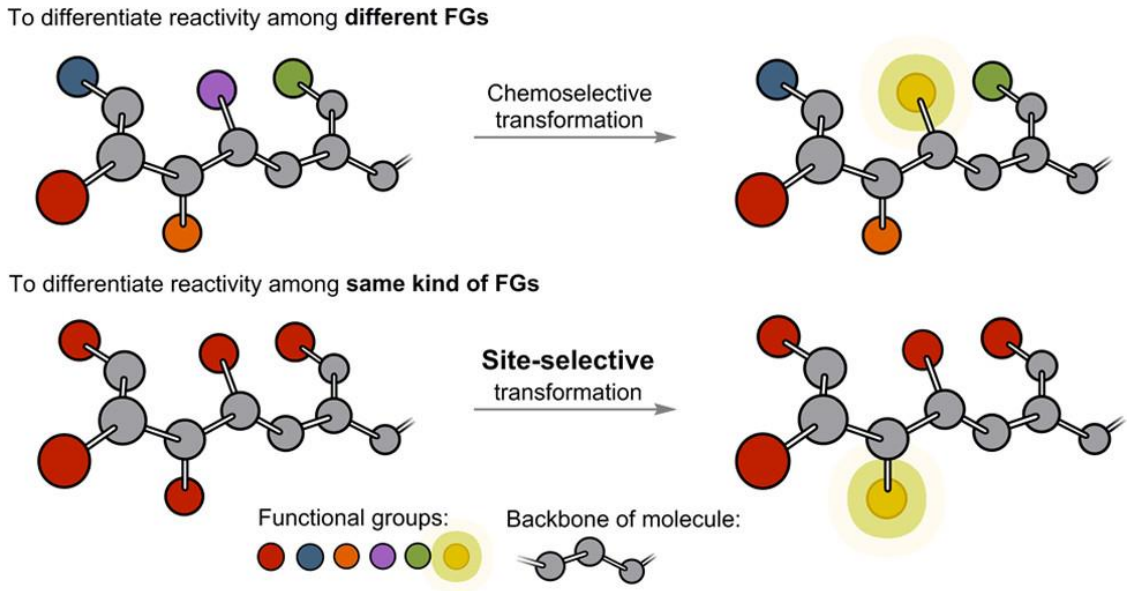
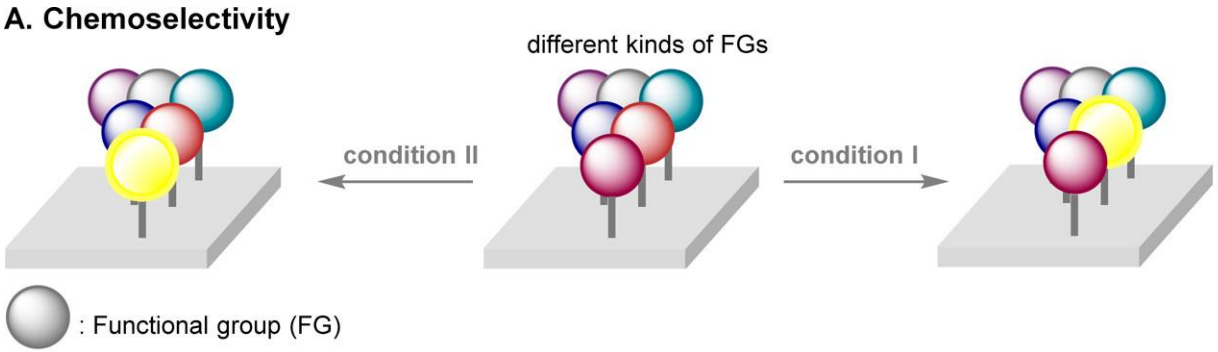
Site-Selectivity Control in Organic Reactions: A Quest To Differentiate Reactivity among the Same Kind of Functional Groups

Reporter: Xin-Hang Jiang
Supervisor: Prof. Yong Huang
Date: 2017. 05. 15

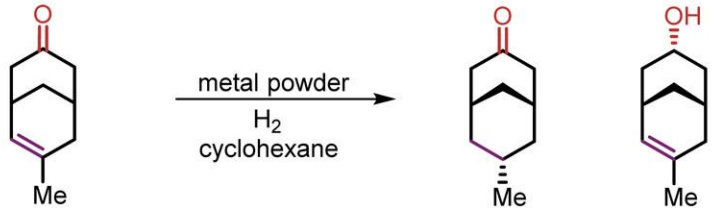


1. Huang, Z. X.; Dong, G. B. *Acc. Chem. Res.* **2017,** 50, 465-471.

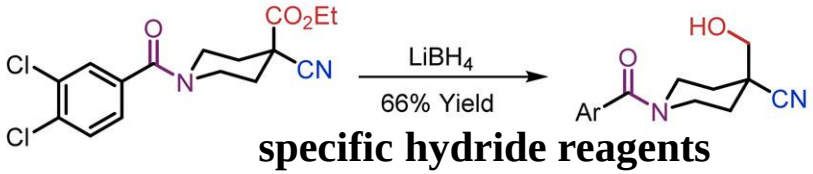
1. Chemoselectivity and site selectivity: Concepts and examples.



the difference in inherent reactivity

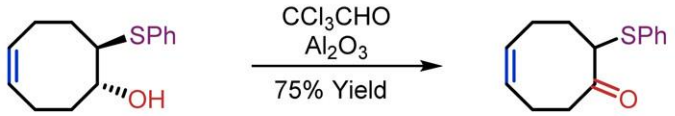


(Eq. 1)



(Eq. 2)

specific hydride reagents



(Eq. 3)

