

Cyclopropanation of Unactivated Olefins

Outline:

I. Isolated olefins

i. Electron-withdrawing group transfer

- a. Carreira (2023)
- b. Giri (2023)
- c. Wickens (2023)
- d. Rovis (2019)

ii. Methylene and alkyl group transfer

- a. Renaud (2019)
- b. Nagib (2024)
- c. Uyeda (2023)

II. Styrenes

- a. Wilkerson-Hill (2022)
- b. Suero (2017)
- c. Molander (2018)
- d. Charette (2018)

Not covered:

- Activated olefins, such as those substituted with electron withdrawing groups
- Simmons-Smith and diazo reagents as carbene precursors
- Classical cyclopropanations made enantioselective
- Highly specific starting materials (i.e. only works on indoles)
- Intramolecular cyclopropanation
- Methods before 2000

Relevant Reviews:

[Visible light mediated cyclopropanation \(2022\)](#)

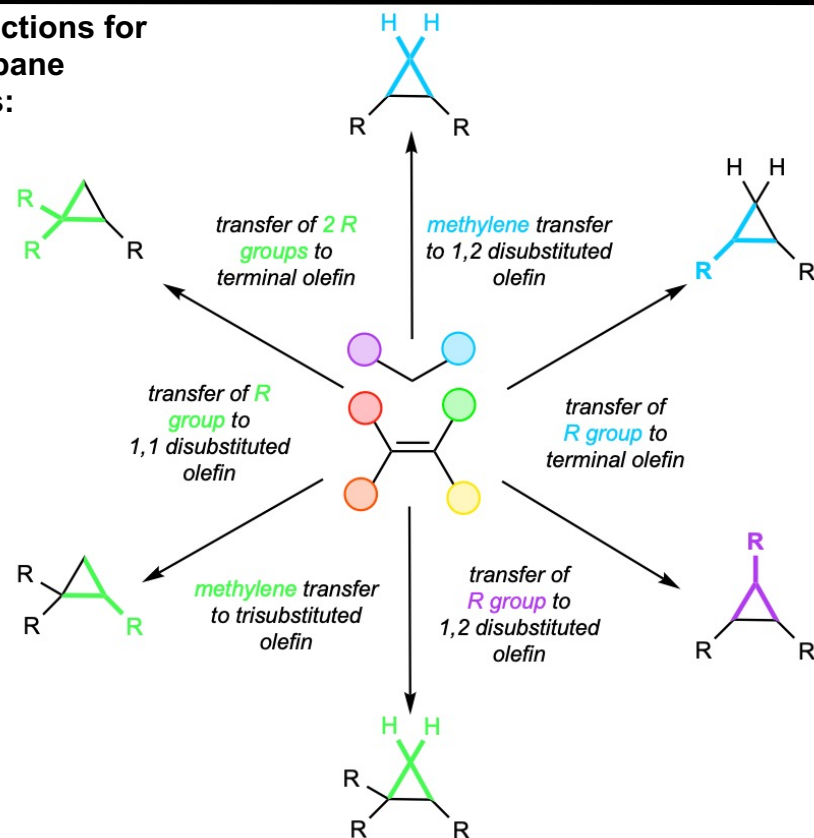
[Stereoselective cyclopropanation \(2003\)](#)

[Asymmetric cyclopropanation \(2007\)](#)

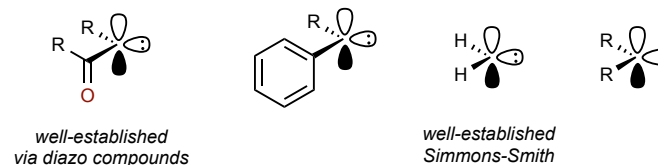
[Organocatalytic cyclopropanation \(2022\)](#)

[Cyclopropanation in total synthesis \(2017\)](#)

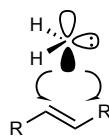
Disconnections for cyclopropane synthesis:



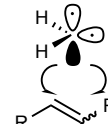
Common methods:



