Literature Report 6

Hydroalkylation of Olefins to Form Quaternary Carbons

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Checker: Xiao-Qing Wang
Date: 2019-6-10

Green, S. A.; Huffman, T. R.; McCourt, R. O.; Puyl, V.; Shenvi, R. A.
J. Am. Chem. Soc. **2019**, *141*, 7709

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CV of Prof. Ryan Ashok Shenvi

Ryan Ashok Shenvi

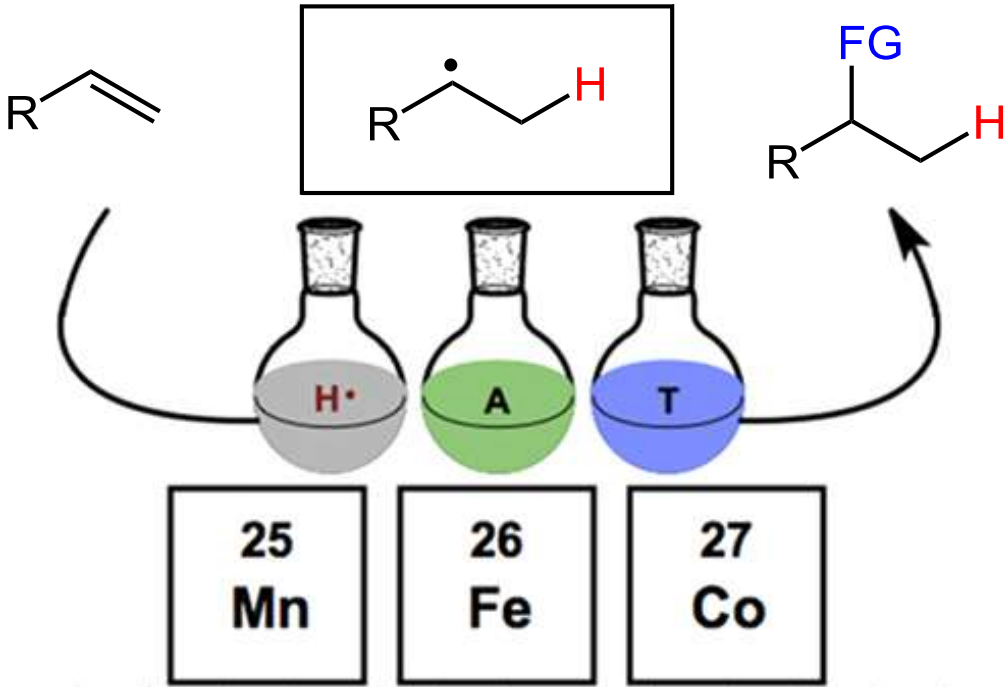
Background:

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

Research Interests:

- Total synthesis of neurotrophic terpenes and unusual pharmacophores
- Hydrogen atom transfer

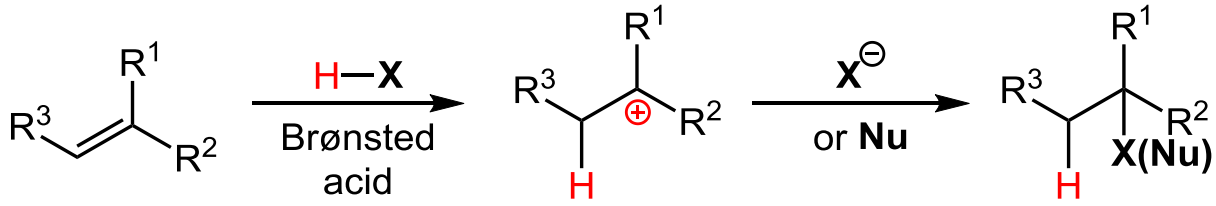
Introduction



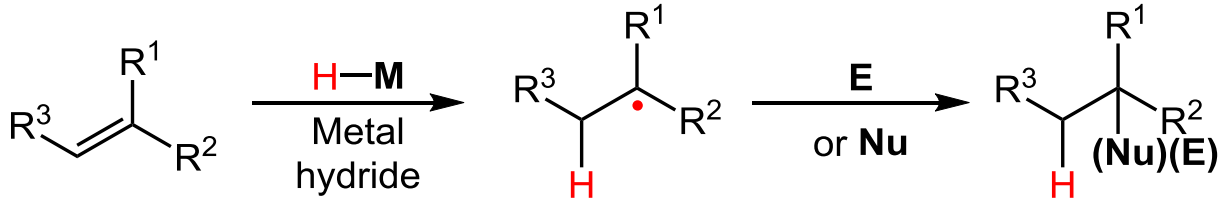
Shenvi, R. A. *et al. Chem. Rev.* **2016**, *116*, 8912

Introduction

A. Brønsted acid proton transfer to an alkene ($R^{1\text{-}3}$ = alkyl)



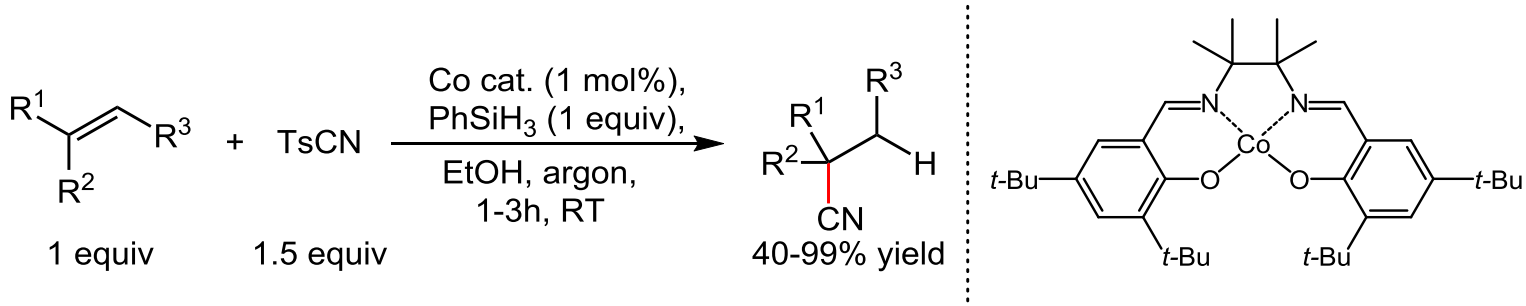
B. Metal hydride hydrogen atom transfer to an alkene ($R^{1\text{-}3}$ = alkyl)



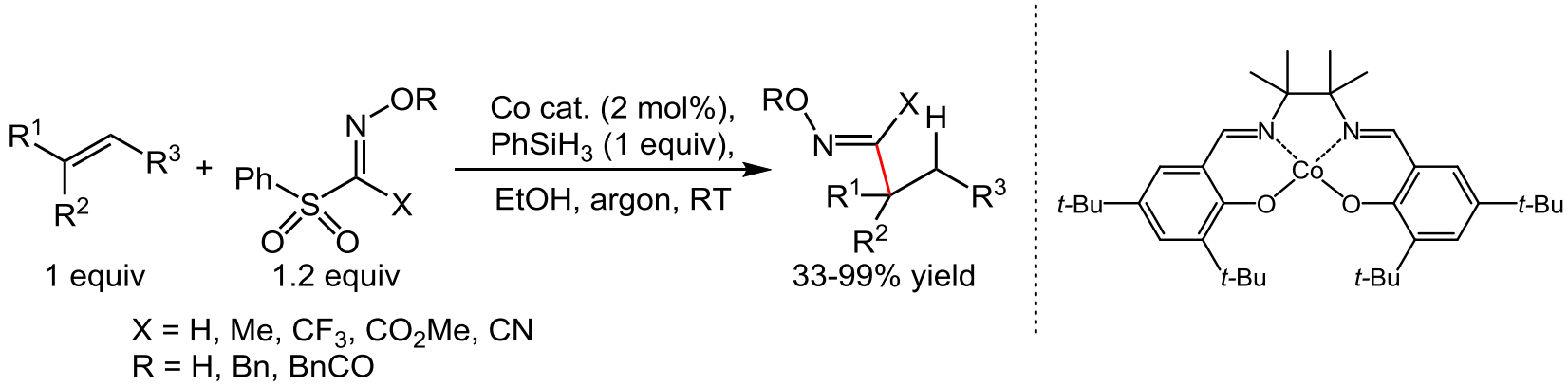
- **Intermolecular C-C formation has been less explored**
- **The reaction largely requires stoichiometric radical traps**

Shenvi, R. A. *et al. Chem. Rev.* **2016**, *116*, 8912

Intermolecular C-C Formation

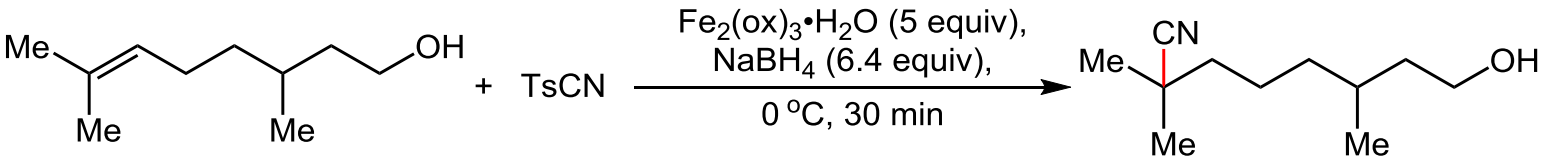


Carreira, E. M. *et al. Angew. Chem. Int. Ed.* **2007**, *46*, 4519



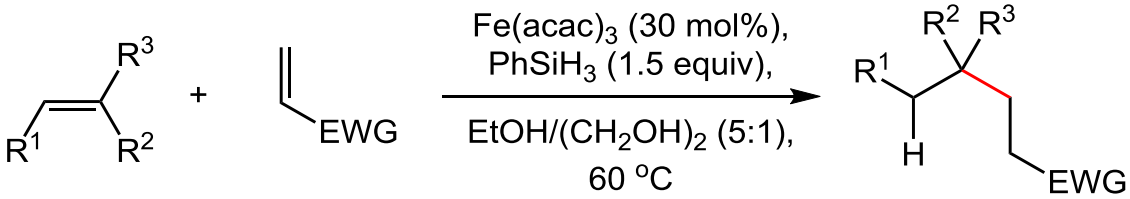
Carreira, E. M. *et al. J. Am. Chem. Soc.* **2009**, *131*, 13214

