



Non-Directed Oxidation of Unactivated C(sp³)-H Bonds

LSPN GROUP SEMINAR BY BALÁZS BUDAI

28.02.2019

Non-Directed C(sp³)-H oxidation

Focus on:

- Non-directed C(sp³)-H oxidation
- Non-activated C(sp³)-H bonds

Challenges

C(sp³)-H bond properties:

1. BDE ~96-101 kcal/mol
2. Lack of high energy n orbital
3. Lack of low energy π^* orbital
4. Very high pKa

Overoxidation

1. Product is often more reactive than SM
2. FG tolerance

Regioselectivity – strategies:

1. Tune redox potential of reagent
2. Play with steric elements
3. ~~Directing group~~
4. ~~Intramolecular reaction~~

Briefly or Not Discussed:

- Activated C(sp³)-H bonds
- Methods with low synthetic utility
- Supramolecular systems
- Enzymatic oxidations
- Heterogeneous methods

Non-Directed C(sp³)-H oxidation

Focus on:

- Non-directed C(sp³)-H oxidation
- Non-activated C(sp³)-H bonds

Challenges

C(sp³)-H bond properties:

1. BDE ~96-101 kcal/mol
2. Lack of high energy n orbital
3. Lack of low energy π^* orbital
4. Very high pKa

Overoxidation

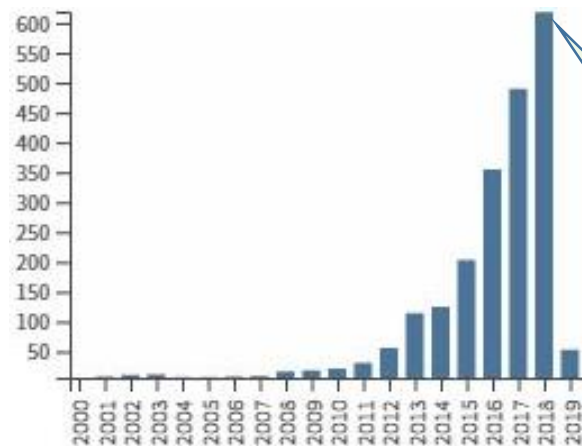
1. Product is often more reactive than SM
2. FG tolerance

Regioselectivity – strategies:

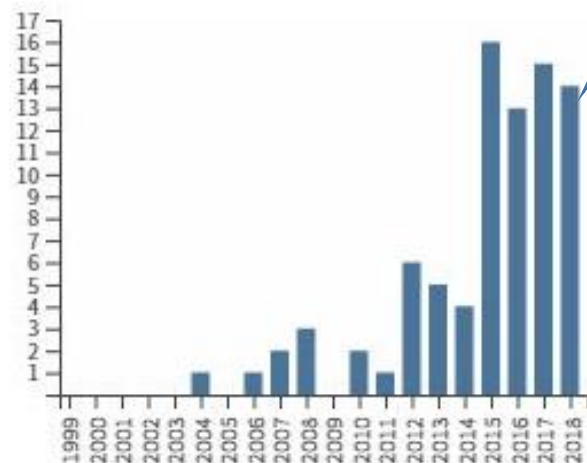
1. Tune redox potential of reagent
2. Play with steric elements
3. ~~Directing group~~
4. ~~Intramolecular reaction~~

“C(sp³)-H oxidation” in the literature

Sum of Times Cited by Year



Total Publications by Year



Briefly or Not Discussed:

- Activated C(sp³)-H bonds
- Methods with low synthetic utility
- Supramolecular systems
- Enzymatic oxidations
- Heterogeneous methods

Note that the numbers are still very small!

Is it the beginning of something bigger?

Non-Directed C(sp³)-H oxidation

Focus on:

- Non-directed C(sp³)-H oxidation
- Non-activated C(sp³)-H bonds

Challenges

C(sp³)-H bond properties:

1. BDE ~96-101 kcal/mol
2. Lack of high energy n orbital
3. Lack of low energy π^* orbital
4. Very high pKa

Overoxidation

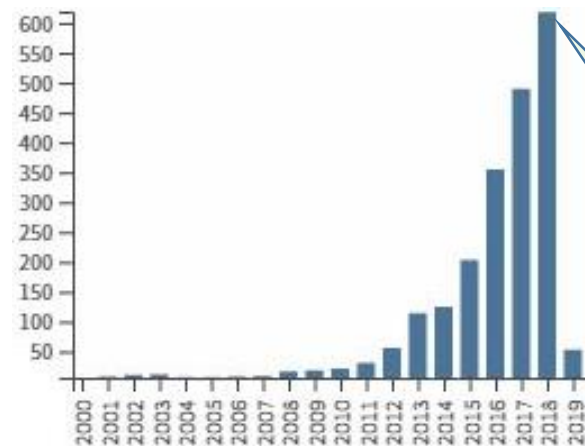
1. Product is often more reactive than SM
2. FG tolerance

Regioselectivity – strategies:

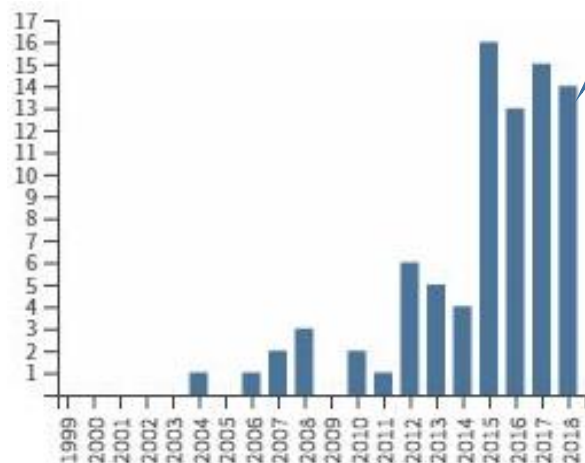
1. Tune redox potential of reagent
2. Play with steric elements
3. ~~Directing group~~
4. ~~Intramolecular reaction~~

“C(sp³)-H oxidation” in the literature

Sum of Times Cited by Year



Total Publications by Year



Briefly or Not Discussed:

- Activated C(sp³)-H bonds
- Methods with low synthetic utility
- Supramolecular systems
- Enzymatic oxidations
- Heterogeneous methods

Note that the numbers are still very small!

Is it the beginning of something bigger?

Booming literature – concept change

Before 2007

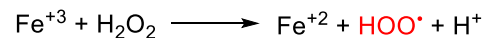
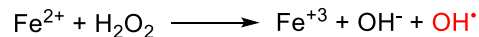
Directing group / molecular recognition is necessary to distinguish between C-H bonds

Following 2007

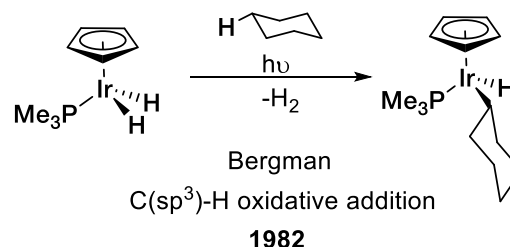
Electronic, steric and stereoelectronic effects together can control selectivity between C-H bonds

Historical overview

Henry J.H. Fenton



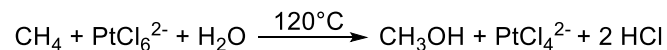
- HO-H bond BDE = 119 kcal/mol
(2nd strongest after H-F BDE 136kcal/mol)
- Oxidizes everything
- Wastewater treatment



1894

1969

Shilov system

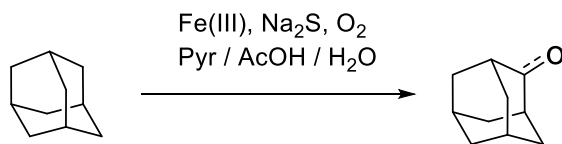


Shilov

stoichiometric in Pt
overoxidation

Periana

catalytic in Pt
no overoxidation
high yield (70% in one pass)



Systems developed later:

Oxaziridine

Stable at r.t.
selective for 3° C-H bonds
easy to prepare

Gif

GO (electrochemical)

GoAgg

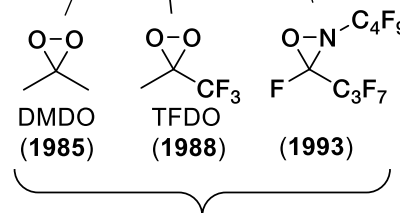
GChAgg

"The nomenclature of the Gif systems is geographically based:
G stands for Gif-sur-Yvette, O is for Orsay, Agg is for Aggieland,
Texas A&M, and Ch is for Chemogolovka, Russia." - Barton, D. H. R.
Acc. Chem. Res., 1992 25 504-512

1998

Shilov-Periana
process

2019



stereoretentive C(sp³)-H ox.

Fenton, *JChemSocTrans* **1894** 899-910

Shilov *Zhurnal Fizicheskoi Khimii* **1969** 2174-2175

Bergman *JACS* **1982** 352

Barton, D. H. R. *Acc. Chem. Res.* **1992**, 25 (11), 504-512.

Barton, D. H. R. *Chem. Soc. Rev.* **1996**, 25 (4), 237.

TFDO / Curci *JOC* **1988** 3890

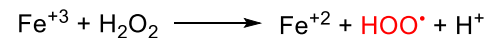
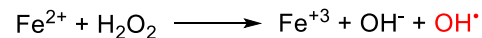
DMDO / Murray, *JOC* **1985** 2847

Oxaziridine / DesMarteau *JOC* **1993** 4754

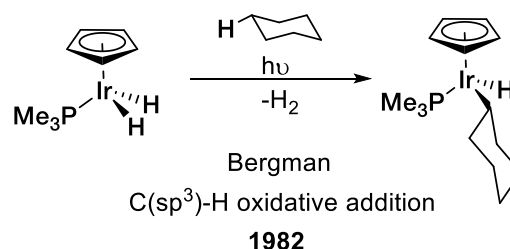
Periana *Science* **1998** 560

Historical overview

Henry J.H. Fenton



- HO-H bond BDE = 119 kcal/mol (2nd strongest after H-F BDE 136kcal/mol)
- Oxidizes everything
- Wastewater treatment

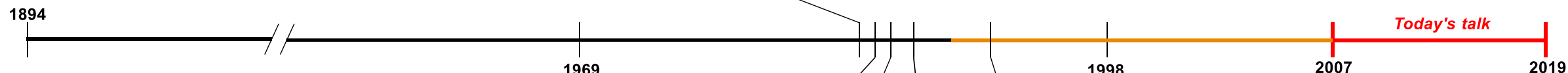


Gif reaction and its varieties by Barton

Heme and non-heme Fe/Mn cat.:

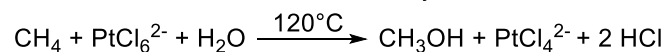
- Bernard Meunier
- John T. Groves
- Lawrence Que
- Miquel Costas
- David Goldberg

C-H oxidative addition (via preexisting function)



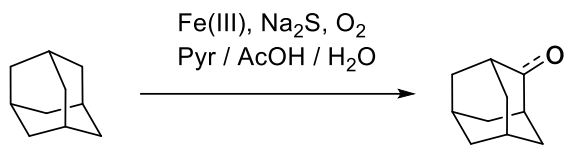
Shilov

stoichiometric in Pt
overoxidation



Periana

catalytic in Pt
no overoxidation
high yield (70% in one pass)



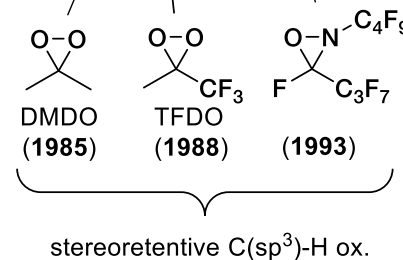
Systems developed later:

Oxaziridine

Stable at r.t.
selective for 3° C-H bonds
easy to prepare

Gif
GO (electrochemical)
GoAgg
GChAgg

"The nomenclature of the Gif systems is geographically based: G stands for Gif-sur-Yvette, O is for Orsay, Agg is for Aggieland, Texas A&M, and Ch is for Chemogolovka, Russia." - Barton, D. H. R. *Acc. Chem. Res.*, 1992 25 504-512



1998
Shilov-Periana process

2007

Today's talk

2019

Fenton, *JChemSocTrans* **1894** 899-910

Shilov *Zhurnal Fizicheskoi Khimii* **1969** 2174-2175

Bergman *JACS* **1982** 352

Barton, D. H. R. *Acc. Chem. Res.* **1992**, 25 (11), 504-512.

Barton, D. H. R. *Chem. Soc. Rev.* **1996**, 25 (4), 237.

TFDO / Curci *JOC* **1988** 3890

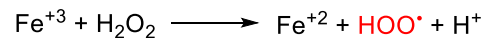
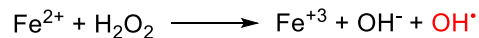
DMDO / Murray, *JOC* **1985** 2847

Oxaziridine / DesMarteau *JOC* **1993** 4754

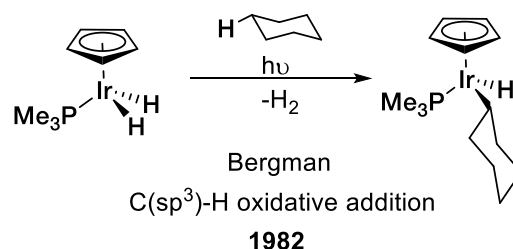
Periana *Science* **1998** 560

Historical overview

Henry J.H. Fenton



- HO-H bond BDE = 119 kcal/mol (2nd strongest after H-F BDE 136kcal/mol)
- Oxidizes everything
- Wastewater treatment



Gif reaction and its varieties by Barton

Heme and non-heme Fe/Mn cat.:

- Bernard Meunier
- John T. Groves
- Lawrence Que
- Miquel Costas
- David Goldberg

C-H oxidative addition (via preexisting function)

1894

Shilov

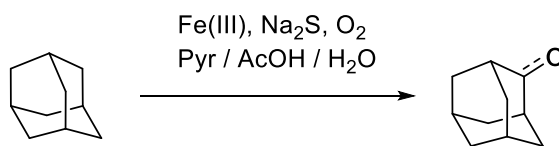
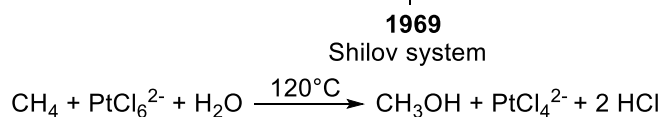
stoichiometric in Pt
overoxidation

Periana

catalytic in Pt
no overoxidation
high yield (70% in one pass)

Oxaziridine

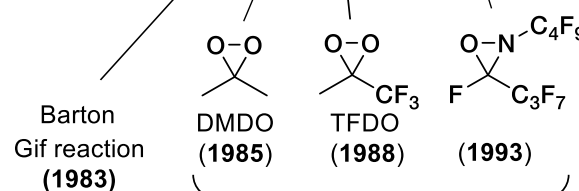
Stable at r.t.
selective for 3° C-H bonds
easy to prepare



Systems developed later:

Gif
GO (electrochemical)
GoAgg
GChAgg

"The nomenclature of the Gif systems is geographically based: G stands for Gif-sur-Yvette, O is for Orsay, Agg is for Aggieland, Texas A&M, and Ch is for Chemogolovka, Russia." - Barton, D. H. R. *Acc. Chem. Res.*, 1992 25 504-512



stereoretentive C(sp³)-H ox.

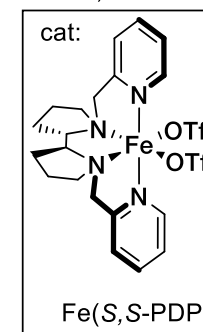
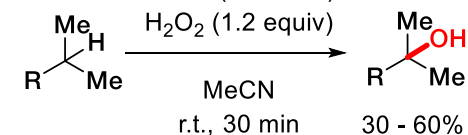
1998

Shilov-Periana
process

2007

White

First preparatively useful C(sp³)-H ox.



2019

Today's talk

Fenton, *JChemSocTrans* **1894** 899-910

Shilov *Zhurnal Fizicheskoi Khimii* **1969** 2174-2175

Bergman *JACS* **1982** 352

Barton, D. H. R. *Acc. Chem. Res.* **1992**, 25 (11), 504-512.

Barton, D. H. R. *Chem. Soc. Rev.* **1996**, 25 (4), 237.

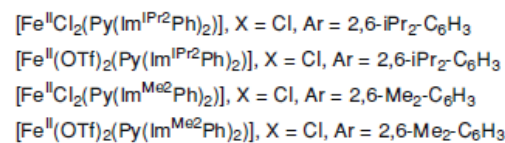
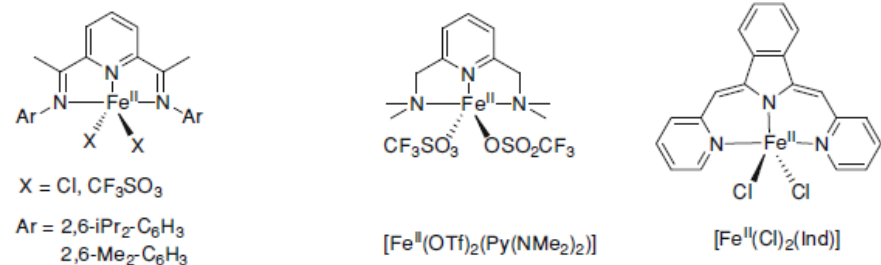
TFDO / Curci *JOC* **1988** 3890

DMDO / Murray, *JOC* **1985** 2847

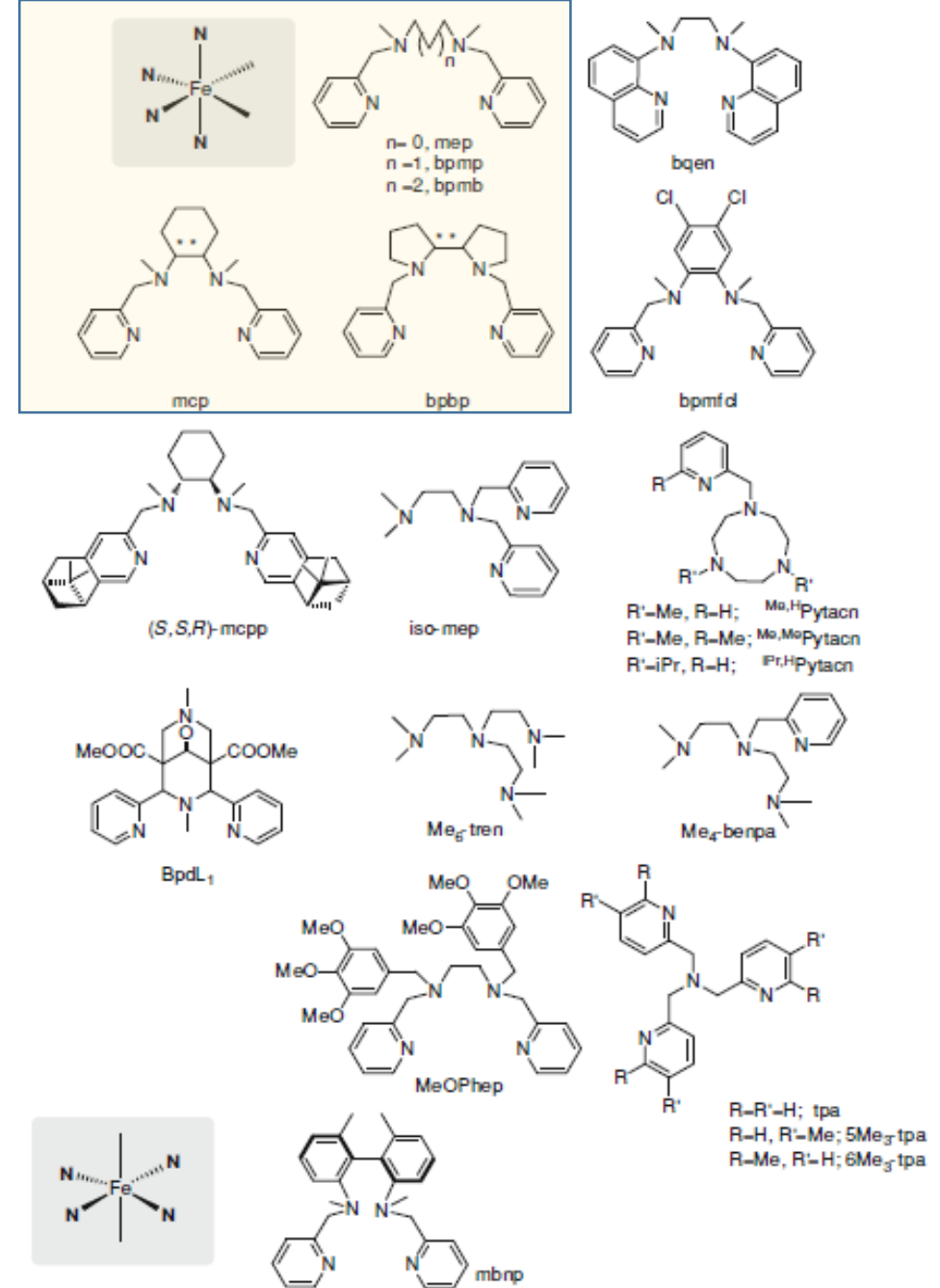
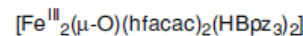
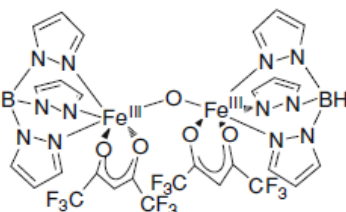
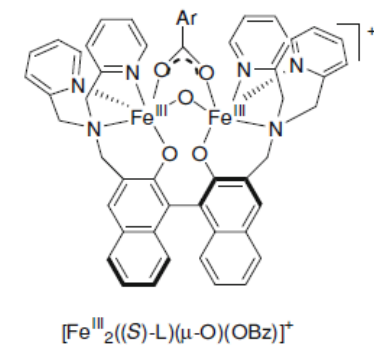
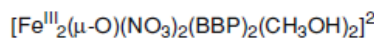
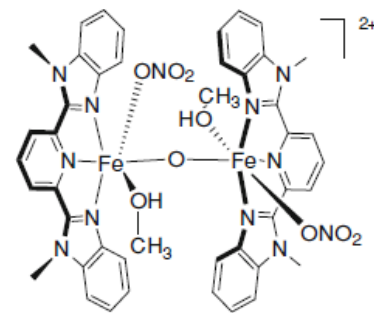
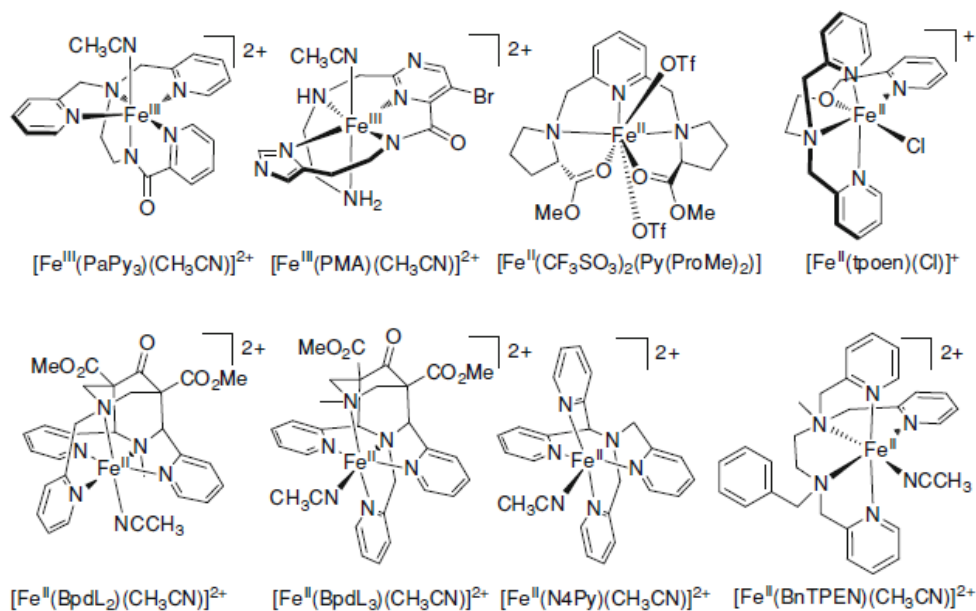
Oxaziridine / DesMarteau *JOC* **1993** 4754

