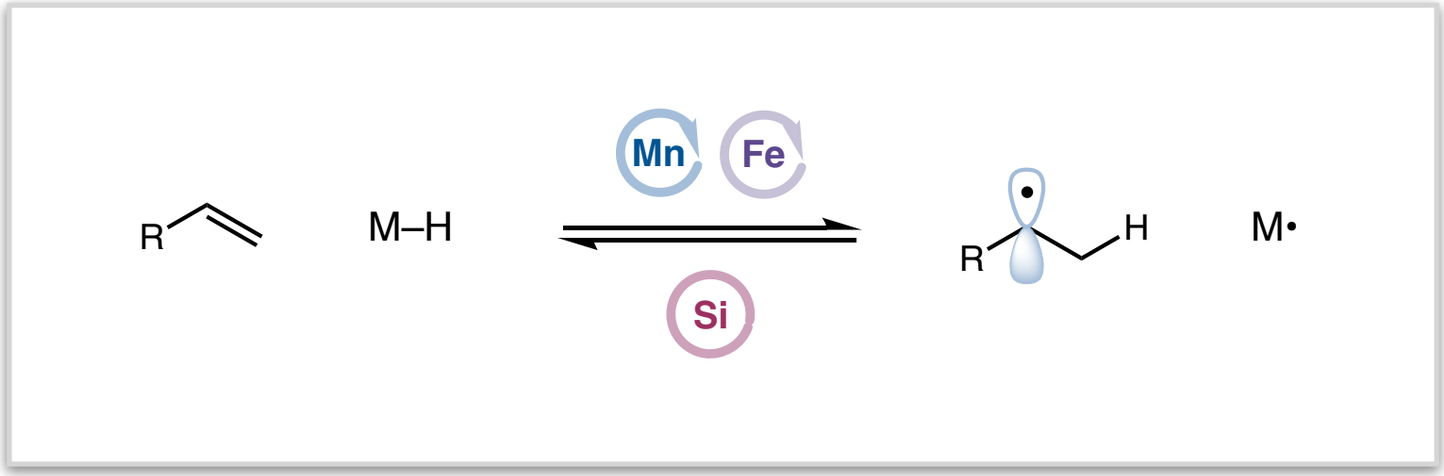
Transition-Metal Hydride HAT: Radical Hydrofunctionalization of Olefins

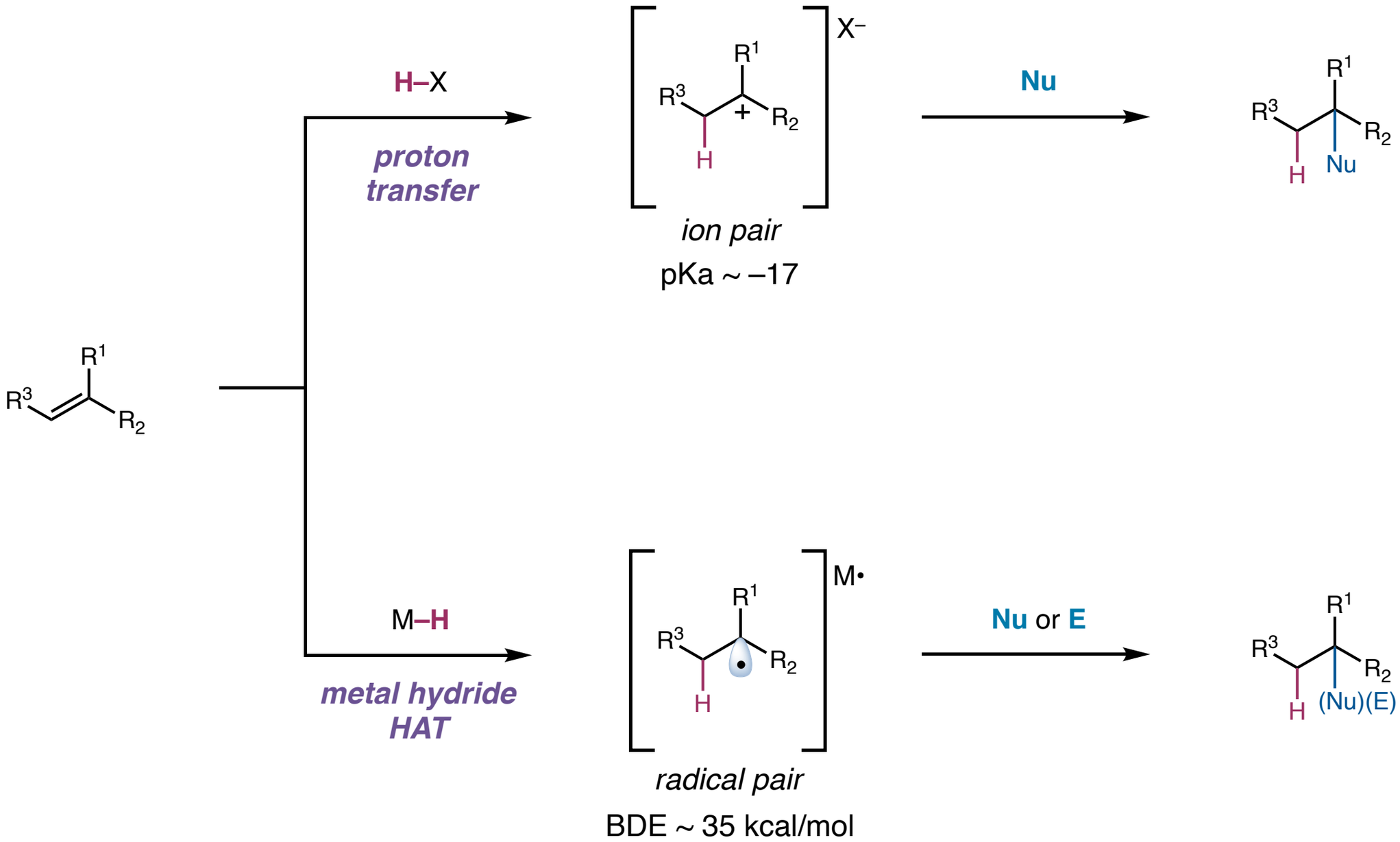


Group Meeting

June 21, 2022

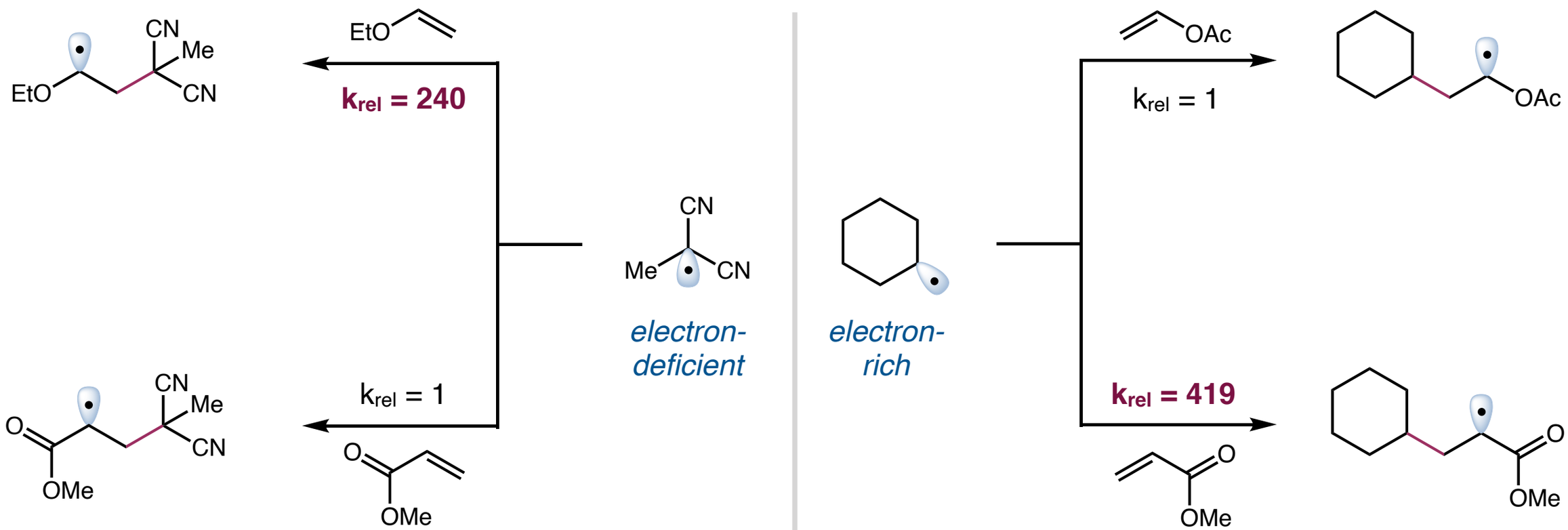
Amy Chan
MacMillan Group
Princeton University

Markovnikov Hydrofunctionalization of Alkenes

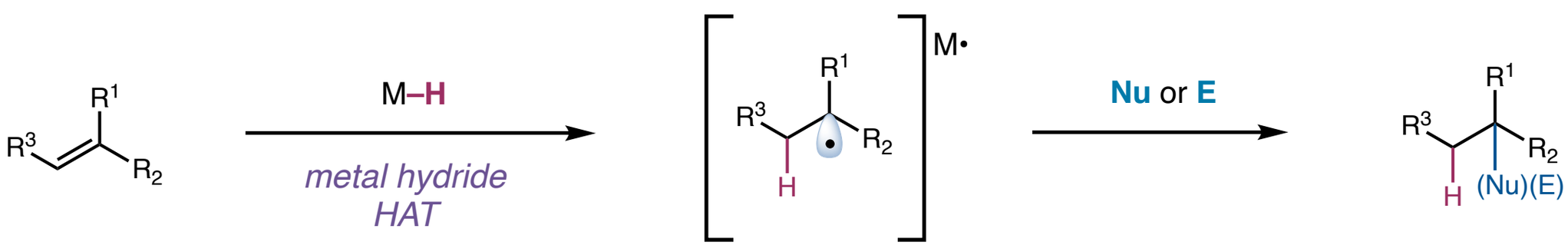


Crossley, S. W. M.; Obradors, C.; Martinez, R. M.; Shenvi, R. A. *Chem. Rev.* **2016**, *116*, 8912–9000.

Relative Rates of Radical Addition

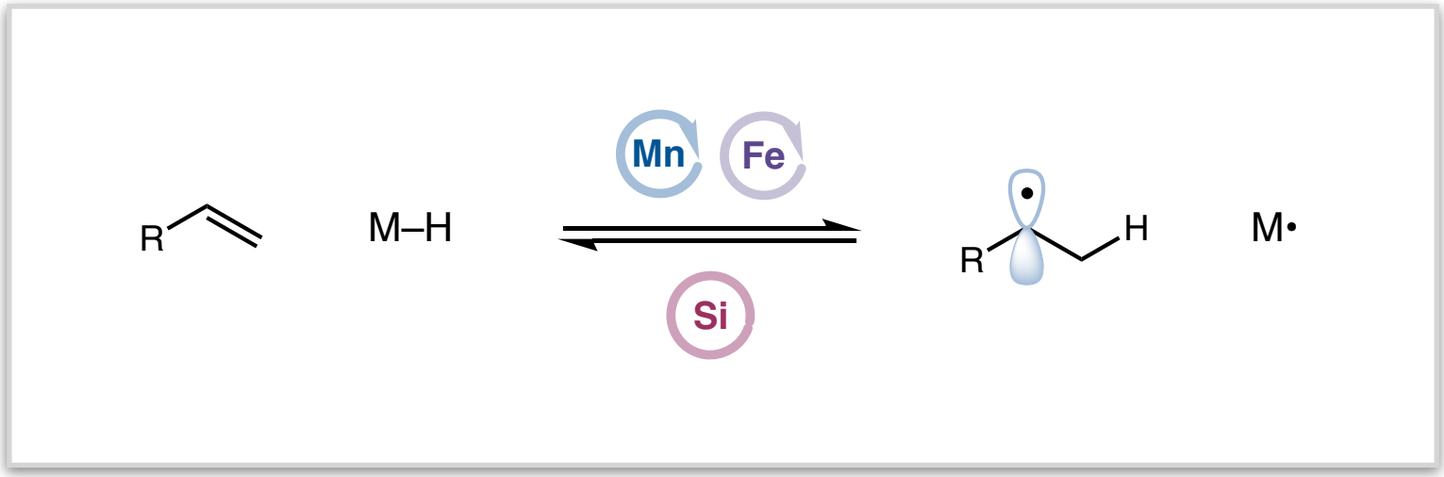


possible polarity reversal in reactivity



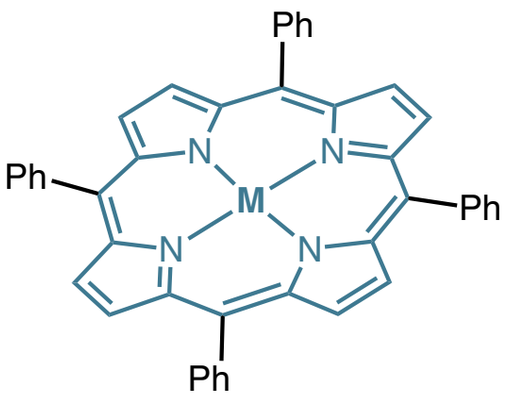
Giese, B. *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 753–764.

Outline

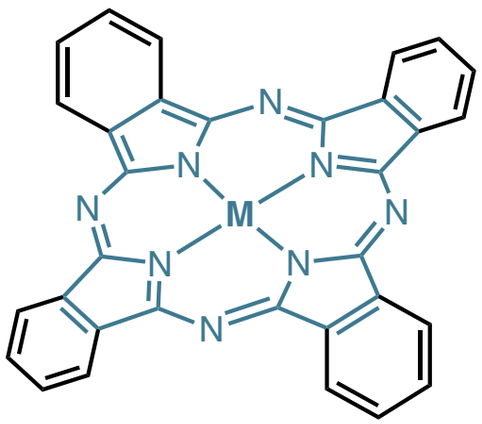


- C–O Bond Formation
- C–N Bond Formation
- C–C Bond Formation
- C–X Bond Formation
- Hydrogenation and Isomerization
- General Mechanistic Considerations

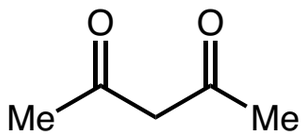
Common Ligand Scaffolds



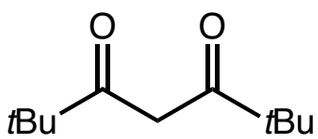
tetraphenylphorphyrin **(TPP)** Mn



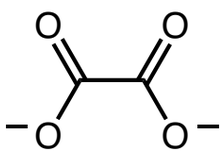
Fe phthalocyanines **(Pc)**



acetoacetonate **(acac)**



dipivaloymethane **(dpm)** Mn

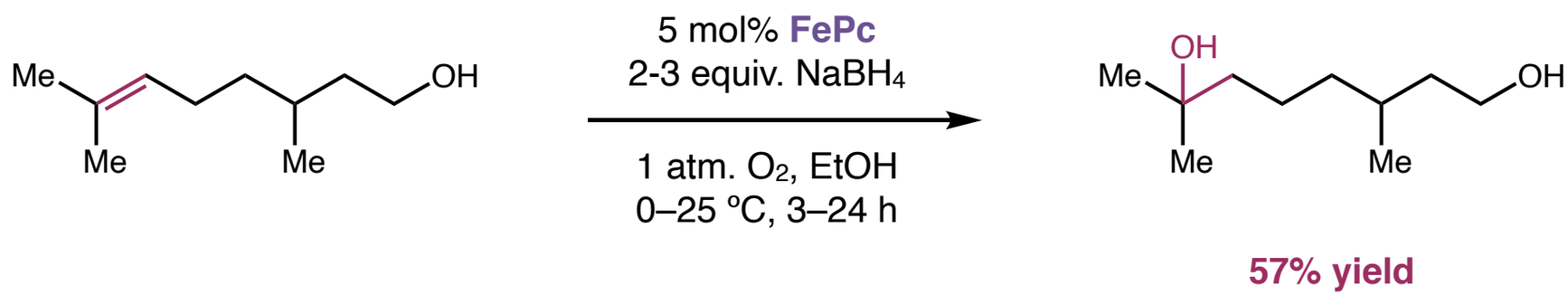


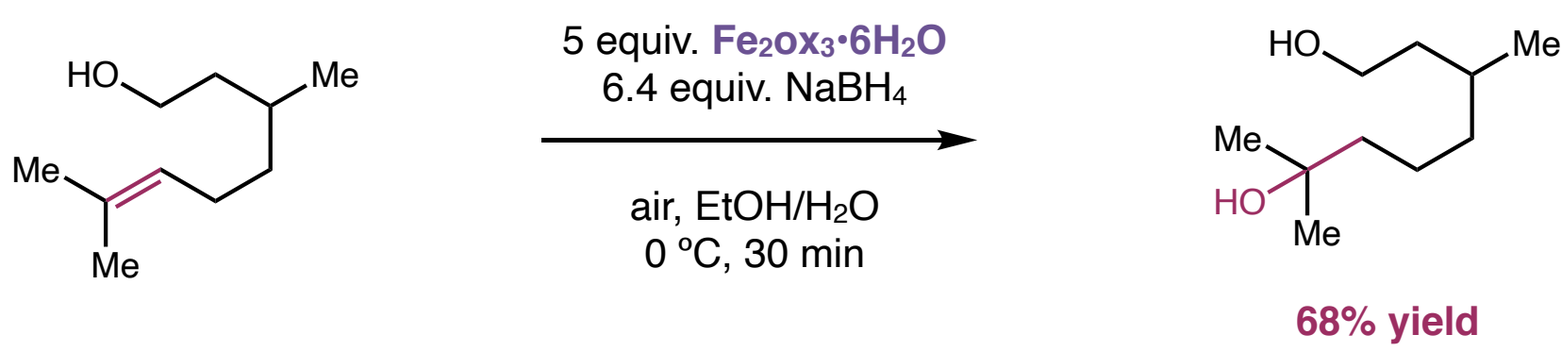
Fe oxalate **(ox)**

Outline

- **C–O Bond Formation**
- C–N Bond Formation
- C–C Bond Formation
- C–X Bond Formation
- Hydrogenation and Isomerization
- General Mechanistic Considerations

Aerobic Hydration of Alkenes

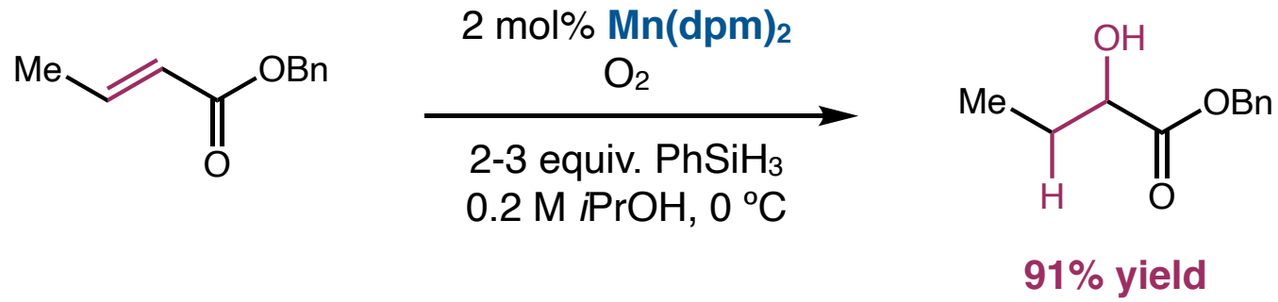




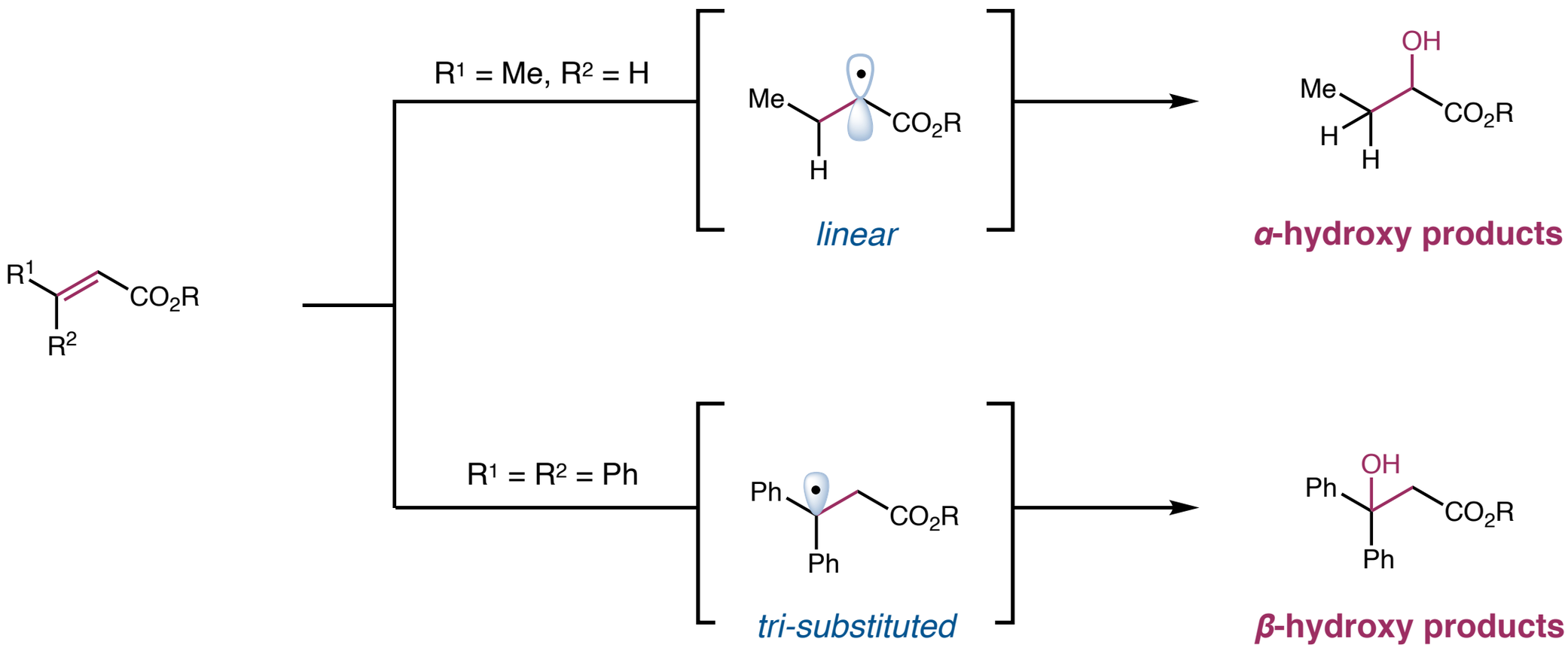
formation of carbon–heteroatom (C, N, O, S, halogen) bonds

Leggans, E. K.; Barker, T. J.; Duncan, K. K.; Boger, D. L. *Org. Lett.* **2012**, *14*, 1428–1431.

