Frontiers in Chemical Synthesis I
Sustainable Chemistry

Seminar Program
May 15, BCH 3303

	Speaker	Title
May 15, 2023, BCH 3303		
Session I: (Chair: Christine Marty)		
10h15-11h15	Emma Robert	*Triplet Energy Transfer for enantioselective transformations*
11h15-12h15	Tak Hin Wong	*Organocatalysis in enantioselective radical reactions*
May 15, 2023, BCH 3303		
Session I: (Chair: Tak Hin Wong)		
13h15-14h15	Cedric Fung	*Palladium-catalyzed cascade reactions*
14h15-15h15	Christine Marty	*Transformation of biologically active compounds via mechanochemistry (TBS)*
15h15-16h15	Vladyslav Smyrnov	*Photocatalytic Late-stage C-H Functionalization*

Palladium-catalyzed cascade reactions in total synthesis

Cedric Fung

15-05-2023

*Laboratory of Synthesis and Natural Products (**LSPN**)*

*Ecole Polytechnique Fédérale de Lausanne (**EPFL**)*

Outline

- 1. Introduction
- 2. Cascades in total synthesis involving palladium
- 3. Summary
- 4. Questions

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- **1. Introduction**
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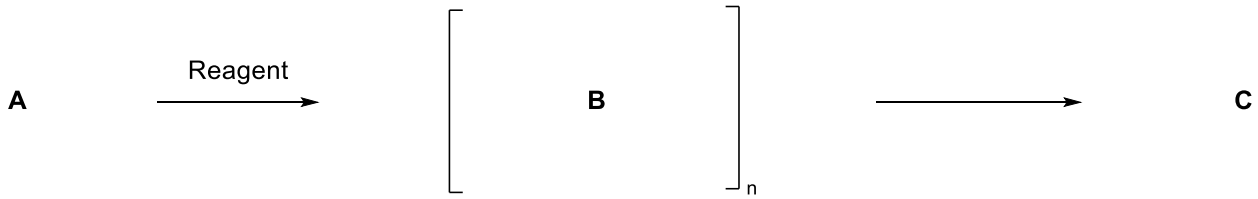
Cascade reaction

- “we understand 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”

Tietze



- Time
- Money
- Atom economy
- Green
- Synthetic beauty

- Substrate design
- Reaction control

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

Palladium overview, classification

- Versatility
- Wide Scope
- Functional group tolerance
- Catalytic amount

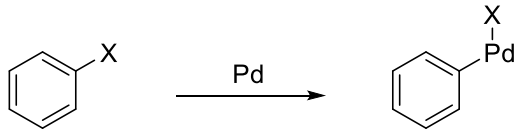
- Toxicity
- Price

Initiation	Propagation	Termination
- Oxidative addition - Nucleopalladation	- Carbopalladation - Benzyne insertion - CO insertion - Isocyanide insertion - Carbene insertion	- Suzuki-Miyaura - Stille - Sonogashira - Mizoroki-Heck - Buchwald-Hartwig - C-H activation - Ion capture - β-H elimination

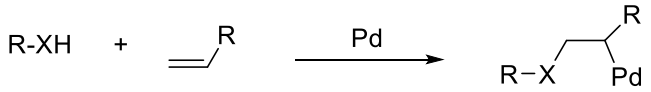
H. A. Döndas, M. de Gracia Retamosa, J. M. Sansano, *Organometallics* **2019**, *38*, 1828-1867.
J. Biemolt, E. Ruijter, *Adv. Synth. Catal.* **2018**, *360*, 3821-3871.

Pd initiation and propagation

Initiation

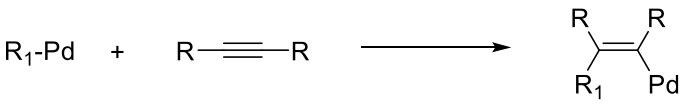


Oxidative addition

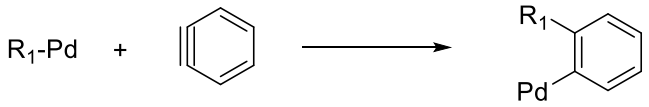


Nucleopalladation

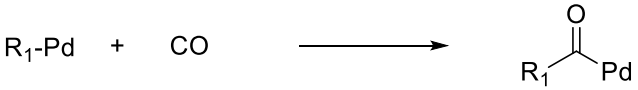
Propagation



Carbopalladation

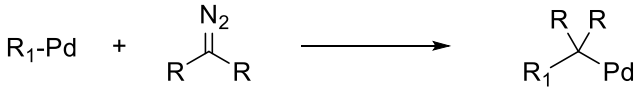


Benzyne insertion



CO insertion

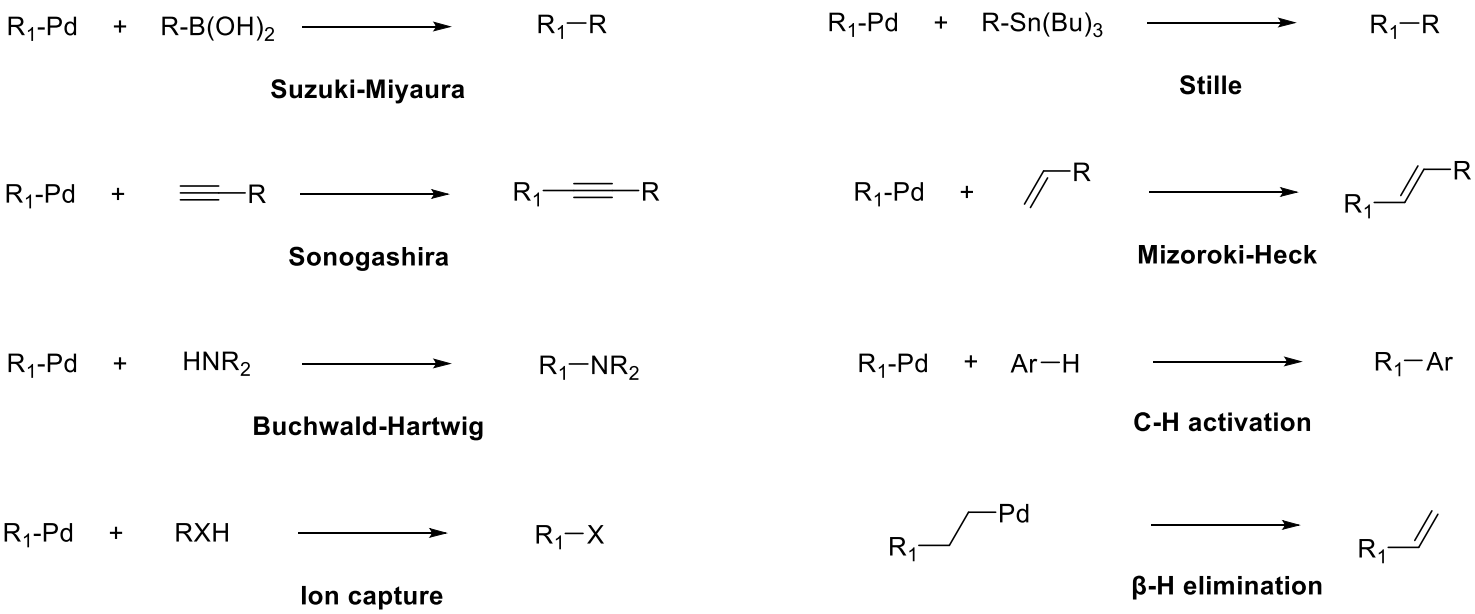
Isocyanide insertion



Carbene insertion

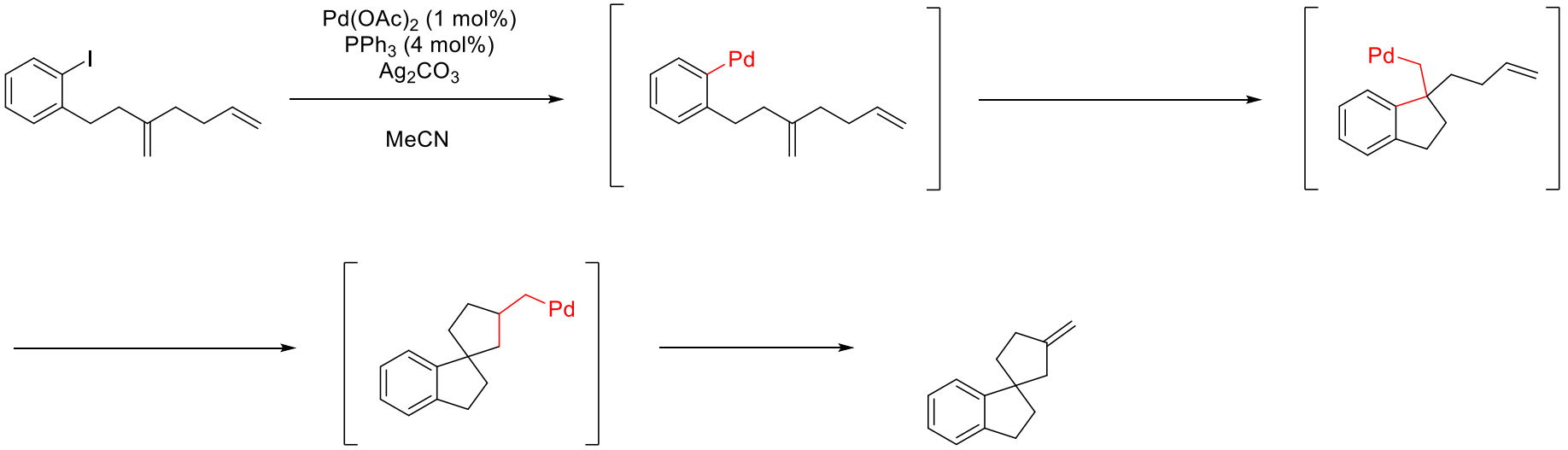
Pd termination

Termination



First examples of Pd-catalyzed cascade reaction

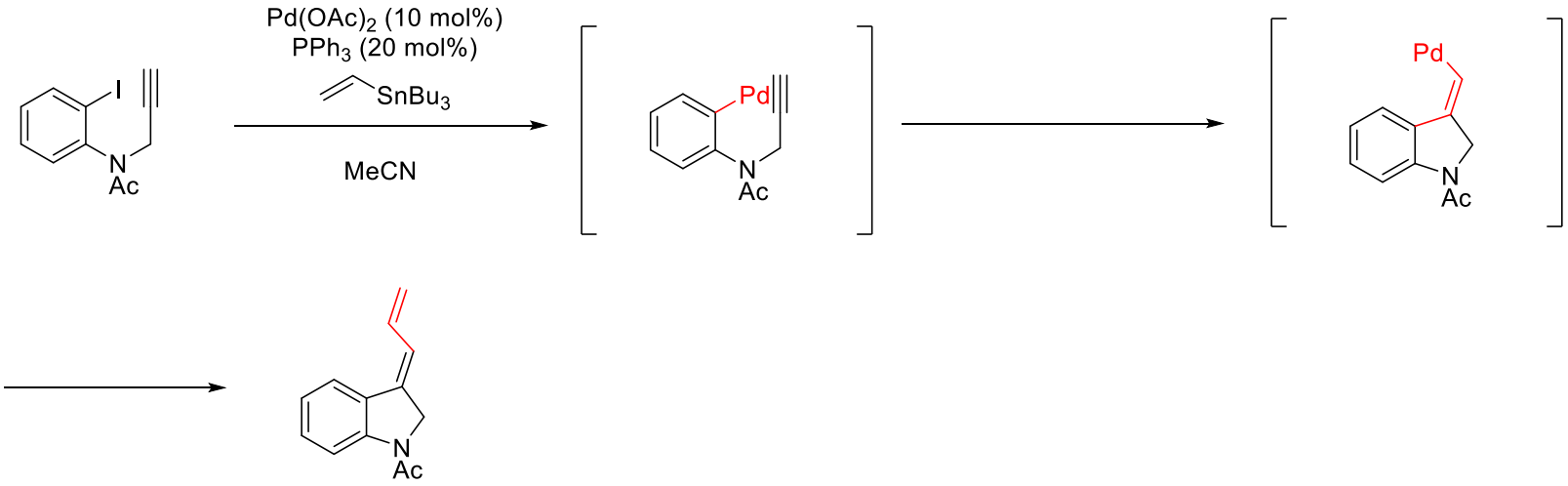
Overman, 1988



M. M. Abelman, L. E. Overman, *J. Am. Chem. Soc.* **1988**, *110*, 2328-2329.

First examples of Pd-catalyzed cascade reaction

Grigg, 1988



B. Burns, P. Ratananukul, V. Sridharan, P. Stevenson, S. Sukirthalingam, T. Worakun, R. Grigg, *Tetrahedron Lett.* **1988**, *29*, 5565-5568.

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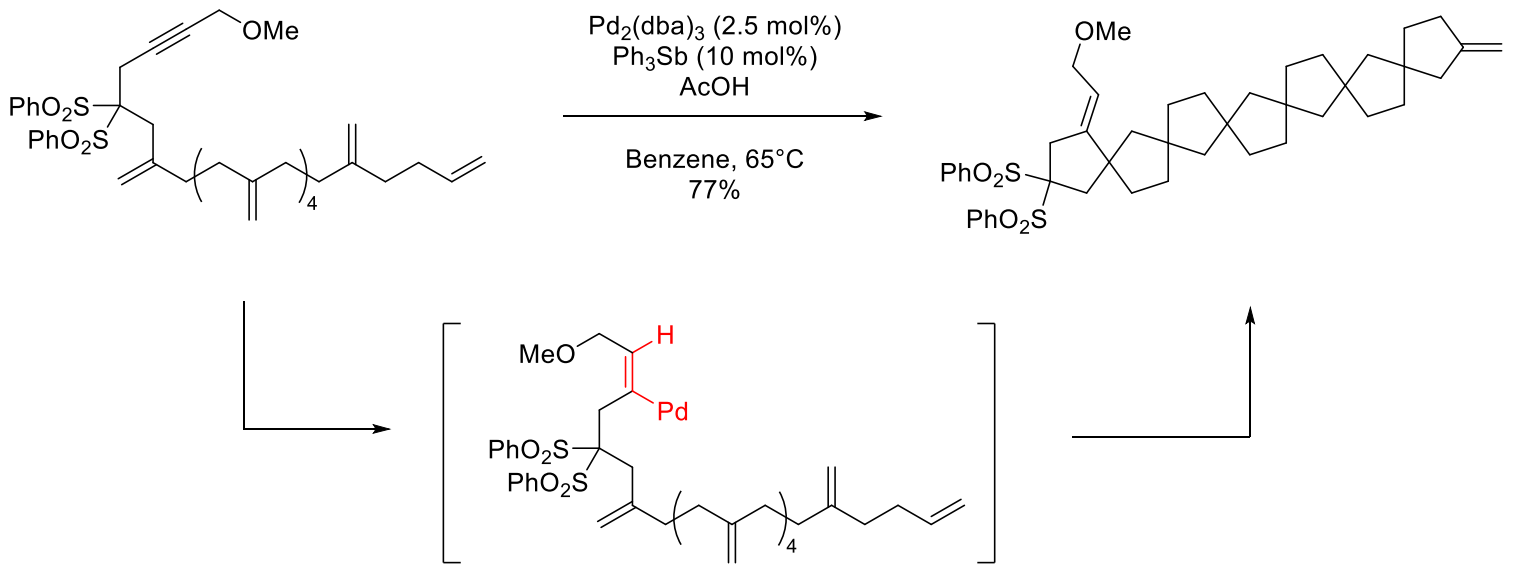
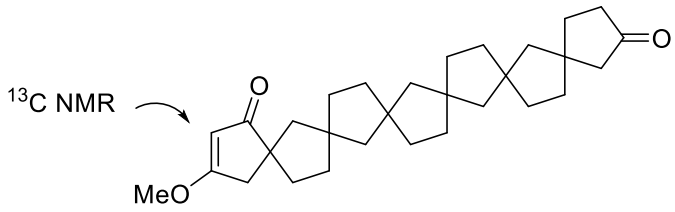
Trost's zipper

Trost, 1993



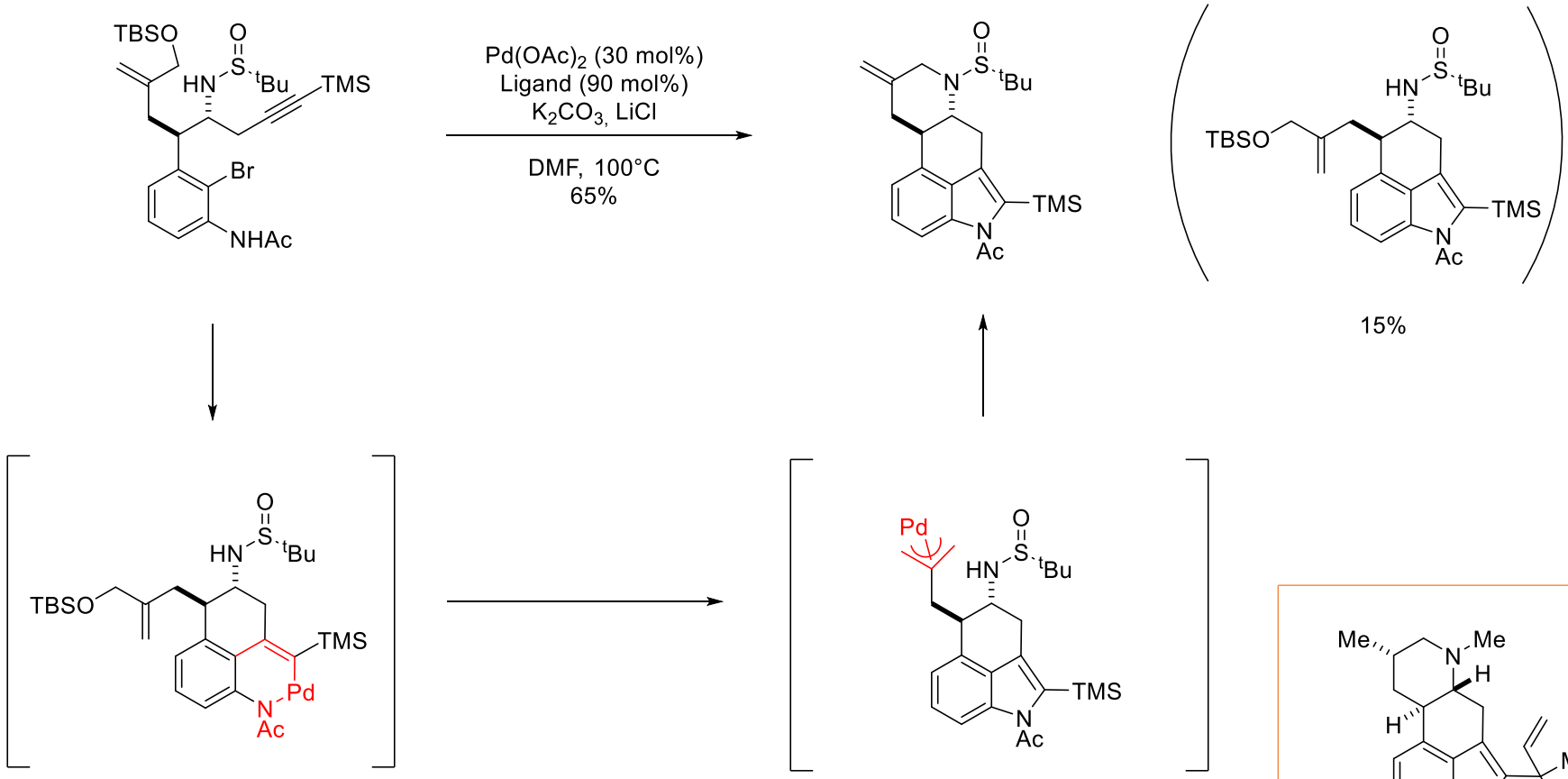
- "Palladium zipper"
- No oxidative addition
- After derivatization, 3:1 isomer (unconfirmed)



Y. Shi, B. M. Trost, *J. Am. Chem. Soc.* **1993**, *115*, 9421-9438.

Larock heteroannulation: Fumiglacavine G

Jia, 2017



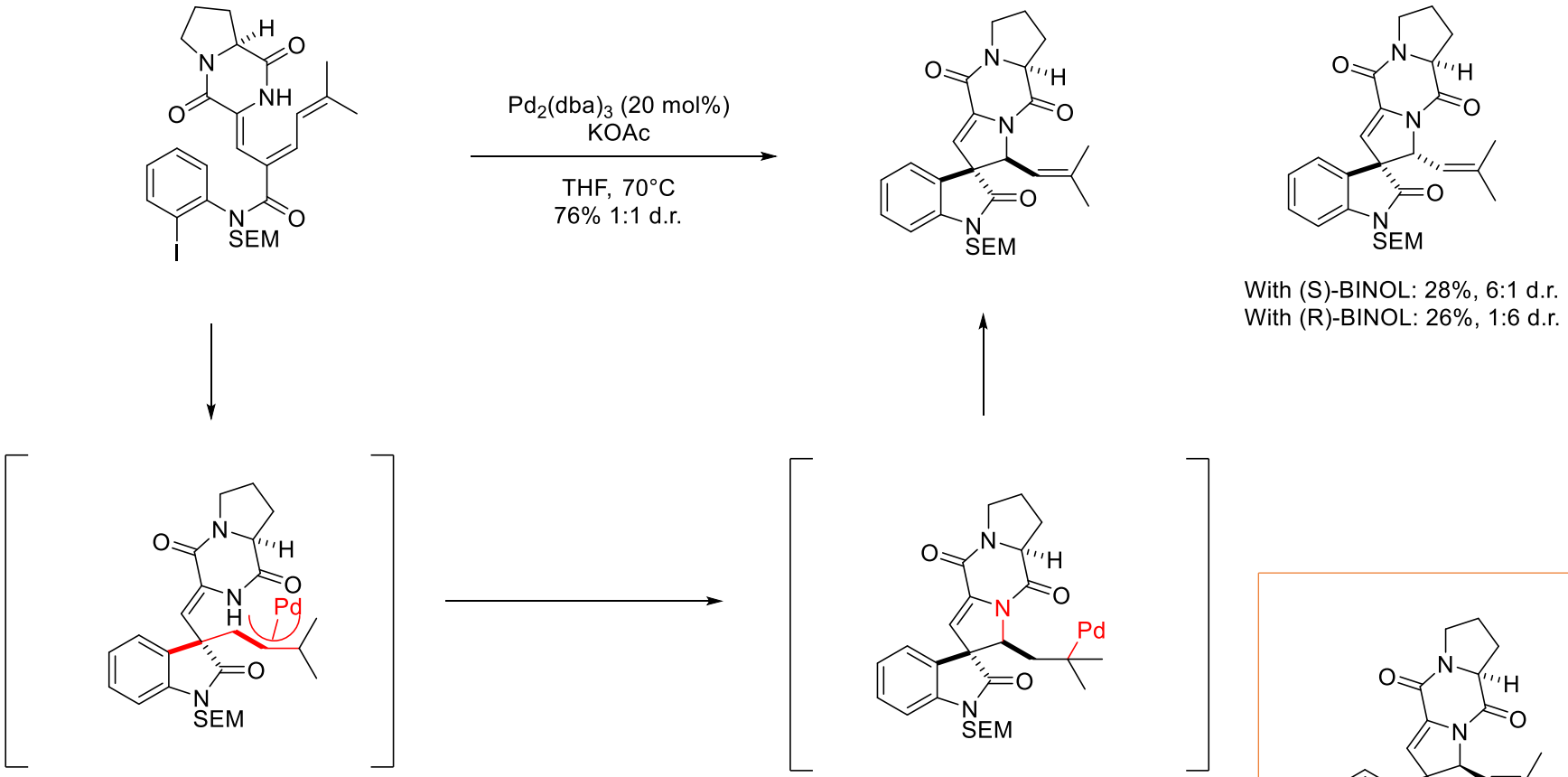
- Larock indole synthesis
- Concomitant formation of π-allyl complex

Fumiglacavine G

H. Liu, X. Zhang, D. Shan, M. Pitchakuntla, Y. Ma, Y. Jia, *Org. Lett.* **2017**, *19*, 3323-3326.

Larock heteroannulation: Spirotryprostatin B

Overman, 2000



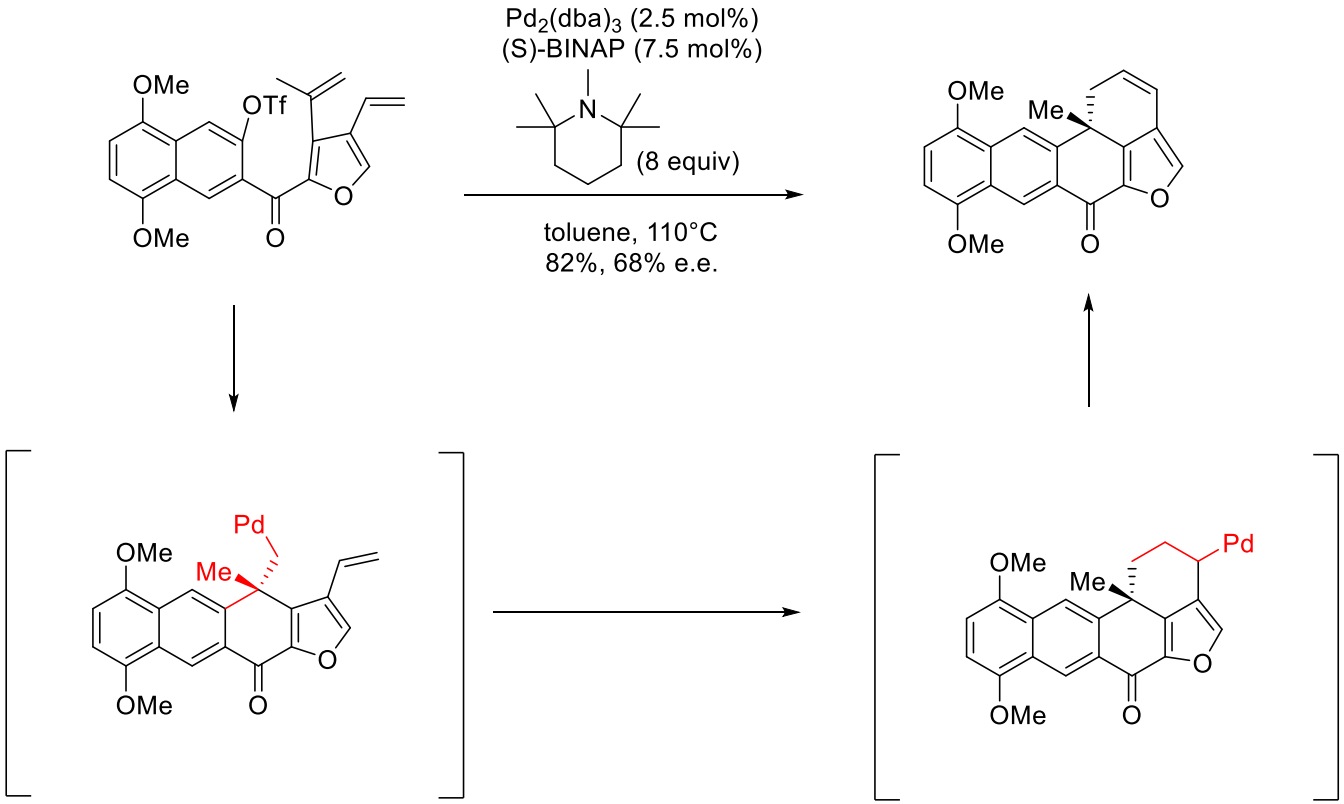
- Diastereoselection
- Subsequent formation of π-allyl complex

Spirotryprostatin B

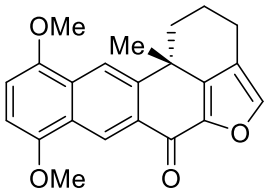
M. D. Rosen, L. E. Overman, *Angew. Chem. Int. Ed.* **2000**, *39*, 4596-4599.

Enantioselectivity: Xestoquinone

Keay, 1996



- Enantioselective
- 6-endo vs 5-exo cyclization

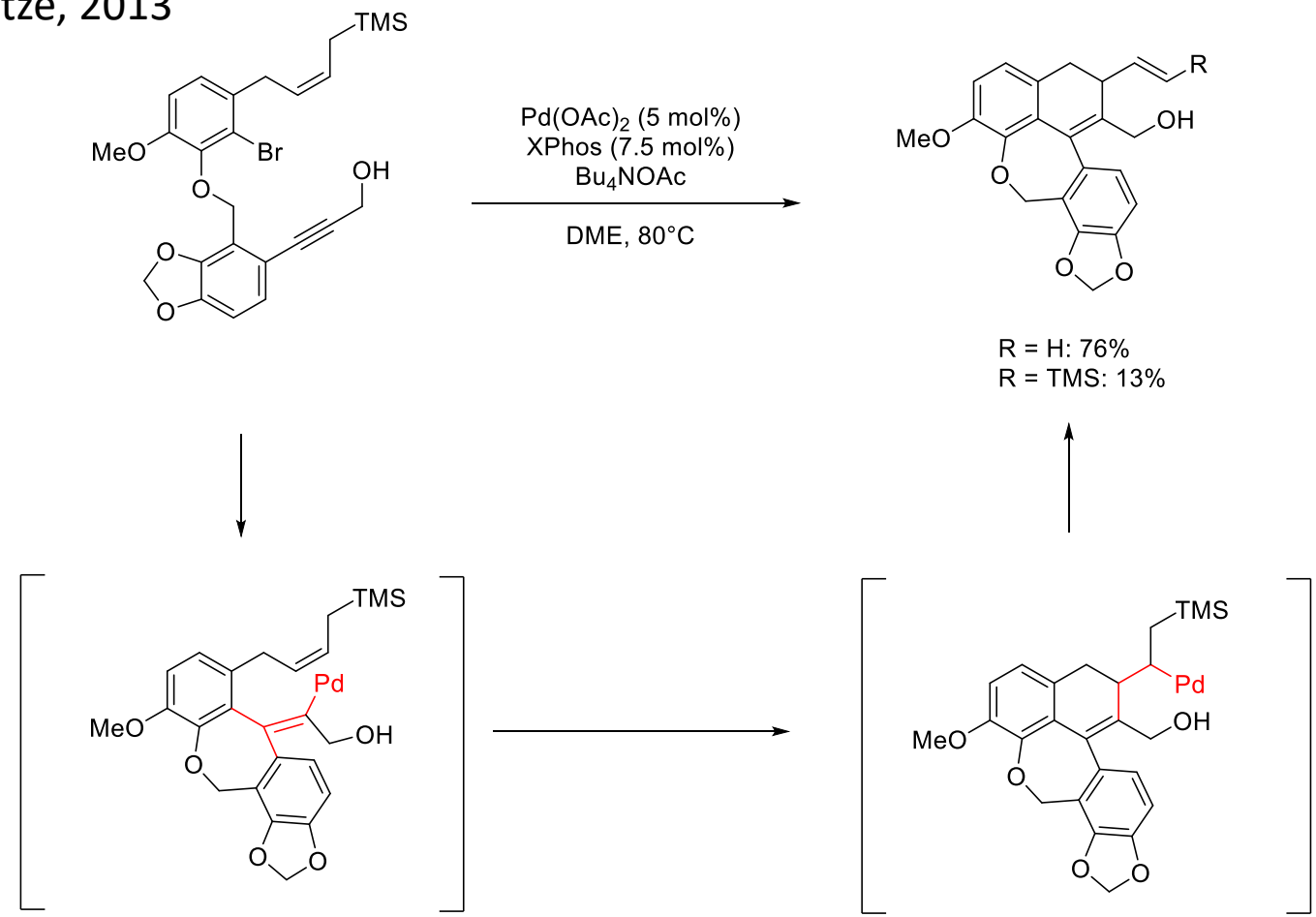


Xestoquinone

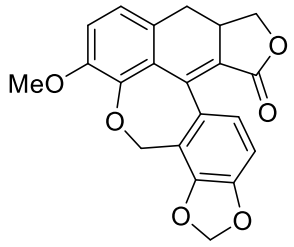
S. P. Maddaford, N. G. Andersen, W. A. Cristofoli, B. A. Keay, *J. Am. Chem. Soc.* **1996**, *118*, 10766-10773.
K. C. Nicolaou, D. J. Edmonds, P. G. Bulger, *Angew. Chem. Int. Ed.* **2006**, *45*, 7134-7186.

Cascade reaction to a natural lignan: Linoxepin

Tietze, 2013



- 7-exo carbopalladation
- TMS promoted reductive elimination

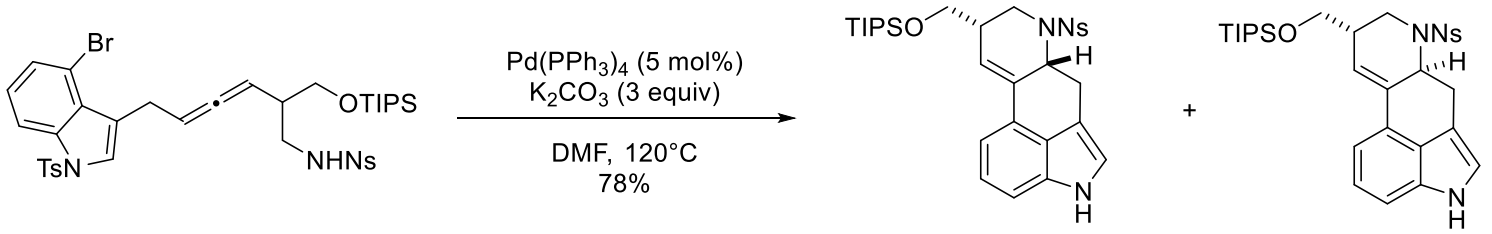


Linoxepin

L. F. Tietze, S.-C. Duefert, J. Clerc, M. Bischoff, C. Maass, D. Stalke, *Angew. Chem. Int. Ed.* **2013**, *52*, 3191-3194.

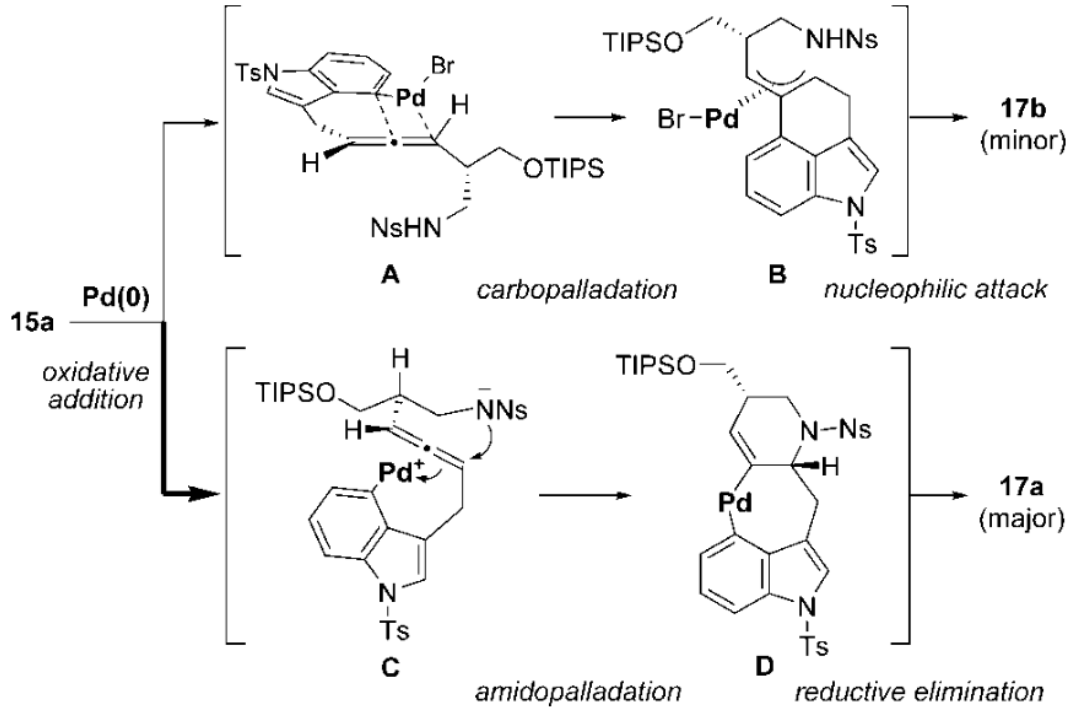
Allenes: Lysergic acid

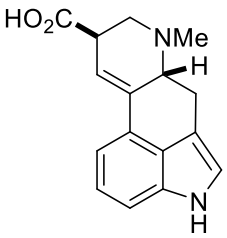
Fujii, Ohno, 2008



(83:17)

Scheme 4. Proposed Mechanism for Domino Cyclization



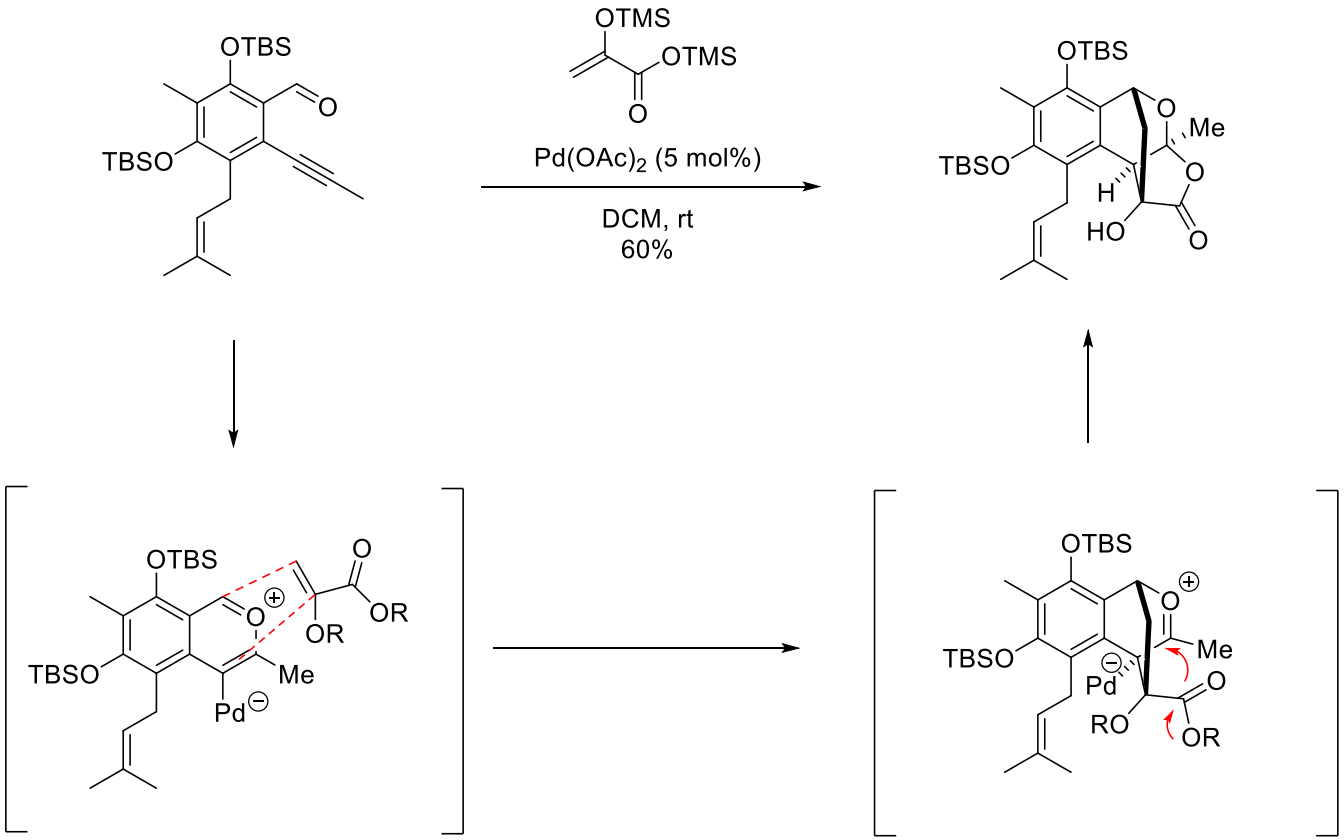


Lysergic acid

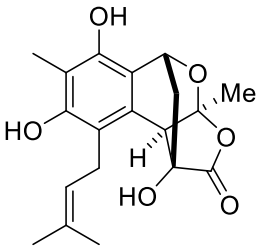
S. Inuki, S. Oishi, N. Fujii, H. Ohno, *Org. Lett.* **2008**, *10*, 5239-5242.

Oxopalladation: Chaetopenol C

Li, Zhai, 2017



- Oxopalladation
- Hetero [4+2] + lactonization cascade

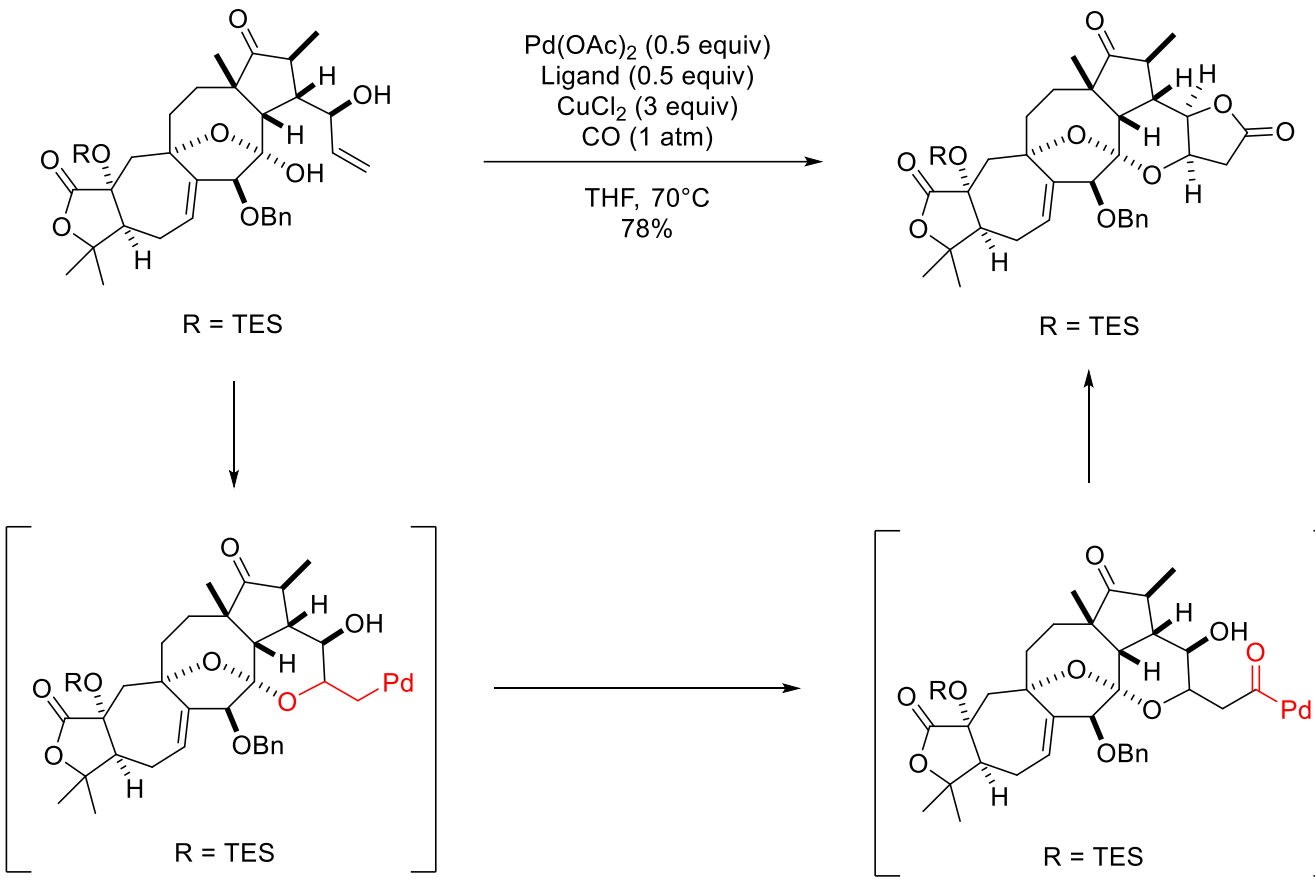


Chaetophenol C

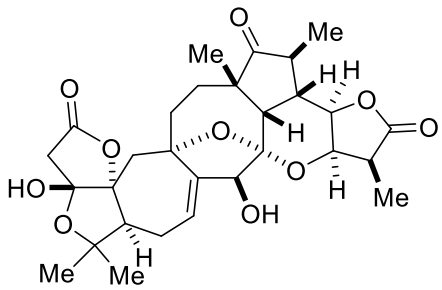
Y. Li, Q. Zhang, H. Wang, B. Cheng, H. Zhai, *Org. Lett.* **2017**, *19*, 4387-4390.

Semmelhack: Schindilactone A

Tang, Chen, Yang, 2011



- Semmelhack reaction

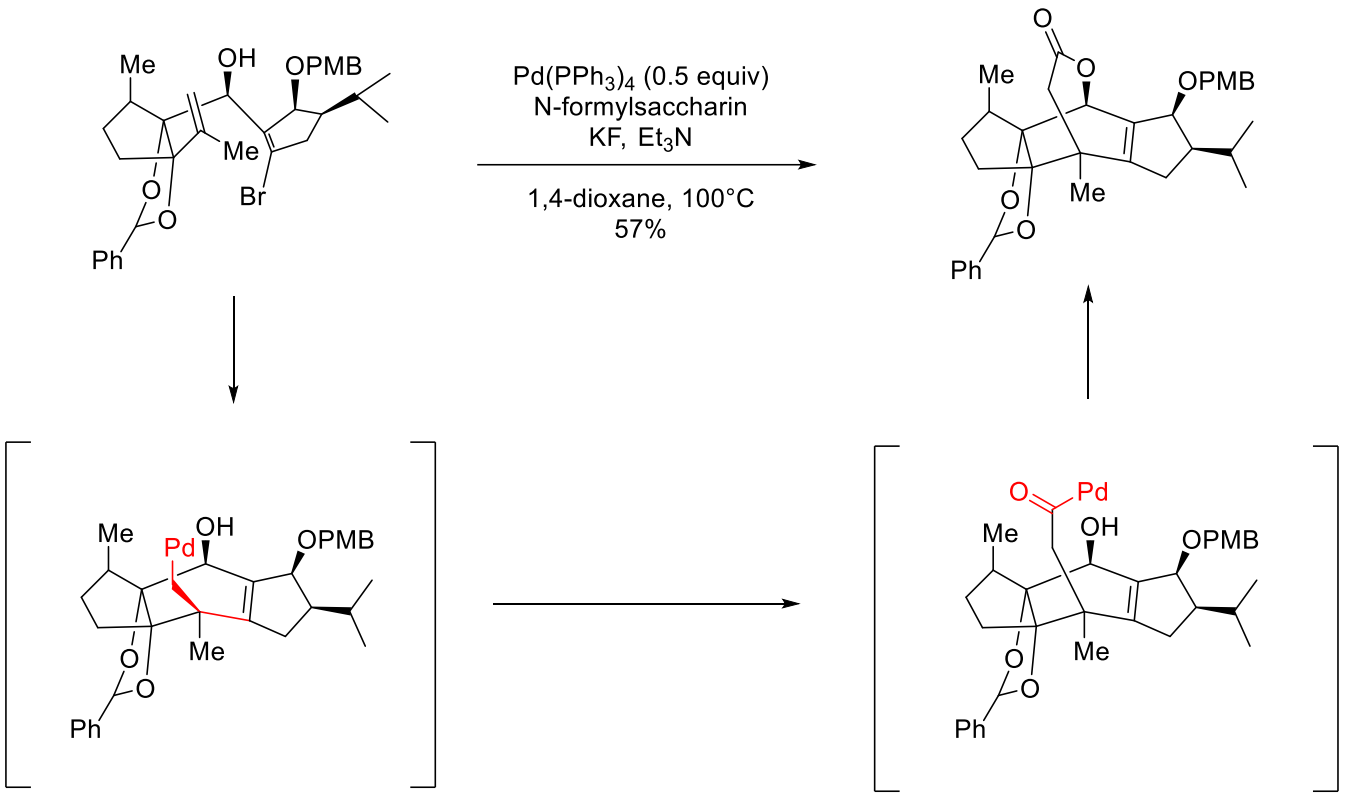


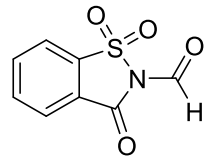
Schindilactone A

Q. Xiao, W.-W. Ren, Z.-X. Chen, T.-W. Sun, Y. Li, Q.-D. Ye, J.-X. Gong, F.-K. Meng, L. You, Y.-F. Liu, M.-Z. Zhao, L.-M. Xu, Z.-H. Shan, Y. Shi, Y.-F. Tang, J.-H. Chen, Z. Yang, *Angew. Chem. Int. Ed.* **2011**, *50*, 7373-7377.

Replacing CO source: Perseanol

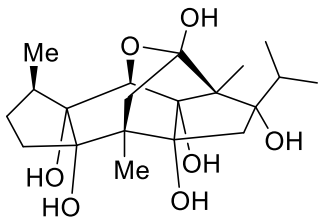
Reisman, 2019





N-formylsaccharin

- N-formylsaccharin as a CO donor
- Need excess Pd when using CO gas

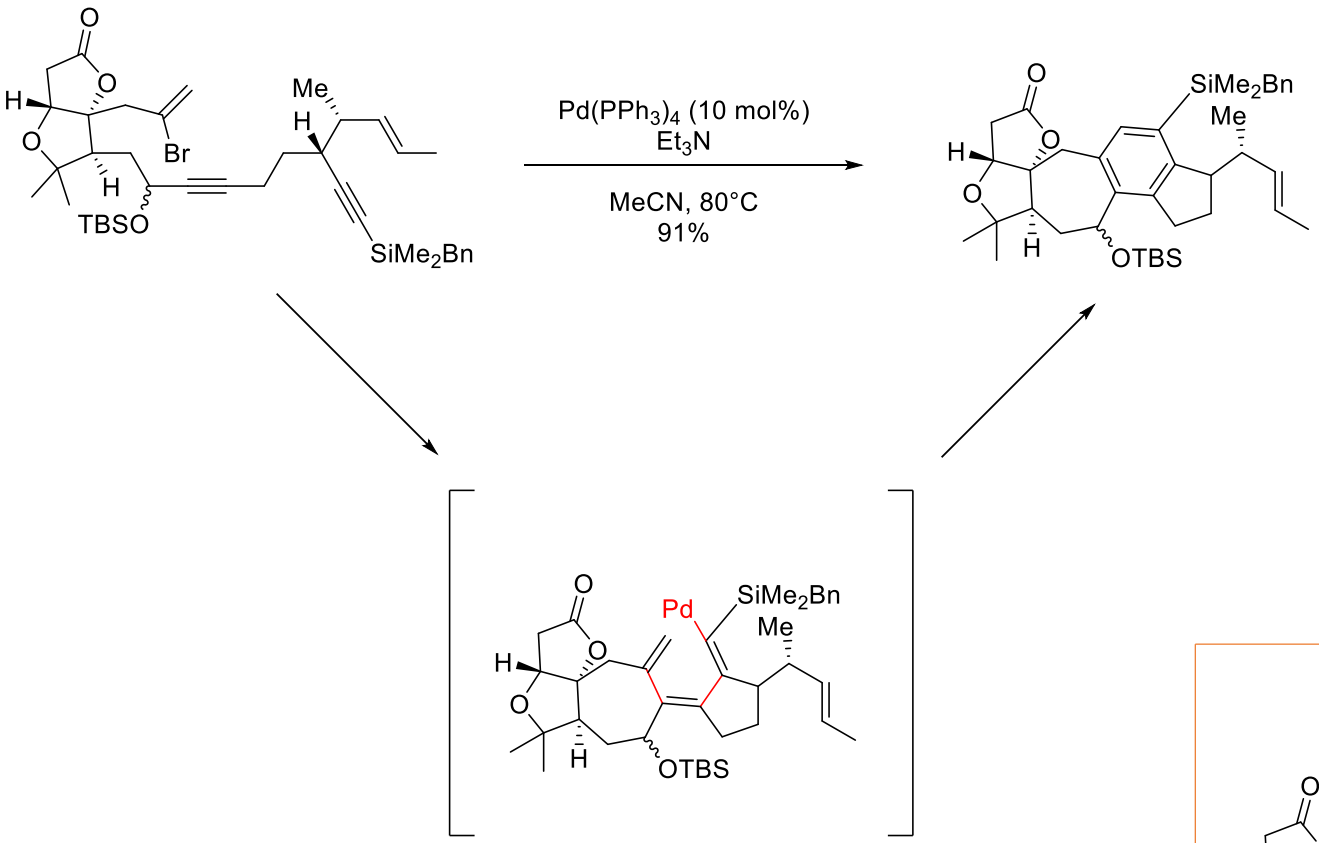


Perseanol

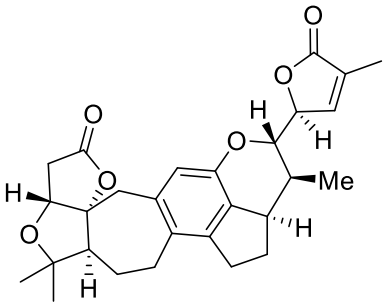
A. Han, Y. Tao, S. Reisman, *Nature* **2019**, *573*, 563-568.