Periana *Science* **1998** 560

Ligands developed for C(sp³)-H oxidation (before 2007)



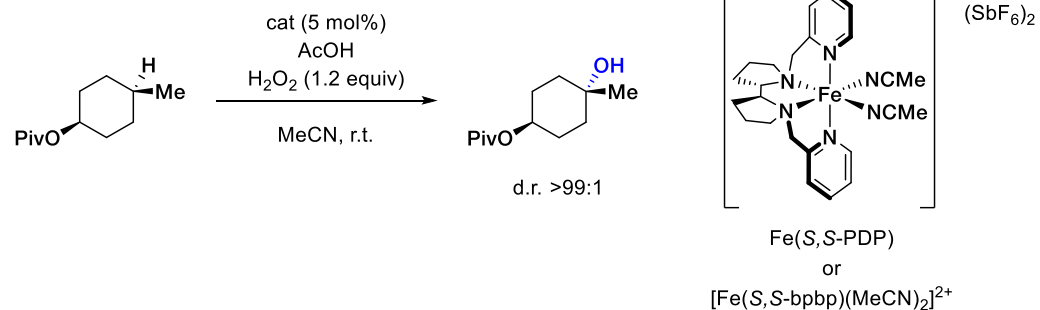
Scheme 5.12 Iron catalysts with tridentate N-based ligands. OTf stands for CF₃SO₃ anion



Scheme 5.14 Schematic representation of relevant tetradentate ligands used to prepare mononuclear iron(II) complexes to perform alkane oxidations

White – the first preparatively useful method

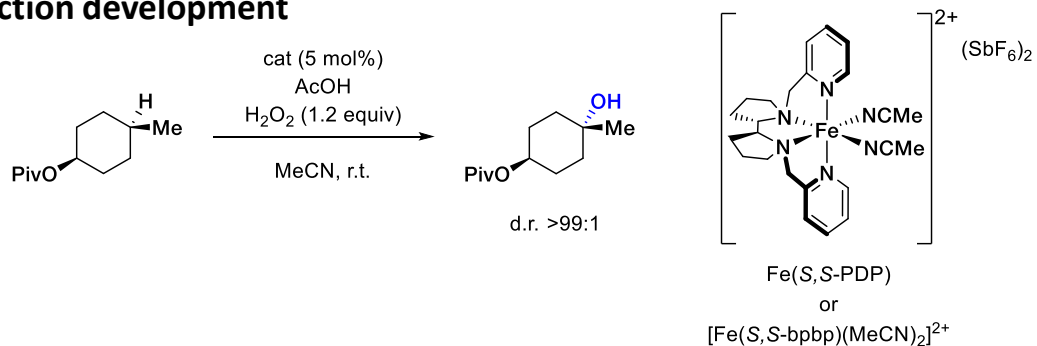
Reaction development



Entry	Catalyst	AcOH(equiv.)	Yield (%)	Conv.(%) ^a	Select (%) ^b
1	[Fe ^{II} (mep)(CH ₃ CN) ₂] ²⁺	0	7	12	56
2	[Fe ^{II} (S,S-bppb)(CH ₃ CN) ₂] ²⁺	0	14	15	92
3	[Fe ^{II} (mep)(CH ₃ CN) ₂] ²⁺	0.5	26	41	62
4	[Fe ^{II} (S,S-bppb)(CH ₃ CN) ₂] ²⁺	0.5	38	42	90
5 ^c	[Fe ^{II} (S,S-bppb)(CH ₃ CN) ₂] ²⁺	0.5	51	–	–

White – the first preparatively useful method

Reaction development

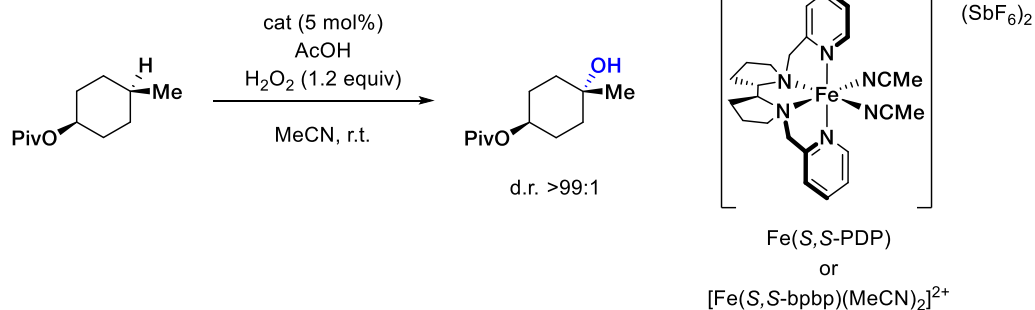


Entry	Catalyst	AcOH(equiv.)	Yield (%)	Conv.(%) ^a	Select (%) ^b
1	[Fe ^{II} (mep)(CH ₃ CN) ₂] ²⁺	0	7	12	56
2	[Fe ^{II} (S,S-bppb)(CH ₃ CN) ₂] ²⁺	0	14	15	92
3	[Fe ^{II} (mep)(CH ₃ CN) ₂] ²⁺	0.5	26	41	62
4	[Fe ^{II} (S,S-bppb)(CH ₃ CN) ₂] ²⁺	0.5	38	42	90
5 ^c	[Fe ^{II} (S,S-bppb)(CH ₃ CN) ₂] ²⁺	0.5	51	–	–

"e) iterative addition protocol" = added 3x(cat+reagent+additive)
Real equivalents are: **cat (15 mol%), AcOH (1.5 equiv.), H₂O₂ (3.6 equiv)**

White – the first preparatively useful method

Reaction development



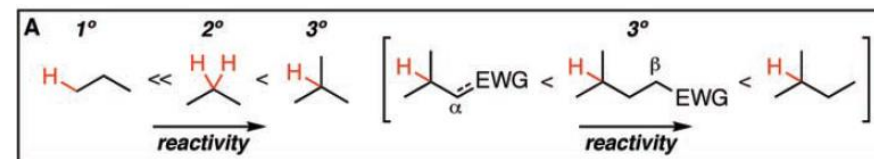
Entry	Catalyst	AcOH(equiv.)	Yield (%)	Conv.(%) ^a	Select (%) ^b
1	[Fe ^{II} (mep)(CH ₃ CN) ₂] ²⁺	0	7	12	56
2	[Fe ^{II} (S,S-bpp)(CH ₃ CN) ₂] ²⁺	0	14	15	92
3	[Fe ^{II} (mep)(CH ₃ CN) ₂] ²⁺	0.5	26	41	62
4	[Fe ^{II} (S,S-bpp)(CH ₃ CN) ₂] ²⁺	0.5	38	42	90
5 ^c	[Fe ^{II} (S,S-bpp)(CH ₃ CN) ₂] ²⁺	0.5	51	–	–

"e) iterative addition protocol" = added 3x(cat+reagent+additive)
Real equivalents are: cat (15 mol%), AcOH (1.5 equiv.), H₂O₂ (3.6 equiv)

Scope and observations

Entry	Product	Isolated % Yield (rsm) [*]	Entry	Product	Isolated % Yield (rsm) [*]
1	5, X = Br	46 (26)	6	(+)-10, Z = H	57 (27)
2	6, X = OAc	53 (43)	7	(+)-11, Z = OAc	43 (42)
3	7	60 (18)	8	(-)-12	33 (67) 90 [†] (8)
4	8	43 (33)	9	13	52 (20)
5	9	52 (21)	10	14	92 [‡]

^{*}rsm = % recovered unoxidized starting material. [†]Starting material was recycled five times. [‡]GC yield.

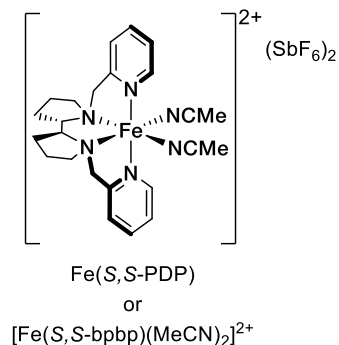
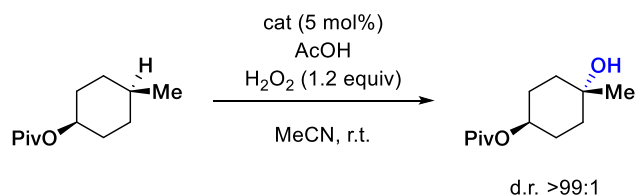


B

Entry	Substrate	Major Product	Isolated %Yield [*] (rsm) [†]	[Remote: Proximal] [‡]	
1	remote	proximal	15, X = H	48 [§] (29)	1:1
2			16, X = OAc	43 (35)	5:1
3			17, X = Br	39 (32)	9:1
4			18, X = F	43 (20)	6:1
5			19, X = OAc	49 (21)	29:1
6			20, X = Br	48 (17)	20:1
7			21, R = CH ₃	52 (18)	>99:1
8			22, R = OCH ₃	56 (32)	>99:1

White – the first preparatively useful method

Reaction development



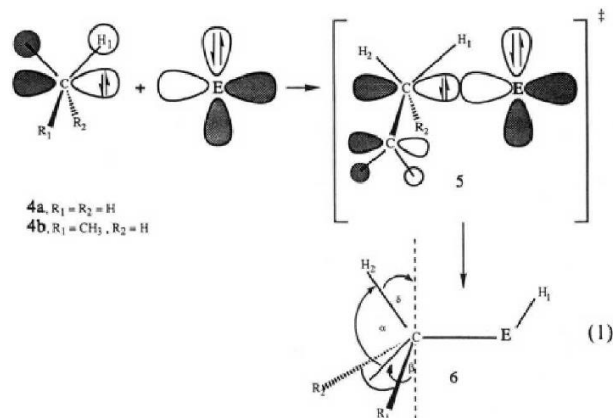
Scope and observations

Entry	Catalyst	AcOH(equiv.)	Yield (%)	Conv. (%) ^a	Select (%) ^b
1	[Fe ^{II} (mep)(CH ₃ CN) ₂] ²⁺	0	7	12	56
2	[Fe ^{II} (S,S-bppb)(CH ₃ CN) ₂] ²⁺	0	14	15	92
3	[Fe ^{II} (mep)(CH ₃ CN) ₂] ²⁺	0.5	26	41	62
4	[Fe ^{II} (S,S-bppb)(CH ₃ CN) ₂] ²⁺	0.5	38	42	90
5 ^c	[Fe ^{II} (S,S-bppb)(CH ₃ CN) ₂] ²⁺	0.5	51	–	–

“e) iterative addition protocol” = added 3x(cat+reagent+additive)
Real equivalents are: cat (15 mol%), AcOH (1.5 equiv.), H₂O₂ (3.6 equiv)

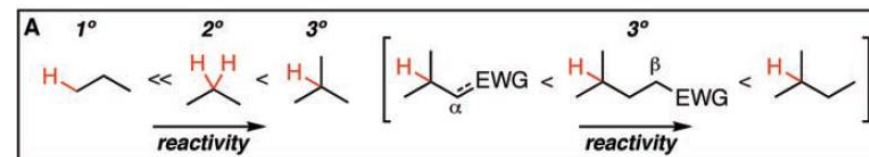
Mechanism – electrophilic oxygen C-H insertion?

- No proposed mechanism
- Cited ref. on mechanism is consistent with DMDO / TMDO oxidation
McDouall, J. J. W. *J. Am. Chem. Soc.* **1993**, *115* (13), 5768–5775.
- Competitors (Que, Costas) has already investigated and proposed mechanism - they are barely mentioned among the references
- Reaction is not exactly stereospecific.



Entry	Product	Isolated % Yield (rsm) [*]	Entry	Product	Isolated % Yield (rsm) [*]
1	5, X = Br	46 (26)	6	(+)-10, Z = H	57 (27)
2	6, X = OAc	53 (43)	7	(+)-11, Z = OAc	43 (42)
3	7	60 (18)	8	(-)-12	33 (67) 90 [†] (8)
4	8	43 (33)	9	13	52 (20)
5	9	52 (21)	10	14	92 [‡]

^{*}rsm = % recovered unoxidized starting material. [†]Starting material was recycled five times. [‡]GC yield.

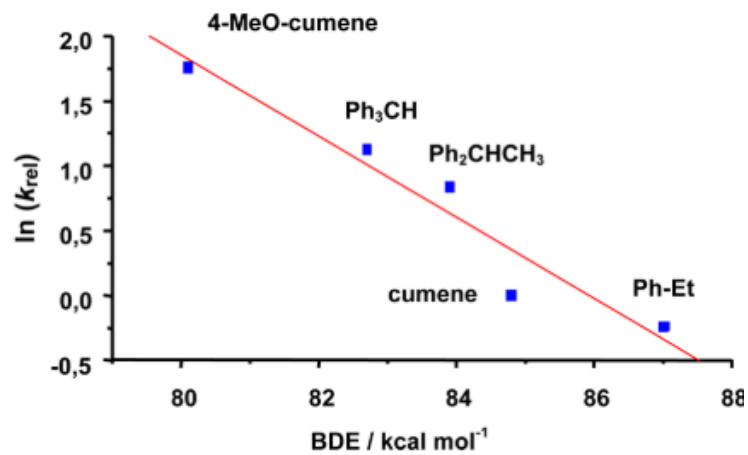
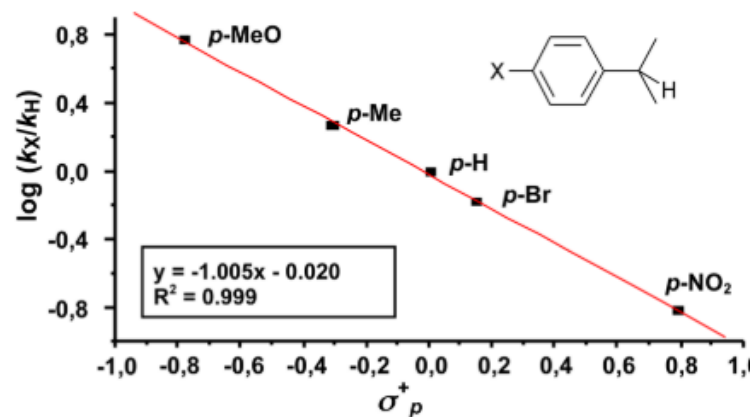


B

Entry	Substrate	Major Product	Isolated %Yield [*] (rsm) [†]	[Remote: Proximal] [‡]
1	remote proximal	15, X = H	48 [§] (29)	1:1
2		16, X = OAc	43 (35)	5:1
3		17, X = Br	39 (32)	9:1
4		18, X = F	43 (20)	6:1
5		19, X = OAc	49 (21)	29:1
6		20, X = Br	48 (17)	20:1
7		21, R = CH ₃	52 (18)	>99:1
8		22, R = OCH ₃	56 (32)	>99:1

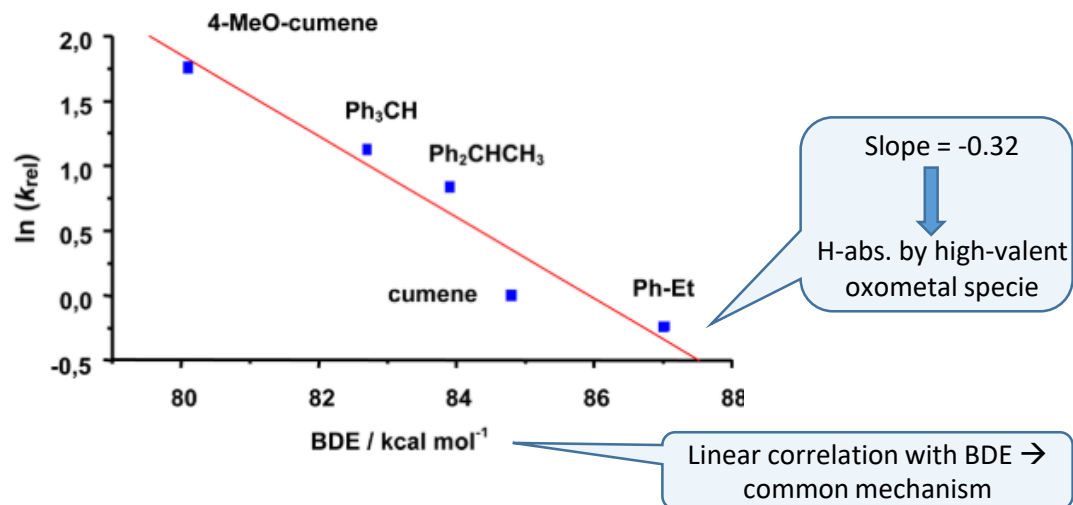
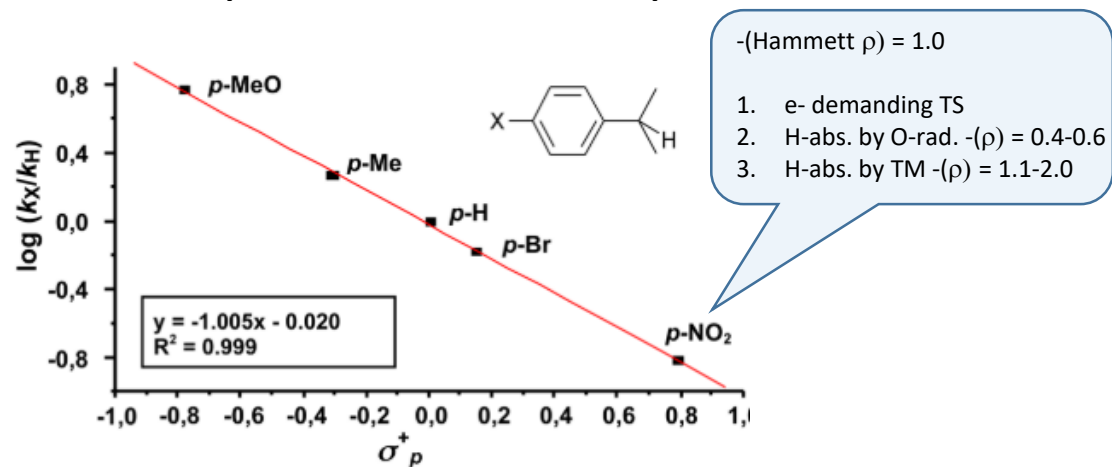
Accepted Mechanism