Hydration of α,β-Unsaturated Esters

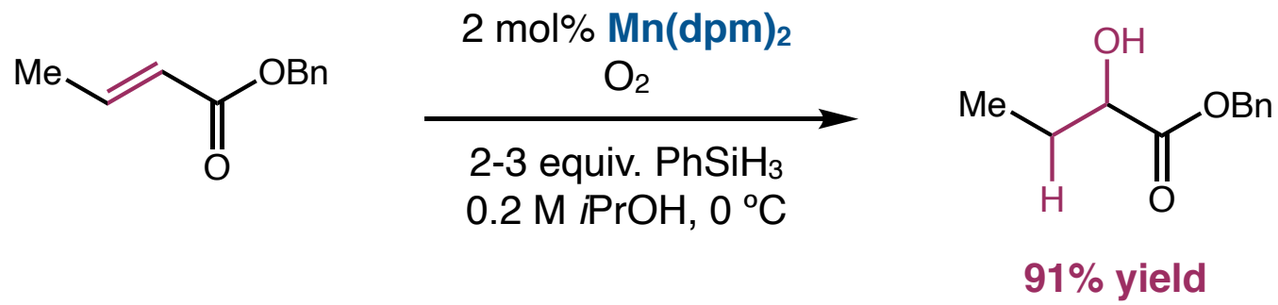


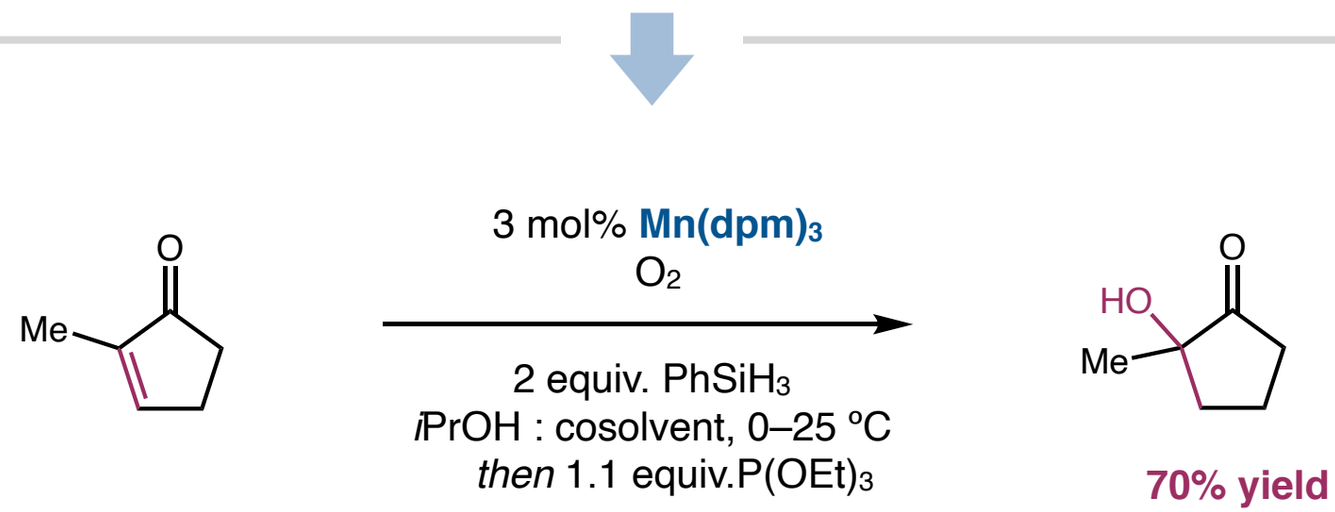
regioselectivity dependent on intermediate radical stability



Inoki, S.; Kato, K.; Isayama, S.; Mukaiyama, T. *Chem. Lett.* ***1990***, *19*, 1869–1872.

Hydration of α,β-Unsaturated Esters



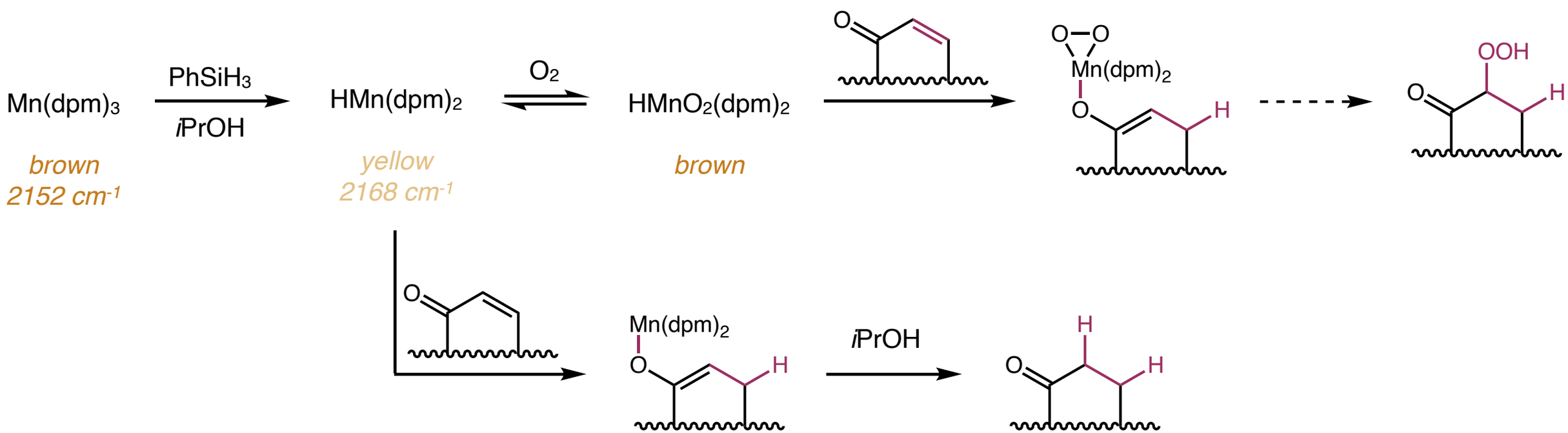


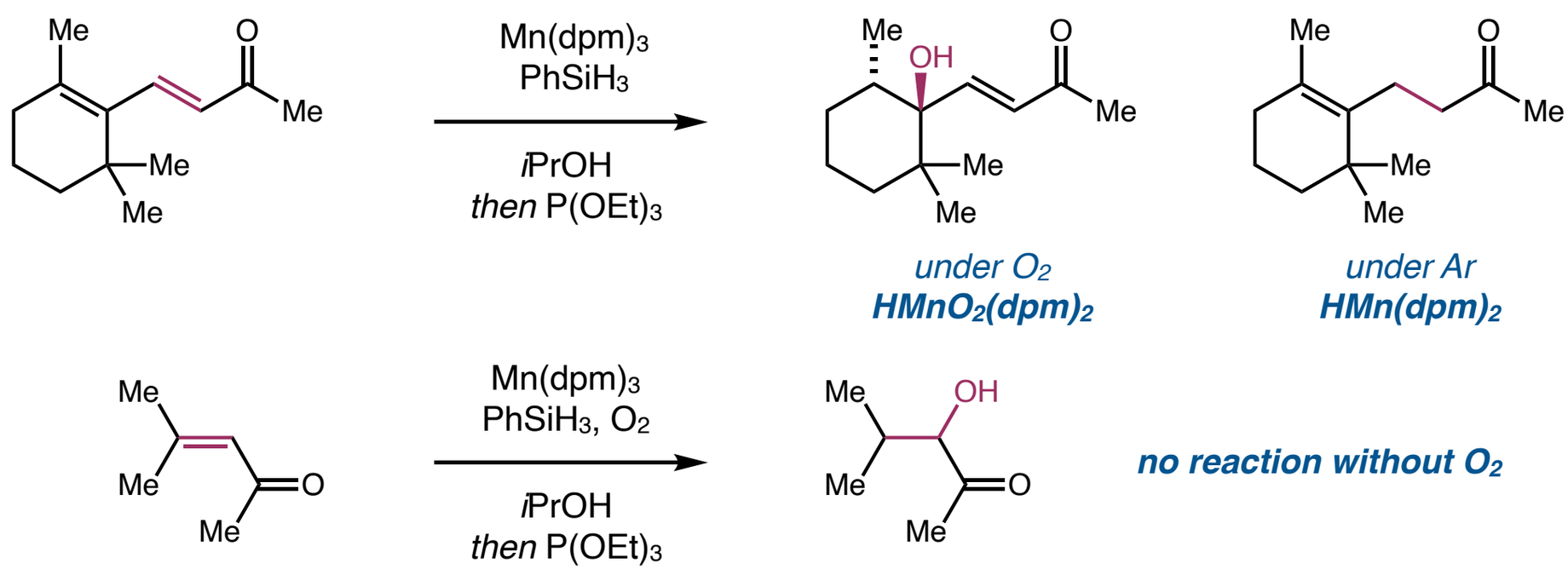
suggests Mn(dpm)$_3$ is the active precatalyst in both cases

Inoki, S.; Kato, K.; Isayama, S.; Mukaiyama, T. *Chem. Lett.* ***1990***, *19*, 1869–1872.

Magnus, P.; Payne, A. H.; Waring, M. J.; Scott, D. A.; Lynch, V. *Tetrahedron Lett.* **2000**, *41*, 9725–9730.

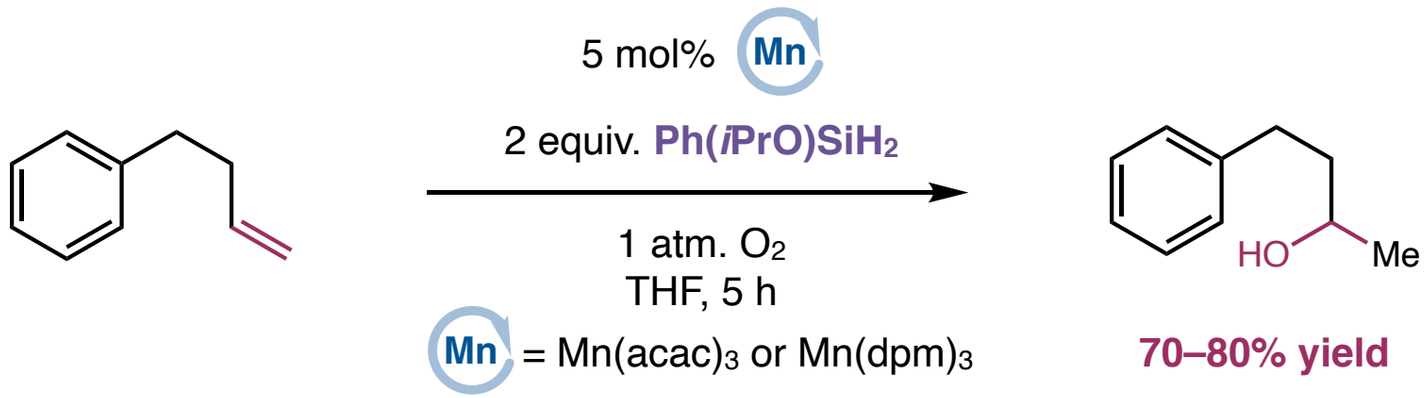
Mechanistic Studies of Manganese Catalysts



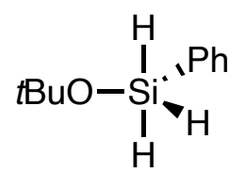


Magnus, P.; Payne, A. H.; Waring, M. J.; Scott, D. A.; Lynch, V. *Tetrahedron Lett.* **2000**, *41*, 9725–9730.

Manganese(III)-catalyzed Mukaiyama Hydration



increases hydridic character of silane



observed by ^{1}H NMR at –70 ºC

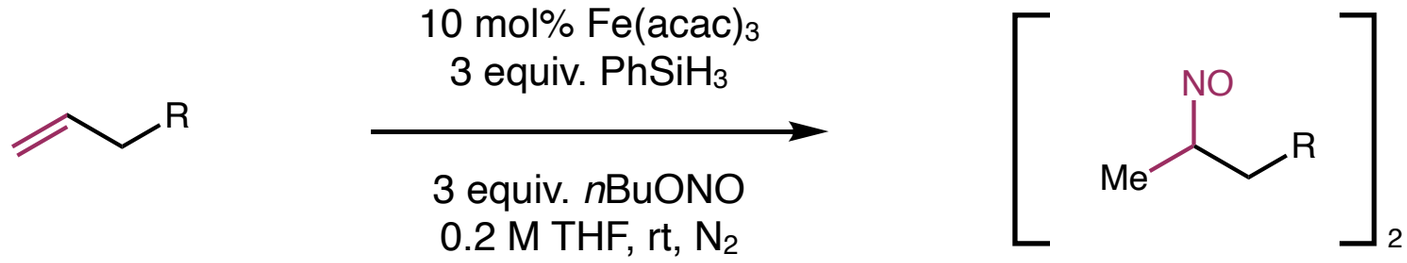
Obradors, C.; Martinez, R. M.; Shenvi, R. A. *J. Am. Chem. Soc.* **2016**, *138*, 4962–4971.

O'Donnell, K.; Bacon, R.; Chellappa, K. L.; Schowen, R. L.; Lee, J. K. *J. Am. Chem Soc.* **1972**, *94* , 2500–2505.

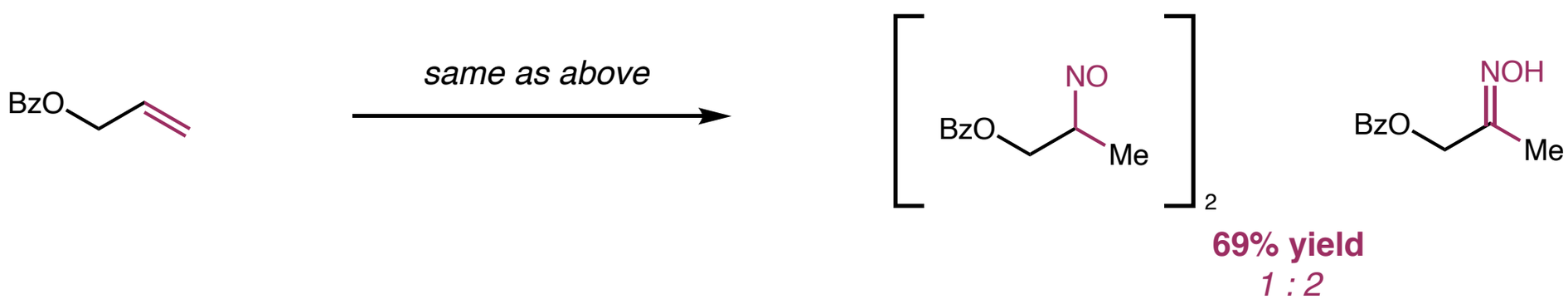
Outline

- C–O Bond Formation
- **C–N Bond Formation**
- C–C Bond Formation
- C–X Bond Formation
- Hydrogenation and Isomerization
- General Mechanistic Considerations

Synthesis of Nitroso Alkanes

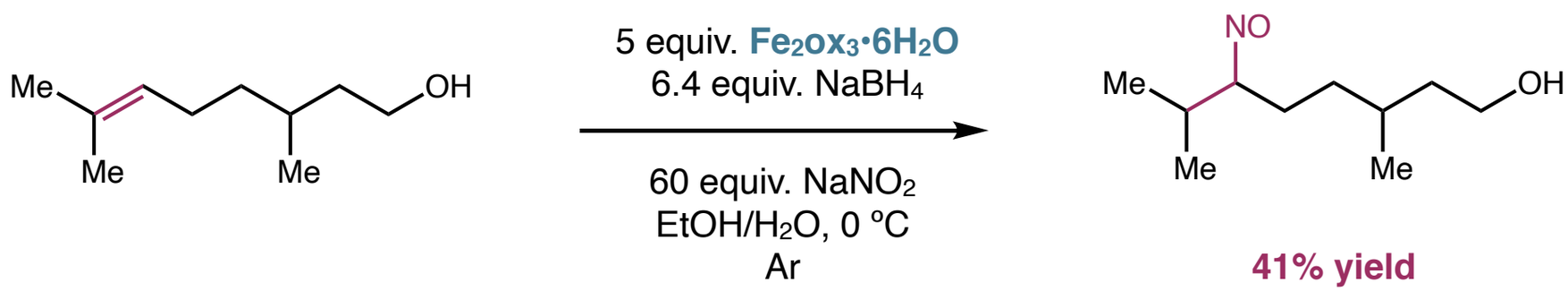


aryl and keto-substituted tautomerize to the oxime



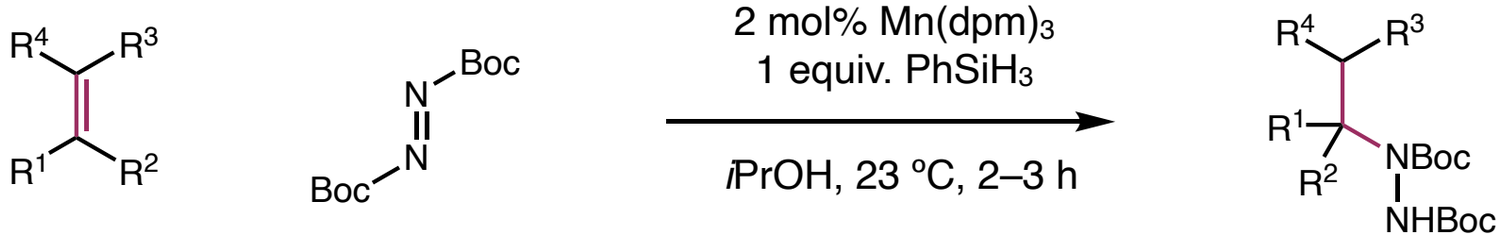
Kato, K.; Mukaiyama, T. *Chem. Lett.* **1992**, *21*, 1137–1140.

