Application of Dihydropyridines in Photochemistry as Radical Precursors

Mikus Puriņš

Laboratory of Catalysis and Organic Synthesis
École Polytechnique Fédérale de Lausanne

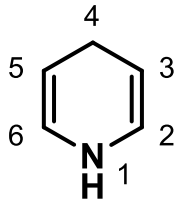
Lausanne – SWITZERLAND
mikus.purins@epfl.ch

Frontiers in Chemical Synthesis II: Heterocyclic chemistry
17.05.2021

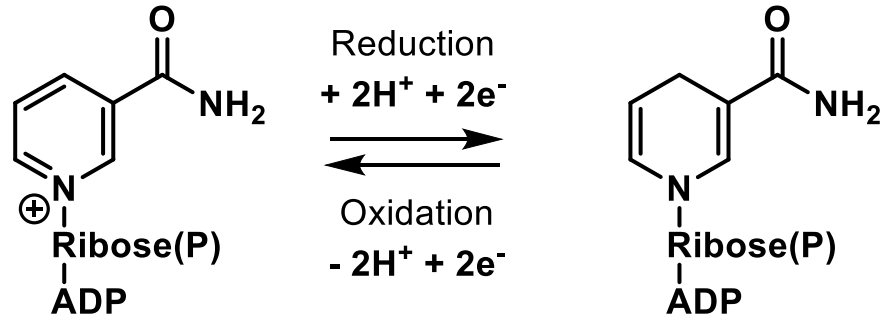
Outline

- **Context and the synthesis of DHPs**
- Application in photocatalysis
  - Photoredox catalysis
  - Metallaphotoredox catalysis
  - Excited state reactivity
- Conclusions and perspectives

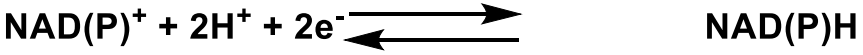
Historical and biological context



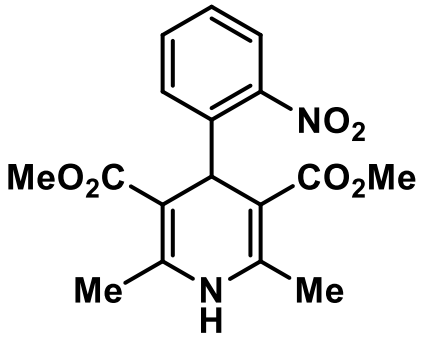
1,4-dihydropyridine



Biochemical Journal **2007**, *402* (2), 205–218.



Calcium channel blockers



Nifedipine
Adalat

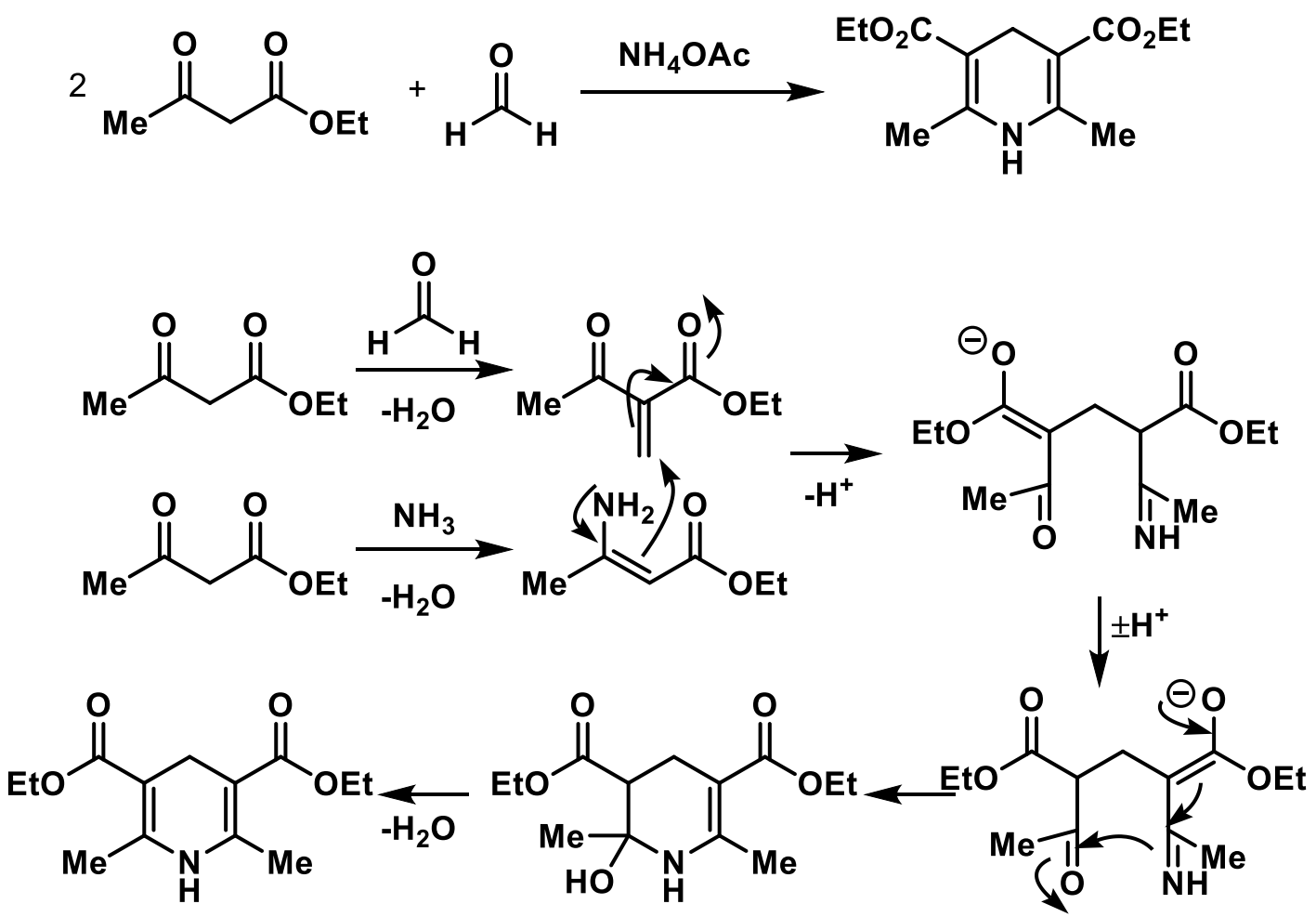
Prof. Gunārs Duburs

Born 1934

- **Candidate of Chemical Sciences dissertation** - *Synthesis and Properties of Dibenzoylenedihydropyridines and Dibenzoylenepyridines*
- **Doctoral dissertation** - *The Reactivity and Biological Properties of 1,4-Dihydropyridines*
- At least **153** papers on dihydropyridines

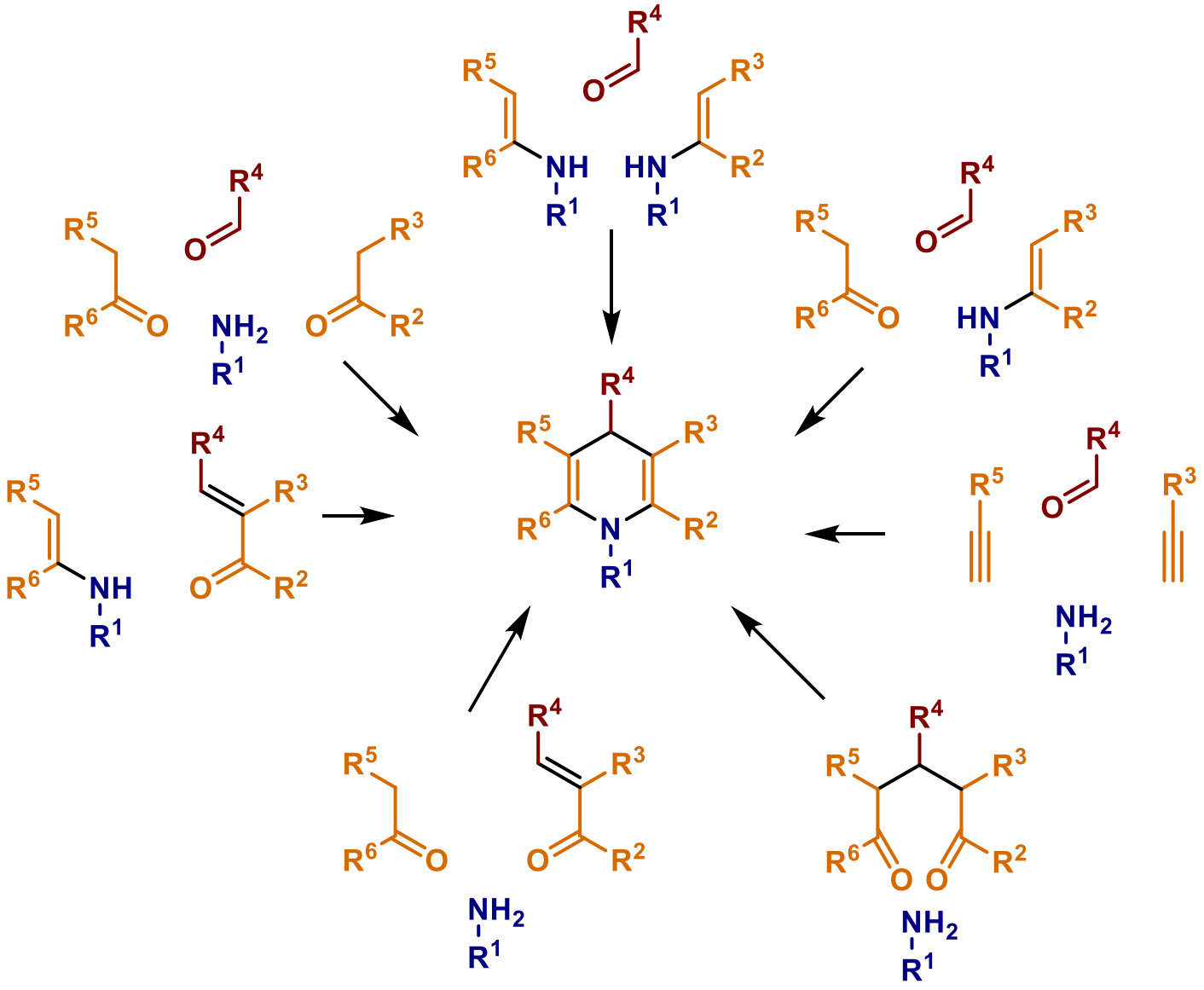
Chem Heterocycl Comp **2015**, *50* (10), 1365–1366.

Synthesis of DHPs - historical



Ber. Dtsch. Chem. Ges. **1881**, *14*, 1637-1638.

Synthesis of DHPs - modern

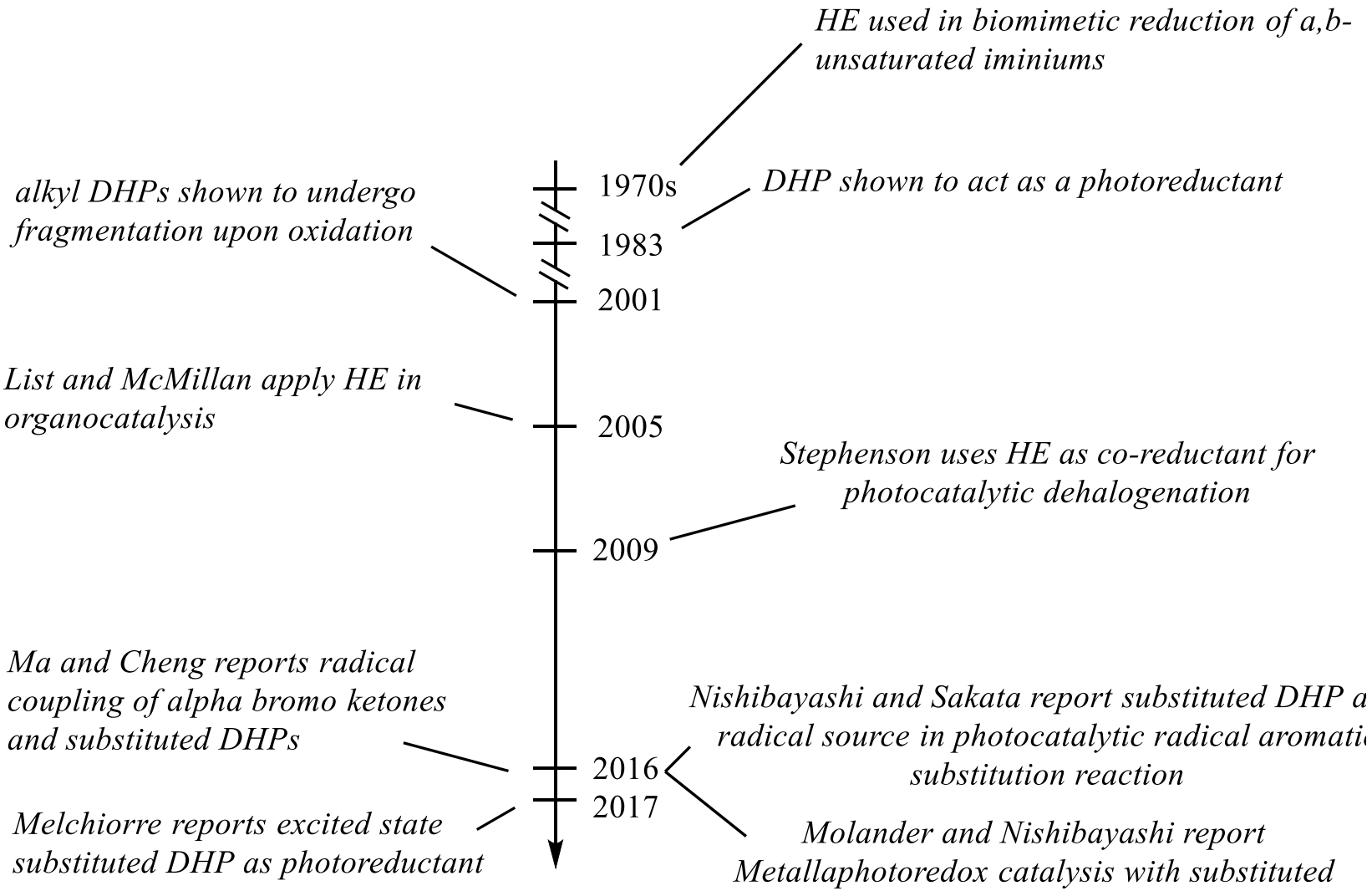


Heterocycles **1988**, *27* (1), 269.
Chem Heterocycl Compd **1992**, *28* (4), 363–391.

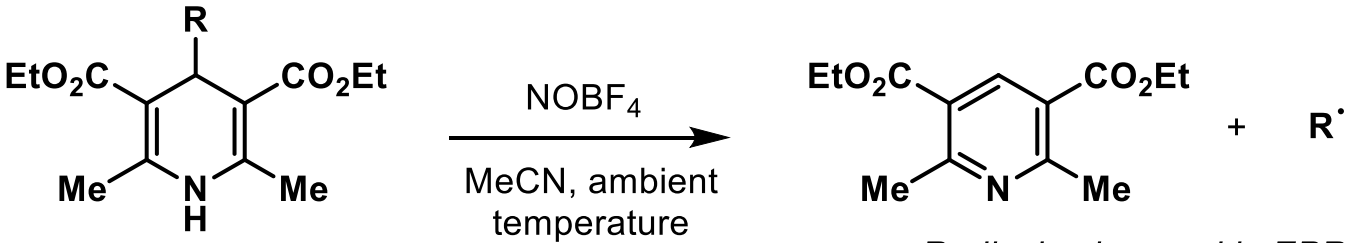
Outline

- Context and the synthesis of DHPs
- **Application in photocatalysis**
  - Photoredox catalysis
  - Metallaphotoredox catalysis
  - Excited state reactivity
- Conclusions and perspectives

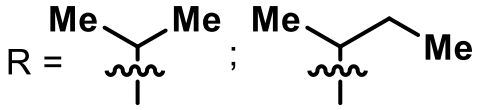
Timeline


HE used in biomimetic reduction of a,b-unsaturated iminiums
1970s
DHP shown to act as a photoreductant
alkyl DHPs shown to undergo fragmentation upon oxidation
1983
2001
List and McMillan apply HE in organocatalysis
2005
Stephenson uses HE as co-reductant for photocatalytic dehalogenation
2009
Ma and Cheng reports radical coupling of alpha bromo ketones and substituted DHPs
Nishibayashi and Sakata report substituted DHP a radical source in photocatalytic radical aromati substitution reaction
2016
2017
Melchiorre reports excited state substituted DHP as photoreductant
Molander and Nishibayashi report Metallaphotoredox catalysis with substituted

Oxidative fragmentation of alkyl substituted DHPs



Radicals observed in EPR

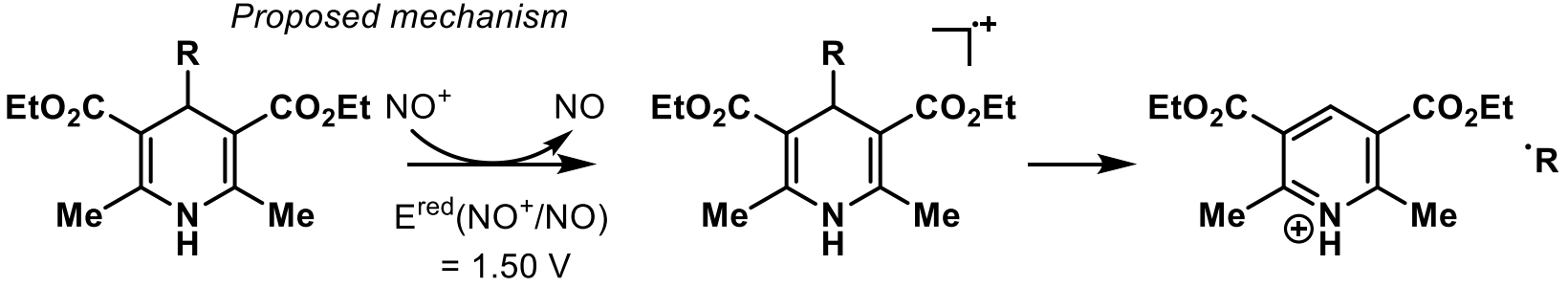


yes

R = H, Me, Et, Aryl, Vinyl

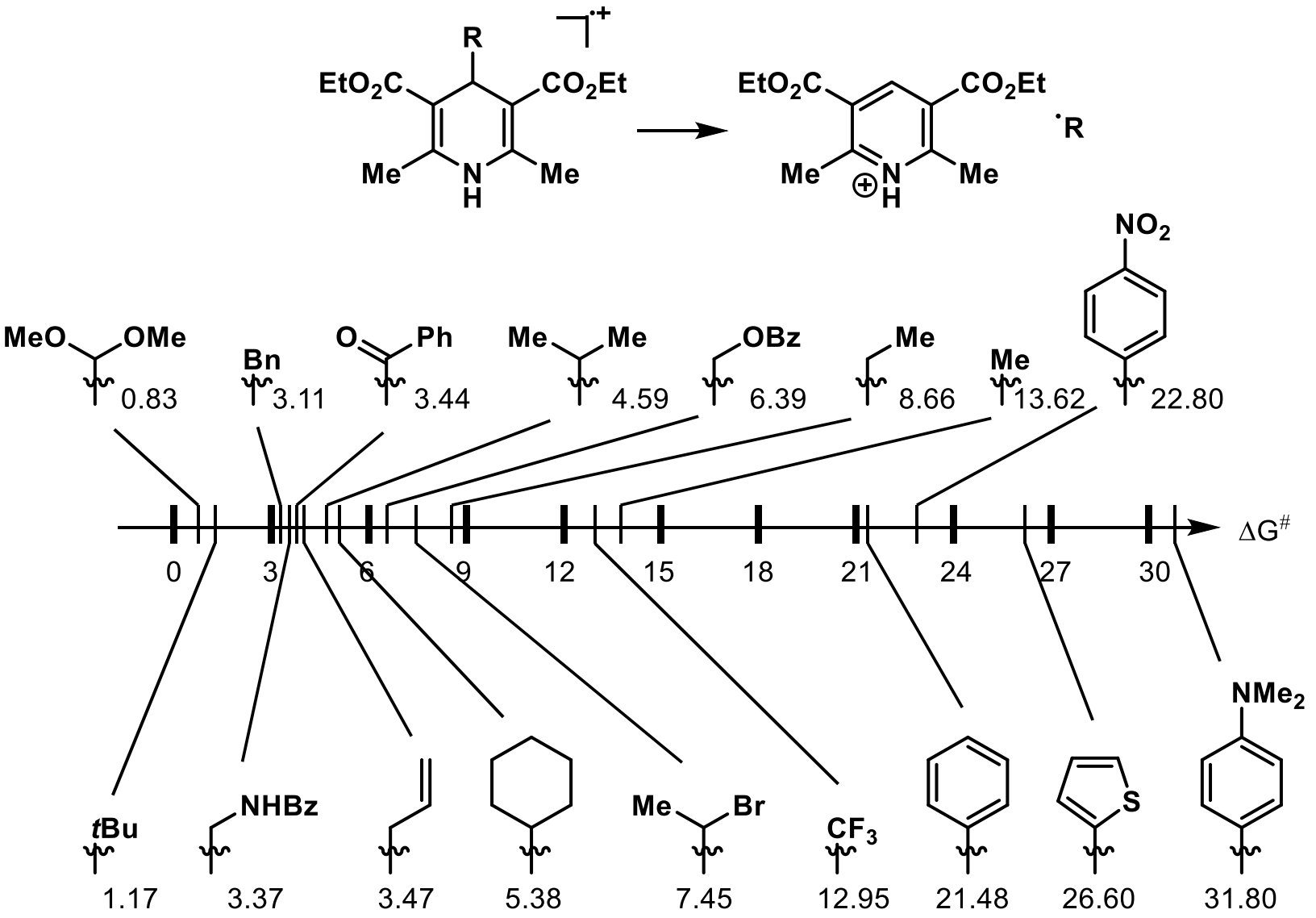
no

Proposed mechanism



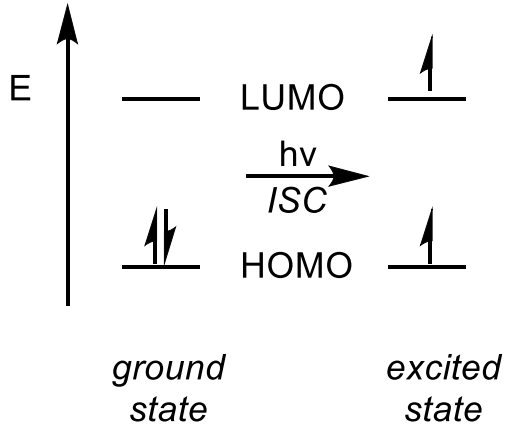
Res. Chem. Intermed. **2001**, *27*, 219–224

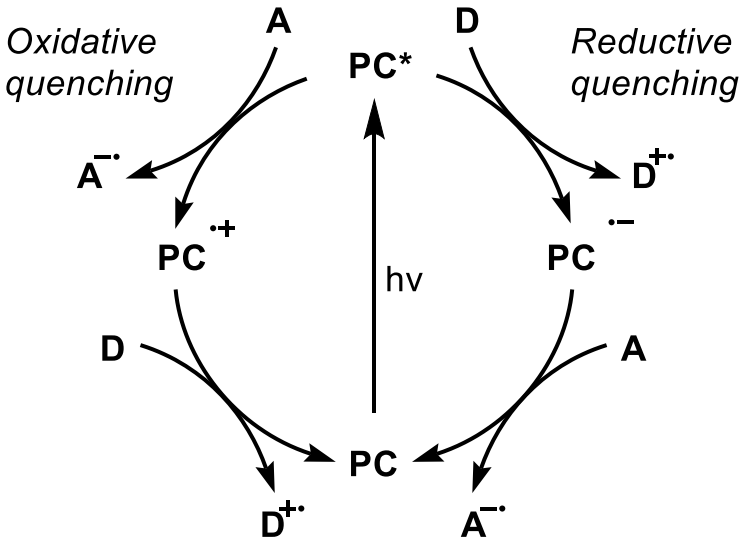
Oxidative fragmentation of alkyl substituted DHPs

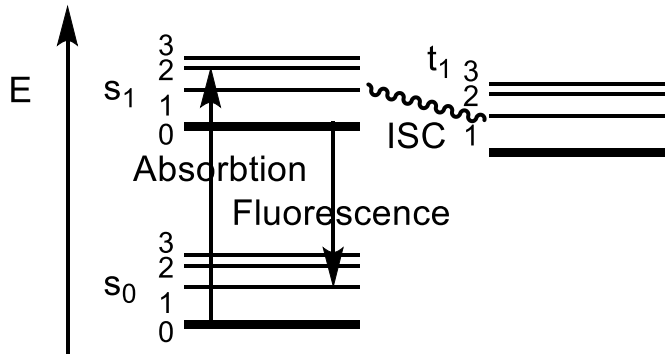


RSC Adv. **2020**, *10* (52), 31425–31434.

Application in photoredox catalysis





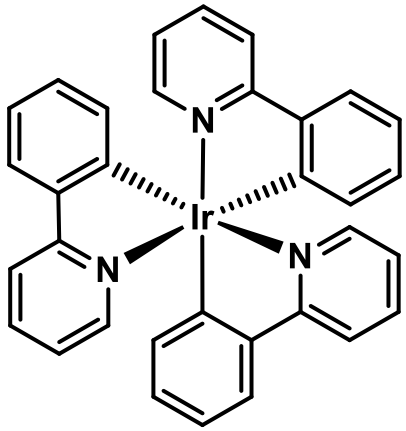


If D = substituted DHP

$E(PC^*/PC^-) > E(D^+/D)$

$E(DHP^+/DHP) \sim 1\ V$

Photocatalysts of this presentation



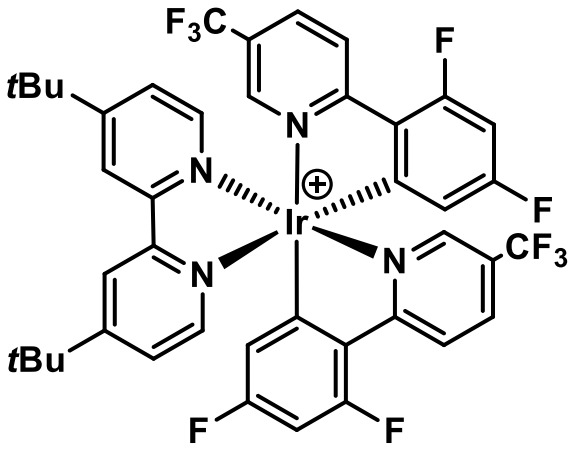
fac-Ir(ppy)$_3$

$E(PC^{\bullet+}/PC^*) = -1.73$ V

$E(PC^*/PC^{\bullet-}) = 0.31$ V

$E(PC^{\bullet+}/PC) = 0.77$ V

$E(PC/PC^{\bullet-}) = -2.19$ V



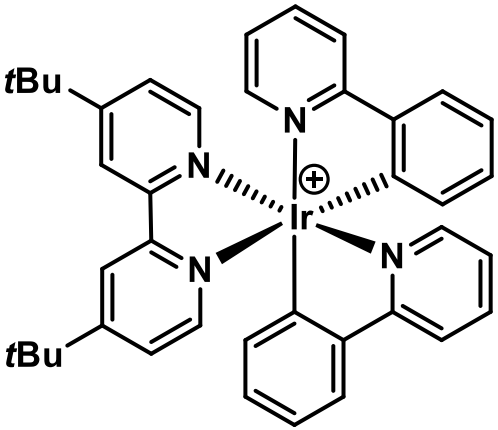
dF-Ir

$E(PC^{\bullet+}/PC^*) = -0.89$ V

$E(PC^*/PC^{\bullet-}) = 1.21$ V

$E(PC^{\bullet+}/PC) = 1.69$ V

$E(PC/PC^{\bullet-}) = -1.37$ V



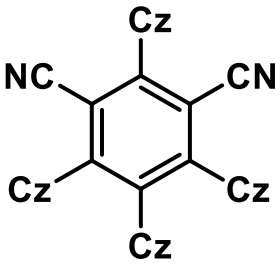
[Ir(ppy)$_2$dtbbpy]

$E(PC^{\bullet+}/PC^*) = -0.96$ V

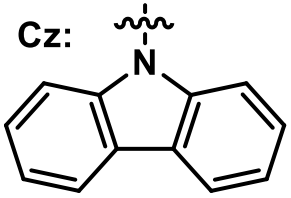
$E(PC^*/PC^{\bullet-}) = 0.66$ V

$E(PC^{\bullet+}/PC) = 1.21$ V

$E(PC/PC^{\bullet-})) = -1.51$ V



4CzIPN



$E(PC^{\bullet+}/PC^*) = -1.04$ V

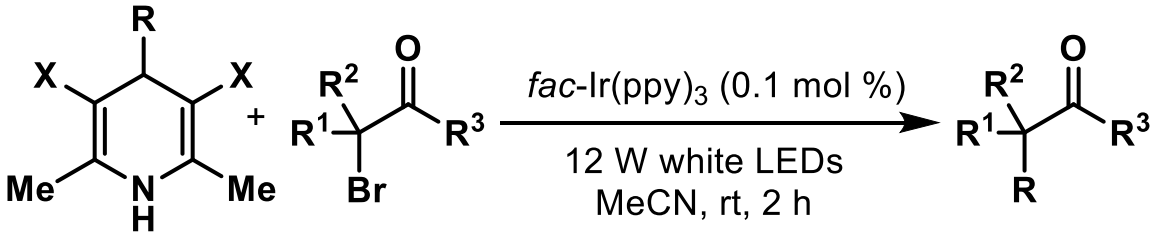
$E(PC^*/PC^{\bullet-}) = 1.35$ V

$E(PC^{\bullet+}/PC) = 1.52$ V

$E(PC/PC^{\bullet-})) = -1.21$ V

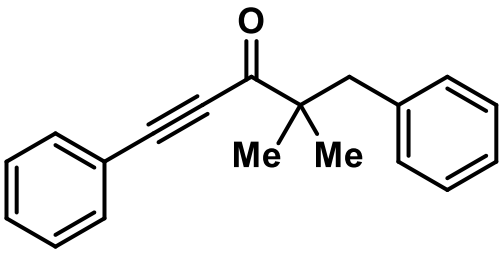
Inorg. Chem. Front. **2014**, *1* (8), 562–576.

Application in photoredox catalysis

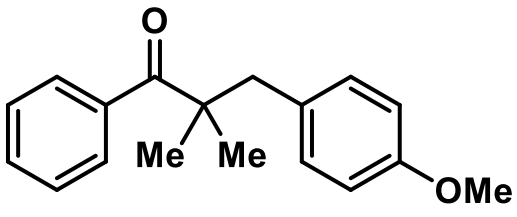


X = CO_2tBu; CN

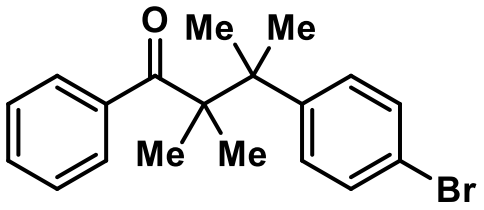
Selected examples



82 %



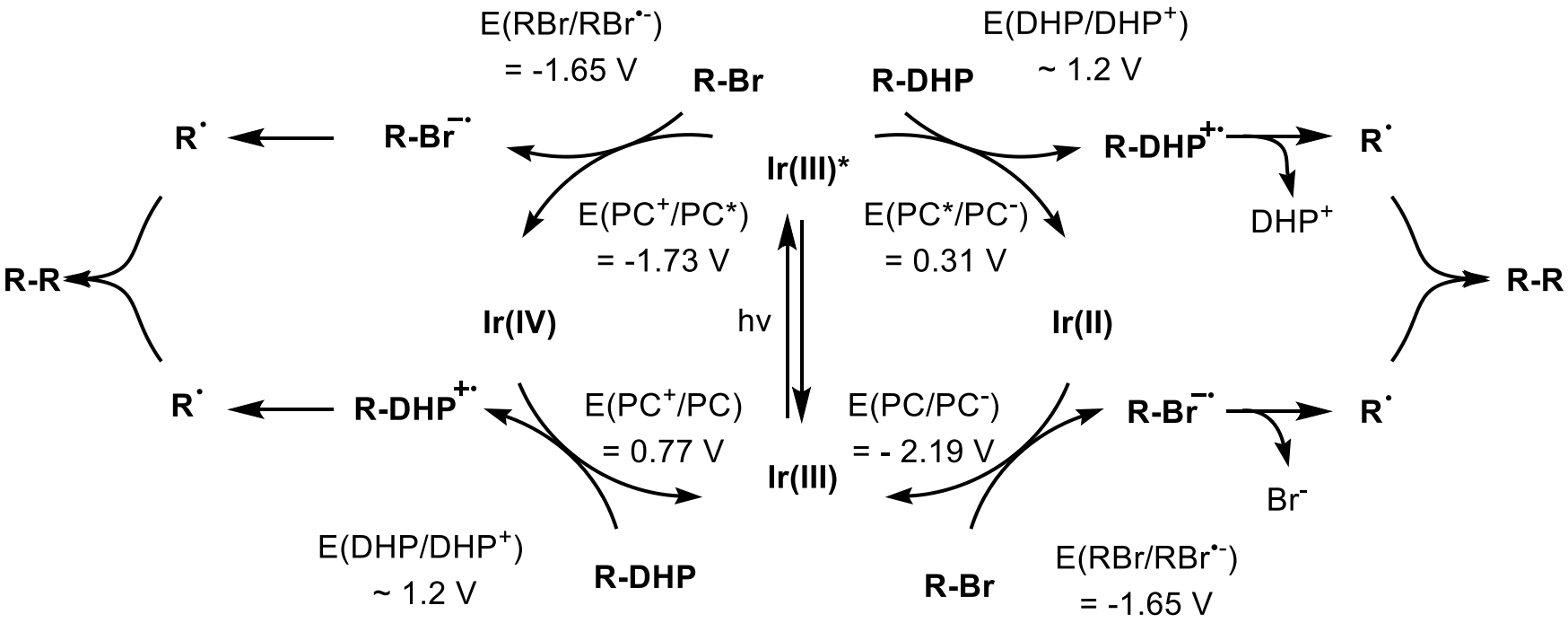
71 %



50 %

J. Am. Chem. Soc. **2016**, *138* (38), 12312–12315.

Application in photoredox catalysis



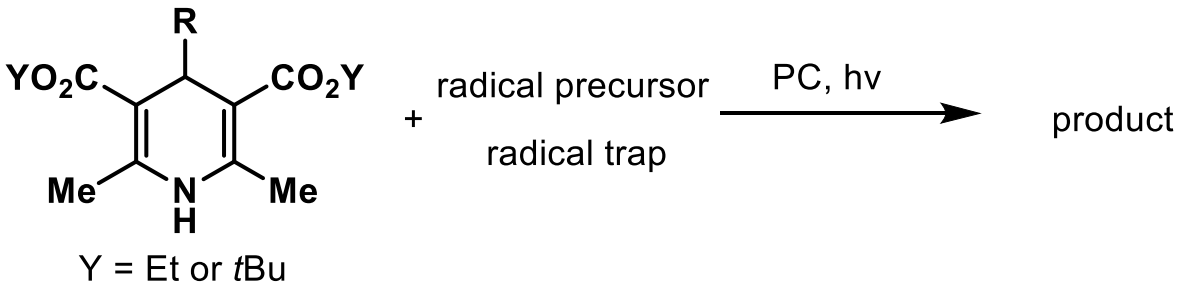
No SV quenching of Ir(III) by R-DHP!

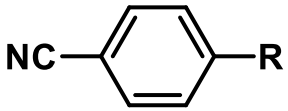
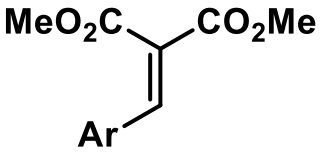
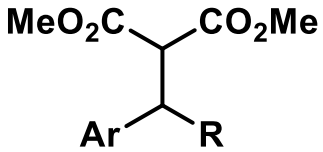
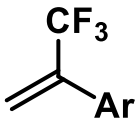
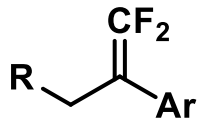
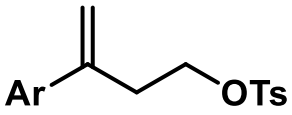
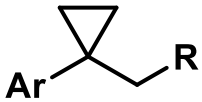
Conversion of DHP in the absence an electron acceptor

Updated mechanism - involving excited state DHP

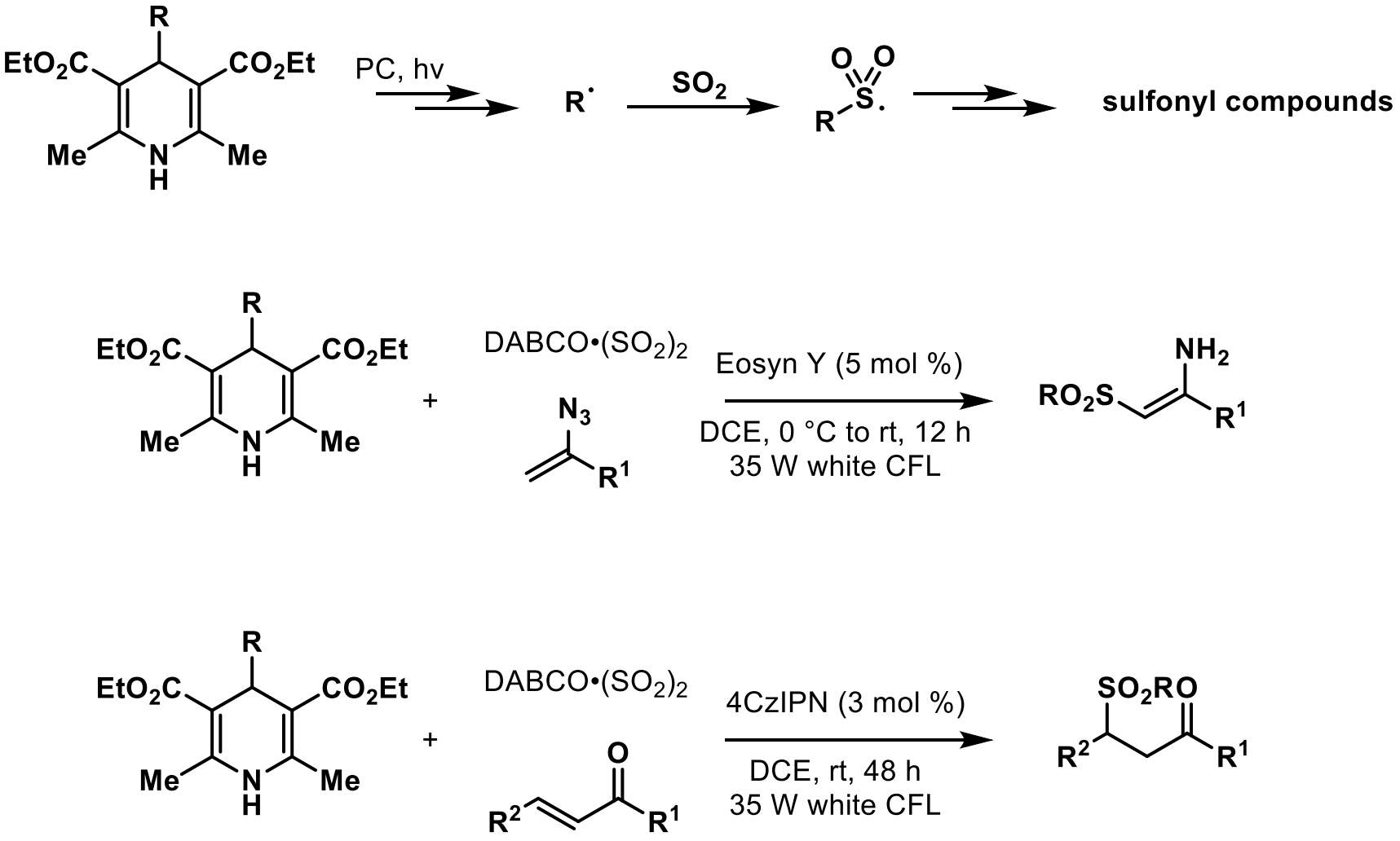
J. Am. Chem. Soc. **2016**, *138* (38), 12312–12315.
Advanced Synthesis & Catalysis **2018**, *360* (5), 925–931.

Application in photoredox catalysis



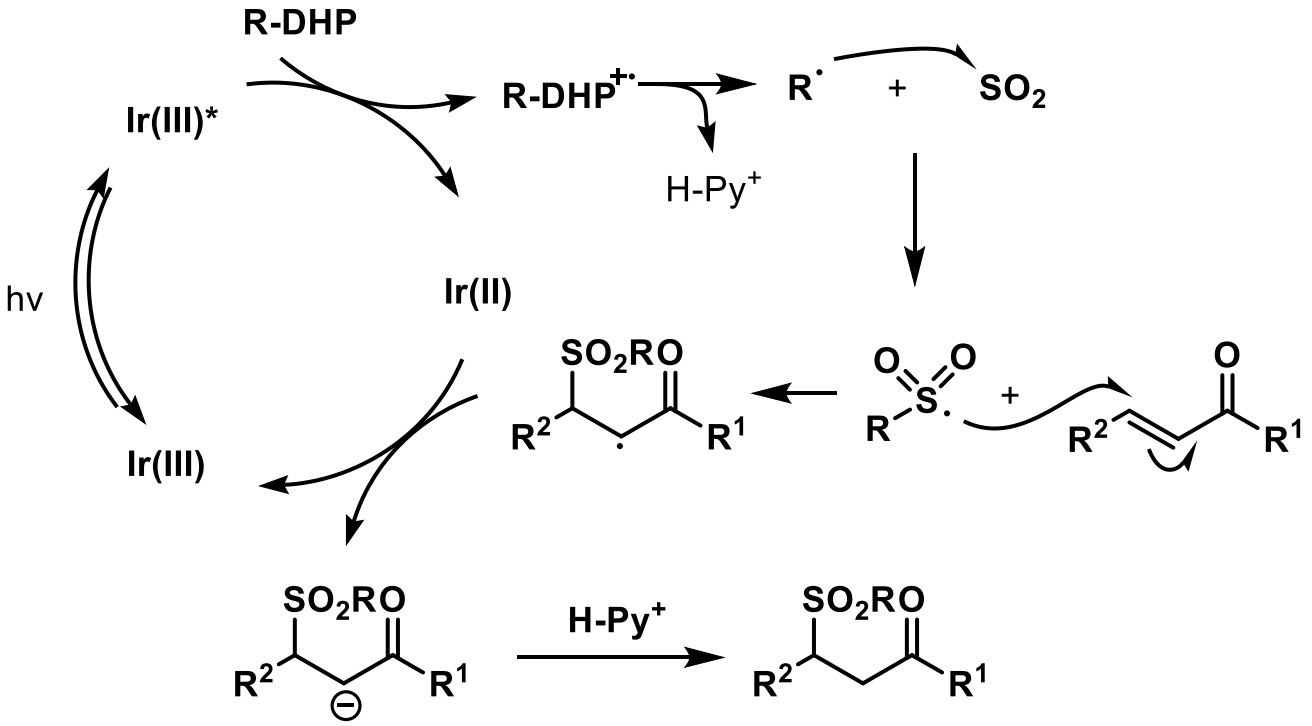
Reagent	Photocatalyst	Product	
	*fac*-Ir(ppy)$_3$		*ChemCatChem* **2016**, *8* (6), 1028–1032.
	dF-Ir + Sc(OTf)$_3$		*Org. Lett.* **2018**, *20* (21), 6877–6881.
	[Ir(ppy)$_2$dtbbpy]PF$_6$		*Asian J. Org. Chem.* **2019**, *8* (5), 661–664.
	4CzIPN		*Org. Lett.* **2018**, *20* (21), 6840–6844.

Application in photoredox catalysis



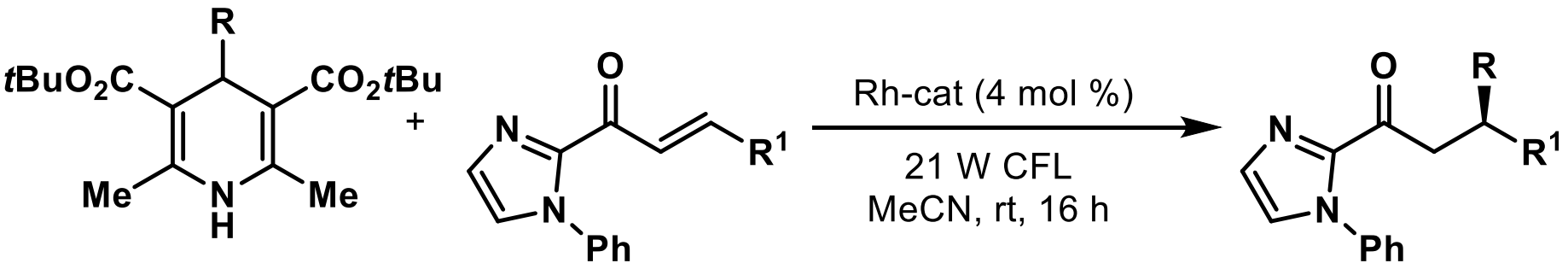
Chem. Commun. **2019**, *55* (14), 2062–2065.
Chem. Commun. **2019**, *55* (43), 6010–6013.

Application in photoredox catalysis

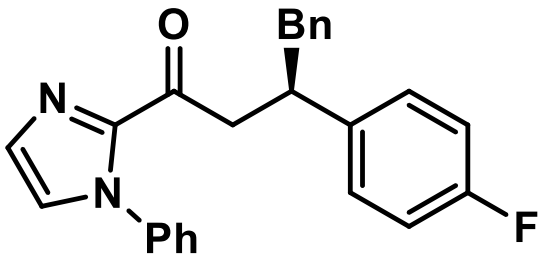


Chem. Commun. **2019**, *55* (14), 2062–2065.
Chem. Commun. **2019**, *55* (43), 6010–6013.

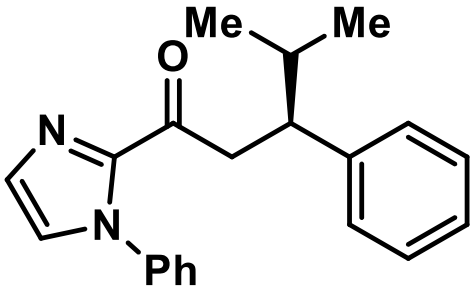
Application in photoredox catalysis



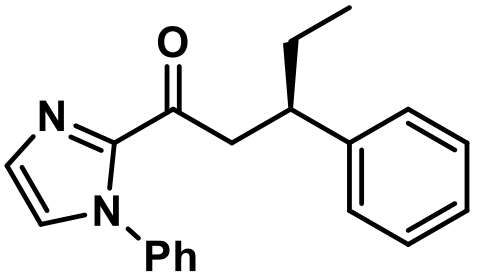
Selected examples



91 %, 95 % ee



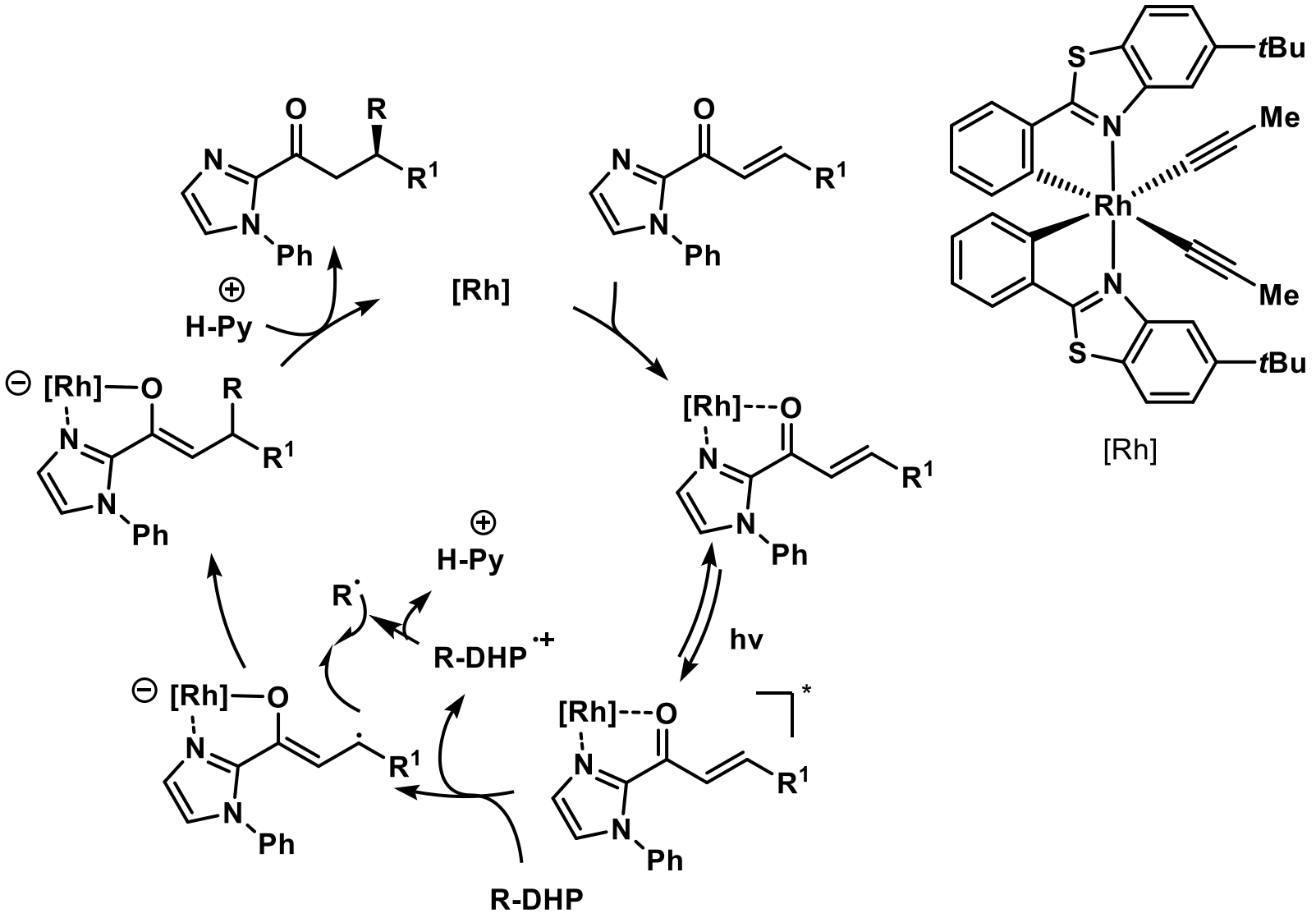
85 %, 97 % ee



85 %, 97 % ee

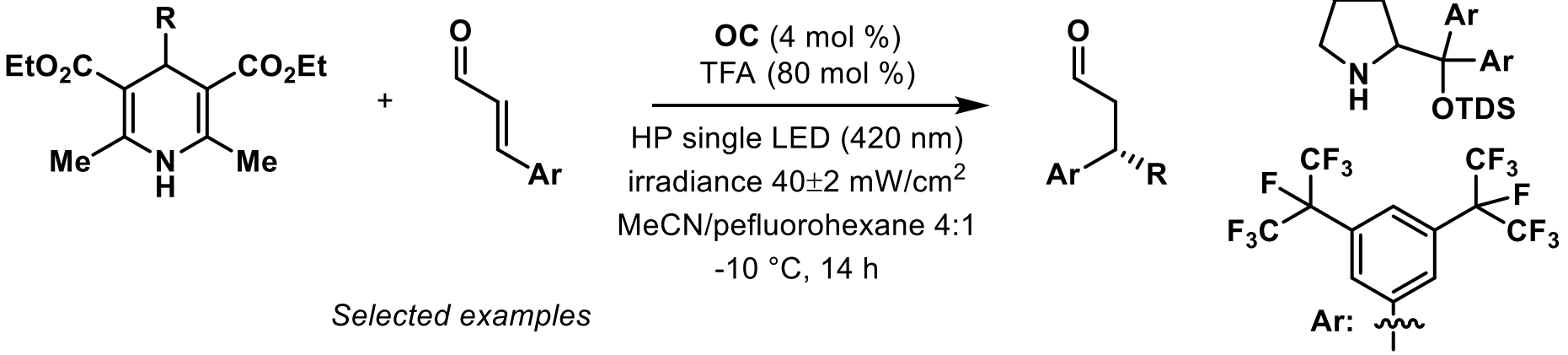
J. Org. Chem. **2018**, *83* (18), 10922–10932.

Application in photoredox catalysis

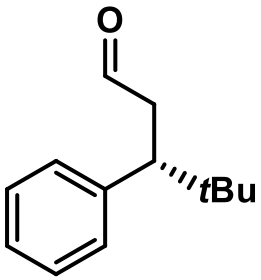


J. Org. Chem. **2018**, *83* (18), 10922–10932.

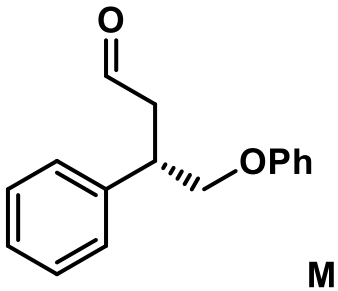
Application in photoredox catalysis



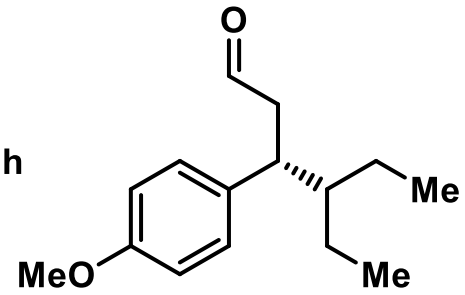
Selected examples



60 %, 74 % ee



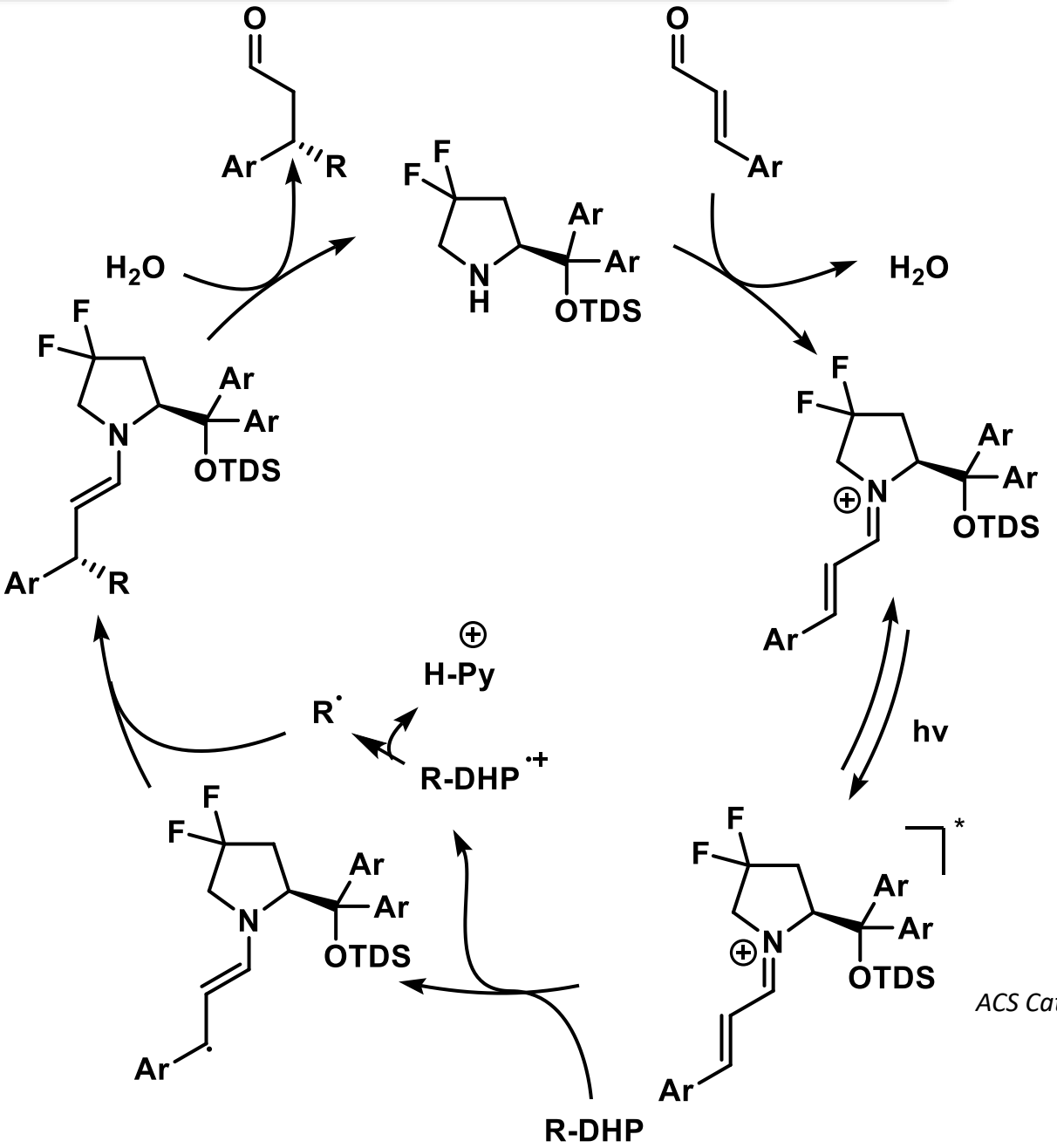
38 %, 83 % ee



69 %, 60 % ee

ACS Catal. **2018**, *8* (2), 1062–1066.

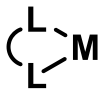
Application in photoredox catalysis



ACS Catal. **2018**, *8* (2), 1062–1066.

Application in metallaphotocatalysis

Metallaphotocatalysis



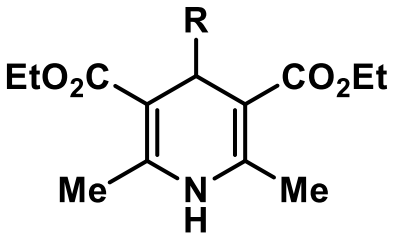
How to modulate reactivity of a transition metal complex?

- *Ligand design*
- *Oxidation state change*
- *Excitation*

Photo(redox) catalysis → *Radical generation via PET*

activated by PC *activated by TM*

Application in metallaphotoredox catalysis



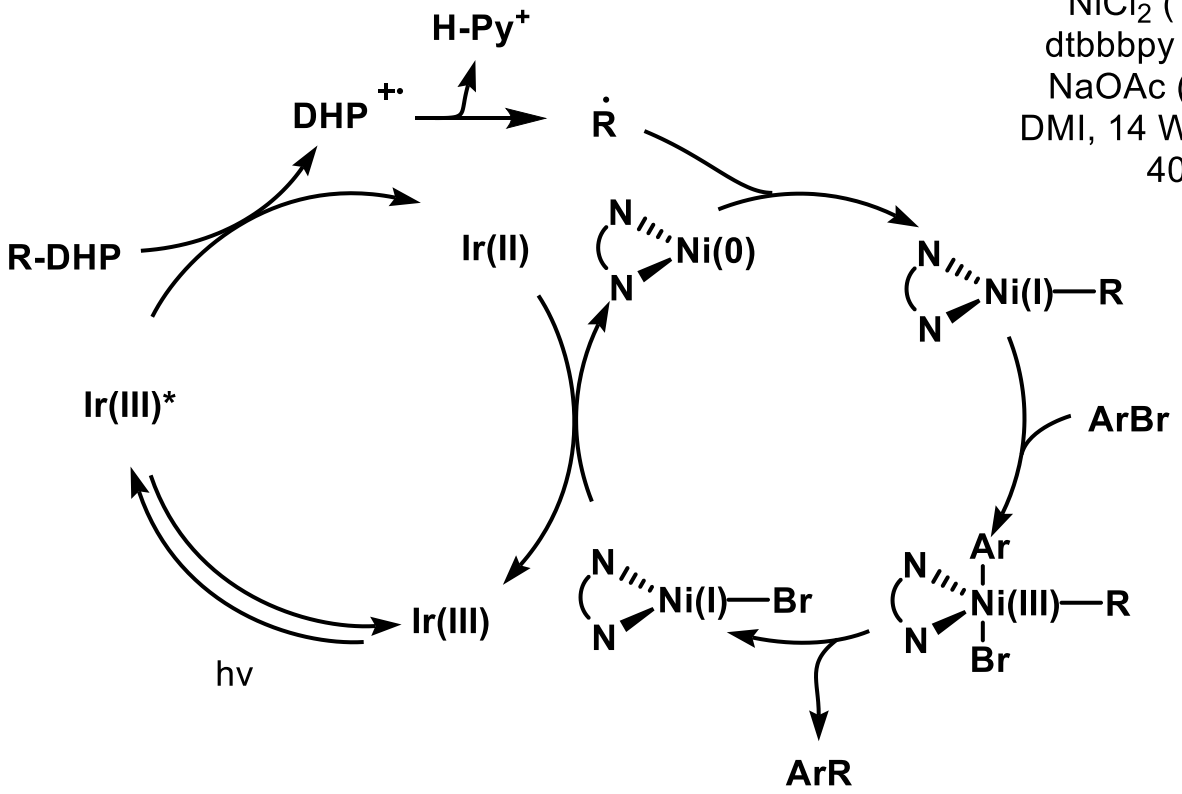
\+ Ar—Br → conditions → Ar—R

Molander:

4CzIPN (3 mol %)
$[Ni(dtbbbpy)(H_2O)_4]Cl_2$ (5 mol %)
acetone, blue LEDs
24 h, rt

Nishibayashi:

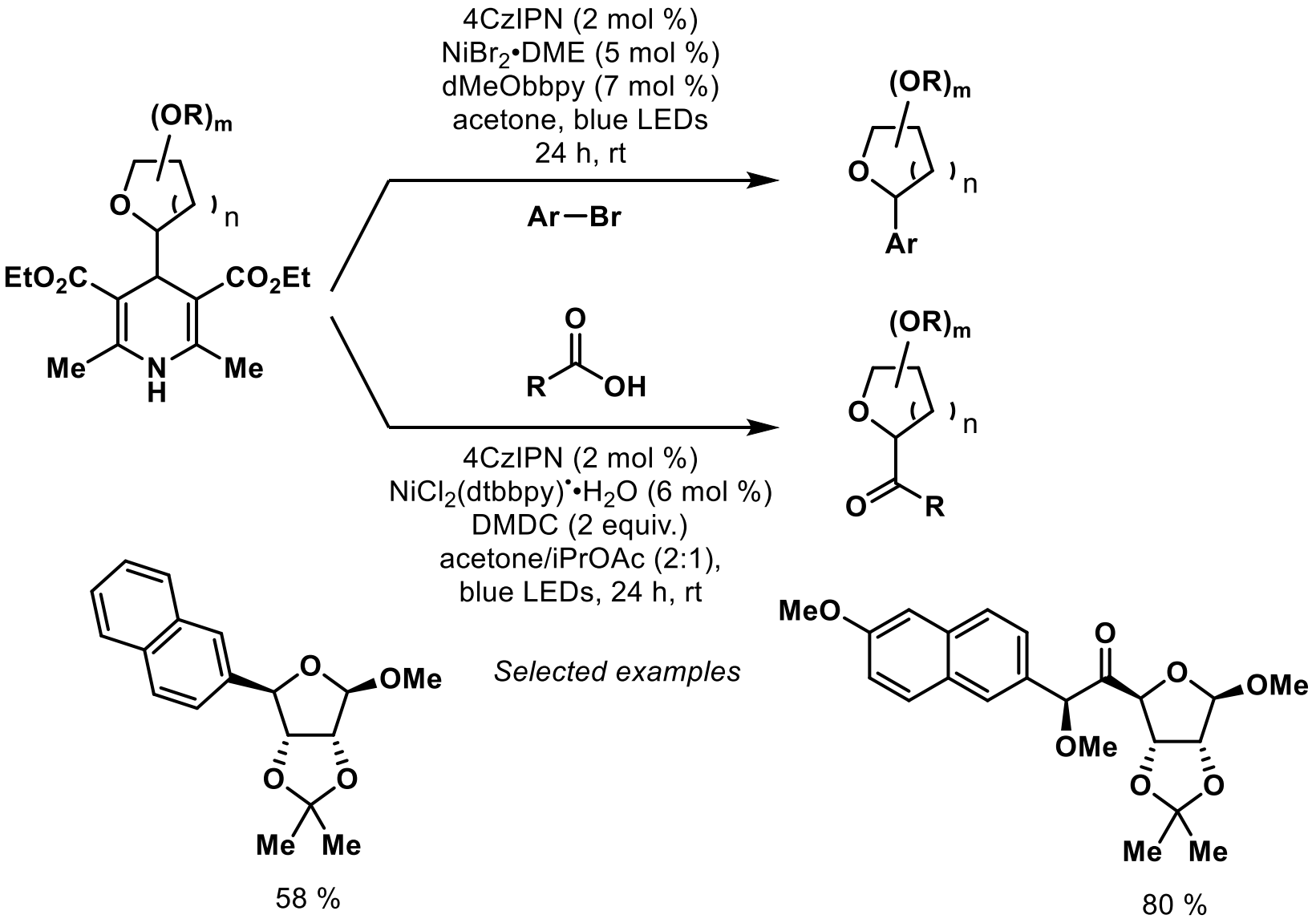
fac-$Ir(ppy)_3$ (1 mol %)
$NiCl_2$ (10 mol %)
dtbbbpy (15 mol %)
NaOAc (1.5 equiv,)
DMI, 14 W white LEDs
40 h, rt



ACS Catal. **2016**, *6* (12), 8004–8008.

Angew. Chem. Int. ed. **2016**, *55* (45), 14106–14110.

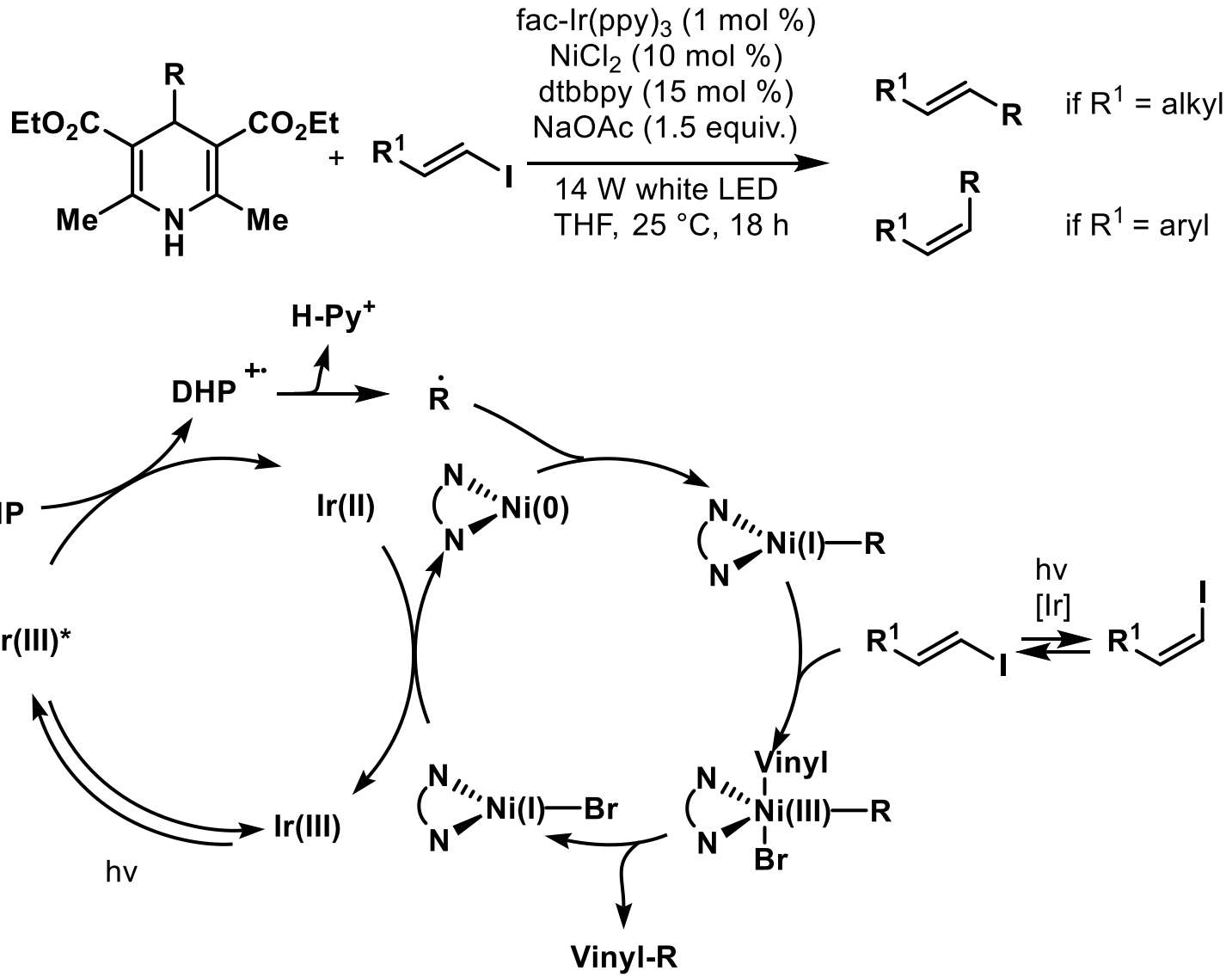
Application in metallaphotoredox catalysis



Angew. Chem. Int. Ed. **2018**, *57* (22), 6610–6613.