Hammett plot and BDE-correlation experiment



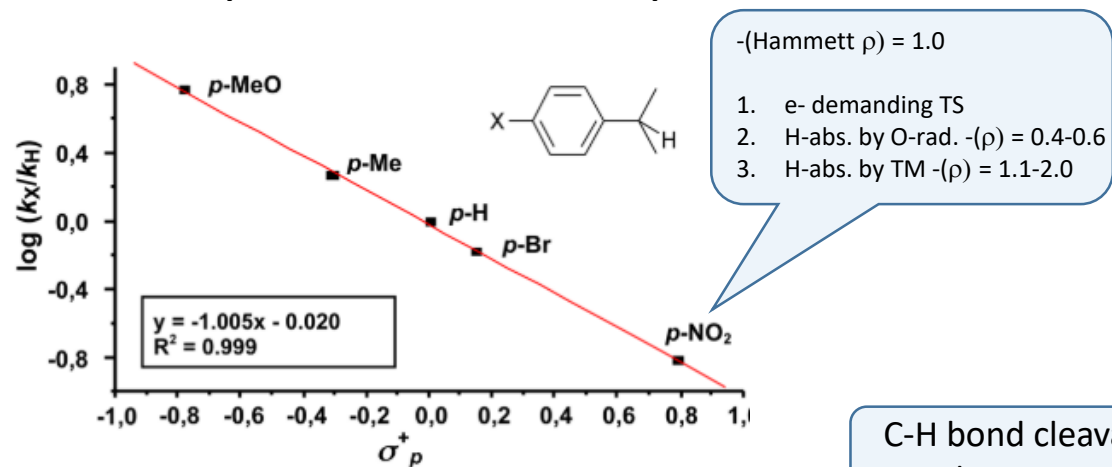
Accepted Mechanism

Hammett plot and BDE-correlation experiment

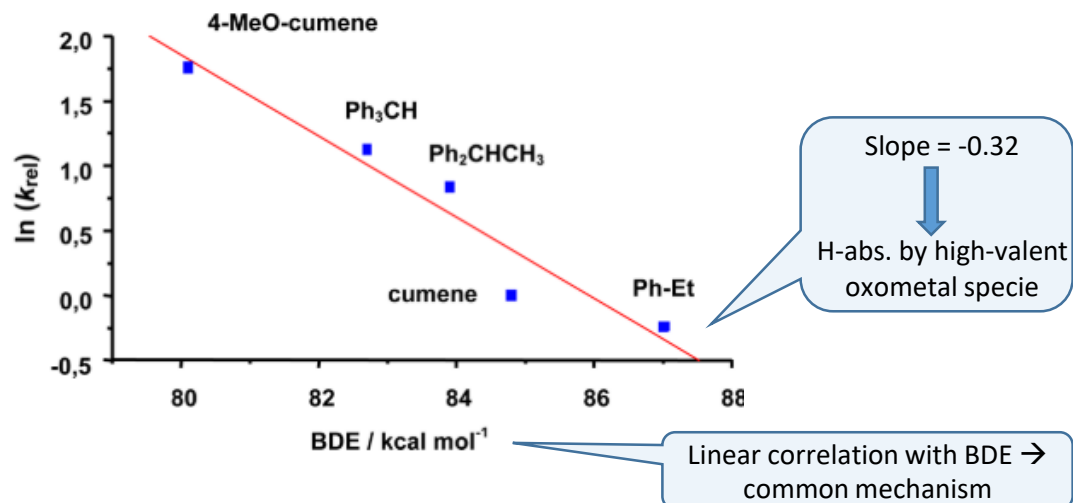


Accepted Mechanism

Hammett plot and BDE-correlation experiment



C-H bond cleavage is rate determining step



Mechanistic studies summary

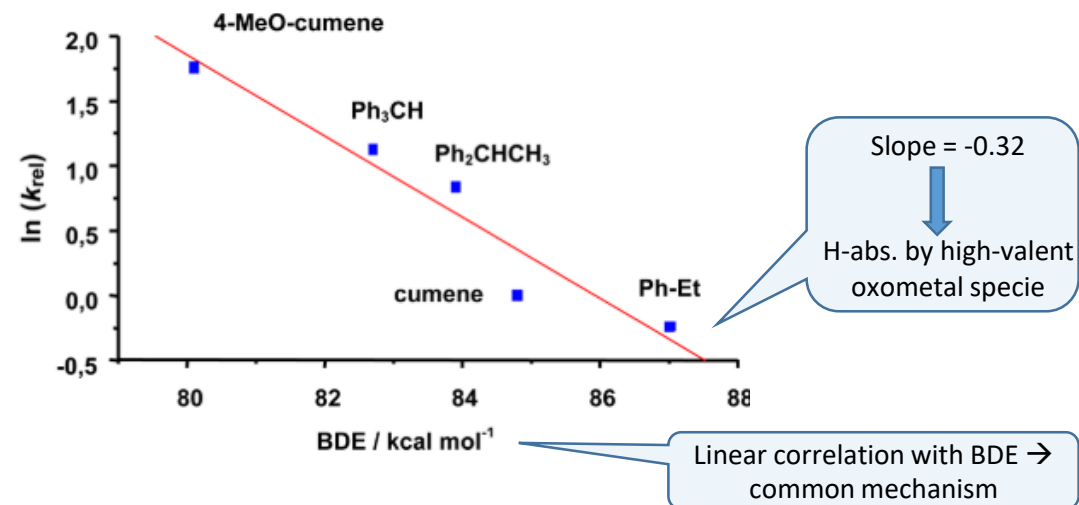
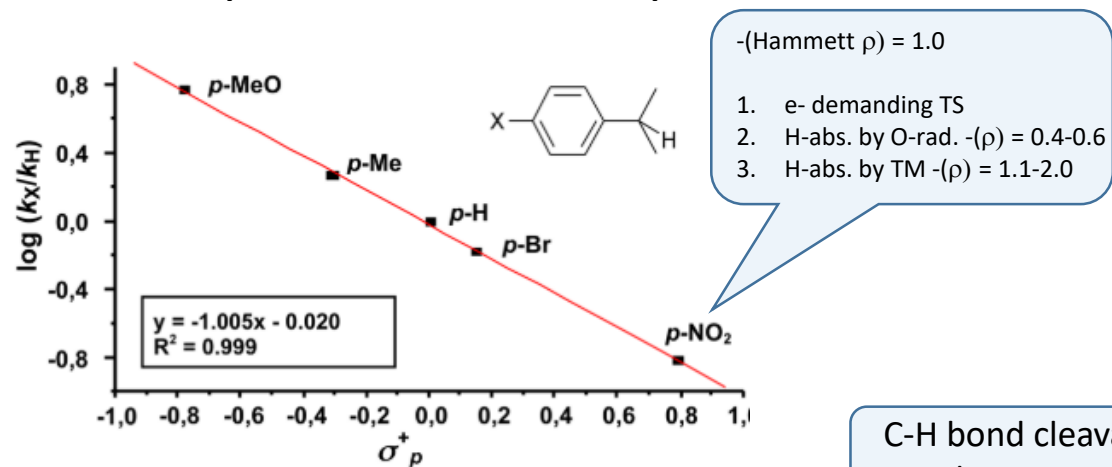
Complex	k_H/k_D^a		RC (%) ^b <i>cis</i> -1,2-DMCH			¹⁸ O (%) from H ₂ ¹⁸ O ^{a,c}		
	Structure	C ₆ H ₁₂ /C ₆ D ₁₂	0 °C	20 °C	30 °C	<i>cis</i> -1,2-DMCH	adamantane	
1		3.5	4.1	> 99	> 99	> 99	–	–
4		3.8	4.7	> 99	98.6	98.6	18 (2.3)	27 (9.1)
5		3.9	3.8	> 99	97.1	94.3	7 (1.5)	18 (21.8)

KIE – characteristic values

Abstracting agent	OH rad.	tBuO rad.	OBt rad.	Fe	Mn	Ru
KIE	1-2	~4	11-27	3.2-4.3	2.2-4.3	4.2-6.5

Accepted Mechanism

Hammett plot and BDE-correlation experiment



Mechanistic studies summary

Complex	k_H/k_D^a		RC (%) ^b <i>cis</i> -1,2-DMCH			¹⁸ O (%) from H ₂ ¹⁸ O ^{a,c}		
	Structure	C ₆ H ₁₂ /C ₆ D ₁₂	0 °C	20 °C	30 °C	<i>cis</i> -1,2-DMCH	adamantane	
1		3.5	4.1	> 99	> 99	> 99	–	–
4		3.8	4.7	> 99	98.6	98.6	18 (2.3)	27 (9.1)
5		3.9	3.8	> 99	97.1	94.3	7 (1.5)	18 (21.8)

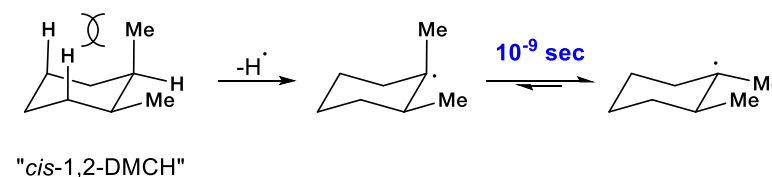
C-H bond cleavage is rate determining step

Partial erosion of stereochemistry

KIE – characteristic values

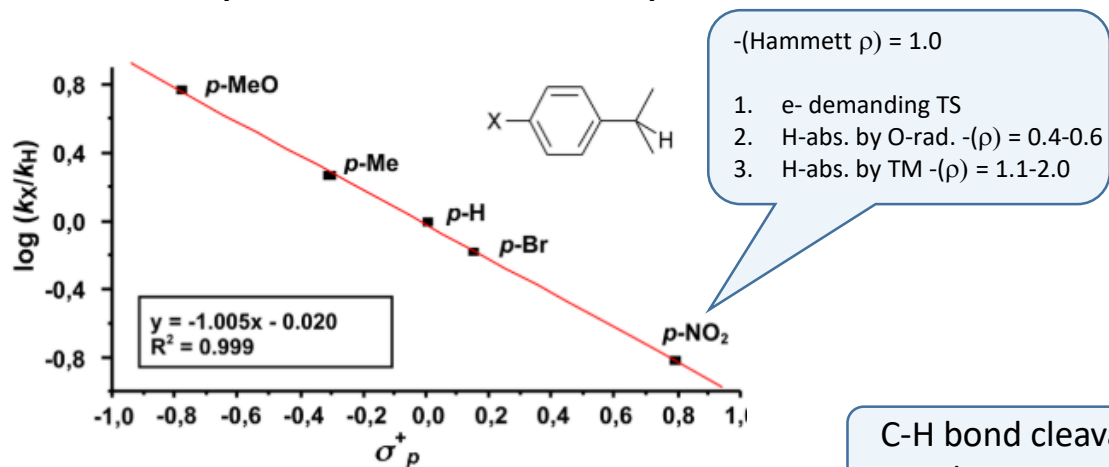
Abstracting agent	OH rad.	tBuO rad.	OBt rad.	Fe	Mn	Ru
KIE	1-2	~4	11-27	3.2-4.3	2.2-4.3	4.2-6.5

Erosion of stereochemistry

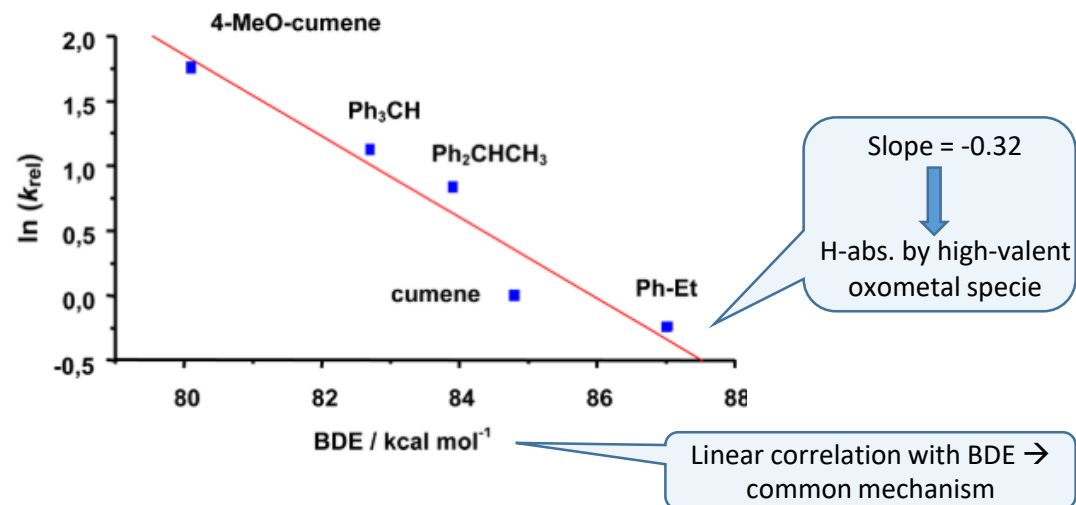


Accepted Mechanism

Hammett plot and BDE-correlation experiment



C-H bond cleavage is rate determining step



Mechanistic studies summary

Complex	k_H/k_D^a		RC (%) ^b <i>cis</i> -1,2-DMCH			¹⁸ O (%) from H ₂ ¹⁸ O ^{a,c}	
		C ₆ H ₁₂ /C ₆ D ₁₂	0 °C	20 °C	30 °C	<i>cis</i> -1,2-DMCH	adamantane
1	3.5	4.1	> 99	> 99	> 99	–	–
4	3.8	4.7	> 99	98.6	98.6	18 (2.3)	27 (9.1)
5	3.9	3.8	> 99	97.1	94.3	7 (1.5)	18 (21.8)

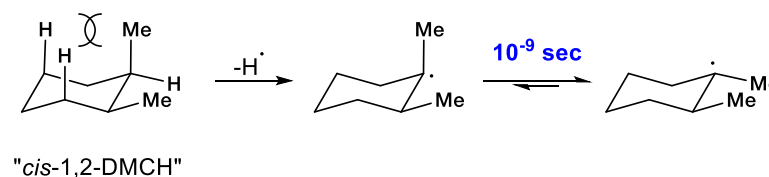
Partial erosion of stereochemistry

¹⁸O incorporation

KIE – characteristic values

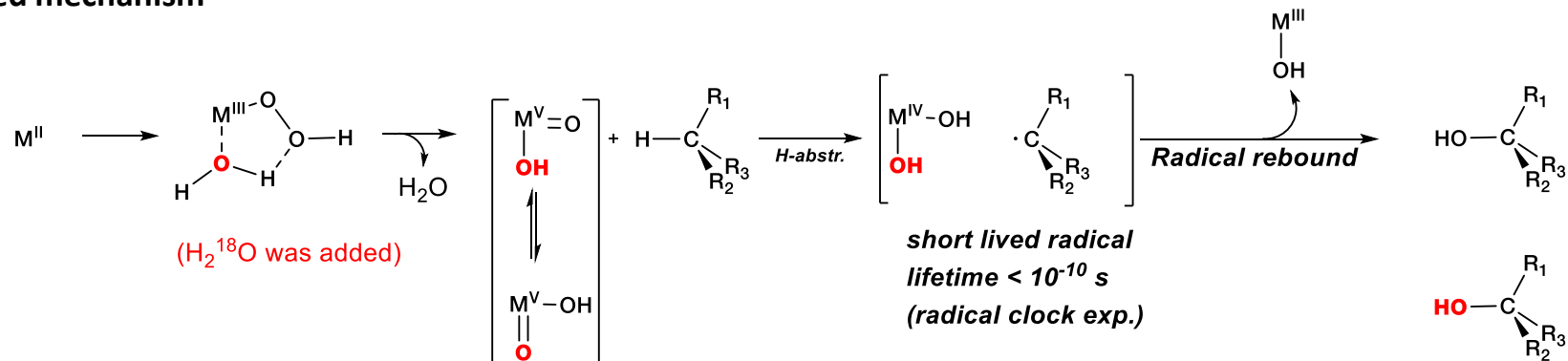
Abstracting agent	OH rad.	tBuO rad.	OBt rad.	Fe	Mn	Ru
KIE	1-2	~4	11-27	3.2-4.3	2.2-4.3	4.2-6.5

Erosion of stereochemistry



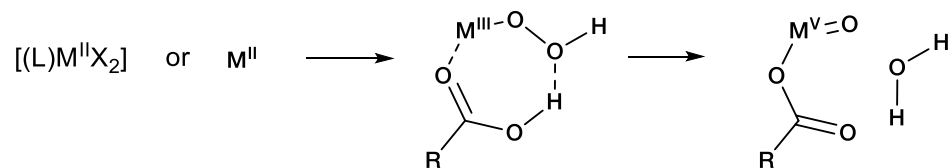
Accepted Mechanism

Proposed mechanism

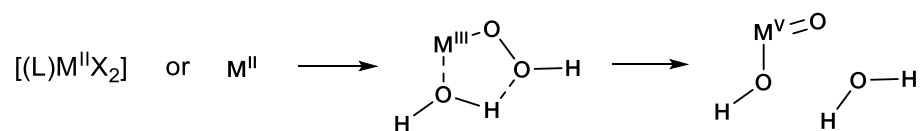


^{18}O incorporation suggest $M=O$ intermediate

Acetic acid mediated Fe(V) generation



Water mediated Fe(V) generation

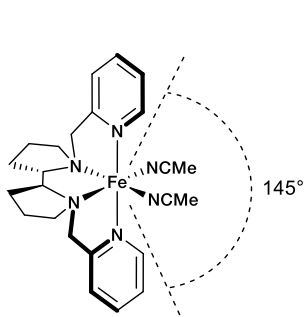


Mechanistic studies:

- (1) Bryliakov, K. P. *ACS Catal.* **2015**, *5* (1), 39–44.
 - (2) Costas, M. *Nat. Chem.* **2011**, *3* (10), 788–793.
 - (4) Que, L. *J. Am. Chem. Soc.* **2002**, *124* (37), 11056–11063.
 - (5) Que, L. *J. Am. Chem. Soc.* **2001**, *123* (26), 6327–6337.
- and many more references therein...

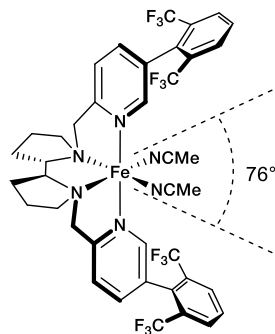
White – further contributions

New catalyst with complimentary reactivity



(S,S)-Fe(PDP) 2007

1

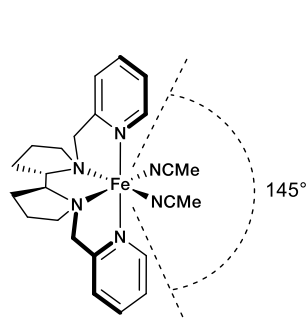


(S,S)-Fe(CF₃-PDP) 2013

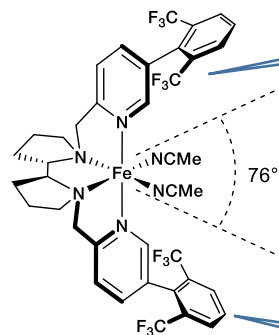
2

White – further contributions

New catalyst with complimentary reactivity



(S,S)-Fe(PDP) 2007
1



(S,S)-Fe(CF₃-PDP) 2013
2

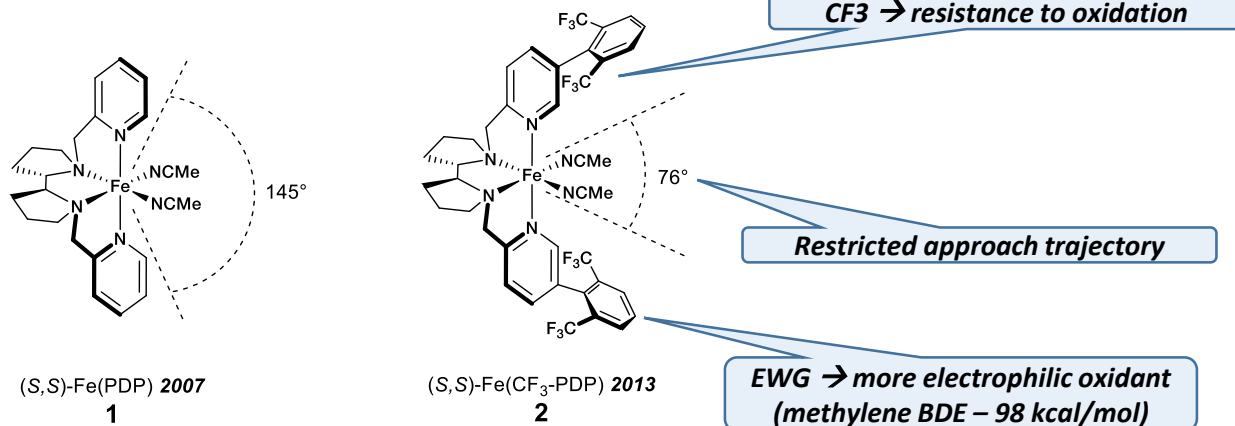
CF₃ → resistance to oxidation

Restricted approach trajectory

**EWG → more electrophilic oxidant
(methylene BDE – 98 kcal/mol)**

White – further contributions

New catalyst with complimentary reactivity

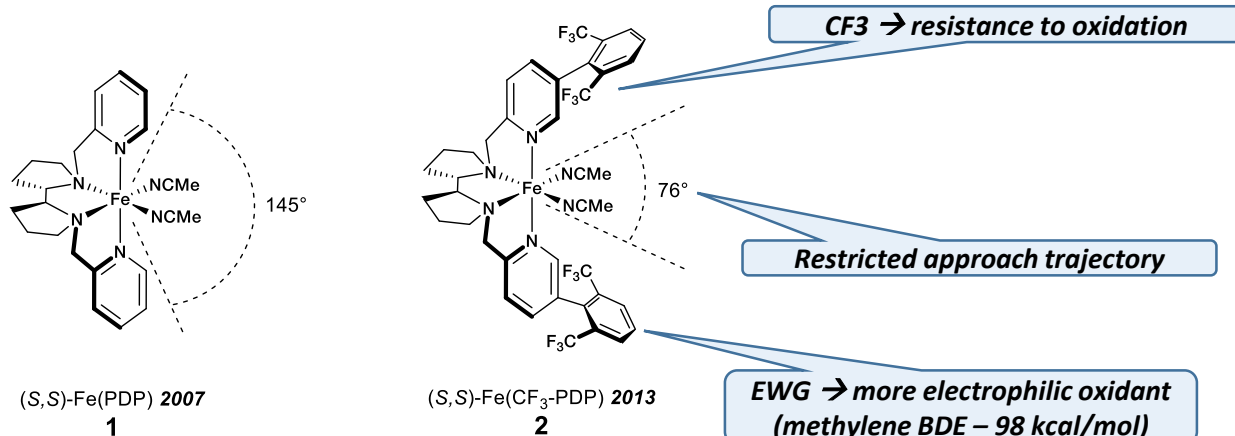


5% Fe(PDP) (1) or Fe(CF₃-PDP) (2)
AcOH, H₂O₂
Method A or B

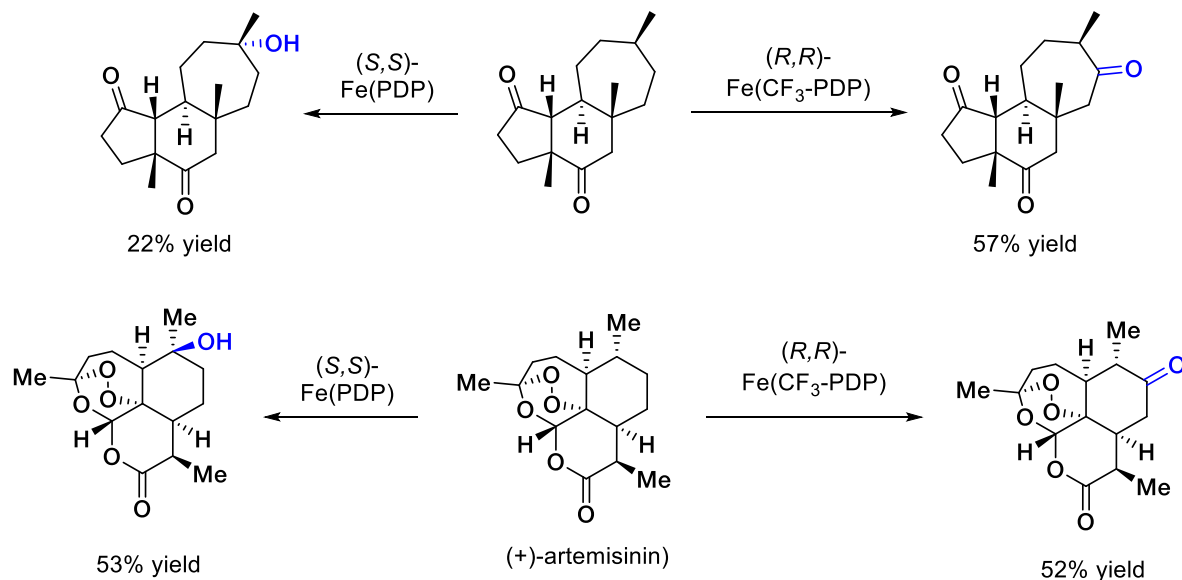
entry (catalyst)	starting material %RSM	oxidation products % yield ^{a,b}		site-selectivity ^c	
					2':3'
1 (1)	16	41	27	1:1	
2 (2)	8	51	11	4:1	
					2':3'
3 (1)	11	28	22	29	2:1
4 (2)	15	44 ^g	26 ^h	7	10:1
					2':3'
5 (1)	0	19	66		1:2
6 (2)	9	51	28		2:1
					2':3'
7 (1)	10	29	43		1:2
8 (2)	8	56	15		4:1
					2':3'
9 (1)	32	24	27		1:1
10 (2)	8	51	6		9:1

