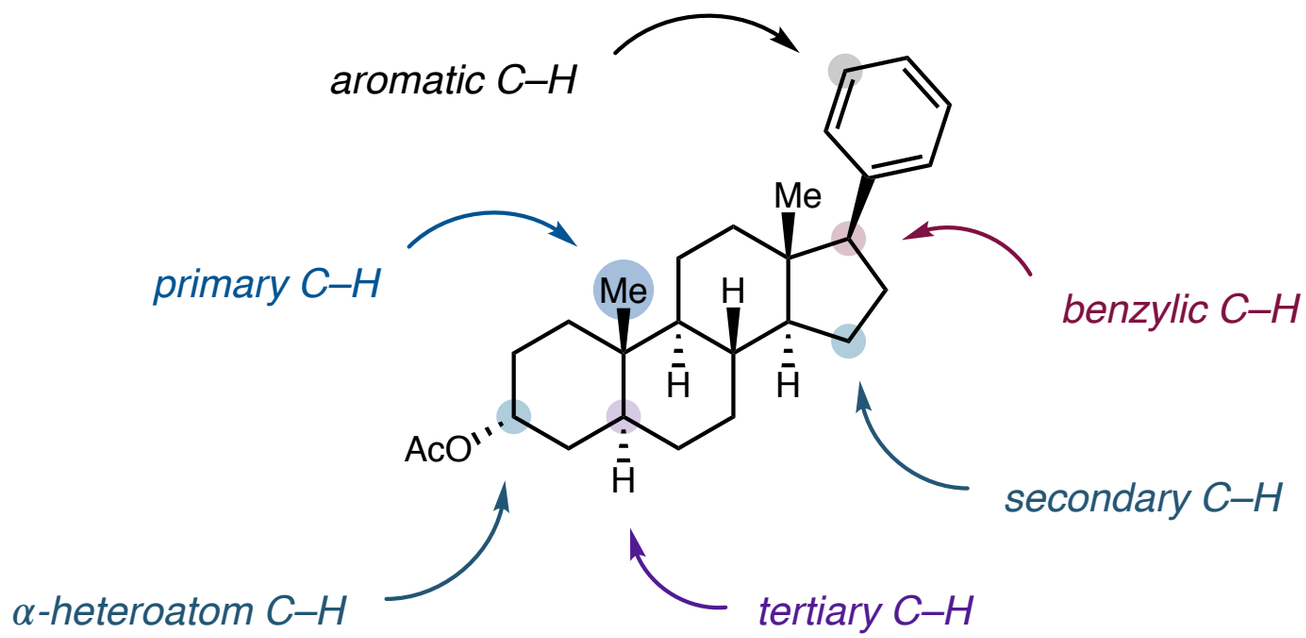
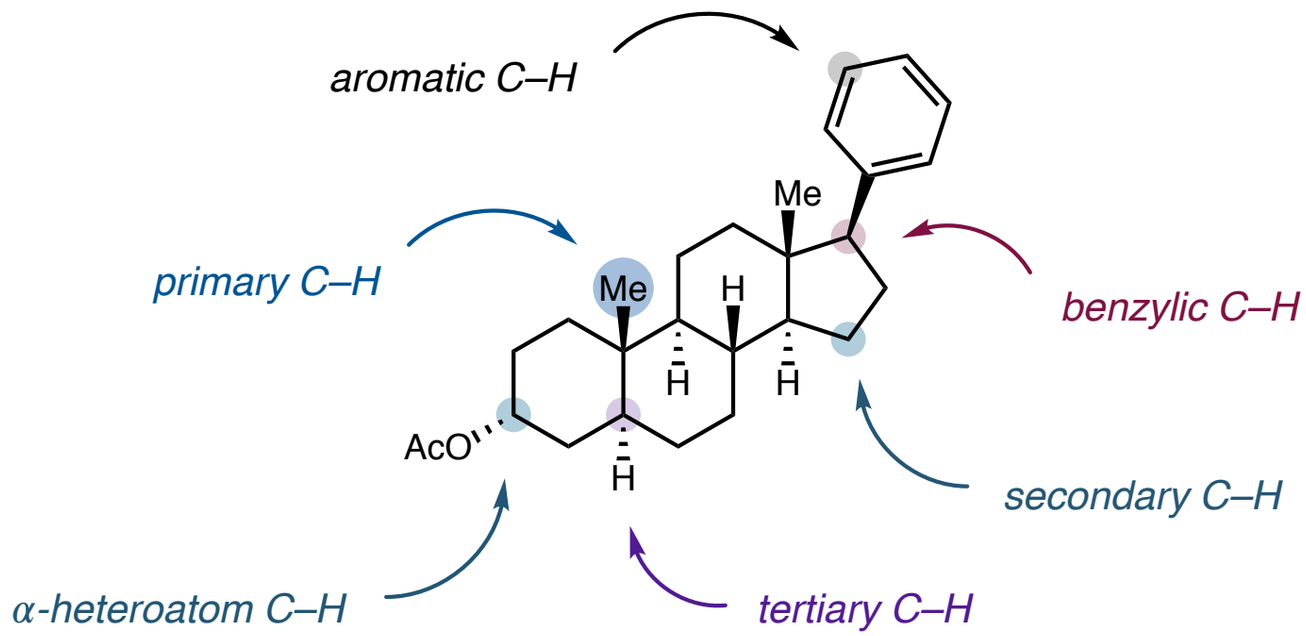
Selectivity in Non-Directed C–H Functionalization of sp^3 C–H Bonds



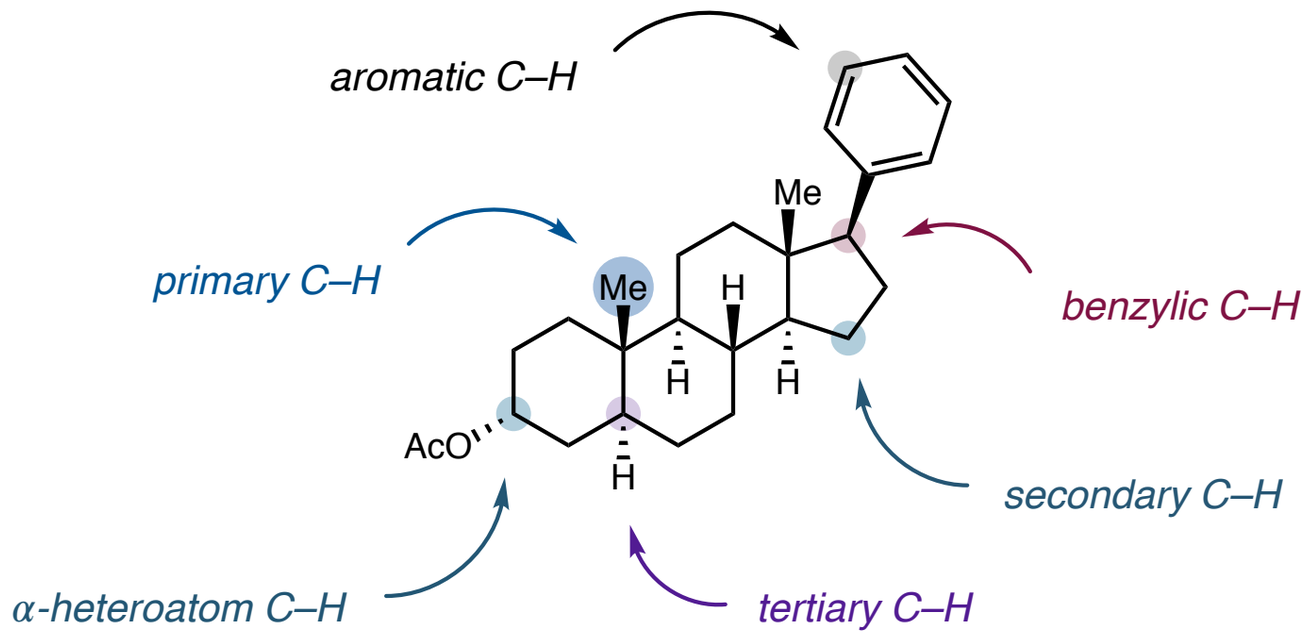
Megan Shaw
MacMillan Group Meeting

C–H Functionalization: Challenges for Selectivity and Reactivity



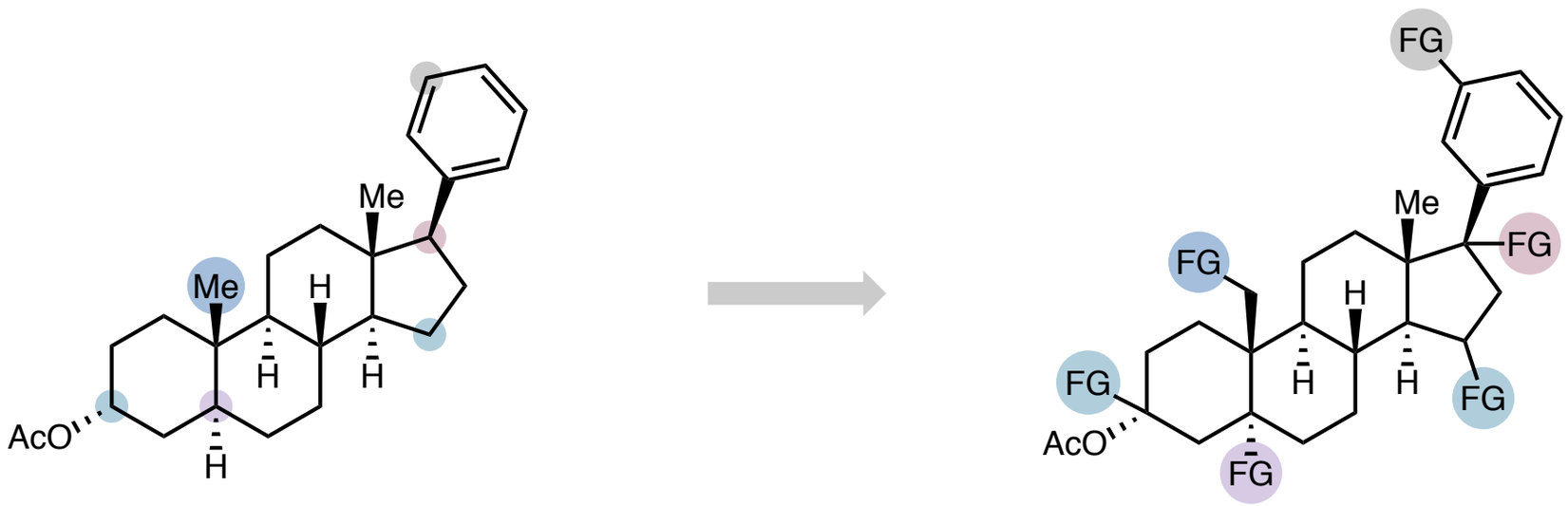
- *unactivated aliphatic bonds have high bond strengths*
- *low bond polarity - no lone pair/π-orbitals to interact with metal catalyst*
- *many C–H bonds in each molecule - hard to target specific bond*
- *non-directed often thermodynamically less favored that directed*

C–H Functionalization: Challenges for Selectivity and Reactivity



Why is so much research effort focused toward C–H activation?

C–H Functionalization: A Strategy for Streamlining Synthetic Sequences



direct C–H functionalization

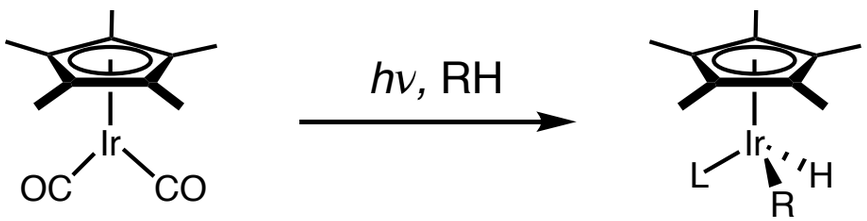
single differentially substituted product

Benefits of C–H Functionalization:

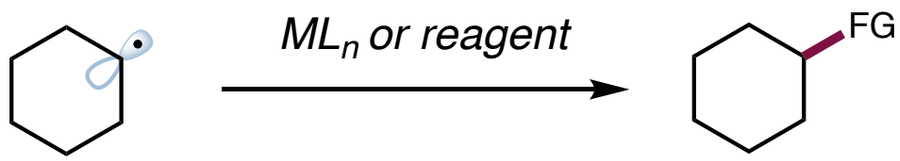
- *allows streamlining of synthetic routes - more atom economical*
- *direct functionalization of light alkanes to valuable feedstocks*
- *late stage functionalization of natural products and pharmaceuticals*
- *no requirement for pre-installation of functional groups*

C–H Functionalization: Presentation Outline

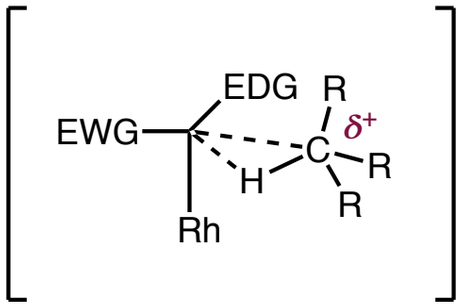
Concerted M–H Bond Formation



Functionalization via Radical Generation

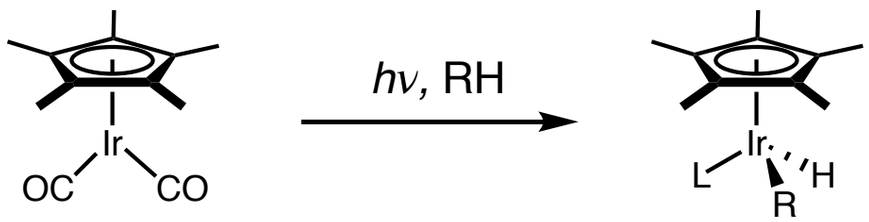


C–H Cleavage via Insertion of Metal Carbenes

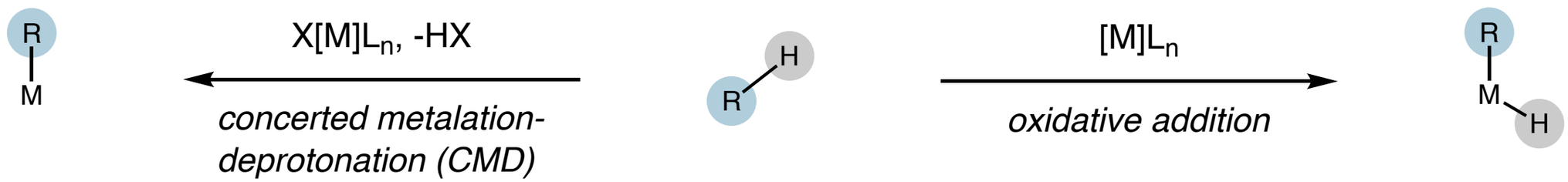


C–H Functionalization: Presentation Outline

Concerted M–H Bond Formation



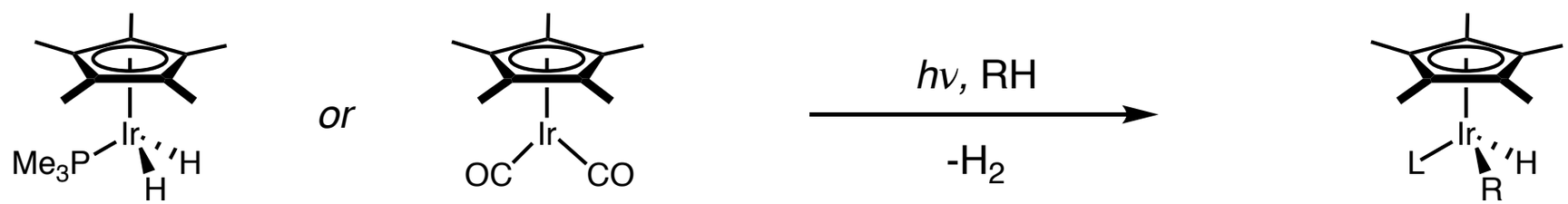
C–H Functionalization via Concerted M–C Bond Formation



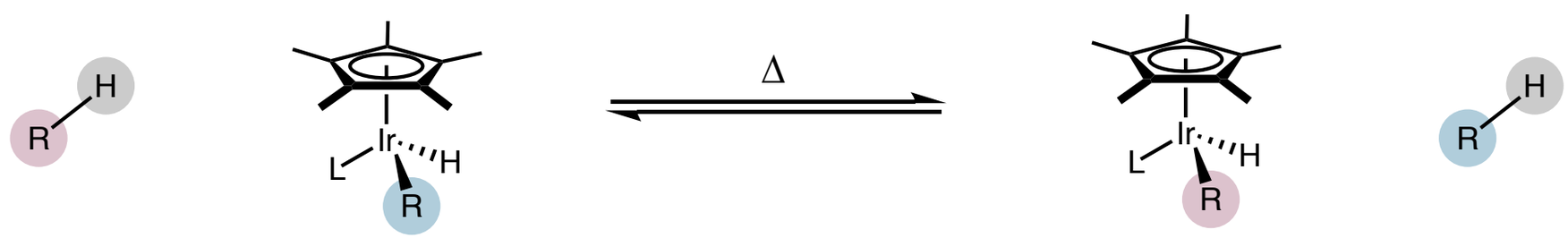
What factors influence selectivity when C–H activation proceeds via concerted M–C bond formation?

C–H Functionalization via Concerted M–C Bond Formation

Bergman and Graham: alkane C–H oxidative addition



JACS **1982**, *104*, 352.; *JACS* **1982**, *104*, 3723



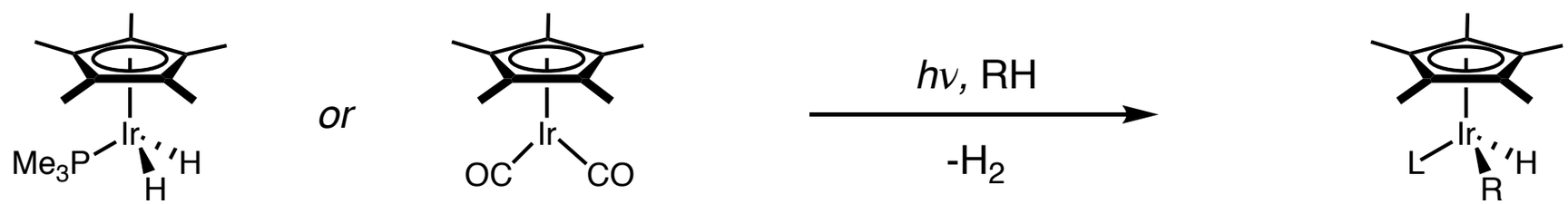
equilibration studies indicated thermodynamic preference for C–H activation:

aryl–H >> primary C–H > secondary C–H

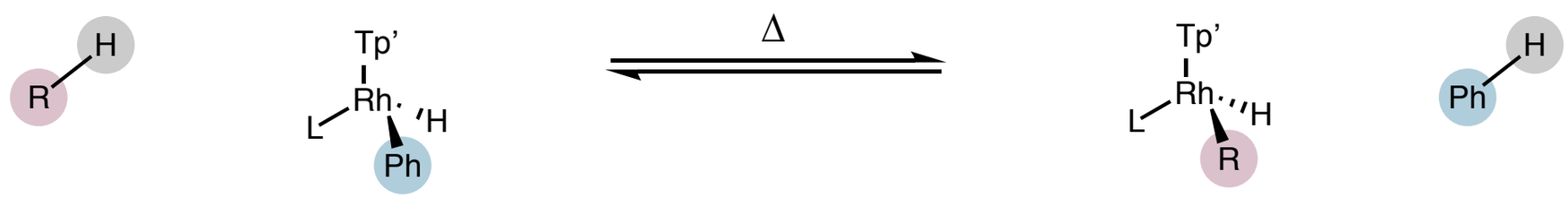
Buchanan, J. M.; Stryker, J. M.; Bergman, R. G. *JACS* ***1986****, 108,* 1537

C–H Functionalization via Concerted M–C Bond Formation

Bergman and Graham: alkane C–H oxidative addition



JACS **1982**, *104*, 352.; *JACS* **1982**, *104*, 3723



R	C–H BDE (kJ mol^{-1})	M–R relative bond strength	k_{rel}
phenyl	474	0	1
methyl	438	-69	2.3
n-pentyl	410	-104	4.7
c-hexyl	401	-121	35.2

increasing C–H BDE

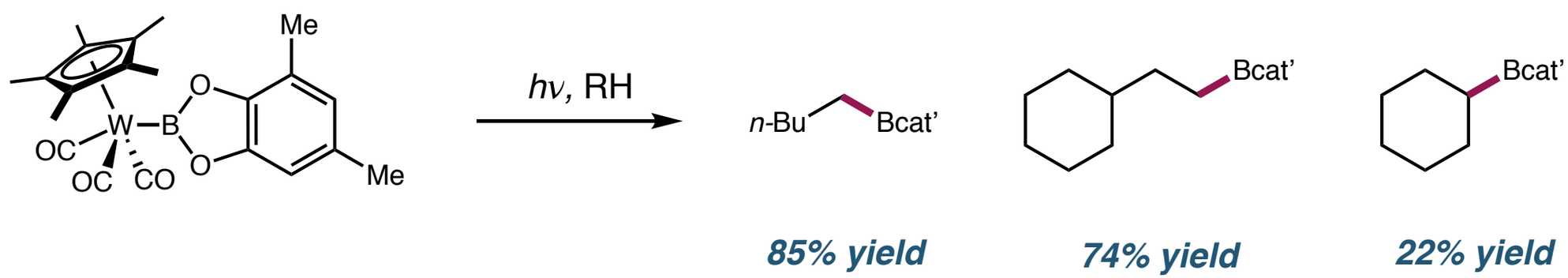
increasing M–R BDE

increasing rate of ox add.

Jones, W. D.; Feher, F. J. *Acc. Chem. Res.* **1989**, *22*, 91.

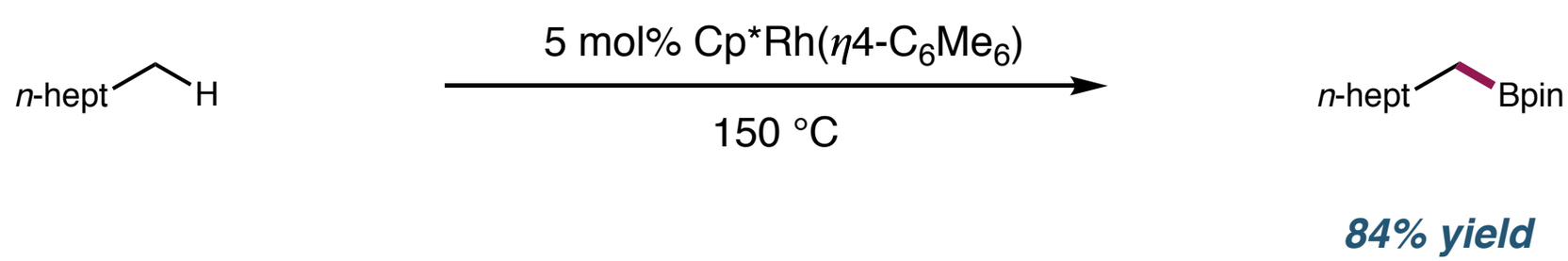
Catalytic C–H Borylation of Alkanes

Stoichiometric Borylation of Alkanes



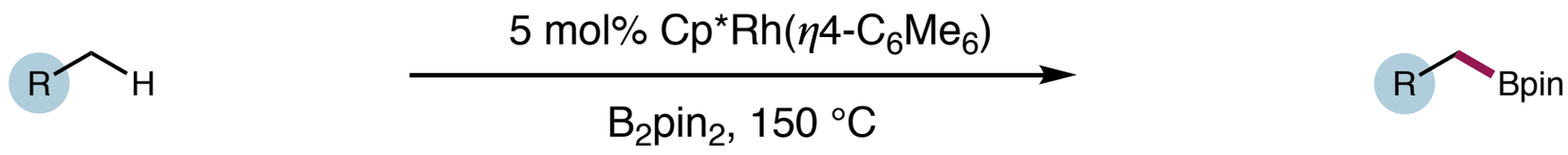
Waltz, K. M.; Hartwig, J. F. *Science* **1997**, *277*, 211.

Catalytic Borylation of Alkanes

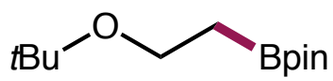


Chen, H.; Schlecht, S.; Semple, T. C.; Hartwig, J. F. *Science* **2000**, *287*, 1995.