unique hydride transfer pathway

1. Huang, Z. X.; Dong, G. B. *Acc. Chem. Res.* **2017,** 50, 465-471.

1. Chemoselectivity and site selectivity: Concepts and examples.

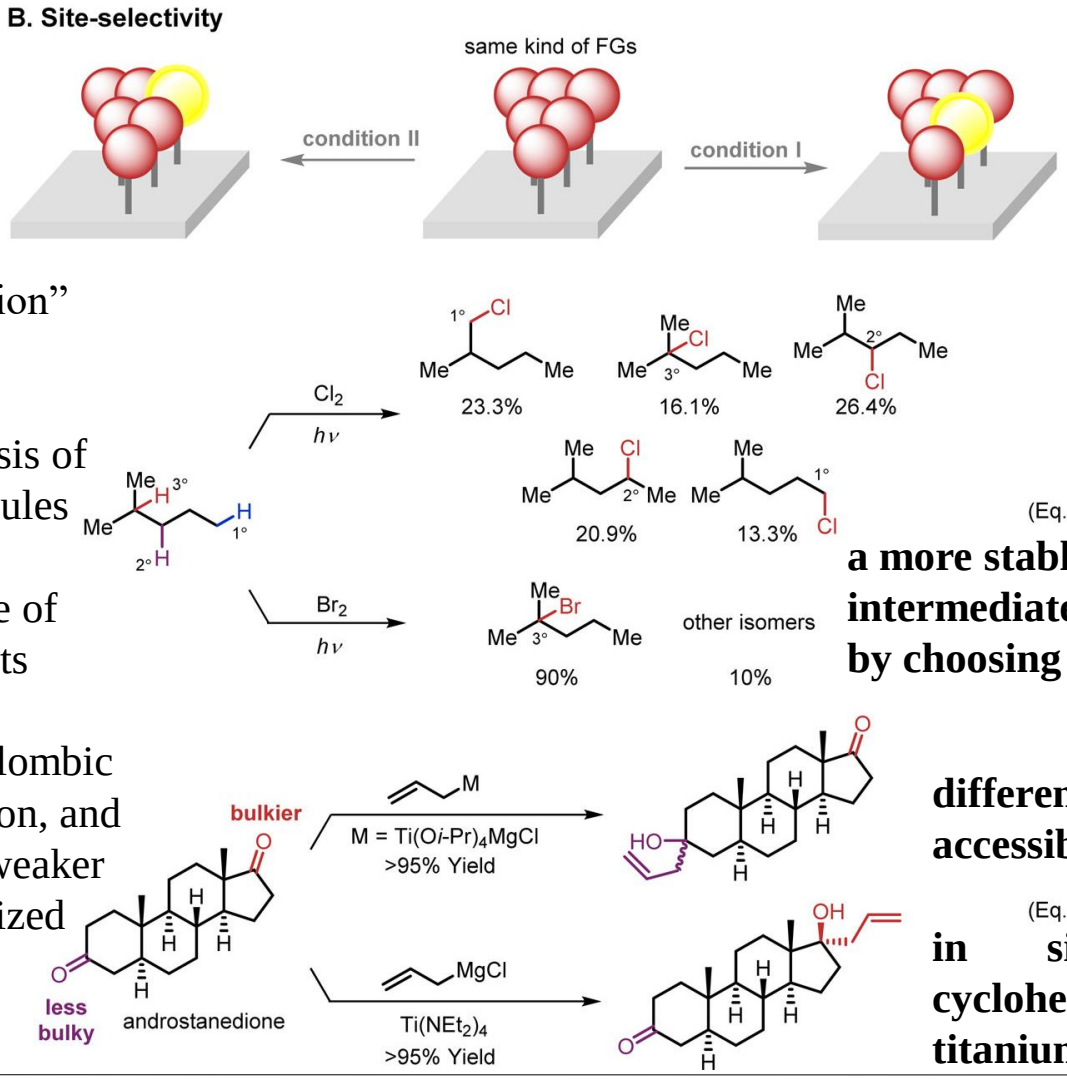
a special scenario of chemoselectivity

eliminate "protection/deprotection" Sequences

streamline the synthesis of complex target molecules

amplify the difference of chemical environments

Induction effect, Coulombic interaction, conjugation, and hyperconjugation, a weaker bond or a more stabilized intermediate



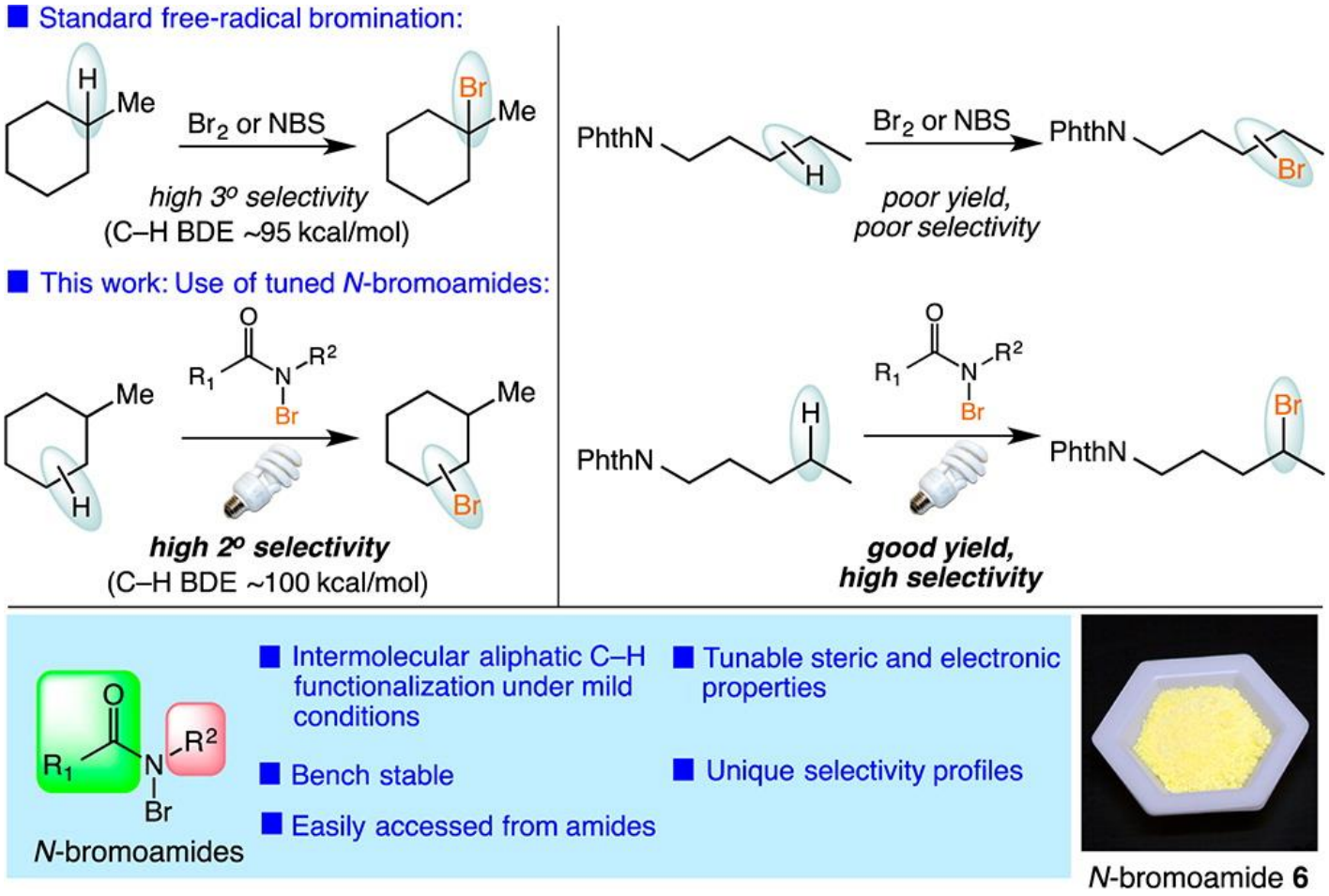
a more stable tertiary alkyl radical intermediate, a late transition state by choosing bromine

different degrees of spatial accessibility,

in situ masking the cyclohexanone carbonyl by titanium complex

1. Huang, Z. X.; Dong, G. B. *Acc. Chem. Res.* **2017,** 50, 465-471.

2. Undirected control of site selectivity: C-H Bromination



Radical-mediated aliphatic C–H brominations using N-bromoamides offer both **high steric** and **electronic selectivities**, enabling C–H brominations inaccessible using standard protocols.

