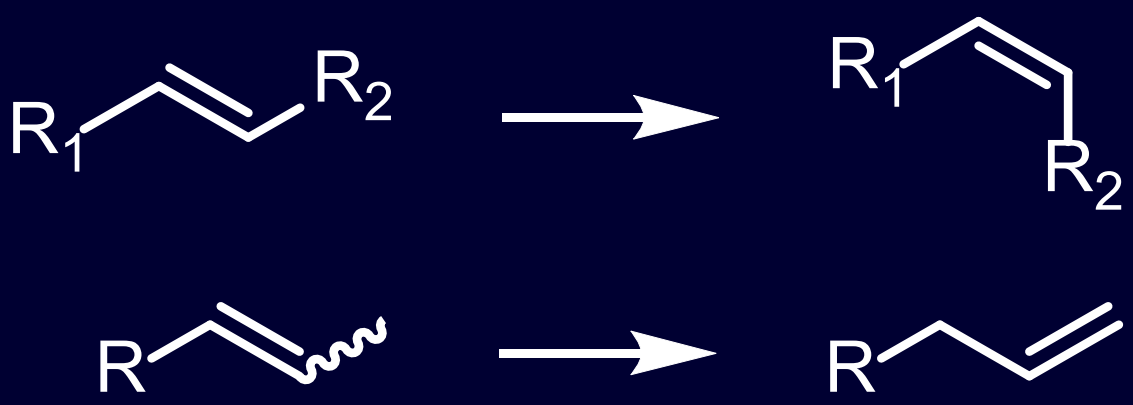


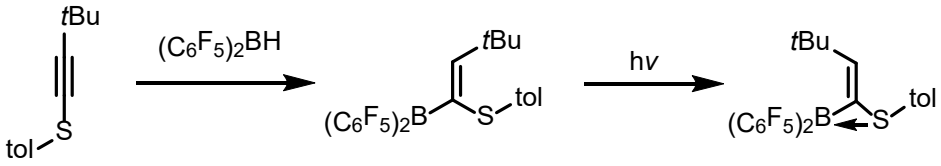
Contra-Thermodynamic Isomerization of Olefins

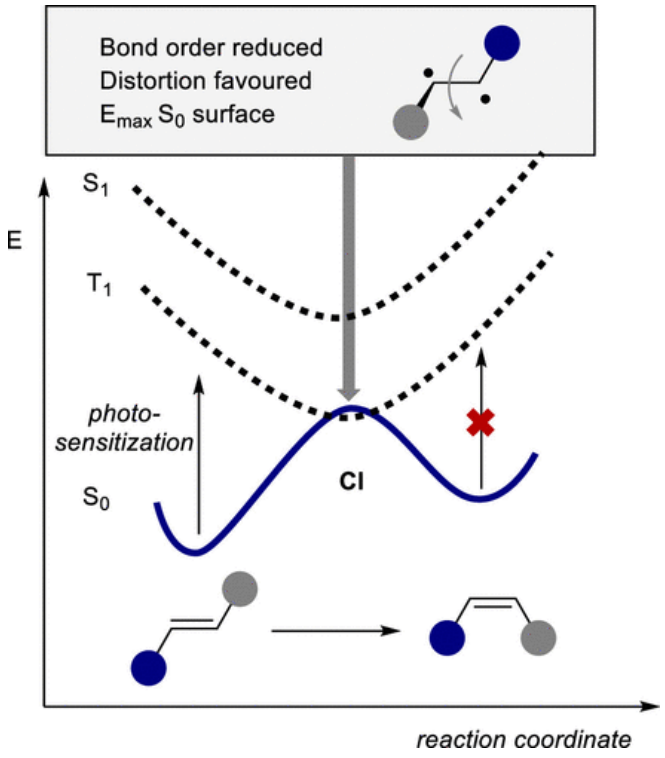
Zijing Chen

College of Chemistry and Molecular Engineering
Aug. 27th 2022

Basic Idea for the Contra-Thermodynamic E→Z Isomerization

The pseudo contra-thermodynamic isomerization of olefins:

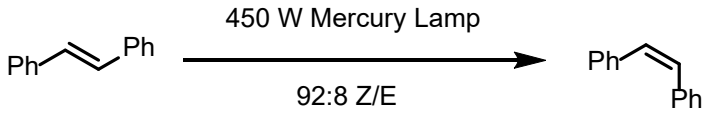




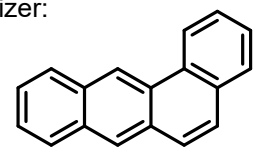
Works from the 20th century:

- Harsh conditions required for irradiation
- Stoichiometric amounts of photosensitizers used
- Results determined by GC, products never isolated

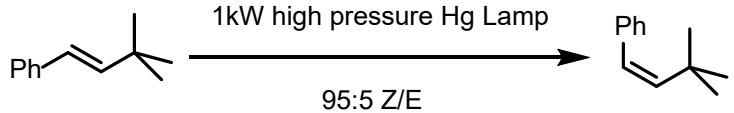
Hammond (1964):



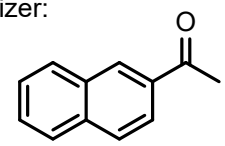
photosensitizer:



Arai (1980):

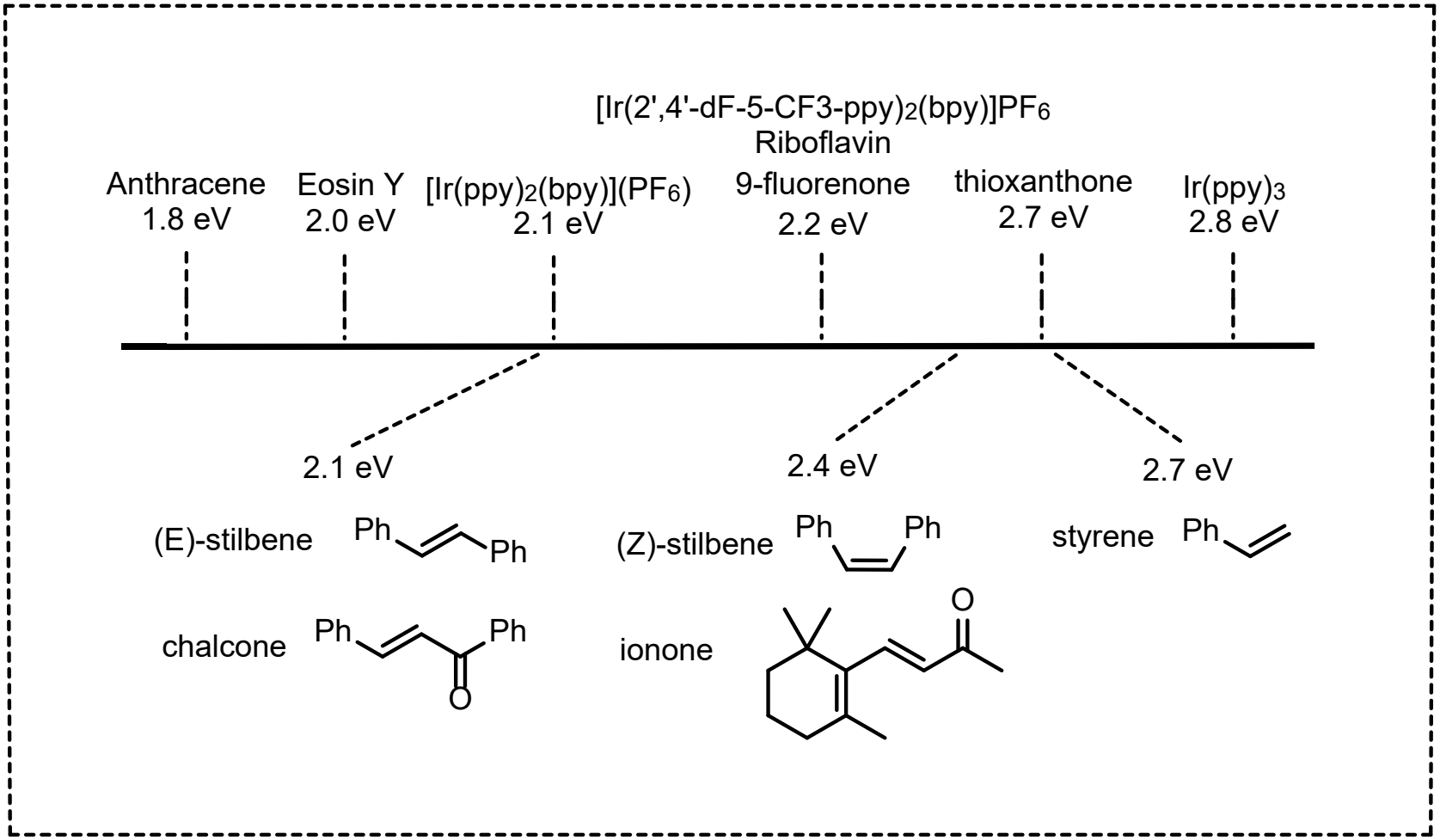


photosensitizer:



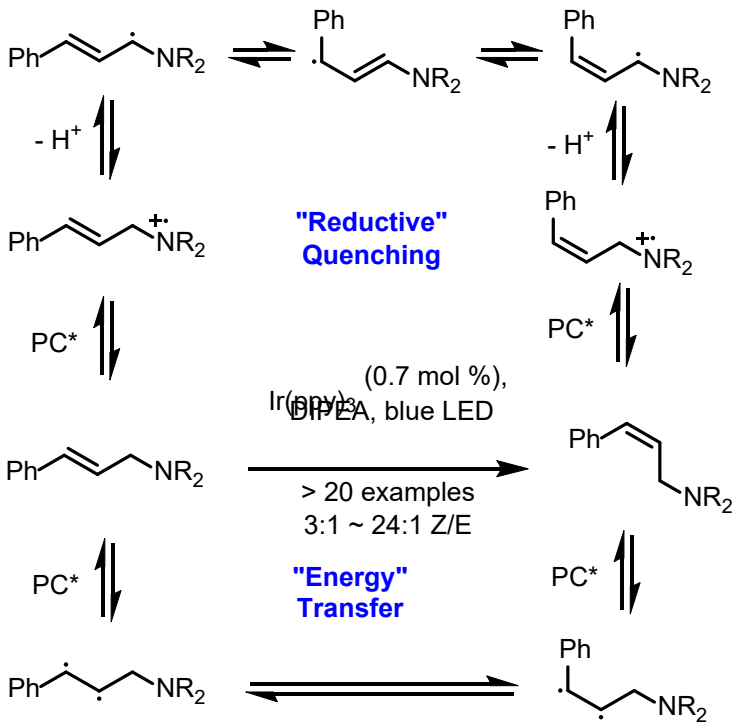
G, Hammond.; J, Saltiel.; A, Lamola.; N, Turro.; J, Bradshaw.; D, Cowan.; R, Counsell.; V, Vogt.; C, Dalton. *J. Am. Chem. Soc.* **1964**, *86*, 3197.
A, Tatsuo.; S, Hirochika.; T, Katsumi.; *Chem. Lett.* **1980**, 261.
L, Fan.; A, Jupp.; D, Stephan. *J. Am. Chem. Soc.* **2018**, *140*, 8119.