Nitrosation of Unactivated Alkenes



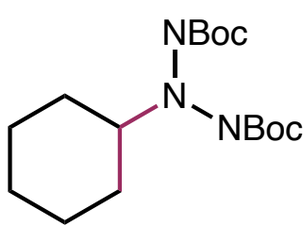
Leggans, E. K.; Barker, T. J.; Duncan, K. K.; Boger, D. L. *Org. Lett.* **2012**, *14*, 1428–1431.

Mn-Catalyzed Hydrohydrazination

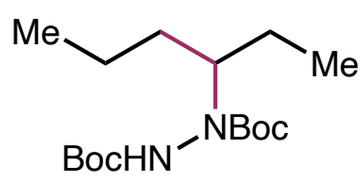


17 examples
45–95% yield

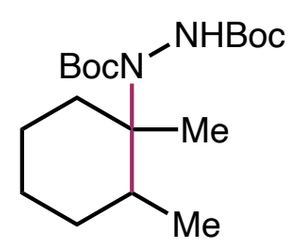
selected scope



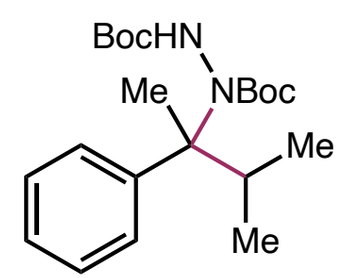
90% yield
24% yield with [Co]



66% yield
16% yield with [Co]



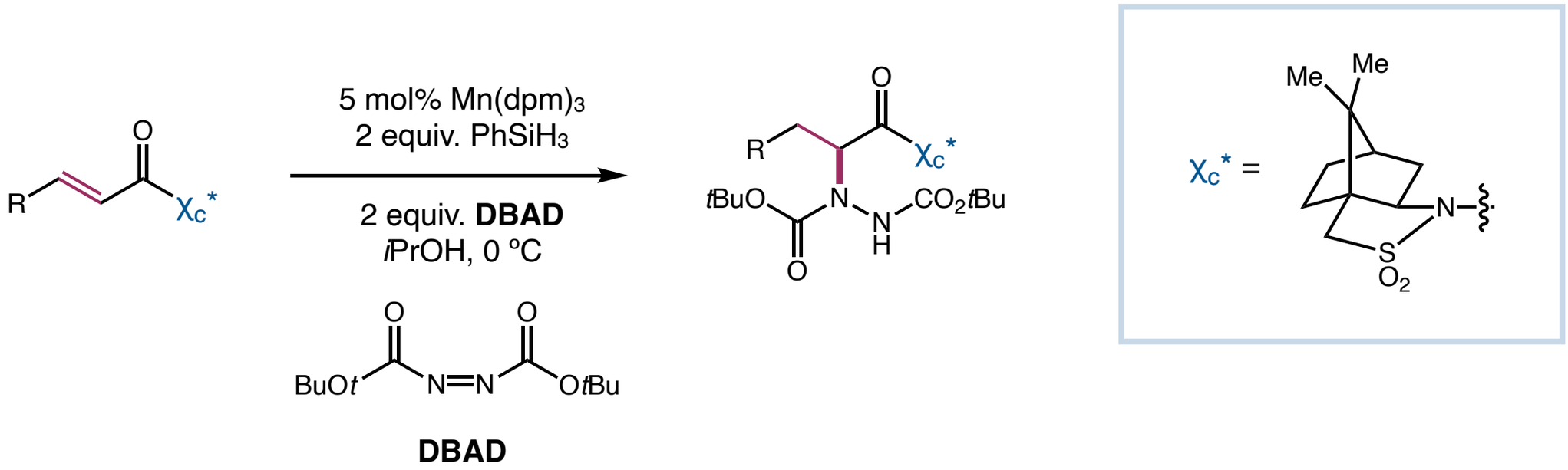
79% yield
18% yield with [Co]

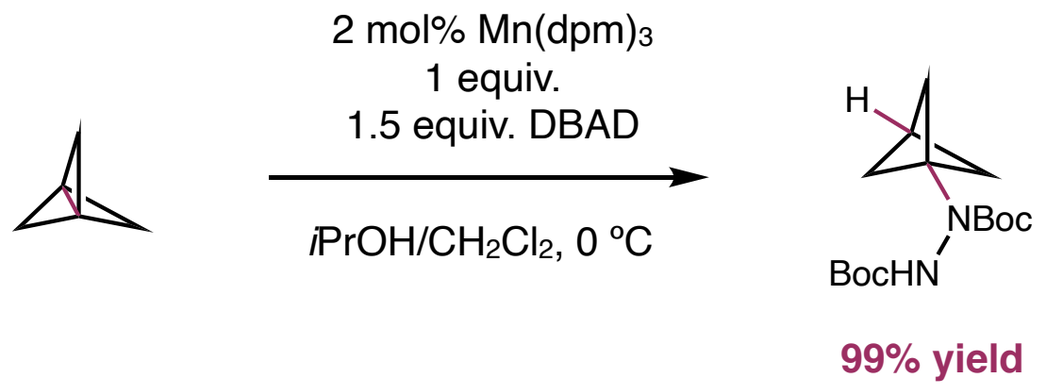


51% yield
13% yield with [Co]

Waser, J.; Carrerira, E. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 4099–4102.

Mn-Catalyzed Hydrohydrazination

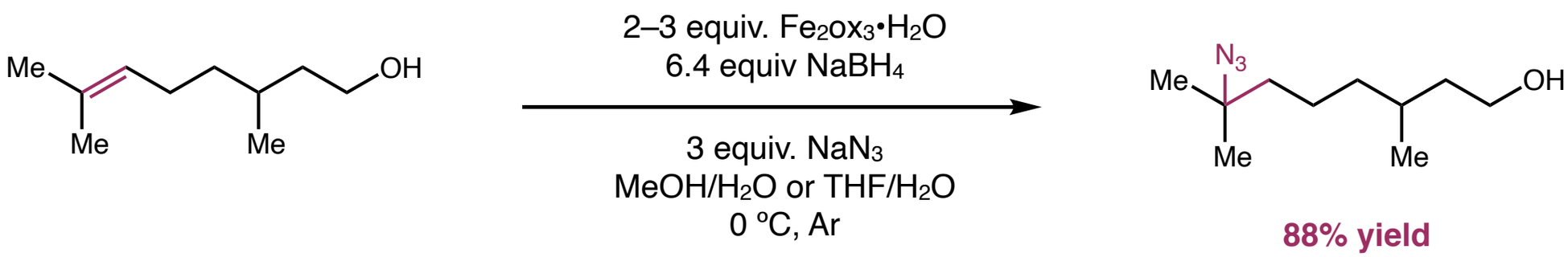




Sato, M.; Gunji, Y.; Ikeno, T.; Yamada, T. *Chem. Lett.* **2005**, *34*, 316–317.

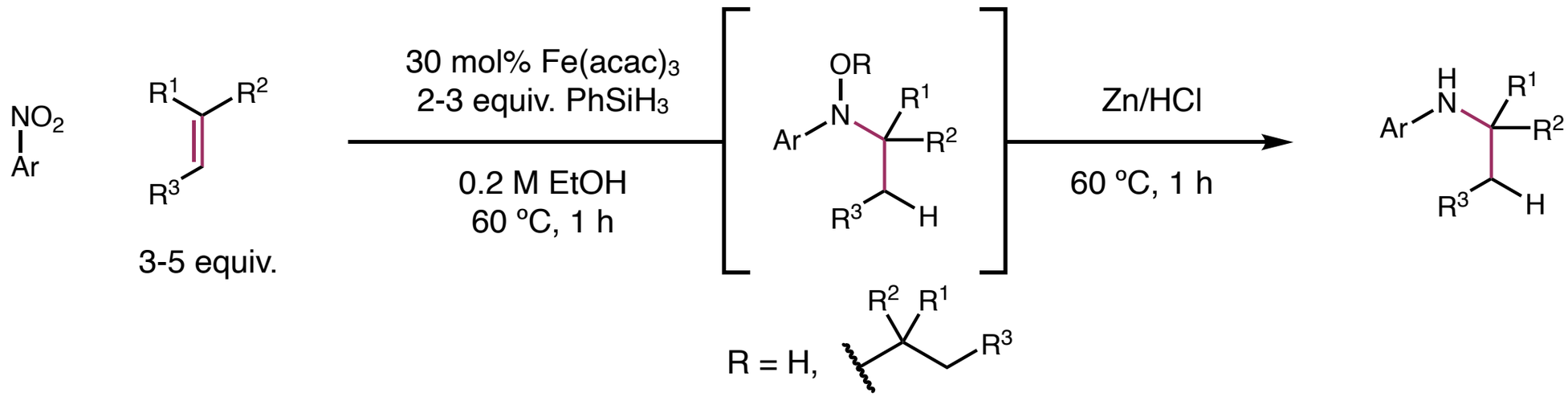
Bunker, K. D.; Sach, N. W.; Huang, Q.; Richardson, P. F. *Org. Lett.* **2011**, *13*, 4746–4748.

Hydroazidation

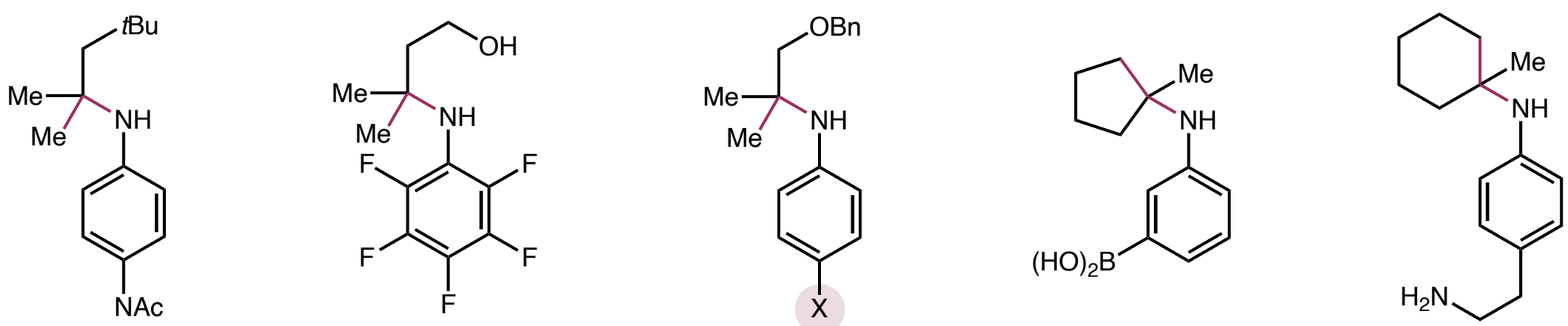


Leggans, E. K.; Barker, T. J.; Duncan, K. K.; Boger, D. L. *Org. Lett.* **2012**, *14*, 1428–1431.

Fe-Catalyzed Hydroamination of Olefins



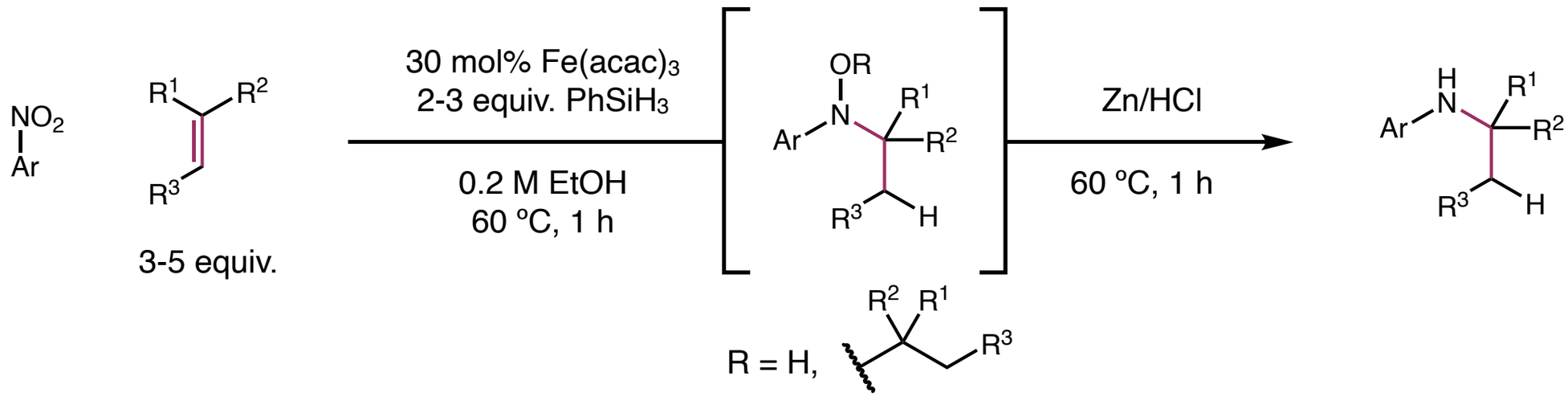
selected substrate scope



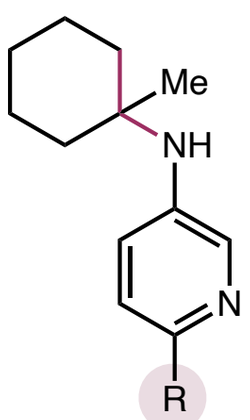
50% yield | **60% yield** | X = OTf **(61% yield)** X = Br **(45% yield)** | **55% yield** | **38% yield**

Gui, J.; et al. *Science* **2015**, *348*, 886–891.

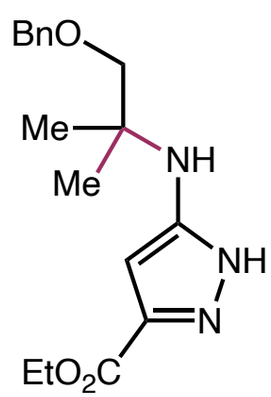
Fe-Catalyzed Hydroamination of Olefins



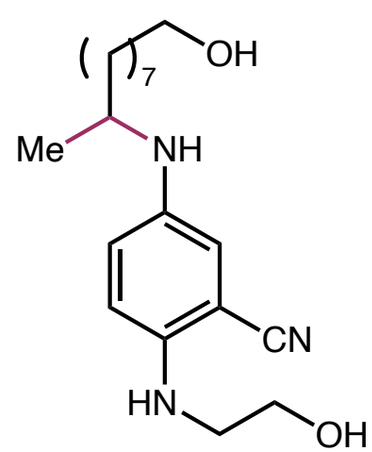
selected substrate scope



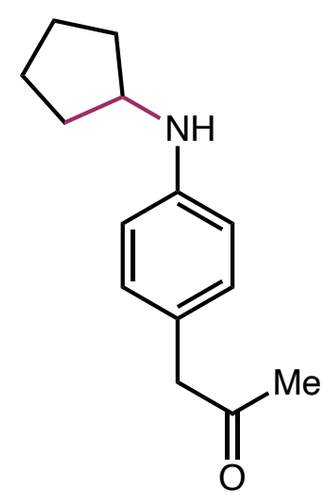
X = OMe **(66% yield)**
X = Cl **(42% yield)**



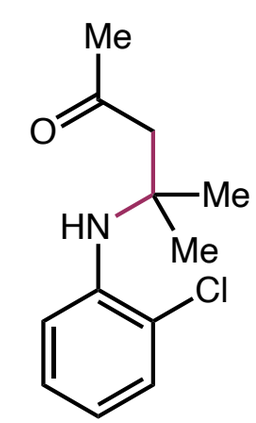
63% yield



53% yield



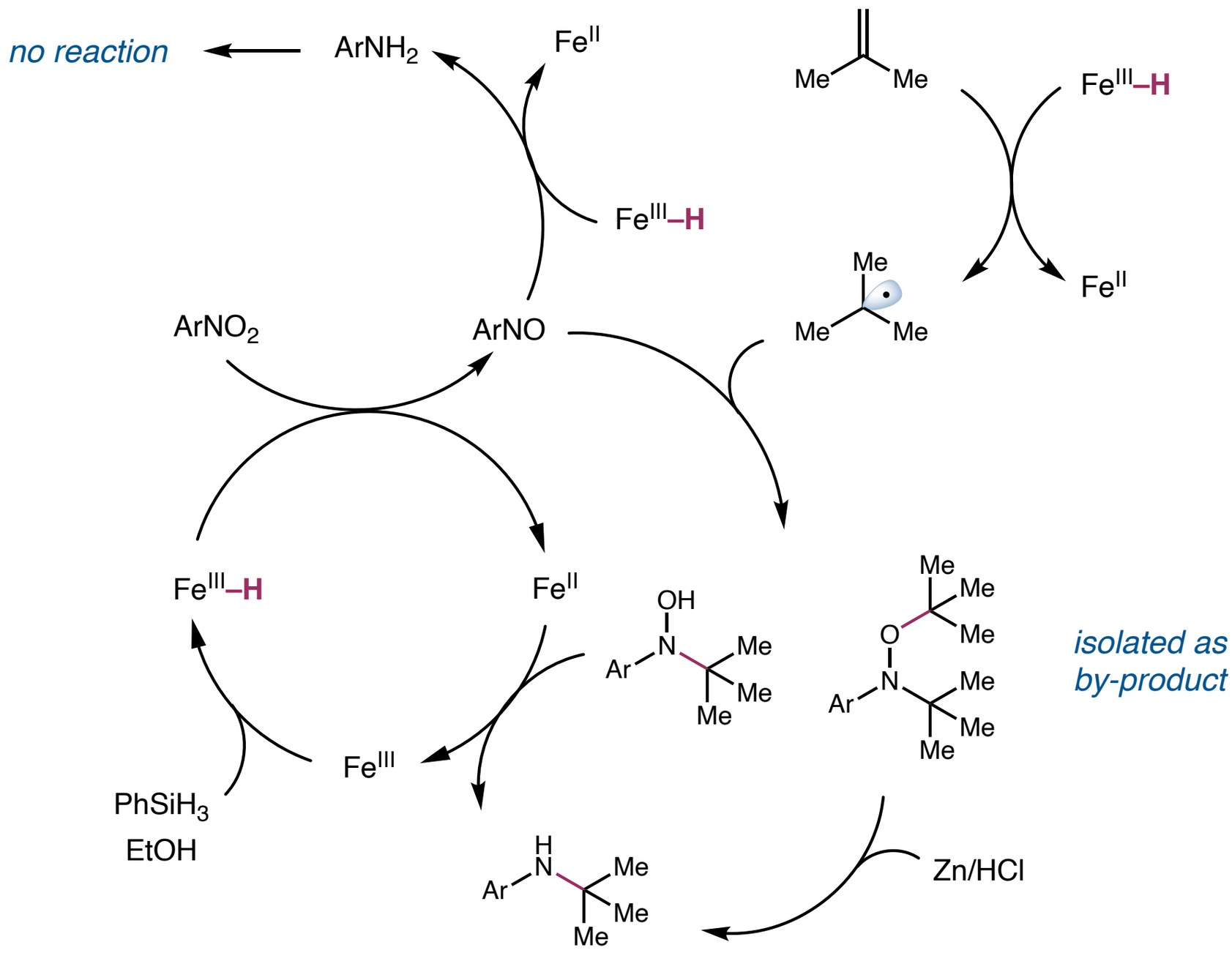
50% yield



41% yield

Gui, J.; et al. *Science* **2015**, *348*, 886–891.

Fe-Catalyzed Hydroamination of Olefins

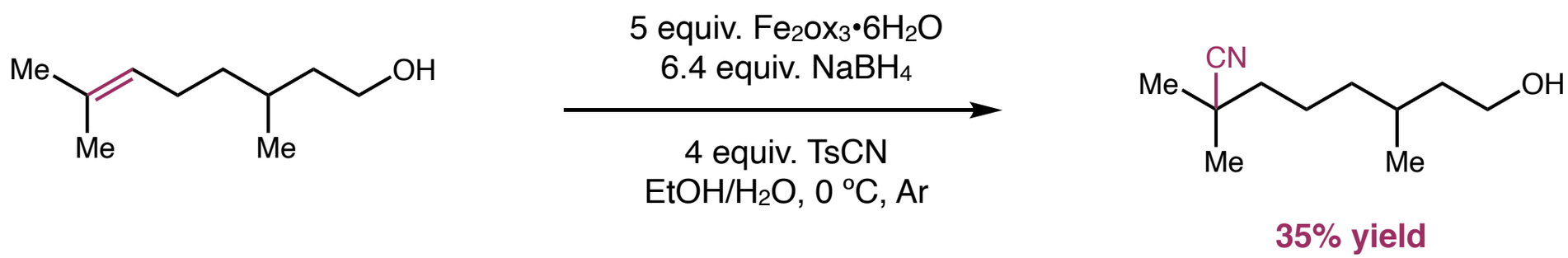


Gui, J.; et al. *Science* **2015**, *348*, 886–891.