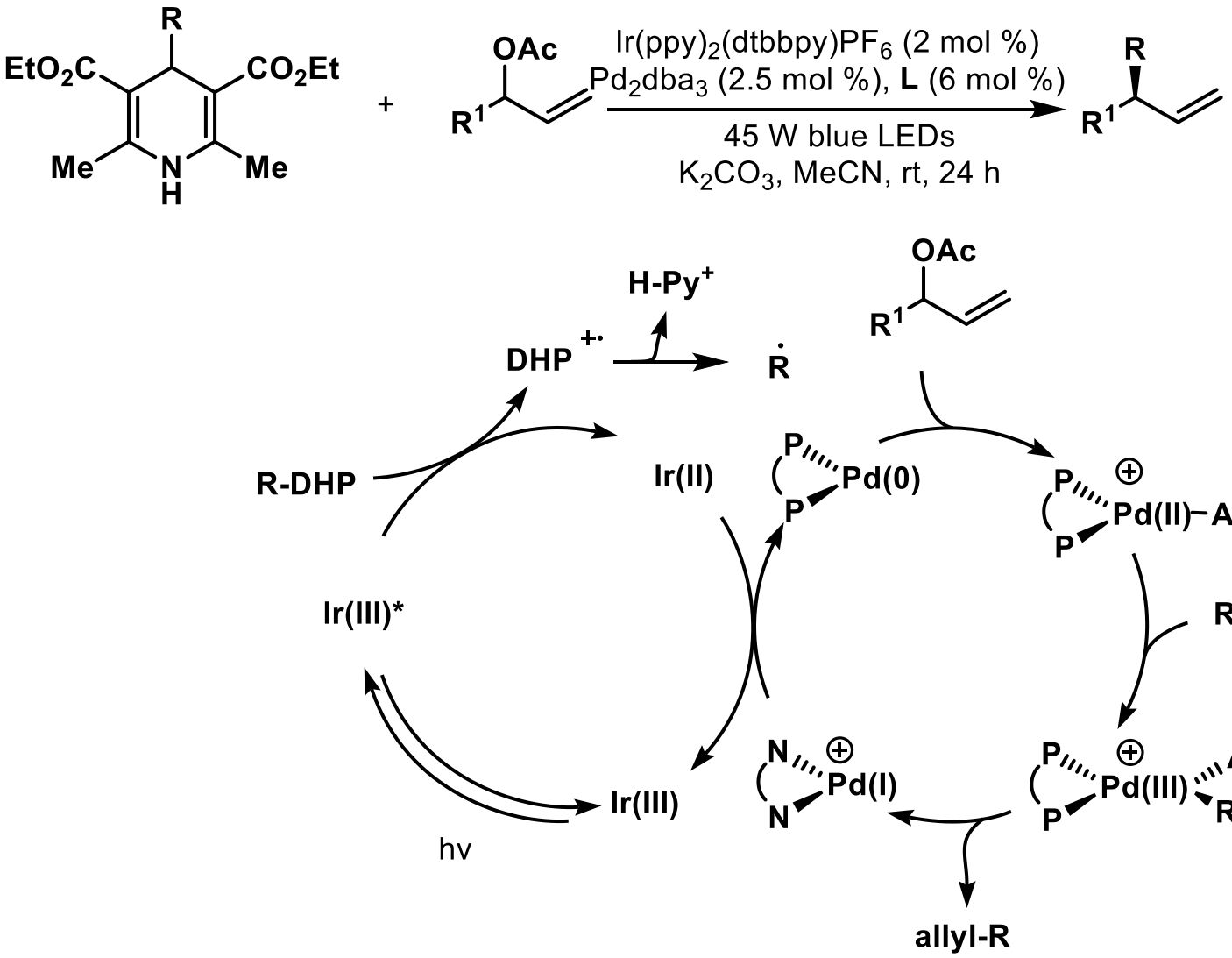
Angew. Chem. Int. Ed. **2018**, *57* (22), 6614–6618.

Application in metallaphotoredox catalysis



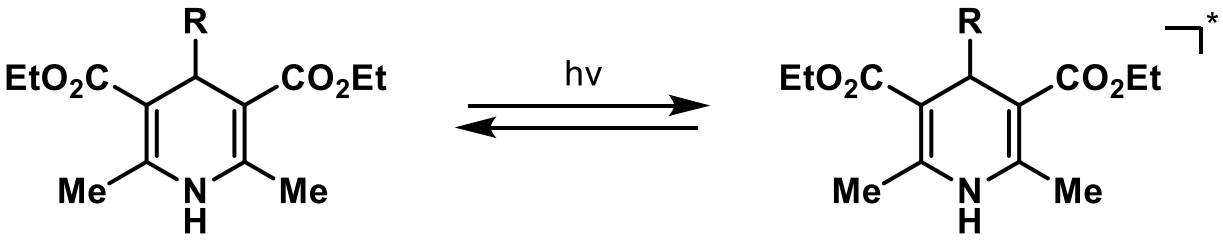
Chemistry – An Asian Journal **2018**, *13* (23), 3653–3657.

Application in metallaphotoredox catalysis



J. Am. Chem. Soc. **2018**, *140* (49), 16914–16919.

Excited state reactivity

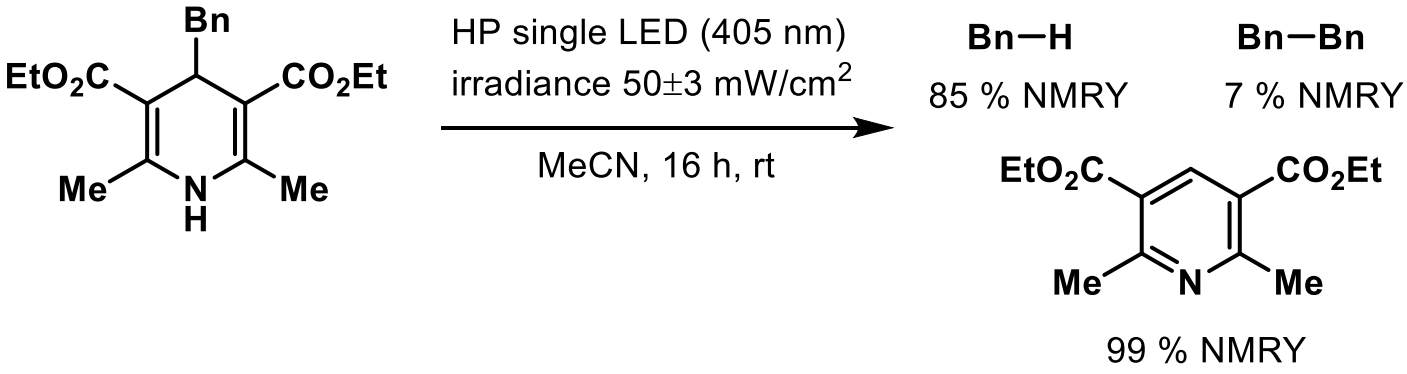


E(R-DHP$^{\bullet+}$/R-DHP) ~ 1 V

by Rehm-Weller approx. ~ E(R-DHP$^{\bullet+}$/R-DHP*) ~ -2 V

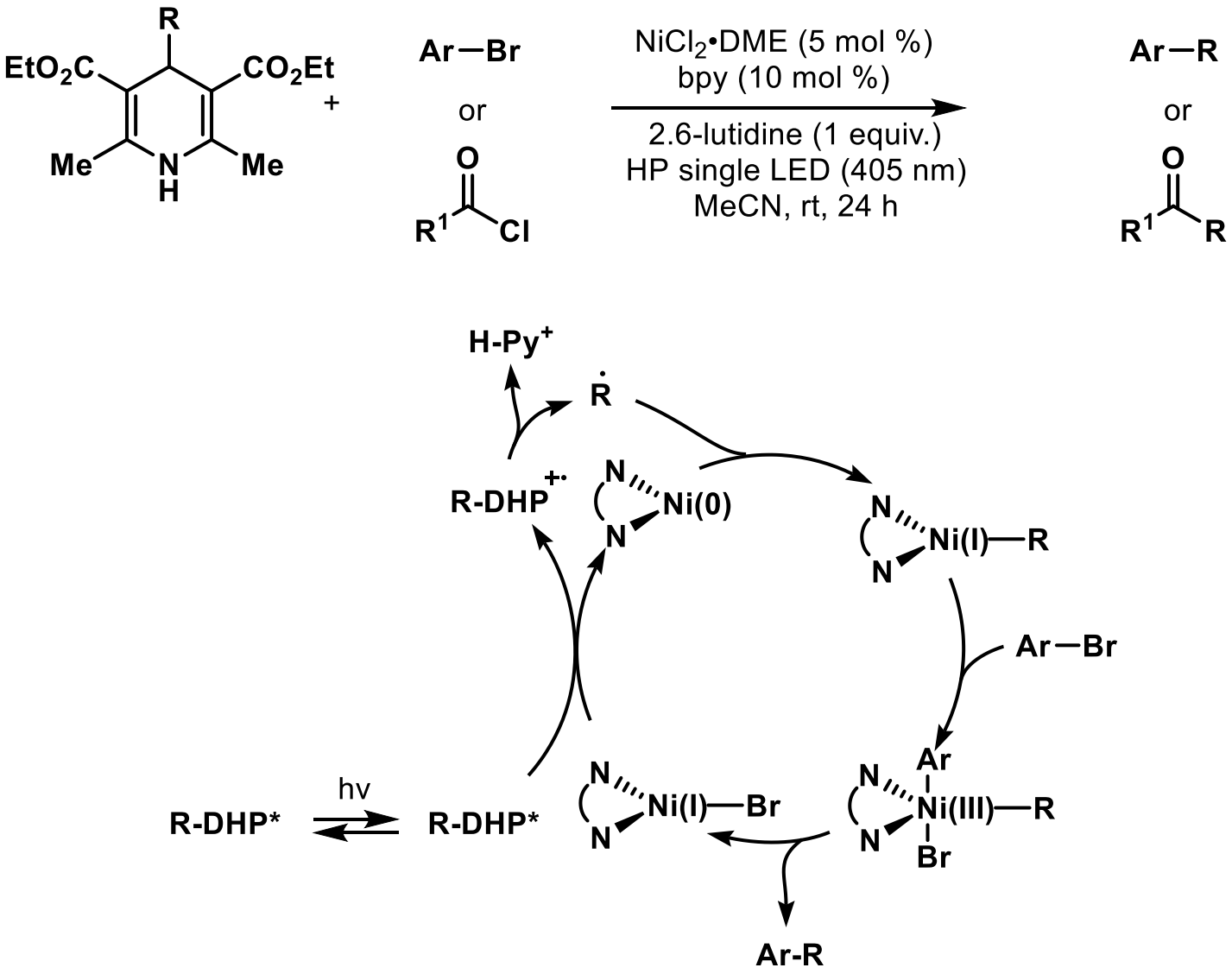
long wave tail in absorbtion spectra = 420 nm ~ 3 eV

Photocatalyst not neccesary?



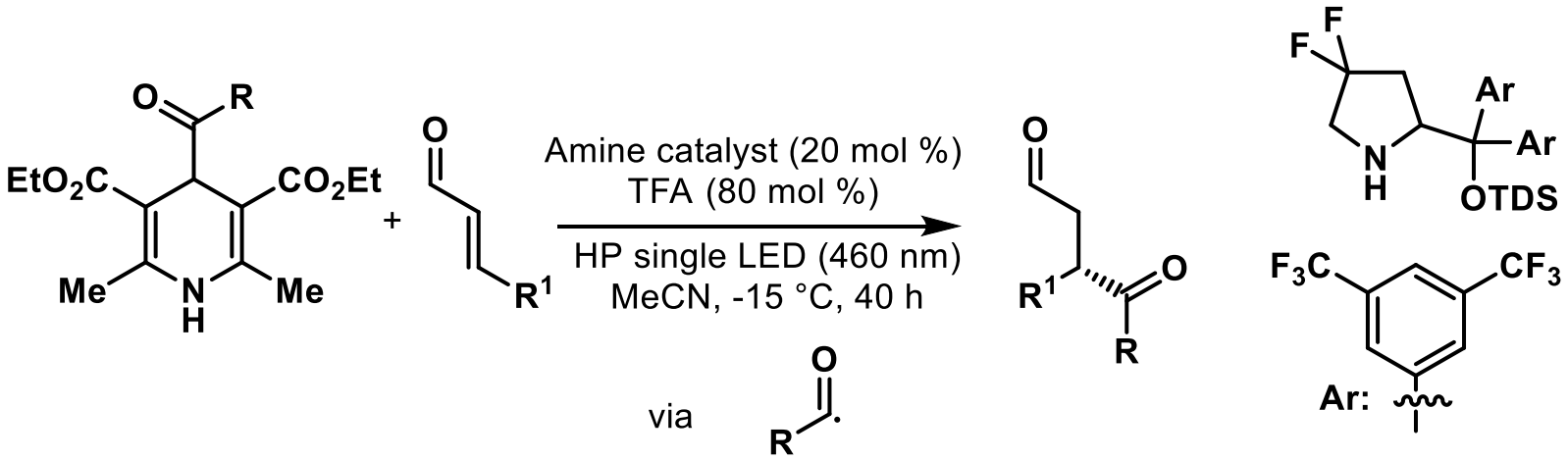
Angew. Chem. Int. Ed. **2017**, *56* (47), 15039–15043.

Excited state reactivity



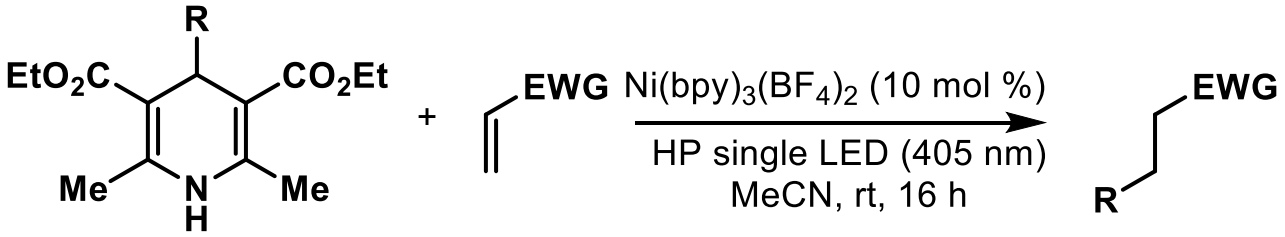
Angew. Chem. Int. Ed. **2017**, *56* (47), 15039–15043.

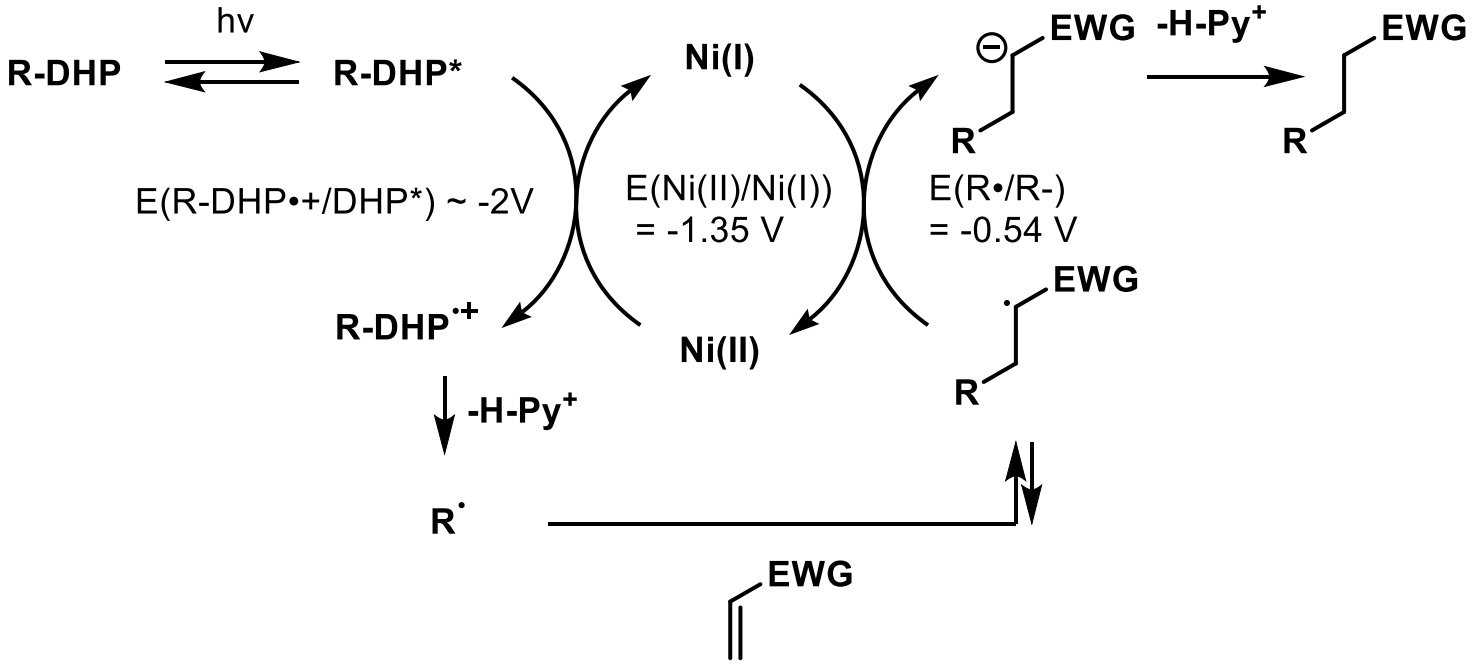
Excited state reactivity



Angew. Chem. Int. Ed. **2020**, *59* (13), 5248–5253.

Excited state reactivity



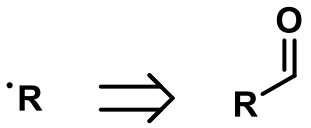


Angew. Chem. Int. Ed. **2019**, *58* (15), 4953–4957.

Outline

- Context and the synthesis of DHPs
- Application in photocatalysis
  - Photoredox catalysis
  - Metallaphotoredox catalysis
  - Excited state reactivity
- **Conclusions and perspectives**

Conclusions

1)  *via* **R-DHP**

2) **$E(R\text{-}DHP^{\bullet+}/R\text{-}DHP) \sim 1\ V$**

3) *R-DHP can be used as radical precursors in photoredox + organo or TM catalysis*

4) 

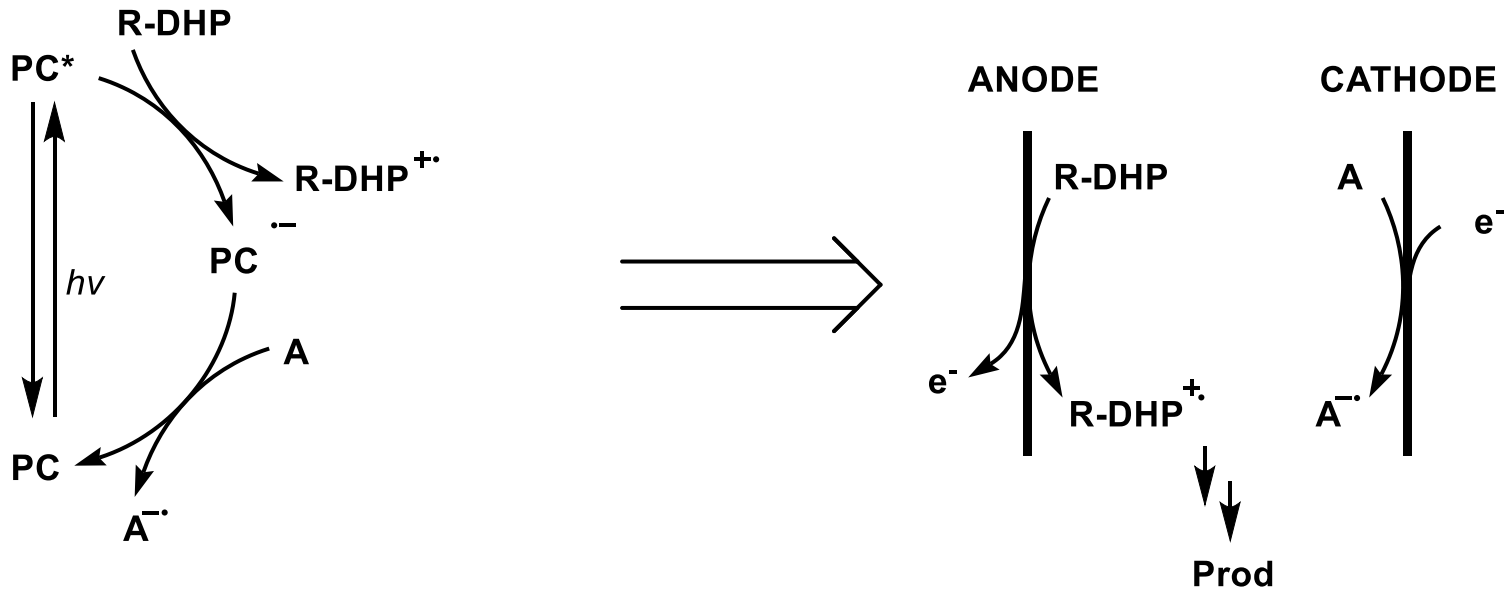
$E(R\text{-}DHP^{\bullet+}/R\text{-}DHP^{*}) \sim -2\ V$

good photoreductant

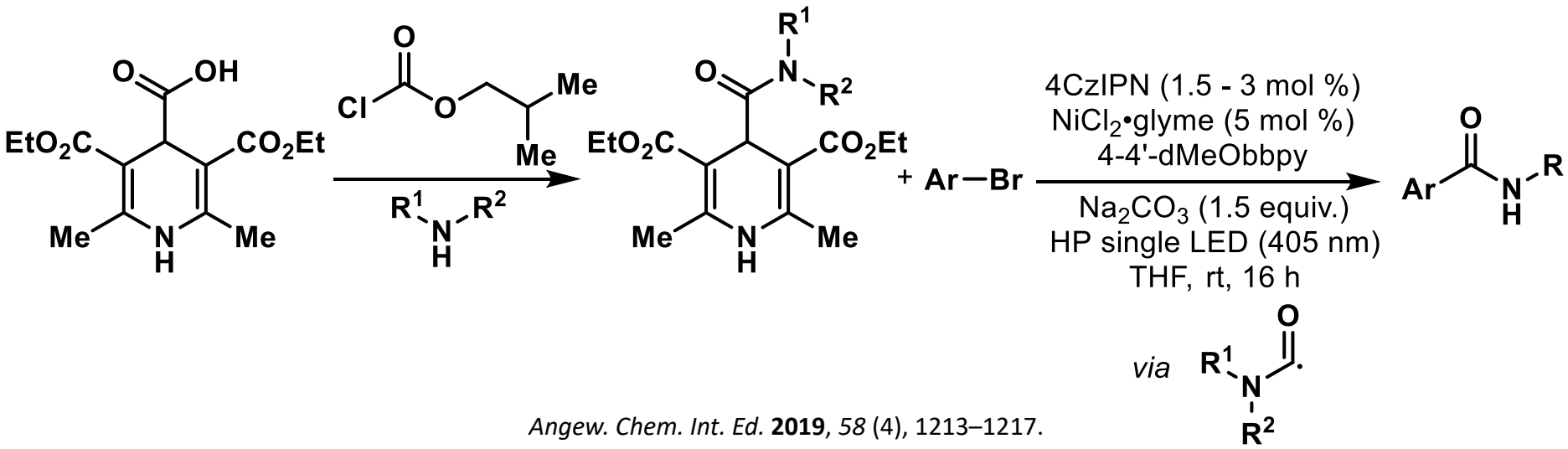
5) Drawback - stoichometric amount of high MW waste

Principial references: *Acta Chimica Sinica*, **2019**, *77* (9): 814-831; *Synlett* **2017**, *28* (2), 148–158.

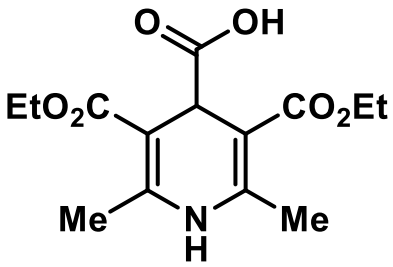
Perspectives – application of R-DHPs in electrochemistry



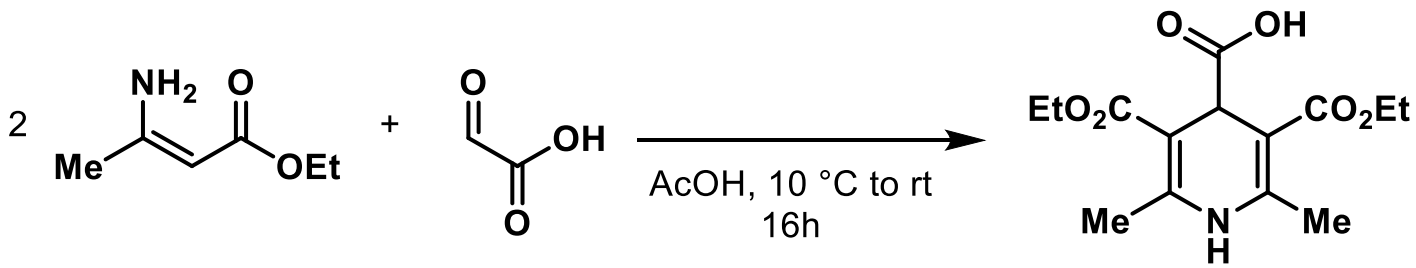
Question 1



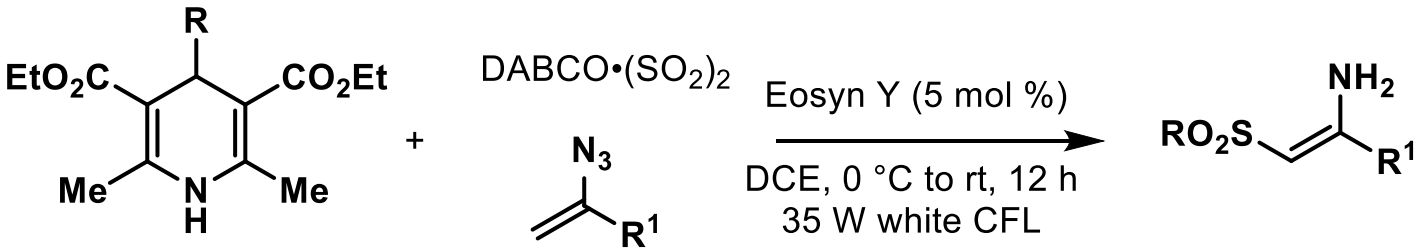
Angew. Chem. Int. Ed. **2019**, *58* (4), 1213–1217.



Propose the starting materials for the synthesis of DHP-carboxylic acid first reported by Dubur et. al. *Chem. Heterocycl. Compd.* **1972**, 5, 762–763

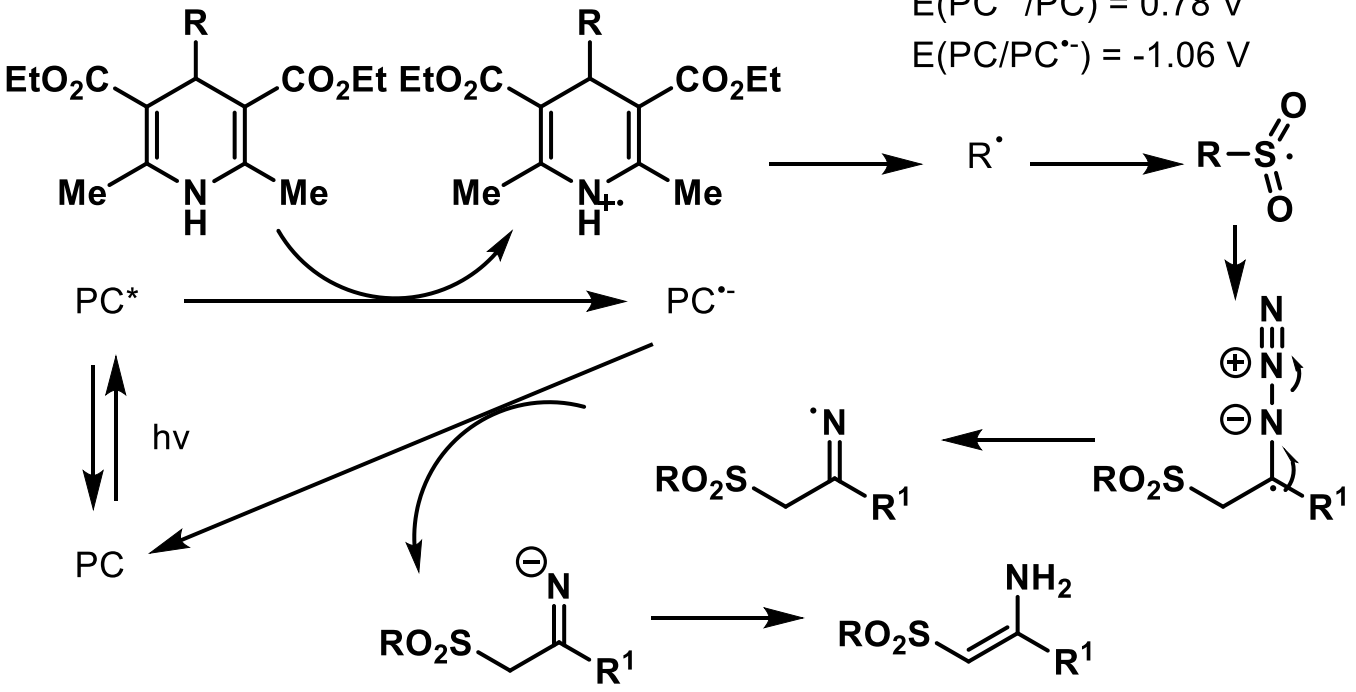


Question 2

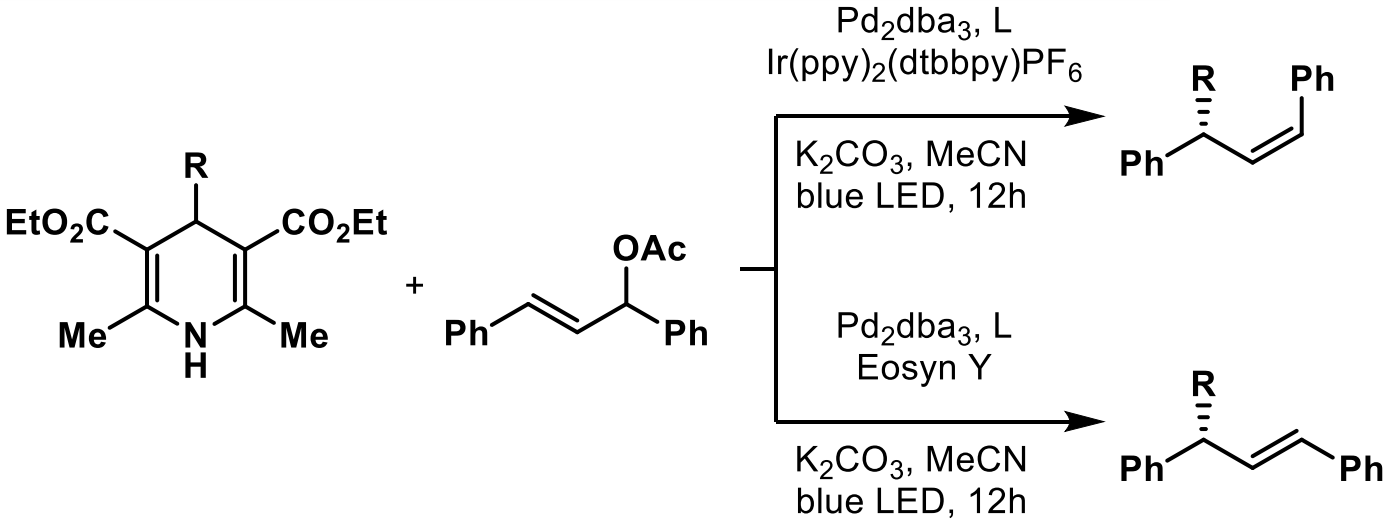


E($PC^{\bullet+}$/PC*) = -1.11 V
E(PC*/$PC^{\bullet-}$) = 0.78 V
E($PC^{\bullet+}$/PC) = 0.78 V
E(PC/$PC^{\bullet-}$) = -1.06 V

propose a catalytic cycle

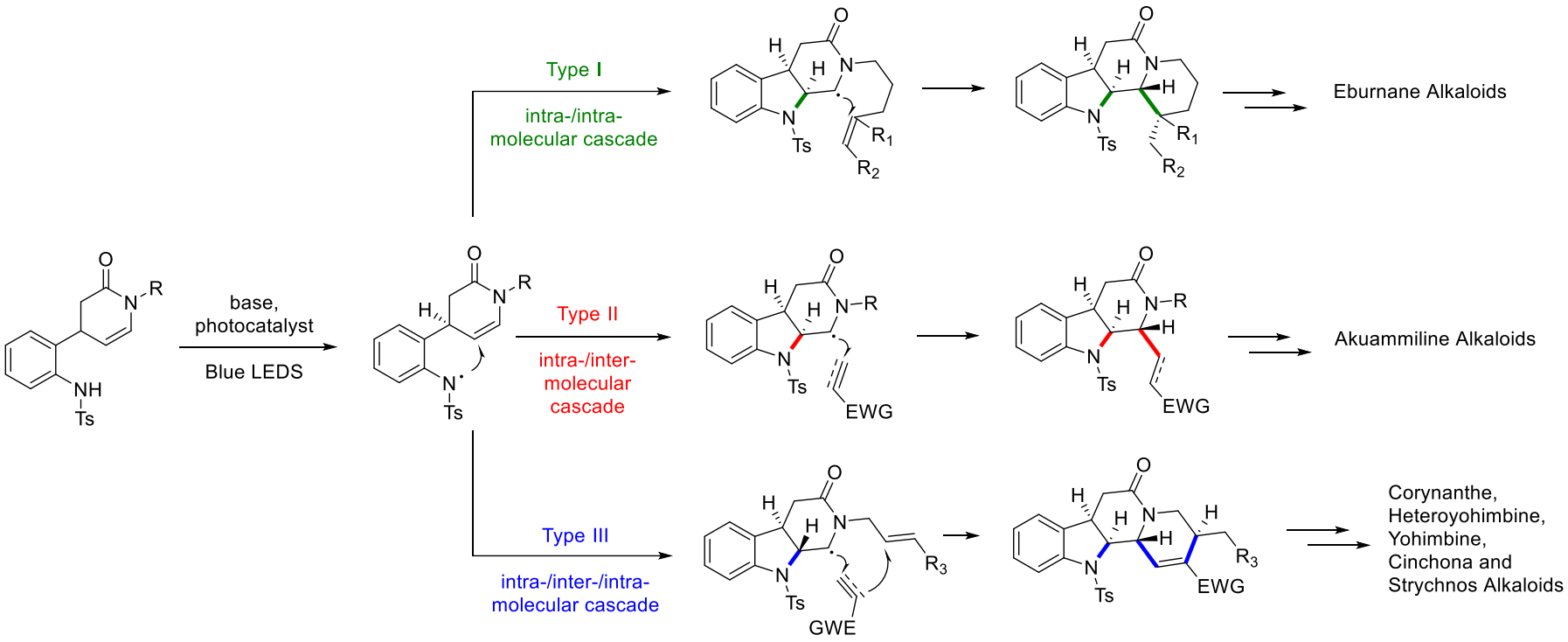


Question 3



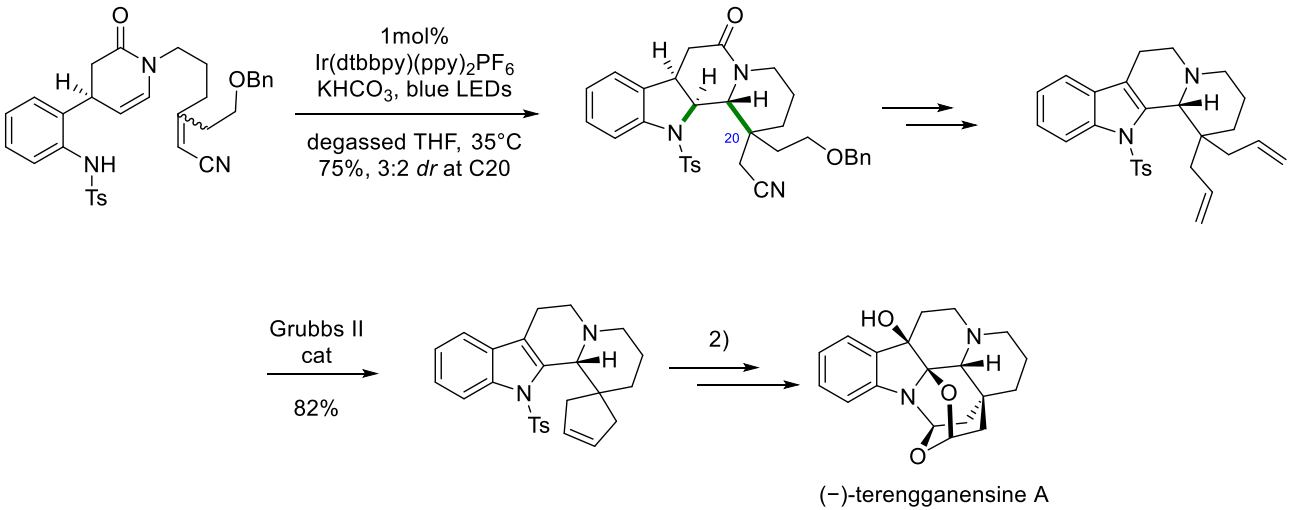
Eosyn Y ~ 44 kcal/mol triplet energy
$Ir(ppy_2)(dtbbpy)PF_6$ ~ 50 kcal/mol triplet energy

N-centered radical initiator



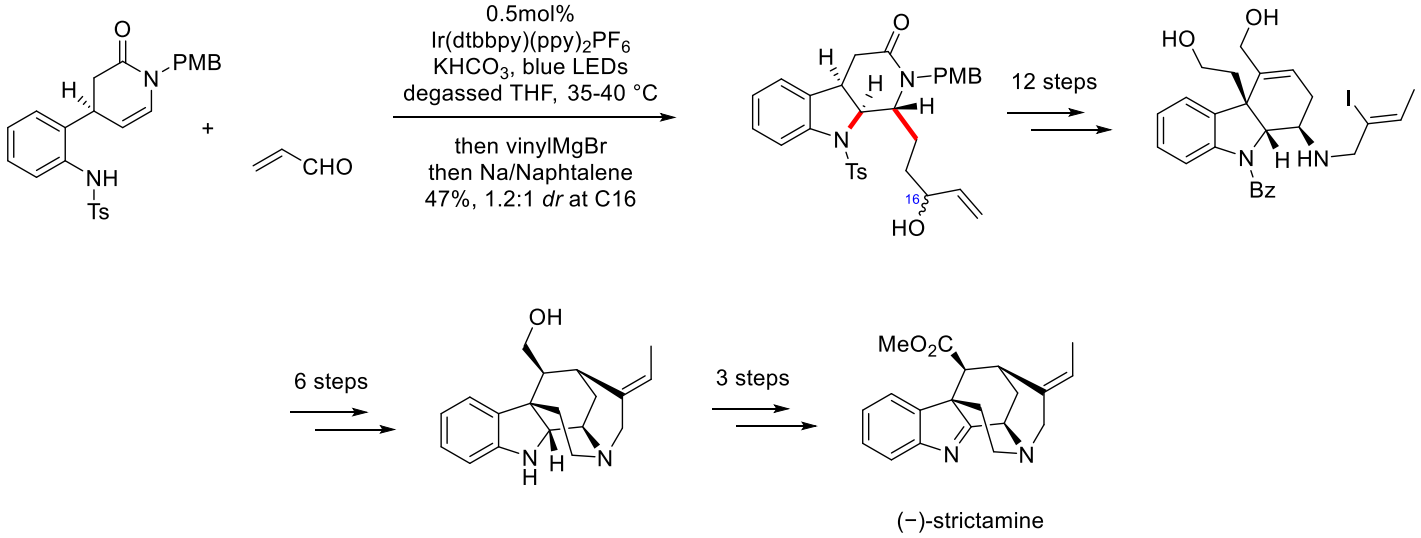
Acc. Chem. Res. 2019, 52, 1877−1891

Eburnane Alkaloids : **(–)-terengganensine A**



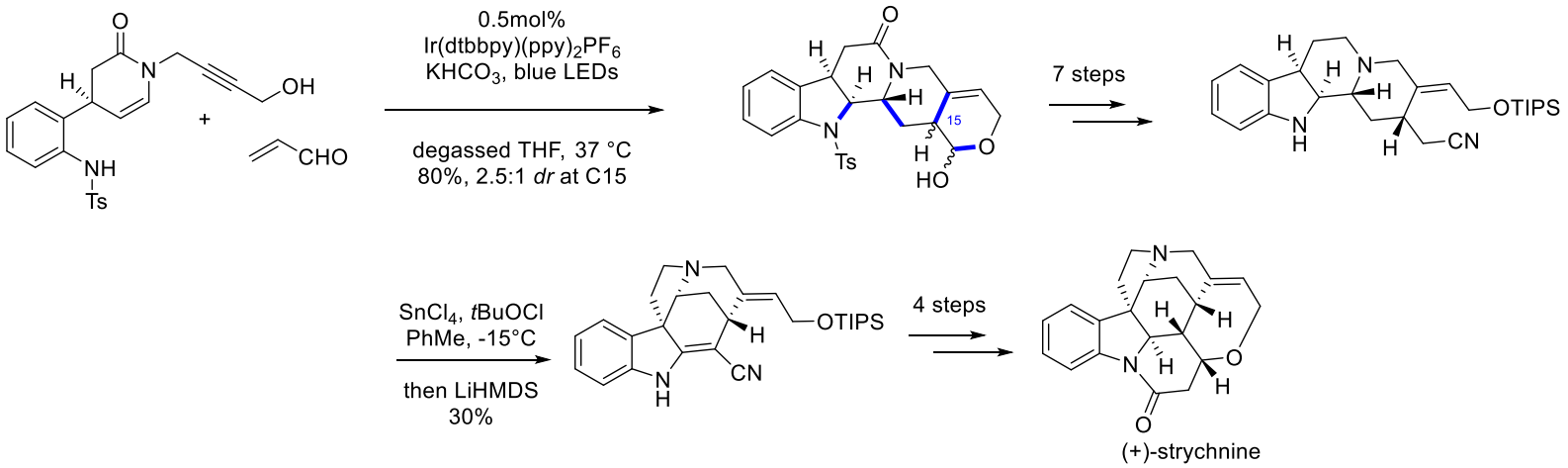
1) Chem. Commun., 2018, 54, 9510
2) Angew. Chem., Int. Ed. 2016, 55, 6556

Akuammiline Alkaloids : **(–)-strictamine**



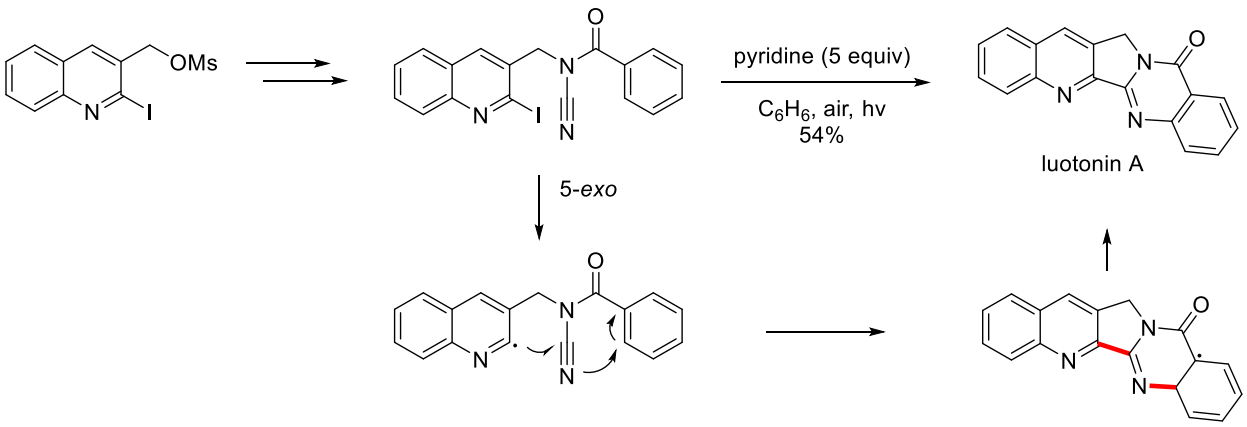
1) Angew.Chem. Int.Ed. 2019, 58,6059 –6063

Strychnos Alkaloids : **(+)-strychnine**



1) *Org. Lett.* 2019, 21, 1, 252–255

First apparition of **N-acylcyanamides** as radical acceptors, N-centered radical intermediate



Luotonine A already synthesized using radical cascades : Bowmann, Org. Biomol. Chem. 2005, 3, 1460 ; Curran, Synlett 2005, 18, 2843

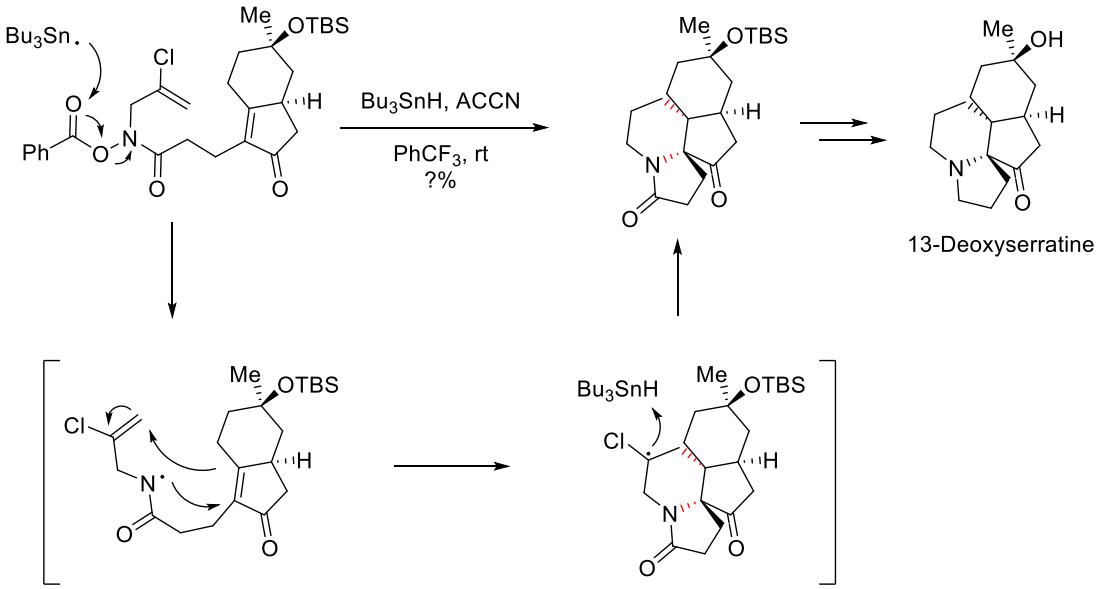
Similar radical cyclization for synthesis of various camptothecine (Curran)

Curran : Bioorg. Med. Chem. Lett. 2005, 15, 4736; Tetrahedron, 1996, 52, 11385; Chem. Eur. J. 1998, 4, 67; J. Am. Chem. Soc. 1991, 113, 2127

M. Malacria : Angew. Chem. Int. Ed. 2007, 46, 576; Tetrahedron, 2013, 69, 7699

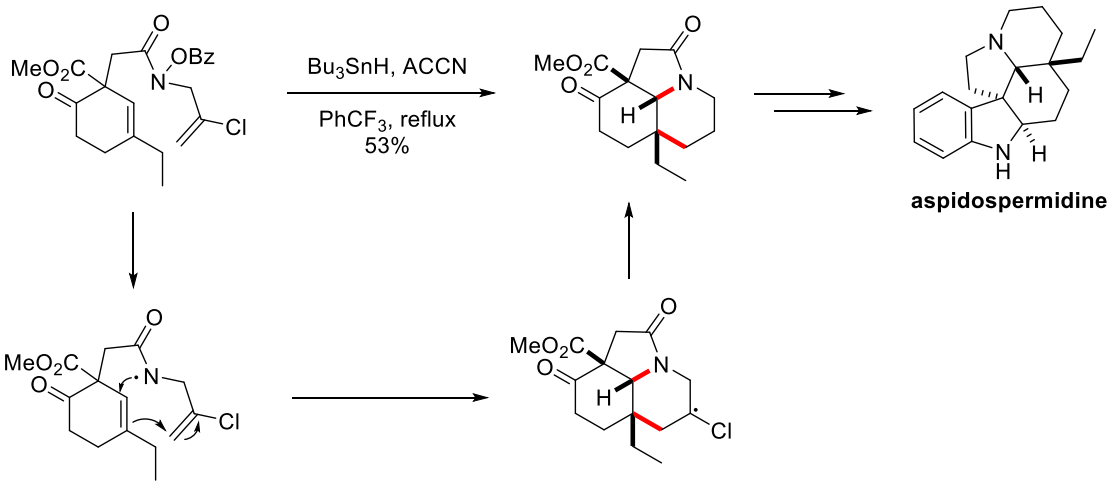
Zard : several methods for generation of amidyl radicals

Synlett 1996, 12, 1148; Tetrahedron lett. 1995, 36, 8791; Tetrahedron Lett. 1999, 39, 2125



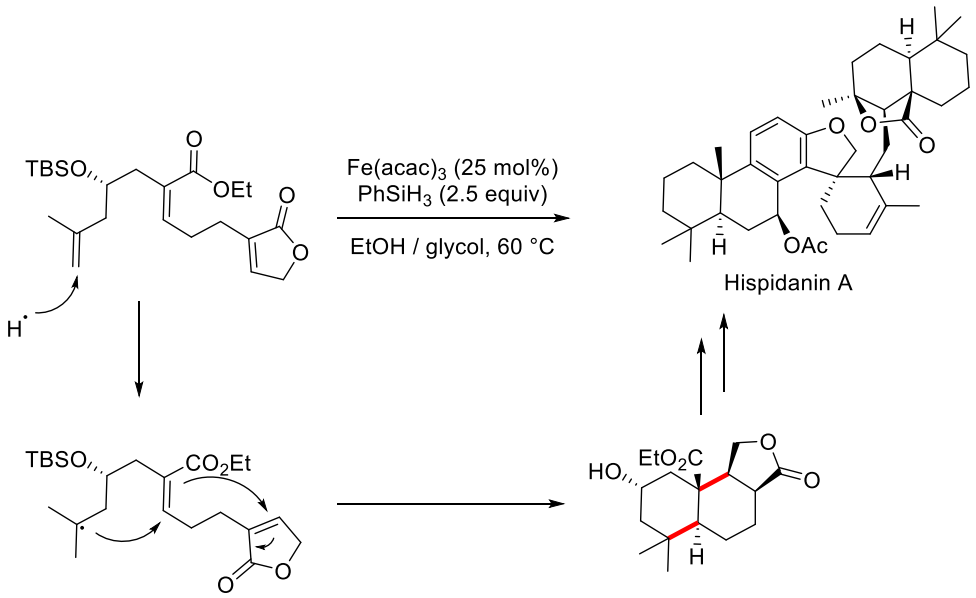
Zard : Angew. Chem. Int. Ed. 2002, 41, No. 10

Amidyl radical initiator

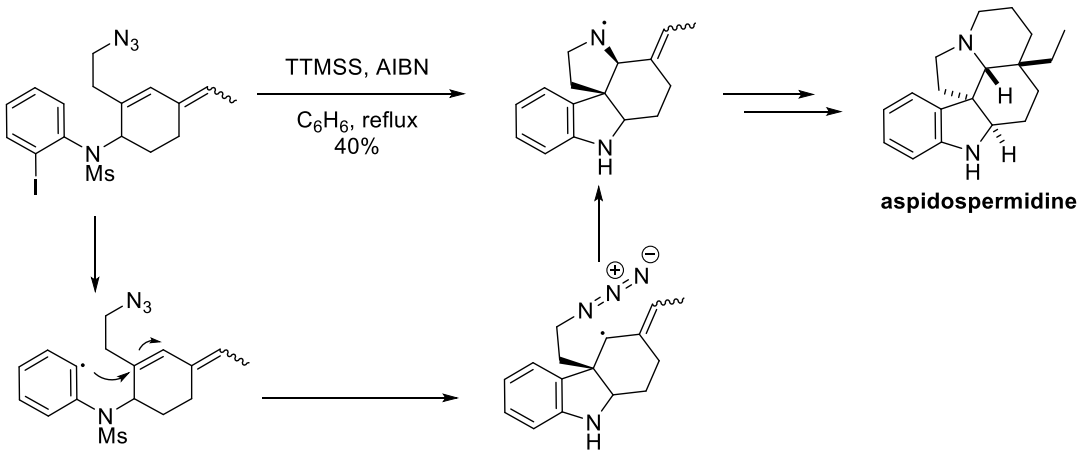


Zard : Org. Lett. 2006, 8, 5, 831–834

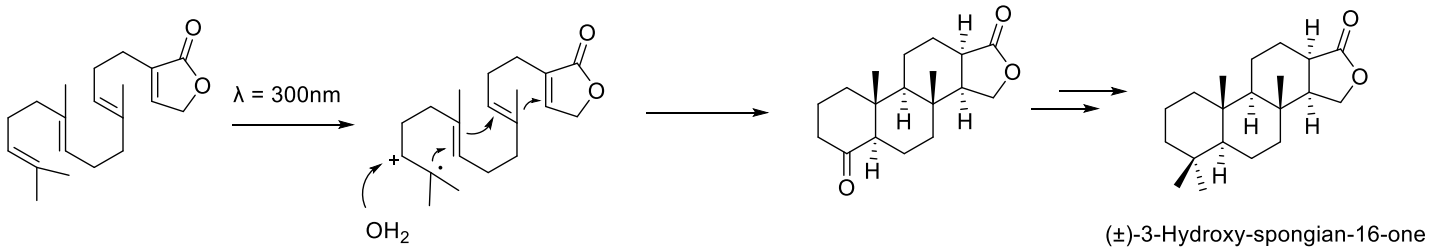
Polyene radical cyclization



Angew. Chem. Int.Ed. 2017, 56,5849 –5852

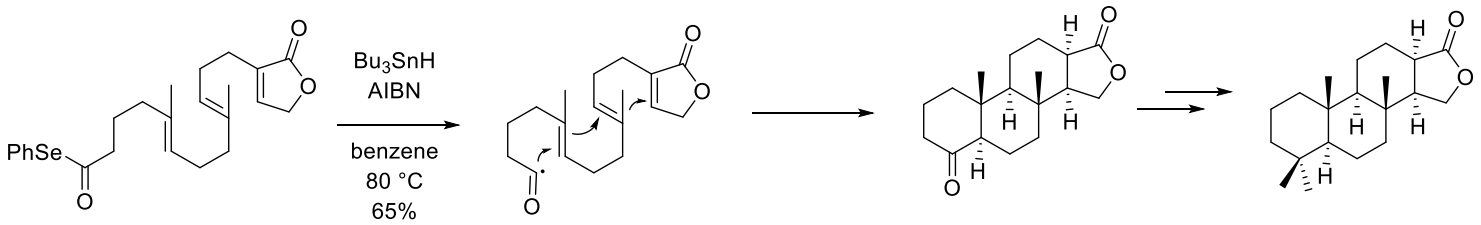


J. Chem. Soc., Perkin Trans. 1, 1999, 995–1001

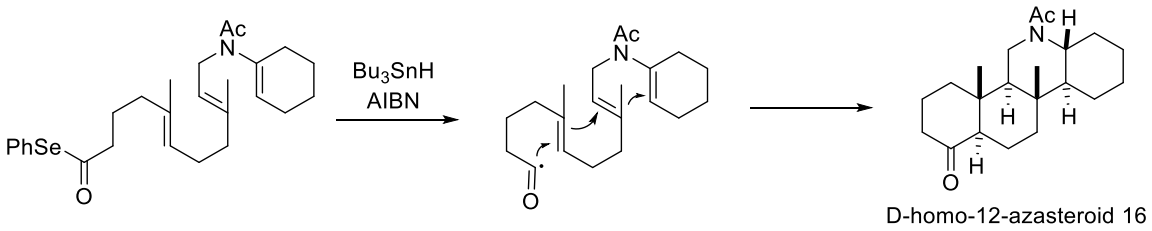


(±)-3-Hydroxy-spongian-16-one

Synthesis 2001, No. 8, 1114–1116

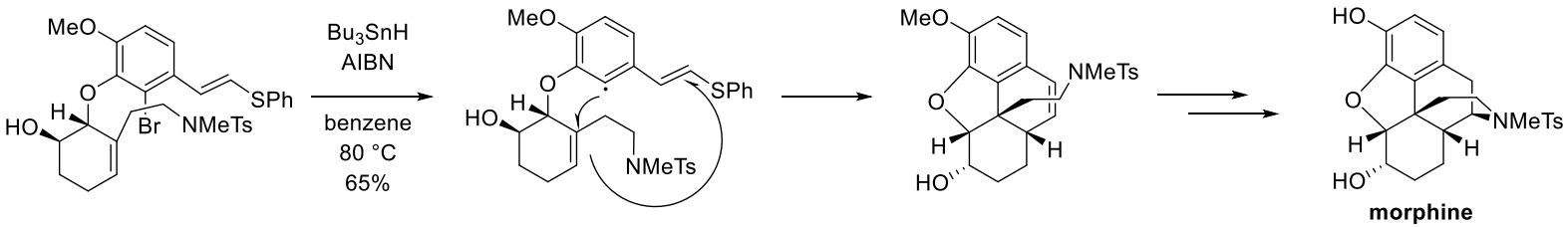


Eur. J. Org. Chem. 2001,5372544

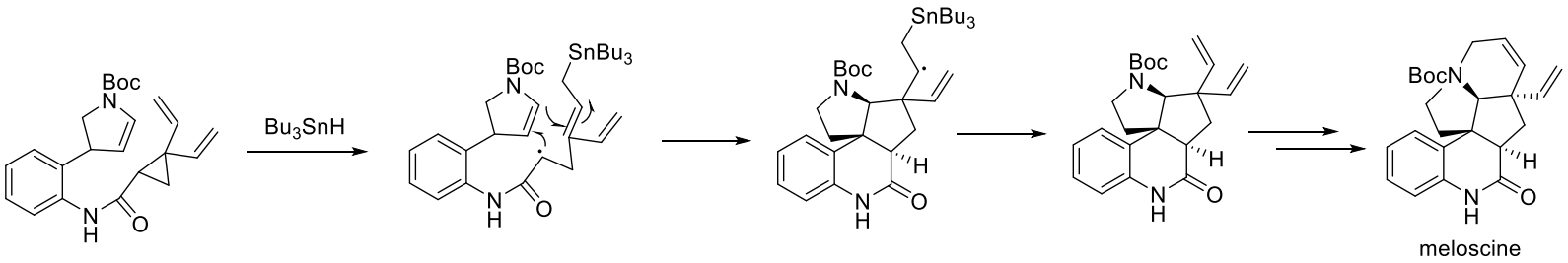


D-homo-12-azasteroid 16

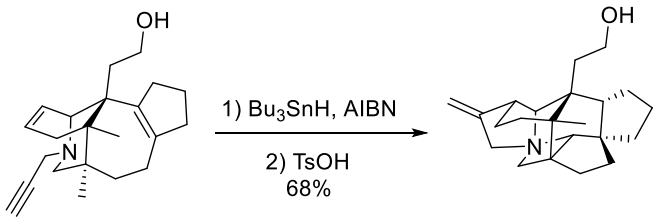
J. Chem. Soc., Perkin Trans. 1, 1998 2



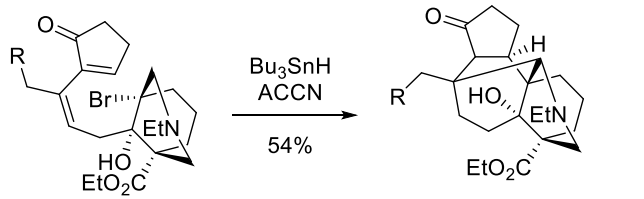
K. A. Parker, D. Fokas, J. Am. Chem. Soc. 1992, 114, 9688–9689



J. Am. Chem. Soc. 2011, 133, 27, 10376–10378

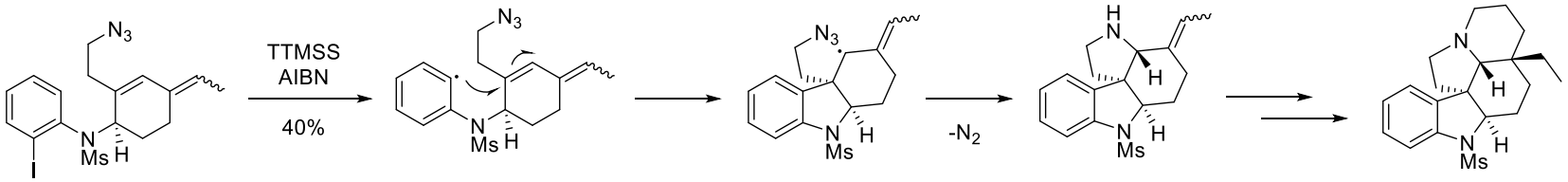


J. Am. Chem. Soc. 2019, 141, 33, 13043–13048

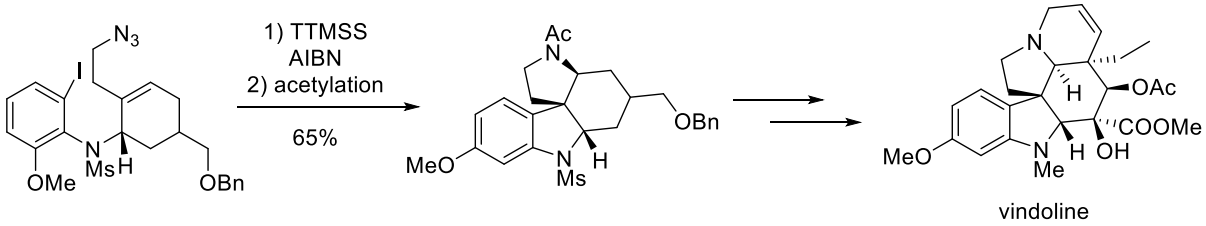


puberuline C framework

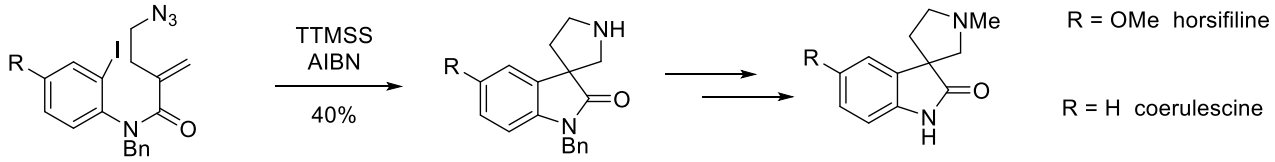
Chem. Sci., 2016, 7, 4372



B. Patro, J. A. Murphy, Org. Lett. 2000, 2, 3599–3601;

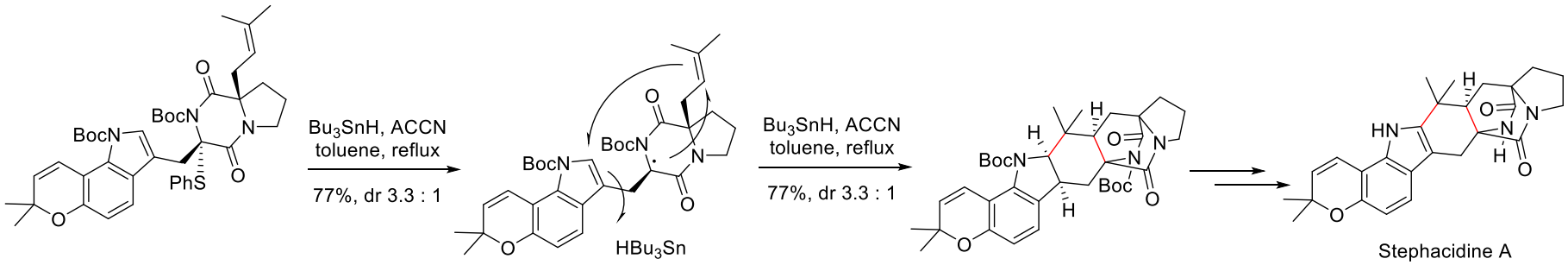


S. Zhou, S. Bommezijn, J. A. Murphy, Org. Lett. 2002, 4, 443–445

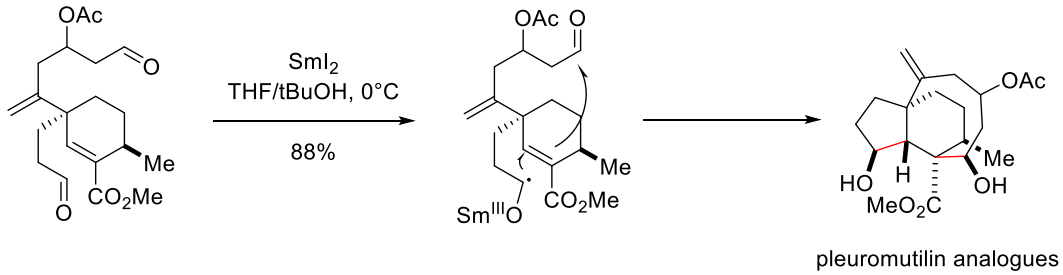


D. Lizos, R. Tri- poli, J. A. Murphy, Chem. Commun. 2001, 2732–2733;

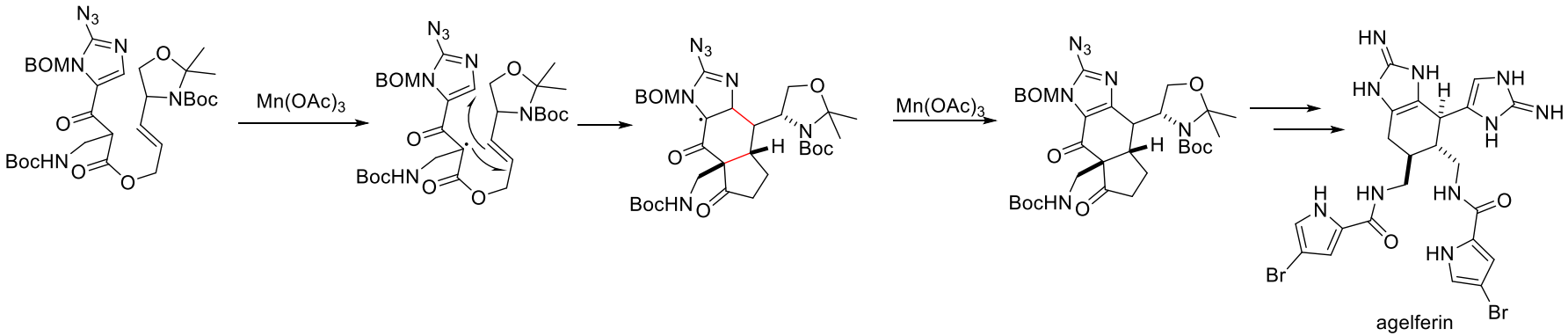
D. E. Lizos, J. A. Murphy, Org. Biomol. Chem. 2003



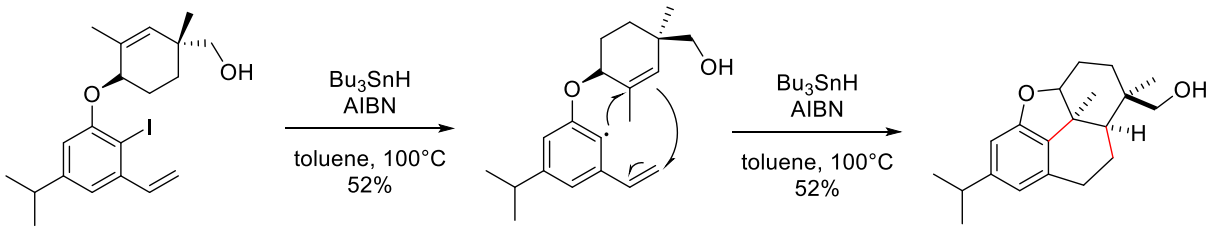
Org. Biomol. Chem., 2013, 11, 4957



Chem. Eur. J. 2013, 19, 6718 – 6723

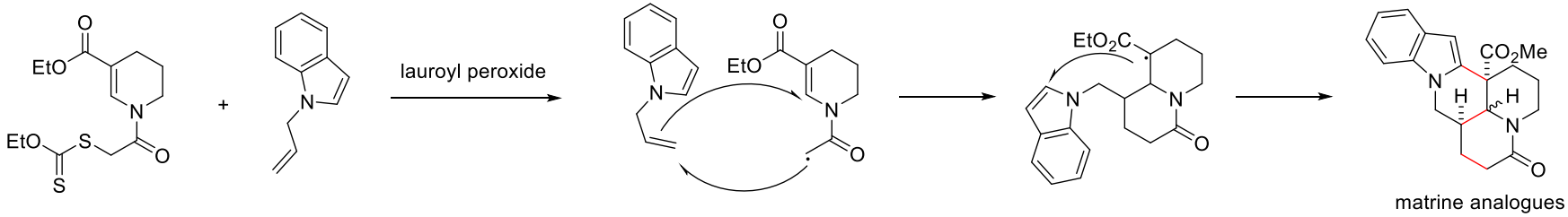


J. Am. Chem. Soc. 2016, 138, 43, 14504

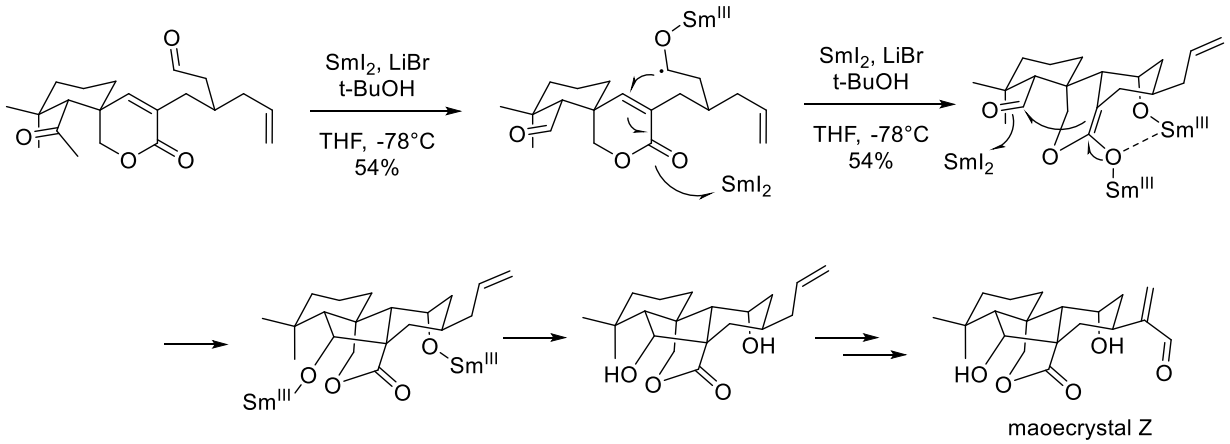


5-epi-7-deoxy-isoabietinin A

Org. Chem. Front., 2017, 4, 2211



Eur. J. Org. Chem. 2017, 2481–2485



J. Am. Chem. Soc. 2011, 133, 14964–14967

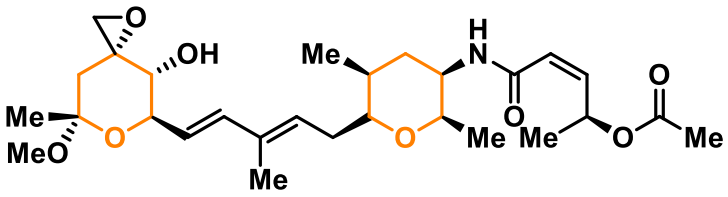
Achmatowicz Reaction and its Use in Total Synthesis

Frontiers in Chemical Synthesis II: Heterocycle Chemistry

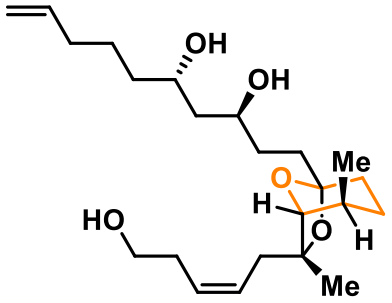
Eliott Le Du
17/05/2021

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

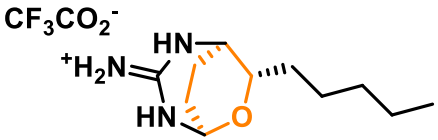
Tetrahydropyran Scaffold Importance



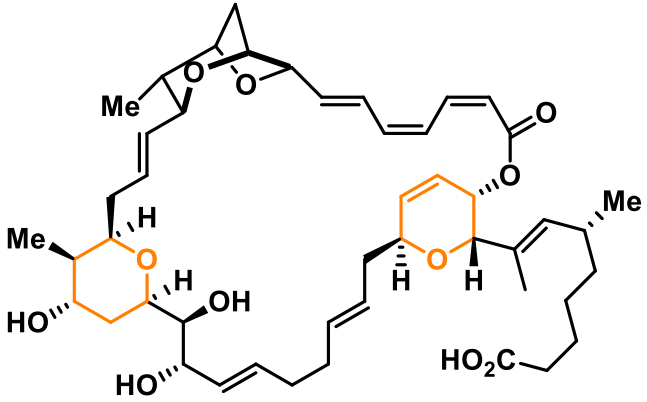
Spliceostatin A
anti-tumor activity



(+)-Attenol B
cytotoxic activity



(+)-Monanchorin
ion-pump inhibitor

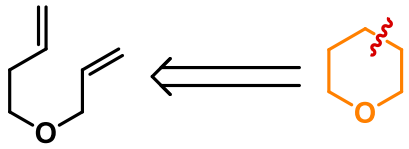


Sorangicine A
antibacterial activity

D. Kaida , H. Motoyoshi , E. Tashiro , T. Nojima , M. Hagiwara , K. Ishigami , H. Watanabe , T. Kitahara , T. Yoshida , H. Nakajima , T. Tani , S. Horinouchi and M. Yoshida, *Nat. Chem. Biol.*, **2007**, 576-583. N. Takada , K. Suenaga , K. Yamada , S.-Z. Zheng , H.-S. Chen and D. Uemura, *Chem. Lett.*, **1999**, 1025-1026. K. M. Meragelman , T. C. McKee and J. B. McMahon, *J. Nat. Prod.*, **2004**, 1165-1167. R. Jansen , V. Wray , H. Irschik , H. Reichenbach and G. Höfle, *Tetrahedron Lett.*, **1985**, 6031-6034.