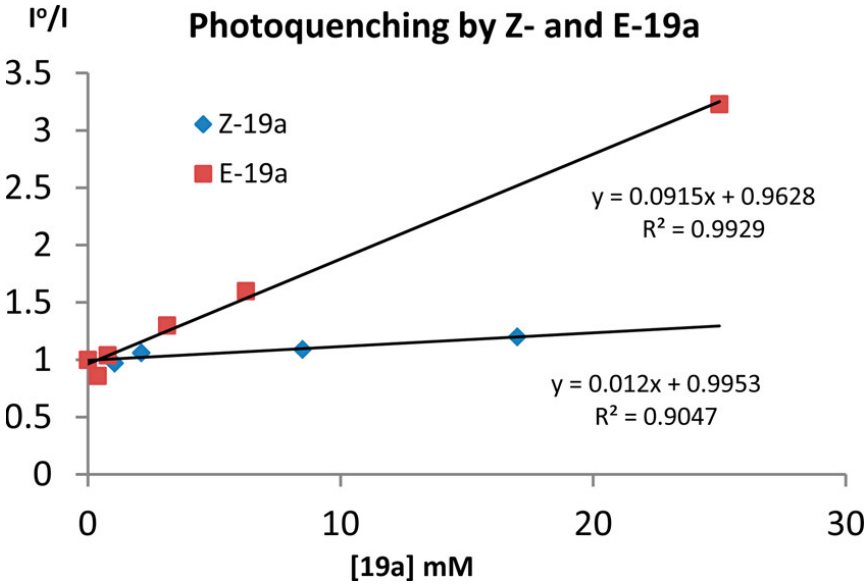
Triplet Energies for PCs and alkenes

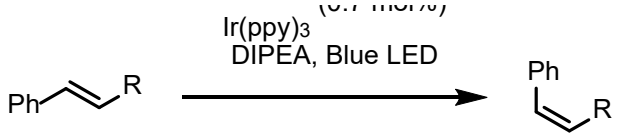


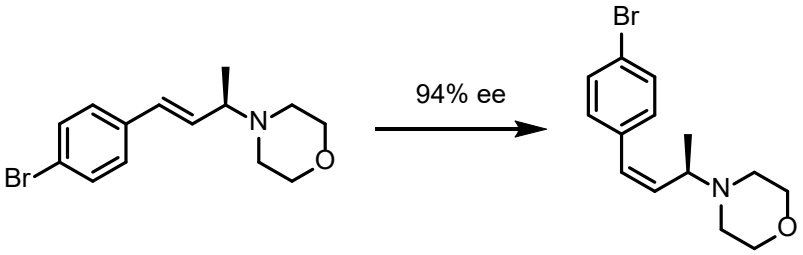
T, Neveselý.; M, Wienhold.; J, Molloy.; R, Gilmour. *Chem. Rev.* **2022**, *122*, 2650.

$Ir(ppy)_3$ As the "Uphill" Catalyst







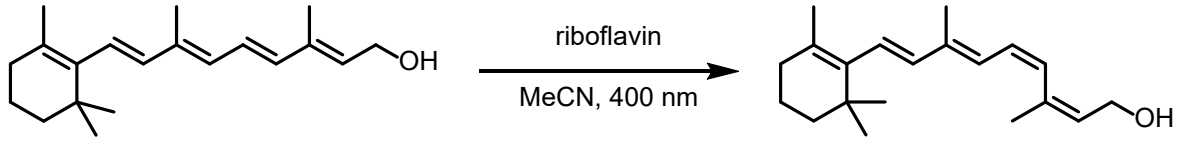


R=Me	80% (^{1}H NMR), 87:13
R=*i*Pr	>99% (^{1}H NMR), 78:22
R=CH_2OH	>99% (^{1}H NMR), 80:20
R=CHMeOH	>99% (^{1}H NMR), 81:19
R=CH_2OAc	>99% (^{1}H NMR), 86:14
R=CHMeOAc	>99% (^{1}H NMR), 87:13

K, Singh.; S, Staig.; J, Weaver. *J. Am. Chem. Soc.* **2014**, *136*, 5275.

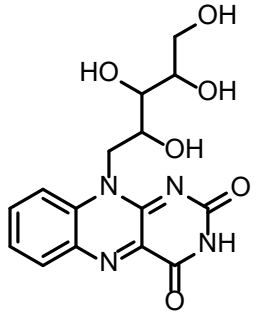
Inspired by Nature's Utilization of Light

Vitamin B2-initiated transformation:



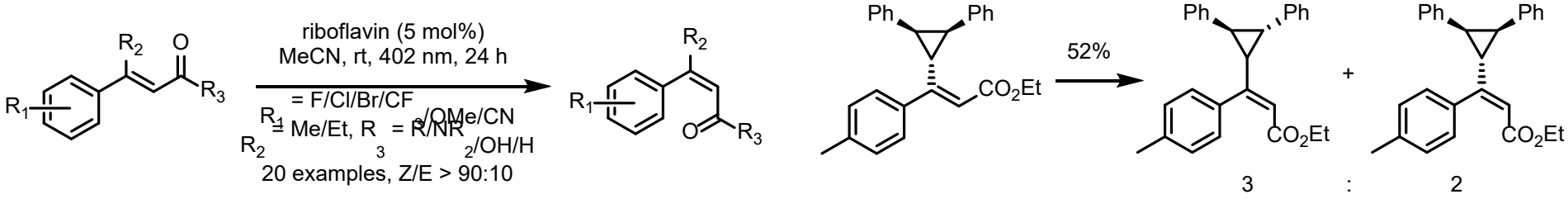
trans-retinol

cis-retinol

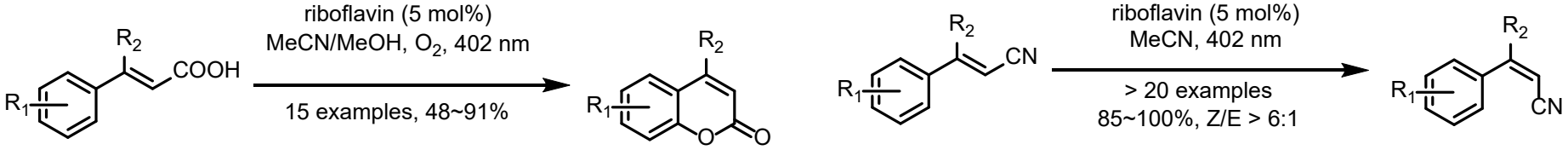


riboflavin

The cinammone derivatives:



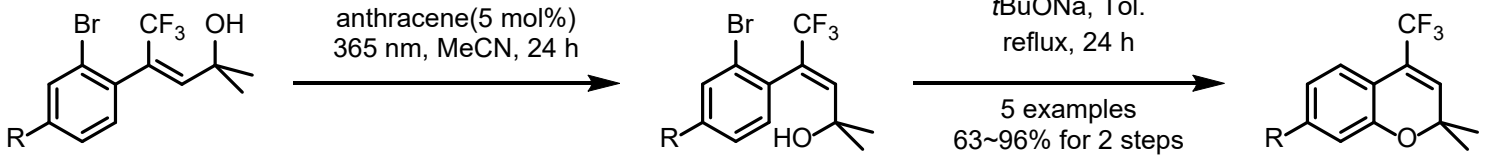
Coumarin synthesis and cinnamonitrile derivatives:



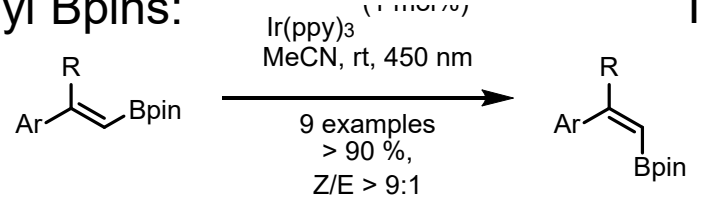
G, Walker.; K, Radda. *Nature* **1967**, 215, 1483.
J, Metternich.; R, Gilmour. *J. Am. Chem. Soc.* **2015**, *137*, 11254.
J, Metternich.; R, Gilmour. *J. Am. Chem. Soc.* **2016**, *138*, 1040.
J, Metternich.; D, Artiukhin.; M, Holland.; M, Bremen-Kühne.; J, Neugebauer.; R, Gilmour. *J. Org. Chem.* **2017**, *82*, 9955.

Erasing Permanent Chromophores

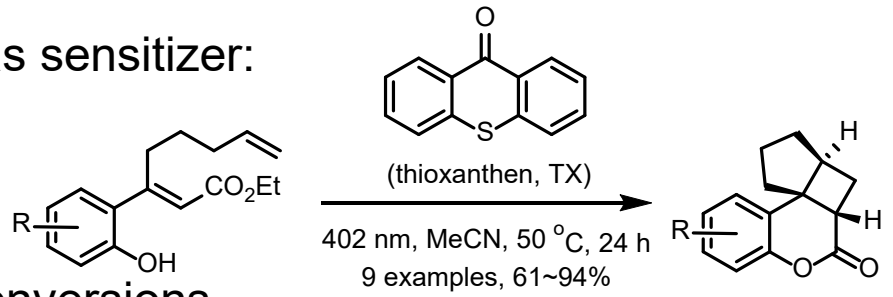
Concise synthesis of 2H-Chromenes:



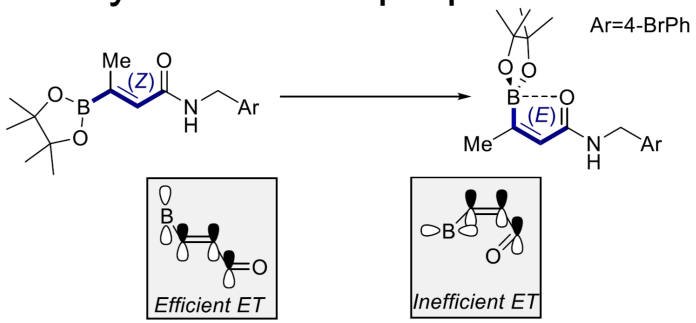
Styrenyl Bpins:

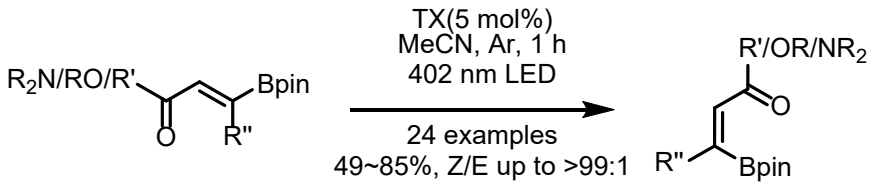


TX as sensitizer:

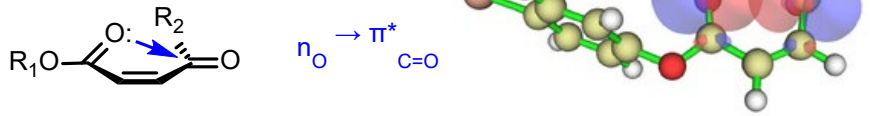


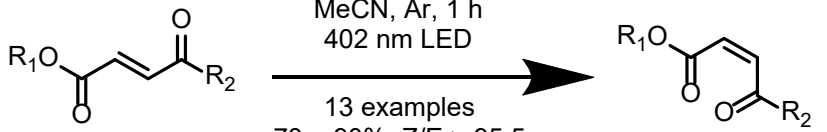
β-boron acrylates: ease preparation and conversions





Fumarates to maleates:





S, Faßbender.; J,Metternich.; R, Gilmour. *Org. Lett.* **2018**, *20*, 724.

T, Neveselý.; C, Daniliuc.; R, Gilmour.; *Org. Lett.* **2019**, *21*, 9724.

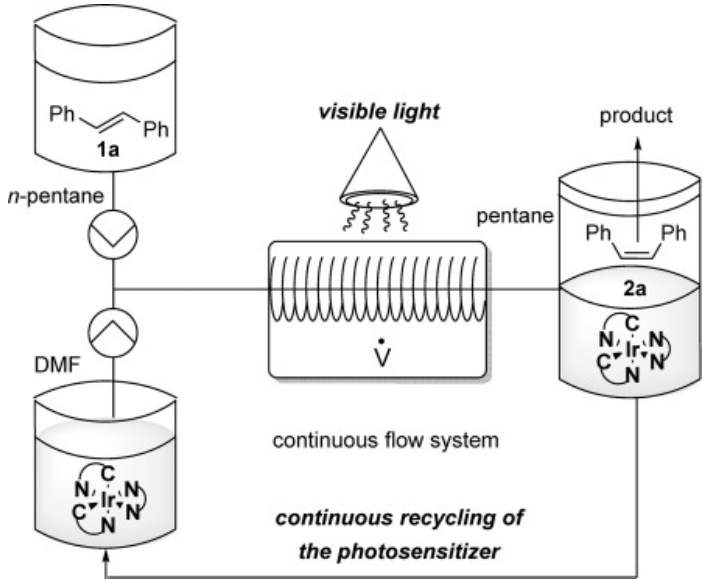
J, Molloy.; J, Metternich.; C, Daniliuc.; A, Watson.; R, Gilmour. *Angew. Chem. Int. Ed.* **2018**, *57*, 3168.

J, Molloy.; M, Schäfer.; M, Wienhold.; T, Morack.; G, Daniliuc.; R, Gilmour. *Science* **2020**, *369*, 302.

