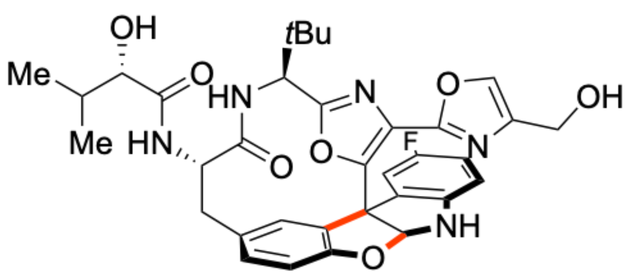
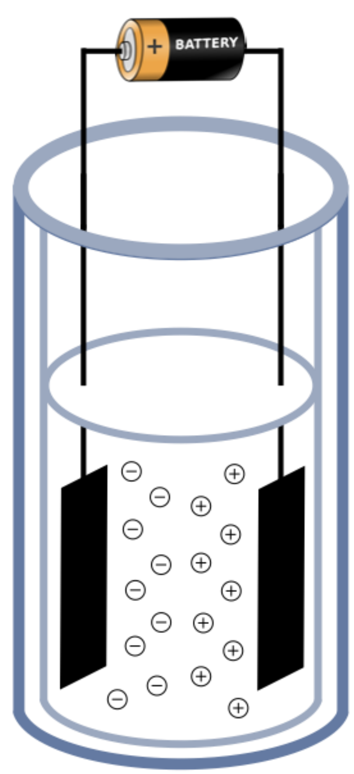
Frontiers in Chemical Synthesis I
Sustainable Chemistry

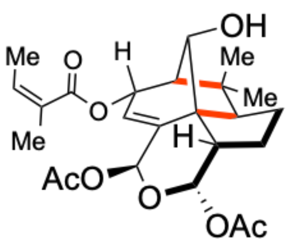
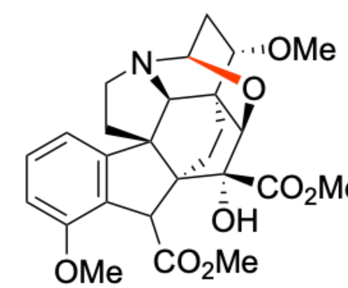
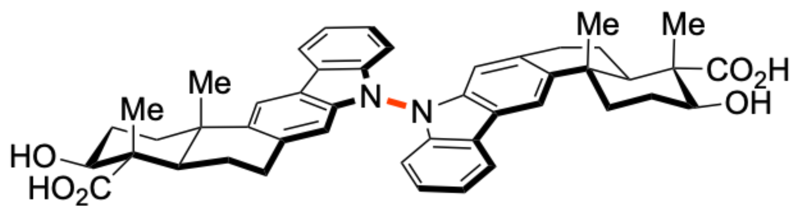
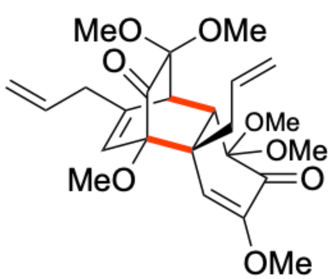
Seminar Program
May 11, Zoom
May 13, Zoom

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

John Reed 11/05/2020

Modernising Total Synthesis through Electrochemistry

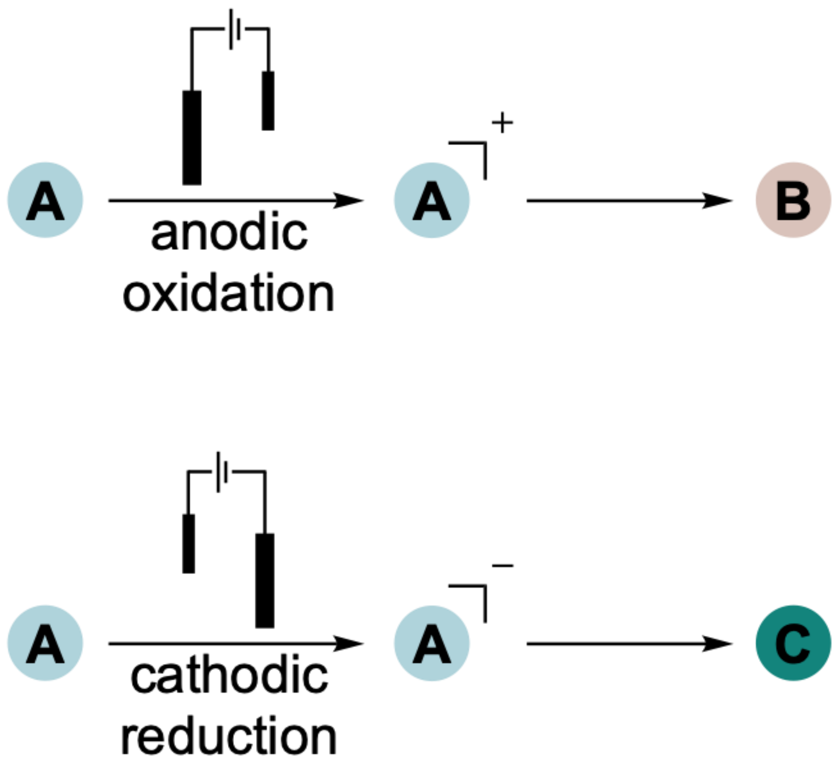



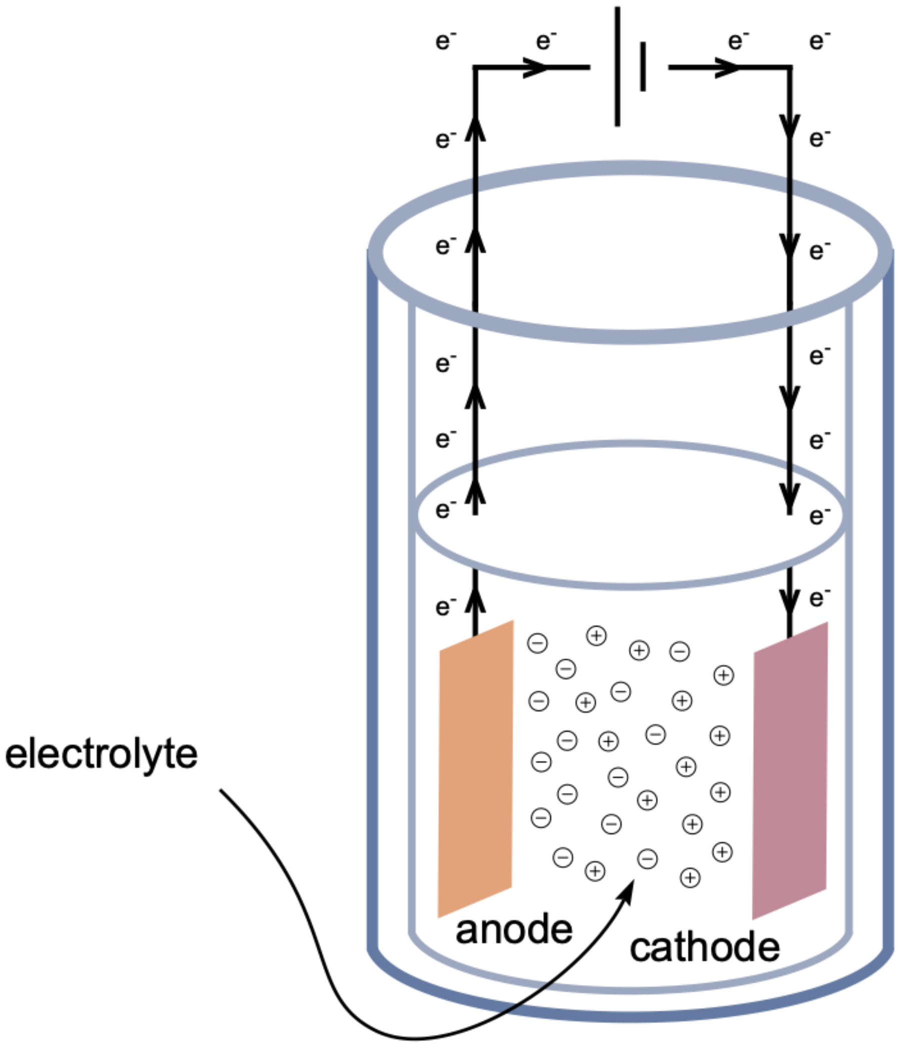





Frontiers in Chemical Synthesis: Towards Sustainable Chemistry

Ecole Polytechnique Fédérale de Lausanne
Laboratory of Asymmetric Catalysis and Synthesis (LCSA)

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

Redox potentials (E_0):

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

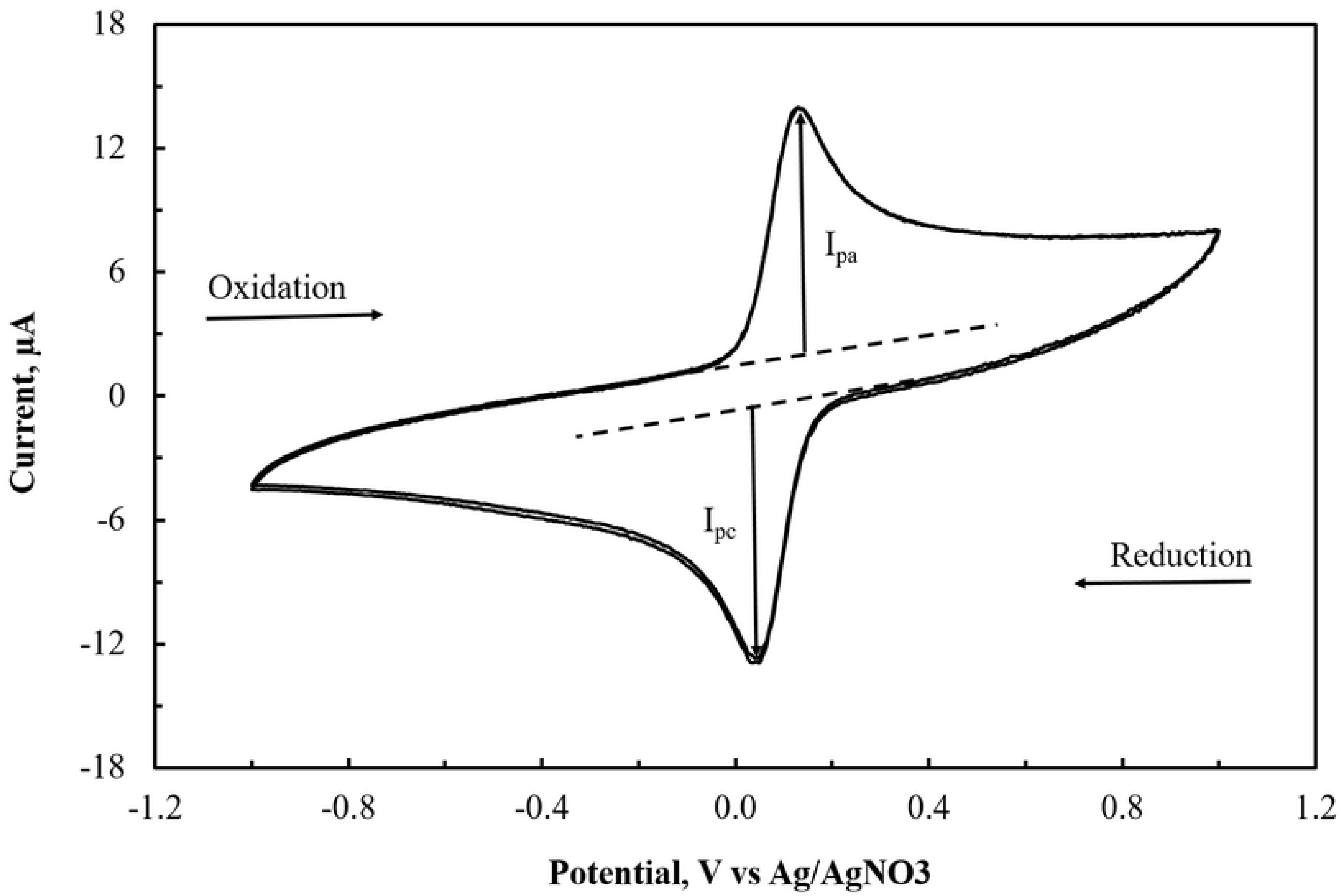
Common reduction potentials (vs SCE)

$F_2 + 2\,e^- \rightarrow 2\,F^-$	+2.87 V
$Cl_2 + 2\,e^- \rightarrow 2\,Cl^-$	+1.36 V
$Pd^{2+} + 2\,e^- \rightarrow Pd(0)$	+0.92 V
$Ni^{2+} + 2\,e^- \rightarrow Ni(0)$	-0.28 V
$Zn^{2+} + 2\,e^- \rightarrow Zn(0)$	-0.76 V
$Ca^{2+} + 2\,e^- \rightarrow Ca(0)$	-2.87 V
$Li^+ \rightarrow Li(0)$	-3.05 V

Experimentally determined using cyclic voltammetry

Reliable for inorganic substrates

Cyclic voltammetry:

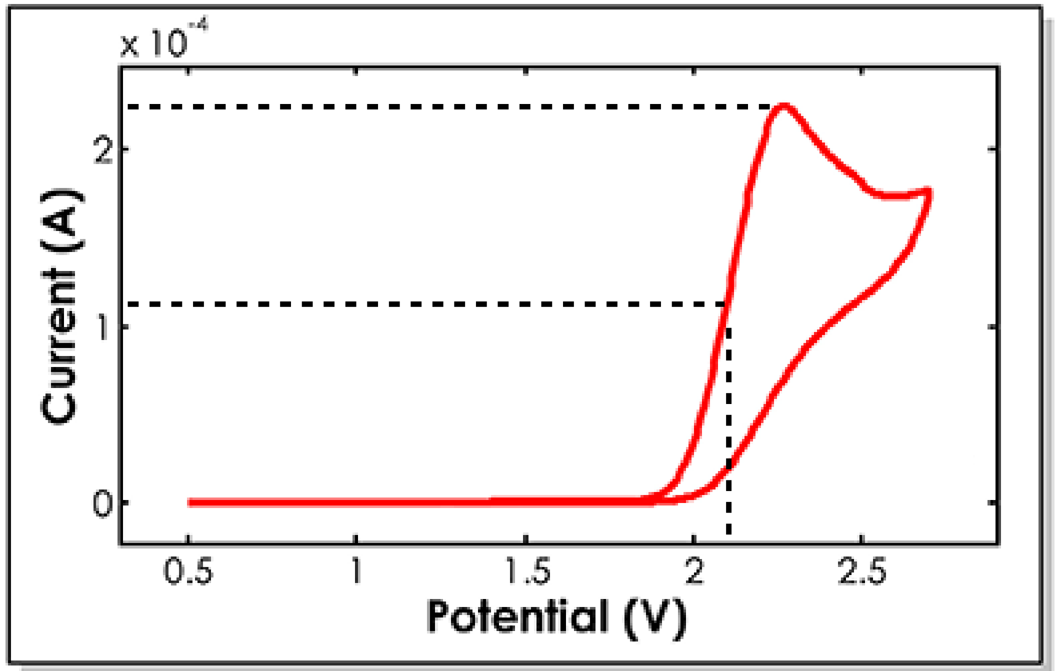


E_0 is given by the average of the oxidative (anodic) and reductive (cathodic) *peak potentials*

Reversible oxidation/reduction necessary!!!

Problematic for organic substrates

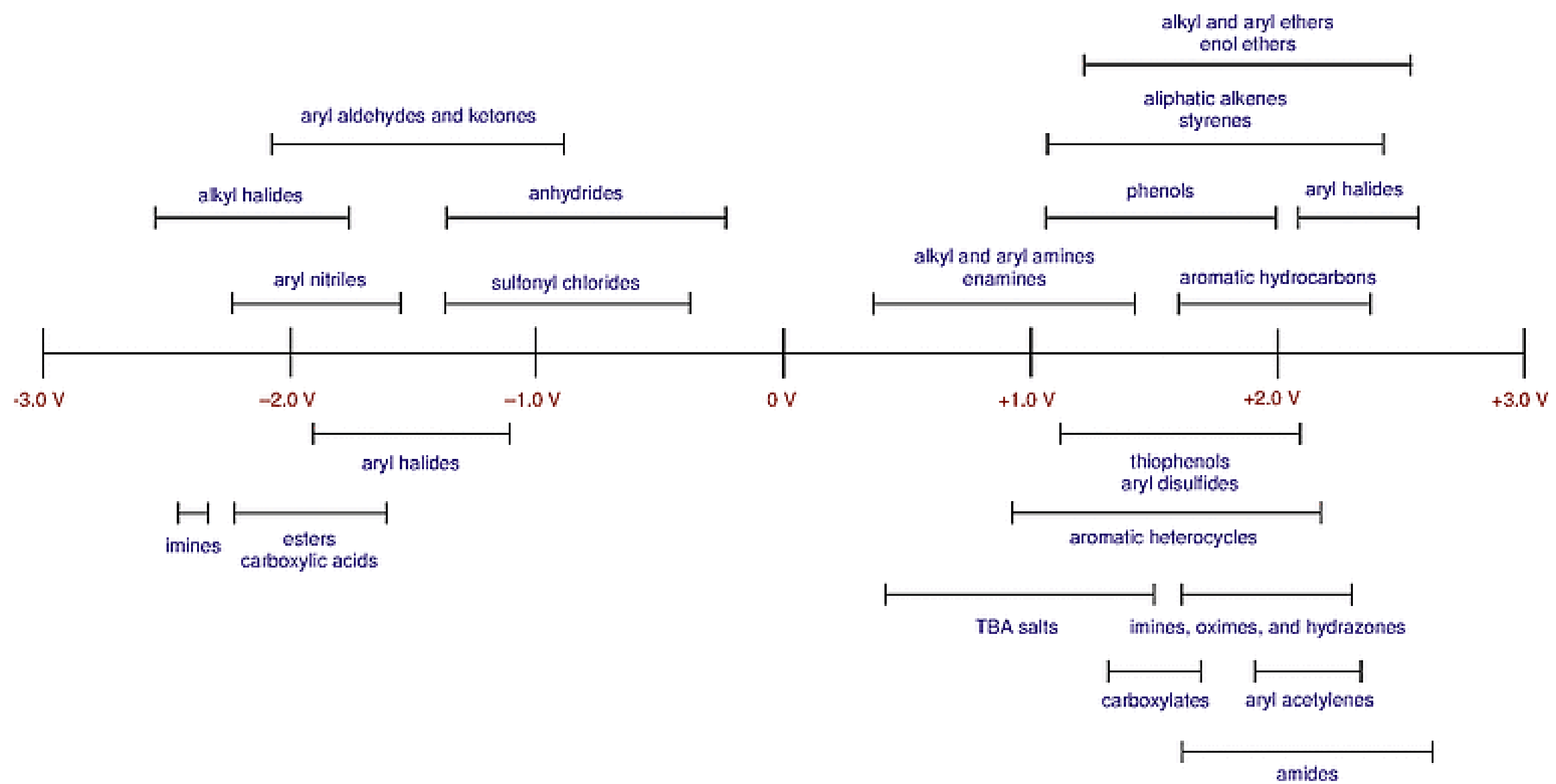
Organic Synthetic Electrochemistry



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



H. G. Roth, N. A. Romero, D. A. Nicewicz, *Synlett.* **2016**, *27*, 714

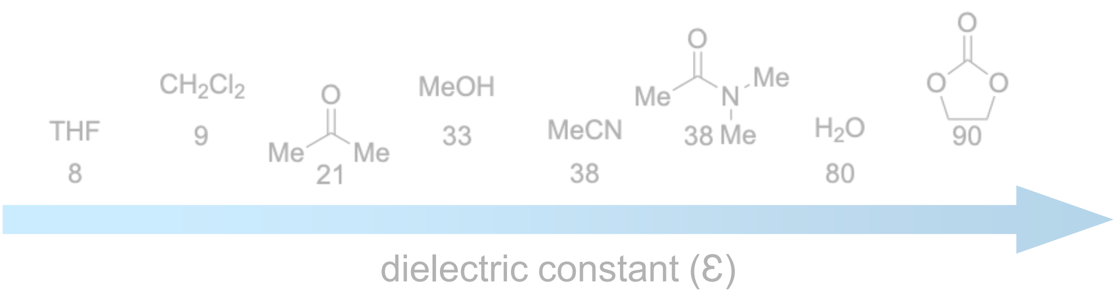
Anode/Cathode Materials:

- Electron transfer occurs at surface
- Different materials have different potential ranges
- Sacrifical 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

Solvent:

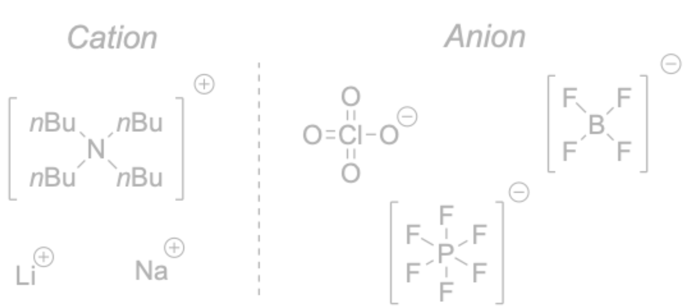
- Stable to electrochemical conditions
- Polar protic solvents most common



- 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

Electrolyte:

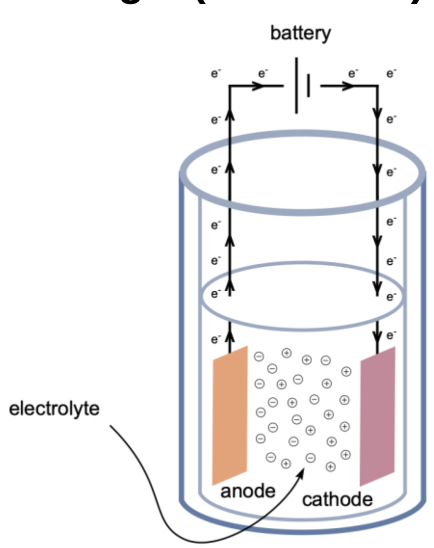
- Source of positive and negative ions
- Carries charge through reaction medium
- Increases conductivity of reaction medium
- Forms an ion layer around electrodes, affecting substrate diffusion



- Li^+ and nBu_4N^+ are common cations: good solubility and chemical inertness
- ClO^{4-} is a common anion: cheap and inert

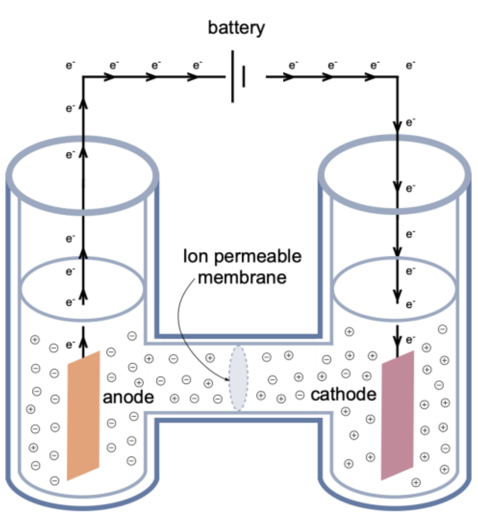
Single Cell vs Split Cell:

Single (Undivided) Cell:



- Lower resistance
- Simpler set-up

Split Cell:

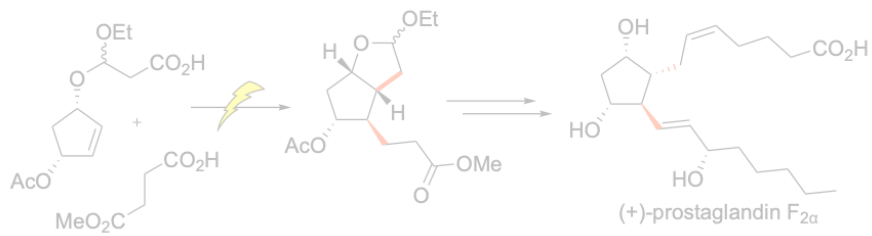


- Higher resistance
- More complicated set-up
- Less undesired reactivity

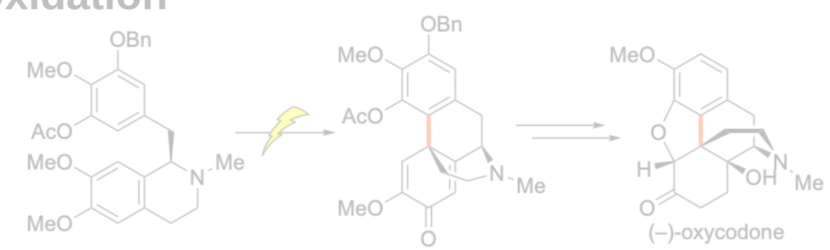
Electrochemistry in Total Synthesis

Anodic Oxidations:

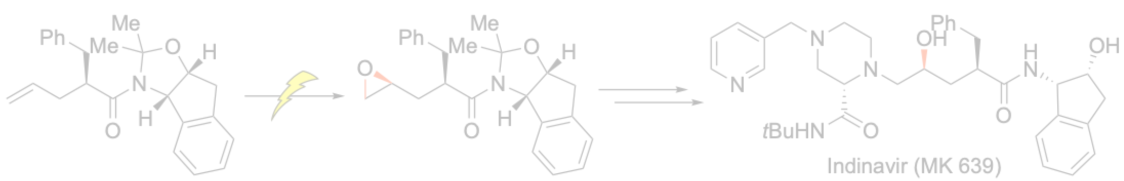
- Oxidative Decarboxylation (Kolbe Reaction)



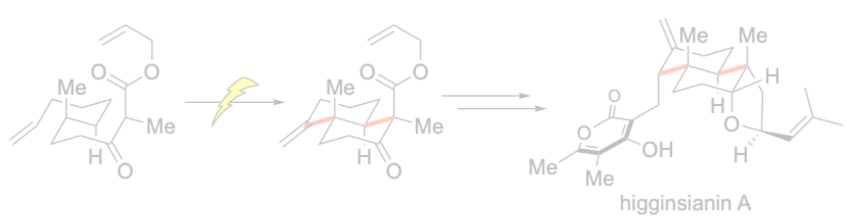
- Arene Oxidation



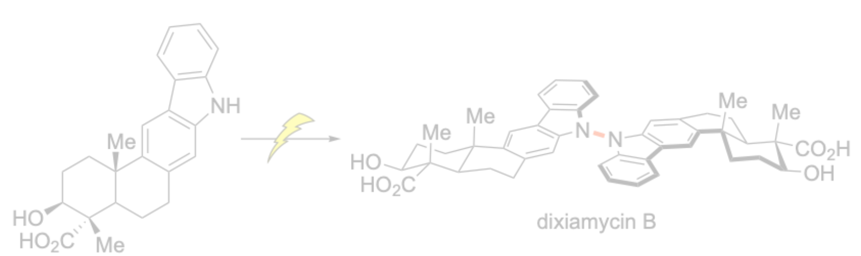
- C=C Bond Oxidation



- C(sp^3)–H Oxidation

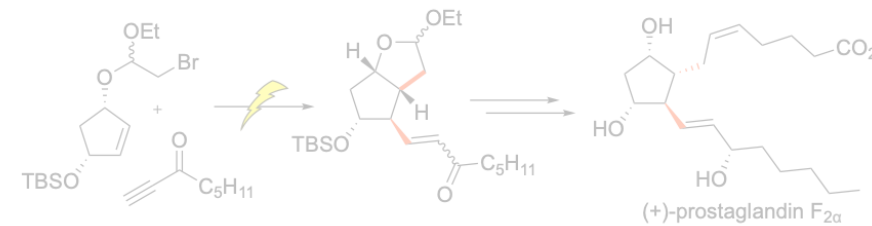


- N–H Bond Oxidation

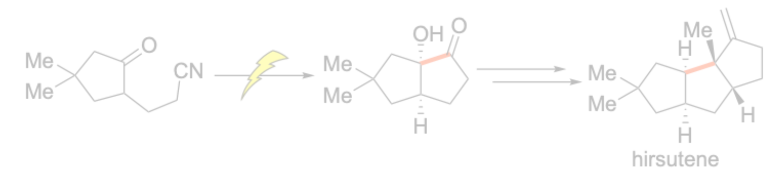


Cathodic Reductions:

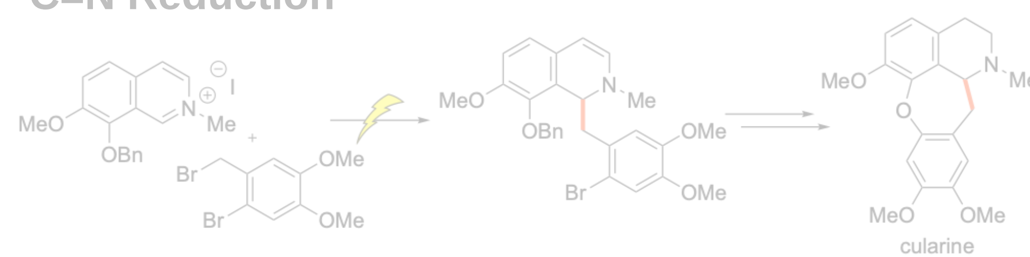
- C–X Reduction



- C=O Reduction

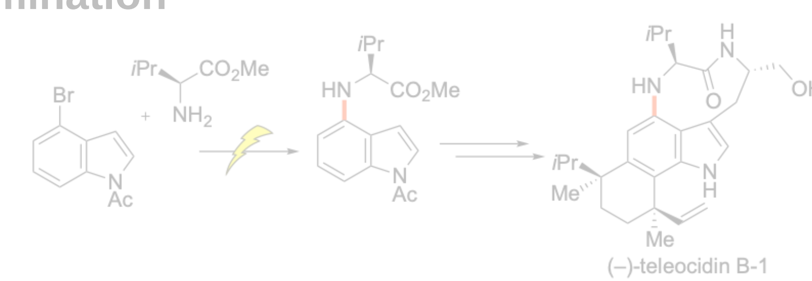


- C=N Reduction

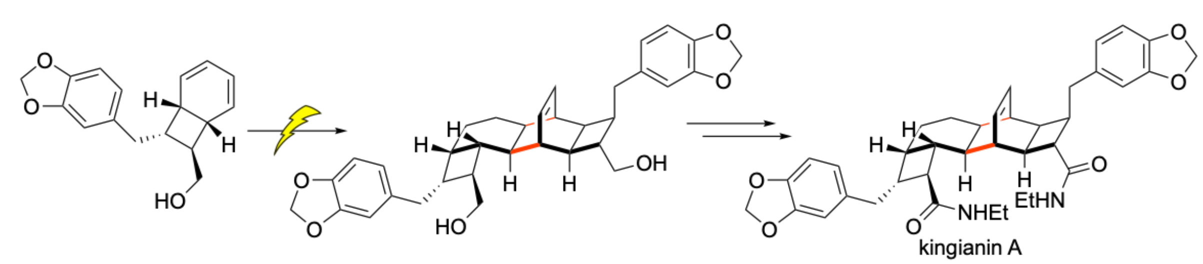


Redox Paired Transformations:

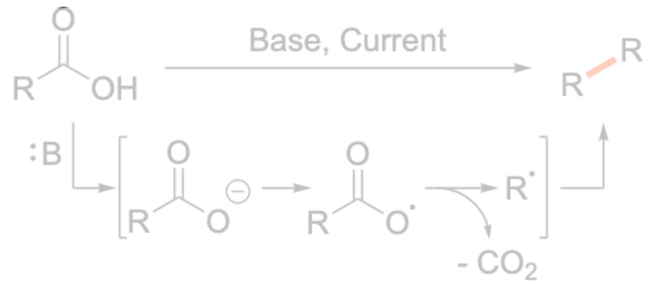
- *e*-Amination



- **Radical Cation Diels-Alder**

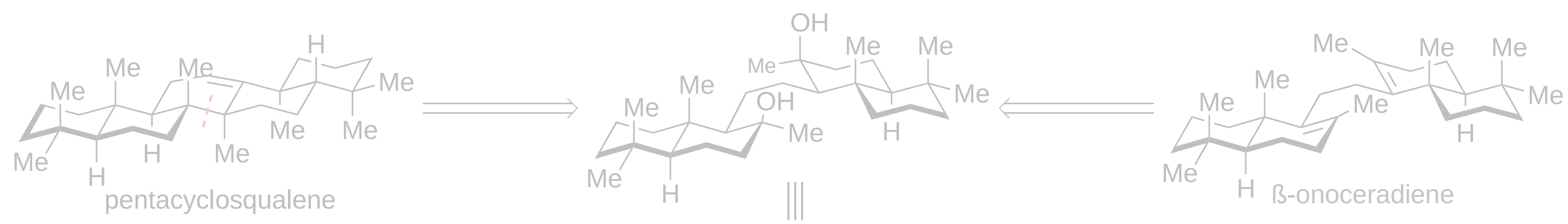


Oxidative Decarboxylation (Kolbe Reaction)

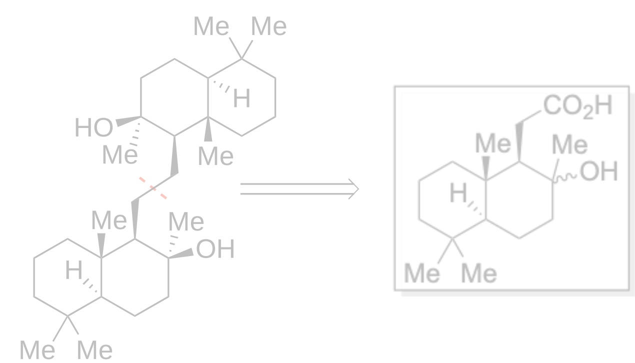


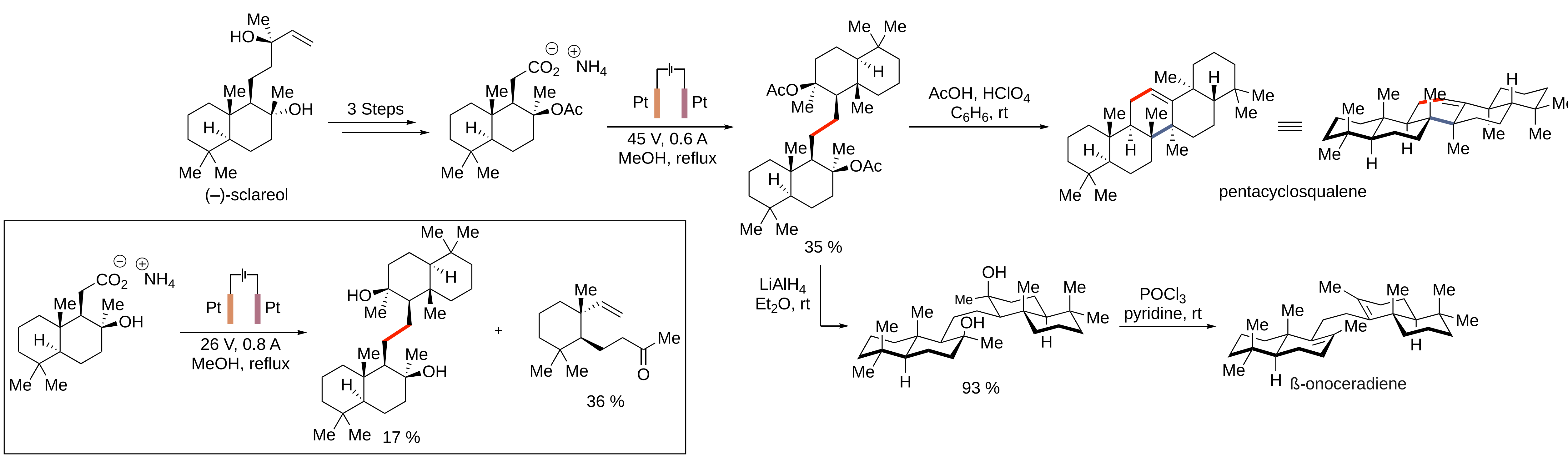
- First reported in 1848[1]
- Single electron oxidation of carboxylate
- Rapid decarboxylation
- Radical coupling gives product

Corey, 1959[2]



- Polar reactivity would require two different coupling units

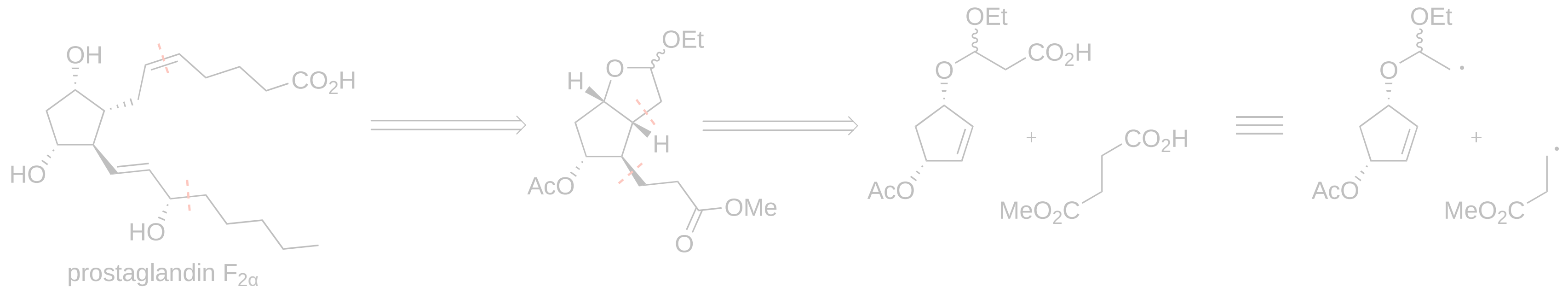


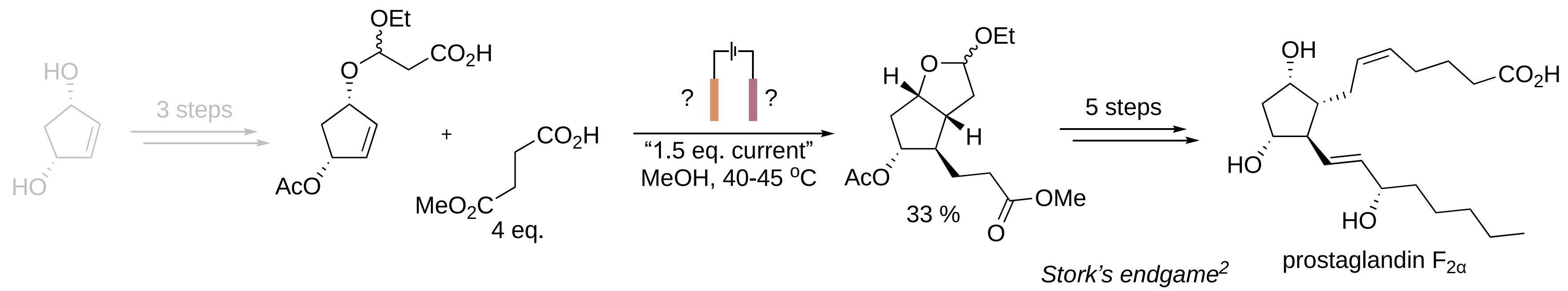


1) H. Kolbe, *Ann. der Chem. & Pharm.* **1848**, *64*, 339
2) E. J. Corey and R. R. Sauers, *J. Am. Chem. Soc.* **1959**, *81*, 1739

Oxidative Decarboxylation (Kolbe Reaction)

Schäfer, 1988[1]



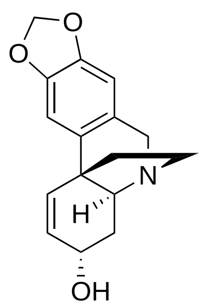


- Reduction of step count by 2
- Obviates the need for tin reagents
- More flexible choice of coupling reagent

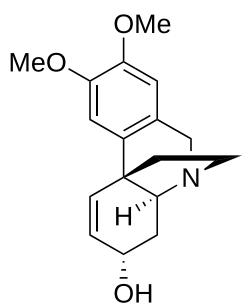
1) L. Becking and H. J. Schäfer, *Tet. Lett.* **1988**, 2801

Arene Oxidation

Tobinaga, 1973[1]

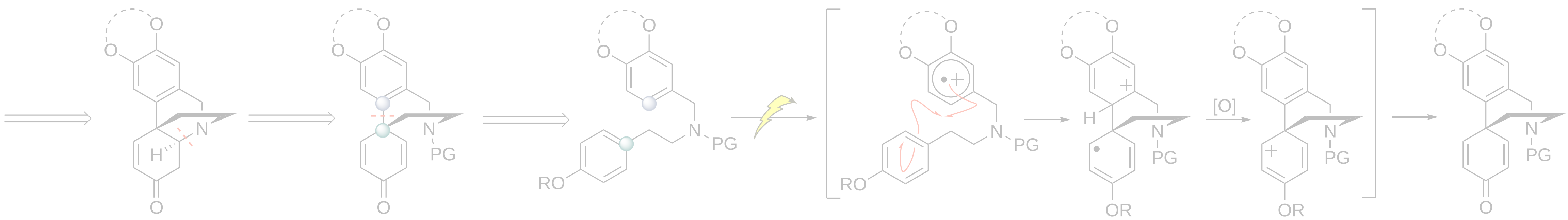


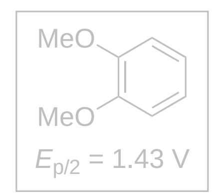
crinine

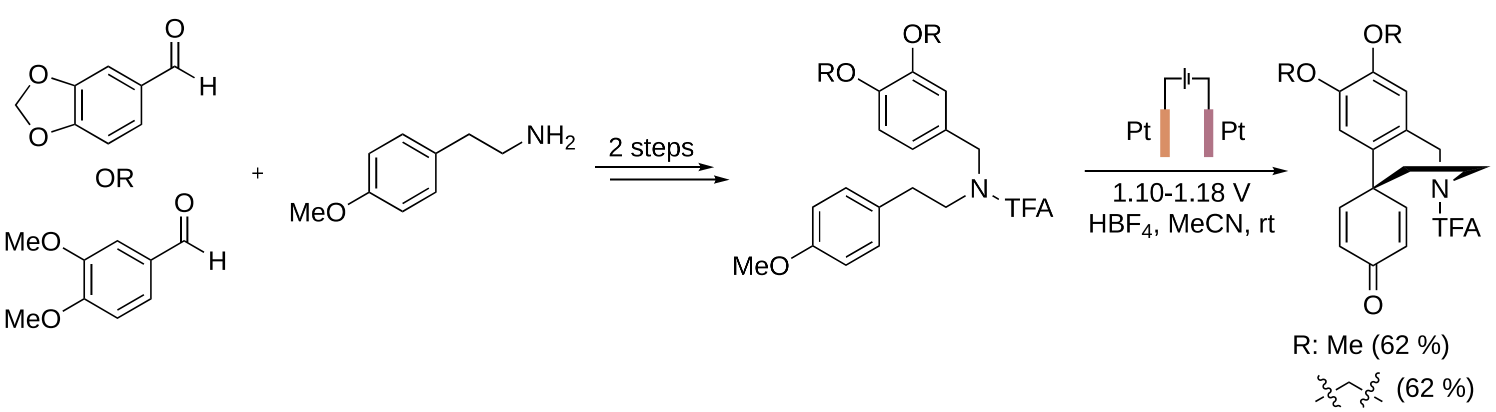


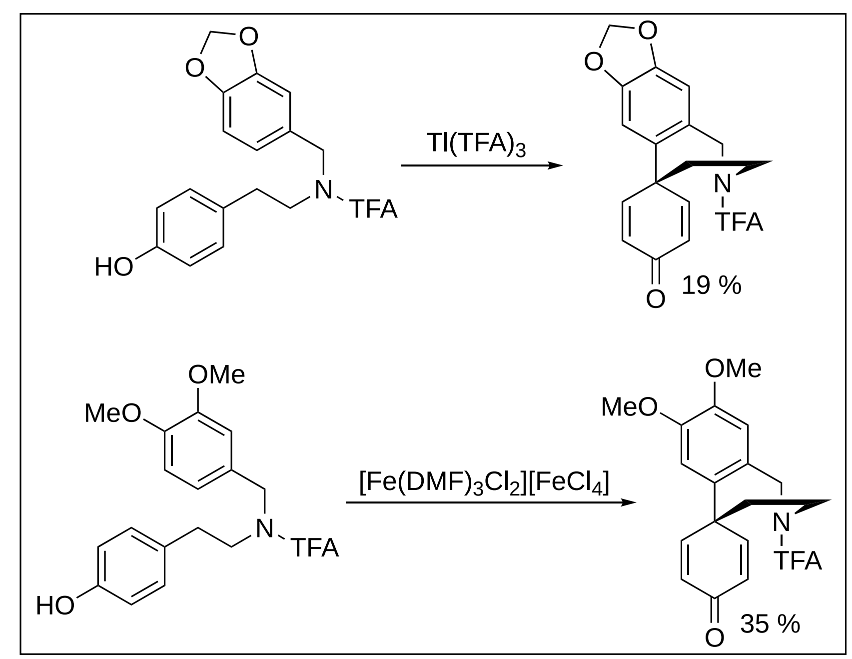
maritidine

Amaryllidaceae alkaloids





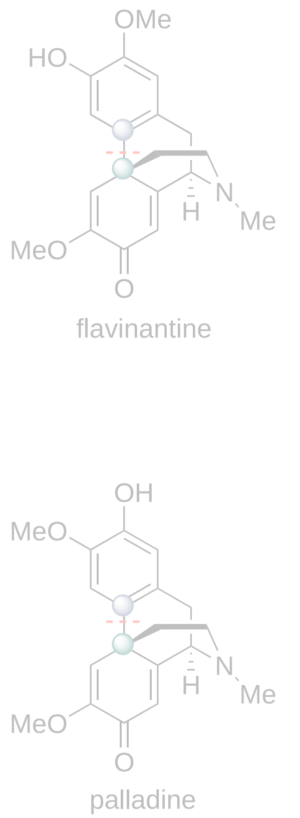




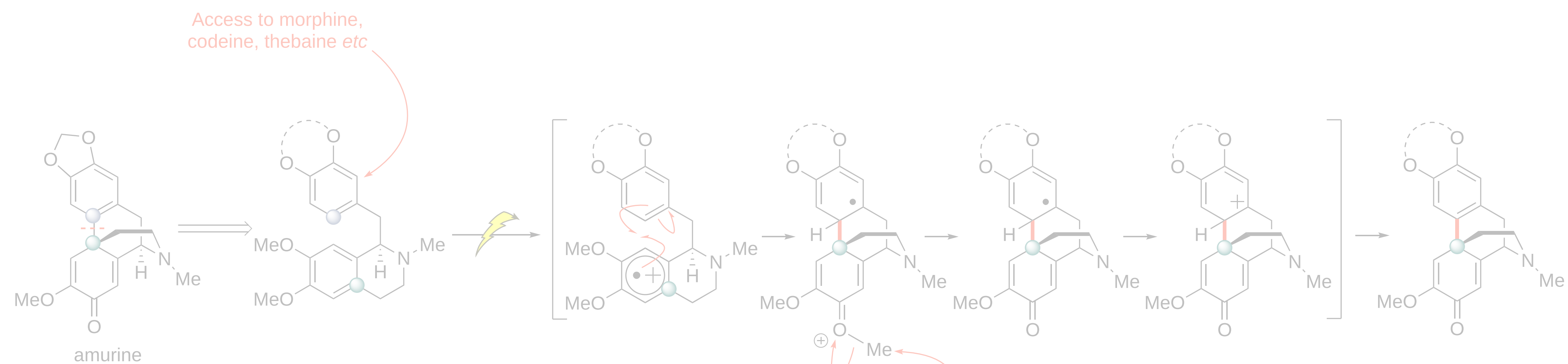
1) E. Kotani, N. Takeuchi, S. Tobinaga, *J. Chem. Soc., Chem. Commun.* **1973**, 550

Arene Oxidation

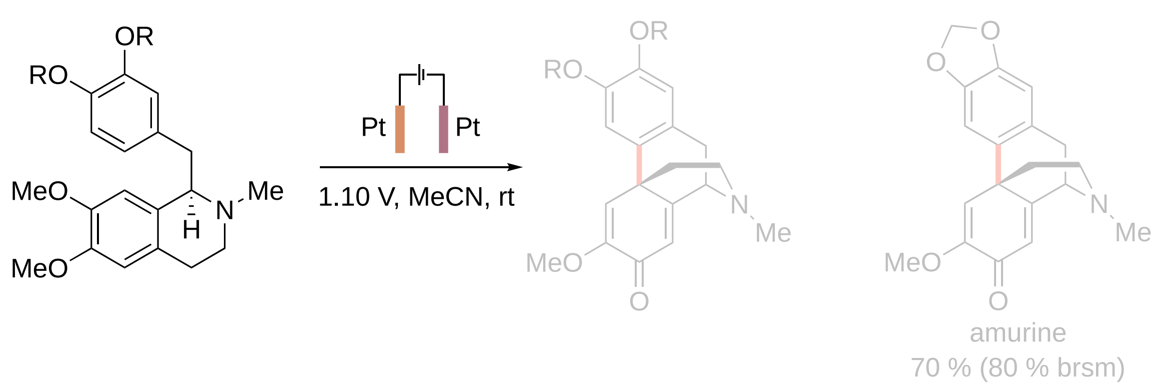
Tobinaga, 1973[1]

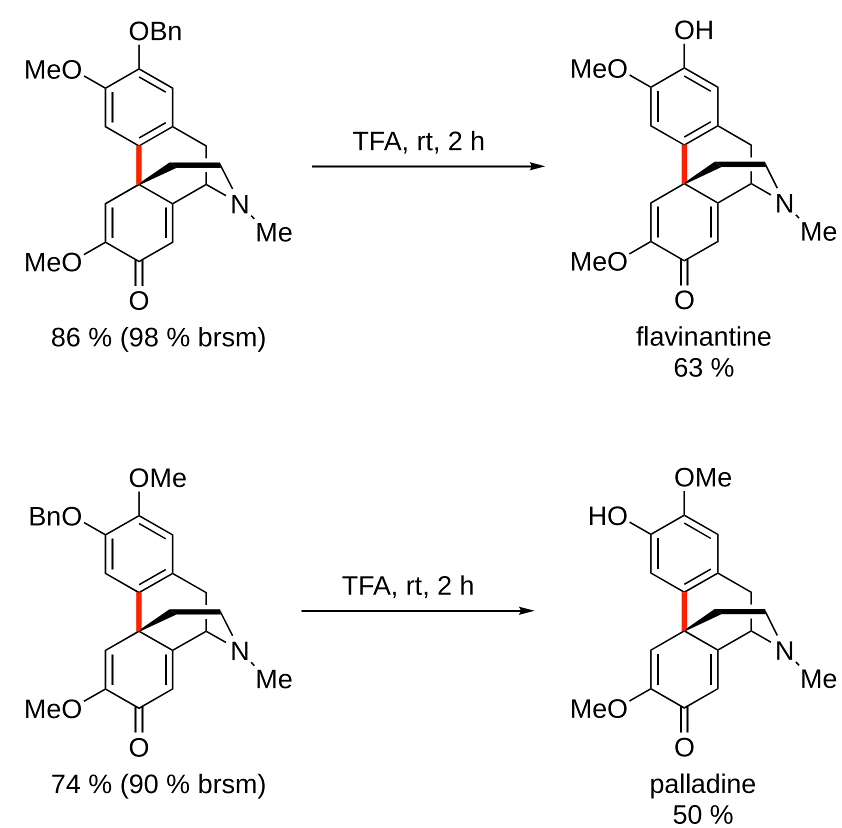


morphinandienone alkaloids



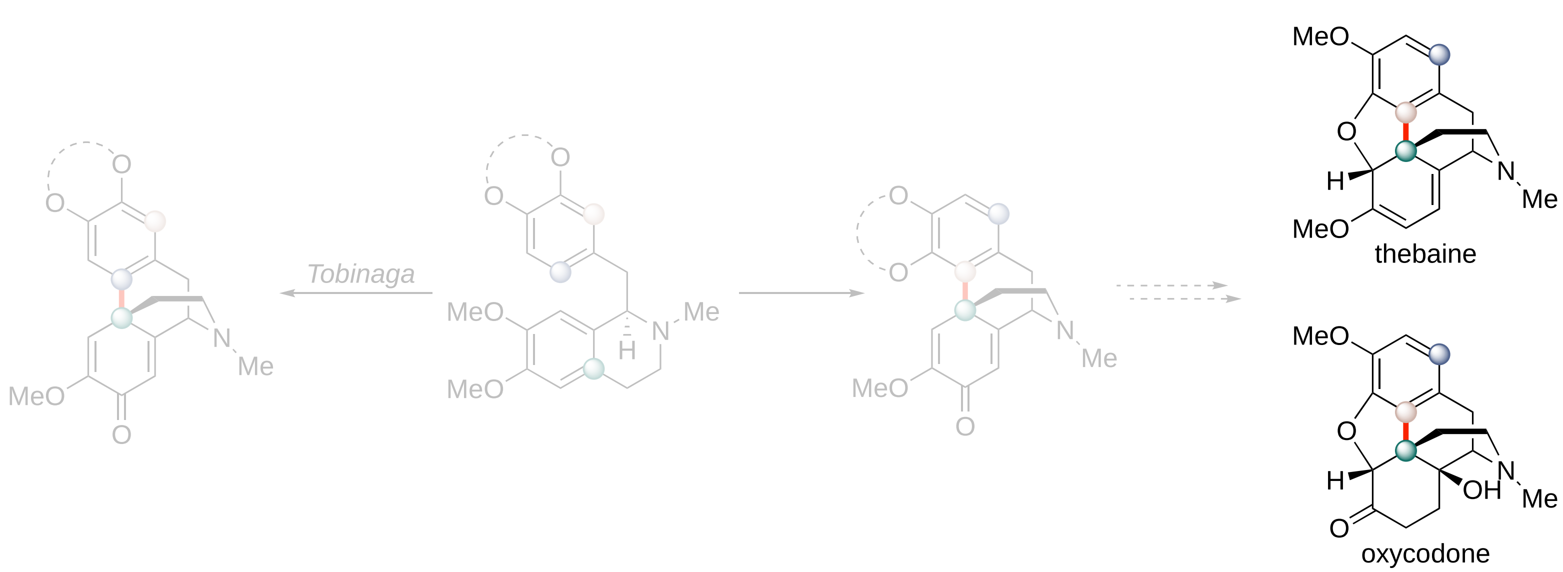
- Biomimetic synthesis
- Well established with [O]-reagents
- Regioselectivity control?





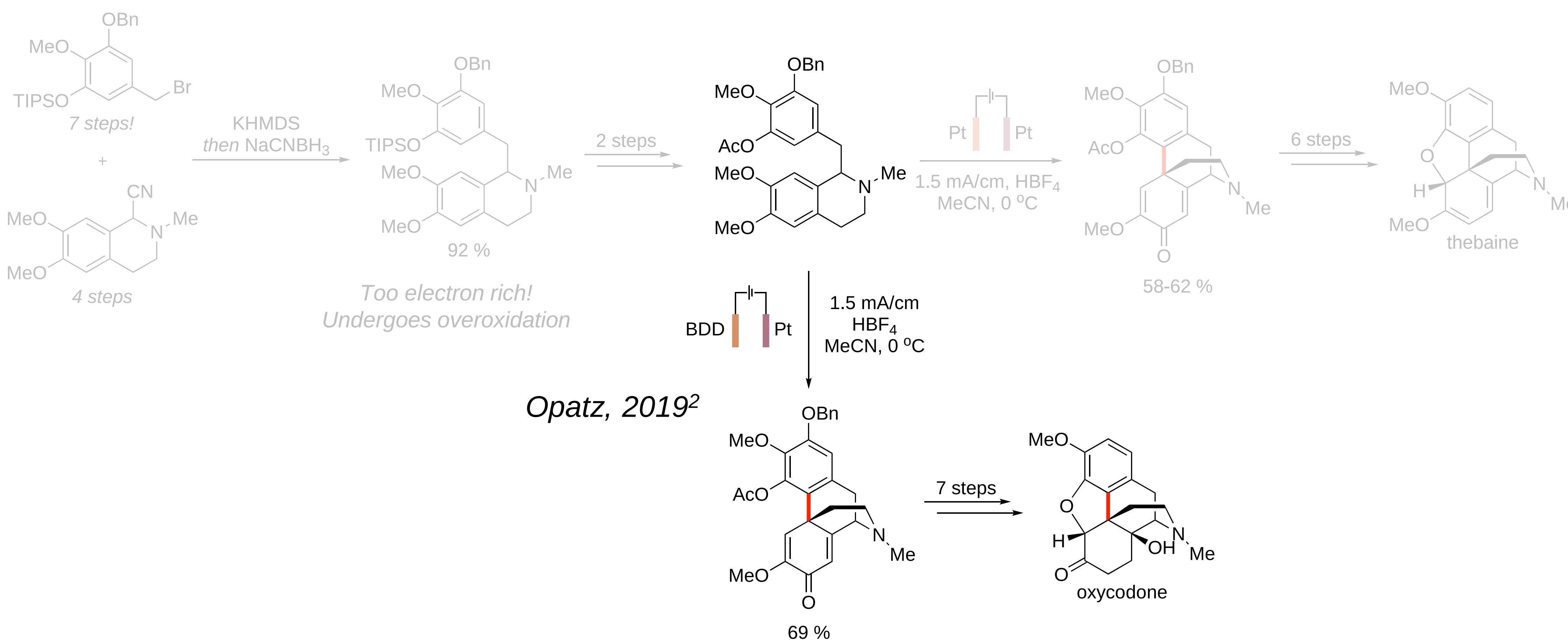
1) E. Kotani, S. Tobinaga, *Tet. Lett.* **1973**, 4759

Arene Oxidation



Regioselectivity difficult to override!

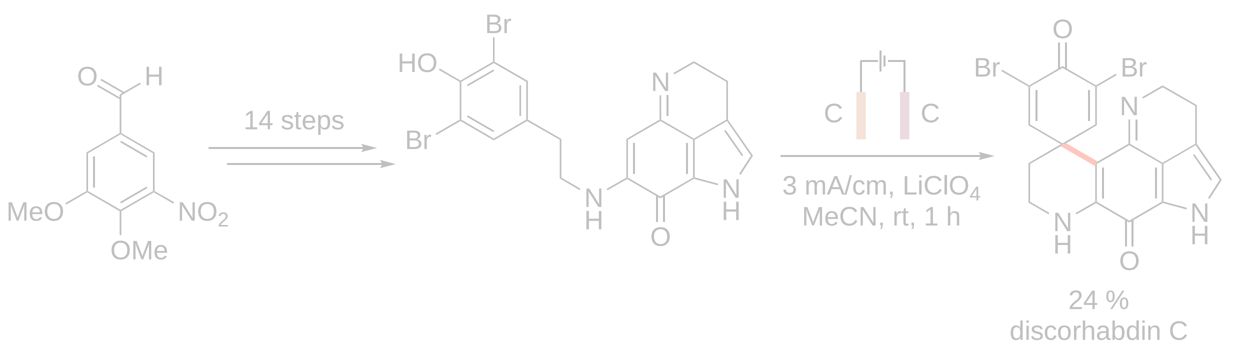
Opatz, 2018[1]



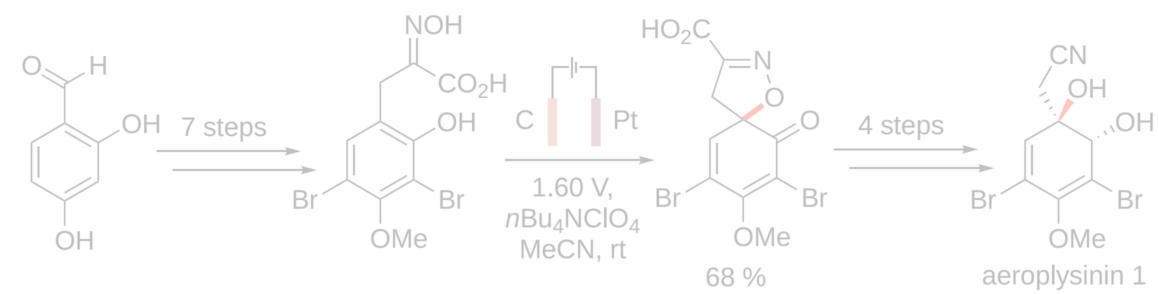
Arene Oxidation

Nishiyama

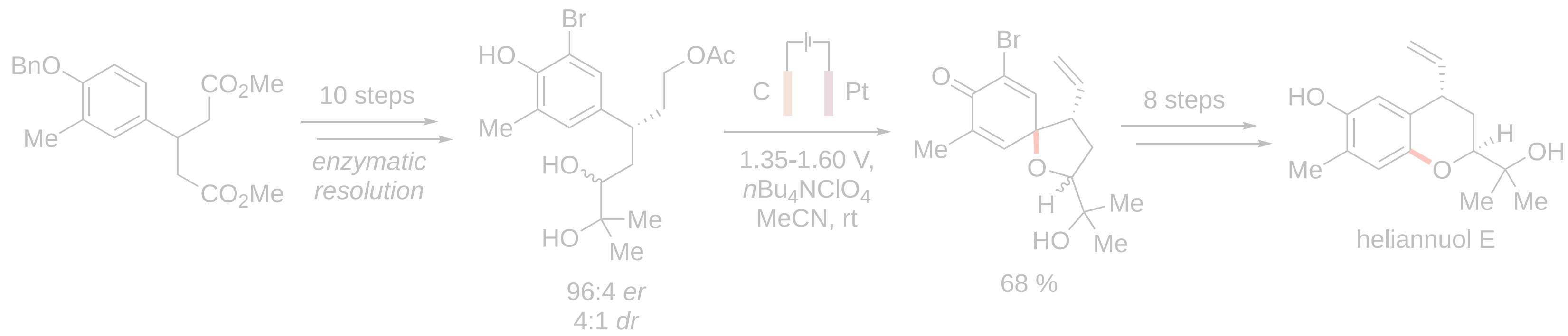
1994[1]



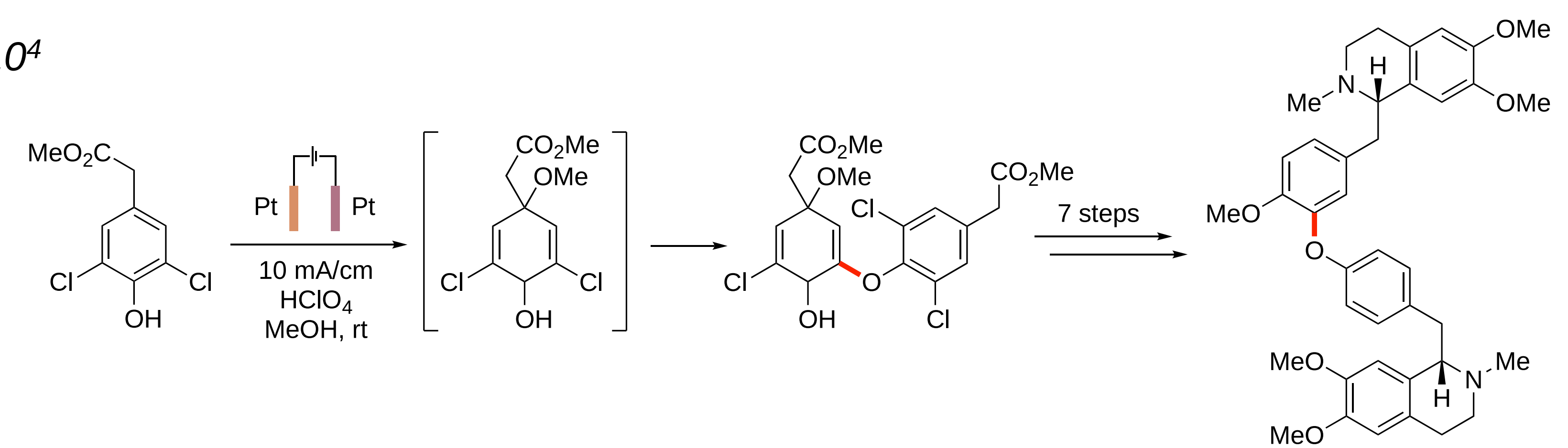
2003[2]



2003[3]



2010[4]



Arene Oxidation

Chiba, 1998[1]

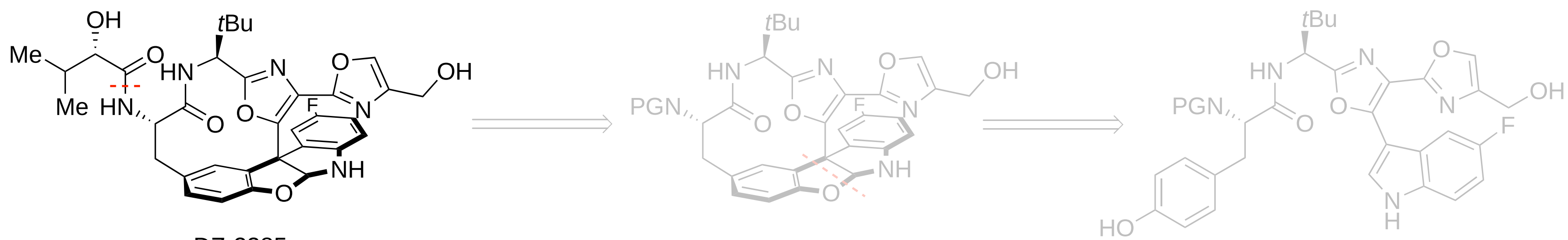
DDQ as redox mediator:

- Oxidises substrate
- Then reoxidised by anode

1) K. Chiba, T. Arakawa, M. Tada *J. Chem. Soc., Perkin Trans. 1*, **1998**, 2939

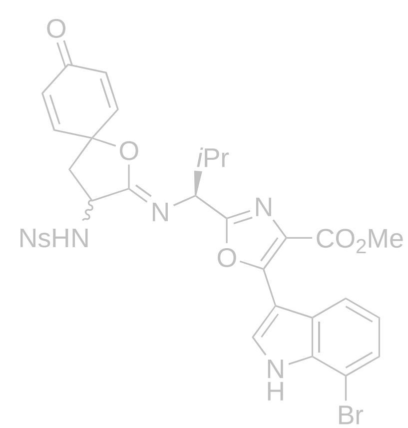
Arene Oxidation

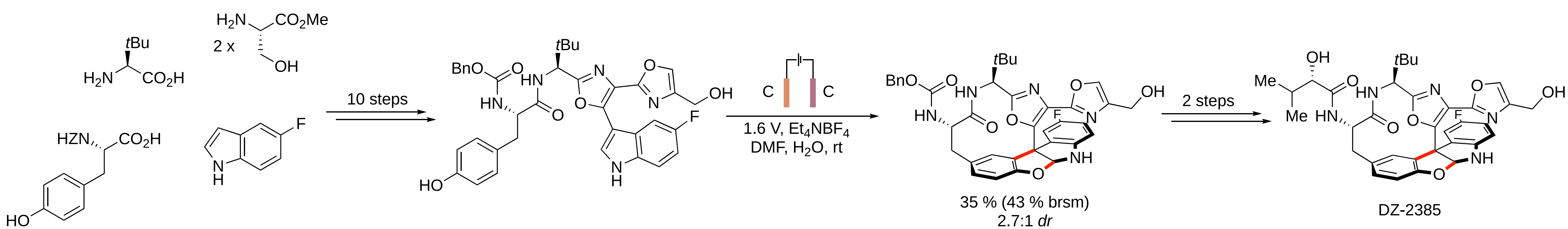
Harran, 2015[1]



DZ-2385

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

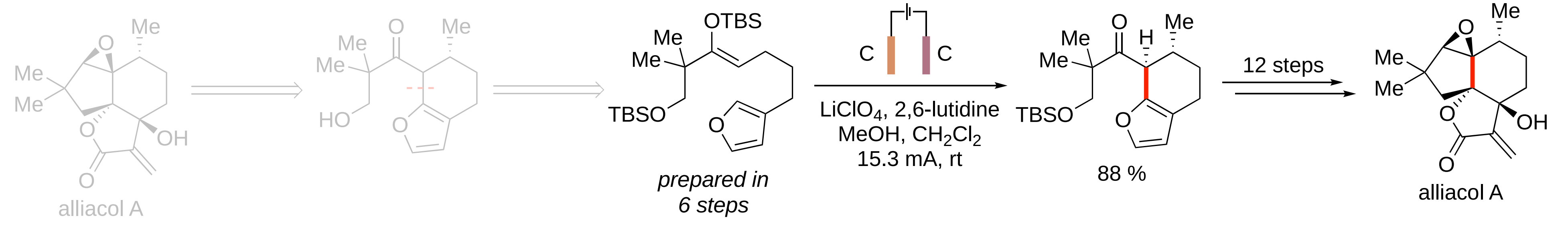




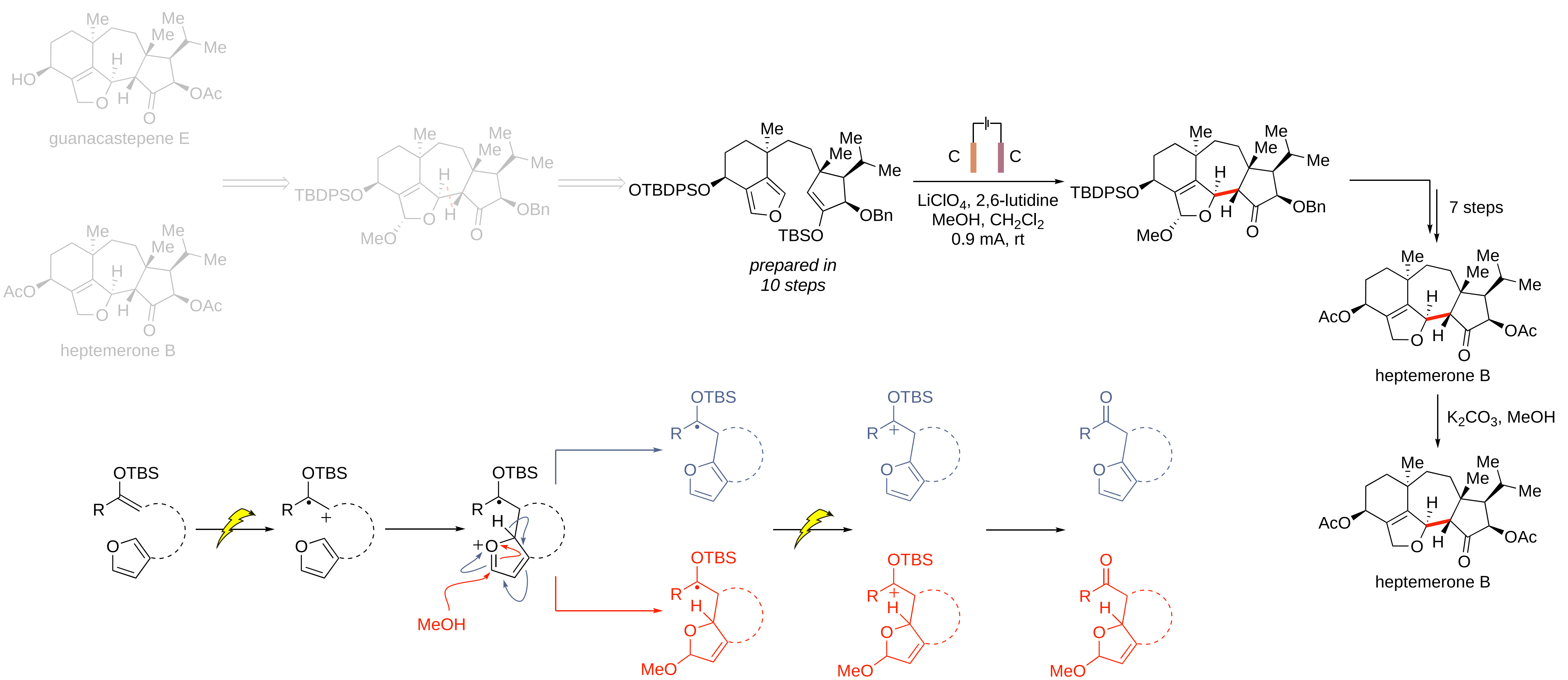
1) Harran *et al. Angew. Chem. Int. Ed.* **2015**, *54*, 4818

C=C Oxidation

Moeller, 2004[1]



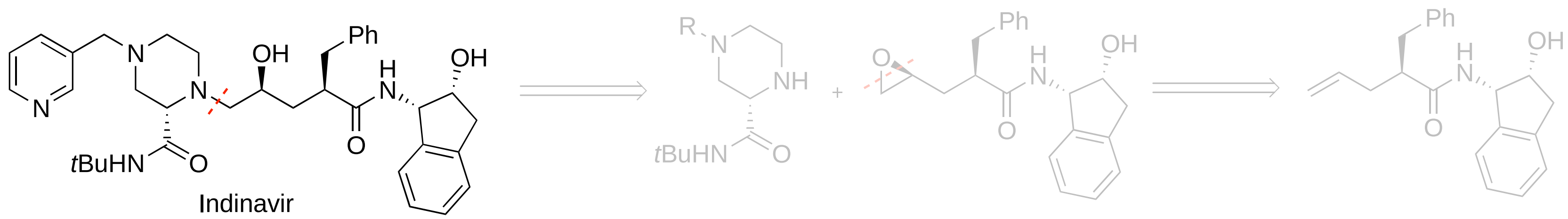
Trauner, 2006[2]

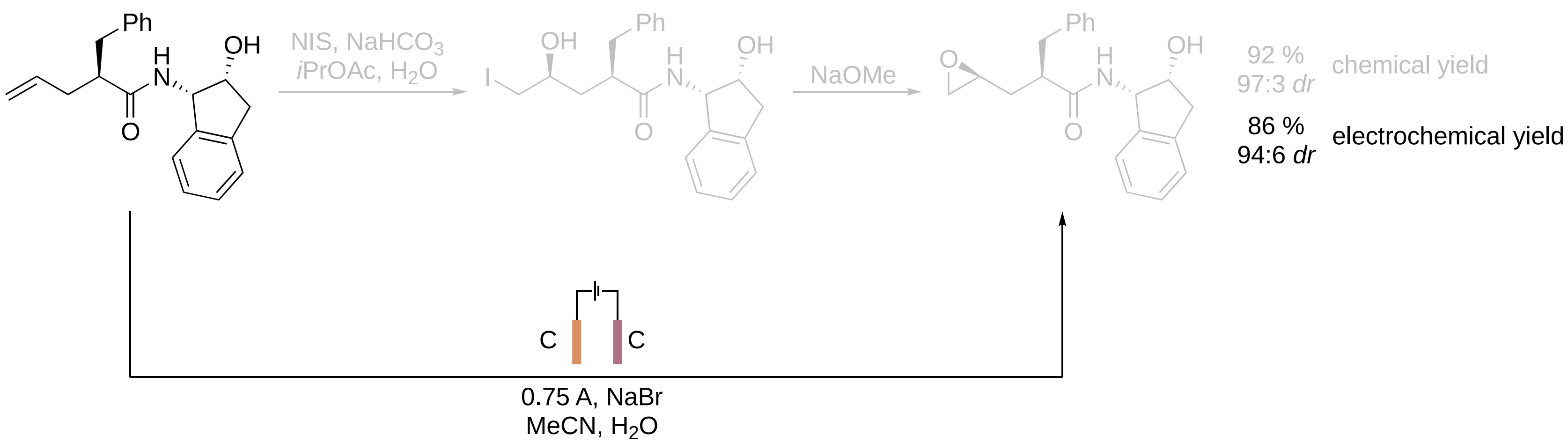


1) J. Mihelcic, K. D. Moeller, *J. Am. Chem. Soc.* **2004**, *126*, 9106

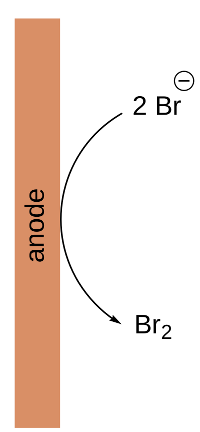
C=C Oxidation

Rossen (Merck), 1997[1]





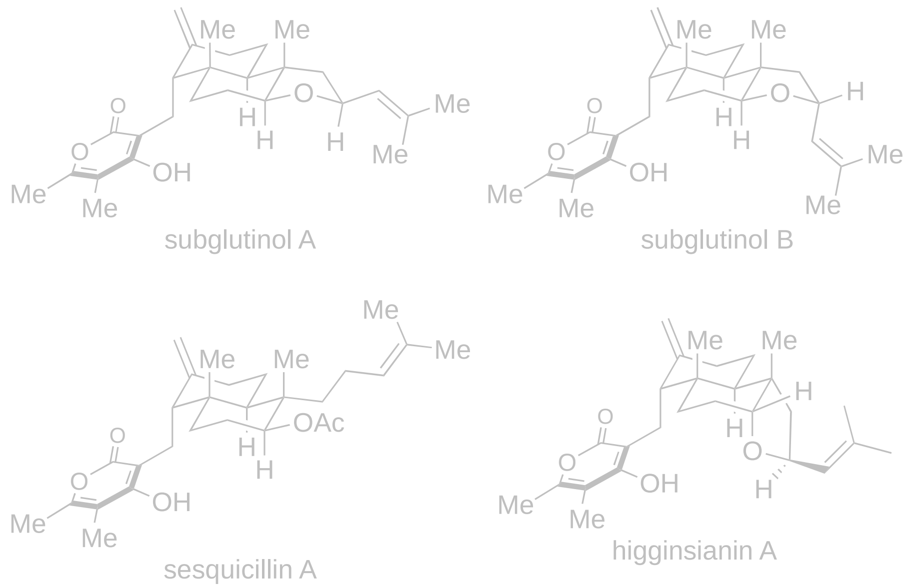
- High yield, *dr*
- Two steps
- Stoich. NIS, NaOMe



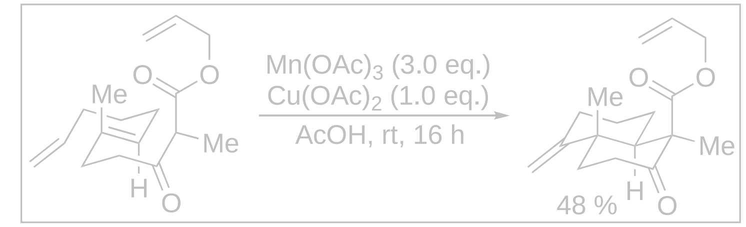
1) K. Rossen, R. P. Volante, P. J. Reider *Tet. Lett.* **1997**, *38*, 777

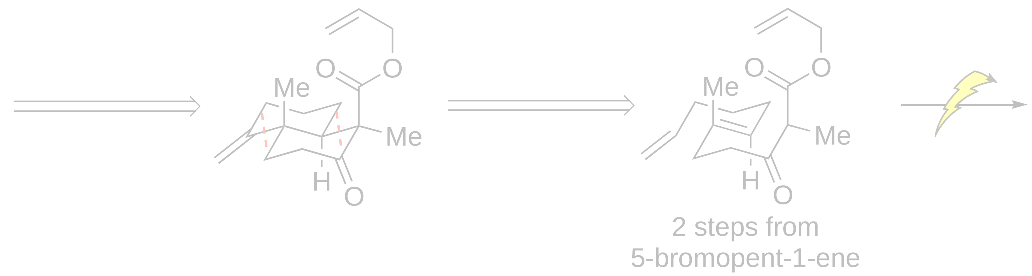
C(sp^3)–H Oxidation

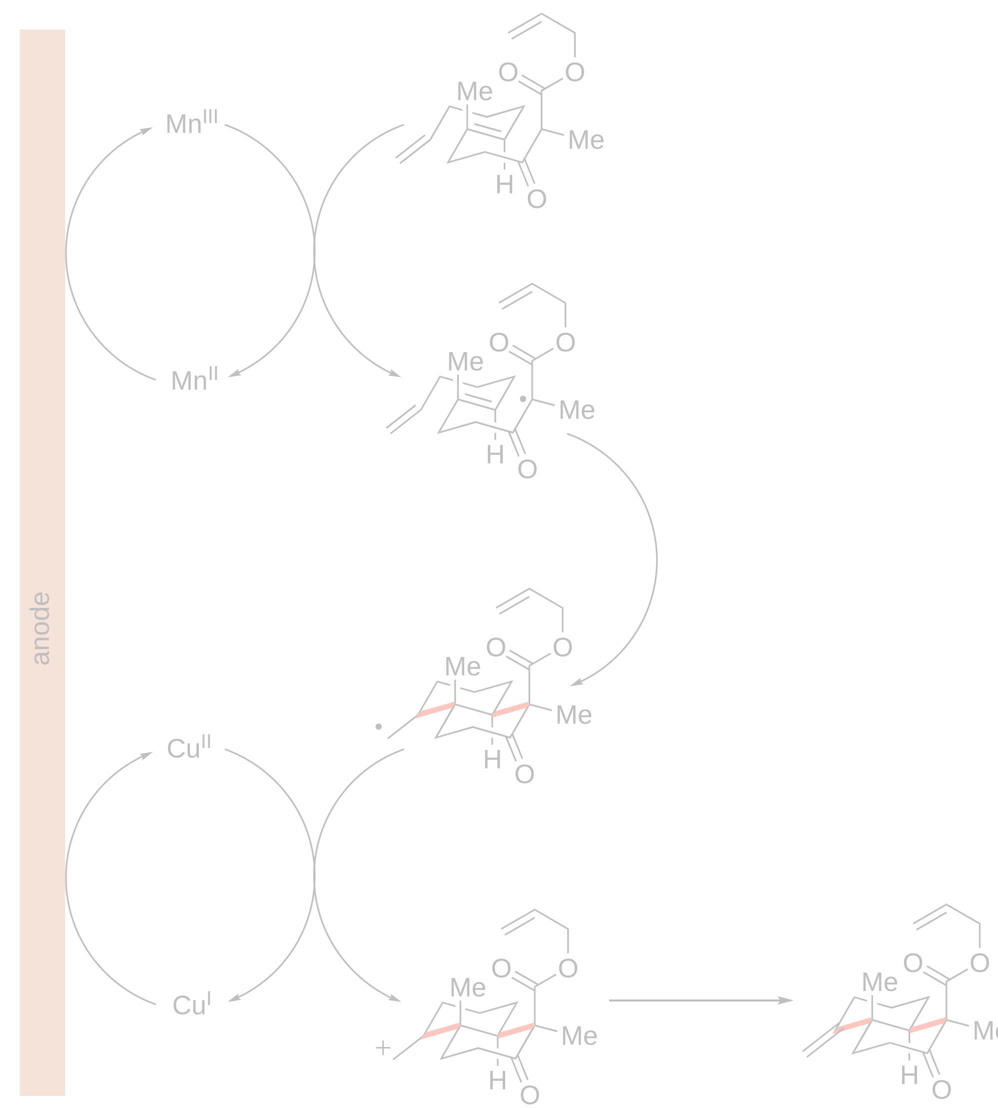
Baran, 2018[1]

