

Frontiers in Chemical Synthesis I

Sustainable Chemistry

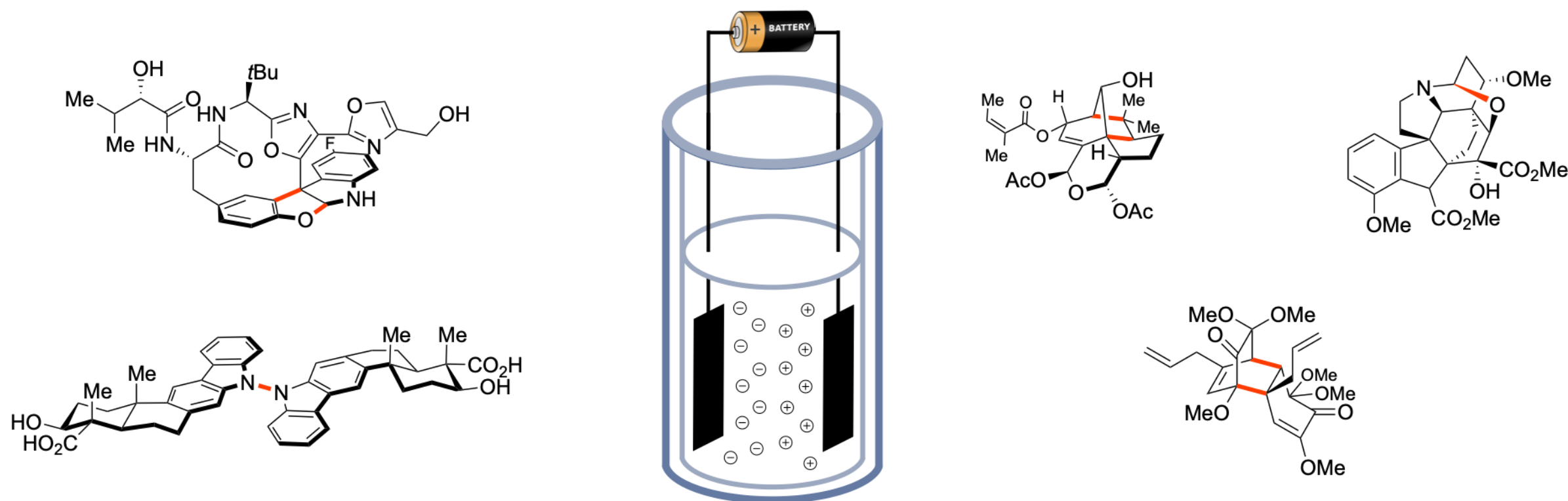
Seminar Program

May 11, Zoom

May 13, Zoom

	Speaker	Title
May 11, 2020, Zoom: https://epfl.zoom.us/j/99900310067		
Session I: (Chair: Stephanie Amos)		
8h15-9h15	John Reed	<i>Use of Electrochemistry in Total Synthesis</i>
9h15-10h15	Raphael Simonet-Davin	<i>Enantioselective Radical Reactions via Transition Metal Catalysis</i>
10h15-11h15	Annabell Martin	<i>Catalytic Cascade Reactions by Radical Relay</i>
May 11, 2020, Zoom: https://epfl.zoom.us/j/94781408031		
Session II: (Chair: John Reed)		
13h15-14h15	Alexandre Leclair	<i>Recent Advances in Iron-Catalyzed Cross Coupling Reactions</i>
14h15-15h15	Stephanie Amos	<i>Enantioselective syntheses and transformations of Cyclopropyl Ketones</i>
May 13, 2020, Zoom: https://epfl.zoom.us/j/97639831812		
Session III: (Chair: Alexandre Leclair)		
9h15-10h15	Anastasia Gitlina	<i>Acid-Mediated Hydroaminomethylation</i>
10h15-11h15	Abhyankar Kedar	<i>Gold-catalyzed C-C bond forming reactions of non-activated olefins</i>

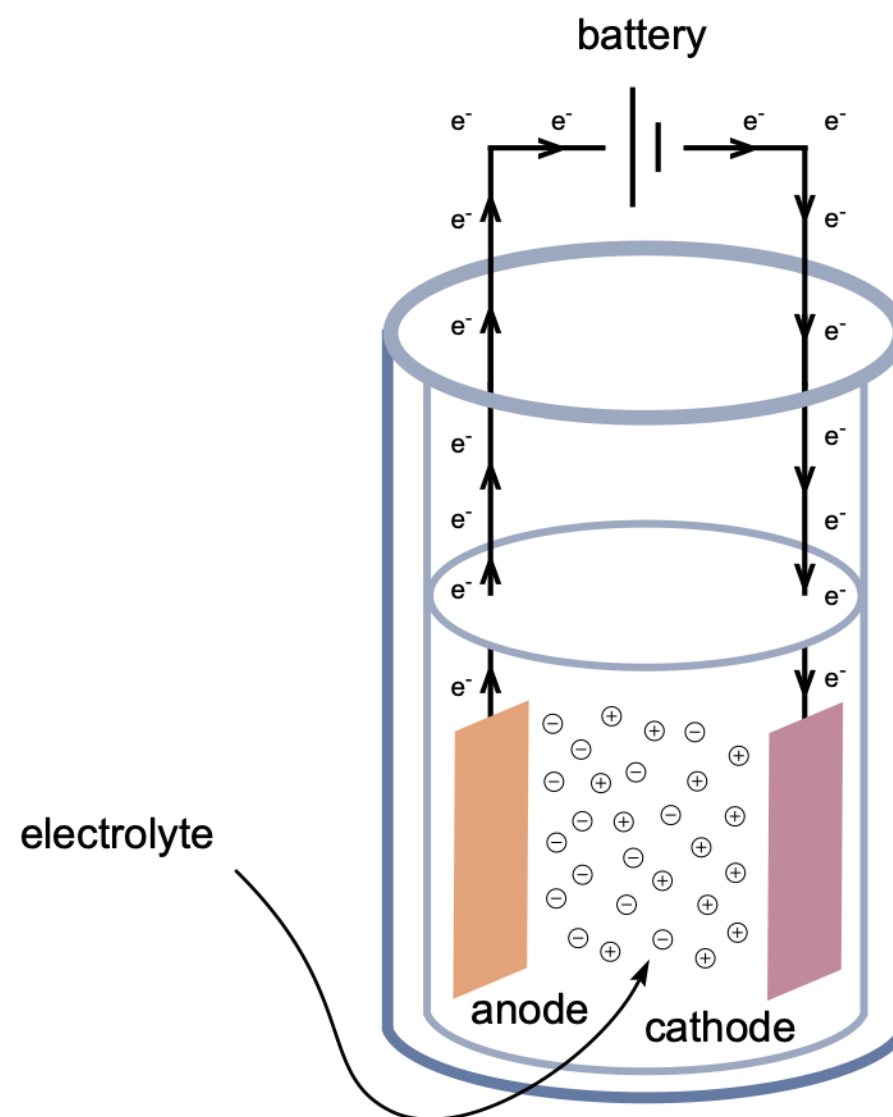
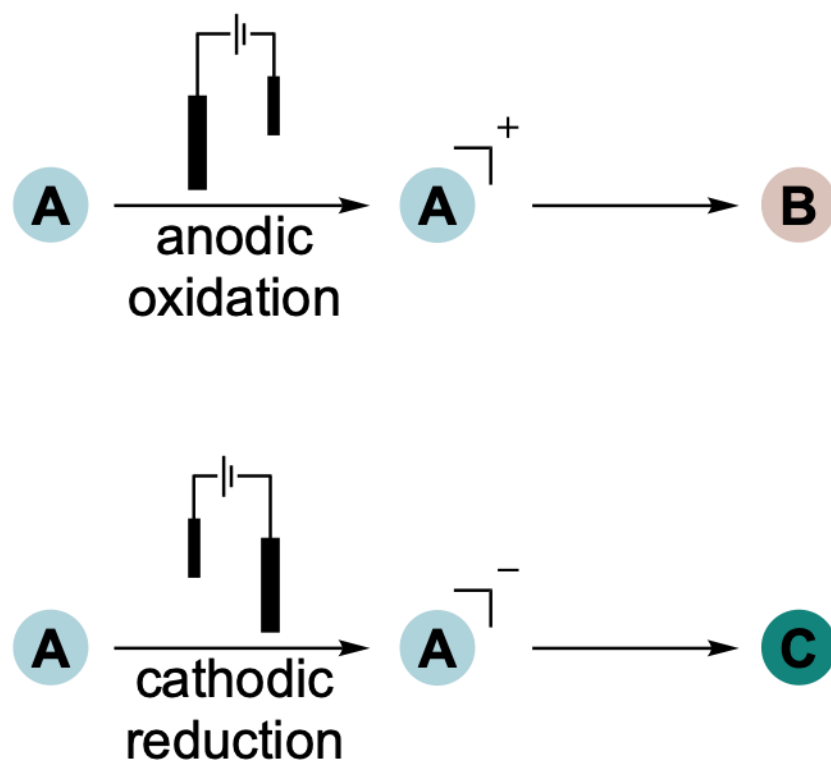
Modernising Total Synthesis through Electrochemistry



Frontiers in Chemical Synthesis:
Towards Sustainable Chemistry

Organic Synthetic Electrochemistry

Redox reactions!



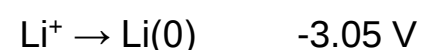
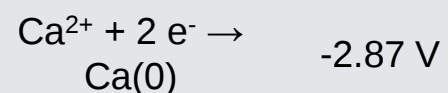
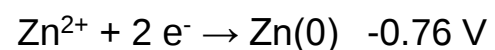
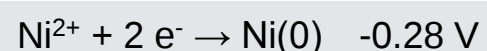
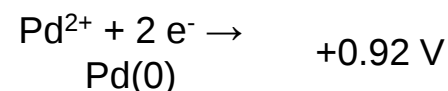
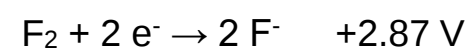
- Battery (or other power source) generates a *potential difference*, measured in volts (V)
- The potential difference drives a *current*, measured in amps (A), through the wire
- Electrons flow from *anode* to *cathode*, resulting in charge accumulation
- If potential difference is large enough for the particular substrate, electron transfer can occur

Organic Synthetic Electrochemistry

Redox potentials (E_0):

A measure of the potential difference needed to oxidise or reduce a compound or functional group

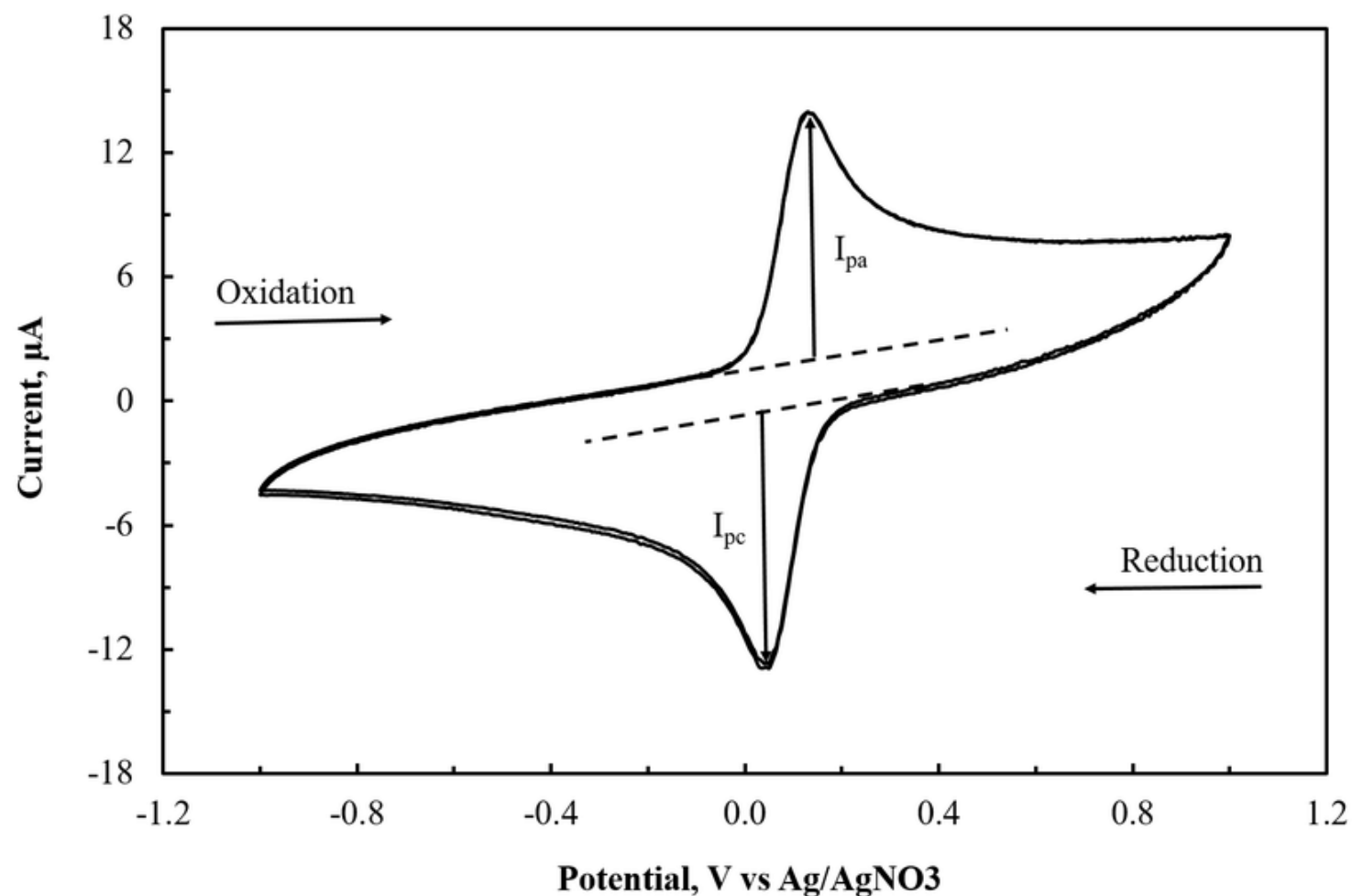
Common reduction potentials (vs SCE)



Experimentally determined using cyclic voltammetry

Reliable for inorganic substrates

Cyclic voltammetry:

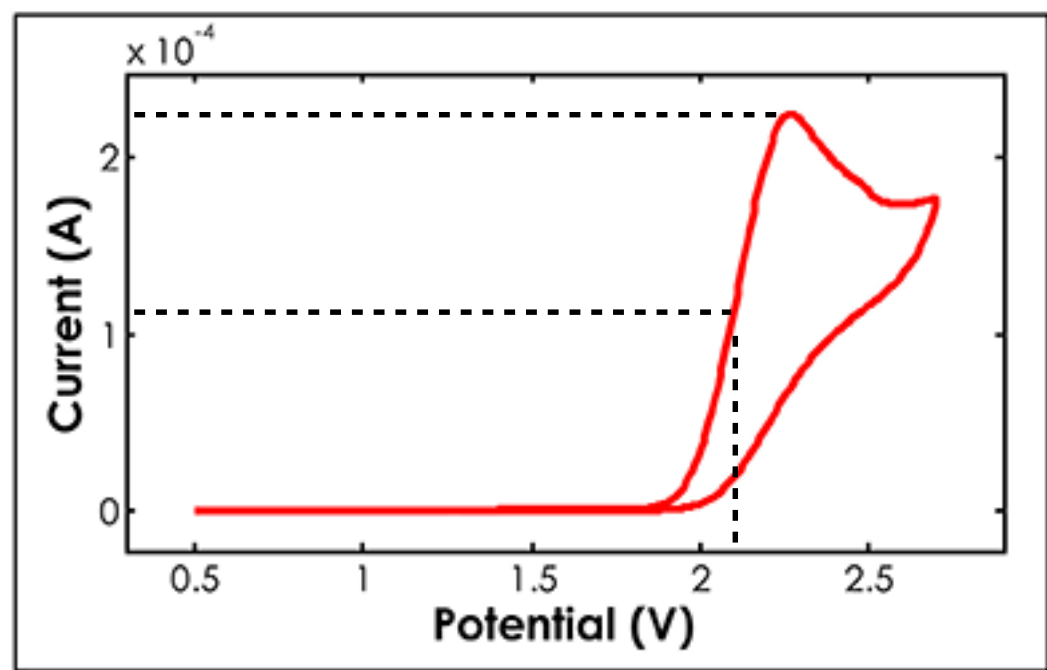


E_0 is given by the average of the oxidative (anodic) and reductive (cathodic) *peak potentials*

Reversible oxidation/reduction necessary!!!

Problematic for organic substrates

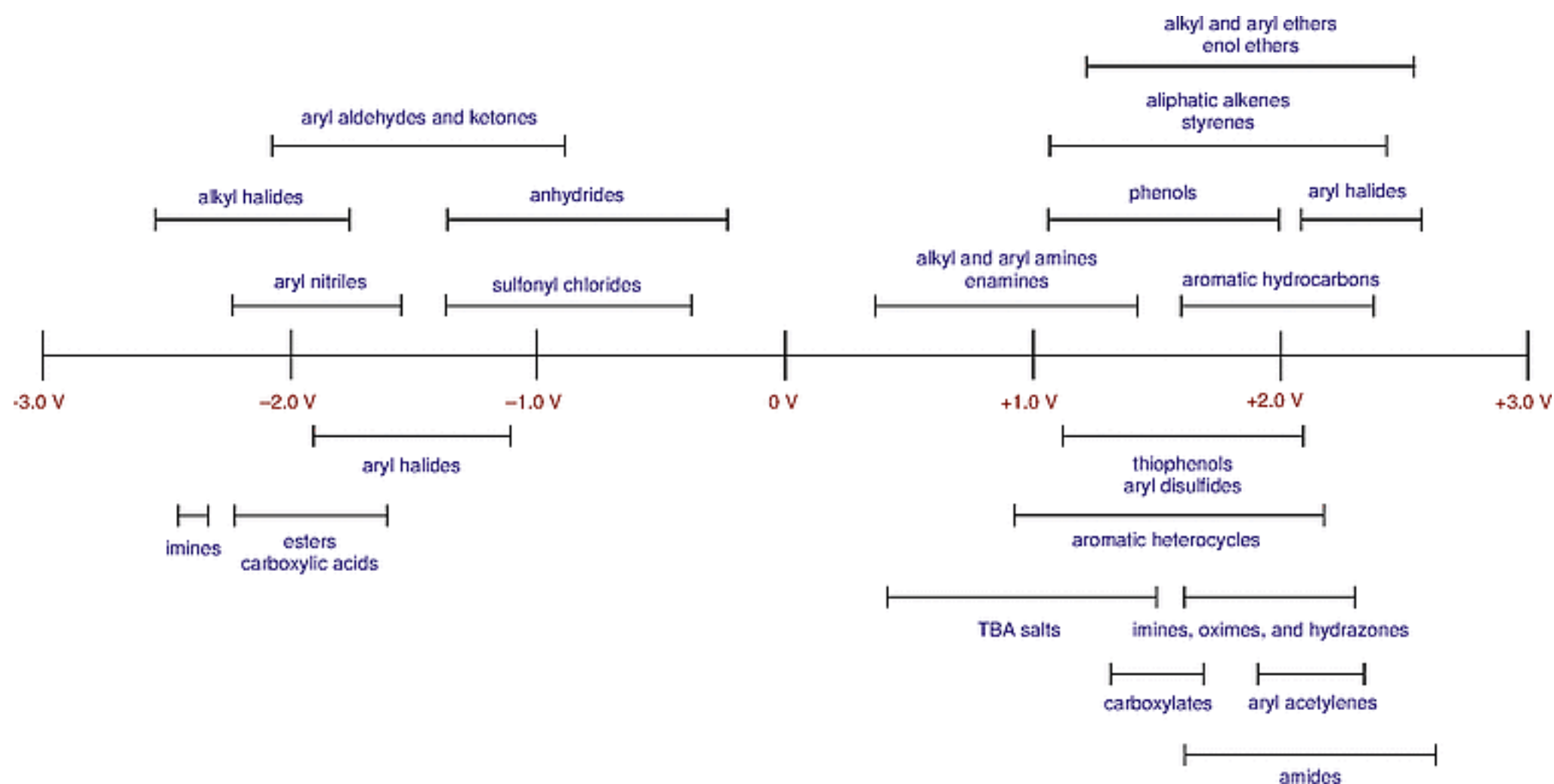
Organic Synthetic Electrochemistry



Single electron oxidations/reductions of organic compounds often lead to unstable intermediates with downstream reactivity

Irreversibility prevents meaningful CV data

Nicewicz has argued that *half-peak potentials* offer close estimates to the true value



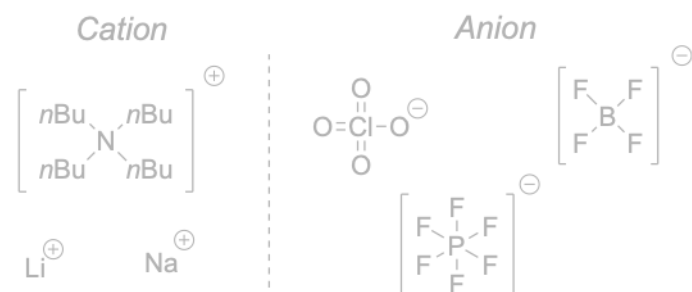
Anode/Cathode Materials:

- Electron transfer occurs at surface
- Different materials have different potential ranges
- Sacrificial anodes can be used when reduction is desired

	Surface Area	Cost/unit
RVC foam	High	€ 26
graphite	Low	€ 185
Ni foam	High	€ 12.5
Pt	Low	€ 621
W	Low	€ 355
BDD	Low	€ 552
Zn	Low	€ 53

Electrolyte:

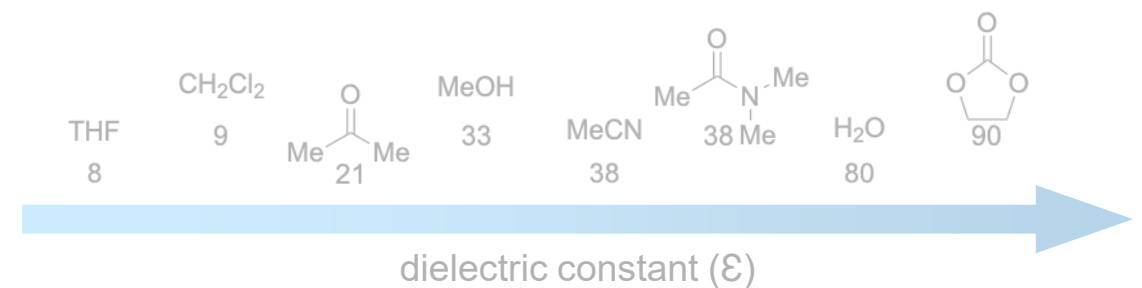
- Source of positive and negative ions
- Carries charge through reaction medium
- Increases conductivity of reaction medium
- Forms an ion layer around electrodes, affecting substrate diffusion



- Li^+ and $n\text{Bu}_4\text{N}^+$ are common cations: good solubility and chemical inertness
- ClO_4^- is a common anion: cheap and inert

Solvent:

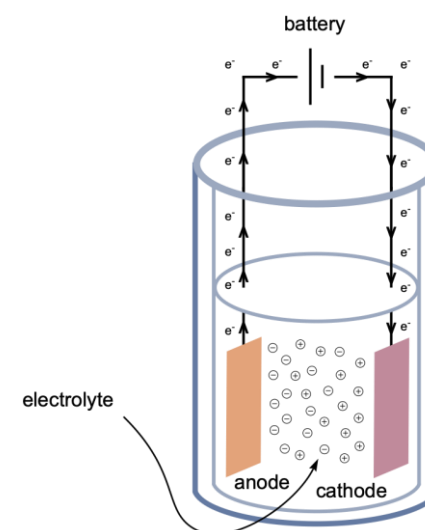
- Stable to electrochemical conditions
- Polar protic solvents most common



- Higher dielectric constant = higher conductivity (lower resistance)
- Protic solvents and CH_2Cl_2 can serve as sacrificial reductants when anodic oxidation is desired
- Choice of solvent affects working potential range

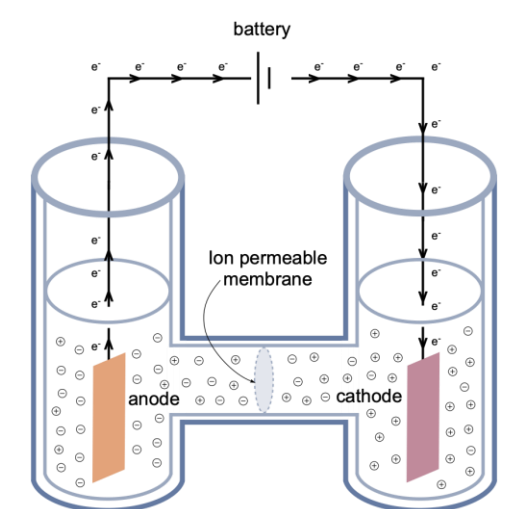
Single Cell vs Split Cell:

Single (Undivided) Cell:



- Lower resistance
- Simpler set-up

Split Cell:

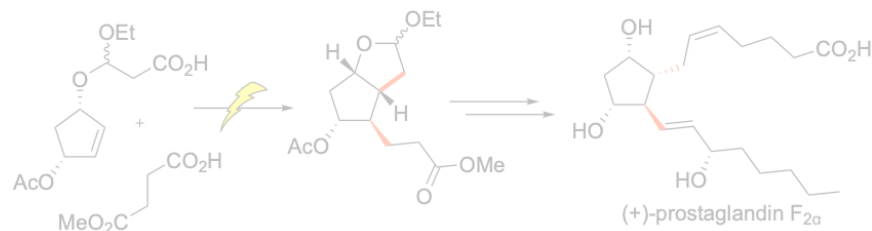


- Higher resistance
- More complicated set-up
- Less undesired reactivity

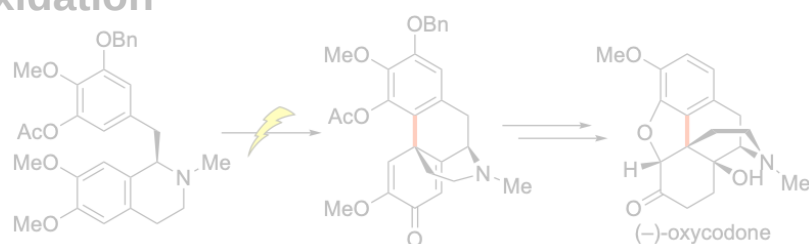
Electrochemistry in Total Synthesis

Anodic Oxidations:

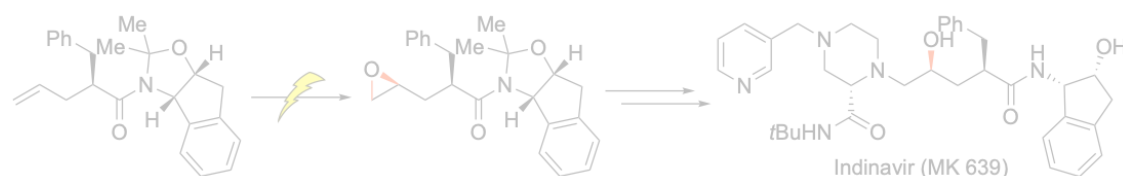
- Oxidative Decarboxylation (Kolbe Reaction)**



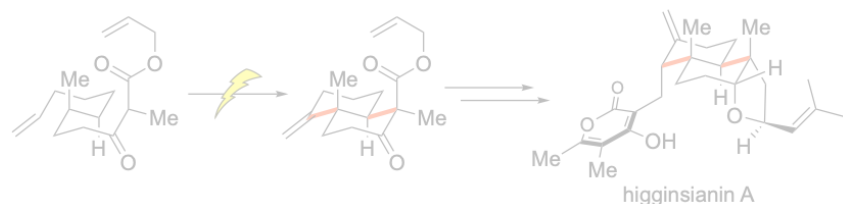
- Arene Oxidation**



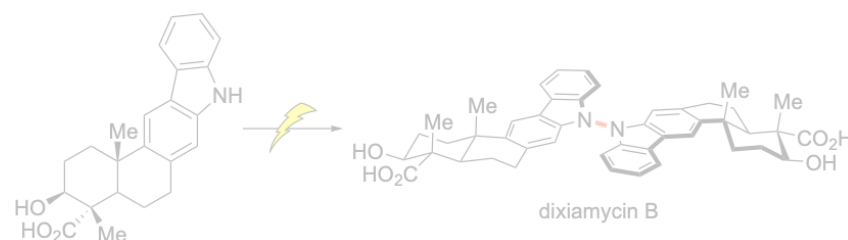
- C=C Bond Oxidation**



- C(sp³)-H Oxidation**

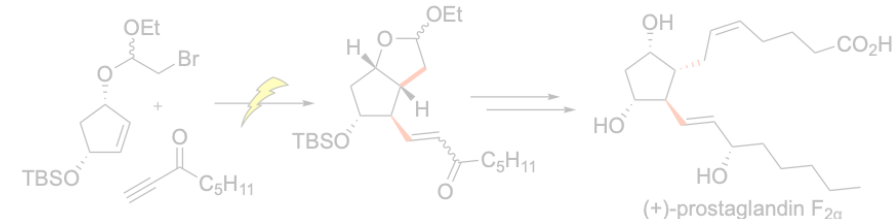


- N-H Bond Oxidation**

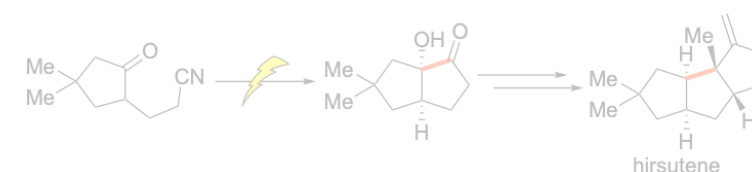


Cathodic Reductions:

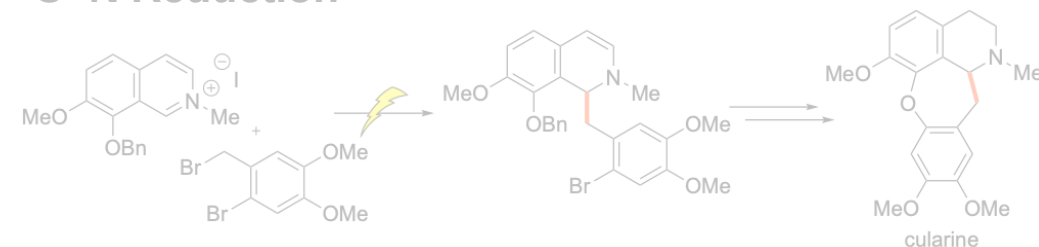
- C-X Reduction**



- C=O Reduction**

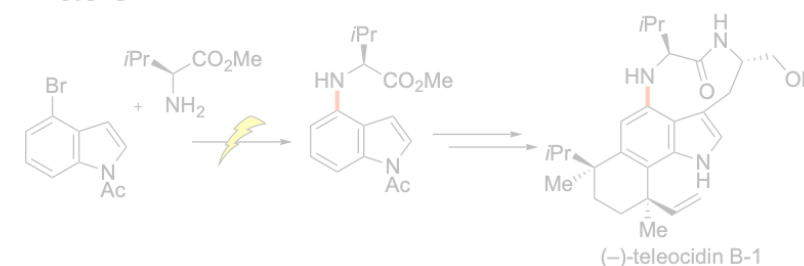


- C=N Reduction**

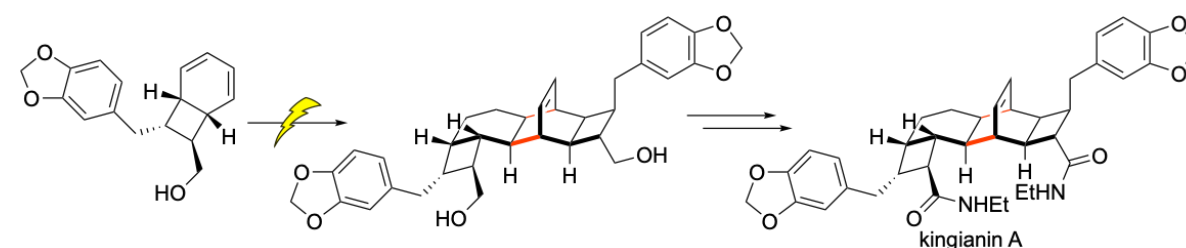


Redox Paired Transformations:

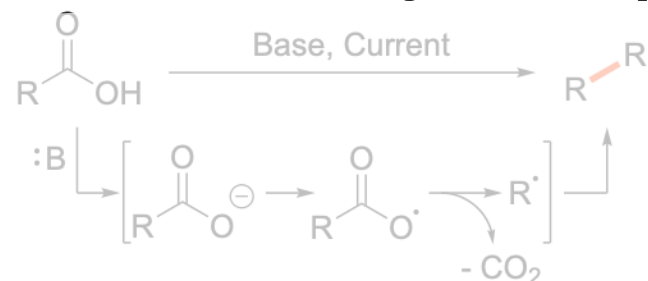
- e-Amination**



- Radical Cation Diels-Alder**

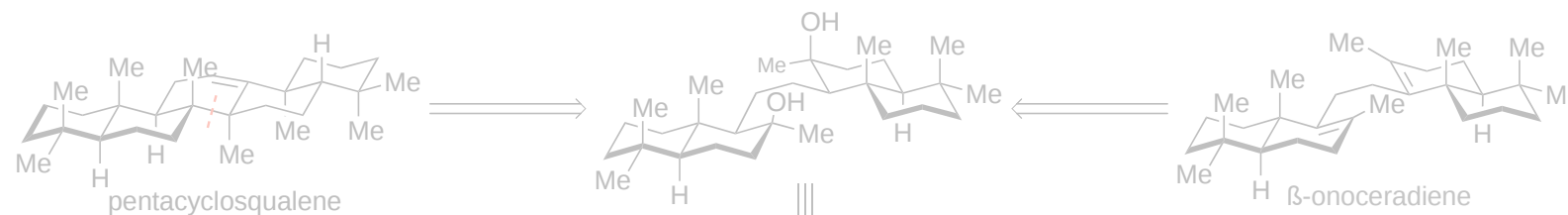


Oxidative Decarboxylation (Kolbe Reaction)

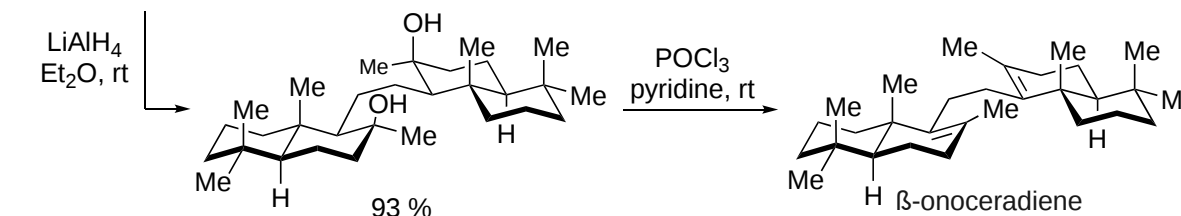
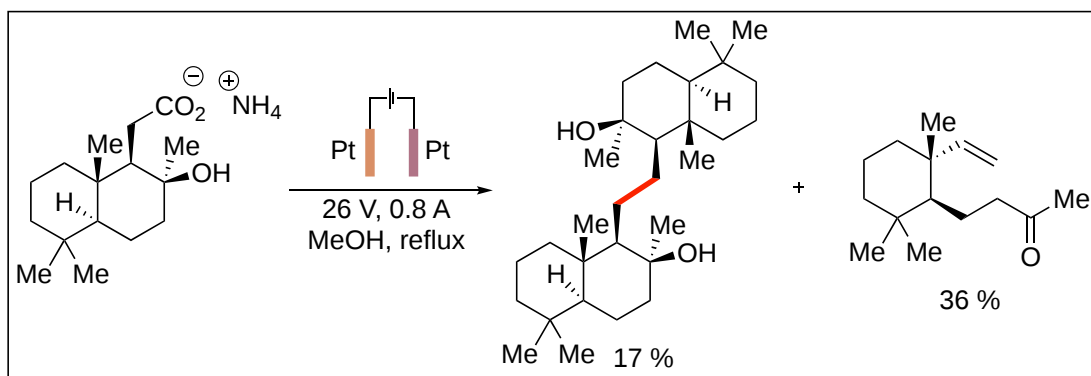
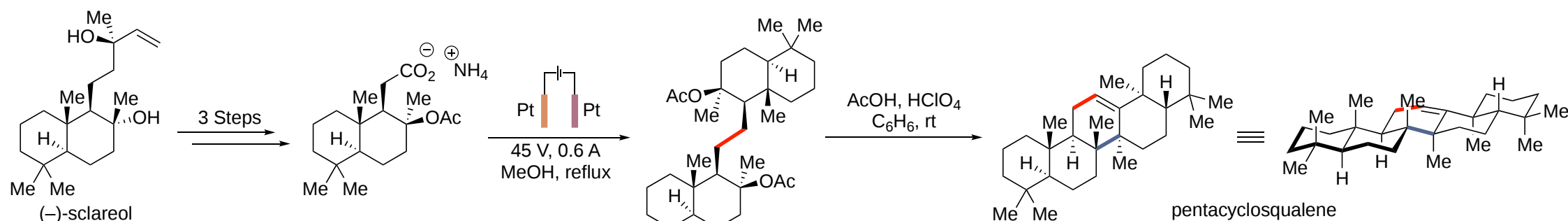
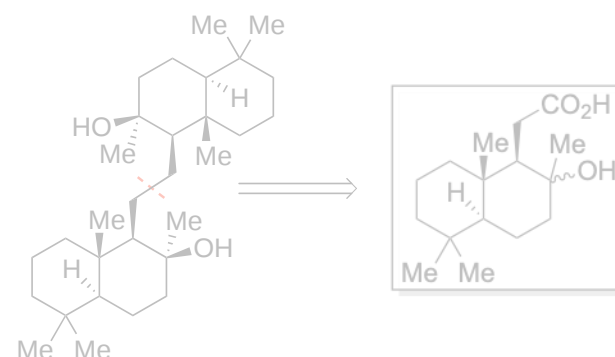


- First reported in 1848¹
- Single electron oxidation of carboxylate
- Rapid decarboxylation
- Radical coupling gives product

Corey, 1959²

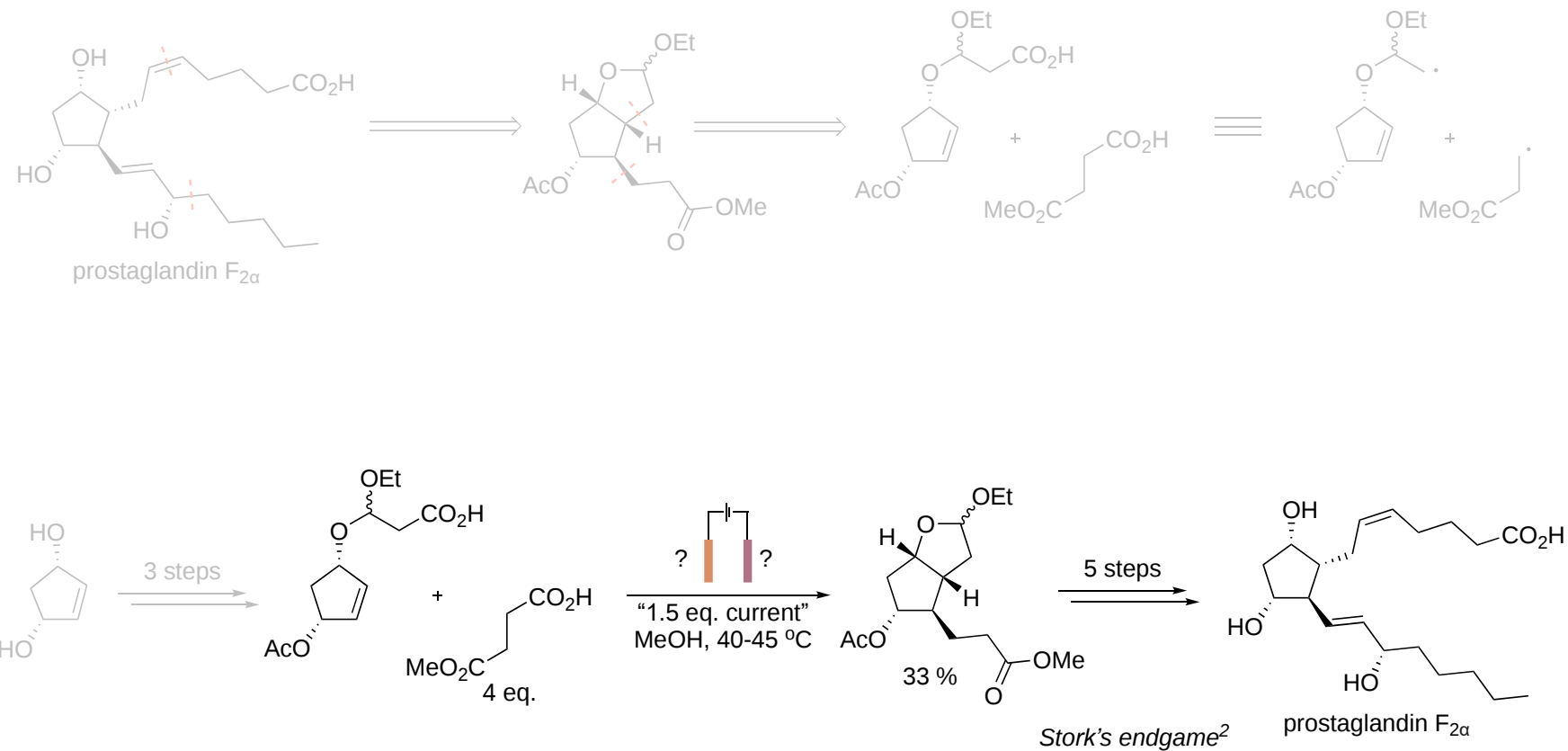


- Polar reactivity would require two different coupling units



Oxidative Decarboxylation (Kolbe Reaction)

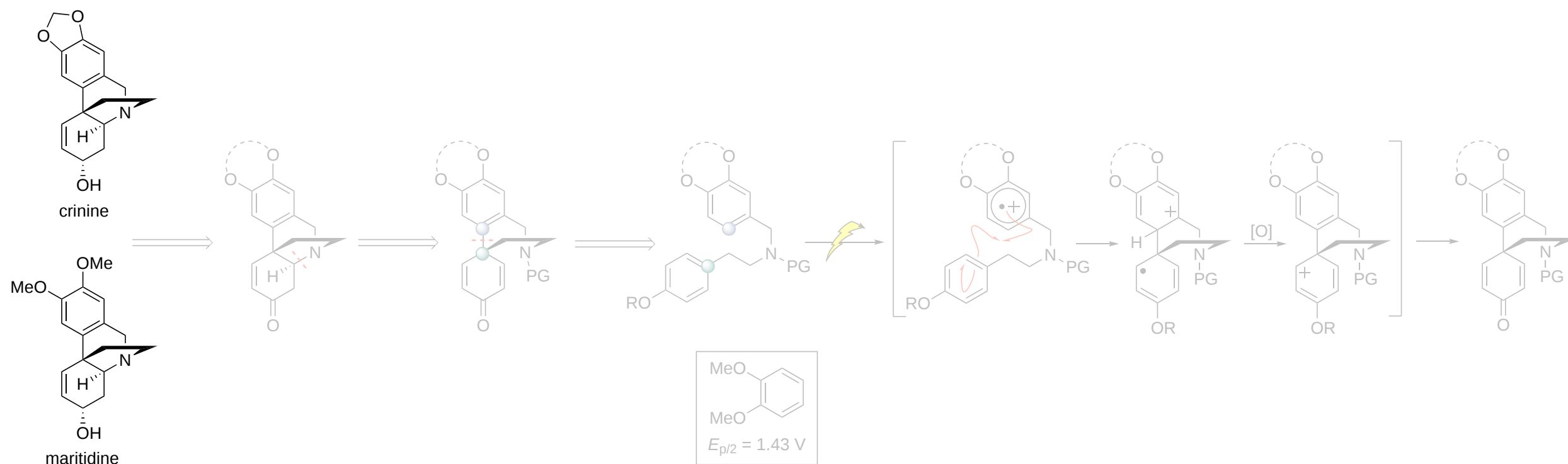
Schäfer, 1988¹



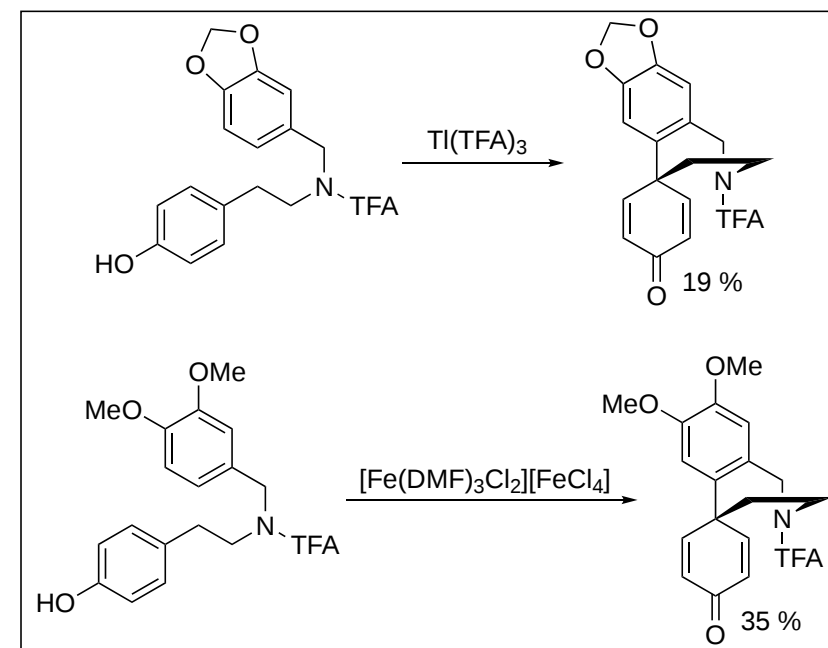
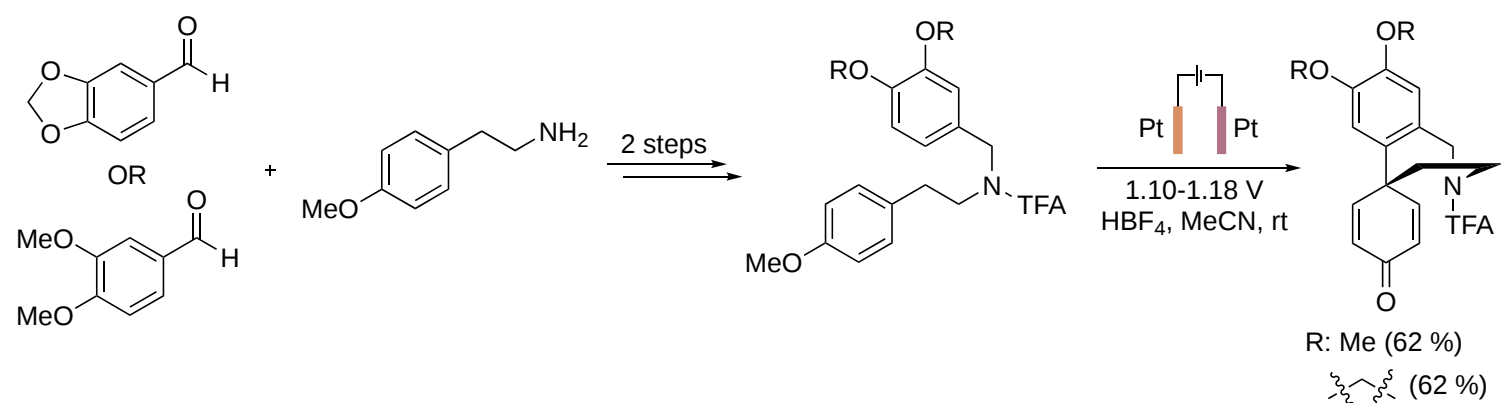
- Reduction of step count by 2
- Obviates the need for tin reagents
- More flexible choice of coupling reagent

Arene Oxidation

Tobinaga, 1973¹

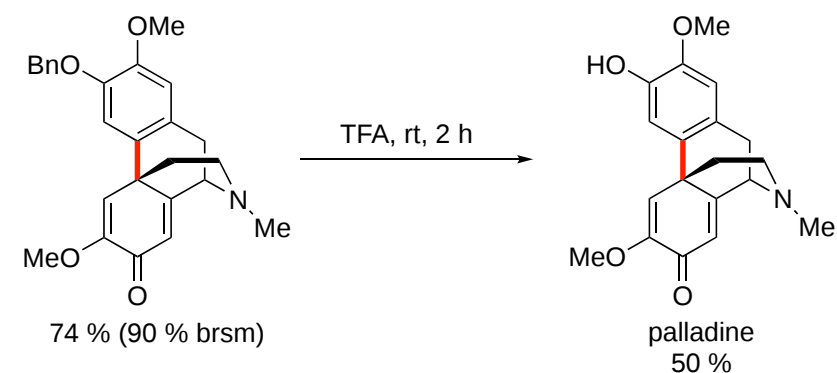
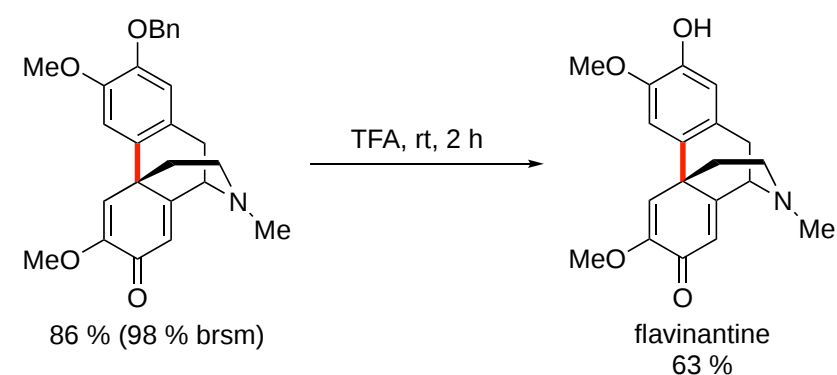
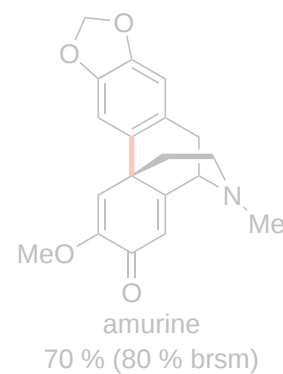
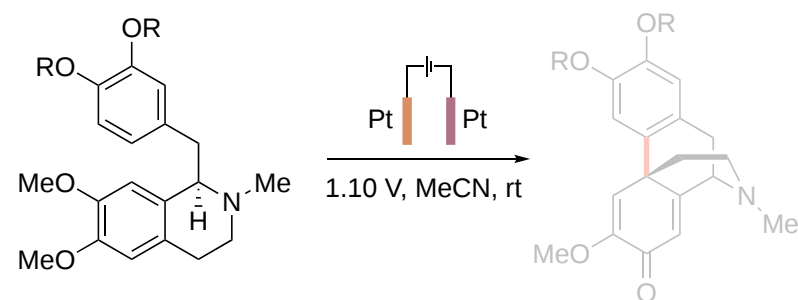
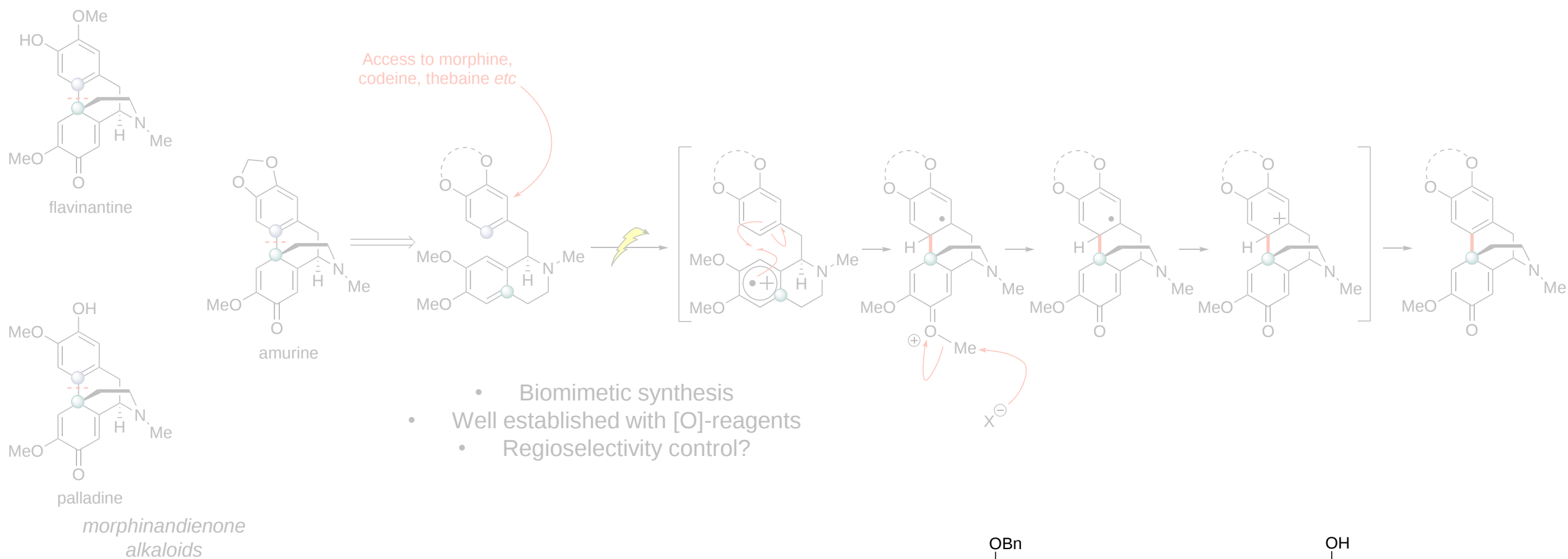


Amaryllidaceae
alkaloids

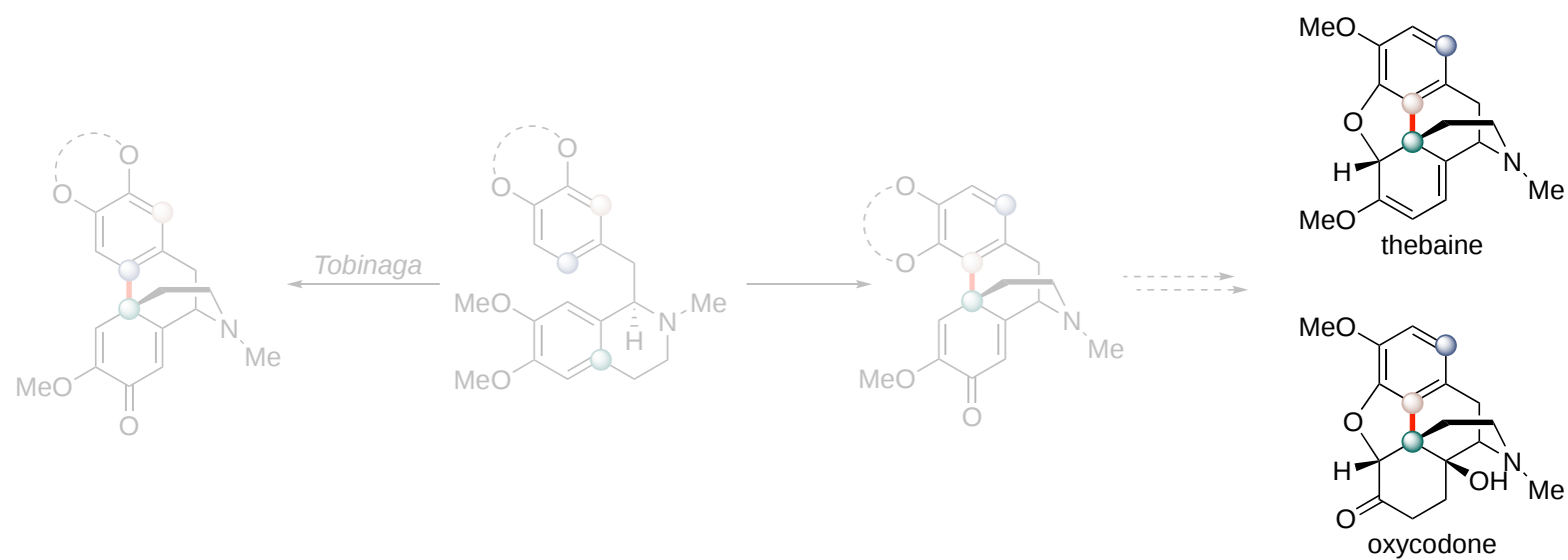


Arene Oxidation

Tobinaga, 1973¹

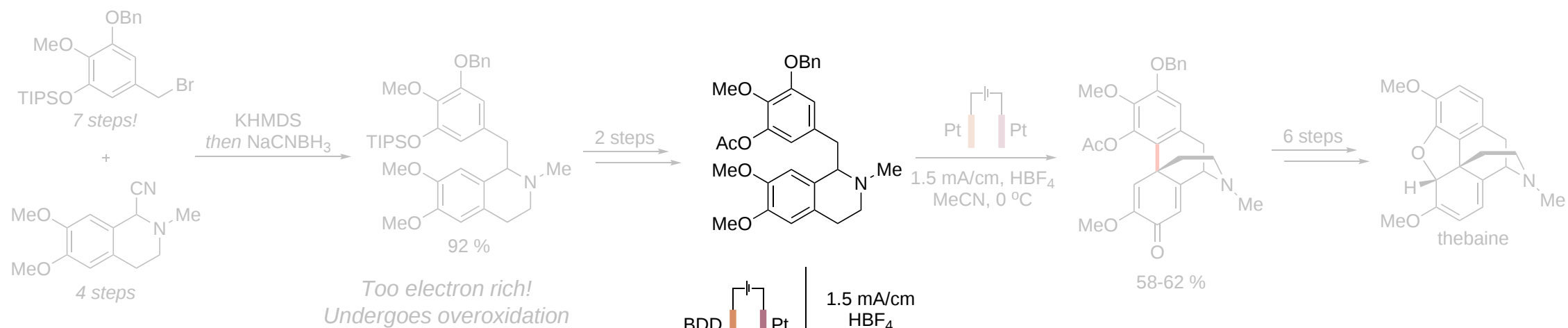


Arene Oxidation



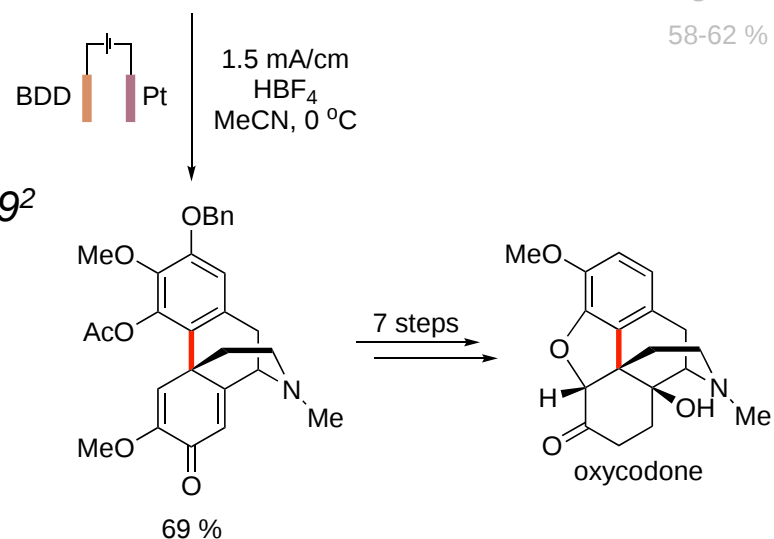
**Regioselectivity
difficult to override!**

Opatz, 2018¹



*Too electron rich!
Undergoes overoxidation*

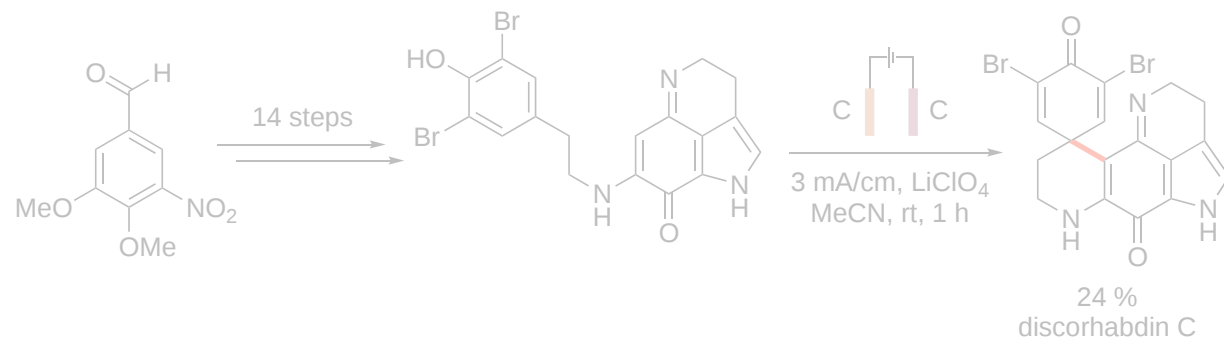
Opatz, 2019²



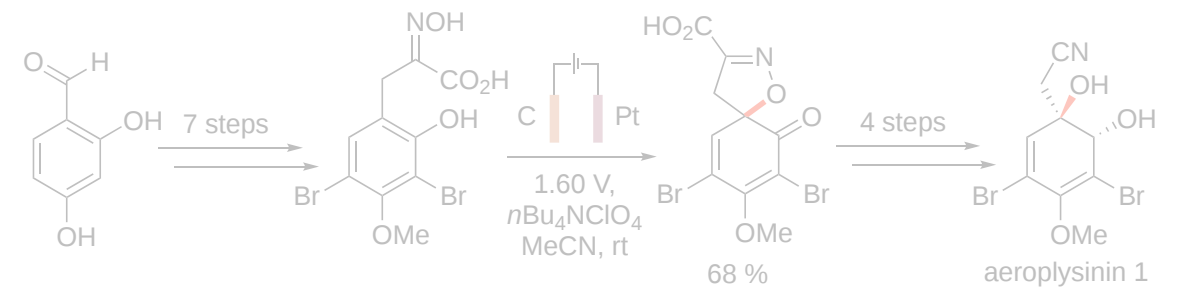
Arene Oxidation

Nishiyama

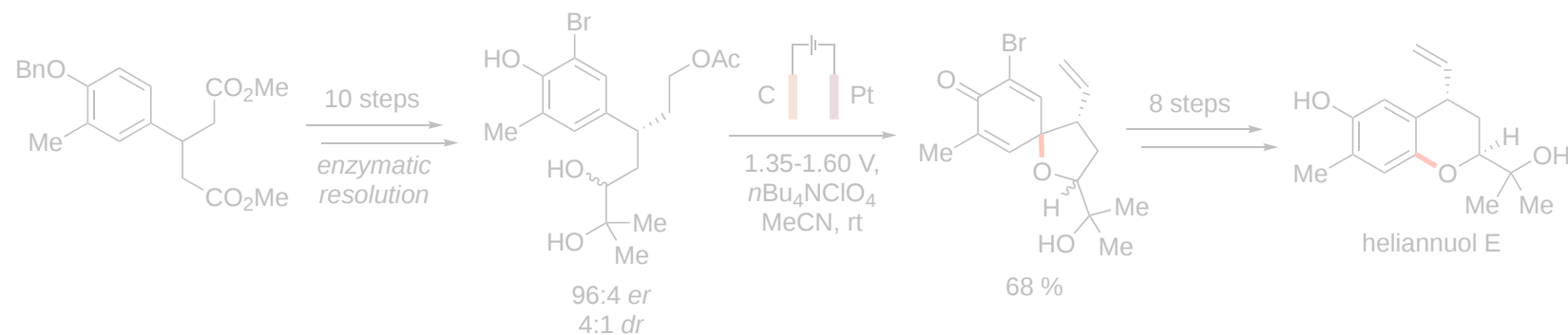
1994¹



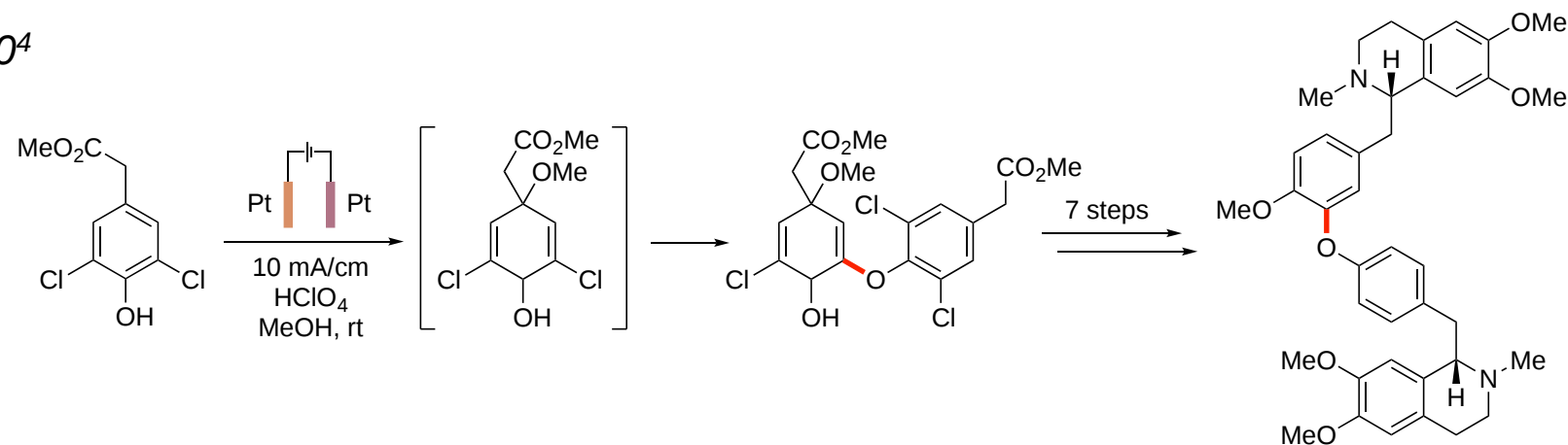
2003²



2003³



2010⁴



Arene Oxidation

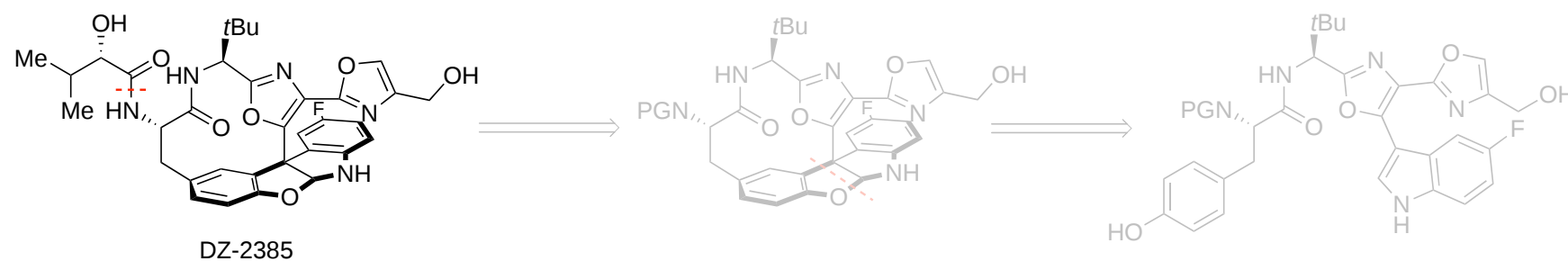
Chiba, 1998¹

DDQ as redox mediator:

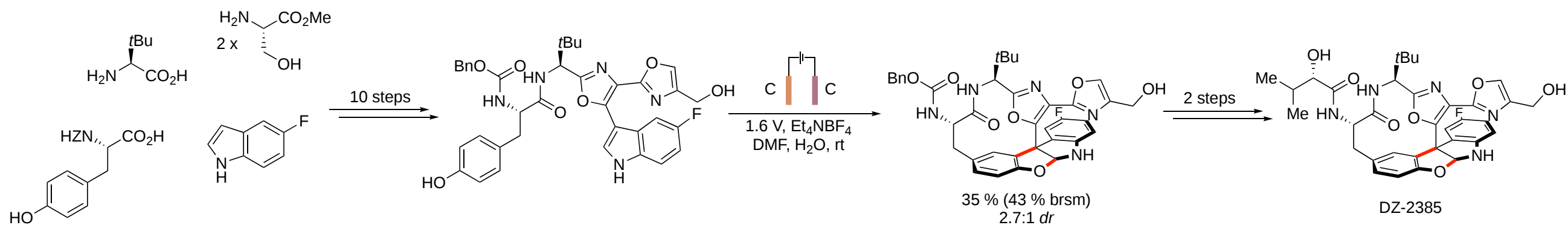
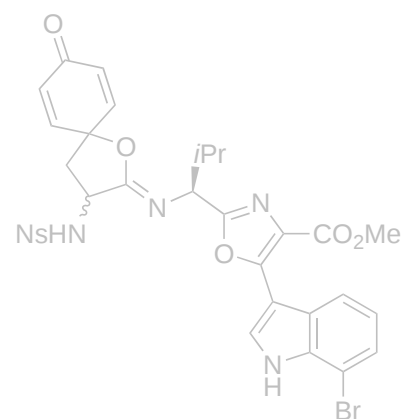
- Oxidises substrate
- Then reoxidised by anode

Arene Oxidation

Harran, 2015¹

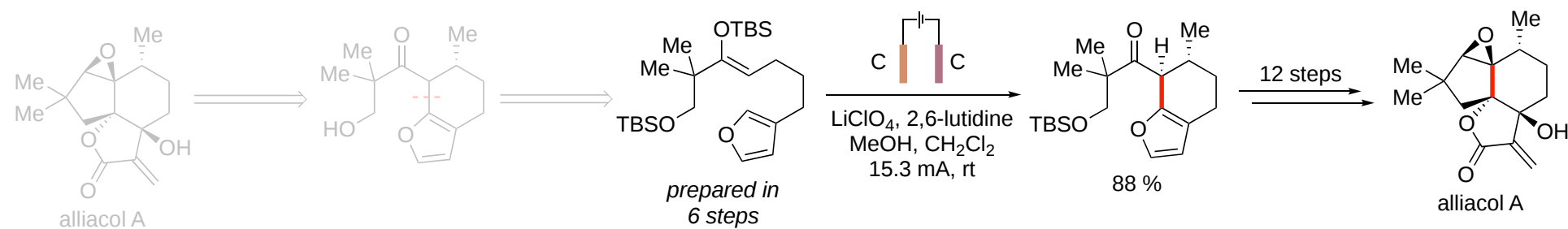


- Similar macrocyclisation achieved with PIDA
- Numerous byproducts: low yield, tricky purification

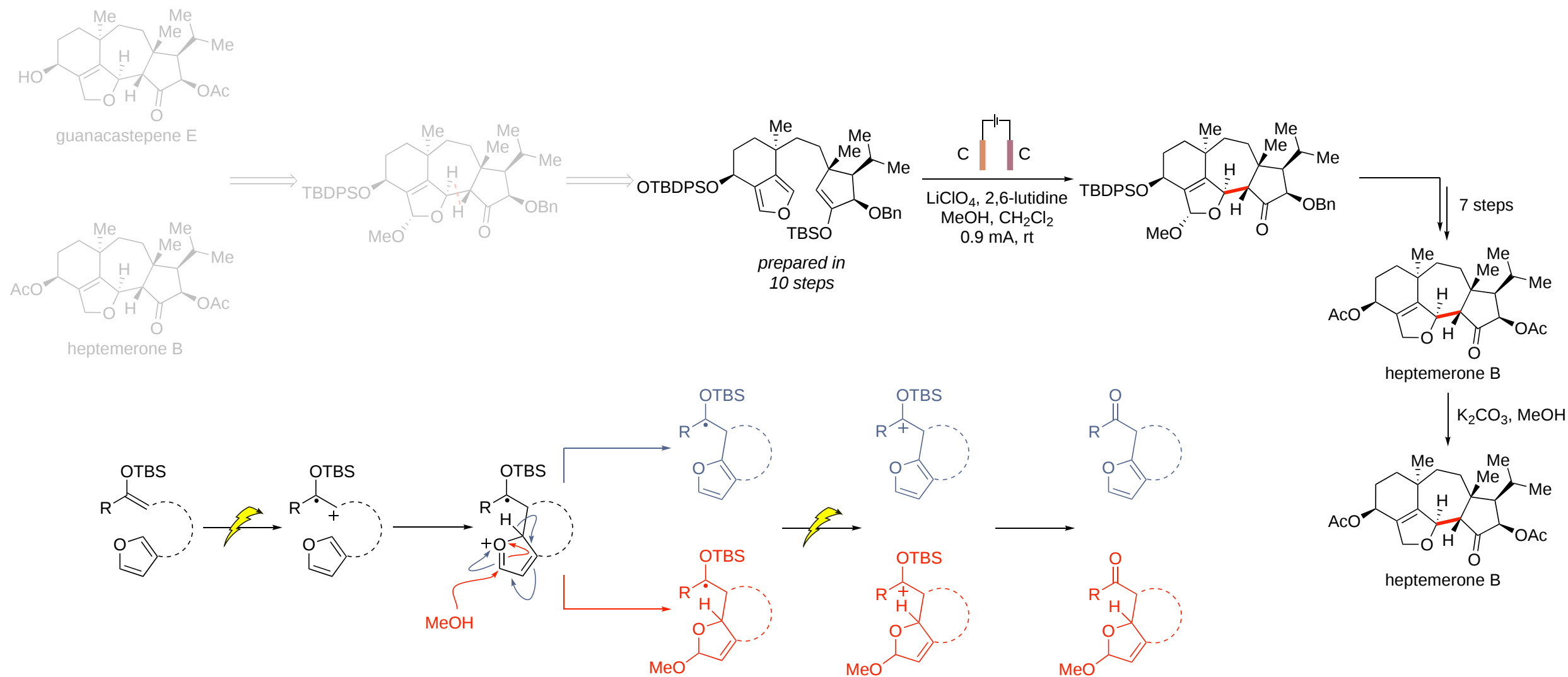


C=C Oxidation

Moeller, 2004¹

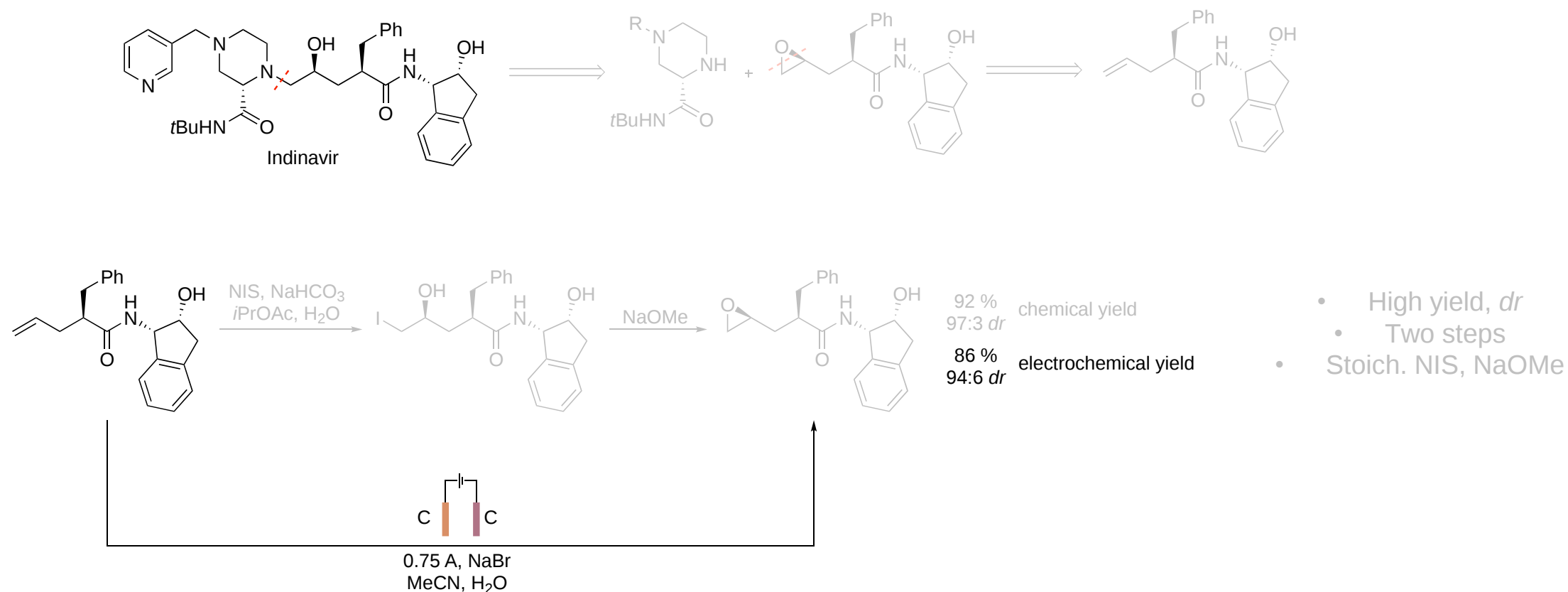


Trauner, 2006²

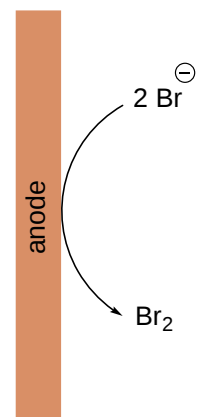


C=C Oxidation

Rossen (Merck), 1997¹

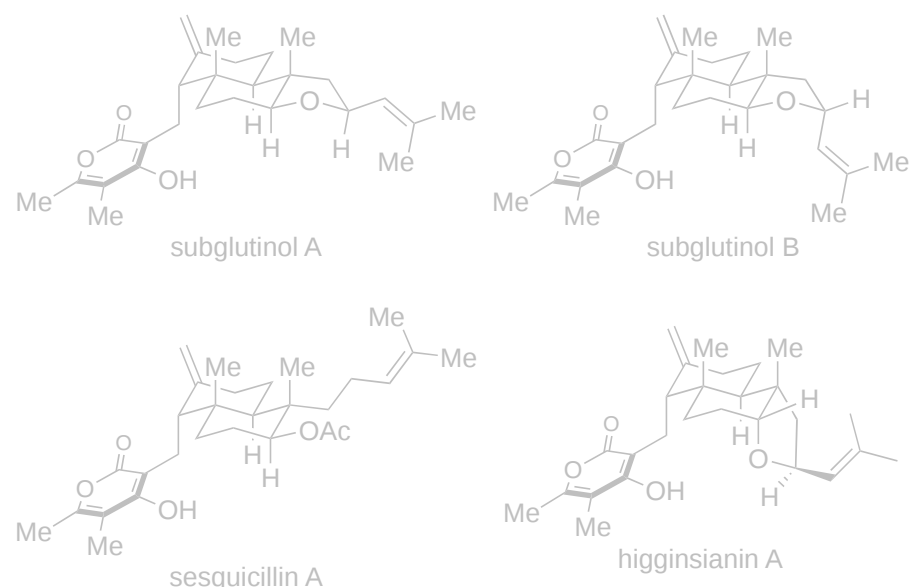


- High yield, *dr*
- Two steps
- Stoich. NIS, NaOMe

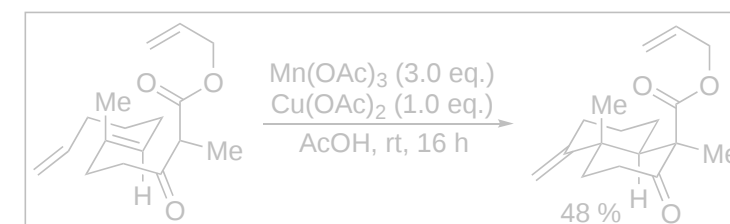


C(sp³)-H Oxidation

Baran, 2018¹



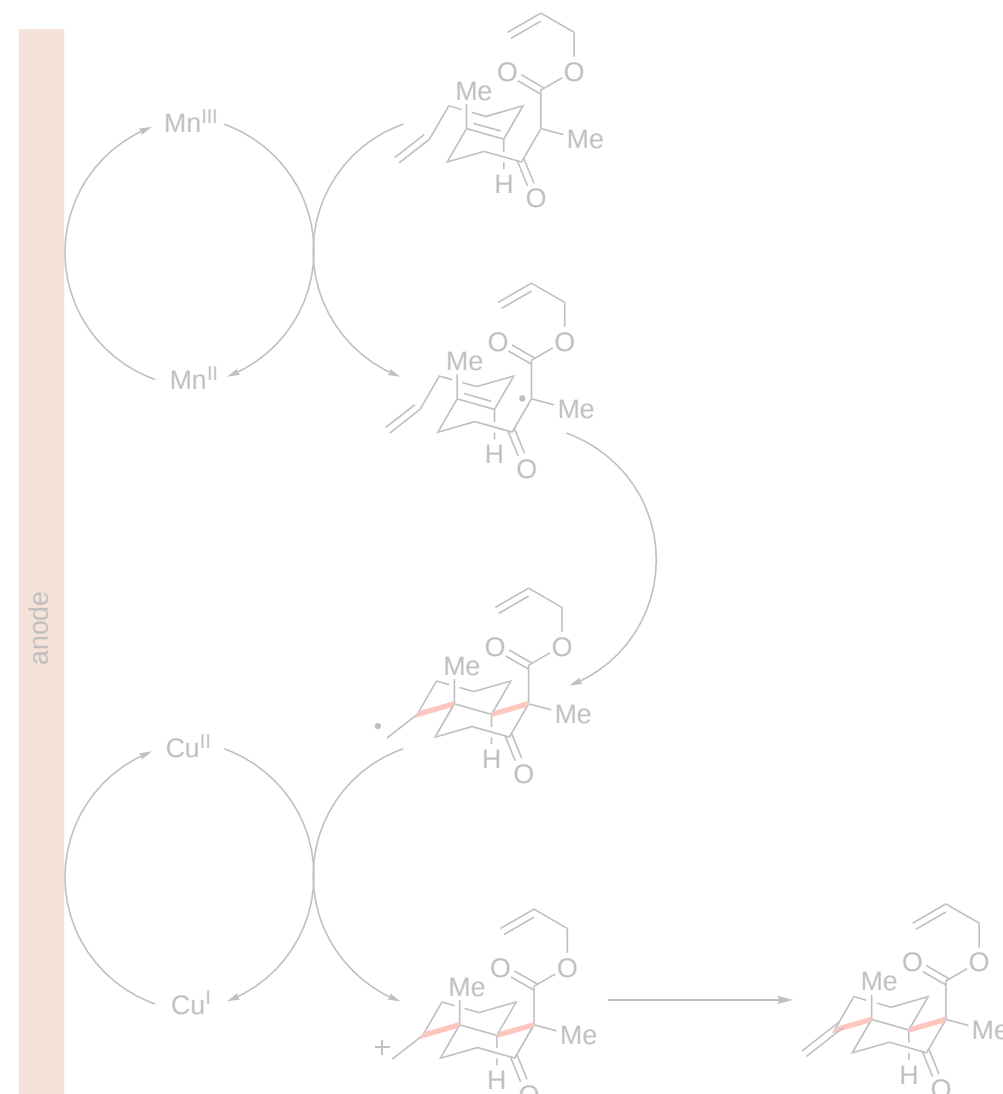
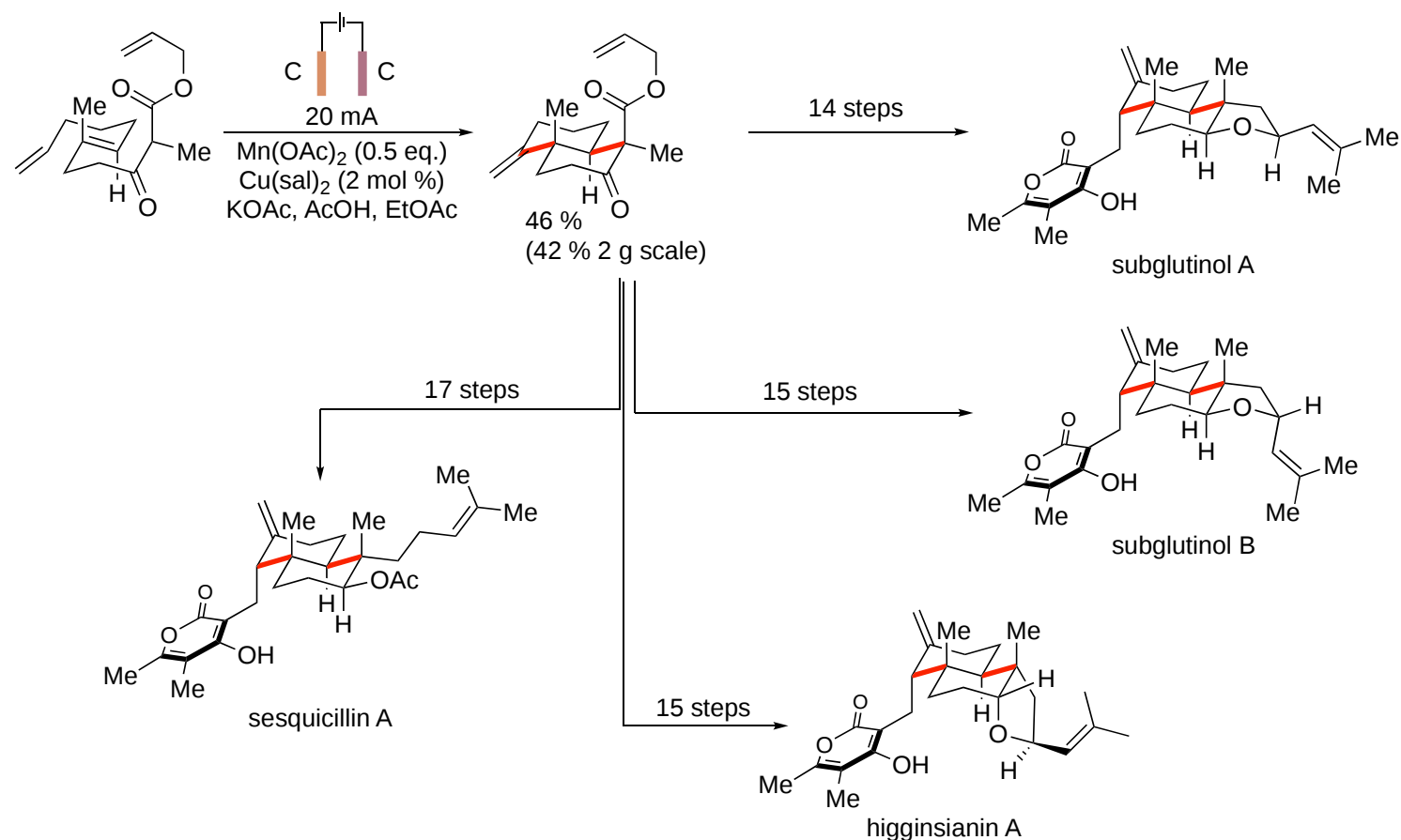
Radical polycyclisation:
-Well developed with
superstoichiometric Mn(III)
and up to 1.0 eq. Cu(II) salts



2 steps from
5-bromopent-1-ene

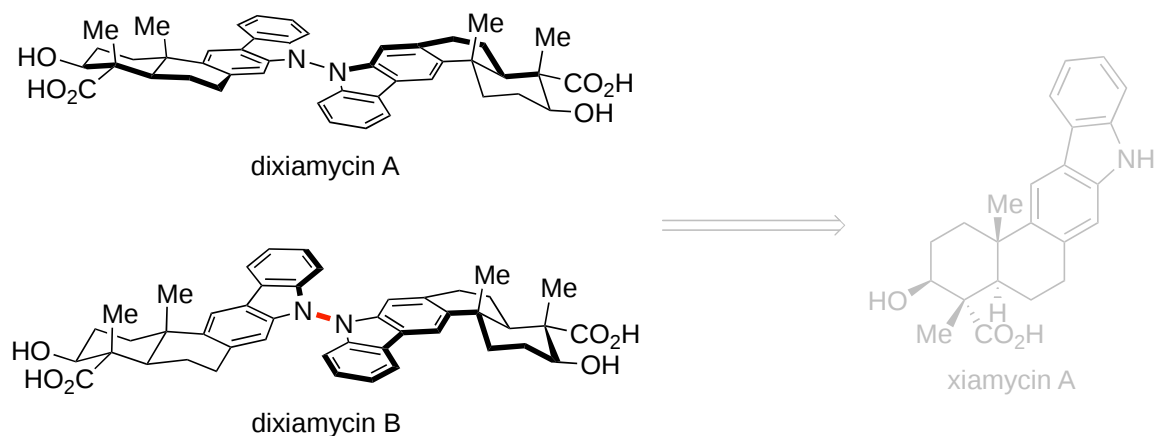
Improved atom-economy
with electrosynthesis?

split-cell setup!