7-exo cascade: Rubriflordilactone A

Anderson, 2015



- 7-exo carbopalladation
- Construction of core 7/6/5 tricycle

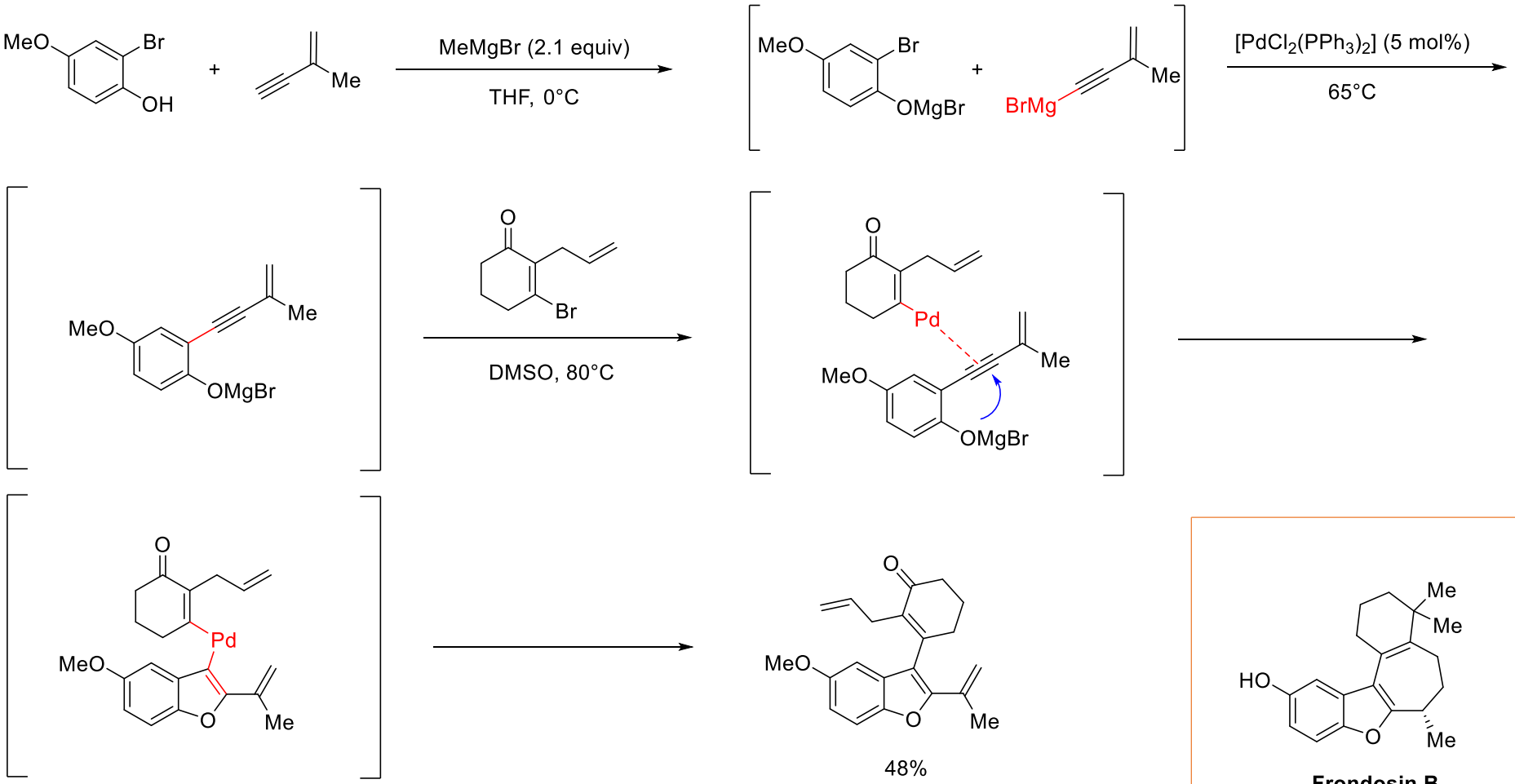


Rubriflordilactone A

S. S. Goh, G. Chaubet, B. Gockel, M.-C. A. Cordonnier, H. Baars, A. W. Phillips, E. A. Anderson, *Angew. Chem. Int. Ed.* **2015**, *54*, 12618-12621.

Multicomponent cascade reaction: Frondosin B

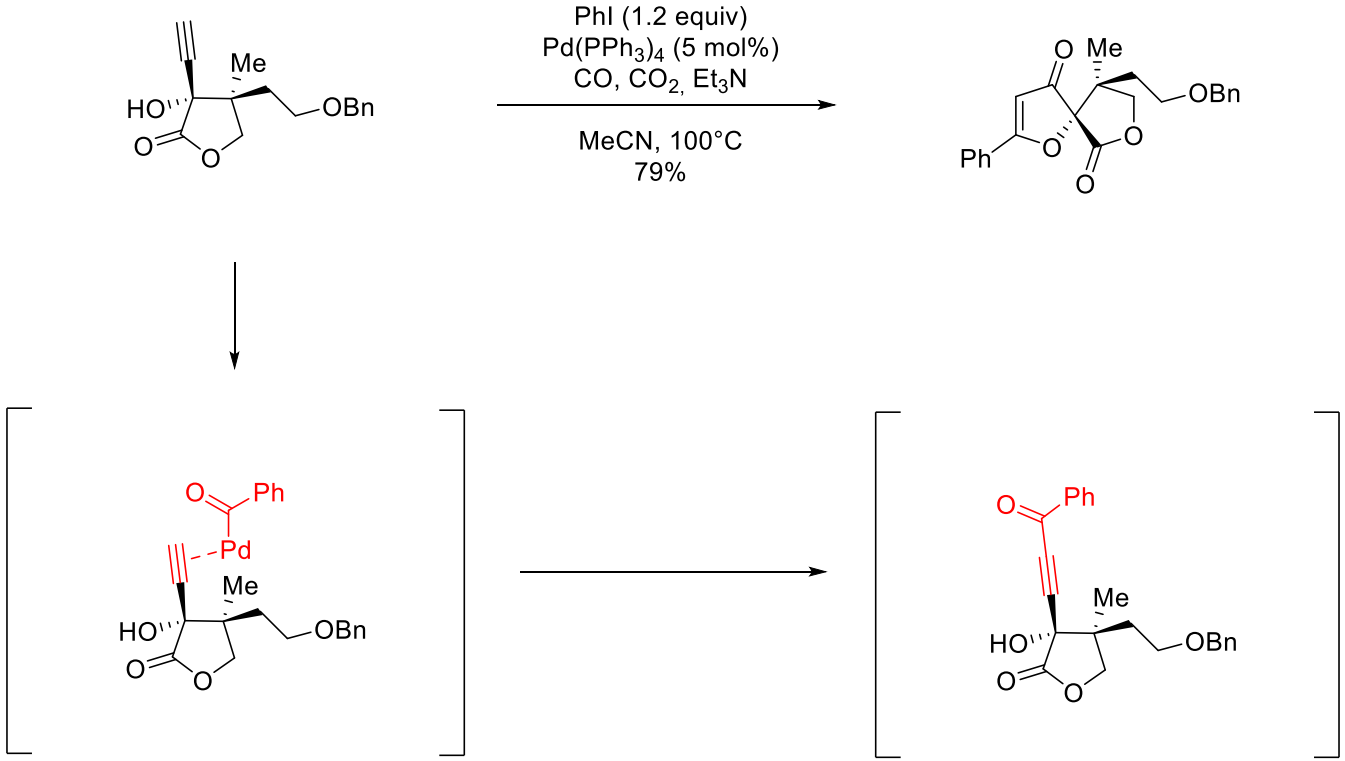
Flynn, 2004

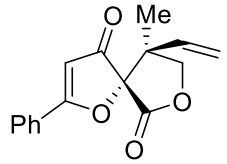


D . J. Kerr, A. C. Willis, B. L. Flynn, *Org. Lett.* **2003**, *6*, 457-460.

Nicolaou's cascade: Hyperolactone C

Nicolaou, 2008

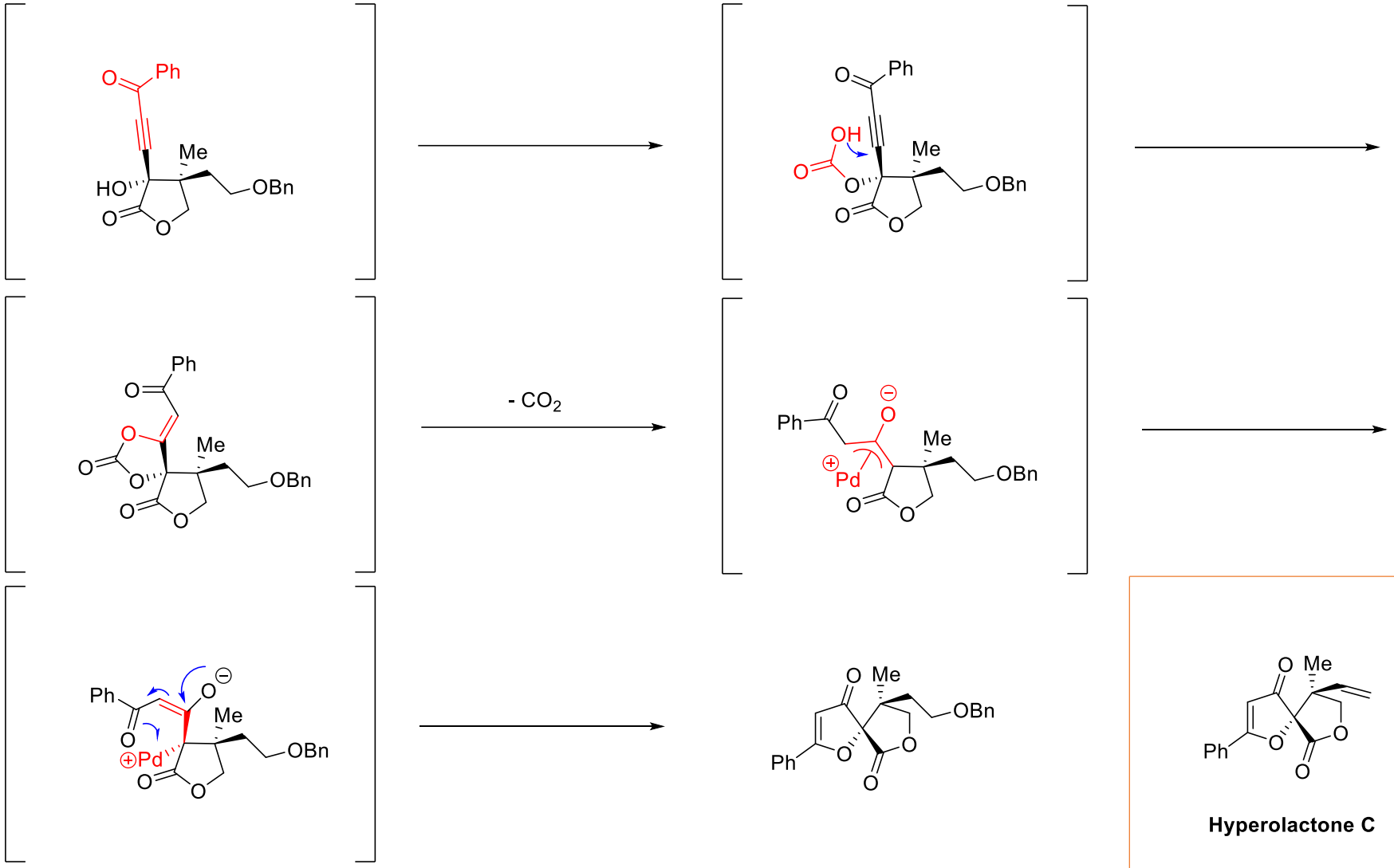




Hyperolactone C

K. C. Nicolaou, T. R. Wu, D. Sarlah, D. M. Shaw, E. Rowcliffe, D. R. Burton, *J. Am. Chem. Soc.* **2008**, *130*, 11114-11121.

Nicolaou's cascade: Hyperolactone C



K. C. Nicolaou, T. R. Wu, D. Sarlah, D. M. Shaw, E. Rowcliffe, D. R. Burton, *J. Am. Chem. Soc.* **2008**, *130*, 11114-11121.

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Summary

Cascade reactions involving palladium

- Very large field
- A lot of versatility
- Multiple bond formation

What's next?

- Better enantiocontrol?
- Even milder conditions?
- Replacing palladium?

Thanks for your attention !

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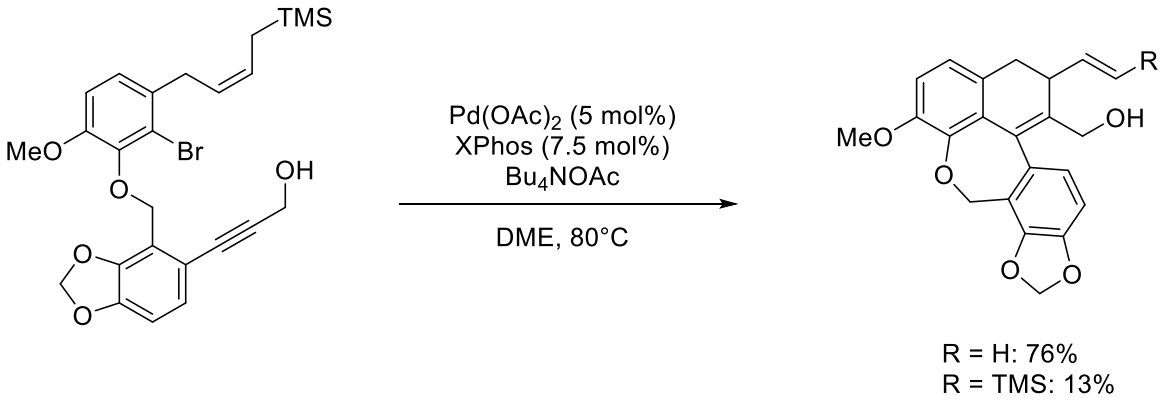
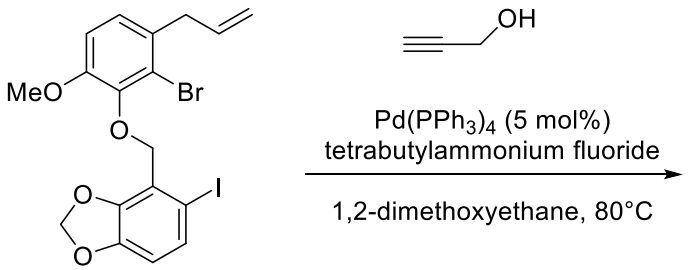
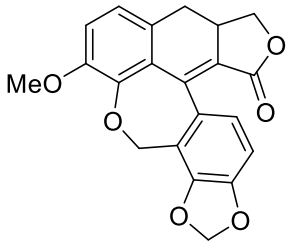
Cascade reaction to a natural lignan: Linoxepin



The authors tried the following reaction first. Why did they abandon it and what product do you expect?

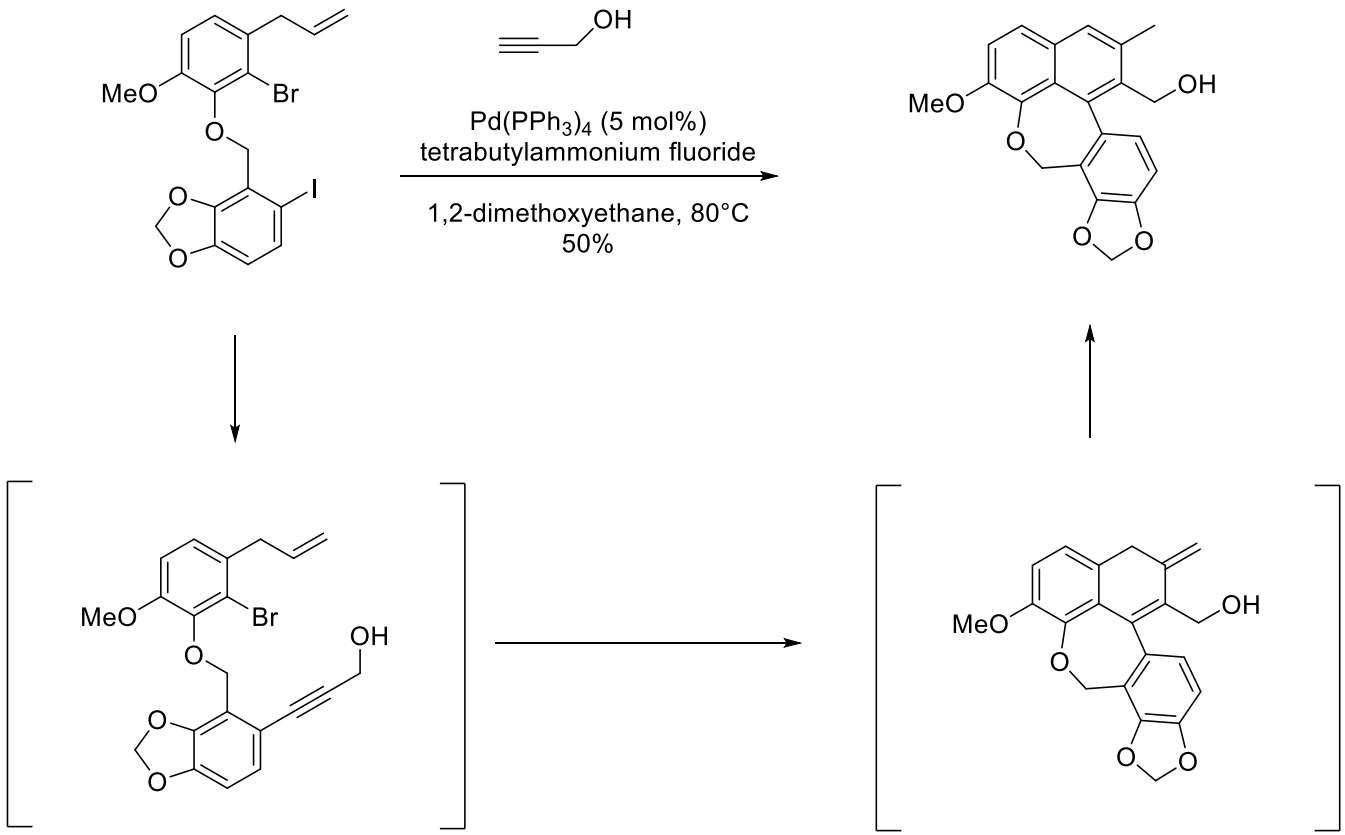


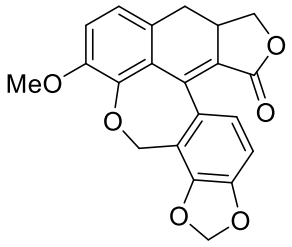


Linoxepin

L. F. Tietze, S.-C. Duefert, J. Clerc, M. Bischoff, C. Maass, D. Stalke, *Angew. Chem. Int. Ed.* **2013**, *52*, 3191-3194.

Cascade reaction to a natural lignan: Linoxepin



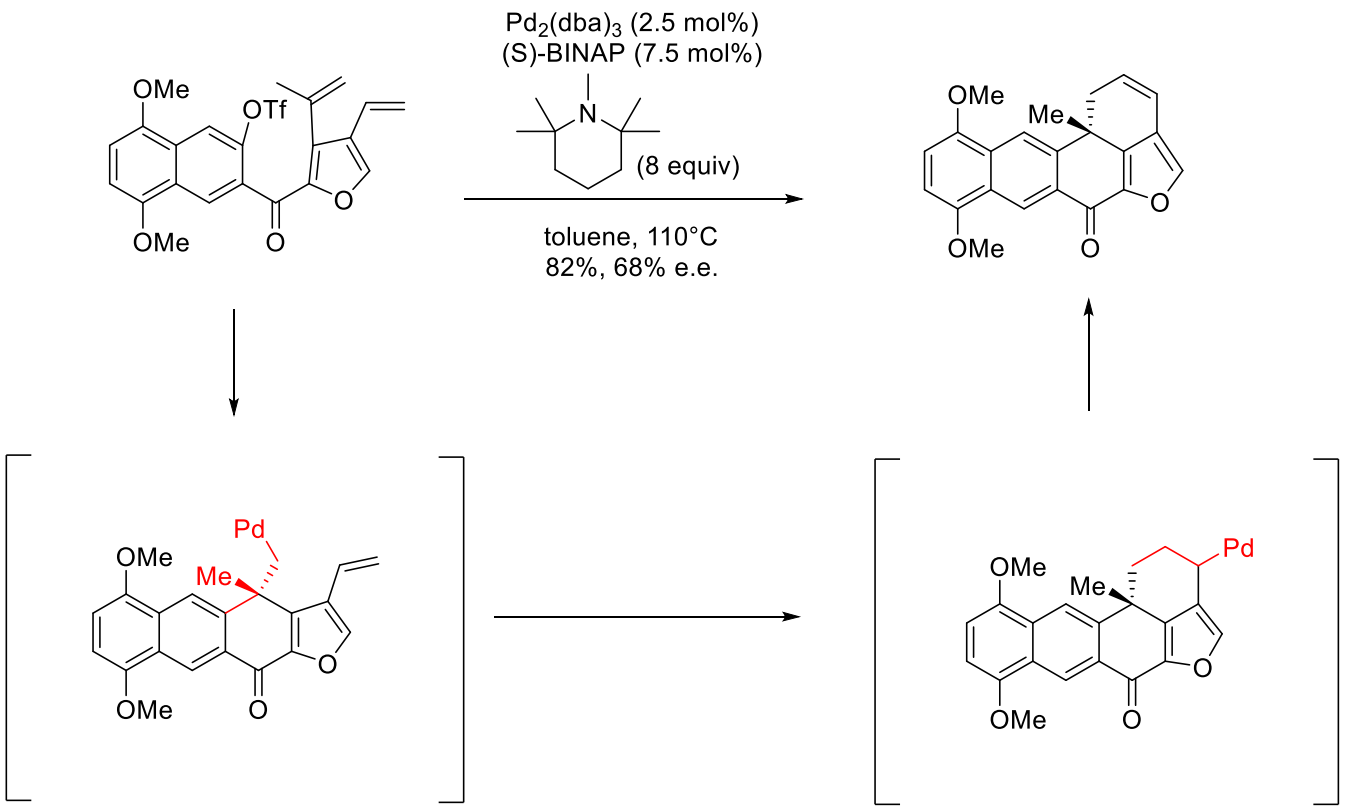


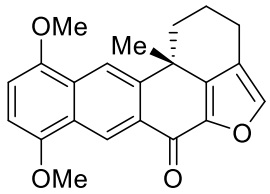
Linoxepin

L. F. Tietze, S.-C. Duefert, J. Clerc, M. Bischoff, C. Maass, D. Stalke, *Angew. Chem. Int. Ed.* **2013**, *52*, 3191-3194.

Enantioselectivity: Xestoquinone

If Br instead of OTf, e.e. = 13%. Explain the poorer enantioselectivity.



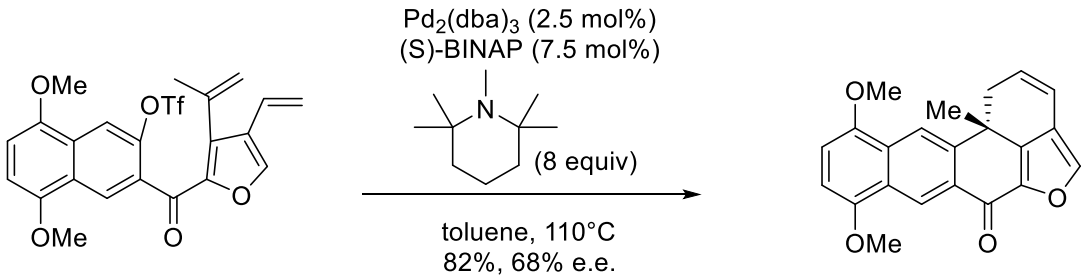


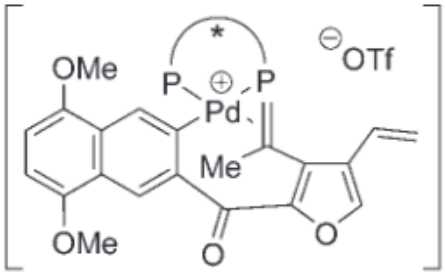
Xestoquinone

S. P. Maddaford, N. G. Andersen, W. A. Cristofoli, B. A. Keay, *J. Am. Chem. Soc.* **1996**, *118*, 10766-10773.
K. C. Nicolaou, D. J. Edmonds, P. G. Bulger, *Angew. Chem. Int. Ed.* **2006**, *45*, 7134-7186.

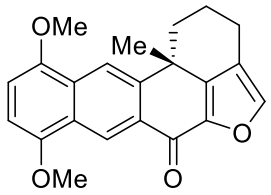
Enantioselectivity: Xestoquinone

If Br instead of OTf, e.e. = 13%. Explain the poorer enantioselectivity.





436



Xestoquinone

S. P. Maddaford, N. G. Andersen, W. A. Cristofoli, B. A. Keay, *J. Am. Chem. Soc.* **1996**, *118*, 10766-10773.
K. C. Nicolaou, D. J. Edmonds, P. G. Bulger, *Angew. Chem. Int. Ed.* **2006**, *45*, 7134-7186.

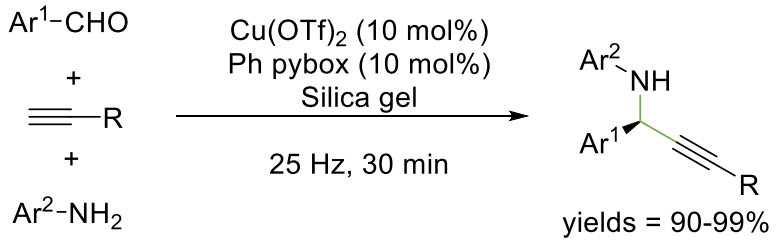
Frontiers in Chemical Synthesis: Towards Sustainable Chemistry

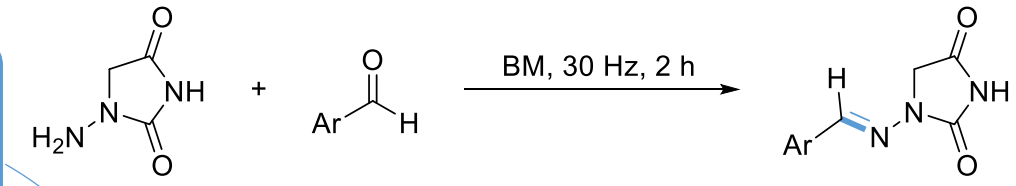
Transformation of biologically active compounds via mechanochemistry

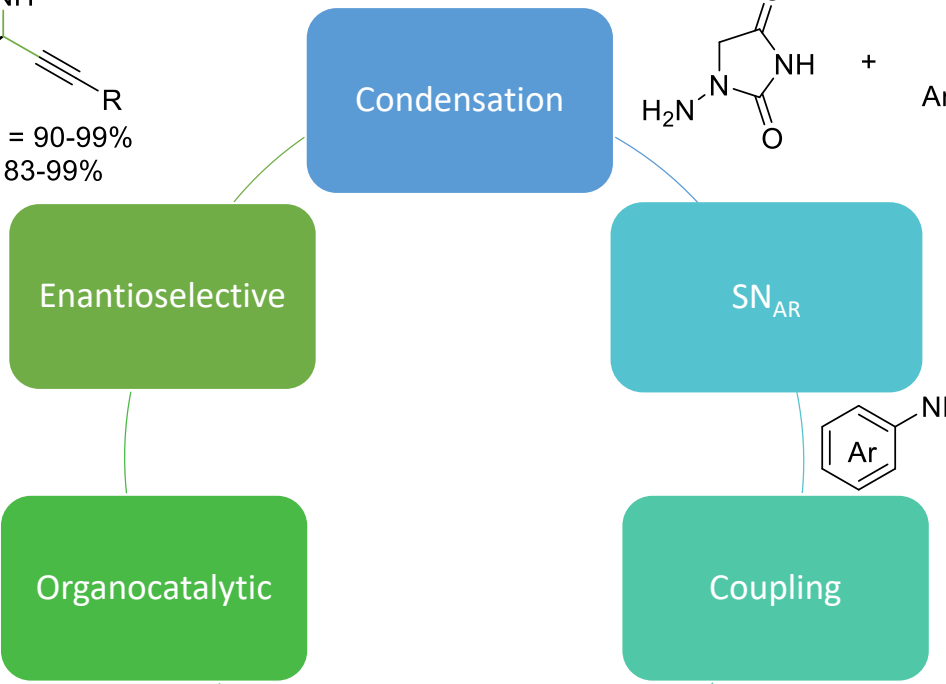
Christine Marty

Laboratory of Catalysis and Organic Synthesis (LCSO)– EPFL

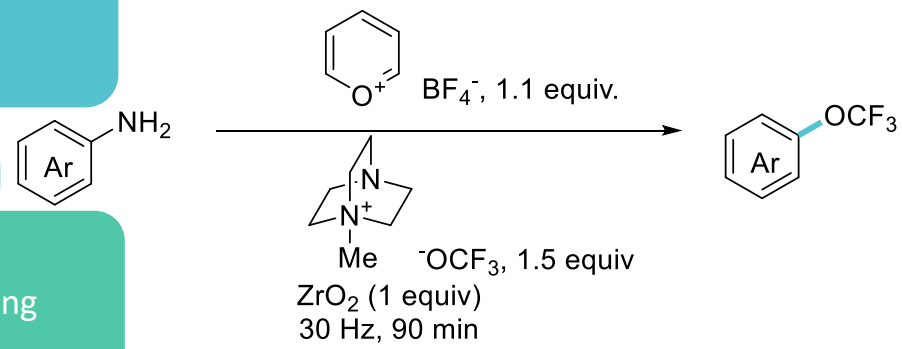
What can you do with mechanochemistry?

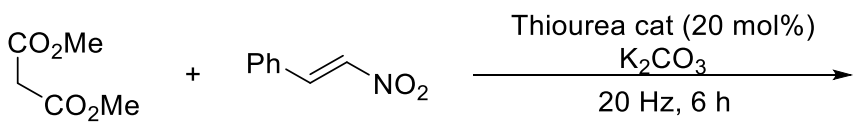


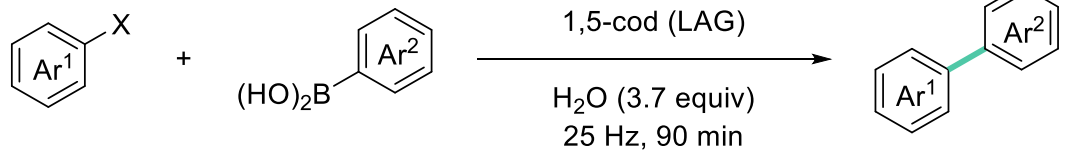


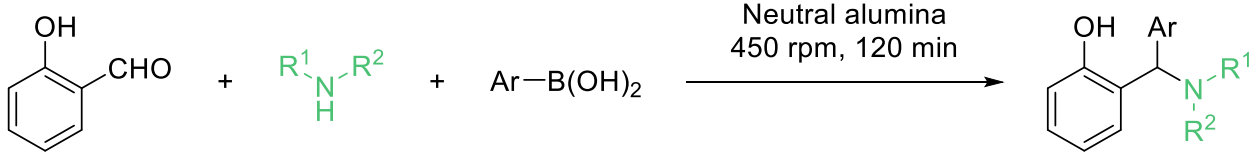


- Preparation of co-crystals
- Inorganic chemistry
- Polymer chemistry
- Organic chemistry





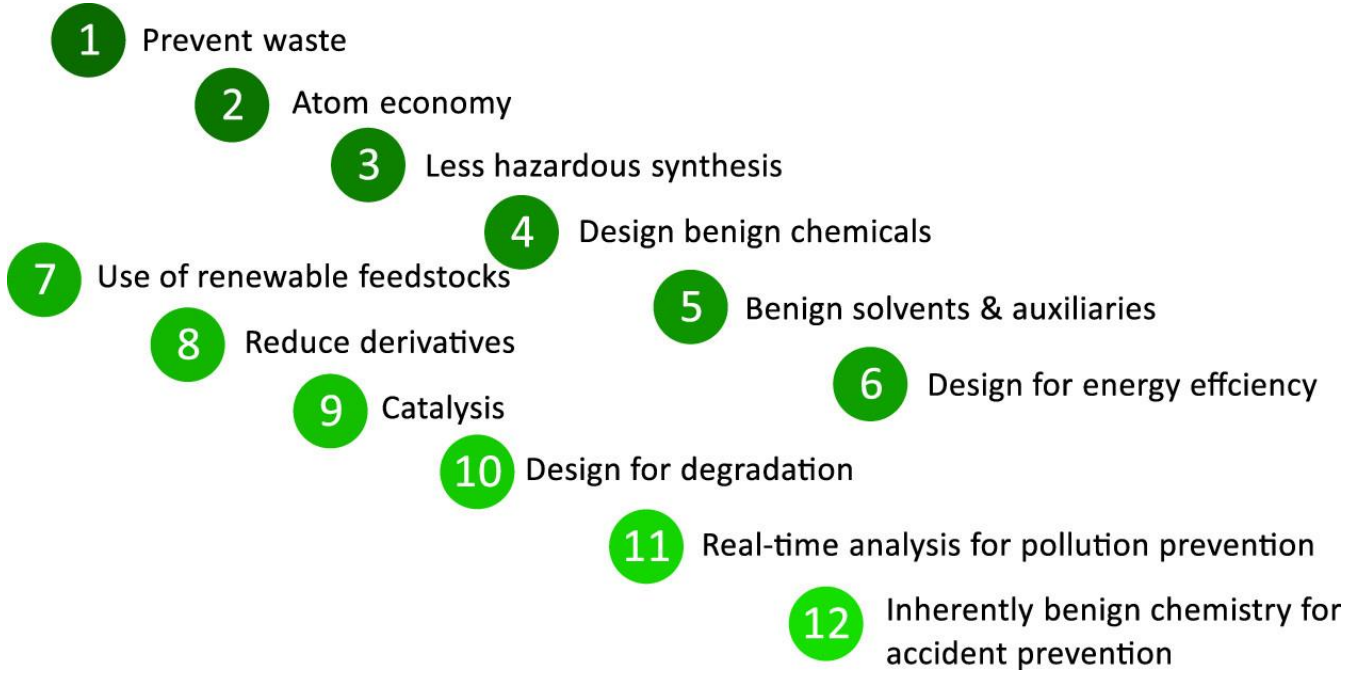




a) Condensation: Green Chem. 2018, 20, 2973. b) SNAR: J. Am. Chem. Soc. 2022, 144, 10438. c) Coupling: Chem. Sci., 2019, 10, 8202.
d) MC: J. Iranian Chem. Soc. 2017, 14, 347. e) Organocat: Tetrahedron 2014, 70,901. f) Enantio: Green Chem., 2015, 17, 2330.

Why mechanochemistry?

Green chemistry



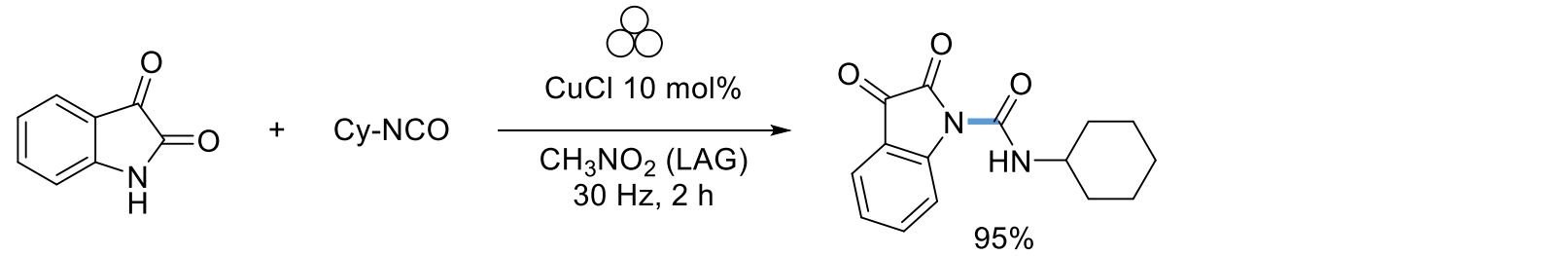
- Solvent free
- Better Atom economy
- Faster Kinetics due to high concentration & Greater surface area

ACS Sustainable Chem. Eng. 2020, 8, 24, 8881.

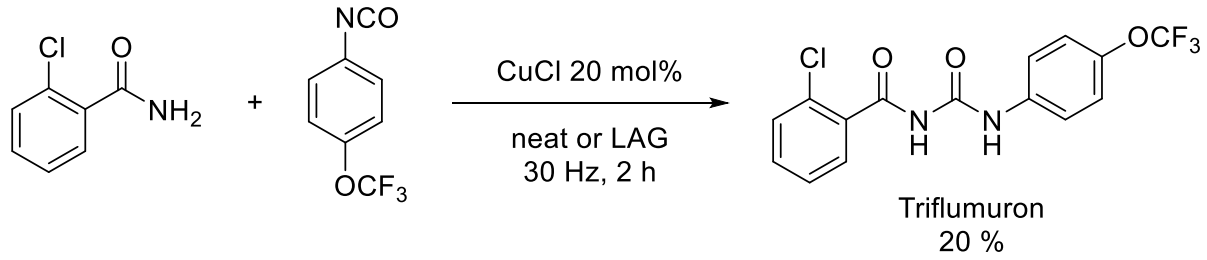
Why mechanochemistry?

Selectivity: C-N coupling to amide

Friscic 2020



Application: Synthesis of insecticides Triflumuron

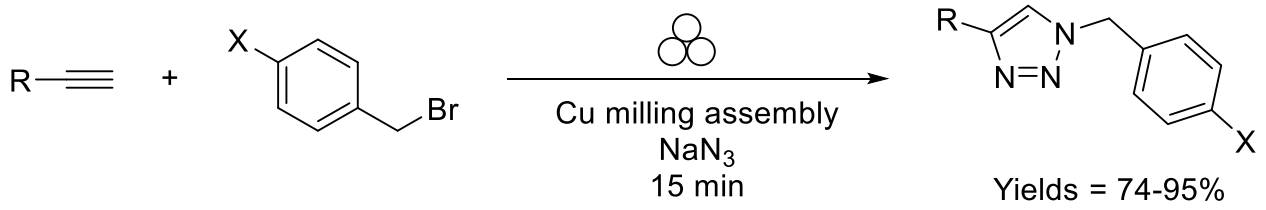


- Selectivity issue
- Poor conversion
- Harsh conditions

ChemSusChem2020,13,2966.

Catalysis in Mechanochemical Reactions

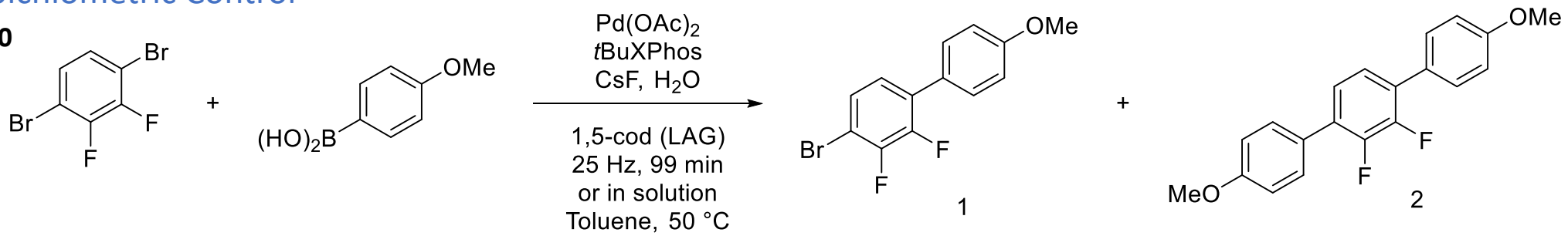
Mack 2013



- Copper vial and copper ball
- No decrease over uses
- NaN_3 stable to mechano

Stoichiometric Control

Ito 2020



BM	Solution
Milling (30 Hz) 72% yield 1/2= 90:10	In toluene 54% yield 1/2= 63:37

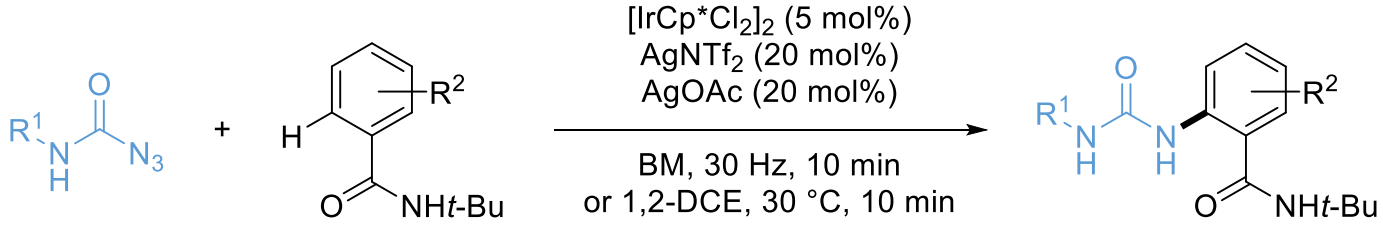
- Mechanochemical desymmetrisation
- Enhance control of reaction stoichiometry

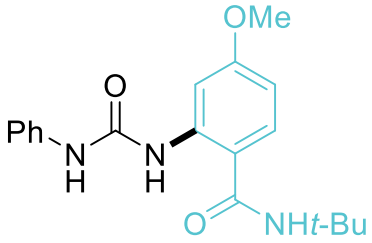
a) CuClick: Green Chem., 2013, 15, 617. b) Stoichiometric control: J. Am. Chem. Soc. 2020, 142,9884.

Why mechanochemistry?

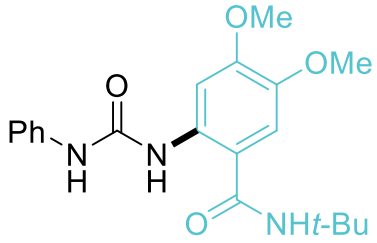
New reactivity: Ir-Catalyzed sp^2 C–H Amidation with Various Carbamoyl Azides

Kim 2021

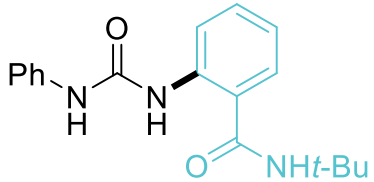




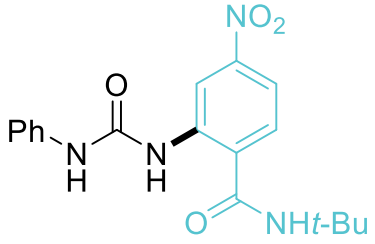
Ball Mill: 63%
Solution: 21%



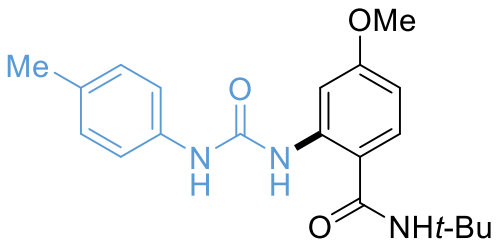
Ball Mill: 71%
Solution: 18%



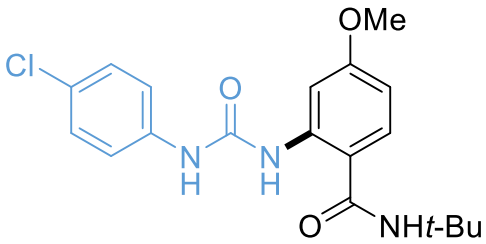
Ball Mill: 33%
Solution:16%



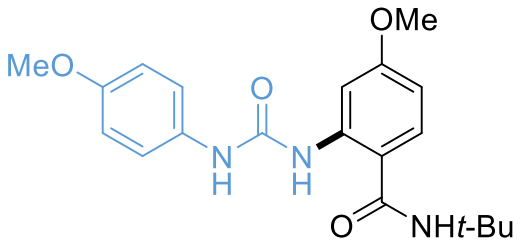
Ball Mill: 11%
Solution: 10%



Ball Mill: 56%
Solution: 21%



Ball Mill: 82%
Solution: 31%



Ball Mill: 49%
Solution: 15%

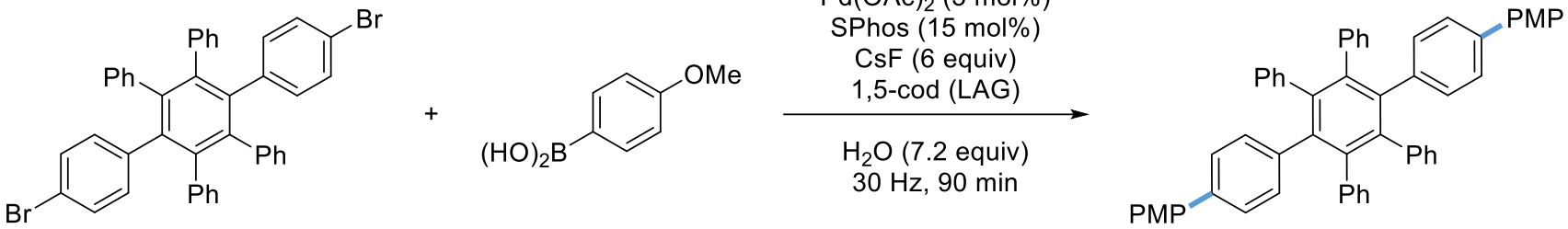
- Acyl azides thermally unstable
- No Curtius side reaction
- Overcompensation with mechanical forces

ACS Sustainable Chem. Eng. 2021, 9, 26, 8679.

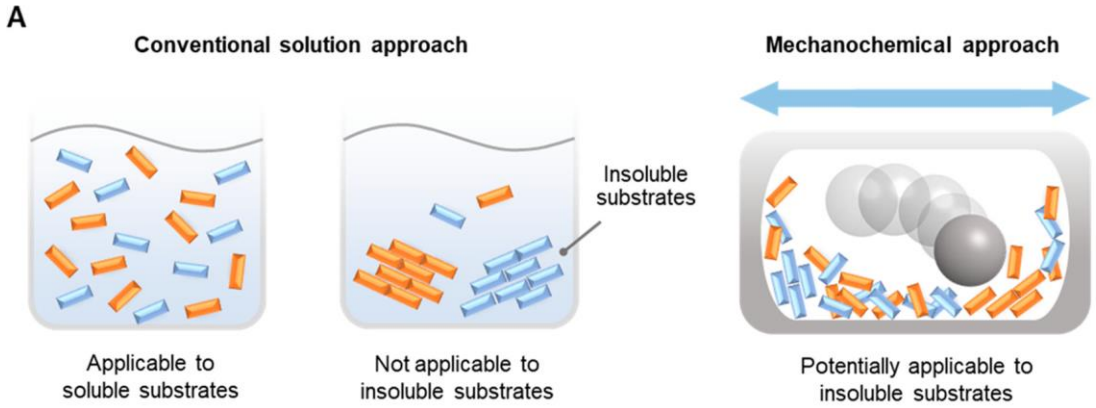
Why mechanochemistry?

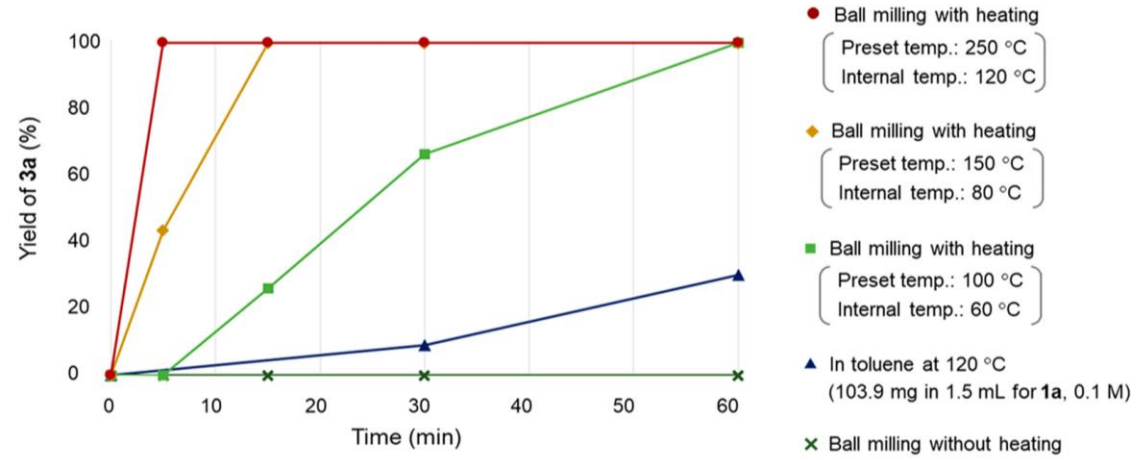
Solid-State Cross-Coupling of Insoluble Aryl Halides

Ito 2021



Solubility in toluene (23 °C)
1.9×10^{-3} M





- Higher yield with mechanochemistry
- Solid state at high temperature

Solubility: *J. Am. Chem. Soc.* 2021, 143, 16, 6165.

