LITERATURE REPORT

Radicals: Reactive Intermediates with Translational Potential

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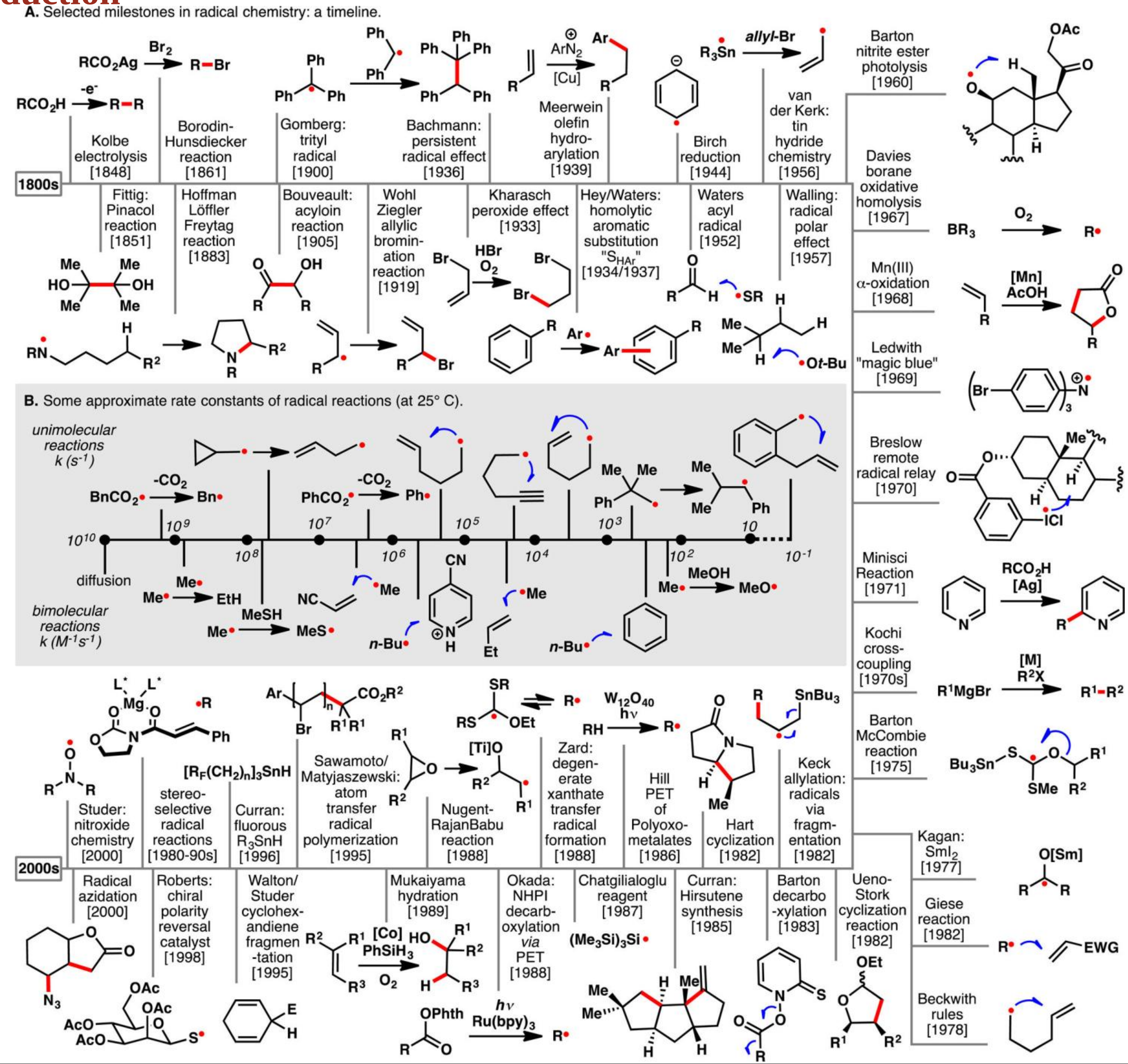
Supervisor: Prof. Yong Huang

2016.10.19

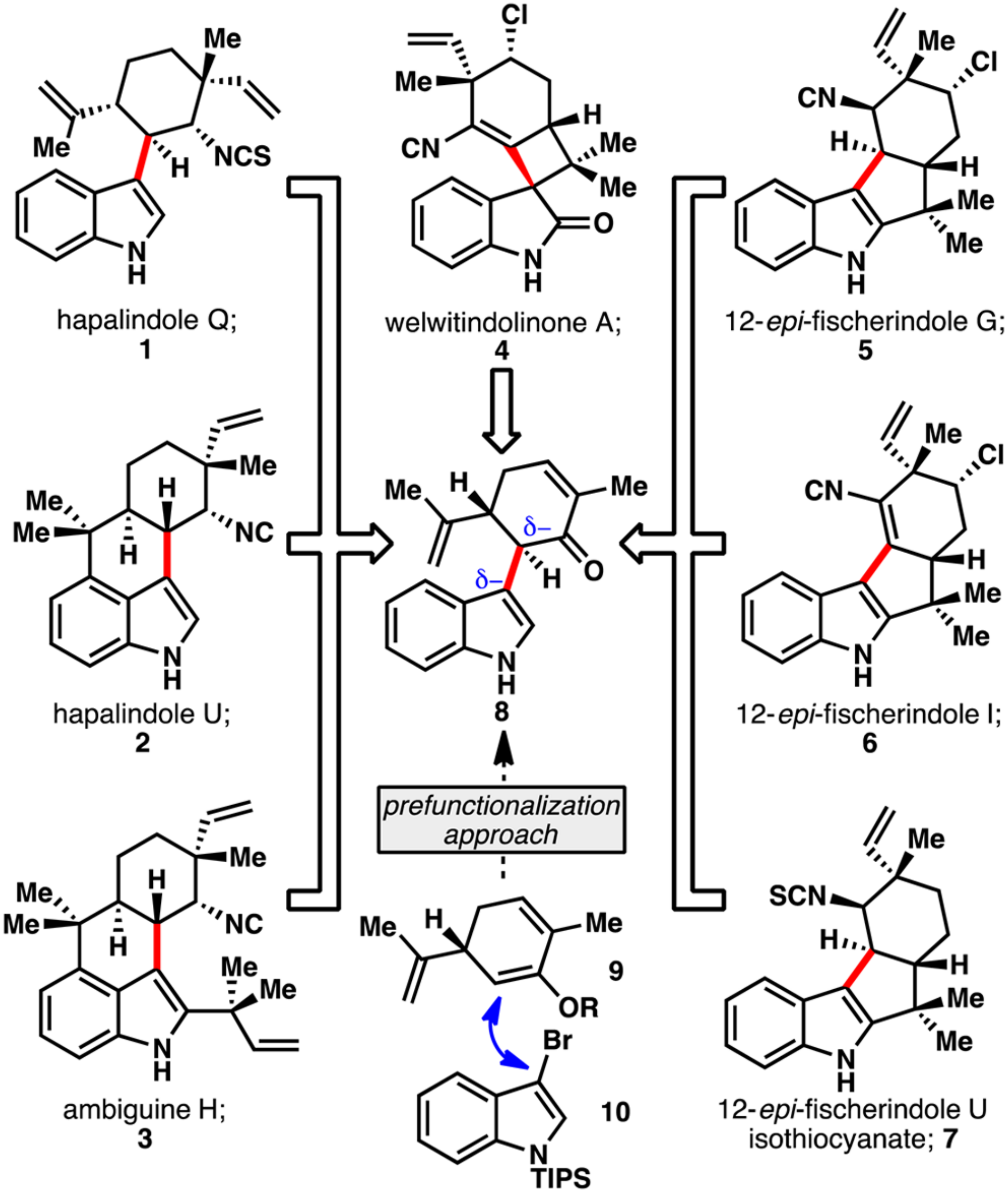
Contents

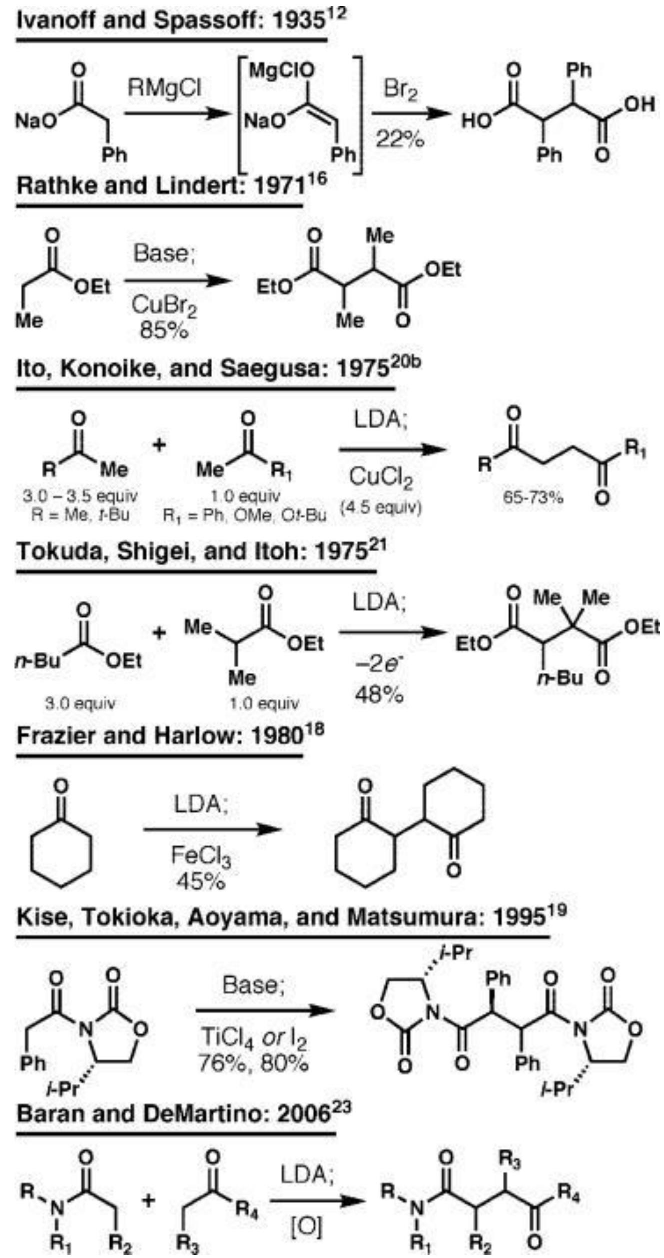
P. S. Baran, *et al. J. Am. Chem. Soc.* **2016**, *138*, 12692

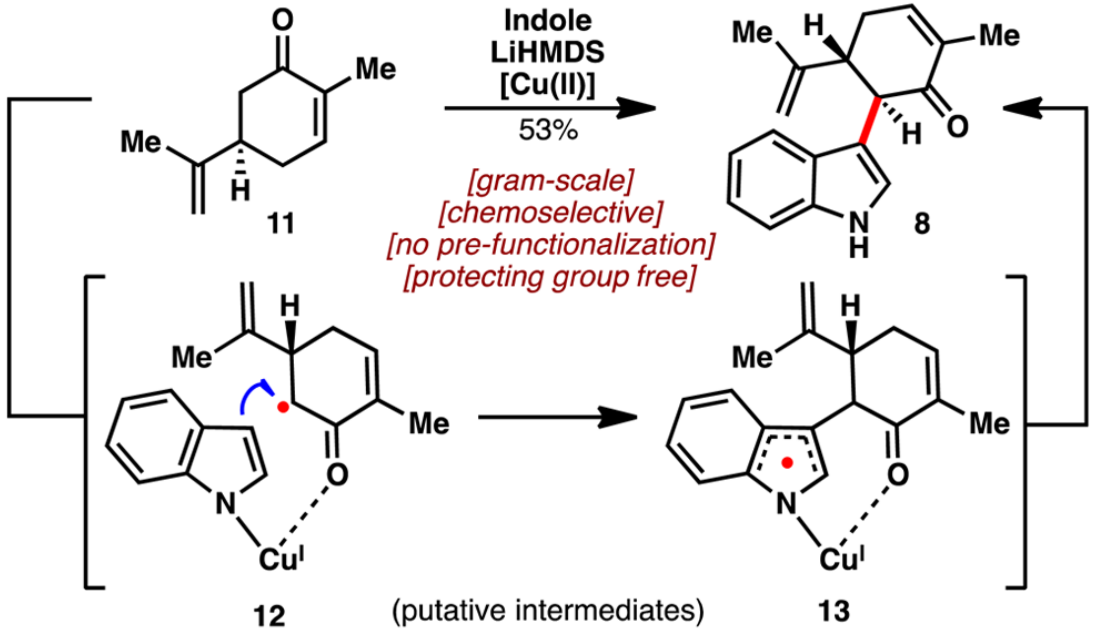
1. Introduction

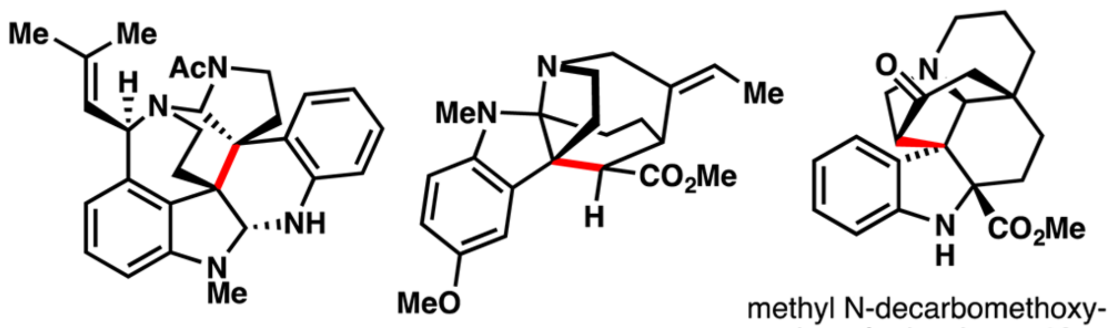


2. A Radical Start: Oxidative Enolate Coupling







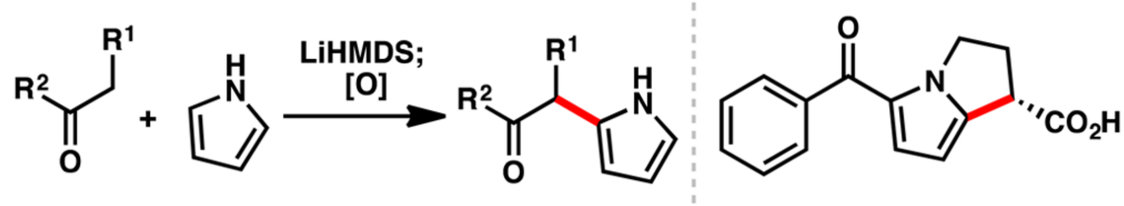


(–)-communesin F; **14**

(–)-vincorine; **15**

methyl N-decarbomethoxy-chanofruticosinate; **16**

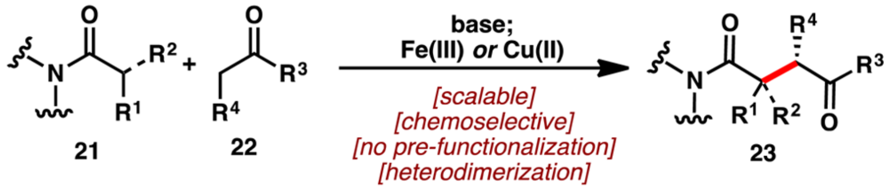
C. Invention of a radical-based pyrrole-carbonyl oxidative coupling

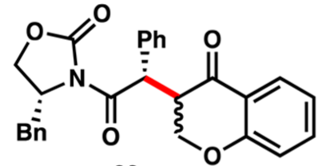


17 **18** **19**

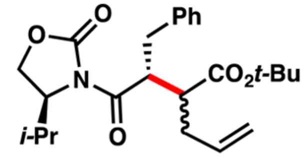
(*S*)-ketorolac; **20**

D. Invention of oxidative enolate heterocoupling.

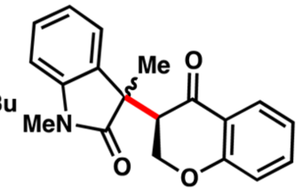




23a
(60%, d.r.=2.6:1.0)

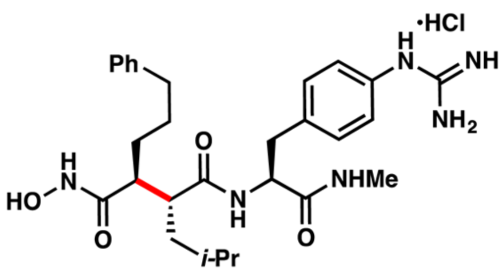


23b
(56%, d.r.=1.2:1.0)

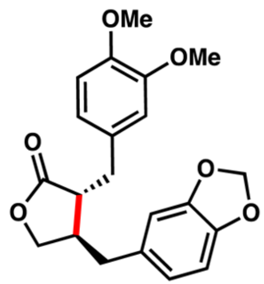


23c
(72%, d.r.=2.6:1.0)

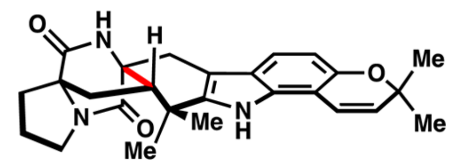
E. Syntheses enabled by oxidative enolate heterocoupling.



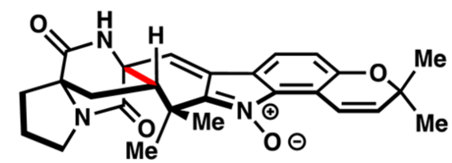
matrix metalloproteinase inhibitor; **24**



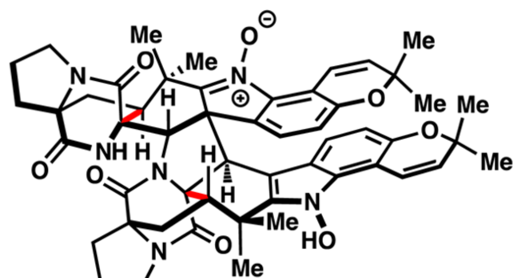
(–)-bursehernin; **25**



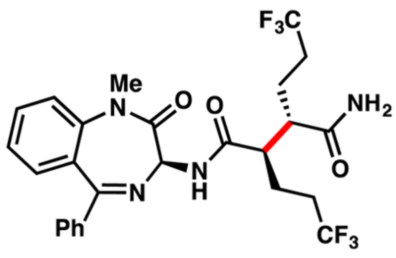
(+)-stephacidin A; **26**



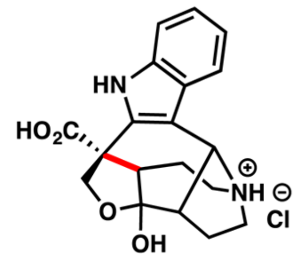
(+)-avrainvillamide; **27**



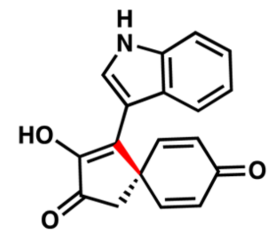
(–)-stephacidin B; **28**



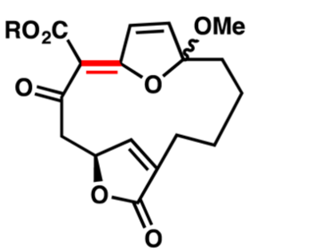
BMS-906024; **29**



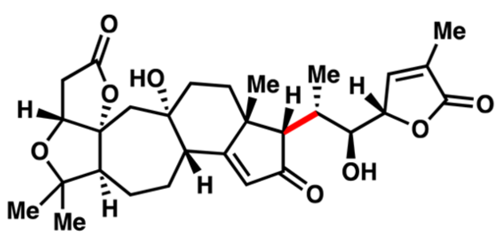
(–)-actinophyllic acid hydrochloride; **30**