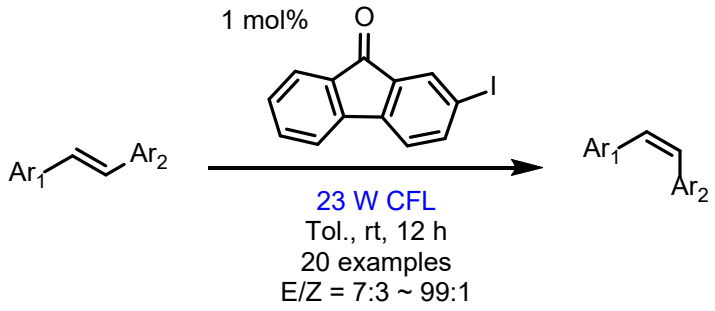
T, Nevesely.; J, Molloy.; C, McLaughlin.; L, Bruss.; G, Daniliuc.; R, Gilmour. *Angew. Chem. Int. Ed.* **2022**, *61*, e202113600.

Other Modifications

Two-phase flow system:
93% conversion at 20 mL/h

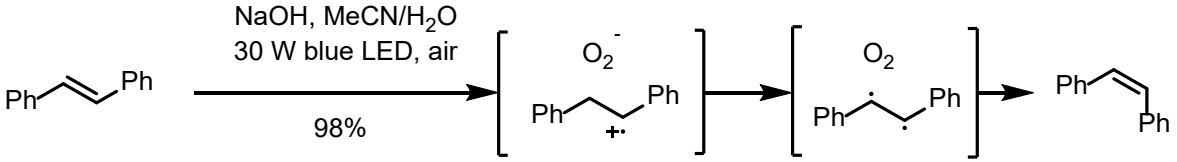


Using household compact fluorescent light (CFL) bulb without metal:



Introduction of a “heavy atom”:
Absorption capacity in visible light region↑
Intersystem crossing efficiency↑

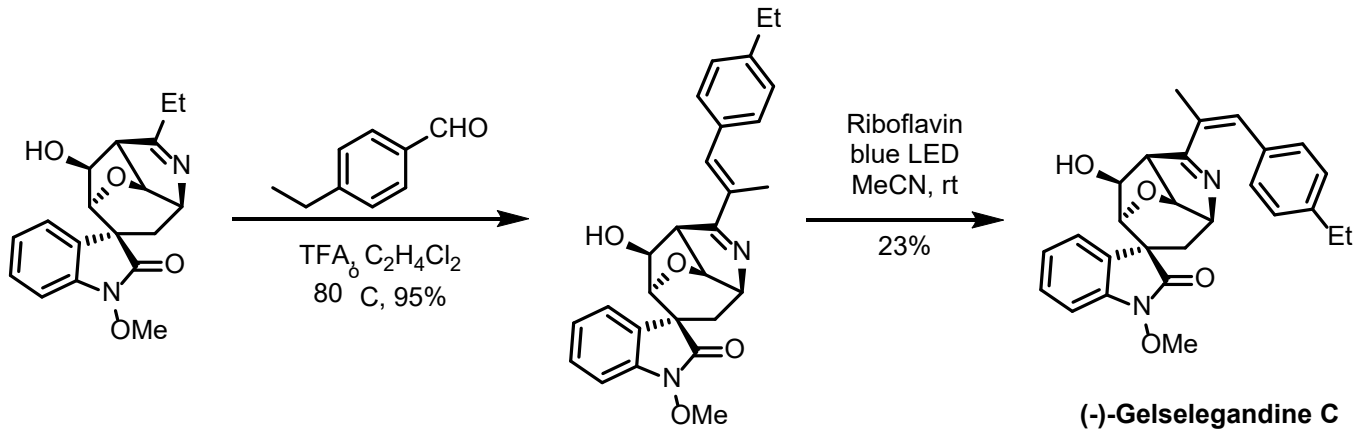
PC-free stilbene isomerization induced by visible light:



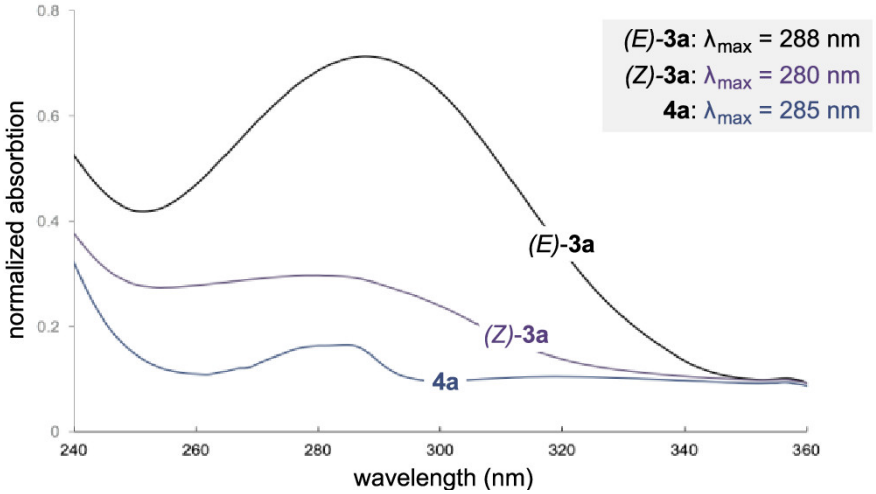
D, Fabry.; M, Ronge.; M, Rueping. *Chem. Eur. J.* **2015**, *21*, 5350.
W, Cai.; H, Fan.; D, Ding.; Y, Zhang.; W, Wang. *Chem. Commun.,* **2017**, *53*, 12918.
J. Xu.; N, Liu.; H, Lv.; C, He.; Z, Liu.; X, Shen.; F, Cheng.; B, Fan.; *Green Chem.* **2020**, *22*, 2739.

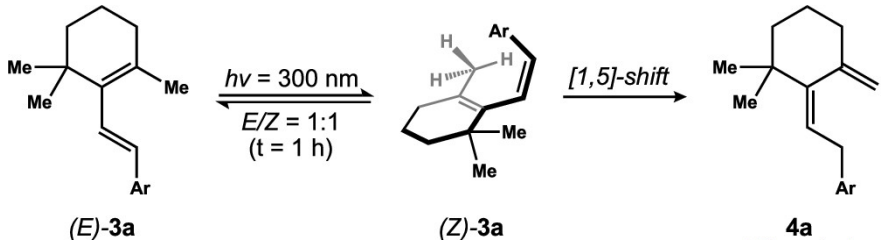
Applications in Total Syntheses

Late-stage geometric isomerization towards *Gelsemium* alkaloid:



To combine with [1,5]-H shift and further transformations:

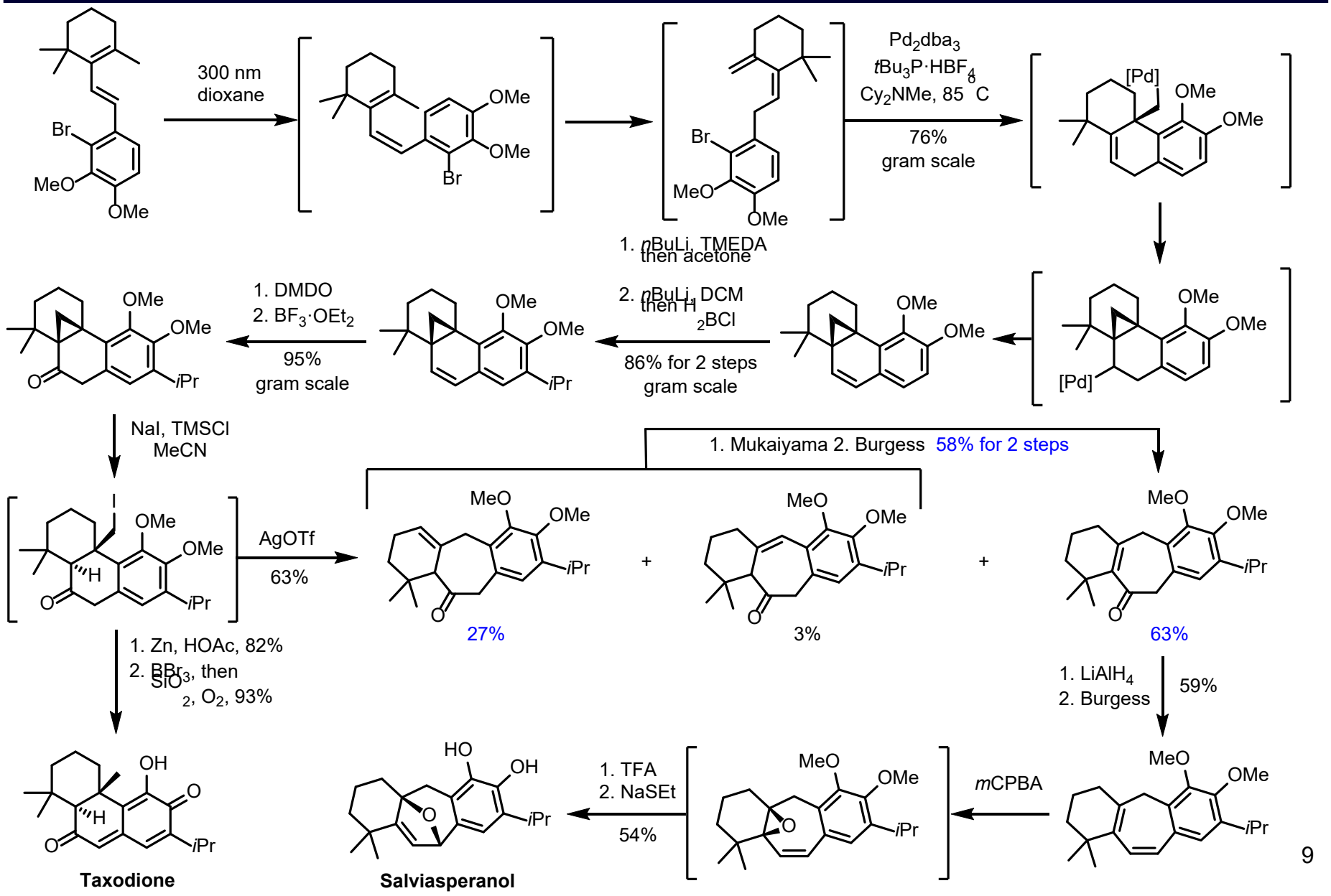




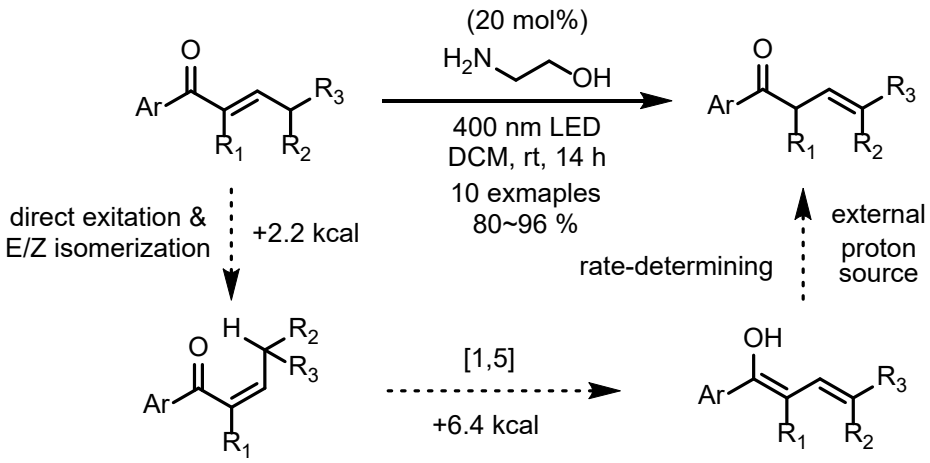
A, Saito.; N, Kogure.; M, Kitajima.; H, Takayama. *Org. Lett.* **2019**, *21*, 7134.

