Cooperative Hydrogen Atom Transfer (cHAT)-Based Hydrogenation Approach

2023. 12. 2. Haruka Fujino

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1. Introduction of cooperative hydrogen atom transfer (cHAT)

2. cHAT Olefin Hydrogenation developed by West group
(*J. Am. Chem. Soc.* 2020, *142*, 19316–19326. and
Chemrxiv 2023, DOI: 10.26434/chemrxiv-2023-b9zdf.)

3. cHAT Olefin Hydrogenation developed by Studer group
(*Nature* 2023, *619*, 506–513.)

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3. cHAT Olefin Hydrogenation developed by Studer group
(*Nature* 2023, *619*, 506–513.)

Profs. Julian G. West and Armido Studer

■ **Prof. Julian G. West**

2012 (?) : BS, The University of British Columbia
Prof. Glenn M. Sammis)
2017 : PhD, Princeton Univarsity (Prof. Erik J. Sorensen)
2017-2019: PD, California Institute of Technology
(Profs. Harry B. Gray and Brian M. Stoltz)
2019- : Assistant Professor, Rice University

Research Topics in the West Group:
Photo-reaction development/catalysis design, and cancer research

■ **Prof. Armido Studer**

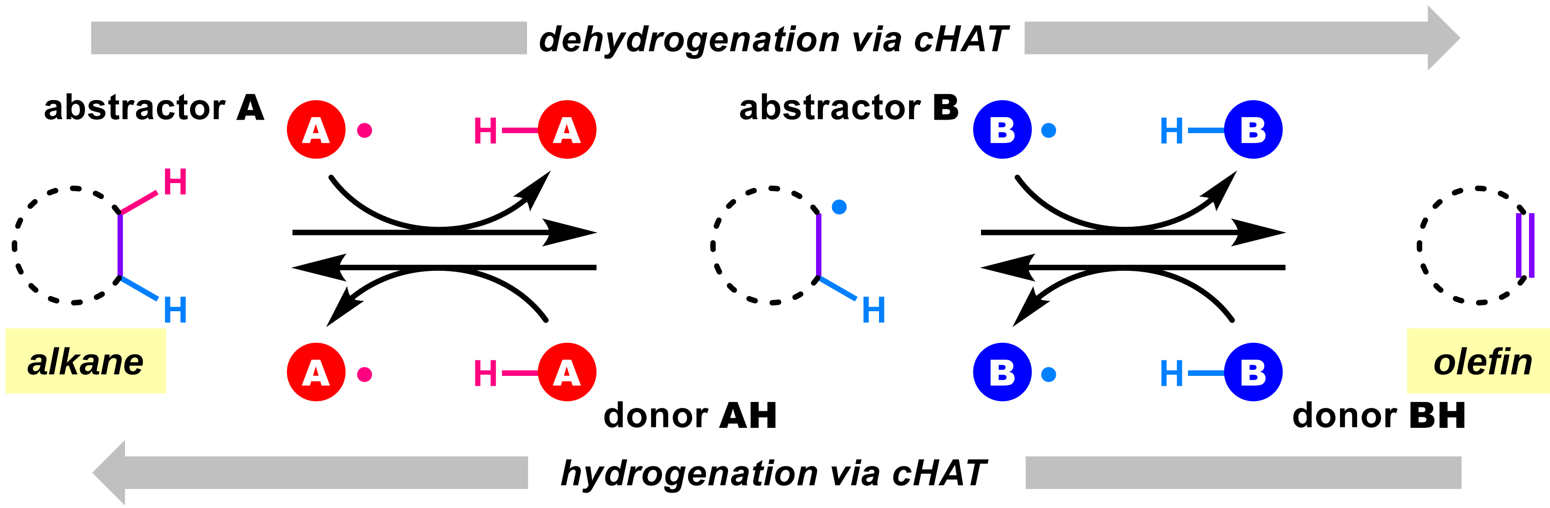
1991 : BS, ETH Zürich (Prof. Dieter Seebach)
1995 : PhD, ETH Zürich (Prof. Dieter Seebach)
1995-1996: PD, University of Pittsburgh (Prof. Dennis P. Curran)
1996-2000: Independent Research, ETH Zürich
2000-2004: Associate Professor, Philipps-Universität Marburg
2004- : Full Professor
Westfälische Wilhelms-Universität-Münster

Research Topics in the Studer Group:
Radical chemistry in organic synthesis, and catalysis for radical reactions

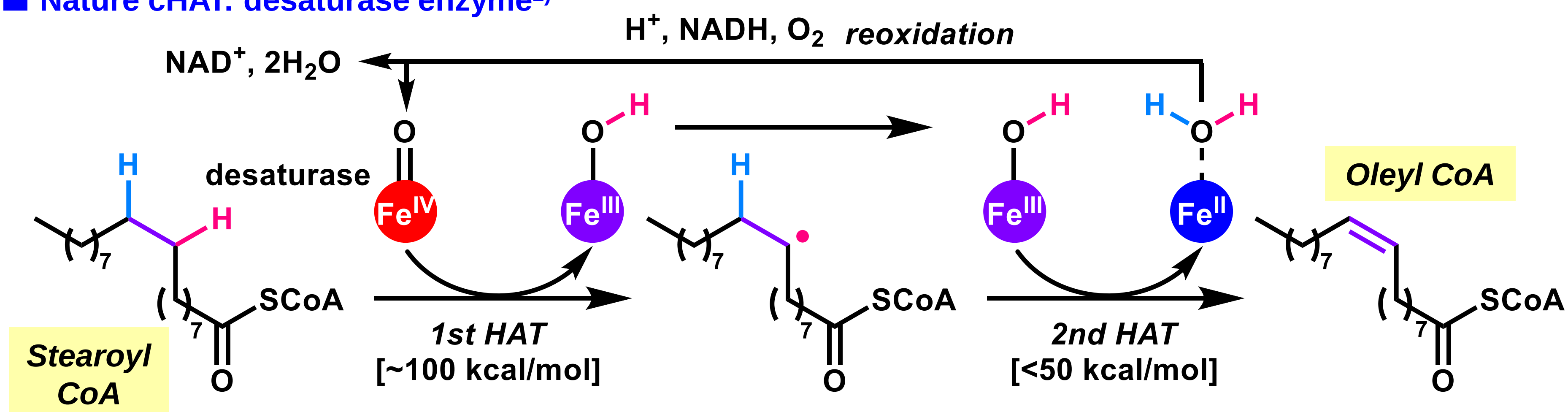
Cooperative Hydrogen Atom Transfer (cHAT)[1]

Cooperative hydrogen atom transfer (cHAT)

a pair of two (or more) HAT processes, each of which is performed by a different donor or abstractor.

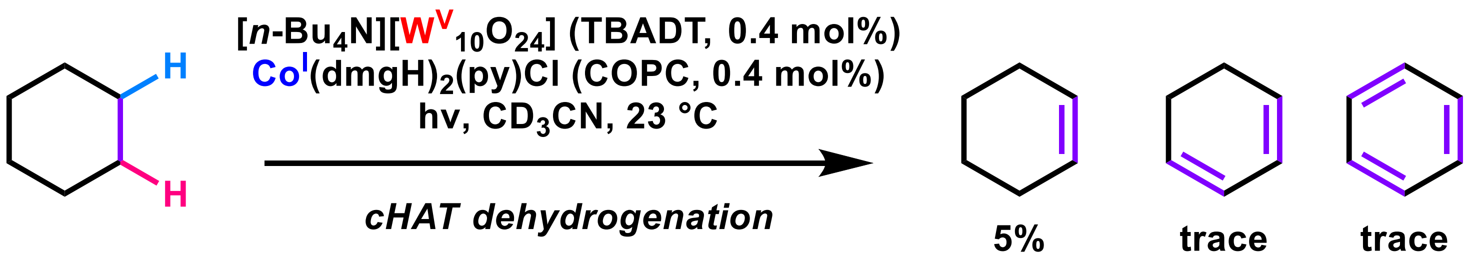


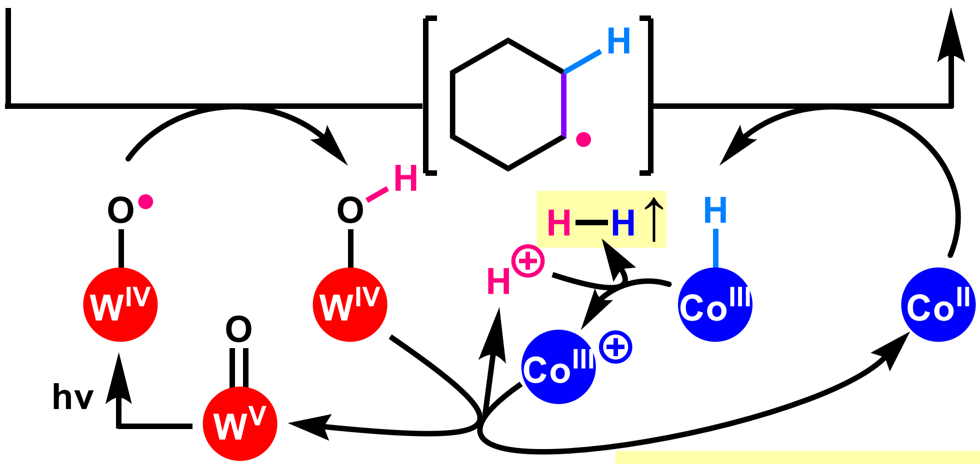
Nature cHAT: desaturase enzyme[2]

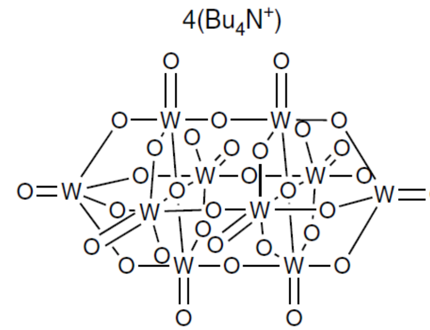


1. Kattamuri, P. V.; West, J. G. *Synlett* **2021**, *32*, 1179.
2. West, J. G.; Sorensen, E. J. *Isr. J. Chem.* **2017**, *57*, 259.

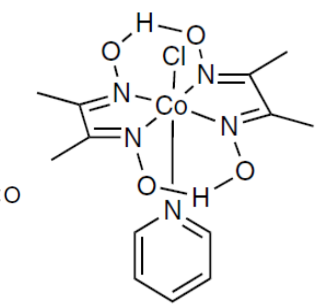
cHAT Dehydrogenation in Organic Synthesis[1)]







TBADT

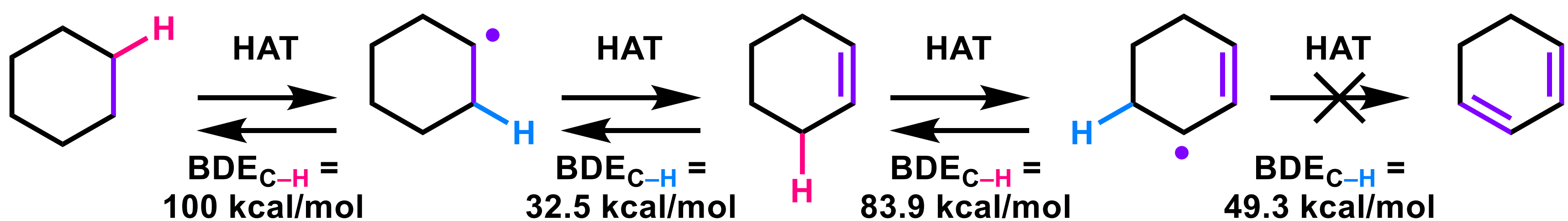


COPC

The release of H_2 gas is the driving force of the reaction.

■ C–H bond dissociation energies (BDE) for each HAT

$BDE_{Co–H}$ ~ 50 kcal/mol

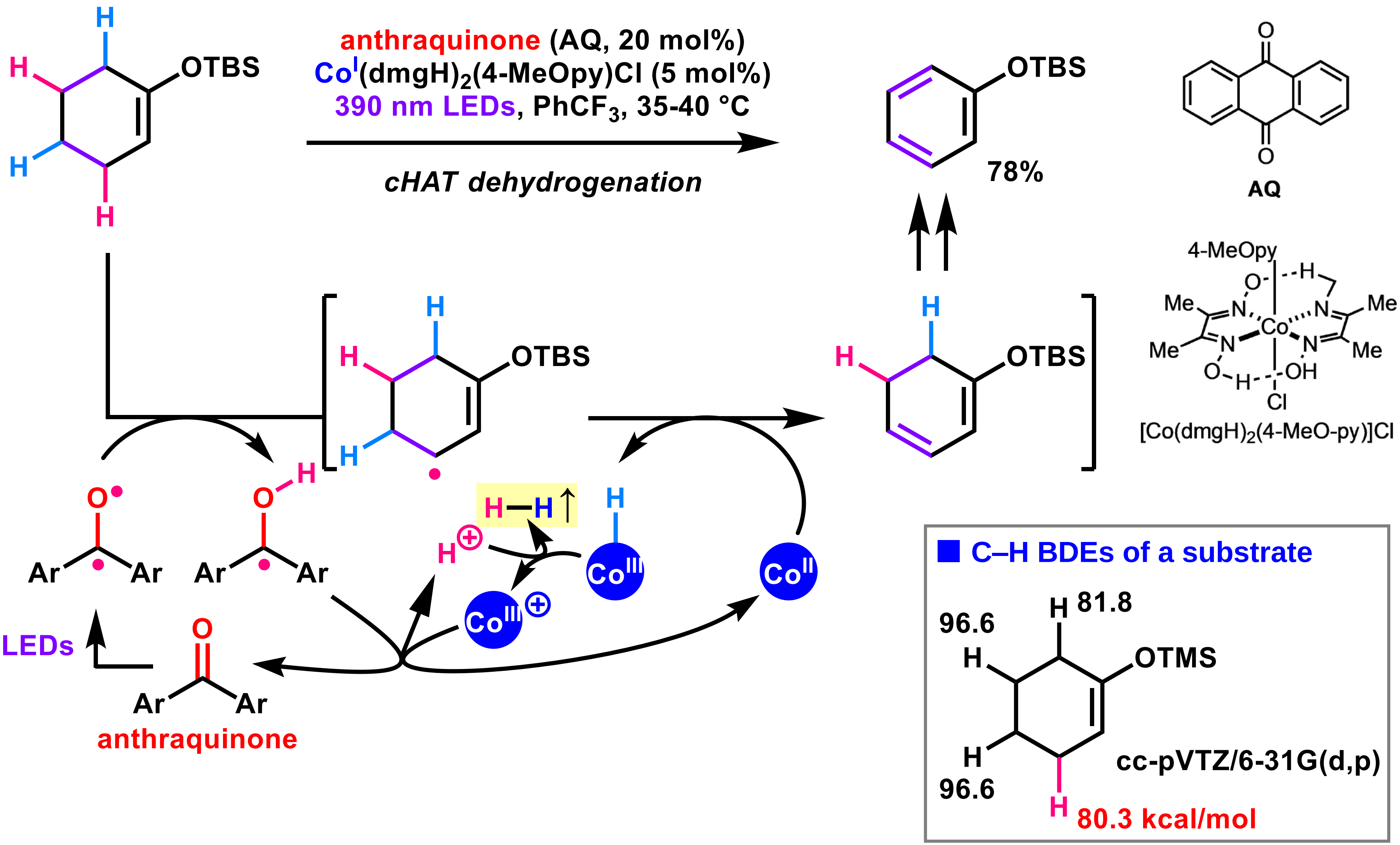


ΔH_{HAT} ~ −17 kcal/mol

ΔH_{HAT} ~ 0 kcal/mol

1. West, J. G.; Huang, D.; Sorensen, E. J. *Nat. Commun.* **2015**, *6*, 10093.

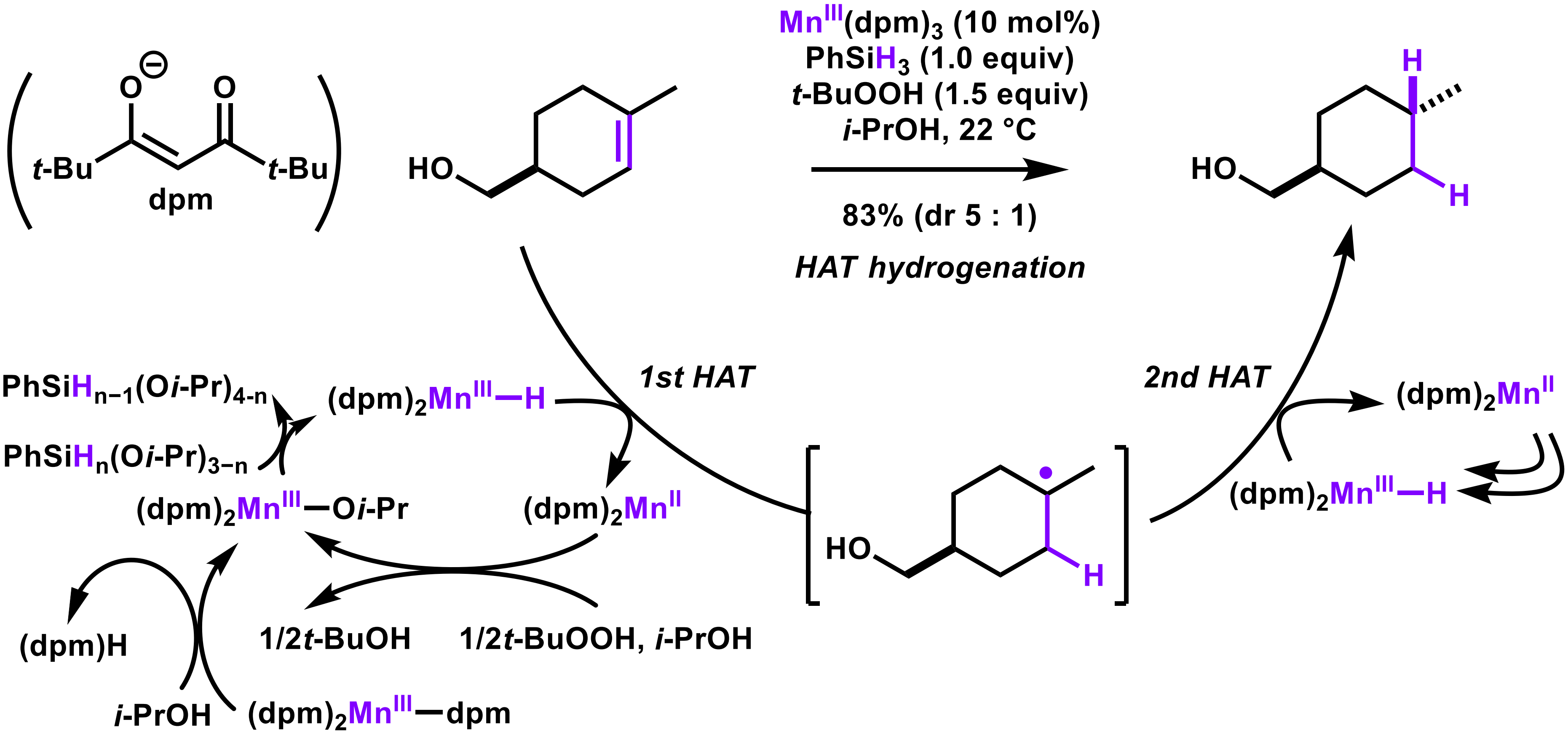
Aromatization via cHAT Dehydrogenation[1)]



The release of H_2 gas and aromatization are the driving forces of the reaction.