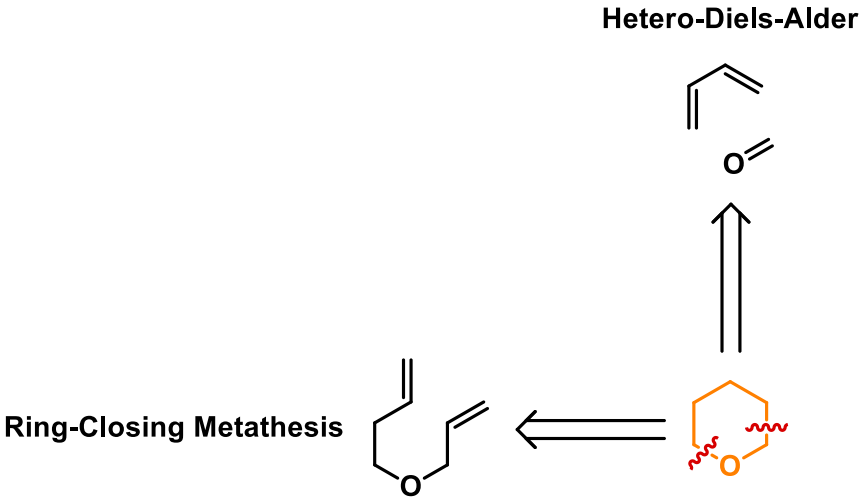
Tetrahydropyran Ring Construction

Ring-Closing Metathesis



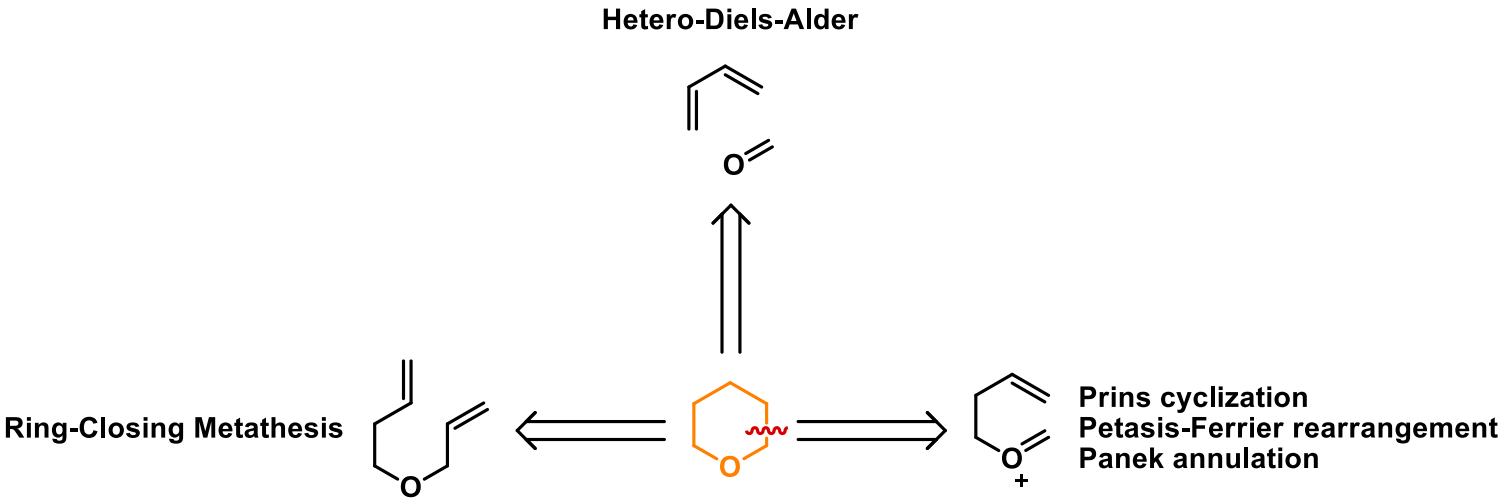
For RCM see: A. Deiters and S. F. Martin, *Chem. Rev.*, **2004**, 2199-2238.

Tetrahydropyran Ring Construction



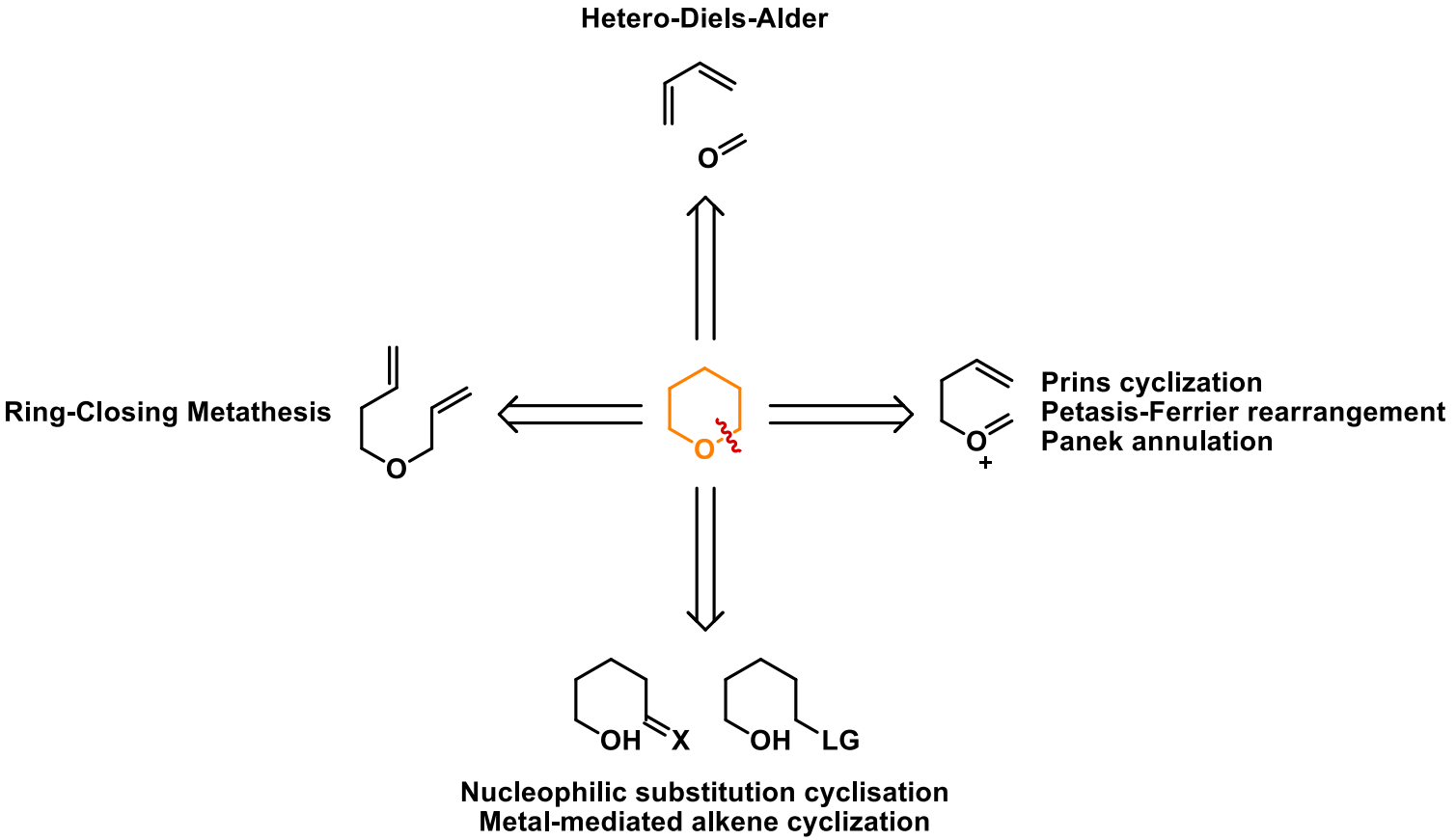
For RCM see: A. Deiters and S. F. Martin, *Chem. Rev.*, **2004**, 2199-2238. For HAD see: M. M. Heravi, T. Ahmadi,M. Ghavidel, B.Heidari and H. Hamidi, *RSC Adv.*, **2015**, 101999-102075.

Tetrahydropyran Ring Construction



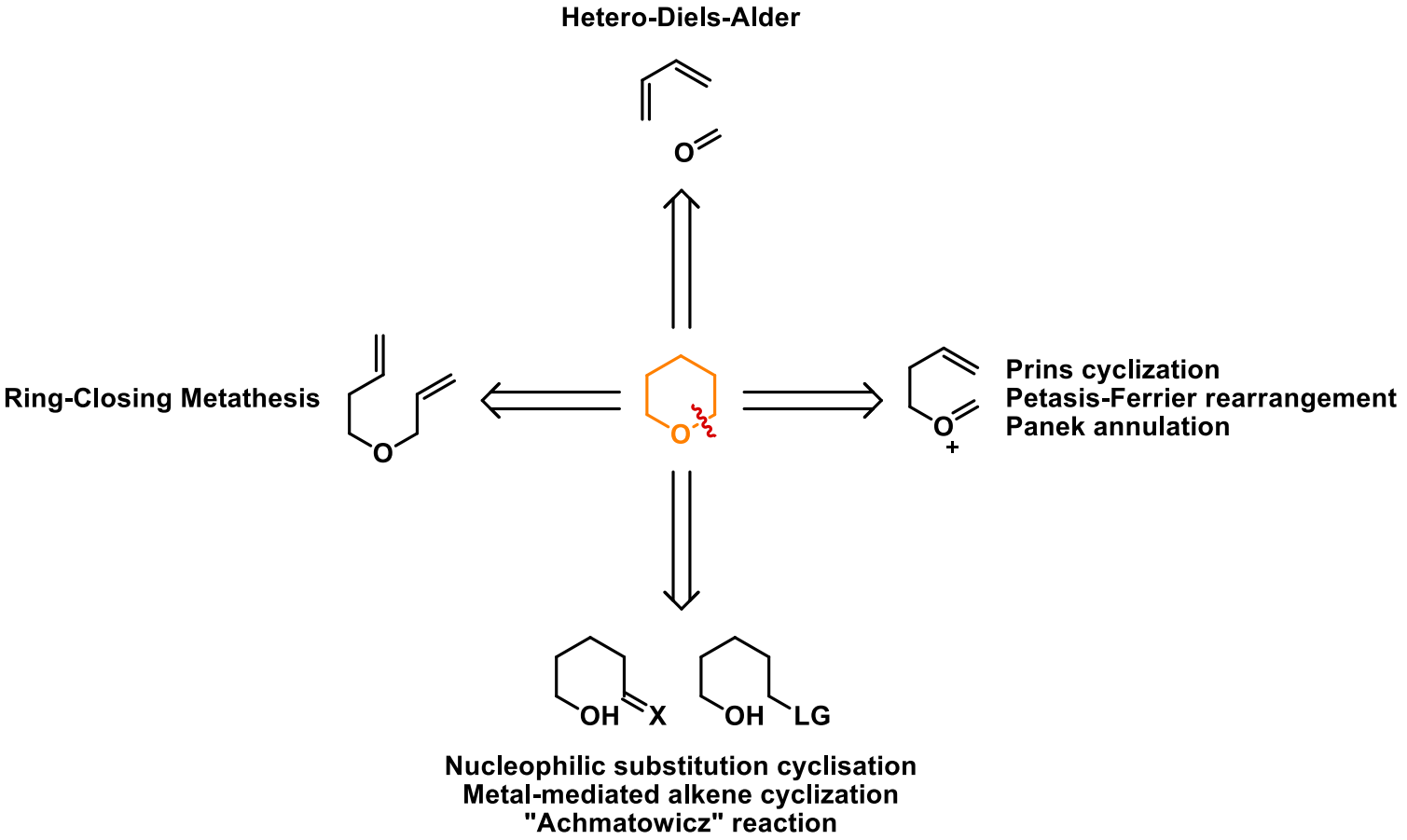
For RCM see: A. Deiters and S. F. Martin, *Chem. Rev.*, **2004**, 2199-2238. For HAD see: M. M. Heravi, T. Ahmadi,M. Ghavidel, B.Heidari and H. Hamidi, *RSC Adv.*, **2015**, 101999-102075. For Prins cyclization see: X. Han, G. R. Peh and P. E. Floreancig, *Eur. J. Org. Chem.*, **2013**, 1193-1208. For Petasis-Ferrier see: E. C. Minbiole and K. P. C Minbiole, *The Journal of Antibiotics* **2016**, 213-219. Seminal work on the Panek annulation: Q. Su and J. S. Panek, *J. Am. Chem. Soc.*, **2004**, 2425-2430.

Tetrahydropyran Ring Construction



For RCM see: A. Deiters and S. F. Martin, *Chem. Rev.*, **2004**, 2199-2238. For HAD see: M. M. Heravi, T. Ahmadi,M. Ghavidel, B.Heidari and H. Hamidi, *RSC Adv.*, **2015**, 101999-102075. For Prins cyclization see: X. Han, G. R. Peh and P. E. Floreancig, *Eur. J. Org. Chem.*, **2013**, 1193-1208. For Petasis-Ferrier see: E. C. Minbiole and K. P. C Minbiole, *The Journal of Antibiotics* **2016**, 213-219. Seminal work on the Panek annulation: Q. Su and J. S. Panek, *J. Am. Chem. Soc.*, **2004**, 2425-2430. For Nucleophilic substitution and metal-mediated alkene cyclization see: M. A. Brimble , K. P. Kaliappan , A. J. Moreno-Vargas , K. Palanichamy , M. A. Perry , J. D. Rainier , S. D. Rychnovsky , N. Sizemore , L. A. Stubbing and P. Vogel , *Synthesis of saturated oxygenated heterocycles. I, 5- and 6-membered rings* , Springer, Berlin, 2014.

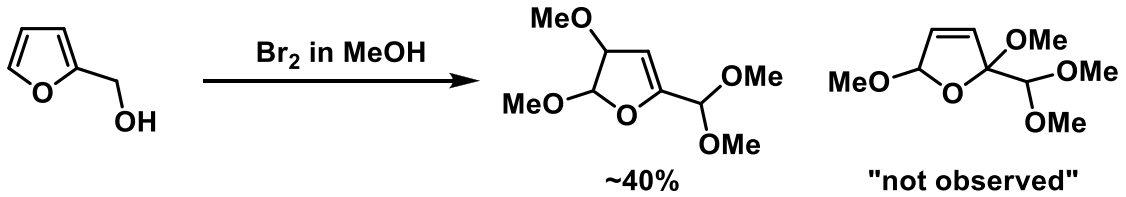
Tetrahydropyran Ring Construction



For RCM see: A. Deiters and S. F. Martin, *Chem. Rev.*, **2004**, 2199-2238. For HAD see: M. M. Heravi, T. Ahmadi,M. Ghavidel, B.Heidari and H. Hamidi, *RSC Adv.*, **2015**, 101999-102075. For Prins cyclization see: X. Han, G. R. Peh and P. E. Floreancig, *Eur. J. Org. Chem.*, **2013**, 1193-1208. For Petasis-Ferrier see: E. C. Minbiole and K. P. C Minbiole, *The Journal of Antibiotics* **2016**, 213-219. Seminal work on the Panek annulation: Q. Su and J. S. Panek, *J. Am. Chem. Soc.*, **2004**, 2425-2430. For Nucleophilic substitution and metal-mediated alkene cyclization see: M. A. Brimble , K. P. Kaliappan , A. J. Moreno-Vargas , K. Palanichamy , M. A. Perry , J. D. Rainier , S. D. Rychnovsky , N. Sizemore , L. A. Stubbing and P. Vogel , *Synthesis of saturated oxygenated heterocycles. I, 5- and 6-membered rings* , Springer, Berlin, 2014.

Seminal Works

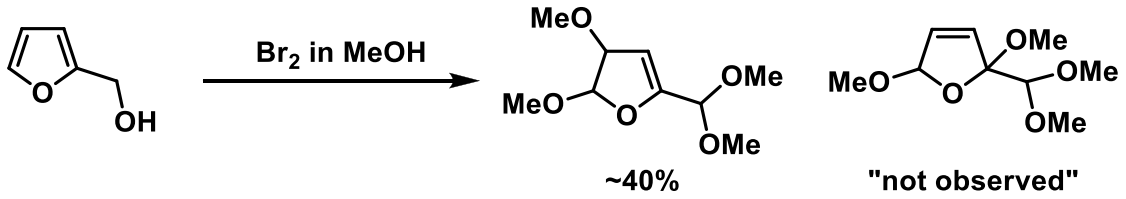
- Meinel (**1935**):



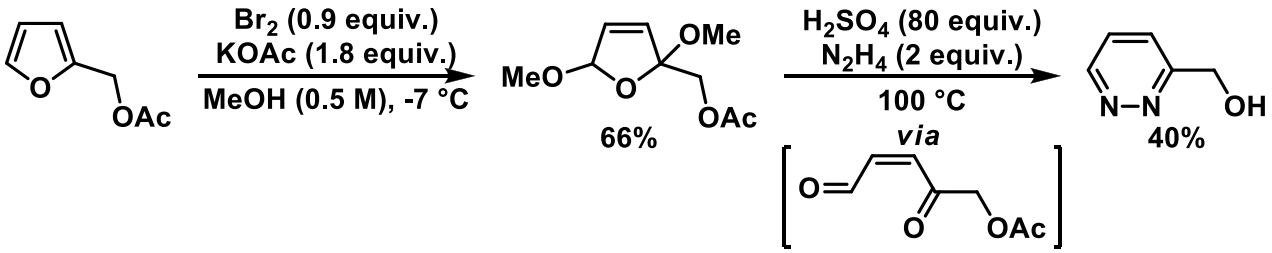
(a) K. Meinel, *Justus Liebigs Ann. Chem.* **1935**, 231–243.

Seminal Works

- Meinel (**1935**):



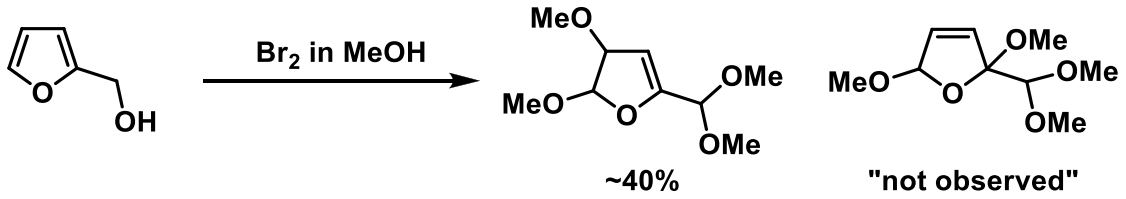
- Clauson-Kaas and coworkers (**1947**):



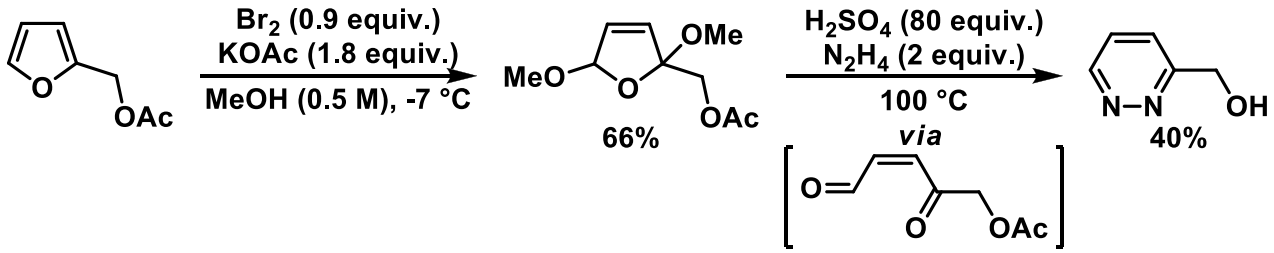
(a) K. Meinel, *Justus Liebigs Ann. Chem.* **1935**, 231–243. (b) N. Clauson-Kaas, F. Limborg, H. Theorell, A. Linnasalmi and P. Laukkanen, *Acta Chem. Scand.* **1947**, 619–623.

Seminal Works

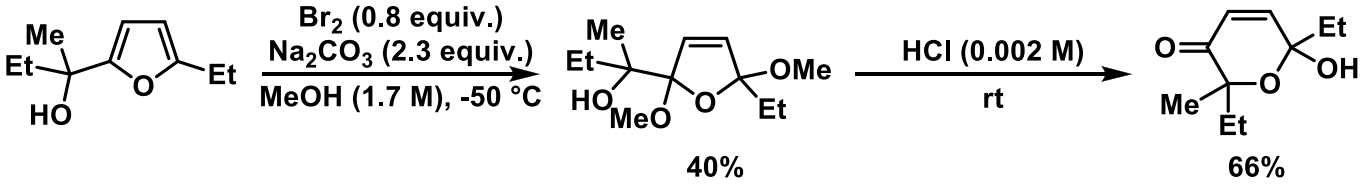
- Meinel (**1935**):



- Clauson-Kaas and coworkers (**1947**):



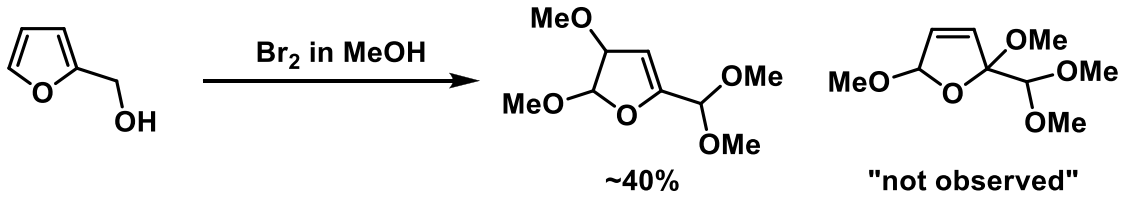
- Cavill and coworkers (**1969**):



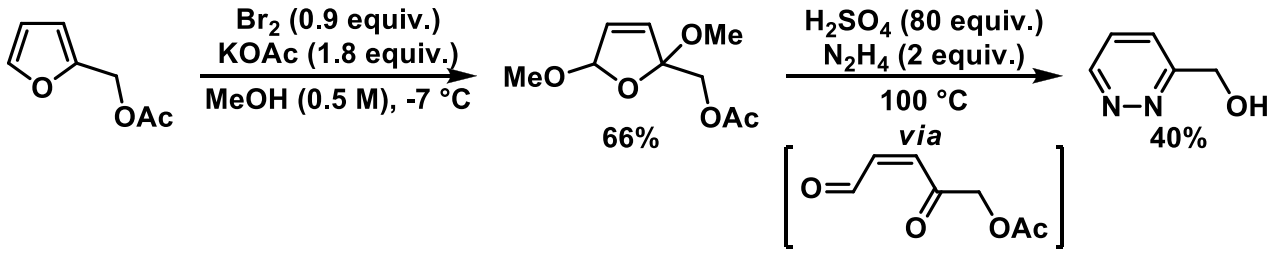
(a) K. Meinel, *Justus Liebigs Ann. Chem.* **1935**, 231–243. (b) N. Clauson-Kaas, F. Limborg, H. Theorell, A. Linnasalmi and P. Laukkanen, *Acta Chem. Scand.* **1947**, 619–623. (c) G. W. K. Cavill , D. G. Laing and P. J. Williams, *Aust. J. Chem.*, **1969**, 2145-2160.

Seminal Works

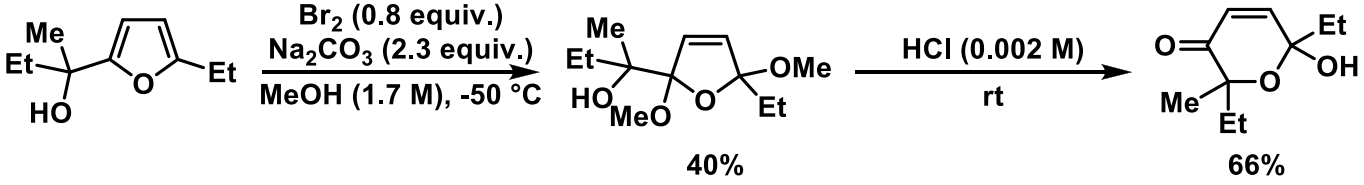
- Meinel (**1935**):



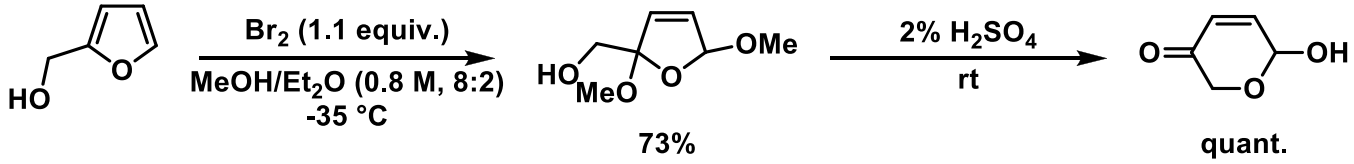
- Clauson-Kaas and coworkers (**1947**):



- Cavill and coworkers (**1969**):

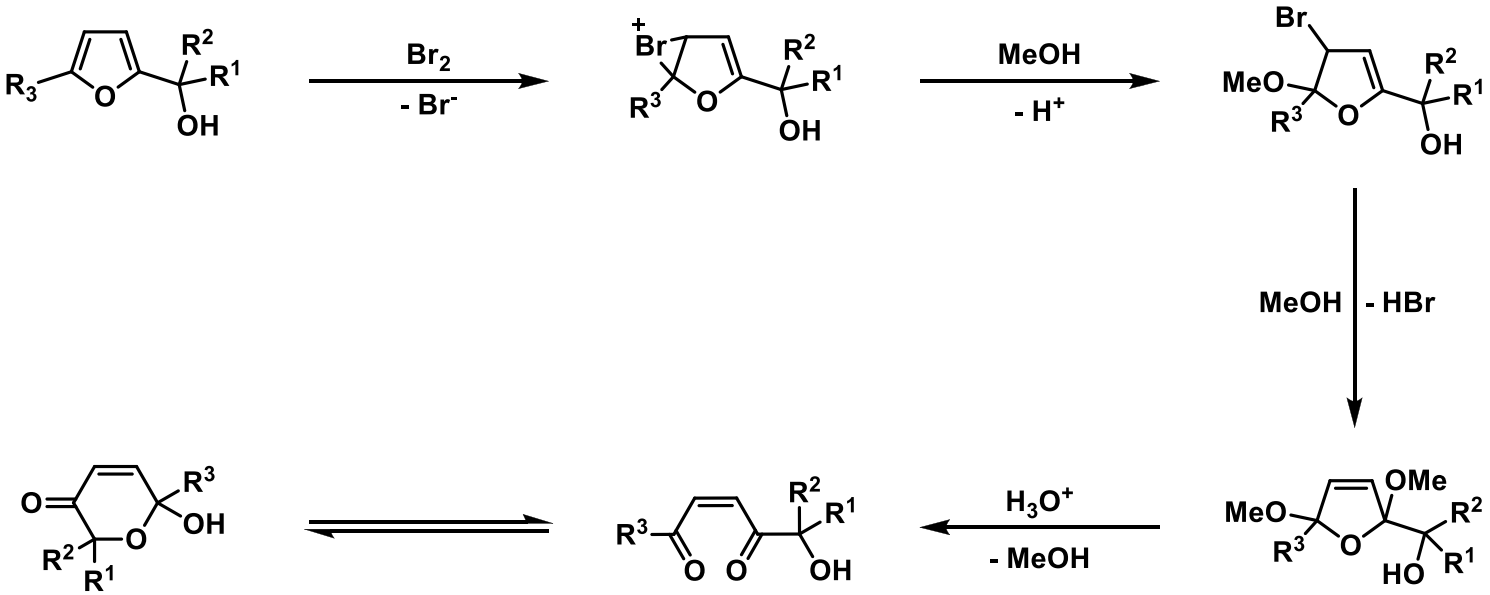


- Achmatowicz and coworkers (**1971**):



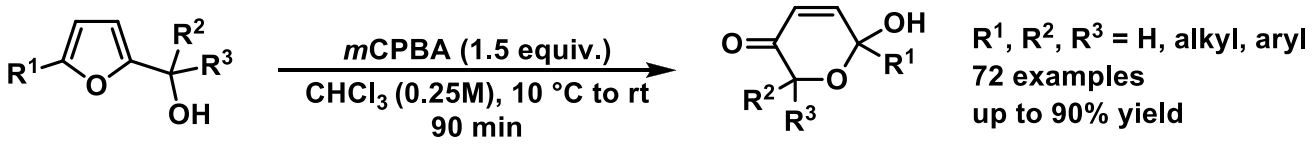
(a) K. Meinel, *Justus Liebigs Ann. Chem.* **1935**, 231–243. (b) N. Clauson-Kaas, F. Limborg, H. Theorell, A. Linnasalmi and P. Laukkanen, *Acta Chem. Scand.* **1947**, 619–623. (c) G. W. K. Cavill , D. G. Laing and P. J. Williams, *Aust. J. Chem.*, **1969**, 2145-2160. (d) O. Achmatowicz, P. Bukowski, B. Szechner, Z. Zwierzchowska and A. Zamojski, *Tetrahedron* **1971**, 1973-1996.

Mechanism


R3
O
R2
R1
OH
Br2
- Br-
+
Br
R3
O
R2
R1
OH
MeOH
- H+
Br
MeO
R3
O
R2
R1
OH
MeOH
- HBr
OMe
MeO
R3
O
R2
R1
HO
H3O+
- MeOH
R3
O
O
R2
R1
OH
O
R2
R1
R3
OH
O
R2
R1

Developments

- mCPBA Lefebvre and coworkers (**1973**):

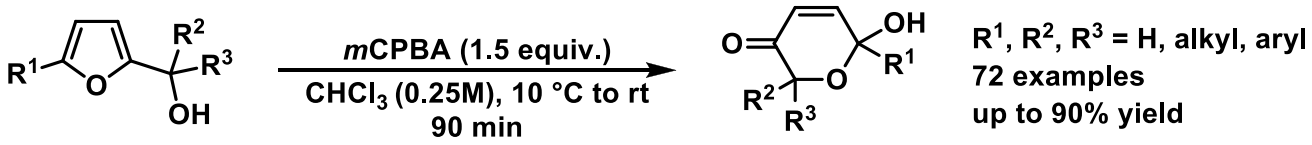


R^1, R^2, R^3 = H, alkyl, aryl
72 examples
up to 90% yield

(a) R. Laliberte, G. Medawar and Y. Lefebvre, *J.Med.Chem.***1973**,1084-1089.

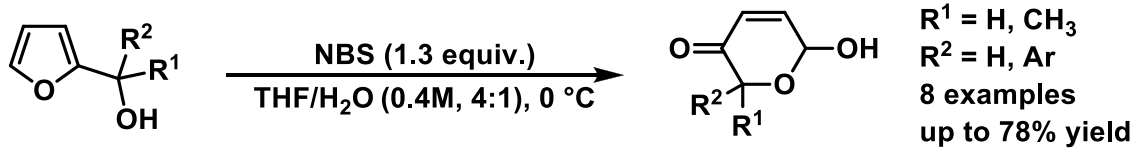
Developments

- mCPBA Lefebvre and coworkers (**1973**):



R^1, R^2, R^3 = H, alkyl, aryl
72 examples
up to 90% yield

- NBS Georgiadis and coworkers (**1986**):

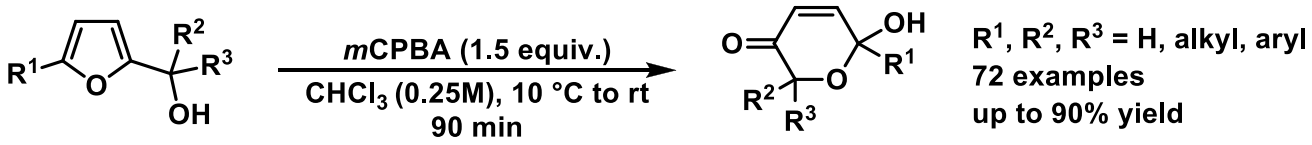


R^1 = H, CH_3
R^2 = H, Ar
8 examples
up to 78% yield

(a) R. Laliberte, G. Medawar and Y. Lefebvre, *J.Med.Chem.***1973**,1084-1089. (b) M. P. Georgiadis and E. A. Couladouros, *J. Org. Chem.*, **1986**, 2725-2727.

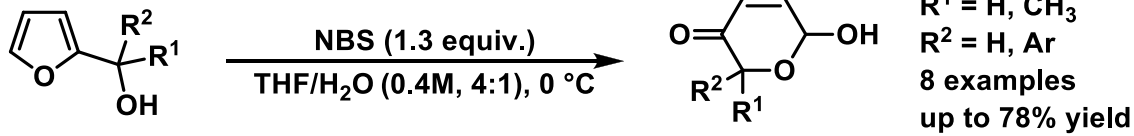
Developments

- mCPBA Lefebvre and coworkers (**1973**):



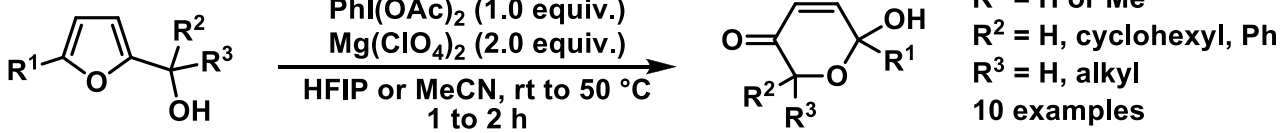
R^1, R^2, R^3 = H, alkyl, aryl
72 examples
up to 90% yield

- NBS Georgiadis and coworkers (**1986**):



R^1 = H, CH_3
R^2 = H, Ar
8 examples
up to 78% yield

- PIDA Piancatelli and coworkers (**1995**):

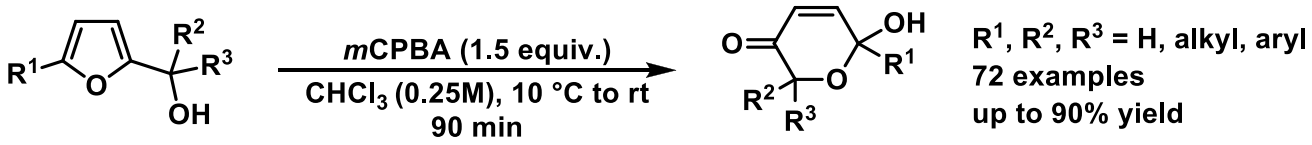


R^1 = H or Me
R^2 = H, cyclohexyl, Ph
R^3 = H, alkyl
10 examples
up to 95% yield

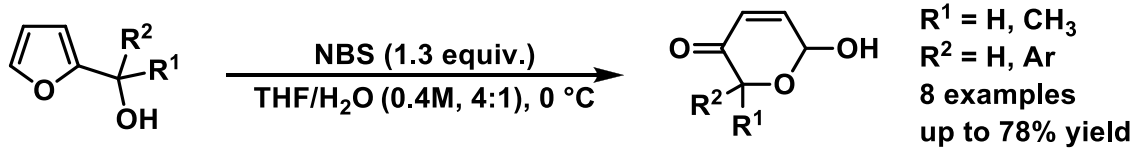
(a) R. Laliberte, G. Medawar and Y. Lefebvre, *J.Med.Chem.***1973**,1084-1089. (b) M. P. Georgiadis and E. A. Couladouros, *J. Org. Chem.*, **1986**, 2725-2727. (c) A. De Mico, R. Margarita and G. Piancatelli, *Tetrahedron Lett.* **1995**, 3553-3556.

Developments

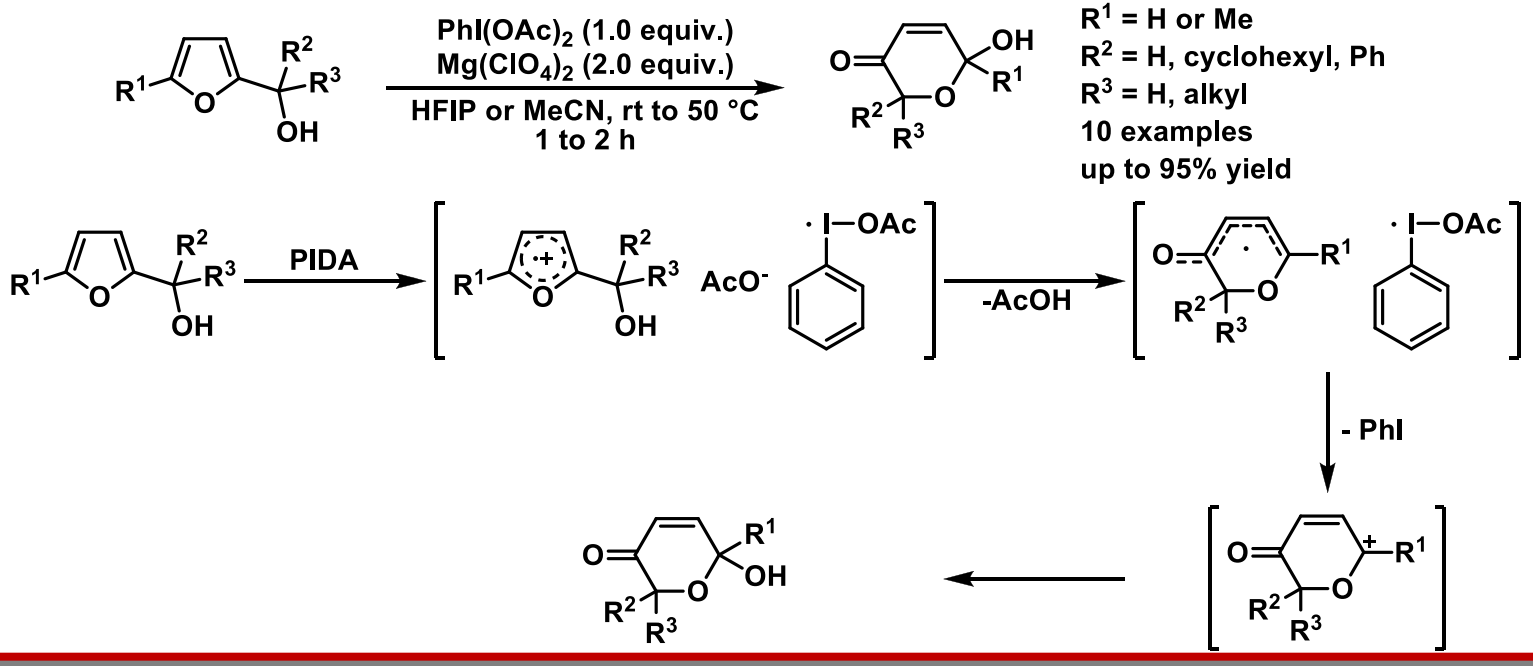
- mCPBA Lefebvre and coworkers (**1973**):



- NBS Georgiadis and coworkers (**1986**):



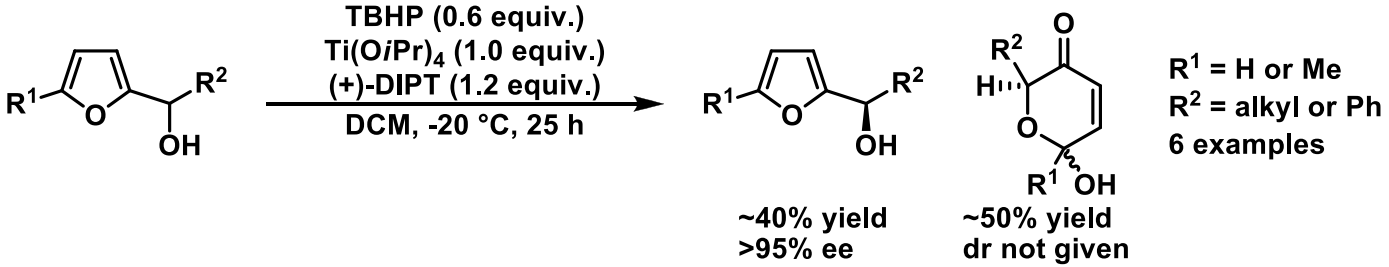
- PIDA Piancatelli and coworkers (**1995**):



(a) R. Laliberte, G. Medawar and Y. Lefebvre, *J.Med.Chem.***1973**,1084-1089. (b) M. P. Georgiadis and E. A. Couladouros, *J. Org. Chem.*, **1986**, 2725-2727. (c) A. De Mico, R. Margarita and G. Piancatelli, *Tetrahedron Lett.* **1995**, 3553-3556.

Developments

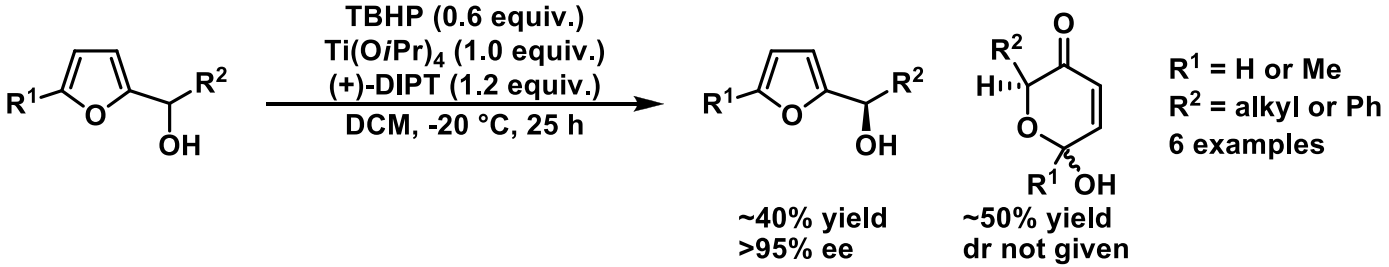
- Sharpless epoxidation Sato and coworkers (**1987**):



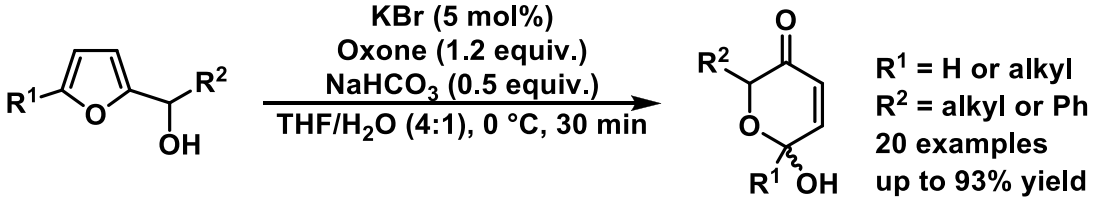
(a) Y. Kobayashi, M. Kusakabe, Y. Kitano and F. Sato, *J. Org. Chem.* **1988**, 1586-1587.

Developments

- Sharpless epoxidation Sato and coworkers (**1987**):



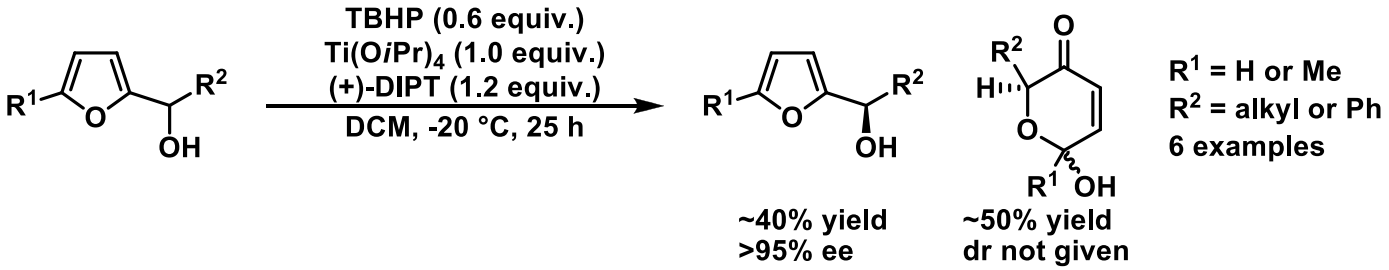
- KBr/Oxone Tong and Li (**2016**):



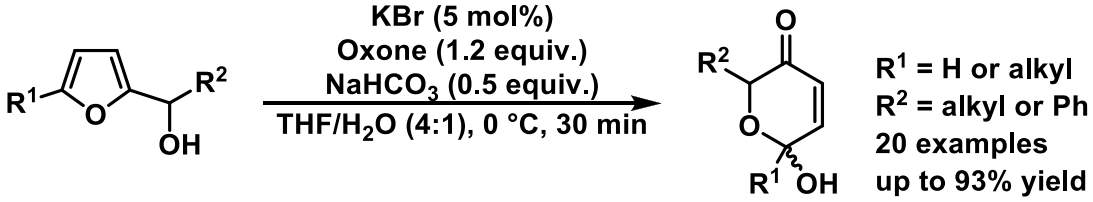
(a) Y. Kobayashi, M. Kusakabe, Y. Kitano and F. Sato, *J. Org. Chem.* **1988**, 1586-1587. (b) Z. L. Li and R. B. Tong, *J. Org. Chem.* **2016**, 4847-4855.

Developments

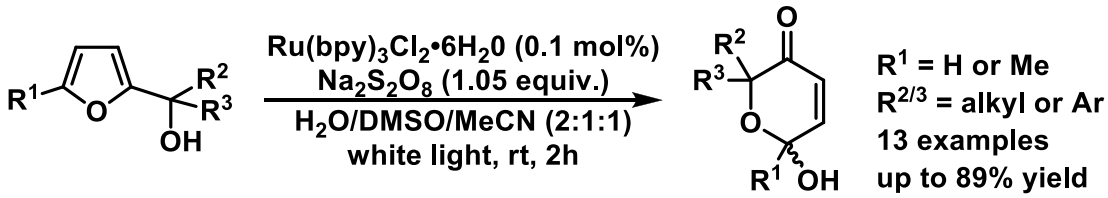
- Sharpless epoxidation Sato and coworkers (**1987**):



- KBr/Oxone Tong and Li (**2016**):



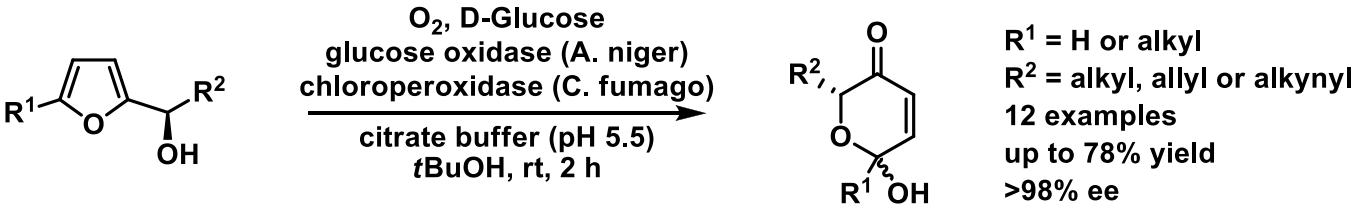
- Photoredox Gilmore and coworkers (**2016**):



(a) Y. Kobayashi, M. Kusakabe, Y. Kitano and F. Sato, *J. Org. Chem.* **1988**, 1586-1587. (b) Z. L. Li and R. B. Tong, *J. Org. Chem.* **2016**, 4847-4855. (c) M. B. Plutschack, P. H. Seeberger and K. Gilmore, *Org. Lett.* **2017**, 30-33.

Developments

- Enzymatic oxidation Deska and coworkers (**2014**):

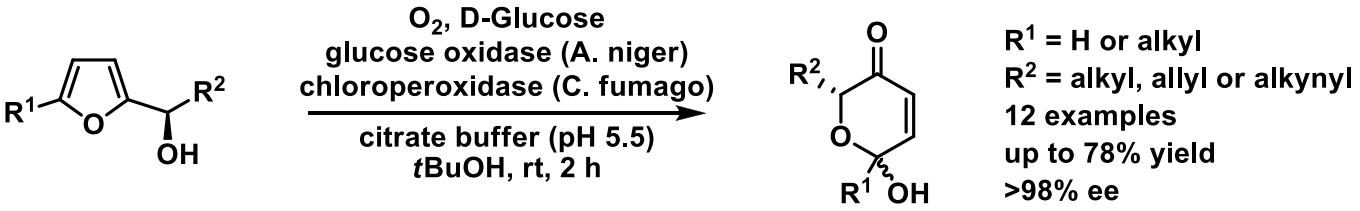


R^1 = H or alkyl
R^2 = alkyl, allyl or alkynyl
12 examples
up to 78% yield
>98% ee

(a) D. Thiel, D. Doknic and J. Deska, *Nat. Commun.* **2014**, 5278-5284.

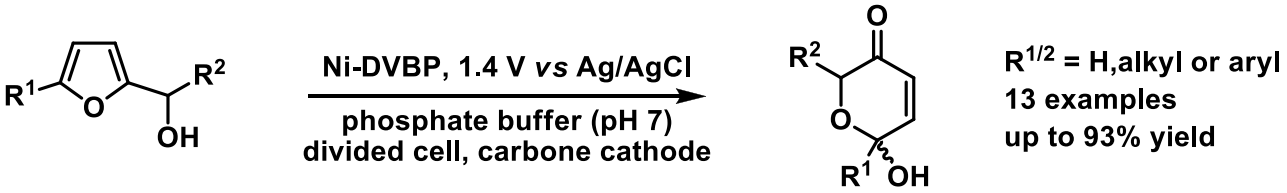
Developments

- Enzymatic oxidation Deska and coworkers (**2014**):



R^1 = H or alkyl
R^2 = alkyl, allyl or alkynyl
12 examples
up to 78% yield
>98% ee

- Electrochemistry Sun and coworkers (**2021**):

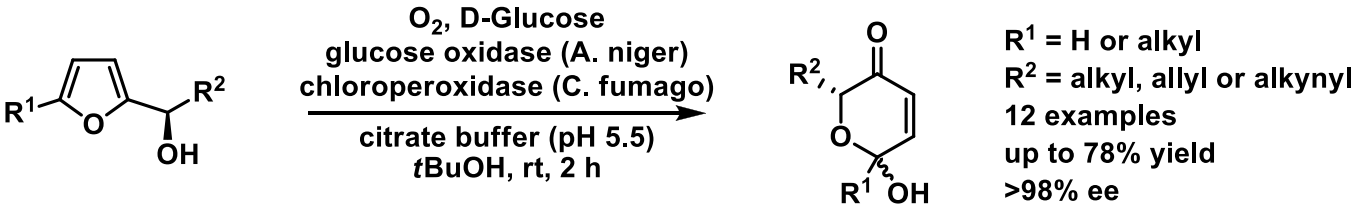


$R^{1/2}$ = H,alkyl or aryl
13 examples
up to 93% yield

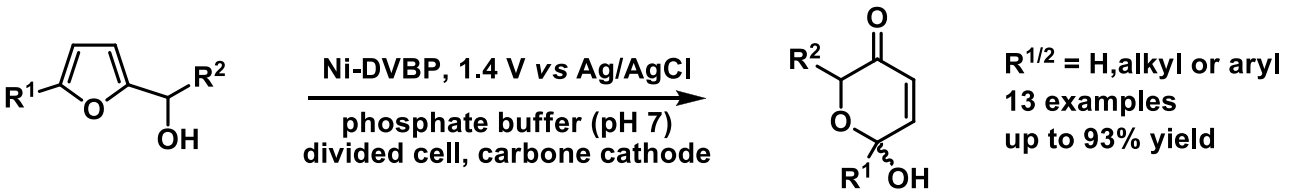
(a) D. Thiel, D. Doknic and J. Deska, *Nat. Commun.* **2014**, 5278-5284. (b) X. Liu, B. Li, G. Han, X. Liu, Z. Cao, D. Jiang and Y. Sun *Nat. Commun.* **2021**, 1868.

Developments

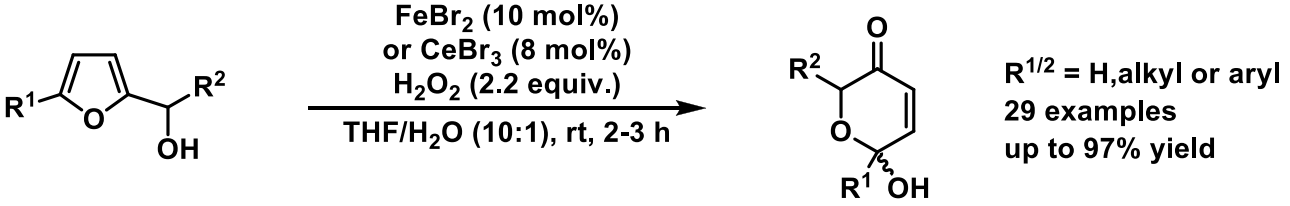
- Enzymatic oxidation Deska and coworkers (**2014**):



- Electrochemistry Sun and coworkers (**2021**):

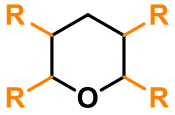


- Fenton chemistry Tong and coworkers (**2021**):

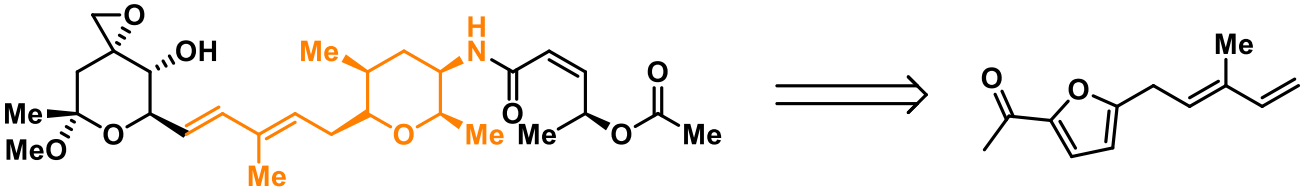


(a) D. Thiel, D. Doknic and J. Deska, *Nat. Commun.* **2014**, 5278-5284. (b) X. Liu, B. Li, G. Han, X. Liu, Z. Cao, D. Jiang and Y. Sun *Nat. Commun.* **2021**, 1868. (c) G. Zhao, L. Liang, E. Wang and R. Tong *ACS. Catal.* **2021**, 3740-3748.

Substituted Tetrahydropyran



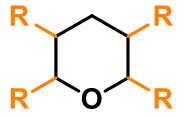
- Synthesis of the Spliceostatin core Ghosh and coworkers (**2020**):



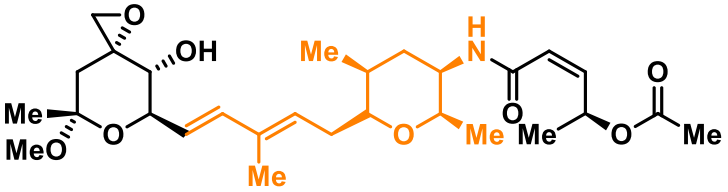
Spliceostatin A
anti-tumor activity

(a) A. K. Ghosh, J. R. Born, A.M. Veitschegger and M. Jurica, *J. Org. Chem.* **2020**, 8111-8120.

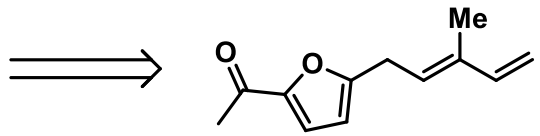
Substituted Tetrahydropyran

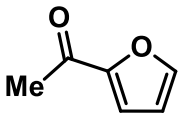


➢ Synthesis of the Spliceostatin core Ghosh and coworkers (**2020**):

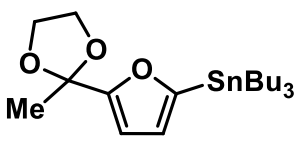


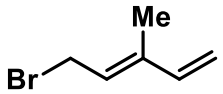
Spliceostatin A
anti-tumor activity



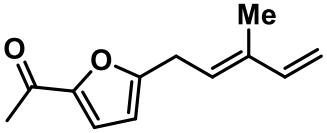


1/ $HOCH_2CH_2OH$, PTSA
2/ *n*-BuLi, THF, nBu_3SnCl, -78 °C
61%

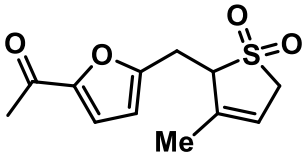




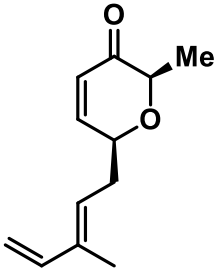
1/ CuI (5 mol%)
Cs_2CO_3 (10 mol%)
MeCN (0.1M), rt, 48 h
2/ PTSA, acetone, 2 h
85%



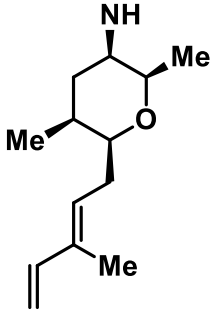
$NaHSO_3$
$KHSO_4$
dioxane
66%



1/ $RuCl_2$[(R,R)-TsDPEN] (1 mol%)
HCO_2H, TEA
2/ KBr, oxone, $NaHCO_3$
3/ BF_3•OEt_2, Et_3SiH
then toluene reflux
66%, >98% ee



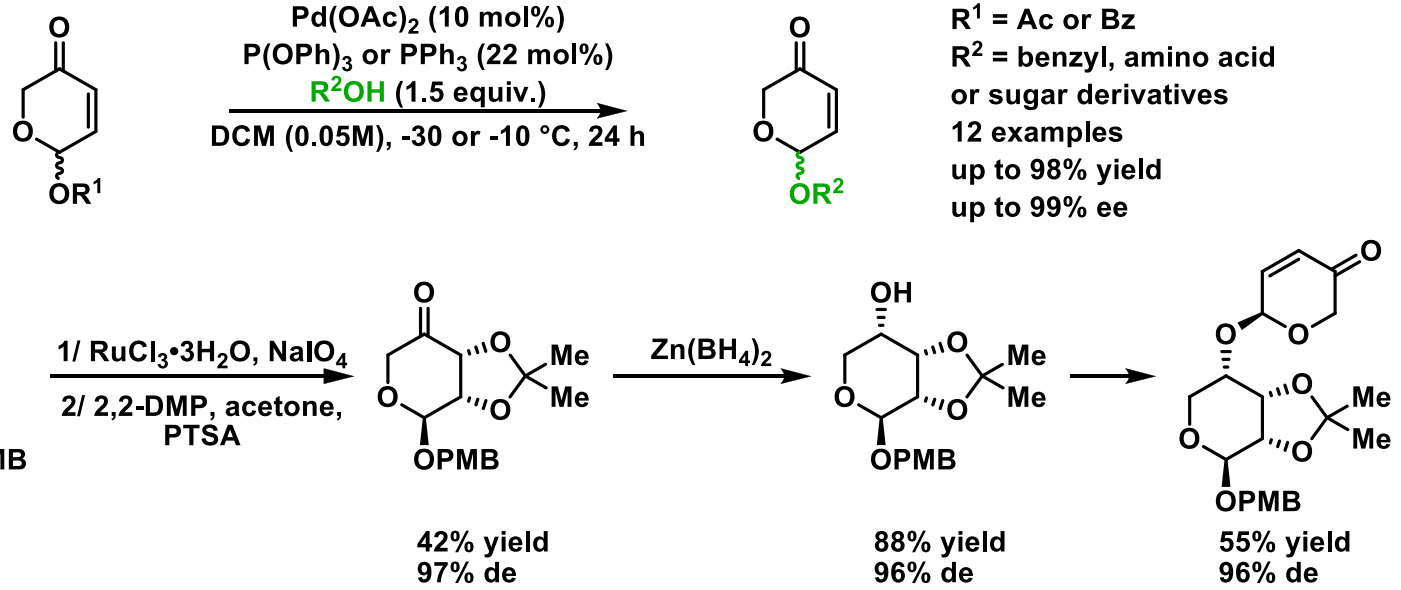
1/ MeLi, Et_2O, CuI
2/ NH_4OAc, $NaBH_3CN$
75%



(a) A. K. Ghosh, J. R. Born, A.M. Veitschegger and M. Jurica, *J. Org. Chem.* **2020**, 8111-8120.

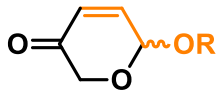
O-Glycosylation

➢ De novo synthesis of saccharide Ferringa and coworkers (**2003**):

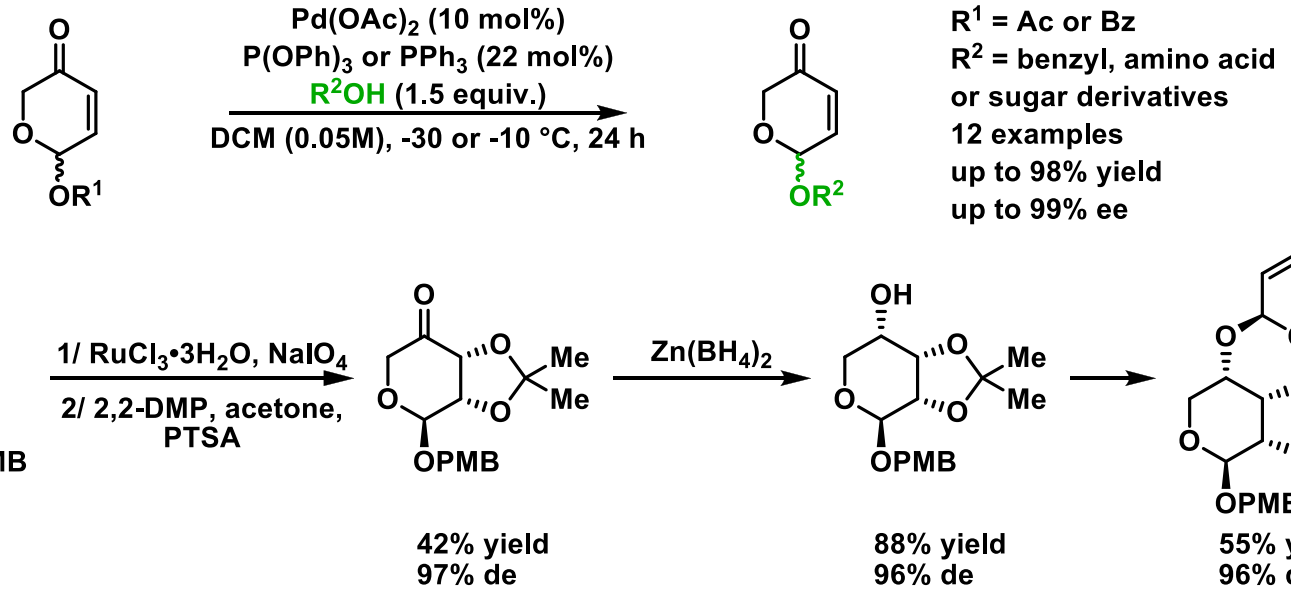


(a) A. C. Comely, R. Eelkema, A. J. Minnaard and B. L. Feringa, *J. Am. Chem. Soc.* **2003**, 8714-8715.

