HAT (Hydrogen Atom Transfer) & MHAT (Metal Hydride Hydrogen Atom Transfer)

Literature seminar

Yu Zhang

2022.12.29

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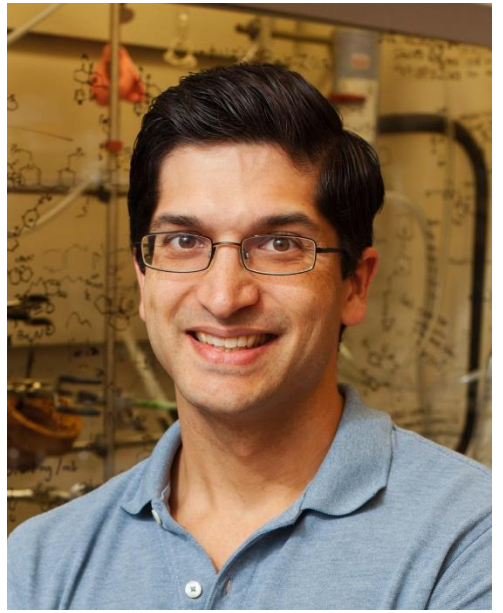
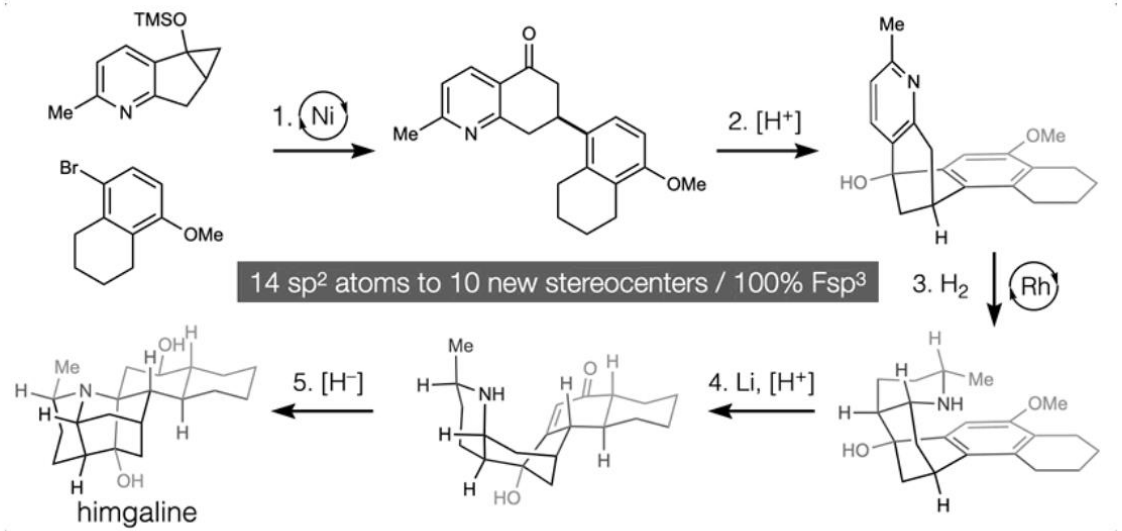
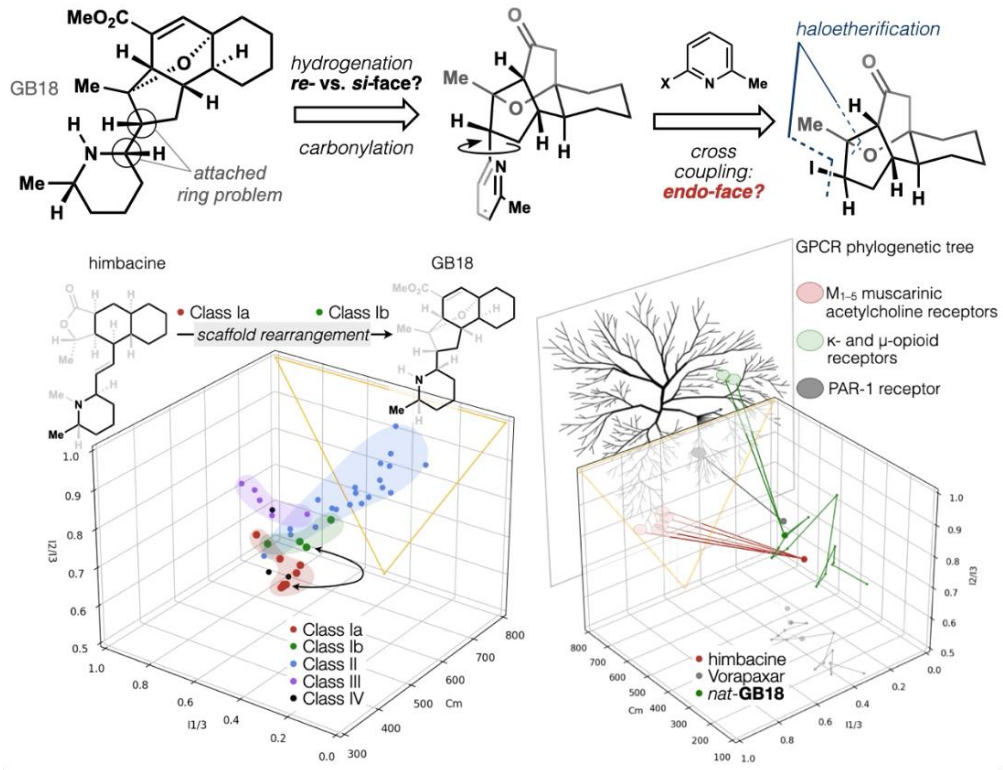
- 1999-2003 B.S., Pennsylvania State University (R.L. Funk)
- 2003-2008 Ph.D., The Scripps Research Institute (P.S. Baran)
- 2008-2010 NIH Postdoctoral Fellow, Harvard University (E.J. Corey)
- 2010-2014 Assistant Professor, The Scripps Research Institute
- 2014-2019 Associate Professor, The Scripps Research Institute
- 2019-present Professor, The Scripps Research Institute



Ryan A. Shenvi



Shenvi *et al.*, *Science* **2022**, *375*, 1270−1274



Shenvi *et al.*, *Nature* **2022**, *606*, 917−921

Website of Shenvi's group: *https://www.shenvilab.org/*

Contents - HAT (Hydrogen Atom Transfer)

1. Concept of HAT
2. Radical Polarity & Polarity Reversal Catalysis (PRC)
3. HAT from Unlikely Sources

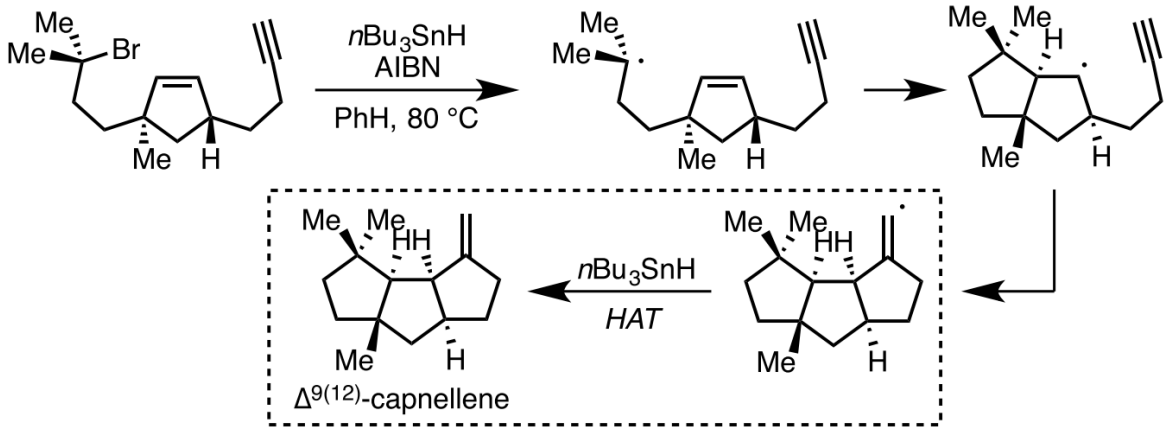
HAT part is according to Baran's group meeting 4/12/14 :
https://www.scripps.edu/baran/images/grpmtgpdf/Lo_Apr_14.pdf

Concept of HAT

HAT: Hydrogen Atom Transfer

A concerted movement of *a proton and an electron (e- + H+ ≡ H•)* in a single kinetic step from one group to another.

$$A{-}H + B^{\bullet} \rightarrow A^{\bullet} + H{-}B$$



example of HAT between alkenyl radical and nBu$_3$SnH

Physical chemistry:

1. Bell–Evans–Polanyi equation :

$$E_a = E_0 + \alpha \Delta H$$

2. Arrhenius equation (阿伦尼乌斯方程) :

$$k = Ae^{-E_a / RT}$$

3. BDE (Bond Dissociation Enthalpy) :

$$\Delta H = BDE(\Delta H) - BDE(\Delta H)$$

(nBu$_3$SnH - BDE = 78 kcal / mol
CH$_3$-H - BDE = 104 kcal / mol CH$_3$O-H – BDE = 105 kcal / mol)

Mayer *et al.*, *J. Am. Chem. Soc.* **2007**, *129*, 5153-5166

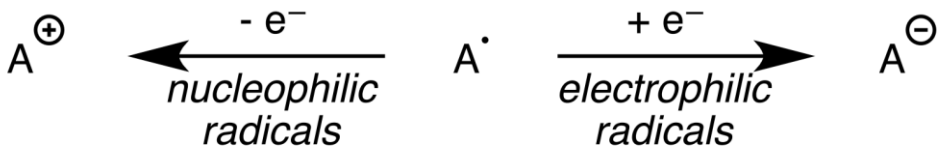
Radical Polarity & Polarity Reversal Catalysis (PRC)

Factors influencing HAT :

Steric effects / Reaction enthalpy / Polar effects

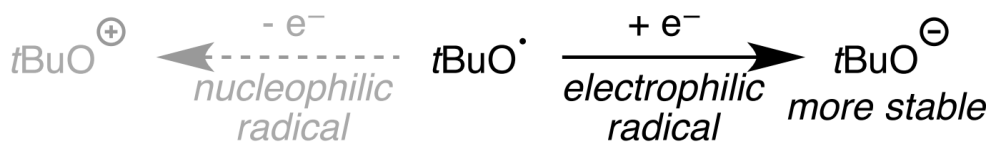
Radical Polarity :

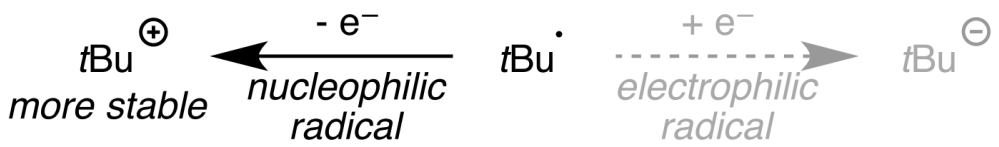
Despite being uncharged species, radicals can have *nucleophilic or electrophilic tendancies*.