← stability of carbene intermediates



singlet carbene
concerted 2+1 cycloaddition
stereospecific



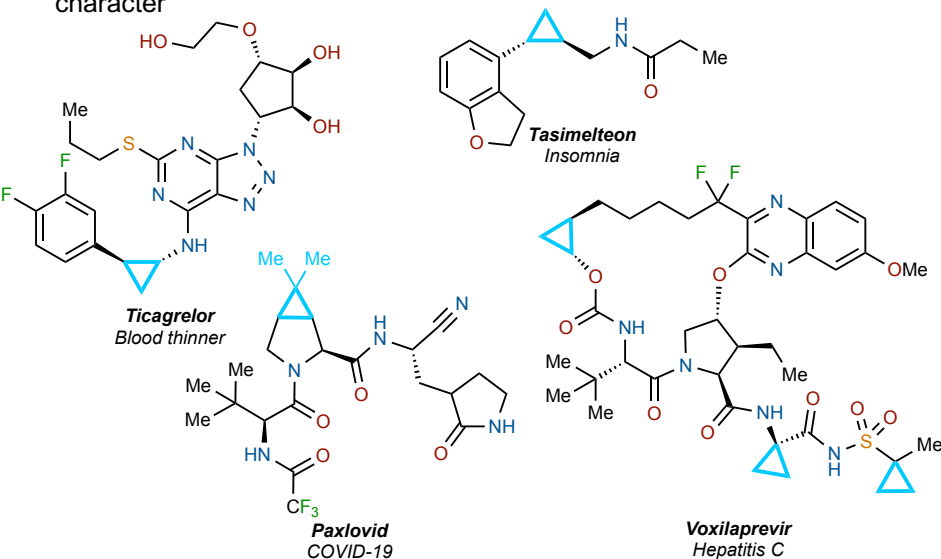
triplet carbene
stepwise bond formation
stereoconvergent

How do different mechanisms allow for different substitution patterns, stereochemistry, and electronics of olefins that react?

Introduction to Cyclopropanes

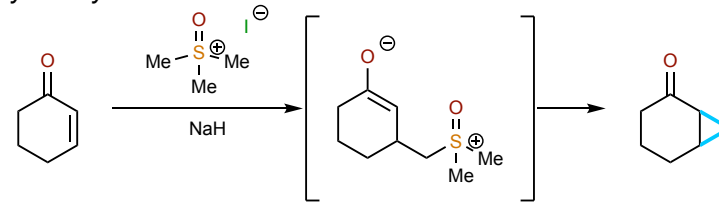
Cyclopropanes in Medicinal Chemistry:

- 6th most common ring and a commonly used bioisostere
- Number of cyclopropane-containing approved small molecule drugs has doubled in last 10 years
- Can modulate the 3D geometry of drug molecules while increasing sp³ character



Common Cyclopropane Syntheses:

Corey-Chaykovsky



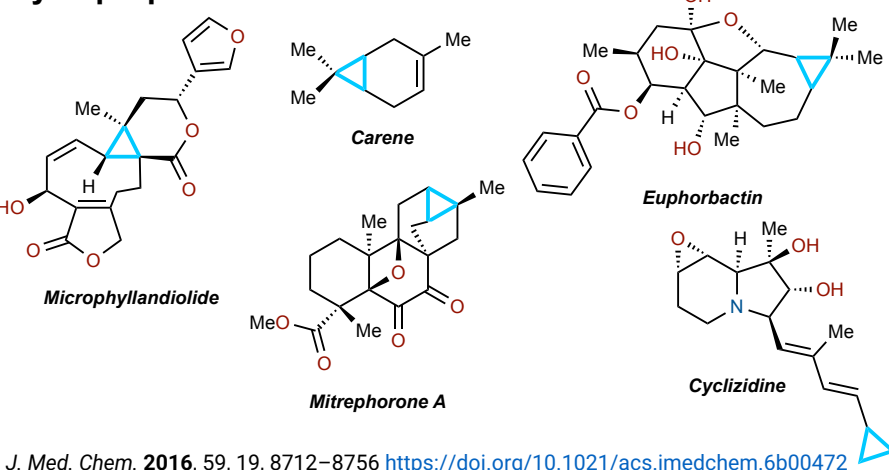
- Requires an electron deficient olefin substituted with ketone, ester, or amide
- Sulfoxonium reagents exhibit better 1,4 selectivity than sulfonium reagents
- Typically only allows for methylene transfer

Double Alkylation

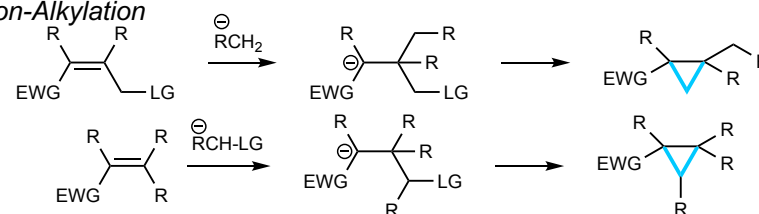


- Requires stabilized carbanion, most often flanked by two electron withdrawing groups
- Introducing additional substitution is challenging due to elimination prone di-halides

Cyclopropanes in Natural Products:



Addition-Alkylation



- Requires electron deficient olefin and specific placement of leaving group

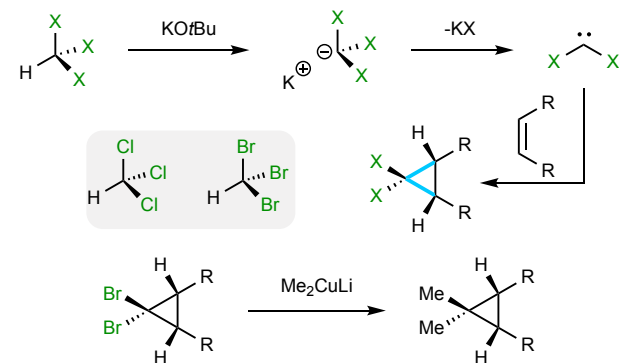
Kulinkovich Reaction



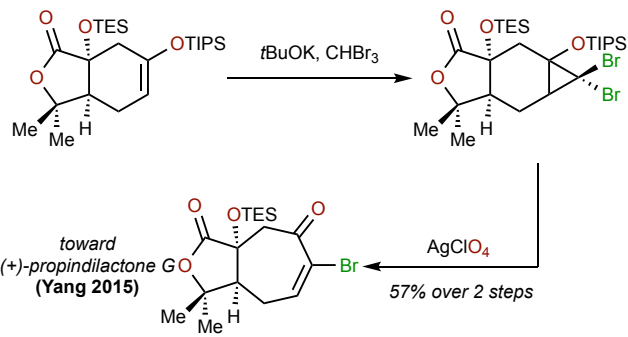
- Generates 1-alkylcyclopropanols
- Possible to exchange ethylene with other olefins to generate more substituted products

Common Ways to Make Cyclopropanes

Free Carbenes

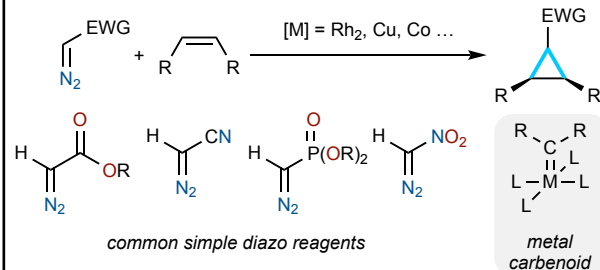


- Haloform reagents form free dihalocarbenes under basic conditions in alcoholic solvents
- Typically results in dibromo- or dichloro-cyclopropanes that can be further elaborated or dehalogenated
- Occurs in a stereospecific and concerted manner
- A common way to install dimethyl cyclopropanes, as dialkylcarbenes are difficult to access
- Often applied to affect a one-carbon ring expansion

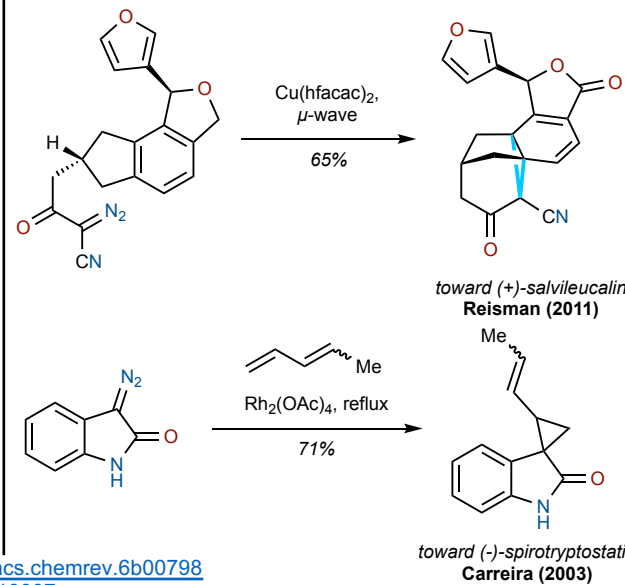


Chem. Rev. **2017**, 117, 11651–11679 <http://dx.doi.org/10.1021/acs.chemrev.6b00798>
 Chem. Rev. **2003**, 103, 4, 977–1050 <https://doi.org/10.1021/cr010007e>

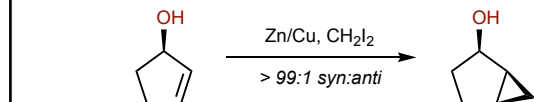
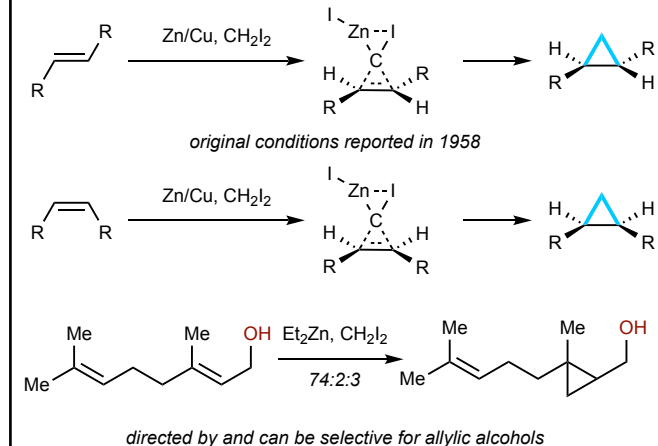
Diazo-derived Carbenoids