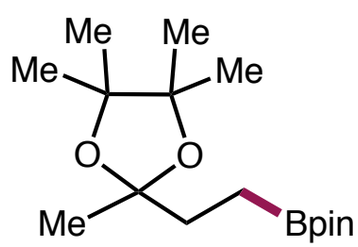
Catalytic C–H Borylation of Alkanes



alkane ***borylated product***

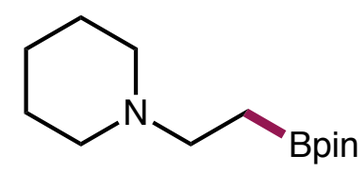


91% yield
(48% yield)

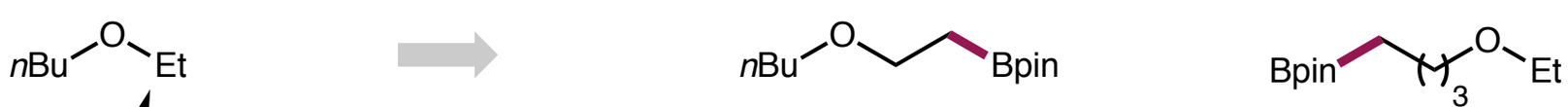


74% yield
(70% yield)

83% yield
(46% yield)



55% yield
(67% yield)

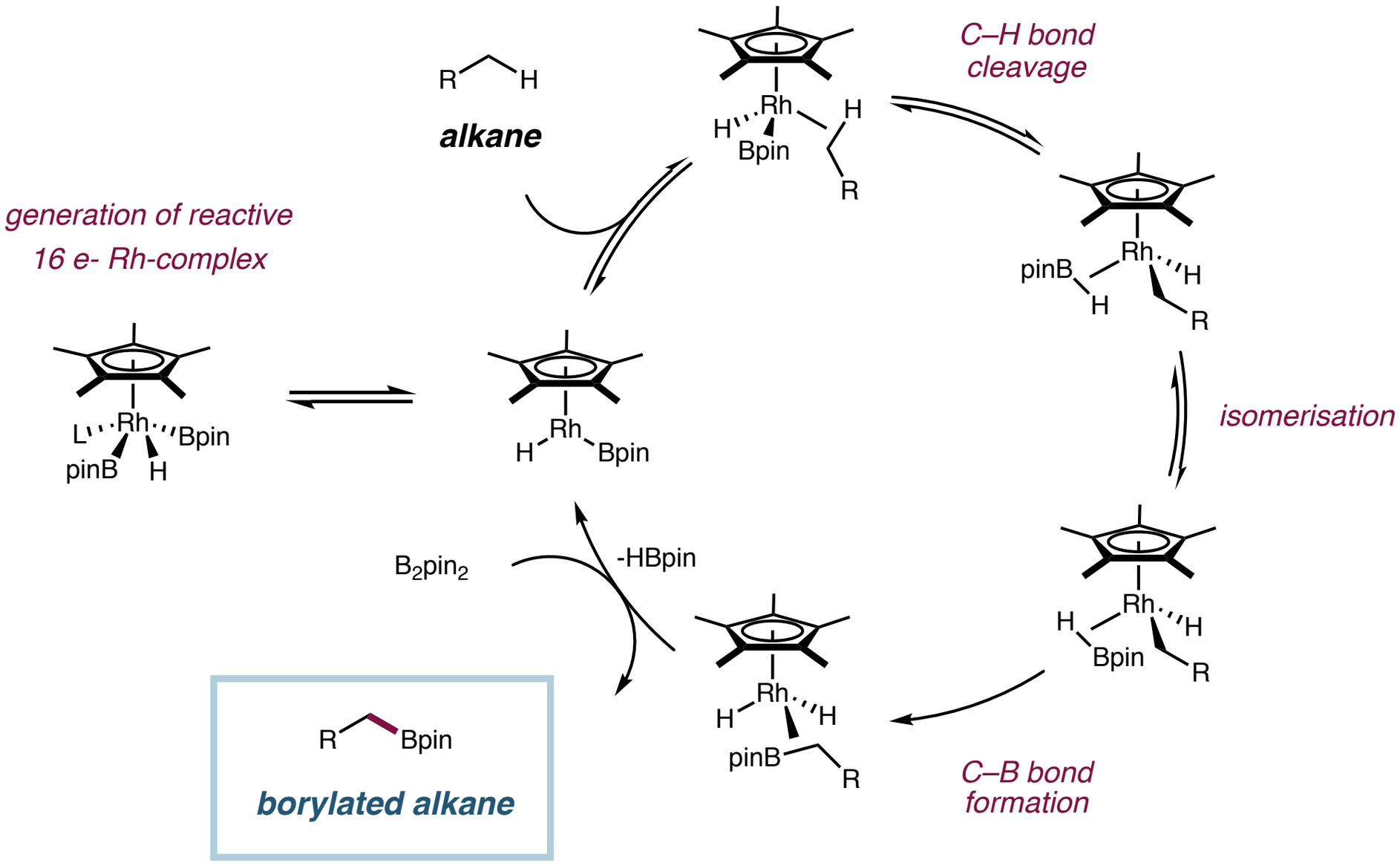


preferential functionalisation of more electron-deficient unhindered C–H bond

4:1 regiomeric ratio

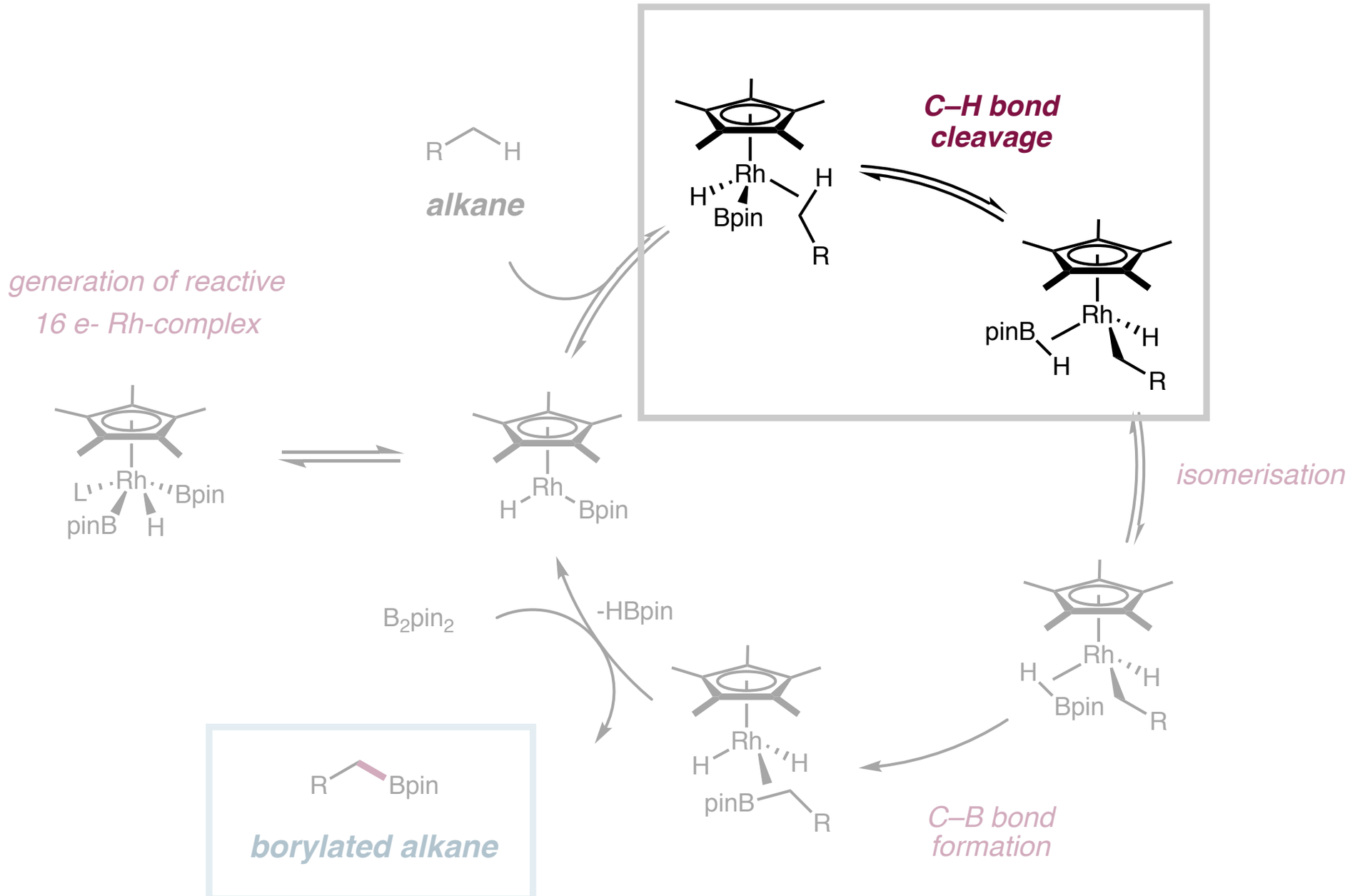
Lawrence, J. D.; Takahashi, M.; Bae, C.; Hartwig, J. F. *JACS* **2004**, *126*, 15334.

Catalytic C–H Borylation of Alkanes



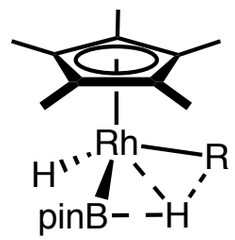
Wei, C. S.; Jimenez-Hoyos, C. A.; Videa, M. F.; Hartwig, J. F.; Hall, M. B. *JACS* **2010**, *132*, 3078.

Selectivity for Primary C–H Borylation

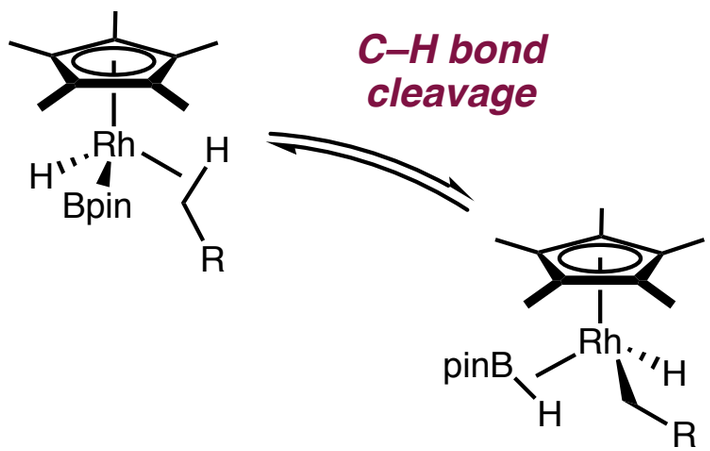


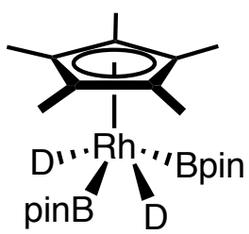
Wei, C. S.; Jimenez-Hoyos, C. A.; Videa, M. F.; Hartwig, J. F.; Hall, M. B. *JACS* **2010**, *132*, 3078.

Selectivity for Primary C–H Borylation

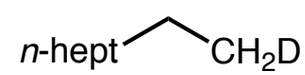


σ-bond metathesis TS
boron p-orbtial implicated

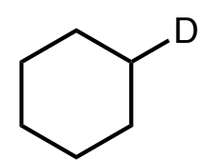




1:1 octane
cyclohexane
→
8 h



0.87 D-incorporation

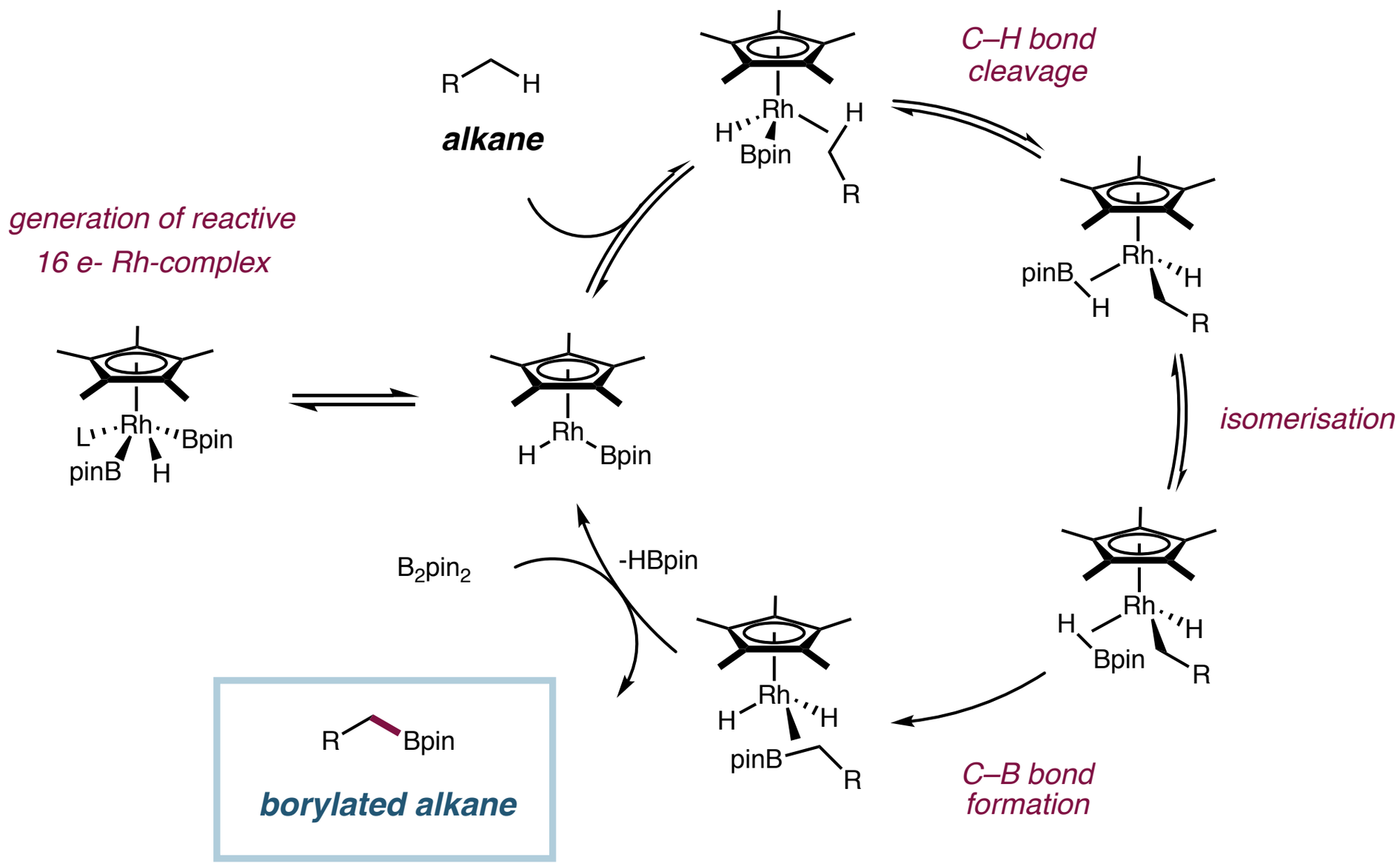


0.15 D-incorporation

reversible insertion enables generation of thermodynamically favoured C–H cleavage complex

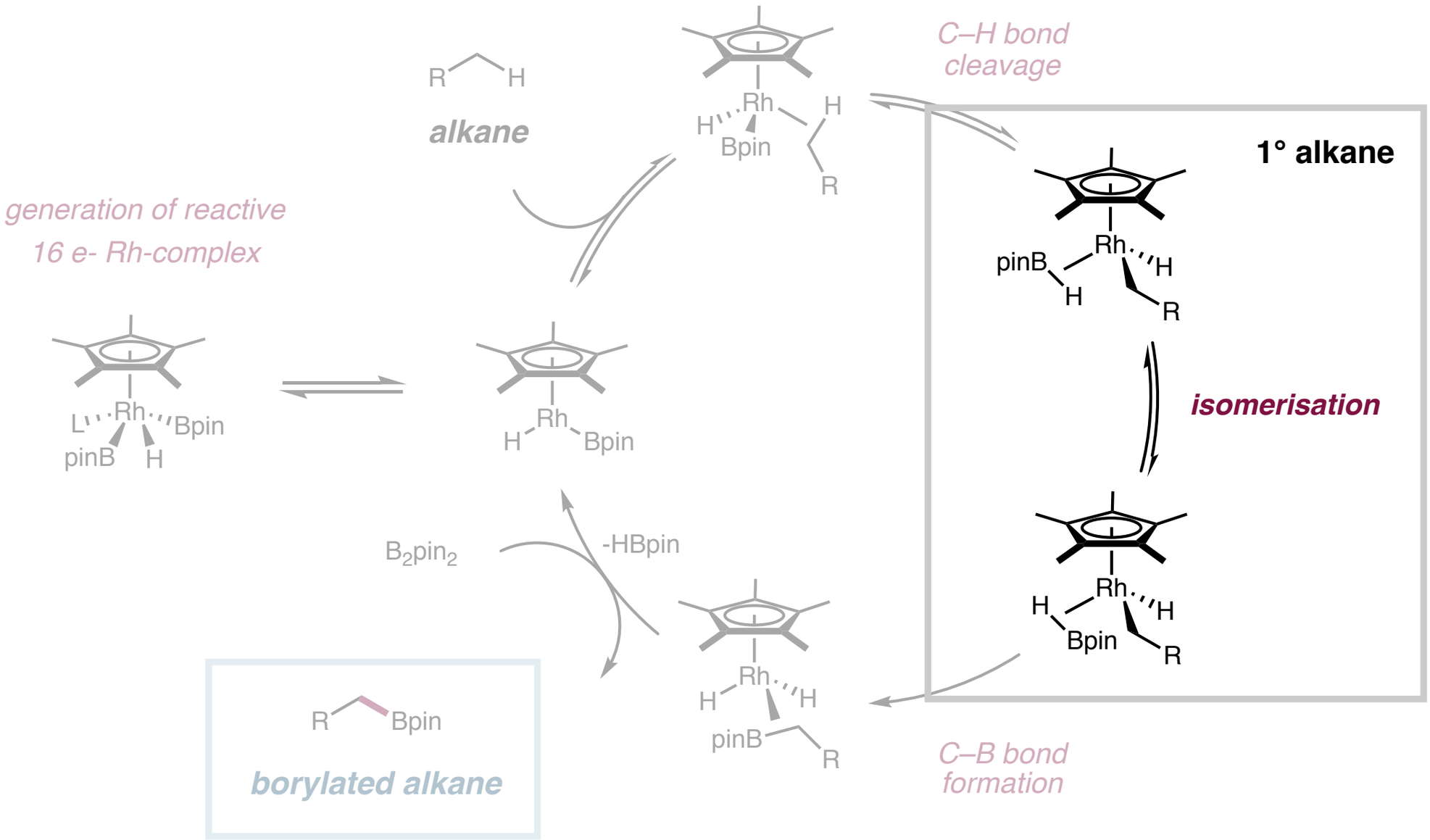
Wei, C. S.; Jimenez-Hoyos, C. A.; Videa, M. F.; Hartwig, J. F.; Hall, M. B. *JACS* **2010**, *132*, 3078.

Catalytic C–H Borylation of Alkanes



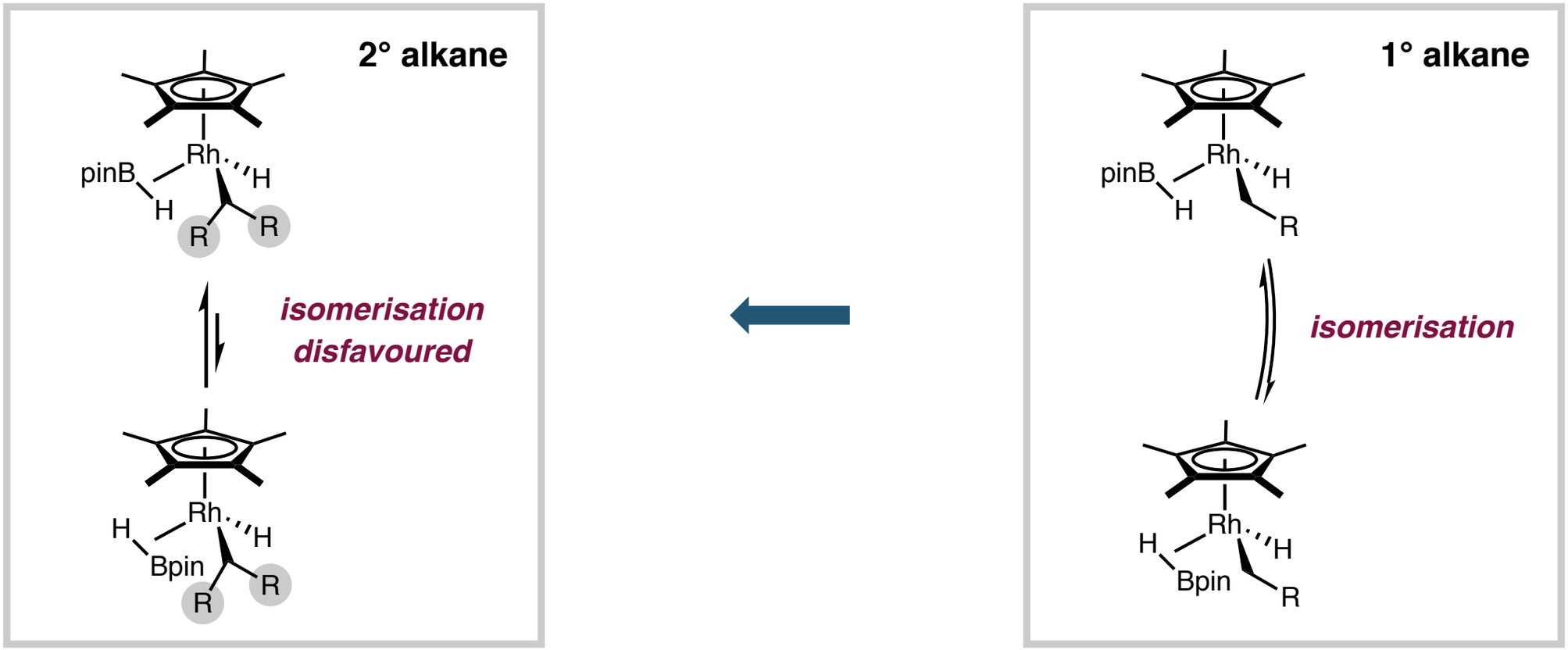
Wei, C. S.; Jimenez-Hoyos, C. A.; Videa, M. F.; Hartwig, J. F.; Hall, M. B. *JACS* **2010**, *132*, 3078.

Catalytic C–H Borylation of Alkanes



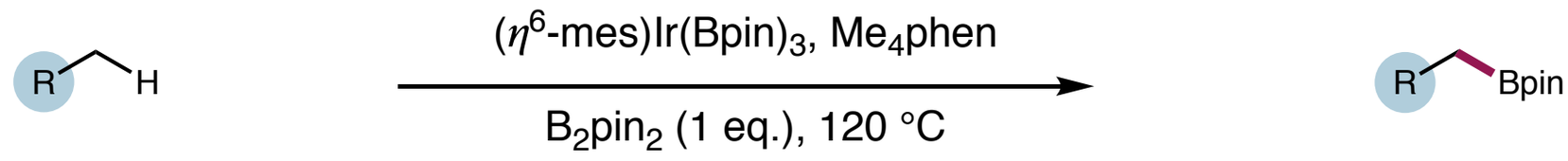
Wei, C. S.; Jimenez-Hoyos, C. A.; Videa, M. F.; Hartwig, J. F.; Hall, M. B. *JACS* **2010**, *132*, 3078.

Catalytic C–H Borylation of Alkanes



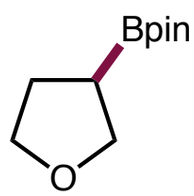
Wei, C. S.; Jimenez-Hoyos, C. A.; Videa, M. F.; Hartwig, J. F.; Hall, M. B. *JACS* **2010**, *132*, 3078.

Catalytic C–H Borylation of Alkanes

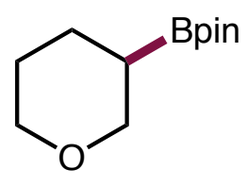


alkane
(9 equiv.)

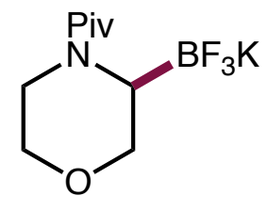
borylated product



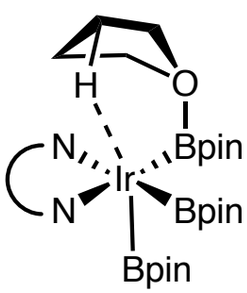
83% yield



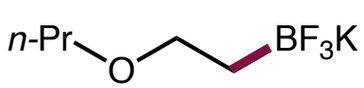
90% yield



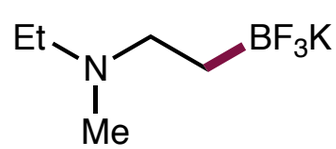
41% yield



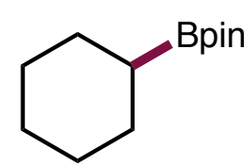
6-membered chelate favours β-cleavage



146% yield



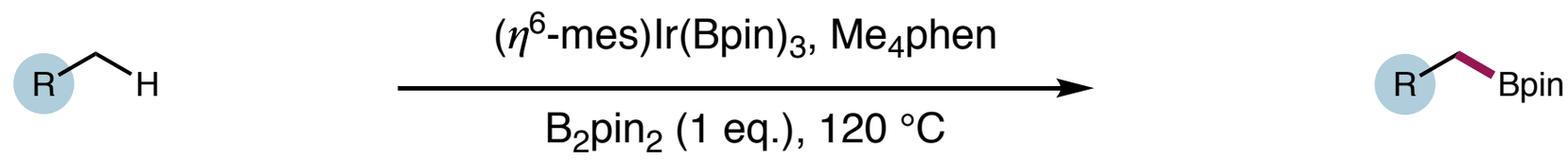
84% yield



39% yield

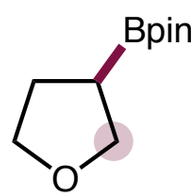
Liskey, C. W.; Hartwig, J. F. *JACS* **2012,** *134*, 12422

Catalytic C–H Borylation of Alkanes

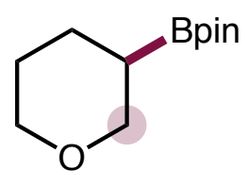


alkane
(9 equiv.)