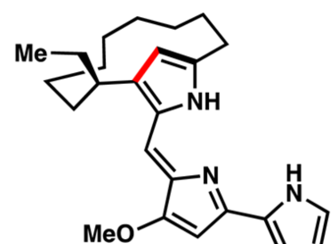
spirobacillene A; **31**



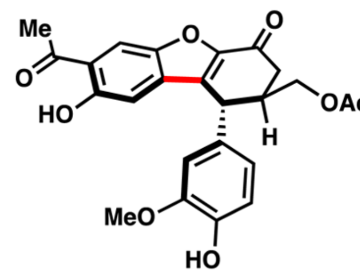
32, toward furanocembranoids



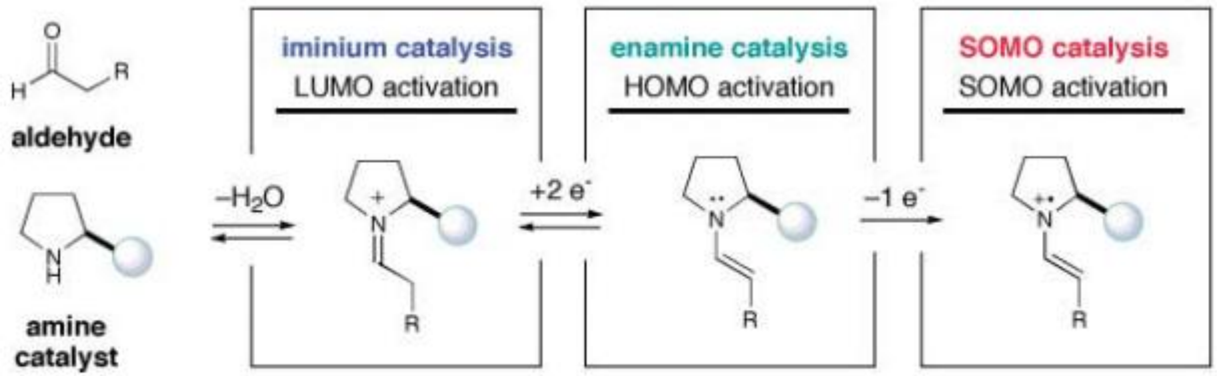
(+)-propindilactone G; **33**

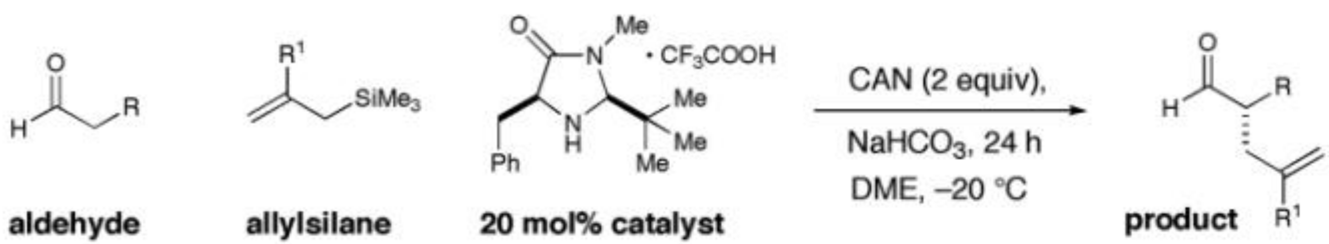


metacycloprodigiosin; **34**

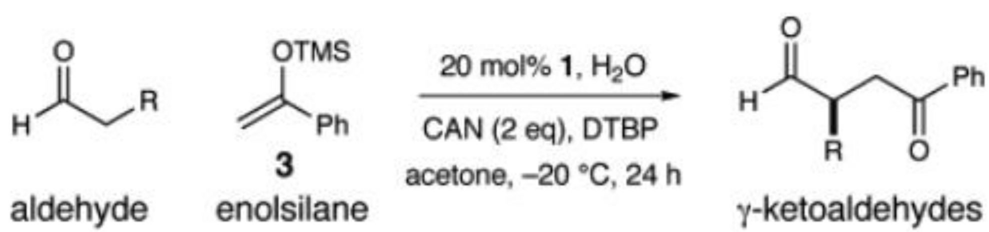


propolisbenzofuran B; **35**



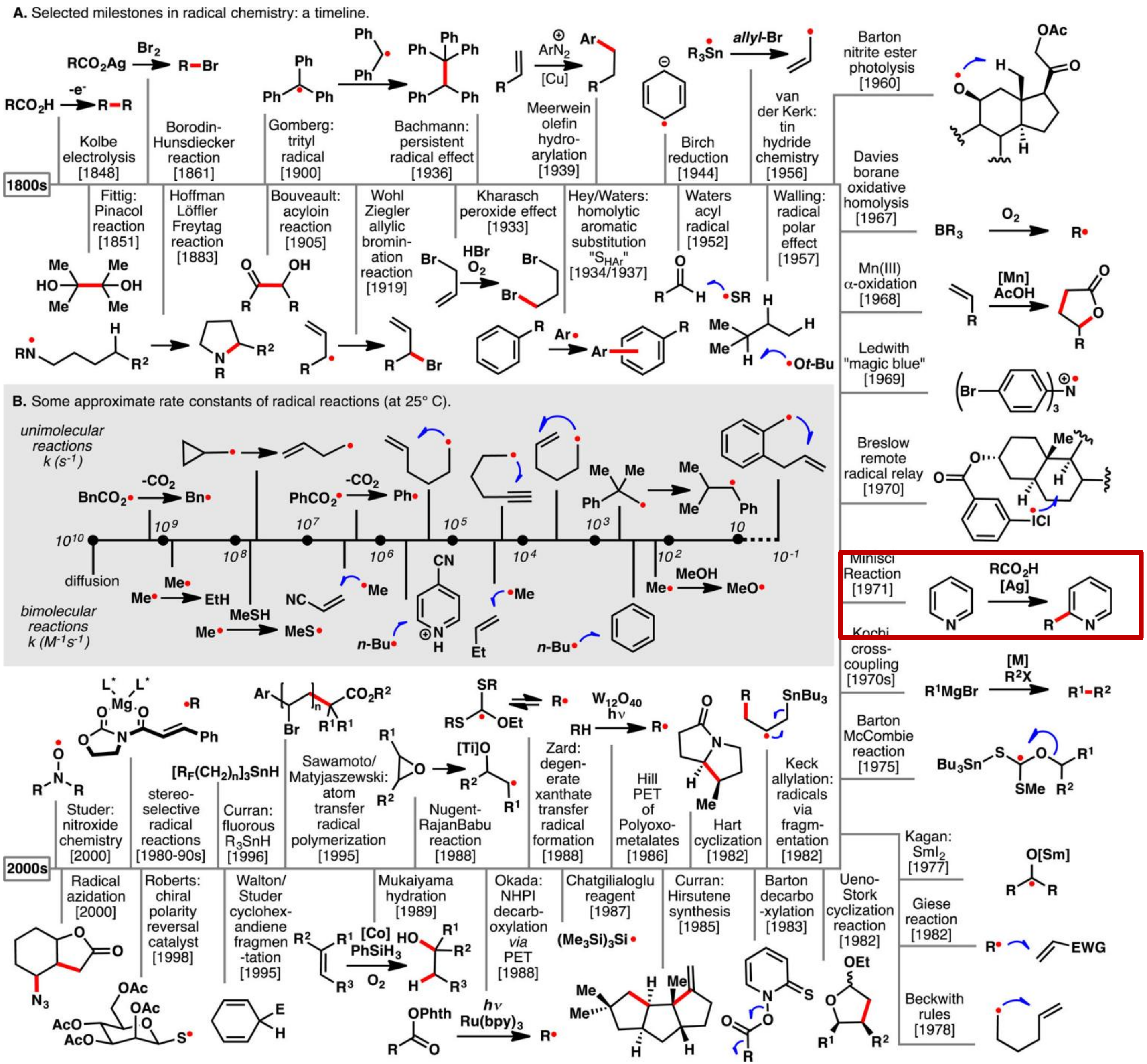


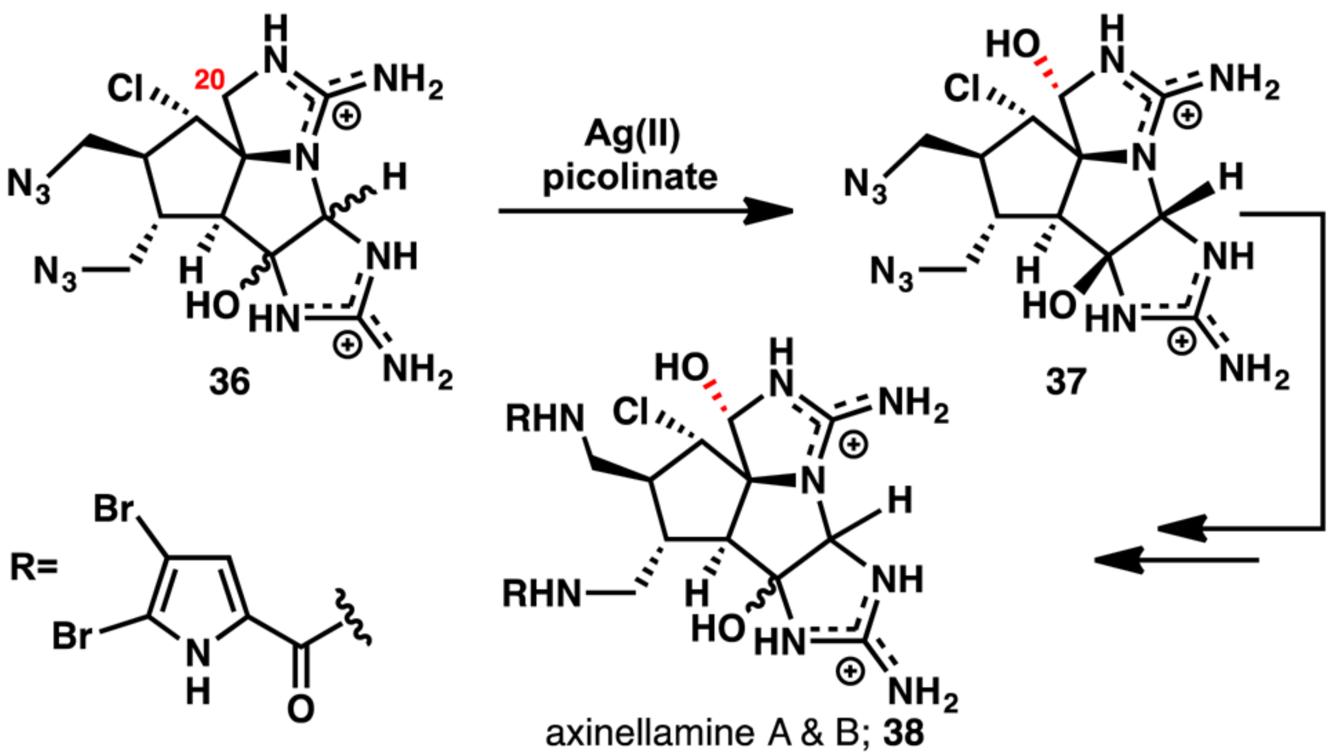
Science **2007**, *316*, 582-585



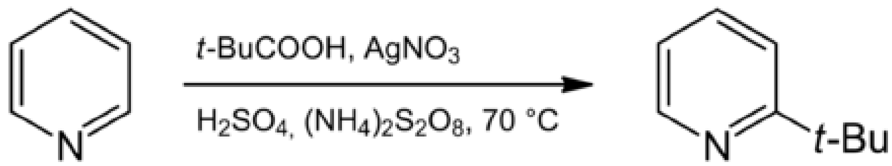
J. Am. Chem. Soc. **2007**, *129*, 7004-7005

3. Developemet of Minisci Type Reaction

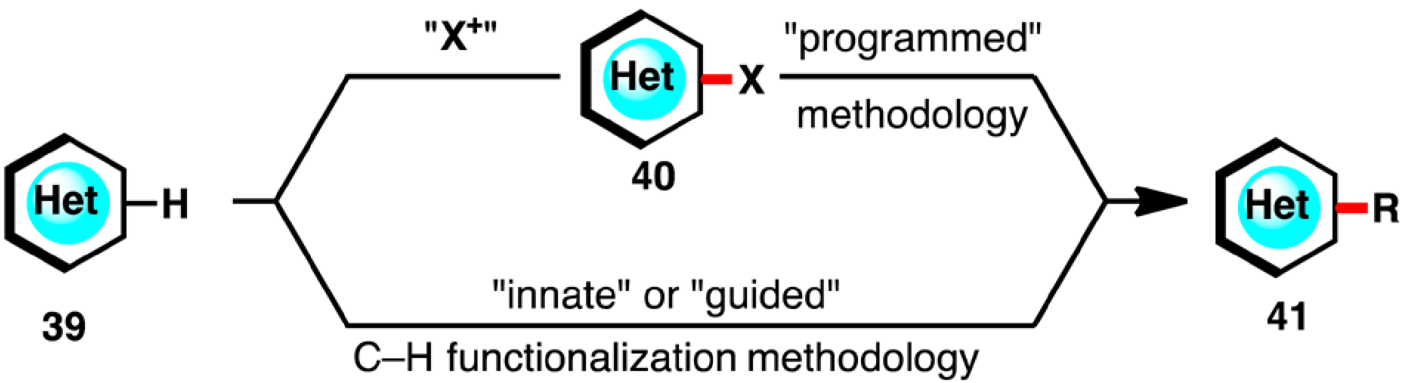




Cl
20
H
N
NH2
N3
N
H
N3
H
NH
HO
HN
NH2
36
Ag(II)
picolinate
HO
Cl
37
RHN
RHN
R=
Br
Br
N
H
O
axinellamine A & B; 38



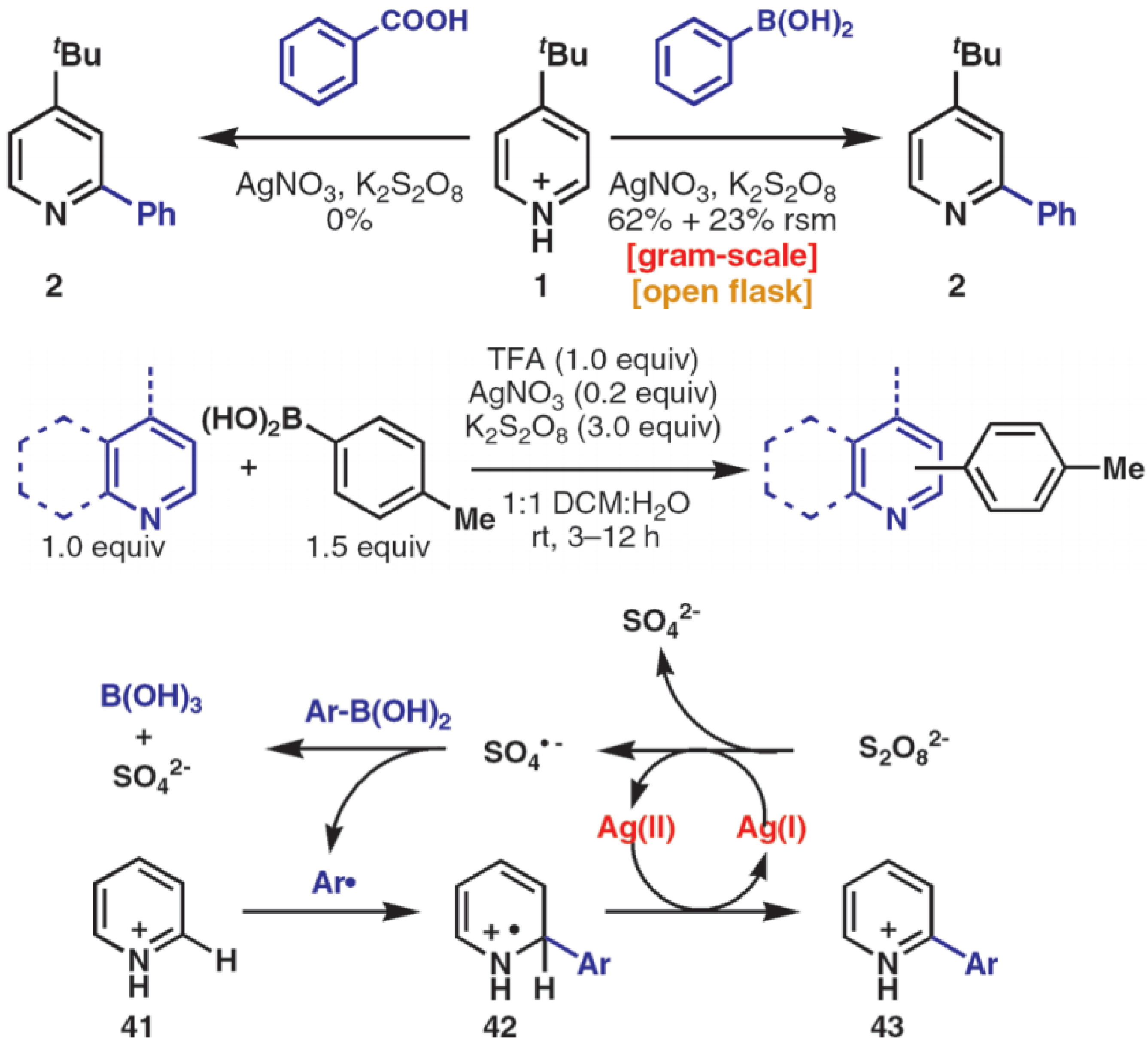
Tetrahedron **1971**, *27*, 3575



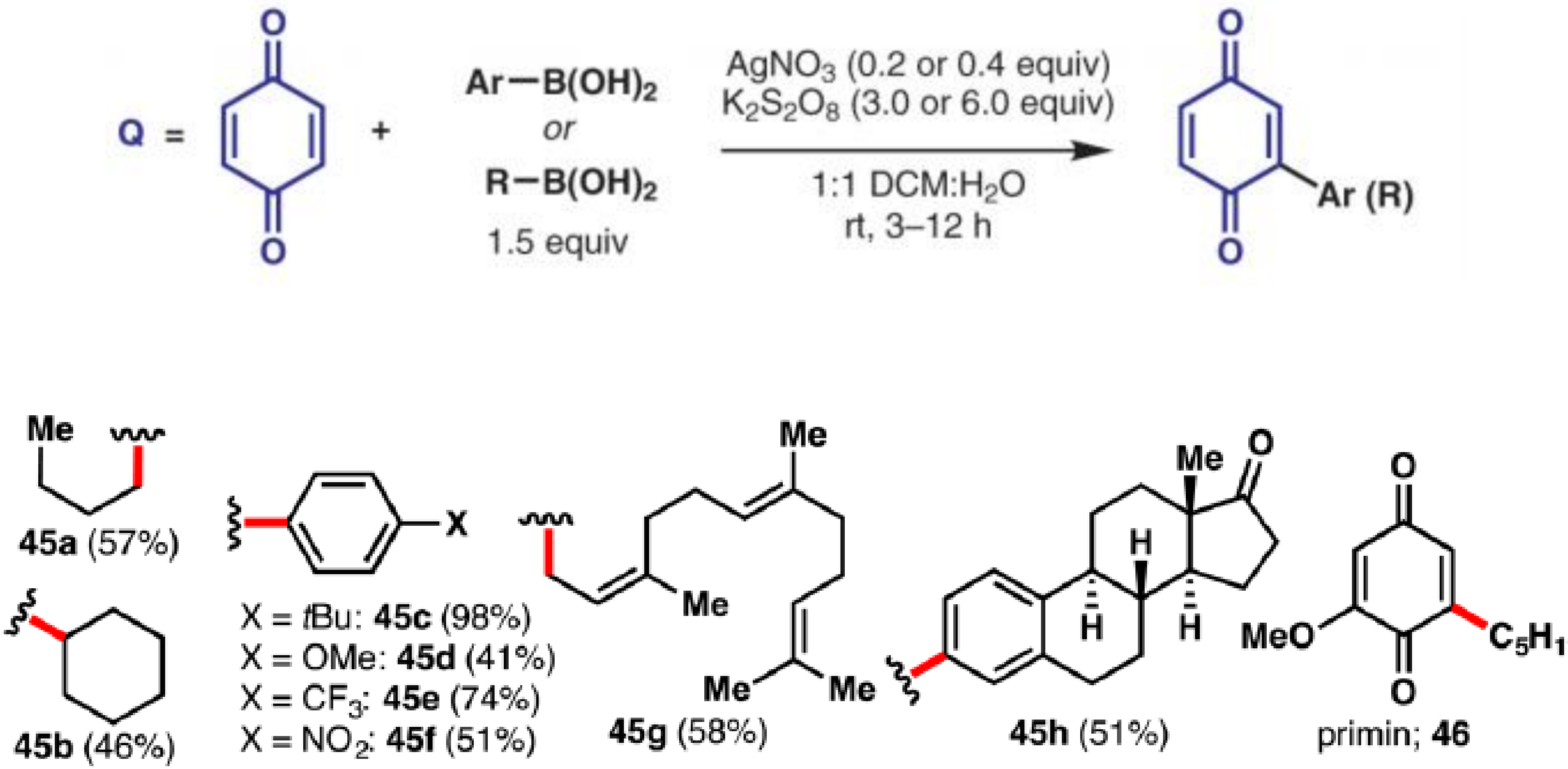
Programmed functionalization:
Halogen–metal (X–M) exchange
Nucleophilic aromatic substitution (S_NAr)
(Metal-catalyzed) cross-coupling

C–H functionalization:
Hydrogen–metal (H–M) exchange
Electrophilic aromatic substitution (S_EAr)
(Metal-catalyzed) C–H activation
Radical C–H functionalization

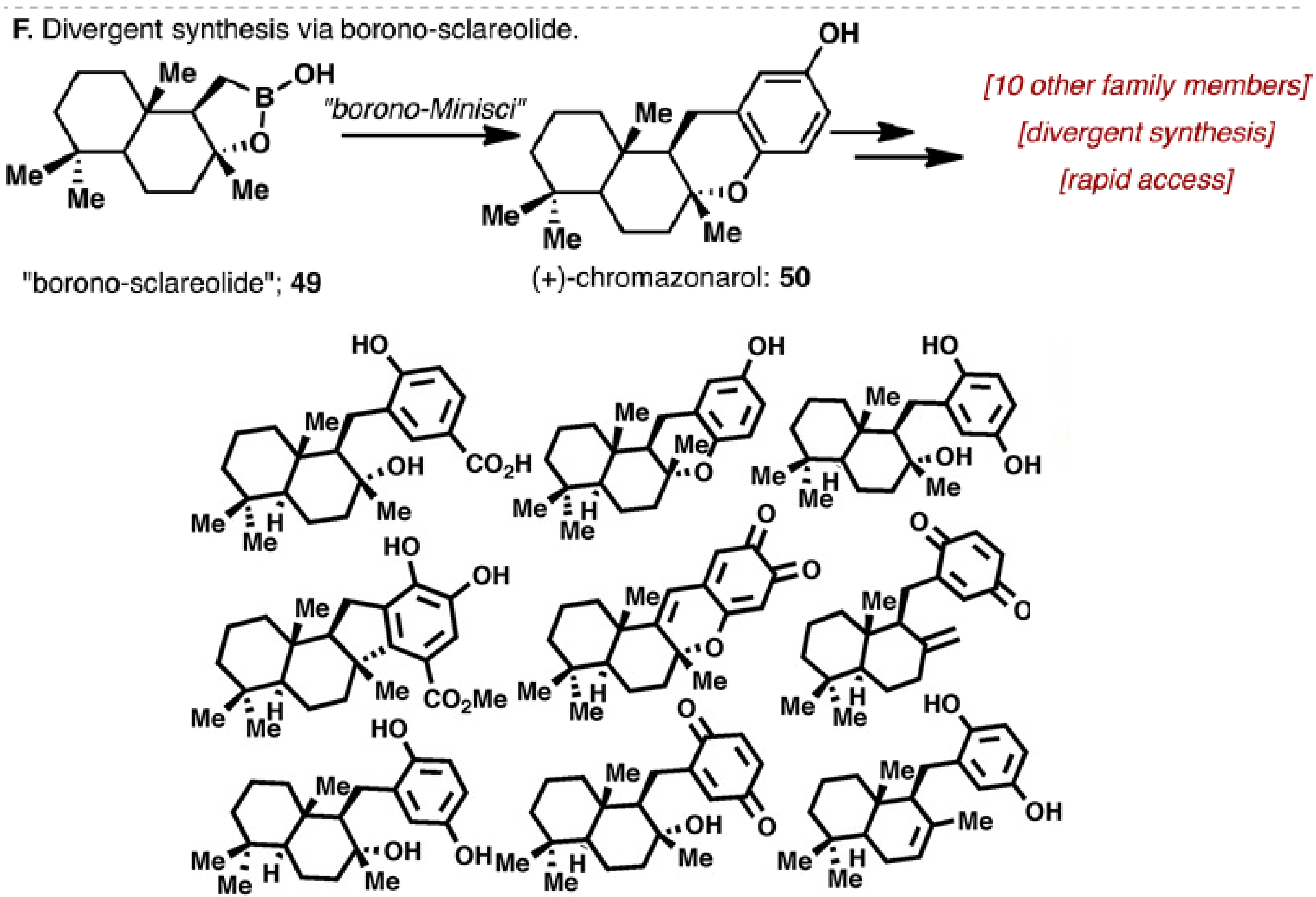
Boronic acid as radical precursors:



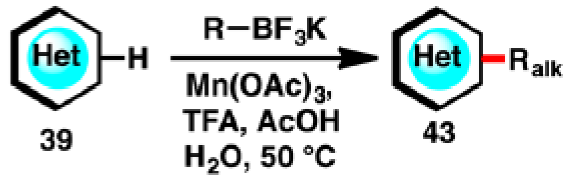
J. Am. Chem. Soc., **2010**, *132*,13194–13196



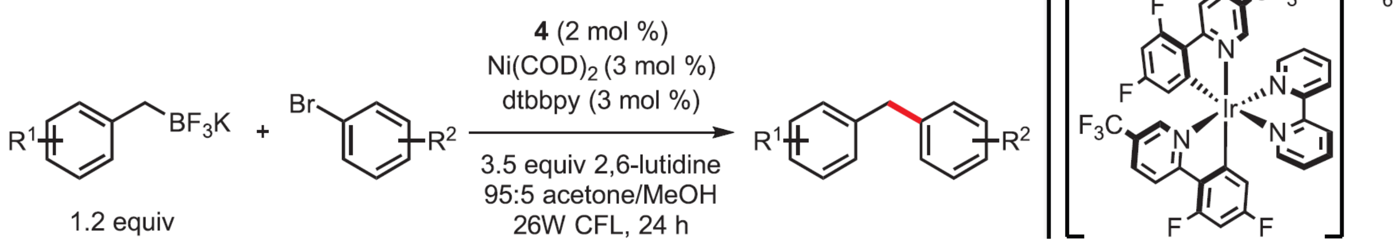
J. Am. Chem. Soc., **2011**, *133*, 3292–3295