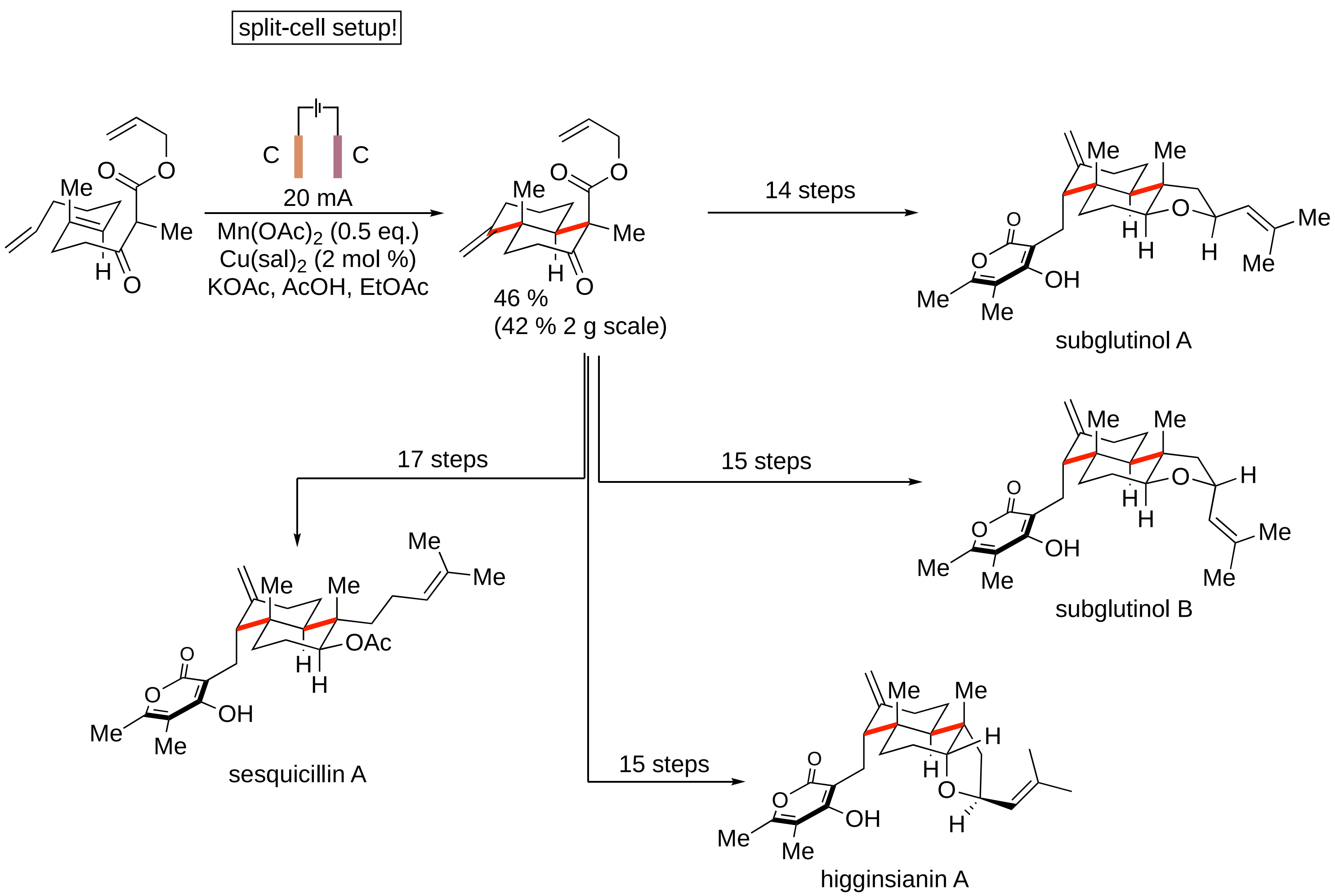


Radical polycyclisation:
-Well developed with superstoichiometric Mn(III) and up to 1.0 eq. Cu(II) salts





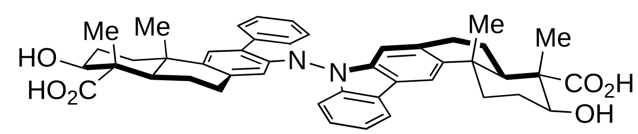




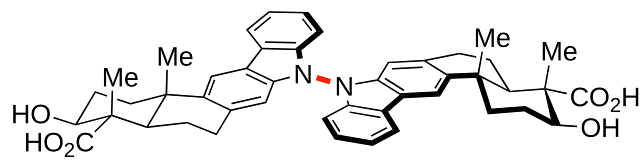
1) Baran *et al.* *J. Am. Chem. Soc.* **2018**, *140*, 7462

N–H Oxidation

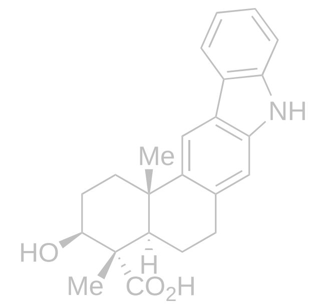
Baran, 2014[1]



dixiamycin A



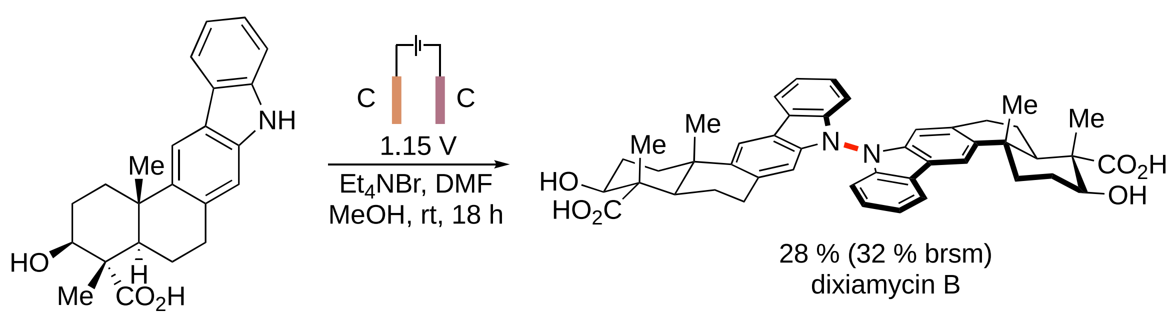
dixiamycin B



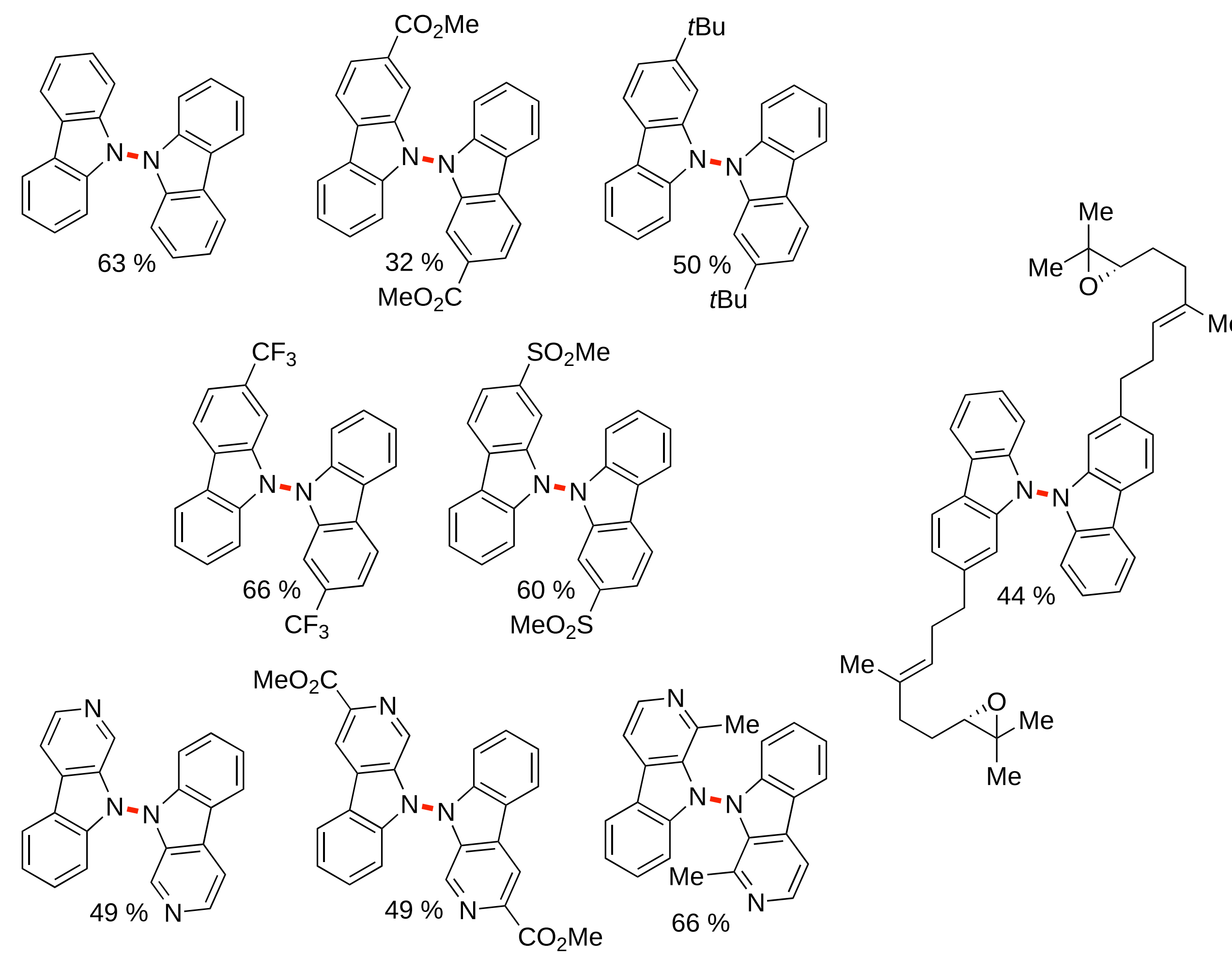
xiamycin A

Chemical dimerization attempts

$KMnO_4$, acetone	<20 %, decomp.
LDA, then [Cu]	no reaction
PIFA, CH_2Cl_2	no reaction
KOtBu, tBuOCl	traces



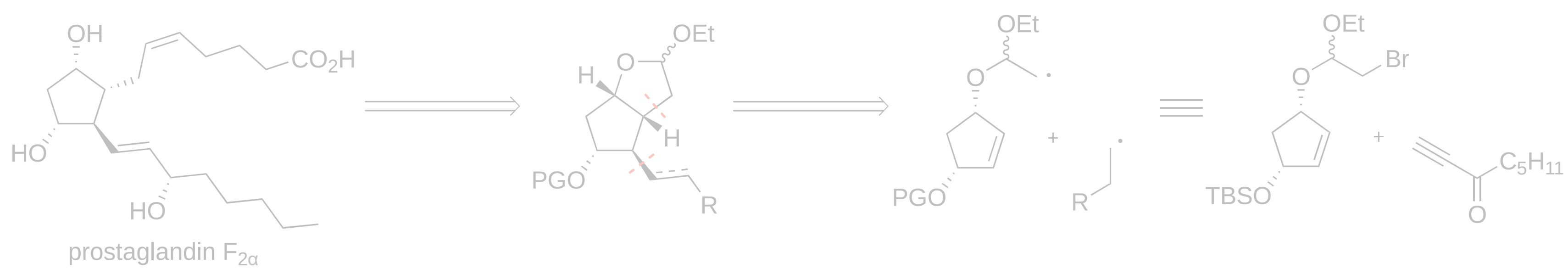
28 % (32 % brsm)
dixiamycin B



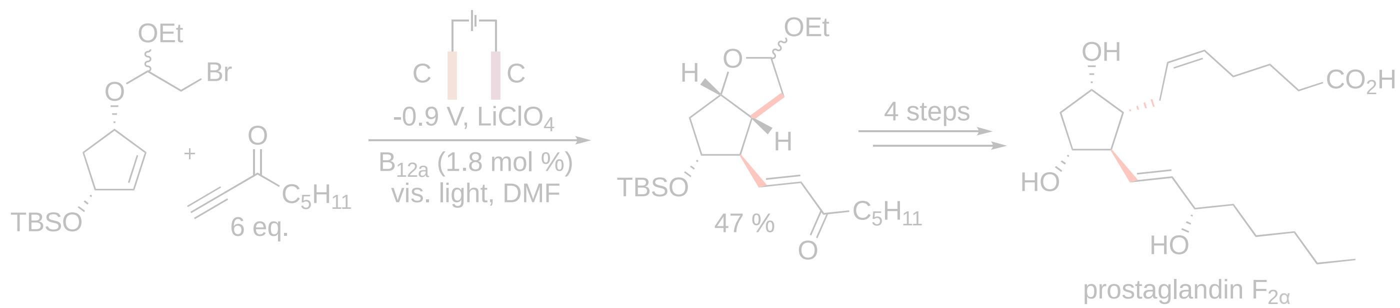
1) Baran *et al. J. Am. Chem. Soc.* **2014**, *136*, 5571

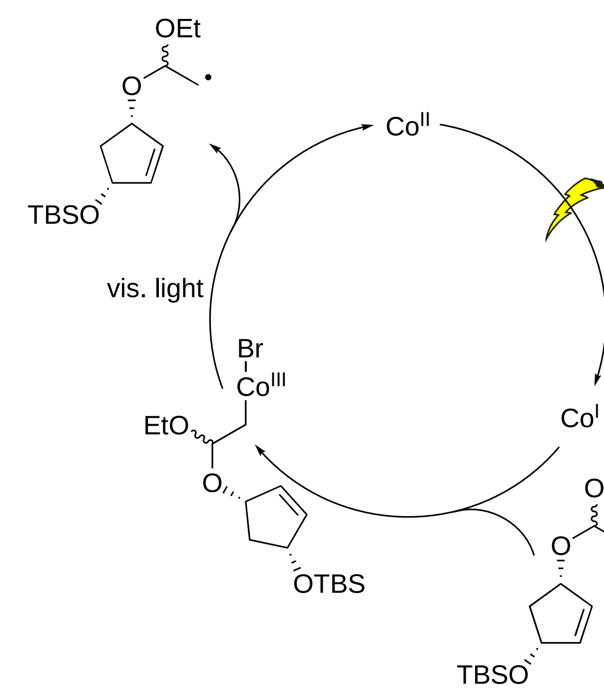
C–X Reduction

Scheffold, 1990[1]

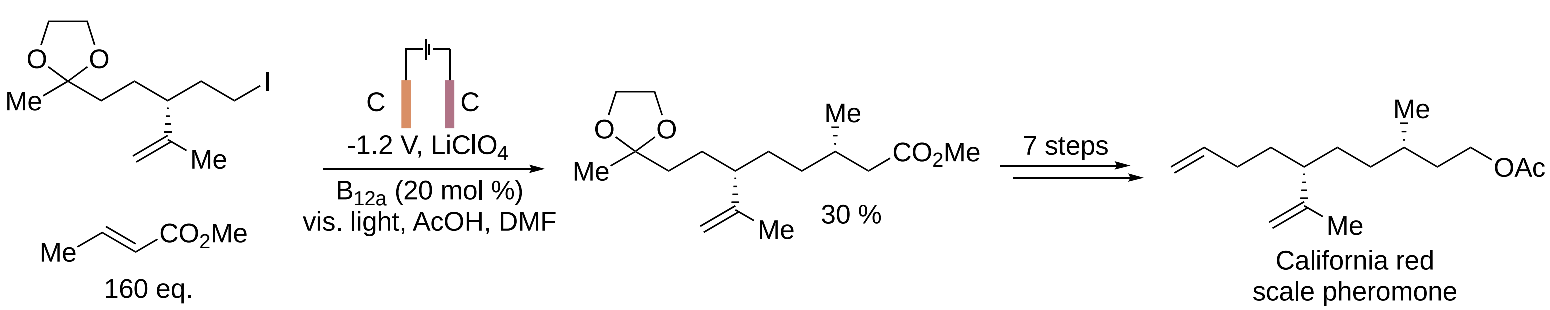


- Single e- C–X reduction known
- Red. potentials 1.9-2.2 V





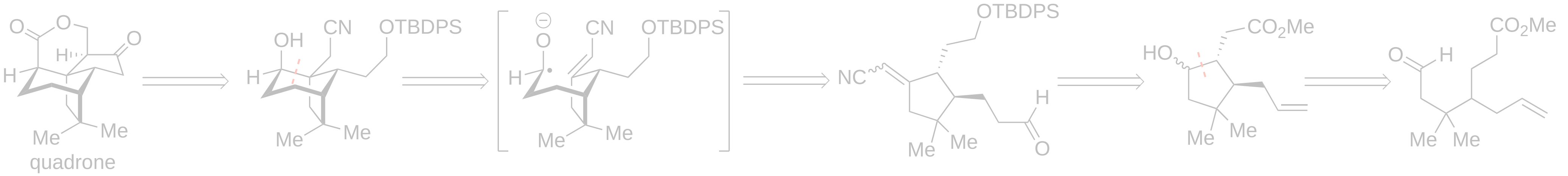
Scheffold, 1993[1]



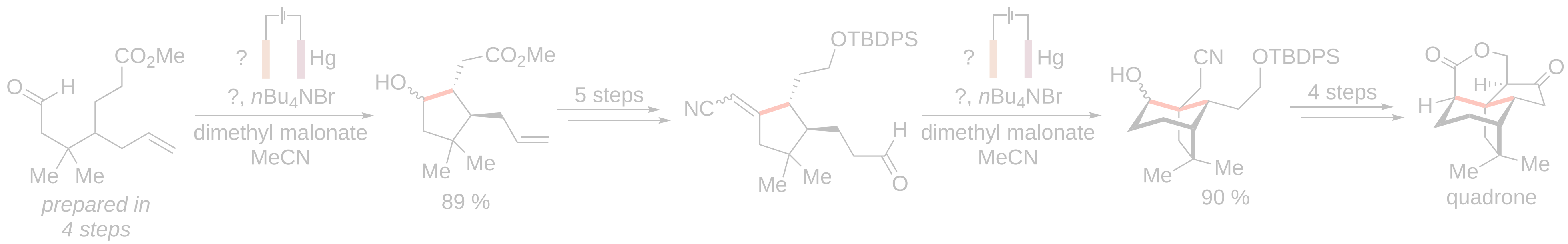
1) Scheffold *et al. Tetrahedron*, **1990**, *46*, 3155

C=O Reduction

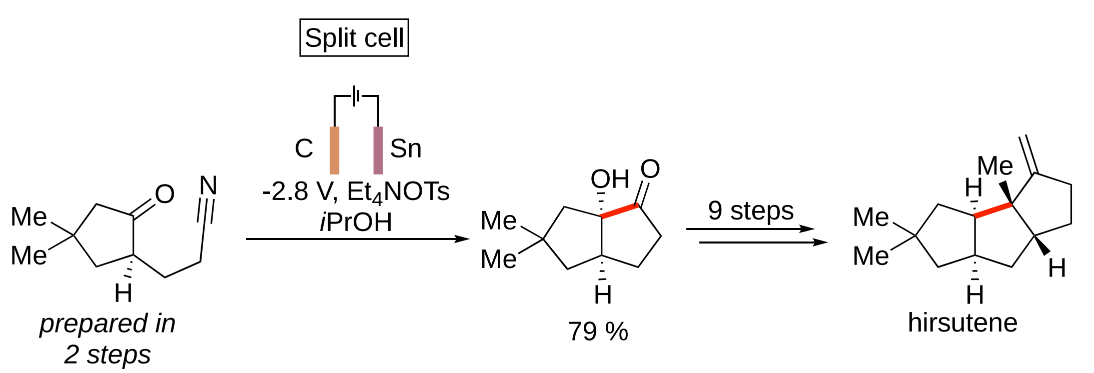
Little, 1990[1]

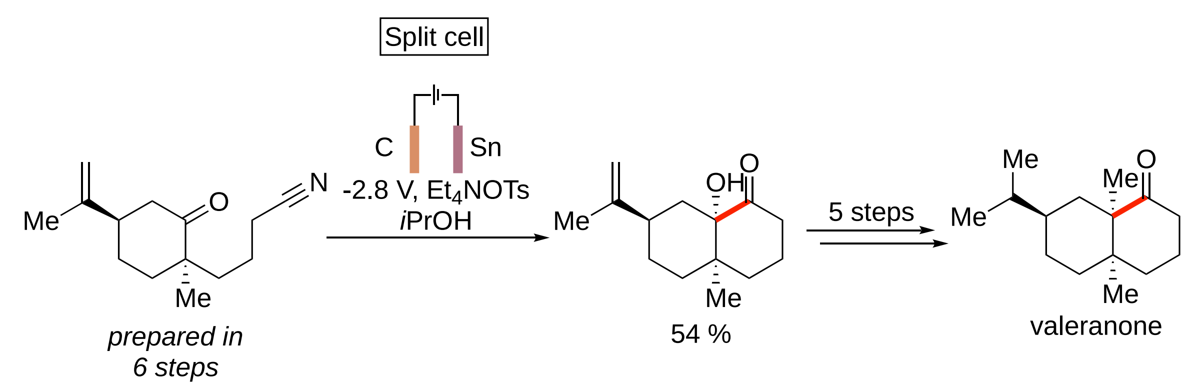


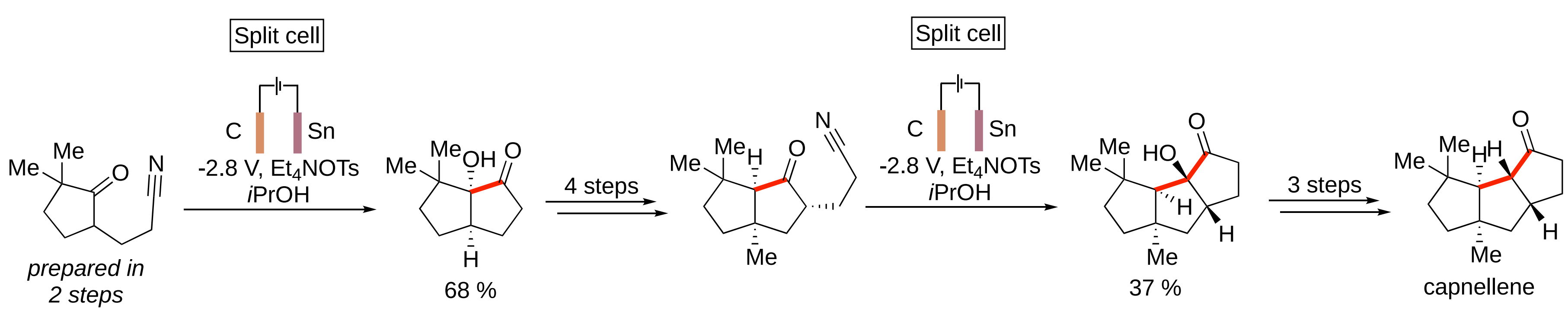
• Well precedented with SmI_2



Shono, 1992[2]



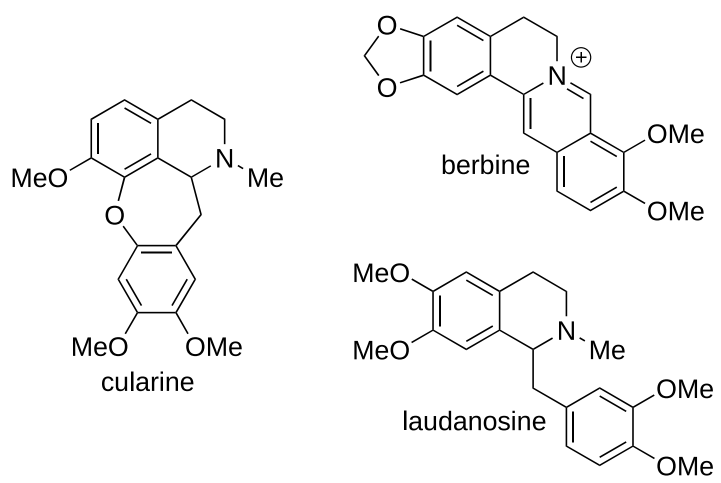




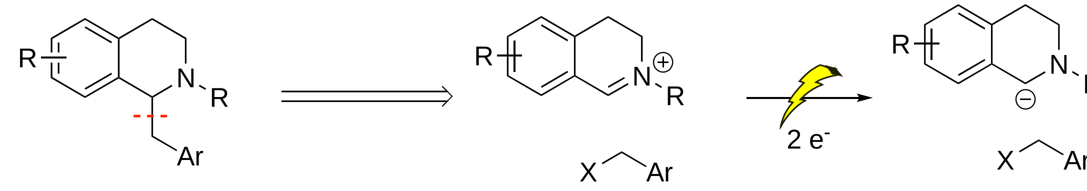
1) Little *et al. Tet. Lett.* **1990**, *31*, 485

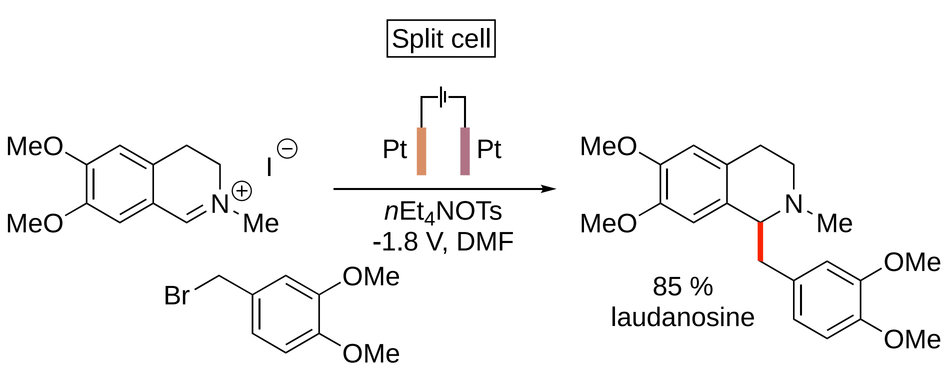
C=N Reduction

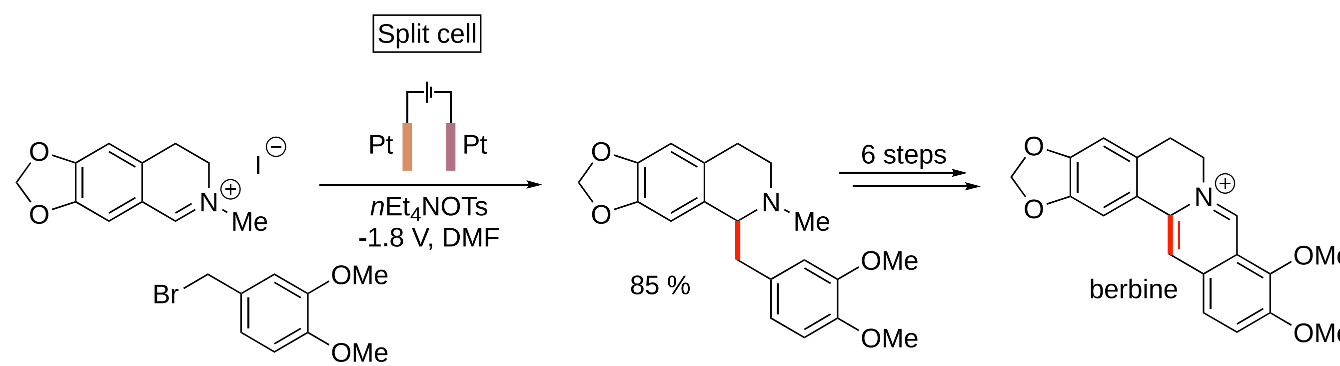
Shono, 1978-81[1-3]

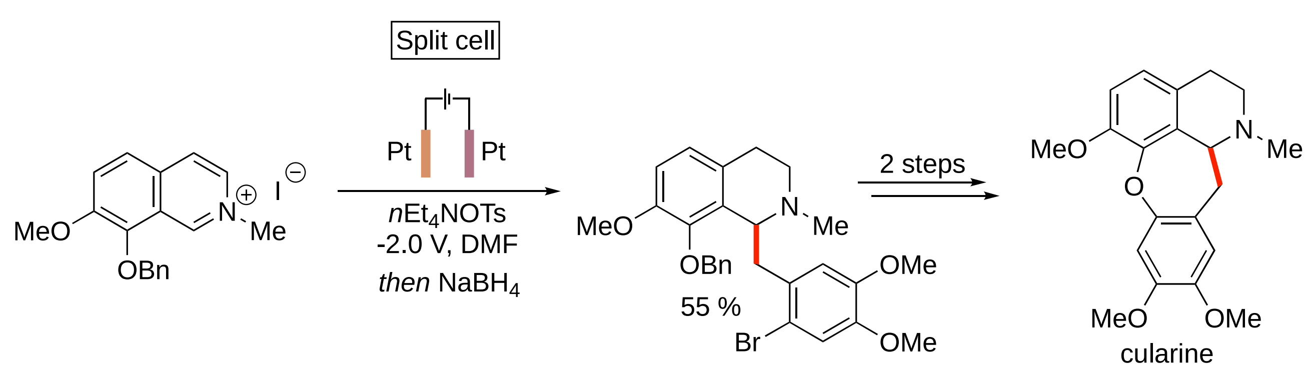


Two intrinsically electrophilic FGs





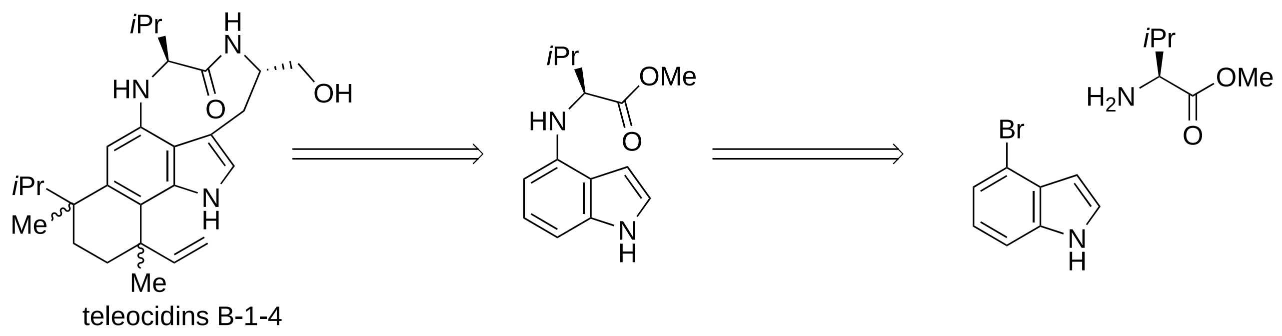


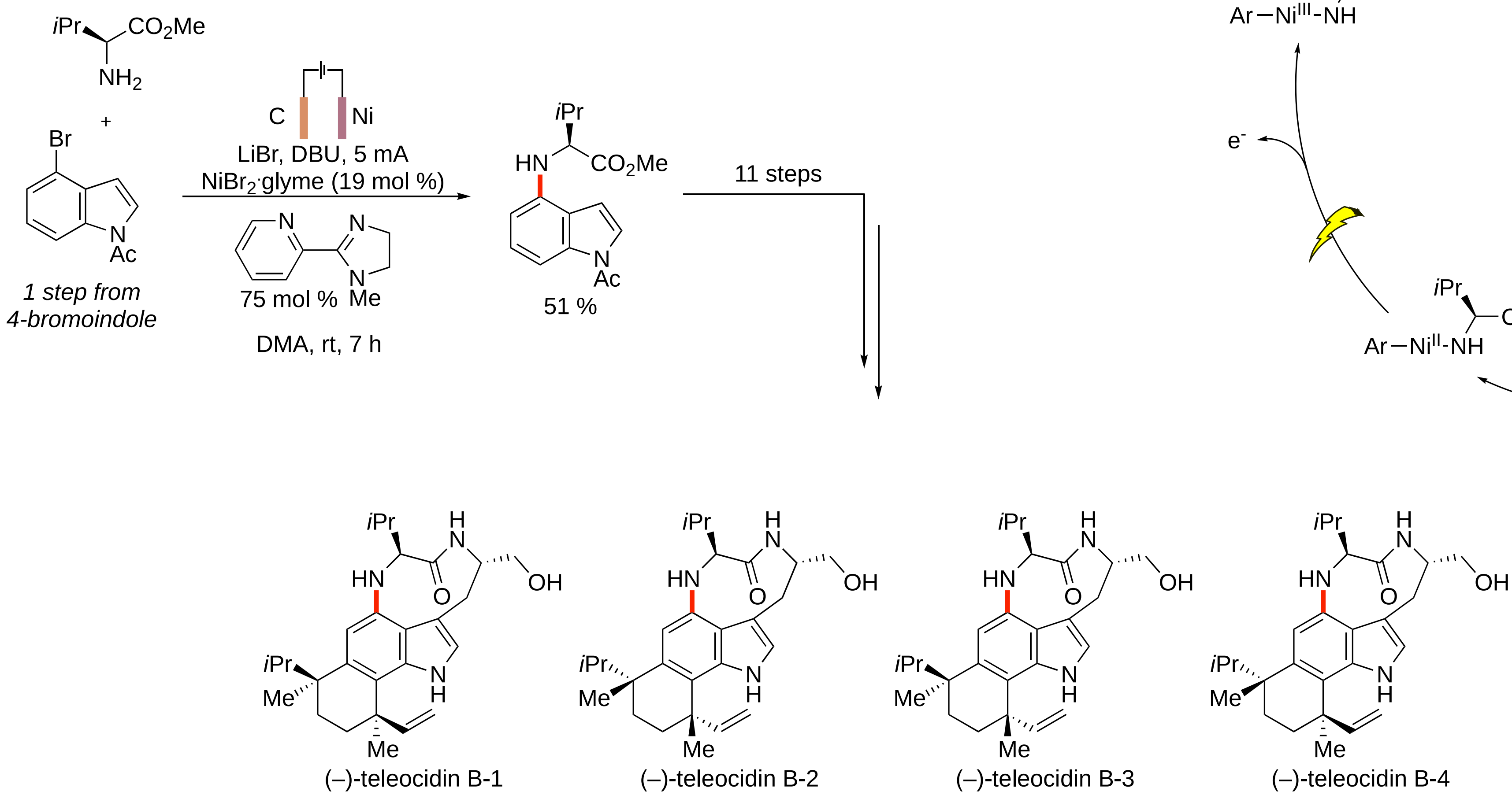


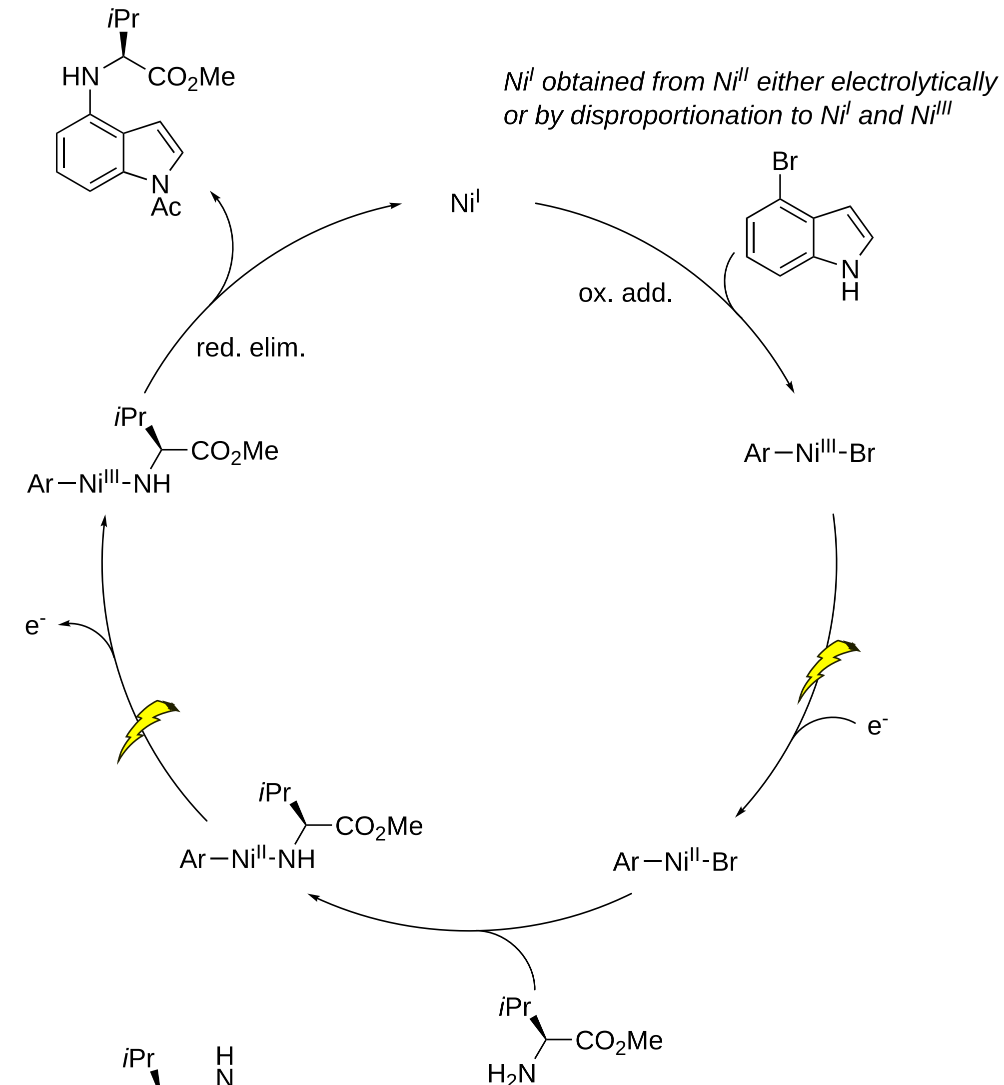
1) Shono *et al. Tet. Lett.* **1978**, *48*, 4819
2) Shono *et al. Tet. Lett.* **1980**, *50*, 3073
3) Shono *et al. Tet. Lett.* **1981**, *51*, 2385

e-Amination

Baran, 2019[1]



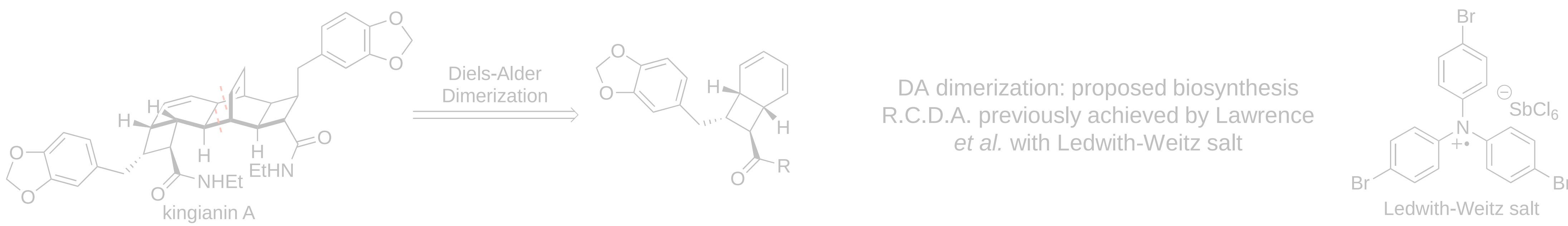


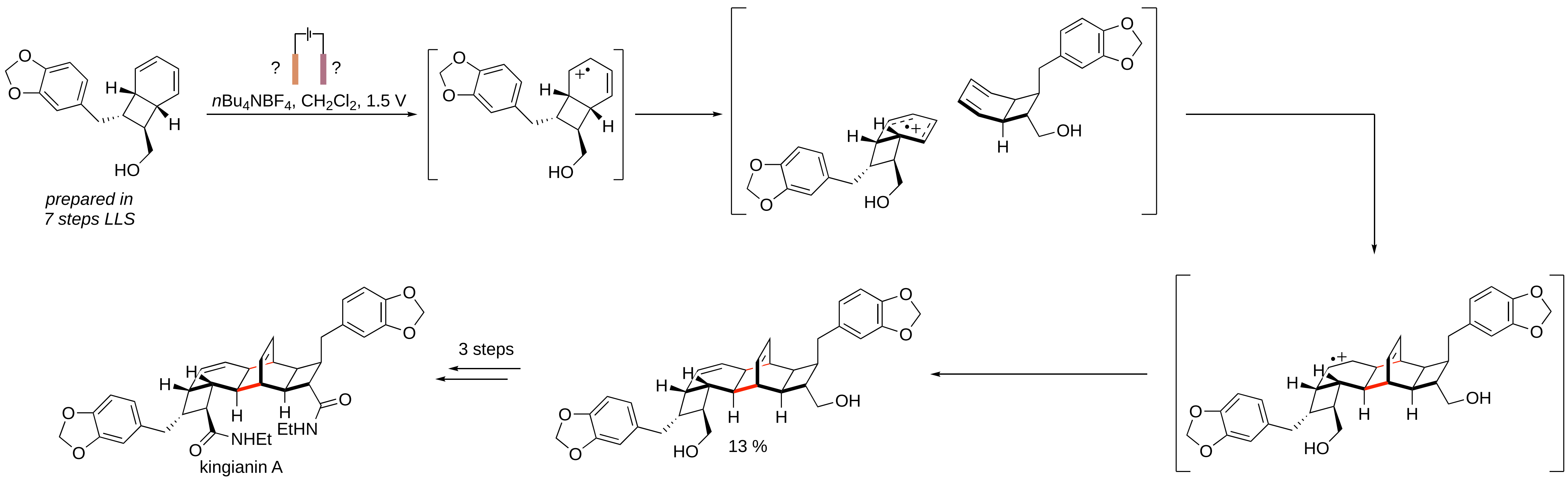


1) Baran *et al. J. Am. Chem. Soc.* **2019**, *141*, 1494

Radical Cation Diels-Alder Reaction

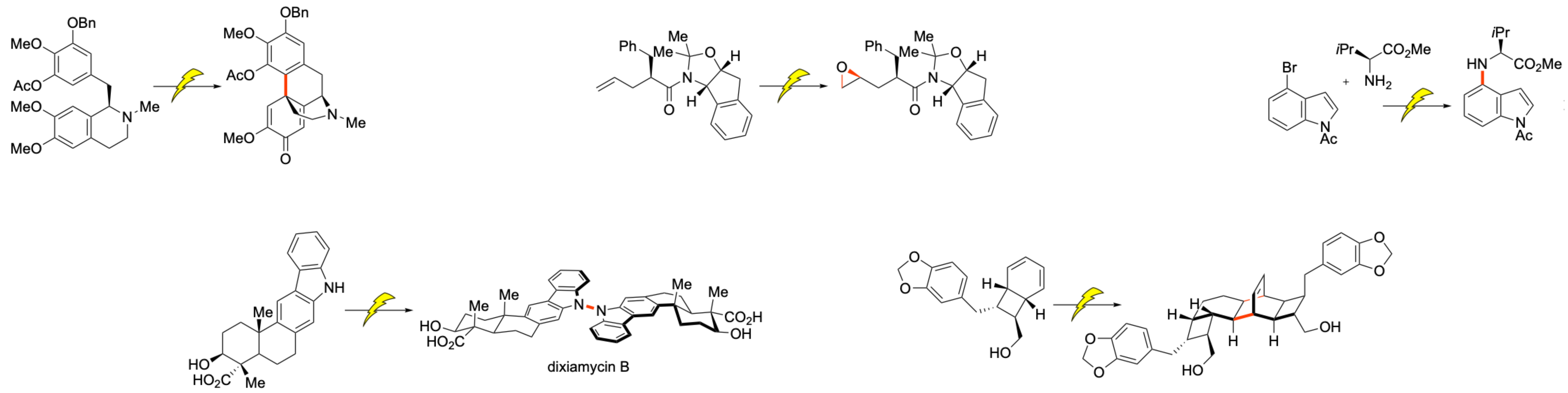
Moses, 2014[1]





1) Moses *et al. Chem. Commun.* **2014**, *50*, 12523

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**

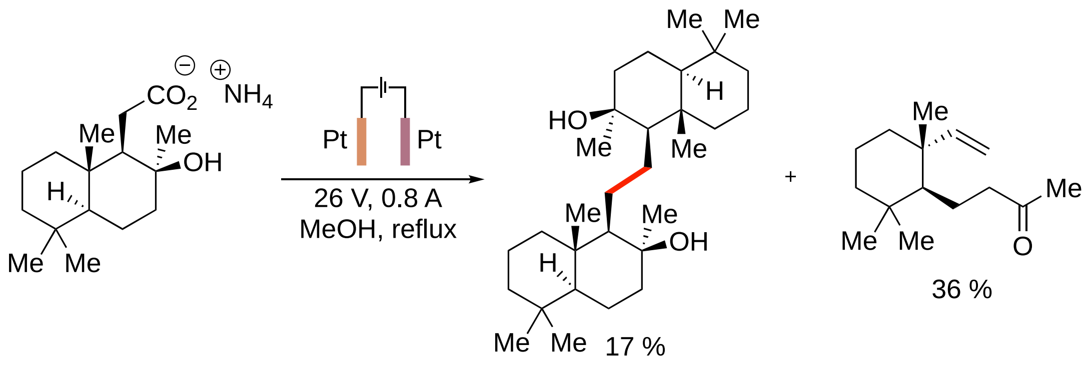
Stoichiometric Oxidants/Reductants Avoided

- **Atom economic electron transfer**

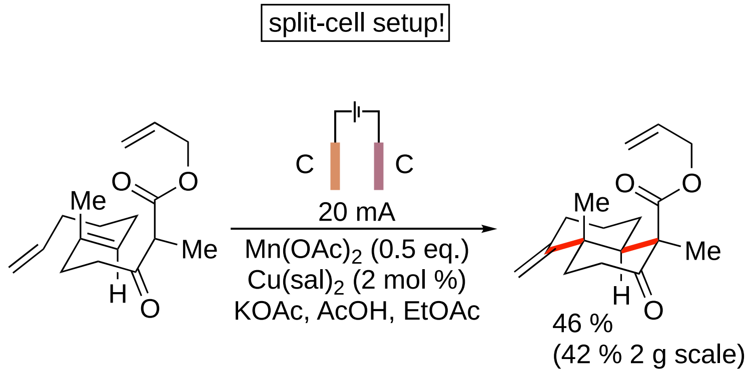
Further Promotion/Education Needed!

- **Electrochemistry still remains a niche option**

Explain the formation of the side-product:



Why is a split cell setup necessary for this transformation?

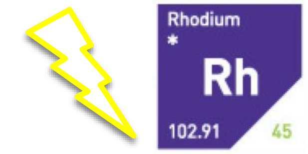


Enantioselective Radical Reactions via Transition Metal Catalysis

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

Simonet-Davin Raphaël
11/05/2020 - Frontiers

Metals Considered



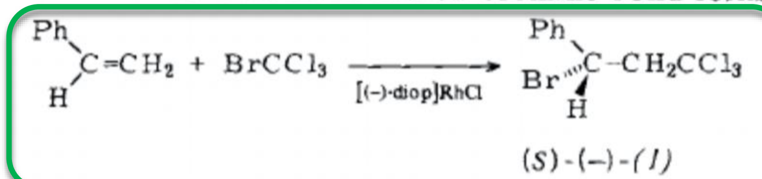
Historical Background

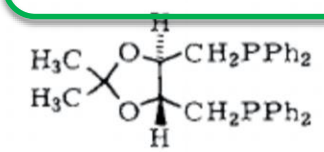
1981, Osaka University, Japan

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

By *Shinji Murai, Ryoji Sugise,* and *Noboru Sonoda*[*]

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.

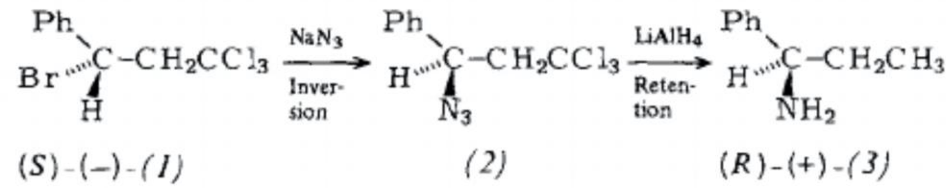




(−)-diop

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.

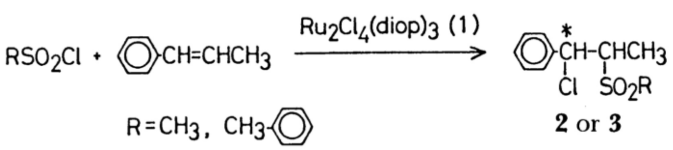
The enantiomeric excess and the absolute configuration were determined in the following way using a sample of *(1)* with $[\alpha]_D = -11.3°$ ($c = 10.3$, C_6H_6) obtained in a separate run. This sample was treated with an excess of NaN_3 to give the azide *(2)*, which was not isolated but directly reduced with $LiAlH_4$ 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 NaN_3 may involve partial racemization[5].

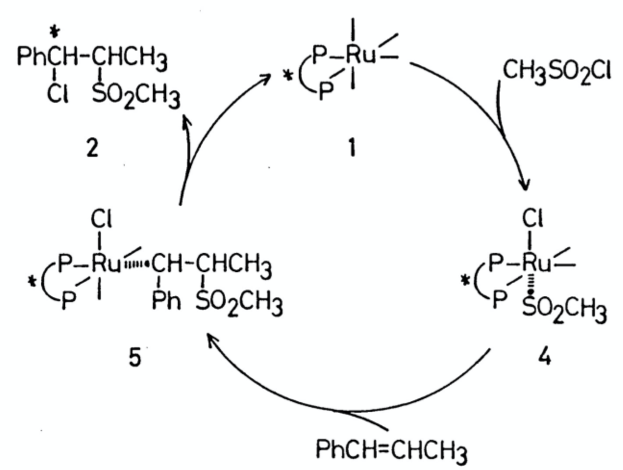


Since various transition metal catalysts for addition of organic halides to olefins are known[6] and a variety of chiral ligands are now available[1], the present result opens up new possibilities for asymmetric synthesis.

1982 → 1983 → 1984 → 1985 → 1986 → 1987 → 1988 →

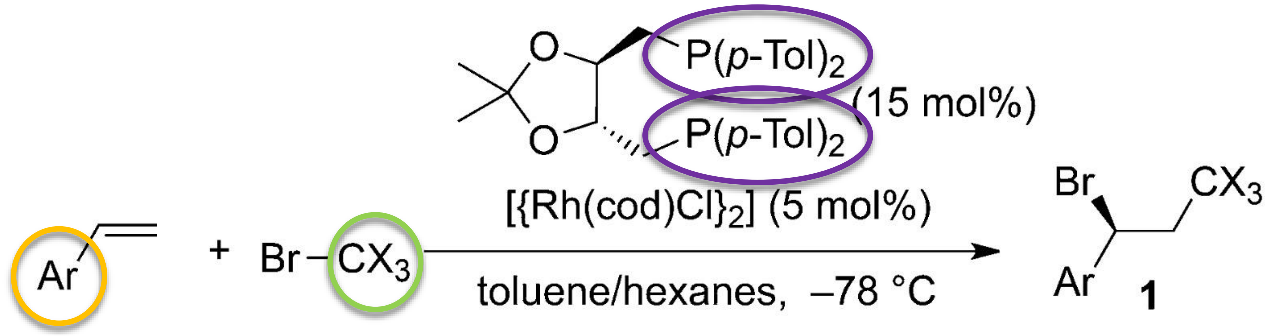
1989, Tokyo University, Japan

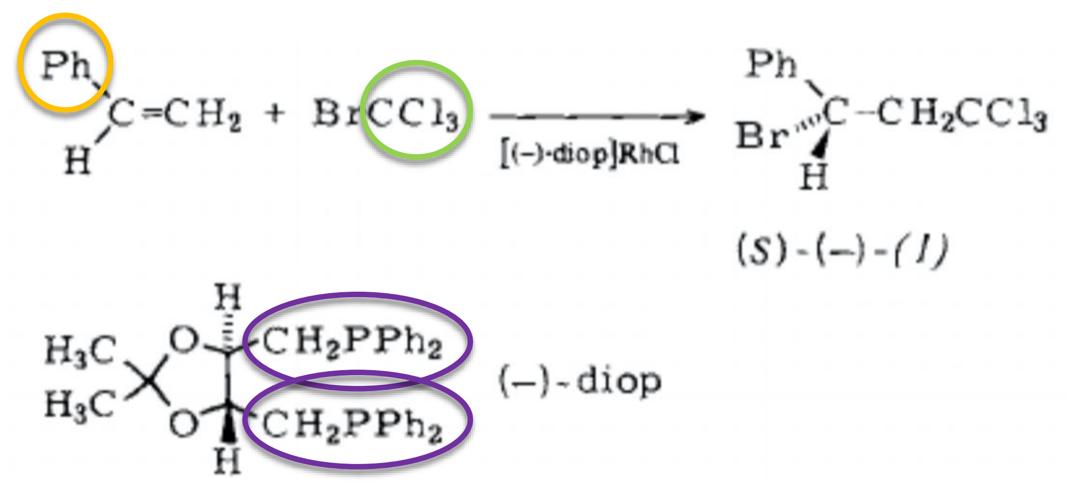




Murai, S.; Sugise, R.; Sonoda, N. *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 475
Kameyama, M.; Kamigata, N.; *Bull. Chem. Soc. Jpn.* **1989**, *62*, 648
To go further: Sibi, M. P.; Manyem, S.; Zimmerman, J. Enantioselective Radical Processes *Chem. Rev.* **2003**, *103*, 3263

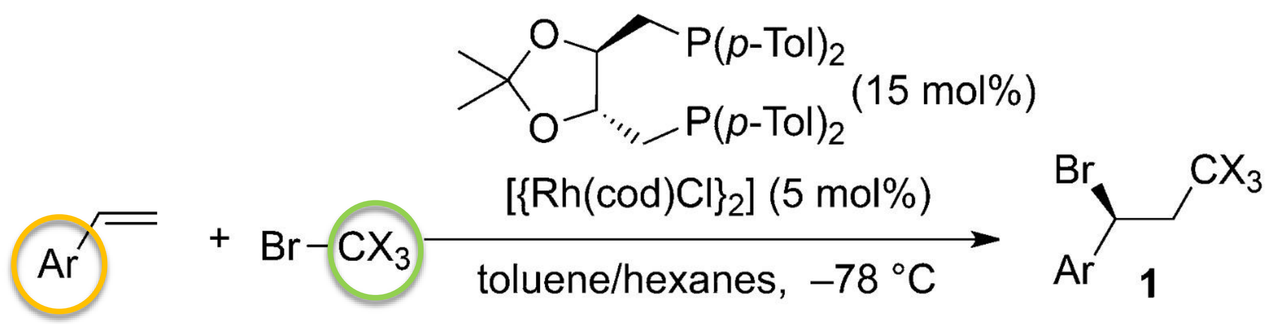
Addition of CX_4 Reagents to Olefins

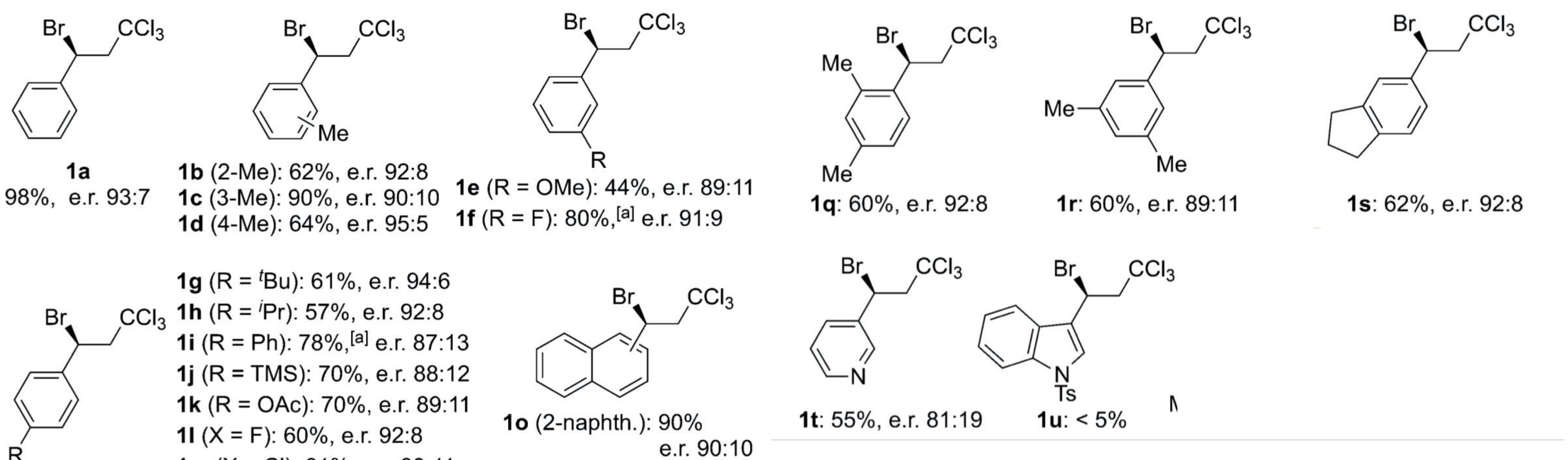




Chen, B.; Fang, C.; Liu, P.; Ready, J. M. *Angew. Chem. Int. Ed.* **2017**, *56,* 8780

Addition of CX_4 Reagents to Olefins





1a 98%, e.r. 93:7

1b (2-Me): 62%, e.r. 92:8
1c (3-Me): 90%, e.r. 90:10
1d (4-Me): 64%, e.r. 95:5

1e (R = OMe): 44%, e.r. 89:11
1f (R = F): 80%,[a] e.r. 91:9

1q: 60%, e.r. 92:8

1r: 60%, e.r. 89:11

1s: 62%, e.r. 92:8

1g (R = ^{t}Bu): 61%, e.r. 94:6
1h (R = ^{i}Pr): 57%, e.r. 92:8
1i (R = Ph): 78%,[a] e.r. 87:13
1j (R = TMS): 70%, e.r. 88:12
1k (R = OAc): 70%, e.r. 89:11
1l (X = F): 60%, e.r. 92:8
1m (X = Cl): 61%, e.r. 89:11
1n (X = Br): 58%, e.r. 86:14

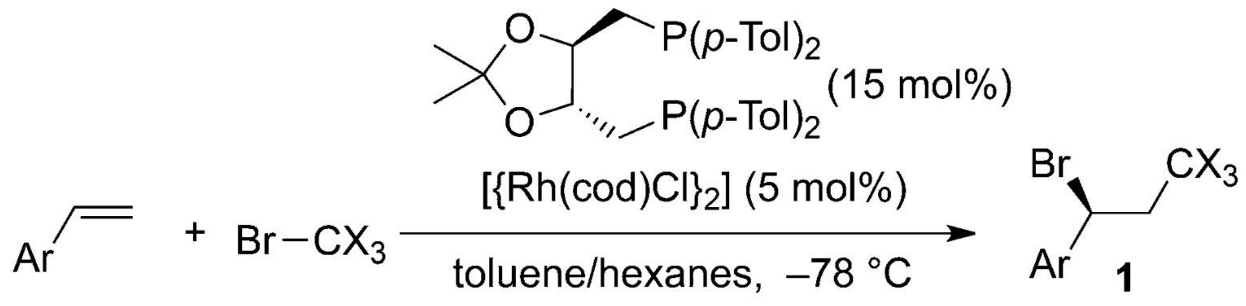
1o (2-naphth.): 90% e.r. 90:10
1p (1-naphth.): <5%

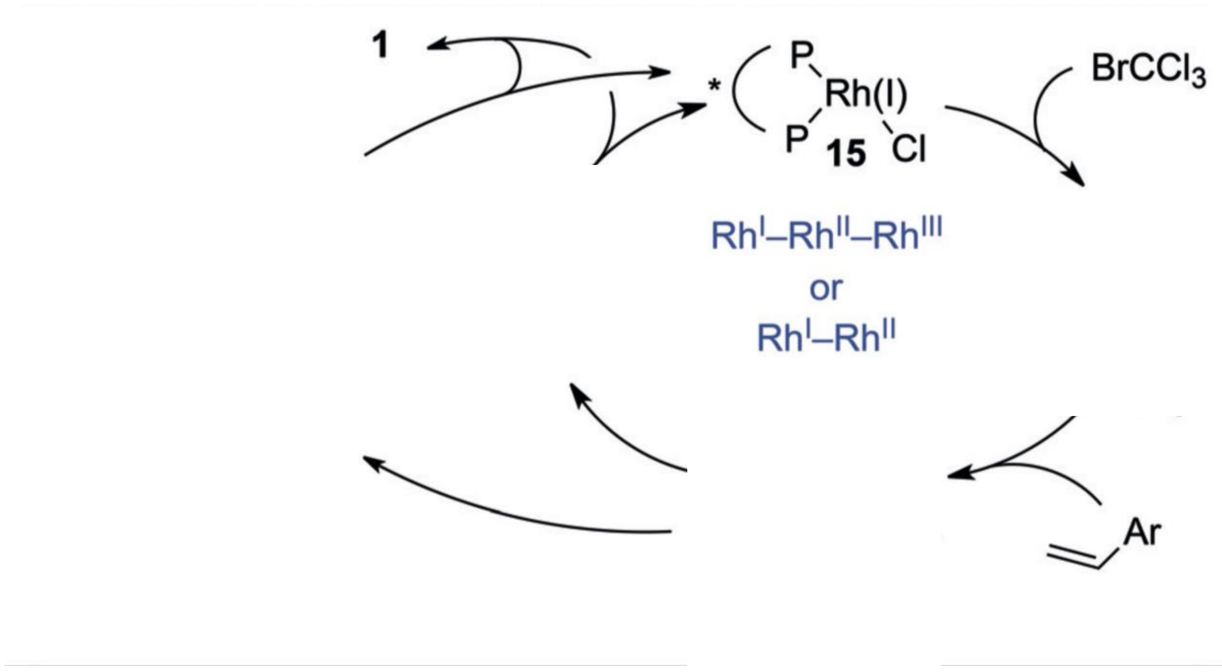
1t: 55%, e.r. 81:19

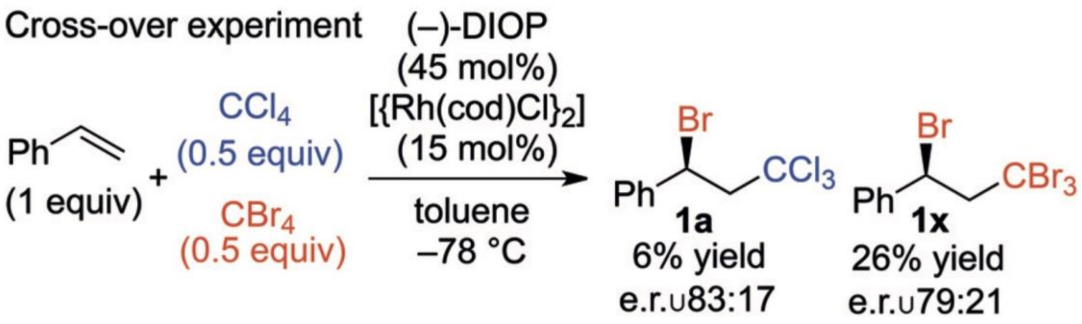
1u: < 5%

Chen, B.; Fang, C.; Liu, P.; Ready, J. M. *Angew. Chem. Int. Ed.* **2017**, *56*, 8780

Addition of CX_4 Reagents to Olefins

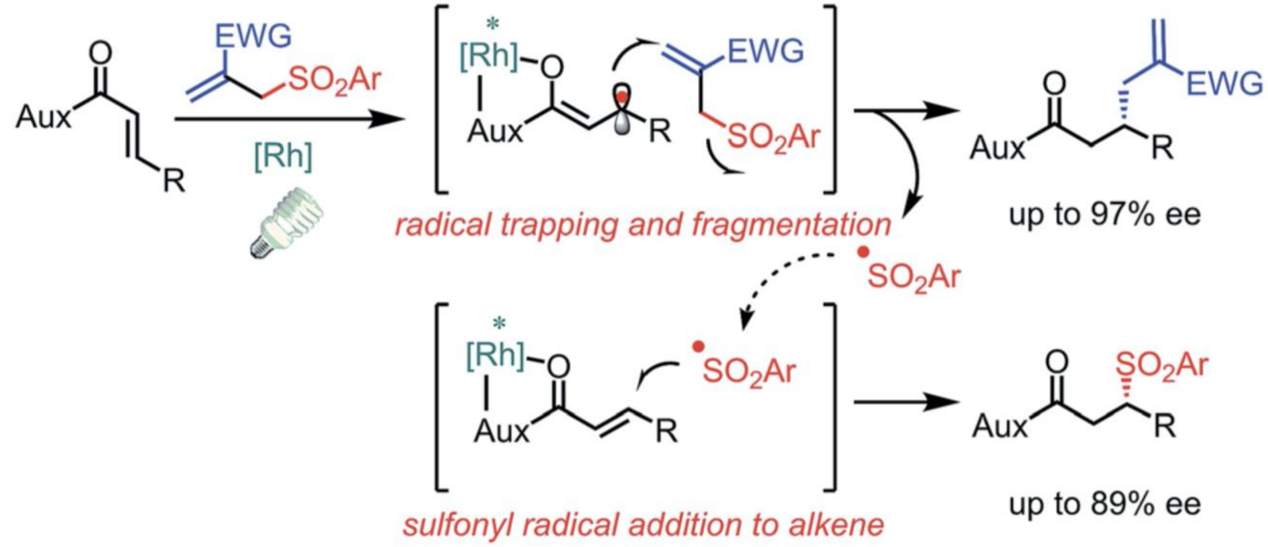


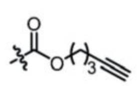
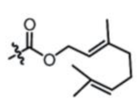
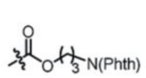




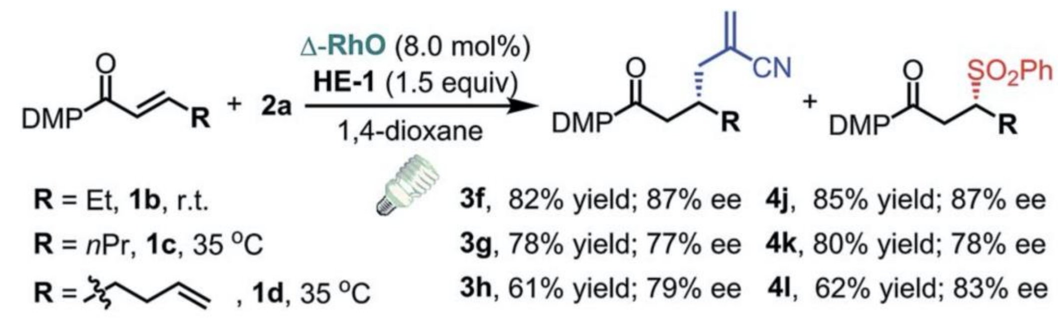
Chen, B.; Fang, C.; Liu, P.; Ready, J. M. *Angew. Chem. Int. Ed.* **2017**, *56*, 8780

One Catalyst – Two Processes

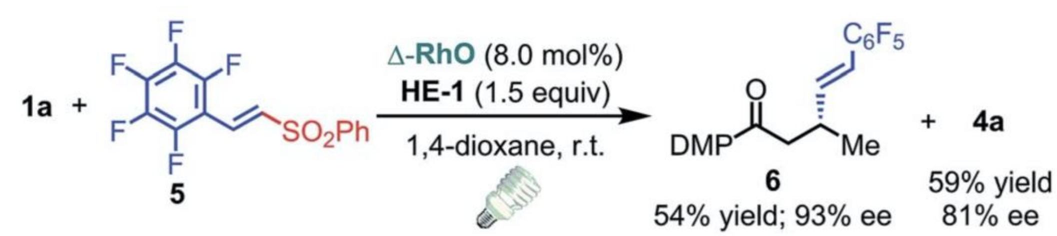


Entry	EWG	Ar	3, Yield[b], ee[c]	4, Yield[b], ee[c]
1	CN	C_6H_5	**3a**, 85%, 96% ee	**4a**, 92%, 85% ee
2	CN	$4\text{-}MeC_6H_4$	**3a**, 68%, 96% ee	**4b**, 70%, 79% ee
3	CN	$4\text{-}BrC_6H_4$	**3a**, 81%, 97% ee	**4c**, 88%, 80% ee
4	CN	$4\text{-}CF_3C_6H_4$	**3a**, 78%, 95% ee	**4d**, 78%, 76% ee
5	CN	$2\text{-}MeC_6H_4$	**3a**, 71%, 95% ee	**4e**, 72%, 86% ee
6[d]	CN	$2,4,6\text{-}Me_3C_6H_2$	**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_6H_5	**3b**, 65%, 94% ee	**4a**, 68%, 84% ee
10[d]	COOEt	$4\text{-}MeOC_6H_4$	**3b**, 65%, 92% ee	**4i**, 63%, 81% ee
11[d]		C_6H_5	**3c**, 60%, 92% ee	**4a**, 69%, 82% ee
12[d]		C_6H_5	**3d**, 62%, 92% ee	**4a**, 72%, 83% ee
13[d]		C_6H_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.



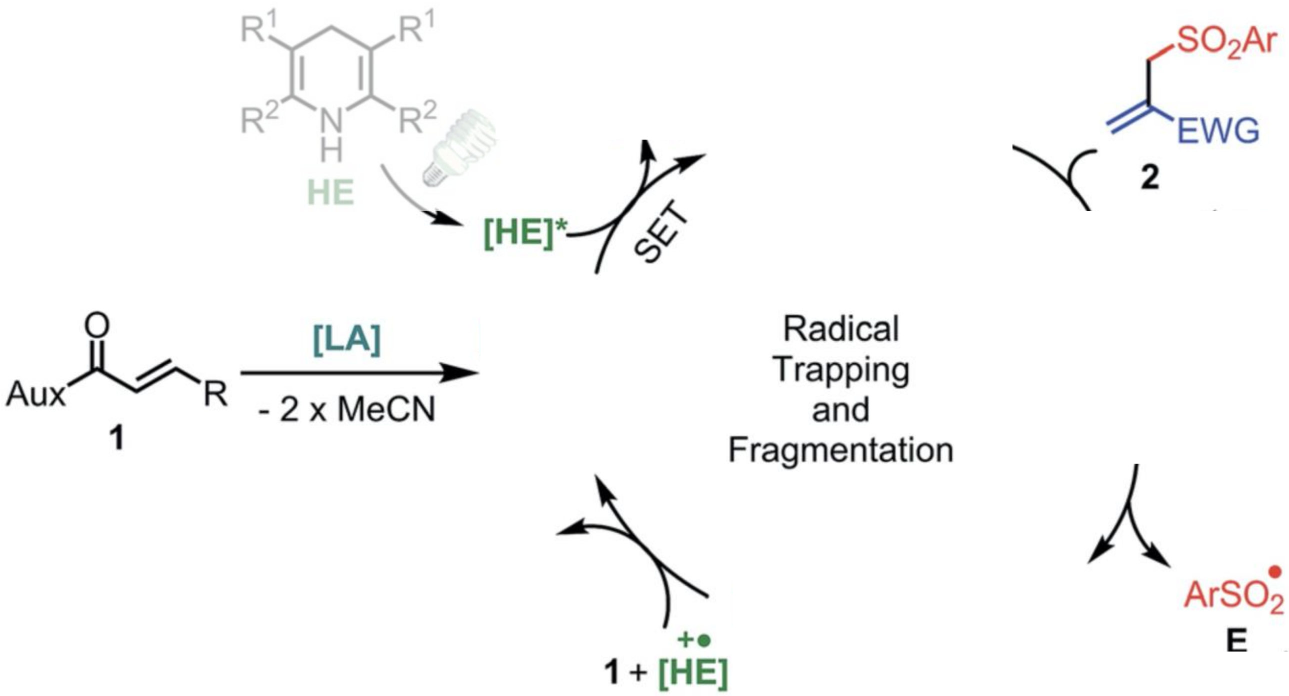
(1)

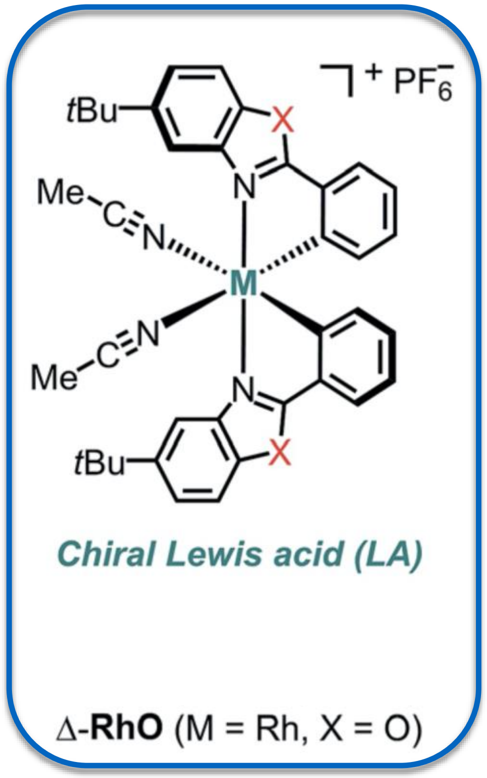


(2)

Huang, X.; Luo, S.; Burghaus, O.; Webster, R. D.; Harms, K.; Meggers, E. *Chem. Sci.* **2017**, *8,* 7126

One Catalyst – Two Processes

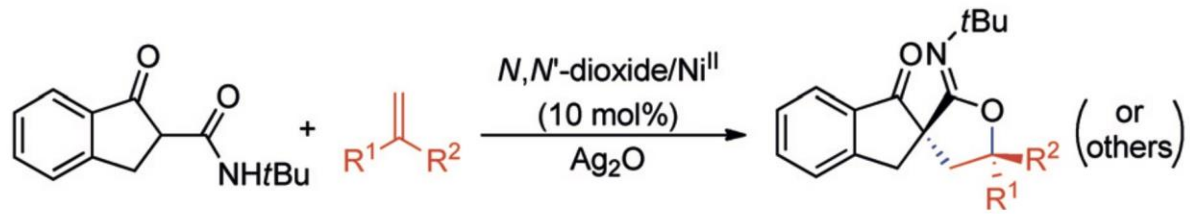


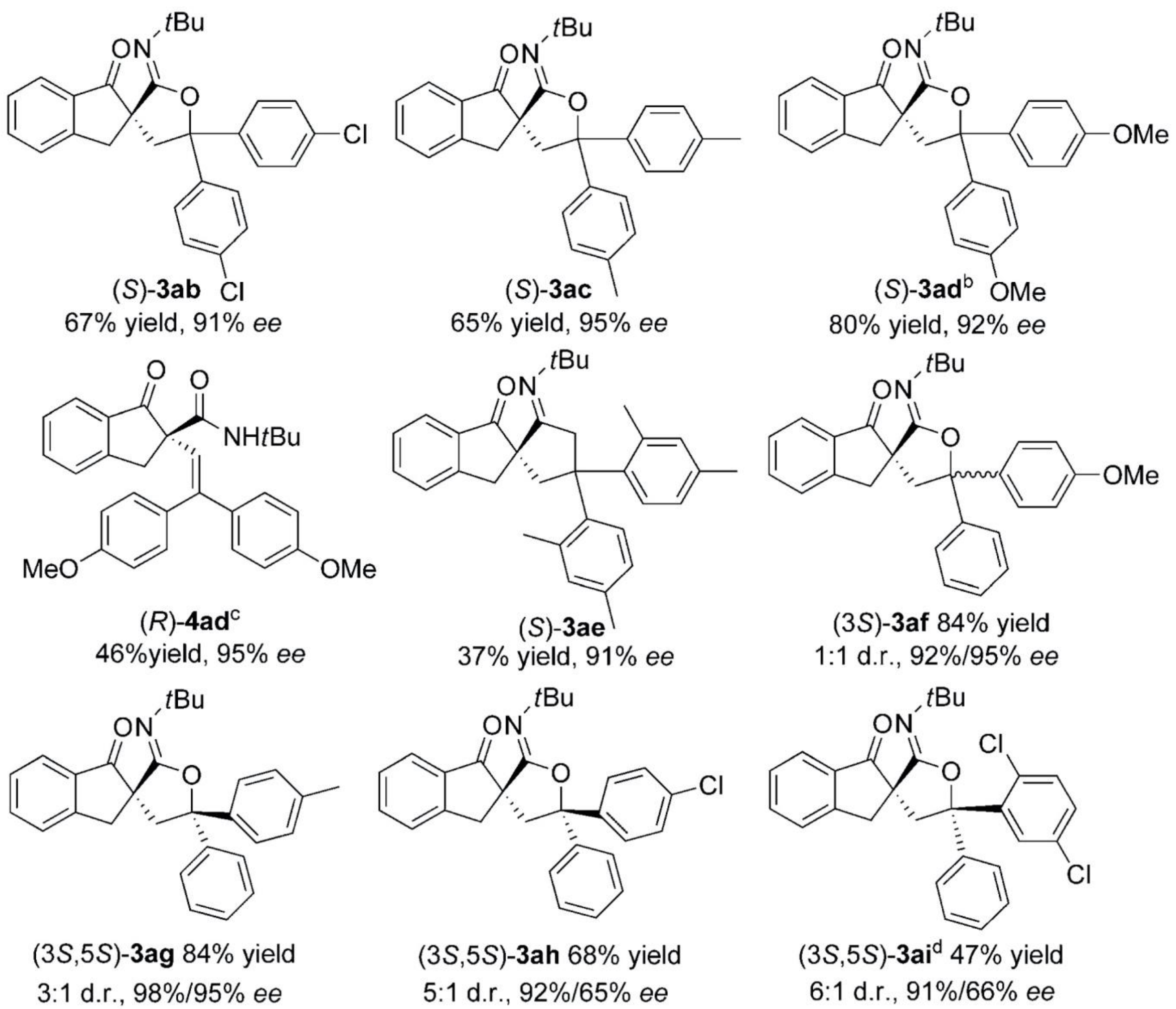


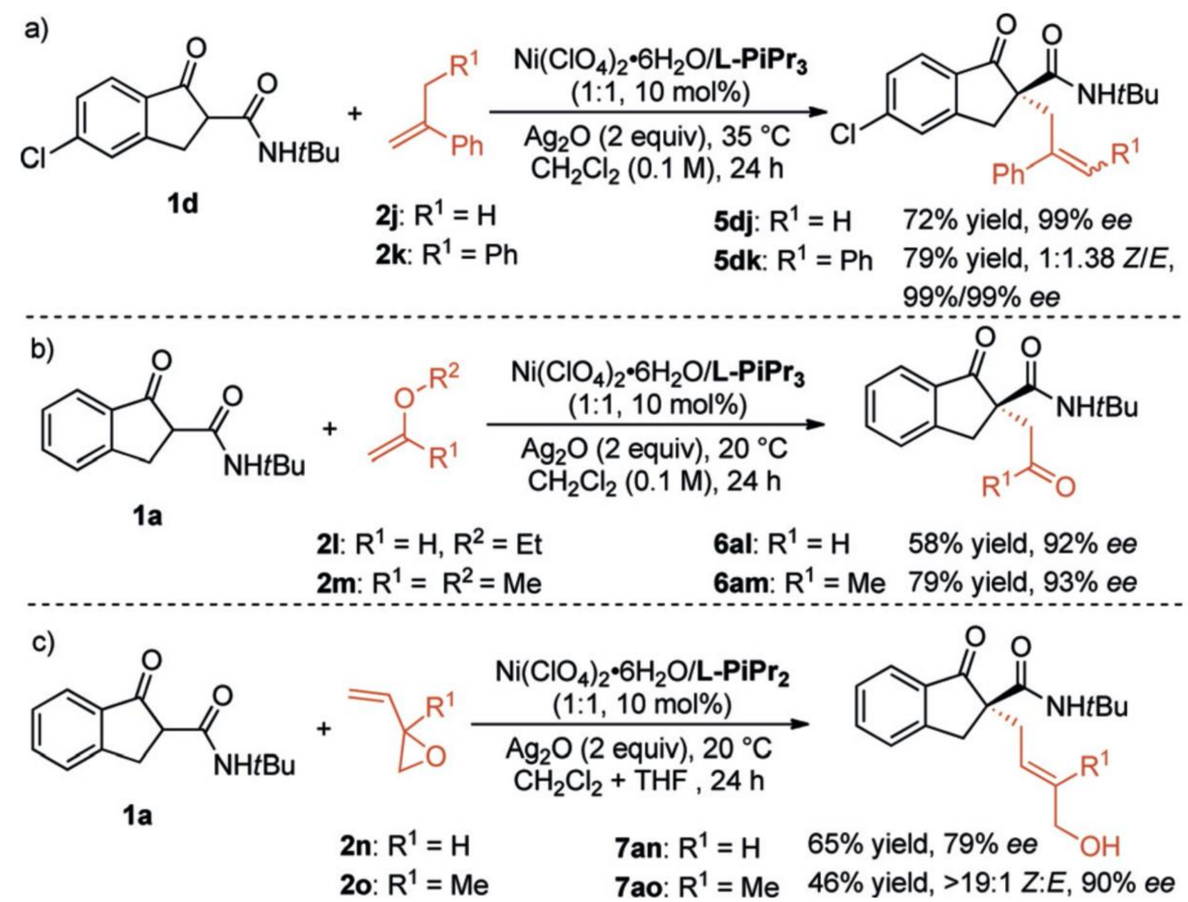
Huang, X.; Luo, S.; Burghaus, O.; Webster, R. D.; Harms, K.; Meggers, E. *Chem. Sci.* **2017**, *8*, 7126