N–H Oxidation

Baran, 2014¹



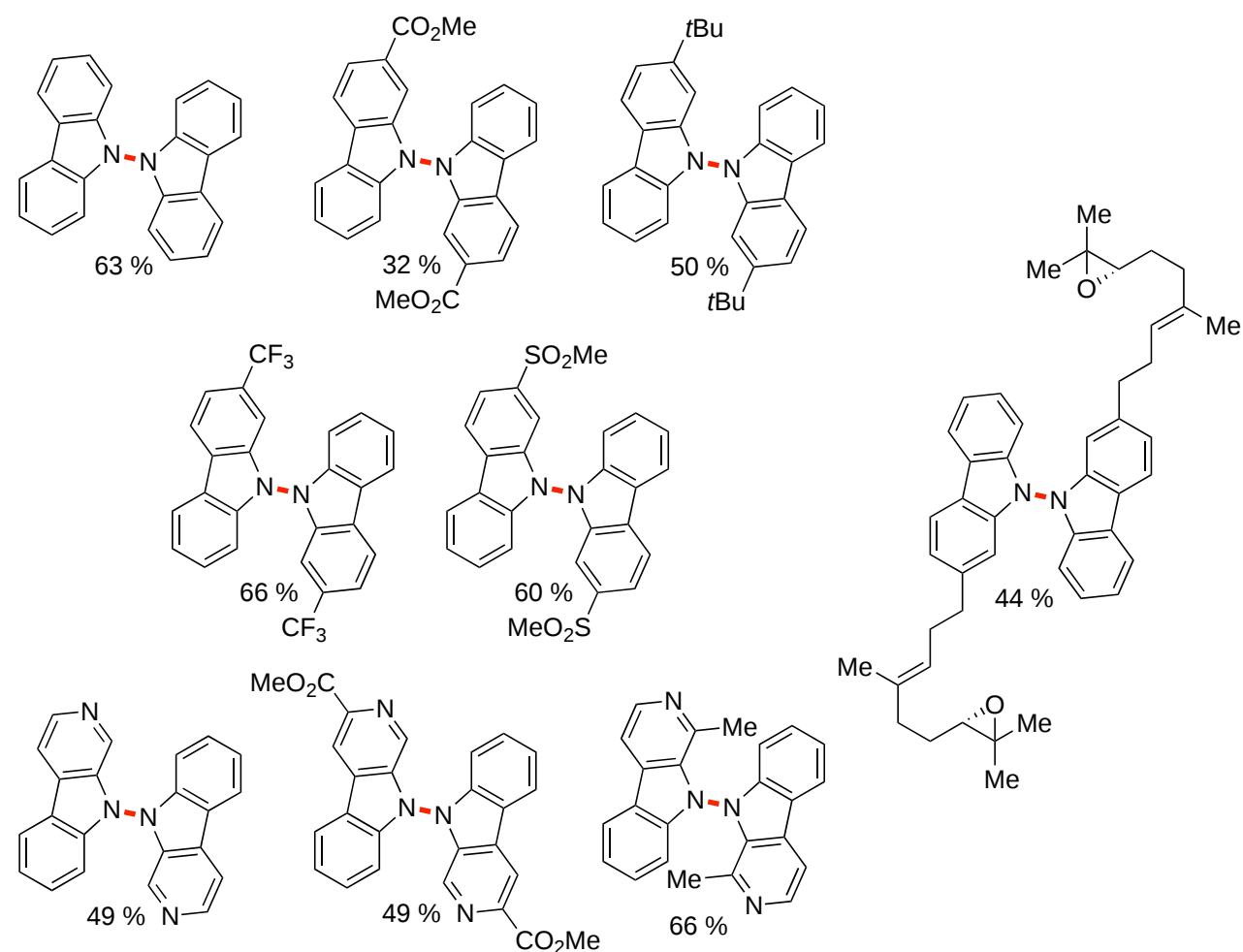
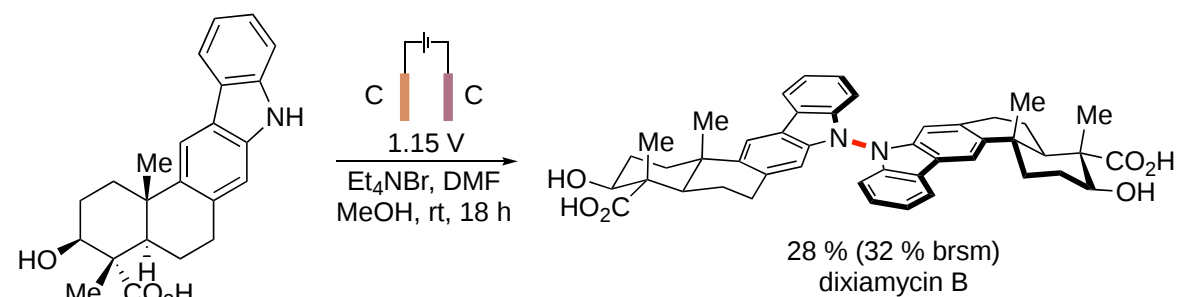
Chemical dimerization attempts

KMnO₄, acetone <20 %, decomp.

LDA, then [Cu] no reaction

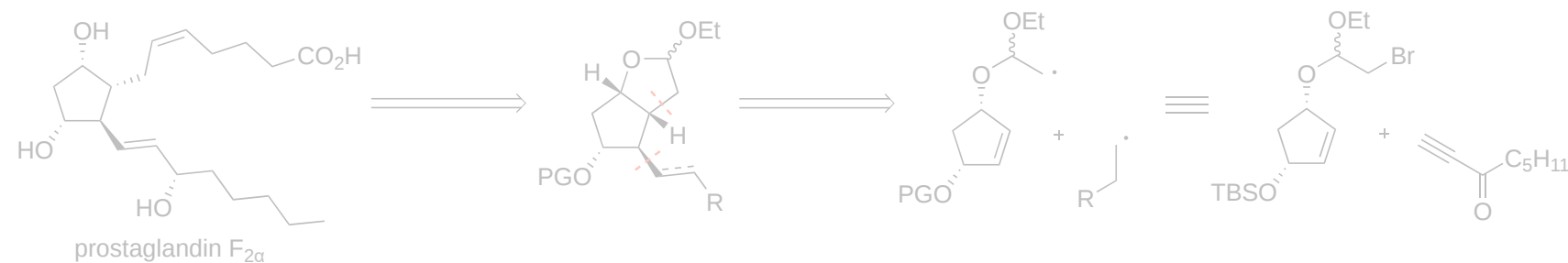
PIFA, CH₂Cl₂ no reaction

KOtBu, tBuOCl traces

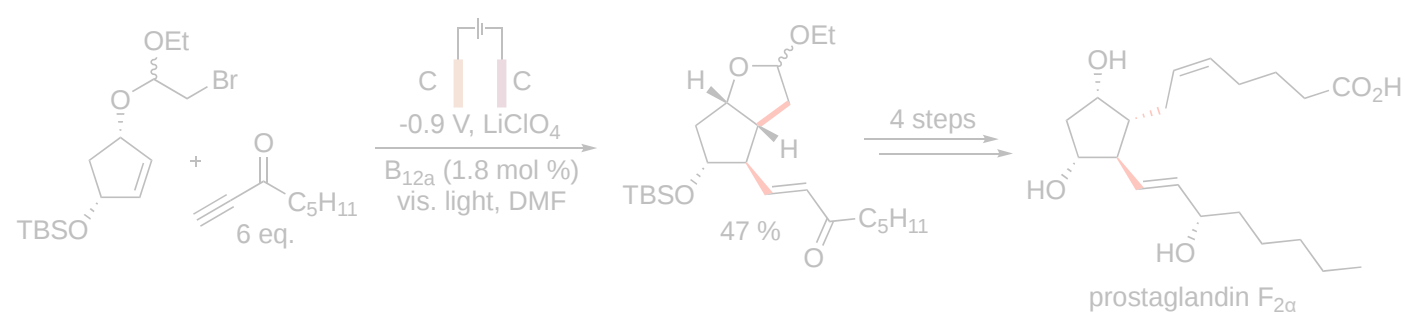


C–X Reduction

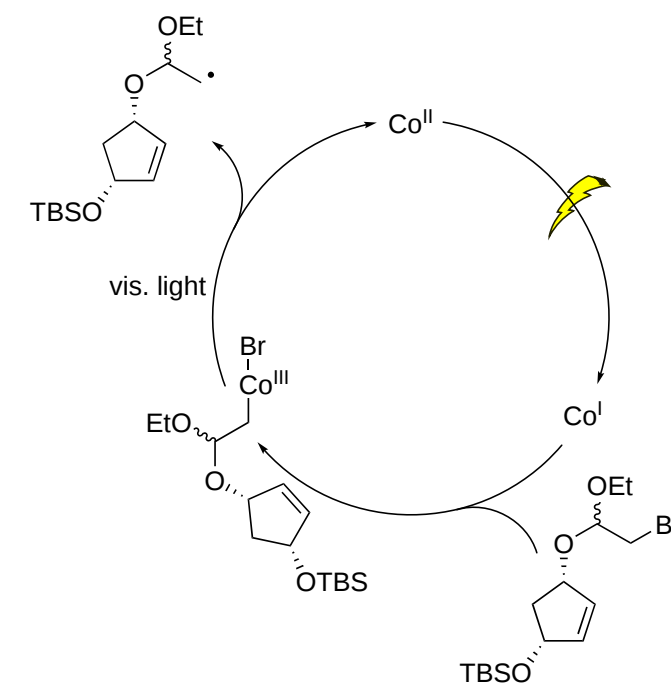
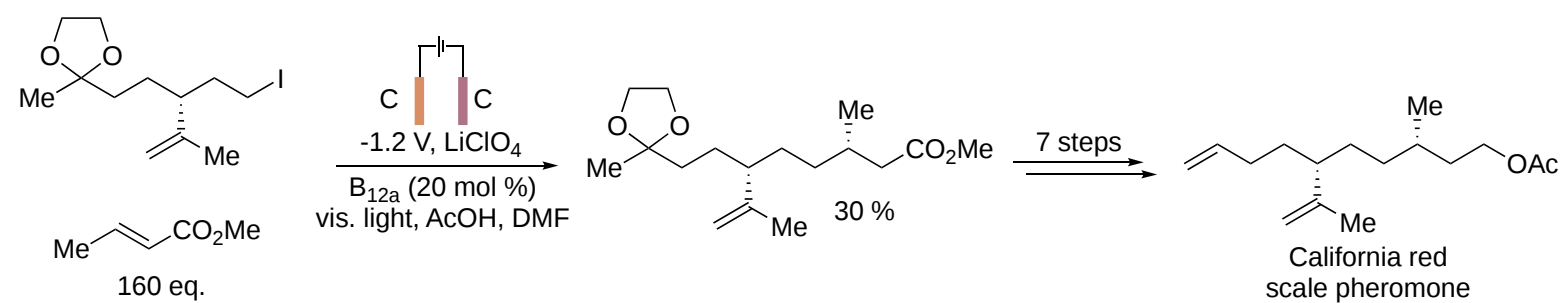
Scheffold, 1990¹



- Single e⁻ C–X reduction known
- Red. potentials 1.9–2.2 V



Scheffold, 1993¹



prepared in 6 steps

54 %

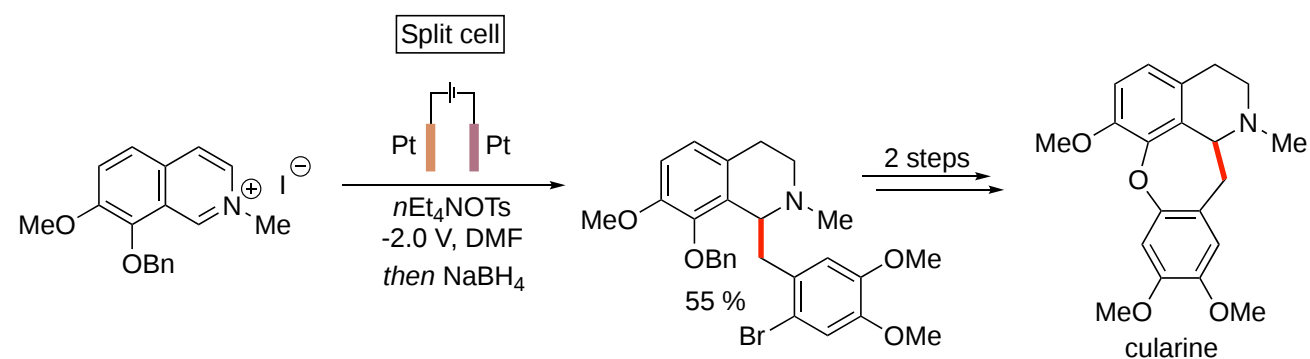
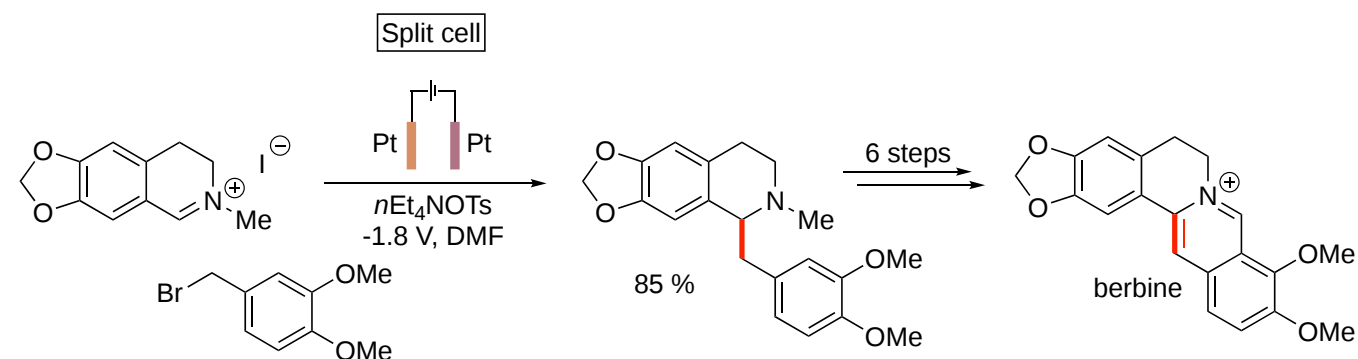
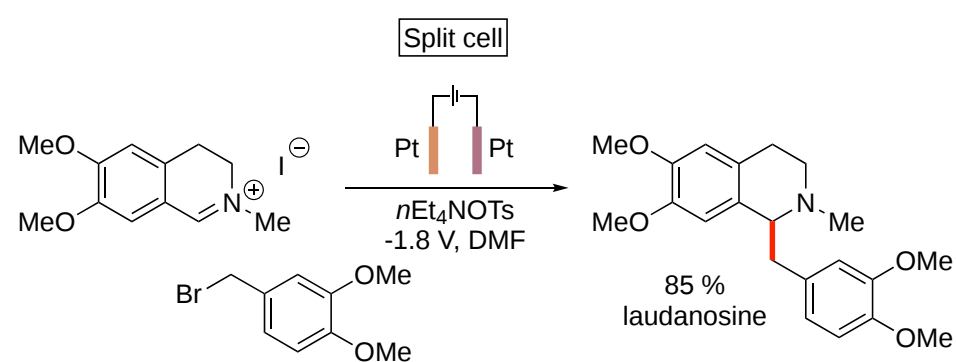
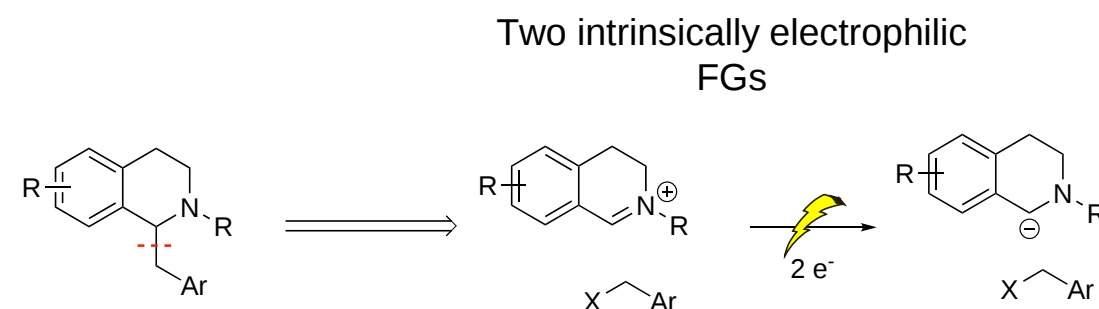
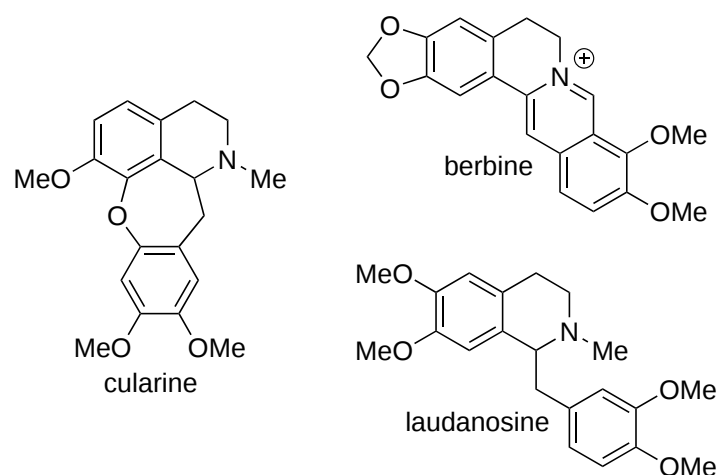
5 steps

valeranone

prepared in 2 steps
 68 %
 4 steps
 37 %
 3 steps
 capnellene

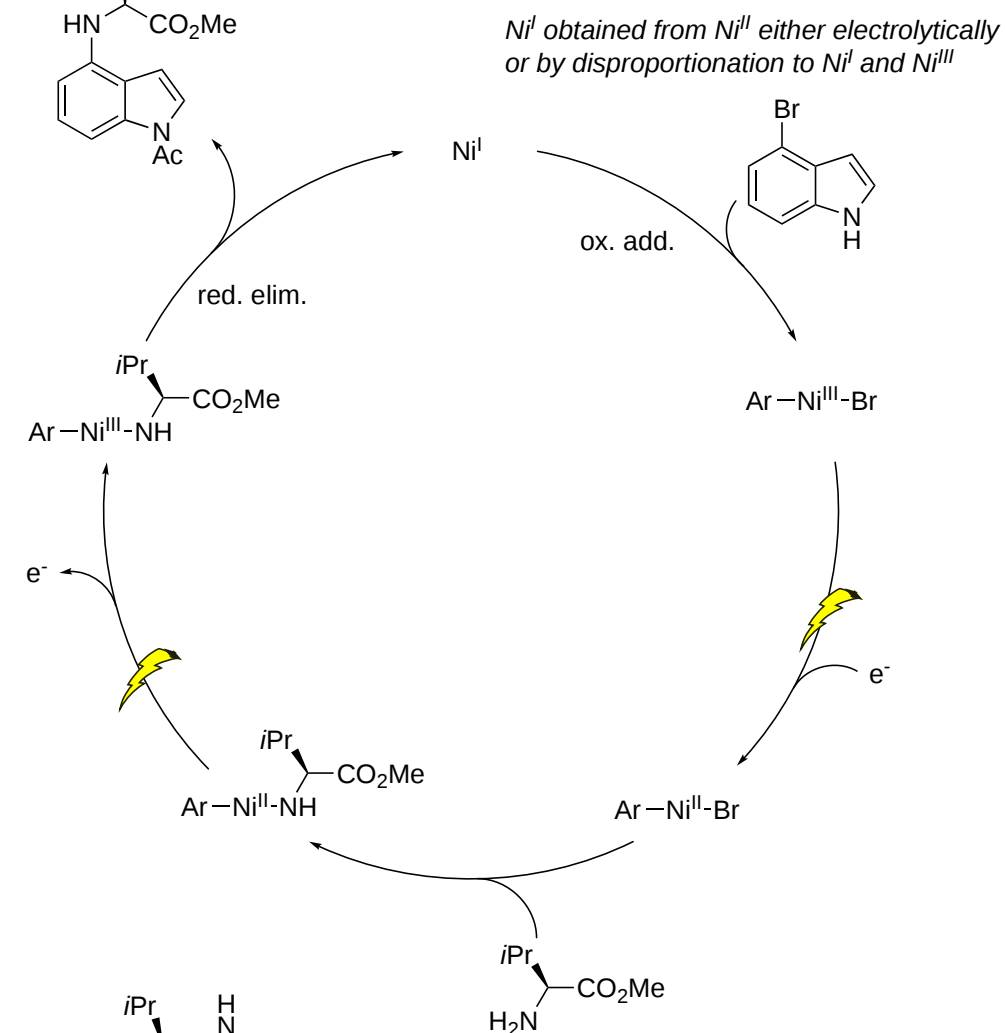
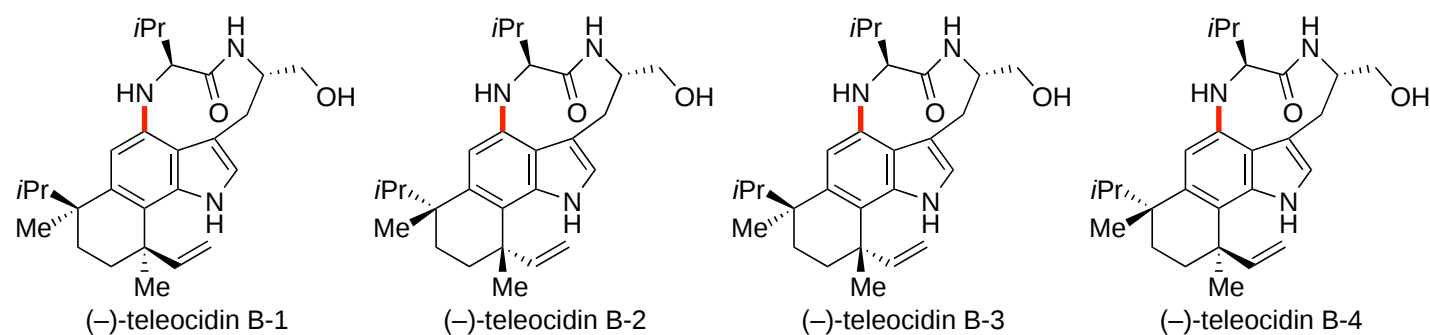
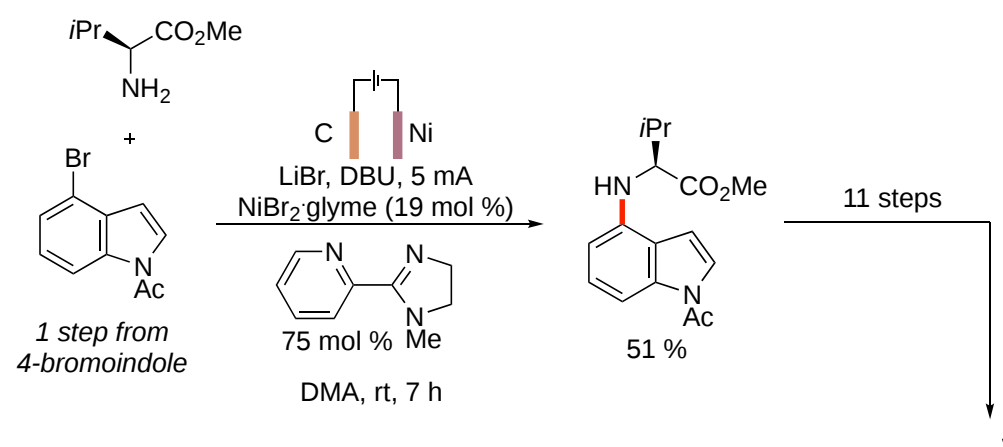
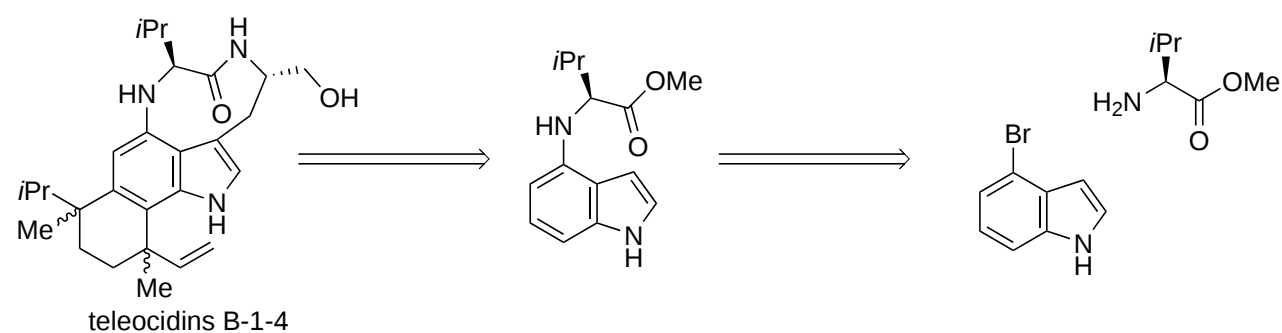
C=N Reduction

Shono, 1978-81¹⁻³

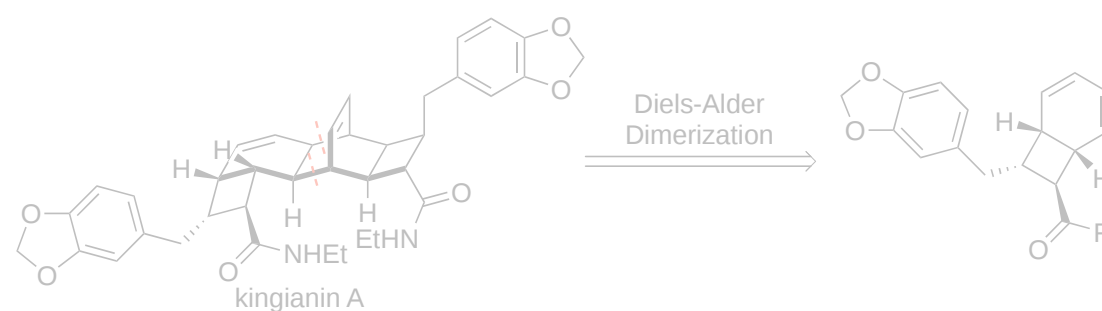


- 1) Shono *et al. Tet. Lett.* **1978**, 48, 4819
- 2) Shono *et al. Tet. Lett.* **1980**, 50, 3073
- 3) Shono *et al. Tet. Lett.* **1981**, 51, 2385

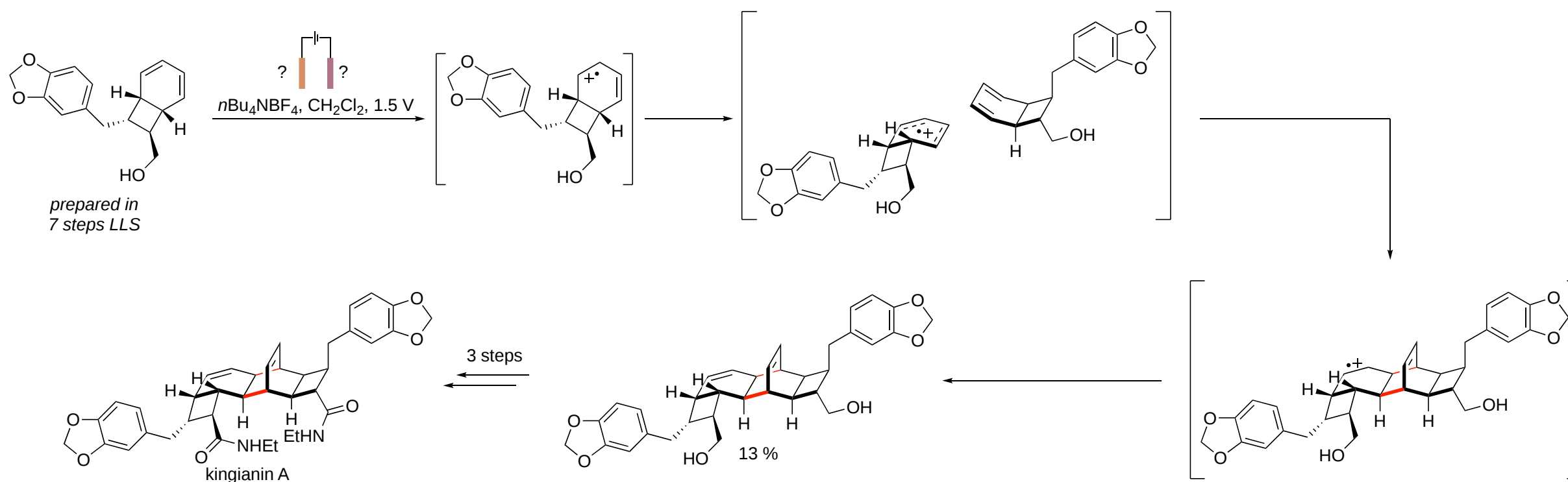
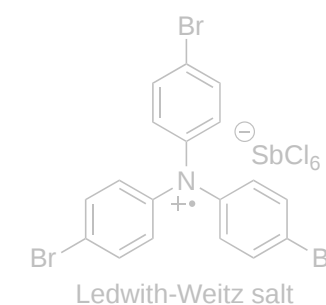
e-Amination

Baran, 2019¹

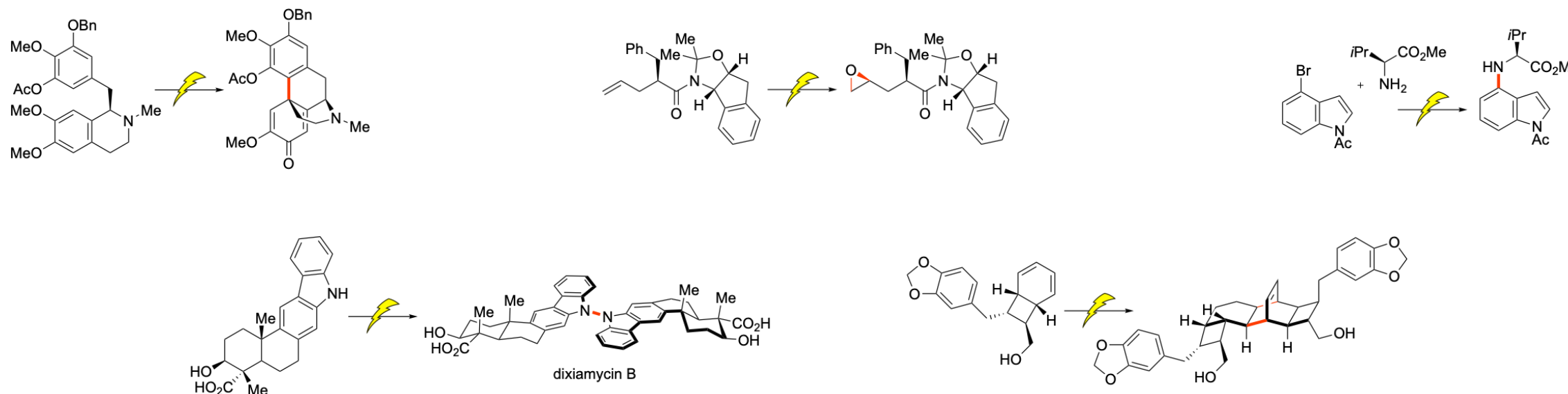
Radical Cation Diels-Alder Reaction

Moses, 2014¹

DA dimerization: proposed biosynthesis
R.C.D.A. previously achieved by Lawrence
et al. with Ledwith-Weitz salt



Wide Variety of Transformations



Conditions Tailored to the Substrate

- Redox potentials can be used to indicate potential reaction pathways
- Choice of materials for the electrodes, solvent and electrolyte

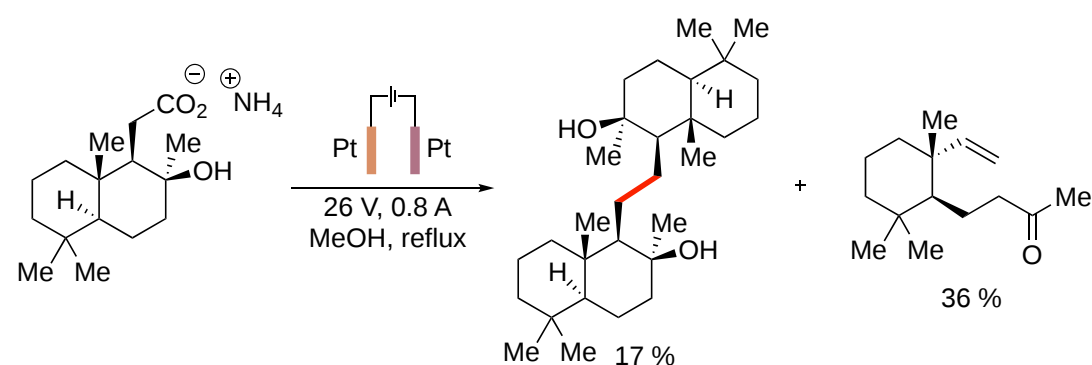
Stoichiometric Oxidants/Reductants Avoided

- Atom economic electron transfer

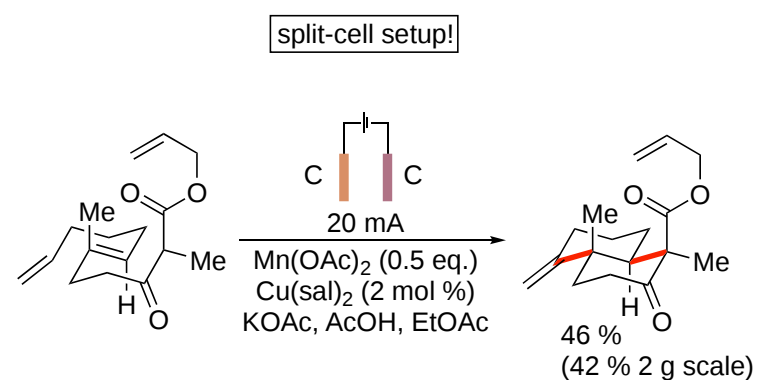
Further Promotion/Education Needed!

- Electrochemistry still remains a niche option

Explain the formation of the side-product:



Why is a split cell setup necessary for this transformation?



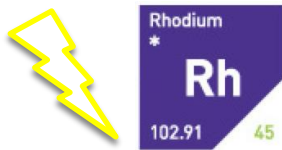


Enantioselective Radical Reactions via Transition Metal Catalysis

PhD within LCSO at EPFL
under the supervision of **Prof. Jérôme WASER**

Simonet-Davin Raphaël
11/05/2020 - Frontiers

Metals Considered



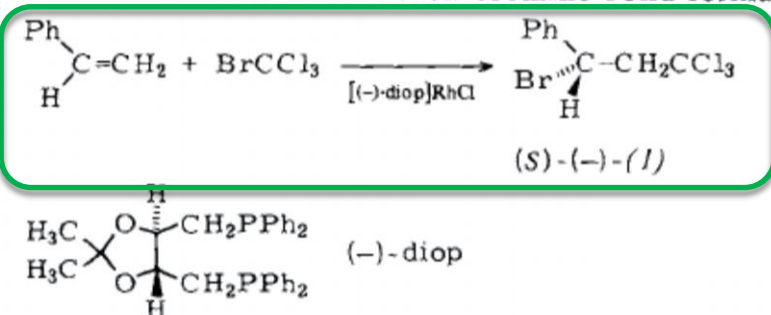
Hydrogen *** H 1.0081										Helium *** He 4.0032																											
Lithium * Li 6.9413		Beryllium * Be 9.0124												Boron * B 10.815		Carbon * C 12.016		Nitrogen *** N 14.017		Oxygen *** O 16.008		Fluorine *** F 19.009		Neon *** Ne 20.1810													
Sodium * Na 22.9911		Magnesium * Mg 24.3112												Aluminium * Al 26.9813		Silicon * Si 28.0914		Phosphorus * P 30.9715		Sulfur * S 32.0716		Chlorine *** Cl 35.4517		Argon *** Ar 39.9518													
Potassium * K 39.1019		Calcium * Ca 40.0820		Scandium * Sc 44.9621		Titanium * Ti 47.8722		Vanadium * V 50.9423		Chromium * Cr 52.0024		Manganese * Mn 54.9425		Iron * Fe 55.8426		Cobalt * Co 58.9327		Nickel * Ni 58.6928		Copper * Cu 63.5529		Zinc * Zn 65.3930		Gallium * Ga 69.7231		Germanium * Ge 72.6332		Arsenic * As 74.9233		Selenium * Se 78.9634		Bromine ** Br 79.9035		Krypton *** Kr 83.8036			
Rubidium * Rb 85.4737		Strontium * Sr 87.6238		Yttrium * Y 88.9139		Zirconium * Zr 91.2240		Niobium * Nb 92.9141		Molybdenum * Mo 95.9442		Technetium * Tc [98]43		Ruthenium * Ru 101.0744		Rhodium * Rh 102.9145		Palladium * Pd 106.4246		Silver * Ag 107.8747		Cadmium * Cd 112.4148		Indium * In 114.8249		Tin * Sn 118.7150		Antimony * Sb 121.7651		Tellurium * Te 127.6052		Iodine * I 126.9053		Xenon *** Xe 131.2954			
Caesium * Cs 132.9155		Barium * Ba 137.3356		LANTHANIDES ▼		Hafnium * Hf 178.4972		Tantalum * Ta 180.9573		Tungsten * W 183.8474		Rhenium * Re 186.2175		Osmium * Os 190.2376		Iridium * Ir 192.2277		Platinum * Pt 195.0878		Gold * Au 196.9779		Mercury ** Hg 200.5980		Thallium * Tl 204.3881		Lead * Pb 207.282		Bismuth * Bi 208.9883		Polonium * Po [209]84		Astatine * At [210]85		Radon *** Rn [222]86			
Francium * Fr [223]87		Radium * Ra [226]88		ACTINIDES ▼		Rutherfordium **** Rf [267]104		Dubnium **** Db [268]105		Seaborgium **** Sg [269]106		Bohrium **** Bh [270]107		Hassium **** Hs [269]108		Meitnerium **** Mt [278]109		Darmstadtium **** Ds [281]110		Roentgenium **** Rg [281]111		Copernicium **** Cn [285]112		Ununtrium **** Uut [286]113		Flerovium **** Fl [289]114		Ununpentium **** Uup [289]115		Livermorium **** Lv [293]116		Ununseptium **** Uus [294]117		Oganesson *** Og [294]118			
Lanthanum * La 138.9157		Cerium * Ce 140.1258		Praseodymium * Pr 140.9159		Neodymium * Nd 144.2460		Promethium * Pm [145]61		Samarium * Sm 150.3662		Europium * Eu 151.9663		Gadolinium * Gd 157.2564		Terbium * Tb 158.9365		Dysprosium * Dy 162.5066		Holmium * Ho 164.9367		Erbium * Er 167.2668		Thulium * Tm 168.9369		Ytterbium * Yb 173.0470		Lutetium * Lu 174.9771									
Actinium * Ac [227]89		Thorium * Th 232.0490		Protactinium * Pa 231.0491		Uranium * U 238.0392		Neptunium * Np [237]93		Plutonium * Pu [244]94		Americium * Am [243]95		Curium * Cm [247]96		Berkelium * Bk [247]97		Californium * Cf [251]98		Einsteinium * Es [252]99		Fermium * Fm [257]100		Mendelevium * Md [258]101		Nobelium * No [259]102		Lawrencium * Lr [262]103									

1981, Osaka University, Japan

[(−)-diop]RhCl—Catalyzed Asymmetric Addition of Bromotrichloromethane to Styrene

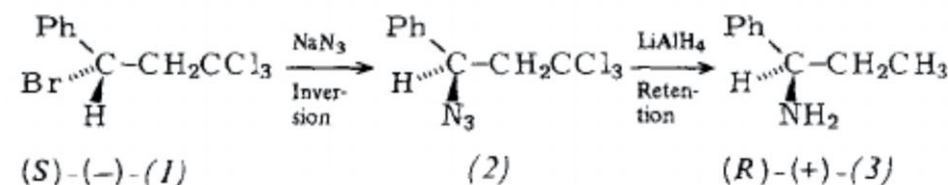
By Shinji Murai, Ryoji Sugise, and Noboru Sonoda^[1]

Although a number of asymmetric reactions catalyzed by transition metal complexes to form C—H, C—C, C—Si, and C—O bonds with creation of chirality have been reported^[1], no reactions of this type which lead to the formation of chiral carbon-halogen bonds have been reported^[2] to the best of our knowledge. We describe here the first example of an asymmetric reaction, catalyzed by a chiral transition metal complex, in which the chiral center is formed as a result of carbon-bromine bond formation.

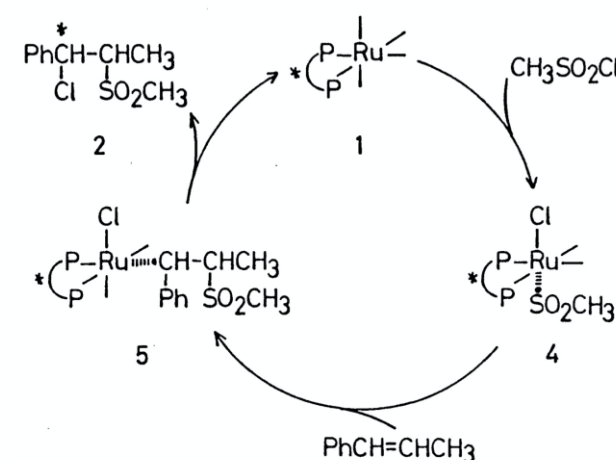
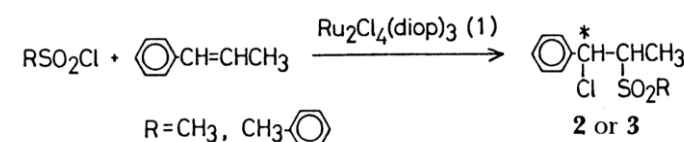


The reaction of bromotrichloromethane with styrene in 2 : 1 ethanol-benzene, in the presence of an optically active phosphane-rhodium complex [(−)-diop]RhCl^[3] (0.30 mmol) at 80 °C for 18 h, gave the 1 : 1-adduct (1) in 26% yield. The adduct (1) showed an optical rotation of $[\alpha]_D = -22.5$ ($c = 10.7$, C_6H_6) which corresponded to > 32% enantiomeric excess and (S)-configuration.

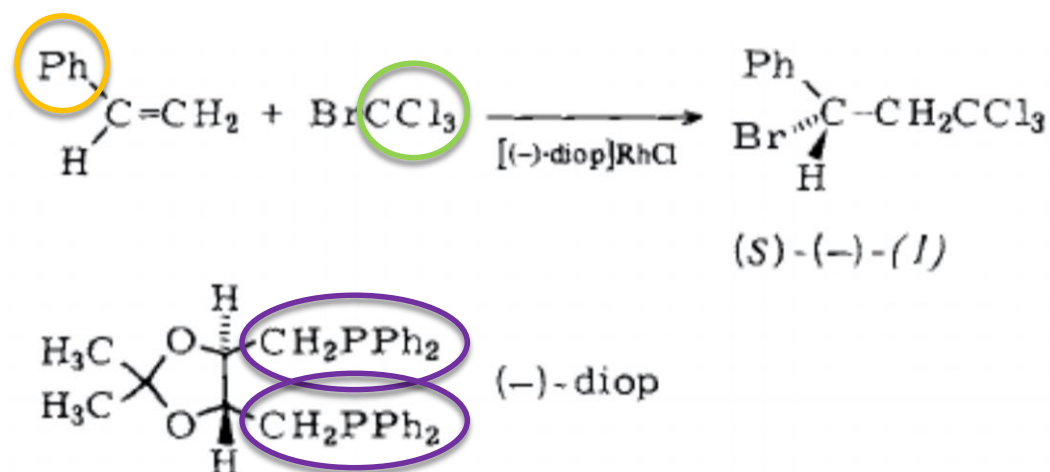
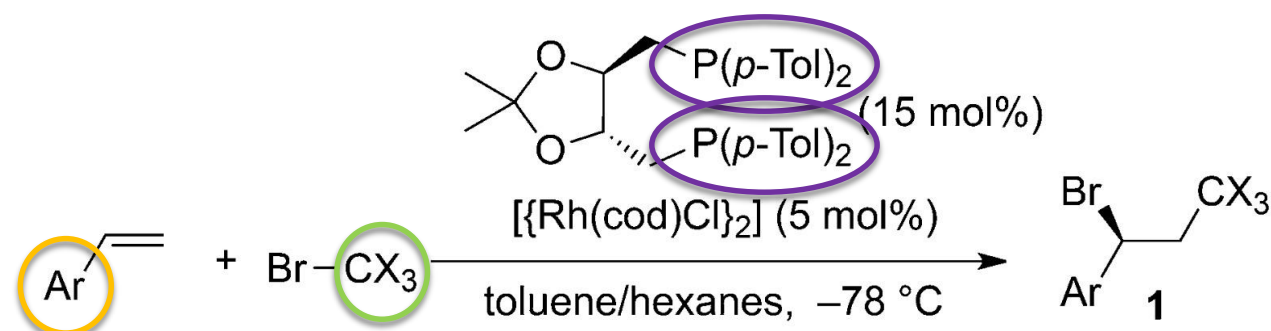
The enantiomeric excess and the absolute configuration were determined in the following way using a sample of (1) with $[\alpha]_D = -11.3^\circ$ ($c = 10.3$, C_6H_6) obtained in a separate run. This sample was treated with an excess of NaN₃ to give the azide (2), which was not isolated but directly reduced with LiAlH₄ to (R)-(+)-1-phenyl-1-propylamine (3) which showed $[\alpha]_D = +3.43$ ($c = 8.4$, C_6H_6) and corresponded to an optical purity of 16%^[4]. Thus, the adduct (S)-(−)-(1) with $[\alpha]_D = -22.5$ corresponds to > 32% enantiomeric excess. It should be noted that the optical purity must be much higher than 32%, since S_N2 displacement of (1) with NaN₃ may involve partial racemization^[5].



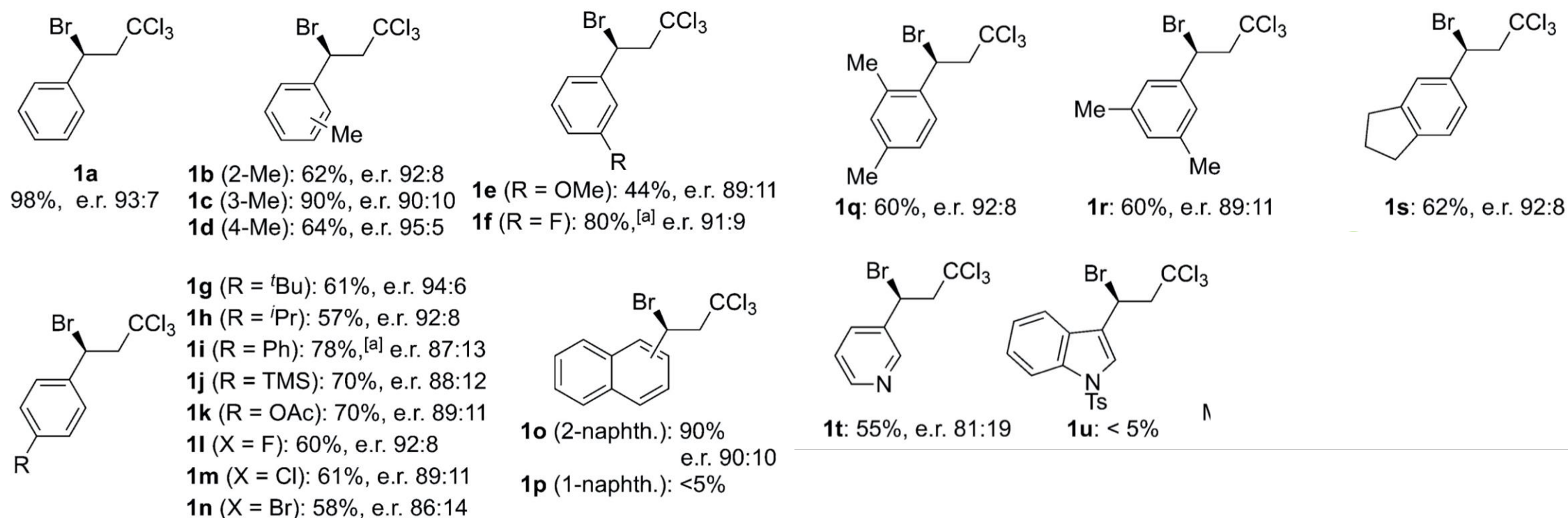
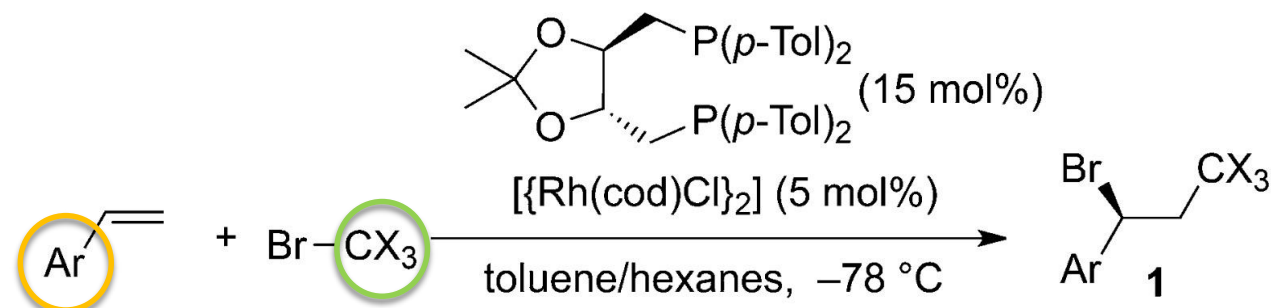
Since various transition metal catalysts for addition of organic halides to olefins are known^[6] and a variety of chiral ligands are now available^[1], the present result opens up new possibilities for asymmetric synthesis.



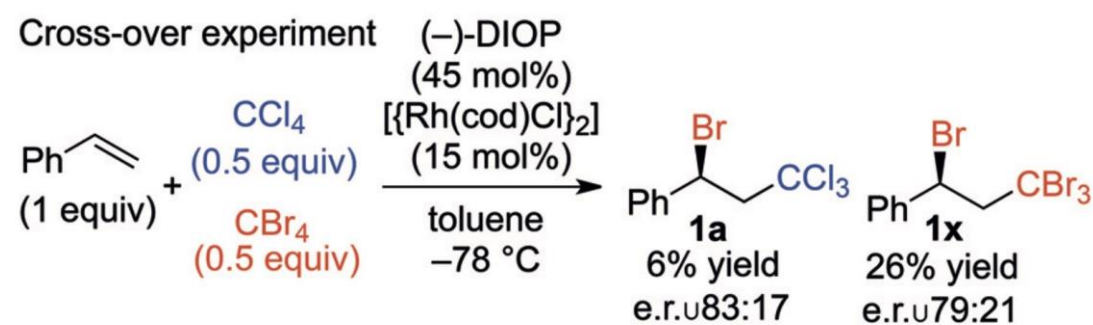
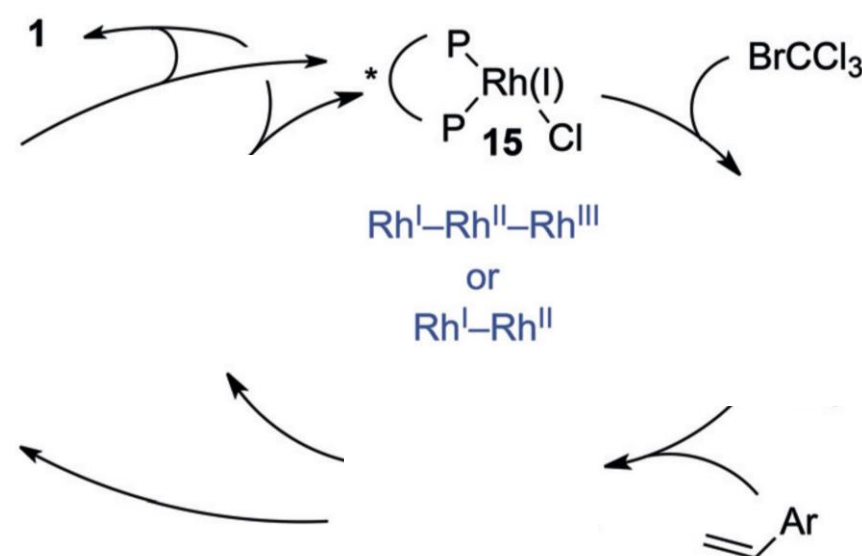
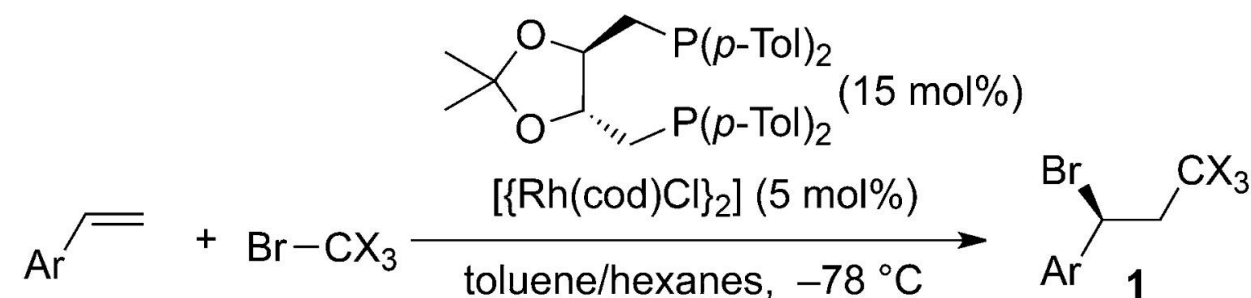
Addition of CX₄ Reagents to Olefins



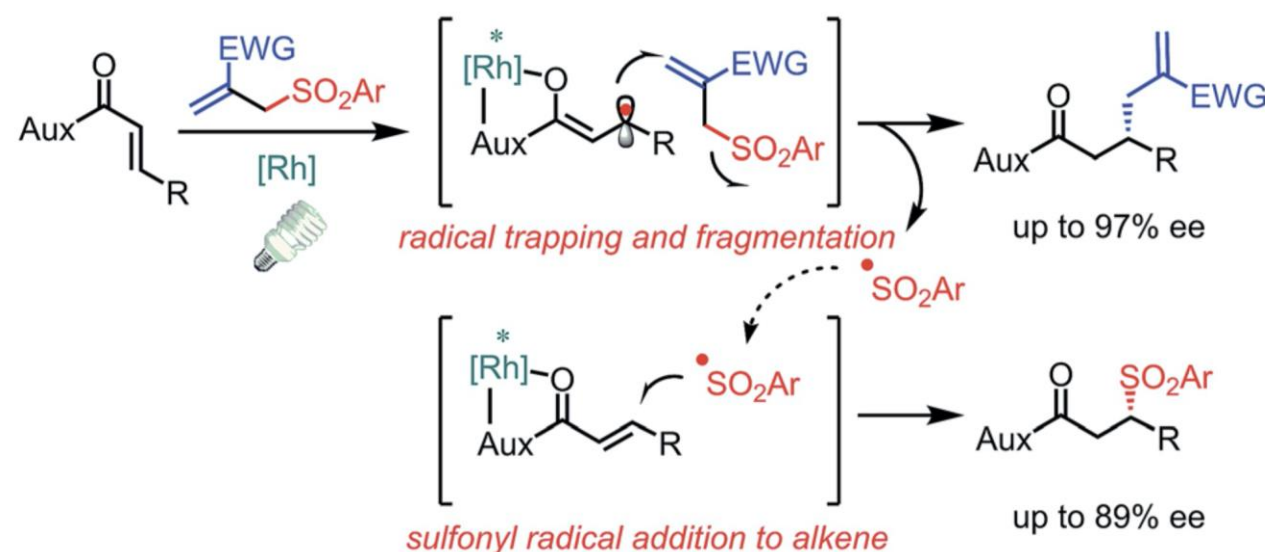
Addition of CX₄ Reagents to Olefins



Addition of CX₄ Reagents to Olefins



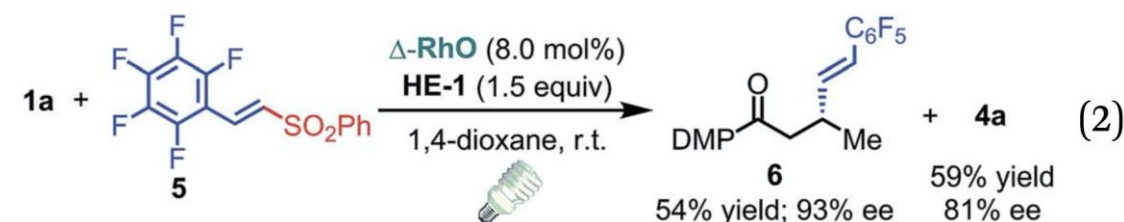
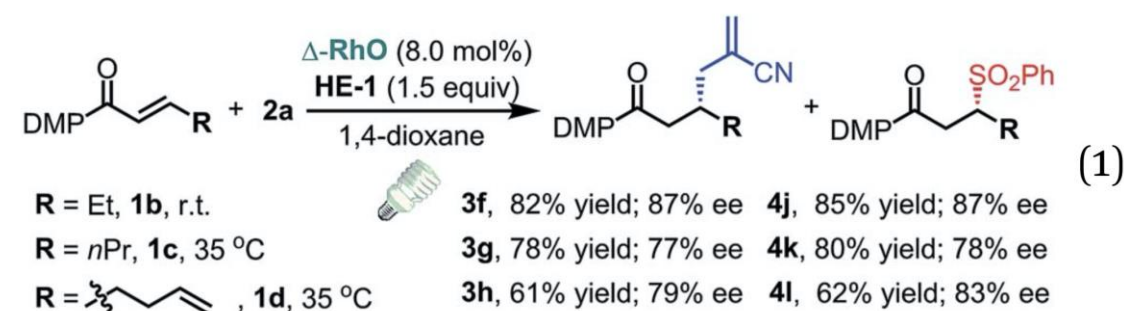
One Catalyst – Two Processes



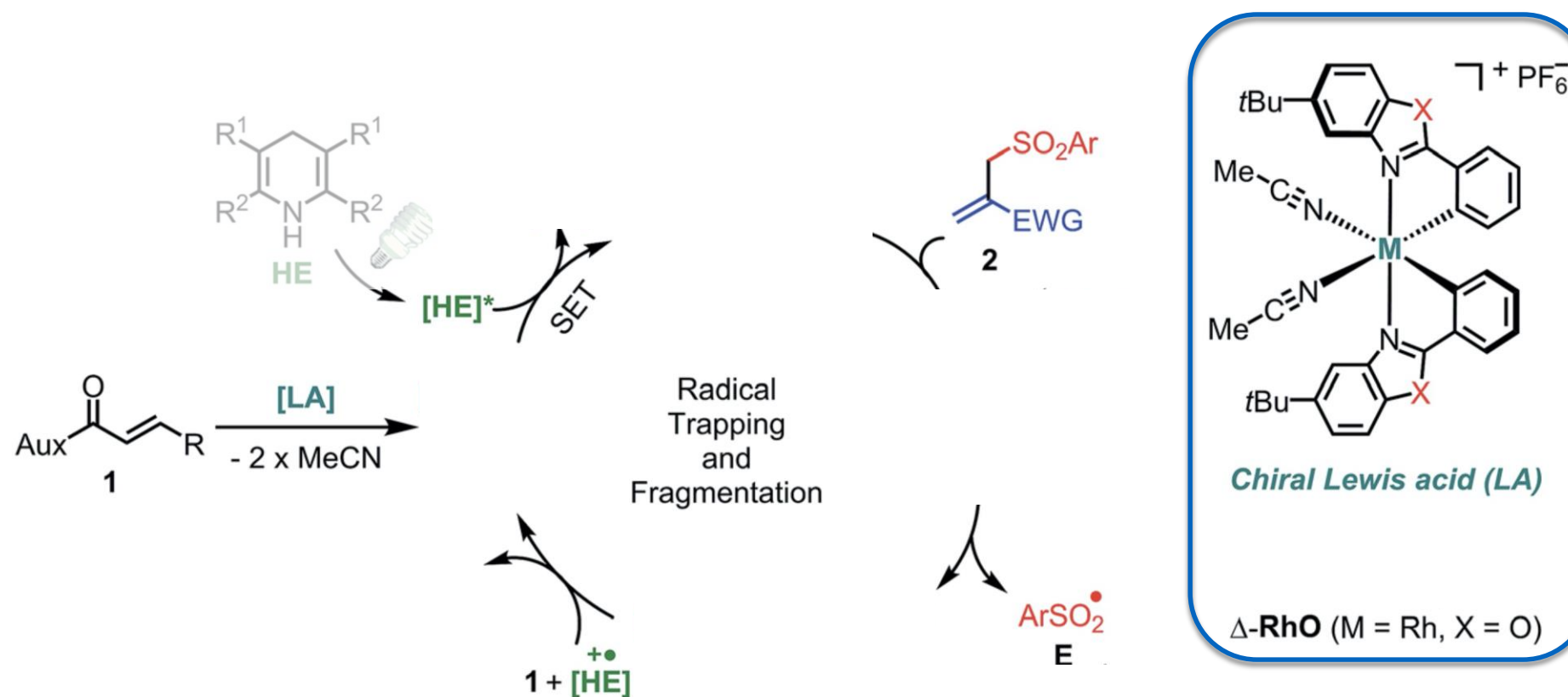
Entry	EWG	Ar	3, Yield ^b , ee ^c	4, Yield ^b , ee ^c
1	CN	C ₆ H ₅	3a , 85%, 96% ee	4a , 92%, 85% ee
2	CN	4-MeC ₆ H ₄	3a , 68%, 96% ee	4b , 70%, 79% ee
3	CN	4-BrC ₆ H ₄	3a , 81%, 97% ee	4c , 88%, 80% ee
4	CN	4-CF ₃ C ₆ H ₄	3a , 78%, 95% ee	4d , 78%, 76% ee
5	CN	2-MeC ₆ H ₄	3a , 71%, 95% ee	4e , 72%, 86% ee
6 ^d	CN	2,4,6-Me ₃ C ₆ H ₂	3a , 57%, 94% ee	4f , 60%, 89% ee
7 ^d	CN	2-Naphthyl	3a , 82%, 94% ee	4g , 88%, 83% ee
8 ^d	CN	1-Naphthyl	3a , 78%, 91% ee	4h , 84%, 80% ee
9	COOEt	C ₆ H ₅	3b , 65%, 94% ee	4a , 68%, 84% ee
10 ^d	COOEt	4-MeOC ₆ H ₄	3b , 65%, 92% ee	4i , 63%, 81% ee
11 ^d		C ₆ H ₅	3c , 60%, 92% ee	4a , 69%, 82% ee
12 ^d		C ₆ H ₅	3d , 62%, 92% ee	4a , 72%, 83% ee
13 ^d		C ₆ H ₅	3e , 73%, 92% ee	4a , 78%, 82% ee

^a Reaction conditions: **1a** (0.20 mmol), **2** (0.10 mmol), Δ -RhO (0.008 mmol) and **HE-1** (0.15 mmol) in 1,4-dioxane (1.0 mL) were stirred at room temperature and irradiated with a 21 W CFL. ^b Isolated yields.

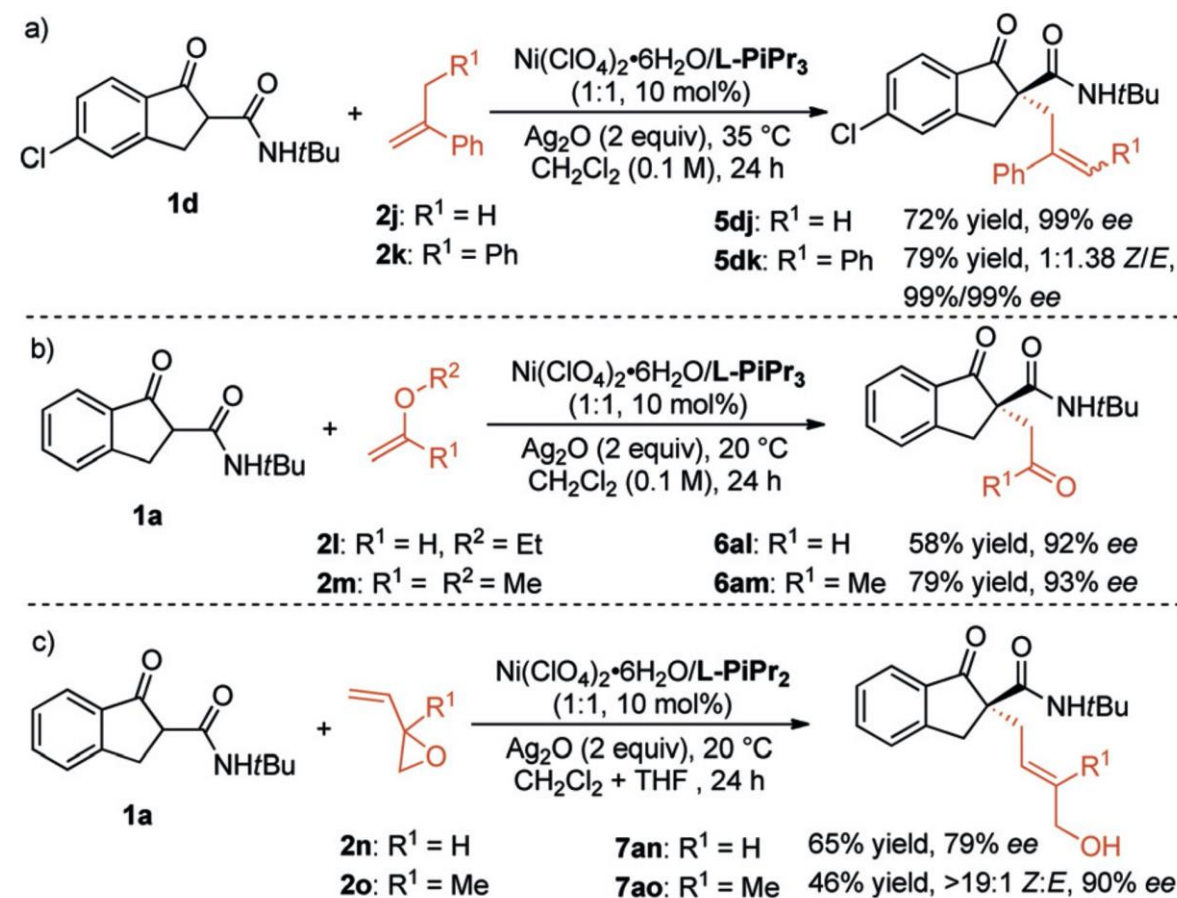
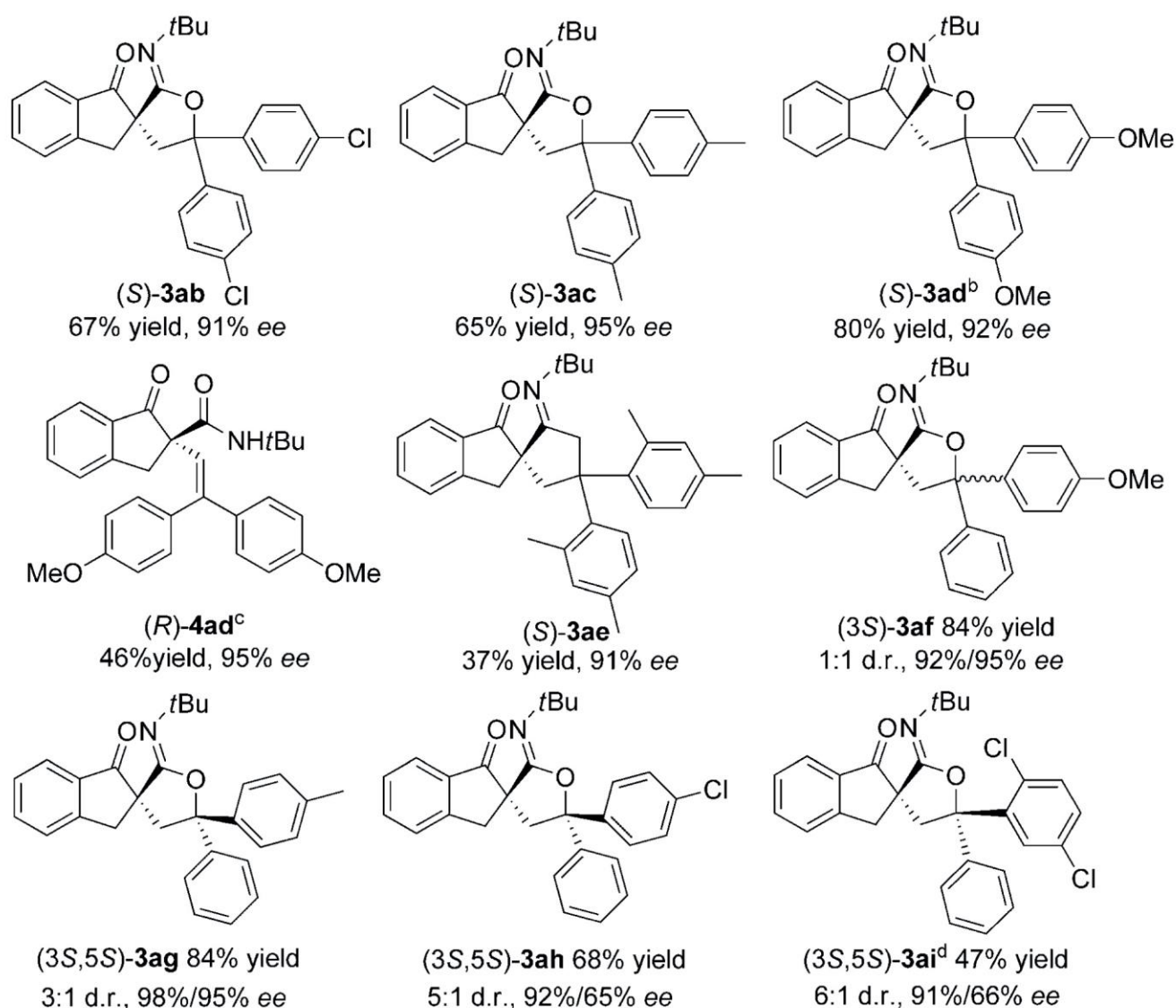
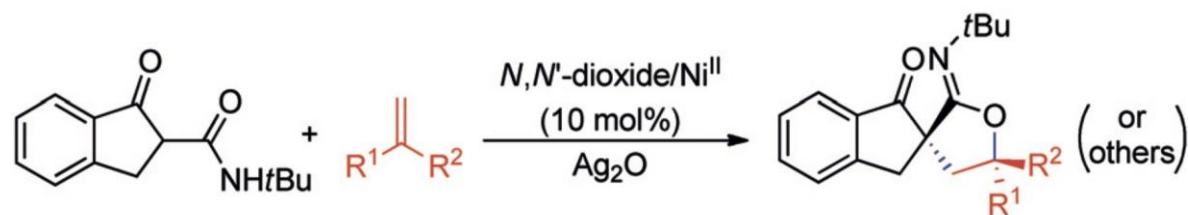
^c Determined by HPLC on a chiral stationary phase. ^d 35 °C.