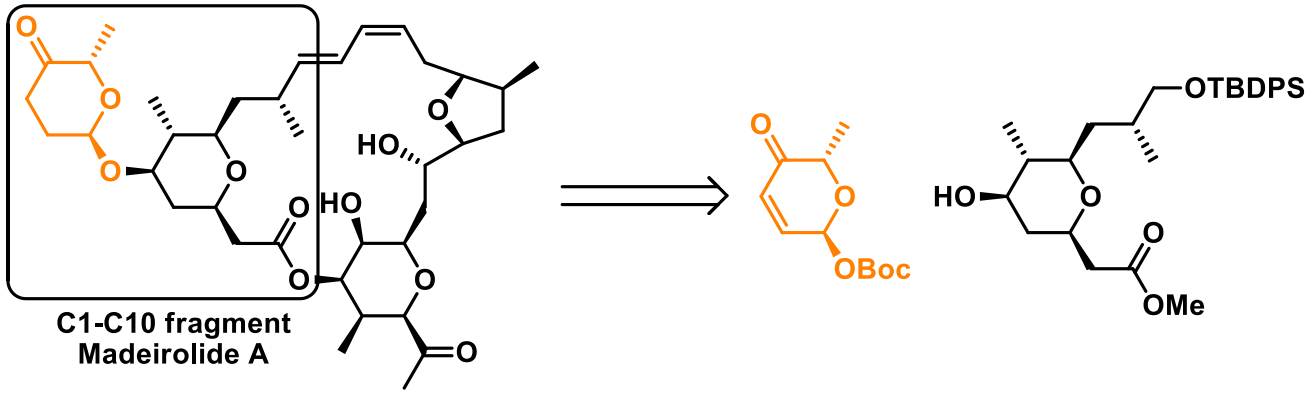
O-Glycosylation



- De novo synthesis of saccharide Ferringa and coworkers (**2003**):

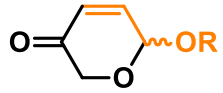


- Application in total synthesis

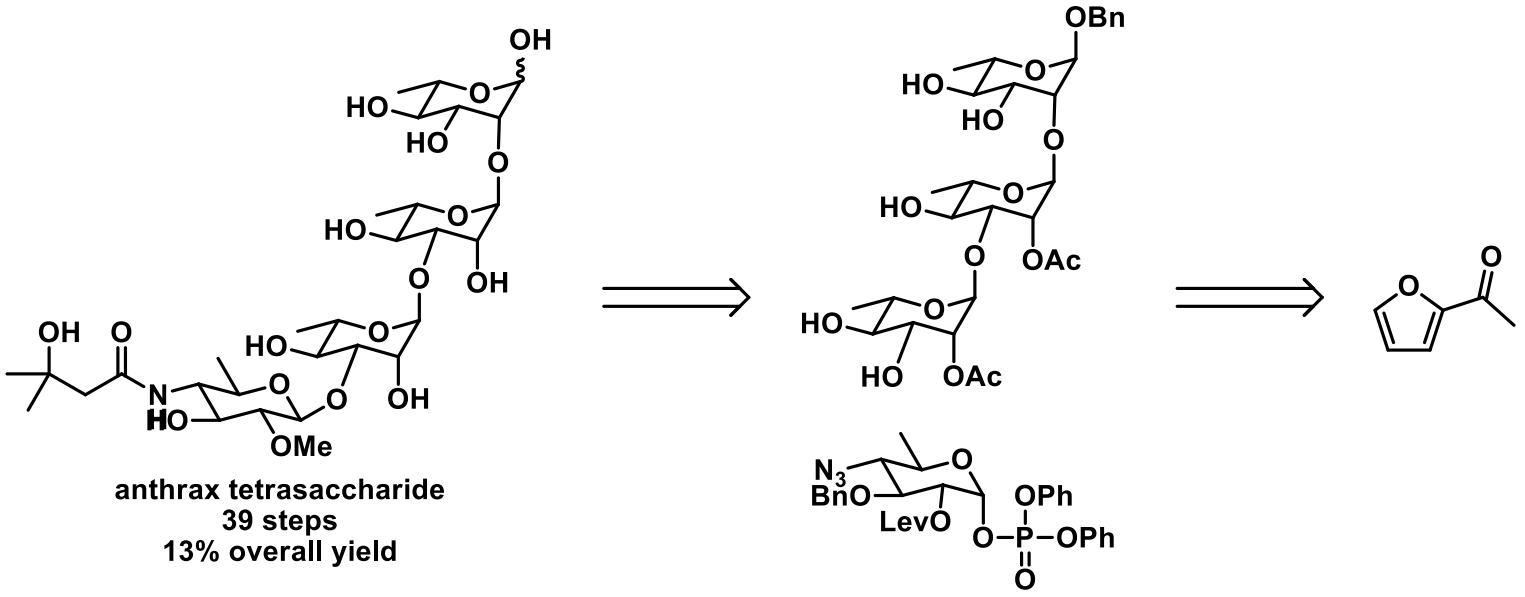


(a) A. C. Comely, R. Eelkema, A. J. Minnaard and B. L. Feringa, *J. Am. Chem. Soc.* **2003**, 8714-8715. (b) S. Hwang, I. Baek and C. Lee, *Org. Lett.* **2016**, 2154-2157.

O-Glycosylation



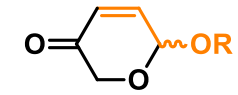
- Anthrax tetrasaccharide Gua and O'Doherty (**2007**)



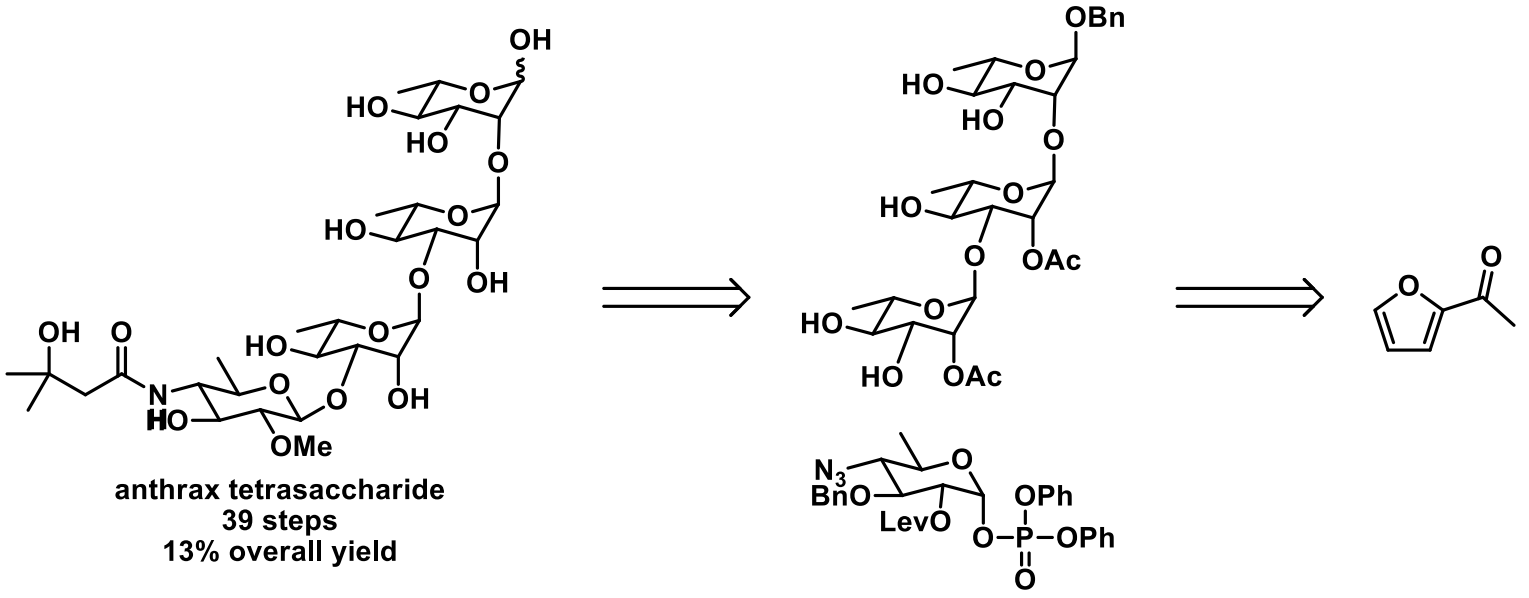
anthrax tetrasaccharide
39 steps
13% overall yield

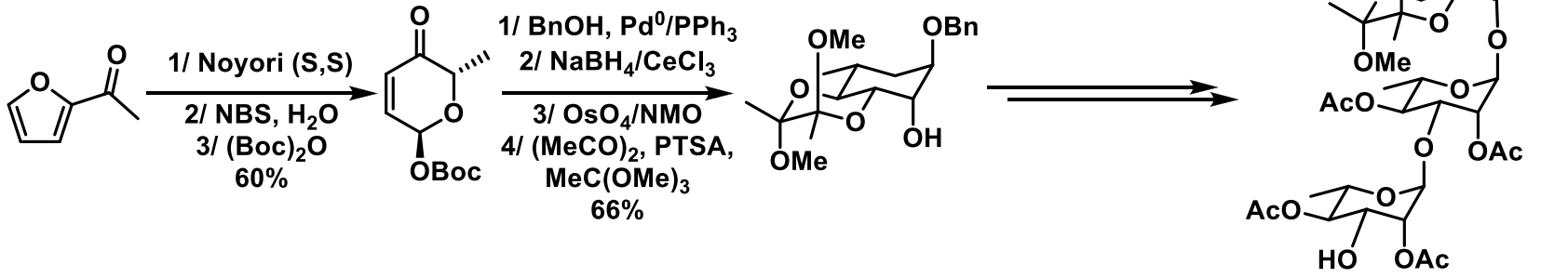
(a) H. Guo and G. A. O'Doherty, *Angew. Chem. Int. Ed. Engl.* **2007**, 5206-5208.

O-Glycosylation



- Anthrax tetrasaccharide Gua and O'Doherty (**2007**)

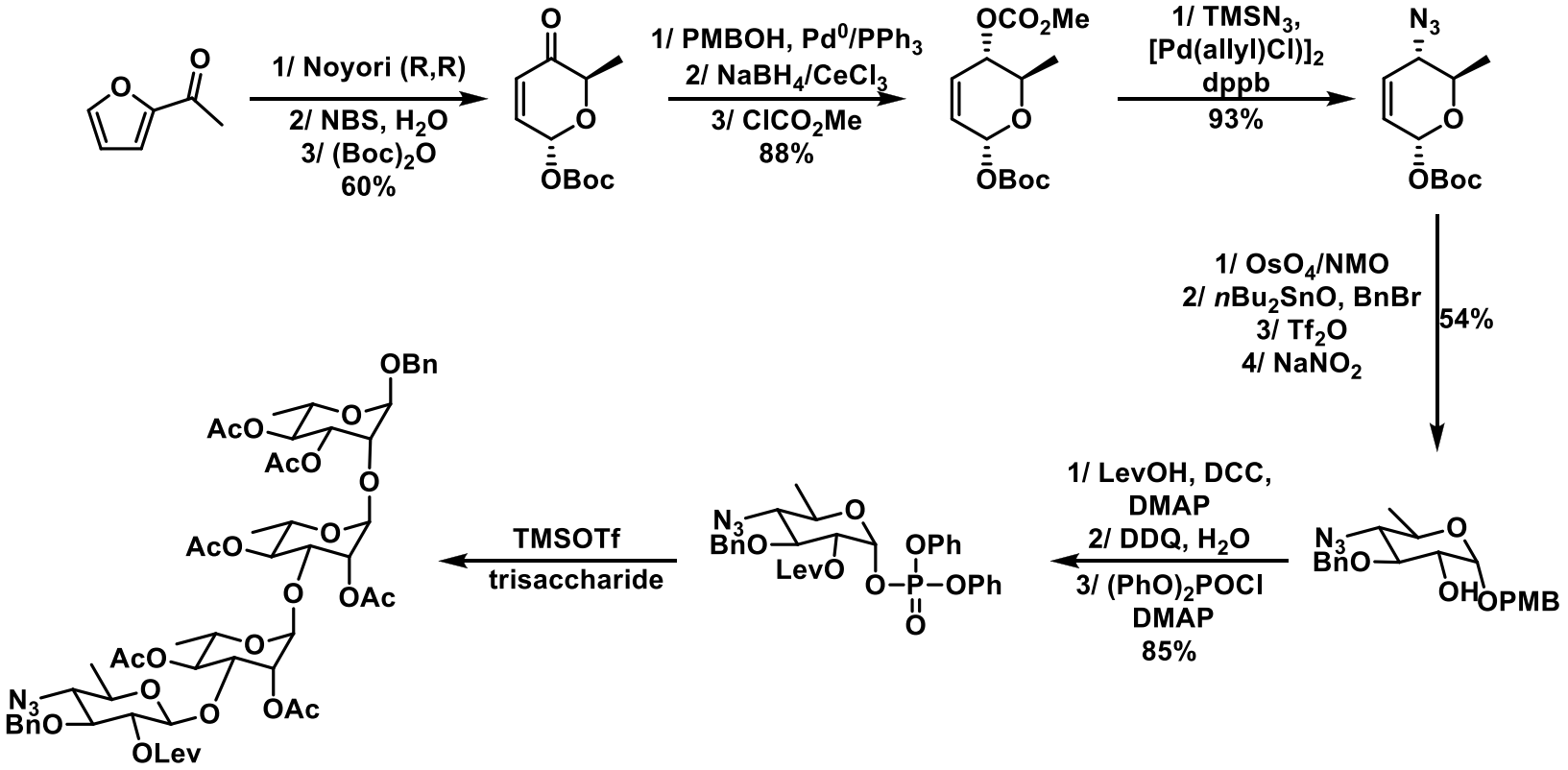




(a) H. Guo and G. A. O'Doherty, *Angew. Chem. Int. Ed. Engl.* **2007**, 5206-5208.

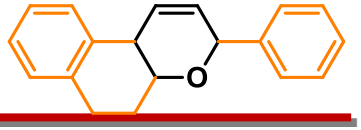
O-Glycosylation

➢ Anthrax tetrasaccharide Gua and O'Doherty (**2007**)

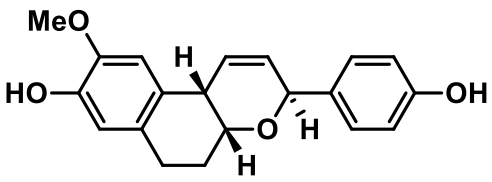


(a) H. Guo and G. A. O'Doherty, *Angew. Chem. Int. Ed. Engl.* **2007**, 5206-5208.

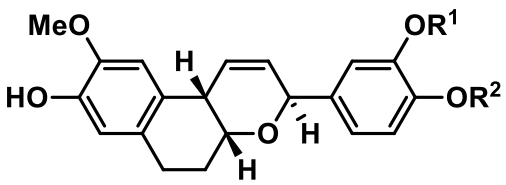
C-Glycosylation



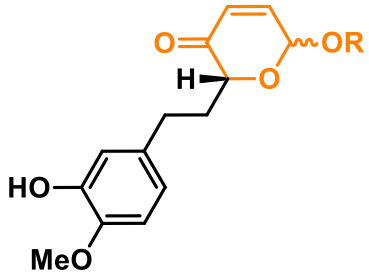
- Asymmetric Total Synthesis (-)-Musellarins A–C and Their Analogues Tong and coworkers (**2015**)



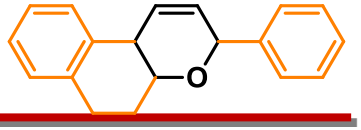
(-)-Muserllarins A



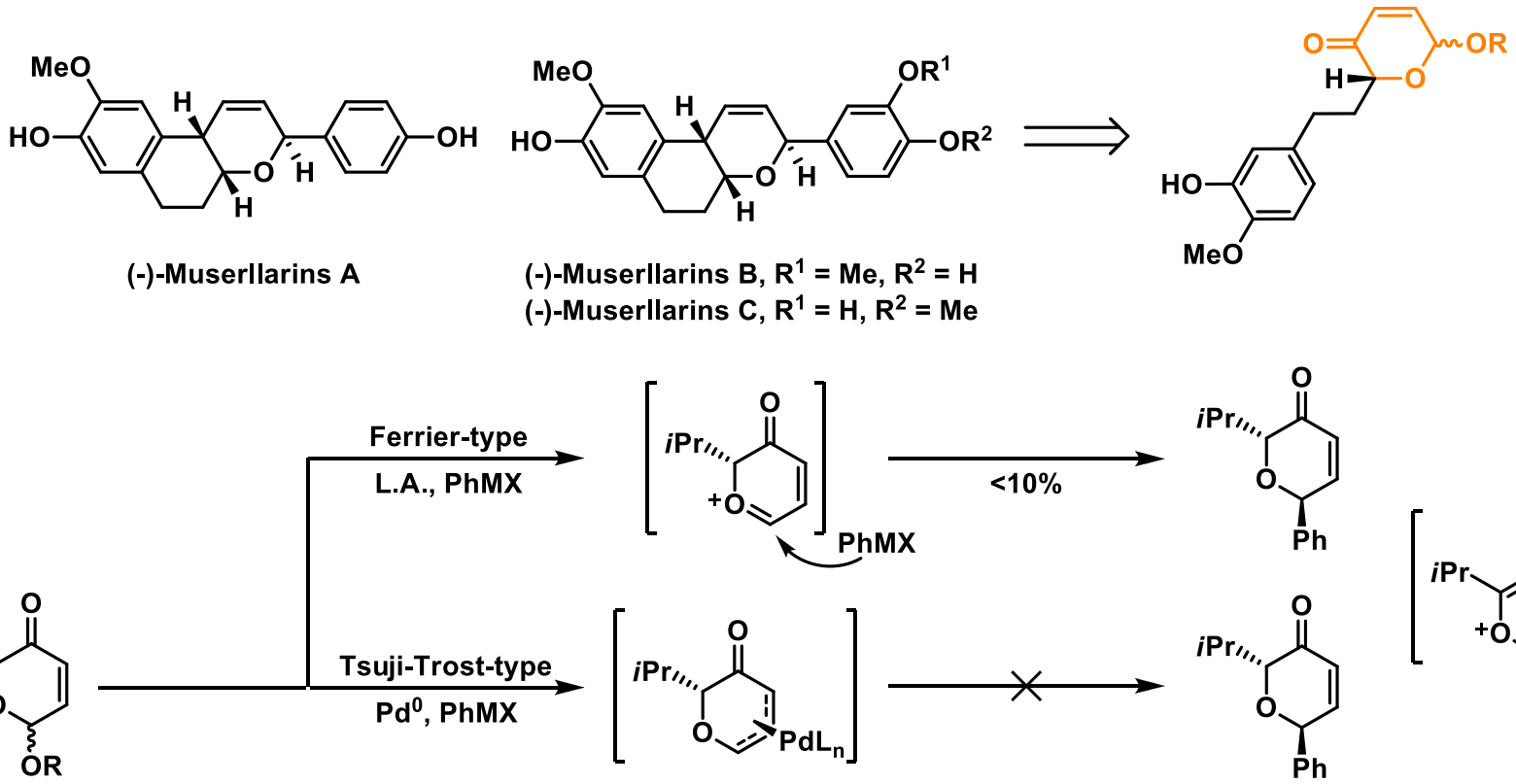
(-)-Muserllarins B, R^1 = Me, R^2 = H
(-)-Muserllarins C, R^1 = H, R^2 = Me



C-Glycosylation

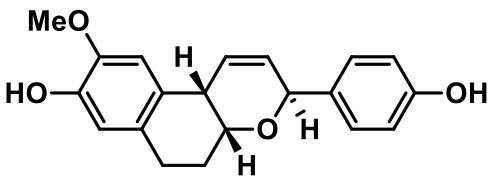


- Asymmetric Total Synthesis (-)-Musellarins A–C and Their Analogues Tong and coworkers (**2015**)

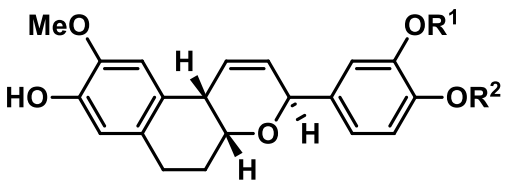


C-Glycosylation

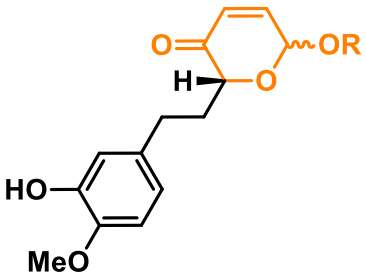
➢ Asymmetric Total Synthesis (-)-Musellarins A–C and Their Analogues Tong and coworkers (**2015**)

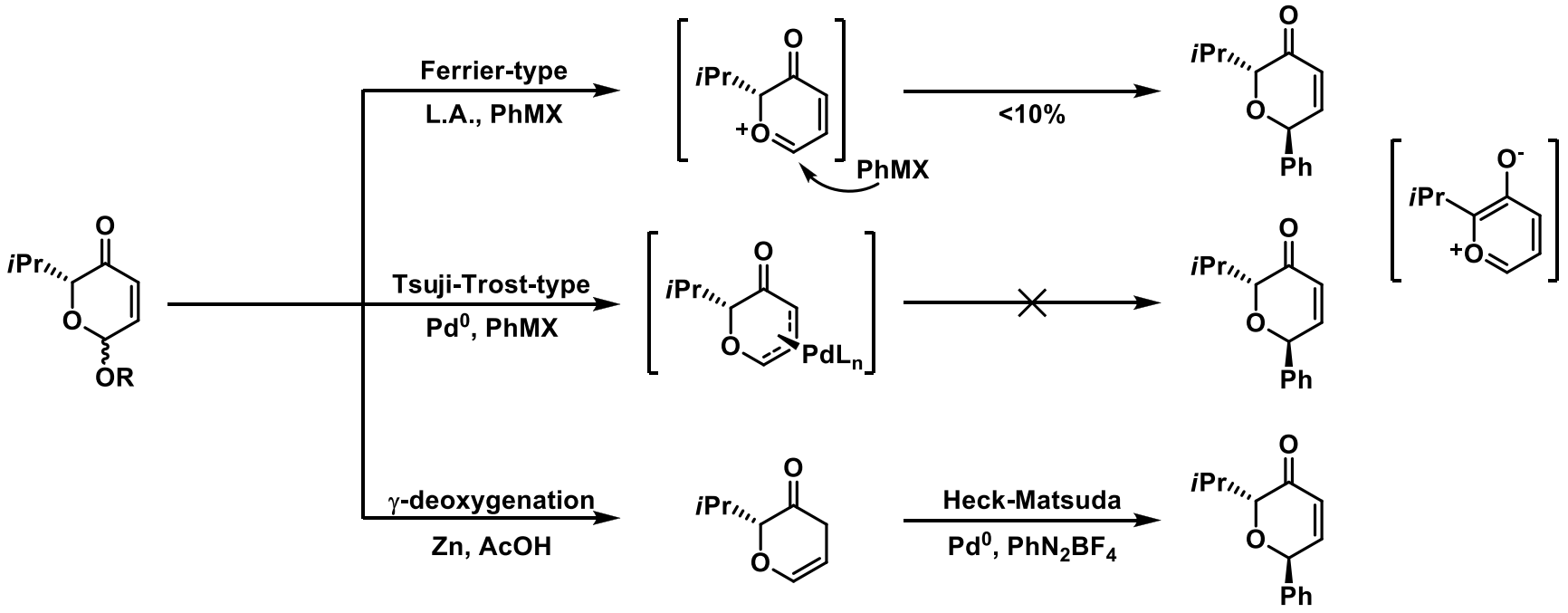


(-)-Muserllarins A



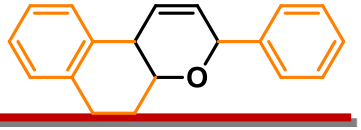
(-)-Muserllarins B, R^1 = Me, R^2 = H
(-)-Muserllarins C, R^1 = H, R^2 = Me



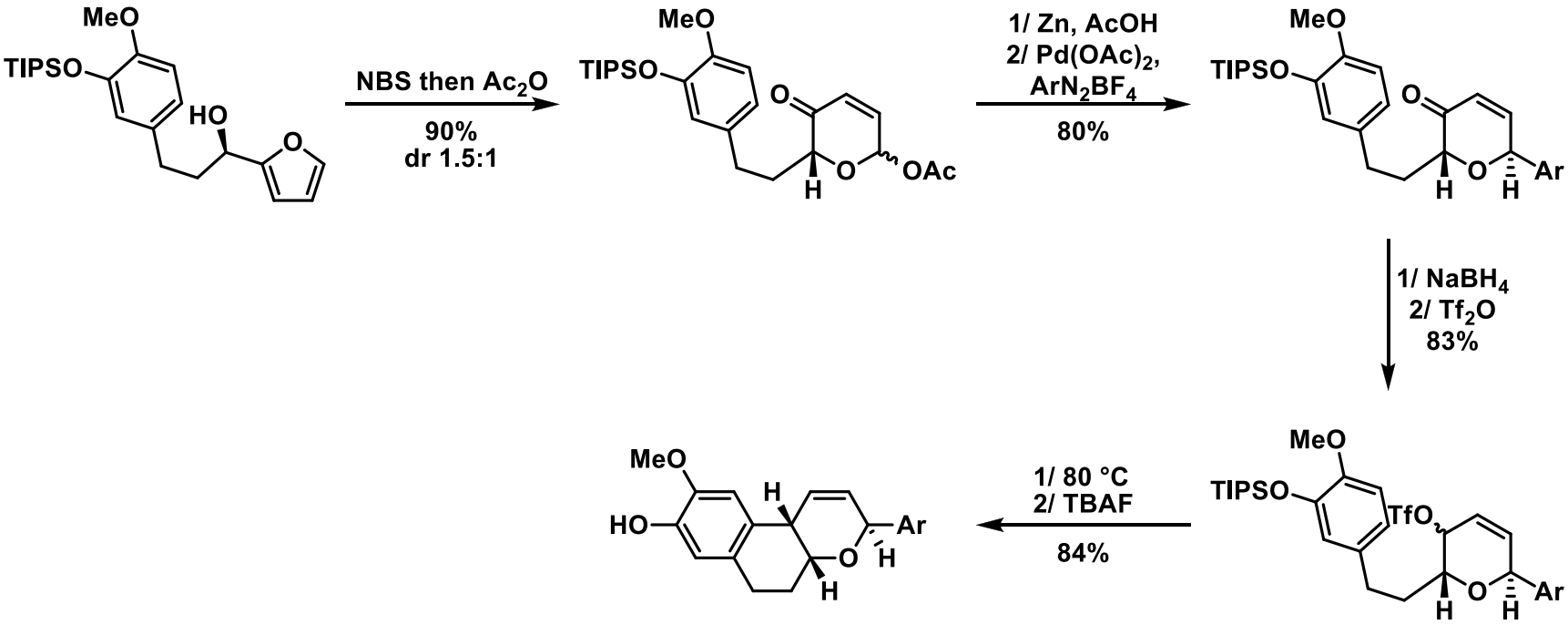


Z. Li, F. C. F. Ip, N. Y. Ip and R. Tong, *Chem. Eur. J.* **2015**, 11152-11157.

C-Glycosylation



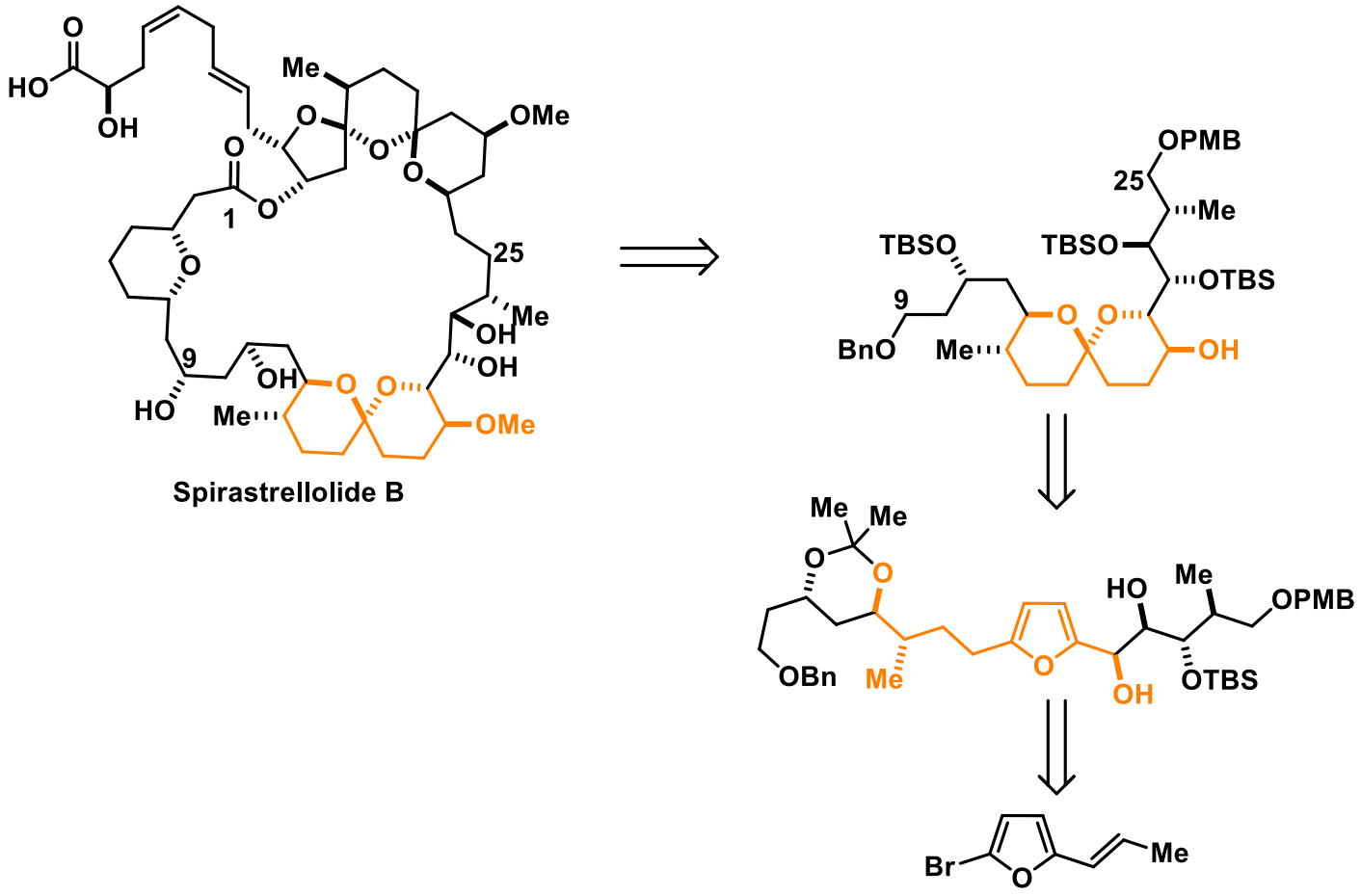
- Asymmetric Total Synthesis (-)-Musellarins A–C and Their Analogues Tong and coworkers (**2015**)



Z. Li, F. C. F. Ip, N. Y. Ip and R. Tong, *Chem. Eur. J.* **2015**, 11152-11157.

Spiroketalization

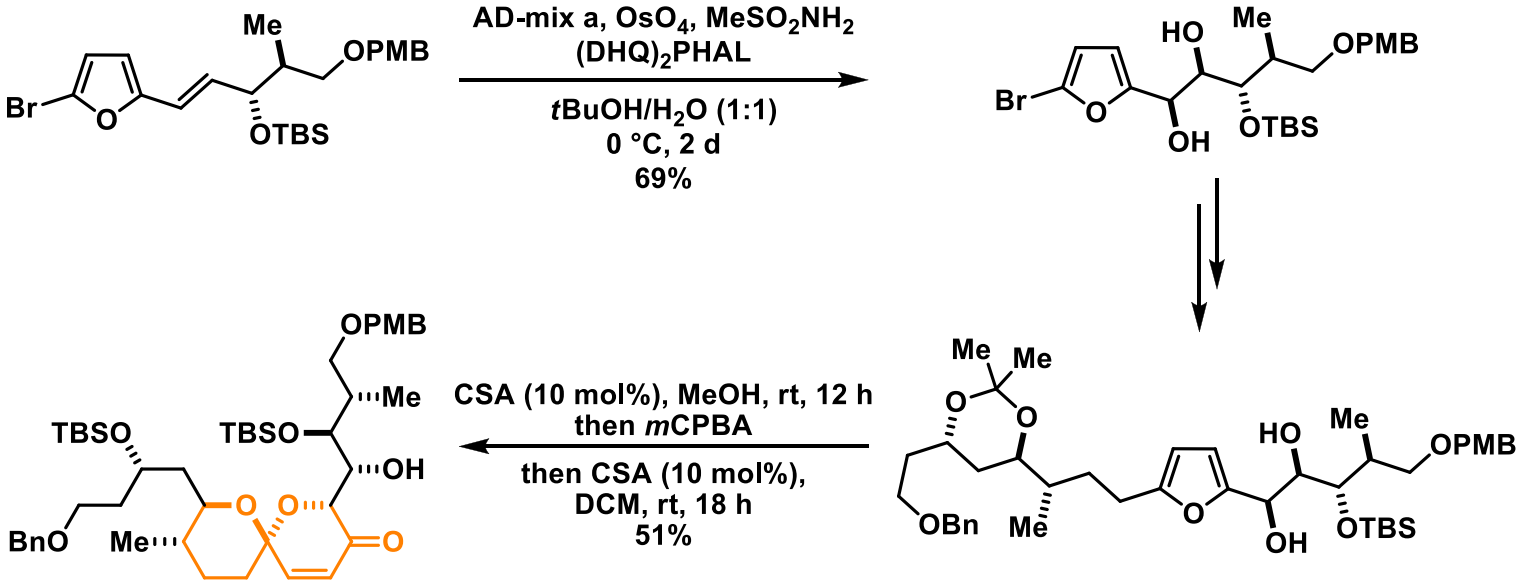
➢ Synthesis of the C9−C25 Subunit of Spirastrellolide B Hanson and coworkers (**2016**)



(a) S. Maitra, M. Bodugam, S. Javed and P. R. Hanson, *Org. Lett.* **2016**, 3094-3097.

Spiroketalization

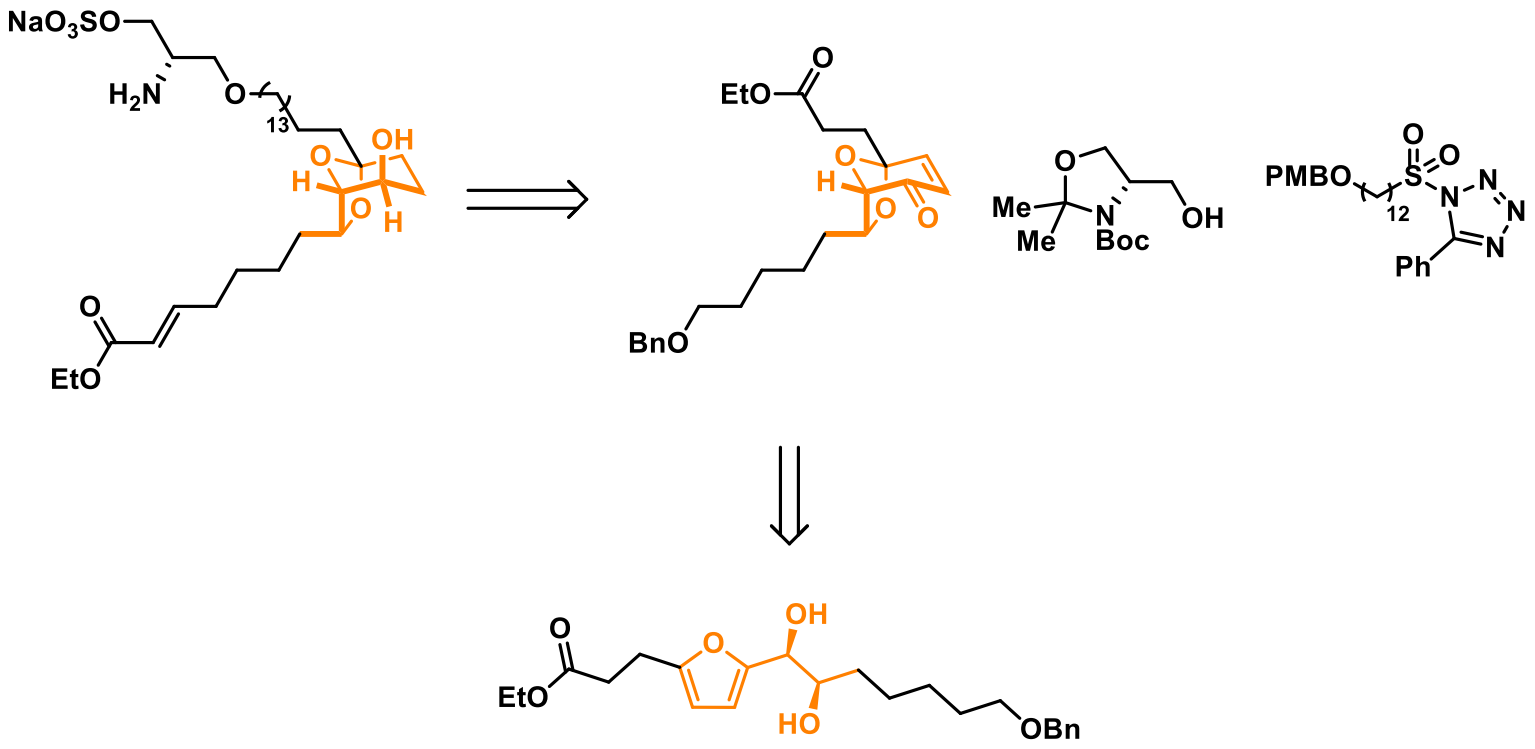
- Synthesis of the C9−C25 Subunit of Spirastrellolide B Hanson and coworkers (**2016**)



(a) S. Maitra, M. Bodugam, S. Javed and P. R. Hanson, *Org. Lett.* **2016**, 3094-3097.

Bicycloketalization

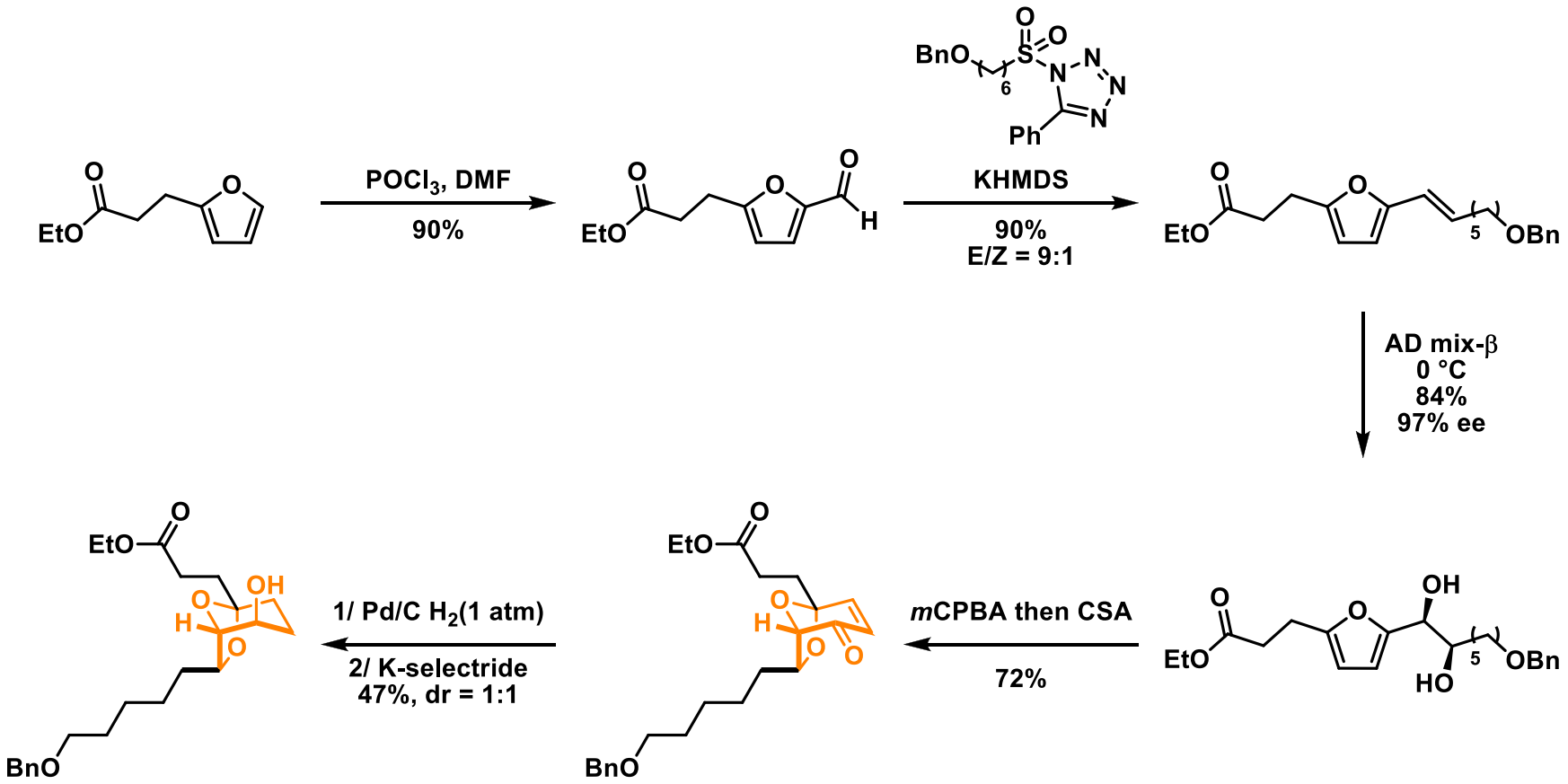
- Asymmetric Total Synthesis of (+)-Didemniserinolipid B Tong and coworkers (**2014**)



J. Ren and R. Tong, *J. Org. Chem.* **2014**, 6987-6995.

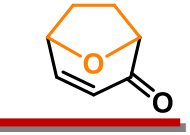
Bicycloketalization

- Asymmetric Total Synthesis of (+)-Didemniserinolipid B Tong and coworkers (**2014**)

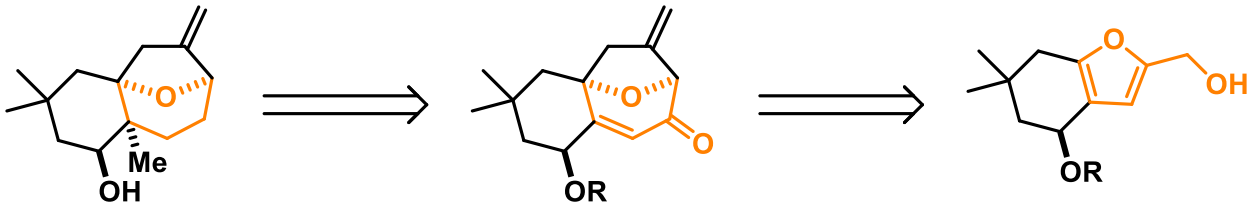


J. Ren and R. Tong, *J. Org. Chem.* **2014**, 6987-6995.

[5+2]-cycloaddition



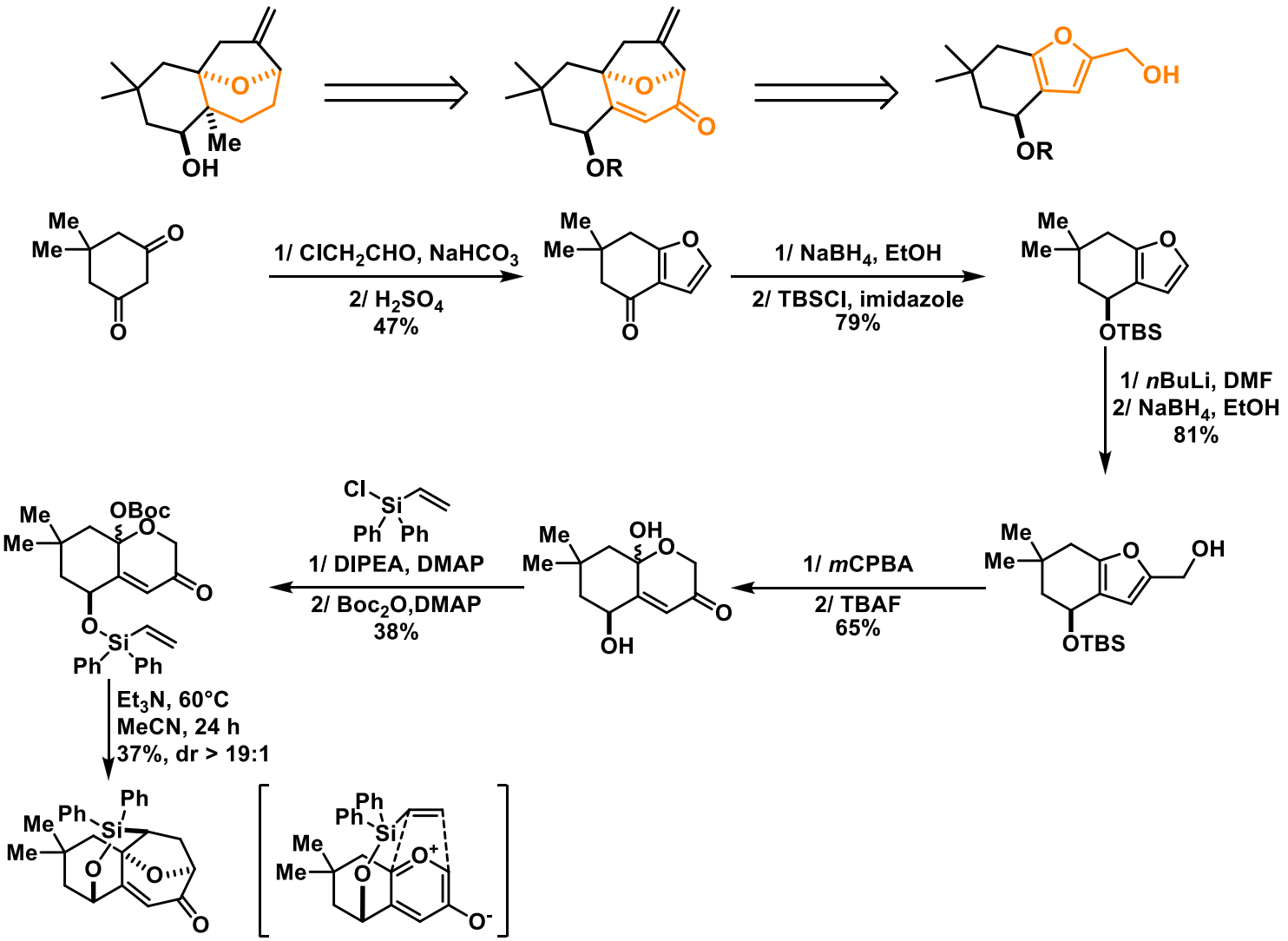
- Synthesis of Toxicodenane A core Mitchell and coworkers (**2020**)



J. P. Grabowski, G. M. Ferrence and T. A. Mitchell, *Tetrahedron Lett.* **2020**, 152324.

[5+2]-cycloaddition

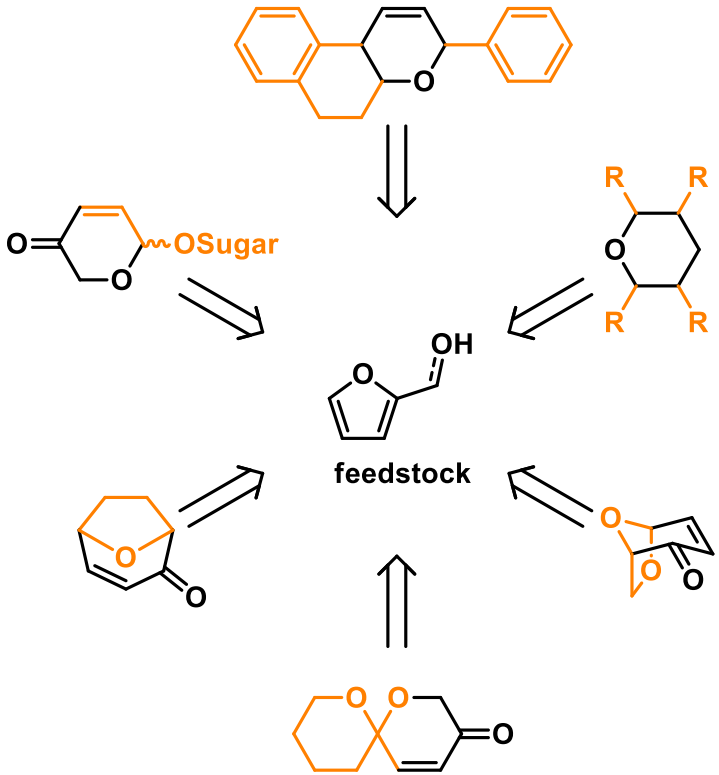
➢ Synthesis of Toxicodenane A core Mitchell and coworkers (**2020**)



J. P. Grabowski, G. M. Ferrence and T. A. Mitchell, *Tetrahedron Lett.* **2020**, 152324.

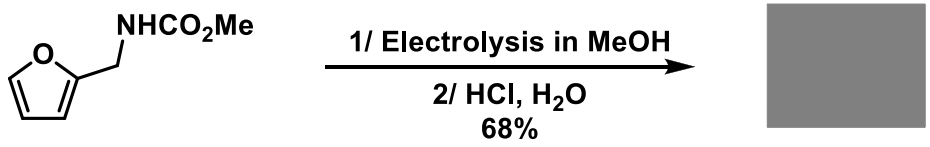
Conclusion

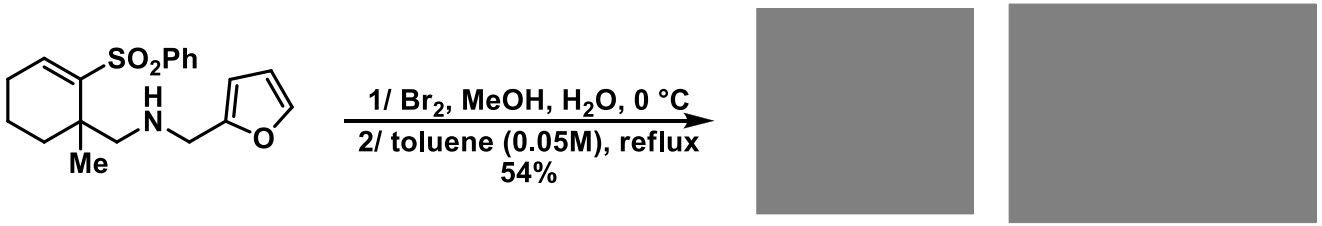
Clauson-Kaas - Cavill - Achmatowicz



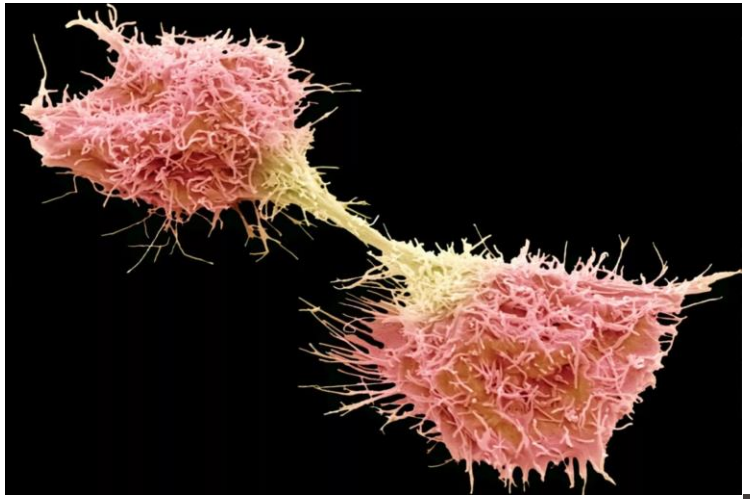
Thank you for your attention!

Questions





(a) N. Clauson-Kaas, N. Elming and Z. Tyle, *Acta Chem. Scand.* **1955**, 1-8. (b) K. M. Peese and D. Y. Gin, *Chem. Eur. J.* **2008**, 1654-1665.



Steve Gschmeissner/Science Photo Library/Getty Images

Heterocycles in Cancer Treatment Drugs

Synthesis of Selected Examples

Johannes Klett

Cancer: Challenges and Progress

- Large group of diseases: rapid creation of abnormal cells
- 10 Mio. deaths/year (2020)
- Prevention

by MACROVECTOR freepik.com

pinterest.ch/pin/346566133832604546/

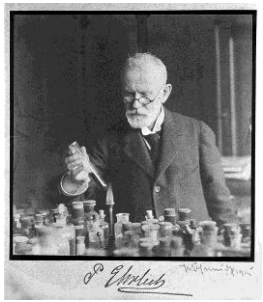
by JCOMP freepik.com

by WIRESTOCK freepik.com

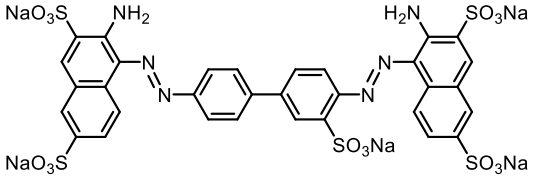
- Developments in Cancer Treatment
  - Surgery, Radiotheraphy, Chemotherapy, Immunotheraphy, Genetheraphy, Nanomedicine

- H. Sung, J. Ferlay, R. L. Siegel, M. Laversanne, I. Soerjomataram, A. Jemal, F. Bray; *CA Cancer J Clin*. **2020**, 1 – 41.
- WHO (2018). Global health estimates 2016: deaths by cause, age, sex, by country and by region, 2000–2016. Geneva, Switzerland: World Health Organization. Available from: https://www.who.int/healthinfo/global_burden_disease/en/ (07.04.2021)
- WHO (2017). Global hepatitis report 2017. Geneva, Switzerland: World Health Organization. Available from: https://www.who.int/hepatitis/publications/global-hepatitis-report2017/en/ (07.04.2021)
- *Curr. Clin. Pharmacol.* **2018**, *13*, 85 – 99.
- *Cancers* **2011**, *3*, 3279 – 3330.

Chemoteraphy

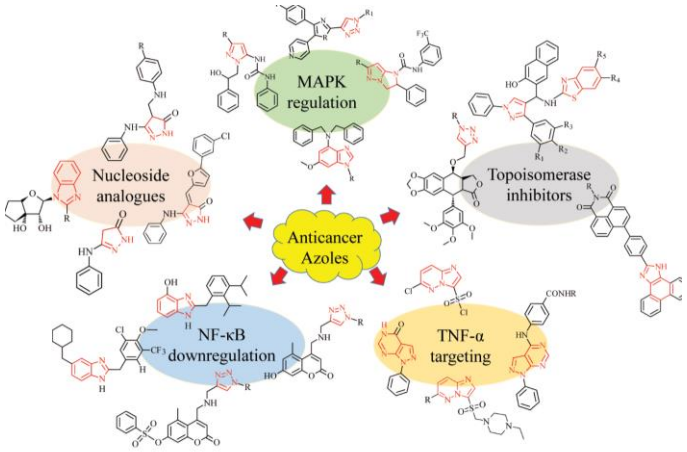


https://wellcomecollection.org/works/y2d2nar6, CC BY-4.0

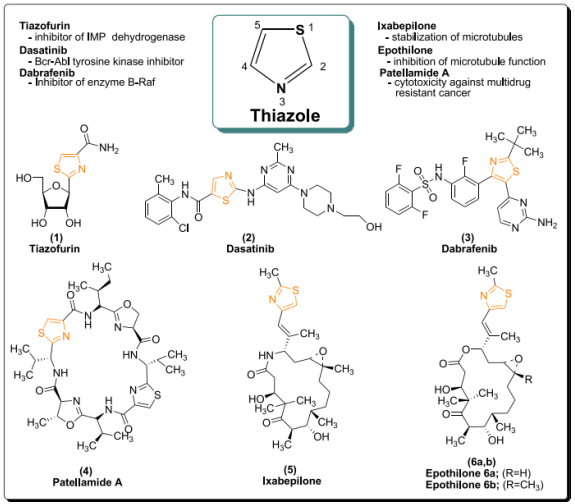


Trypan red

- Paul Ehrlich (1854 – 1915)
- Heterocylces in anticancer drugs



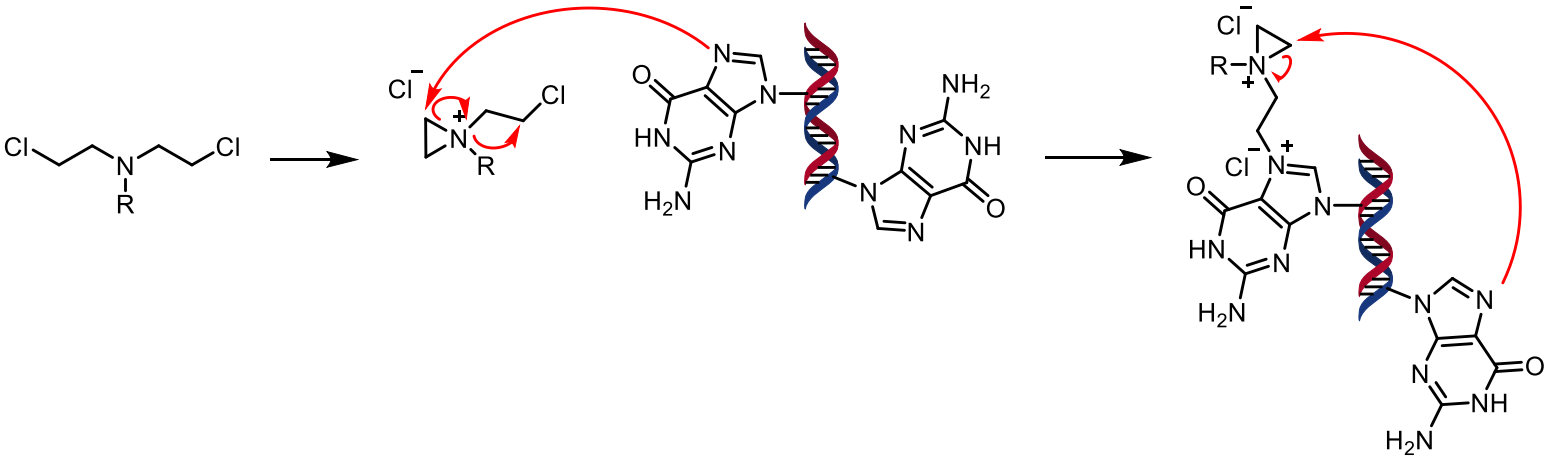
'Azole' based advanced anticancer chemotherapeutics.



- *Berliner Klinische Wochenschrift*, **1907**, *44*, 233–236.
- *Eur. J. Med. Chem.* **2020**, *188*, 112016.
- *Curr. Org. Chem.* **2021**, *25*, 654 – 668.

Chemotherapy

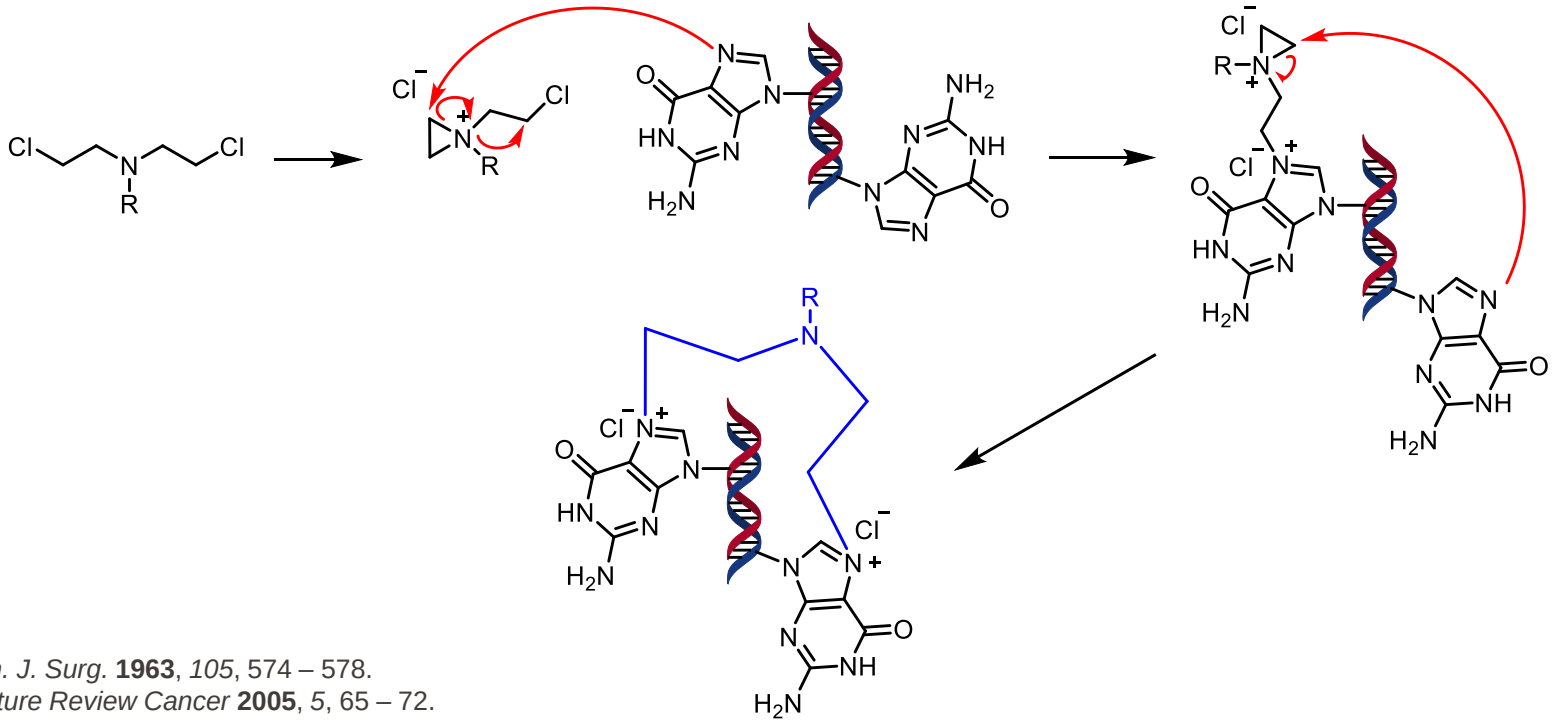
- Nitrogen Mustard as 1st chemotherapeutic agent against cancer



- *Am. J. Surg.* **1963**, *105*, 574 – 578.
- *Nature Review Cancer* **2005**, *5*, 65 – 72.
- *Cancer Res.*, **2008**, *68*, 8643 – 8653.
- *J. Am. Chem. Soc.* **1990**, *112*, 2459 – 2460.
- *J. Am. Chem. Soc.* **1993**, *115*, 2551 – 2557.

Chemotherapy – Alkylating Agents

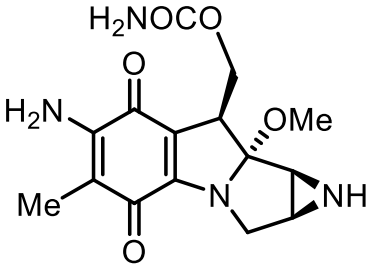
- Nitrogen Mustard as 1st chemotherapeutic agent against cancer



Interstrand Cross Linking

- *Am. J. Surg.* **1963**, *105*, 574 – 578.
- *Nature Review Cancer* **2005**, *5*, 65 – 72.
- *Cancer Res.*, **2008**, *68*, 8643 – 8653.
- *J. Am. Chem. Soc.* **1990**, *112*, 2459 – 2460.
- *J. Am. Chem. Soc.* **1993**, *115*, 2551 – 2557.