Radical-Polar Crossover Reactions

Nickel
Ni
58.69
28



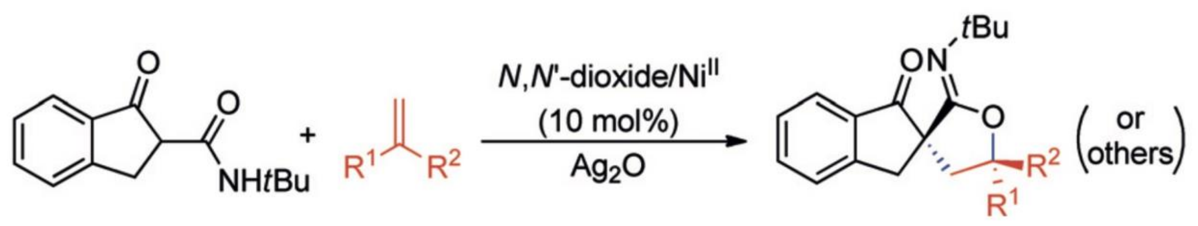


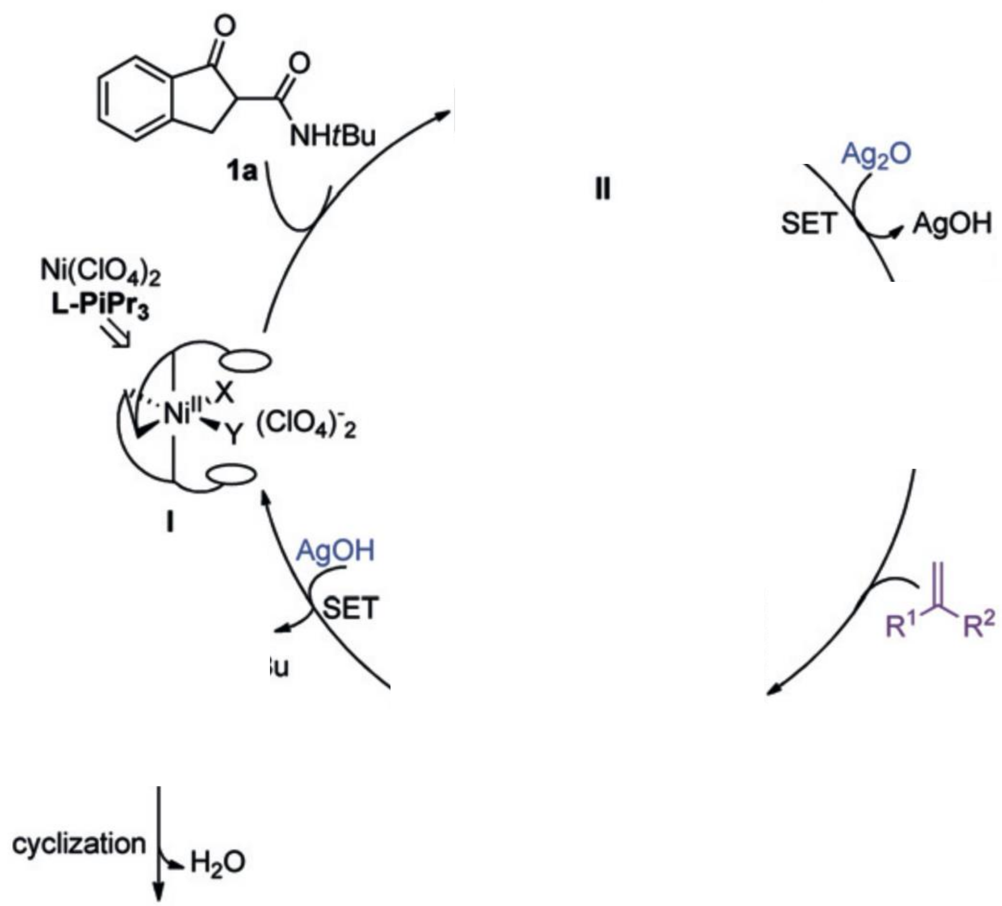


EPFL

Zhang, X.; Wu, W.; Cao, W.; Yu, H.; Xu, X.; Liu, X.; Feng, X. *Angew. Chem. Int. Ed.* **2020**, *59*, 4846

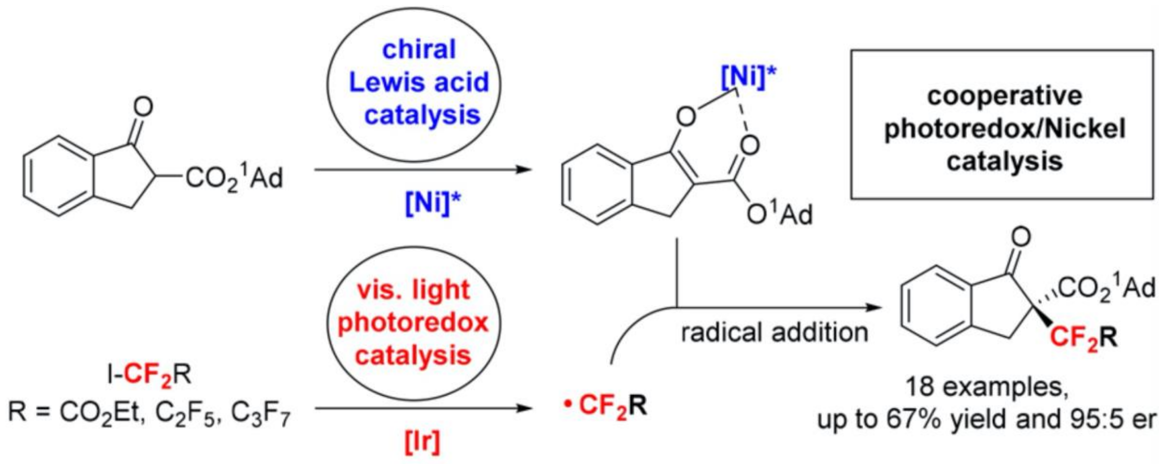
Radical-Polar Crossover Reactions

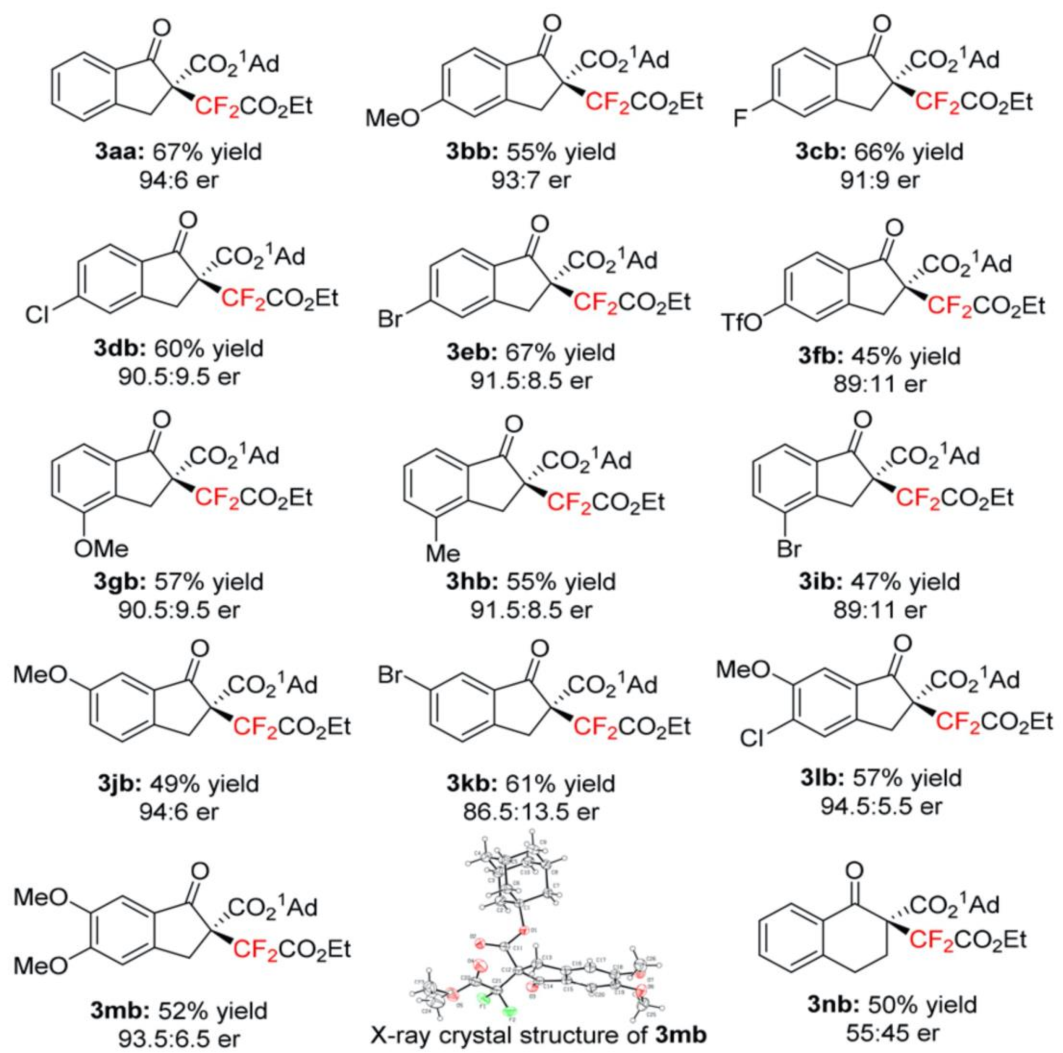




Zhang, X.; Wu, W.; Cao, W.; Yu, H.; Xu, X.; Liu, X.; Feng, X. *Angew. Chem. Int. Ed.* **2020**, *59,* 4846

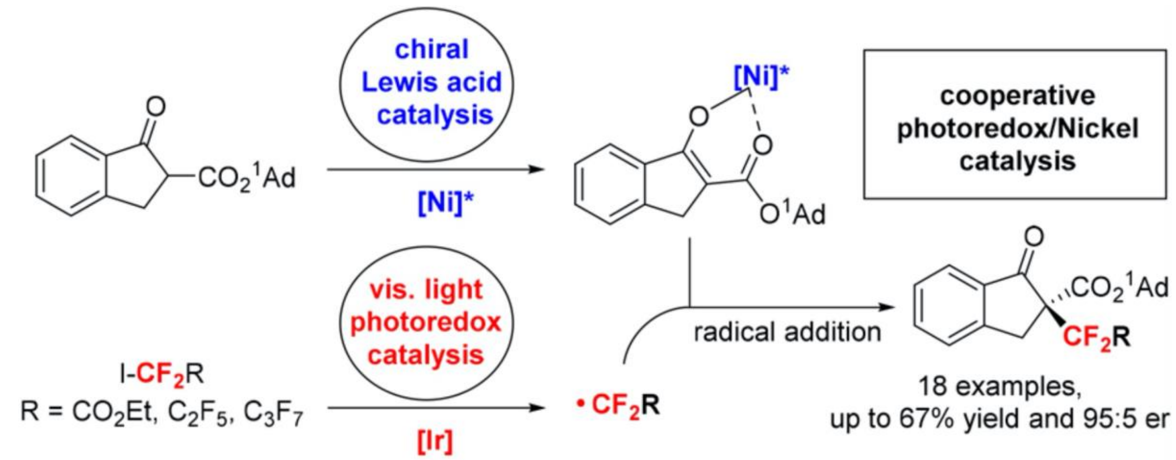
Difluoroalkylation of β-Ketoesters

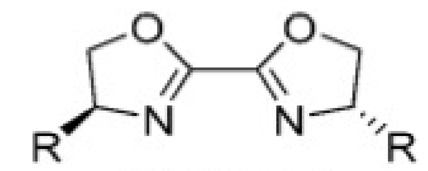




Liu, J.; Ding, W.; Zhou, Q.-Q.; Liu, D.; Lu, L.-Q.; Xiao, W.-J. *Org. Lett.* **2018**, *20,* 461

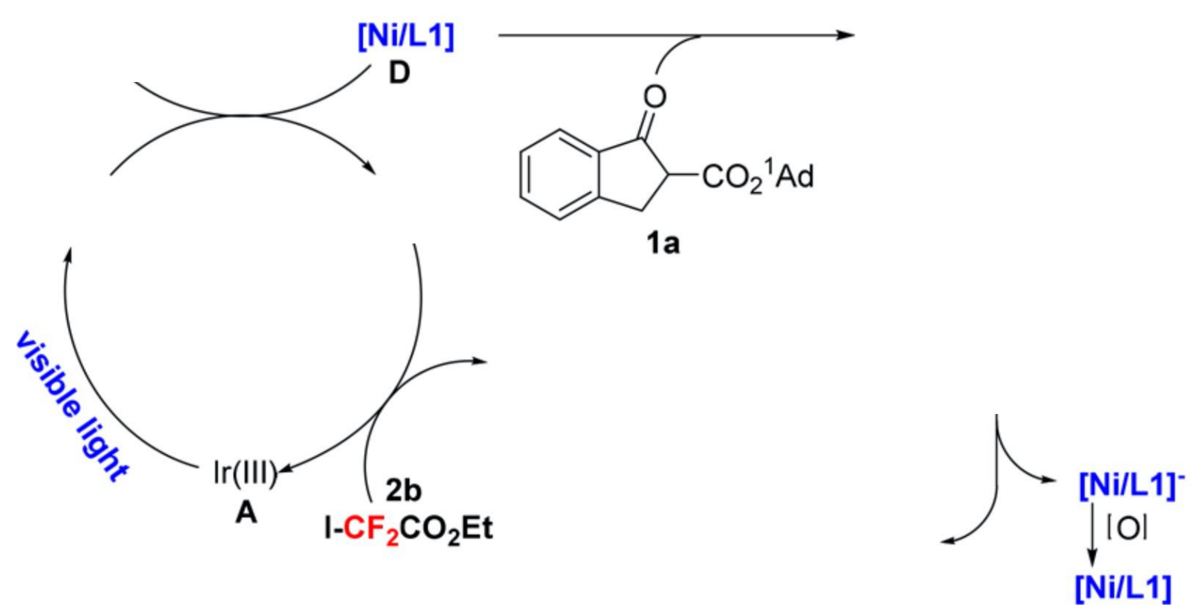
Difluoroalkylation of β-Ketoesters





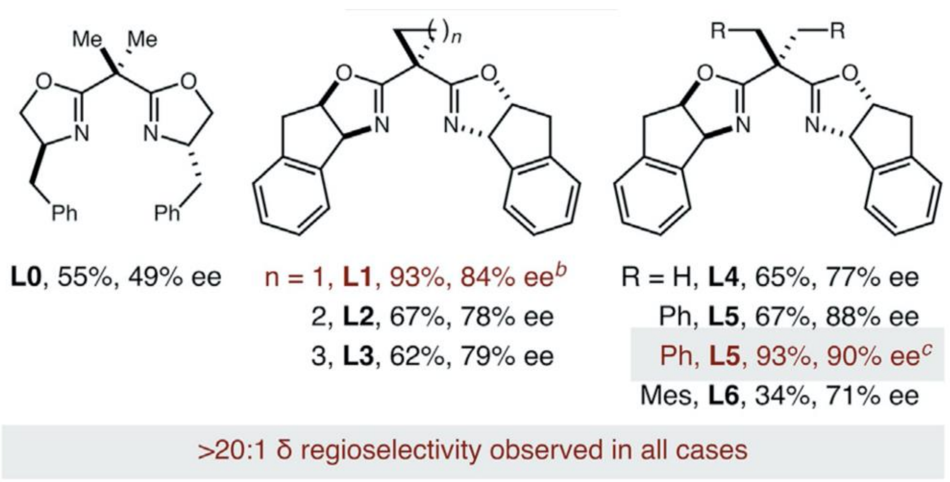
L1: R = Bn
L2: R = ^{i}Pr

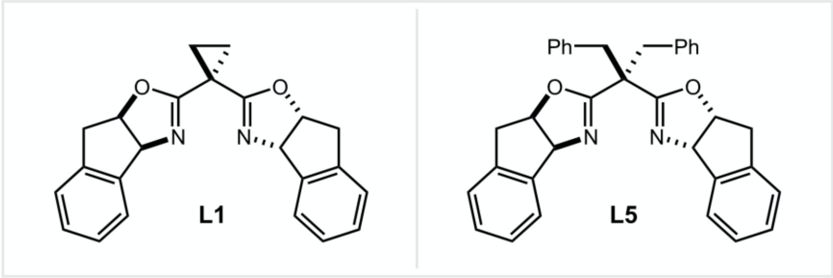
$Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$



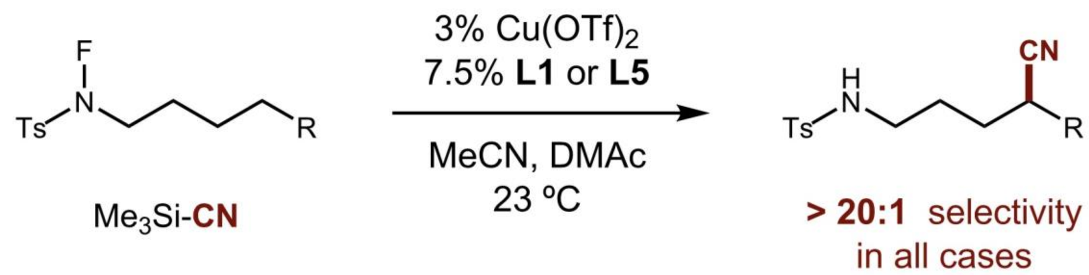
Liu, J.; Ding, W.; Zhou, Q.-Q.; Liu, D.; Lu, L.-Q.; Xiao, W.-J. *Org. Lett.* **2018**, *20,* 461

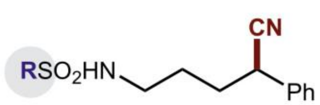
Acyclic Amines Cyanation



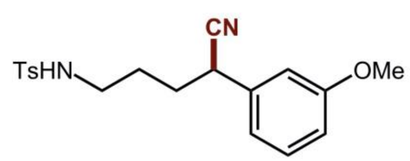


Acyclic Amines Cyanation

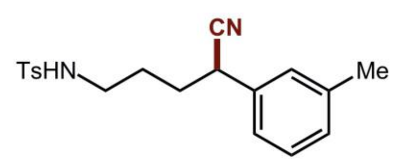




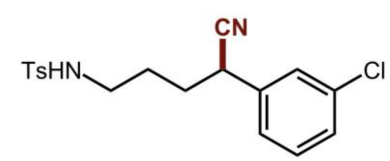
R = *p*-MePh, **1**, 89%, **90% ee**
p-OMePh, **2**, 67%, **92% ee**



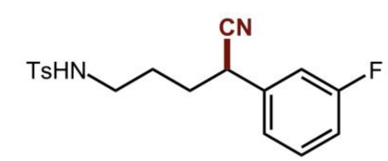
3, 82%, **92% ee**



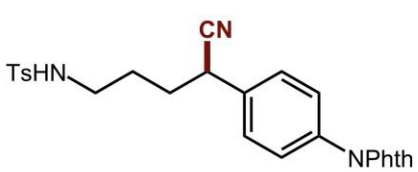
4, 84%, **88% ee**



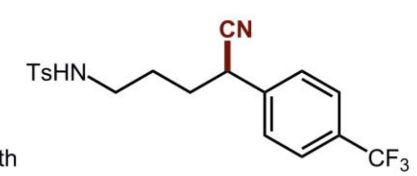
5, 78%, **89% ee**



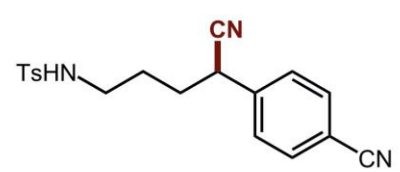
6, 66%, **90% ee**



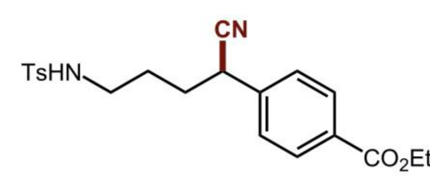
7, 83%, **91% ee**



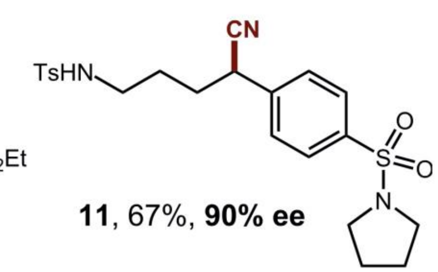
8, 91%, **91% ee**



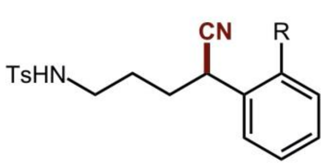
9, 95%, **95% ee**



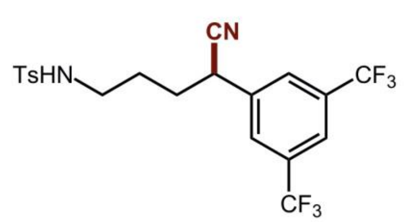
10, 56%, **93% ee**



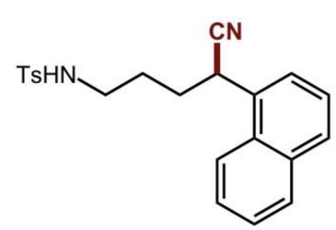
11, 67%, **90% ee**



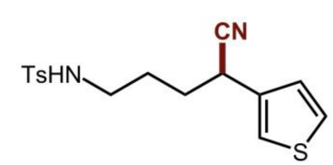
R = Me, **12**, 76%, **86% ee**
F, **13**, 68%, **89% ee**



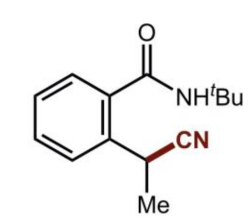
14, 69%, **87% ee**



15, 80%, **92% ee**



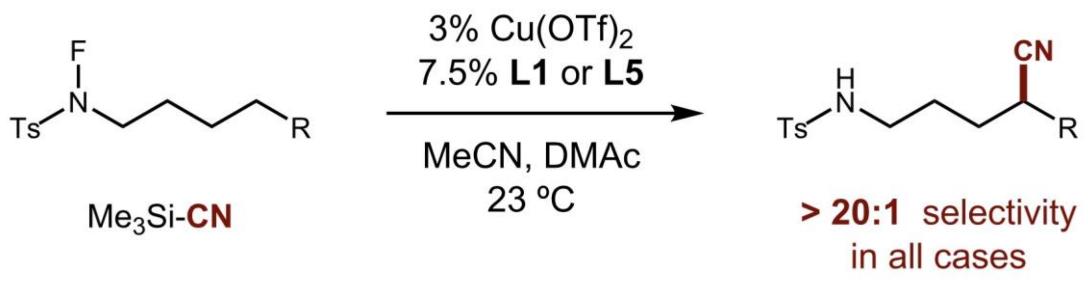
16, 70%, **92% ee**

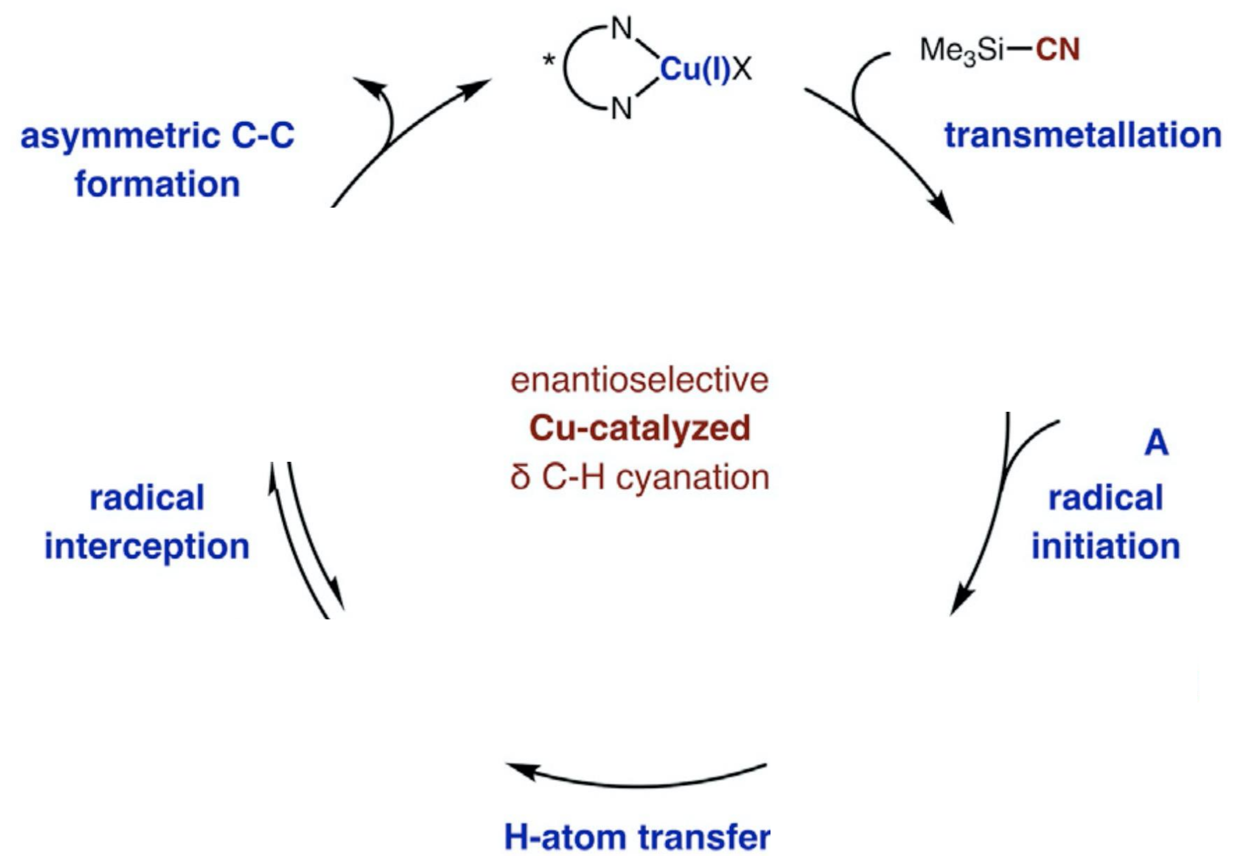


17, 82%, **93% ee**

Zhang, Z.; Zhang, X.; Nagib, D. A. *Chem.* **2019**, *5*, 3127

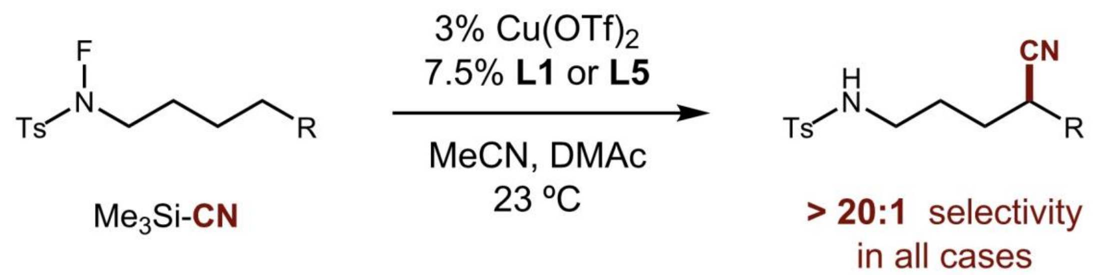
Acyclic Amines Cyanation

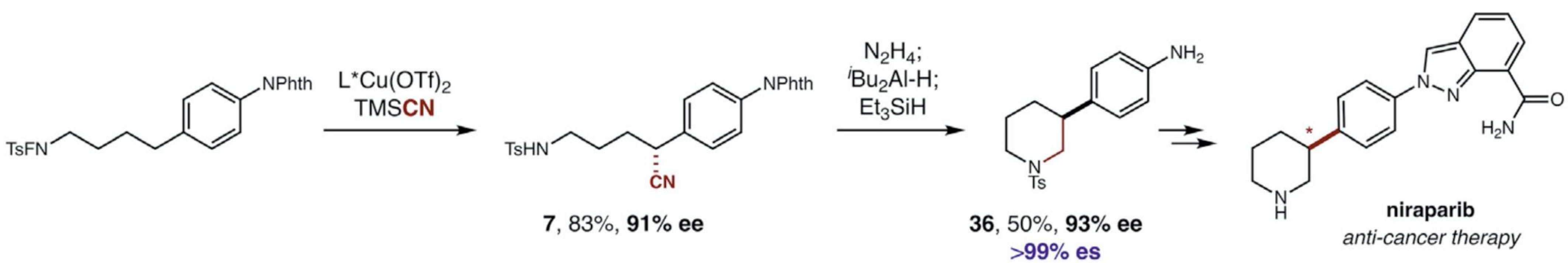




Zhang, Z.; Zhang, X.; Nagib, D. A. *Chem.* **2019**, *5*, 3127

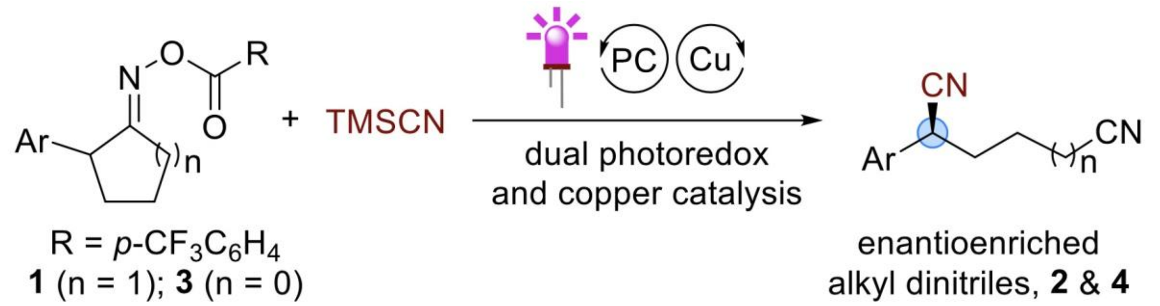
Acyclic Amines Cyanation

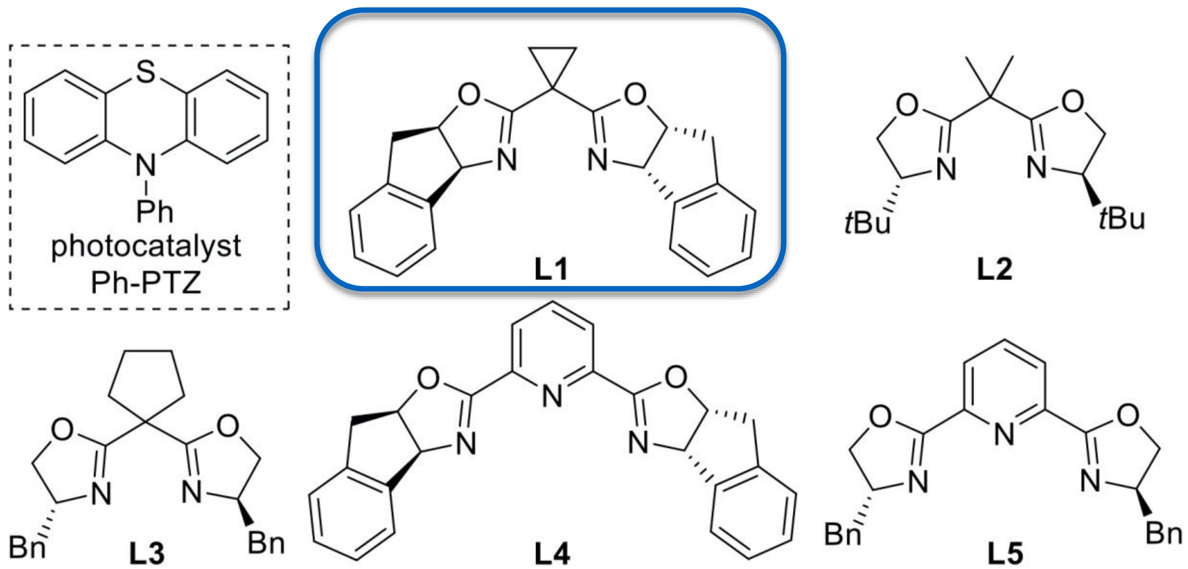




Zhang, Z.; Zhang, X.; Nagib, D. A. *Chem.* **2019**, *5*, 3127

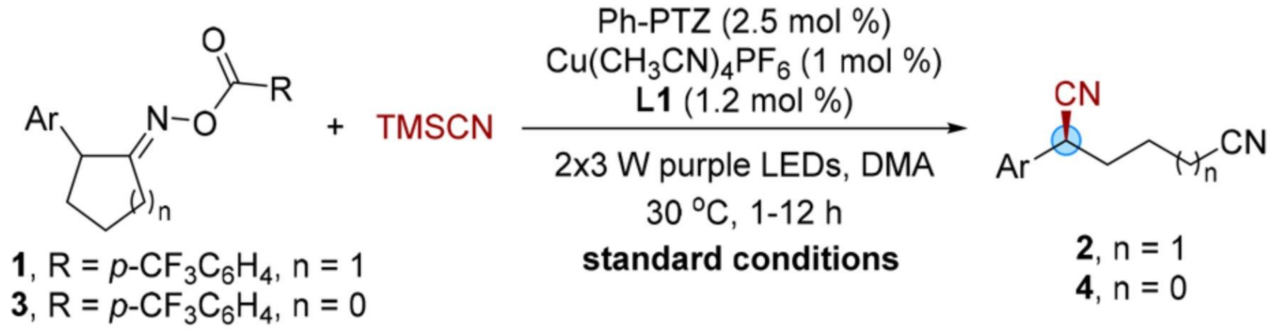
Ring-Opening Cyanation of Oxime

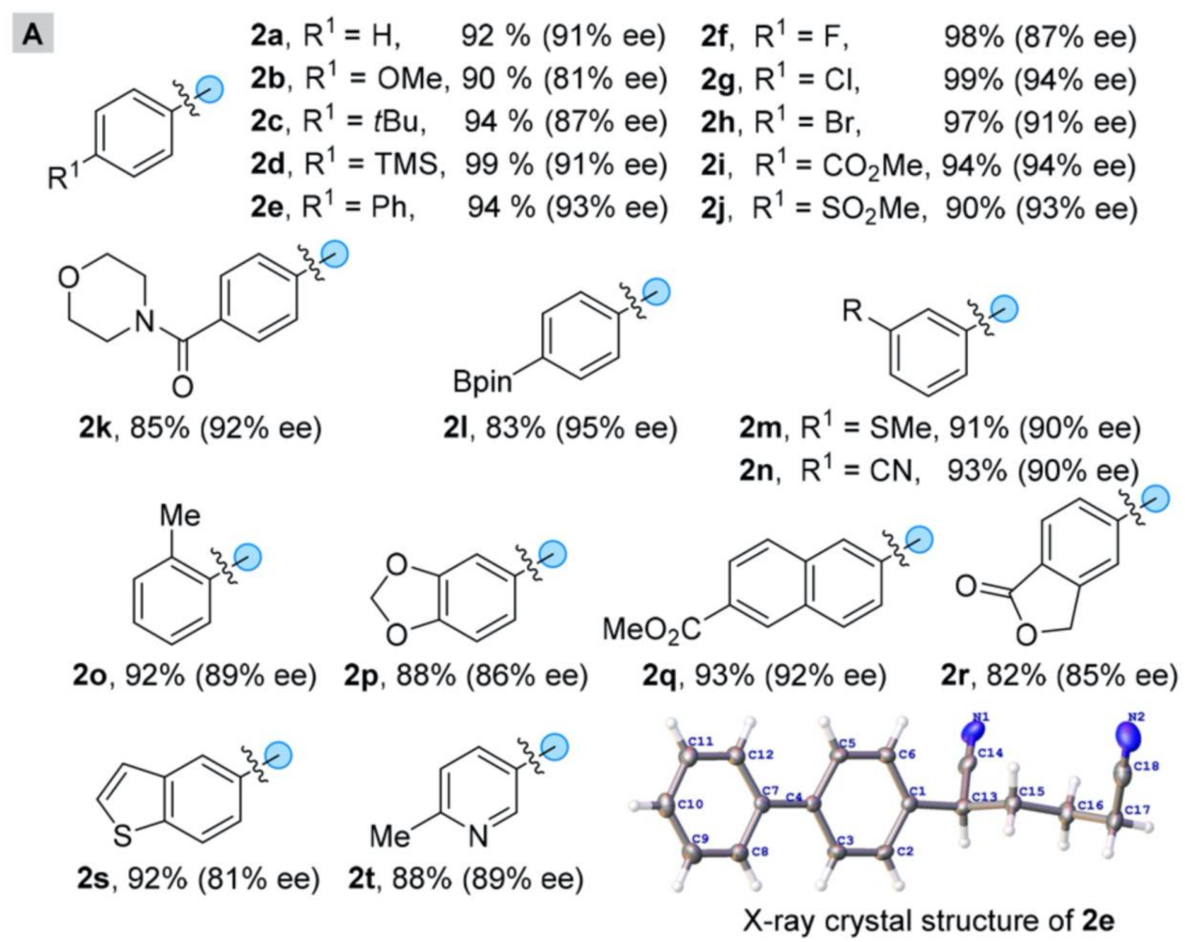




Chen, J.; Wang, P.-Z.; Lu, B.; Liang, D.; Yu, X.-Y.; Xiao, W.-J.; Chen, J.-R. *Org. Lett.* **2019**, *21,* 9763

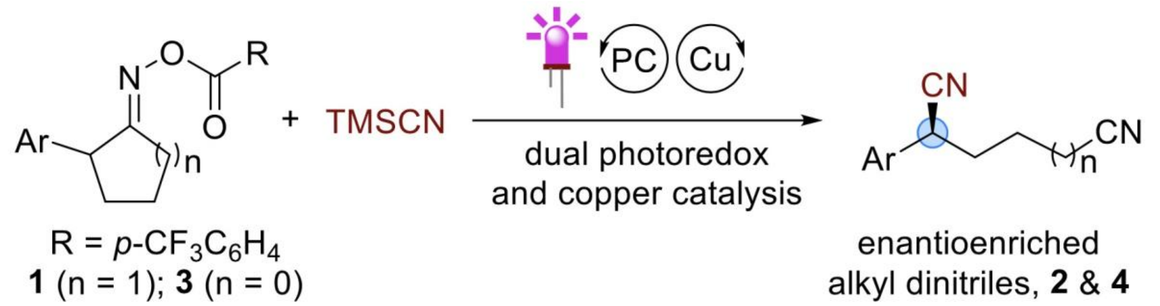
Ring-Opening Cyanation of Oxime

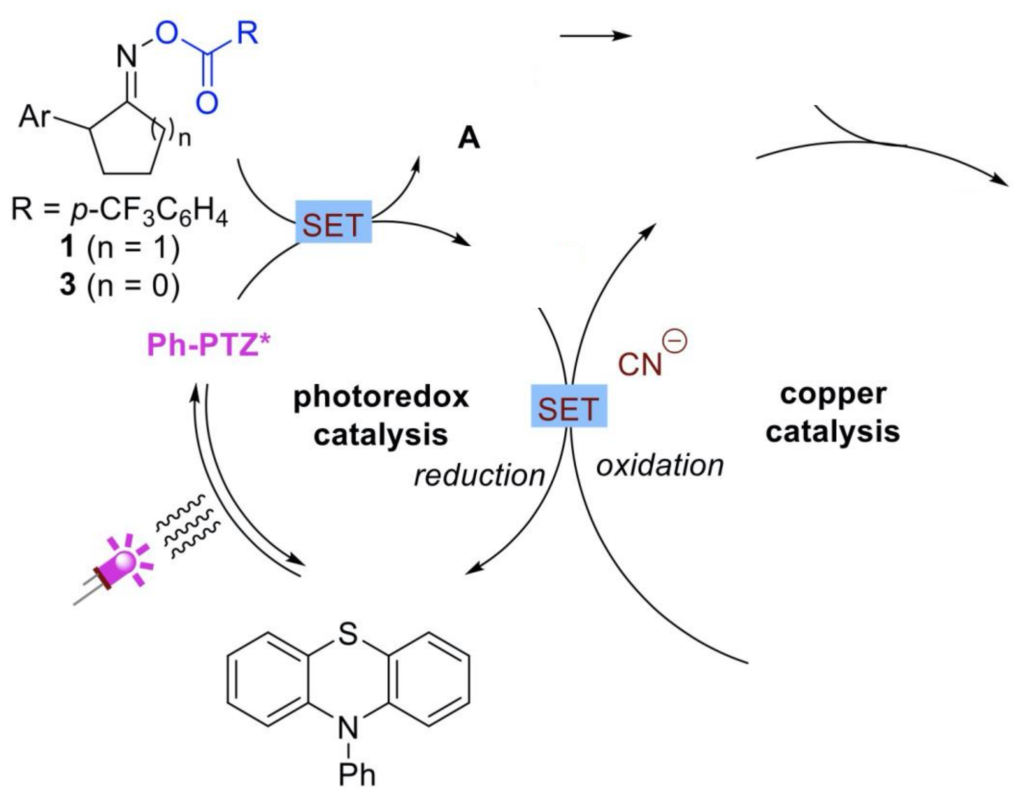




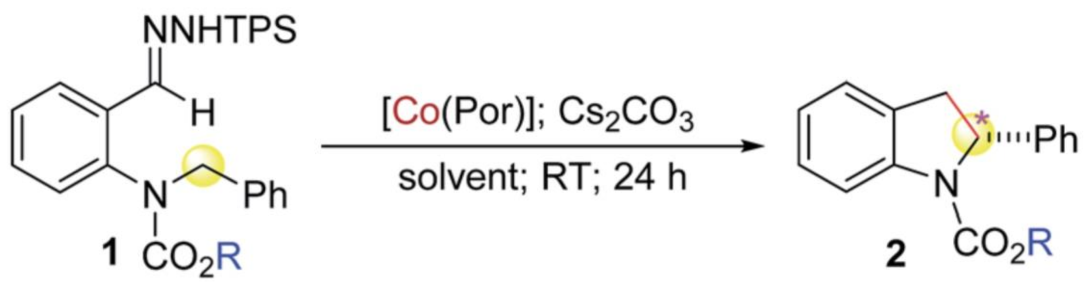
Chen, J.; Wang, P.-Z.; Lu, B.; Liang, D.; Yu, X.-Y.; Xiao, W.-J.; Chen, J.-R. *Org. Lett.* **2019**, *21*, 9763

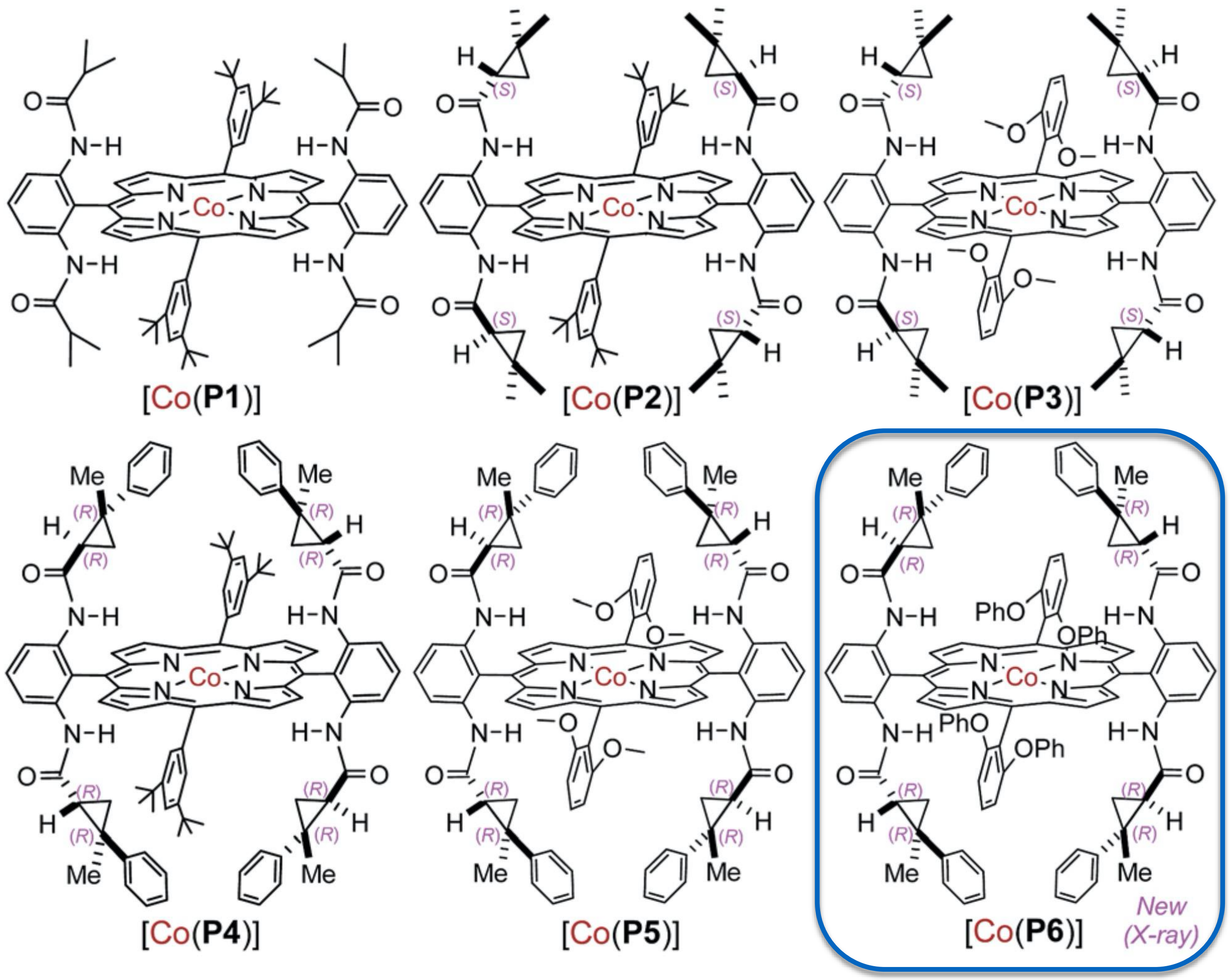
Ring-Opening Cyanation of Oxime





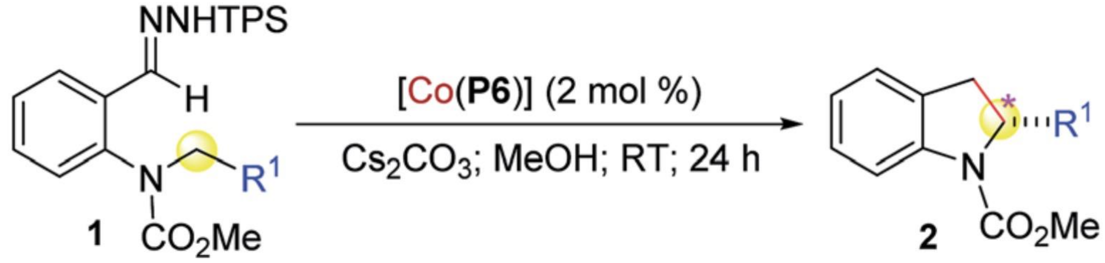
C(sp³)–H Alkylation for Indoline

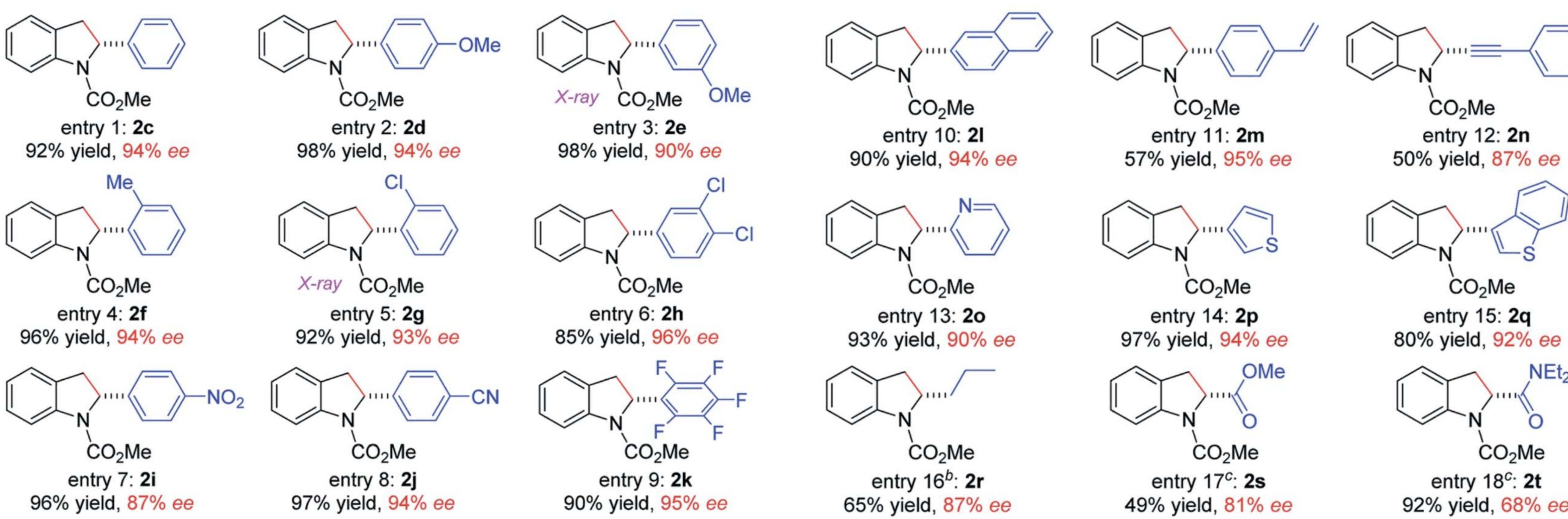




Wen, X.; Wang, Y.; Zhang, X. P. *Chem. Sci.* ***2018***, *9,* 5082

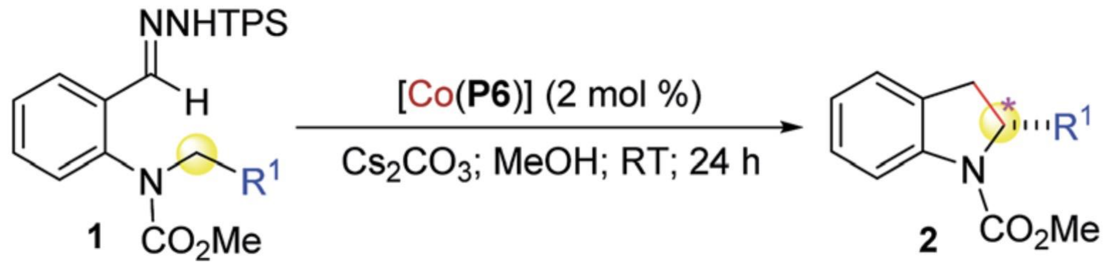
C(sp³)–H Alkylation for Indoline

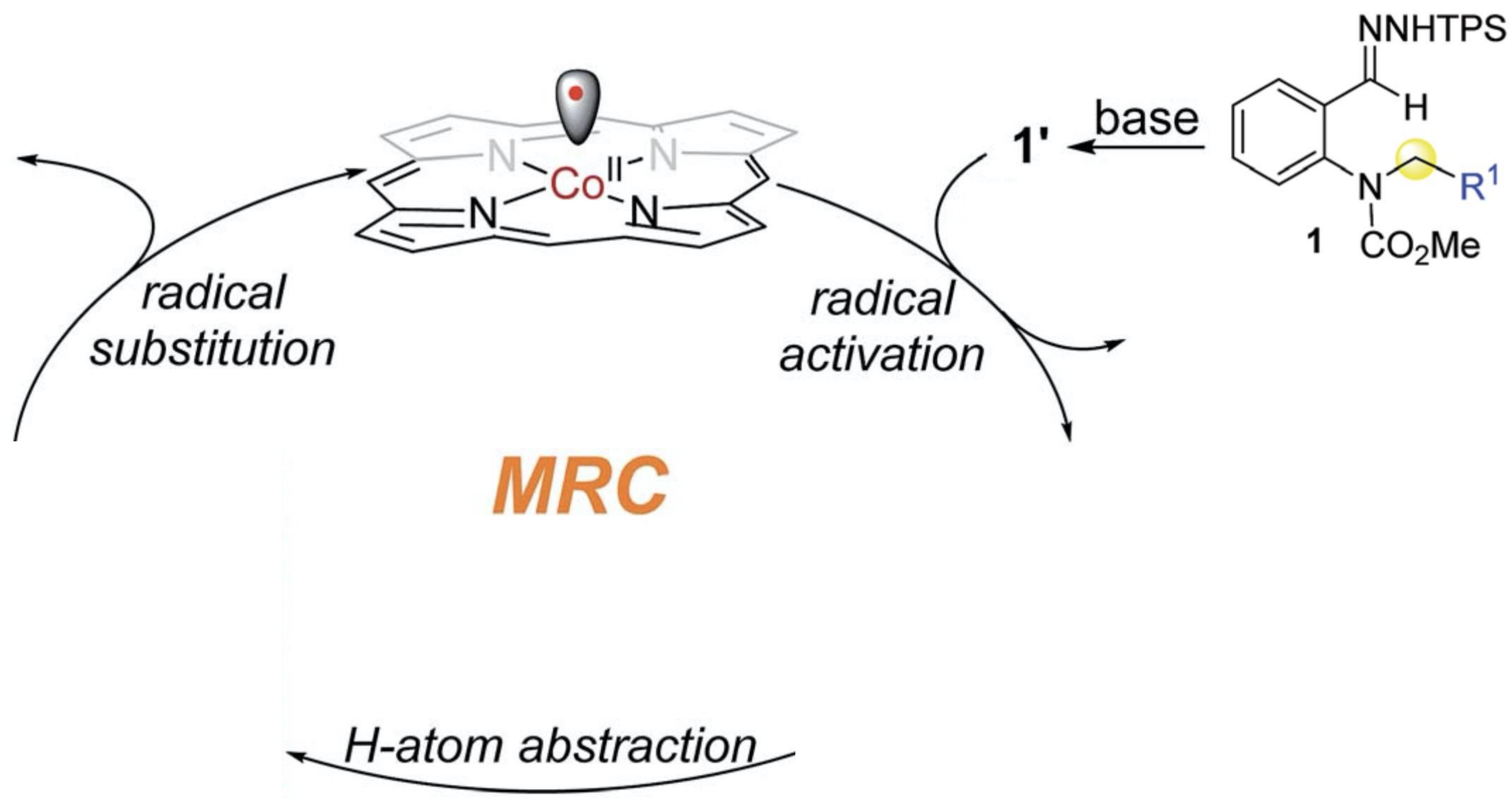




Wen, X.; Wang, Y.; Zhang, X. P. *Chem. Sci.* ***2018***, *9*, 5082

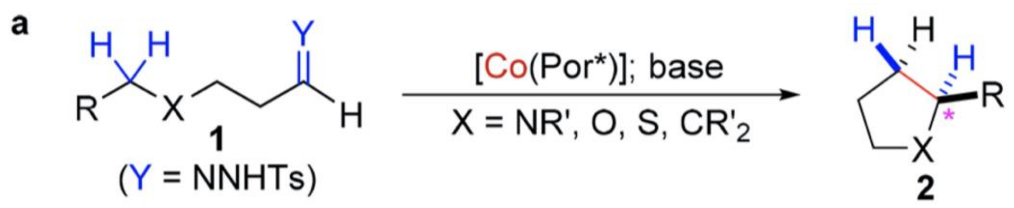
C(sp^3)–H Alkylation for Indoline

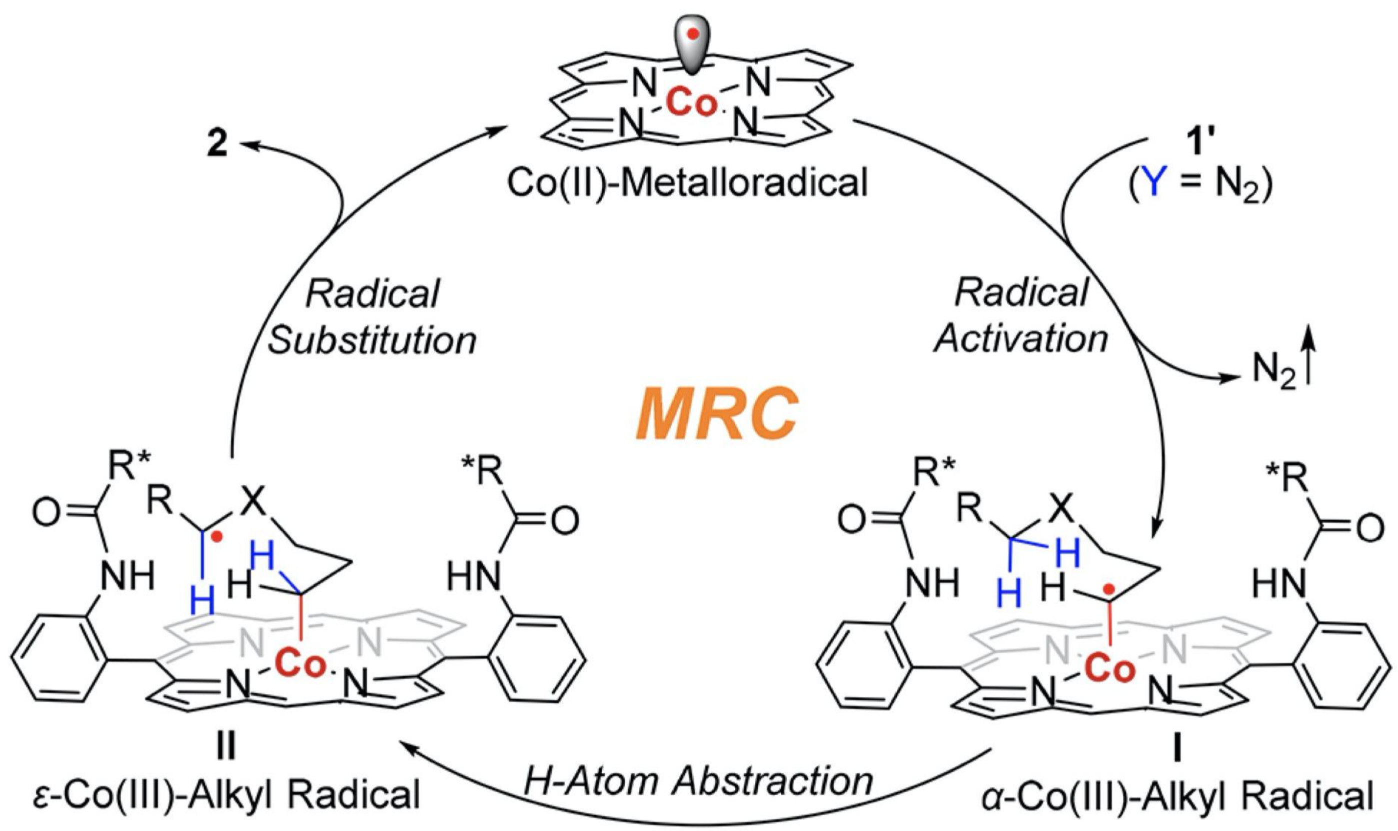




Wen, X.; Wang, Y.; Zhang, X. P. *Chem. Sci.* ***2018***, *9*, 5082

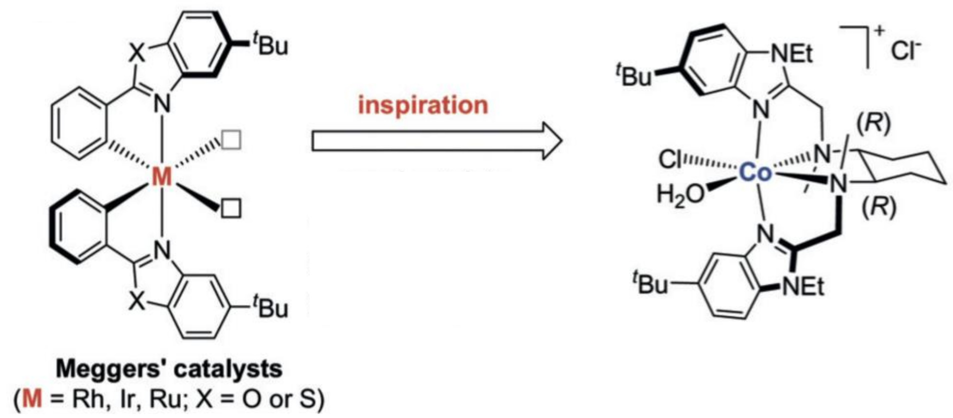
C(sp³)–H Alkylation for 5-Membered Ring Structures

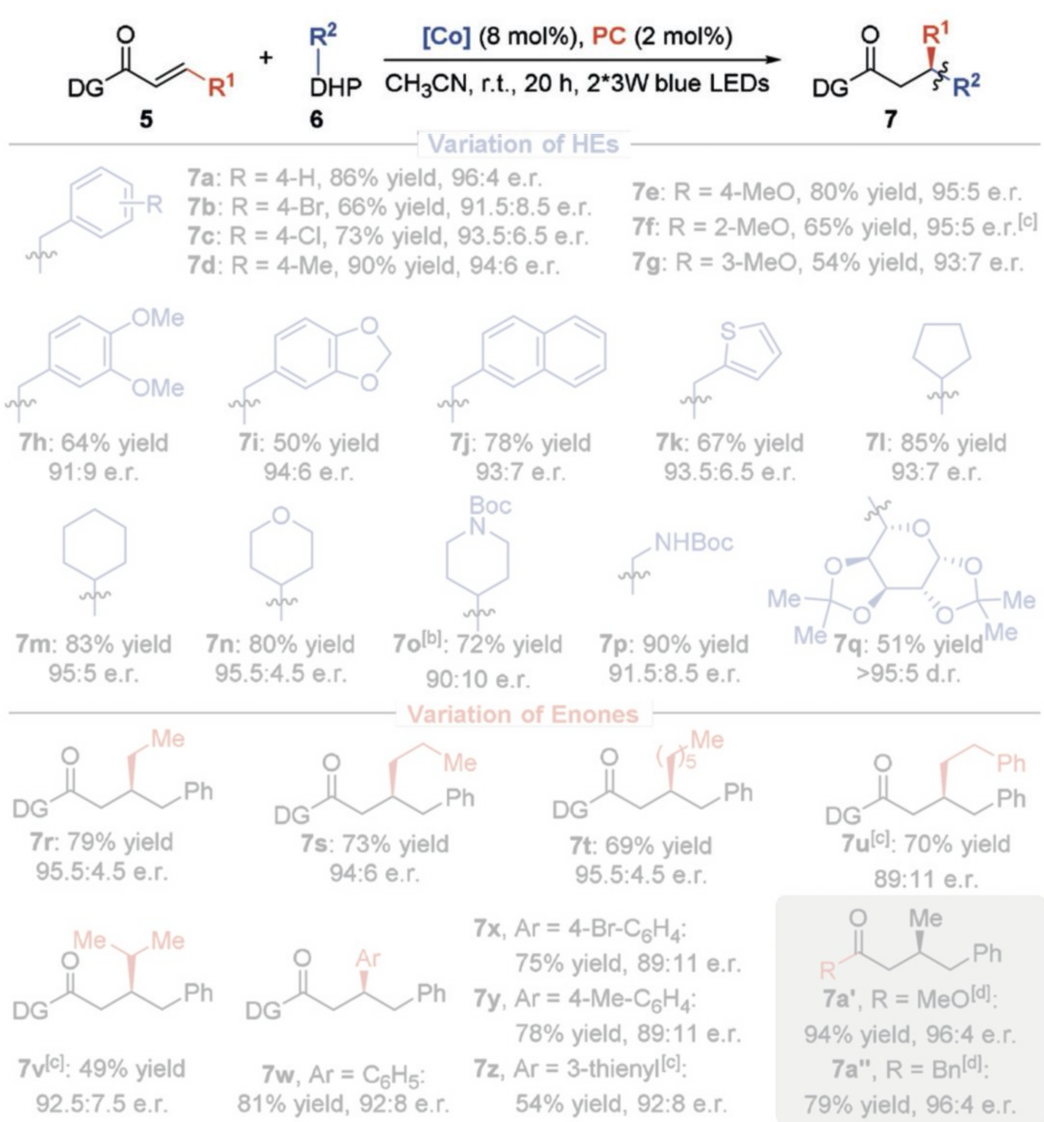


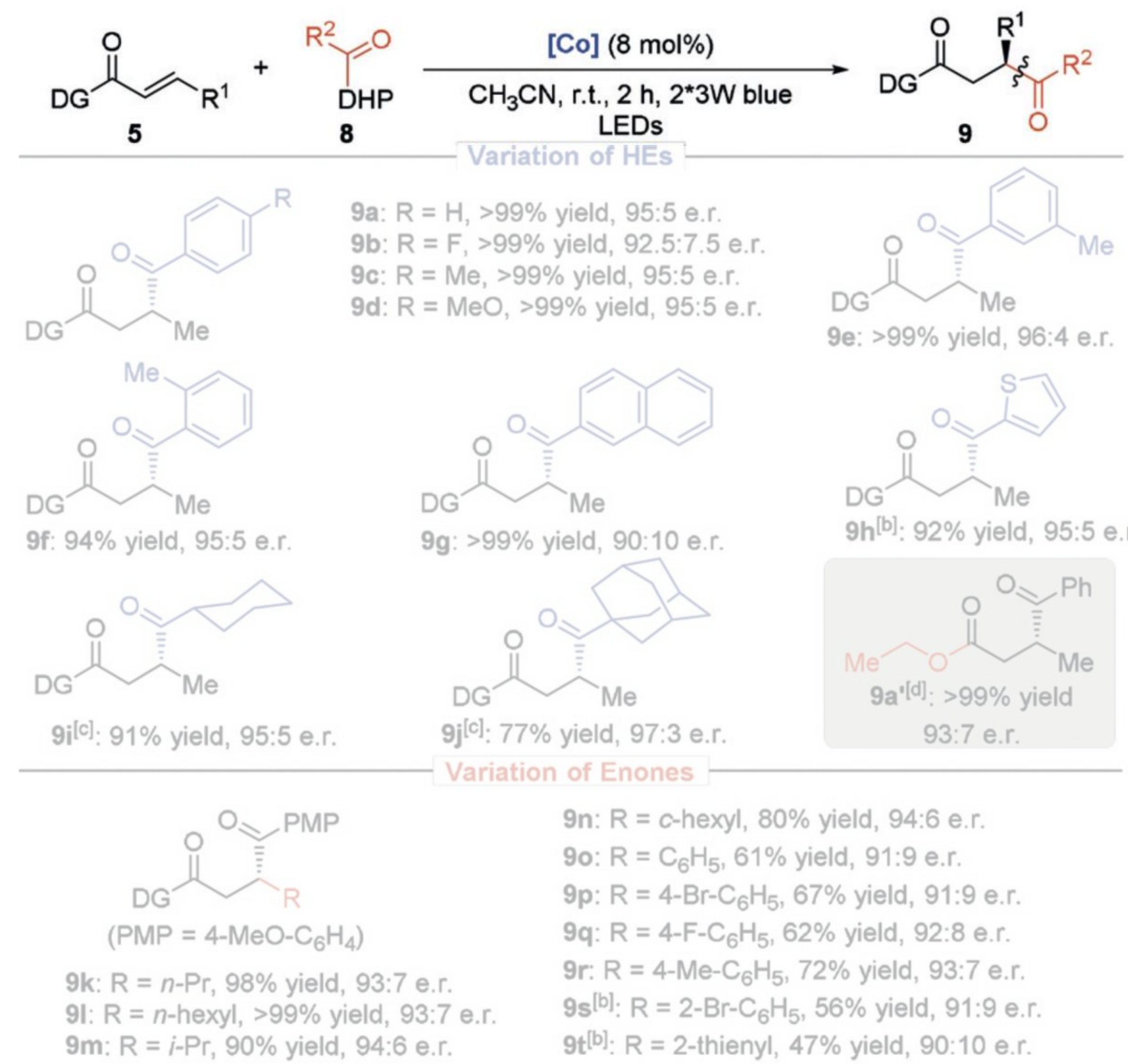


Wang, Y.; Wen, X.; Cui, X.; Zhang, X. P. *J. Am. Chem. Soc.* **2018**, *140*, 4792

Enone Acylation and Alkylation

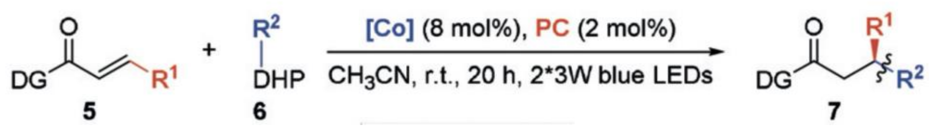


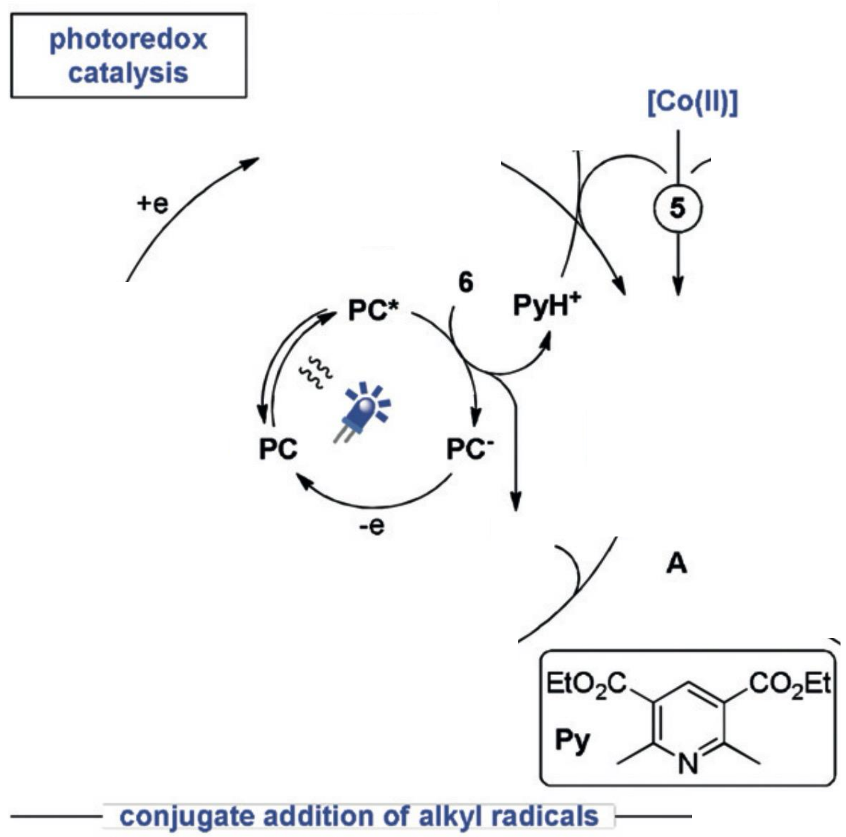


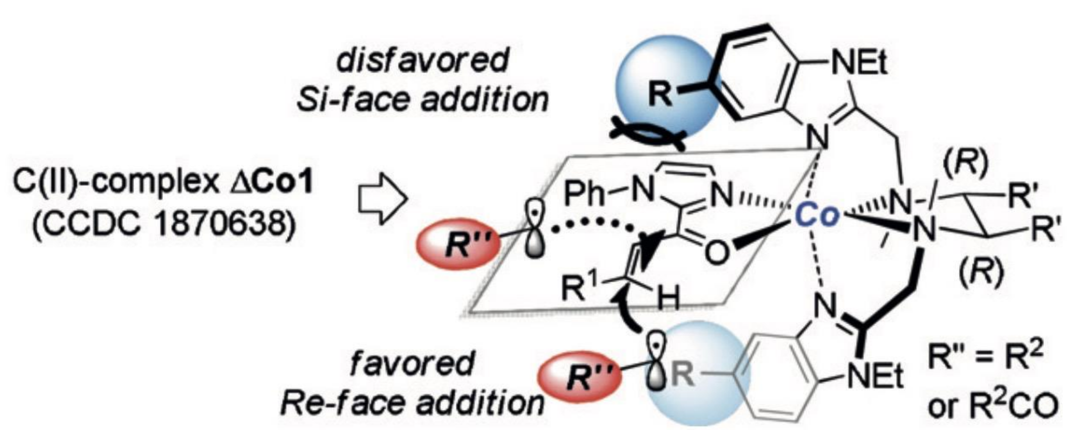


Zhang, K.; Lu, L.-Q.; Jia, Y.; Wang, Y.; Lu, F.-D.; Pan, F.; Xiao, W.-J. *Angew. Chem. Int. Ed.* **2019**, *58,* 13375

Enone Acylation and Alkylation



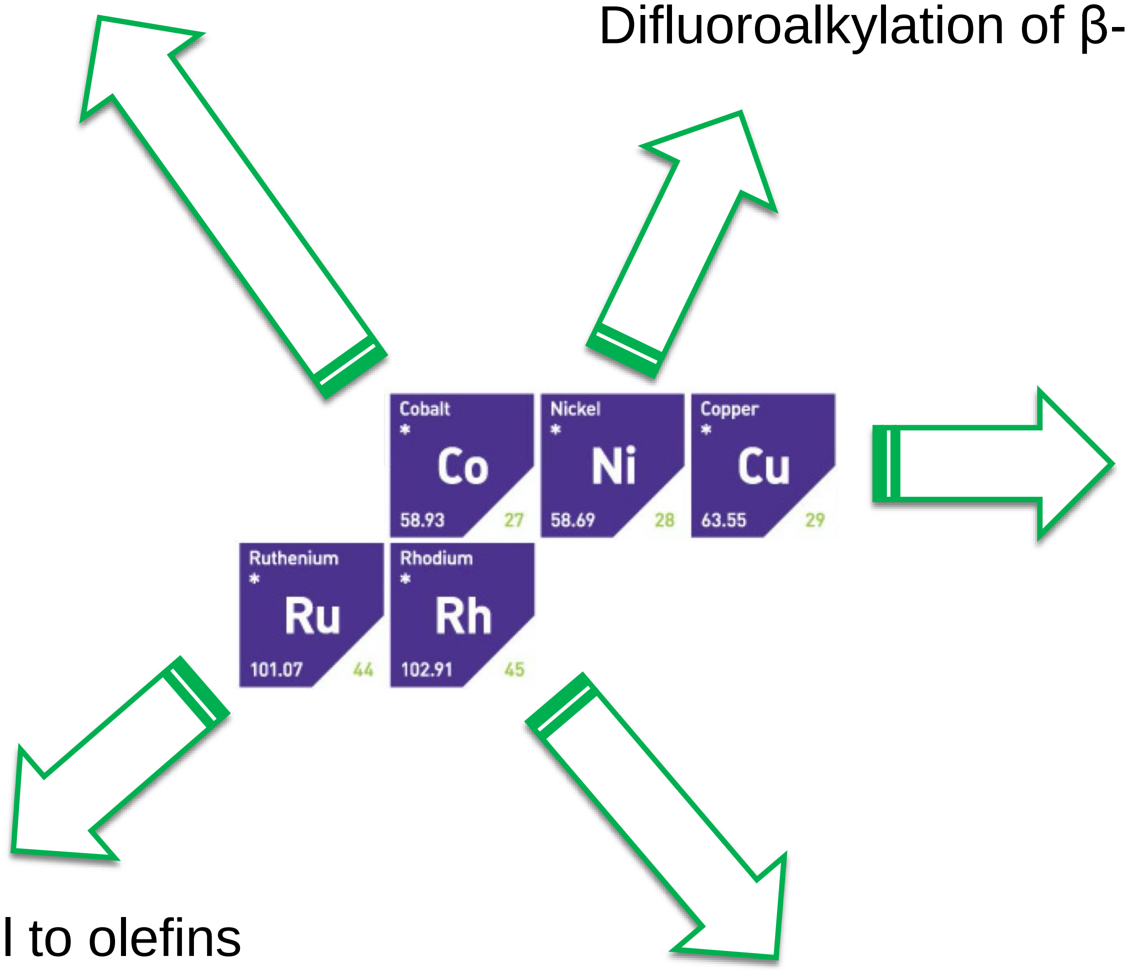




Conclusion

Alkylation of C(sp^3)–H Bonds
Alkylation and acylation of enones
Access to 5-membered ring structures

Radical-polar crossover reactions
Difluoroalkylation of β-ketoesters



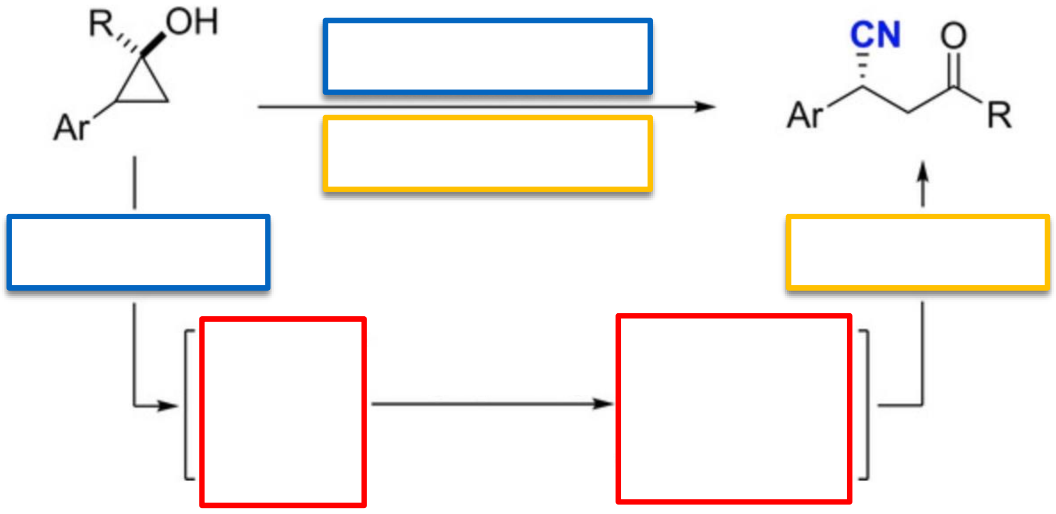
Cyanation of acyclic amines
Ring-opening cyanation of oxime
Ring-opening cyanation of cyclopropanols

Addition of RSO_2Cl to olefins

Addition of CX_4 reagents to olefins
Alkene and sulfonyl addition to olefins

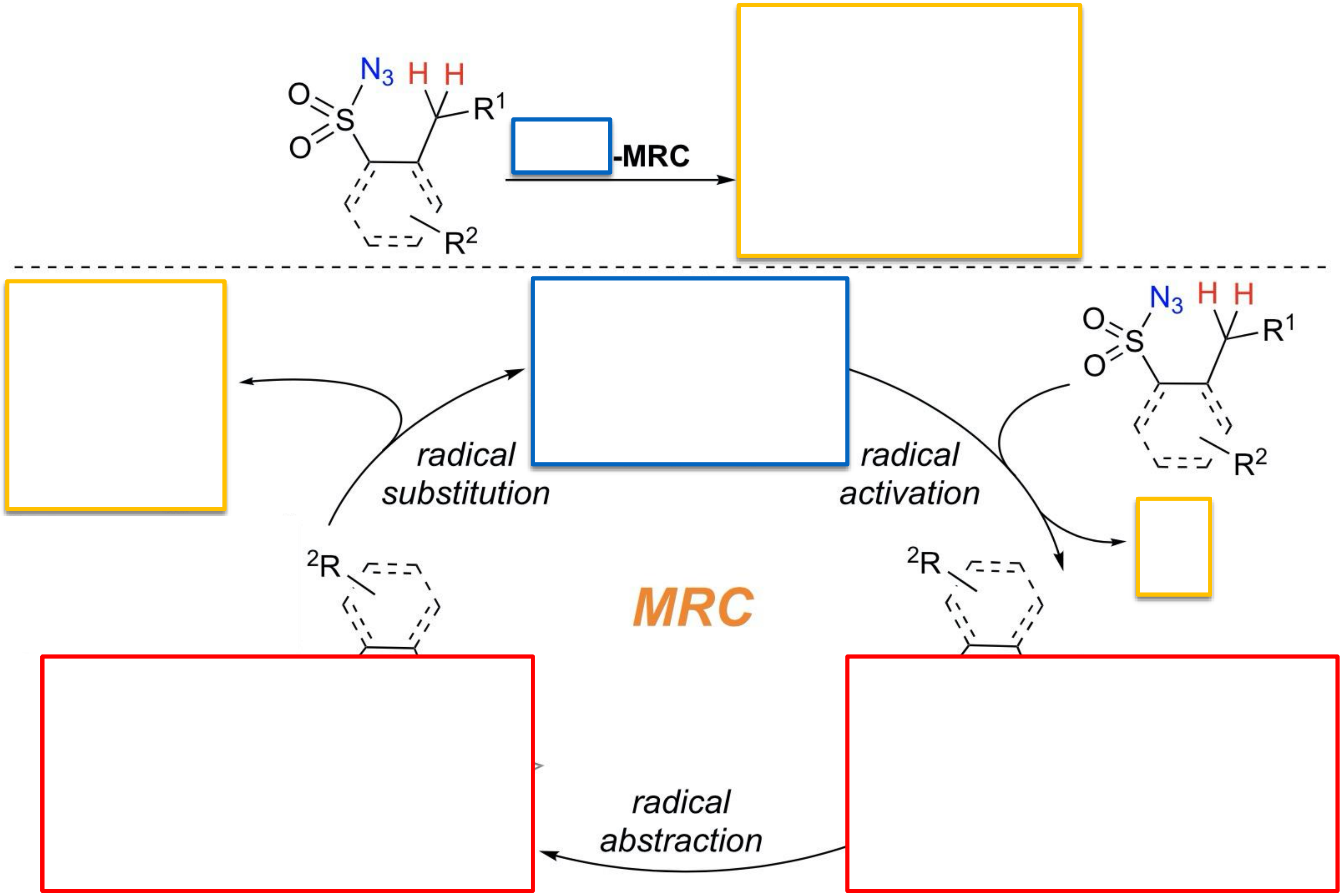
Exercice 1

? 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

Exercice 2

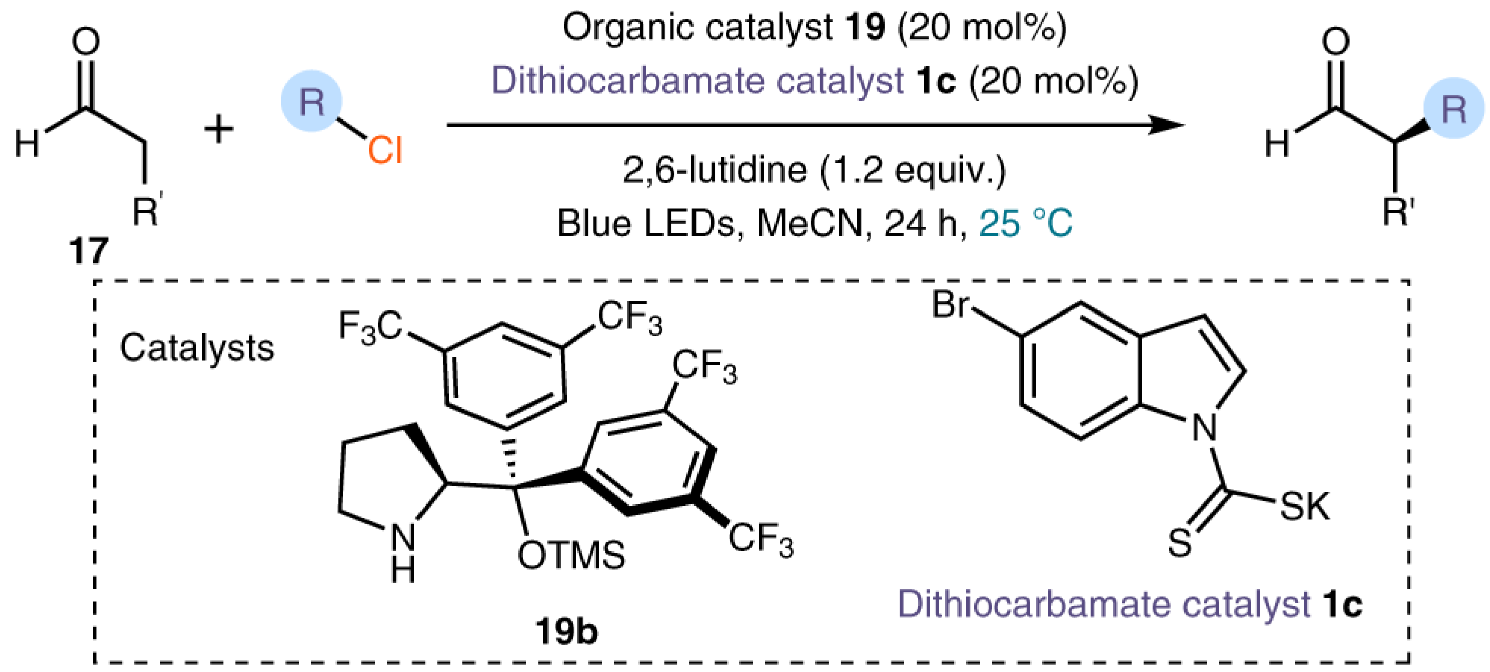


1/ Propose a metal/ligand for this reaction

2/ Propose a product for the MRC

3/ Propose the missing intermediates

Outlook - Beyond Metals



Scheitzer-Chaput, B.; Horwitz, M. A.; de Pedro Beato, E.; Melchiorre, P. *Nat. Chem.* **2019**, *11,* 129
Perego, L. A.; Bonilla, P.; Melchiorre, P. *Adv. Synth. Catal.* **2019**, *362,* 302