2. Schmidt, V. A.; Quinn, R. K.; Brusoe, A. T.; Alexanian, E. J. *J. Am. Chem. Soc.* **2014**, 136, 14389−14392..

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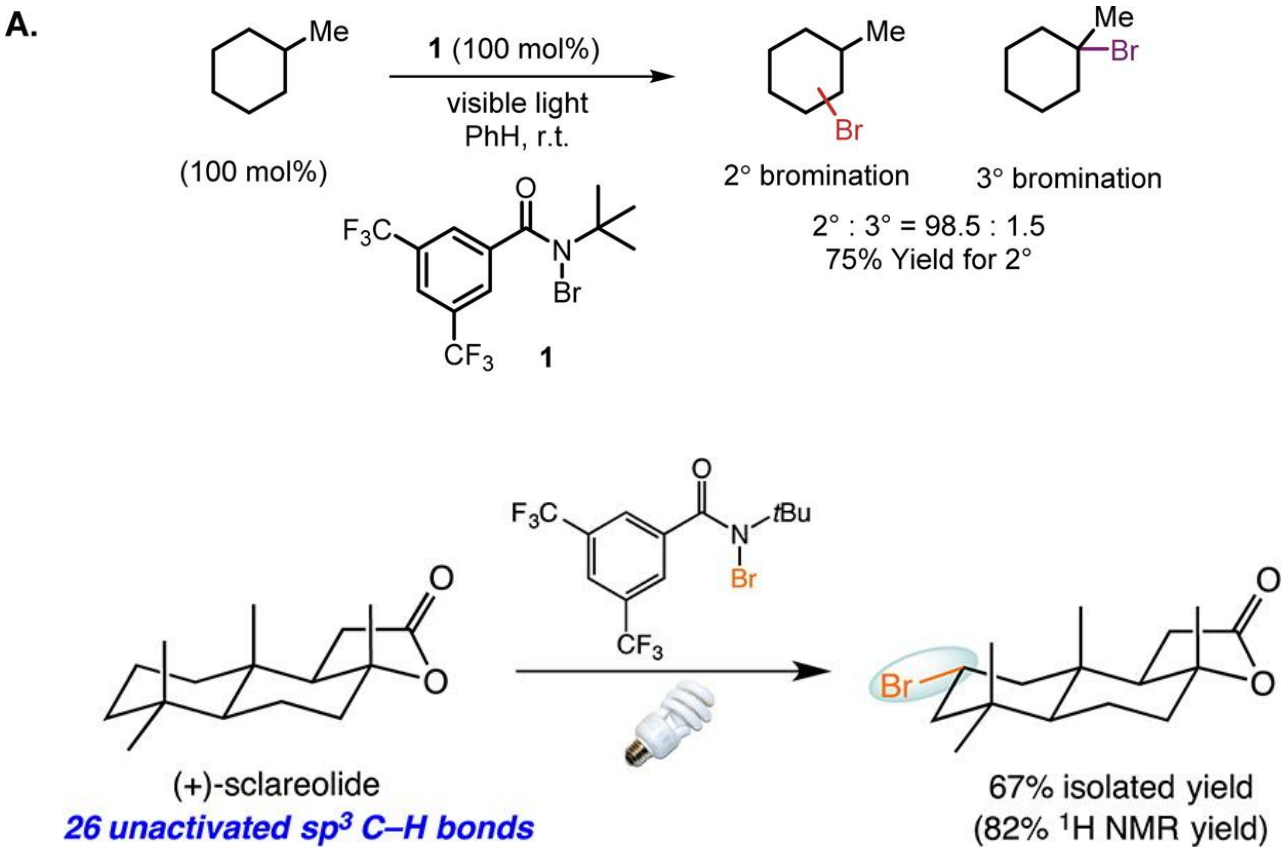
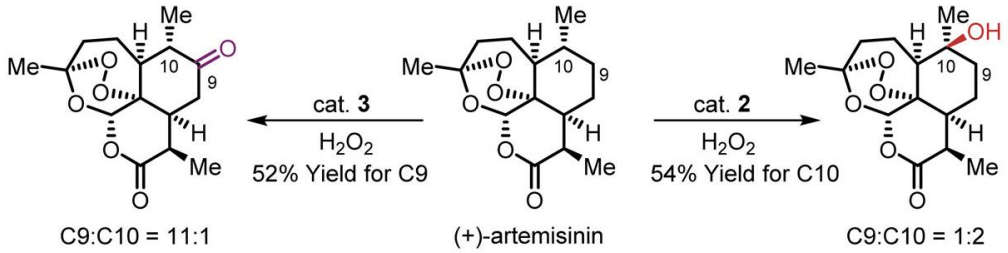


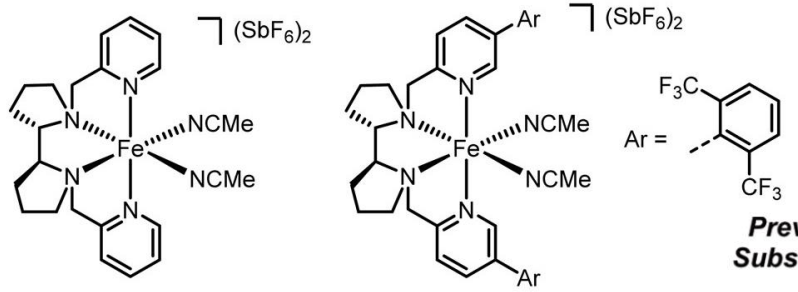
Radical-mediated aliphatic C–H brominations using N-bromoamides offer both **high steric** and **electronic selectivities**, enabling C–H brominations inaccessible using standard protocols.

2. Schmidt, V. A.; Quinn, R. K.; Brusoe, A. T.; Alexanian, E. J. *J. Am. Chem. Soc.* **2014**, 136, 14389−14392..

2. Undirected control of site selectivity: C-H Oxidation

B.





Fe(*S*,*S*-PDP), **2**

Fe(*S*,*S*-CF_3-PDP), **3**

tertiary C-H versus secondary C-H:

electronic (favors electron-rich sites), steric (favors unhindered sites), and stereoelectronic factors (favors sites where strain relief is possible)

5-position ortho-CF_3:

deactivate the ligand toward oxidation, narrow the cone of possible approach trajectories to 76°

6-CF_3: greatly diminished C-H oxidation reactivity

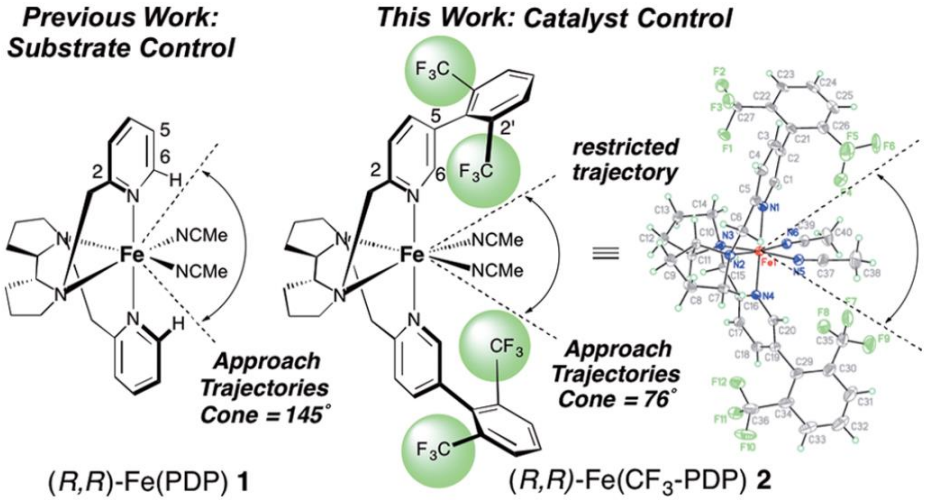
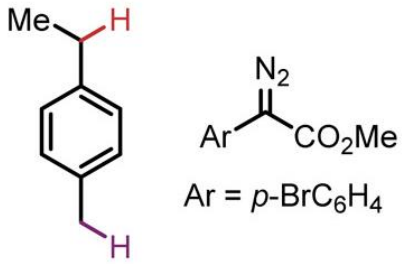


Figure 1. Trajectory Restriction Strategy

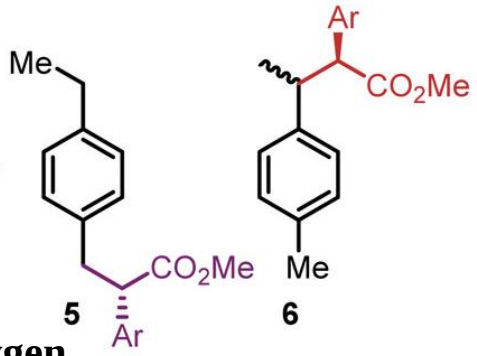
3. Gormisky, P. E.; White, M. C. *J. Am. Chem. Soc.* **2013**, 135, 14052−14055.