Equipments

Mortar and pestle
(Operator dependent)

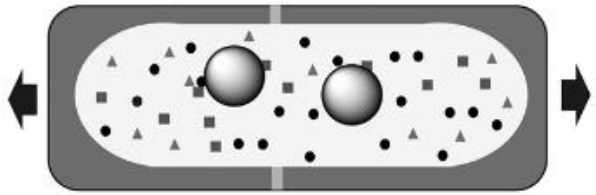
First exemple 315 B.C

Vibratory Mills

Scale < 2.0g

- No Temperature control
- Cryomilling available

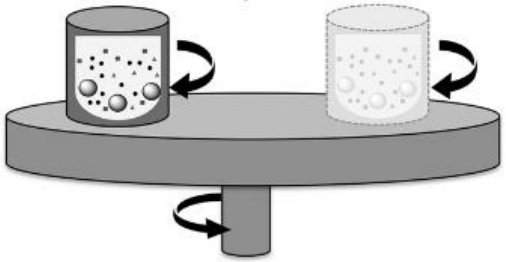
Mixer mill



Scale < 1.0 Kg

- No Temperature control
- Multi-station device available

Planetary ball mill



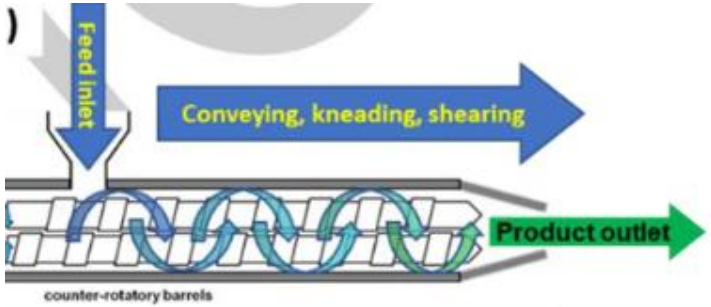
Planetary Mills

Scale < 10 Kg

- No Temperature control
- Large scale batch process

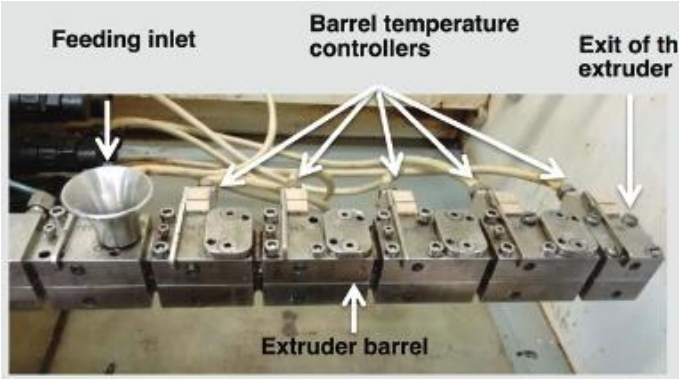
Simoloyer

Eccentric Mill



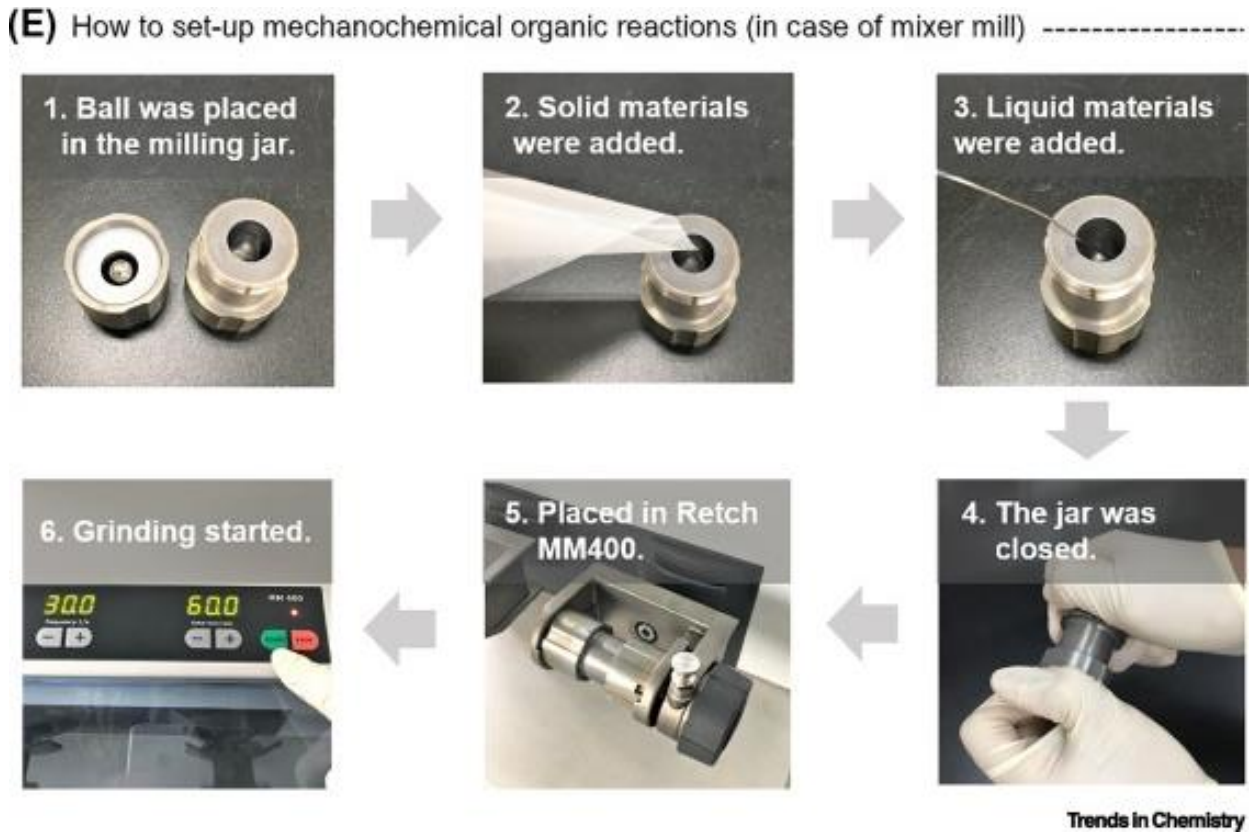
Scale: grams to tonnes

- Continuous
- Accurate temperature control



Angew. Chem. Int. Ed. 2023, e202300819

Set up and Parameters



Control of impact and mixing

- Grinding speed (Hz or rpm)
- Size and number of balls
- Materials of jar and ball
- Jar filling degree
- Ball to reagent ratio

Grinding additive

- Unreactive liquid

(LAG, η= μL/mg)-> better homogeneity

- Unreactive solid -> lower concentration

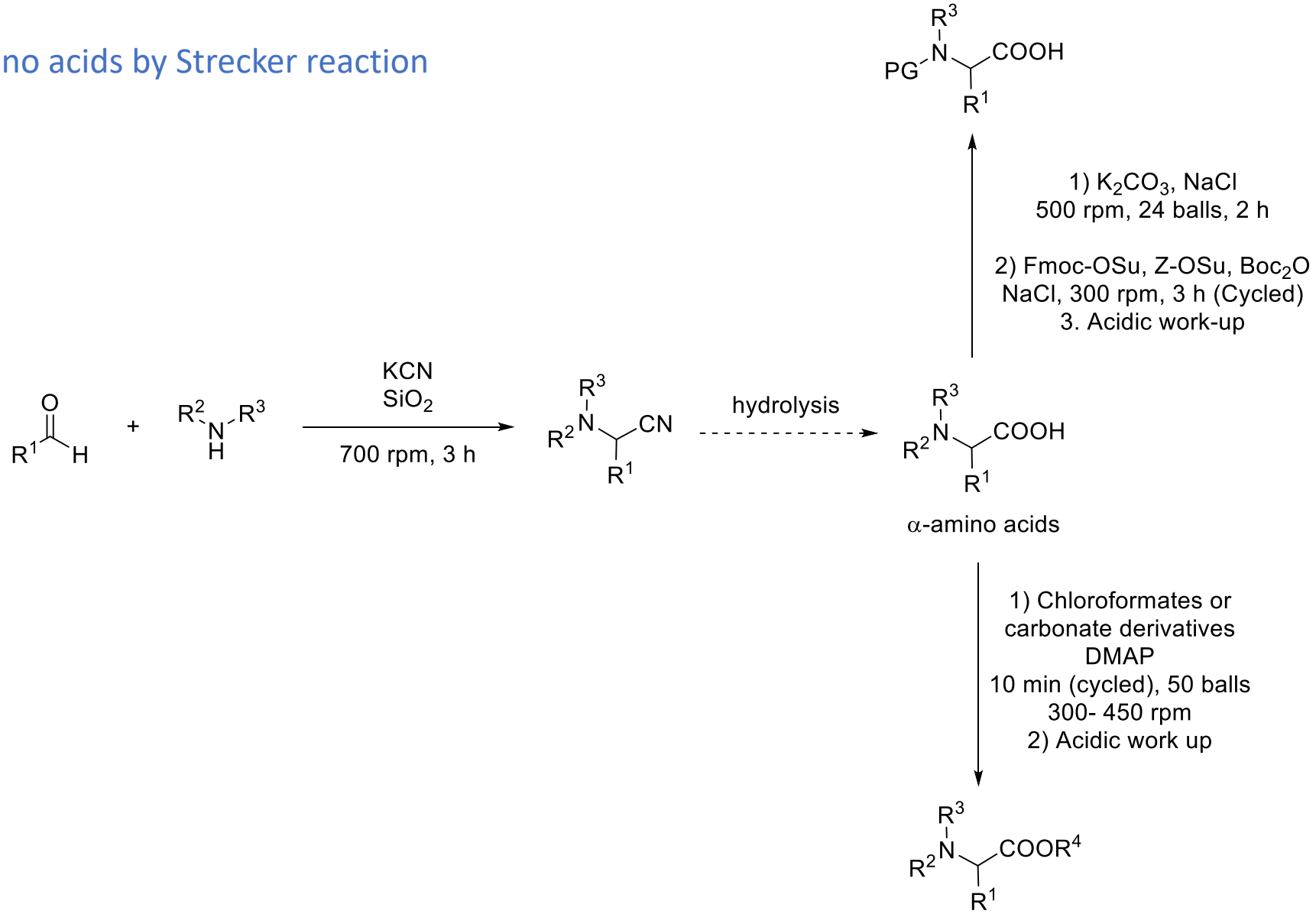
Monitoring

- Temperature (viscosity)
- Ex situ: common techniques (NMR, MS, IR…)
- In situ monitoring (X-Ray diffraction, solid state HR-MAS NMR, Raman spectroscopy)

https://doi.org/10.1016/j.trechm.2020.09.006

Synthesis of amino acids by Strecker reaction

Bolm 2016

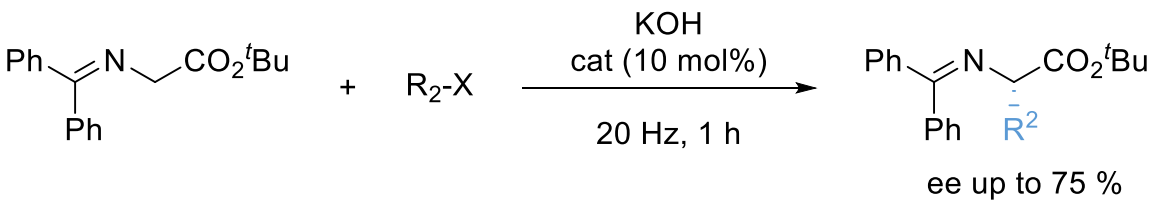


a) Strecker: Chem.Eur.J. 2016, 22,1451. b) *N*-terminus: ACS Sustainable Chem. Eng. 2013, 1, 1186. c) *C*-terminus: J. Org. Chem. 2014, 79, 9, 4008.

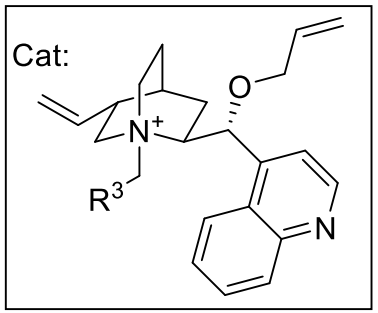
Synthesis of unnatural amino acids

Lamathy & Metro

Phase transfer catalyst

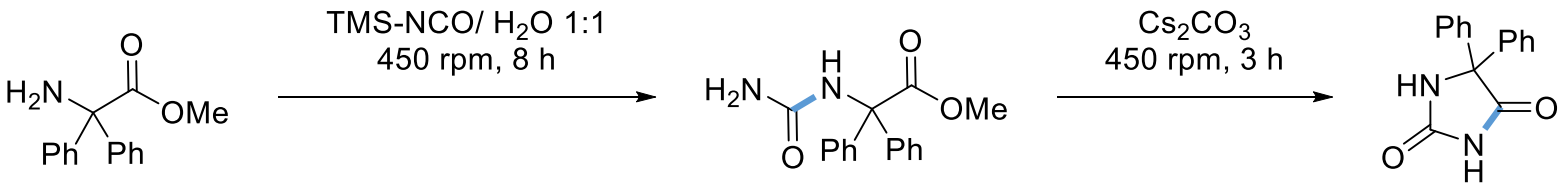


ee up to 75 %



- Enantiomeric excess values lower than in solution

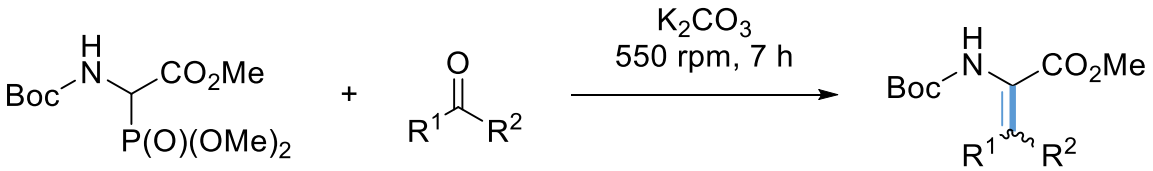
Bioactive hydantoins



Phenyltoin
84 %

- Anti epileptic drug
- Solvent free
- No purification needed

Unsaturated amino acids



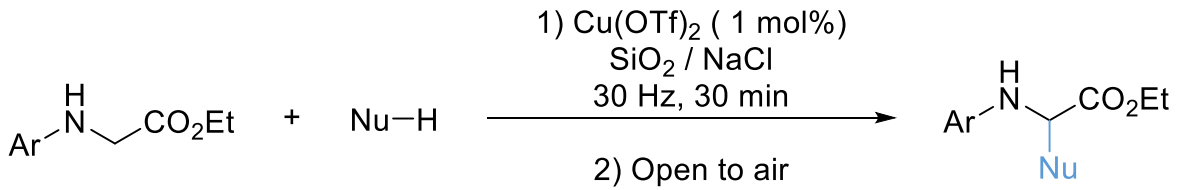
- Mild base
- Good Z selectivity

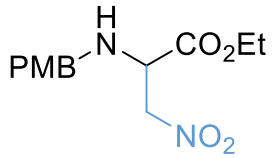
a) PTC: Chem. Eur.J.2012, 18,3773. b) J. Org. Chem. 2014, 79, 10132. c) Tetrahedron Lett. 2010, 51, 6246.

Synthesis of unnatural amino acids

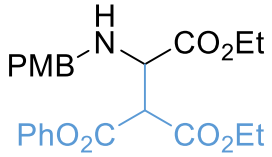
Cross Dehydrogenative coupling

Yu 2023

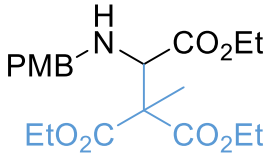




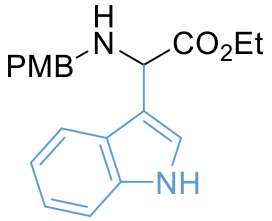
65%



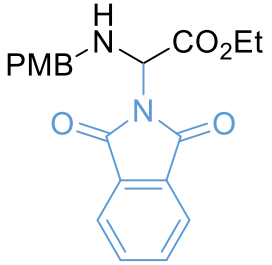
62%



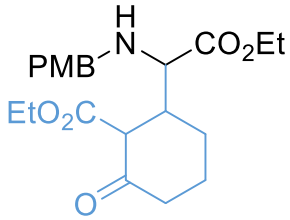
80%



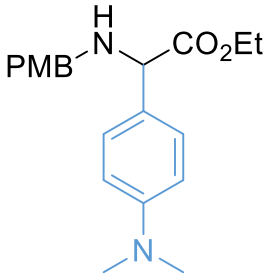
83%



88%



84%



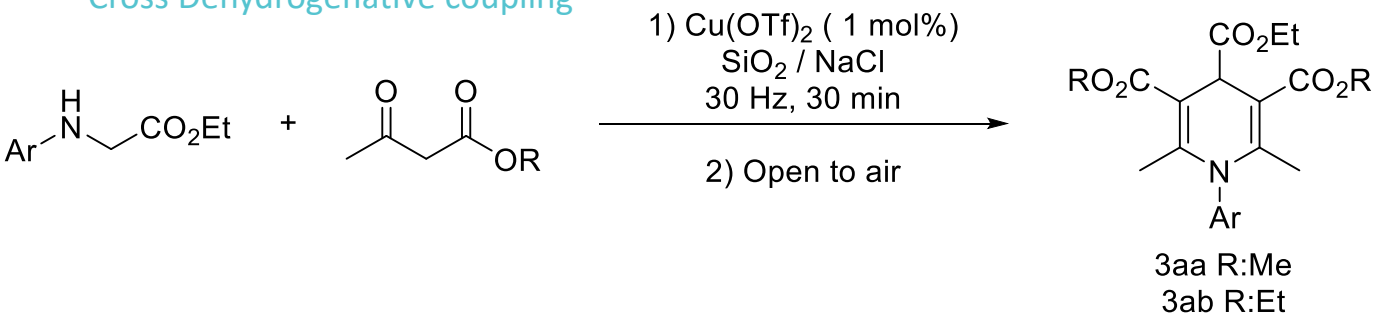
62%

a) Mechano: Green Chem., 2023,25, 2853.

Mechanochemistry of amino acids

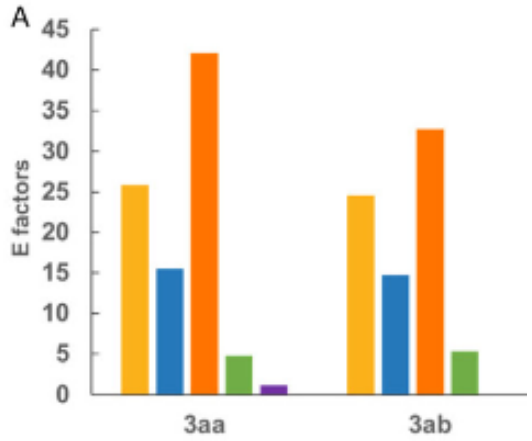
Synthesis of unnatural amino acids

Cross Dehydrogenative coupling

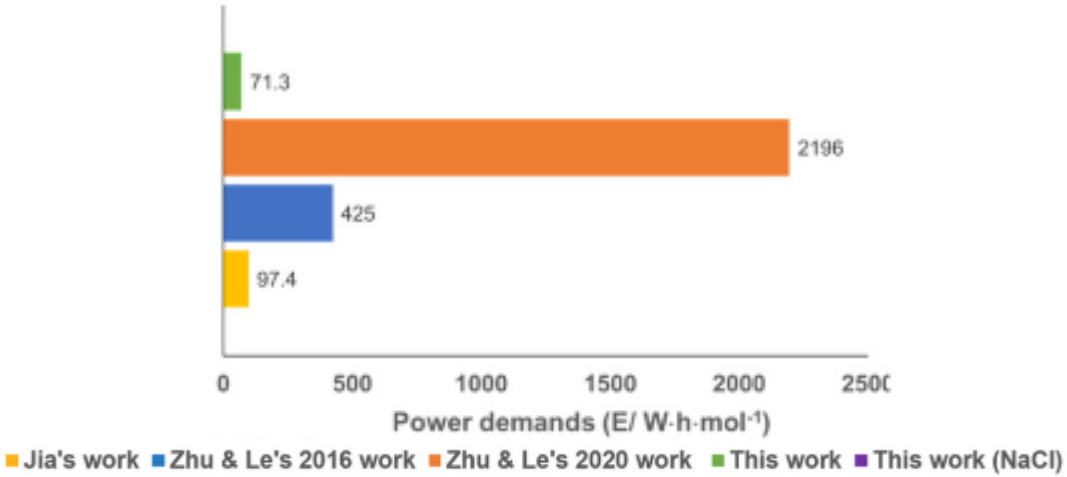


3aa R:Me
3ab R:Et

	Jia	Zhu 2016	Zhu 2020	This work (Yu)
Catalyst	TMSCl	$Cu(OTf)_2$	$Ir(ppy)_3$	$Cu(OTf)_2$
Oxidant	$TBPA^{+\bullet}$ O_2 (1 atm)	O_2 (1 atm)	DCP	O_2 (air)
Solvent	MeCN	Toluene	Toluene	None
Conditions	60 °C 4 h	60 °C 12 h	Blue LED (18 W) 12 h	BM: 30 Hz 0.5 h



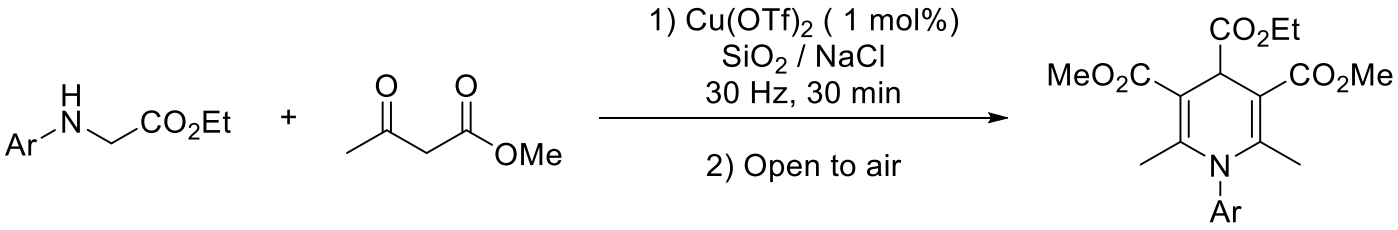
$$\text{E-factor} = \left(\frac{\sum(\text{mass of waste})}{\text{mass of product}} \right) \times 100$$



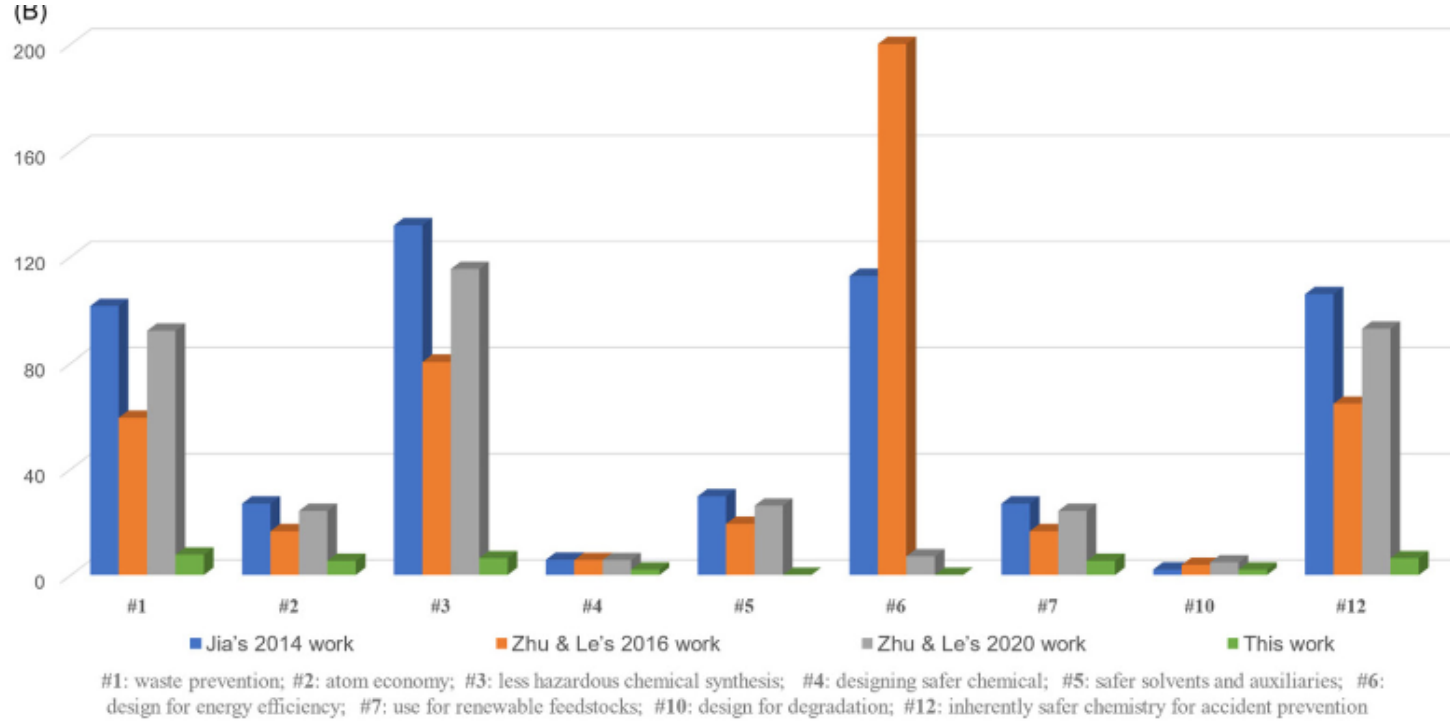
a) Mechano: Green Chem., 2023,25, 2853. b) Jia's: Adv. Synth. Catal., 2014, 356, 1210. c) J.Org. Chem., 2016, 81, 9449. d) Tetrahedron, 2020, 76, 131353.

Synthesis of unnatural amino acids

Cross Dehydrogenative coupling



	Jia	Zhu 2016	Zhu 2020	Yu
Catalyst	TMSCl	$Cu(OTf)_2$	$Ir(ppy)_3$	$Cu(OTf)_2$
Oxidant	$TBPA^{+\bullet}$ O_2 (1 atm)	O_2 (1 atm)	DCP	O_2 (air)
Solvent	MeCN	PhMe	Toluene	None
Conditions	60 °C 4 h	60 °C 12 h	Blue LED (18 W) 12 h	BM: 30 Hz 0.5 h
Yield	78%	73%	56%	71%

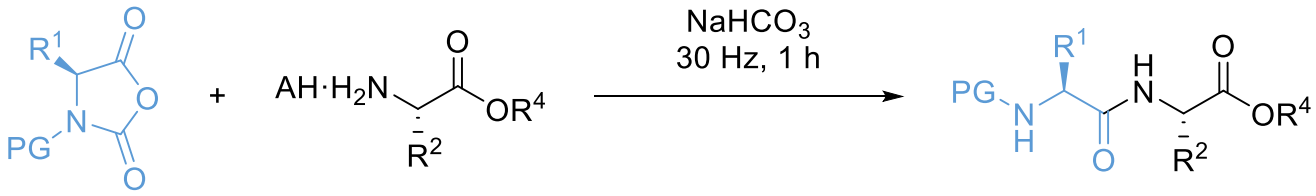


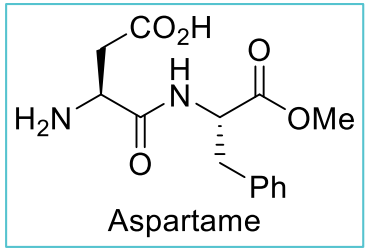
a) Mechano: Green Chem., 2023,25, 2853. b) Jia's: Adv. Synth. Catal., 2014, 356, 1210. c) J.Org. Chem., 2016, 81, 9449. d) Tetrahedron, 2020, 76, 131353.

Amino acid N-carboxyanhydride (UNCA)

α-amino acid N-carboxyanhydrides (UNCAs)

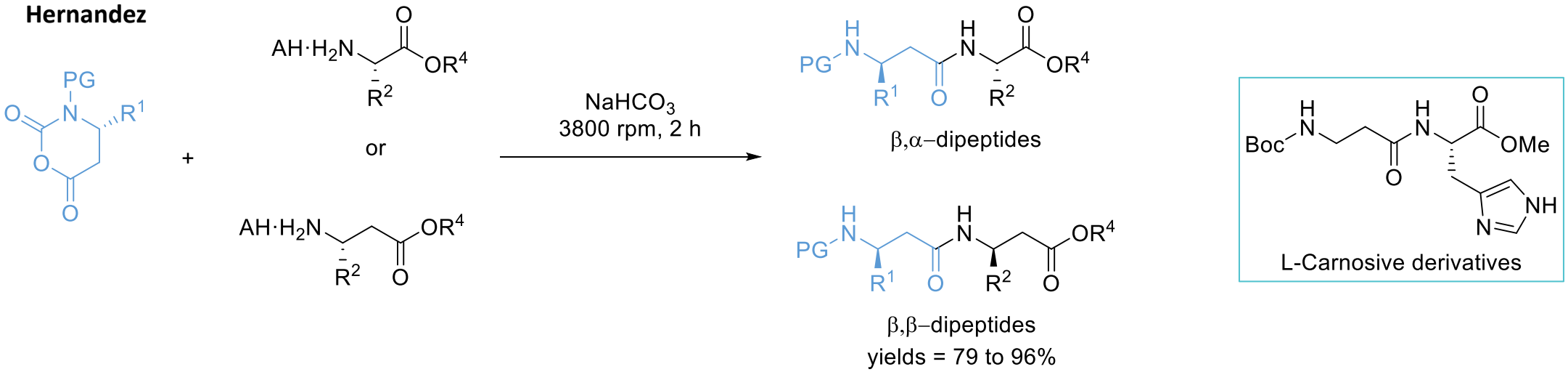
Lamathy & Metro





β-amino acid N-carboxyanhydrides (UNCAs)

Hernandez



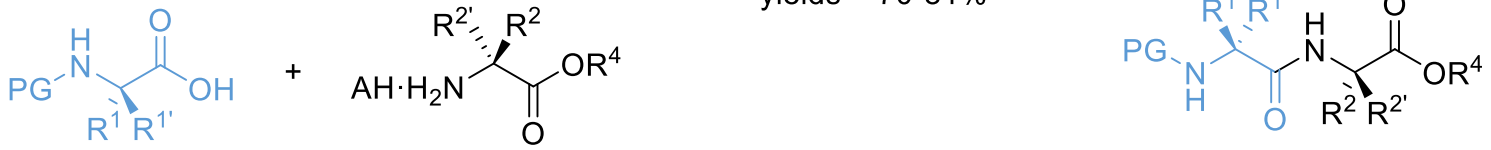
a) Angew. Chem., Int. Ed., 2009, 48 , 9318. b) J. Org. Chem., 2010, 75 , 7107.

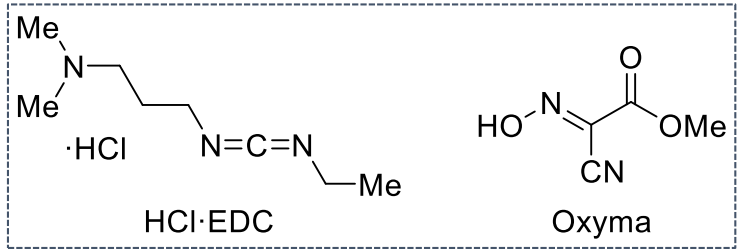
Mechanochemistry of Peptide bond formation

Carbodiimide peptide coupling

EDC coupling

Strukil 2012

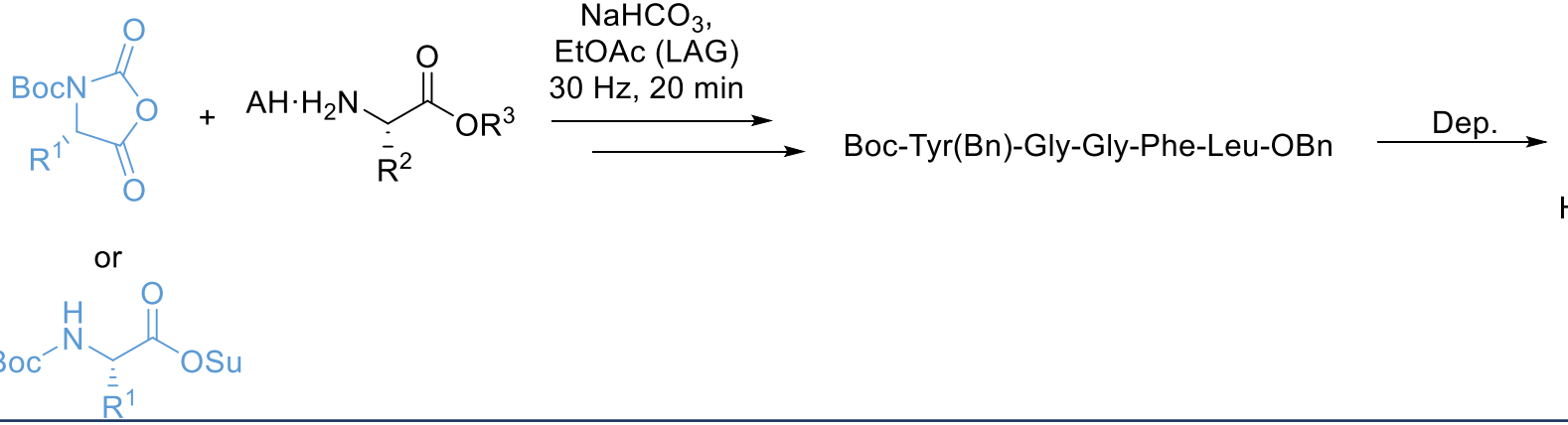




Oxyma
- Reduction of frequency and time
- Up to tetrapeptide

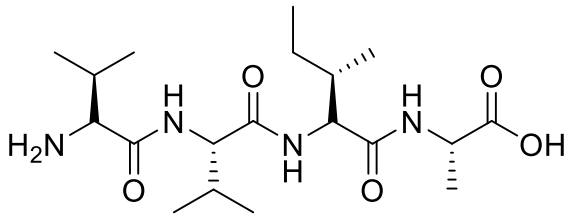
Activated ester

Lamathy 2013



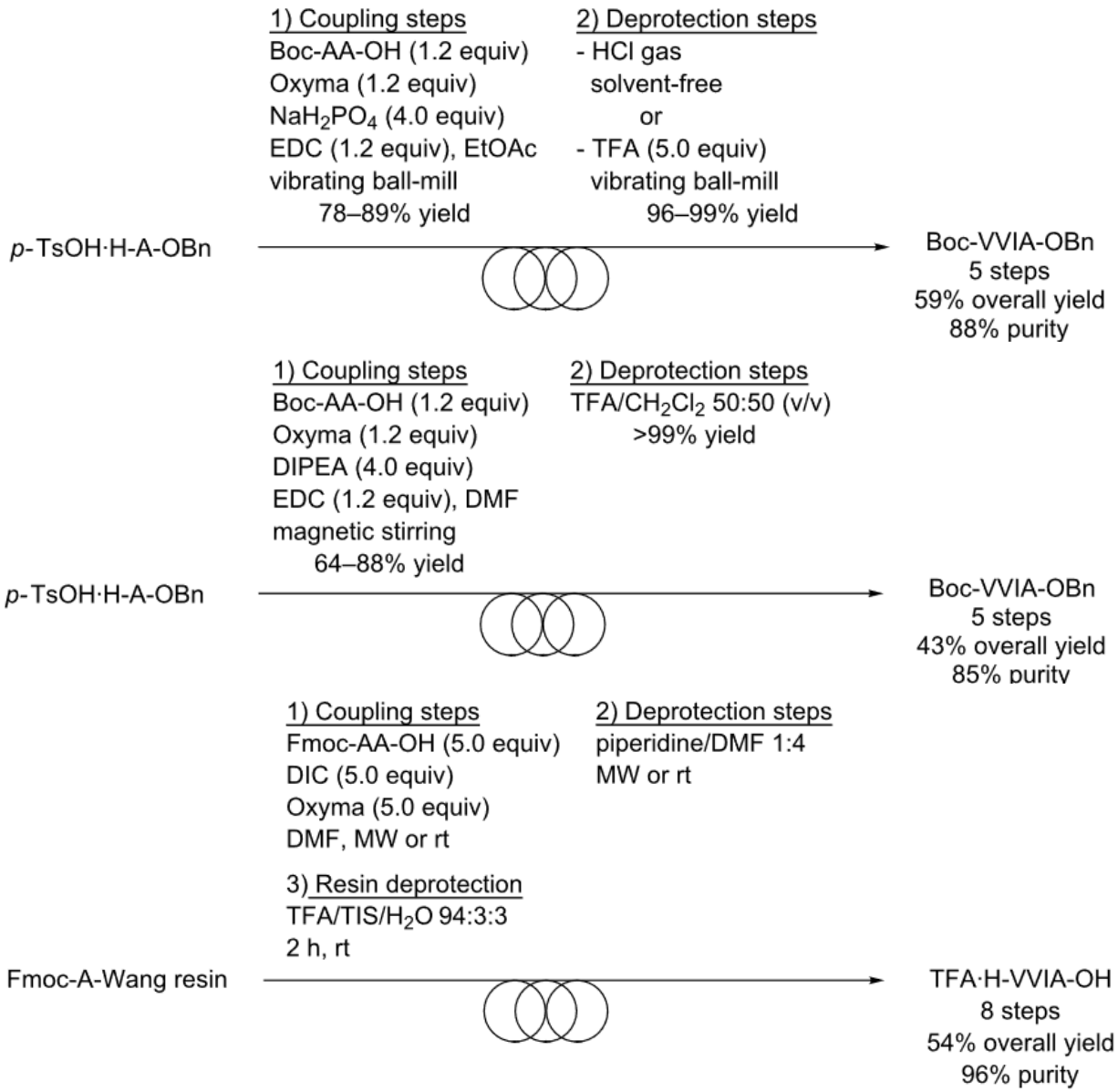
a) Chem. Commun., 2012, 48 , 12100. b) Eur. J. Org. Chem., 2016, 3505. c) Green Chem., 2013, 15, 1116–1120.

Case study: peptide coupling



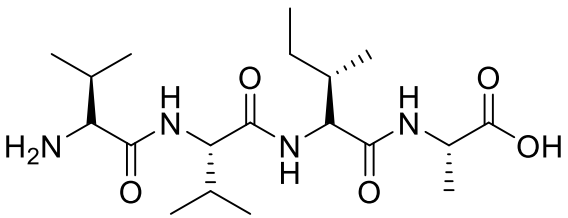
VVIA

Therapeutic peptide
High hydrophobicity
High steric hindrance



Beilstein J.Org. Chem. 2017, 13,2087

Case study: peptide coupling



VVIA

Ball-Mill (BM)	Solution	SPPS
Boc **No solvent** Extractions and washing needed	Boc **DMF** Extractions and washing needed	Fmoc DMF/NMP Resin deprotection step

Efficiency, yield:
SSPS > BM > solution

Efficiency

	Ball-Mill (BM)	Solution	Solid phase (SPPS)
Total of steps	**5**	**5**	8
Overall Yield	**59 %**	43 %	54 %
Purity	88 %	85 %	**96 %**
Reaction time Deprotection Total:	5 min (coupling) 1 h Few days	3 hrs (coupling) 2-3 h Few days	30 min x2 coupling 5 min x2 6 h

Beilstein J.Org. Chem. 2017, 13,2087

Case study: peptide coupling

Environmental impact

E-Factor

	Ball-Mill	Solution	Solid phase
P-IA-OR	**4.9**	7.3	95.5
TFA. H-IA-OR	**1.3**	5.9	1406.6
P-VIA-OR	**5.0**	7.1	81.0
P-VVIA-OR	**9.4**	17.8	68.1

$$\text{E-factor} = \left(\frac{\sum(\text{mass of waste})}{\text{mass of product}} \right) \times 100$$

Amount of waste
BM > solution >> SPPS

Toxicity of reagents
BM > solution >> SPPS
Due to DMF

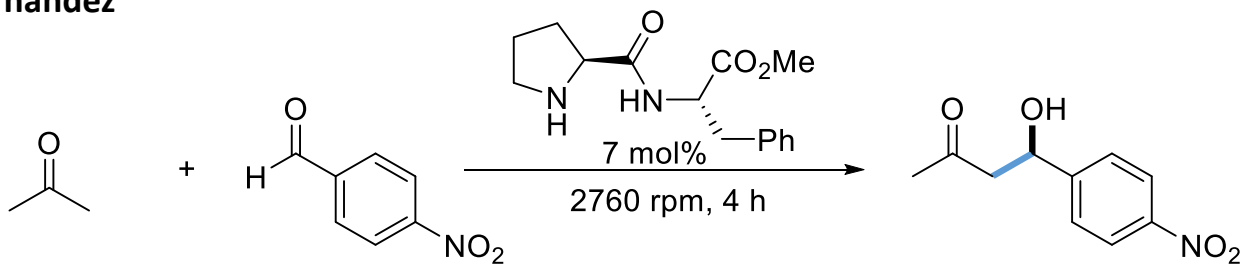
Cumulative Number of Hazard Phrases

	Ball-Mill (BM)	Solution	Solid phase
Coupling	**4**	11	12
Deprotection with TFA	**3**	9	-
Deprotection with Pip	-	-	11

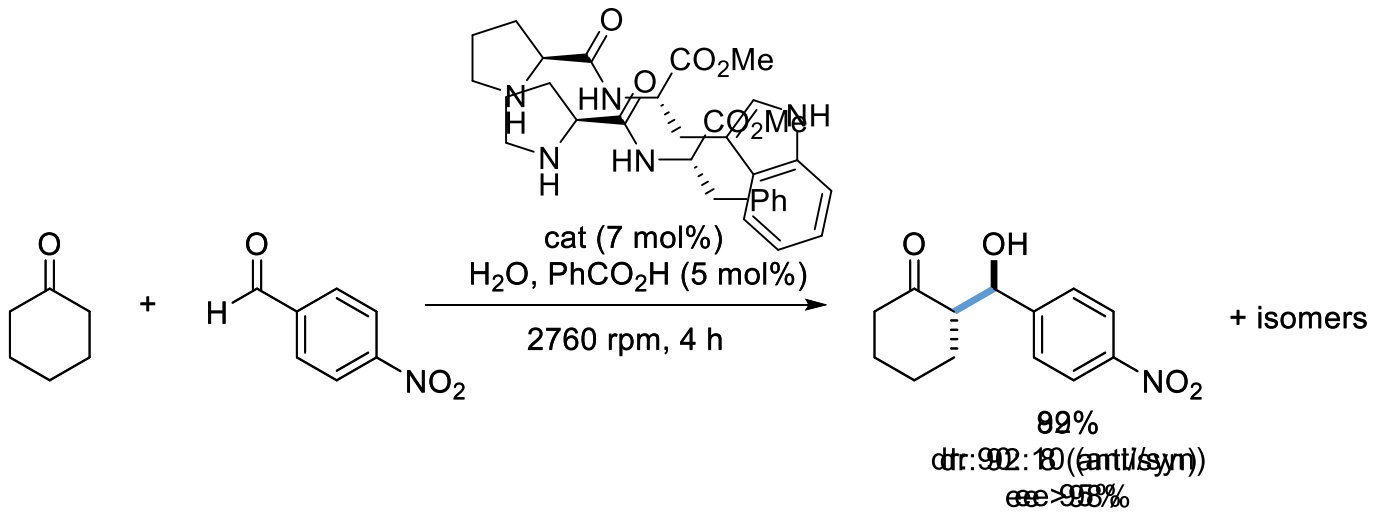
Beilstein J.Org. Chem. 2017, 13,2087

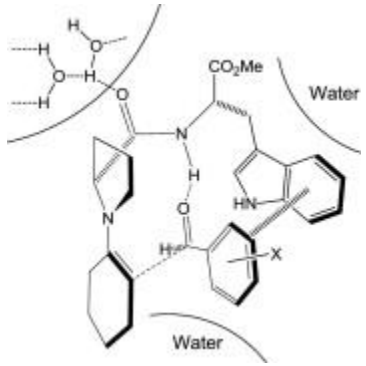
Catalyst for enantioselective reactions

Hernandez



BM	Solution
ketone 2 equiv 4 h 82% ee: 69%	Excess ketone 27 equiv 24 -48 h 88% ee: 28%





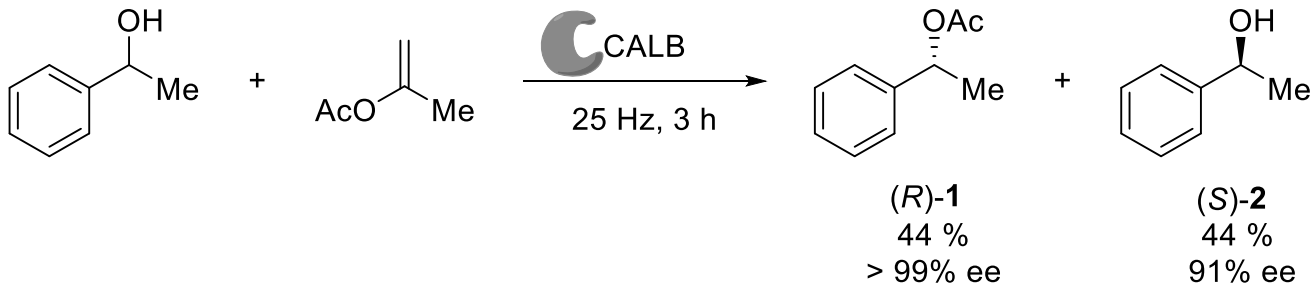
- Reinforcement non covalent int.
- Maximizing π-π stacking

a) J.Org.Chem. 2011, 76, 1464. b). Tetrahedron 2011, 67,695.

Kinetic Resolution

Enzymatic resolution of 2nd alcohol

Hernandez 2016



(*R*)-**1**
44 %
> 99% ee

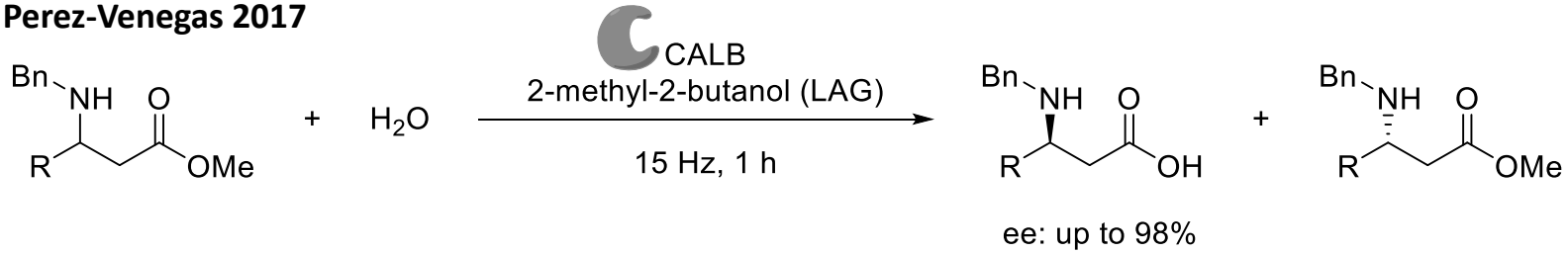
(*S*)-**2**
44 %
91% ee

Recyclability of immobilized CALB

Cycle	Conv. [%]	ee (*R*)-1	ee (*S*)-2
1	49	> 99	91
2	42	> 99	64
3	37	> 99	51
4	27	99	37

Enzymatic resolution of β-amino esters

Perez-Venegas 2017



ee: up to 98%

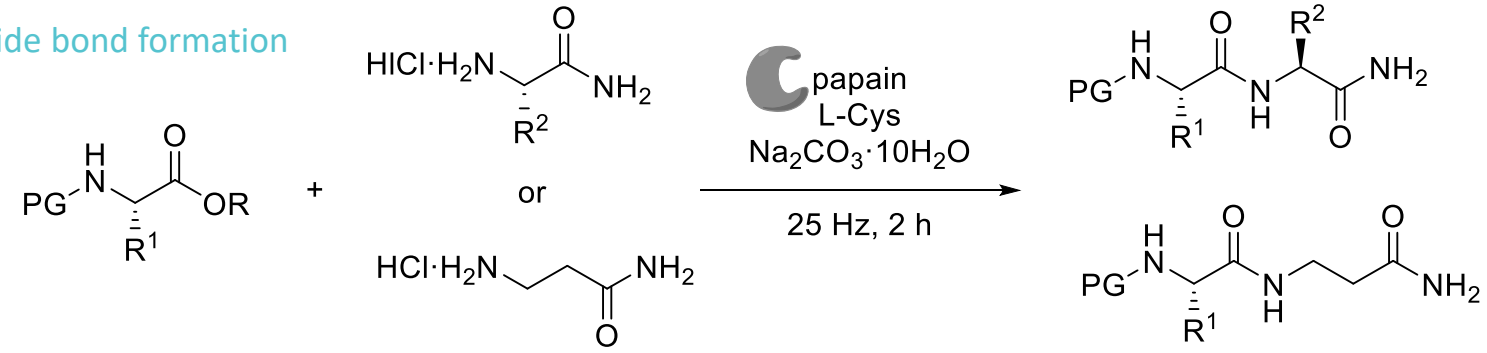
- Immobilized enzyme
- Recovery of the lipase
- ee up to 99%

a) ChemCatChem 2016, 8,1769. b). Beilstein J.Org. Chem. 2017, 13,1728.

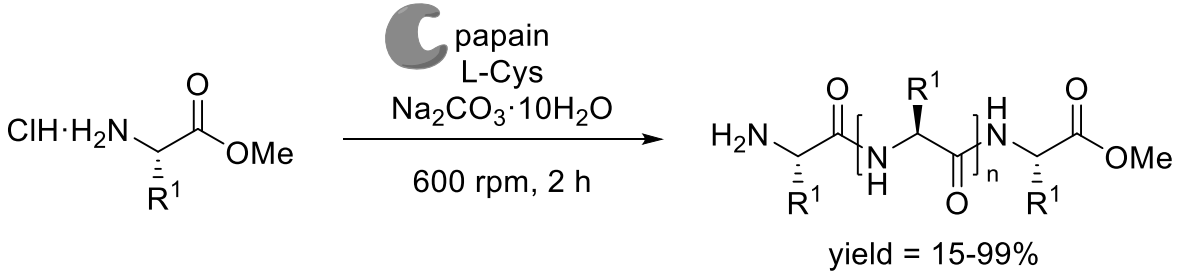
Papain-catalysed mechanochemical synthesis

Hernandez

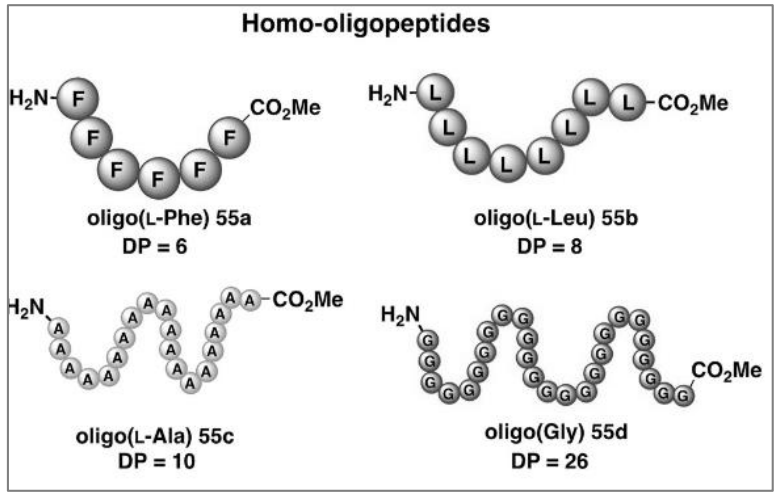
Peptide bond formation



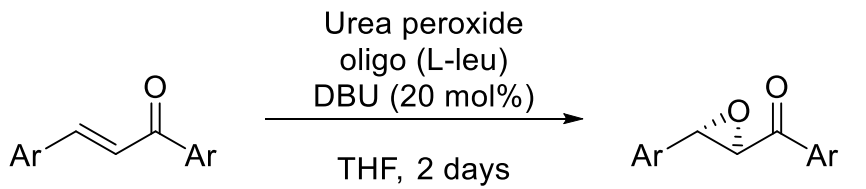
Homo-oligomerization of amino acids



yield = 15-99%



Application: Asymmetric Julia-Colonna epoxidation



yield = up to 85%
ee= 45-92%

a) Green Chem. 2017, 19,2620. b). GreenChem. 2018, 20,1262.