Outline

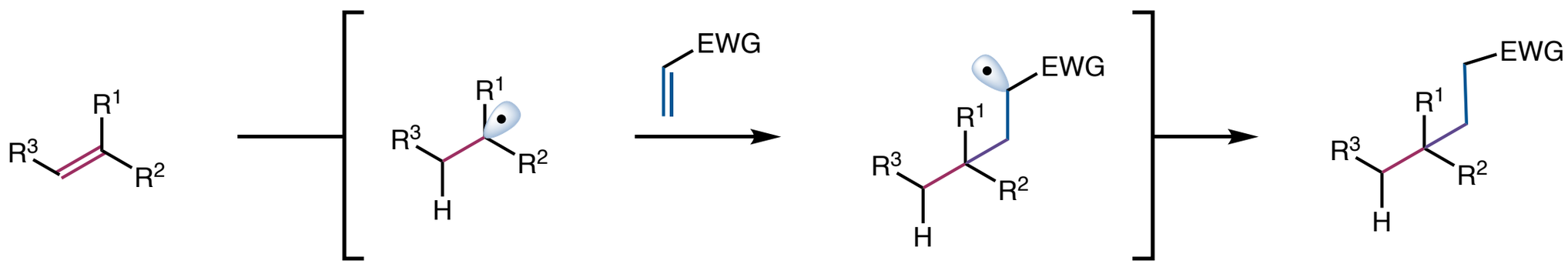
- C–O Bond Formation
- C–N Bond Formation
- **C–C Bond Formation**
- C–X Bond Formation
- Hydrogenation and Isomerization
- General Mechanistic Considerations

Hydrocyanation of Alkenes



Leggans, E. K.; Barker, T. J.; Duncan, K. K.; Boger, D. L. *Org. Lett.* **2012**, *14*, 1428–1431.

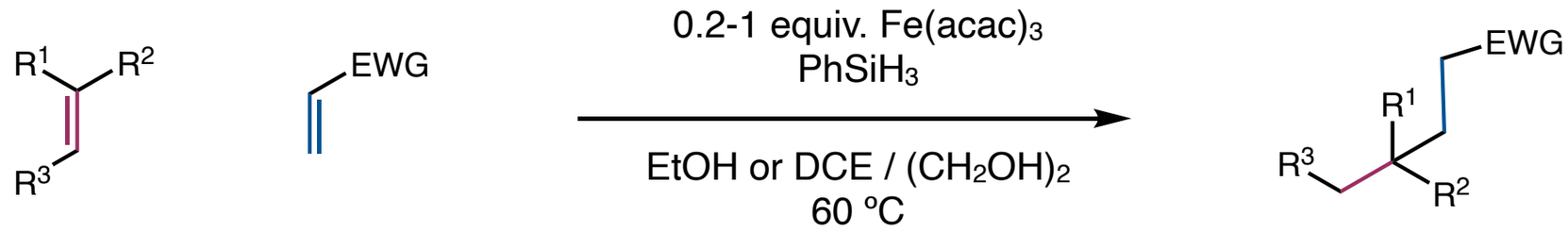
Radical Conjugate Addition



Lo, J. C.; Yabe,Y.; Baran, P. S. *J. Am. Chem. Soc.* **2014**, *136*, 1304–1307.

Lo, J. C.; Gui, J.; Yabe, Y.; Pan, C.-M.; Baran, P. S. *Nature* **2014**, *516*, 343–348.

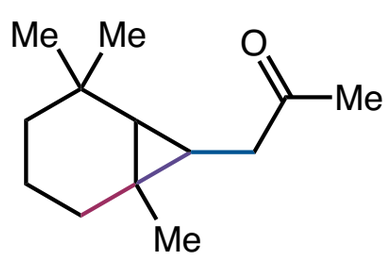
First-Generation Conjugate Addition



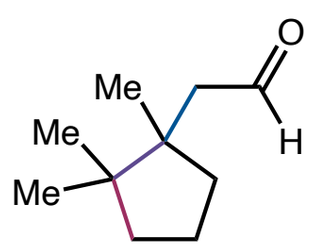
R = carbon/hydrogen

29 examples

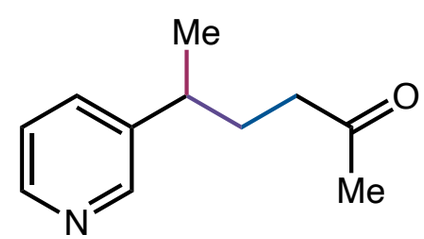
selected scope



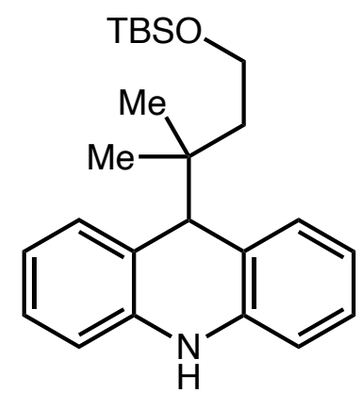
97% yield



76% yield



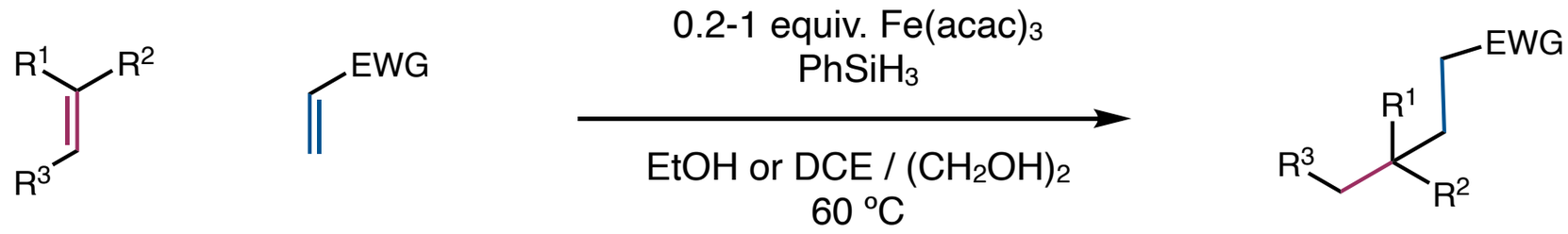
42% yield



48% yield

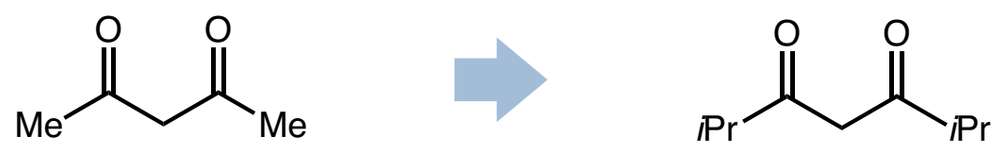
Lo, J. C.; Yabe,Y.; Baran, P. S. *J. Am. Chem. Soc.* **2014**, *136*, 1304–1307.

Second-Generation Conjugate Addition

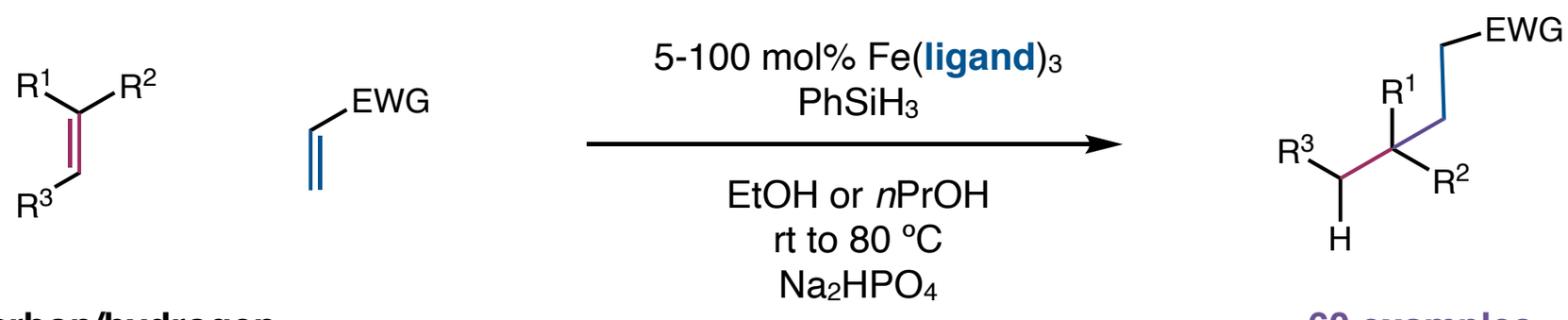


R = carbon/hydrogen

29 examples



acetoacetonate (acac) diisobutyrylmethane (dibm)



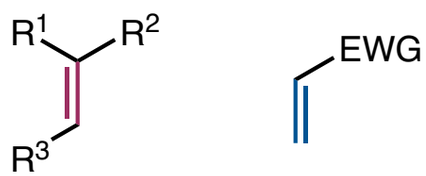
R = carbon/hydrogen and *heteroatom*

60 examples

Lo, J. C.; Yabe,Y.; Baran, P. S. *J. Am. Chem. Soc.* **2014**, *136*, 1304–1307.

Lo, J. C.; Gui, J.; Yabe, Y.; Pan, C.-M.; Baran, P. S. *Nature* **2014**, *516*, 343–348.

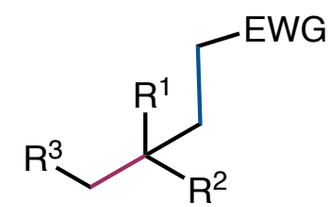
Second-Generation Conjugate Addition



R = carbon/hydrogen
and *heteroatom*

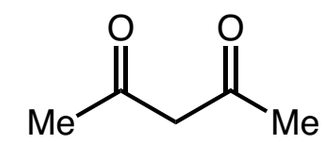
5-100 mol% Fe(**ligand**)$_3$
$PhSiH_3$

EtOH or *n*PrOH
rt to 80 °C
Na_2HPO_4

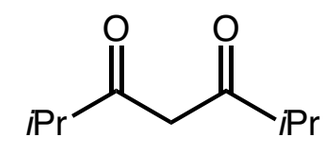


60 examples

ligand

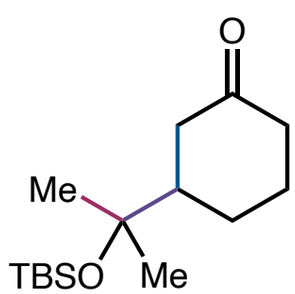


(acac)

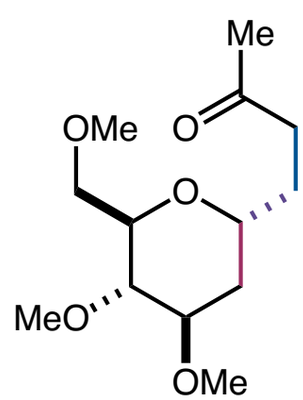


(dibm)

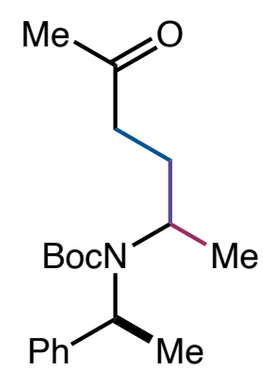
selected scope



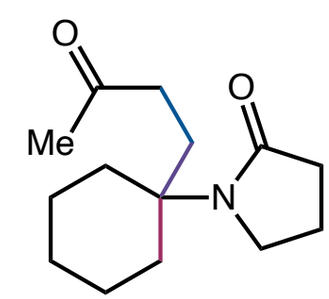
78% yield



64% yield
>99:1 *dr*



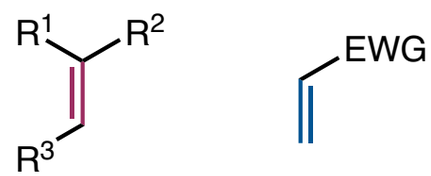
42% yield
1.4:1 *dr*



48% yield

Lo, J. C.; Gui, J.; Yabe, Y.; Pan, C.-M.; Baran, P. S. *Nature* **2014**, *516*, 343–348.

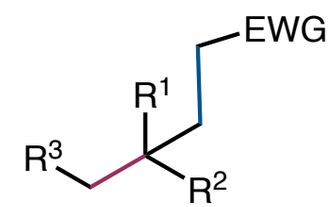
Second-Generation Conjugate Addition



R = carbon/hydrogen
and *heteroatom*

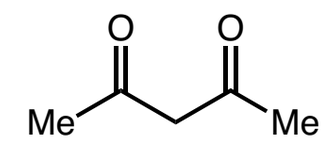
5-100 mol% Fe(ligand)$_3$
$PhSiH_3$

EtOH or *n*PrOH
rt to 80 °C
Na_2HPO_4

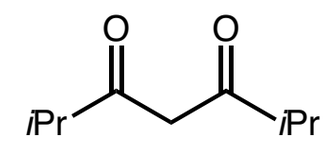


60 examples

ligand

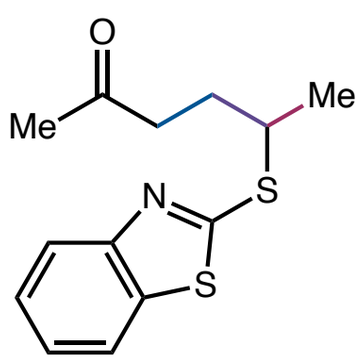


(acac)

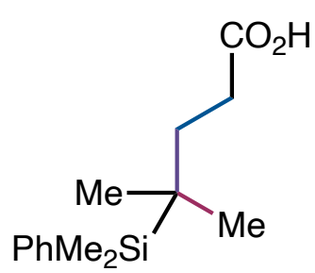


(dibm)

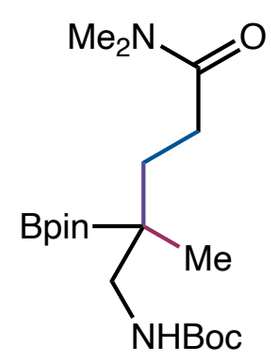
selected scope



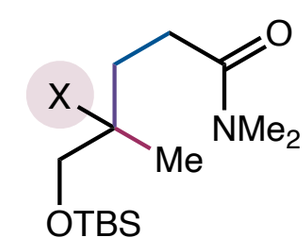
54% yield



53% yield



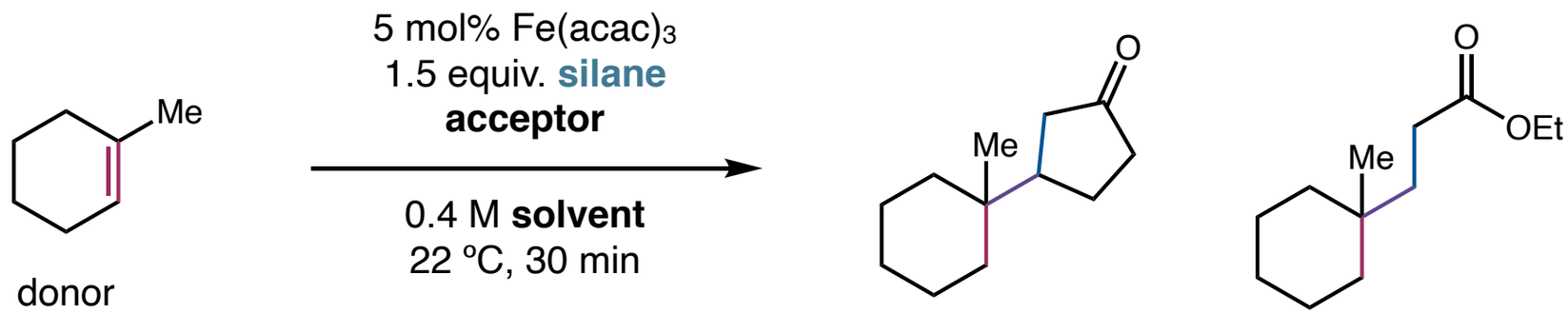
32% yield



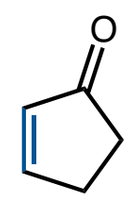
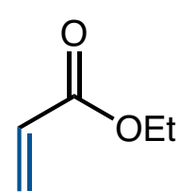
X = F **(48% yield)**
X = Cl **(60% yield)**
X = Br **(42% yield)**
X = I **(37% yield)**

Lo, J. C.; Gui, J.; Yabe, Y.; Pan, C.-M.; Baran, P. S. *Nature* **2014**, *516*, 343–348.

Comparison of Silane in Conjugate Addition

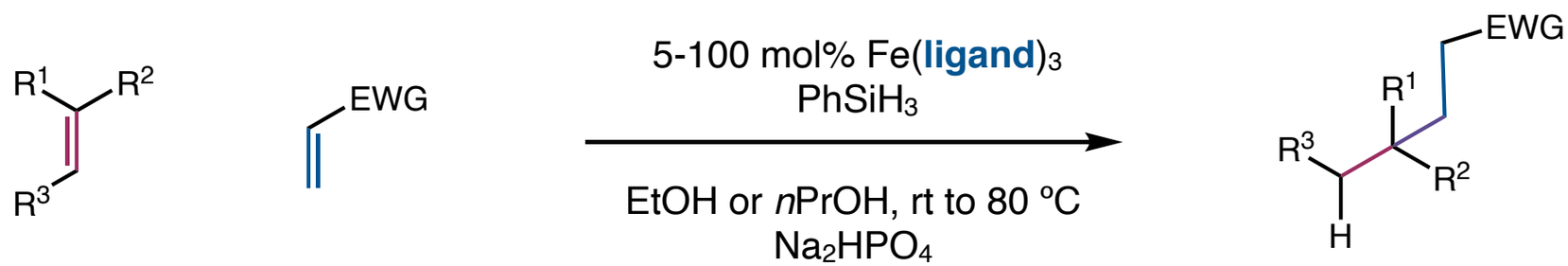


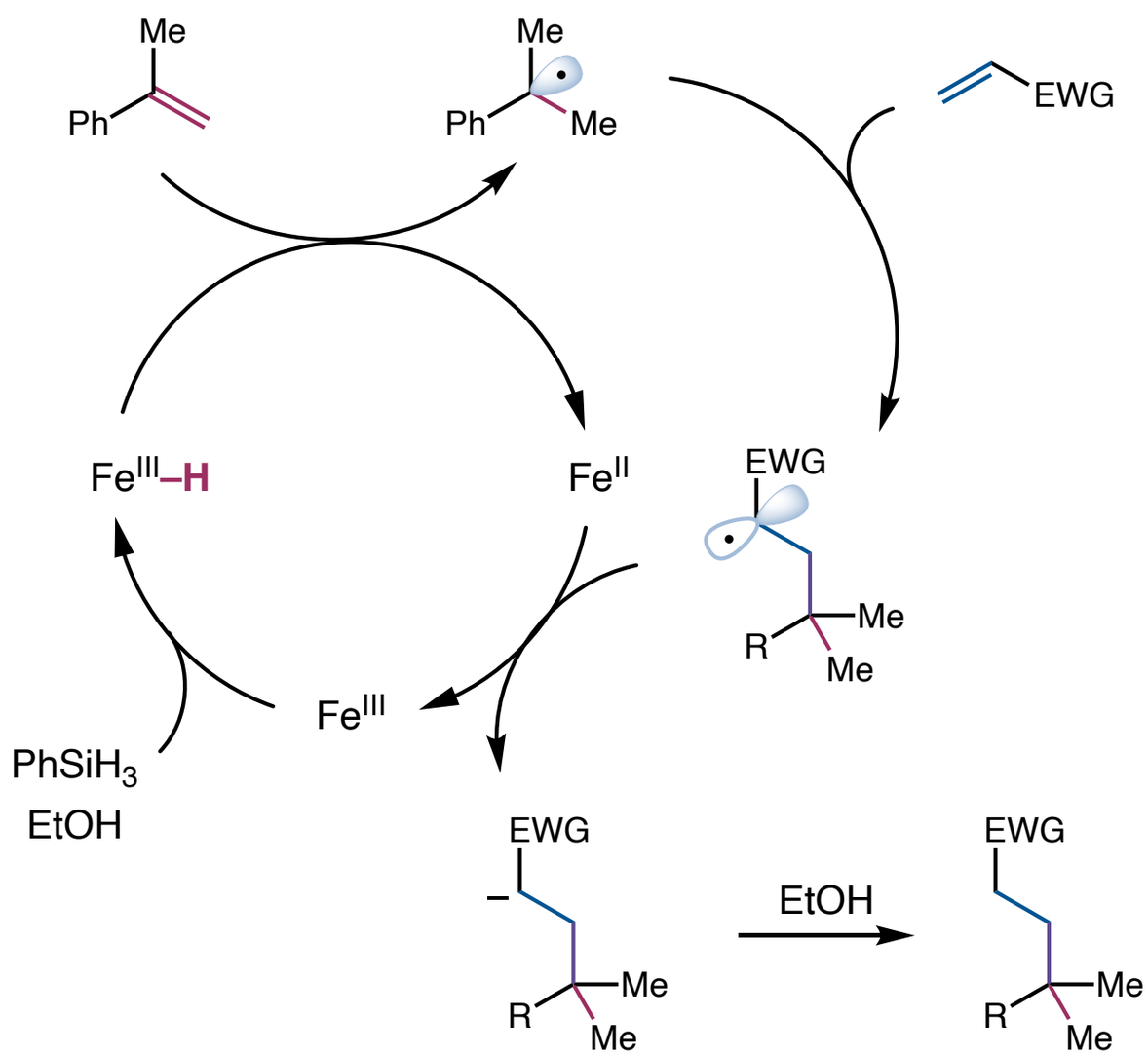
$PhSiH_3$ → *$Ph(iPrO)SiH_2$*

solvent	silane	acceptor	yield
*i*PrOH	$PhSiH_3$		13%
***i*PrOH : DCM 1:1**	**$Ph(iPrO)SiH_2$**		**69%**
*i*PrOH	$PhSiH_3$		22%
***i*PrOH : DCM 1:1**	**$Ph(iPrO)SiH_2$**		**89%**

Obradors, C.; Martinez, R. M.; Shenvi, R. A. *J. Am. Chem. Soc.* **2016**, *138*, 4962–4971.