Mitomycin C



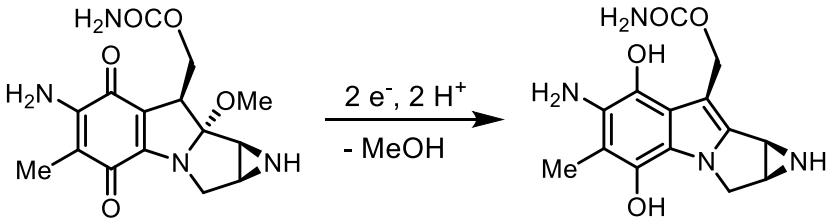
Mitomycin C

http://www.hpfiedler-group.de/metabolites.php?metabolite_id=26 (27.04.2021)

- Produced by *Streptomyces Lavendulae*
- Isolated in 1958, only 2 total synthesis (1979 KISHI and 1987 FUKUYAMA)
- Very effective against bladder and non-small-cell lung carcinoma

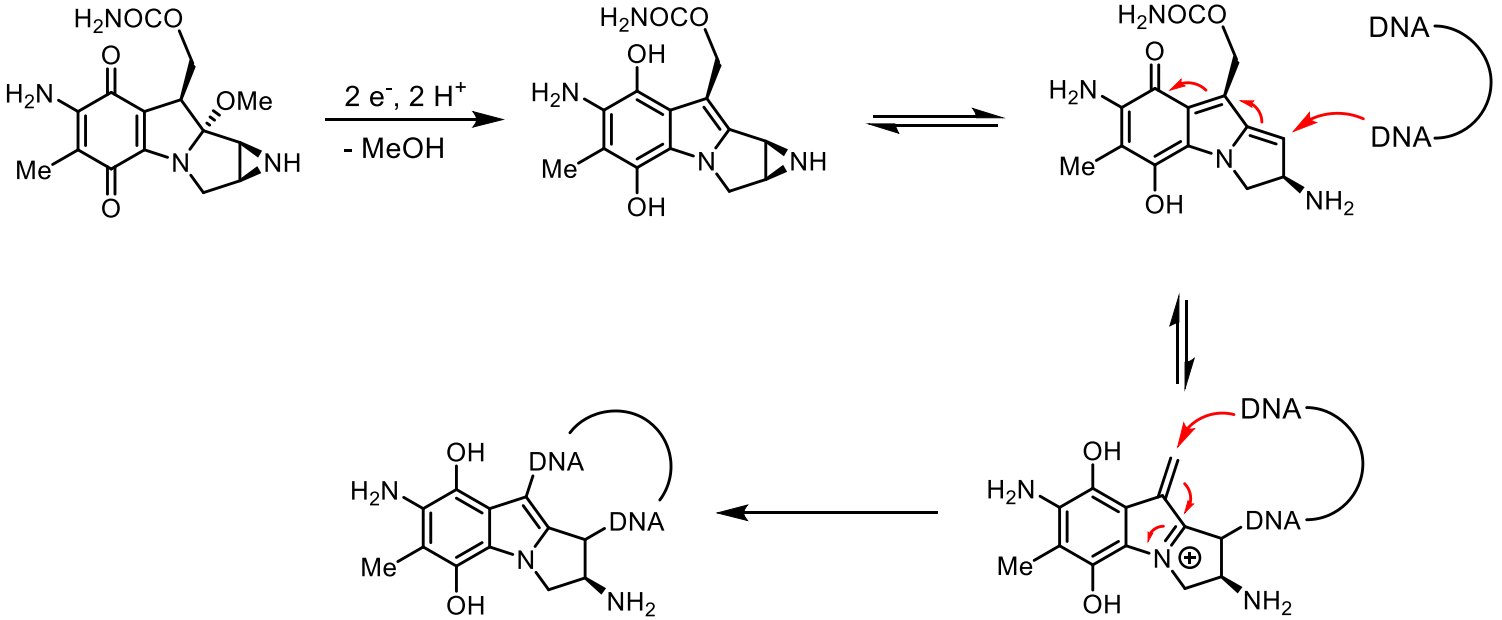
- *Antibiot. Chemother.* **1958**, *8*, 228 – 240.
- *J. Nat. Prod.* **1979**, *42*, 549 – 568.
- *J. Am. Chem. Soc.* **1987**, *109*, 7881 – 7882.
- *Cancer Treat. Rev*., **2001**, *27*, 35 – 50.
- *Beilstein J. Org. Chem.* **2009**, *5,* No. 33

Mitomycin C – Mechanism of Action



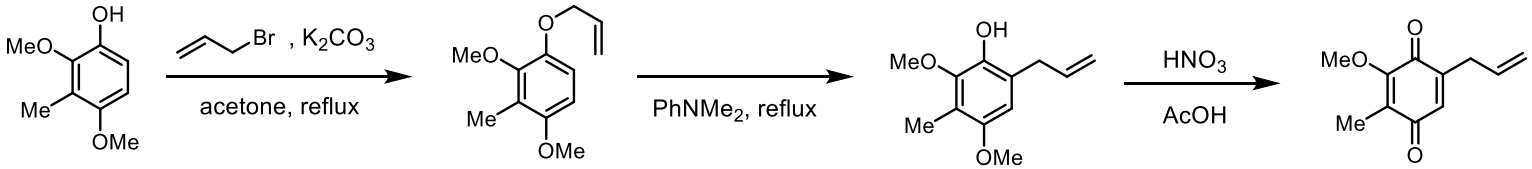
- *Science*, **1964**, *145*, 55 – 58.
- *Beilstein J. Org. Chem.* **2009**, *5,* No. 33

Mitomycin C – Mechanism of Action



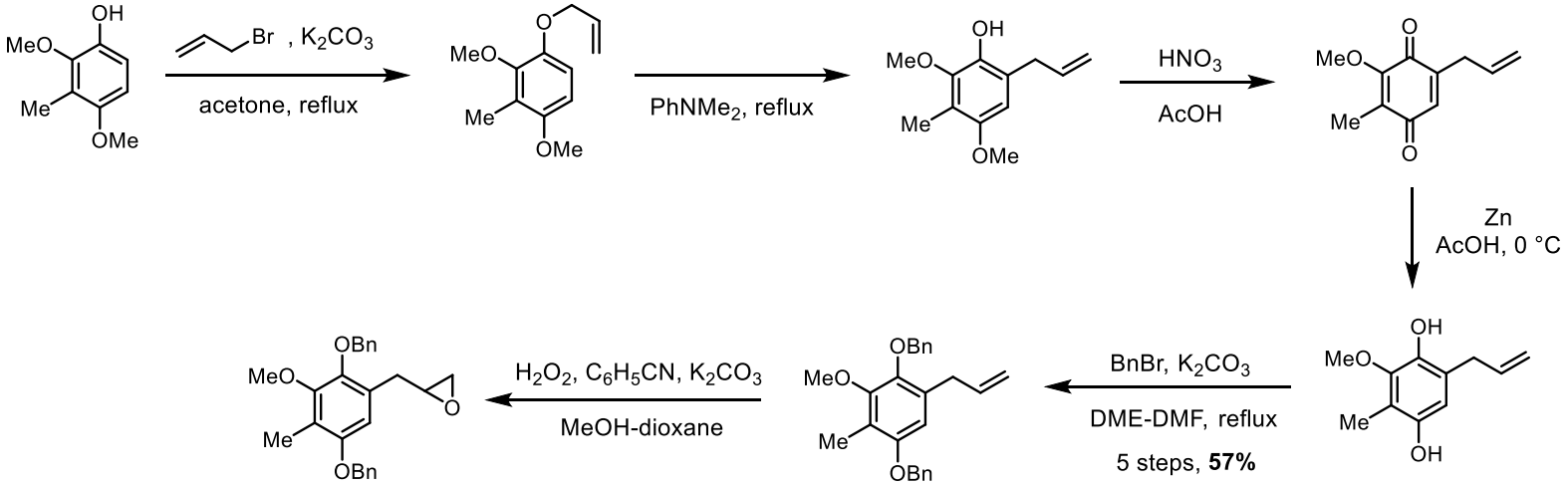
- *Science*, **1964**, *145*, 55 – 58.
- *Beilstein J. Org. Chem.* **2009**, *5*, No. 33

Mitomycin C - Synthesis



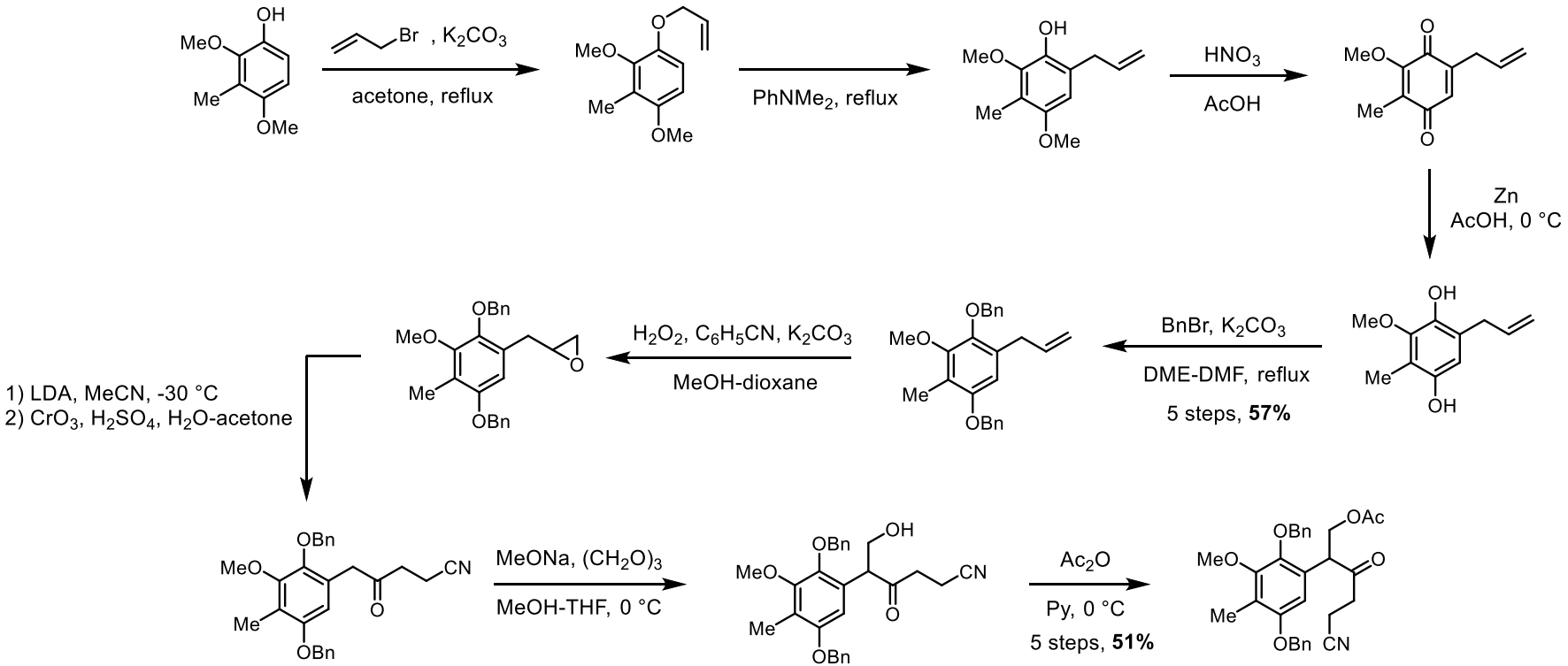
- *J. Am. Chem. Soc.* **1977**, *99*, 4835 – 4836.
- *J. Am. Chem. Soc.* **1977**, *99*, 8115 – 8116.
- *J. Nat. Prod.* **1979**, *42*, 549 – 568.
- *Beilstein J. Org. Chem.* **2009**, *5,* No. 33

Mitomycin C - Synthesis



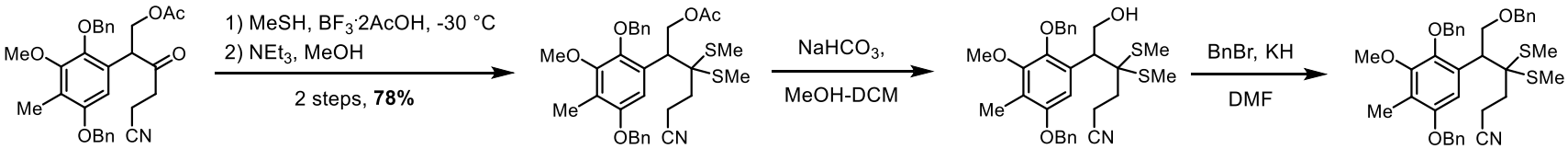
- *J. Am. Chem. Soc.* **1977**, *99*, 4835 – 4836.
- *J. Am. Chem. Soc.* **1977**, *99*, 8115 – 8116.
- *J. Nat. Prod.* **1979**, *42*, 549 – 568.
- *Beilstein J. Org. Chem.* **2009**, *5,* No. 33

Mitomycin C - Synthesis



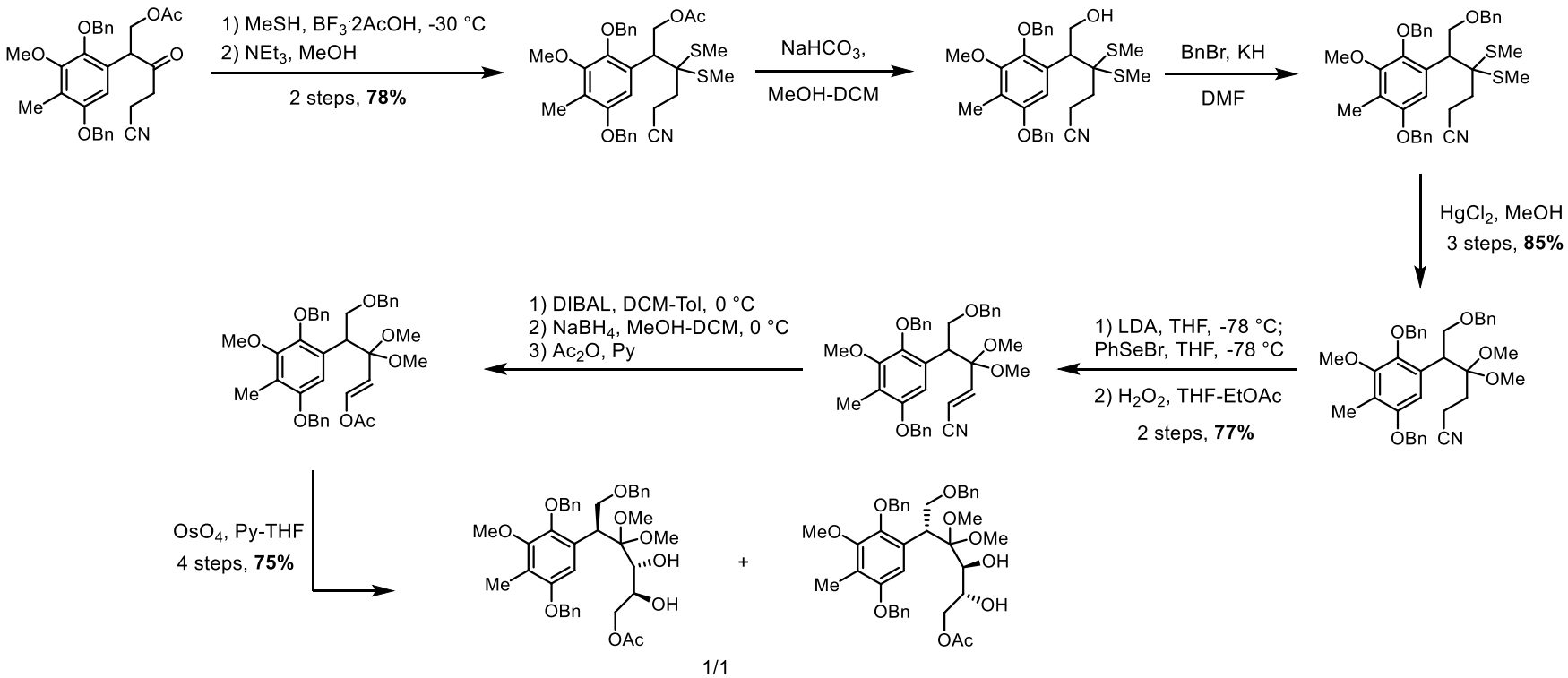
- *J. Am. Chem. Soc.* **1977**, *99*, 4835 – 4836.
- *J. Am. Chem. Soc.* **1977**, *99*, 8115 – 8116.
- *J. Nat. Prod.* **1979**, *42*, 549 – 568.
- *Beilstein J. Org. Chem.* **2009**, *5,* No. 33

Mitomycin C - Synthesis



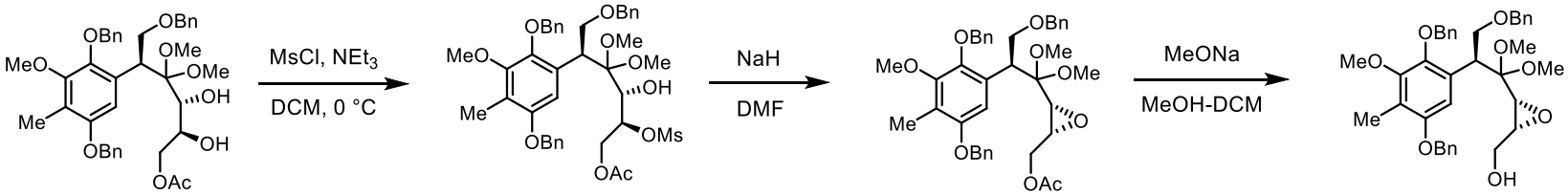
- *J. Am. Chem. Soc.* **1977**, *99*, 4835 – 4836.
- *J. Am. Chem. Soc.* **1977**, *99*, 8115 – 8116.
- *J. Nat. Prod.* **1979**, *42*, 549 – 568.
- *Beilstein J. Org. Chem.* **2009**, *5,* No. 33

Mitomycin C - Synthesis



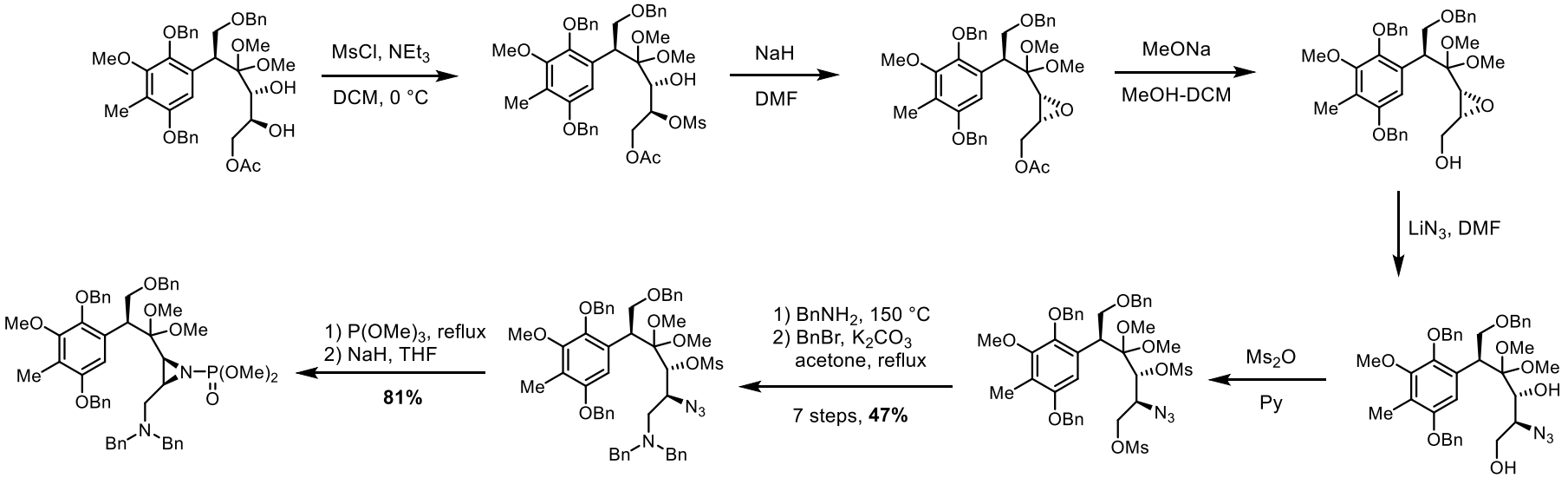
- *J. Am. Chem. Soc.* **1977**, *99*, 4835 – 4836.
- *J. Am. Chem. Soc.* **1977**, *99*, 8115 – 8116.
- *J. Nat. Prod.* **1979**, *42*, 549 – 568.
- *Beilstein J. Org. Chem.* **2009**, *5,* No. 33

Mitomycin C - Synthesis



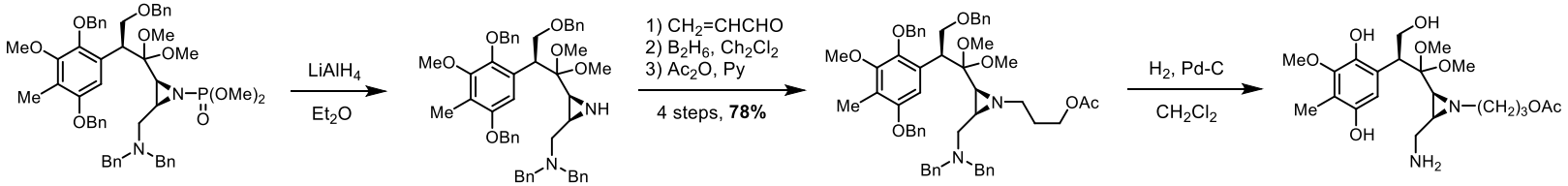
- *J. Am. Chem. Soc.* **1977**, *99*, 4835 – 4836.
- *J. Am. Chem. Soc.* **1977**, *99*, 8115 – 8116.
- *J. Nat. Prod.* **1979**, *42*, 549 – 568.
- *Beilstein J. Org. Chem.* **2009**, *5,* No. 33

Mitomycin C - Synthesis



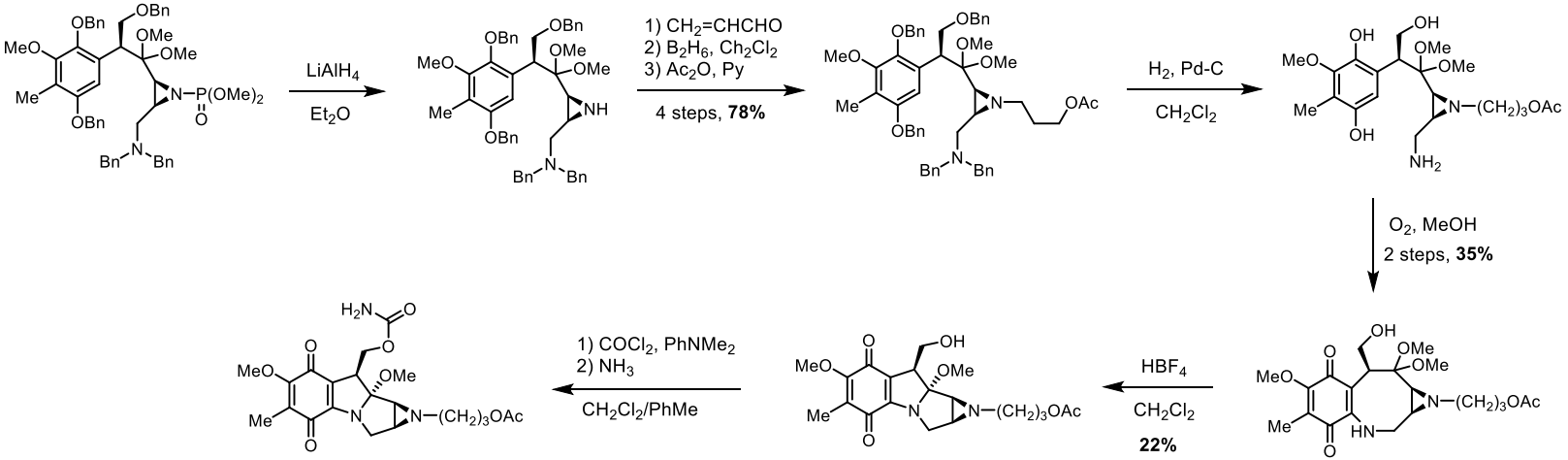
- *J. Am. Chem. Soc.* **1977**, *99*, 4835 – 4836.
- *J. Am. Chem. Soc.* **1977**, *99*, 8115 – 8116.
- *J. Nat. Prod.* **1979**, *42*, 549 – 568.
- *Beilstein J. Org. Chem.* **2009**, *5,* No. 33

Mitomycin C - Synthesis



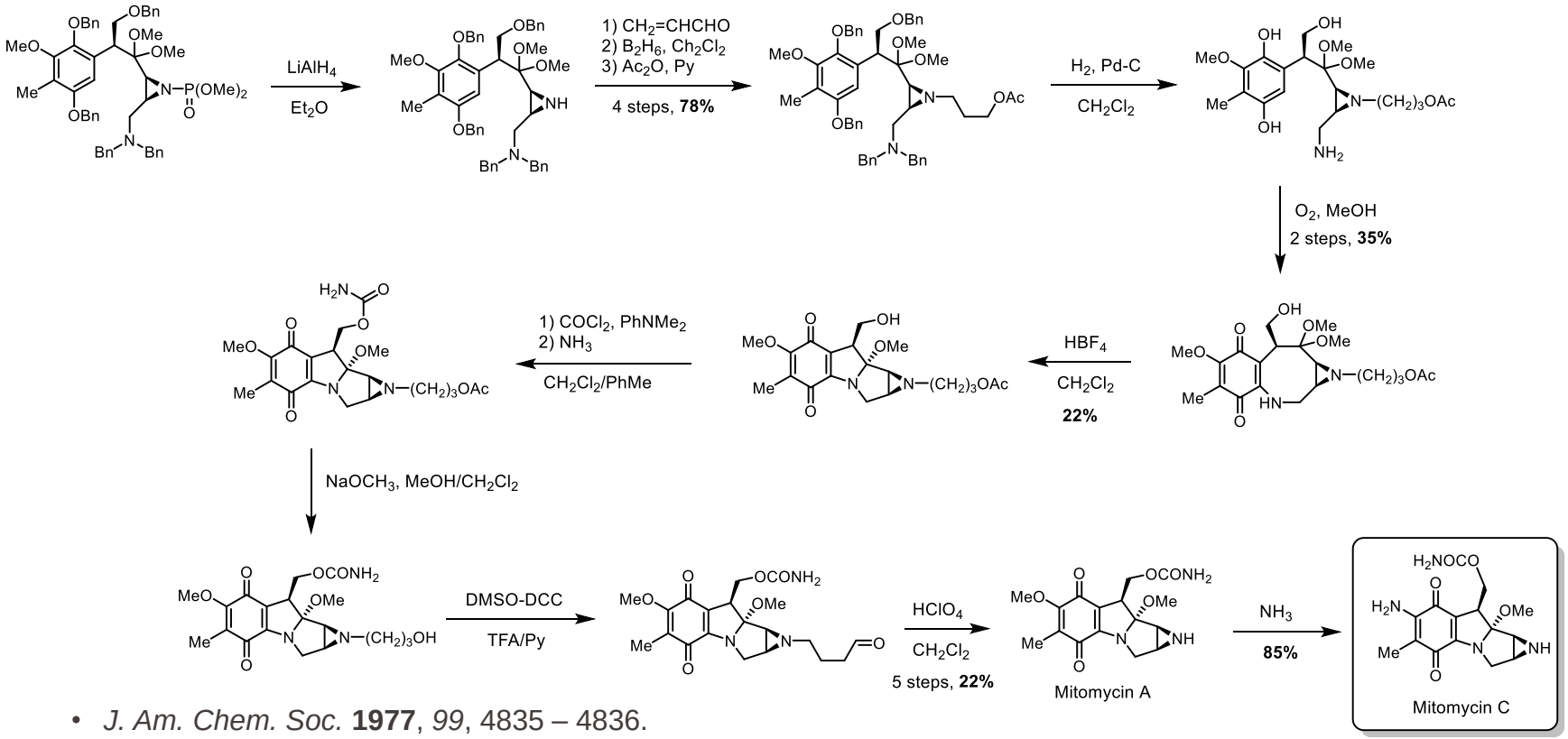
- *J. Am. Chem. Soc.* **1977**, *99*, 4835 – 4836.
- *J. Am. Chem. Soc.* **1977**, *99*, 8115 – 8116.
- *J. Nat. Prod.* **1979**, *42*, 549 – 568.
- *Beilstein J. Org. Chem.* **2009**, *5,* No. 33

Mitomycin C - Synthesis



- *J. Am. Chem. Soc.* **1977**, *99*, 4835 – 4836.
- *J. Am. Chem. Soc.* **1977**, *99*, 8115 – 8116.
- *J. Nat. Prod.* **1979**, *42*, 549 – 568.
- *Beilstein J. Org. Chem.* **2009**, *5,* No. 33

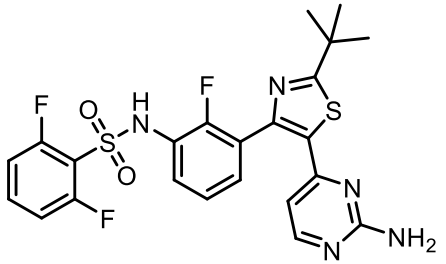
Mitomycin C - Synthesis



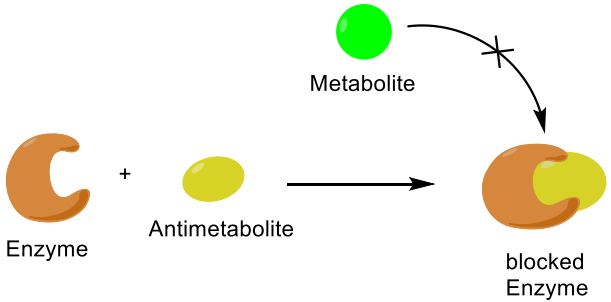
- *J. Am. Chem. Soc.* **1977**, *99*, 4835 – 4836.
- *J. Am. Chem. Soc.* **1977**, *99*, 8115 – 8116.
- *J. Nat. Prod.* **1979**, *42*, 549 – 568.
- *Beilstein J. Org. Chem.* **2009**, *5,* No. 33

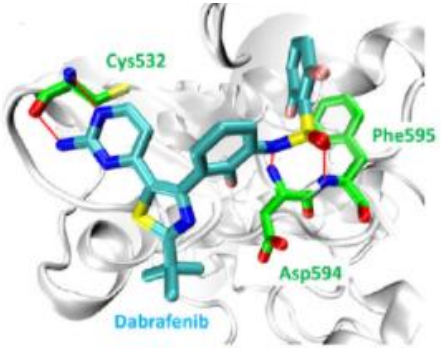
Dabrafenib

- Synthesized in 2013
- Inhibits enzyme BRaf^{V600E}



Dabrafenib

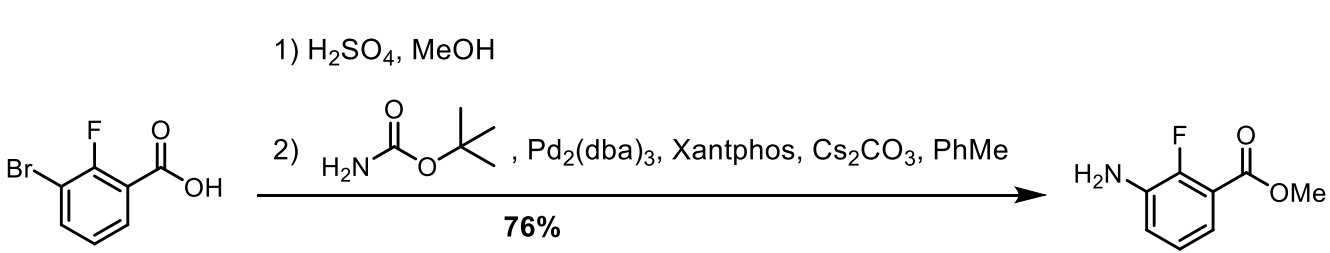


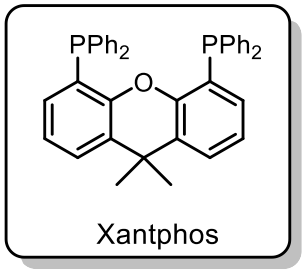


- Treatment of melanoma and lung cancer

- *ACS Med. Chem. Lett.* **2013**, *4*, 358 – 362.
- *Clin. Pharmacol. Ther.* **2014**, *95*, 24 – 31.
- *Med. Res. Rev.* **2017**, *37*, 98 – 148.
- *Chem. Rev.* **2009**, *109*, 2880 – 2893.
- *PNAS*, **2002**, *99*, 13481 – 13486.

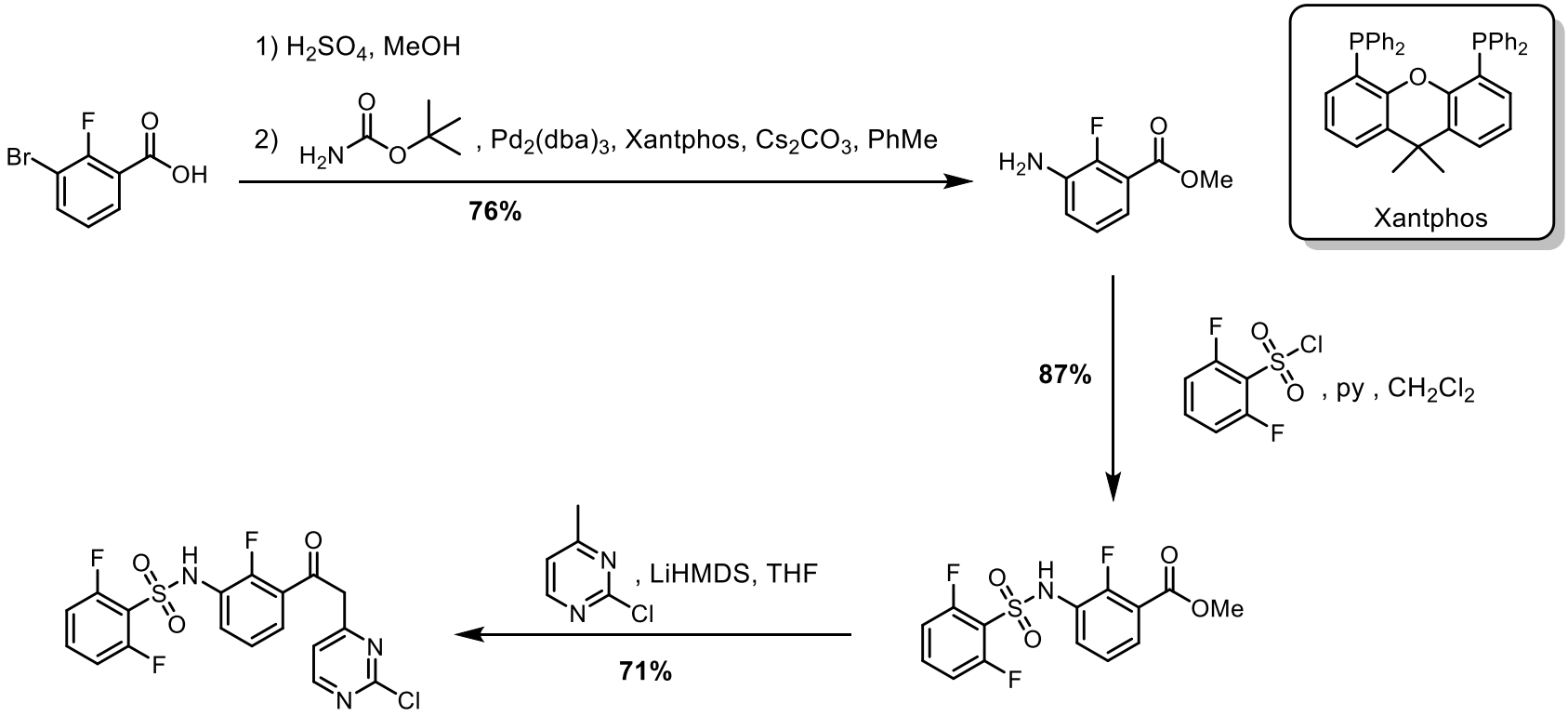
Dabrafenib – Synthesis





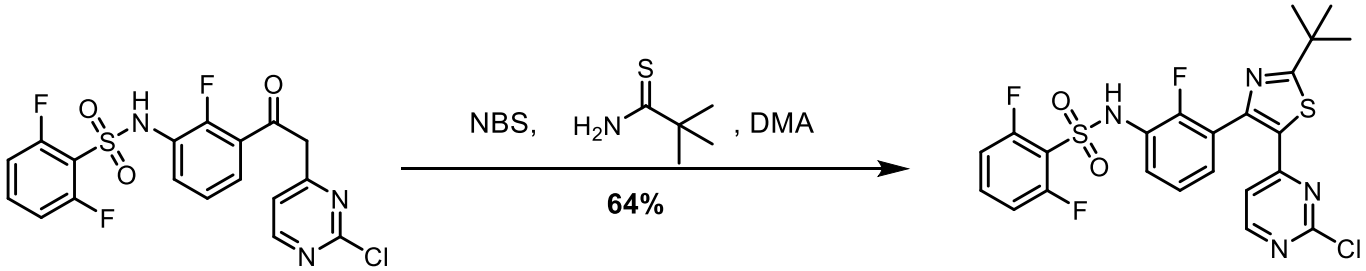
- *ACS Med. Chem. Lett.* **2013**, *4*, 358 – 362.
- *Med. Res. Rev.* **2017**, *37*, 98 – 148.

Dabrafenib – Synthesis



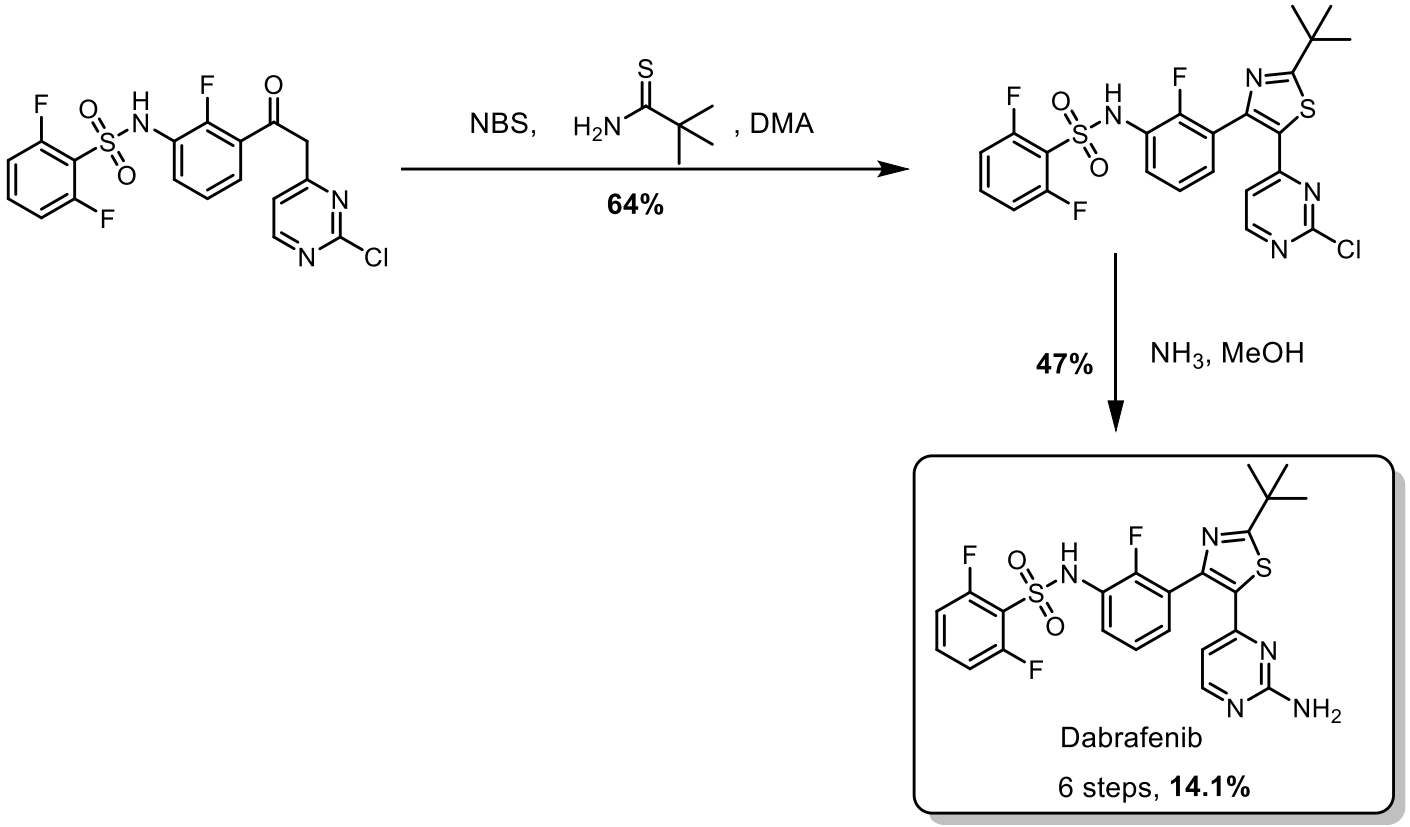
- *ACS Med. Chem. Lett.* **2013**, *4*, 358 – 362.
- *Med. Res. Rev.* **2017**, *37*, 98 – 148.

Dabrafenib – Synthesis



- *ACS Med. Chem. Lett.* **2013**, *4*, 358 – 362.
- *Med. Res. Rev.* **2017**, *37*, 98 – 148.

Dabrafenib – Synthesis

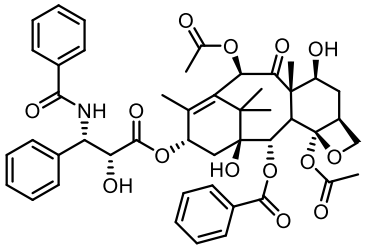


- *ACS Med. Chem. Lett.* **2013**, *4*, 358 – 362.
- *Med. Res. Rev.* **2017**, *37*, 98 – 148.

Paclitaxel

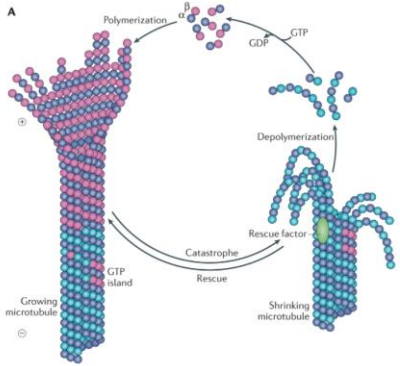
- Isolated in 1971 from the pacific yew
- Anti-Microtubule Agent
- 1st total synthesis in 1994

  (HOLTON group and NICOLAOU group)
- Used against breast, lung, prostate and bladder cancer



Paclitaxel (Taxol®)

brewbrooks-www.flickr.com/photos/brewbooks/263660629



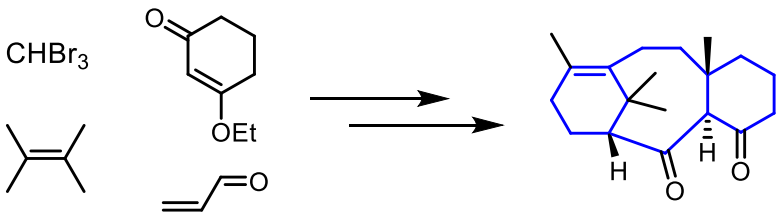
Microtubule

Pacific yew by JASON HOLLINGER, CC BY 2.0

- *J. Am. Chem. Soc.* **1994**, *116*, 1597 – 1598.
- *J. Am. Chem. Soc.* **1994**, *116*, 1599 – 1600.
- *Nature,* **1994**, *367*, 630 – 634.
- *J. Am. Chem. Soc.* **1971**, *93*, 2325 – 2327.
- *Pharmac. Ther.* **1991**, *52*, 35 – 84.
- *Nat. Rev. Mol. Cell Biol.* **2015**, *16*, 711 – 726.
- *Nat. Rev. Mol. Cell Biol.* **2018**, *19*, 451 – 463.
- *Pharm. Unserer Zeit* **2005**, *34*, 98 – 103.

Paclitaxel – Two Phase Synthesis

1st phase:
Construction of
taxane skeleton

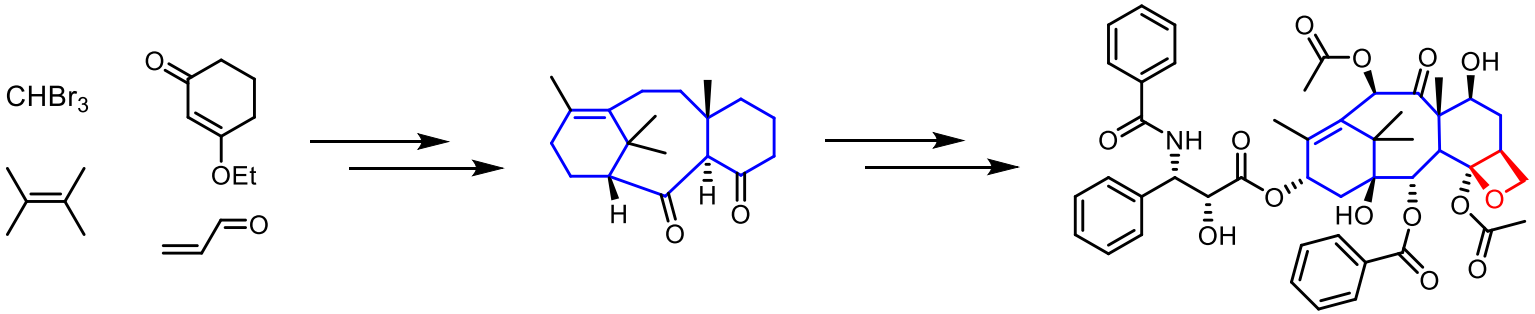


- *Nat. Chem.* **2012**, *4*, 21 – 25.
- *Org. Process Res. Dev.* **2015**, *19*, 284 – 289.
- *J. Am. Chem. Soc.* **2020**, *142*, 10526 – 10533.

Paclitaxel – Two Phase Synthesis

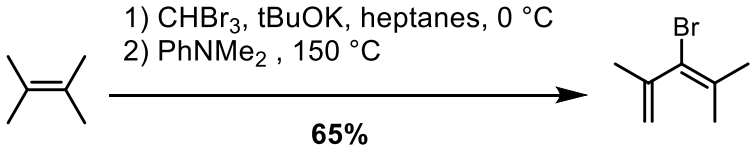
1st phase:
Construction of
taxane skeleton

2nd phase:
Oxidation
manipulations



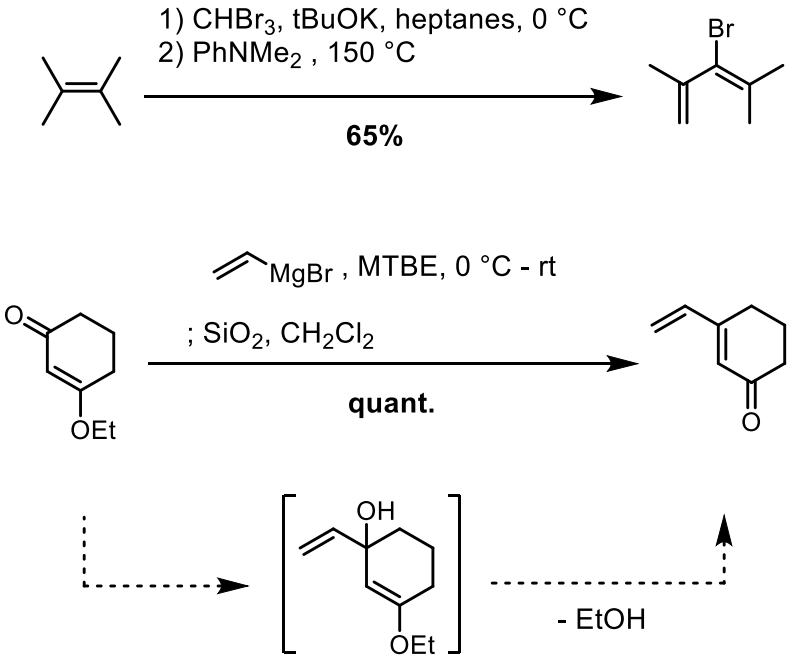
- *Nat. Chem.* **2012**, *4*, 21 – 25.
- *Org. Process Res. Dev.* **2015**, *19*, 284 – 289.
- *J. Am. Chem. Soc.* **2020**, *142*, 10526 – 10533.

Paclitaxel – Two Phase Synthesis – 1st Phase



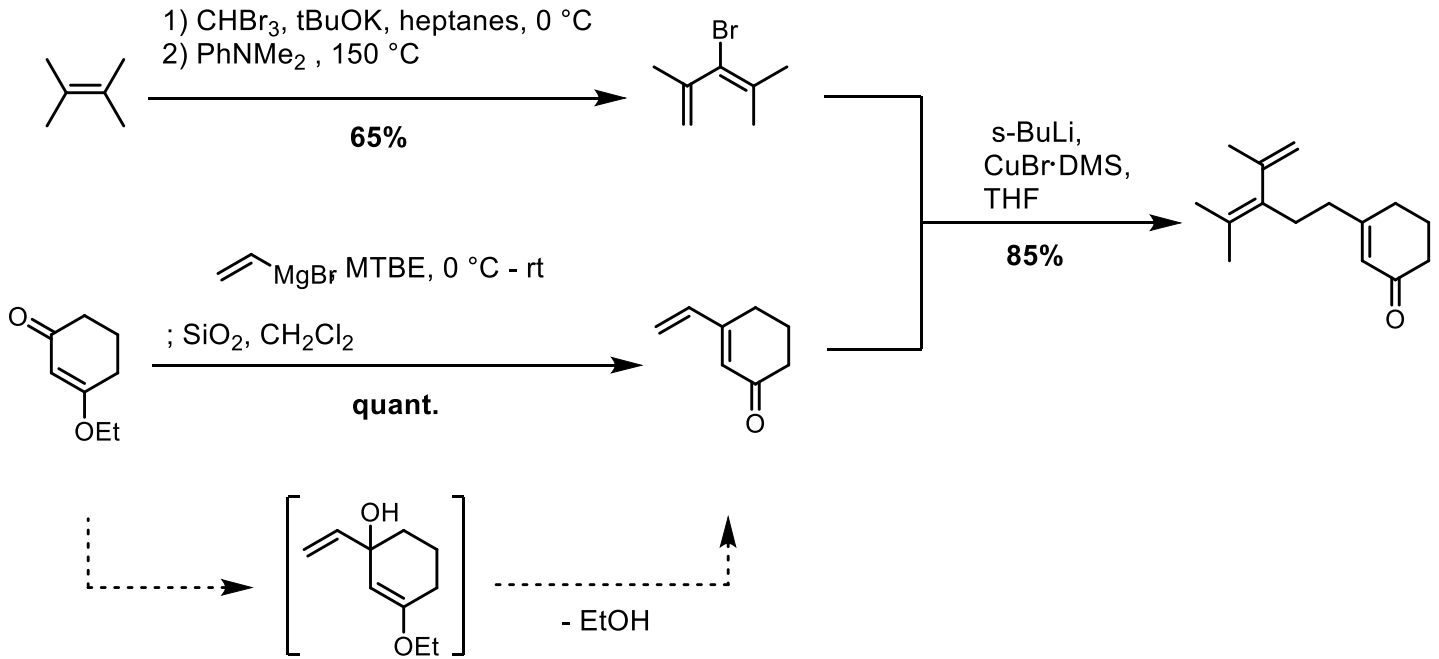
- *Nat. Chem.* **2012**, *4*, 21 – 25.
- *Org. Process Res. Dev.* **2015**, *19*, 284 – 289.
- *J. Am. Chem. Soc.* **2020**, *142*, 10526 – 10533.

Paclitaxel – Two Phase Synthesis – 1st Phase



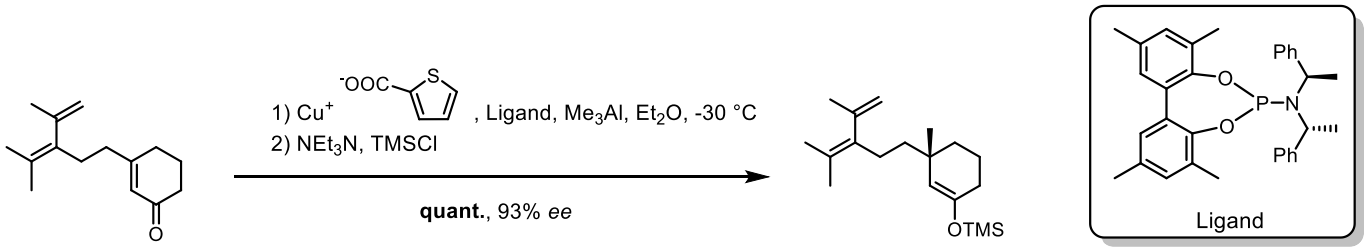
- *Nat. Chem.* **2012**, *4*, 21 – 25.
- *Org. Process Res. Dev.* **2015**, *19*, 284 – 289.
- *J. Am. Chem. Soc.* **2020**, *142*, 10526 – 10533.

Paclitaxel – Two Phase Synthesis – 1st Phase



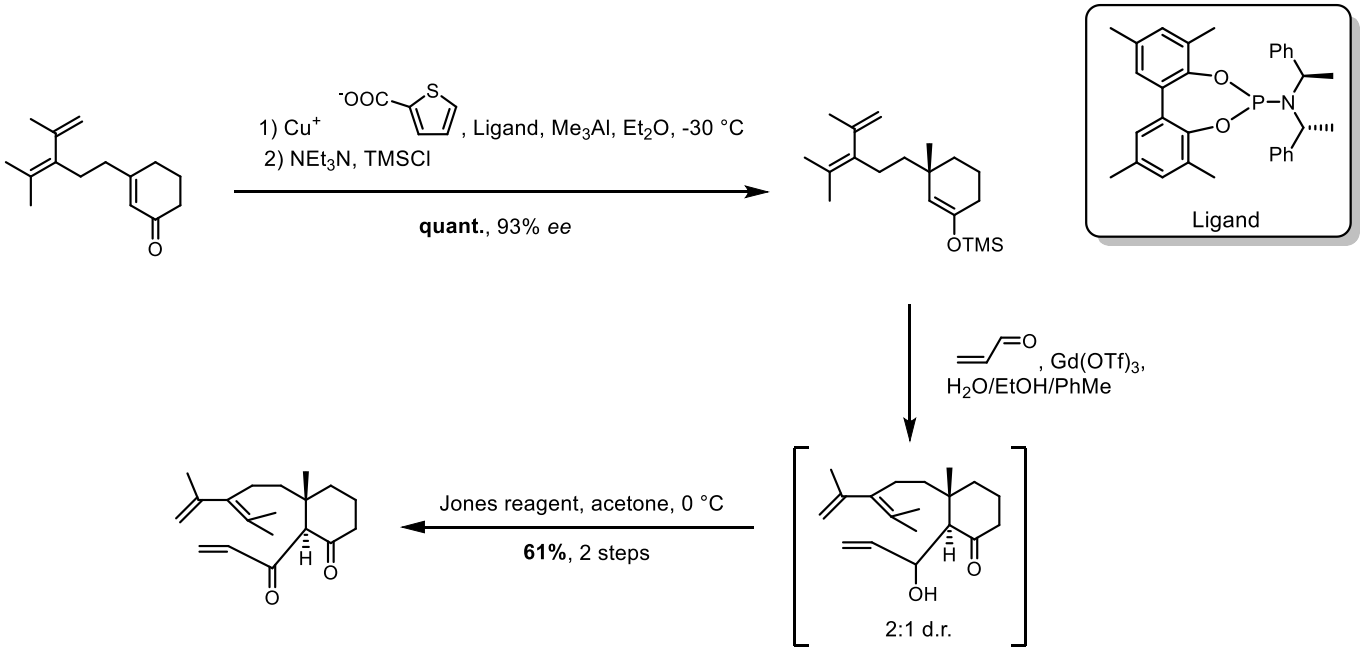
- *Nat. Chem.* **2012**, *4*, 21 – 25.
- *Org. Process Res. Dev.* **2015**, *19*, 284 – 289.
- *J. Am. Chem. Soc.* **2020**, *142*, 10526 – 10533.

Paclitaxel – Two Phase Synthesis – 1st Phase



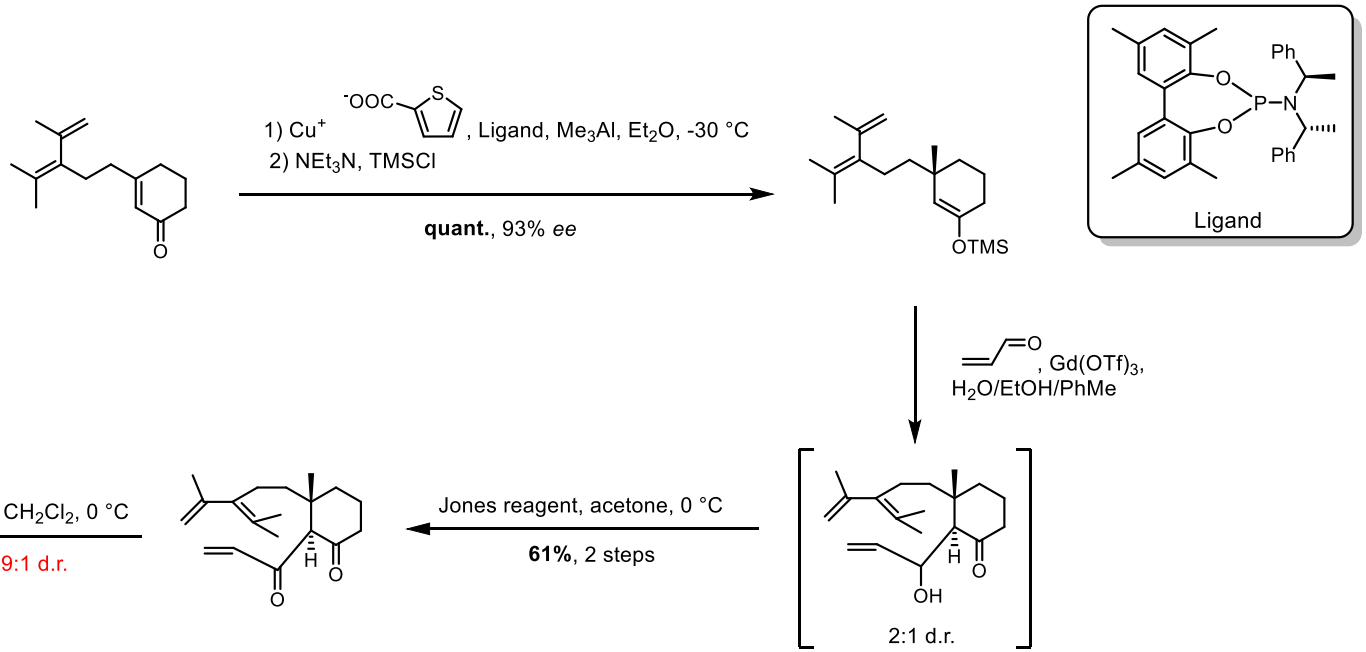
- *Nat. Chem.* **2012**, *4*, 21 – 25.
- *Org. Process Res. Dev.* **2015**, *19*, 284 – 289.
- *J. Am. Chem. Soc.* **2020**, *142*, 10526 – 10533.

Paclitaxel – Two Phase Synthesis – 1st Phase



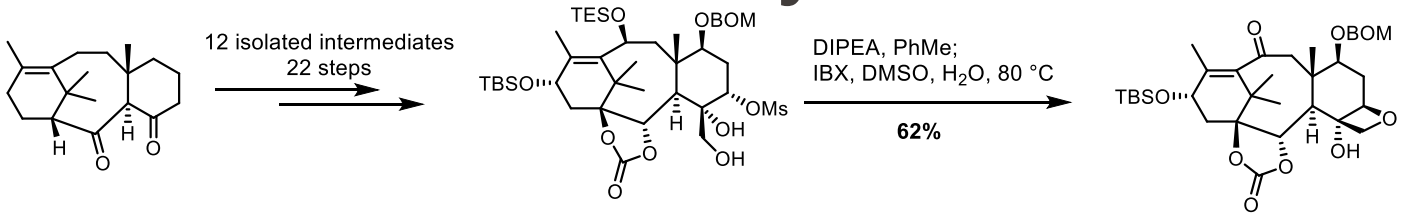
- *Nat. Chem.* **2012**, *4*, 21 – 25.
- *Org. Process Res. Dev.* **2015**, *19*, 284 – 289.
- *J. Am. Chem. Soc.* **2020**, *142*, 10526 – 10533.

Paclitaxel – Two Phase Synthesis – 1st Phase



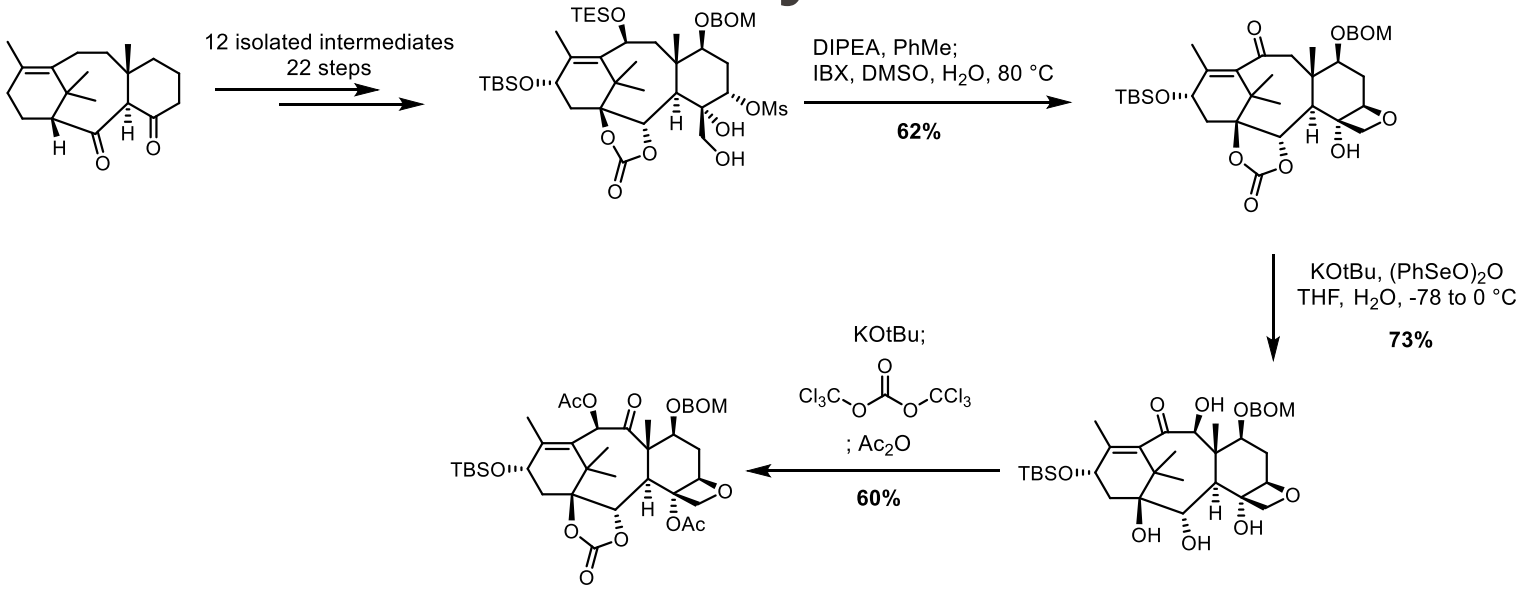
- *Nat. Chem.* **2012**, *4*, 21 – 25.
- *Org. Process Res. Dev.* **2015**, *19*, 284 – 289.
- *J. Am. Chem. Soc.* **2020**, *142*, 10526 – 10533.

Paclitaxel – Two Phase Synthesis – 2nd Phase



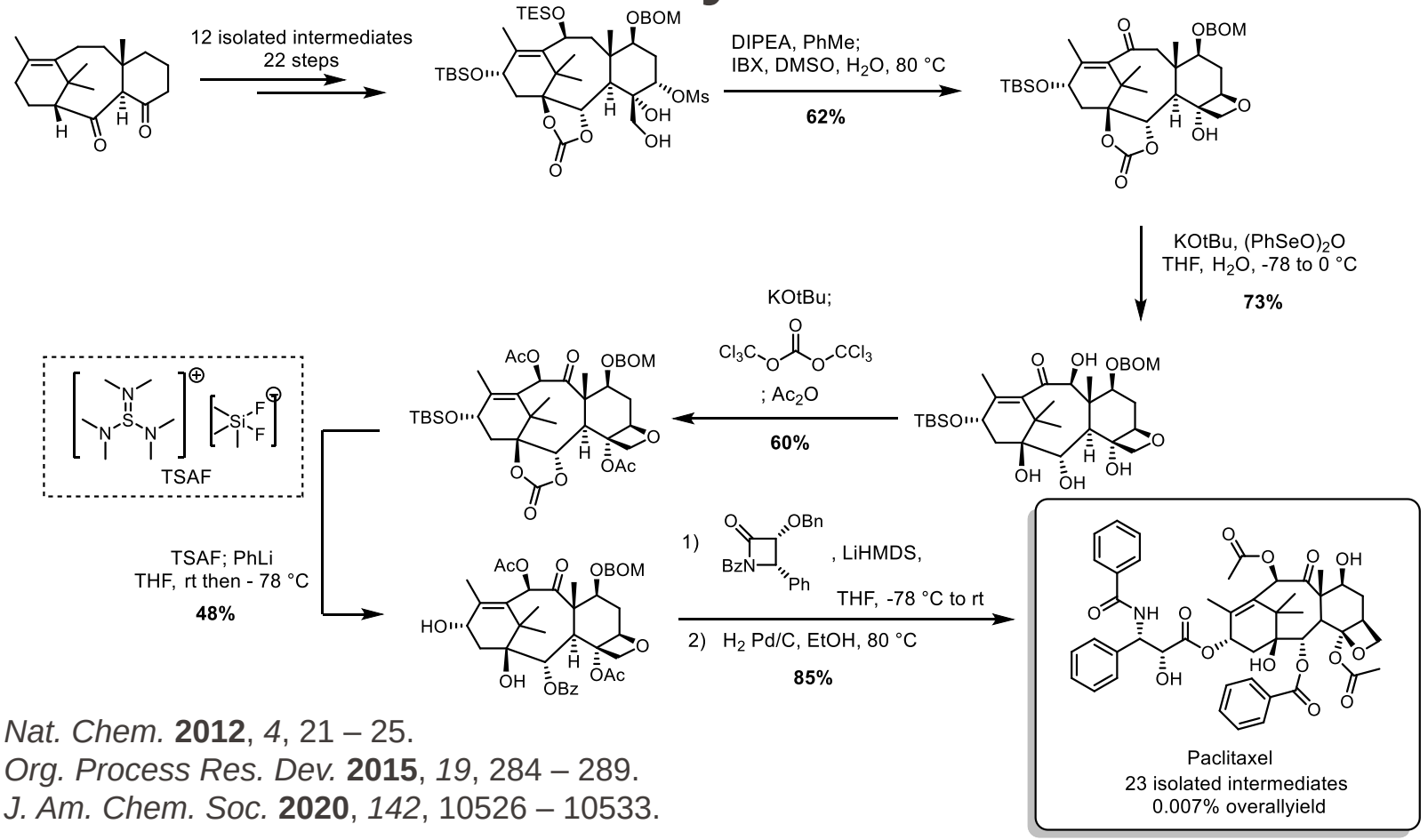
- *Nat. Chem.* **2012**, *4*, 21 – 25.
- *Org. Process Res. Dev.* **2015**, *19*, 284 – 289.
- *J. Am. Chem. Soc.* **2020**, *142*, 10526 – 10533.

Paclitaxel – Two Phase Synthesis – 2nd Phase



- *Nat. Chem.* **2012**, *4*, 21 – 25.
- *Org. Process Res. Dev.* **2015**, *19*, 284 – 289.
- *J. Am. Chem. Soc.* **2020**, *142*, 10526 – 10533.

Paclitaxel – Two Phase Synthesis – 2nd Phase



- *Nat. Chem.* **2012**, *4*, 21 – 25.
- *Org. Process Res. Dev.* **2015**, *19*, 284 – 289.
- *J. Am. Chem. Soc.* **2020**, *142*, 10526 – 10533.

Conclusion and Outlook

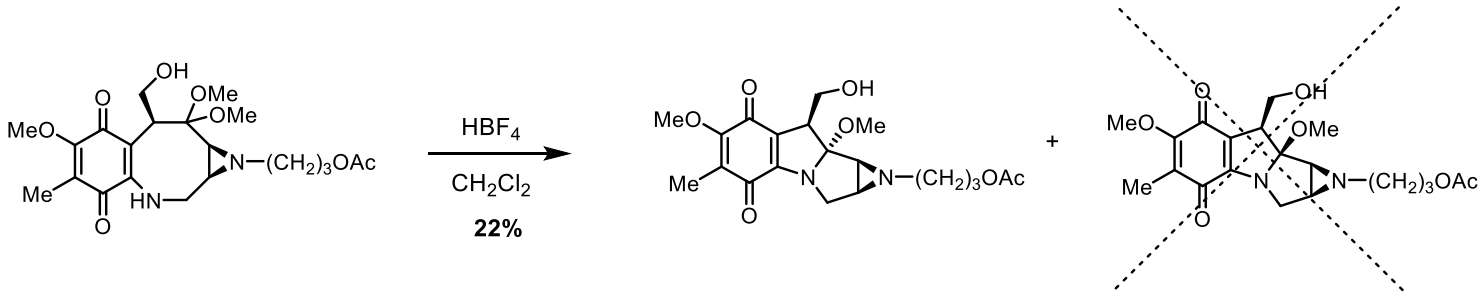
- Heterocycles: important motif in (anti-cancer) drugs
- Challenging structures
- Total synthetic, semi synthetic or biosynthetic access
- Future derivatization of existing molecules to enhance their bioactivity
- Based on mechanism of action: design of new compounds

- *RSC Adv.* **2020**, *10*, 44247 – 44311.
- *J. Am. Chem. Soc.* **2020**, *142*, 10526 – 10533.

Thank you very much for your attention!

Questions

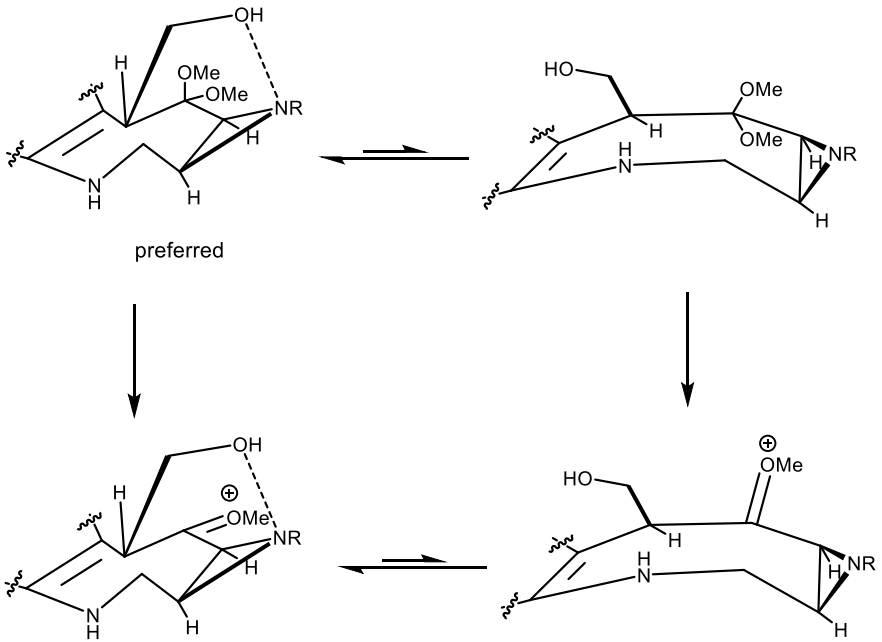
1) Key Transannulation: Why only 1 diasteromer?



- *J. Nat. Prod.* **1979**, *42*, 549 – 568.

Questions

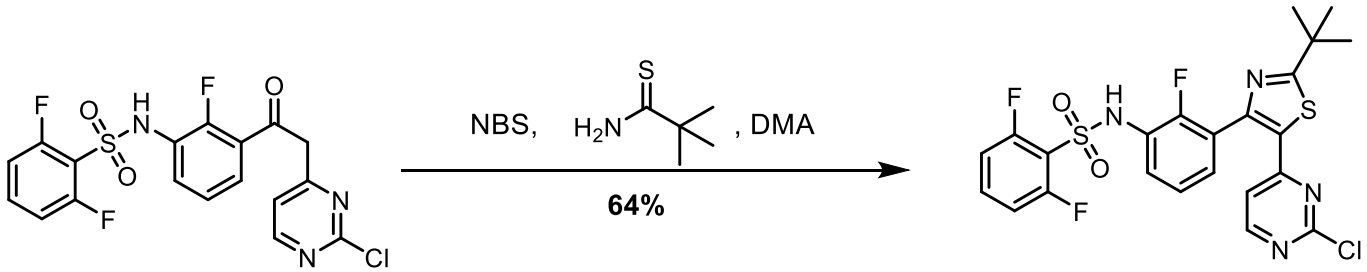
1) Key Transannulation: Why only 1 diasteromer?



- *J. Nat. Prod.* **1979**, *42*, 549 – 568.

Questions

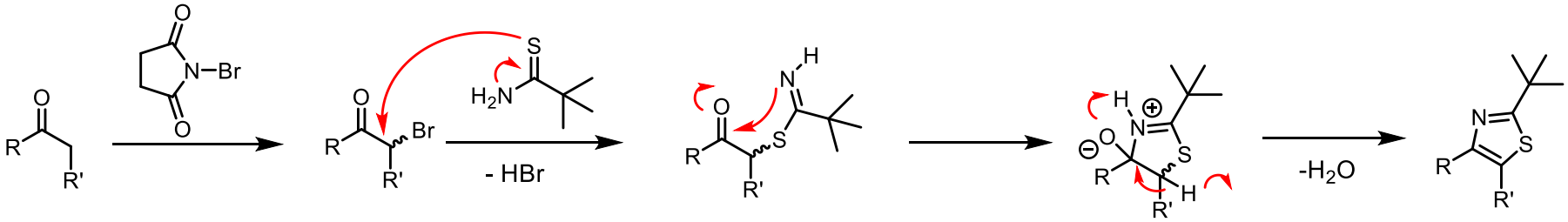
2) Name and reaction mechanism of thiazole core synthesis of Dabrafenib ?



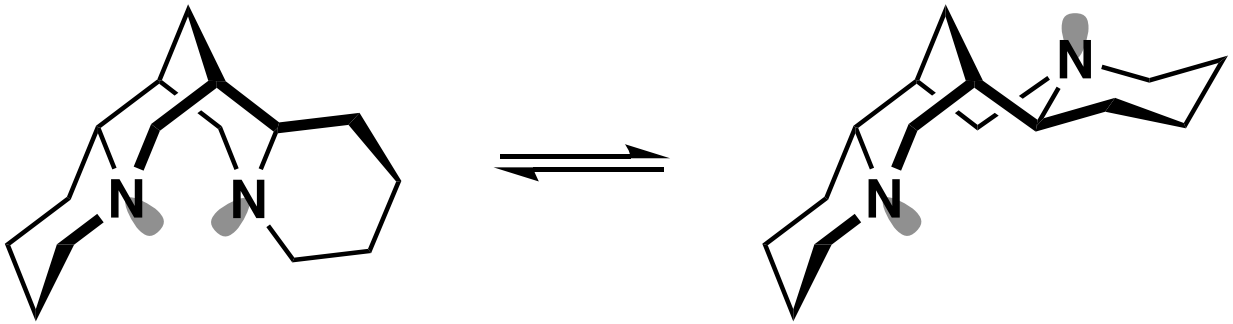
- *ACS Med. Chem. Lett.* **2013**, *4*, 358 – 362.
- *Med. Res. Rev.* **2017**, *37*, 98 – 148.

Questions

2) 2) Name and reaction mechanism of thiazole core synthesis of Dabrafenib ?
-> Hantzsch Thiazole Synthesis



- *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 3118 – 3132.
- *The Chemistry of Heterocycles: Chapter 5 - Five-Membered Heterocycles*, Elsevier, **2019**, p. 415.