2. Undirected control of site selectivity: Carbenoid Insertion

C.

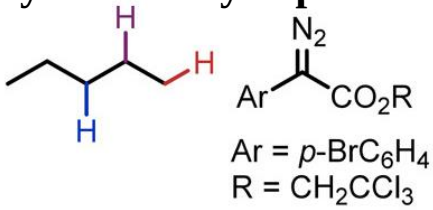


cat. **4a** or **4b**

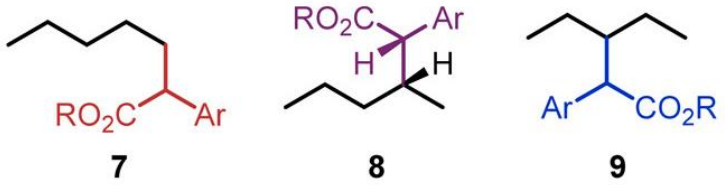


Catalyst	Site-selectivity		Yield (%)
	5	**6**	
4a	<1	20	75
4b	5	1	74

at benzylic and allylic positions and α to oxygen

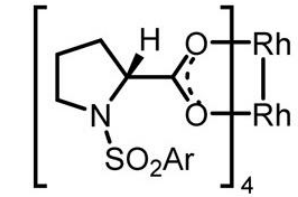


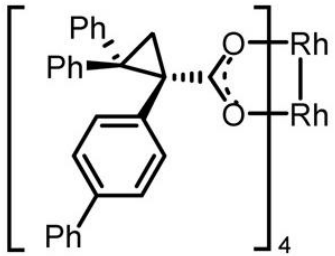
cat. **4c**

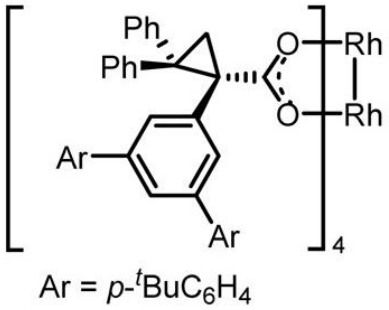


site-selectivity **7**:**8**:**9** = 1:25:0
99% Yield

unactivated C–H bonds



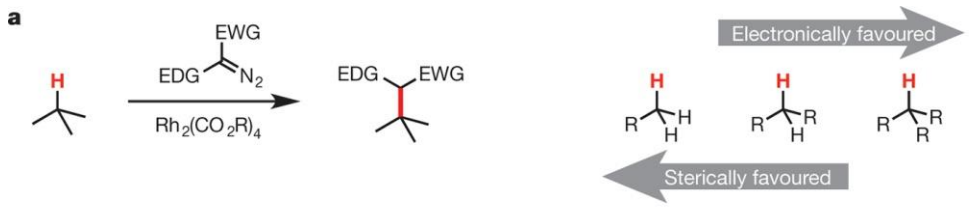




4a, Rh_2(*R*-DOSP)$_4$ **4b**, Rh_2(*R*-BPCP)$_4$ **4c**, Rh_2[*R*-3,5-di(*p*-^{t}BuC$_6$H$_4$)TPCP]$_4$

4. Qin, C.; Davies, H. M. L. *J. Am. Chem. Soc.* **2014**, 136, 9792−9796.
5. Liao, K.; Negretti, S.; Musaev, D. G.; Bacsa, J.; Davies, H. M. L. *Nature* **2016**, 533, 230.234.

2. Undirected control of site selectivity: Carbenoid Insertion



rhodium-bound donor/acceptor carbenes:

reactivity: < acceptor-only substituted carbenes

enabling highly selective C−H functionalization by balance of steric and electronic effects.

electronically favored highly substituted sites

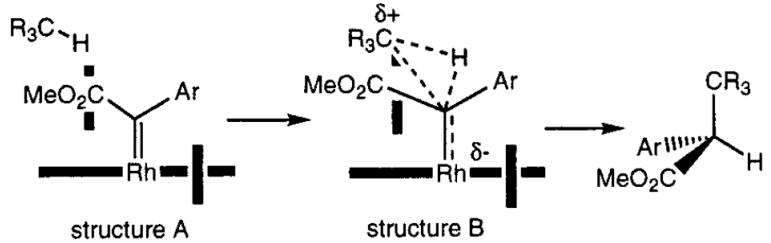
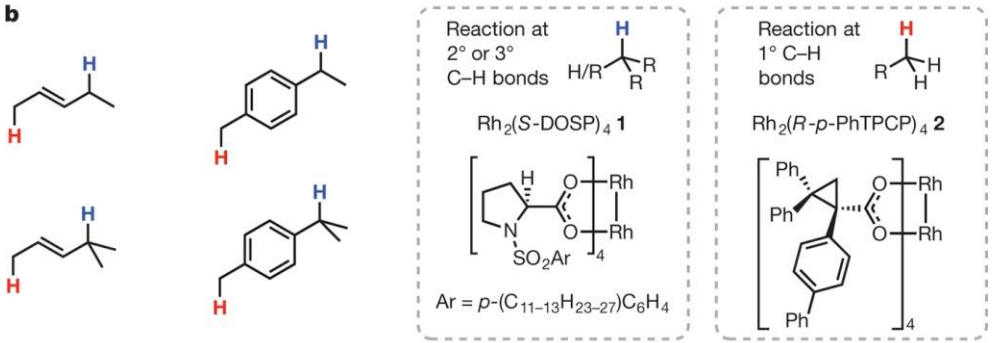
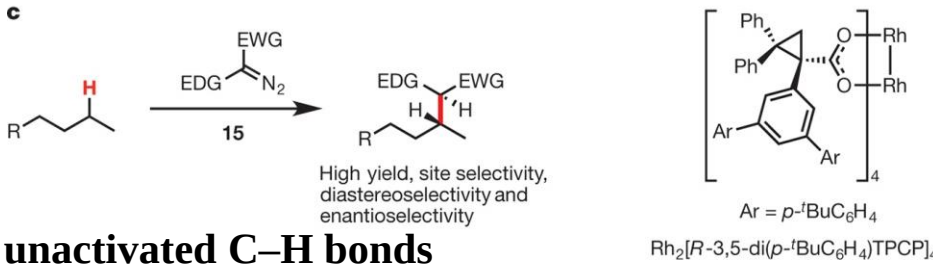