Mechanism of Conjugate Addition

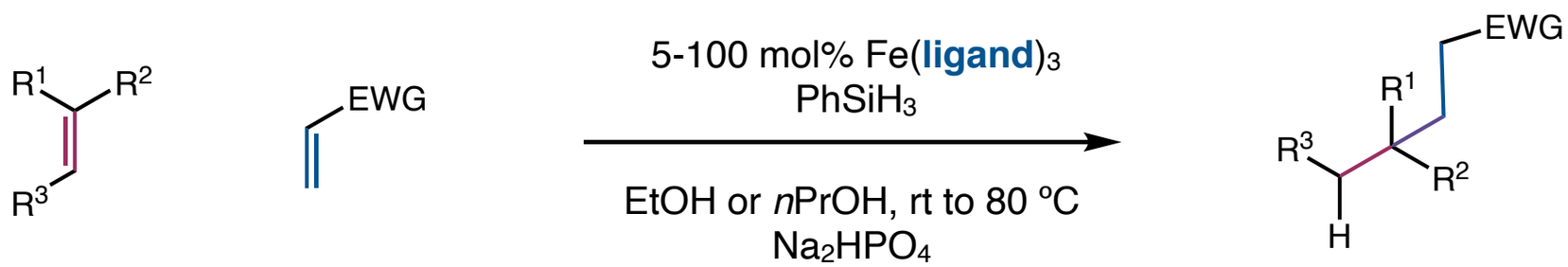




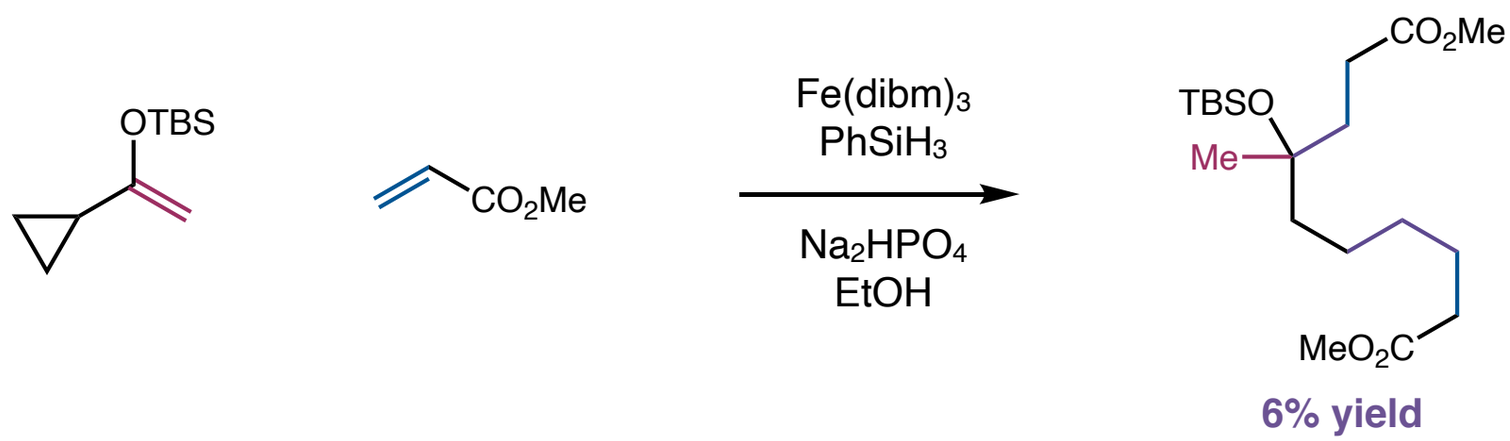
Lo, J. C.; Yabe,Y.; Baran, P. S. *J. Am. Chem. Soc.* **2014**, *136*, 1304–1307.

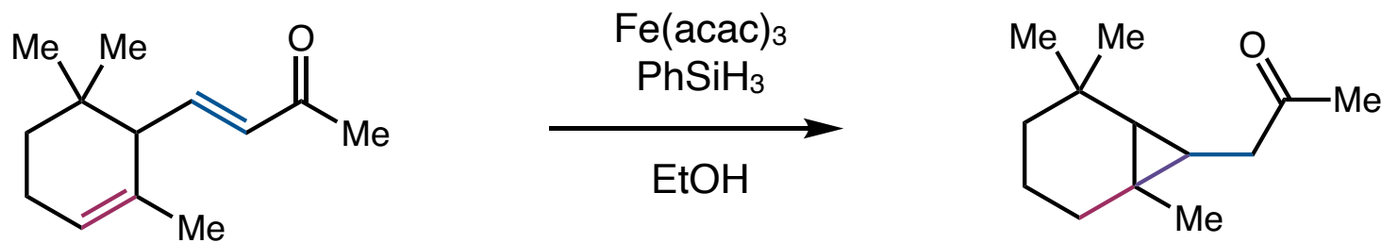
Lo, J. C.; Gui, J.; Yabe, Y.; Pan, C.-M.; Baran, P. S. *Nature* **2014**, *516*, 343–348.

Mechanism of Conjugate Addition



radical trap experiments

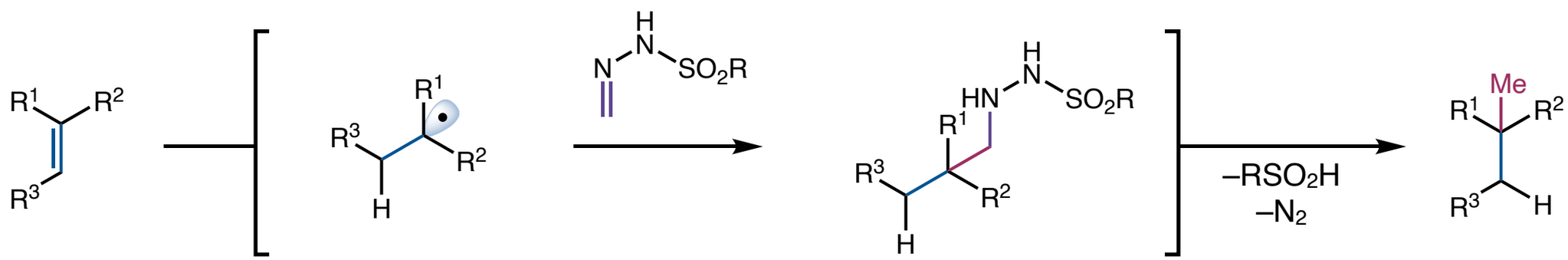




Lo, J. C.; Yabe,Y.; Baran, P. S. *J. Am. Chem. Soc.* **2014**, *136*, 1304–1307.

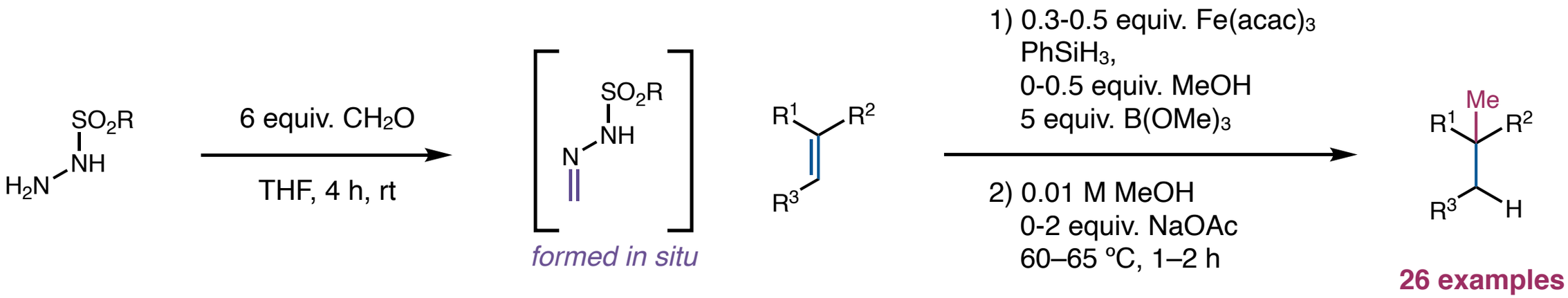
Lo, J. C.; Gui, J.; Yabe, Y.; Pan, C.-M.; Baran, P. S. *Nature* **2014**, *516*, 343–348.

Hydromethylation

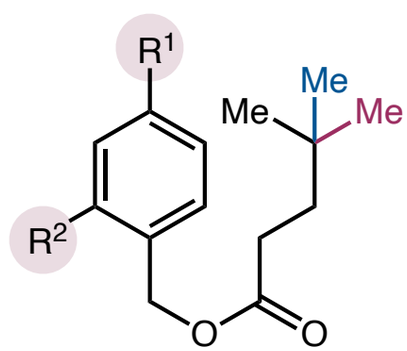


Dao, H. T.; Li, C.; Michaudel, Q.; Maxwell, B. D.; Baran, P. S. *J. Am. Chem. Soc.* **2015**, *137*, 8046–8049.

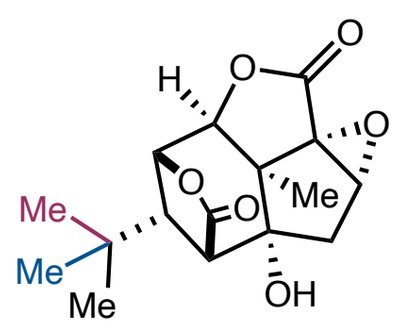
Hydromethylation



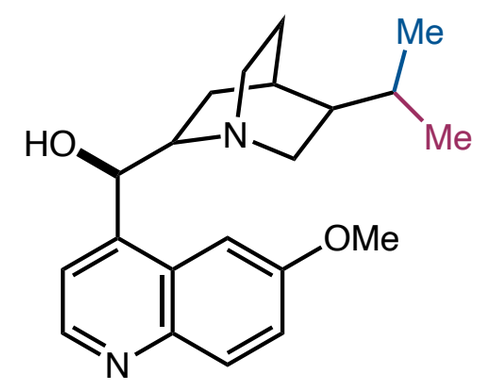
selected scope



$R^1 = N_3$, $R^2 = H$ **(42% yield)**
$R^1 = Bpin$, $R^2 = H$ **(47% yield)**
$R^1 = H$, $R^2 = C^oC–TMS$ **(55% yield)**
$R^1 = H$, $R^2 = CH_2OH$ **(61% yield)***



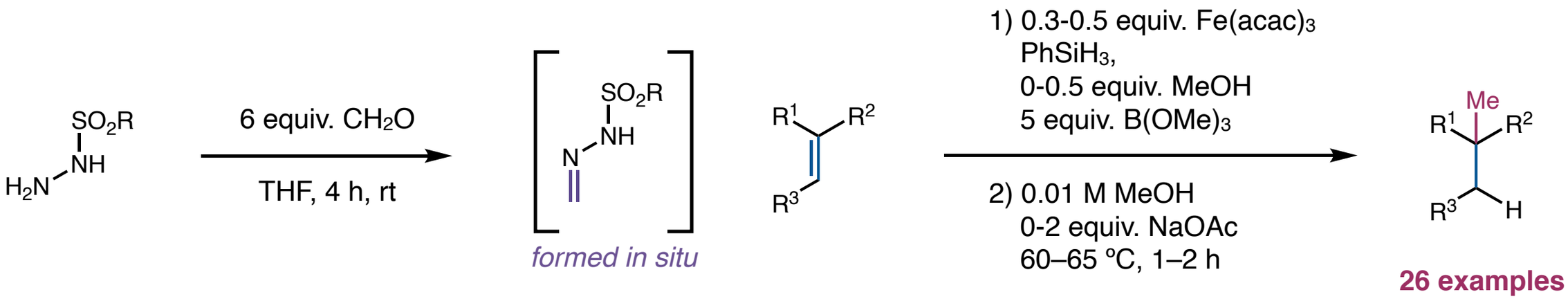
32% yield*



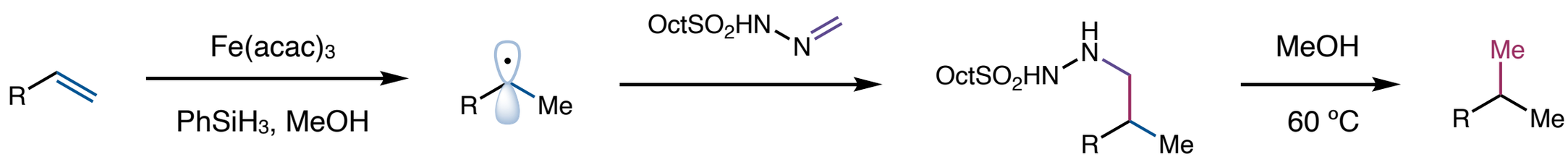
32% yield*

Dao, H. T.; Li, C.; Michaudel, Q.; Maxwell, B. D.; Baran, P. S. *J. Am. Chem. Soc.* **2015**, *137*, 8046–8049.

Hydromethylation



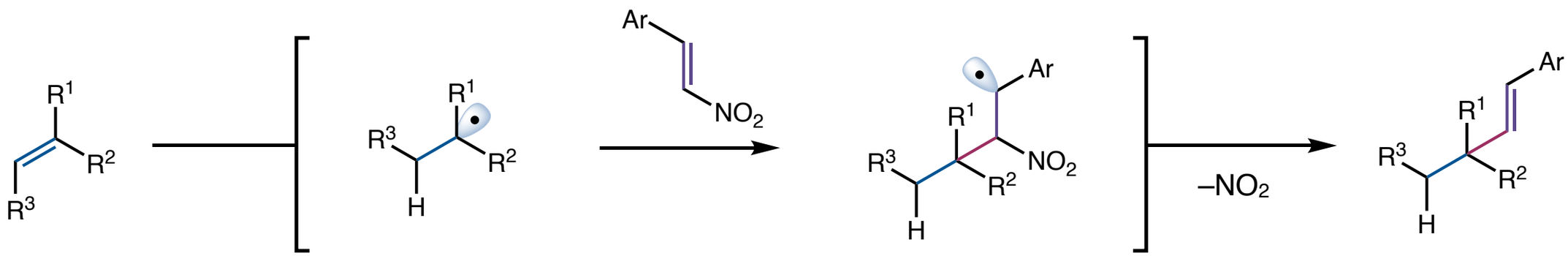
mechanistic studies



supported by isotope labeling experiments

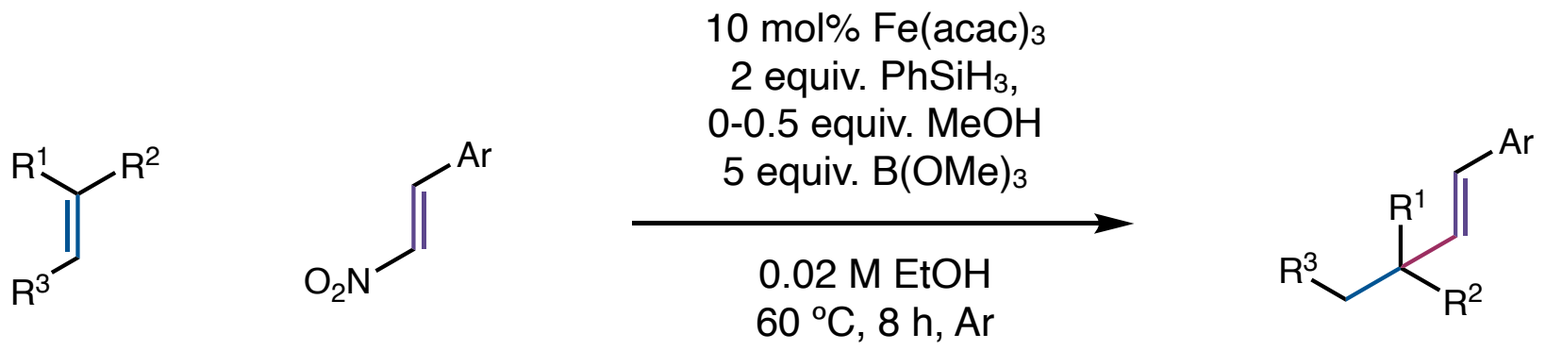
Dao, H. T.; Li, C.; Michaudel, Q.; Maxwell, B. D.; Baran, P. S. *J. Am. Chem. Soc.* **2015**, *137*, 8046–8049.

Hydrostyrenylation



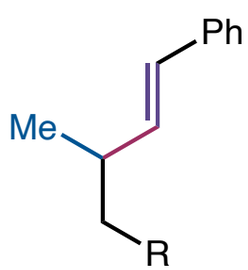
Zheng, J.; Wang, D.; Cui, S. *Org. Lett.* **2015**, *17*, 4572–4575.