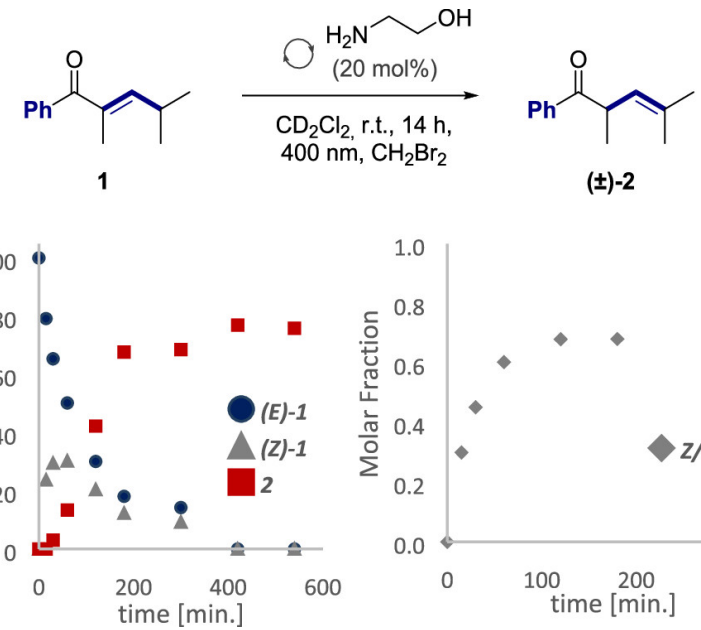
M,Solans.; V, Basistyi.; J, Law.; N, Bartfield.; J, Frederich. *J. Am. Chem. Soc.* **2022**, *144*, 6193.

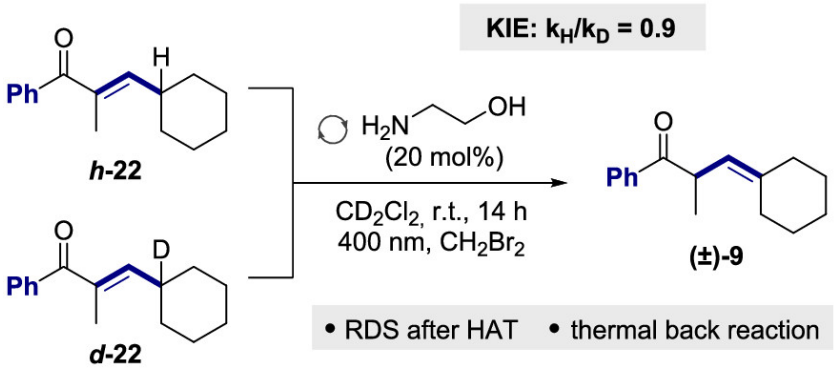
Z/*E* Isomerization-[1,5] Hydride Shift-Heck Cascade

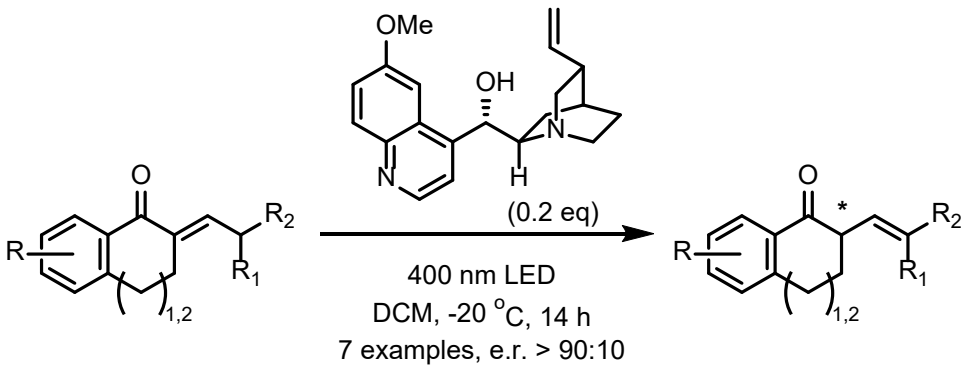


Deconjugative Isomerization



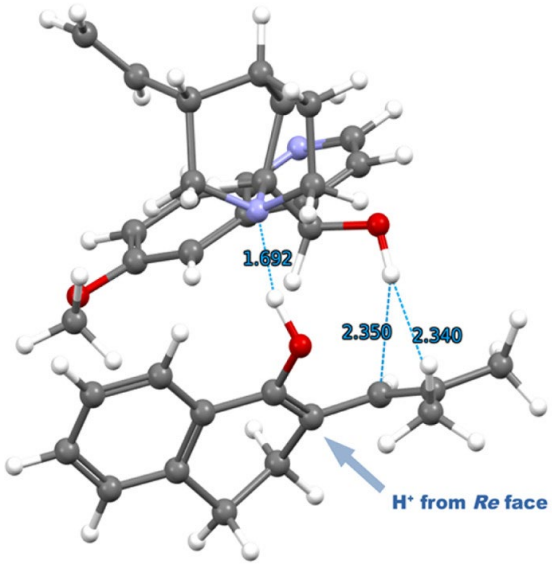




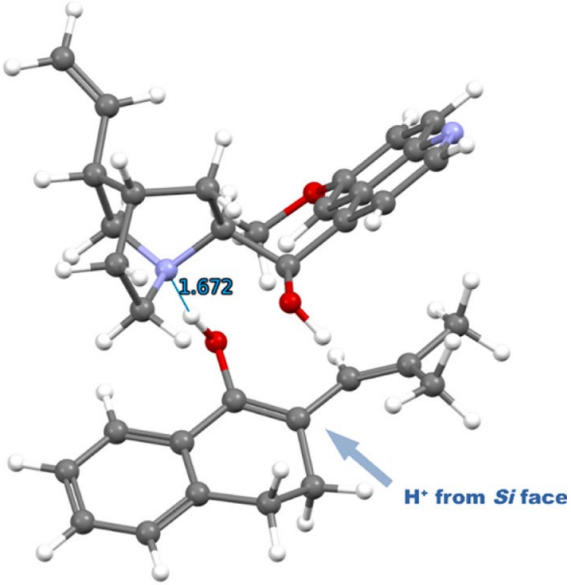


T, Morack.; C, Onneken.; H, Nakakohara.; C, Mück-Lichtenfeld.; R, Gilmour. *ACS Catal.* **2021**, *11*, 11929.

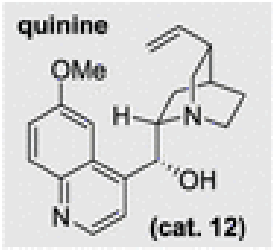
For Enantioselective Protonation

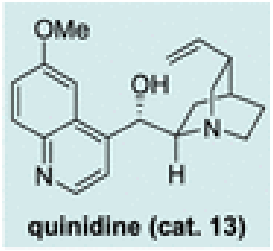


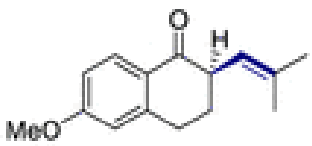
catalyst on the *Si* face of enol-**12**
ΔG_{298} = +1.9 kcal/mol



catalyst on the *Re* face of enol-**12**
ΔG_{298} = 0.0 kcal/mol

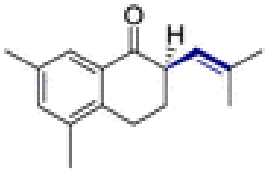






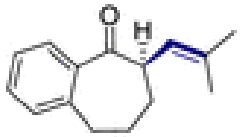
(-)-**11** 88%
e.r. 93:7

(+)-**11** 97%
e.r. 8:92



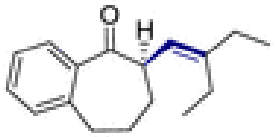
(-)-**15** 86%
e.r. 93:7

(+)-**15** 85%
e.r. 7:93



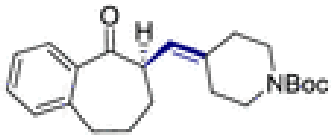
(+)-**18** 91%
e.r. 95:5

(-)-**18** 99%
e.r. 7:93



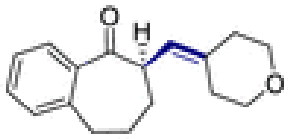
(+)-**19** 91%
e.r. 93:7

(-)-**19** 85%
e.r. 6:94



(+)-**20** 89%
e.r. 90:10

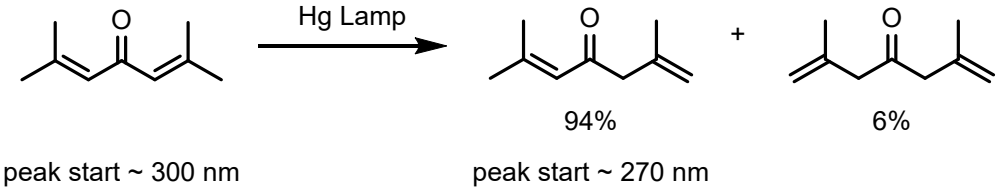
(-)-**20** 99%
e.r. 8:92



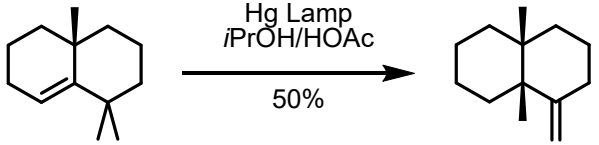
(+)-**21** 90%
e.r. 91:9

(-)-**21** 97%
e.r. 9:91

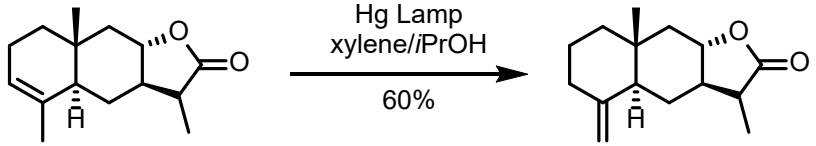
From Geometric Isomerization to Positional Isomerization



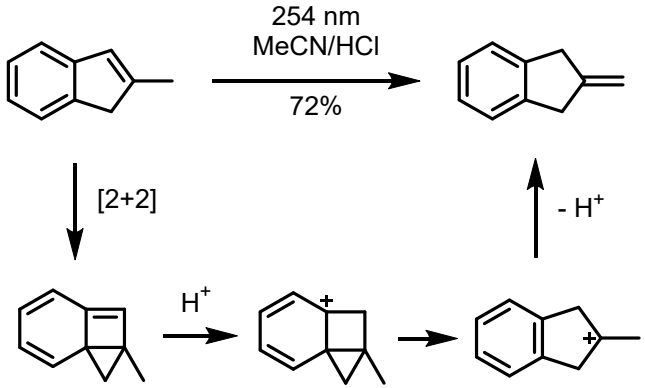
K, Crowley.; R, Schneider.; J, Meinwald. *J. Chem. Soc.* **1966**, 571.



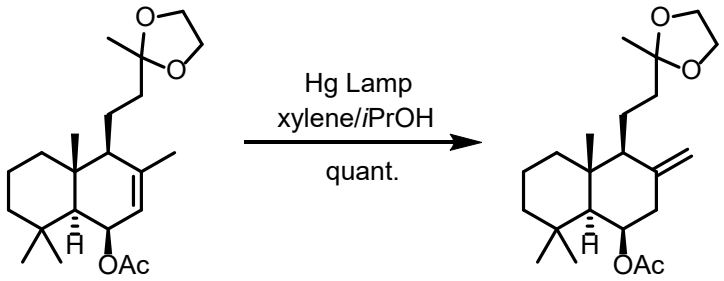
J, Marshall.; A, Hochstetler. *J. Am. Chem. Soc.* **1969**, *91*, 3.



G, Blay.; L, Cardona.; B, Garcia.; J, Pedro.; A, Serrano. *Tetrahedron* **1992**, *48*, 5265.

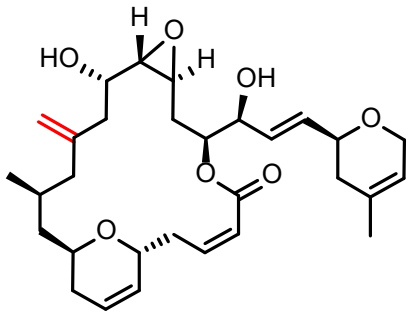


H, Morrison.; D, Giacherio. *J. Org. Chem.* **1982**, *47*, 1059.

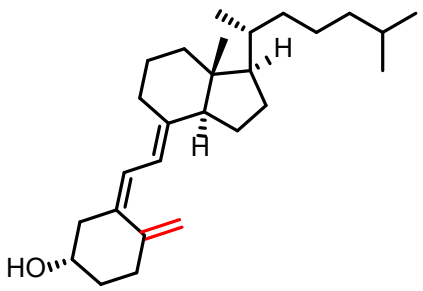


A, Abad.; M, Arno.; C, Agullo.; A, Cuñat.; B, Meseguer.; R, Zaragoza. *J. Nat. Prod.* **1993**, *56*, 2133.