Figure 1. initiated by a hydride transfer event



at benzylic and allylic positions and α to oxygen



unactivated C–H bonds

high regio-, diastereo- and enantioselectivity

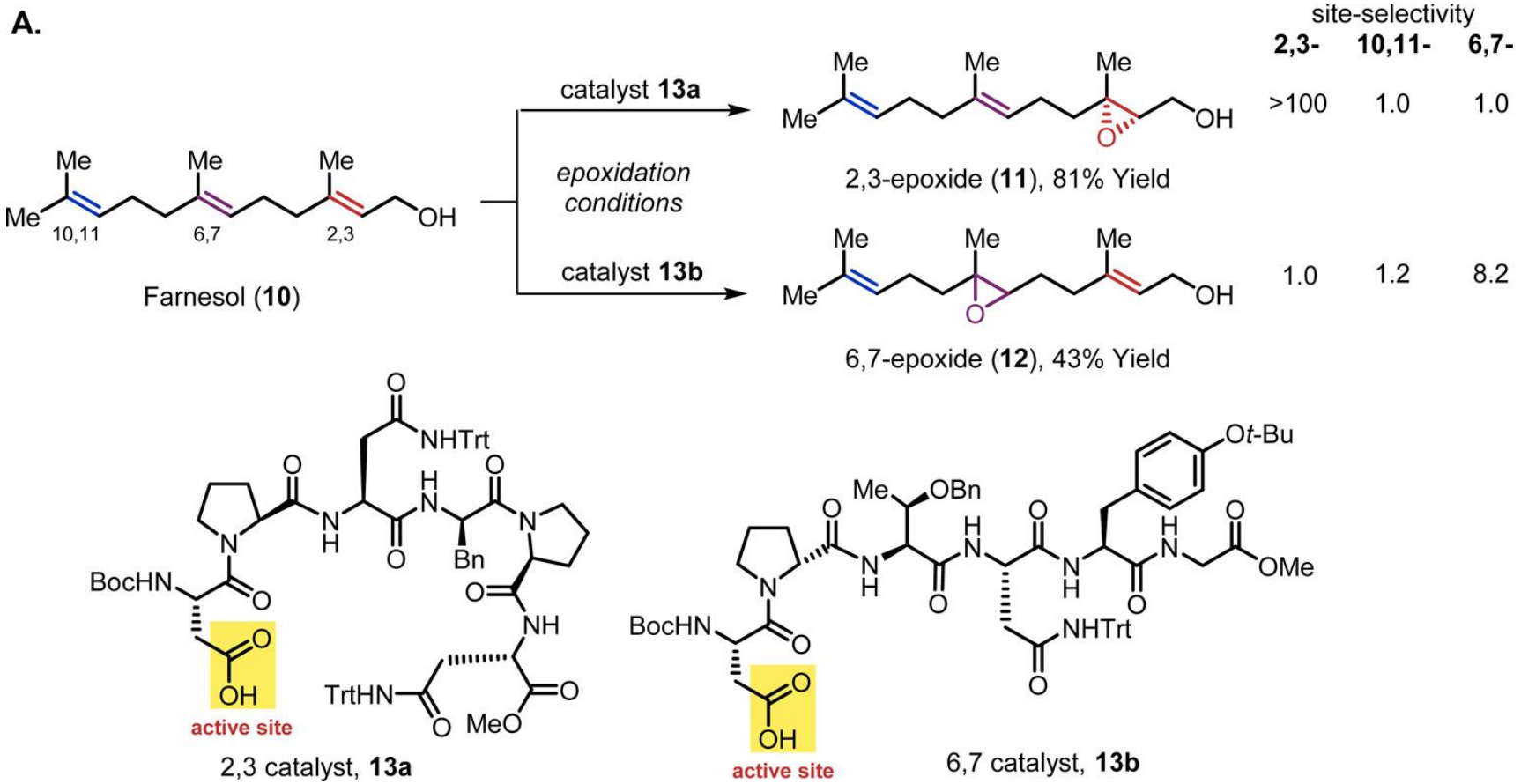
larger and more electrophilic catalysts

counterbalanced by the **steric demands** of the **carbene complex**.

on steric grounds the primary C–H bond would be preferred.

4. Qin, C.; Davies, H. M. L. *J. Am. Chem. Soc.* **2014**, 136, 9792−9796.
5. Liao, K.; Negretti, S.; Musaev, D. G.; Bacsa, J.; Davies, H. M. L. *Nature* **2016**, 533, 230.234.
6. Davies, H. M. L.; Hansen, J. *J. Am. Chem. Soc.* **1997**, 119, 9075.

3. Directed control of site selectivity: Peptide Catalysis

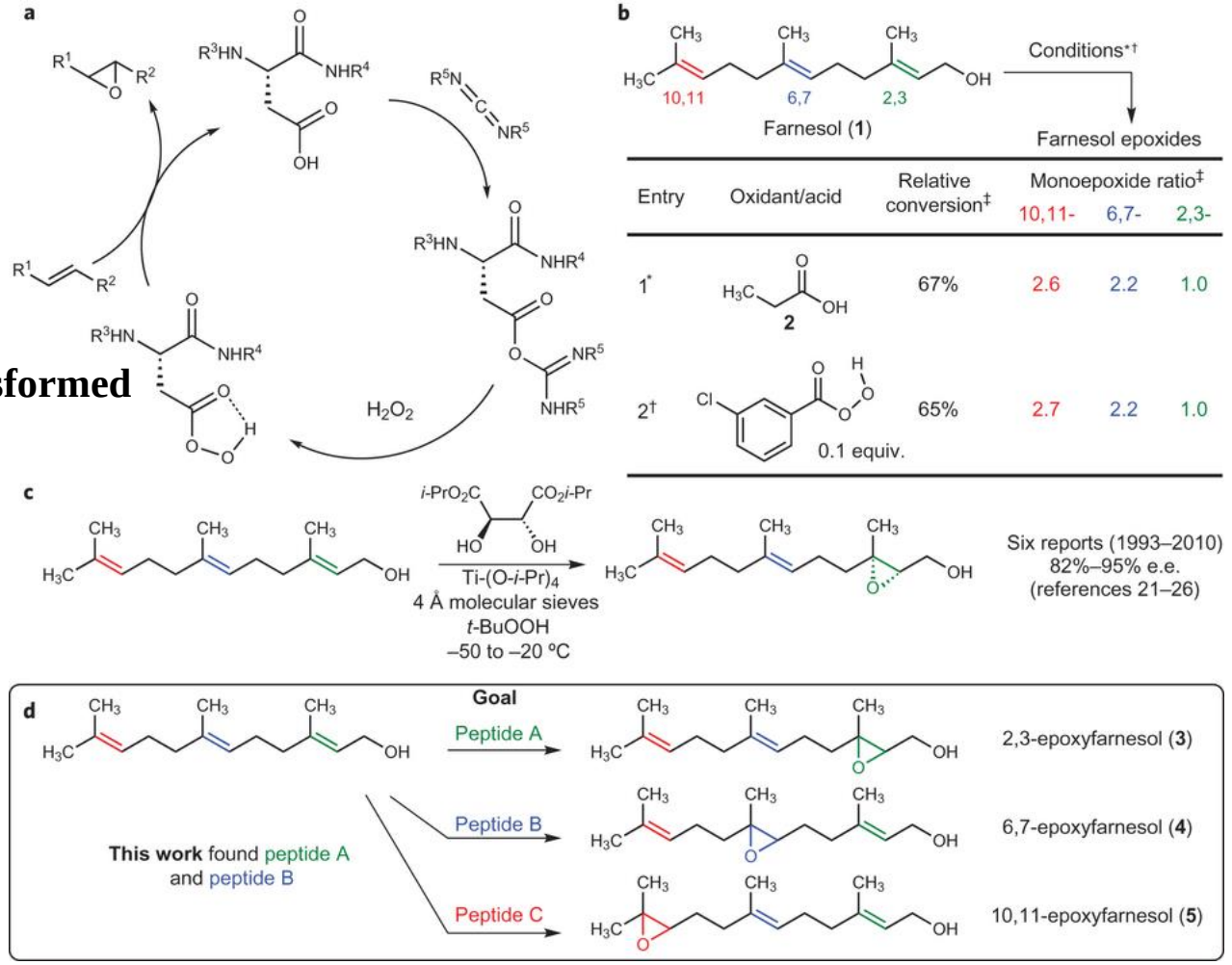


The **steric hindrance**, **hydrogen bonding**, **π-interactions**, and other characters of the backbone can be fine-tuned by replacing the amino-acid residues.