Radical Conjugate Addition-Elimination

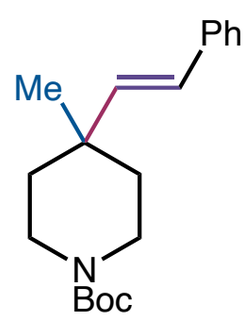


26 examples

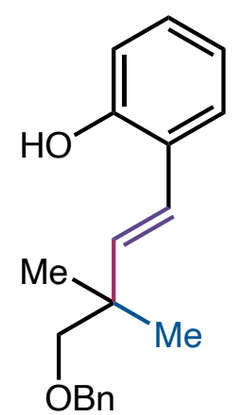
selected scope



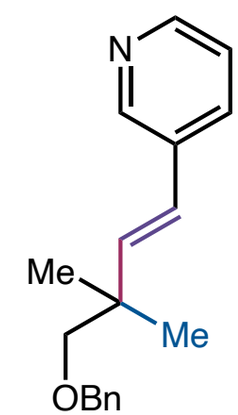
R = TMS **(45% yield)**
R = CN **(56% yield)**



42% yield



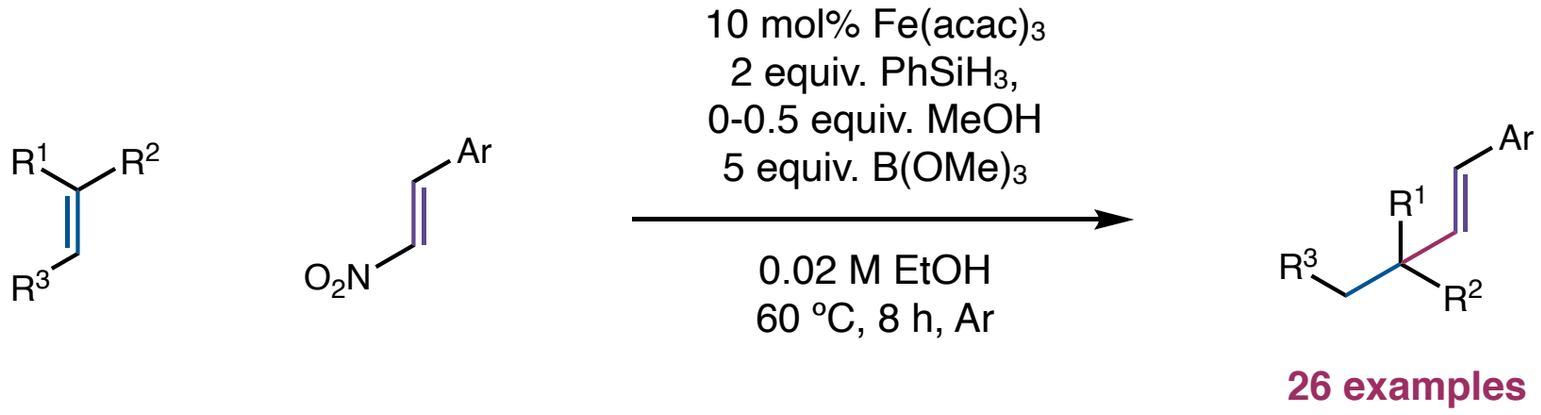
50% yield



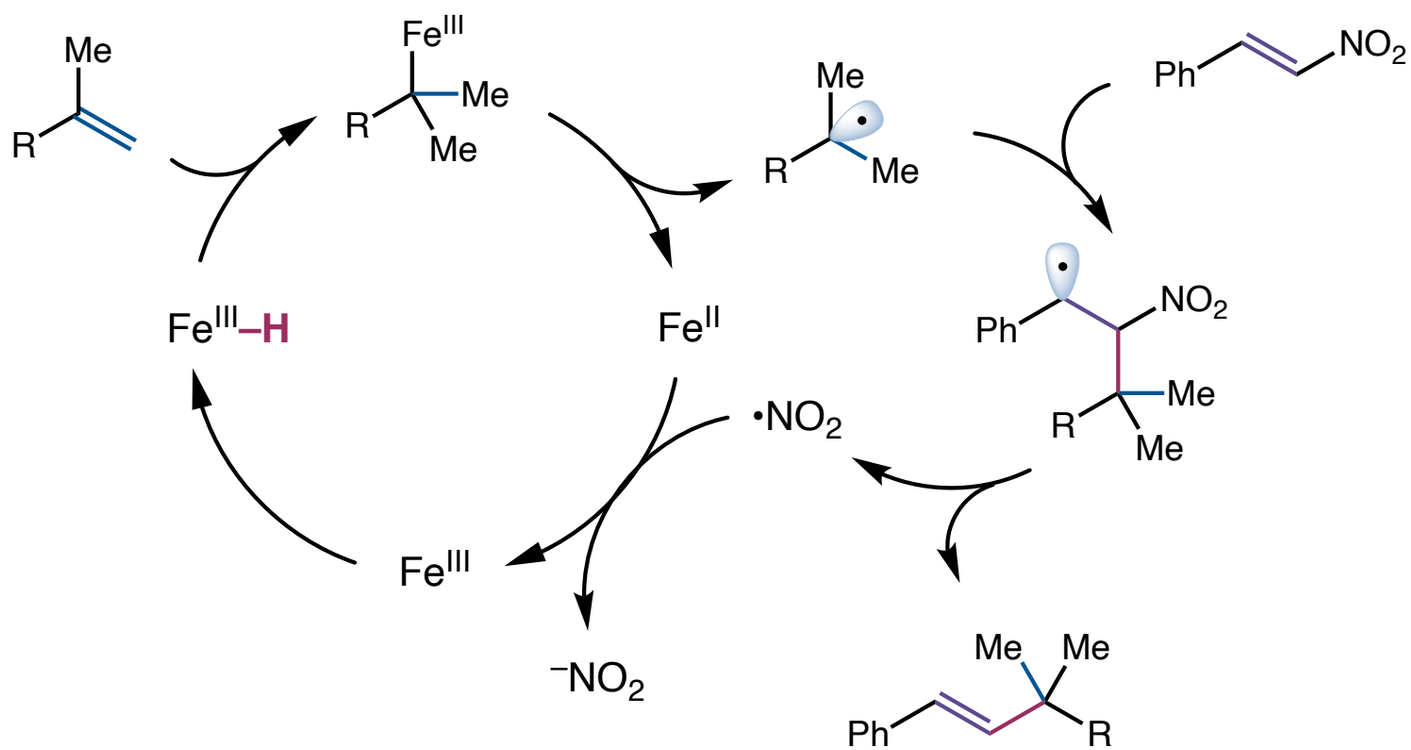
48% yield

Zheng, J.; Wang, D.; Cui, S. *Org. Lett.* **2015**, *17*, 4572–4575.

Radical Conjugate Addition-Elimination

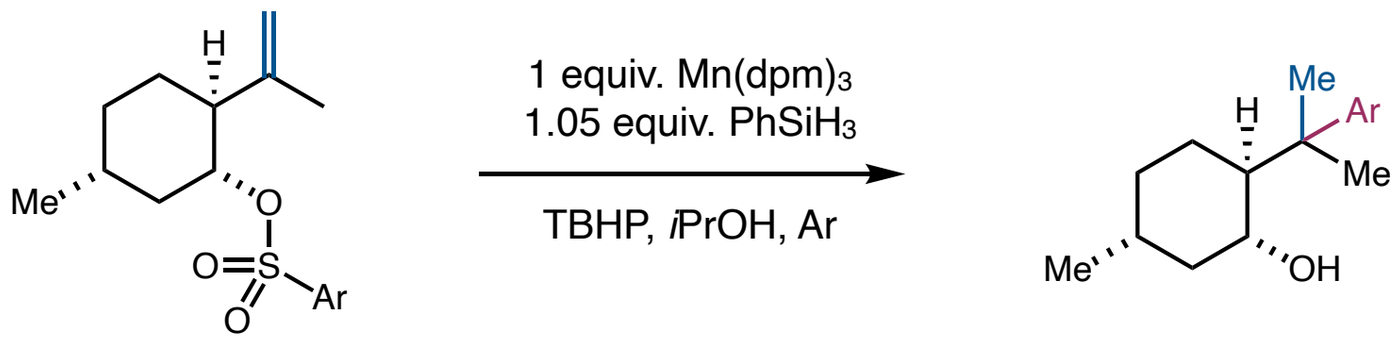


proposed mechanism



Zheng, J.; Wang, D.; Cui, S. *Org. Lett.* **2015**, *17*, 4572–4575.

HAT Initiated Smiles-Truce Rearrangement



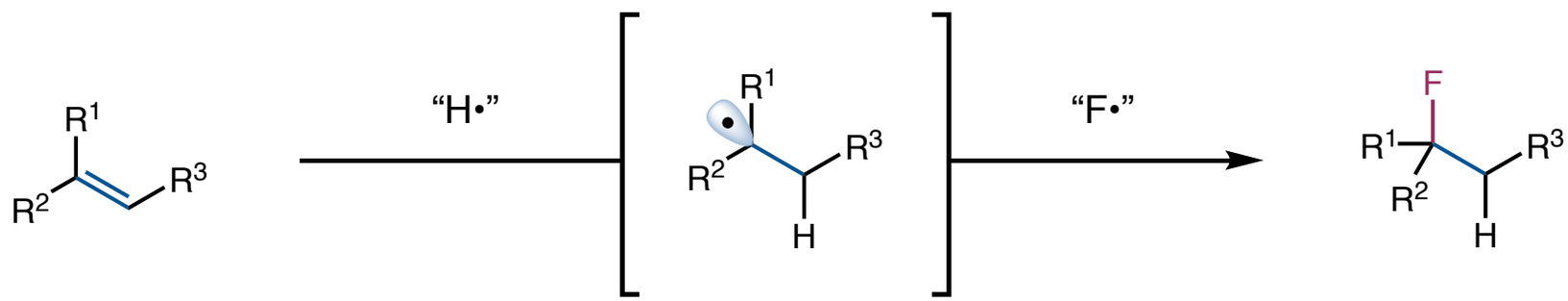
21 substrates
15–91% yield

Crossley, S. W. M.; Martinez, R. M.; Guevara-Zuluaga, S.; Shenvi, R. A. *Org. Lett.* **2016**, *18*, 2620–2623.

Outline

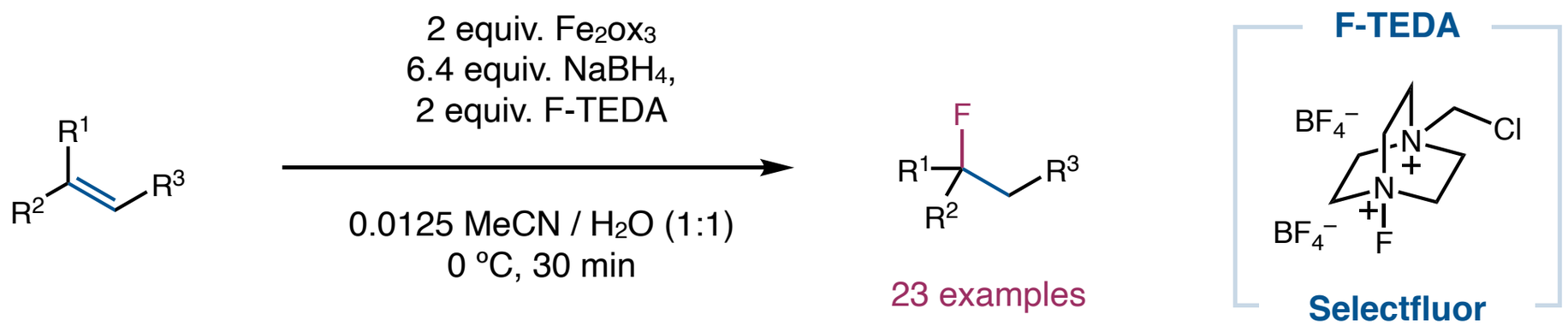
- C–O Bond Formation
- C–N Bond Formation
- C–C Bond Formation
- **C–X Bond Formation**
- Hydrogenation and Isomerization
- General Mechanistic Considerations

Radical Hydrofluorination of Olefins

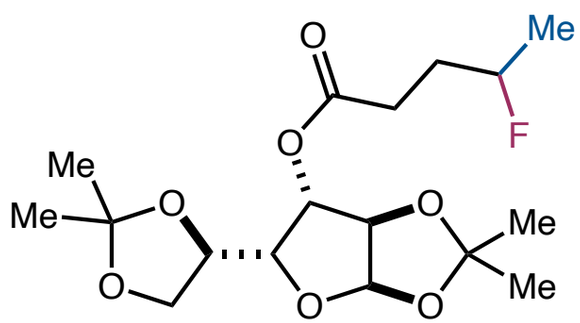


Barker, T. J.; Boger, D. L. *J. Am. Chem. Soc.* **2012**,*134*, 10401–10404.

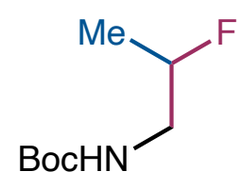
Radical Hydrofluorination of Olefins



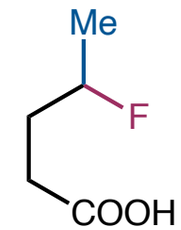
selected scope



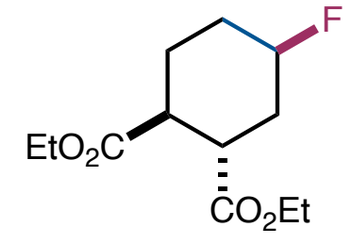
72% yield



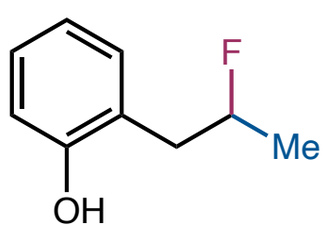
61% yield



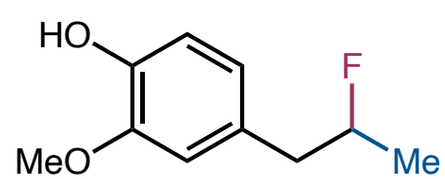
66% yield



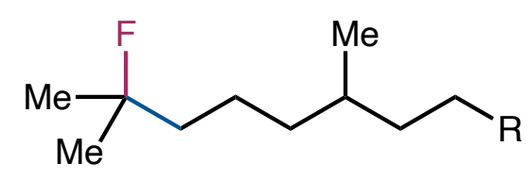
52% yield
5:1 *dr*



60% yield



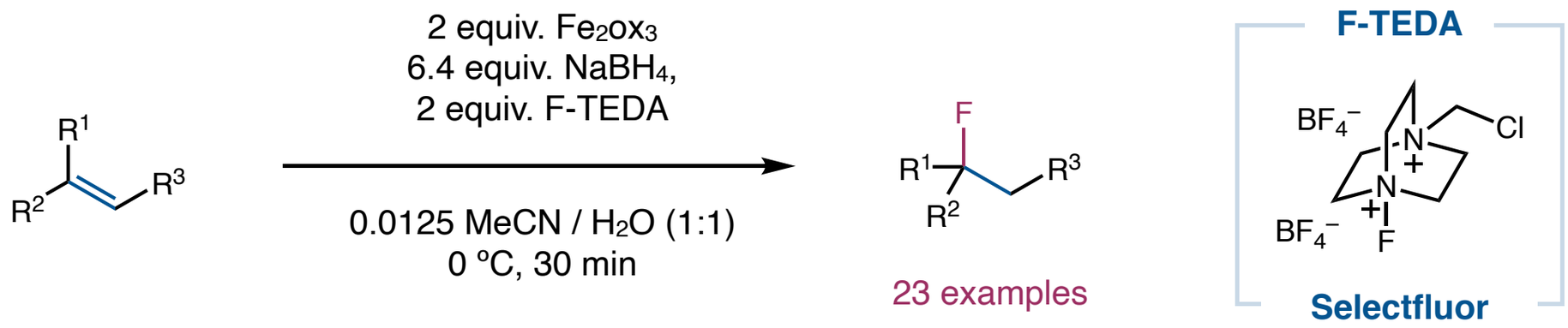
54% yield



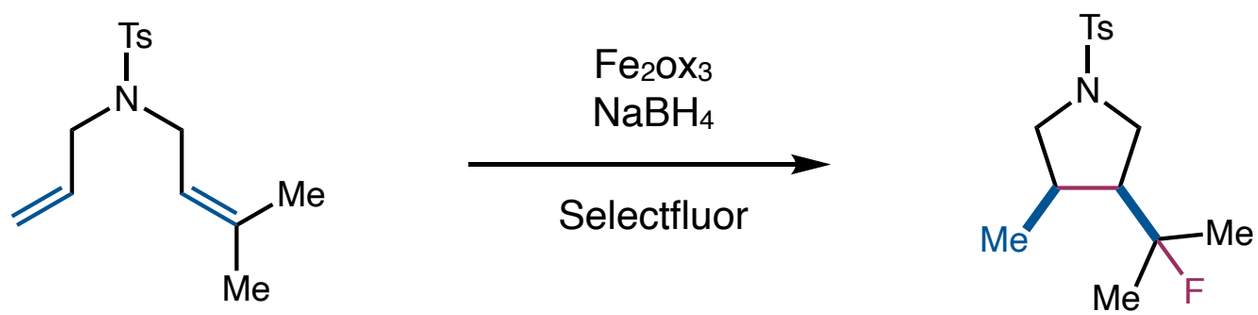
R = NH_2 **(52% yield)**
R = OH **(70% yield)**

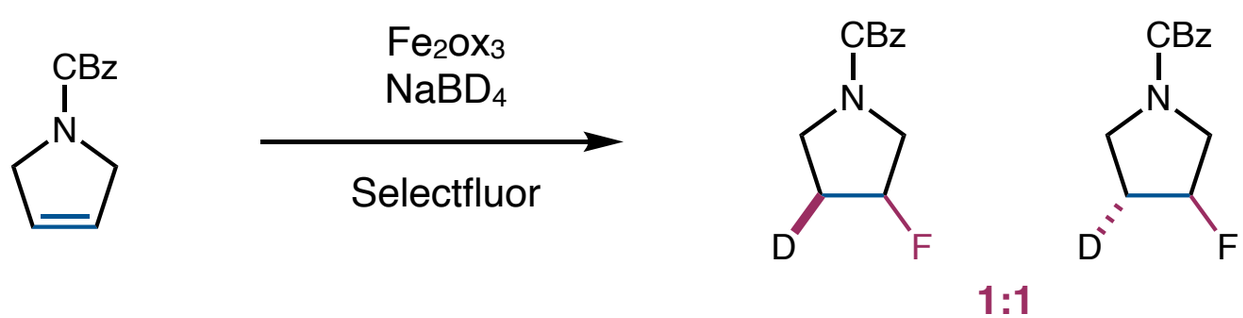
Barker, T. J.; Boger, D. L. *J. Am. Chem. Soc.* **2012**, *134*, 10401–10404.

Radical Hydrofluorination of Olefins



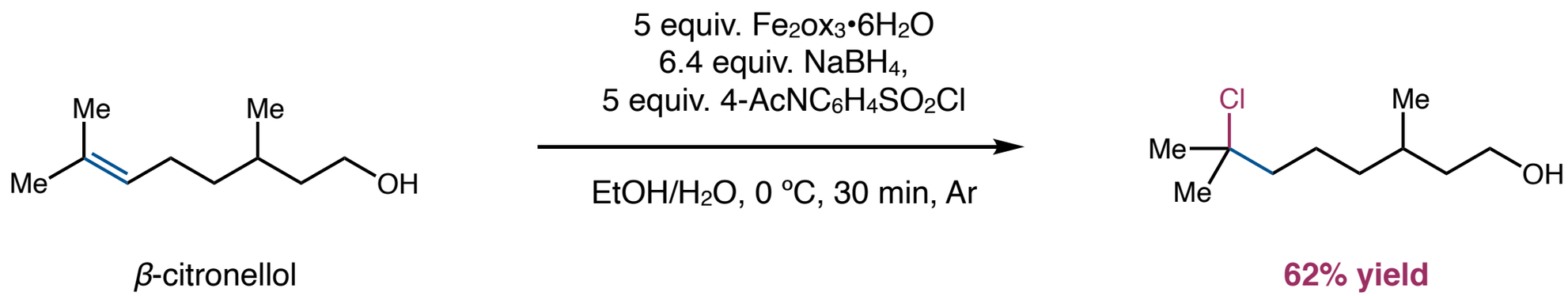
mechanistic studies





Barker, T. J.; Boger, D. L. *J. Am. Chem. Soc.* **2012**, *134*, 10401–10404.

Hydrochlorination

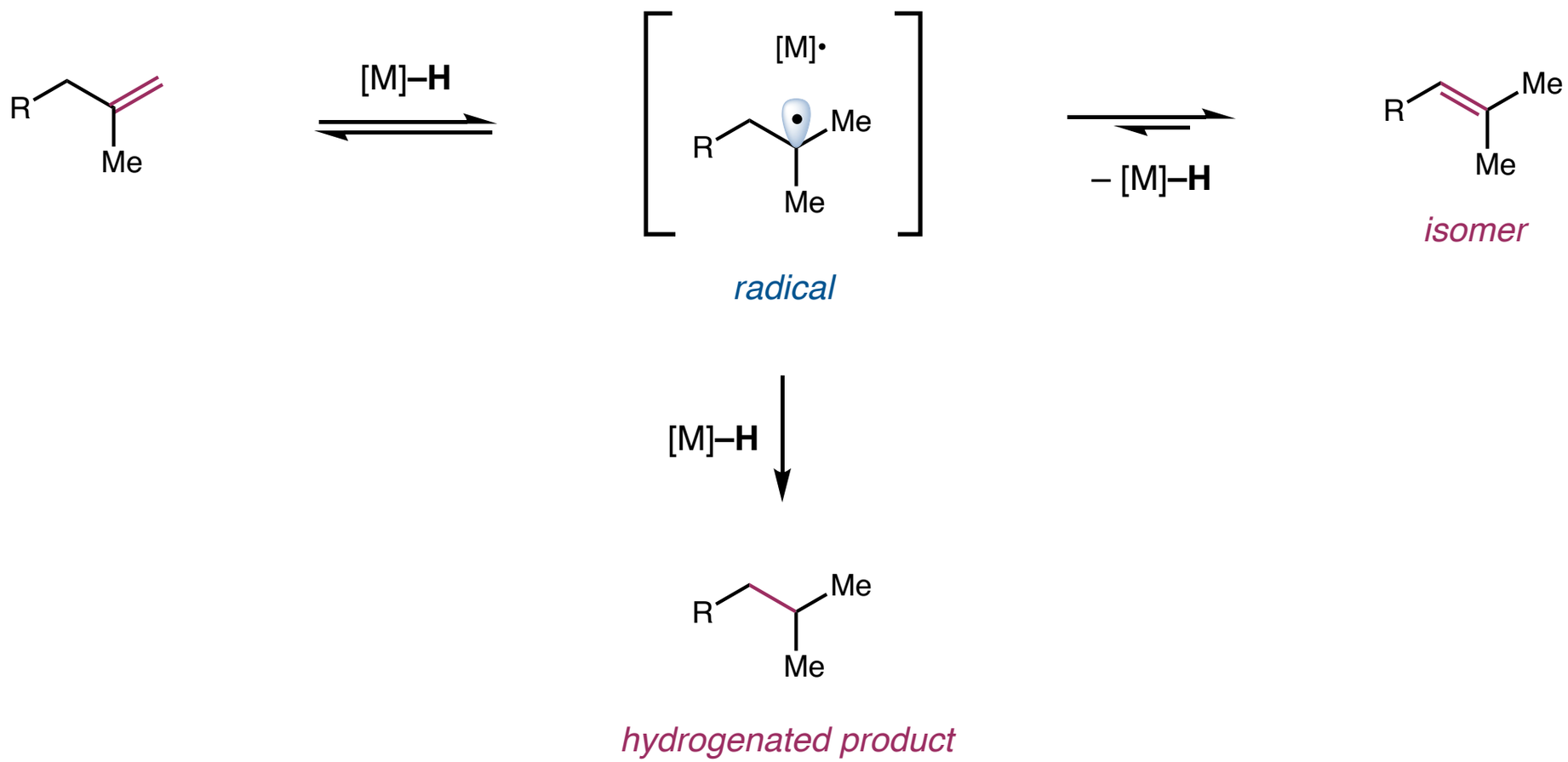


Leggans, E. K.; Barker, T. J.; Duncan, K. K.; Boger, D. L. *Org. Lett.* **2012**, *14*, 1428–1431.