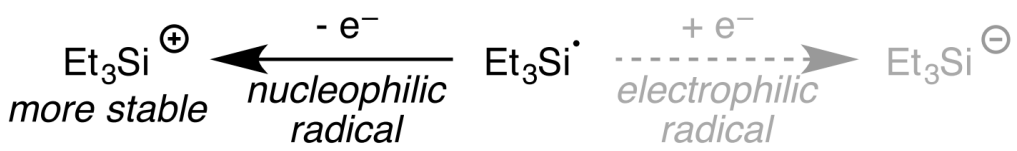


If A^+ is more stable, $A^\bullet$ is a nucleophilic radical because it wants to lose an e^-.

If A^- is more stable, $A^\bullet$ is an electrophilic radical because it wants to gain an e^-.



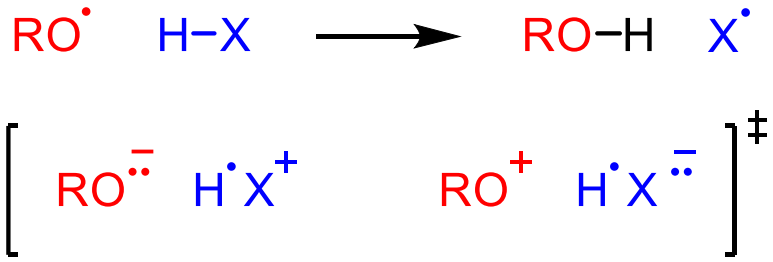




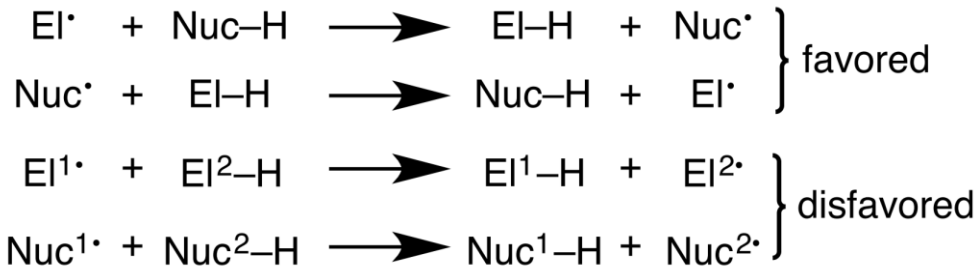
Lopata *et al.*, *J. Org. Chem.* **1998**, *63*, 8646-8653

Radical Polarity & Polarity Reversal Catalysis (PRC)

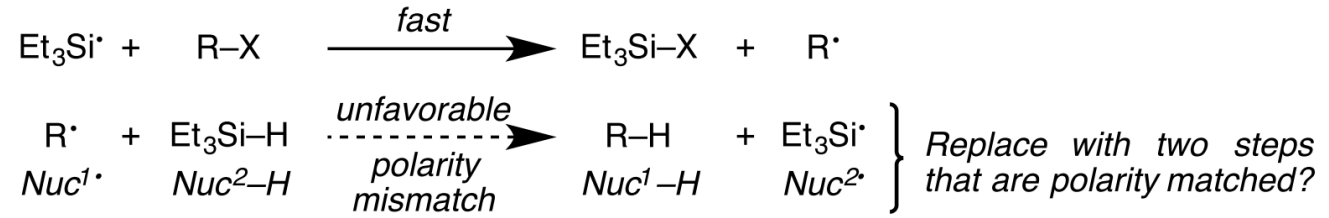
HAT transition state :

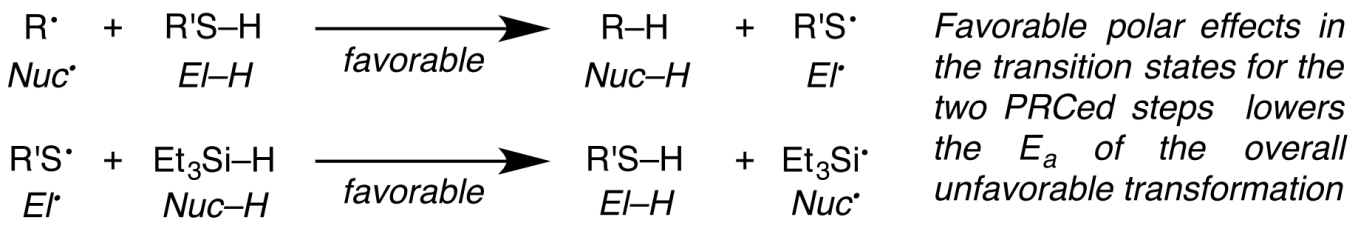


Polarity match / mismatch



Et_3Si-H – BDE = 90 kcal / mol; MeS-H – BDE = 92 kcal / mol





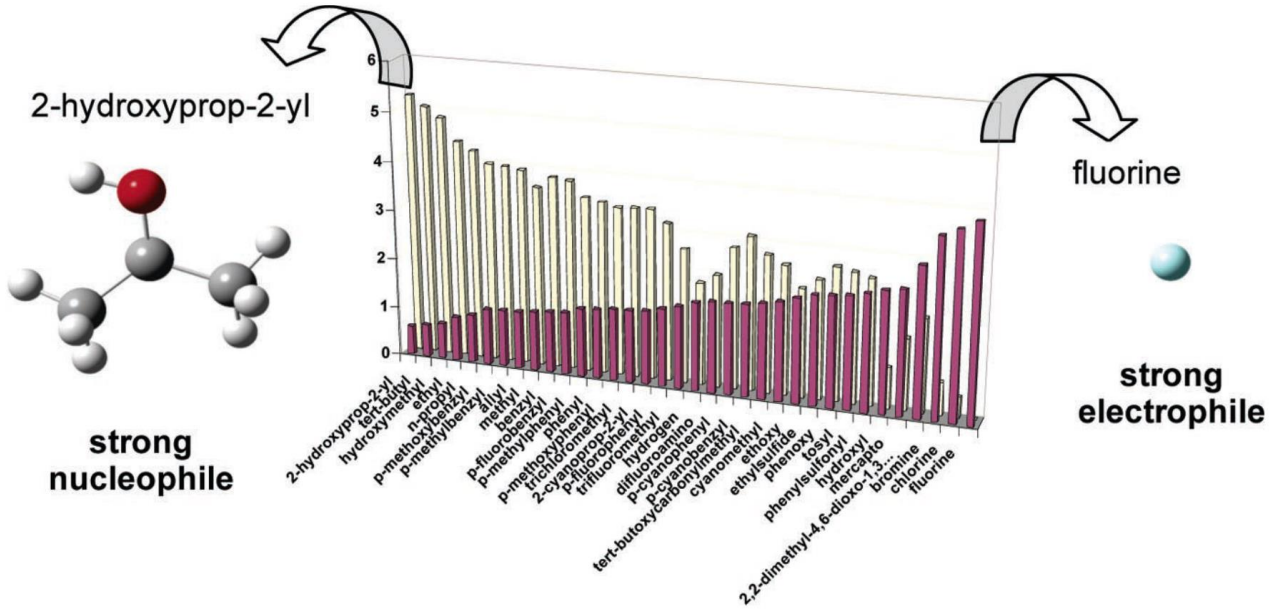
Polarity Reversal Catalysis (PRC) :

Adding a catalyst that replaces the polarity mismatched step with *two polarity matched ones* should yield a net favorable reaction.

Roberts *et al.*, *J. Chem. Soc., Chem. Commun.*, **1989**, 1387

Radical Polarity & Polarity Reversal Catalysis (PRC)

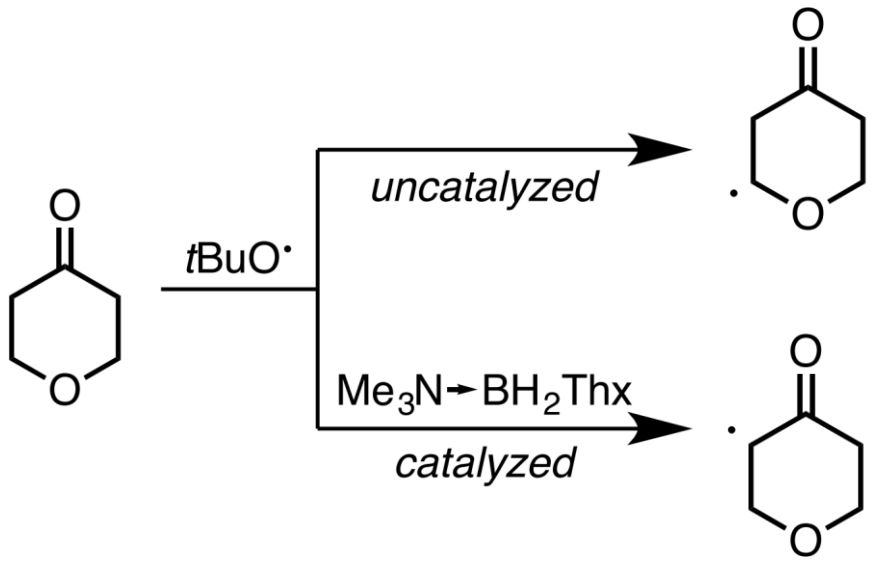
character	PCA	ω
strong nucleophile	2-hydroxyprop-2-yl tert-butyl hydroxymethyl	2-hydroxyprop-2-yl tert-butyl hydroxymethyl
moderate nucleophile	p-methoxybenzyl p-fluorobenzyl p-methylbenzyl benzyl methyl	p-methoxybenzyl p-methylbenzyl methyl benzyl p-fluorobenzyl
weak nucleophile	p-cyanobenzyl 2-cyanoprop-2-yl tert-butoxycarbonylmethyl cyanomethyl	2-cyanoprop-2-yl p-cyanobenzyl tert-butoxycarbonylmethyl cyanomethyl
moderate electrophile	tosyl phenylsulfonyl	tosyl phenylsulfonyl
strong electrophile	2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl	2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl



Classification of 15 Radicals According to Electrophilicity / Nucleophilicity: Comparison between PCA and the Global Electrophilicity Index ω

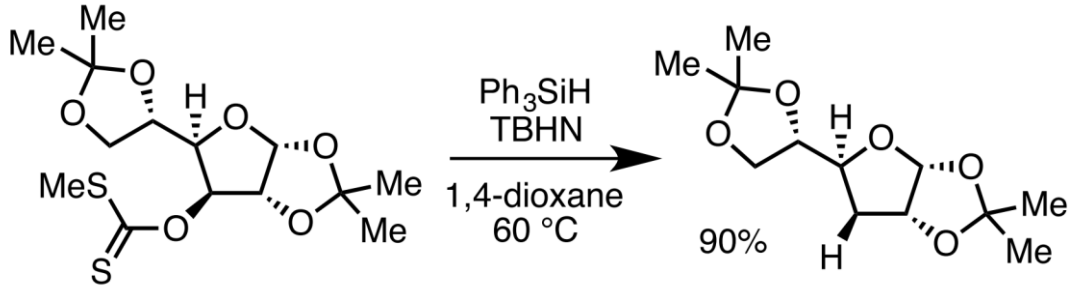
Proft *et al.*, *Org. Lett.* **2007**, *9*, 2721-2724

Radical Polarity & Polarity Reversal Catalysis (PRC)

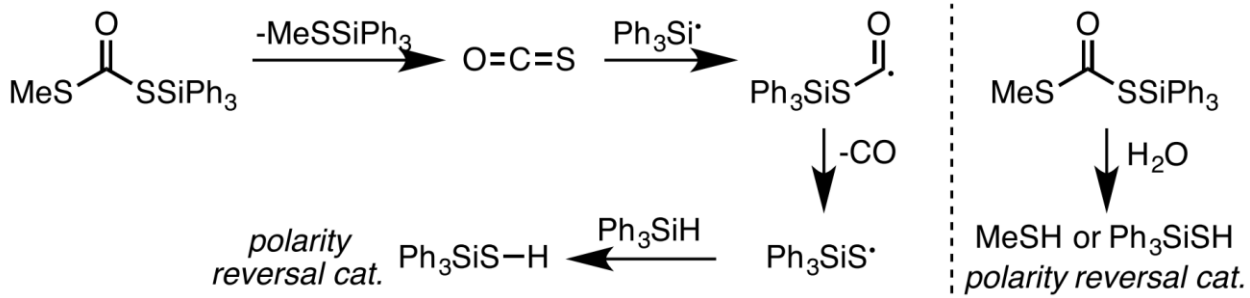


Roberts *et al.*, *J. Chem. Soc., Chem. Commun.* **1987**, 1322

using R_3SiH in *Barton-McCombie* reactions proceeds efficiently

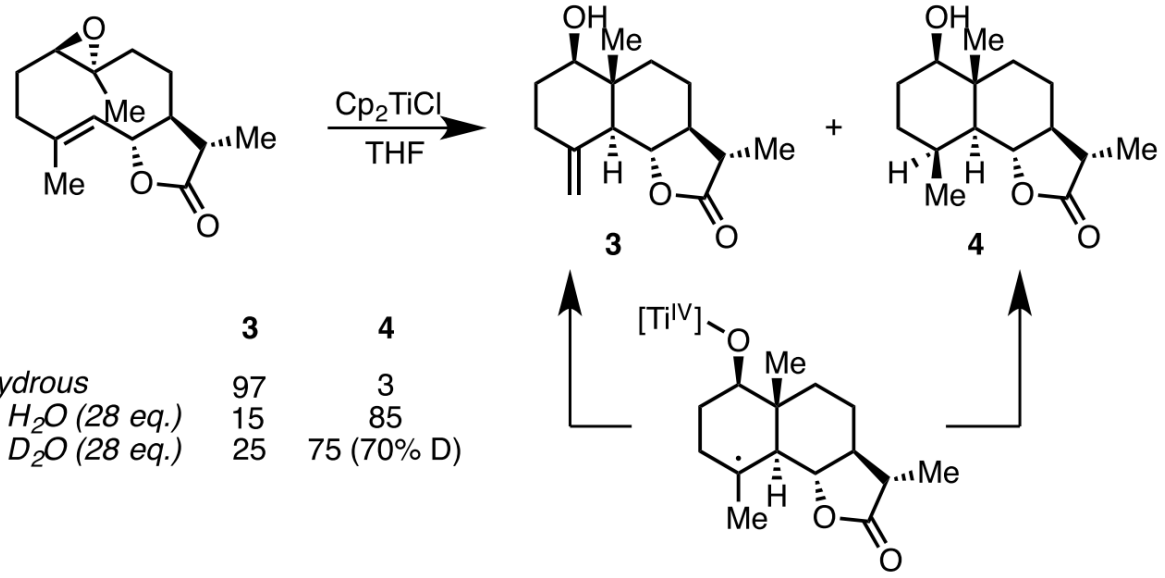


In situ formation of polarity reversal catalyst:



Roberts *et al.*, *Tetrahedron Lett.* **2001**, *42*, 763

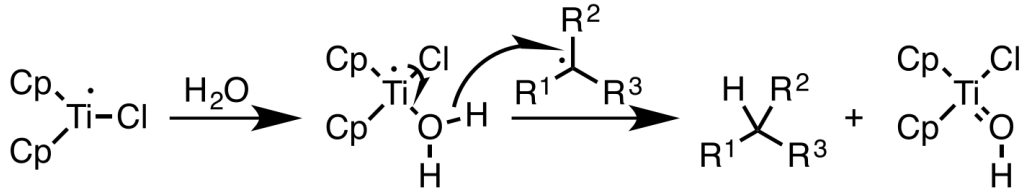
HAT from Unlikely Sources



	3	4
anhydrous	97	3
with H_2O (28 eq.)	15	85
with D_2O (28 eq.)	25	75 (70% D)

Oltra *et al.*, *J. Org. Chem.* **2002**, *67*, 2566

The BDE of H_2O was proposed to decrease upon complexation with Ti^{III}.

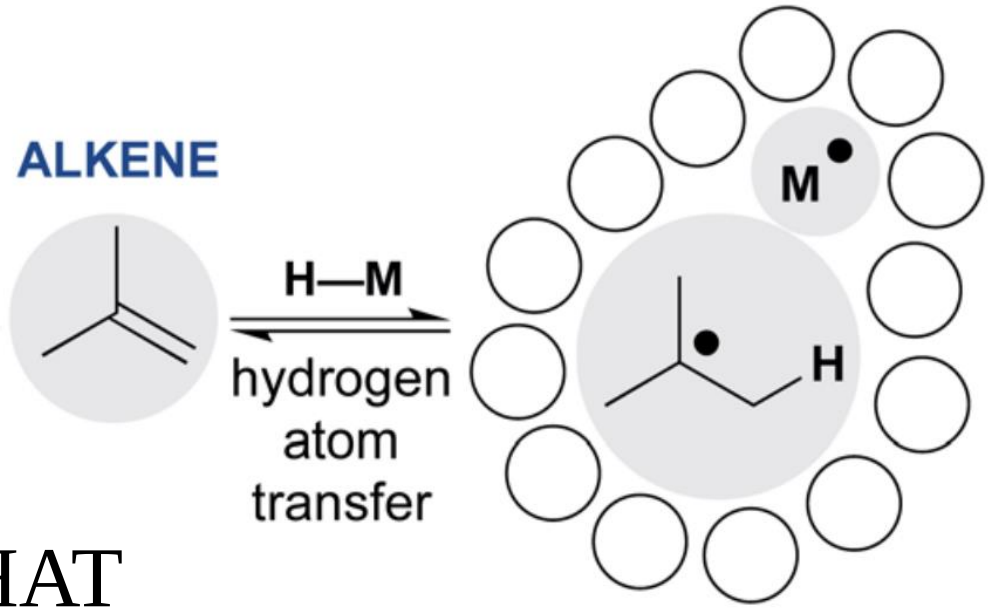


BDE_{calc} = 49.4 kcal/mol

Oltra *et al.*, *Angew. Chem. Int. Ed.* **2006**, *45*, 5522

Contents - MHAT (Metal Hydride Hydrogen Atom Transfer)

1. Introduction of MHAT
2. Mechanism of MHAT
3. Versatile applications of MHAT



Introduction - Classification of MHAT

Classification of MHAT :

- bearing strong-field (SF) ligands --- SF systems

Mo, W, V, Cr, Mn, Fe, Co / strong-field ligands (*carbonyls*)