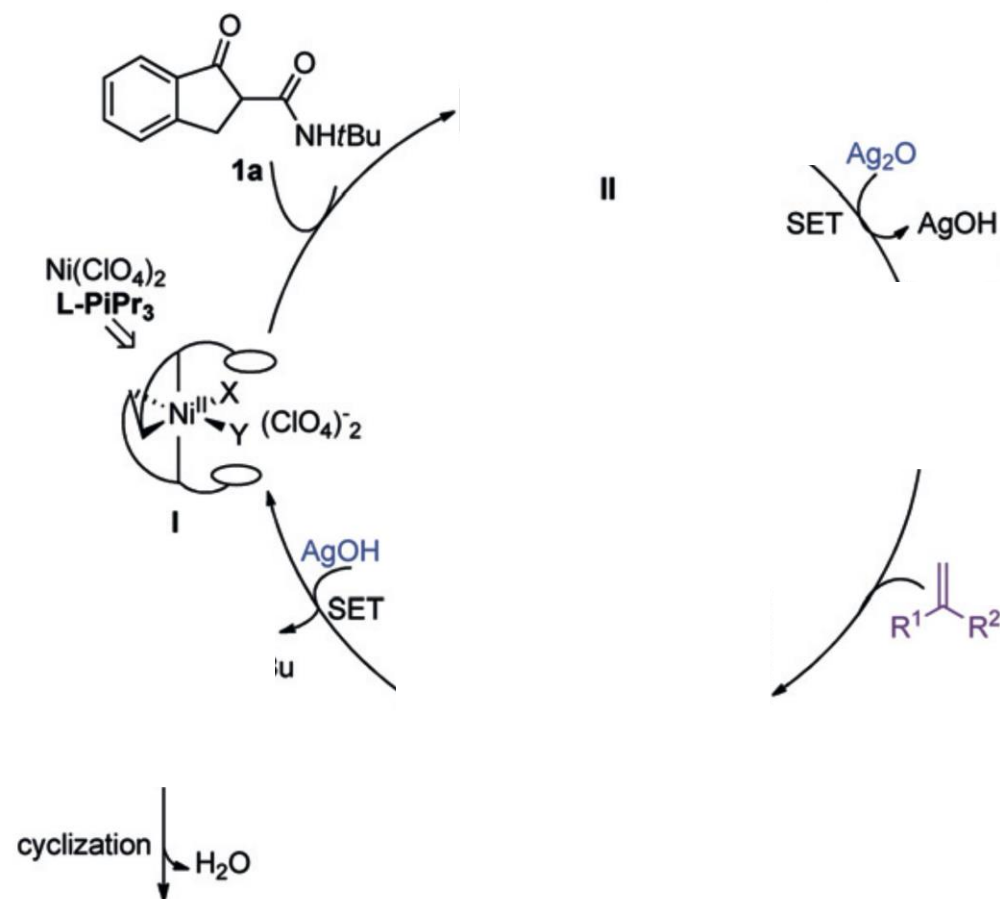
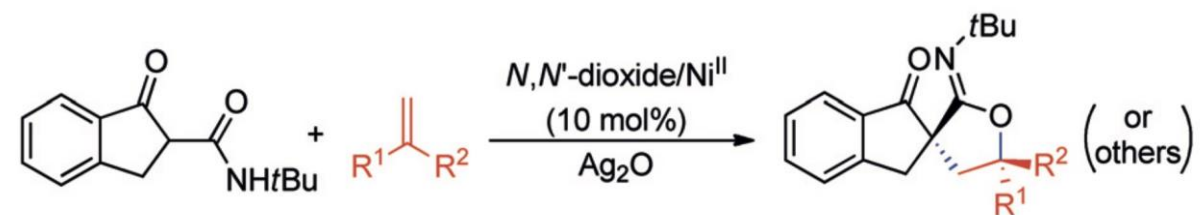
One Catalyst – Two Processes



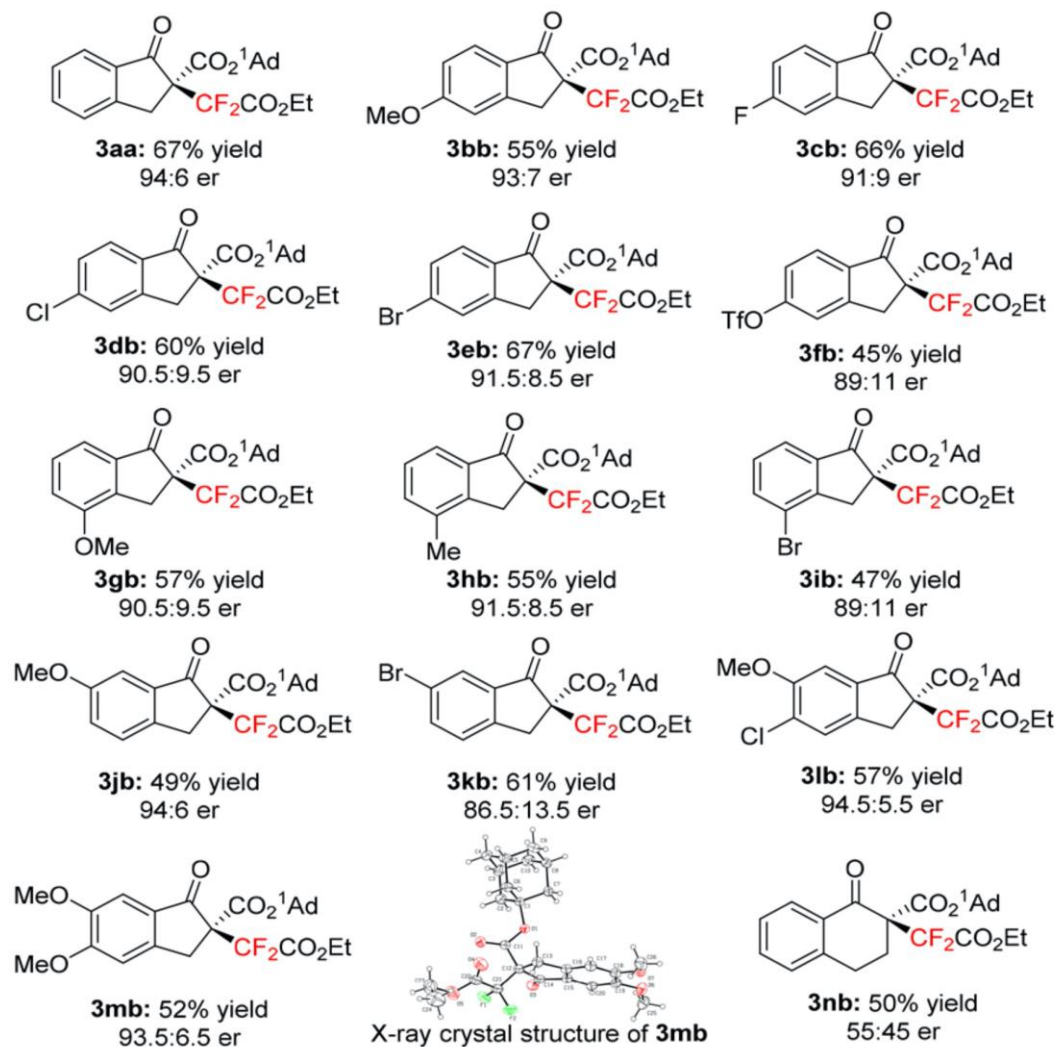
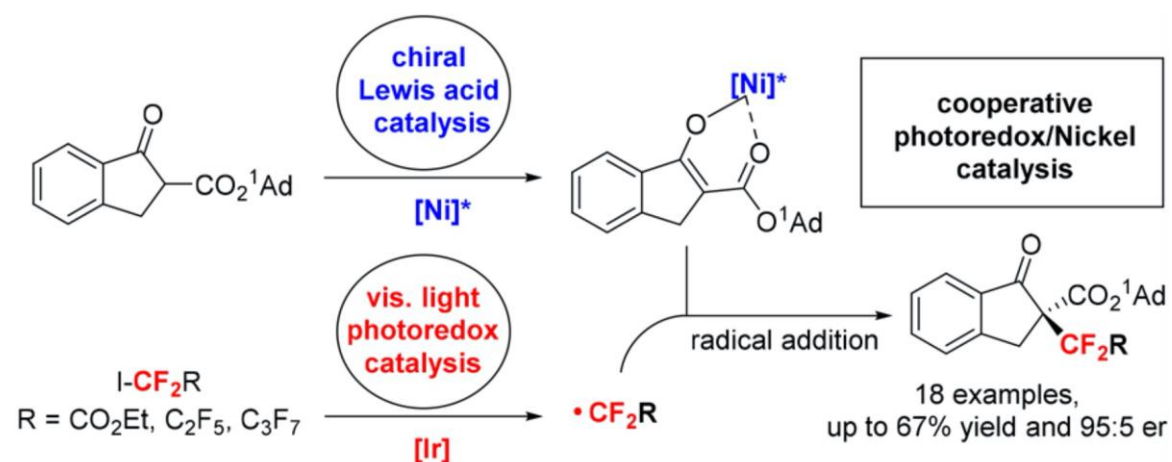
Radical-Polar Crossover Reactions



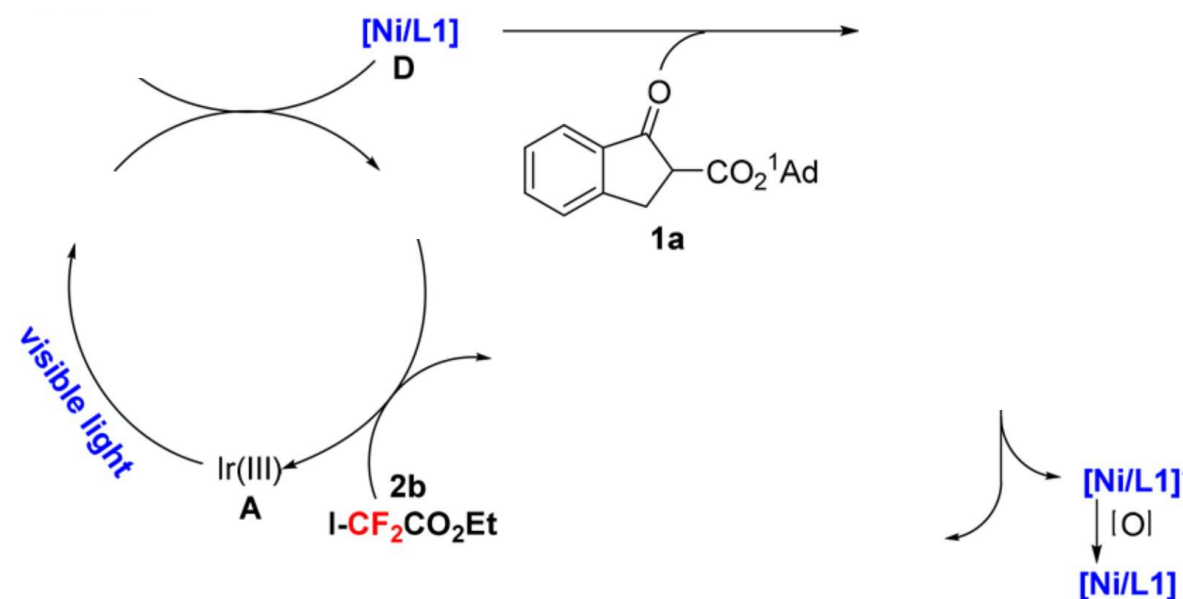
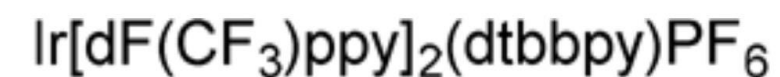
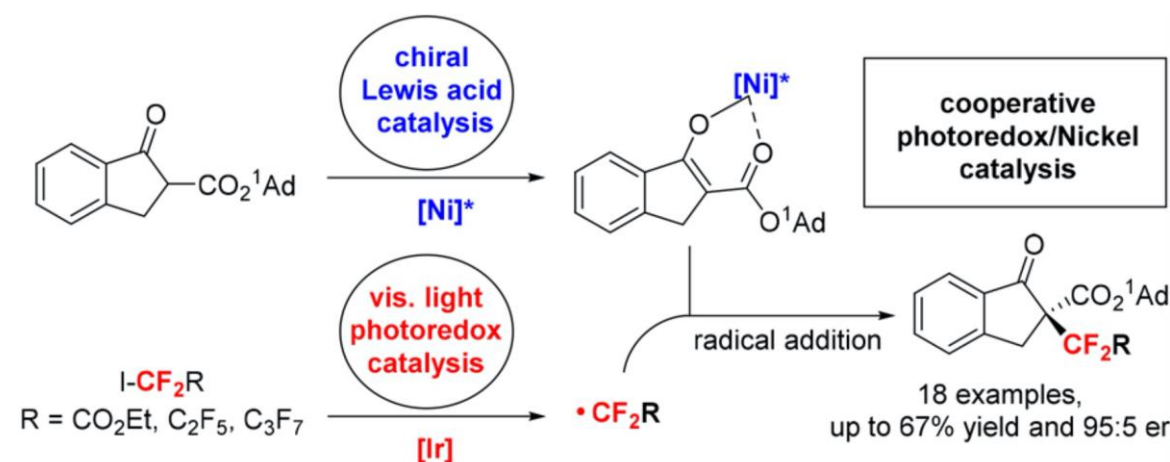
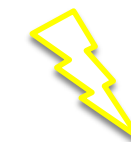
Radical-Polar Crossover Reactions



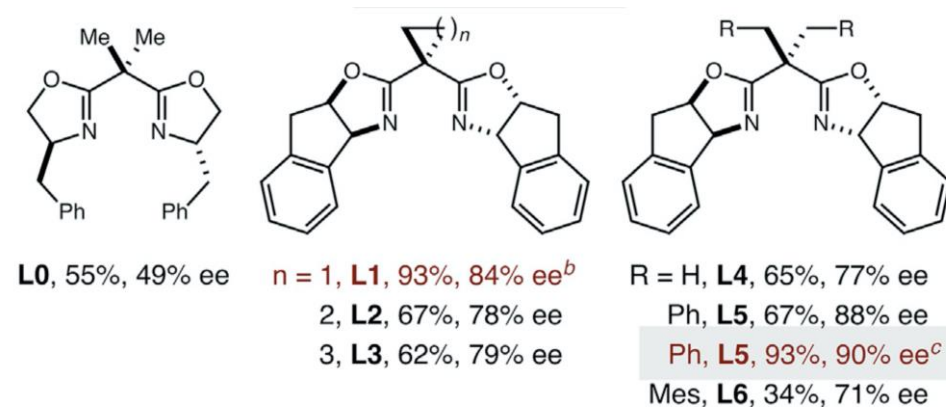
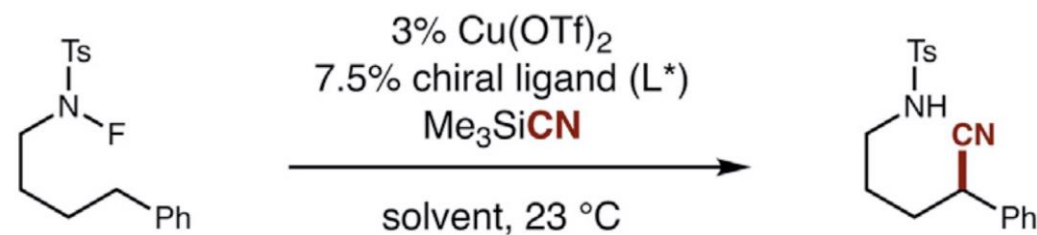
Difluoroalkylation of β -Ketoesters



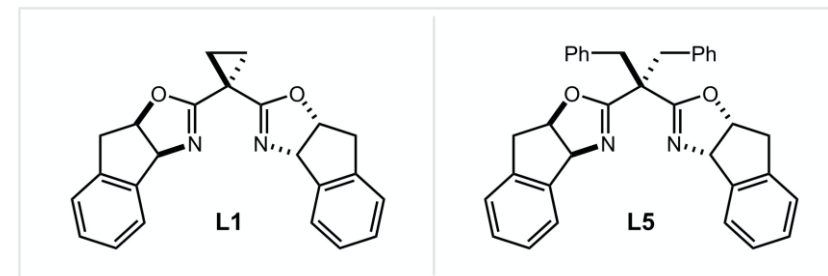
Difluoroalkylation of β -Ketoesters



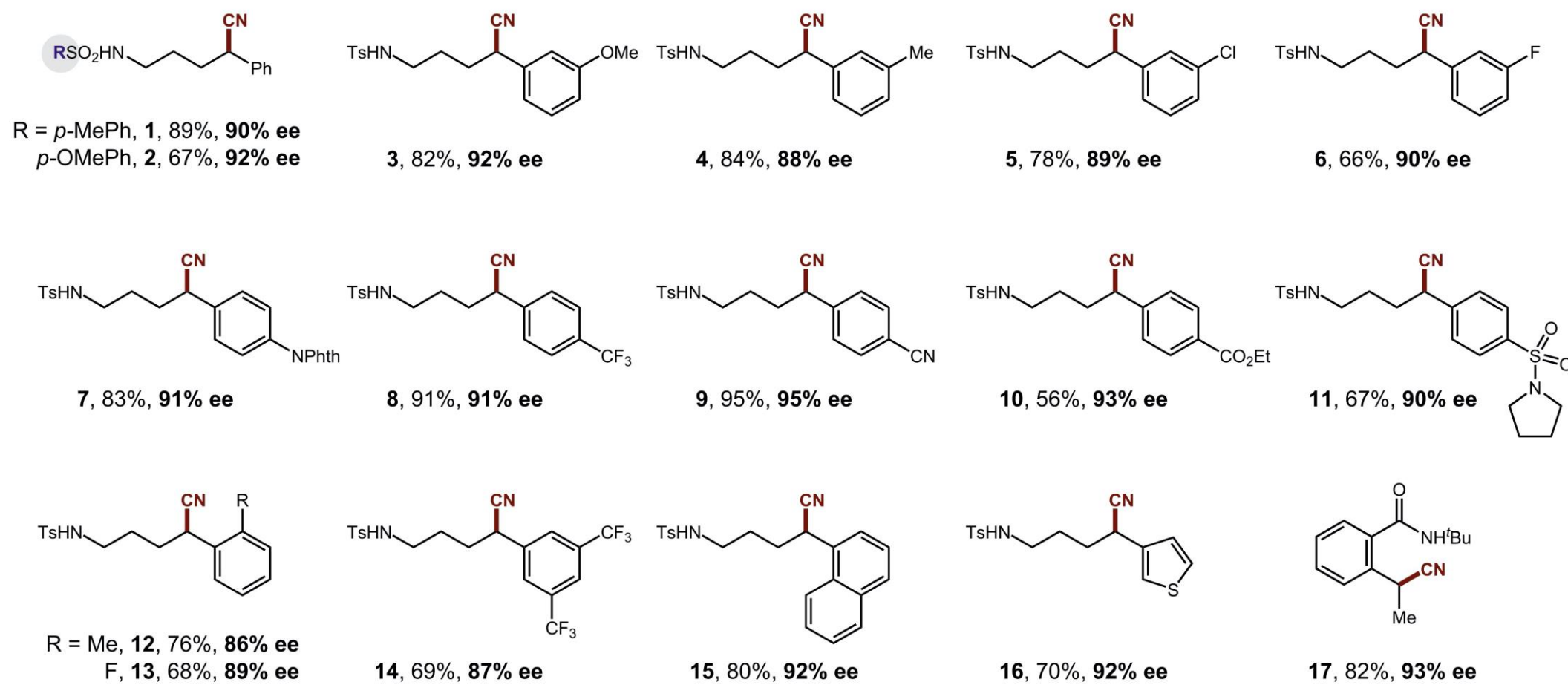
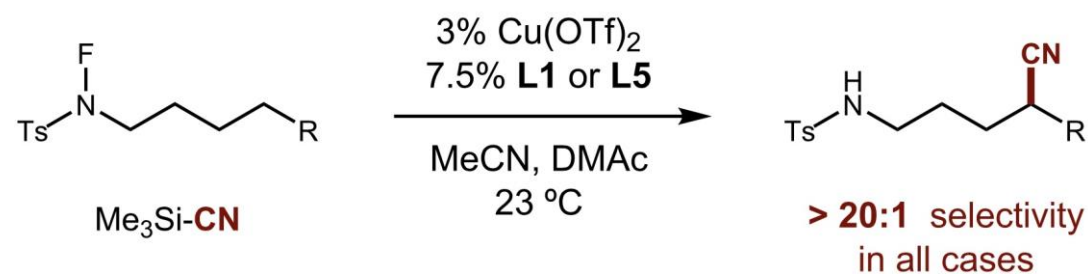
Acyclic Amines Cyanation



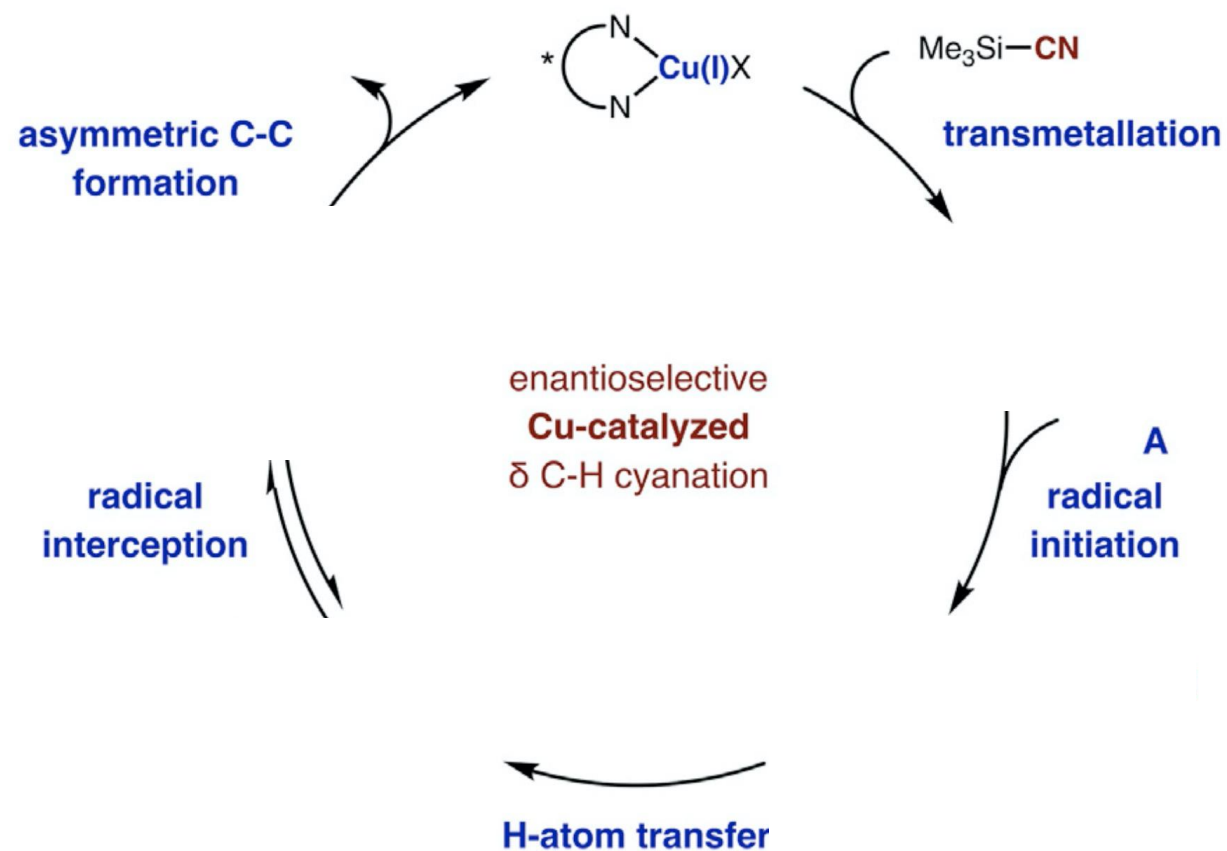
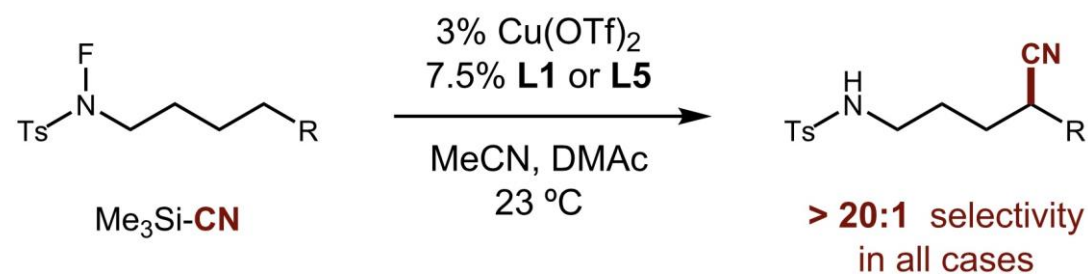
>20:1 δ regioselectivity observed in all cases



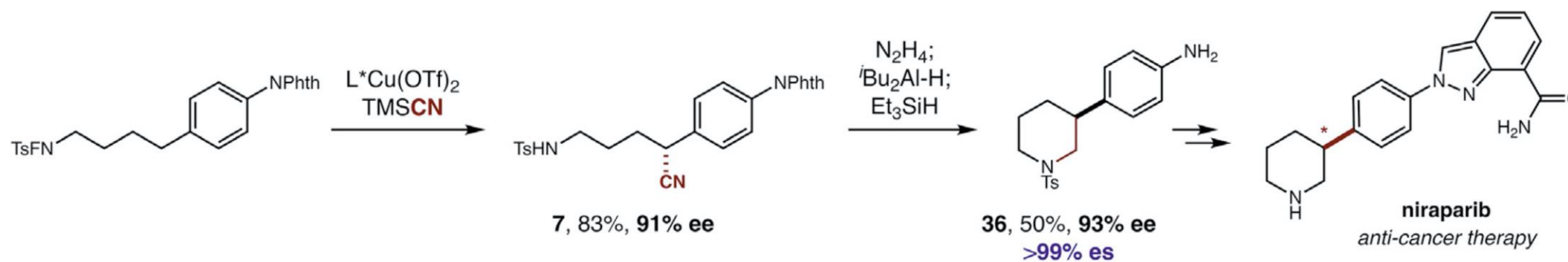
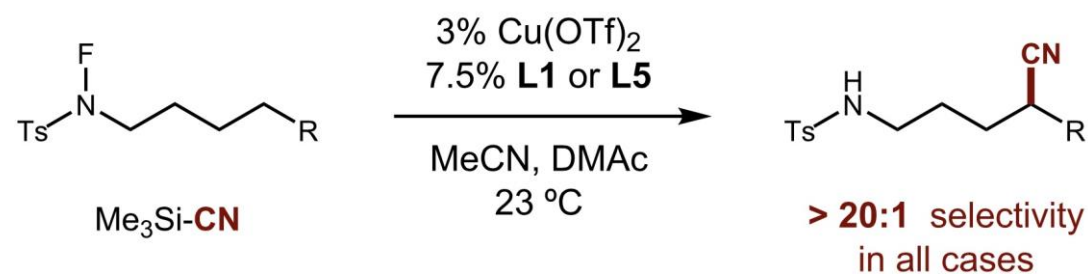
Acyclic Amines Cyanation



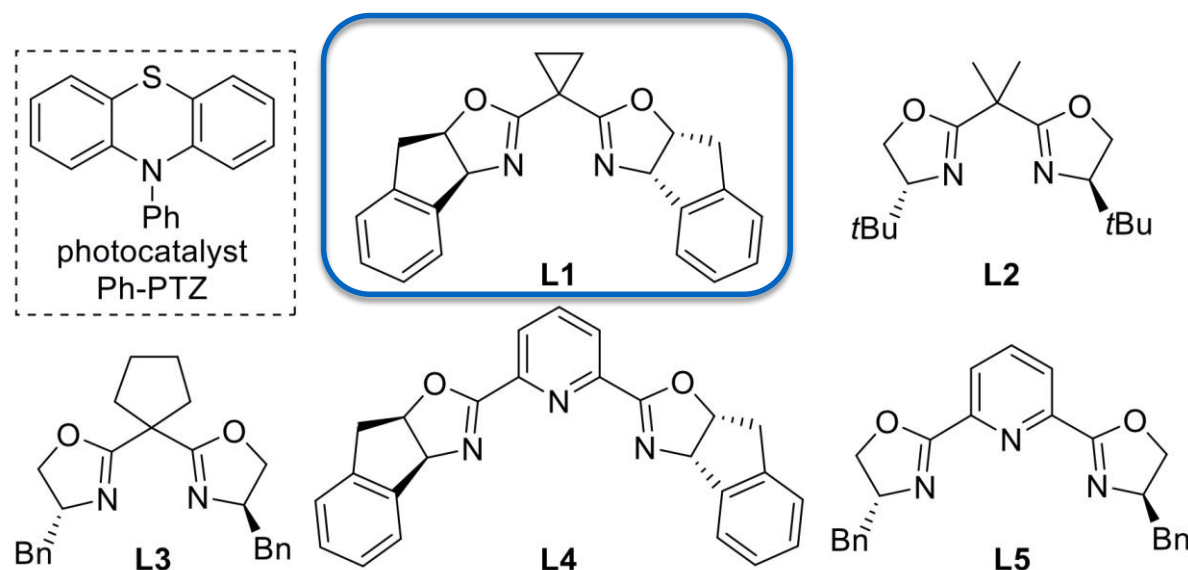
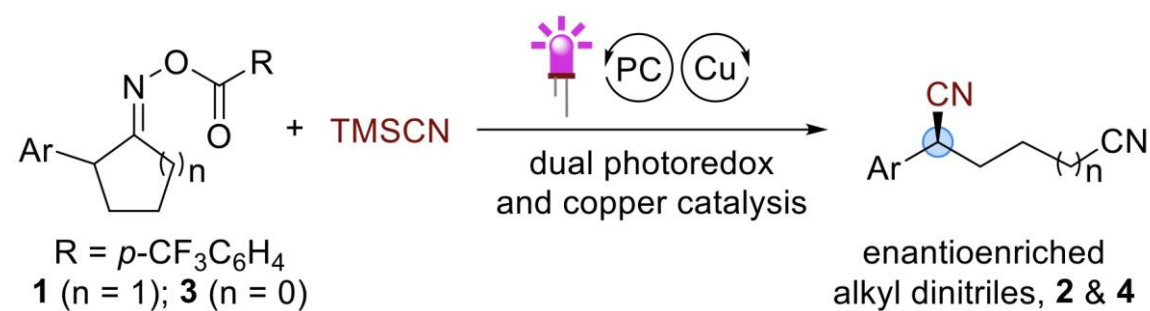
Acyclic Amines Cyanation



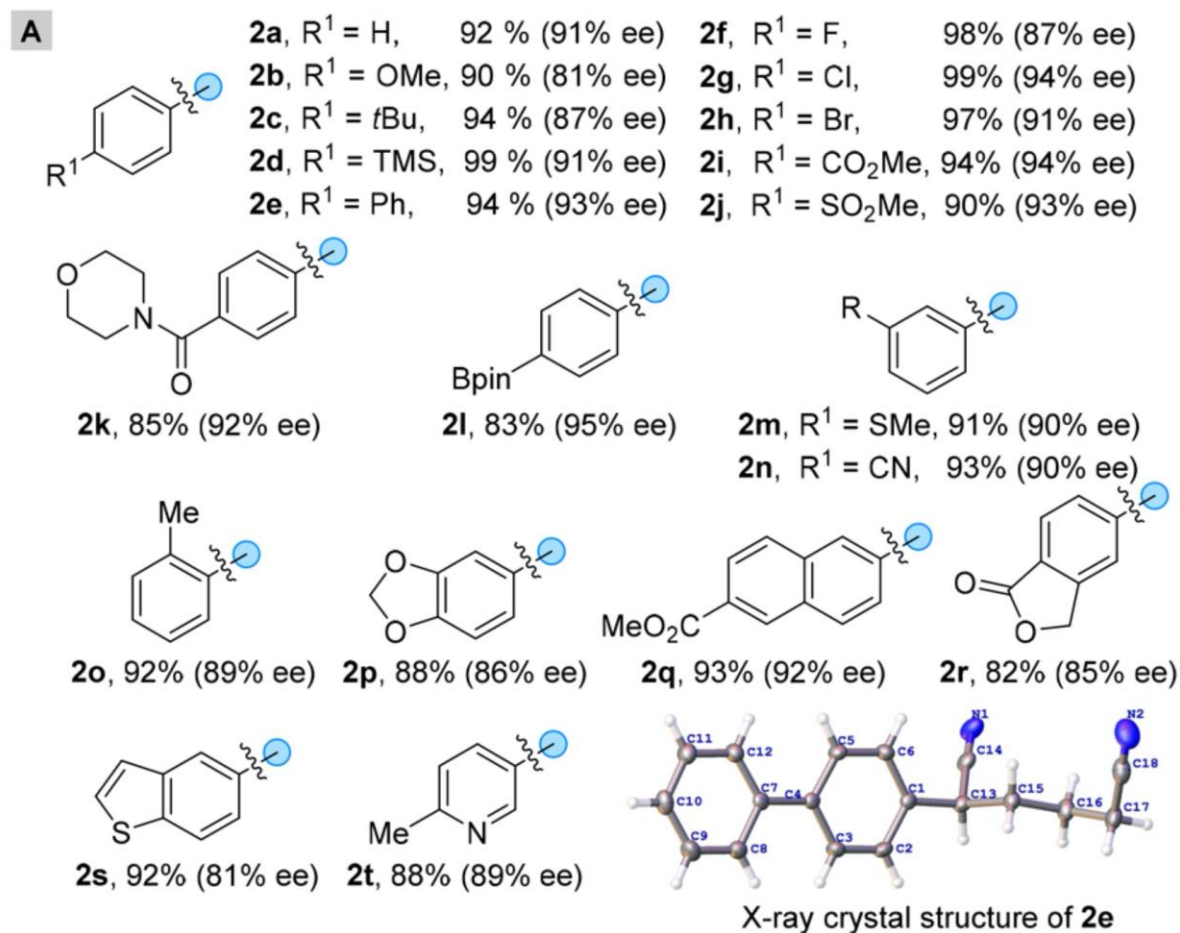
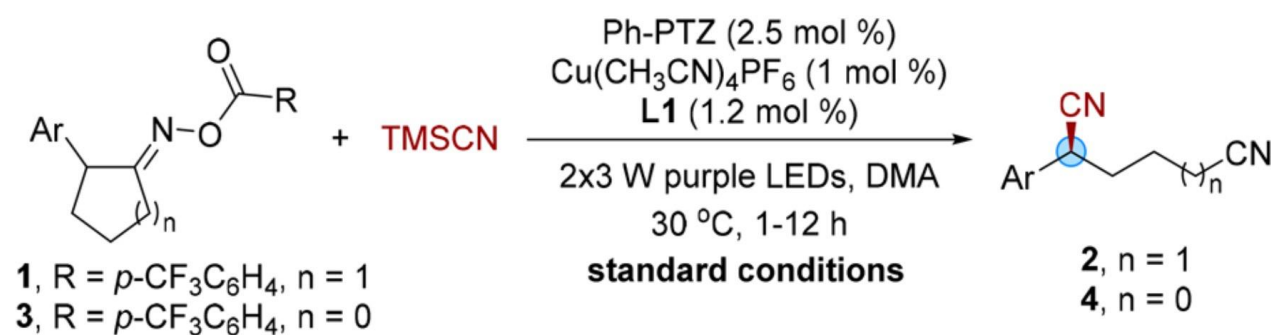
Acyclic Amines Cyanation



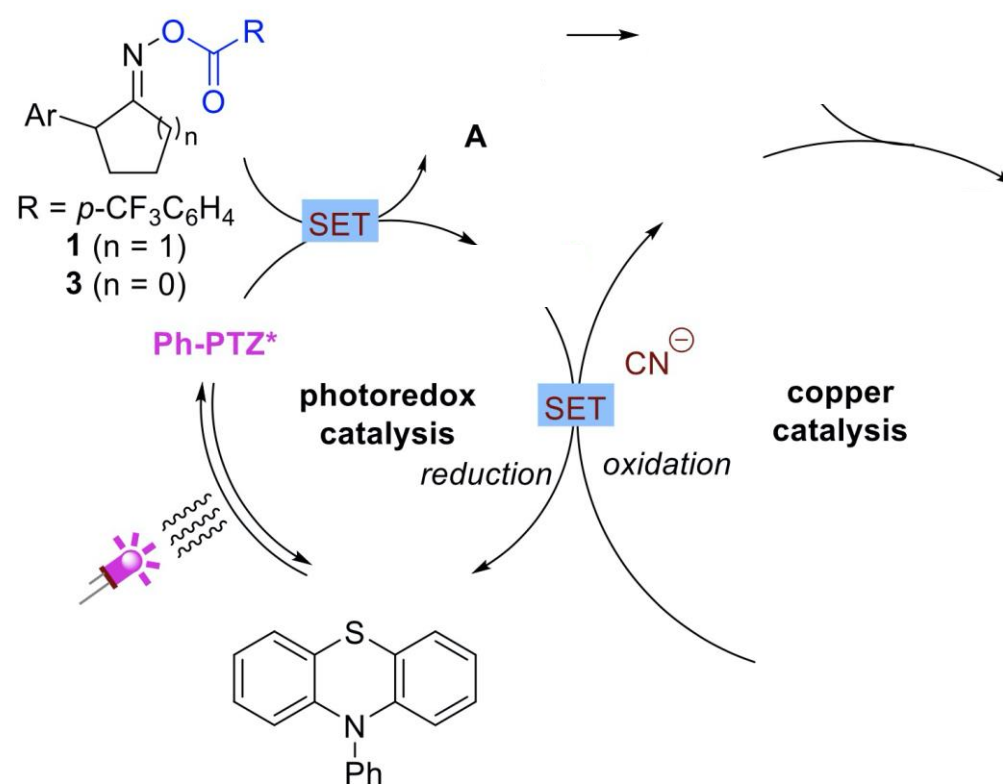
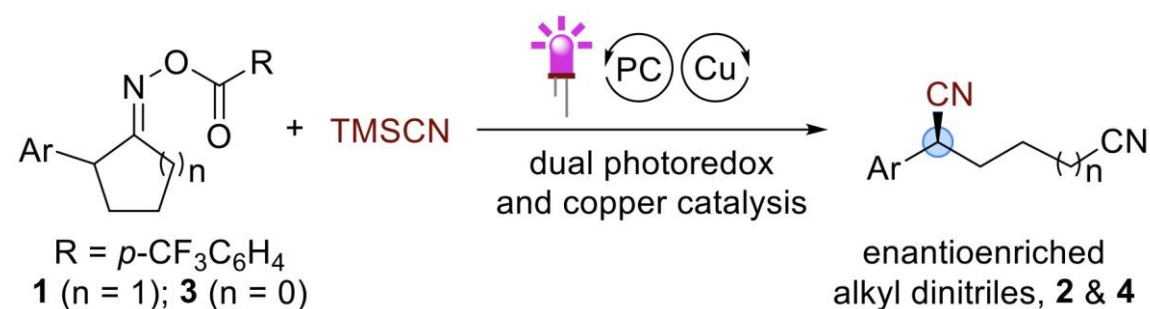
Ring-Opening Cyanation of Oxime



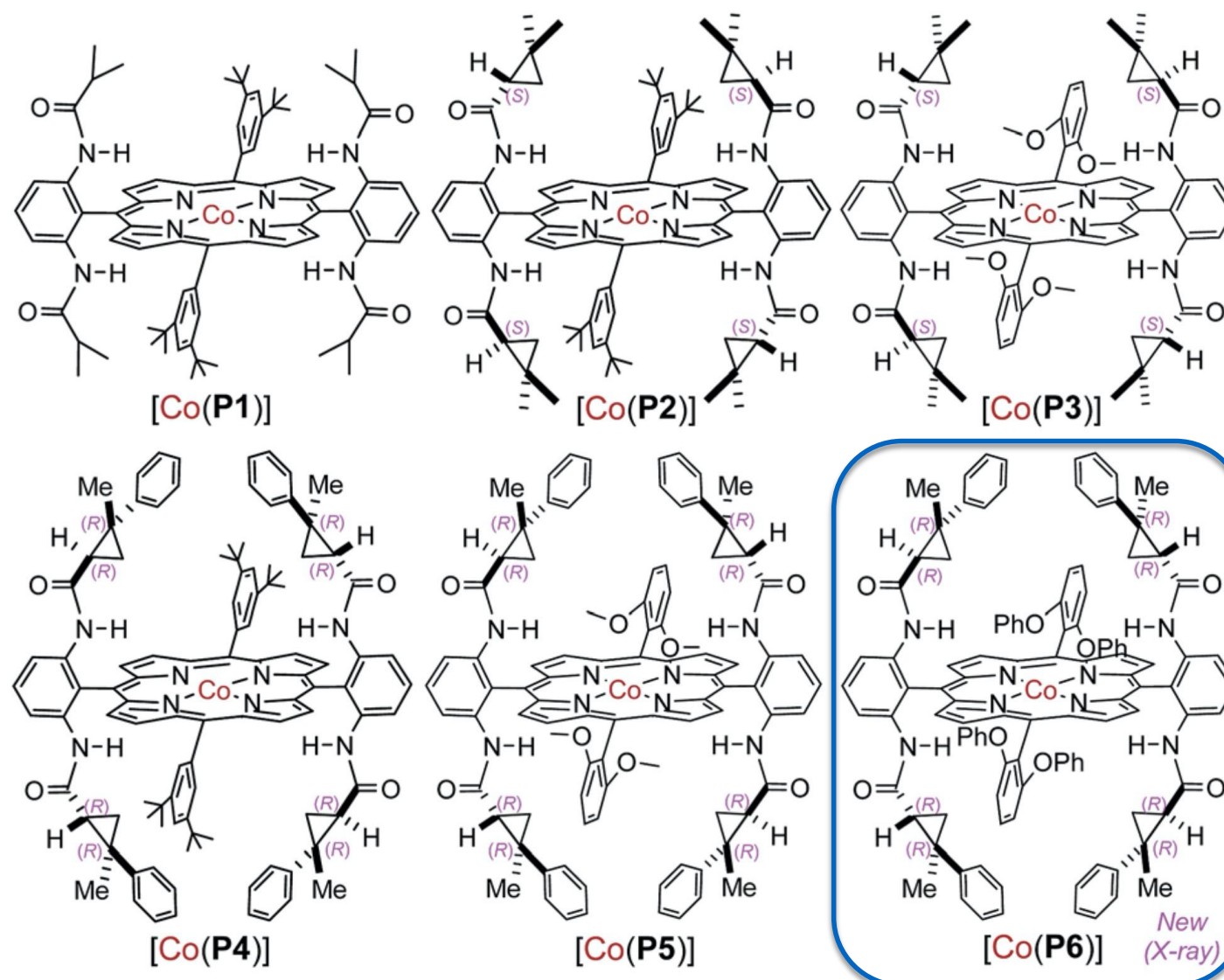
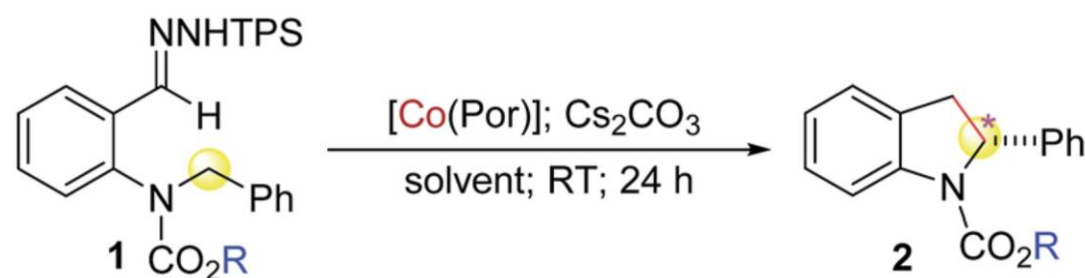
Ring-Opening Cyanation of Oxime



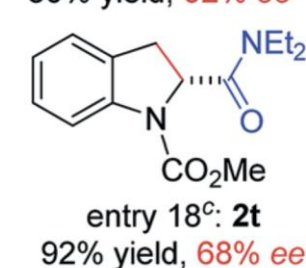
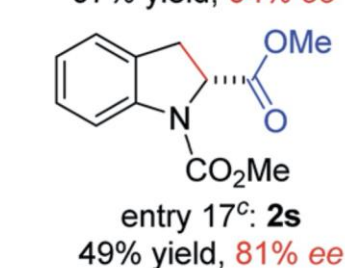
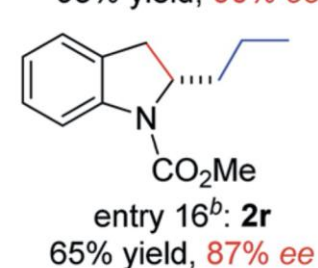
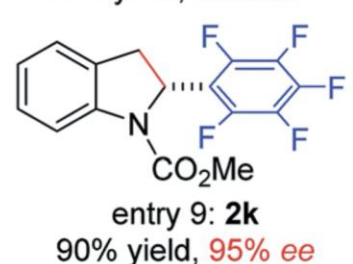
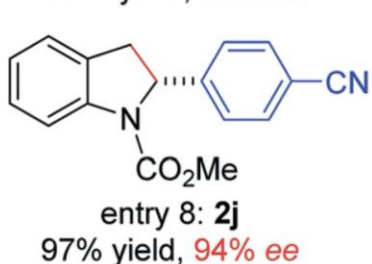
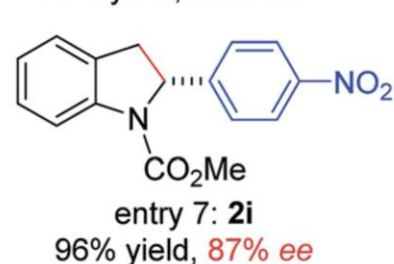
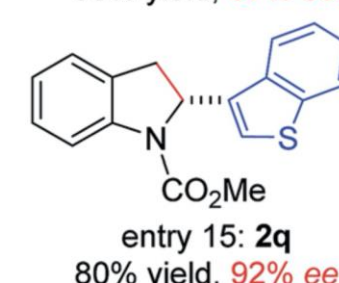
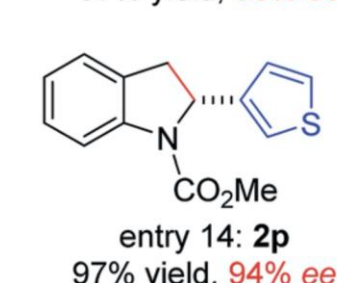
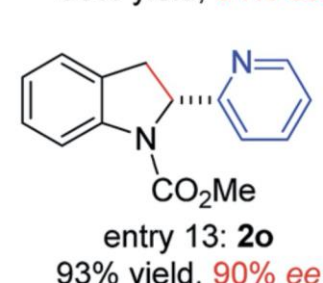
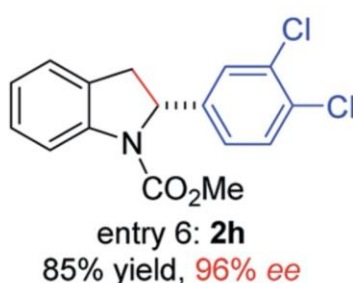
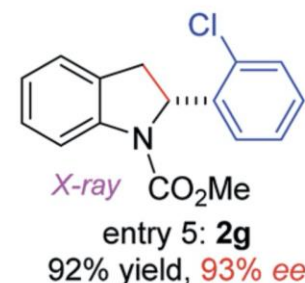
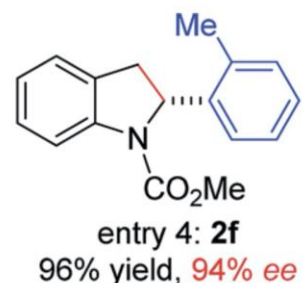
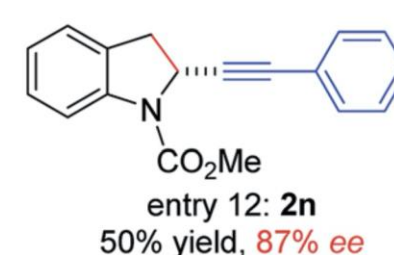
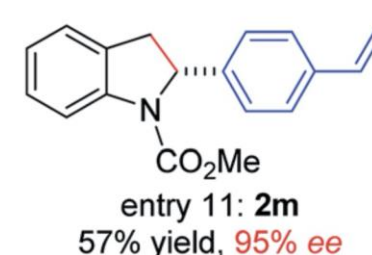
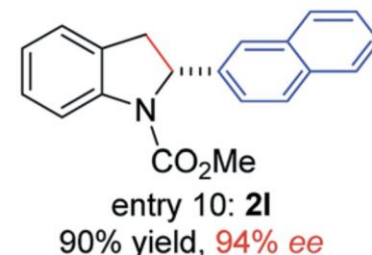
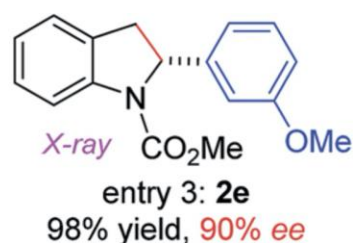
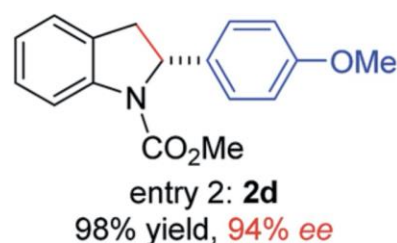
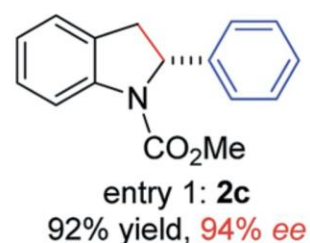
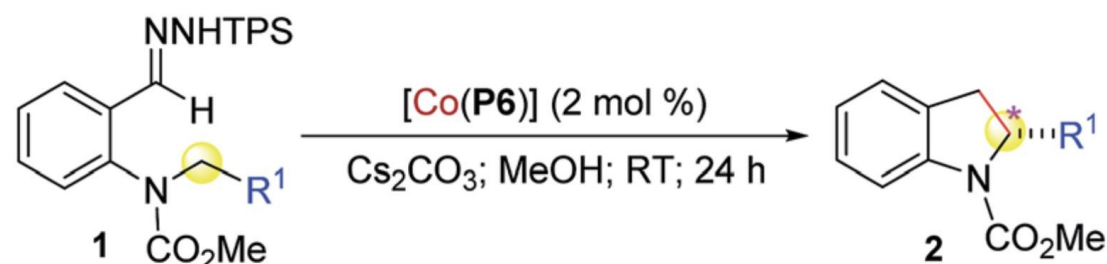
Ring-Opening Cyanation of Oxime



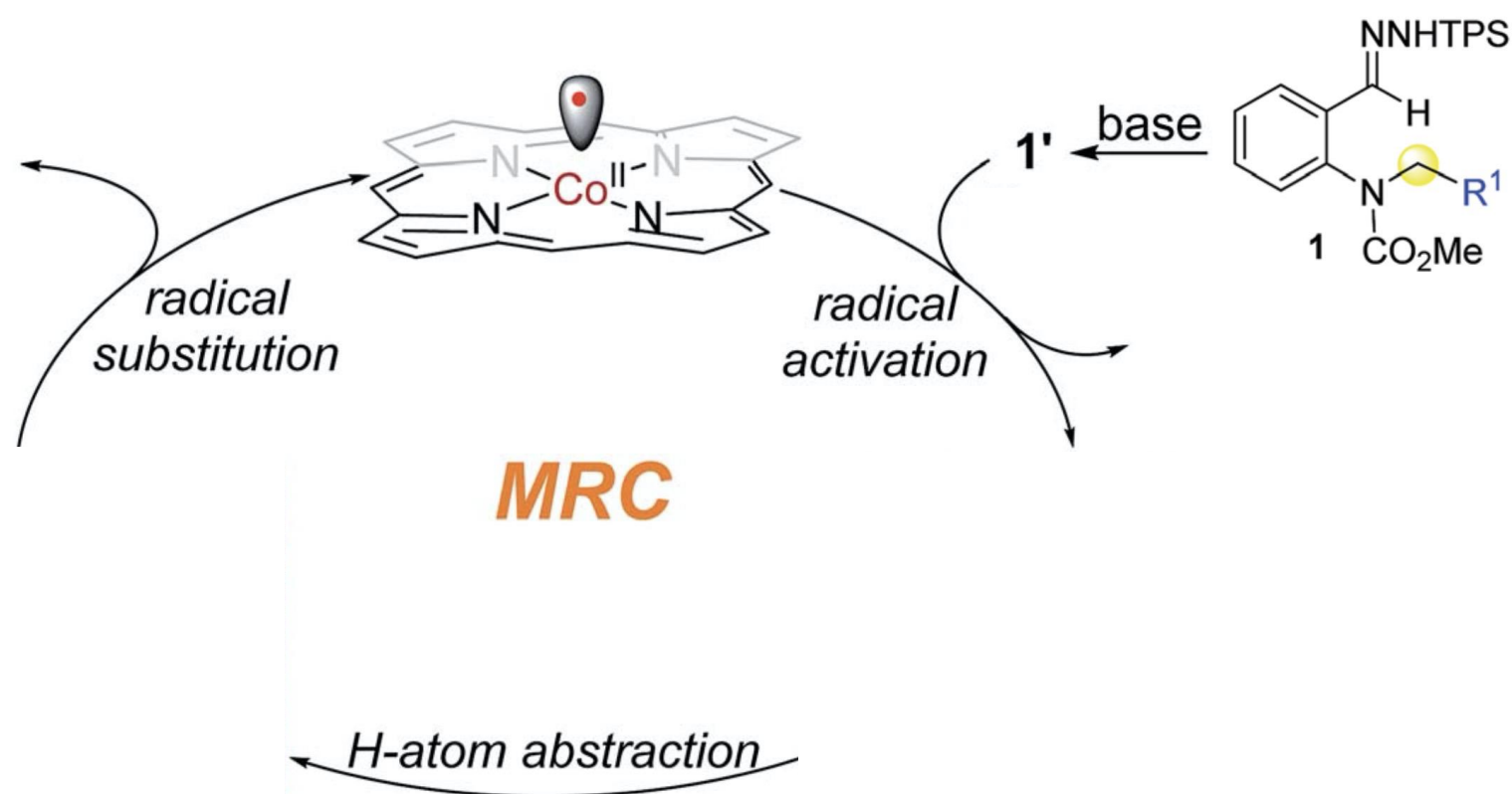
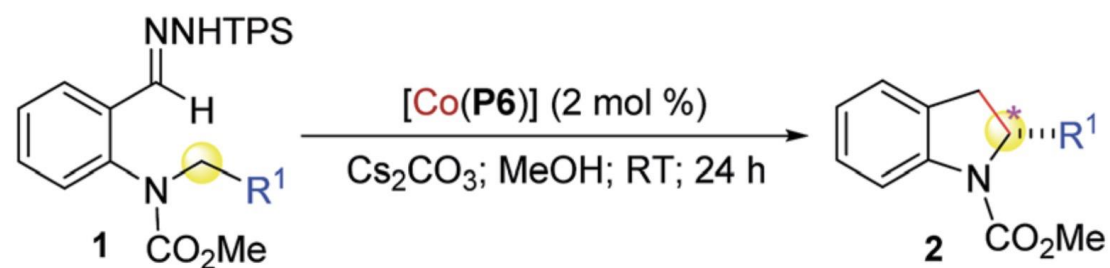
C(sp³)-H Alkylation for Indoline



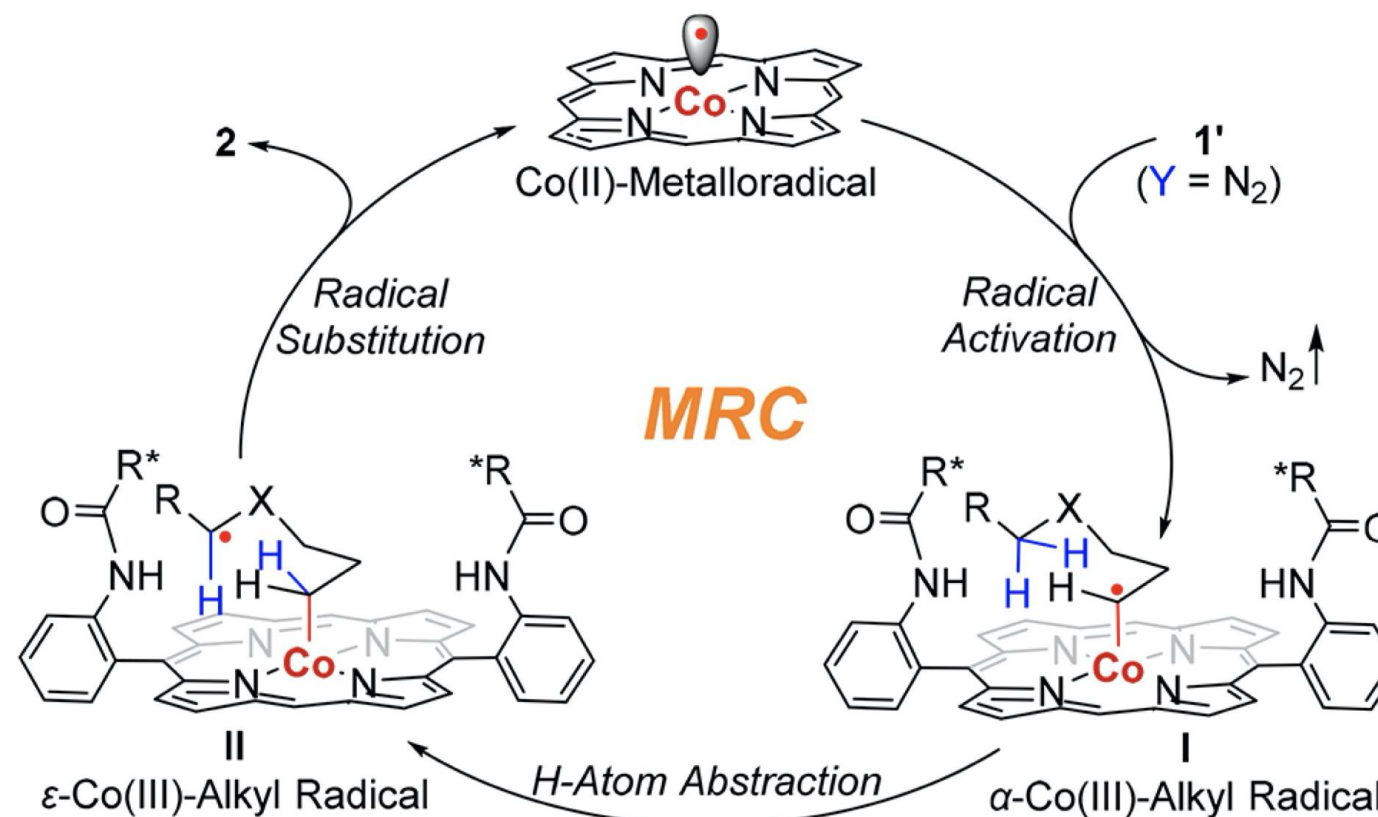
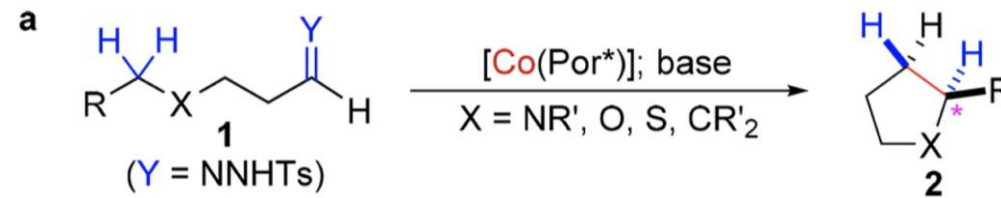
C(sp³)-H Alkylation for Indoline



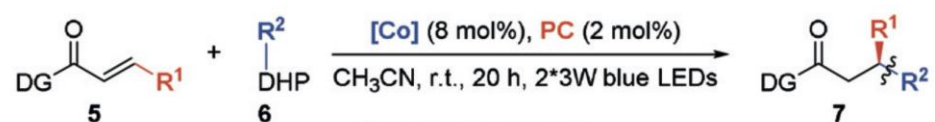
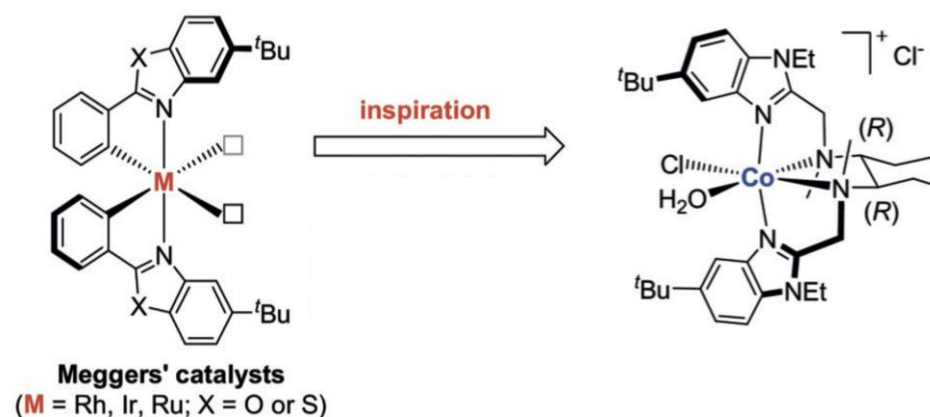
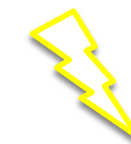
C(sp³)-H Alkylation for Indoline



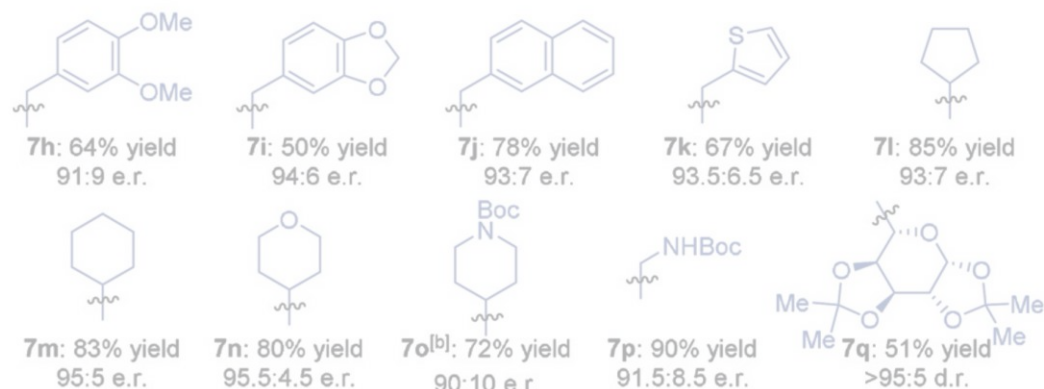
C(sp³)-H Alkylation for 5-Membered Ring Structures



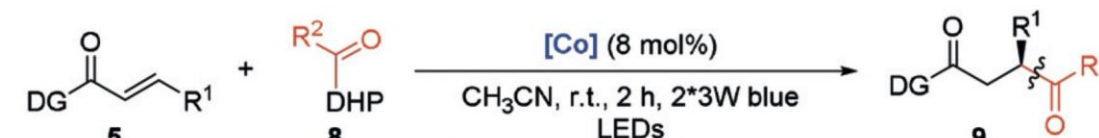
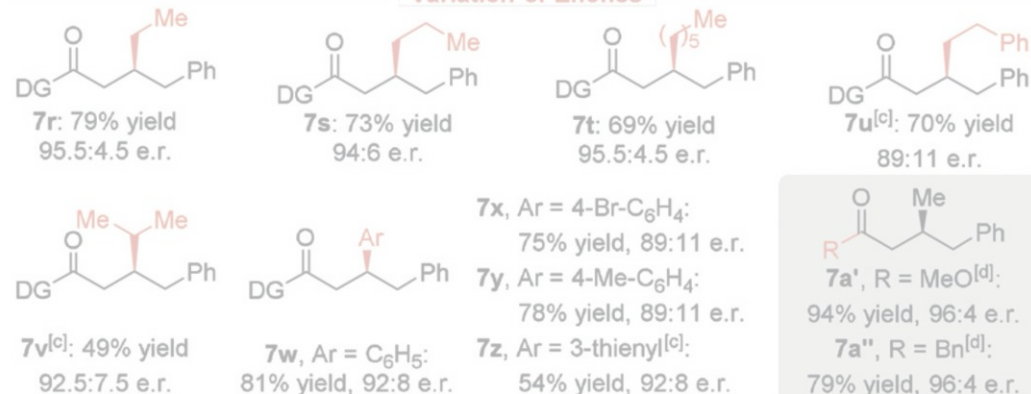
Enone Acylation and Alkylation



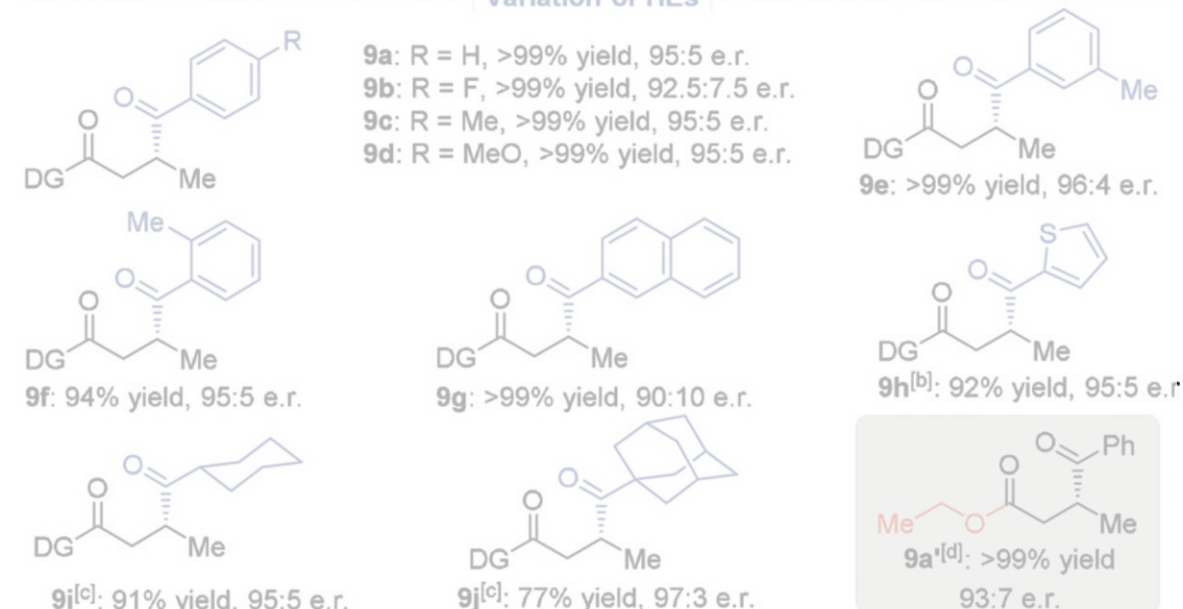
Variation of HEs



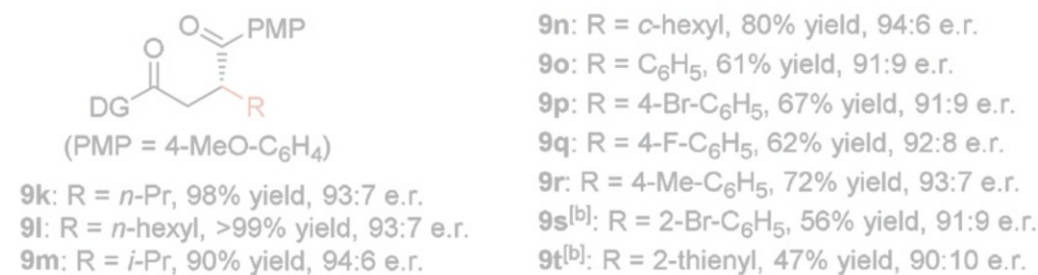
Variation of Enones



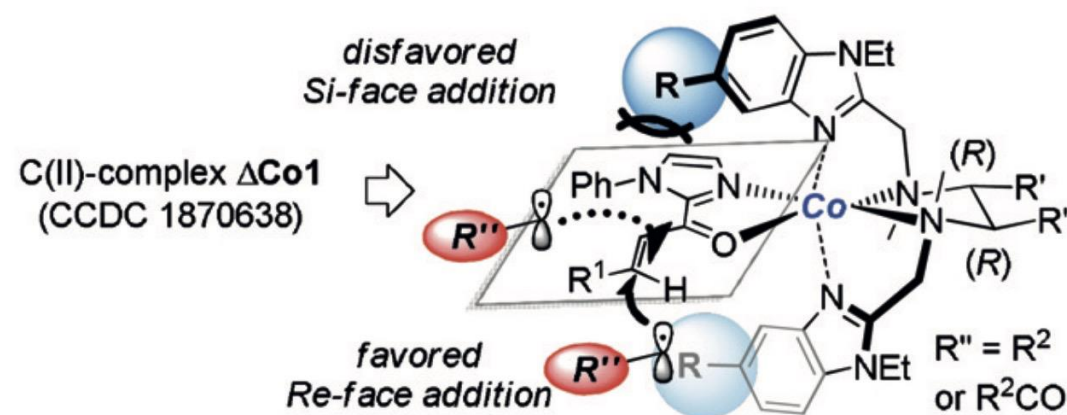
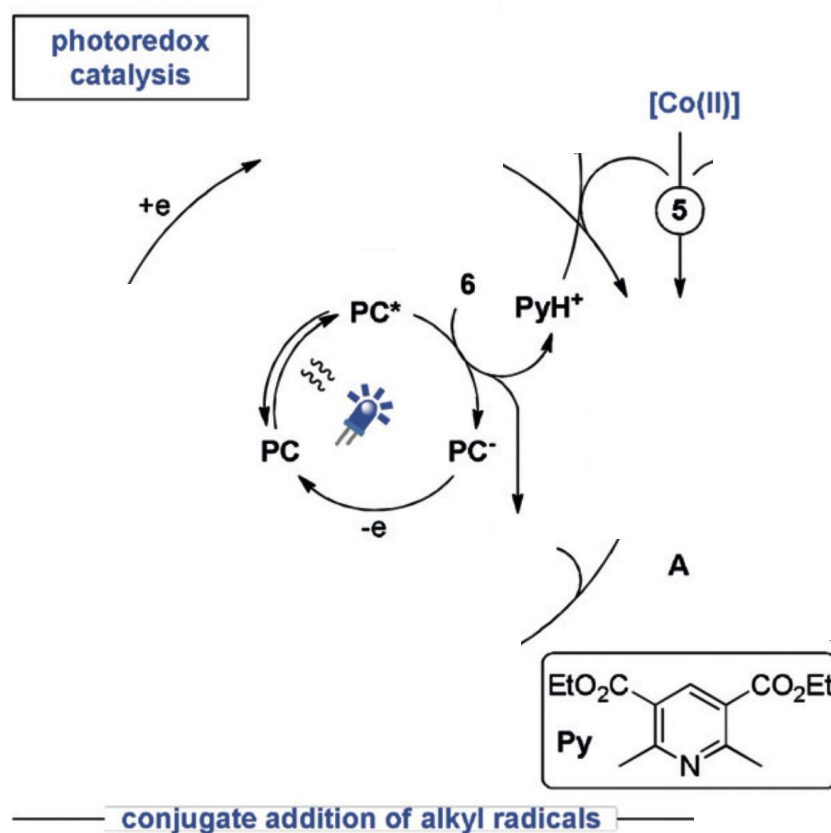
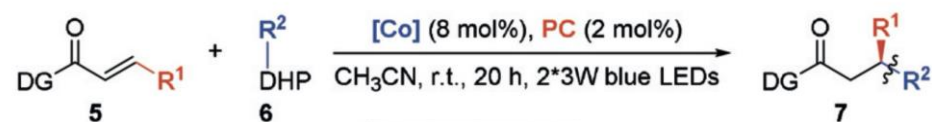
Variation of HEs



Variation of Enones



Enone Acylation and Alkylation



Conclusion

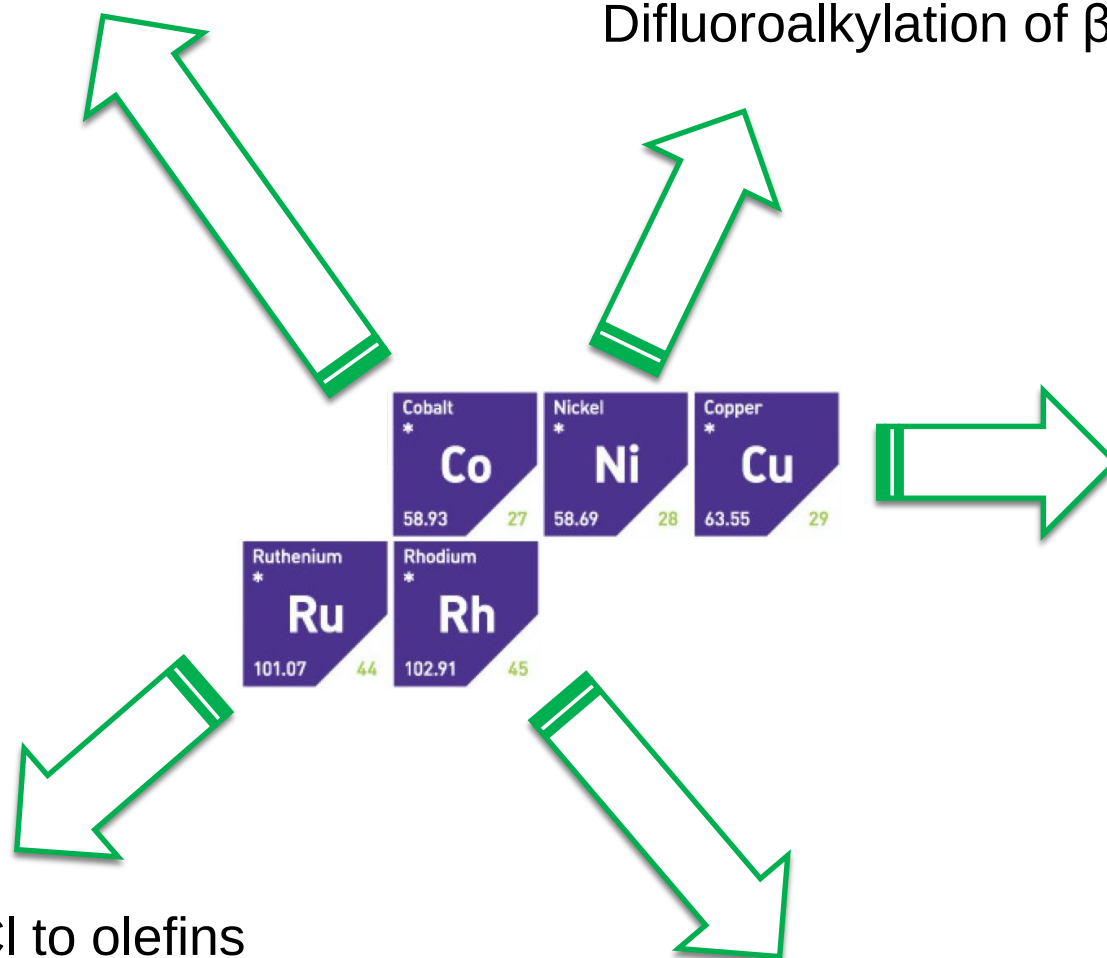
Alkylation of C(sp³)–H Bonds
Alkylation and acylation of enones
Access to 5-membered ring structures

Radical-polar crossover reactions
Difluoroalkylation of β -ketoesters

Cyanation of acyclic amines
Ring-opening cyanation of oxime
Ring-opening cyanation of cyclopropanols

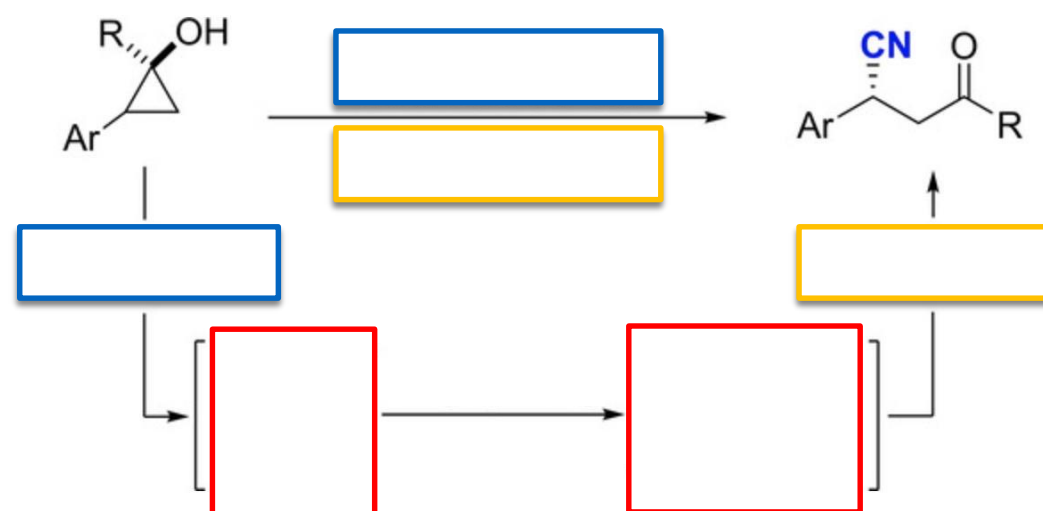
Addition of RSO₂Cl to olefins

Addition of CX₄ reagents to olefins
Alkene and sulfonyl addition to olefins



Exercise 1

? catalyzed radical relay for enantioselective cyanation of cyclopropanols

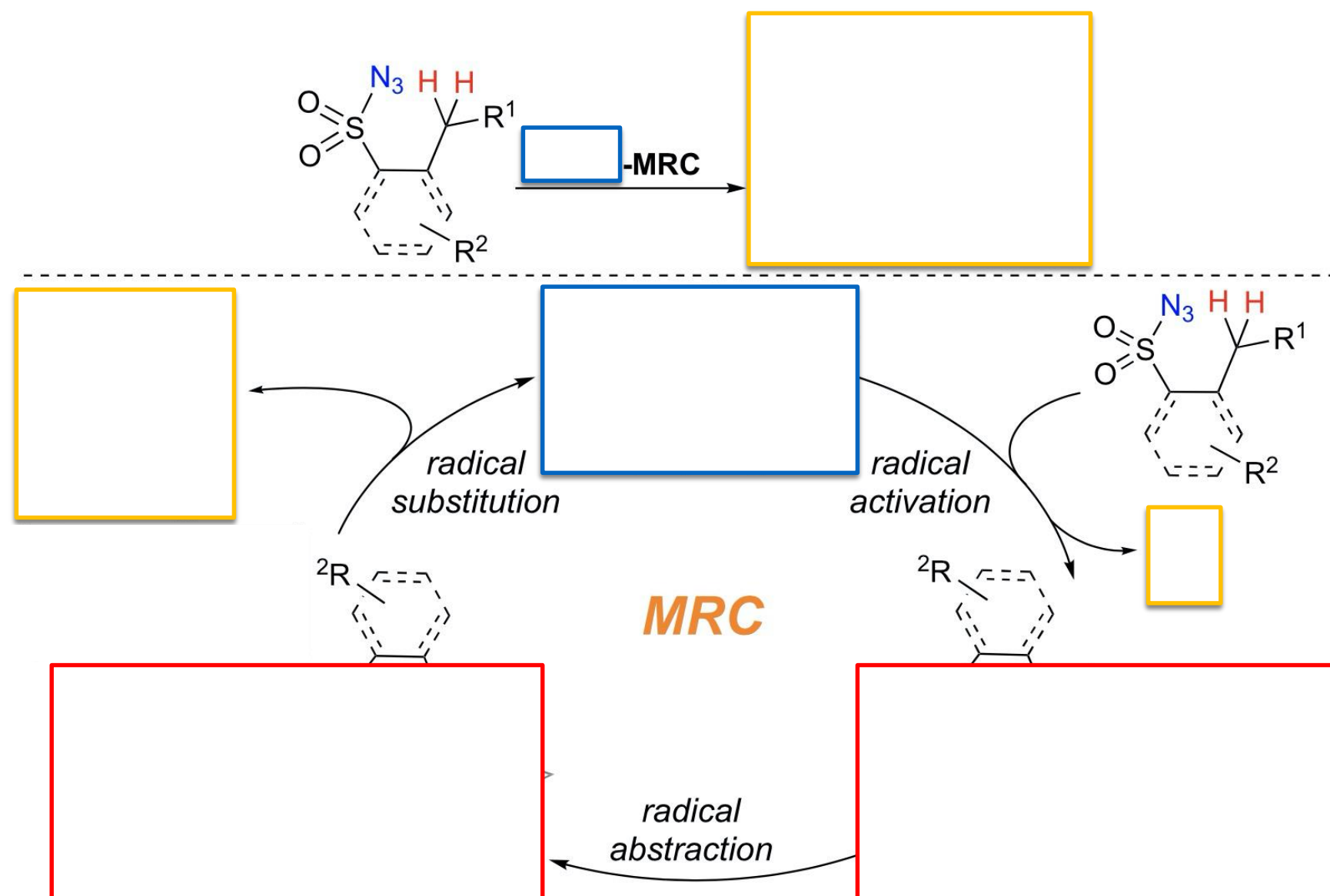


1/ Propose a metal/ligand for this reaction

2/ Propose a CN source

3/ Propose the missing intermediates

Exercise 2

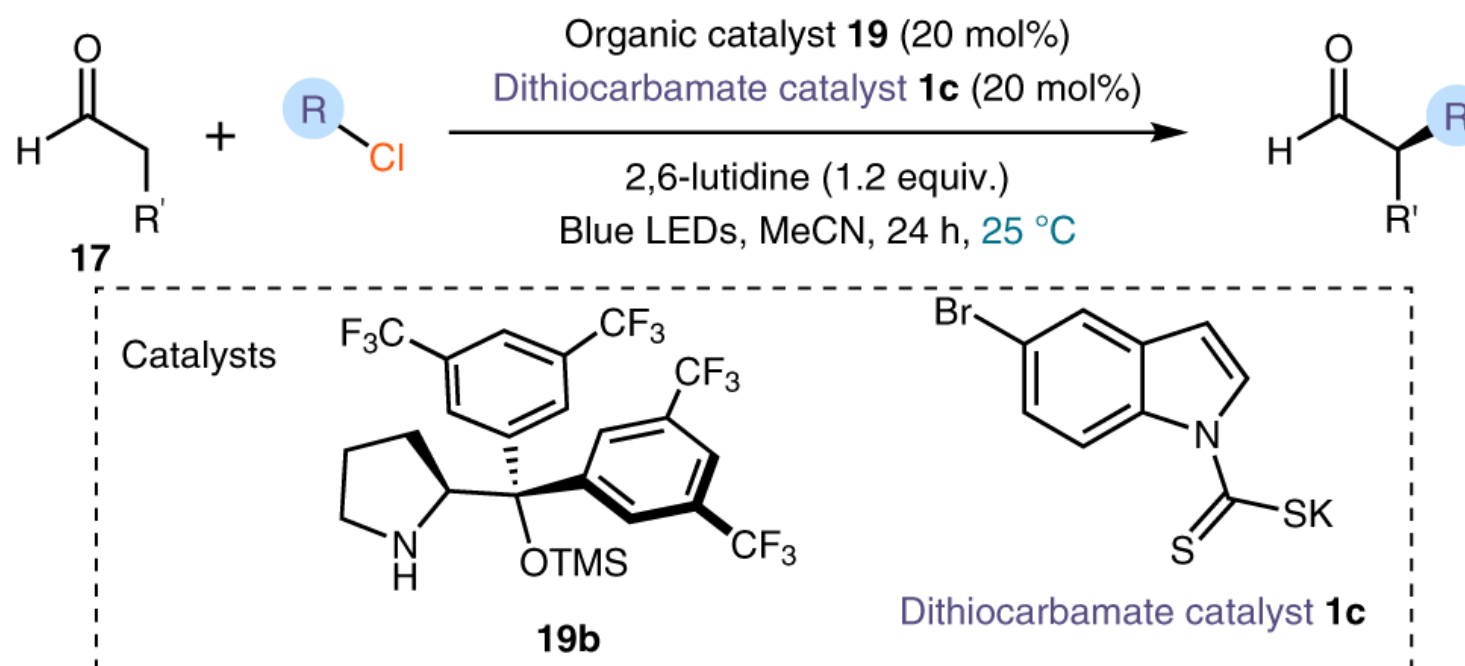
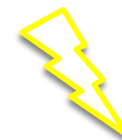


1/ Propose a metal/ligand for this reaction

2/ Propose a product for the MRC

3/ Propose the missing intermediates

Outlook - Beyond Metals



Acknowledgements

Thank you for your attention!