Outline

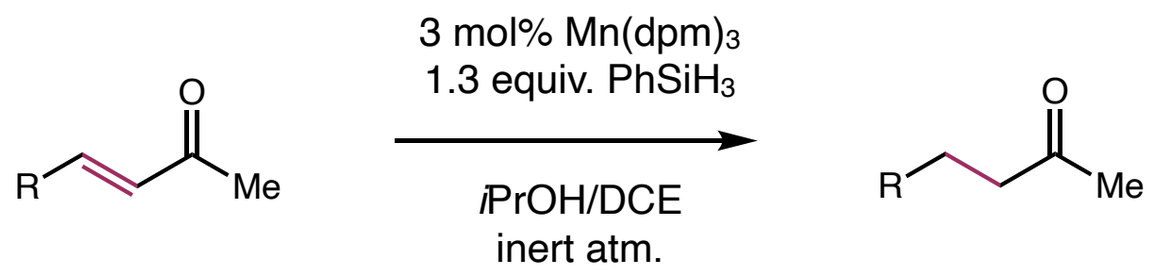
- C–O Bond Formation
- C–N Bond Formation
- C–C Bond Formation
- C–X Bond Formation
- **Hydrogenation and Isomerization**
- General Mechanistic Considerations

Hydrogenation versus Isomerization Pathways

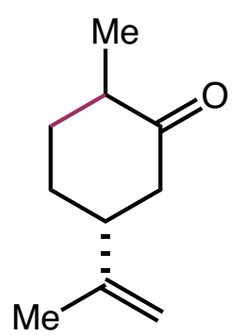


Crossley, S. W. M.; Obradors, C.; Martinez, R. M.; Shenvi, R. A. *Chem. Rev.* **2016**, *116*, 8912–9000.

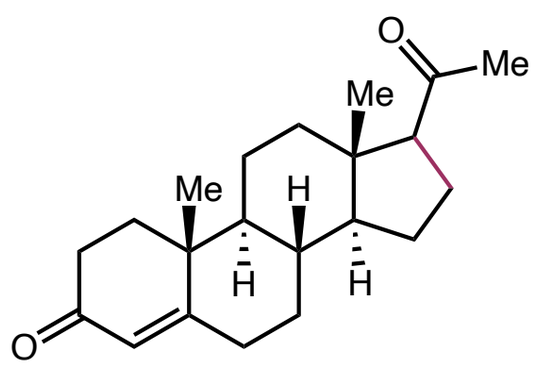
Conjugate Reduction



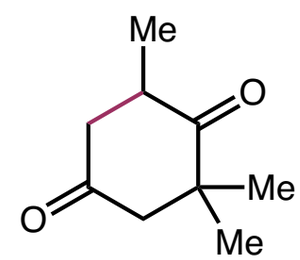
selected scope



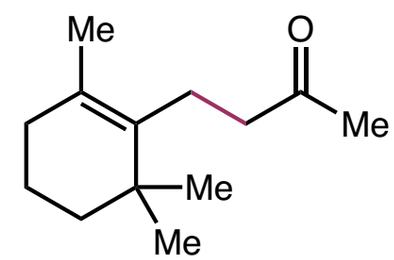
50% yield



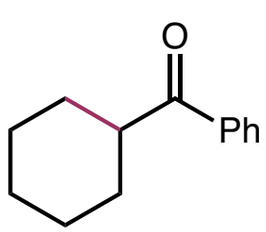
99% yield



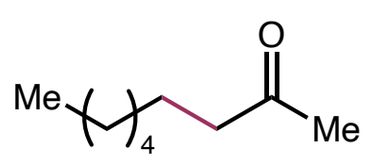
99% yield



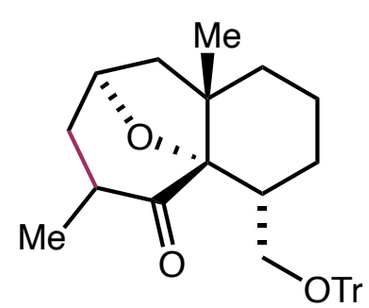
25% yield



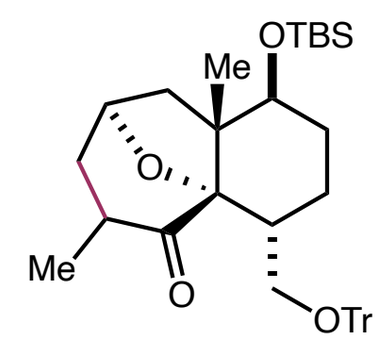
50% yield



74% yield



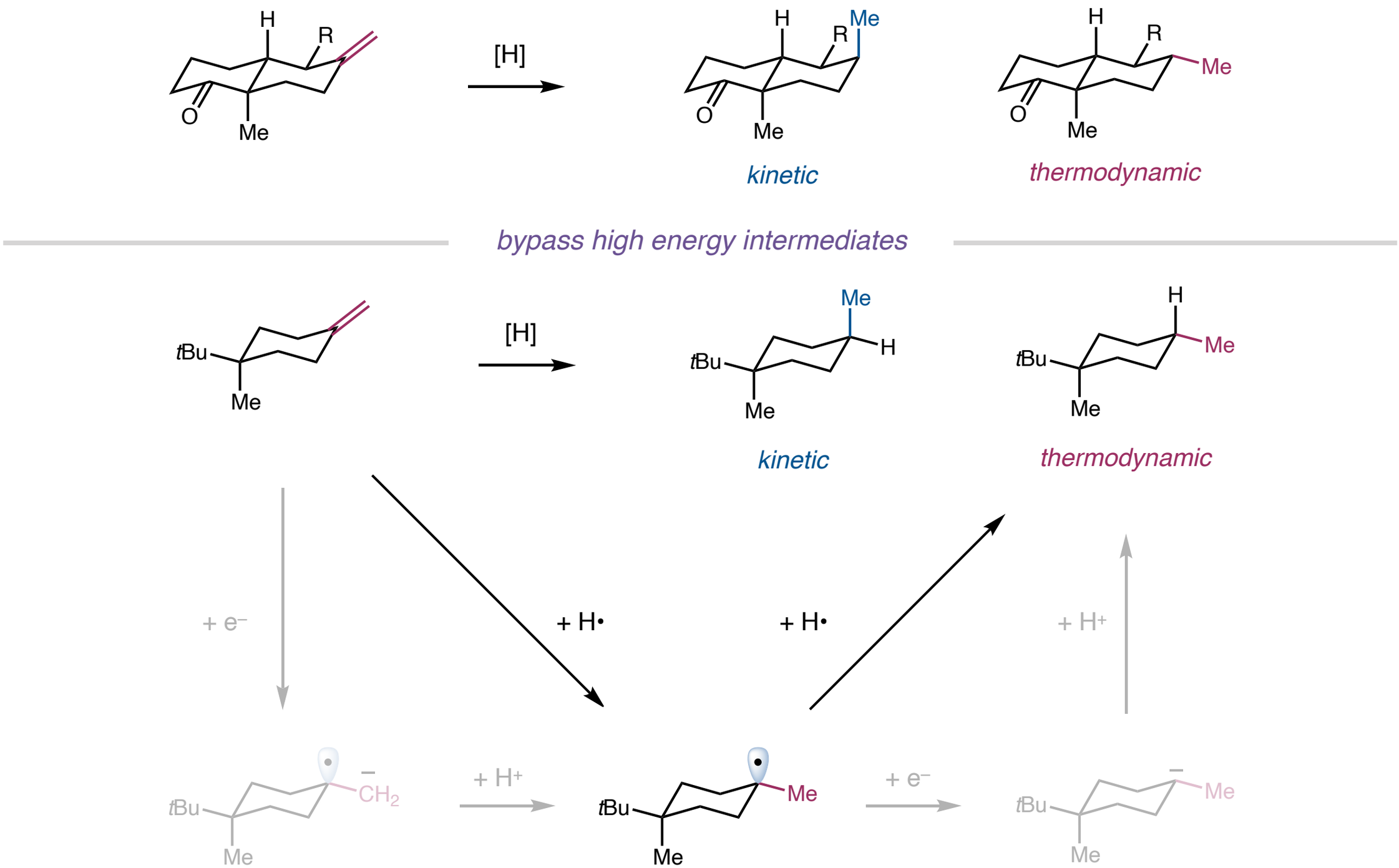
100% yield



100% yield

Magnus, P.; Waring, M. J.; Scott, D. A. *Tetrahedron Lett.* **2020**, *41*, 9731–9733.

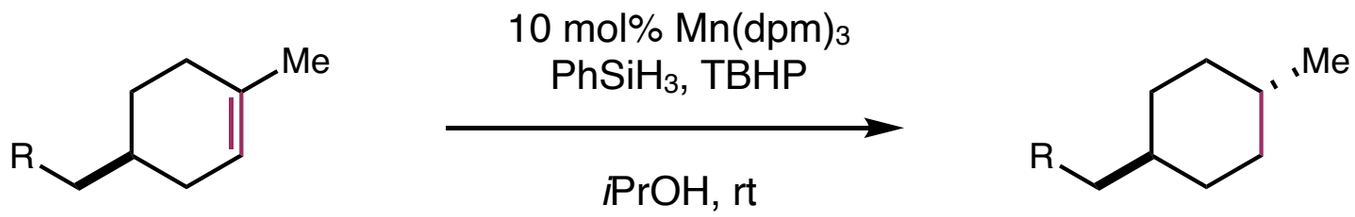
Chemo- and Stereoselective HAT Hydrogenation



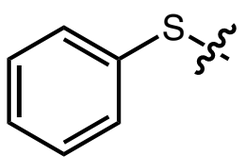
Wan, K. K.; Iwasaki, K.; Umotoy, J. C.; Wolan, D. W.; Shenvi, R. A. *Angew. Chem. Int. Ed.* **2015**, *27*, 1145–1164.

Wan, K. K.; Shenvi, R. A. *Synlett* **2016**, *27*, 1145–1164.

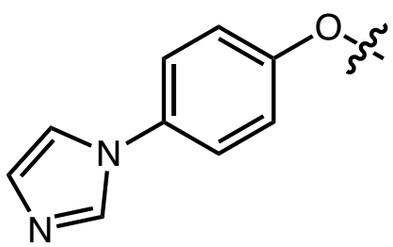
Hydrogenation of Unactivated Alkenes



selected scope

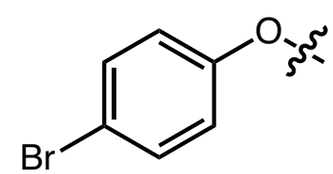


82% yield
5:1 *dr*



84% yield
5:1 *dr*

83% yield
5:1 *dr*

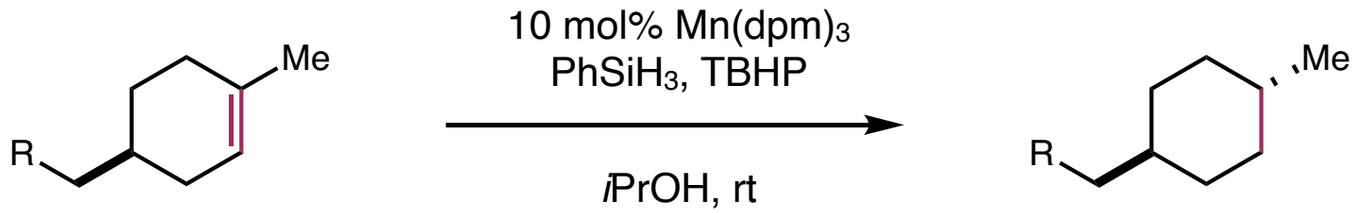


80% yield
5:1 *dr*

Wan, K. K.; Iwasaki, K.; Umotoy, J. C.; Wolan, D. W.; Shenvi, R. A. *Angew. Chem. Int. Ed.* **2015**, *27*, 1145–1164.

Wan, K. K.; Shenvi, R. A. *Synlett* **2016**, *27*, 1145–1164.

Hydrogenation of Unactivated Alkenes



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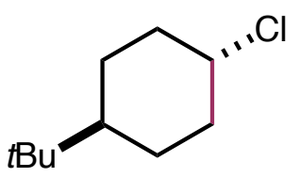
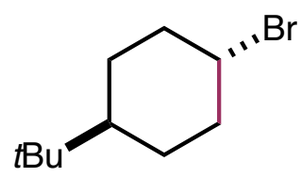
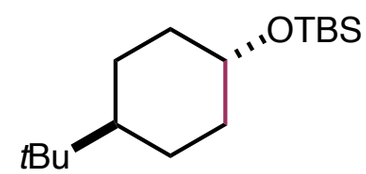


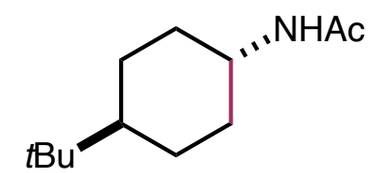
71% yield
3.7:1 *dr*



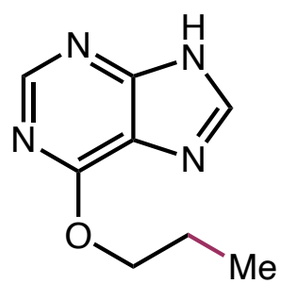
67% yield
3.7:1 *dr*



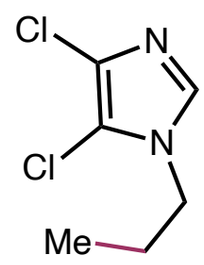
78% yield
3.9:1 *dr*



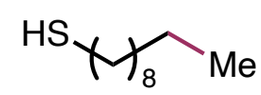
72% yield
6.7:1 *dr*



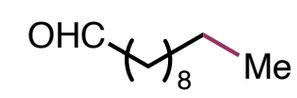
71% yield
3.7:1 *dr*



67% yield
3.7:1 *dr*



78% yield
3.9:1 *dr*

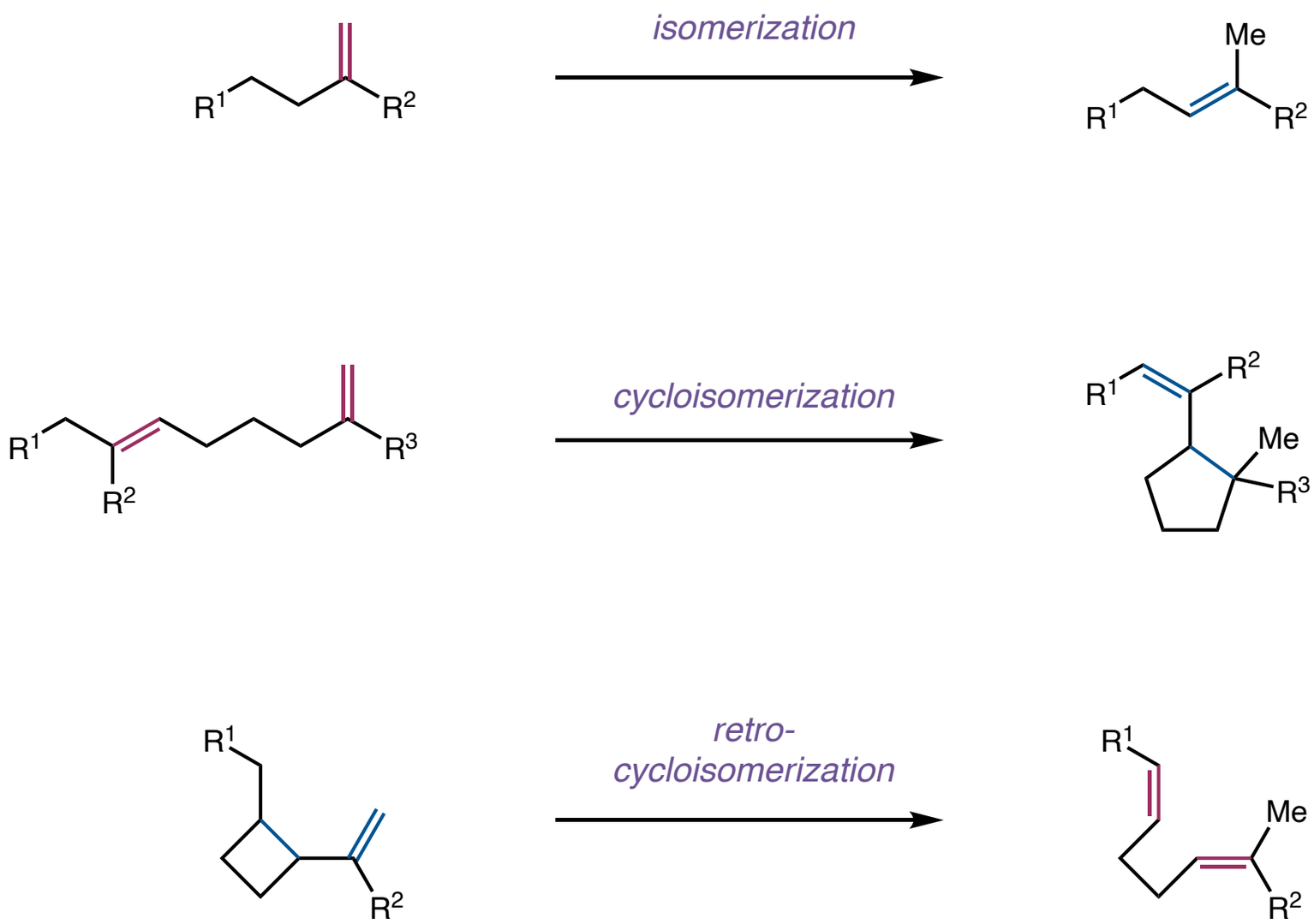


72% yield
6.7:1 *dr*

Wan, K. K.; Iwasaki, K.; Umotoy, J. C.; Wolan, D. W.; Shenvi, R. A. *Angew. Chem. Int. Ed.* **2015**, *27*, 1145–1164.