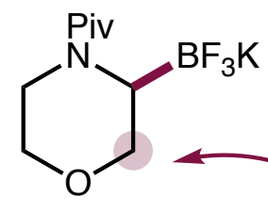
borylated product



83% yield



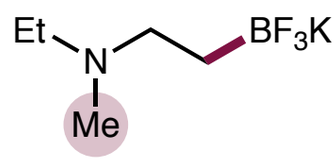
90% yield



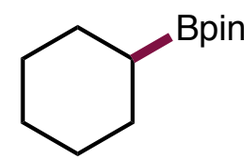
41% yield

anticipated site selectivity via radical generation

146% yield



84% yield

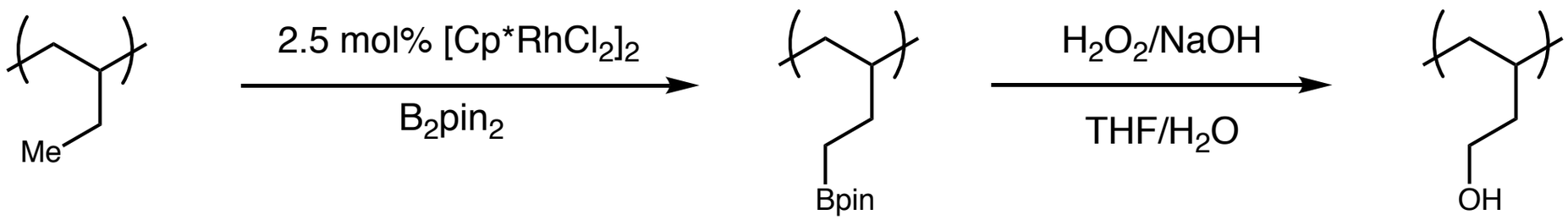


39% yield

Liskey, C. W.; Hartwig, J. F. *JACS* **2012,** *134*, 12422

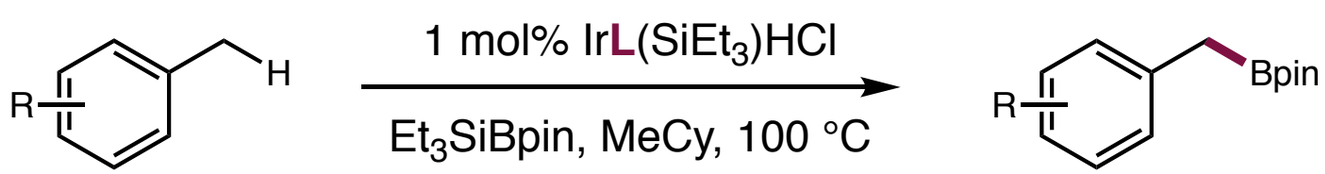
Catalytic C–H Borylation of Alkanes

Polymer functionalisation via borylation

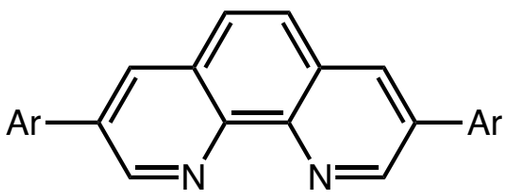


Kondo, Y.; Garcia-Cuadrado, D.; Hartwig, J. F.; Boaen, N. K.; Wagner, N. L.; Hillmyer, M. A. *JACS* **2002**, *124*, 1164

Direct Functionlization of Benzylic C–H Bonds



1.7-99:1 rr



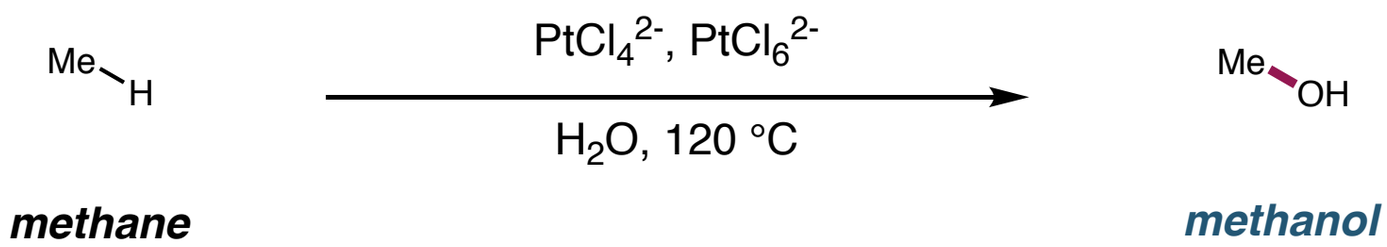
L

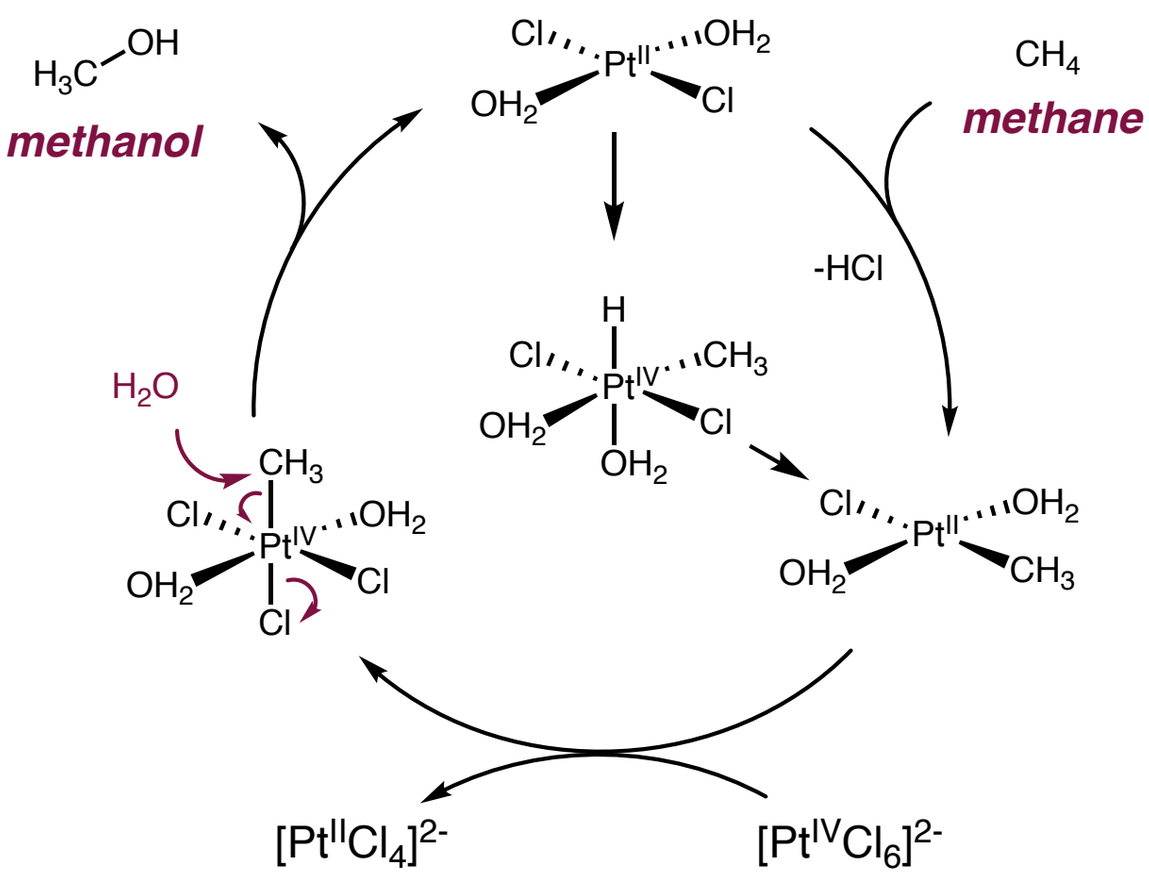
Ar = 3,5-$(CF_3)_2C_6H_3$

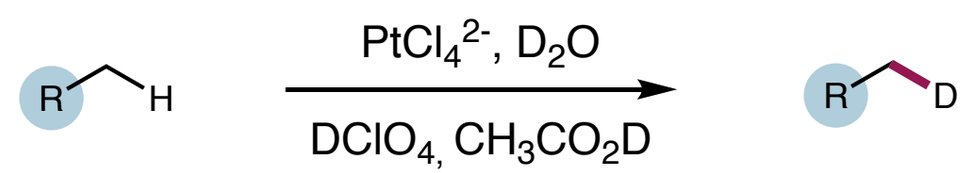
Larsen, M. A.; Wilson, C. V.; Hartwig, J. F. *JACS* **2015**, *137*, 8633-8643

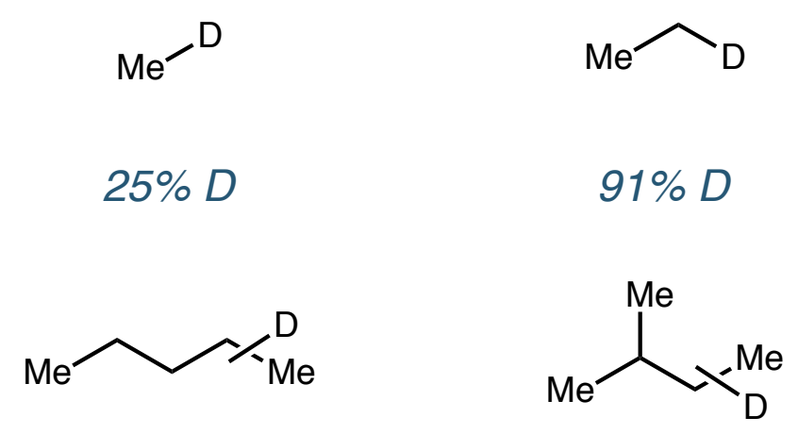
Pt-Catalyzed C–H Functionalization

Shilov process, 1972:









25% D

91% D

75% D

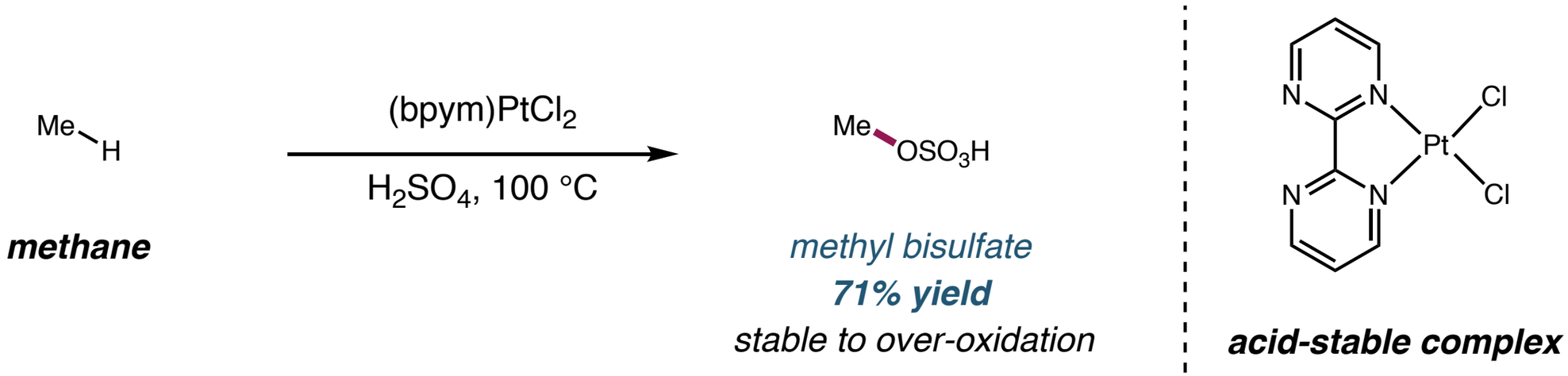
1.6:1 1°:2°

69% D

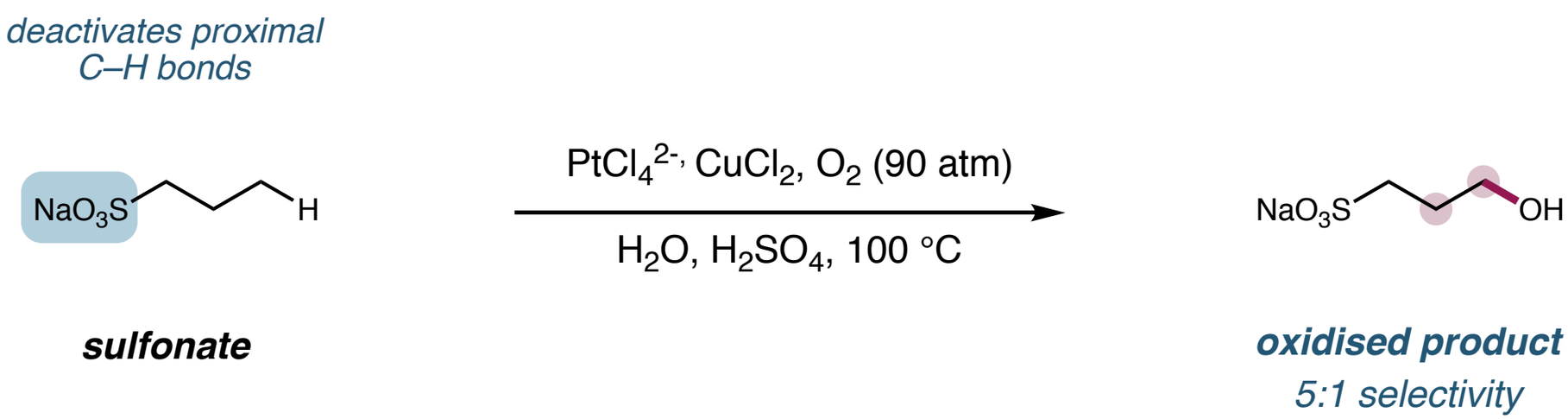
9:4:1 1°:2°:3°

Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2979

Pt-Catalyzed C–H Functionalization

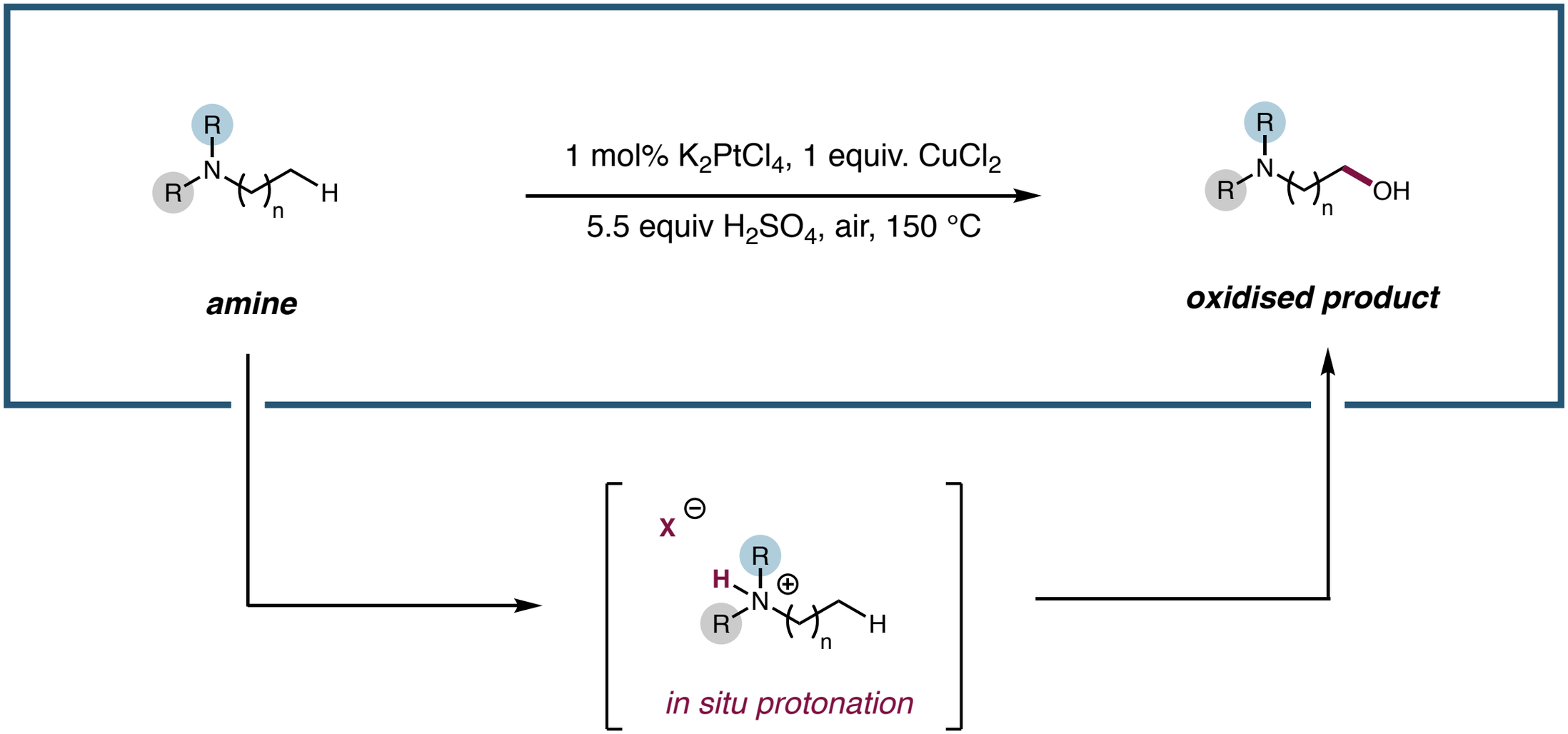


Periana, R. A.; Taube, D. J.; Gamble, S.; Taube, H.; Satoh, T.; Fujii, H. *Science* **1998**, *280*, 560



Lin, M.; Shen, C.; Garcia-Zayas, E. A.; Sen, A. *JACS* **2001**, *123*, 1000.

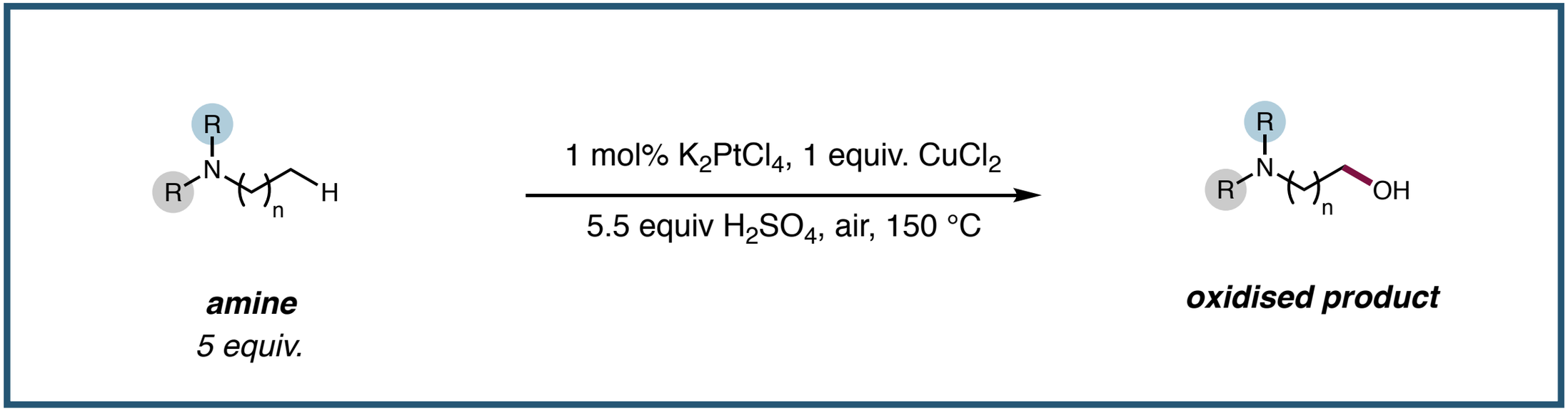
Pt-Catalyzed C–H Functionalization

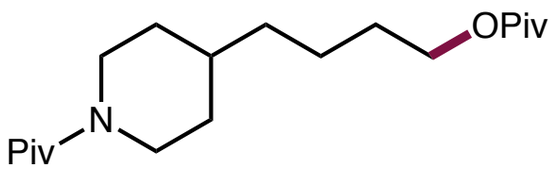


- ***renders substrate soluble in aq reaction medium***
- ***protects catalysts from coordination to basic amine functionality***
- ***electronically deactivates proximal C–H bonds***

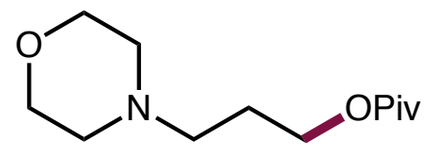
Lee, M.; Sanford, M. S. *JACS*, **2015**, *137*, 12796

Pt-Catalyzed C–H Functionalization

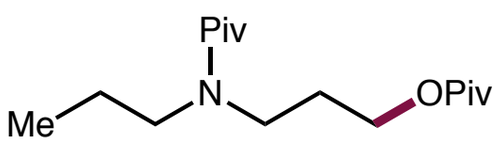




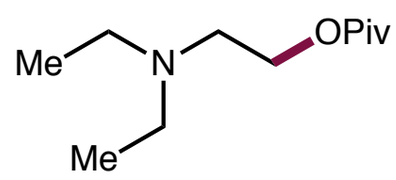
65% yield
5:1 rr



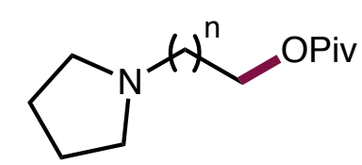
122% yield
10:1 rr



87% yield
8:1 rr



88% yield
>20:1 rr

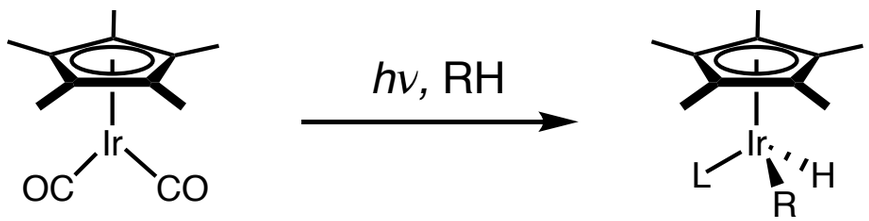


n = 1	***25% yield, >20:1 rr***
n = 2	***85% yield, 10:1 rr***
n = 3	***126% yield, 4:1 rr***
n = 4	***73% yield, 2:1 rr***

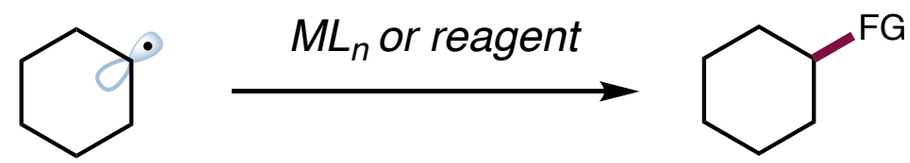
Lee, M.; Sanford, M. S. *JACS*, **2015**, *137*, 12796

C–H Functionalization: Presentation Outline

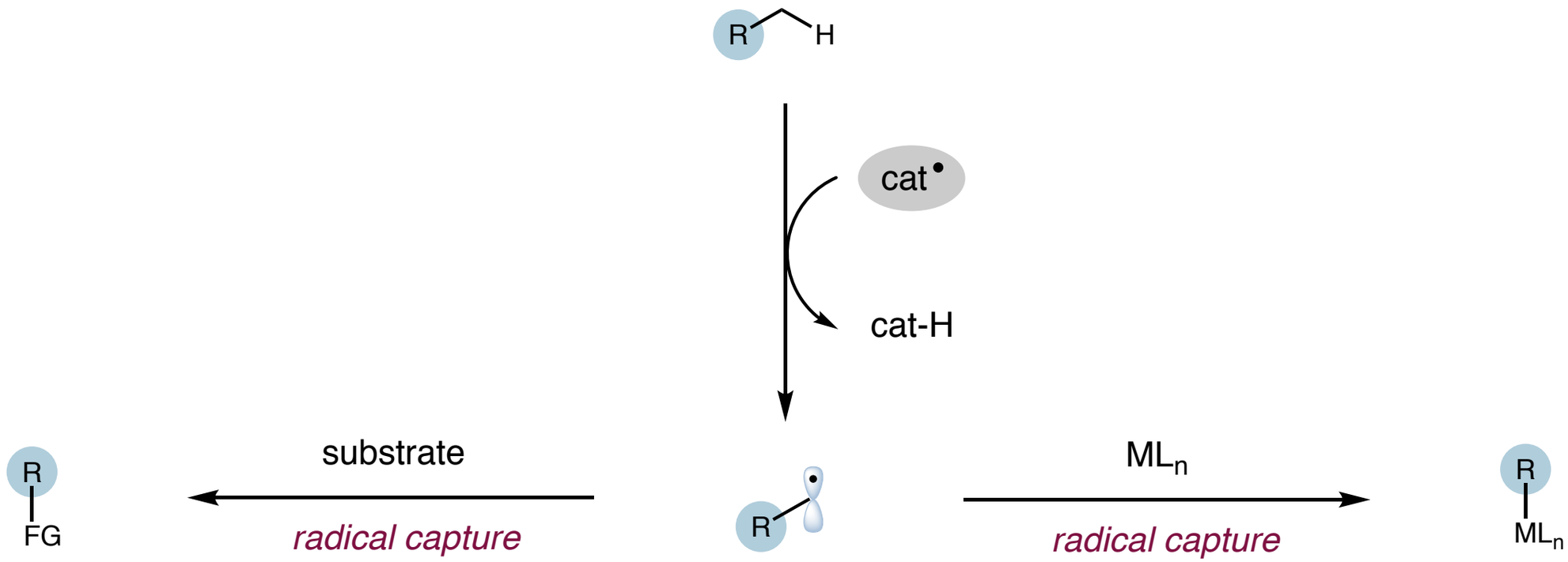
Concerted M–H Bond Formation



Functionalization via Radical Generation



C–H Functionalization via Radical Generation

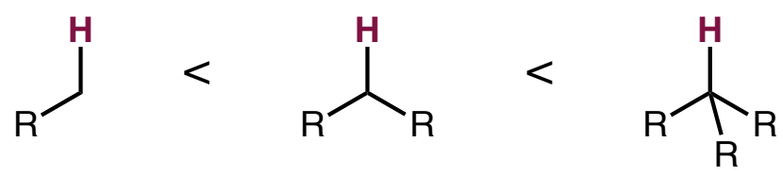


What factors influence selectivity when C–H activation proceeds through the generation of an alkyl radical?