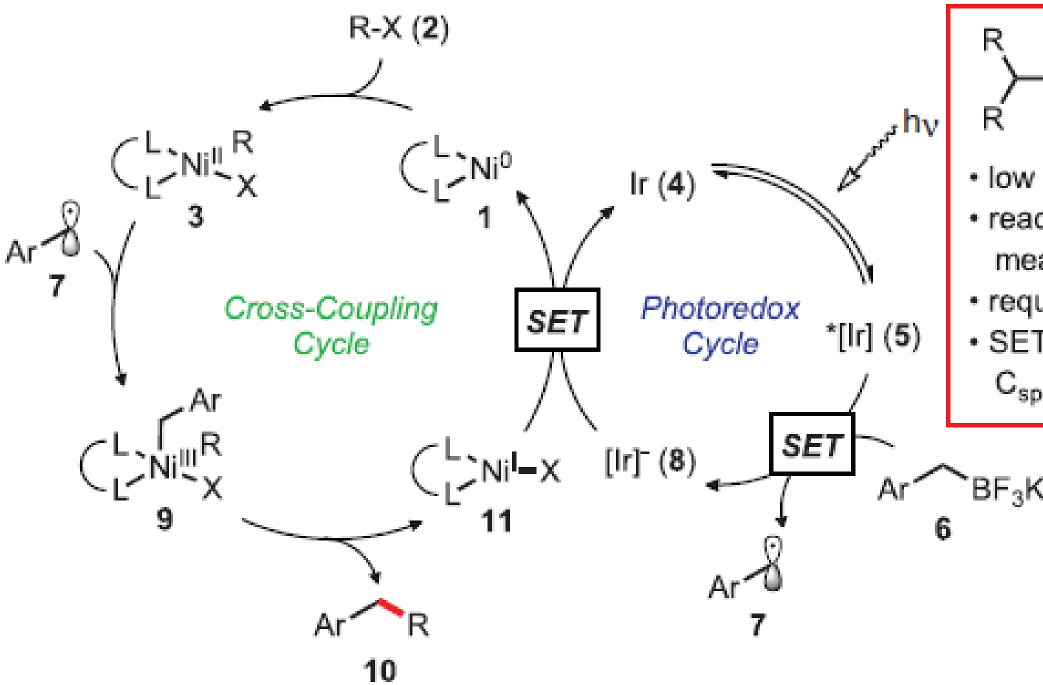
J. Am. Chem. Soc. **2012**, *134*, 8432–8435



Org. Lett. **2011**, *13*, 1852–1855



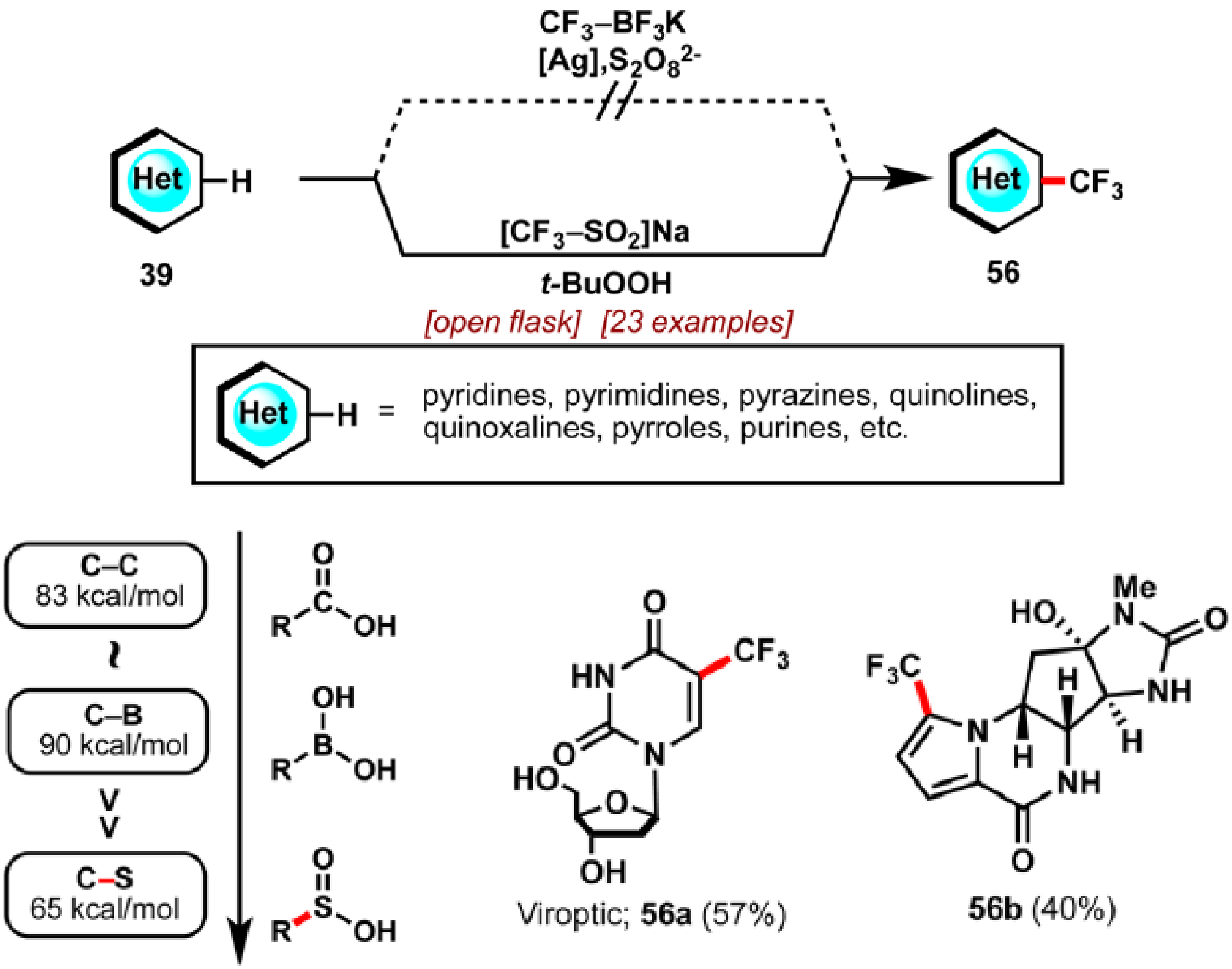
Photoredox Cross-Coupling: Single-Electron Transmetalation



- low activation energy
- reactivity dictated by measurable redox potentials
- requires no base or heat
- SET rate: $C_{sp3} > C_{sp2} > C_{sp}$

Science **2014**, *345*, 433

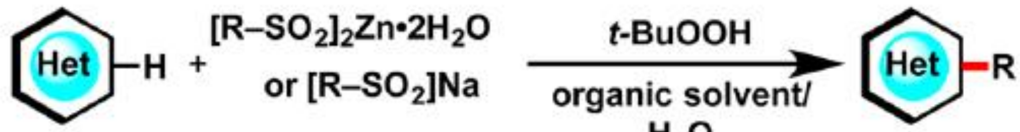
Sulfinates as radical precursors:



PNAS **2011**, *108*, 14411-14415

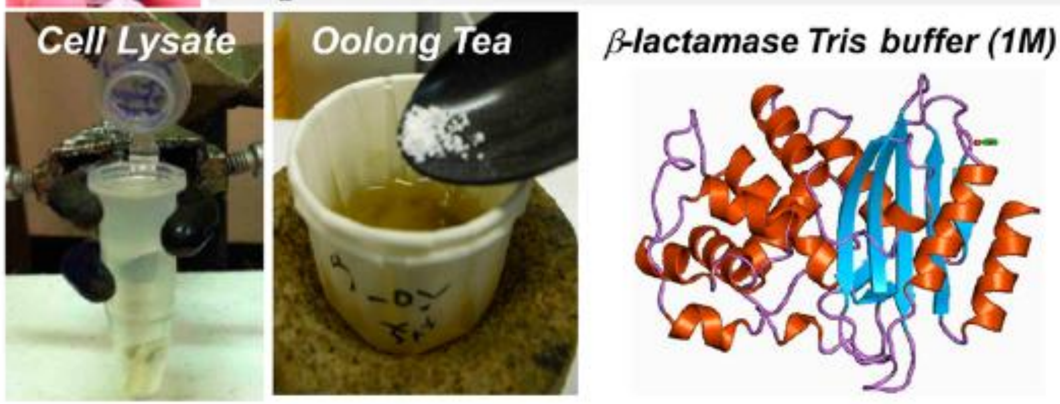
Nature **2012**, *492*, 95–99

B. Development of zinc sulfinate toolbox for drug discovery.



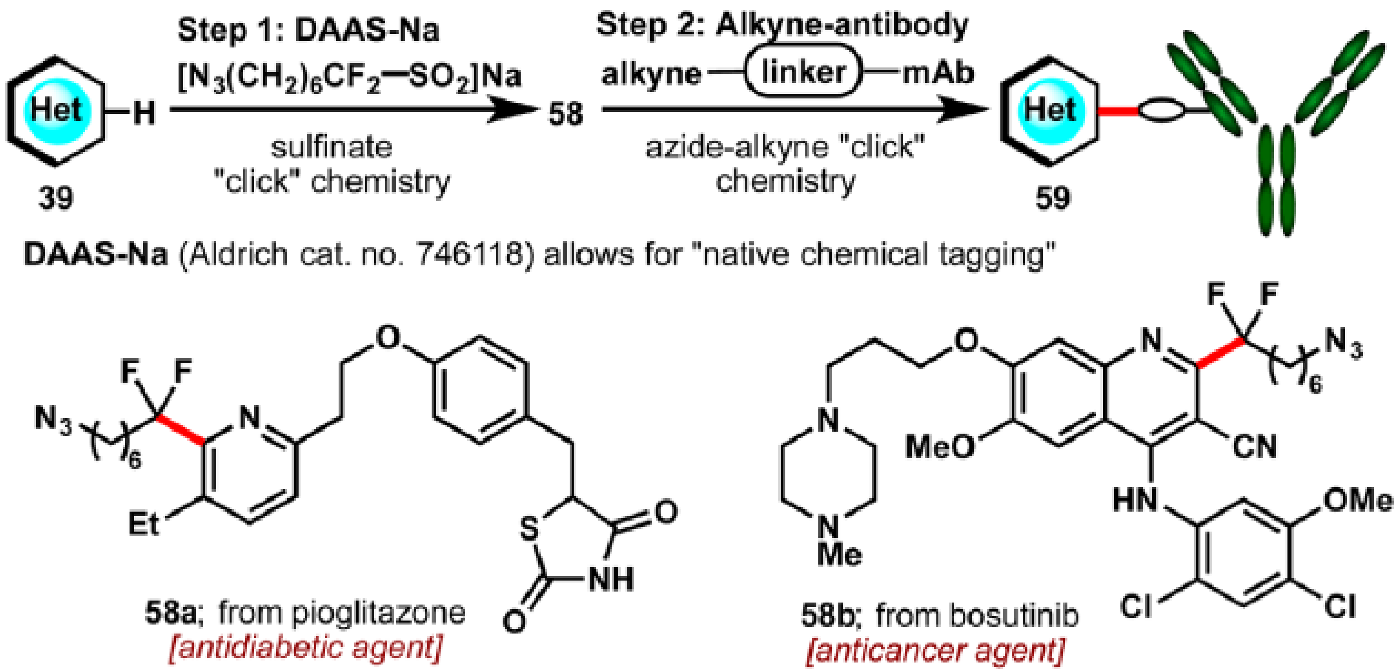
39 57

R group	Acronym of zinc sulfinate reagent	Sigma–Aldrich catalog number
CF_3	TFMS	771406
CF_2H	DFMS	767840
CH_2Cl	MCMS	791105
CH_2SO_2Ph	PSMS	792187
CF_2CH_3 (Na salt)	DFES-Na	745405
CH_2CF_3	TFES	745499
CH_2CH_2Cl	MCES	790788
$CH_2CH_2CH_3$	NPS	791040
$CH(CH_3)_2$	IPS	745480
CH_2Ph	BNS	790796



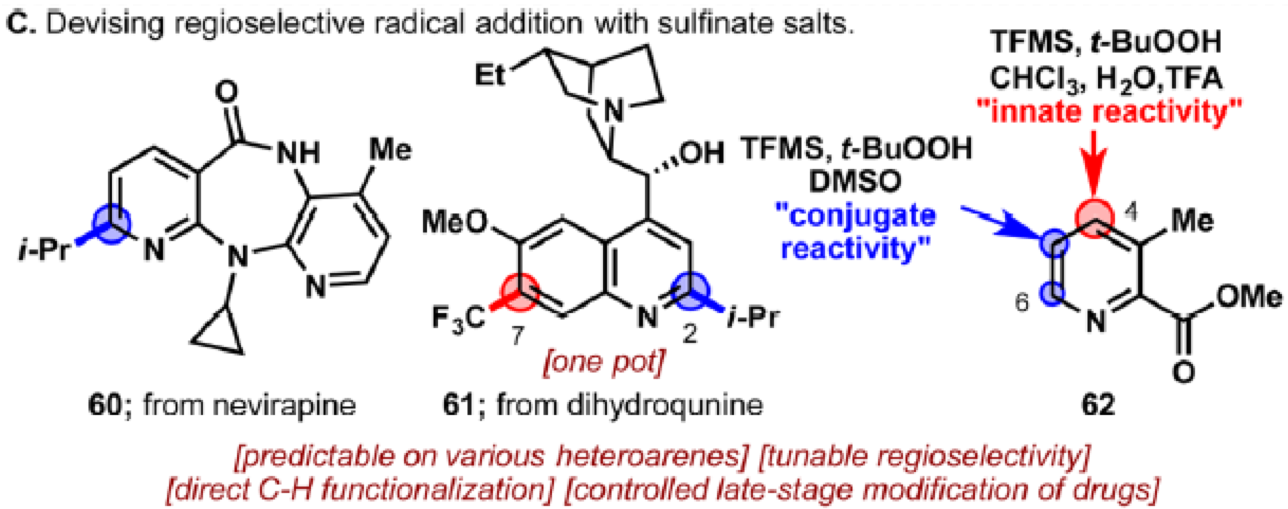
Nature **2012**, *492*, 95–99 *J. Am. Chem. Soc.*, **2012**, *134*, 1494–1497

Angew. Chem. Int. Ed. **2013**, *52*, 3949 –3952

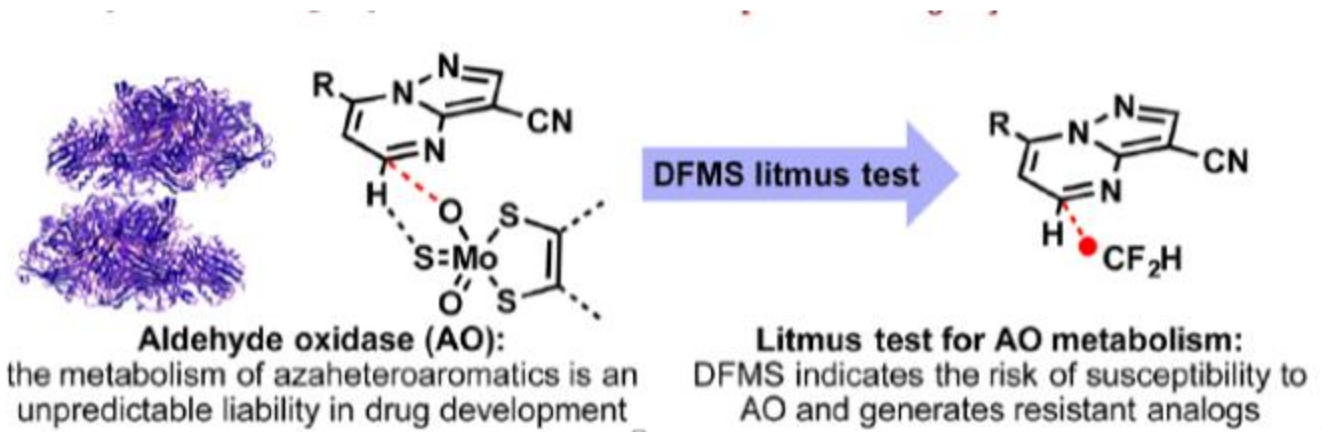


Angew. Chem. Int. Ed. **2013**, *52*, 3949 –3952

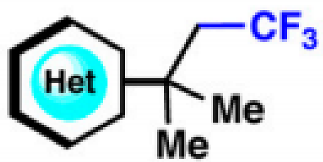
J. Am. Chem. Soc., **2013**, *135*, 12994–12997



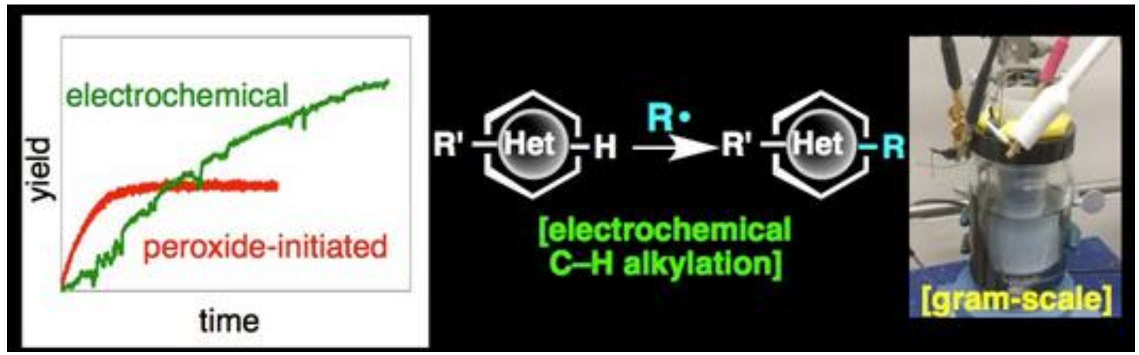
J. Am. Chem. Soc. **2013**, *135*, 12122–12134



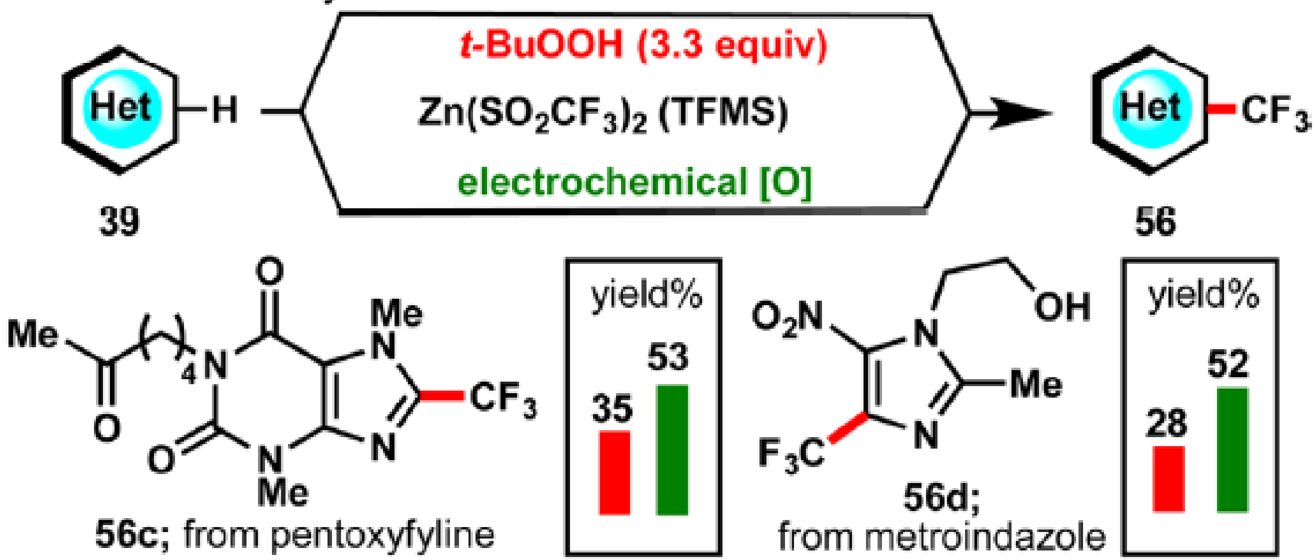
J. Med. Chem. **2014**, *57*, 1616–1620



byproduct "A"

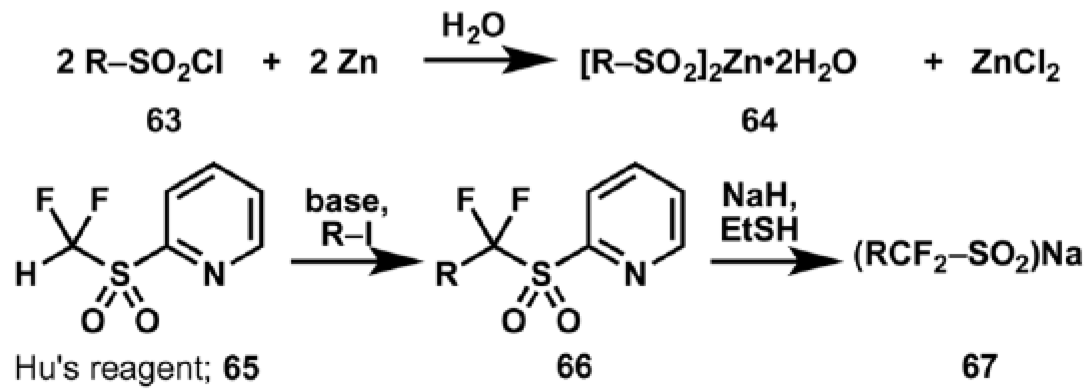


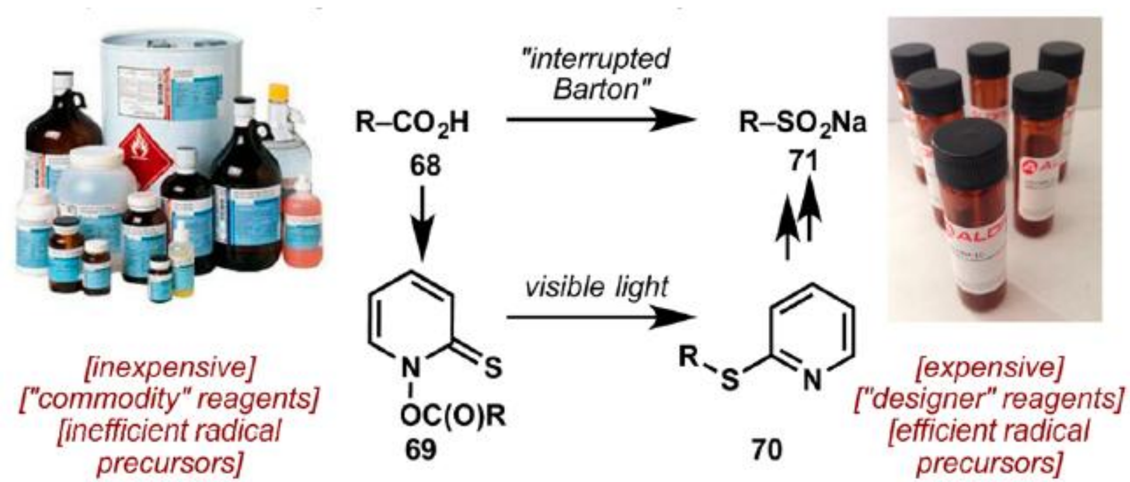
D. "Process-friendly" electrochemical initiation.



Angew. Chem. Int. Ed. **2014**, *53*, 11868 –11871

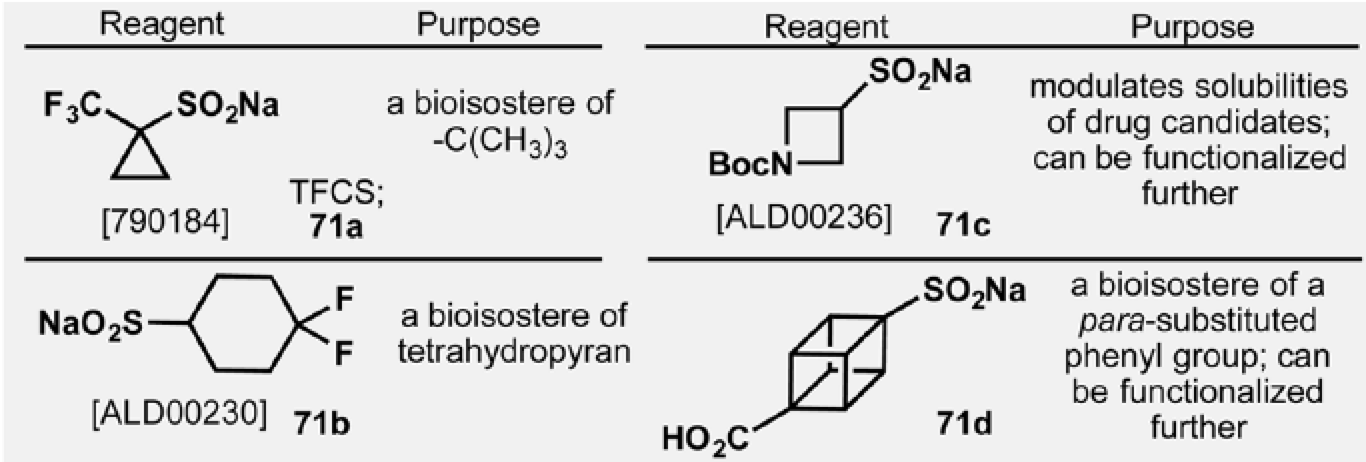
E. Syntheses of sulfinate reagents.