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

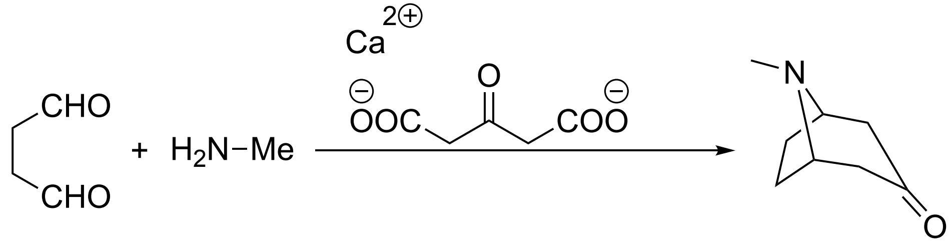
→ **any cascade reaction = one-pot reaction**

→ **any one-pot reaction ≠ cascade reaction**

L. F. Tietze, U. Beifuss, *Angew. Chem. Int. Ed.* **1993**, *32*, 131–163

Introduction – Cascade Reactions

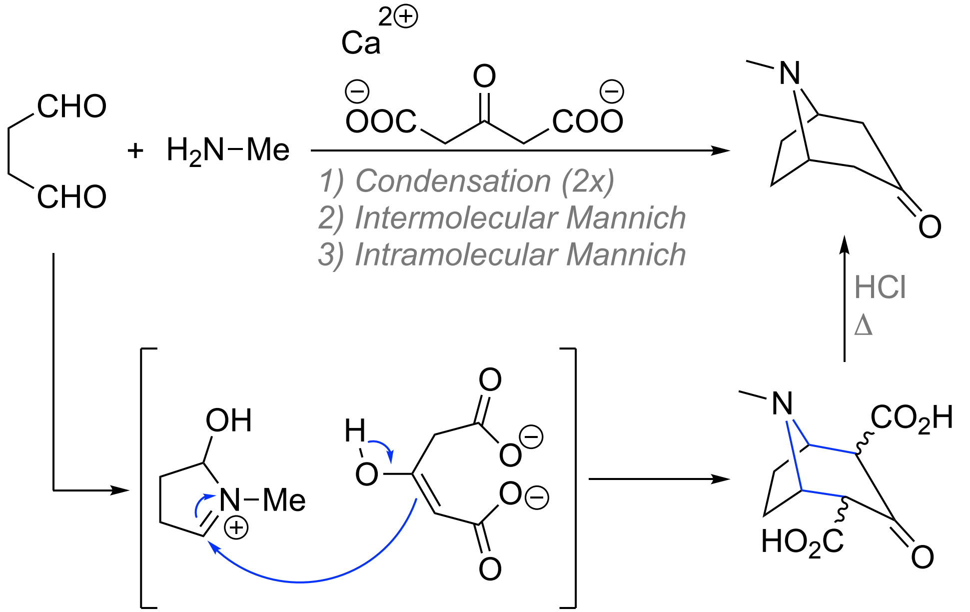
First example: Synthesis of Tropinone (Robinson, 1917)



R. Robinson, *J. Chem. Soc.* **1917**, 762–768

Introduction – Cascade Reactions

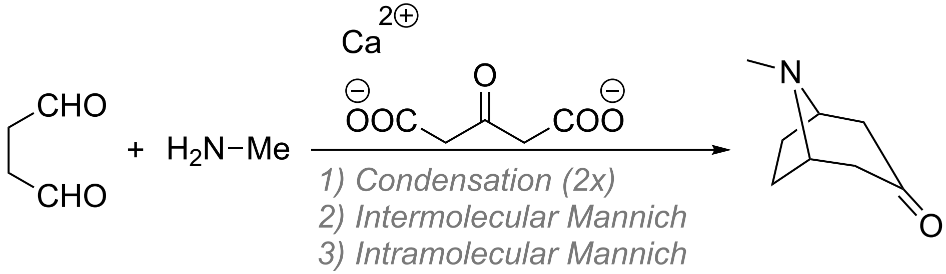
First example: Synthesis of Tropinone (Robinson, 1917)



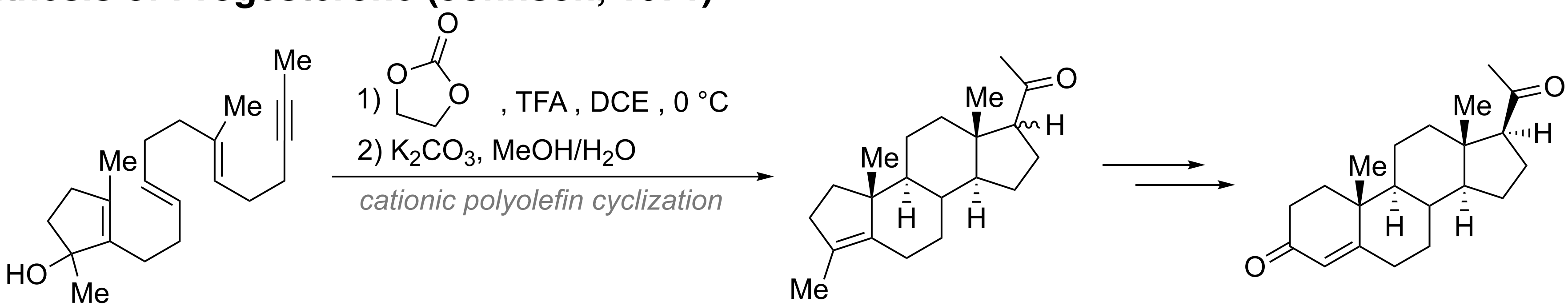
R. Robinson, *J. Chem. Soc.* **1917**, 762–768

Introduction – Cascade Reactions

First reported: Synthesis of Tropinone (Robinson, 1917)



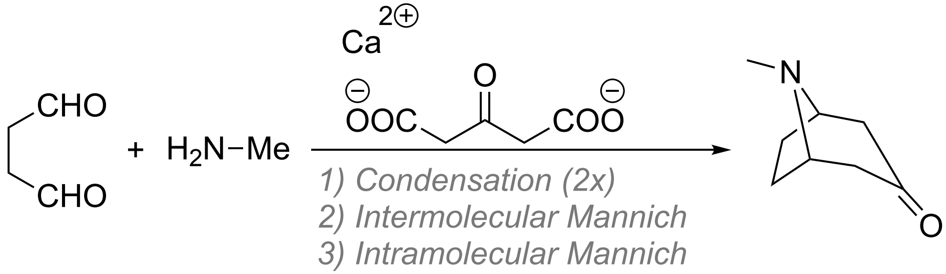
Synthesis of Progesterone (Johnson, 1971)



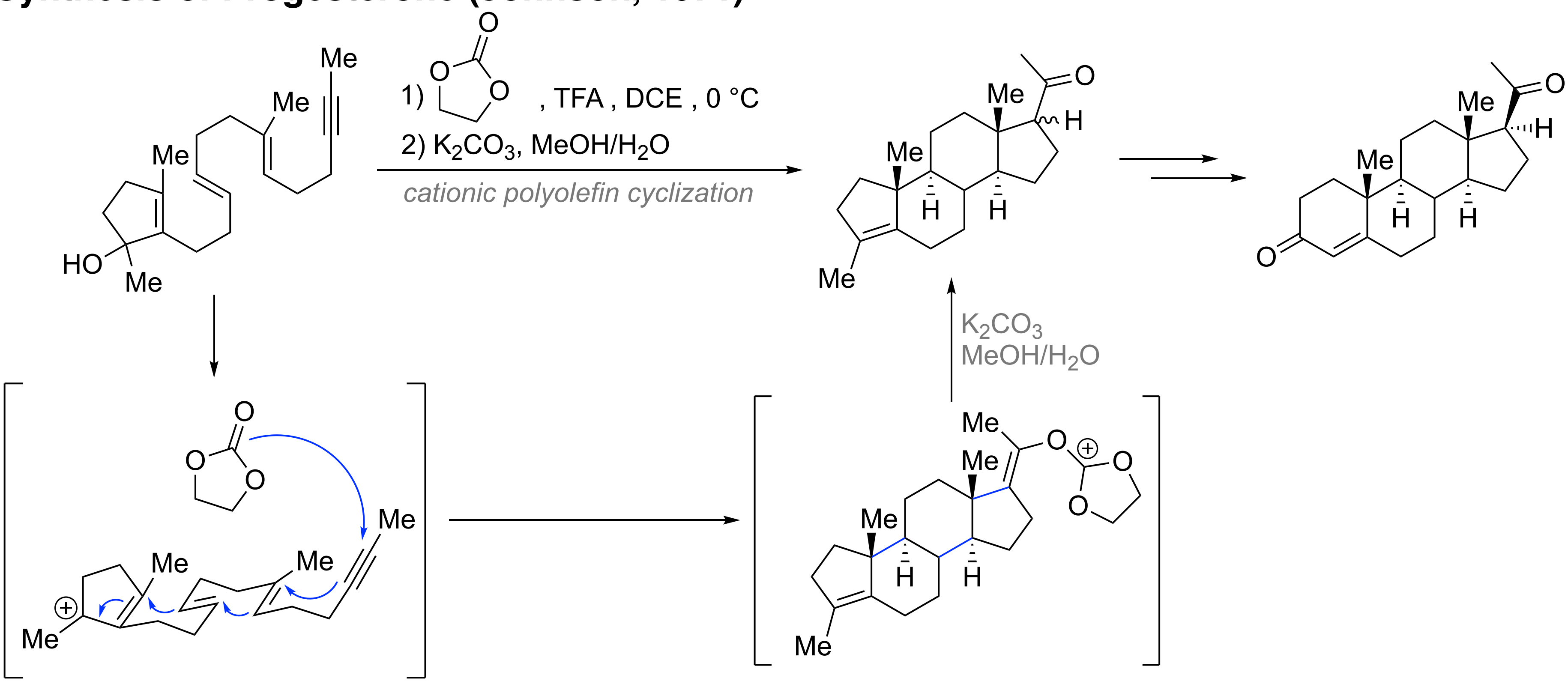
W. S. Johnson, M. B. Gravestock, B. E. McCarry, *J. Am. Chem. Soc.* **1971**, *93*, 4332–4334

Introduction – Cascade Reactions

First reported: Synthesis of Tropinone (Robinson, 1917)



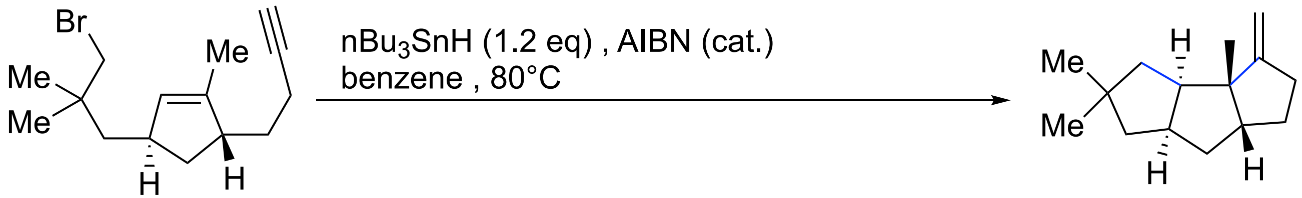
Synthesis of Progesterone (Johnson, 1971)



W. S. Johnson, M. B. Gravestock, B. E. McCarry, *J. Am. Chem. Soc.* **1971**, *93*, 4332–4334

Introduction – Radical Cascade Reactions

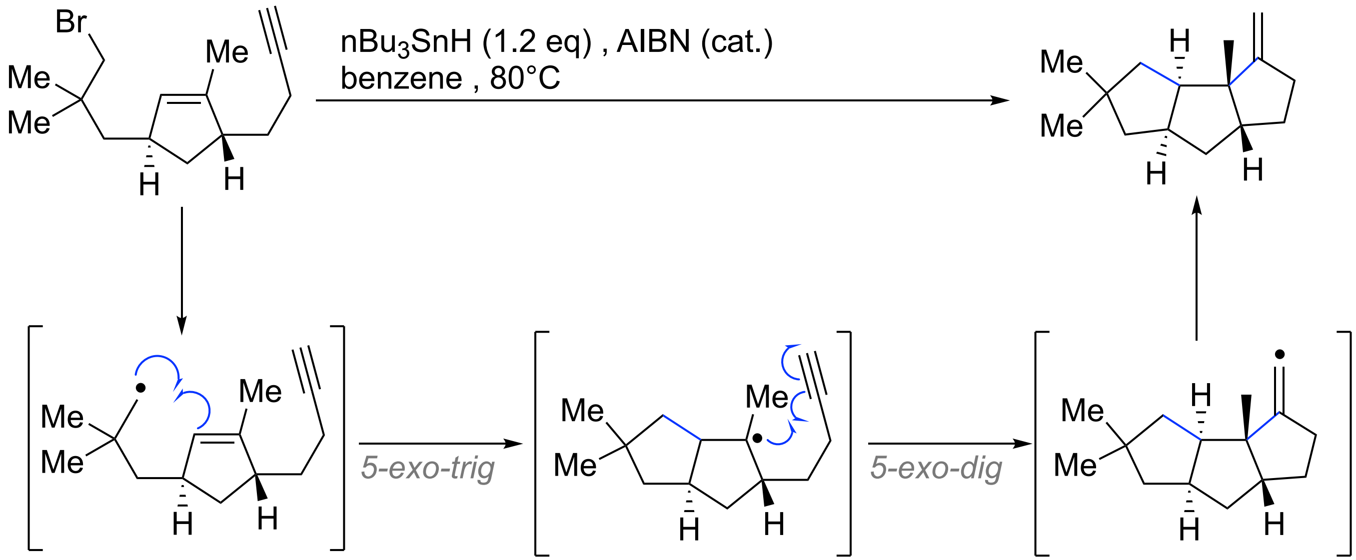
Total synthesis of (+/–)-Hirsutene (Curran, 1985) – Key step constitutes a radical



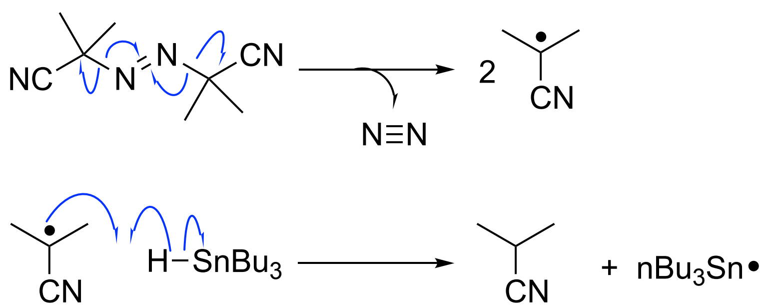
D. P. Curran, M.-H. Chen, *Tetrahedron Lett.* **1985**, *26,* 4991–4994

Introduction – Radical Cascade Reactions

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



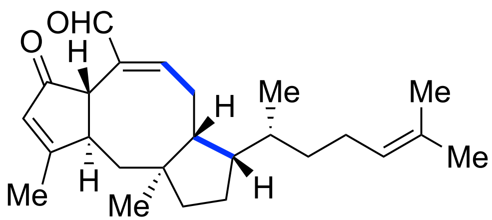
Initiation:



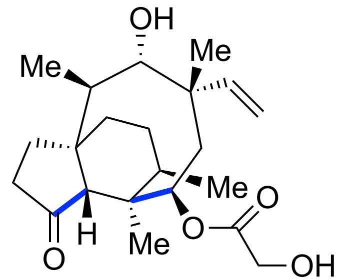
D. P. Curran, M.-H. Chen, *Tetrahedron Lett.* **1985**, *26,* 4991–4994

Introduction – Radical Cascade Reactions

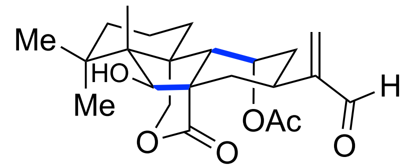
Achieving rapid complexity in total syntheses of natural products and complex materials:



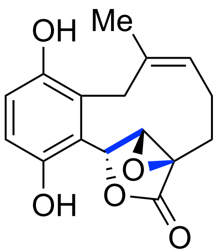
(–)-6-epi-ophiobolin N



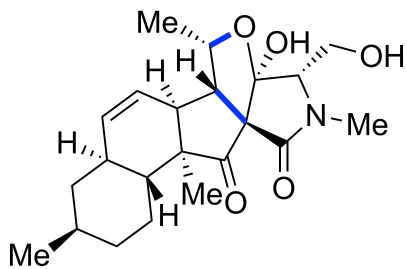
(+)-pleuromutilin



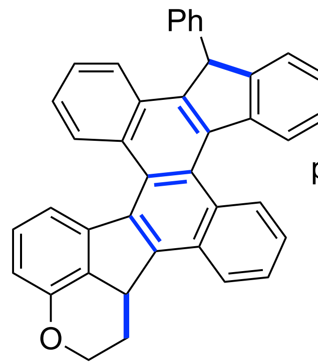
(–)-maoecrystal Z



(+/–)-clavilactone



(+)-fusarisetin



polyaromatic nanoribbon

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

M. Yan, J. C. Lo, J. T. Edwards, P. S. Baran, *J. Am. Chem. Soc.* **2016**, *138,* 12692–12714

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

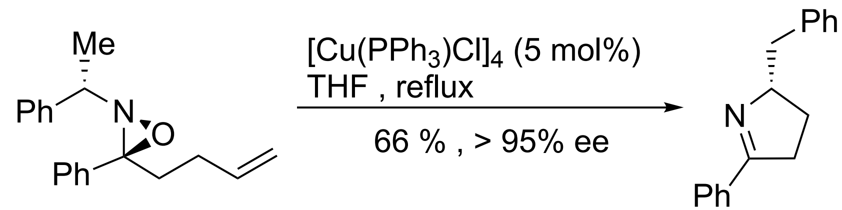
2) Radical Relocation: Radical character is propagated during a bond-forming / breaking sequence

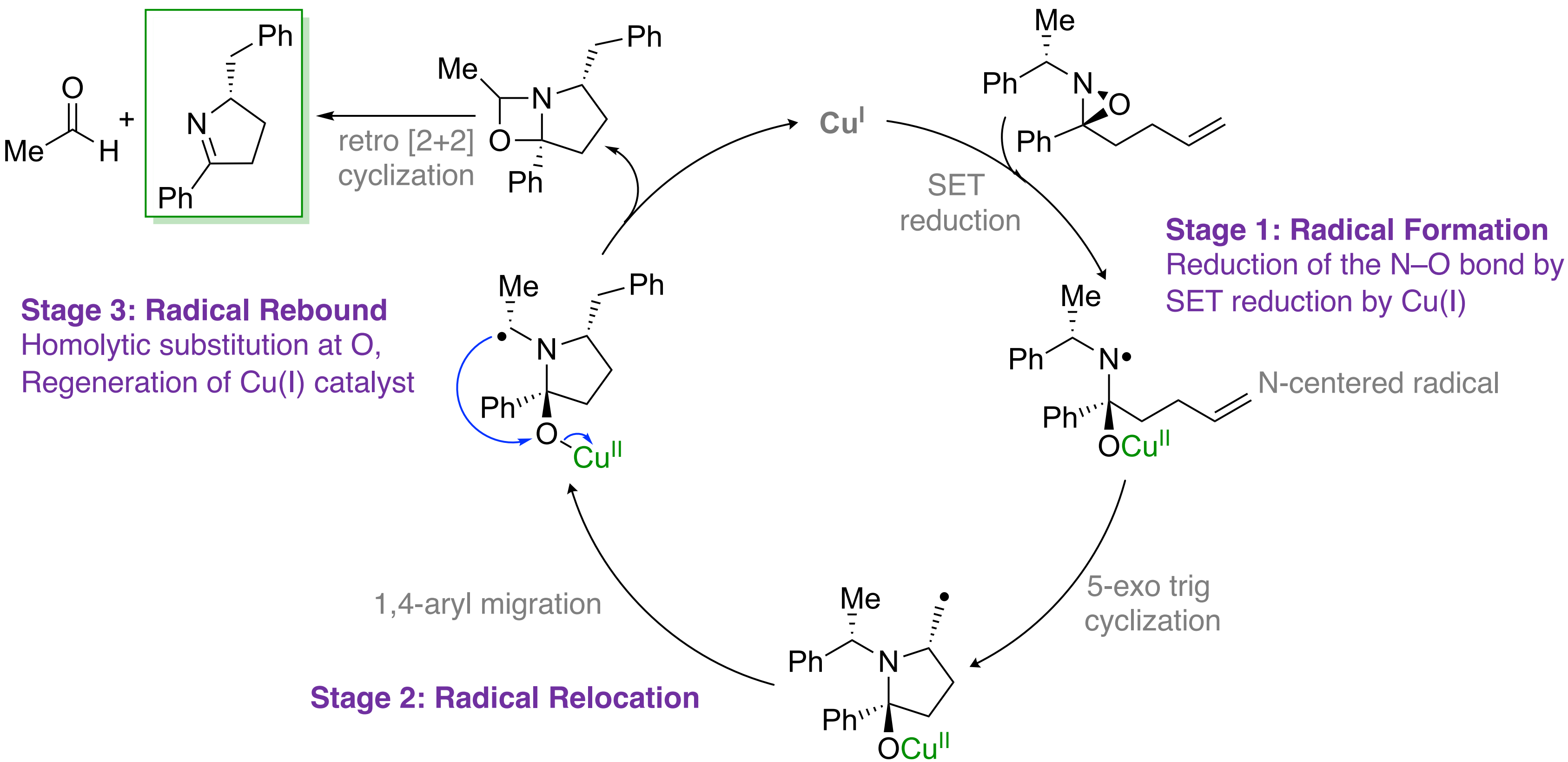
3) Radical Rebound: Radical character is recycled, typically by SET back to metal catalyst or expulsion of a radical that acts as a catalyst

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

Examples – Intramolecular Radical Relays

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





J. Aubé, X. Ping, Y. Wang, F. Takusagawa, *J. Am. Chem. Soc.* **1992**, *114*, 5466–5467

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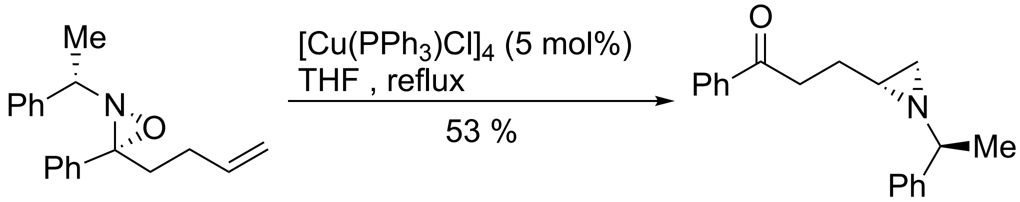

QUESTION: Why does the diastereoisomeric oxaziridine lead to an azirine instead of the pyrroline?

J. Aubé, X. Ping, Y. Wang, F. Takusagawa, *J. Am. Chem. Soc.* **1992**, *114,* 5466–5467

Examples – Intramolecular Radical Relays

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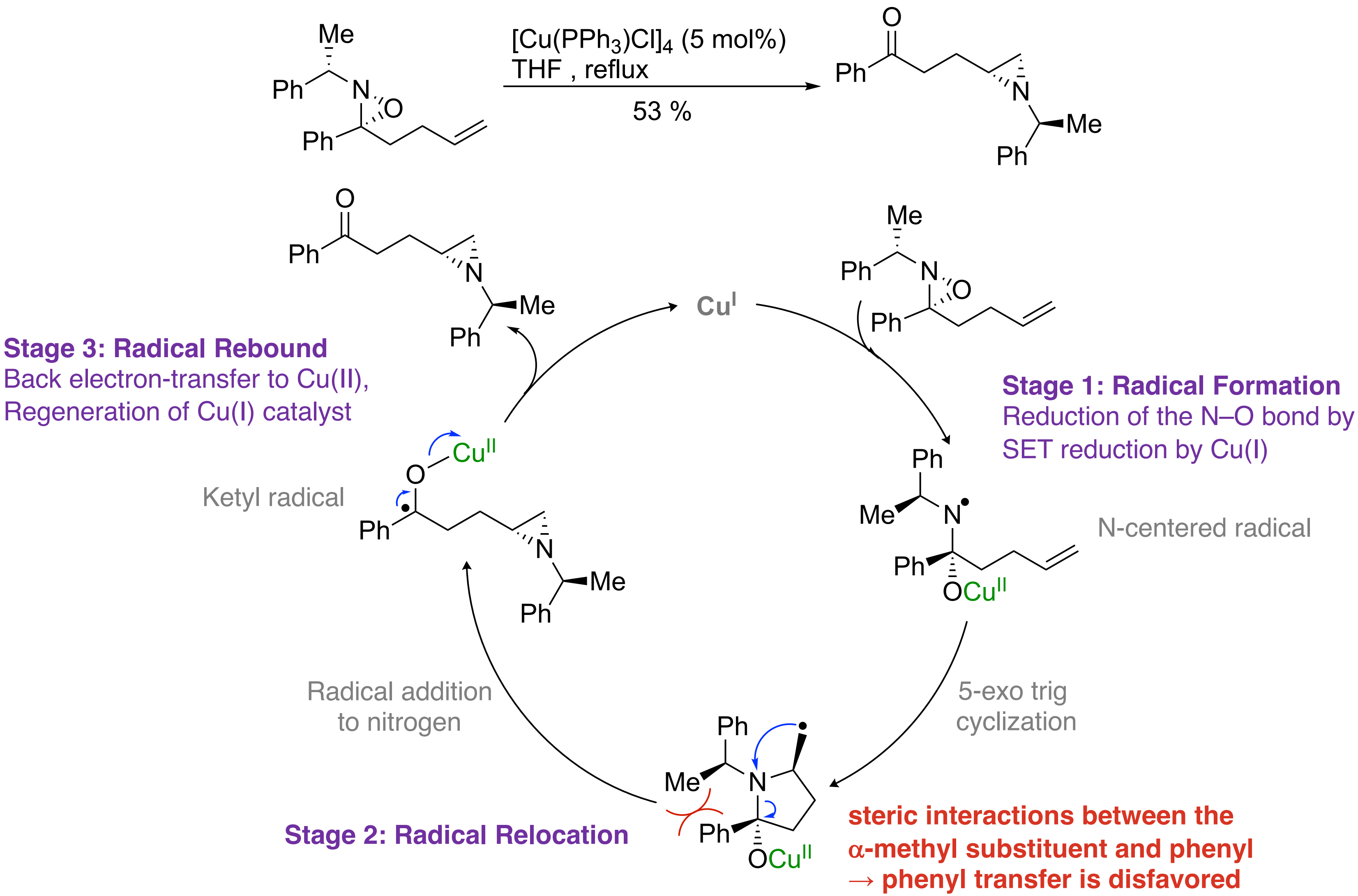
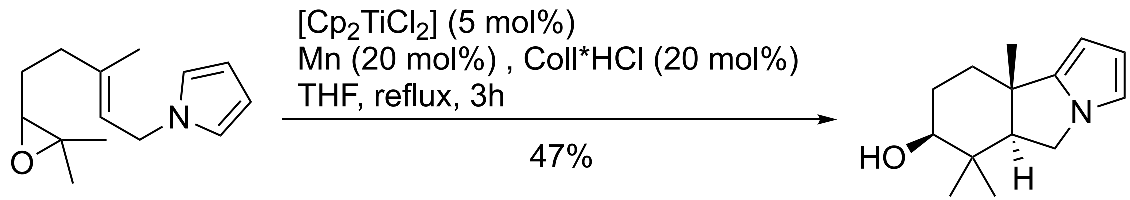
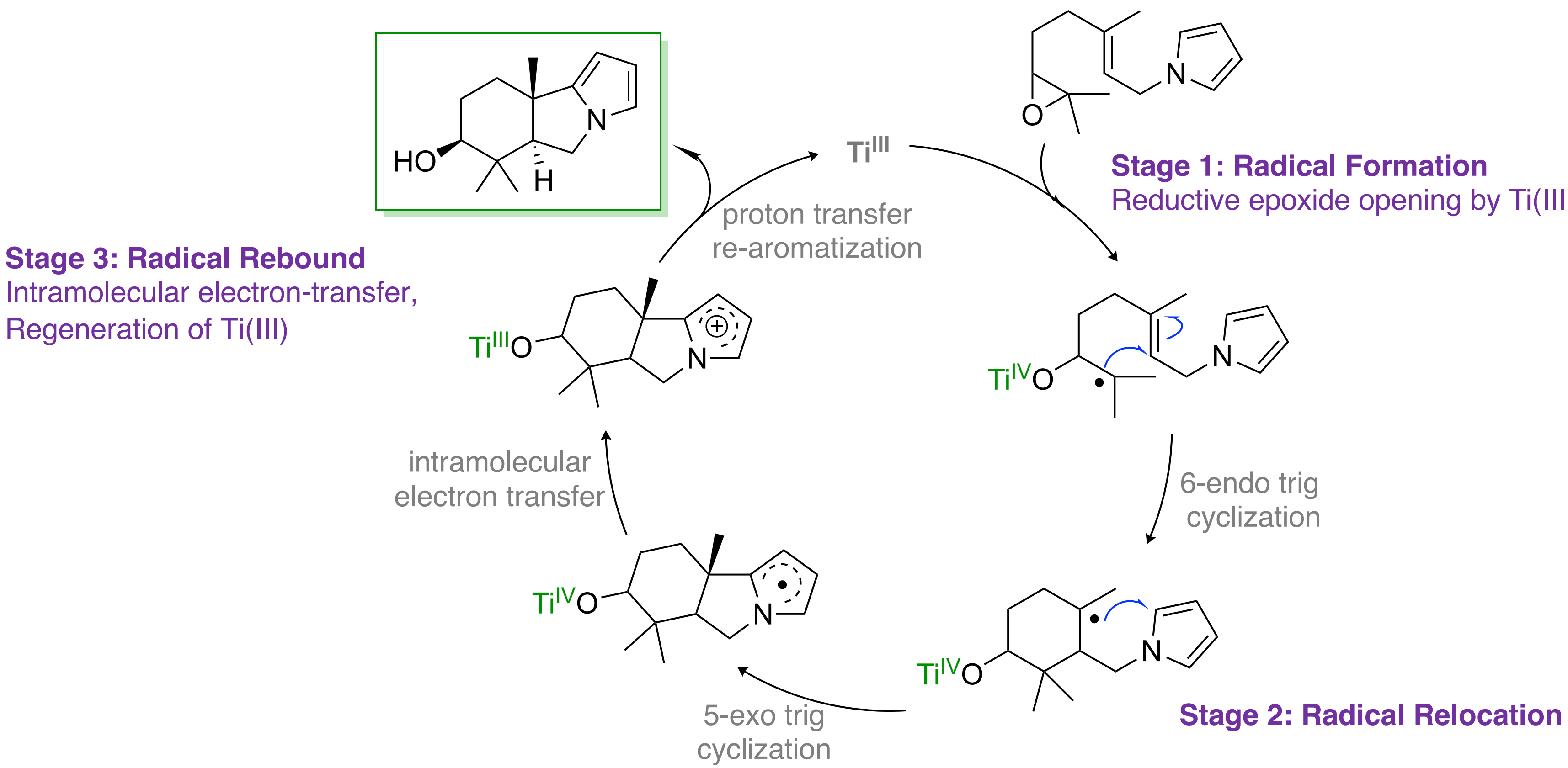


J. Aubé, X. Ping, Y. Wang, F. Takusagawa, *J. Am. Chem. Soc.* **1992**, *114,* 5466–5467

Examples – Intramolecular Radical Relays

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

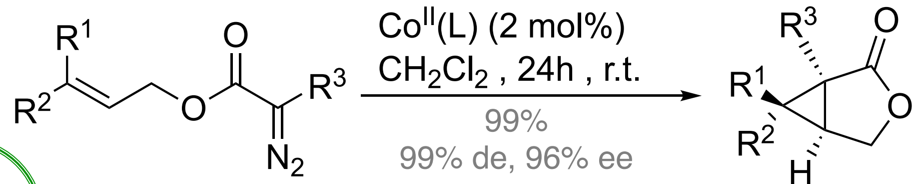


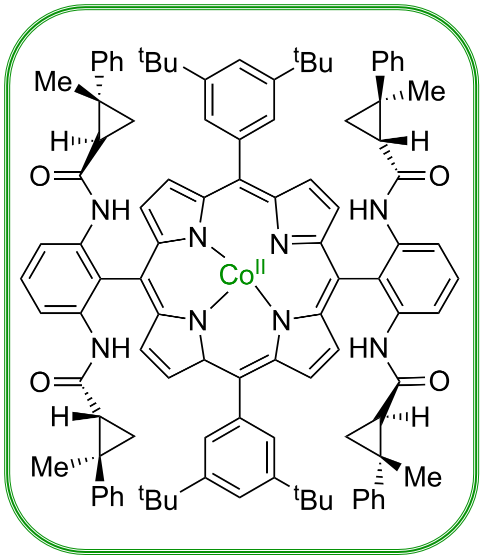


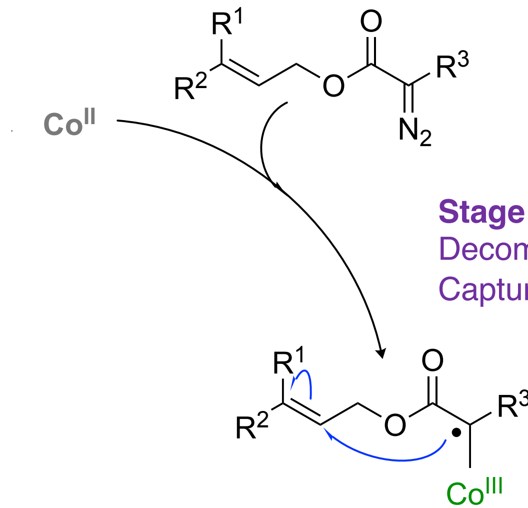
S. Hildebrandt, A. Gansäuer, *Angew. Chem. Int. Ed.* **2016**, *55,* 9719–9722

Examples – Intramolecular Radical Relays

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







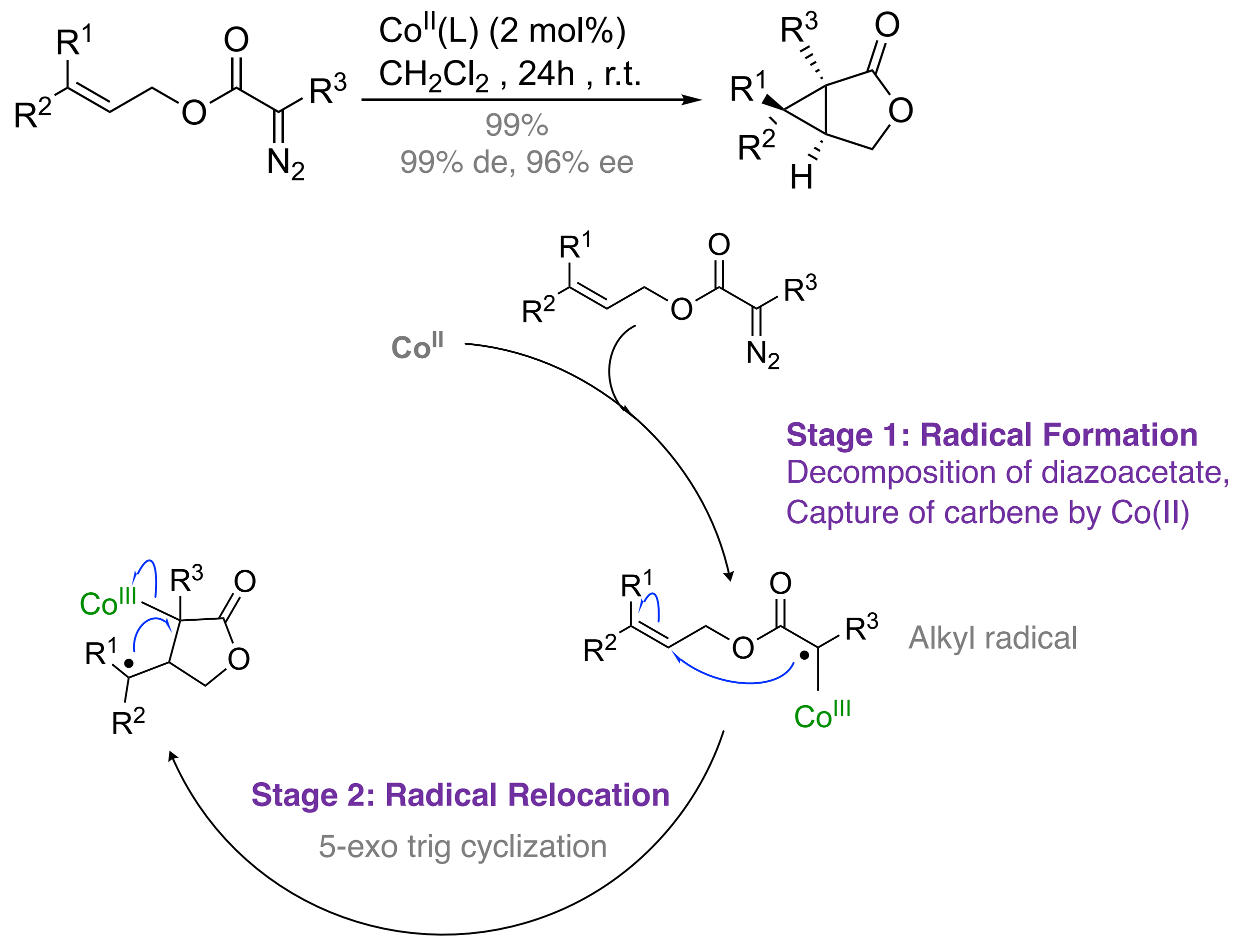
Stage 1: Radical Formation
Decomposition of diazoacetate,
Capture of carbene by Co(II)

Alkyl radical

X. Xu, H. Lu *et al.*, *J. Am. Chem. Soc.* **2011**, *133,* 15292–15295

Examples – Intramolecular Radical Relays

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



X. Xu, H. Lu *et al.*, *J. Am. Chem. Soc.* **2011**, *133,* 15292–15295

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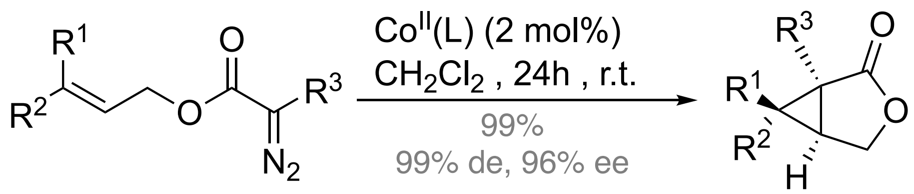
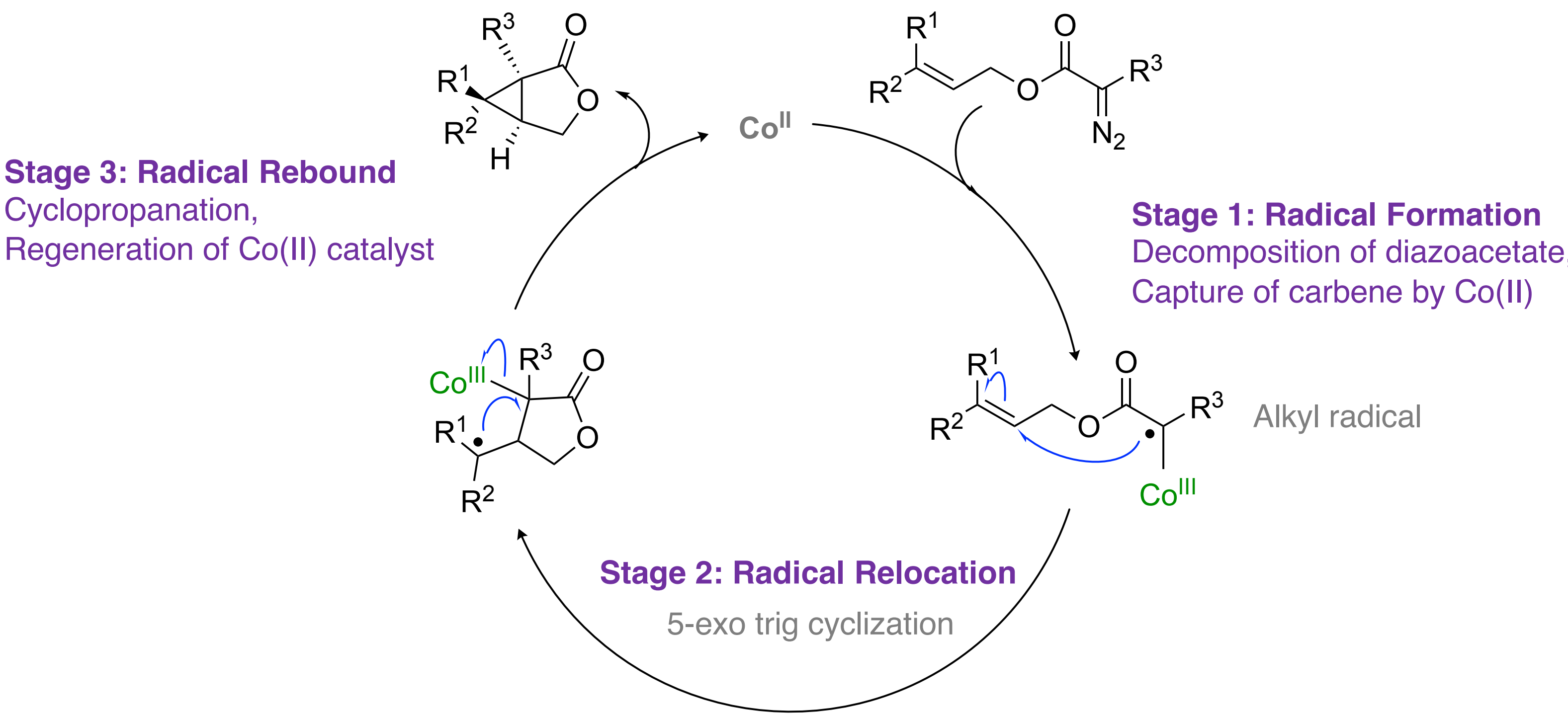
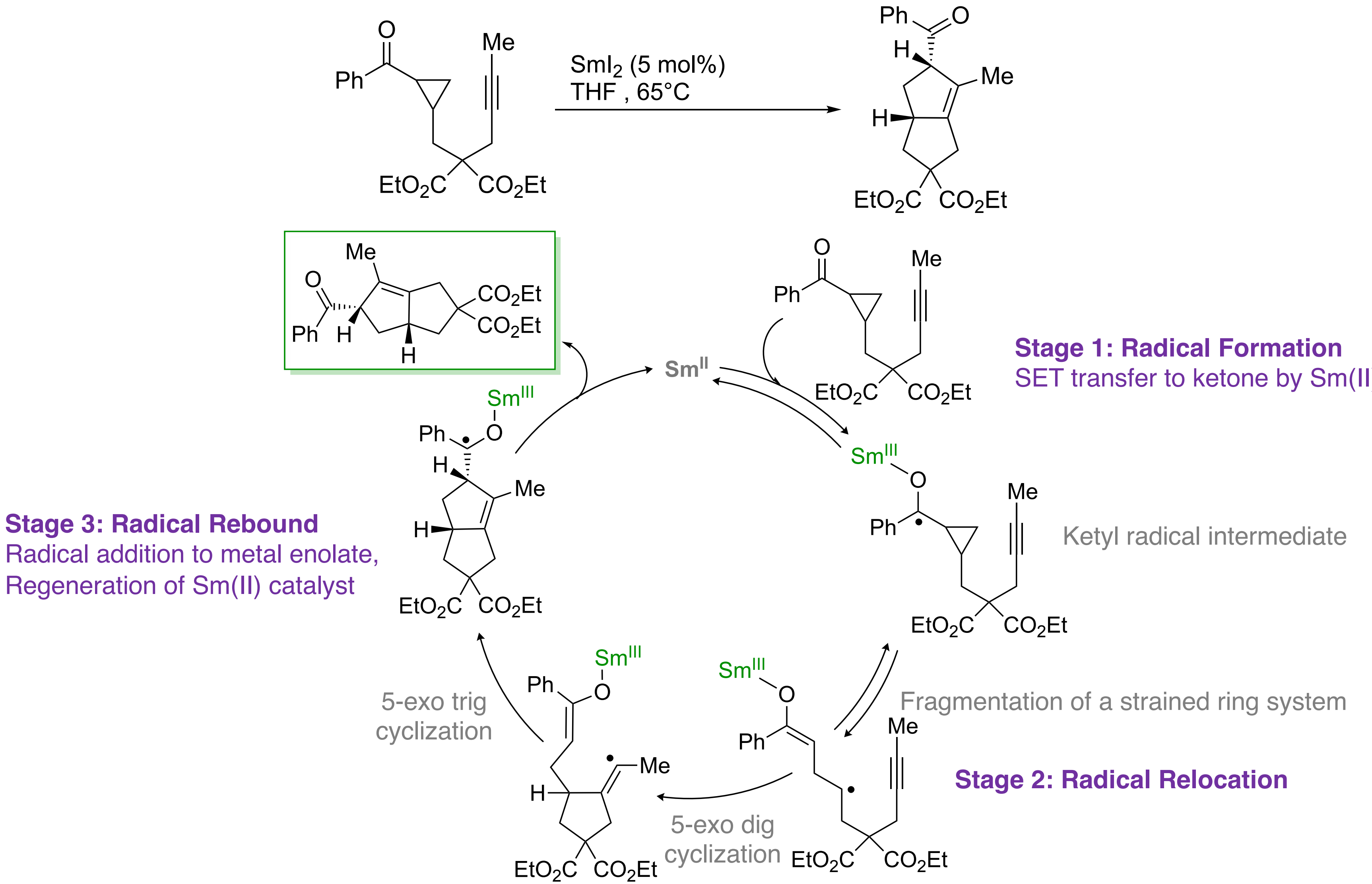




X. Xu, H. Lu *et al.*, *J. Am. Chem. Soc.* **2011**, *133,* 15292–15295

Examples – Intramolecular Radical Relays

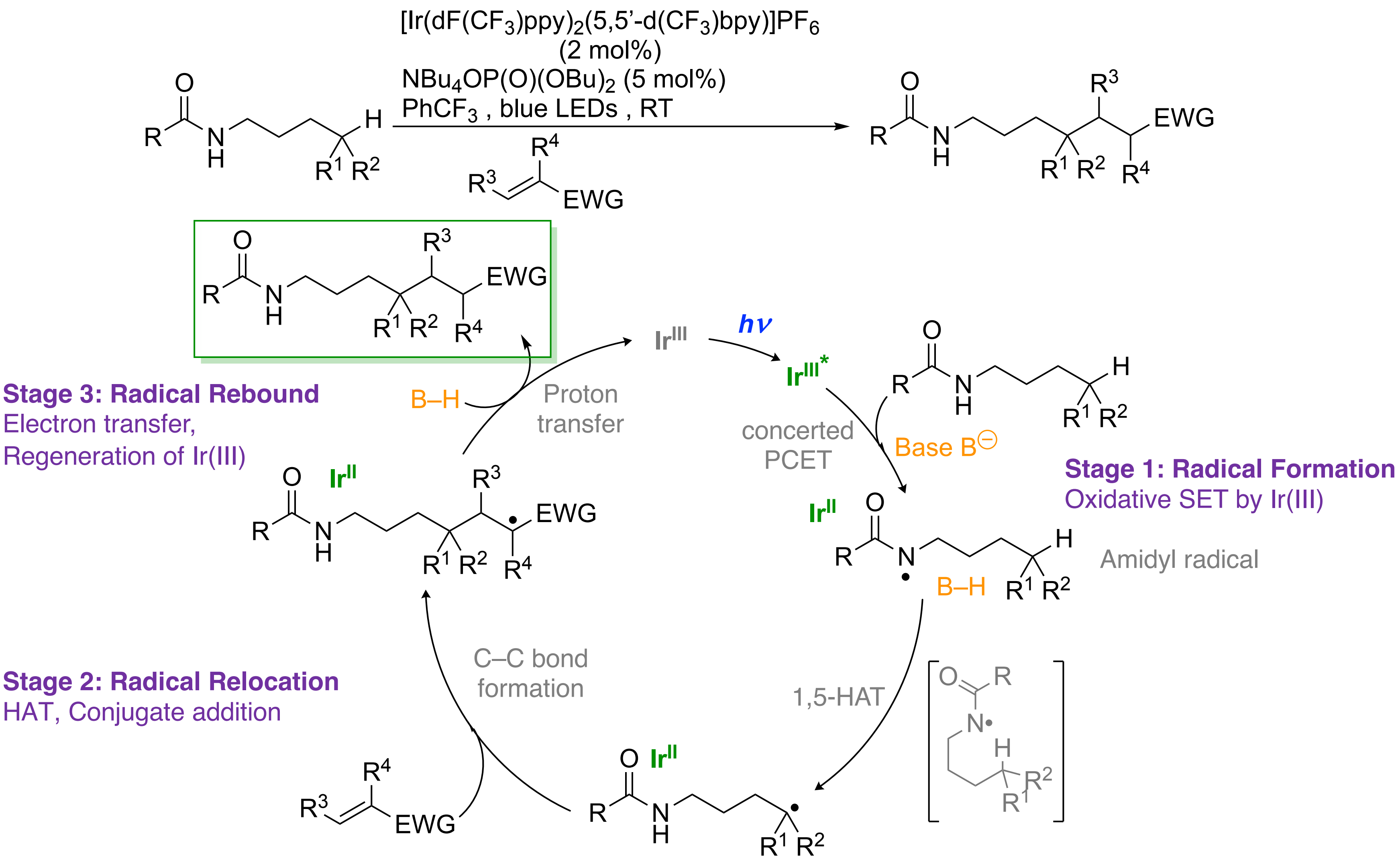
Sm(II)-catalyzed cyclization cascade (Procter 2019)



H.-M. Huang, J. J. W. McDouall, D. J. Procter, *Nat. Catal.* **2019**, *2,* 211–218

Examples – Radical Relays involving HAT

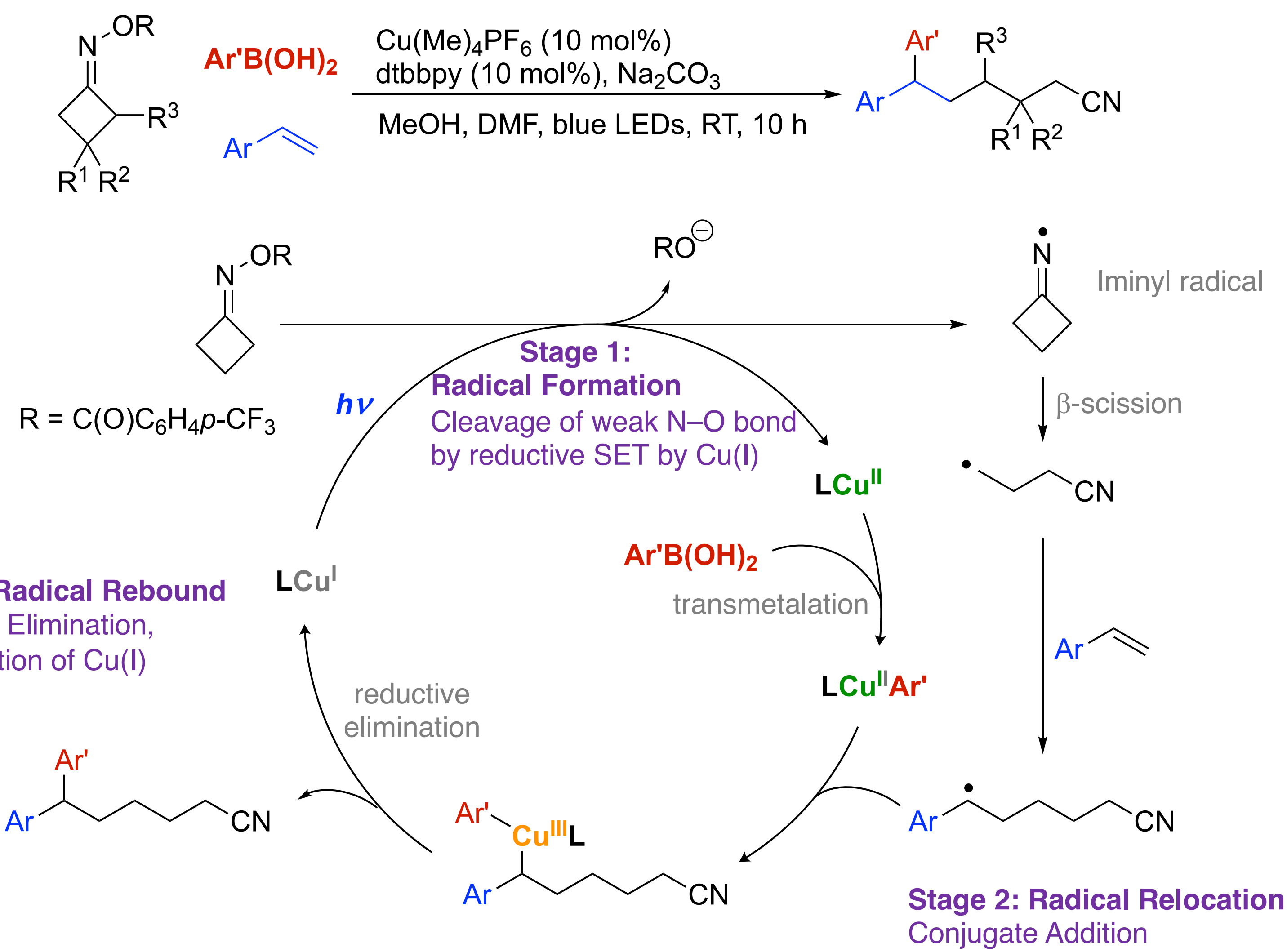
Ir(III)-catalyzed cascade reaction (Knowles and Rovis, 2016)



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

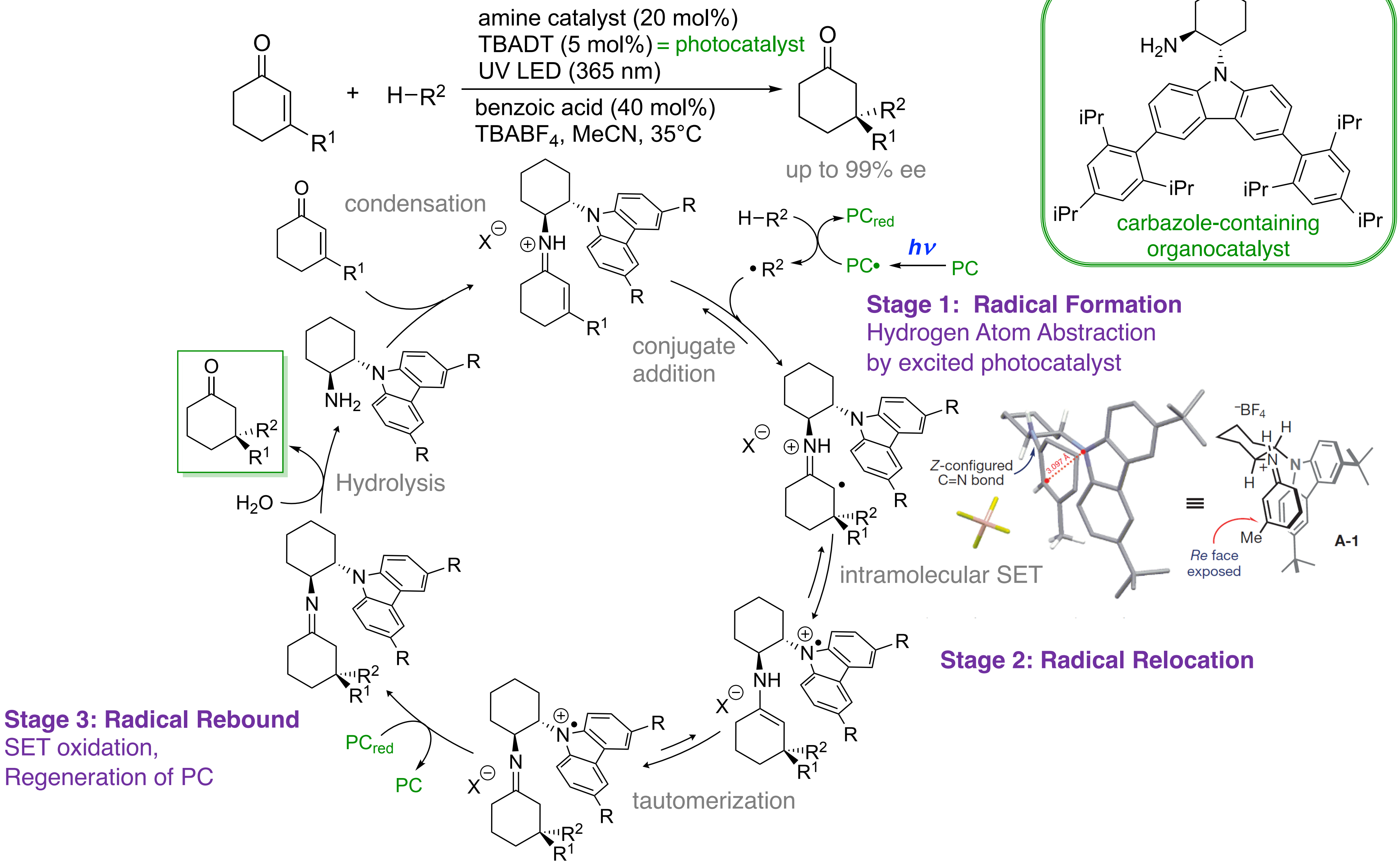
Cu(I)-catalyzed multicomponent coupling (Xiao and Chen, 2018)



X. Y. Yu, Q. Q. Zhao, J. Chen, J. R. Chen, W. J Xiao, *Angew. Chem. Int. Ed.* **2018**, *57,* 15505–15509

Examples – Intermolecular Radical Relays

Merging organocatalysis and photoredox catalysis (Melchiorre, 2016)



J. J. Murphy D. Bastida, S. Paria, M. Fagnoni, P. Melchiorre, *Nature* **2016**, *532,* 218–222

Examples – Intermolecular Radical Relays

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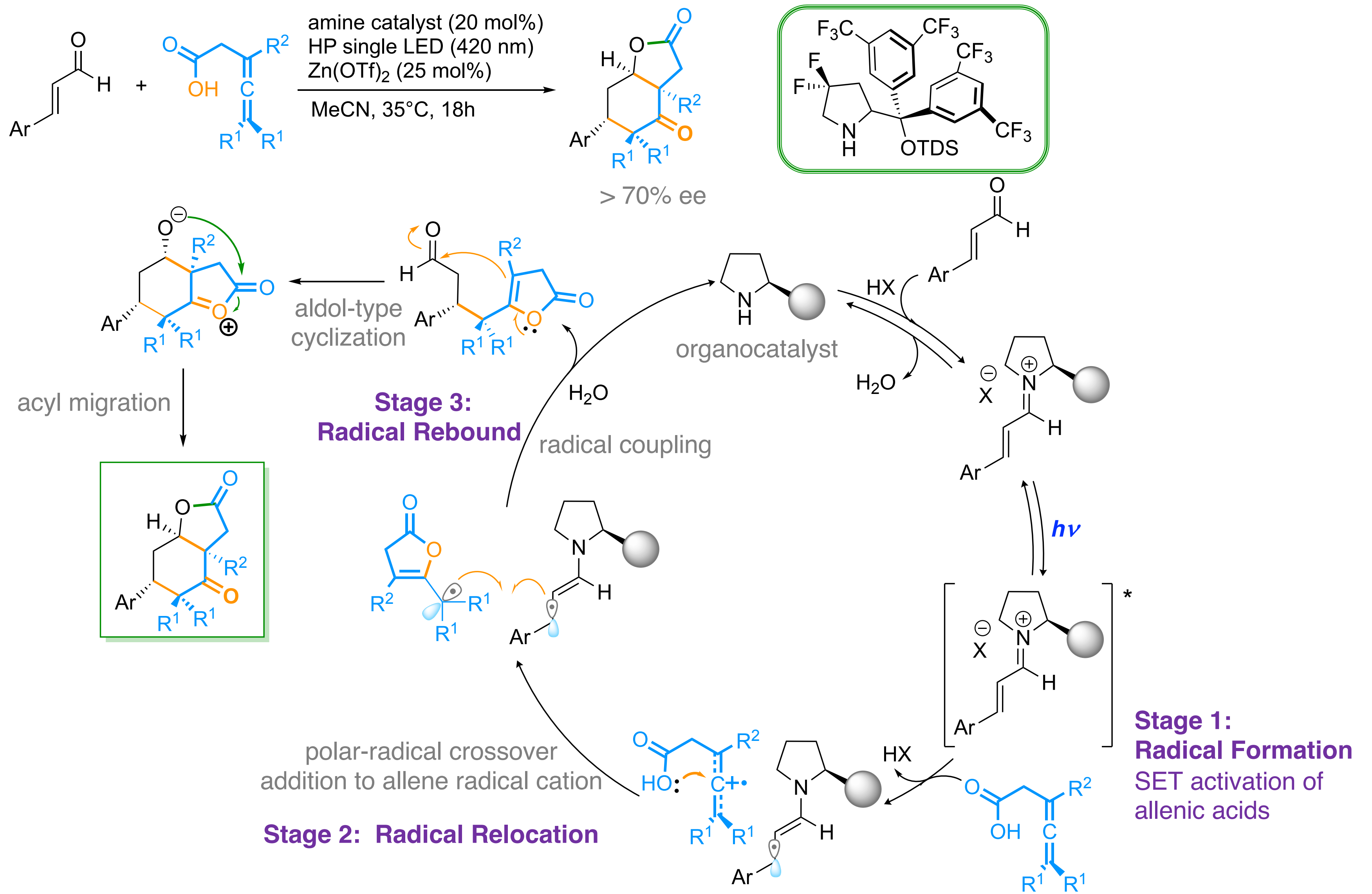


L. A. Perego, P. Bonilla, P. Melchiorre, *Adv. Synth. Catal.* **2020**, *362*, 302–307

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

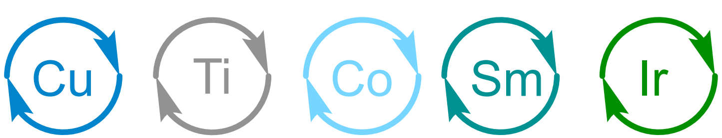
Strategies for radical relocation:

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

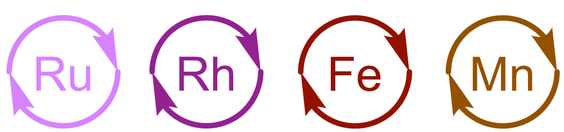
Following the Baldwin Rules

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!

EPFL

ISIC - LSPN

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.

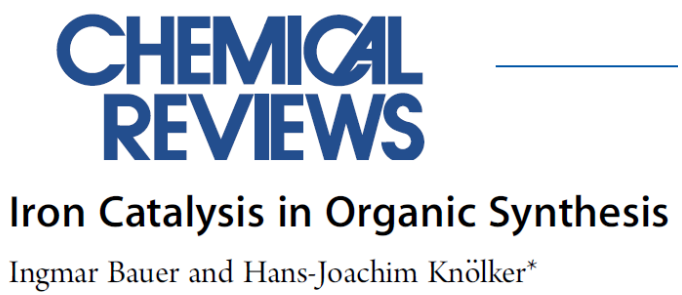
E. Bauer, Ed. , *Iron Catalysis II*, Springer International Publishing, Cham, **2015**.

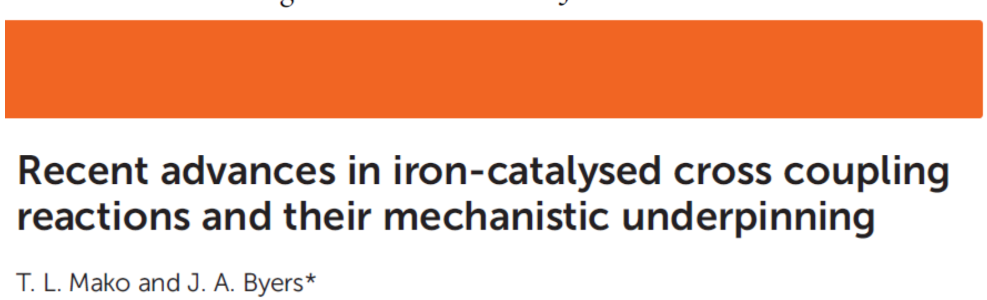
Reviews:

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





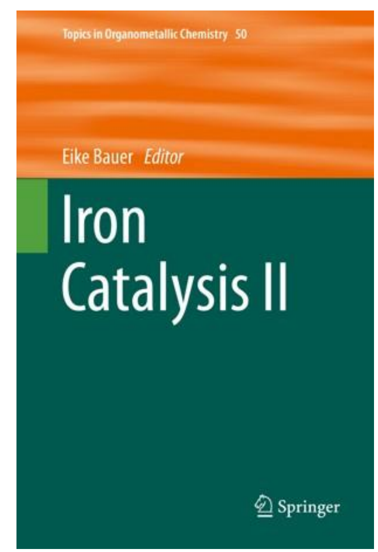


Table of contents

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

Fe

[Ar] $3d^6$ $4s^2$

Transition metal

Stable isotopes: ^{54}Fe, **^{56}Fe**, ^{57}Fe, ^{58}Fe

$FeCl_2$, $FeCl_3$, $Fe(acac)_3$

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

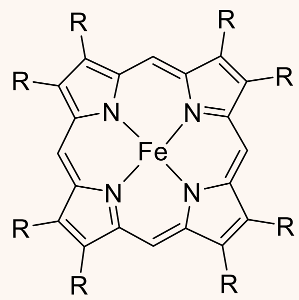
Readily available: 4th more abundant element in the Earth's crust

Cheap: 0.081 €/kg

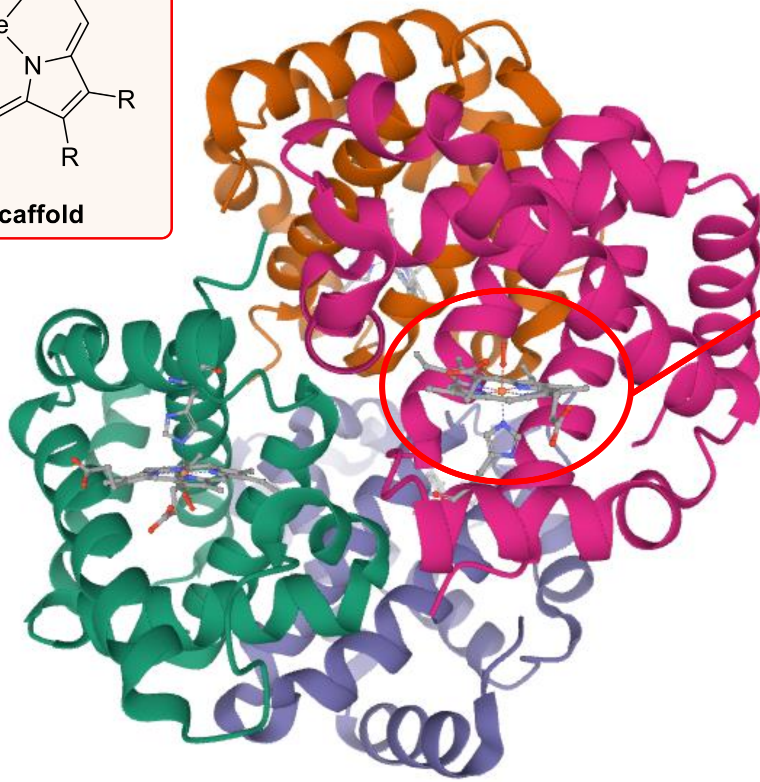
Relatively non-toxic:
Acceptable level in drugs → 1300 ppm Vs ≤10 ppm for most transition metals

A. Fürstner *et al.*, *ACS Cent. Sci.* **2016**, *2*, 778–789
European Medicines Agency, Guideline on the Specification: Limits for Residues of Metal Catalysts or Metal Reagents, EMEA/CHMP/SWP/4446/2000, London, February 21, 2008.

In biology: Transport of oxygen in vertebrates

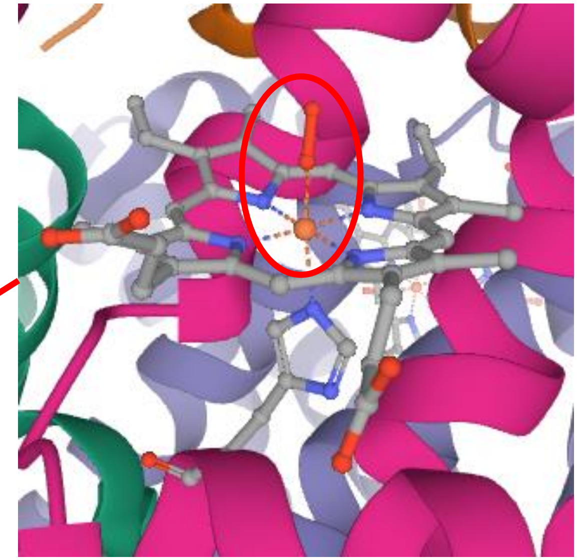


Heme scaffold



Hemoglobin

Oxygen complexation



<u>Structure of hemoglobin</u>: https://www.rcsb.org/3d-view/1GZX/1

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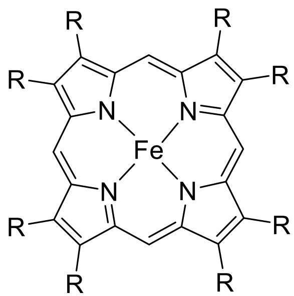

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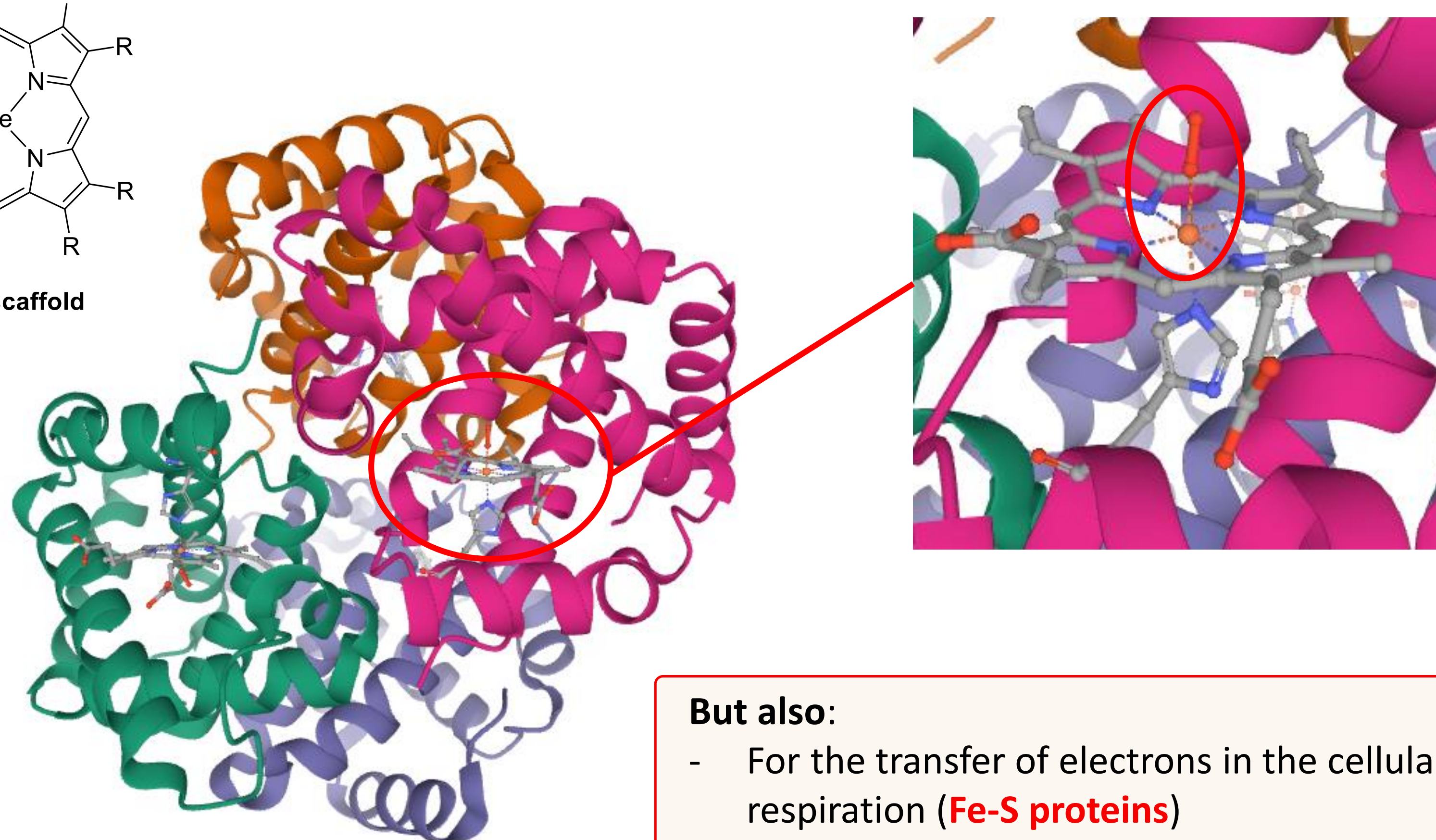

Hemoglobin

But also:

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

Structure of hemoglobin: https://www.rcsb.org/3d-view/1GZX/1

Introduction

Applications in industrial productions:

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

$$N_2 + 3\,H_2 \xrightarrow[\substack{450\text{-}550\ ^\circ C \\ 250\text{-}350\ \text{bar}}]{\textbf{Fe cat.}} 2\,NH_3$$

  → Main source of ammonia for nitrogen fertilizer

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

$$n\,CO + (2n{+}1)\,H_2 \xrightarrow[150\text{-}300\ ^\circ C]{\textbf{Fe, Co or Ru cat.}} C_nH_{2n+2} + n\,H_2O$$

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

$$CO + H_2O \xrightarrow[\substack{\text{ii) Cu/Zn/Al cat.} \\ 200\text{-}250\ ^\circ C}]{\substack{\text{i) } \textbf{Fe/Cr/Mg}\text{ cat.} \\ 310\text{-}450\ ^\circ C}} CO_2 + H_2$$

A. Fürstner *et al.*, *ACS Cent. Sci.* **2016**, *2*, 778–789
S. Gangula *et al.*, *Org. Process Res. Dev.* **2015**, *19*, 470–475

Introduction

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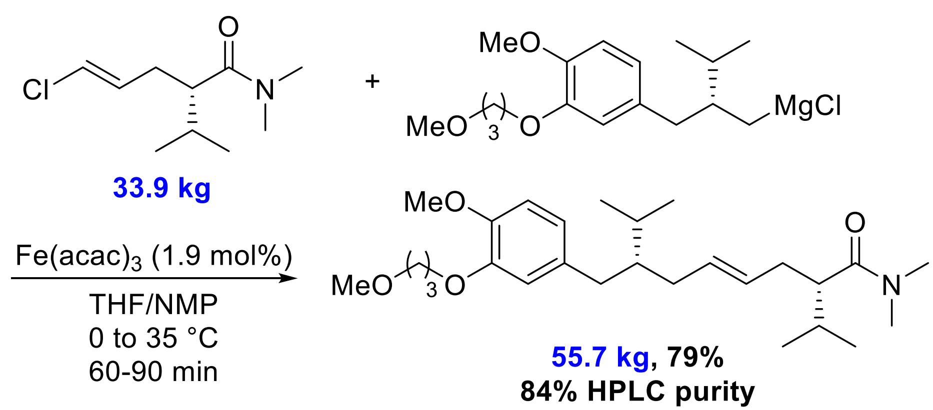
$$CO + H_2O \xrightarrow[\text{ii) Cu/Zn/Al cat., 200-250 °C}]{\text{i) Fe/Cr/Mg cat., 310-450 °C}} CO_2 + H_2$$

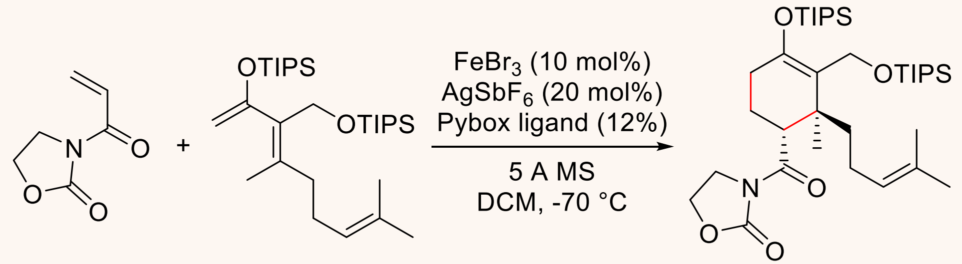
- Current investigations in cross-couplings:



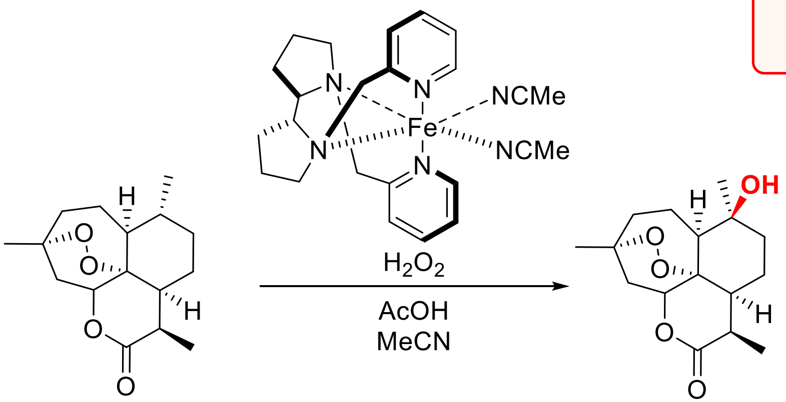
A. Fürstner *et al.*, *ACS Cent. Sci.* **2016**, *2*, 778–789
S. Gangula *et al.*, *Org. Process Res. Dev.* **2015**, *19*, 470–475

Broad range of applications:

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



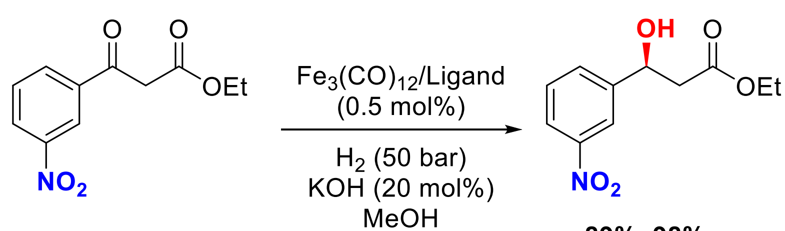
99%, > 33:1 exo/endo
87% ee



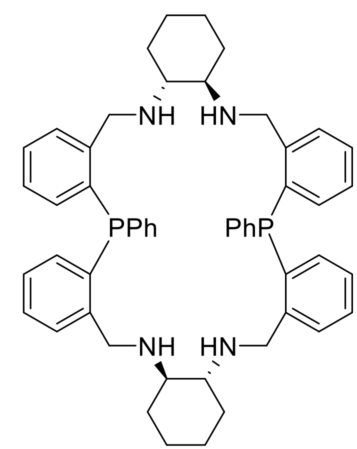
54%

As catalyst in oxidation: C-H functionalization

In catalytic hydrogenation:



89%, 98% ee



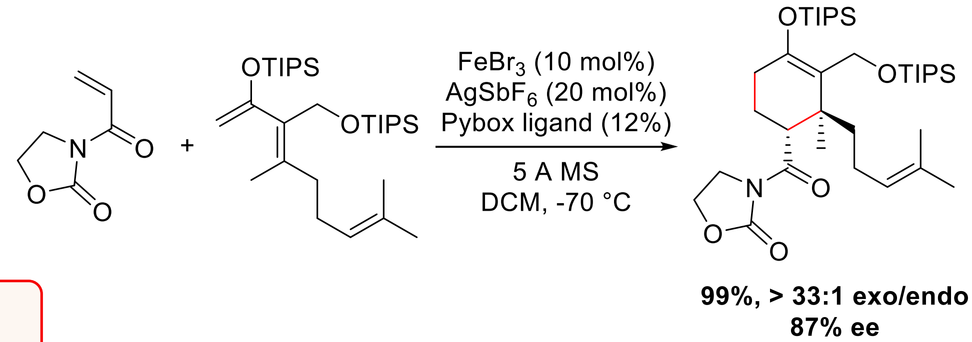
Ligand

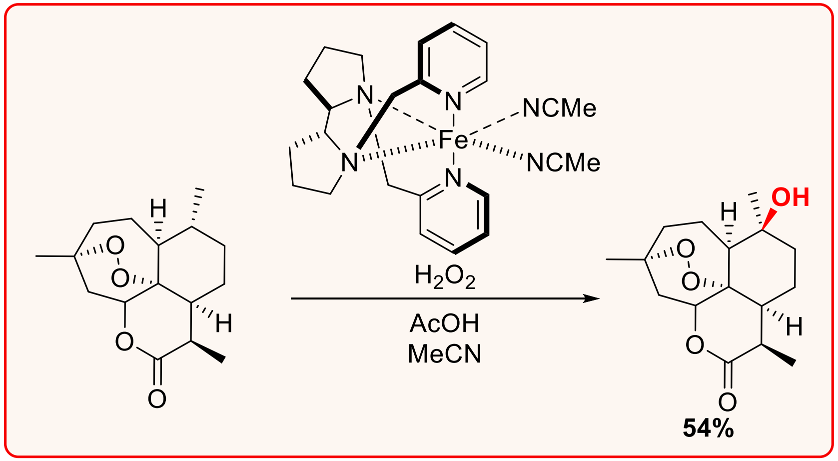
M. Shibasaki *et al., Org. Lett.* **2004**, *6,* 4387-4390
M. S. Chen and M. C. White, *Science* **2007**, *318*, 783-787
J. Gao *et al., J. Am. Chem. Soc.* **2014**, *136*, 4031–4039