Intermolecular C-C Formation



1 equiv 4 equiv 35% yield

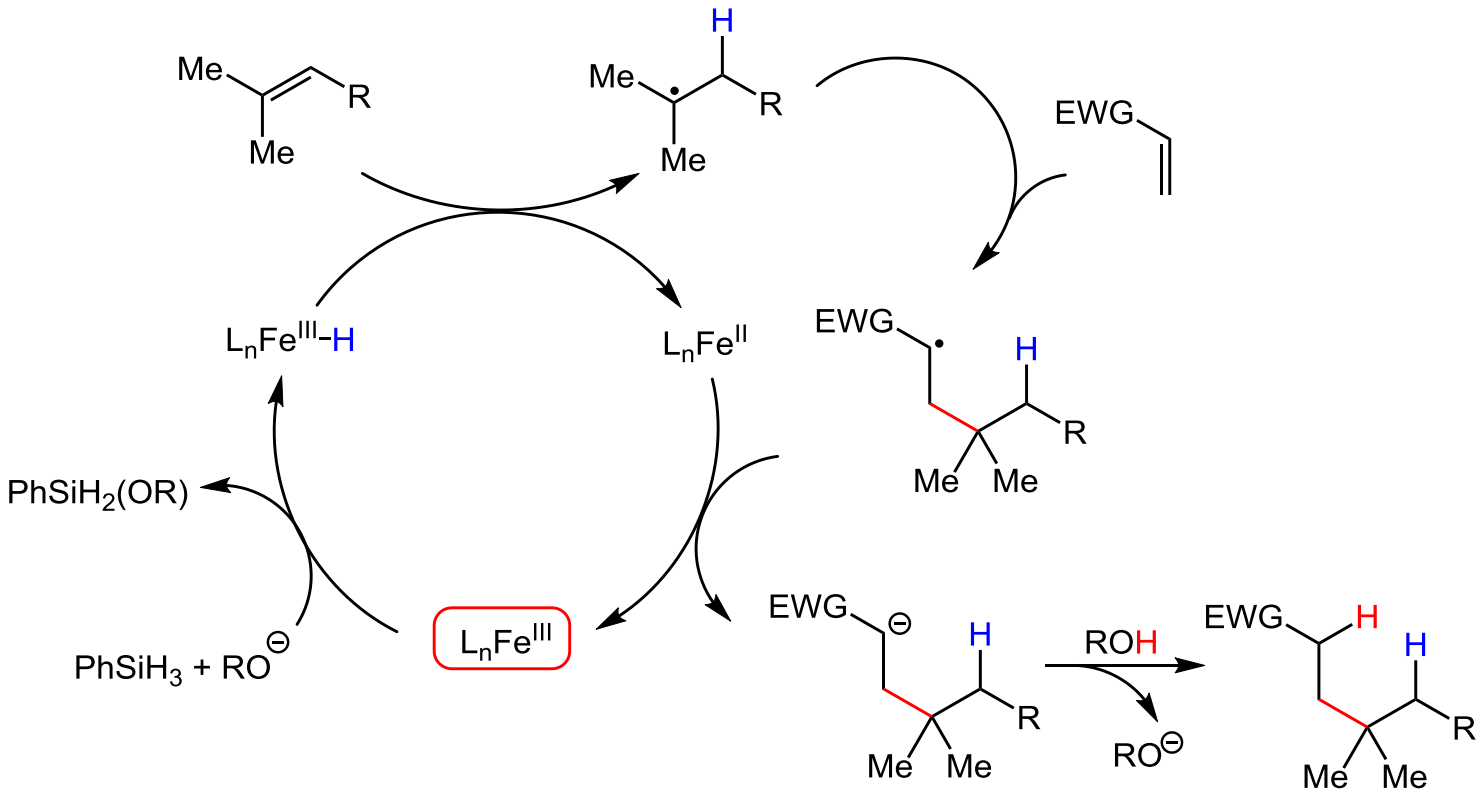
Boger, D. L. *et al. Org. Lett.* **2012**, *14*, 1428



1 equiv 3 equiv 34-93% yield

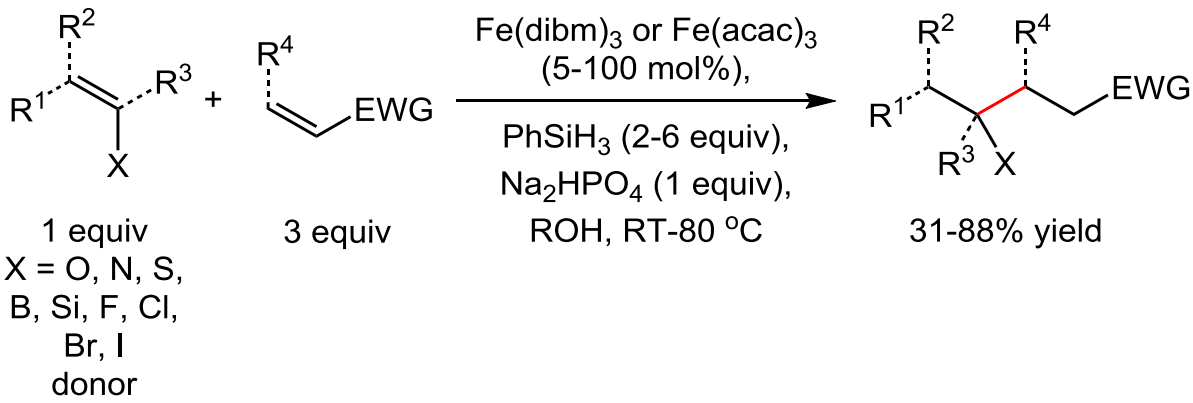
Baran, P. S. *et al. J. Am. Chem. Soc.* **2014**, *136*, 1304

Proposed Mechanism

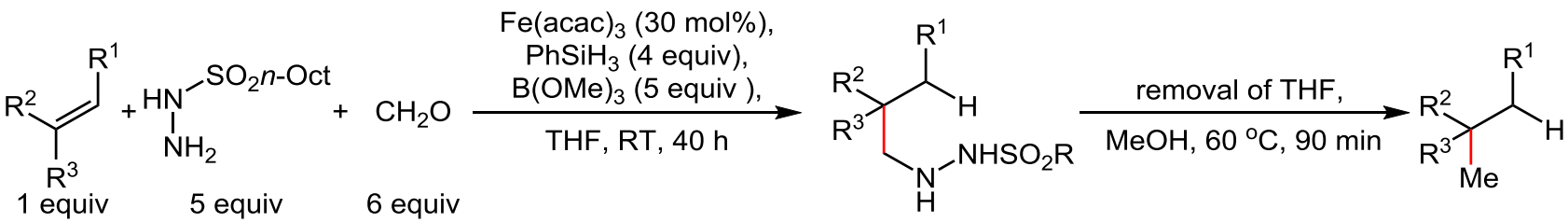


Baran, P. S. *et al. J. Am. Chem. Soc.* **2014**, *136*, 1304

Intermolecular C-C Formation

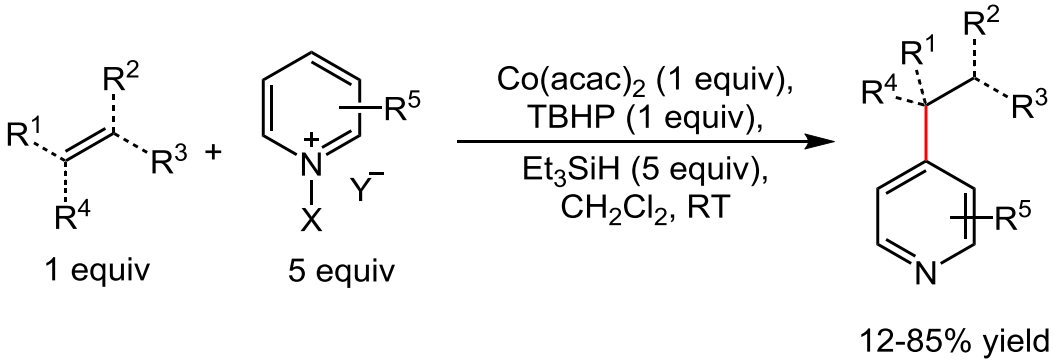


Baran, P. S. *et al. Nature* **2014**, *516*, 343



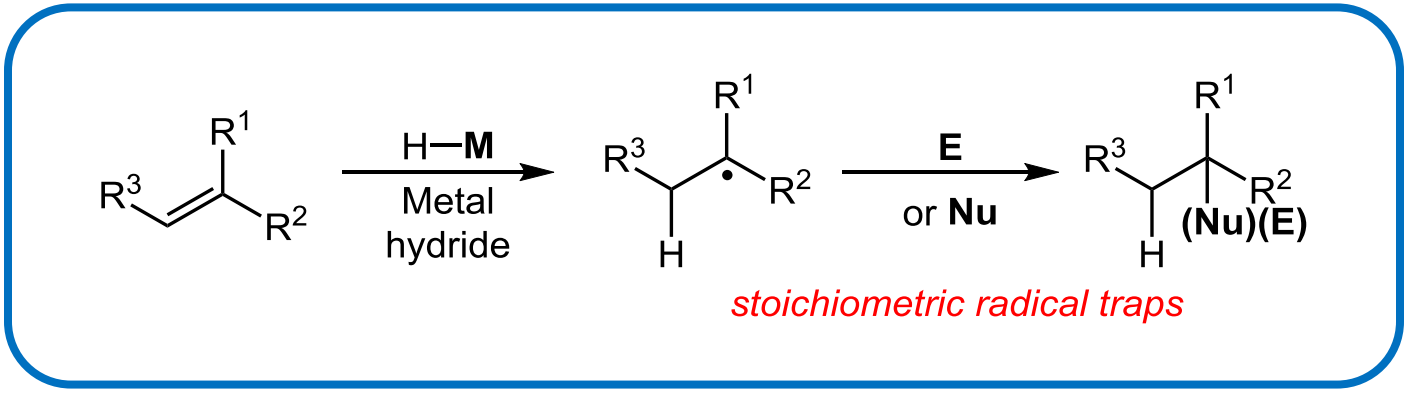
Baran, P. S. *et al. J. Am. Chem. Soc.* **2015**, *137*, 8046

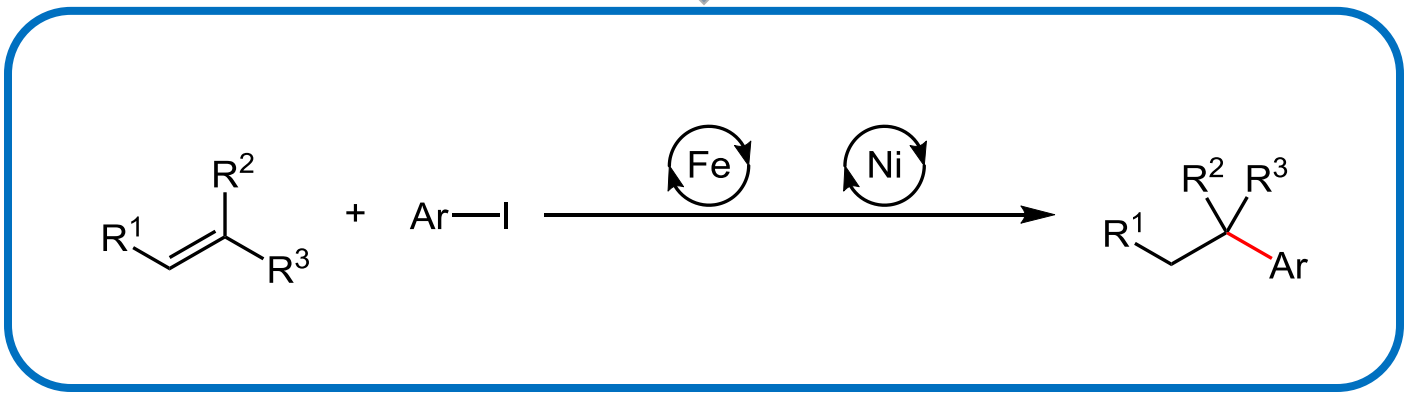
Intermolecular C-C Formation



Herzon, S. B. *et al. J. Am. Chem. Soc.* **2016**, *138*, 8718

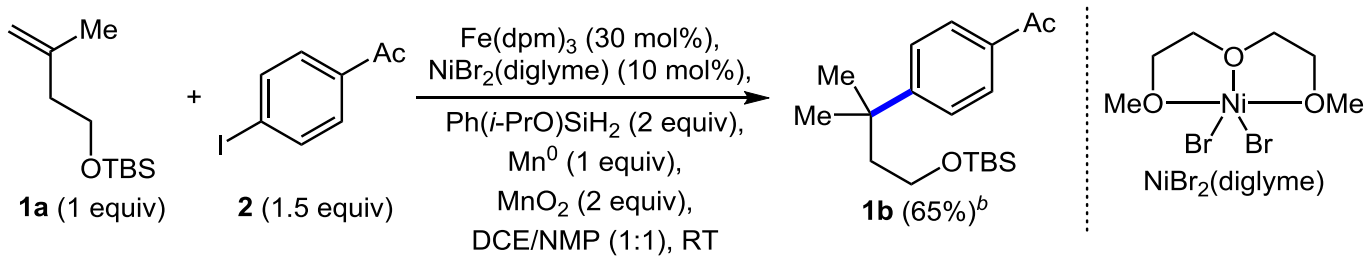
A Dual Catalytic Platform for Hydroarylation