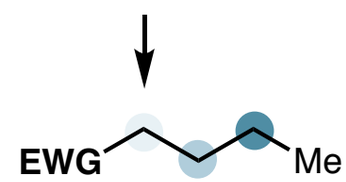
C–H Functionalization via Radical Generation

Inductive effects

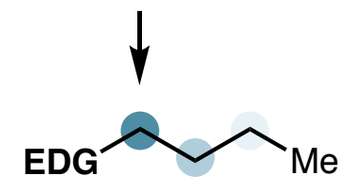
radical stability influences reactivity



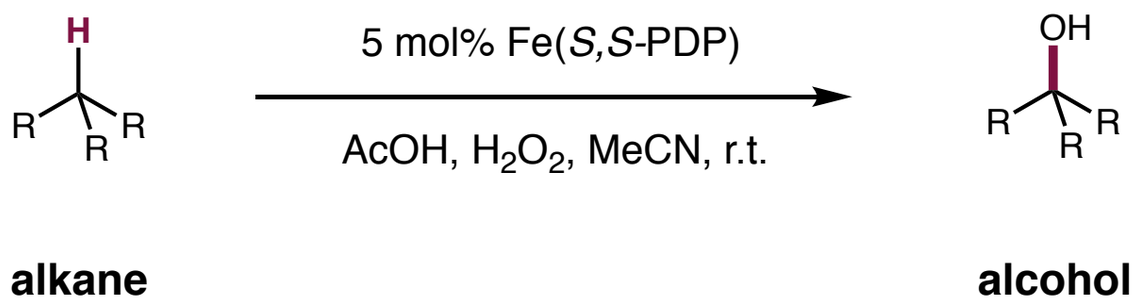
electron-deficient
deactivated

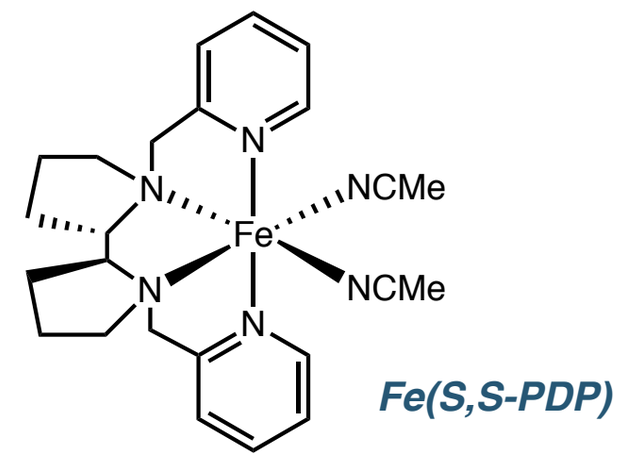


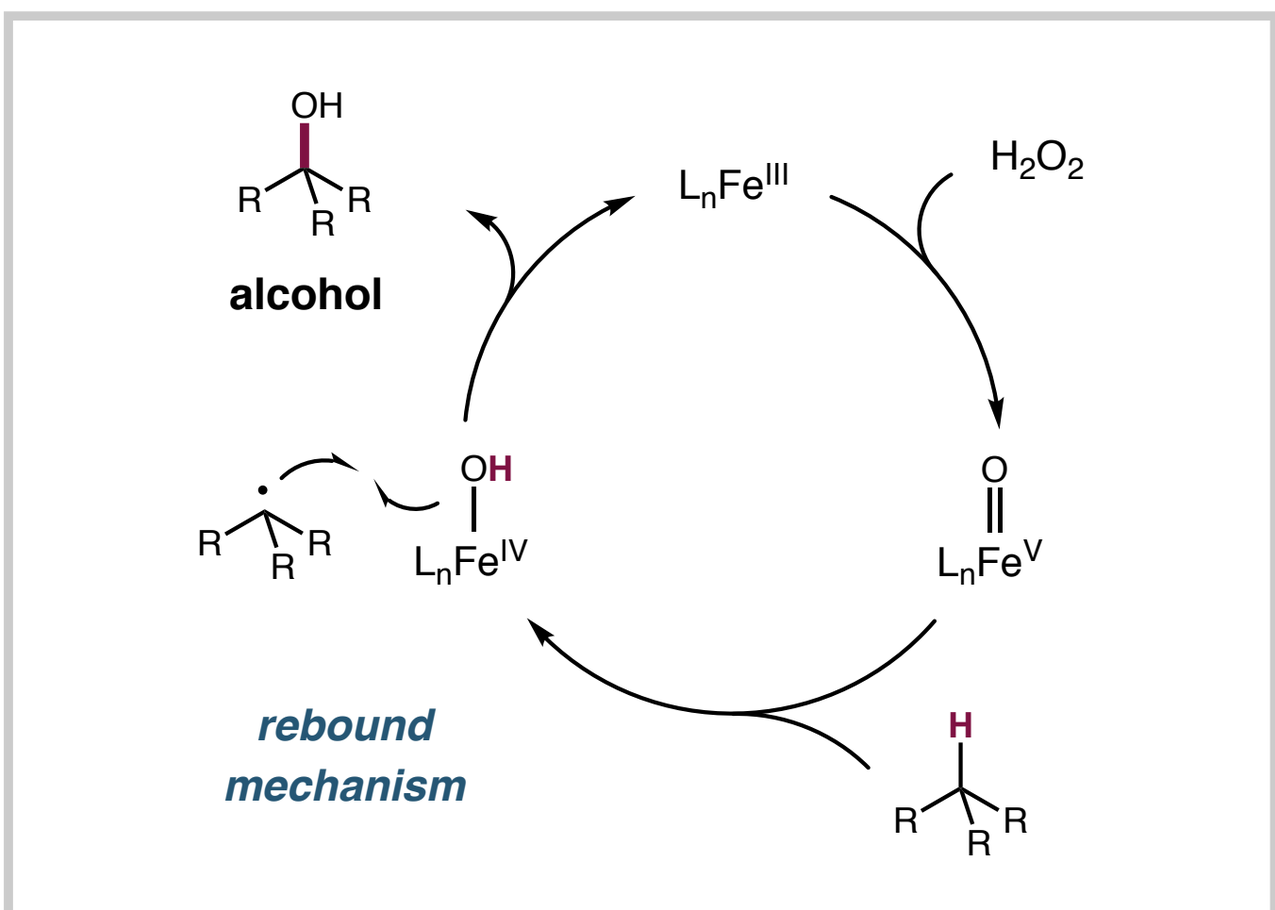
electron-rich
activated



Inductive Effects Influence Site Selectivity for Oxidation

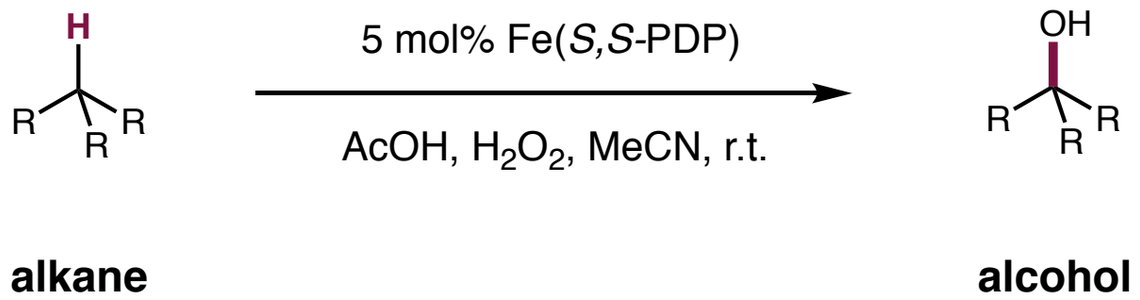


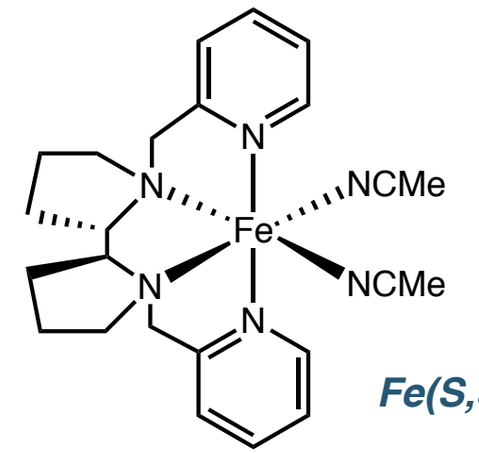




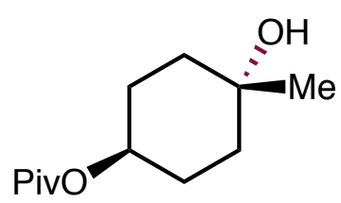
mechanistically similar to metalloporphyrin oxidation pathway

Inductive Effects Influence Site Selectivity for Oxidation

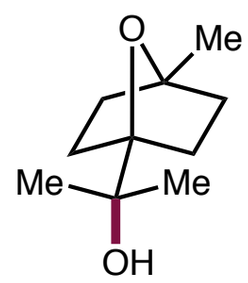




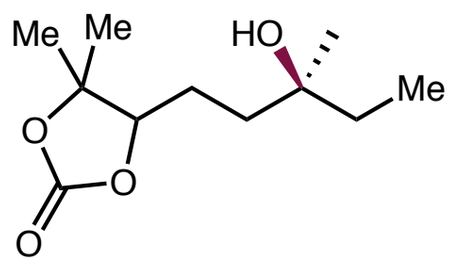
Fe(S,S-PDP)



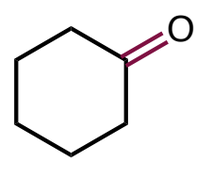
51% yield



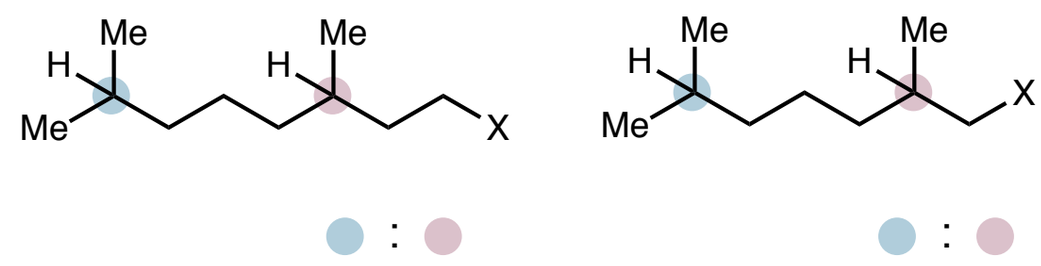
52% yield



57% yield



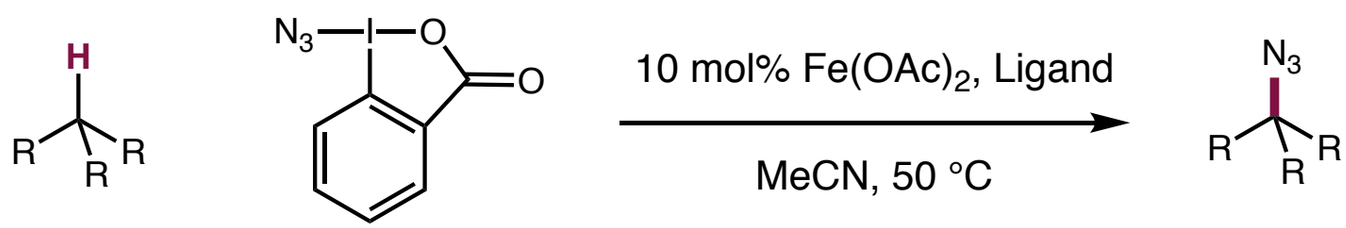
92% yield



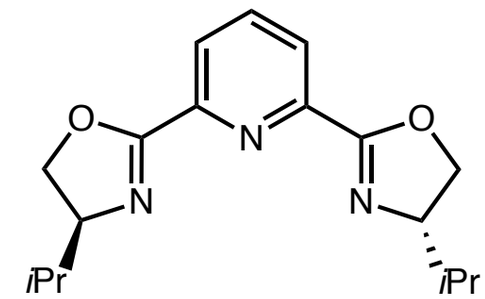
X = H	*1:1*	*X = OAc*	*29:1*
X = OAc	*5:1*	*X = Br*	*20:1*
X = Br	*9:1*		

Chen, M. S.; White, M. C. *Science* **2007**, *381*, 783

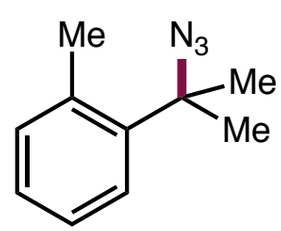
Inductive Effects Influence Site Selectivity for Oxidation



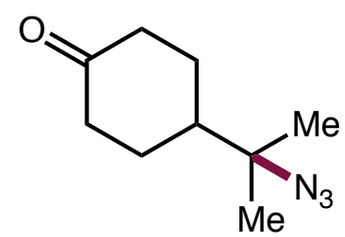
alkane **azide**



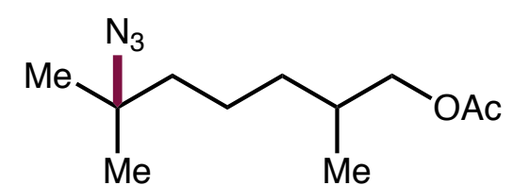
Ligand



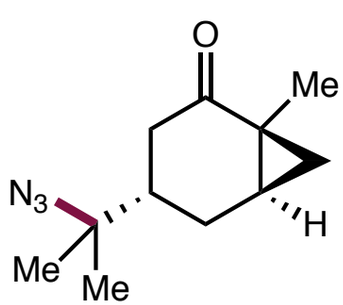
67% yield, 12:1 r.r



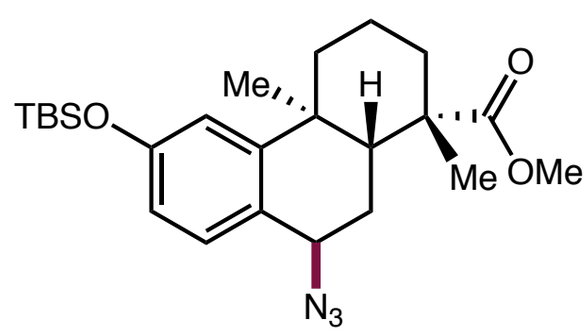
53% yield, 5:1 r.r



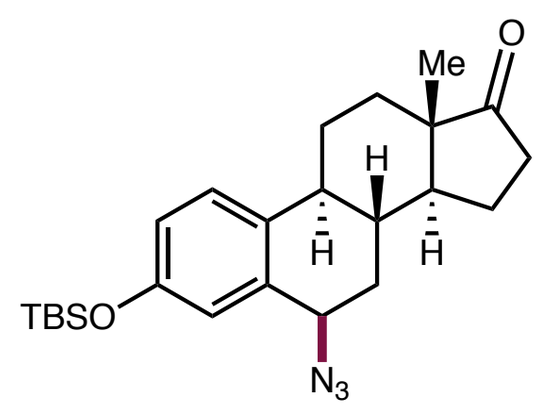
50% yield, 10:1 r.r



53% yield, 10:1:1 r.r



75% yield, 6:1 r.r



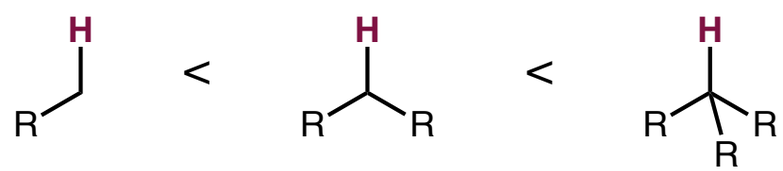
24% yield, 5:1 r.r

Sharma, A.; Hartwig, J. F. *Nature* **2015**, *517*, 600.

C–H Functionalization via Radical Generation

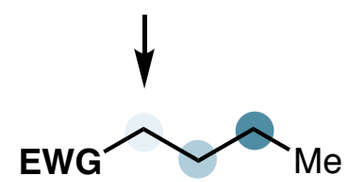
Inductive effects

radical stability influences reactivity

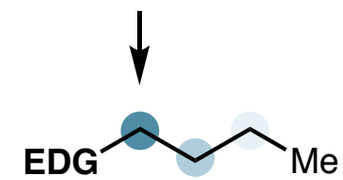


1° **2°** **3°**

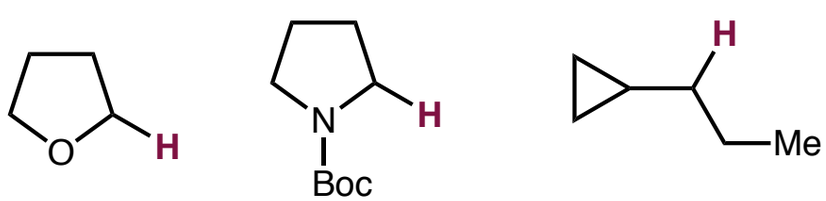
electron-deficient
deactivated



electron-rich
activated

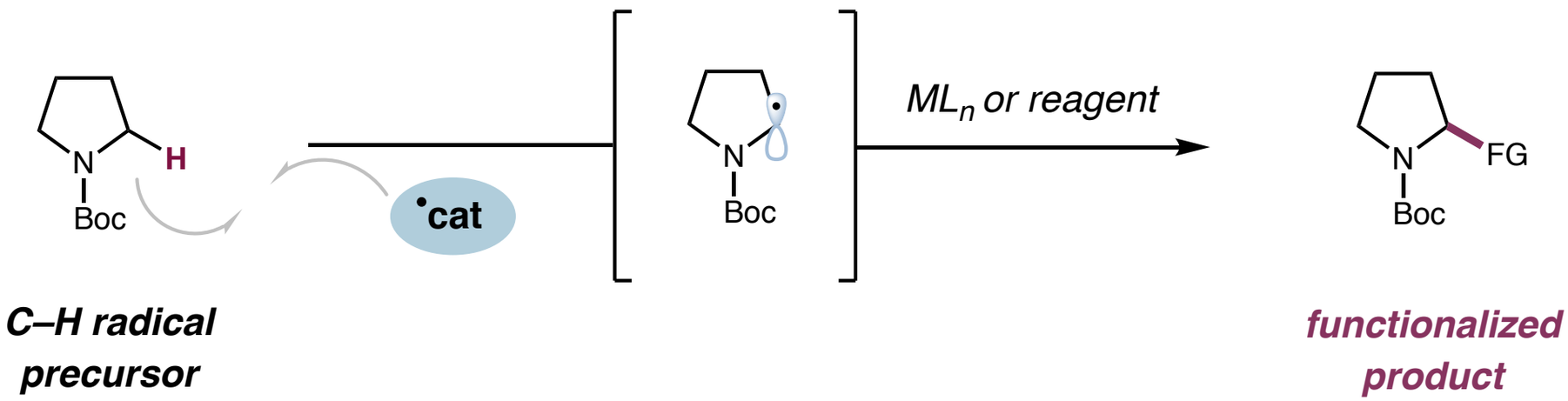


Hyperconjugation

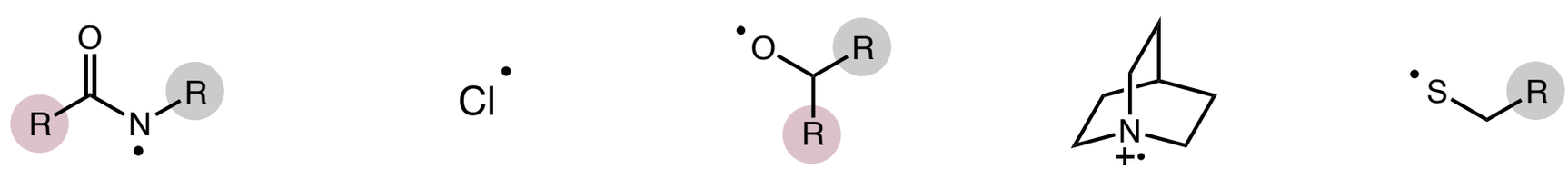


n → $\sigma^*_{C–H}$ σ_{C-C} → $\sigma^*_{C–H}$

Hyperconjugation Favors Selectivity Adjacent to Heteroatoms



HAT catalysts

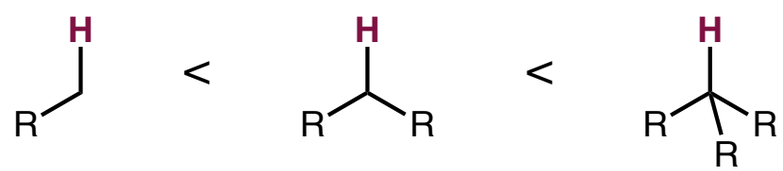


amidyl radical ***halide radical*** ***O-centred radical*** ***amine radical cation*** ***thiyl radical***

C–H Functionalization via Radical Generation

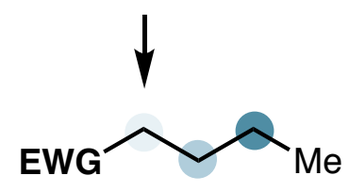
Inductive effects

radical stability influences reactivity

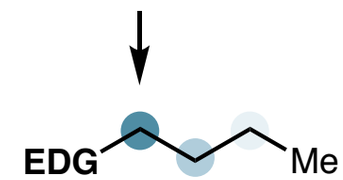


1° **2°** **3°**

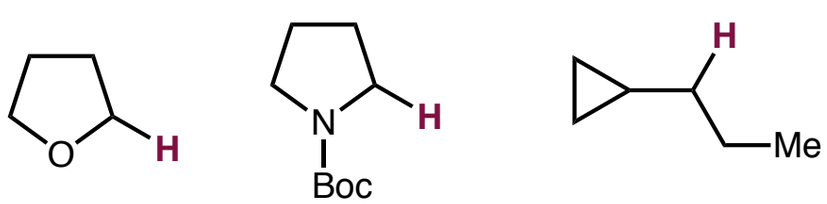
electron-deficient
deactivated



electron-rich
activated

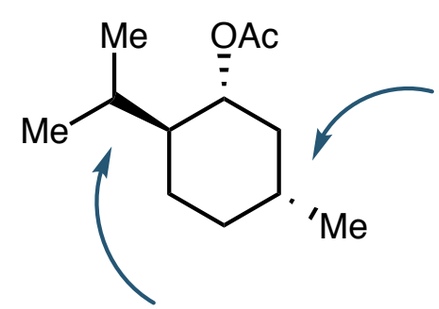


Hyperconjugation



n → $\sigma^*_{C–H}$ σ_{C-C} → $\sigma^*_{C–H}$

Steric effects

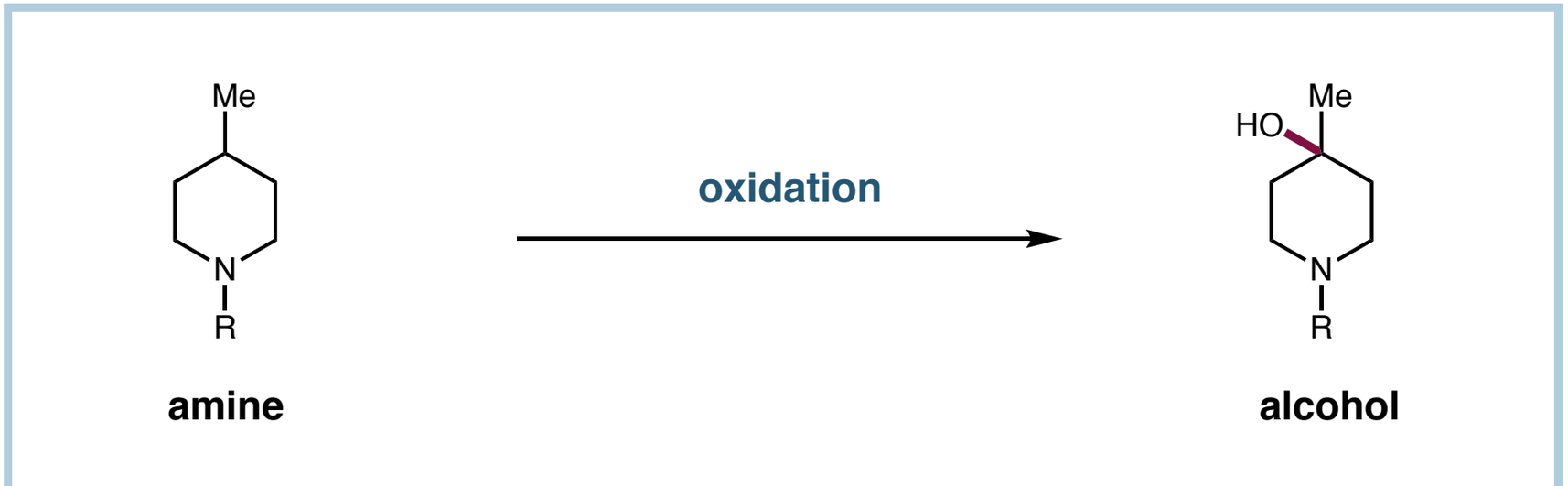


primary site of oxidation

secondary site of oxidation

[Fe(mcpp)]
17:1 r.r.