Conclusion

Advantages of mechanochemistry
- Greener chemistry
- Better Selectivity
- New reactivity

Amino Acids → Peptide → Enzymes

Mechanochemistry of Amino Acids

- Strecker reaction
- Unnatural amino acids (α–functionalization or unsaturated)
- Case study: heating, photochemistry and BM

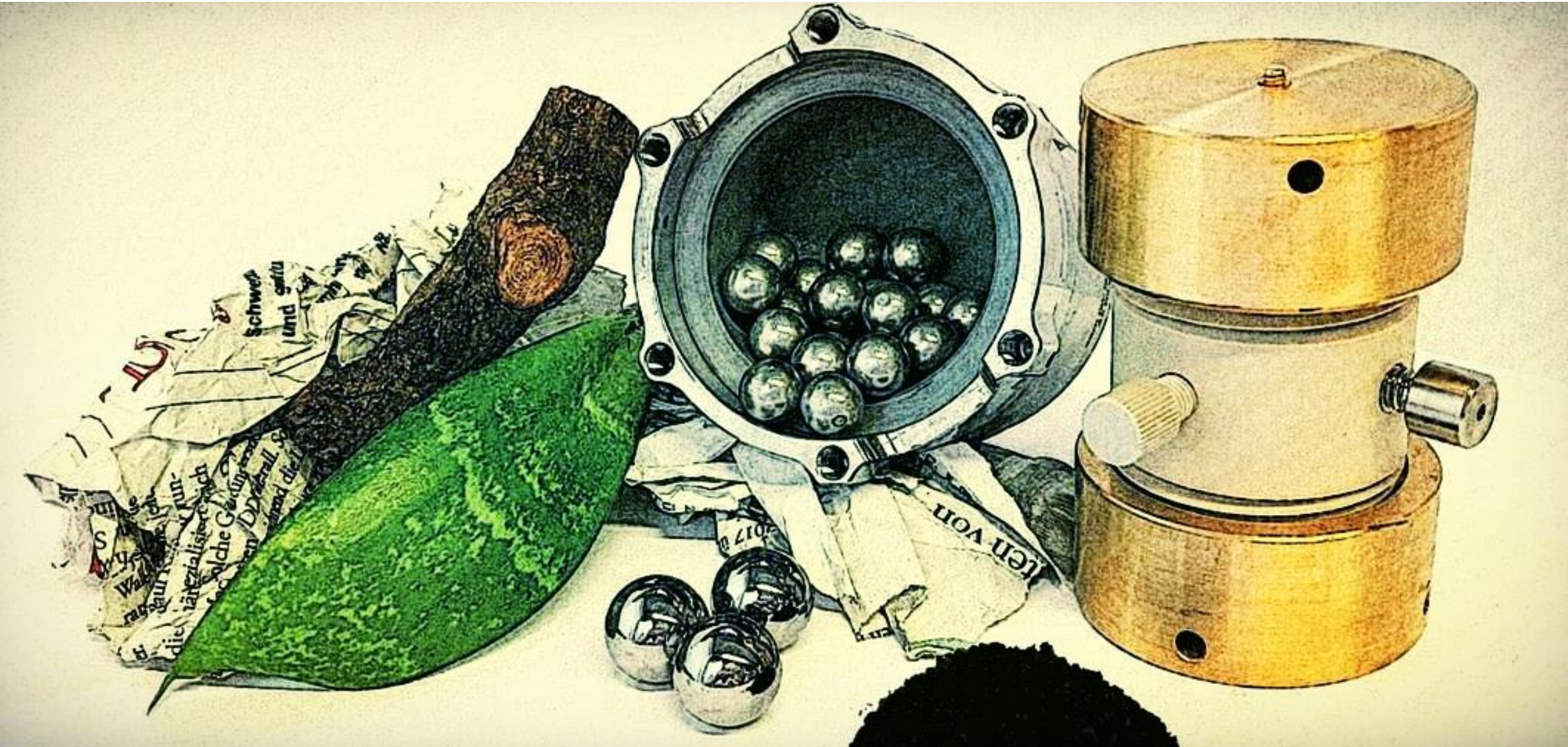
Mechanochemistry of Peptide Bonds

- UNCA or EDC coupling
- Up to pentapeptides
- Case study: between BM, solution and SPPS

Catalysis by Peptides and Enzymes

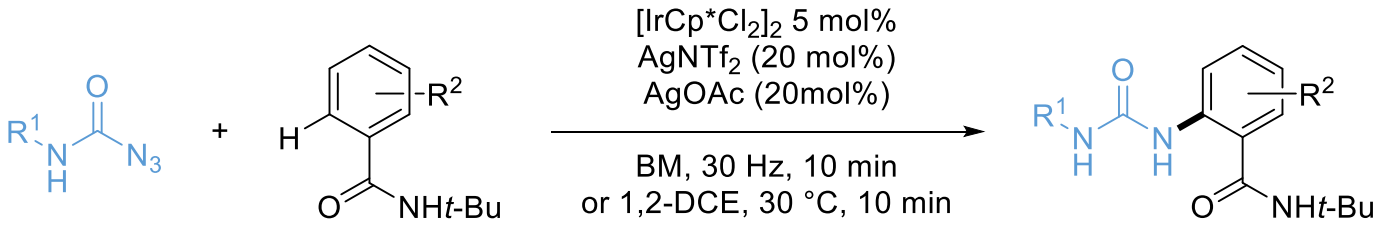
- Lipase for resolution
- Protease for peptide synt
- Recycling of peptide and enzymes

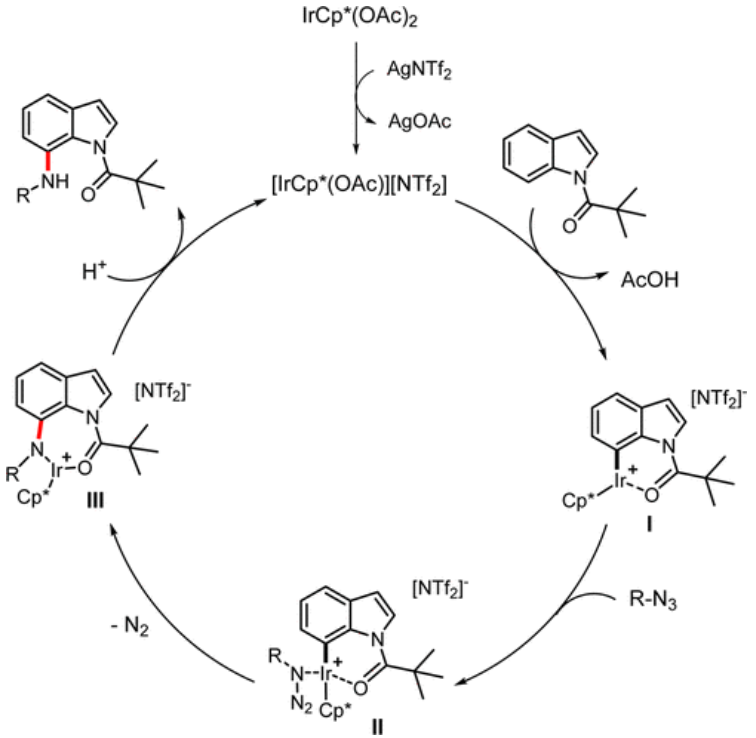
Thank you for your attention



Question 1

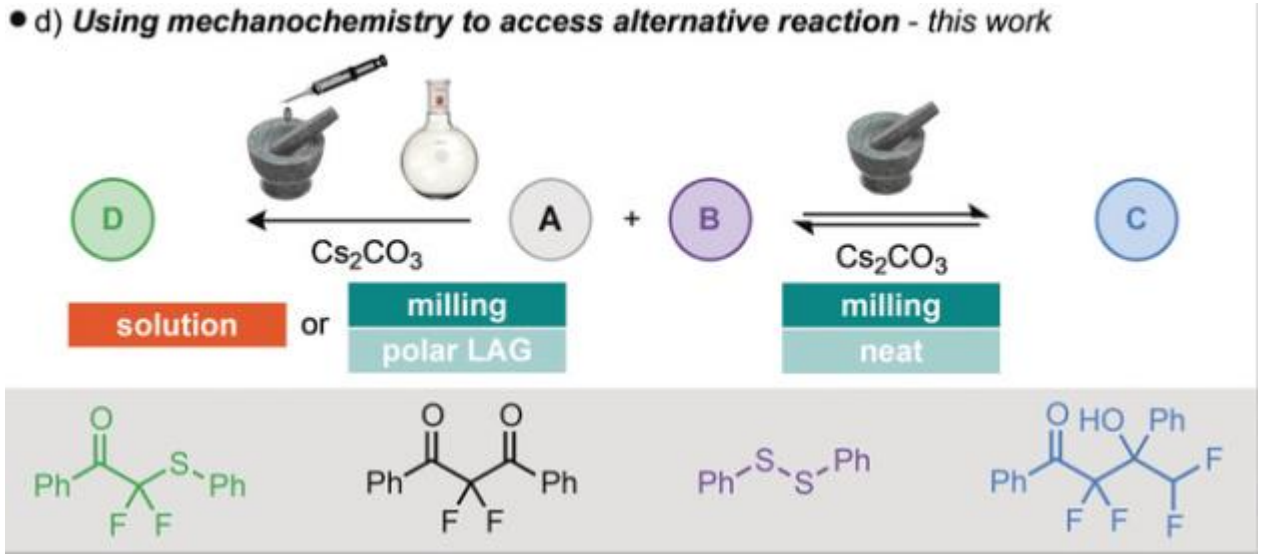
Mechanism?

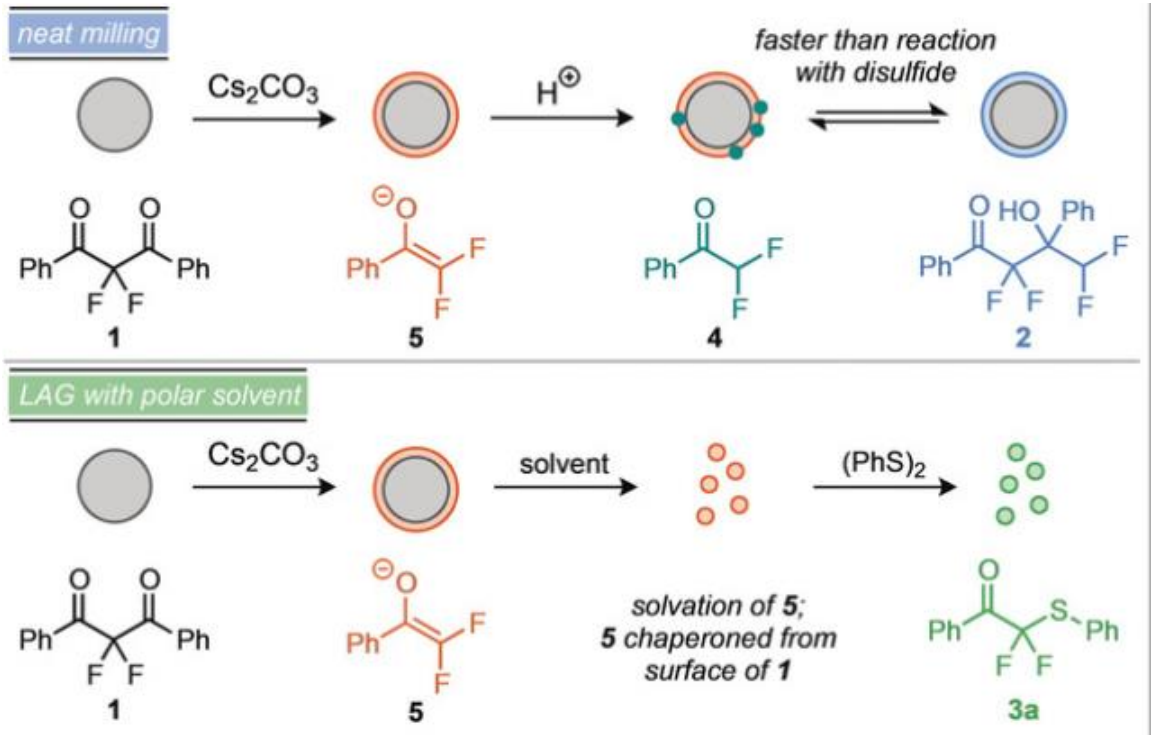




a)

Influence of LAGs- Can you comment of the results?





a) Angew.Chem.Int.Ed.2018,57,16104.

Photocatalytic Late-stage C-H Functionalization

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Laboratory of Catalysis and Organic Synthesis
École Polytechnique Fédérale de Lausanne

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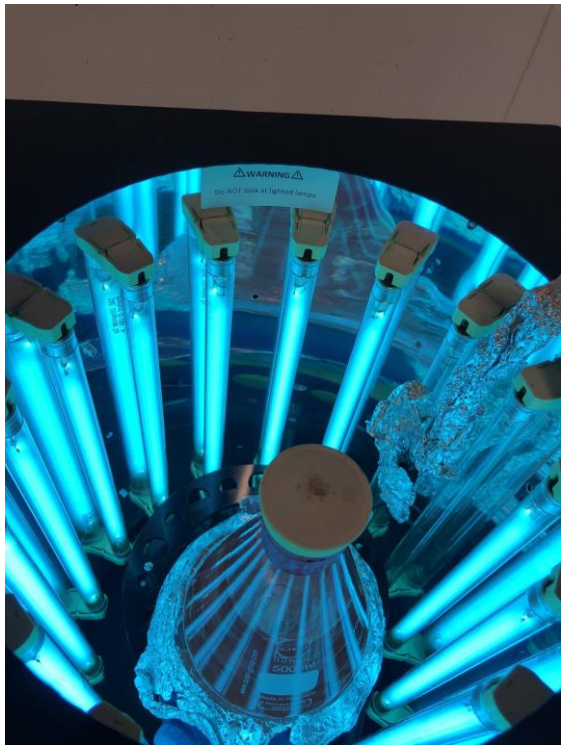
Frontiers in Chemical Synthesis: Towards Sustainable Chemistry
15.05.2023

Photochemistry

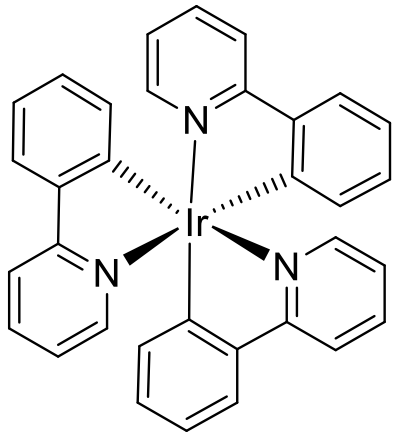
The study of chemical reactions, isomerizations and physical behavior that may occur under the influence of visible and/or ultraviolet light is called ***Photochemistry.***



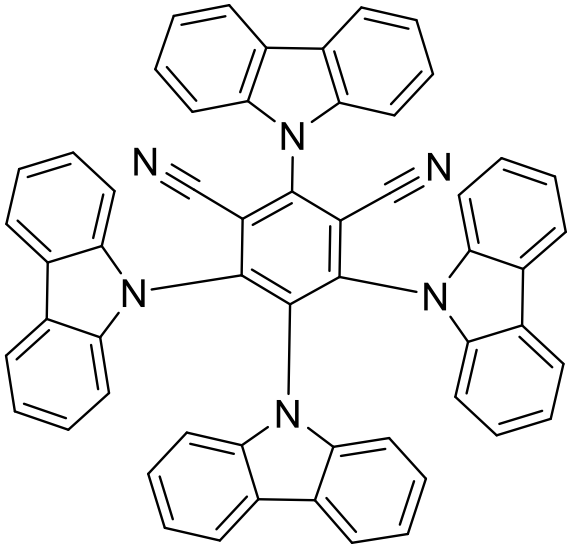
Modern photochemical reaction setups

Reaction modes:

1. Excitation of electron donor-acceptor complexes
2. Single-electron transfer (SET)
3. Energy transfer (EnT)

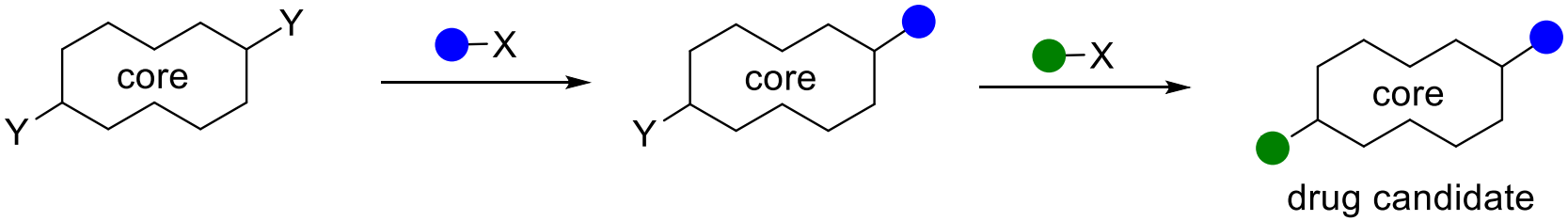


fac-Ir(ppy)$_3$



4CzIPN

Late-stage functionalization



Late-stage functionalization is a desired chemoselective transformation on a complex molecule to provide at least one analog in sufficient quantity and purity for a given purpose without the necessity for installation of a functional group that exclusively serves the purpose to enable said transformation

Advantages:

- Access to complex products, which are tough to access by other means
- Rapid access to drug analogs for SAR

Requirements:

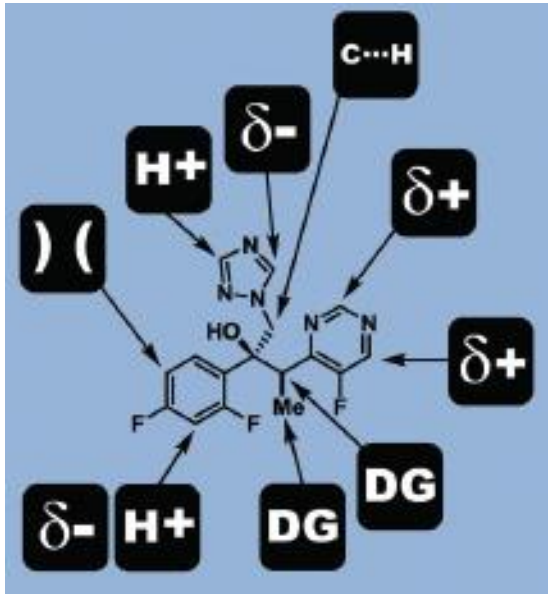
- Good functional group tolerance
- Reasonable selectivity (several products can be good)

P. Bellotti, H.-M. Huang, T. Faber, F. Glorius, *Chem. Rev.* **2023**, *123*, 4237–4352.

Site-selectivity in late-stage C-H functionalizations

Site selectivity of C-H functionalization reactions strongly depends from reaction used:

1. H-abstraction or insertion (usually the weakest C-H bond) C···H
2. Deprotonation (most acidic) H+
3. Addition-elimination at electrophilic carbon δ+
4. Addition-elimination at nucleophilic carbon δ-
5. Directed C-H activation DG
6. Guided by sterics) (



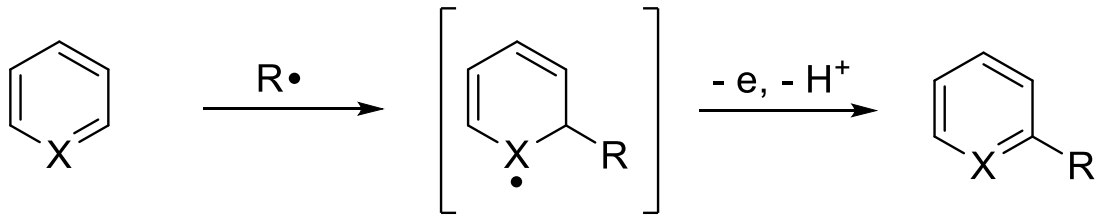
Possible C-H functionalization sites of voriconazole

T. Cernak, K. D. Dykstra, S. Tyagarajan, P. Vachal, S. W. Krska, *Chem. Soc. Rev.* **2016**, *45*, 546–576.

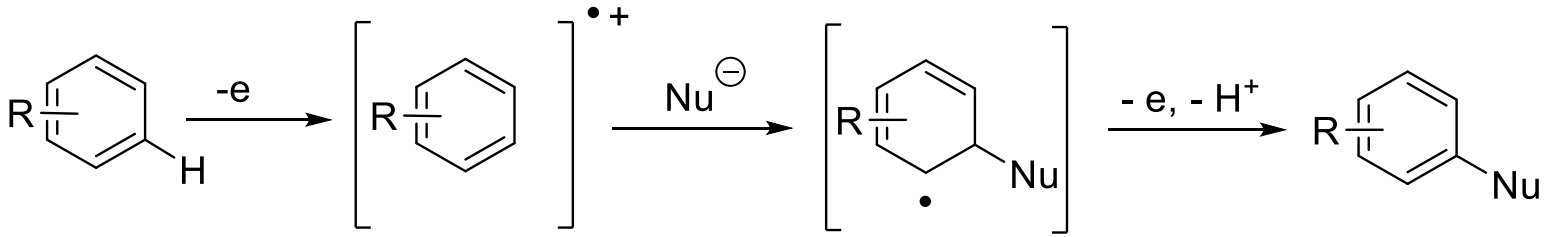
Photocatalytic C(sp^2)-H functionalizations

Three main mechanism types are operable (HAT is unaccessible):

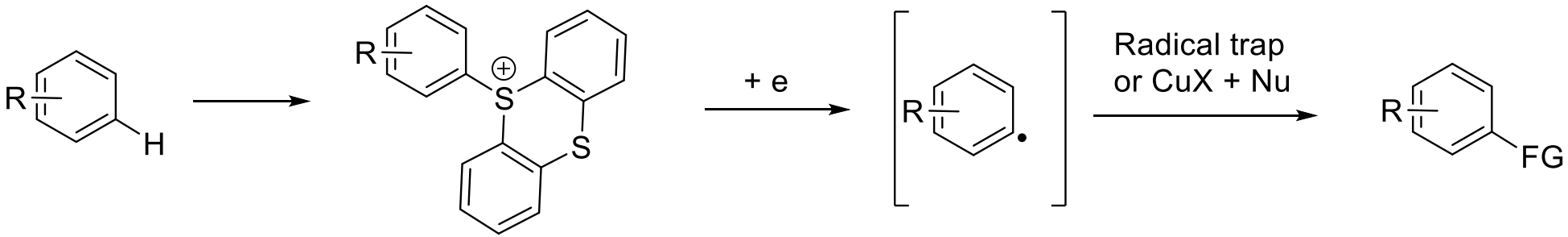
1. Minisci-type reactions



2. Oxidation of (Het)Ar, followed by addition of nucleophile



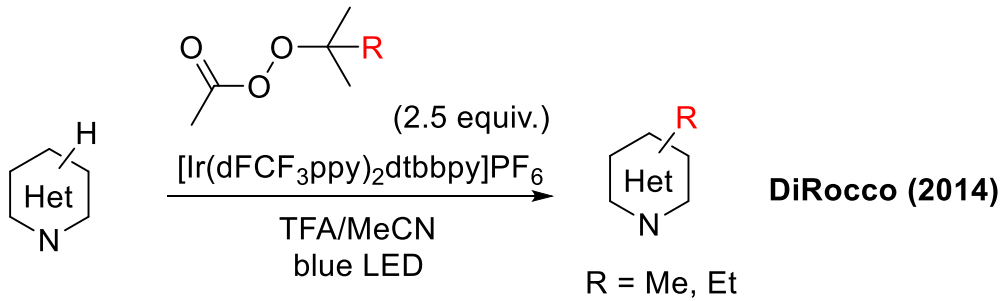
3. Thianthrenation/photoinduced functionalization



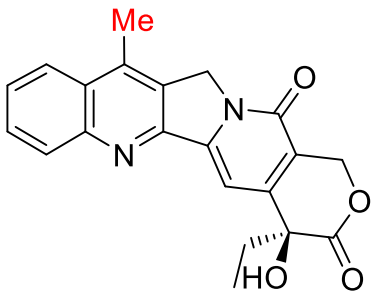
P. Bellotti, H.-M. Huang, T. Faber, F. Glorius, *Chem. Rev.* **2023**, *123*, 4237–4352.

Minisci-type reactions: polarity-matching

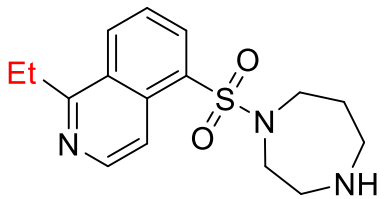
Nucleophilic radical additions:



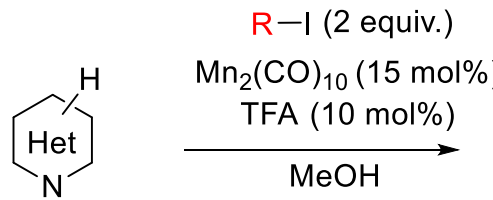
DiRocco (2014)



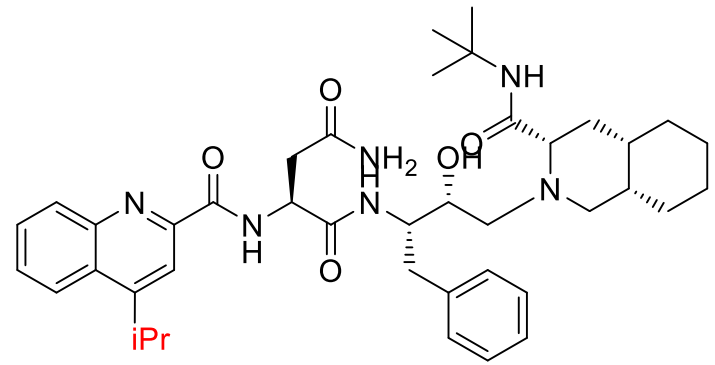
77%
from camptothecin



56%
from Fasudil



Fadeyi, Frenette (2017)

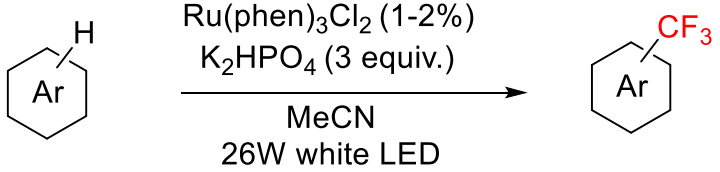


31%
from Saquinavir

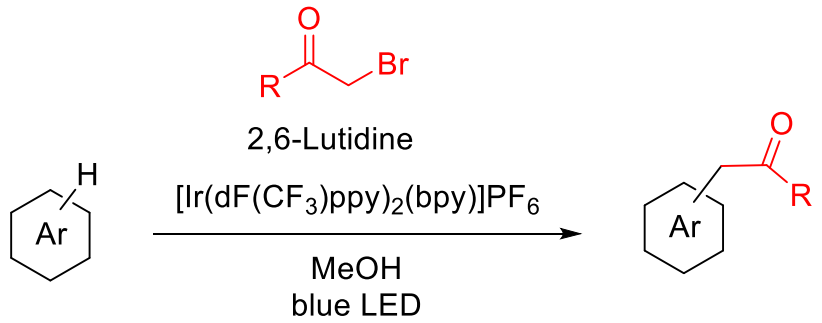
1) DiRocco, D. A.; Dykstra, K.; Krska, S.; Vachal, P.; Conway, D. V.; Tudge, M. *Angew. Chem. Int. Ed.* **2014**, *53*, 4802−4806. 2) Nuhant, P.; Oderinde, M. S.; Genovino, J.; Juneau, A Allais, C.; Chinigo, G. M.; Choi, C.; Sach, N. W.; Bernier, L.; Fobian, Y. M.; Bundesmann, M. W.; Khunte, B.; Frenette, M.; Fadeyi, O. O. *Angew. Chem. Int. Ed.* **2017**, *56*, 15309−153

Minisci-type reactions: polarity-matching

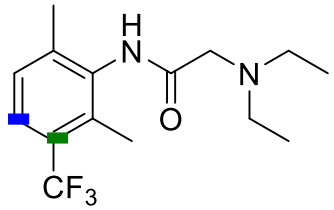
Electrophilic radical additions:



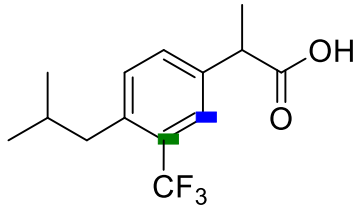
MacMillan (2011)



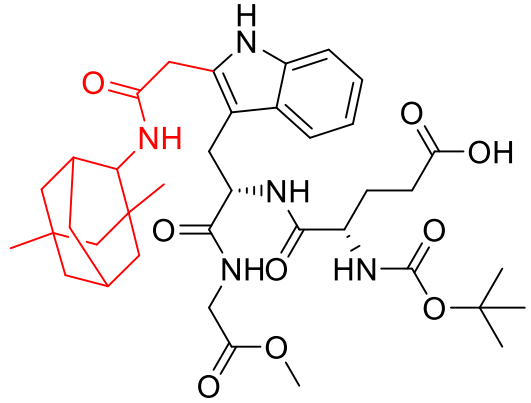
Paixao (2021)



78% (2:1 r.r)
from lidocaine



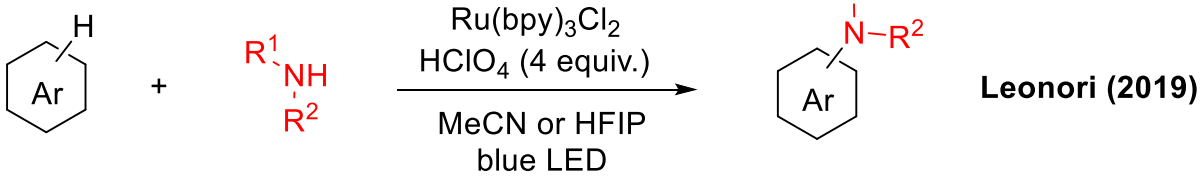
78% (1.4:1 r.r)
from ibuprofen



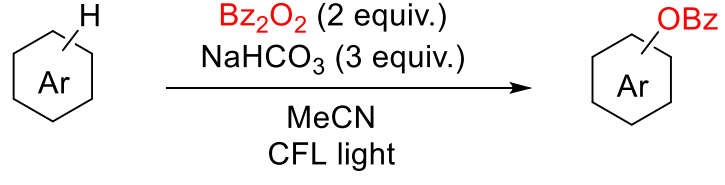
51%

1) D. A. Nagib, D. W. C. MacMillan, *Nature* **2011**, *480*, 224–228. 2) R. N. Lima, J. A. C. Delgado, D. I. Bernardi, R. G. S. Berlinck, N. Kaplaneris, L. Ackermann, M. W. Paixão, *Chem. Commun.* **2021**, *57*, 5758–5761.

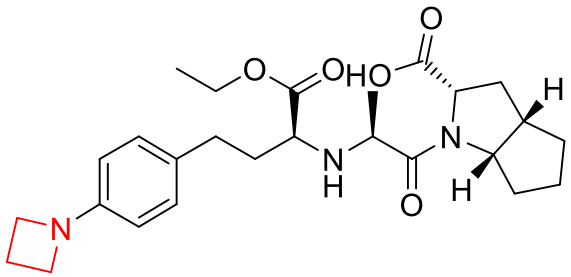
Minisci-type reactions: heteroatom-centered radicals



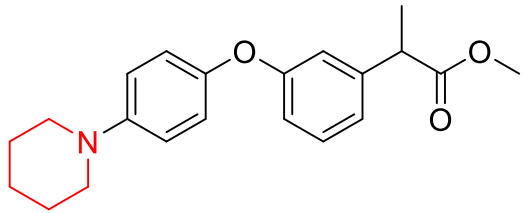
Leonori (2019)



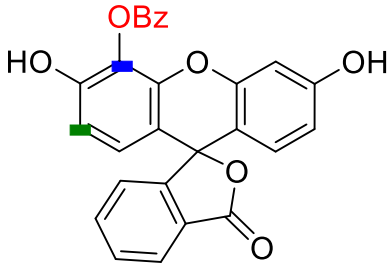
Li (2012)



59%
from ramipril



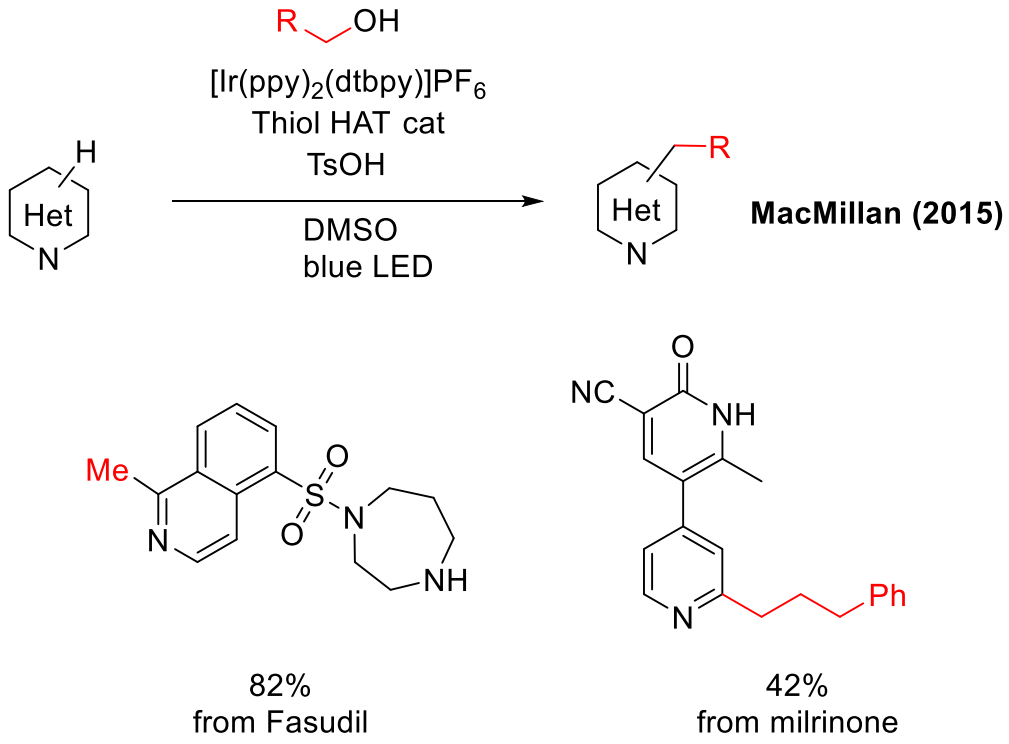
68%
from fenoprofen

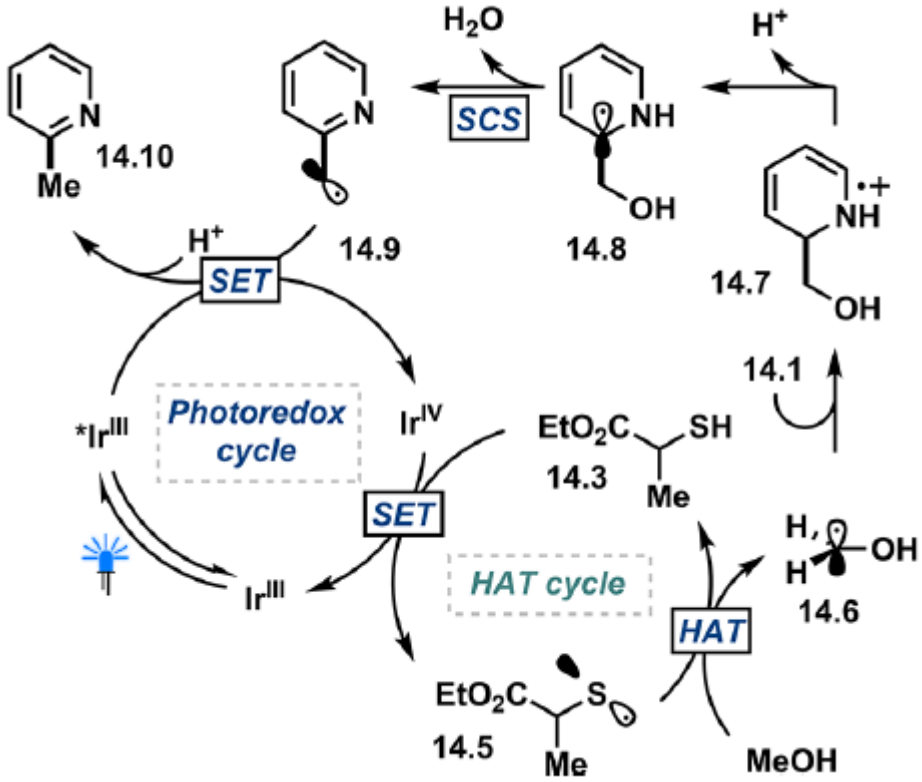


51% (2.19:1 rr)
from fluorescein

1) A. Ruffoni, F. Juliá, T. D. Svejstrup, A. J. McMillan, J. J. Douglas, D. Leonori, *Nat. Chem.* **2019**, *11*, 426–433. 2) H. Rao, P. Wang, C.-J. Li, *Eur. J. Org. Chem.* **2012**, *2012*, 6503–6507.

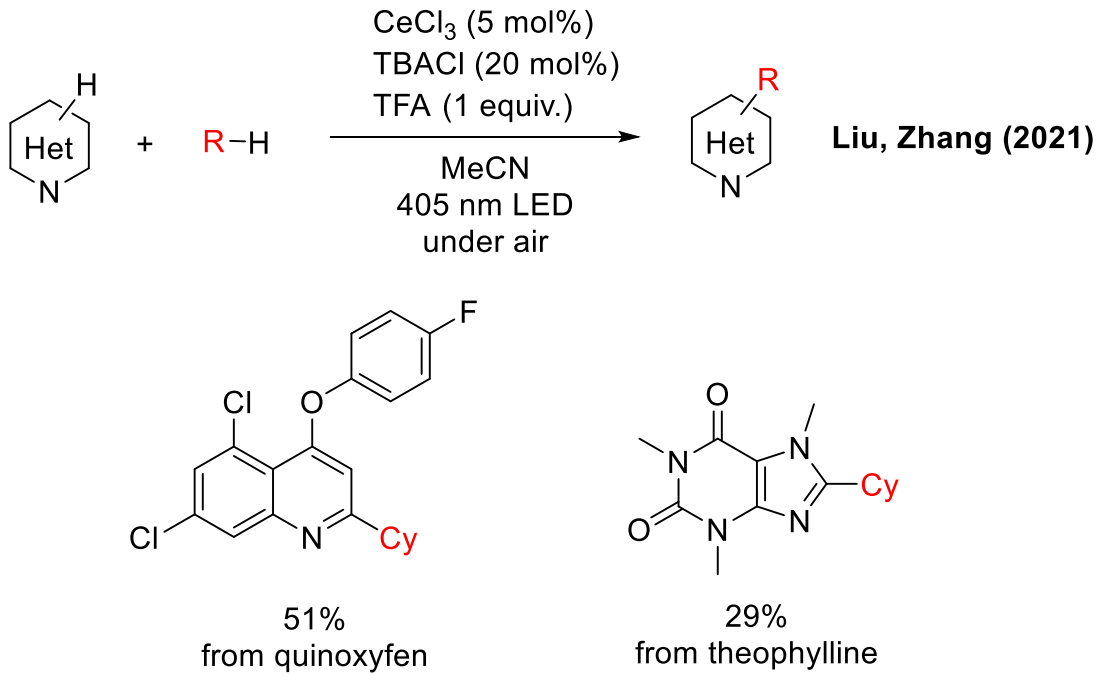
Minisci-type reactions: spin-center shift

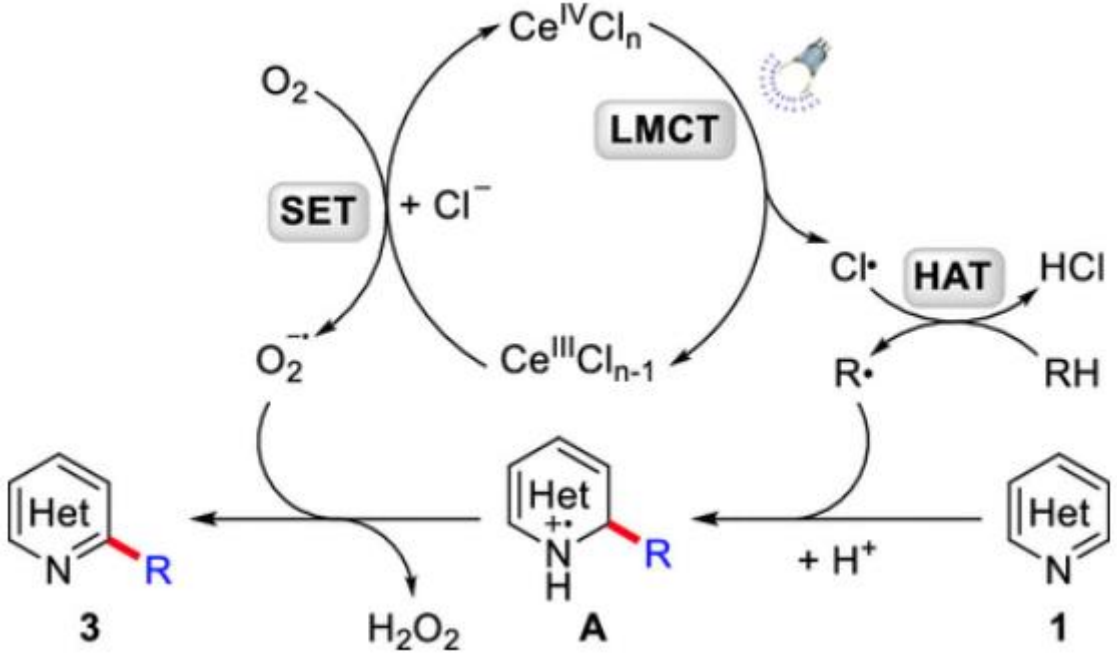




J. Jin, D. W. C. MacMillan, *Nature* **2015**, *525*, 87–90.

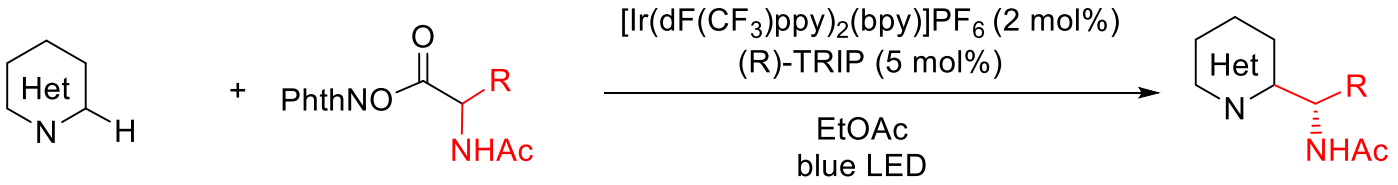
Minisci-type reactions: dehydrogenative reactions



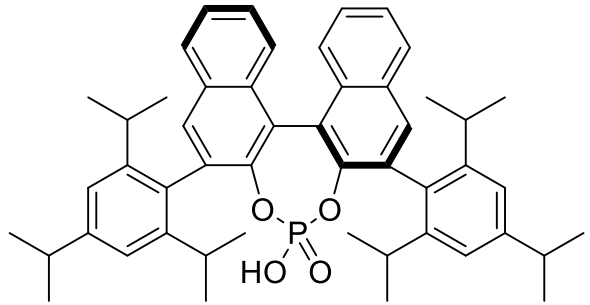


J. Xu, H. Cai, J. Shen, C. Shen, J. Wu, P. Zhang, X. Liu, *J. Org. Chem.* **2021**, *86*, 17816–17832.

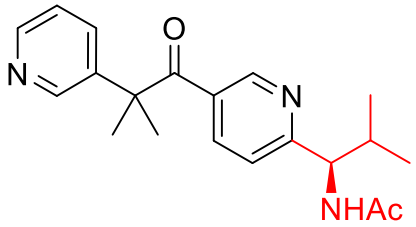
Minisci-type reactions: enantioselective variation



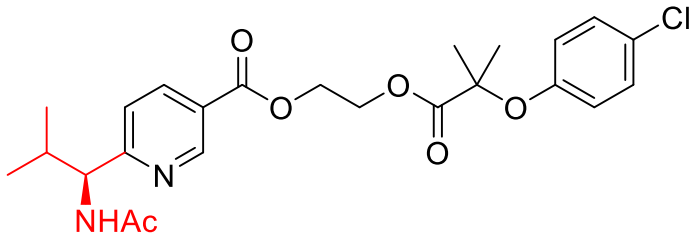
Phipps (2018)



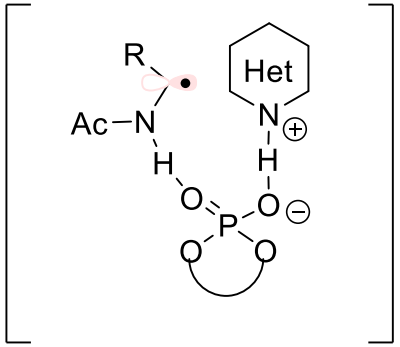
(R)-TRIP



70% (95% ee)
from metyrapone

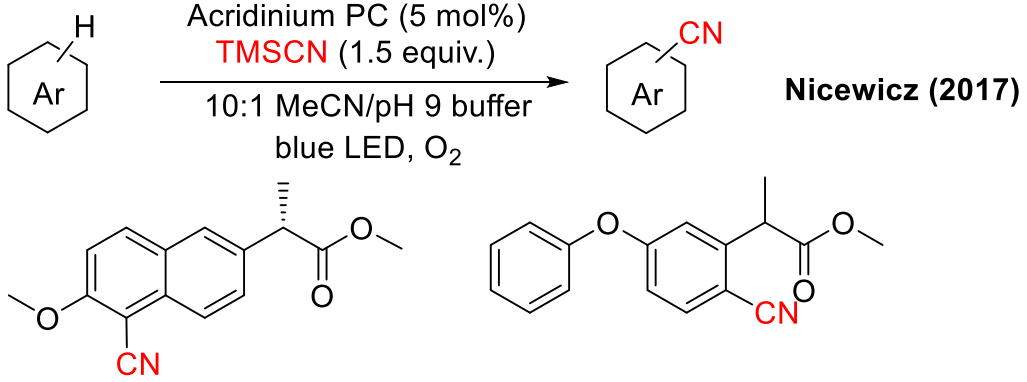


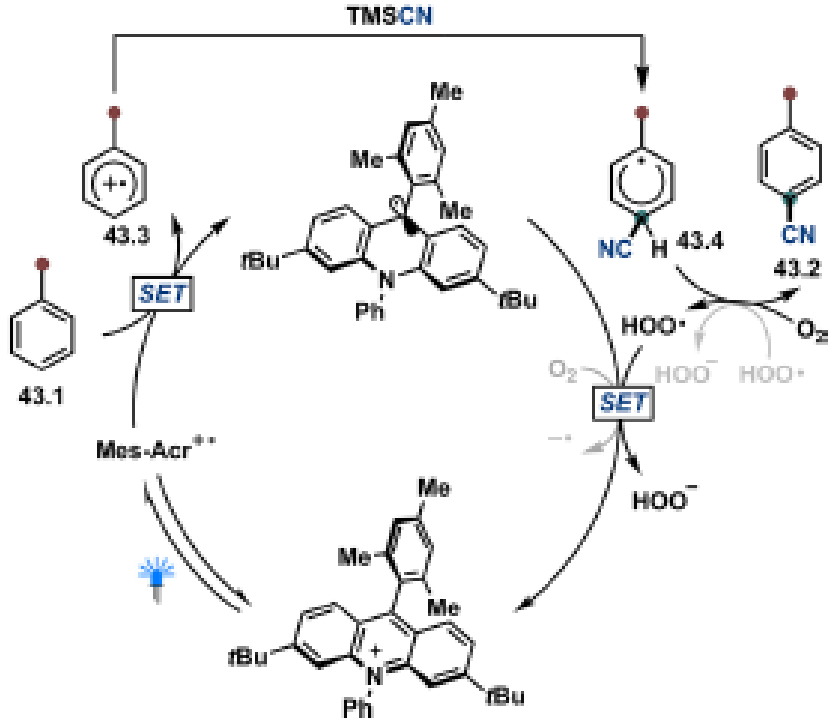
86% (93% ee)
from etofibrate

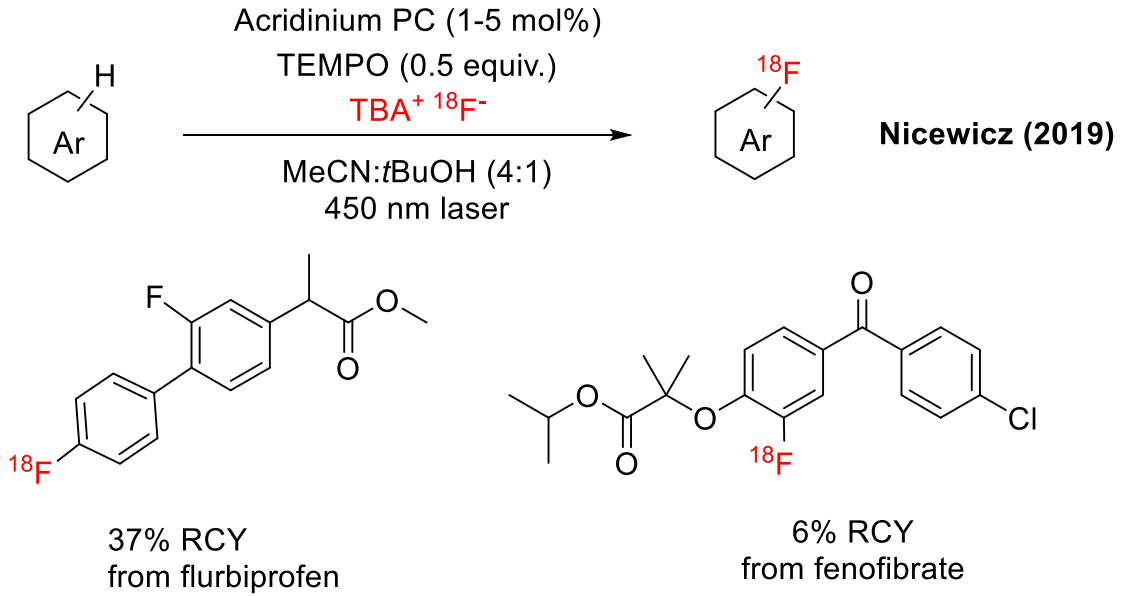


R. S. J. Proctor, H. J. Davis, R. J. Phipps, *Science* **2018**, *360*, 419–422.

Oxidation of aromatic compounds followed by nucleophilic attack

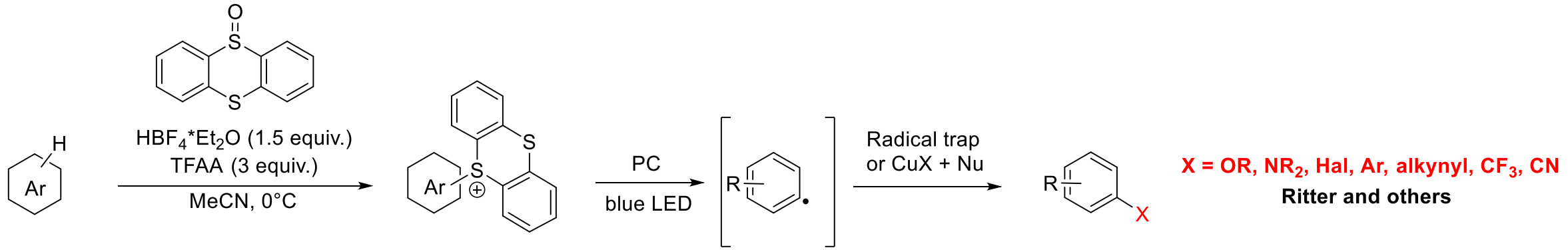


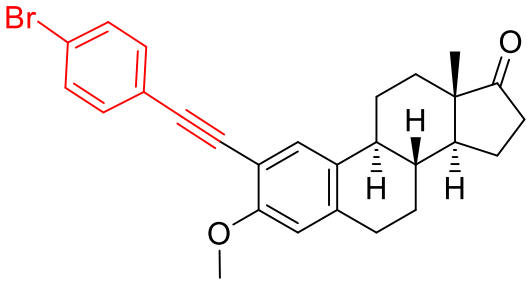




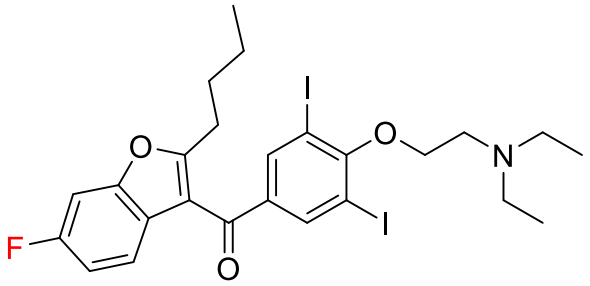
1) J. B. McManus, D. A. Nicewicz, *J. Am. Chem. Soc.* **2017**, *139*, 2880–2883. 2) W. Chen, Z. Huang, N. E. S. Tay, B. Giglio, M. Wang, H. Wang, Z. Wu, D. A. Nicewicz, Z. Li, *Science* **2019**, *364*, 1170–1174.