Green, S. A.; Shenvi, R. A.* *et al. J. Am. Chem. Soc.* **2018**, *140*, 11317

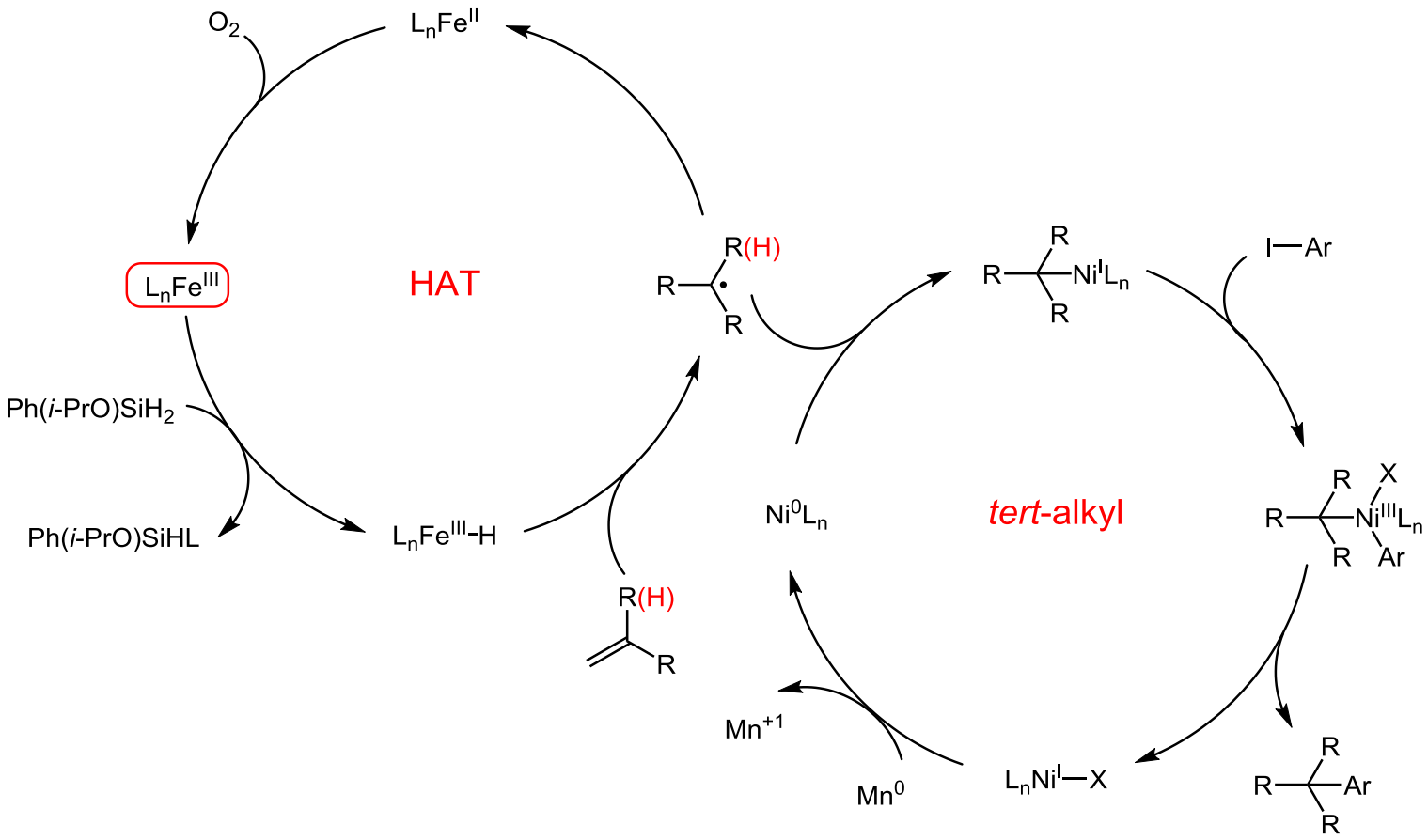
Deviations from Standard Conditions



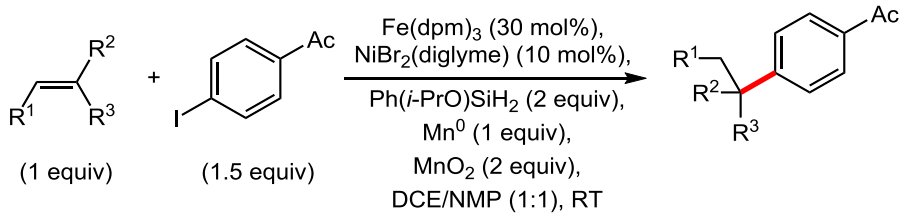
Entry	Deviations from Above	Yield (%)[a]
1	10 mol% $NiBr_2$(dtbbpy)	none
2	No NMP	none
3	No MnO_2	20
4	Under O_2 instead of air	trace[c]
5	1 equiv H_2O	none
6	5 mol% $NiBr_2$(diglyme)	54
7	2 equiv Mn	43
8	1 equiv Ph(*i*-PrO)SiH_2	28
9	No $NiBr_2$(diglyme)	none
10	No Fe(dmp)$_3$	none

[a] 0.1 mmol scale, yield determined by FID using dodecane as an internal standard. [b] 0.3 mmol scale, isolated yield. [c] Under an O_2 balloon, the olefin was predominantly consumed to hydration via Drago-Mukaiyama Hydration.

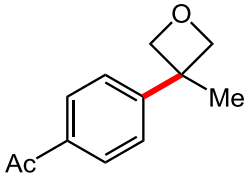
Proposed Mechanism



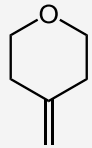
Olefin Scope[a]



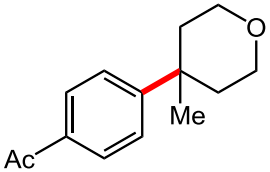
3a



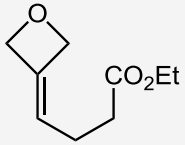
3b (53%[b])



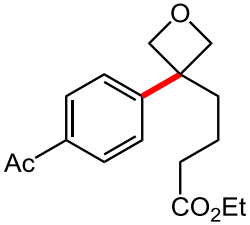
4a



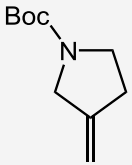
4b (54%)



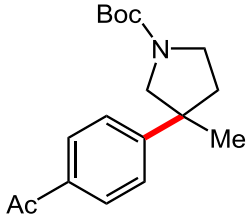
5a



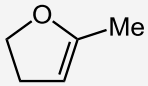
5b (59%)



6a



6b (72%)



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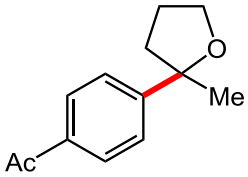
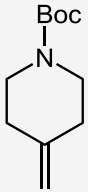
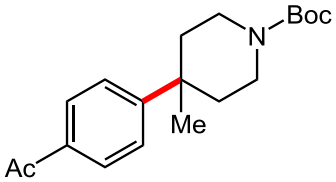


7b (30%[c])

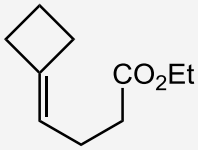


8a

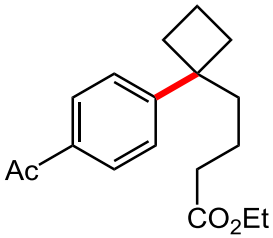


8b (57%, 11:1 *b*:*l*)

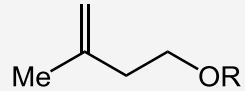
Olefin Scope



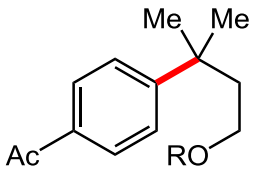
9a



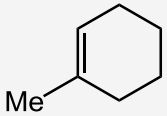
9b (62%, 10:1 *b*:*l*)



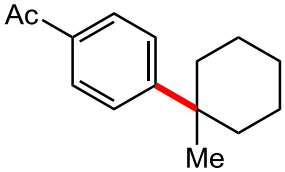
10a R = TBS
11a R = Ac



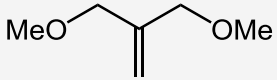
10b R = TBS (65%)
11b R = Ac (57%)



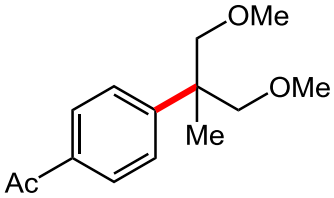
12a



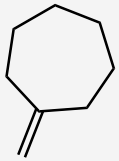
12b (60%)



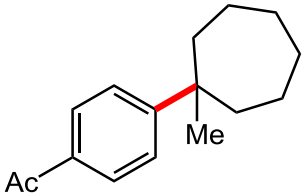
13a



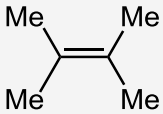
13b (39%)



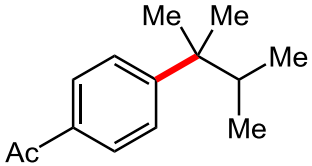
14a



14b (62%, 4:1 *b*:*l*)

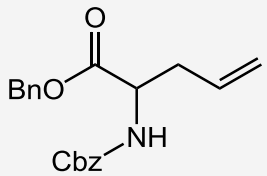


15a

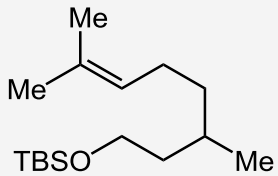


15b (21%[c])

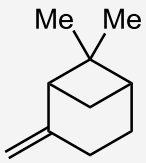
Olefin Scope



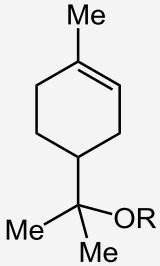
16a from allyl glycine



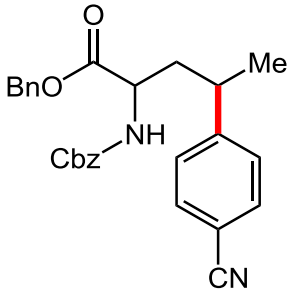
17a from (+/-)-citronellol



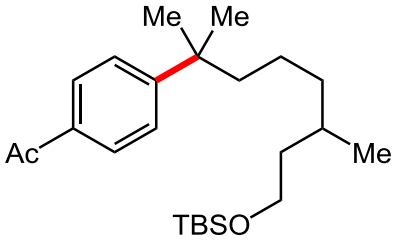
18a β-pinene



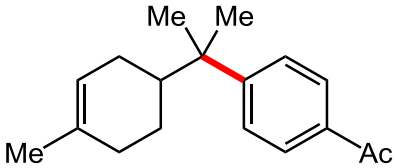
19a R = H α-terpineol
20a R = TMS



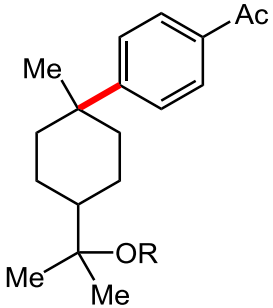
16b (71%, 2:1 d.r.)