7. Lichtor, P. A.; Miller, S. J. *Nat. Chem.* **2012**, 4, 990.995.

3. Directed control of site selectivity: Peptide Catalysis

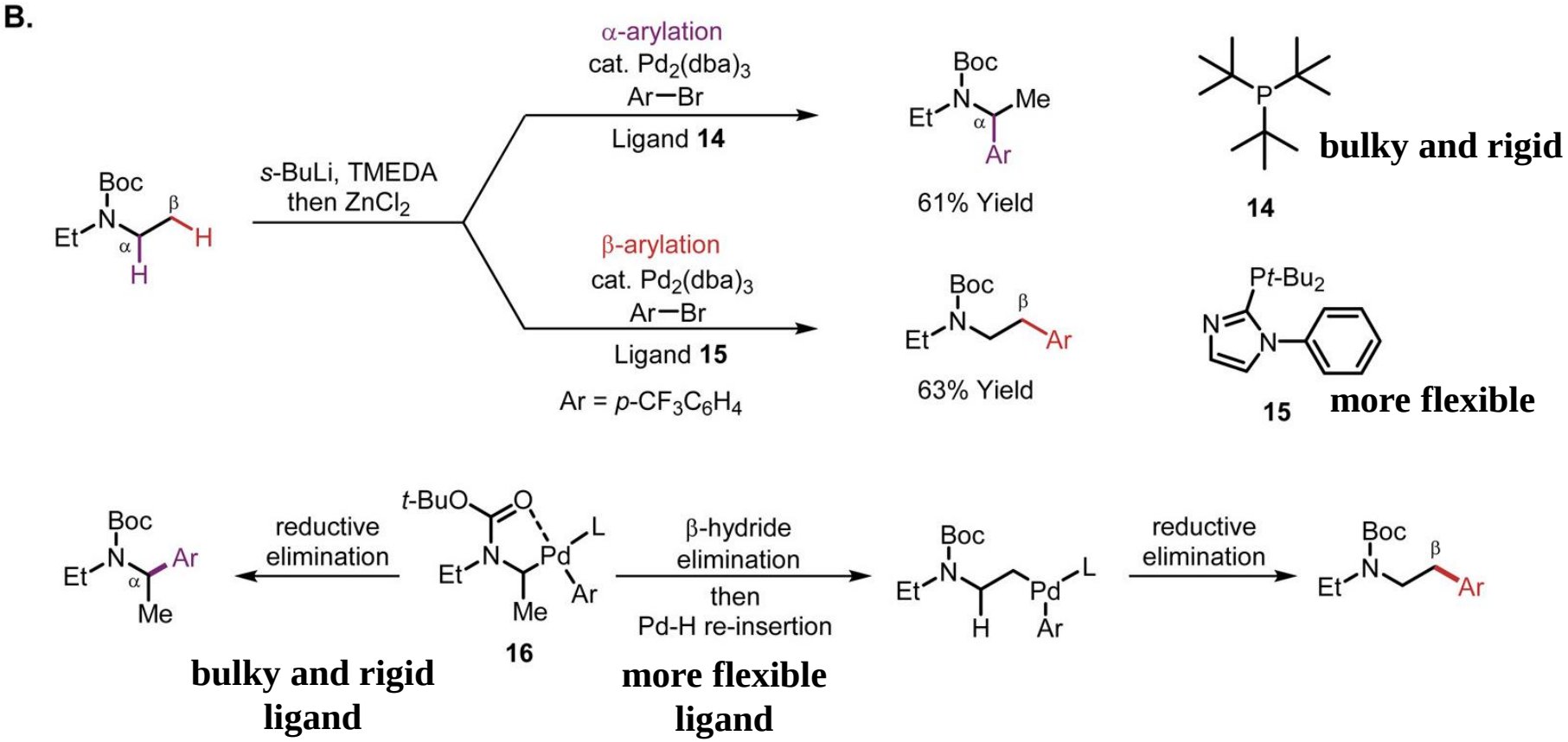
in situ transformed to a peracid



contrary site selectivity : conformational difference upon forming hydrogen bonds

7. Lichtor, P. A.; Miller, S. J. *Nat. Chem.* **2012**, 4, 990.995.

3. Directed control of site selectivity: Ligand effect



a **bulky and rigid P(t-Bu)3 (14)** ligand favored the **direct reductive elimination** of intermediate 16 to give the **α-arylated amine**, a **more flexible** ligand, such as **15**, promoted a **β-hydrogen elimination/Pd−hydride reinsertion sequence** to eventually yield the **β-arylation product**.

8. Millet, A.; Dailler, D.; Larini, P.; Baudoin, O. *Angew. Chem., Int. Ed.* **2014**, 53, 2678−2682.
9. For an earlier case where the site selectivity was controlled by substrates, see: Seel, S.; Thaler, T.; Takatsu, K.; Zhang, C.; Zipse, H.; Straub, B. F.; Mayer, P.; Knochel, P. *J. Am. Chem. Soc.* **2011**, 133, 4774−4777.

3. Directed control of site selectivity: Ligand effect

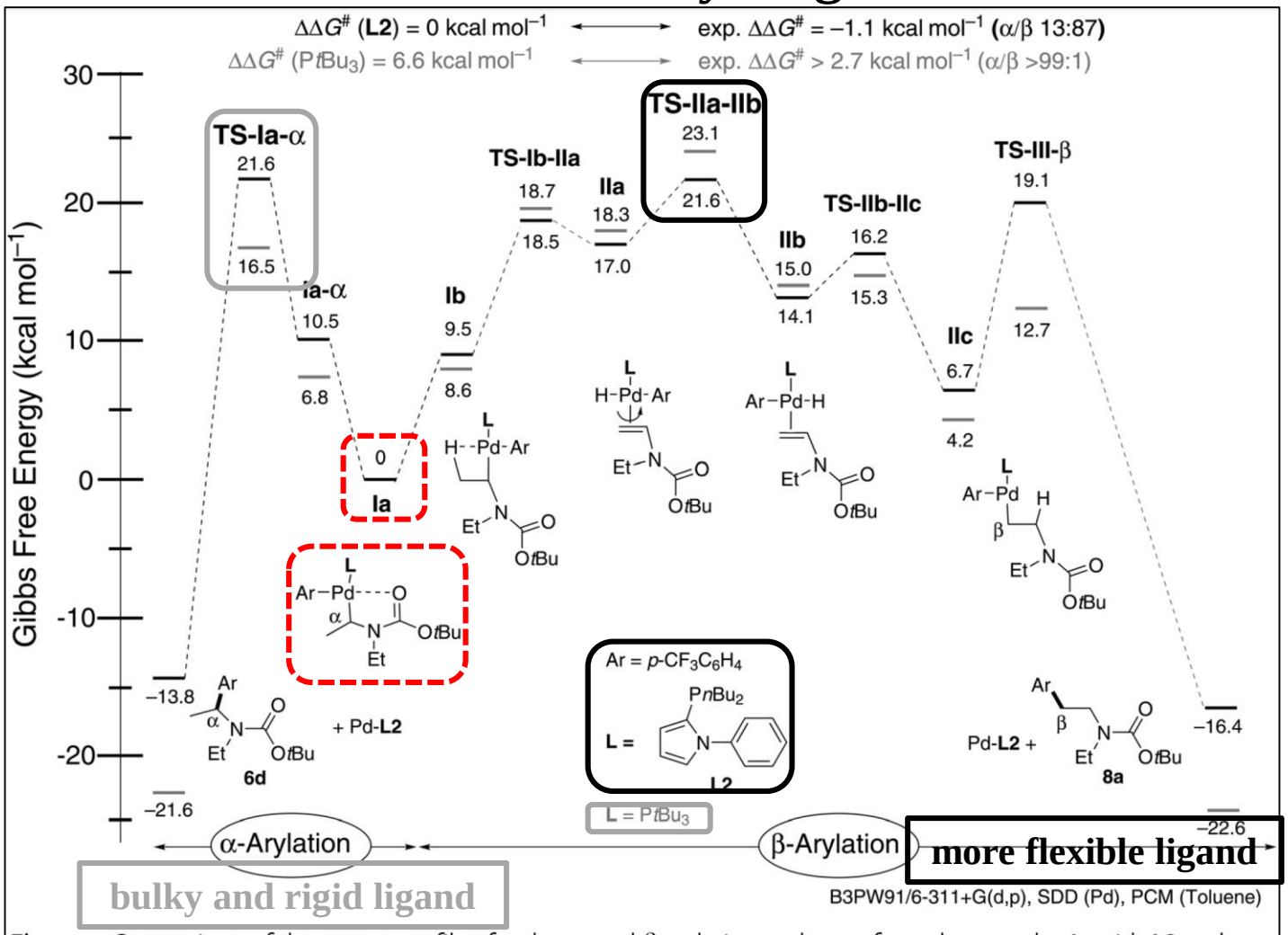


Figure 2. Comparison of the energy profiles for the α- and β-arylation pathways from the complex **Ia** with **L2** and $PtBu_3$ as the ligands.