Strategies for Overcoming Substrate Control: N-Complexation

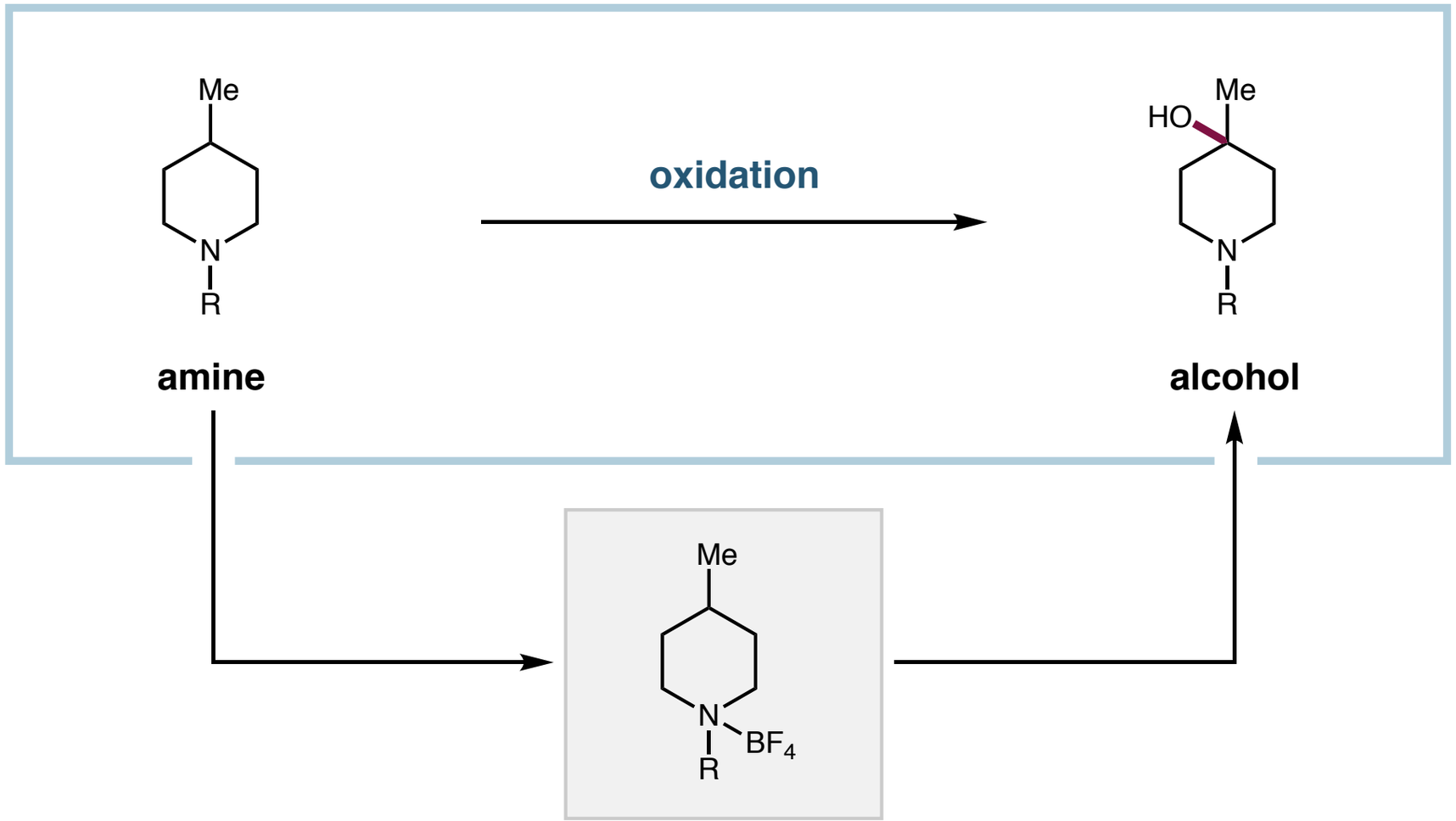


Challenges of N-Heterocycle Remote Oxidation

N-heterocycles prone to catalyst complexation and/or oxidation to N-oxide

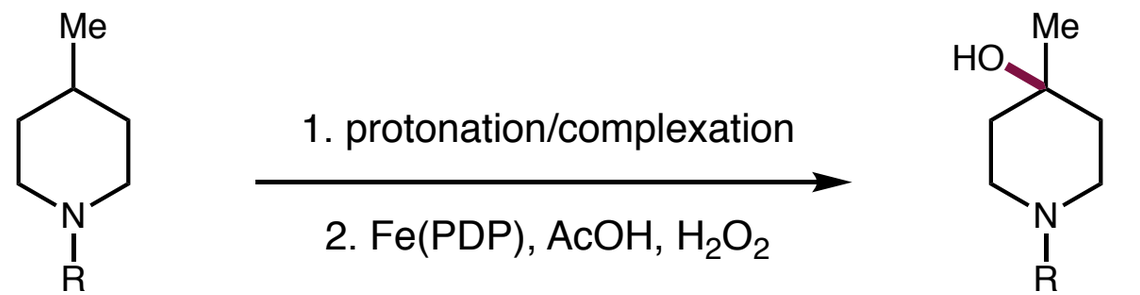
C–H bonds adjacent to nitrogen are activated toward functionalization

Strategies for Overcoming Substrate Control: N-Complexation

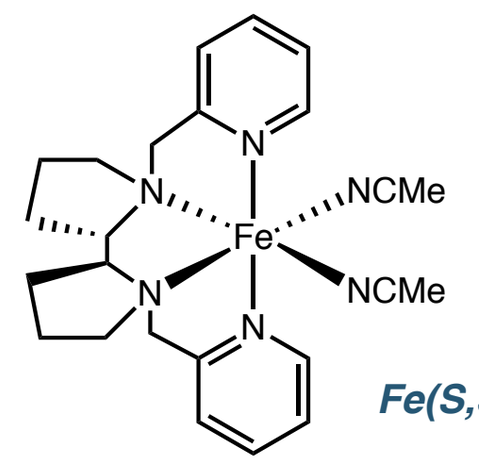


Lewis acid complexation renders basic nitrogen strongly withdrawing

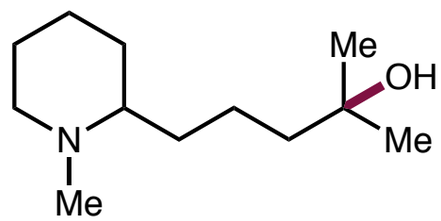
Strategies for Overcoming Substrate Control: N-Complexation



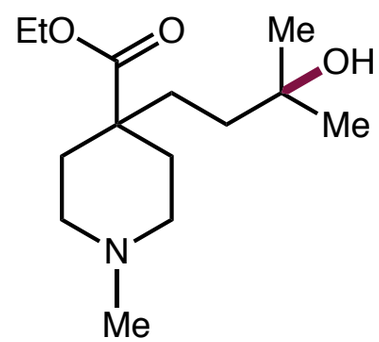
amine **alcohol**



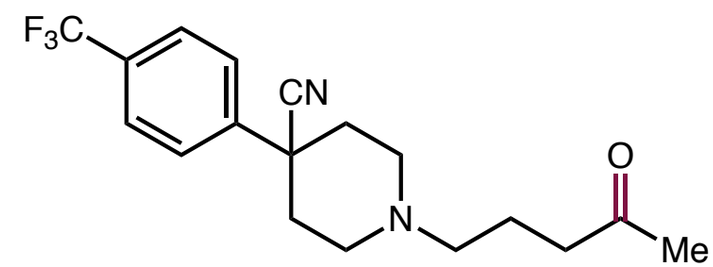
Fe(S,S-PDP)



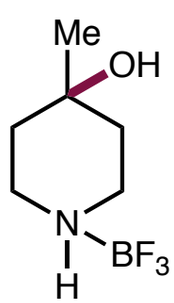
52% yield



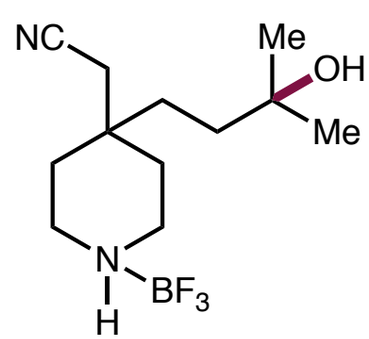
55% yield



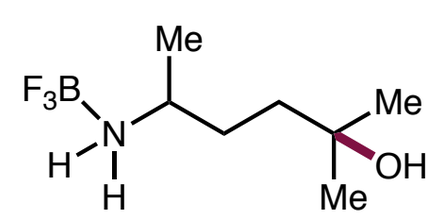
40% yield



65% yield



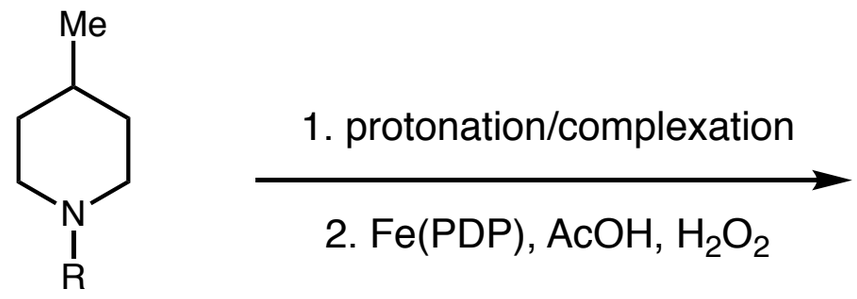
60% yield



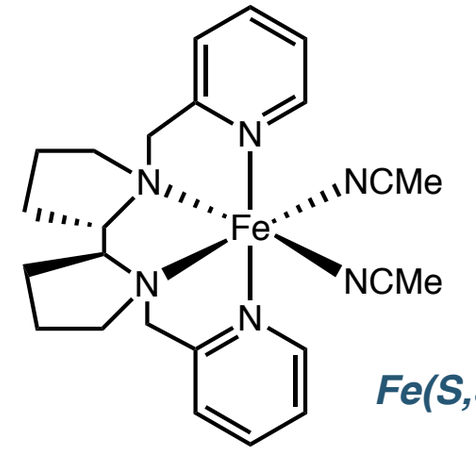
56% yield

Howell, J. M.; Feng, K.; Clark, J. R.; Trzepkowski, L. J.; White, M. C. *JACS* **2015**, *137*, 14590.

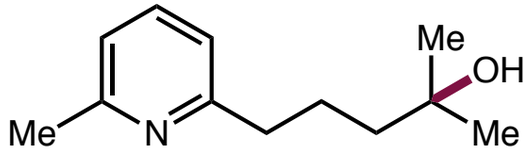
Strategies for Overcoming Substrate Control: N-Complexation



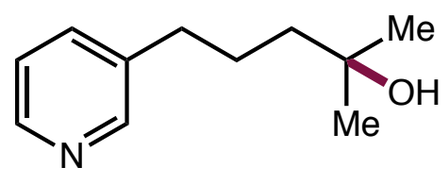
amine **alcohol**



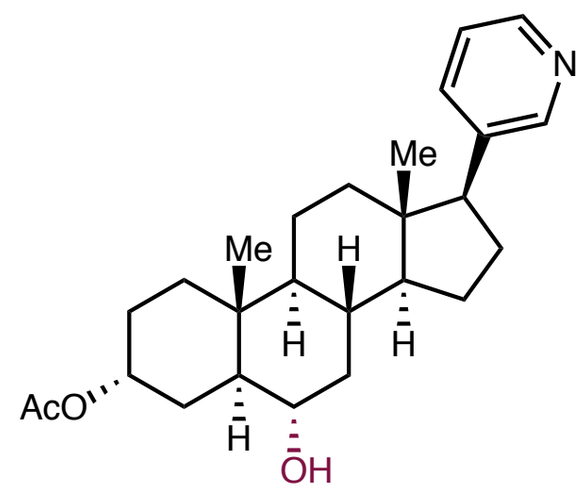
Fe(S,S-PDP)



61% yield

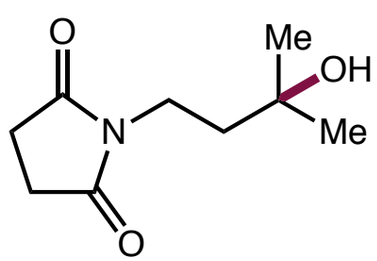


50% yield

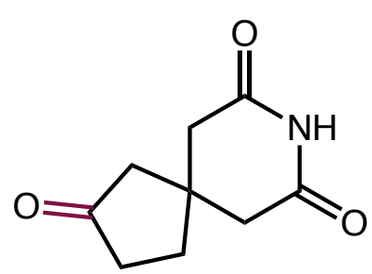


42% yield

6:1 ketone:alcohol



66% yield

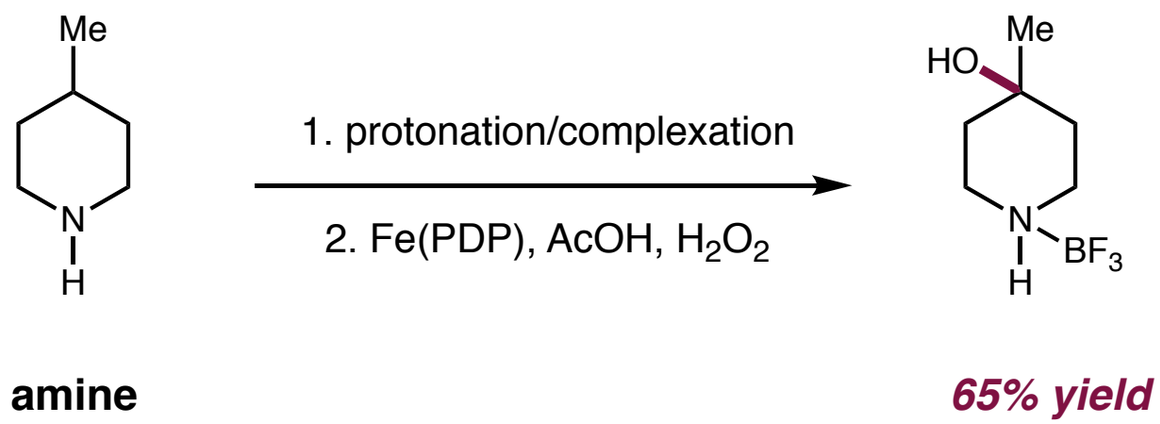


57% yield

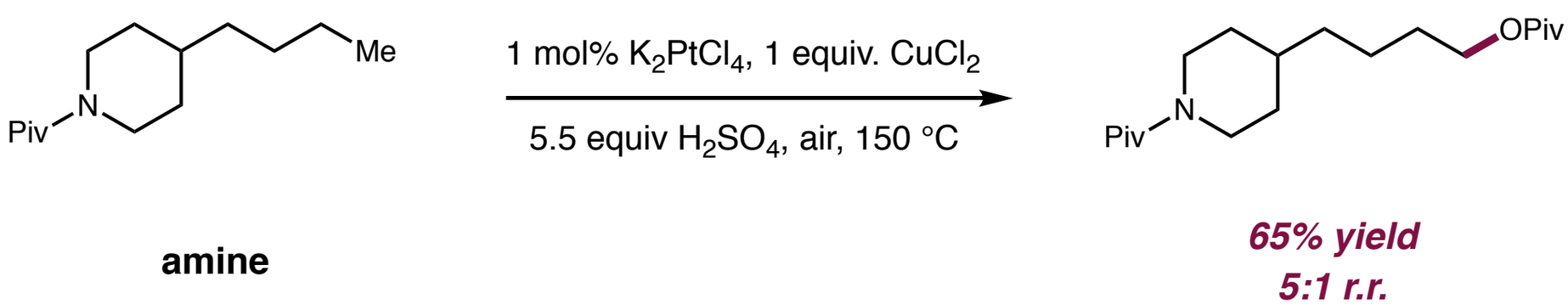
Howell, J. M.; Feng, K.; Clark, J. R.; Trzepkowski, L. J.; White, M. C. *JACS* **2015**, *137*, 14590.

Strategies for Overcoming Substrate Control: N-Complexation

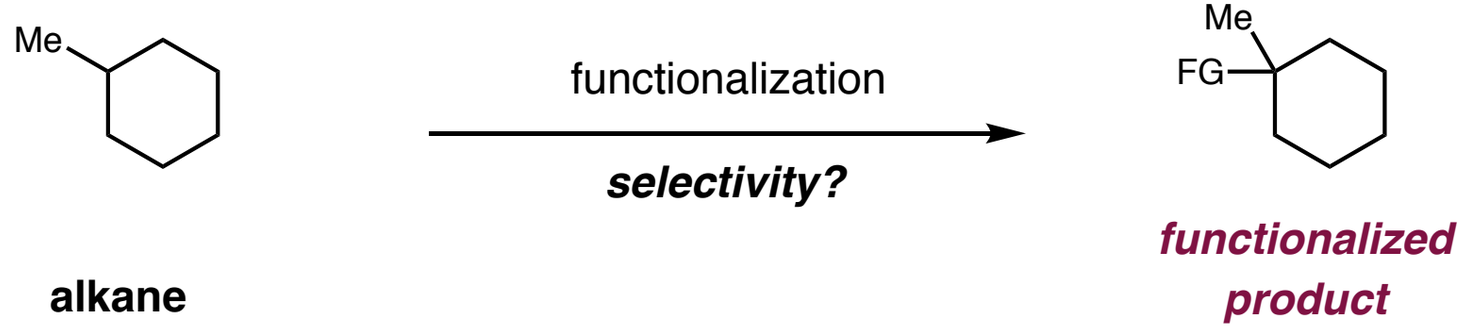
White: Oxidation via radical generation

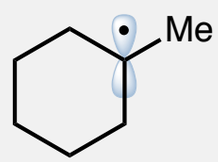


Sanford: Oxidation via metal C–H insertion



Strategies for Overcoming Substrate Control: Sterically Bulky Catalysts

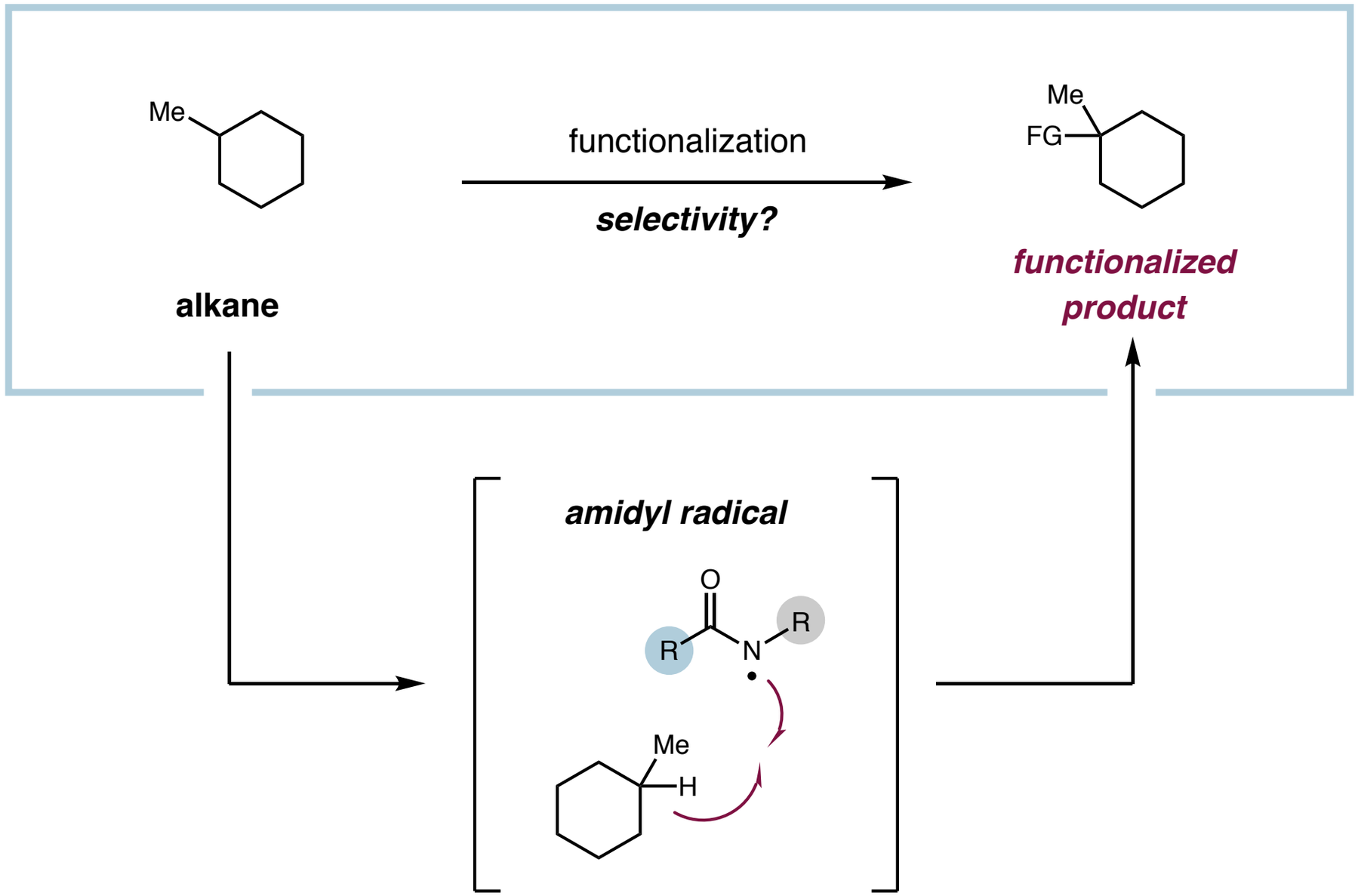




typically radical stability favors HAT at tertiary centre

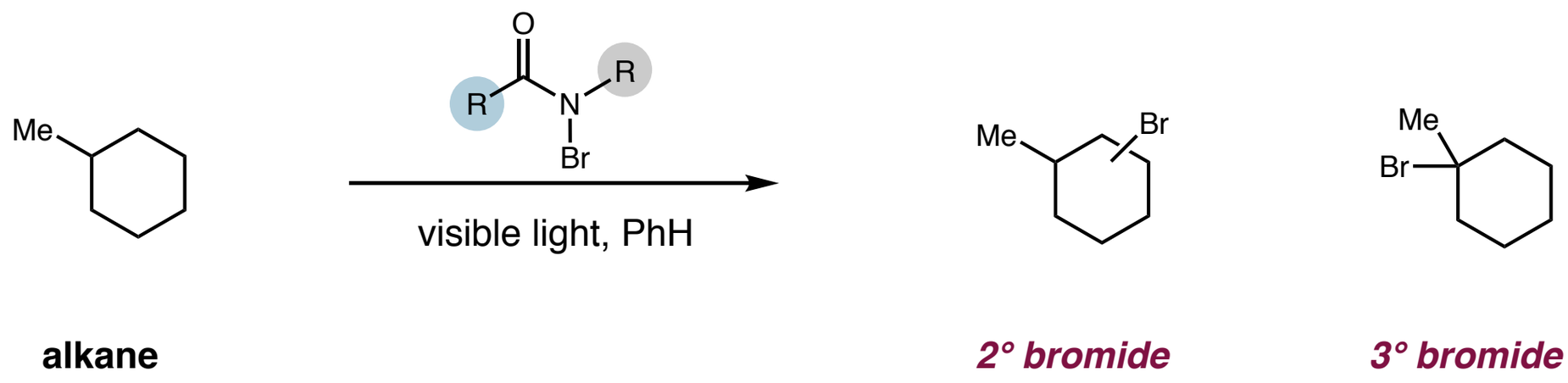
Can catalyst design override substrate selectivity in radical functionalizations?

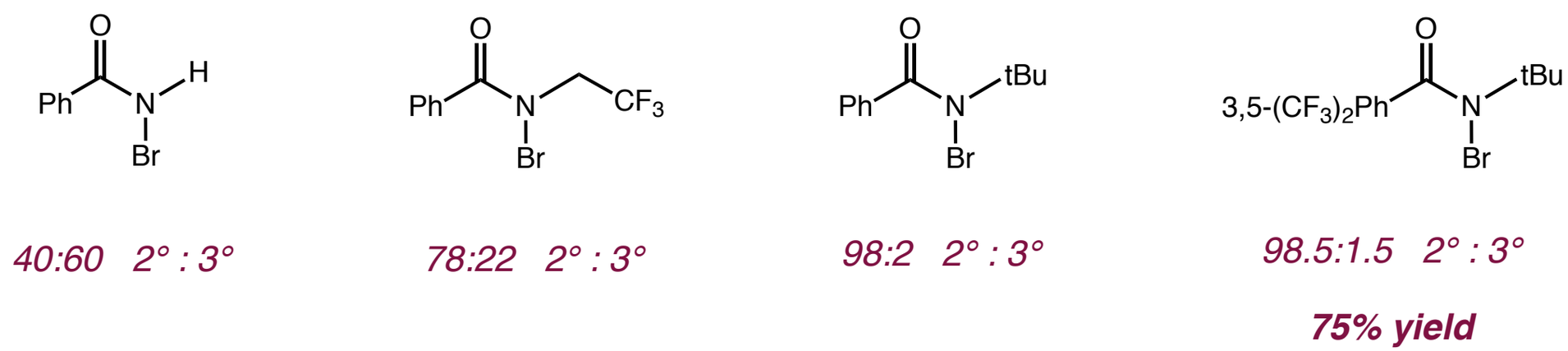
Strategies for Overcoming Substrate Control: Sterically Bulky Catalysts



Schmidt, V. A.; Quinn, R. K.; Brusoe, A. T.; Alexanian, E. J. *JACS* **2014**, *136*, 14389

Strategies for Overcoming Substrate Control: Sterically Bulky Catalysts

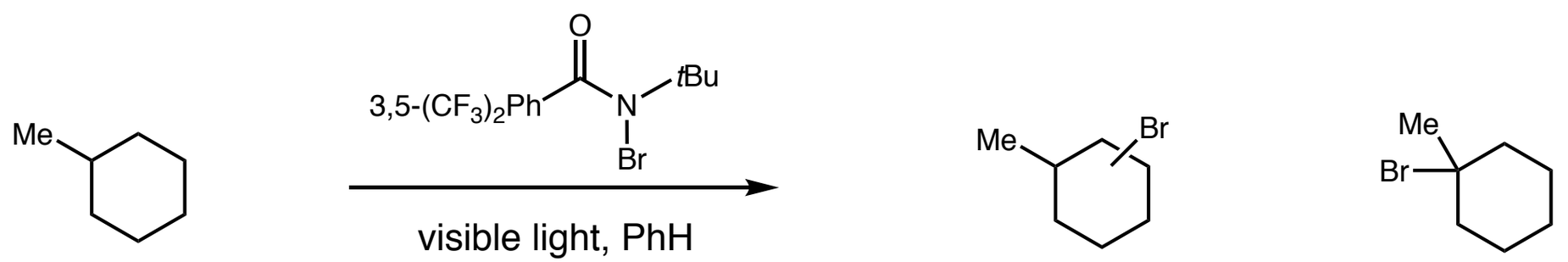




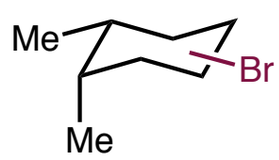
increasing steric bulk, increasing selectivity

Schmidt, V. A.; Quinn, R. K.; Brusoe, A. T.; Alexanian, E. J. *JACS* **2014**, *136*, 14389