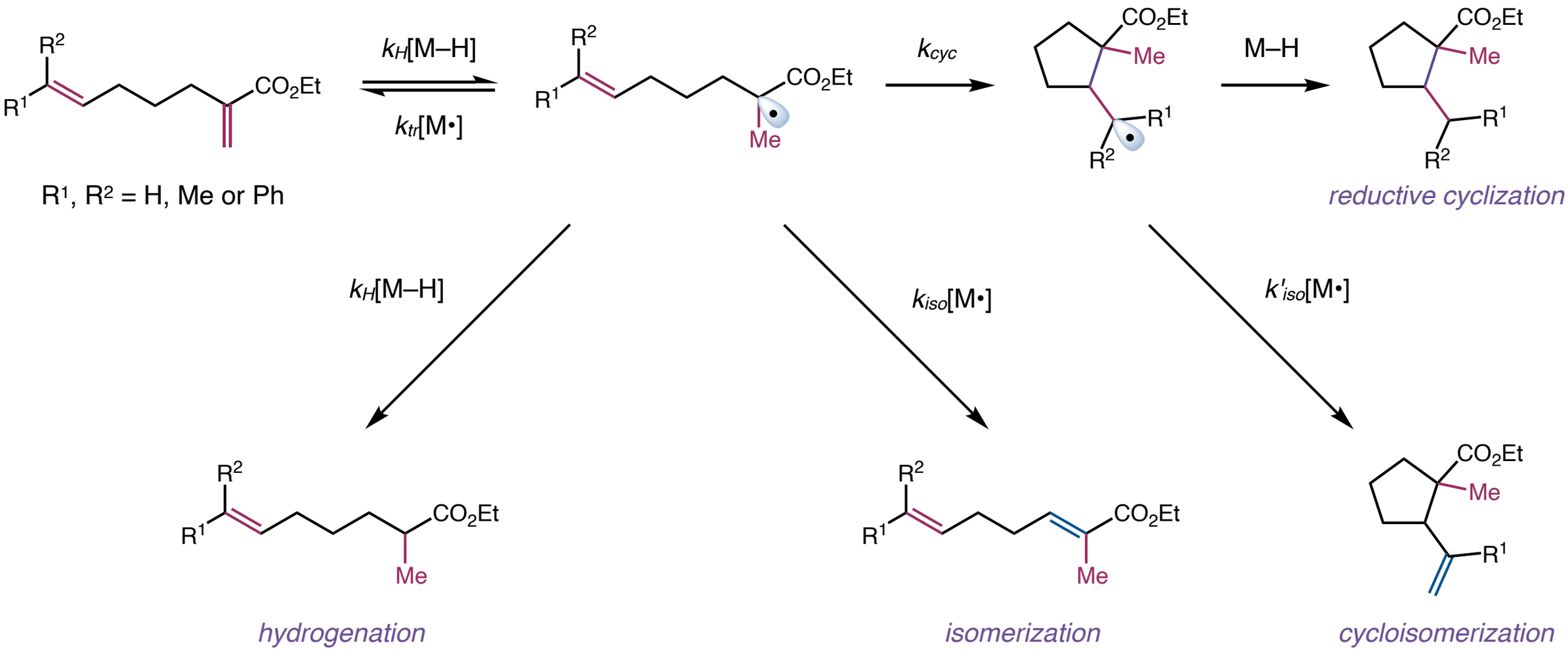
Wan, K. K.; Shenvi, R. A. *Synlett* **2016**, *27*, 1145–1164.

Isomerization



Biswas, S. *Comments Inorg. Chem.* **2015**, *35*, 300–330.

Possible Pathways via TM HAT

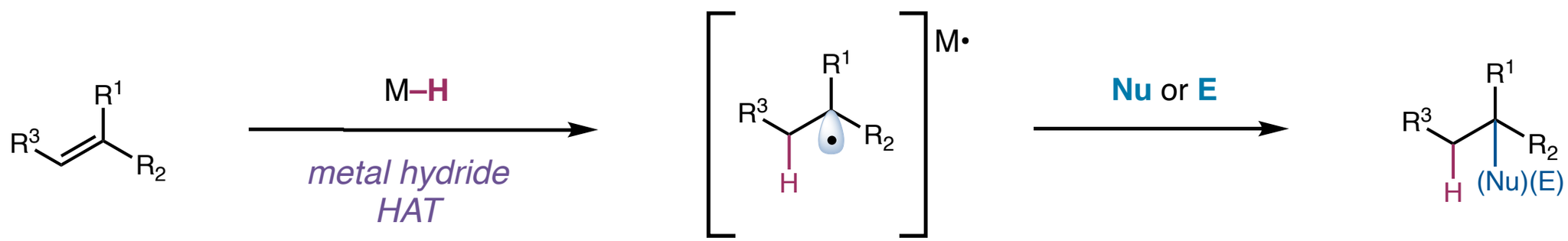


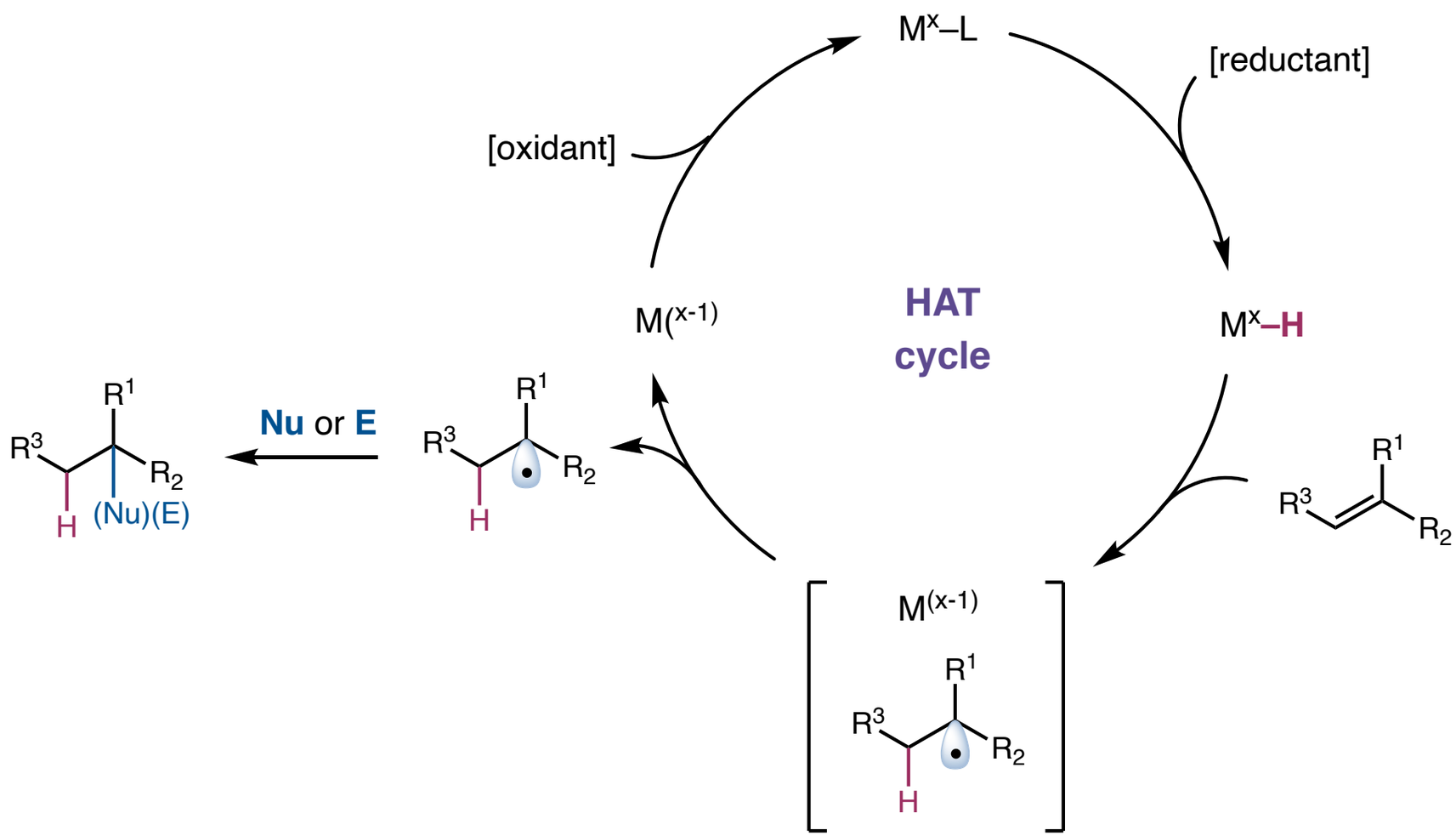
Han, A.; Spartaru, T.; Hartung, J., Jr.; Li, G.; Norton, J. R. *J. Org. Chem.* **2014**, *79*, 1938–1946.

Outline

- C–O Bond Formation
- C–N Bond Formation
- C–C Bond Formation
- C–X Bond Formation
- Hydrogenation and Isomerization
- **General Mechanistic Considerations**

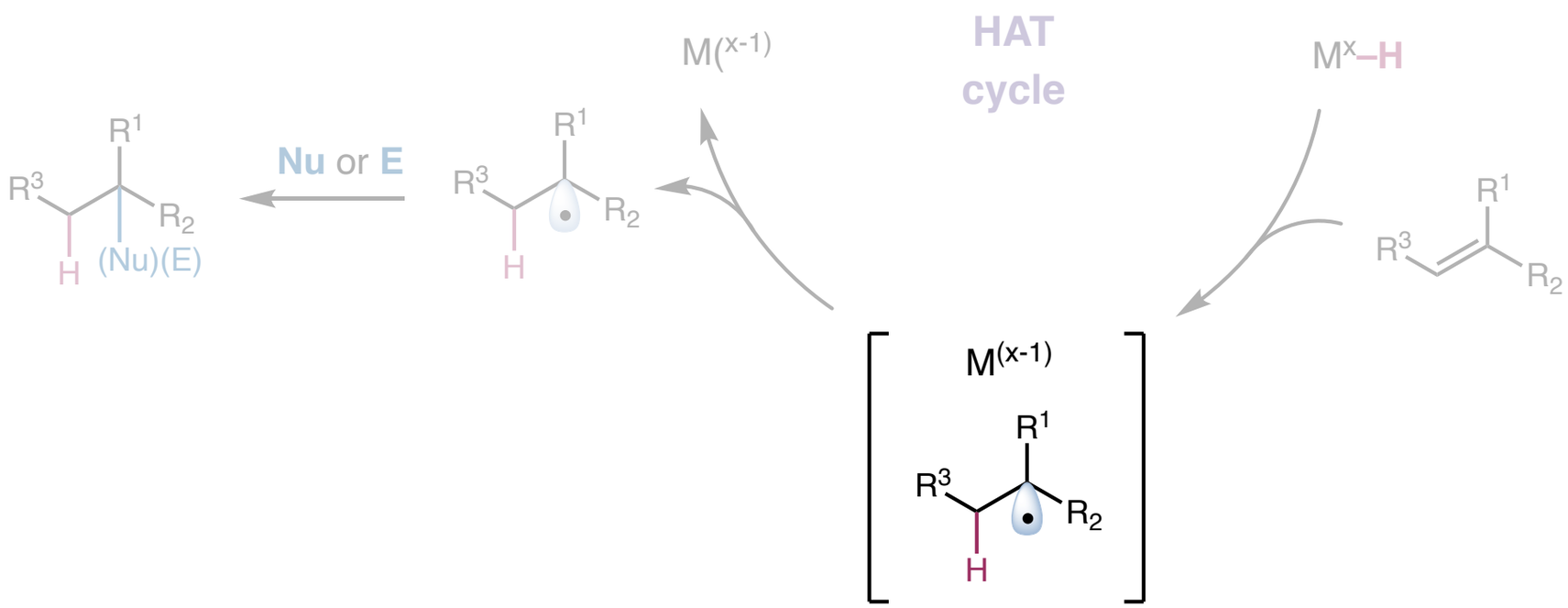
Reductive-Oxidative Cycle Towards Alkene Hydrofunctionalization

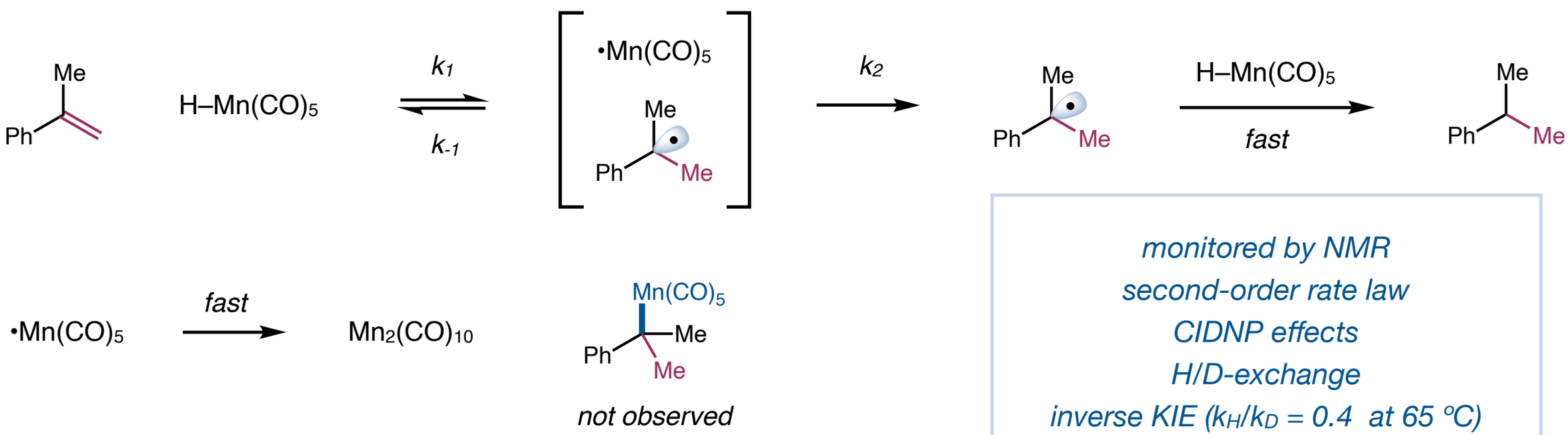




Crossley, S. W. M.; Barabé, F.; Shenvi, R. A. *J. Am. Chem. Soc.* **2014**, *136*, 16788–16791.

Formation of a Radical Pair

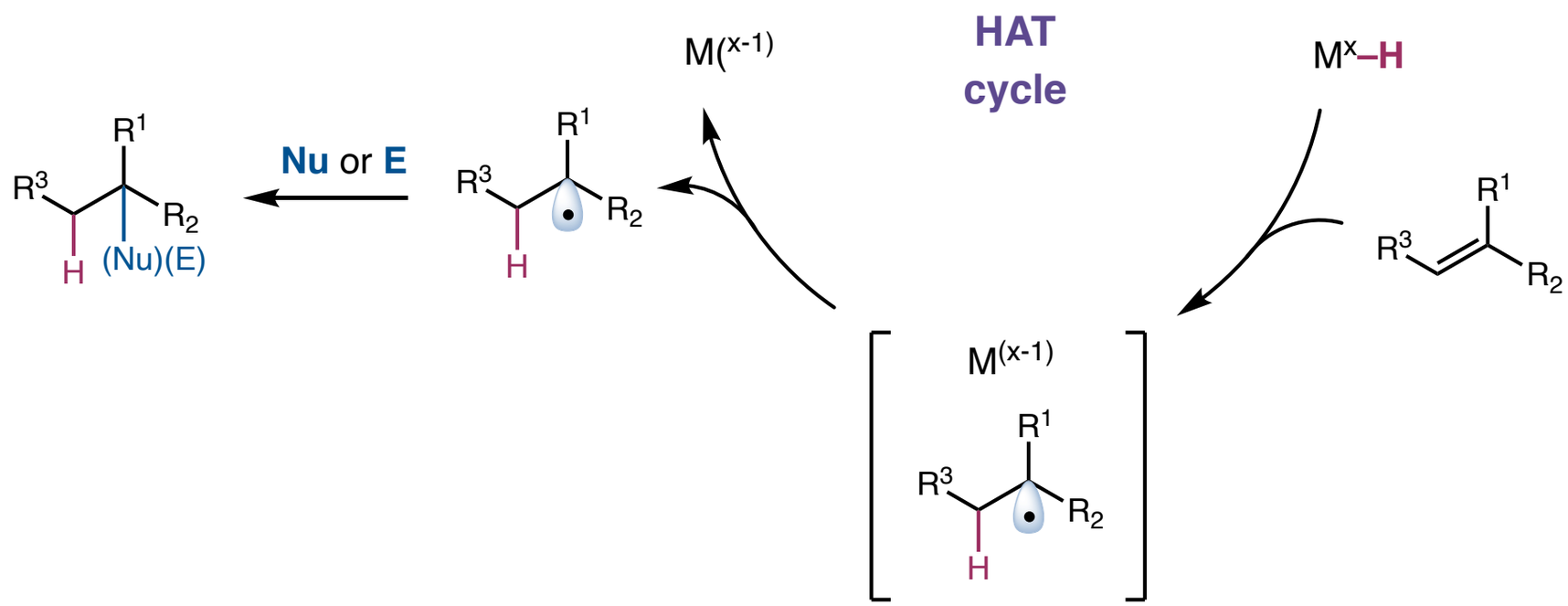




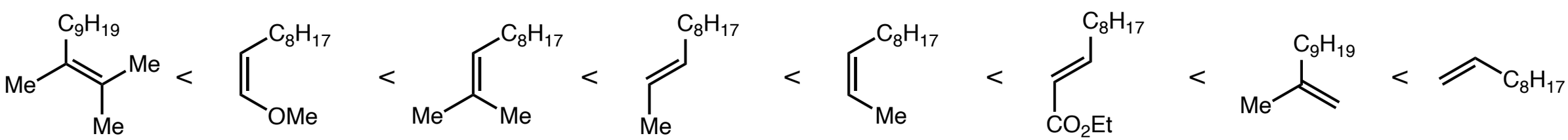
monitored by NMR
second-order rate law
CIDNP effects
H/D-exchange
inverse KIE (k_H/k_D = 0.4 at 65 °C)

Sweany, R. L.; Halpern, J. *J. Am. Chem. Soc.* **1977**, *99*, 8335–8337.

Reactivity of Alkenes



relative rates using $Mn(dpm)_3/PhSiH_3$ + TBHP – competitive consumption



decreased substitution increases rate of alkene consumption

EWG minorly accelerate rate of the reaction

Crossley, S. W. M.; Barabé, F.; Shenvi, R. A. *J. Am. Chem. Soc.* **2014**, *136*, 16788–16791.

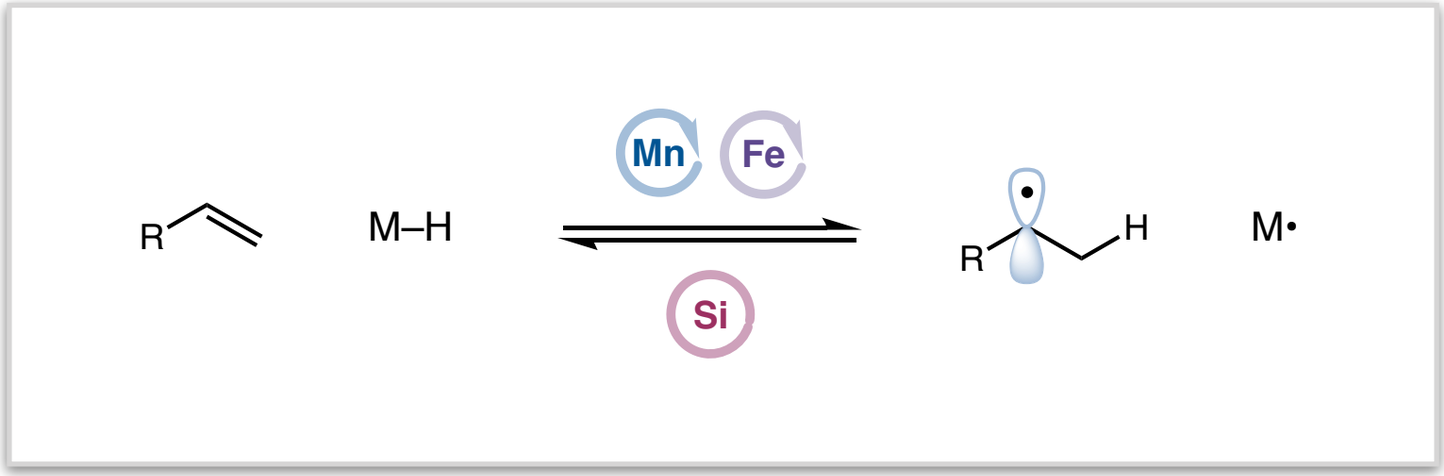
Key Reaction Conditions for Consideration

Mn	Fe
$Mn(dpm)_2$	$Fe_2ox_3 \cdot H_2O$
$Mn(dpm)_3$	FePc
$Mn(acac)_3$	$Fe(acac)_3$

reductant	**solvent**
$PhSiH_3$	iPrOH
$Ph(iPrO)SiH_2$	EtOH
	MeOH

Transition-Metal Hydride HAT:

Radical Hydrofunctionalization of Olefins



Questions?