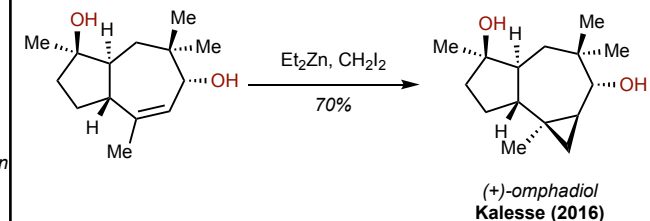
- Decomposes to form stabilized metal carbenoid intermediates
- Diazo reagents potentially explosive
- Alkyl diazo compounds lacking stabilizing groups can be generated in situ
- Carbene dimerization and C-H insertion are possible side reactions
- Chiral ligands allow for enantioselective variants
- **Common way to cyclopropanate unactivated olefins**



Simmons-Smith



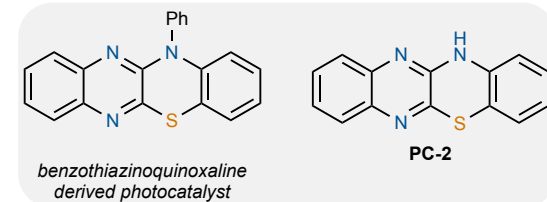
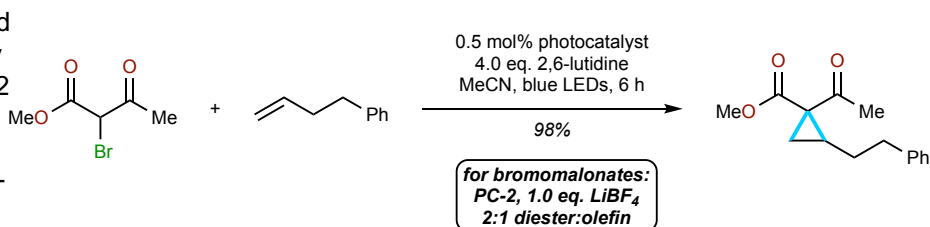
- Works well to transfer non-stabilized carbenes
- Stereospecific depending on geometry of starting olefin
- Alkyl substituted carbenes prone to 1,2 hydride shifts
- Often low selectivity in presence of several olefin
- Can be accelerated by Lewis acids
- Chiral Lewis acids can allow for enantioselective variants, but largely limited to allylic alcohols
- **Common way to cyclopropanate unactivated olefins**



Photocatalytic Cyclopropanation

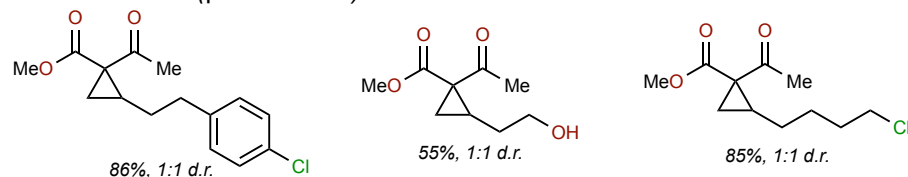
Carreira (2023)

- Cyclopropanation of unactivated olefins known photocatalytically both intramolecularly and over 2 steps
- Intermolecular reaction with unactivated olefin and α -bromo- β -ketoesters still challenging

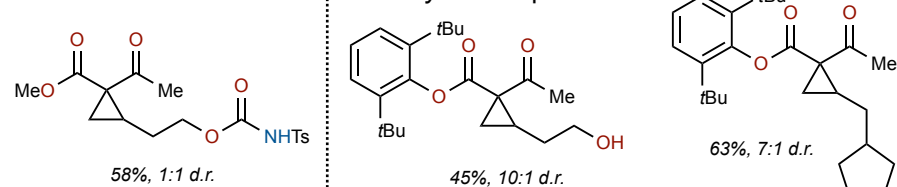


Substrate scope:

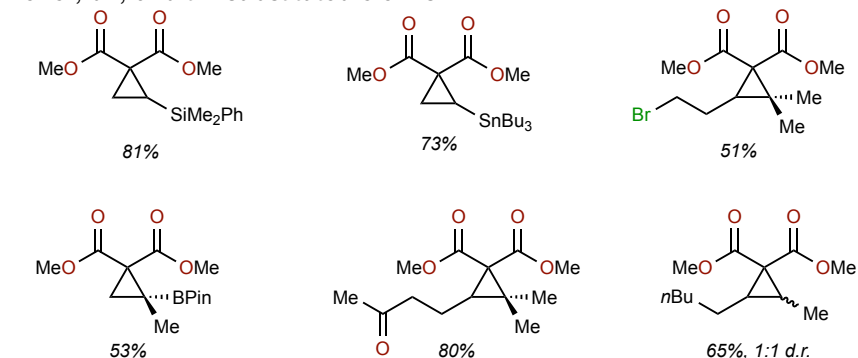
terminal olefins (β -ketoesters)



sterically biased β -ketoesters:

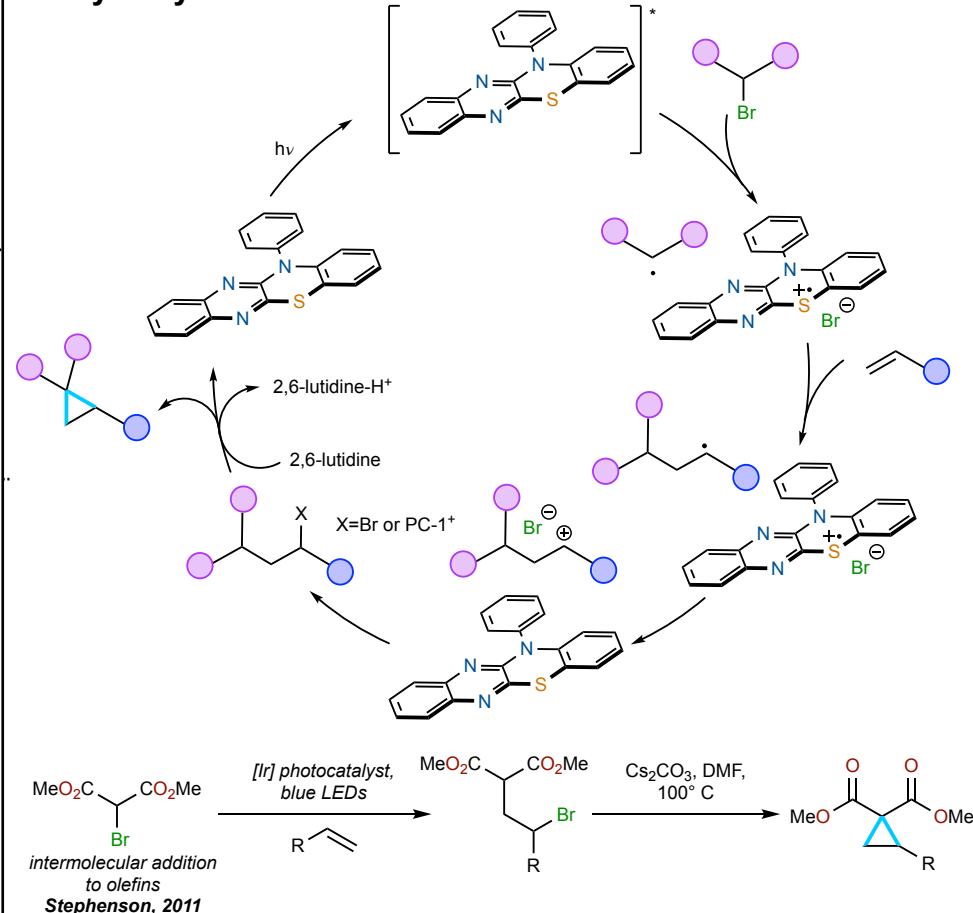


mono-, di-, and tri-substituted olefins



isolated as mixtures, major diastereomers not determined

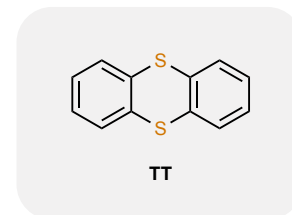
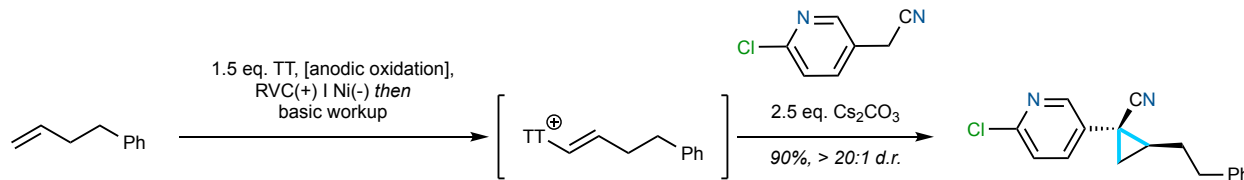
Catalytic cycle:



Thianthrenium Salts

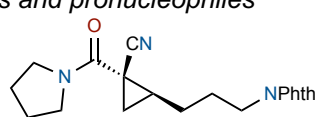
Wickens (2023)

- Dihalides bearing substitution generally fail in double-alkylation reactions
- Thianthrenium salts allow olefins to behave as dielectrophiles

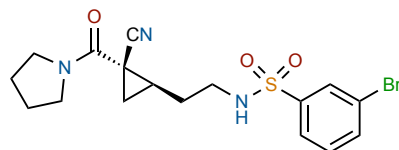


Substrate scope:

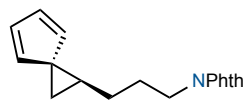
olefins and pronucleophiles



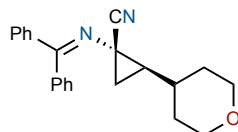
79%, > 20:1 d.r.



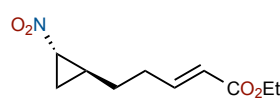
54%, > 20:1 d.r.



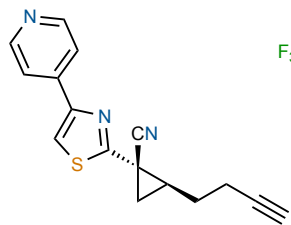
45%



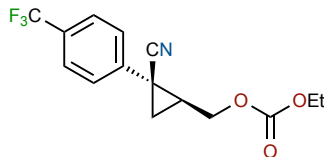
68%, 2:1 d.r.



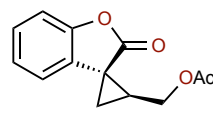
55%, > 20:1 d.r.



47%, 6:1 d.r.

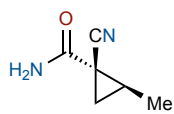


70%, > 20:1 d.r.

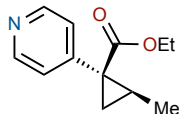


54%, 4:1 d.r.

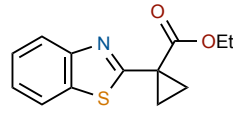
feedstock olefins



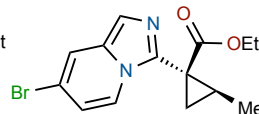
74%, > 20:1 d.r.



83%, 4:1 d.r.

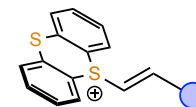
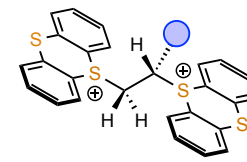
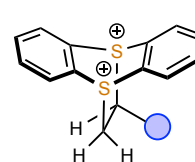


67%



50%, > 20:1 d.r.

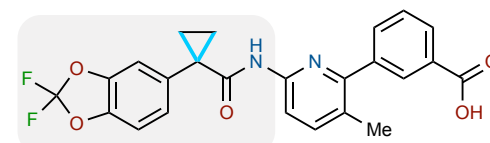
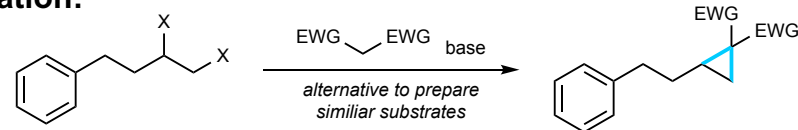
Reaction intermediates:



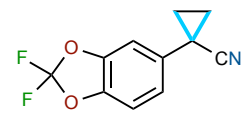
Intermediates before addition of Cs₂CO₃

Key di-electrophile intermediate

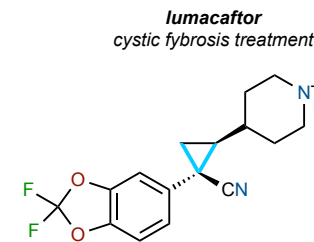
Application:



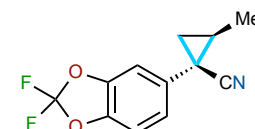
lumacaftor
cystic fibrosis treatment



87%
yield from dihalide: 88-100%



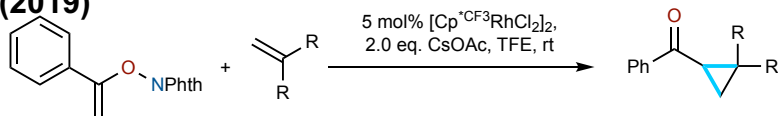
75%, > 20:1 d.r.
yield from dihalide: < 5%