17b (53%)



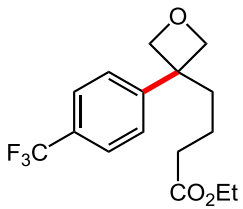
18b (34%, 10:1 *b*:*l*)



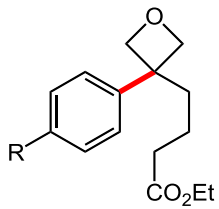
19b R = H (25%, 2:1 d.r.)
20b R = TMS (40%, 2:1 d.r.)
(13:1 *b*:*l*)

[a] 0.3 mmol scale, isolated yield, reaction time 16 h. 1.5 mL 1,2-DCE and 1.5 mL NMP. N_2 atmosphere for 1.5 h, then open to air. All substrates gave >20:1 branched: linear (*b*:*l*) ratio except where notated. [b] 0.1 mmol scale, isolated yield. [c] Run under an air ballon.

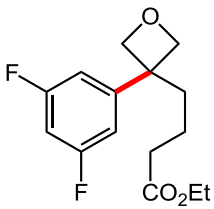
Alkyl Halide Scope[a]



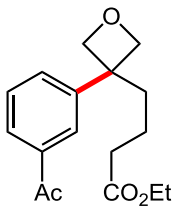
21 from Ar-I (54%)
from Ar-Br (41%)



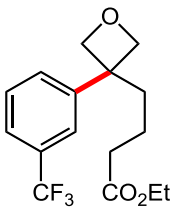
22 R = Bdan (38%)
(7:3 *b*:*l*)
23 R = OMe (45%)



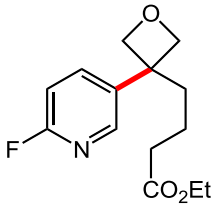
24 (51%)



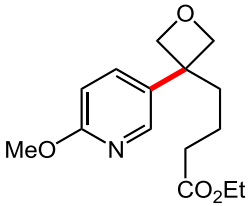
25 (55%)



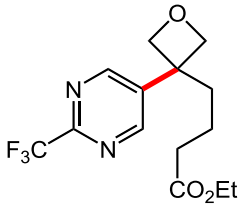
26 (41%)



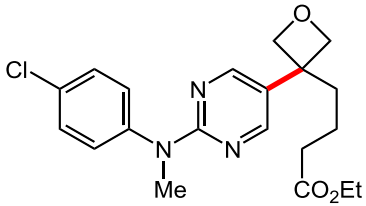
27 (58%)



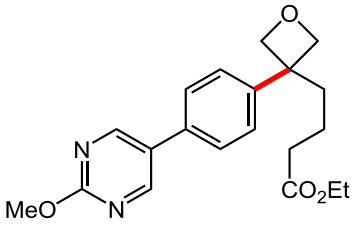
28 (40%)
(9:1 *b*:*l*)



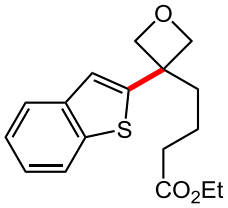
29 from bromide (53%)



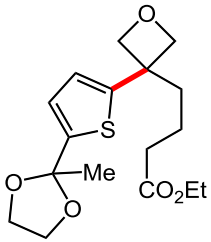
30 from bromide (31%)



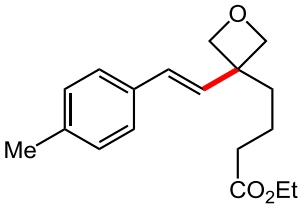
31 (24%)
(13:1 *b*:*l*)



32 (33%)



33 (53%)



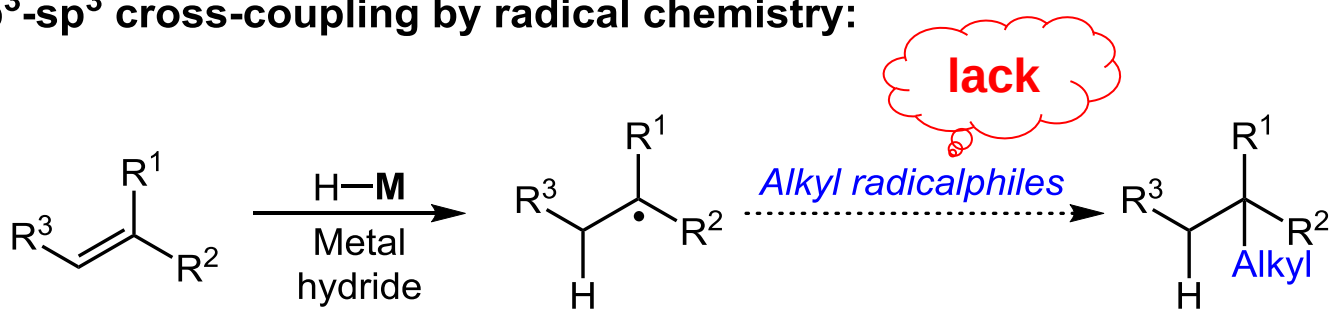
34 from bromide (23%)

[a] 0.3 mmol scale, isolated yield, reaction time 16 h. 1.5 mL 1,2-DCE and 1.5 mL NMP. N_2 atmosphere for 1.5 h, then open to air. All substrates gave >20:1 branched : linear ratio except where notated.

Hydroalkylation

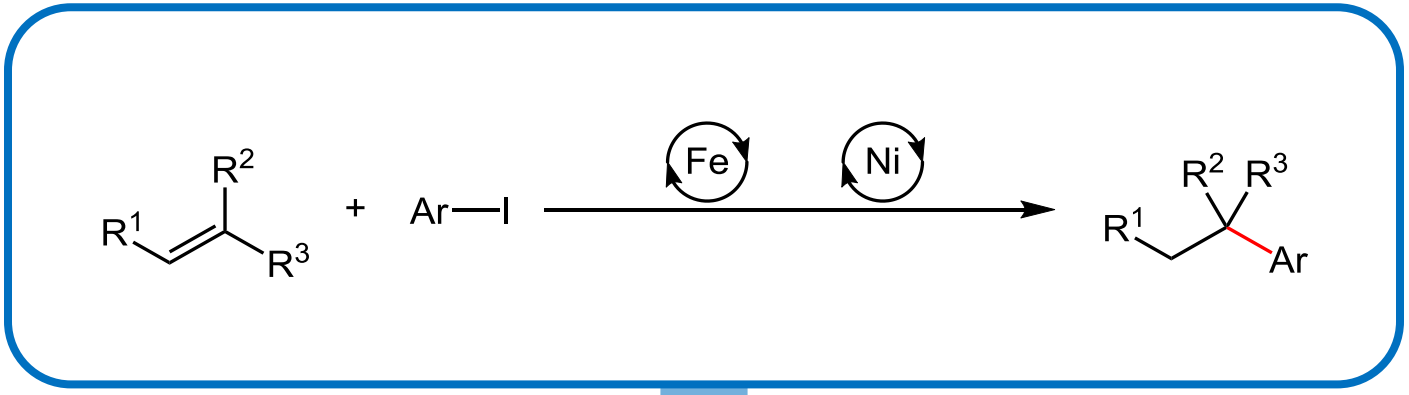
Transition metal-catalyzed alkyl-alkyl bond formation:

Sp^3-sp^3 cross-coupling by radical chemistry:

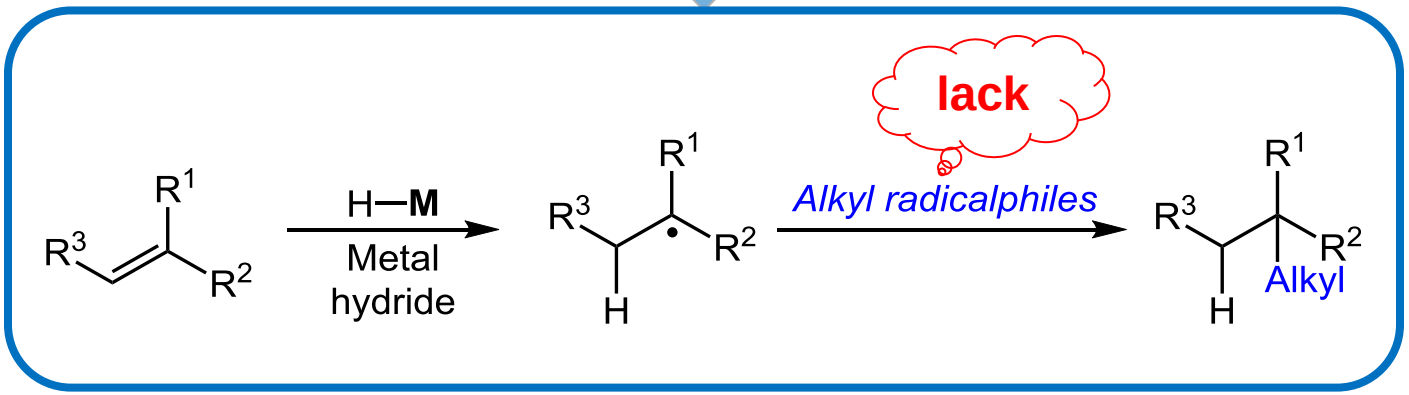


Fu, G. C. *et al. Science* **2017**, *356*, 7230

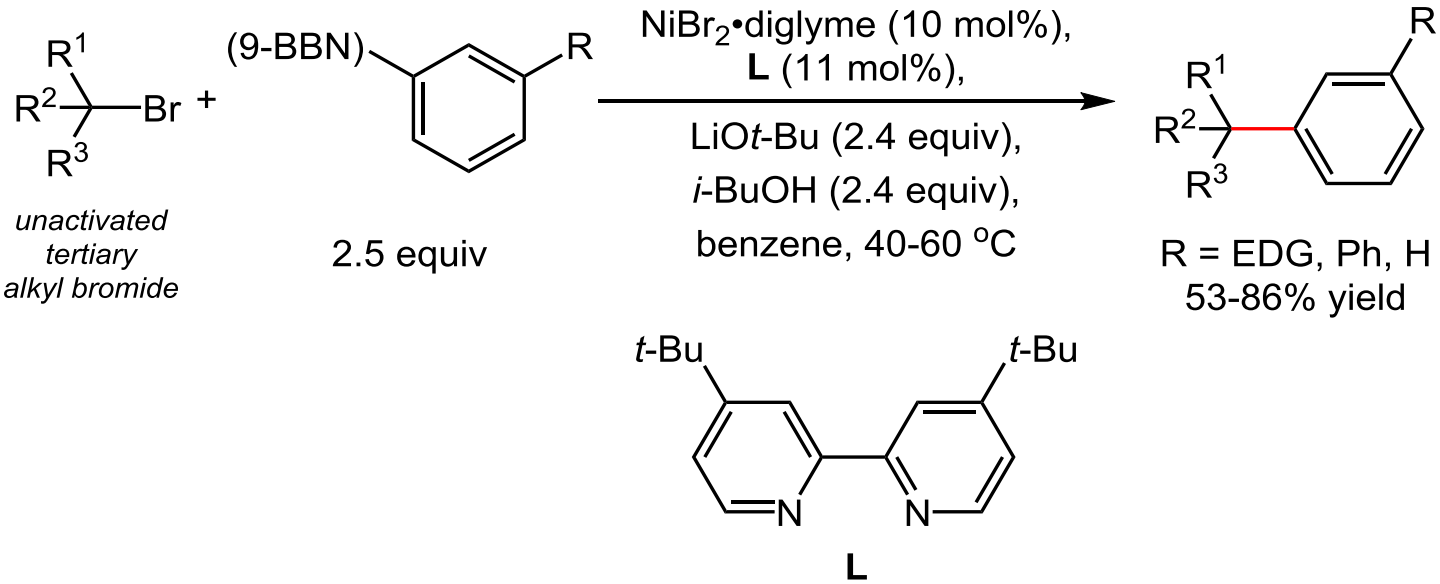
A Dual Catalytic Platform for Hydroalkylation?



Application?

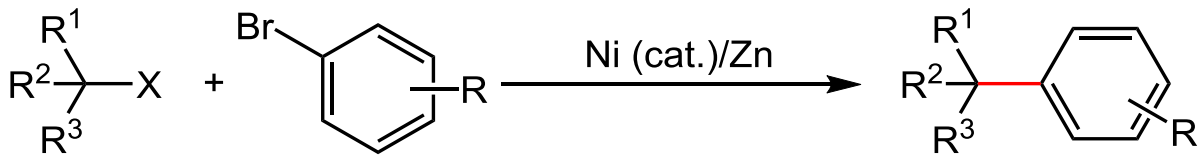


Construction of Quaternary Carbons

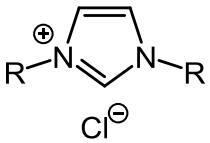


Fu, G. C. *et al. J. Am. Chem. Soc.* **2013**, *135*, 624

Construction of Quaternary Carbons



R = EWG
21-95% yield



L1: R = *i*-Pr
L2: R = *t*-Bu

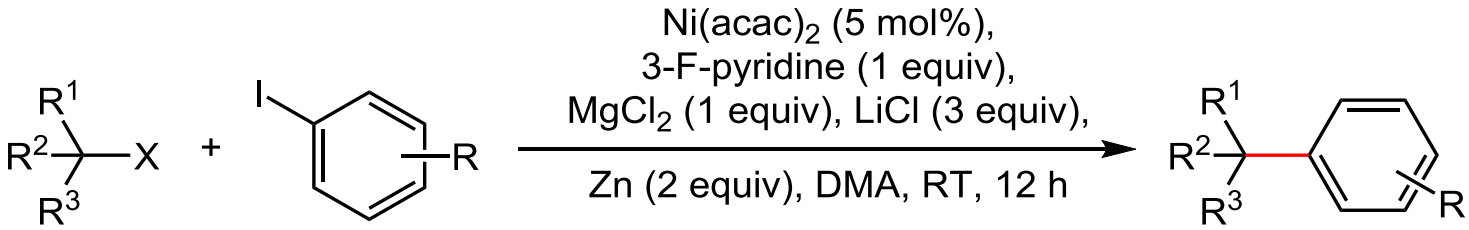
Method 1: 2 equiv 1 equiv

$Ni(acac)_2$ (10 mol%), **L1** (0 or 30 mol%), DMAP (1 equiv), $MgCl_2$ (1.5 equiv), Zn (2 equiv), DMA, 25 ^oC, 12 h

Method 2: 1 equiv 2 equiv

$Ni(acac)_2$ (10 mol%), **L2** (0 or 30 mol%), Py or DMAP (30 mol%), $MgCl_2$ (1 equiv), Zn (2 equiv), DMA, 25 ^oC, 12 h

Gong, H. *et al. J. Am. Chem. Soc.* **2015**, *137*, 11562

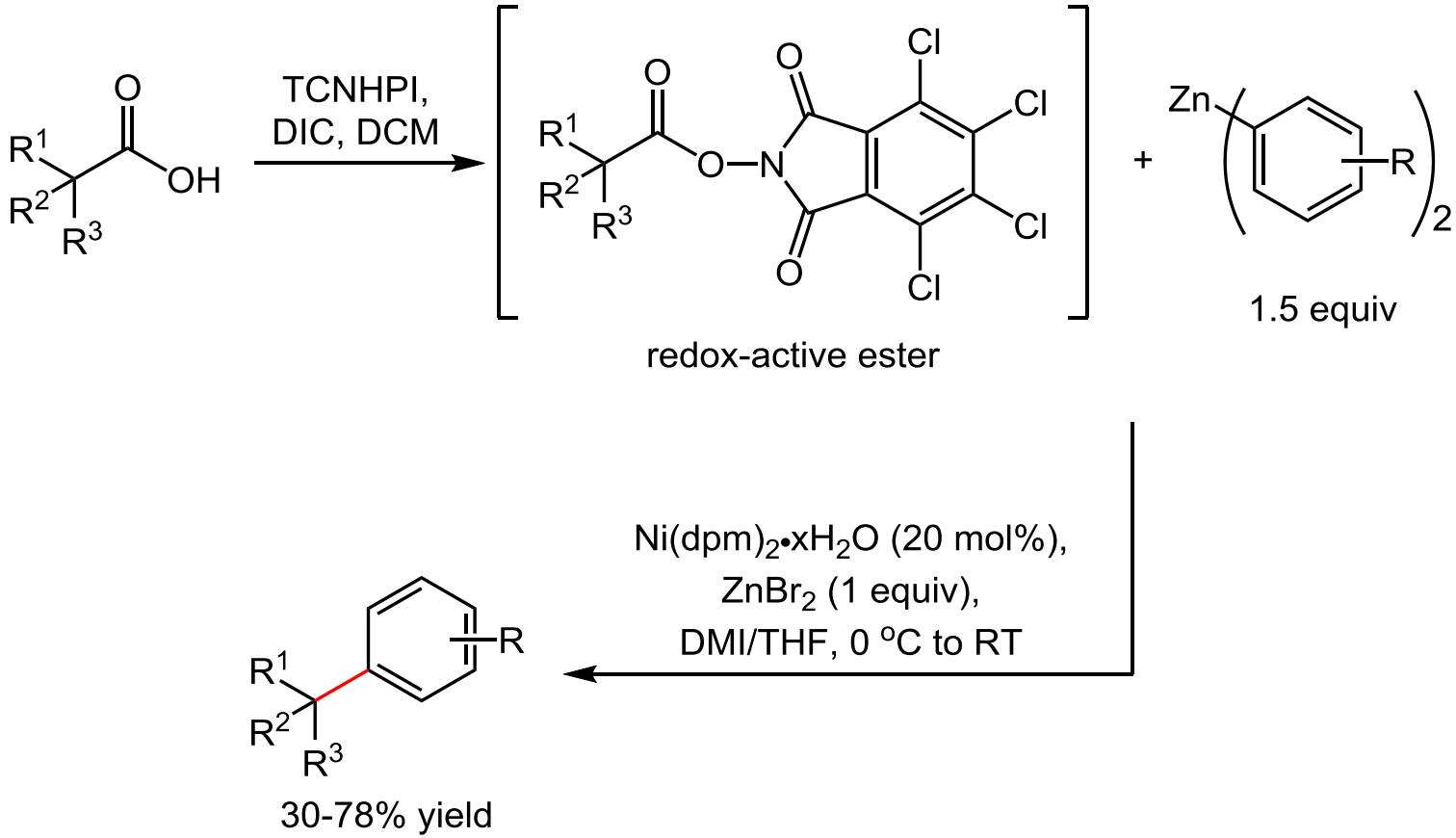


1 equiv 2 equiv

R = EDG, H
13-82% yield

Gong, H. *et al. J. Am. Chem. Soc.* **2018**, *140*, 14490

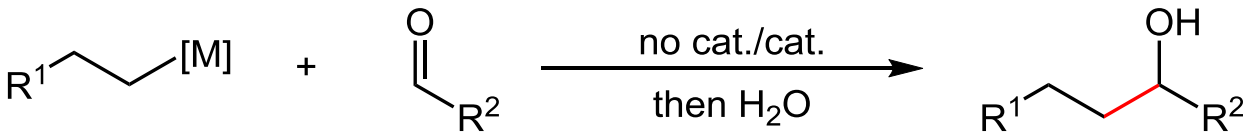
Construction of Quaternary Carbons



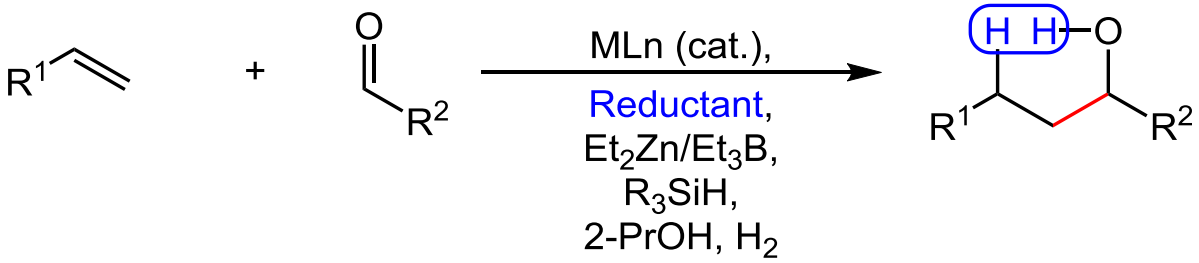
Baran, P. S. *et al. Angew. Chem. Int. Ed.* **2019**, *58*, 2454

Reductive Coupling with Olefins

Classical C=O addition - Stoichiometric metals:



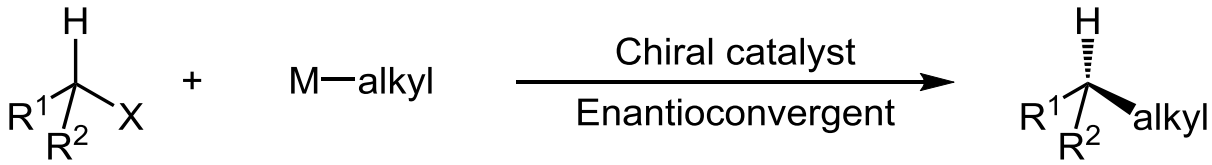
Metal catalyzed C=O reductive coupling:



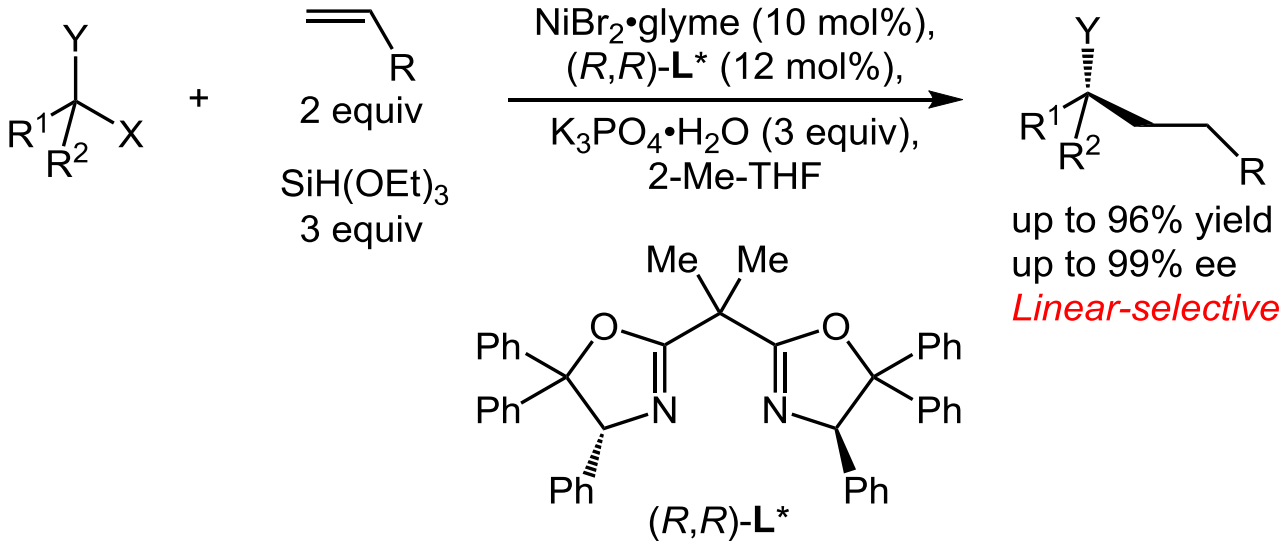
Krische, M. J. *et al. Science* **2016**, *354*, 300

Nickel Catalysis with Olefins

Nickel catalysis with organometallic reagent:

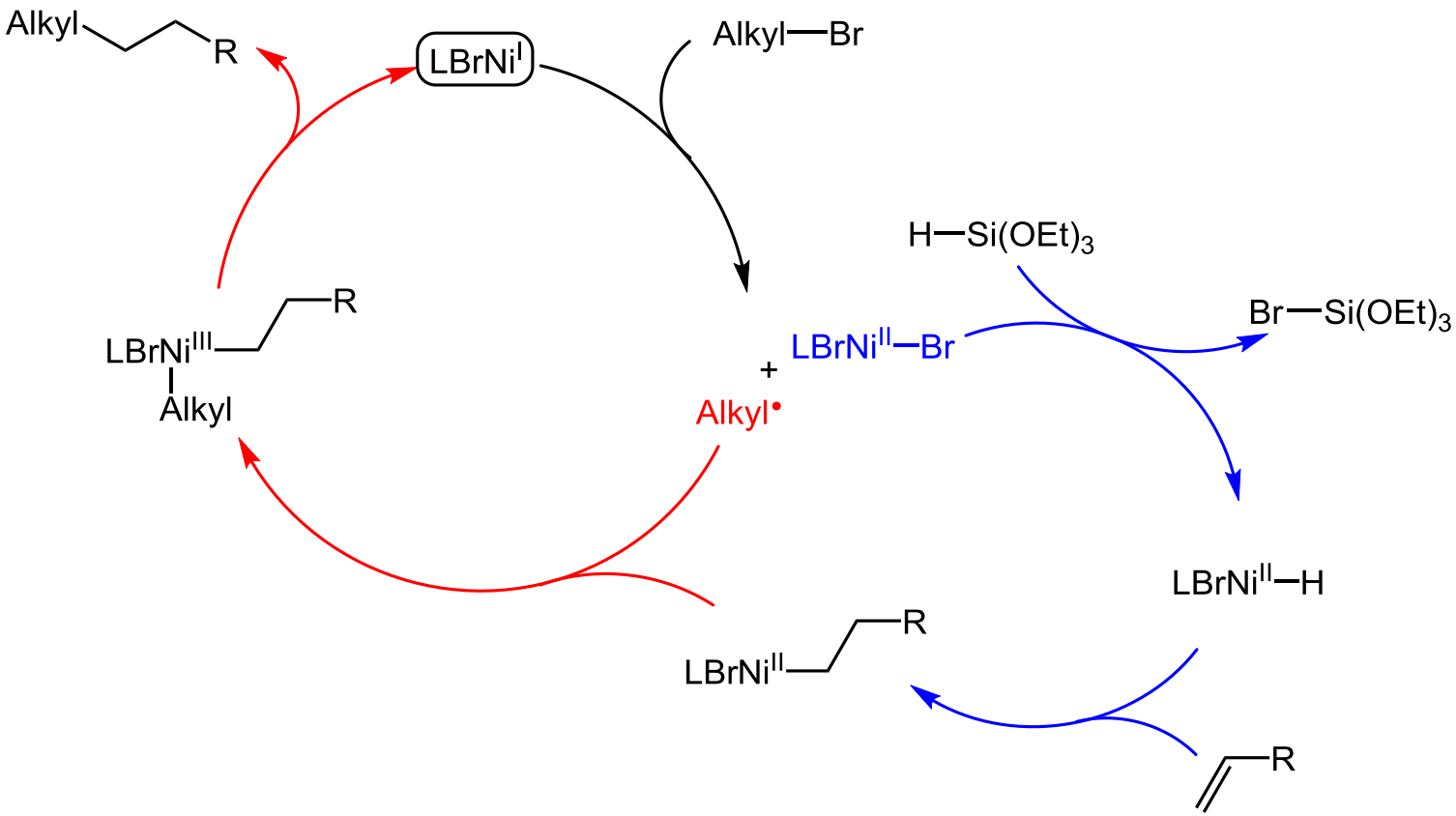


Nickel catalysis with olefins:



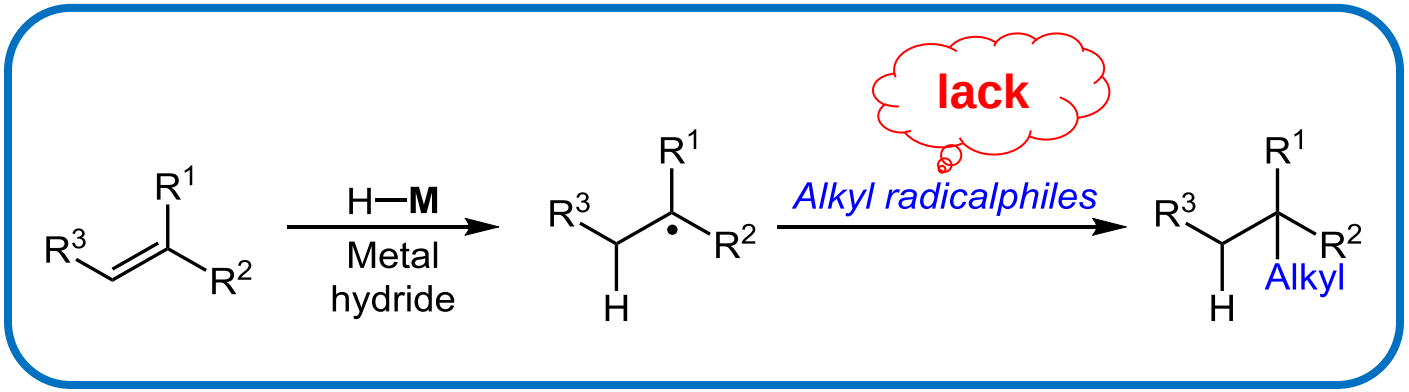
Fu, G. C. *et al. Nature* **2018**, *563*, 379

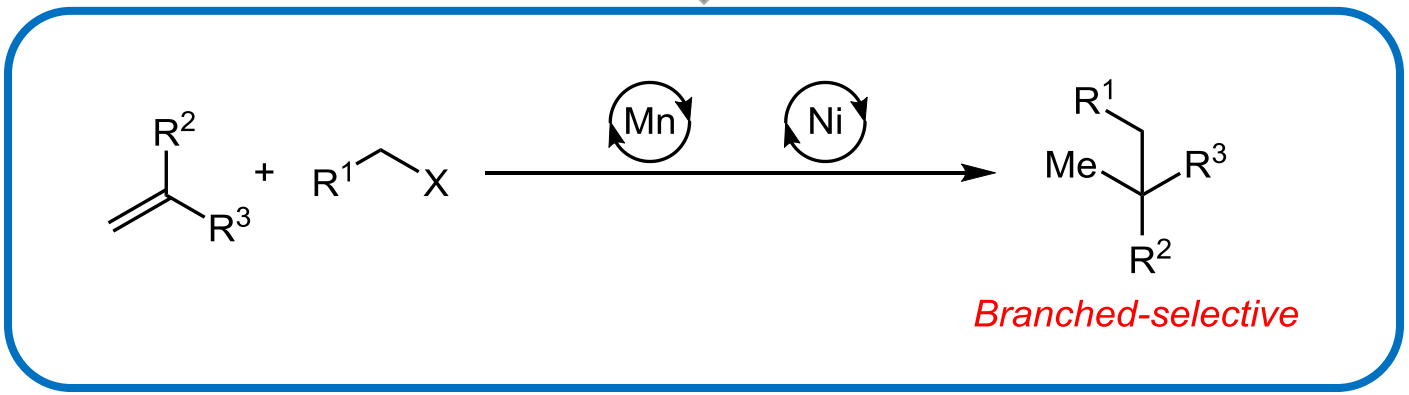
Proposed Mechanism



Fu, G. C. *et al. Nature* **2018**, *563*, 379

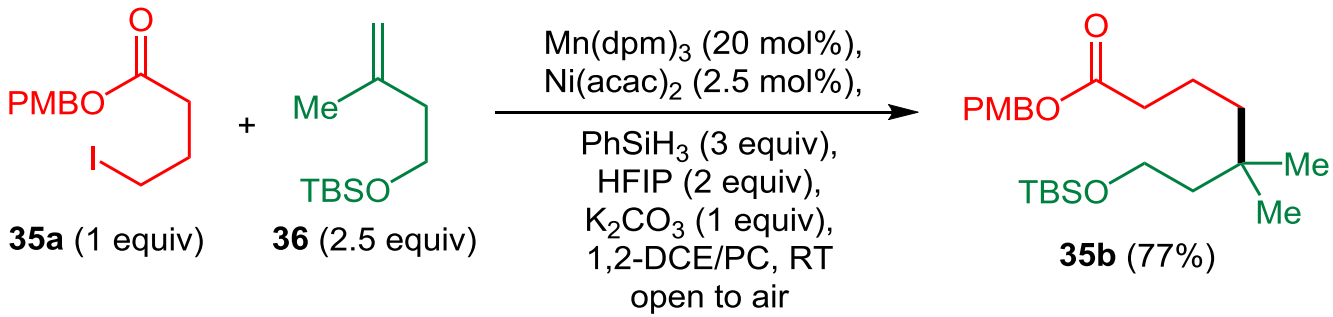
A Dual Catalytic Platform for Hydroalkylation