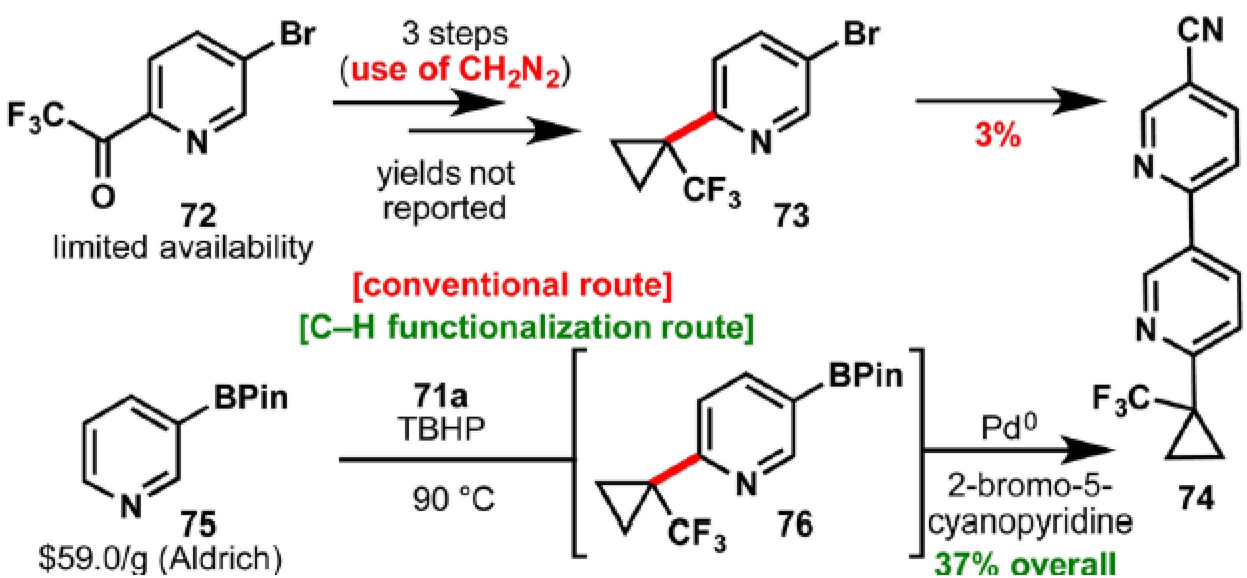




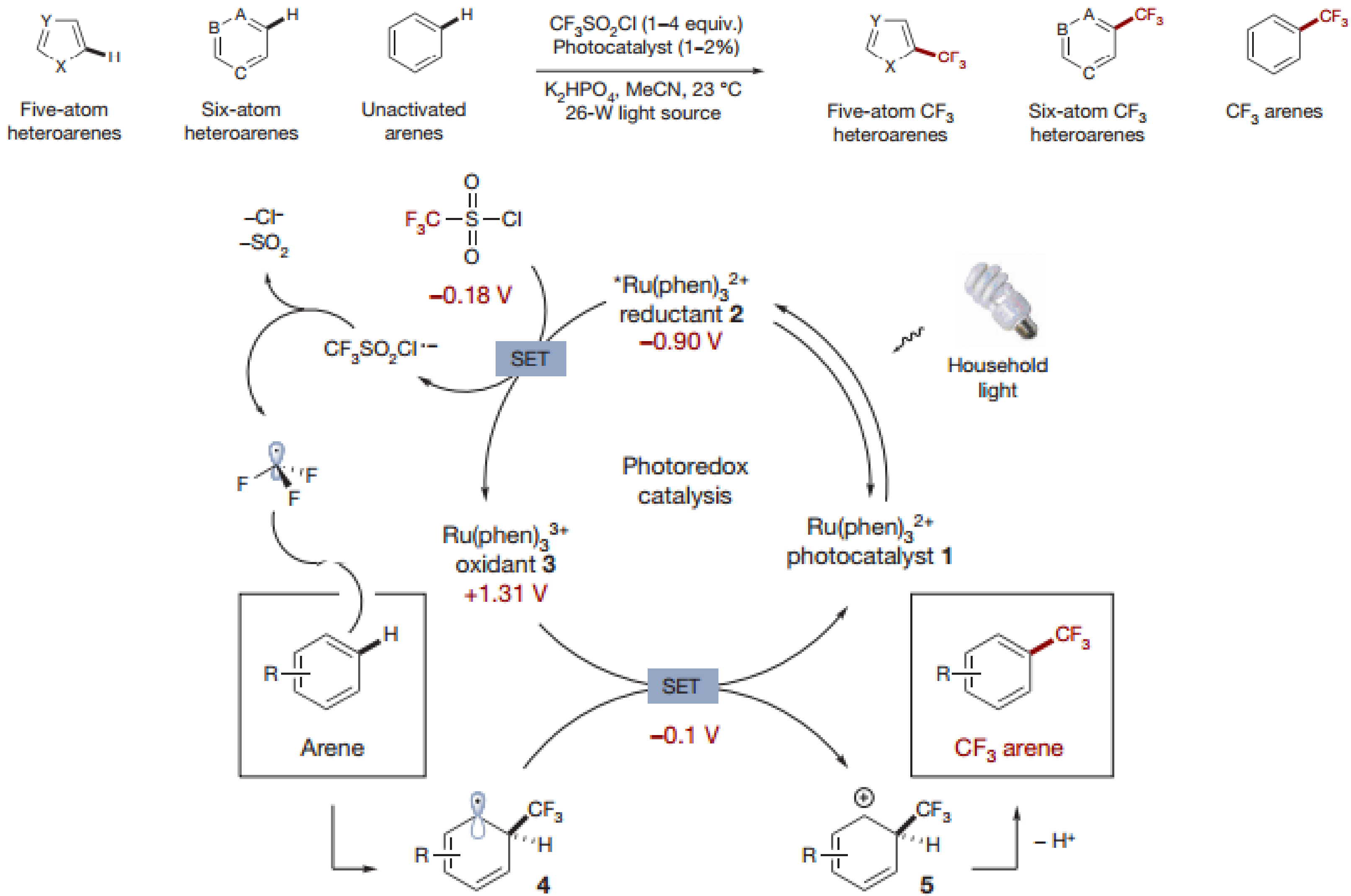
Nature Protocols **2013**, *8*, 1042–1047

Angew. Chem. Int. Ed. **2014**, *53*, 9851 –9855



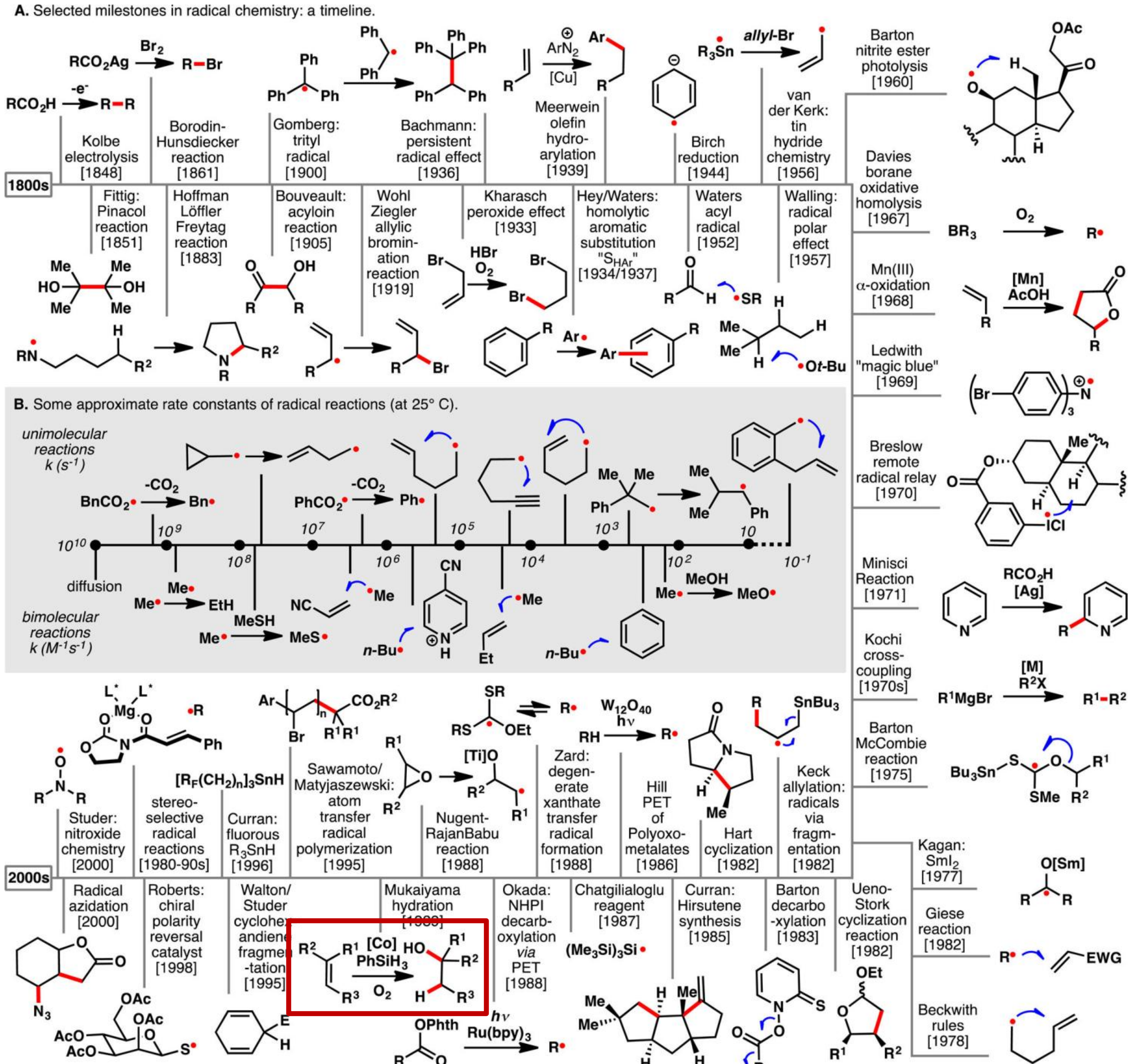


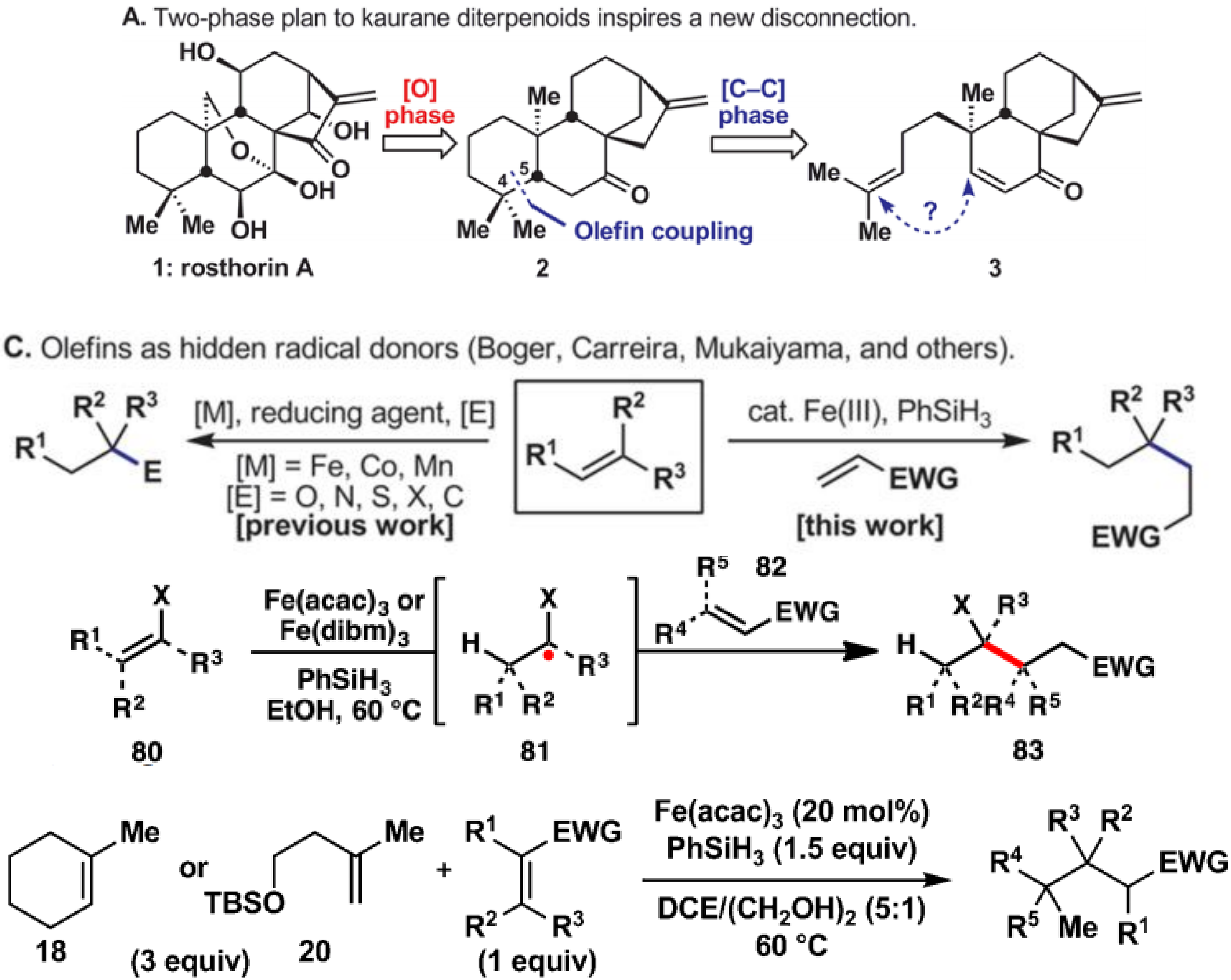
Angew. Chem. Int. Ed. **2014**, *53*, 9851 –9855



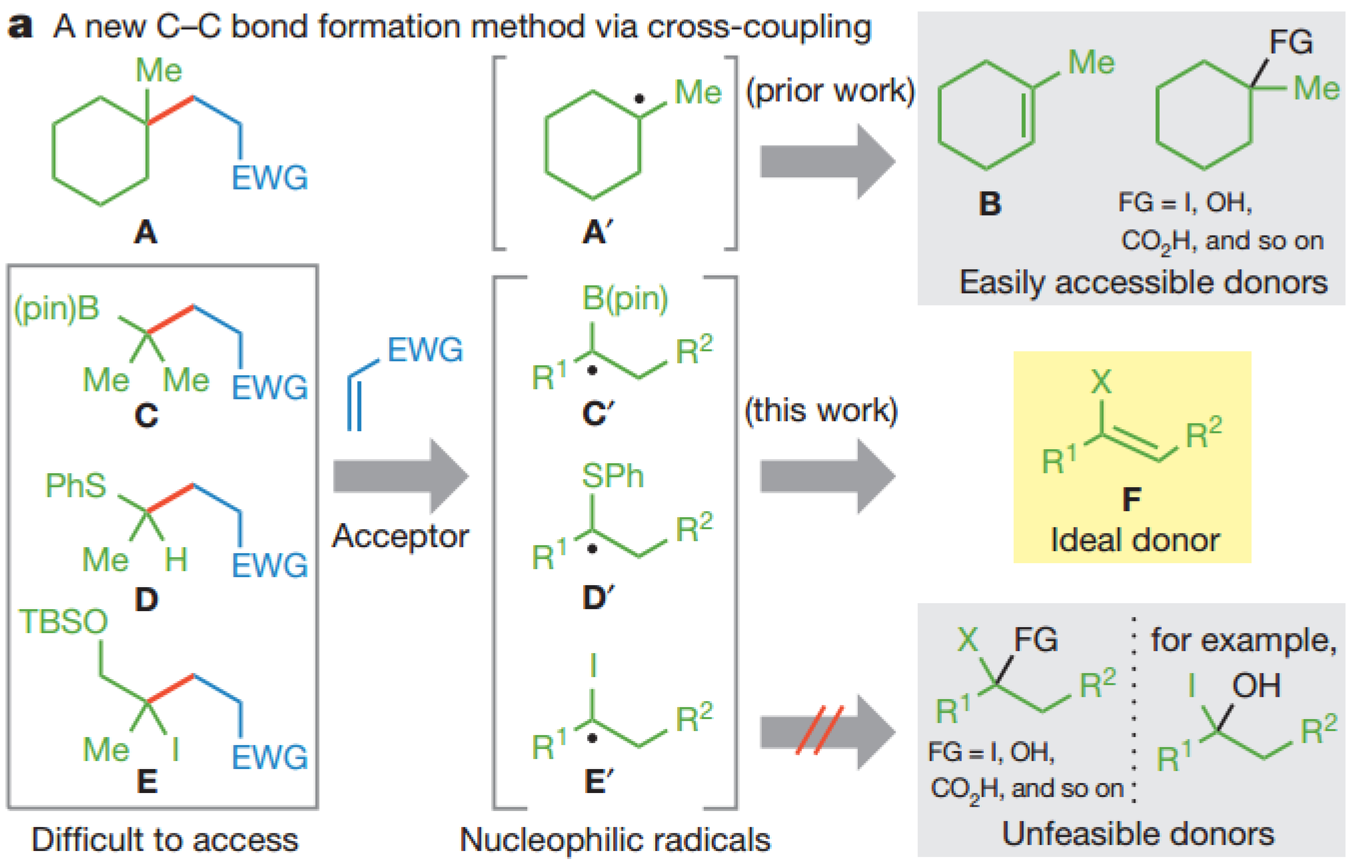
Nature **2011**, *480*, 224-228

1.4. Olefins As Radical Progenitors



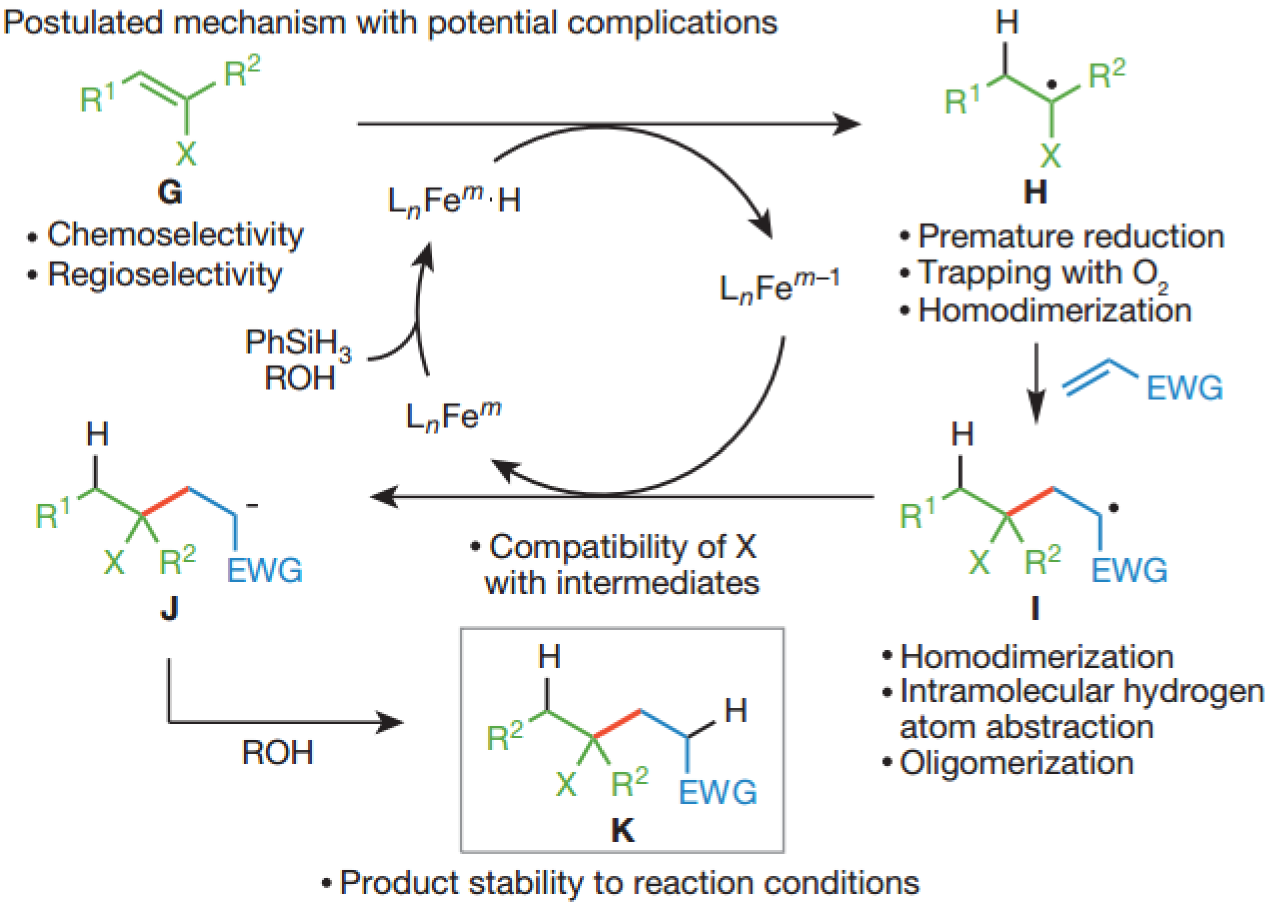


J. Am. Chem. Soc., **2014**, *136*, 1304–1307

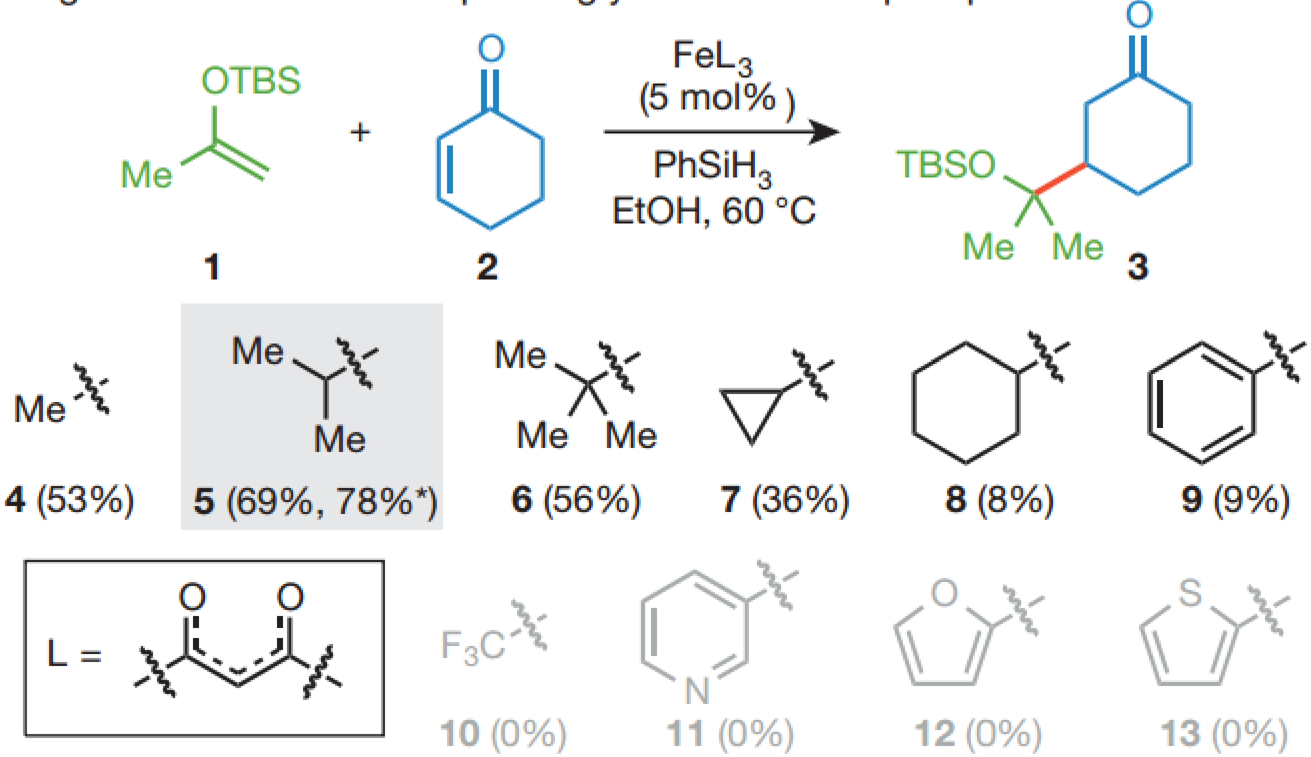


Nature **2014**, *516*, 343–348.