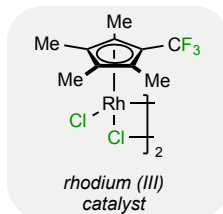
74%, > 20:1 d.r.
yield from dihalide: < 5%

C-H Activation and Radical Addition

Rovis (2019)



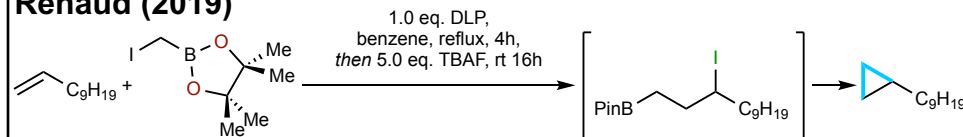
N-enoxyphthalimides



rhodium (III) catalyst

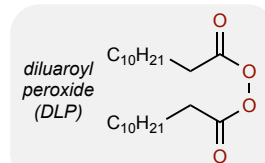
- Allows for different substitution on carbenoid
- Known previously on electron deficient olefins and on allylic alcohols

Renaud (2019)



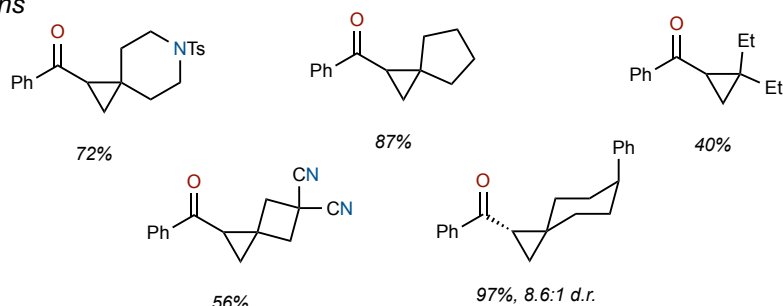
2.0 eq.

- 3-haloalkylboronates as cyclopropane precursors
- Known via hydroboration of allylic chlorides but represents first use of boronic ester

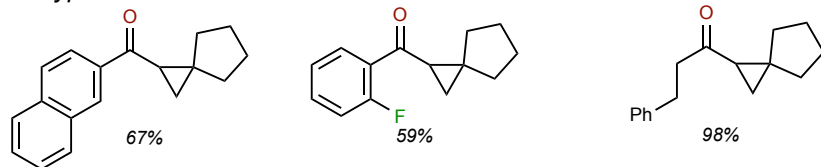


Substrate scope:

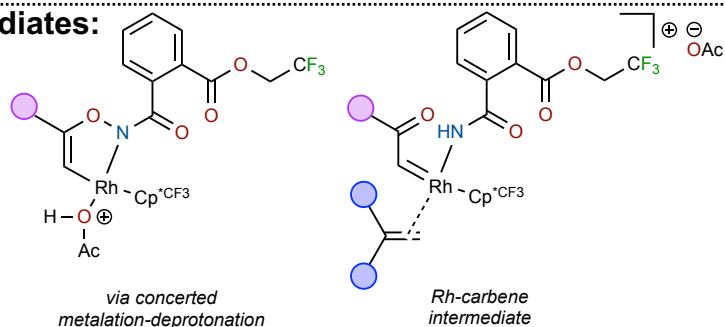
olefins



N-enoxyphthalamide substituent



Key intermediates:



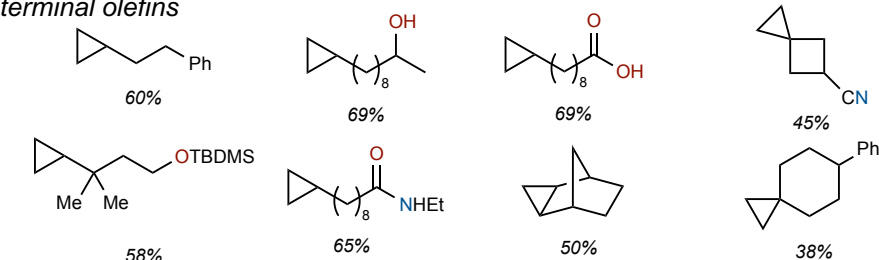
via concerted metalation-deprotonation

Rh-carbene intermediate

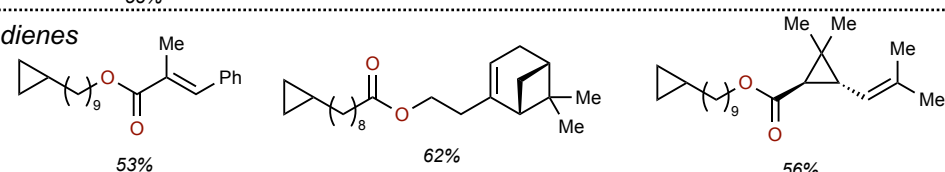
Synlett 2019, 30, 1787–1790 <https://doi.org/10.1055/s-0039-1690130>