Thianthrenation/photoinduced functionalization

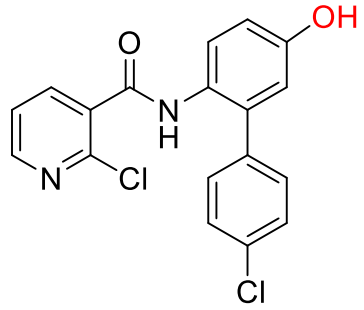




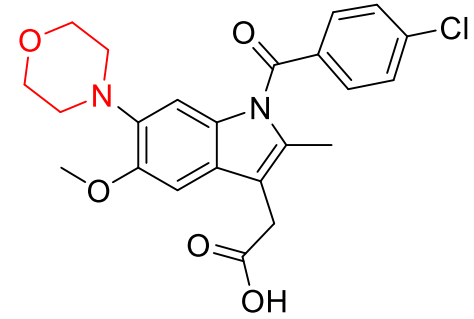
67%
from estrone



35%
from amiodarone



57%
from boscalid



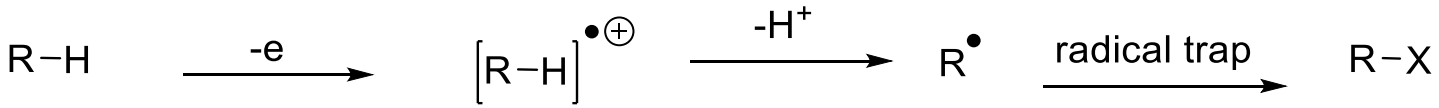
44%
from indomethacin

F. Berger, M. B. Plutschack, J. Riegger, W. Yu, S. Speicher, M. Ho, N. Frank, T. Ritter, *Nature* **2019**, *567*, 223–228.

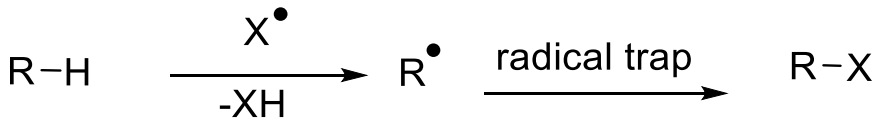
Photocatalytic C(sp^3)-H functionalizations

Two main mechanism types are operable:

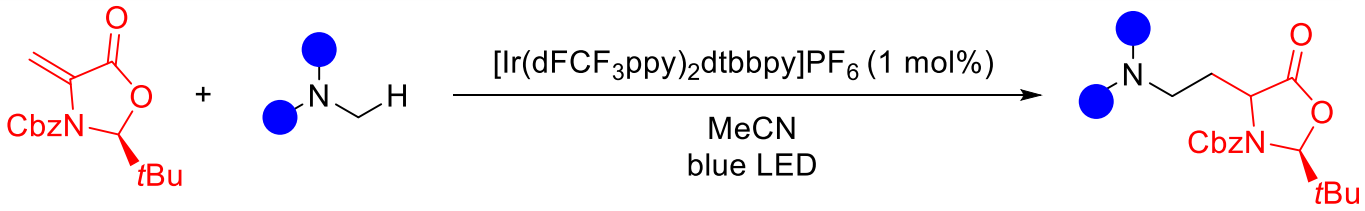
1. Single-electron oxidation/deprotonation



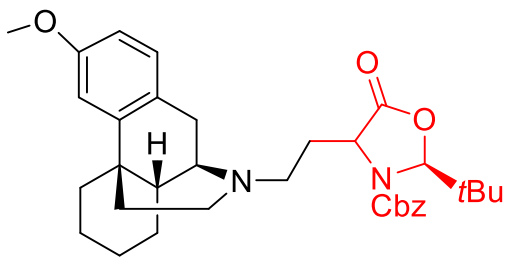
2. Hydrogen atom abstraction (HAT)



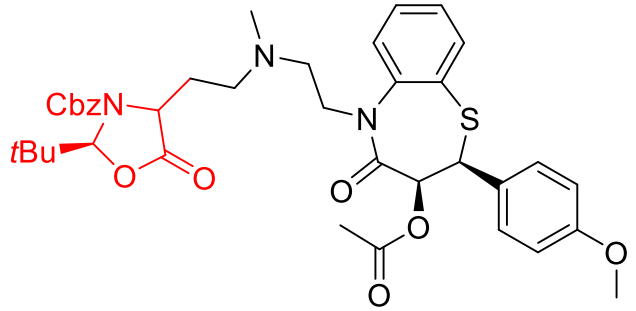
α-Amino radicals by oxidation/deprotonation



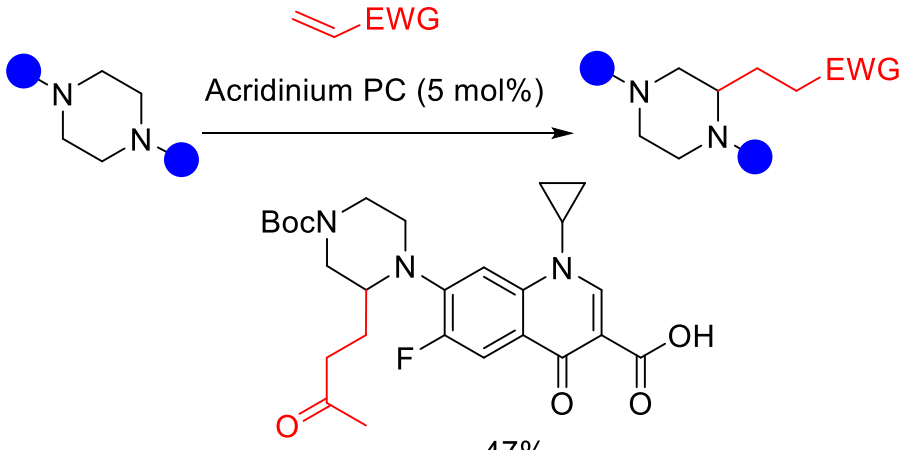
Jui (2018)



64%
from dextromethorphan

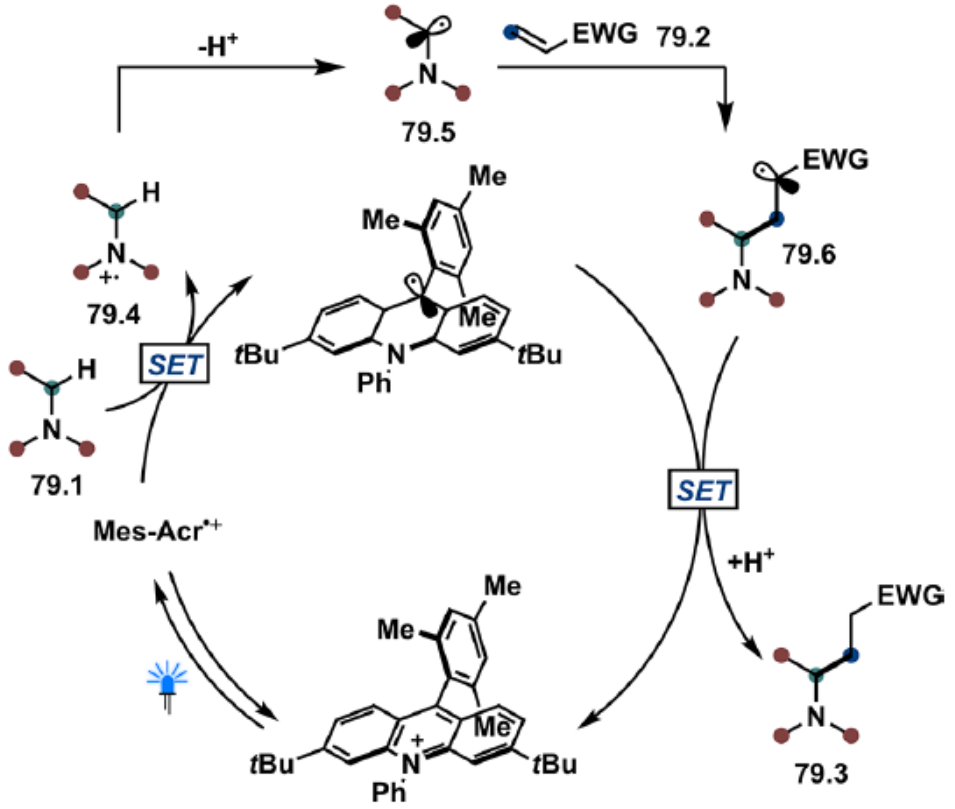


62%
from diltiazem



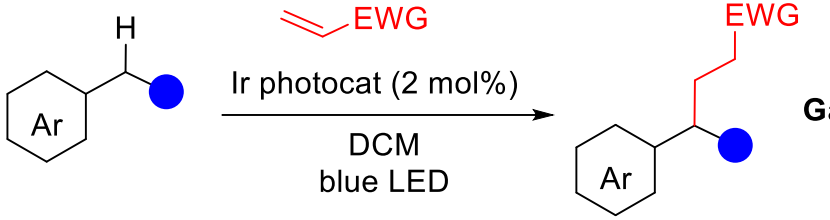
Nicewicz (2020)

47%
from ciprofloxacin

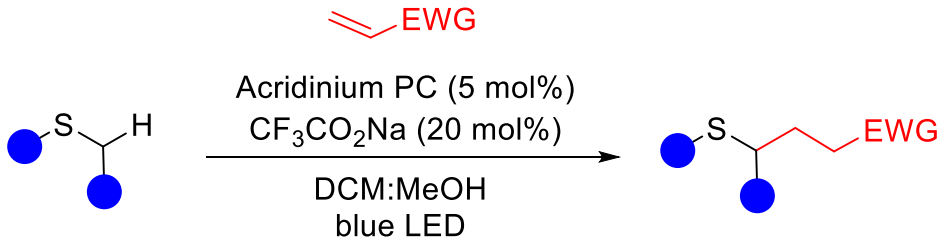


1) R. A. Aycock, C. J. Pratt, N. T. Jui, *ACS Catal.* **2018**, *8*, 9115–9119. 2) J. B. McManus, N. P. R. Onuska, M. S. Jeffreys, N. C. Goodwin, D. A. Nicewicz, *Org. Lett.* **2020**, *22*, 679–683.

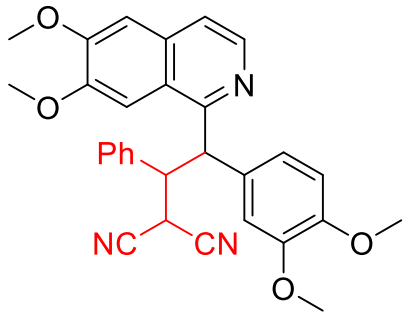
Oxidation/deprotonation: other examples



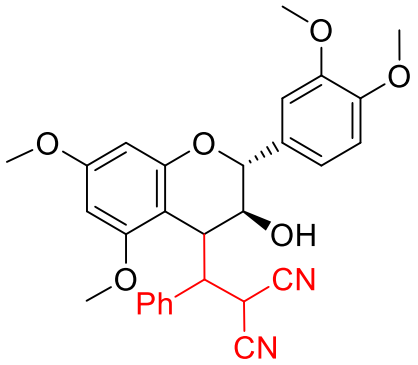
Garcia-Mancheno (2021)



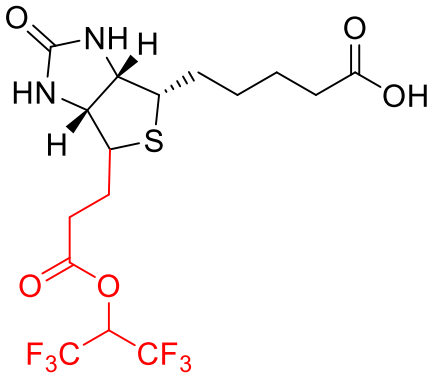
Alfonzo, Hande (2020)



85%
from papaverine



58%
from cathecin



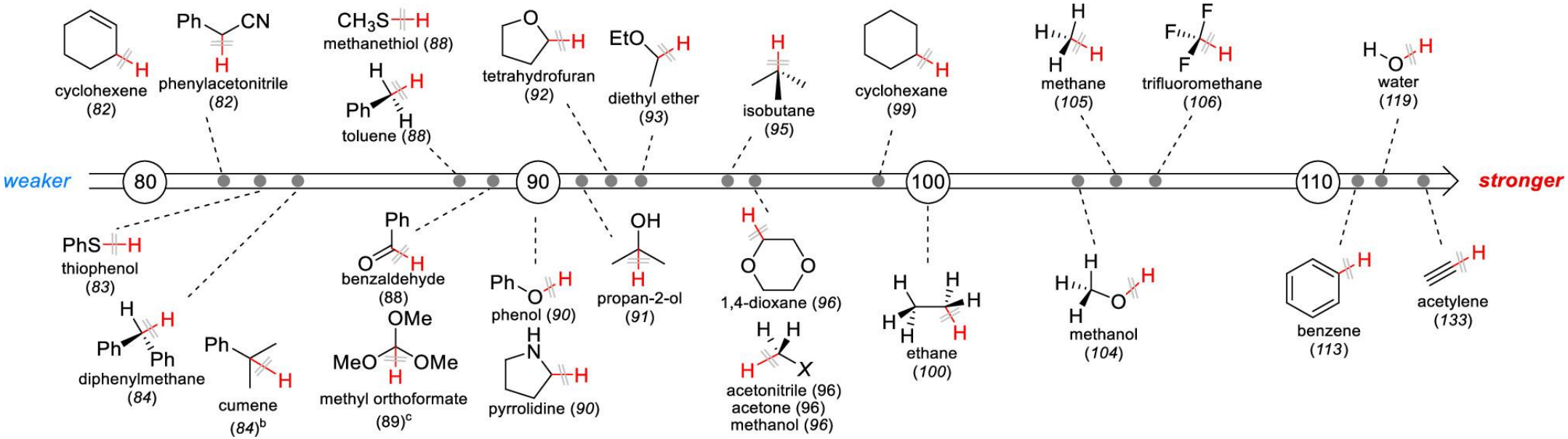
69%
from biotin

1) T. Brandhofer, M. Stinglhamer, V. Derdau, M. Méndez, C. Pöverlein, O. G. Mancheño, *Chem. Commun.* **2021**, *57*, 6756–6759. 2) E. Alfonzo, S. M. Hande, *ACS Catal.* **2020**, *10*, 12590–12595.

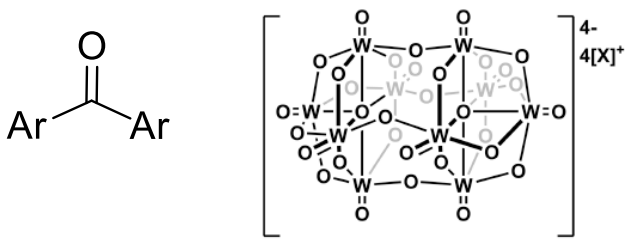
HAT-based methods

Factors influencing HAT:

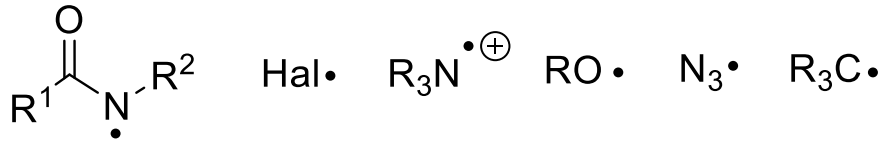
1. BDE of C-H bond
2. Polarity match between HAT donor and acceptor



Commonly used hydrogen abstractors:



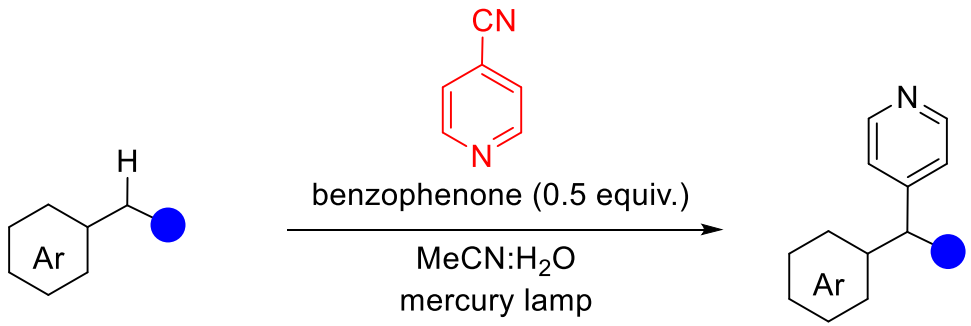
direct HAT



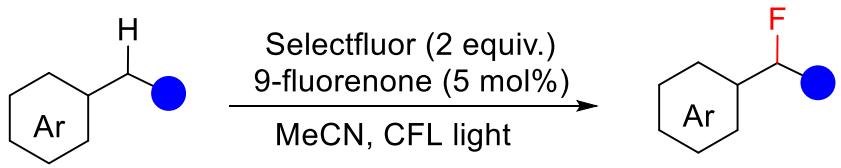
indirect HAT

L. Capaldo, D. Ravelli, M. Fagnoni, *Chem. Rev.* **2022**, *122*, 1875–1924.

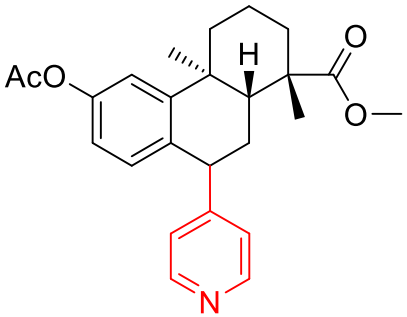
Functionalization of benzylic C-H bonds



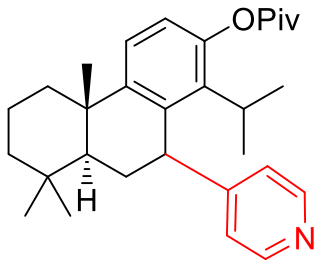
Inoue (2013)



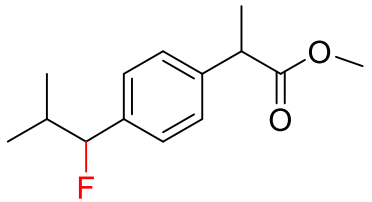
Chen (2013)



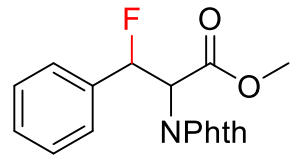
71%
from podocarpic acid



72%
from totarol



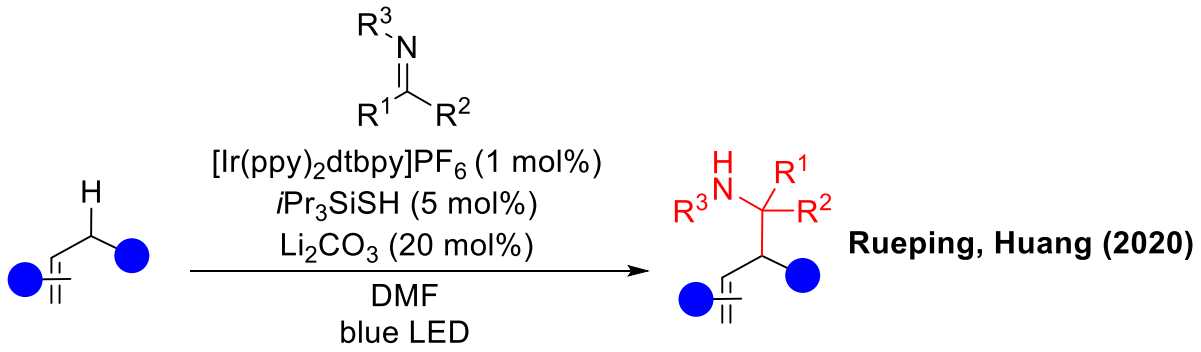
64%
from ibuprofen



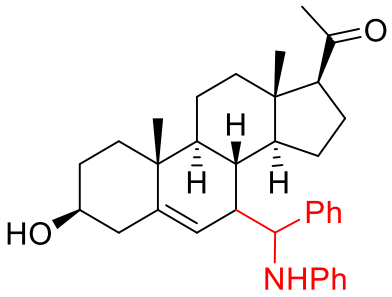
52%
from phenylalanine

1) T. Hoshikawa, M. Inoue, *Chem. Sci.* **2013**, *4*, 3118–3123. 2) J.-B. Xia, C. Zhu, C. Chen, *J. Am. Chem. Soc.* **2013**, *135*, 17494–17500.

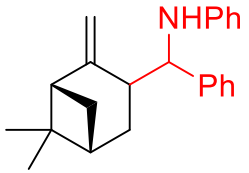
Functionalization of allylic C-H bonds



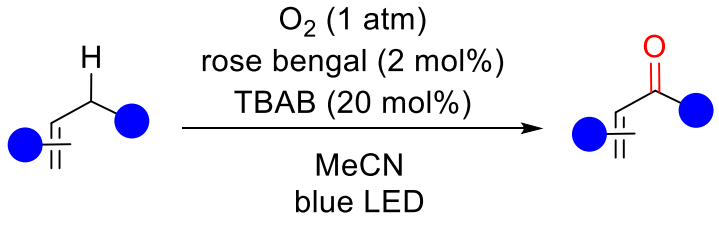
Rueping, Huang (2020)



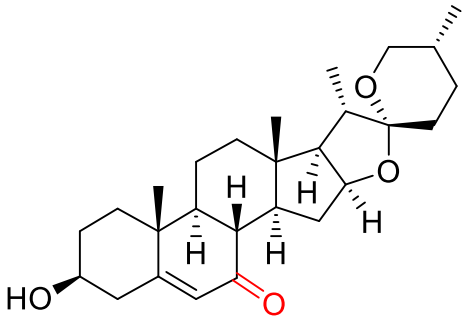
79%
from pregnenolone



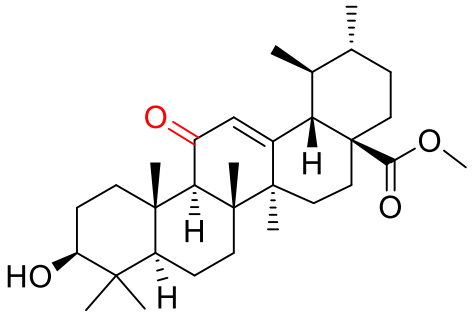
69%
from β-pinene



Cai (2022)



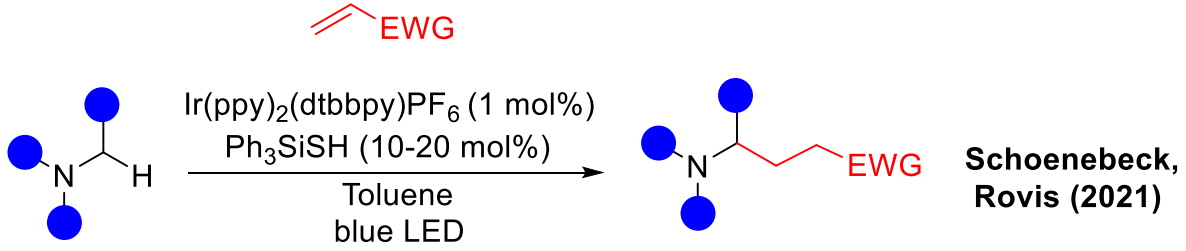
89%
from diosgenin



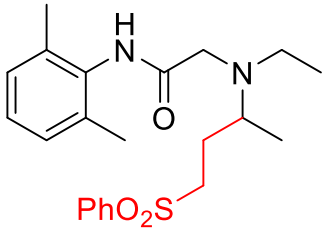
73%
from ursolic acid

1) J. Jia, R. Kancherla, M. Rueping, L. Huang, *Chem. Sci.* **2020**, *11*, 4954–4959. 2) C. Liu, H. Liu, X. Zheng, S. Chen, Q. Lai, C. Zheng, M. Huang, K. Cai, Z. Cai, S. Cai, *ACS Catal.* **2022**, *12*, 1375–1381.

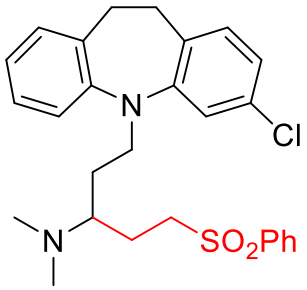
Functionalization of α-Amino C-H bonds by HAT



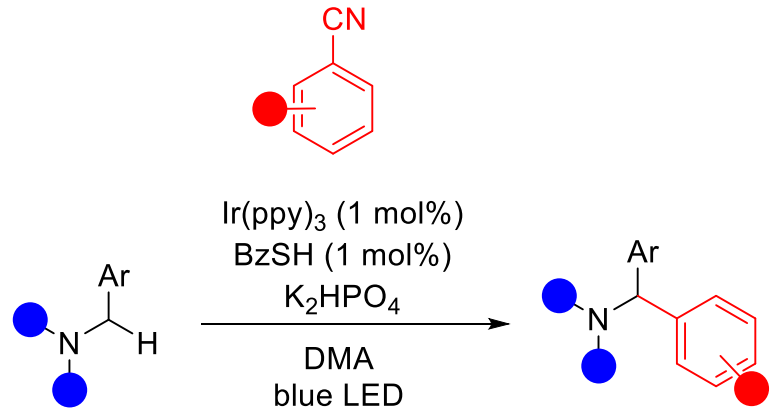
Schoenebeck, Rovis (2021)



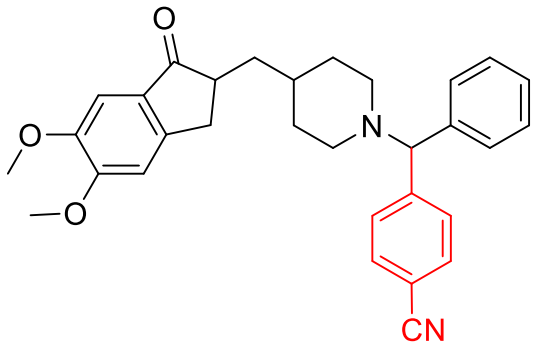
65%
from lidocaine



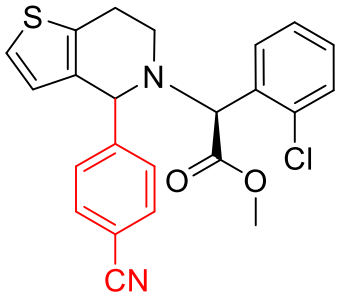
62%
from clomipramine



Hamashima (2018)



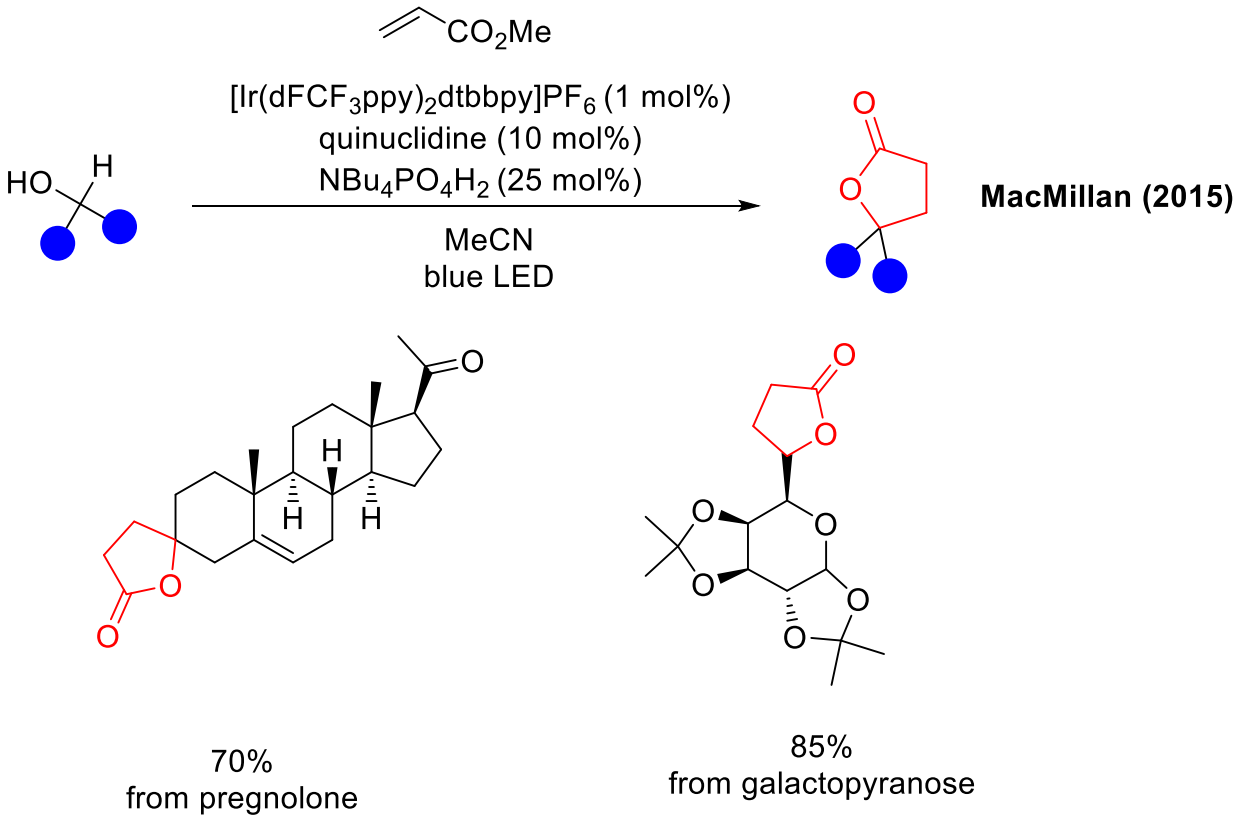
74%
from donepezil



96%
from clopidogrel

1) Y. Shen, I. Funez-Ardoiz, F. Schoenebeck, T. Rovis, *J. Am. Chem. Soc.* **2021**, *143*, 18952–18959. 2) T. Ide, J. P. Barham, M. Fujita, Y. Kawato, H. Egami, Y. Hamashima, *Chem. Sci.* **2018**, *9*, 8453–8460.

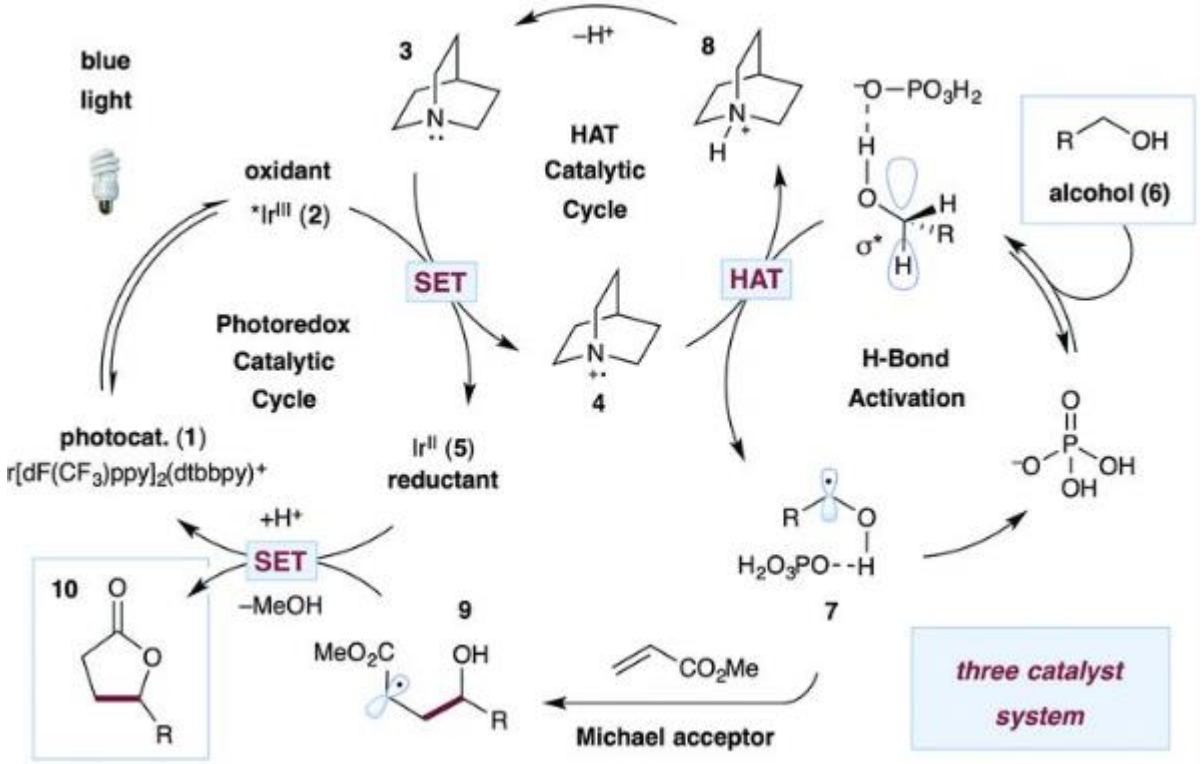
Alcohol activation favoring α-Oxy C-H bonds HAT



MacMillan (2015)

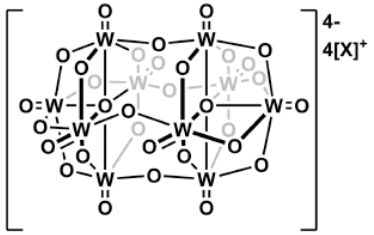
70%
from pregnolone

85%
from galactopyranose

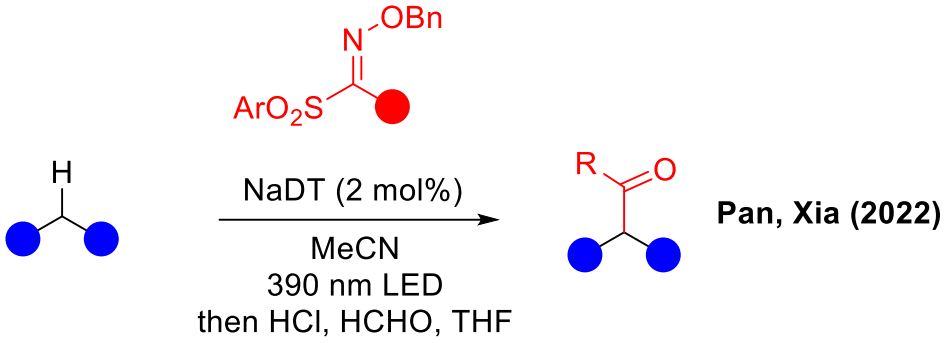


J. L. Jeffrey, J. A. Terrett, D. W. C. MacMillan, *Science* **2015**, *349*, 1532–1536.

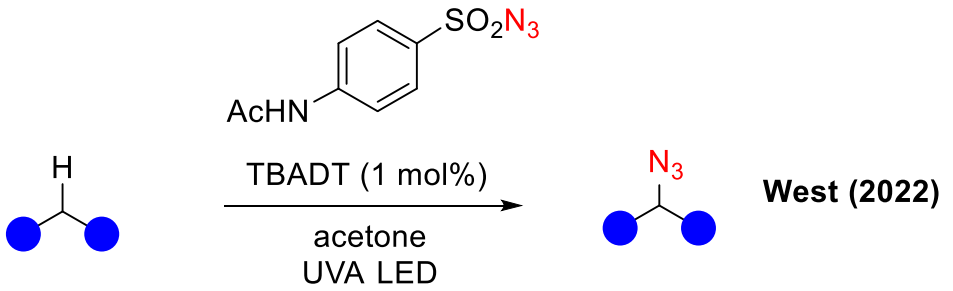
Decatungstate catalysed HAT reactions



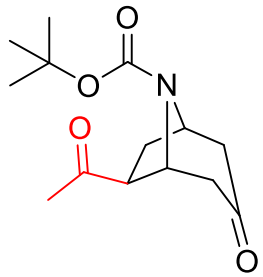
Decatungstate anion



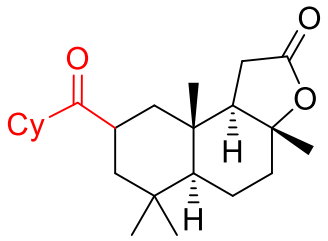
Pan, Xia (2022)



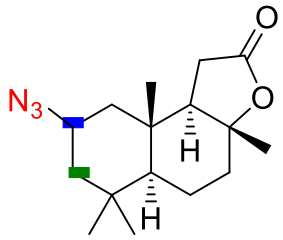
West (2022)



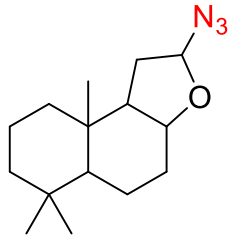
56%
from Boc-tropinone



62%
from sclareolide



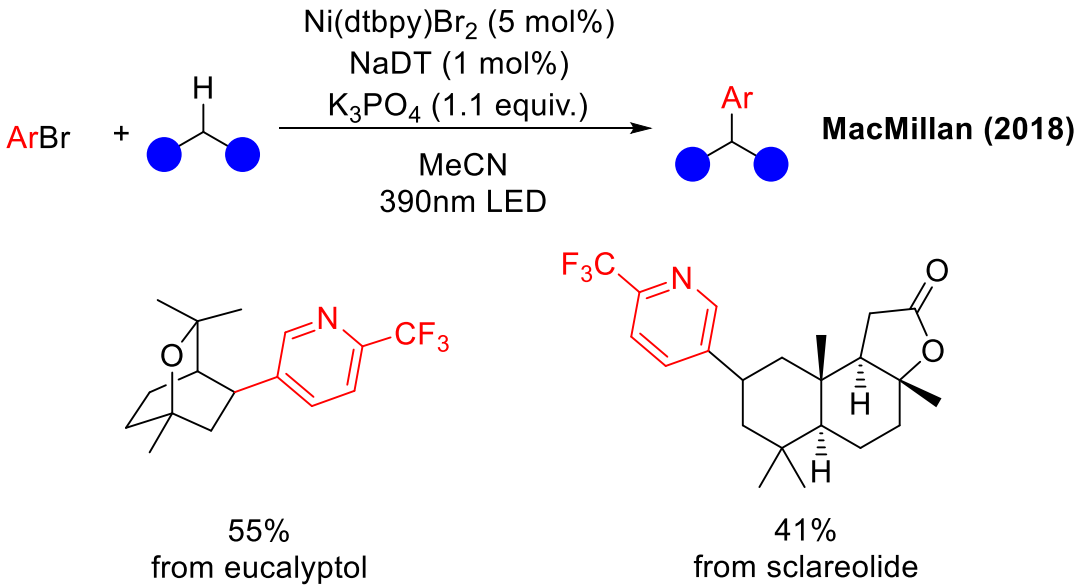
44% (2.4:1 rr)
from sclareolide

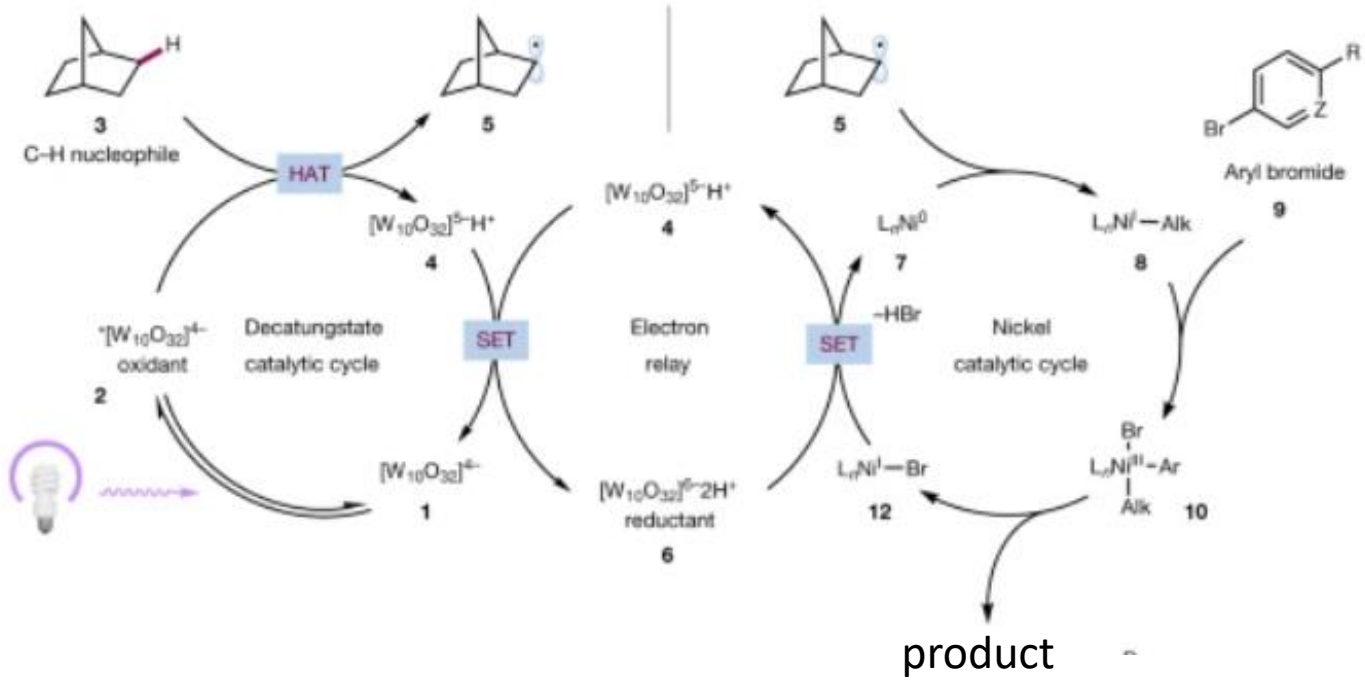


35%
from ambroxide

1) Q. Liu, Y. Ding, Y. Gao, Y. Yang, L. Gao, Z. Pan, C. Xia, *Org. Lett.* **2022**, *24*, 7983–7987. 2) Y.-C. Lu, S.-C. Kao, J. G. West, *Chem. Commun.* **2022**, *58*, 4869–4872.

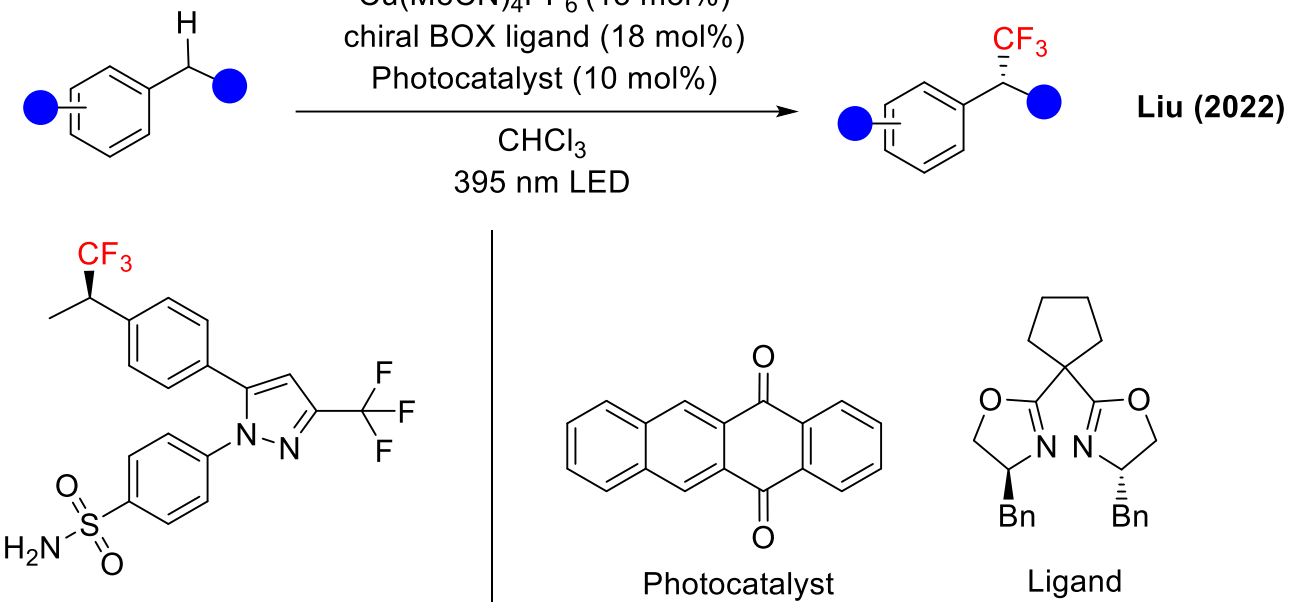
Metallaphotoredox chemistry for LSF



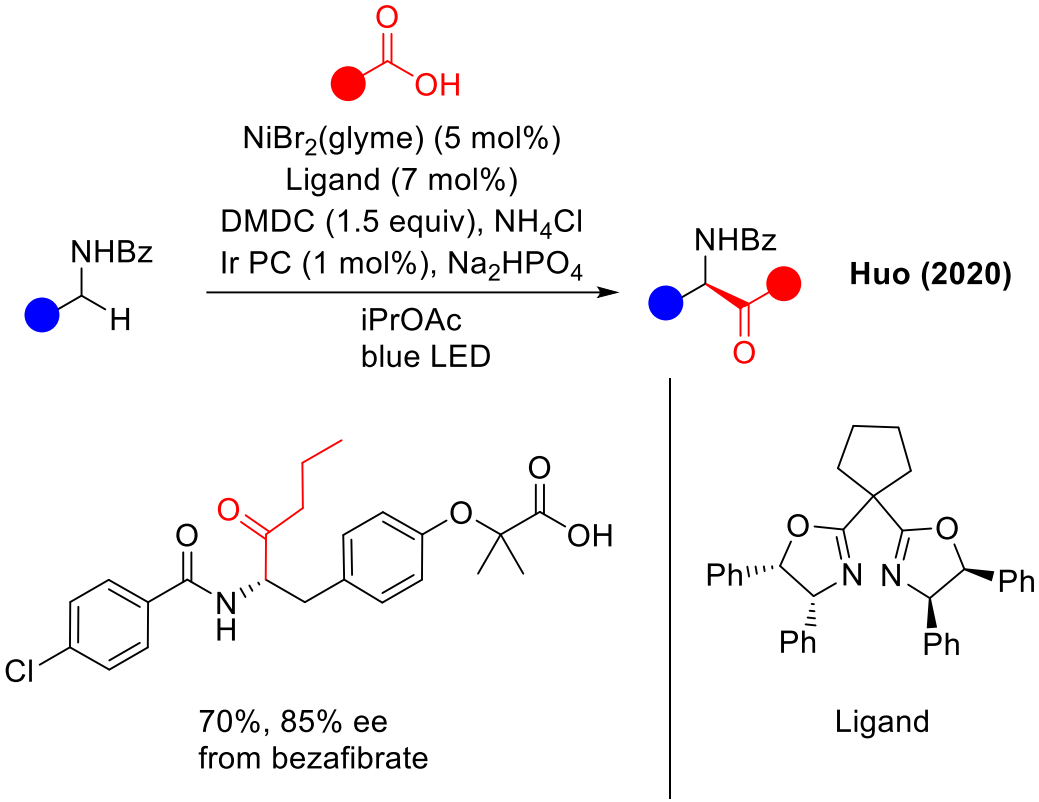


I. B. Perry, T. F. Brewer, P. J. Sarver, D. M. Schultz, D. A. DiRocco, D. W. C. MacMillan, *Nature* **2018**, *560*, 70–75.

Metallaphotoredox – access to enantioselectivity



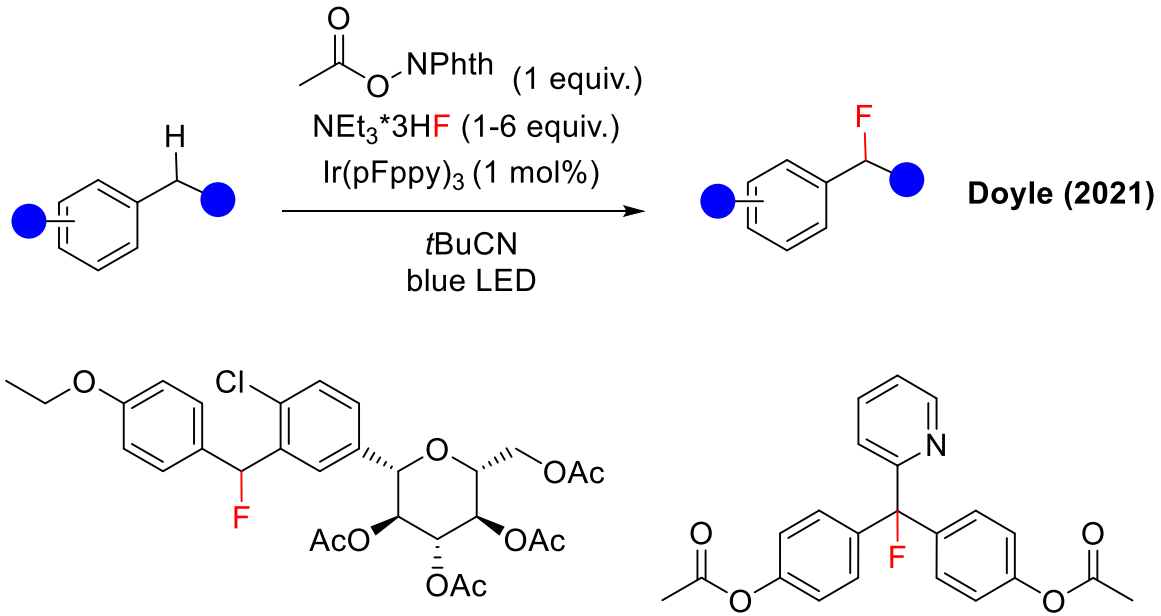
41%, 92% ee
from ethyl colecoxib

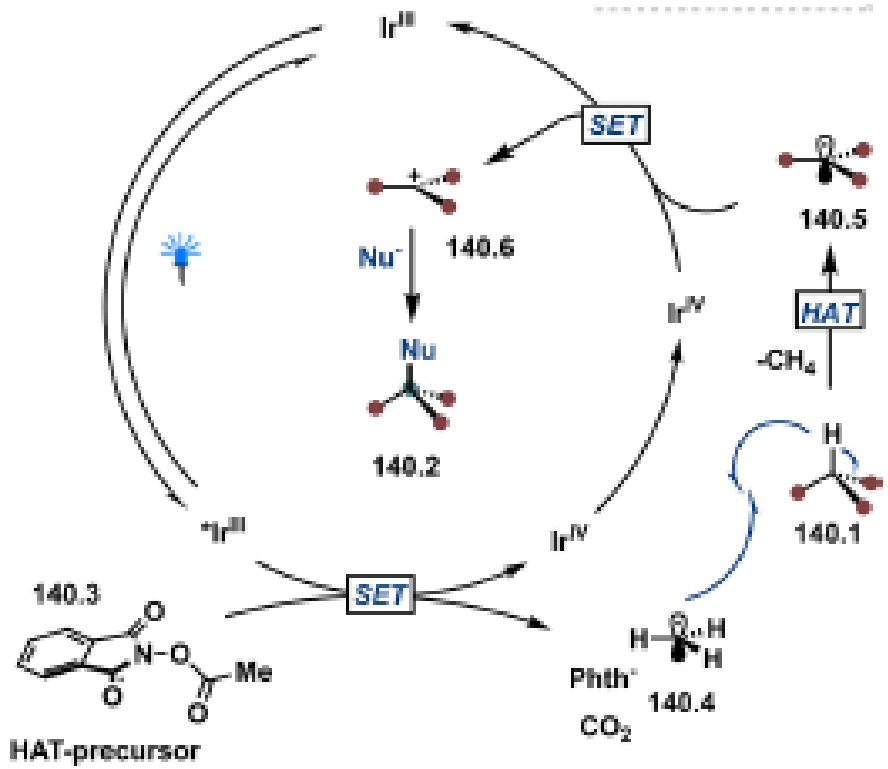


70%, 85% ee
from bezafibrate

1) P. Xu, W. Fan, P. Chen, G. Liu, *J. Am. Chem. Soc.* **2022**, *144*, 13468–13474. 2) X. Shu, L. Huan, Q. Huang, H. Huo, *J. Am. Chem. Soc.* **2020**, *142*, 19058–19064.

Radical-polar crossover for LSF





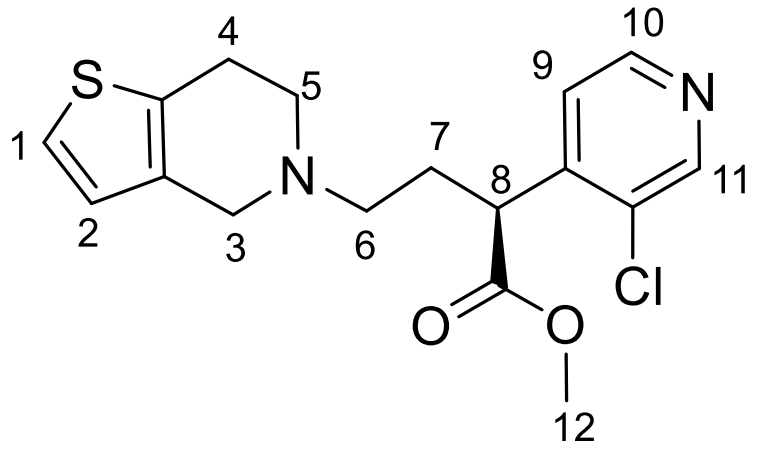
I. N.-M. Leibler, M. A. Tekle-Smith, A. G. Doyle, *Nat Commun* **2021**, *12*, 6950.