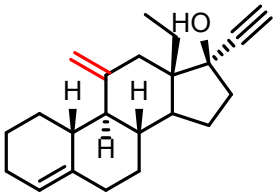
Molecules with Terminal Olefin Structure



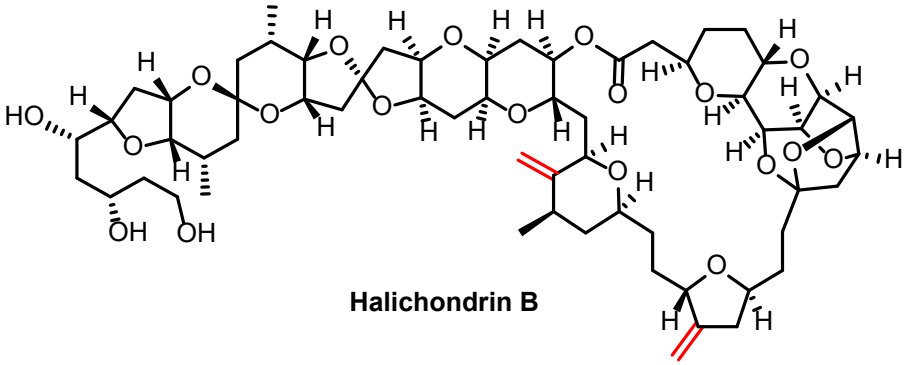
Laulimalide



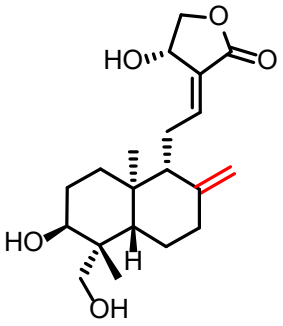
Vitamin D3



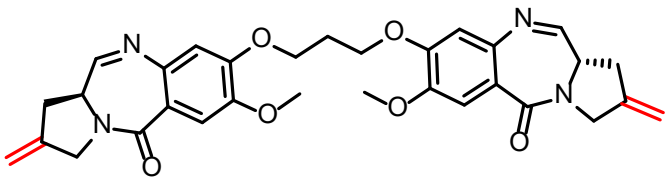
Desogestrel



Halichondrin B

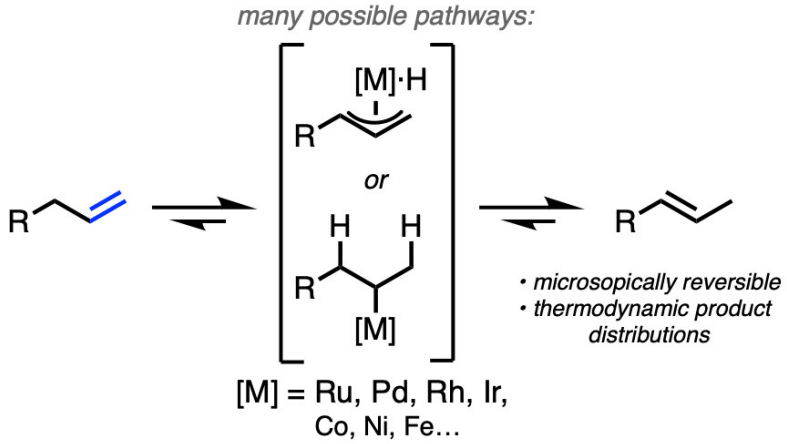


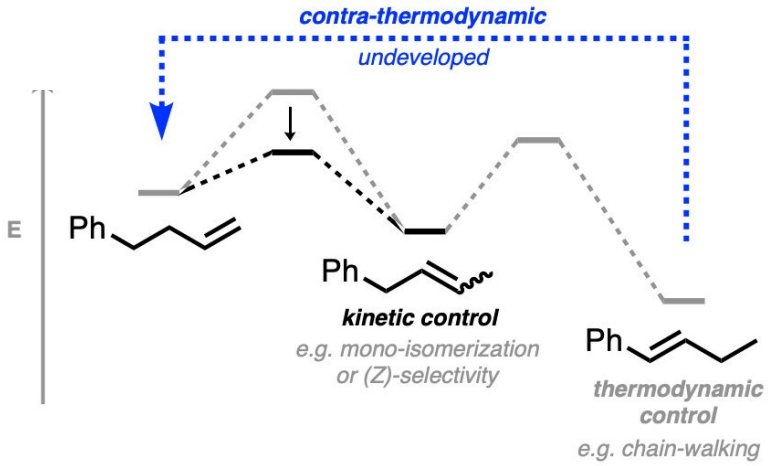
Andrographolide



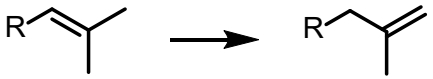
SJG 136
DNA crosslinker

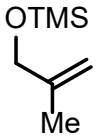
The Contra-Thermodynamic Positional Isomerization



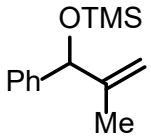


Calculated □G(kcal/mol)
at 298K (by CBS-QB3):

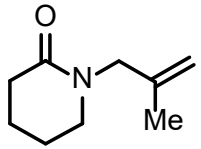




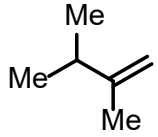
+5.82



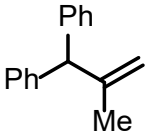
+4.81



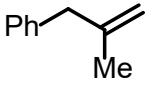
+1.14



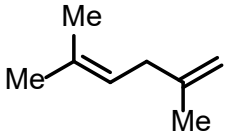
+2.51



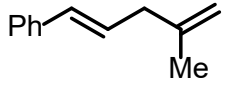
+5.83



+1.85



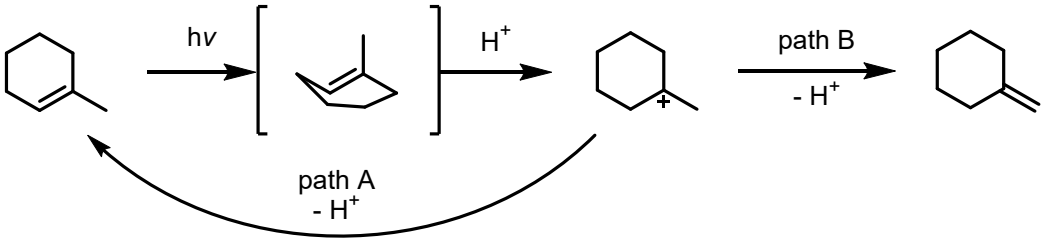
+5.36



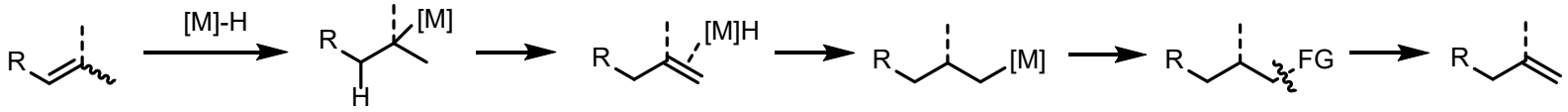
+5.64

Strategies for Non-conjugated Alkenes

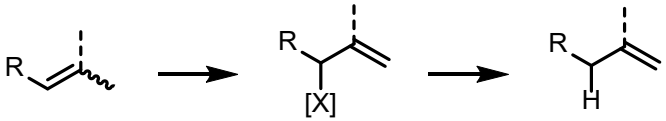
E/Z isomerization/Acid Catalyzed Double Bond Migration Sequence:



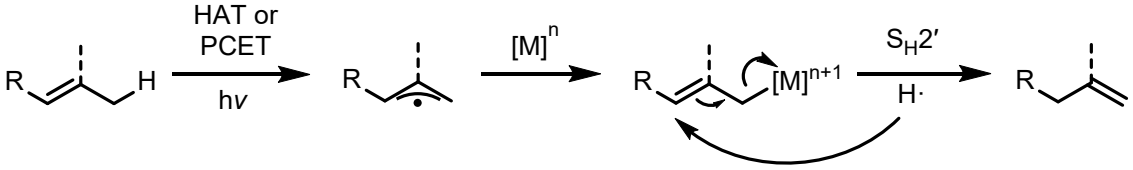
Hydrofunctionalization/Chain Walking/Dehydrofunctionalization Sequence:



Ene-type Allylic Substitution/Reduction Sequence:

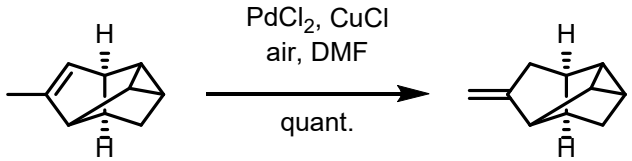


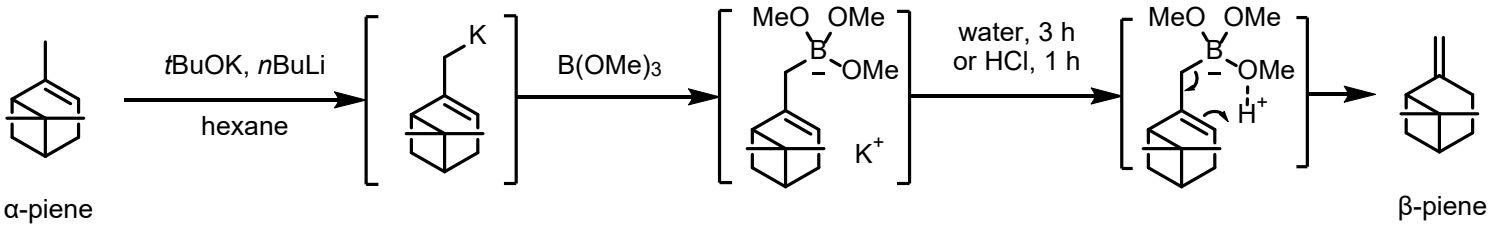
Photoactivation/Regiospecific Bimolecular Homolytic Substitution(S_H2') Sequence:

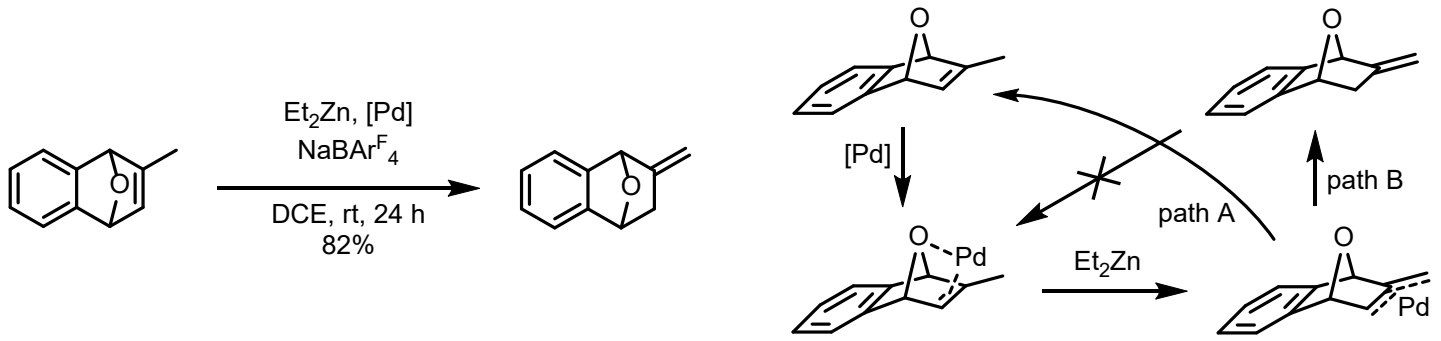


Base-Catalyzed Isomerization

The Pseudo-Contrathermodynamic Situation:





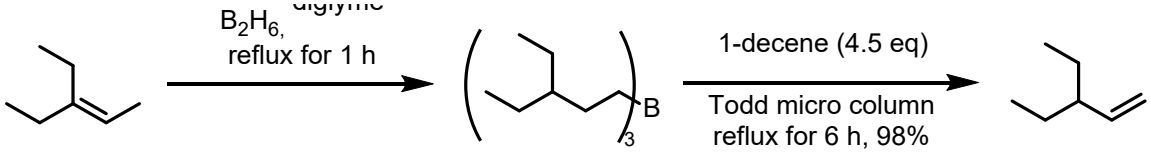


G, Dzhemileva.; V, Odinokov.; U, Dzhemilev. *Bull. Acad. Sci. USSR Div. Chem. Sci.* **1987**, *36*, 131.