Green, S. A.; Shenvi, R. A.* *et al. J. Am. Chem. Soc.* **2019**, *141*, 7709

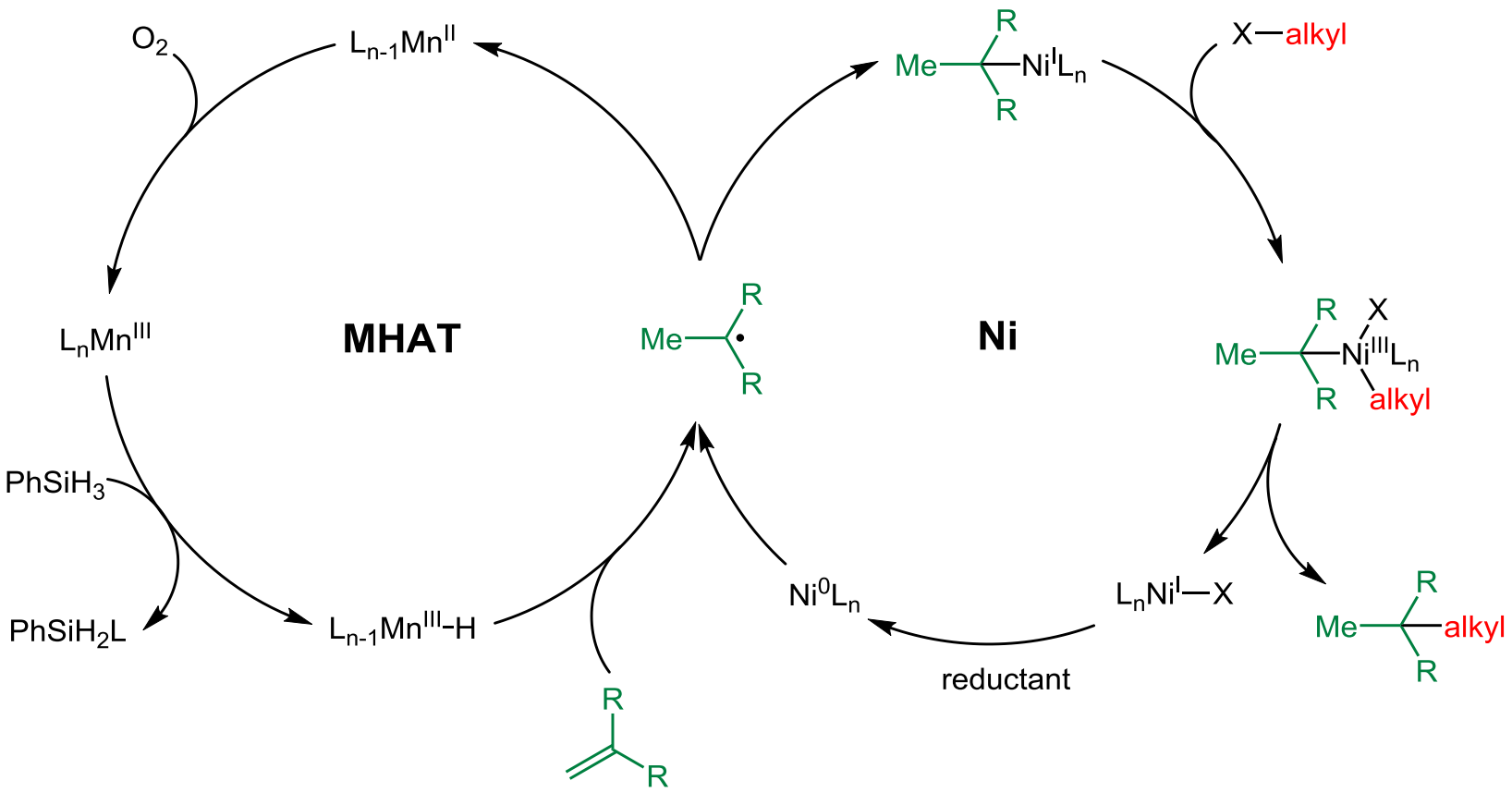
Deviations from Standard Conditions



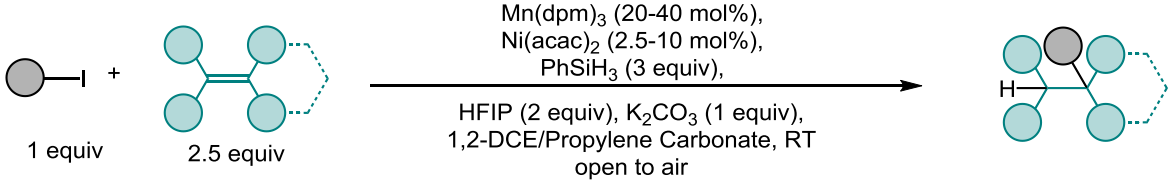
Entry	Deviations from Above	Yield (%)[a]
1	None	77 (72)[b]
2	$Fe(dpm)_3$ instead of $Mn(dmp)_3$	0 (20)[c]
3	no $Mn(dmp)_3$	none
4	no $Ni(acac)_2$	20 (trace)[d]
5	no K_2CO_3	55
6	no HFIP	36
7	no propylene carbonate (PC)	55
8	*i*-PrOH instead of HFIP	54
9	Ph(*i*-PrO)SiH_2 instead of $PhSiH_3$	50 (27)[c]

[a] 0.1 mmol scale, yield determined by GC-FID using 1,3,5-trimethoxybenzene as an internal standard. [b] 0.3 mmol scale, isolated yield 15:1 branched (*b*) : linear (*l*) product. [c] No HFIP. [d] Using 2-iodoethyl benzoate of **35a**. dpm = dipivaloylmethane; HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol; 1,2-DCE = 1,2-dichloroethane; PC = propylene carbonate.

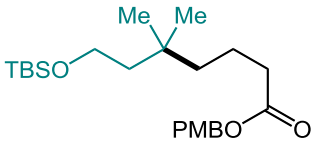
Proposed Mechanism



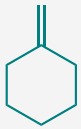
Olefin Scope[a]



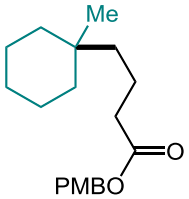
37a 1,1 acyclic



37b (73%, 15:1 *b:l*)

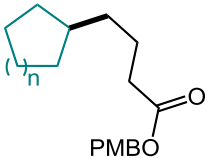


40a 1,1 cyclic

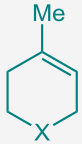


40b (53%, 2:1 *b:l*)

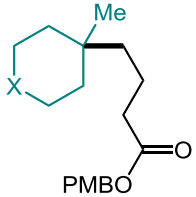
di **42a** n = 1
43a n = 2



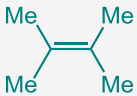
42b n = 1 (68%)[b]
43b n = 2 (57%)



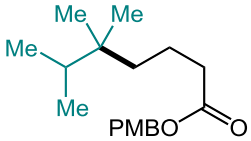
tri **38a** X = CH_2
39a X = NBoc



38b (65%, >20:1 *b:l*)
39b (58%, >20:1 *b:l*)

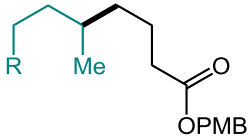


41a tetra



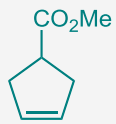
41b (40%, >20:1 *b:l*)

mono **44a** R = C_4H_9
45a R = Ph
46a R = OTBS

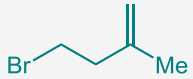


44b R = C_4H_9 (55%, 1.5:1 *b:l*)
45b R = Ph (64%, 2.5:1 *b:l*)
46b R = OTBS (71%, 1.5:1 *b:l*)

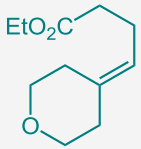
Olefin Scope



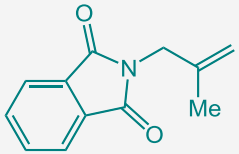
47a



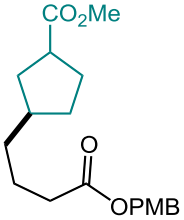
48a



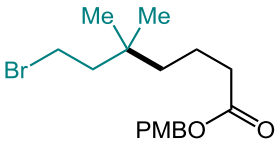
49a



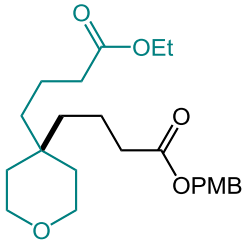
50a



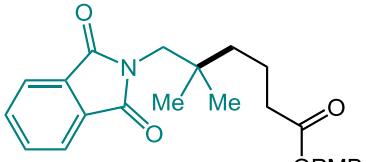
47b (73%, 1.6:1 d.r.)



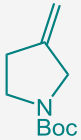
48b (70%, >20:1 *b:l*)



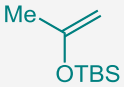
49b (58%, 4:1 *b:l*)



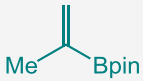
50b (51%, >20:1 *b:l*)



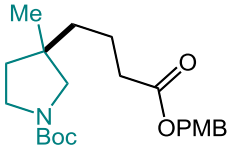
51a



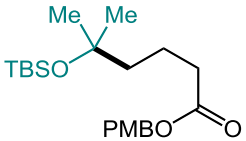
52a



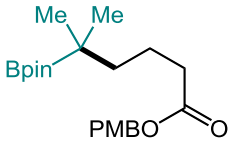
53a



51b (76%, 8:1 *b:l*)

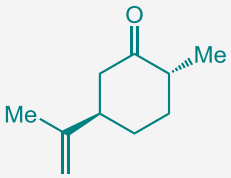


52b (45%, >20:1 *b:l*[c])

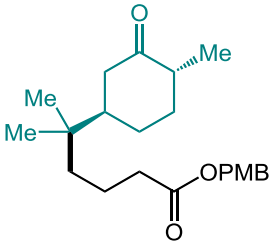


53b (31%, >20:1 *b:l*)

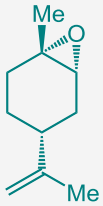
Olefin Scope



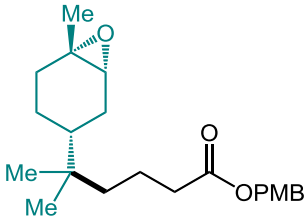
54a dihydrocarvone



54b (78%, >20:1 *b:l*)