Stay safe

Catalytic Cascade Reactions by Radical Relay

CH-707 Frontiers in Organic Chemistry I

Annabell Martin

Laboratory of Chemical and Biological Probes (LOCBP)

Supervisor: Prof. Rivera-Fuentes

11.05.2020

H.-M. Huang, M. H. Garduño-Castro, C. Morrill, D. J. Procter,
Chem. Soc. Rev. **2019**, 48, 4626–4638

Outline

1. Introduction

- * (Radical) Cascade Reactions
- * Radical Relay

2. Examples

- * Intramolecular Radical Relays
- * Radical Relays involving Hydrogen Atom Transfer (HAT)
- * Intermolecular Radical Relays

3. Summary – Strategies for radical formation, relocation and rebound

4. Outlook

Introduction – Cascade Reactions

Cascade/Domino Reactions: a process involving **two or more** consecutive reactions in which subsequent reactions result as a consequence of the functionality formed by bond formation or fragmentation in the previous step

- each reaction composing the sequence occurs spontaneously
- no isolation of intermediates
- same reaction conditions throughout the consecutive cascade steps
- no addition of reagents after the initial step

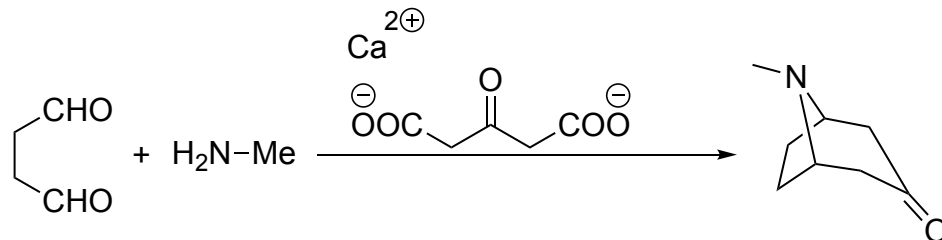
vs

One-pot Reactions: a process in which another reagent, mediator or catalyst is **added after** the first transformation without isolation of the first formed product

- **any cascade reaction = one-pot reaction**
- **any one-pot reaction $\neq$ cascade reaction**

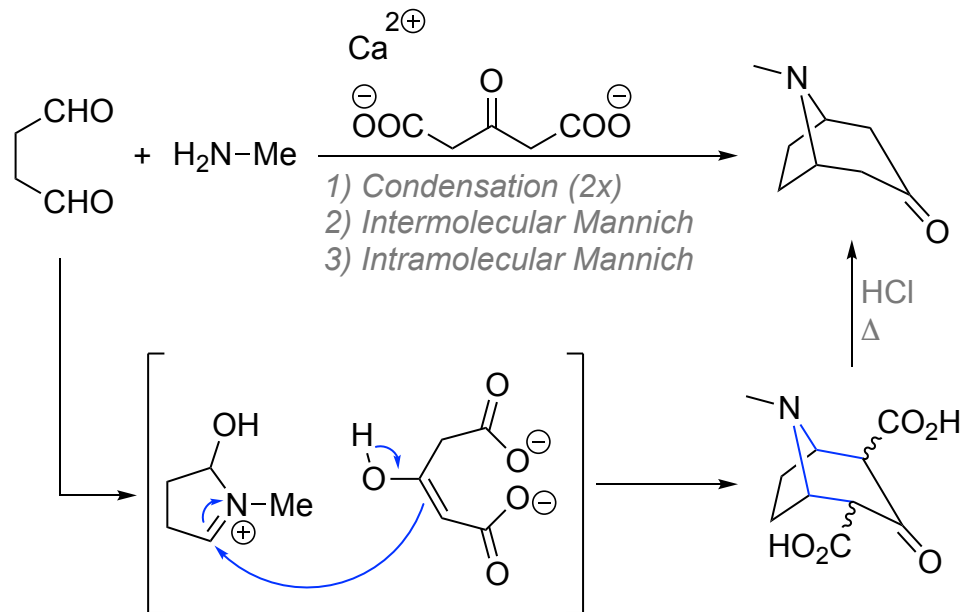
Introduction – Cascade Reactions

First example: Synthesis of Tropinone (Robinson, 1917)



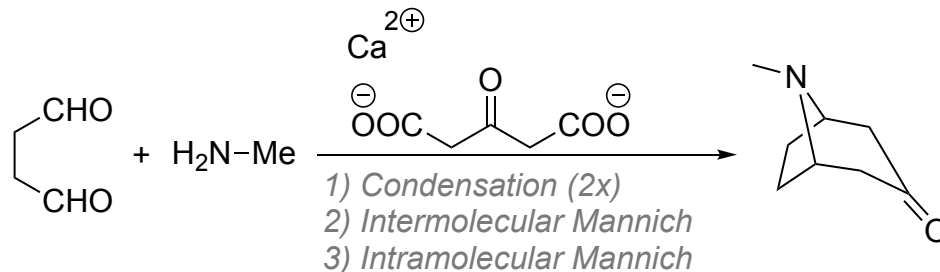
Introduction – Cascade Reactions

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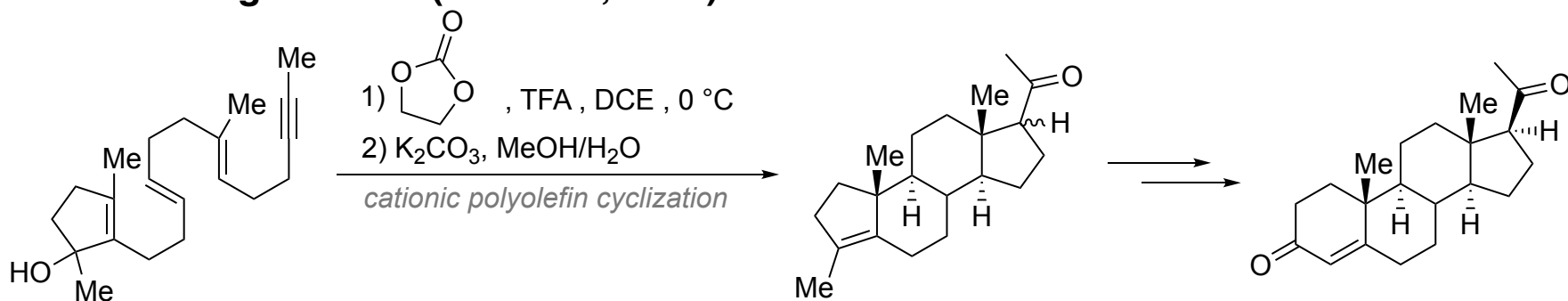


Introduction – Cascade Reactions

First reported: Synthesis of Tropinone (Robinson, 1917)

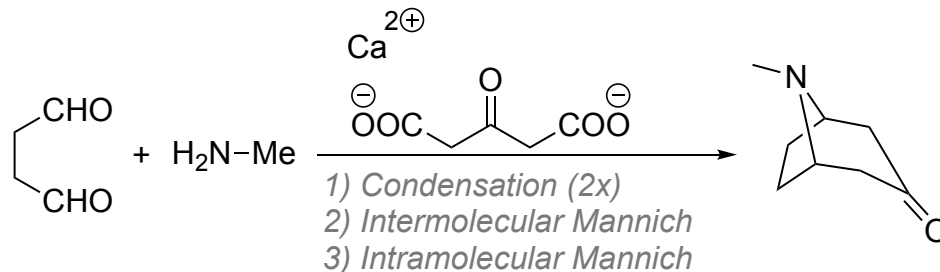


Synthesis of Progesterone (Johnson, 1971)

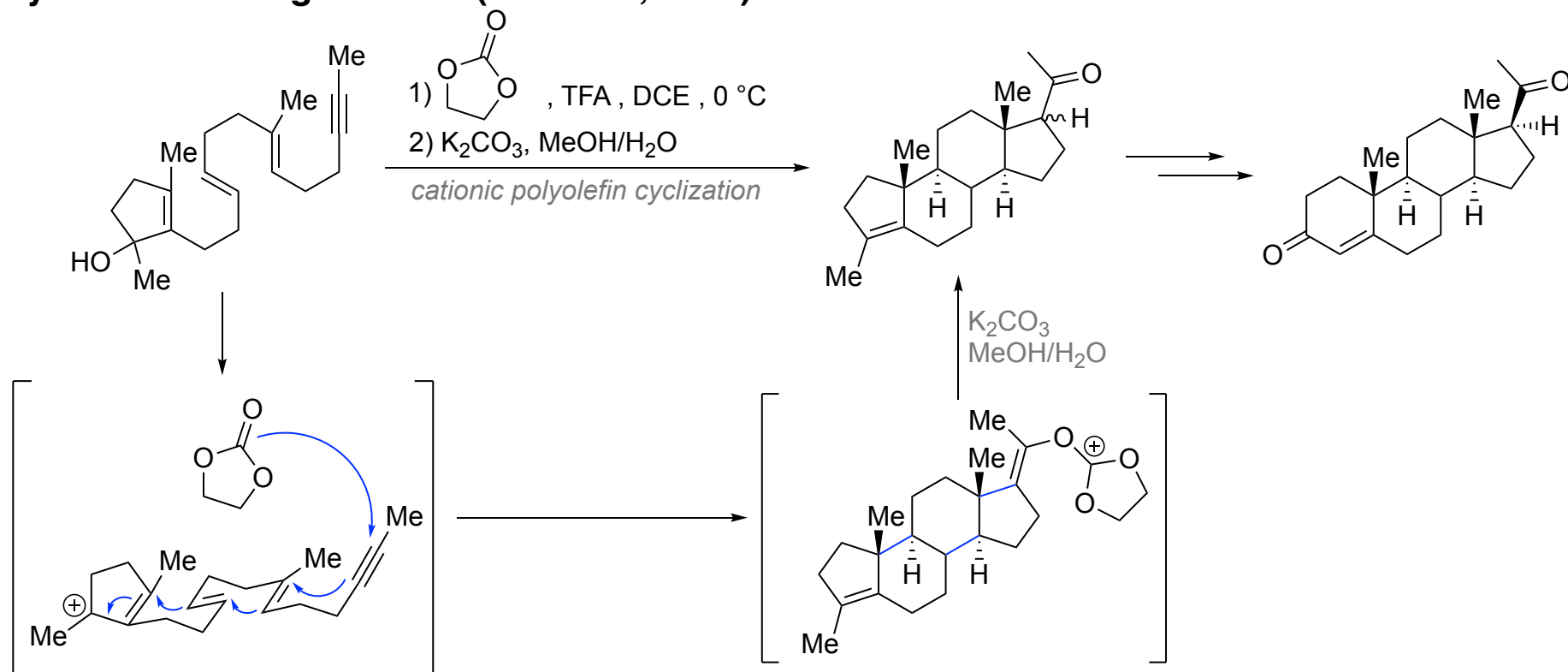


Introduction – Cascade Reactions

First reported: Synthesis of Tropinone (Robinson, 1917)

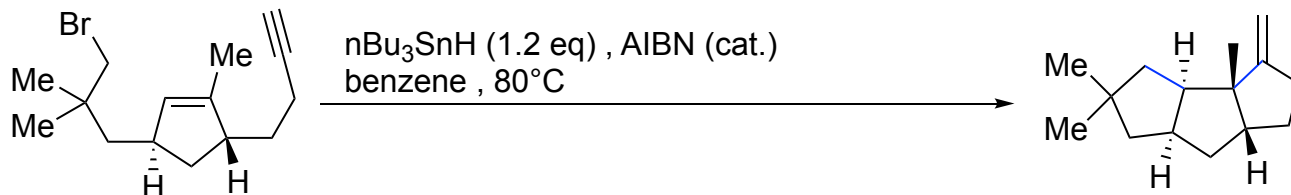


Synthesis of Progesterone (Johnson, 1971)



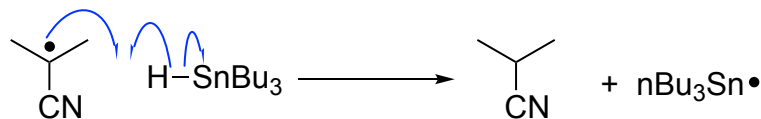
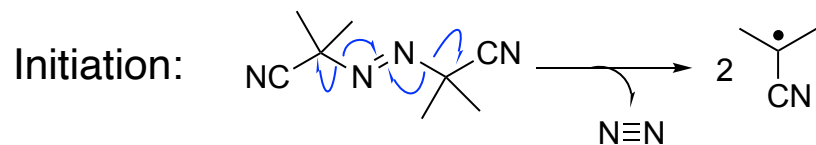
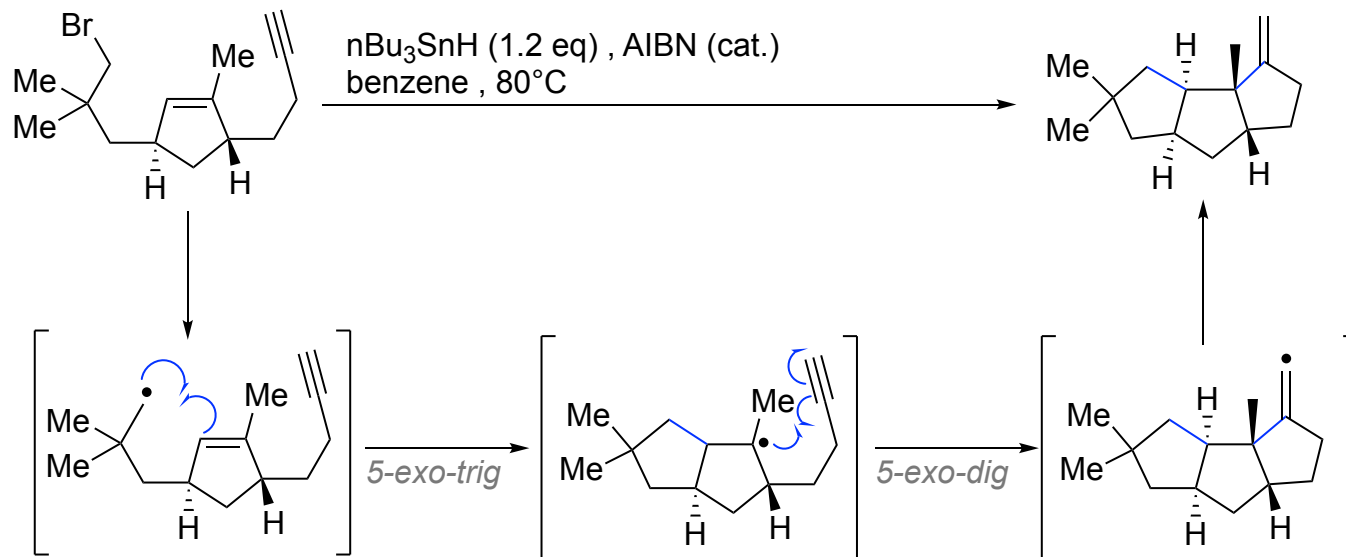
Introduction – Radical Cascade Reactions

Total synthesis of (+/-)-Hirsutene (Curran, 1985) – Key step constitutes a radical



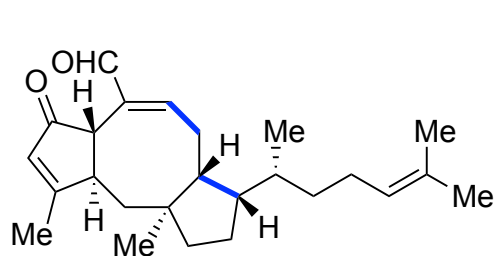
Introduction – Radical Cascade Reactions

Total synthesis of (+/-)-Hirsutene (Curran, 1985)

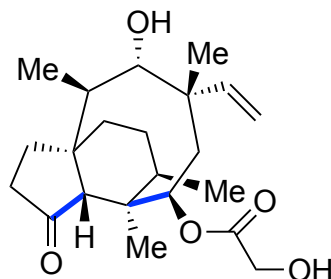


Introduction – Radical Cascade Reactions

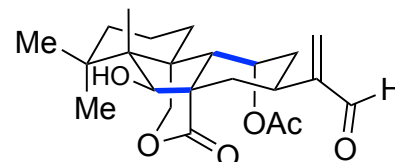
Achieving rapid complexity in total syntheses of natural products and complex materials:



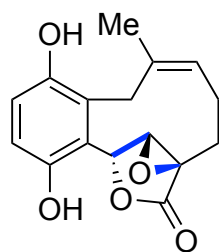
(-)-6-epi-ophiobolin N



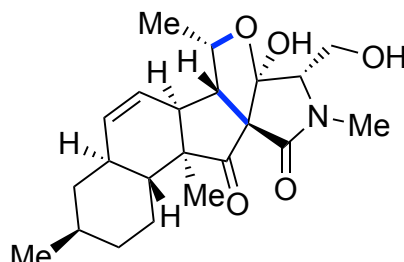
(+)-pleuromutilin



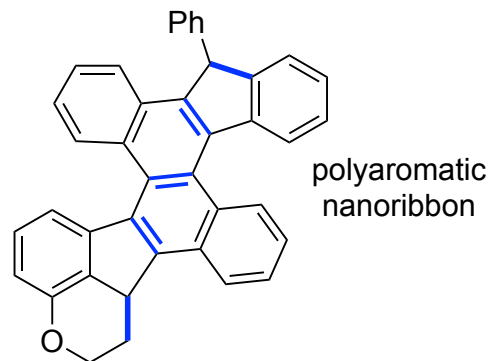
(-)-maoecrystal Z



(+/-)-clavilactone



(+)-fusarisetin



polyaromatic
nanoribbon



stoichiometric amounts of reagents and/or additives required to mediate these strategies

Introduction – Radical Relay

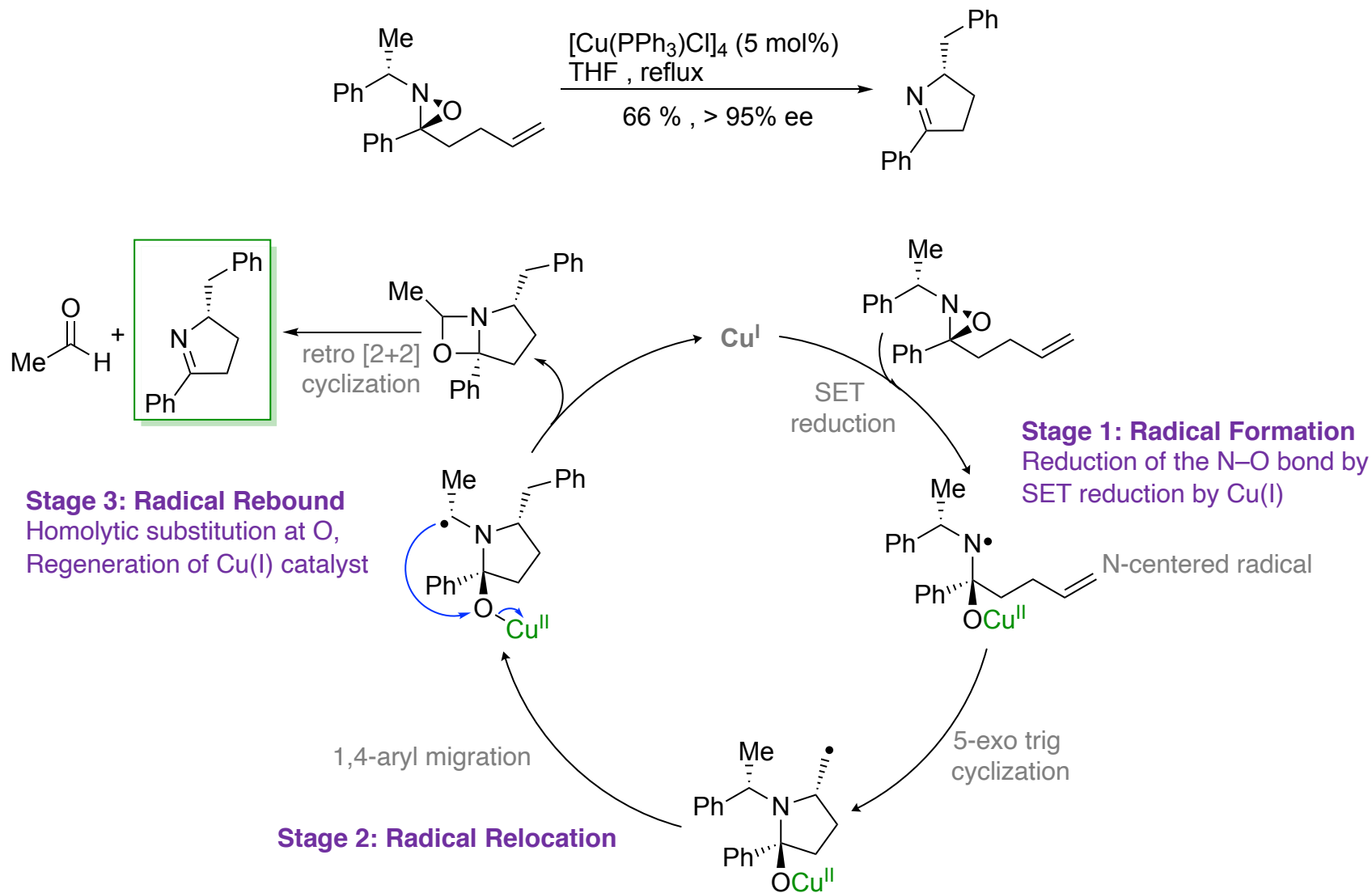
Definition: redox-neutral process in which radical character is re-generated and thus
(by Procter) only a catalytic amount of radical-generating reagent is required

3 key stages:

- 1) Radical Formation: Radical character is generated by SET or addition of radical
- 2) Radical Relocation: Radical character is propagated during a bond-forming / breaking sequence
- 3) Radical Rebound: Radical character is recycled, typically by SET back to metal catalyst or expulsion of a radical that acts as a catalyst

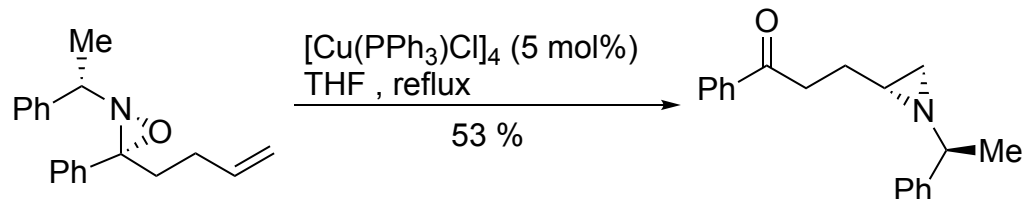
Examples – Intramolecular Radical Relays

Cu(I)-catalyzed cascade synthesis of pyrrolines (Aubé 1992)



Examples – Intramolecular Radical Relays

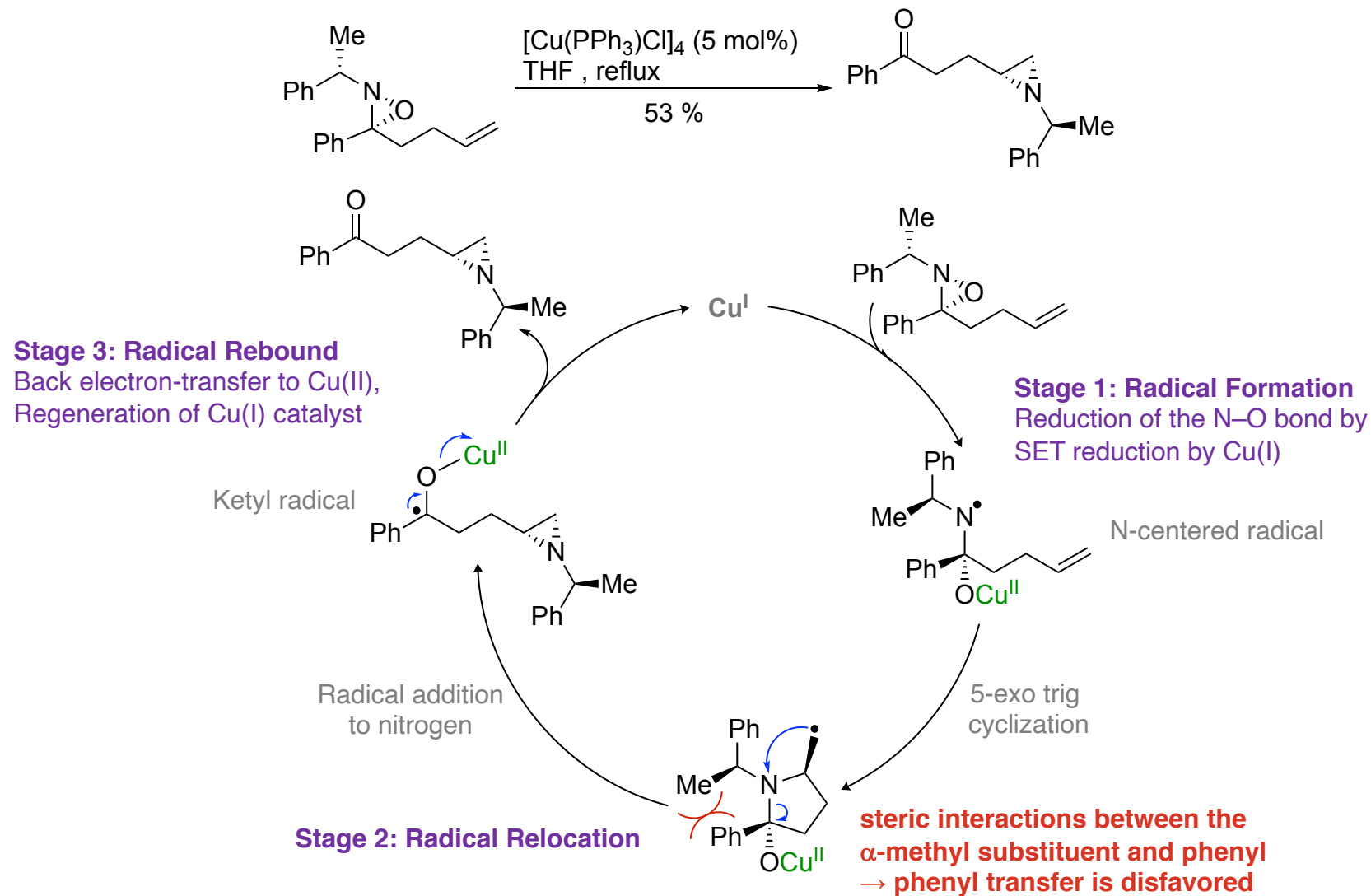
Cu(I)-catalyzed cascade synthesis of pyrrolines (Aubé 1992)



QUESTION: Why does the diastereoisomeric oxaziridine lead to an azirine instead of the pyrroline?

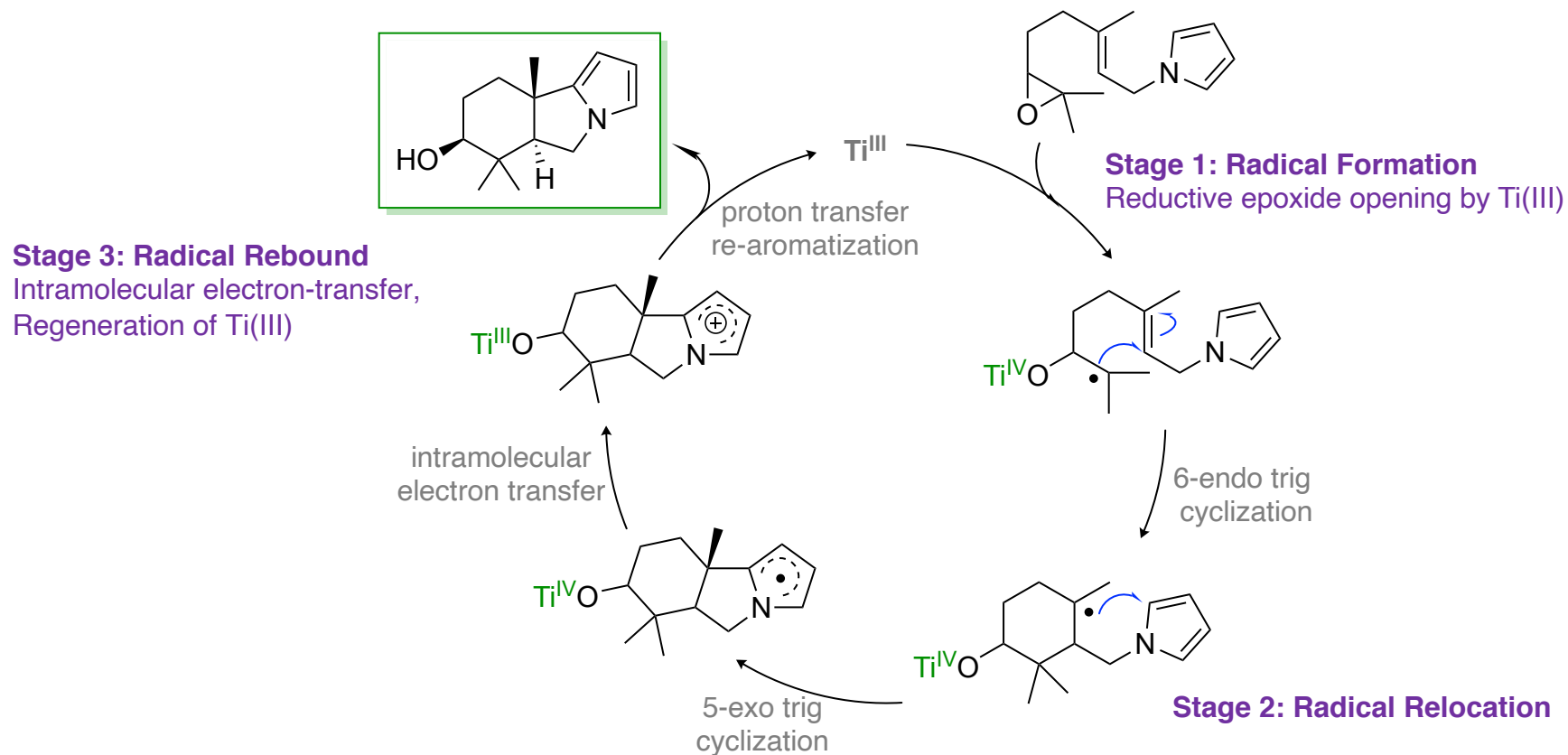
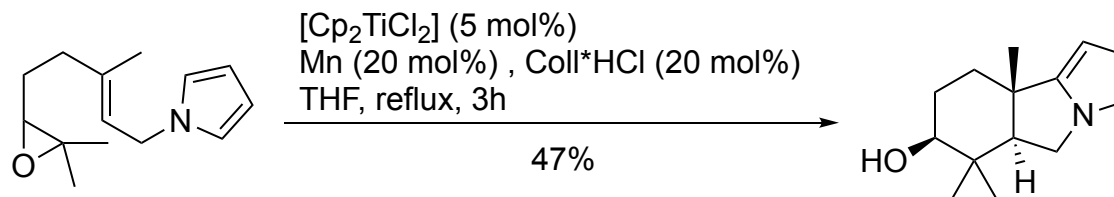
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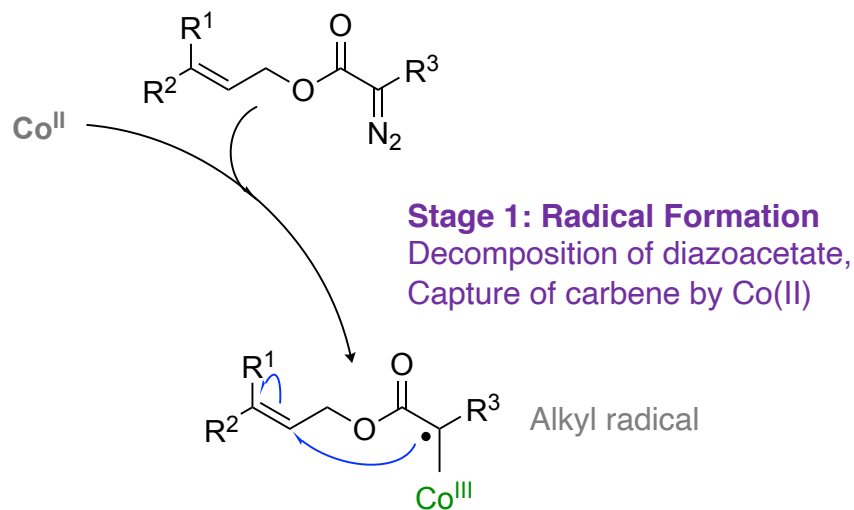
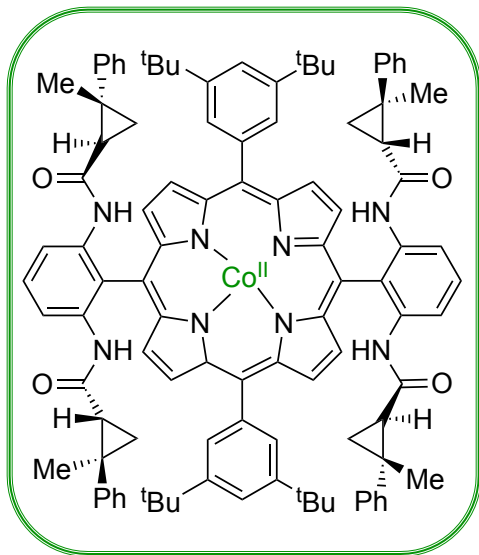
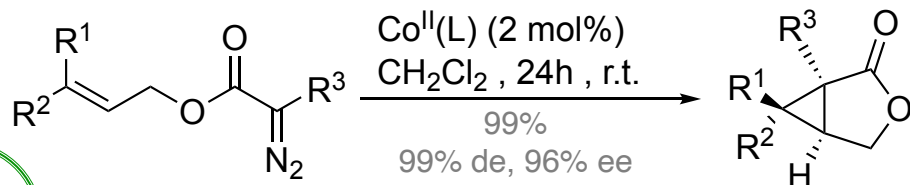
Examples – Intramolecular Radical Relays

Ti(III)-catalyzed cascade synthesis of dihydropyrrolizine scaffolds (Gansäuer 2016)



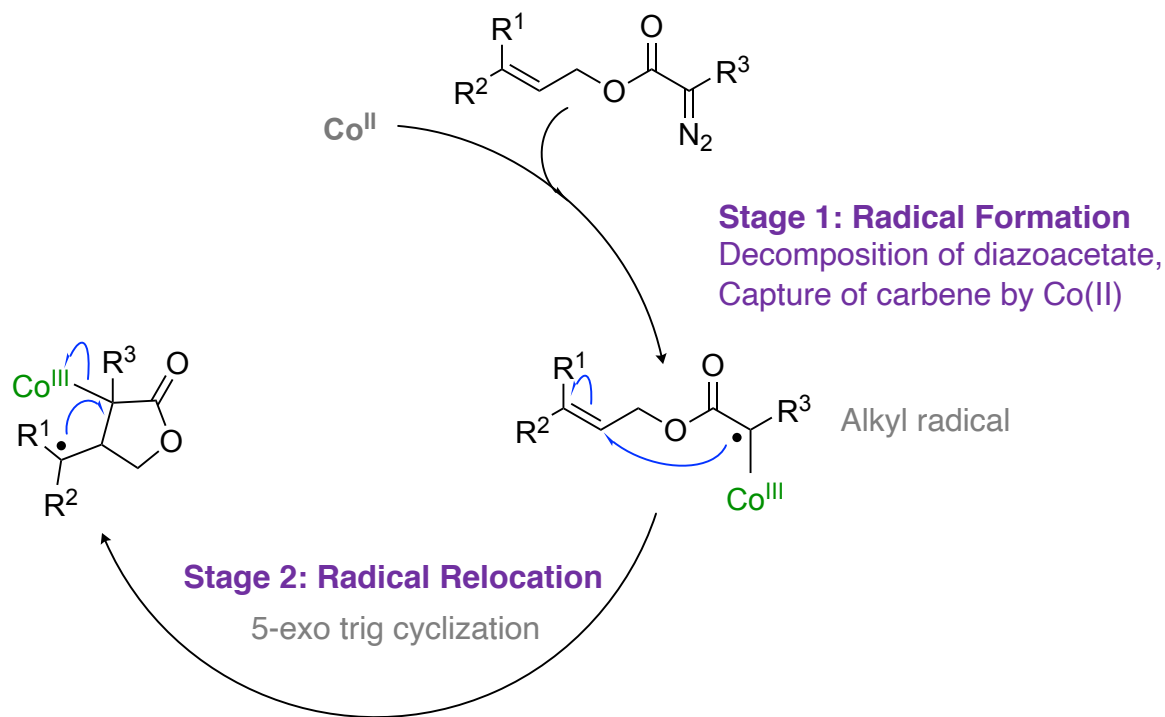
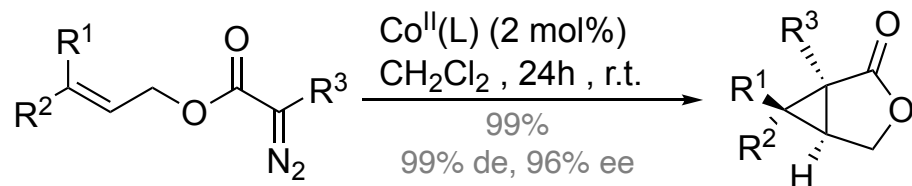
Examples – Intramolecular Radical Relays

Co(II)-catalyzed enantioselective cascade synthesis of cyclopropanes (Zhang 2011)



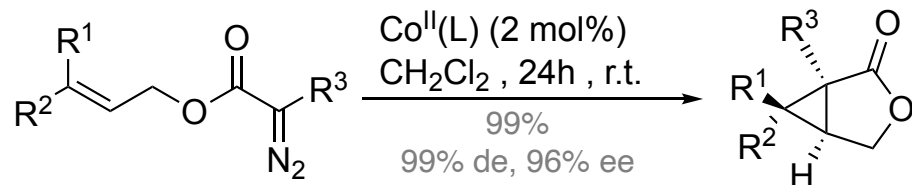
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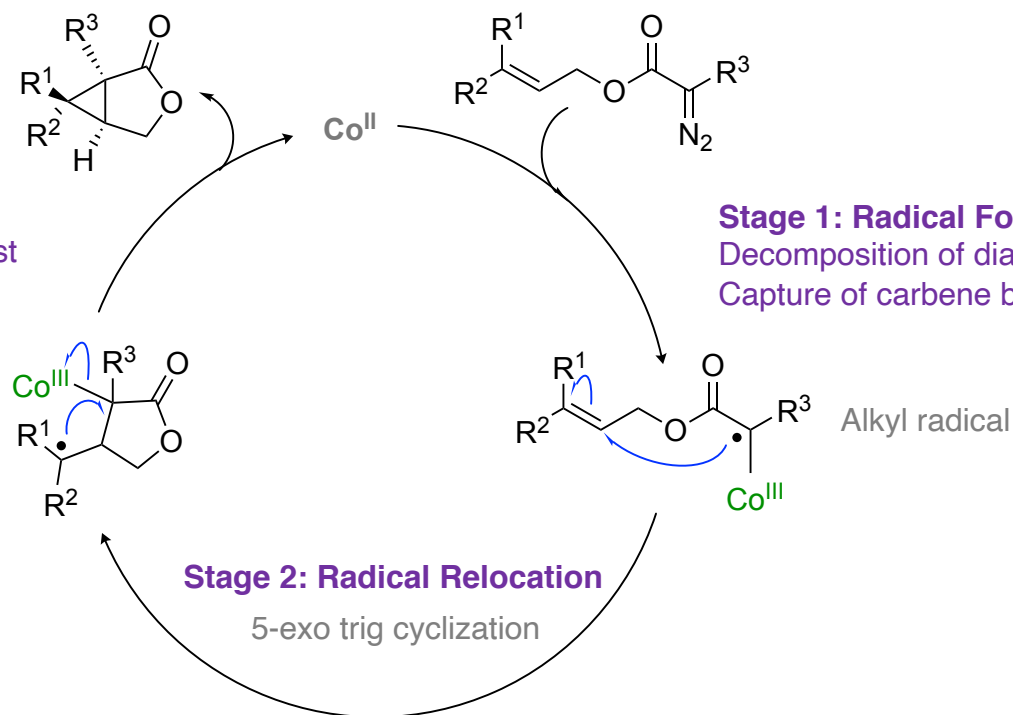
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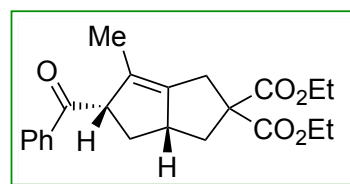
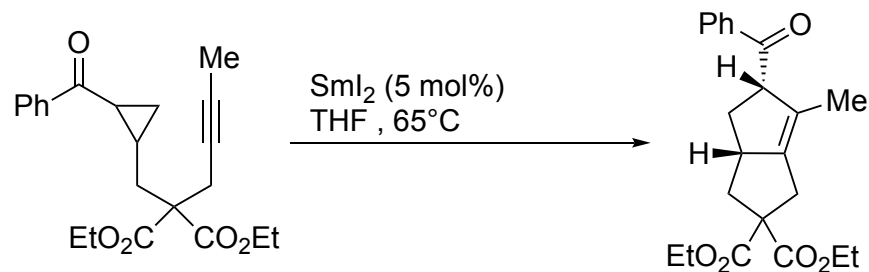
Stage 3: Radical Rebound
Cyclopropanation,
Regeneration of Co(II) catalyst

Stage 1: Radical Formation
Decomposition of diazoacetate,
Capture of carbene by Co(II)

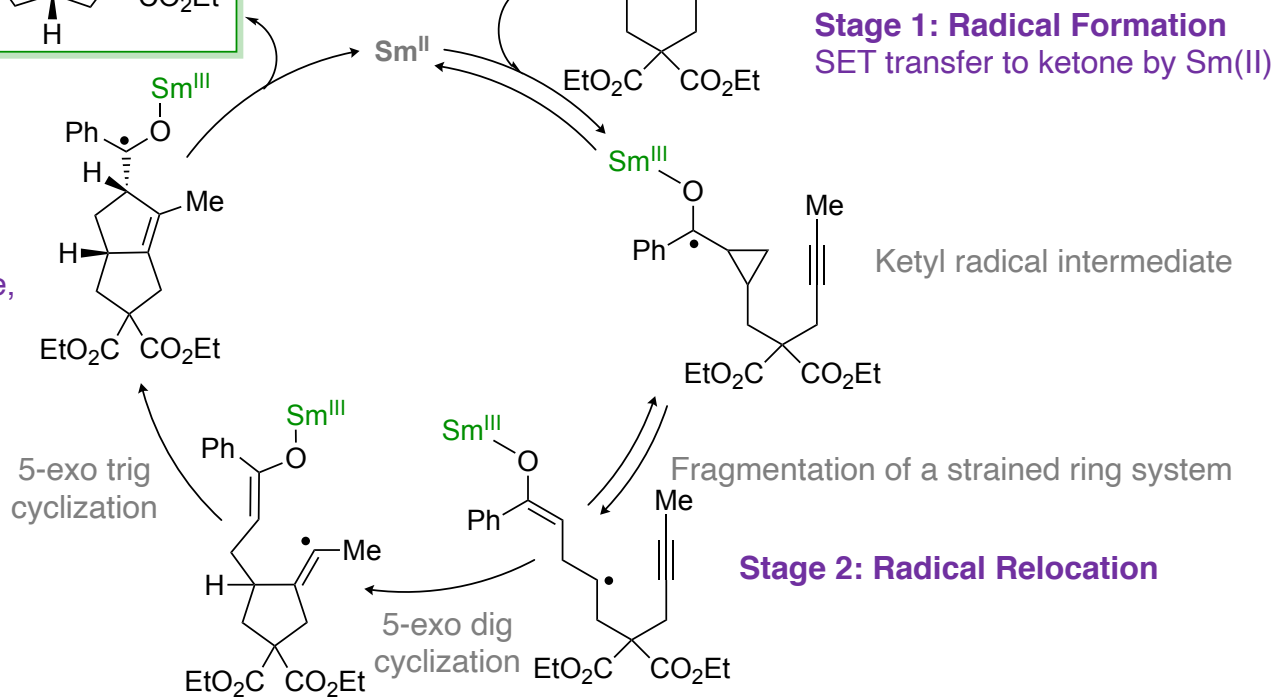


Examples – Intramolecular Radical Relays

Sm(II)-catalyzed cyclization cascade (Procter 2019)

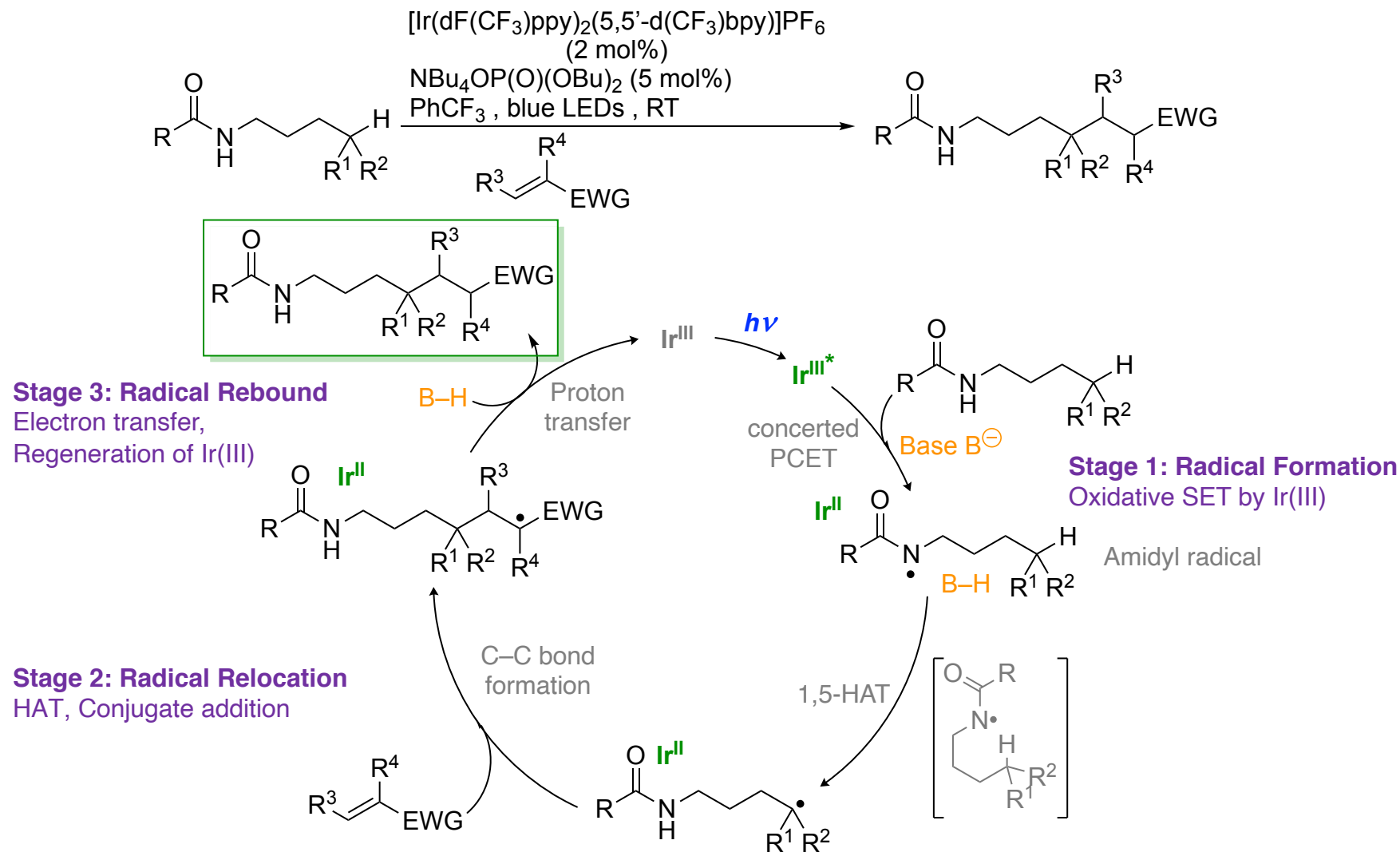


Stage 3: Radical Rebound
Radical addition to metal enolate,
Regeneration of Sm(II) catalyst



Examples – Radical Relays involving HAT

Ir(III)-catalyzed cascade reaction (Knowles and Rovis, 2016)

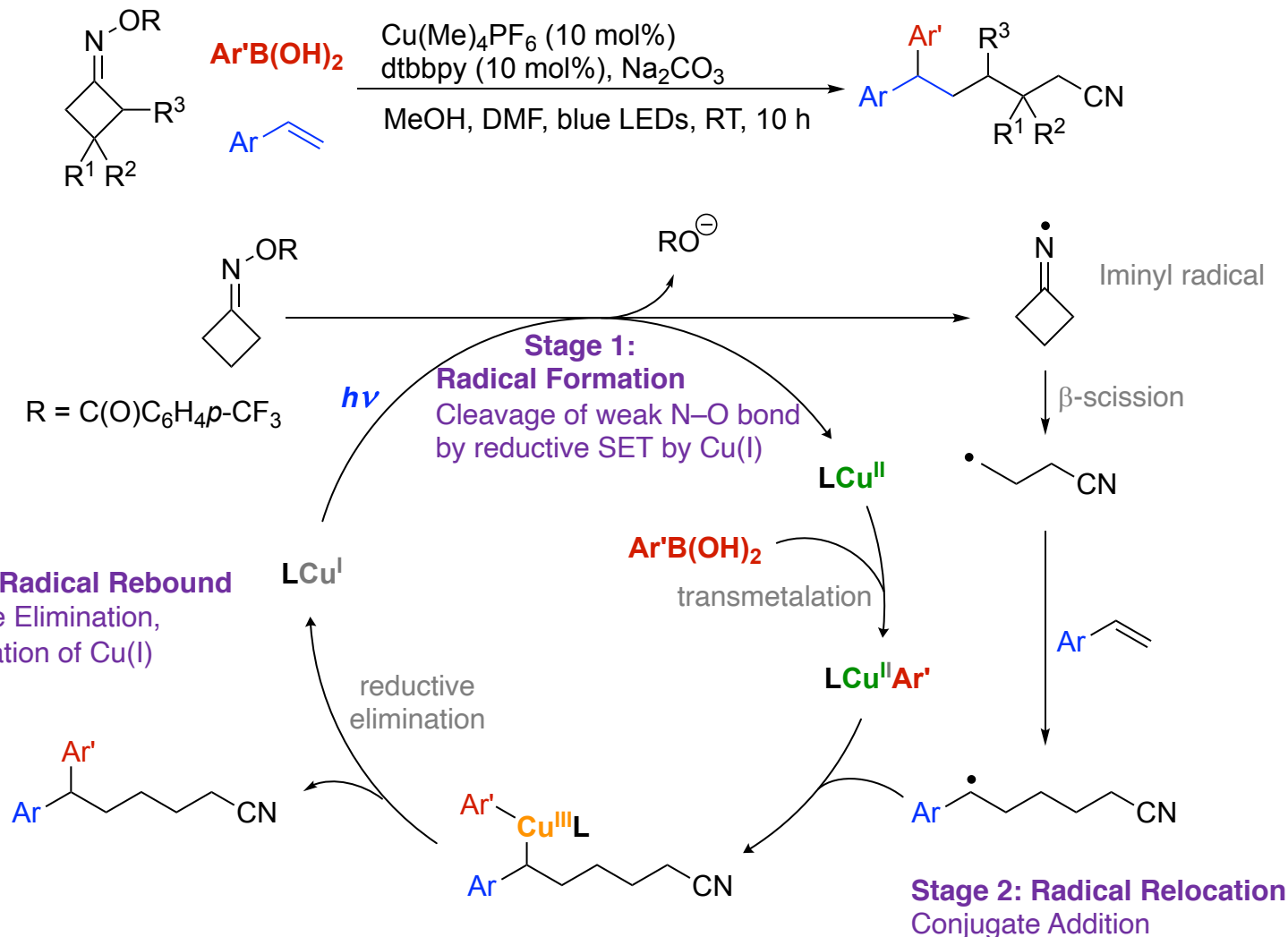


G. J. Choi, Q. Zhu, D. C. Miller, C. J. Gu, R. R. Knowles, *Nature* **2016**, 539, 268–271

J. C. K. Chu, T. Rovis, *Nature* **2016**, 539, 272–275

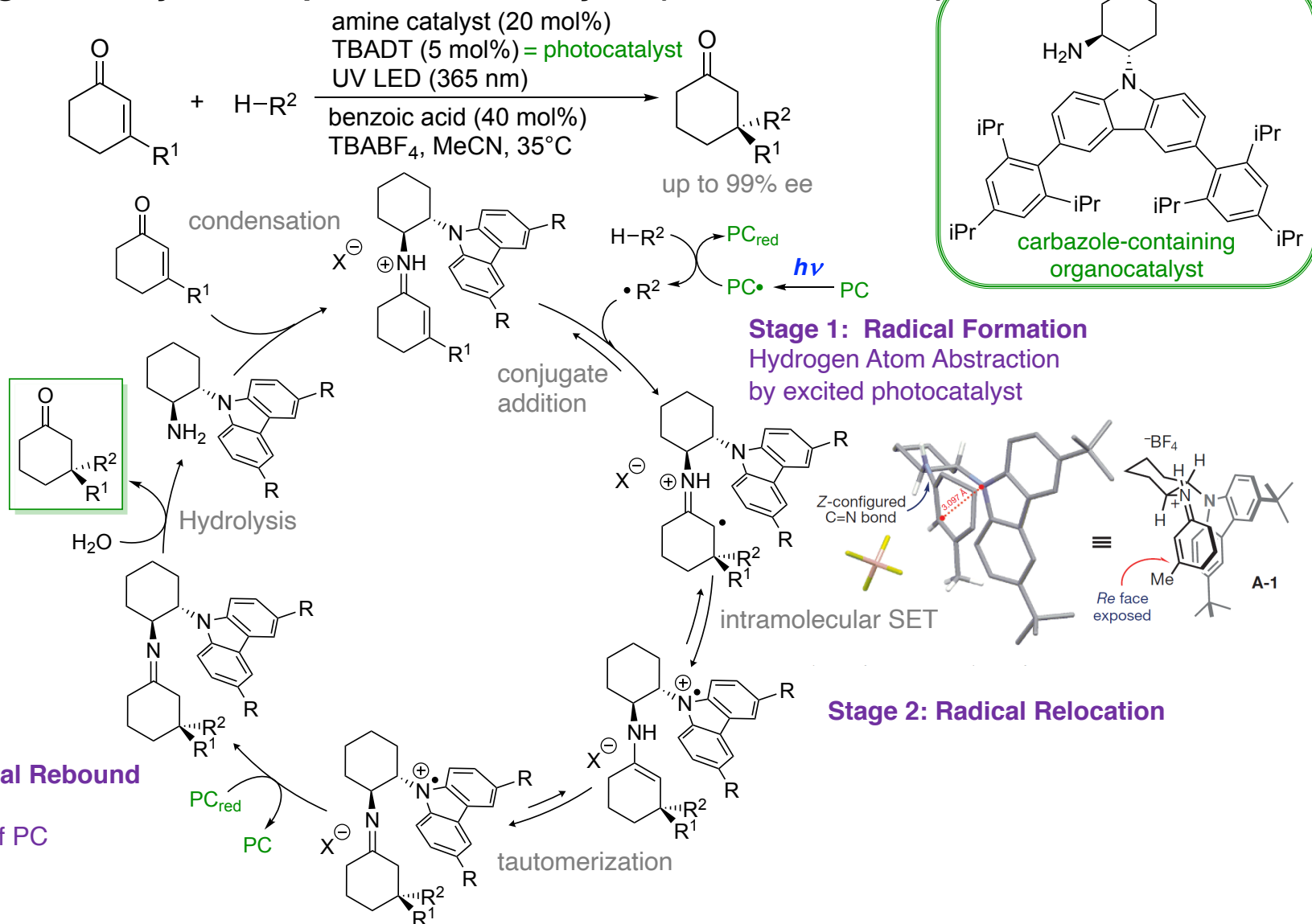
Examples – Intermolecular Radical Relays

Cu(I)-catalyzed multicomponent coupling (Xiao and Chen, 2018)



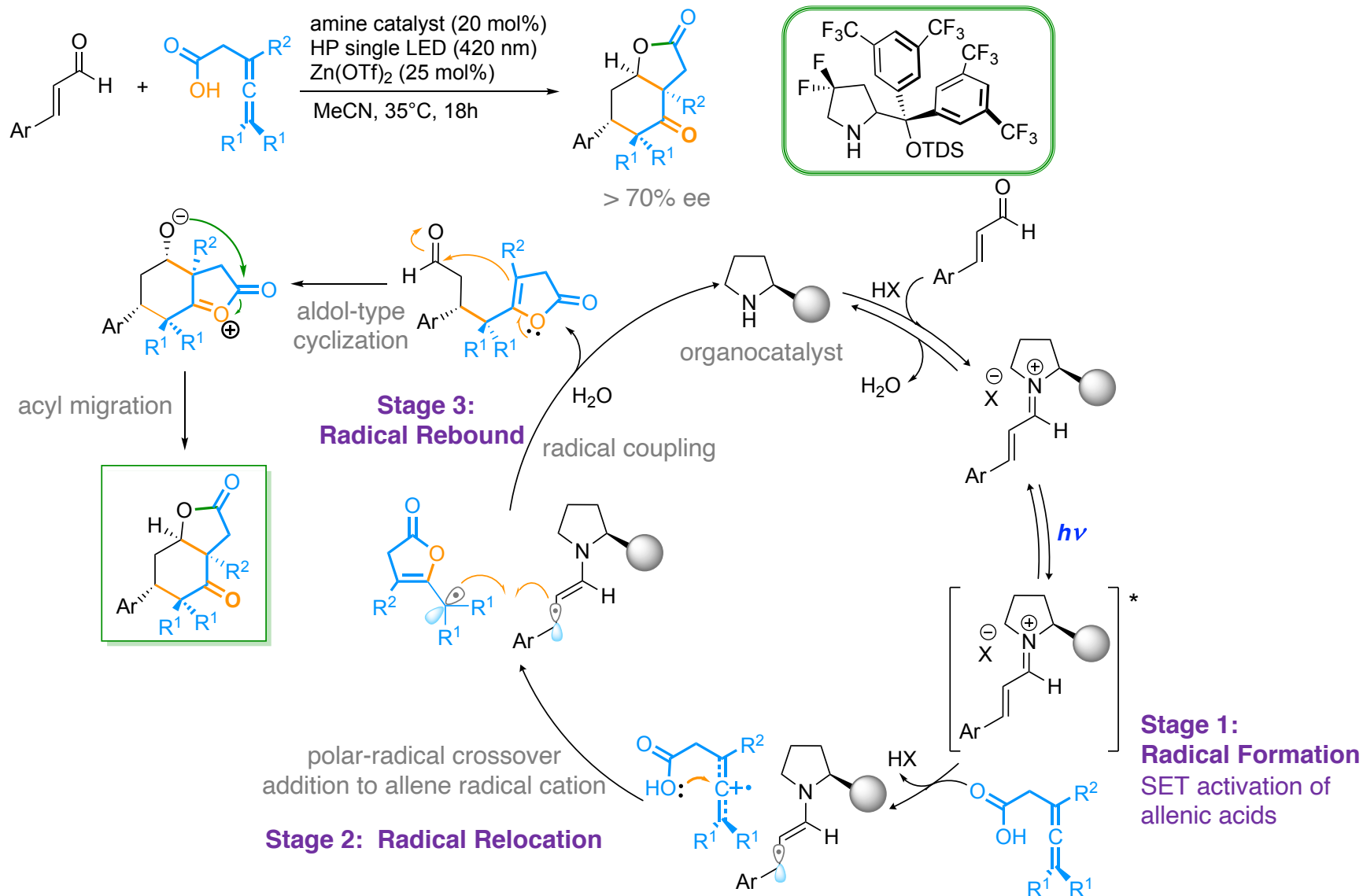
Examples – Intermolecular Radical Relays

Merging organocatalysis and photoredox catalysis (Melchiorre, 2016)



Examples – Intermolecular Radical Relays

Merging organocatalysis and photoredox catalysis (Melchiorre, 2019)



Summary – Cascade Reactions by Radical Relay

Strategies for radical formation:

1. Cleavage of a weak bond by reductive SET from a low valent metal
2. Fragmentation of a strained ring system
3. Capture of a carbene by a low valent metal catalyst
4. Fragmentation promoted by visible light

Strategies for radical relocation:

1. Driven by release of ring strain
2. Hydrogen Atom Transfer (HAT)
3. Conjugate Addition

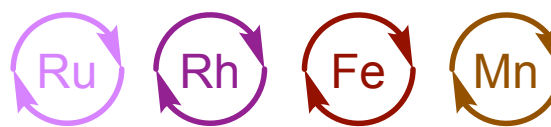
Following the Baldwin Rules

Strategies for radical rebound:

1. Homolytic substitution (at oxygen)
2. Intramolecular electron-transfer to regenerate the catalyst
3. Radical addition to a metal enolate



Enantioselective Radical Relays



Metal-free Radical Relays using organocatalysts

Outlook

- * (radical) cascades as versatile tools for the construction of complex, molecular architectures
- * high sustainability: atom-economic
 energy-efficient
 waste minimization (only catalytic amounts)
- * challenging starting materials – strained ring systems, diazo-compounds etc.

Can more general starting materials serve as an input?

Can general design principles be developed to upgrade any radical process to a catalytic relay process?

Thank you very much for your attention!

Recent advances in iron-catalyzed cross-coupling reactions

CH-707: Frontiers in Chemical Synthesis -
Towards Sustainable Chemistry

11.05.2020

Alexandre Leclair

Important literature

Books:

M. Nakamura *et al.*, in *Org. React.*, American Cancer Society, **2014**, pp. 1–210.

E. Bauer, Ed. , *Iron Catalysis II*, Springer International Publishing, Cham, **2015**.

Reviews:

I. Bauer and H.-J. Knölker, *Chem. Rev.* **2015**, *115*, 3170–3387

T. L. Mako and J. A. Byers, *Inorg. Chem. Front.*, **2016**, *3*, 766

M. L. Neidig *et al.*, *J. Am. Chem. Soc.* **2018**, *140*, 11872–11883 / *Acc. Chem. Res.* **2019**, *52*, 140–150

**CHEMICAL
REVIEWS**

Iron Catalysis in Organic Synthesis

Ingmar Bauer and Hans-Joachim Knölker*

Recent advances in iron-catalysed cross coupling reactions and their mechanistic underpinning

T. L. Mako and J. A. Byers*

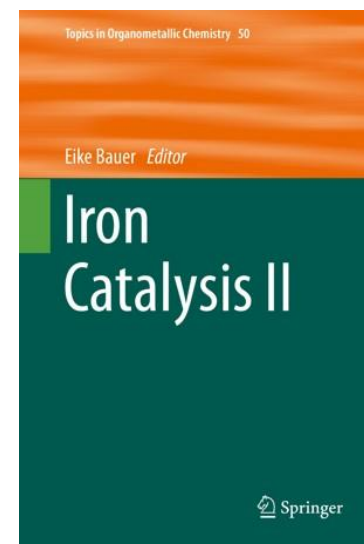


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III. Recent progress for classical cross-coupling reactions

→ Focus on mechanism investigations

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III. Recent progress for classical cross-coupling reactions

→ Focus on mechanism investigations

IV. Conclusion and outlooks

Introduction

25 Mn	26 Fe	27 Co	28 Ni
43 Tc	44 Ru	45 Rh	46 Pd



Fe

[Ar] 3d⁶ 4s²

Transition metal



Stable isotopes: ⁵⁴Fe, ⁵⁶Fe, ⁵⁷Fe, ⁵⁸Fe

Oxidation states: -II, -I, 0, +I, +II, +III, +IV, +V, +VI

FeCl₂, FeCl₃, Fe(acac)₃

Readily available: 4th more abundant element in the Earth's crust

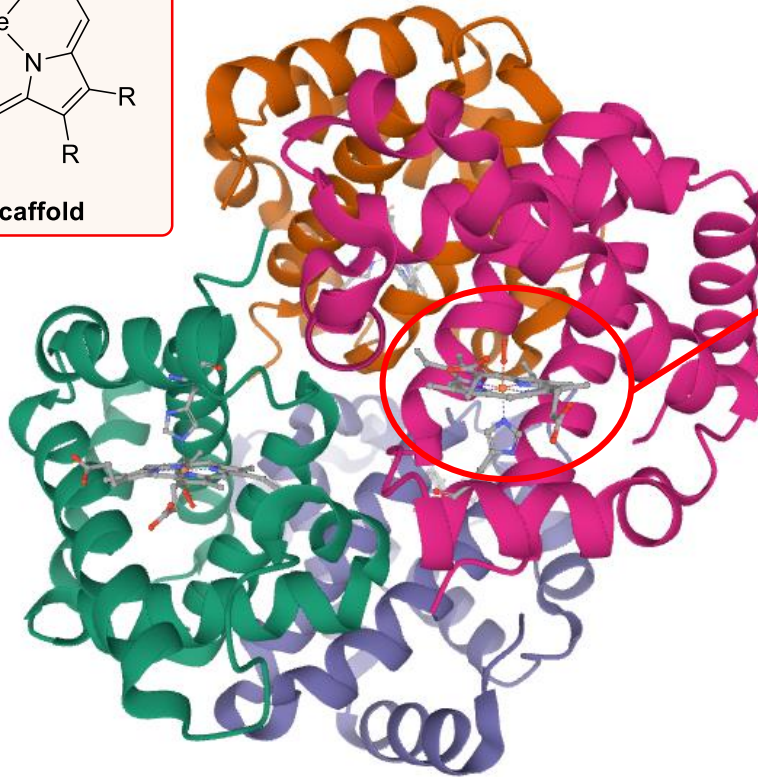
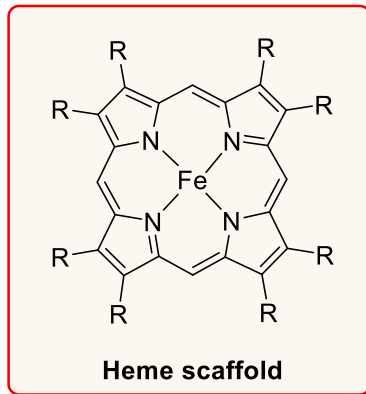
Cheap: 0.081 €/kg

Relatively non-toxic:

Acceptable level in drugs → 1300 ppm Vs ≤10 ppm for most transition metals

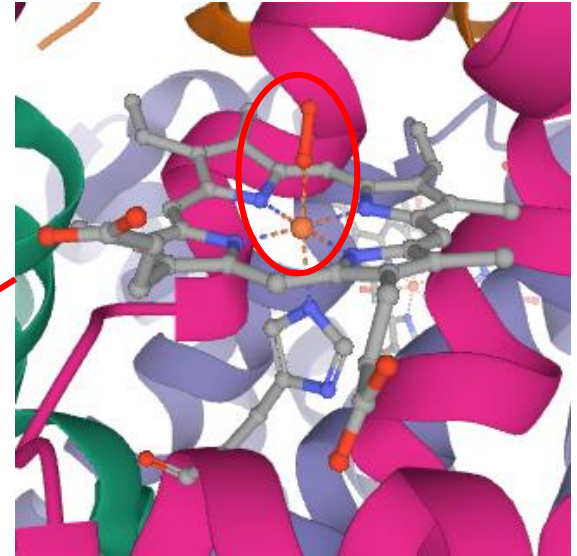
Introduction

In biology: Transport of oxygen in vertebrates



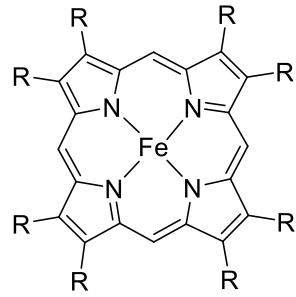
Hemoglobin

Oxygen complexation

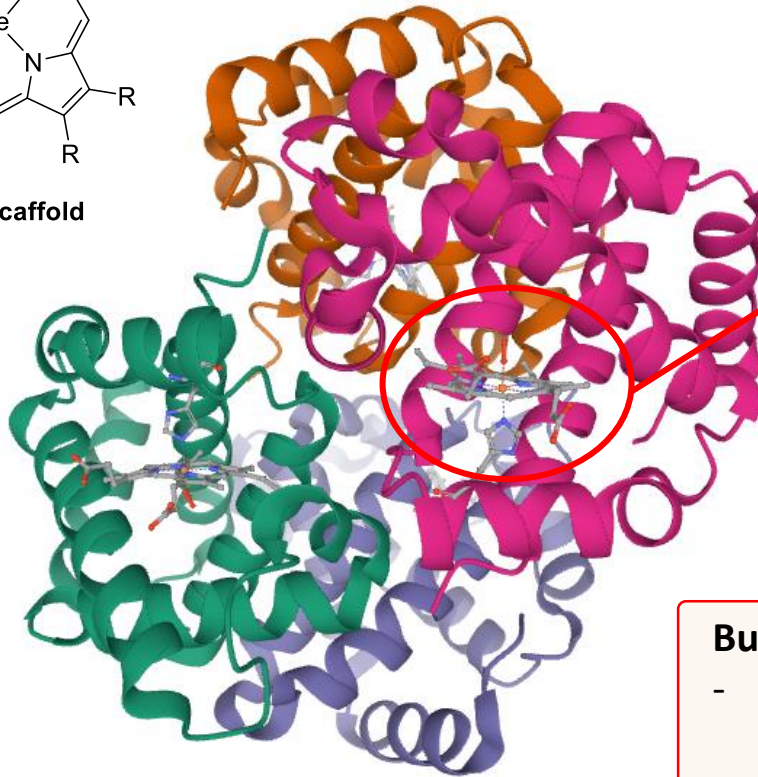


Introduction

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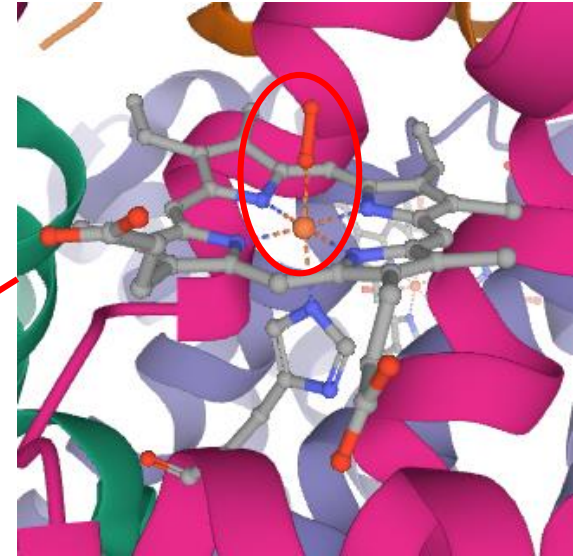


Heme scaffold



Hemoglobin

Oxygen complexation



But also:

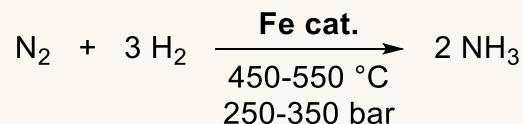
- For the transfer of electrons in the cellular respiration (**Fe-S proteins**)
- For the immune system (**lactoferrin**)
- ...

Introduction

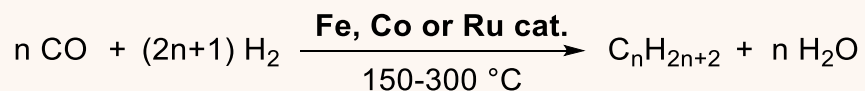
Applications in industrial productions:

- Production of ammonia (**Haber-Bosch process**):

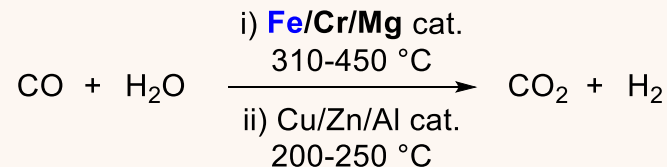
→ Main source of ammonia for nitrogen fertilizer



- Production of alkanes (**Fischer-Tropsch process**):



- Production of hydrogen gas (**Water-gas shift reaction**):

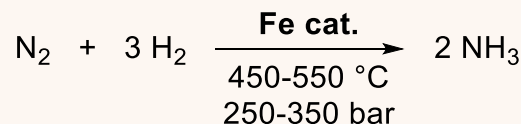


Introduction

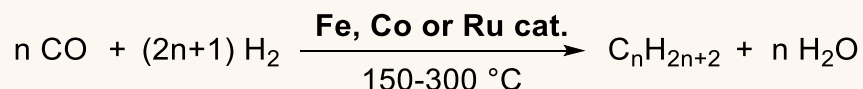
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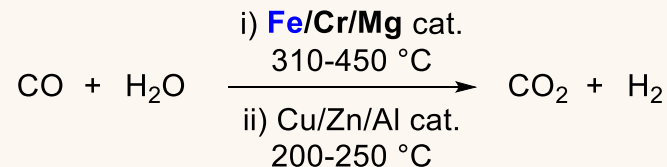
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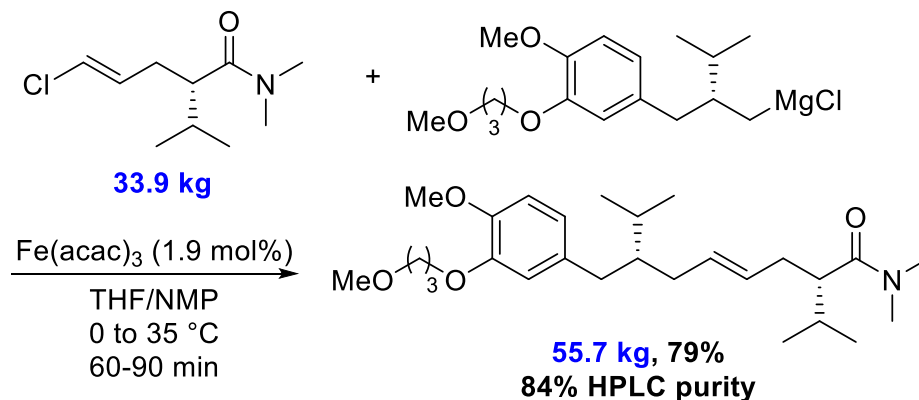
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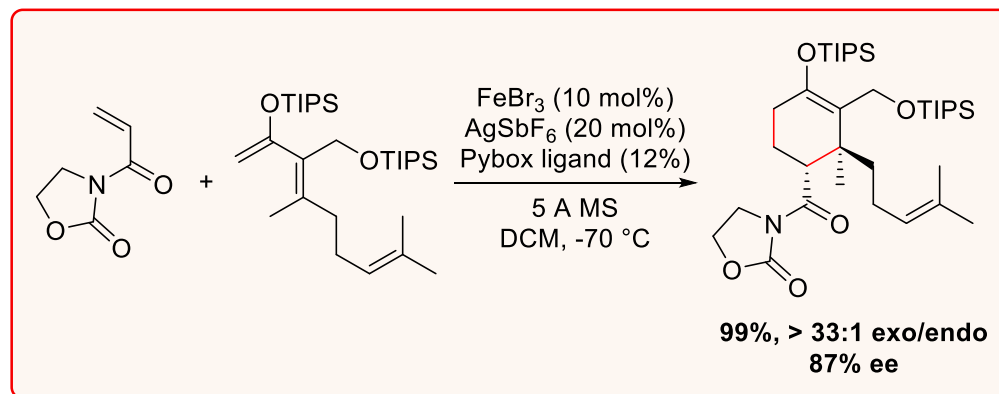
- Current investigations in cross-couplings:



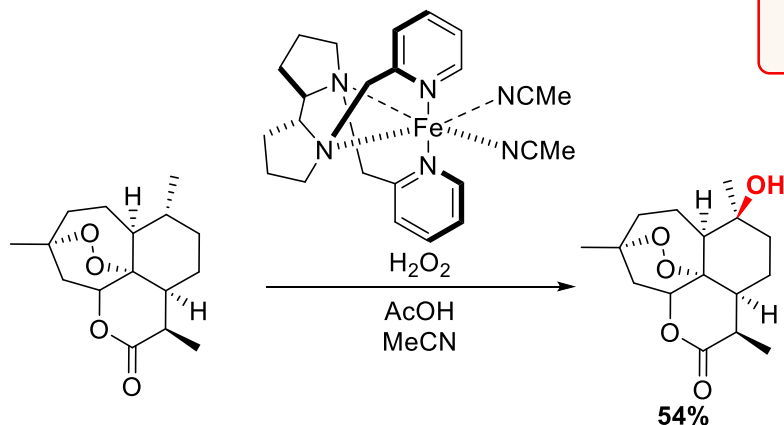
Introduction

Broad range of applications:

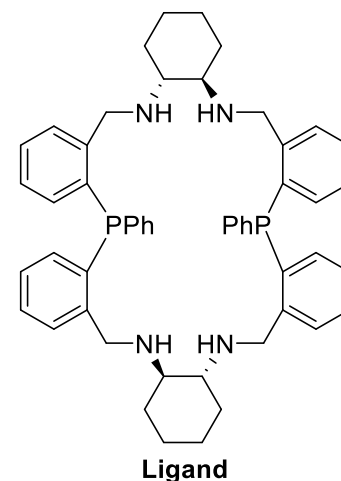
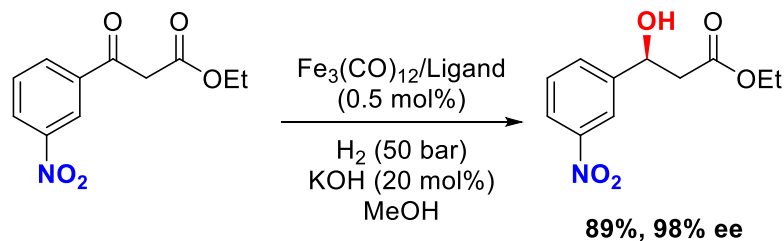
As Lewis acid: Diels-Alder, Friedel-Crafts, ...