Introduction

Broad range of applications:

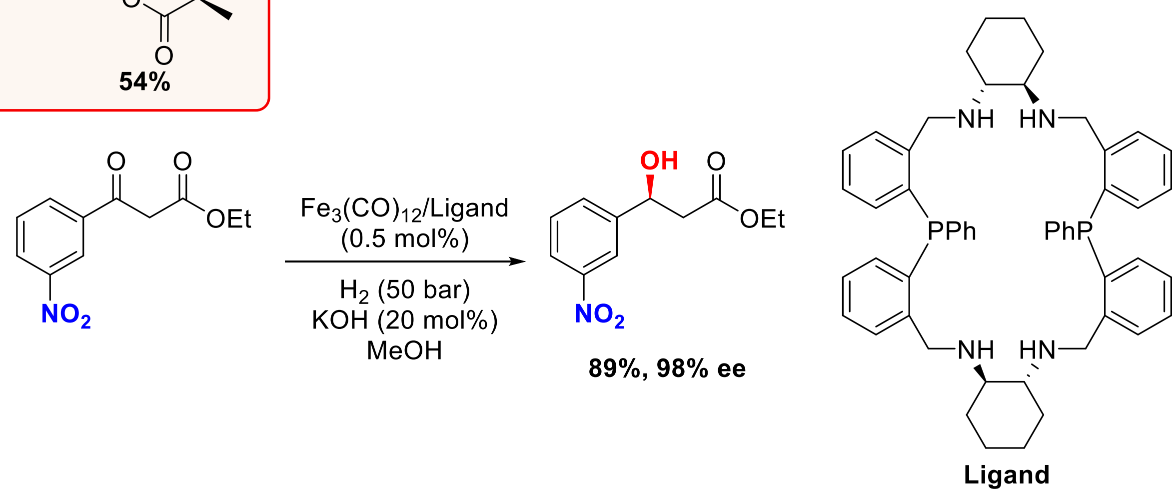
As Lewis acid: Diels-Alder, Friedel-Crafts, …





As catalyst in oxidation: C-H functionalization

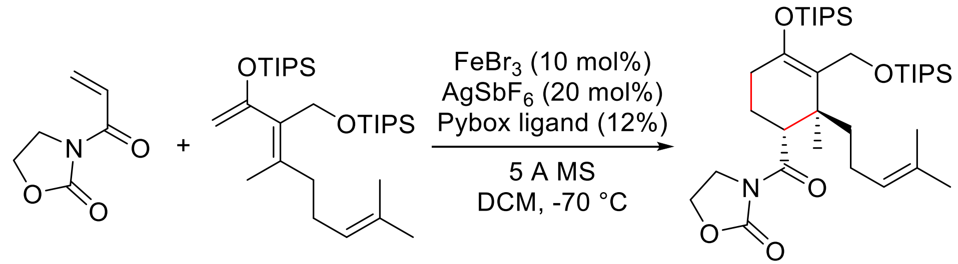
In catalytic hydrogenation:



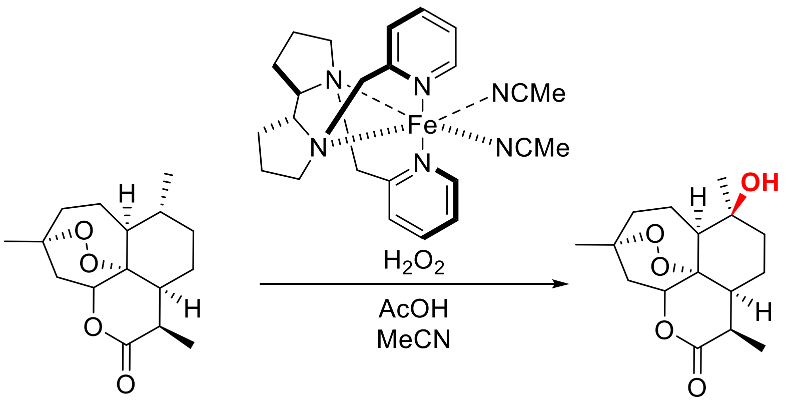
M. Shibasaki *et al., Org. Lett.* **2004**, *6,* 4387-4390
M. S. Chen and M. C. White, *Science* **2007**, *318*, 783-787
J. Gao *et al., J. Am. Chem. Soc.* **2014**, *136*, 4031–4039

Broad range of applications:

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



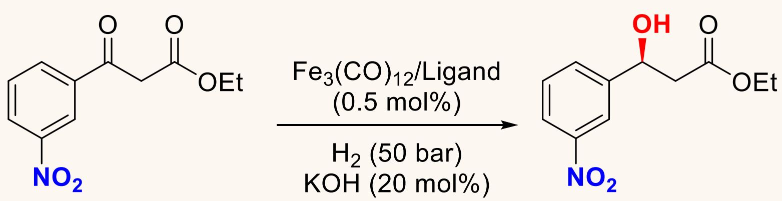
99%, > 33:1 exo/endo
87% ee



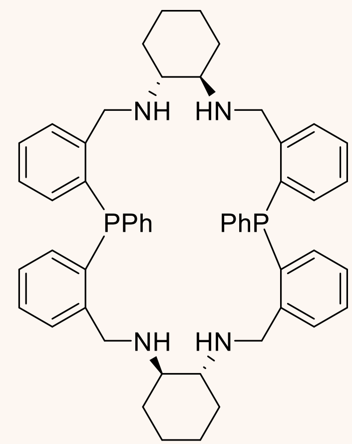
54%

As catalyst in oxidation: C-H functionalization

In catalytic hydrogenation:



89%, 98% ee



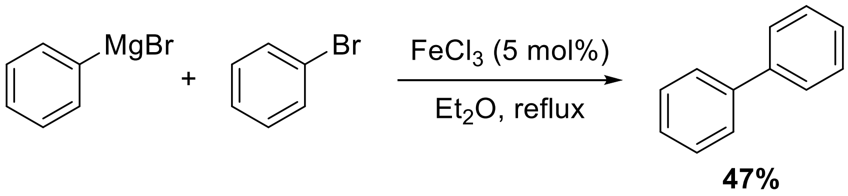
Ligand

M. Shibasaki *et al., Org. Lett.* **2004**, *6,* 4387-4390
M. S. Chen and M. C. White, *Science* **2007**, *318*, 783-787
J. Gao *et al., J. Am. Chem. Soc.* **2014**, *136*, 4031–4039

Preliminary work

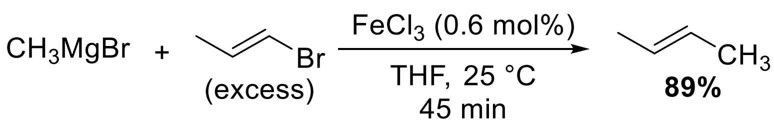
Initial report by Kharash, 1941

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

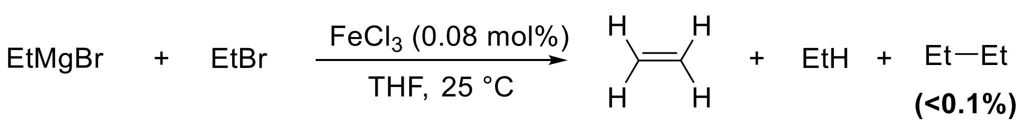


Development of Fe-catalyzed Kumada-Corriu cross coupling (Kochi, 1971)

- Applicable to alkenyl bromide and Grignard reagents



- Alkyl bromides converted in corresponding alkenes

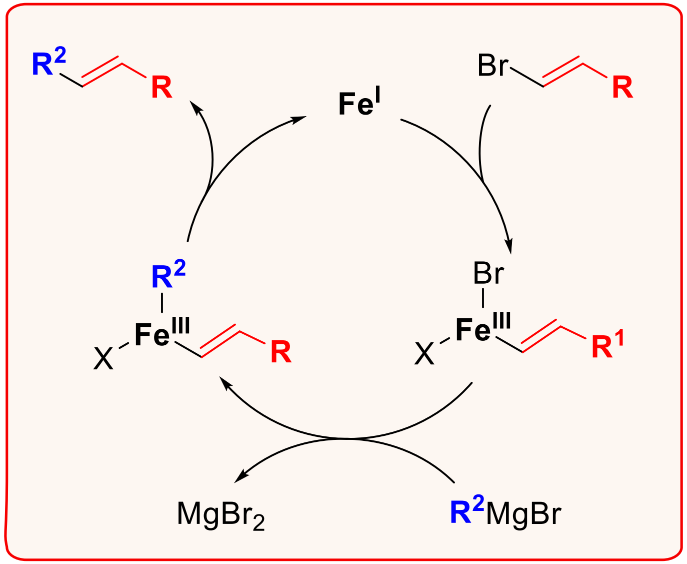


Further developed only 27 years later by Cahiez

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

Proposed mechanism:

Fe^{I}/Fe^{III} catalytic cycle



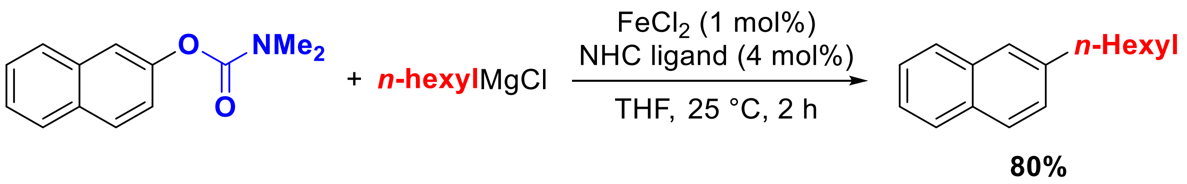
→ Intense ESR spectrum comparable with the one of **$HFe^{I}(dppe)_2$**

R. S. Smith, J. K. Kochi, *J. Org. Chem.* **1976**, *41*, 502-509

Recent progress in Kumada-Corriu cross-coupling

Applied to a broad range of electrophiles R-X:

→ X= Cl, Br, I, F, OTs, OTf, OPiv, OCO_2R, $OCONMe_2$, $OPO(OR)_2$, SO_2Cl, SO_2R, …



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

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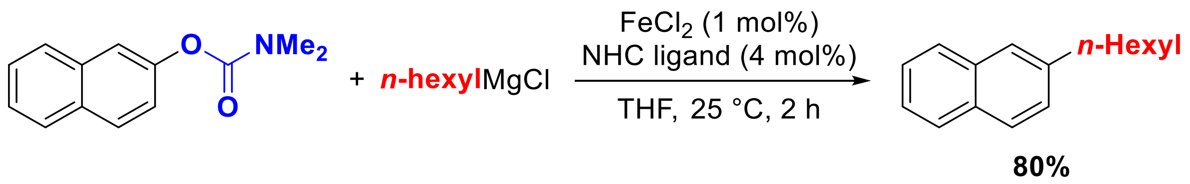
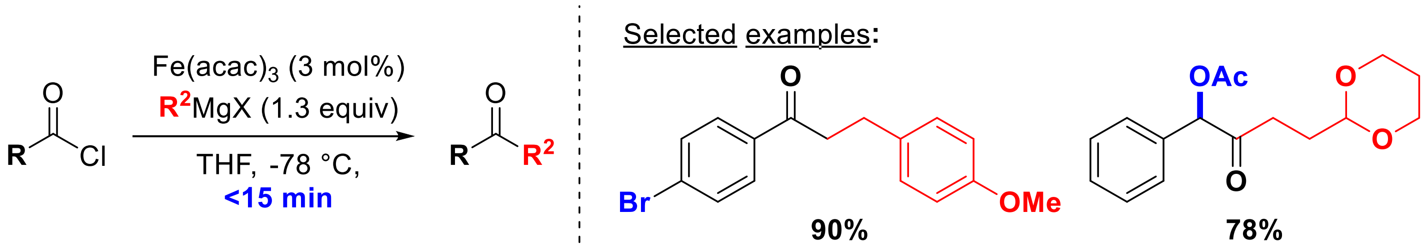


Very reactive but selective:



Z.-J. Shi et al., *J. Am. Chem. Soc.* **2009**, *131*, 14656-14657
Fürstner et al., *J. Org. Chem.* **2004**, *69*, 3943-3949
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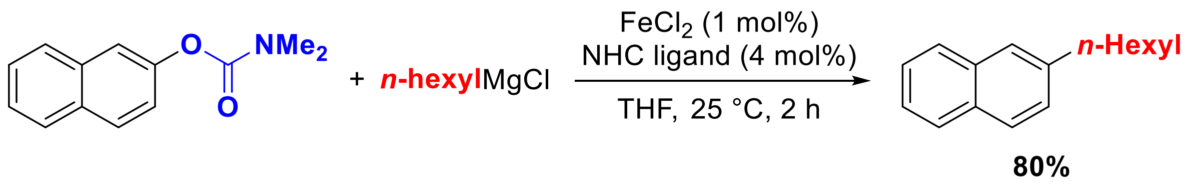

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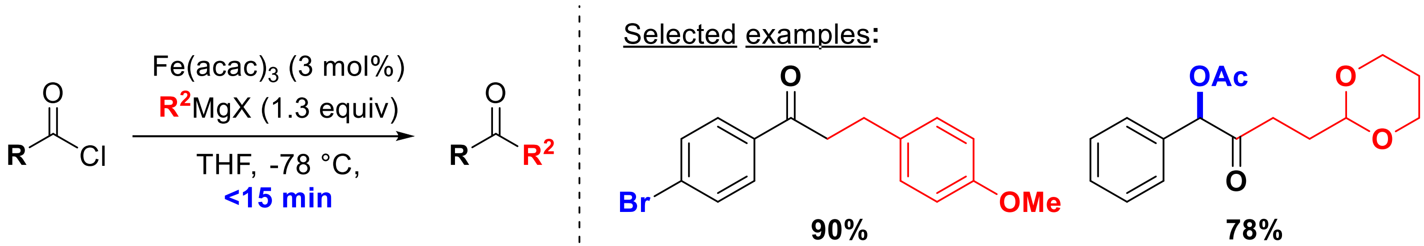
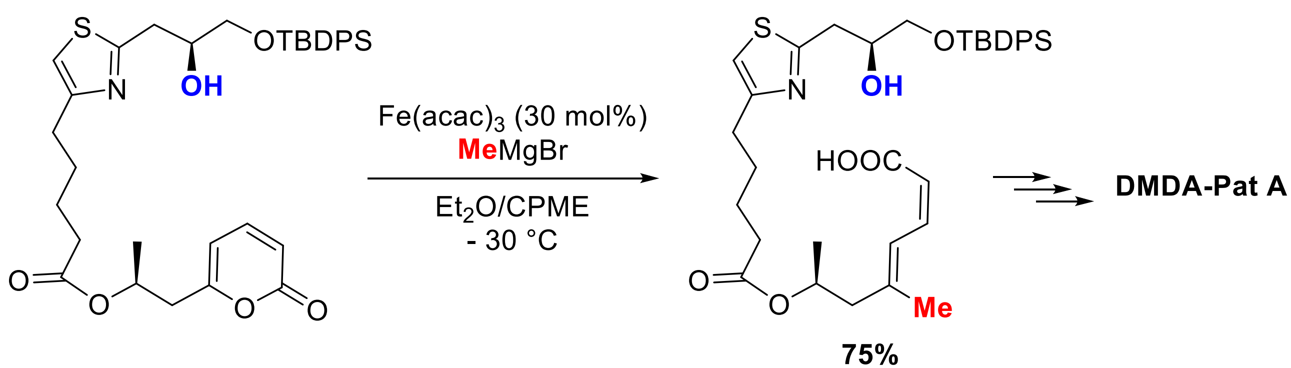


New reactivity:



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Fürstner et al., *J. Org. Chem.* **2004**, *69*, 3943-3949
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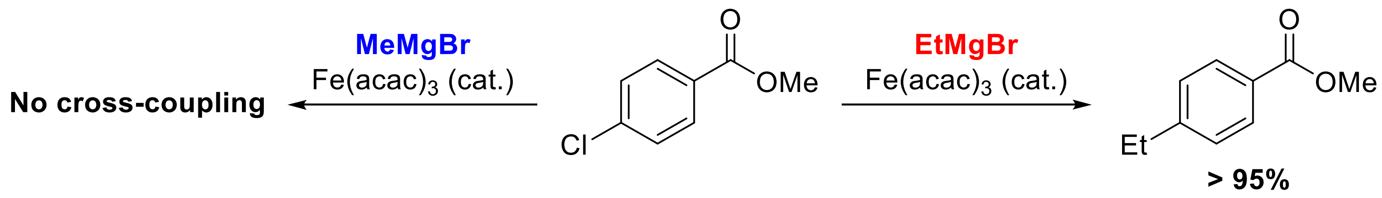
Centered on the mechanism:

→ Several proposed: Fe^{-II}/Fe^{0}, Fe^{0}/Fe^{II}, Fe^{I}/Fe^{III}, Fe^{II}/Fe^{III}, Fe^{II}/Fe^{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, …

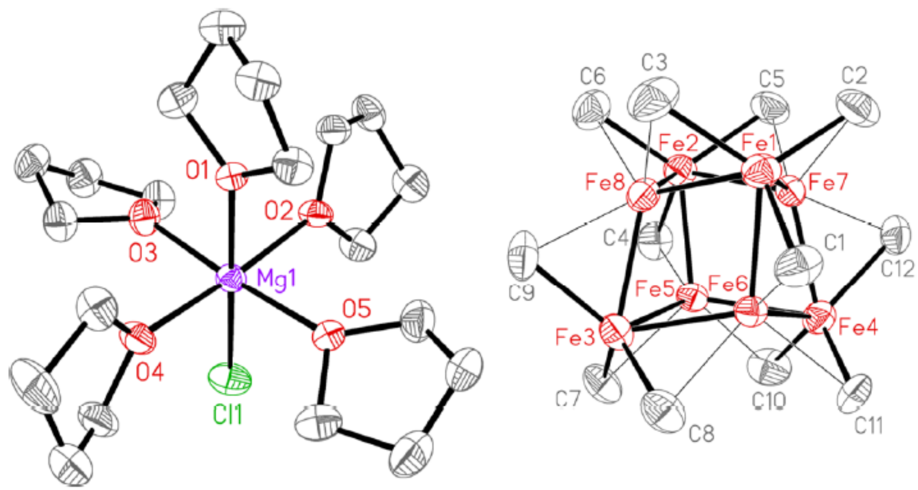
A. Fürstner *et al., J. Am. Chem. Soc.* **2008**, *130*, 8773-8787
M. L. Neidig *et al., J. Am. Chem. Soc.* **2018**, *140*, 11872−11883

Recent progress in Kumada-Corriu cross-coupling

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

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

→ Low activity alone, **require additional MeMgBr**



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

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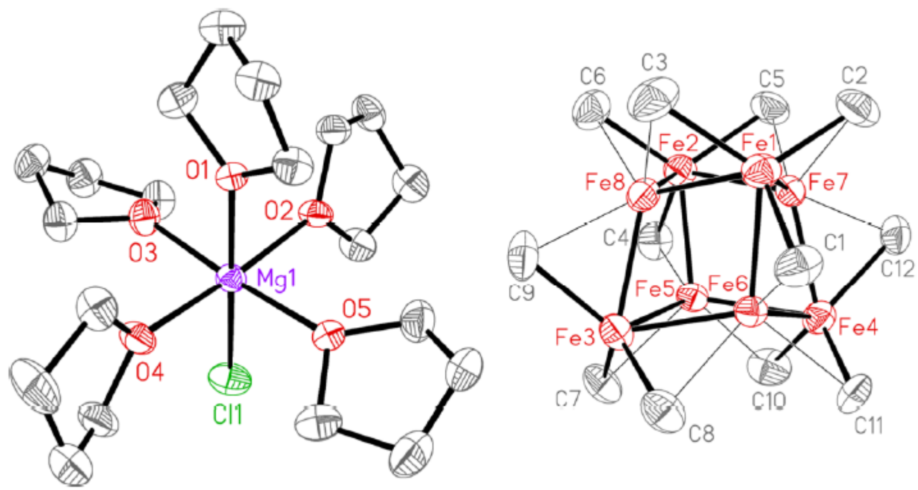
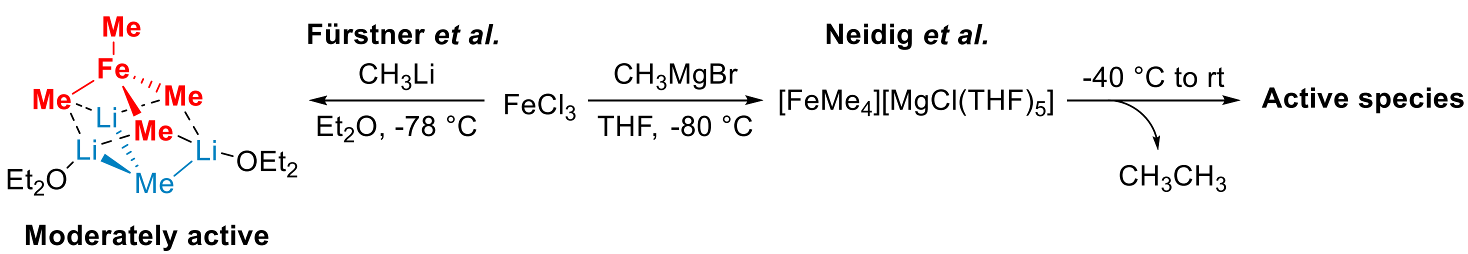


- Several organoferrates isolated upon reaction of $FeCl_3$ with RMetal



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M. L. Neidig *et al., J. Am. Chem. Soc.* **2016**, *138*, 7492–7495/
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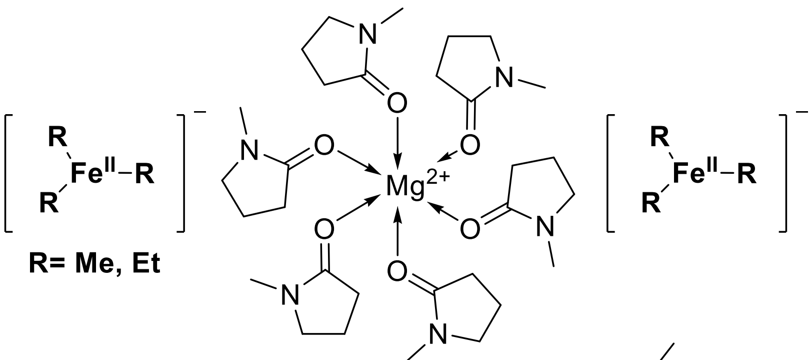
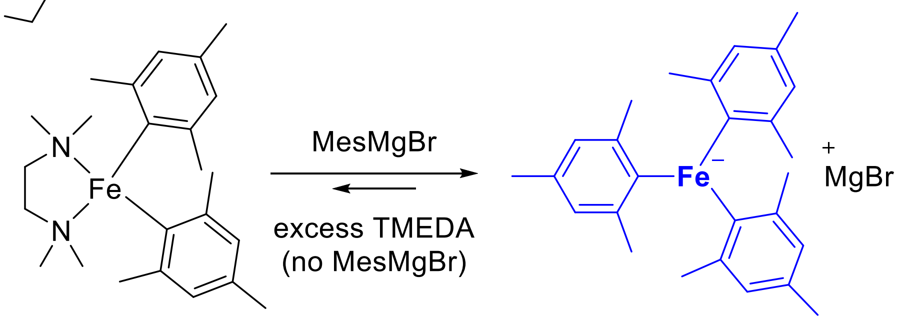
- Switch in presence of NMP or TMEDA:
    - Trialkyl ferrates isolated by Neidig → **catalytically active**



- TMEDA as chaperone



More active

Same observation With BnMgBr

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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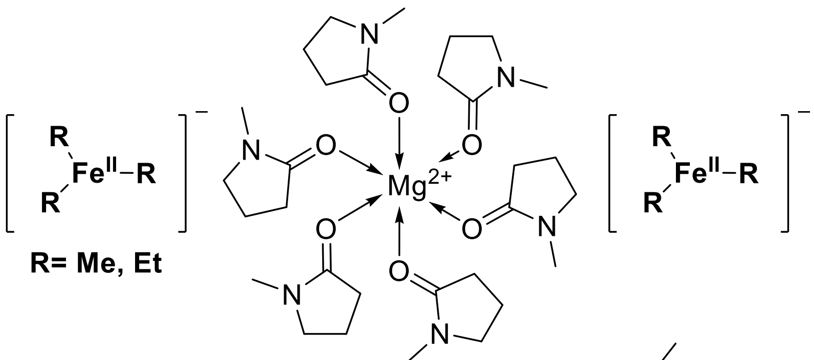

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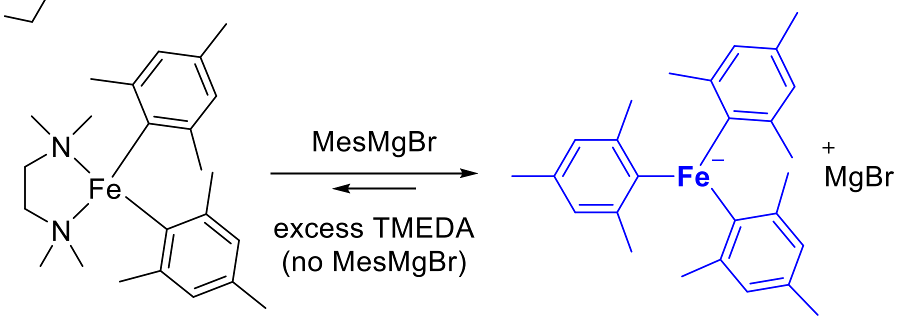


More active
Same observation With BnMgBr

→ **Exact mechanism not fully understood…** (≠ for trialkyl ferrate than iron cluster)

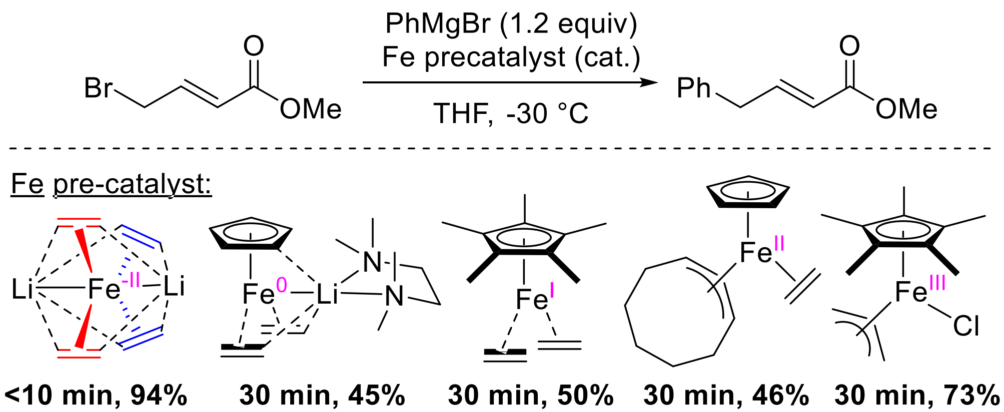
R. B. Bedford et al., *Angew. Chem. Int. Ed*. **2014**, *53*, 1804 –1808
M. L. Neidig *et al*., *Angew. Chem. Int. Ed.* **2018**, *57*, 6496 –6500 / *Angew.Chem. Int. Ed.* **2019**, *58*,2769 –2773
S. Sandt, A. J. von Wangelin, *Angew. Chem. Int. Ed*. **2020**, *59*, 5434 – 5437

Recent progress in Kumada-Corriu cross-coupling

Fe^{-II}/Fe^{0} mechanism proposed with R^1MgX (R^1 with β-H)

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

→ Several pre-catalysts synthesized and tried



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

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

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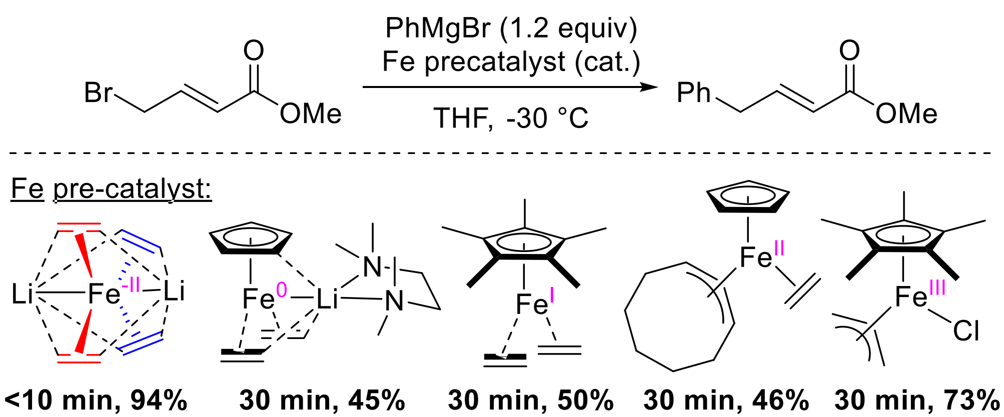

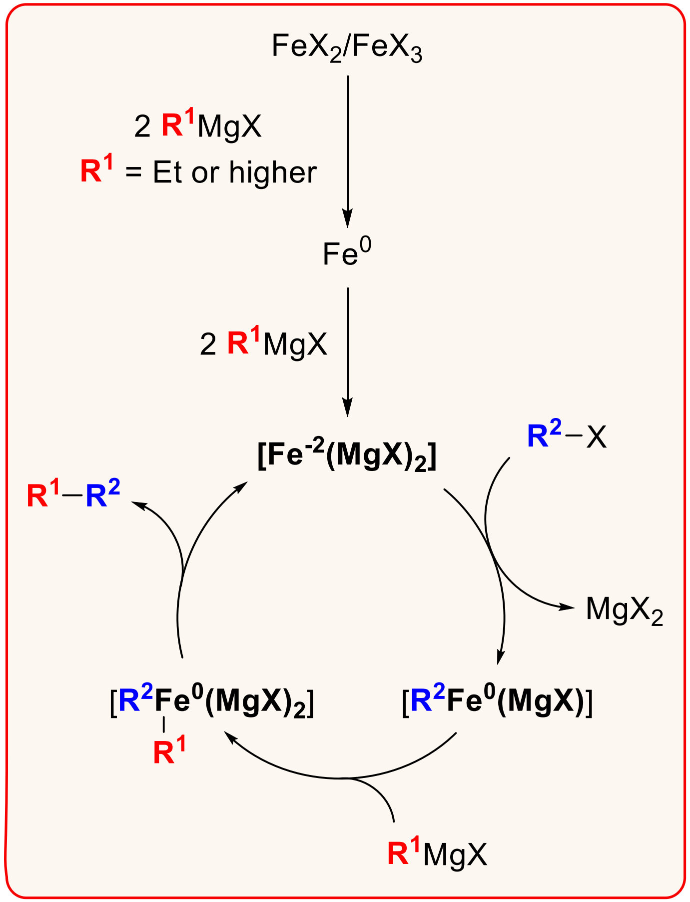

⇒ Higher activity for Fe^{-II} pre-catalyst

→ **Proposed mechanism:**

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

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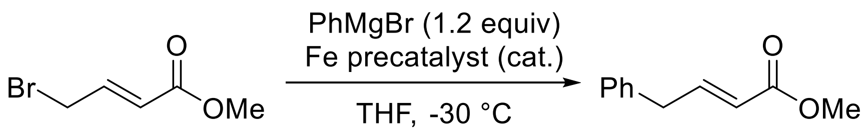
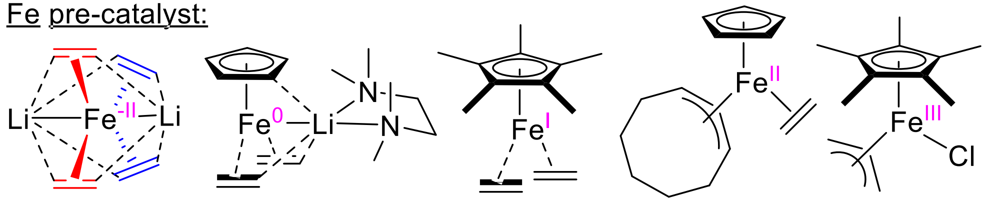


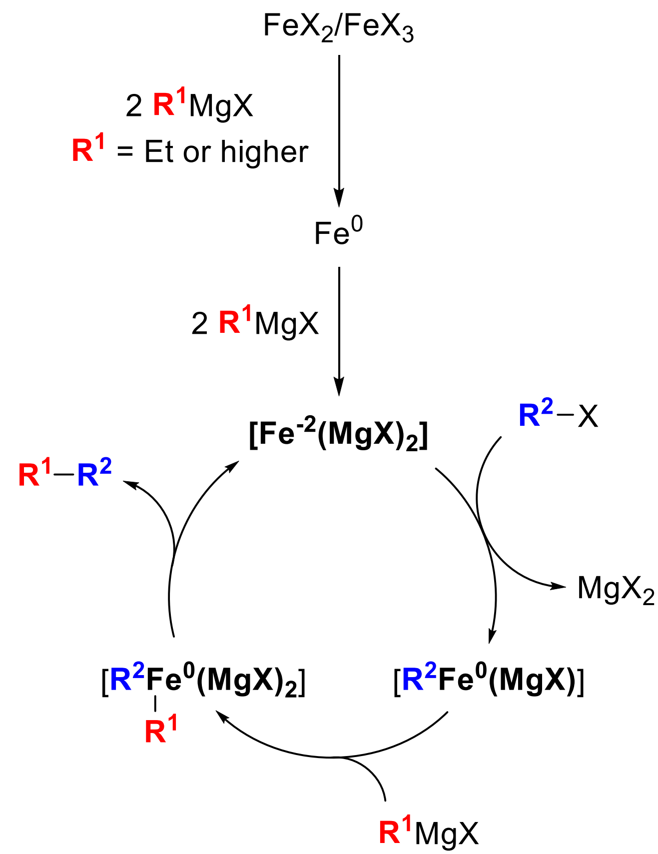
Fe pre-catalyst:



<10 min, 94%	**30 min, 45%**	**30 min, 50%**	**30 min, 46%**	**30 min, 73%**

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

→ Proposed mechanism:

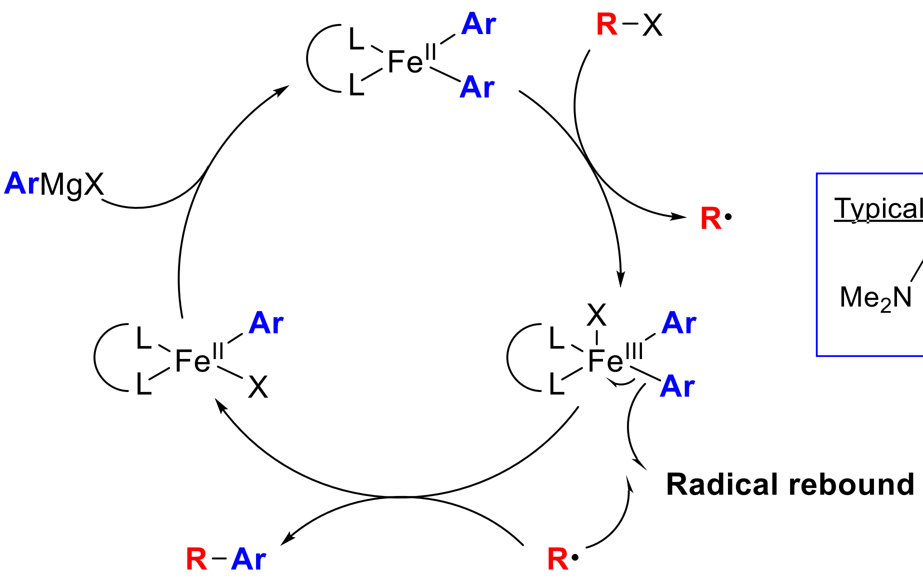


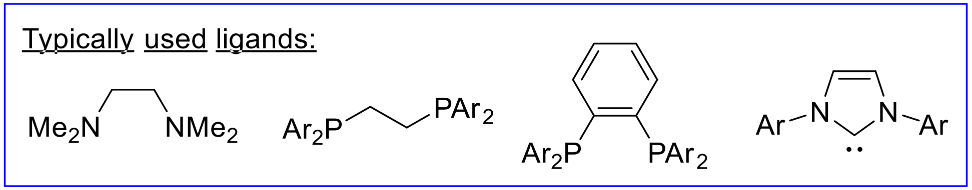
However:
- **Possible concomitant mechanisms**
- Only **pre-catalysts**
- **Different ligands** → strong influence

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

Recent progress in Kumada-Corriu cross-coupling

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





C.-J. Wallentin *et al.*, *ACS Catal.* **2016**, *6*, 1640–1648
M. Nakamura et al., *J. Am. Chem. Soc.* **2004**, *126*, 3686–3687.
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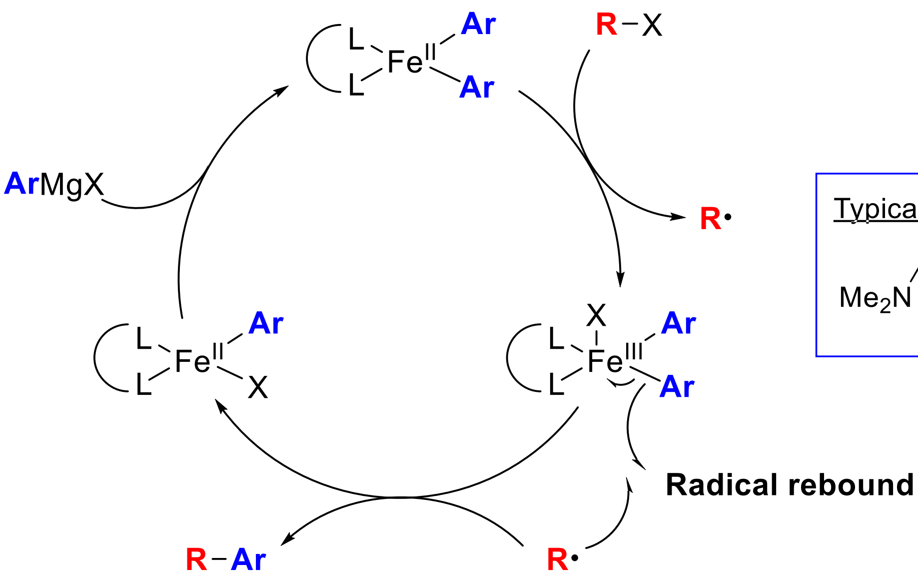
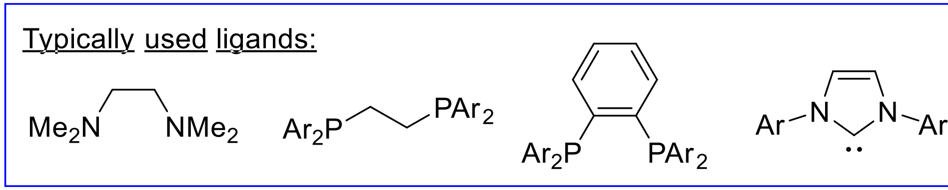
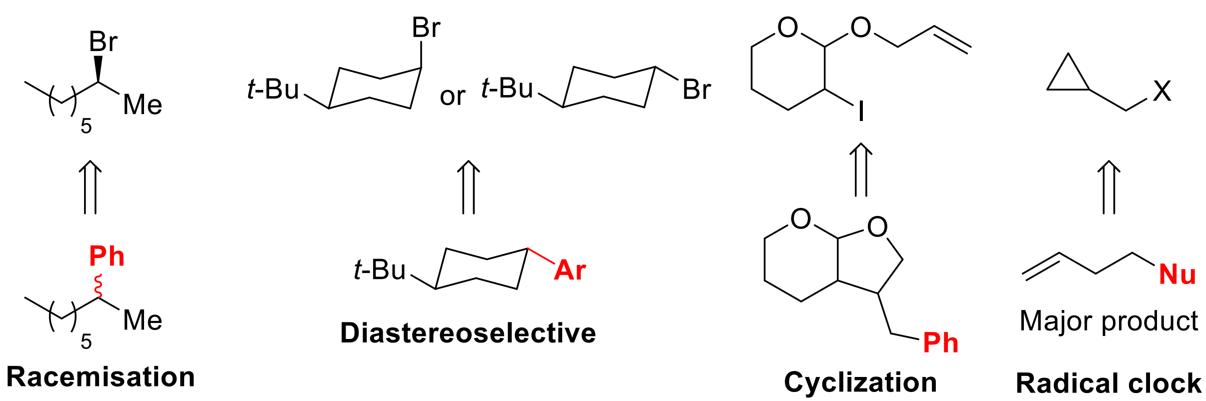




→ Whatever the mechanism, several experiments in favor of alkyl radicals:



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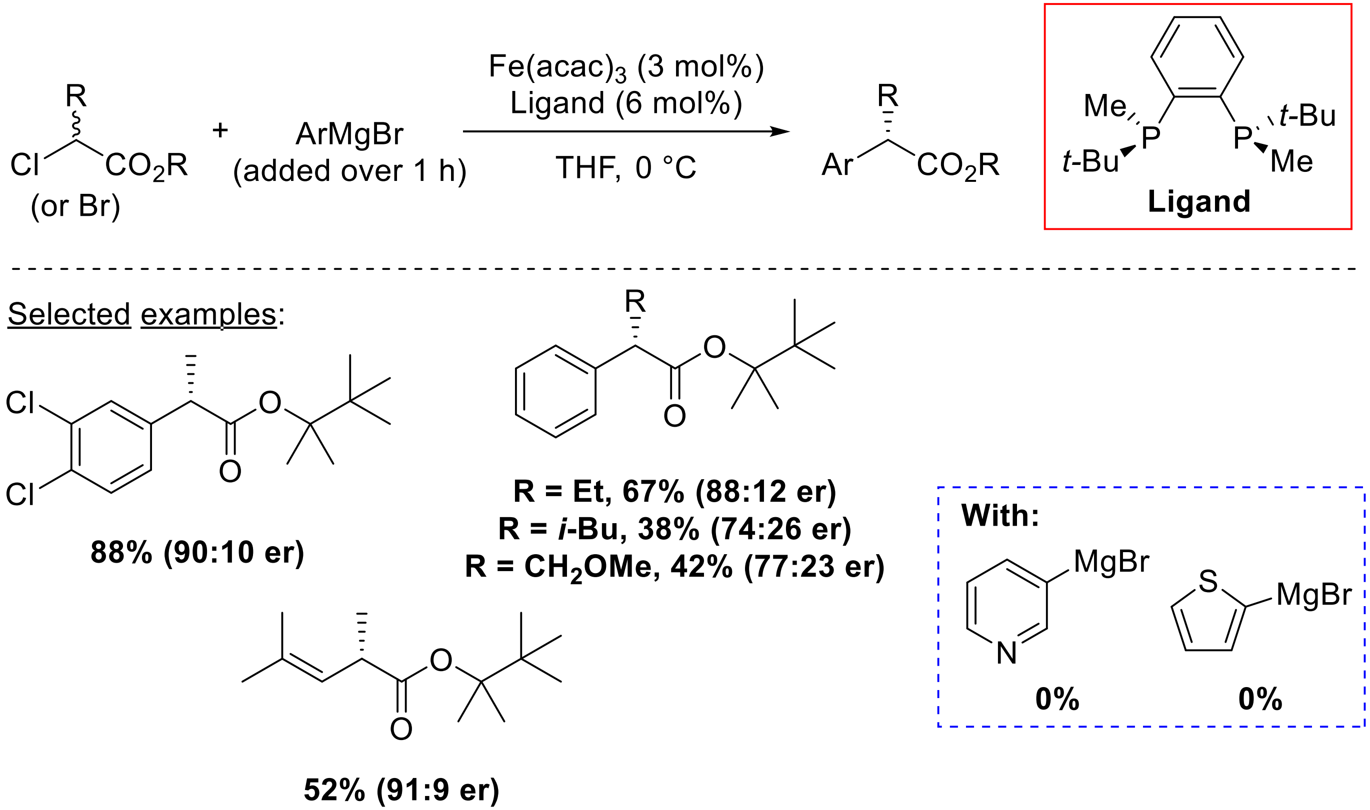
A. Fürstner et al., *Angew. Chem. Int. Ed.* **2004**, *43*, 3955 –3957

Enantioselective Kumada-Corriu cross-coupling

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

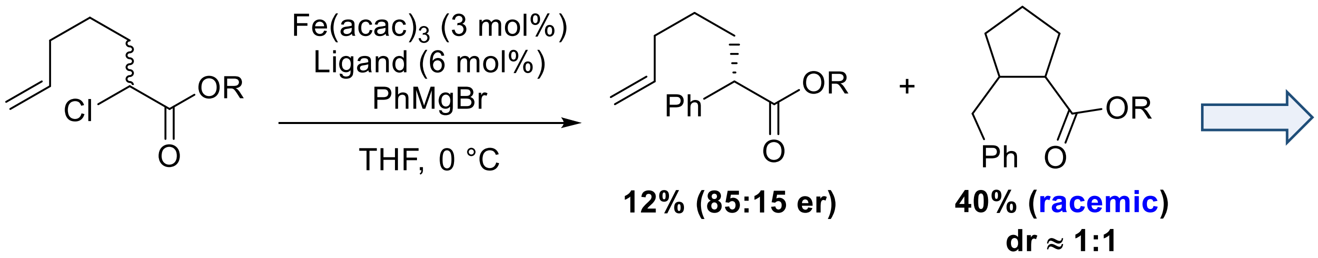
- Enantioconvergent coupling of aryl Grignard reagents with α-chloroesters



M. Nakamura *et al.*, *J. Am. Chem. Soc.* **2015**, *137*, 7128-7134

Enantioselective Kumada-Corriu cross-coupling

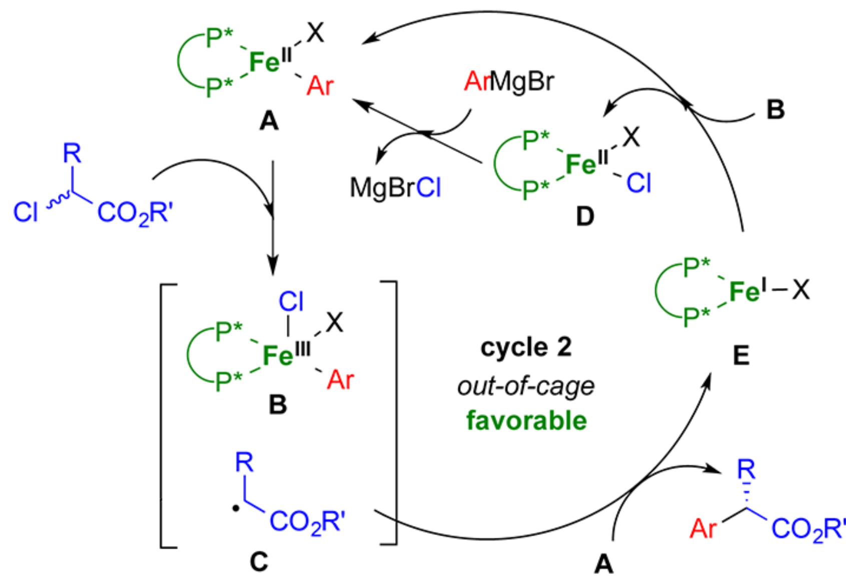
Mechanistic investigations:



Out-of-cage mechanism proposed

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

Bimetallic mechanism proposed:

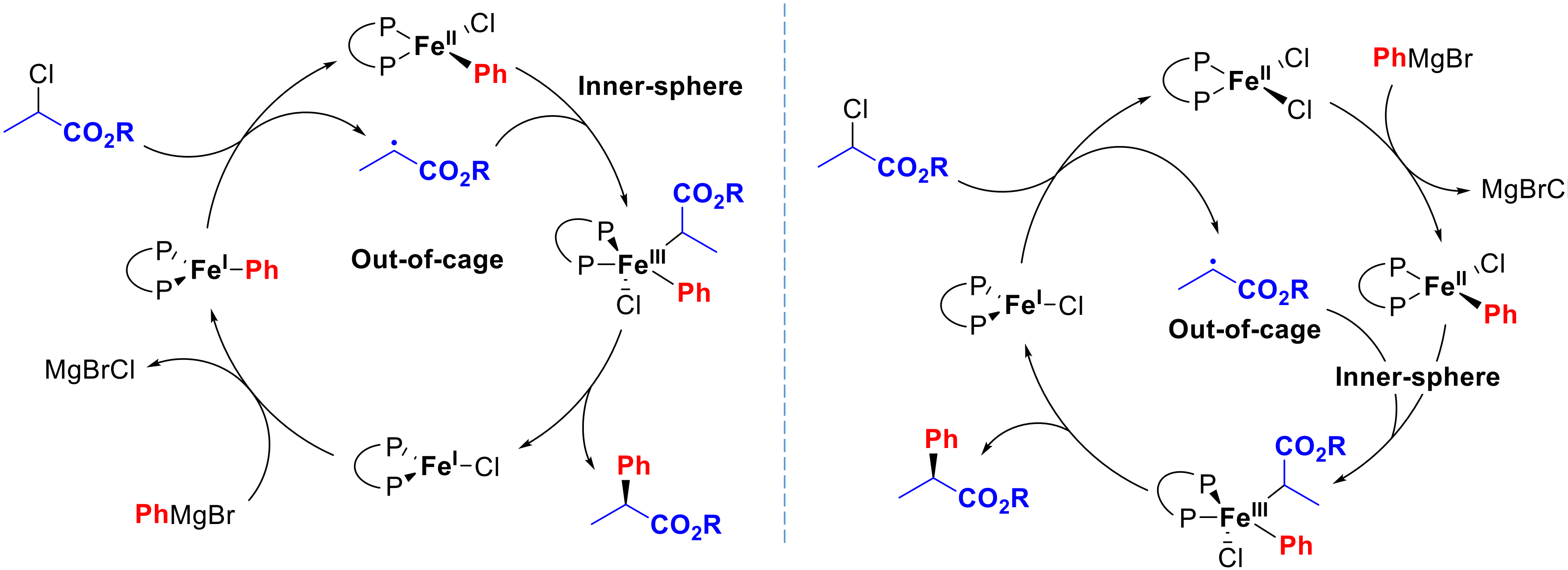


M. Nakamura *et al.*, *J. Am. Chem. Soc.* **2015**, *137*, 7128-7134

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

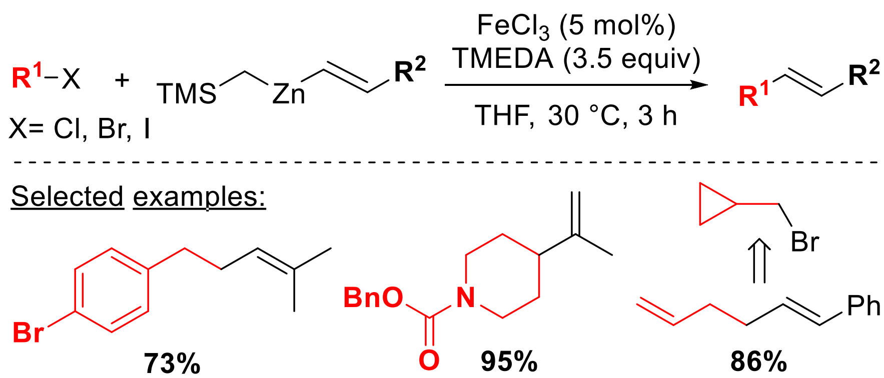
→ Dropwise addition of Grignard reagent important to avoid Fe^{II}PhPh (biphenyl formation)

→ Inner-sphere out-of-cage mechanism

O. Gutierrez *et al.*, *J. Am. Chem. Soc.* **2017**, *139*, 16126–16133
M. Nakamura, K. Morokuma *et al.*, *J. Am. Chem. Soc.* **2017**, *139*, 16117–16125

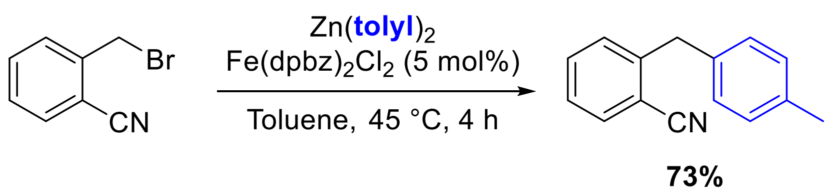
New development in Negishi cross-coupling

First reported with vinyl zinc reagents

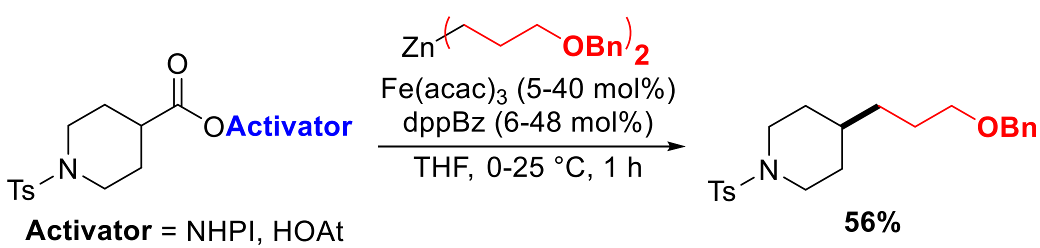


Only scarce numbers of reports

- With benzyl-X:



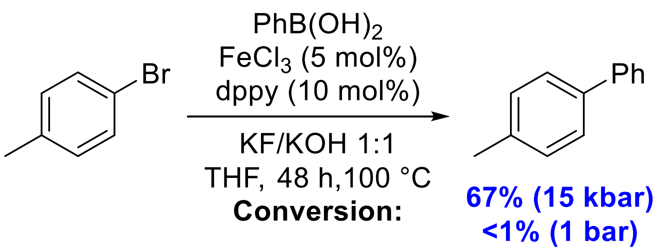
- Extended further with redox-active esters (1°, 2°, 3° alkyl-COOH/ Ar- and R_2Zn):



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

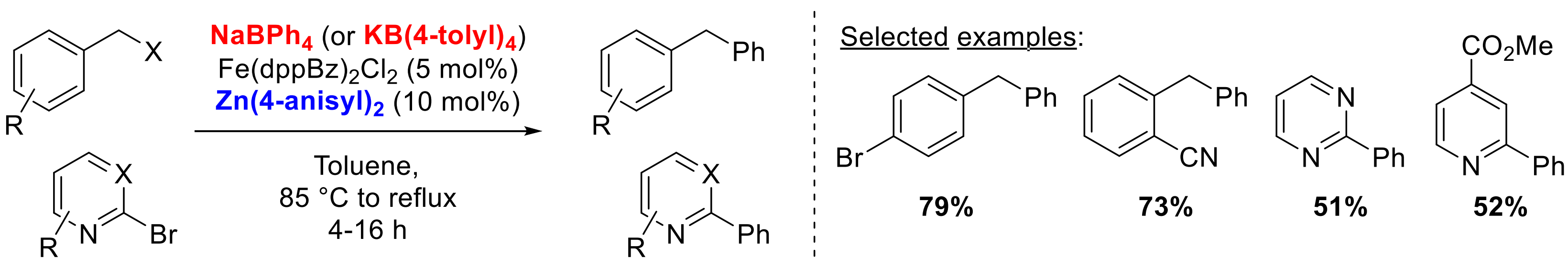
Few reports → Difficulty with the transmetallation/reduction step

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



High pressure required

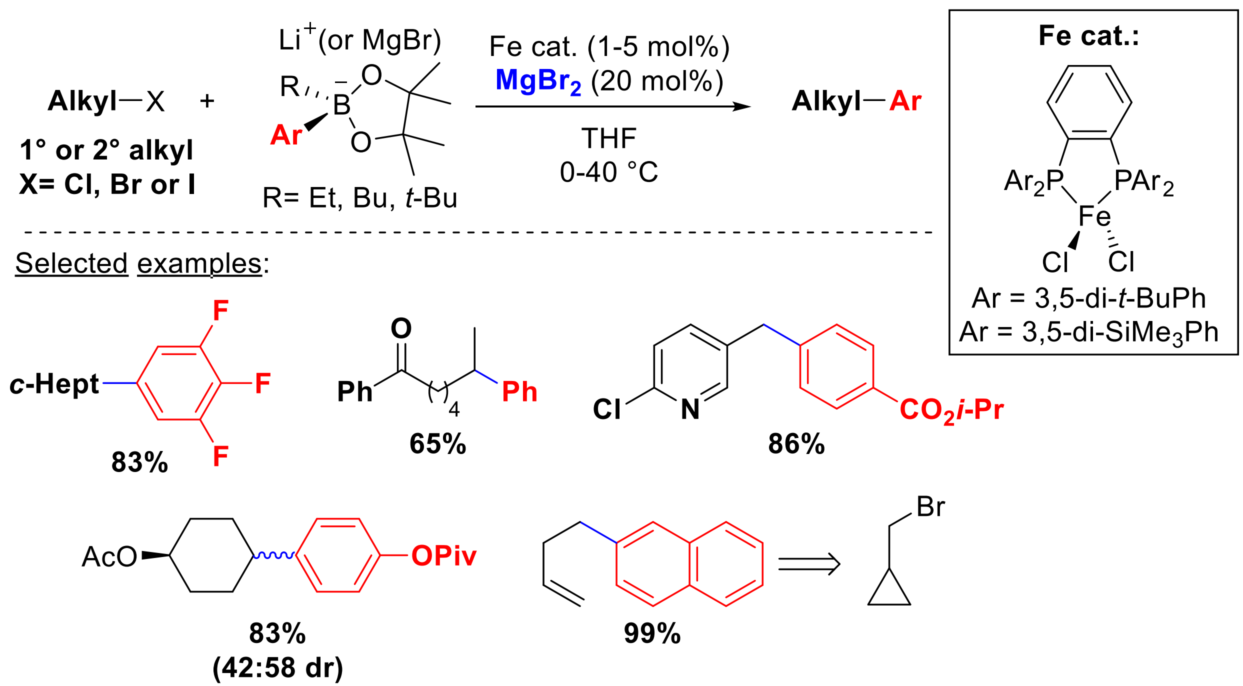
Solution: Use activated borate as nucleophile (Bedford et al., 2009)



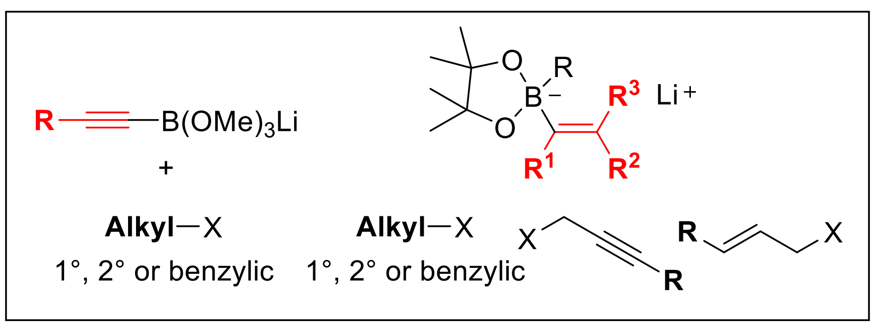
D. J. Young *et al.*, *Tetrahedron Lett.* **2008**, *49*, 5620-5621
R. B. Bedford *et al.*, *Chem. Commun.* **2009**, 6430–6432 / *Organometallics* **2014**, *33*, 5767-5780

Progress in Suzuki-Miyaura cross-coupling

Nakamura 2010



Extension of the scope

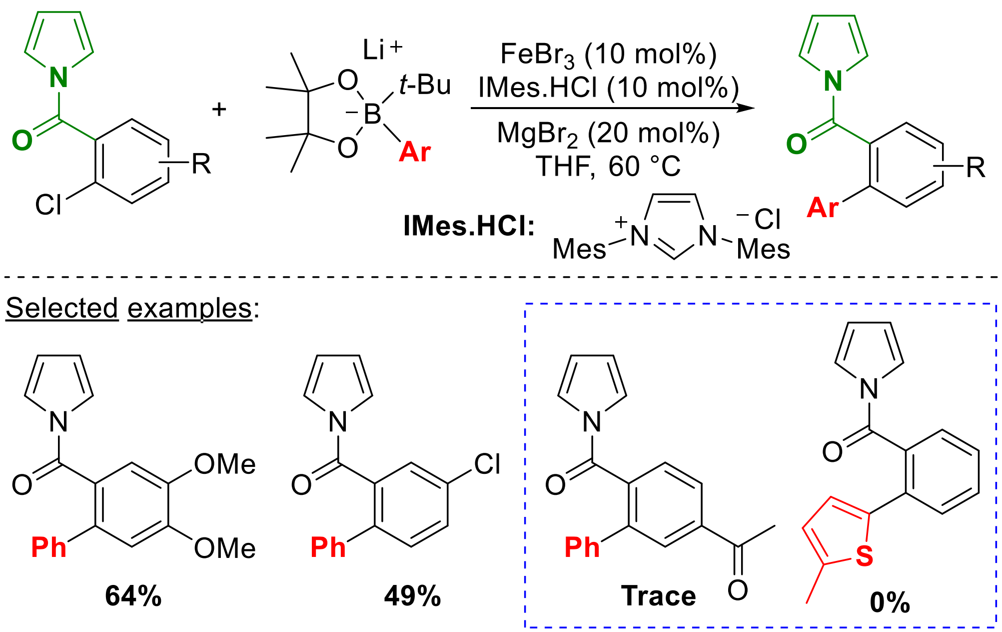


M. Nakamura *et al.*, *J. Am. Chem. Soc.* **2010**, *132*, 10674-10676 / *J. Org. Chem.* **2012**, *77*, 1168-1173 / *Chem. Lett.* **2015**, *44*, 486-488 / *Org. Biomol. Chem.* **2020**,*18*, 3022-3026
R. B. Bedford *et al.*, *Chem. Eur. J.* **2014**, *20,* 7935-7938

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)

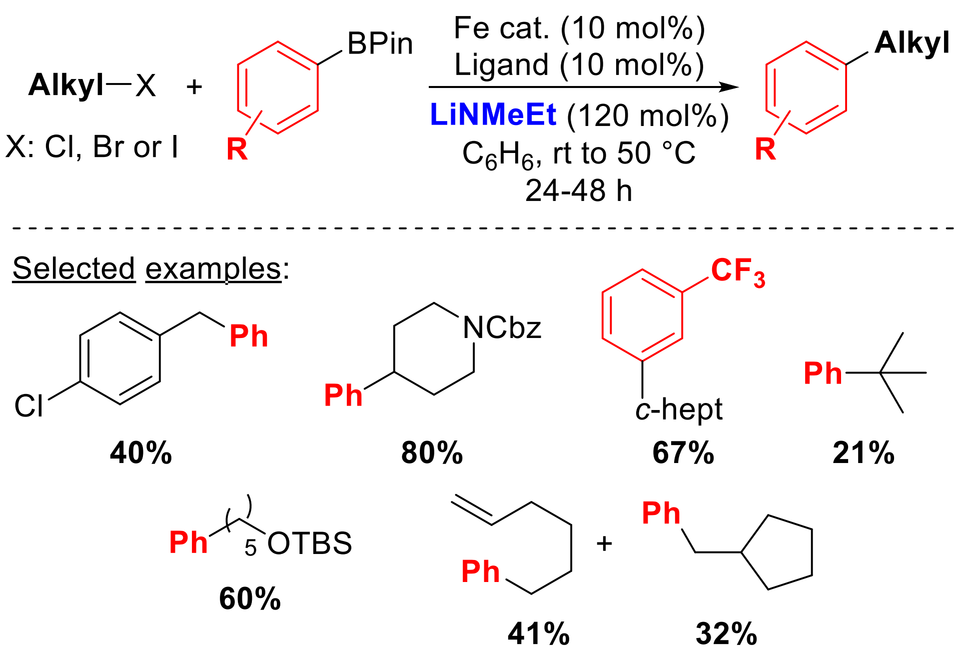


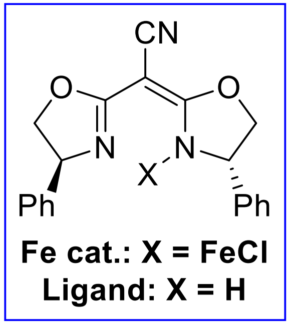
Proof of contaminations: R. B. Bedford, M. Nakamura *et al., Tetrahedron Lett.* **2009**, *50*, 6110-6111
R. B. Bedford *et al.,* Synthesis **2015**, *47*, 1761-1765 / *Nat. Catal.* **2018**, *1,* 429–437

Progress in Suzuki-Miyaura cross-coupling

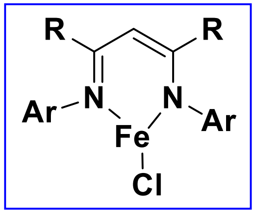
Byers's work with ligand tuning

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





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

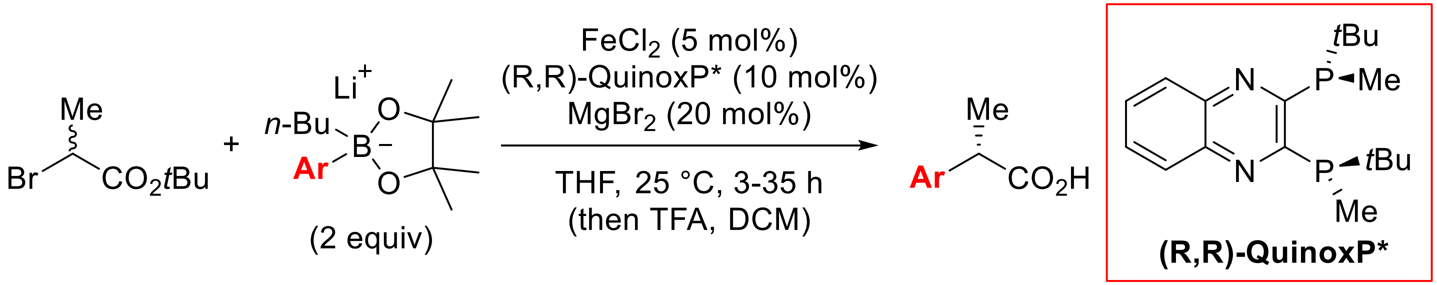


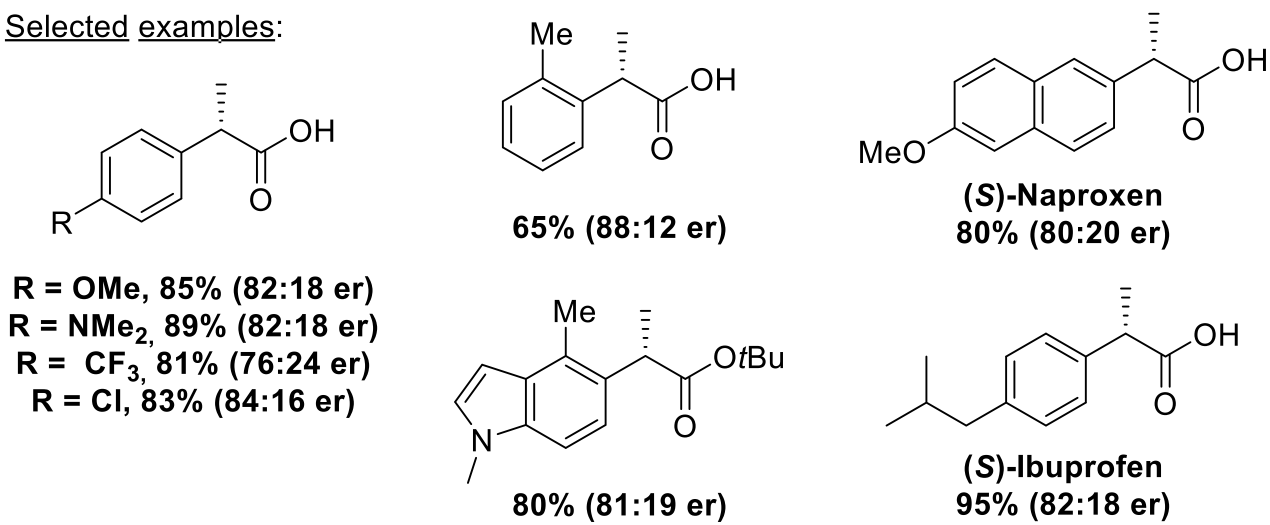
Byers *et al.*, *Org. Lett.* **2018**, *20*, 5233-5237 / *Angew. Chem. Int. Ed.* **2020**, *59*, 5392-5397

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



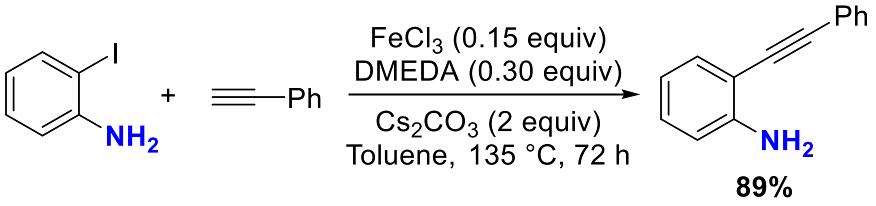


M. Nakamura *et al.*, *Chem. Commun.* **2019**, 55, 1128-1131

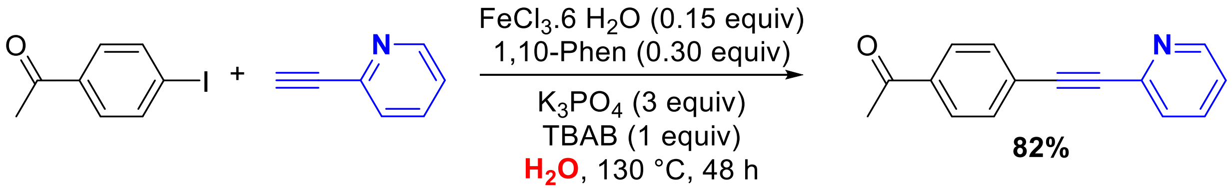
Point on Fe-catalyzed Sonogashira

Still under developed …

- First report by Bolm and coworkers



- Designed in water



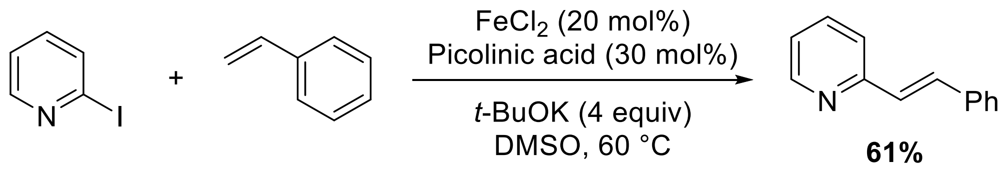
→ Few other reports but only very high temperature

C. Bolm *et al., Angew. Chem. Int. Ed.* **2008***, 47,* 4862 –4865
G. Anilkumar *et al., ChemistrySelect* **2016**, *3*, 556 –559

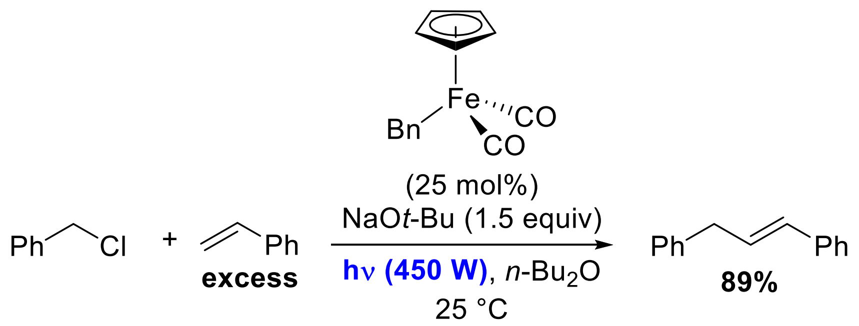
Fe catalysis in Heck-type cross-coupling

Only few reports

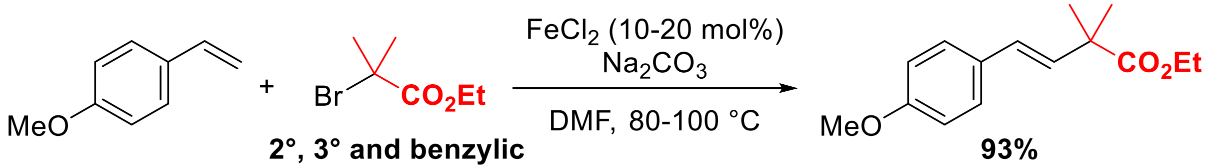
- Initial report by Vogel



- 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**

Conclusion and Outlooks

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⇨ However, **mechanisms still not fully understood …**

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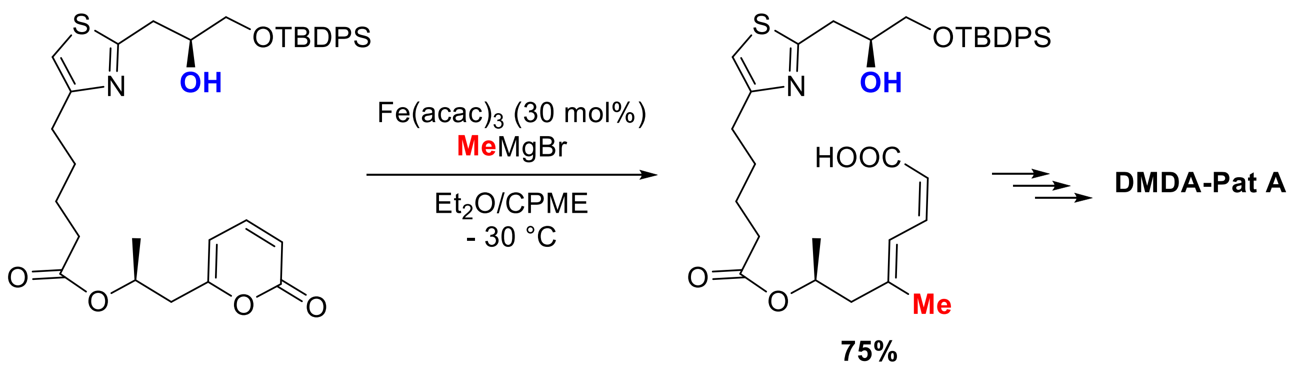
⇨ **Tuning of the ligands might be key …**

Thank you for your attention

Questions

Questions 1

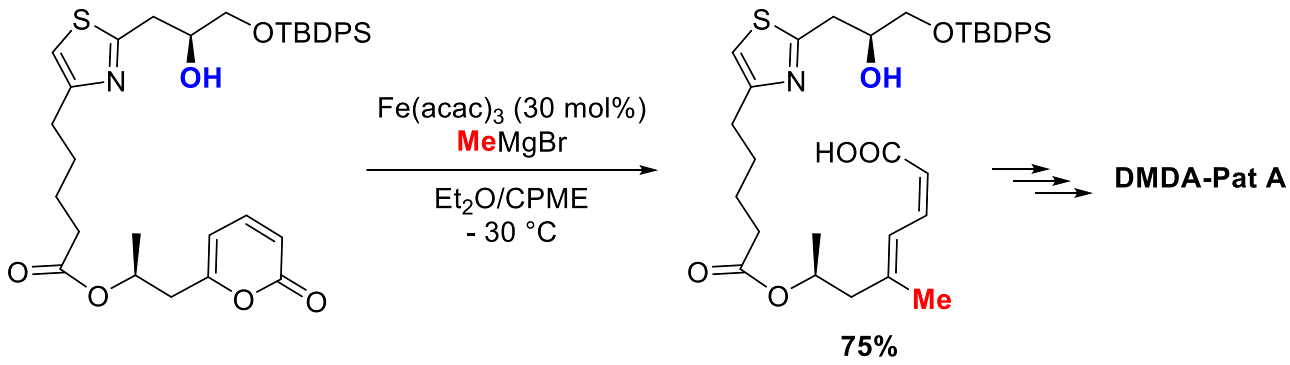
Can you suggest a mechanism for this transformation ?

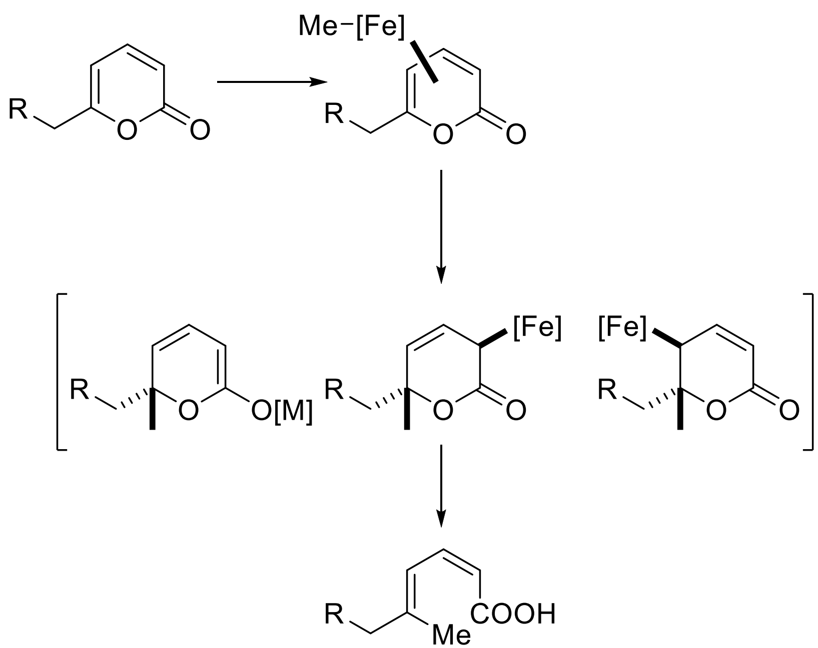


Fürstner et al., *Angew. Chem. Int. Ed.* **2013**, *52*, 13071 –13075

Questions 1

Can you suggest a mechanism for this transformation ?





Fürstner et al., *Angew. Chem. Int. Ed.* **2013**, *52*, 13071 –13075

Questions 2

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

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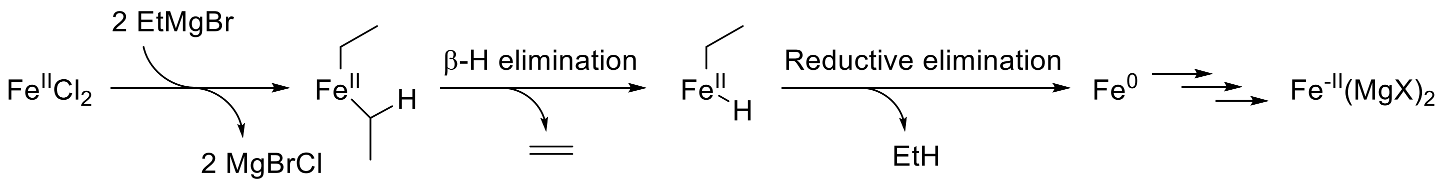
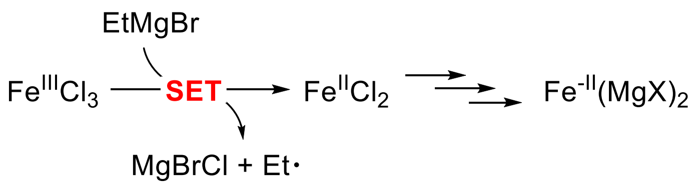
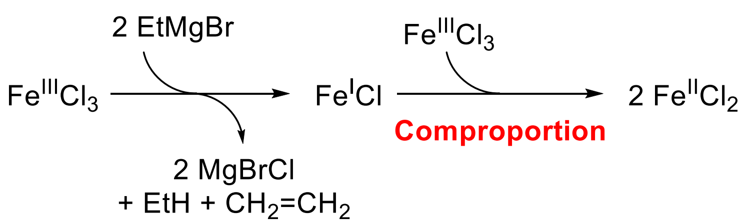
Propose a mechanism for the reduction of Fe^{II} to Fe^{-II} and Fe^{III} to Fe^{-II}



1.


2.