1. Caldora, H. P.; Zhang, Z.; Tilby, M. J.; Turner, O.; Leonori, D. *Angew. Chem. Int. Ed.* **2023**, *62*, e202301656.

HAT Hydrogenation (Radical-Based Hydrogenation)[1)]

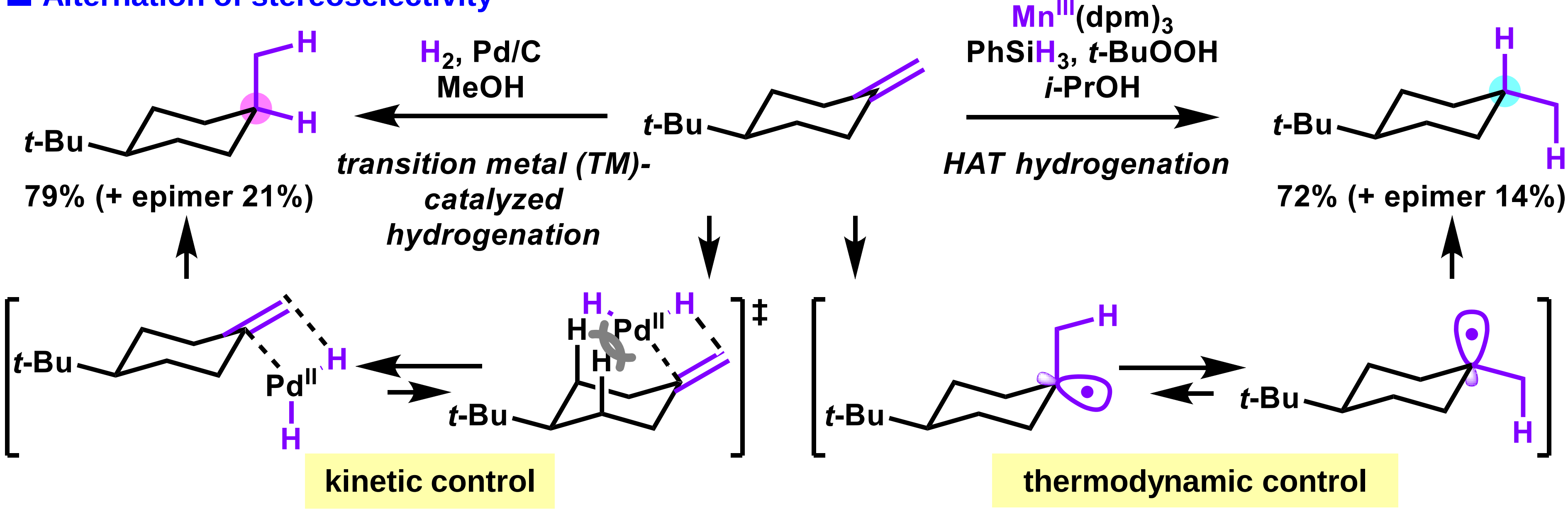


According to the Sorensen and West's definition, This reaction is NOT cHAT dehydrogenation because the same hydrogen donor participates twice in the HAT process.

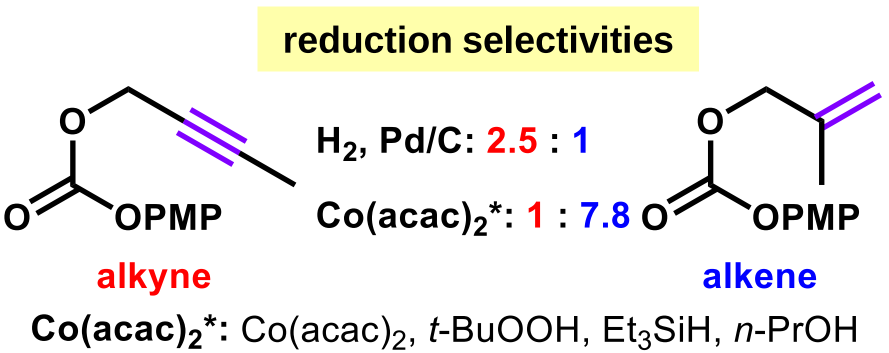
1. Iwasaki, K.; Wan, K. K.; Shenvi, R. A. *J. Am. Chem. Soc.* **2014**, *136*, 1300.
2. For a related reaction, see: King, S. M.; Ma, X.; Herzon, S. B. *J. Am. Chem. Soc.* **2014**, *136*, 6884.

Characteristics of HAT Hydrogenation[1), 2)]

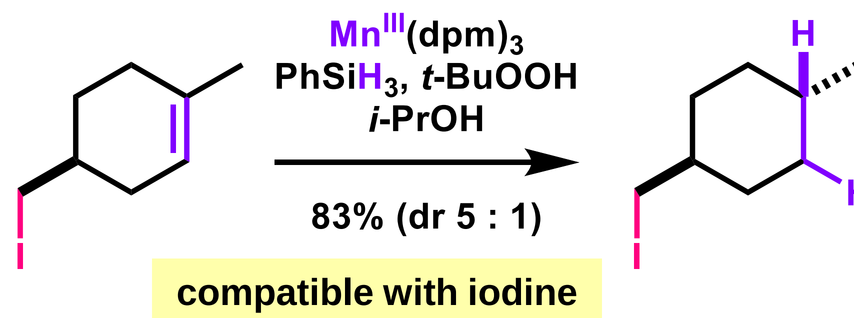
■ Alternation of stereoselectivity



■ Alternation of chemoselectivity



■ Functional group tolerance



1. Iwasaki, K.; Wan, K. K.; Shenvi, R. A. *J. Am. Chem. Soc.* **2014**, *136*, 1300.
2. King, S. M.; Ma, X.; Herzon, S. B. *J. Am. Chem. Soc.* **2014**, *136*, 6884.

HAT Hydrogenation in Natural Product Syntheses

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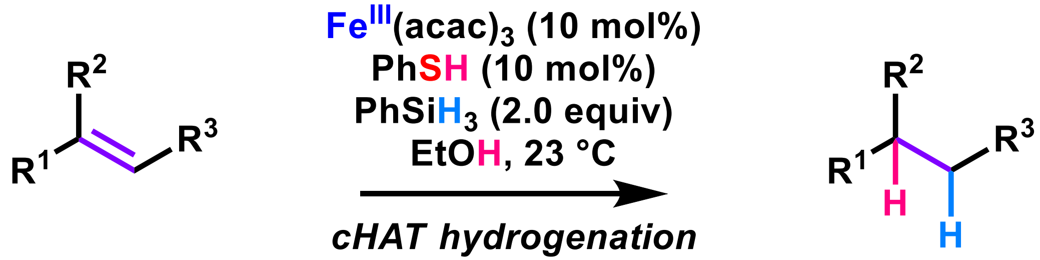
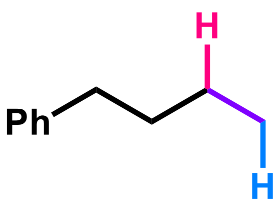
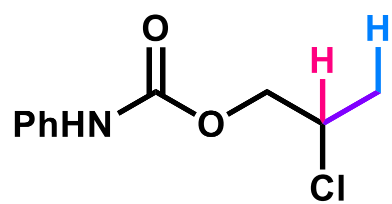
Exogenous Oxidant-Free cHAT Hydrogenation[1)]



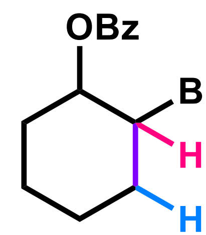
■ **Structures, yields, and if applicable stereoselectivities of products, and reaction time**



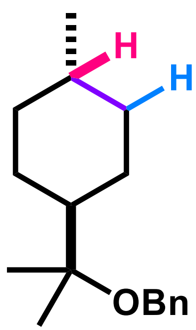
93% [26 h]



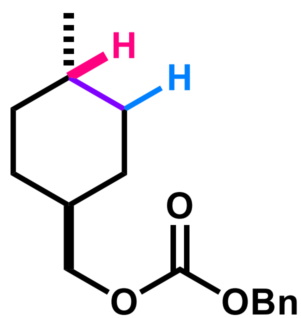
78% [5.5 d]



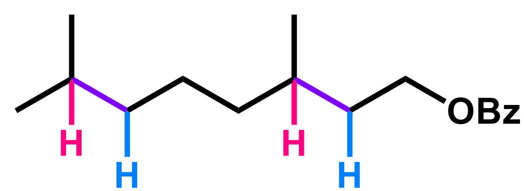
64% (dr 1 : 1) [6 d]



83% (dr 6.7 : 1) [5.5 d]



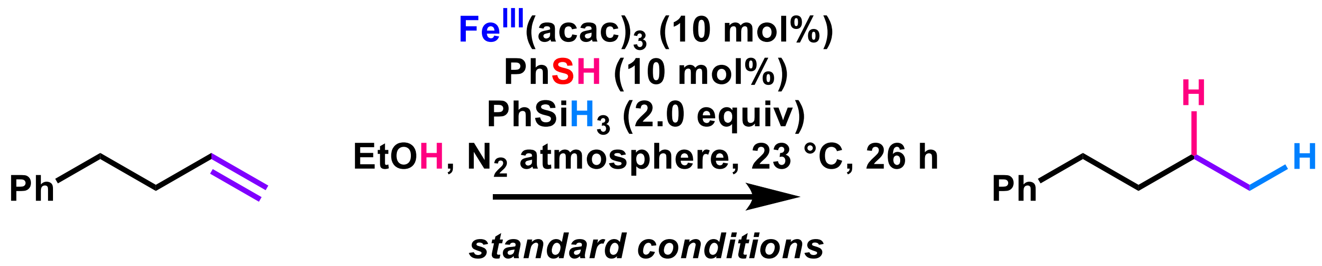
83% (dr 6.7 : 1) [46 h]



82% [36 h]

1. Kattamuri, P. V.; West, J. G. *J. Am. Chem. Soc.* **2020**, *142*, 19316.

Control Experiments[1)]



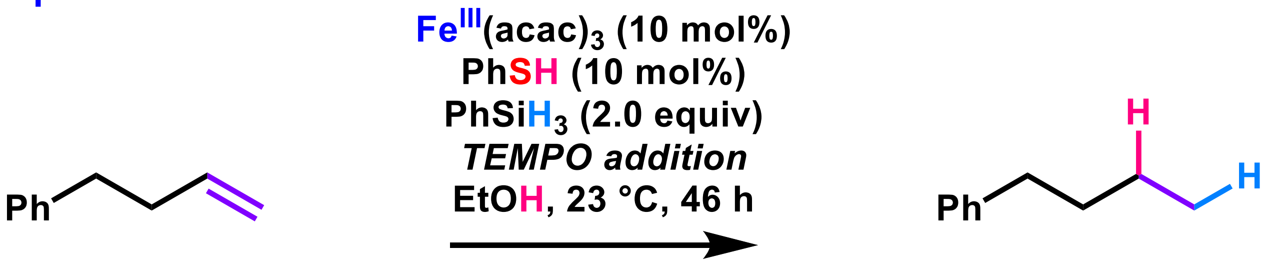
entry	deviation from the standard conditions	yield
1	none	93%
2	no $Fe^{III}(acac)_3$	n.d.
3	$Mn^{III}(dpm)_3$ instead of $Fe^{III}(acac)_3$	30%
4	$Co^{III}(acac)_3$ instead of $Fe^{III}(acac)_3$	14%
5	no PhSH	27%
6	*n*-$C_{12}H_{25}S$–H instead of PhSH, 72 h	43%
7	$PhSiH_3$ (1.2 equiv)	49%
8	50 ºC	49%
9	under air	48%

[a] BDE: Co^{III}–H ~ 50 kcal/mol, (acac)Fe^{III}–H ~ 16 kcal/mol.
[b] BDE: PhS–H ~ 82 kcal/mol, *n*-$C_{12}H_{25}S$–H ~ 88 kcal/mol.

1. Kattamuri, P. V.; West, J. G. *J. Am. Chem. Soc.* **2020**, *142*, 19316.

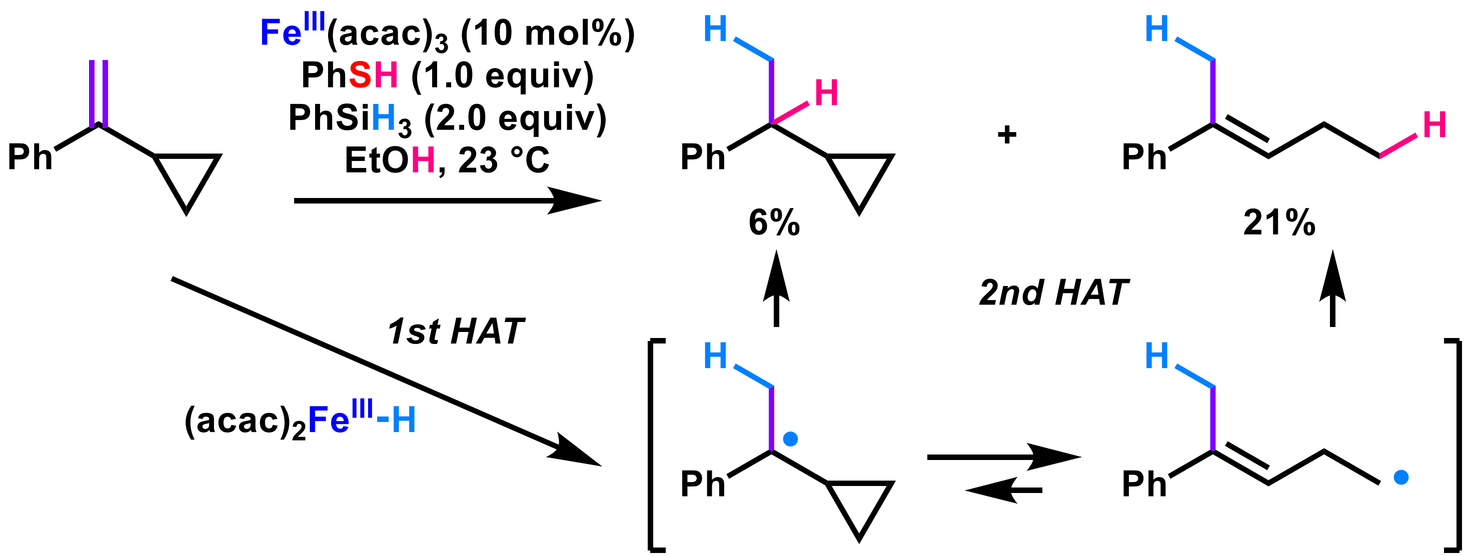
Confirmation of a Radical-Based Mechanism[1)]

■ Radical trap experiment with TEMPO



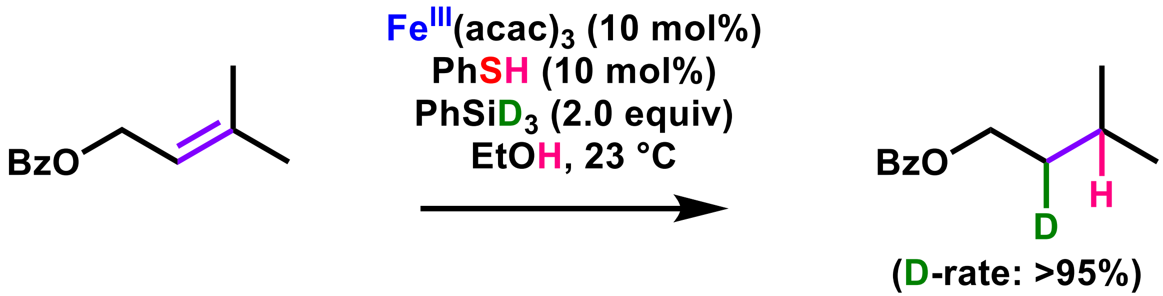
entry	*TEMPO addition*	yield
1	none	93%
2	0.2 equiv at t = 0 min	n.d.
3	0.2 equiv at t = 3 h	43%

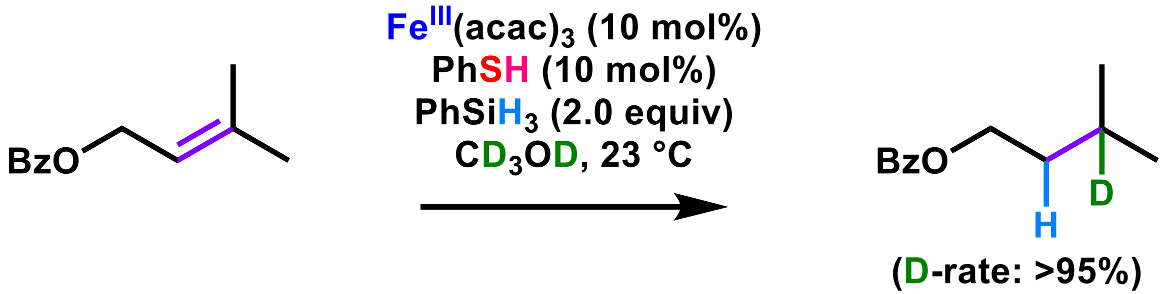
■ Ring-opening experiment

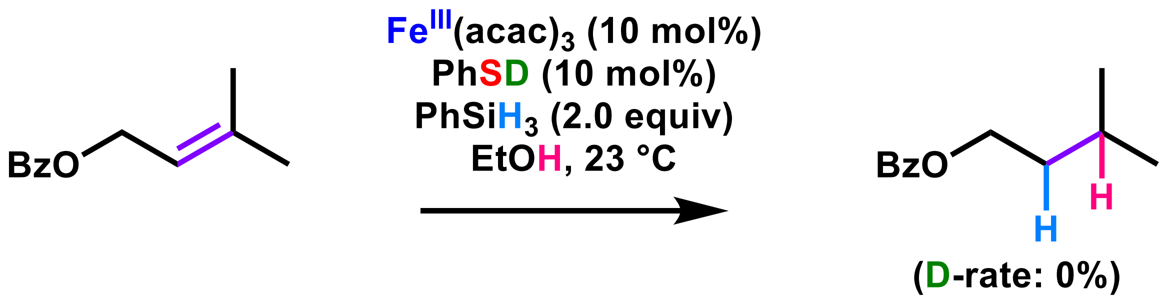


1. Kattamuri, P. V.; West, J. G. *J. Am. Chem. Soc.* **2020**, *142*, 19316.

Deuterium Labelling Experiments[1)]