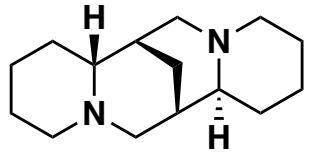
Sparteine-Mediated Enantioselective Lithiation

Diana Cavalli

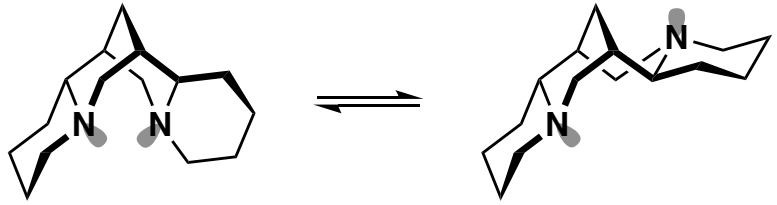
17.05.2021

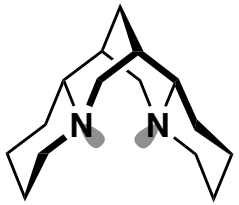
Table of Contents

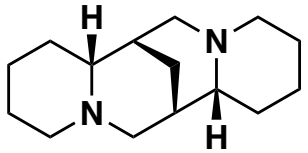
(–)-Sparteine and its diastereomers



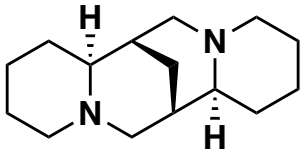
(–)-sparteine



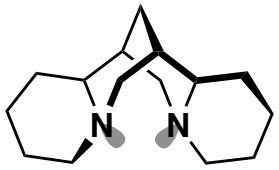




(–)-α-isosparteine

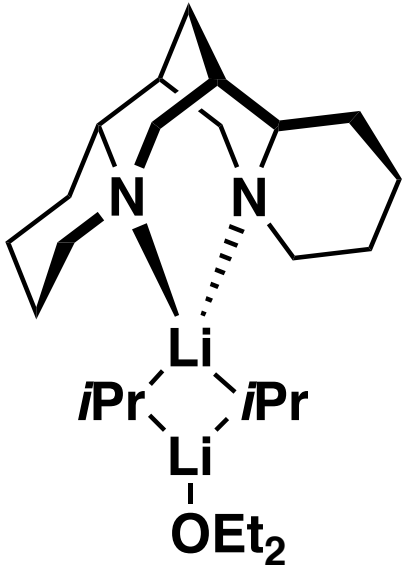


(–)-β-isosparteine



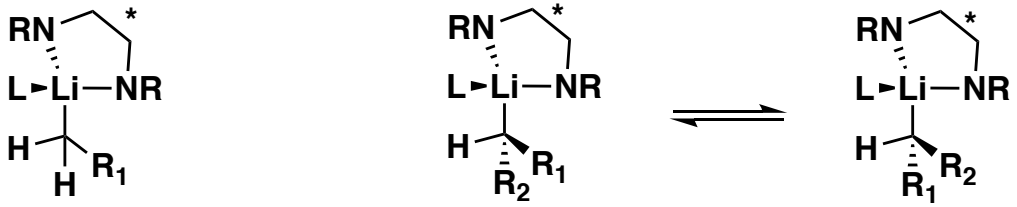
- D. Hoppe, T. Hense, *Angew. Chem. Int. Ed. Engl.*, **1997**, *36*, 2282
  Synthesis: 1) N. Maulide, B. Peng, A. C. A. Mateus, F. R. F. Machado, EP2808326A1, 2014. 2) J. D. Firth, S. J. Canipa, L. Ferris, P. O'Brien, *Angew. Chem. Int. Ed.*, **2018**, *57*, 223.

Lithium/Sparteine Configuration



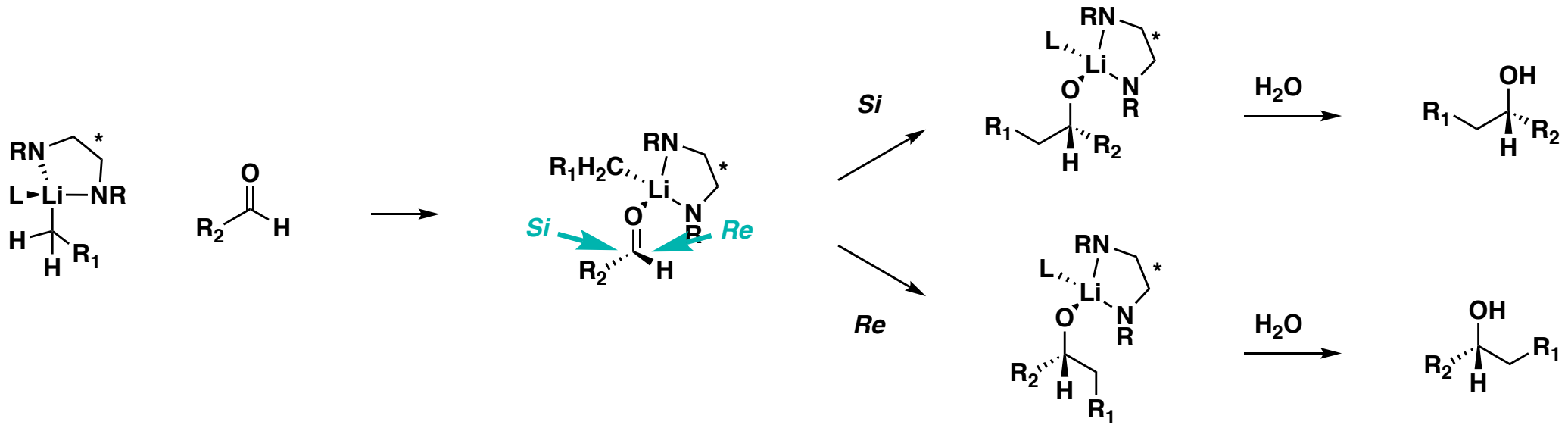
- C. Strohmann, K. Strohfeldt, D. Schildbach, *J. Am. Chem. Soc.*, **2003**, *125*, 13672.

Lithium/Sparteine Carbanion Pairs



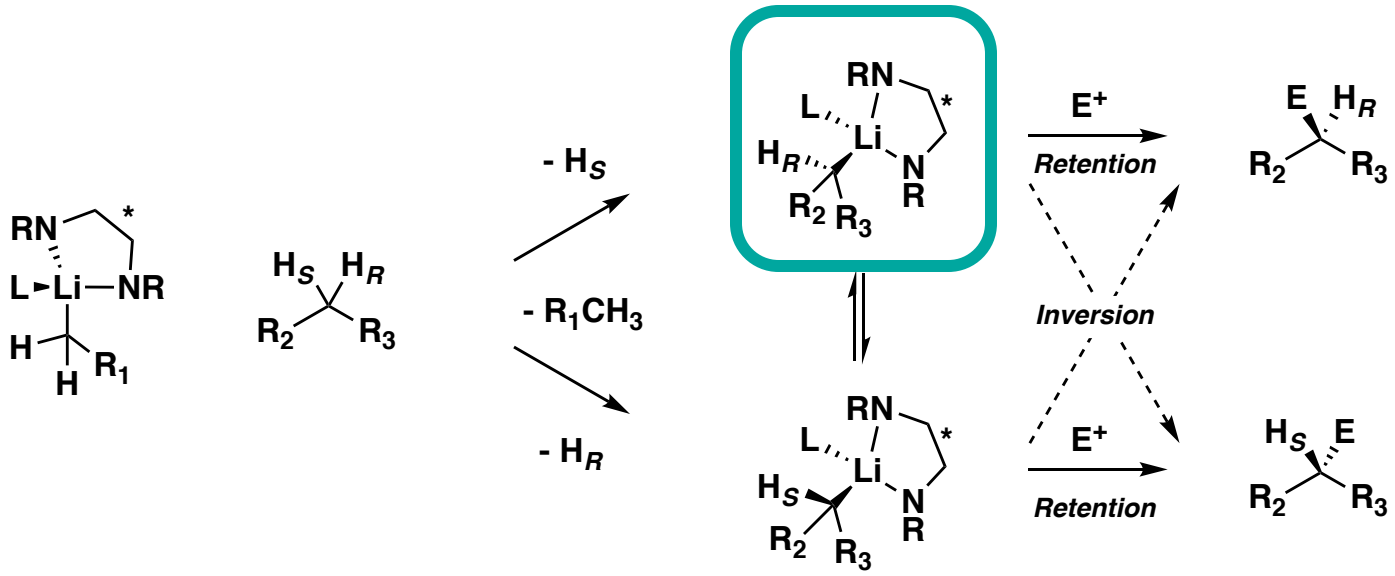
- D. Hoppe, T. Hense, *Angew. Chem. Int. Ed. Engl.*, **1997**, *36*, 2282

Enantiofacial Selectivity



- D. Hoppe, T. Hense, *Angew. Chem. Int. Ed. Engl.*, **1997**, *36*, 2282

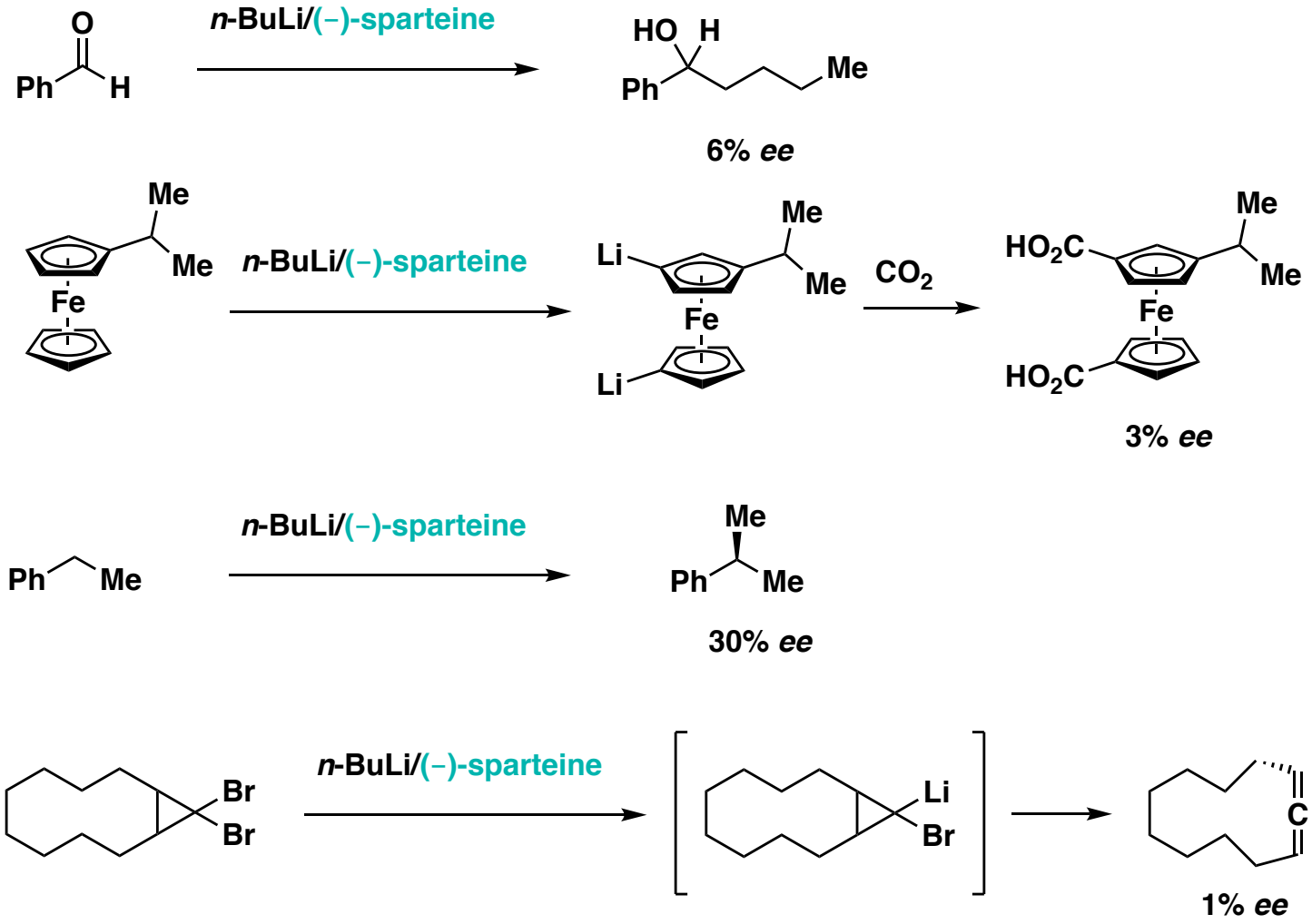
Stereoselective Deprotonation



- D. Hoppe, T. Hense, *Angew. Chem. Int. Ed. Engl.*, **1997**, *36*, 2282

Pioneering Works

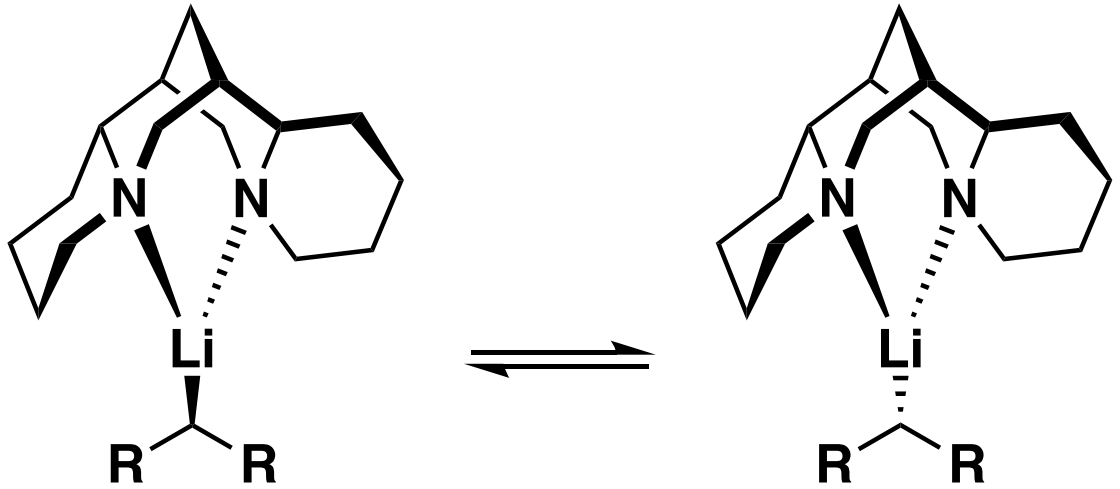
Nozaki, Aratani, Toraya and Noyori, 1968 - 1970



1) T. Aratani, T. Gonda, H. Nozaki, *Tetrahedron*, **1970**, *26*, 5453. 2) H. Nozaki, T. Aratani, T. Toraya, R. Noyori, *Tetrahedron*, **1971**, *27*, 905.

Configurationally Labile Li/Sparteine-Carbanion Pairs

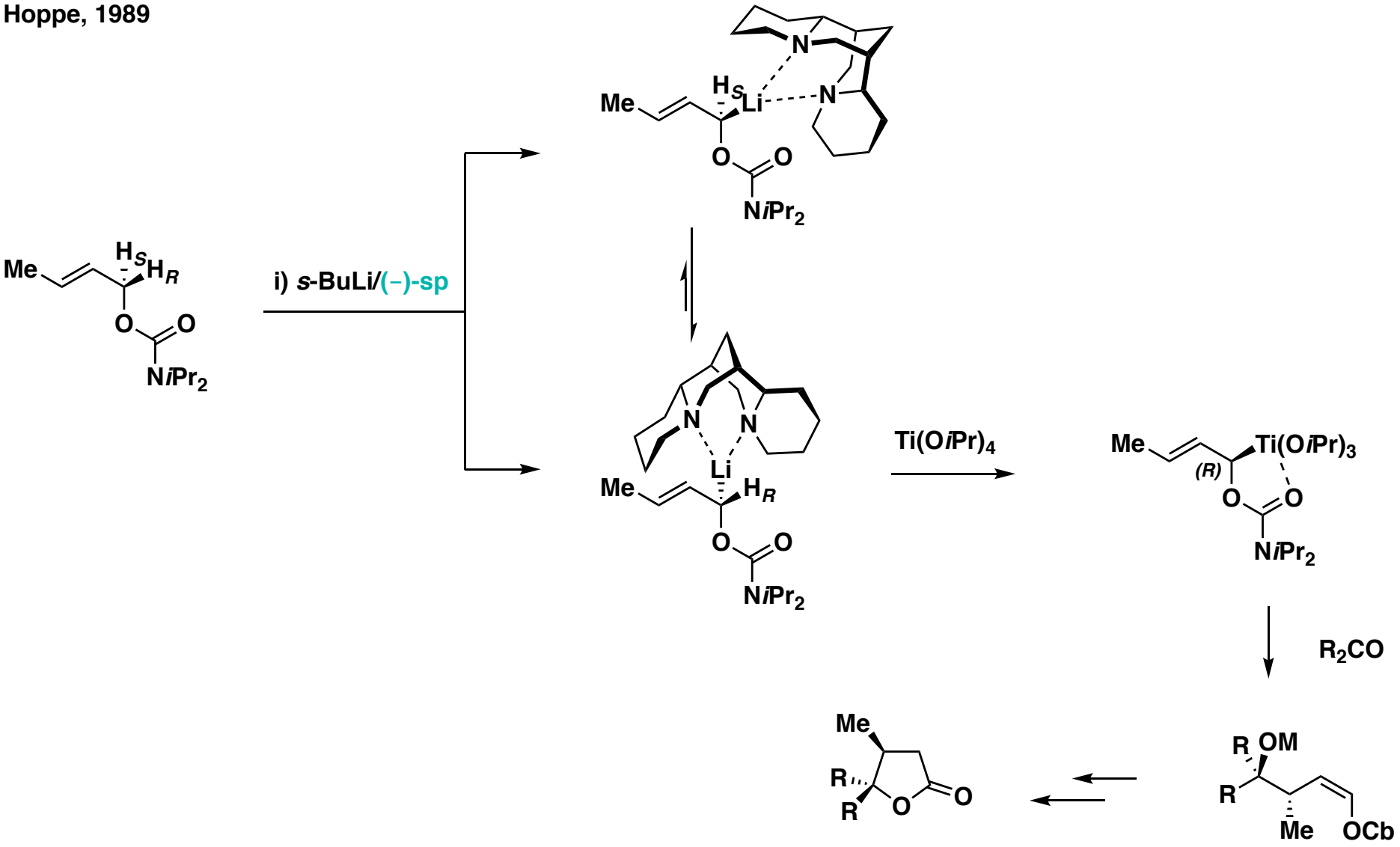
Configurationally labile Li/sp-carbanion pairs



- D. Hoppe, T. Hense, *Angew. Chem. Int. Ed. Engl.*, **1997**, *36*, 2282

Allylic Compounds

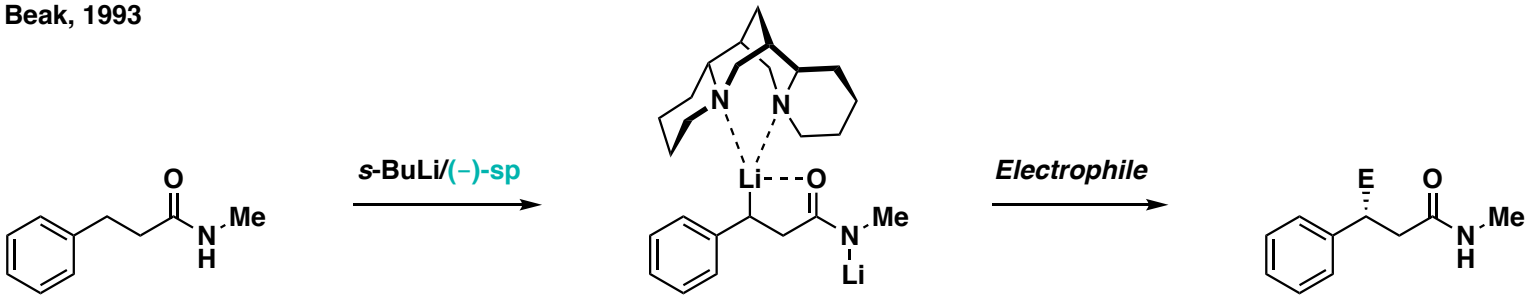
Hoppe, 1989



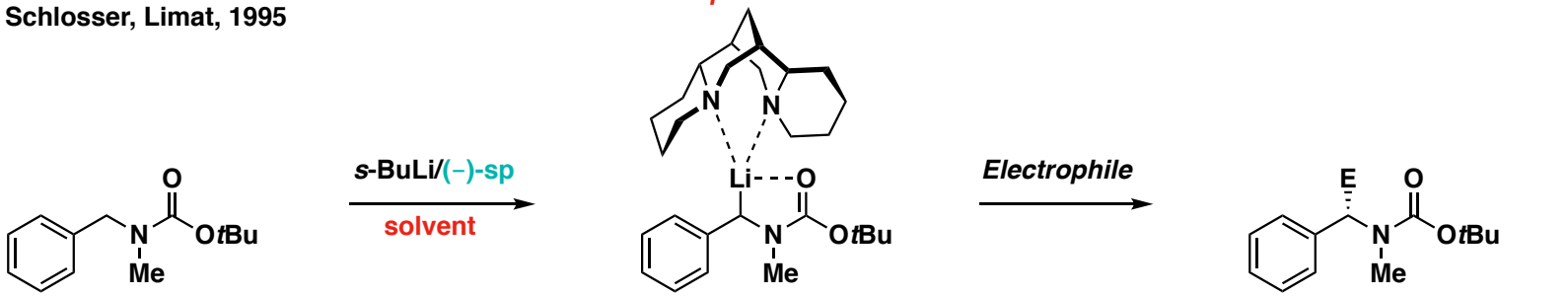
D. Hoppe, O. Zschange, *Angew. Chem. Int. Ed. Engl.*, **1989**, *28*, 69.

Benzylic Compounds

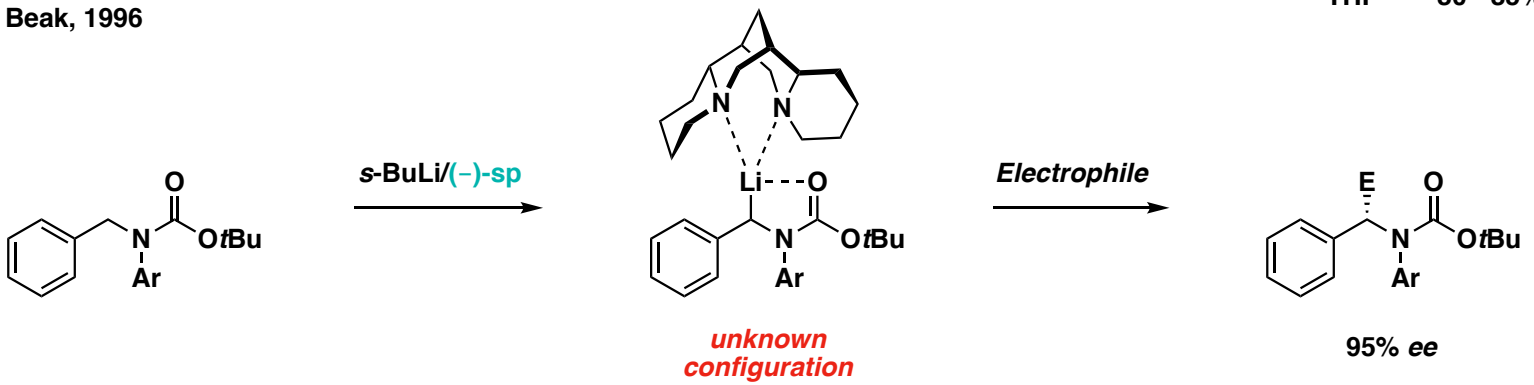
Beak, 1993



Schlosser, Limat, 1995



Beak, 1996

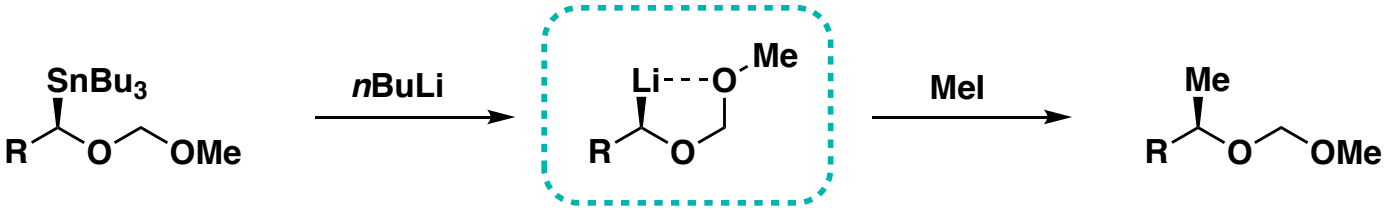


1) P. Beak, H. Du, *J. Am. Chem. Soc.*, **1993**, *115*, 2516. 2) M. Schlosser, D. Limat, *J. Am. Chem. Soc.*, **1995**, *117*, 12342. 3) Y. S. Park, M. L. Boys, P. Beak, *J. Am. Chem. Soc.*, **1996**, *126*, 1887.

Configurationally Stable Li/Sparteine-Carbanion Pairs

Configurationally stable Li/sp-carbanion pairs

Still, Sreekumar, 1980



Examples of configurationally stable lithium/sparteine carbanion pairs:

α to an Oxygen Atom:

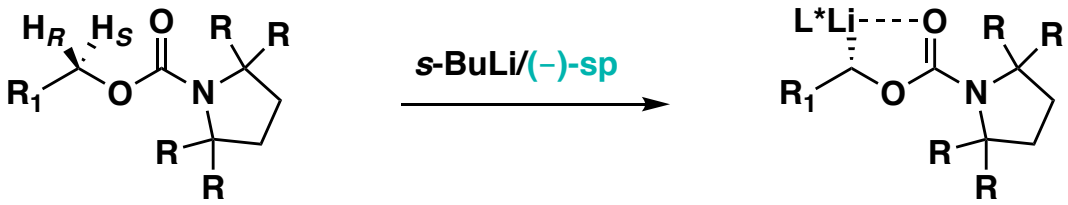
- **Hoppe's Alkyl Carbamates**
- **Hoppe's Aryl Carbamates**

α to a Nitrogen Atom:

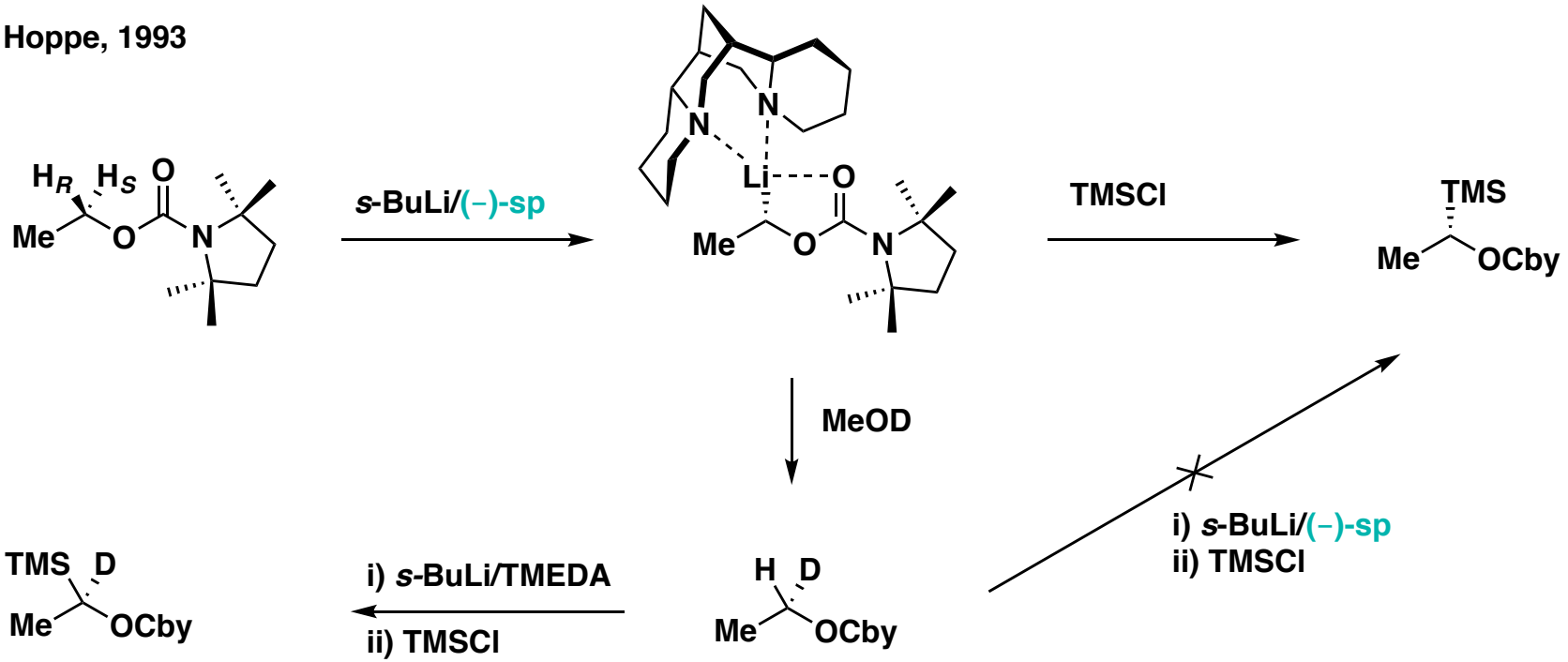
- **Heterocyclic substrates**

W. C. Still, C. Streekumar, *J. Am. Chem. Soc.*, **1980**, *102*, 1201.

Lithiation α to an Oxygen Atom

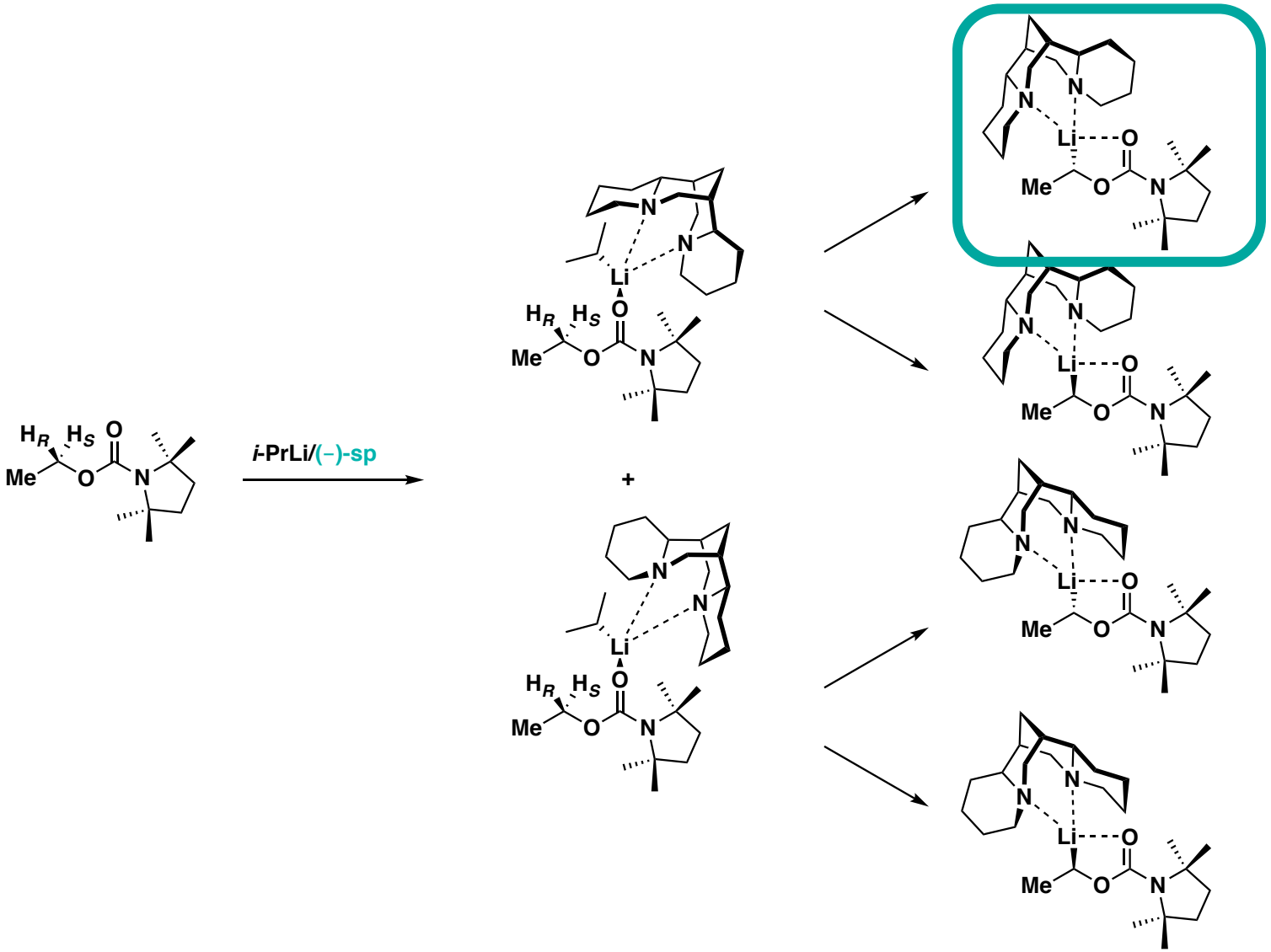


Hoppe, 1993



D. Hoppe, M. Paetow, F. Hintze, *Angew. Chem. Int. Ed. Engl.*, **1993**, *32*, 394

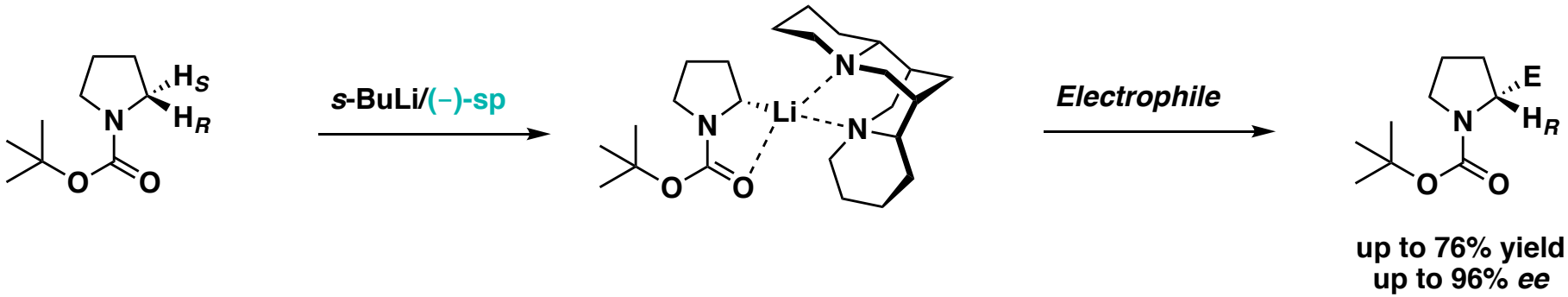
Lithiation α to an Oxygen Atom



- E. U. Würtwein, D. Hoppe, *J. Org. Chem.*, **2005**, *70*, 4443.

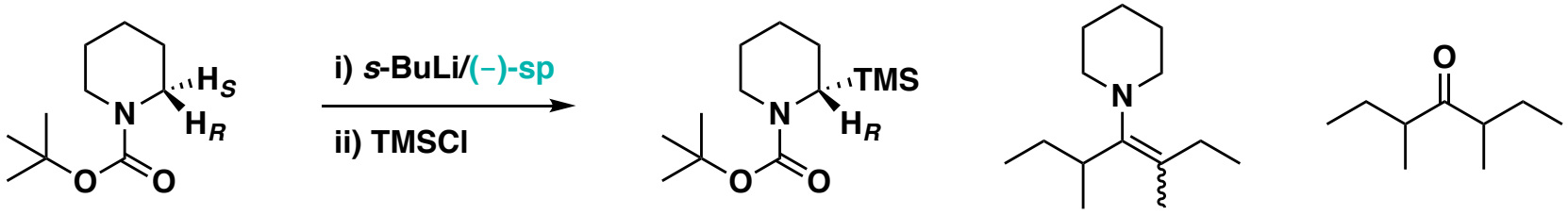
Lithiation α to a Nitrogen Atom

Beak, 1991



up to 76% yield
up to 96% *ee*

Bailey, Beak, 2002



8%
87:13 e.r.

43%

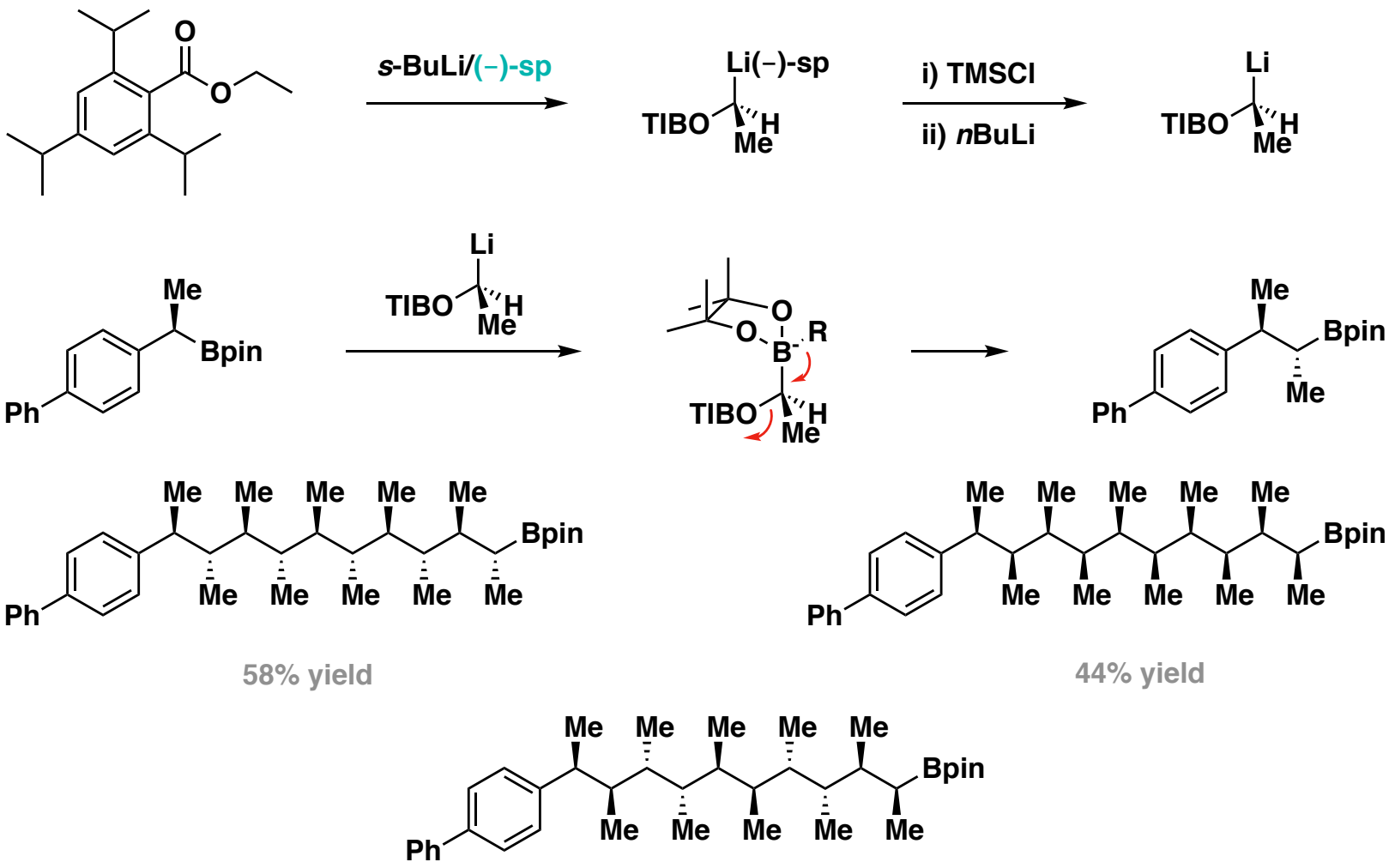
9%

1) S. T. Kerrick, P. Beak, *J. Am. Chem. Soc.*, **1991**, *113*, 9708. 2) W. F. Bailey, P. Beak, S. T. Kerrick, S. Ma, K. B. Wiberg, *J. Am. Chem. Soc.*, **2002**, *124*, 1889.

Recent Applications

Recent Applications

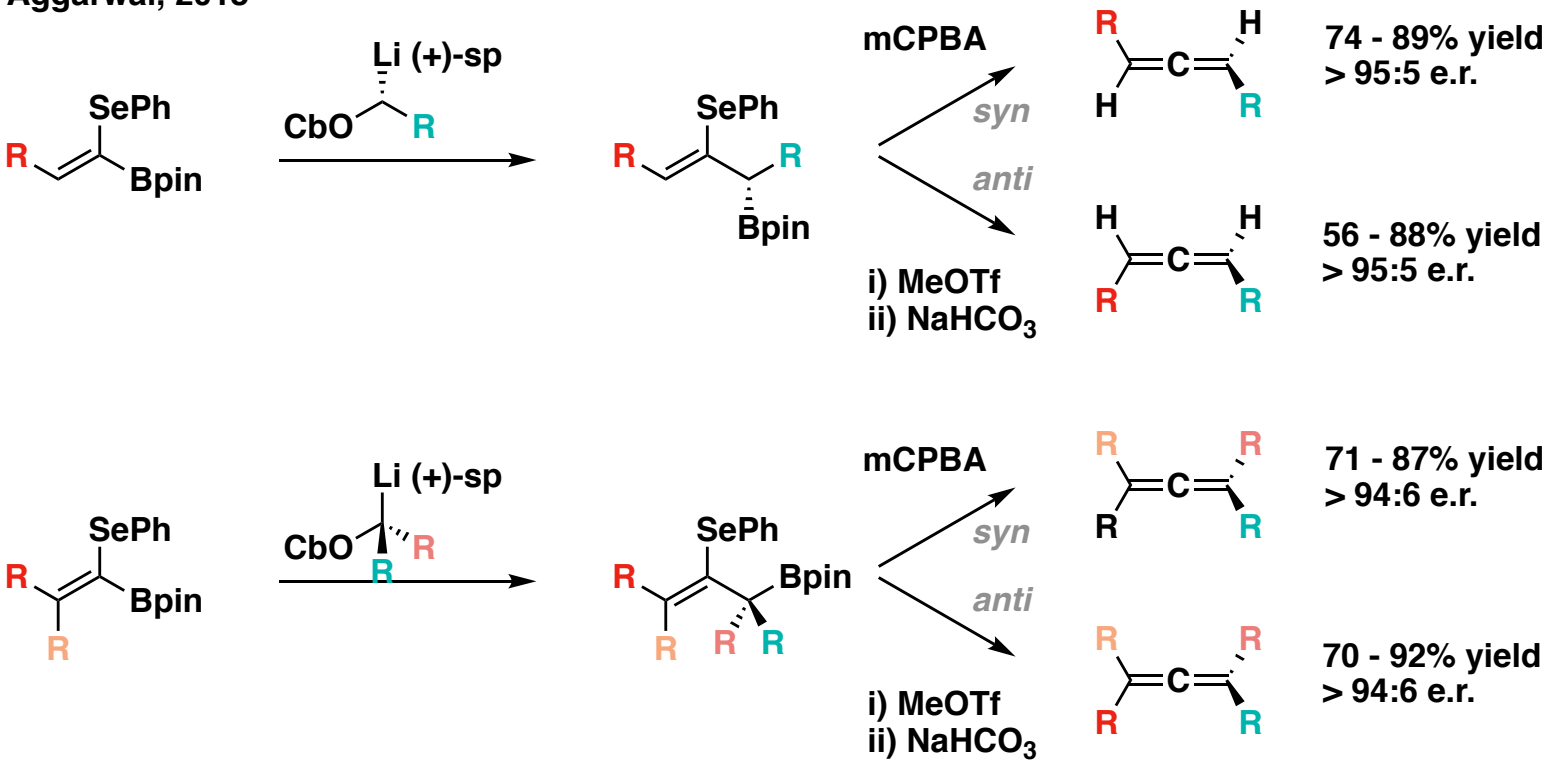
Aggarwal, 2014



M. Burns, S. Essafi, J. R. Bame, S. P. Bull, M. P. Webster, S. Balieu, J. W. Dale, C. P. Butts, J. N. Harvey, V. K. Aggarwal, *Nature*, **2014**, *513*, 183.

Recent Applications

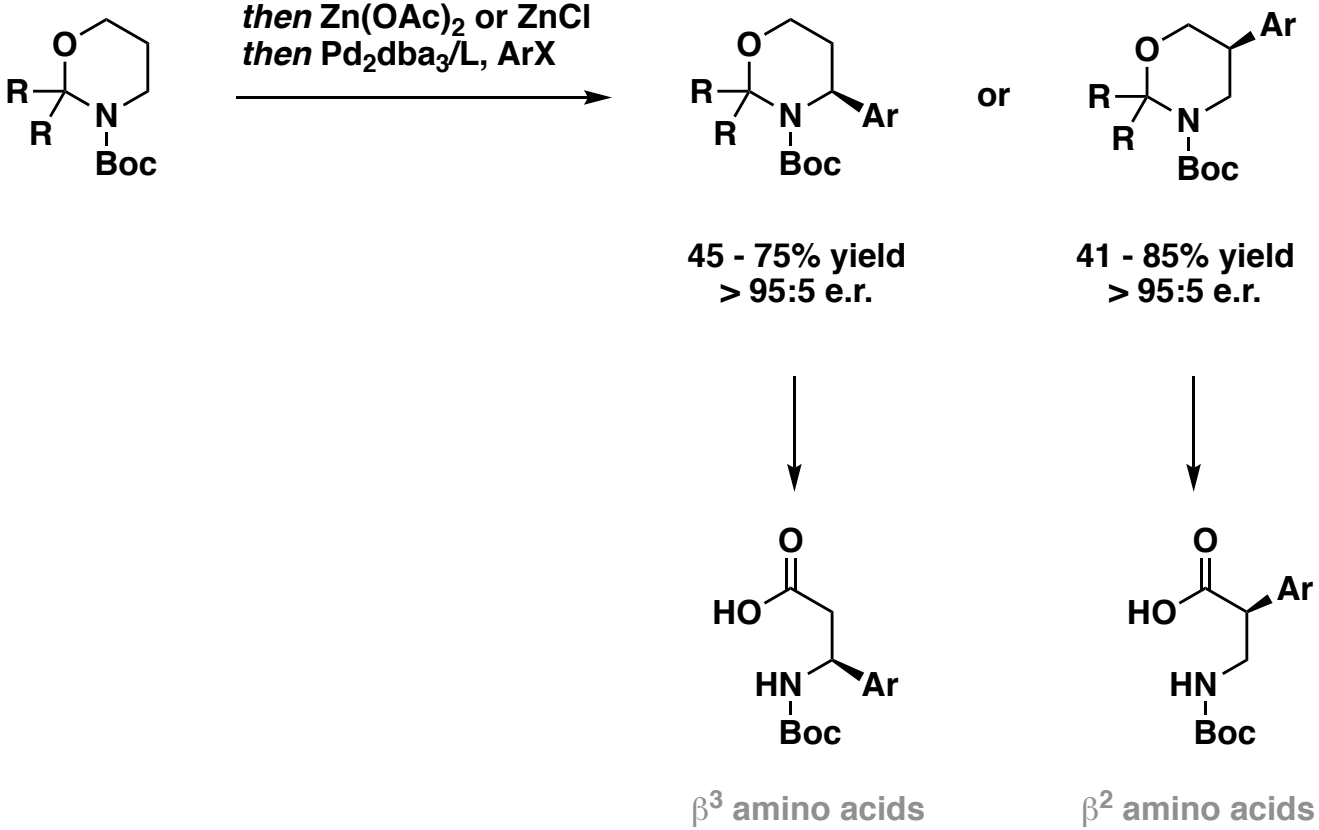
Aggarwal, 2018



R. J. Armstrong, M. Nandakumar, R. M. P. Dias, A. Noble, E. L. Myers, V. K. Aggarwal, *Angew. Chem. Int. Ed.*, **2018**, *57*, 8203.

Recent Applications

Baudoin, 2019



W. Lin, K. F. Zhang, O. Baudoin, *Nature Cat.*, **2019**, *2*, 882.

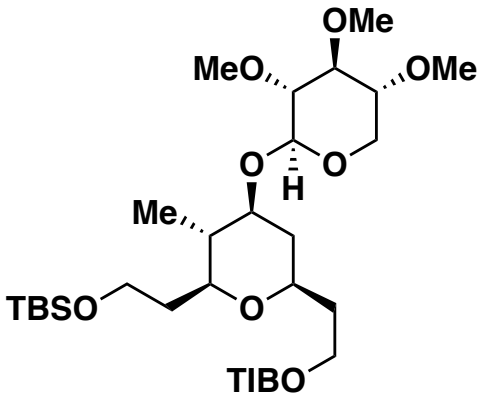
Conclusions

- Highly enantioselective deprotonation of carbamates
- Can be combined to a various arrange of electrophiles
  - Various enantioselective transformations could be achieved
- (+)-sparteine (and analogs) is suitable as well

Questions

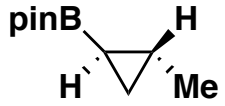
Questions

Aggarwal, *Angew. Chem. Int. Ed.* 2016



i) *s*BuLi (1.1 equiv)
(+)-sparteine
Et_2O, -78 °C, 1 h

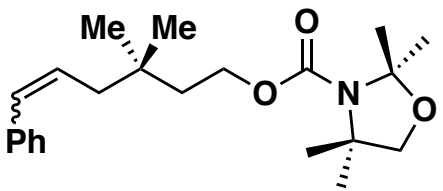
→ ?

ii) 

(1.2 equiv)
-78 °C, 1 h, then reflux 2 h

iii) NaOH (2 M):H_2O_2 (30%) (2:1)
RT, 2 h

Hoppe, *Angew. Chem. Int. Ed.* 1997



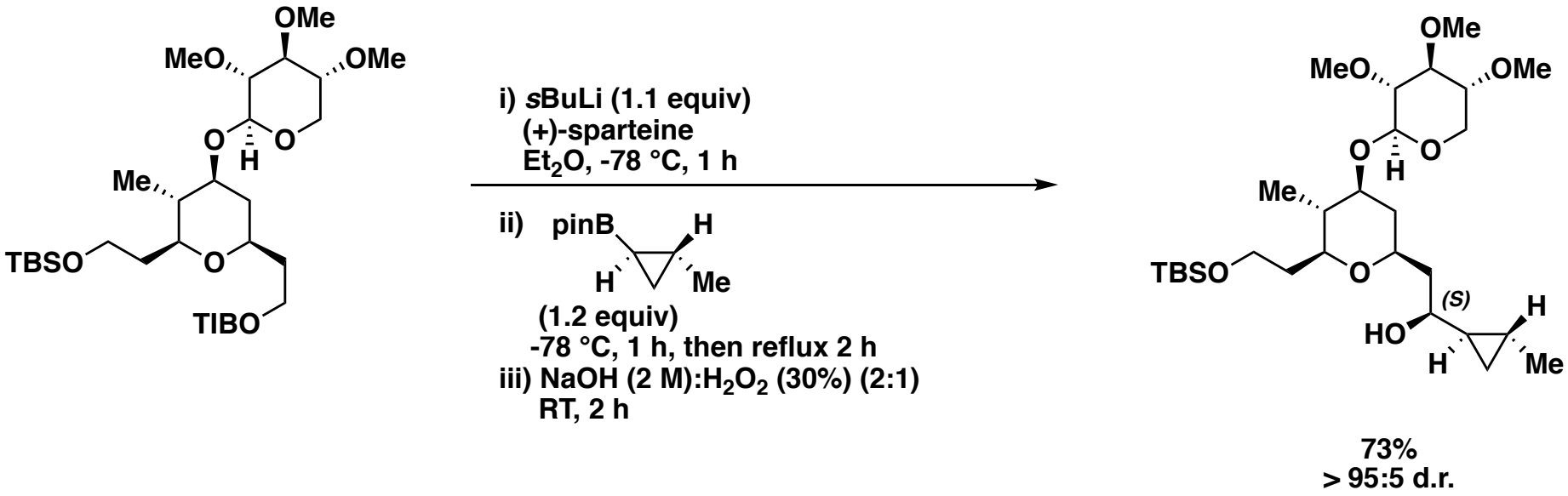
i) *s*BuLi, (-)-sparteine
Et_2O, -78 °C, 24 h

→ ?

ii) $PhMe_2SiCl$, -78 °C to rt

Answer 1

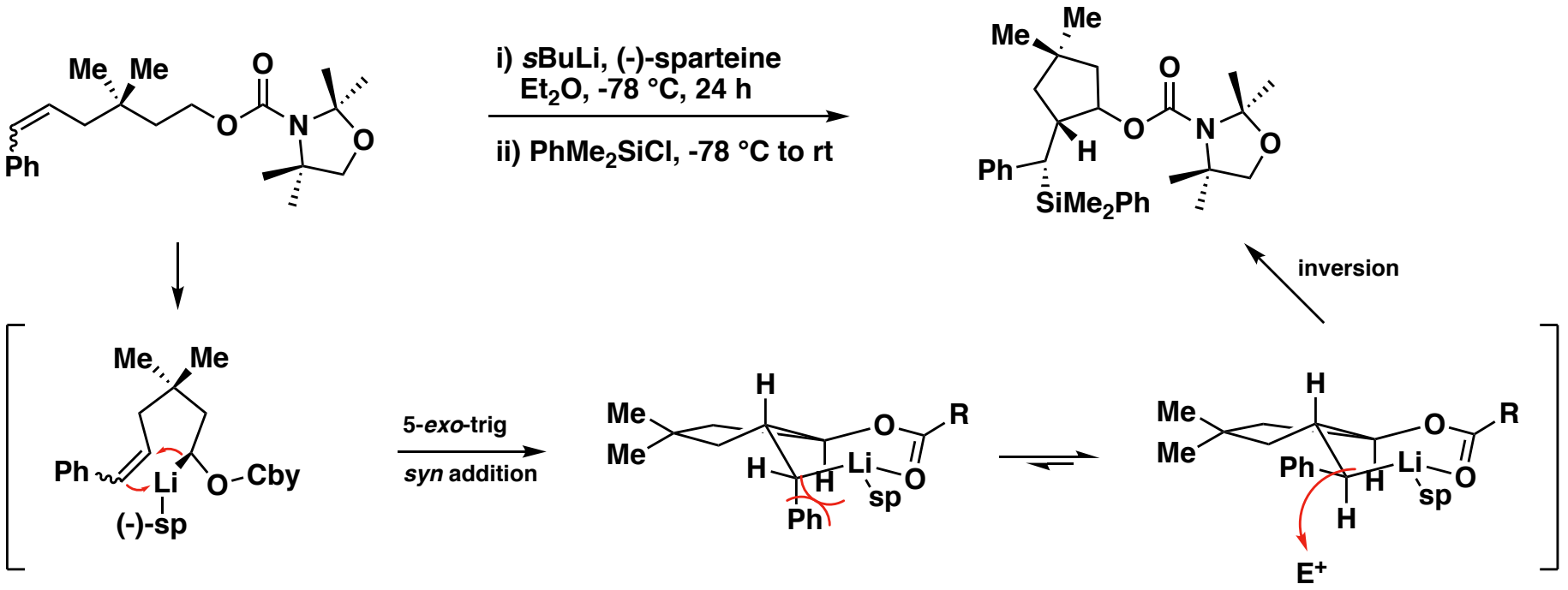
Aggarwal, ***Angew. Chem. Int. Ed.*** 2016



73%
> 95:5 d.r.

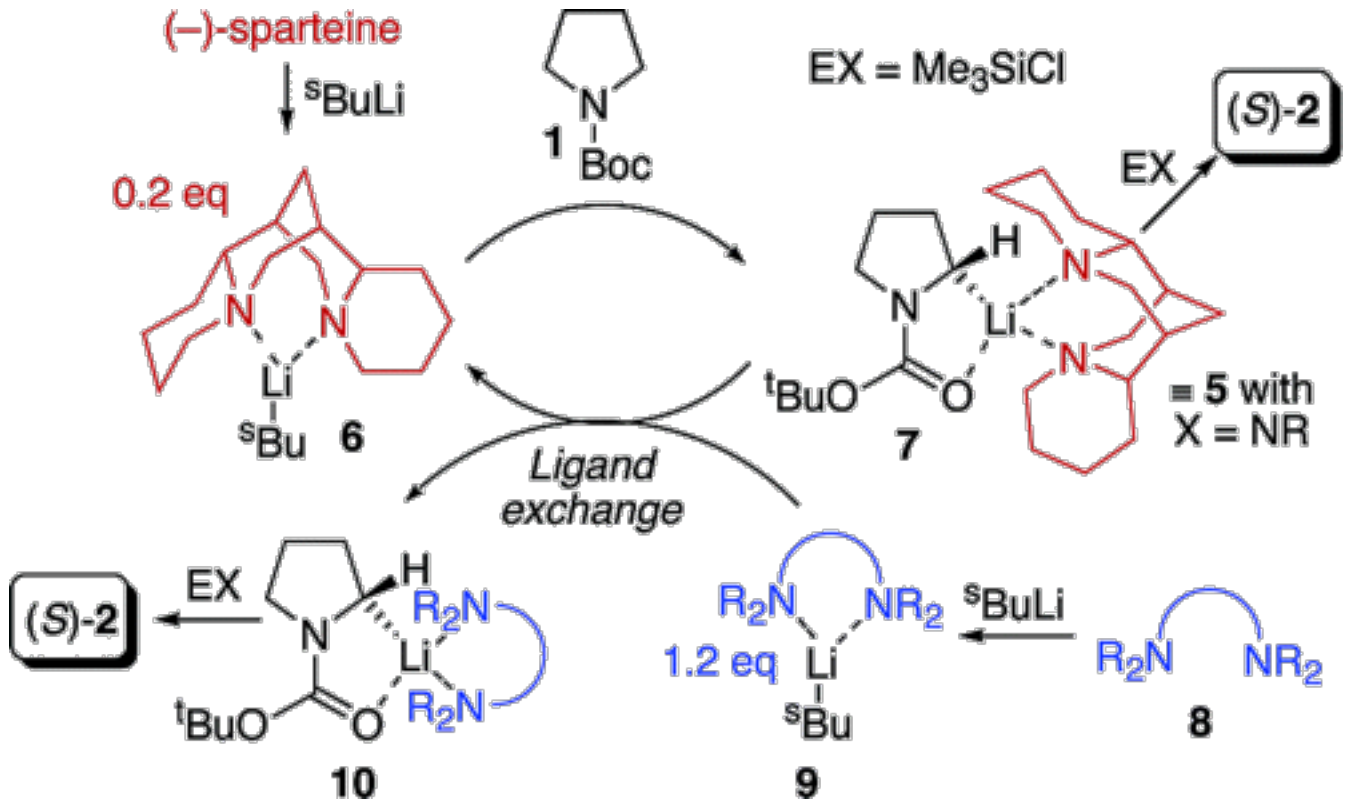
Answer 2

Hoppe, *Angew. Chem. Int. Ed.* 1997



Thank you for your attention

Questions?



- M. J. McGrath, P. O'Brien, *J. Am. Chem. Soc.*, **2005**, *127*, 16378.

Heterocycle Synthesis *via* Enantioselective NHC-Catalysed Annulations

Frontiers in Chemical Synthesis:
Heterocyclic Chemistry

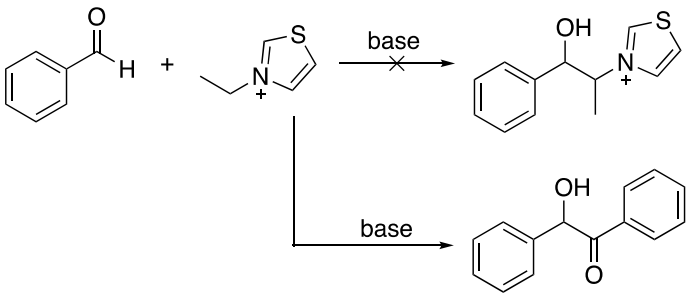
Lara Lavrenčič
1st year PhD student at LSCI
20.05.2021

Presentation Outline

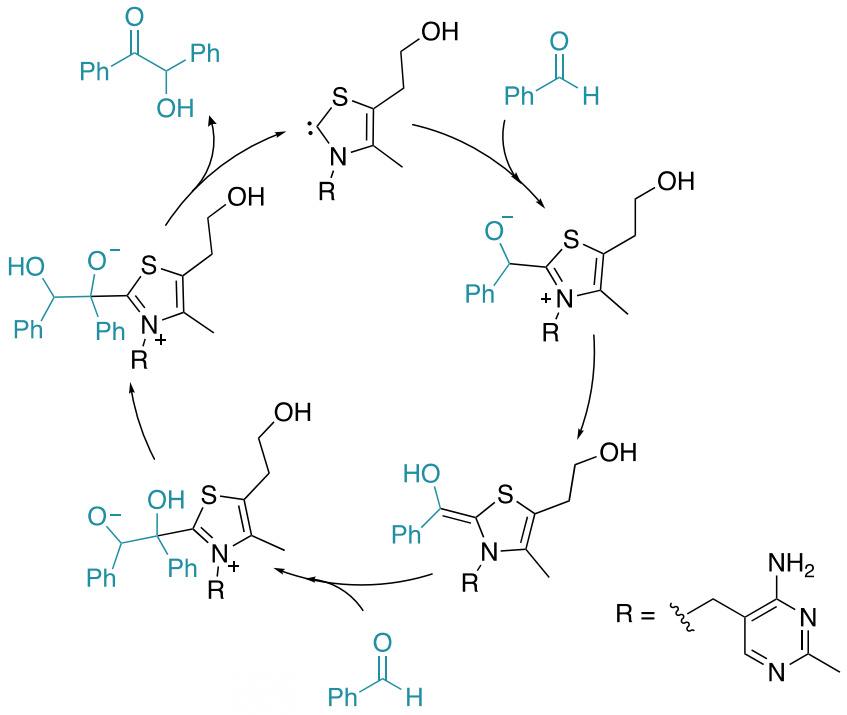
1. Background and Main Innovations
2. Reactivity Overview
3. Selected Examples:
    - 3.1. Homoenolate Equivalents
    - 3.2. (Conjugated) Enolate Equivalents
    - 3.3. α,β-Unsaturated Acyl Azoliums
    - 3.4 Cooperative NHC/Metal Catalysis
4. Conclusion and Questions

Early Historical Background

Ugai:

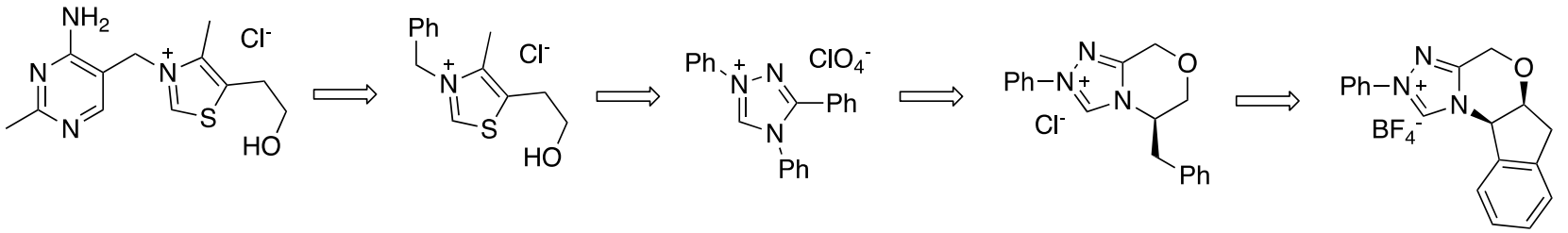


Breslow:



1) P.-C. Chiang, J. W. Bode*, in *Catalysis Series*, S. Diez-Gonzalez, Ed. (Royal Society of Chemistry, Cambridge, 2010, pp. 399–435. 2) J. Mahatthananchai, J. W. Bode, in *Contemporary Carbene Chemistry*, R. A. Moss, M. P. Doyle, Eds. (John Wiley & Sons, Inc, Hoboken, NJ, 2013, pp. 237–273. 3) R. Breslow, *J. Am. Chem. Soc.* **80**, 3719–3726 (1958).

NHC Precatalyst Development



Thiamine (Vitamin B1)

Ugai and Breslow, 1943

Stetter, 1976

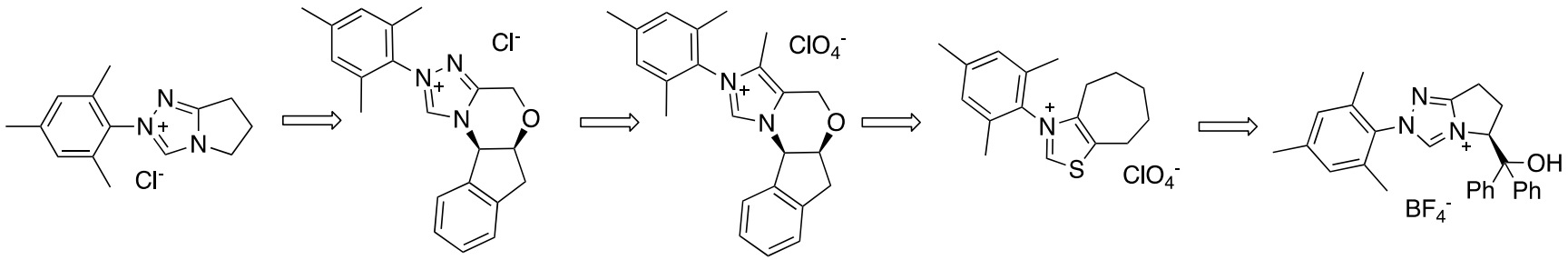
Enders and Tesla, 1996

Knight and Leeper, 1998

Rovis, 2002

J. Mahatthananchai, J. W. Bode, in *Contemporary Carbene Chemistry*, R. A. Moss, M. P. Doyle, Eds. (John Wiley & Sons, Inc, Hoboken, NJ, 2013, pp. 237–273.

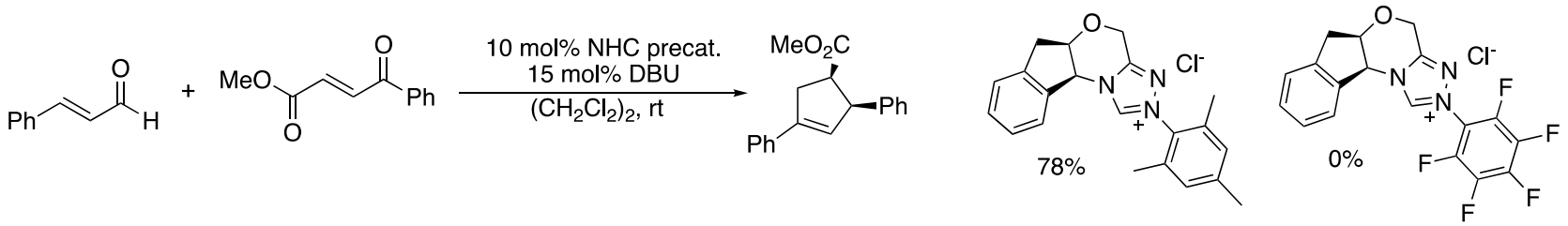
NHC Precatalyst Development

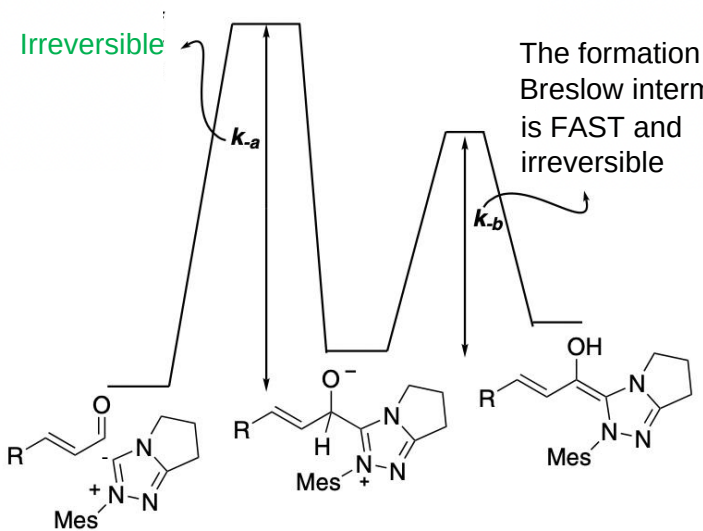


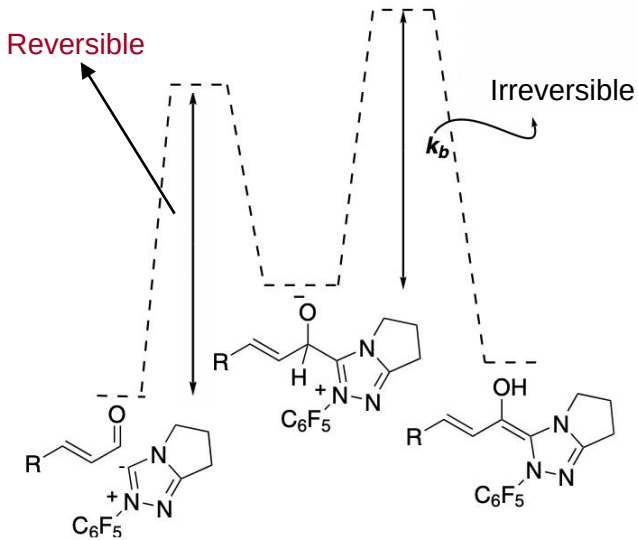
Bode, 2005 | Bode, 2005 | Bode, 2008 | Glorius, 2008 | Ye, 2009

J. Mahatthananchai, J. W. Bode, in *Contemporary Carbene Chemistry*, R. A. Moss, M. P. Doyle, Eds. (John Wiley & Sons, Inc, Hoboken, NJ, 2013, pp. 237–273.