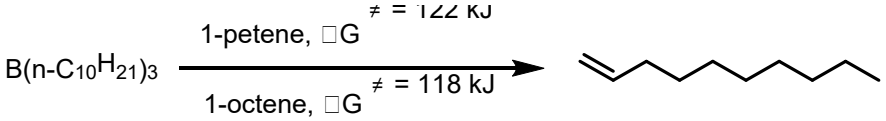
G, Newkome.; K, Theriot.; V, Gupta.; F, Fronczek.; G, Baker. *J. Org. Chem.* **1989**, *54*, 1766

S, Cabrera.; R, Arraya.; I, Alonso.; J, Carretero. *J. Am. Chem. Soc.* **2005**, *127*, 17943.

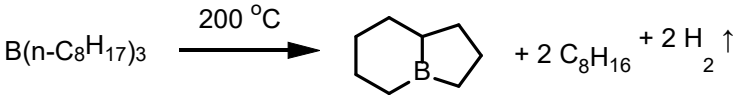
Olefin Isomerization through Borane?

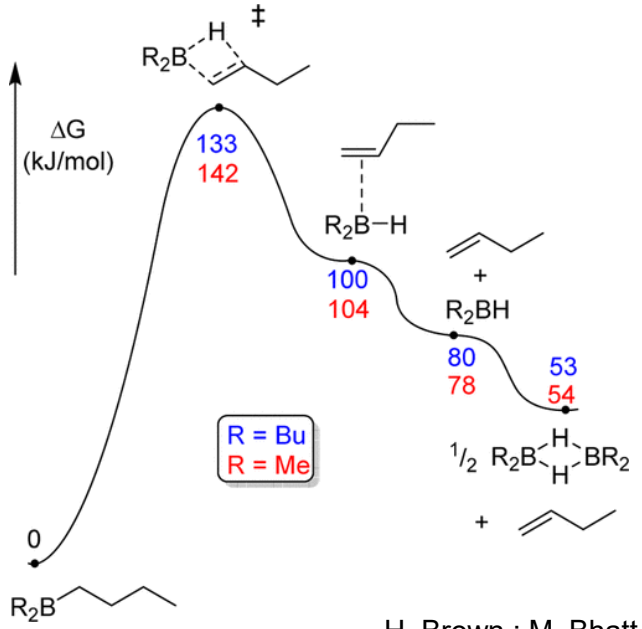


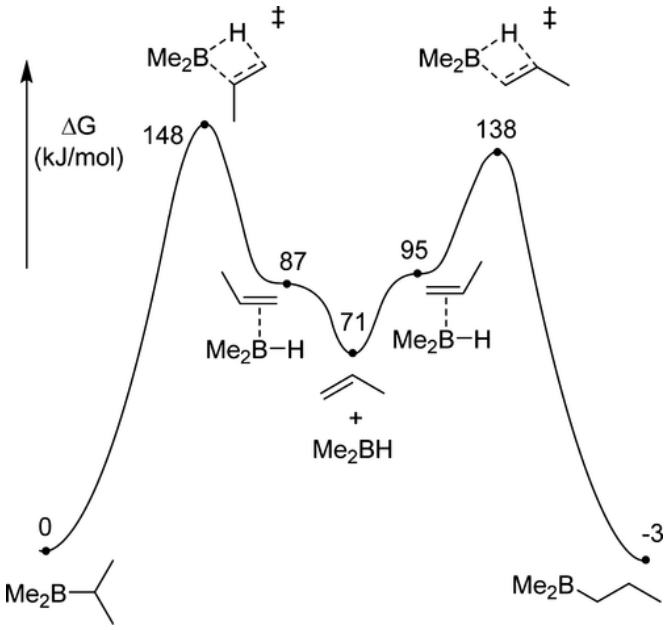
displacement √



thermal dehydroboration ×





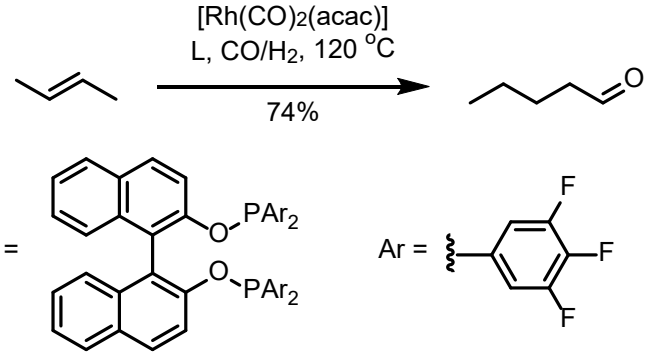


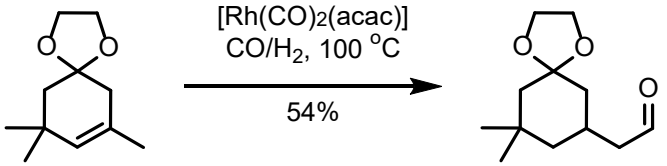
H, Brown.; M, Bhatt.; *J. Am. Chem. Soc.* **1960**, *82*, 2074.

N, Weliange.; D, McGuinness.; J, Patel. *Organometallics* **2014**, *33*, 4251.

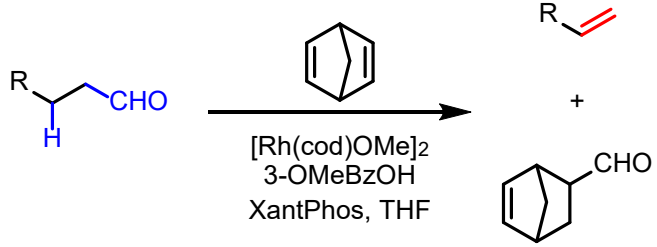
Chain-Walking to the Terminal Followed by Elimination

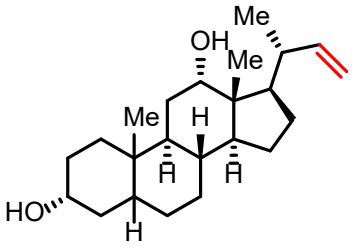
Hydroformylation:



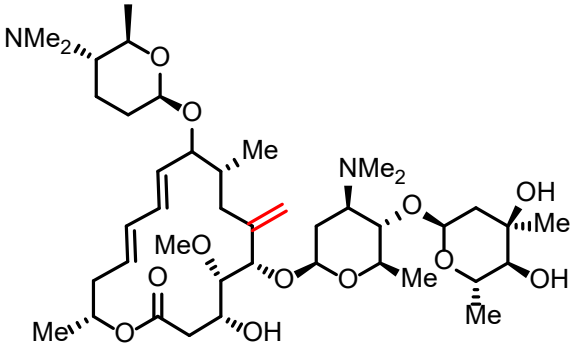


Dehydroformylation:



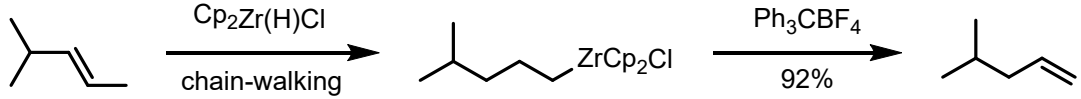


68%

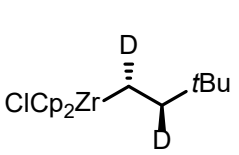


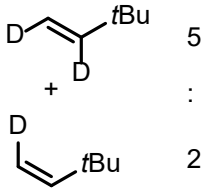
78%

Hydrozirconation and hydride elimination:



via *trans*-hydride abstraction





H, Klein.; R, Jackstell.; K, Wiese.; C, Borgmann.; M, Beller. *Angew. Chem. Int. Ed.* **2001**,*40*,1.

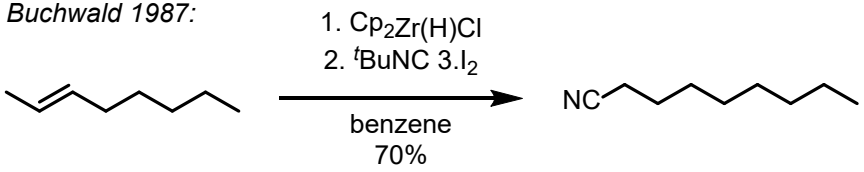
S, Murphy.; J, Park.; F, Cruz.; V, Dong. *Science*, **2015**, *347*, 56. J, Schwartz.; J, Labinger. *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 333.

S, Paganelli.; F, Battois.; M, Marchetti.; R, Lazzaroni.; R, Settambolo.; S, Rocchiccioli. *J. Mol. Cat. A: Chemical* **2006**, *246*, 195.

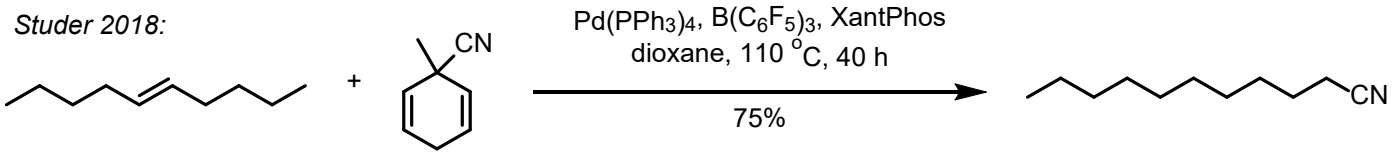
Chain Walking and Reversible Hydrocyanation

Hydrocyanation:

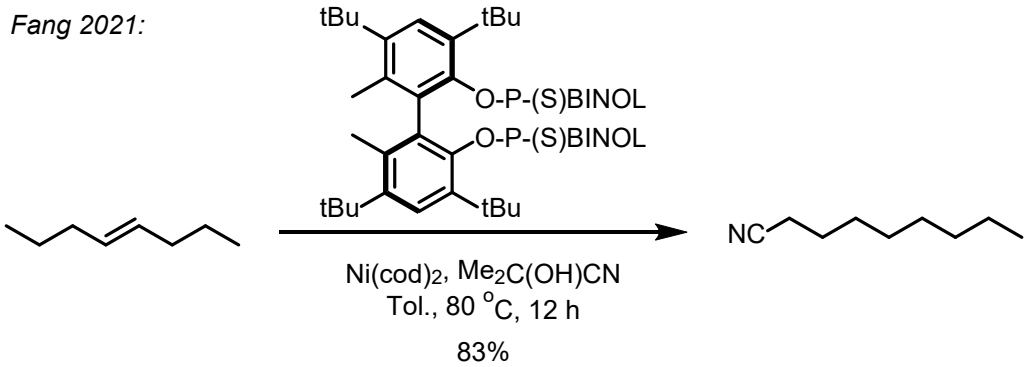
Buchwald 1987:



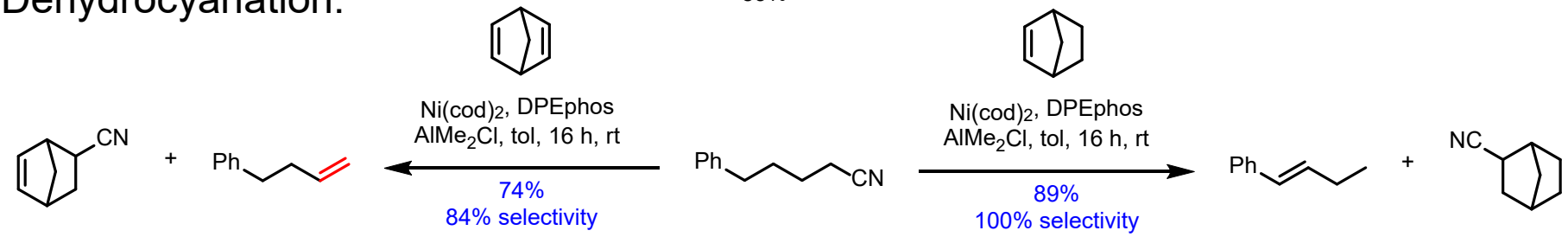
Studer 2018:



Fang 2021:



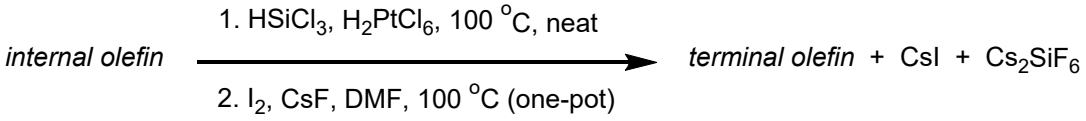
Dehydrocyanation:



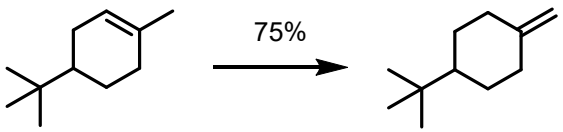
L, Buchwald.; J, LaMaire. *Tetrahedron Lett.* **1987**, *28*, 295.
A, Bhunia.; K, Bergander.; A, Studer**.** *J. Am. Chem. Soc.* **2018**, *140*, 16353.
J, Gao.; J, Ni.; R, Yu.; G, Cheng.; X, Fang. *Org. Lett.* **2021**, *23*, 486.
X, Fang.; P, Yu.; B, Morandi. *Science* **2016**, *351*, 832.