Metal hydride often *isolable* / hydrogen atom source often H_2

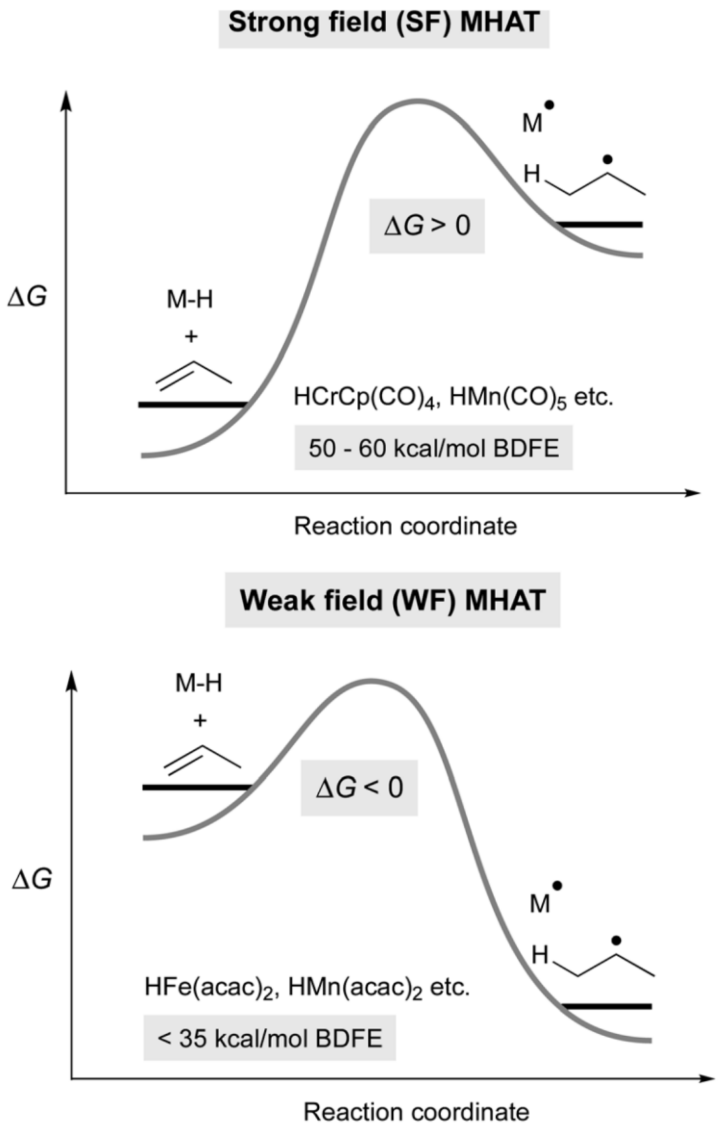
/ rates of catalysis generally *slow*

- bearing weak-field (WF) ligands --- WF systems

Mn, Fe, Co / weak-field ligands (*based on N or O donors*) /

Metal hydride often *inseparable* / hydrogen atom source

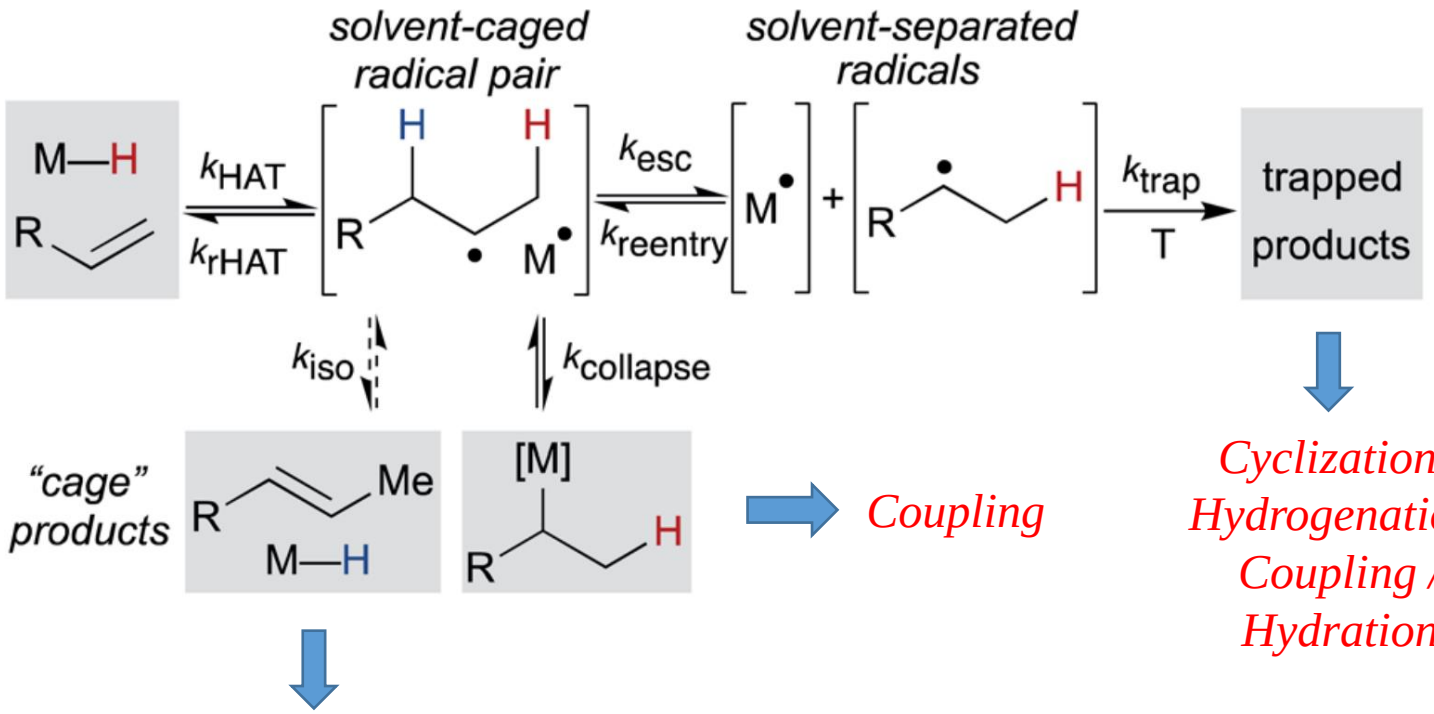
often *$PhSiH_3$ or $NaBH_4$* / rates of catalysis *rapid*



Shenvi *et al.*, *Chem. Sci.*,**2020**, *11*,12401–12422

Mechanism of MHAT

Mechanism of MHAT :



MHAT Formation ---

- *Carbon-Metal bond ?*
- *Free radical ?*

Shenvi *et al.*, *Chem. Sci.*,**2020**, *11*,12401–12422

Mechanism of MHAT

Complete catalytic cycle :

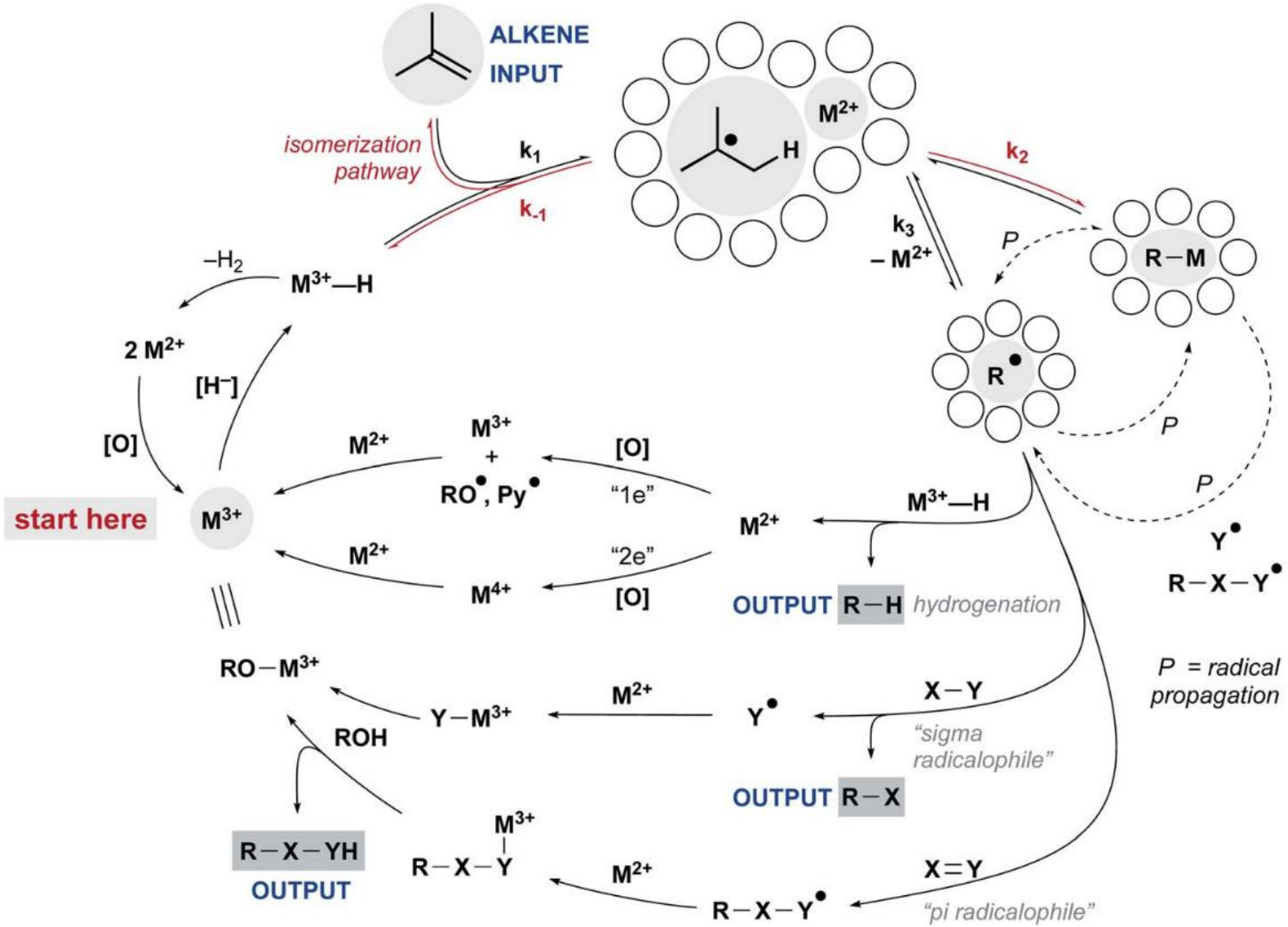
Why M^{3+}-H ?