As catalyst in oxidation: C-H functionalization



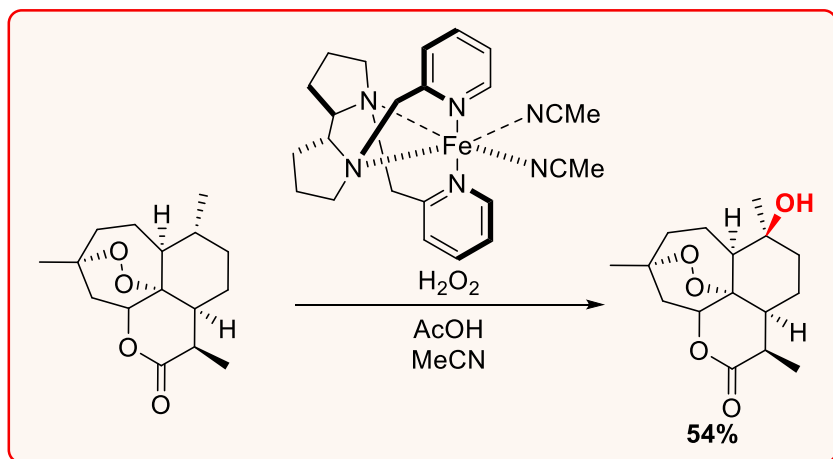
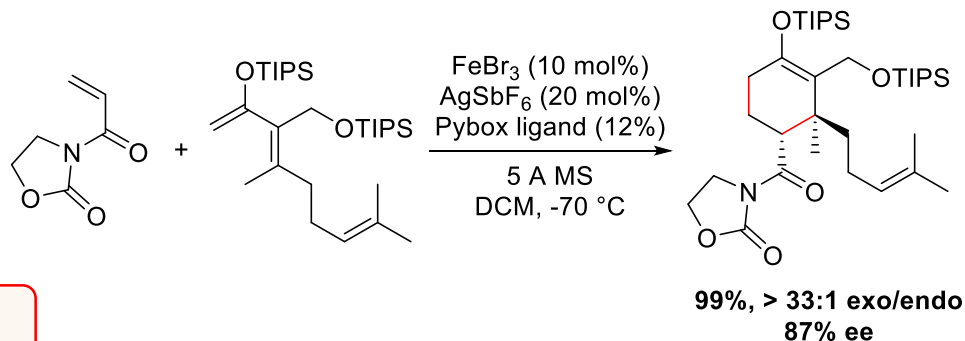
In catalytic hydrogenation:



Introduction

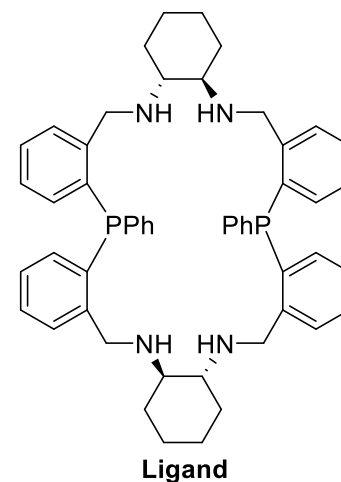
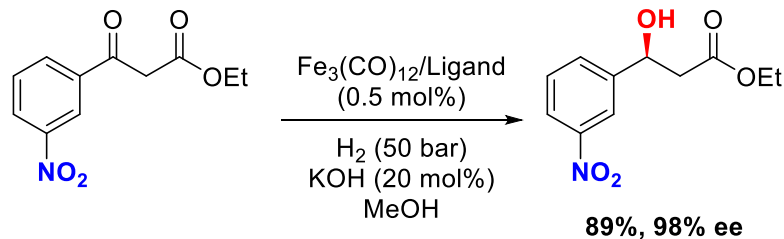
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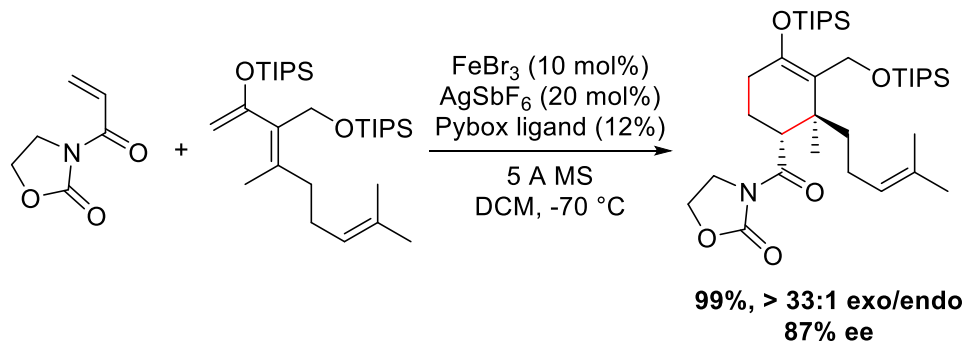
In catalytic hydrogenation:



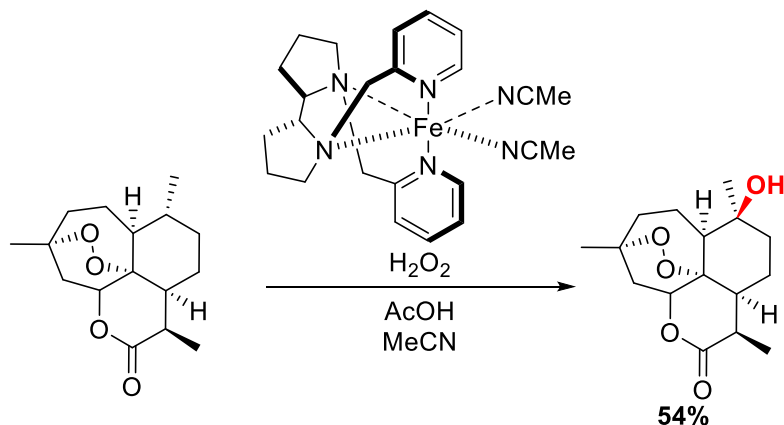
Introduction

Broad range of applications:

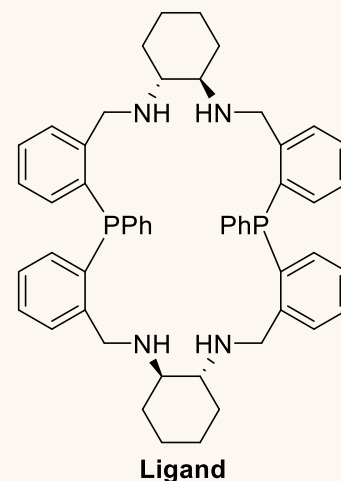
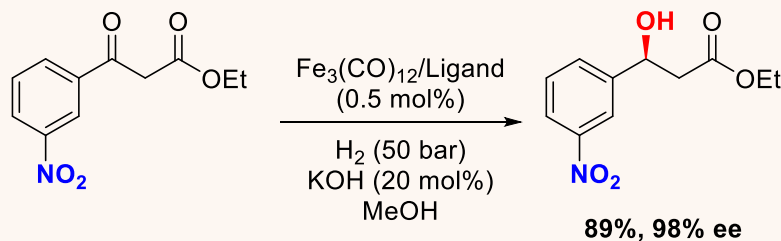
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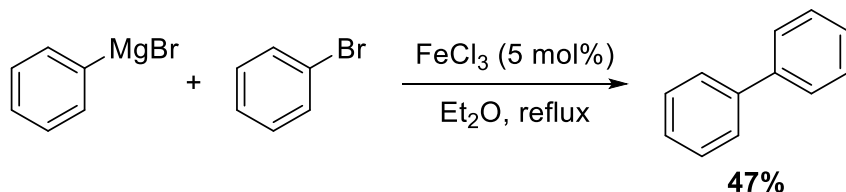
In catalytic hydrogenation:



Preliminary work

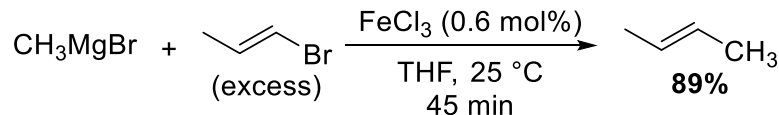
Initial report by Kharash, 1941

- Exploring the effect of metallic halides (Fe, Co, Ni, ...) on the reaction of ArMgBr and RX

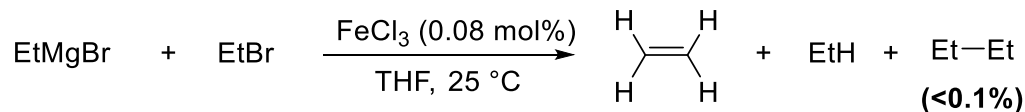


Development of Fe-catalyzed Kumada-Corriu cross coupling (Kochi, 1971)

- Applicable to alkenyl bromide and Grignard reagents



- Alkyl bromides converted in corresponding alkenes



Further developed only 27 years later by Cahiez

M. S. Kharash, E. K. Fields, *J. Am. Chem. Soc.* **1941**, 63, 2316-2320

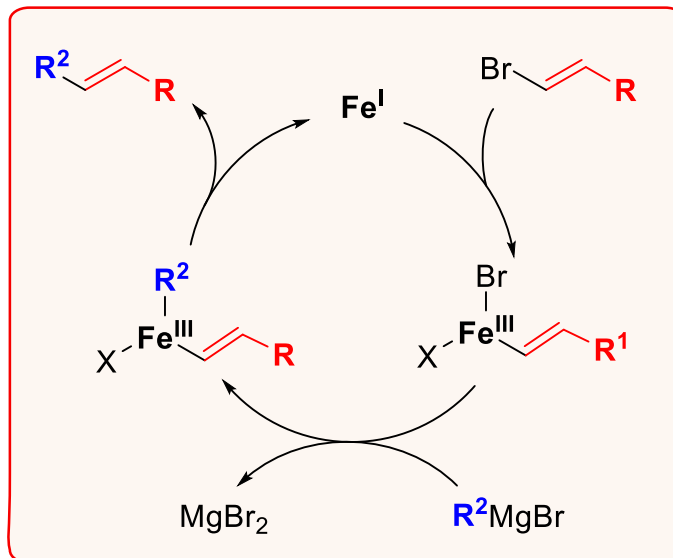
M. Tamura, J. K. Kochi, *J. Am. Chem. Soc.* **1971**, 93, 1487-1489

G. Cahiez, H. Avedissian, *Synthesis* **1998**, 8, 1199-1205

Preliminary work

Proposed mechanism:

Fe^I/Fe^{III} catalytic cycle

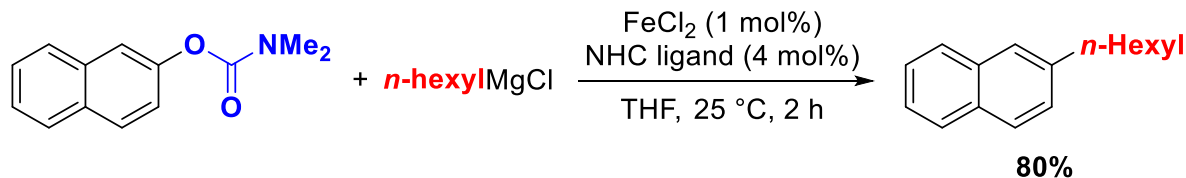


→ Intense ESR spectrum comparable with the one of **HFe^I(dppe)₂**

Recent progress in Kumada-Corriu cross-coupling

Applied to a broad range of electrophiles R-X:

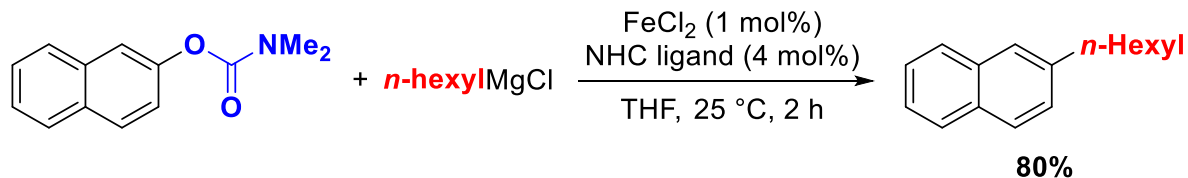
→ X= Cl, Br, I, F, OTs, OTf, OPiv, OCO₂R, OCONMe₂, OPO(OR)₂, SO₂Cl, SO₂R, ...



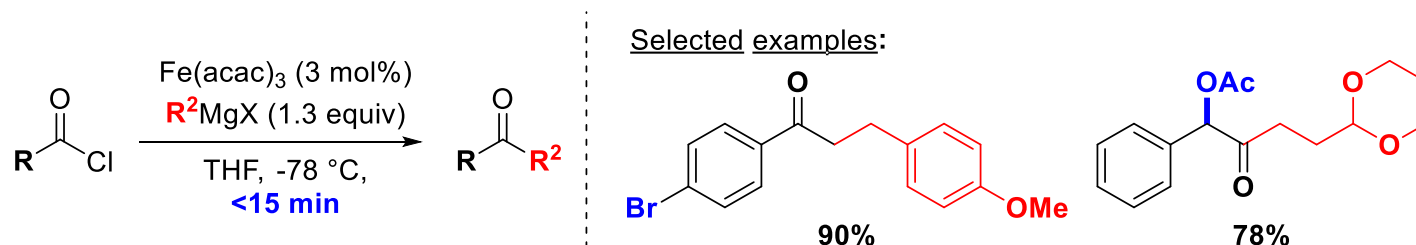
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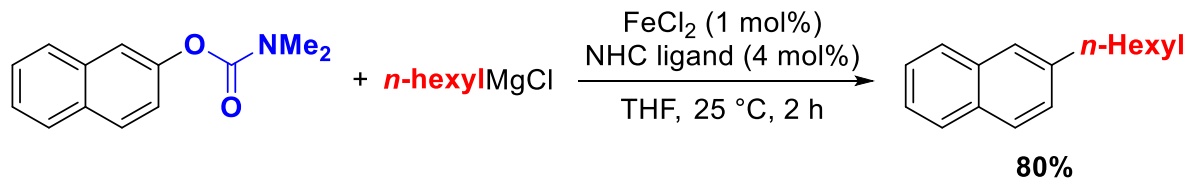
Very reactive but selective:



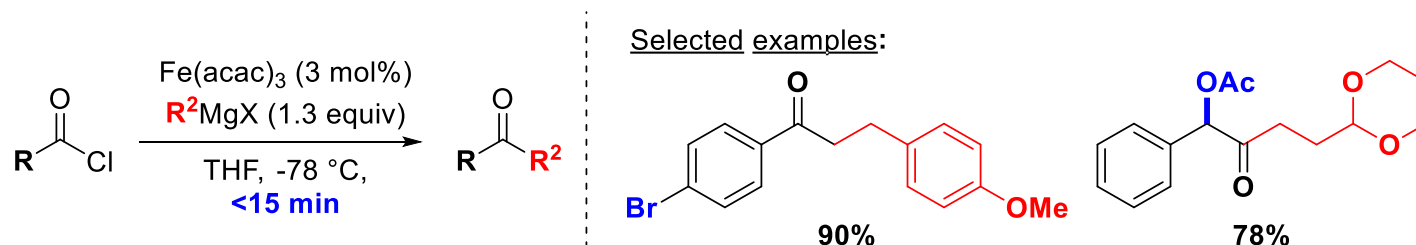
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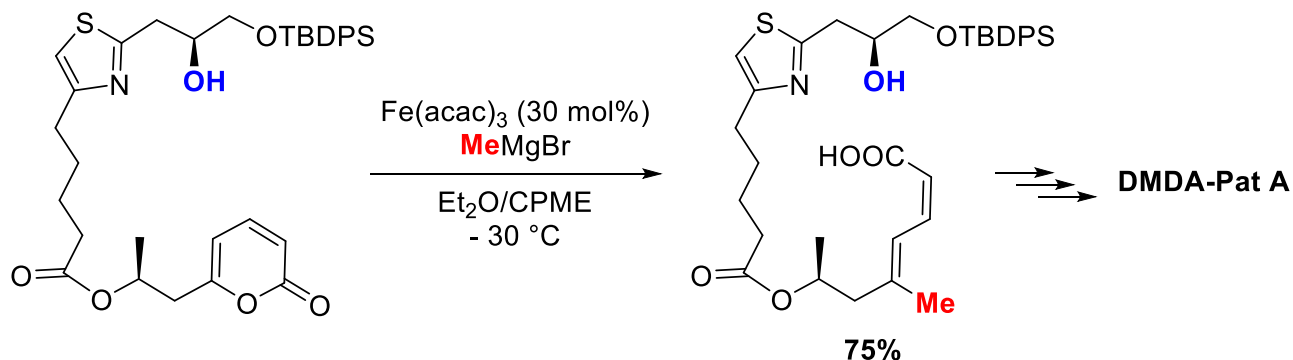
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Very reactive but selective:



New reactivity:



Z.-J. Shi et al., *J. Am. Chem. Soc.* **2009**, 131, 14656-14657

Fürstner et al., *J. Org. Chem.* **2004**, 69, 3943-3949

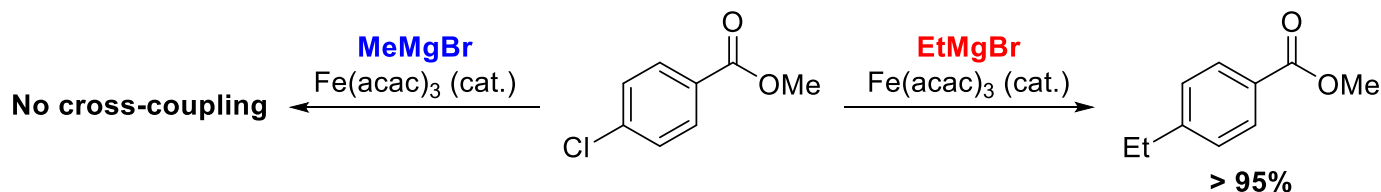
Fürstner et al., *Angew. Chem. Int. Ed.* **2016**, 55, 6051-6056

Recent progress in Kumada-Corriu cross-coupling

Centered on the mechanism:

→ Several proposed: $\text{Fe}^{\text{II}}/\text{Fe}^0$, $\text{Fe}^0/\text{Fe}^{\text{II}}$, $\text{Fe}^{\text{I}}/\text{Fe}^{\text{III}}$, $\text{Fe}^{\text{II}}/\text{Fe}^{\text{III}}$, $\text{Fe}^{\text{II}}/\text{Fe}^{\text{IV}}$

→ Highly dependent on the conditions (Nucleophiles, ligands, solvents, additives)



→ Both one- and two-electron process possible

→ Difficult elucidation of the mechanism:

- Paramagnetic nature of many iron species
- Air/thermal sensitivity of most reactive iron intermediates



Numerous techniques applied:

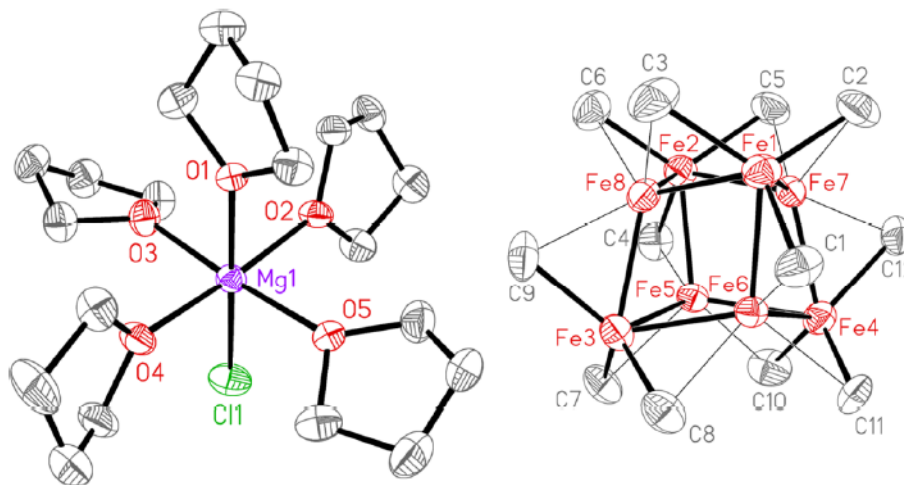
- Electron paramagnetic resonance (EPR)
- Magnetic circular dichroism (MCD)
- ^{57}Fe Freeze-trapped Mössbauer spectroscopy
- X-ray diffraction, ...

Recent progress in Kumada-Corriu cross-coupling

Organoferrate intermediates with R^1MgBr without β -hydrogen (Me, Ph, ...)

- Fe^I species detected by Kochi $\rightarrow [Fe_8Me_{12}]^- [MgCl(THF)_5]^+$ isolated by Neidig *et al.*

$\rightarrow$ Low activity alone, **require additional MeMgBr**

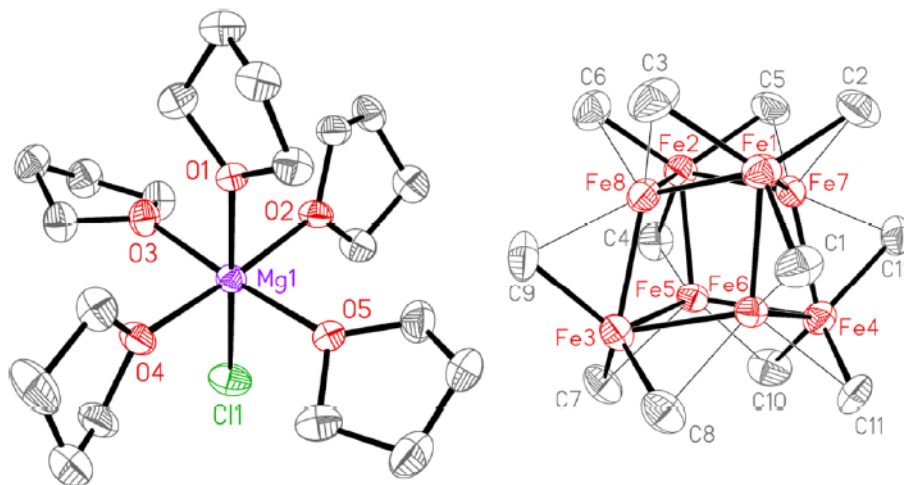


Recent progress in Kumada-Corriu cross-coupling

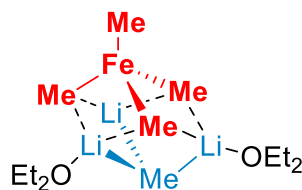
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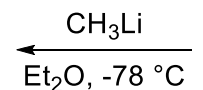


- Several organoferrates isolated upon reaction of $FeCl_3$ with RMetal

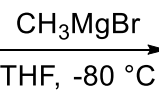


Moderately active

Fürstner *et al.*

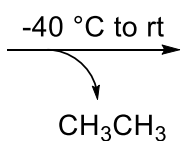


$FeCl_3$



Neidig *et al.*

$[FeMe_4][MgCl(THF)_5]$



Active species

A. Fürstner *et al.*, *J. Am. Chem. Soc.* **2008**, *130*, 8773-8787

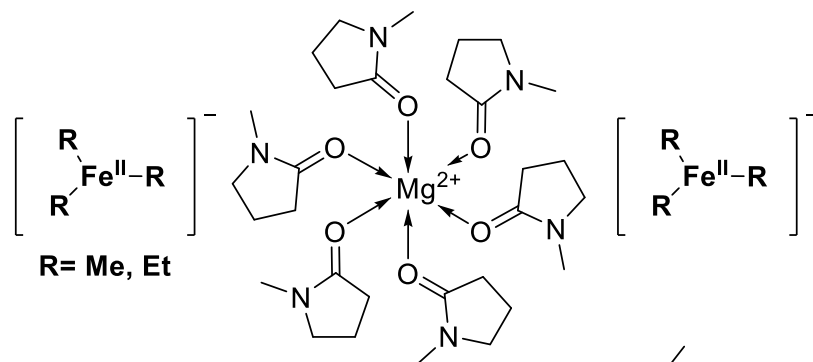
M. L. Neidig *et al.*, *J. Am. Chem. Soc.* **2016**, *138*, 7492-7495/

S. Sandt, A. J. von Wangelin, *Angew. Chem. Int. Ed.* **2020**, *59*, 5434 – 5437

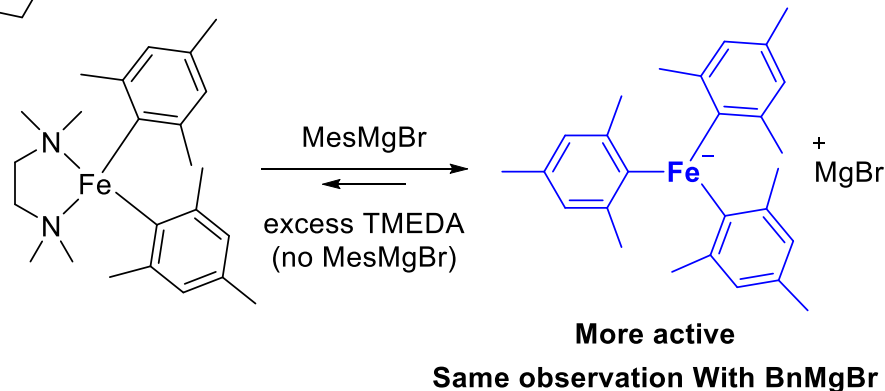
Recent progress in Kumada-Corriu cross-coupling

Organoferrate intermediates with R^1MgBr without β -hydrogen (Me, Ph, ...)

- Switch in presence of NMP or TMEDA:
 - Trialkyl ferrates isolated by Neidig $\rightarrow$ **catalytically active**



- TMEDA as chaperone



R. B. Bedford et al., *Angew. Chem. Int. Ed.* **2014**, 53, 1804–1808

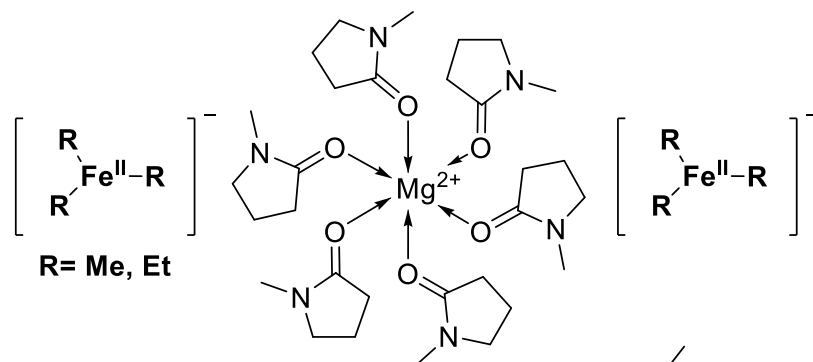
M. L. Neidig et al., *Angew. Chem. Int. Ed.* **2018**, 57, 6496–6500 / *Angew. Chem. Int. Ed.* **2019**, 58, 2769–2773

S. Sandt, A. J. von Wangelin, *Angew. Chem. Int. Ed.* **2020**, 59, 5434–5437

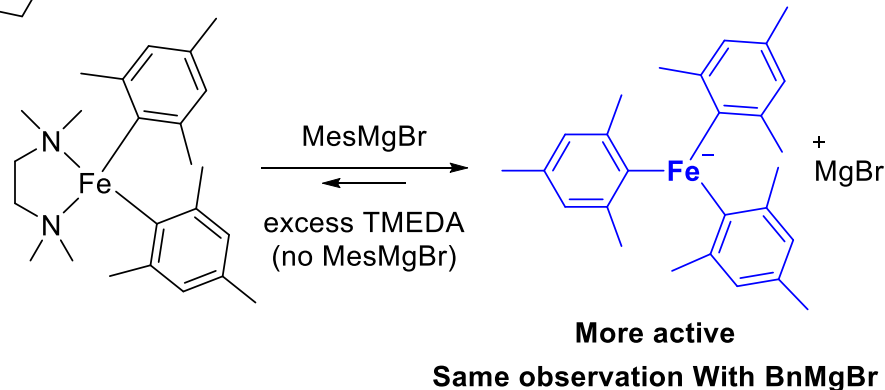
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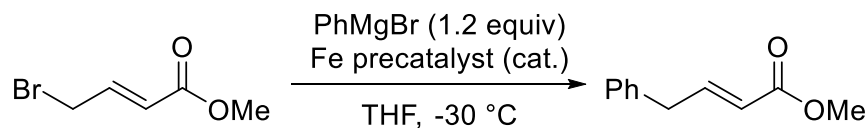
→ **Exact mechanism not fully understood...** ($\neq$ for trialkyl ferrate than iron cluster)

Recent progress in Kumada-Corriu cross-coupling

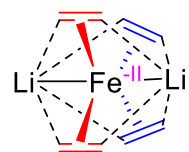
$\text{Fe}^{-\text{II}}/\text{Fe}^0$ mechanism proposed with R^1MgX (R^1 with $\beta\text{-H}$)

→ $\text{Fe}^{-\text{II}}(\text{MgX})_2$ speculated (first by Bogdanovic)

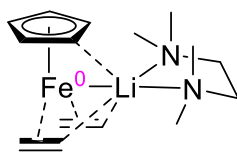
→ Several pre-catalysts synthesized and tried



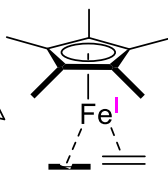
Fe pre-catalyst:



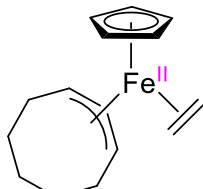
<10 min, 94%



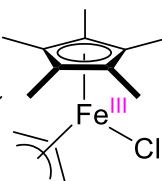
30 min, 45%



30 min, 50%



30 min, 46%



30 min, 73%



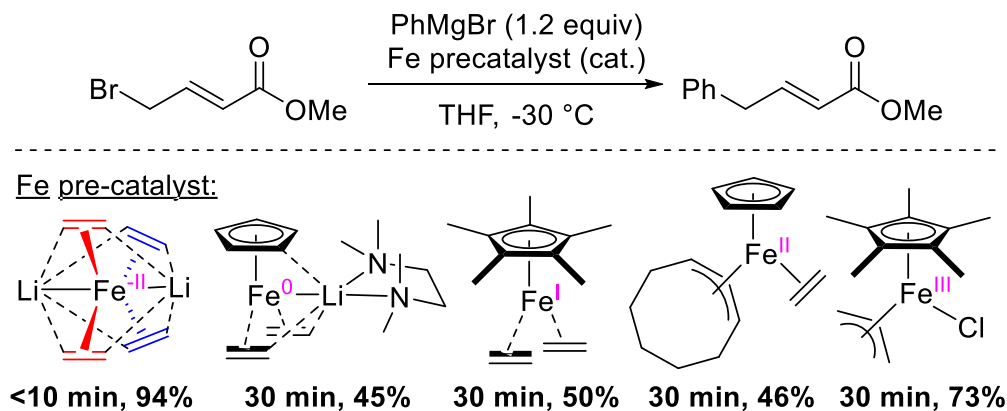
Higher activity for $\text{Fe}^{-\text{II}}$ pre-catalyst

Recent progress in Kumada-Corriu cross-coupling

Fe^{II}/Fe⁰ mechanism proposed with R¹MgX (R¹ with β-H)

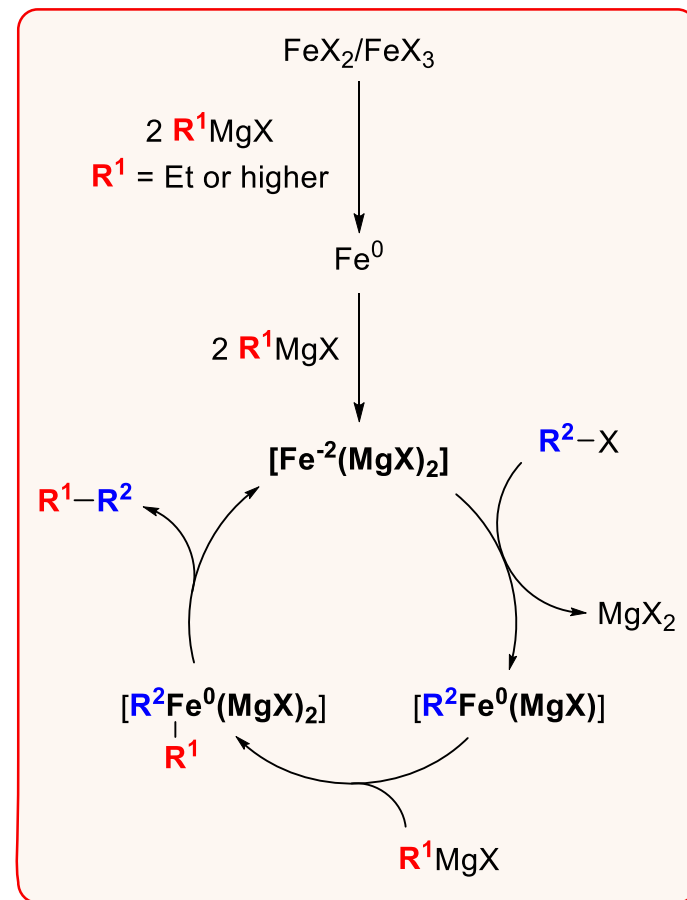
→ Fe^{II}(MgX)₂ speculated (first by Bogdanovic)

→ Several pre-catalysts synthesized and tried



➡ Higher activity for Fe^{II} pre-catalyst

→ Proposed mechanism:

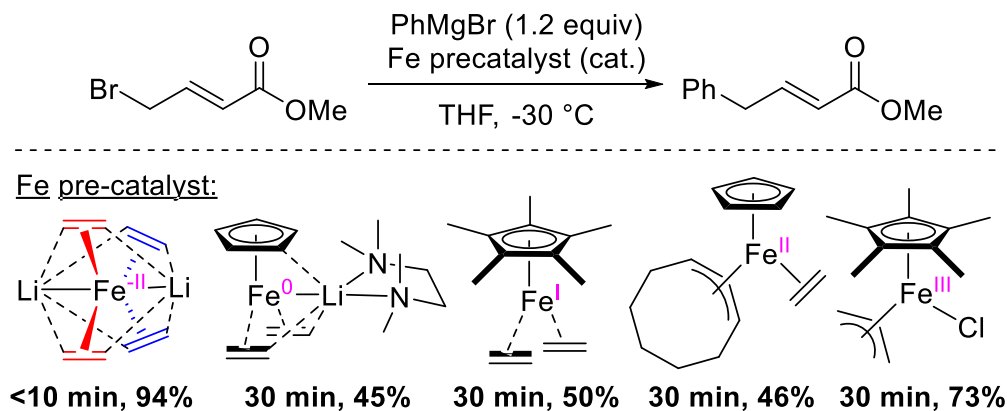


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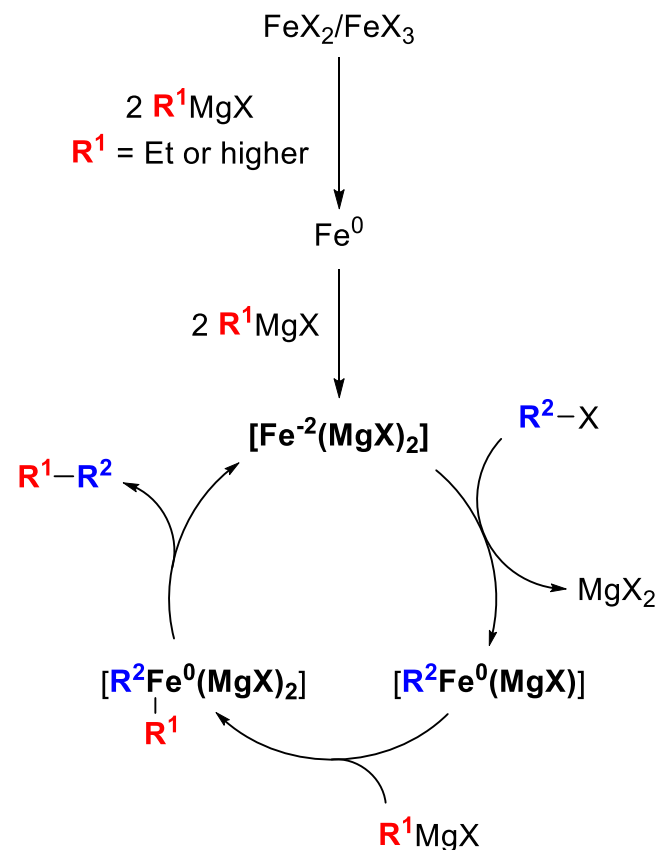
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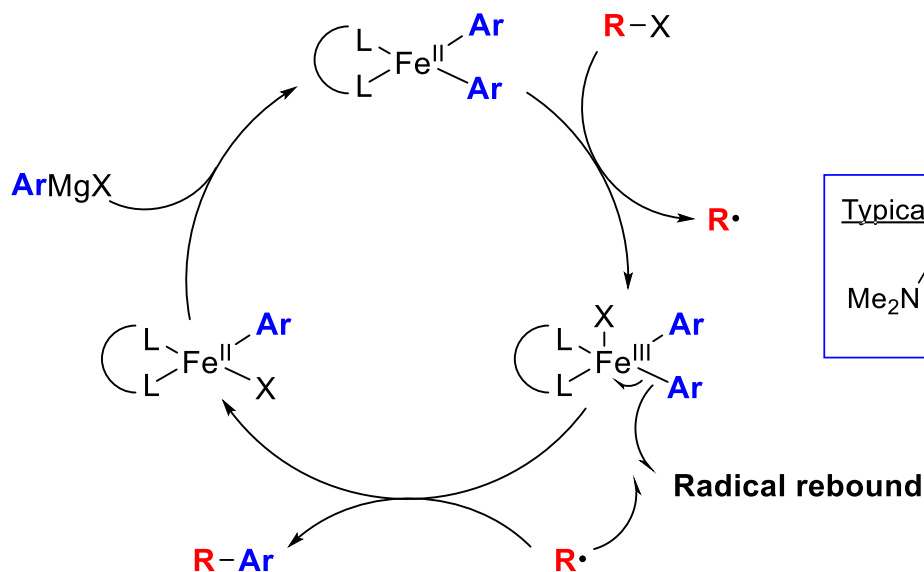
→ Proposed mechanism:

- However:
- Possible concomitant mechanisms
 - Only pre-catalysts
 - Different ligands → strong influence

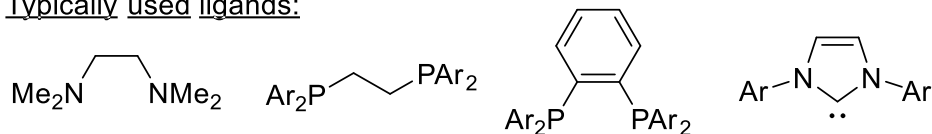


Recent progress in Kumada-Corriu cross-coupling

$\text{Fe}^{\text{II}}/\text{Fe}^{\text{III}}$ catalytic cycle proposed in many cases

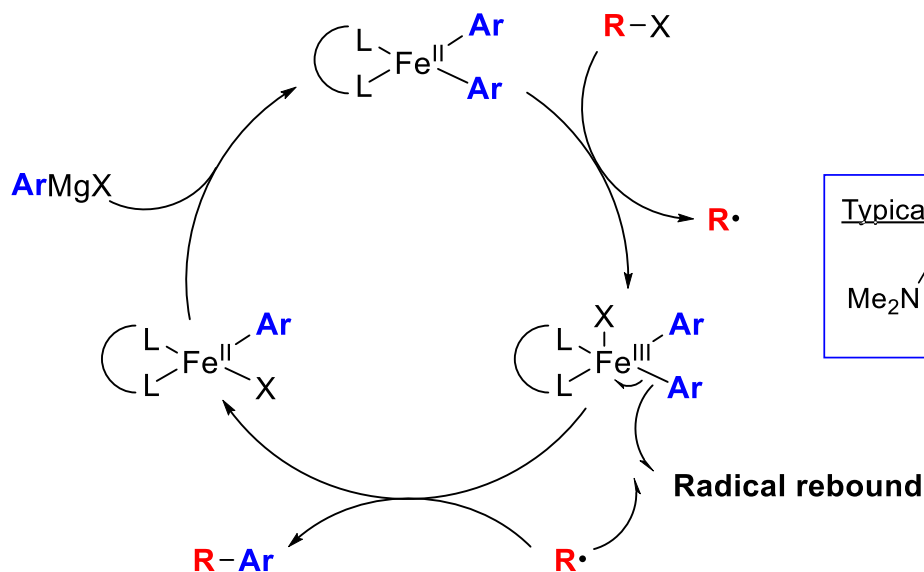


Typically used ligands:

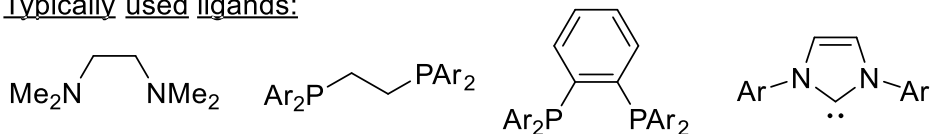


Recent progress in Kumada-Corriu cross-coupling

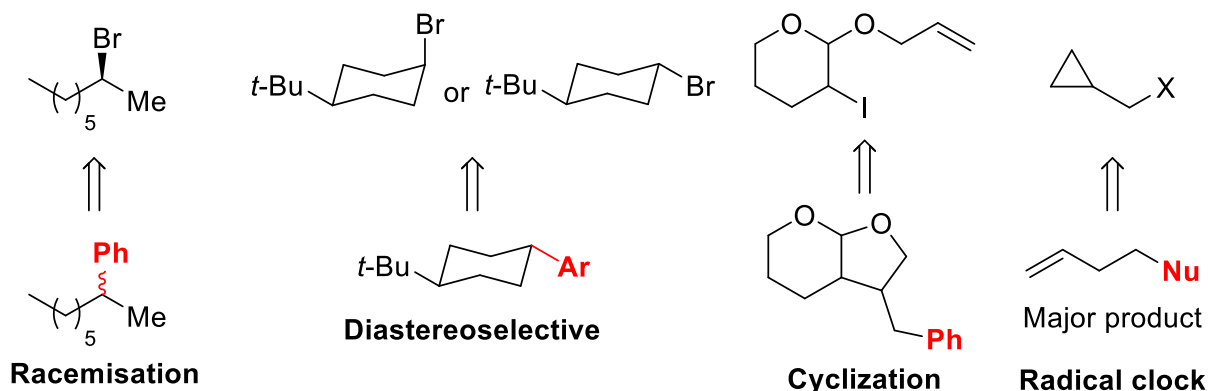
$\text{Fe}^{\text{II}}/\text{Fe}^{\text{III}}$ catalytic cycle proposed in many cases



Typically used ligands:



→ Whatever the mechanism, several experiments in favor of alkyl radicals:

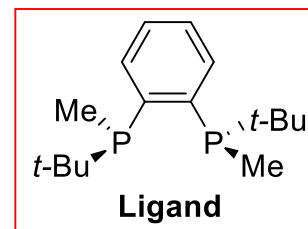
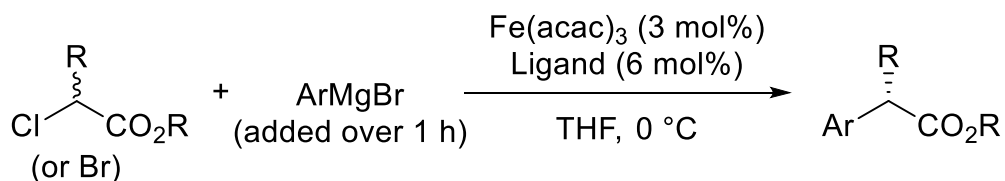


C.-J. Wallentin *et al.*, *ACS Catal.* **2016**, 6, 1640–1648
 M. Nakamura *et al.*, *J. Am. Chem. Soc.* **2004**, 126, 3686–3687.
 A. Fürstner *et al.*, *Angew. Chem. Int. Ed.* **2004**, 43, 3955–3957

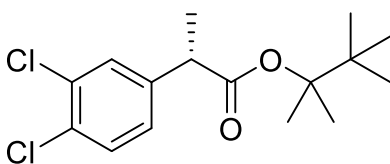
Enantioselective Kumada-Corriu cross-coupling

Only one report to date (Nakamura *et al.* 2015)

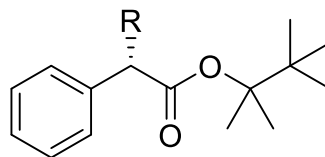
- Enantioconvergent coupling of aryl Grignard reagents with α -chloroesters



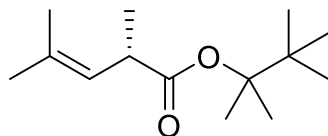
Selected examples:



88% (90:10 er)

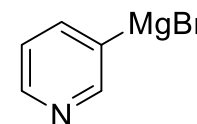


R = Et, 67% (88:12 er)
R = *i*-Bu, 38% (74:26 er)
R = CH_2OMe , 42% (77:23 er)

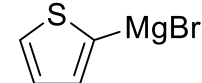


52% (91:9 er)

With:



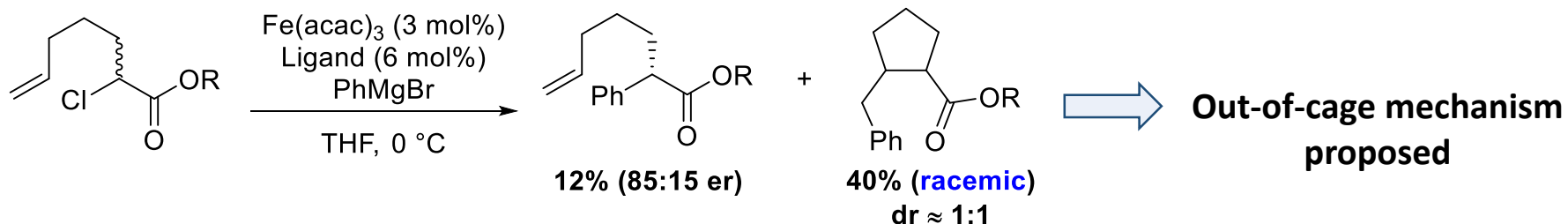
0%



0%

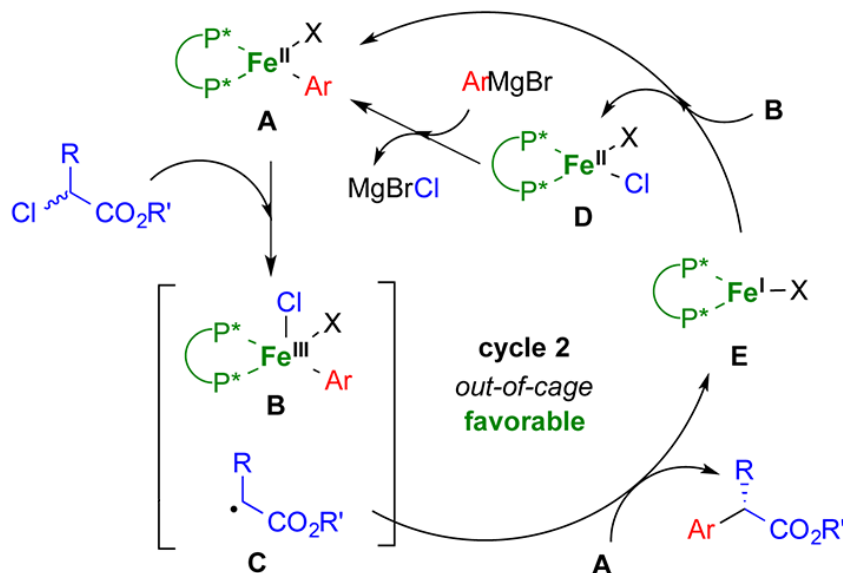
Enantioselective Kumada-Corriu cross-coupling

Mechanistic investigations:



→ First-order relationship between [Fe cat.] and ratio not cyclized-cyclized

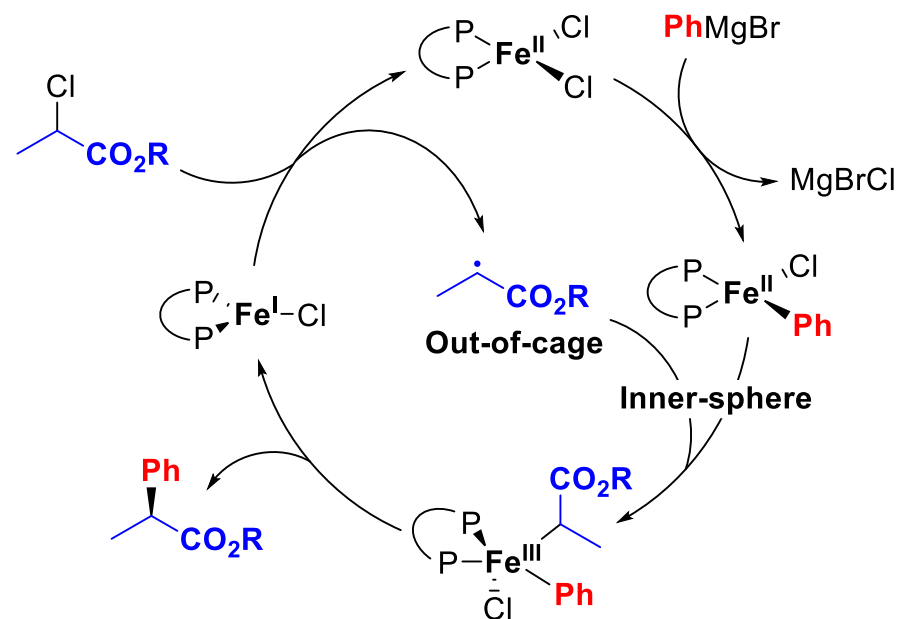
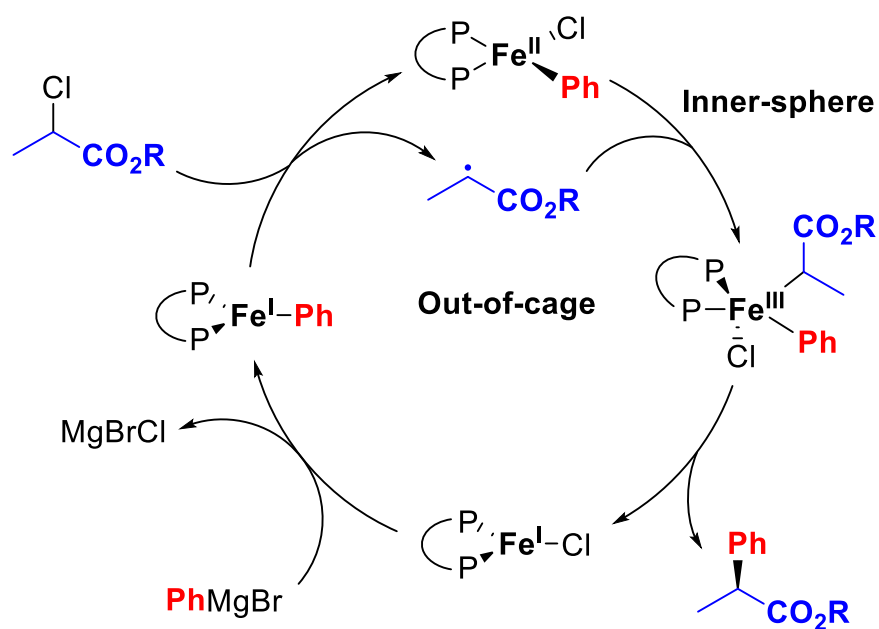
Bimetallic mechanism proposed:



Enantioselective Kumada-Corriu cross-coupling

Computational studies:

→ 2 slightly different mechanisms proposed



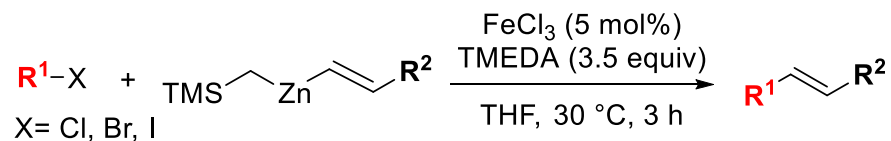
→ C-Cl activation high in energy for Fe^{II} species → Fe^I more favorable

→ Dropwise addition of Grignard reagent important to avoid $Fe^{II}PhPh$ (biphenyl formation)

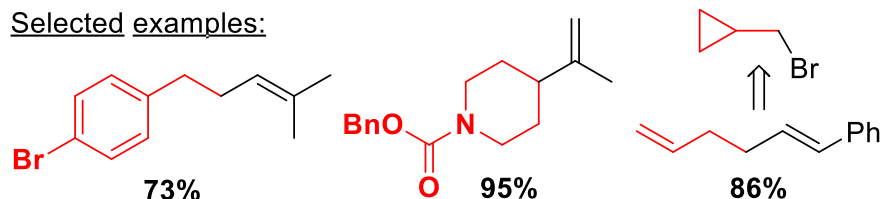
→ Inner-sphere out-of-cage mechanism

New development in Negishi cross-coupling

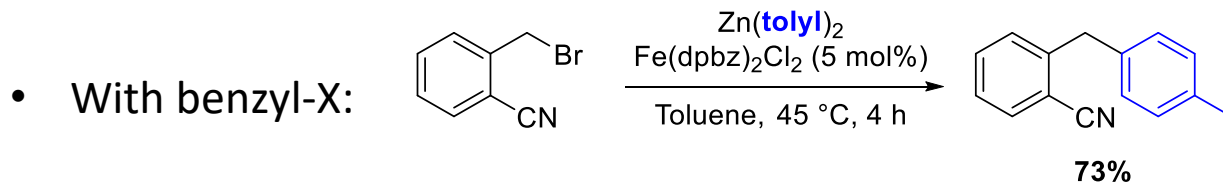
First reported with vinyl zinc reagents



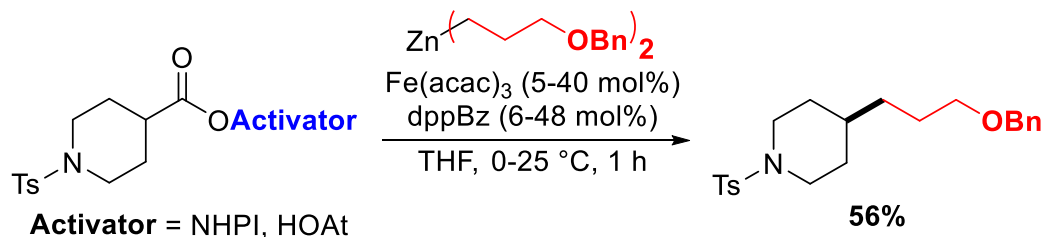
Selected examples:



Only scarce numbers of reports



- Extended further with redox-active esters (1°, 2°, 3° alkyl-COOH/ Ar- and R₂Zn):



M. Nakamura *et al.*, *Org. Lett.* **2009**, 11, 4496-4499

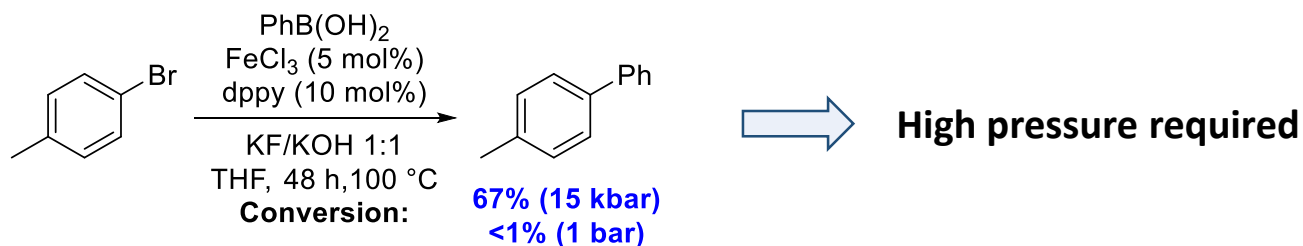
R. B. Bedford *et al.*, *Chem. Commun.* **2009**, 600-602 / *Angew. Chem. Int. Ed.* **2013**, 52, 1285-1288

P. S. Baran *et al.*, *J. Am. Chem. Soc.* **2016**, 138, 11132-11135

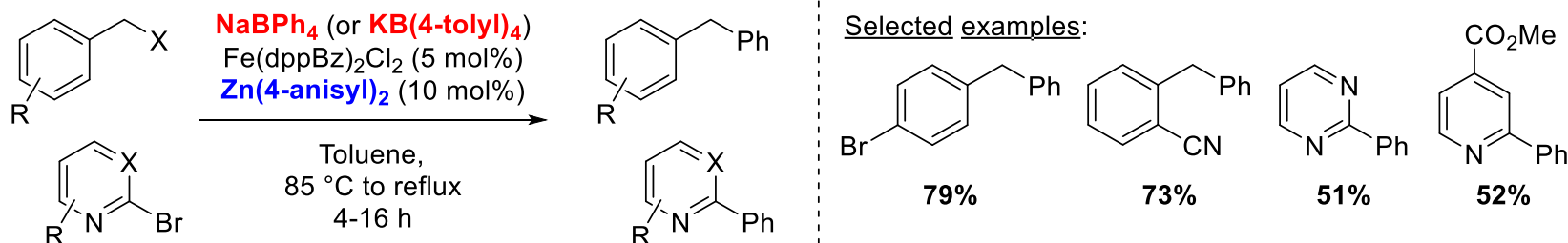
Progress in Suzuki-Miyaura cross-coupling

Few reports → Difficulty with the transmetallation/reduction step

First report of Fe-catalyzed Suzuki-Miyaura cross-coupling (Hor *et al.*, 2008)

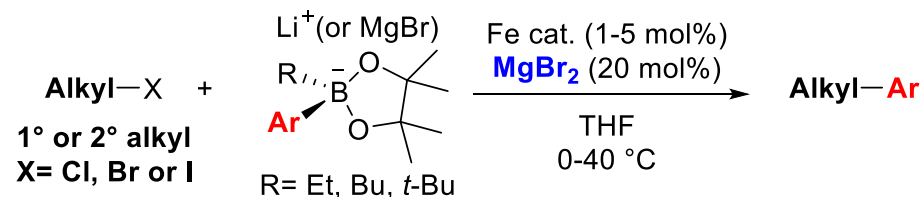


Solution: Use activated borate as nucleophile (Bedford *et al.*, 2009)

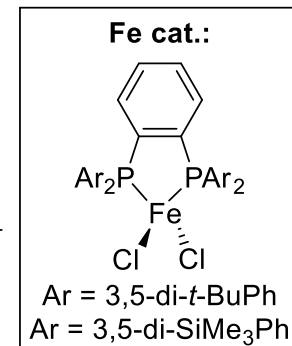
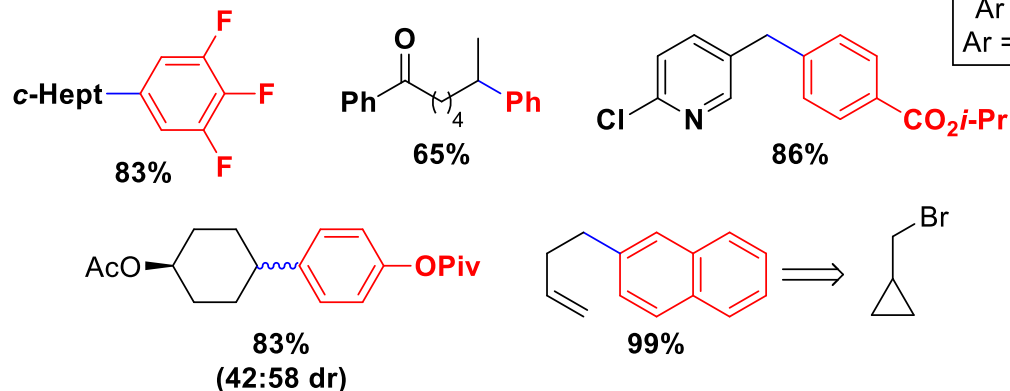


Progress in Suzuki-Miyaura cross-coupling

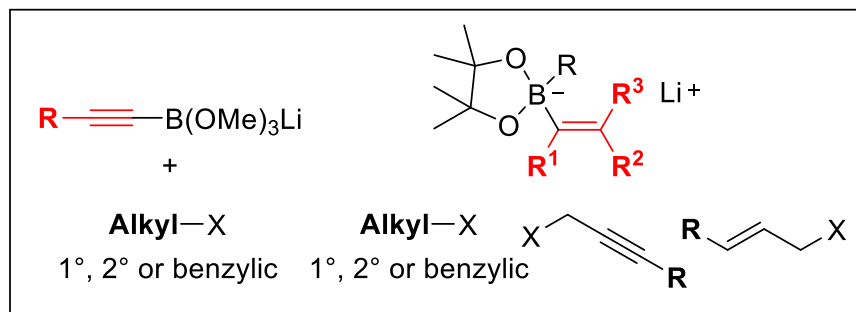
Nakamura 2010



Selected examples:



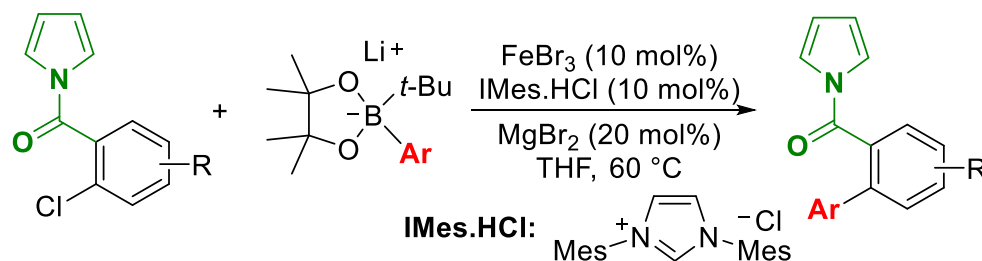
Extension of the scope



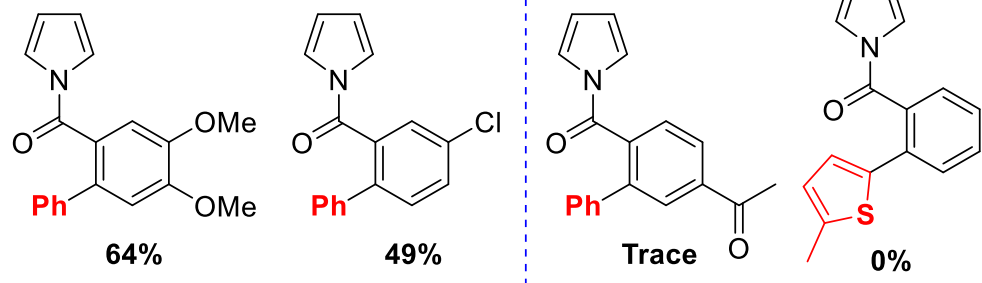
Progress in Suzuki-Miyaura cross-coupling

Only few reports with aryl electrophile

- First reports → Due to palladium contaminations (articles retracted later)
- Observed as side-product with 2-halobenzyl halides (< 41%)
- Directing group required (Bedford et al., 2018)



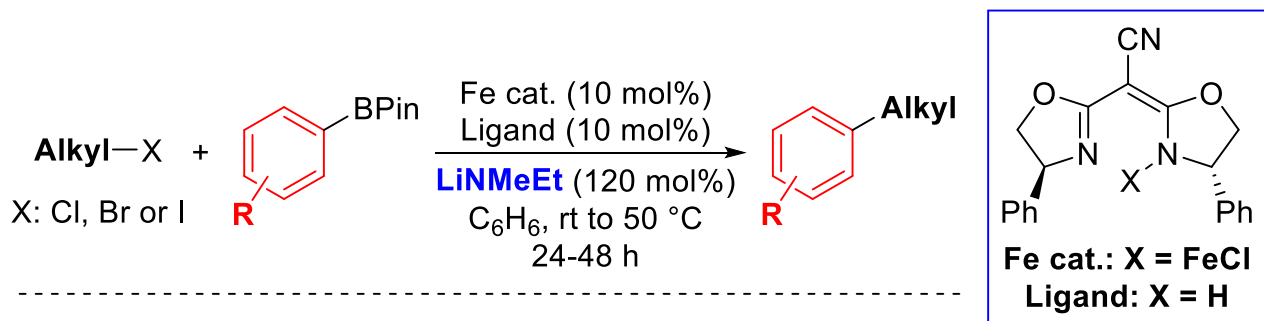
Selected examples:



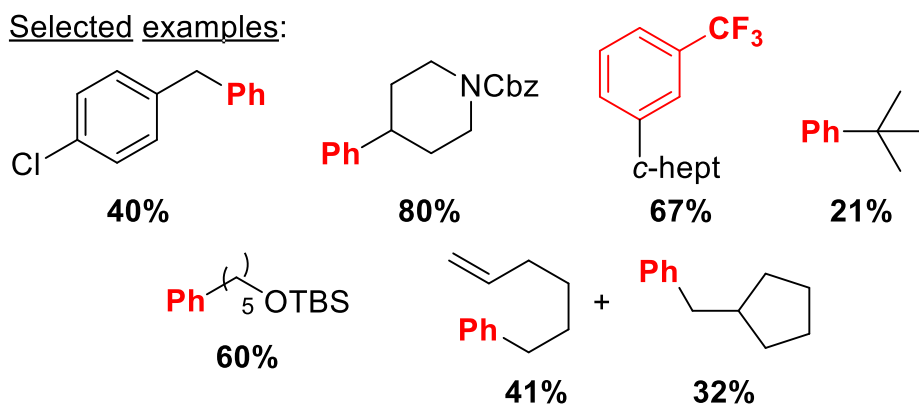
Progress in Suzuki-Miyaura cross-coupling

Byers's work with ligand tuning

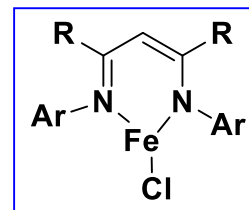
- Alkoxide to help the transmetallation → Iron aggregates: inactive
- Anionic ligand and amide base → improved transmetallation / monomeric iron species



Selected examples:



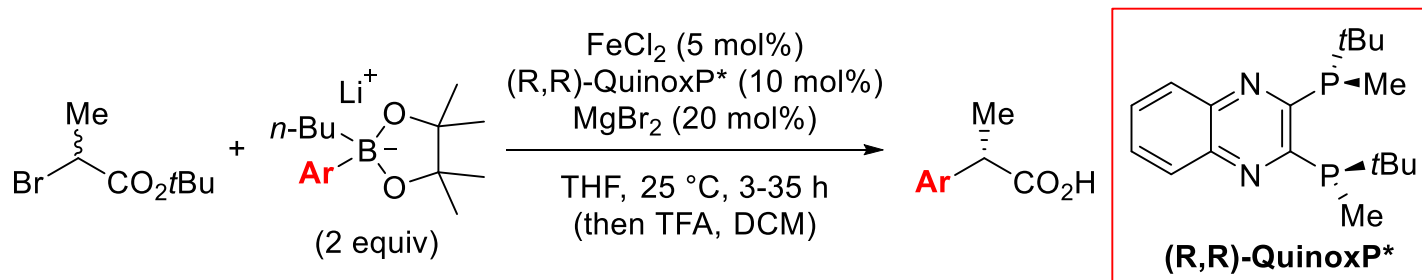
- Improvement of the scope (heteroaromatic-BPin, 3° alkyl) and efficiency with:



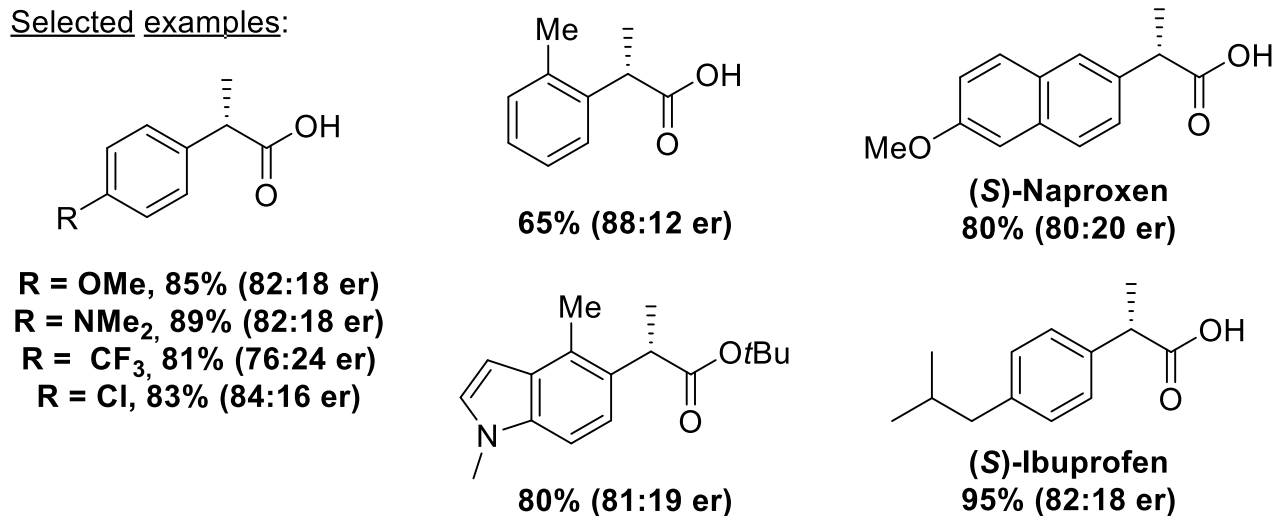
Enantioselective cross-coupling

First report of enantioselective Fe-catalyzed Suzuki-Miyaura cross-coupling (Nakamura *et al.* 2019)

- Enantioconvergent coupling of lithium arylborates with α -bromoesters



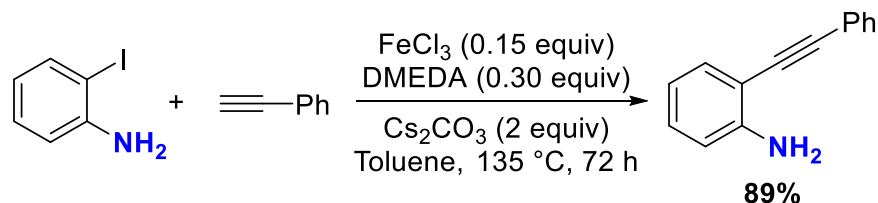
Selected examples:



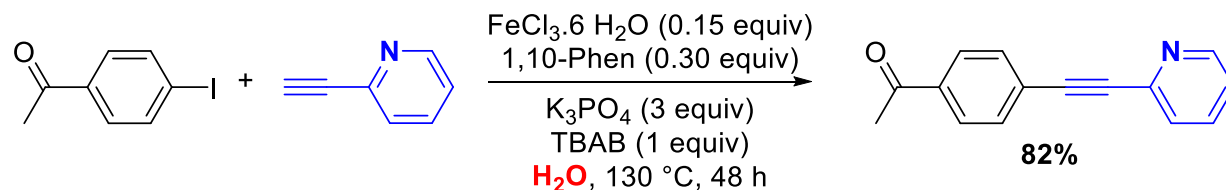
Point on Fe-catalyzed Sonogashira

Still under developed ...

- First report by Bolm and coworkers



- Designed in water

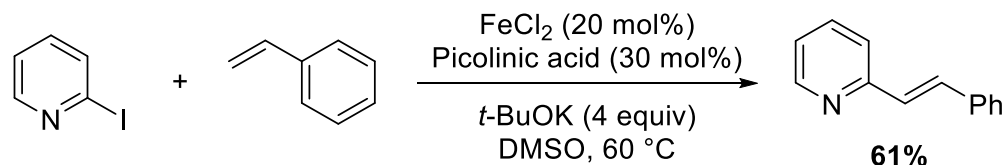


→ Few other reports but only very high temperature

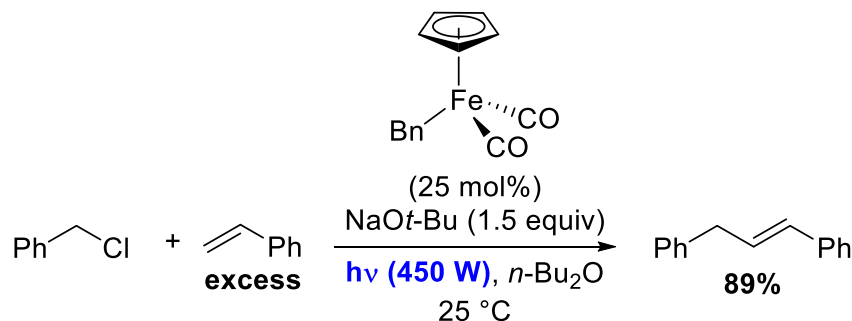
Fe catalysis in Heck-type cross-coupling

Only few reports

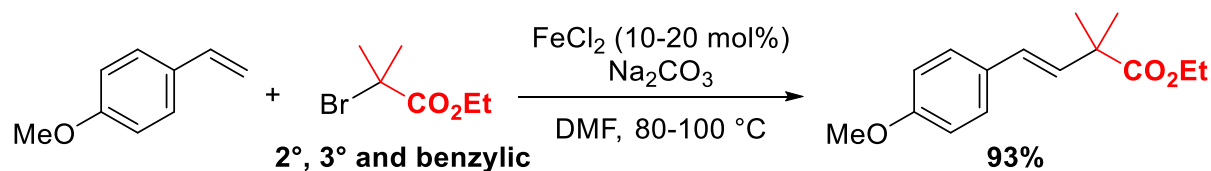
- Initial report by Vogel



- Extended to benzylic substrates via UV-irradiated iron catalyst



- Applied in 2017 to alkyl electrophiles



P. Vogel *et al.*, *Adv. Synth. Catal.* **2008**, 350, 2859–2864
G. W. Waldhart, N. P. Mankad, *J. Organomet. Chem.* **2015**, 793, 171-174
S. P. Thomas *et al.*, *ACS Catal.* **2017**, 7, 2353–2356

Conclusion and Outlooks

- Iron-catalyzed Kumada-Corriu cross-coupling **well developed**
 - Very **fast** reaction, even at low temperature
 - Highly **chemoselective**
 - Cheap catalyst, often **without ligand**
 - Less-sensitive to β -hydride elimination



However, **mechanisms still not fully understood ...**

- Almost **no enantioselective version**
- Use of less-nucleophilic partner **still underdeveloped**

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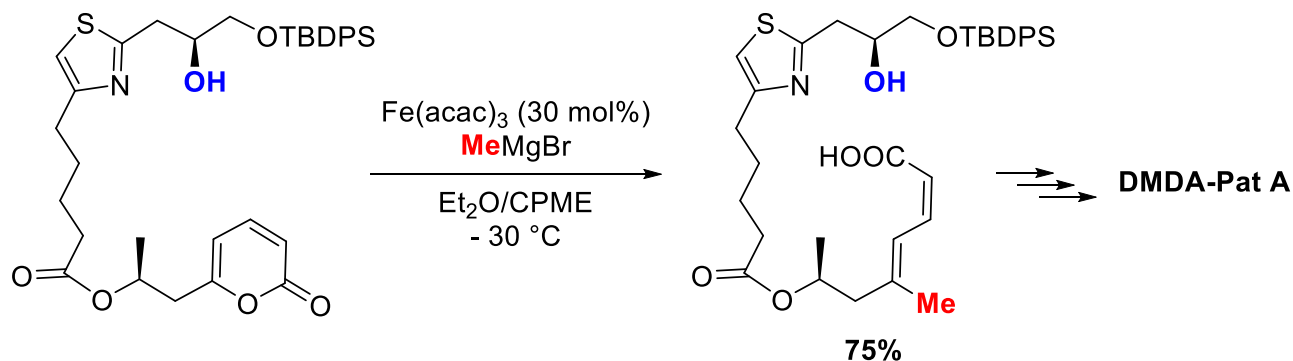
Tuning of the ligands might be key ...

Thank you for your attention

Questions

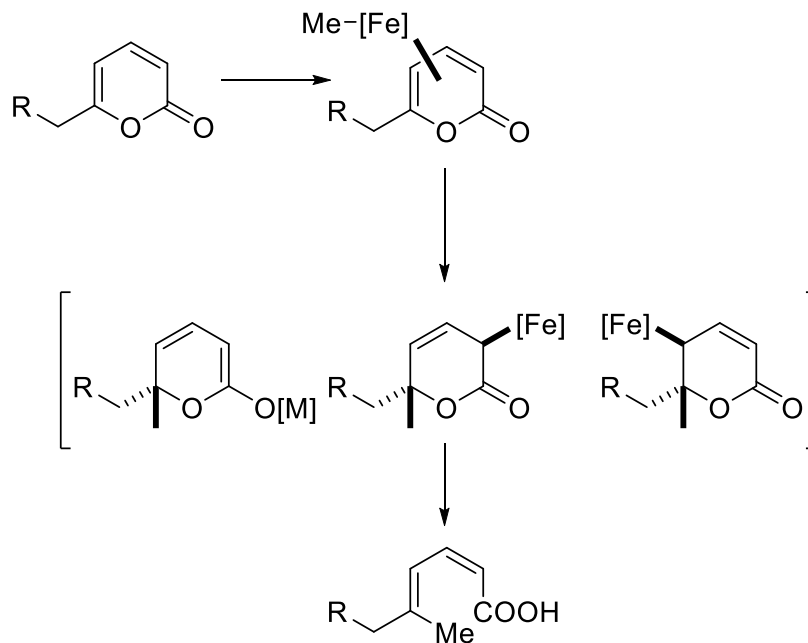
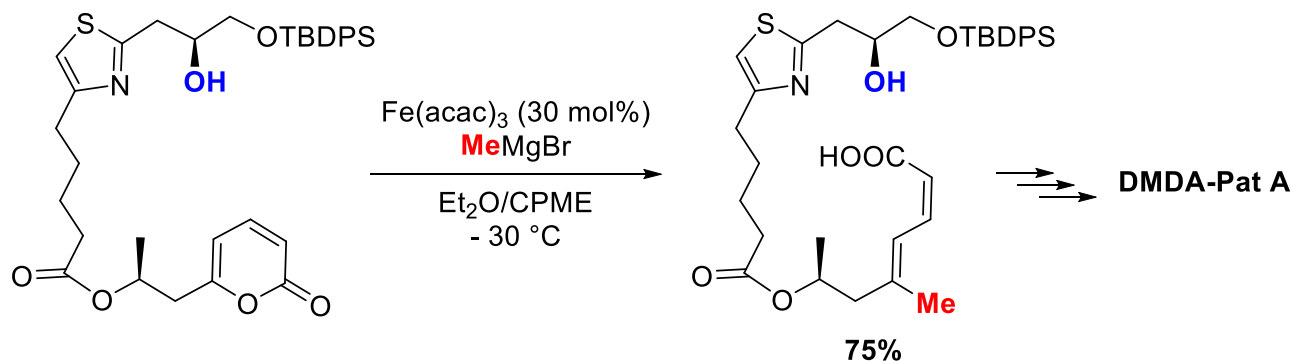
Questions 1

Can you suggest a mechanism for this transformation ?