White – further contributions

New catalyst with complimentary reactivity



More complex examples

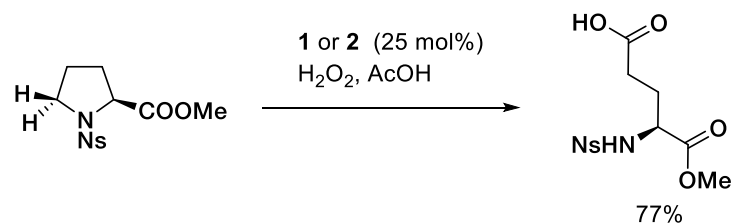


5% Fe(PDP) (1) or Fe(CF₃-PDP) (2)
AcOH, H₂O₂
Method A or B

entry (catalyst)	starting material %RSM	oxidation products % yield ^{a,b}		site-selectivity ^c
1 (1)	16	41	27	1:1
2 (2)	8	51	11	4:1
3 (1)	11	28	22	2:1
4 (2)	15	44 ^g	26 ^h	10:1
5 (1)	0	19	66	1:2
6 (2)	9	51	28	2:1
7 (1)	10	29	43	1:2
8 (2)	8	56	15	4:1
9 (1)	32	24	27	1:1
10 (2)	8	51	6	9:1

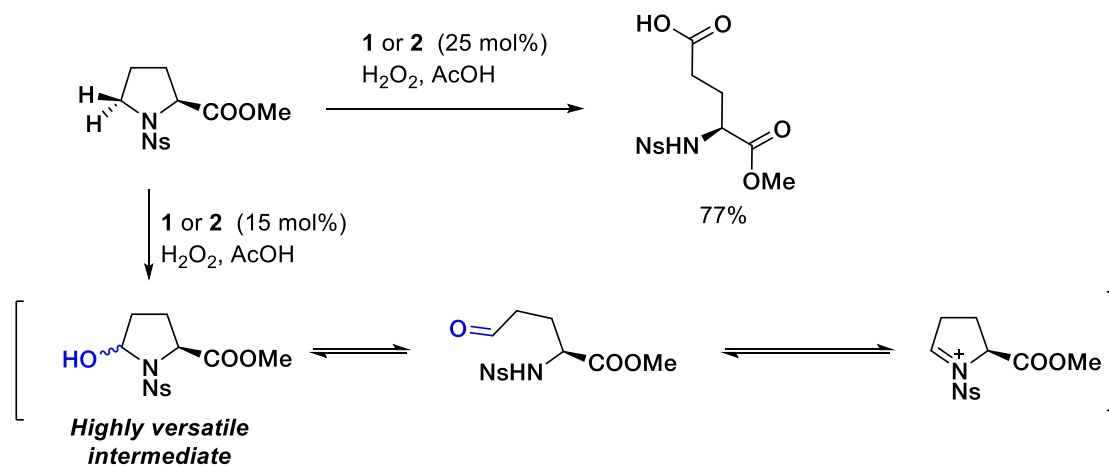
White – further contributions

Diversification of peptides and amino acids



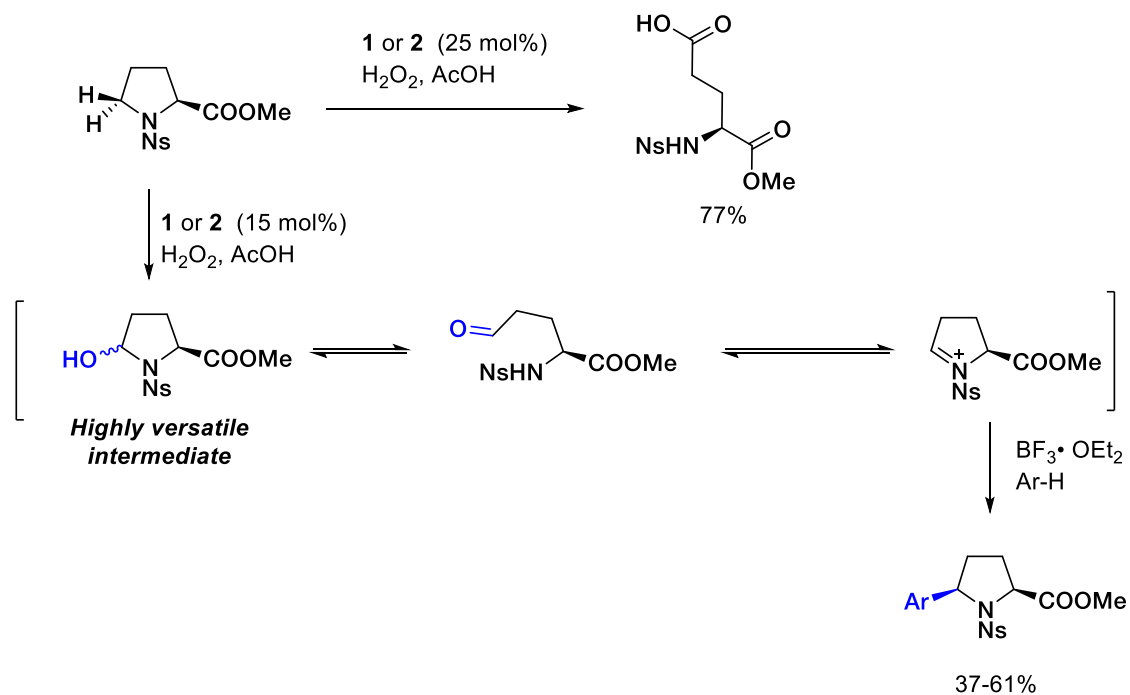
White – further contributions

Diversification of peptides and amino acids



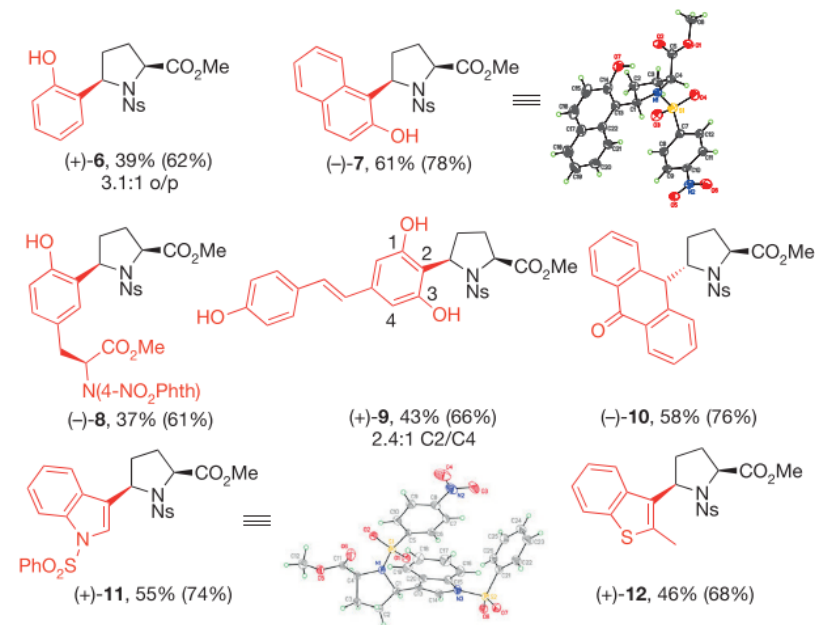
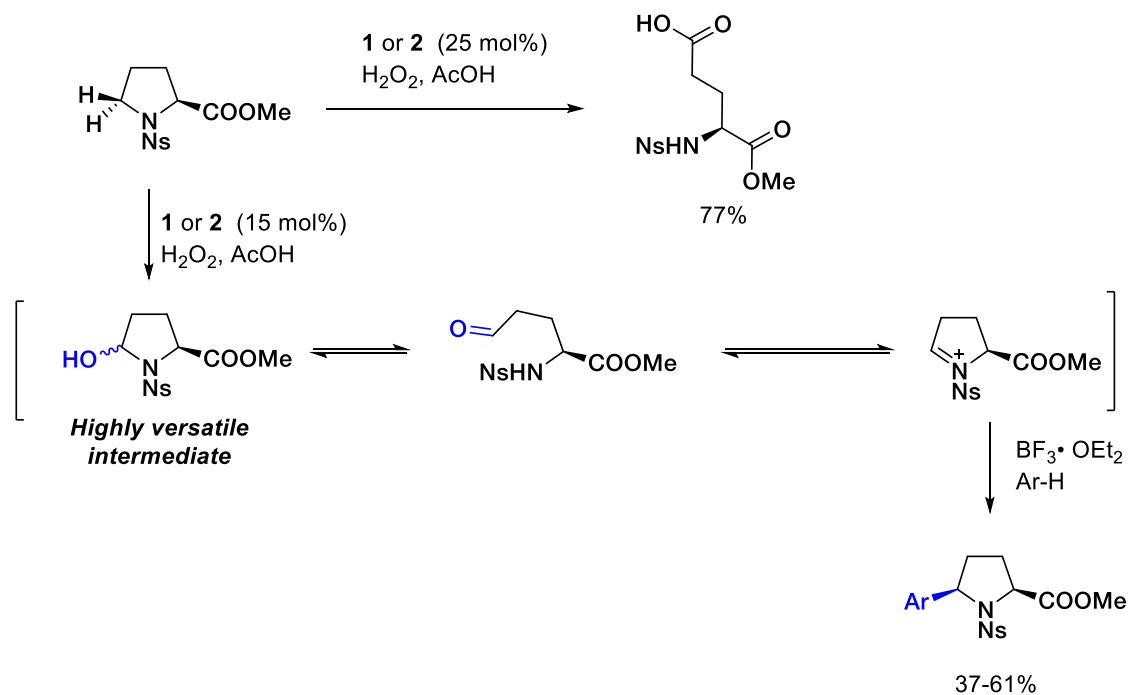
White – further contributions

Diversification of peptides and amino acids



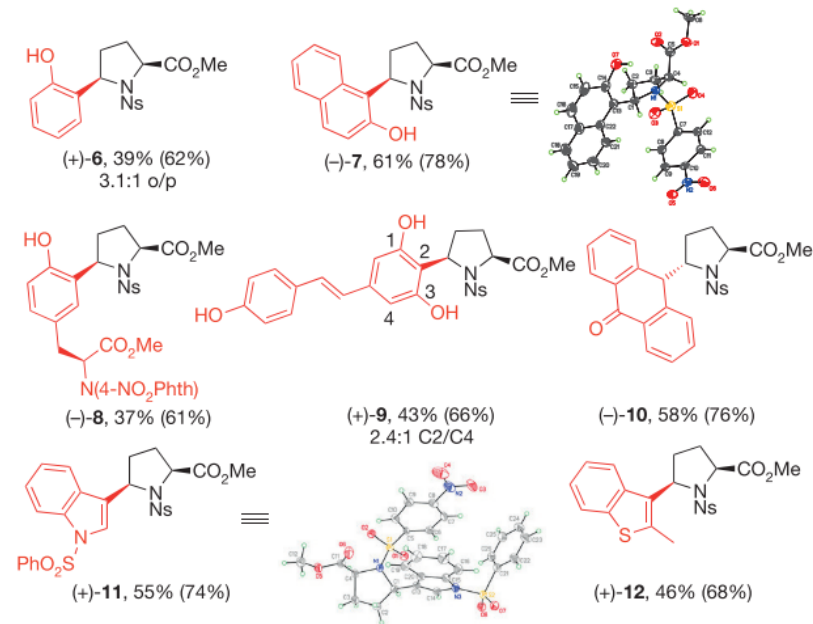
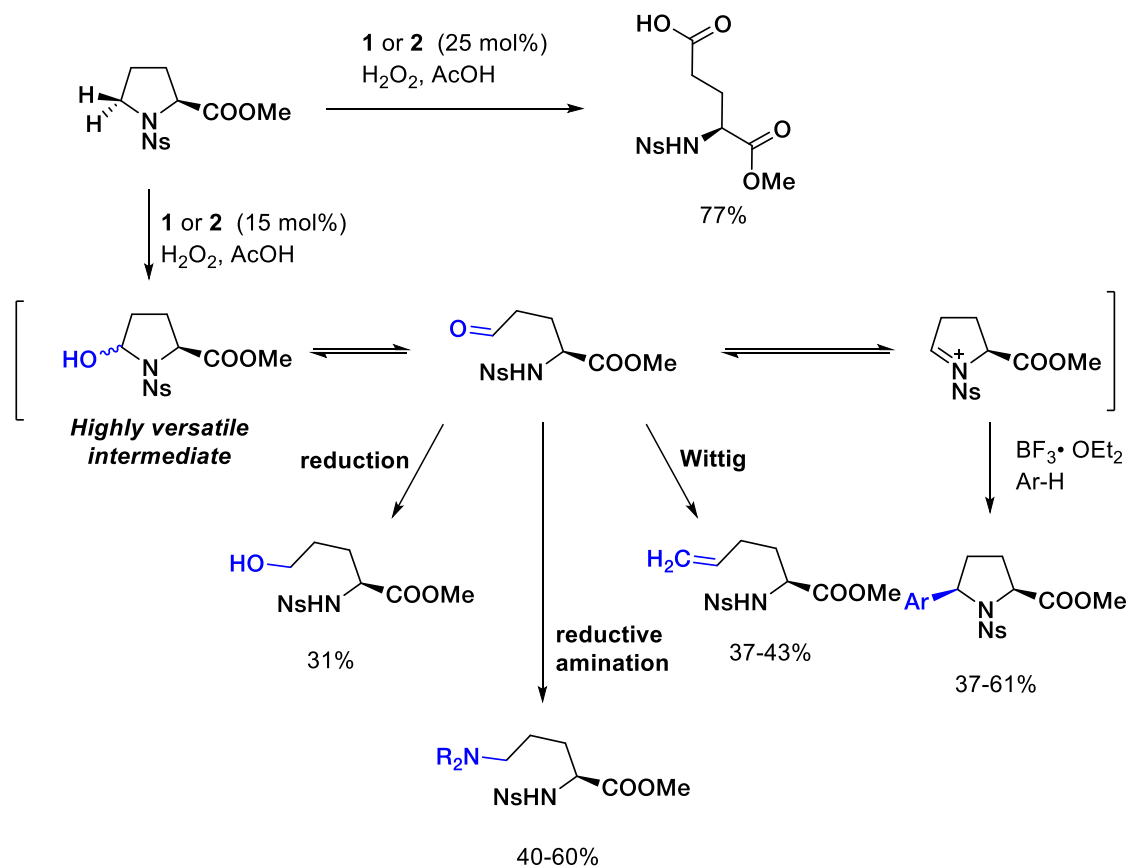
White – further contributions

Diversification of peptides and amino acids



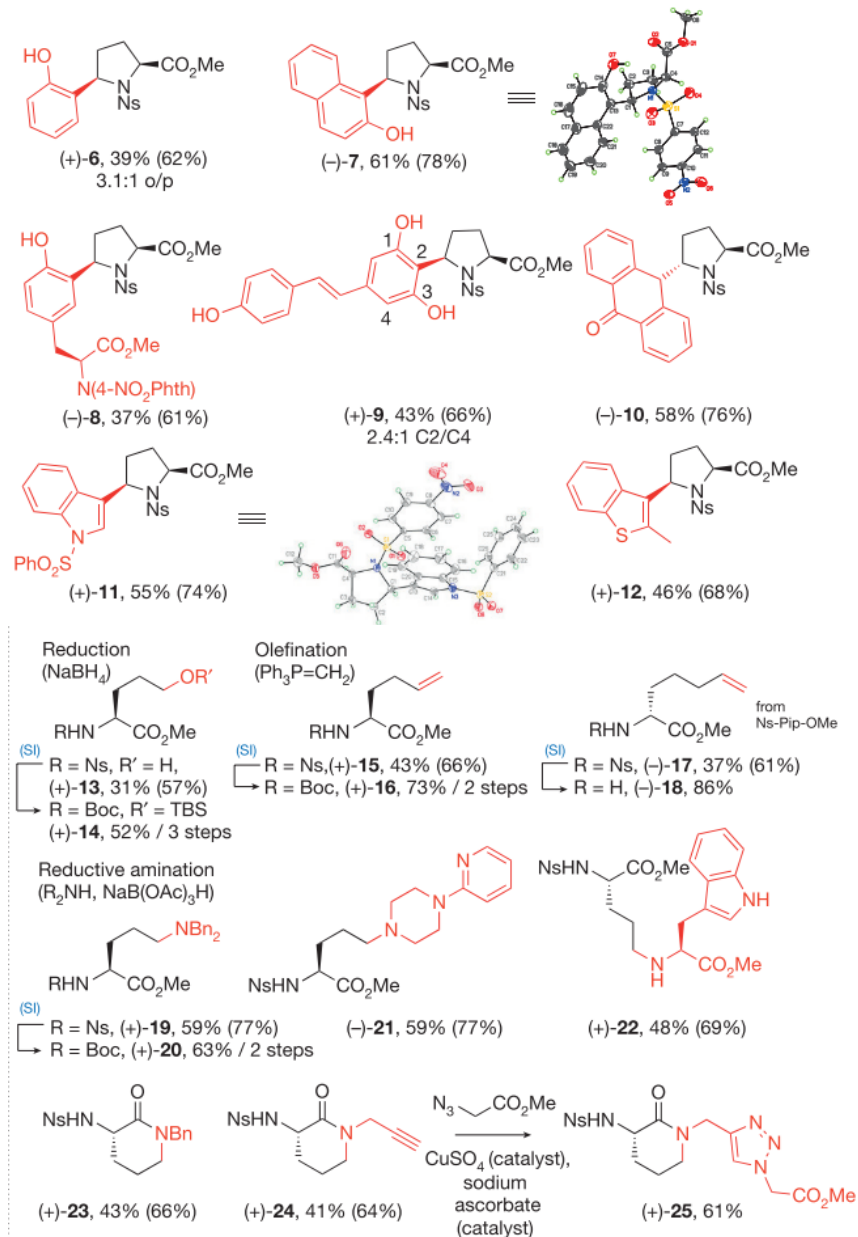
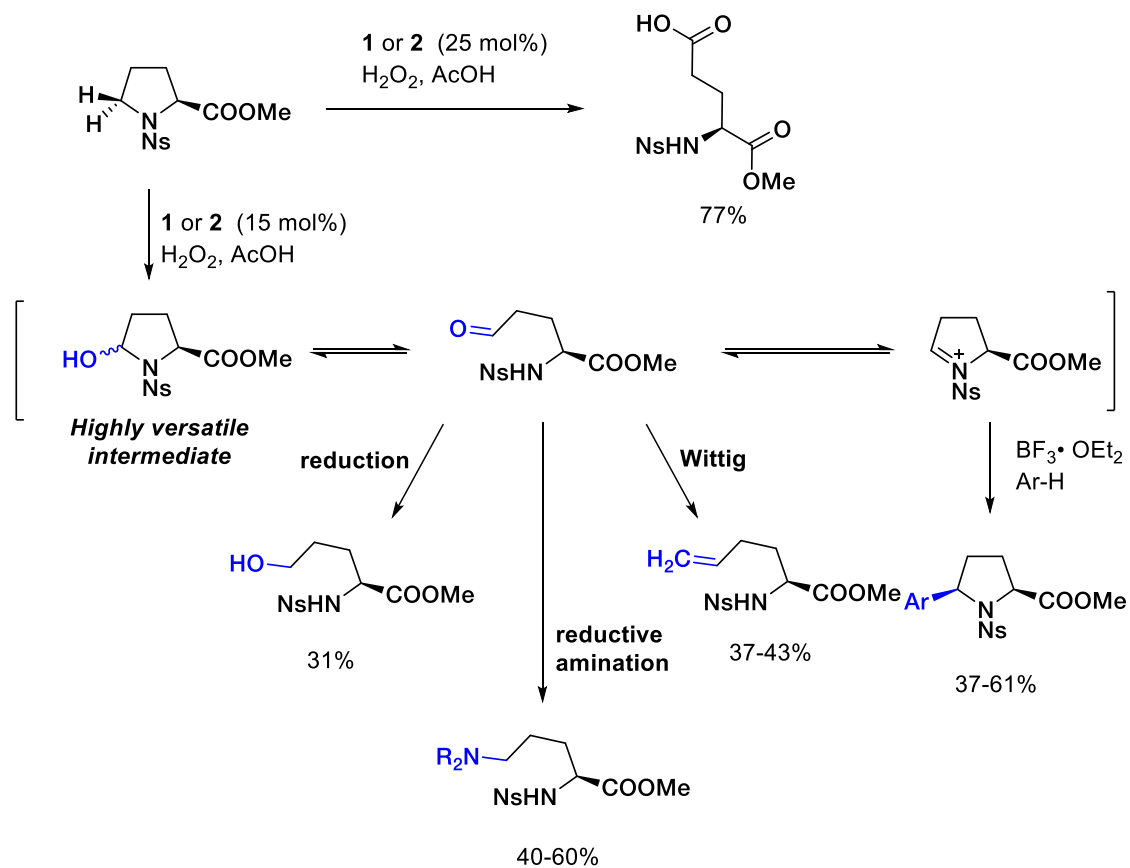
White – further contributions