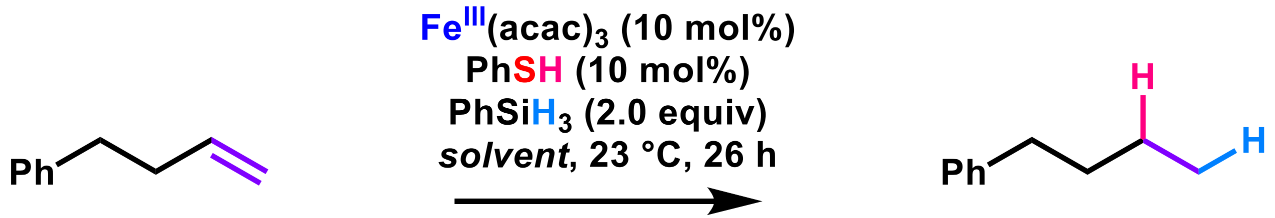






1. Kattamuri, P. V.; West, J. G. *J. Am. Chem. Soc.* **2020**, *142*, 19316.

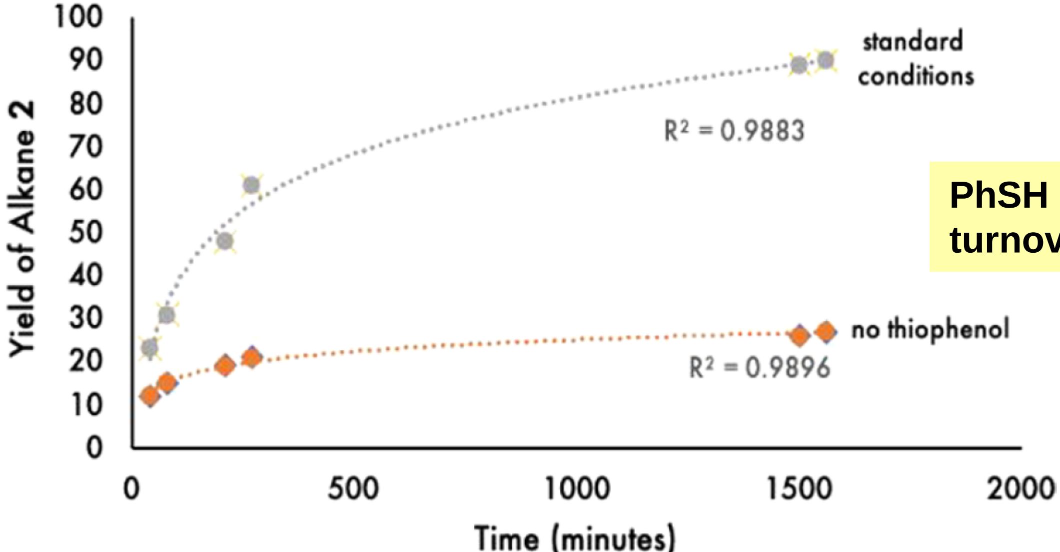
Effect of EtOH and PhSH on cHAT Hydrogenation[1)]



Effect of EtOH

entry	*solvent*	yield
1	C_6D_6	trace
2	C_6D_6 + 10 v/v% EtOH	41%
3	EtOH	93%

Reaction Profile with or without PhSH (*solvent* = EtOH)

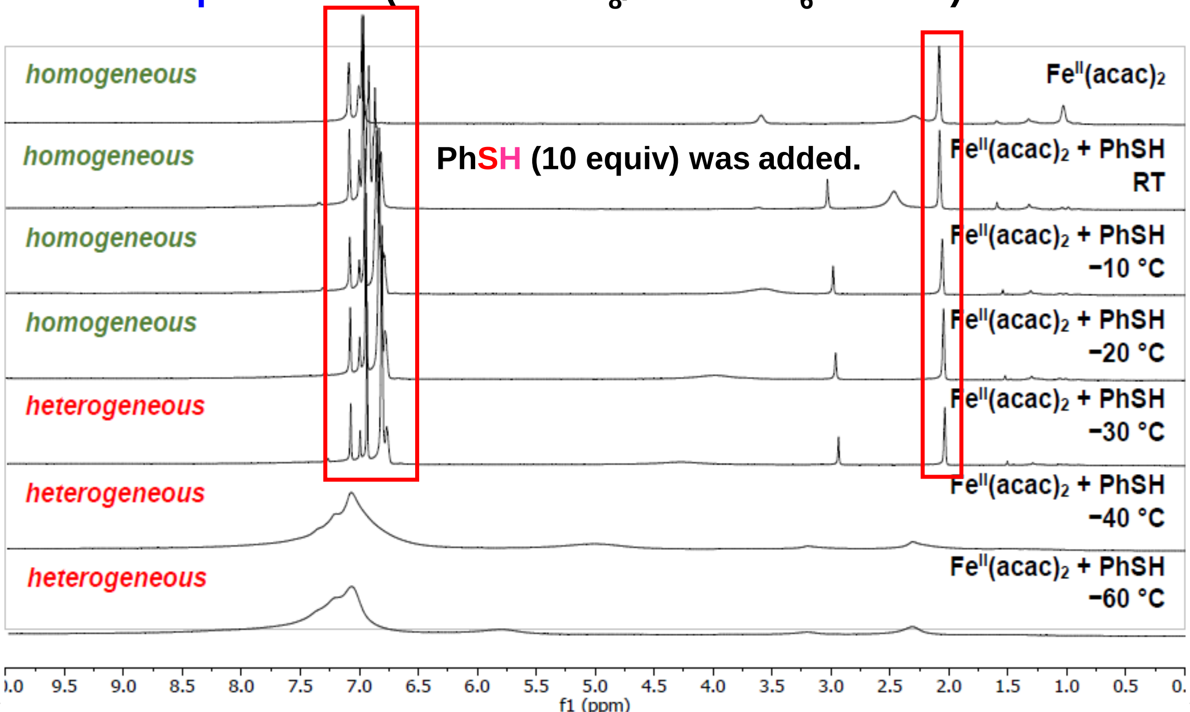


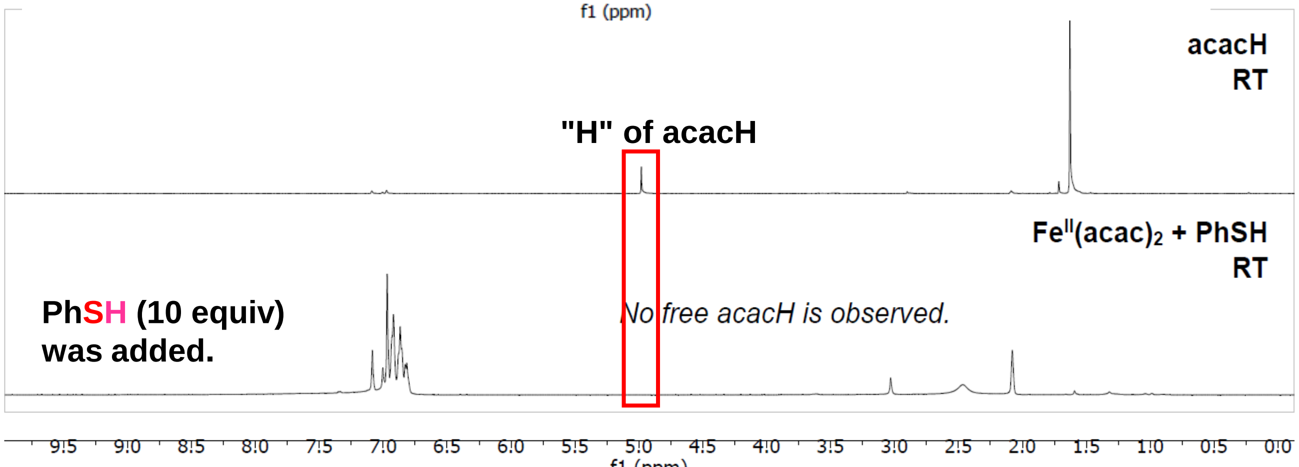
PhSH participates not only in an iron catalyst turnover but also in a HAT process.

1. Kattamuri, P. V.; West, J. G. *J. Am. Chem. Soc.* **2020**, *142*, 19316.

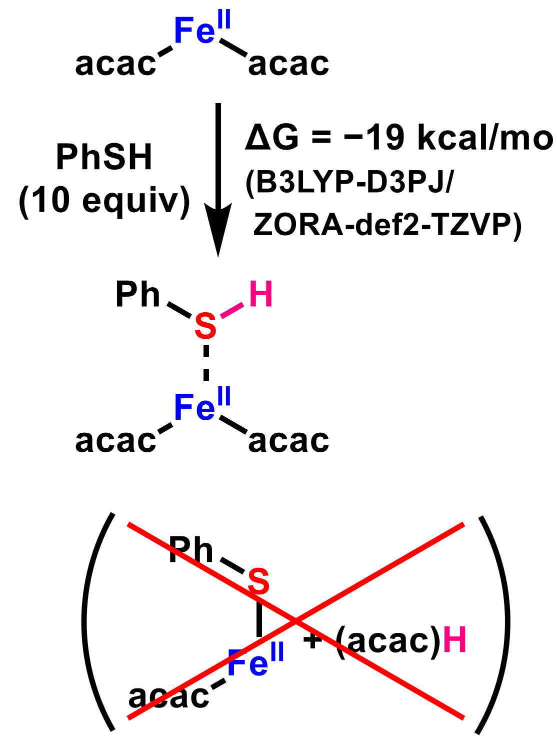
PhSH Binding to $Fe^{II}(acac)_2(EtOH)_2$[1)]

■ ^1H NMR experiments (in toluene-d_8/ethanol-d_6 = 95 : 5)

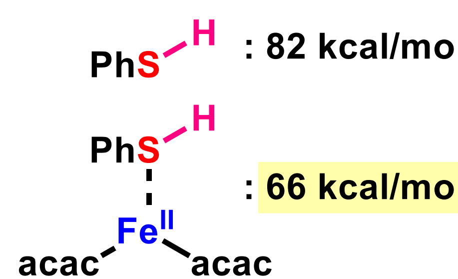




■ Plausible transformation

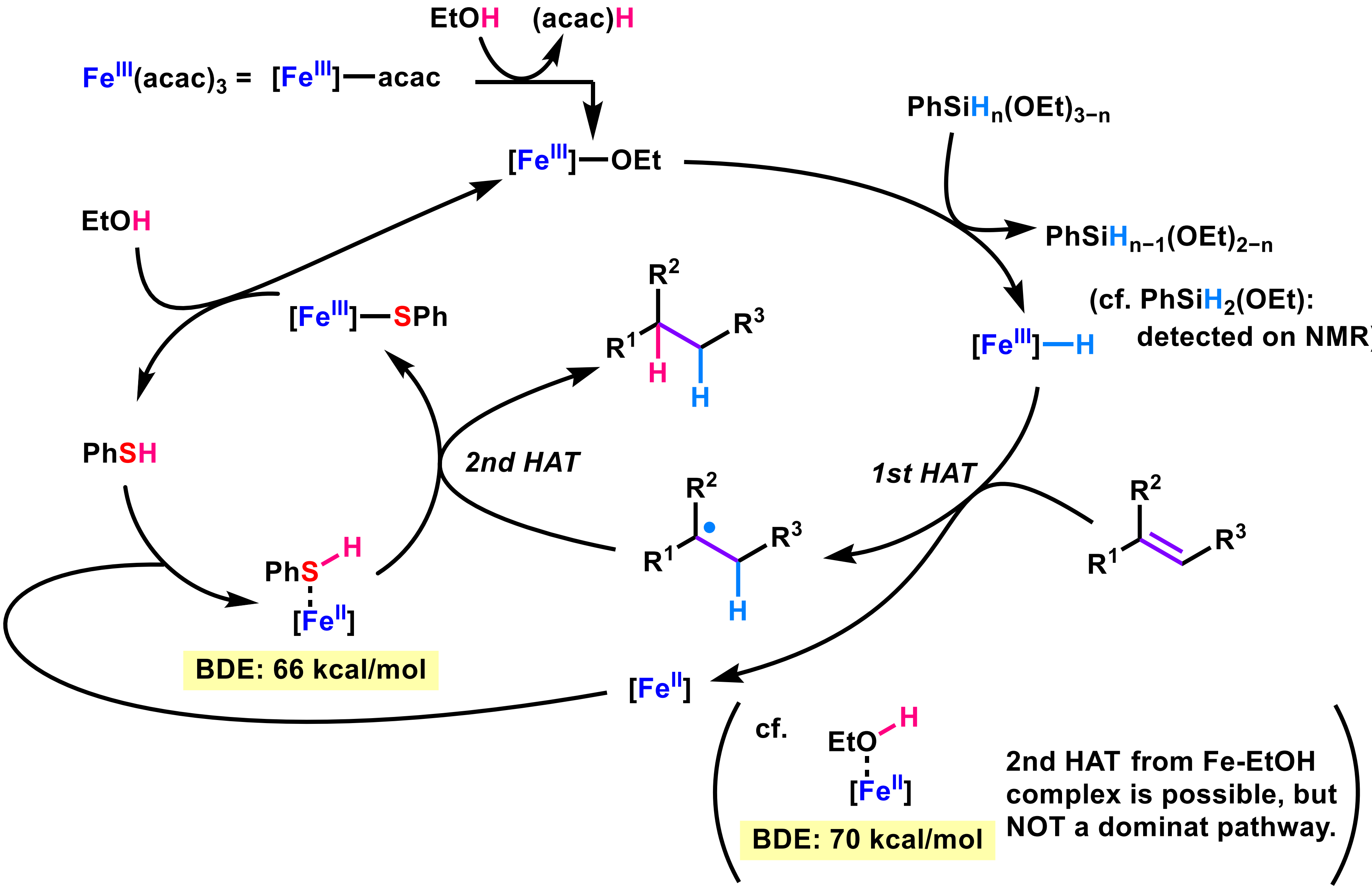


■ Decrease in BDE of PhS–H[2)]



1. West, J. G.; Miller, S. J.; Holland, P. L. et al. *Chemrxiv* **2023**, DOI: 10.26434/chemrxiv-2023-b9zdf.
2. Boekell, N, G.; Flowers, R. A. *Chem. Rev.* **2022**, *122*, 13447.

The Most Plausible Reaction Mechanism[1]

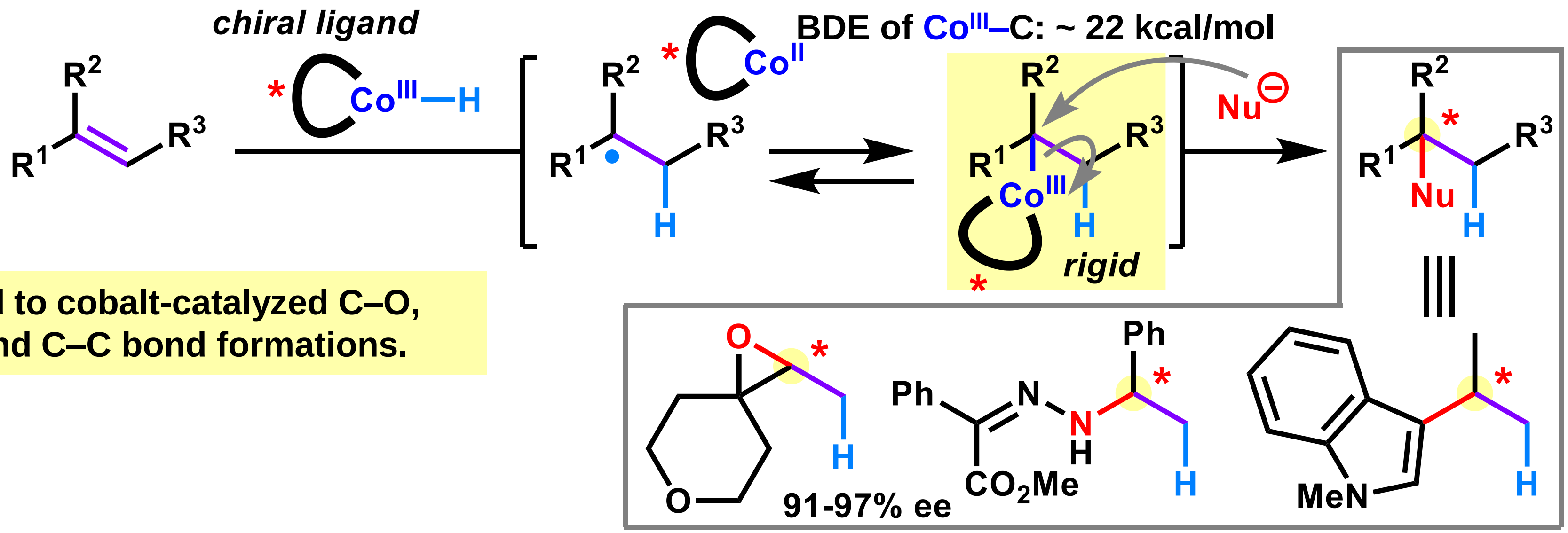


→ **Hypothesis:** **If a chiral thiol is employed, asymmetric HAT hydrogenation, which has been regarded as a quite challenging reaction mode would occur?**

1. West, J. G.; Miller, S. J.; Holland, P. L. et al. *Chemrxiv* **2023**, DOI: 10.26434/chemrxiv-2023-b9zdf.

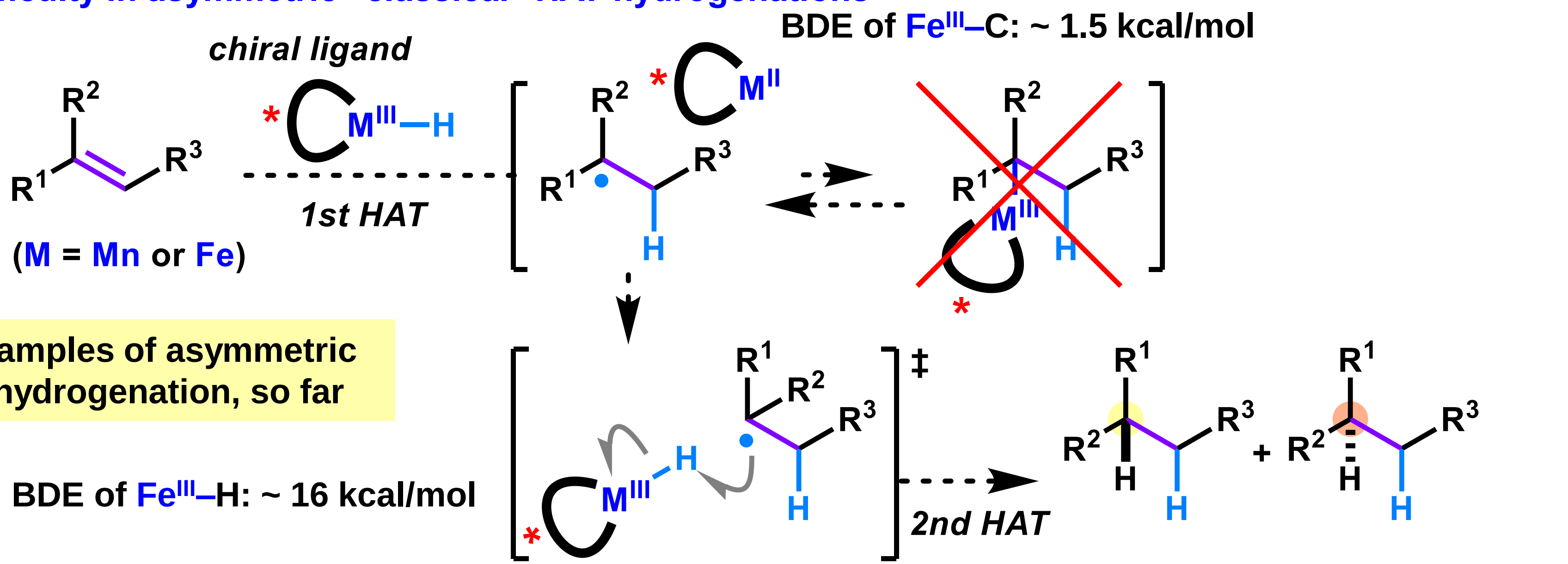
The Difficulty in Asymmetric HAT Hydrogenation

■ The precedented asymmetric metal HAT reactions



Limited to cobalt-catalyzed C–O, C–N, and C–C bond formations.