8. Millet, A.; Dailler, D.; Larini, P.; Baudoin, O. *Angew. Chem., Int. Ed.* **2014**, 53, 2678−2682.

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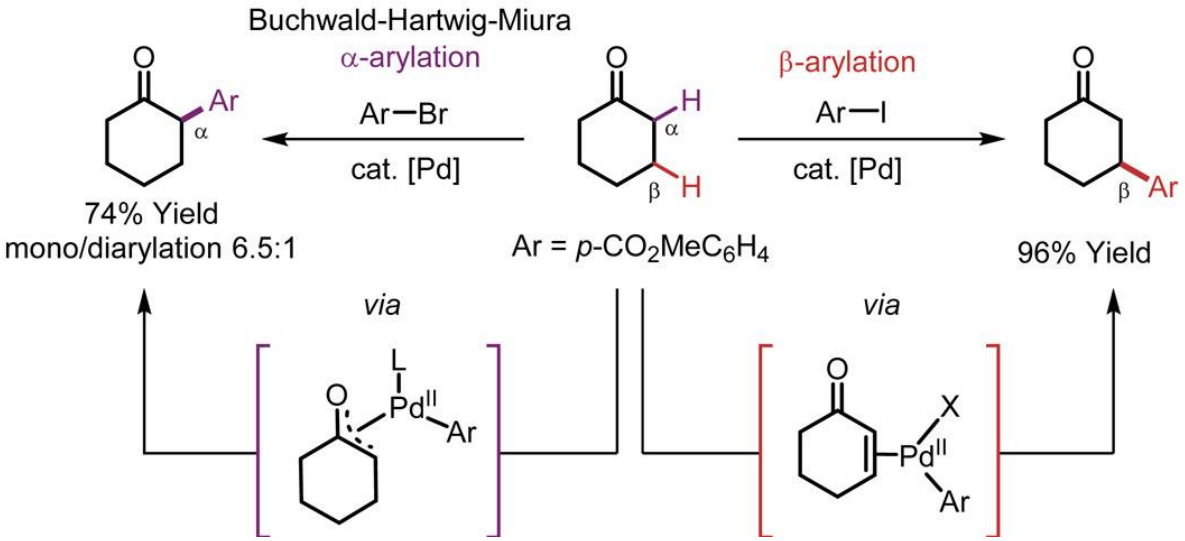
3. Directed control of site selectivity: Change of the Reaction Pathway

C.



	α-arylation	β-arylation
[Pd]	$Pd_2(dba)_3$	$Pd(TFA)_2$
Ligand	Xantphos	$P(i\text{-}Pr)_3$
Additive	K_3PO_4	AgTFA
Solvent	Toluene	HFIP/Dioxane

aryl halides: oxidant and aryl source

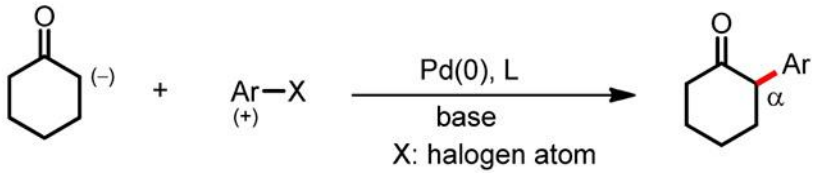
Direct β-arylation: palladium-catalyzed dehydrogenation and conjugate addition/reductive Heck

Buchwald-Hartwig-Miura α-arylation: oxidative addition, ligand exchange with the enolate, reductive elimination

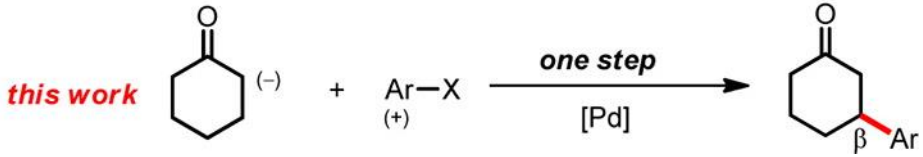
10. Huang, Z.; Dong, G. *J. Am. Chem. Soc.* **2013**, 135, 17747−17750.
11. Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, 122, 1360−1370.
12. For a recent review, see: Johansson, C. C. C.; Colacot, T. J. *Angew. Chem., Int. Ed.* **2010**, 49, 676−707.