Diversification of peptides and amino acids



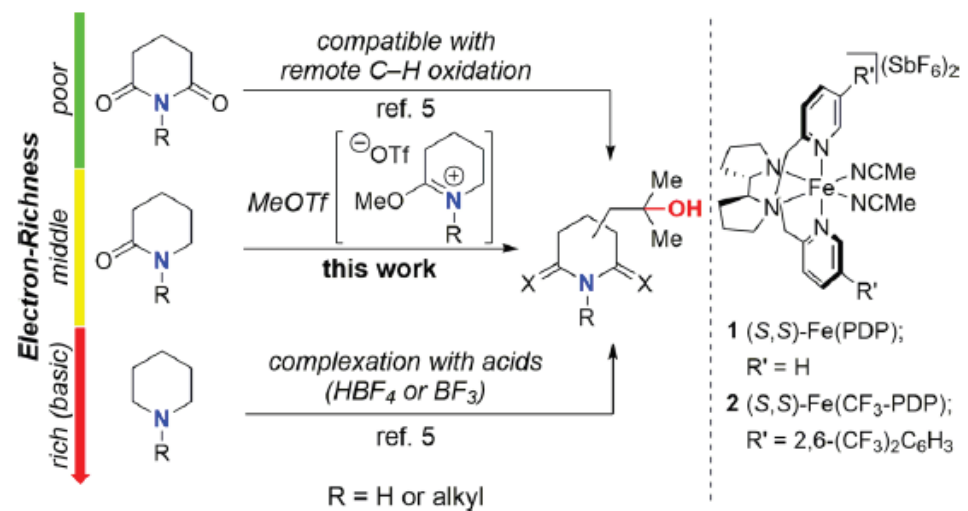
White – further contributions

Diversification of peptides and amino acids



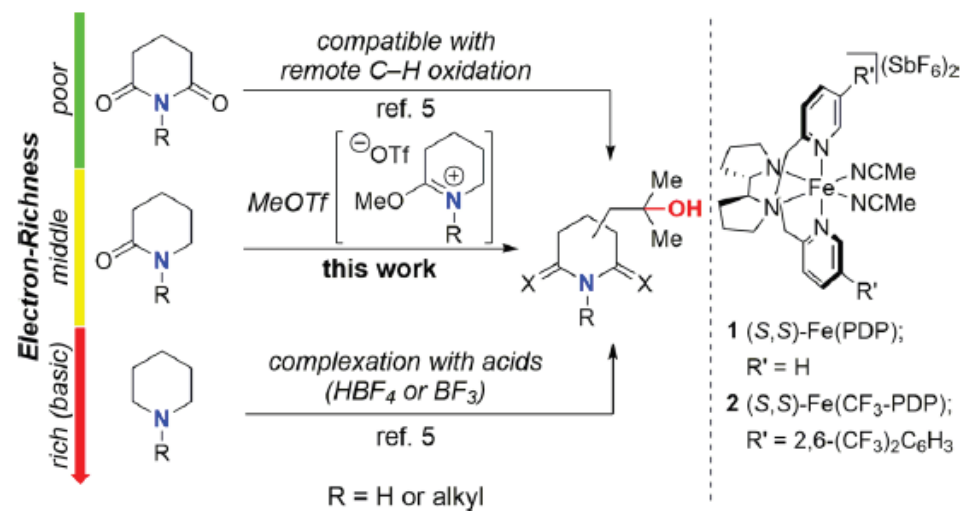
The Nitrogen Problem

White - overcoming amide and amine incompatibility

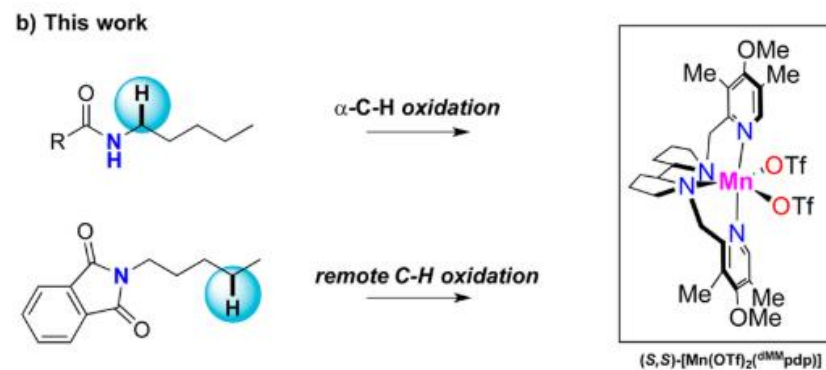


The Nitrogen Problem

White - overcoming amide and amine incompatibility

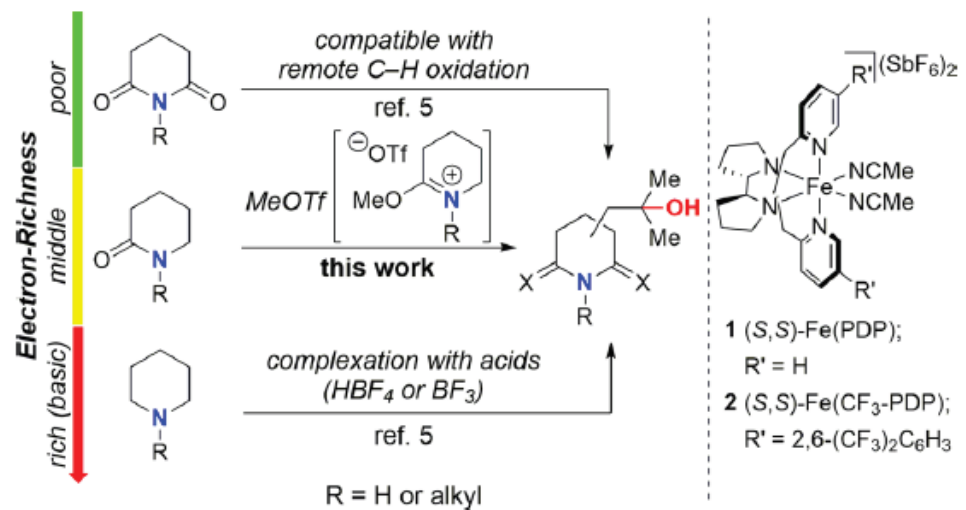


Costas – importance of α -substituents

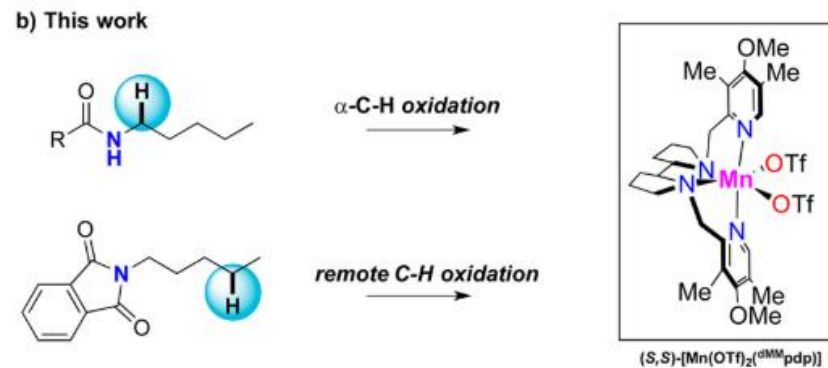


The Nitrogen Problem

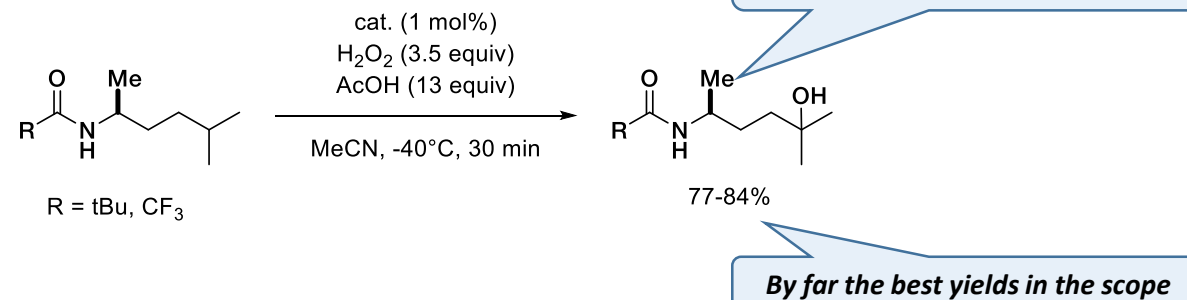
White - overcoming amide and amine incompatibility



Costas – importance of α -substituents

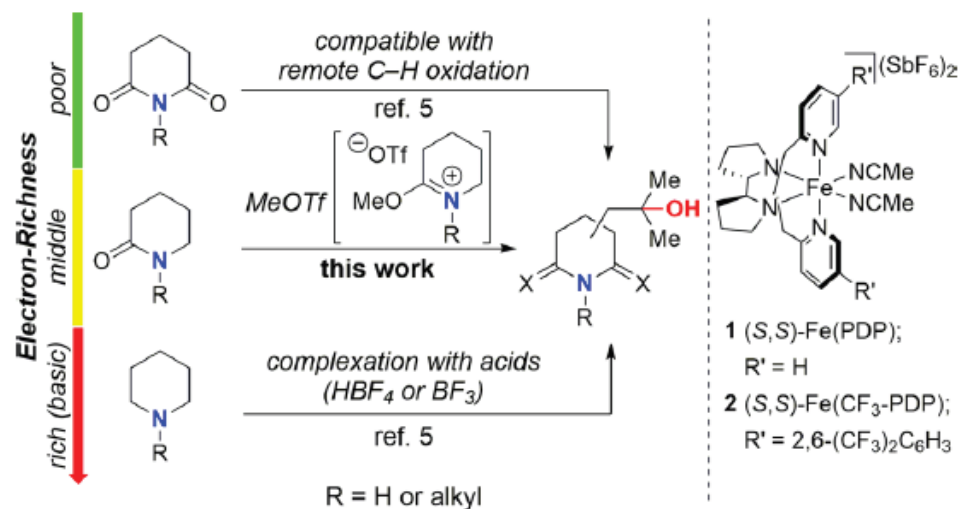


Important observation

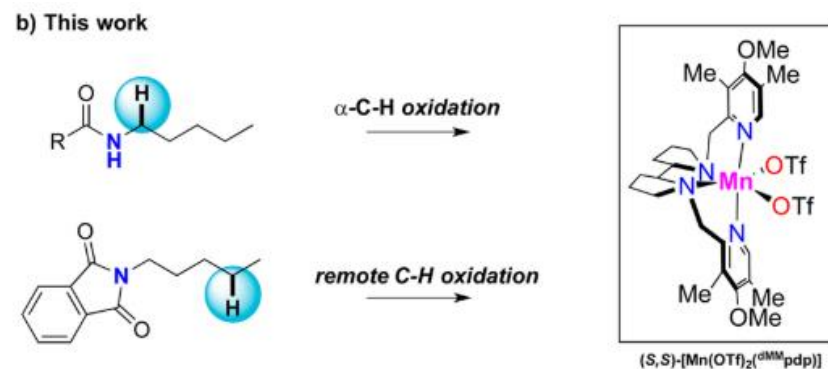


The Nitrogen Problem

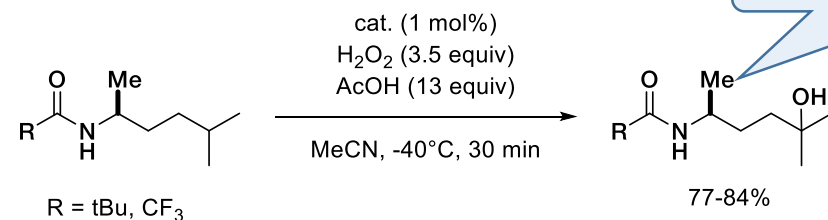
White - overcoming amide and amine incompatibility



Costas – importance of α -substituents

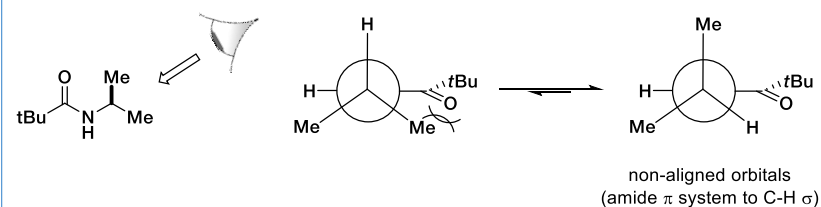


Important observation



α -position remains intact!

Rationalization

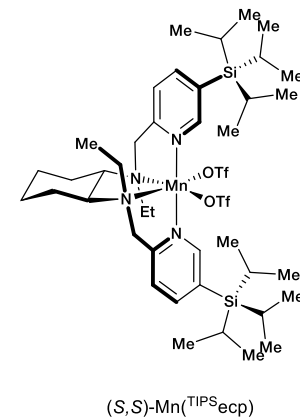
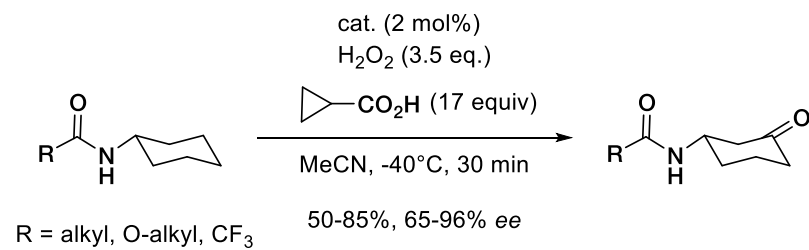


By far the best yields in the scope

Does the amide function "activates and deactivates" at the same time?

Costas – First enantioselective example

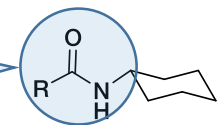
Important factors



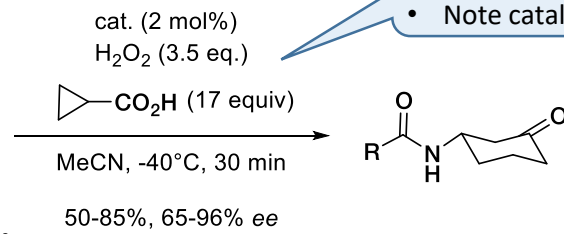
Costas – First enantioselective example

Important factors

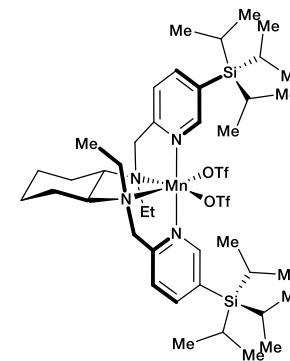
Significant improvement in conversion and yield (Carbamate and acetyl groups are also OK)



R = alkyl, O-alkyl, CF₃



- Oxidatively robust acid additive
- Propionic acid gave similar results
- Note catalyst loading



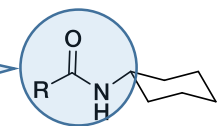
(S,S)-Mn(TIPSecp)

ecp-type ligands were not successful with iron catalysis, whereas the ligands are very often “interchangeable”

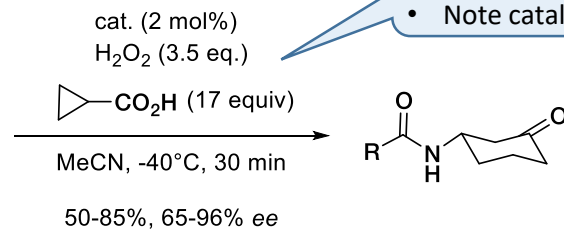
Costas – First enantioselective example

Important factors

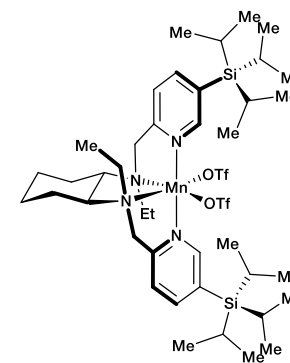
Significant improvement in conversion and yield (Carbamate and acetyl groups are also OK)



R = alkyl, O-alkyl, CF₃



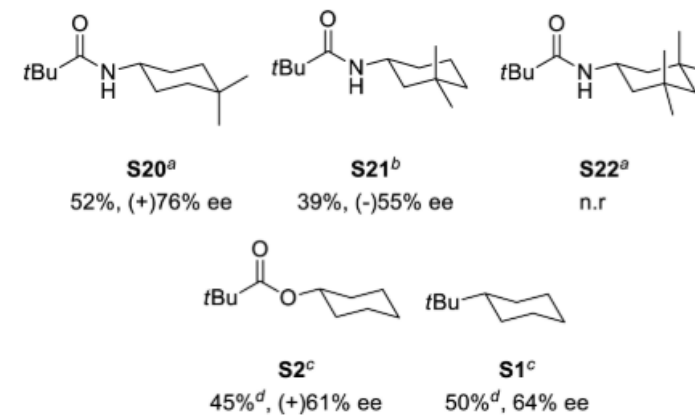
- Oxidatively robust acid additive
- Propionic acid gave similar results
- Note catalyst loading



(S,S)-Mn(TIPSecp)

ecp-type ligands were not successful with iron catalysis, whereas the ligands are very often “interchangeable”

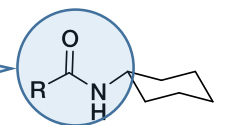
Scope – substituents on the cyclohexyl ring



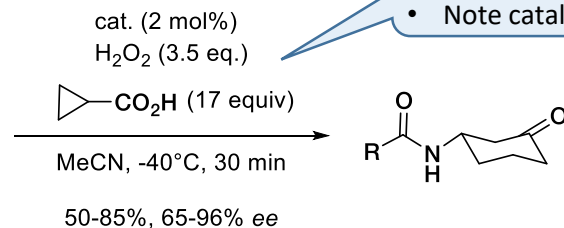
Costas – First enantioselective example

Important factors

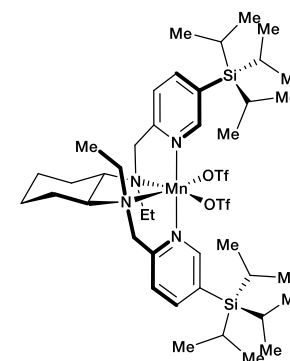
Significant improvement in conversion and yield (Carbamate and acetyl groups are also OK)



R = alkyl, O-alkyl, CF₃



- Oxidatively robust acid additive
- Propionic acid gave similar results
- Note catalyst loading

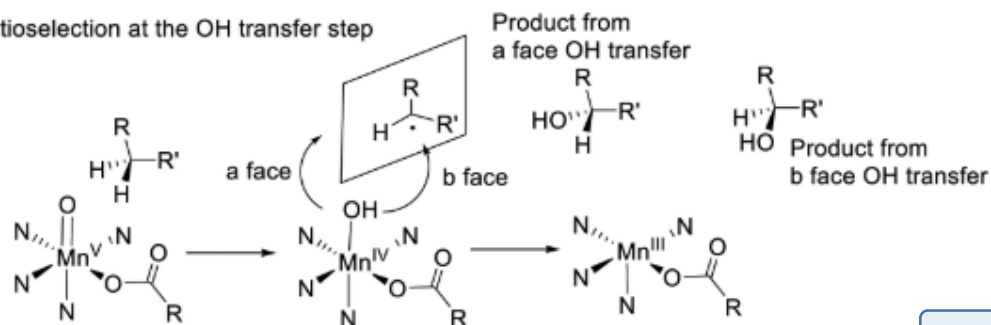


(S,S)-Mn(TIPSecp)

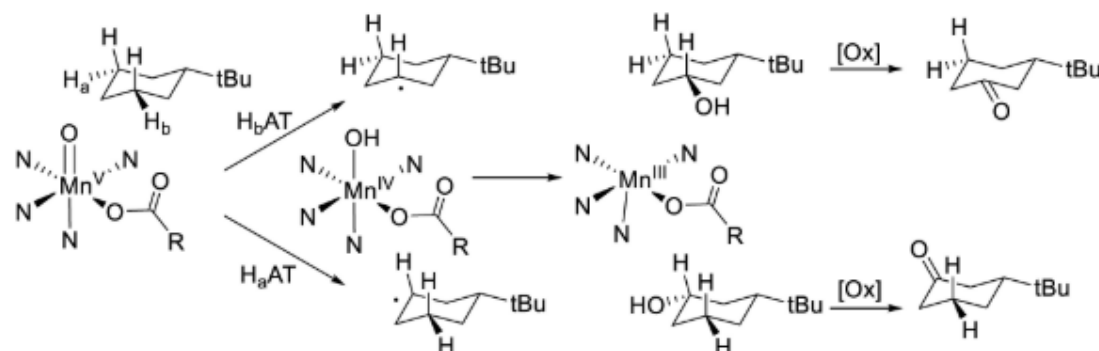
ecp-type ligands were not successful with iron catalysis, whereas the ligands are very often “interchangeable”

Enantiodetermining step

A) Enantioselection at the OH transfer step

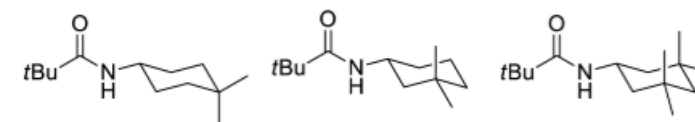


B) Enantioselection at the HAT transfer step



- Compare with Fu, Jacobsen, Lee&Tan

Scope – substituents on the cyclohexyl ring



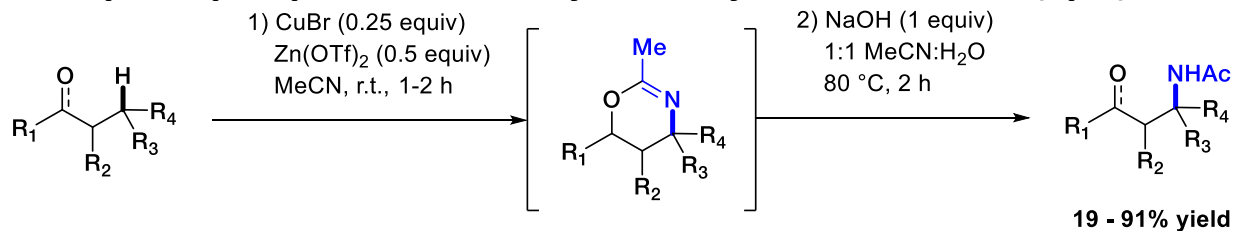
S20^a 52%, (+)76% ee S21^b 39%, (-)55% ee S22^a n.r.