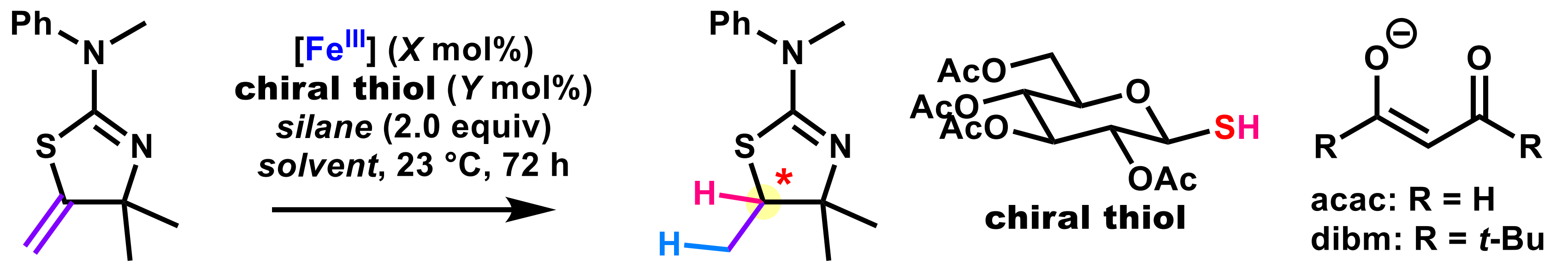
■ The difficulty in asymmetric "classical" HAT hydrogenations



No examples of asymmetric HAT hydrogenation, so far

weak BDE of M^{III}–H bond and hard controll to the enantionselectivity

Asymmetric cHAT Hydrogenation[1)]



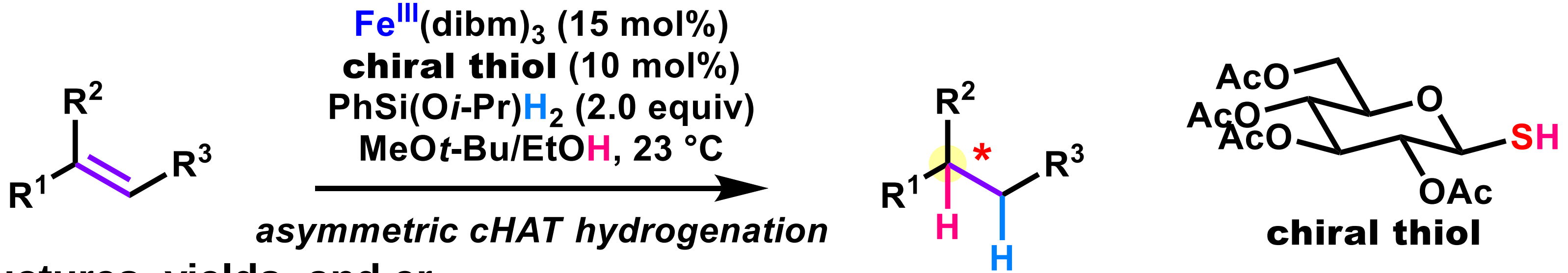
entry	[Fe^{III}] (X mol%)	silane	thiol (Y mol%)	solvent	yield and er
1	Fe^{III}(acac)$_3$ (15 mol%)	PhSiH$_3$	10 mol%	EtOH	91% (52 : 48)
2	Fe^{III}(acac)$_3$ (15 mol%)	PhSiH$_3$	10 mol%	*i*-PrOH	58% (53 : 47)
3	Fe^{III}(acac)$_3$ (15 mol%)	PhSiH$_3$	10 mol%	1,4-dioxane/EtOH = 95 : 5	37% (61 : 39)
4	Fe^{III}(acac)$_3$ (15 mol%)	PhSiH$_3$	50 mol%	1,4-dioxane/EtOH = 95 : 5	40% (63 : 37)
5	Fe^{III}(dibm)$_3$ (15 mol%)	PhSi(O*i*-Pr)H$_2$^{b}	10 mol%	1,4-dioxane/EtOH = 95 : 5	63% (58.5 : 41.5)
6	Fe^{III}(dibm)$_3$ (15 mol%)	PhSi(O*i*-Pr)H$_2$^{b}	10 mol%	MeO*t*-Bu/EtOH = 95 : 5	74% (61 : 39)

[a] Reaction time was 7 h (entries 5 and 6).

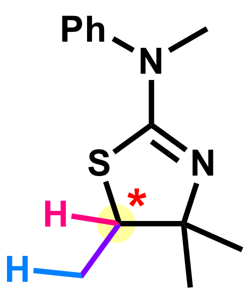
→ **The first example of asymmetric HAT hydrogenation**

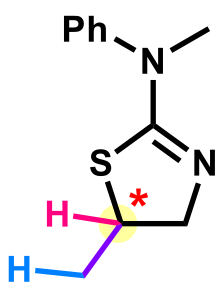
1. West, J. G.; Miller, S. J.; Holland, P. L. et al. *Chemrxiv* **2023**, DOI: 10.26434/chemrxiv-2023-b9zdf.

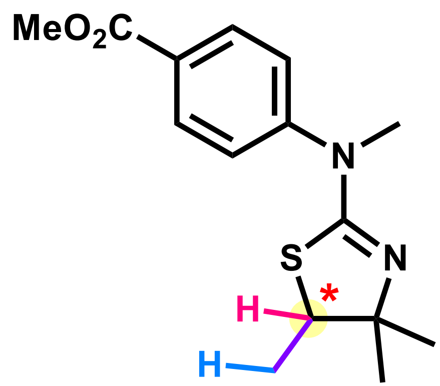
Substrate Scope of Asymmetric cHAT Hydrogenation[1)]

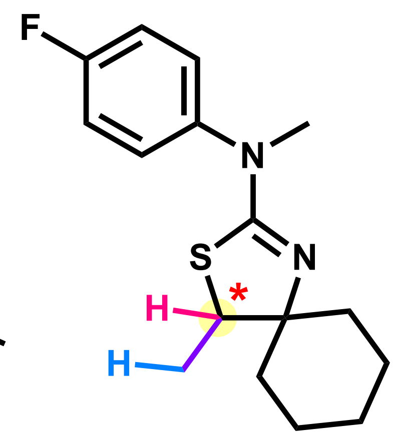


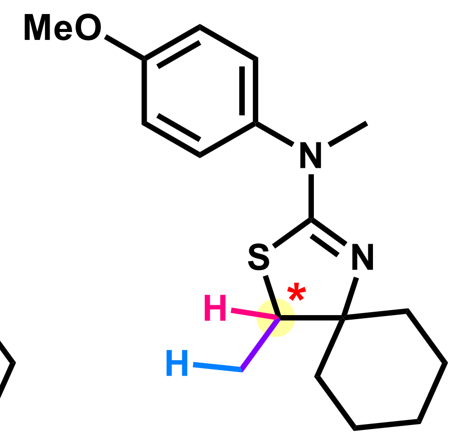
■ Structures, yields, and er

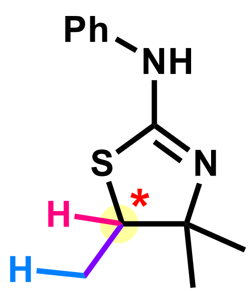

74% (61 : 39)

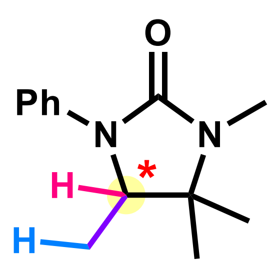

36% (52 : 48)

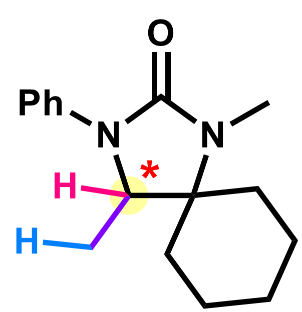

56% (51 : 49)

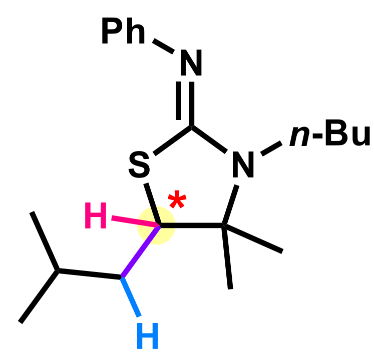

34% (69 : 31)

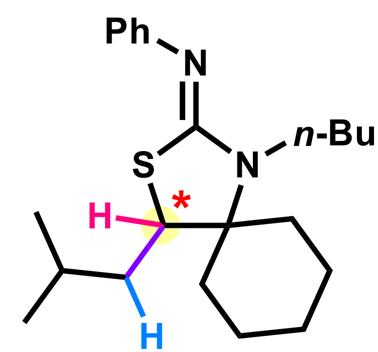

63% (62.5 : 37.5)


30% (52 : 48)


40% (56 : 44)


22% (56 : 44)


13% (75 : 25)


14% (80 : 20)

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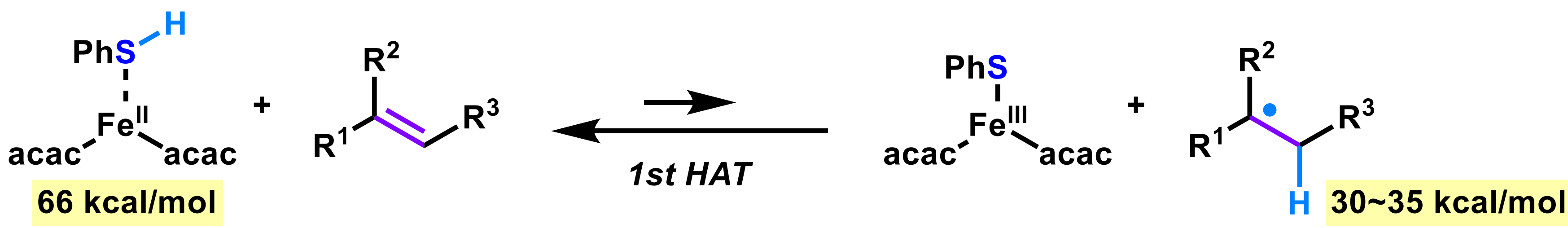
3. **cHAT Olefin Hydrogenation developed by Studer group**
(*Nature* 2023, *619*, 506–513.)

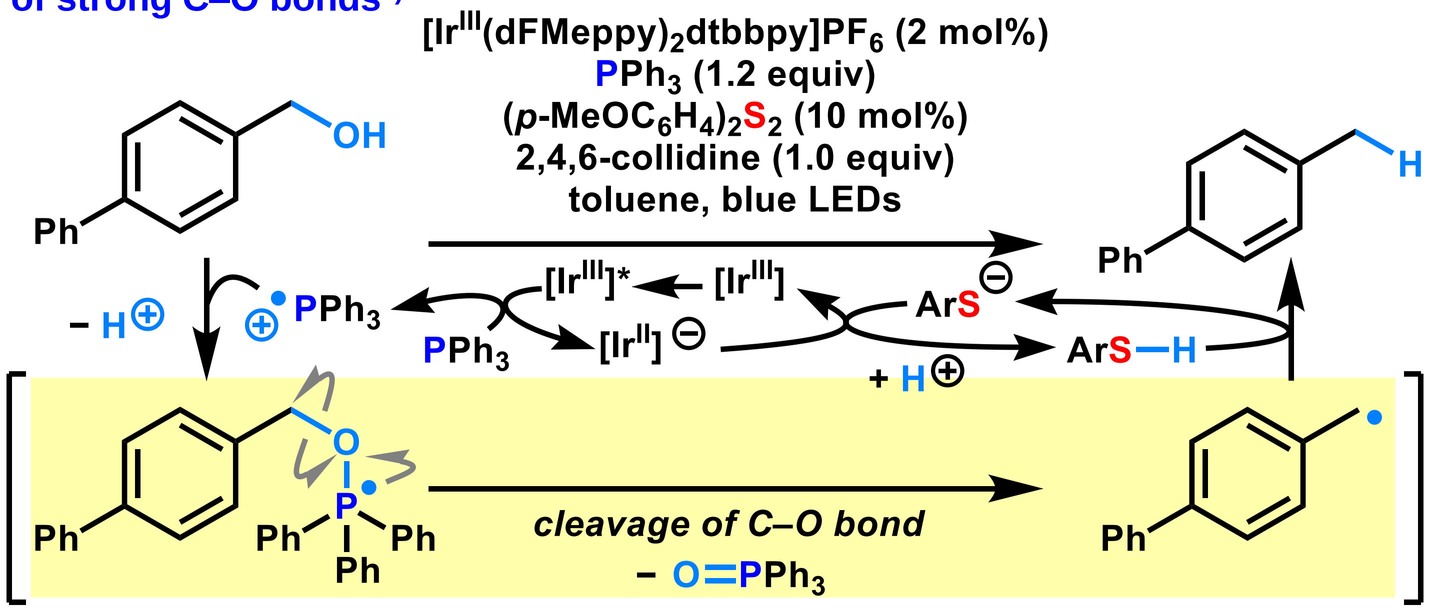
O–H Serves as a Hydrogen Donor of the First HAT?

West cHAT hydrogenation



The BDE of the hydrogen donor in the first HAT should be ca. 35 kcal/mol or less.
Accordingly, hydride species of Fe, Mn, and occasionally Co have been utilized for this particular purpose.

Activation of strong C–O bonds[1)]

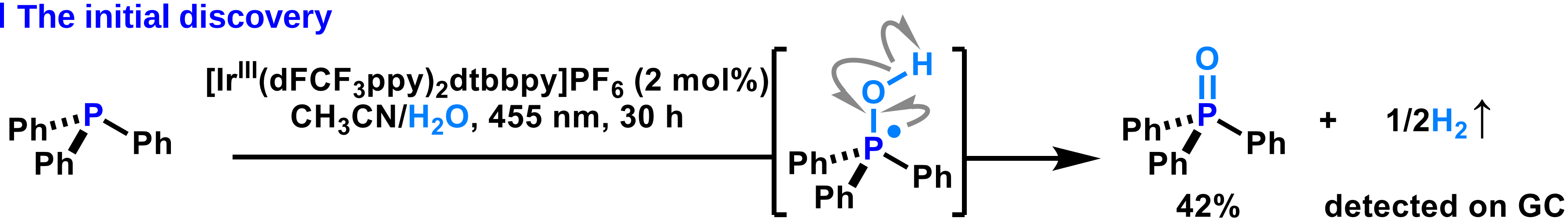


The formation of stable O=PPh$_3$ phosphoryl decreases the BDE of strong CO bonds in an alcohol.

1. Stache, E. E.; Ertel, A. B.; Rovis, T.; Doyle, A. G. *ACS Catal.* **2018**, *8*, 11134.

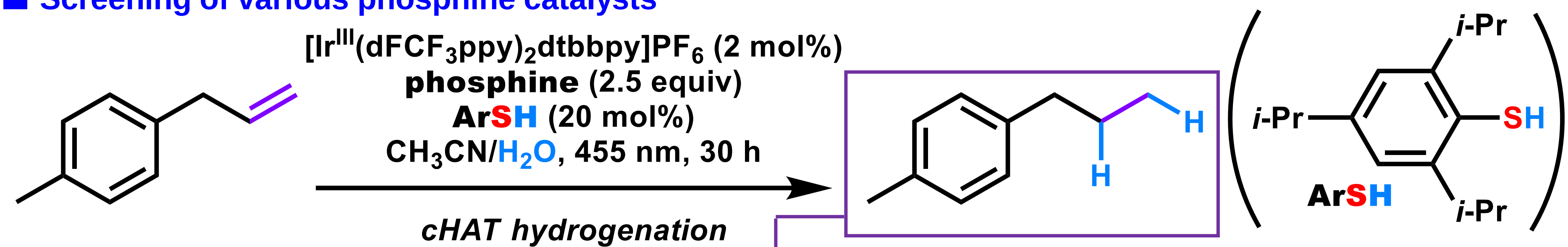
The Initial Discovery and Phosphines Screening[1)]

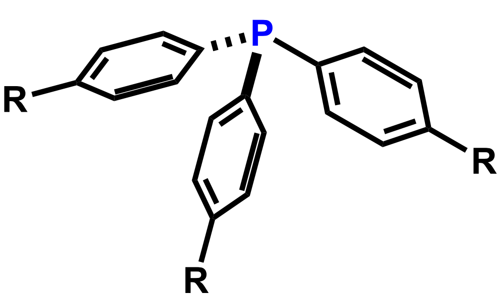
■ The initial discovery



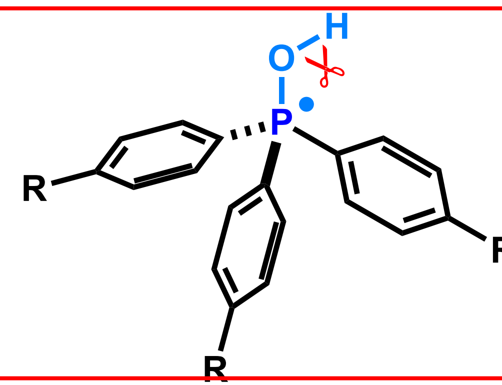
Two O–H bonds on H_2O were successfully activated in the presence of iridium catalysts and phosphine.