$(acac)_2Fe–H$

BDE = 17-20 kcal / mol

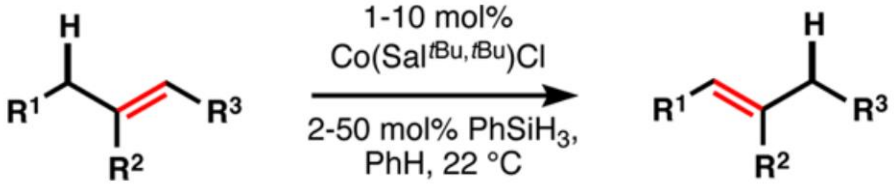
$[(acac)_2Fe–H]^-$

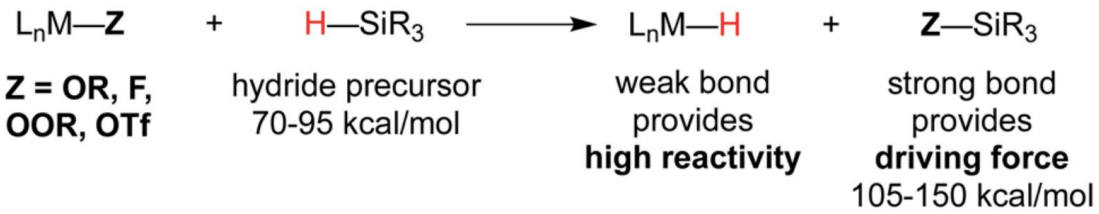
BDE = 66 kcal / mol

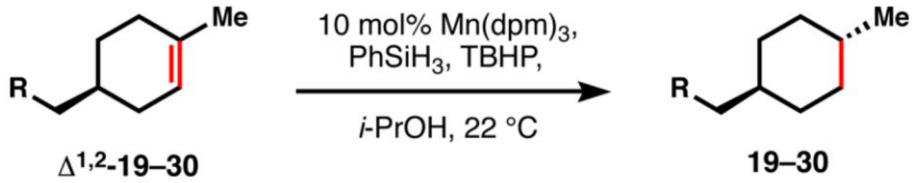


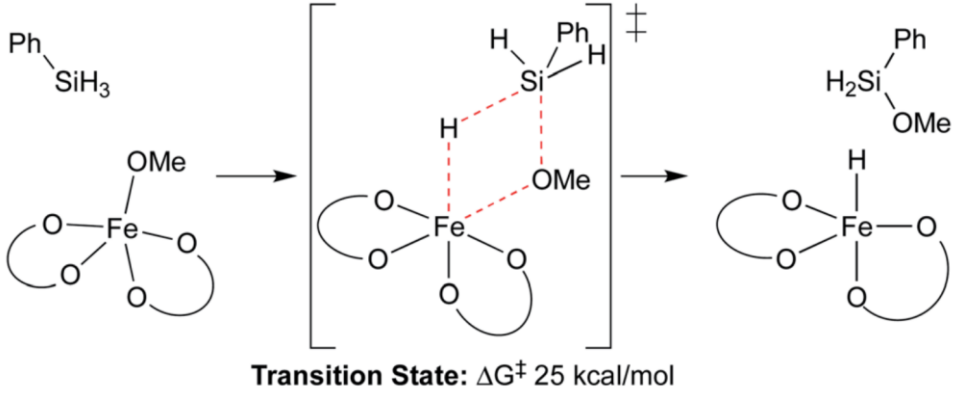
Mechanism of MHAT – Formation of Metal Hydride

M^{3+}-H : *low BDE / active species*

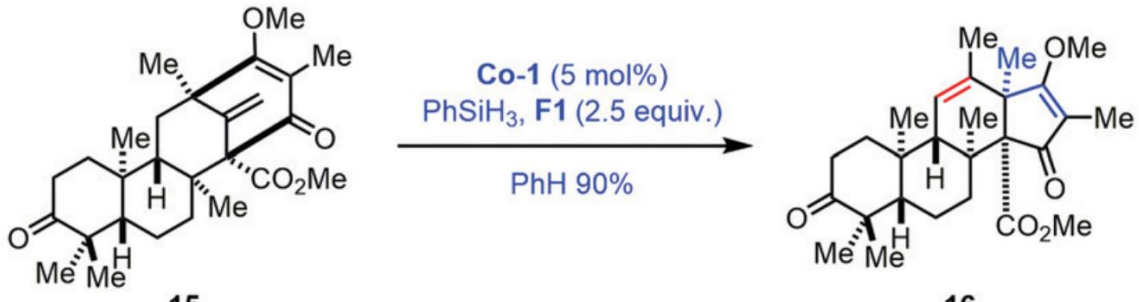


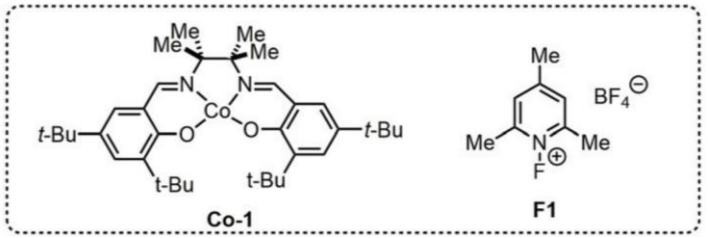






Potential mechanisms of metal-hydride formation.



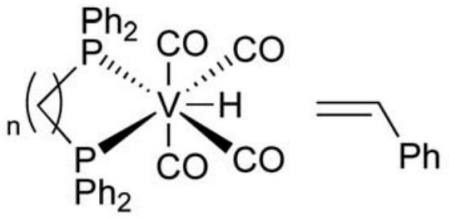


Shenvi *et al.*, *Chem. Sci.*,**2020**, *11*,12401–12422

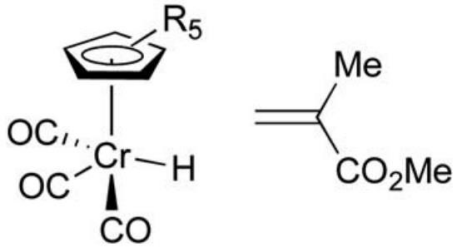
Mechanism of MHAT – Trends in alkene selectivity

Strong-Field systems:

a. Influence of M-H Sterics on MHAT rate

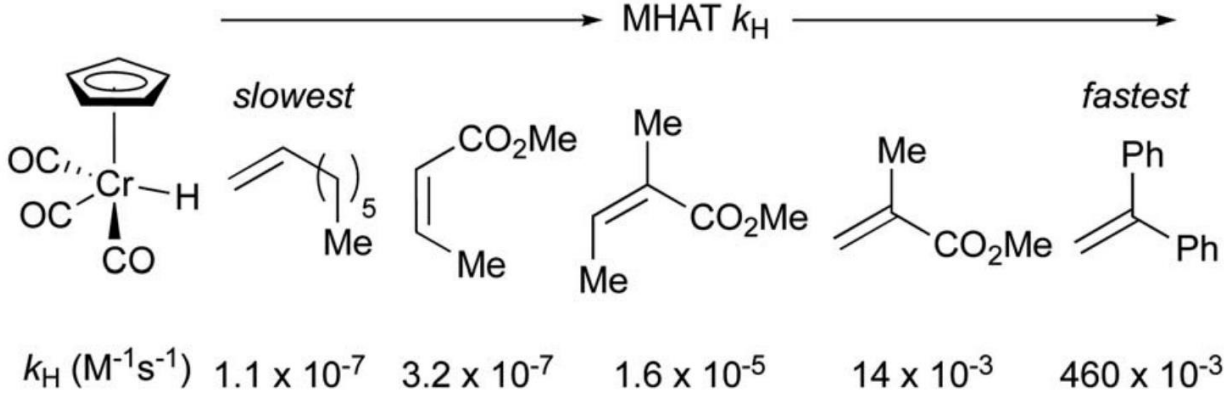


n	k_H ($M^{-1}s^{-1}$)	*M-H* BDE (kcal/mol)
1	17×10^{-3}	57.9
2	9.0×10^{-3}	57.5
3	7.5×10^{-3}	56.0
4	5.0×10^{-3}	54.9



R	k_H ($M^{-1}s^{-1}$)	*M-H* BDE (kcal/mol)
H	4.0×10^{-3}	61.5
Me	0.6×10^{-3}	62.3
Ph	0.5×10^{-3}	59.6

b. Influence of Olefin Sterics and Electronics on MHAT rate

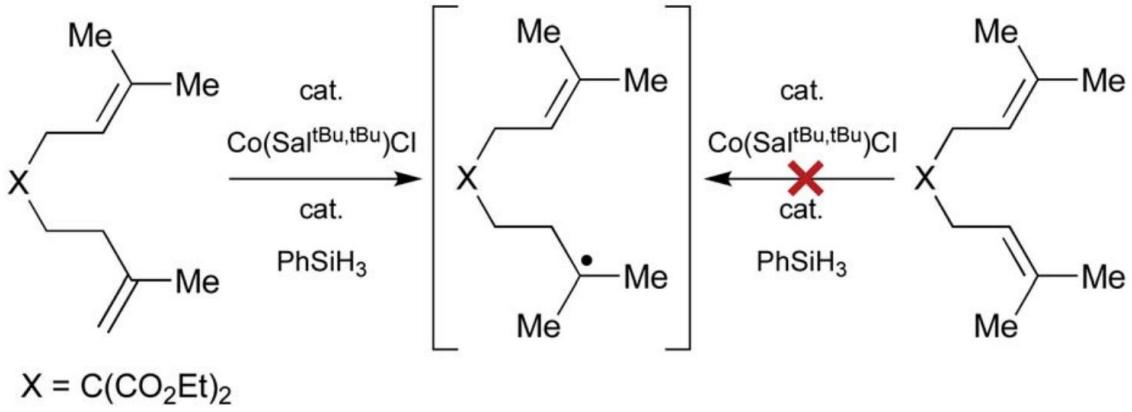


k_H ($M^{-1}s^{-1}$)	1.1×10^{-7}	3.2×10^{-7}	1.6×10^{-5}	14×10^{-3}	460×10^{-3}

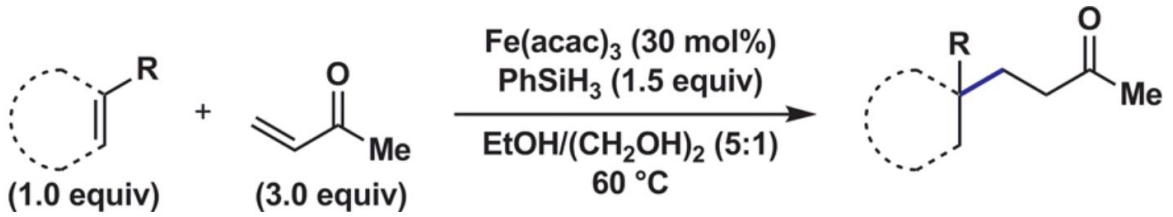
Shenvi *et al.*, *Chem. Sci.*,**2020**, *11*,12401–12422