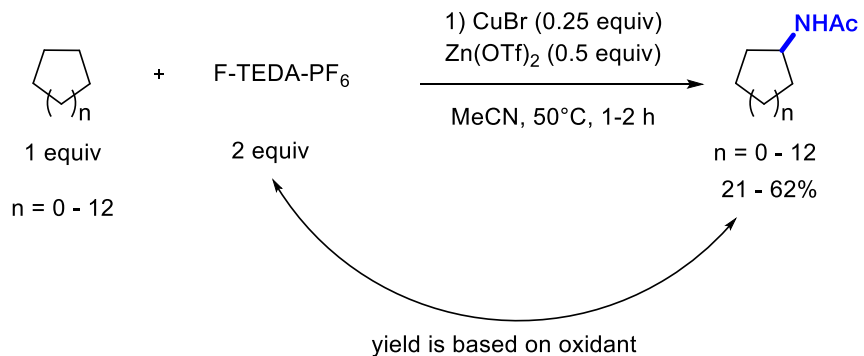
S2^c 45%^d, (+)61% ee S1^c 50%^d, 64% ee

Baran

2-step / 1-pot protocol – only tertiary or activated C(sp³)-H bond ox.

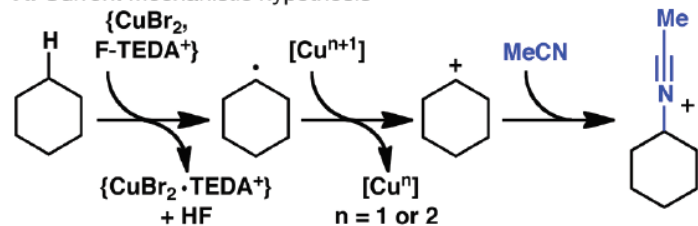


Unactivated C(sp³)-H bond ox.



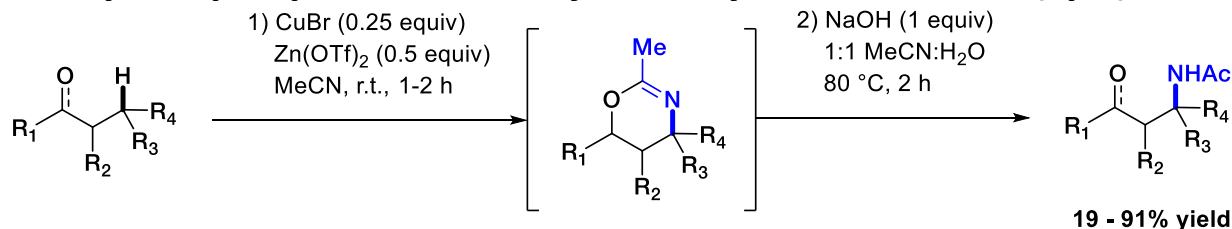
Proposed mechanism

A. Current mechanistic hypothesis

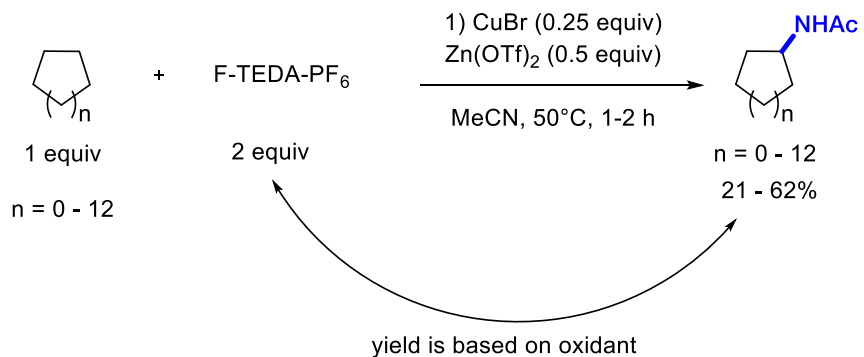


Baran

2-step / 1-pot protocol – only tertiary or activated C(sp³)-H bond ox.

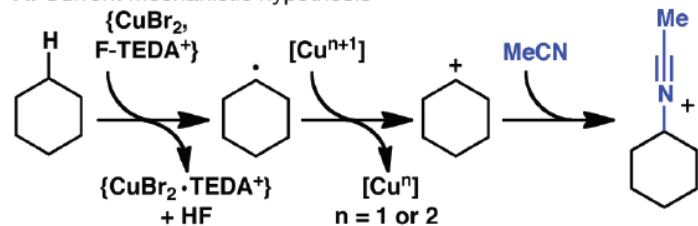


Unactivated C(sp³)-H bond ox.



Proposed mechanism

A. Current mechanistic hypothesis



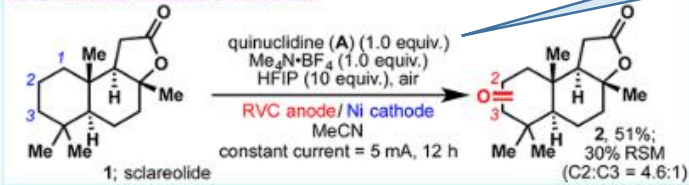
Substrate	Product	Yield ^a (%)
		91 81 [gram-scale]
		84
		53
		42 (dr 2:1)
		61 ^b [X-ray]
		19 ^b , 89 ^{b,c}
		23 ^b , 0 ^{b,c} [X-ray]
		65 ^d

Substrate	Product	Yield ^a	Yield ^b
		90 ^c	88 ^c
		39	63
		51	72
		41	62
		62	90
		25 ^d	28 ^d
		36 ^e	55 ^e
		5	15
		16 ^f	31 ^f

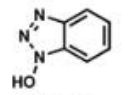
Optimization and important factors

Key: choice of redox mediator

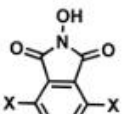
Electrochemical oxidation of sclareolide



Entry ^a	Deviation from above	Yield%	C2/C3
1	B as the mediator	39	2.1/1
2	C as the mediator	9	2.0/1
3	D as the mediator	19	1.1/1
4	E, F, G, or H as the mediator/no mediator	<5	n.d.
5	0.4 equiv. of A	30	5.4/1
6	added A portionwise (0.5 equiv. x 2)	42	4.6/1
7	LiClO ₄ instead of Me ₄ NBF ₄	<5	n.d.
8	Et ₄ NClO ₄ instead of Me ₄ NBF ₄	57	4.8/1
9	no HFIP	<5	n.d.
10	TFA (1.0 equiv.) instead of HFIP	<5	n.d.
11	AcOH (2.0 equiv.) instead of HFIP	15	3.9/1
12	under Ar	<5	n.d.
13	stainless steel cathode	49	2.8/1
14	Cu cathode	45	6/1
15	Al cathode	36	2.1/1
16	10 mA, 6 h	39	4.9/1



HFIP was also essential

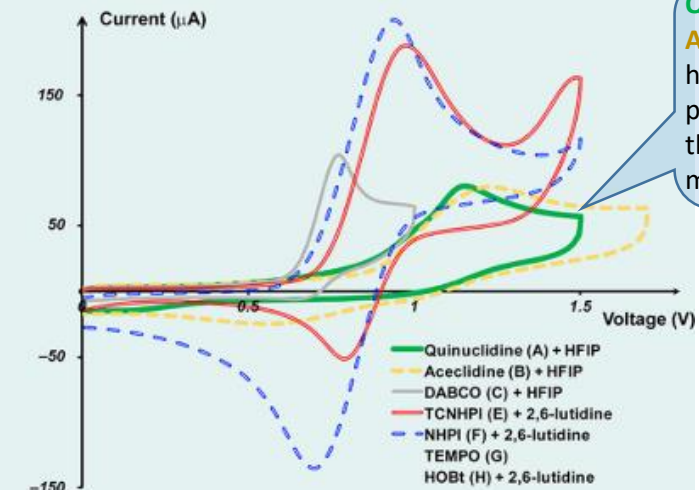


Mediators



^a reactions conducted on 0.2 mmol scales.

C. Cyclic voltammograms of selected mediators.



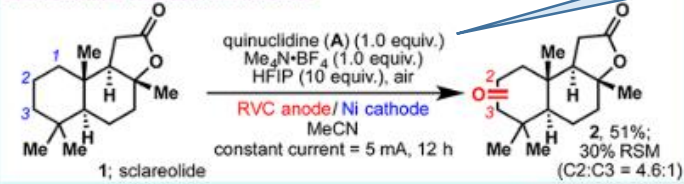
Quinuclidine (green) and Aceclidine (yellow) has the highest thermodynamic potential ($E_{1/2}$) → they are the best performing mediators

Baran

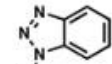
Optimization and important factors

Key: choice of redox mediator

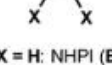
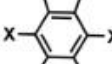
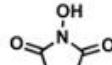
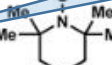
Electrochemical oxidation of sclareolide



Entry ^a	Deviation from above	Yield%	C2/C3
1	B as the mediator	39	2.1/1
2	C as the mediator	9	2.0/1
3	D as the mediator	19	1.1/1
4	E, F, G, or H as the mediator/no mediator	<5	n.d.
5	0.4 equiv. of A	30	5.4/1
6	added A portionwise (0.5 equiv. x 2)	42	4.6/1
7	LiClO ₄ instead of Me ₄ NBF ₄	<5	n.d.
8	Et ₄ NClO ₄ instead of Me ₄ NBF ₄	57	4.8/1
9	no HFIP	<5	n.d.
10	TFA (1.0 equiv.) instead of HFIP	<5	n.d.
11	AcOH (2.0 equiv.) instead of HFIP	15	3.9/1
12	under Ar	<5	n.d.
13	stainless steel cathode	49	2.8/1
14	Cu cathode	45	6/1
15	Al cathode	36	2.1/1
16	10 mA, 6 h	39	4.9/1



HFIP was also essential

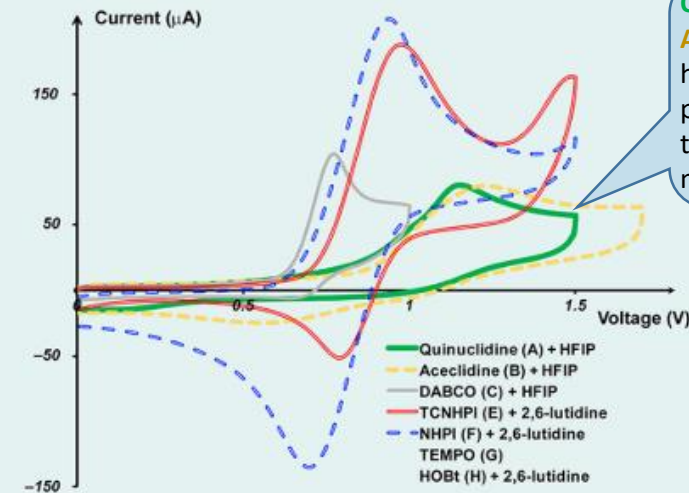


Mediators



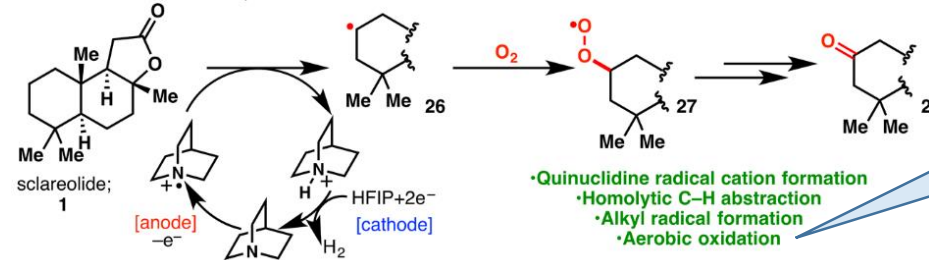
^a reactions conducted on 0.2 mmol scales.

C. Cyclic voltammograms of selected mediators.



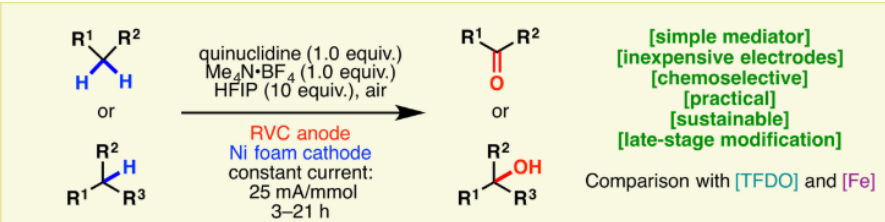
Quinuclidine (green) and Aceclidine (yellow) has the highest thermodynamic potential ($E_{1/2}$) → they are the best performing mediators

Proposed mechanism

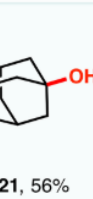
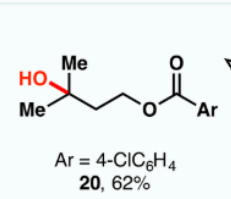
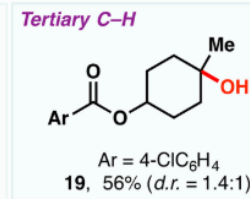
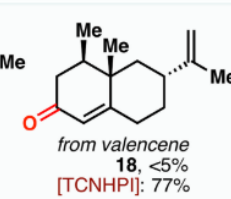
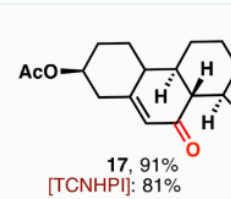
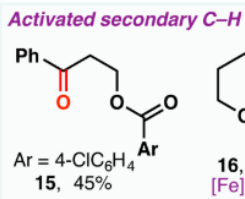
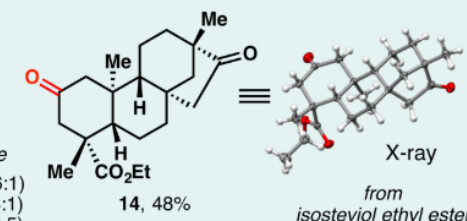
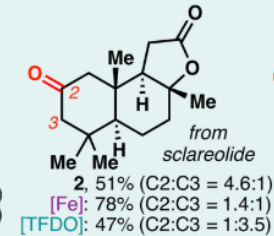
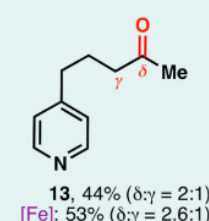
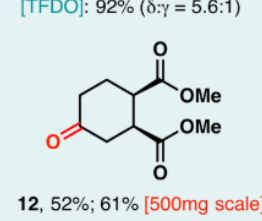
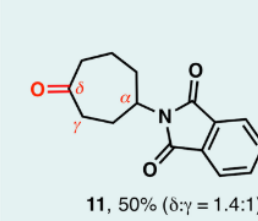
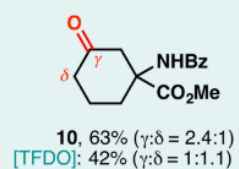
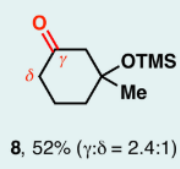
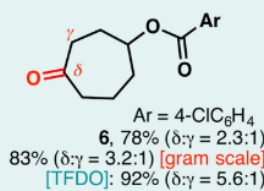
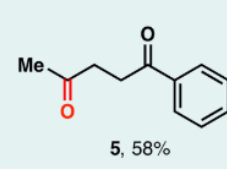
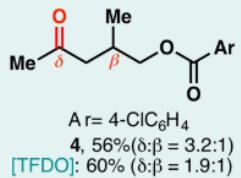
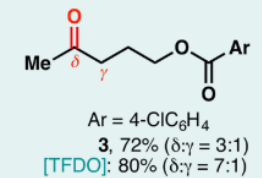


How safe it is to run the cell filled with MeCN and air?

Scope of the reaction

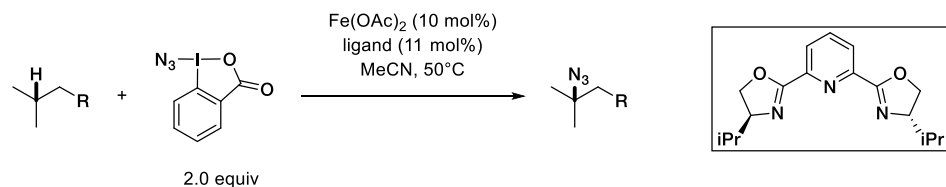


Secondary C-H

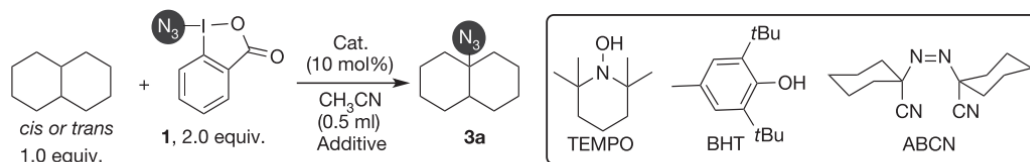


Hartwig – C-N bond formation

Method



Mechanism



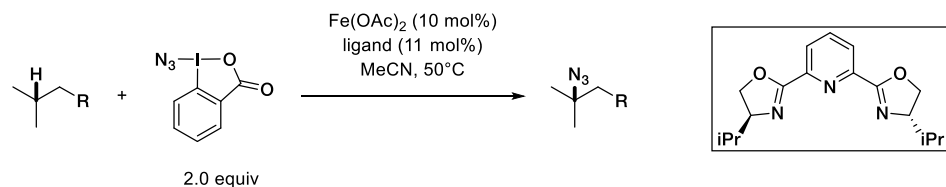
Entry	Substrate	Catalyst	Temperature (°C)	Additive	Yield (%)	Selectivity
1	<i>cis</i>	$\text{Fe}(\text{OAc})_2/\mathbf{L11}$	23	TEMPO*	3	NA
2	<i>cis</i>	$\text{Fe}(\text{OAc})_2/\mathbf{L11}$	23	BHT*	3	NA
3†	<i>cis</i>	$\text{Fe}(\text{OAc})_2/\mathbf{L11}$	80	NA	55	3.2
4†	<i>trans</i>	$\text{Fe}(\text{OAc})_2/\mathbf{L11}$	80	NA	43	3.2
5†	<i>cis</i>	BzOOBz	80	ABCN‡	40	1.7
6†	<i>trans</i>	BzOOBz	80	ABCN‡	33	1.7

Conclusions from preliminary studies

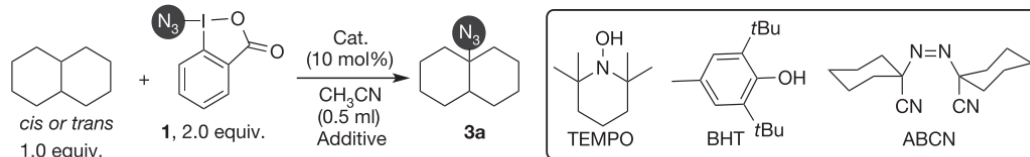
1. Tertiary alkyl radical is generated (lifetime $<10^{-9}$ sec)
2. C-H bond cleavage is turnover limiting step (KIE = 5)
3. Iron is involved in C-N bond formation (Fe-N₃ intermediate)
4. In MeCN, C-H lysis is faster, radical rebound is slower
5. In EtOAc, C-H lysis is slower, radical rebound is faster

Hartwig – C-N bond formation

Method



Mechanism



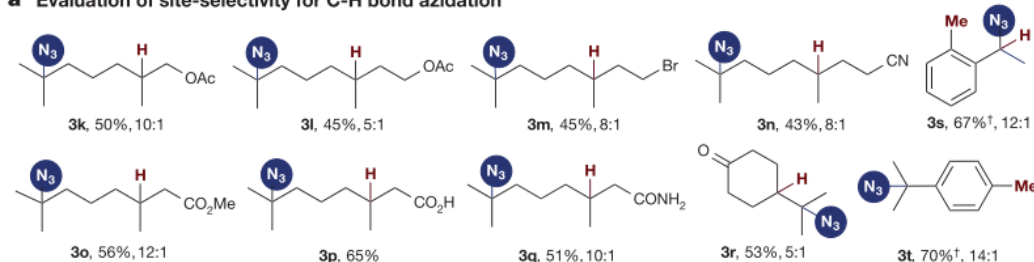
Entry	Substrate	Catalyst	Temperature (°C)	Additive	Yield (%)	Selectivity
1	<i>cis</i>	Fe(OAc) ₂ /L11	23	TEMPO*	3	NA
2	<i>cis</i>	Fe(OAc) ₂ /L11	23	BHT*	3	NA
3†	<i>cis</i>	Fe(OAc) ₂ /L11	80	NA	55	3.2
4†	<i>trans</i>	Fe(OAc) ₂ /L11	80	NA	43	3.2
5†	<i>cis</i>	BzOOBz	80	ABCN‡	40	1.7
6†	<i>trans</i>	BzOOBz	80	ABCN‡	33	1.7

Conclusions from preliminary studies

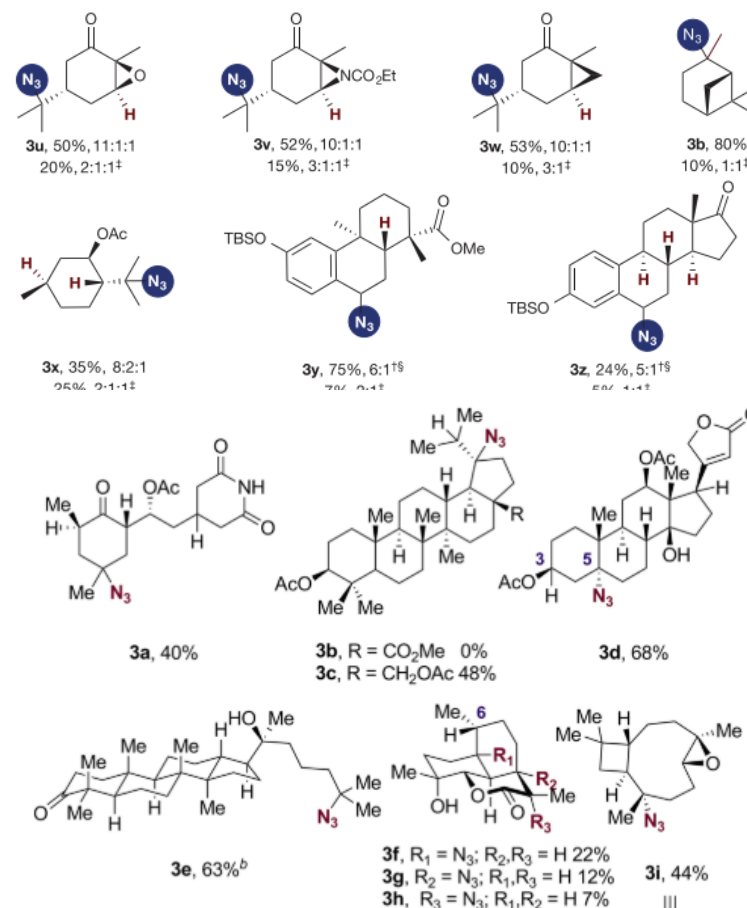
1. Tertiary alkyl radical is generated (lifetime <math><10^{-9}</math> sec)
2. C-H bond cleavage is turnover limiting step (KIE = 5)
3. Iron is involved in C-N bond formation (Fe-N₃ intermediate)
4. In MeCN, C-H lysis is faster, radical rebound is slower
5. In EtOAc, C-H lysis is slower, radical rebound is faster