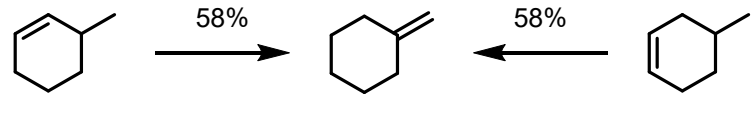
One-pot Hydrosilylation and Retrohydrosilylation

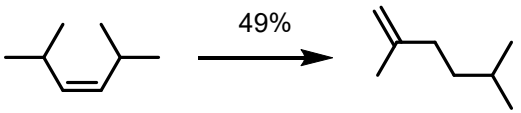
Benefit：high *n/iso* rate; neat reaction
Challenges: C-Si bond difficult for oxidative addition; microscopic reverse
Solution: coupling to additional exergonic processes

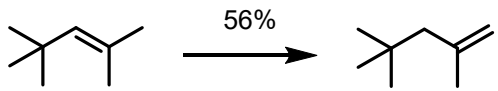


strong Si-F bond formation, I_2 reduction as driving force

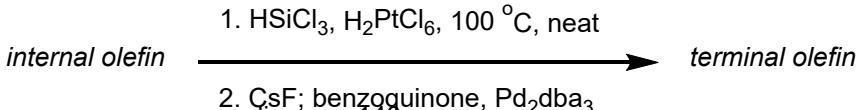


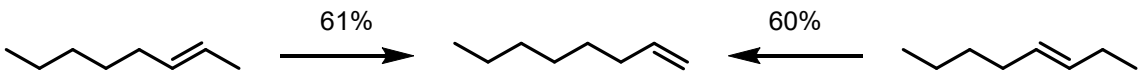


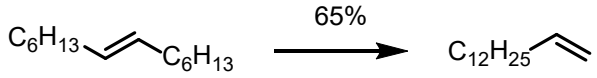




Catalytic version: more atom-efficient

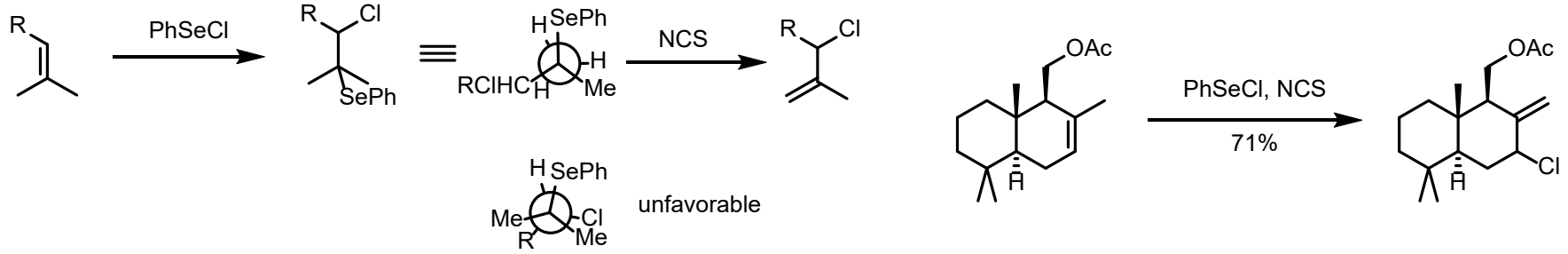


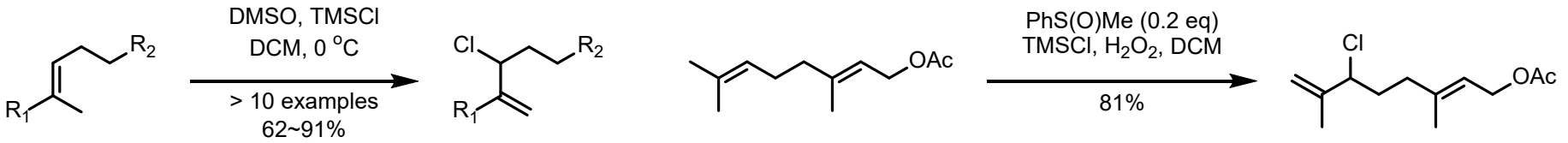


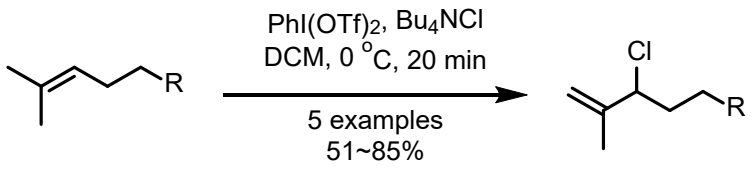


S, Hanna.; T, Butcher.; J, Hartwig. *Org. Lett.* **2019**, *21*, 7129.
S, Hanna.; T, Wills.; T, Butcher.; J, Hartwig. *ACS Catal.* **2020**, *10*, 8736.

Ene-type Allylic Substitutions







V, Delgado.; V, Armstrong.; M, Cortésa.; A, Barrerob. *J. Braz. Chem. Soc.* **2008**, *19*, 1258.

V, Demertzidou.; S, Pappa.; V, Sarli.; A, Zografos. *J. Org. Chem.* **2017**, *82*, 8710.

N, Iordanidis.; A, Zografos.; J, Gallos.; T, Koftis.; C, Stathakis. *Eur. J. Org. Chem.* **2021**, 5058.

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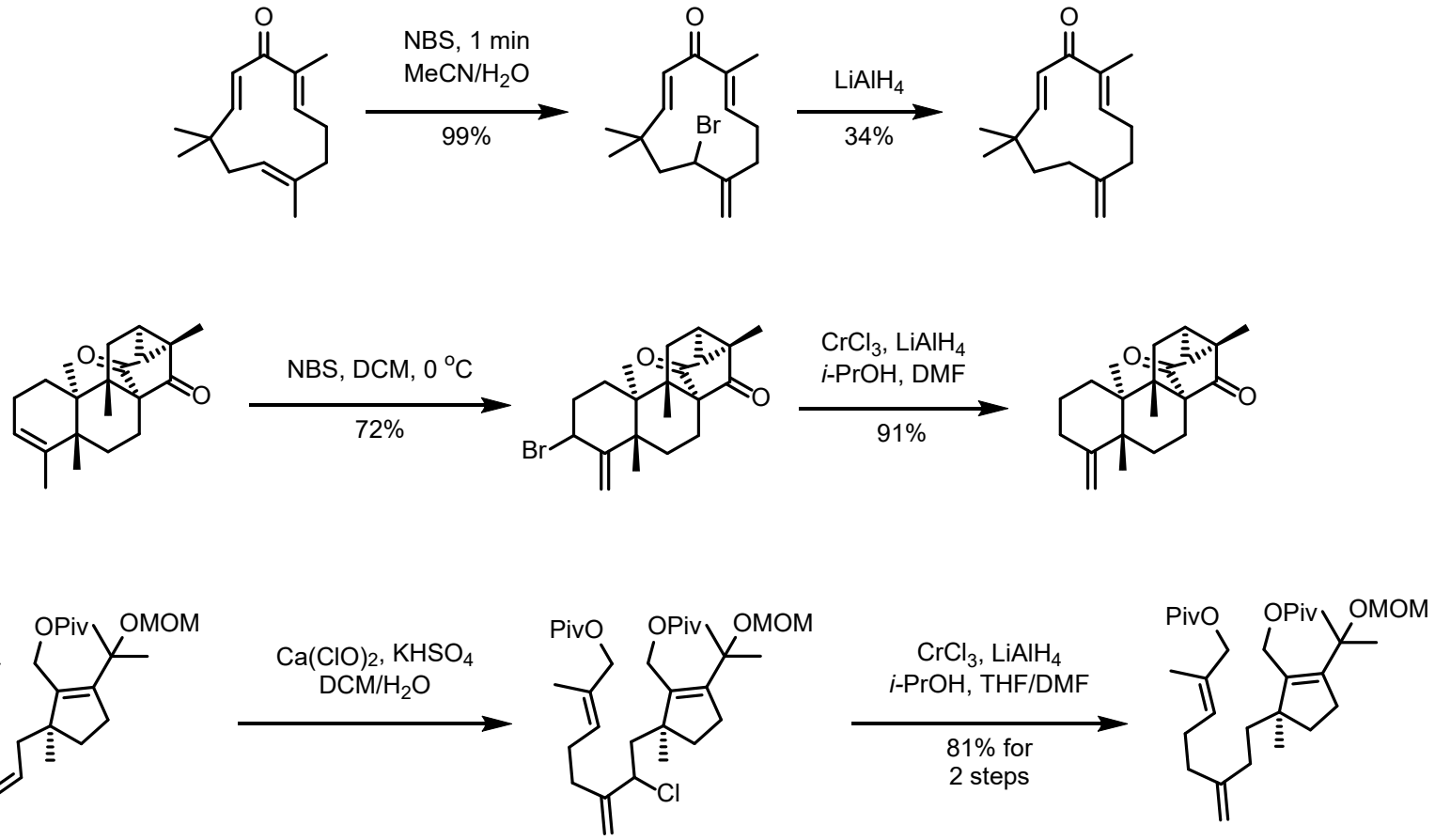
Double Bond Migrative Reduction



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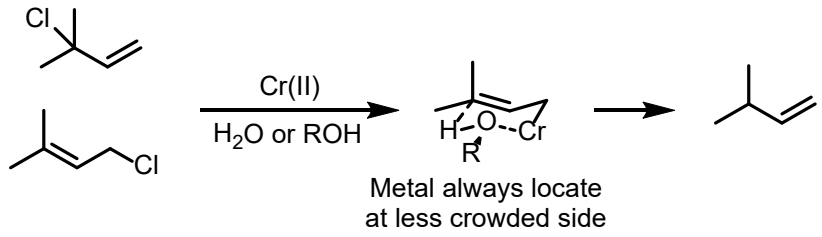
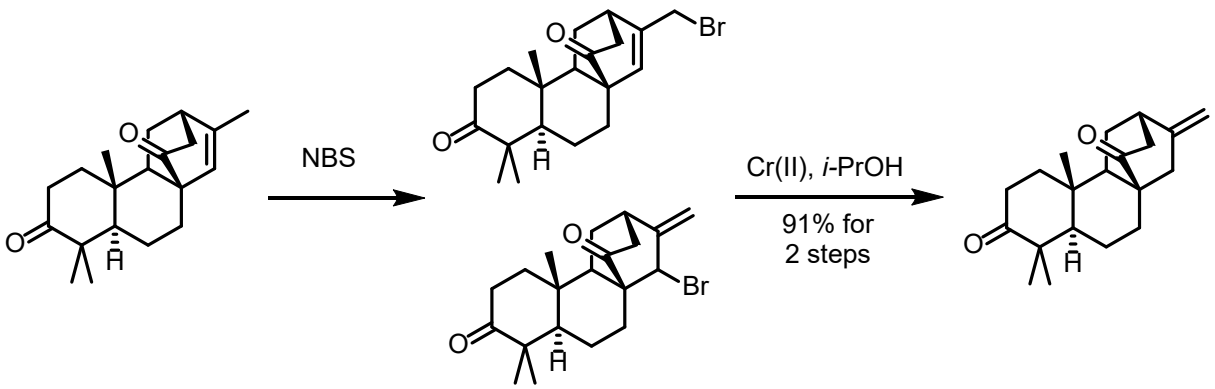
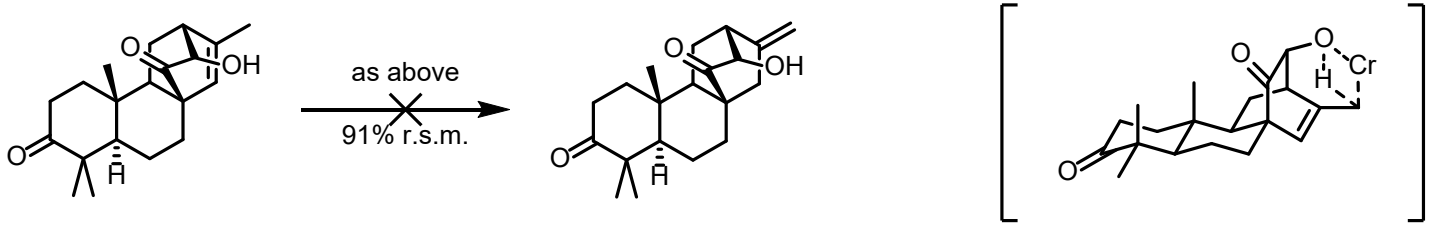
Impacts of Nearby Substitutions