■ Screening of various phosphine catalysts





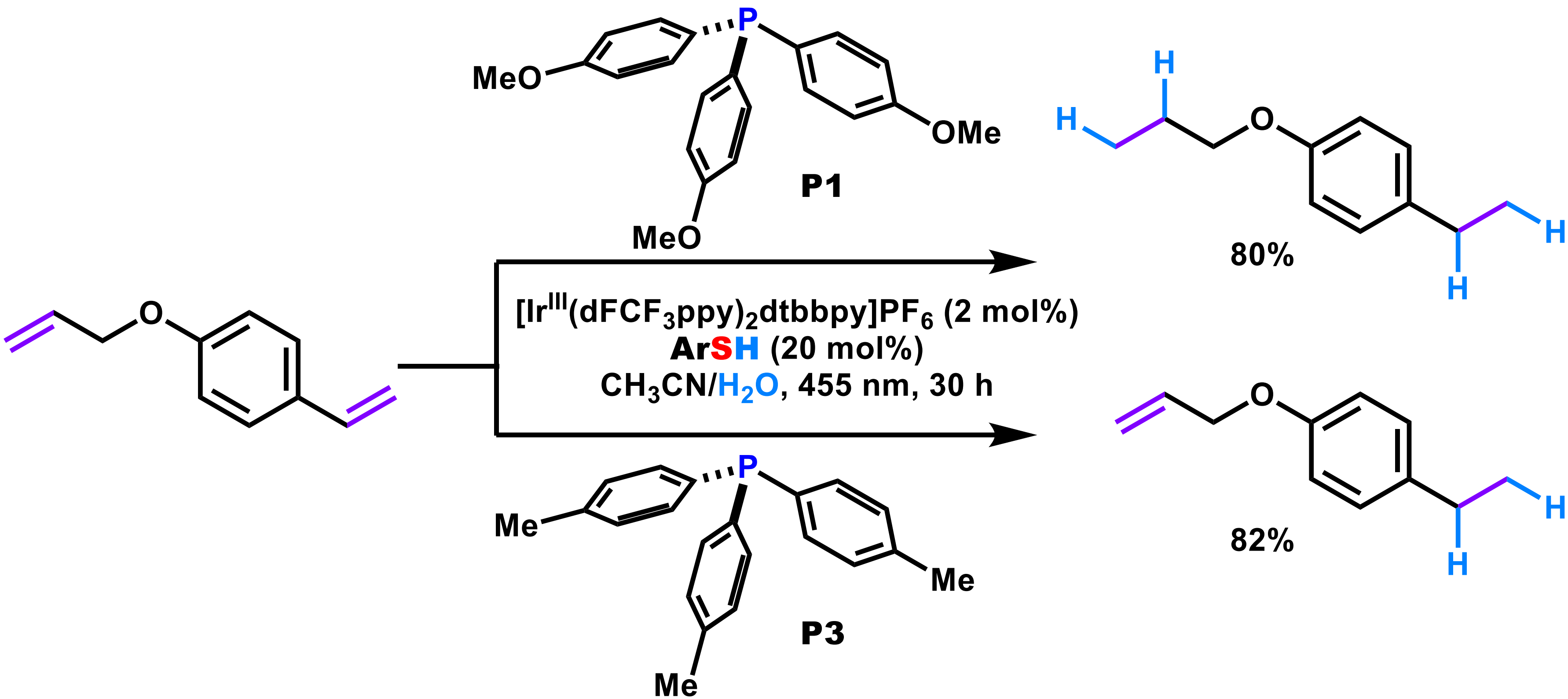
phosphine	yield	BDE[a]
P1 (R = OMe)	92%	5.0 kcal/mol
P2 (R = F)	50%	6.9 kcal/mol
P3 (R = Me)	9%	8.3 kcal/mol
P4 (R = H)	6%	9.4 kcal/mol
P5 (R = CF_3)	7%	13.4 kcal/mol

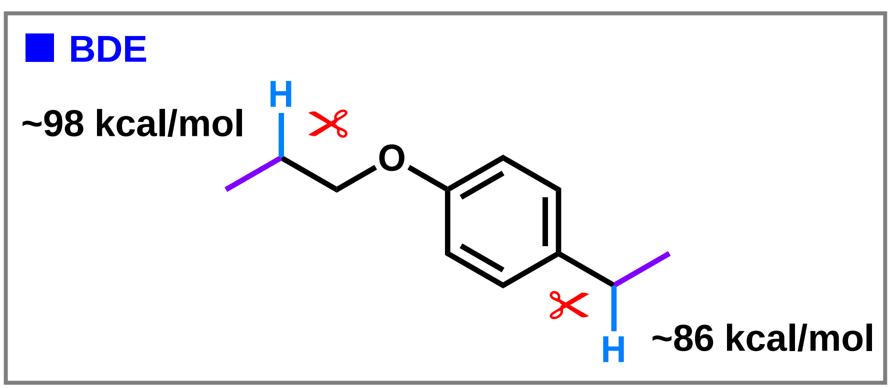


[a]Calculated by PWPB95-D3/def2TZVP/COSMO-RS (CH_3CN)

1. Zhang, J.; Mück-Lichtenfeld, C.; Studer, A. *Nature* **2023**, *619*, 506.

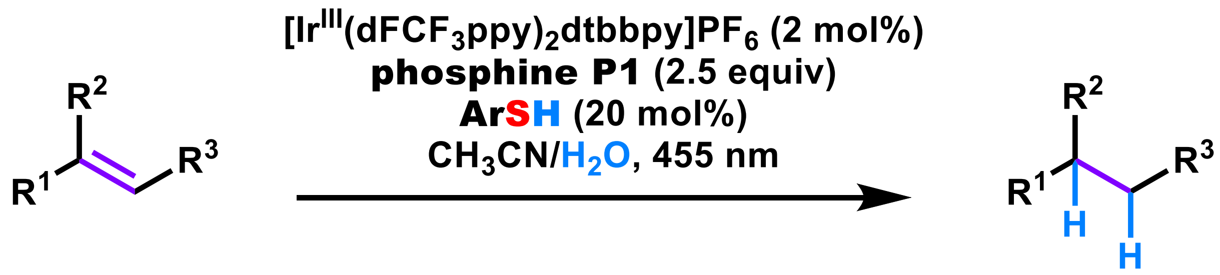
Phosphine-Dependent Tuning of Reactivities[1]

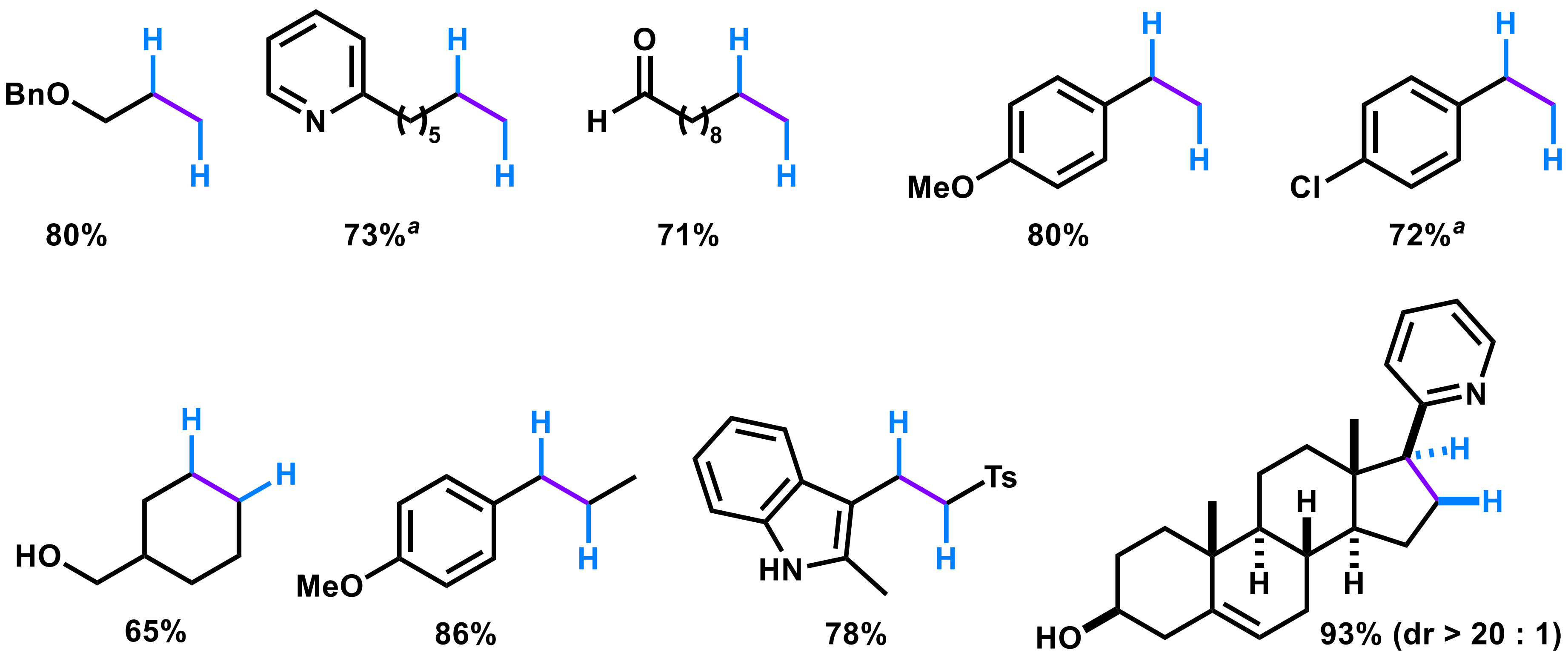




By selecting an appropriate phosphine, a more reactive olefin can be selectively hydrogenated.

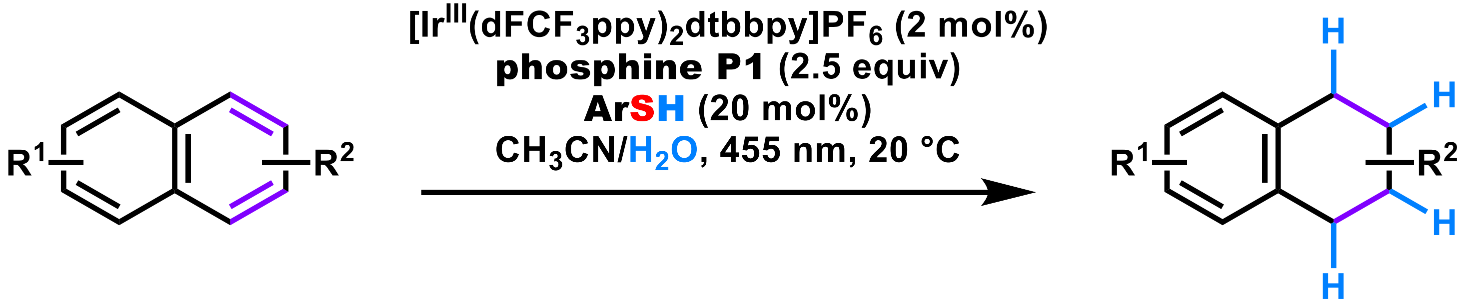
Substrate Scope (1)[1]

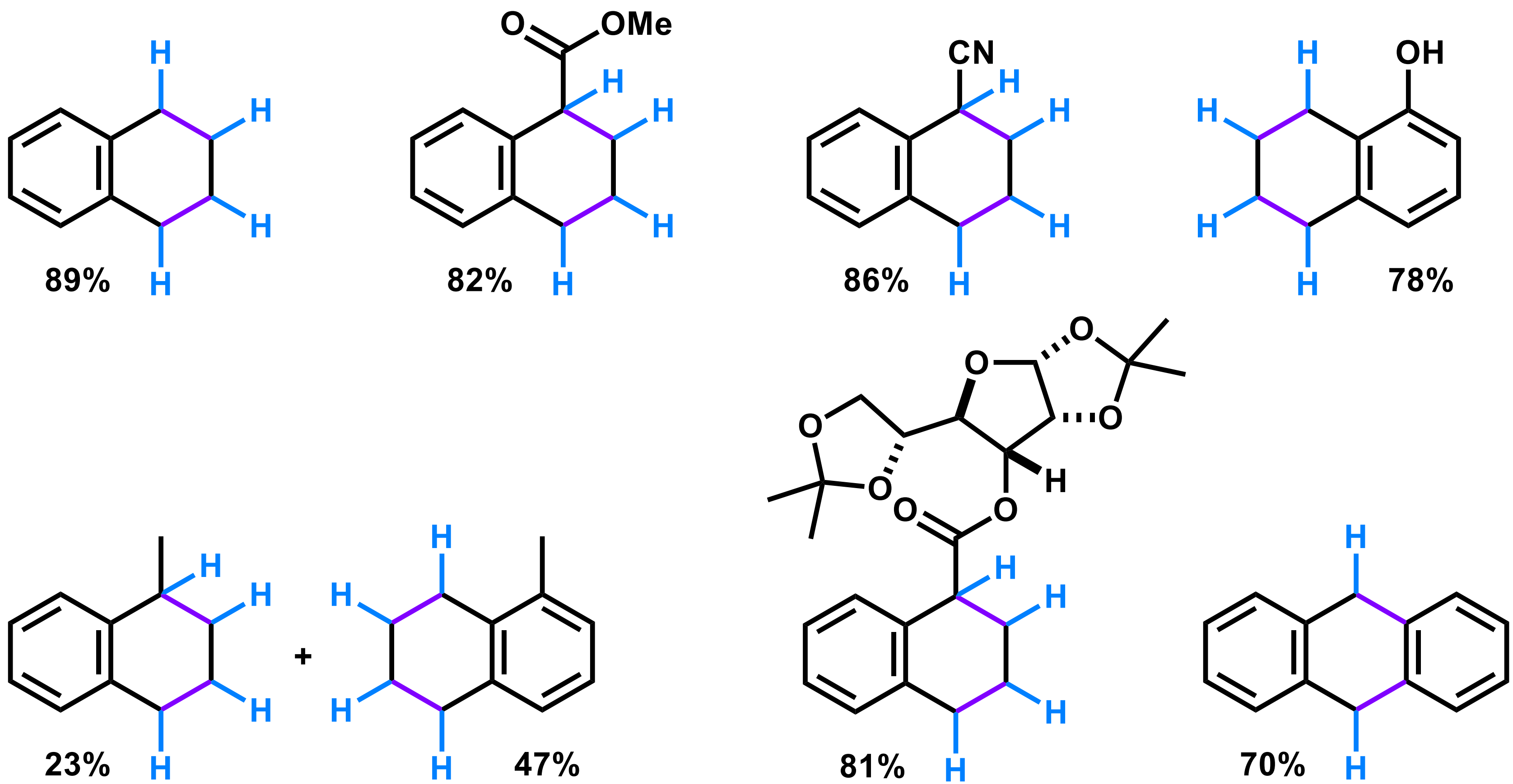




1. Zhang, J.; Mück-Lichtenfeld, C.; Studer, A. *Nature* **2023**, *619*, 506.

Substrate Scope (2): Dearomatization of Naphthalene[1)]

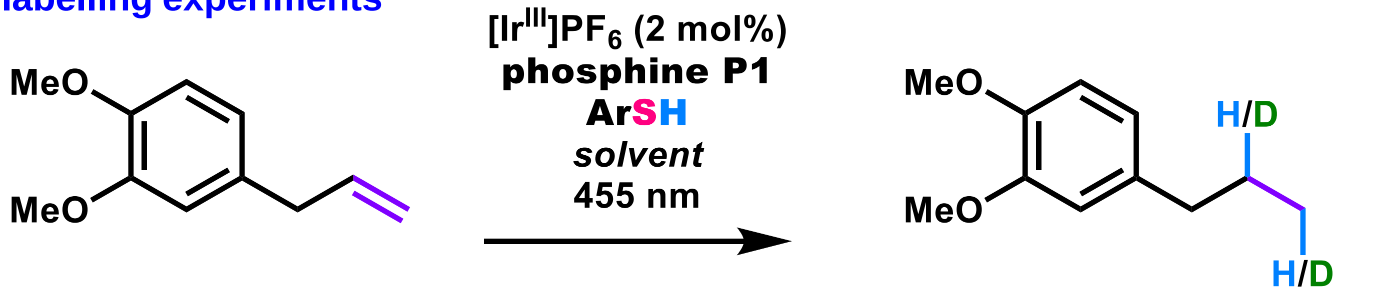




1. Zhang, J.; Mück-Lichtenfeld, C.; Studer, A. *Nature* **2023**, *619*, 506.

Deuterium Labelling Experiments[1)]

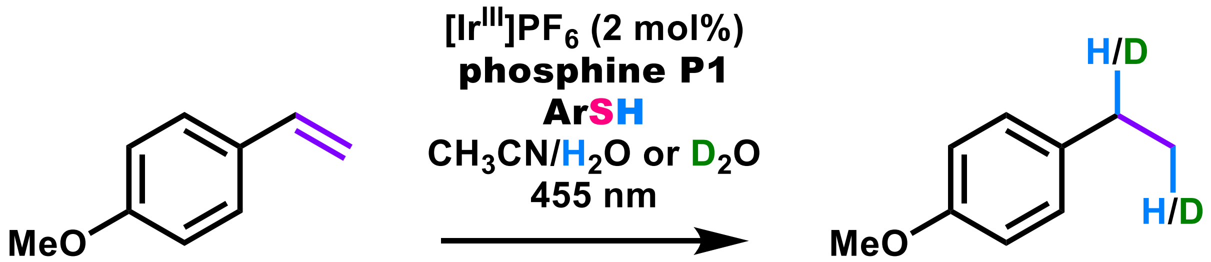
■ Deuterium labelling experiments



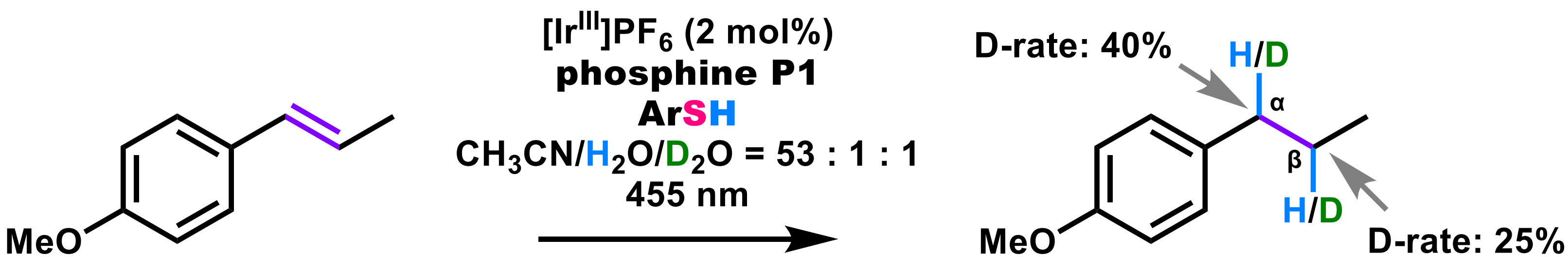
Both hydrogen atoms come from H_2O.