Catalytic Enantioselective Syntheses and Transformations of Cyclopropyl Ketones and Derivatives

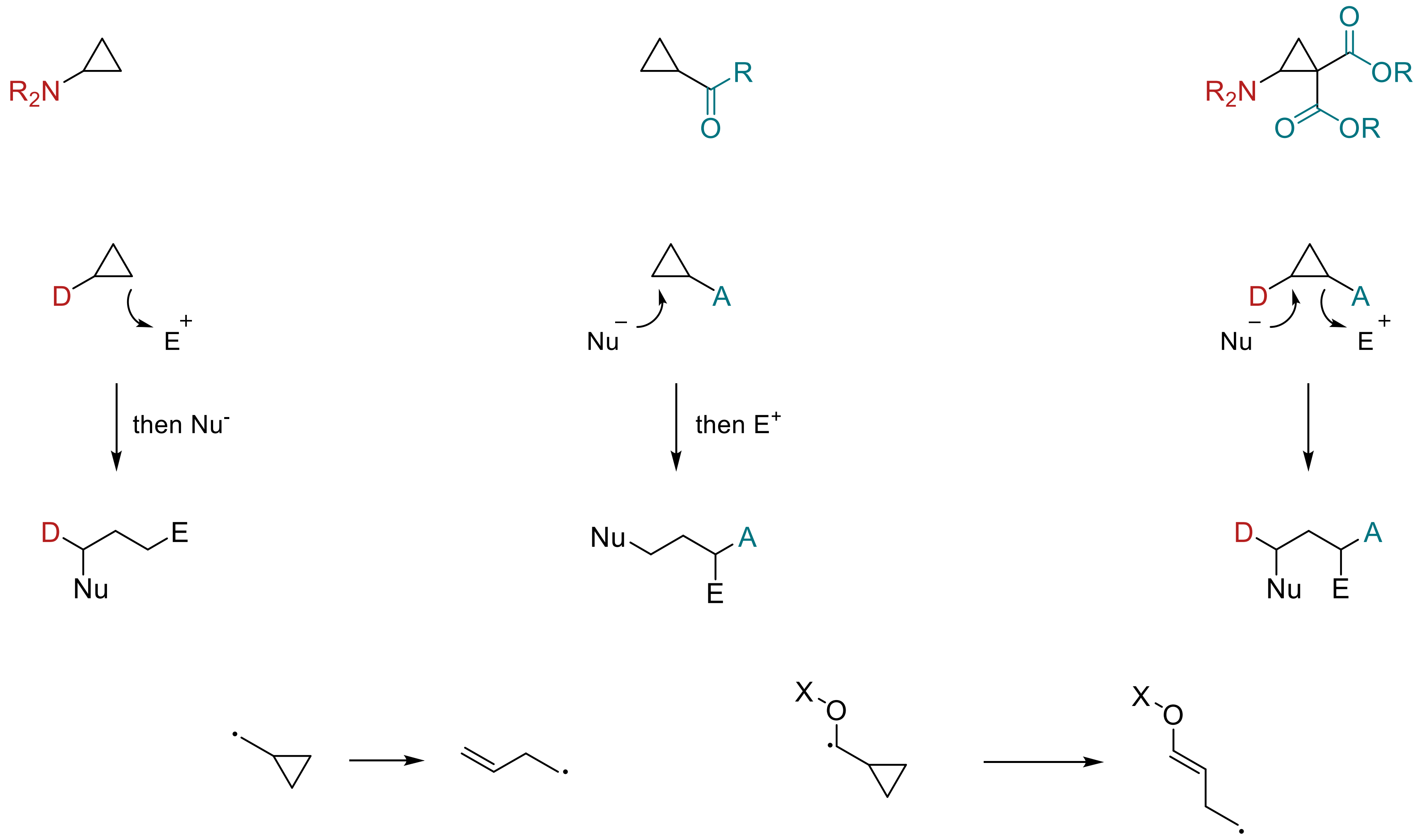
Frontiers in Chemical Synthesis I: Towards Sustainable Chemistry

Stephanie AMOS

11 May 2020

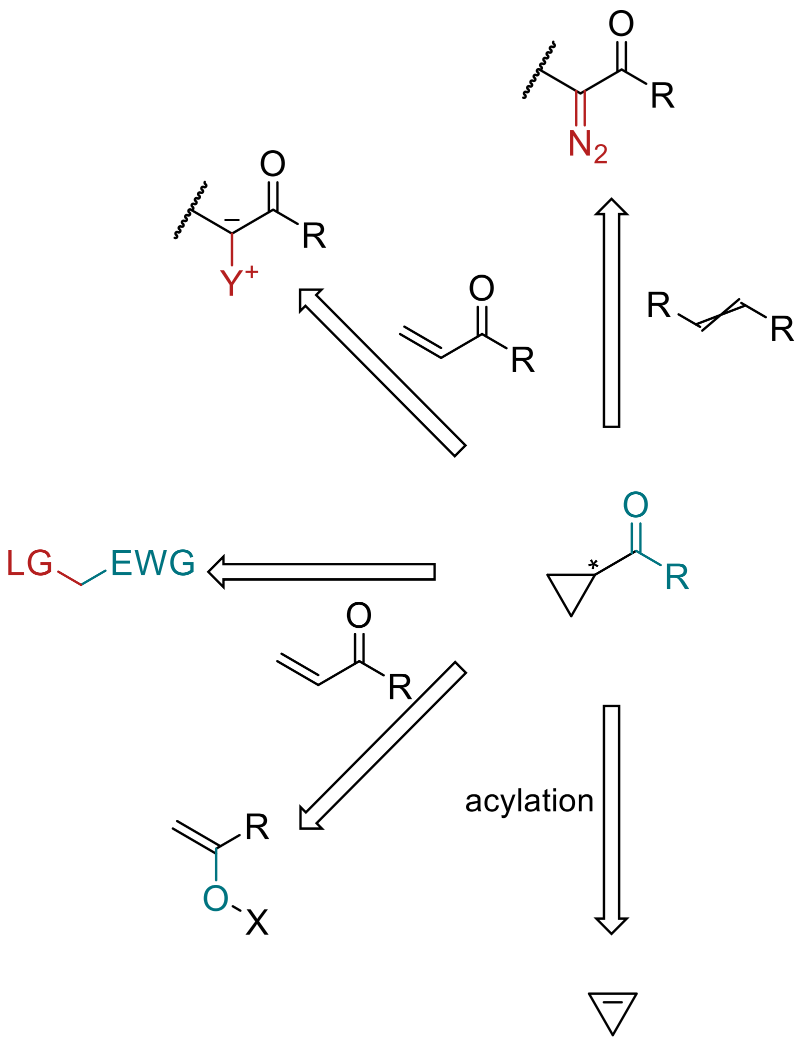
Ecole Polytechnique Fédérale de Lausanne
Laboratory of Catalysis and Organic Synthesis (LCSO)

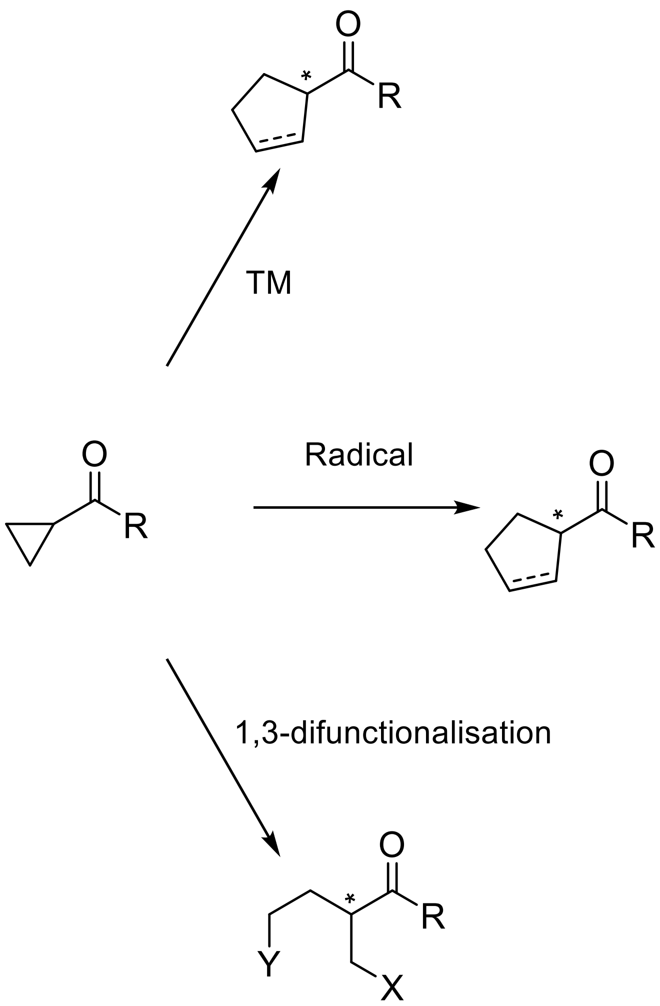
Cyclopropanes for difunctionalisation



H. N. C. Wong et al. *Chem. Rev.* **1989**, *89*, 165-198; O. G. Kulinkovich, Cyclopropanes in Synthesis; **2015**, John Wiley & Sons, Inc.; E. M. Carreira et. al. *Chem. Rev.* **2017**, *117*, 11651−11679.

General strategies

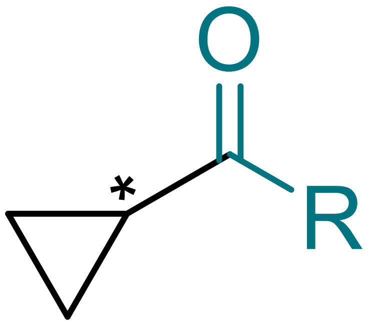




- Chiral lewis acids
- Organocatalysis
- Chiral ligands

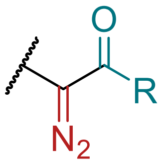
07/10/2020

H. Péllissier, Tetrahedron, **2008**, *64*, 7041-7095. A. B. Charette et al. *Chem. Rev.* **2003,** *103,* 977-1050; O. G. Kulinkovich, Cyclopropanes in Synthesis; **2015**, John Wiley & Sons, Inc.



Synthesis of chiral cyclopropyl ketones

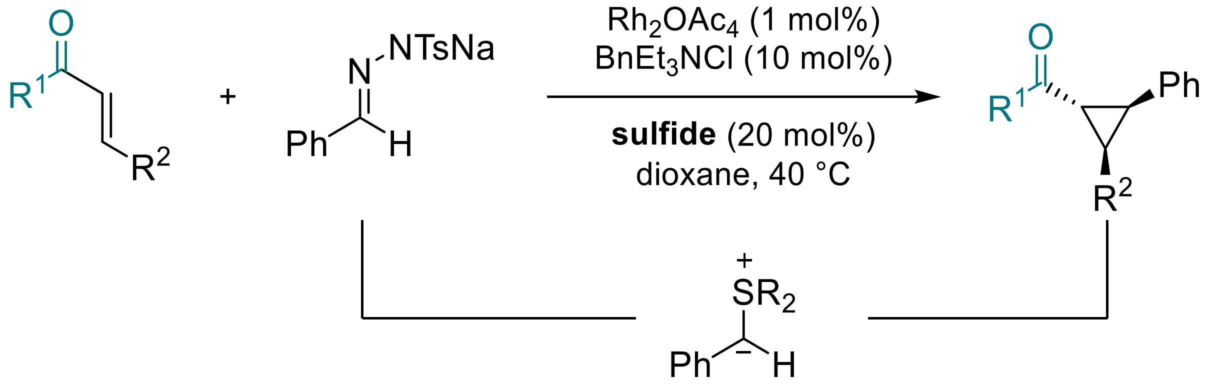
Traditionnal strategies: diazo ketones



M. A. McKervey, *Chem. Rev.* **2015**, *115*, 9981−10080; O. Reiser et al. *Chem. Commun.* **2012**, *48*, 3457–3459; M. Tilset et al. *Org. Lett.* **2009**, *11*, 547-550; X. P. Zhang et al. *J. Am. Chem. Soc.* **2007**, *129*, 12074-12075; L. K. Woo et al. *Organometallics*, **2012**, *31*, 3628−3635.

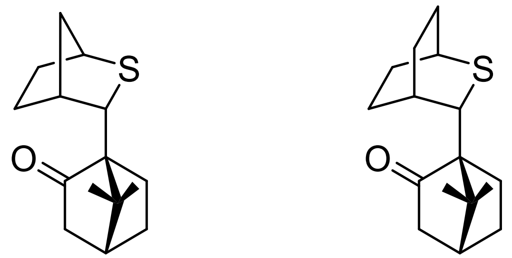
MIRC with ylides

Aggarwal, ACIE, 2001

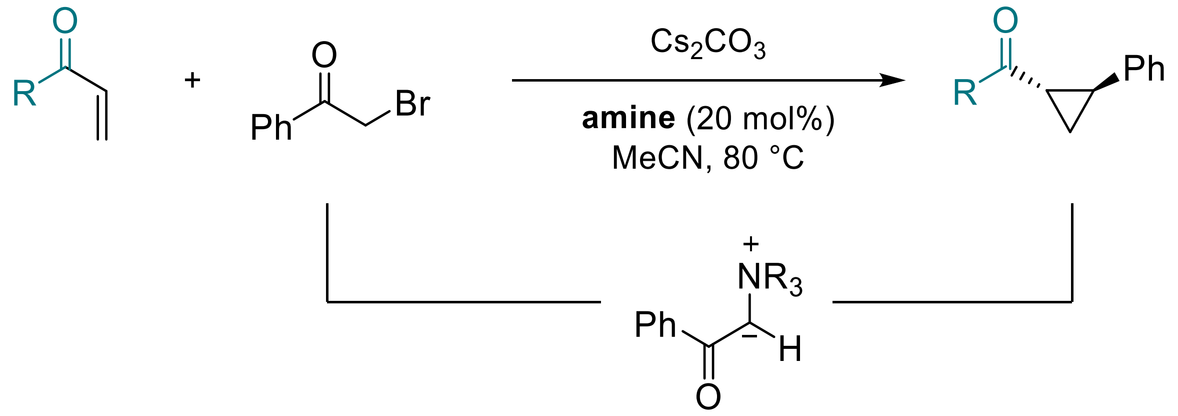


30-73% yield
up to 5:1 dr.
up to 92% ee

sulfide

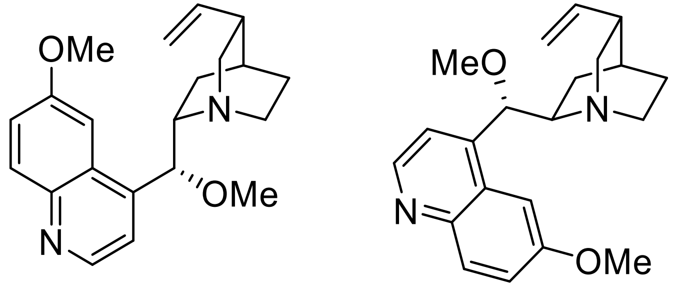


Gaunt, ACIE, 2004



63-96% yield
up to 97% ee

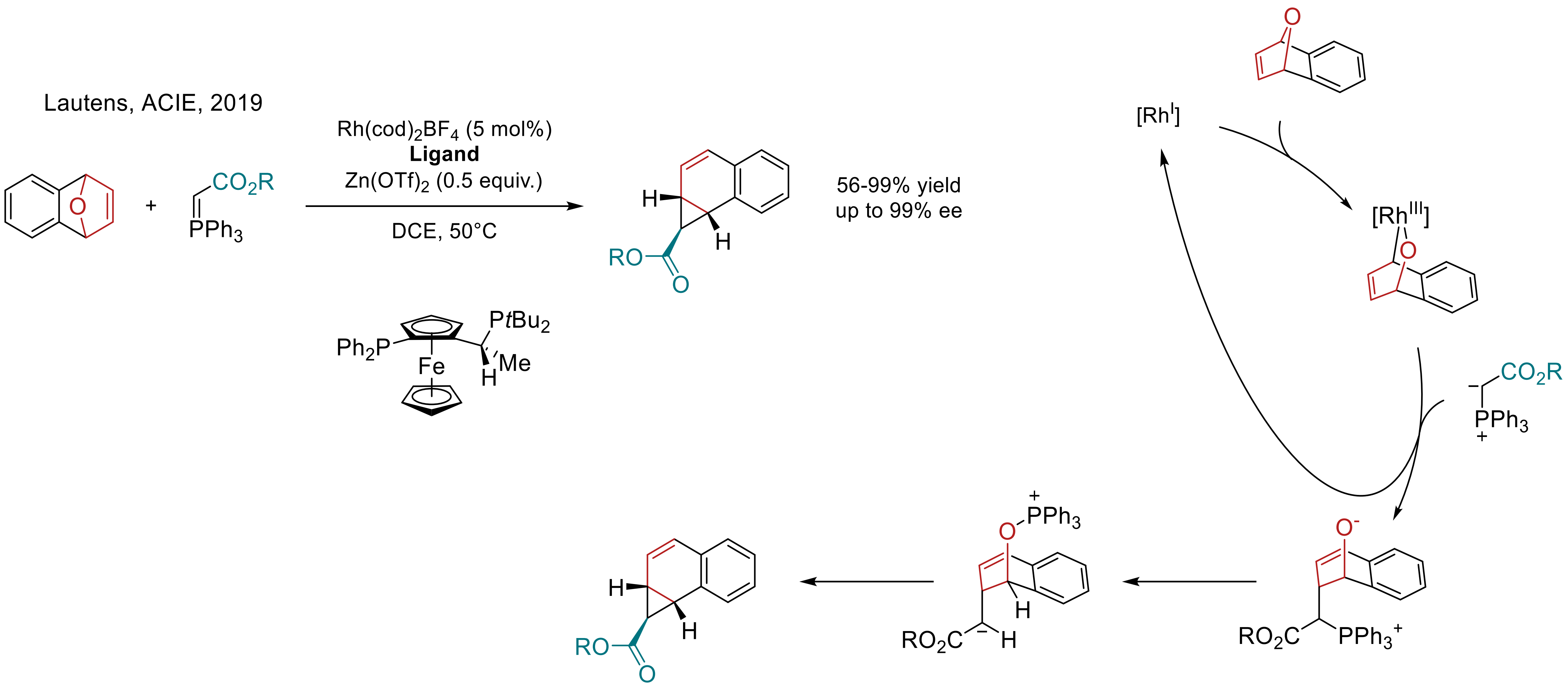
amine



V. K. Aggarwal et al. *Angew. Chem. Int. Ed.* **2001**, *40*, 1433–1436; M. J. Gaunt et al. *Angew. Chem. Int. Ed.* **2004**, *43*, 4641–4644.

Rh-catalysed phosphorus ylide promoted cyclopropanation

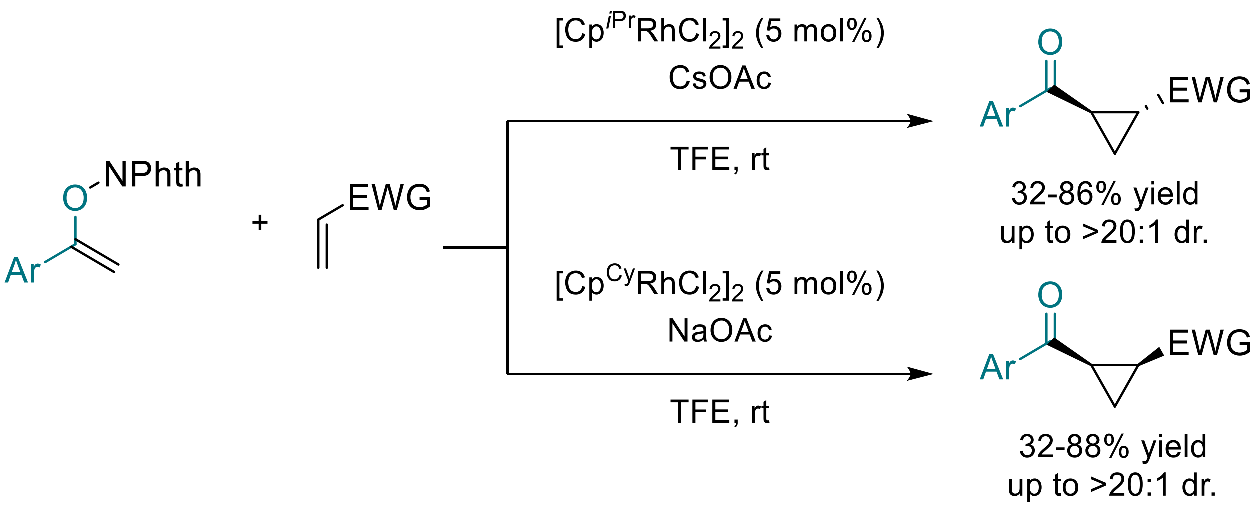
Lautens, ACIE, 2019



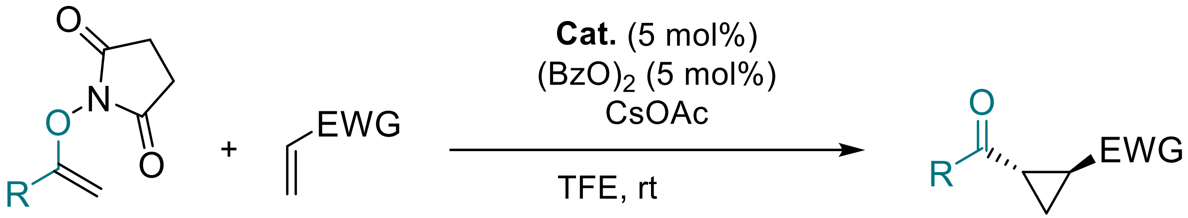
M. Lautens et al. *Angew. Chem. Int. Ed.* **2019**, *58*, 15819–15823.

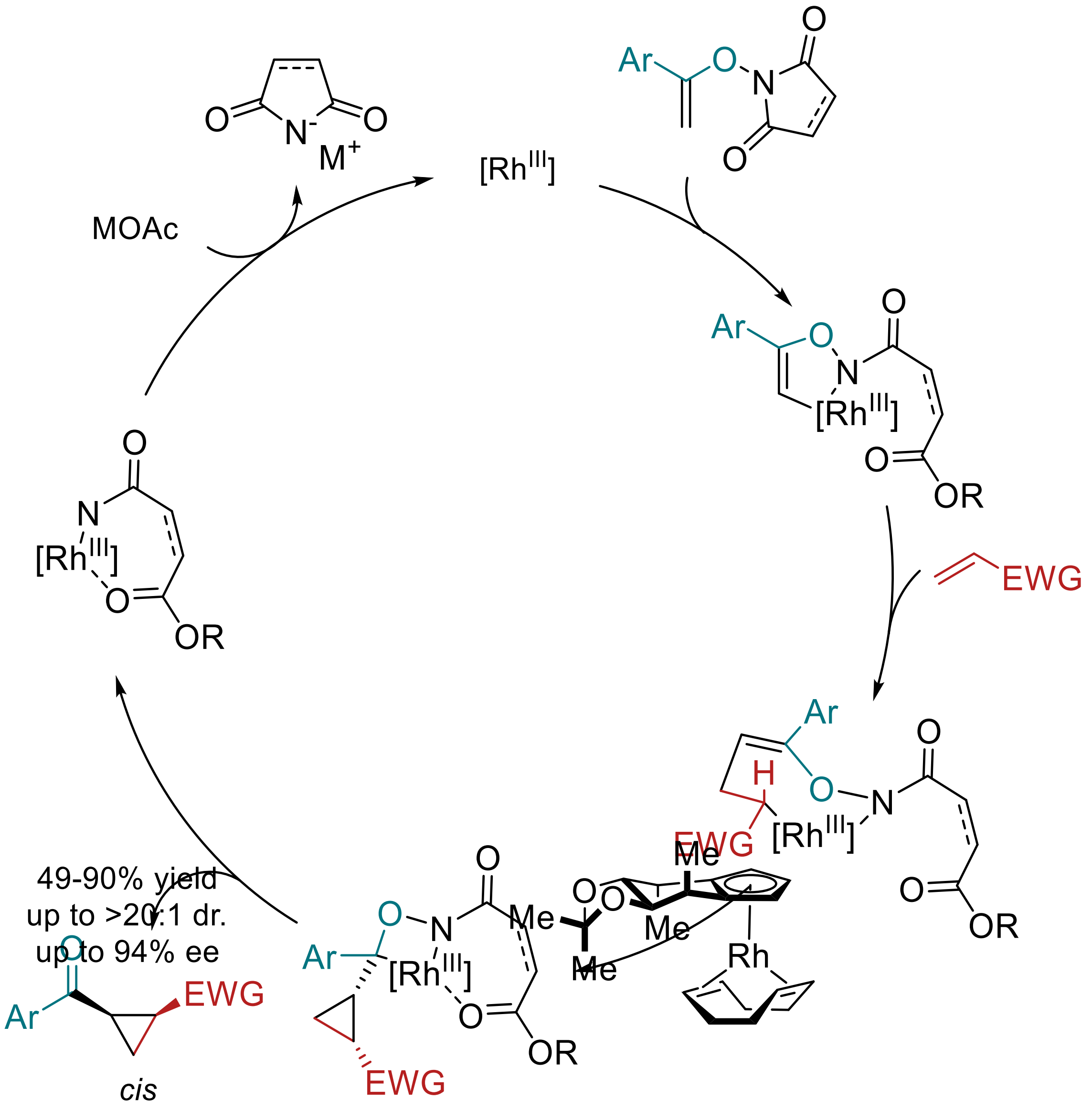
N-Enoxyimide mediated cyclopropanations

Rovis, JACS, 2014 and 2016



Cramer, Chem. Sci. 2019

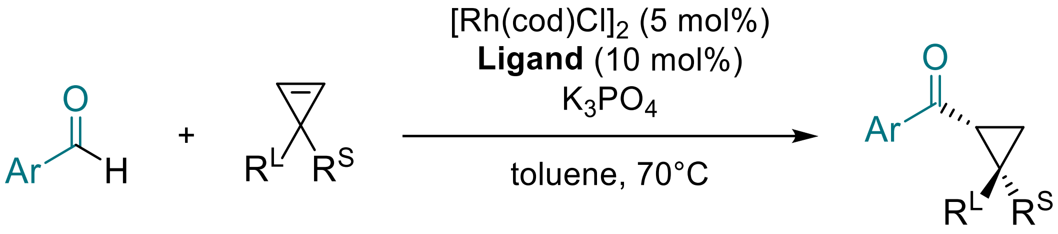




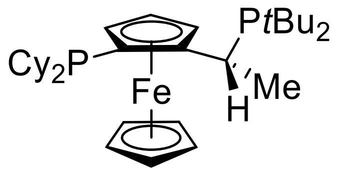
T. Rovis et al. *J. Am. Chem. Soc.* **2014**, *136*, 11292−11295; T. Rovis et al. *J. Am. Chem. Soc.* **2018**, *140*, 9587−9593; N. Cramer et al. *Chem. Sci.* **2019**, *10*, 2773-2777..

Transition metal catalysed cyclopropene difunctionalisation

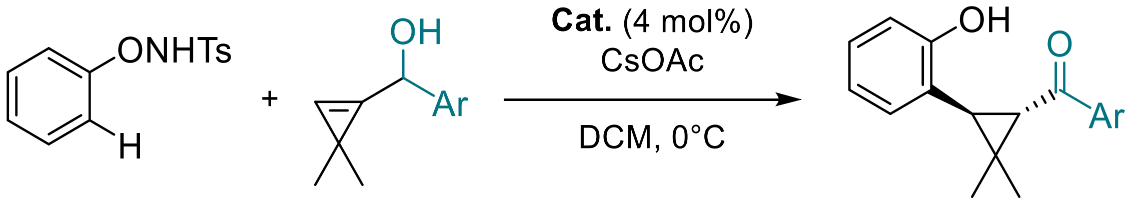
Dong, JACS, 2010



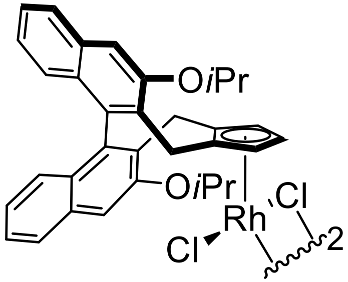
76-92% yield
up to >20:1 dr.
up to 99% ee



Li, ACIE, 2020



46-81% yield
up to 98% ee



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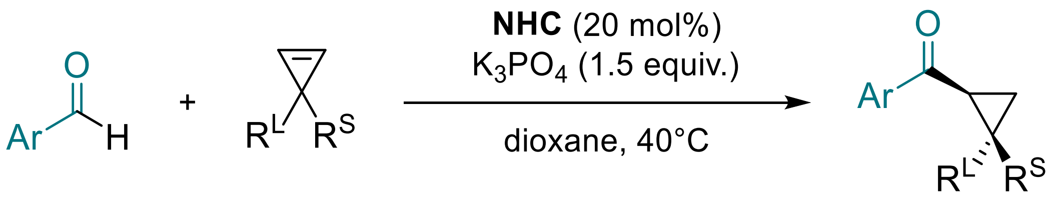
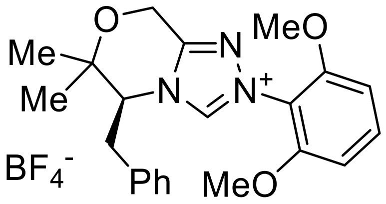
V. M. Dong et al. *J. Am. Chem. Soc.* **2010**, *132*, 16354–16355; F. Glorius et al. *Angew. Chem. Int. Ed.* **2011**, *50*, 12626–12630.

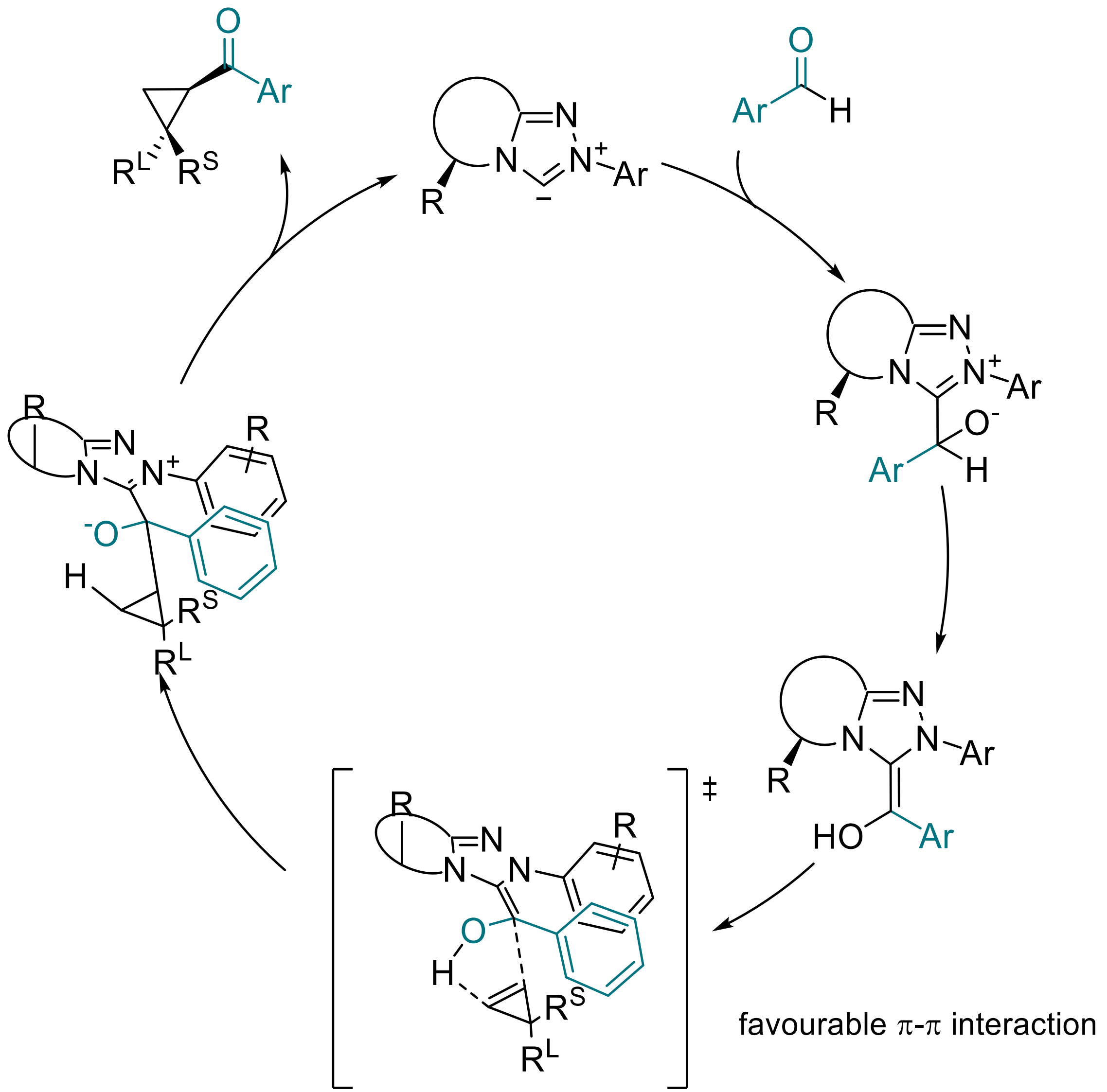
Organocatalytic cyclopropene difunctionalisation

Glorius, ACIE, 2011

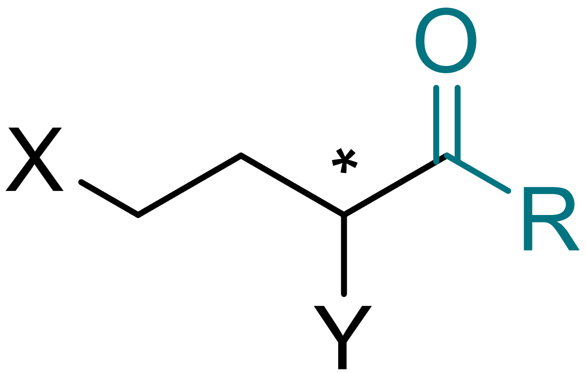


31-93% yield
up to >20:1 dr.
up to 96% ee





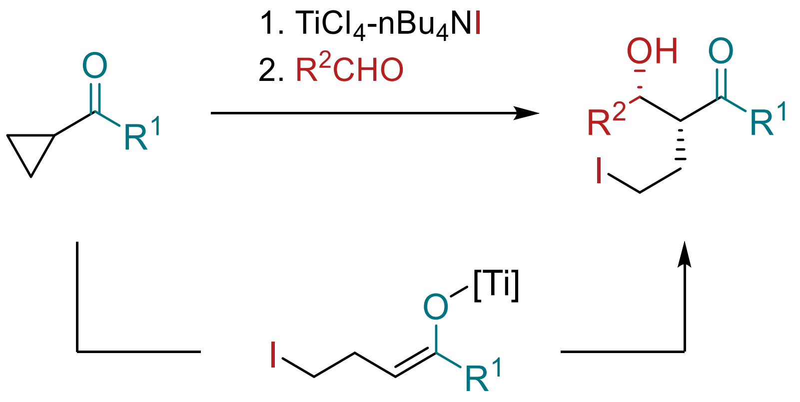
X. Li et al. *Angew. Chem. Int. Ed.* **2020**, *59*, 2890–2896



Enantioselective cyclopropyl ketone ring-opening

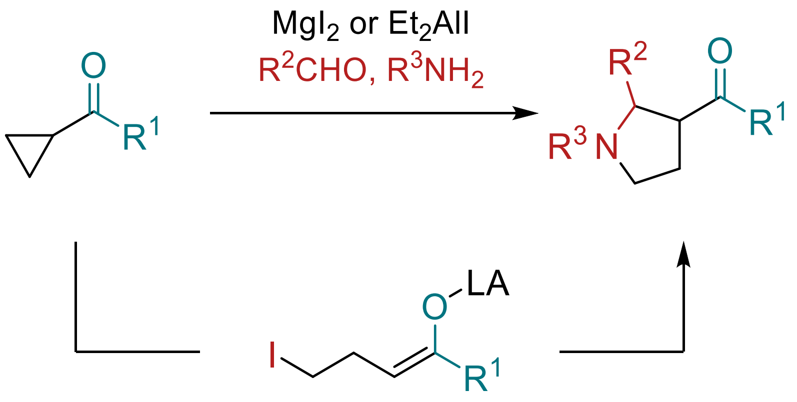
Diastereoselective transformations

Oshima, Tetrahedron, 2001



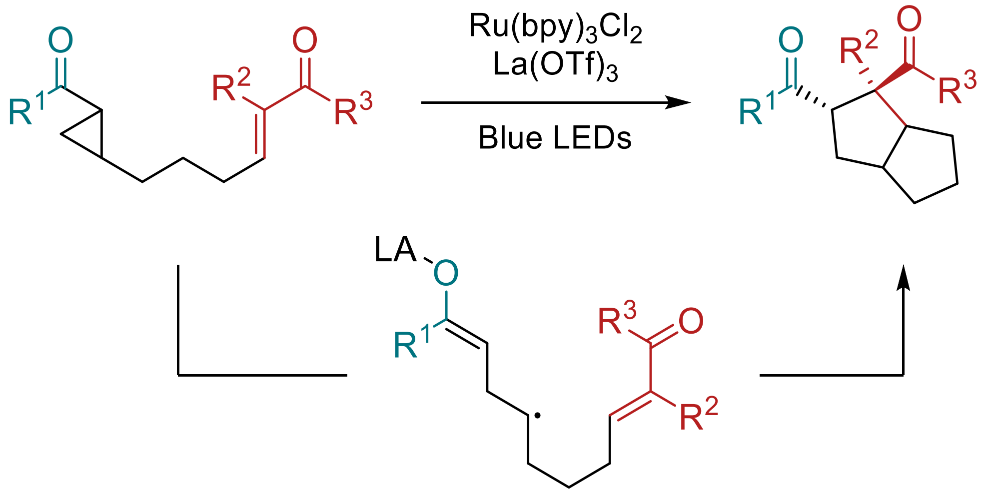
54-85% yield
up to >99:1 dr.

Olsson, Org. Lett., 2002



16-75% yield
up to >99:1 dr.

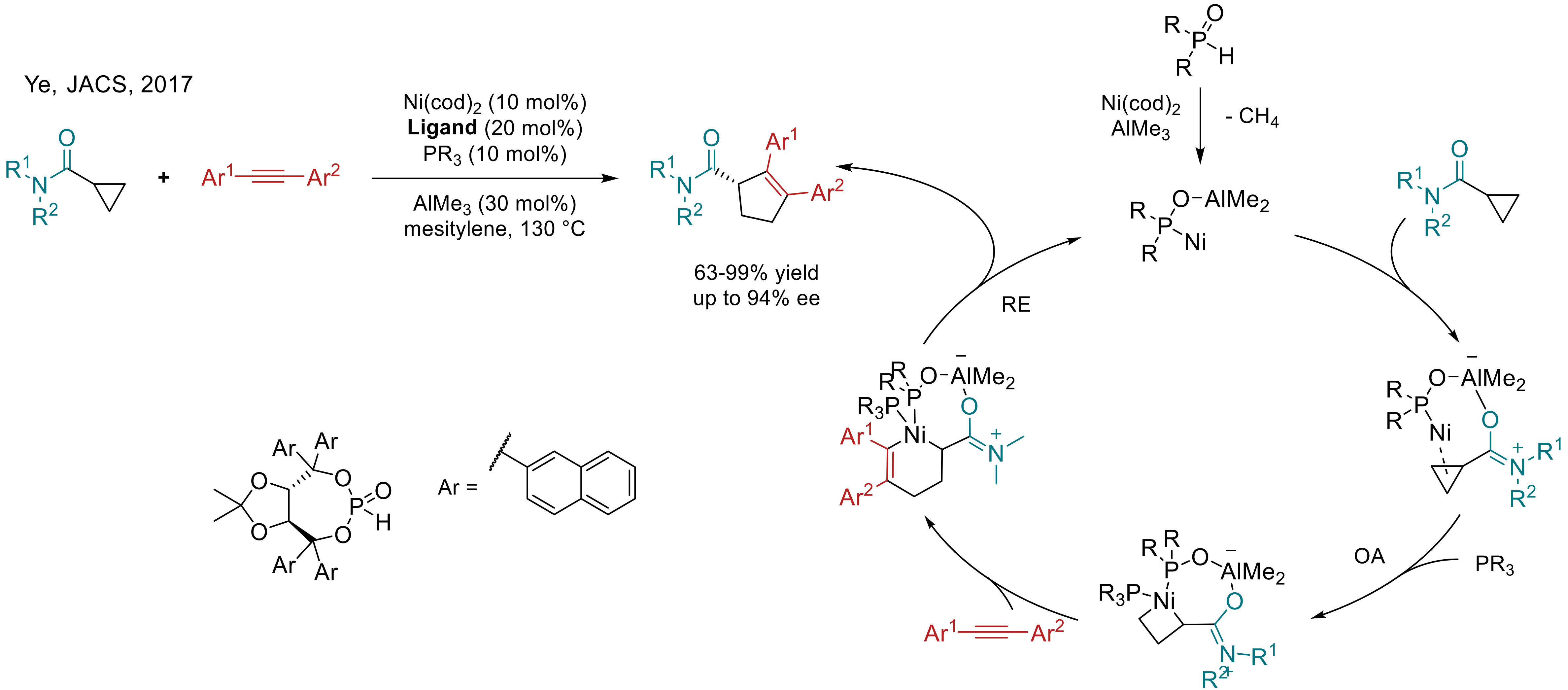
Yoon, JACS, 2011



55-86% yield
up to >10:1 dr.

K. Oshima et al. Tetrahedron, 2001, 57, 987-995; R. Olsson et al. Org Lett. 2002, 4, 3147-3150; T. P. Yoon et al. *J. Am. Chem. Soc.* **2011**, *133*, 1162–1164

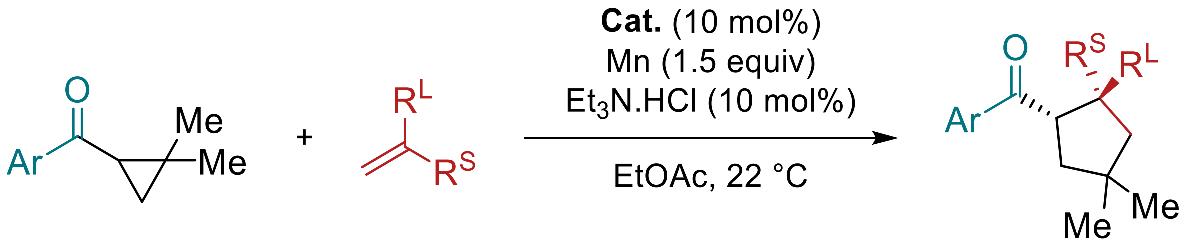
Ye, JACS, 2017



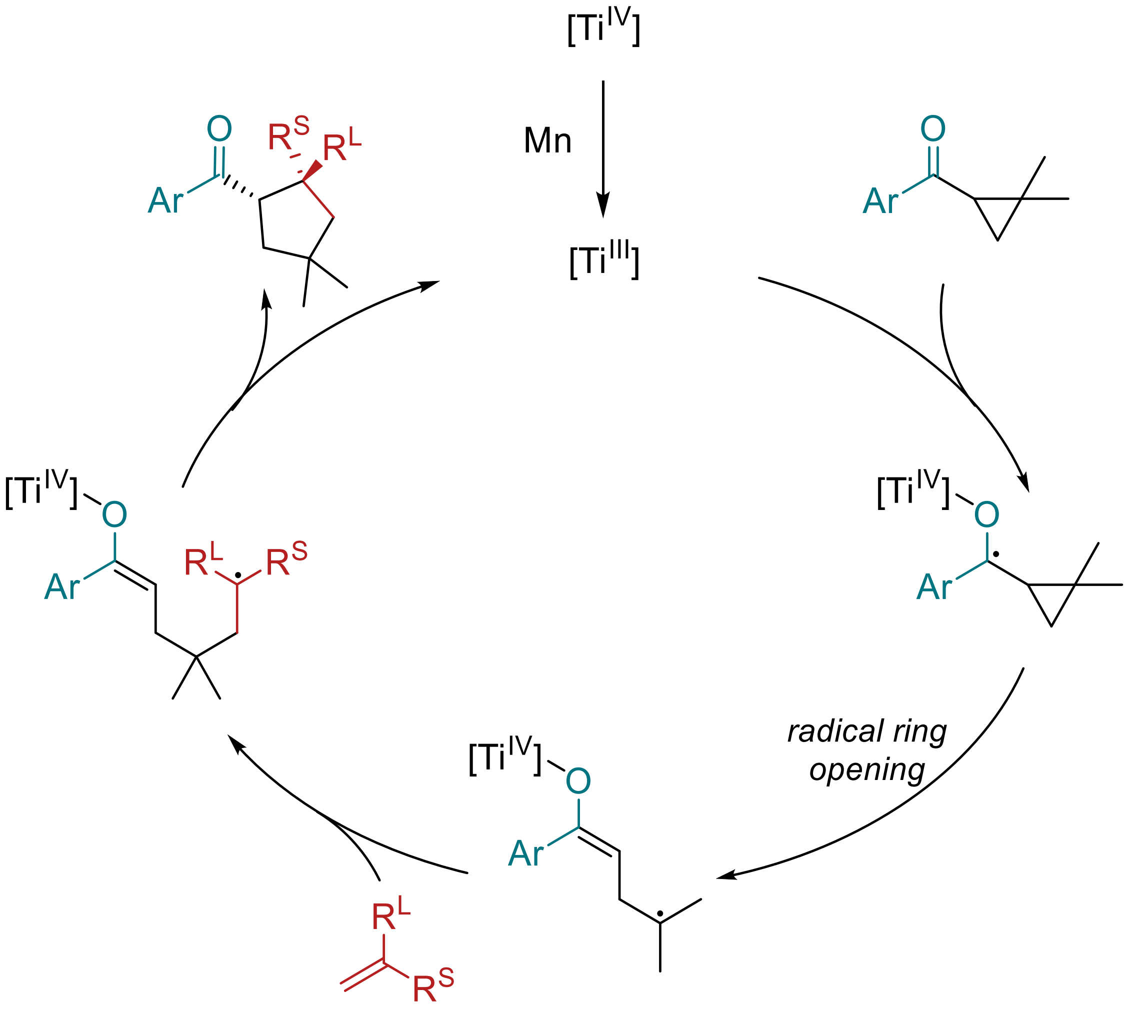
M. Ye et al. *J. Am. Chem. Soc.* **2017**, *139*, 18150−18153.

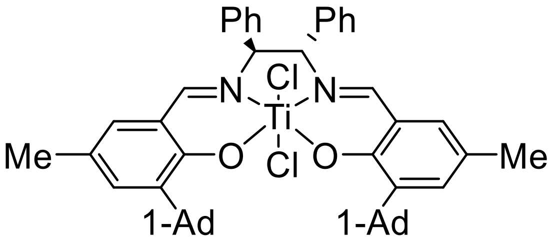
Radical ring-opening with Ti-based catalyst

Lin, JACS, 2018



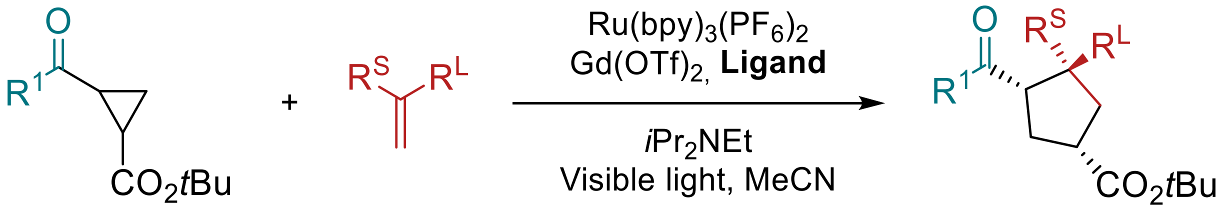
53-98% yield
up to 96% ee
up to >19:1 dr.



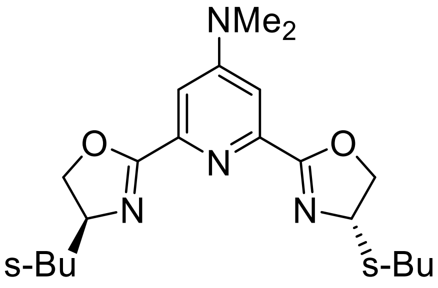


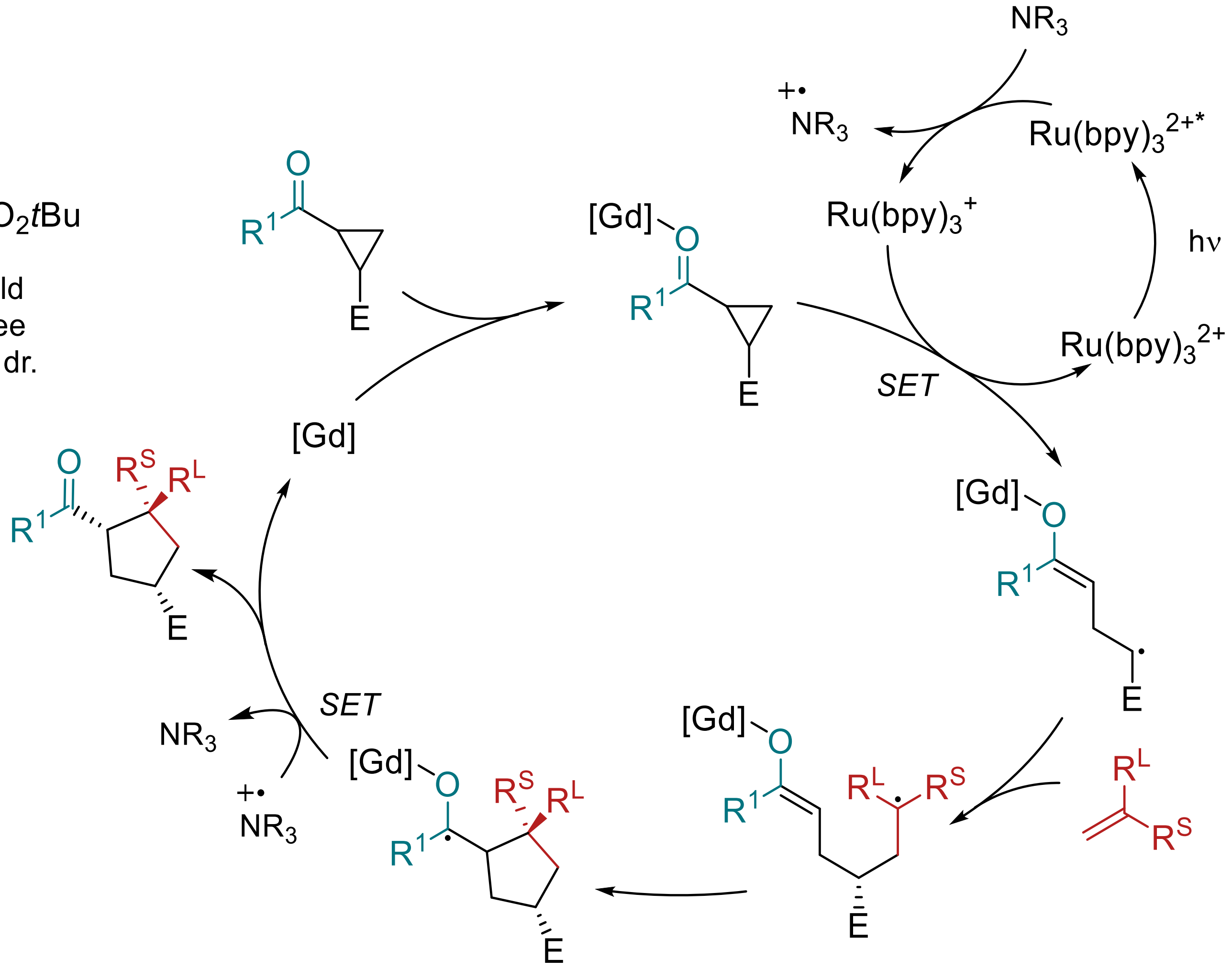
Lewis acid and photocatalysed radcial [3+2] cycloaddition

Yoon, JACS, 2016



55-95% yield
up to 97% ee
2:1 to >20:1 dr.

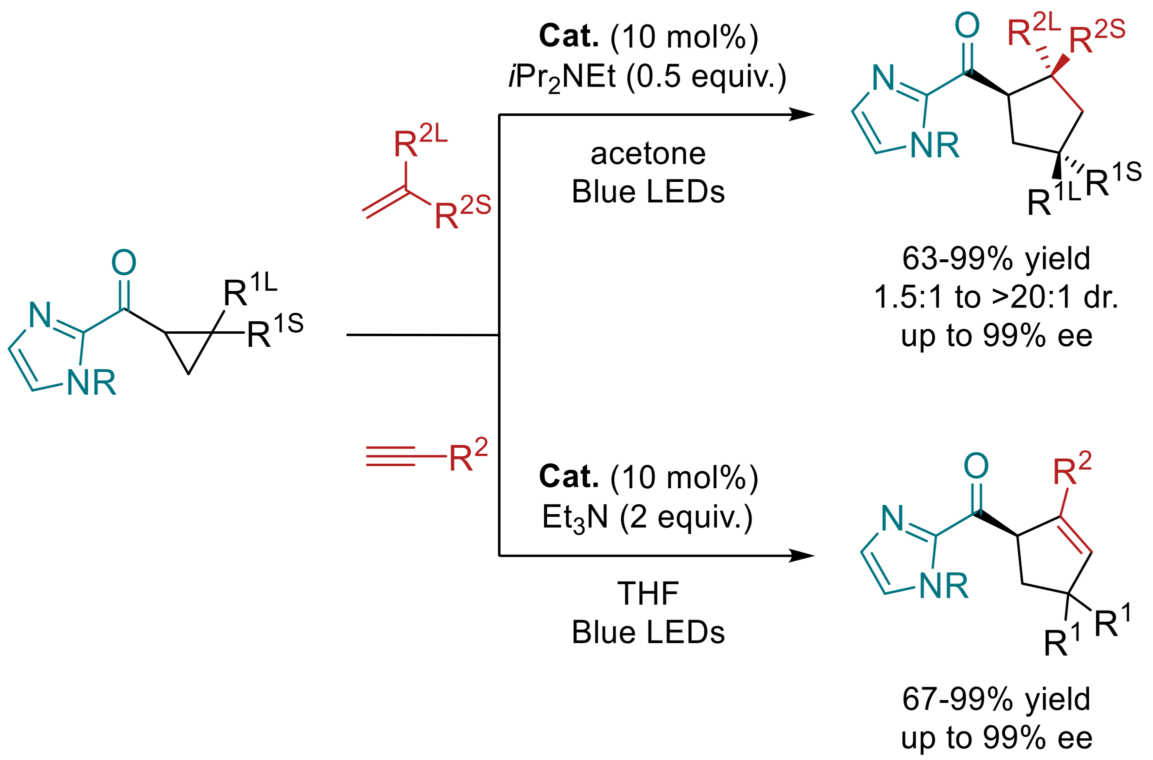


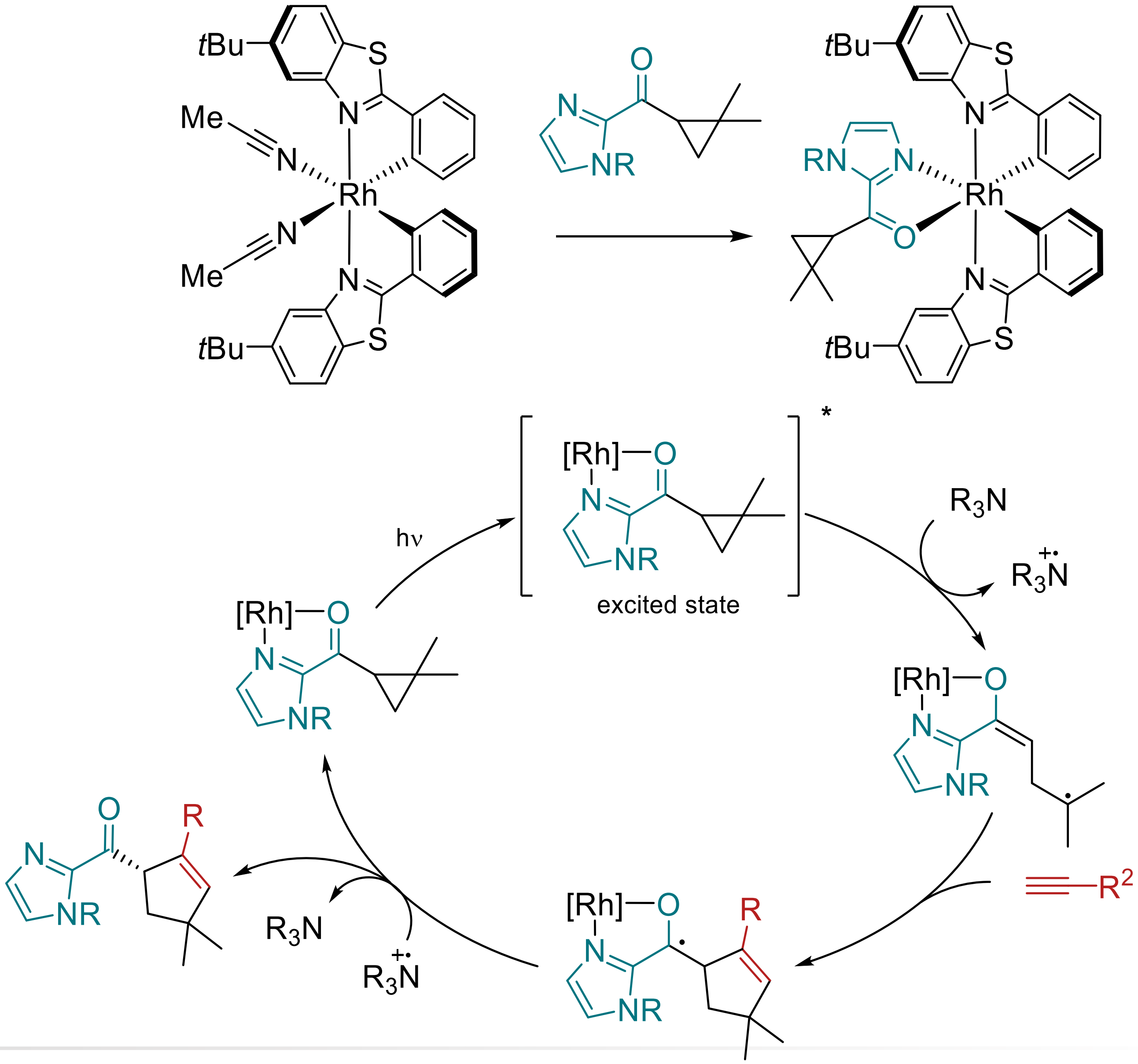


T. P. Yoon et al. *J. Am. Chem. Soc.* **2016**, *138*, 4722−4725

[3+2] photocycloaddition

Meggers, ACIE, 2018

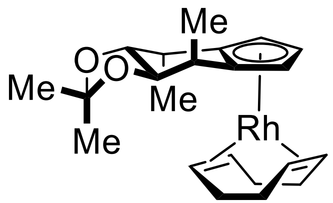




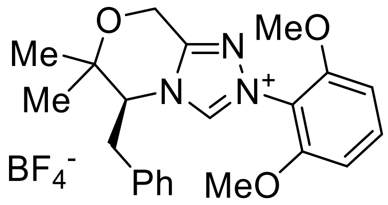
E. Meggers, et al. *Angew. Chem. Int. Ed.* **2018**, *57*, 5454–5458

Conclusion: enantioselective syntheses of cyclopropyl ketones

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

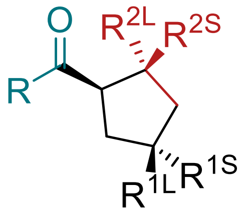


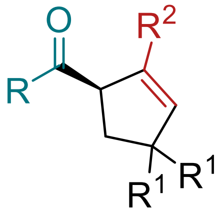
- Transition metal catalysis with chiral ligand design



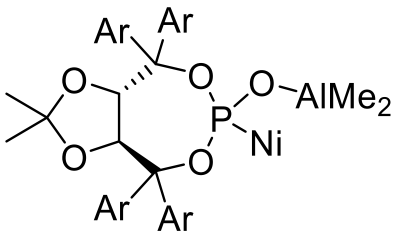
- Organocatalysis
- but also radical ring closures or rearrangements

Conclusion: enantioselective transformations of cyclopropyl ketones

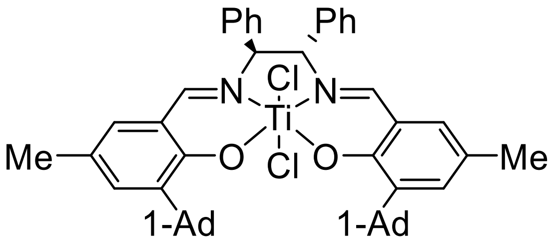




- Enantioselctive transformations limited to [3+2] cycloadditions



- Transition metal C-C activation

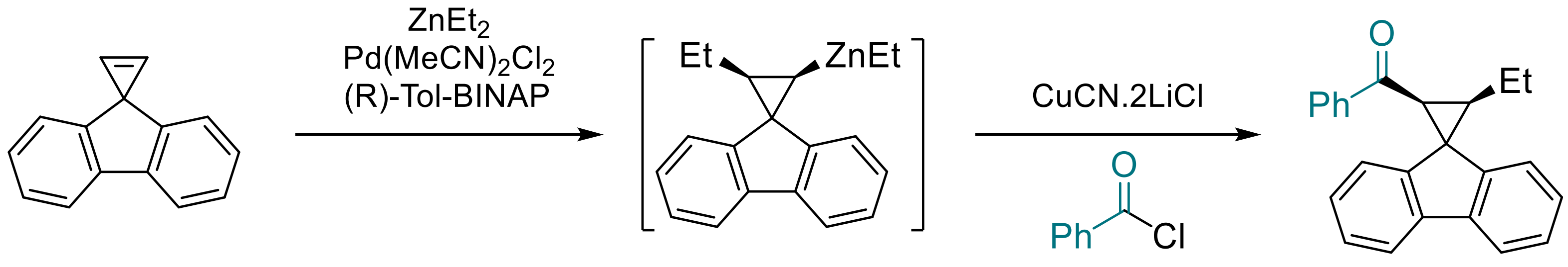


- Radical/LA dual catalysis

Questions?

- Propose the starting material and a mechanism for this transformation

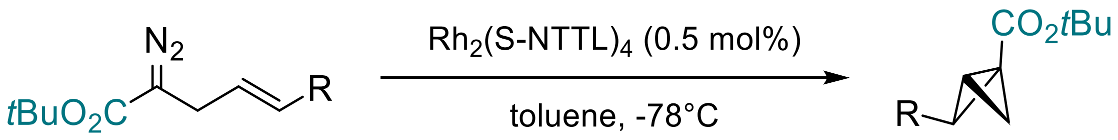
Lautens, OL, 2011



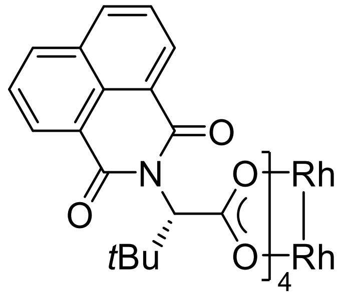
75% yield
>95:5 dr.
93% ee

- Propose a structure for the following transformation

Fox, JACS, 2013



65-88% yield
up to 95% ee

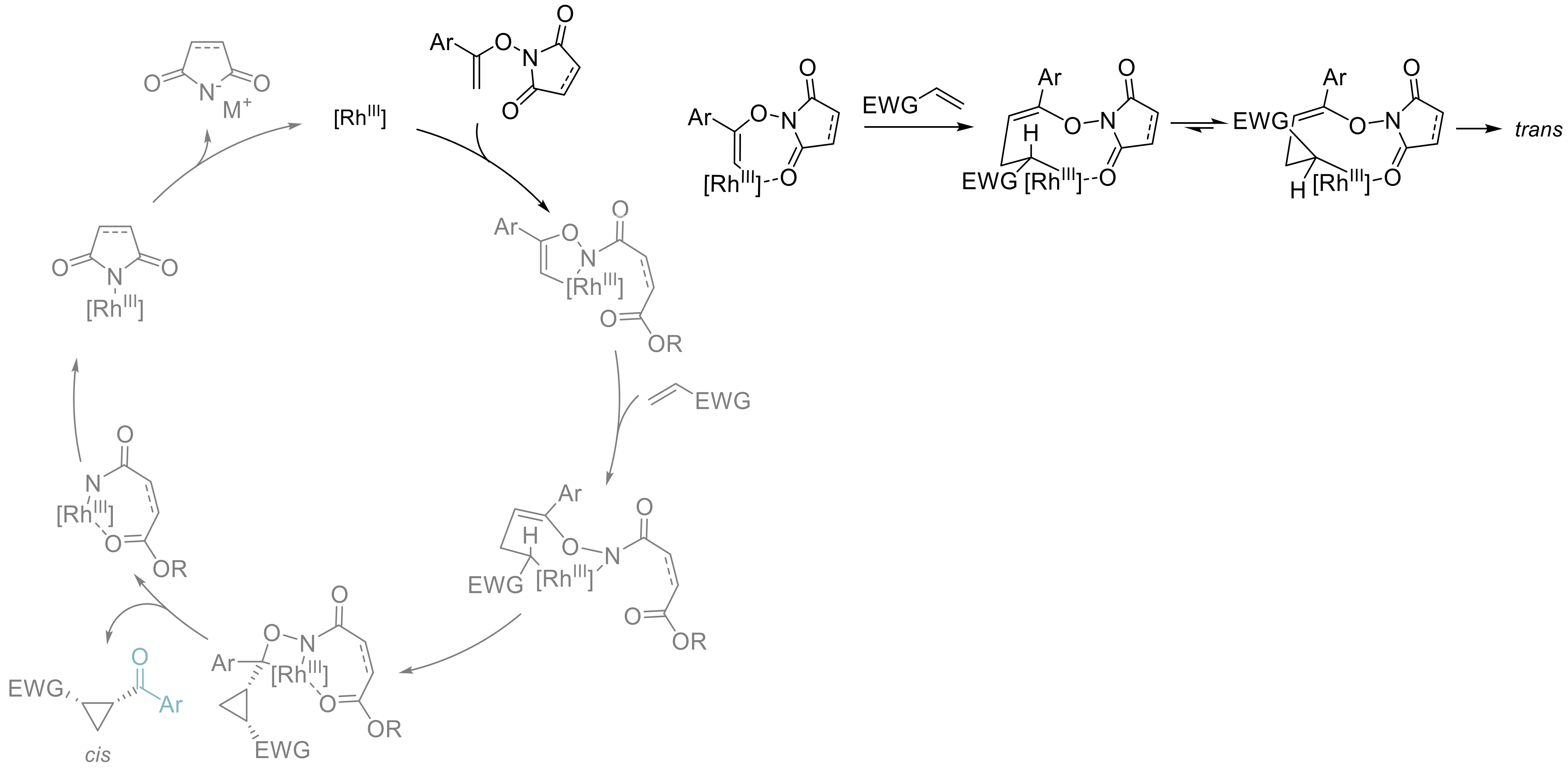


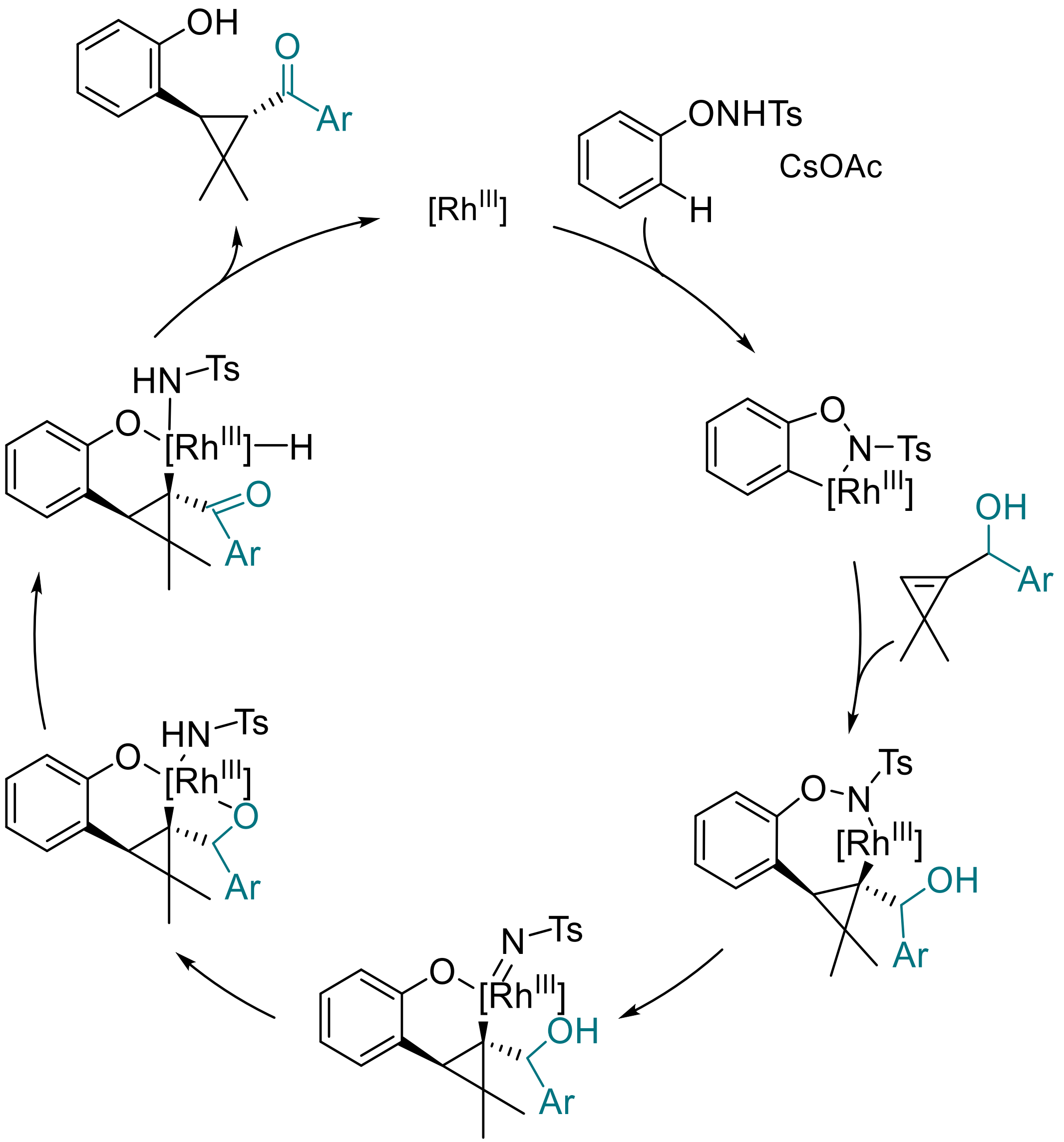
M. Lautens et al. *Org. Lett.* **2011**, *13*, 819-821; J. M. Fox et al. *J. Am. Chem. Soc.* **2013**, *135*, 9283−9286.

Thank you for your attention!

Any questions?

Rovis trans cyclopropanation




OH
O
Ar
ONHTs
CsOAc
H
[Rh^{III}]
O
N–Ts
[Rh^{III}]
OH
Ar
Ts
O–N
[Rh^{III}]
OH
Ar
N–Ts
O
[Rh^{III}]
OH
Ar
HN–Ts
O
[Rh^{III}]
O
Ar
HN–Ts
O
[Rh^{III}]–H
O
Ar

Acid-mediated hydroaminomethylation

Gitlina Anastasia

PhD student, LCS, Prof. Kay Severin

EPFL

13th May 2020

Amines

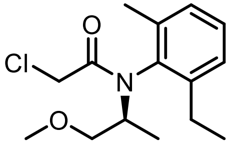
Lubricants

Antiseptics

Textiles

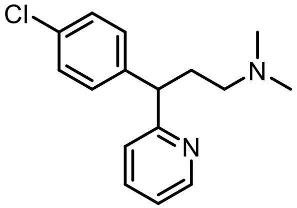
Solvents

Agrochemicals

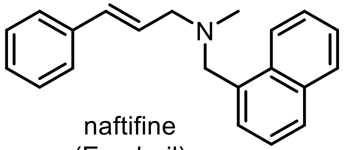


(*S*)-metolachor

Pharmaceutics

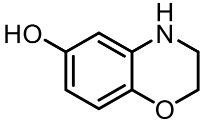


chlorphenamine
(Piriton)



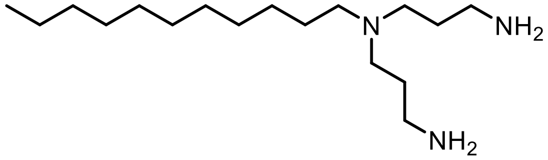
naftifine
(Exoderil)

Cosmetics



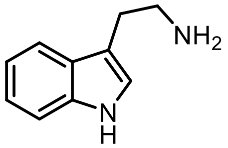
hydroxybenzomorpholine

Detergents



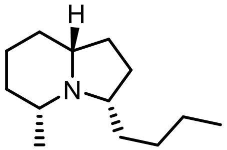
N,*N*-di(propylamino)dodecylamine

Food-additives

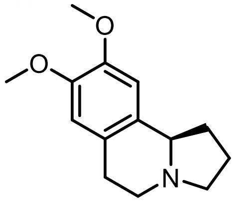


tryptamine

Natural products



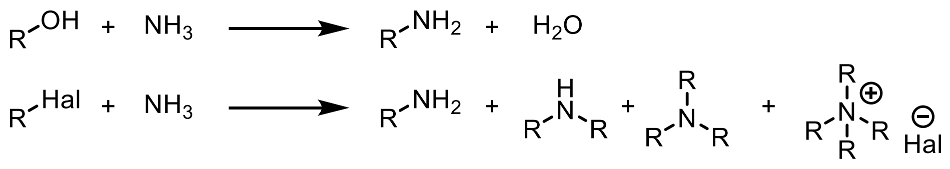
monomorine I



crispine A

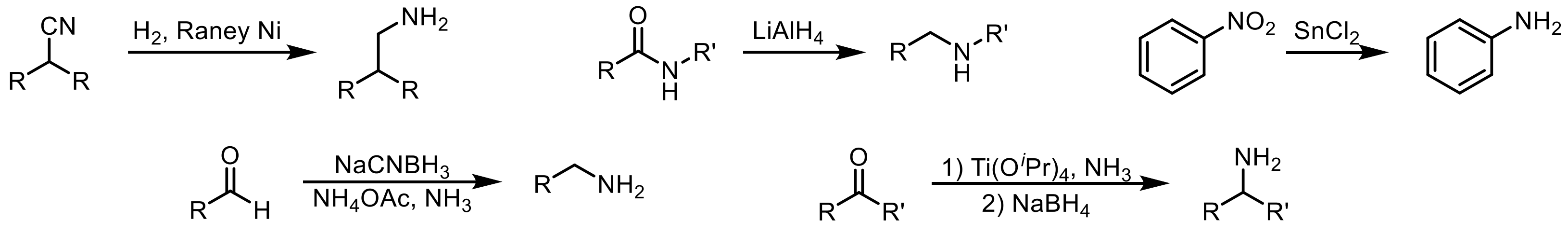
Summary of amines synthesis

Classical S_N2 reactions:



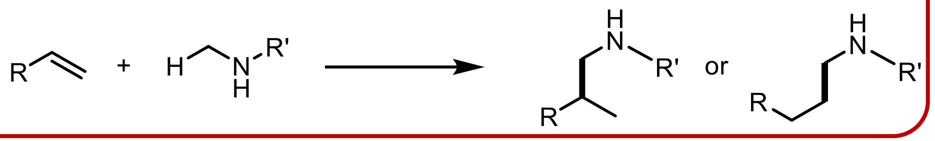
+ Gabriele synthesis
+ Delépine reaction
+ Mitsunobu reaction

Reductive routes:



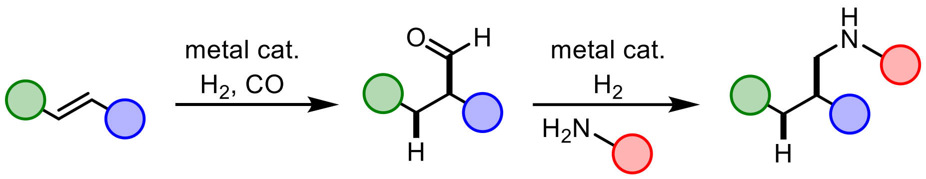
Hydroamination:

Hydroaminomethylation (HAM):

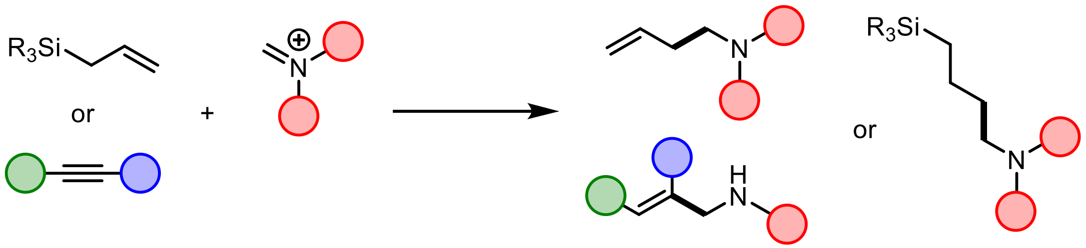


HAM methods

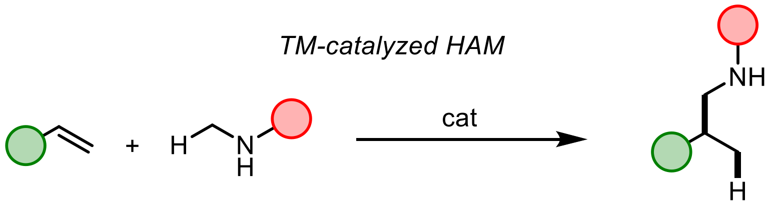
Tandem HAM via hydroformylation



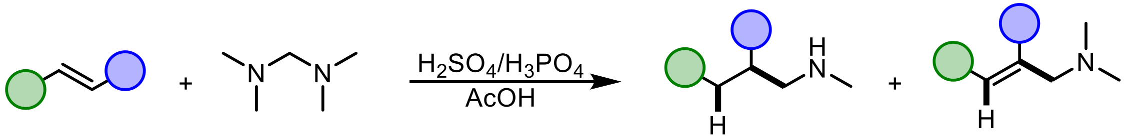
HAM with iminium salts



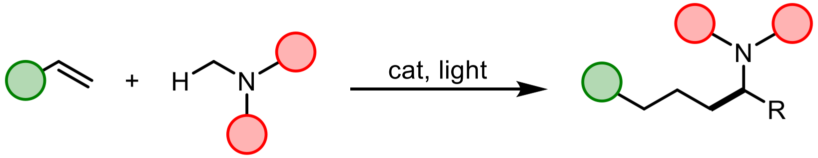
TM-catalyzed HAM



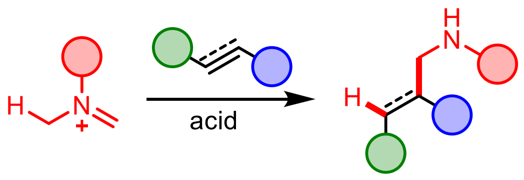
HAM with aminals



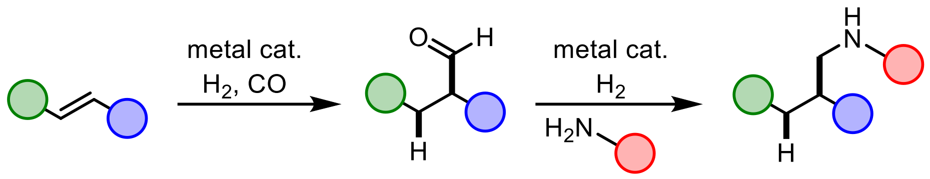
Photoredox HAM



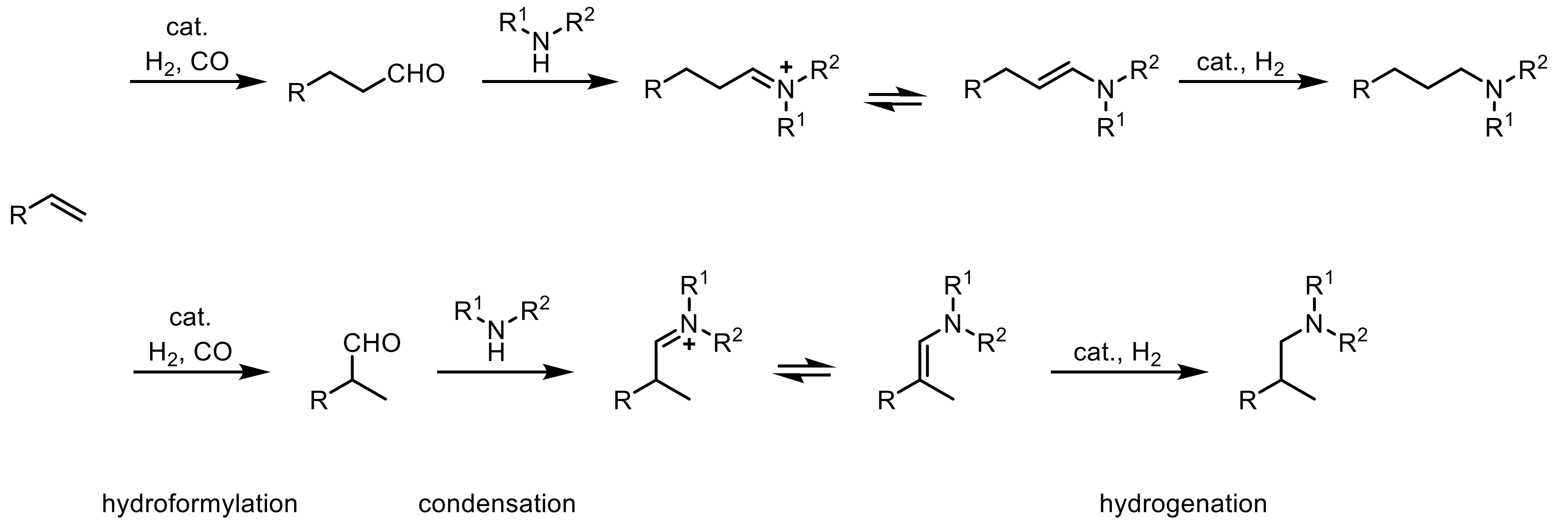
Acid-mediated HAM



Tandem HAM *via* hydroformylation

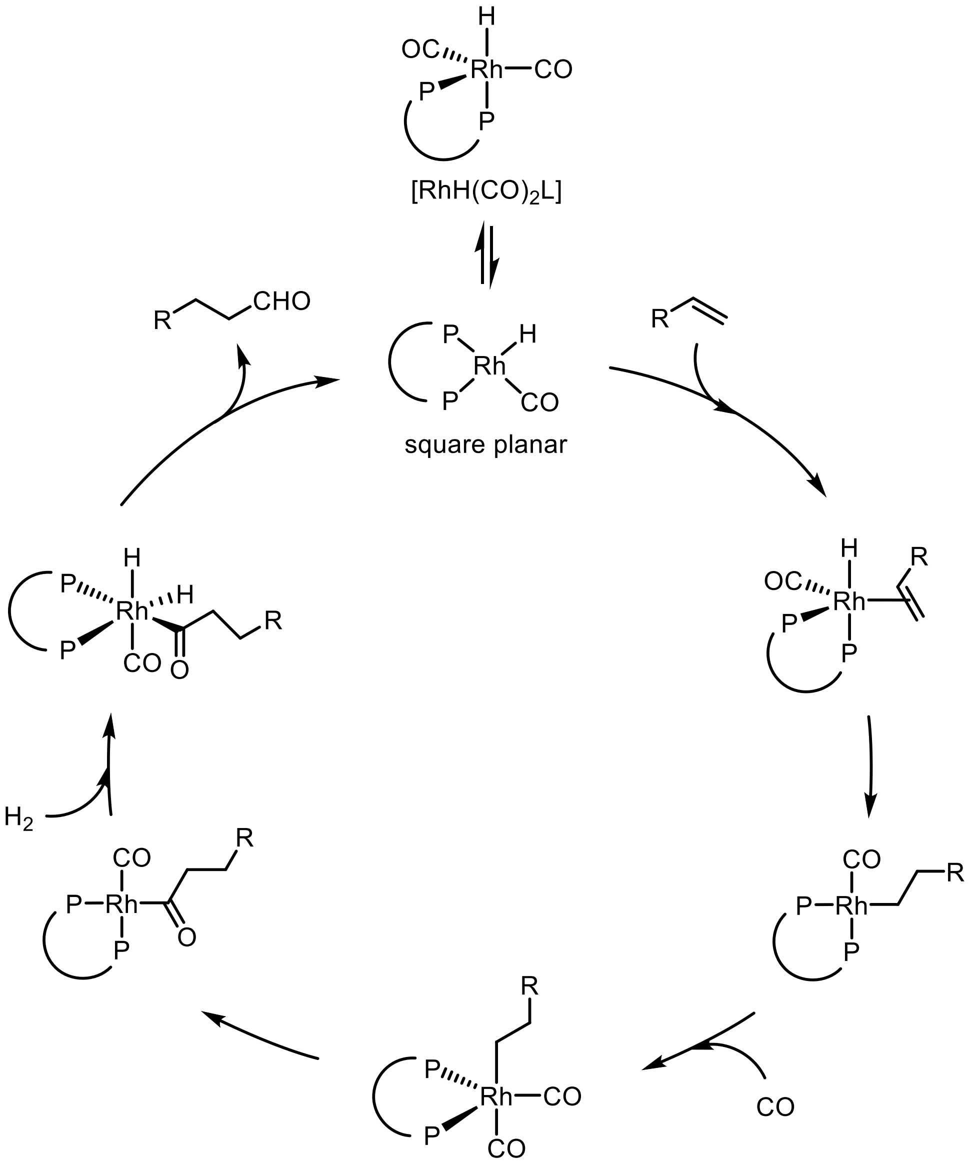


Kaiser et al., *Angew. Chem. In. Ed.*, **2019**, 58, 14639

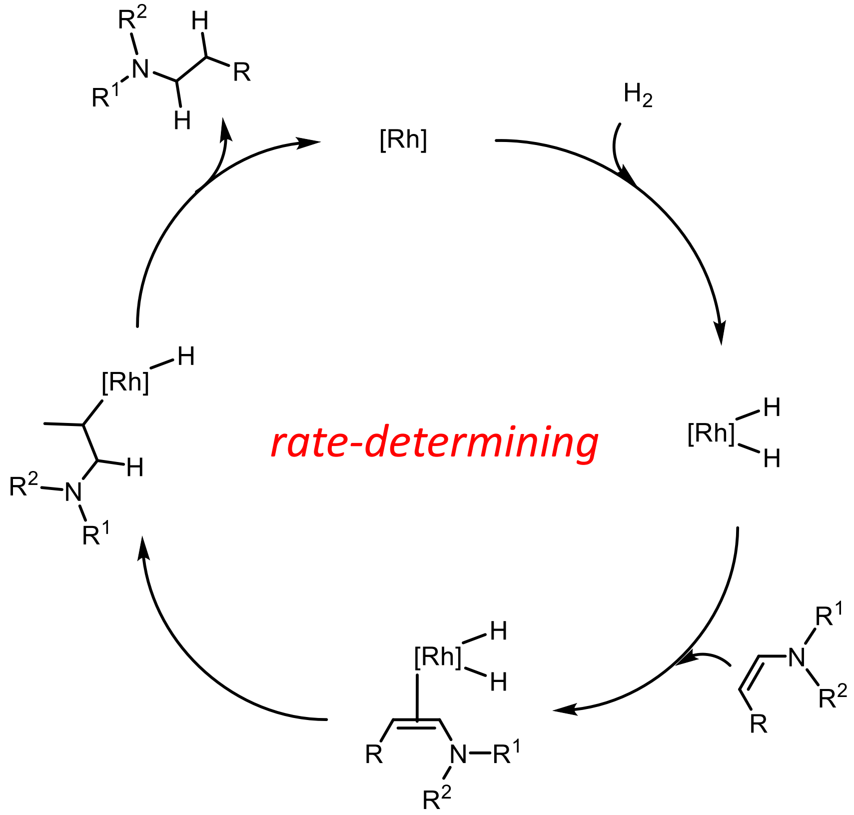


Kalck et al., *Chem. Rev.*, **2018**, 118, 3861

Catalytic cycle of hydroformylation step

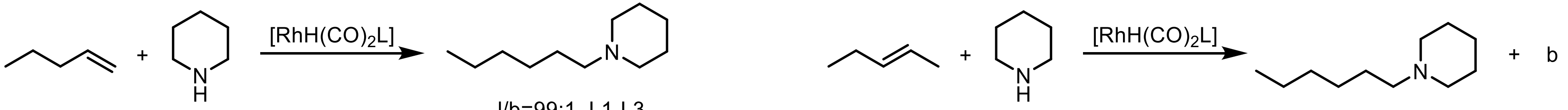


Catalytic cycle of hydragenation step



General conditions:
90 to 130 °C, 30 to 60 bar
CO/H_2 (1:1 to 1:5)
30 min to 72 h