Scope

a Evaluation of site-selectivity for C-H bond azidation

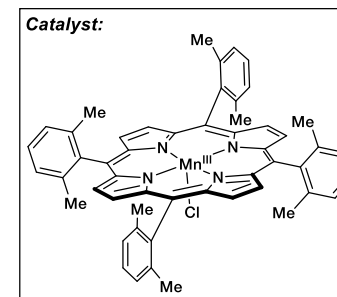
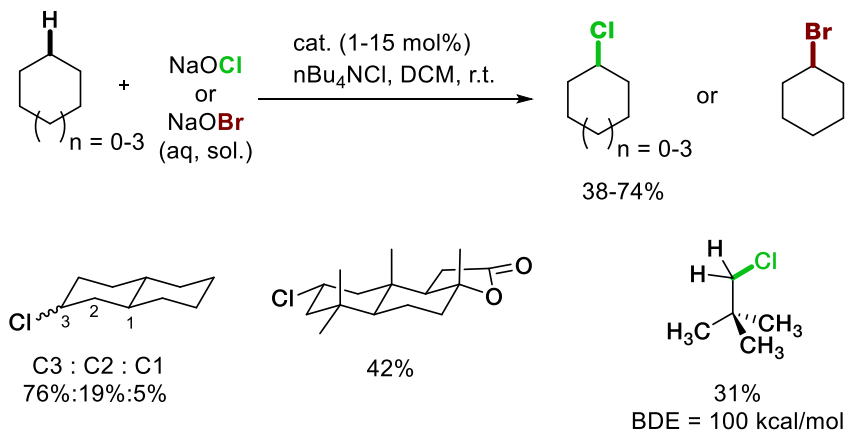


b C-H bond azidation complex molecular scaffolds containing multiple tertiary centres

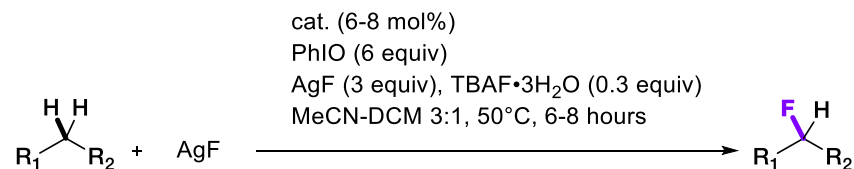


Groves

C-H chlorination and bromination



C-H fluorination

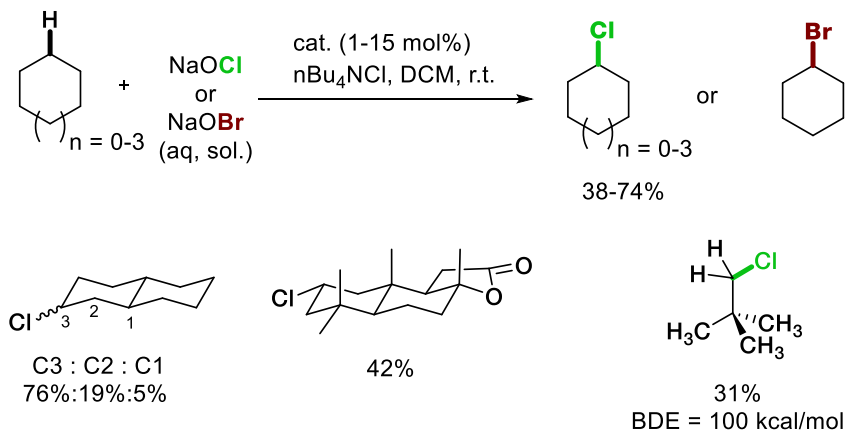


Liu, W.; Groves, J. T. *J. Am. Chem. Soc.* **2010**, *132* (37), 12847–12849.

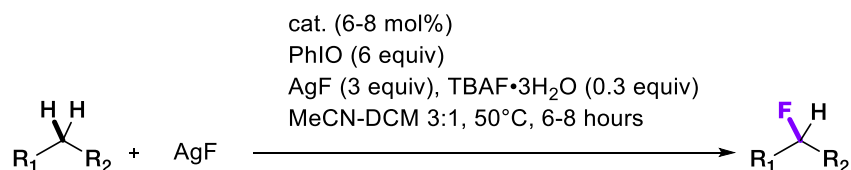
Liu, W.; Groves, J. T. *Science* (80-.). **2012**, *337* (6100), 1322–1325.

Groves – C-H halogenation

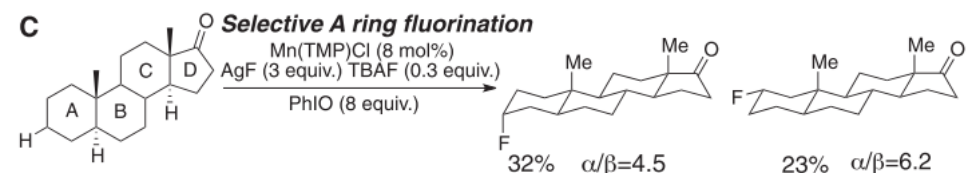
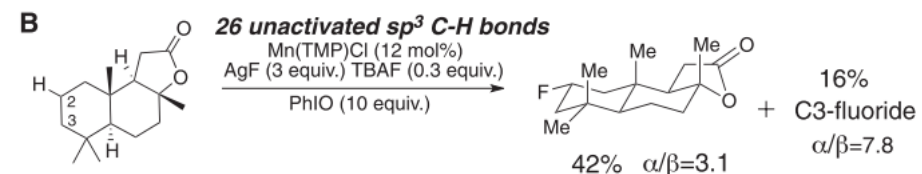
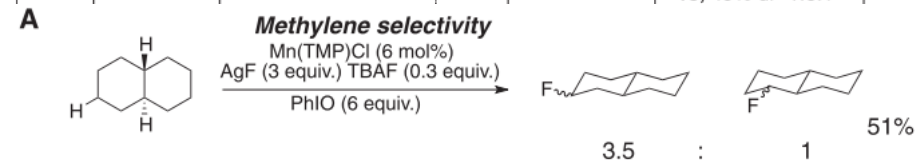
C-H chlorination and bromination



C-H fluorination



Entry	Substrate	Fluorination product	Entry	Substrate	Major fluorination product	Minor sites
1		 2, 49%	7		 8, 46% dr=6:1	C4 14%
2		 3, 51%	8		 9, 44% dr=8:1	C4 12%
3		 4, 55%	9		 10, 42%	C3 11%
4		 5, 53% 1:1.4	10		 11, 51% dr=1.5:1	C2 <2%
5		 6, 49% exo: endo=5.7	11		 12a, 30% cis/trans=1:1	12b, C3 27% cis/trans=2:1
6		 7, 2:1*	12		 13, 49% dr=1.6:1†	C3 9%

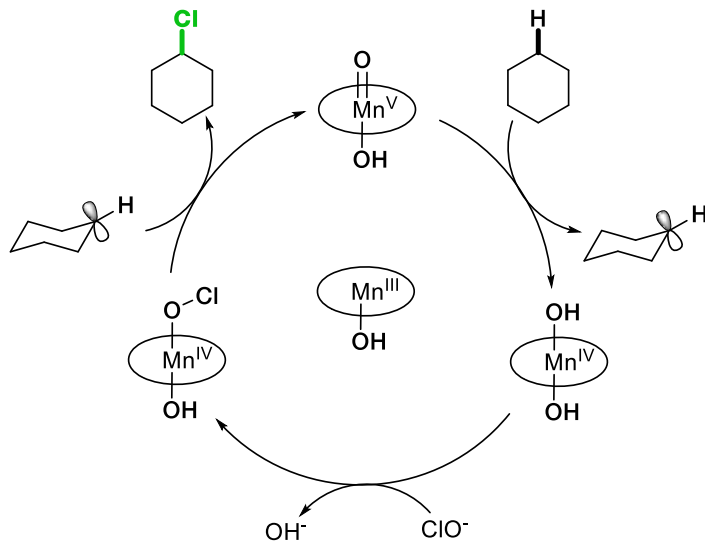


Liu, W.; Groves, J. T. *J. Am. Chem. Soc.* **2010**, *132* (37), 12847–12849.

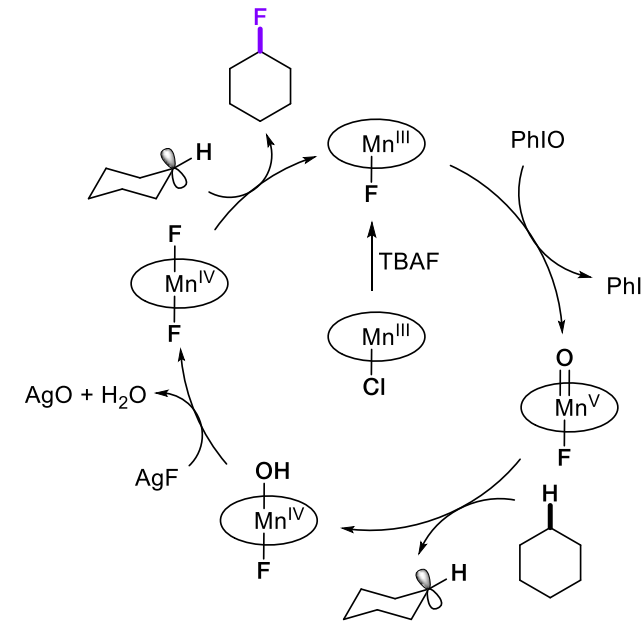
Liu, W.; Groves, J. T. *Science* (80-.). **2012**, *337* (6100), 1322–1325.

Mechanism – “heteroatom rebound catalysis”

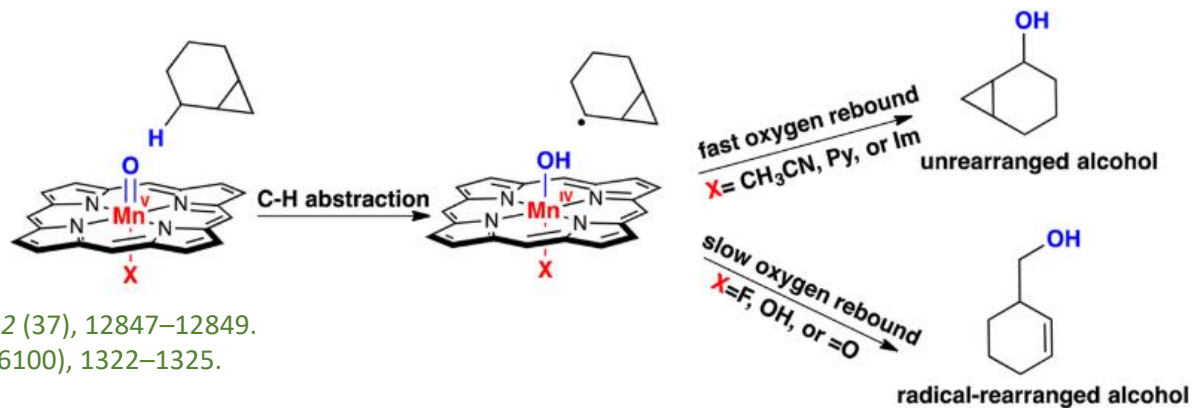
C-H chlorination / bromination



C-H fluorination



Effect of apical – trans ligands

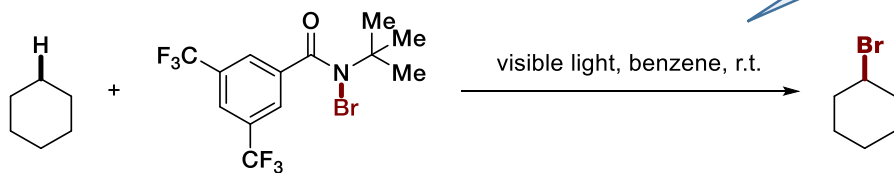


Liu, W.; Groves, J. T. *J. Am. Chem. Soc.* **2010**, *132* (37), 12847–12849.

Liu, W.; Groves, J. T. *Science* (80-). **2012**, *337* (6100), 1322–1325.

Alexanian, Vanderwal – HLF-type halogenation

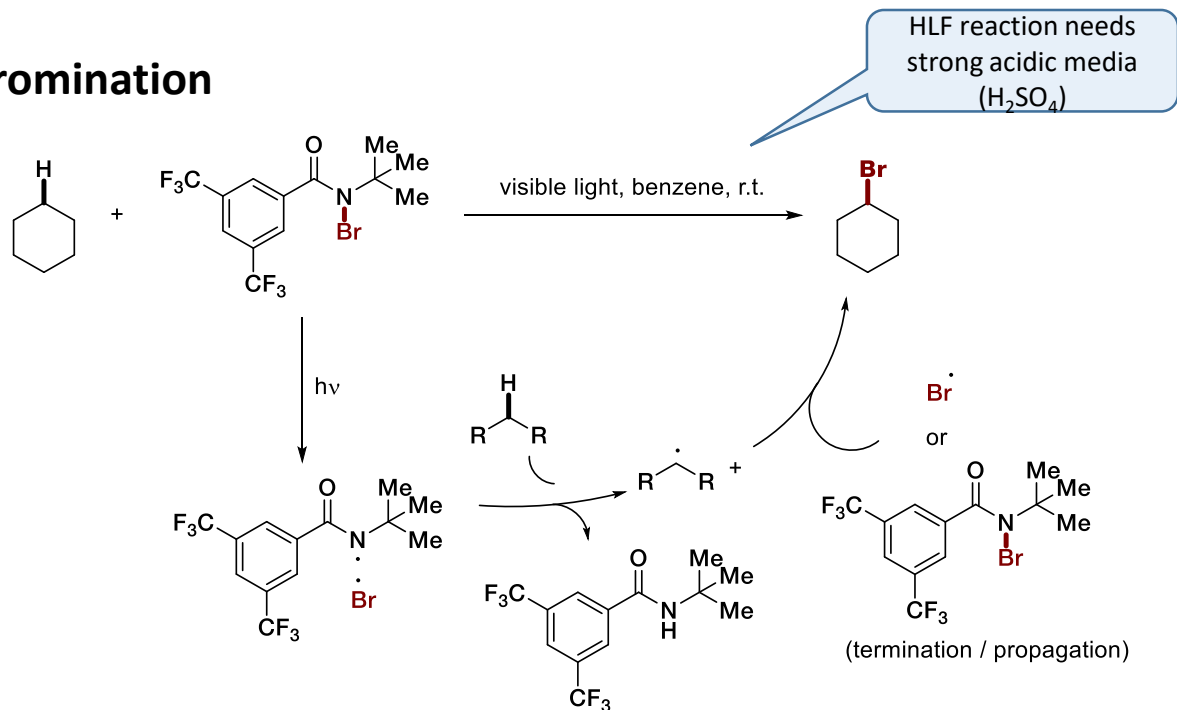
C-H bromination



HLF reaction needs strong acidic media (H_2SO_4)

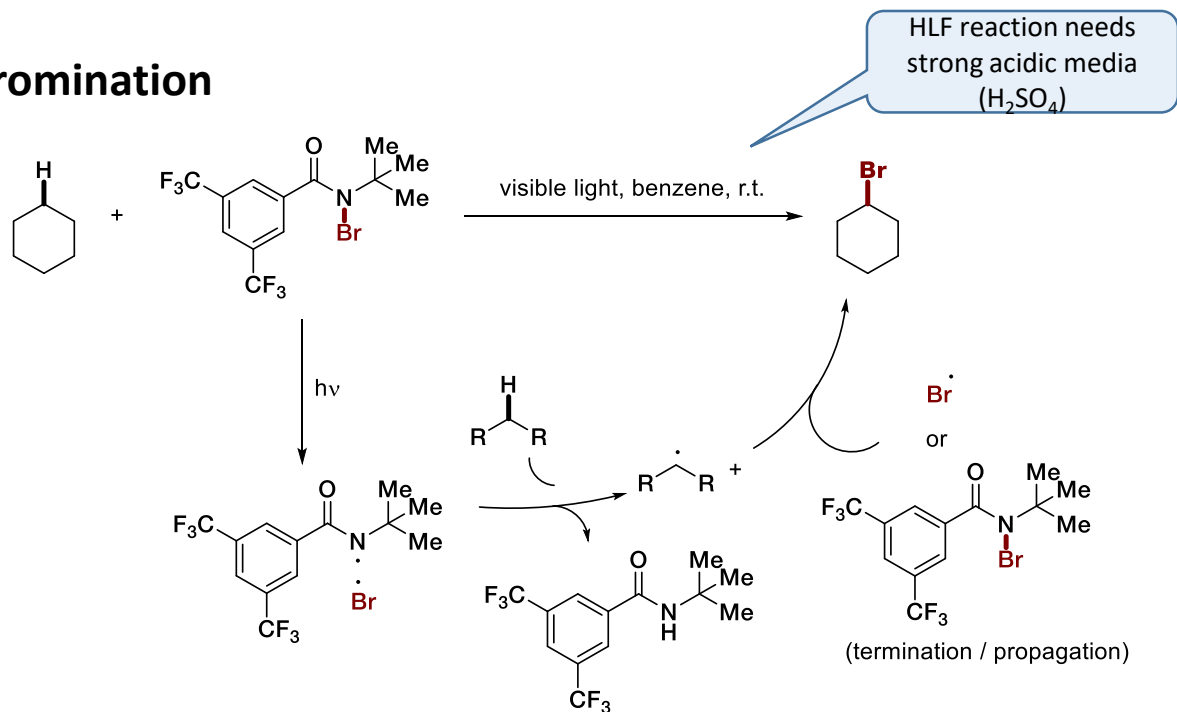
Alexanian, Vanderwal – HLF-type halogenation

C-H bromination

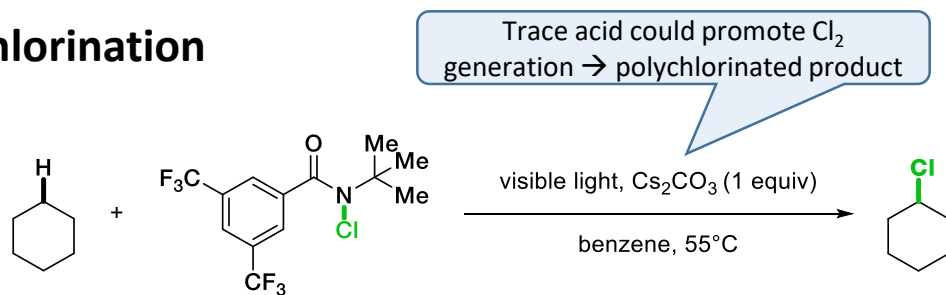


Alexanian, Vanderwal – HLF-type halogenation

C-H bromination

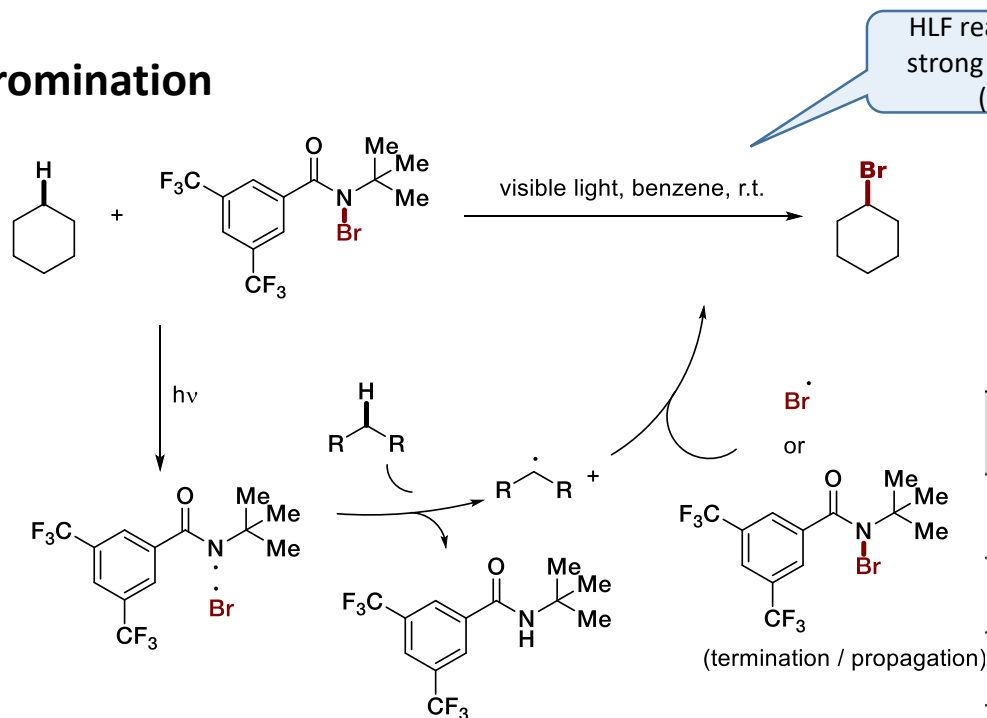


C-H chlorination



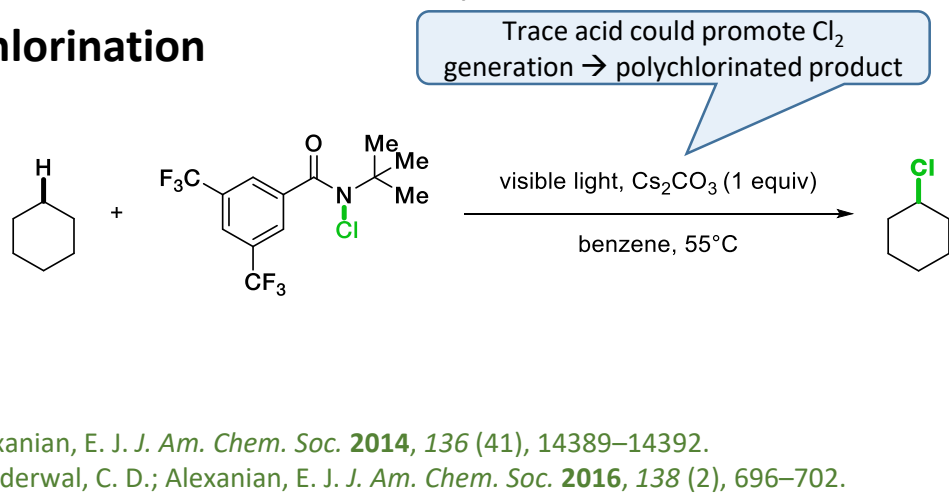
Alexanian, Vanderwal – HLF-type halogenation