Thank you for attention!

Question 1

What will be the site-selectivity of C-H functionalization of this compound if it will be treated with:

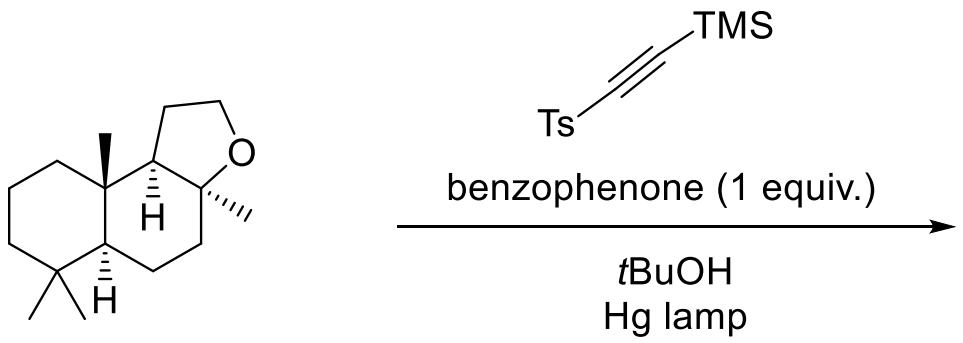
a) Nucleophilic radical
b) Electrophilic radical
c) Strongly oxidizing photocatalyst + nucleophile
d) Electrophilic HAT abstractor
e) Nucleophilic HAT abstractor



Analog of clopidogrel

Question 2

Propose the product and the mechanism of the reaction:



ambroxide

Triplet Energy Transfer for Enantioselective Transformation

Emma Robert

Frontiers in Chemical Synthesis I

Toward Sustainable Chemistry

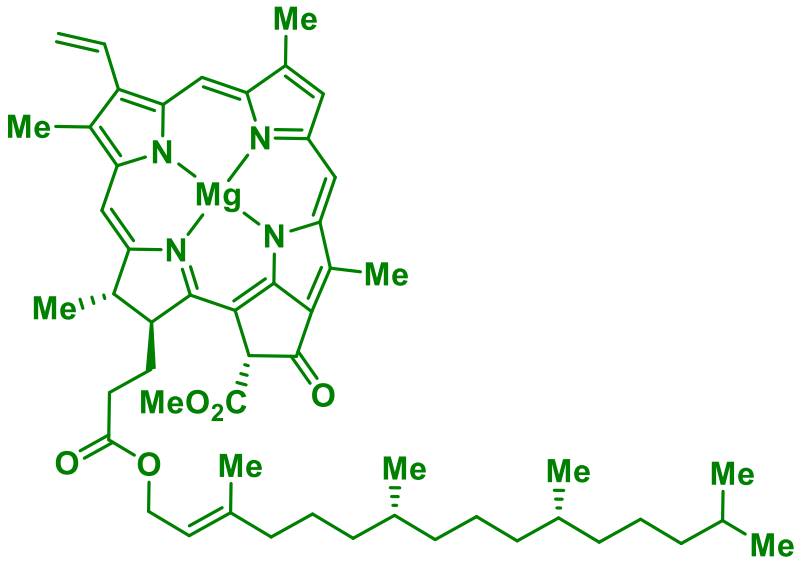
15.05.2023

Biomimicry

- Sun to generate radicals
- Coloured catalysts
- Activate stable molecules
- Enable new reactions

Green chemistry principles

- Light irradiation → Photons
- No harsh conditions
- Catalytic quantities
- Mild and controlled



Enantioselective transformations

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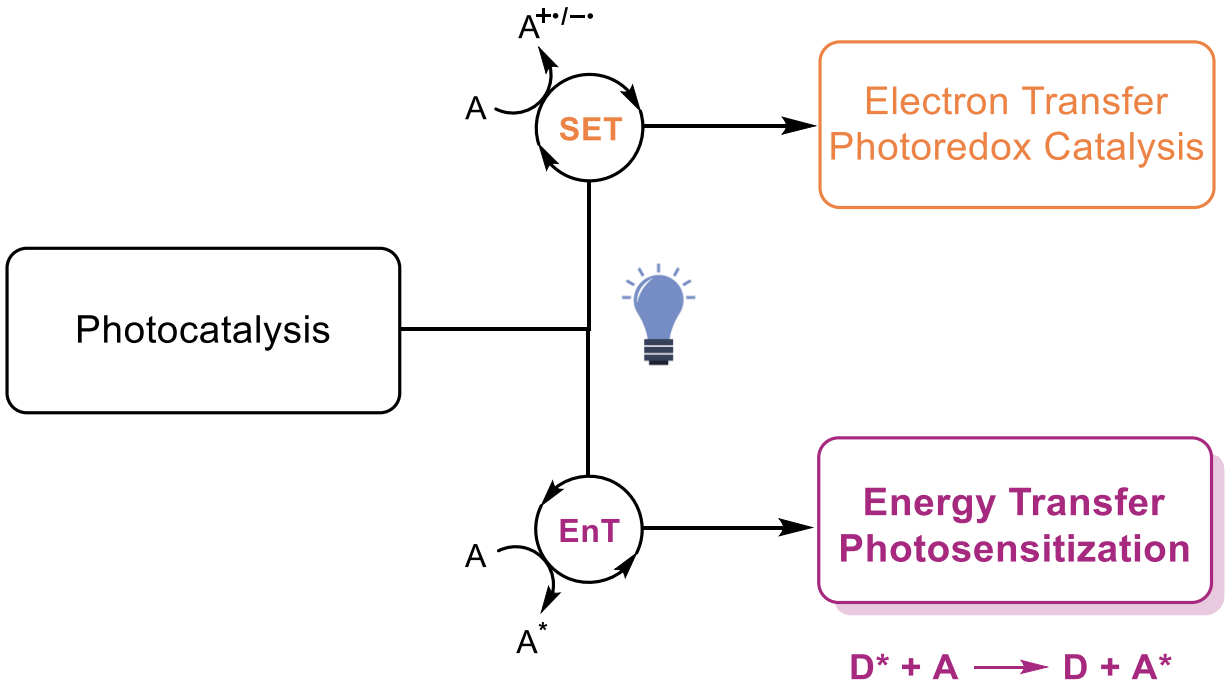
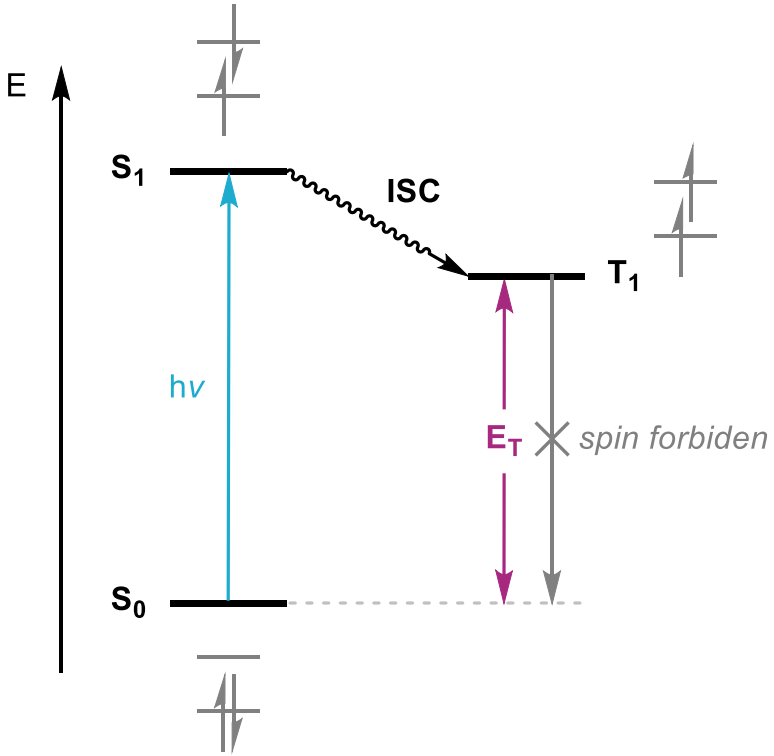
Photoredox / Energy Transfer ?

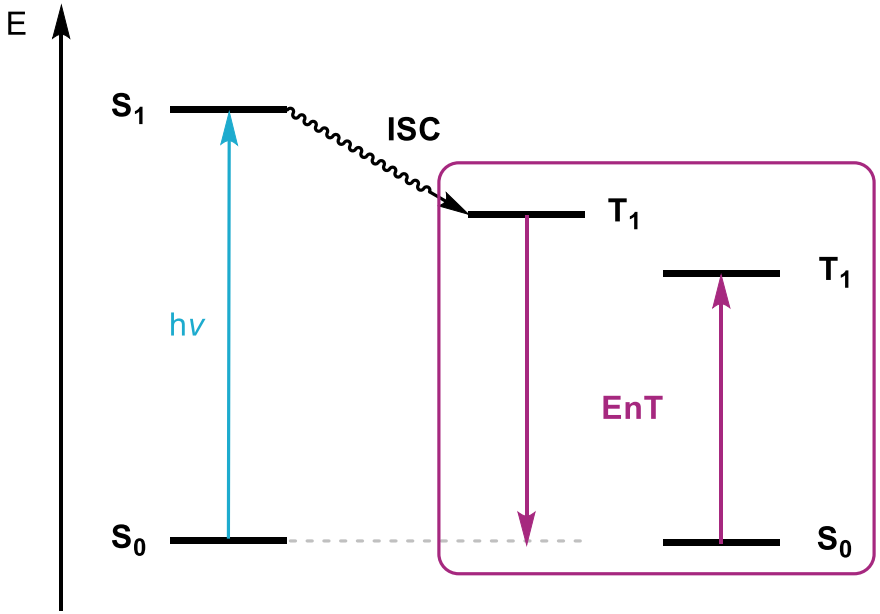


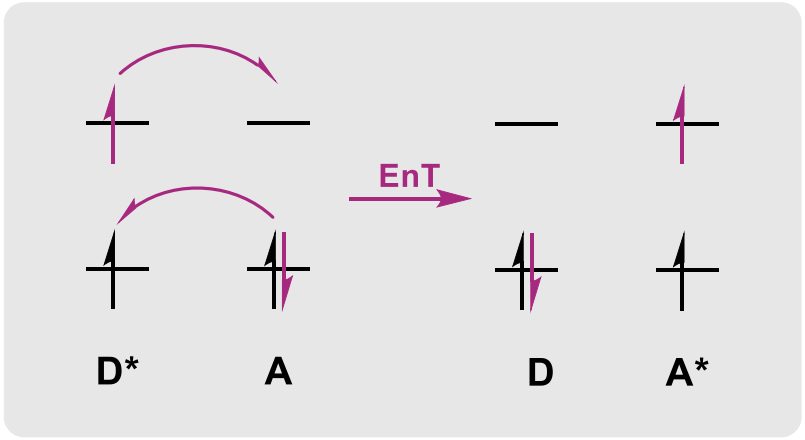
Strieth-Kalthoff, F.; James, M. J.; Teders, M.; Pitzer, L.; Glorius, F. *Chem. Soc. Rev.* **2018**, *47*, 7190−7202.

Dexter Mechanism

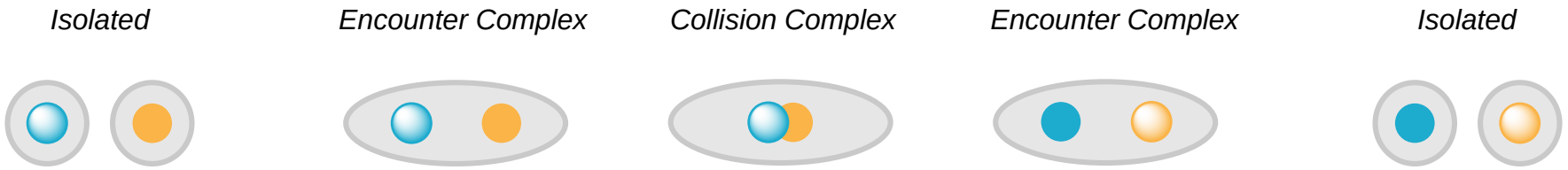


Strieth-Kalthoff, F.; James, M. J.; Teders, M.; Pitzer, L.; Glorius, F. *Chem. Soc. Rev.* **2018**, *47*, 7190−7202.





Strieth-Kalthoff, F.; James, M. J.; Teders, M.; Pitzer, L.; Glorius, F. *Chem. Soc. Rev.* **2018**, *47*, 7190−7202.

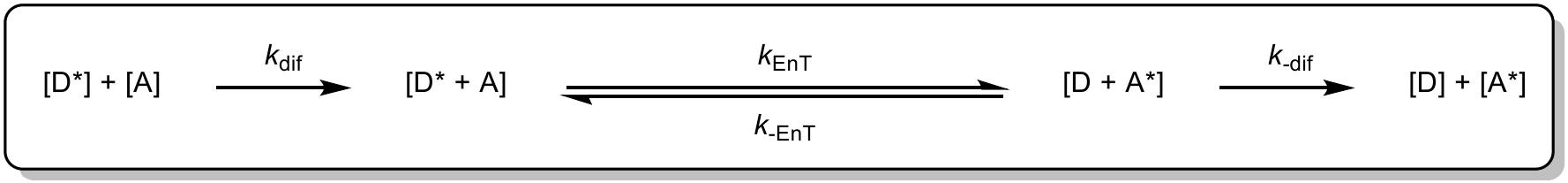


$$[D^*] + [A] \xrightarrow{k_{dif}} [D^* + A] \underset{k_{-EnT}}{\overset{k_{EnT}}{\rightleftharpoons}} [D + A^*] \xrightarrow{k_{-dif}} [D] + [A^*]$$

Fast energy transfer
$k_{EnT} >> k_{dif}$
↓
Diffusion-limited overall rate
$k_{obs} \approx k_{dif}$

Slow energy transfer
$k_{EnT} << k_{dif}$
↓
EnT-limited overall rate
$k_{obs} \propto k_{EnT}$

Strieth-Kalthoff, F.; James, M. J.; Teders, M.; Pitzer, L.; Glorius, F. *Chem. Soc. Rev.* **2018**, *47*, 7190−7202.



Fast energy transfer
$k_{EnT} >> k_{dif}$

Diffusion-limited overall rate
$k_{obs} \approx k_{dif}$

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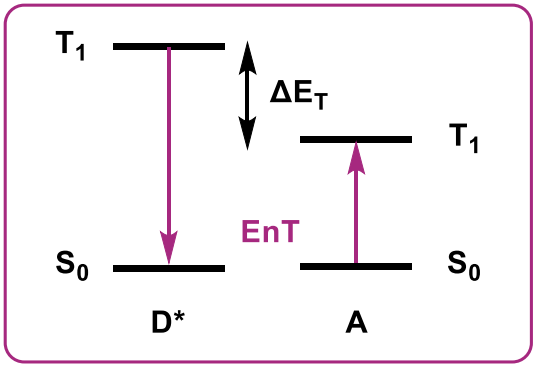
$k_{EnT} << k_{dif}$

EnT-limited overall rate
$k_{obs} \propto k_{EnT}$



$$k_{EnT} = K \cdot J \cdot e^{-\frac{2RDA}{L}}$$

K: parameter for specific orbital interactions

R_{DA}/L: distance between Donor and Acceptor

J: spectral overlap integral (number of T_1-S_0 transition of the excited donor which can induce a S_0-T_1 transition of the acceptor)

«rules of thumb» for the magnitude of *J*

$$\Delta E_T = E_T(D) - ET(A)$$

$$\Delta E_T > 0$$

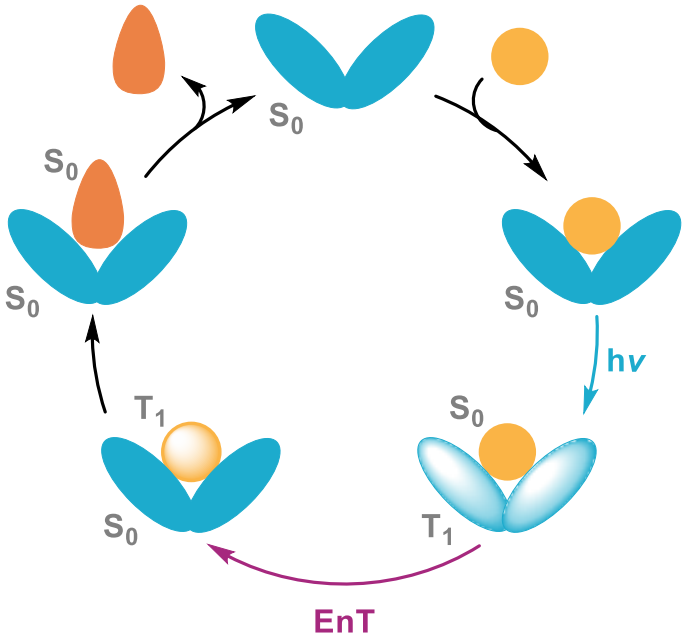
exergonic, large number of transitions, *J* large

$$\Delta E_T < 0$$

endergonic, *J* becomes negligible for large ΔE_T

Strieth-Kalthoff, F.; James, M. J.; Teders, M.; Pitzer, L.; Glorius, F. *Chem. Soc. Rev.* **2018**, *47*, 7190−7202.

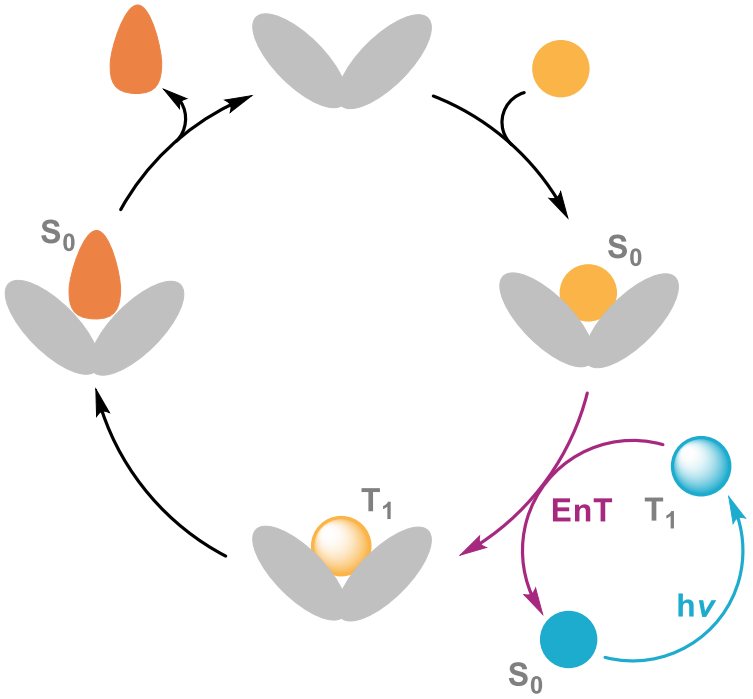
Single Catalyst Regime



Chiral Triplet Sensitizer

Asymmetric induction from the sensitizer

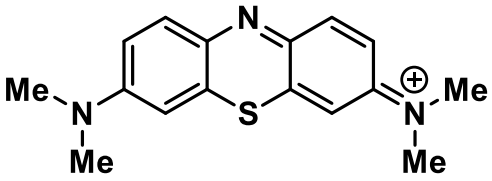
Dual Catalysis



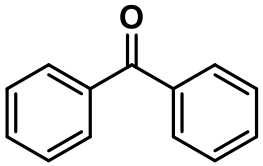
Photochemically inactive chiral catalyst

EnT by an achiral sensitizer

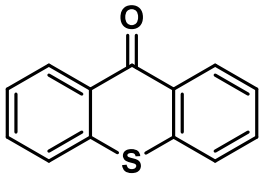
Literature-known Photosensitizer



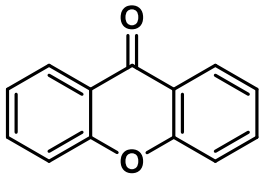
Methylene blue
E_T = 32.0 kcal/mol



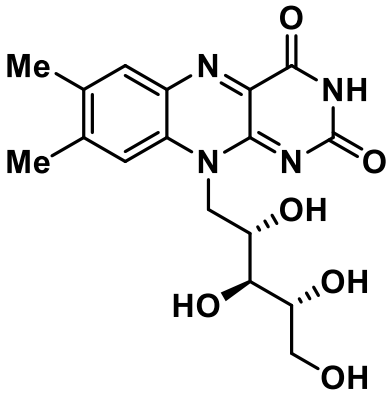
Benzophenone
E_T = 69.1 kcal/mol



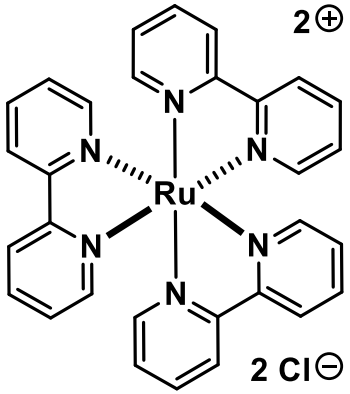
Thioxanthone
E_T = 63.4 kcal/mol



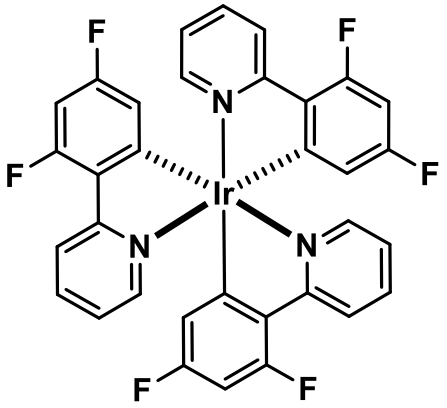
Xanthone
E_T = 74.0 kcal/mol



Riboflavine
E_T = 50.0 kcal/mol



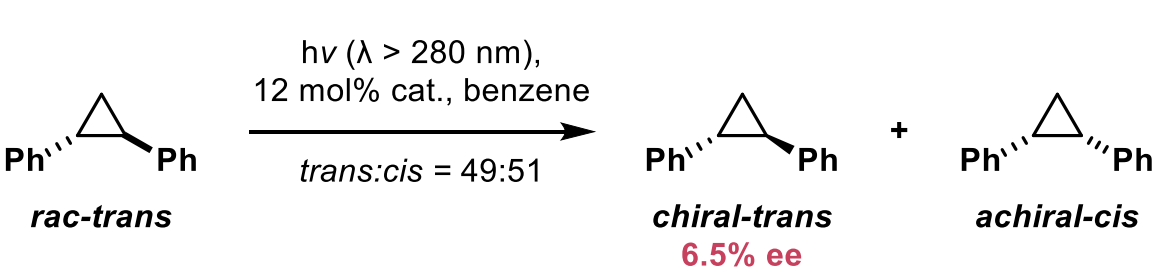
$[Ru(bpy)_3]Cl_2$
E_T = 49.0 kcal/mol

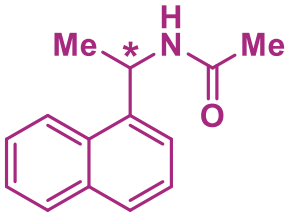


***fac*-$[Ir(dF\text{-}ppy)_3]$**
E_T = 63.5 kcal/mol

Table of Content

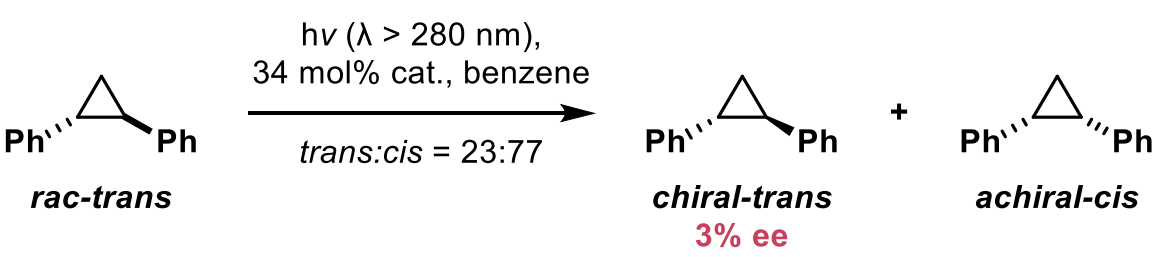
Cole & Hammond (1965)

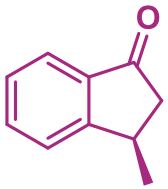




Reaction at the singlet level

Ouannès (1973)



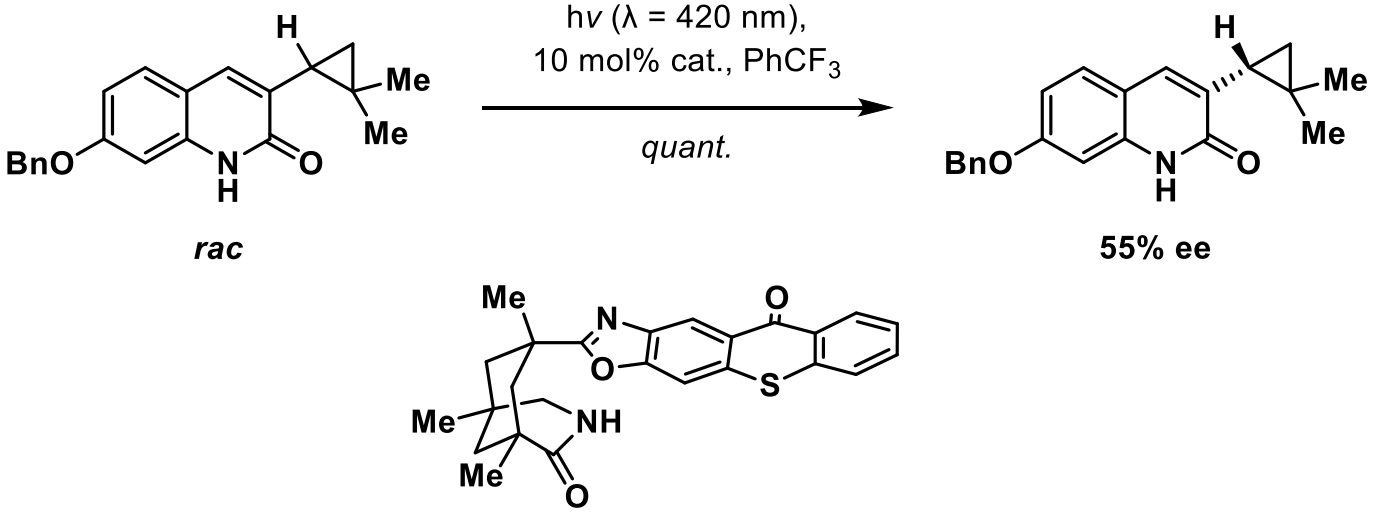


First enantioselective triplet sensitized reaction!

Hammond, G. S.; Cole, R. S. *J. Am. Chem. Soc.* **1965**, *87*, 3256−3257.
Ouannès, C.; Beugelmans, R.; Roussi, G. *J. Am. Chem. Soc.* **1973**, *95*, 8472− 8474.

EnT Deracemization Principle

T. Bach (2019)



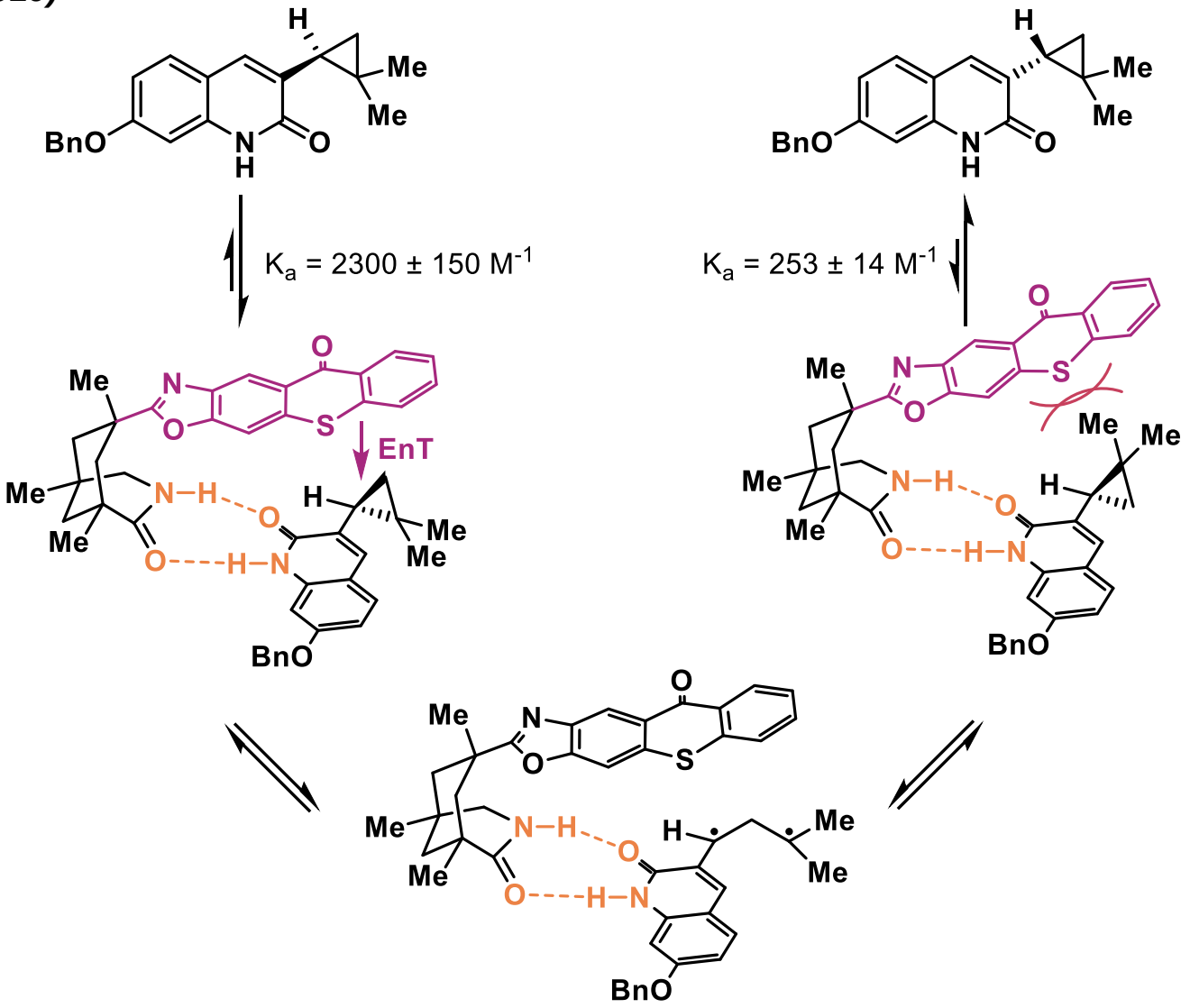
rac

55% ee

Tröster, A.; Bauer, A.; Jandl, C.; Bach, T. *Angew. Chem. Int. Ed.* **2019**, *58*, 3538−3541.

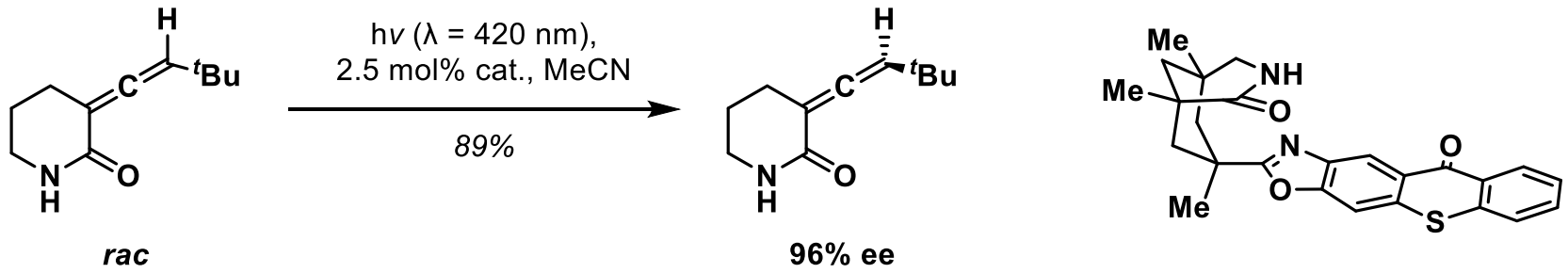
EnT Deracemization Principle

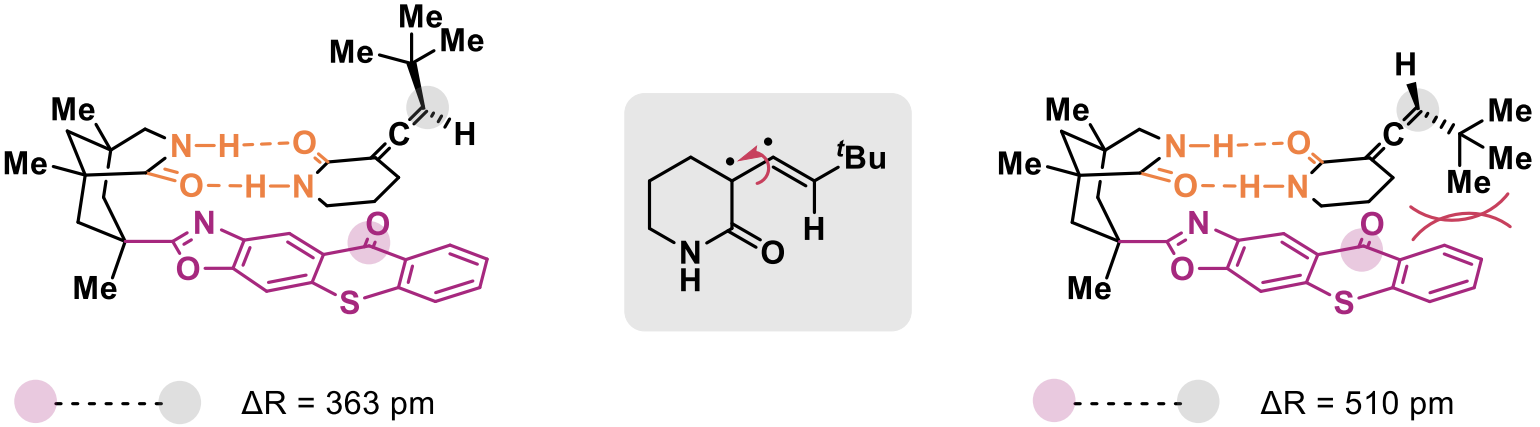
T. Bach (2019)



Tröster, A.; Bauer, A.; Jandl, C.; Bach, T. *Angew. Chem. Int. Ed.* **2019**, *58*, 3538−3541.

T. Bach (2018)

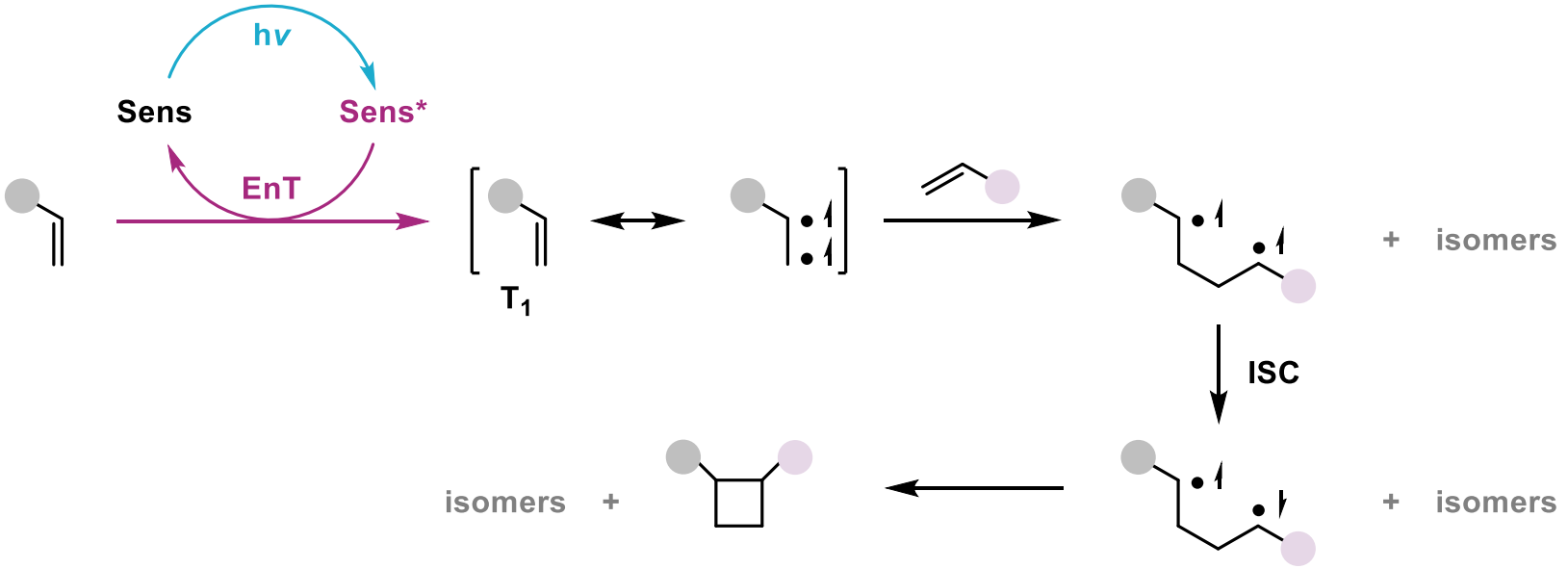




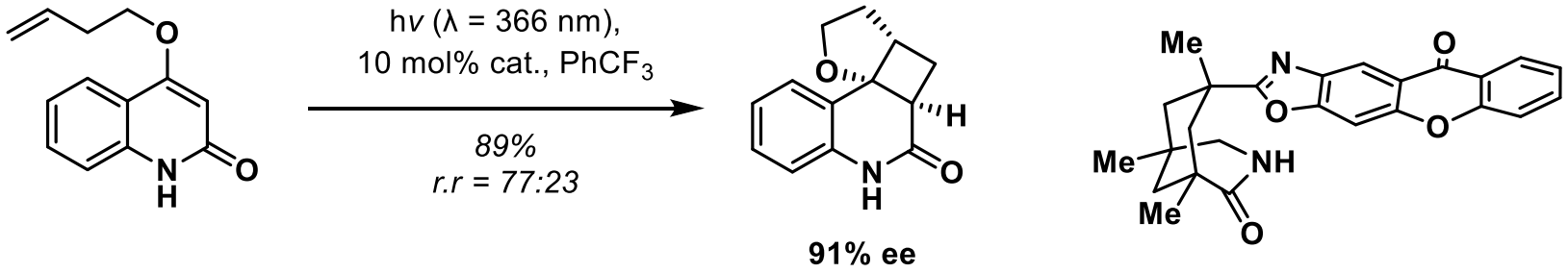
Hölzl-Hobmeier, A.; Bauer, A.; Silva, A. V.; Huber, S. M.; Bannwarth, C.; Bach, T. *Nature* **2018**, *564*, 240− 243.

EnT [2+2] Cycloaddition

[2+2] General Mechanism

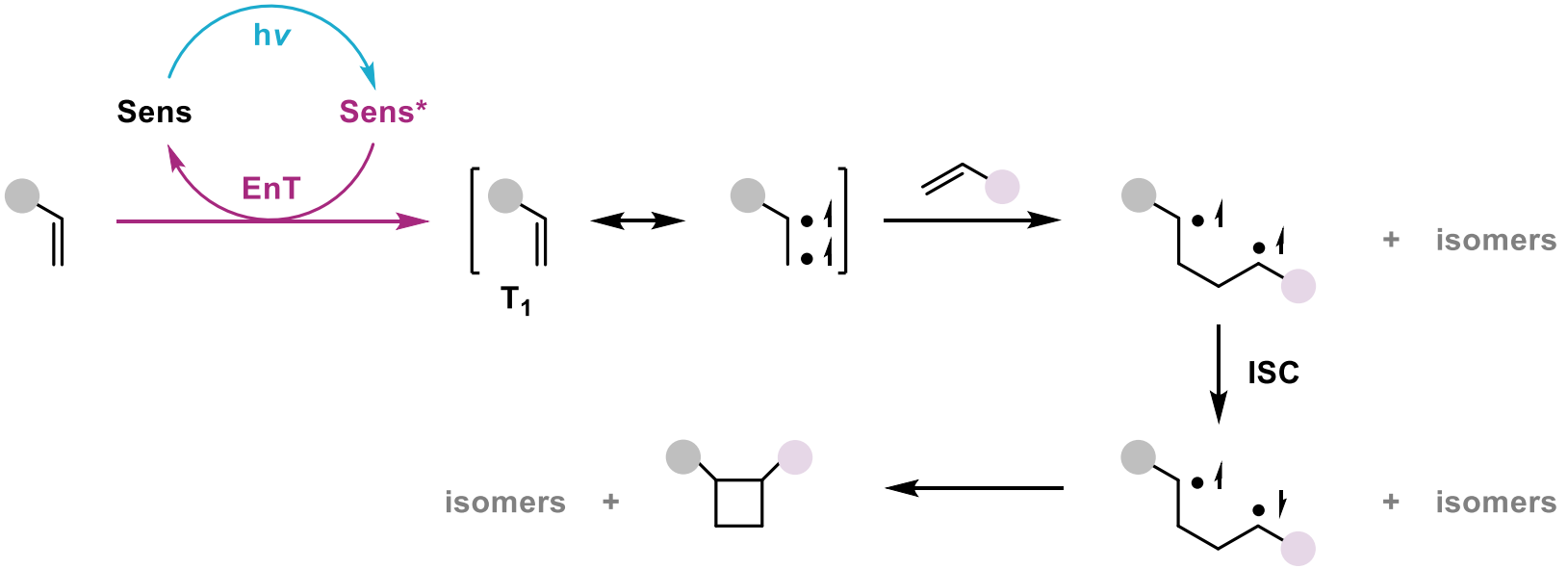


T. Bach (2009)

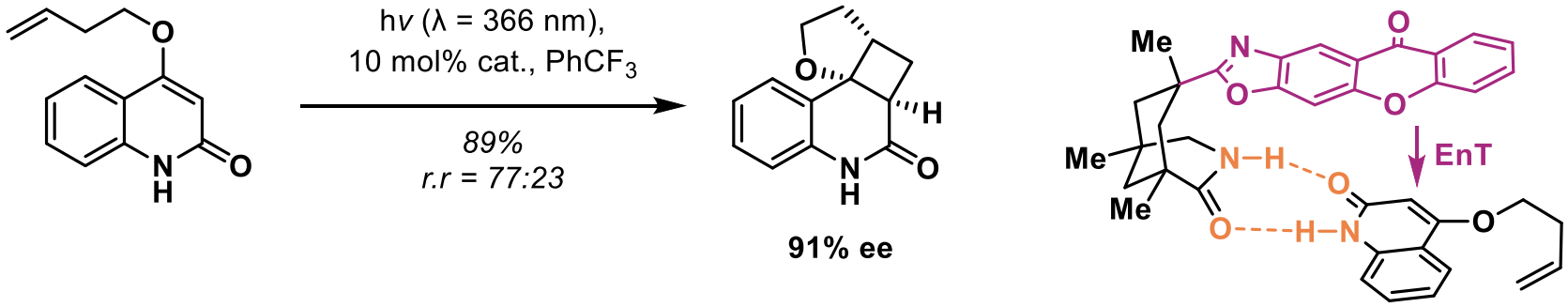


Müller, C.; Bauer, A.; Bach, T. *Angew. Chem. Int. Ed*. **2009**, *48*, 6640−6642.

[2+2] General Mechanism

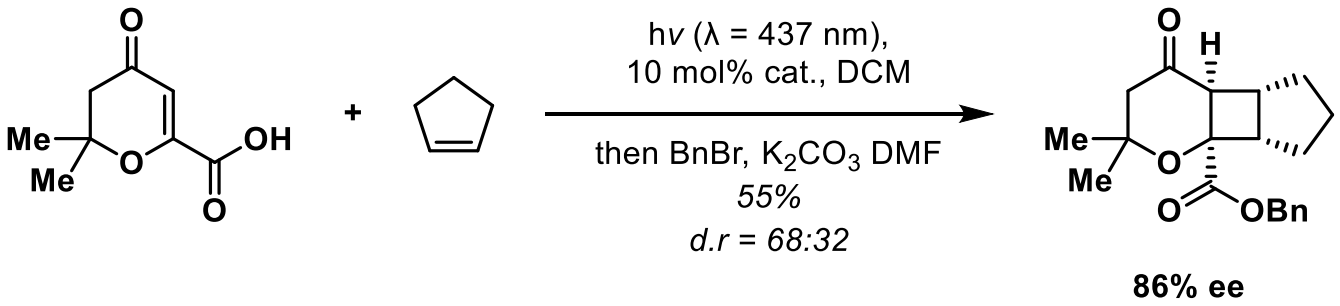


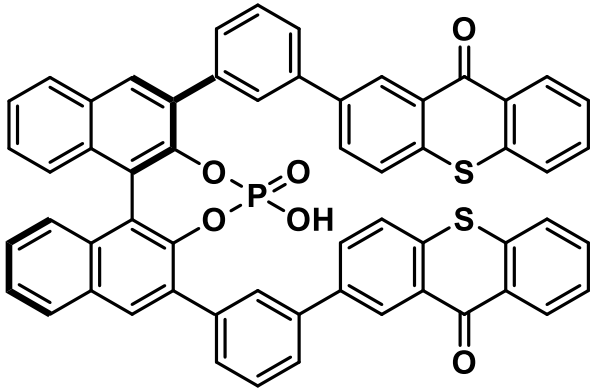
T. Bach (2009)



Müller, C.; Bauer, A.; Bach, T. *Angew. Chem. Int. Ed*. **2009**, *48*, 6640−6642.

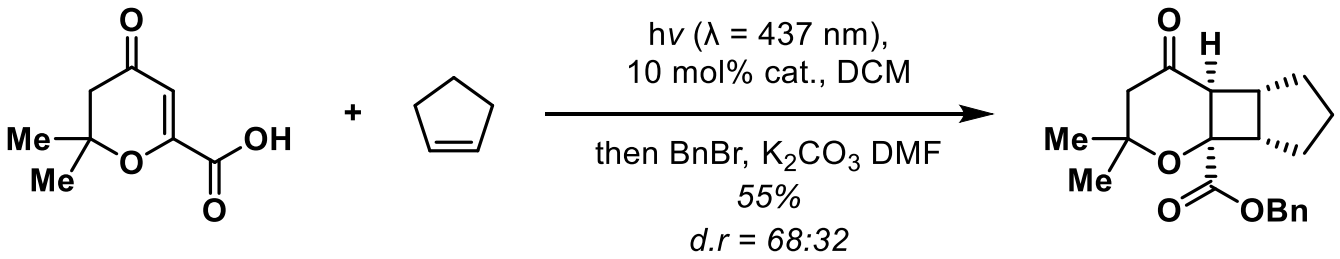
T. Bach (2020)

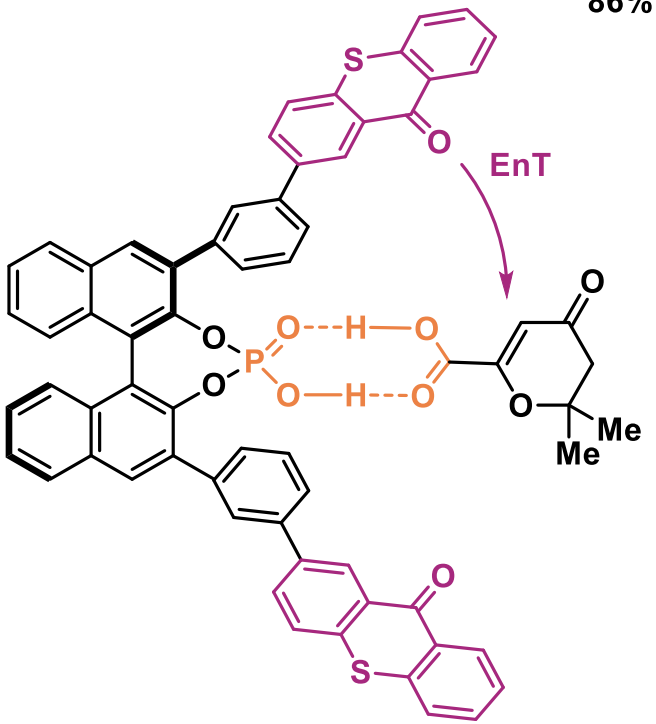




Pecho, F.; Zou, Y.-Q.; Gramüller, J.; Mori, T.; Huber, S. M.; Bauer, A.; Gschwind, R. M.; Bach. *Chem. Eur. J.* **2020**, *26*, 5190−5194.

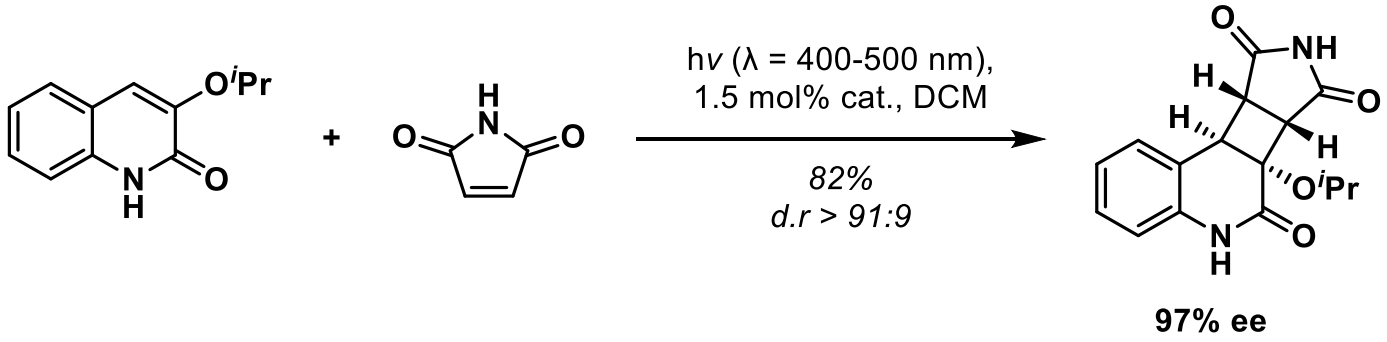
T. Bach (2020)

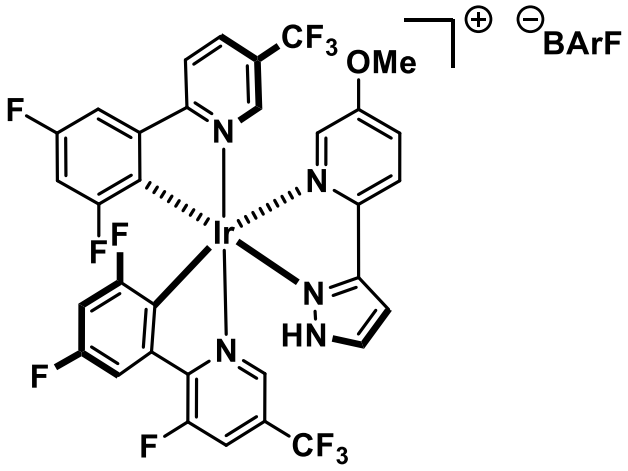




Pecho, F.; Zou, Y.-Q.; Gramüller, J.; Mori, T.; Huber, S. M.; Bauer, A.; Gschwind, R. M.; Bach. *Chem. Eur. J.* **2020**, *26*, 5190−5194.