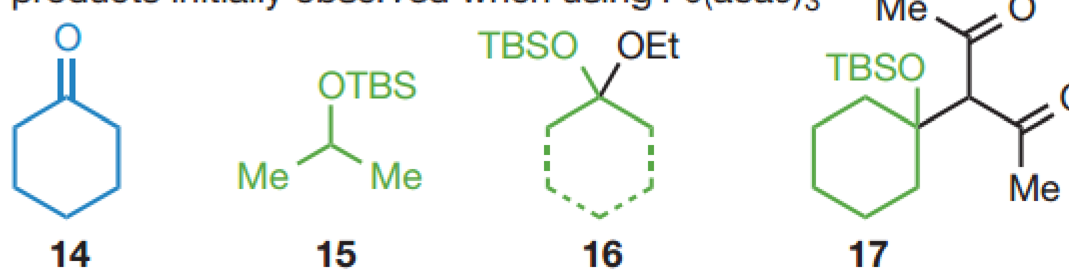
b Postulated mechanism with potential complications

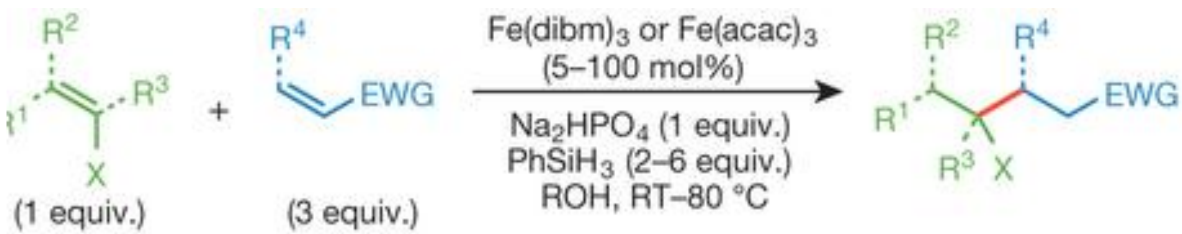


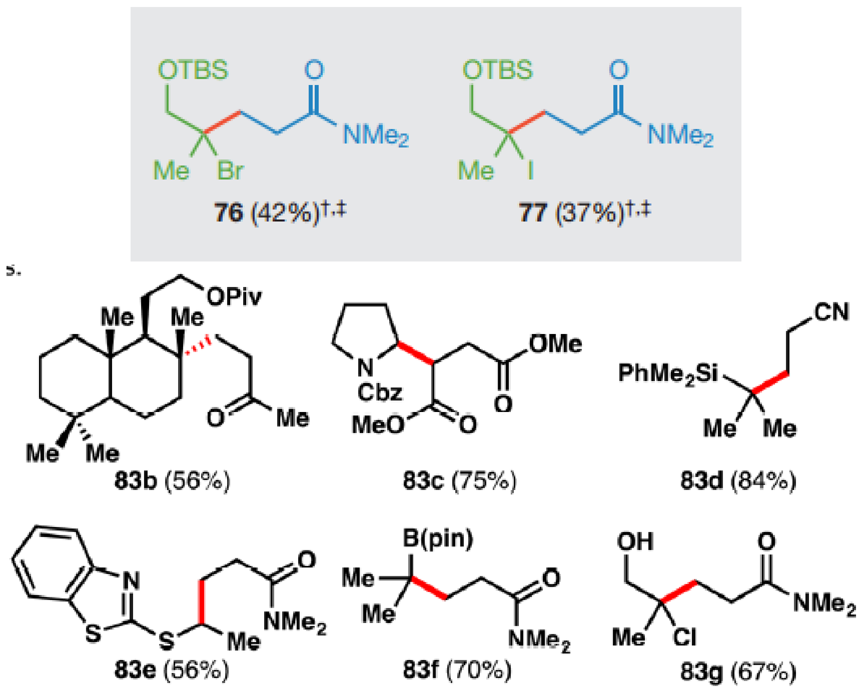
a Ligand screen with corresponding yields of the coupled product

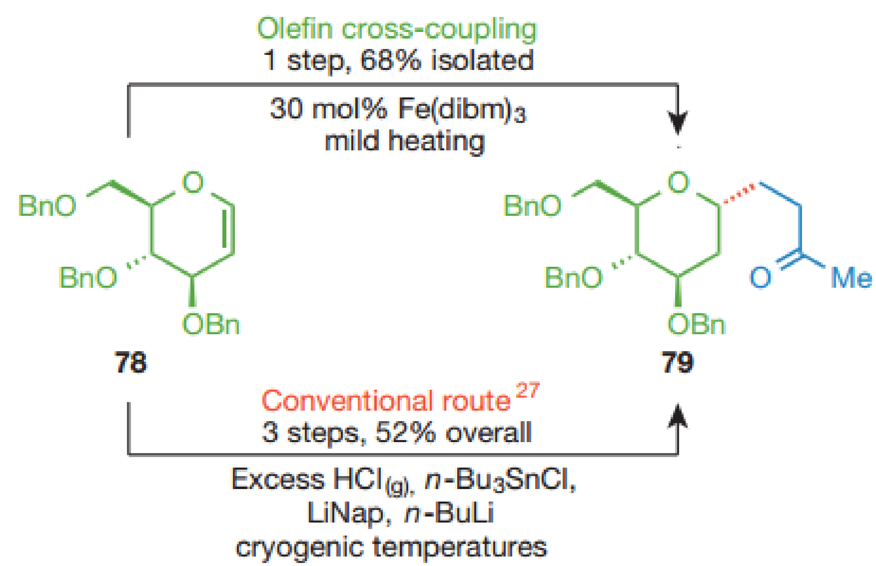


b Side products initially observed when using $Fe(acac)_3$

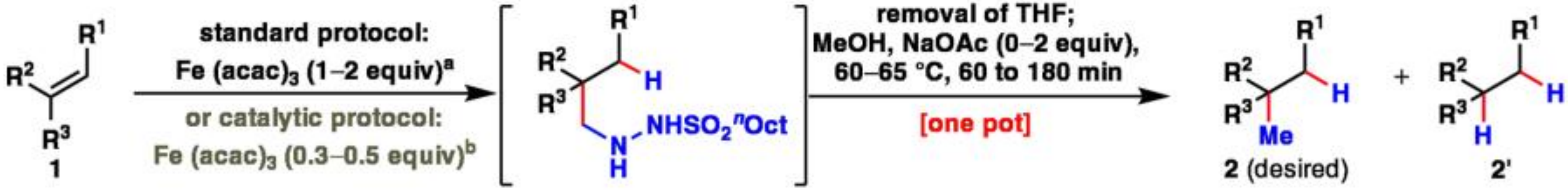




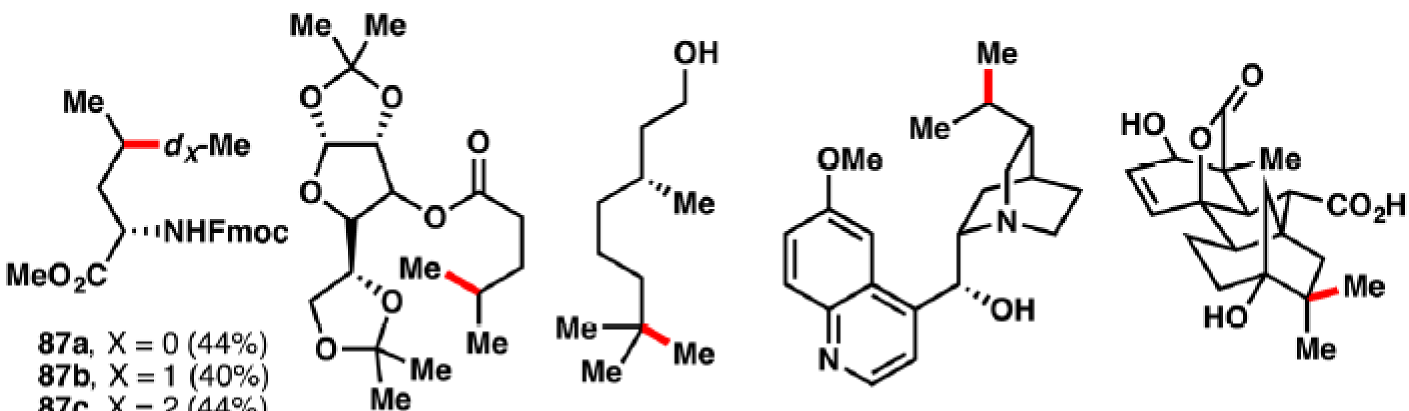




[>90 examples] [performed under air]
[C, O, N, S, Si, B, F, Cl, Br, and I substitutents tolerated on donor olefin]
[-C(O)R, -CO_2R, -CHO, -$CONR_2$, -SO_2R, -CO_2H tolerated on acceptor olefin]



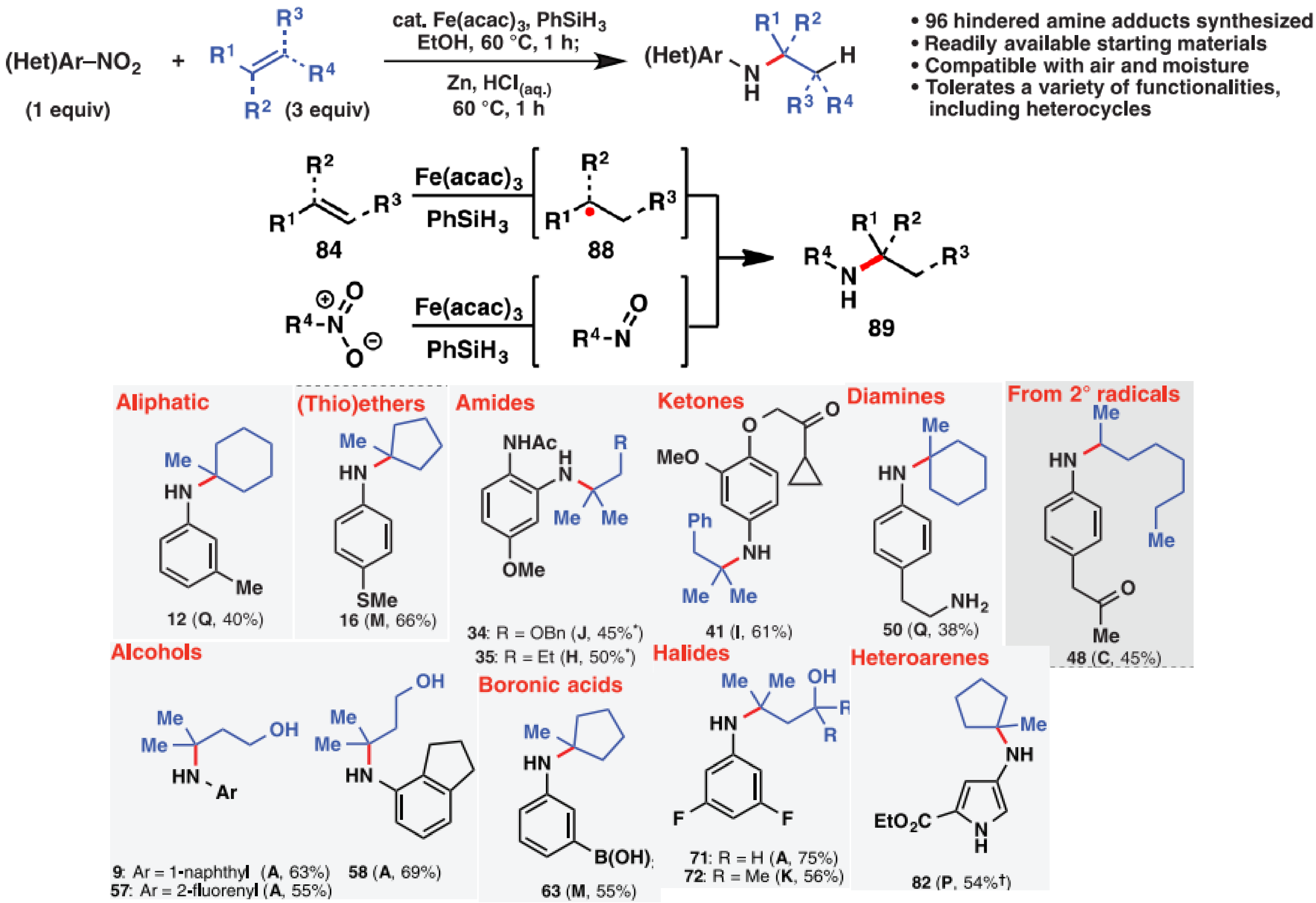
[one pot sequence] *[mono-, di-, and trisubstutitued olefins]*



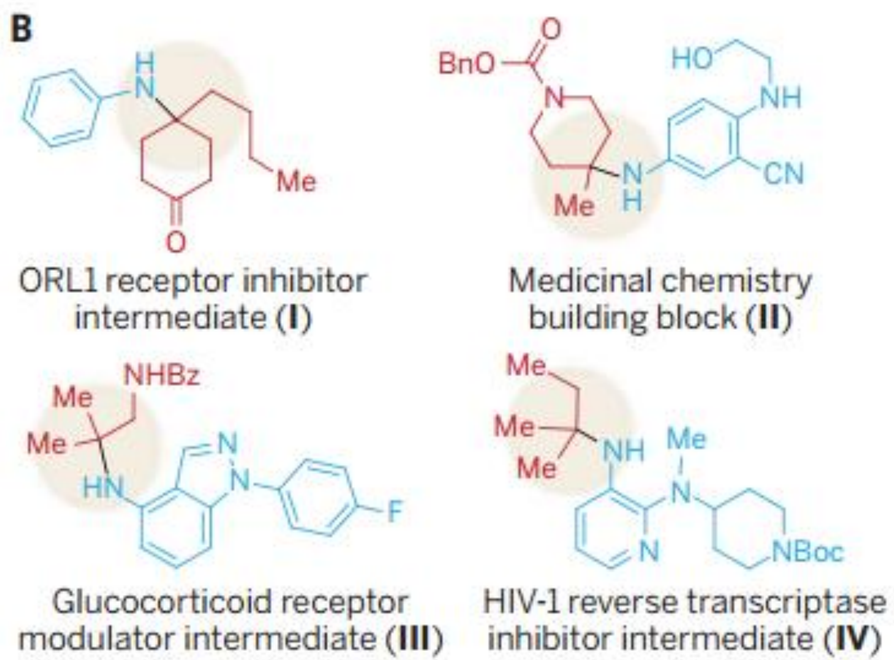
87a, X = 0 (44%)
87b, X = 1 (40%)
87c, X = 2 (44%)
87d, X = 3 (40%)

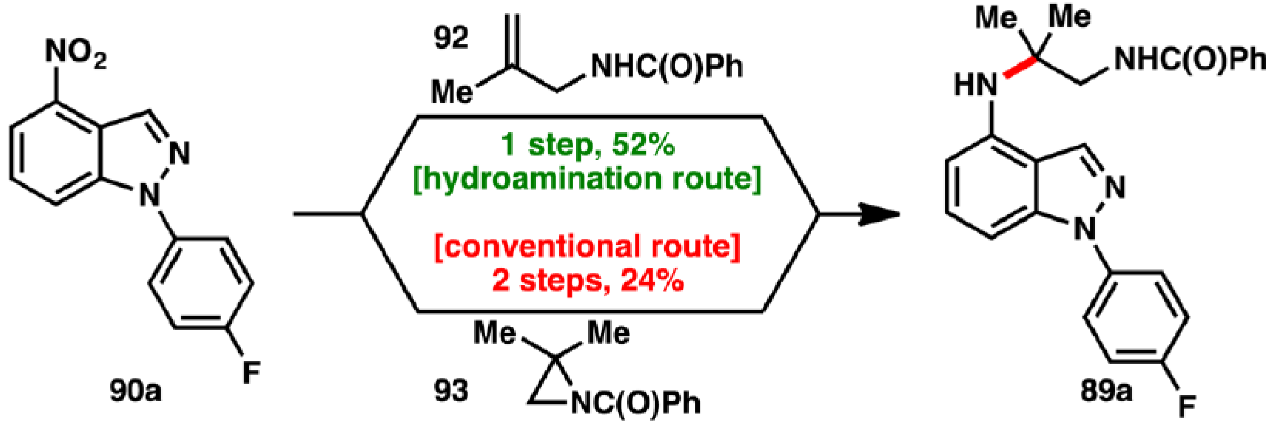
87e (68%) **87f** (68%) **87g** (32%) **87h** (13%)

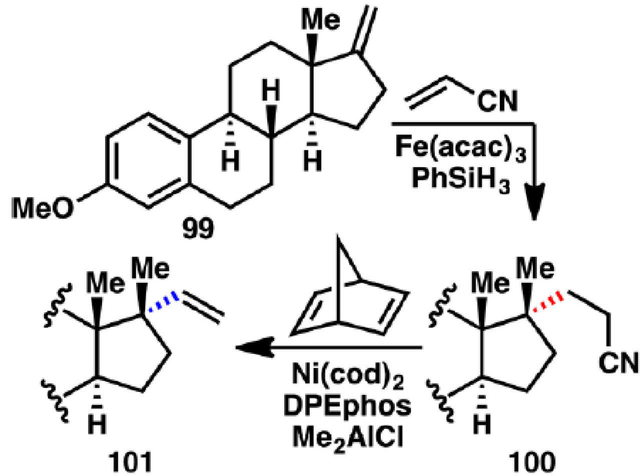
J. Am. Chem. Soc., **2015**, *137*, 8046–8049



Science **2015**, *348*, 886–891.

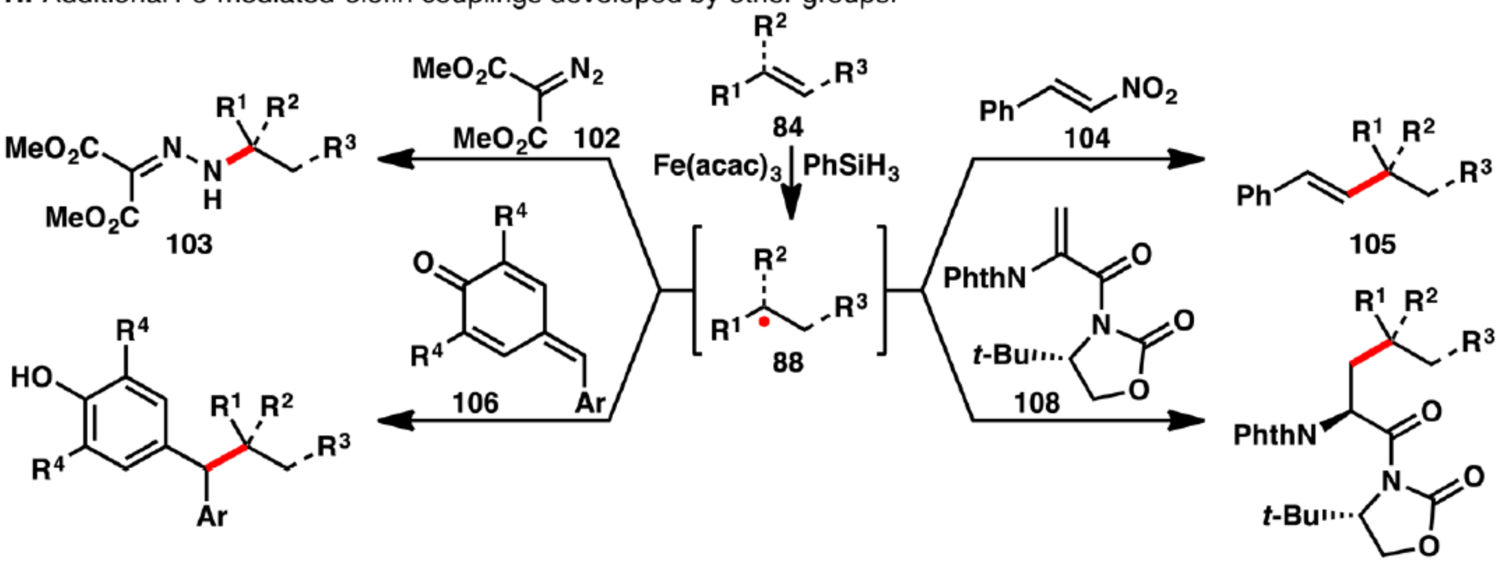

B
H
N
Me
O
ORL1 receptor inhibitor
intermediate (I)
BnO
O
N
HO
NH
N
H
Me
CN
Medicinal chemistry
building block (II)
NHBz
Me
Me
HN
N
N
F
Glucocorticoid receptor
modulator intermediate (III)
Me
Me
Me
NH
Me
N
N
NBoc
HIV-1 reverse transcriptase
inhibitor intermediate (IV)


NO2
N
N
F
90a
92
Me
NHC(O)Ph
1 step, 52%
[hydroamination route]
[conventional route]
2 steps, 24%
Me
Me
93
NC(O)Ph
Me
Me
HN
NHC(O)Ph
N
N
89a
F

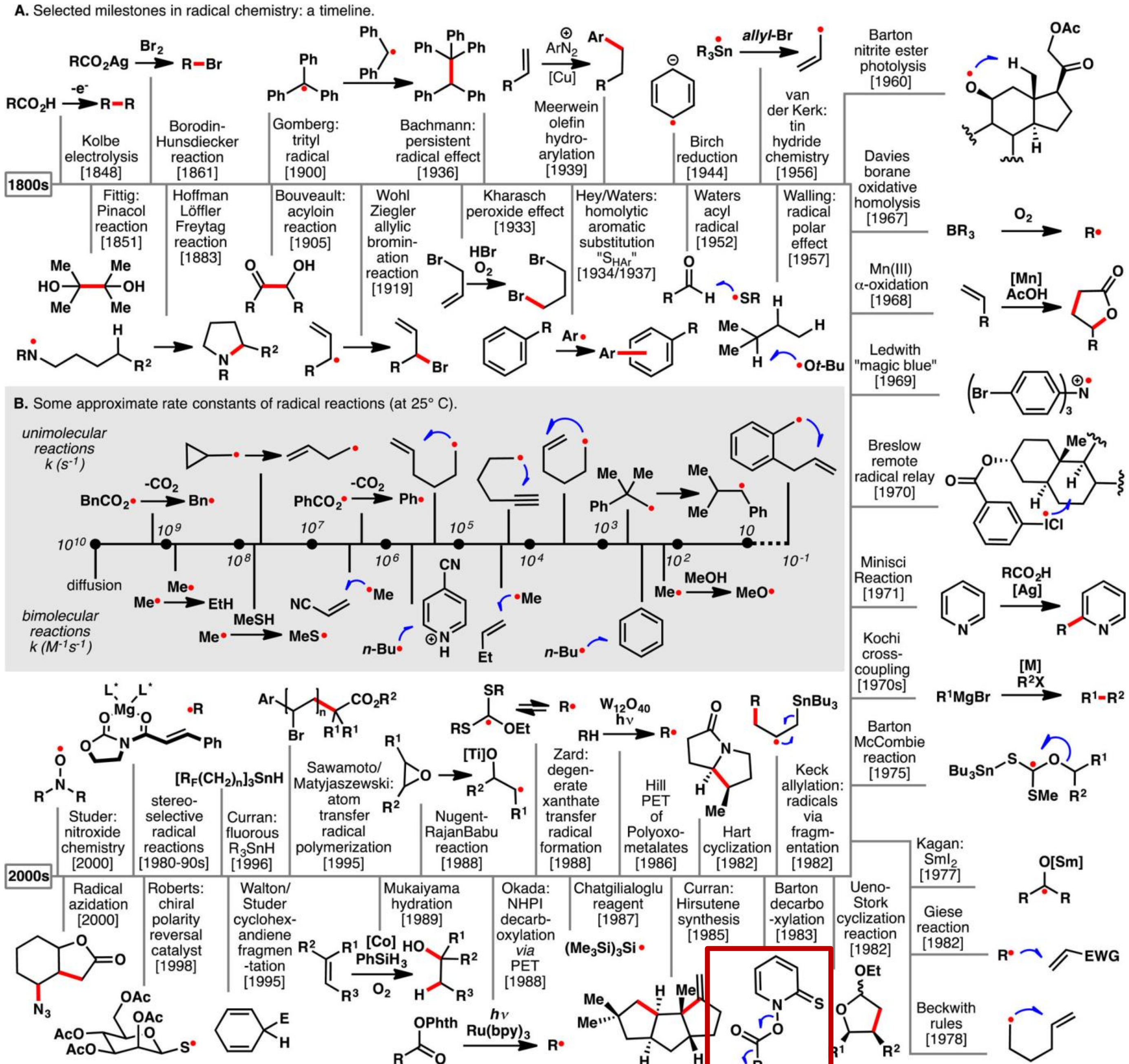


Science **2016**, *351*, 832

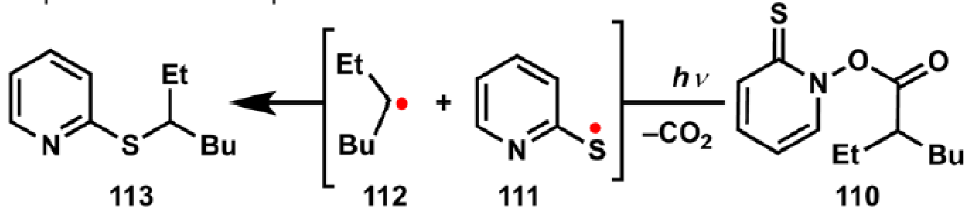
H. Additional Fe-mediated olefin couplings developed by other groups.