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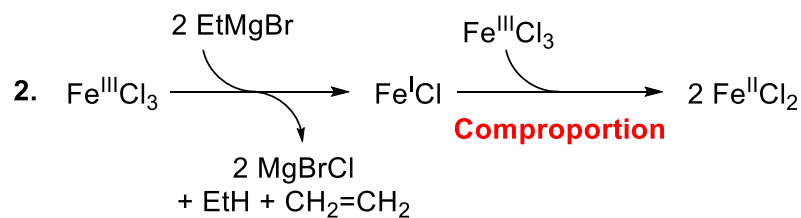
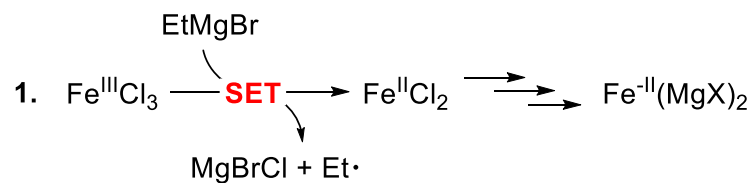
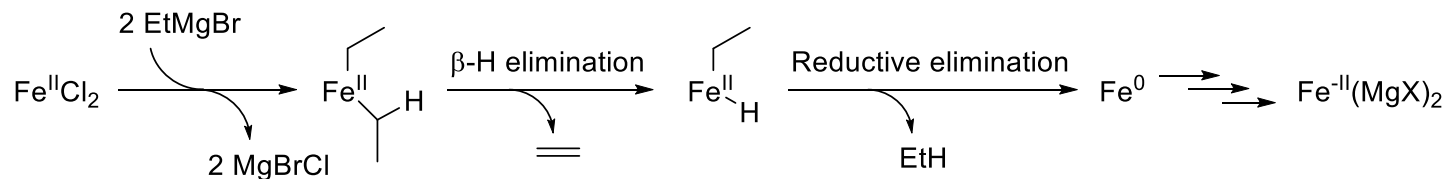


Questions 2

Propose a mechanism for the reduction of Fe^{II} to $\text{Fe}^{-\text{II}}$ and Fe^{III} to $\text{Fe}^{-\text{II}}$

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Catalytic Enantioselective Syntheses and Transformations of Cyclopropyl Ketones and Derivatives

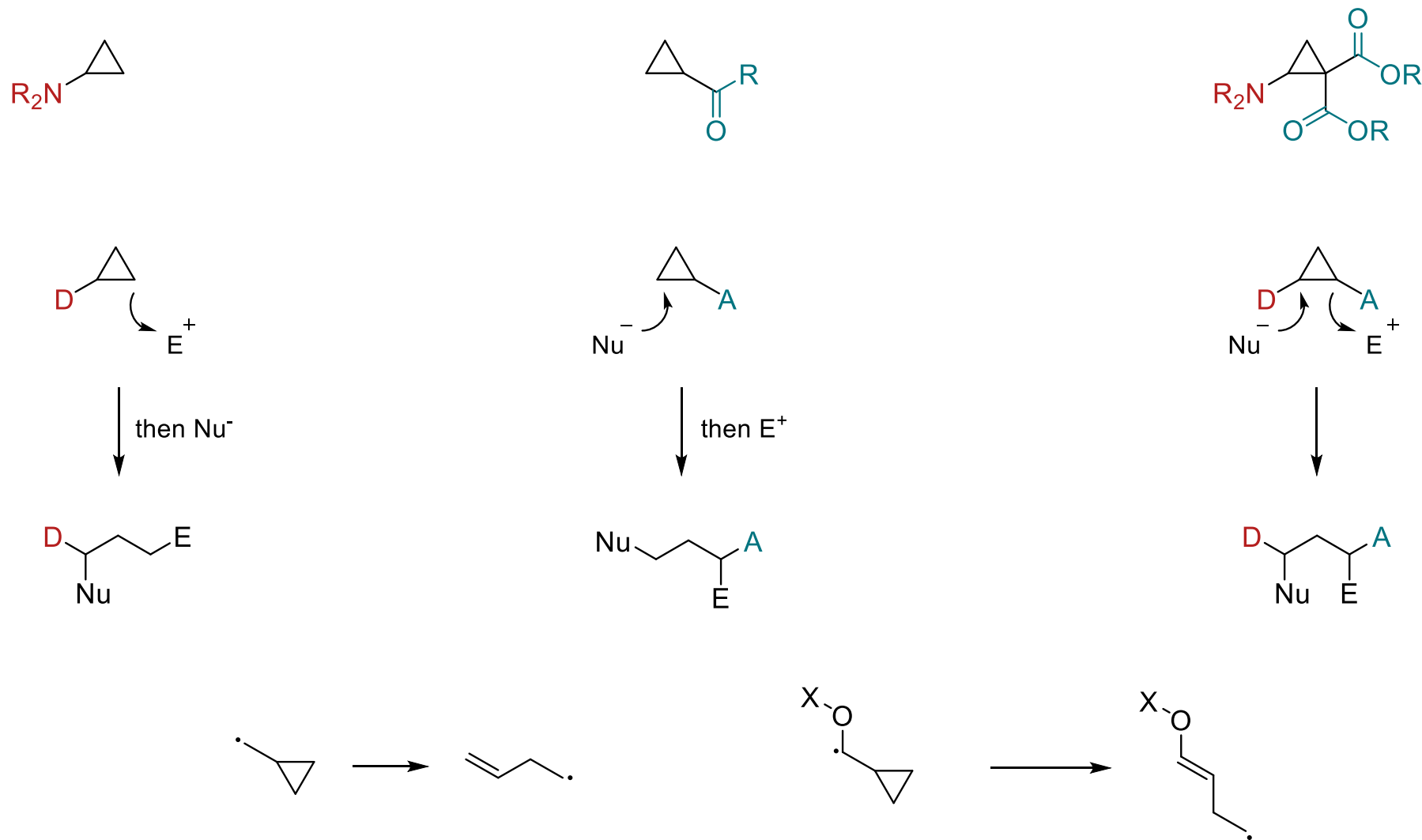
Frontiers in Chemical Synthesis I: Towards Sustainable Chemistry

Stephanie AMOS

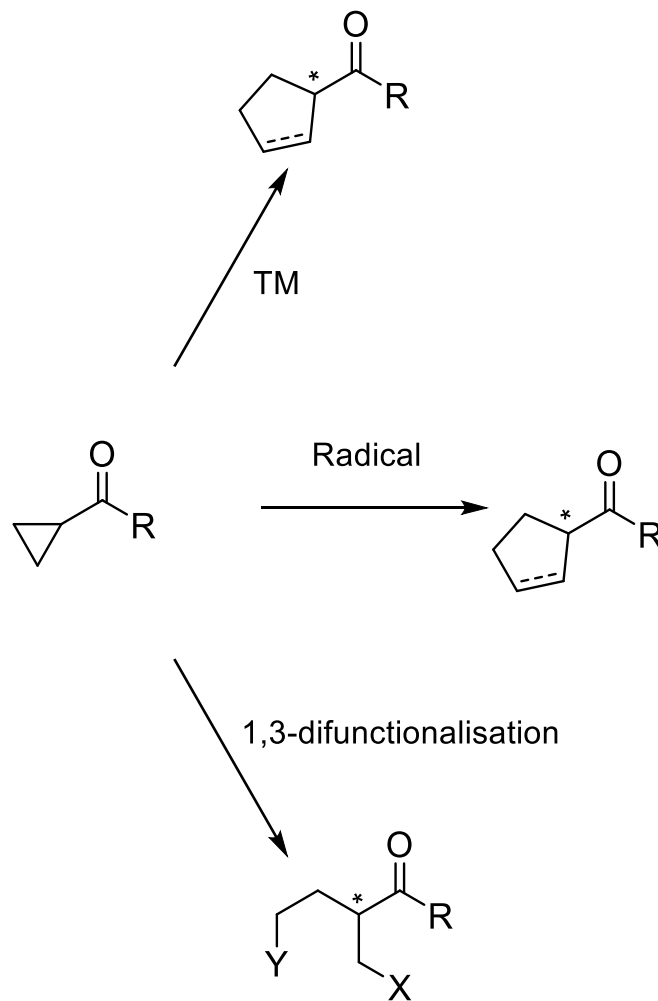
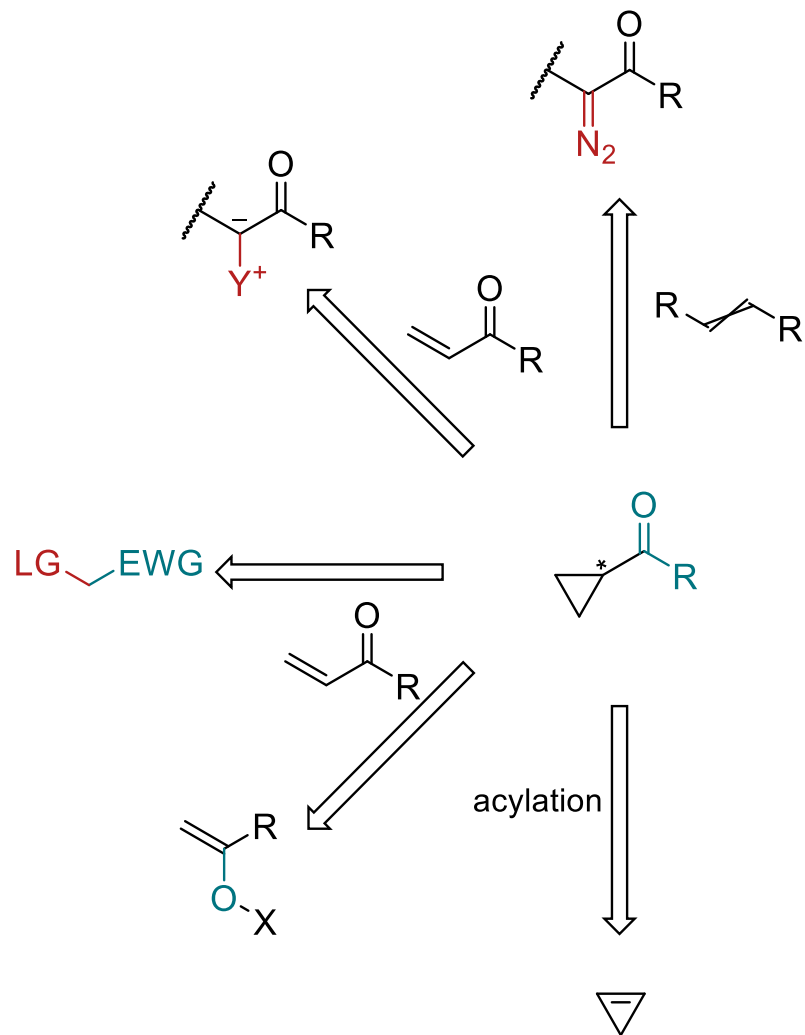
11 May 2020

Ecole Polytechnique Fédérale de Lausanne
Laboratory of Catalysis and Organic Synthesis (LCSO)

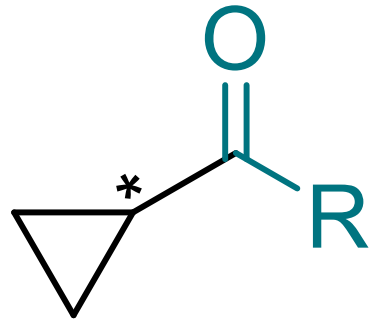
EPFL ■ Cyclopropanes for difunctionalisation



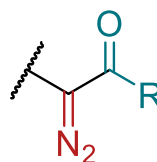
07/10/2020



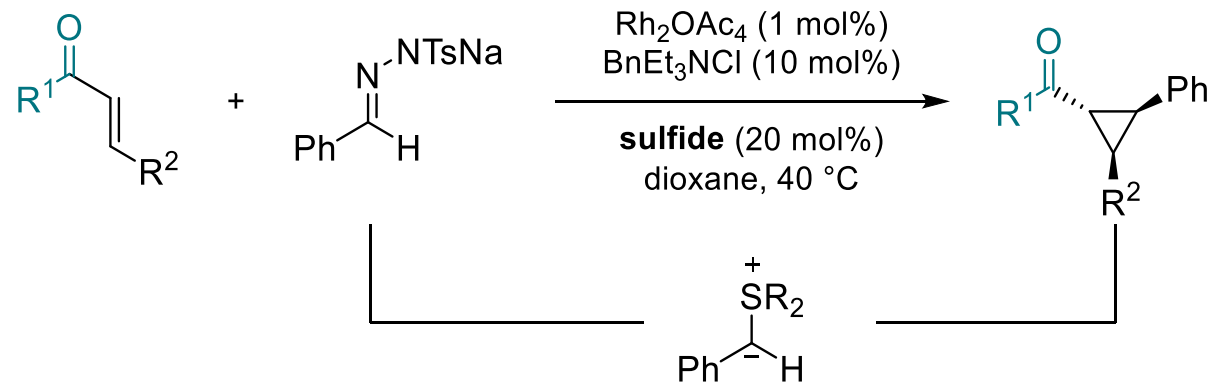
- Chiral lewis acids
- Organocatalysis
- Chiral ligands



Synthesis of chiral cyclopropyl ketones

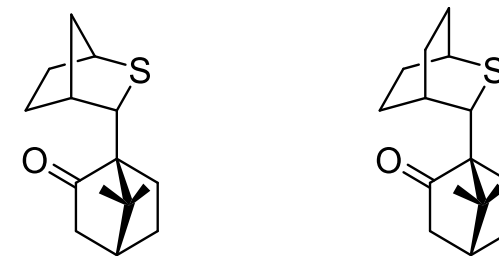


Aggarwal, ACIE, 2001

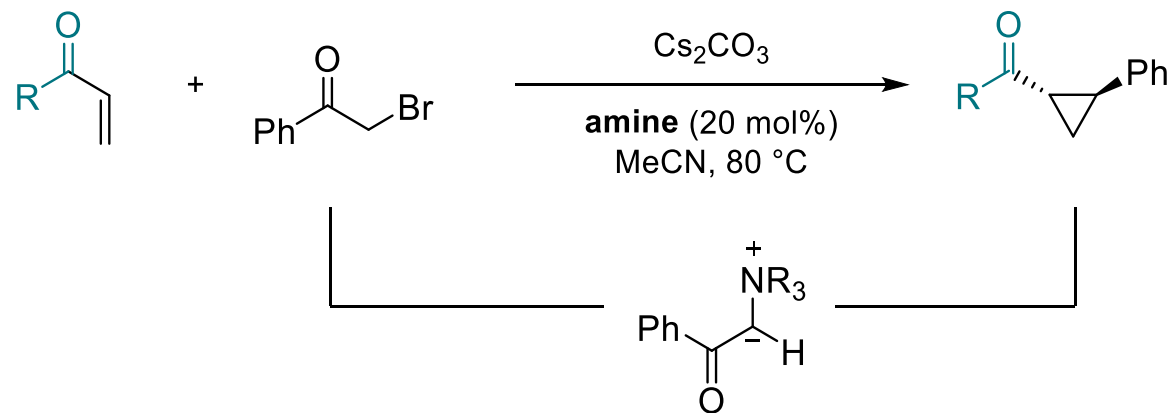


30-73% yield
up to 5:1 dr.
up to 92% ee

sulfide

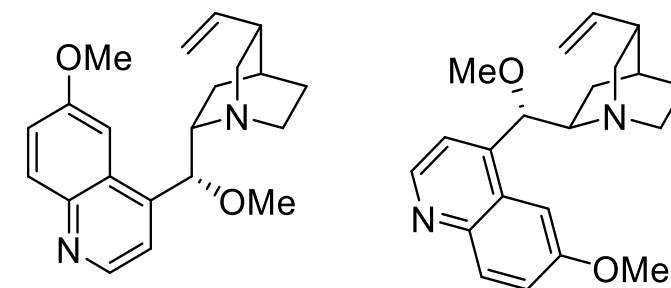


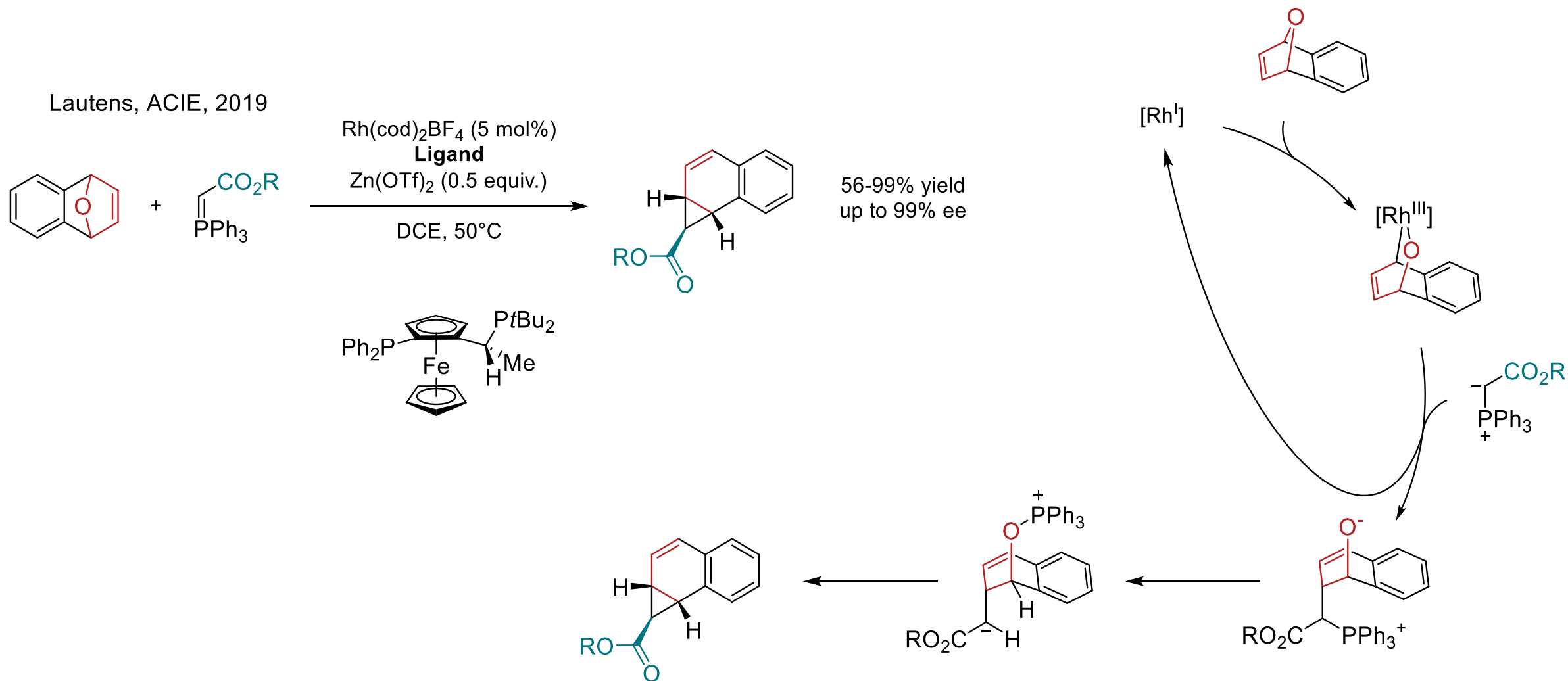
Gaunt, ACIE, 2004



63-96% yield
up to 97% ee

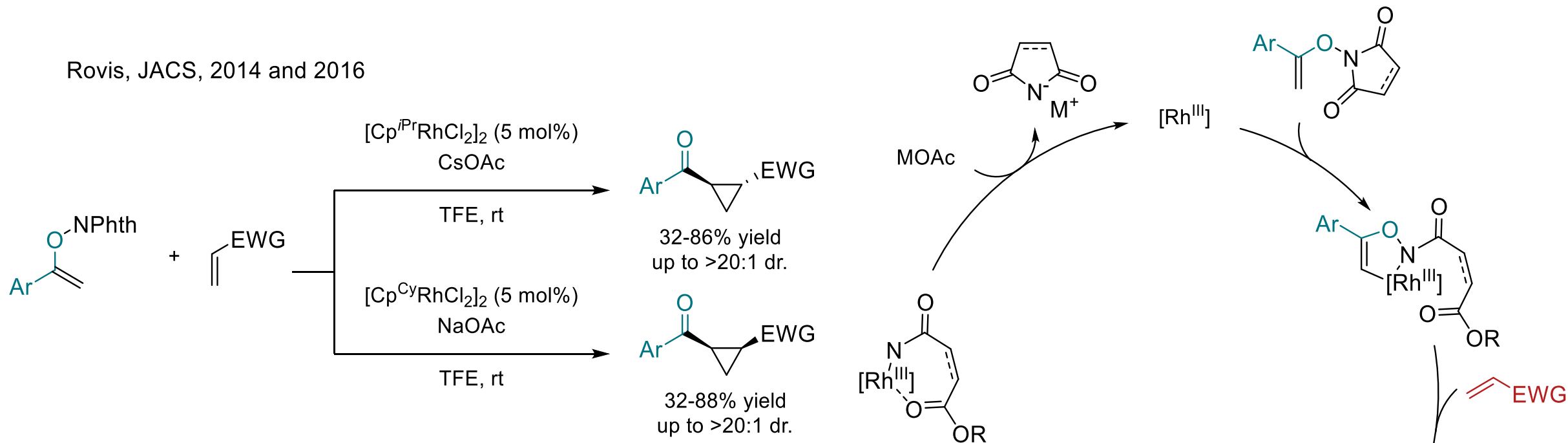
amine



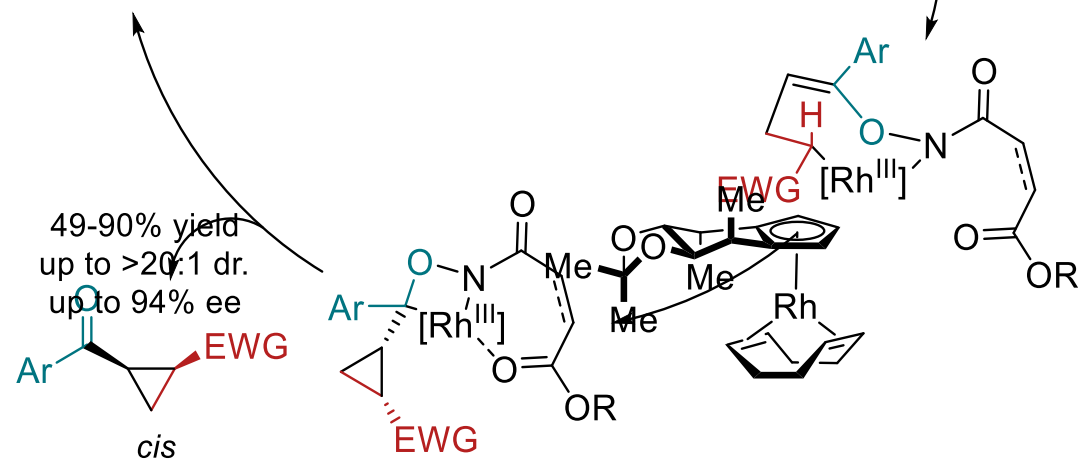
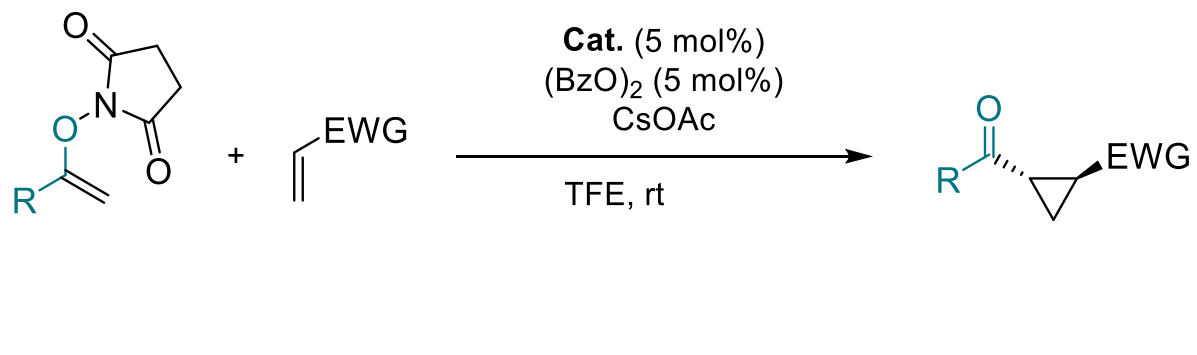


EPFL ■ N-Enoxyimide mediated cyclopropanations

Rovis, JACS, 2014 and 2016

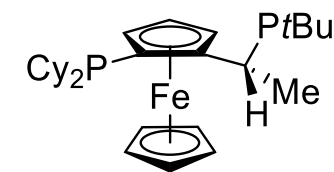
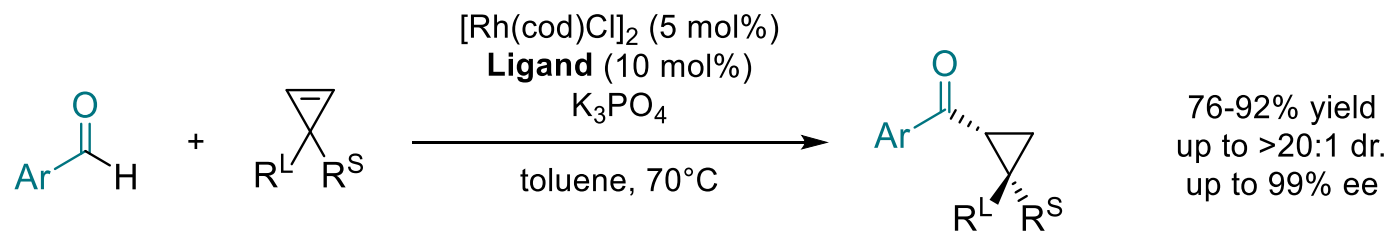


Cramer, Chem. Sci. 2019

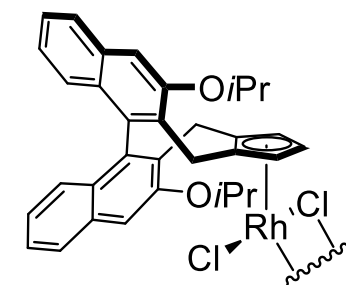
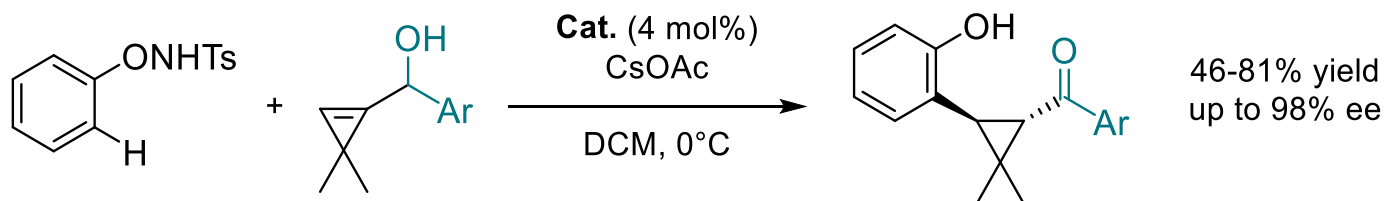


07/10/2020

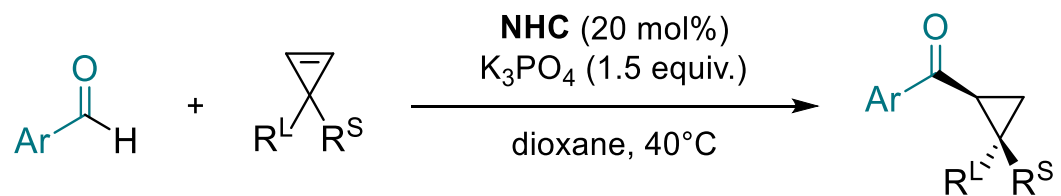
Dong, JACS, 2010



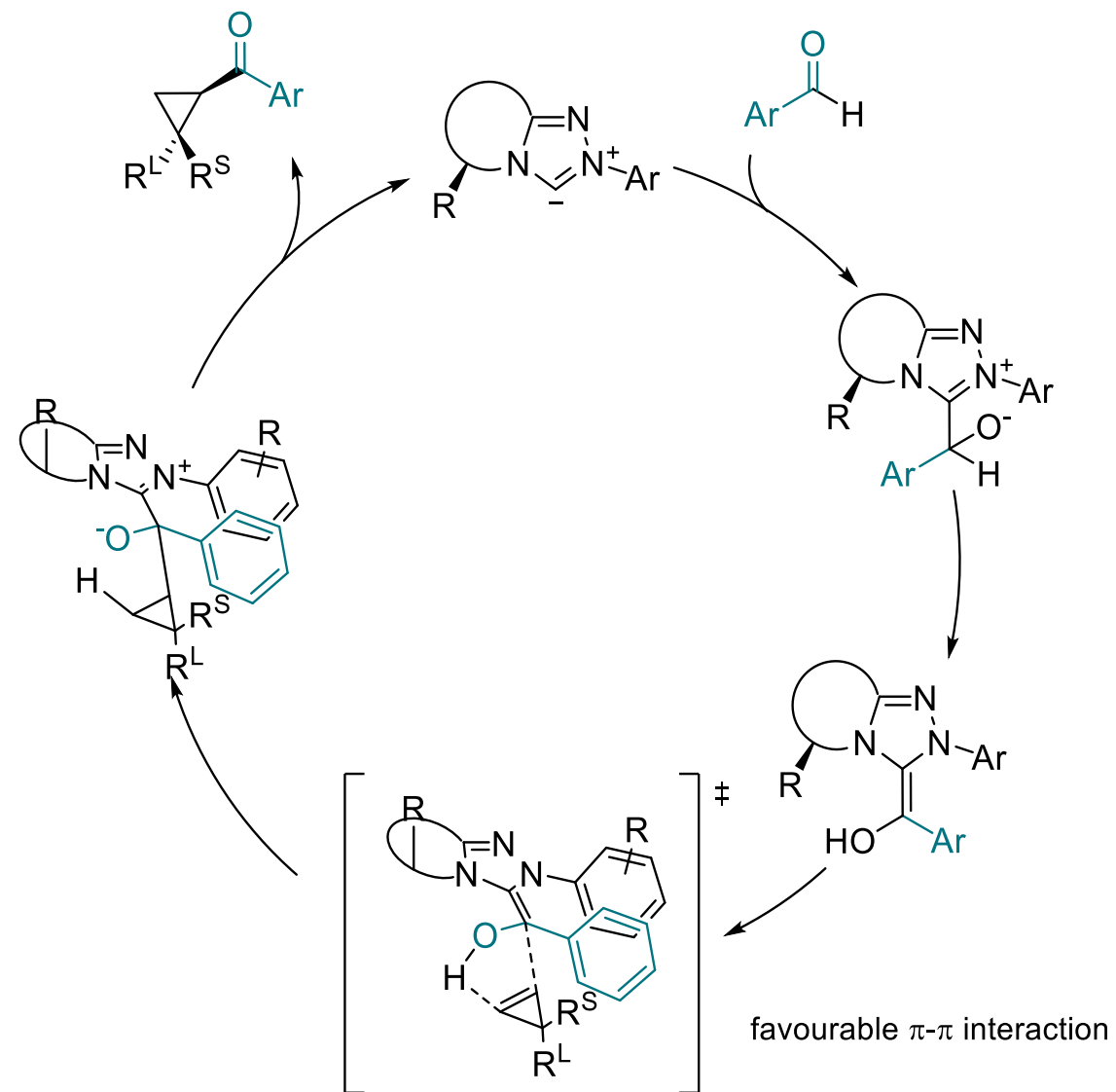
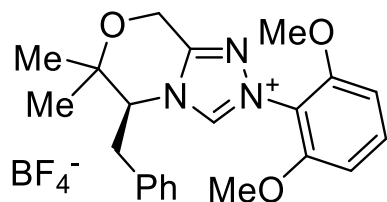
Li, ACIE, 2020

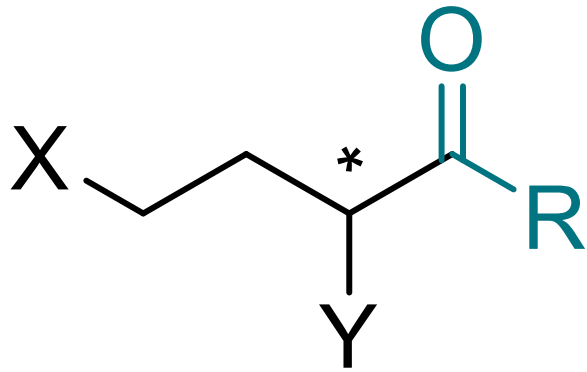


Glorius, ACIE, 2011



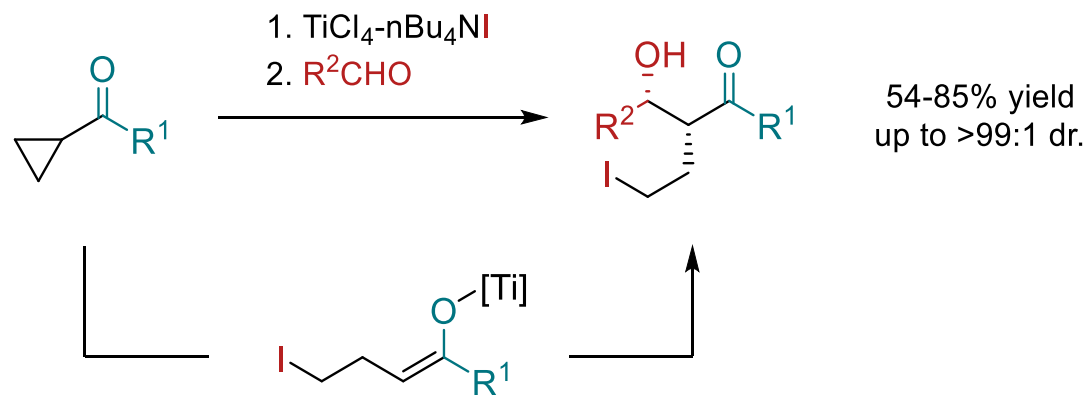
31-93% yield
up to >20:1 dr.
up to 96% ee



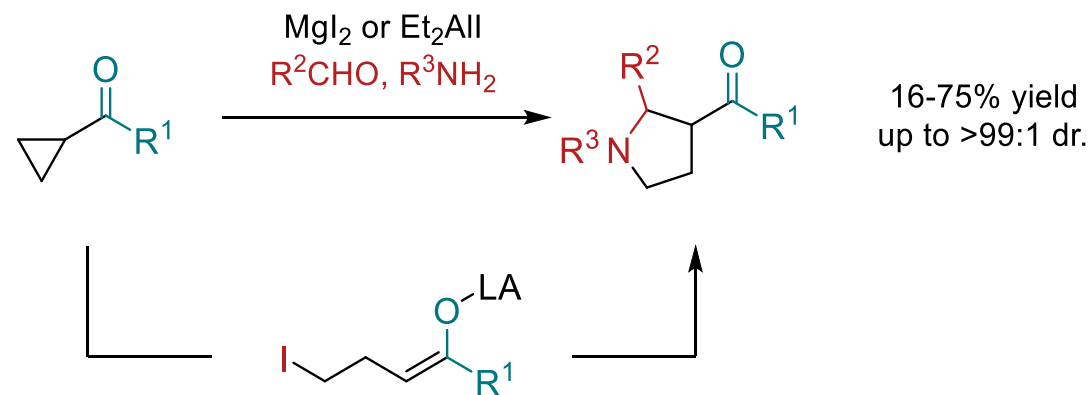


Enantioselective cyclopropyl ketone ring-opening

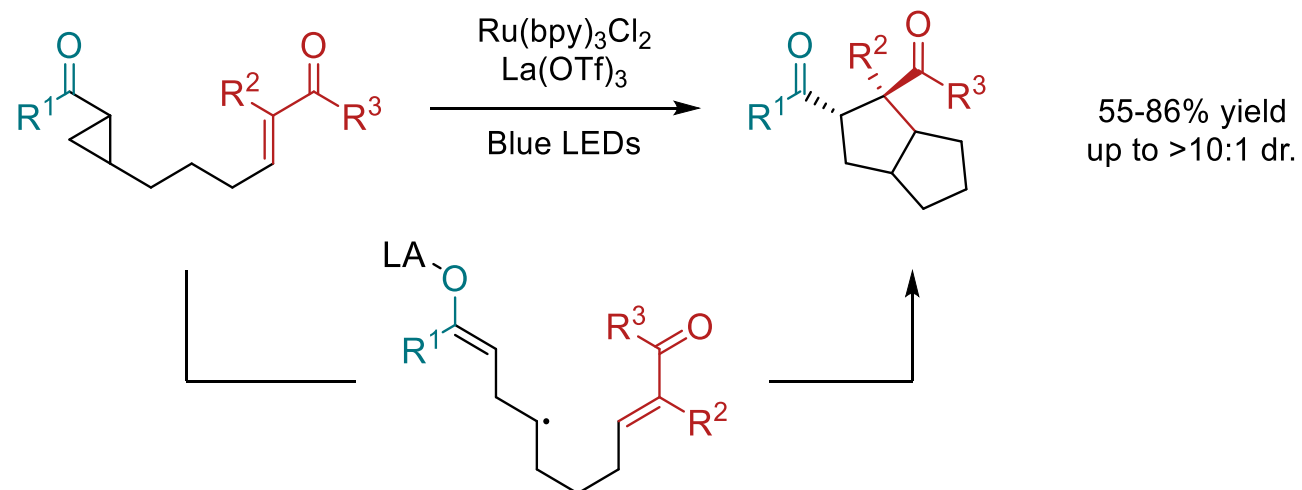
Oshima, Tetrahedron, 2001



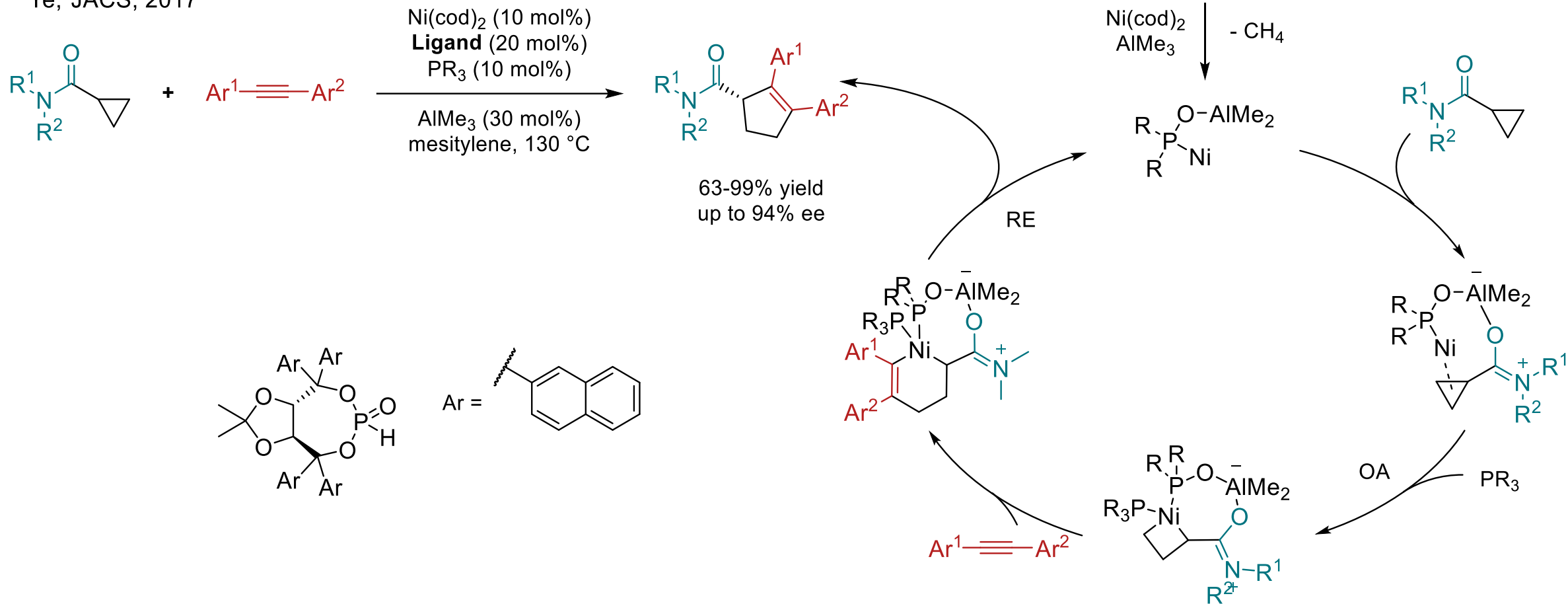
Olsson, Org. Lett., 2002



Yoon, JACS, 2011



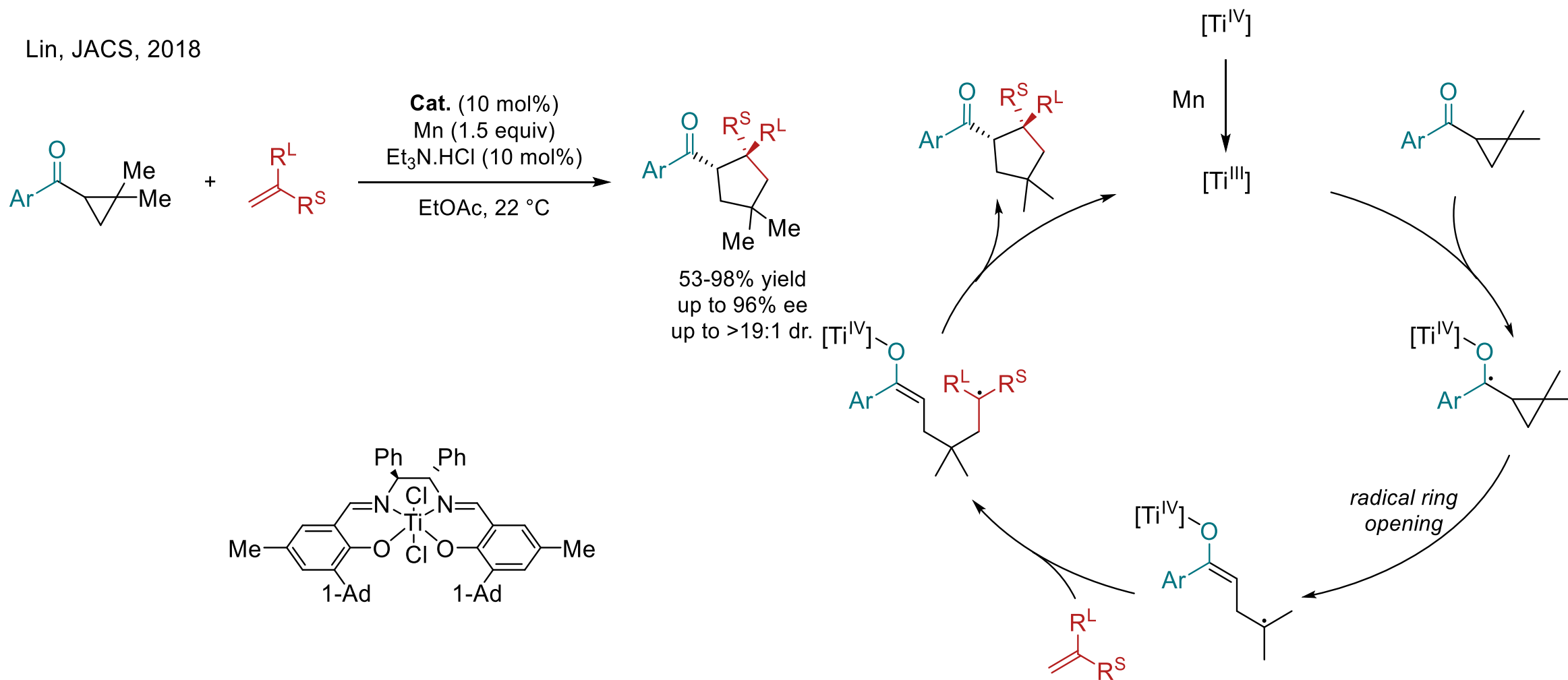
Ye, JACS, 2017



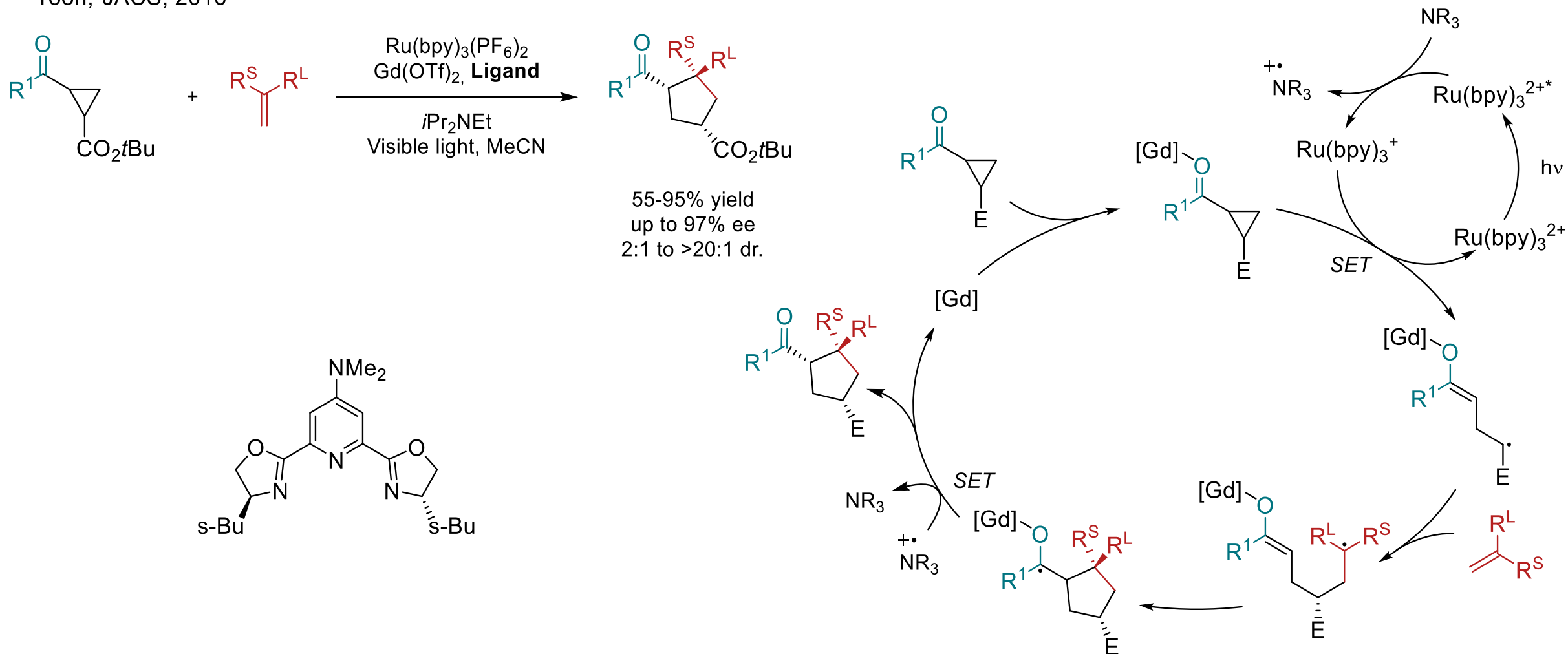
07/10/2020

EPFL ■ Radical ring-opening with Ti-based catalyst

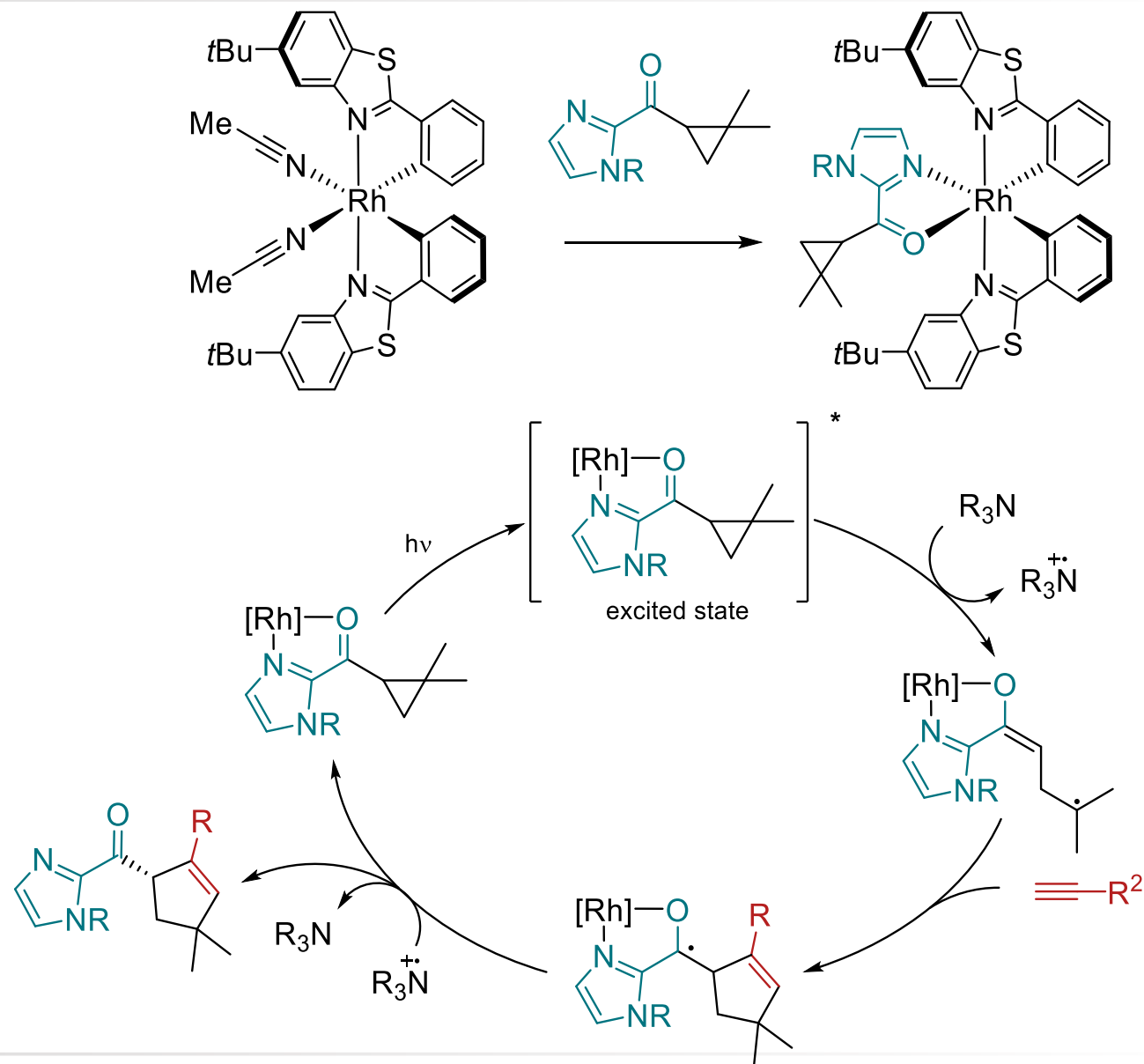
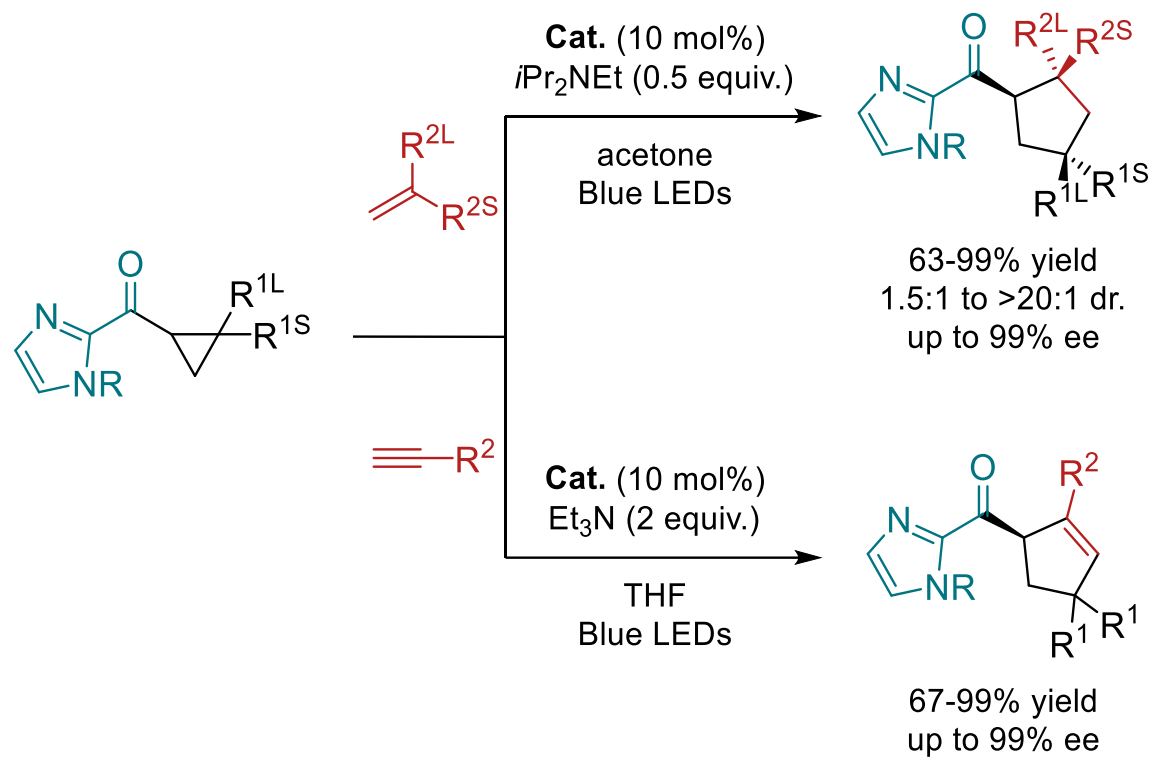
Lin, JACS, 2018



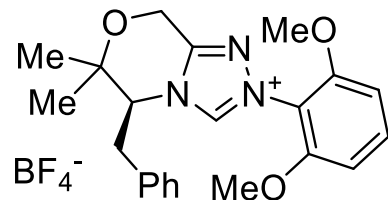
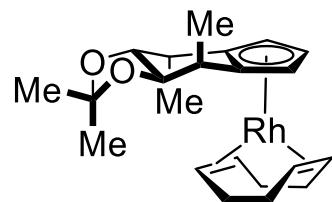
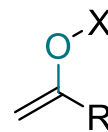
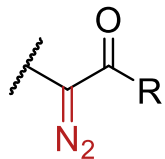
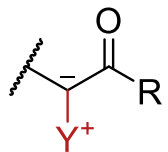
Yoon, JACS, 2016



Meggers, ACIE, 2018



Conclusion: enantioselective syntheses of cyclopropyl ketones



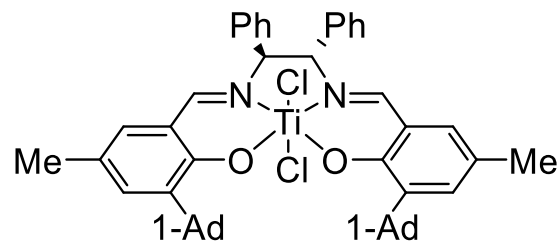
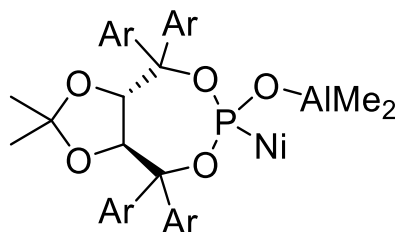
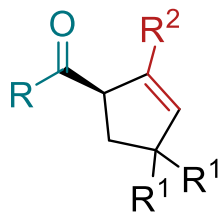
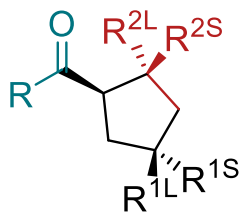
- Variety of different C1 building blocks
- trans* and *cis* cyclopropanes

- Transition metal catalysis with chiral ligand design

- Organocatalysis

- but also radical ring closures or rearrangements

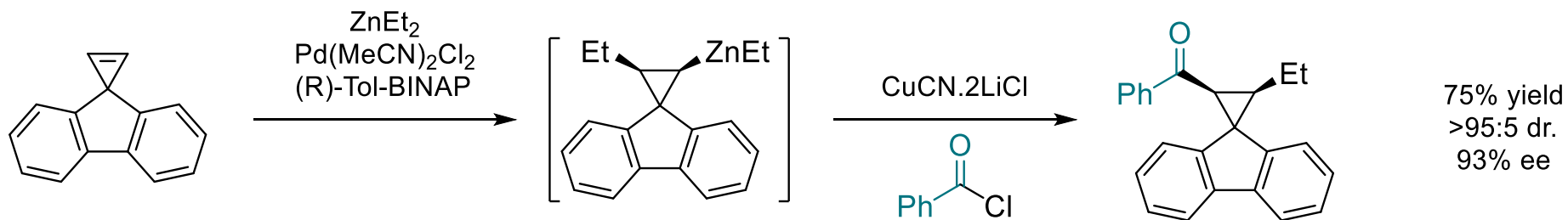
Conclusion: enantioselective transformations of cyclopropyl ketones



- Enantioselective transformations limited to [3+2] cycloadditions
- Transition metal C-C activation
- Radical/LA dual catalysis

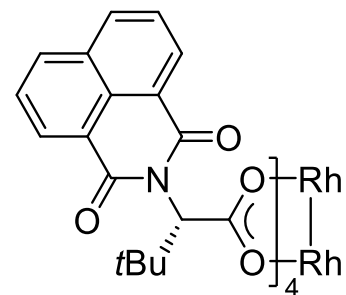
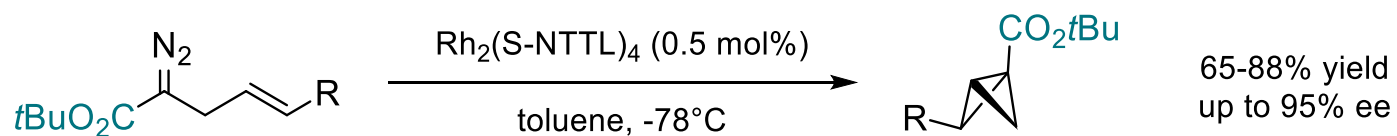
- Propose the starting material and a mechanism for this transformation

Lautens, OL, 2011



- Propose a structure for the following transformation

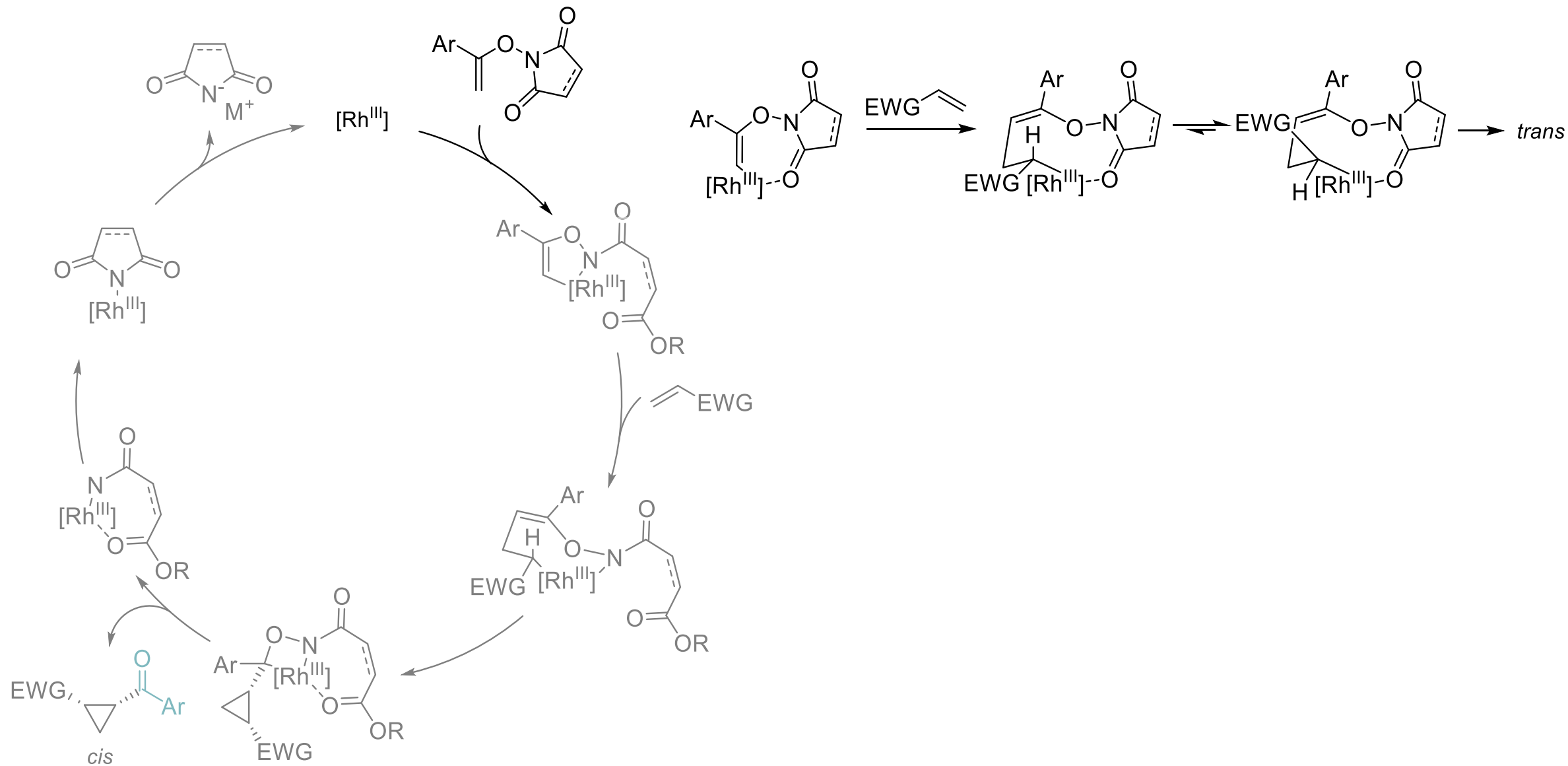
Fox, JACS, 2013

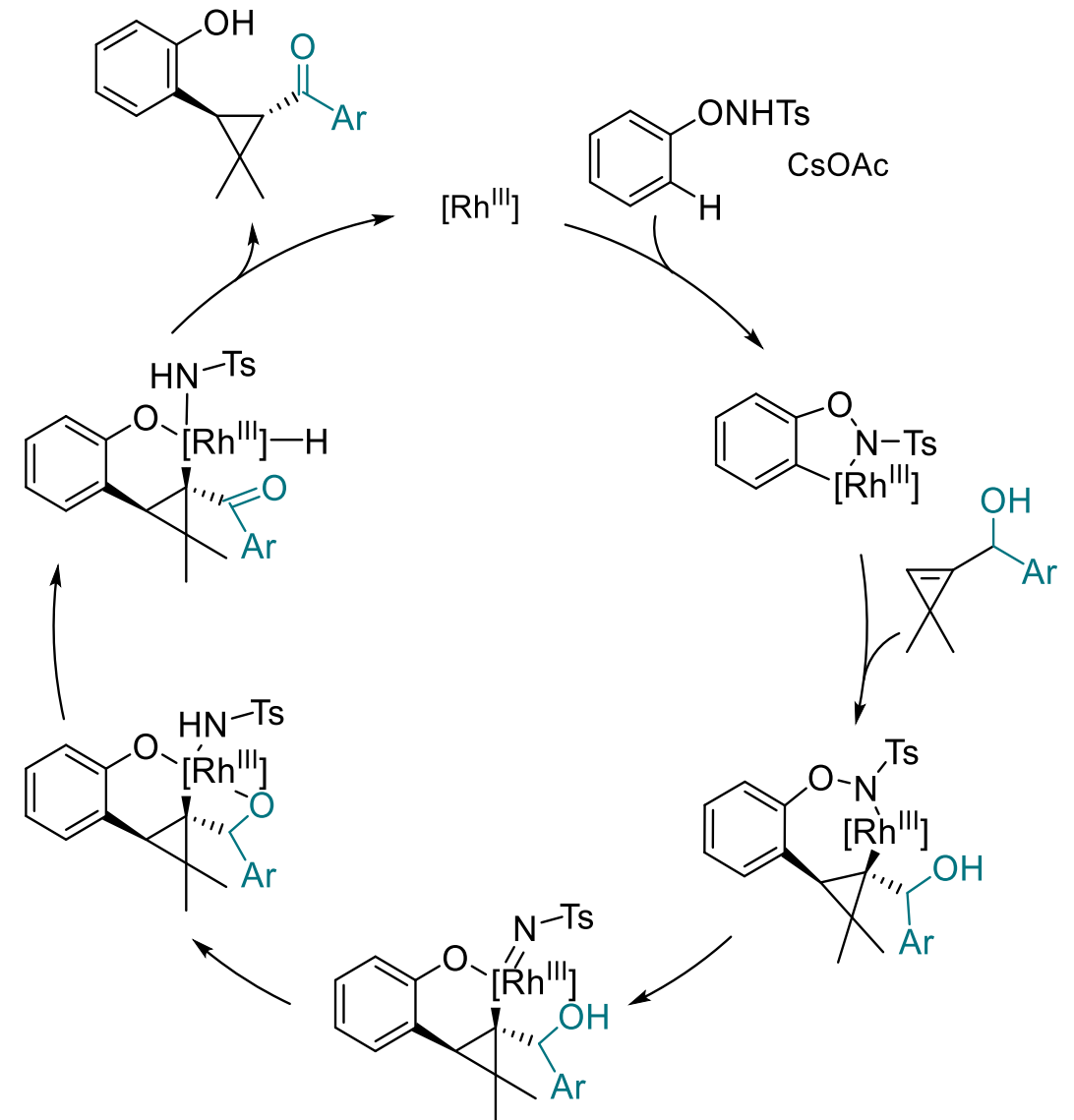


Thank you for your attention!

Any questions?

EPFL ■ Rovis trans cyclopropanation





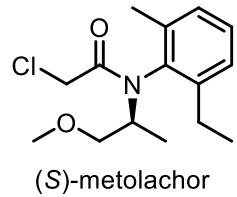
Acid-mediated hydroaminomethylation

Gitlina Anastasia

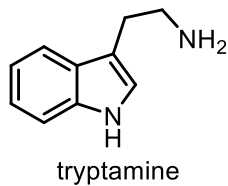
PhD student, LCS, Prof. Kay Severin

Amines

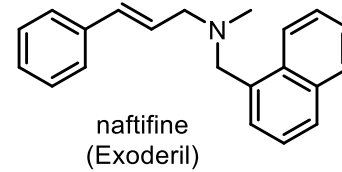
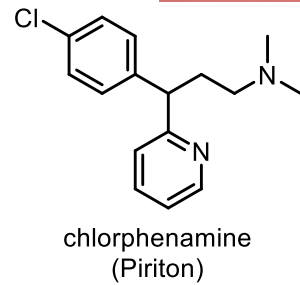
Agrochemicals



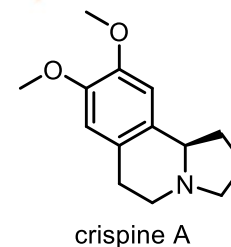
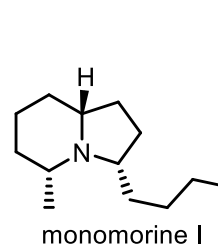
Food-additives



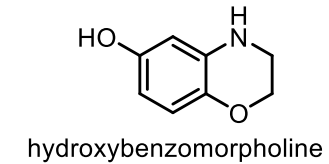
Pharmaceuticals



Natural products



Cosmetics



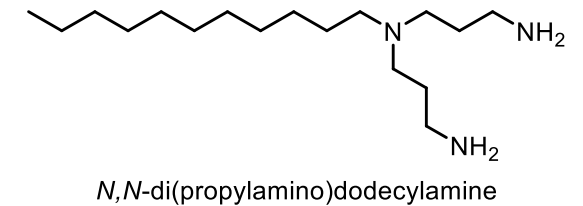
Lubricants

Antiseptics

Textiles

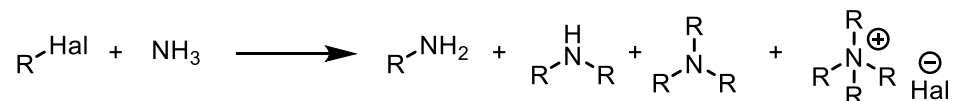
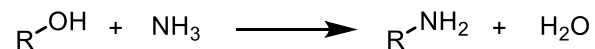
Solvents

Detergents



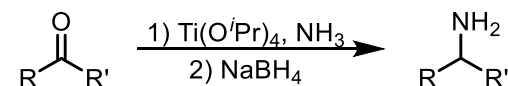
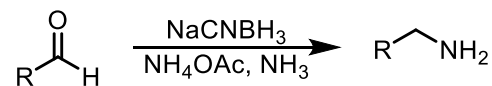
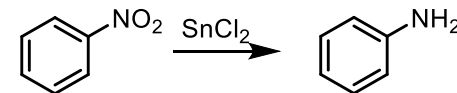
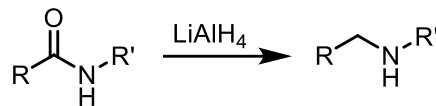
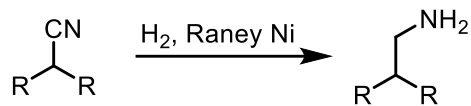
Summary of amines synthesis

Classical S_N2 reactions:

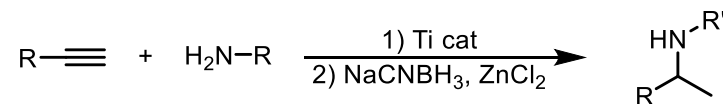
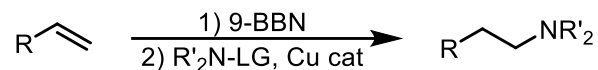


+ Gabriele synthesis
+ Delépine reaction
+ Mitsunobu reaction

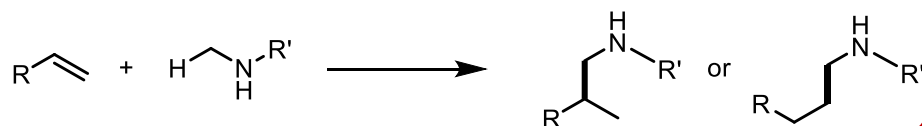
Reductive routes:



Hydroamination:

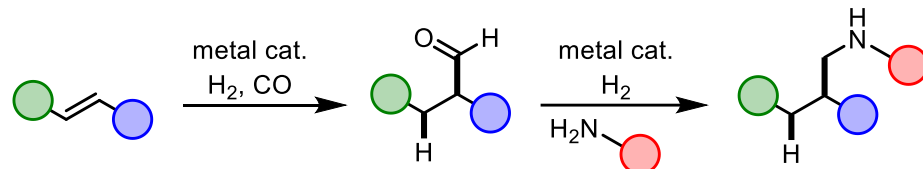


Hydroaminomethylation (HAM):

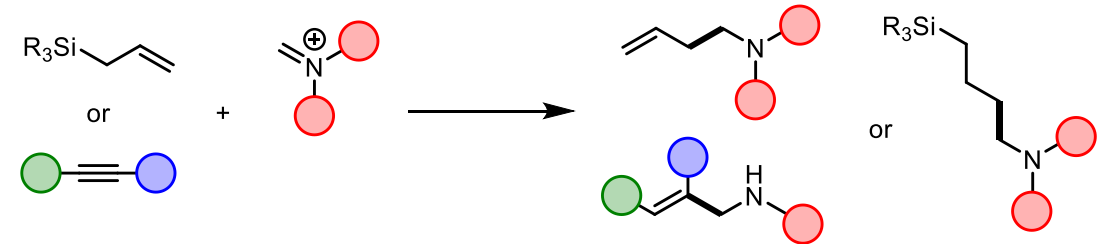


HAM methods

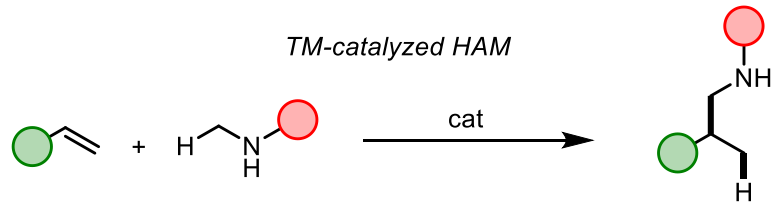
Tandem HAM via hydroformylation



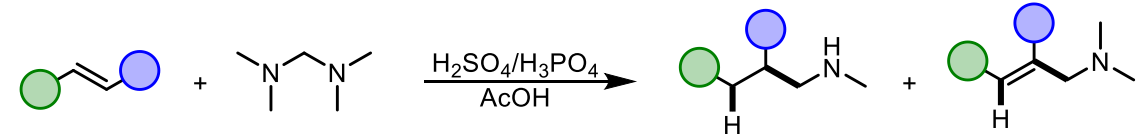
HAM with iminium salts



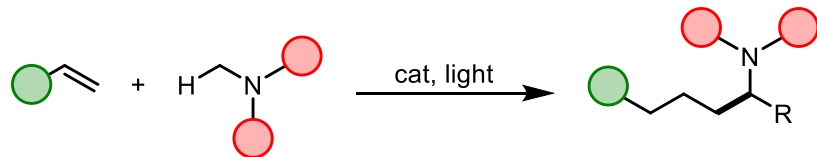
TM-catalyzed HAM



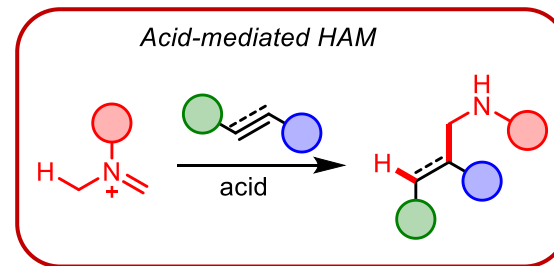
HAM with aminals



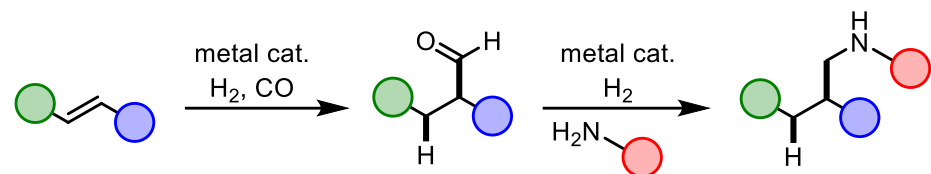
Photoredox HAM



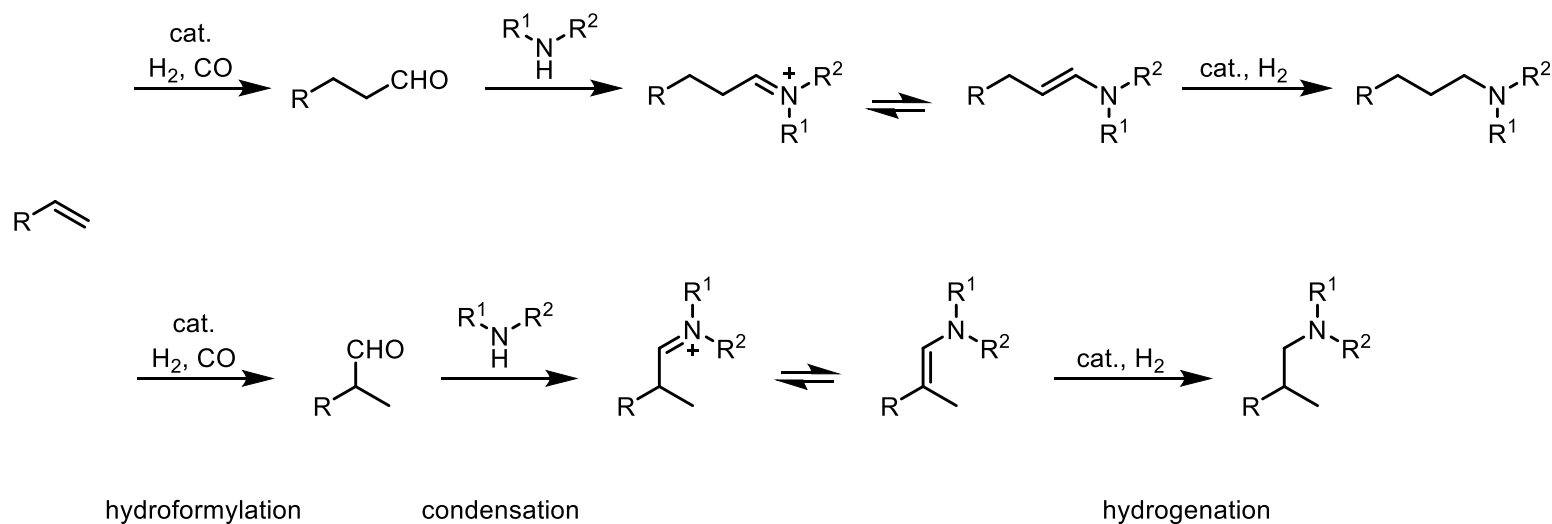
Acid-mediated HAM



Tandem HAM *via* hydroformylation

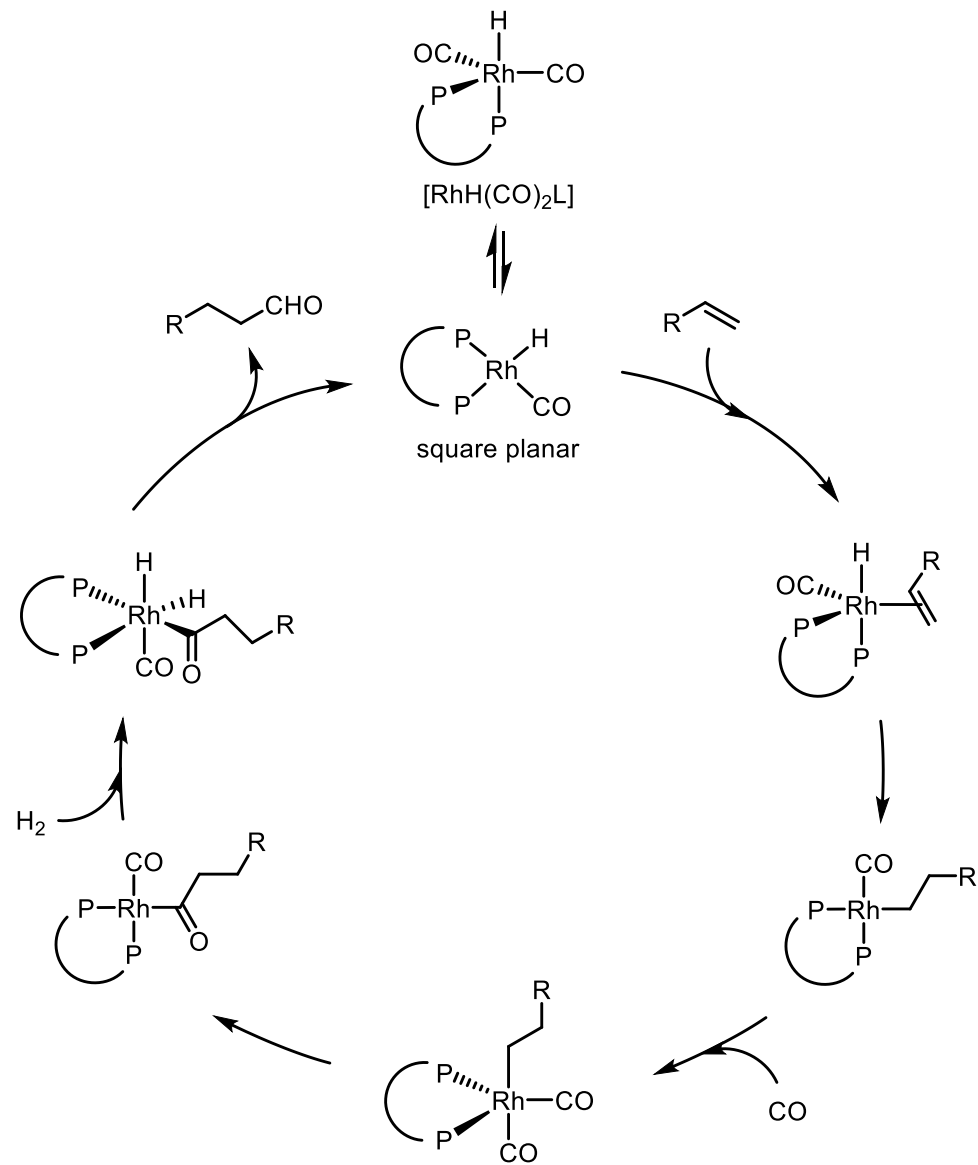


Kaiser et al., *Angew. Chem. Int. Ed.*, **2019**, 58, 14639

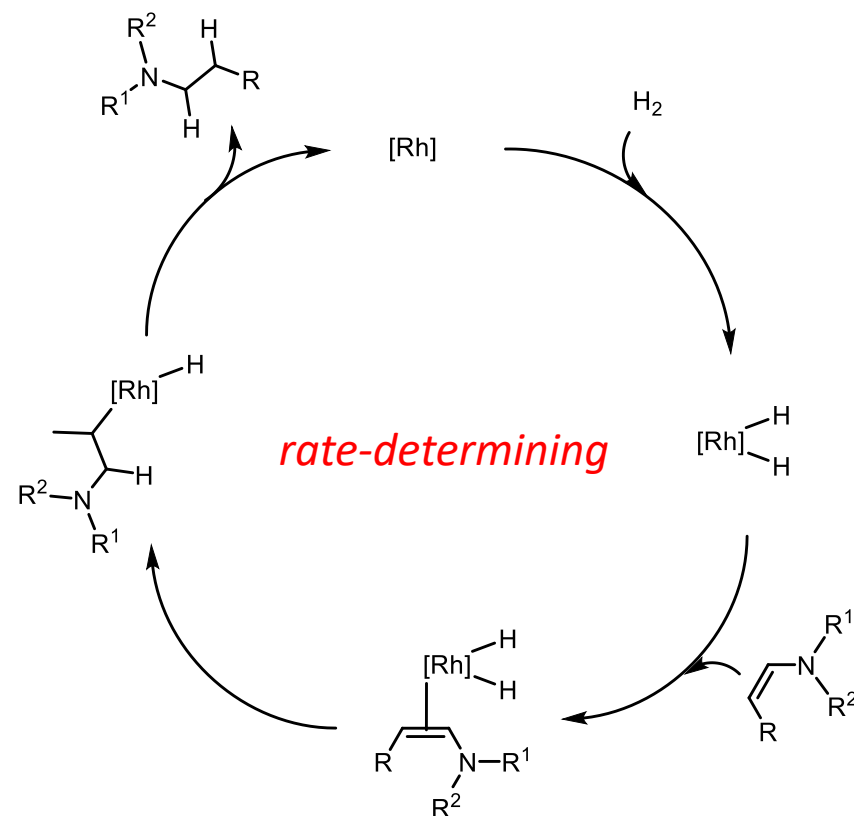


Kalck et al., *Chem. Rev.*, **2018**, 118, 3861

Catalytic cycle of hydroformylation step



Catalytic cycle of hydrogenation step

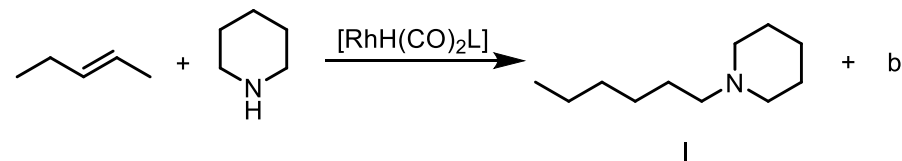
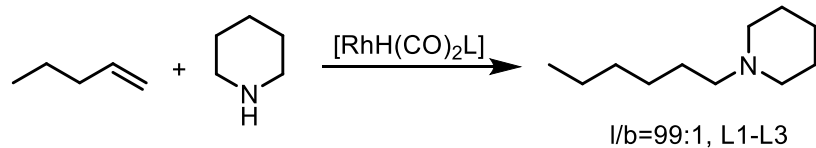
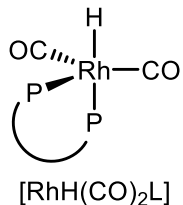