CD_3CN/H_2O: 90% (D-rate: 0%)
CH_3CN/D_2O: 90% (D-rate: 92%)

■ Kinetic isotope effect (KIE) experiments



KIE = k_{H2O}/k_{D2O} = 3.2

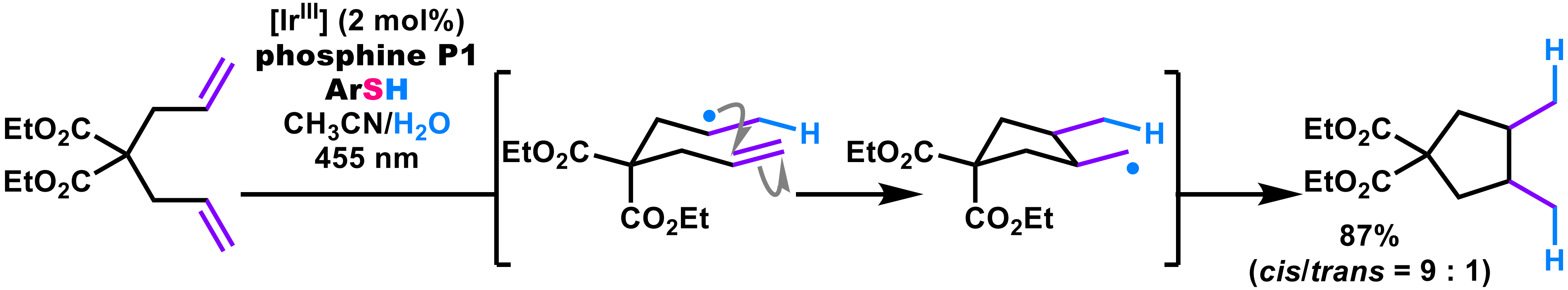


Hydrogenation at β position is the rate determining step of this reaction.

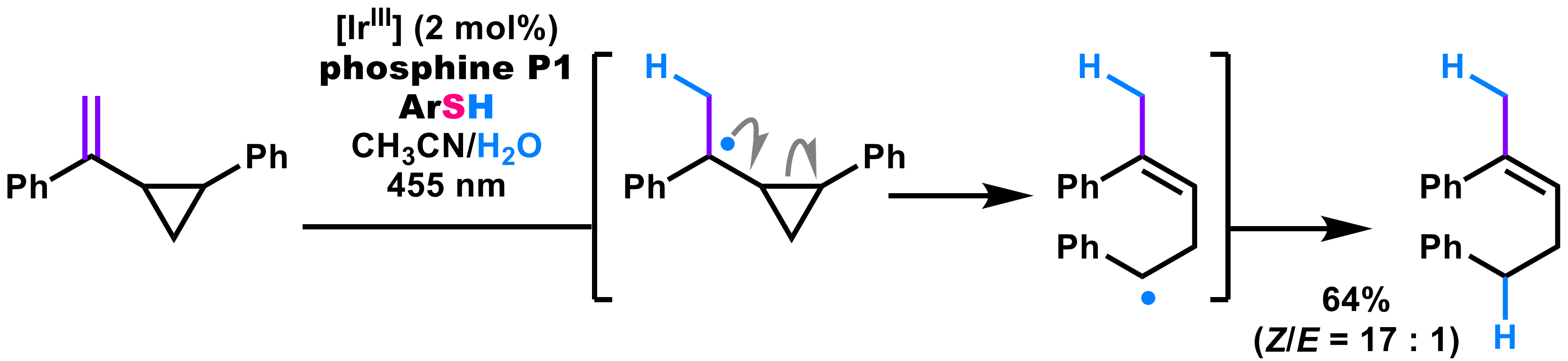
1. Zhang, J.; Mück-Lichtenfeld, C.; Studer, A. *Nature* **2023**, *619*, 506.

Confirmation of Radical-Based Mechanism[1)]

Radical cyclization

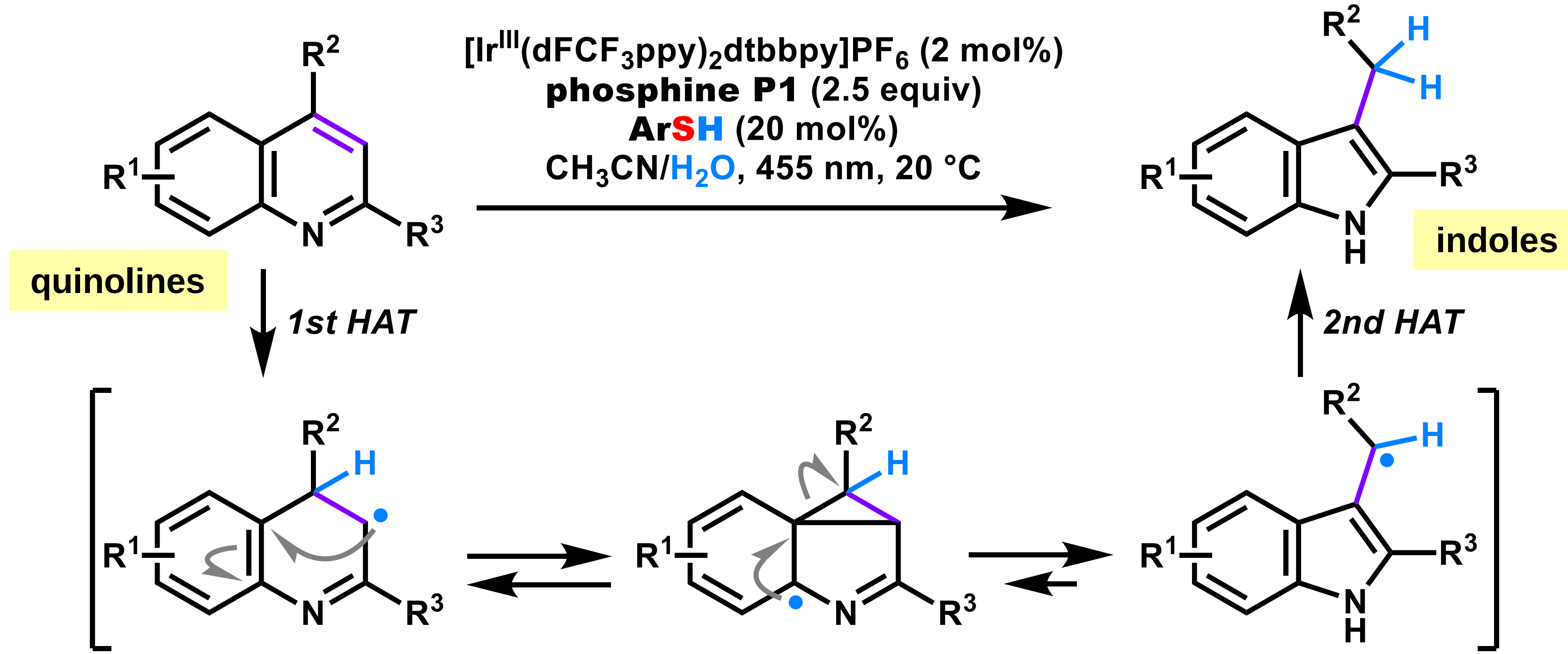


Ring-opening experiment

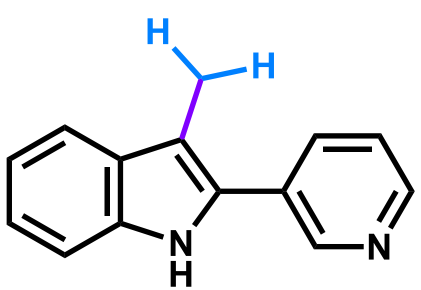


1. Zhang, J.; Mück-Lichtenfeld, C.; Studer, A. *Nature* **2023**, *619*, 506.

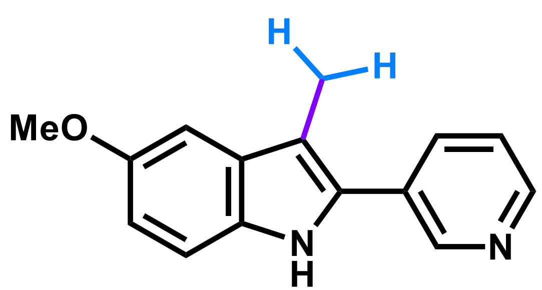
An Application: Skeletal Editing of Quinolines[1)]



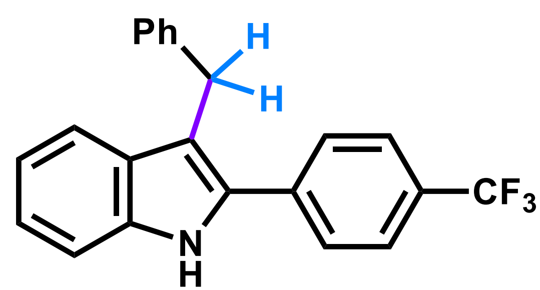
■ **Substrate scope**



61%



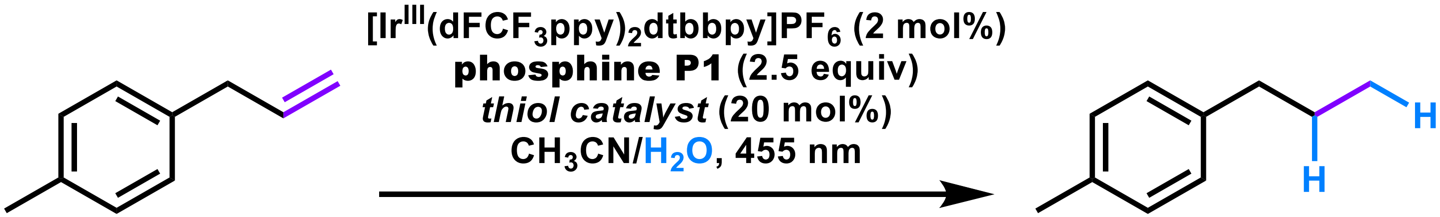
46%



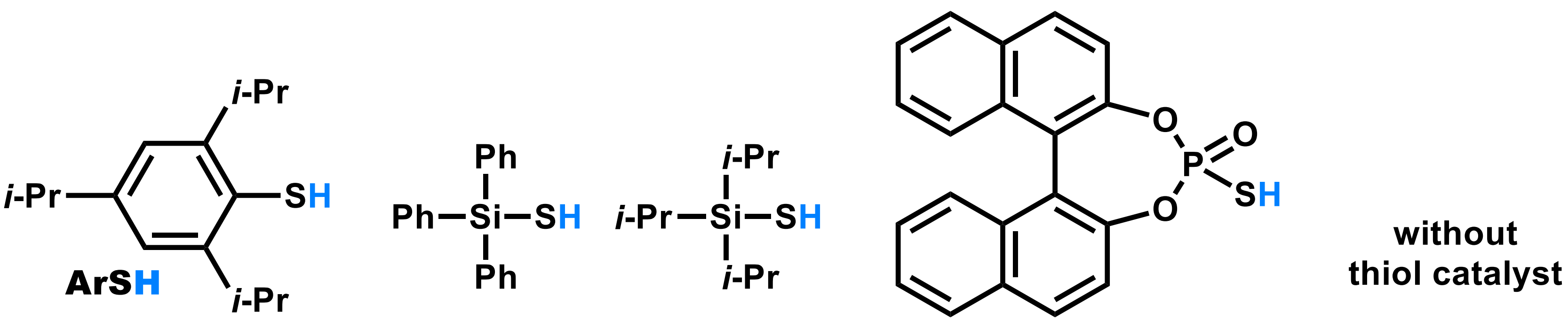
52%

1. Zhang, J.; Mück-Lichtenfeld, C.; Studer, A. *Nature* **2023**, *619*, 506.

The Significance of Thiol Catalyst[1)]



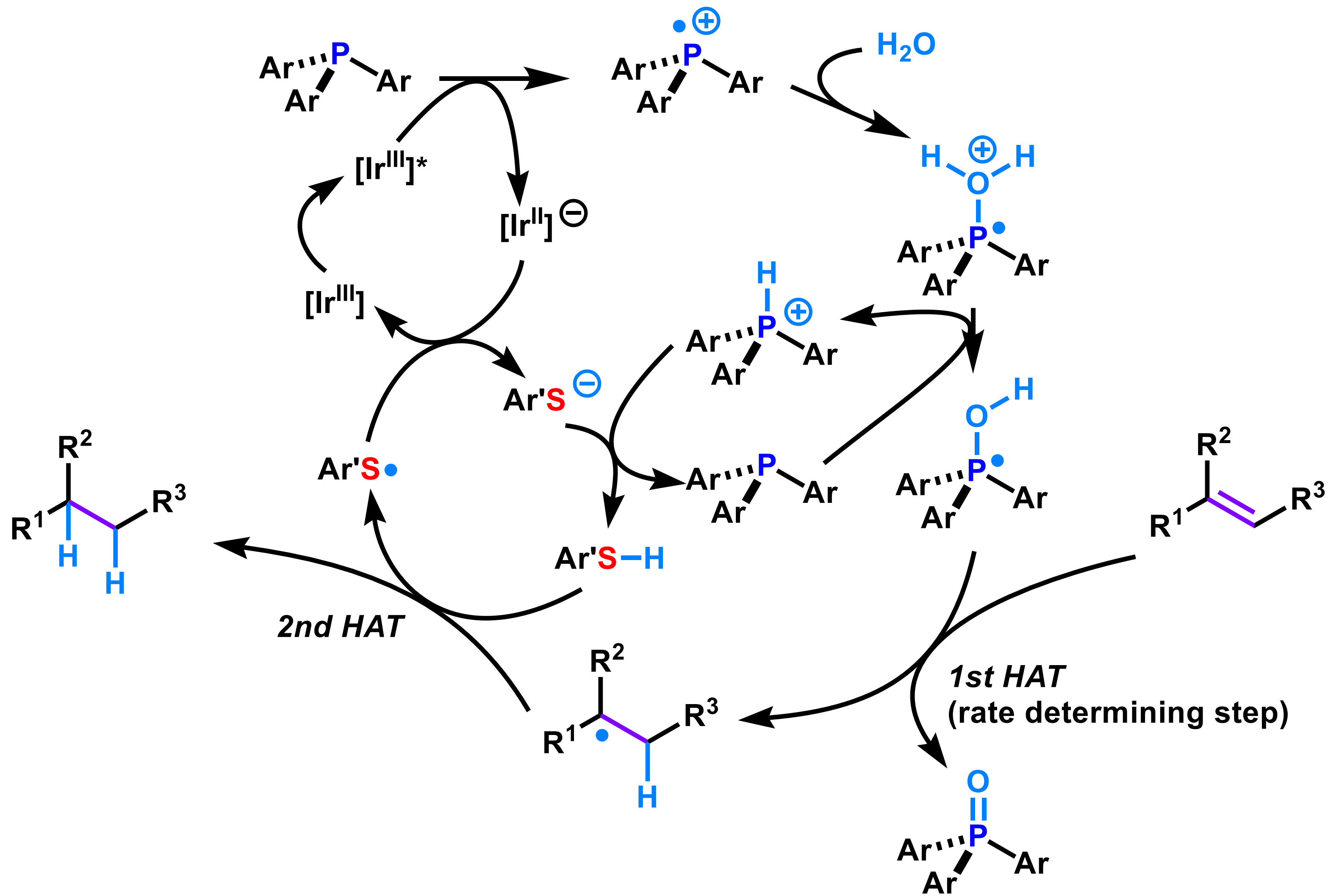
■ **Structures of thiol catalysts and yields of hydrogenated products**



92%	0%	0%	0%	0%
BDE ~ 80 kcal/mol	BDE ~ 88 kcal/mol		BDE ~ 87 kcal/mol	

1. Zhang, J.; Mück-Lichtenfeld, C.; Studer, A. *Nature* **2023**, *619*, 506.

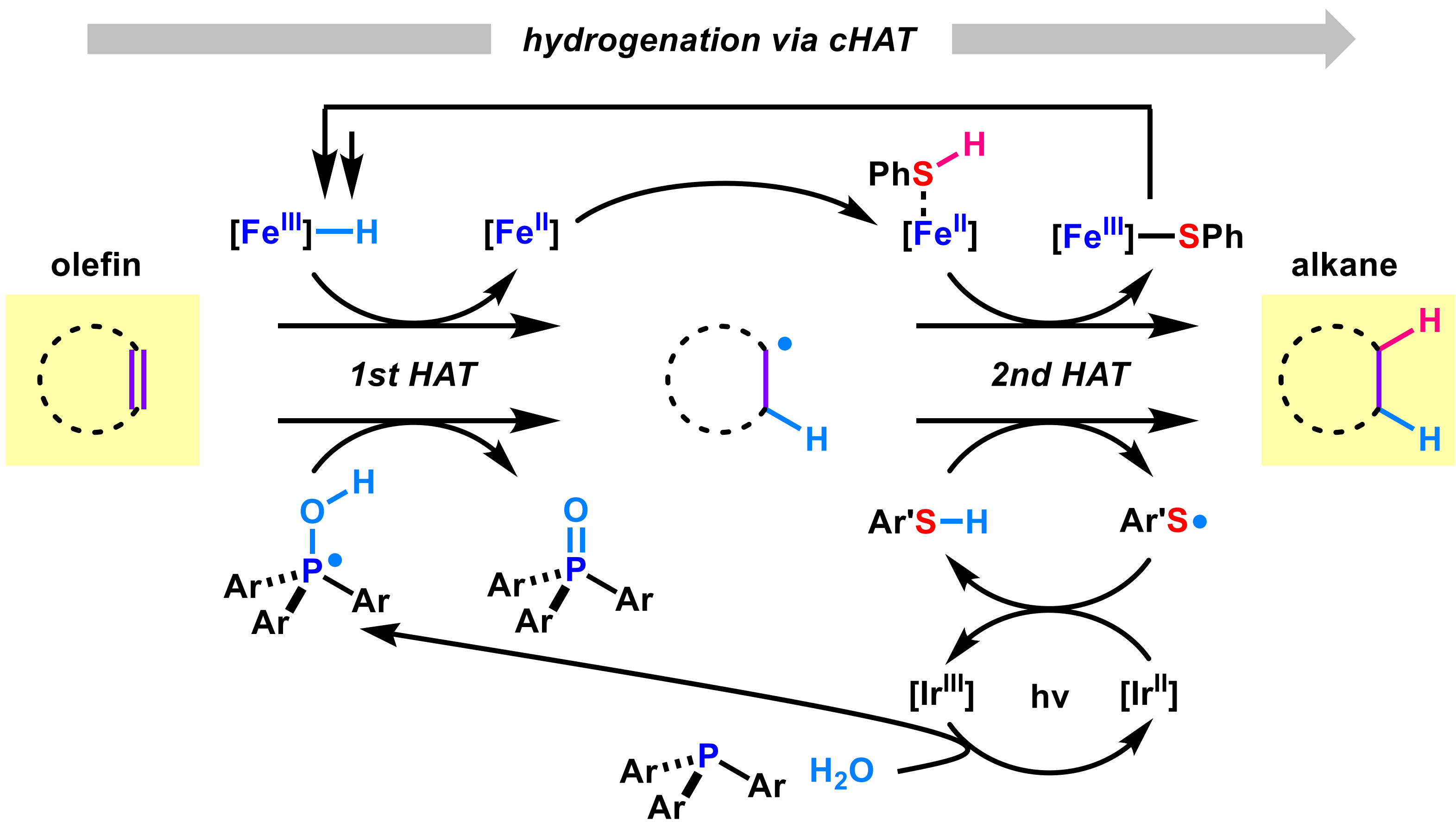
The Proposed Reaction Mechanism[1)]