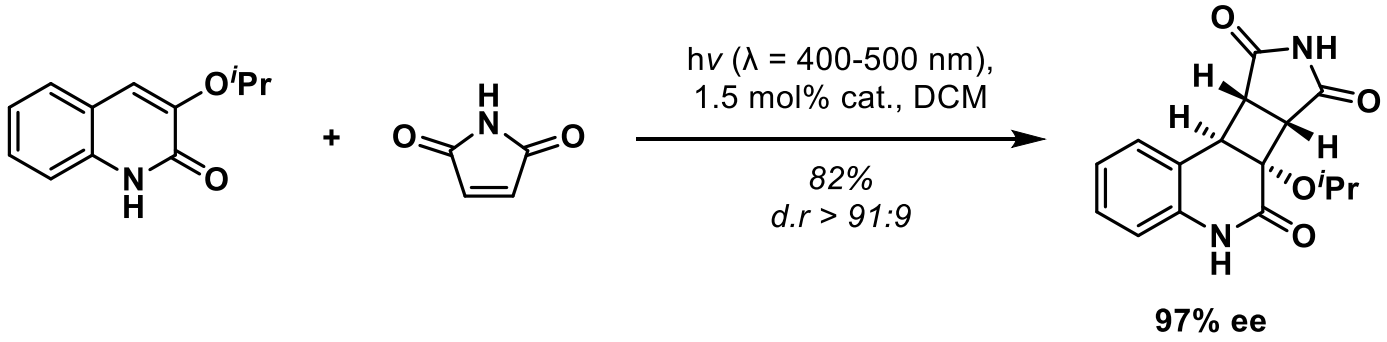
Yoon (2019)

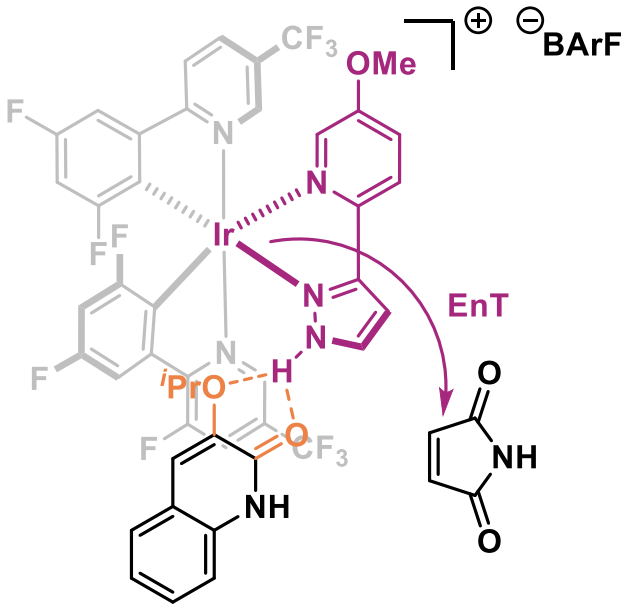




Zheng, J.; Swords, W. B.; Jung, H.; Skubi, K. L.; Kidd, J. B.; Meyer, G. J.; Baik, M.-H.; Yoon, T. P. *J. Am. Chem. Soc.* **2019**, *141*, 13625−13634.

Yoon (2019)



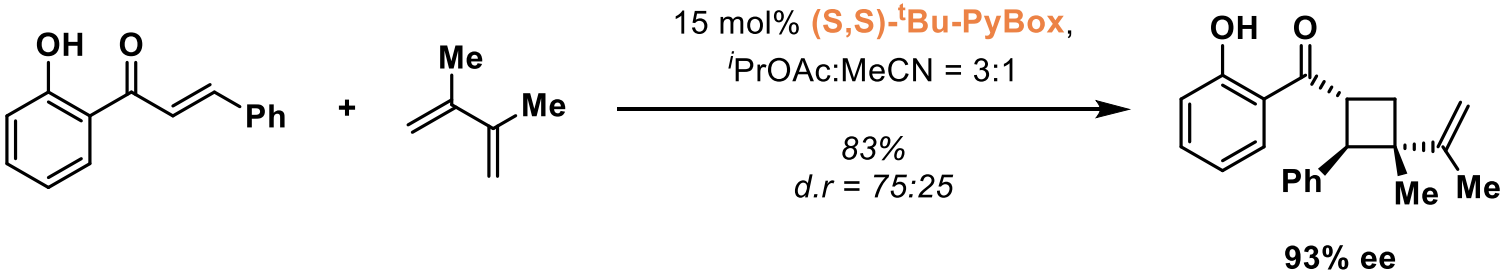


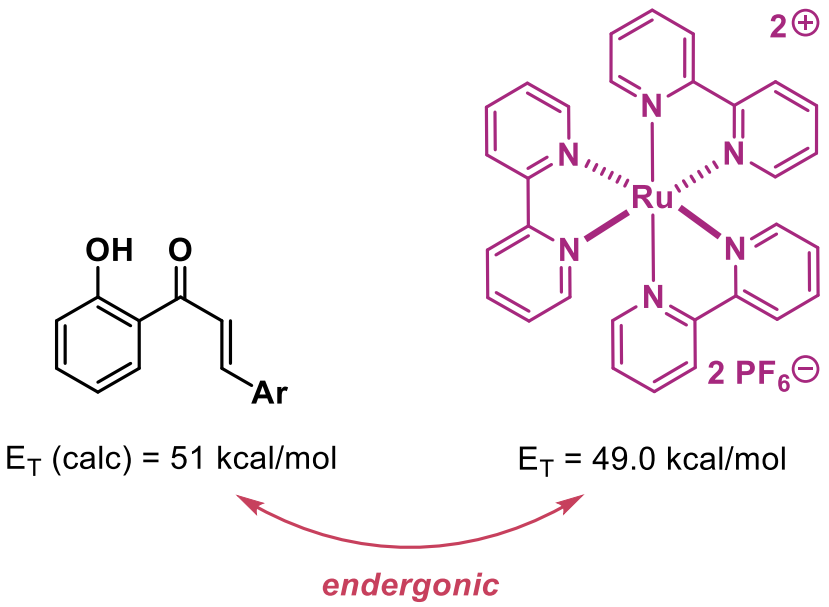
Zheng, J.; Swords, W. B.; Jung, H.; Skubi, K. L.; Kidd, J. B.; Meyer, G. J.; Baik, M.-H.; Yoon, T. P. *J. Am. Chem. Soc.* **2019**, *141*, 13625−13634.

Table of Content

Key Role of the Lewis Acid

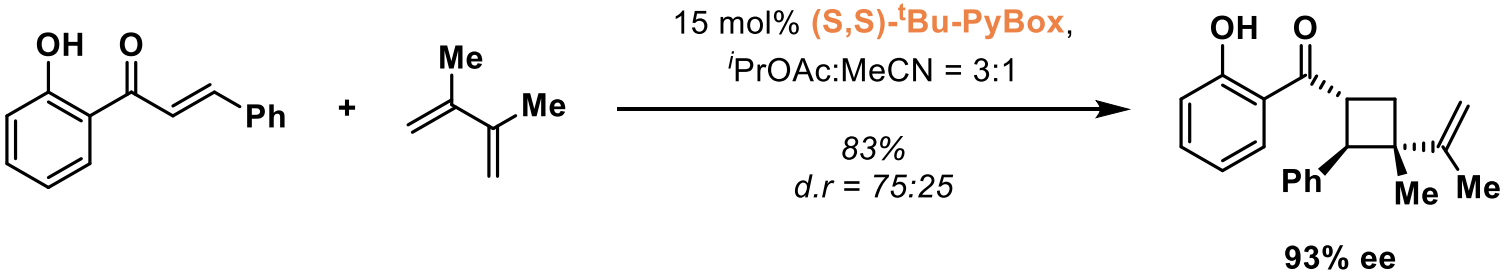
Yoon (2016)

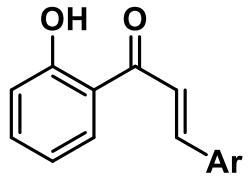




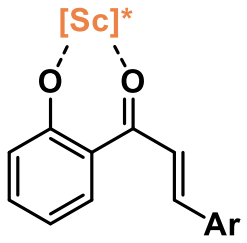
Blum, T. R.; Miller, Z. D.; Bates, D. M.; Guzei, I. A.; Yoon, T. P. *Science* **2016**, *354*, 1391−1395.

Yoon (2016)

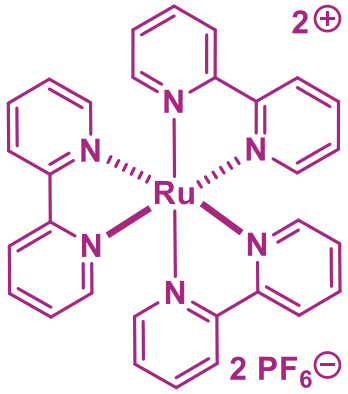




E_T (calc) = 51 kcal/mol



E_T (calc) = 32 kcal/mol



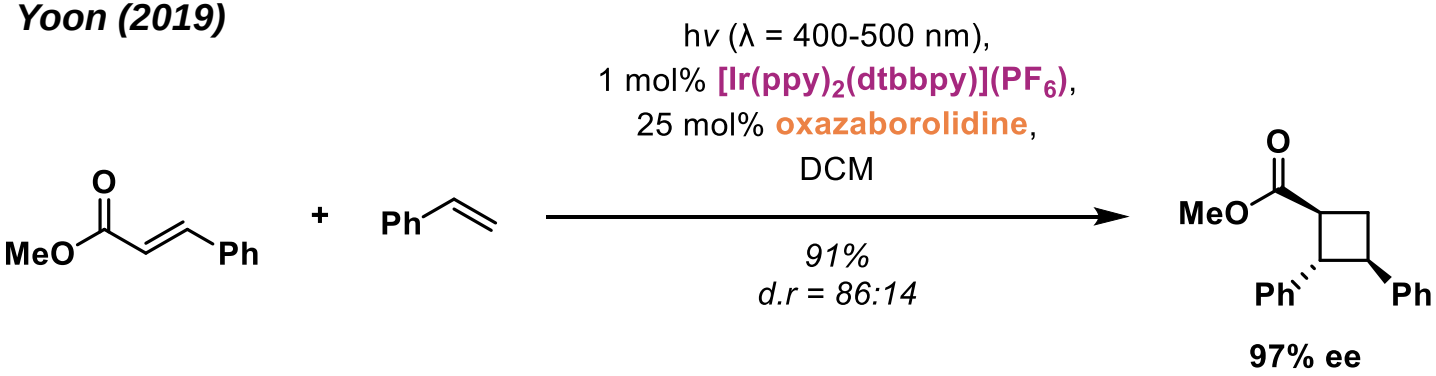
E_T = 49.0 kcal/mol

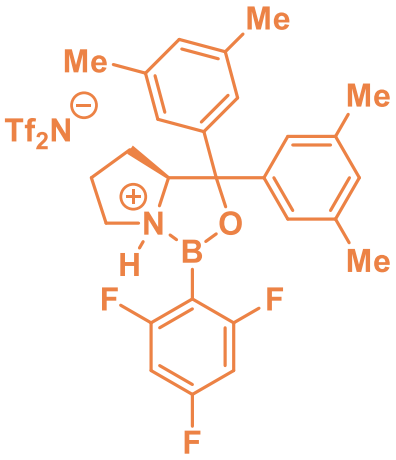
exergonic

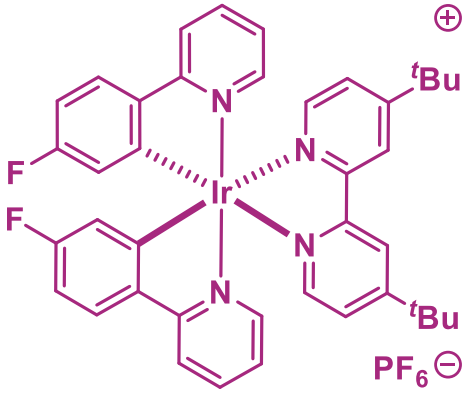
Blum, T. R.; Miller, Z. D.; Bates, D. M.; Guzei, I. A.; Yoon, T. P. *Science* **2016**, *354*, 1391−1395.

Key Role of the Lewis Acid

Yoon (2019)







Daub, M. E.; Jung, H.; Lee, B. J.; Won, J.; Baik, M.-H.; Yoon, T. P. *J. Am. Chem. Soc.* **2019**, *141*, 9543−9547.

Key Role of the Lewis Acid

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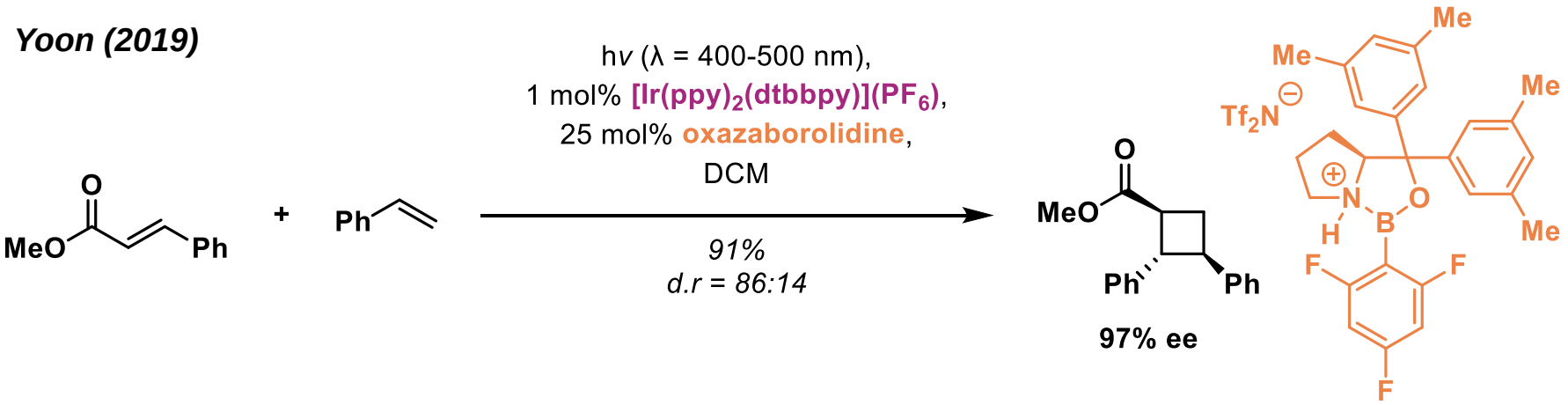
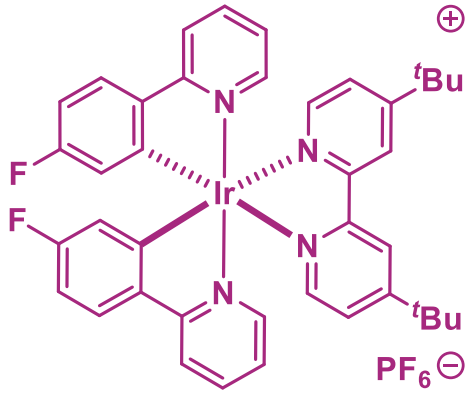




E_T (calc) = 48.5 kcal/mol

E_T (calc) = 42.0 kcal/mol

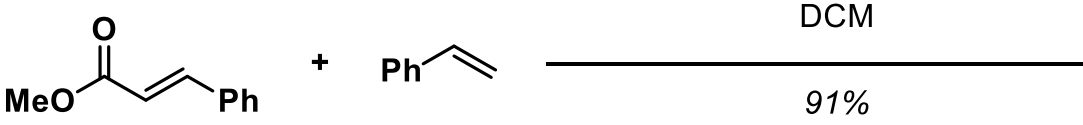
E_T (calc) = 54.3 kcal/mol

exergonic

Daub, M. E.; Jung, H.; Lee, B. J.; Won, J.; Baik, M.-H.; Yoon, T. P. *J. Am. Chem. Soc.* **2019**, *141*, 9543−9547.

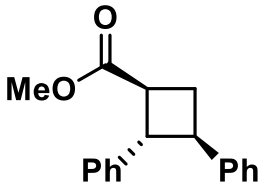
Key Role of the Lewis Acid

Yoon (2019)

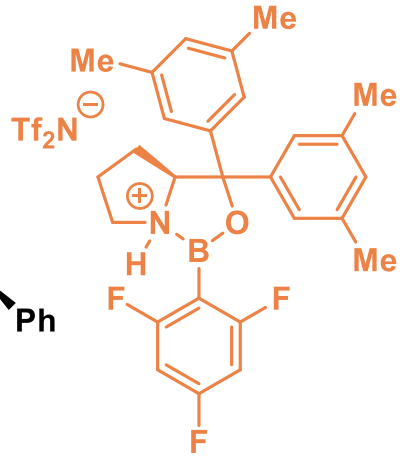


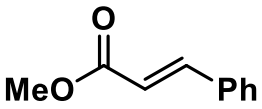
hν (λ = 400-500 nm),
1 mol% **[Ir(ppy)$_2$(dtbbpy)](PF$_6$)**,
25 mol% **oxazaborolidine**,
DCM

91%
d.r = 86:14

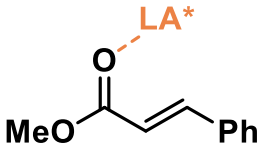


97% ee

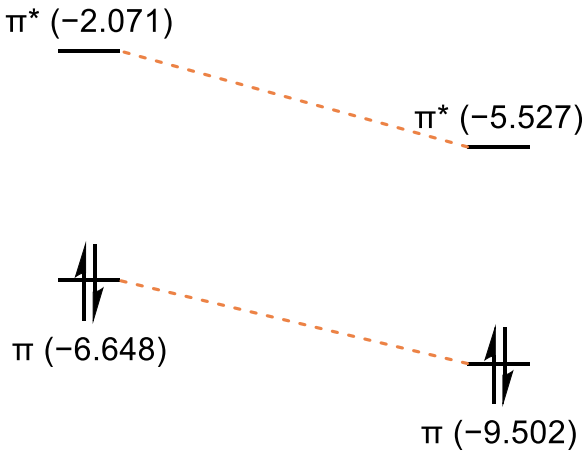




E_T (calc) = 48.5 kcal/mol

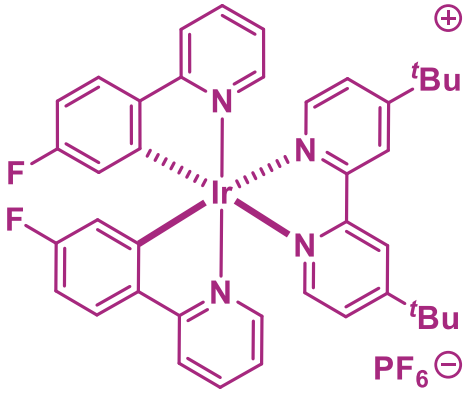


E_T (calc) = 42.0 kcal/mol



SOMO 2
(−5.656)

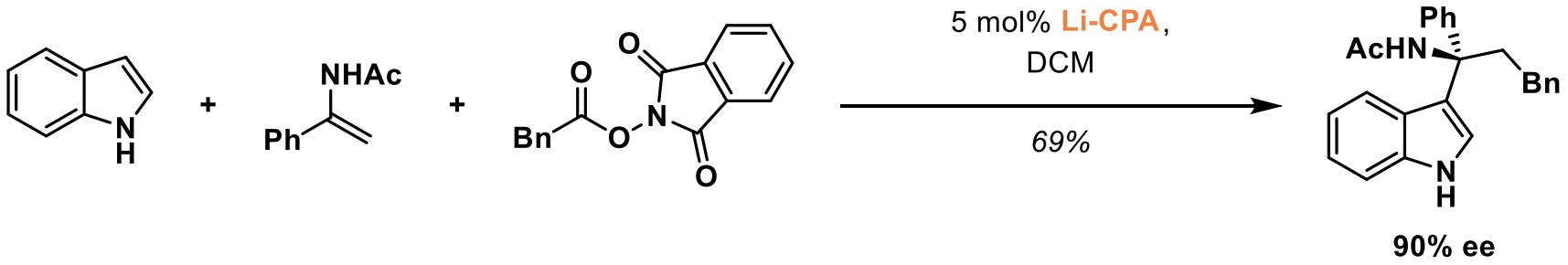
SOMO 1
(−8.921)

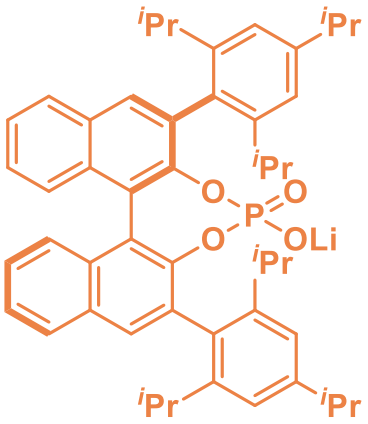


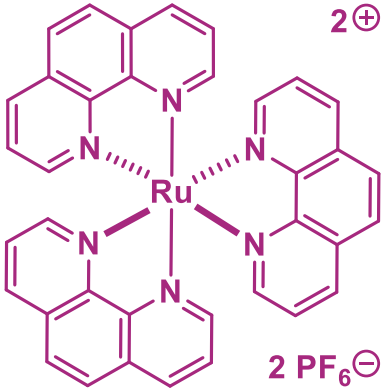
E_T (calc) = 54.3 kcal/mol

Daub, M. E.; Jung, H.; Lee, B. J.; Won, J.; Baik, M.-H.; Yoon, T. P. *J. Am. Chem. Soc.* **2019**, *141*, 9543−9547.

Wang (2020)



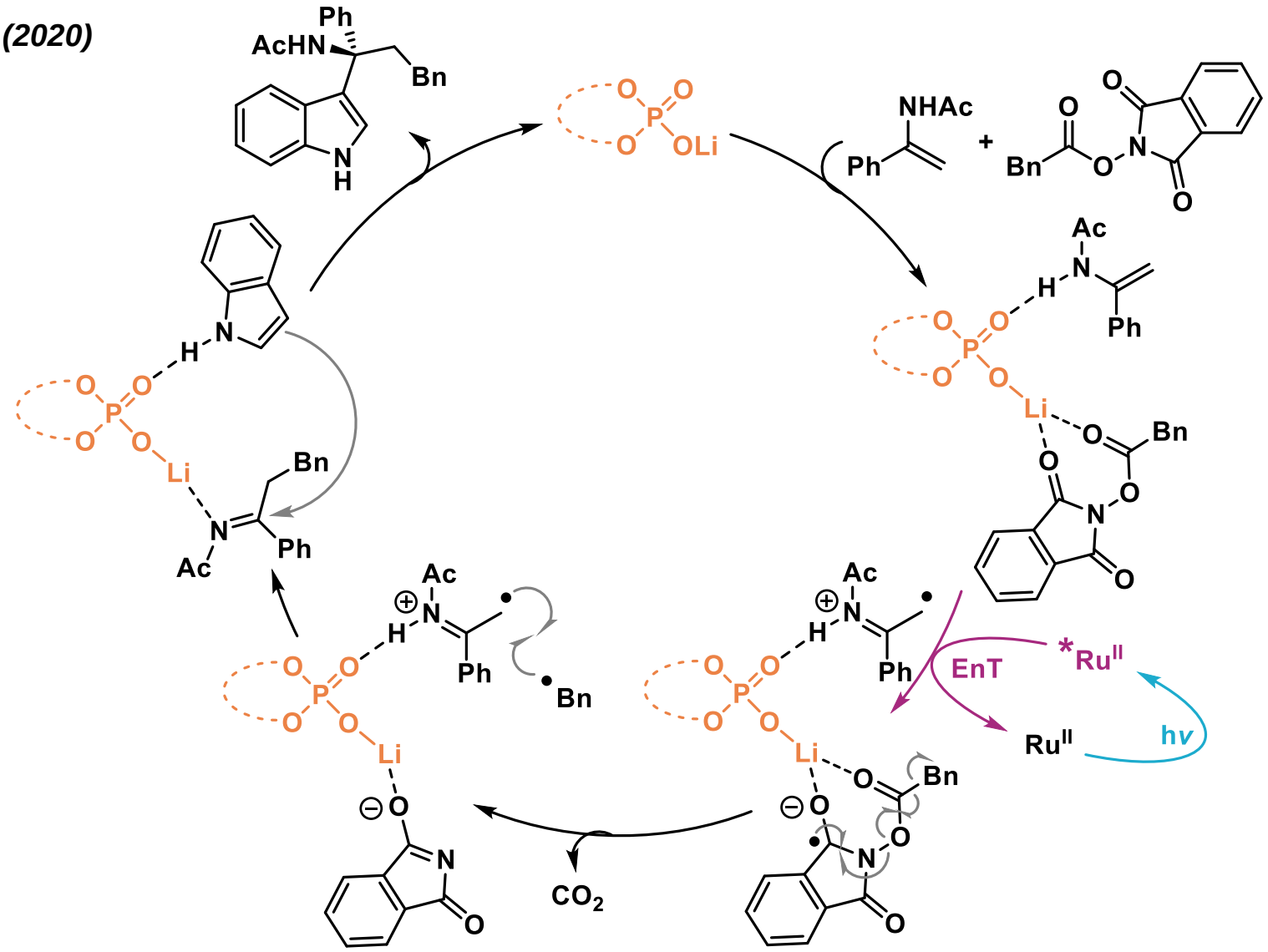




Shen, Y.; Shen, M.-L.; Wang, P.-S. *ACS Catal.* **2020**, *10*, 8247−8253.

Asymmetric Friedel-Craft

Wang (2020)

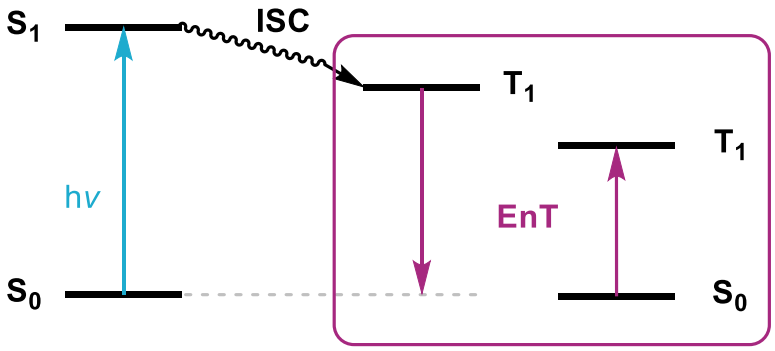


Shen, Y.; Shen, M.-L.; Wang, P.-S. *ACS Catal.* **2020**, *10*, 8247−8253.

EnT: using a sensitizer to access T_1

Visible light instead of direct UV excitation

✓ milder and more selective

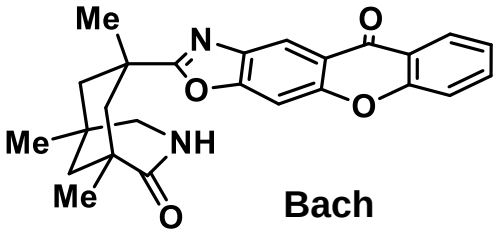


BUT enantioselective reactions remain difficult due to the **rapidity of the EnT**

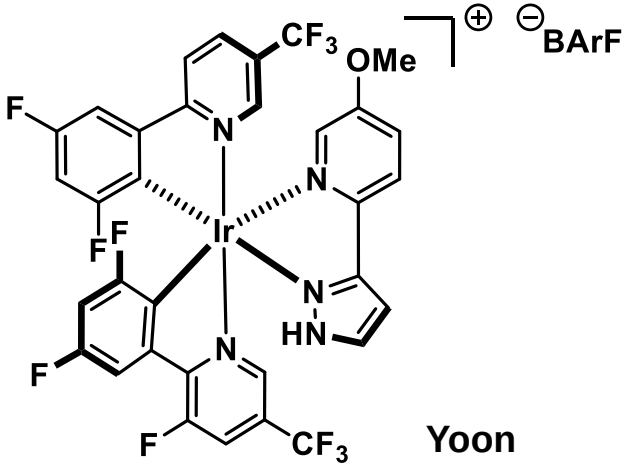
2 strategies:

✓ chiral sensitizer with non covalent binding site

✓ Dual catalytic systems (chiral LA + achiral sensitizer)



Bach



Yoon

Major challenges of EnT:

Designing new catalyst

- with higher E_T
- Replace Ru and Ir

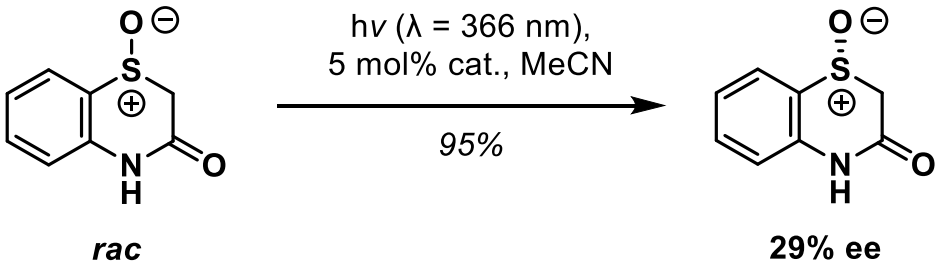
✓ New photocatalyst: quantum dots, heterogenous catalysis.

Expanding the range of enantioselective transformation using EnT

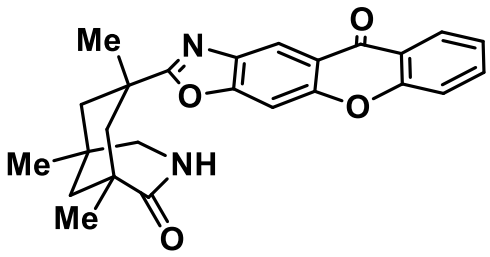
Adapting to industry (long reaction times, limited scalability…)

Thank you for your attention!

Propose a rationale for the reaction:

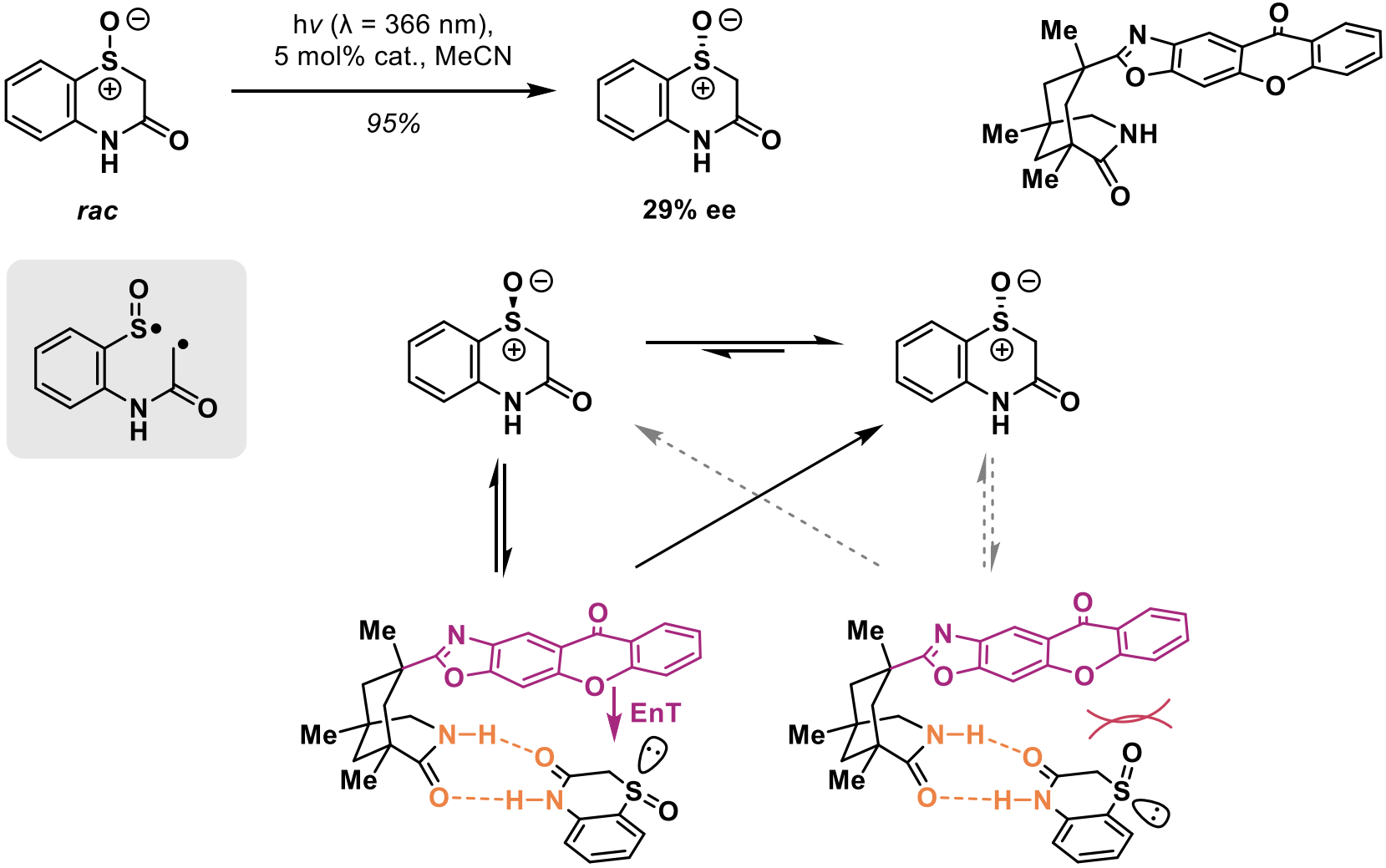


rac **29% ee**



Wimberger, L.; Kratz, T.; Bach, T. *Synthesis* **2019**, *51*, 4417−4424.

Propose a rationale for the reaction:



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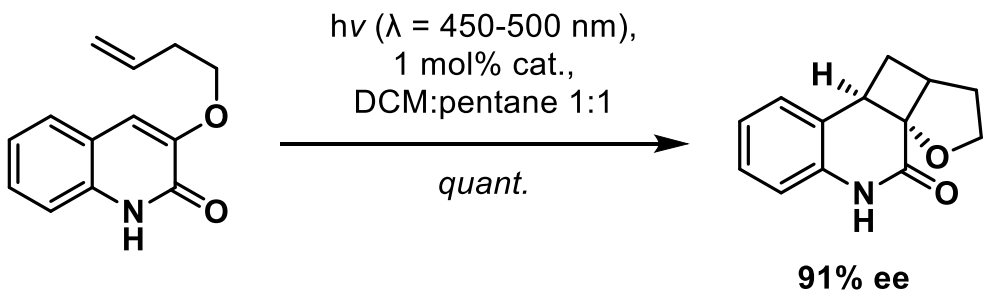

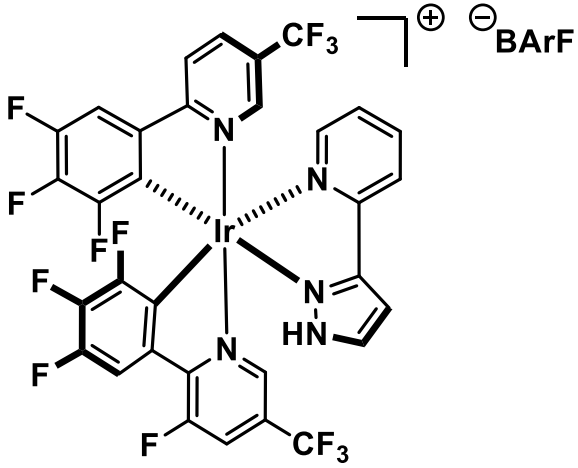

Skubi, K. L.; Kidd, J. B.; Jung, H.; Guzei, I. A.; Baik, M.-H.; Yoon, T. P. *J. Am. Chem. Soc.* **2017**, *139*, 17186−17192.

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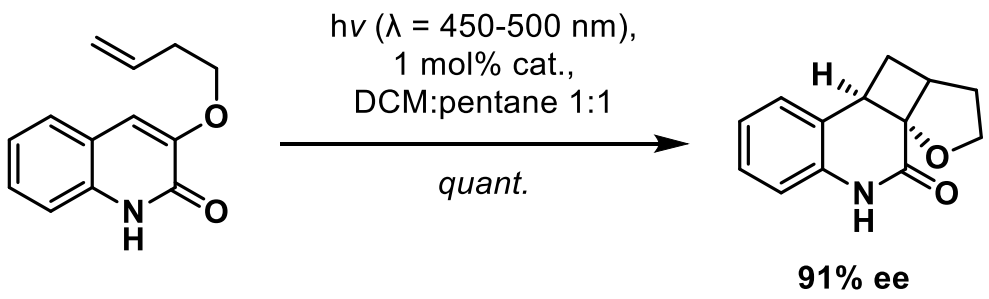
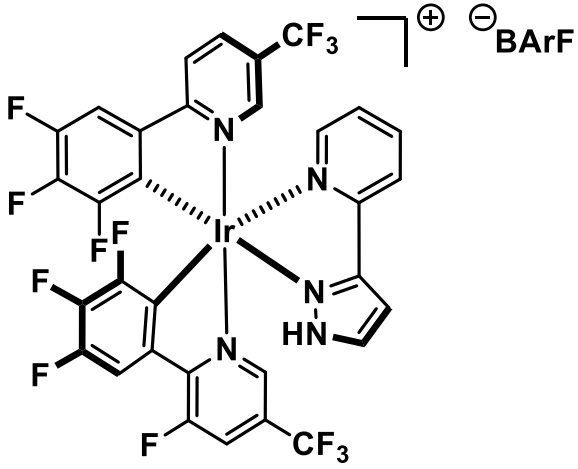
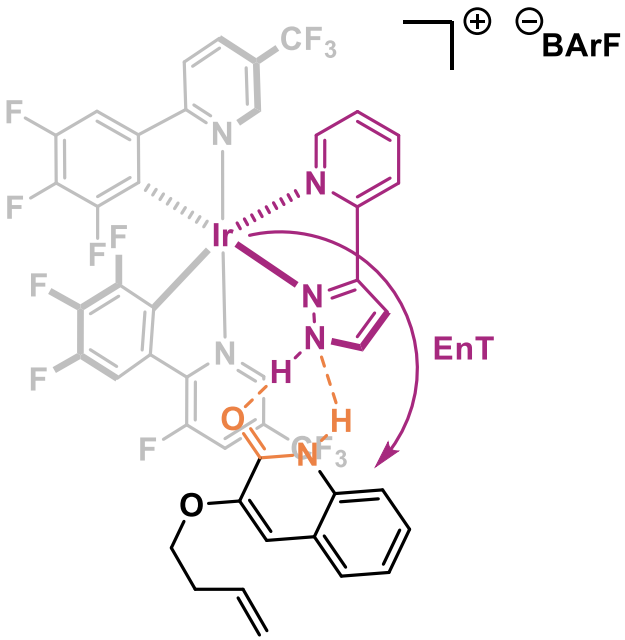






Skubi, K. L.; Kidd, J. B.; Jung, H.; Guzei, I. A.; Baik, M.-H.; Yoon, T. P. *J. Am. Chem. Soc.* **2017**, *139*, 17186−17192.

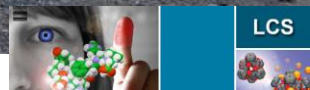
Organocatalysis in Enantioselective Radical Reactions

Dicky Wong

LCS

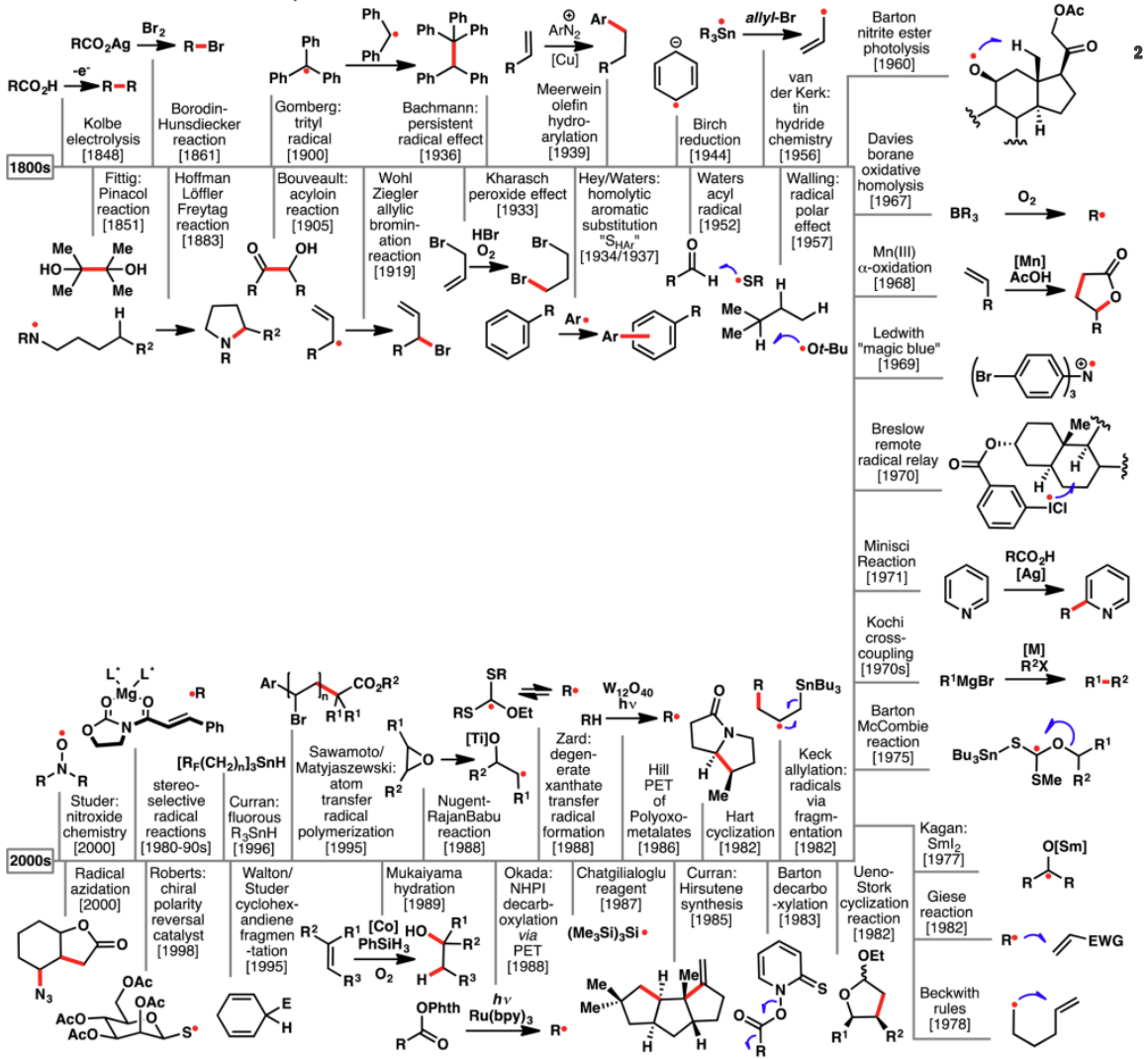
Prof. Kay Severin's group

Cancale, France



Introduction

- Frémy's salt (1845)
- First man-made persistent radical
- Advantage: Stereoselective preparation of radical precursor is not required
- Disadvantage: Stereochemical information lost upon formation of radical species



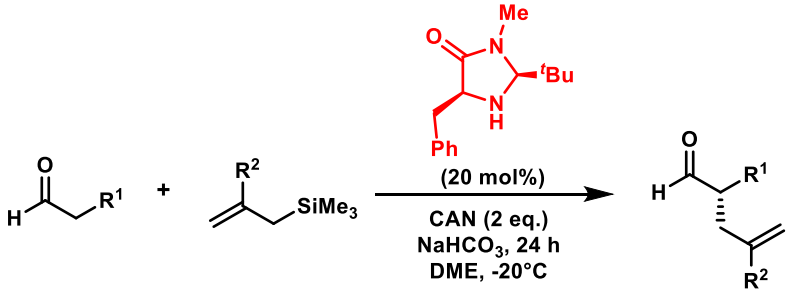
- M. Yan, J. C. Lo, J. T. Edwards, P. S. Baran, *J. Am. Chem. Soc.* **2016**, *138*, 12692–12714.

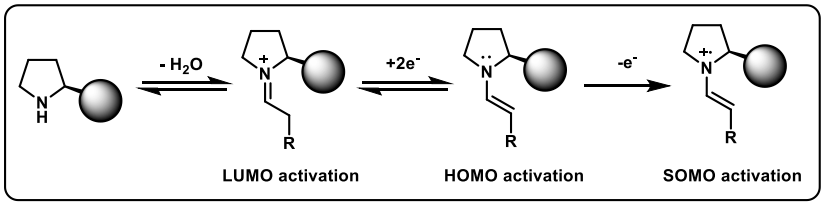
Modes of activation

1. Iminium/enamine formation
2. (Iminium) photocatalysis
3. NHC catalysis
4. Thiol catalyst
5. H-bonding catalyst
6. Lewis/Brønsted acid catalyst
7. Ion pairing

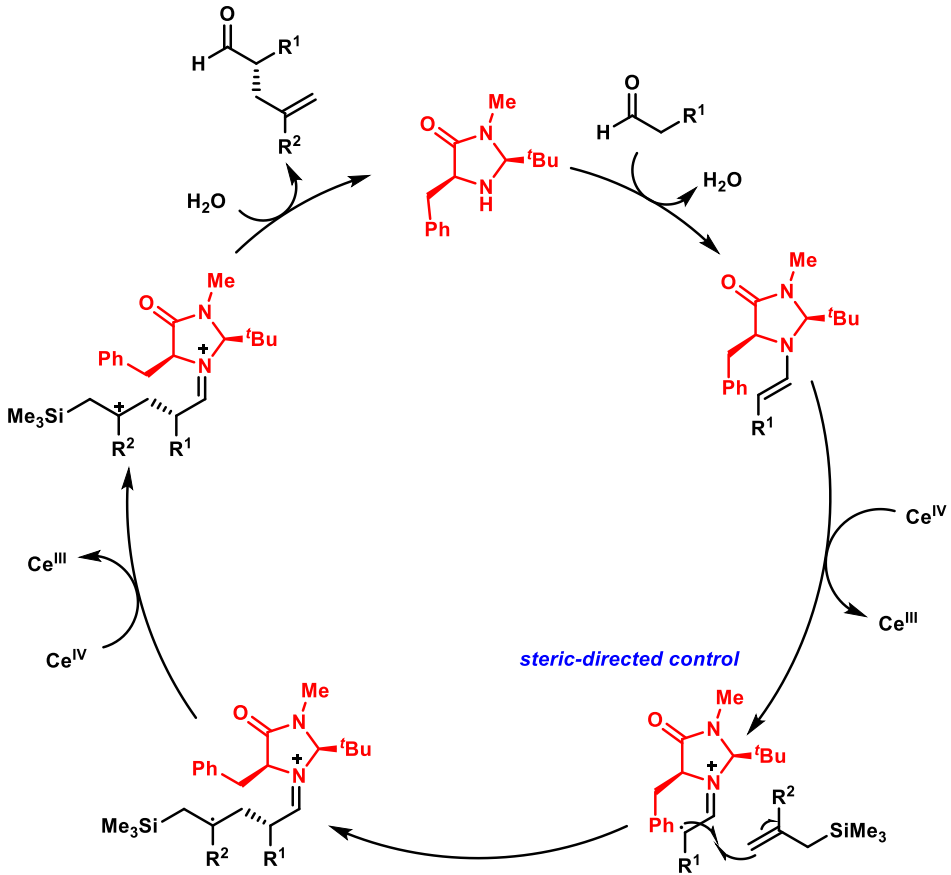
Early example: Iminium/Enamine

α-Allylation of aldehyde (MacMillan, 2007)



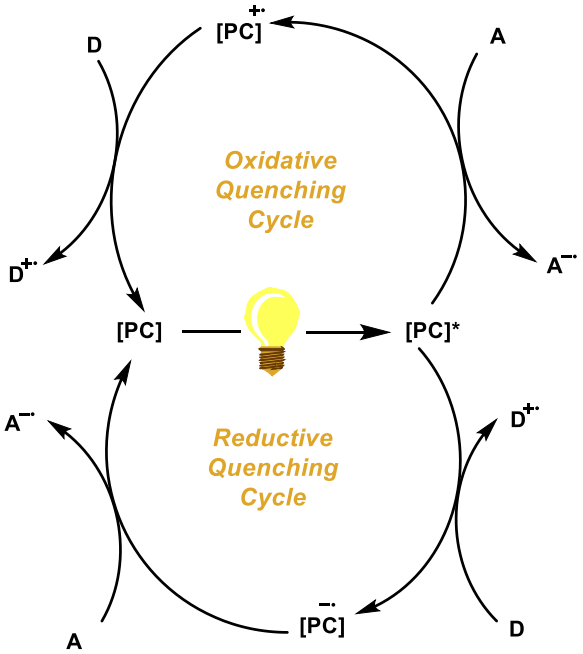


- Formation of iminium radical through SET activation with oxidant
- Pioneer work involving radical formation in enantioselective catalysis

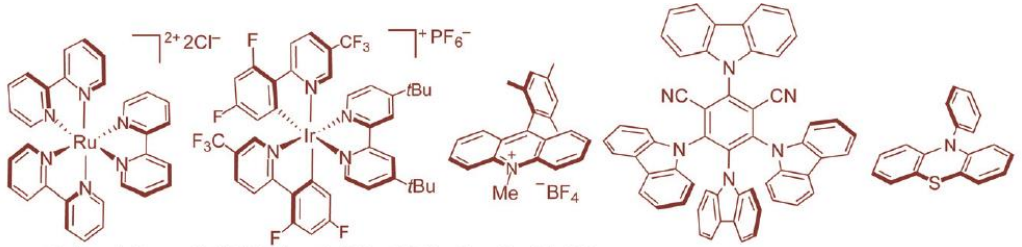


C. H. Bennett, G. Brassard, T. D. Beeson, A. Mastracchio, J.-B. Hong, K. Ashton, D. W. C MacMillan, *Science* **2007**, *316*, 582–585.

Photocatalysis



Common photoredox catalysts

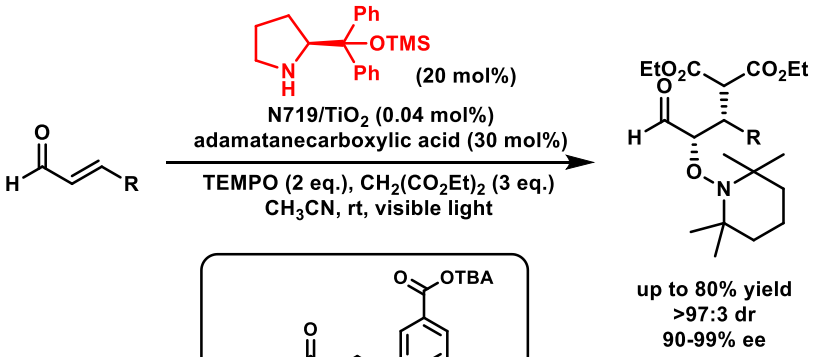


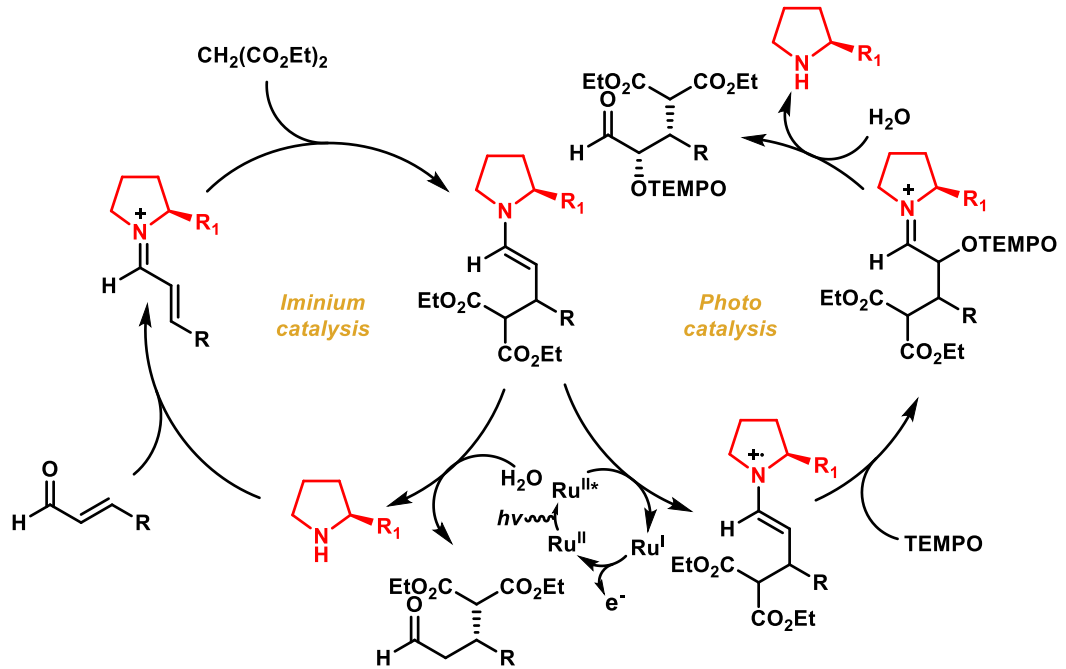
	$Ru(bpy)_3Cl_2$		$[Ir\{dF(CF_3)ppy\}_2(dtbpy)]PF_6$		Mes-Acr-Me BF_4		4CzIPN		Ph-PTH	
λ_{max} (nm)	454		380		429	in DCE	435		<300	
λ_{em} (nm)	605	in MeCN	470	in MeCN	509		539	in MeCN	443	in MeCN
ET (kcal/mol)	47.3		60.8		48.5		56.4		none	
$E_{1/2}(PC^+/PC^*)$	−0.81		−0.89		−0.55	in MeCN	−1.18		−2.10	
$E_{1/2}(PC^*/PC^-)$	+0.77		+1.21		+2.12		+1.43		+0.68	

- Y. Sumida, H. Ohmiya, *Chem. Soc. Rev.* **2021**, *50*, 6320–6332.