Strategies for Overcoming Substrate Control: Sterically Bulky Catalysts

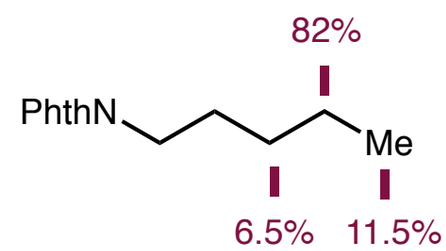


alkane ***2° bromide*** ***3° bromide***

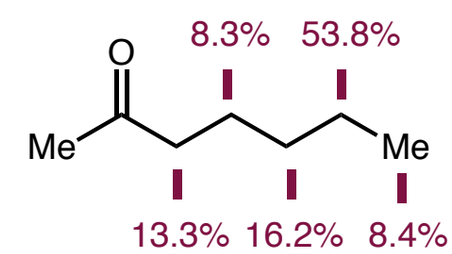


50% yield,
12:1 2° : 3°

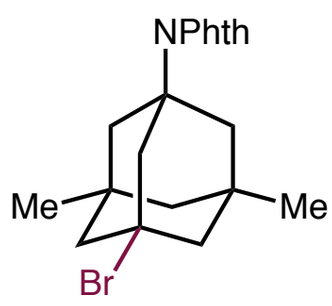
45% yield,
>99:1 2° : 3°



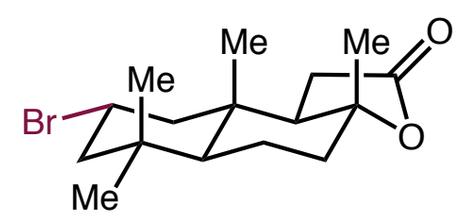
56% yield



72% yield



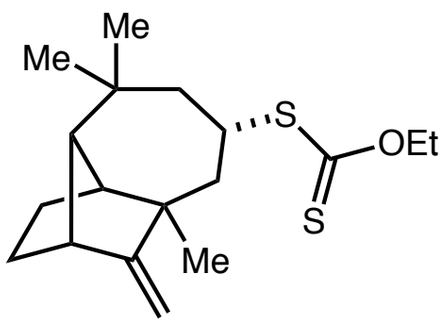
70% yield



67% yield

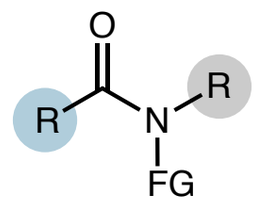
Schmidt, V. A.; Quinn, R. K.; Brusoe, A. T.; Alexanian, E. J. *JACS* **2014**, *136*, 14389

Strategies for Overcoming Substrate Control: Sterically Bulky Catalysts



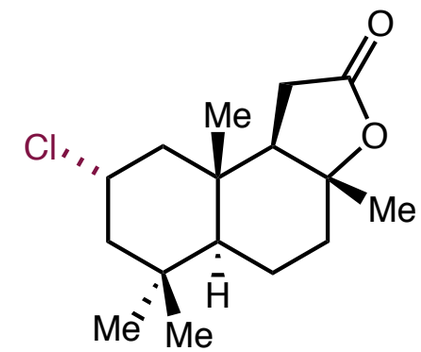
54% yield

xanthylation



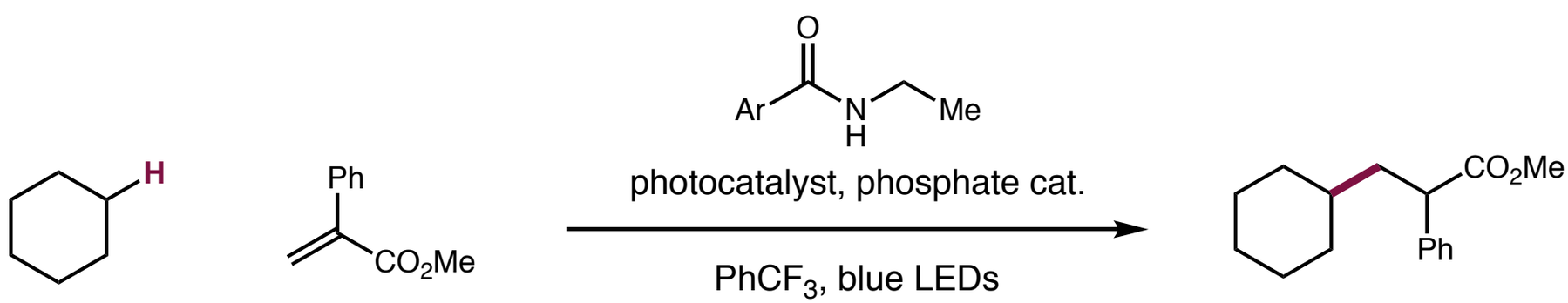
amidyl radical strategy

chlorination



82% yield

Photoredox-mediated C–C bond formation via amidyl radical

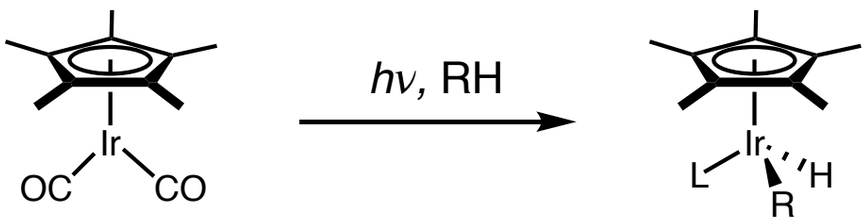


Choi, G. J.; Zhu, Q.; Miller, D. C.; Gu, C. J.; Knowles, R. R. *Nature*, **2016**, *539*, 268

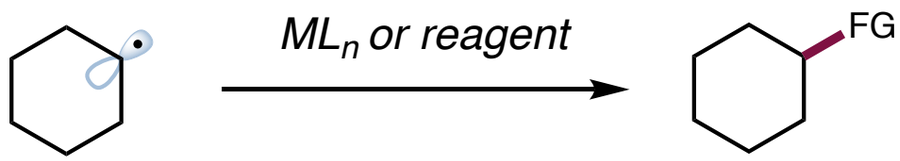
JACS, **2016**, *138,* 13854; JACS, **2016**, *138*, 698

C–H Functionalization: Presentation Outline

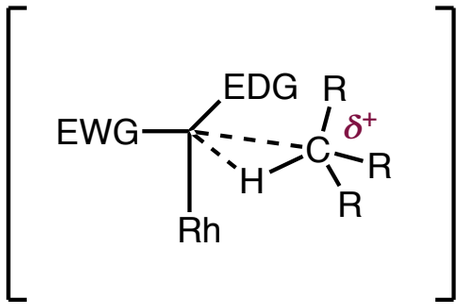
Concerted M–H Bond Formation



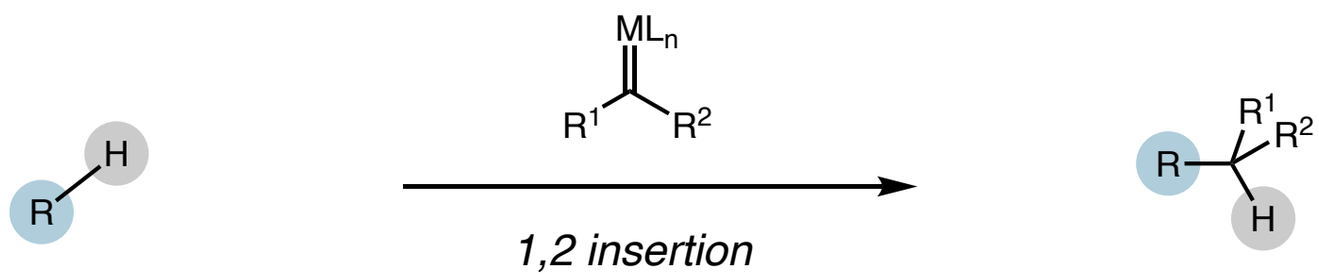
Functionalization via Radical Generation



C–H Cleavage via Insertion of Metal Carbenes

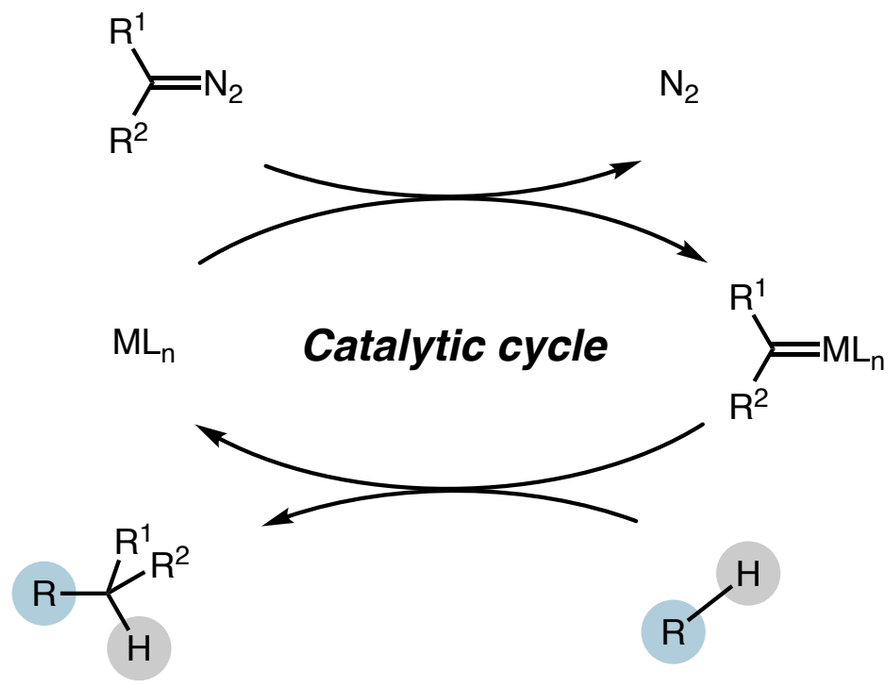


C–H Functionalization via Metal Carbene Insertion



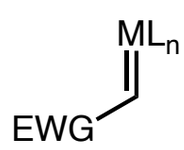
What factors influence selectivity when C–H activation proceeds via insertion of a metal carbene?

C–H Functionalization via Metal Carbene Insertion

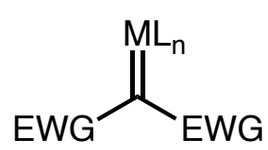


M–C bond formation does not occur during C–H bond functionalization

intermolecular C–H functionalization with C–M bond formation exhibits different chemoselectivity



acceptor-carbene

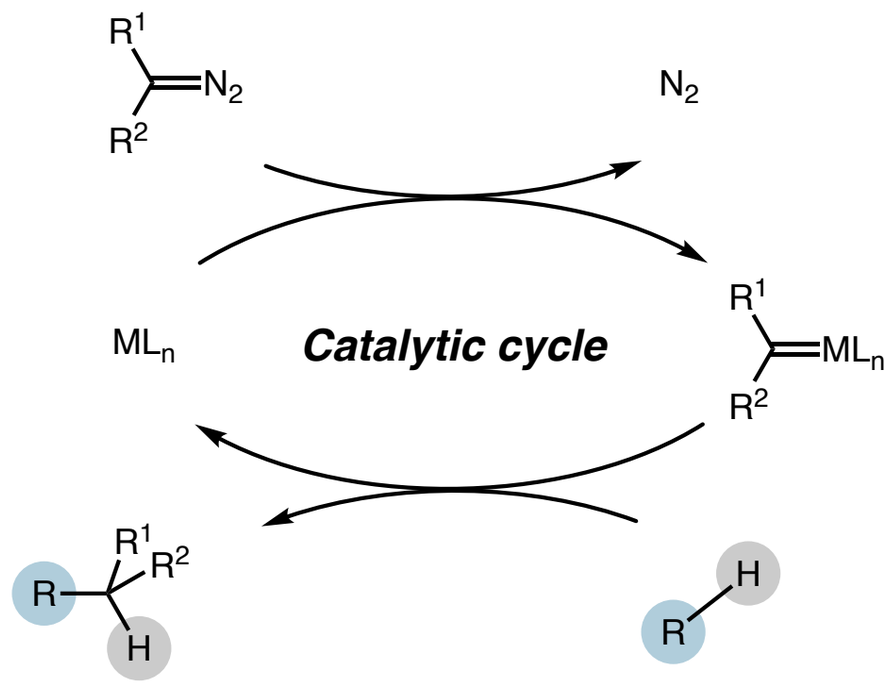


acceptor/acceptor -carbene

highly reactive and electrophilic

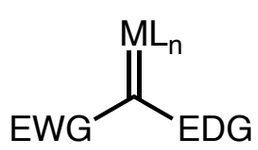
low selectivity and substantial dimerisation observed in intermolecular C–H functionalizations

C–H Functionalization via Metal Carbene Insertion



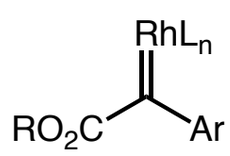
M–C bond formation does not occur during C–H bond functionalization

intermolecular C–H functionalization with C–M bond formation exhibits different chemoselectivity



donor/acceptor -metal carbene

≡

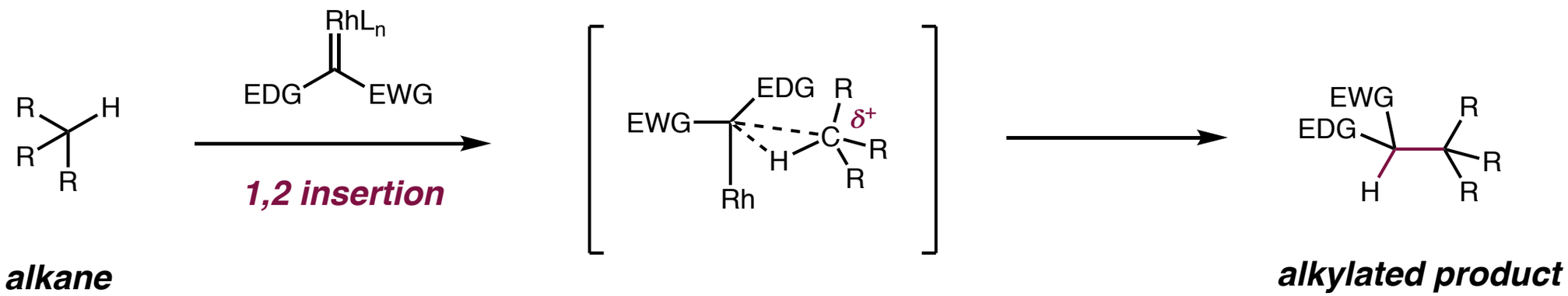


typical structure

reactivity modulated by EDG

regio-, diastereo- and stereo-selective intermolecular C–H functionalizations have been developed

C–H Functionalization via Metal Carbene Insertion



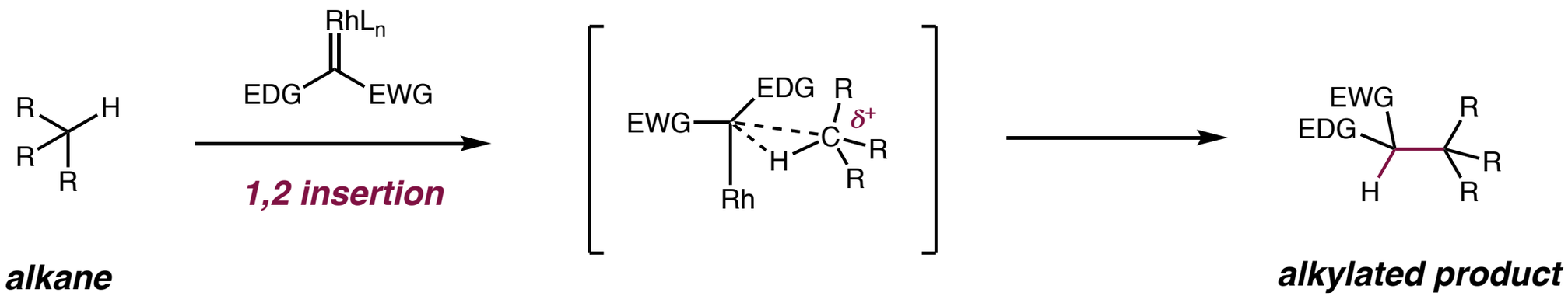
Key factors effecting regioselectivity

highly electrophilic carbene complex

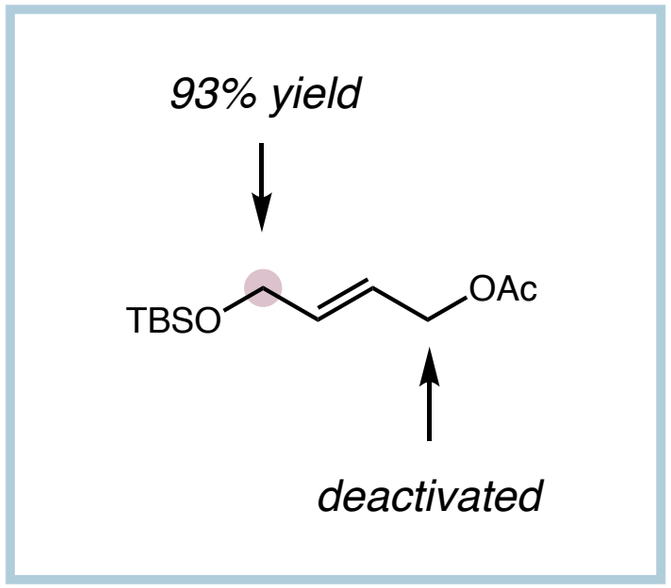
build up of partial positive charge in transition state

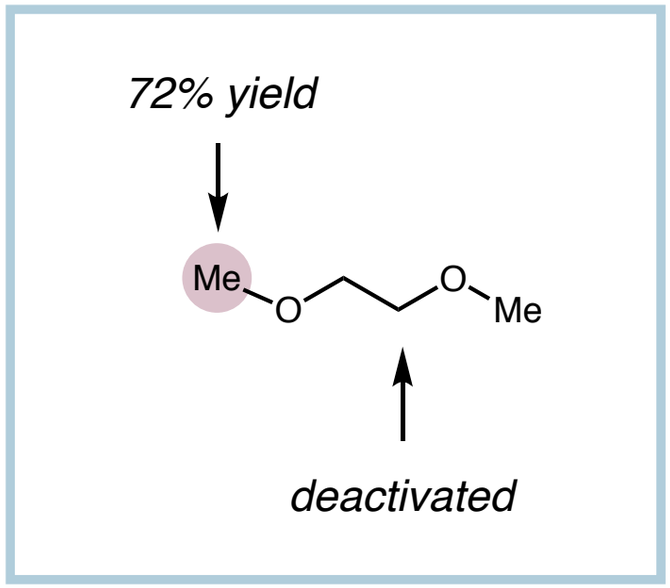
very hindered $Rh_2(DOSP)_4$ catalyst commonly used

C–H Functionalization via Metal Carbene Insertion



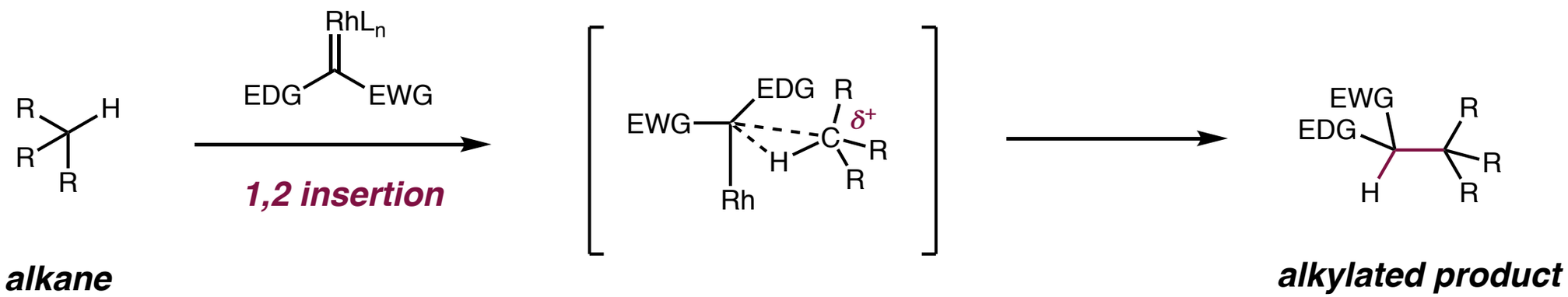
Electronic factors: stabilisation of positive charge



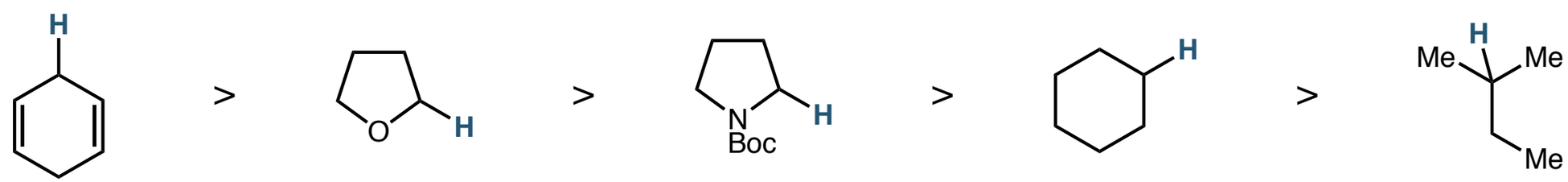


Davies, H. M. L.; Morton, D. *Chem. Soc. Rev.* **2011** *40*, 1857

C–H Functionalization via Metal Carbene Insertion



Electronic factors: stabilisation of positive charge

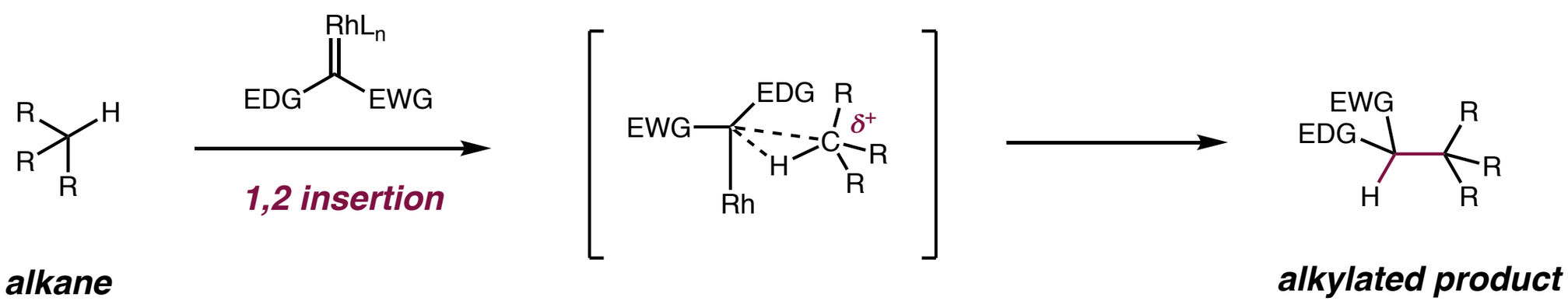


26,000 > *2700* > *1700* > *1.0* > *0.078*

relative rates of rhodium carbene insertion

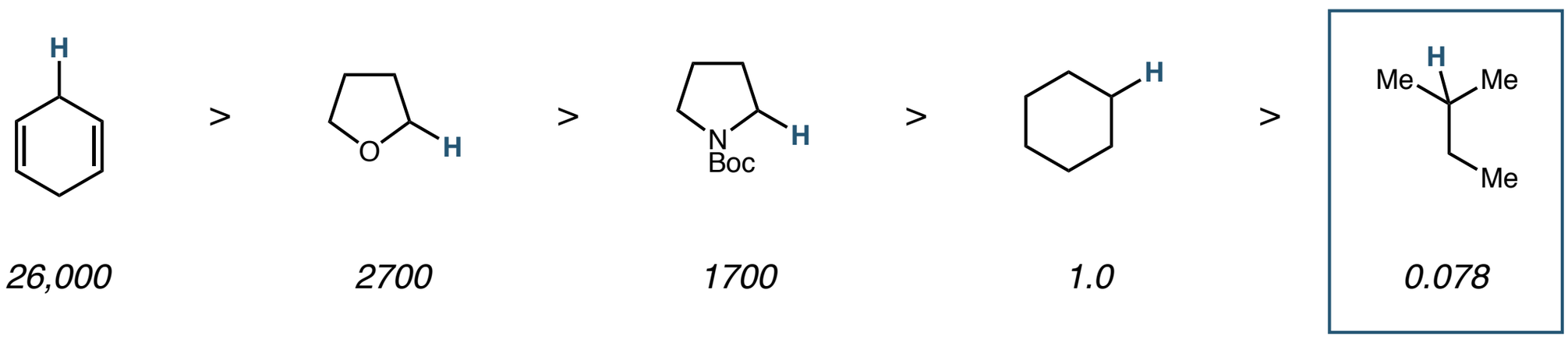
Davies, H. M. L.; Morton, D. *Chem. Soc. Rev.* **2011** *40*, 1857

C–H Functionalization via Metal Carbene Insertion



Electronic factors: stabilisation of positive charge

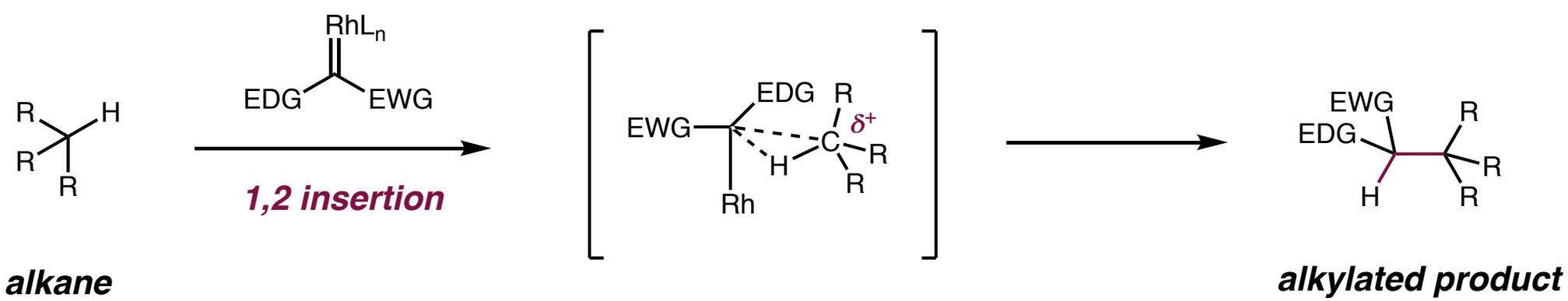
Steric factors: bulky Rh-ligands favours primary C–H insertion



relative rates of rhodium carbene insertion

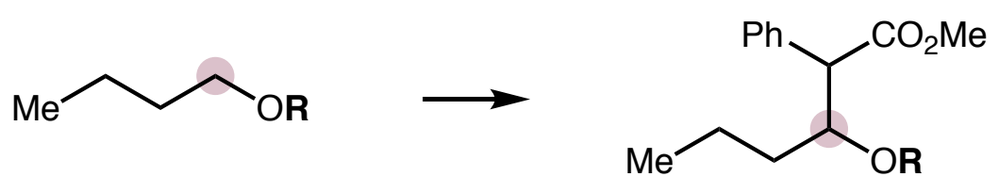
Davies, H. M. L.; Morton, D. *Chem. Soc. Rev.* **2011** *40*, 1857