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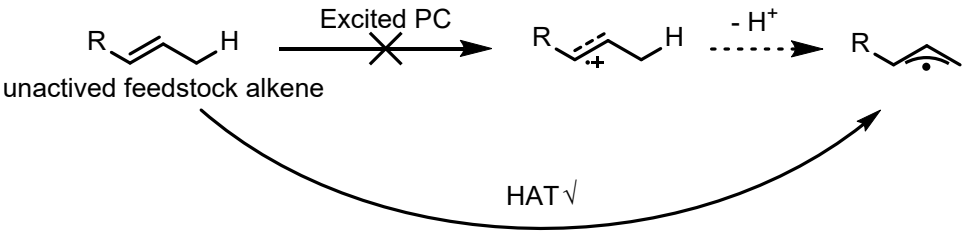
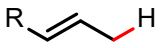
Photocatalyst-Induced Activation

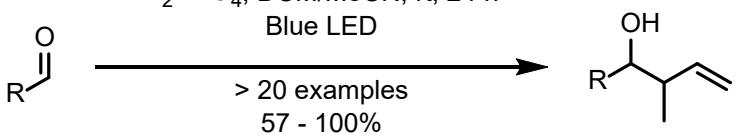


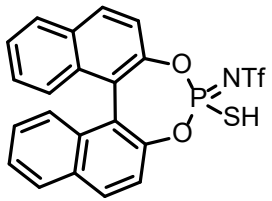


BDE ~ 85 kcal/mol

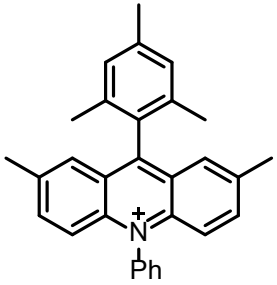
S-H

BDE ~ 87 kcal/mol



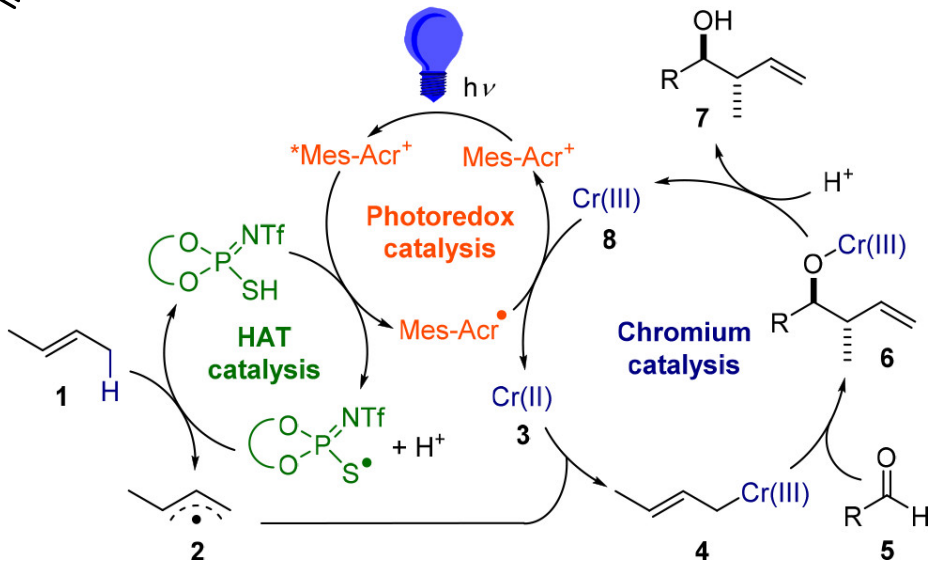


HAT1



PC1

φ ~ 2.1 V vs SCE



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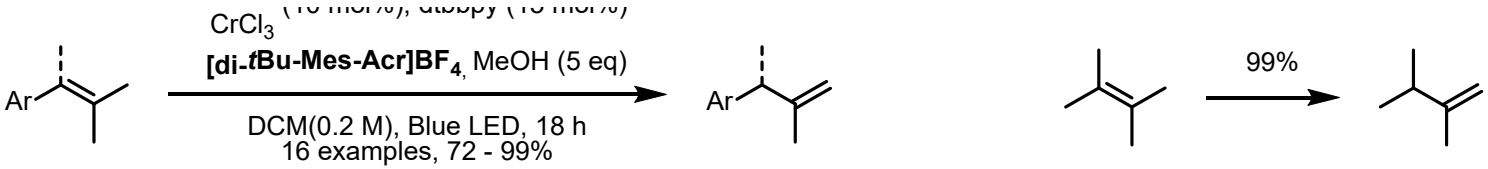
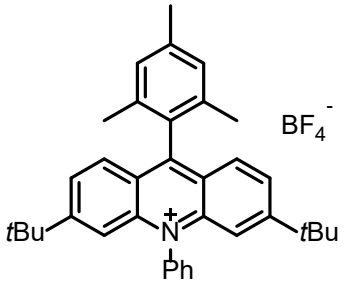
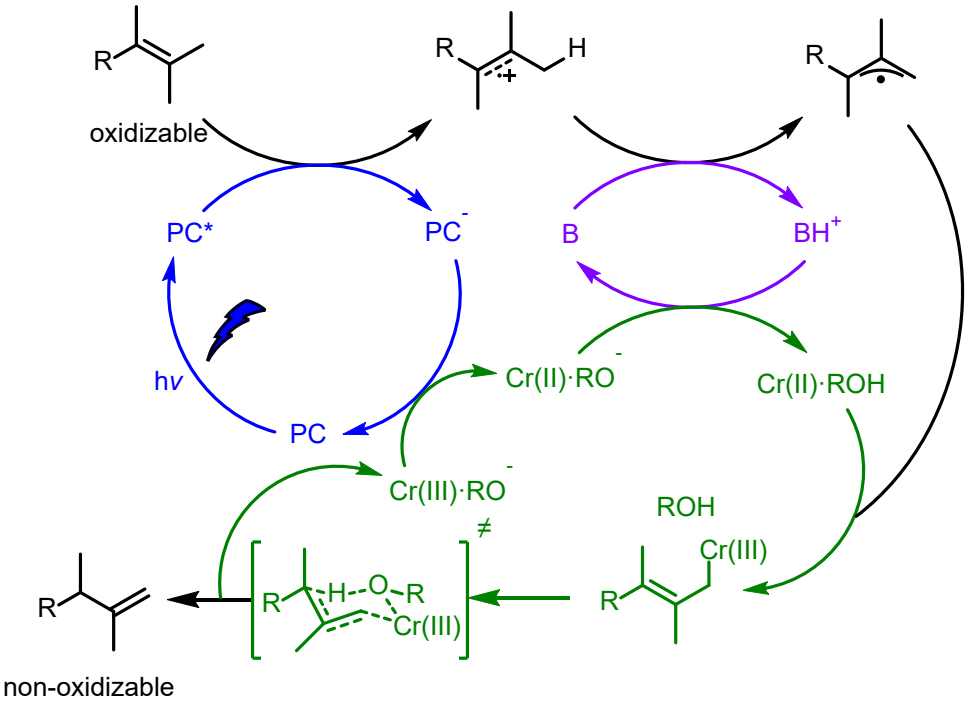
For Alkenes with Lower Oxidation Potentials





[di-*t*Bu-Mes-Acr]BF_4



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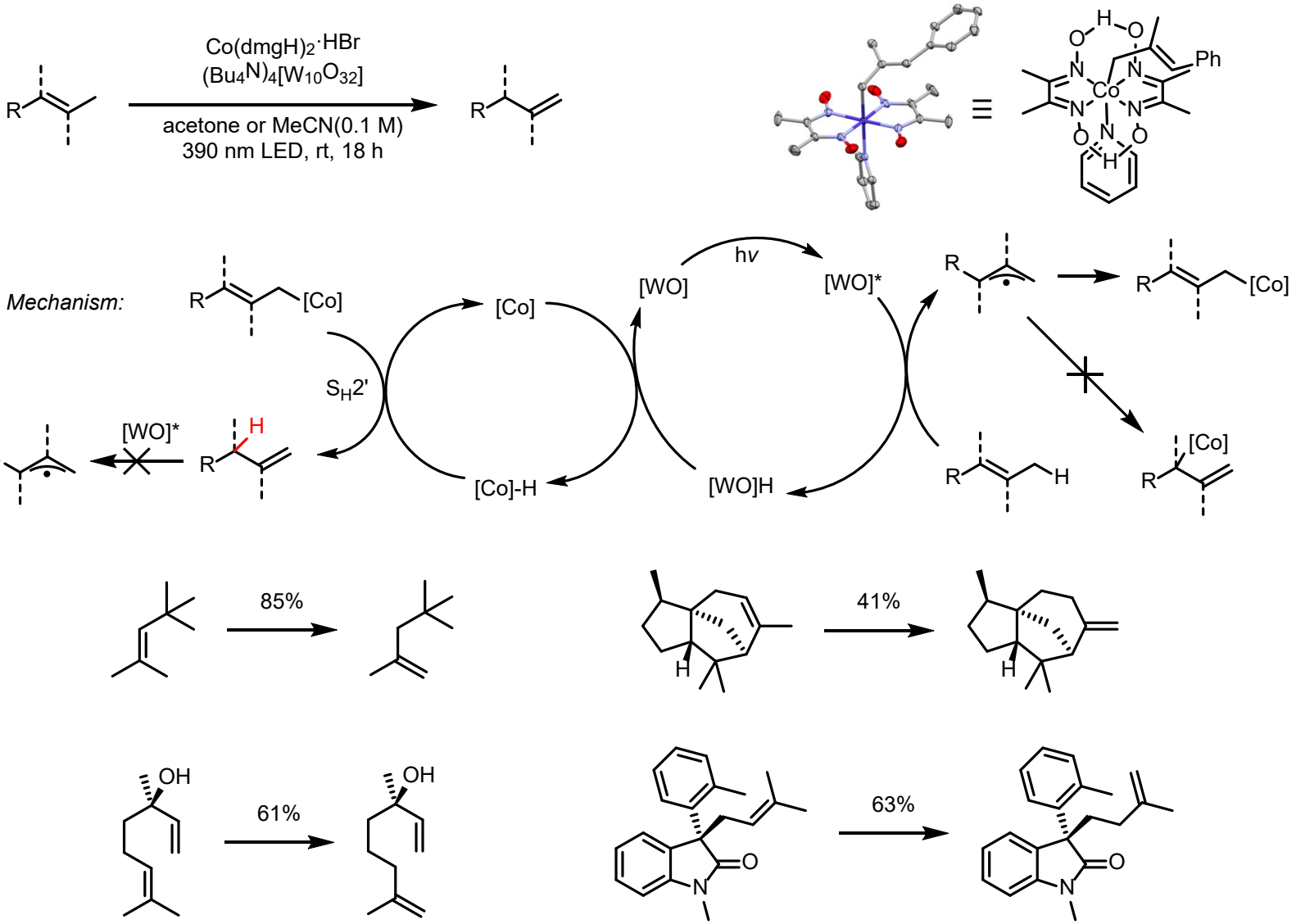
The First Universal Solution?



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Summary

Fighting against thermodynamics:

- Selective excitation of alkenes with better conjugation
- Kinetic-controlled protonation at specific position
- Addition——chain walking——defunctionalization
- Ene-type allylic substitution and reduction
- Metals' favorability of terminal location
- Selective hydrogen atom extraction for non-oxidizable olefins
- Applications in total syntheses and late-stage transformations