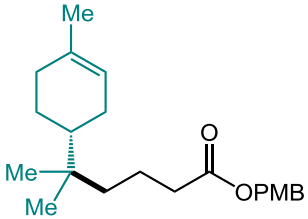


56a limonene oxide

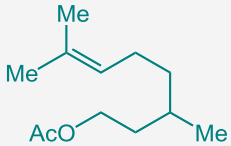


56b (63%, >20:1 *b:l*)

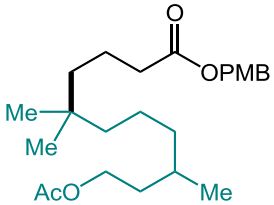
58a α- & **58a'** β-pinene



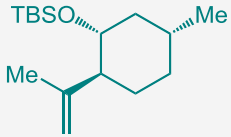
58b (61% from α
65% from β
3:1 ring open: ring closed)



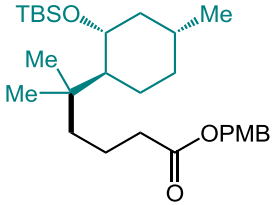
55a β-citronellol



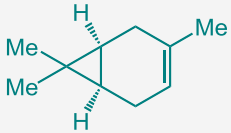
55b (71%, >20:1 *b:l*)



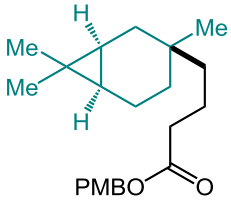
57a isopulegol



57b (30%, 7:1 *b:l*)

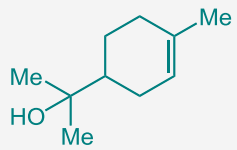


59a 3-carene

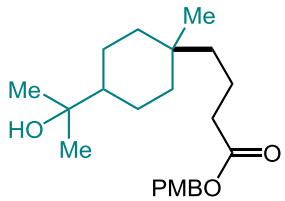


59b (42%, 4:1 d.r., 7:1 *b:l*)

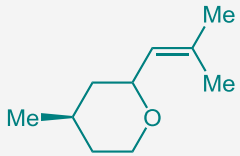
Olefin Scope



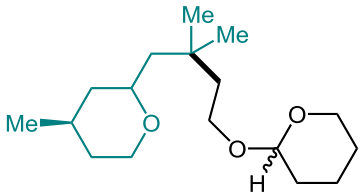
60a α-terpineol



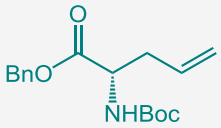
60b (60%, 4:1 d.r., >20:1 *b:l*)



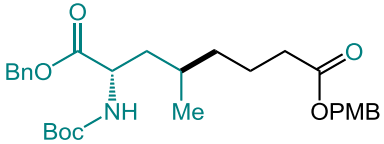
61a rose-oxide 11:1 d.r.



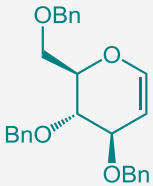
61b (52%, 11:1 d.r., >20:1 *b:l*[c])



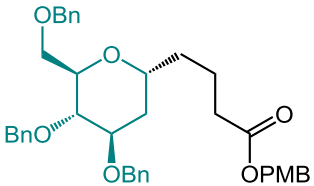
62a allyl glycine



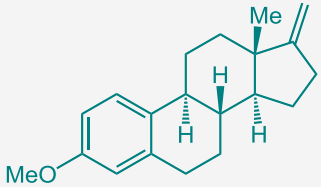
62b (75%, 1:1 d.r., 1.5:1 *b:l*)



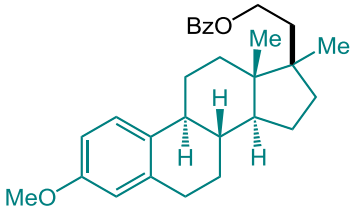
63a glucal



63b (50%, >20:1 *b:l*)



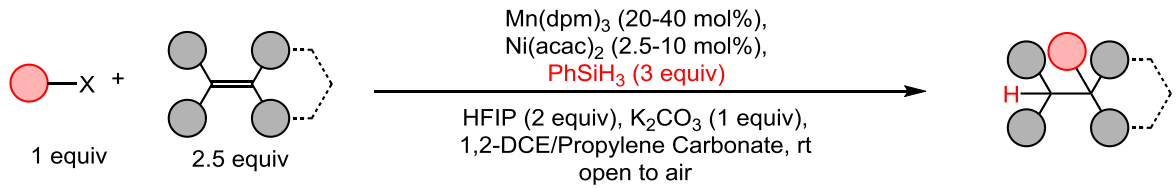
64a estrone



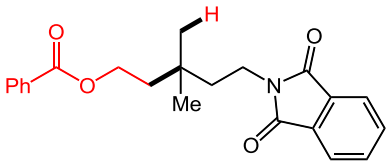
64b (28%, 3:1 *b:l*)

[a] 0.3 mmol scale, isolated yield, *b:l* = branched/linear ratio. [b] Reaction run under an air balloon. [c] 5 equiv of olefin added in two portions (2.5 equiv at start and 2.5 equiv at 24 h).

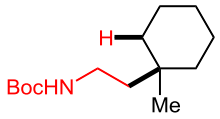
Alkyl Halide Scope[a]



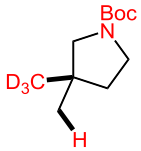
Alkyl Iodides



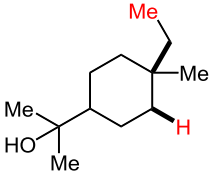
65 (72%, 13:1 *b:l*)



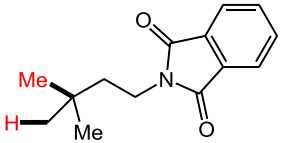
66 (75%, >20:1 *b:l*)



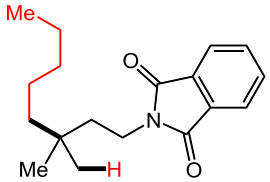
67 (39%, >20:1 *b:l*)



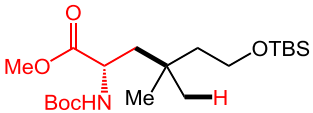
68 (47%, 4:1 d.r., >20:1 *b:l*[b])



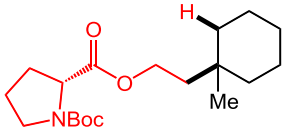
69 (64%, 10:1 *b:l*[c])



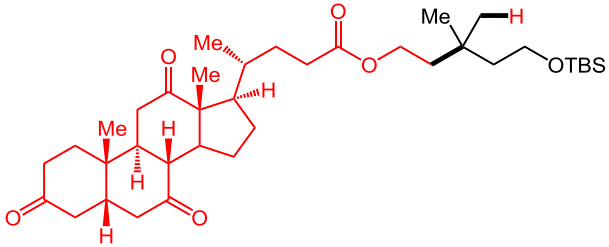
70 (56%, >20:1 *b:l*)



71 (51%, >20:1 *b:l*)

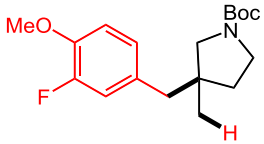


72 (53%, >20:1 *b:l*)

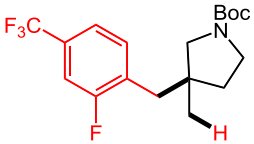


73 (41%, >20:1 *b:l*)

Benzyl Bromides

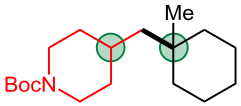


74 (43%, >20:1 *b:l*)

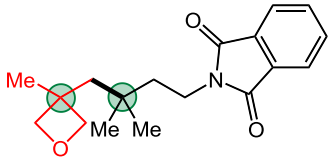


75 (45%, >20:1 *b:l*)

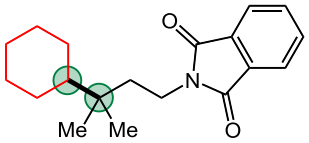
Congested Centers (Limitations: 1-10%)



76



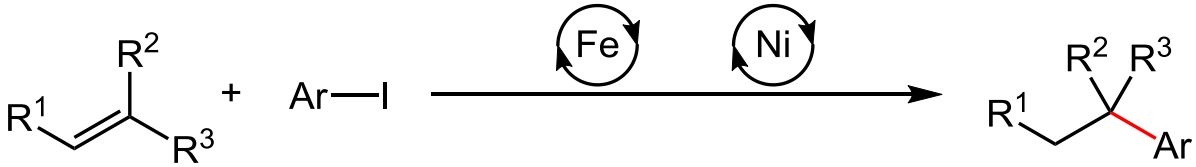
77



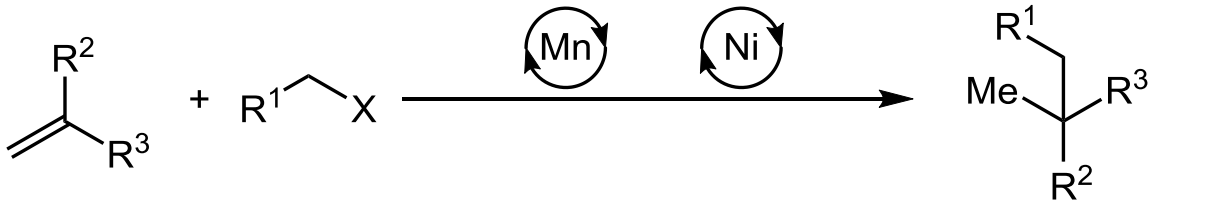
78

[a] 0.3 mmol scale, isolated yield, *b:l* = branched/linear ratio. [b] 0.1 mmol scale. [c] Isolated as a mixture with hydrogenation, yield determined by NMR. Further purified by prep HPLC.

Summary



Green, S. A.; Shenvi, R. A.* *et al. J. Am. Chem. Soc.* **2018**, *140*, 11317



Branched-selective

Green, S. A.; Shenvi, R. A.* *et al. J. Am. Chem. Soc.* **2019**, *141*, 7709

The first paragraph

Olefins represent versatile feedstocks and intermediates for chemical synthesis. Metal-hydride hydrogen atom transfer (MHAT) has emerged as a useful reaction platform for the branched-selective hydrofunctionalization of olefins. Its high chemoselectivity for olefins and mild reaction conditions have allowed its deployment in medicinal chemistry and natural product synthesis. The bulk of these transformations involve carbon−heteroatom bond formation, whereas intermolecular C−C formation has been less explored and has largely required stoichiometric radical traps like π-electrophiles. Pioneering advances in the formation of C−C bonds are represented by hydrocyanations and hydrooximation from Carreira and Boger. More recently, Baran and co-workers developed a powerful variant of the Giese reaction as well as a creative protocol for hydromethylation. Finally, our group and others have investigated the branched-selective hydroarylation of olefins using MHAT, establishing olefins as progenitors of arylated quaternary centers.

The last paragraph

In summary, we have reported a Markovnikov-selective hydroalkylation of unbiased olefins using diverse alkyl iodides and benzyl bromides. The combination of Mn mediated MHAT catalysis and Ni catalysis enable an unprecedented synthesis of quaternary carbons. The mild reaction conditions and robust functional group compatibility support its utility for late stage modification of small molecules. Efforts are underway to expand this chemistry to more sterically congested centers and complex natural products.

Thanks
for your attention