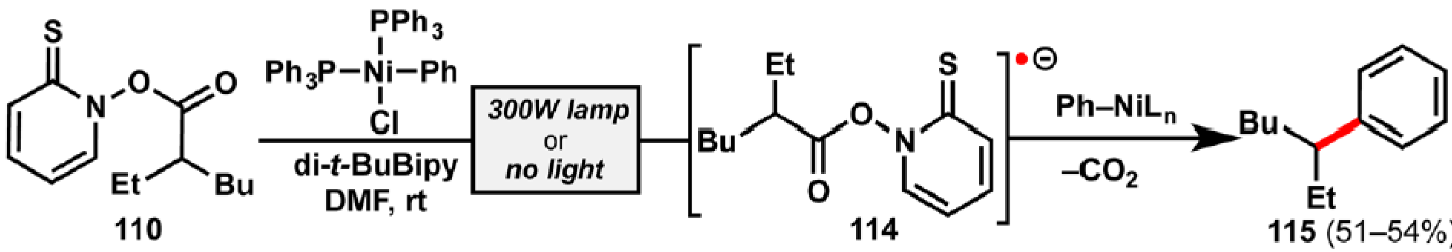


5. Redox-Active Esters As Electrophiles for Cross-Coupling:

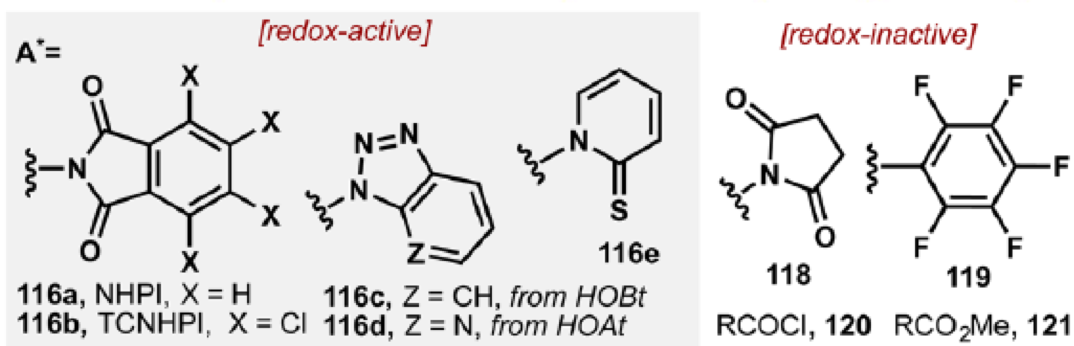


Inspiration based on prior work with Barton esters.

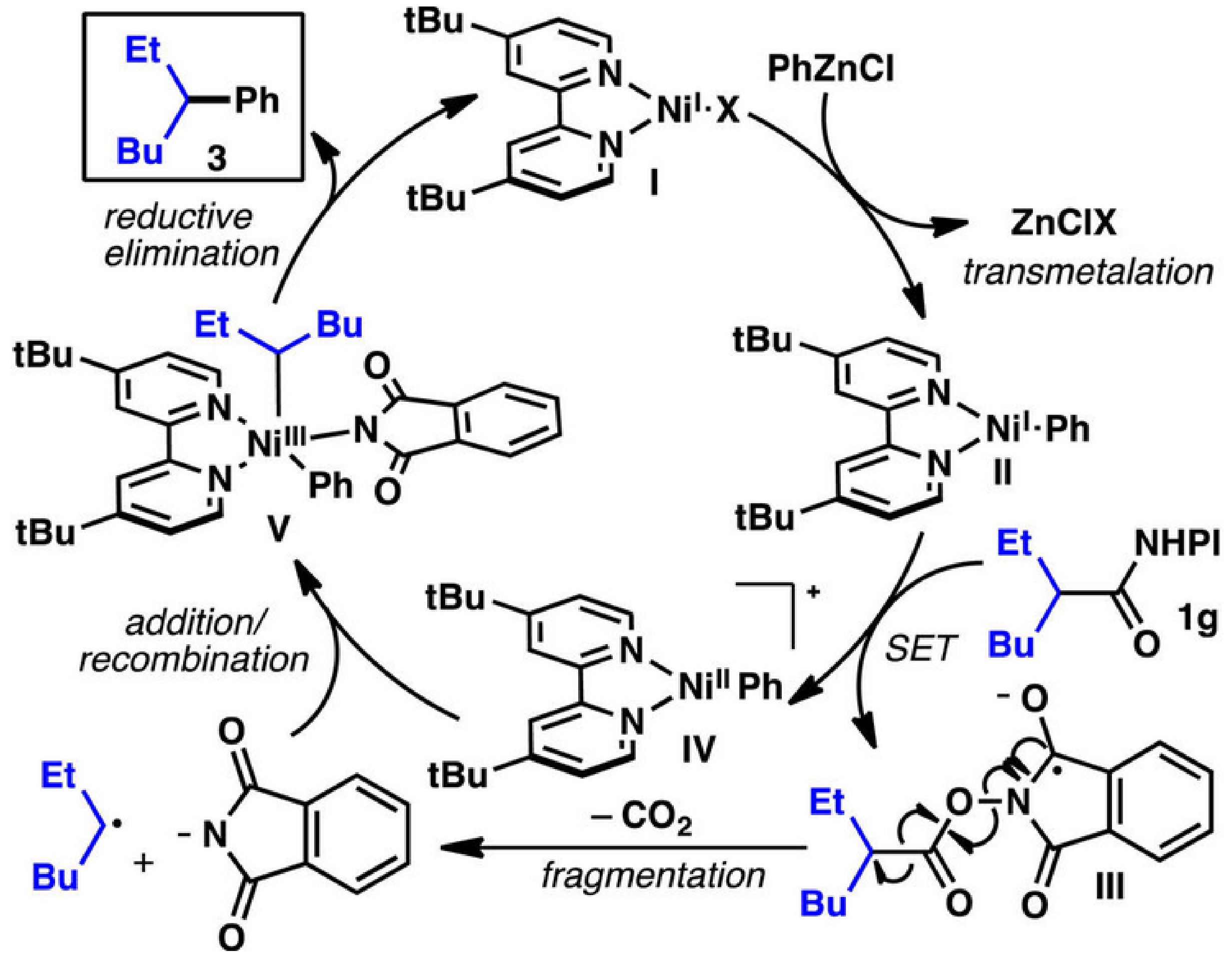




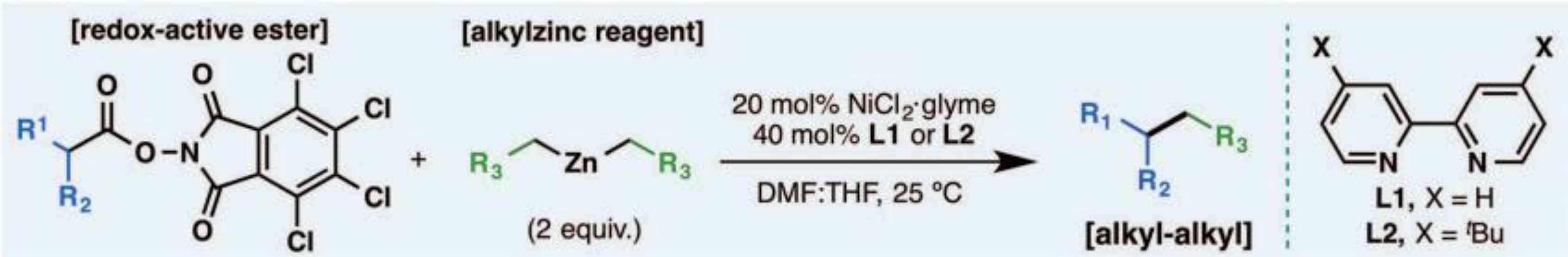
- 28 examples
- cyclic and acyclic substrates
- Lewis-basic heteroatoms
- unactivated (non-heteroatom stabilized) acids
- simple setup, room temp

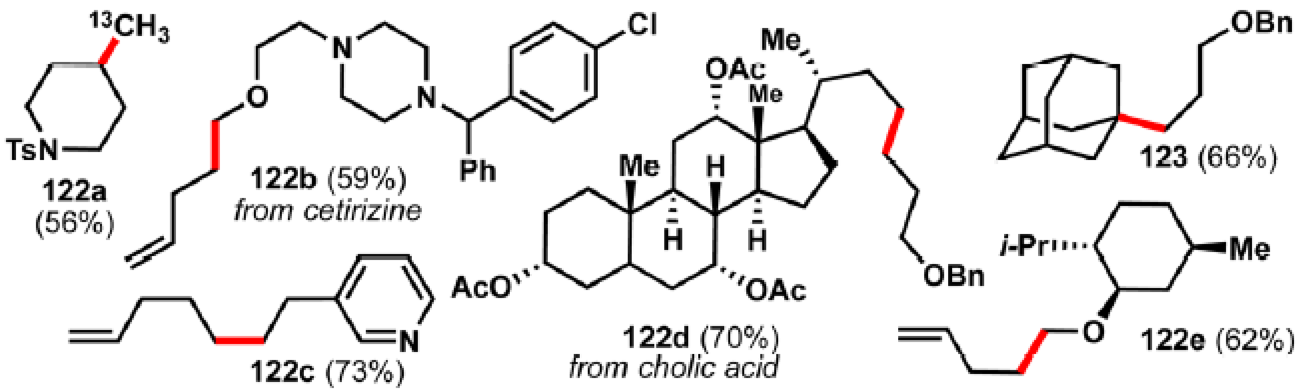


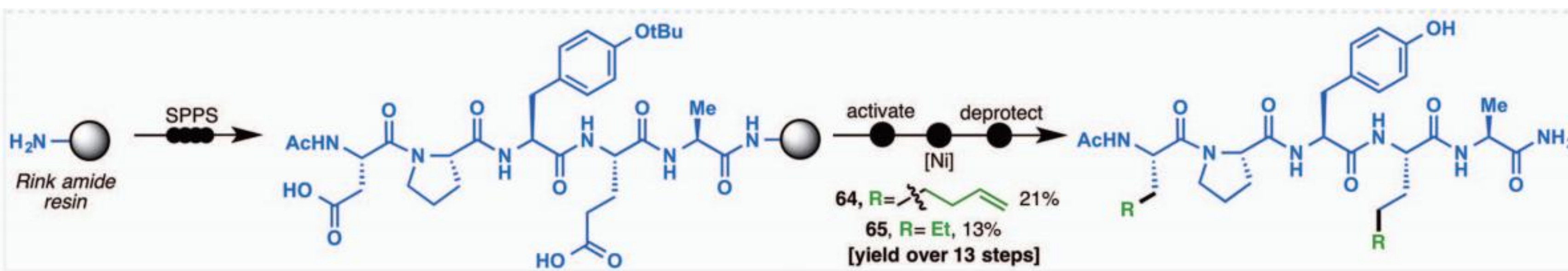
J. Am. Chem. Soc., **2016**, *138*, 2174–2177



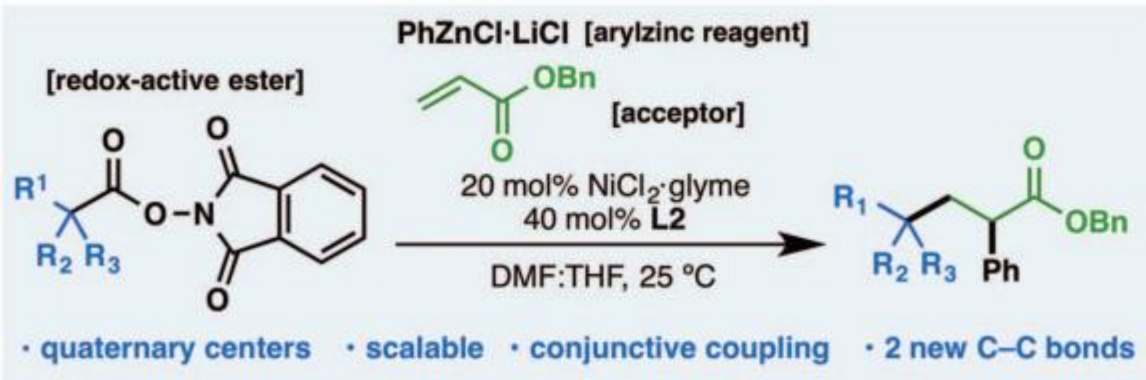
Et
Ph
Bu
3
reductive elimination
tBu
N
Ni^{I}·X
N
tBu
I
PhZnCl
ZnClX
transmetalation
tBu
N
Ni^{I}·Ph
N
II
tBu
Et
NHPI
Bu
O
1g
SET
Et
Bu
O
N
Ni^{III}
N
Ph
O
tBu
tBu
V
addition/ recombination
tBu
N
Ni^{II} Ph
N
IV
tBu
+
- O
Et
O
N
Bu
O
O
III
– CO_2
fragmentation
Et
Bu
+
- N
O
O

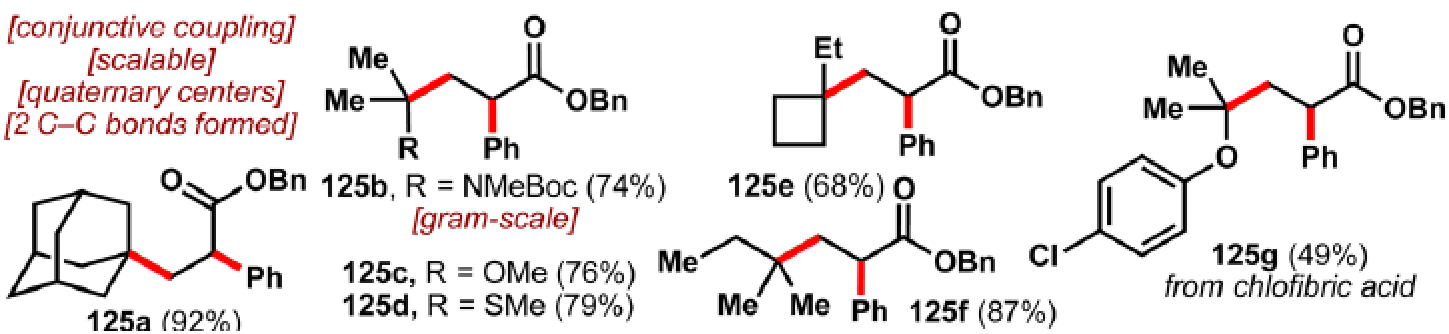


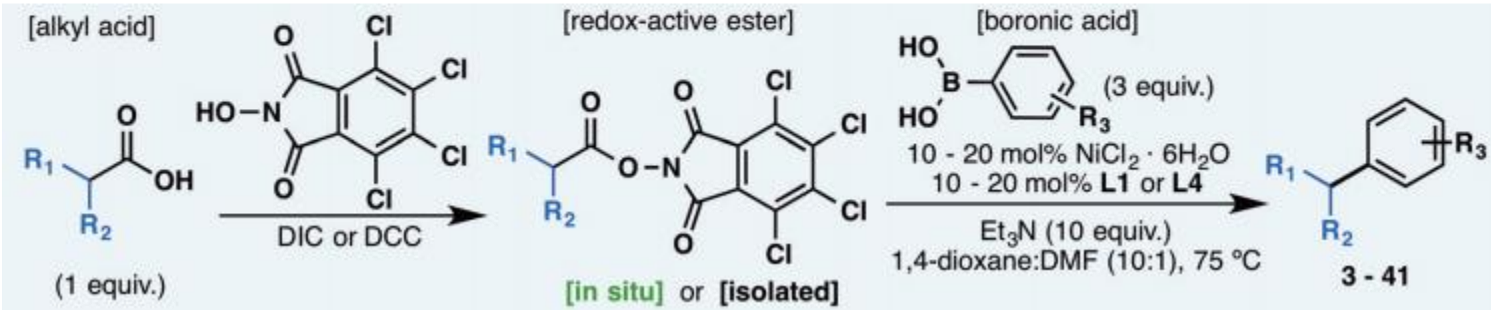




Science **2016**, *352*, 801-805.


PhZnCl·LiCl [arylzinc reagent]
[redox-active ester]
OBn
[acceptor]
20 mol% NiCl2·glyme
40 mol% L2
DMF:THF, 25 °C
R1
R2 R3
OBn
Ph
· quaternary centers · scalable · conjunctive coupling · 2 new C–C bonds

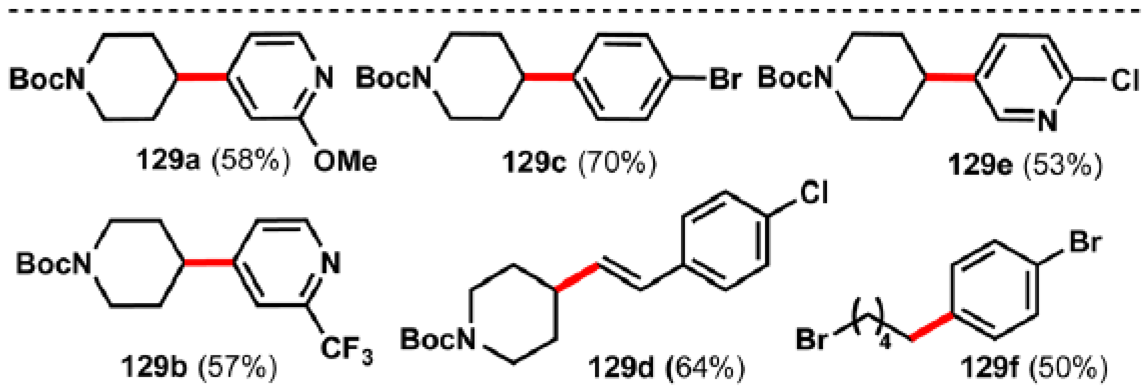

[conjunctive coupling]
[scalable]
[quaternary centers]
[2 C–C bonds formed]
OBn
Ph
125a (92%)
Me
Me
R
Ph
OBn
125b, R = NMeBoc (74%)
[gram-scale]
125c, R = OMe (76%)
125d, R = SMe (79%)
Et
Ph
OBn
125e (68%)
Me
Me Me
Ph
OBn
125f (87%)
Me
Me
Cl
Ph
OBn
125g (49%)
from chlofibric acid



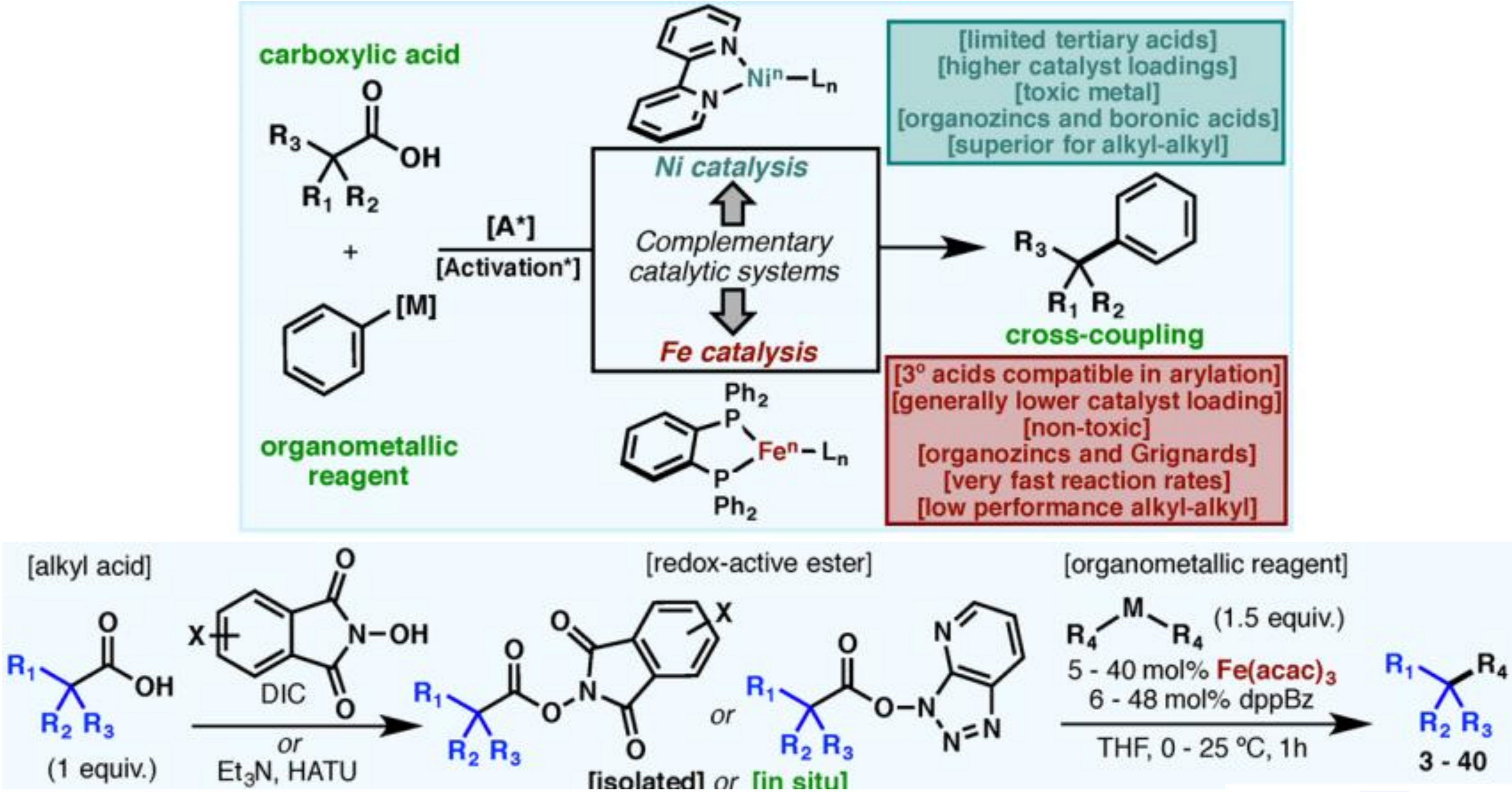
[commercially-available]
[1° and 2° alkyl acids]
[mild conditions]