C–H Functionalization via Metal Carbene Insertion

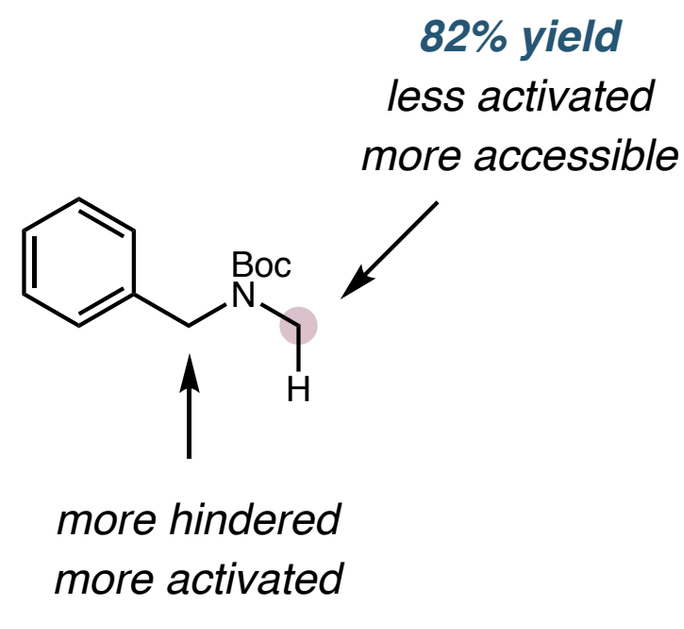


Electronic factors: stabilisation of positive charge

Steric factors: bulky Rh-ligands favours primary C–H insertion

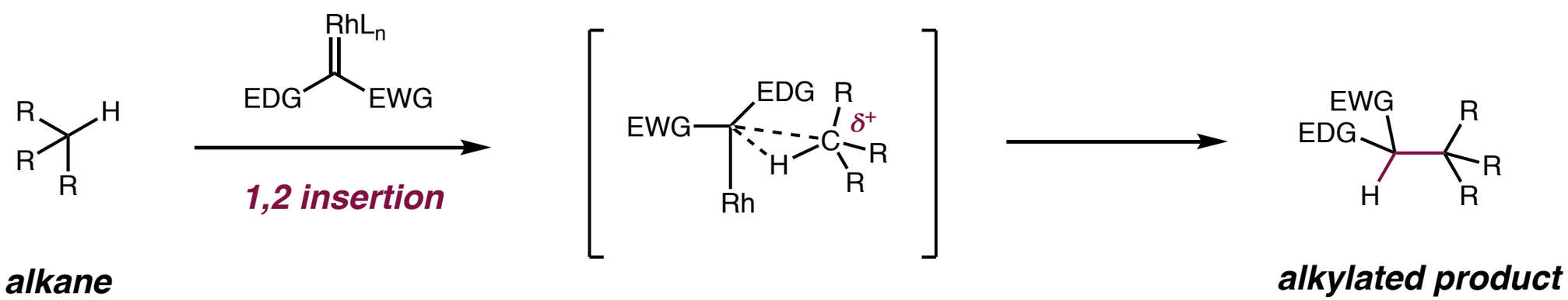


R	Relative rate
TMS	102
TES	39
TBS	14
TIPS	1.7
TBDPS	1



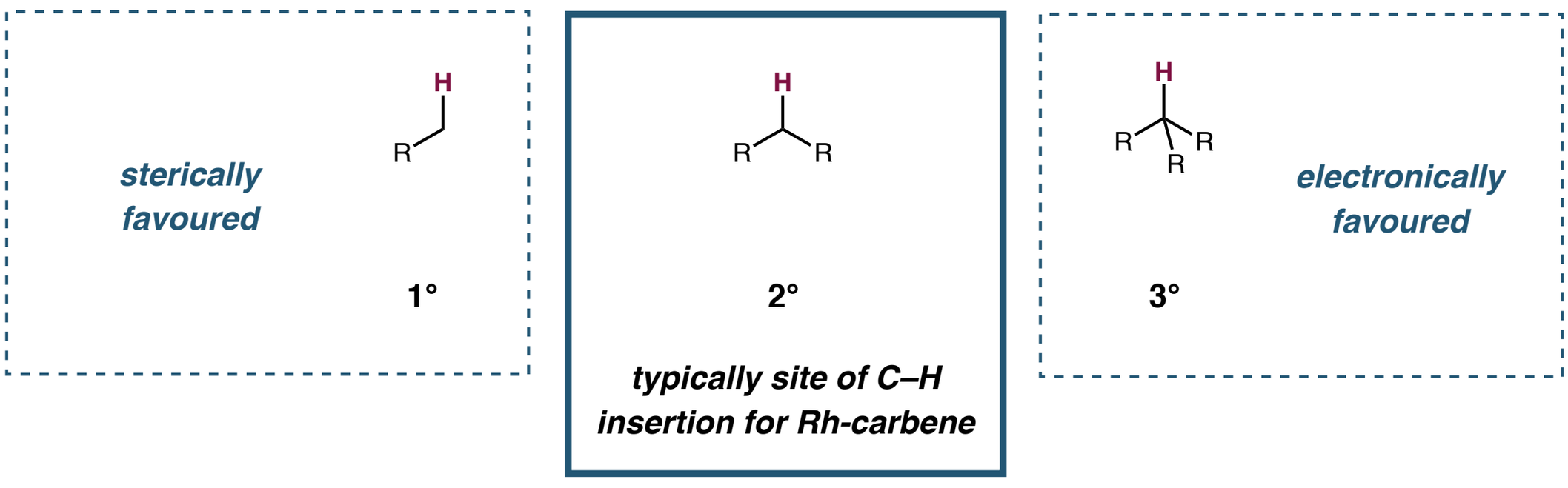
Davies, H. M. L.; Beckwith, R. E. J.; Antoulinakis, E. G.; Jin, Q. *JOC* **2003**, *68*, 6126.

C–H Functionalization via Metal Carbene Insertion



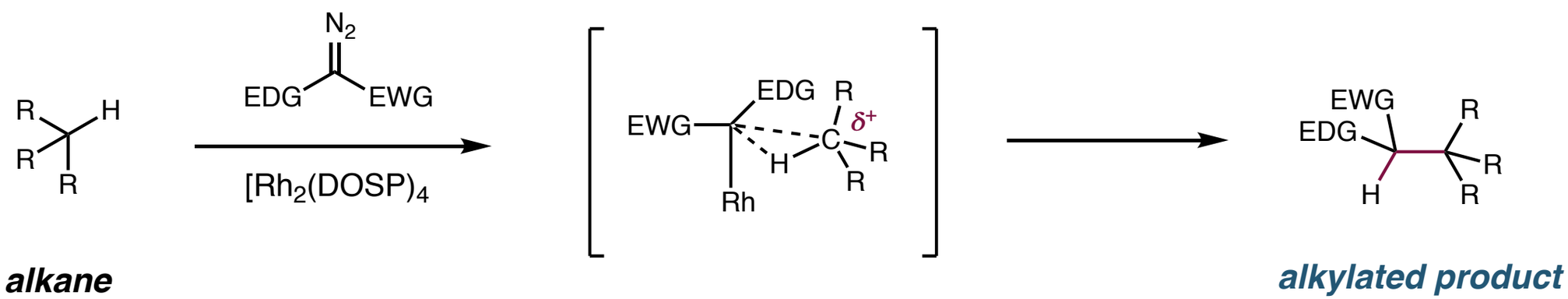
Electronic factors: stabilisation of positive charge

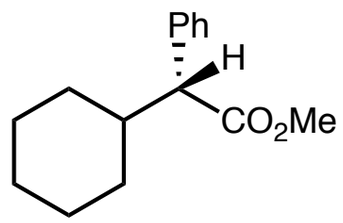
Steric factors: bulky Rh-ligands favours primary C–H insertion



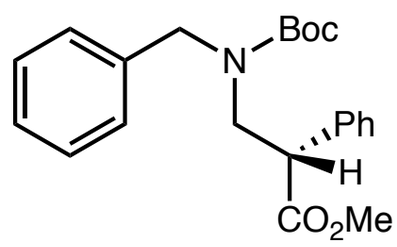
Davies, H. M. L.; Beckwith, R. E. J.; Antoulinakis, E. G.; Jin, Q. *JOC* **2003**, *68*, 6126.

C–H Functionalization via Metal Carbene Insertion

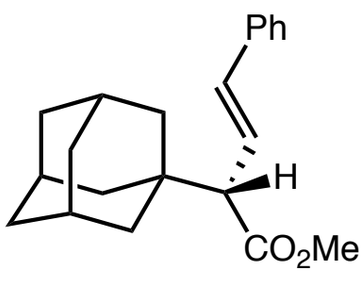




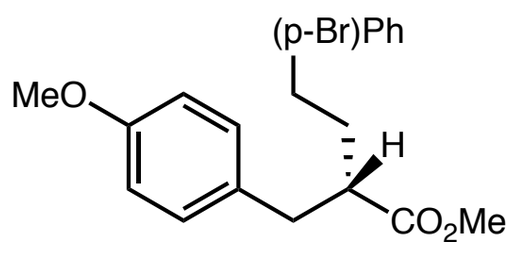
80% yield, 95% ee



67% yield, 91% ee



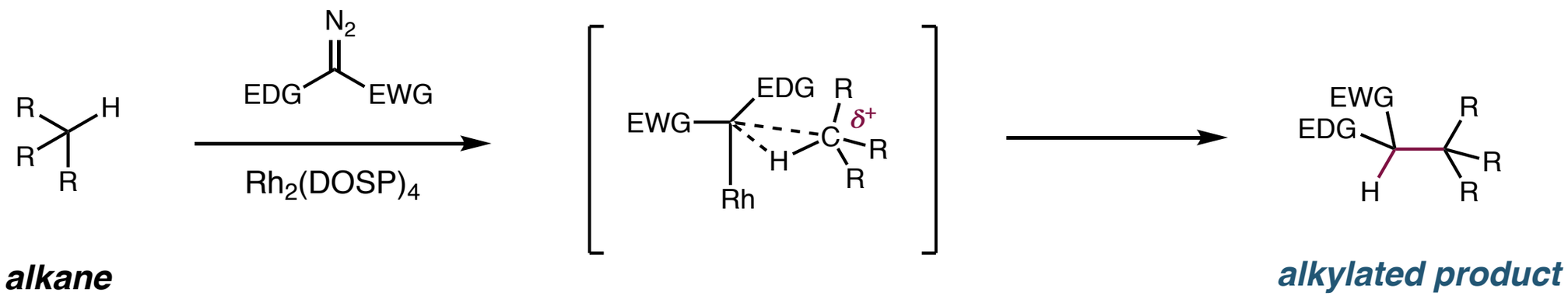
58% yield, 91% ee

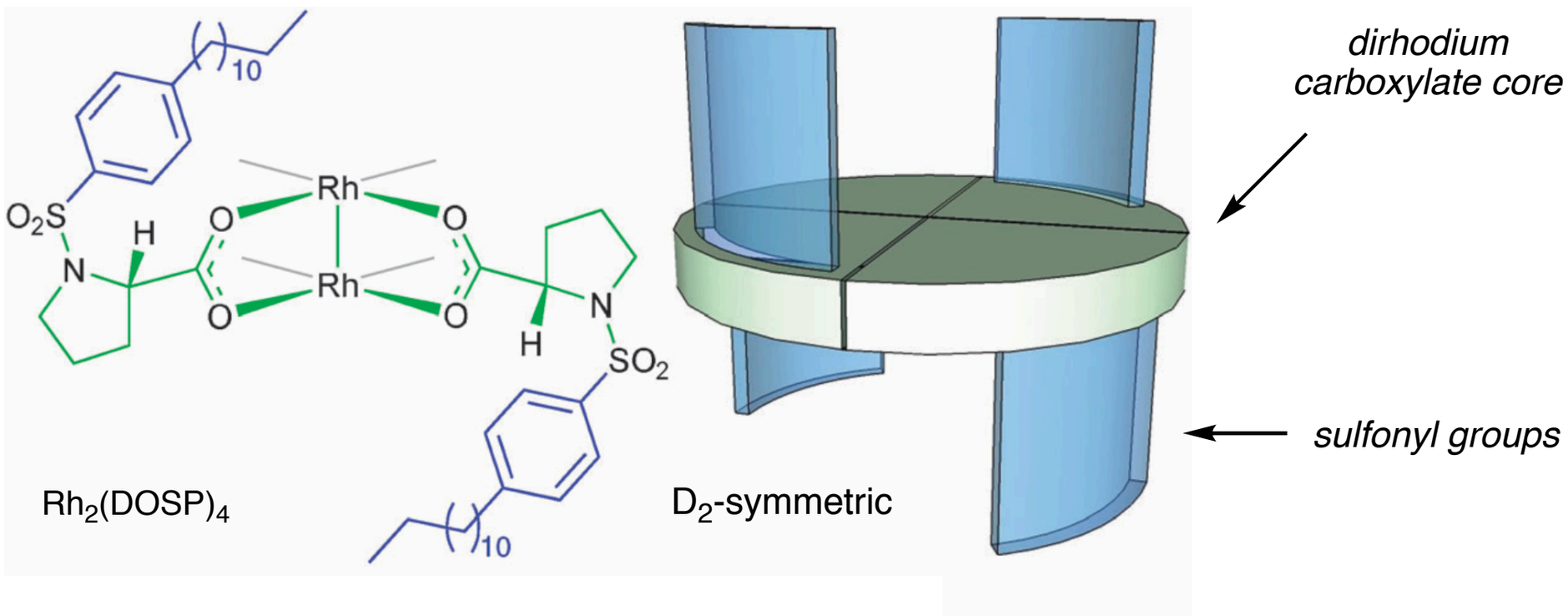


51% yield, 94% ee

Davies, H. M. L.; Morton, D. *Chem. Soc. Rev.* **2011** *40*, 1857

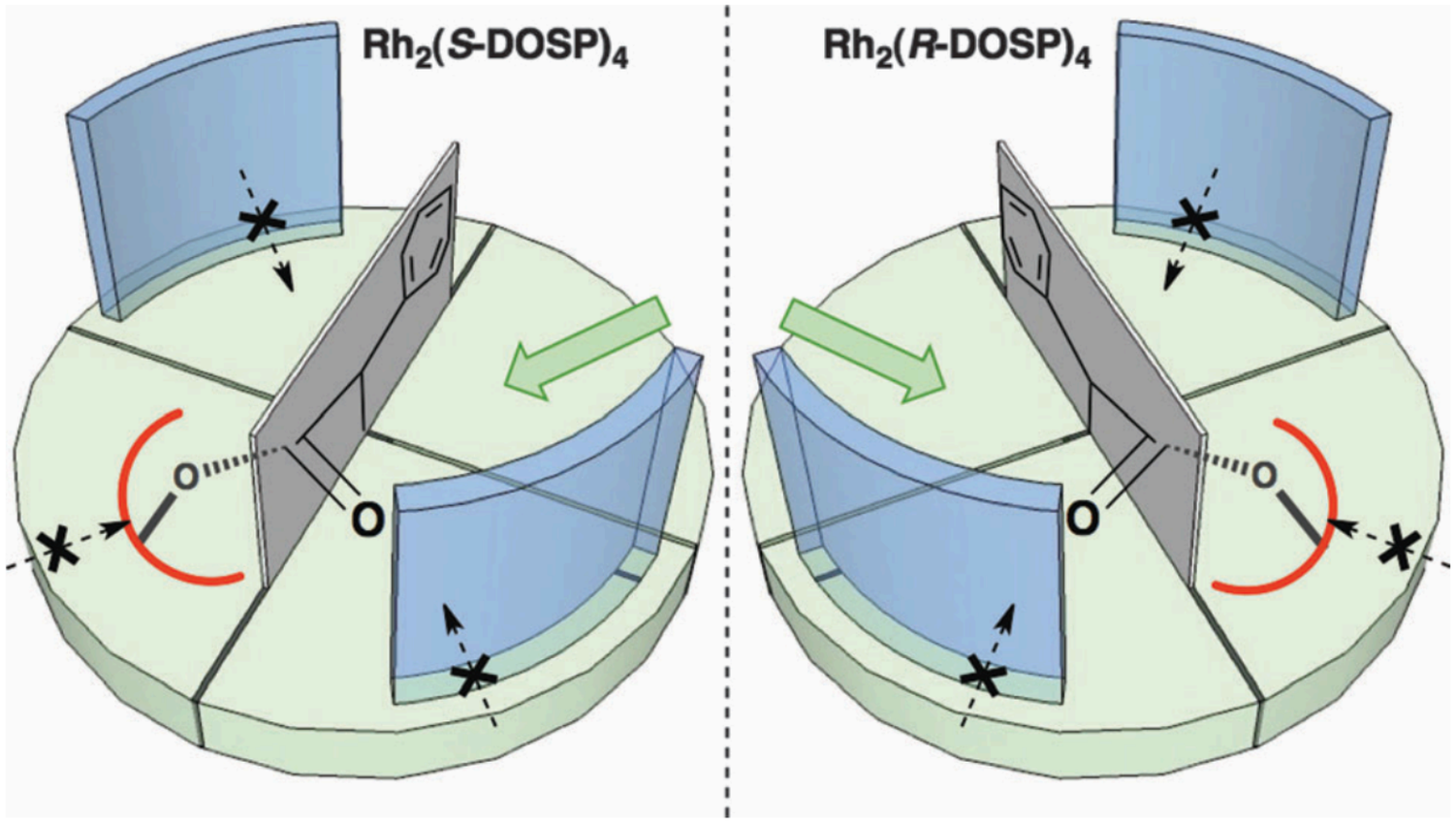
Enantiocontrol in Rh-Carbene Functionalizations





Davies, H. M. L.; Morton, D. *Chem. Soc. Rev.* **2011** *40*, 1857

Enantiocontrol in Rh-Carbene Functionalizations

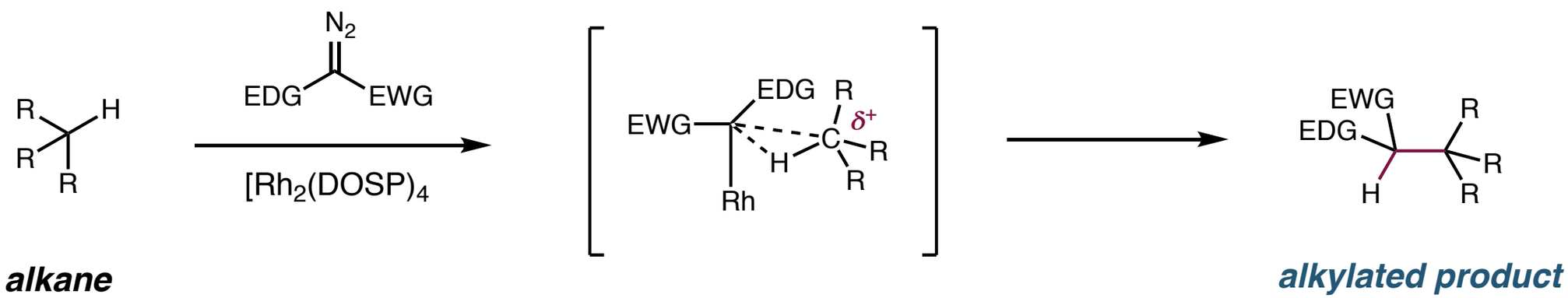


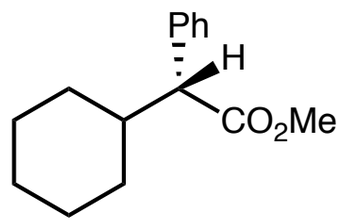
DOSP sulfonate groups block two approach vectors

perpendicular ester functionality blocks third vector

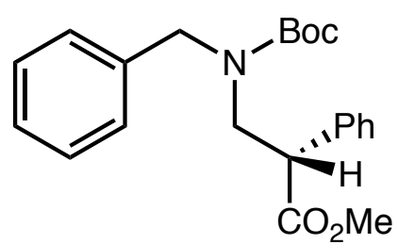
Davies, H. M. L.; Morton, D. *Chem. Soc. Rev.* **2011** *40*, 1857

C–H Functionalization via Metal Carbene Insertion

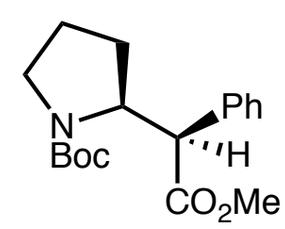




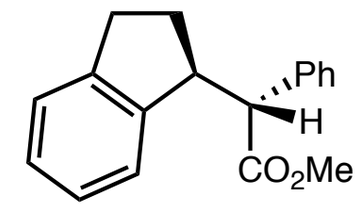
80% yield, 95% ee



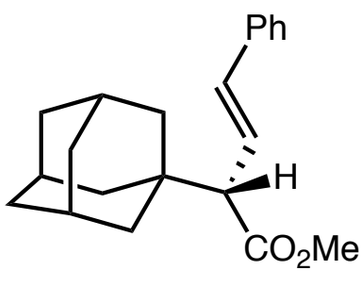
67% yield, 91% ee



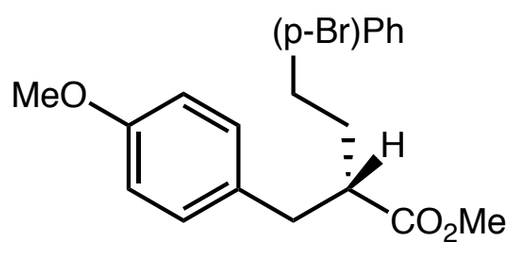
72% yield, 94% ee
96:4 d.r.



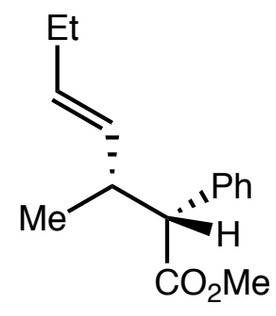
62% yield, 85% ee
80:20 d.r.



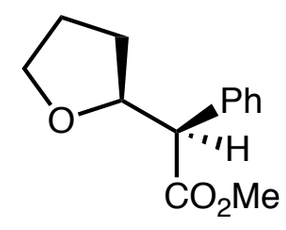
58% yield, 91% ee



51% yield, 94% ee



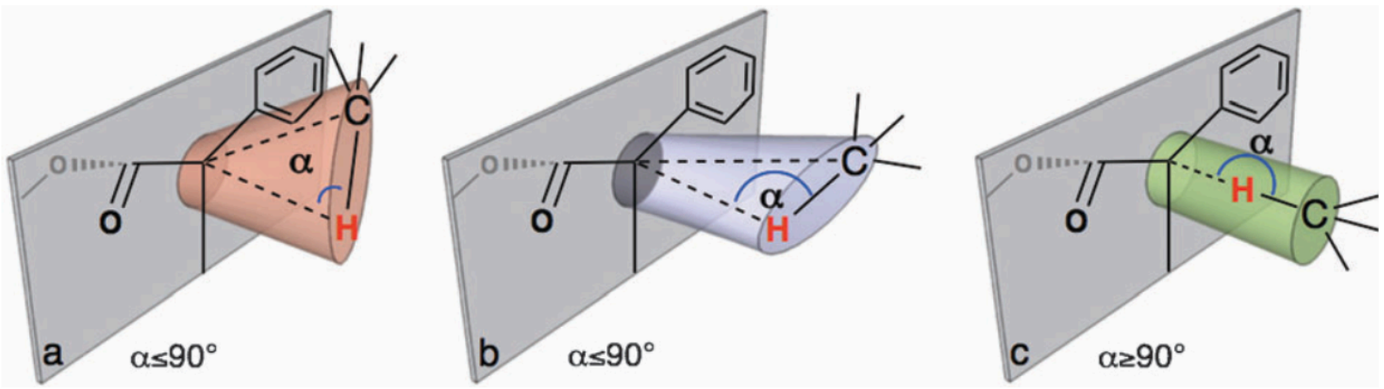
56% yield, 92% ee
56:44 d.r.



67% yield, 97% ee
74:26 d.r.