C-H bromination



entry	major chlorination product	% selectivity	combined yield (%) ^b	sites of minor chlorination (% selectivity)
	EWG α β γ δ ω Me			
1	23: EWG = PhthN	75.4	88	$\gamma = 8.8$; $\omega = 15.7$
2	24: EWG = $\text{Ph-SO}_2\text{O}^{\ominus}\text{K}^{\oplus}$	68.3	76	$\gamma = 18.3$; $\omega = 13.6$
3	PhthN α β γ δ ω Me	63.6	69	$\beta = 2.4$; $\gamma = 7.5$; $\omega = 26.5$
4	PhthN α β γ δ ω CO ₂ Me	77.5	66	$\omega = 22.5$
5	PhthN α β γ δ ω Ph	67.9	81	$\gamma = 14.9$; $\omega = 17.1$
6	PhthN α β γ δ ω Me	74.0	78	$\alpha = 6.5$; $\omega = 18.9$
7	MsO α β γ δ ω Cl	100	65 ^c	

C-H chlorination



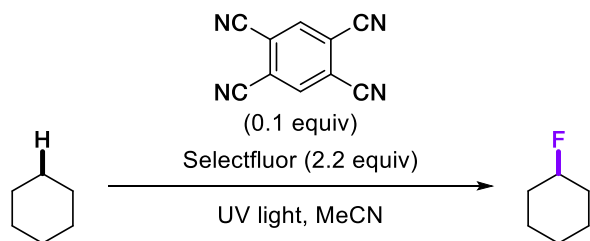
entry	substrate (1 equiv)	bromination products	yield (%)
1 ^b	11	12	63 exo:endo >99:1
2 ^b	13	14, 15	53 ^c 14:15 >99:1
3 ^b	16	17, 18	50 ^c 17:18 12:1
4	19	20, 21	58 20:21 36:1
5	trans decalin 22	23, 24	45 ^c 23:24 >99:1
6 ^b	cis decalin 25	26, 27	55 ^c 26:(24+27) >99:1
entry	substrate (1 equiv)	chlorination products	yield (%)
9	5	6	54 exo:endo >99:1
10 ^b	7	8, 9	79 8:9 >99:1
11 ^b	10	11, 12	73 11:12 11:1
12	13	14, 15, 20	69 14:15 19:1

Alexanian, E. J. *J. Am. Chem. Soc.* **2014**, *136* (41), 14389–14392.

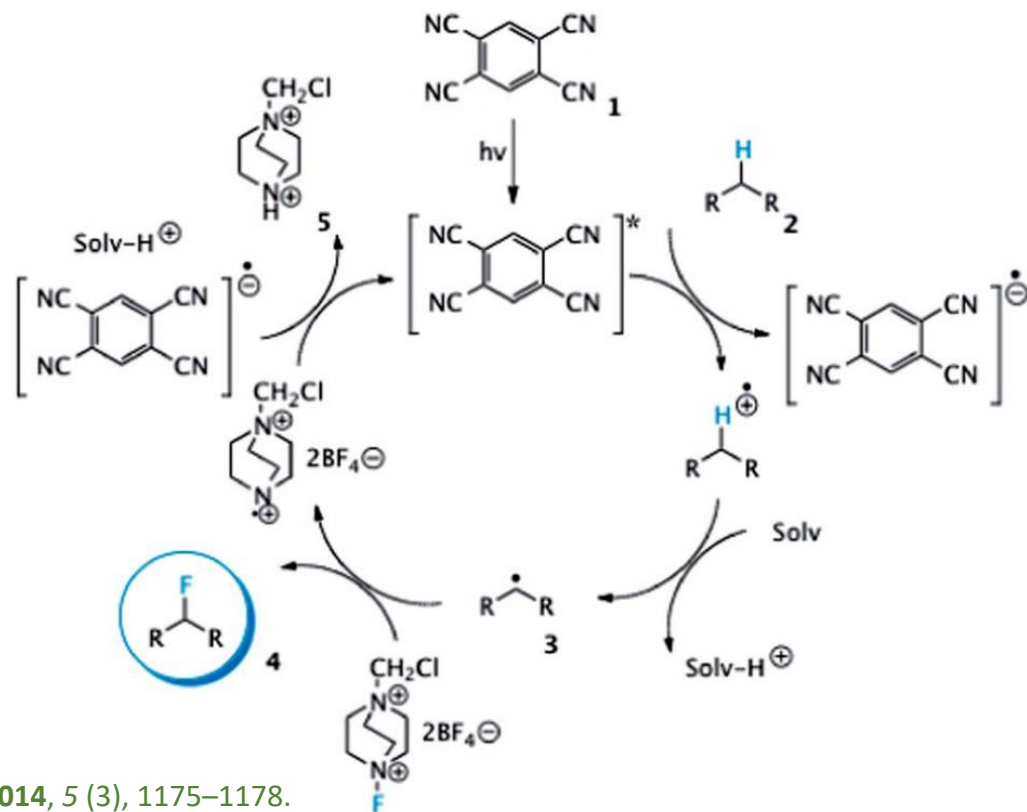
Vanderwal, C. D.; Alexanian, E. J. *J. Am. Chem. Soc.* **2016**, *138* (2), 696–702.

Lectka – photocatalyzed C-H fluorination

Conditions

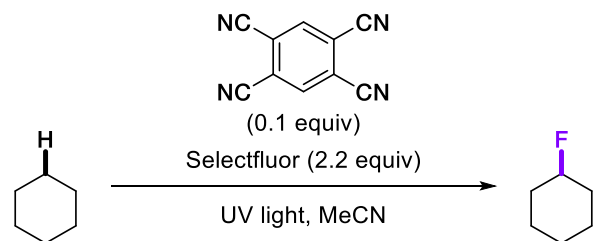


Working hypothesis for mechanism

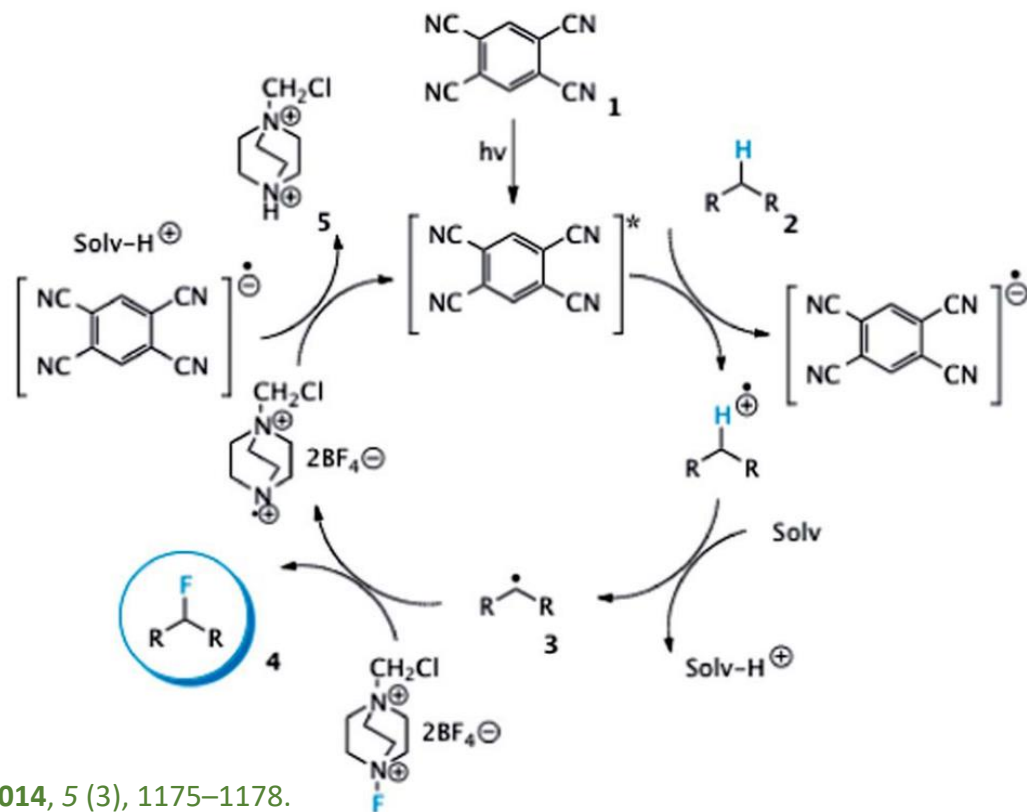


Lectka – photocatalyzed C-H fluorination

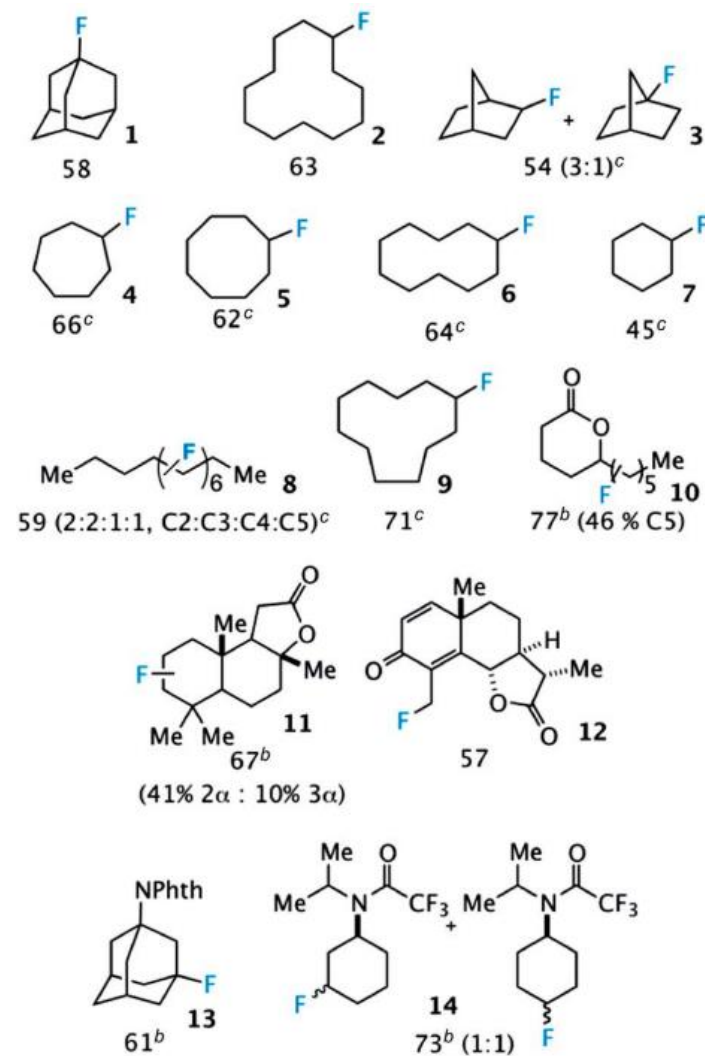
Conditions



Working hypothesis for mechanism



Scope of transformation



Overview



Major branches of C(sp³)-H oxidation chemistry

1. C-O bond formation

1. Heme or Non-heme Fe / Mn catalytic systems (White, Groves, Costas)
2. Electrochemical methods (Baran)
3. Hypervalent iodine based systems (Maruoka – not presented)

2. C-N bond formation

1. Iron / Hypervalent iodine system (Hartwig)
2. Metal-nitrenoid chemistry (Du Bois – not presented)

1. C-X bond formation

1. Heme or Non-heme Fe / Mn catalytic systems (Groves)
2. Intermolecular HLF reaction based halogenation (Alexanian)
3. Photocatalyzed halogenation (Lectka and others)

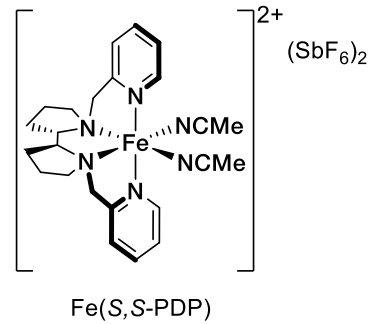
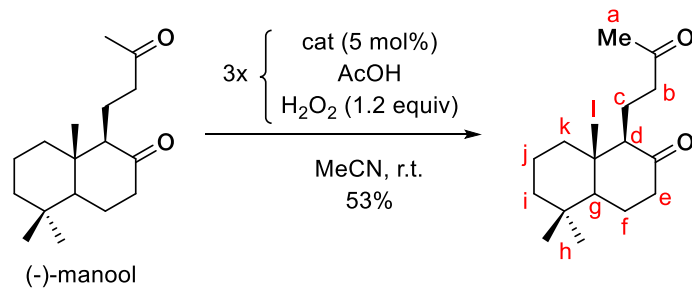


Take home message

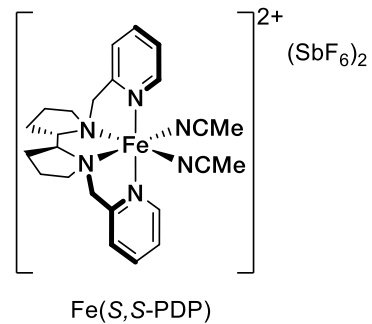
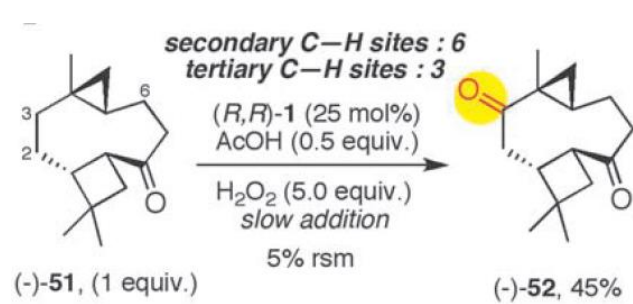
1. *Subtle electronic, steric and stereoelectronic factors determine the reaction outcome*
2. *Fe / Mn – based systems dominate the field*
3. *Short-lived radicals allow asymmetric C-H functionalization*

Questions

Where will the oxidation take place?



Explain the selectivity!



Literature

Important reviews/perspectives:

1. Cheng, J.-P. *Chem. Rev.* **2017**, *117* (13), 8622–8648.
2. White, M. C. *J. Am. Chem. Soc.* **2018**, *140* (C), 13988–14009.
3. Costas, M., Que, L. *Chem. Rev.* **2004**, *104* (2), 939–986.
4. Theopold, K. H. *Chem. Rev.* **2010**, *110* (2), 1060–1081.
5. Ackermann, L. *Chem. Rev.* **2018**, acs.chemrev.8b00507.
6. Shi, Z. J. *Chem. Rev.* **2011**, *111* (3), 1293–1314.
7. Perez, P. J. *ChemInform* **2008**, *39* (48), 3379–3394.
8. Maimone, T. J. *J. Am. Chem. Soc.* **2019**.
9. Baran, P. S. *Angew. Chemie - Int. Ed.* **2011**, *50* (15), 3362–3374.
10. Nakamura, E. *Chem. Rev.* **2017**, *117* (13), 9086–9139.
11. Nagib, D. A. *Synth.* **2018**, *50* (8), 1569–1586.
12. Lei, A. *Chem. Rev.* **2017**, *117* (13), 9016–9085.
13. Krska, S. W. *Chem. Soc. Rev.* **2016**, *45* (3), 546–576.

Fe / Mn

1. Barton D. H. R., & Doller, D. The Selective Functionalization of Saturated Hydrocarbons: Gif Chemistry. *Acc. Chem. Res.* **25**, 504–512 (1992).
2. Font, D. *et al.* Readily Accessible Bulky Iron Catalysts exhibiting Site Selectivity in the Oxidation of Steroidal Substrates. *Angew. Chemie Int. Ed.* **55**, 5776–5779 (2016).
3. Visser, S. P. De, Kumar, D., Cohen, S., Shacham, R. & Shaik, S. A Predictive Pattern of Computed Barriers for C - H Hydroxylation by Compound I of Cytochrome P450. 8362–8363 (2004). doi:10.1021/ja048528h
4. Clark, J. R., White, M. C., Feng, K., Howell, J. M. & Trzepkowski, L. J. Remote Oxidation of Aliphatic C–H Bonds in Nitrogen-Containing Molecules. *J. Am. Chem. Soc.* **137**, 14590–14593 (2015).
5. Nanjo, T., De Lucca, E. C. & White, M. C. Remote, Late-Stage Oxidation of Aliphatic C-H Bonds in Amide-Containing Molecules. *J. Am. Chem. Soc.* **139**, 14586–14591 (2017).
6. Liu, W. & Groves, J. T. Manganese Catalyzed C-H Halogenation. *Acc. Chem. Res.* **48**, 1727–1735 (2015).
7. Rana, S. *et al.* Selective C-H halogenation over hydroxylation by non-heme iron(IV)-oxo. *Chem. Sci.* **9**, 7843–7858 (2018).
8. Bassan, A., Blomberg, M. R. A., Siegbahn, P. E. M. & Que, L. A density functional study of O-O bond cleavage for a biomimetic non-heme iron complex demonstrating an FeV-intermediate. *J. Am. Chem. Soc.* **124**, 11056–11063 (2002).
11. Qiu, B., Xu, D., Sun, Q., Lin, J. & Sun, W. Manganese-Catalyzed Asymmetric Oxidation of Methylene C-H of Spirocyclic Oxindoles and Dihydroquinolinones with Hydrogen Peroxide. *Org. Lett.* **21**, 618–622 (2019).
12. Chen, M. S. & White, M. C. A Predictably Selective Aliphatic C H Oxidation Reaction for Complex Molecule Synthesis. *Science (80-.)*. **318**, 783–787 (2007).
13. Milan, M., Carboni, G., Salamone, M., Costas, M. & Bietti, M. Tuning Selectivity in Aliphatic C–H Bond Oxidation of N -Alkylamides and Phthalimides Catalyzed by Manganese Complexes. *ACS Catal.* **7**, 5903–5911 (2017).
14. Osberger, T. J., Rogness, D. C., Kohrt, J. T., Stepan, A. F. & White, M. C. Oxidative diversification of amino acids and peptides by small-molecule iron catalysis. *Nature* **537**, 214–219 (2016).
15. White, M. C. & Zhao, J. Aliphatic C-H Oxidations for Late-Stage Functionalization. *J. Am. Chem. Soc.* **140**, 13988–14009 (2018).
16. Gormisky, P. E. & White, M. C. Catalyst-Controlled Aliphatic C–H Oxidations with a Predictive Model for Site-Selectivity. *J. Am. Chem. Soc.* **135**, 14052–14055 (2013).
17. Milan, M., Bietti, M. & Costas, M. Highly Enantioselective Oxidation of Nonactivated Aliphatic C–H Bonds with Hydrogen Peroxide Catalyzed by Manganese Complexes. *ACS Cent. Sci.* **3**, 196–204 (2017).
18. Ottenbacher, R. V., Talsi, E. P. & Bryliakov, K. P. Mechanism of Selective C–H Hydroxylation Mediated by Manganese Aminopyridine Enzyme Models. *ACS Catal.* **5**, 39–44 (2015).
19. Chen, K. & Que, L. Stereospecific alkane hydroxylation by non-heme iron catalysts: Mechanistic evidence for an FeV=O active species. *J. Am. Chem. Soc.* **123**, 6327–6337 (2001).
20. Barton, D. H. R. On the mechanism of Gif reactions. *Chem. Soc. Rev.* **25**, 237 (1996).
21. Kawamata, Y. *et al.* Scalable, Electrochemical Oxidation of Unactivated C–H Bonds. *J. Am. Chem. Soc.* **139**, 7448–7451 (2017).

C-N and C-X bond

1. Sharma, A. & Hartwig, J. F. Metal-catalysed azidation of tertiary C-H bonds suitable for late-stage functionalization. *Nature* **517**, 600–604 (2015).
2. Karimov, R. R., Sharma, A. & Hartwig, J. F. Late stage azidation of complex molecules. *ACS Cent. Sci.* **2**, 715–724 (2016).
3. Liu, W. & Groves, J. T. Manganese Catalyzed C-H Halogenation. *Acc. Chem. Res.* **48**, 1727–1735 (2015).
4. Liu, W.; Groves, J. T. *J. Am. Chem. Soc.* **2010**, *132* (37), 12847–12849.
5. Liu, W.; Groves, J. T. *Science (80-.)*. **2012**, *337* (6100), 1322–1325.
6. Liu, W. & Groves, J. T. Manganese Catalyzed C-H Halogenation. *Acc. Chem. Res.* **48**, 1727–1735 (2015).
7. Rana, S. *et al.* Selective C-H halogenation over hydroxylation by non-heme iron(IV)-oxo. *Chem. Sci.* **9**, 7843–7858 (2018).
8. Sathyamoorthi, S., Banerjee, S., Du Bois, J., Burns, N. Z. & Zare, R. N. Site-selective bromination of sp³C-H bonds. *Chem. Sci.* **9**, 100–104 (2017).
9. Schmidt, V. A., Quinn, R. K., Brusoe, A. T. & Alexanian, E. J. Site-selective aliphatic C-H bromination using N -bromoamides and visible light. *J. Am. Chem. Soc.* **136**, 14389–14392 (2014).
10. Quinn, R. K. *et al.* Site-Selective Aliphatic C-H Chlorination Using N-Chloroamides Enables a Synthesis of Chlorolissoclimide. *J. Am. Chem. Soc.* **138**, 696–702 (2016).

Thank you for your attention !