3. Directed control of site selectivity: Change of the Reaction Pathway

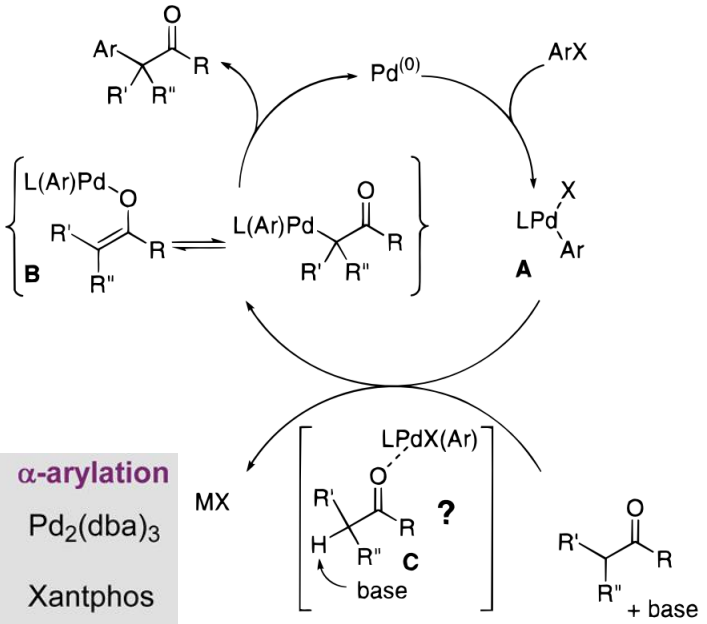
A. Buchwald–Hartwig–Miura α-arylation



B. β-arylation of simple ketones with aryl halides

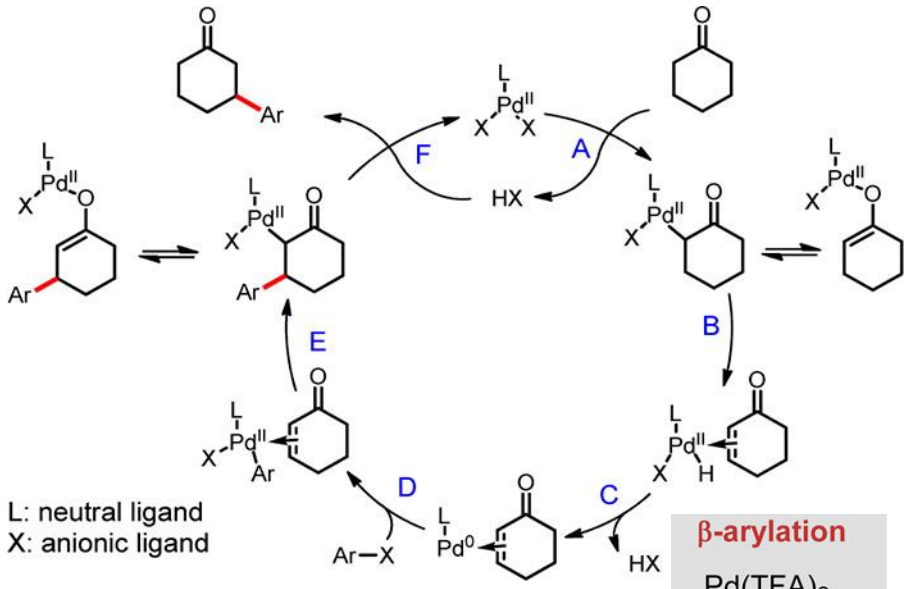


Scheme 1



	α-arylation
[Pd]	$Pd_2(dba)_3$
Ligand	Xantphos
Additive	K_3PO_4
Solvent	Toluene

strong base: deprontonation, ligand exchange



acidic medium, iodide extractor

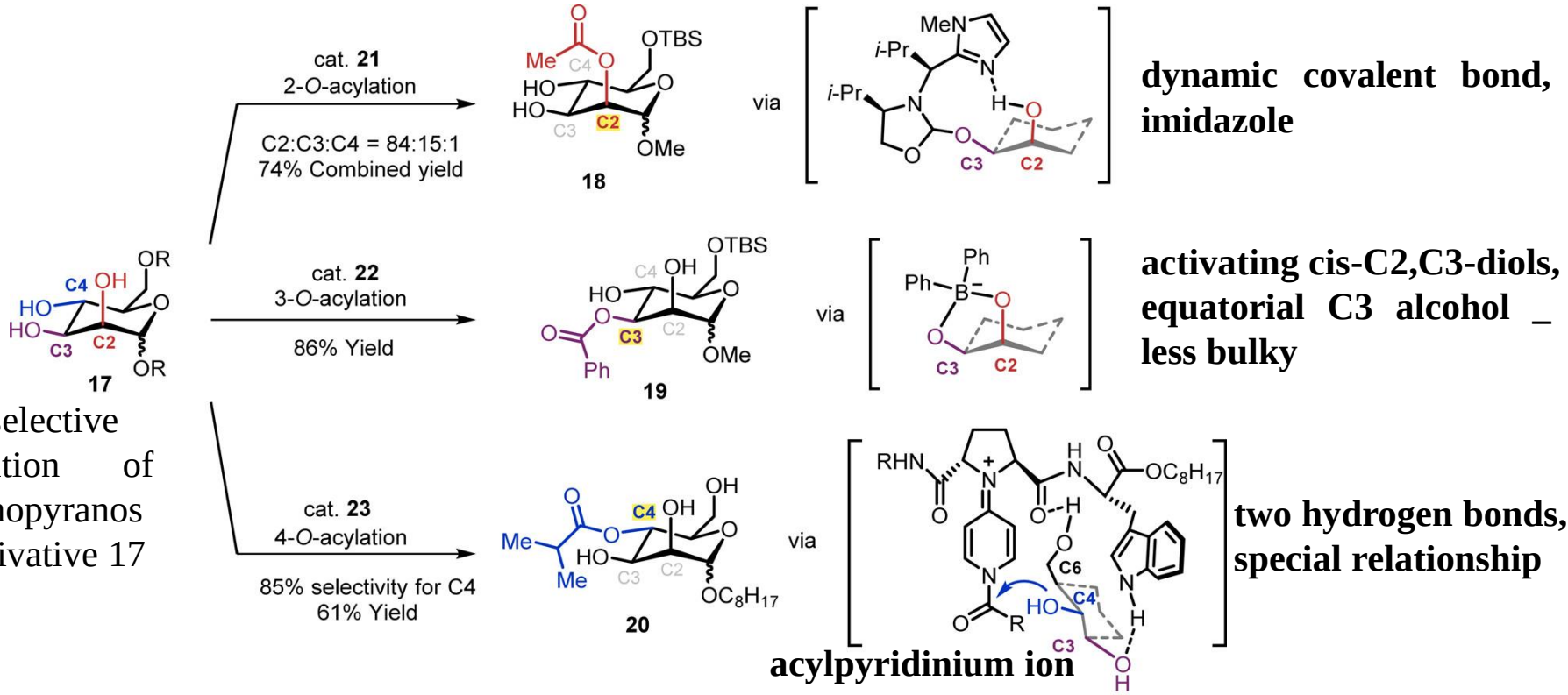
copper(II) trifluoroacetate

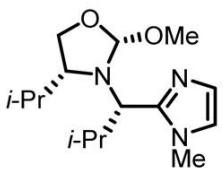
	β-arylation
	$Pd(TFA)_2$
	$P(i\text{-}Pr)_3$
	AgTFA
	HFIP/Dioxane

10. Huang, Z.; Dong, G. *J. Am. Chem. Soc.* **2013**, 135, 17747−17750.
11. Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, 122, 1360−1370.
12. For a recent review, see: Johansson, C. C. C.; Colacot, T. J. *Angew. Chem., Int. Ed.* **2010**, 49, 676−707.

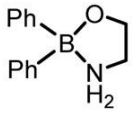
3. Directed control of site selectivity: Sugar Chemistry

site-selective acylation of mannopyranose derivative 17

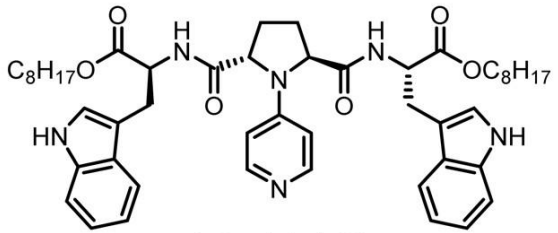




2-*O* catalyst, **21**
Tan



3-*O* catalyst, **22**
Taylor



4-*O* catalyst, **23**
Kawabata

13. Sun, X.; Lee, H.; Lee, S.; Tan, K. L. *Nat. Chem.* **2013**, 5, 790−795.
14. Lee, D.; Taylor, M. S. *J. Am. Chem. Soc.* **2011**, 133, 3724−3727.
15. Kawabata, T.; Muramatsu, W.; Nishio, T.; Shibata, T.; Schedel, H. *J. Am. Chem. Soc.* **2007**, 129, 12890−12895.

4. Conclusion and outlook

1. Compared with the advancement of selectivity control among different kinds of FGs as well as the monument of controlling regio-, diastereo-, and enantioselectivity, the development of **site-selective approaches** is still in its infant stage.

2. To breed more general, practical, and broadly applicable methods, it is envisaged that future endeavors will focus on (1) **expanding the substrate scope** that can undergo site-selective transformations and (2) **precisely controlling** the site of reaction **in less biased settings**.

3. Clearly, the needs cannot be met without the availability of more powerful catalysts, reagents, strategies, and even new tactics. It is expected that Mother Nature will continue providing inspirations to design **biomimetic or supramolecular catalysts**.

4. To enable more precise site selectivity control and broader reaction scope would require **better modeling** and **deeper mechanistic understanding** of these catalytic processes.

1. Huang, Z. X.; Dong, G. B. *Acc. Chem. Res.* **2017,** 50, 465-471.

4. Conclusion and outlook

5. In addition, **cooperative catalysis** through **combining two or more activation modes** might be another trend for the incoming efforts. Vigorous development in recent years has demonstrated that **merger of multiple catalysis** is able to **activate substrates once considered inert or functionalize sites previously inaccessible.**

6. Furthermore, **practical applications** of site-selective transformations in **complex molecule synthesis** are anticipated to be illustrated more frequently in the future.

1. Huang, Z. X.; Dong, G. B. *Acc. Chem. Res.* **2017,** 50, 465-471.

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