Mechanism of MHAT – Trends in alkene selectivity

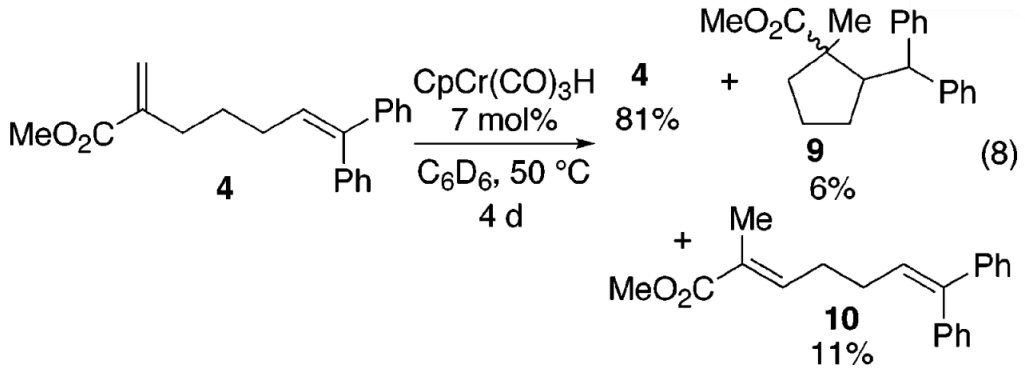
Weak-Field systems:



Shenvi *et al.*, *Chem. Sci.*,**2020**, *11*,12401–12422

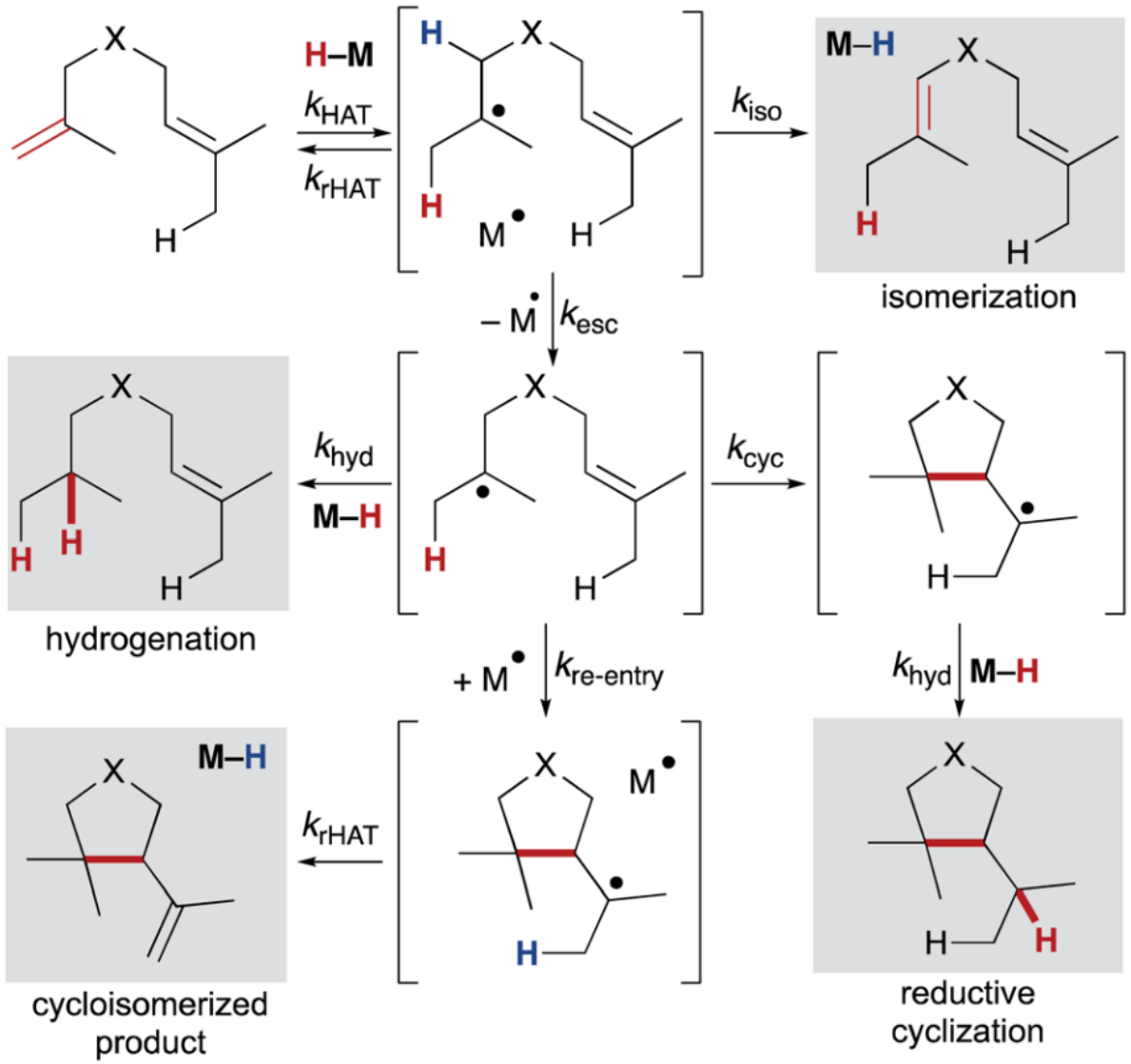


Baran *et al.*, *J. Am. Chem. Soc.*, **2014**, *136*, 1304–1307



Norton *et al.*, *J. Am. Chem. Soc.*, **2007**, *129*, 770–771

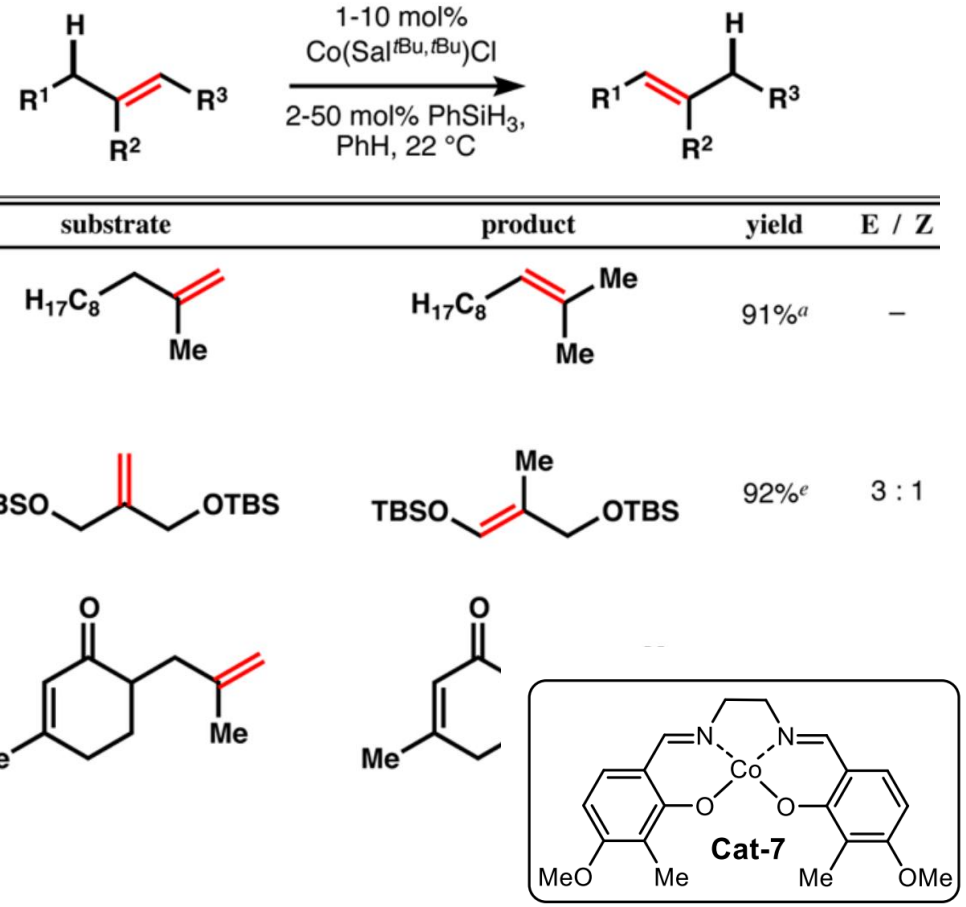
Versatile applications of MHAT



Versatile applications of MHAT :