Photocatalysis

Michael Addition/Oxyamination via TiO_2/N719 Dye-Sensitized Organophotocatalysis (Jang, 2012)



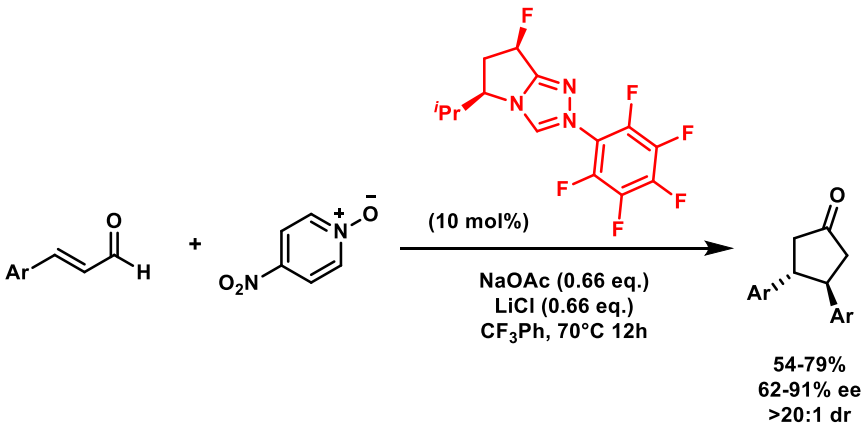


- Multicatalytic system: asymmetric iminium catalysis combined with photoinduced SOMO catalysis

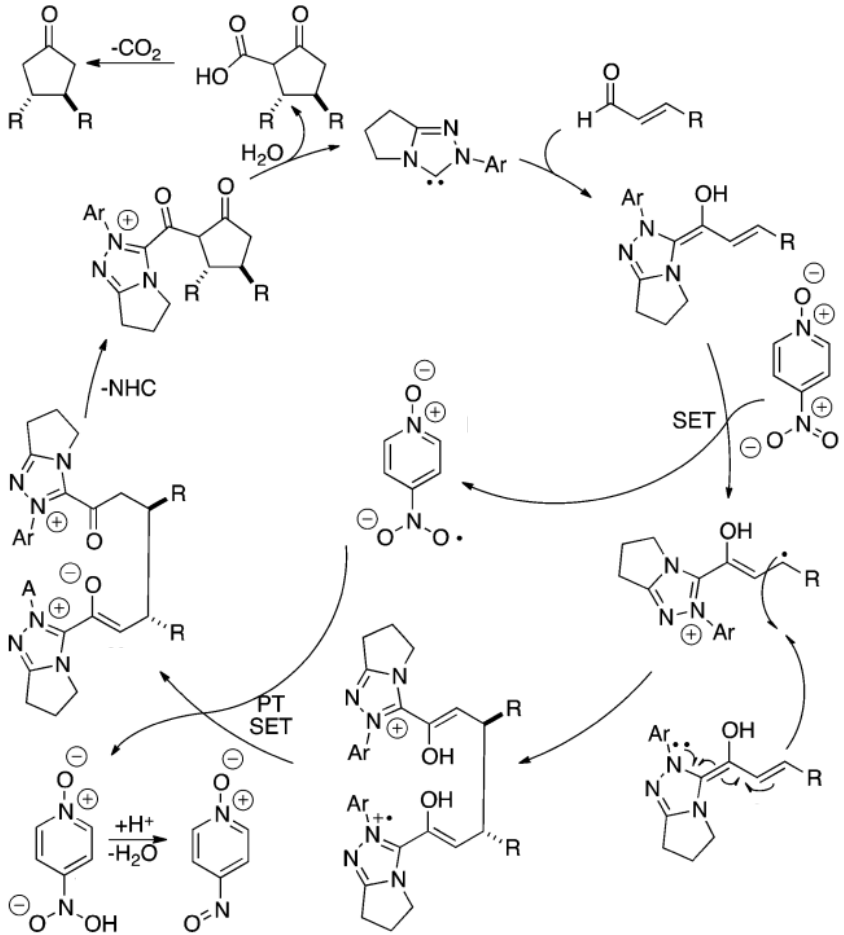
H. S. Yoon, X. H. Ho, J. Jang, H. J. Lee, S. J. Kim, H. Y. Jang, *Org. Lett.* **2012**, *14*, 3272–3275.

Enantioselective NHC catalysis

Oxidatively initiated NHC-catalyzed synthesis of cyclopentanones from enals (Rovis, 2015)



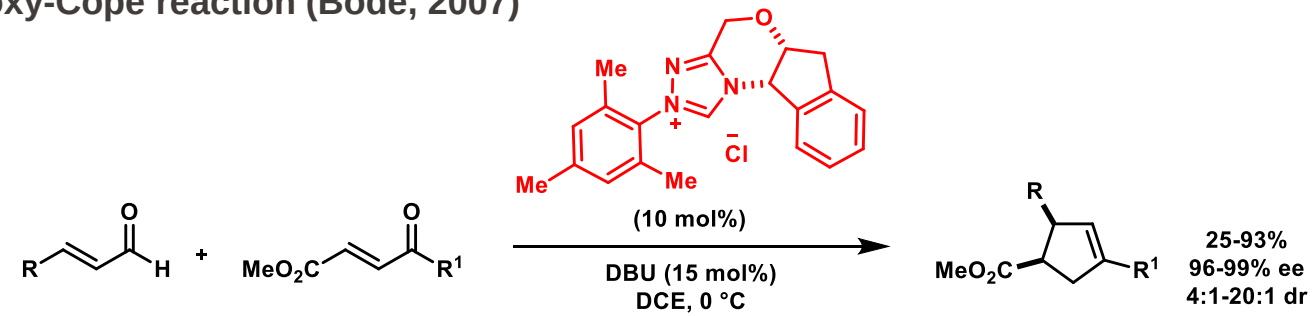
- Formation of Breslow intermediate
- SET from Breslow intermediate to 4-nitropyridine N-oxide to generate radical cation species
- Steric-control enantioselectivity



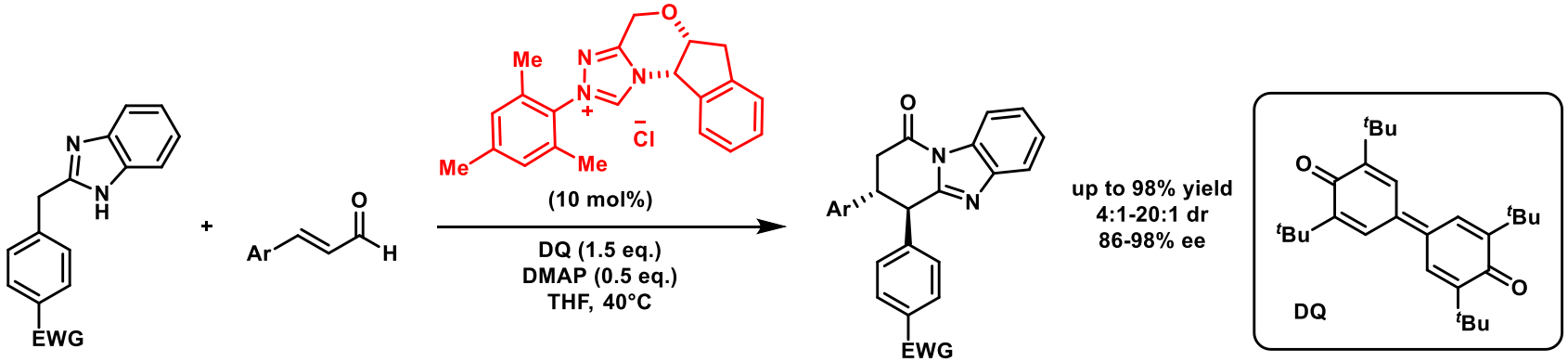
N. A. White, T. Rovis, *J. Am. Chem. Soc.* **2015**, *137*, 10112–10115.

Enantioselective NHC catalysis

Benzoin-oxy-Cope reaction (Bode, 2007)



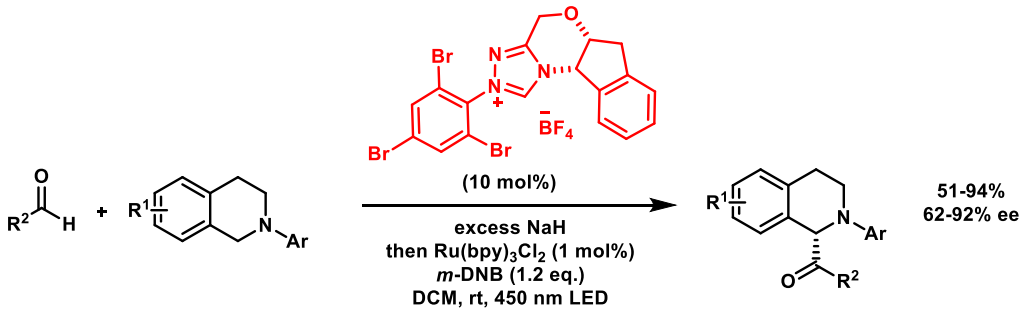
Enantioselective oxidative coupling of enals and di(hetero)arylmethanes (Chi, 2018)



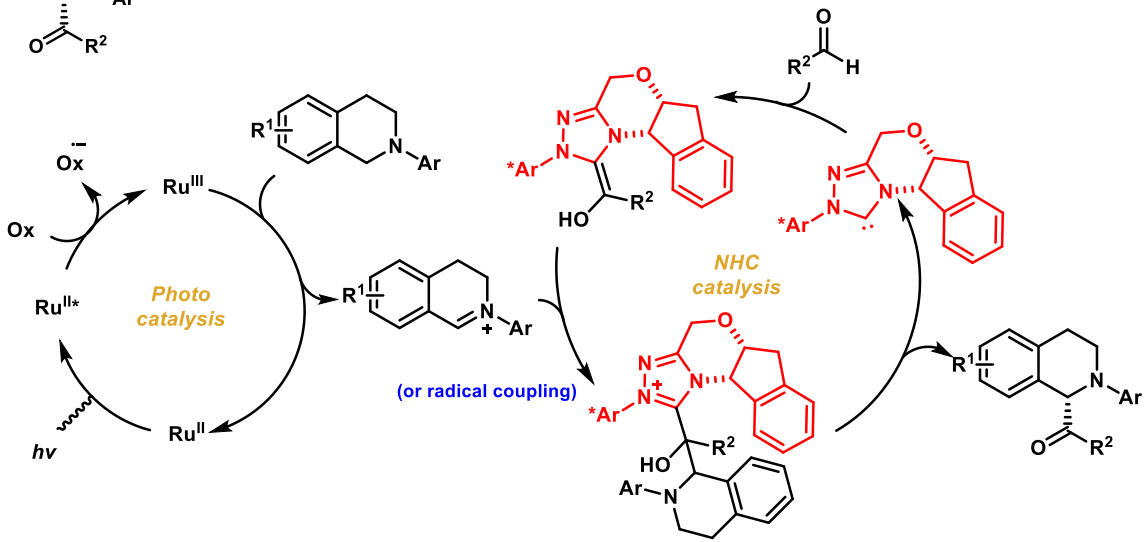
P. C. Chiang, J. Kaeobamrung, J. W. Bode, *J. Am. Chem. Soc.* **2007**, *129*, 3520–3521.
Q. Chen, T. Zhu, P. K. Majhi, C. Mou, H. Chai, J. Zhang, S. Zhuo, Y. R. Chi, *Chem. Sci.* **2018**, *9*, 8711–8715.

Enantioselective NHC/photocatalysis

Asymmetric α-acylation of tertiary amines by dual catalysis (Rovis, 2012)



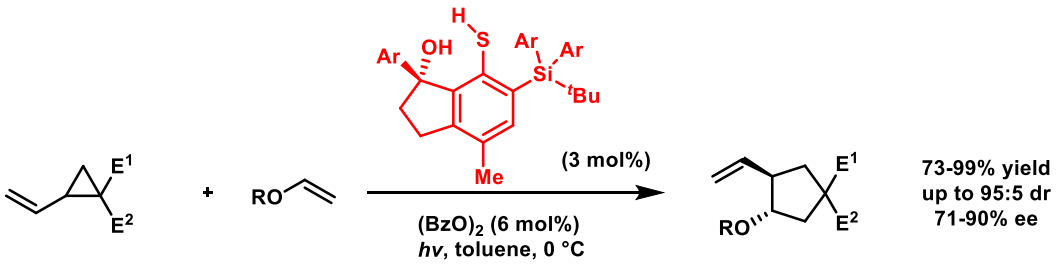
- First example of enantioselective NHC/photocatalysis
- *m*-DNB: act as oxidant to oxidize Ru^{II}* and consecutively oxidizes the amine to iminium ion



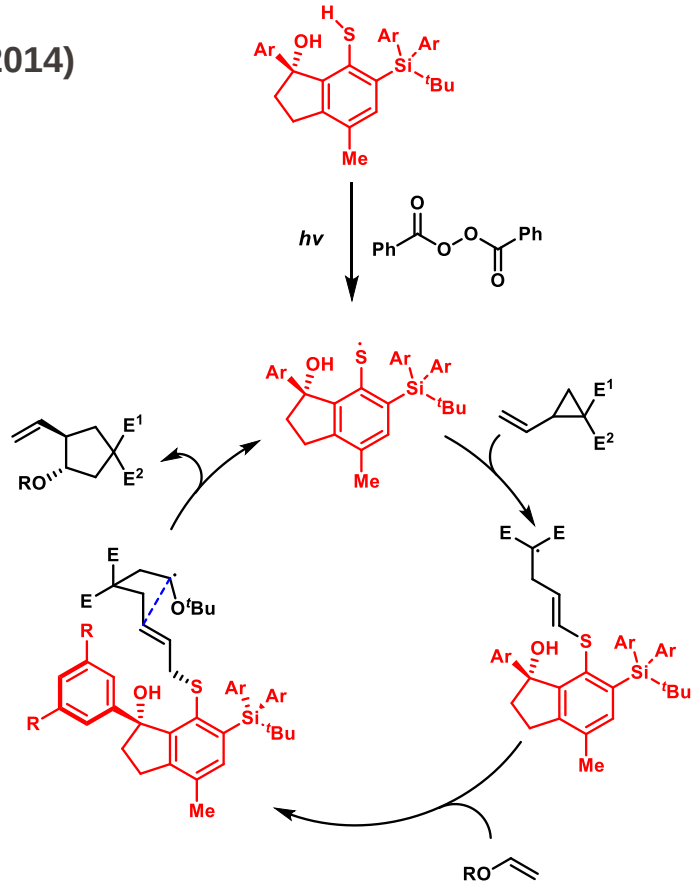
D. A. DiRocco, T. Rovis, *J. Am. Chem. Soc.* **2012**, *134*, 8094–8097.

Chiral Thiol Catalyst

Chiral thiols in the synthesis of vinylcyclopentanes (Maruoka, 2014)



73-99% yield
up to 95:5 dr
71-90% ee

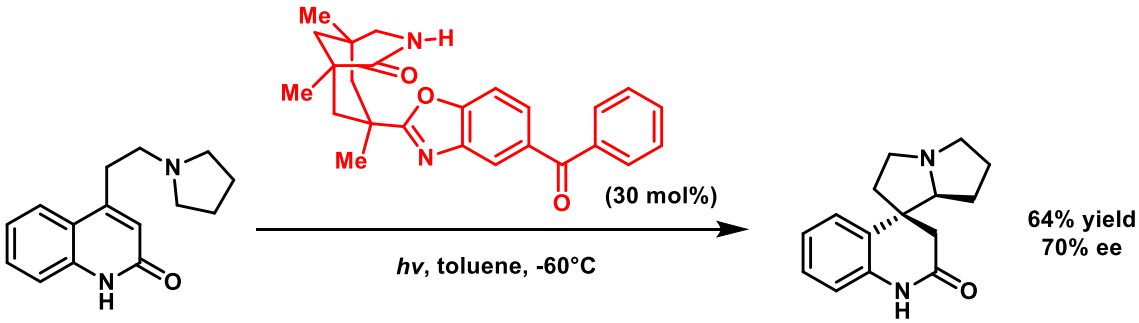


- Asymmetric radical C-C bond formation
- Inability of conventional chiral scaffolds to provide an efficient chiral environment

T. Hashimoto, Y. Kawamata, K. Maruoka, *Nat. Chem.* **2014**, *6*, 702–705.

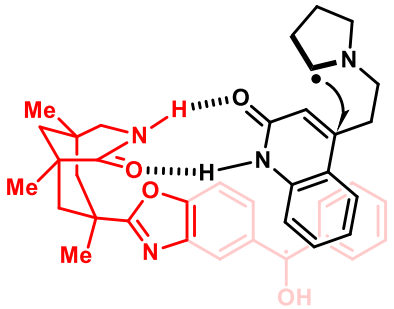
H-Bonding catalyst

Chiral H-bond-mediated radical conjugate addition (Bach, 2005)



- Excitation (λ > 300 nm) of the benzophenone catalyst and SET with quinolone substrate (or remote HAT)
- Followed by enantioselective radical conjugate addition of α-amino alkyl radical to enone moiety

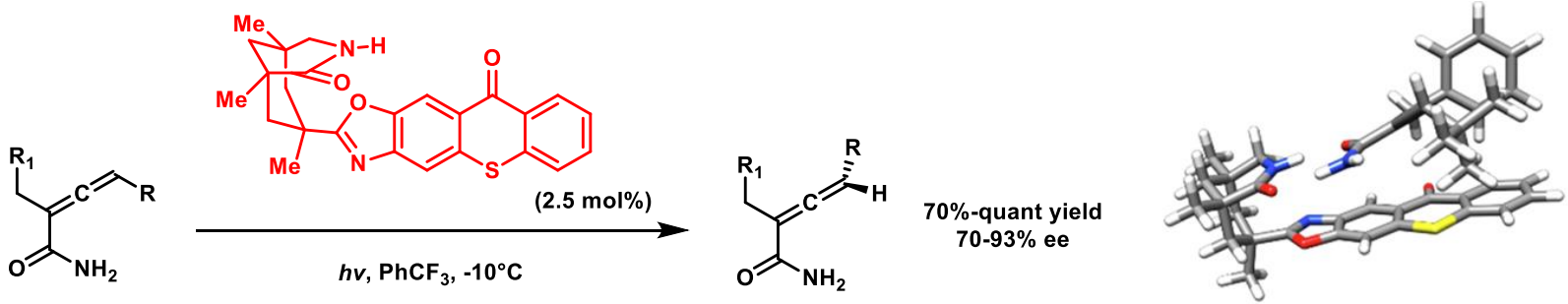
Possible transition state:



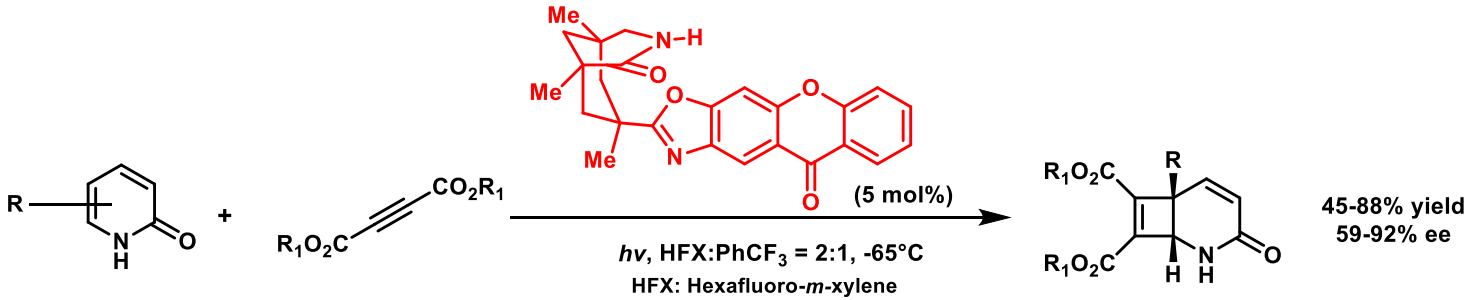
A. Bauer, F. Westkämper, S. Grimme, T. Bach, *Nature* **2005**, *436*, 1139–1140.

H-Bonding catalyst

Photochemical deracemization of primary allene amides by triplet energy transfer (Bach, 2021)



Intermolecular [2+2] photocycloaddition between 2-pyridines and acetylenedicarboxylates (Bach, 2014)

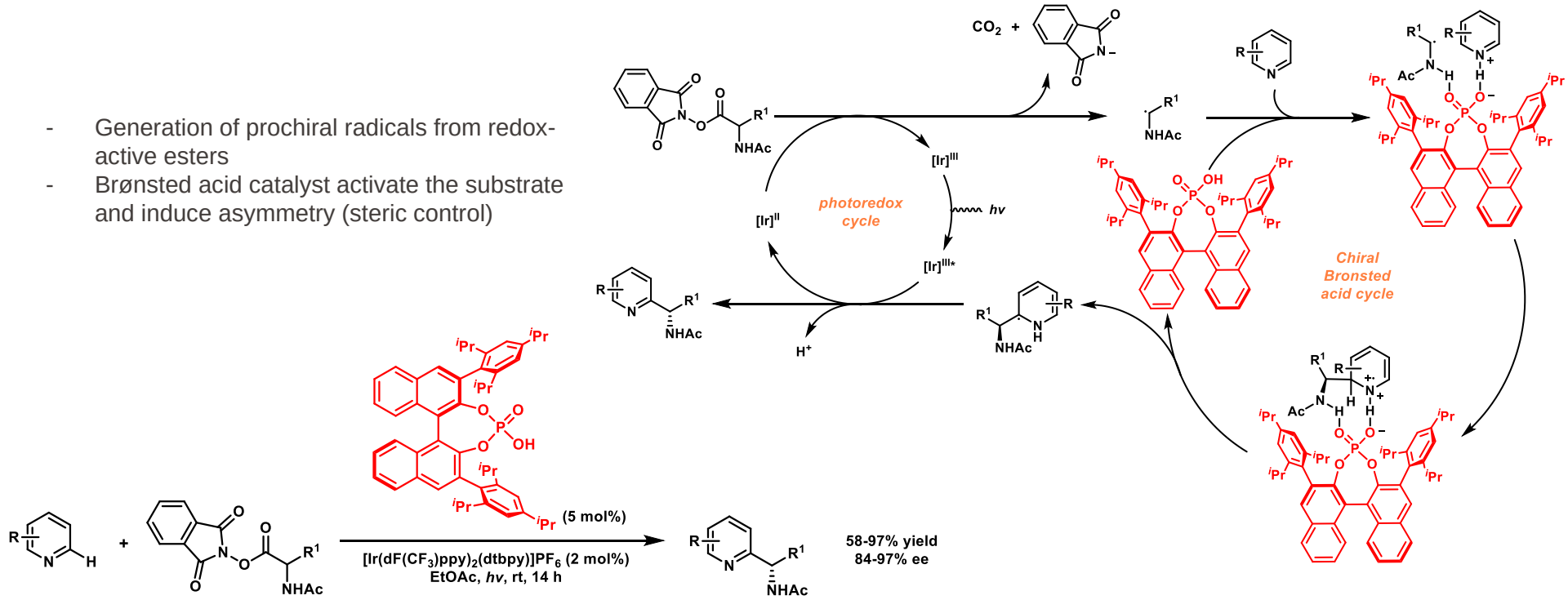


- M. Plaza, J. Großkopf, S. Breitenlechner, C. Bannwarth, T. Bach, *J. Am. Chem. Soc.* **2021**, *143*, 11209–11217.
  M. M. Maturi, T. Bach, *Angew. Chem. Int. Ed.* **2014**, *53*, 7661–7664.

Lewis/Brønsted acid catalyst

Catalytic enantioselective Minisci-type addition to heteroarenes (Phipps, 2018)

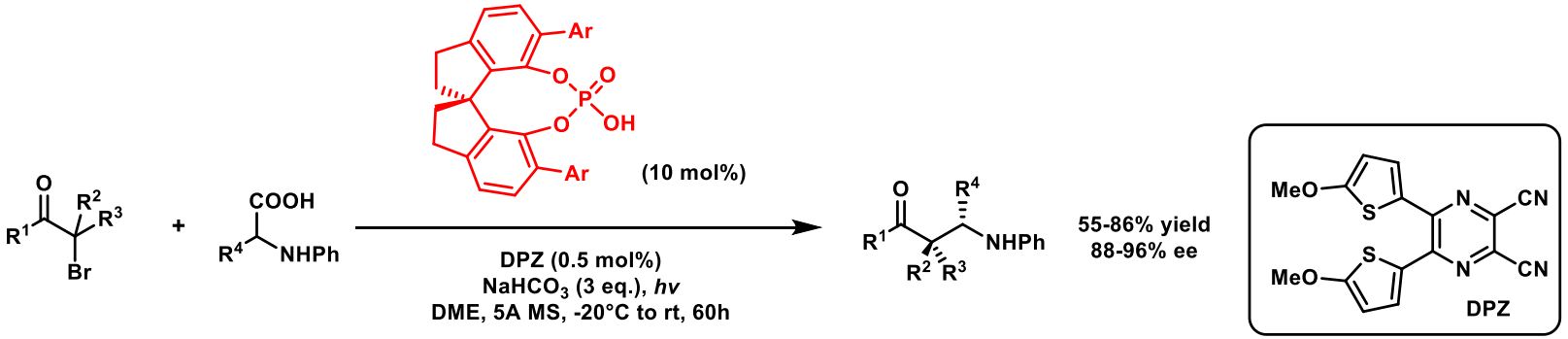
- Generation of prochiral radicals from redox-active esters
- Brønsted acid catalyst activate the substrate and induce asymmetry (steric control)



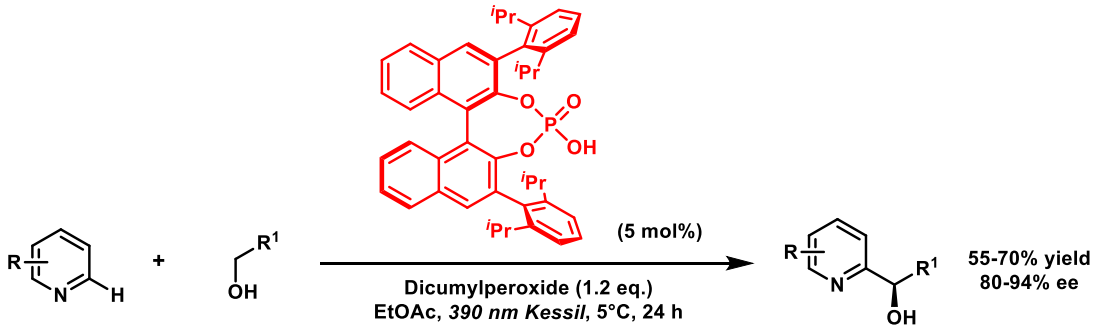
R. S. J. Proctor, H. J. Davis, R. J. Phipps, *Science* **2018**, *360*, 419–422.

Lewis/Brønsted acid catalyst

SPINOL-phosphoric acid as Lewis acid catalyst in the synthesis of β-amino acids (Jiang, 2018)



HAT-driven enantioselective Minisci Reaction of alcohols (Ermanis & Phipps, 2022)

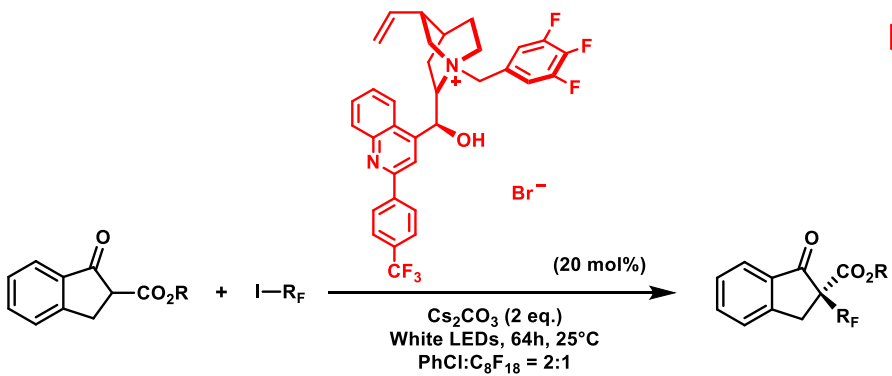


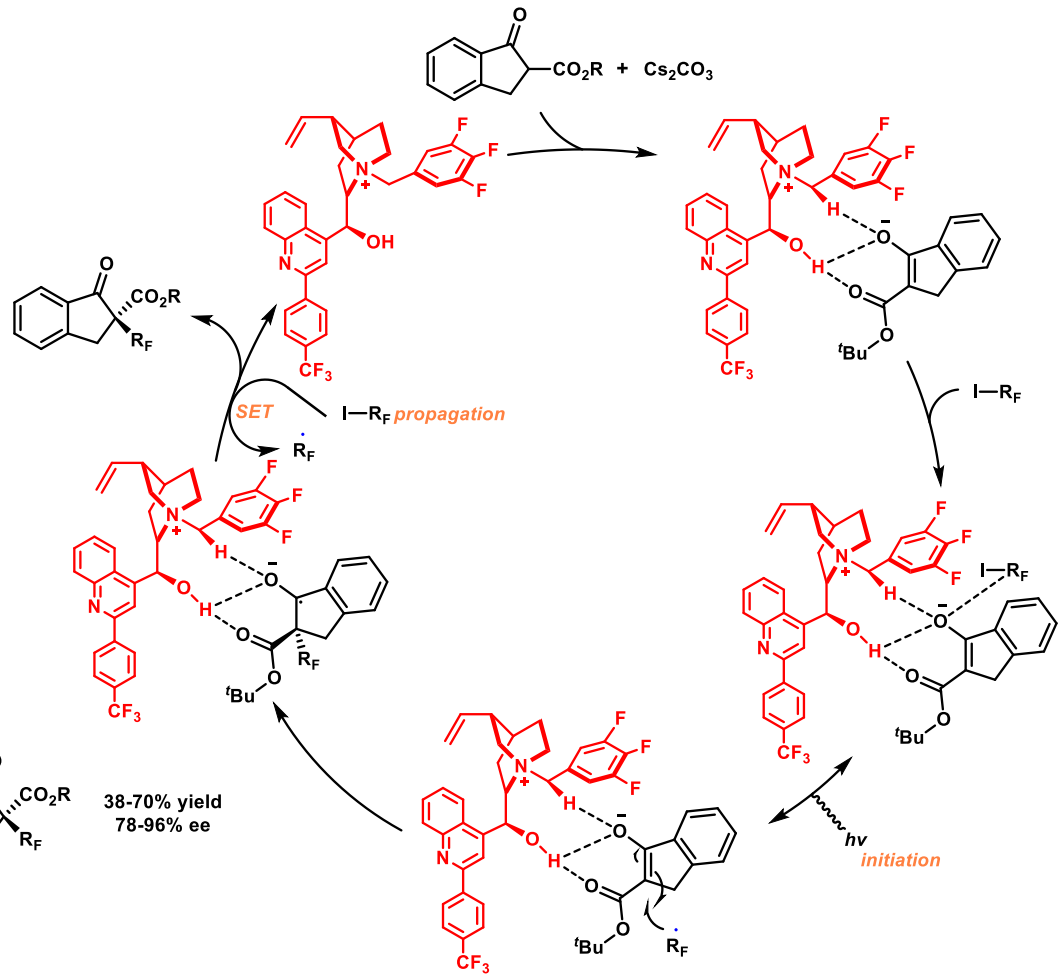
- J. Li, M. Kong, B. Qiao, R. Lee, X. Zhao, Z. Jiang, *Nat. Comm.* **2018**, *9*, 1–9.
- A. C. Colgan, R. S. J. Proctor, D. C. Gibson, P. Chuentragool, A. S. K. Lahdenperä, K. Ermanis, R. J. Phipps, *Angew. Chem. Int. Ed.* **2022**, *61*, e202200266.

Ion-pairing

Enantioselective perfluoroalkylation of β-ketoesters (Melchiorre, 2015)

- Generation of enolate–chiral cation complex to form EDA complex (π-σ* orbital interaction) with perfluoroalkyl iodides
- Chiral PTC provides steric to allow the enantioselective R_F radical cation for attacking the enolate

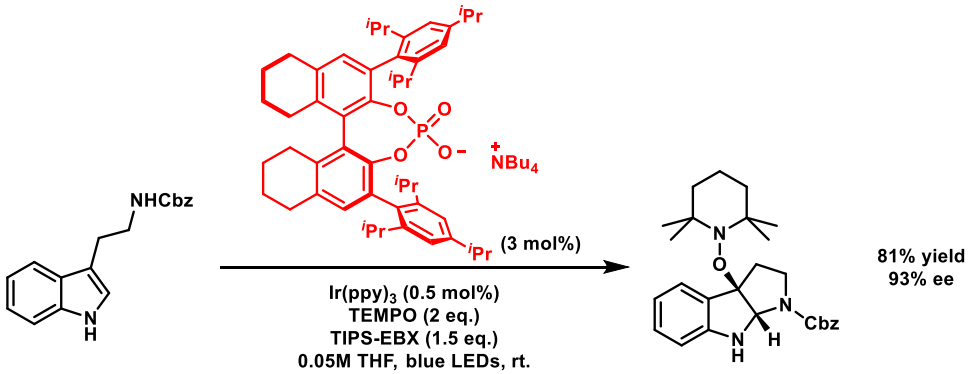




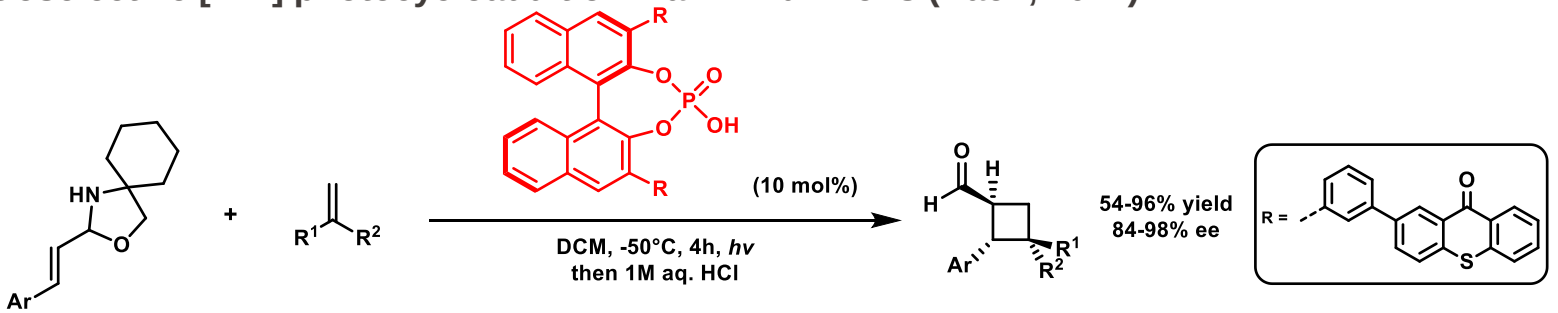
Ł. Woźniak, J. J. Murphy, P. Melchiorre, *J. Am. Chem. Soc.* **2015**, *137*, 5678–5681.

Ion-pairing

Synthesis of Pyrroloindolines via non-covalent stabilization of indole radical cations(Knowles, 2018)

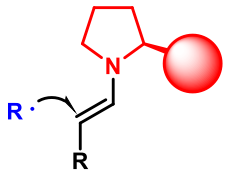


Enantioselective [2+2] photocycloaddition via iminium ions (Bach, 2021)

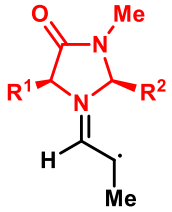


- E. C. Gentry, L. J. Rono, M. E. Hale, R. Matsuura, R. R. Knowles, *J. Am. Chem. Soc.* **2018**, *140*, 3394–3402.
  F. Pecho, Y. Sempere, J. Gramüller, F. M. Hörmann, R. M. Gschwind, T. Bach, *J. Am. Chem. Soc.* **2021**, *143*, 9350–9354.

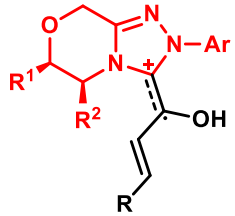
Conclusion & Outlook



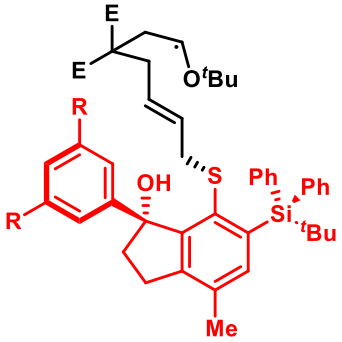
Iminium/enamine



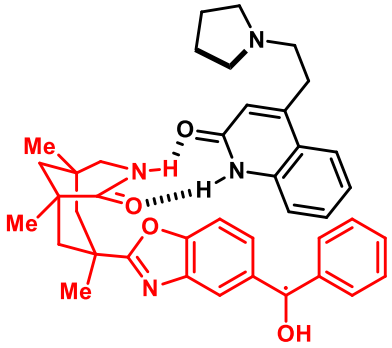
Photocatalysis



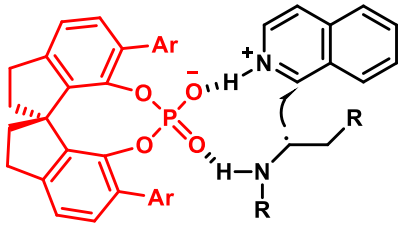
NHC catalysis



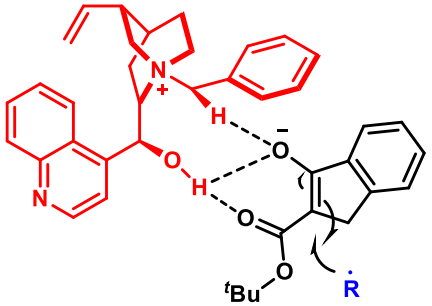
Thiol catalyst



H-bonding catalyst

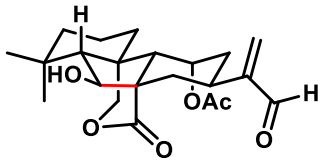


Lewis acid catalysis

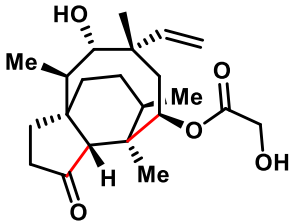


Ion pairing

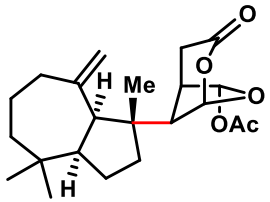
Conclusion & Outlook



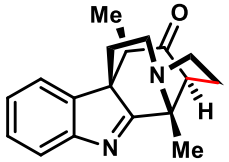
(-)-Maoecrystal Z



(+)-Pleuromutlin



(-)-Aplyviolene



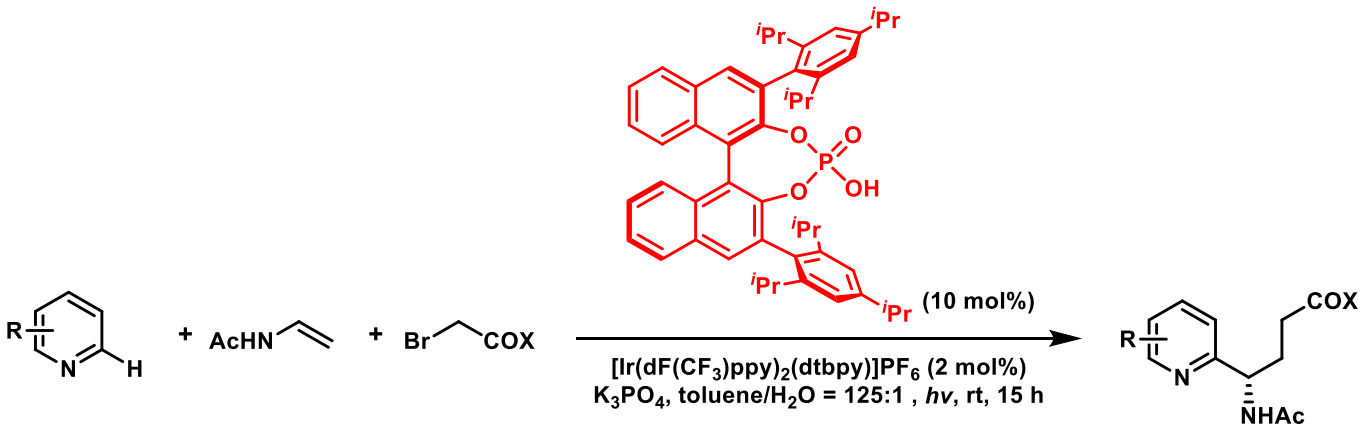
(-)-Arborisidine

- Rapid generation of complexity in total synthesis
- Enantioselective radical reactions can open a new route to various applications, including drugs and natural products

M. Yan, J. C. Lo, J. T. Edwards, P. S. Baran, *J. Am. Chem. Soc.* **2016**, *138*, 12692–12714.
F.-Y. Wang, L. Jiao, F.-Y. Wang, L. Jiao, *Angew. Chem. Int. Ed.* **2021**, *60*, 12732–12736.

Question 1

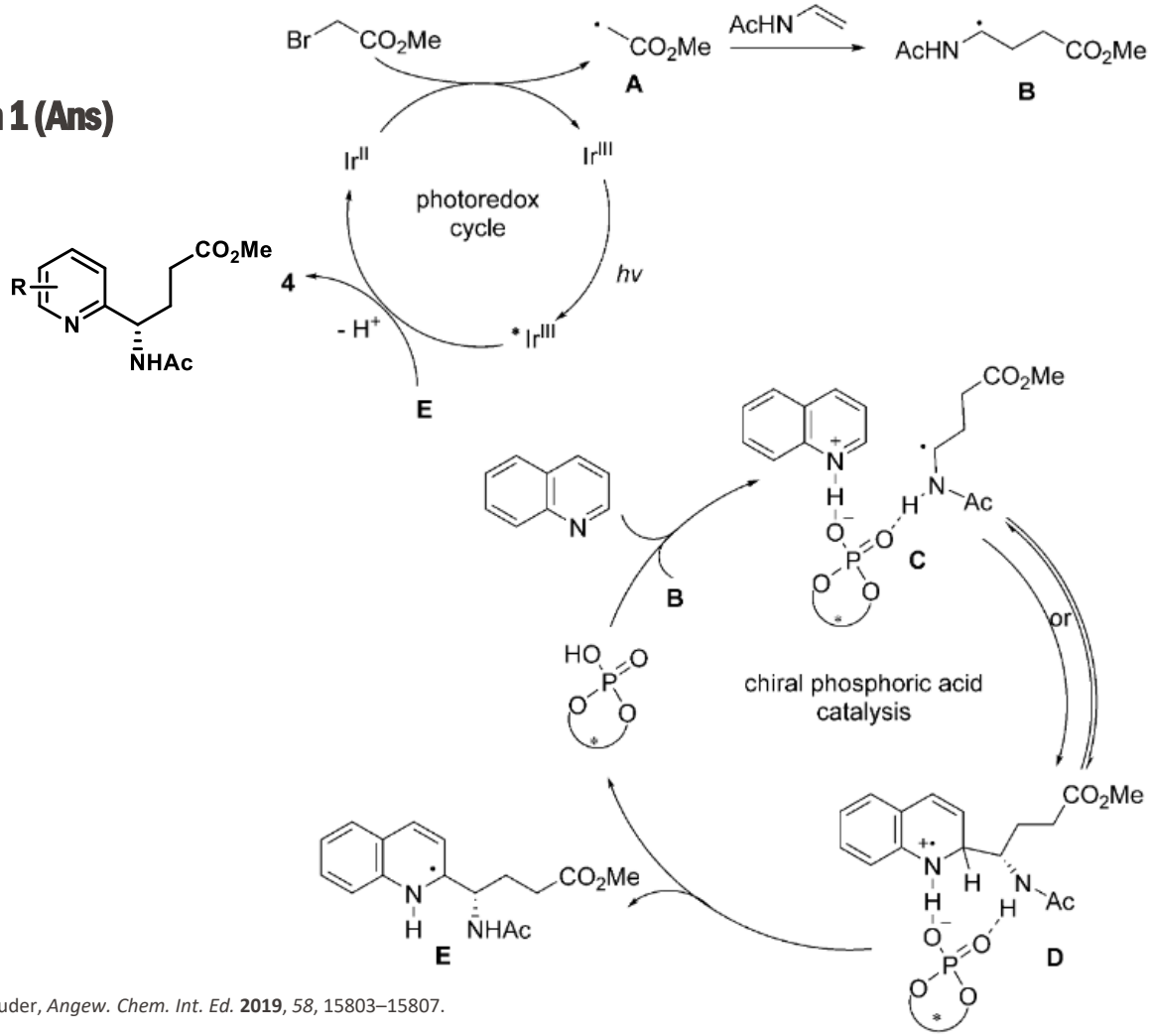
In 2019, Studer's group reported an asymmetric synthesis of heterocyclic γ-amino-acid and diamine derivatives by three-component radical cascade reactions. The general reaction is shown in the following scheme:



Identify the mode of activation, and provide the full catalytic cycle of this reaction.

- D. Zheng, A. Studer, *Angew. Chem. Int. Ed.* **2019**, *58*, 15803–15807.

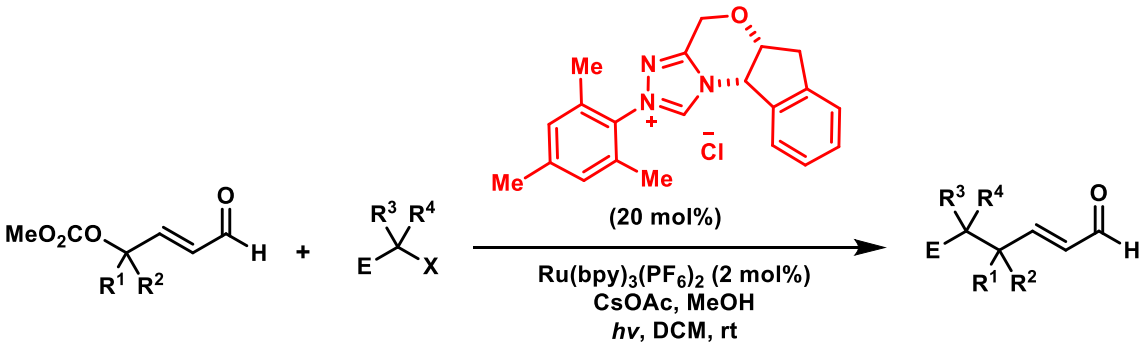
Question 1 (Ans)



D. Zheng, A. Studer, *Angew. Chem. Int. Ed.* **2019**, *58*, 15803–15807.

Question 2

In 2019, Ye's group reported visible-light-driven NHC catalyzed γ- and ε-alkylation with alkyl radicals with chiral NHC precursors as the pre-catalyst. The general reaction is shown in the following scheme:

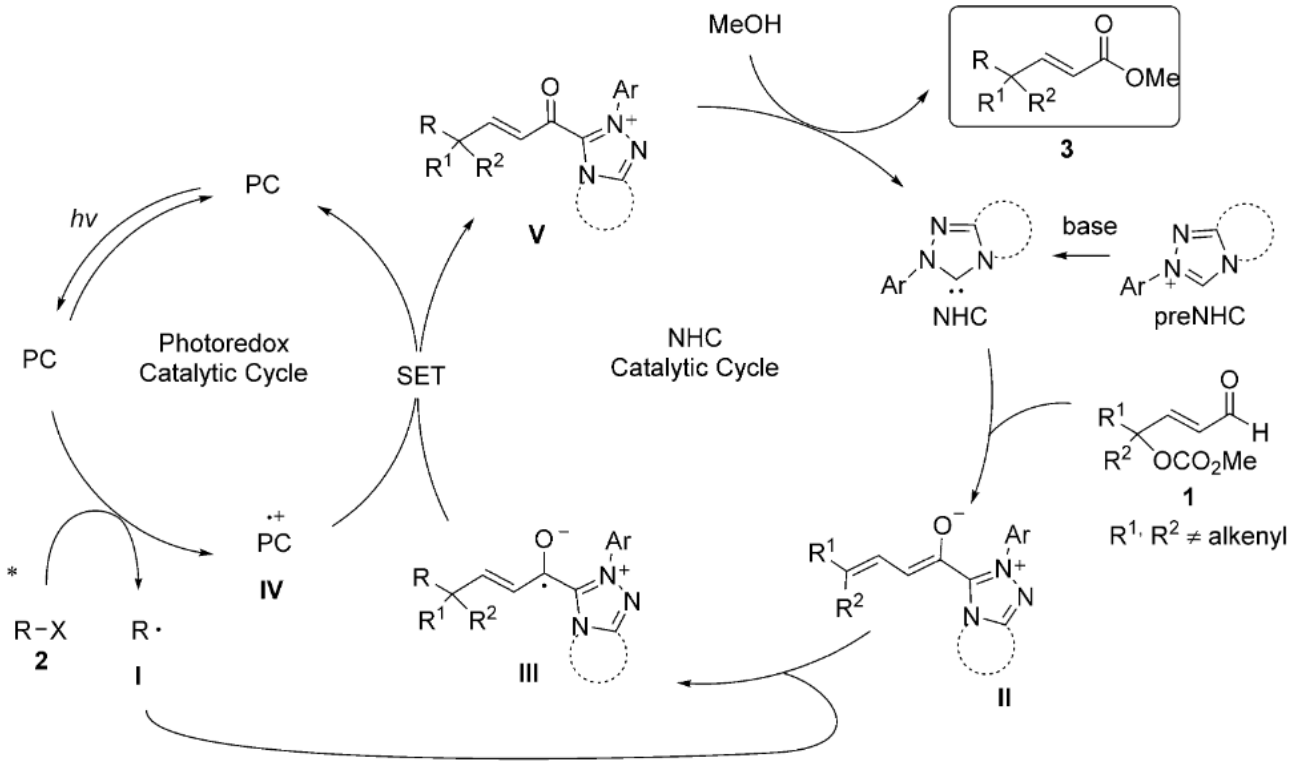


(a) Identify the mode of activation, and provide the full catalytic cycle of this reaction.

(b) (Open question) From the paper, they used the same R^1/R^2 and R^3/R^4 group. When they used different R^1/R^2 and R^3/R^4 group and generate chiral carbons, low enantioselectivity (12-29% ee) was observed. What could be the reason?

L. Dai, Z. H. Xia, Y. Y. Gao, Z. H. Gao, S. Ye, *Angew. Chem. Int. Ed.* **2019**, *58*, 18124–18130.

Question 2 (Ans)



(b) Possible explanation: R^1R^2 selectivity to from olefin in II is low, or the distance of the conjugated Breslow intermediate is too long, which the enantiopure NHC cannot control the enantioselectivity efficiently

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