N-Mesityl Catalysts

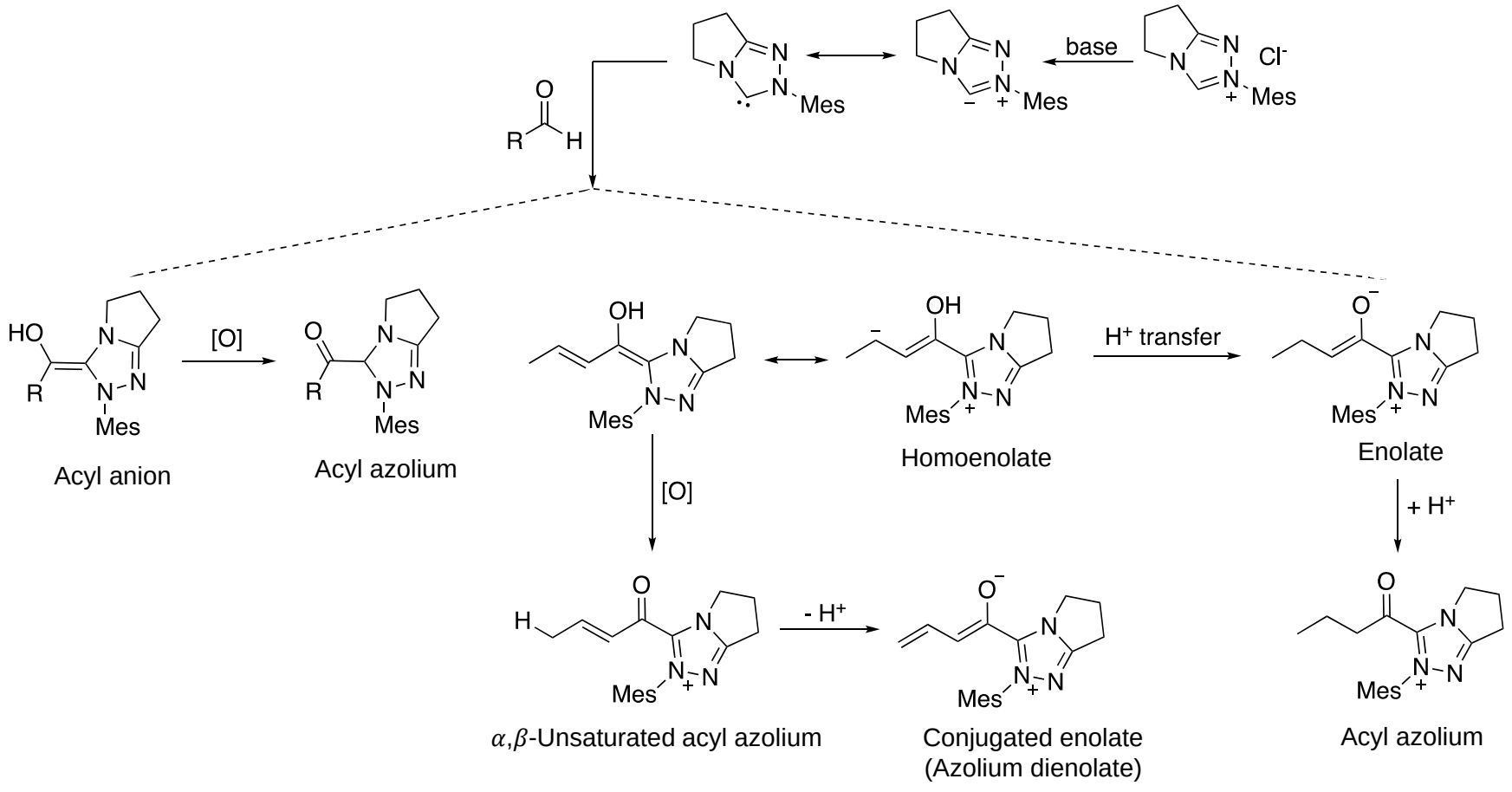






J. Mahatthananchai, J. W. Bode, in *Contemporary Carbene Chemistry*, R. A. Moss, M. P. Doyle, Eds. (John Wiley & Sons, Inc, Hoboken, NJ, 2013, pp. 237–273.

Types of Reactive Intermediates

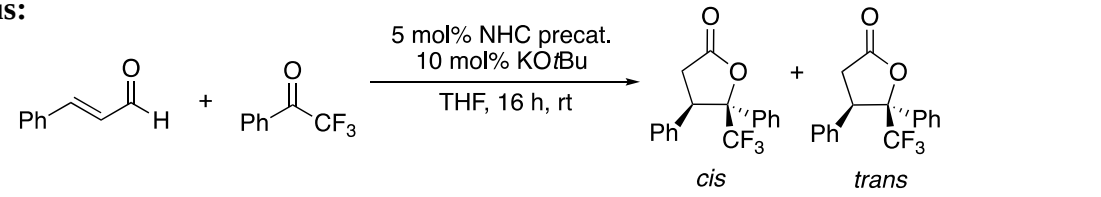


Presentation Outline

1. Background and Main Innovations
2. Reactivity Overview
3. Selected Examples:
    - 3.1. Homoenolate Equivalents
    - 3.2. (Conjugated) Enolate Equivalents
    - 3.3. α,β-Unsaturated Acyl Azoliums
    - 3.4 Cooperative NHC/Metal Catalysis
4. Conclusion and Questions

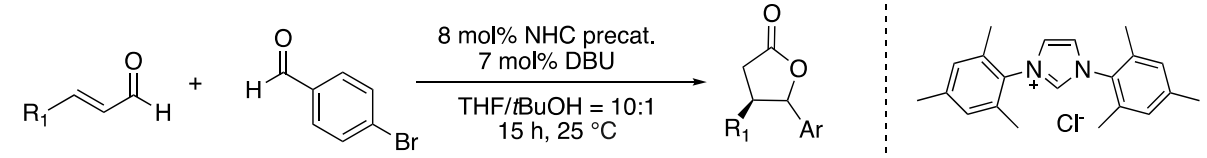
Annulations *via* Formal 1,2-Additions

Glorius:



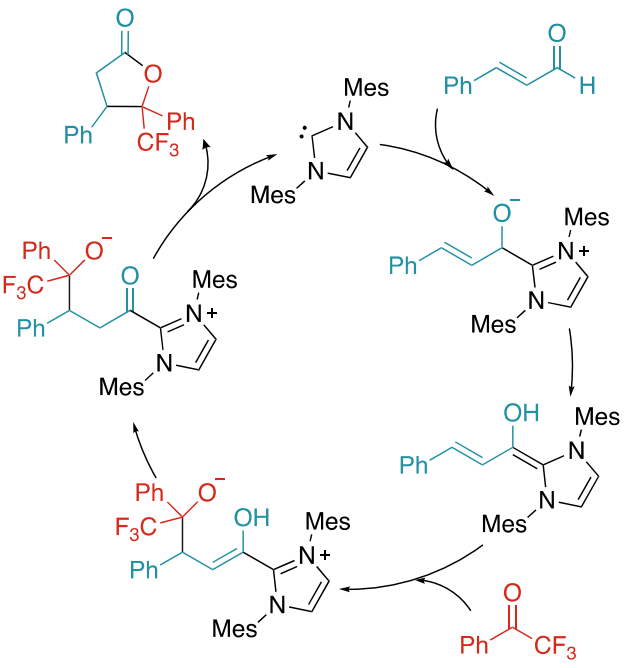
84%, 1.9:1 *dr* | 0% | 10% | 70%, 2.8:1 *dr*, 12/25 *ee*

Bode:



R_1 = Ar or Alkynylsilane

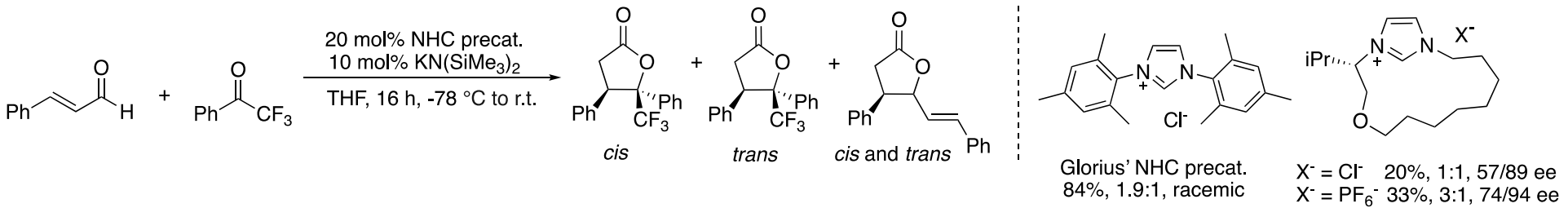
~ 80%
dr (cis/trans) = from 4:1 to 8:1



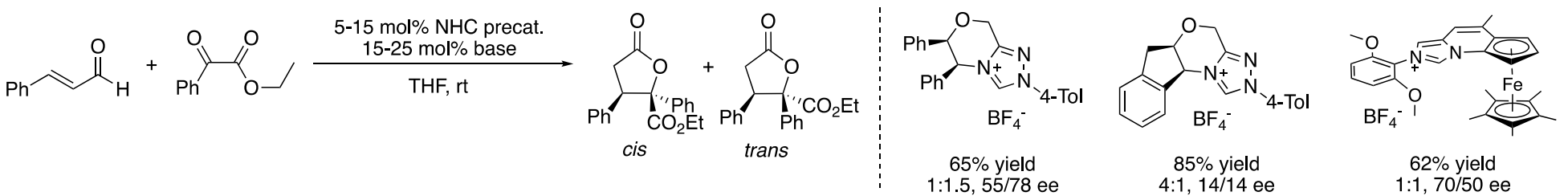
1) C. Burstein, F. Glorius, *Angew. Chem. Int. Ed.* **43**, 6205–6208 (2004), 2) S. S. Sohn, E. L. Rosen, J. W. Bode, *J. Am. Chem. Soc.* **126**, 14370–14371 (2004).

Annulations *via* Formal 1,2-Additions

Saigo:



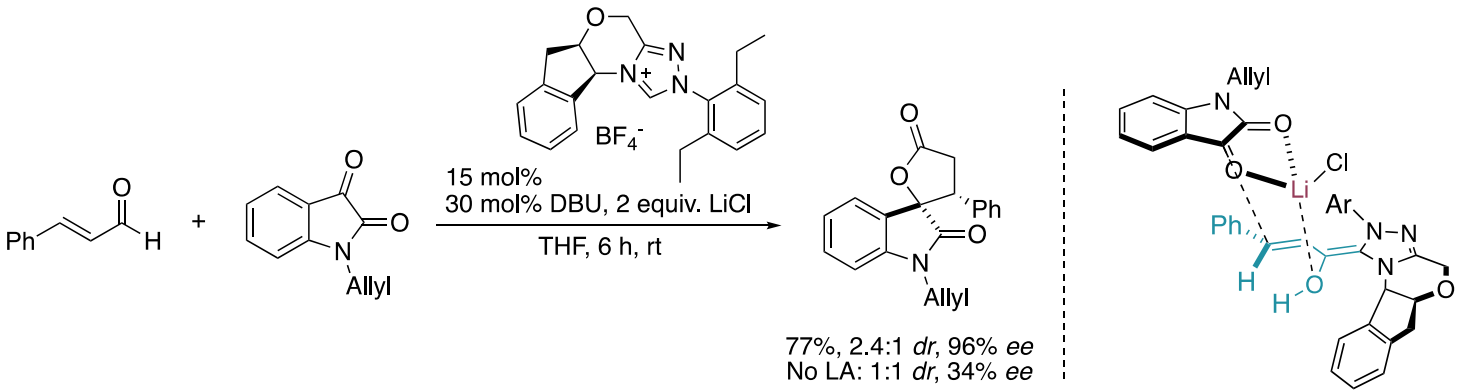
You:



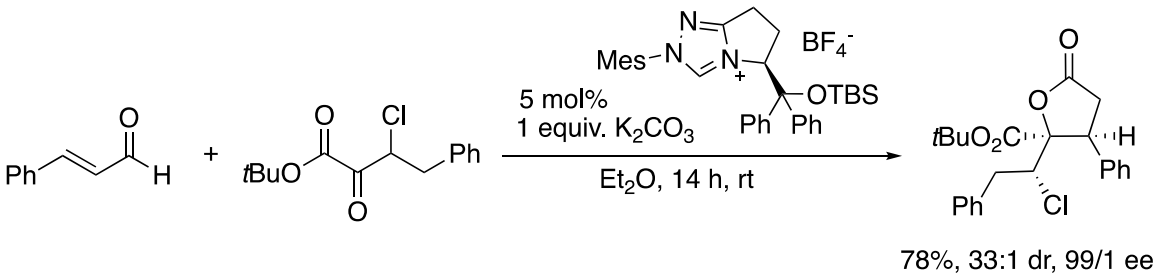
1) Y. Matsuoka, Y. Ishida, D. Sasaki, K. Saigo, *Chem. Eur. J.* **14**, 9215–9222 (2008), 2) Y. Li, Z.-A. Zhao, H. He, S.-L. You, *Adv. Synth. Catal.* **350**, 1885–1890 (2008).

Annulations *via* Formal 1,2-Additions

Scheidt:



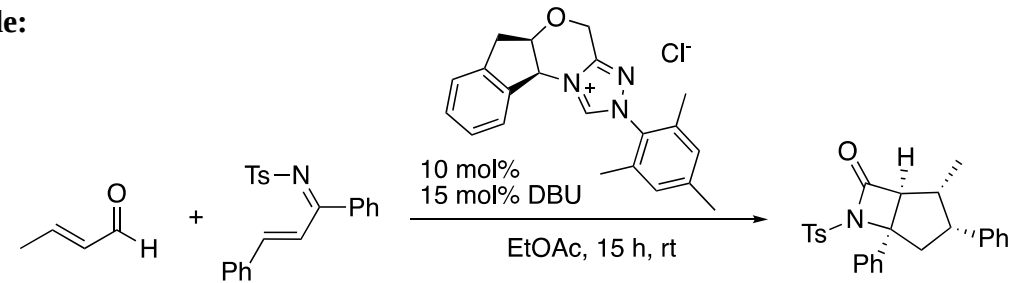
Johnson:



1) J. Dugal-Tessier, E. A. O'Bryan, T. B. H. Schroeder, D. T. Cohen, K. A. Scheidt, *Angew. Chem. Int. Ed.* **51**, 4963–4967 (2012). 2) C. G. Goodman, M. M. Walker, J. S. Johnson, *J. Am. Chem. Soc.* **137**, 122–125 (2015).

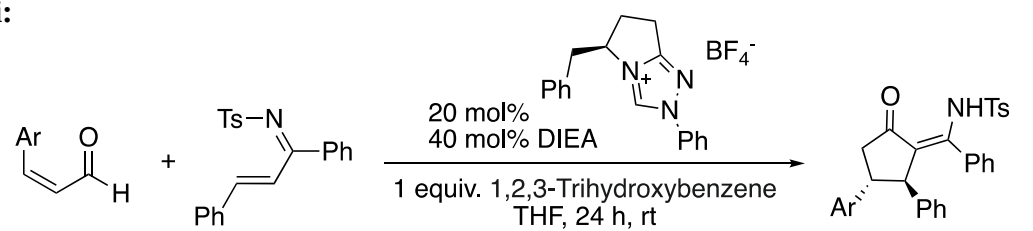
Annulations *via* Formal 1,4-Additions

Bode:

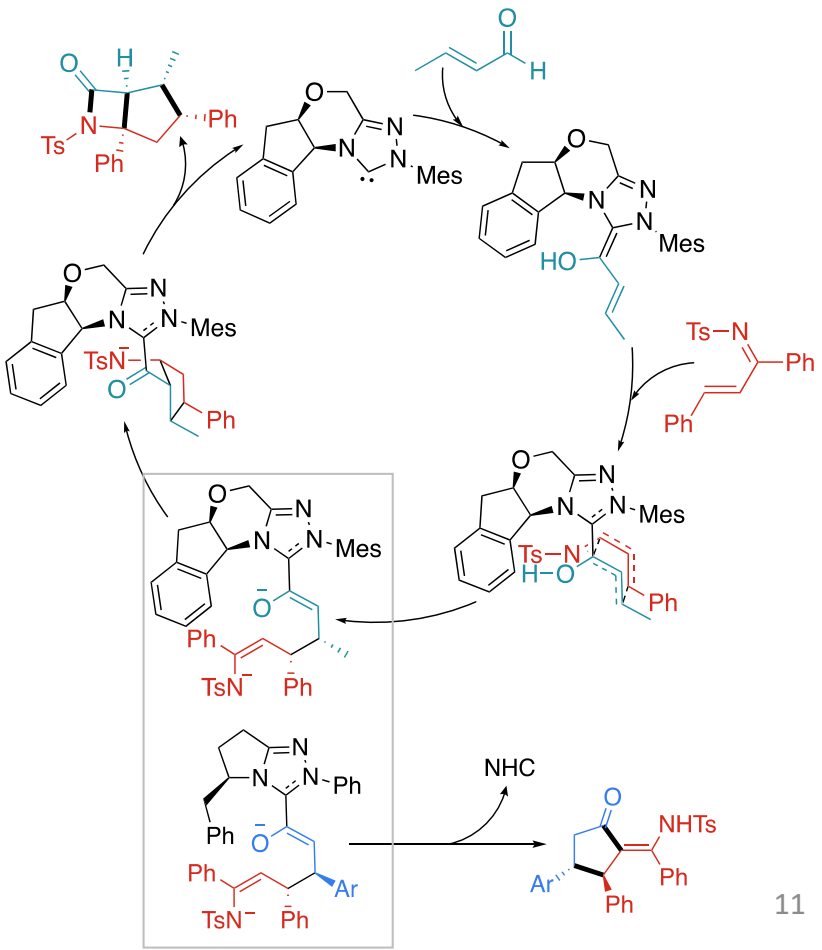


94%, 10:1 dr, 99% ee

Chi:



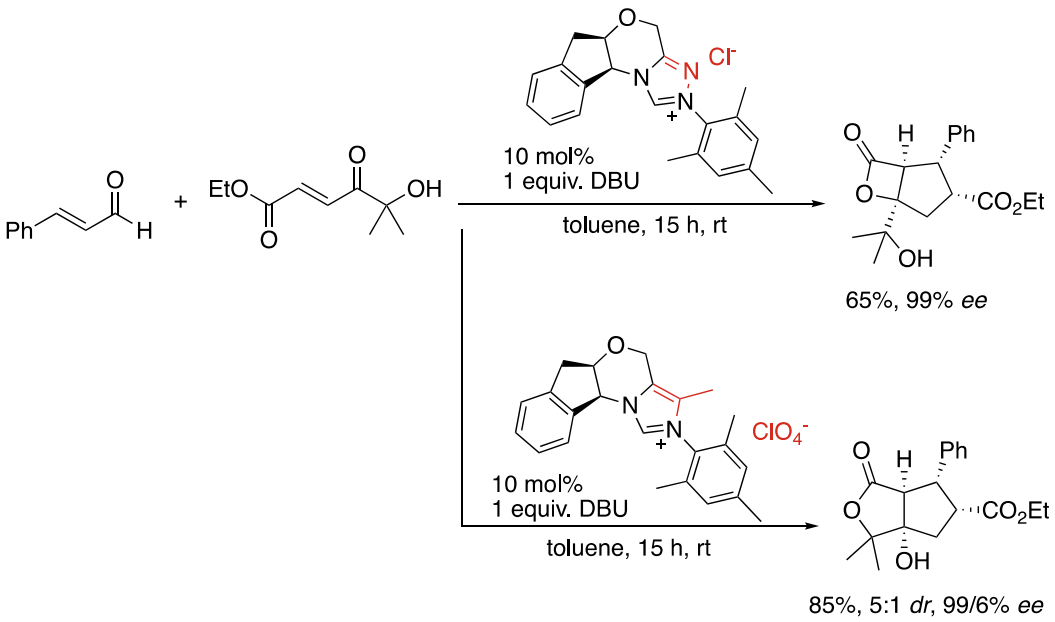
94%, 10:1 dr, 99% ee

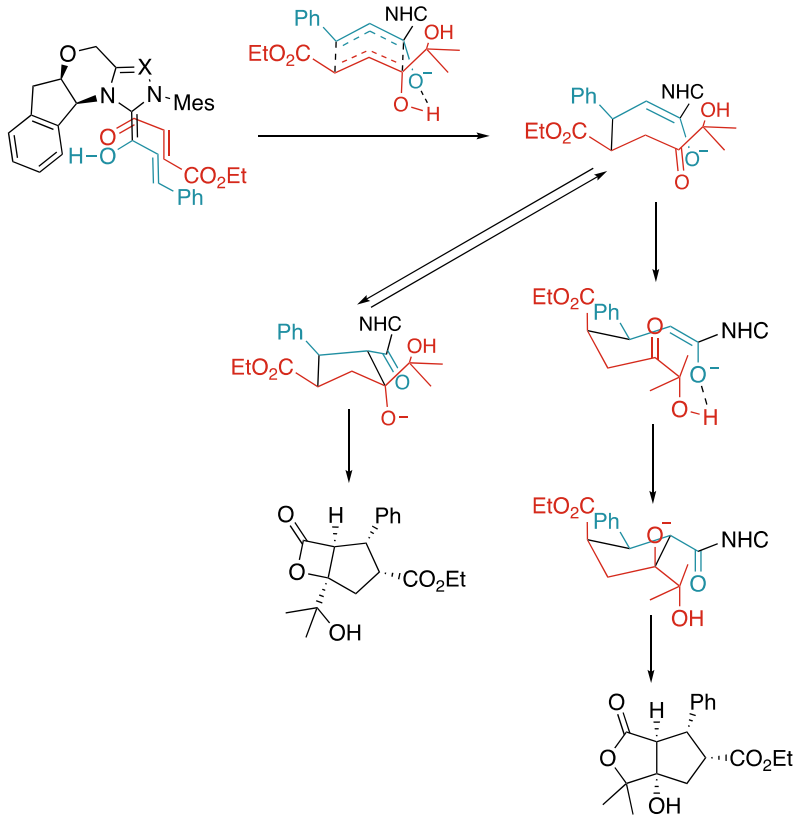


1) M. He, J. W. Bode, *J. Am. Chem. Soc.* **130**, 418–419 (2008), 2) X. Chen, X. Fang, Y. R. Chi, *Chem. Sci.* **4**, 2613 (2013).

Annulations *via* Formal 1,4-Additions

Bode:





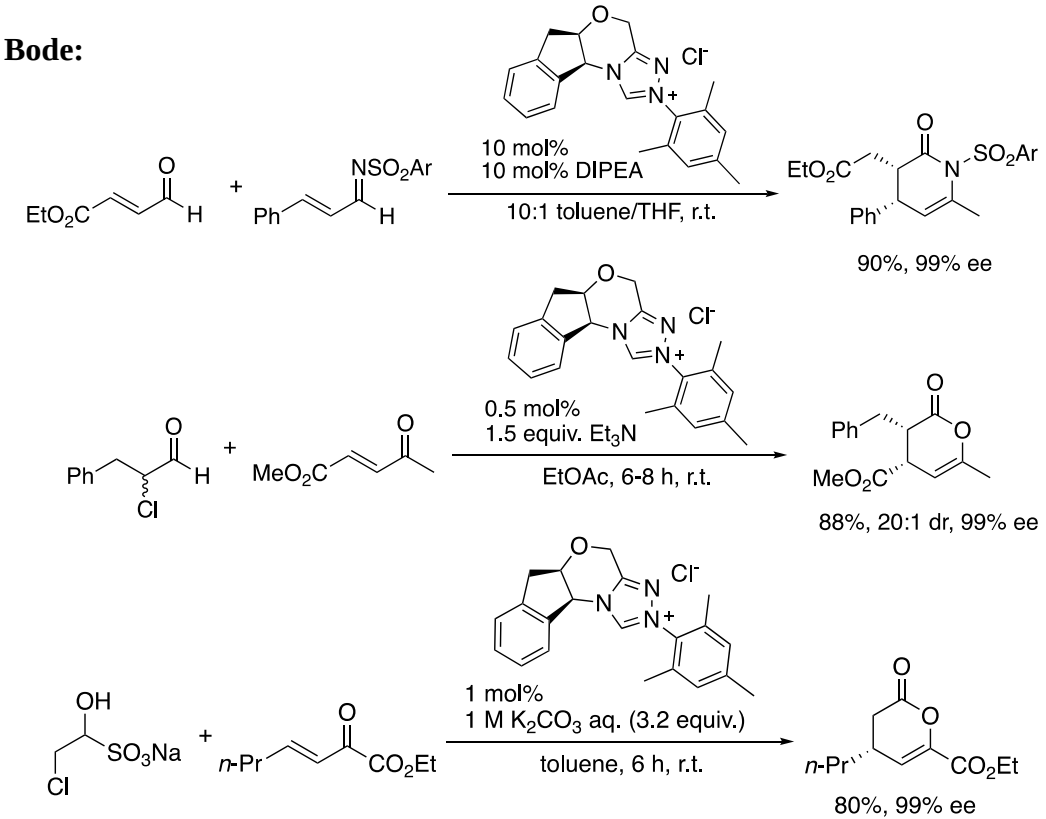
J. Kaeobamrung, J. W. Bode, *Org. Lett.* **11**, 677–680 (2009).

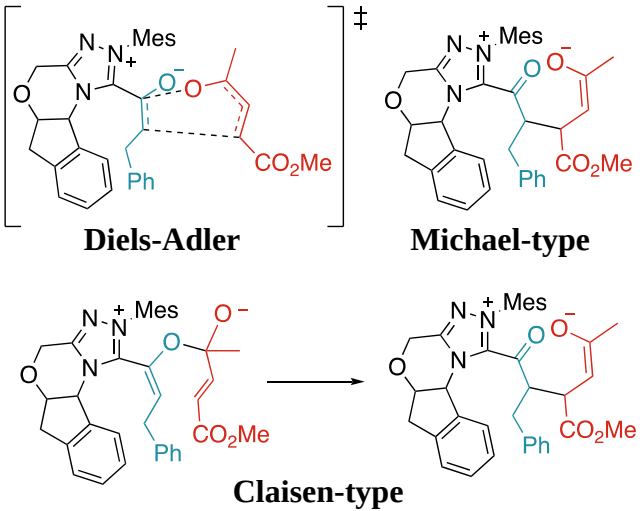
Presentation Outline

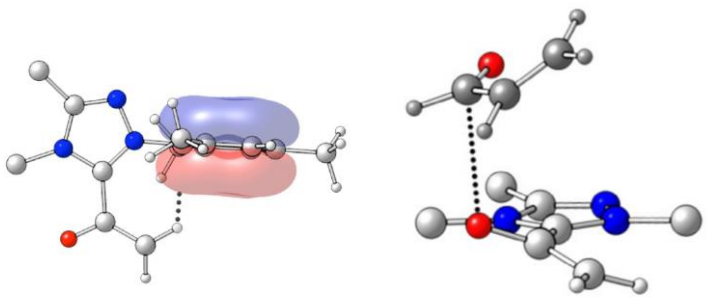
1. Background and Main Innovations
2. Reactivity Overview
3. Selected Examples:
    - 3.1. Homoenolate Equivalents
    - 3.2. (Conjugated) Enolate Equivalents
    - 3.3. α,β-Unsaturated Acyl Azoliums
    - 3.4 Cooperative NHC/Metal Catalysis
4. Conclusion and Questions

[4+2] Annulations

Bode:



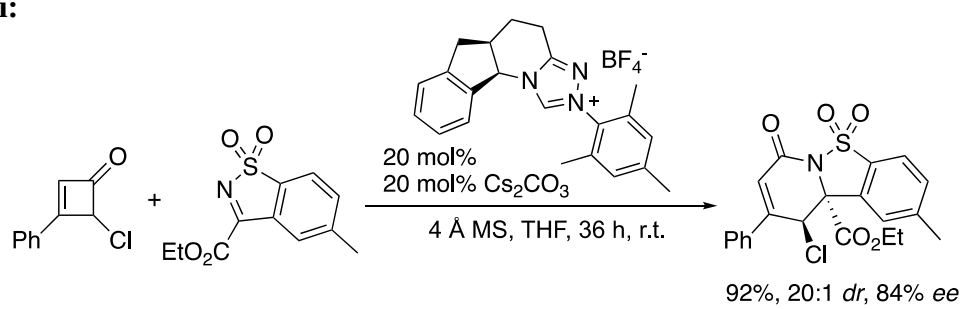


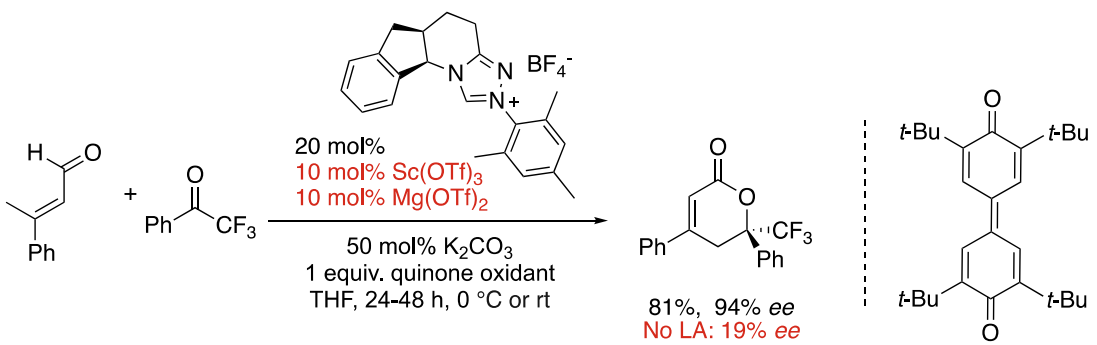


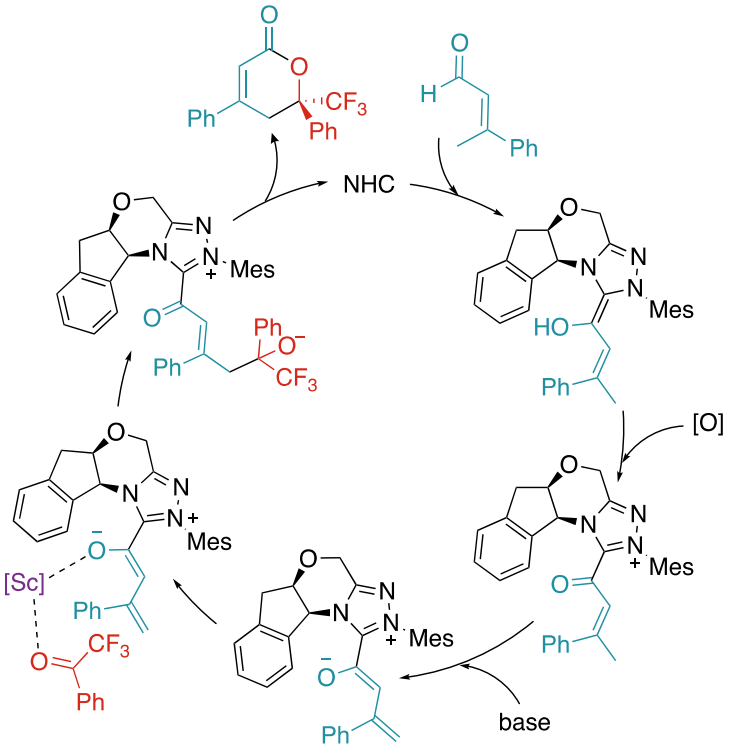
1) M. He, J. R. Struble, J. W. Bode, *J. Am. Chem. Soc.* **128**, 8418–8420 (2006). 2) M. He, G. J. Uc, J. W. Bode, *J. Am. Chem. Soc.* **128**, 15088–15089 (2006). 3) M. He, B. J. Beahm, J. W. Bode, *Org. Lett.* **10**, 3817–3820 (2008), 4) S. E. Allen, J. Mahatthananchai, J. W. Bode, M. C. Kozlowski, *J. Am. Chem. Soc.* **134**, 12098–12103 (2012).

[4+2] Annulations

Chi:





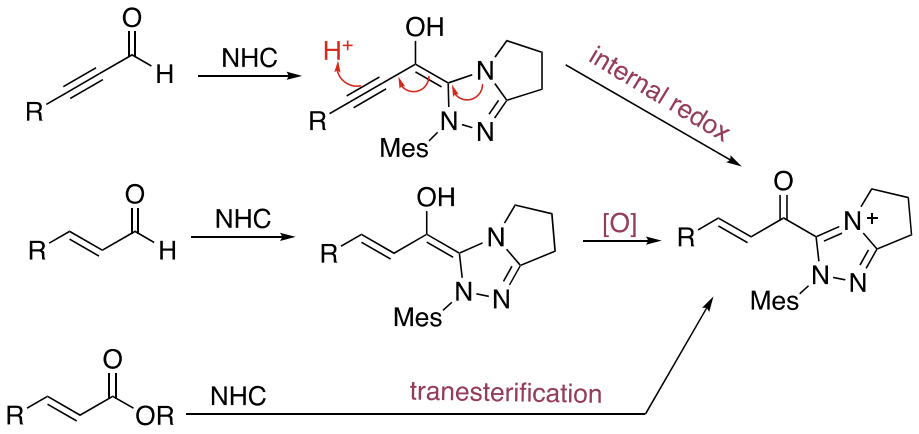


1) B.-S. Li *et al.*, *Nat Commun.* **6**, 6207 (2015)., 2) J. Mo, X. Chen, Y. R. Chi, *J. Am. Chem. Soc.* **134**, 8810–8813 (2012).

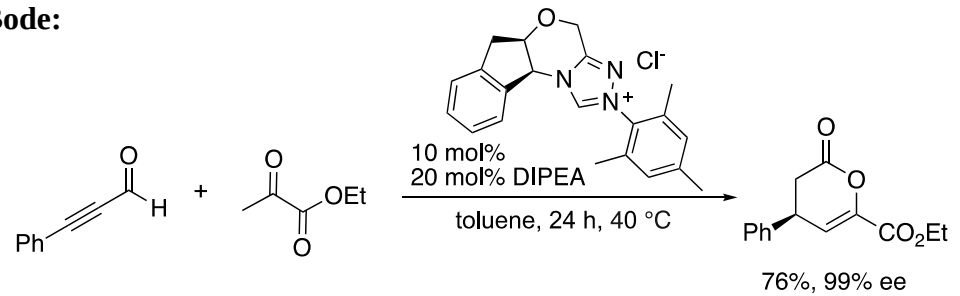
Presentation Outline

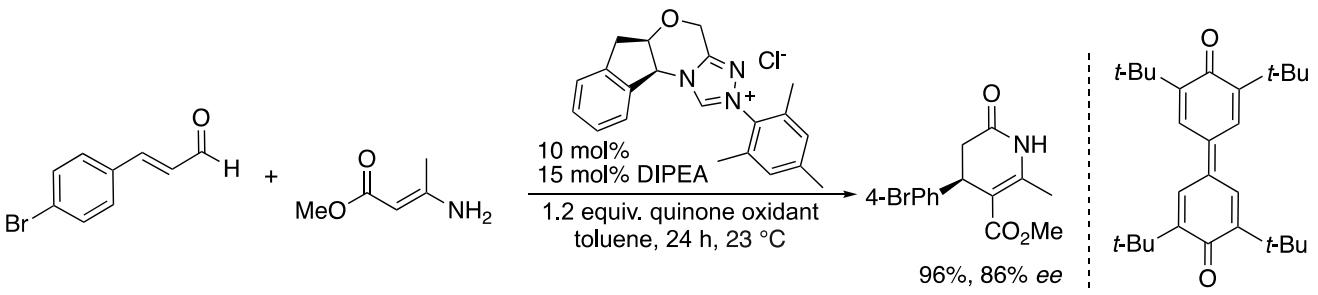
1. Background and Main Innovations
2. Reactivity Overview
3. Selected Examples:
    - 3.1. Homoenolate Equivalents
    - 3.2. (Conjugated) Enolate Equivalents
    - 3.3. α,β-Unsaturated Acyl Azoliums
    - 3.4 Cooperative NHC/Metal Catalysis
4. Conclusion and Questions

Activated Carboxylate Equivalents



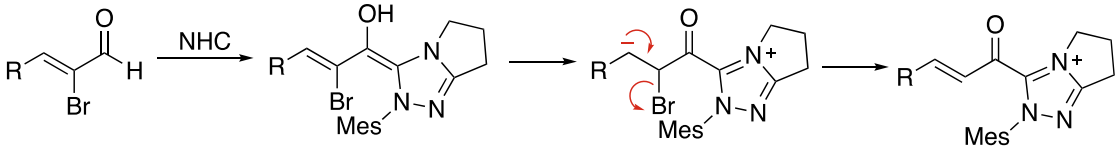
Bode:



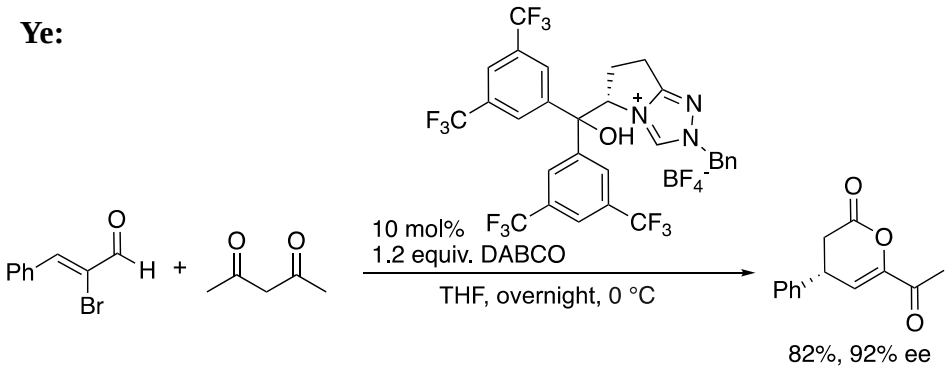


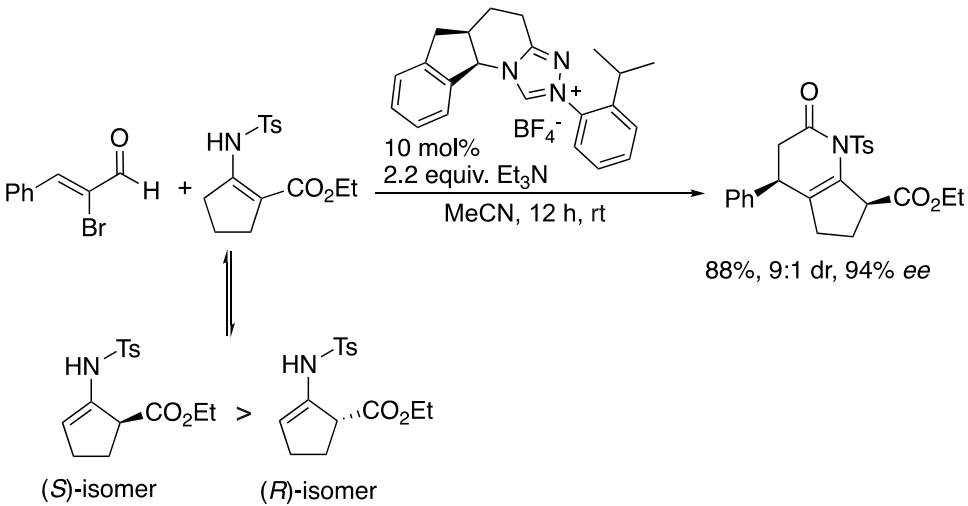
1) B. Wanner, J. Mahatthananchai, J. W. Bode, *Org. Lett.* **13**, 5378–5381 (2011)., 2) J. Kaeobamrung, J. Mahatthananchai, P. Zheng, J. W. Bode, *J. Am. Chem. Soc.* **132**, 8810–8812 (2010).

Bromoenal Substrates



Ye:

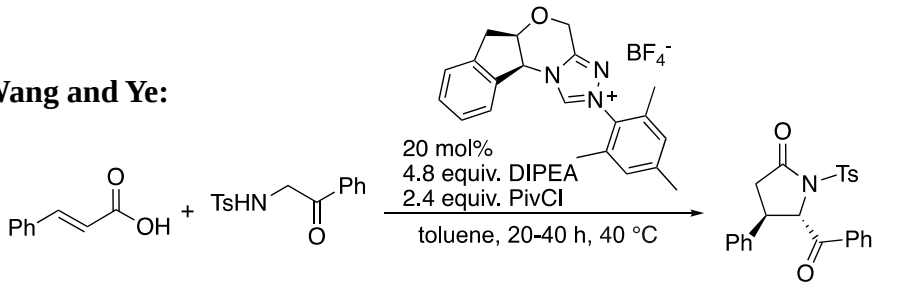




1) F.-G. Sun, L.-H. Sun, S. Ye, *Adv. Synth. Catal.* **353**, 3134–3138 (2011). 2) K. Chen, Z. Gao, S. Ye, *Angew. Chem.* **131**, 1195–1199 (2019).

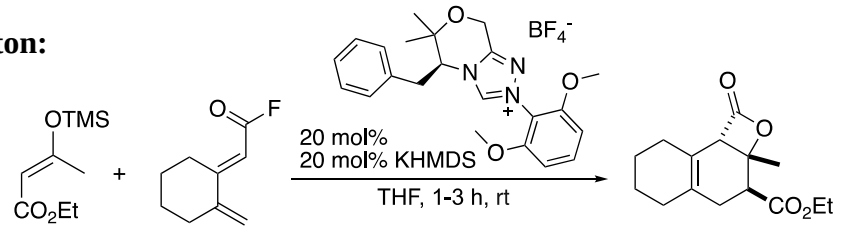
Acids and Acyl Fluorides

Wang and Ye:

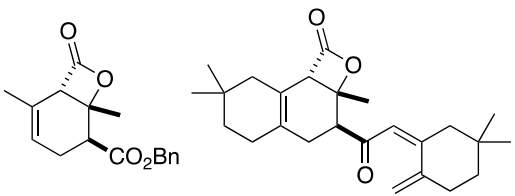


64%, 5:1 dr, 96% ee

Lupton:



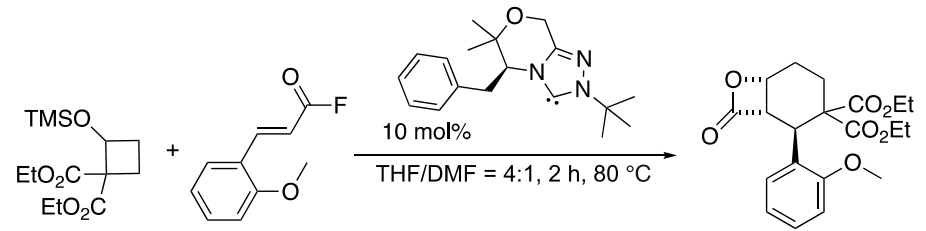
55%, >20:1 dr, 94% *ee*



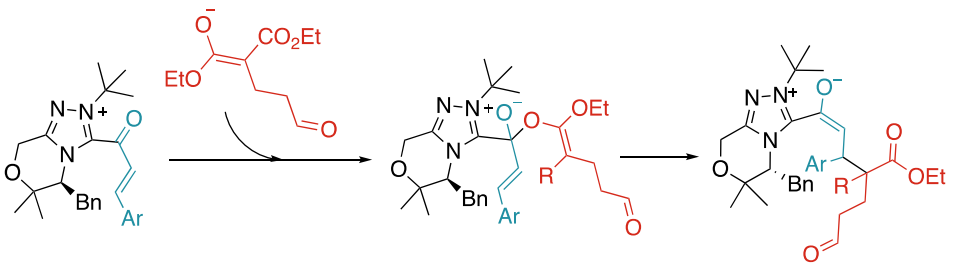
45%, >20:1 dr, 92% *ee*

68%, >20:1 dr, 92% *ee*

Lupton:



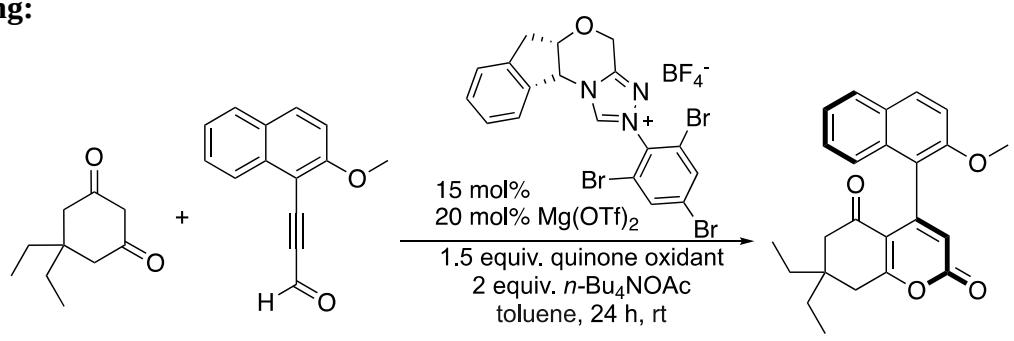
87%, >20:1 dr, 94% *ee*



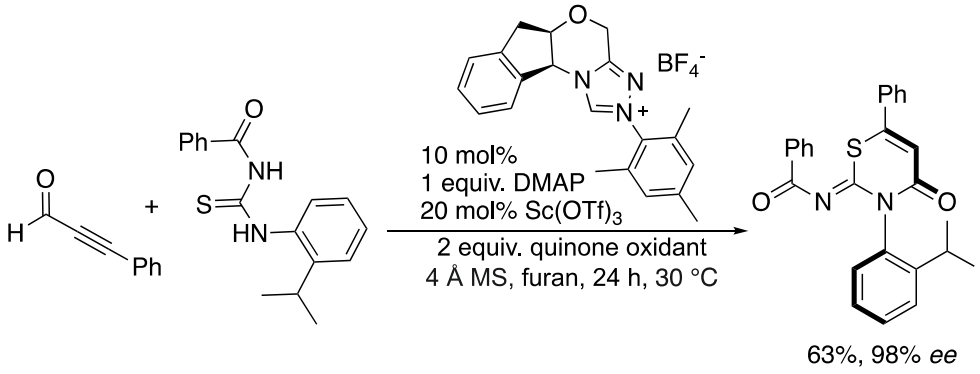
1) A. Lee *et al.*, *Angew. Chem.* **131**, 6002–6006 (2019). 2) A. Levens, A. Ametovski, D. W. Lupton, *Angew. Chem. Int. Ed.* **55**, 16136–16140 (2016). 3) R. M. Gillard, J. E. M. Fernando, D. W. Lupton, *Angew. Chem. Int. Ed.* **57**, 4712–4716 (2018).

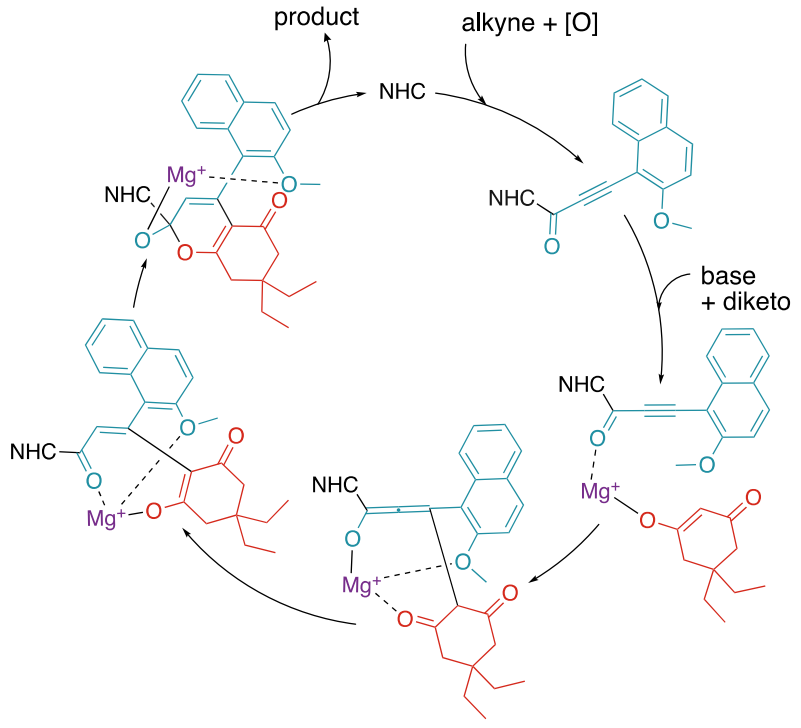
Alkynyl Acyl Azoliums

Wang:



Jin:





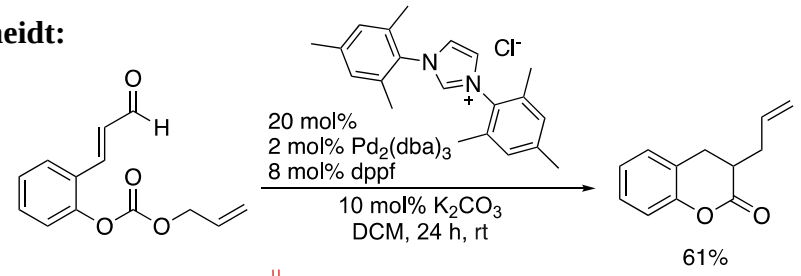
1) C. Zhao *et al.*, *Nat Commun.* **9**, 611 (2018). 2) T. Li *et al.*, *Angew. Chem.* **133**, 9448–9453 (2021).

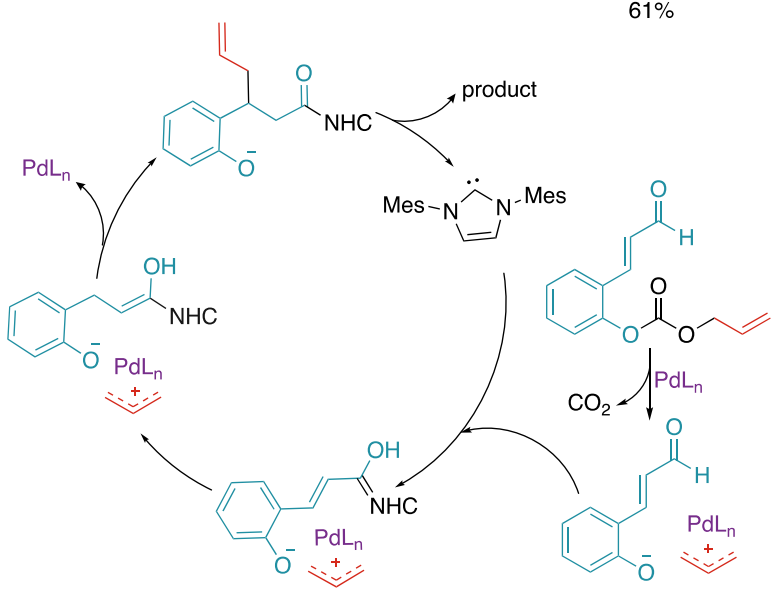
Presentation Outline

1. Background and Main Innovations
2. Reactivity Overview
3. Selected Examples:
    - 3.1. Homoenolate Equivalents
    - 3.2. (Conjugated) Enolate Equivalents
    - 3.3. α,β-Unsaturated Acyl Azoliums
    - 3.4 Cooperative NHC/Metal Catalysis
4. Conclusion and Questions

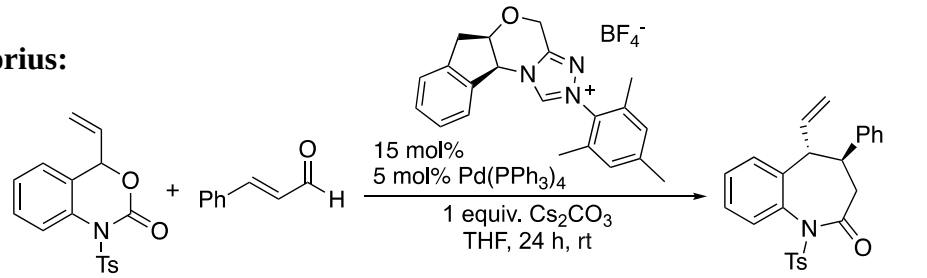
Cooperative NHC/Pd Catalysis

Scheidt:

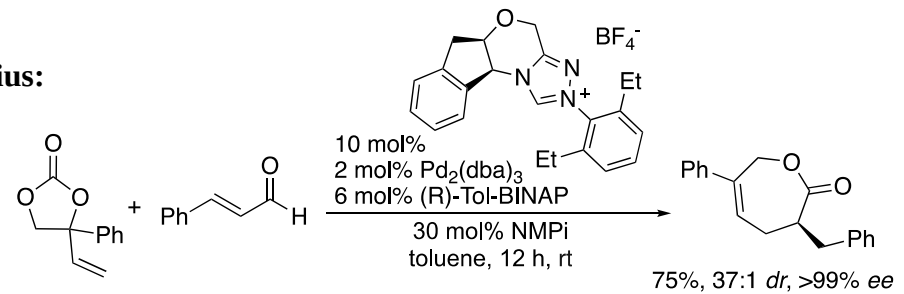


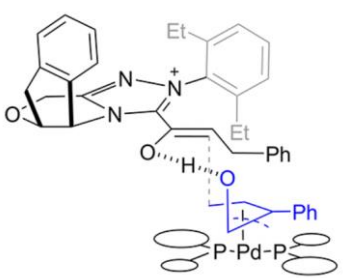


Glorius:



Glorius:

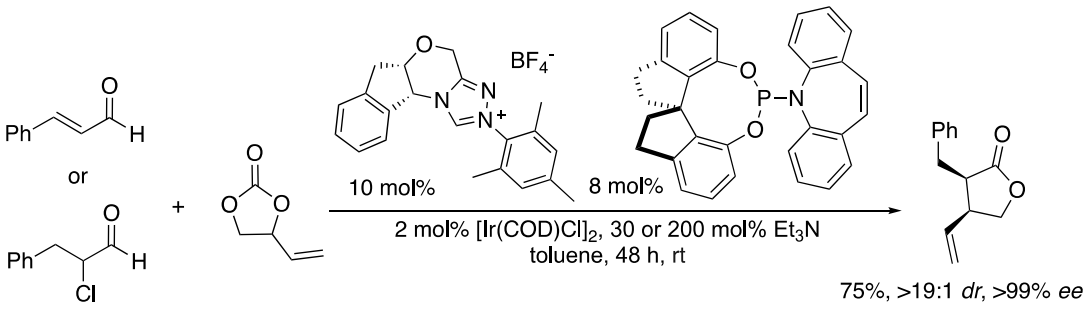


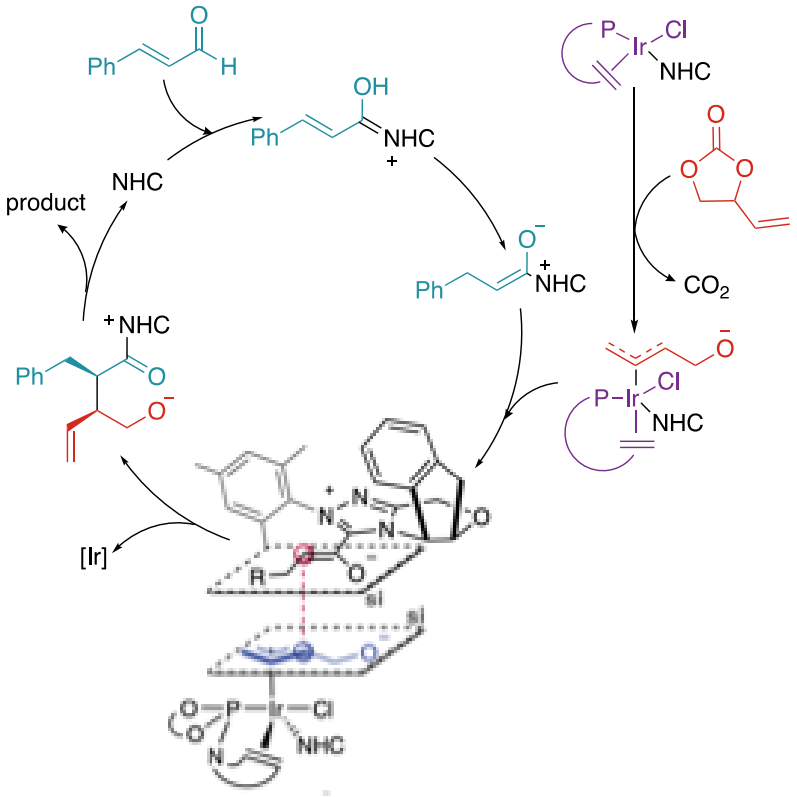


1) K. Liu, M. T. Hovey, K. A. Scheidt, *Chem. Sci.* **5**, 4026 (2014). 2) C. Guo, M. Fleige, D. Janssen-Müller, C. G. Daniliuc, F. Glorius, *J. Am. Chem. Soc.* **138**, 7840–7843 (2016). 3) S. Singha, T. Patra, C. G. Daniliuc, F. Glorius, *J. Am. Chem. Soc.* **140**, 3551–3554 (2018).

Cooperative NHC/Ir Catalysis

Glorius:





S. Singha, E. Serrano, S. Mondal, C. G. Daniliuc, F. Glorius, *Nat Catal*. **3**, 48–54 (2020).

Conclusion and Outlook

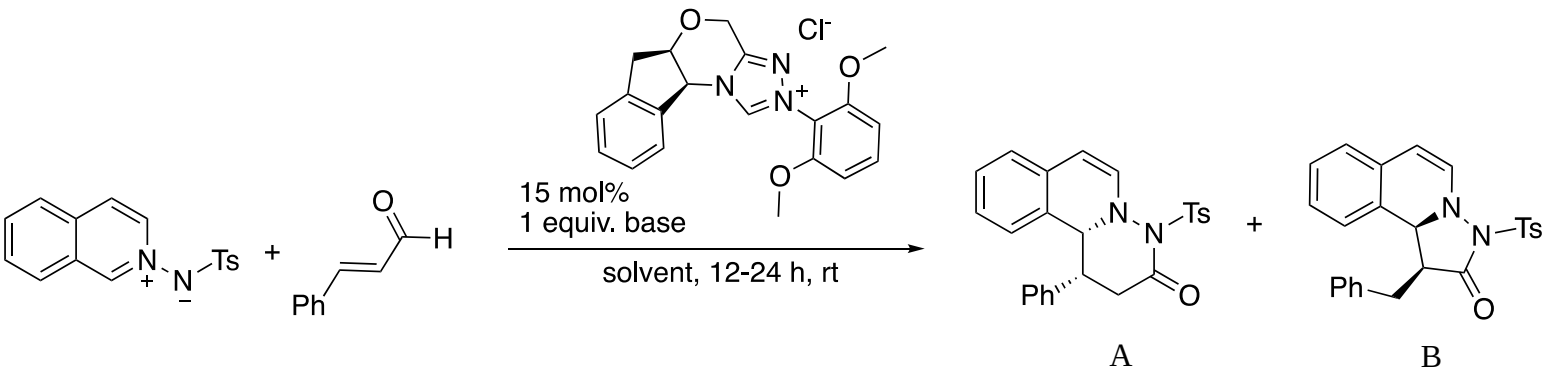
1. *N*-mesityl catalysts as (one of) the most important developments in the field
2. With essentially one class of catalysts we can drive so many different transformations
3. Since mid 2000's a large number of enantioselective transformations has been reported

4. Further progress needed with "ordinary" ketones and other simple carbonyl electrophiles
5. Further progress in cooperative NHC/metal catalysis

Thank you for your attention!

Questions

Question 1: How would you explain the following switchable selectivity?

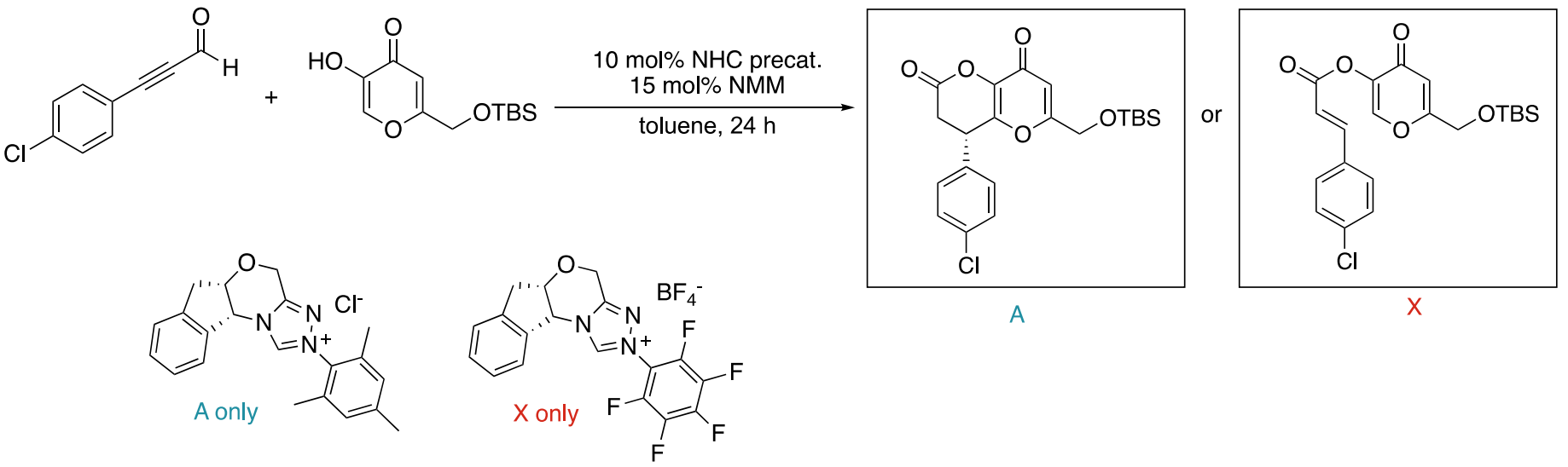


Toluene, K_2CO_3: A/B = 1:10
Toluene, DBU: A/B = 15:1
THF, K_2CO_3: A/B = 10:1

C. Guo, M. Fleige, D. Janssen-Müller, C. G. Daniliuc, F. Glorius, *Nature Chem.* **7**, 842–847 (2015).

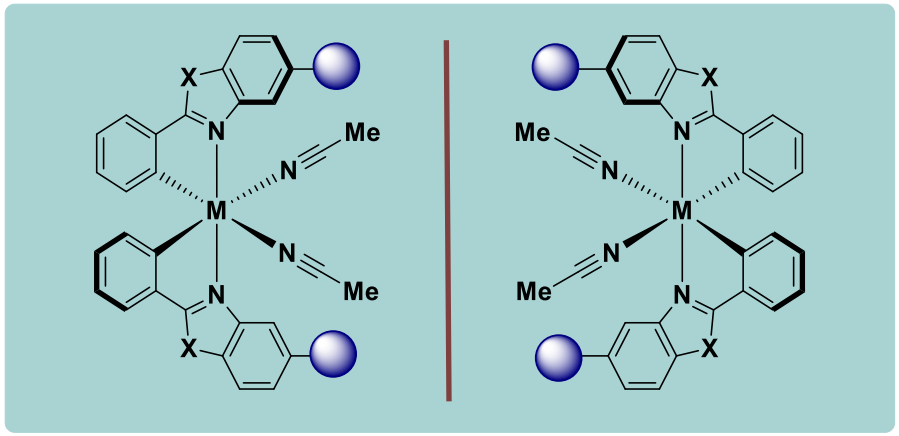
Questions

Question 2: Products? How can you explain the difference in reaction outcomes?



J. Kaeobamrung, J. Mahatthananchai, P. Zheng, J. W. Bode, *J. Am. Chem. Soc.* **132**, 8810–8812 (2010).

Application of Octahedral Metal-Centered Chirality based on Heterocyclic Ligands in Asymmetric Catalysis

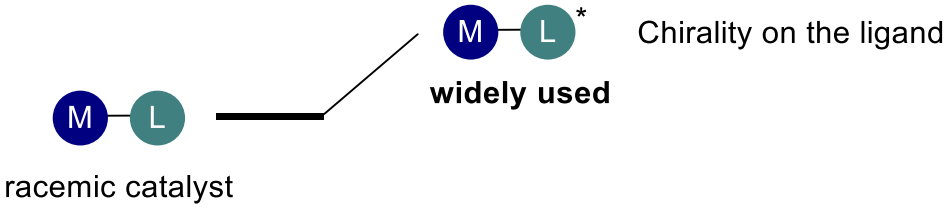


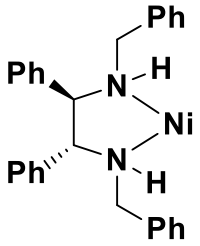
Xingyu Liu

20/05/2021

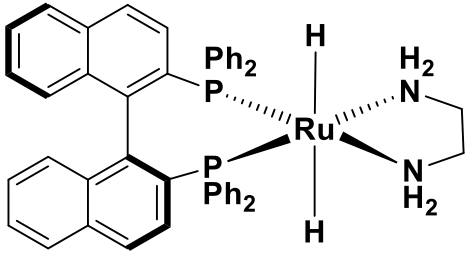
Table of content

1. Metal-assisted enantioselective reaction

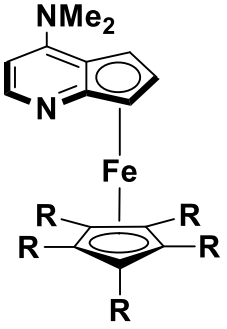




Kobayashi
Central Chirality



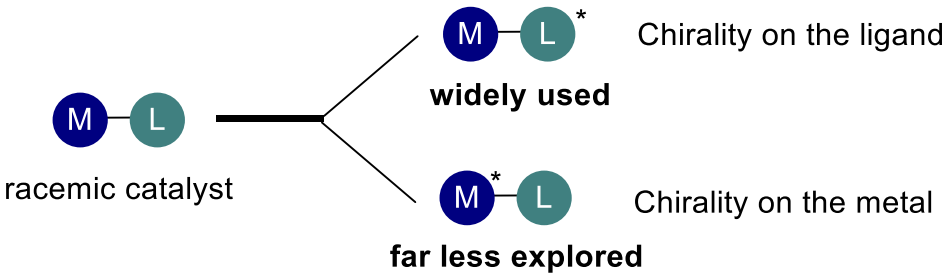
Noyori
Atropisomeric Chirality

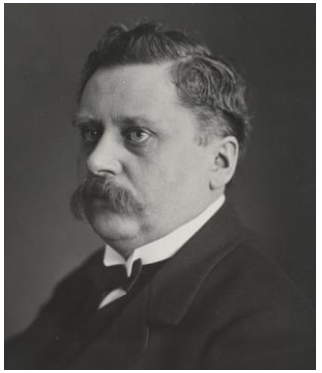


Fu
Planar Chirality

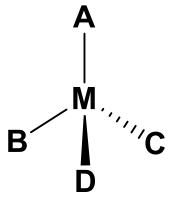
Review: *Catal. Sci. Technol*., **2015**, *5*, 3441.
Top. Organomet. Chem. **2005**, *15*, 271.

1. Metal-assisted enantioselective catalytic reaction

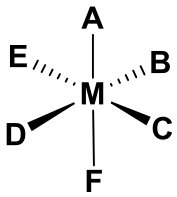




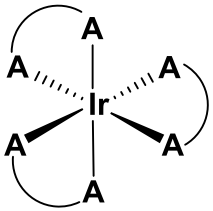
Alfred Werner



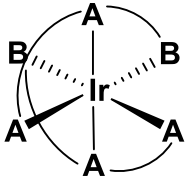
Tetrahedral



Octahedral



Bidentate



Tridentate

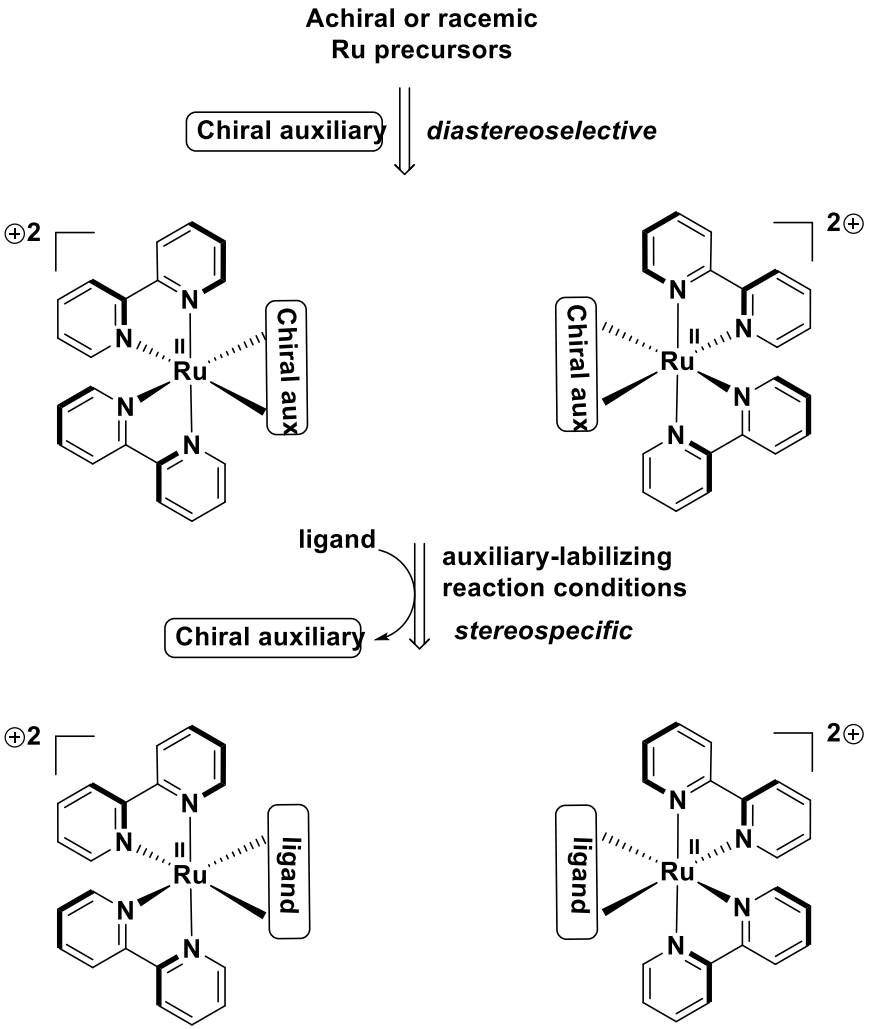
Central Chirality (*R/S*)

Propeller chirality (Λ/Δ)

Werner, A. On the constitution and configuration of compounds of a higher order. *From Nobel Lectures, Chemistry 1901*.

2. Synthesis of chiral-at-metal complexes

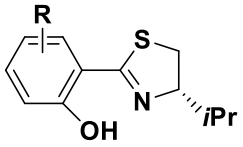
Chiral induction with chiral auxiliaries

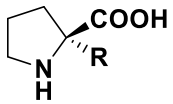


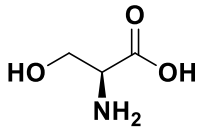
Chem. Eur. J. **2010,** *16*, 752.