1. Zhang, J.; Mück-Lichtenfeld, C.; Studer, A. *Nature* **2023**, *619*, 506.

Summary: cHAT towards Natural Product Syntheses

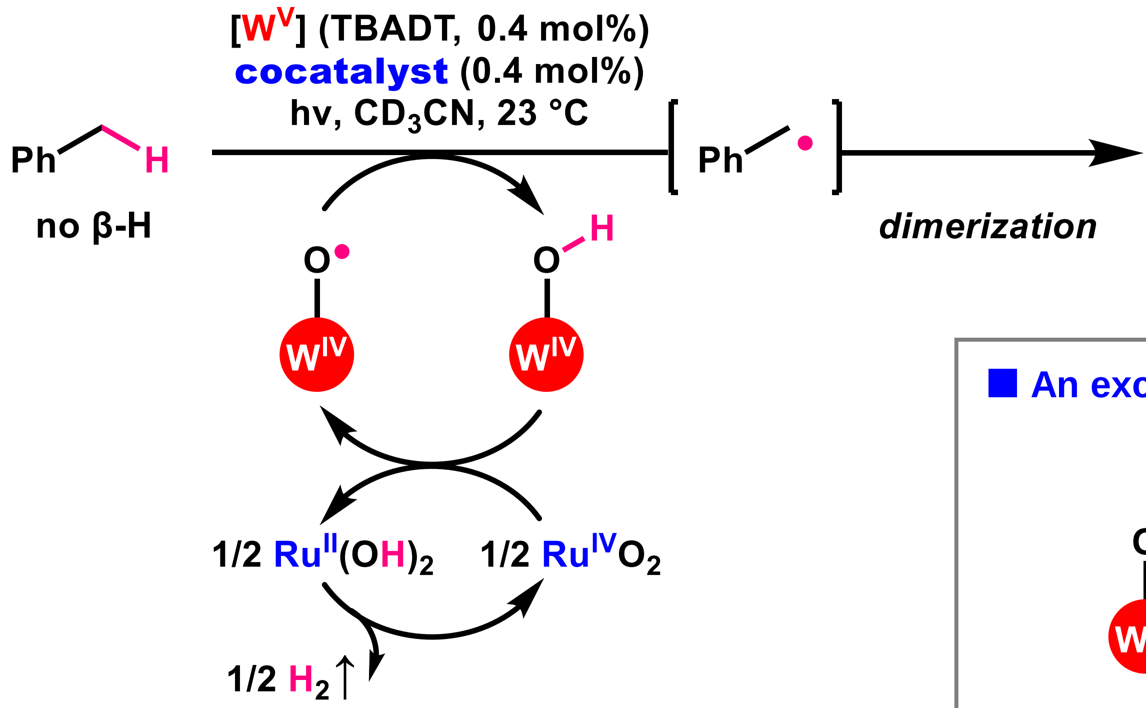
■ **West (2020)**
✓ The absence of an exogenous oxidant
✓ Asymmetric HAT hydrogenation



■ **Studer (2023)**
✓ The absence of a stoichiometric oxidant
✓ Environmentally-benign conditions using H_2O as a hydrogen source
✓ cHAT hydrogenative dearomatization

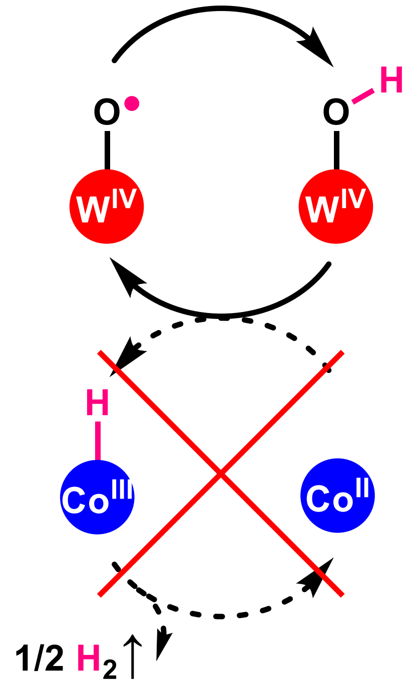
Appendix

Evidence of a cHAT mechanism in Dehydrogenation[1)]



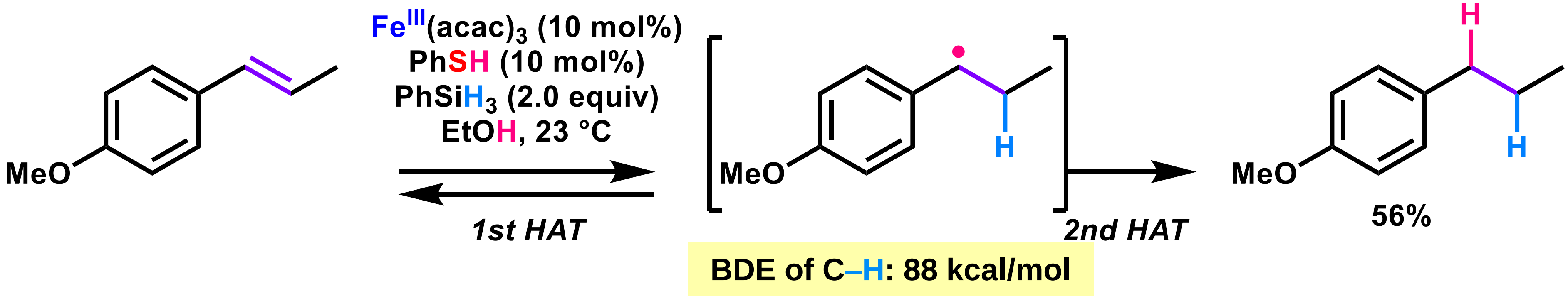
cocatalysts	results
$Ru^{IV}O_2$	multiple turnovers
$Co^{I}(dmgH)_2(py)Cl$	~ 1% (no turnover)
no catalyst	~ 1% (no turnover)

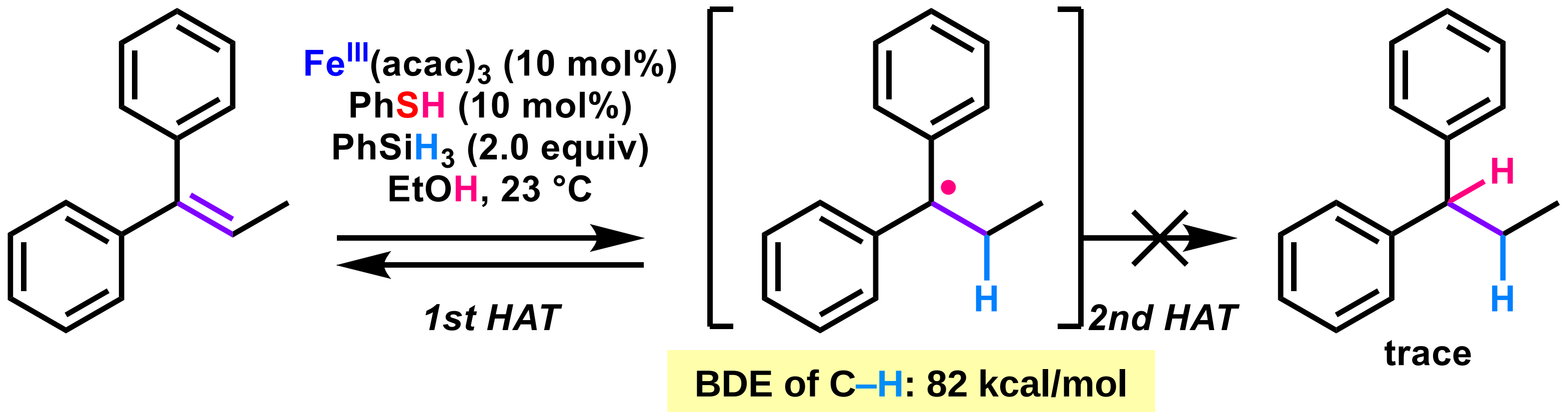
■ An excluded catalytic cycle



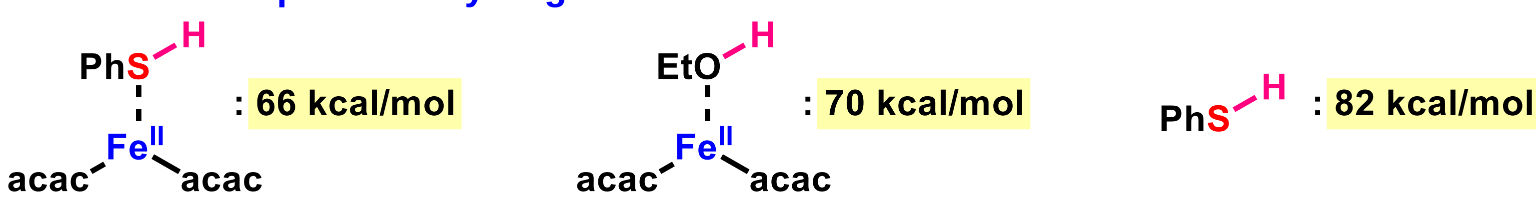
1. West, J. G.; Huang, D.; Sorensen, E. J. *Nat. Commun.* **2015**, *6*, 10093.

Stability of Radical Intermediate and Limitation[1)]





■ BDE of some potential hydrogen donors



While the authors mentioned that the BDE of radical intermediates affects the 2nd HAT,
In my opinion, kinetic barrier with bulky aryl groups in the 1st HAT should not be overlooked.

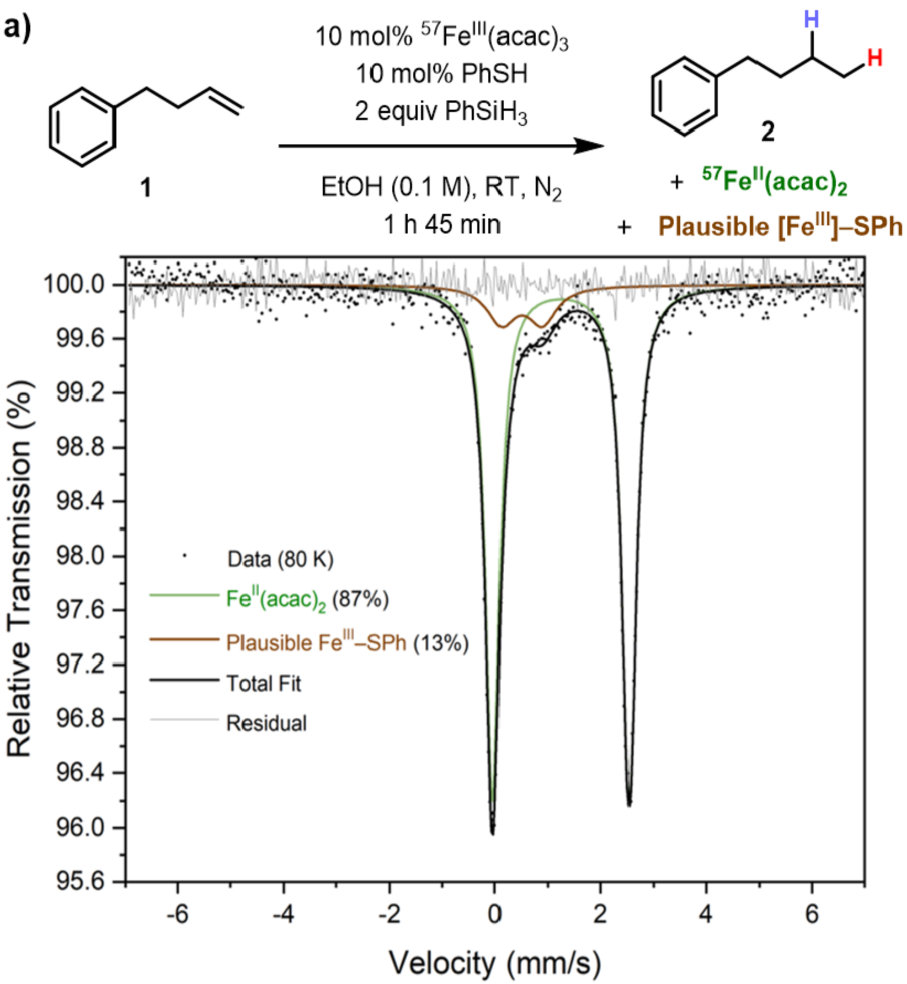
1. Kattamuri, P. V.; West, J. G. *J. Am. Chem. Soc.* **2020**, *142*, 19316.

Partial Decomposition of $Fe(acac)_3$ with PhSH[1)]

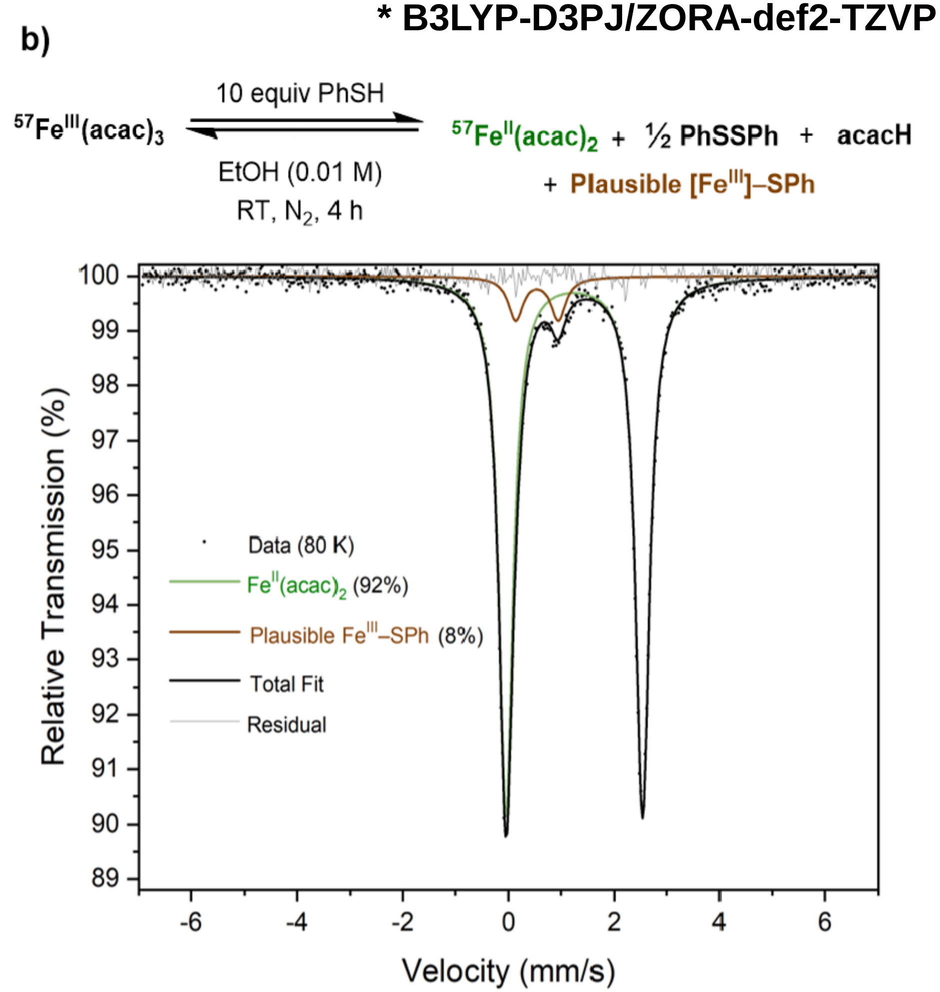
■ Mössbauer spectroscopy of the reaction mixture (experimental) and [Fe^{III}]–SPh species (computational*)

* B3LYP-D3PJ/ZORA-def2-TZVP

a)



b)

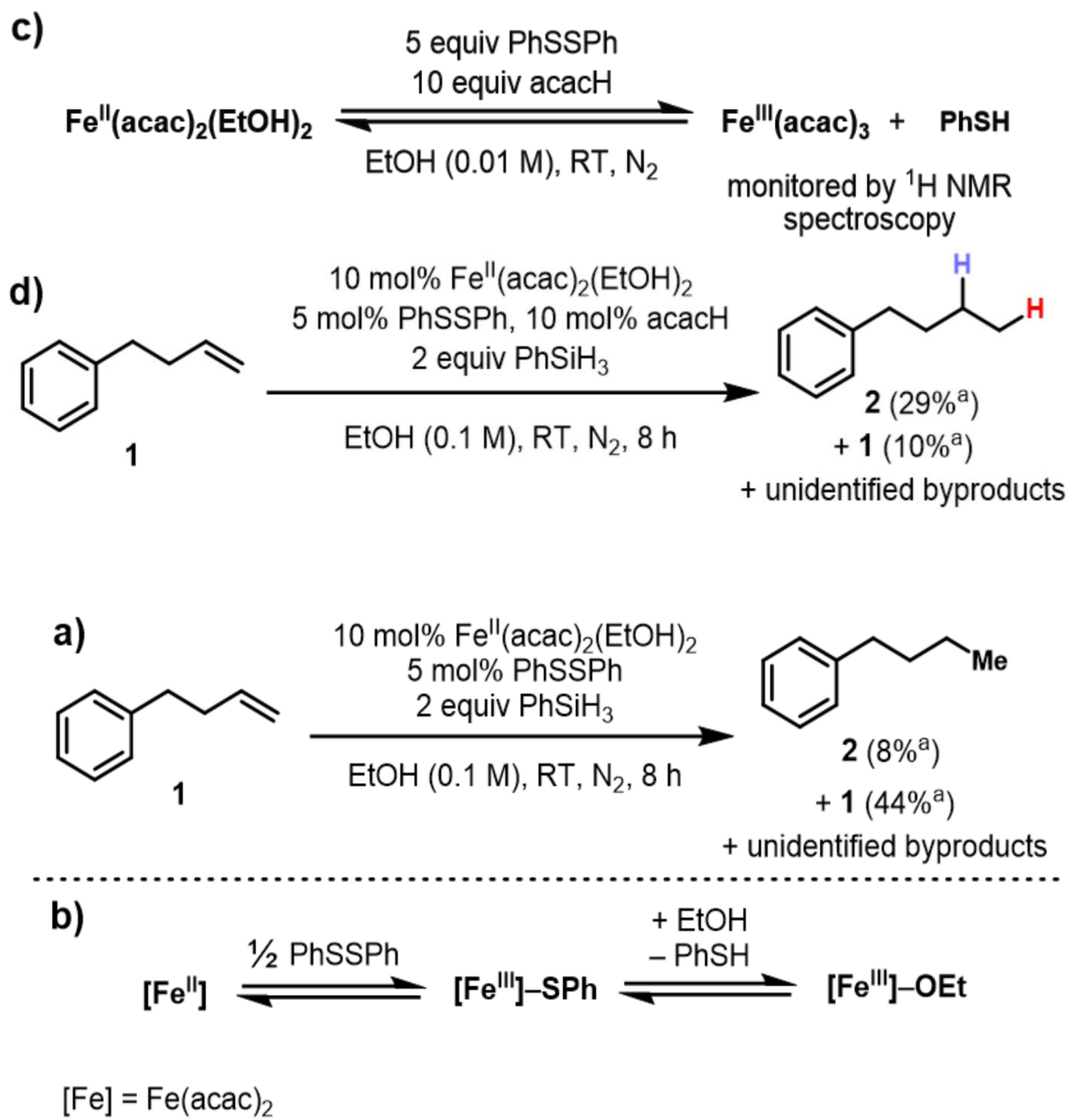


[Fe^{III}]–SPh species are seemingly formed in situ.