General conditions:

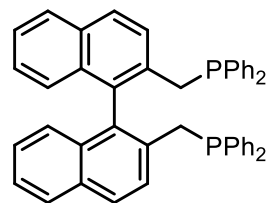
90 to 130 °C, 30 to 60 bar

CO/H₂ (1:1 to 1:5)

30 min to 72 h

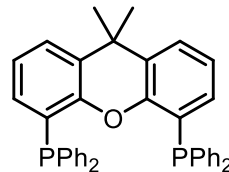
HAM reaction of terminal and internal alkenes**Unmodified catalysts:**Rh₂O₃[Ru₃(CO)₁₂][Rh(acac)(CO)₂][Rh₂(μ-Cl)₂(COD)₂]**Ligand-decorated catalysts:**

L =



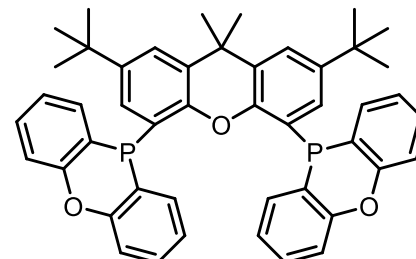
L1, 120°

yield (I) 6%, I/b=99:1



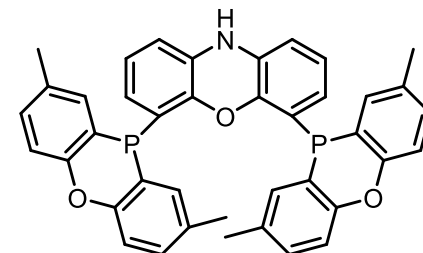
L2, 111°

yield (I) quant, I/b=93:7



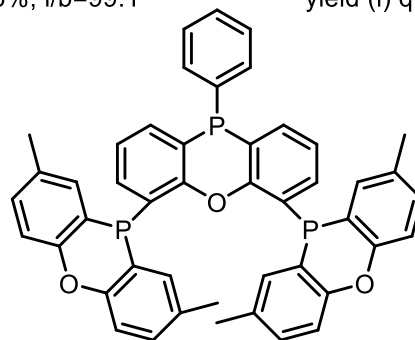
L3, 123°

yield (I) 67%, I/b=73:27



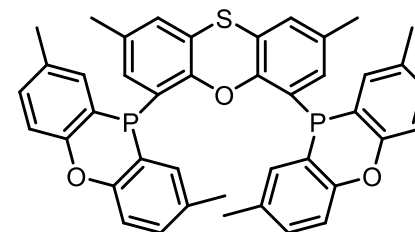
L4, 125°

yield (I) 56%, I/b=73:27



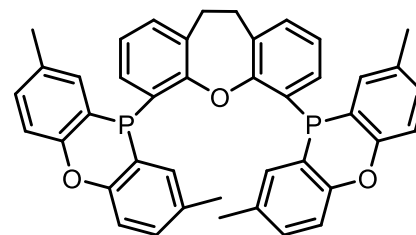
L5, 131°

yield (I) 40%, I/b=51:49



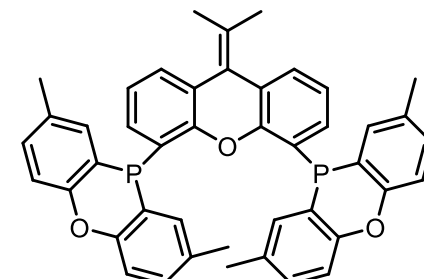
L6, 113°

yield (I) 43%, I/b=45:55



L7, 106°

yield (I) 15%, I/b=20:80



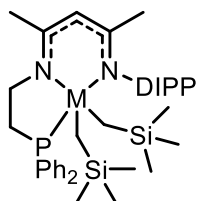
L8, 114°

yield (I) 67%, I/b=68:32

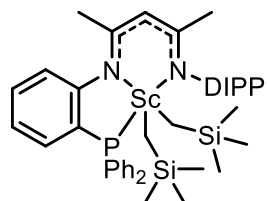
Metal-catalyzed HAM of alkenes

Recent catalytic systems:

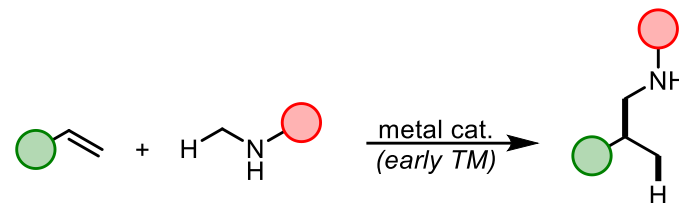
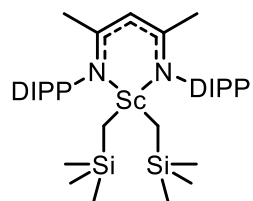
3 group



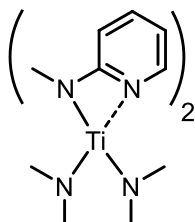
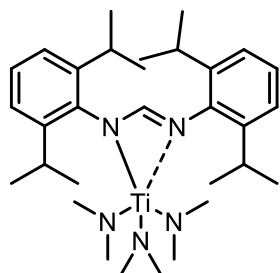
M = Sc, Y



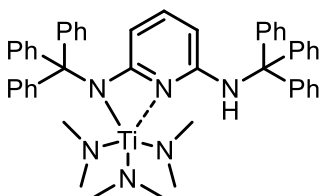
Gao *et al*, *Org. Chem. Front.*, **2018**, 5, 59



4 group



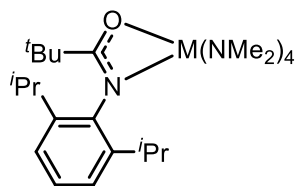
Lehning *et al*, *Chem. Eur. J.*, **2017**, 23, 4197
Bielefeld *et al*, *Angew. Chem. Int. Ed.*, **2017**, 56, 15155



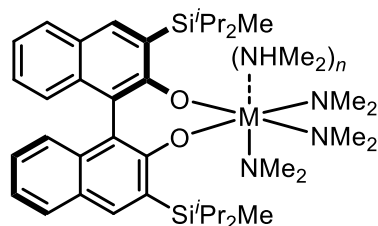
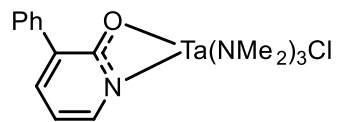
Overall:

- + 1°, 2°, 3° amines
- + activated and nonactivated alkenes
- + moderate to good yields
- terminal alkenes
- double HAM
- mixture of linear and branched products
- moderate FG tolerance
- air sensitivity

5 group



M = Nb, Ta

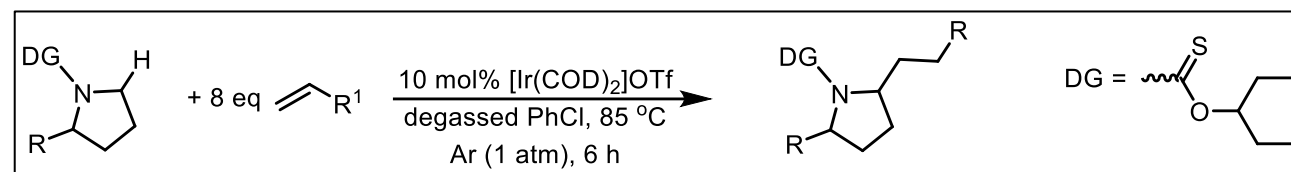
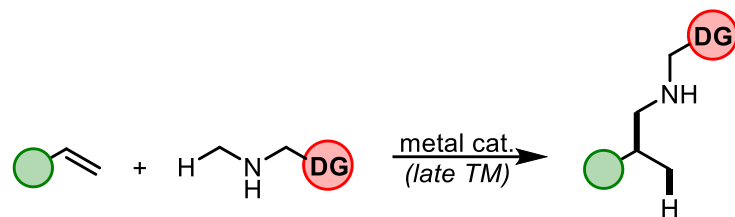


M = Ta, n = 1
M = Nb, n = 0

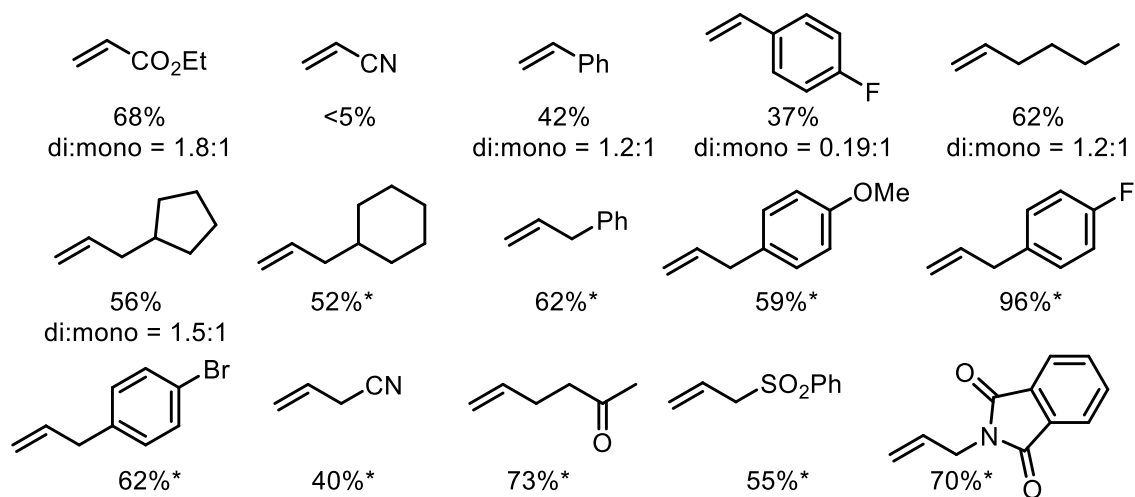
Lauzon *et al*, *ACS Catal.*, **2017**, 7, 5921

Chong *et al*, *J. Am. Chem. Soc.*, **2014**, 136, 10898

Reznichenko *et al*, *J. Am. Chem. Soc.*, **2012**, 134, 3300

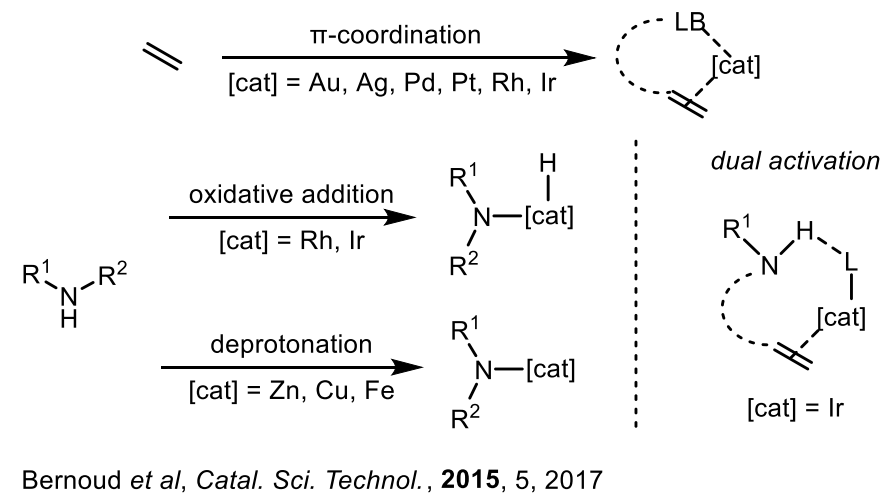
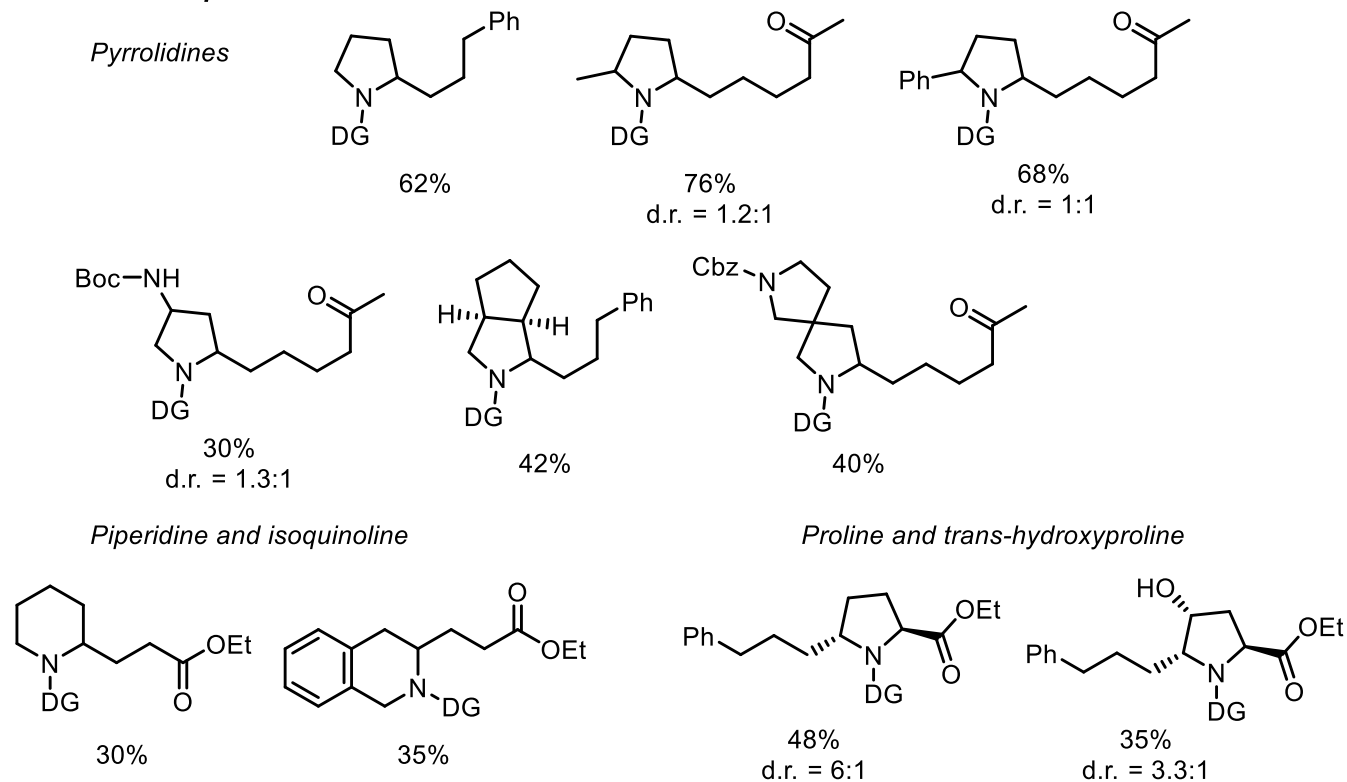


Olefins scope, R = H

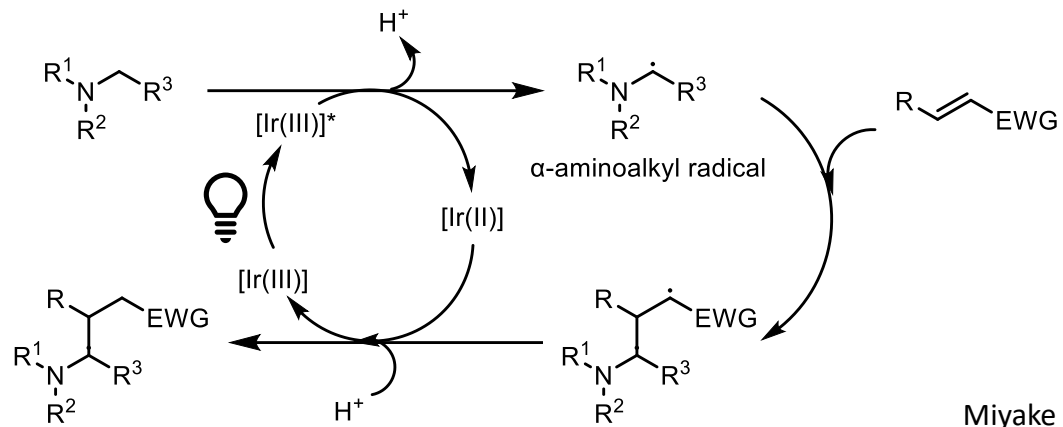
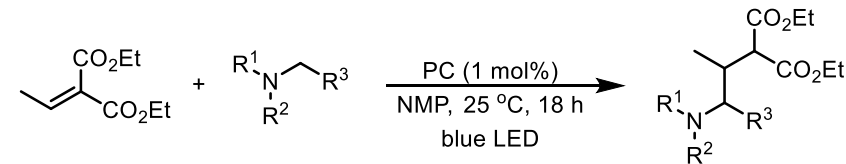
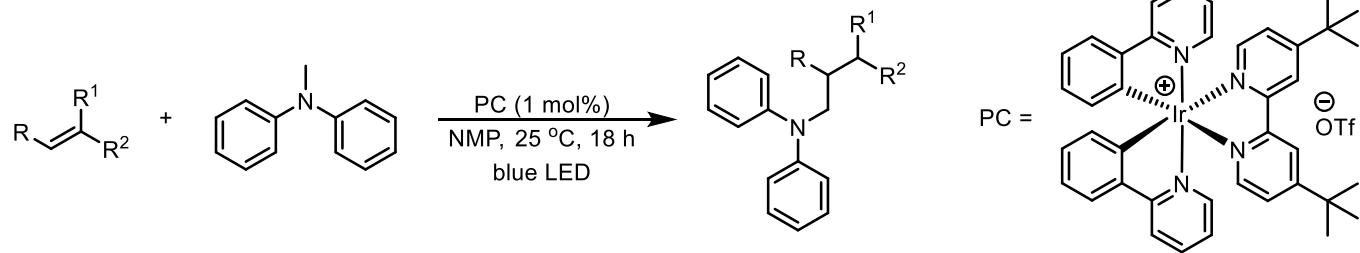


*only dialkylated products (d.r. > 20:1) were obtained for these substrates

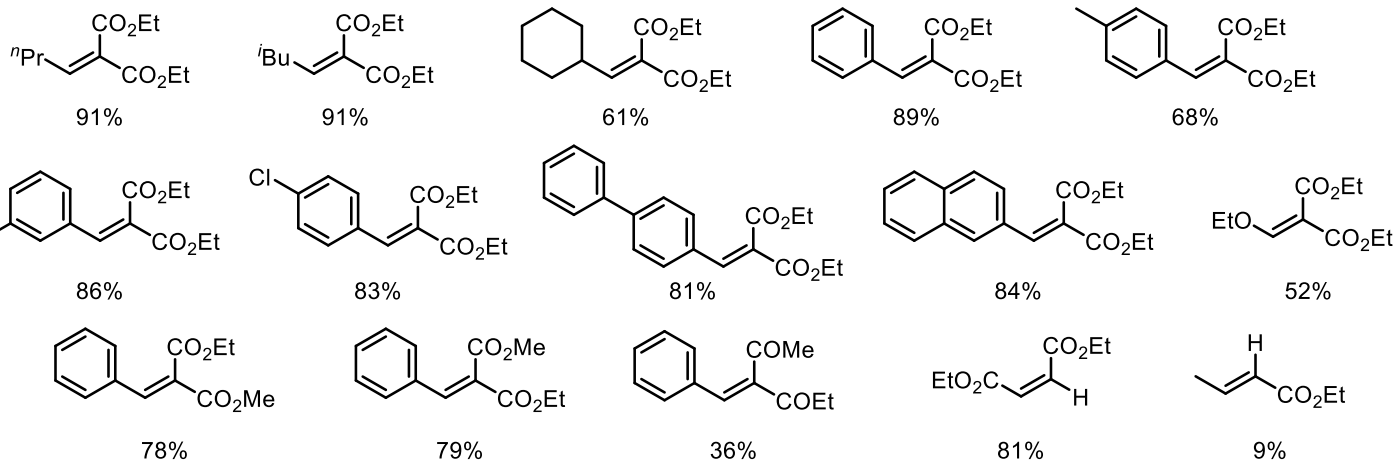
Amines scope



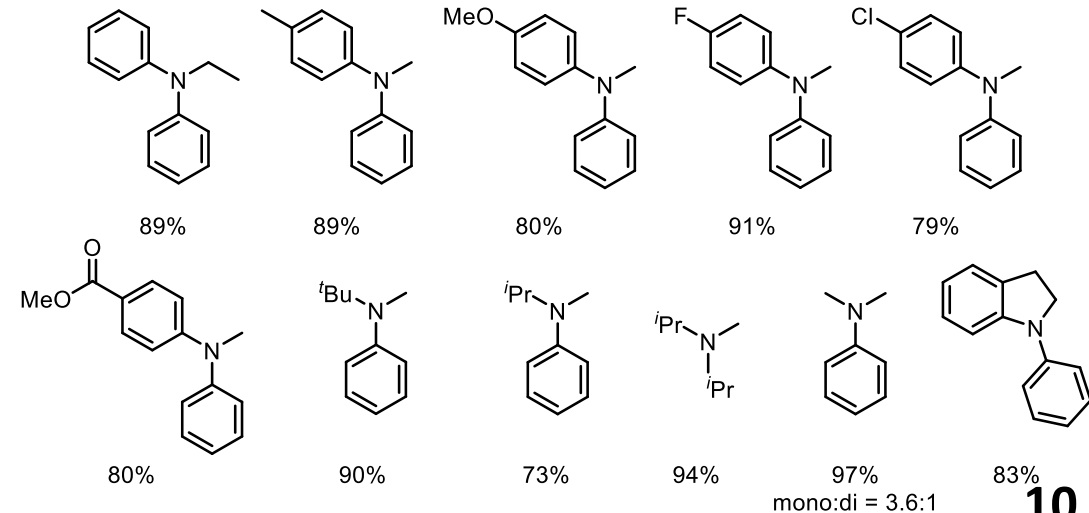
Photocatalytic approach to HAM

Miyake *et al*, *J. Am. Chem. Soc.*, **2012**, 134, 3338

Olefins scope



Amines scope



Pros vs Cons of metal-catalyzed methods of HAM of alkenes



one-pot
atom economy
orthogonal/autotandem catalysis
high yields*
high chemo-, regio-, enantioselectivity*
good functional group tolerance*

**if catalyst is well-designed*



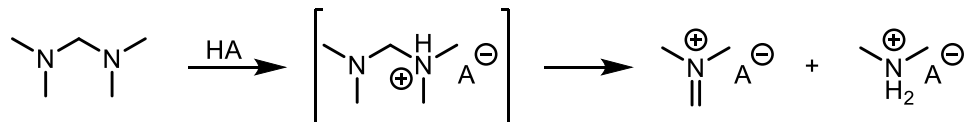
moderate yields in general
catalyst design
catalyst-based substrate design
early TM incompatible with air conditions
limited olefins scope (nonactivated, terminal)
selectivity restrictions
double alkylation
metal or oxidant additives in principle



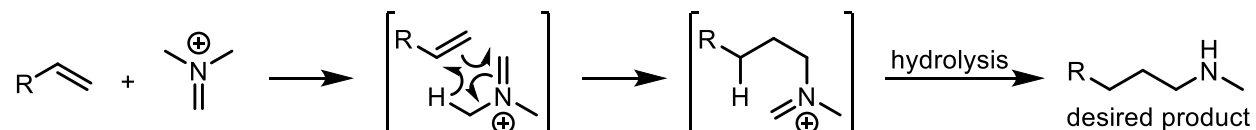
metal-free?
activated π -systems?

Acid-mediated HAM with animals

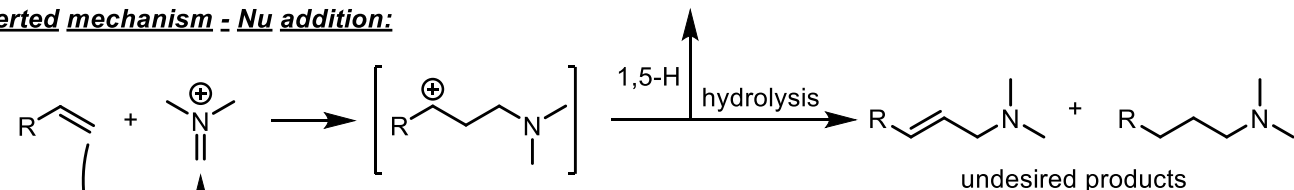
Formation of iminium salts - cleavage of amins with mineral acid:



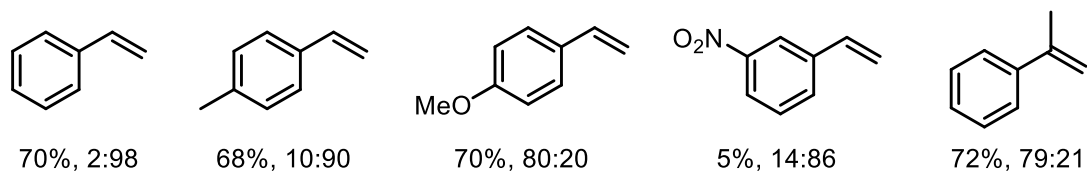
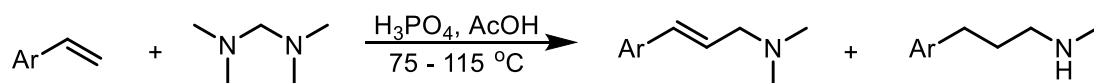
Concerted mechanism - ene reaction:



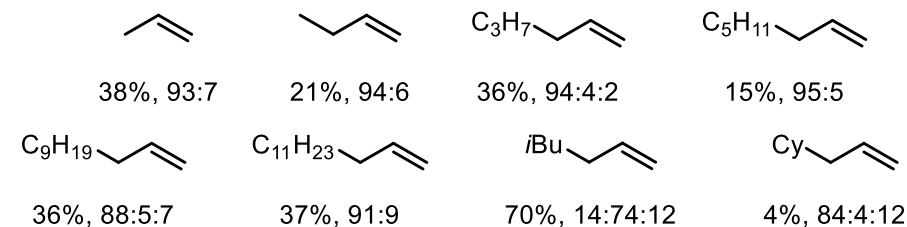
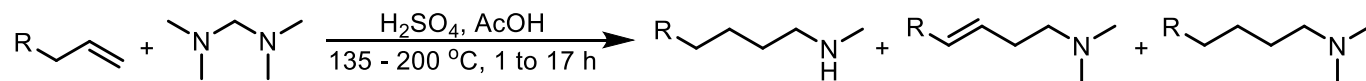
Unconcerted mechanism - Nu addition:



Aryl olefins

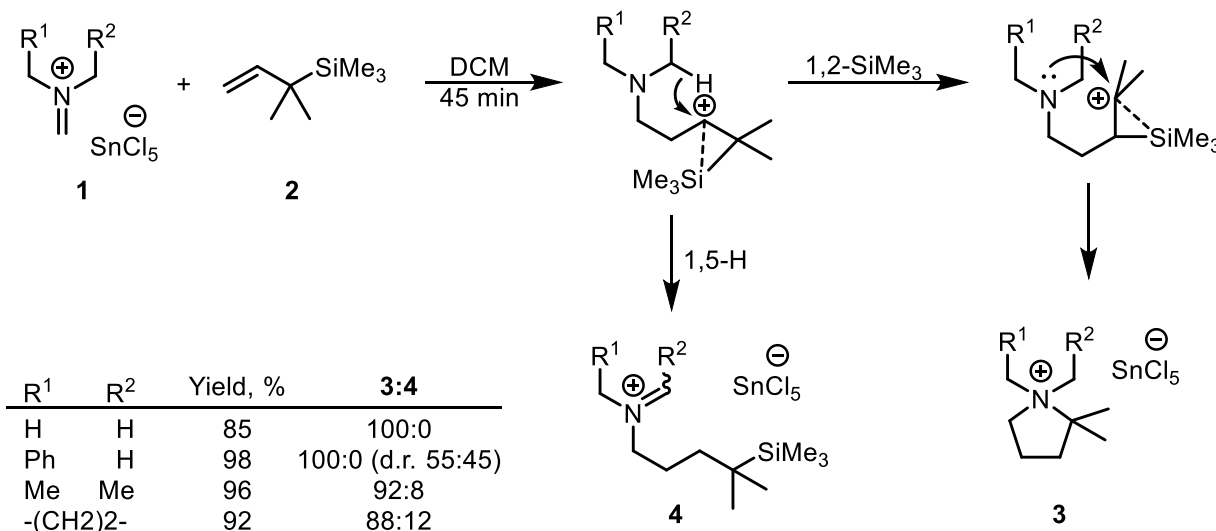
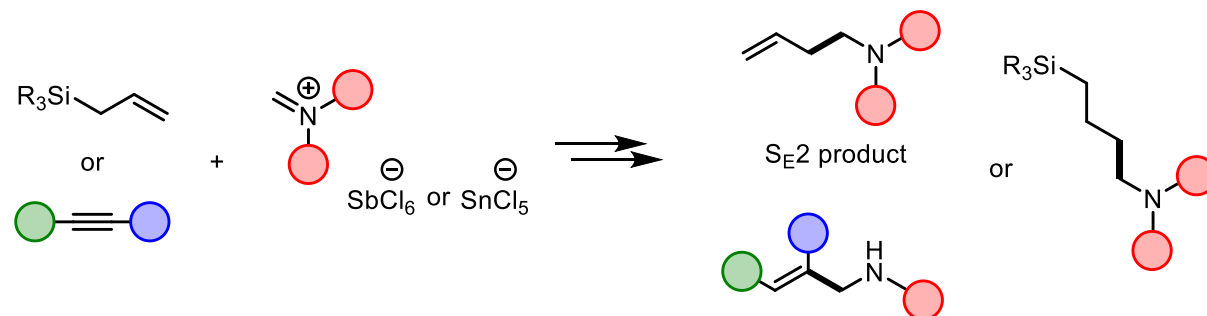
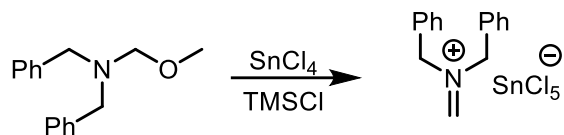


Nonconjugated olefins



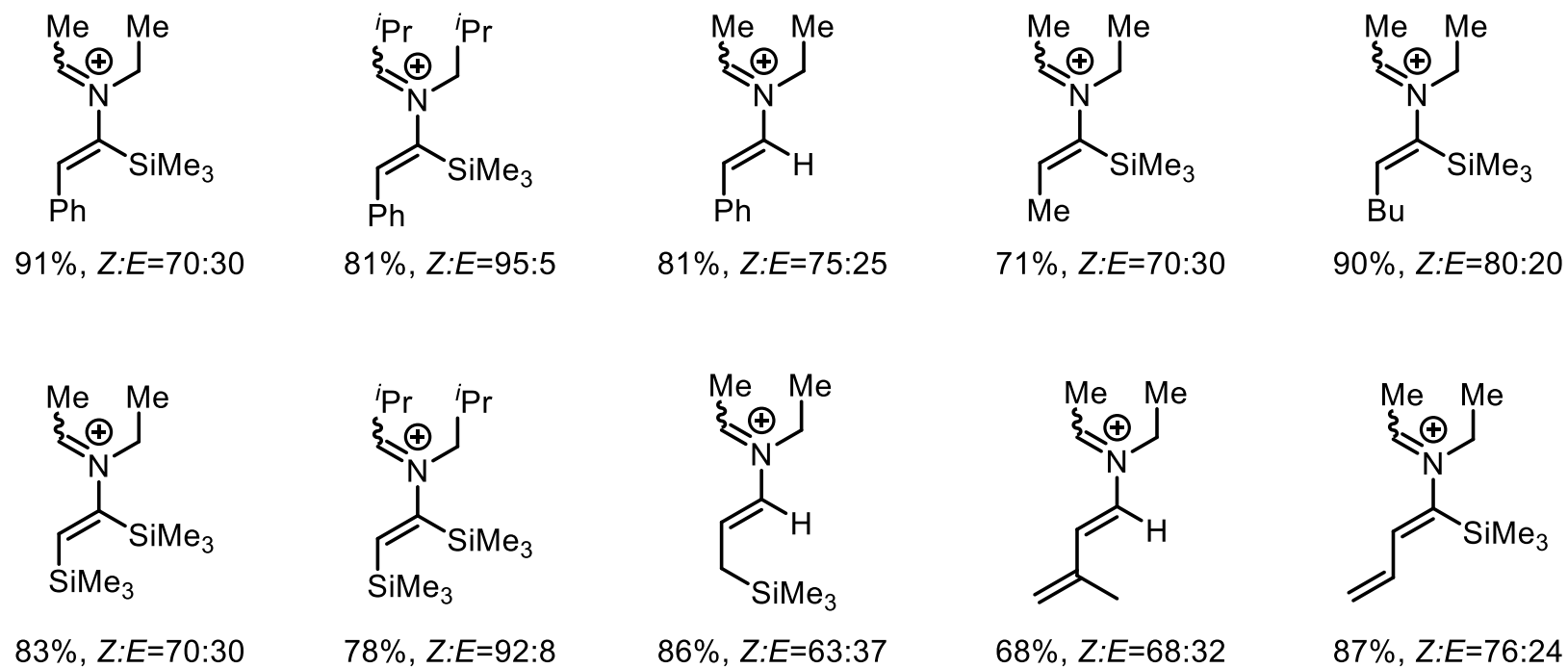
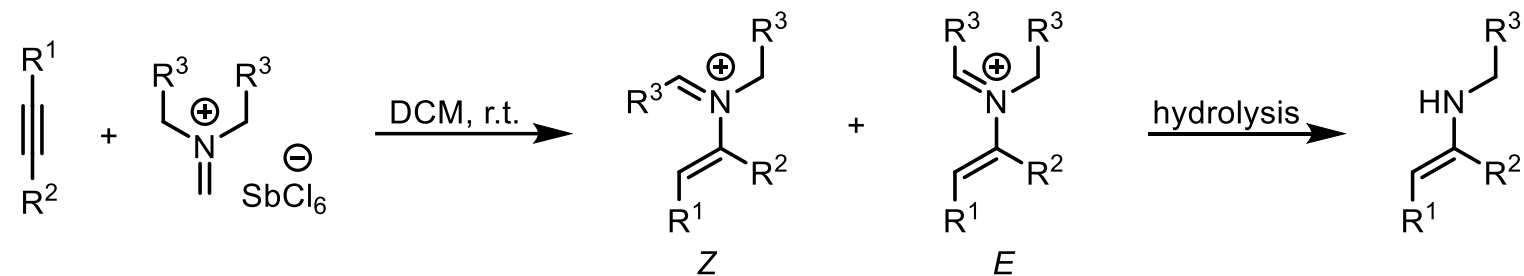
HAM of activated substrates with N,O-acetals

Formation of iminium salts - cleavage of N,O-acetals with Lewis acids:



- β -silyl effect
- poor chemoselectivity
- poor regioselectivity
- only activated alkenes

R ¹	R ²	Yield, %	3:4
H	H	85	100:0
Ph	H	98	100:0 (d.r. 55:45)
Me	Me	96	92:8
-(CH ₂) ₂ -		92	88:12

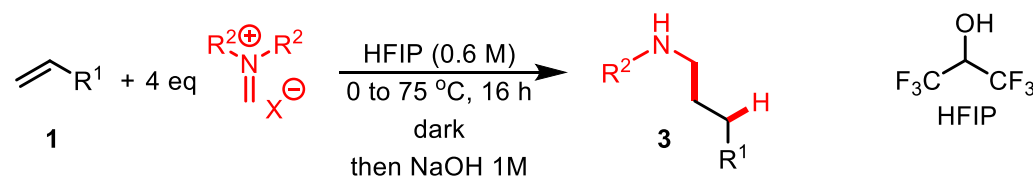
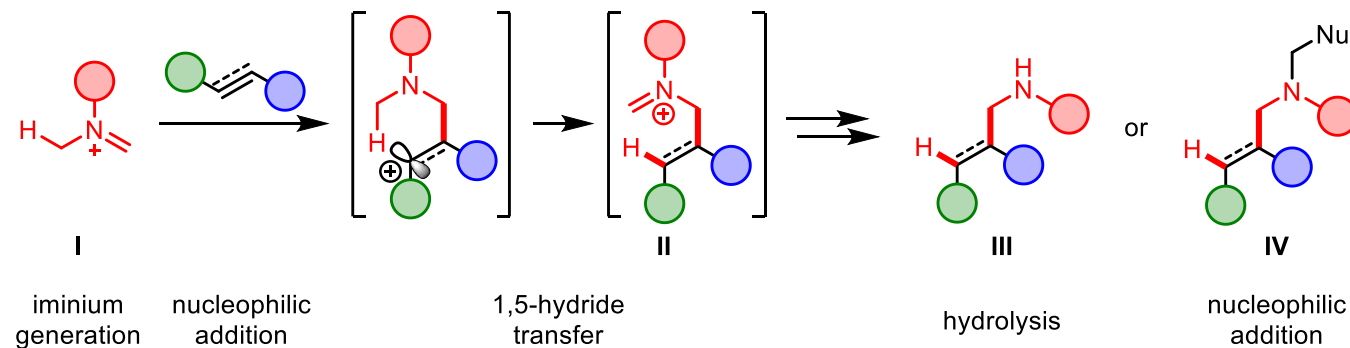


Acid-mediated HAM

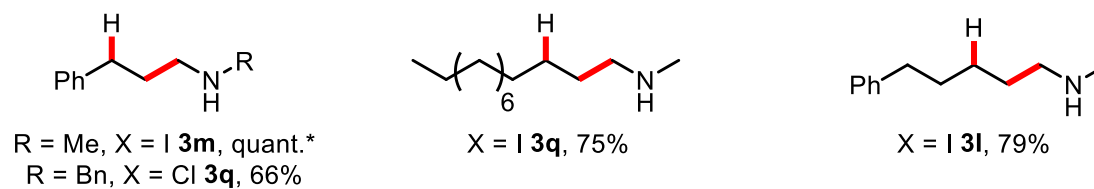


Prof. Nuno Maulide
University of Vienna

The concept

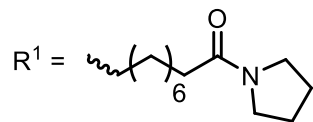
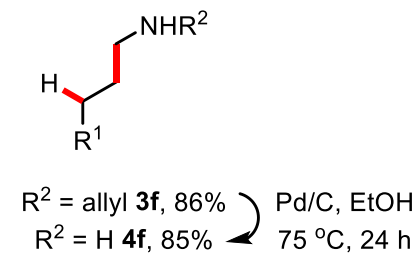
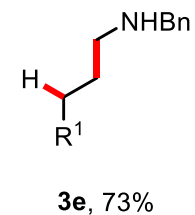
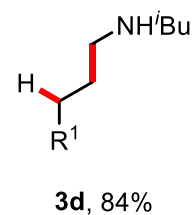
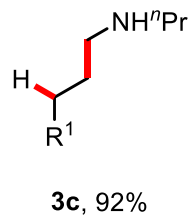
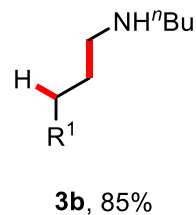
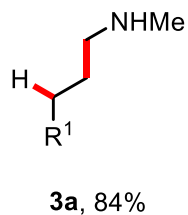
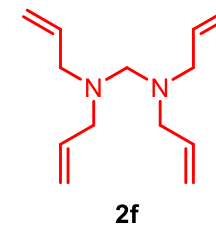
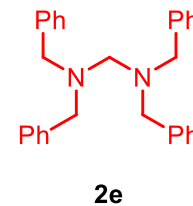
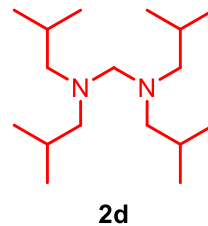
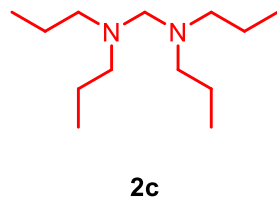
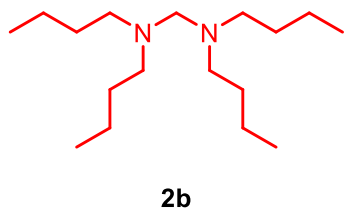
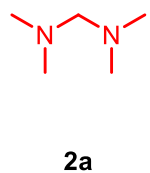
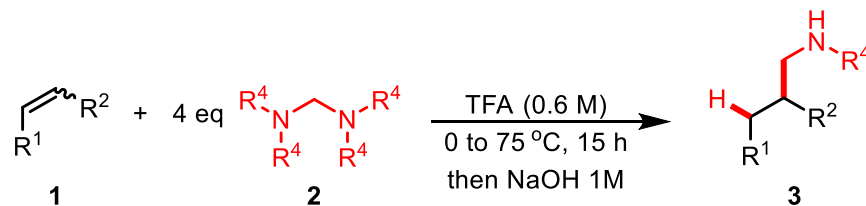


First steps

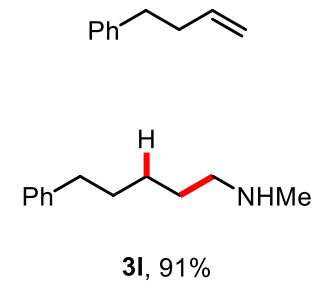
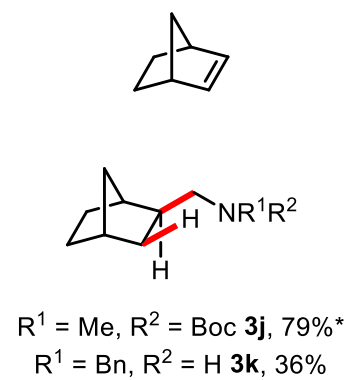
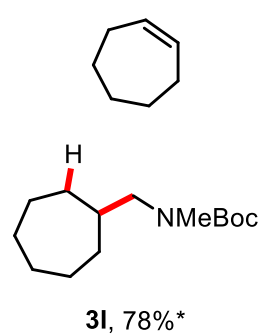
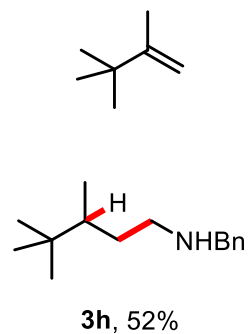
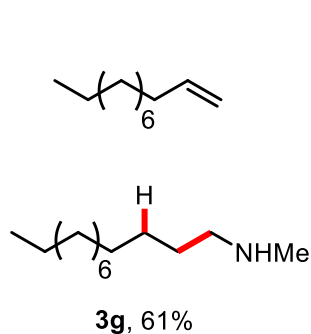
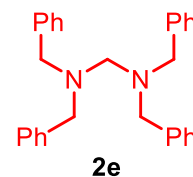
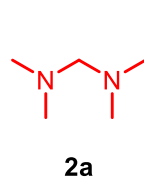
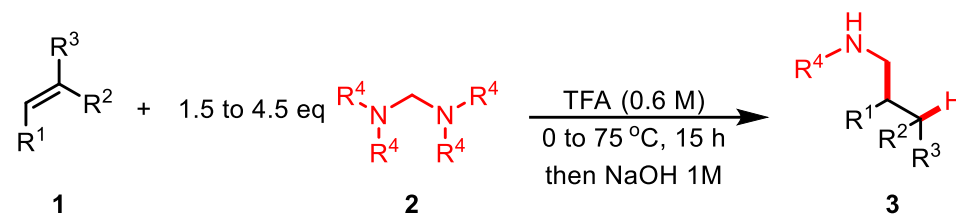


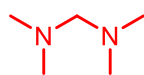
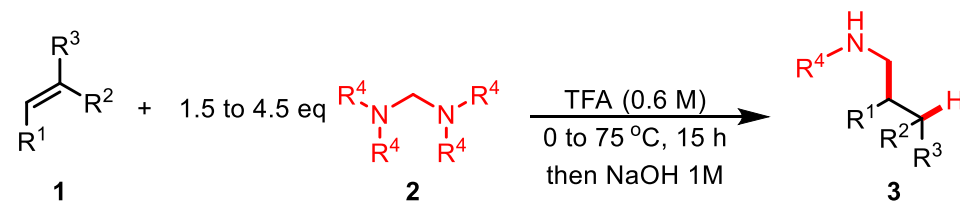
unsuccessful substrates:
internal alkenes, alkynes

Aminals scope

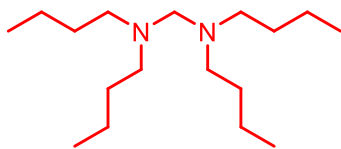


Olefins scope

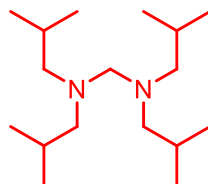




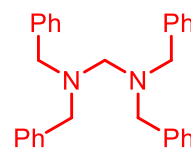
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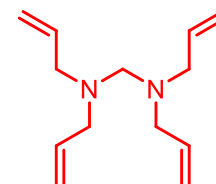
2b



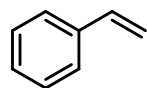
2d



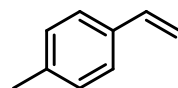
2e



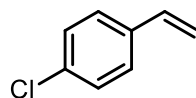
2f



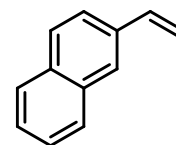
R = Me **3m**, 82%
(86% on 50 mmol)



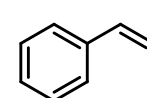
3n, 85%



3o, 86%



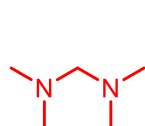
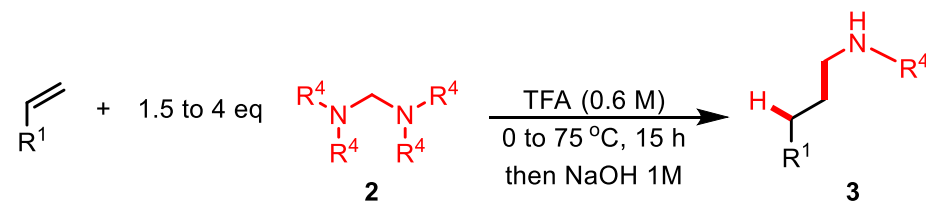
3p, 55%



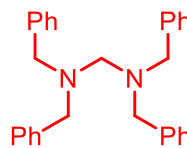
R = *i*Bu **3t**,
61% from *cis*- and 60% from *trans*-
R = Me **3u**,
39% from *cis*-

R = Bn **3q**, 42%
R = *n*Bu **3r**, 86%
R = allyl **3s**, 69%

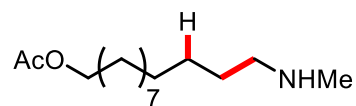
Functional group tolerance



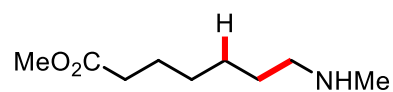
2a



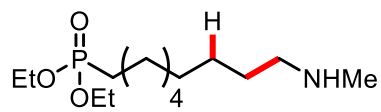
2e



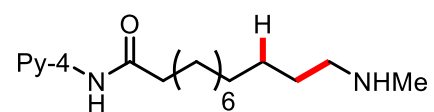
3v, 93%



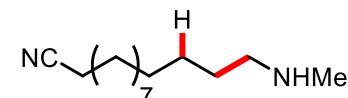
3w, 64%



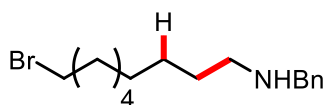
3x, 80%



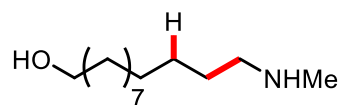
3y, 72%



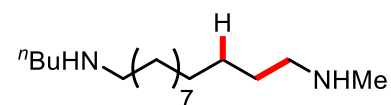
3z, 84%



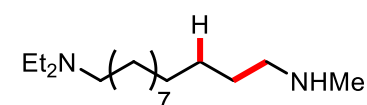
3aa, 40%



3ab, 82%
(71% on 20 mmol)

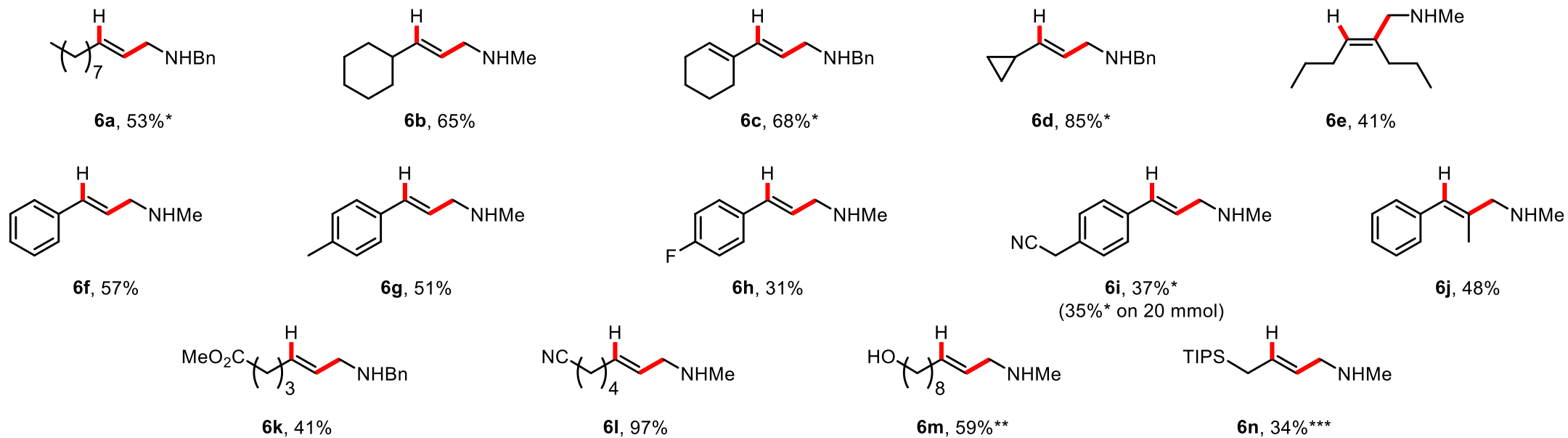
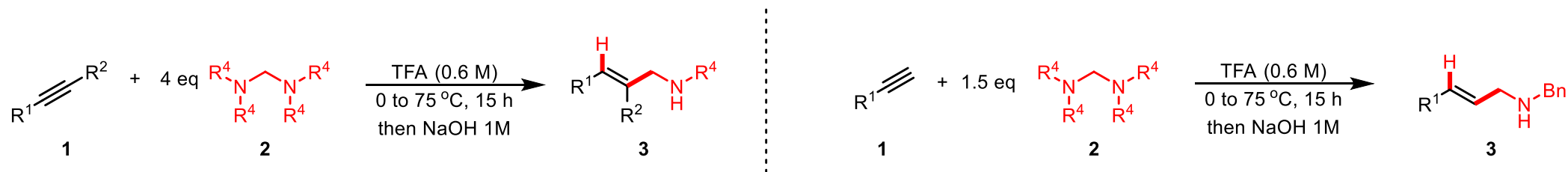


3ac, 60%



3ad, 75%

Alkynes scope

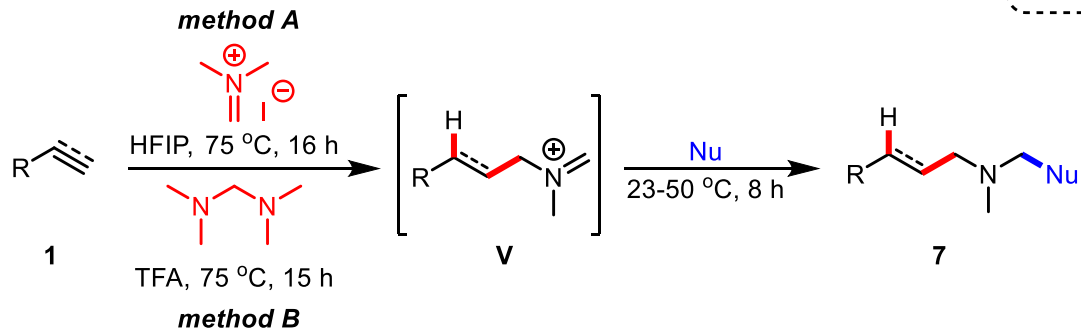
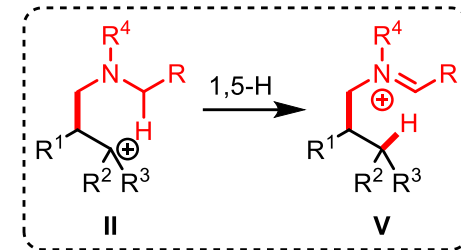


*DCE used as co-solvent

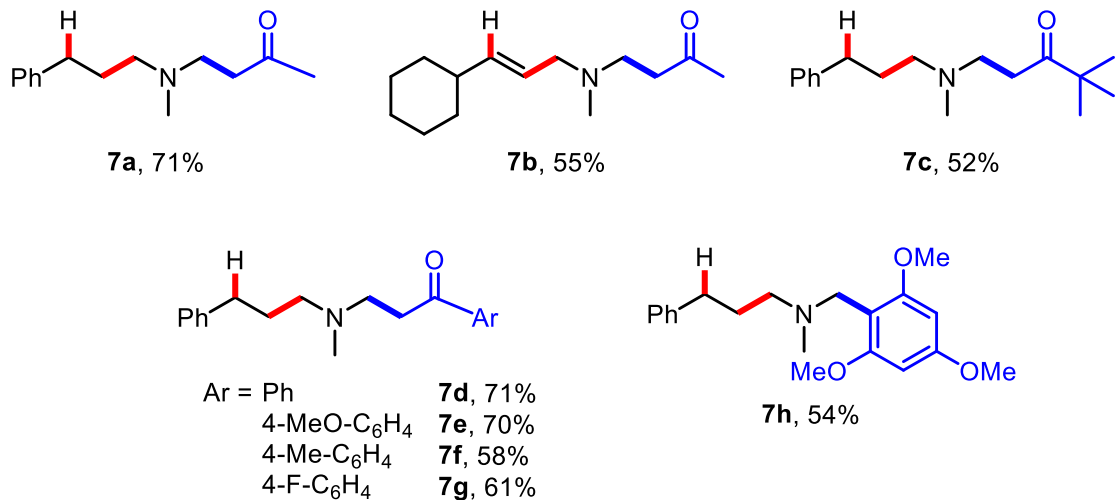
**Reaction was run for 5 h

***Reaction was run at room temperature

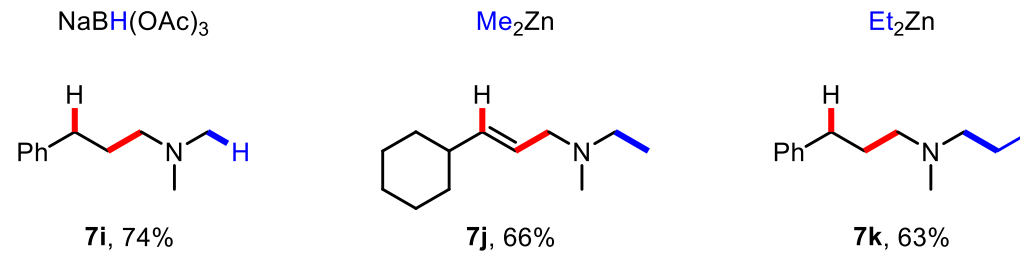
Domino functionalization



following method B, in TFA

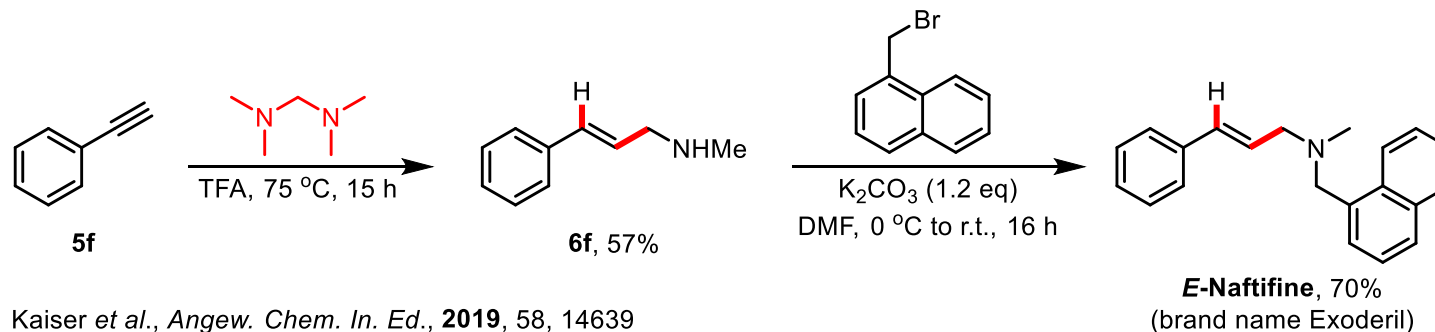


following method A, in HFIP

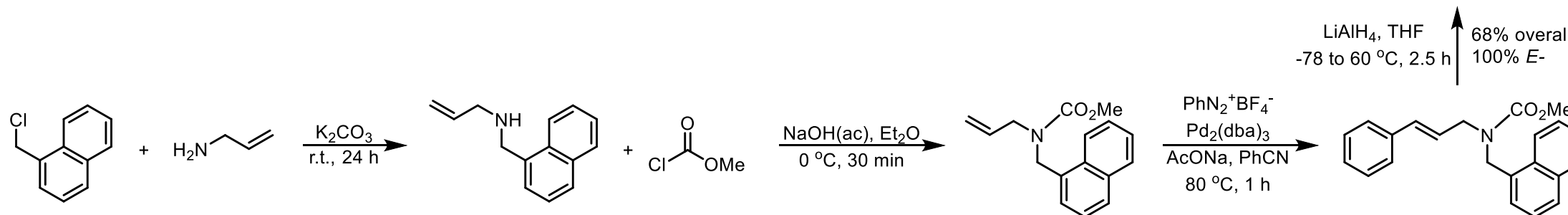
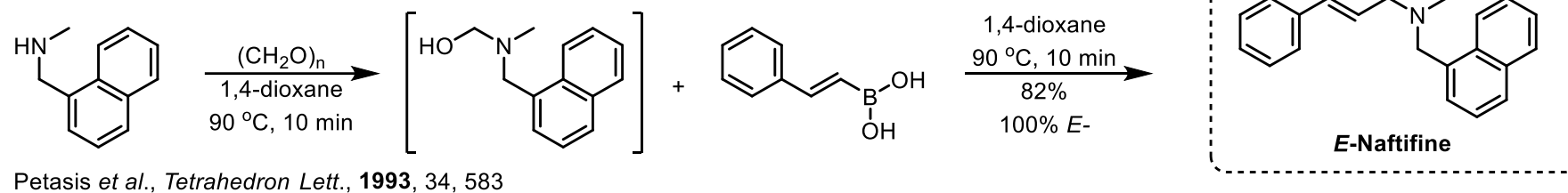
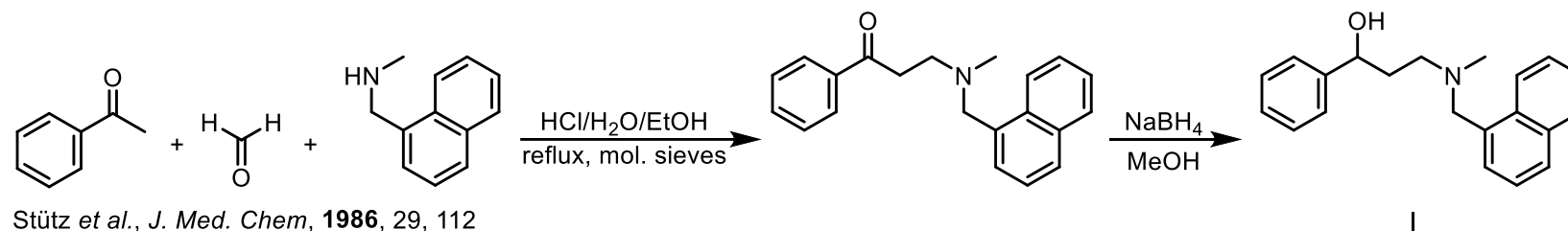


Pharmaceutical products synthesis

This work:

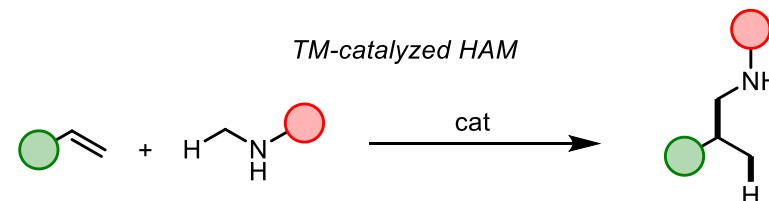
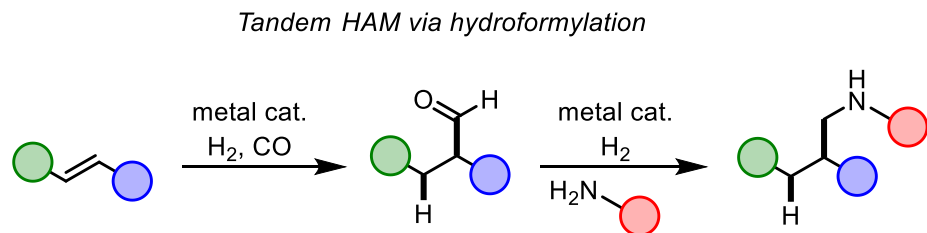
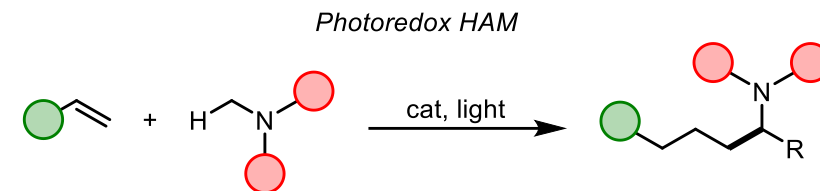


Previous works:

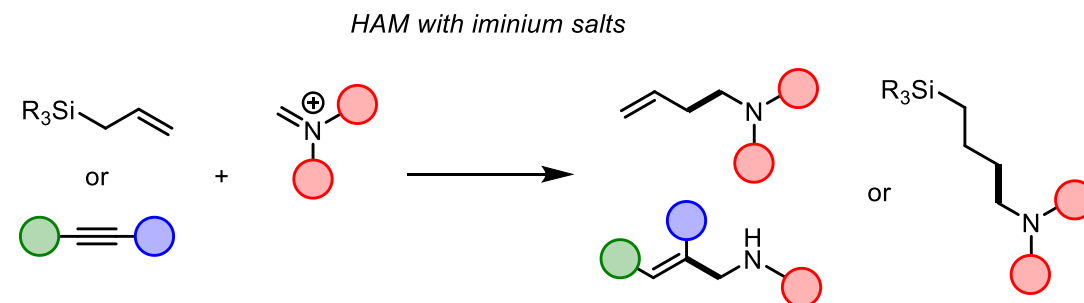
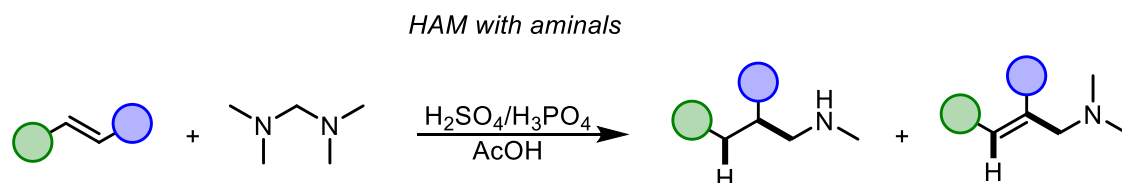


Conclusion

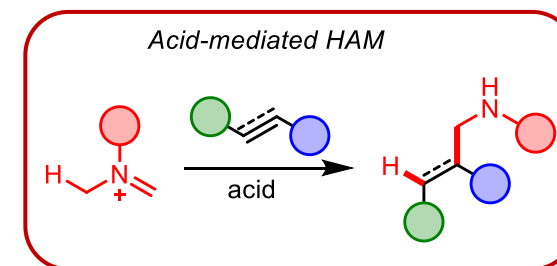
- lots of limited TM-catalyzed HAM methods



- number of limited metal-free HAM procedures



- one general acid-mediated HAM method



References

Reviews

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2. Agbossou-Niedercorn, Recent metal-catalysed asymmetric hydroamination of alkenes *Journal of Organometallic Chemistry*, **2017**, 847, 13.
3. Boutevin, Biobased amines: from synthesis to polymers; present and future *Chem. Rev.*, **2016**, 116, 14181.
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Articles

1. Maulide, A general acid-mediated hydroaminomethylation of unactivated alkenes and alkynes *Angew. Chem. Int. Ed.*, **2019**, 58, 14639.
2. Zacchino, Design of two alternative routes for the synthesis of naftifine and analogues as potential antifungal agents *Molecules* **2018**, 23, 520.
3. Xu, Scandium-catalyzed C(sp³)-H alkylation of N,N-dimethyl anilines with alkenes *Org. Chem. Front.*, **2018**, 5, 59.
4. Doye, Hydroaminoalkylation of allylsilanes and a one-pot procedure for the synthesis of 1,5-benzoazasilepines *Chem. Eur. J.*, **2017**, 23, 4197.

5. Doye, Dimethylamine as a substrate in hydroaminoalkylation reactions *Angew. Chem. Int. Ed.*, **2017**, 56, 15155.
6. Schafer, Amidate complexes of tantalum and niobium for the hydroaminoalkylation of unactivated alkenes **2017**, *ACS Catal.*, 7, 5921.
7. Yu, Practical alkoxythiocarbonyl auxiliaries for iridium(I)-catalyzed C–H alkylation of azacycles *Angew. Chem. Int. Ed.*, **2017**, 56, 10530.
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9. Nishibayashi, Visible-light-mediated utilization of α -aminoalkyl radical: addition to electron-deficient alkenes using photoredox catalysts *J. Am. Chem. Soc.*, **2012**, 134, 3338.
10. Correia, Substrate-directable Heck reactions with arenediazonium salts. The regio- and stereoselective arylation of allylamine derivatives and application in the synthesis of naftifine and abamides *J. Org. Chem.* **2011**, 76, 7737.
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12. Mayr, Synthesis of allylamines from alkynes and iminium ions *Synthesis*, **2003**, 12, 1790.
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16. Petasis, The boronic acid Mannich reaction: a new method for the synthesis of geometrically pure allylamines *Tetrahedron Letters*, **1993**, 34 (4), 583.
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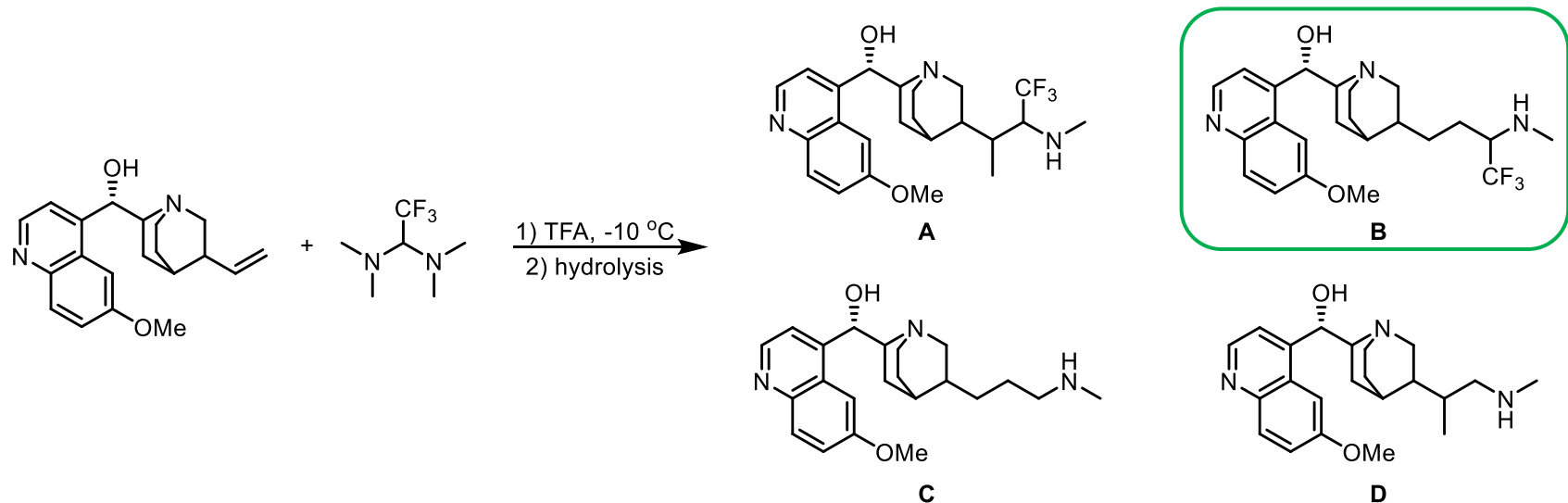
Thank you for your kind attention!

Question + Exercise

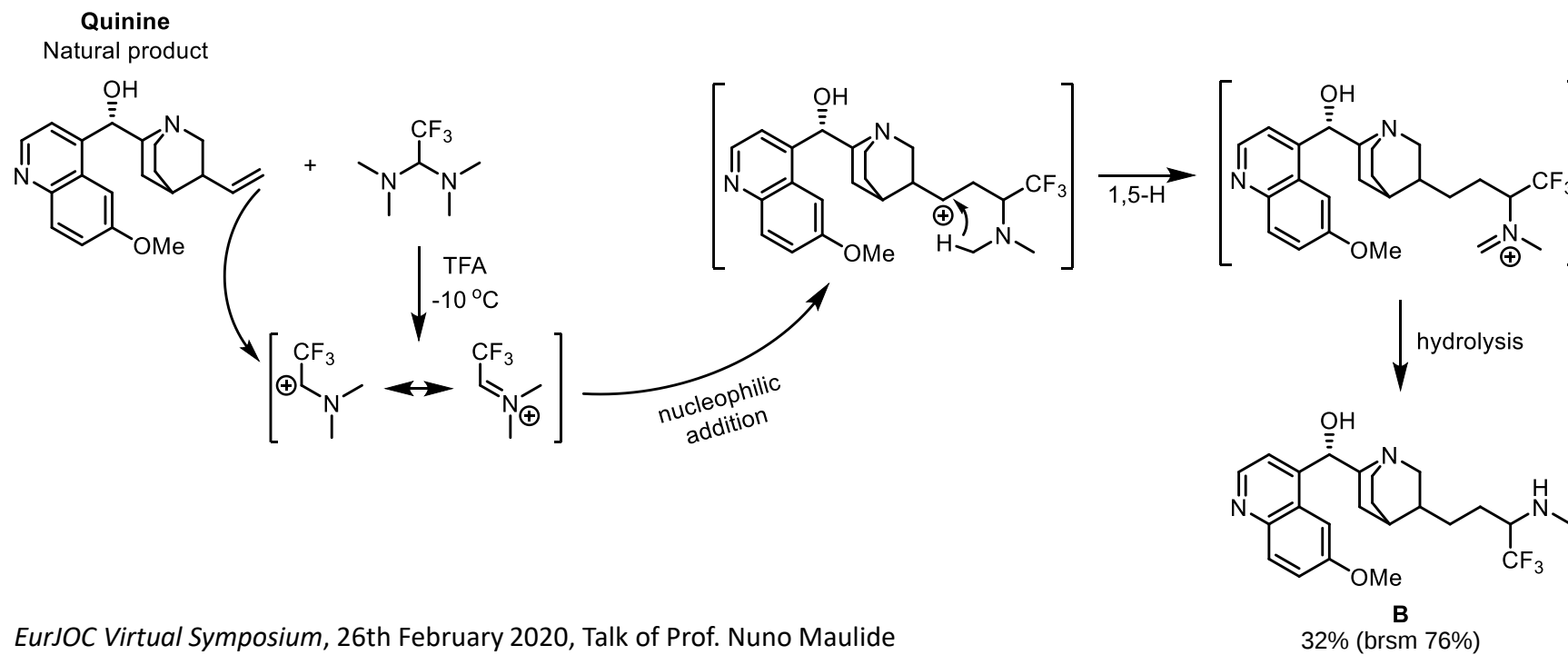
- Do you have any ideas regarding the choice of TFA in the work of Prof. Maulide group?

"...we suspect the solvating properties of TFA, as well as the low nucleophilicity and low basicity of the corresponding conjugate base play important roles in dictating the reaction outcome by facilitating the hydride transfer event."