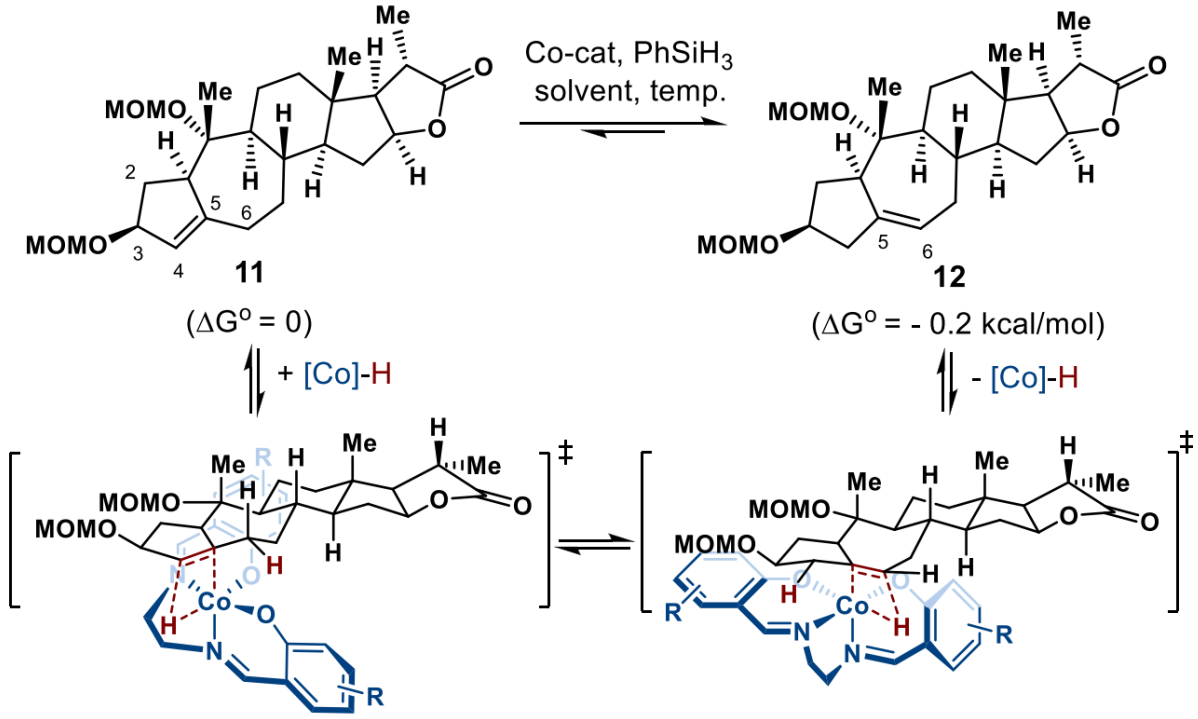
- Olefin Isomerization
- Thermodynamic Hydrogenation
- Cyclization

Versatile applications of MHAT - Olefin Isomerization



Shenvi *et al.*, *J. Am. Chem. Soc.* **2014**, *136*, 16788−16791

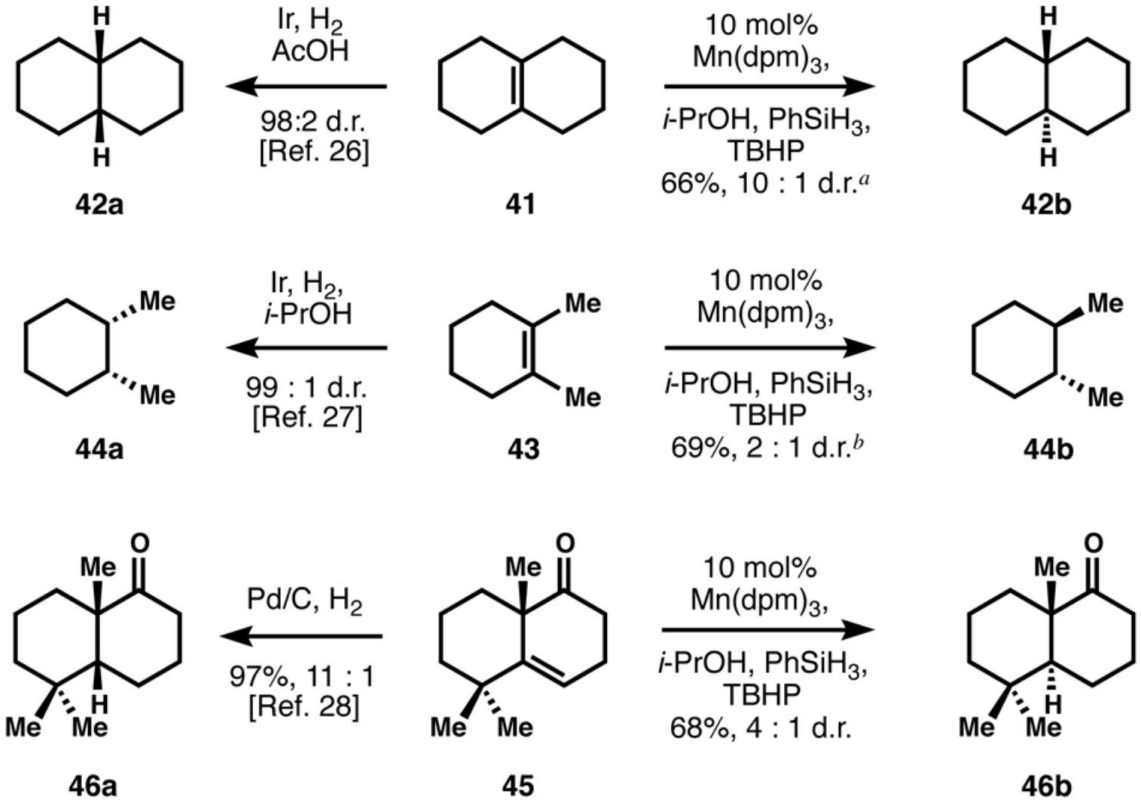
Semisynthesis of (−) - **Bufospirostenin A**

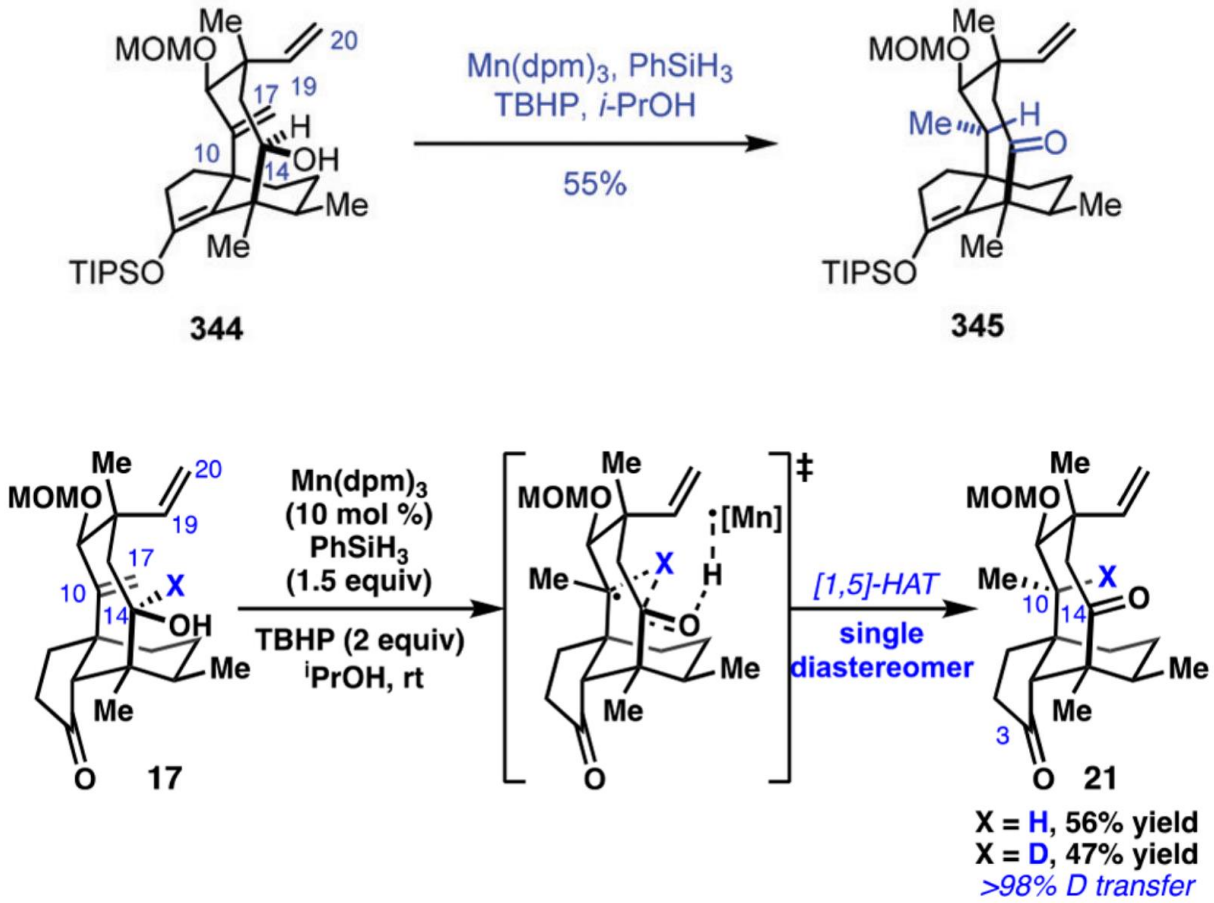


Catalyst (0.2 equiv), $PhSiH_3$ (0.8 equiv), acetone (degassed)

Zhen Yang *et al.*, *J. Am. Chem. Soc.* **2022**, *144*, 2479−2483

Versatile applications of MHAT - Hydrogenation

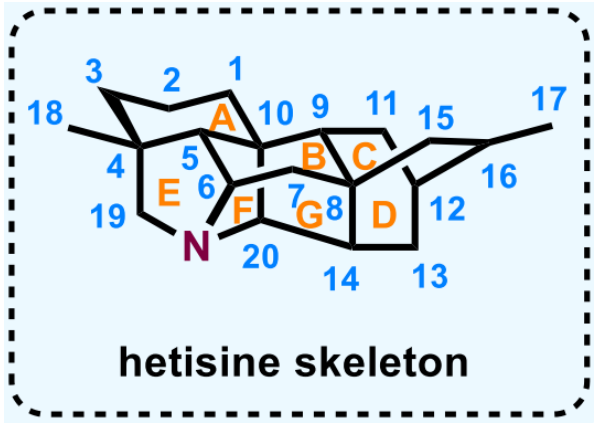


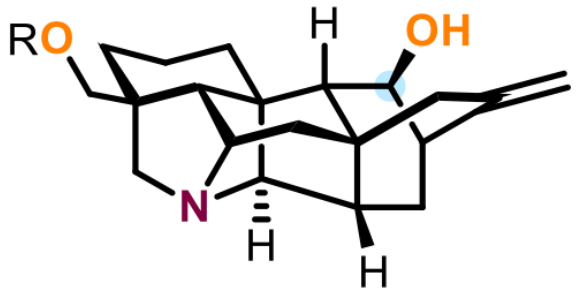


Shenvi *et al.*, *J. Am. Chem. Soc.* **2014**, *136*, 1300−1303

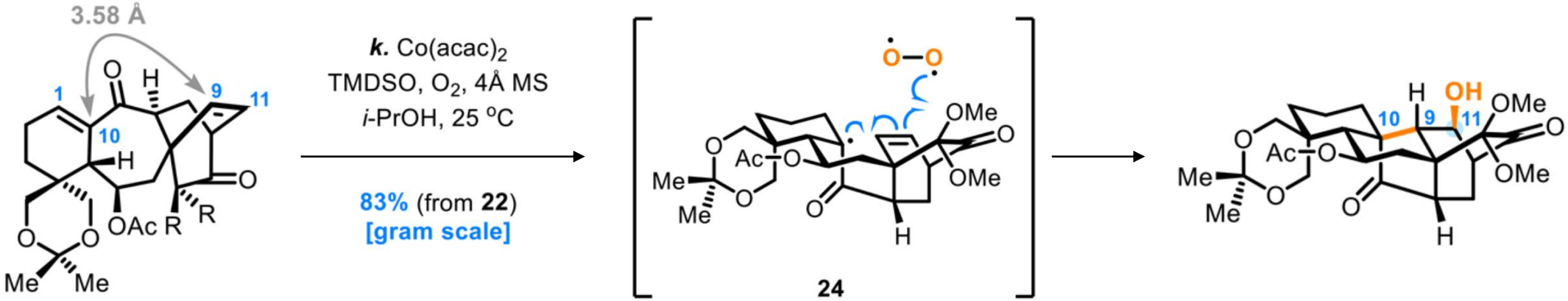
Reisman *et al.*, *J. Am. Chem. Soc.* **2018**, *140*, 1267−1270