Excess amount of PhSH damages $Fe^{III}(acac)_3$, leading to the formation of Fe^{II} $(acac)_2$ and $(PhS)_2$.

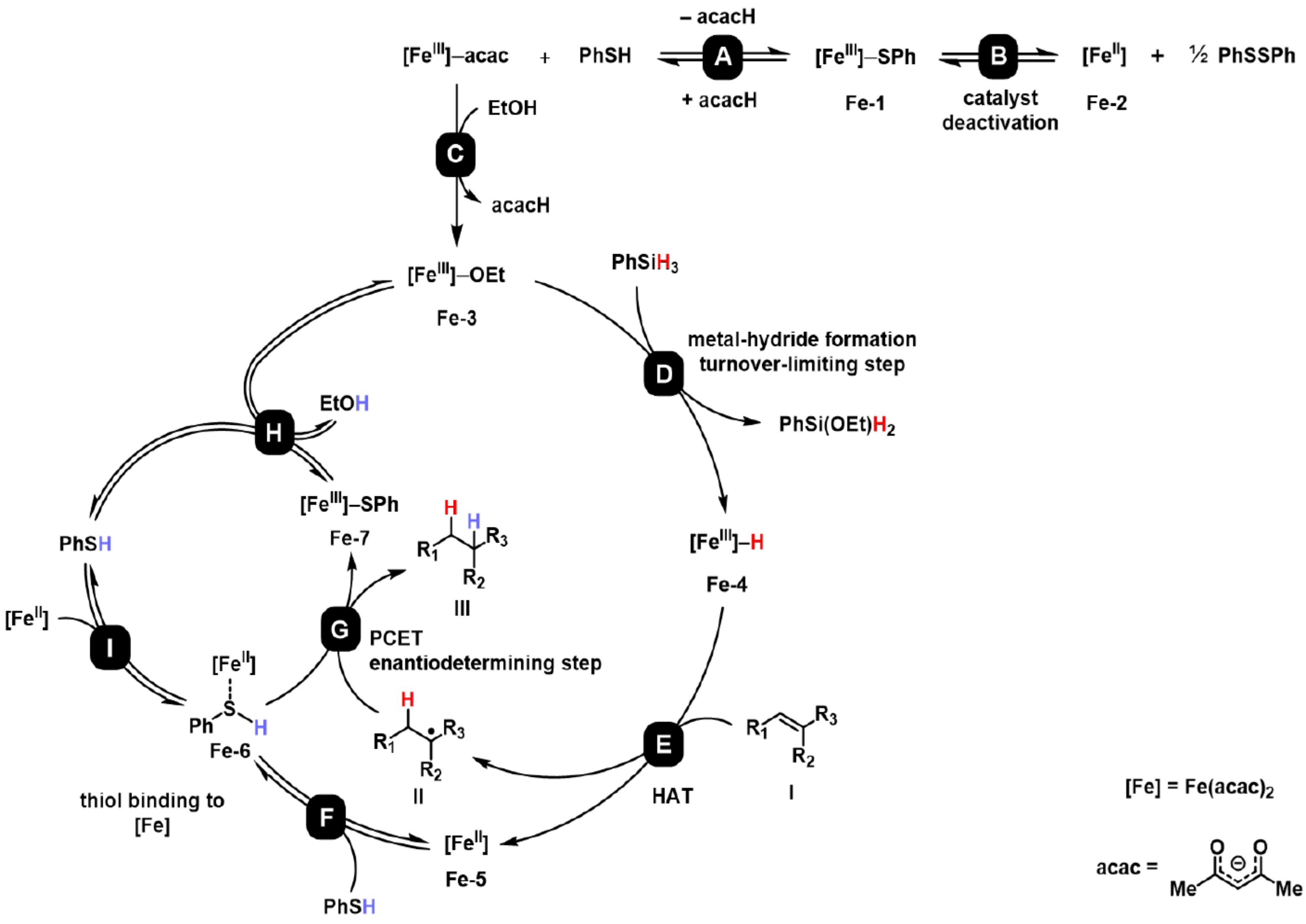
1. West, J. G.; Miller, S. J.; Holland, P. L. et al. *Chemrxiv* **2023**, DOI: 10.26434/chemrxiv-2023-b9zdf.

Reversible Formation of Fe(acac)$_3$ from Fe^{II}(acac)$_2$[1)]



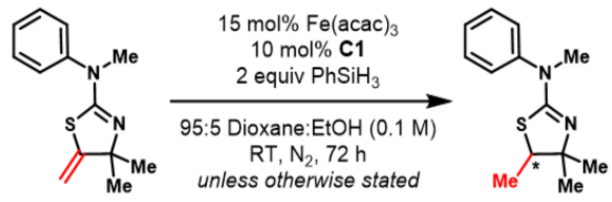
1. West, J. G.; Miller, S. J.; Holland, P. L. et al. *Chemrxiv* **2023**, DOI: 10.26434/chemrxiv-2023-b9zdf.

More Detailed Mechanism of Fe-Catalyzed cHAT[1)]



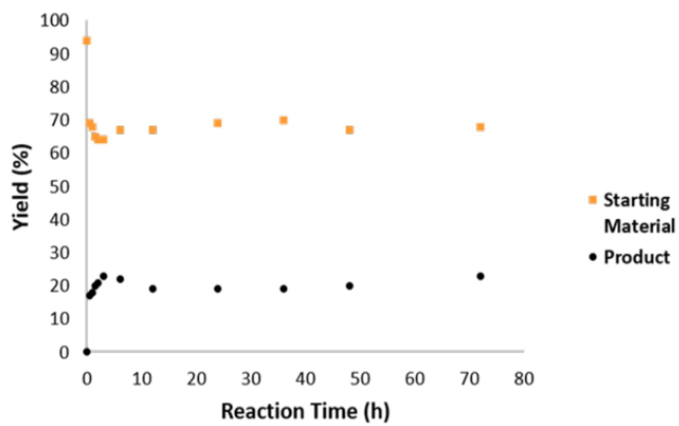
1. West, J. G.; Miller, S. J.; Holland, P. L. et al. *Chemrxiv* **2023**, DOI: 10.26434/chemrxiv-2023-b9zdf.

Iron and/or Silane Spiking Experiments[1)]

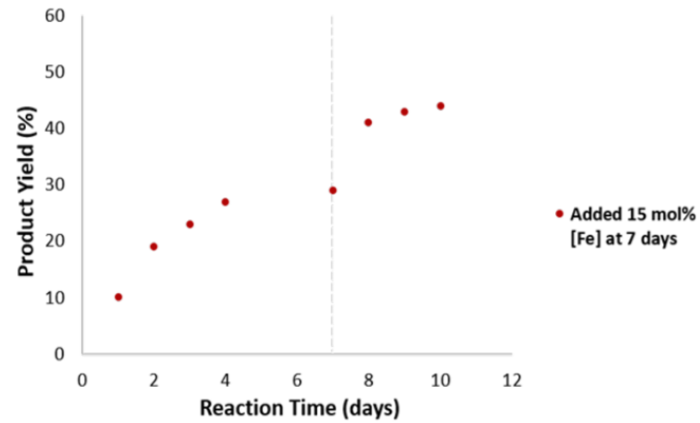


3d **4d**

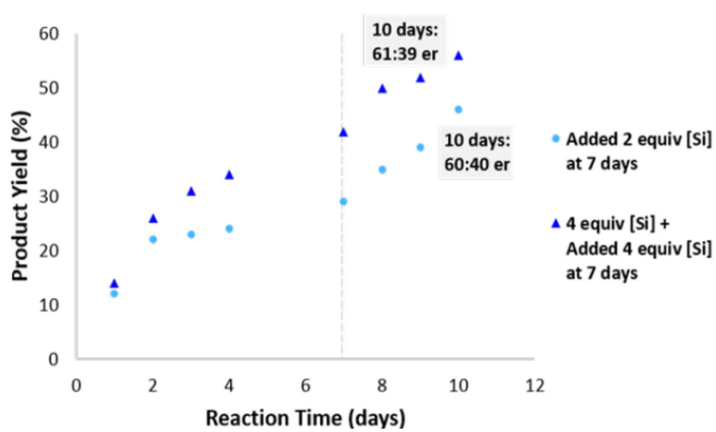
a) Reaction profile[1]



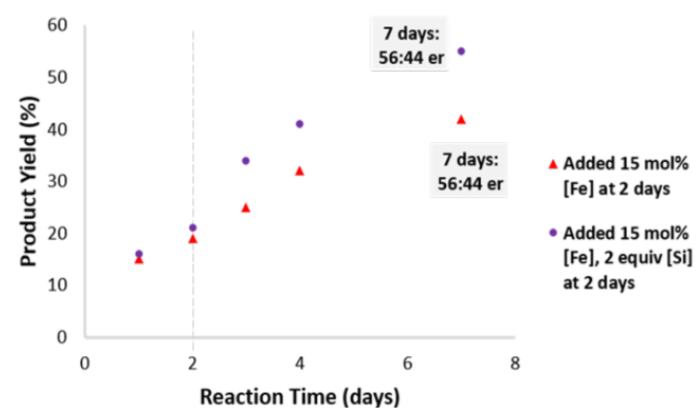
b) Iron spiking



c) Silane spiking

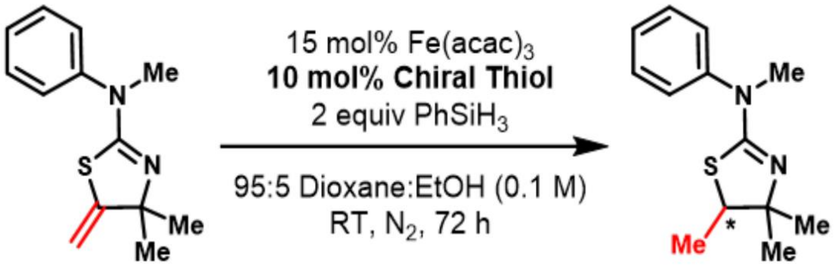


d) Iron and silane spiking

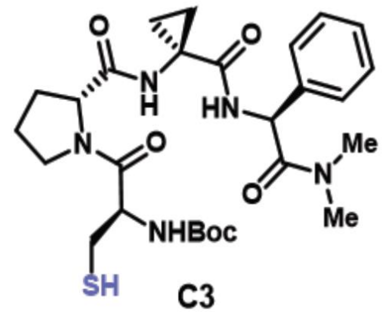


1. West, J. G.; Miller, S. J.; Holland, P. L. et al. *Chemrxiv* **2023**, DOI: 10.26434/chemrxiv-2023-b9zdf.

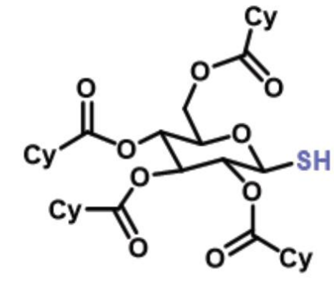
Thiol Screening in Asymmetric cHAT Hydrogenation[1)]



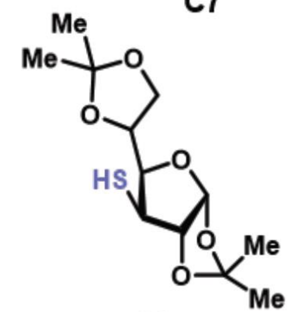
Entry	Chiral Thiol	Yield (%)[a]	er[b]
1	**C1**	26	61:39
2	Boc-Cys-OMe (**C2**)	48	51:49
3[c]	Boc-Cys-^{D}Pro-Acpc-Phg-NMe_2 (**C3**)	16	49:51
4	Boc-Cys-^{D}Pro-Aib-Phe-Pip (**C4**)	45	47:53
5	[Boc-Cys-^{D}Pro-Aib-Phe-Pip]$_2$ (**C5**)	12	49:51
6[d]	2-thio-Bz-^{D}Pro-Acpc-Cha-NMe_2 (**C6**)	51	48:52
7	**C7**	31	61:39
8	**C8**	29	58:42
9	**C9**	35	37:63



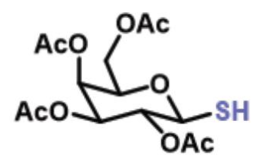
C3



C7

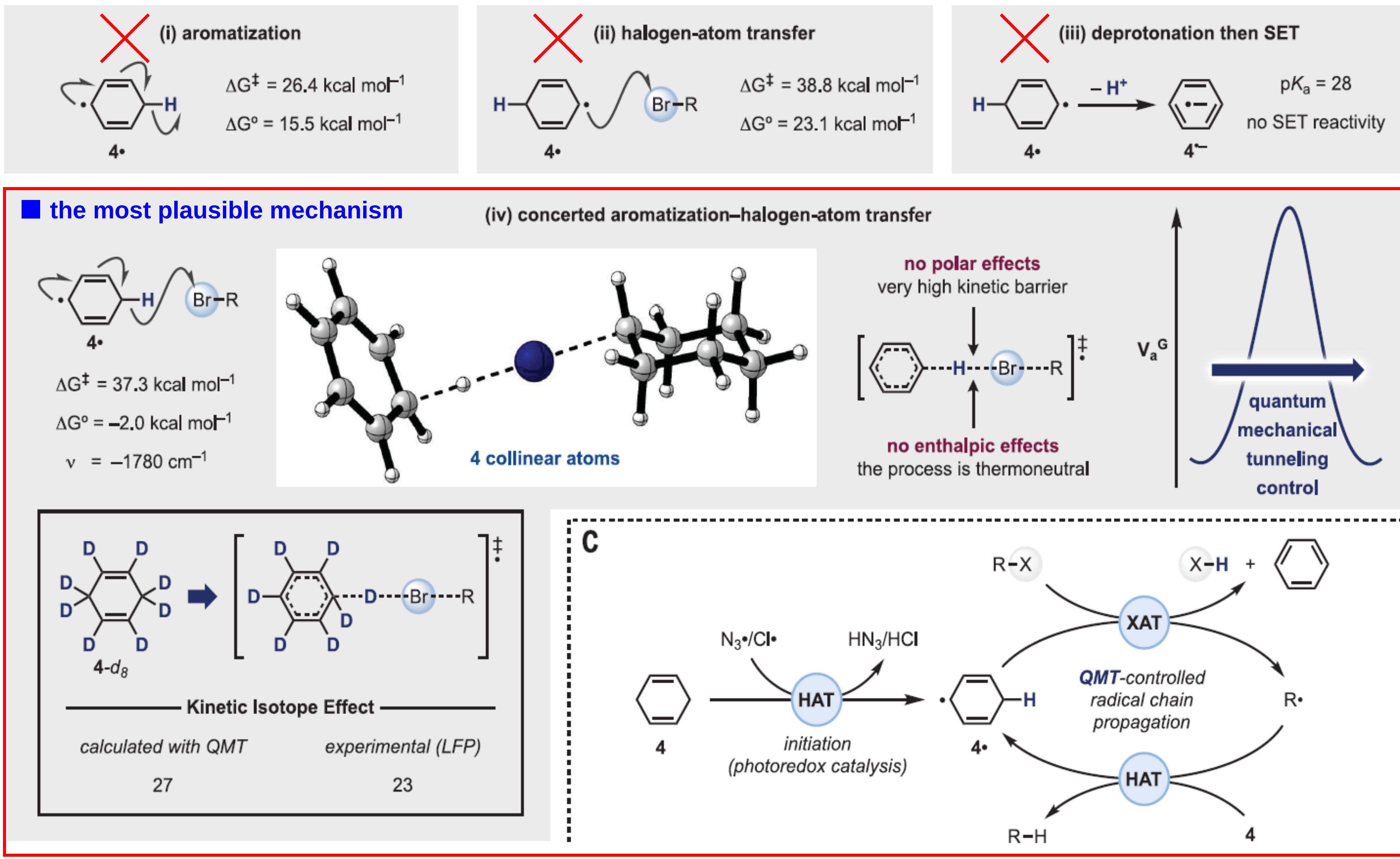


C9



C8

A Hydrogen Radical Sometimes Have High Reactivity Due to The Quantum Tunnelling Effect[1]



1. Lakhdar, S.; Leonori, D. et al. *Science* **2022**, *377*, 1323.