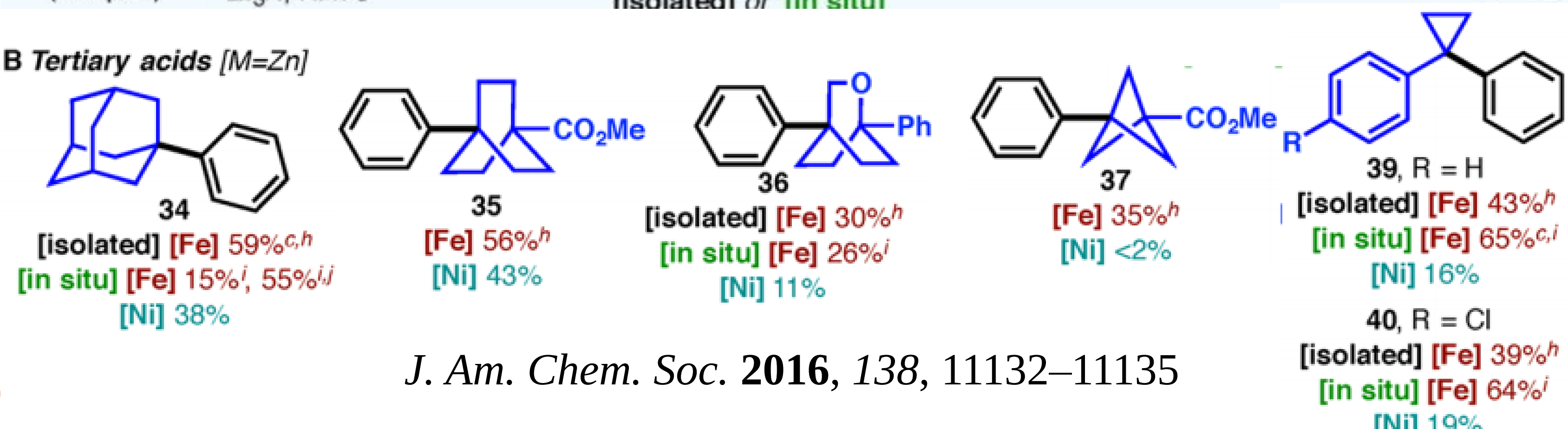
[functional group tolerant]
[in situ activation]
[monocatalytic]

[> 30 examples]
[heteroaromatic boronic acids]
[practical and scalable]

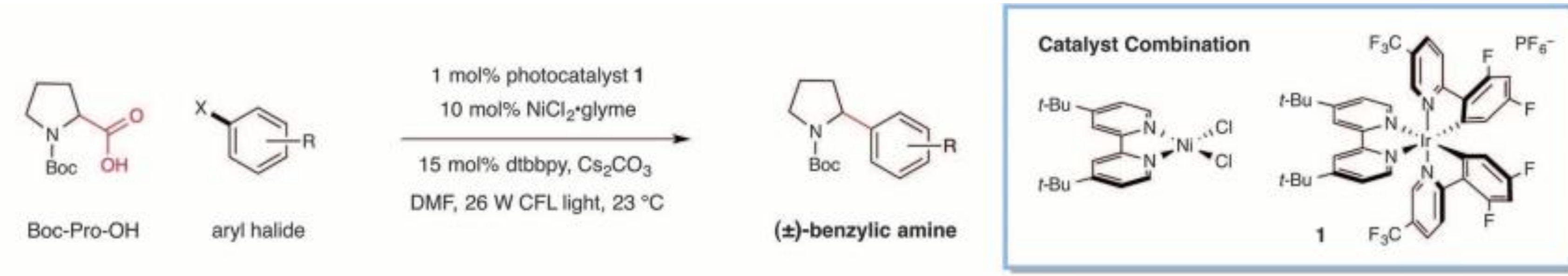


Angew. Chem. Int. Ed. **2016**, *55*, 9676-9679.

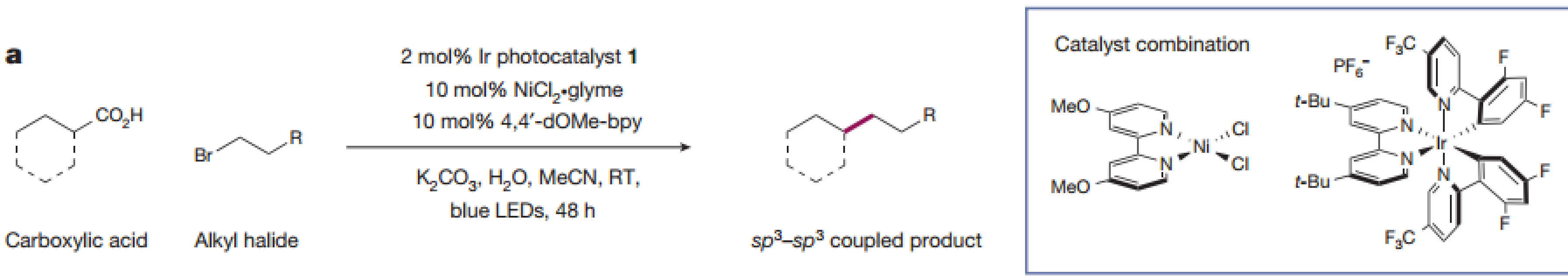




J. Am. Chem. Soc. **2016**, *138*, 11132–11135

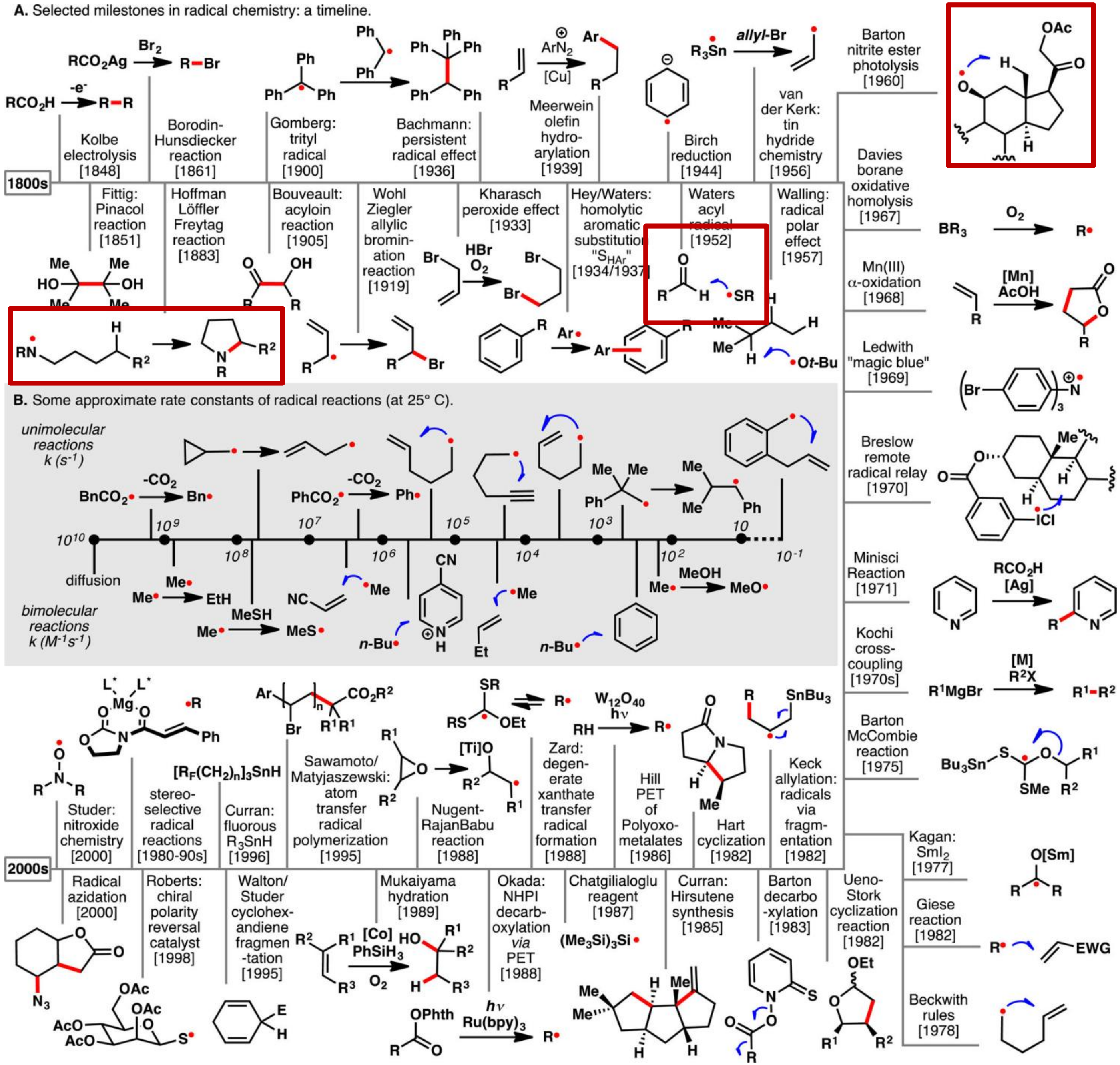


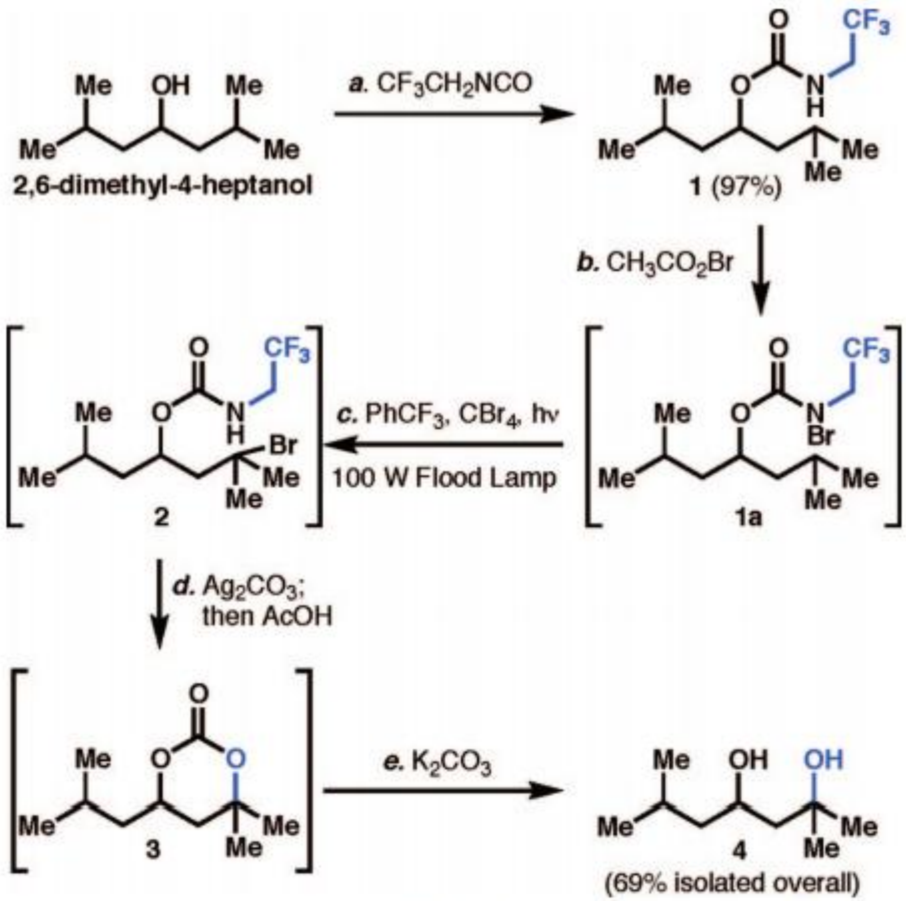
Science **2014**, *345*, 437-440



Nature **2016**, *535*, 322–325

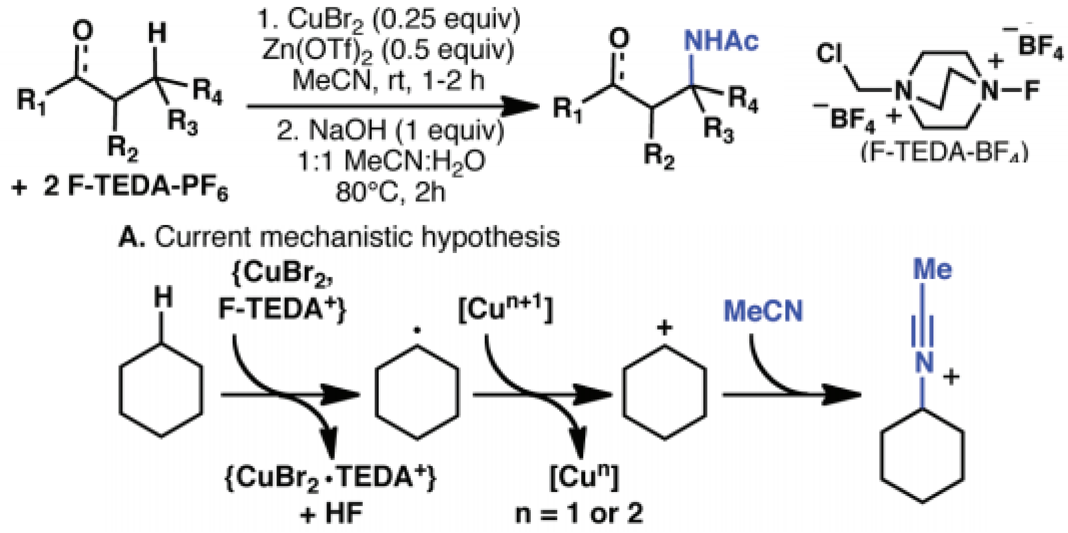
6. Hydrogen Atom Transfer reaction



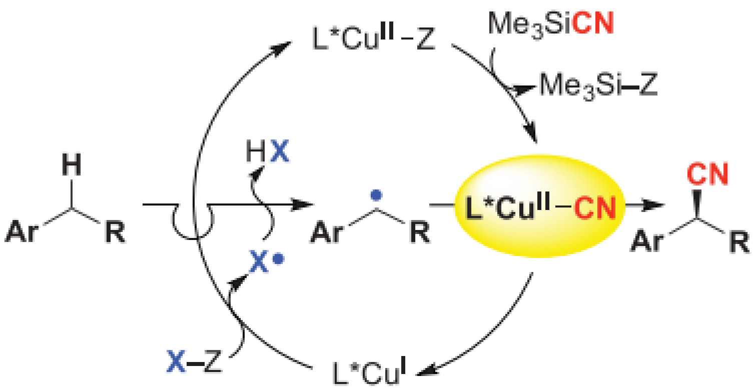


[a] Reagents and conditions: (a) CF_3CH_2NCO (1.0 equiv), DCM, Pyr (1.0 equiv), 23 °C, 2 h, 97%; (b) CH_3CO_2Br (1.0 equiv), DCM, 0 °C, 5 min; (c) $PhCF_3$ (0.05 M), CBr_4 (1.0 equiv), 23 °C, hν, 7 min; (d) Ag_2CO_3 (1.25 equiv), DCM, 23 °C, 1 h; then AcOH, 15 min; (e) K_2CO_3 (5.0 equiv), MeOH, 23 °C, 2 h, 69% overall. DCM = dichloromethane, Pyr = pyridine.

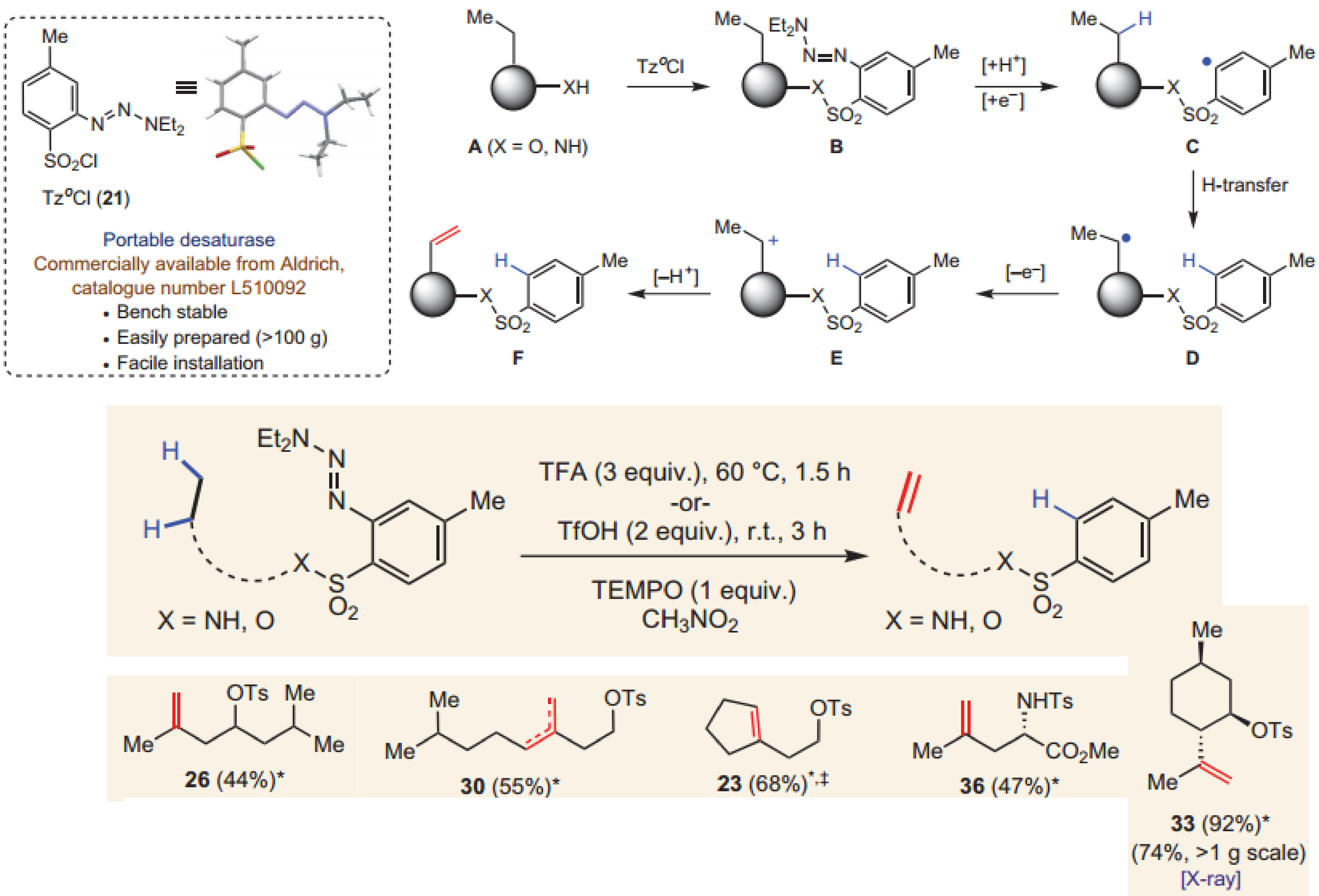
J. Am. Chem. Soc., **2008**, *130*, 7247–7249



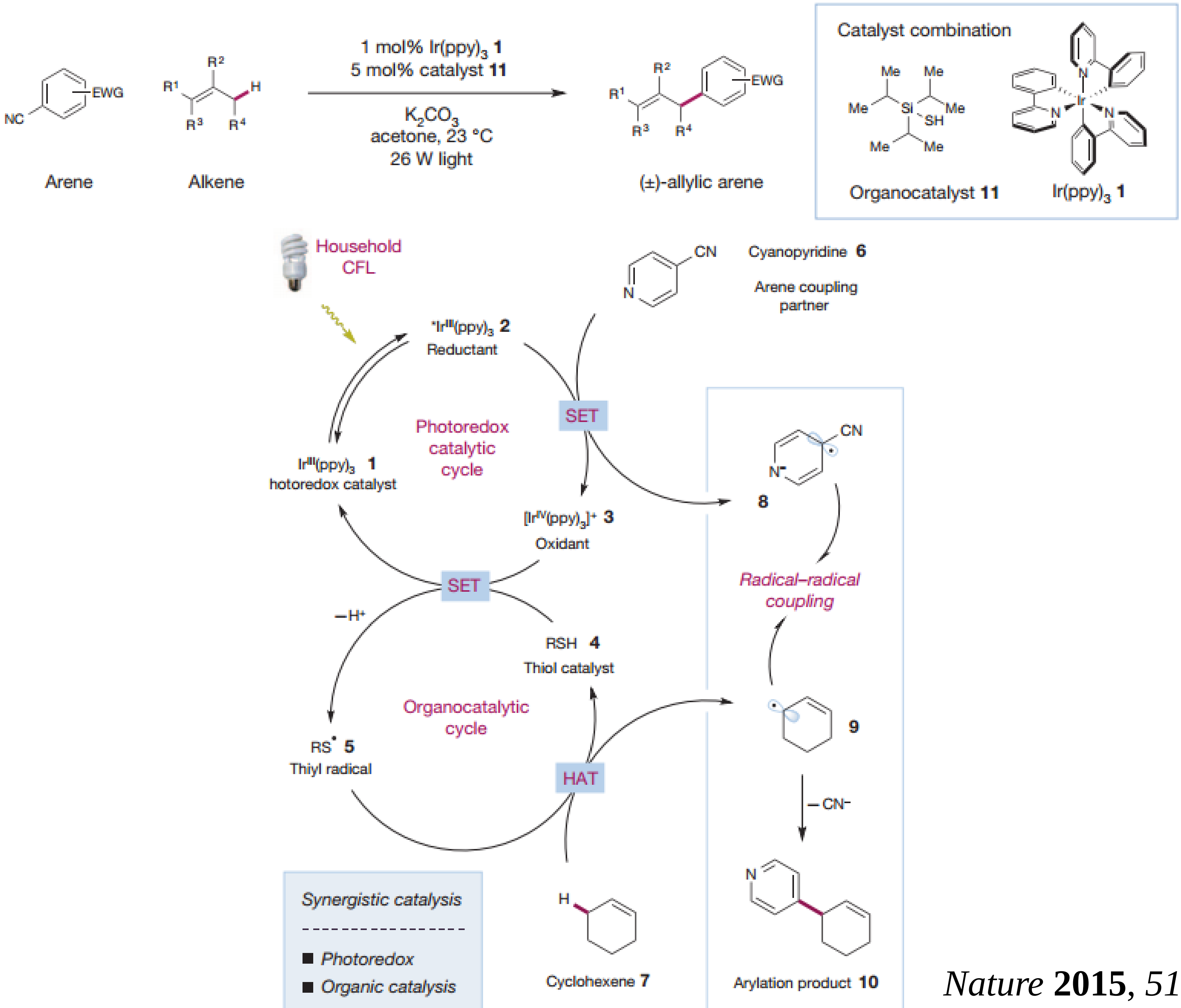
J. Am. Chem. Soc. **2012**, *134*, 2547–2550