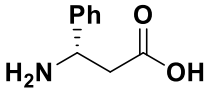
Commonly used chiral auxiliaries

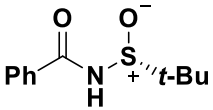
Bidentate ligand

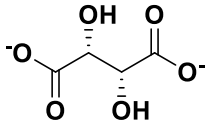






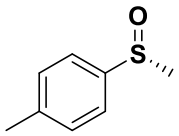






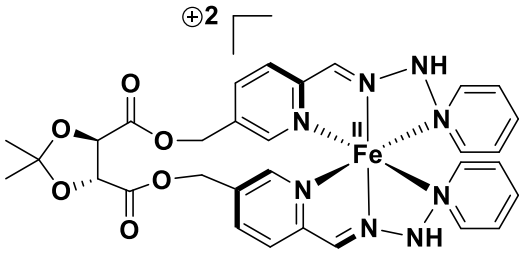
Monodentate ligand

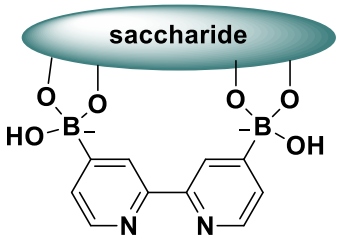
Hydrogen bonding



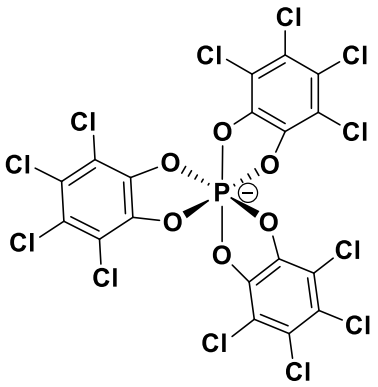
π-π interaction

Cleavable chiral linkers



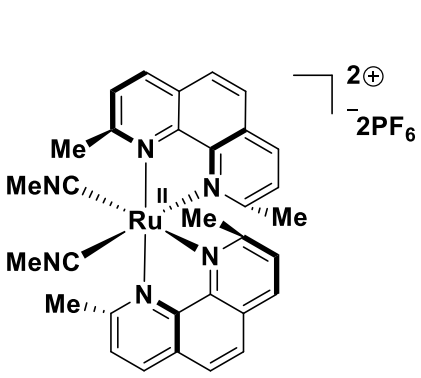


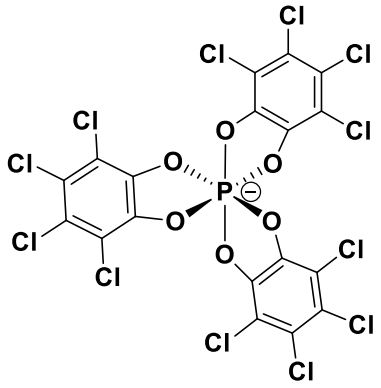
Chiral anion

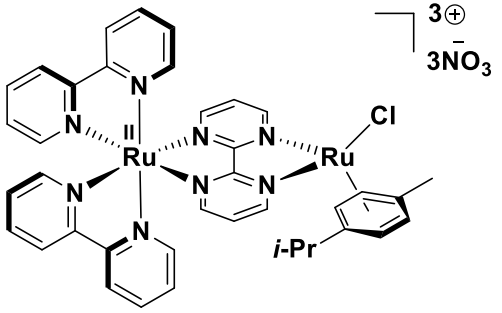


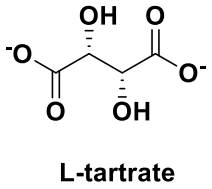
Δ-TRISPHAT

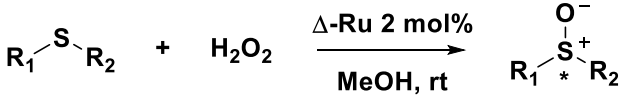
3.1 Early attempts in asymmetric catalysis

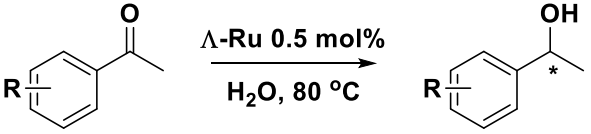


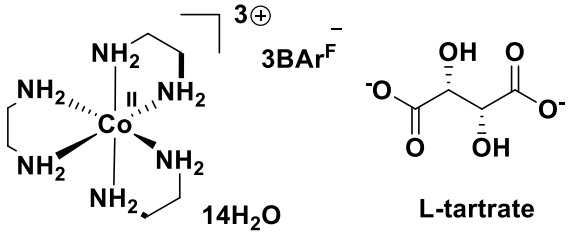


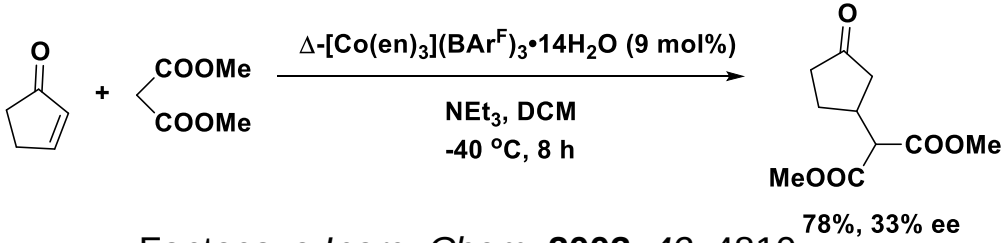






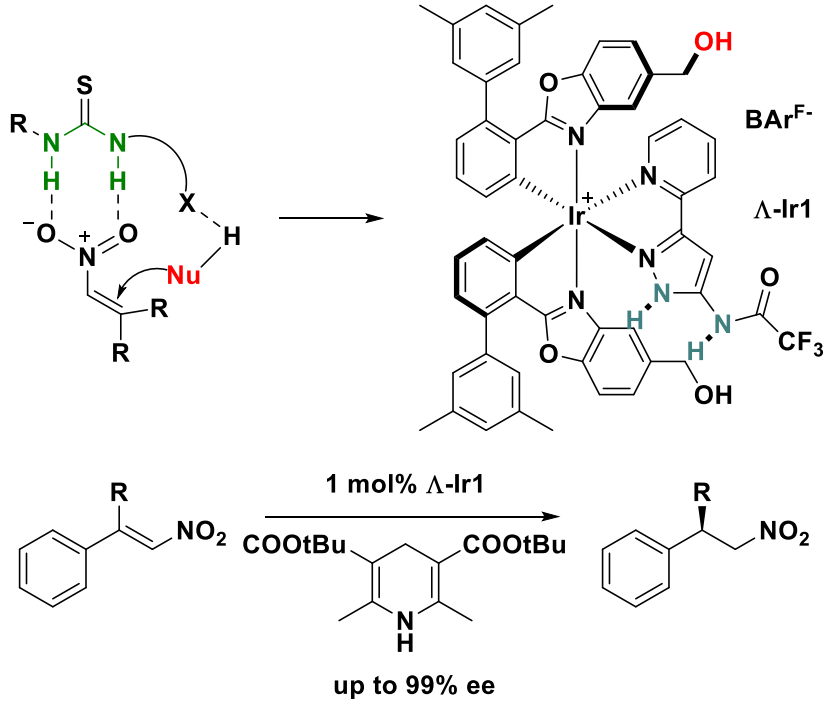


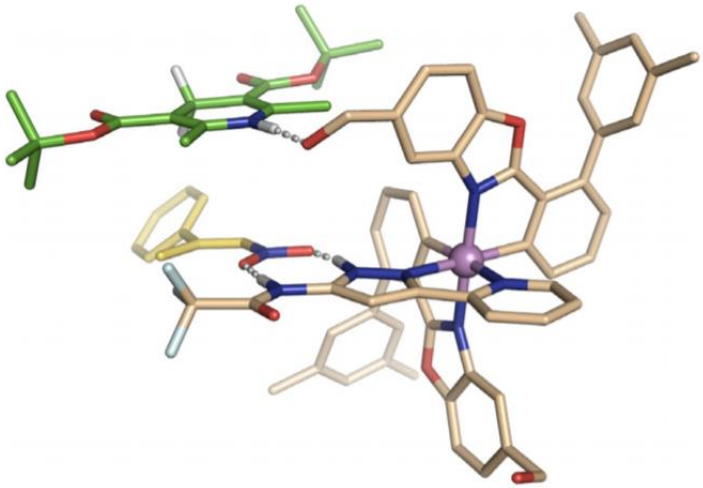




Fontecave *Inorg. Chem.* **2003**, *42*, 4810.
Inorg. Chem. **2007**, *46*, 5354.
Gladysz *Chem. Eur. J.* **2008**, *14*, 5397.

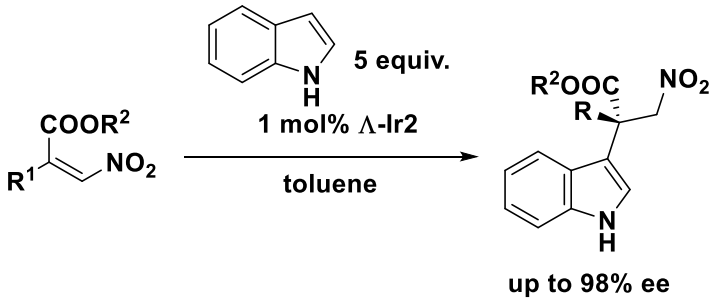
3.2 Simulation of organocatalyst

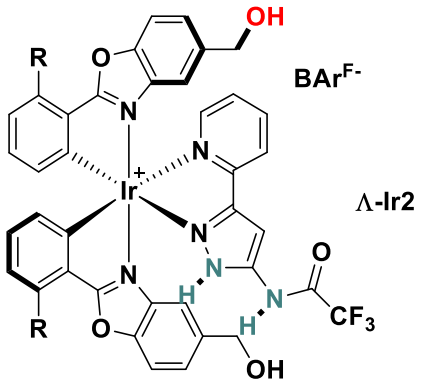


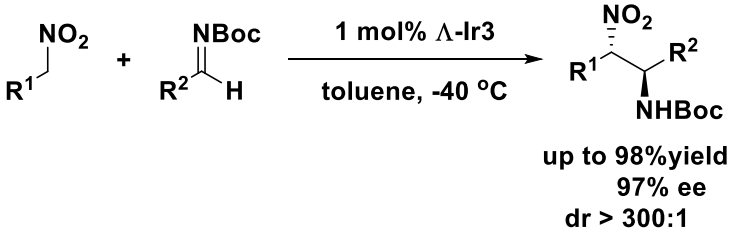


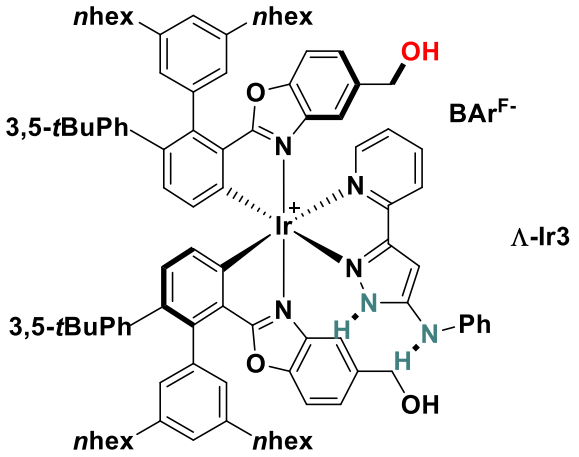
Eric, Meggers, *J. Am. Chem. Soc.* **2013**, *135*, 10598.

3.2 Simulation of organocatalyst







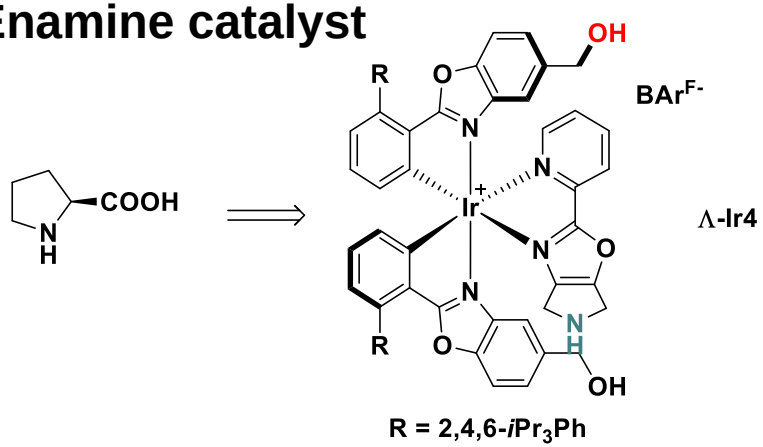


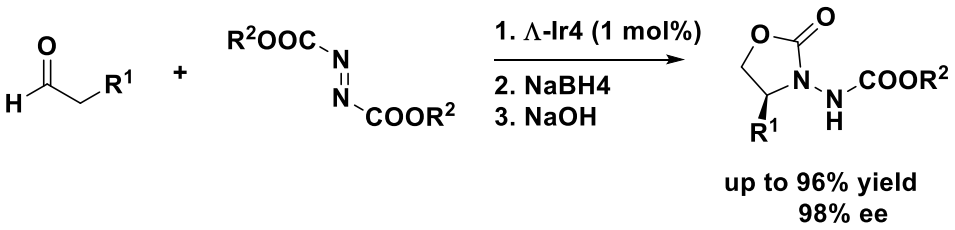
Ir1 and Ir2 didn't catalyze this reaction

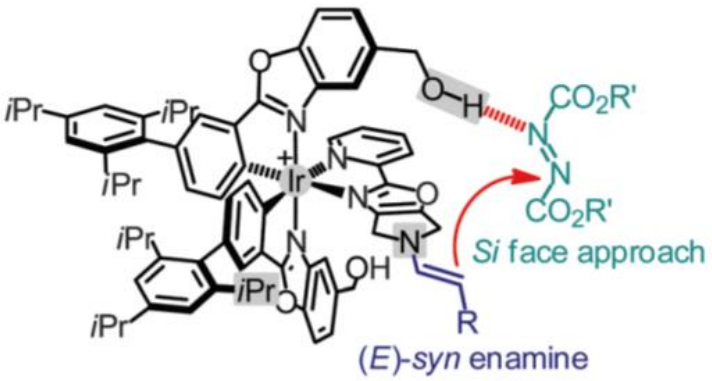
Angew. Chem. Int. Ed. **2013**, *52*, 14021, *Nat. Commun.* **2014**, *5*, 4531.

3.2 Simulation of organocatalyst

Enamine catalyst



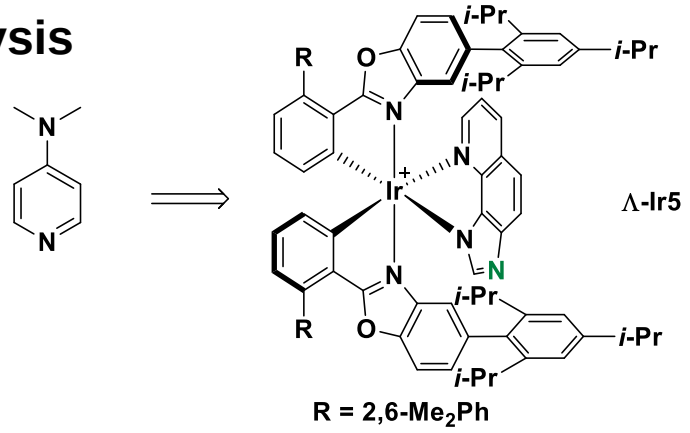


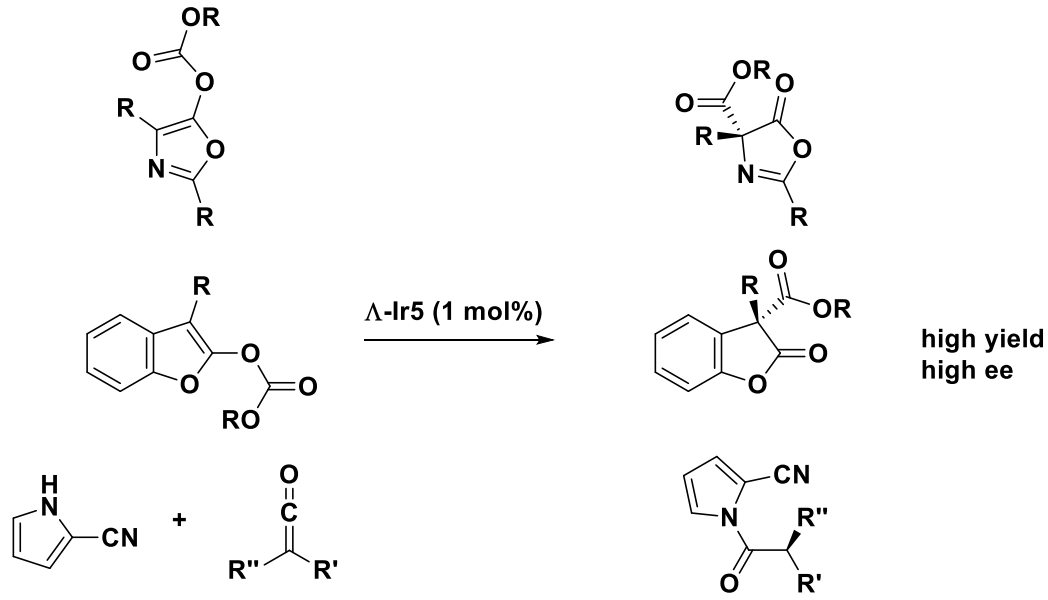


Chem. Commun., **2014**, *50*, 10409.

3.2 Simulation of organocatalyst

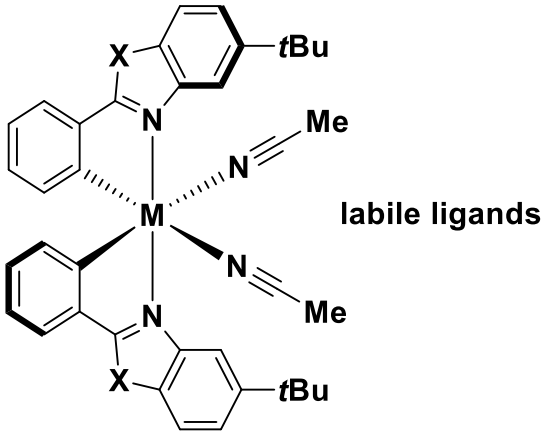
Nucleophilic Catalysis





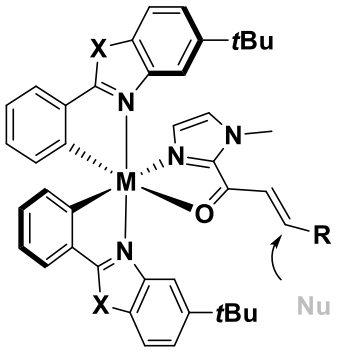
ACS Catal. **2017**, *7*, 5151.

3.3 Chiral Lewis acid catalysis



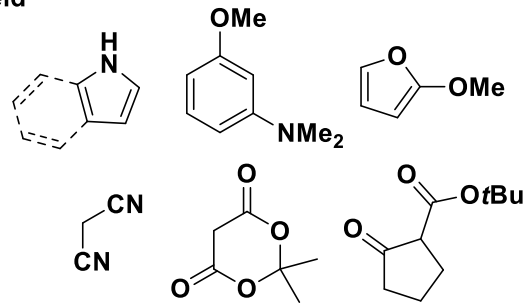
labile ligands

M= Ir, Rh
Rh usually has better ee and yield than Ir

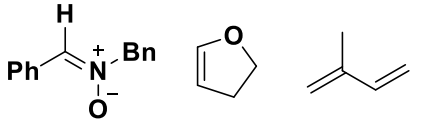


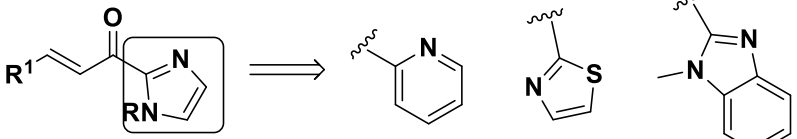
X= O, S
S usually has better ee and yield than O

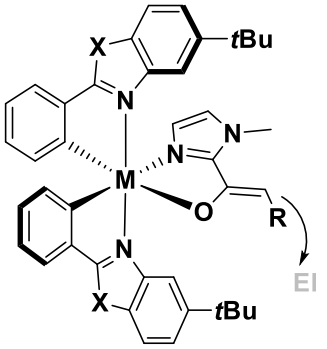
Asymmetric Micheal additions

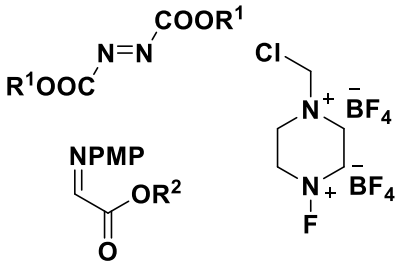


Asymmetric cycloadditions



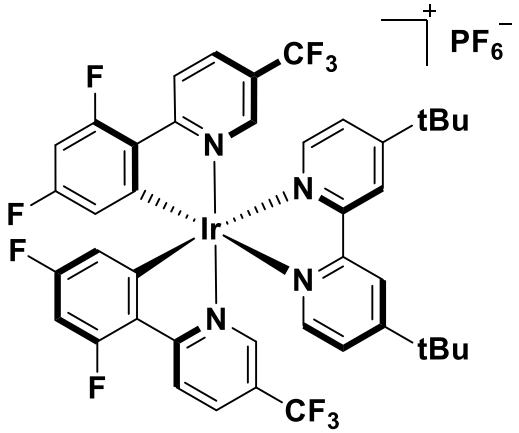




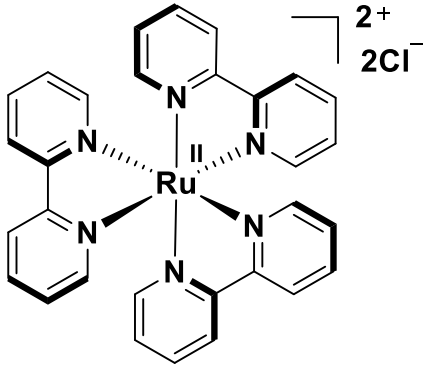


J. Am. Chem. Soc. 2014, 136, 8, 2990, *Chem. Eur. J.* **2015**, *21*, 9720, *Chem. Sci.* **2015**, *6*, 1094. *Chem. Asian J.* **2016**, *11*,3355.

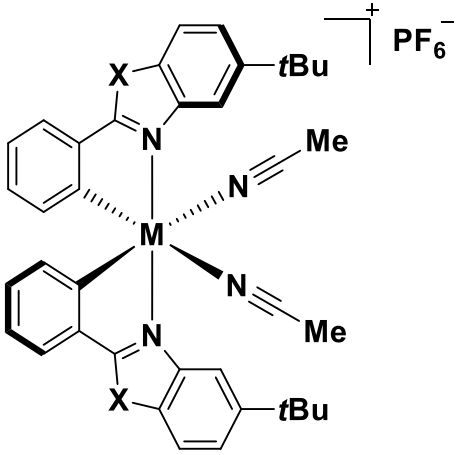
3.4 Visible-light-induced asymmetric reactions

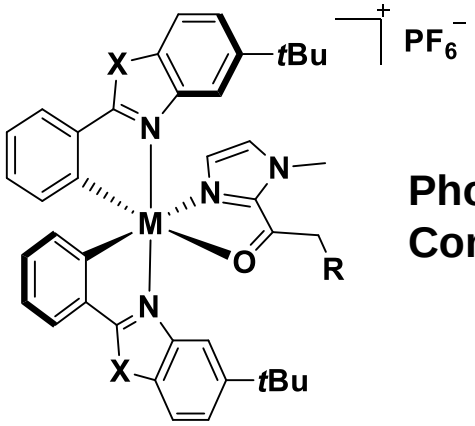


[Ir{dF(CF3)ppy}2(dtbpy)]PF6



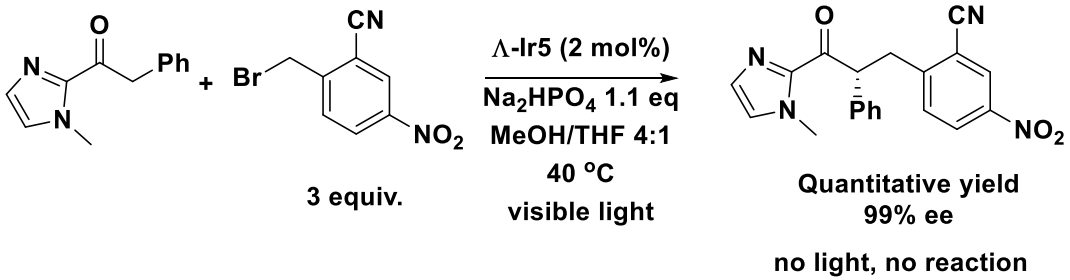
Ru(bpy)3Cl2

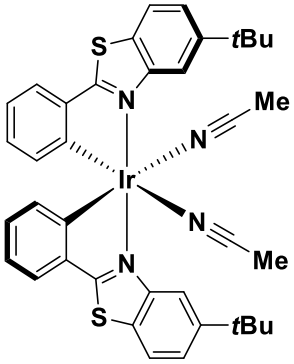




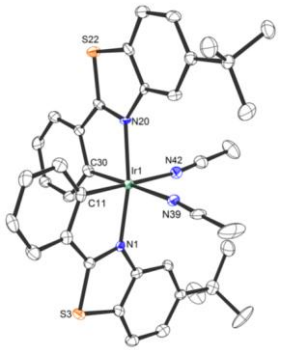
Photosensitizer
Compactible under photoredox condition

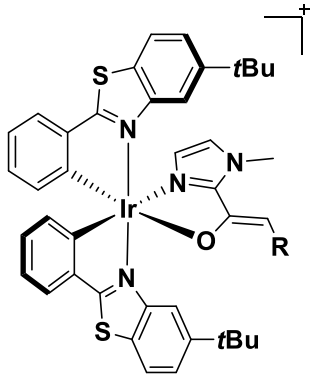
3.4 Visible-light-induced asymmetric reactions



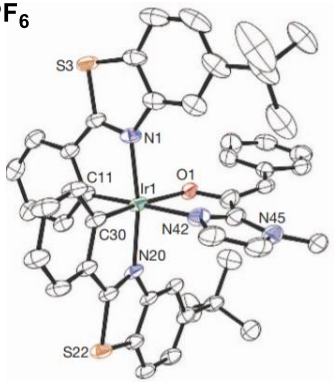


Λ-Ir5



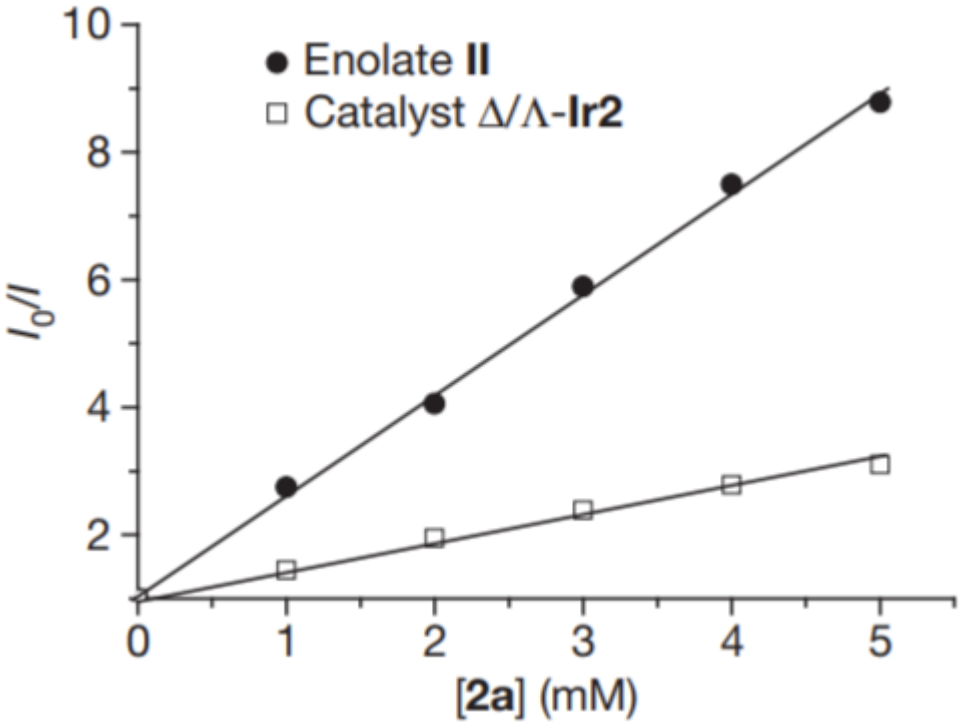


Enolate-Ir5

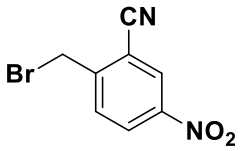


Nature *2014*, **515**, 100.

3.4 Visible-light-induced asymmetric reactions



Stern-Volmer plot

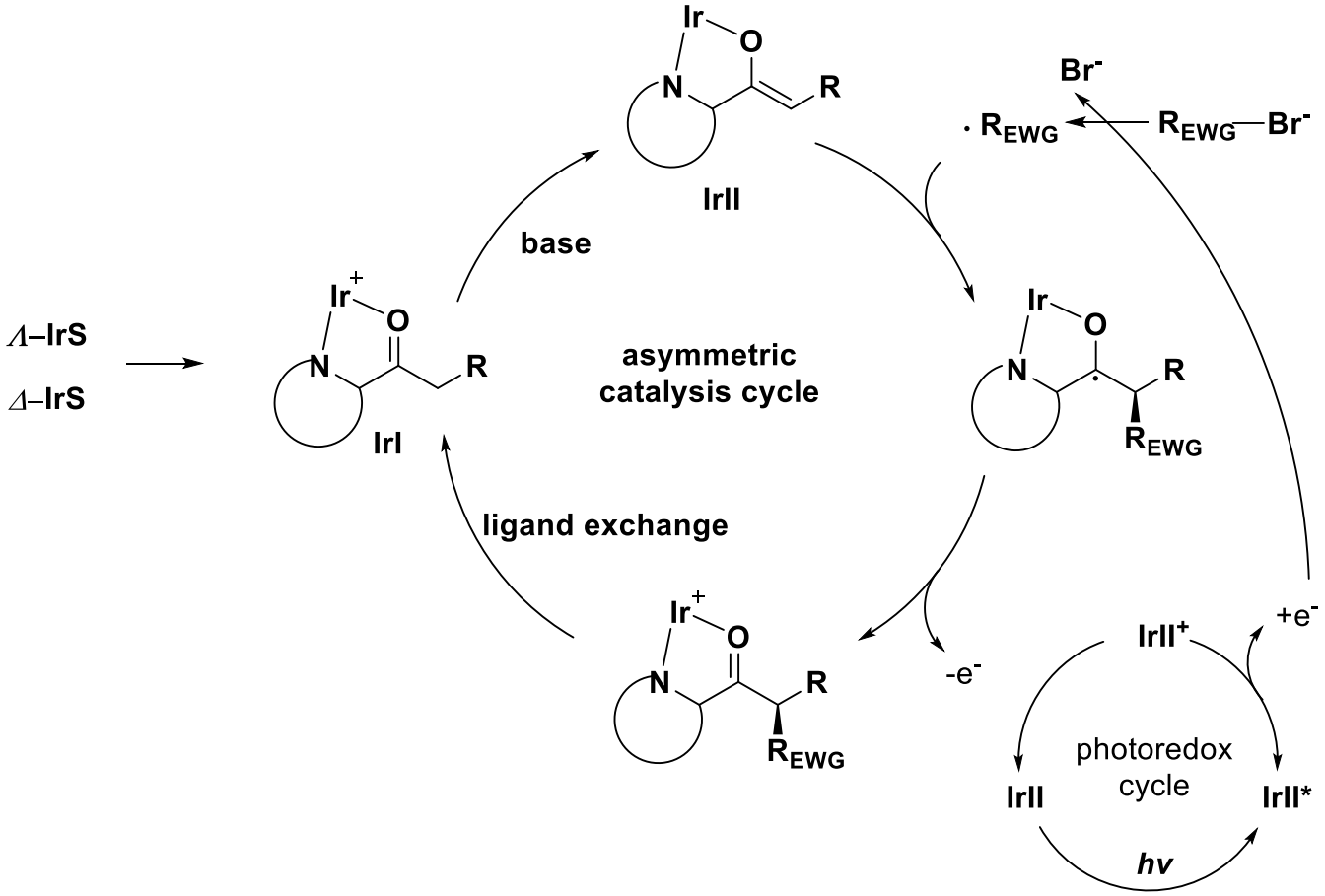


2a

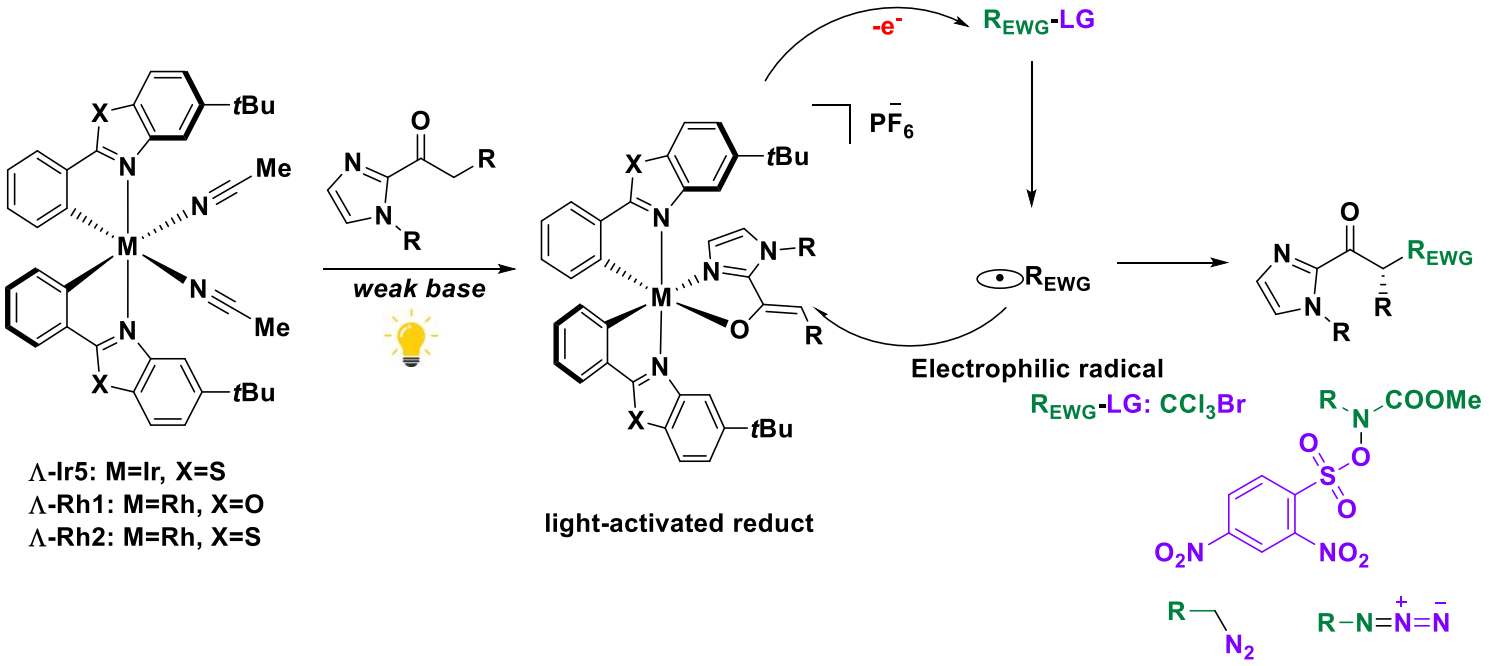
Complex	Absorbance λ_{max}	Emission λ_{max} (E^{00})	$E_{1/2}(PS^+/PS)$	$E_{1/2}(PS^+/PS^*)$
Δ/Λ-**Ir2**	425 nm	560 nm (2.21 eV)	> +1.5 V	> −0.71 V
Enolate **II**	440 nm	550 nm (2.25 eV)	+0.51 V	−1.74 V

3.4 Visible-light-induced asymmetric reactions

Proposed mechanism



3.4 Visible-light-induced asymmetric reactions

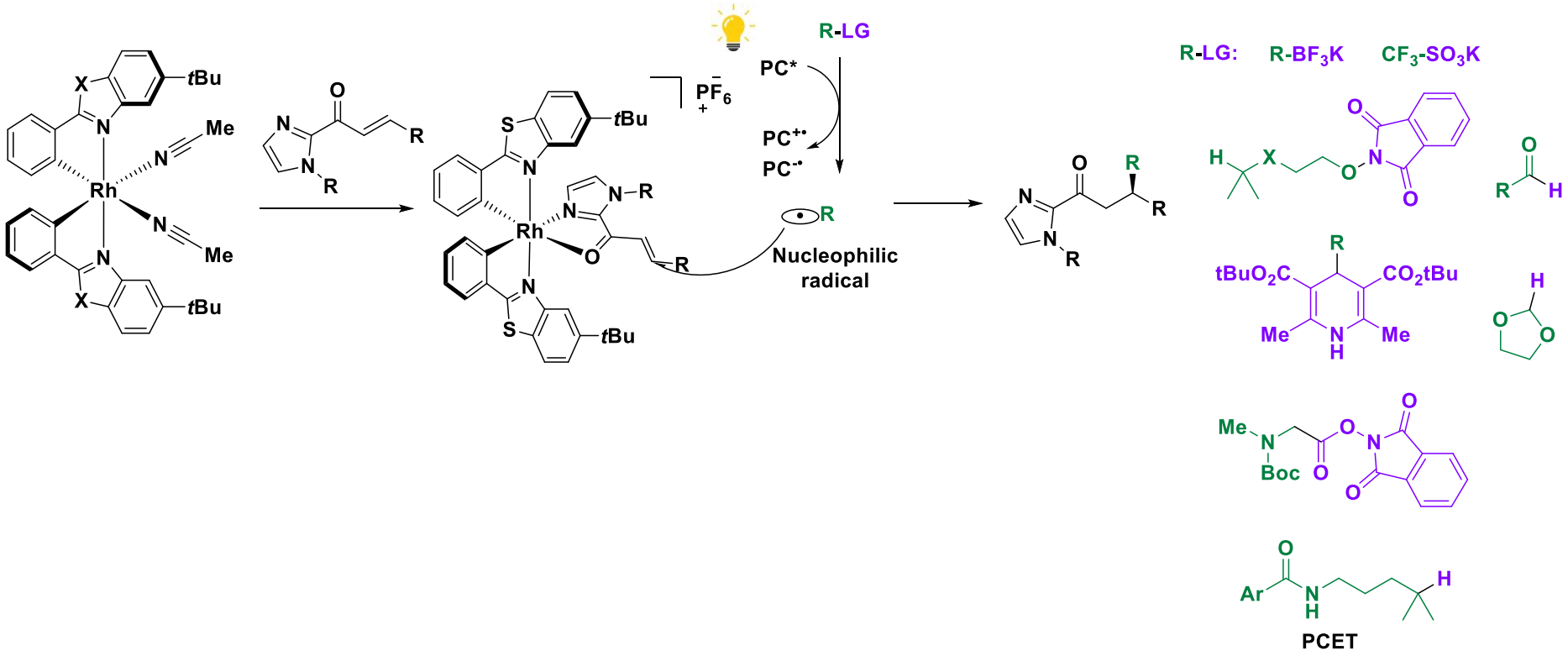


Λ-Ir5: M=Ir, X=S
Λ-Rh1: M=Rh, X=O
Λ-Rh2: M=Rh, X=S

light-activated reduct

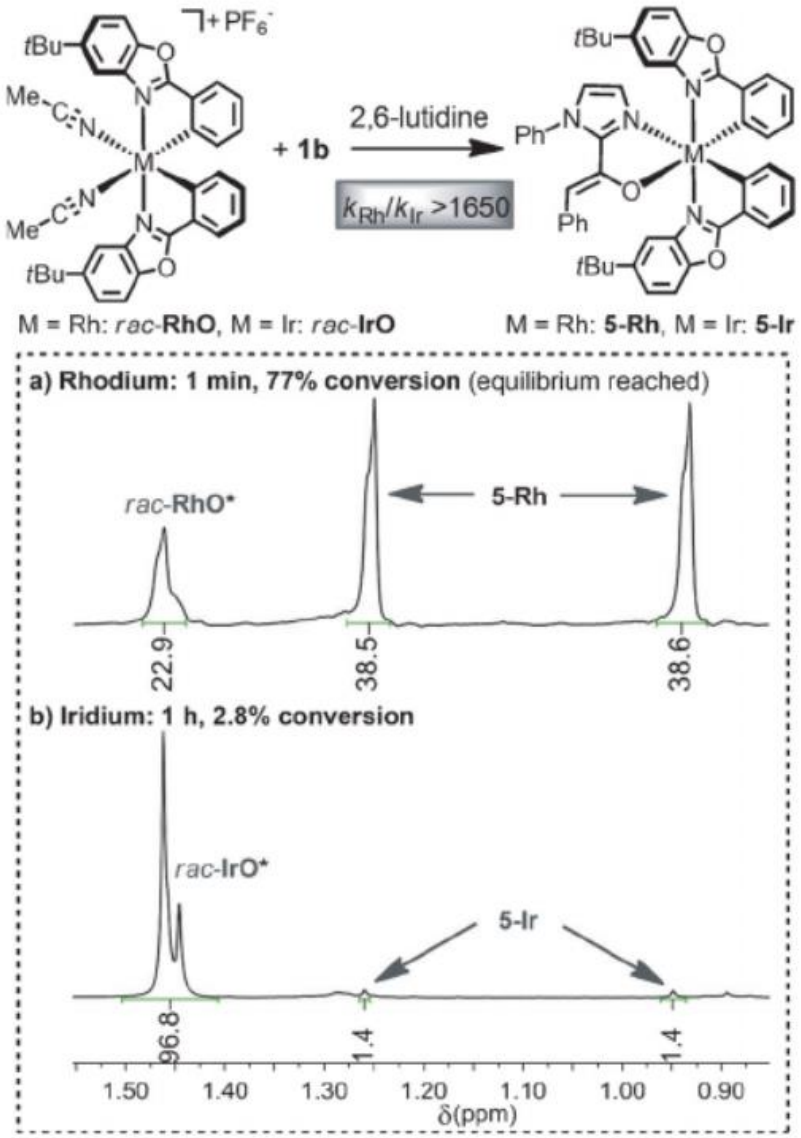
Chem. Eur. J. **2016**, *22*, 9102, *Nat. Protocols* **2018**, *13*, 605,
J. Org. Chem. **2018**, 83, 18, 10922, *J. Am. Chem. Soc.* **2016**, 138, 38, 12636.

3.4 Visible-light-induced asymmetric reactions



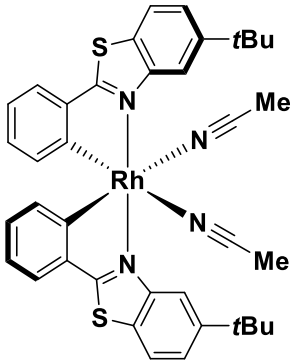
J. Am. Chem. Soc. **2016**, *138*, 6936, *J. Am. Chem. Soc.* **2015**, *137*, 9551, *Angew. Chem. Int. Ed.* **2018**, *57*, 11193. *Angew. Chem., Int. Ed.* **2016**, *55*, 13495, *Angew. Chem. Int. Ed.* **2019**, *58*, 16859, *Chem. Commun.* **2017**, *53*, 8964.

3.4 Visible-light-induced asymmetric reactions

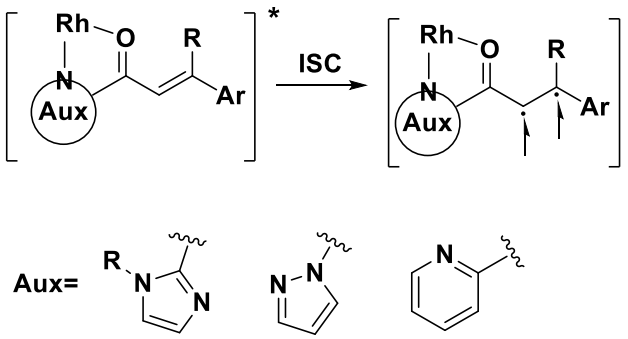


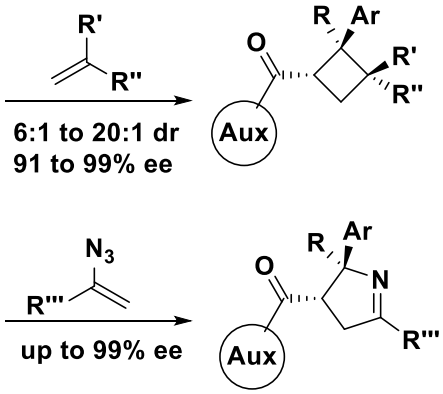
3.4 Visible-light-induced asymmetric reactions

Photocycloaddition

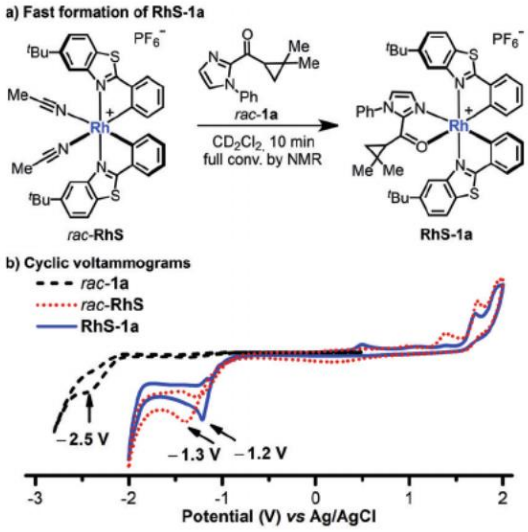


direct visible light activation

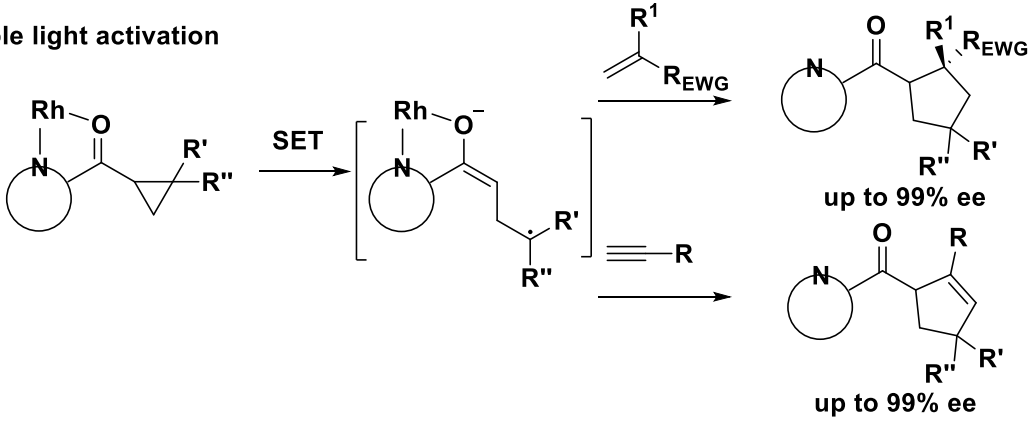




Aux=

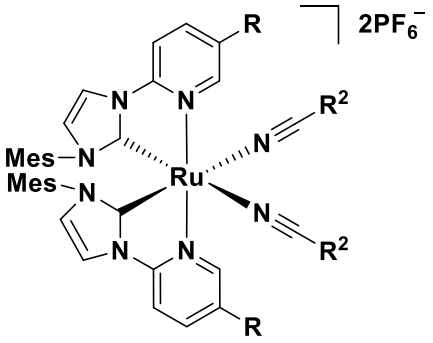


direct visible light activation

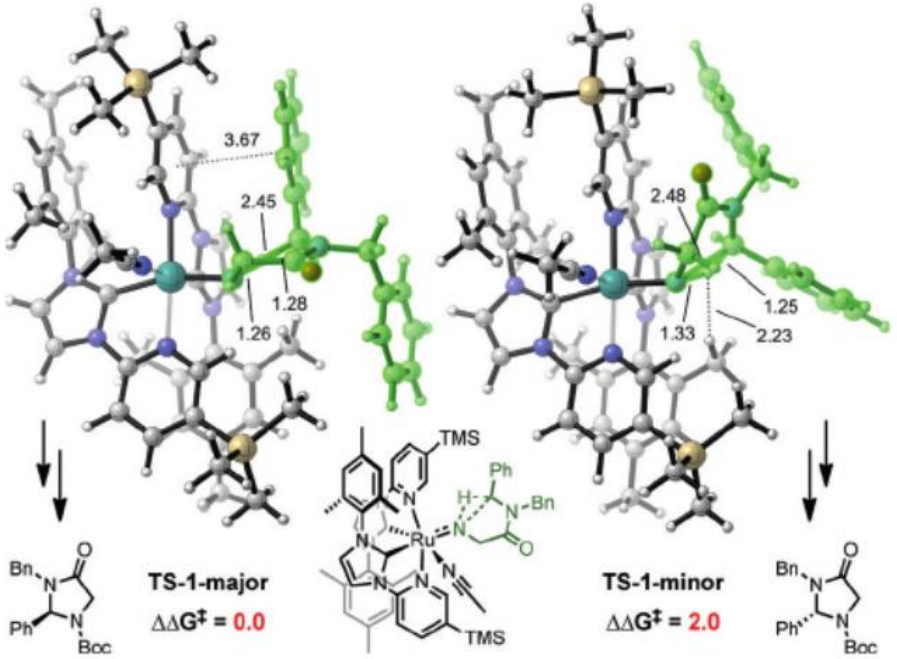


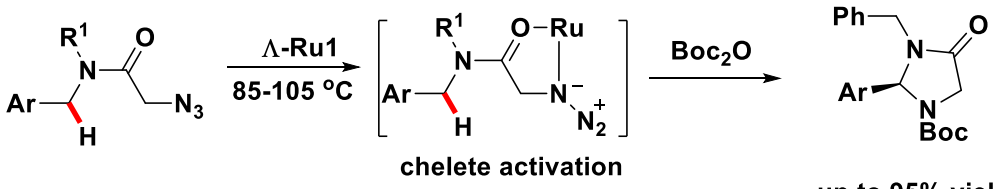
J. Am. Chem. Soc. **2017**, *139*, 9120,
Nat. Commun. **2017**, *8*, 2245,
Angew. Chem. Int .Ed. **2018**, *57*, 5454.

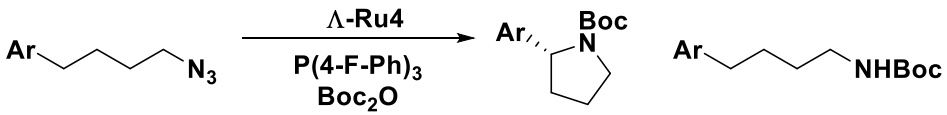
3.5 C-H insertion reactions through metal-nitrenoids



Λ-Ru1: R=TMS
Λ-Ru2: R=TES
Λ-Ru3: R=CF_3

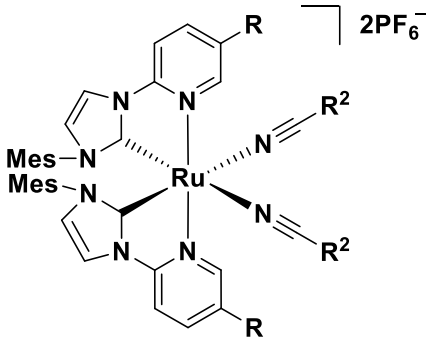




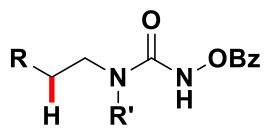


Angew. Chem. Int. Ed. **2019**, *58*, 1088, *Chem. Sci.*, **2019**, *10*, 3202.

3.5 C-H insertion reactions through metal-nitrenoids

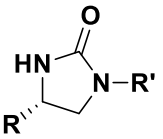


Λ-Ru1: R=TMS
Λ-Ru2: R=TES
Λ-Ru3: R=CF_3
Λ-Ru4: R=C_6H_5*p*-CF_3

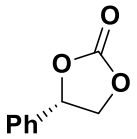


R'= alkyl, H

Λ-Ru1
0.05-0.1 mol%
K_2CO_3 3 equiv.

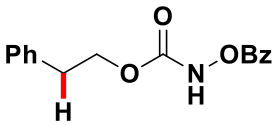


up to 99% yield
99% ee

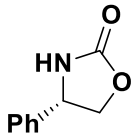


88% yield
78% ee

Λ-Ru2
K_2CO_3 3 equiv.



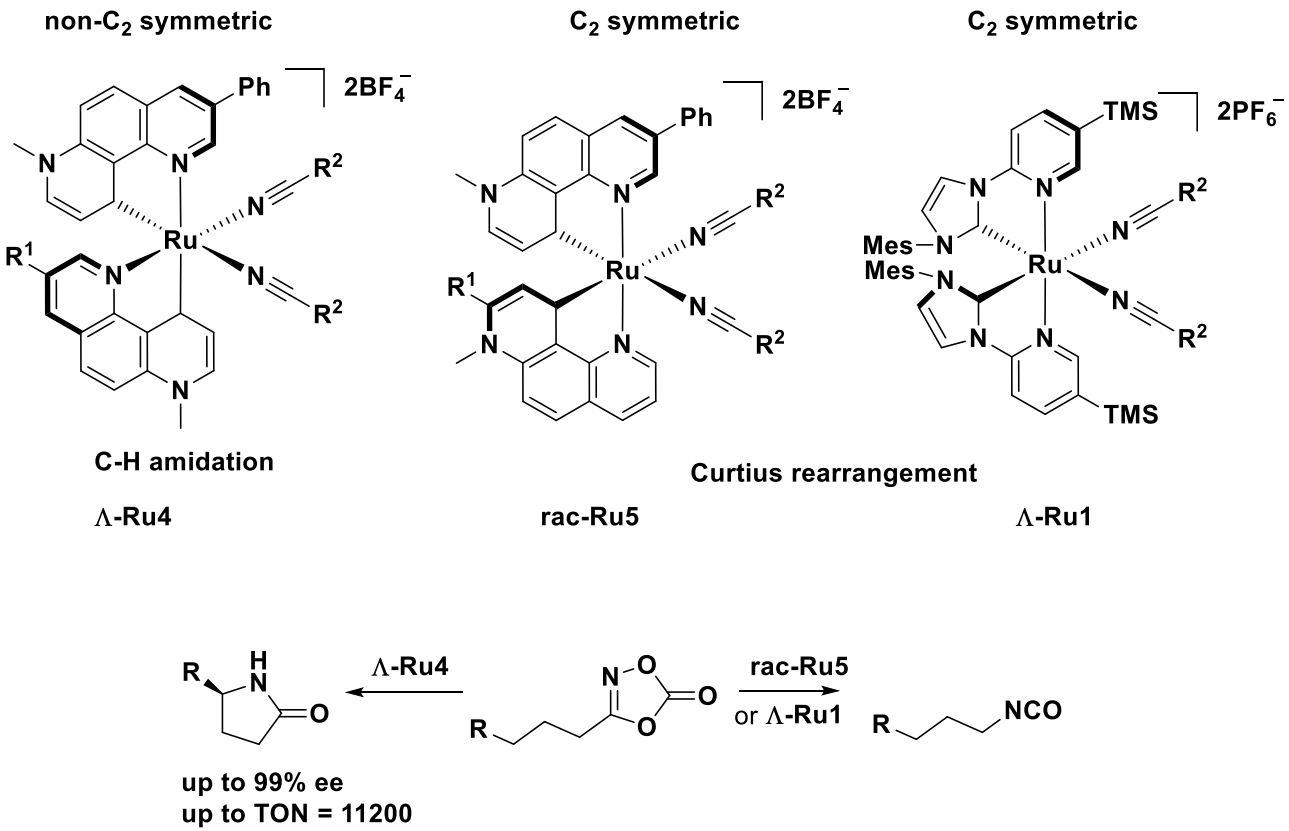
Λ-Ru3
K_2CO_3 3 equiv.



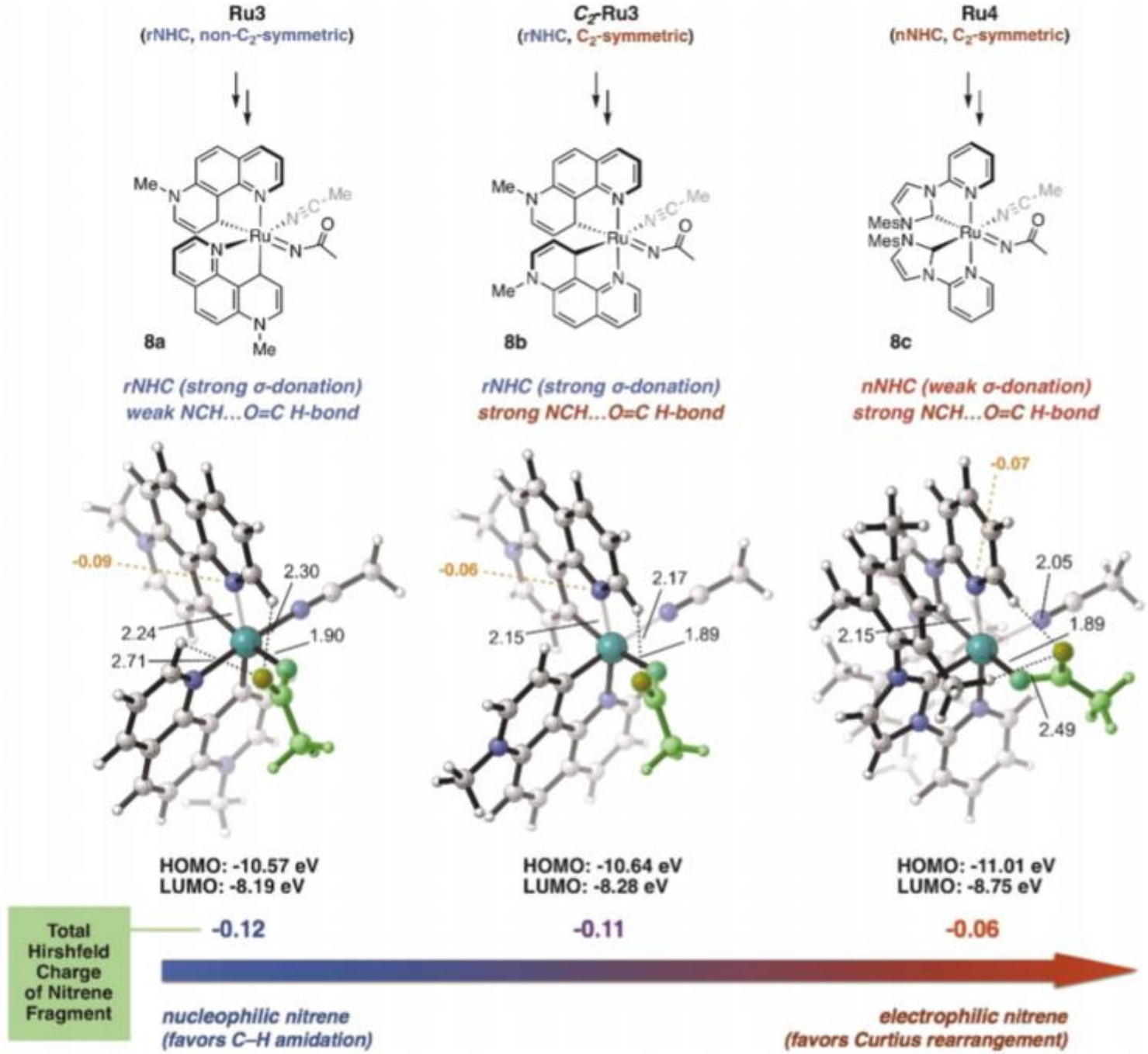
84% yield
80% ee

Chem **2020**, *6*, 2024,
Angew. Chem. Int. Ed. **2020**, *132*, 21890.

3.5 C-H insertion reactions through metal-nitrenoids

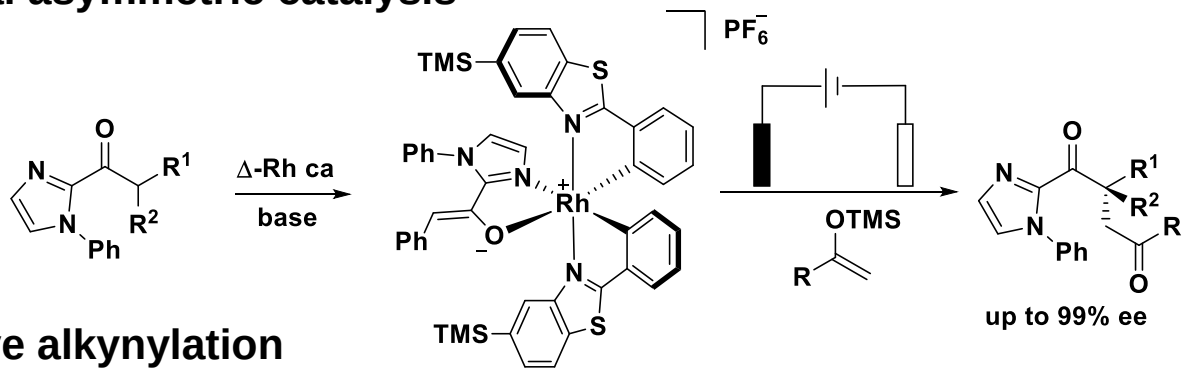


J. Am. Chem. Soc. **2019**, *141*, 19048.

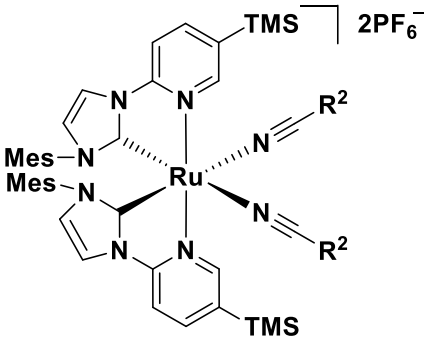

Ru3
(rNHC, non-C2-symmetric)
C2-Ru3
(rNHC, C2-symmetric)
Ru4
(nNHC, C2-symmetric)
8a
8b
8c
rNHC (strong σ-donation)
weak NCH…O=C H-bond
rNHC (strong σ-donation)
strong NCH…O=C H-bond
nNHC (weak σ-donation)
strong NCH…O=C H-bond
-0.09
2.30
2.24
1.90
2.71
-0.06
2.17
2.15
1.89
-0.07
2.05
2.15
1.89
2.49
HOMO: -10.57 eV
LUMO: -8.19 eV
HOMO: -10.64 eV
LUMO: -8.28 eV
HOMO: -11.01 eV
LUMO: -8.75 eV
Total Hirshfeld Charge of Nitrene Fragment
-0.12
-0.11
-0.06
nucleophilic nitrene
(favors C–H amidation)
electrophilic nitrene
(favors Curtius rearrangement)

3.6 Other types of reactions

Electrochemical asymmetric catalysis

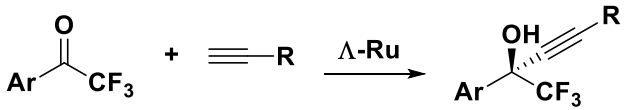


Enantioselective alkynylation

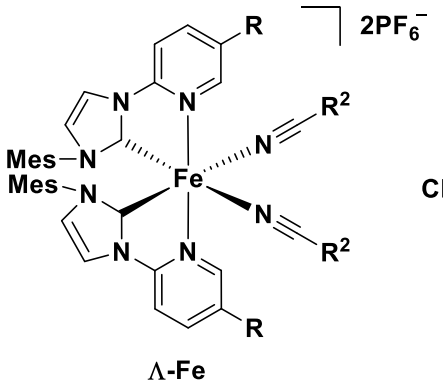


Λ-Ru

Nat. Catal. **2019**, *2*, 34



J. Am. Chem. Soc. **2017**, *139*, 4322



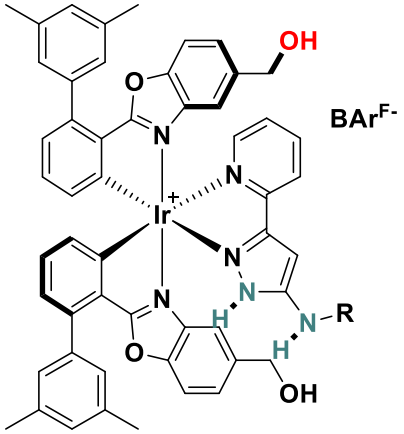
Λ-Fe

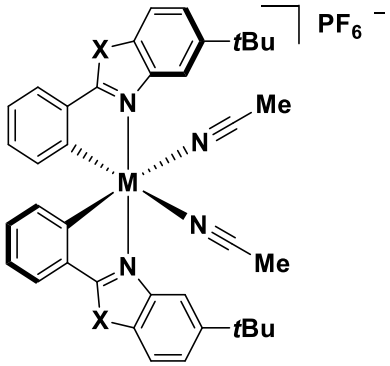
Chiral Lewis Acid

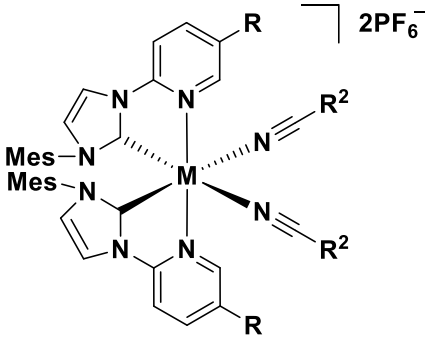
J. Am. Chem. Soc. **2019**, *141*, 4569.
Chem. Eur. J, DOI: 10.1002/chem.202100703.

4. Summary and outlook

Summary

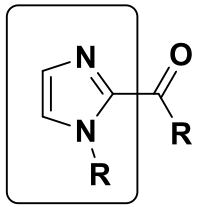






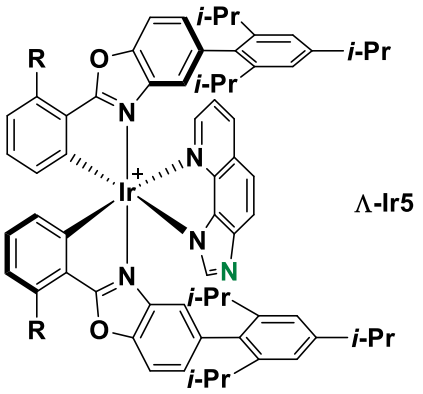
1. Simulation of organocatalyst
2. Chiral Lewis acid catalysis and visible light induced asymmetric catalysis
3. C-H insertion through metal-nitrenoids

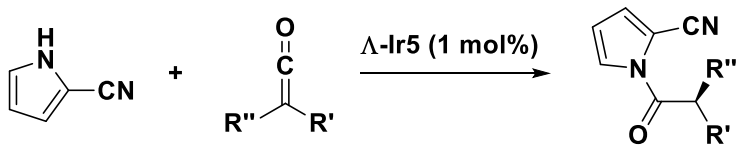
Outlook



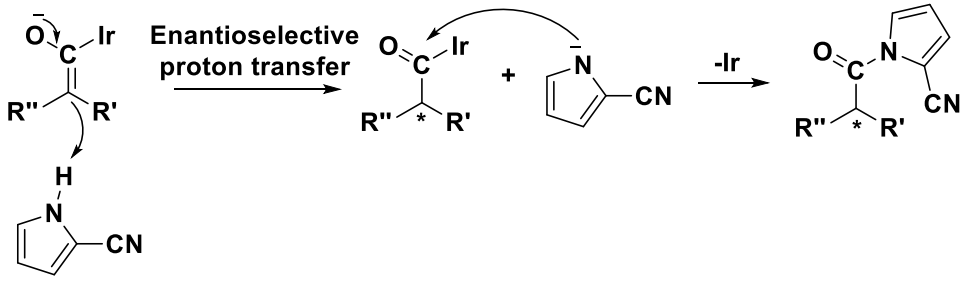
1. More reactions without relying on the 2-acyl imidazole moiety?
2. Further transformations of the 2-acyl imidazole product?

Question 1.

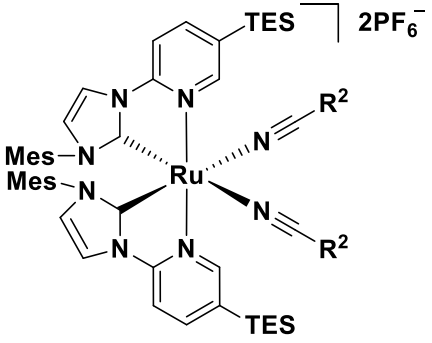




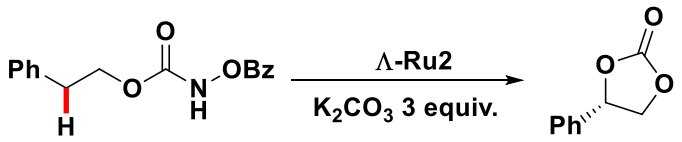
Mechanism?



Question 2.



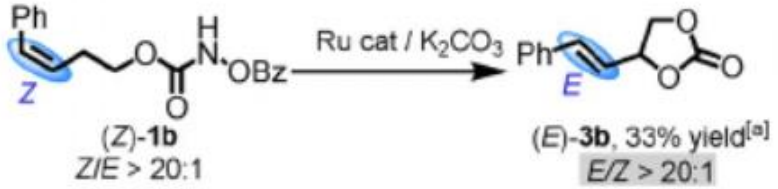
Λ-Ru2: R=TES



Mechanism?

88% yield
78% ee

b) Olefin isomerization



(*Z*)-**1b**
Z/*E* > 20:1

(*E*)-**3b**, 33% yield[a]
E/*Z* > 20:1

■ **Proposed mechanism**