- Choose the product of HAM

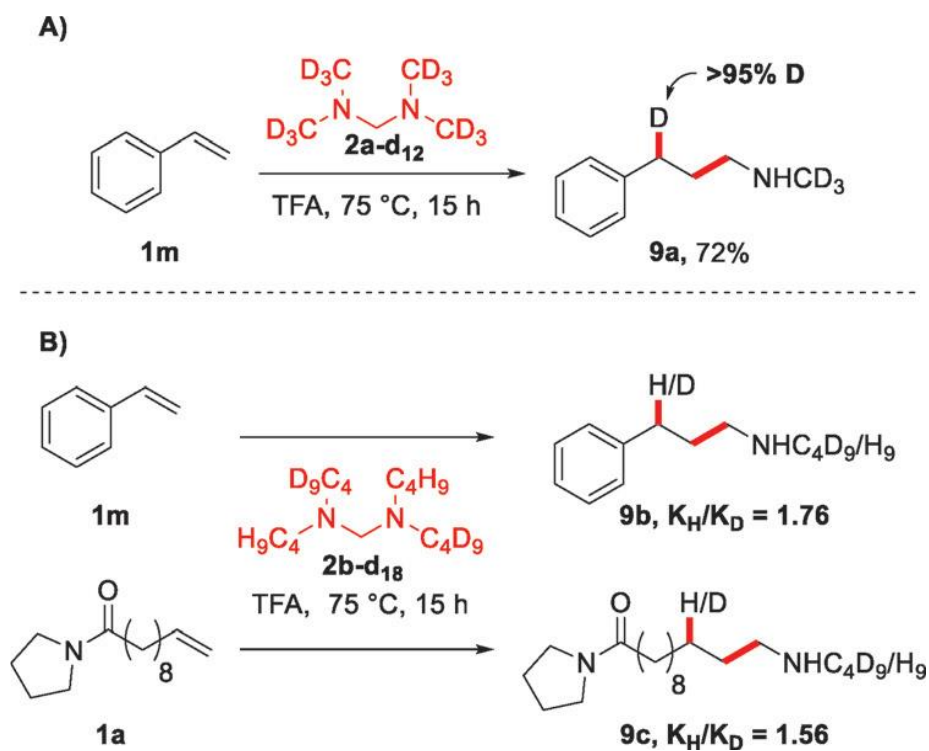


Exercise



EurJOC Virtual Symposium, 26th February 2020, Talk of Prof. Nuno Maulide

Additional slide – mechanistic studies of acid-mediated hydroaminomethylation

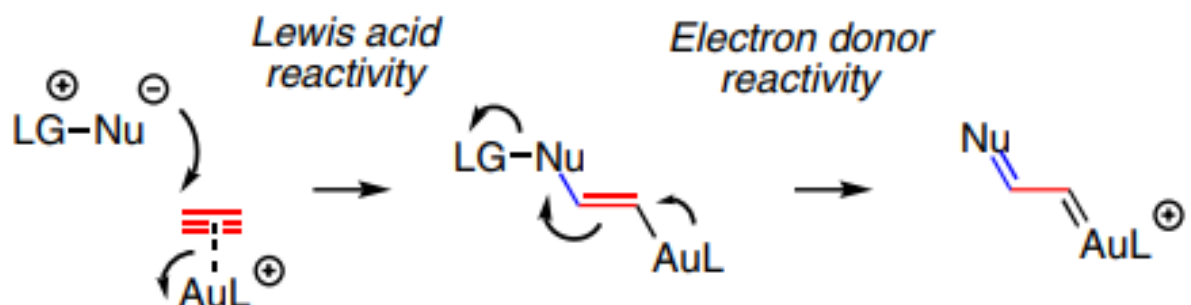
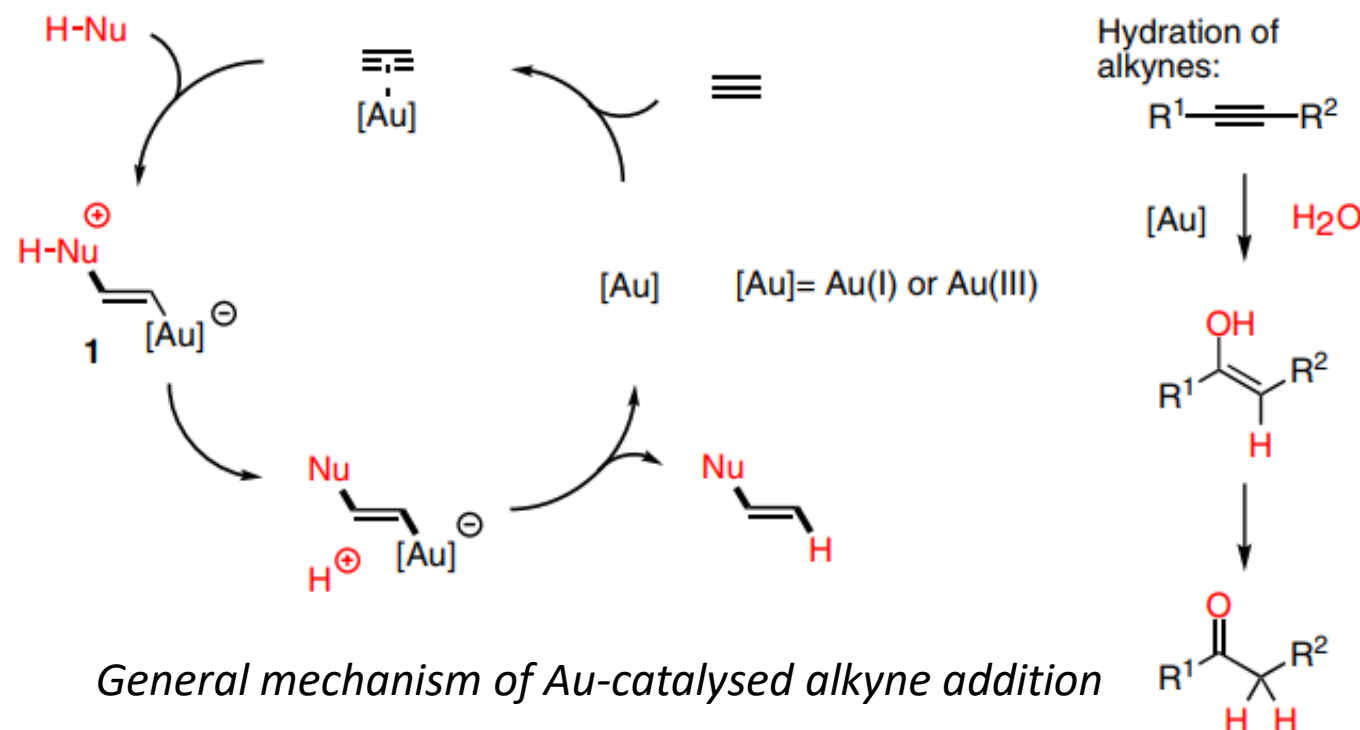


Gold catalysed C-C bond forming reactions of unactivated olefins

Kedar Abhyankar
Prof. Dyson Group

Gold catalysis: Introduction

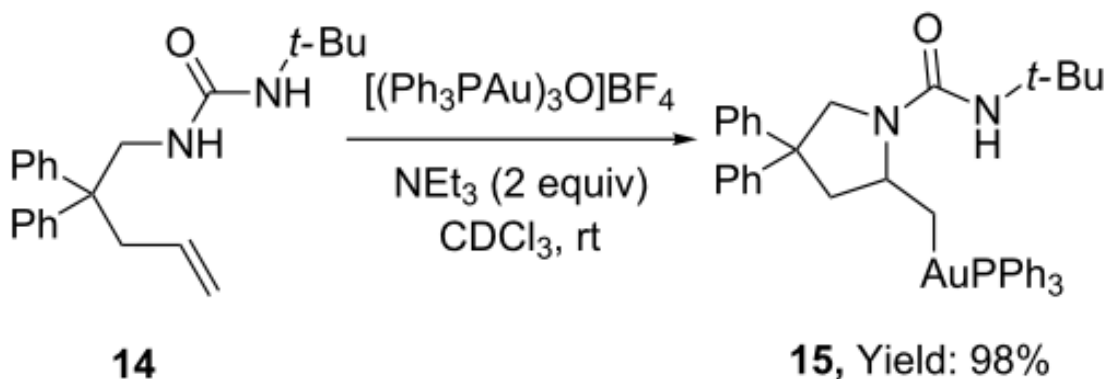
- Relatively less scarce
- Gold is commonly recycled
- Hydrolytically/aerobically stable
- Rational catalyst design less developed
- Alkynes and allenes common substrates
- Typically formulated as pi-acid catalysis



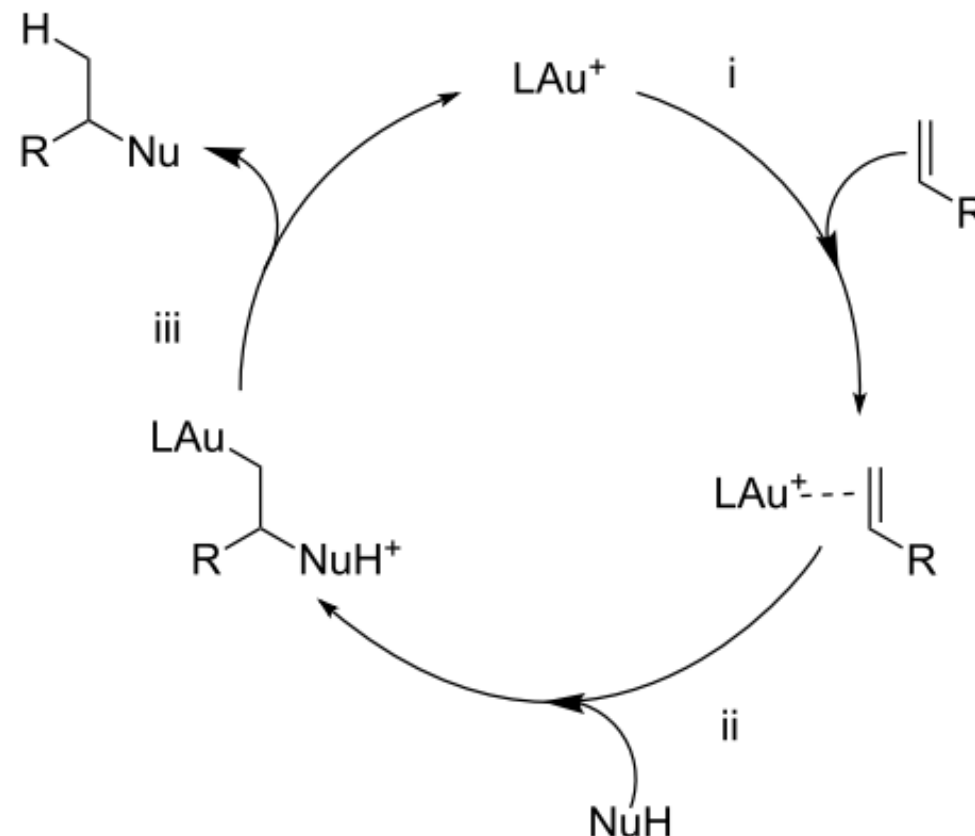
- However:
- Oxidative coupling processes /cross-coupling processes
- Au carbene species invoked as intermediates
- 6s contraction, 5d expansion
- Dual behaviour

Olefins as substrates

- Alkenes: key petrochemical feedstock
- Less reactive than alkynes
- Functionalisation of high synthetic utility
- C-C bond forming reactions always in vogue
- Focus here is on unactivated alkenes: not dienes, ene-ynes, allenes



Isolation of alkyl species in Au-catalysed hydroamination

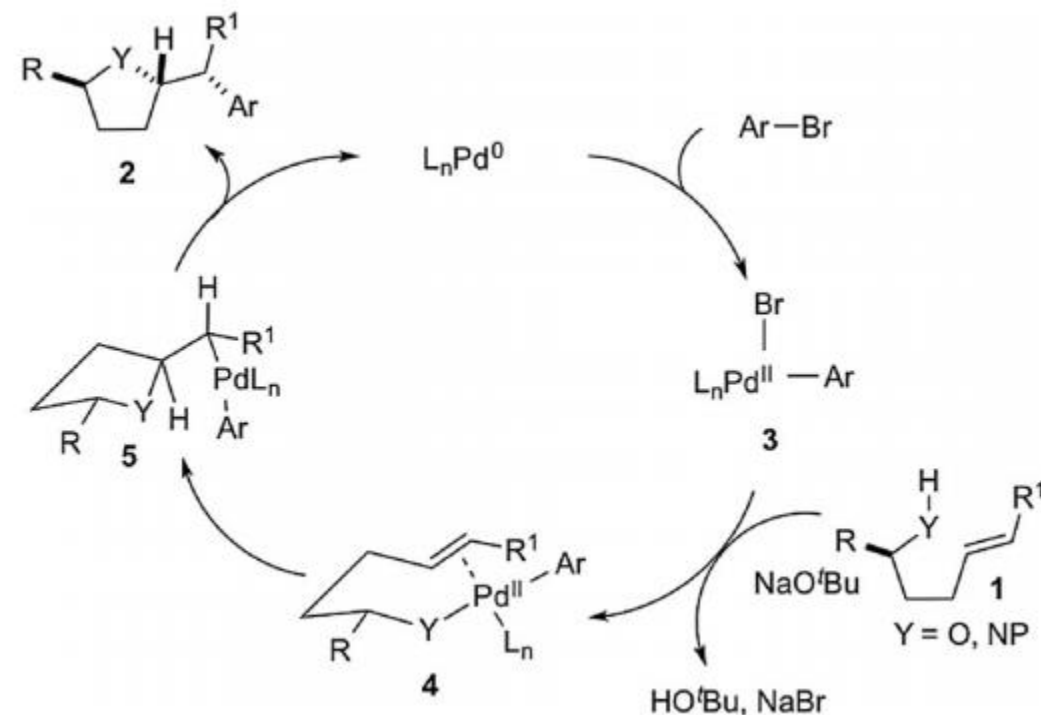
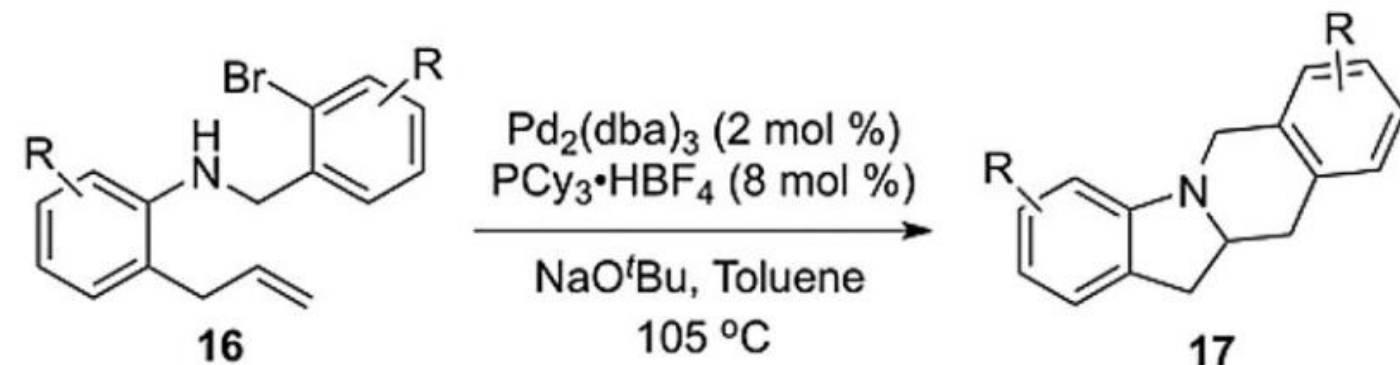
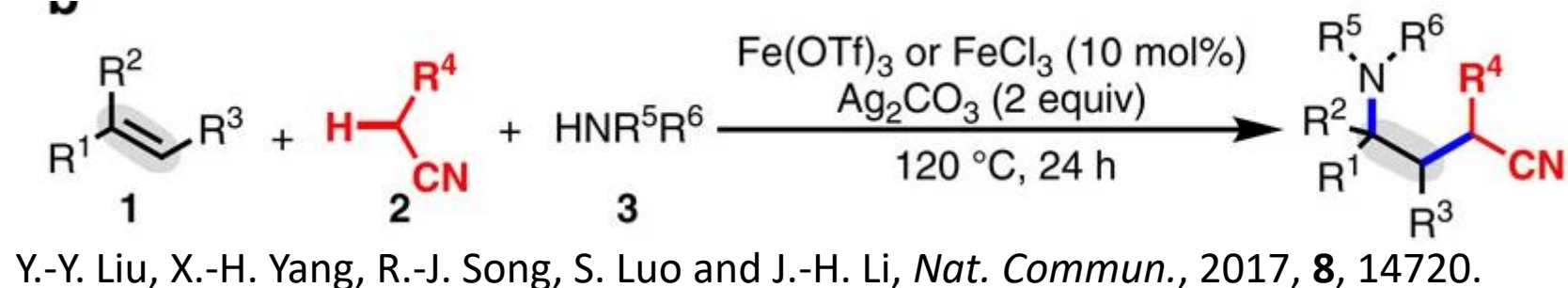


General mechanism of Au catalysed addition to alkenes

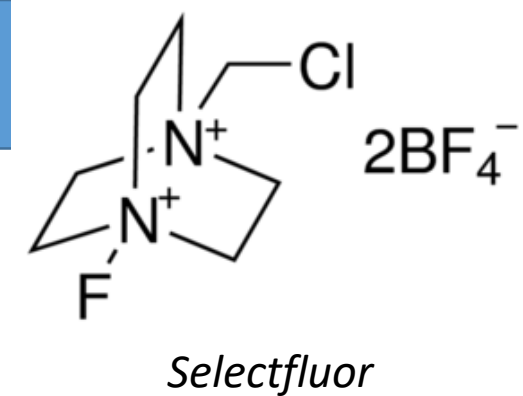
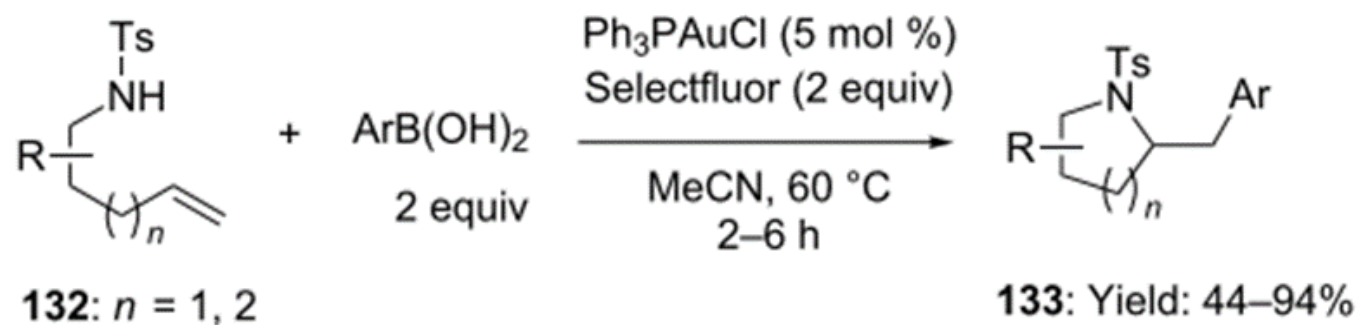
- Inertness of alkyl intermediates accounts for scarce reactivity
- Focus: C-C bond forming reactions that feature i) powerful transformations ii) novel catalytic systems

Carboheterofunctionalisation of alkenes

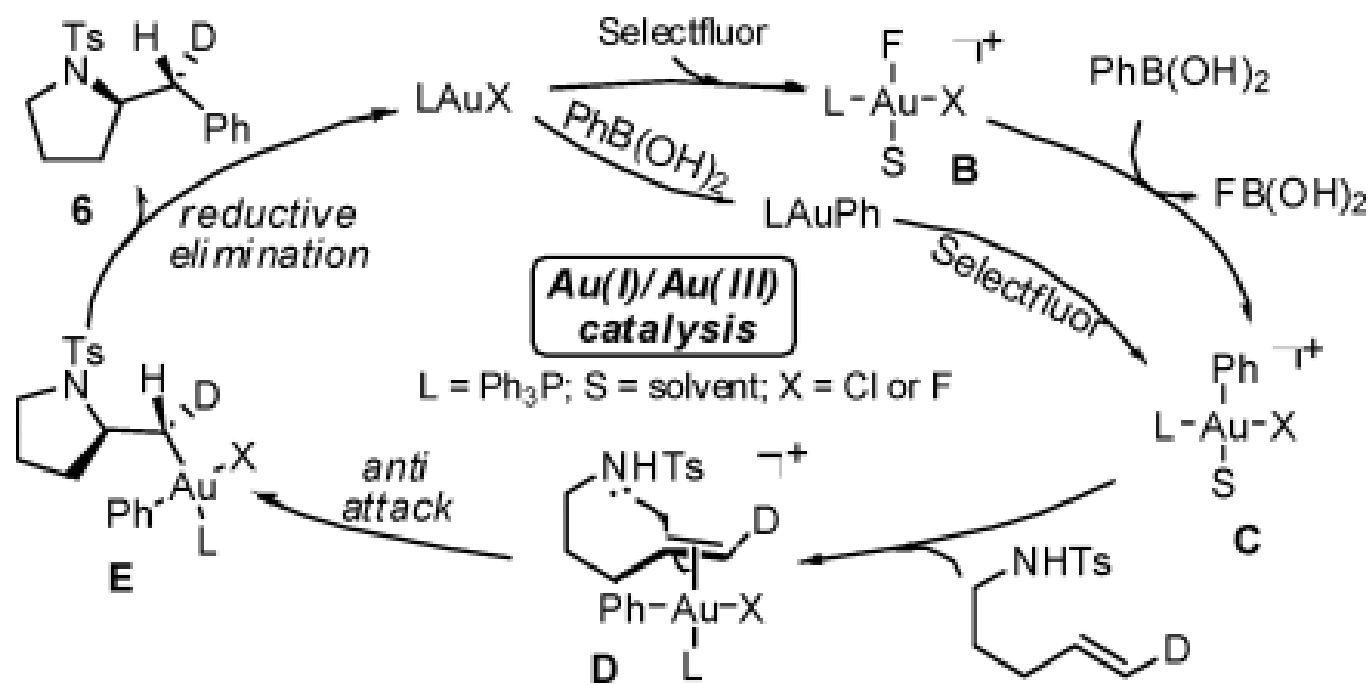
- Controlled heterocycles synthesis is of immense value
- As well as direct conversion of alkenes
- Limited intermolecular variants/multi-component couplings
- Au(I) hasn't lagged behind: development has been alongside more common Pd and Rh systems



Carboamination



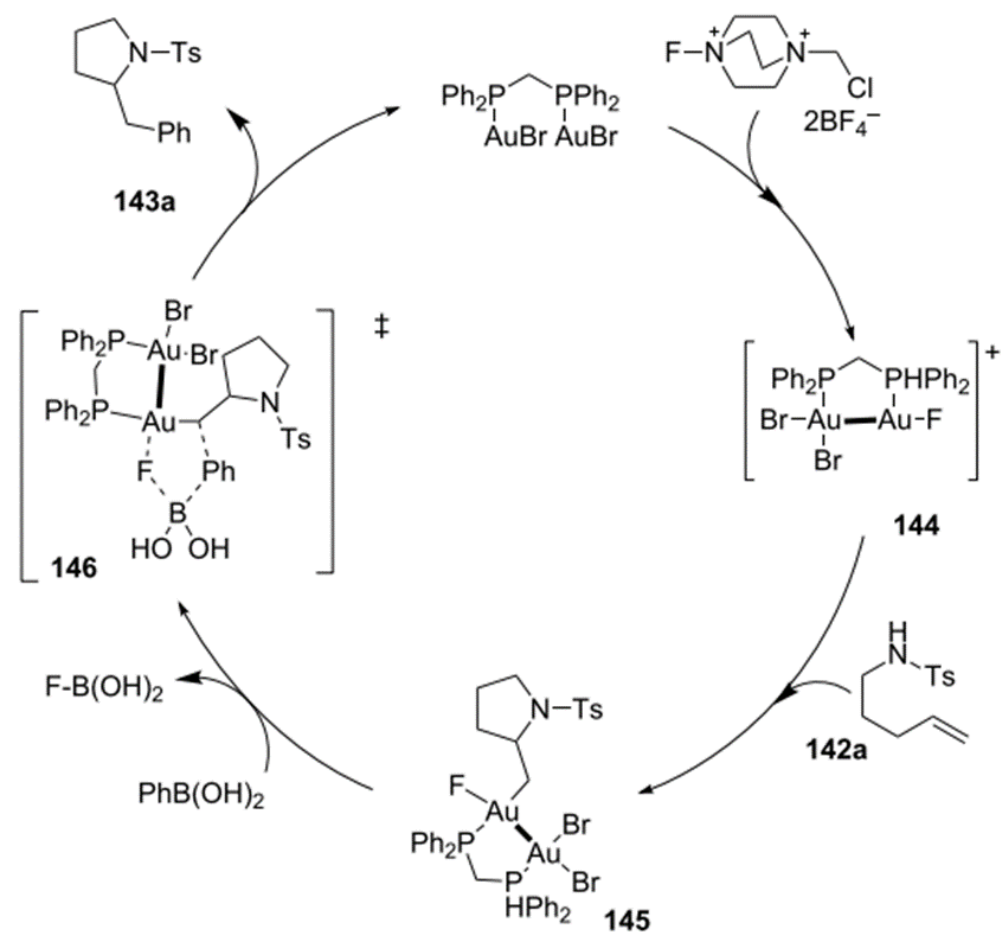
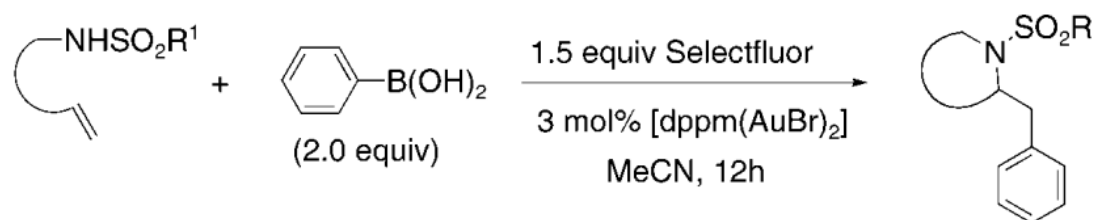
- Reported by Zhang et al
- Potential intermediacy of LAuPh hypothesised but contradicted by Toste (JACS 2010)



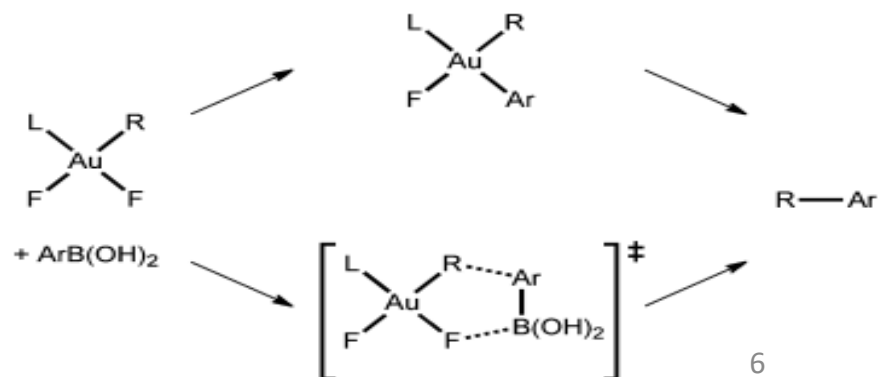
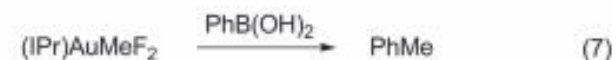
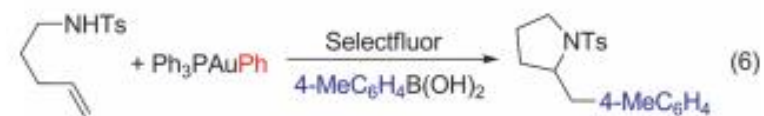
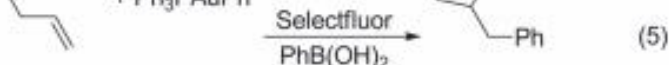
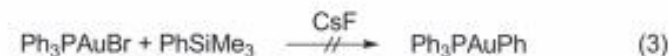
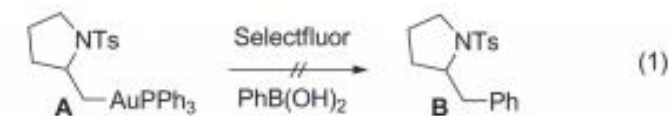
G. Zhang, L. Cui, Y. Wang and L. Zhang, *J. Am. Chem. Soc.*, 2010, **132**, 1474–1475.

S. Zhu, L. Ye, W. Wu and H. Jiang, *Tetrahedron*, 2013, **69**, 10375–10383.

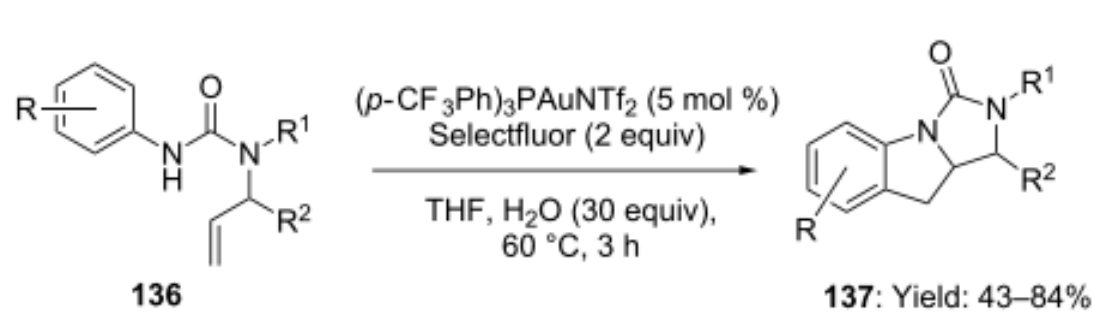
Carboamination: A new mechanistic proposal



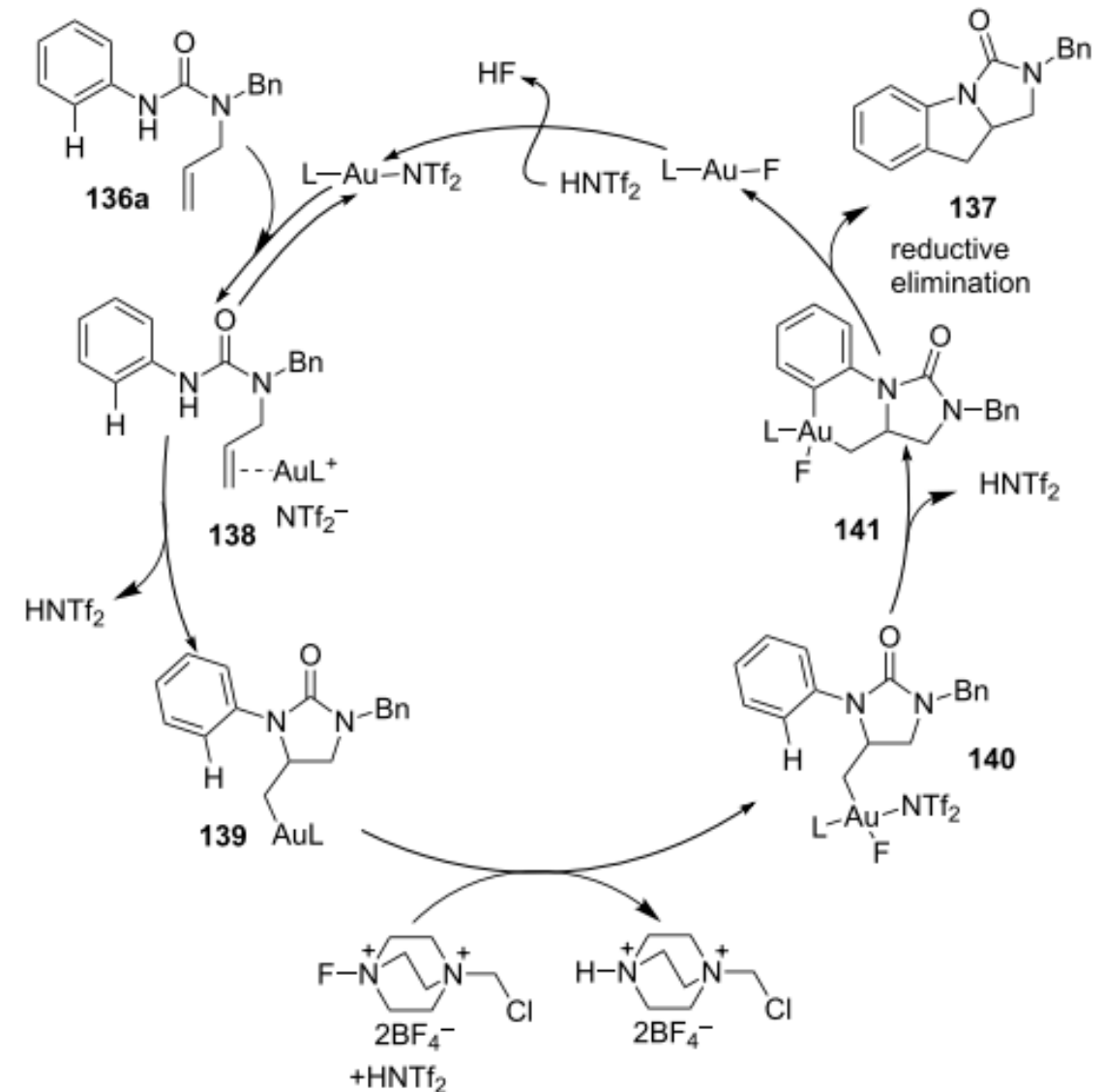
- Bimetallic system by Toste
- Catalytically superior (milder conditions)
- Tolerates a wide range of substituted sulphonamides
- Even those without Thorpe-Ingold driving force
- 6-membered rings cyclised at slightly elevated temperatures



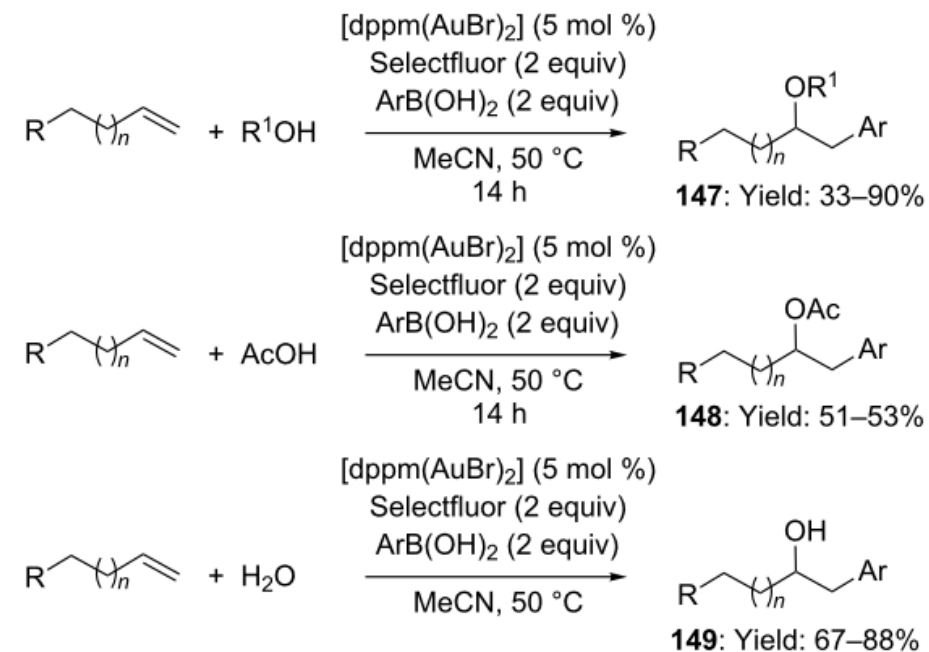
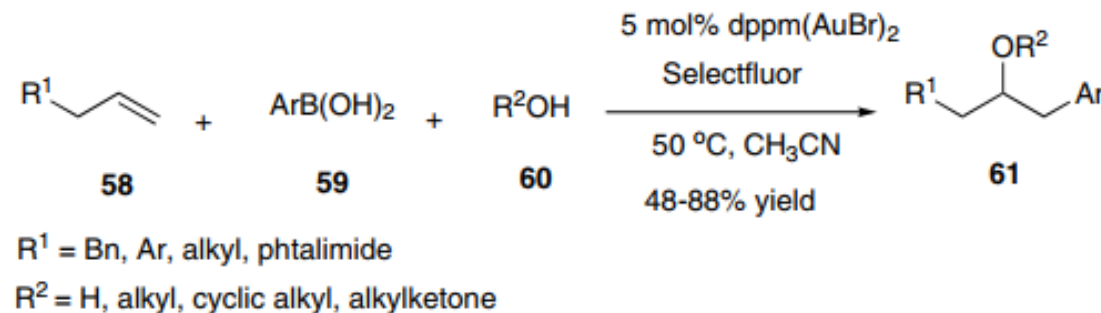
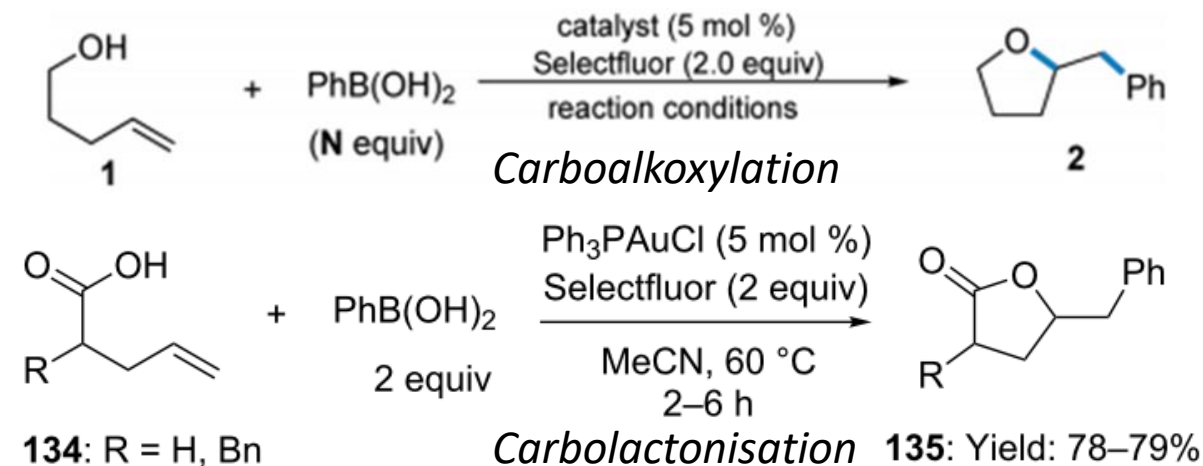
Intramolecular variant: Aryl C-H functionalisation



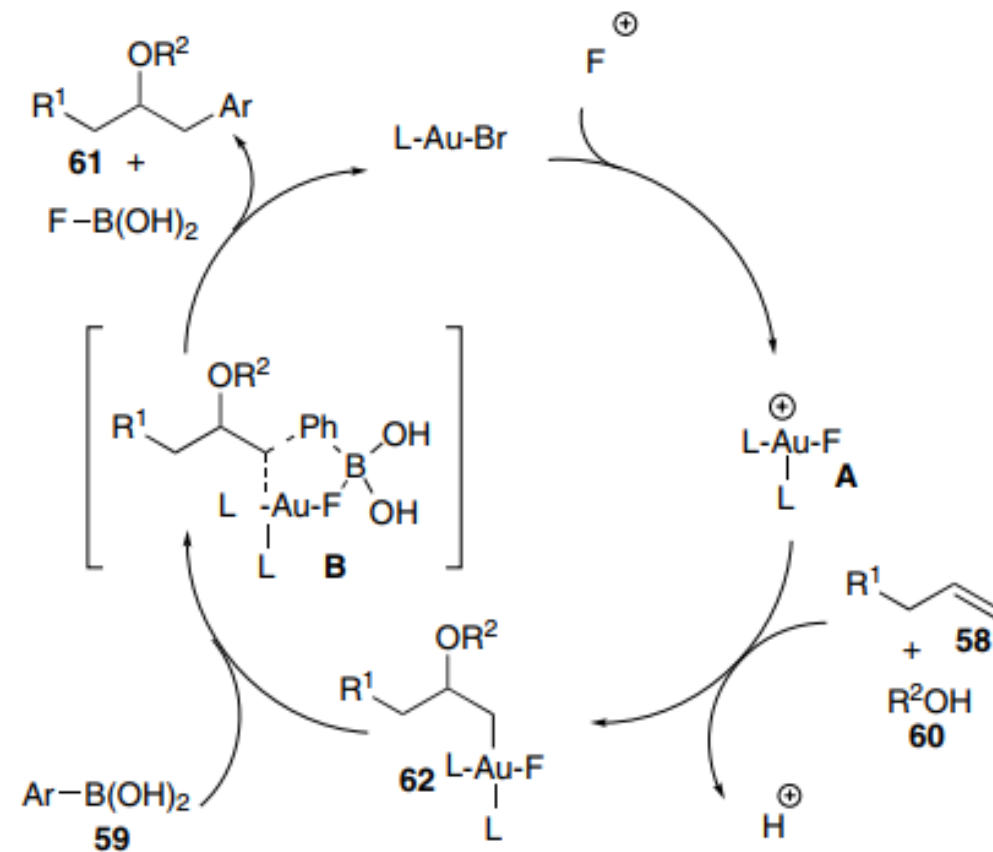
- In conflict mechanistically with prior approach
- First example of C-H functionalisation with Au-alkyl
- 30eq H₂O required
- cf. *ortho*-metalation by platinum group metals



Carboalkoxylation



- Mechanistically similar
- 3 component intermolecular coupling
- Range of terminal alkenes functionalised

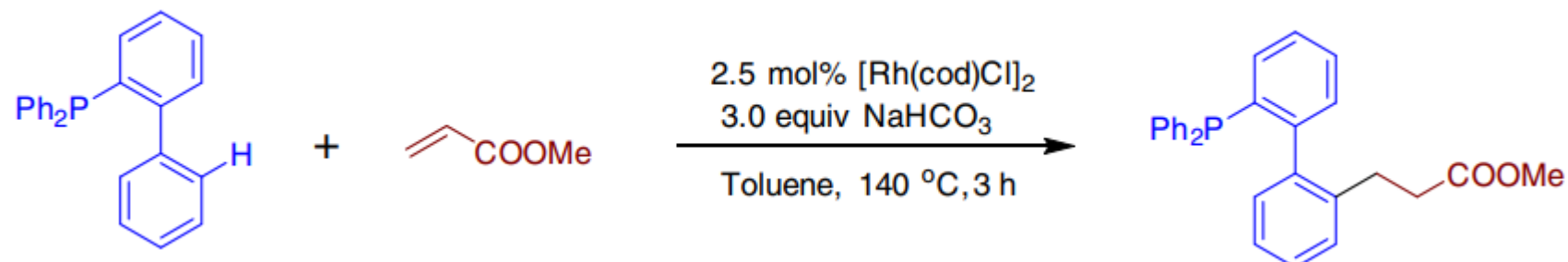


A. D. Melhado, W. E. Brenzovich, A. D. Lackner and F. D. Toste, *J. Am. Chem. Soc.*, 2010, **132**, 8885–8887.

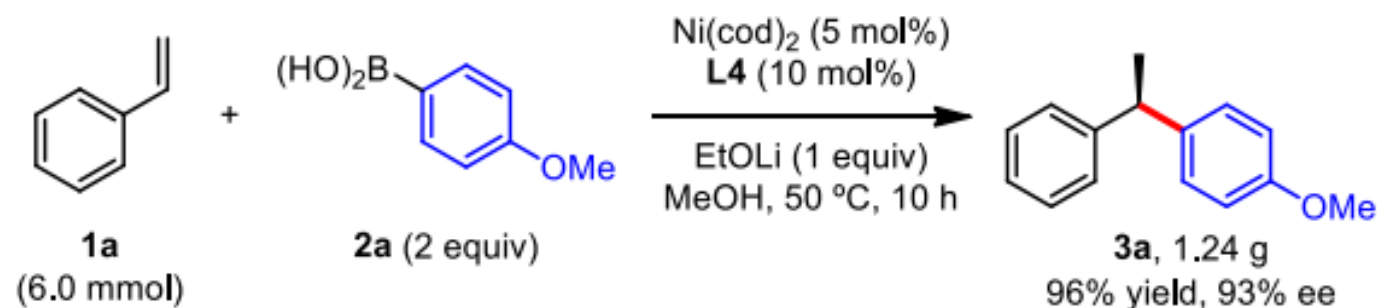
B. G. Zhang, L. Cui, Y. Wang and L. Zhang, *J. Am. Chem. Soc.*, 2010, **132**, 1474–1475.

Hydroarylation

- A tertiary centre bearing 2 aryl groups is an essential structural motif in both natural and pharmaceutical products
- Direct access from alkenes is would be of immense synthetic value

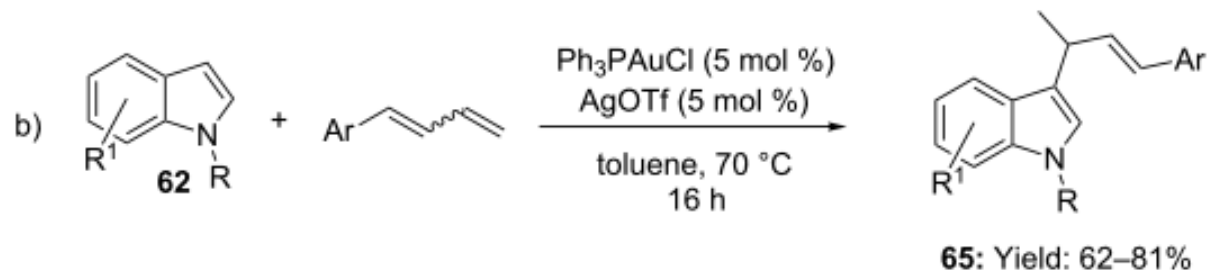
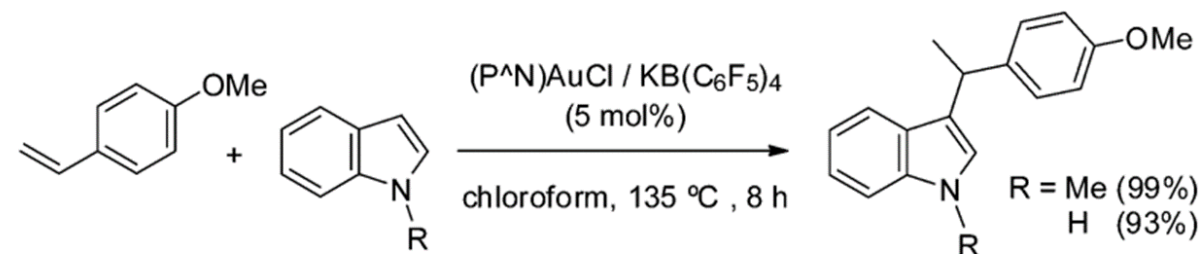
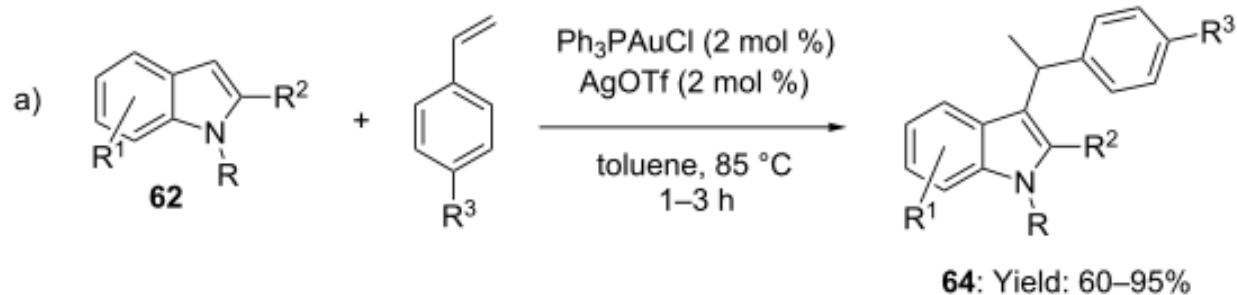


D. Wang, B. Dong, Y. Wang, J. Qian, J. Zhu, Y. Zhao and Z. Shi, *Nat. Commun.*, 2019, **10**, 3539.

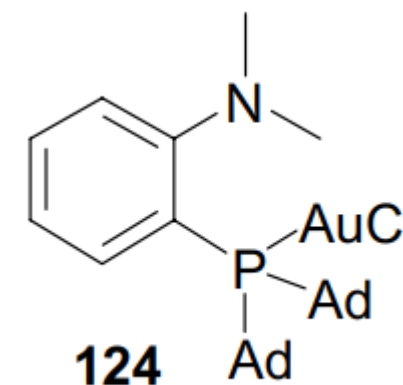
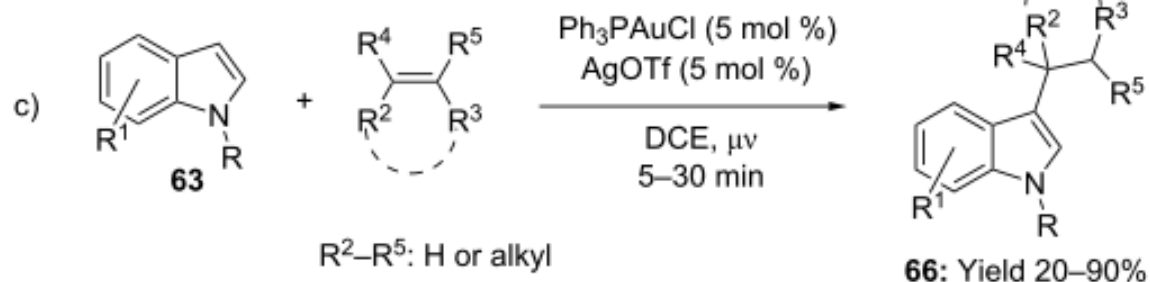


Y.-G. Chen, B. Shuai, X.-T. Xu, Y.-Q. Li, Q.-L. Yang, H. Qiu, K. Zhang, P. Fang and T.-S. Mei, *J. Am. Chem. Soc.*, 2019, **141**, 3395–3399.

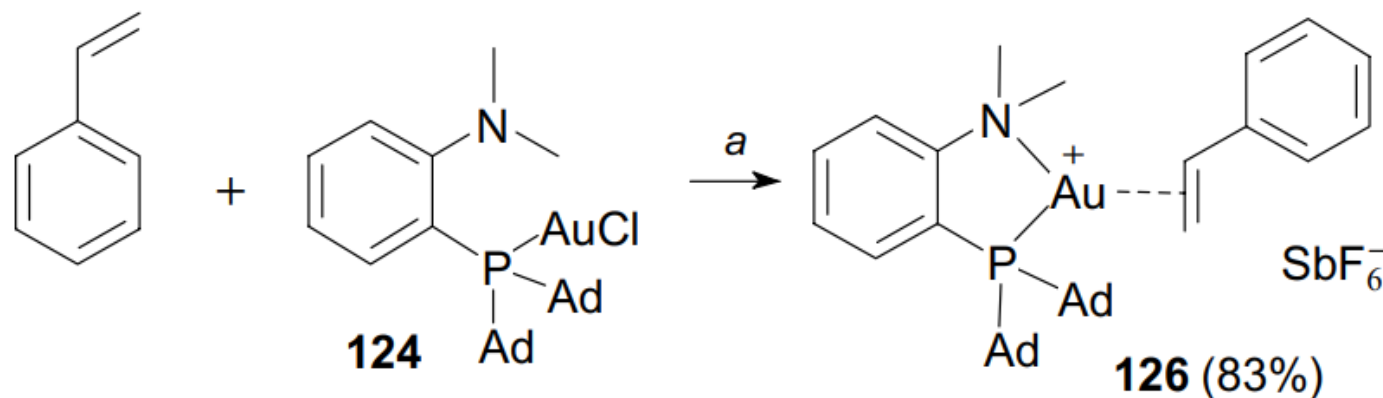
Addition of indoles to alkenes using Au(I)



- Reasonable substrate scope
- Styrenes react under thermal conditions, aliphatic alkenes only under microwave irradiation (but with C=C isomerisation)
- Alkene activation prior to nucleophilic attack from indole C3

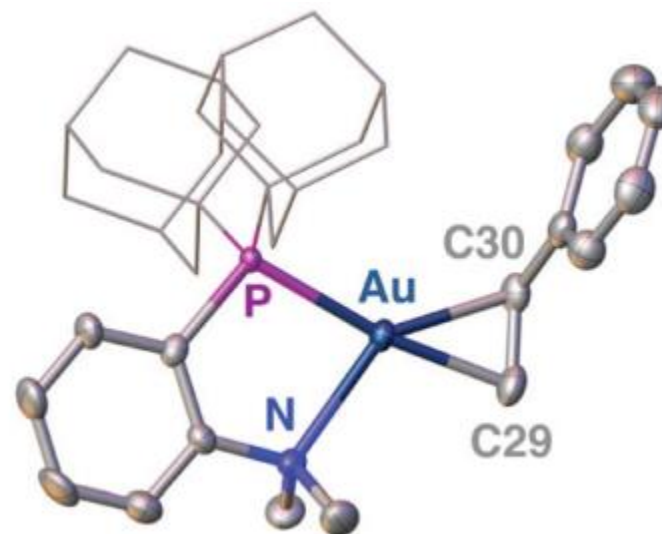


Isolation of intermediate Au(I) alkene complex

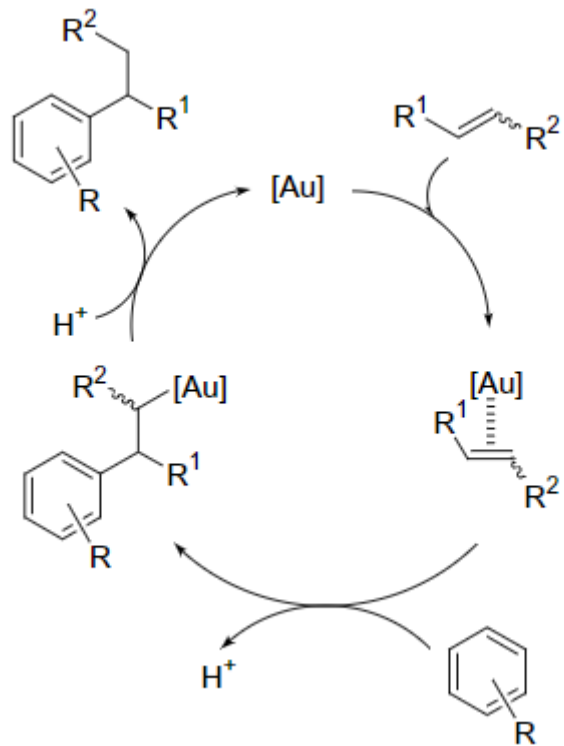
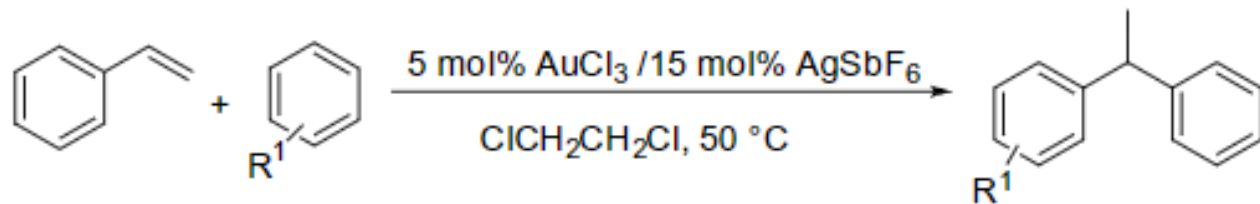


(a) AgSbF_6 , DCM, from -30 to 0°C , 0.5 h

- Recently isolated (Bourissou 2019)
- Interesting geometry and bonding (between T and Y)
- Increased metallacyclopropane character relative to monodentate species
- Key catalytic intermediate

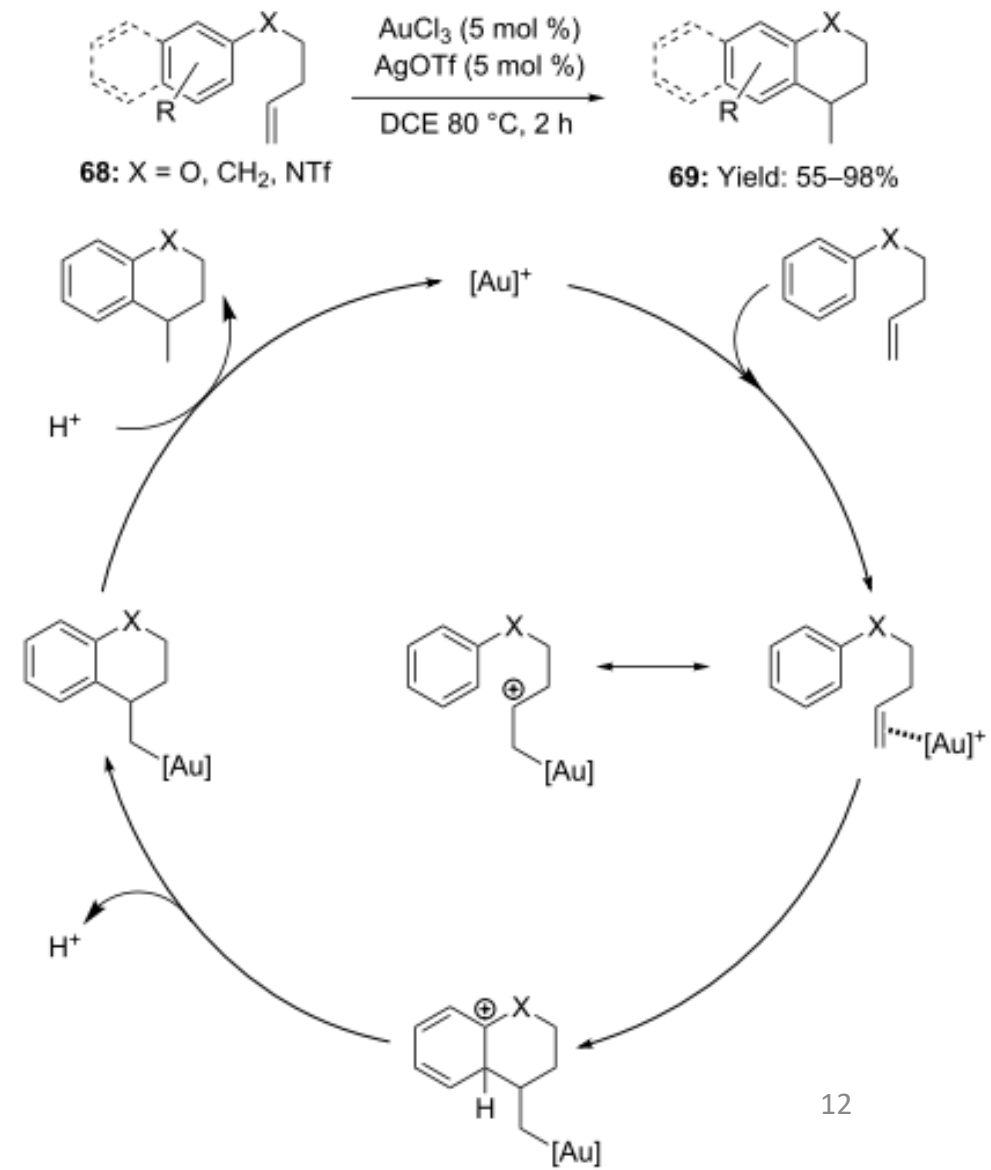


Au(III) catalysed hydroarylation of alkenes with benzene derivatives

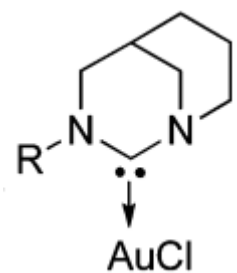
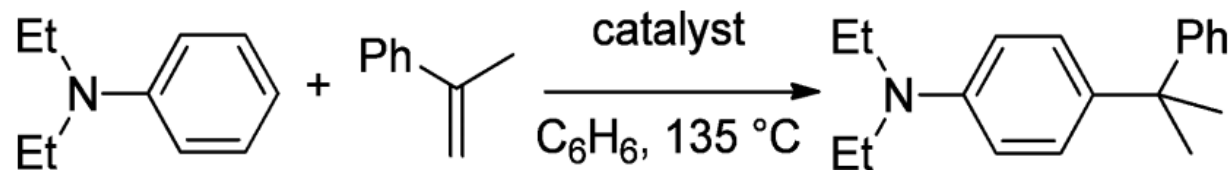


- Au(III) with silver, conceptually similar to classic Lewis acid
- Thiophene also utilised

Y.-P. Xiao, X.-Y. Liu and C.-M. Che, *J. Organomet. Chem.*, 2009, **694**, 494–501.
Jean, M.; van de Weghe, P. *Tetrahedron Lett.* **2011**, 52, 3509–3513.

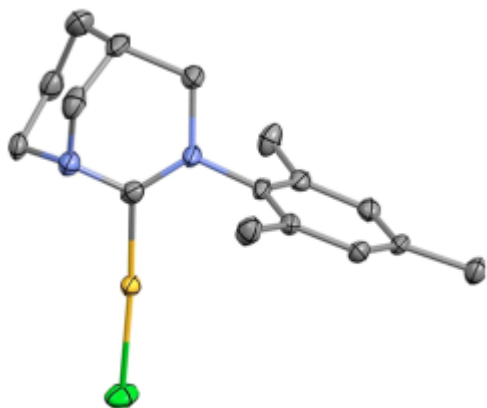


Au(I) catalysed hydroarylation with dialkylanilines

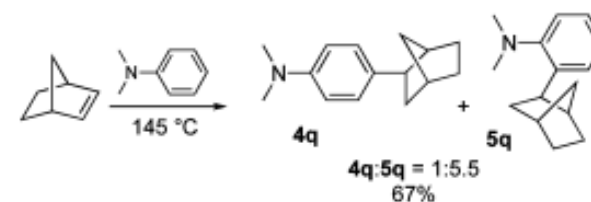
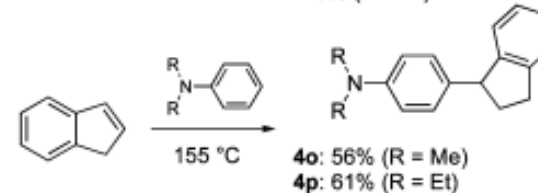
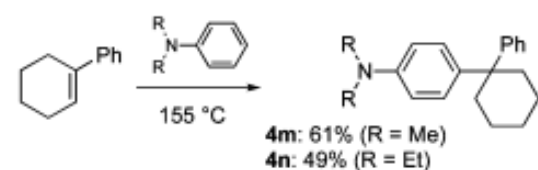
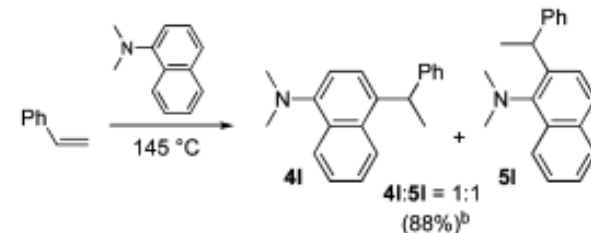
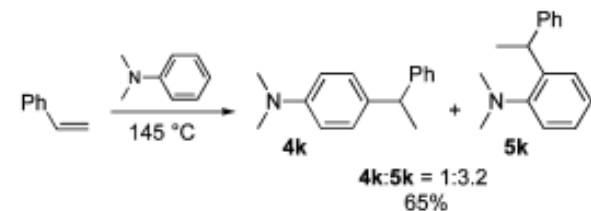
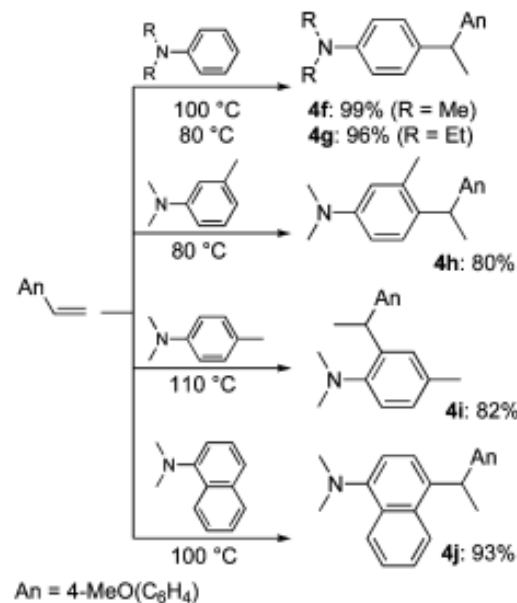
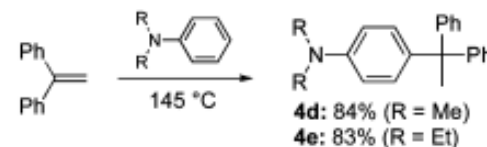
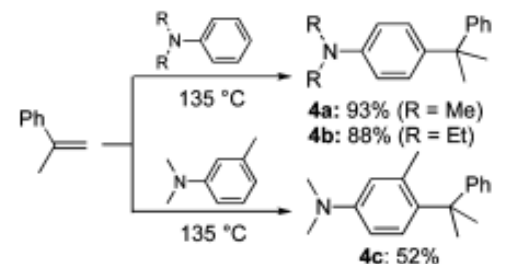


Suggest a synthesis of this NHC-Au motif

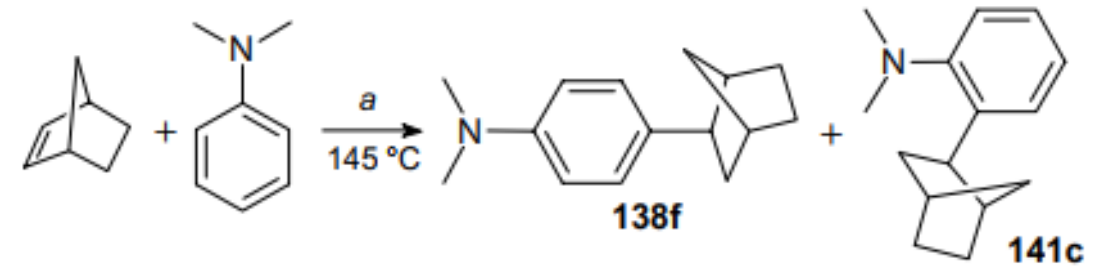
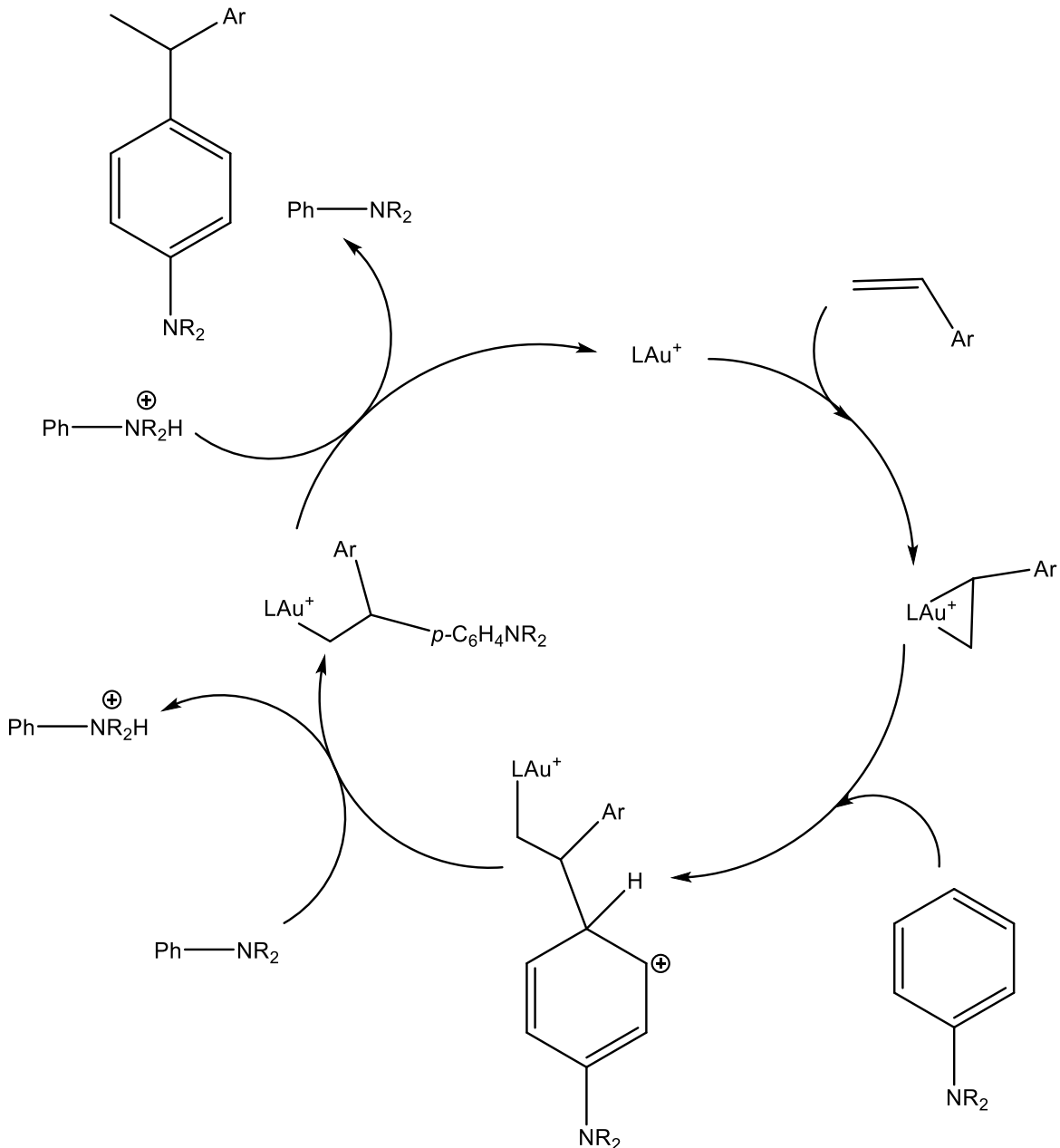
Precatalyst (R=Mes)



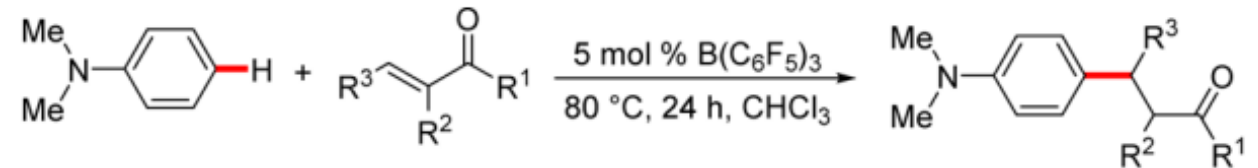
- Hydroarylation catalysts not usually compatible with dialkylanilines and other Lewis basic substrates
- para*-selective
- Markovnikov and anti markovnikov pattern observed, depending on alkene substrate



Au(I) catalysed hydroarylation with dialkylanilines (cont.)

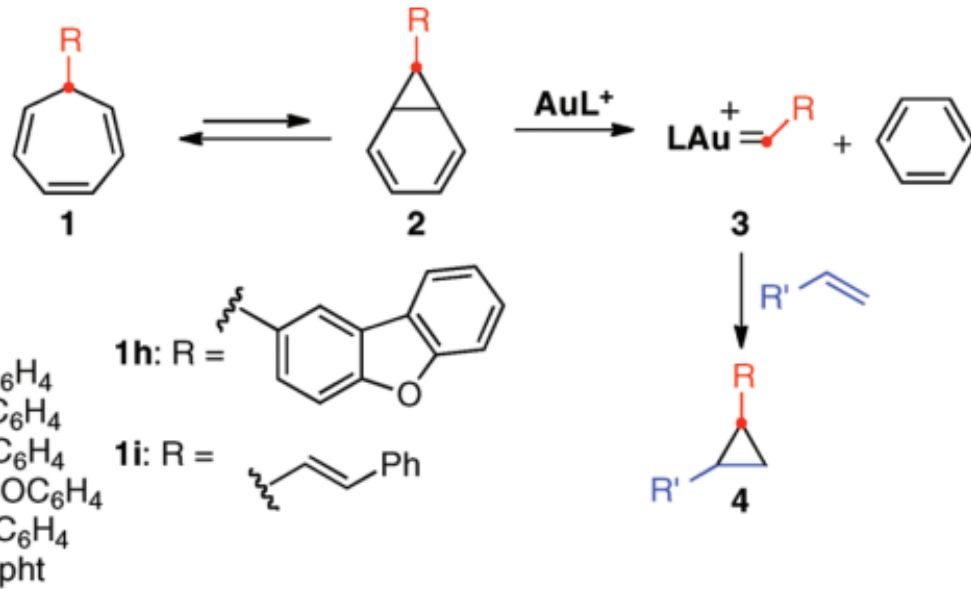


- *Para*-selective in majority of cases, occasional *ortho*-competition
- Borane-catalysed variant, only active with Michael acceptors. Same anti-markovnikov product

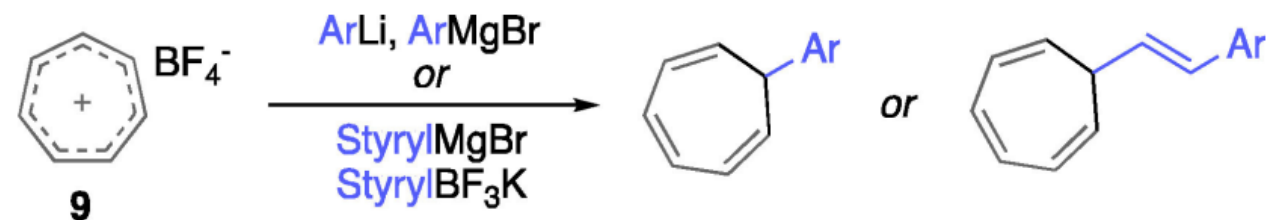
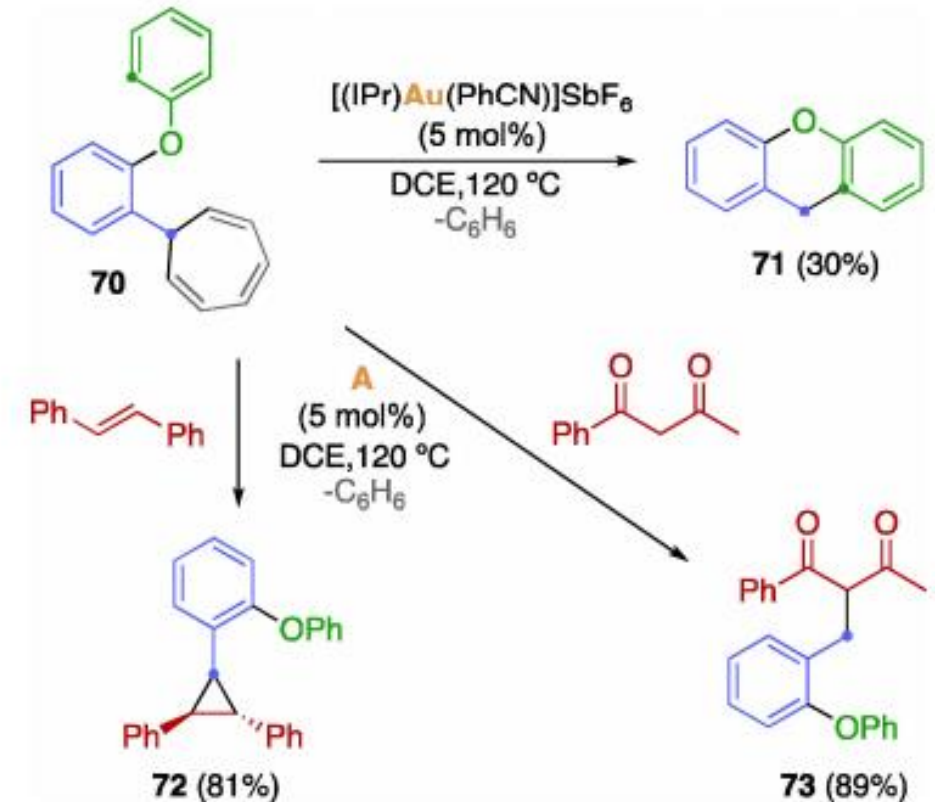


H. Wu, T. Zhao and X. Hu, *Sci. Rep.*, 2018, **8**, 11449.
W. Li and T. Werner, *Org. Lett.*, 2017, **19**, 2568–2571.

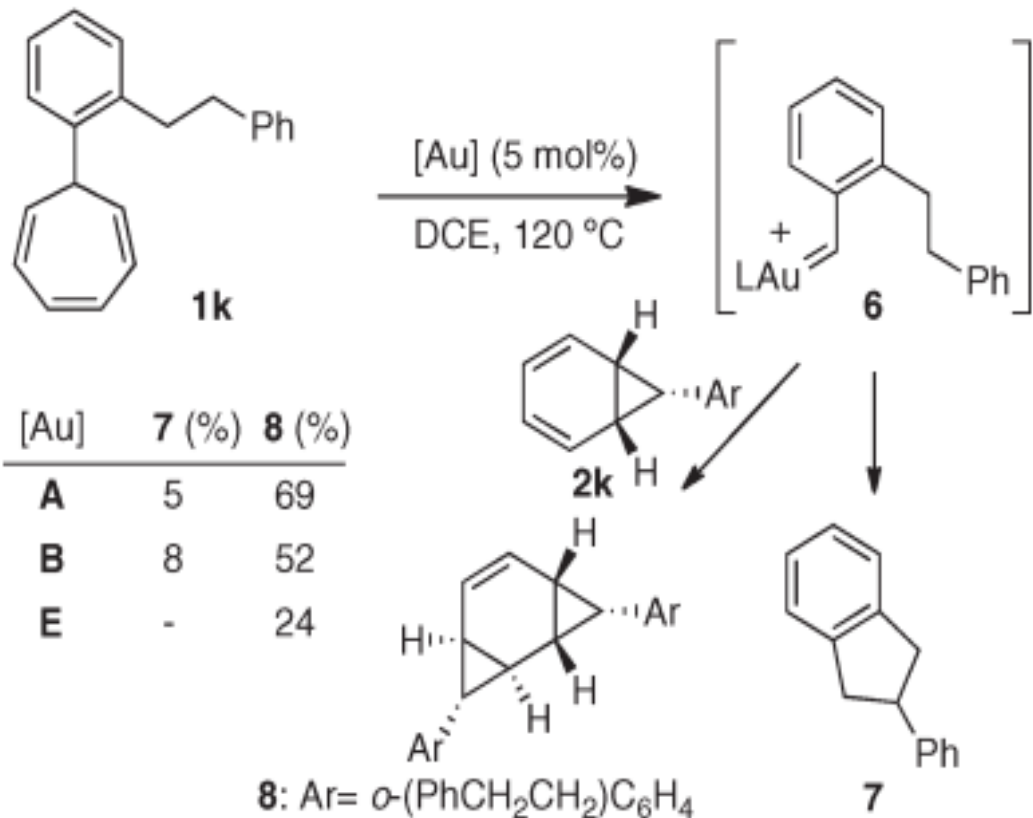
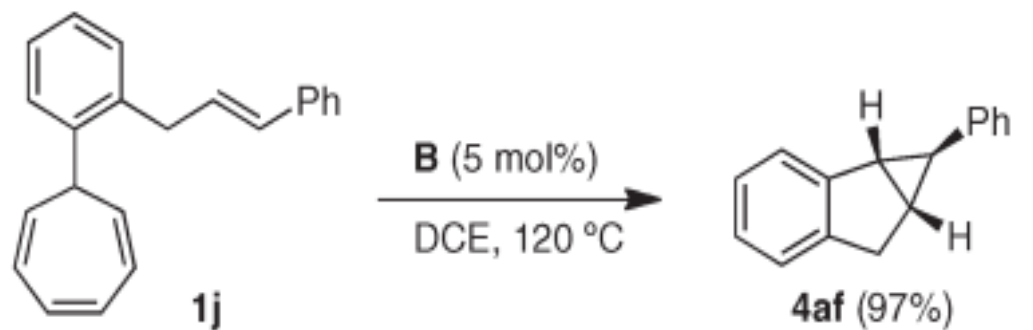
Cyclopropanation: Au carbenes from cycloheptatrienes



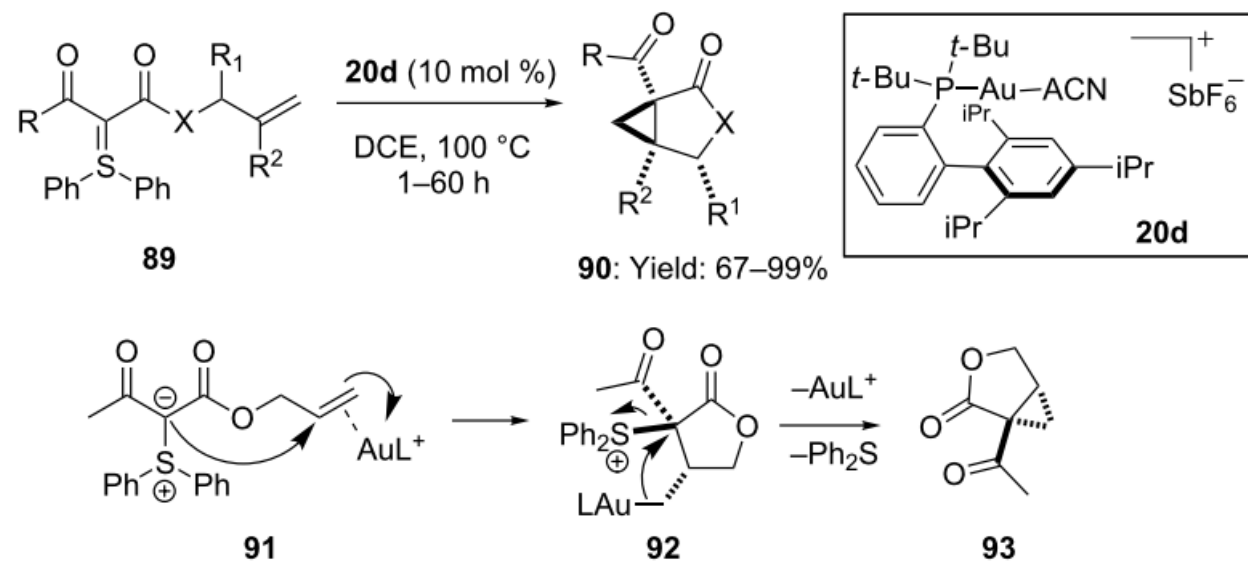
- Trisubstituted arylcyclopropanes easily prepared via Au(I) catalysed Retro-Buchner reaction
- Utilising cycloheptatrienes as carbene/carbenoid sources
- A methodology well developed work with Au(I) systems
- Starting aryl or styryl cycloheptatrienes are easily prepared from tropylium
- Potentially wide substrate scope



Cyclopropanation cont.



- Favours reaction with alkene over C-H insertion
- Intramolecular ylid cyclisation another methodology (activation of olefin by Au(I))

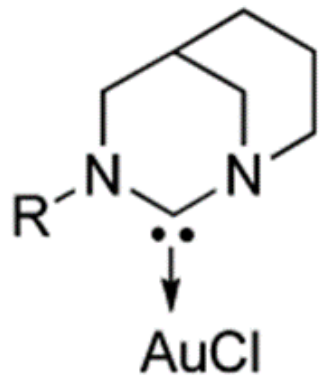


M. Mato, C. García-Morales and A. M. Echavarren, *ChemCatChem*, 2019, **11**, 53–72.
 . R. Solorio-Alvarado, Y. Wang and A. M. Echavarren, *J. Am. Chem. Soc.*, 2011, **133**, 11952–11955
 1X. Huang, S. Klimczyk, L. F. Veiros and N. Maulide, *Chem. Sci.*, 2013, **4**, 1105–1110..

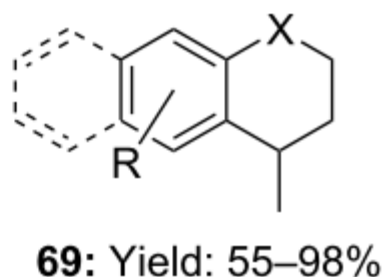
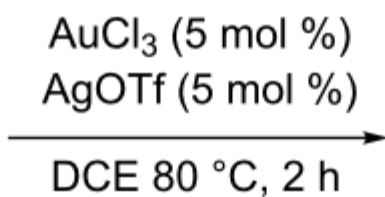
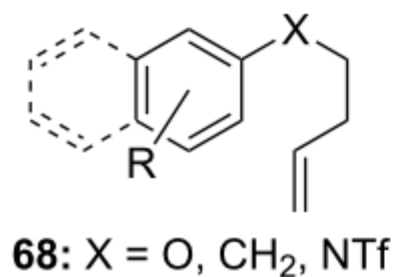
Summary

- Gold mediated C-C bond forming reactions of unactivated olefins: some key reactions of interest (carboheterofunctionalisation, hydroarylation, Retro-Buchner reaction of cycloheptatrienes in formation of Au carbenes)
- By no means exhaustive: the utility of allylic alcohols, addition of active methylene compounds, hydroalkylation, Au-Heck with aryldiazonium salts and dual photoredox/Au catalysed processes

Exercises



Suggest a synthesis of this precatalyst. Given that the free ligand is relatively less stable, the preparation utilised constructs the ligand within the protective environment of the metal coordination sphere.



Suggest a plausible catalytic cycle for this transformation

Answers