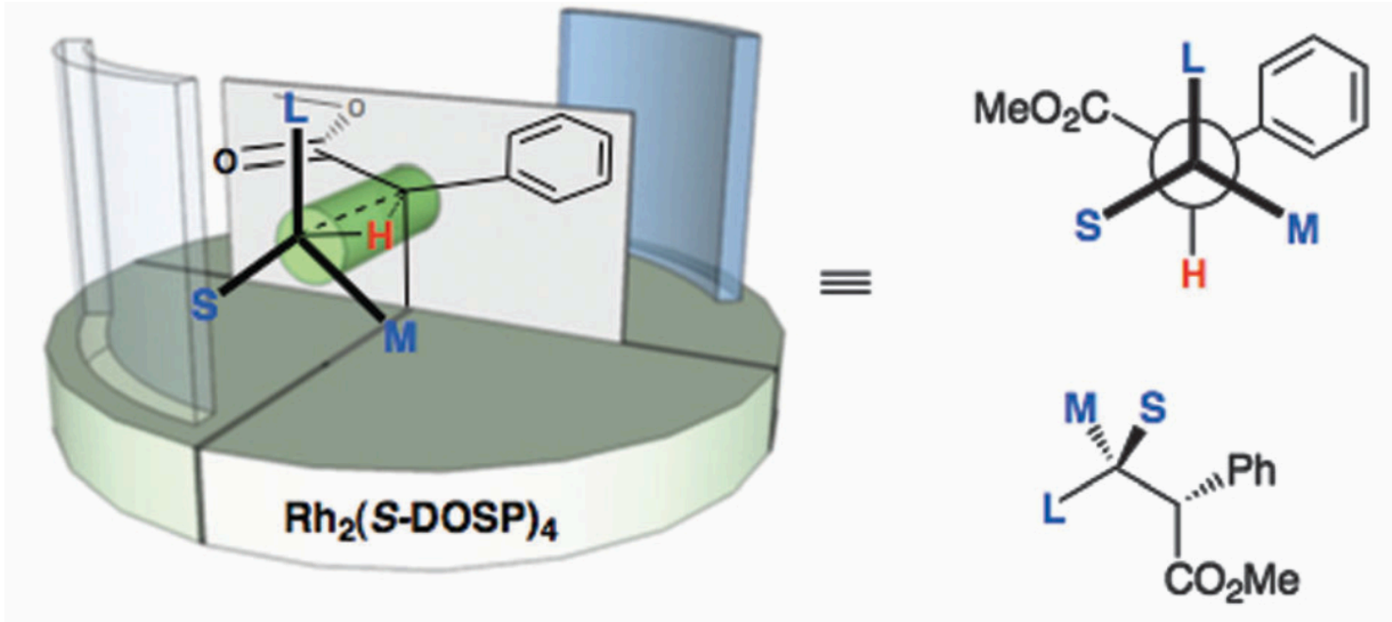
Davies, H. M. L.; Morton, D. *Chem. Soc. Rev.* **2011** *40*, 1857

Diastereocontrol in Rh-Carbene Functionalizations



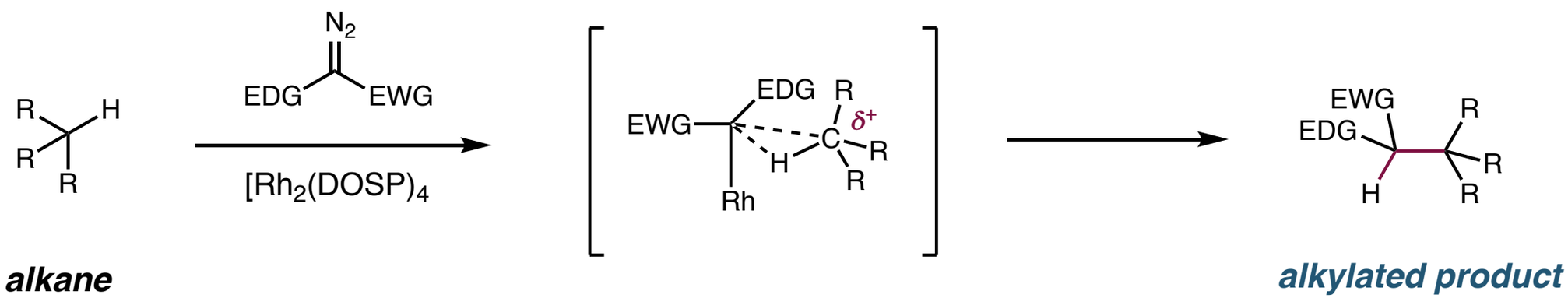
calculated favoured approach

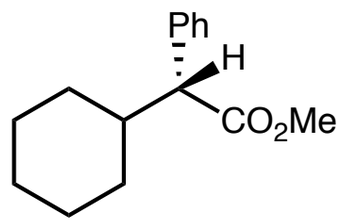
Model for diastereocontrol



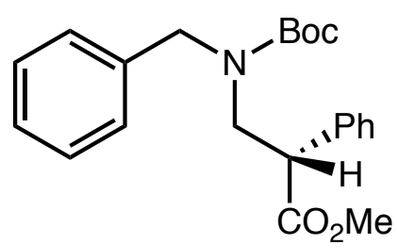
Davies, H. M. L.; Morton, D. *Chem. Soc. Rev.* **2011** *40*, 1857

C–H Functionalization via Metal Carbene Insertion

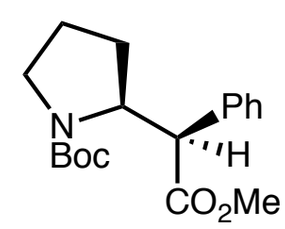




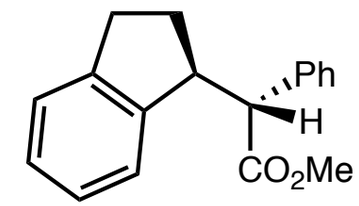
80% yield, 95% ee



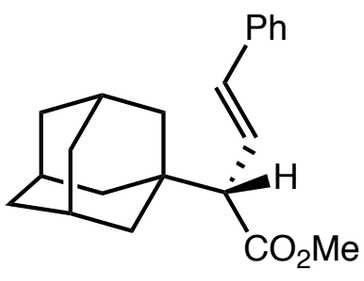
67% yield, 91% ee



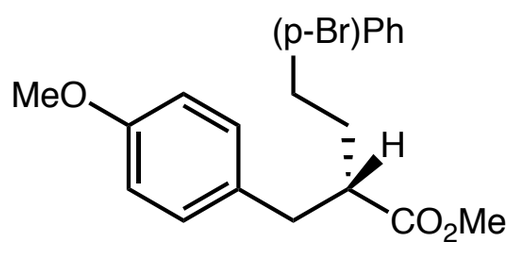
72% yield, 94% ee
96:4 d.r.



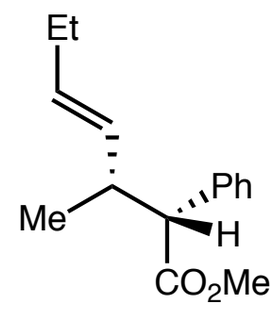
62% yield, 85% ee
80:20 d.r.



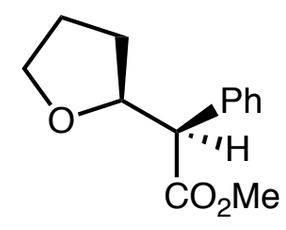
58% yield, 91% ee



51% yield, 94% ee



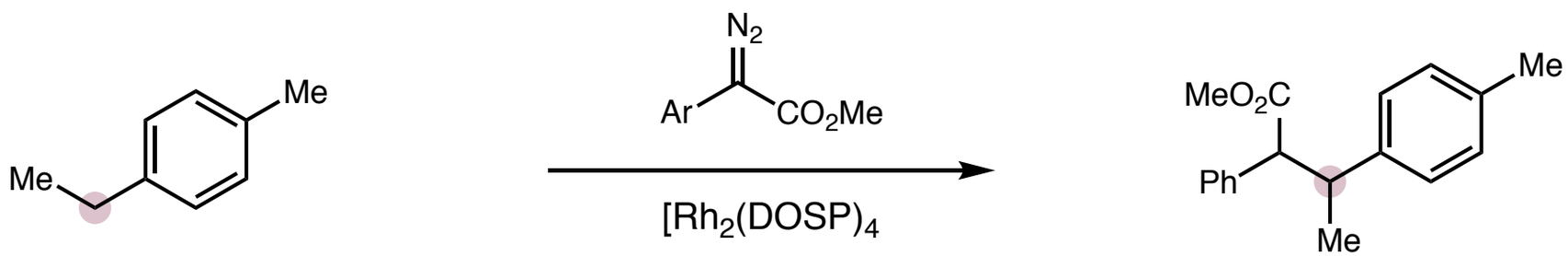
56% yield, 92% ee
56:44 d.r.



67% yield, 97% ee
74:26 d.r.

Davies, H. M. L.; Morton, D. *Chem. Soc. Rev.* **2011** *40*, 1857

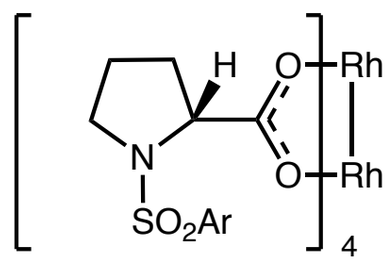
C–H Functionalization via Metal Carbene Insertion



C–H substrate

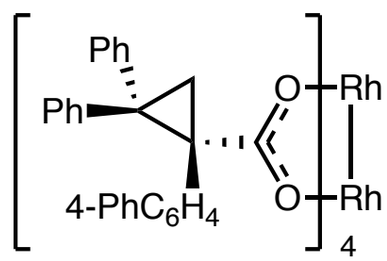
secondary selective

Can the regioselectivity be altered through catalyst design?



Ar = 4-($C_{12}H_{25}$)C_6H_4

Rh_2(*R*-DOSP)$_4$

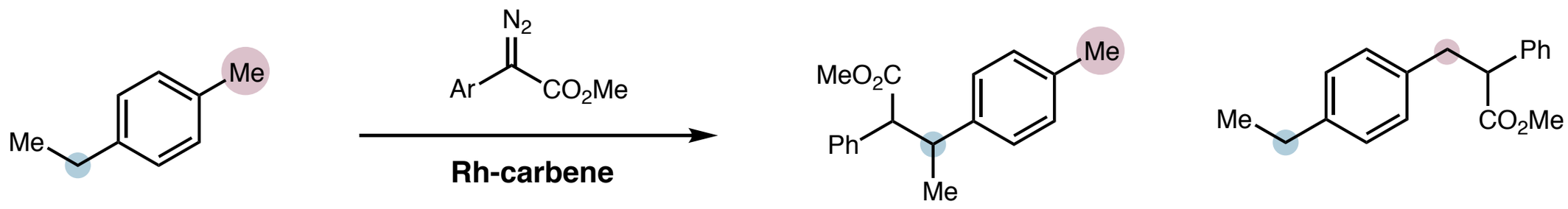


increased steric bulk

Rh_2(*R*-BPCP)$_4$

Qin, C.; Davies, H. M. L. *JACS*, **2014**, *136*, 9792

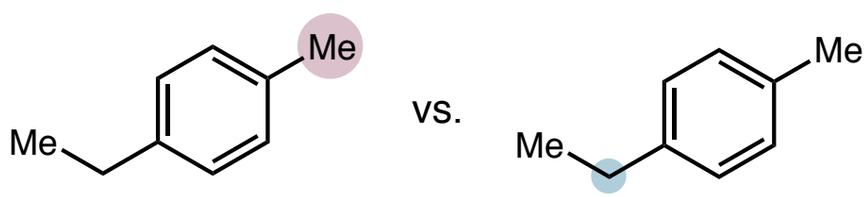
C–H Functionalization via Metal Carbene Insertion



C–H substrate

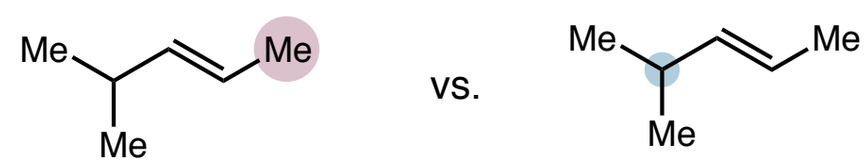
secondary *vs.* ***primary***

Benzylic



Rh_2(*R*-DOSP)$_4$	**<1:20 1°:2°**
Rh_2(*R*-BPCP)$_4$	**5:1 1°:2°** *74% yield, 92% ee*

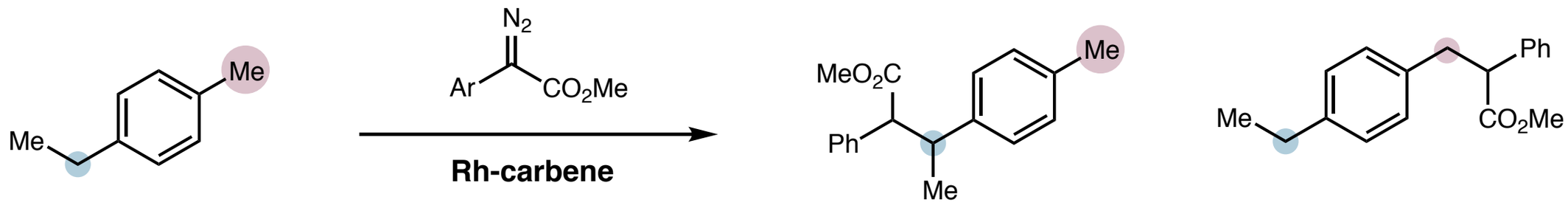
Allylic



Rh_2(*R*-DOSP)$_4$	**1:7 1°:3°**
Rh_2(*R*-BPCP)$_4$	**17:1 1°:3°** *60% yield, 94% ee*

Qin, C.; Davies, H. M. L. *JACS*, **2014**, *136*, 9792

C–H Functionalization via Metal Carbene Insertion



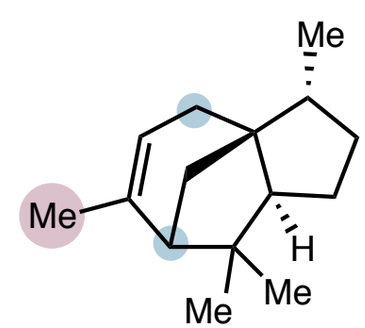
C–H substrate

secondary *vs.* ***primary***

α-oxy

Rh_2(*R*-DOSP)$_4$	**3:2 1°:2°**
Rh_2(*R*-BPCP)$_4$	**>20:1 1°:2°** *86% yield, 64% ee*

allylic



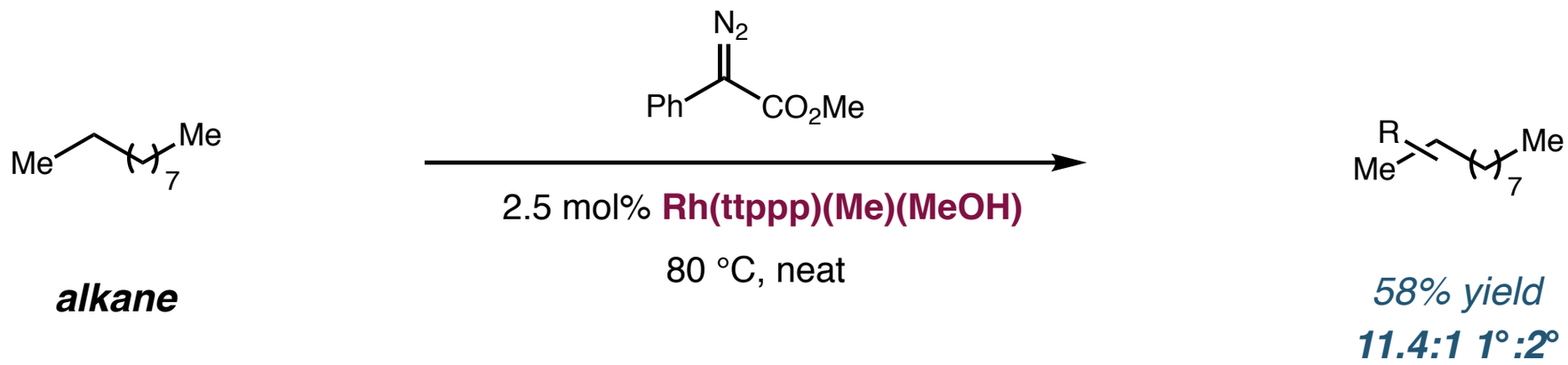
Rh_2(*R*-BPCP)$_4$

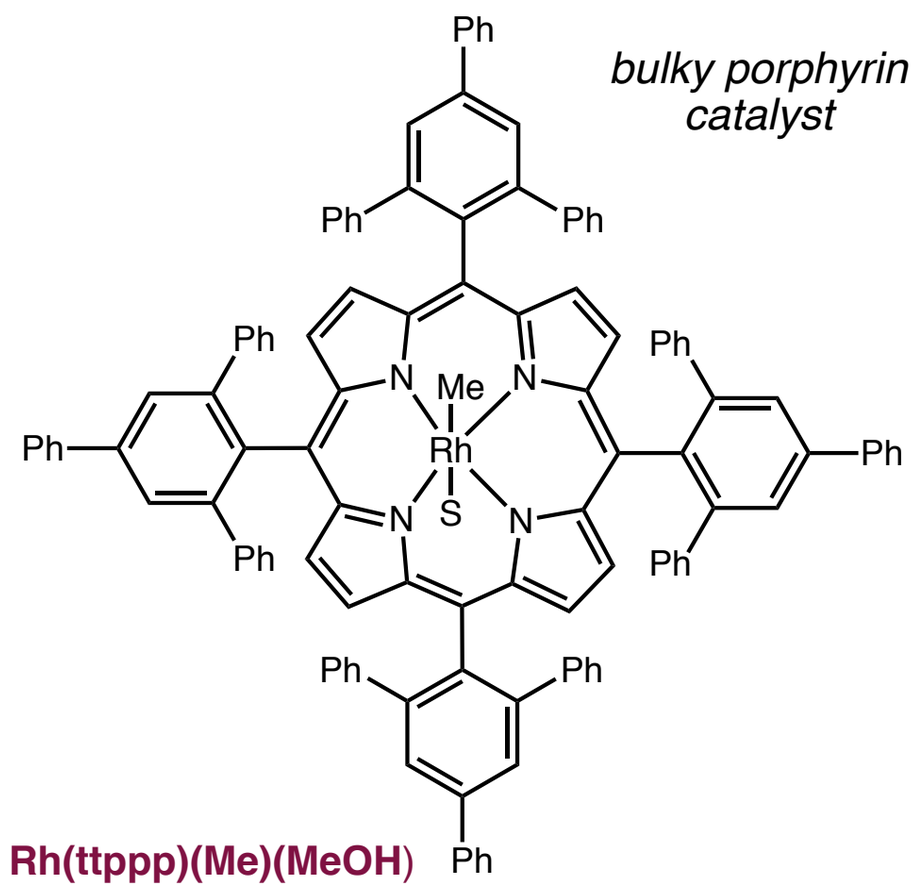
single regioisomer

88% yield, >20:1 d.r.

Qin, C.; Davies, H. M. L. *JACS*, **2014**, *136*, 9792

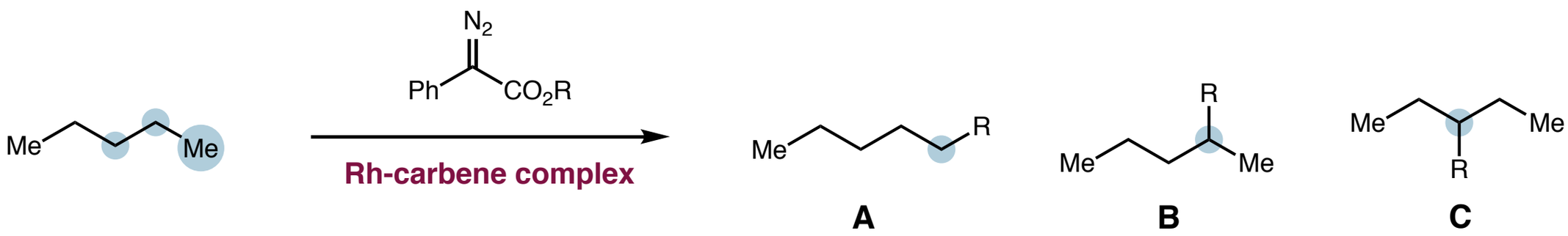
C–H Functionalization via Metal Carbene Insertion





Thu, H-T; Tong, G. S.-M.; Huang, J.-S.; Chan, S. L.-F.; Deng, Q.-H.; Che, C.-M. *ACIE* **2008**, *47*, 9747

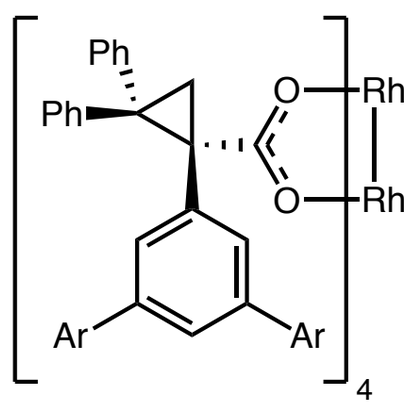
C–H Functionalization via Metal Carbene Insertion



alkane

regioisomeric functionalized products

Selective functionalization of unactivated bonds via catalyst design?



Ar = p-tBuC_6H_4

Rh_2(*R-3,5-di(p-tBuC_6H_4)TPCP*)$_4$

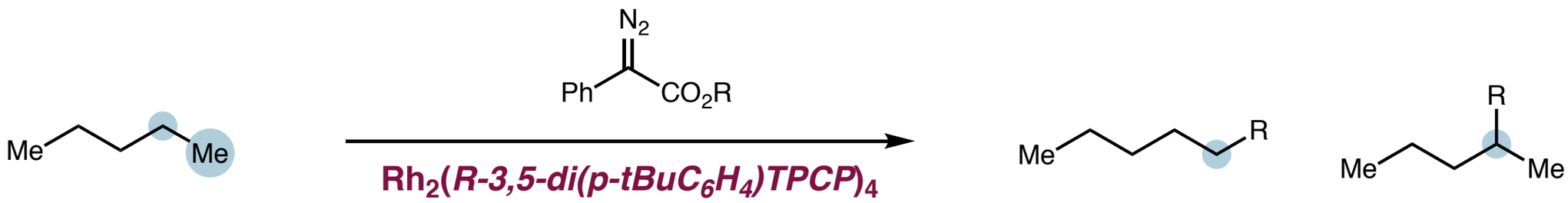
1 : 25 : n.d. ***A : B : C***

20:1 d.r., 99% ee

99% yield

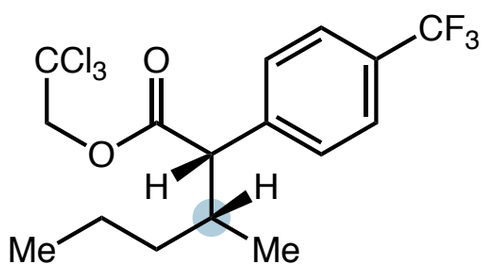
Liao, K.; Negretti, S.; Musaev, D. G.; Basca, J.; Davies, H. M. L. *Nature* **2016**, *230*, 533

C–H Functionalization via Metal Carbene Insertion

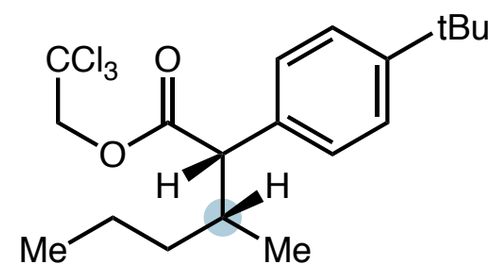


alkane

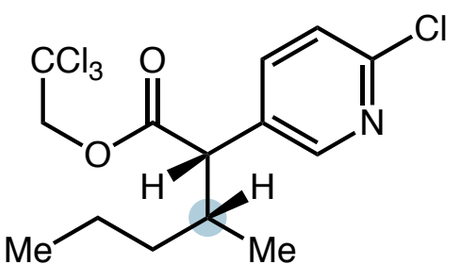
regioisomeric functionalized products



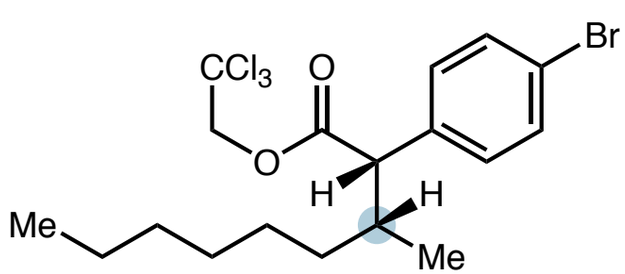
91% yield, 97% ee
15:1 r.r., 14:1 d.r.



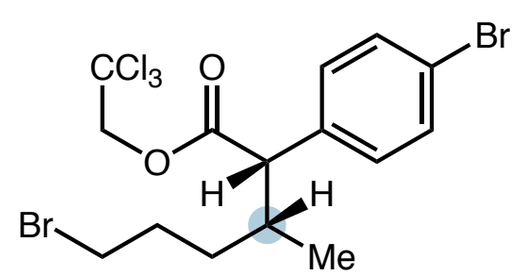
91% yield, 99% ee
22:1 r.r., 24:1 d.r.



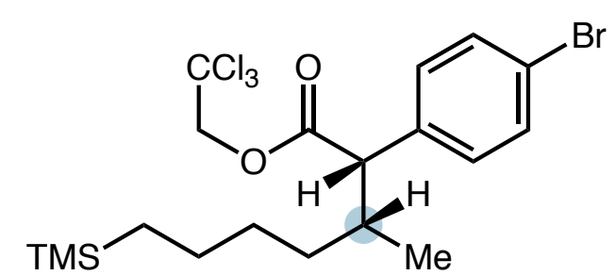
87% yield, 91% ee
28:1 r.r., 55:1 d.r.



82% yield, 91% ee
27:1 r.r., 9:1 d.r.



65% yield, 95% ee
9:1 r.r., 9:1 d.r.

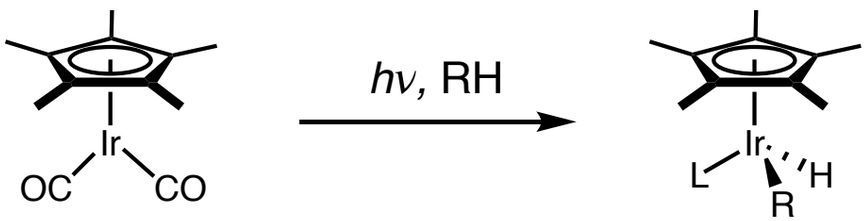


85% yield, 90% ee
20:1 r.r., 9:1 d.r.

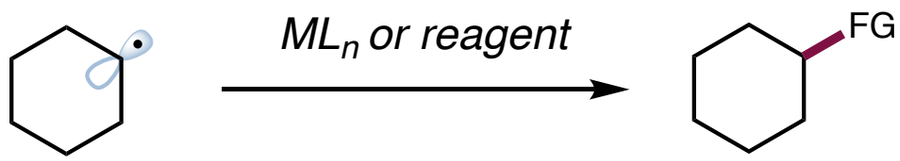
Liao, K.; Negretti, S.; Musaev, D. G.; Basca, J.; Davies, H. M. L. *Nature* **2016**, *230*, 533

C–H Functionalization: Summary

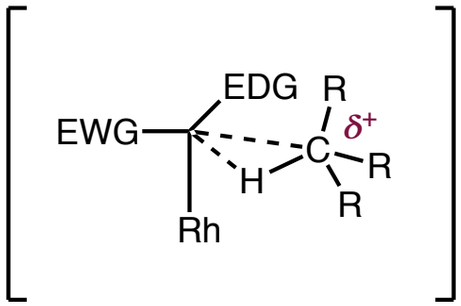
Concerted M–H Bond Formation



Functionalization via Radical Generation



C–H Cleavage via Insertion of Metal Carbenes



C–H Functionalization: Summary

Concerted M–H Bond Formation

highly selective for primary C–H functionalization

currently limited in breadth of functionalizations

offers opportunity to modulate catalyst reactivity

Functionalization via Radical Generation

highly predictable site of C–H functionalisation

wide breadth of transformations developed

only moderate catalyst control has been achieved

C–H Cleavage via Insertion of Metal Carbenes

catalyst design can provide regioselectivity

narrower scope of potential products

high diastereo- and stereoselectivity achieved