HAM reaction of terminal and internal alkenes

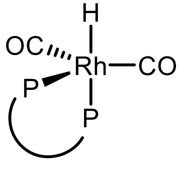


l/b=99:1, L1-L3

l

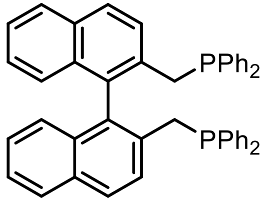
Unmodified catalysts:
Rh_2O_3
$[Ru_3(CO)_{12}]$
[Rh(acac)$(CO)_2$]
$[Rh_2(\mu\text{-}Cl)_2(COD)_2]$

Ligand-decorated catalysts:

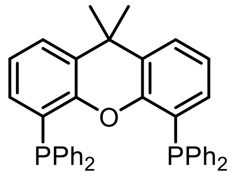


$[RhH(CO)_2L]$

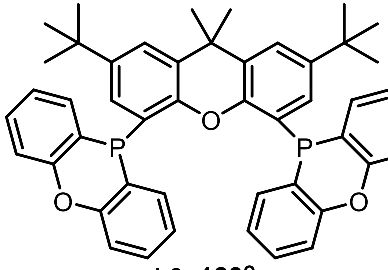
L =



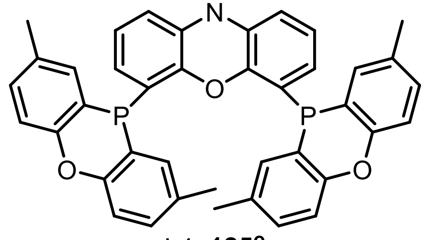
L1, **120°**
yield (l) 6%, l/b=99:1



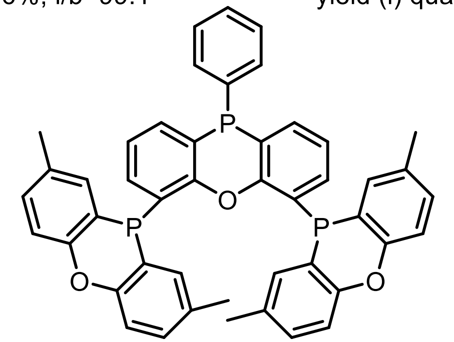
L2, **111°**
yield (l) quant, l/b=93:7



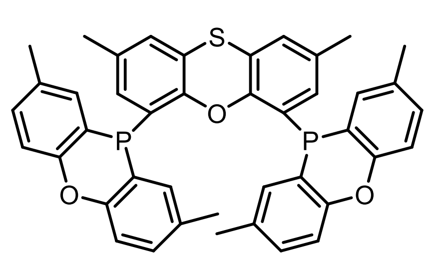
L3, **123°**
yield (l) 67%, l/b=73:27



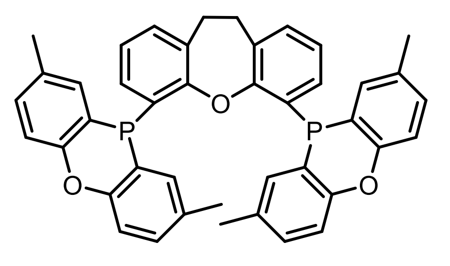
L4, **125°**
yield (l) 56%, l/b=73:27



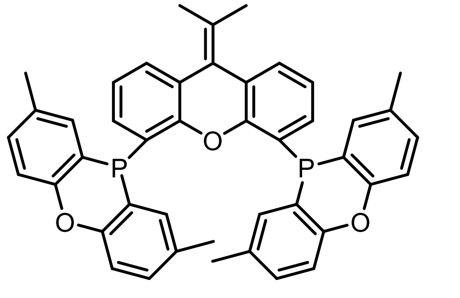
L5, **131°**
yield (l) 40%, l/b=51:49



L6, **113°**
yield (l) 43%, l/b=45:55



L7, **106°**
yield (l) 15%, l/b=20:80



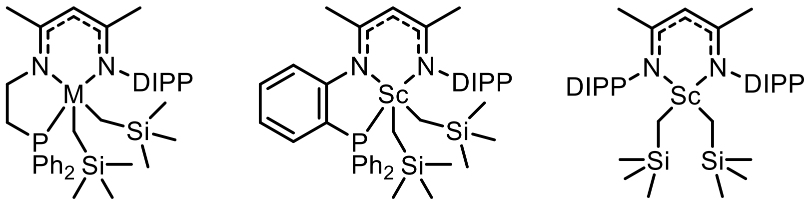
L8, **114°**
yield (l) 67%, l/b=68:32

Raymond et al., *Organometallics,* **2003**, 22 (25), 5358

Metal-catalyzed HAM of alkenes

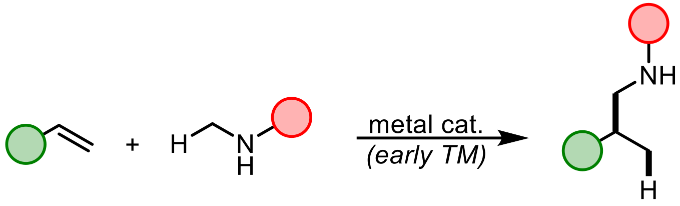
Recent catalytic systems:

3 group

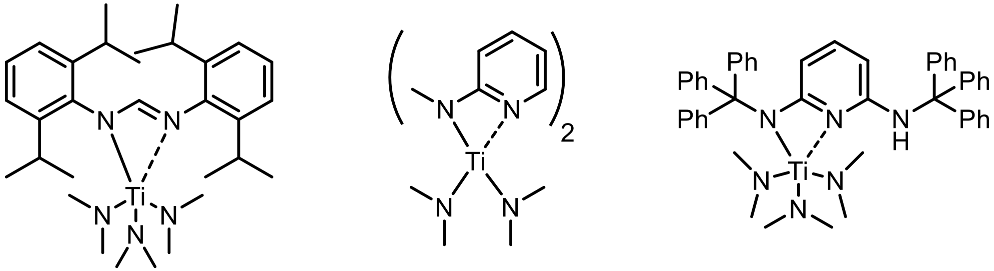


M = Sc, Y

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

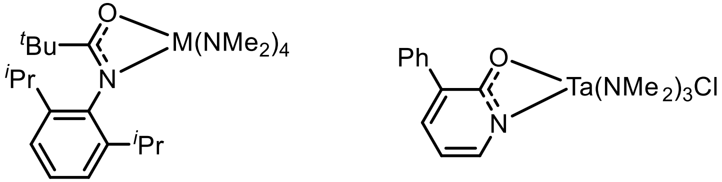


4 group

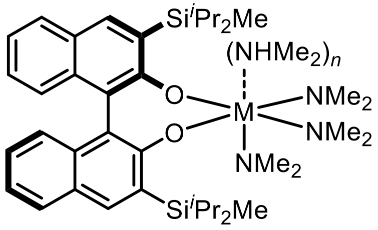


Lehning *et al*, *Chem. Eur. J.*, **2017**, 23, 4197
Bielefeld *et al*, *Angew. Chem. Int. Ed.*, **2017**, 56, 15155

5 group



M = Nb, Ta

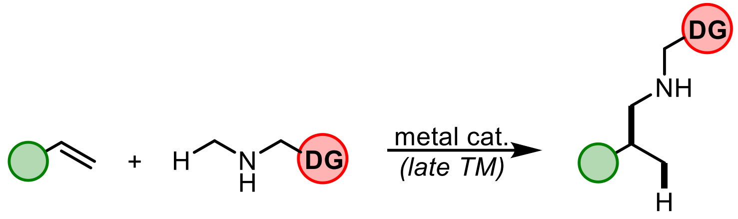


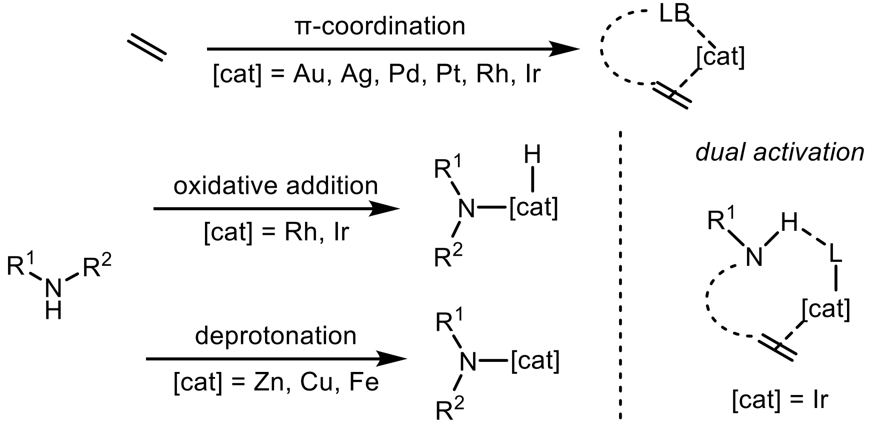
M = Ta, n = 1
M = Nb, n = 0

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

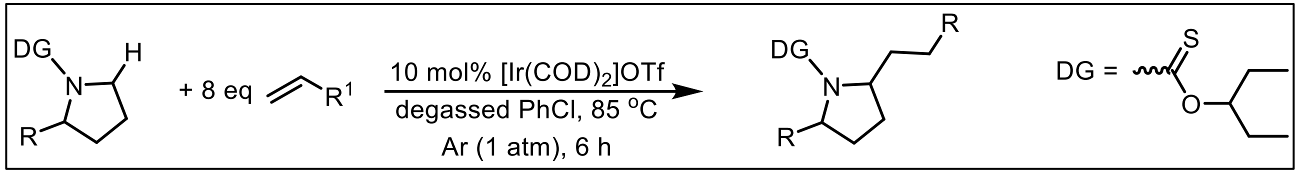
Overall:

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

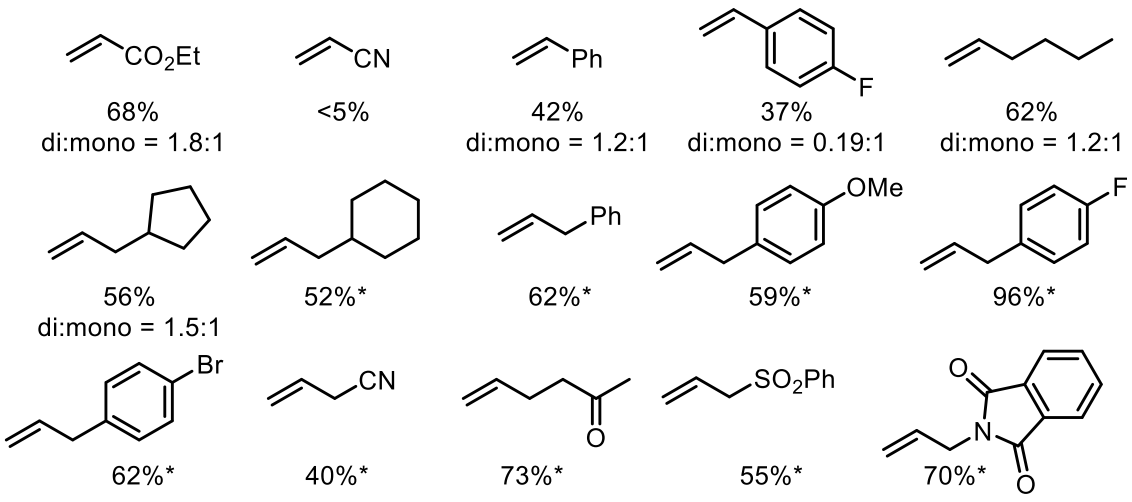




Bernoud *et al*, *Catal. Sci. Technol.*, **2015**, 5, 2017

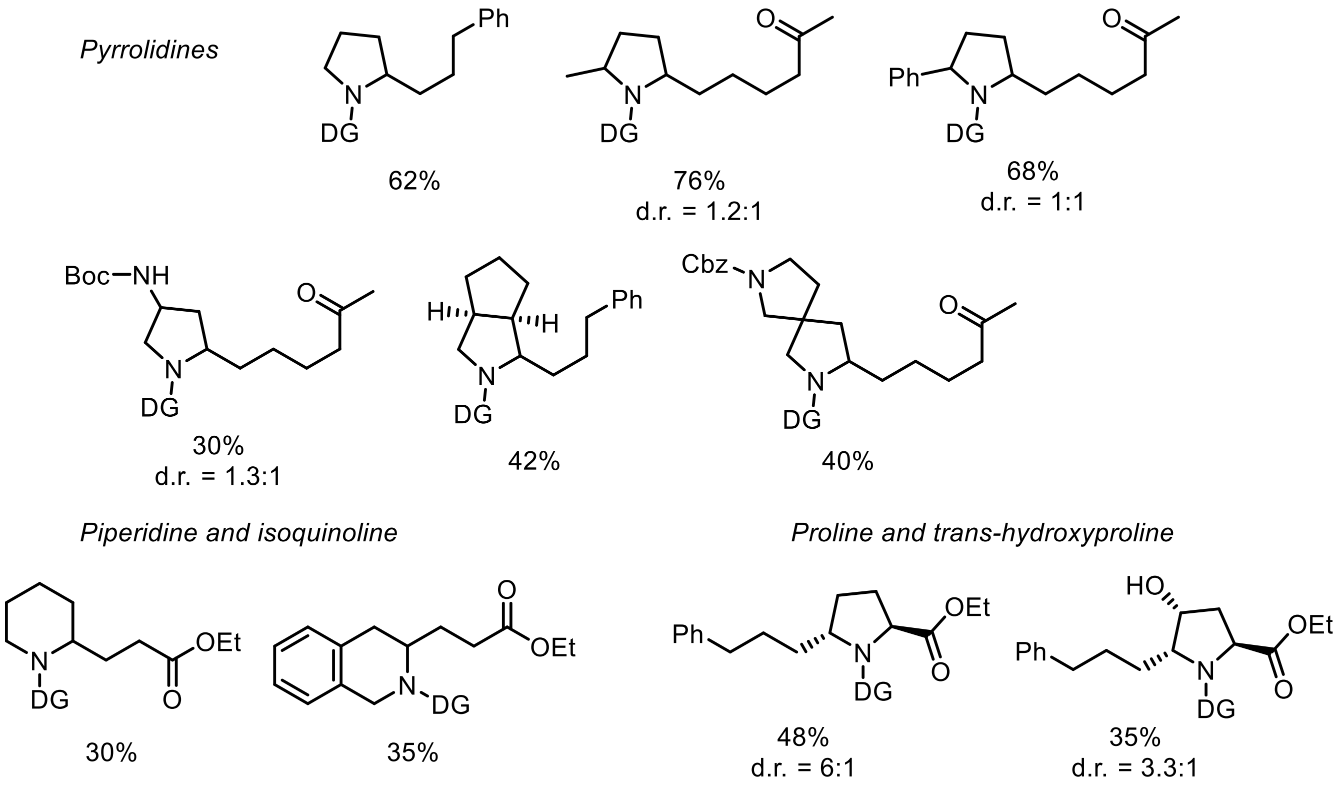


Olefins scope, R = H



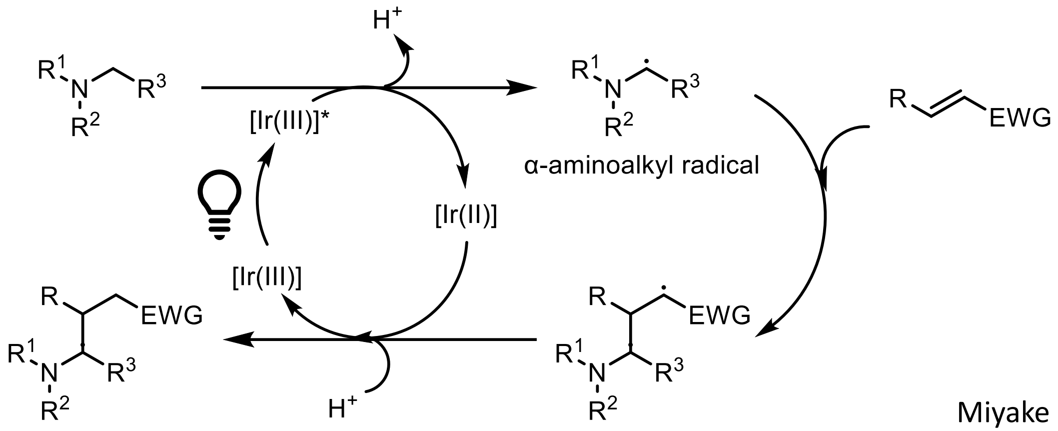
*only dialkylated products (d.r. > 20:1) were obtained for these substrates

Amines scope

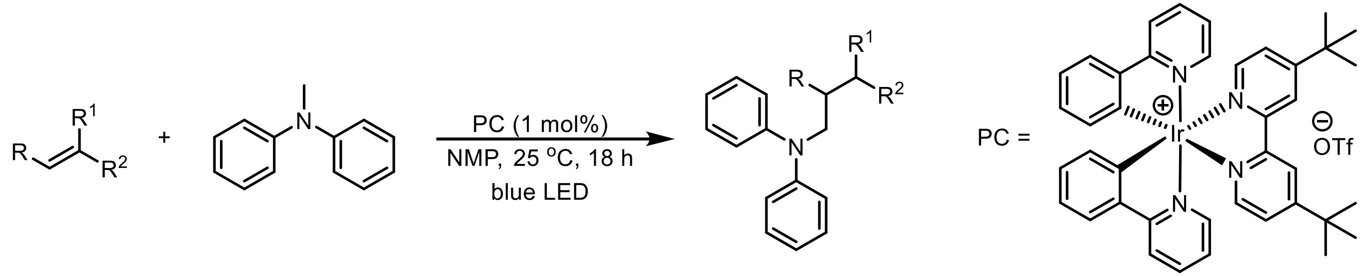


Tran *et al*, *Angew. Chem. Int. Ed.*, **2017**, 56, 10530

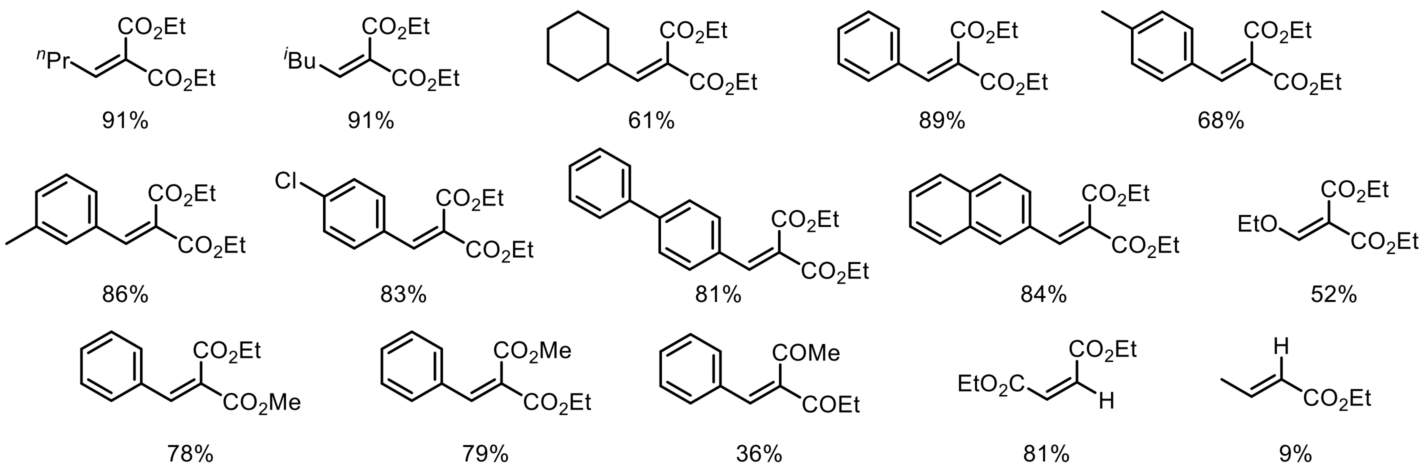
Photocatalytic approach to HAM

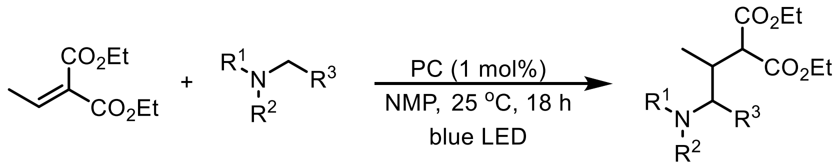


Miyake *et al*, *J. Am. Chem. Soc.*, **2012**, 134, 3338

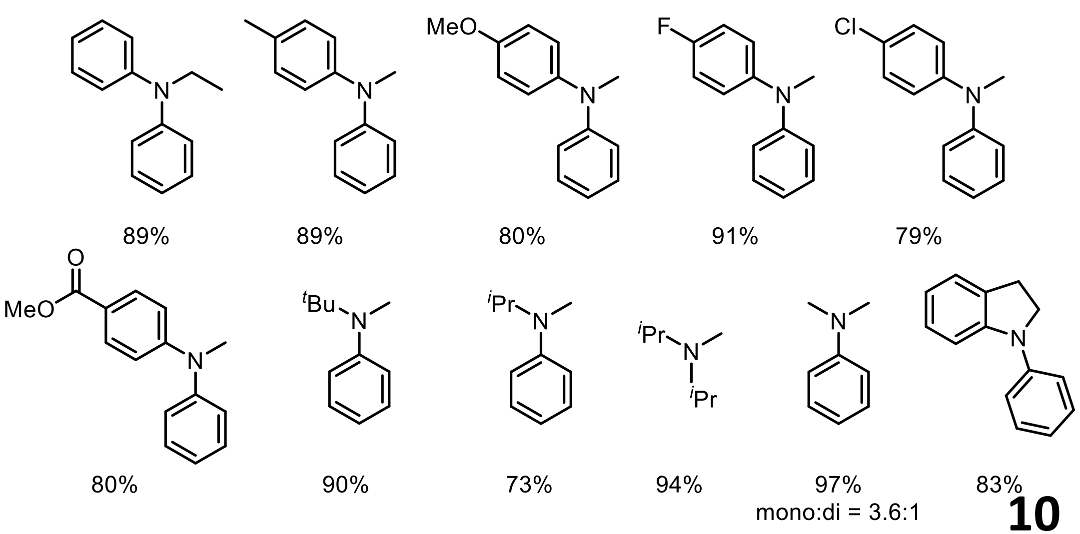


Olefins scope





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*

☹

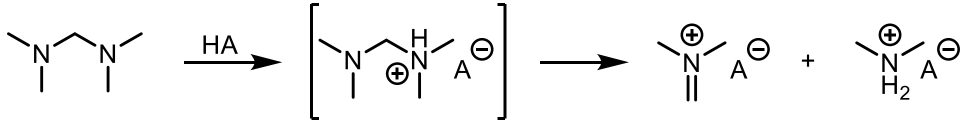
moderate yields in general
catalyst design
catalyst-based substrate design
early TM incompatible with air conditions
limited olefins scope (nonactivated, terminal)
selectivity restrictions
double alkylation
metal or oxidant additives in principle

↓

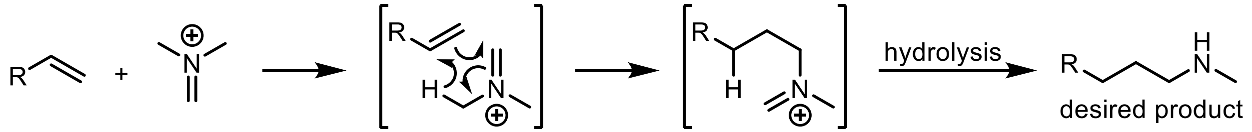
metal-free?
activated π-systems?

Acid-mediated HAM with aminals

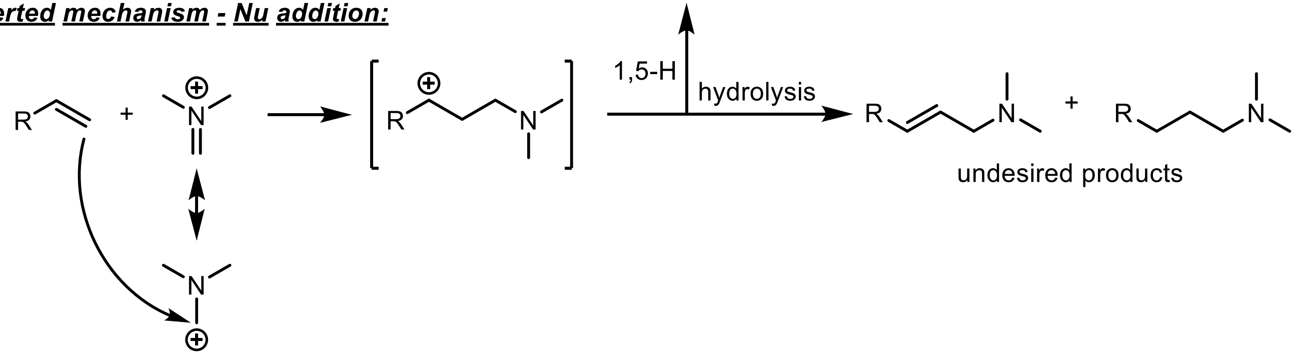
Formation of iminium salts - cleavage of aminals with mineral acid:



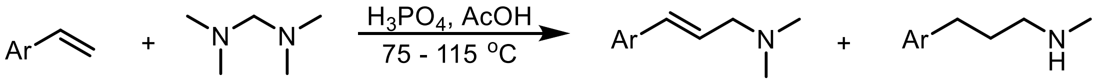
Concerted mechanism - ene reaction:

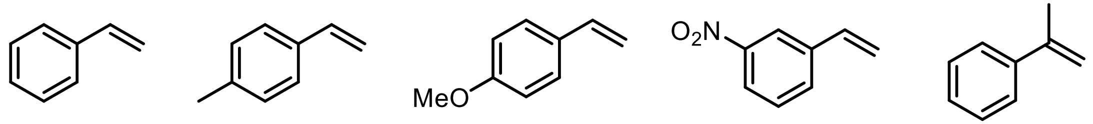


Unconcerted mechanism - Nu addition:



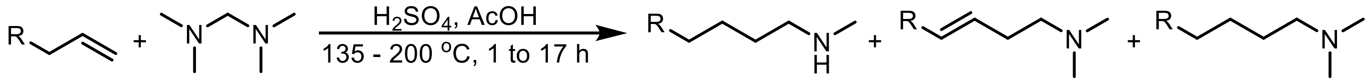
Aryl olefins

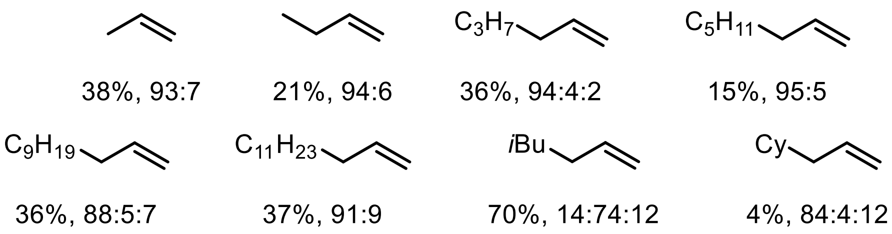




70%, 2:98   68%, 10:90   70%, 80:20   5%, 14:86   72%, 79:21

Nonconjugated olefins

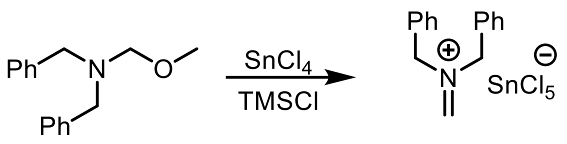


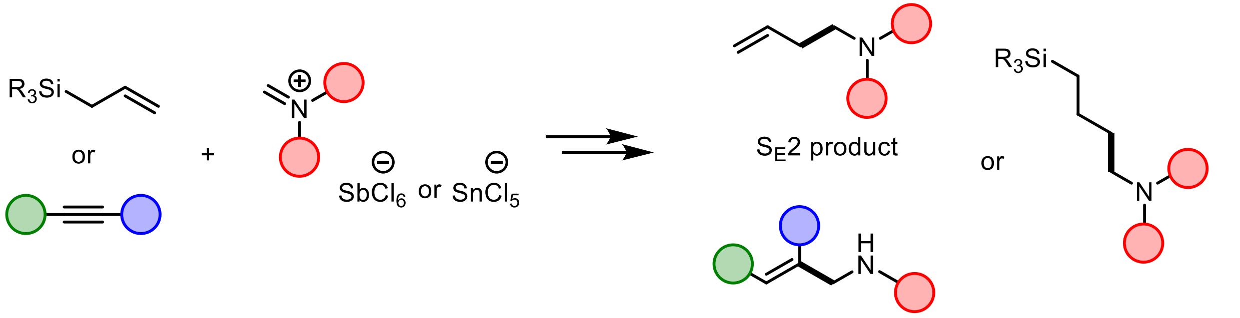


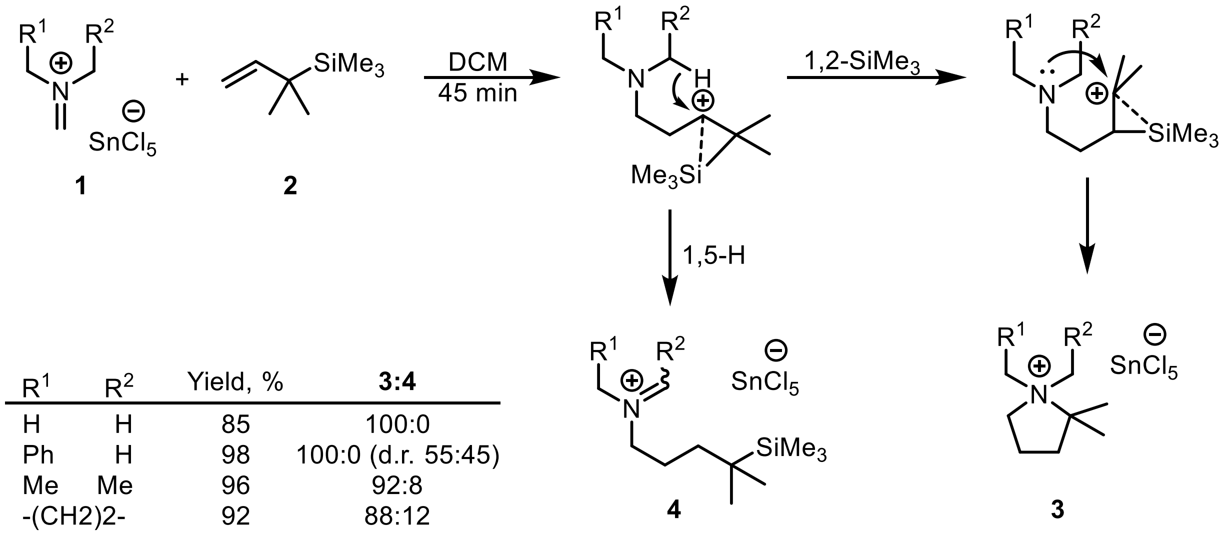
T. Cohen, A. Onopchenko, *J. Org. Chem.*, **1983**, 48 (24), 4531

HAM of activated substrates with N,O-acetals

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



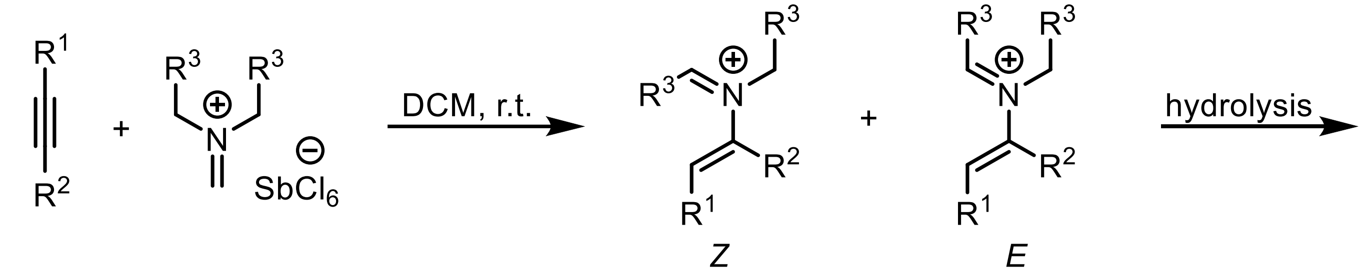


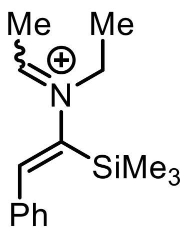


R^1	R^2	Yield, %	**3:4**
H	H	85	100:0
Ph	H	98	100:0 (d.r. 55:45)
Me	Me	96	92:8
-(CH2)2-		92	88:12

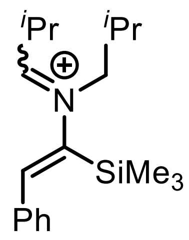
- β-silyl effect
- poor chemosectivity
- poor regioselectivity
- only activated alkenes

Rehn *et al*, *Synthesis*, **2003**, 12, 1790

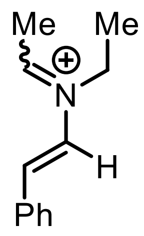




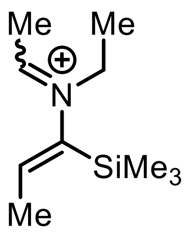
91%, *Z:E*=70:30



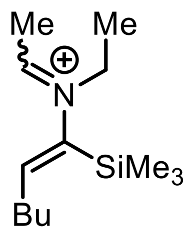
81%, *Z:E*=95:5



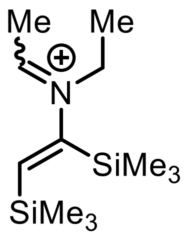
81%, *Z:E*=75:25



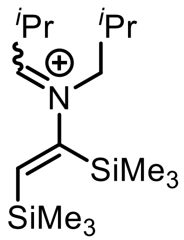
71%, *Z:E*=70:30



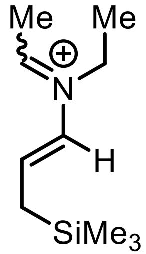
90%, *Z:E*=80:20



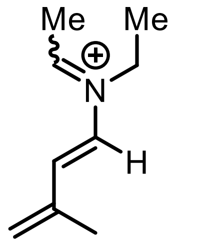
83%, *Z:E*=70:30



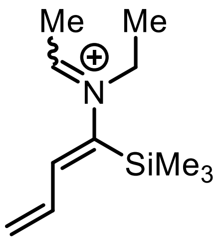
78%, *Z:E*=92:8



86%, *Z:E*=63:37



68%, *Z:E*=68:32

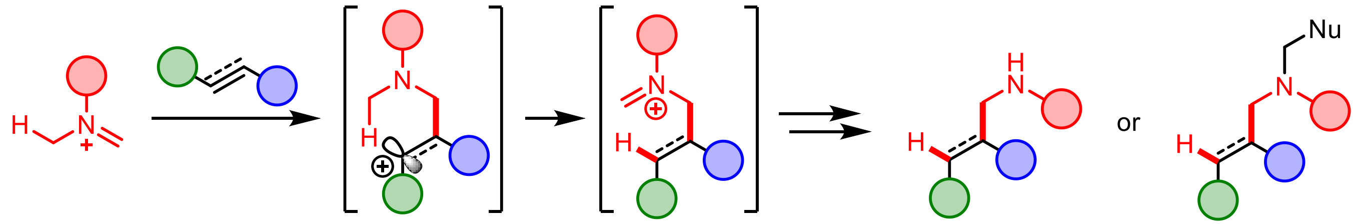


87%, *Z:E*=76:24

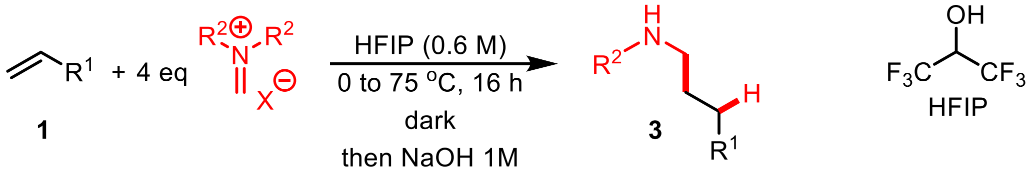
Ofial *et al*, *Angew. Chem. Int. Ed.*, **1997**, 36, 143

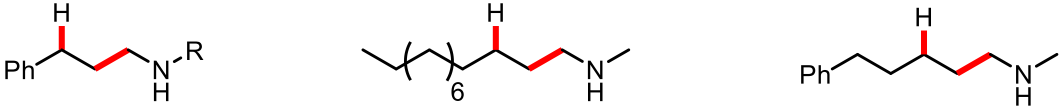
Acid-mediated HAM

The concept



First steps



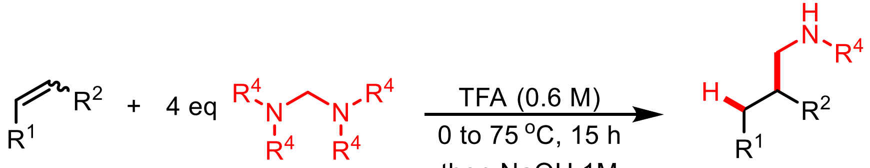


unsuccessful substrates: internal alkenes, alkynes

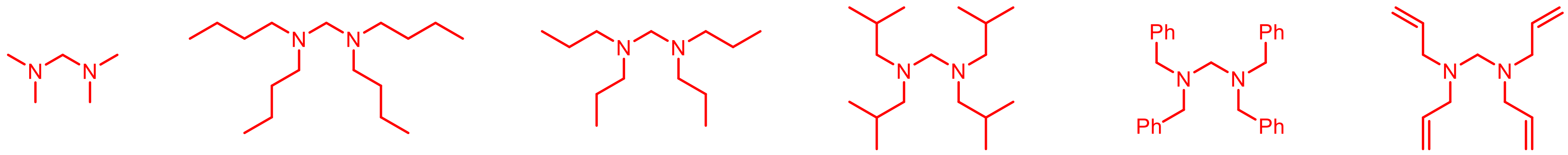
*Yield determined by [1]H NMR analysis using an internal standard

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

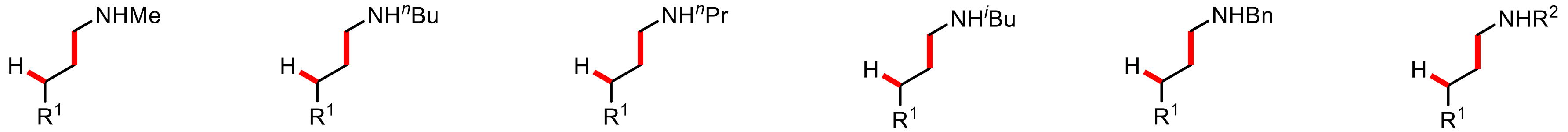
Aminals scope



1 2 3

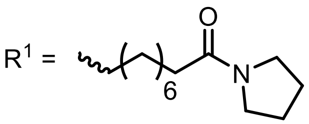


2a 2b 2c 2d 2e 2f

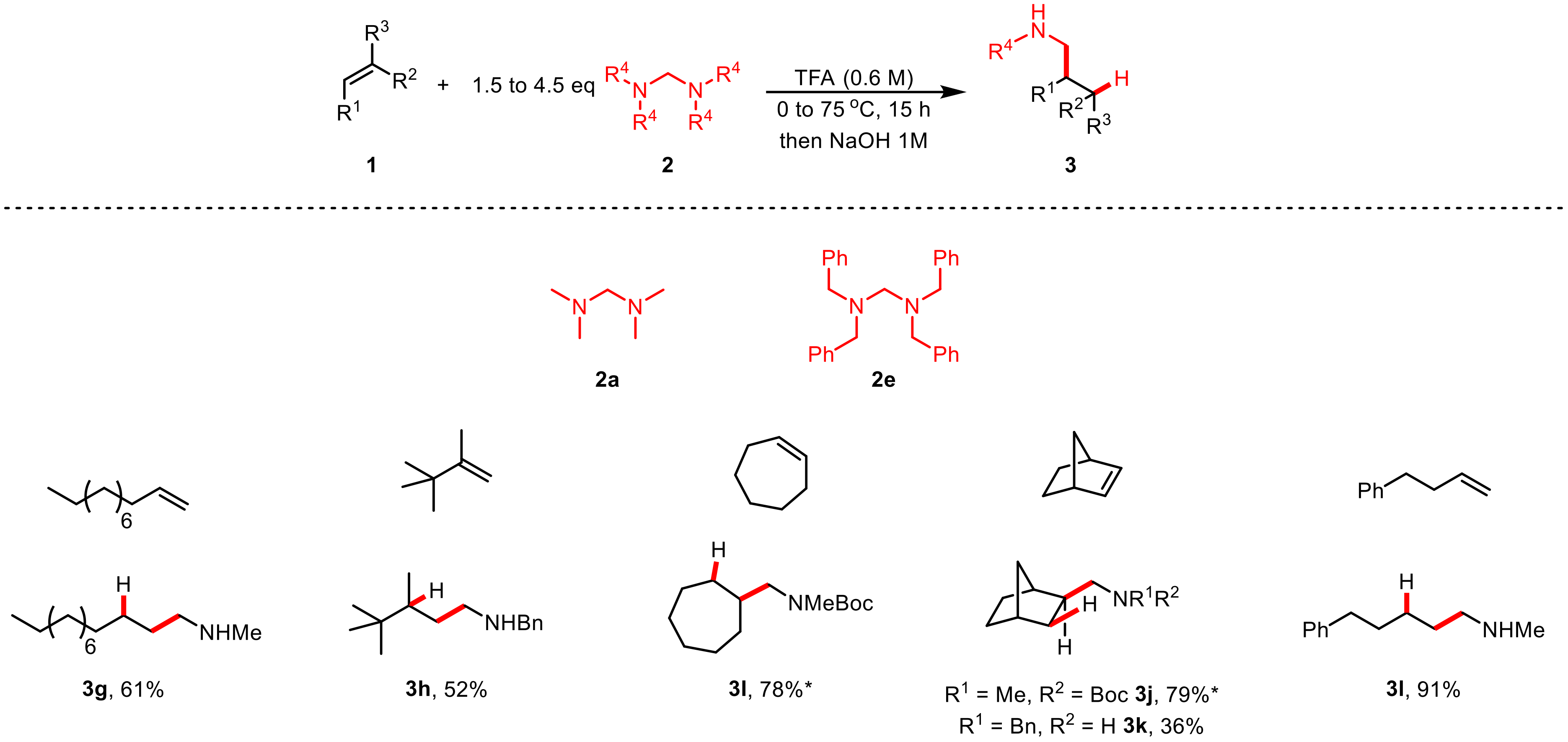


3a, 84% **3b**, 85% **3c**, 92% **3d**, 84% **3e**, 73%

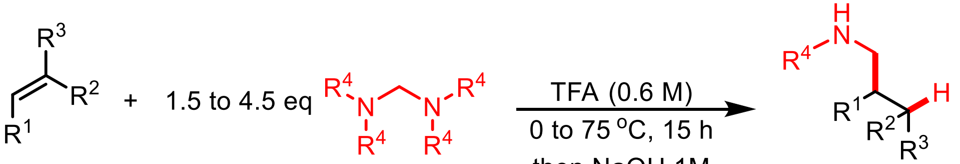
R^2 = allyl **3f**, 86% Pd/C, EtOH
R^2 = H **4f**, 85% 75 °C, 24 h



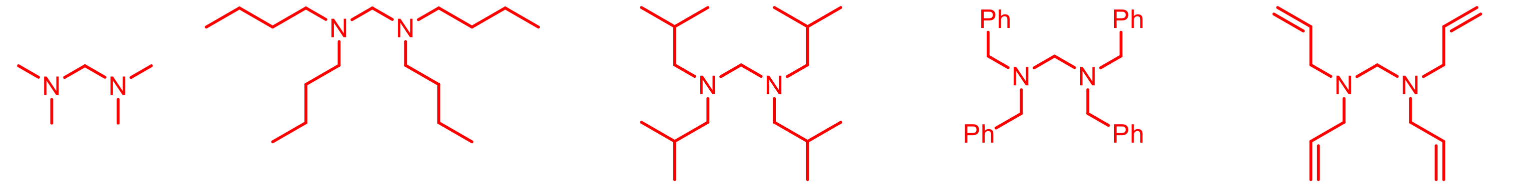
Olefins scope



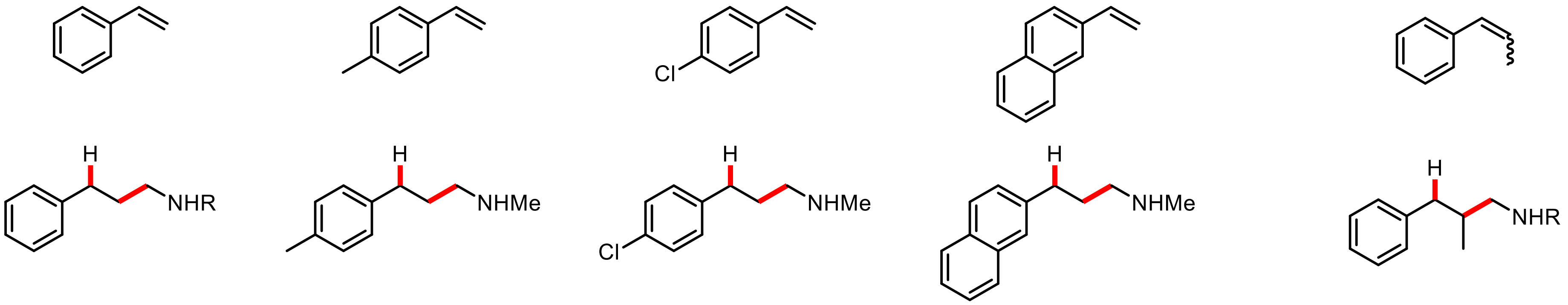
*Yield after acylative protection with Boc_2O to facilitate isolation



1 **2** **3**



2a **2b** **2d** **2e** **2f**



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

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

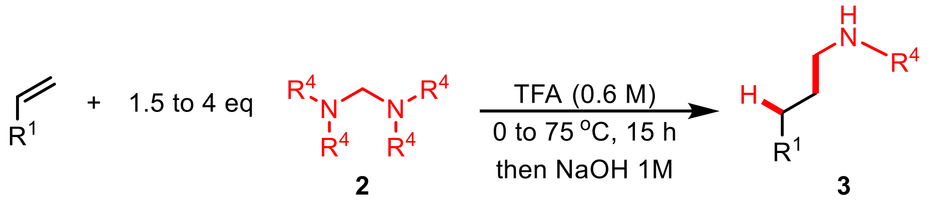
3n, 85%

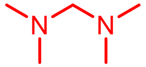
3o, 86%

3p, 55%

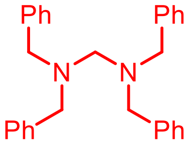
R = ^{i}Bu **3t**,
61% from *cis*- and 60% from *trans*-
R = Me **3u**,
39% from *cis*-

Functional group tolerance

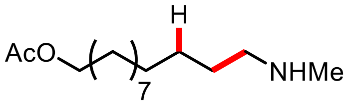




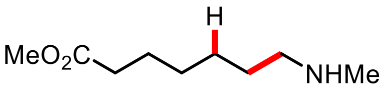
2a



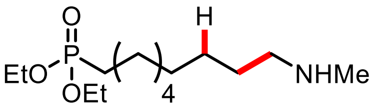
2e



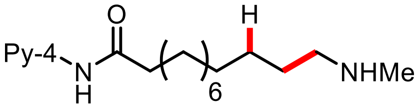
3v, 93%



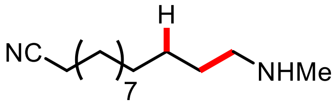
3w, 64%



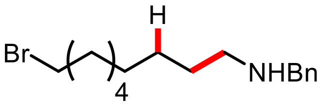
3x, 80%



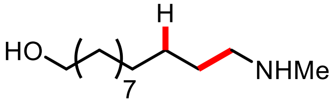
3y, 72%



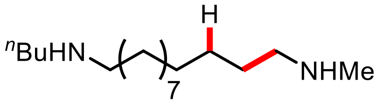
3z, 84%



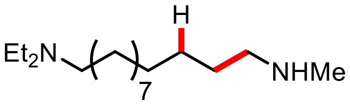
3aa, 40%



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

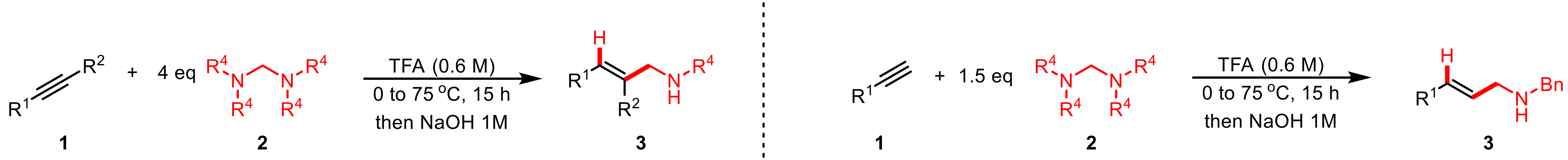


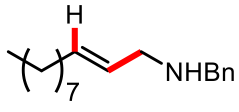
3ac, 60%



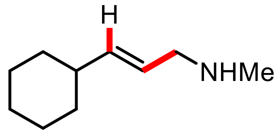
3ad, 75%

Alkynes scope

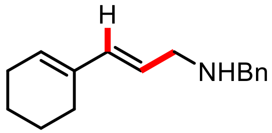




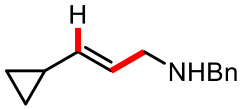
6a, 53%*



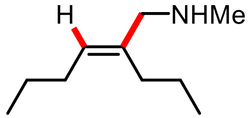
6b, 65%



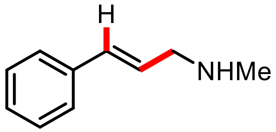
6c, 68%*



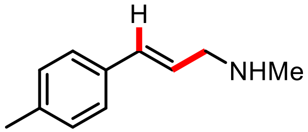
6d, 85%*



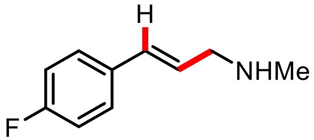
6e, 41%



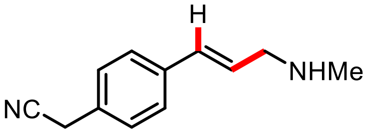
6f, 57%



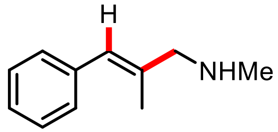
6g, 51%



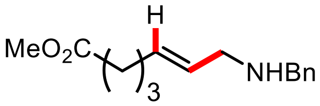
6h, 31%



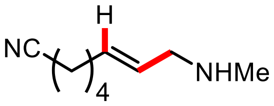
6i, 37%*
(35%* on 20 mmol)



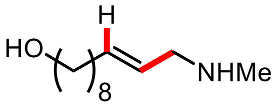
6j, 48%



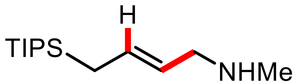
6k, 41%



6l, 97%



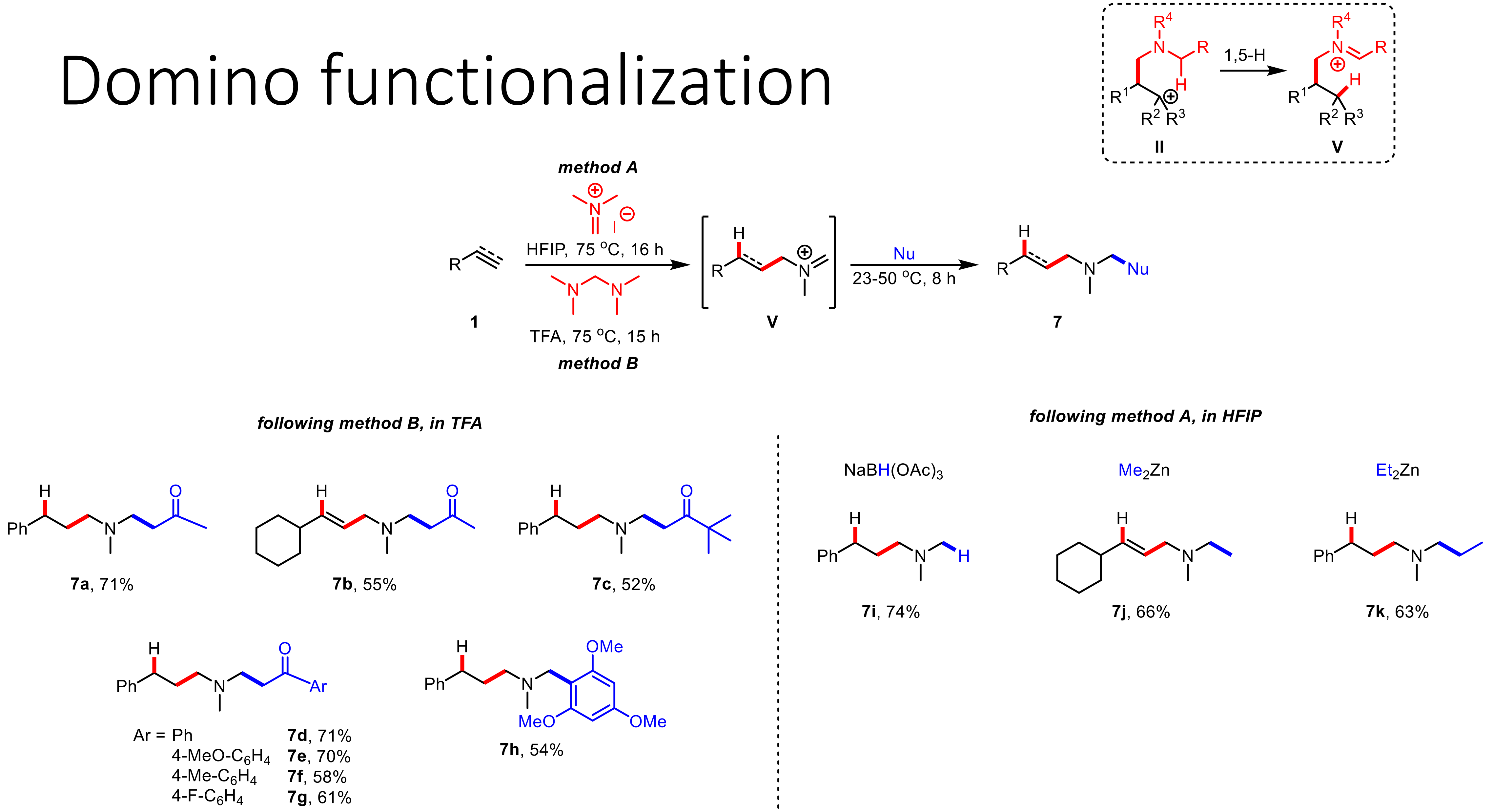
6m, 59%**



6n, 34%***

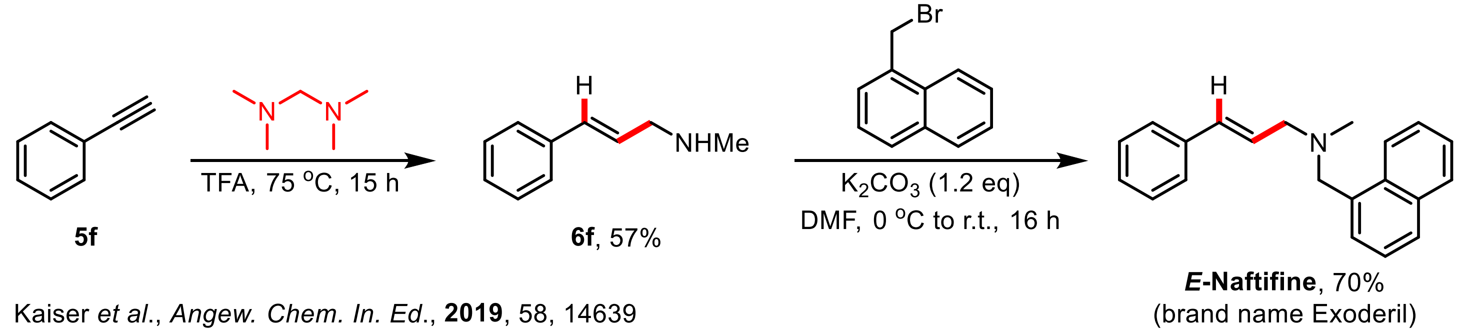
*DCE used as co-solvent
**Reaction was run for 5 h
***Reaction was run at room temperature

Domino functionalization

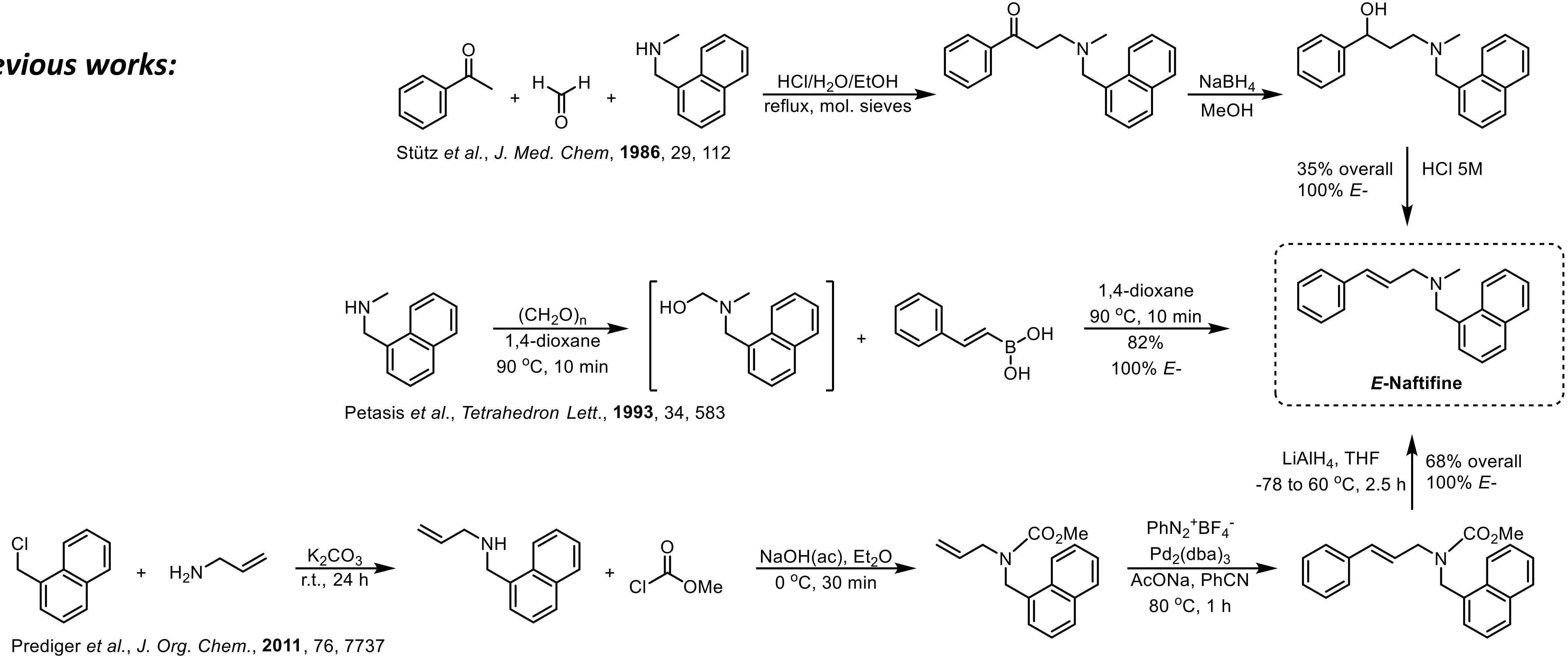


Pharmaceutical products synthesis

This work:



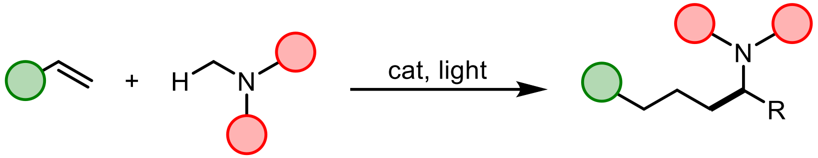
Previous works:



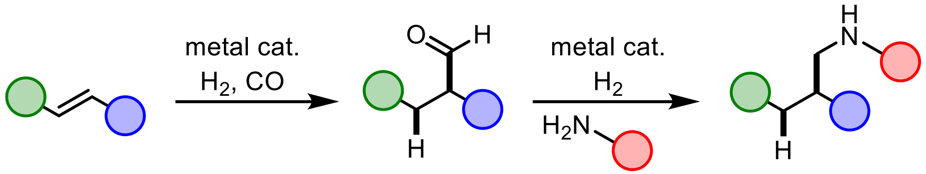
Conclusion

- lots of limited TM-catalyzed HAM methods

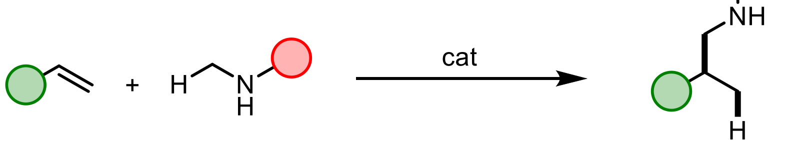
Photoredox HAM



Tandem HAM via hydroformylation

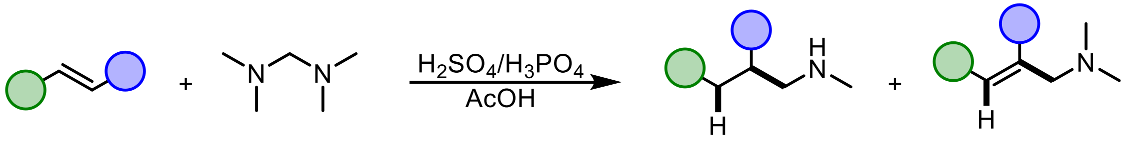


TM-catalyzed HAM

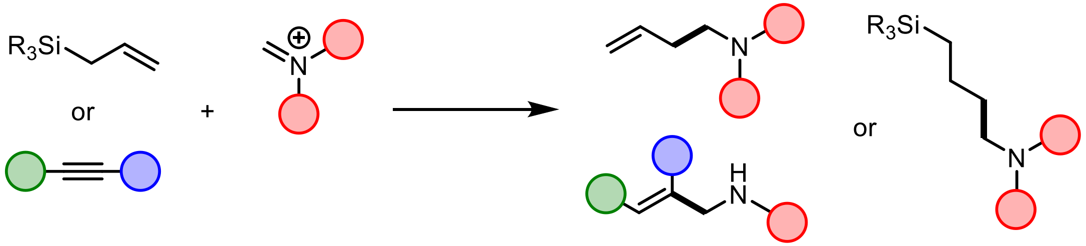


- number of limited metal-free HAM procedures

HAM with aminals

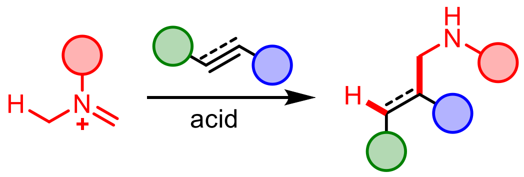


HAM with iminium salts



- one general acid-mediated HAM method

Acid-mediated HAM



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2. Agbossou-Niedercorn, Recent metal-catalysed assymetric hydroamination of alkenes *Journal of Organometallic Chemistry*, **2017**, 847, 13.
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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(sp^3)–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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14. Mayr, Reactions of allylsilanes with iminium salts: ene reactions with inverse electron demand *J. Org. Chem*., **1996**, 61, 5823.

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18. Cohen, Onopchenko, Competing hydride transfer and ene reactions in the aminoalkylation of 1-alkenes with *N,N*-dimethylmethyleniminium ions. A literature correction *J. Org. Chem*., **1983**, 48, 4531.

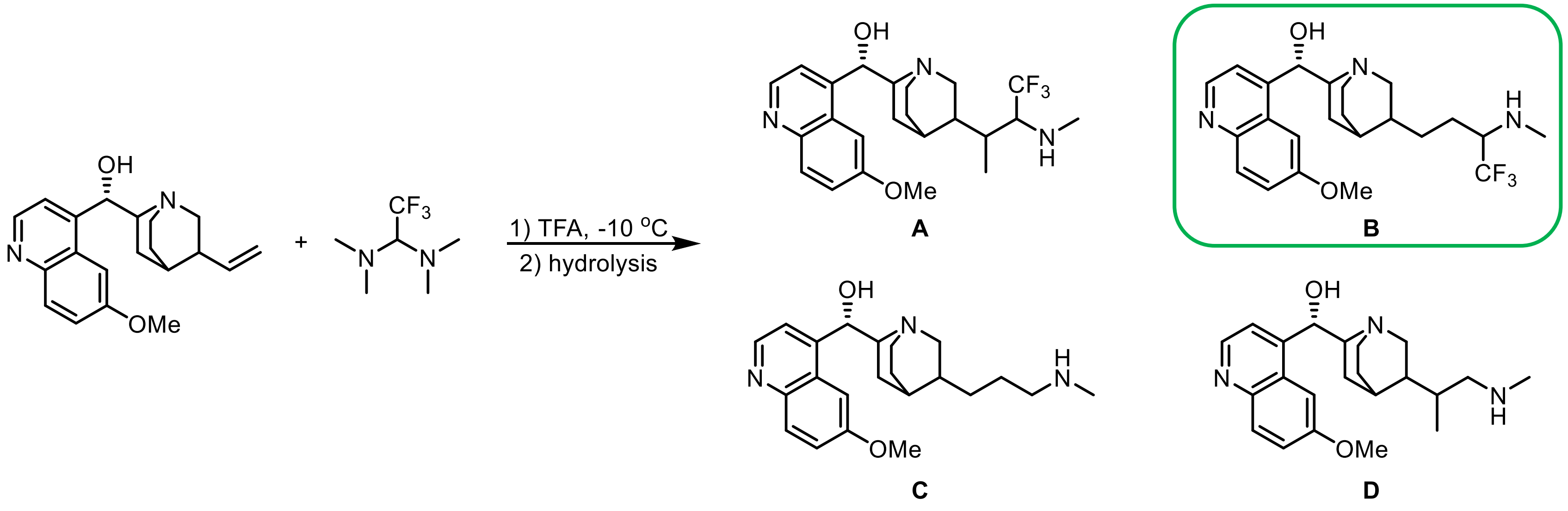
Thank you for your kind attention!

Question + Exercise

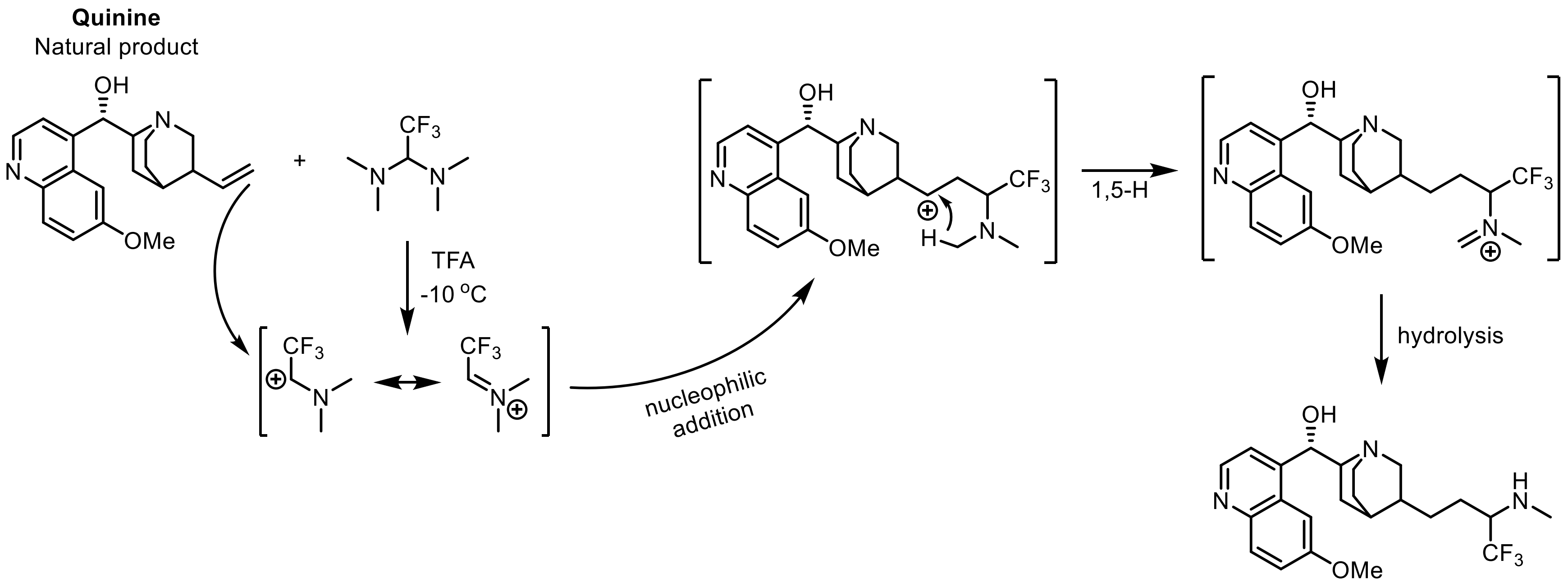
- Do you have any ideas regarding the choice of TFA in the work of Prof. Maulide group?

"…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



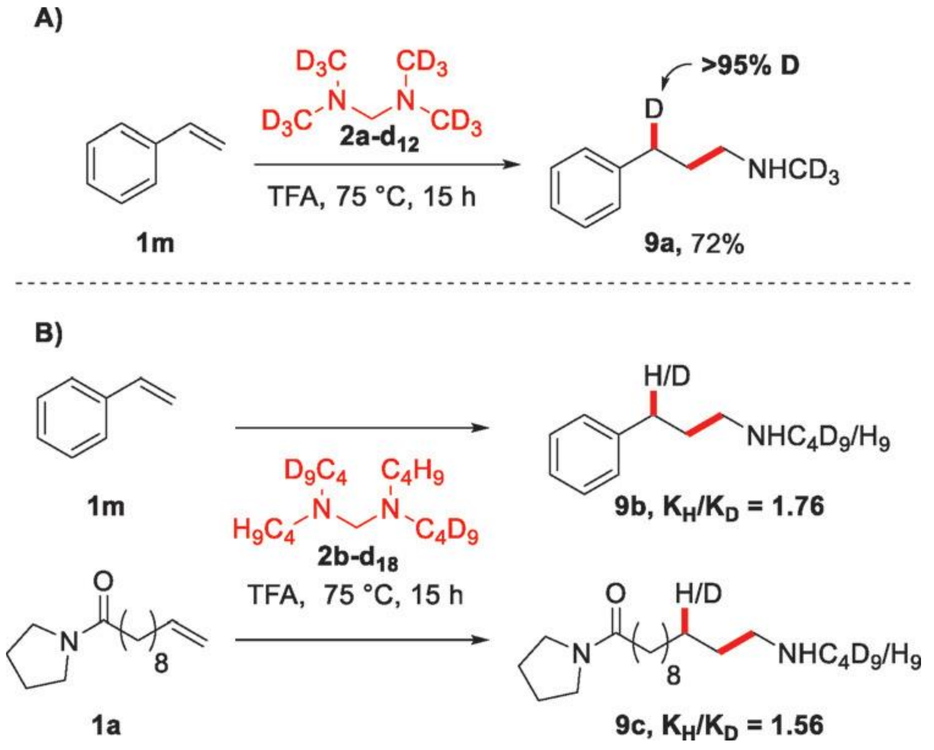
Exercise



B
32% (brsm 76%)

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

Additional slide – mechanistic studies of acid-mediated hydroaminomethylation



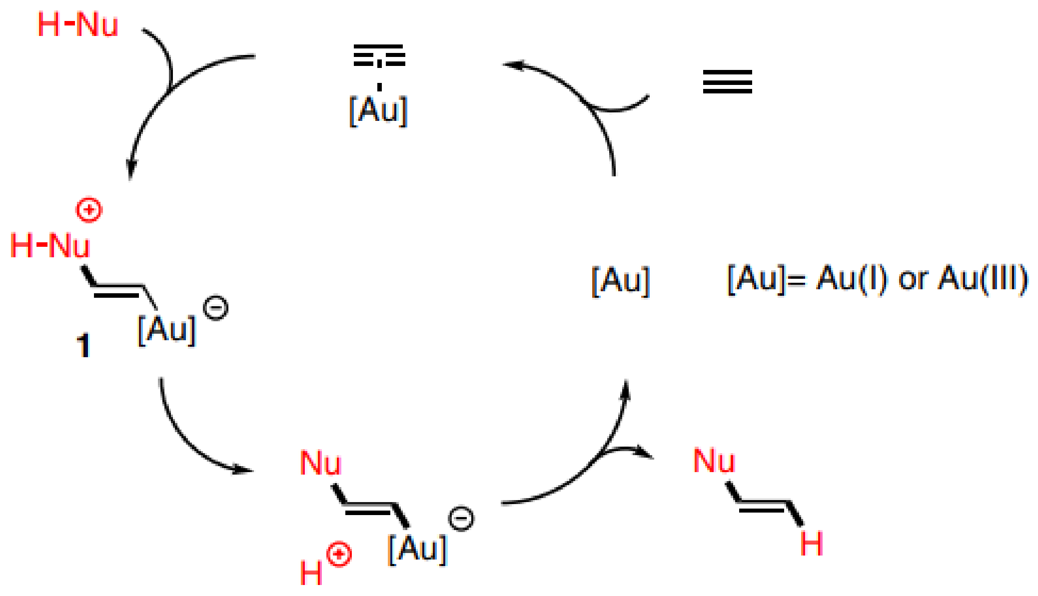
Gold catalysed C-C bond forming reactions of unactivated olefins

Kedar Abhyankar

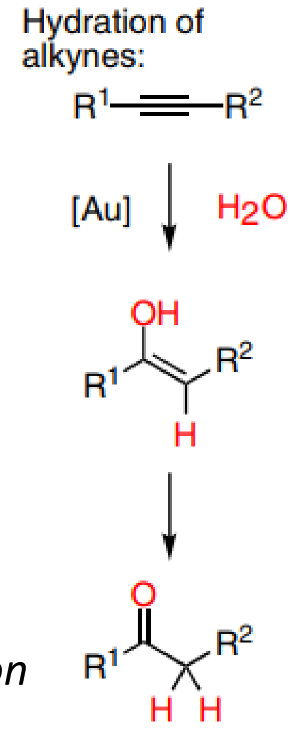
Prof. Dyson Group

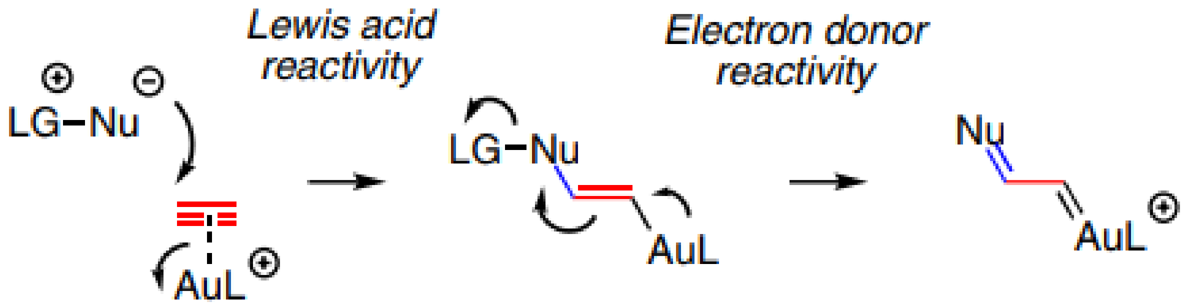
Gold catalysis: Introduction

- 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



General mechanism of Au-catalysed alkyne addition



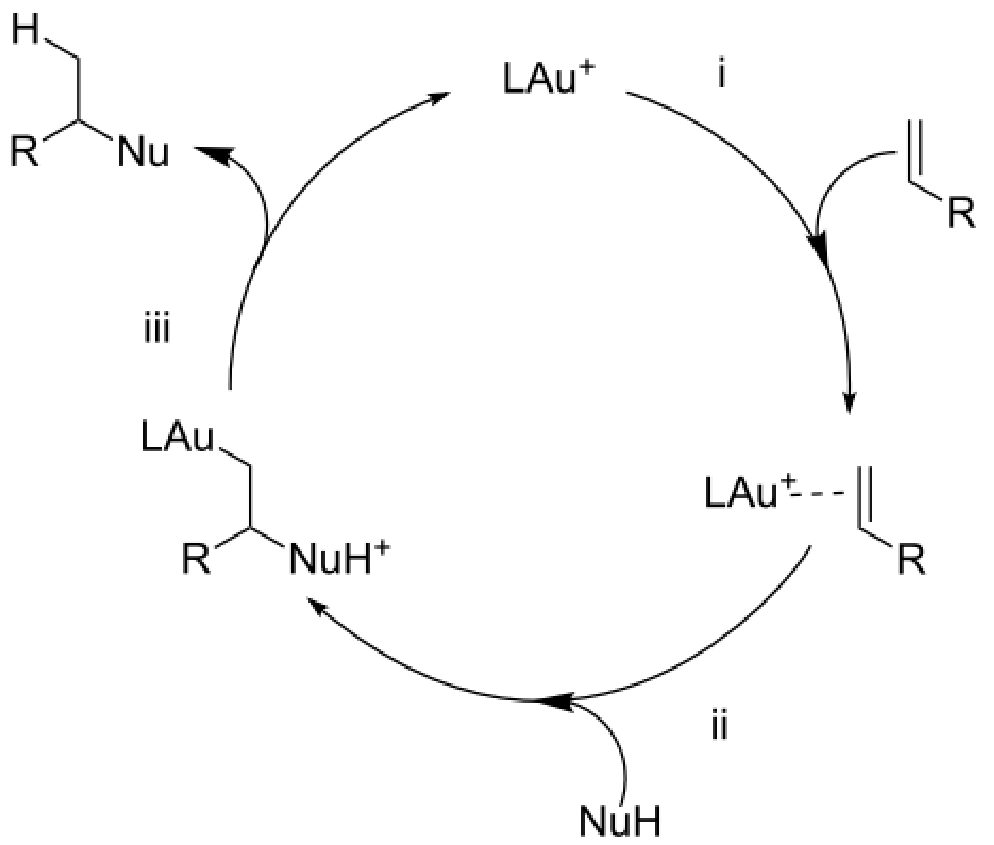


- However:
- Oxidative coupling processes /cross-coupling processes
- Au carbene species invoked as intermediates
- 6s contraction, 5d expansion
- Dual behaviour

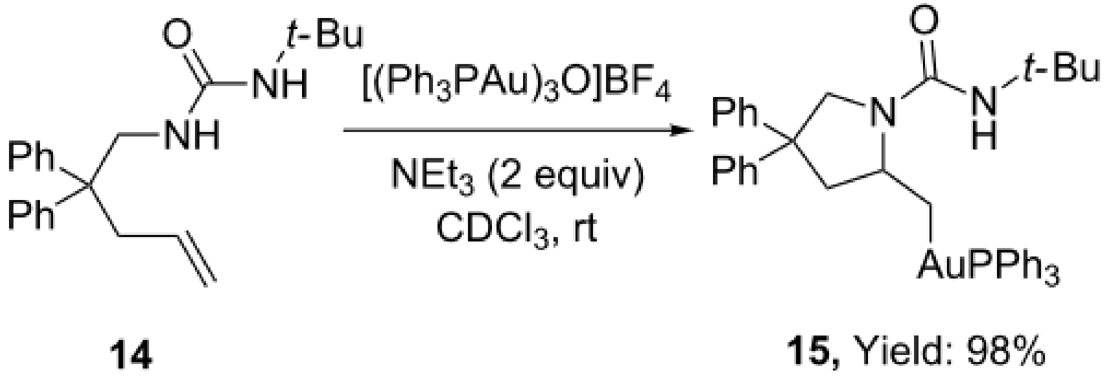
M. Veronique and D. T. Francisco, *Gold Catalysis: An Homogeneous Approach*, World Scientific Publishing Company, 2014.