Versatile applications of MHAT - Cyclization



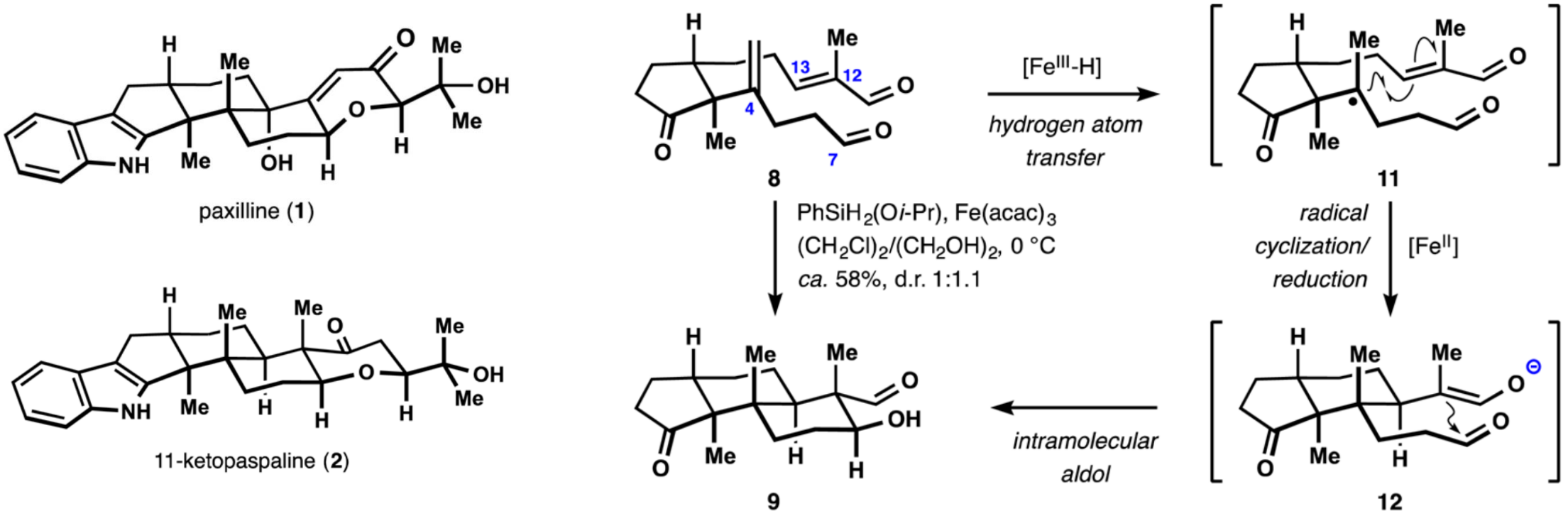


R = H: (+)-davisinol (**7**)
R = Bz: (+)-18-benzoyldavisinol (**8**)



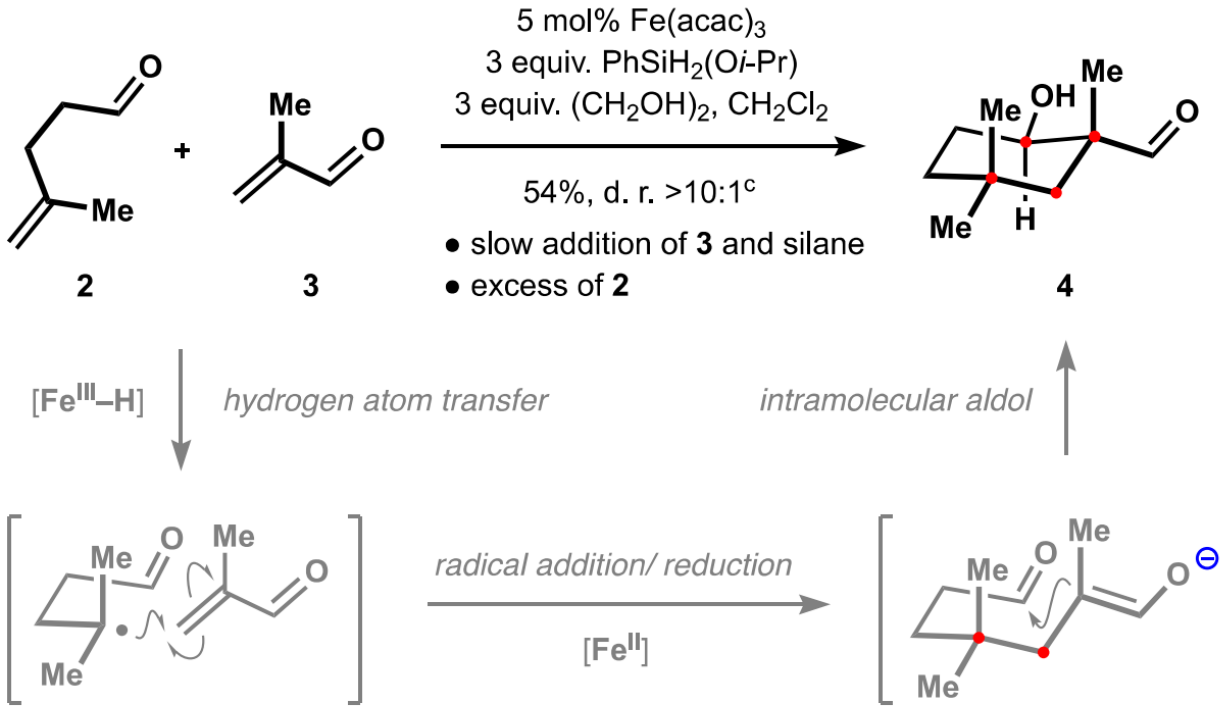
Hanfeng Ding *et al.*, *J. Am. Chem. Soc.* **2021**, *143*, 10576−10581

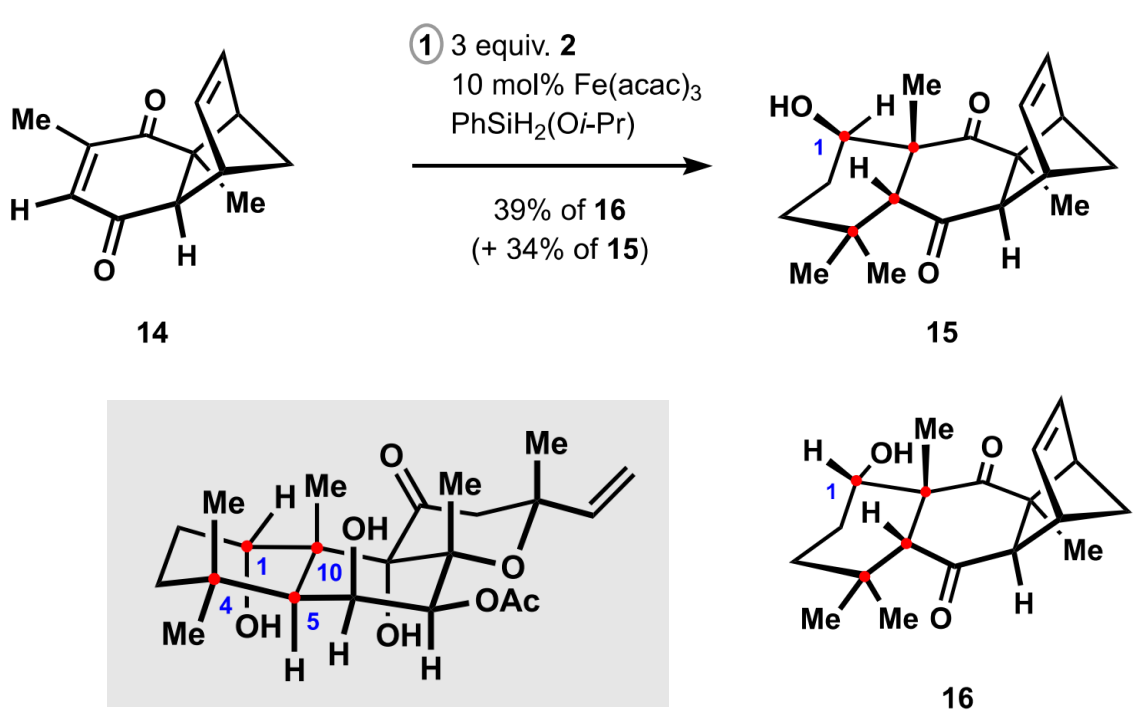
Versatile applications of MHAT - Cyclization



Pronin *et al.*, *J. Am. Chem. Soc.* **2015**, *137*, 15410−15413

Versatile applications of MHAT - Cyclization





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Pronin *et al.*, *J. Am. Chem. Soc.* **2019**, *141*, 12246−12250