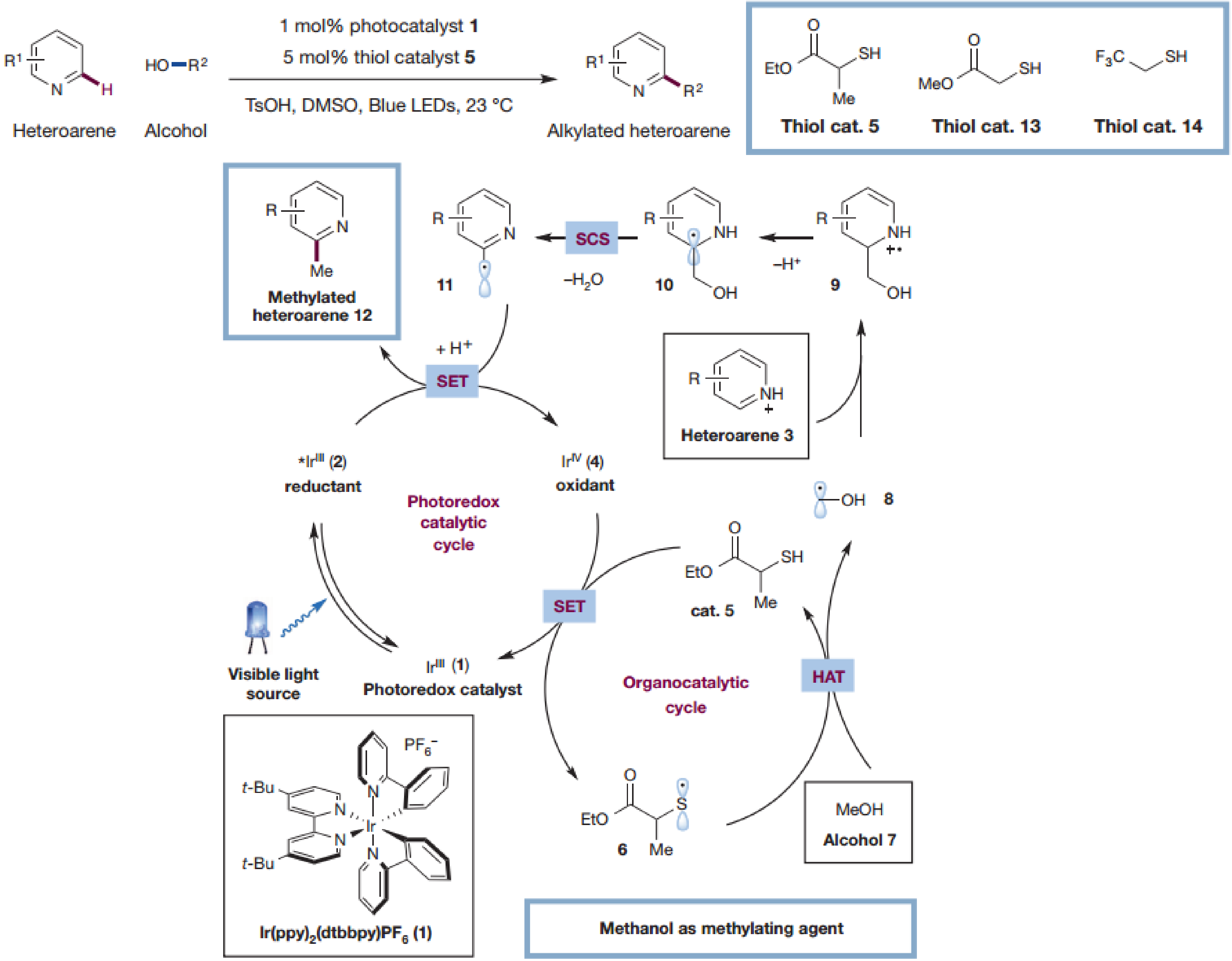
Science **2016,** ASAP



Nat. Chem. **2012**, *4*, 629–635



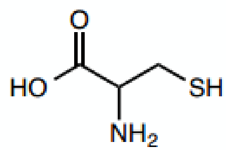
Nature **2015**, *519*, 74-77



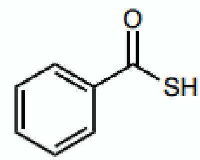
Nature **2015**, *525*, 87-90

S-H Bond Dissociation Energies in Thiols

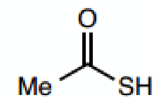
- Alkanethiols: similar S–H BDEs around 87 kcal mol^{-1} regardless of the structure of the alkyl residue



86 kcal mol^{-1}

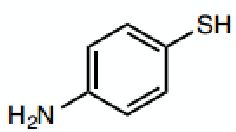


87 kcal mol^{-1}

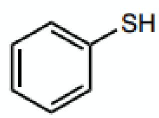


88 kcal mol^{-1}

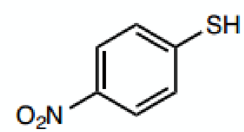
- Thiophenols: weaker S–H BDEs due to the stabilization by resonance of the corresponding arenethiyl radical



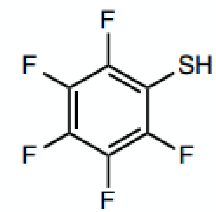
70 kcal mol^{-1}



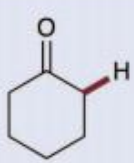
79 kcal mol^{-1}



82 kcal mol^{-1}

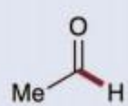


84 kcal mol^{-1}

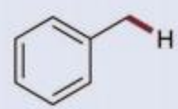


88.0 kcal/mol

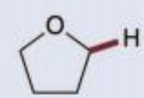
88.8 kcal/mol



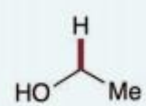
89.4 kcal/mol



89.8 kcal/mol

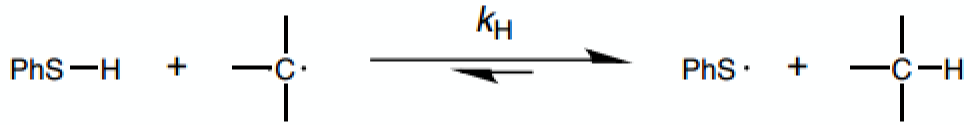


92.0 kcal/mol



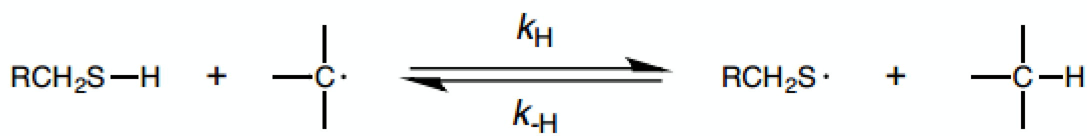
92.0 kcal/mol

Rate Constants for the Reduction of Various Alkyl Radicals by Thiophenol



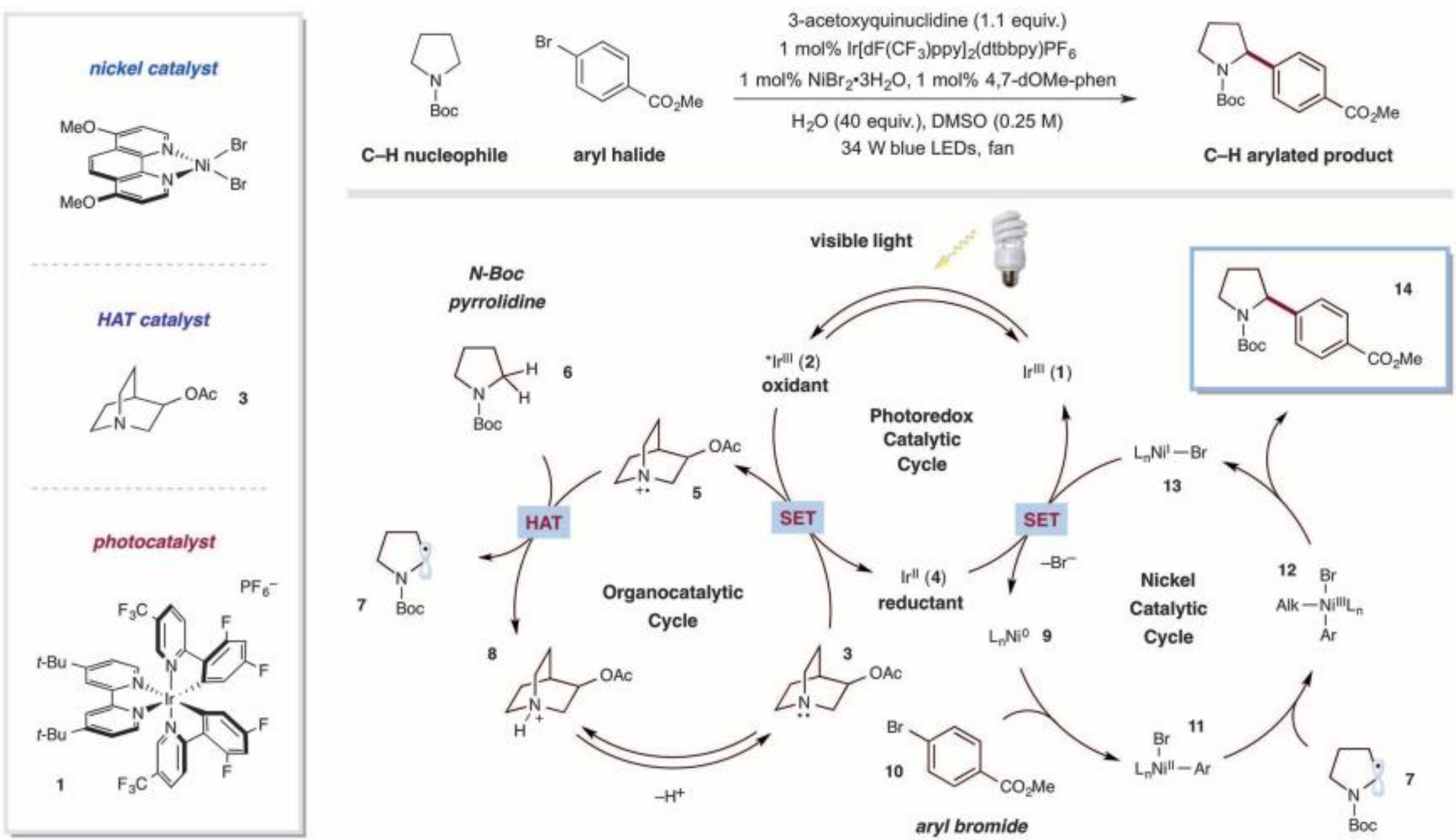
entry	radical	k_H/[M^{-1} s^{-1}] (T/K)	ΔH/[kcal mol^{-1}]
1	n-C_3H_7-**CH_2**·	1.3×10^8 (298)	-17
2	$(CH_3)_2$**CH**·	1.0×10^8 (298)	-15
3	$(CH_3)_3$**C**·	1.4×10^8 (298)	-12
4	n-C_6F_{13}-**CF_2**·	2.8×10^5 (303)	-20
5	$ROCH_2$**CH_2**·	7.6×10^7 (353)	-18
6	Ph**CH_2**·	3.0×10^5 (298)	-5

Rate Constants for the Reduction of Various Alkyl Radicals by Alkanethiol

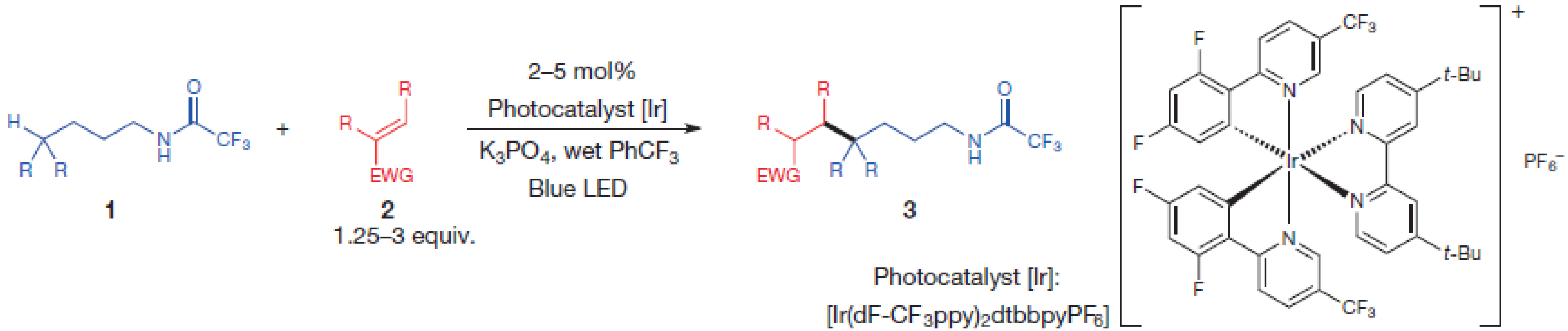


entry	radical	k_H/[M^{-1} s^{-1}] (T/K)	k_{-H}/[M^{-1} s^{-1}] (T/K)	ΔH/[kcal mol^{-1}]
1	R-**CH_2**·	2×10^7 (298)		-13
2	R_3**C**·	4×10^6 (303)	2×10^4 (353)	-8
3	R-**CH**(OMe)·	2×10^7 (298)		-4
4	R-**C**(=O)·	7×10^6 (353)		-1
5	Ph-**CHR**·	7×10^2 (333)	1×10^6 (353)	+2
6	Ph-**CH**(OMe)·		2×10^7 (353)	+2

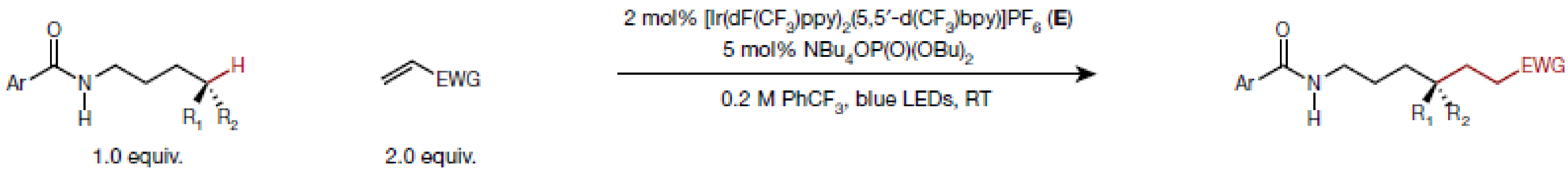
Chem. Rev. **2014**, *114*, 2587



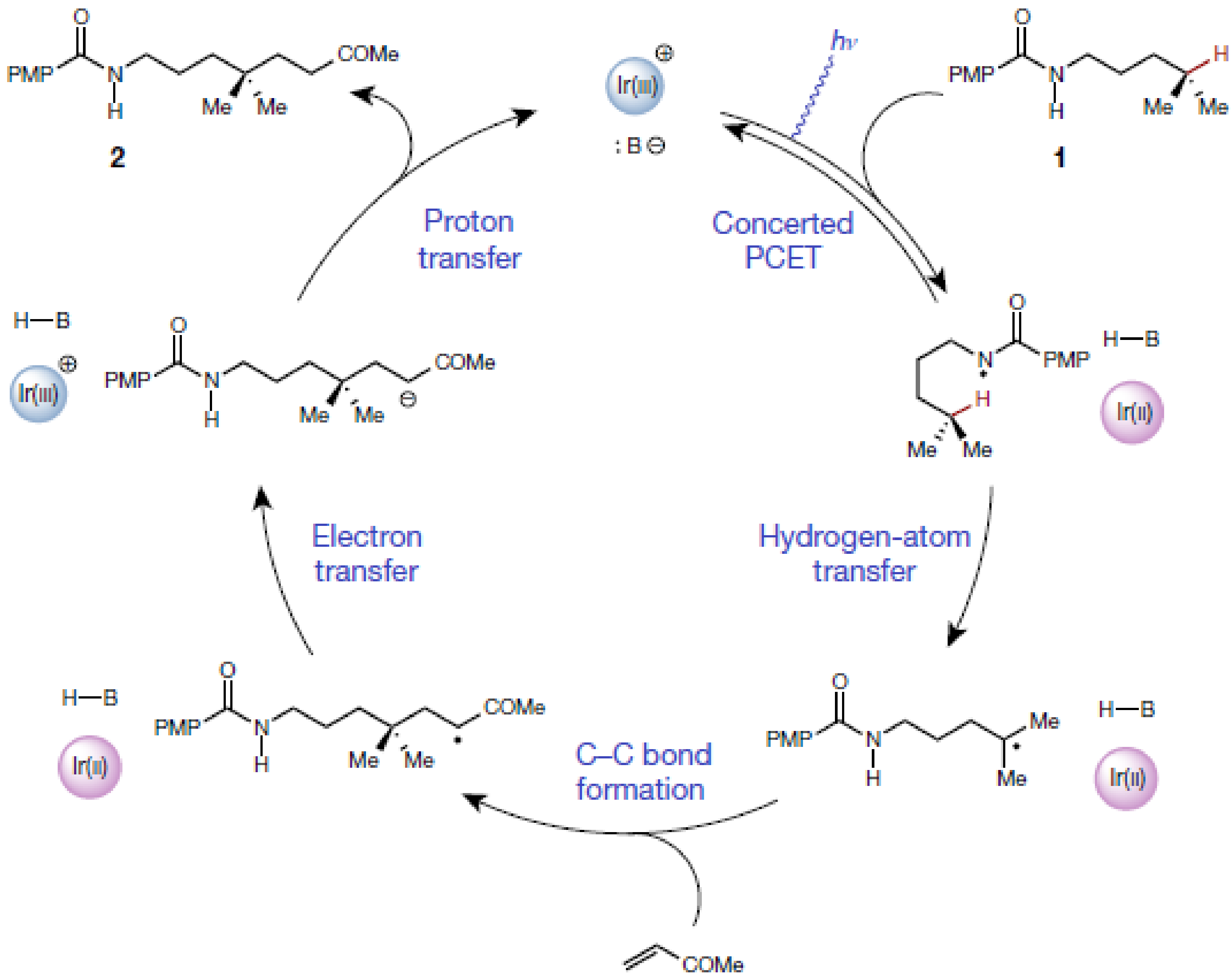
Science **2016**, *352*, 1304-1308



T. Rovis, *Nature* **2016**, ASAP

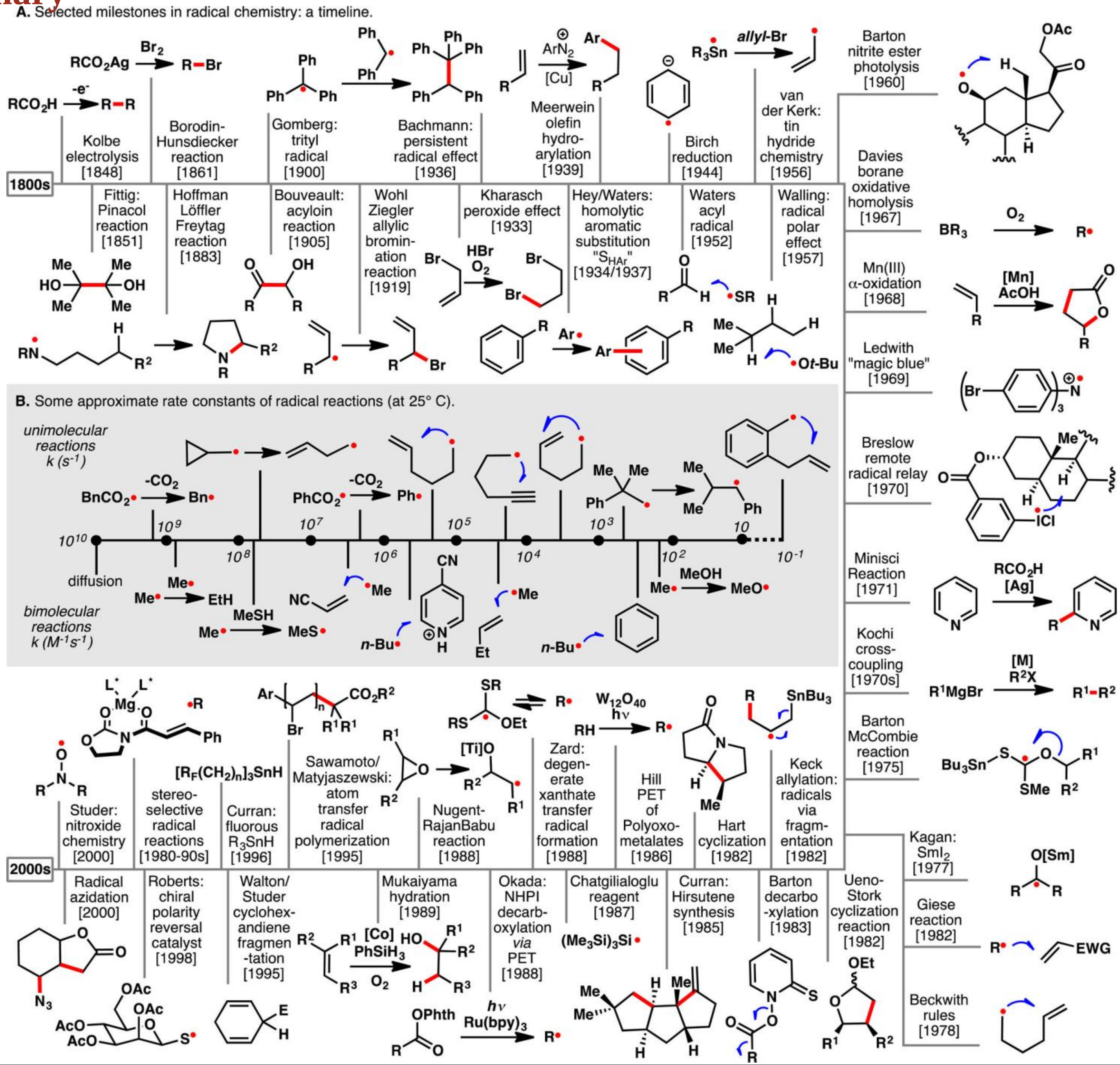


R. R. Knowles, *Nature* **2016**, ASAP



Ir(III)
:B⊖
hν
PMP
N
H
O
Me
H
1
COMe
2
Proton transfer
Concerted PCET
H—B
Ir(II)
Hydrogen-atom transfer
Electron transfer
C–C bond formation

7. Summary



A. Selected milestones in radical chemistry: a timeline.
1800s
Kolbe electrolysis [1848]
Fittig: Pinacol reaction [1851]
Borodin-Hunsdiecker reaction [1861]
Hoffman Löffler Freytag reaction [1883]
Gomberg: trityl radical [1900]
Bouveault: acyloin reaction [1905]
Wohl Ziegler allylic bromination reaction [1919]
Kharasch peroxide effect [1933]
Bachmann: persistent radical effect [1936]
Meerwein olefin hydroarylation [1939]
Hey/Waters: homolytic aromatic substitution "S_HAr" [1934/1937]
Birch reduction [1944]
Waters acyl radical [1952]
van der Kerk: tin hydride chemistry [1956]
Walling: radical polar effect [1957]
Barton nitrite ester photolysis [1960]
Davies borane oxidative homolysis [1967]
Mn(III) α-oxidation [1968]
Ledwith "magic blue" [1969]
Breslow remote radical relay [1970]
Minisci Reaction [1971]
Kochi cross-coupling [1970s]
Barton McCombie reaction [1975]
Kagan: SmI2 [1977]
Beckwith rules [1978]
Giese reaction [1982]
Ueno-Stork cyclization reaction [1982]
Keck allylation: radicals via fragmentation [1982]
Hart cyclization [1982]
Barton decarboxylation [1983]
Curran: Hirsutene synthesis [1985]
Hill PET of Polyoxometalates [1986]
Chatgilialoglu reagent [1987]
Zard: degenerate xanthate transfer radical formation [1988]
Okada: NHPI decarboxylation via PET [1988]
Nugent-RajanBabu reaction [1988]
Mukaiyama hydration [1989]
Sawamoto/Matyjaszewski: atom transfer radical polymerization [1995]
Walton/Studer cyclohexandiene fragmentation [1995]
Curran: fluorous R3SnH [1996]
Roberts: chiral polarity reversal catalyst [1998]
stereoselective radical reactions [1980-90s]
Studer: nitroxide chemistry [2000]
Radical azidation [2000]
2000s
B. Some approximate rate constants of radical reactions (at 25° C).
unimolecular reactions k (s-1)
bimolecular reactions k (M-1s-1)
diffusion
10^10 10^9 10^8 10^7 10^6 10^5 10^4 10^3 10^2 10 10^-1

Thanks for Your Attention！