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



General mechanism of Au catalysed addition to alkenes



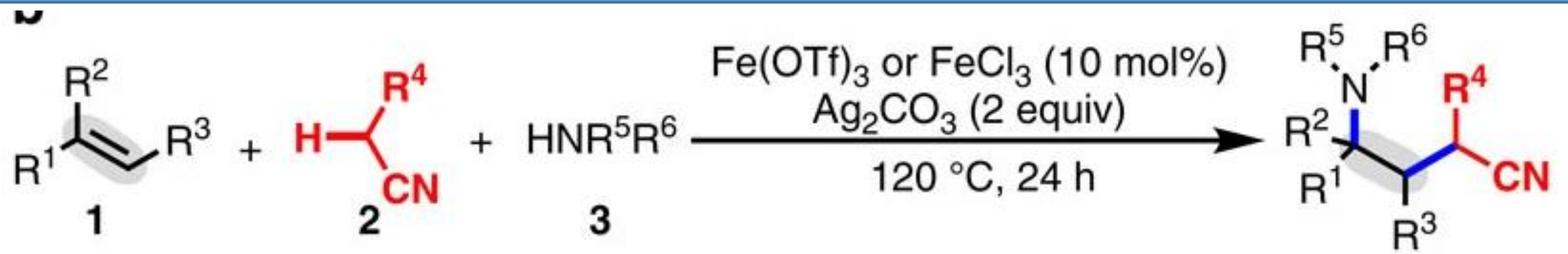
Isolation of alkyl species in Au-catalysed hydroamination

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

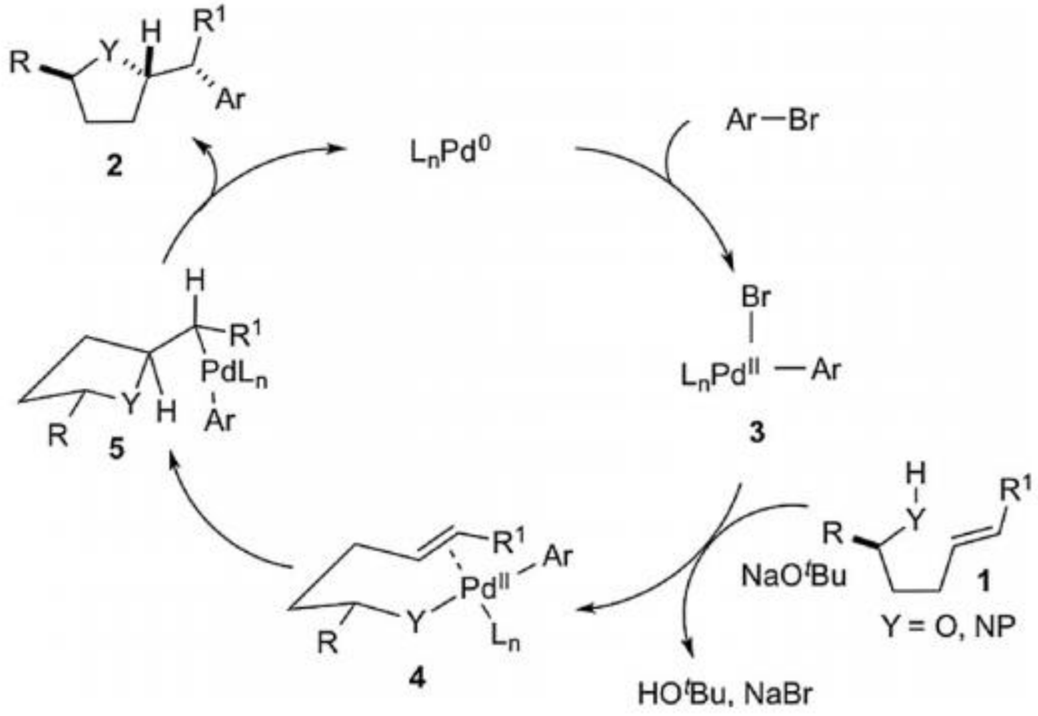
R. L. LaLonde, J. Brenzovich William E., D. Benitez, E. Tkatchouk, K. Kelley, I. I. I. Goddard William A. and F. D. Toste, *Chem. Sci.*, 2010, **1**, 226–233.

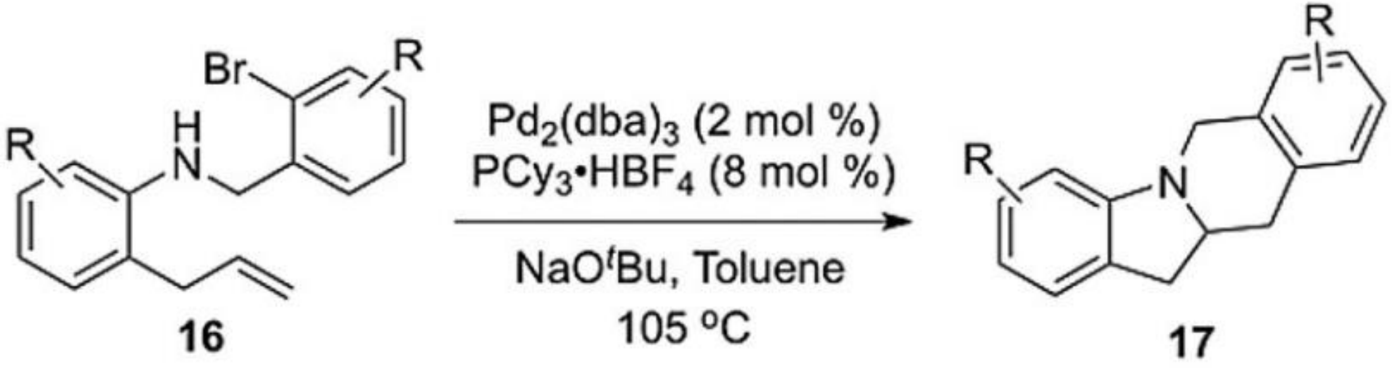
Carboheterofunctionalisation of alkenes

- 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



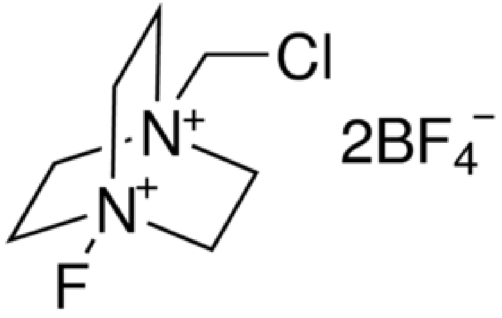
Y.-Y. Liu, X.-H. Yang, R.-J. Song, S. Luo and J.-H. Li, *Nat. Commun.*, 2017, **8**, 14720.



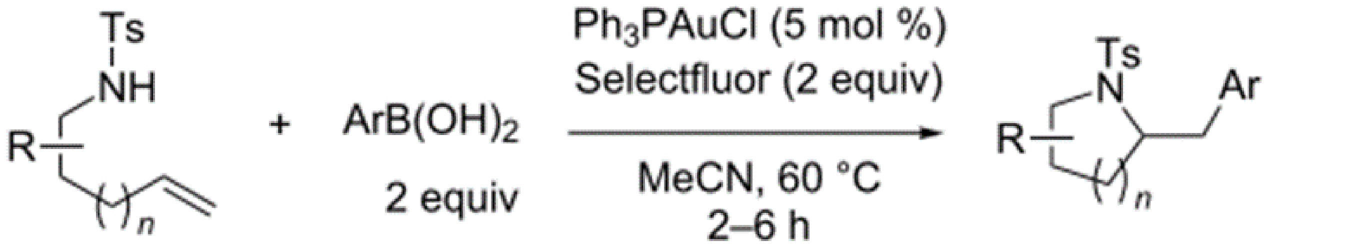


J. Alicea and J. P. Wolfe, *J. Org. Chem.*, 2014, **79**, 4212–4217.

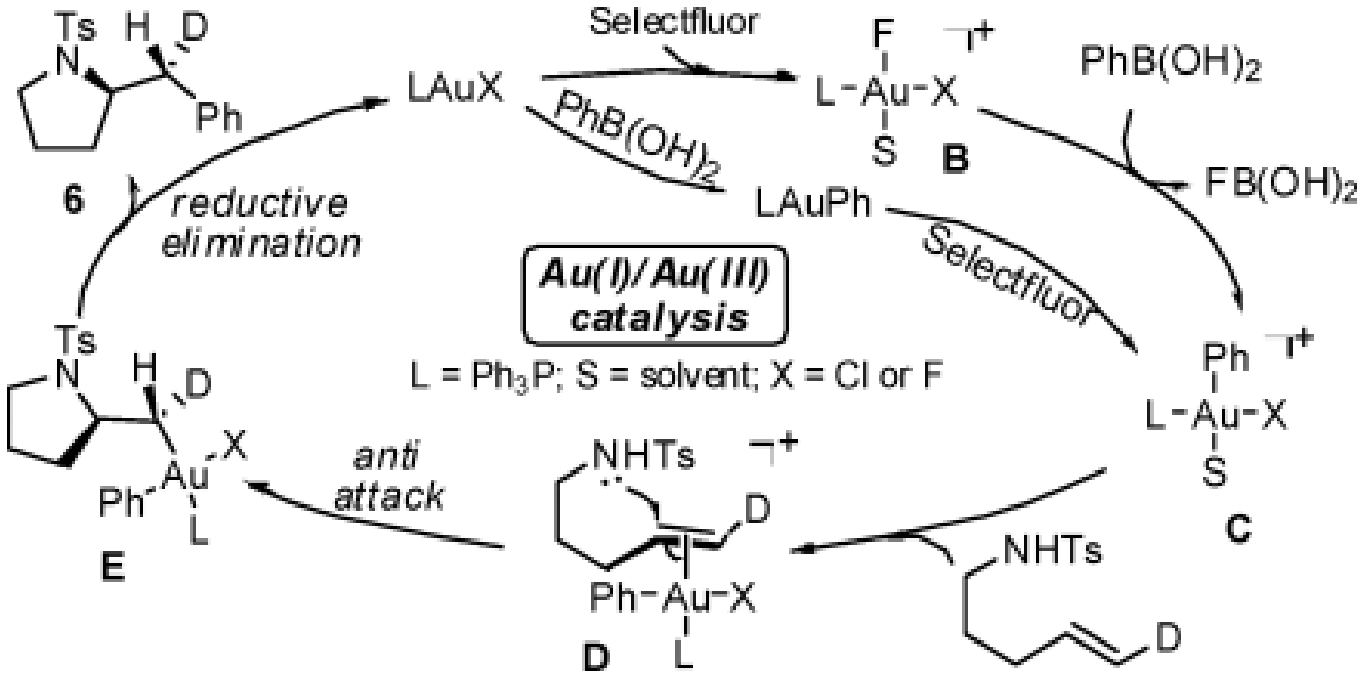
Carboamination



Selectfluor

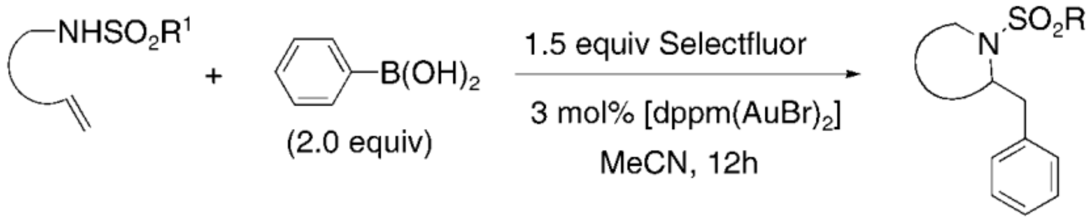


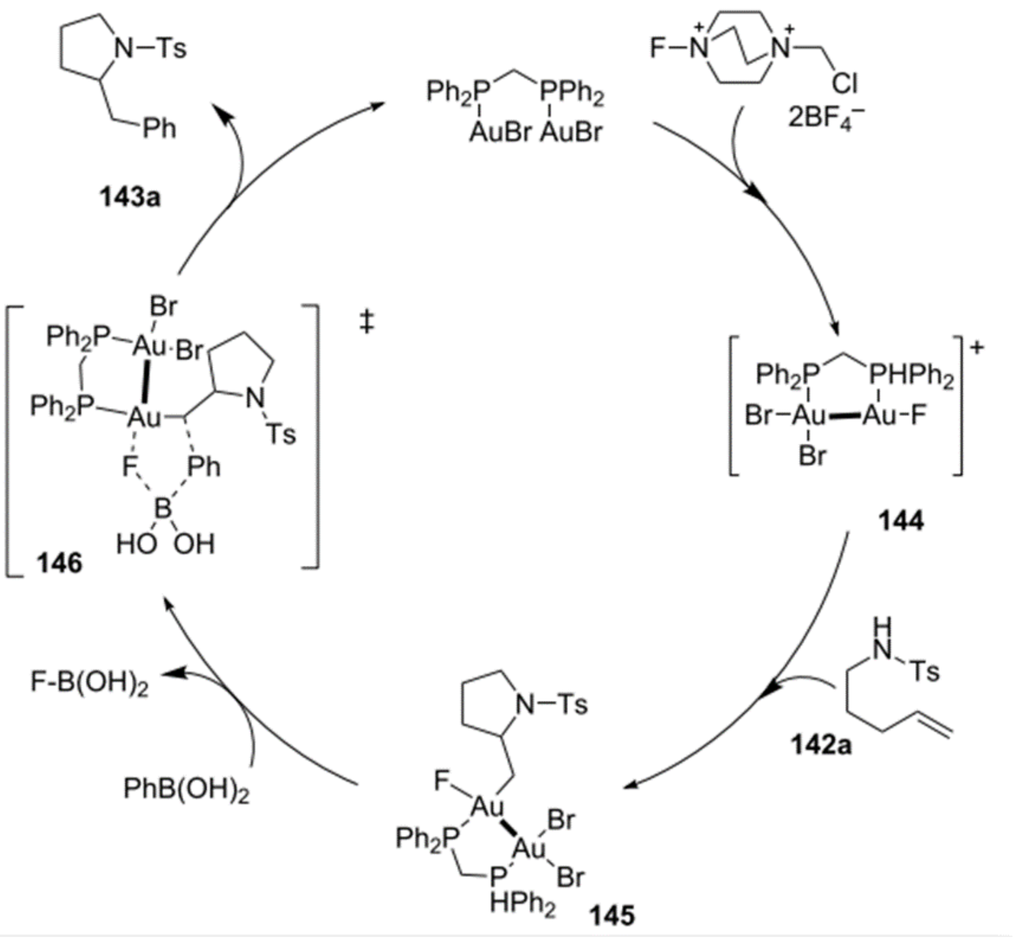
- Reported by Zhang et al
- Potential intermediacy of LAuPh hypothesised but contradicted by Toste (JACS 2010)



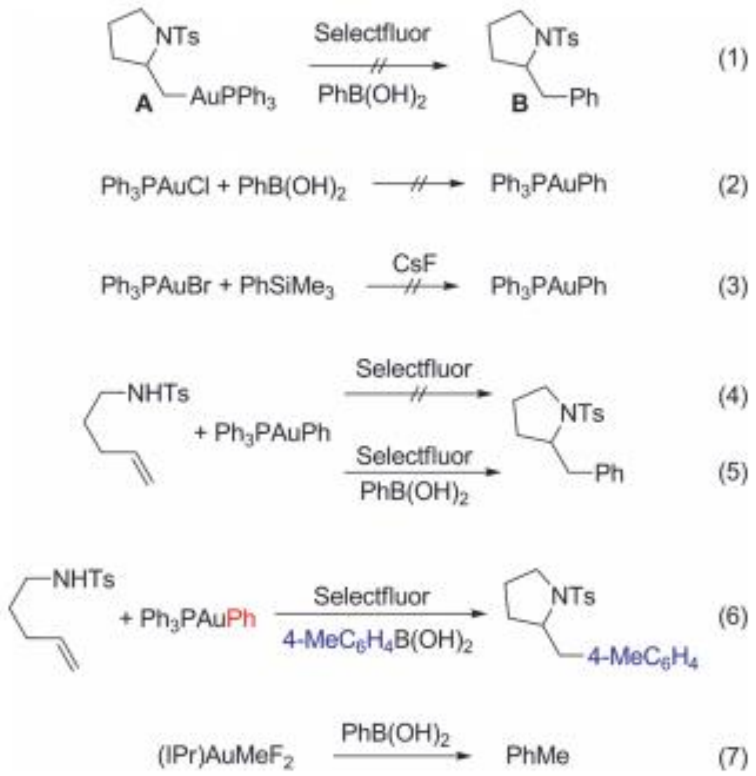
G. Zhang, L. Cui, Y. Wang and L. Zhang, *J. Am. Chem. Soc.*, 2010, **132**, 1474–1475.
S. Zhu, L. Ye, W. Wu and H. Jiang, *Tetrahedron*, 2013, **69**, 10375–10383.

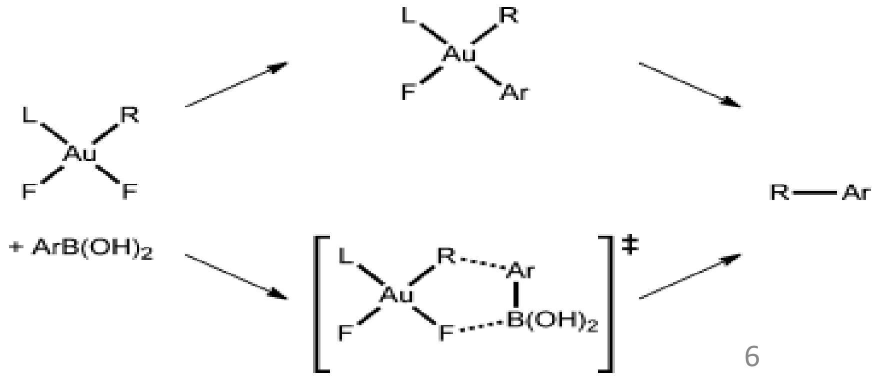
Carboamination: A new mechanistic proposal



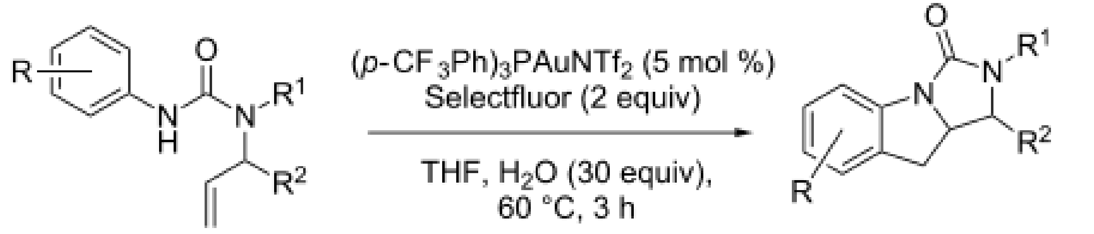


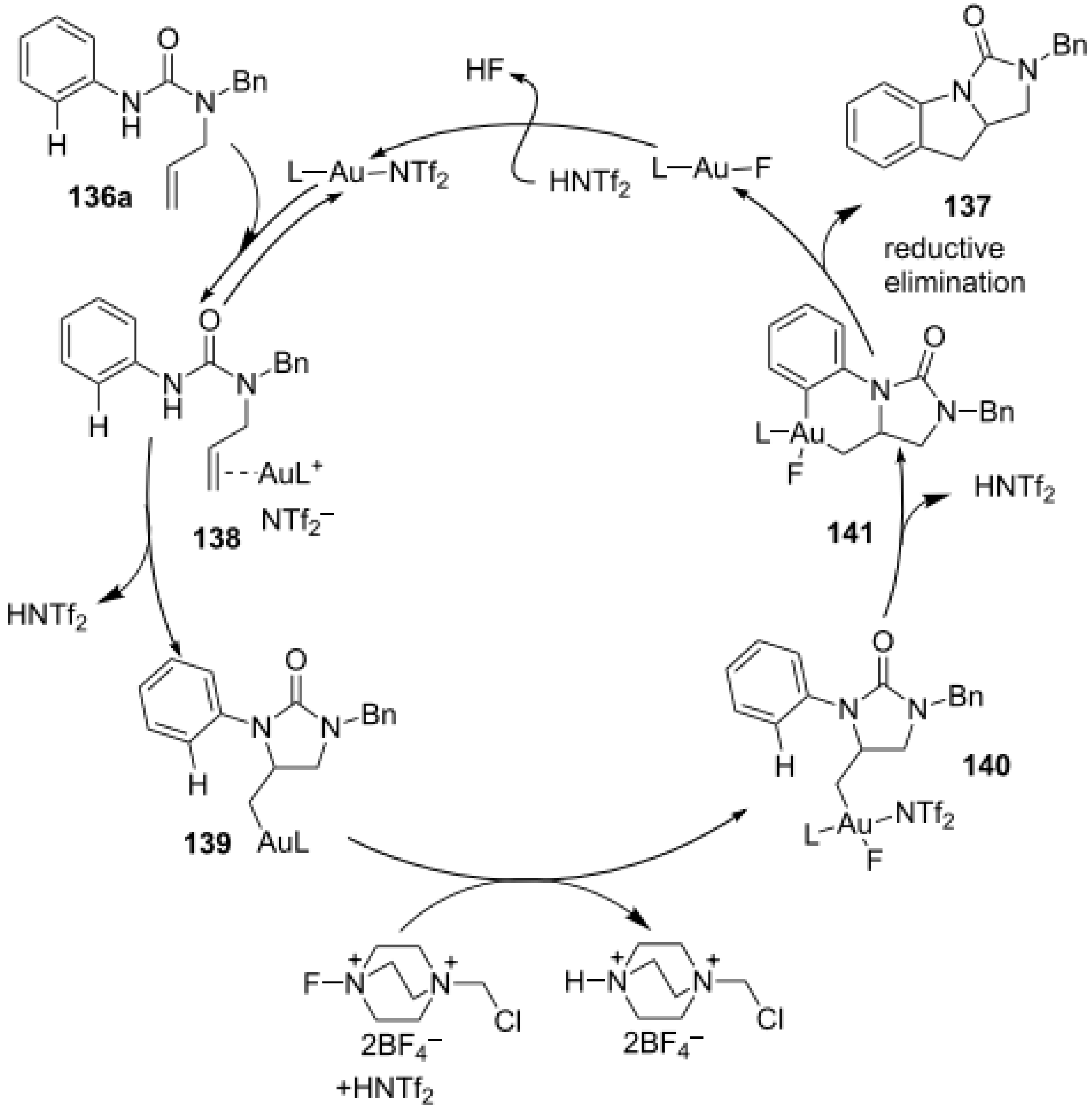
- Bimetallic system by Toste
- Catalytically superior (milder conditions)
- Tolerates a wide range of substituted sulphonamides
- Even those without Thorpe-Ingold driving force
- 6-membered rings cyclised at slightly elevated temperatures





Intramolecular variant: Aryl C-H functionalisation

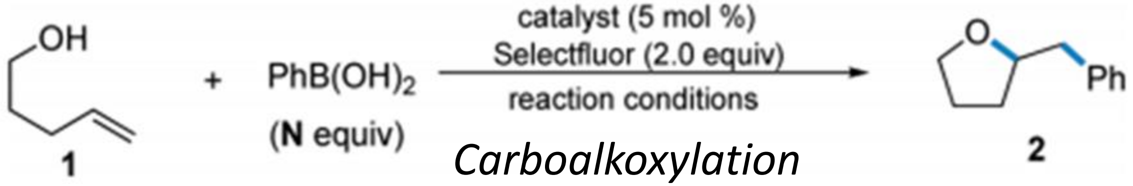


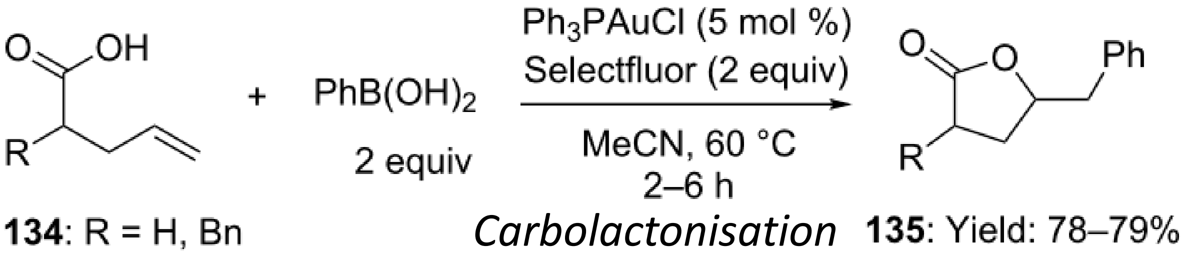


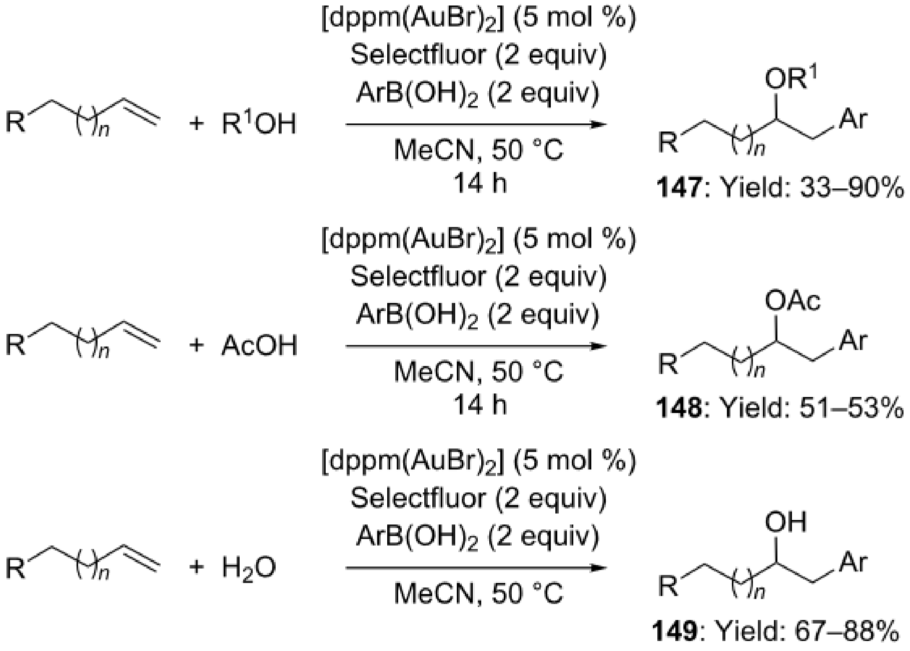
- In conflict mechanistically with prior approach
- First example of C-H functionalisation with Au-alkyl
- 30eq H_2O required
- cf. *ortho*-metalation by platinum group metals

G. Zhang, Y. Luo, Y. Wang and L. Zhang, *Angew. Chemie Int. Ed.*, 2011, **50**, 4450–4454.

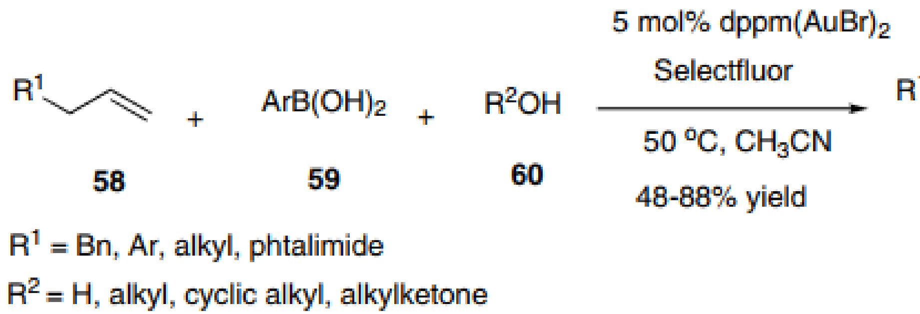
Carboalkoxylation

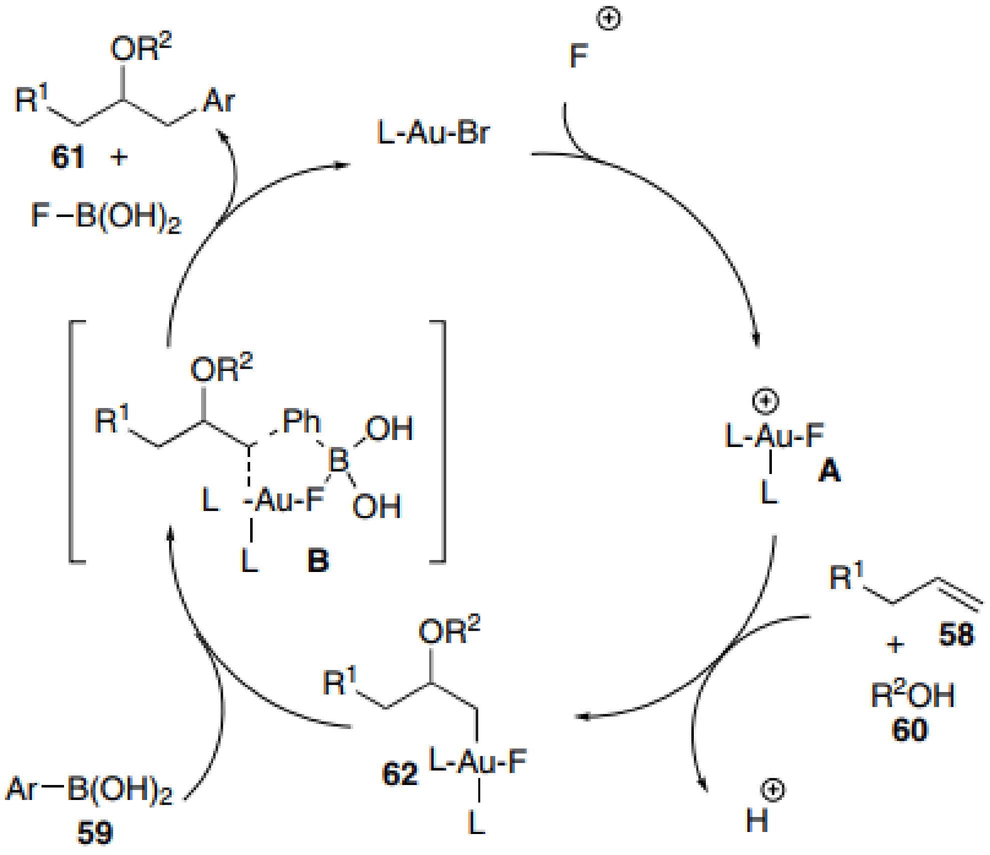






- *Mechanistically similar*
- *3 component intermolecular coupling*
- *Range of terminal alkenes functionalised*

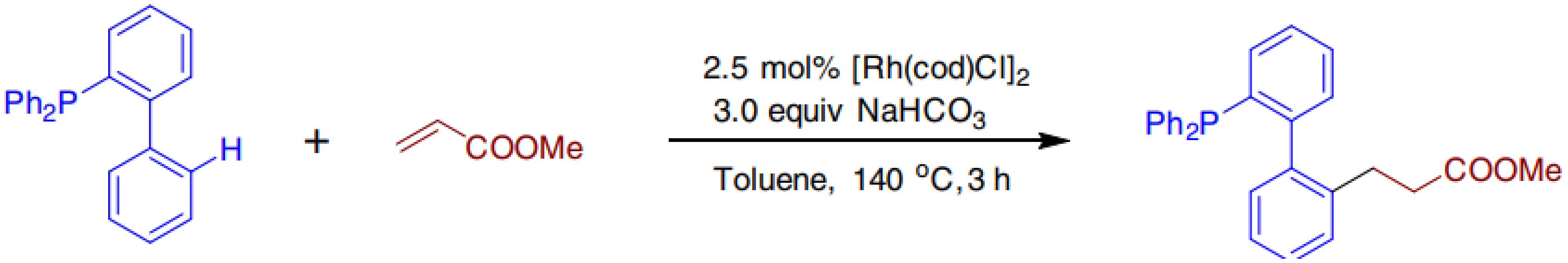




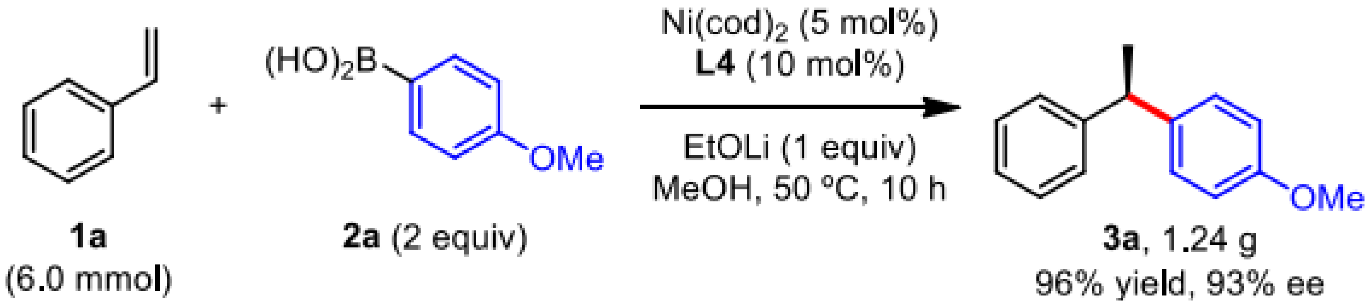
A. D. Melhado, W. E. Brenzovich, A. D. Lackner and F. D. Toste, *J. Am. Chem. Soc.*, 2010, **132**, 8885–8887.
B. G. Zhang, L. Cui, Y. Wang and L. Zhang, *J. Am. Chem. Soc.*, 2010, **132**, 1474–1475.

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

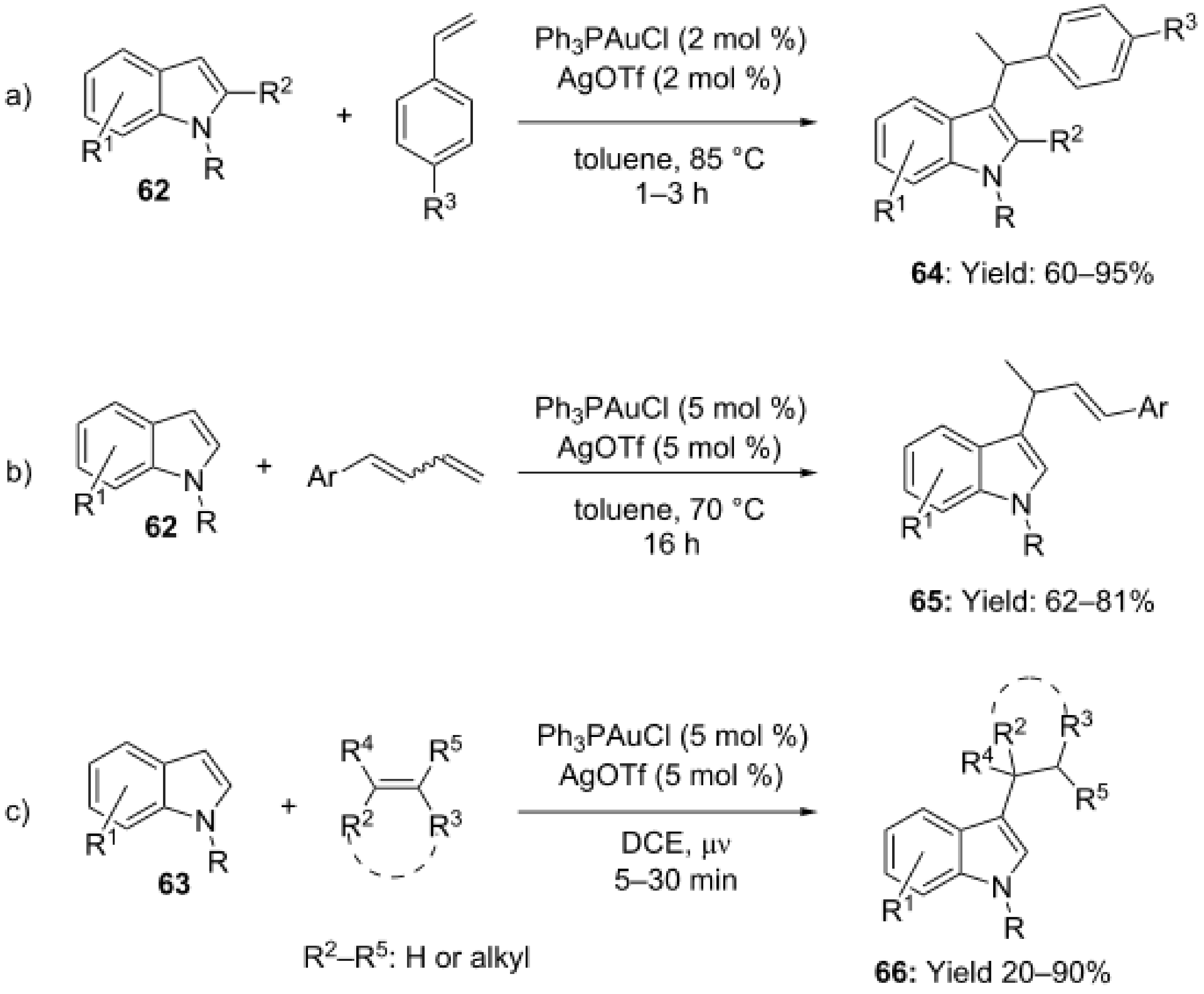


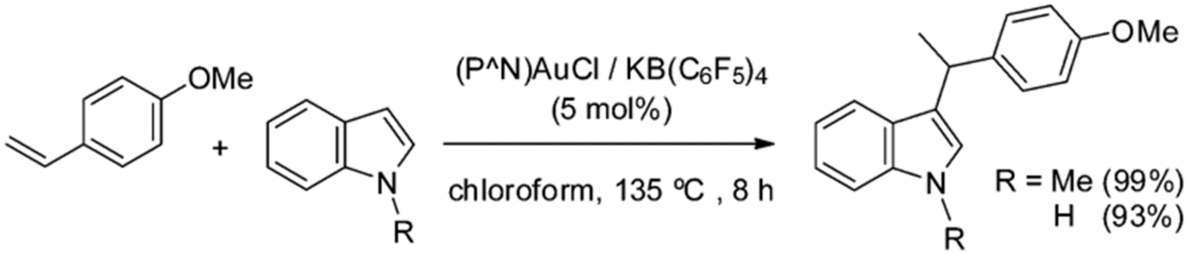
D. Wang, B. Dong, Y. Wang, J. Qian, J. Zhu, Y. Zhao and Z. Shi, *Nat. Commun.*, 2019, **10**, 3539.



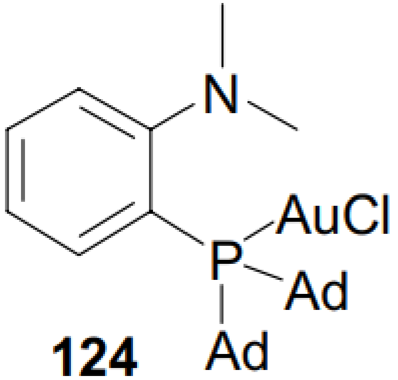
Y.-G. Chen, B. Shuai, X.-T. Xu, Y.-Q. Li, Q.-L. Yang, H. Qiu, K. Zhang, P. Fang and T.-S. Mei, *J. Am. Chem. Soc.*, 2019, **141**, 3395–3399.

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



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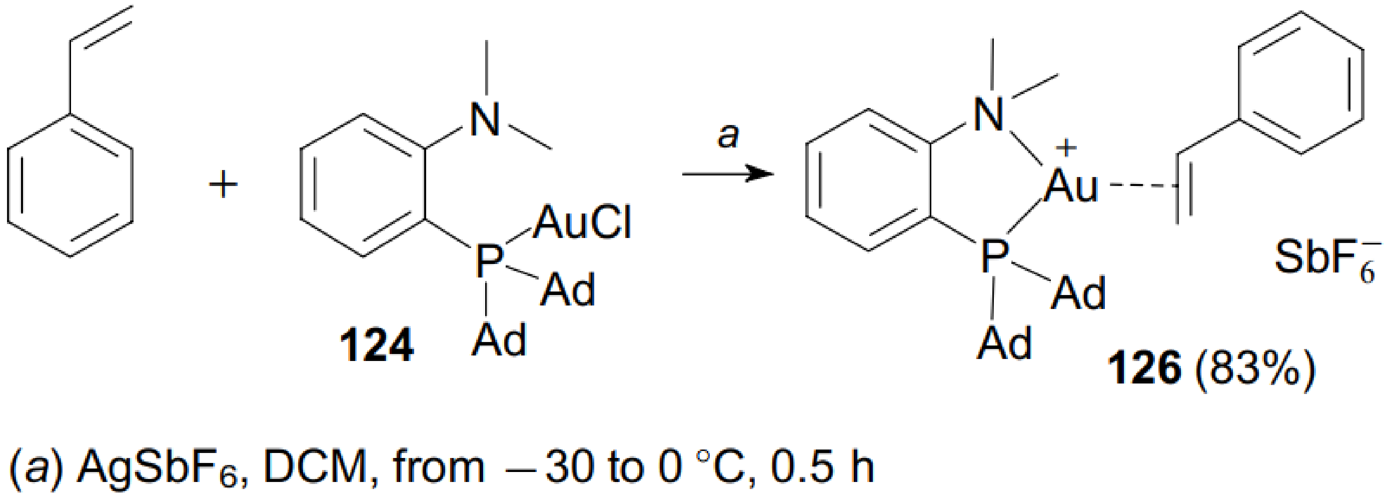
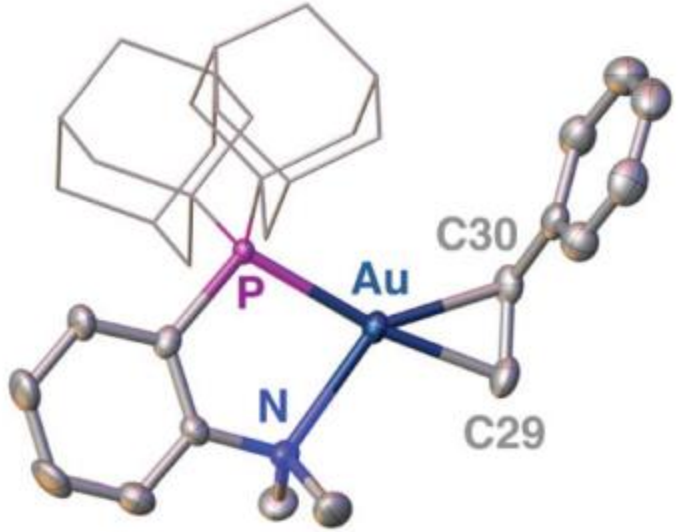
M.-Z. Wang, M.-K. Wong and C.-M. Che, *Chem. – A Eur. J.*, 2008, **14**, 8353–8364.
M. Navarro, A. Toledo, M. Joost, A. Amgoune, S. Mallet-Ladeira and D. Bourissou, *Chem. Commun.*, 2019, **55**, 7974–7977.

Isolation of intermediate Au(I) alkene complex

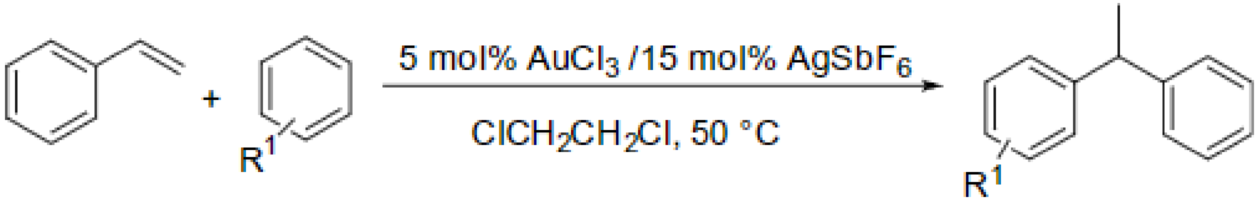


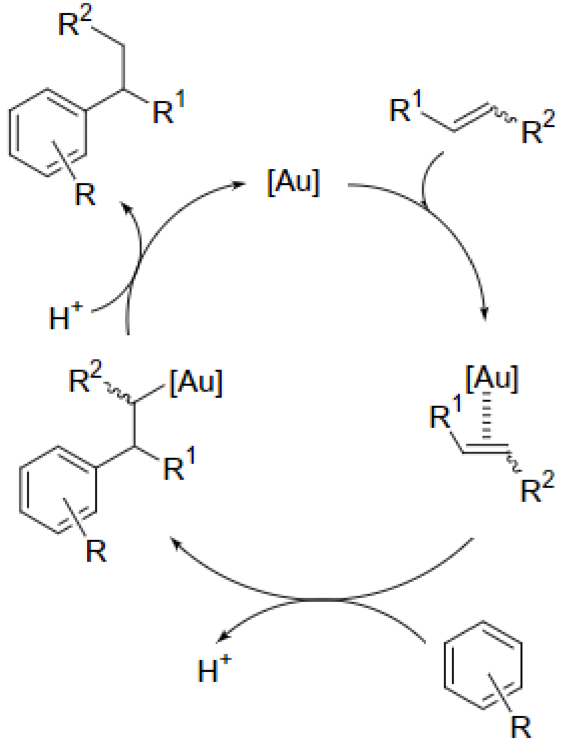
- Recently isolated (Bourissou 2019)
- Interesting geometry and bonding (between T and Y)
- Increased metallacyclopropane character relative to monodentate species
- Key catalytic intermediate



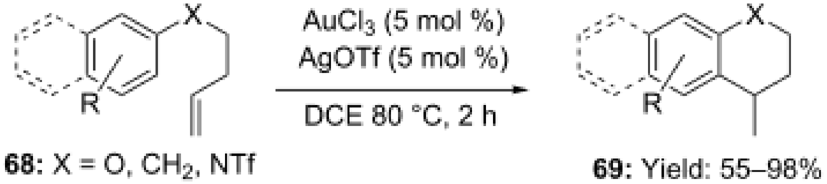
M. Navarro, A. Toledo, M. Joost, A. Amgoune, S. Mallet-Ladeira and D. Bourissou, *Chem. Commun.*, 2019, **55**, 7974–7977.

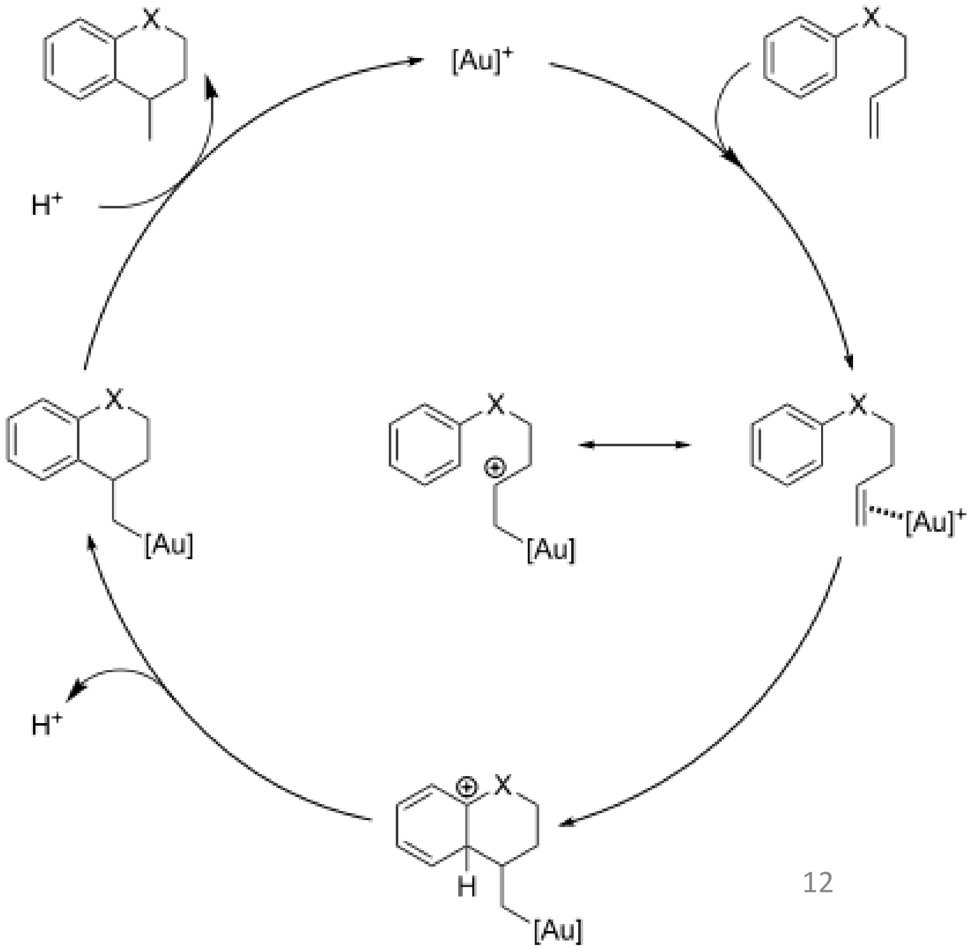
Au(III) catalysed hydroarylation of alkenes with benzene derivatives





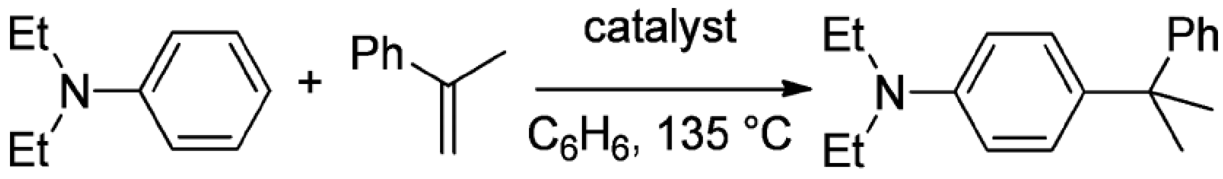
- Au(III) with silver, conceptually similar to classic Lewis acid
- Thiophene also utilised

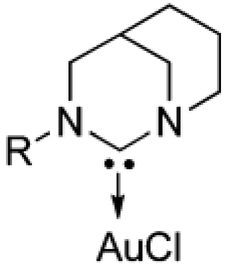




Y.-P. Xiao, X.-Y. Liu and C.-M. Che, *J. Organomet. Chem.*, 2009, **694**, 494–501.
Jean, M.; van de Weghe, P. *Tetrahedron Lett.* **2011,** *52,* 3509–3513.

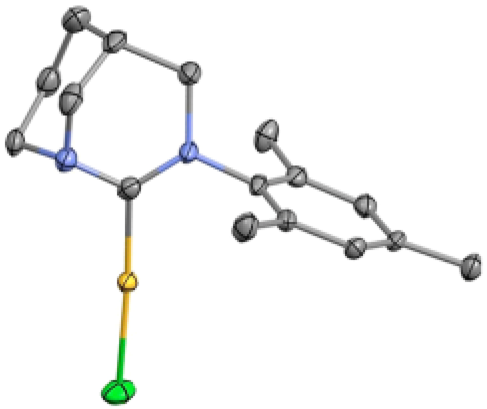
Au(I) catalysed hydroarylation with dialkylanilines



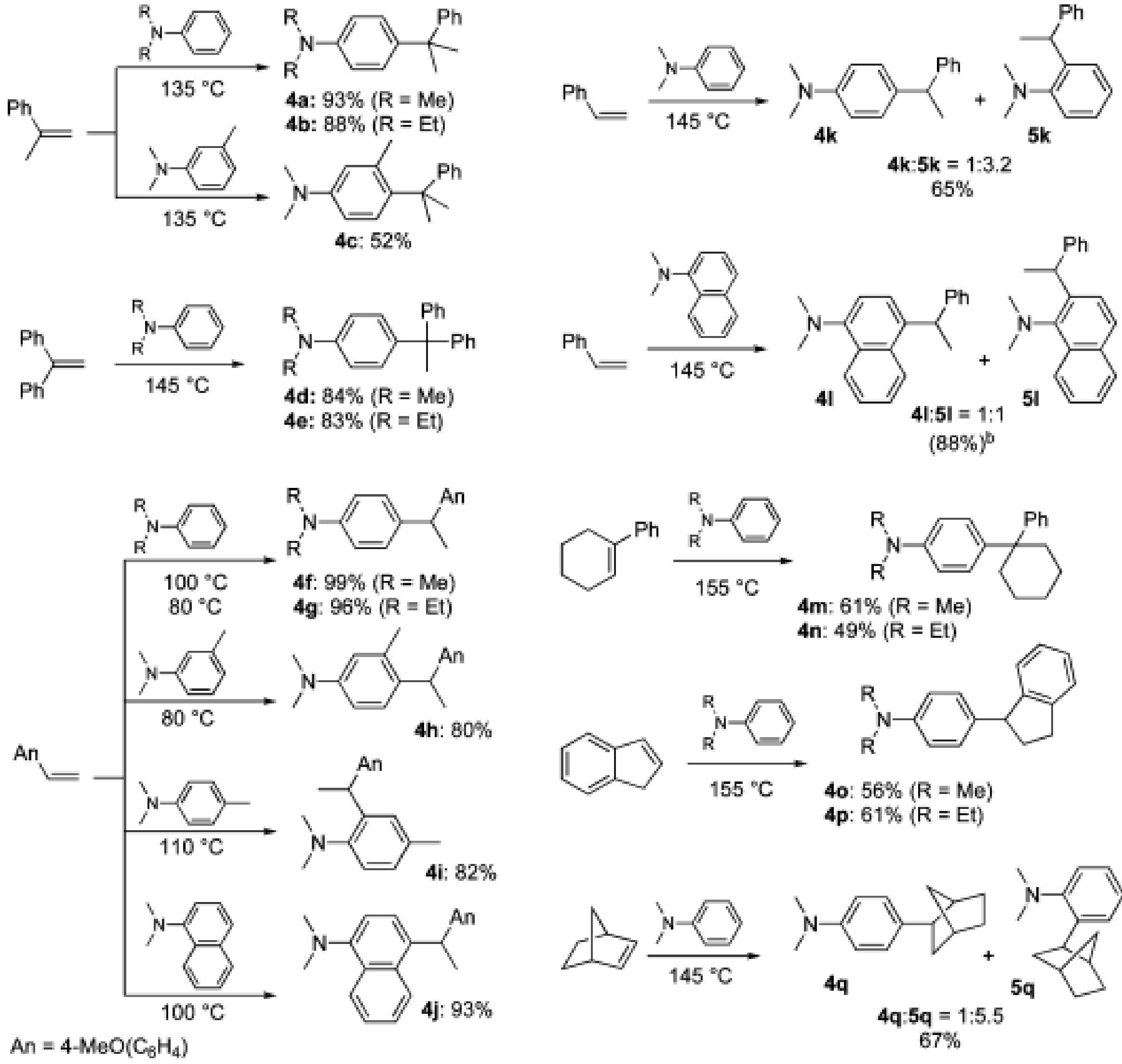


Suggest a synthesis of this NHC-Au motif

<u>*Precatalyst (R=Mes)*</u>

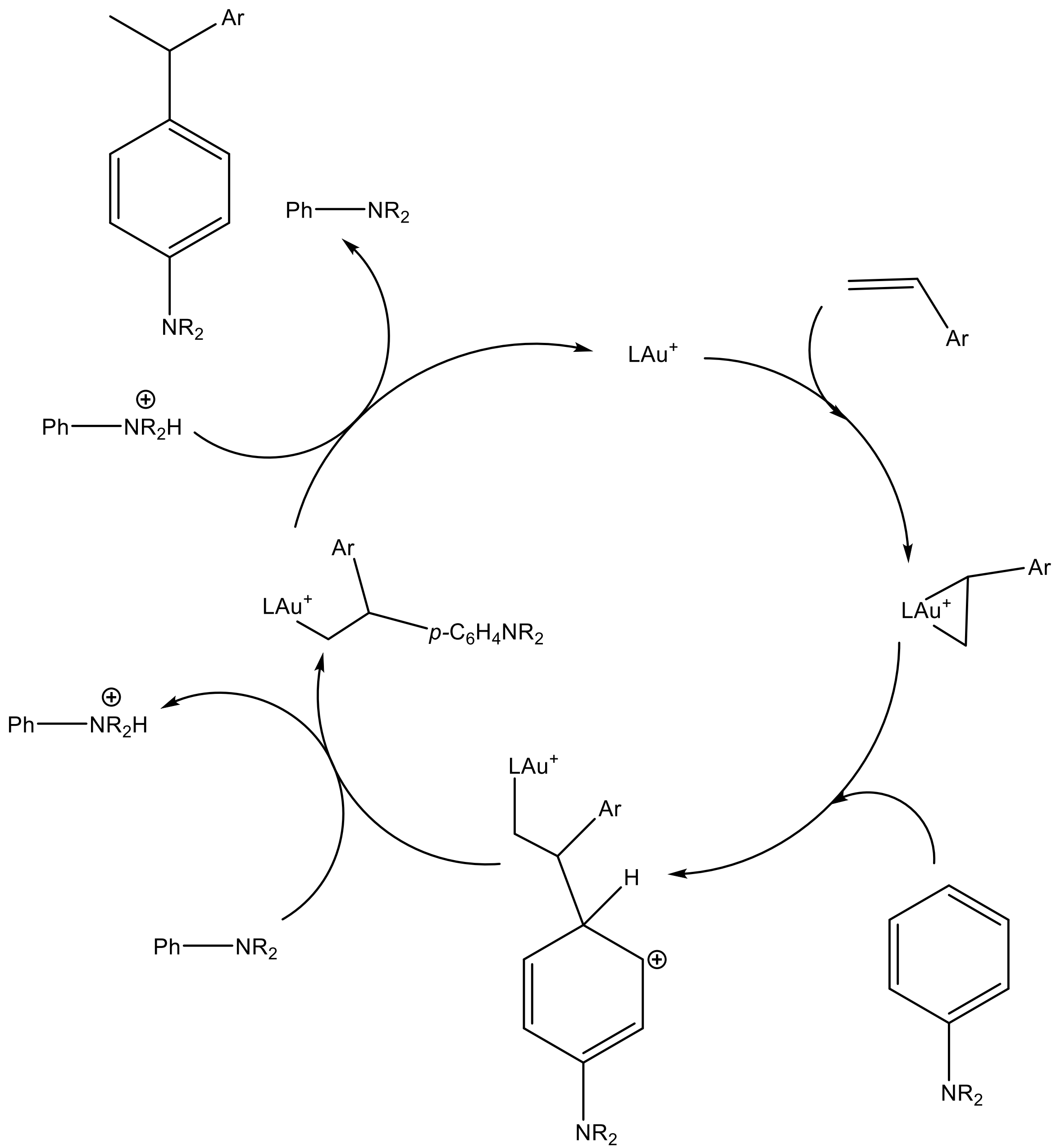


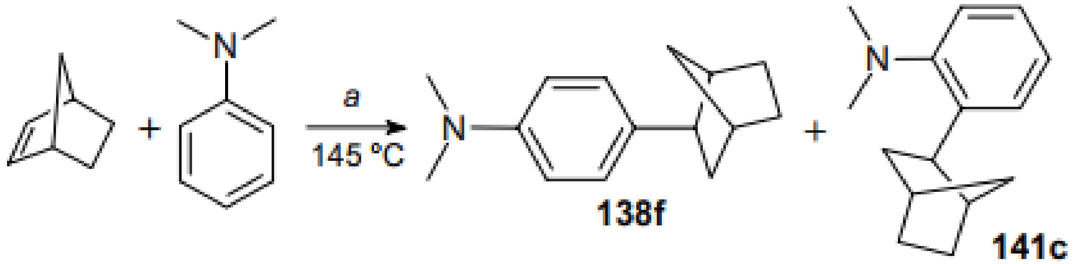
- Hydroarylation catalysts not usually compatible with dialkylanilines and other Lewis basic substrates
- *para*-selective
- Markovnikov and anti markovnikov pattern observed, depending on alkene substrate



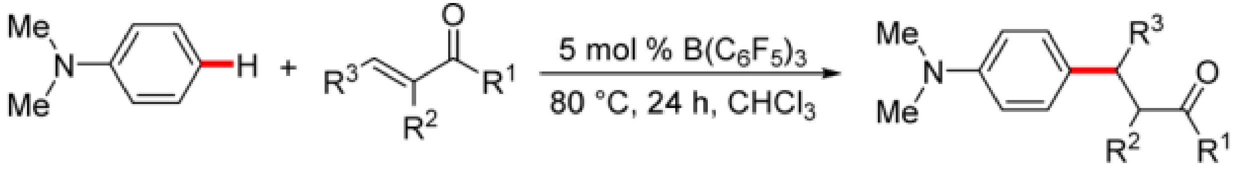
X. Hu, D. Martin, M. Melaimi and G. Bertrand, *J. Am. Chem. Soc.*, 2014, **136**, 13594–13597.

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



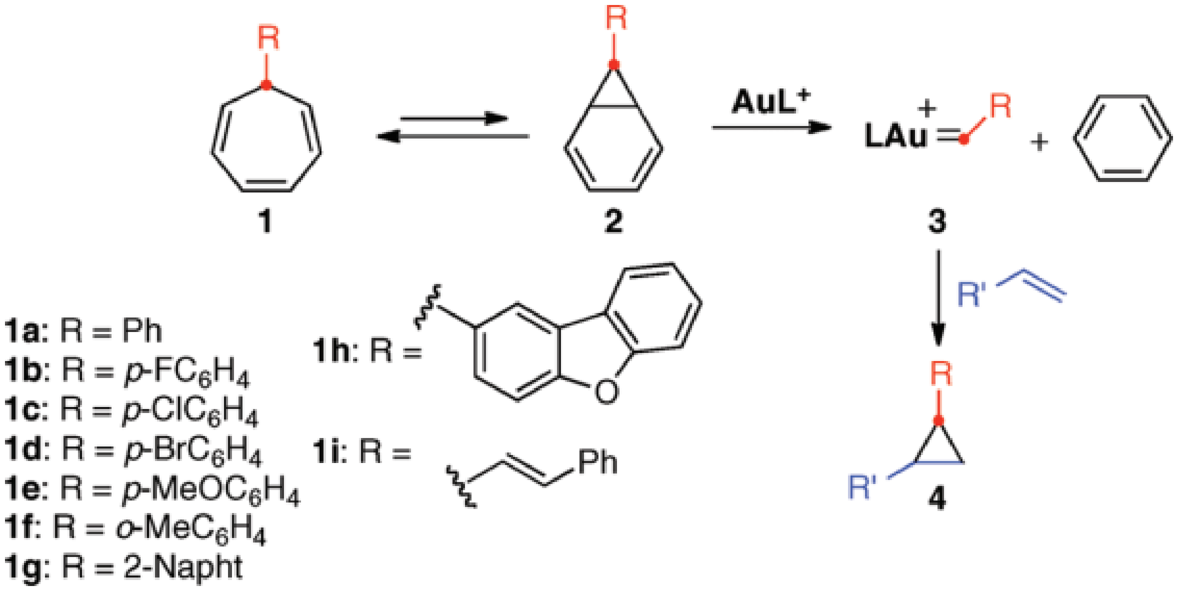


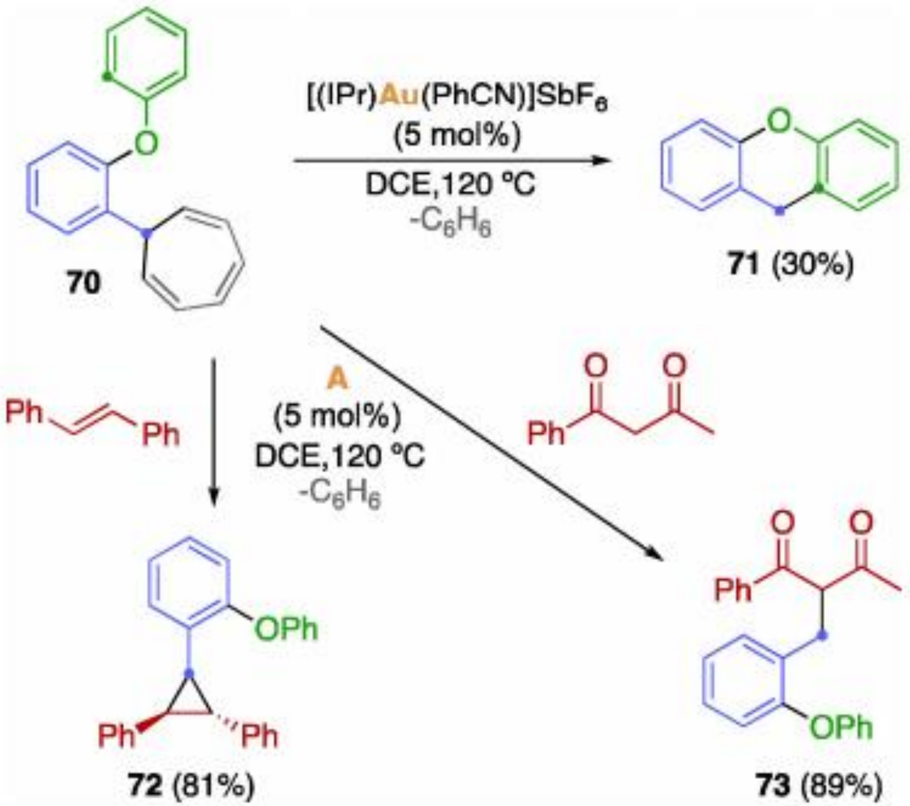
- *Para*-selective in majority of cases, occasional *ortho*-competition
- Borane-catalysed variant, only active with Michael acceptors. Same anti-markovnikov product



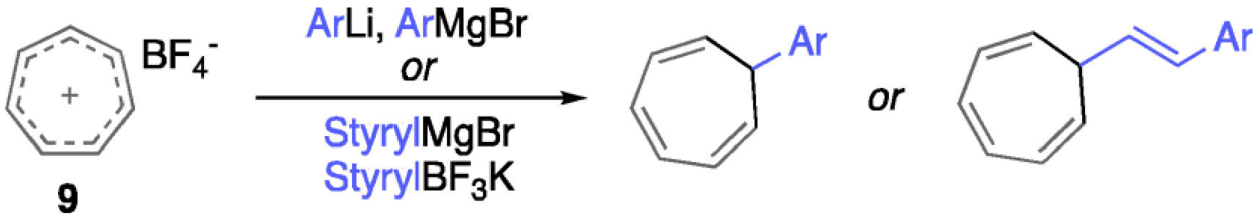
H. Wu, T. Zhao and X. Hu, *Sci. Rep.*, 2018, **8**, 11449.
W. Li and T. Werner, *Org. Lett.*, 2017, **19**, 2568–2571.

Cyclopropanation: Au carbenes from cycloheptatrienes



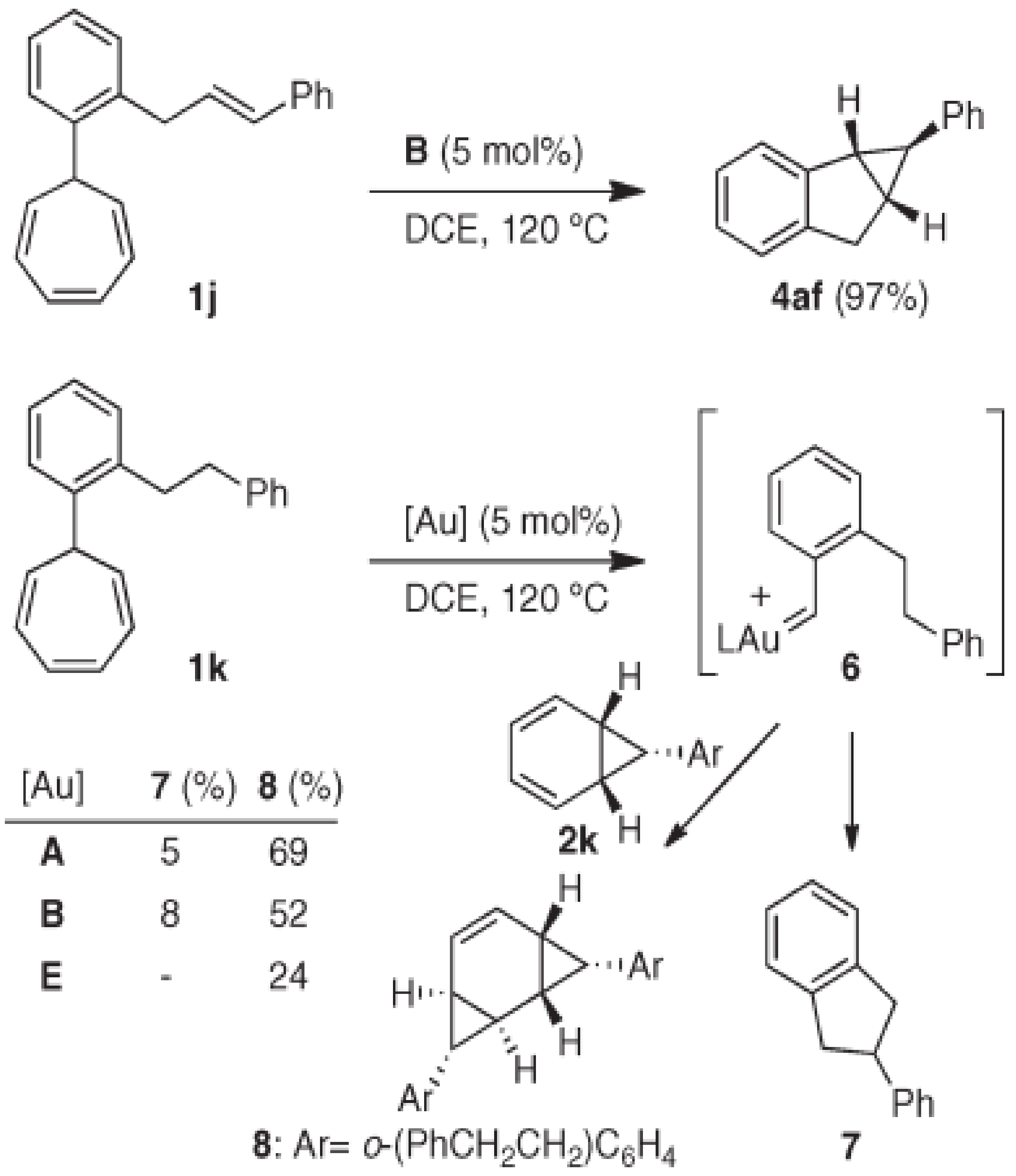


- Trisubstituted arycyclopropanes easily prepared via Au(I) catalysed Retro-Buchner reaction
- Utilising cycloheptatrienes as carbene/carbenoid sources
- A methodology well developed work with Au(I) systems
- Starting aryl or styryl cycloheptatrienes are easily prepared from tropylium
- Potentially wide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



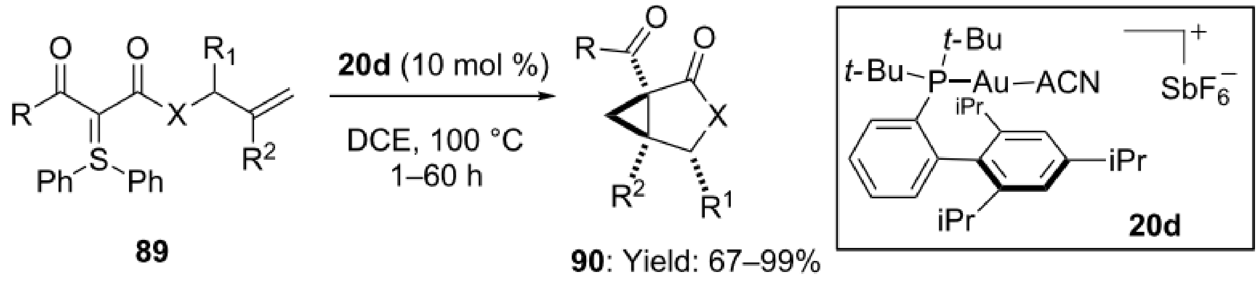
C. R. Solorio-Alvarado, Y. Wang and A. M. Echavarren, *J. Am. Chem. Soc.*, 2011, **133**, 11952–1195M. Mato, C. García-Morales and A. M. Echavarren, *ChemCatChem*, 2019, **11**, 53–72.

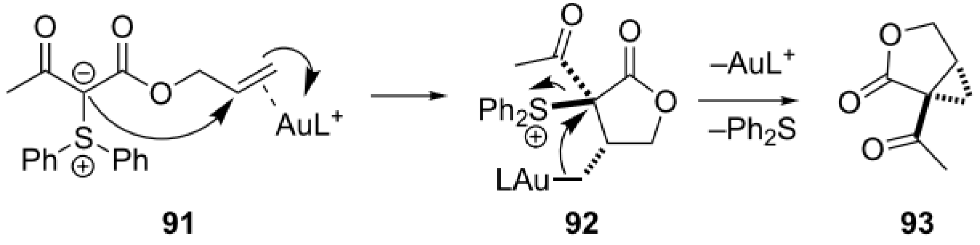
Cyclopropanation cont.



[Au]	7 (%)	8 (%)
A	5	69
B	8	52
E	-	24

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





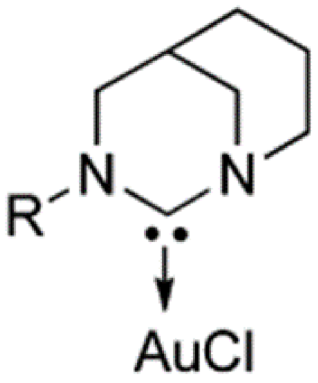
M. Mato, C. García-Morales and A. M. Echavarren, *ChemCatChem*, 2019, **11**, 53–72.
. R. Solorio-Alvarado, Y. Wang and A. M. Echavarren, *J. Am. Chem. Soc.*, 2011, **133**, 11952–11955
1X. Huang, S. Klimczyk, L. F. Veiros and N. Maulide, *Chem. Sci.*, 2013, **4**, 1105–1110..

Summary

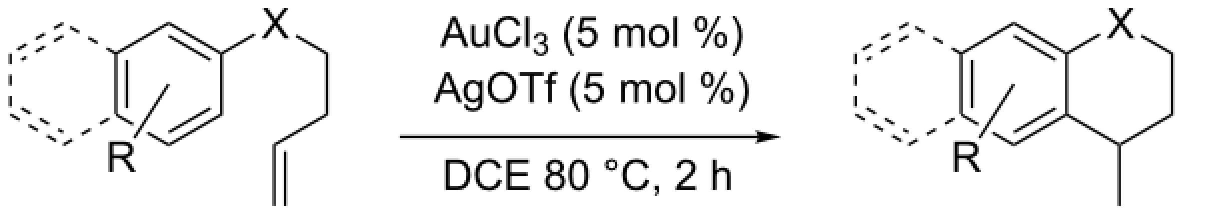
- Gold mediated C-C bond forming reactions of unactivated olefins: some key reactions of interest (carboheterofunctionalisation, hydroarylation, Retro-Buchner reaction of cycloheptatrienes in formation of Au carbenes

- 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.

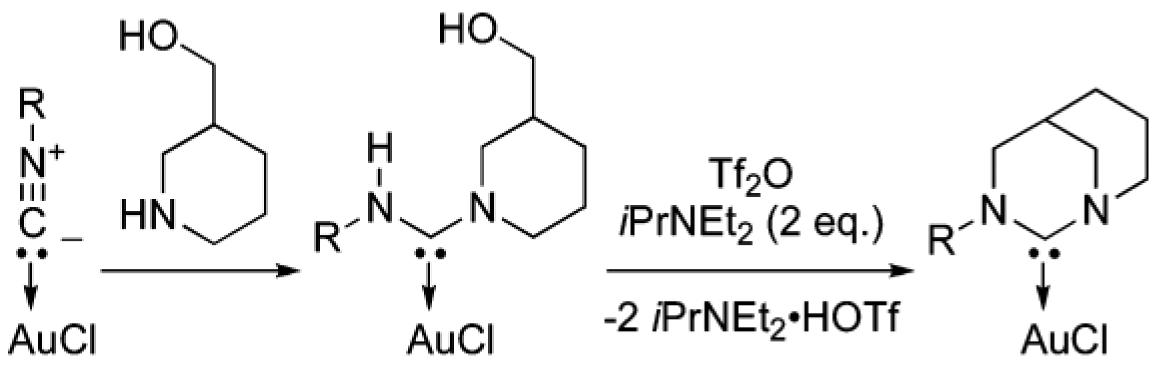


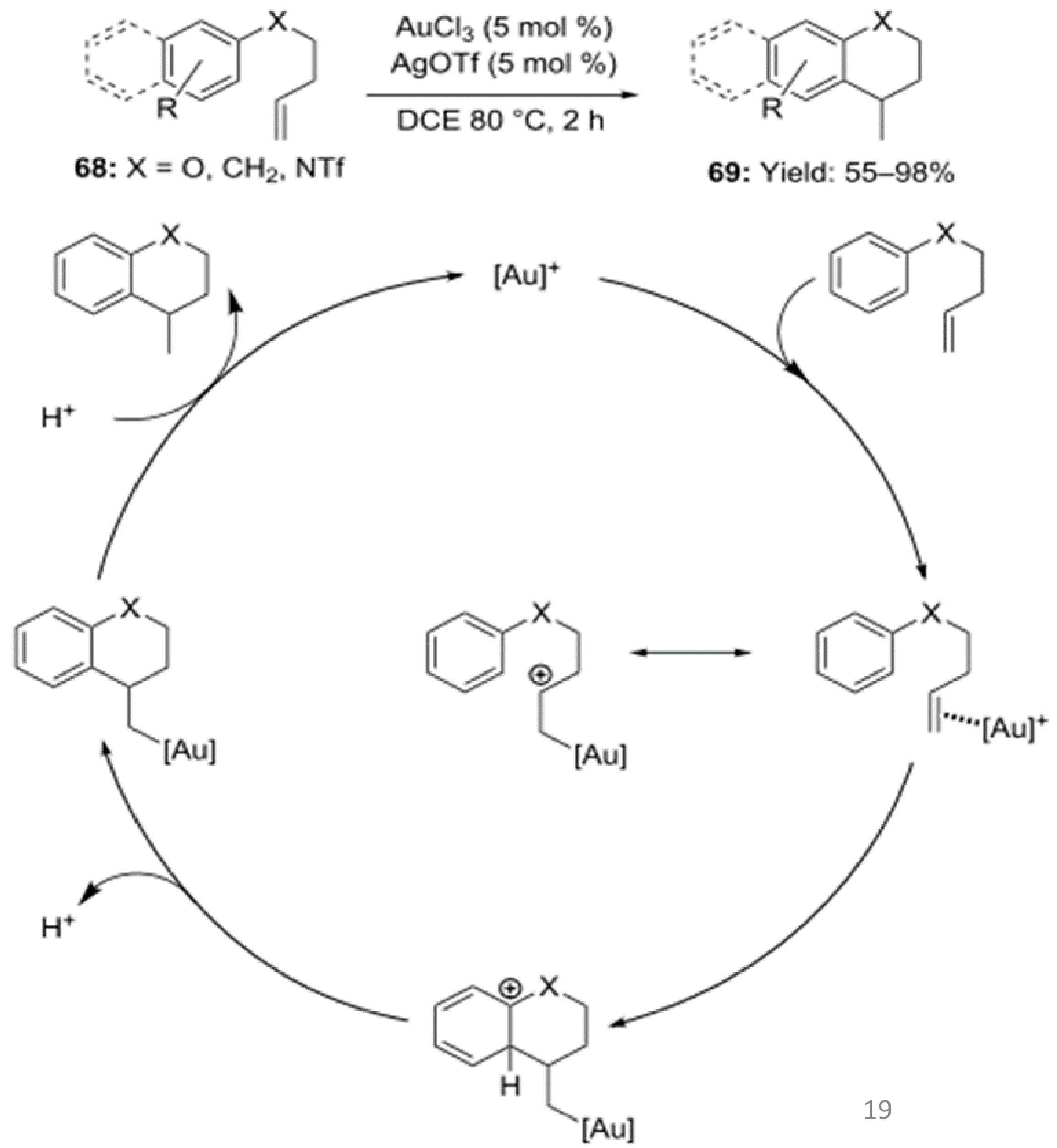
68: X = O, CH_2, NTf

69: Yield: 55–98%

Suggest a plausible catalytic cycle for this transformation

Answers


R
HO
HN
H
N
R
AuCl
Tf2O
iPrNEt2 (2 eq.)
-2 iPrNEt2•HOTf


X
R
AuCl3 (5 mol %)
AgOTf (5 mol %)
DCE 80 °C, 2 h
68: X = O, CH2, NTf
69: Yield: 55–98%
[Au]+
H+
[Au]
H