Substrate scope:

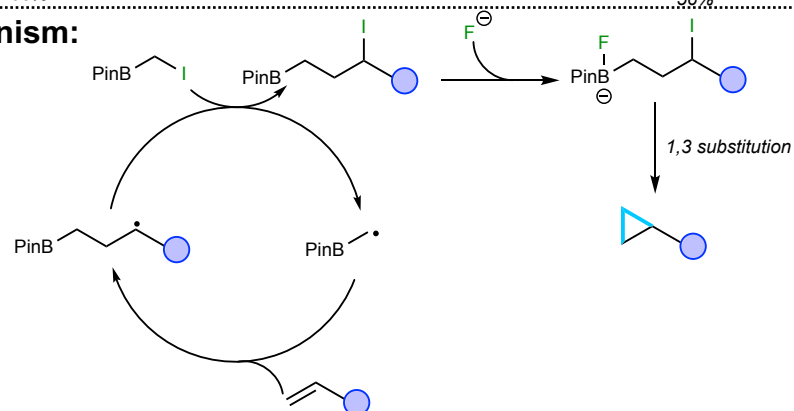
terminal olefins



dienes



Mechanism:

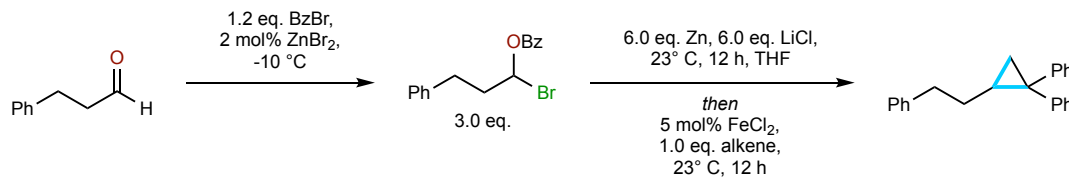


Angew. Chem. Int. Ed. 2019, 58, 14240–14244 <https://doi.org/10.1002/anie.201907962>

Iron Carbenes

Nagib (2024)

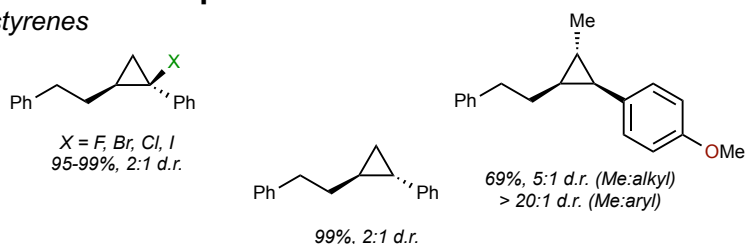
- Works on unactivated, alkyl olefins
- Via a non-stabilized iron carbene
- LiCl necessary as activator



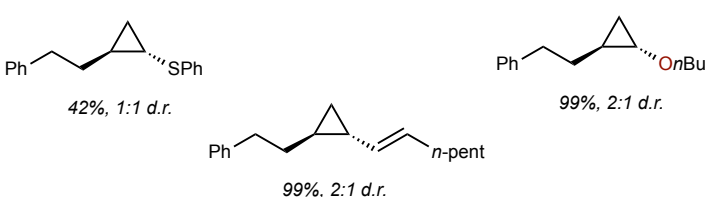
One-pot procedure possible with 10 mol% FeCl₂ and olefin added after 3 hours

Substrate scope:

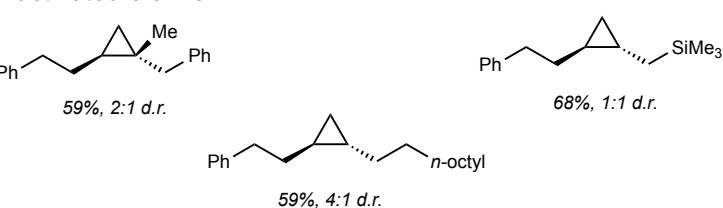
styrenes



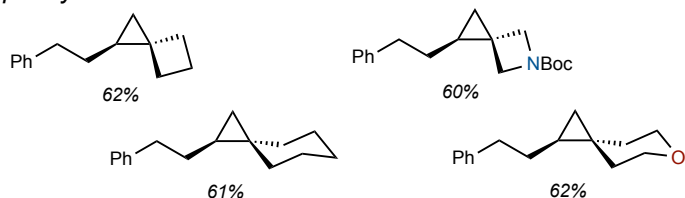
α -heteroatom and dienes



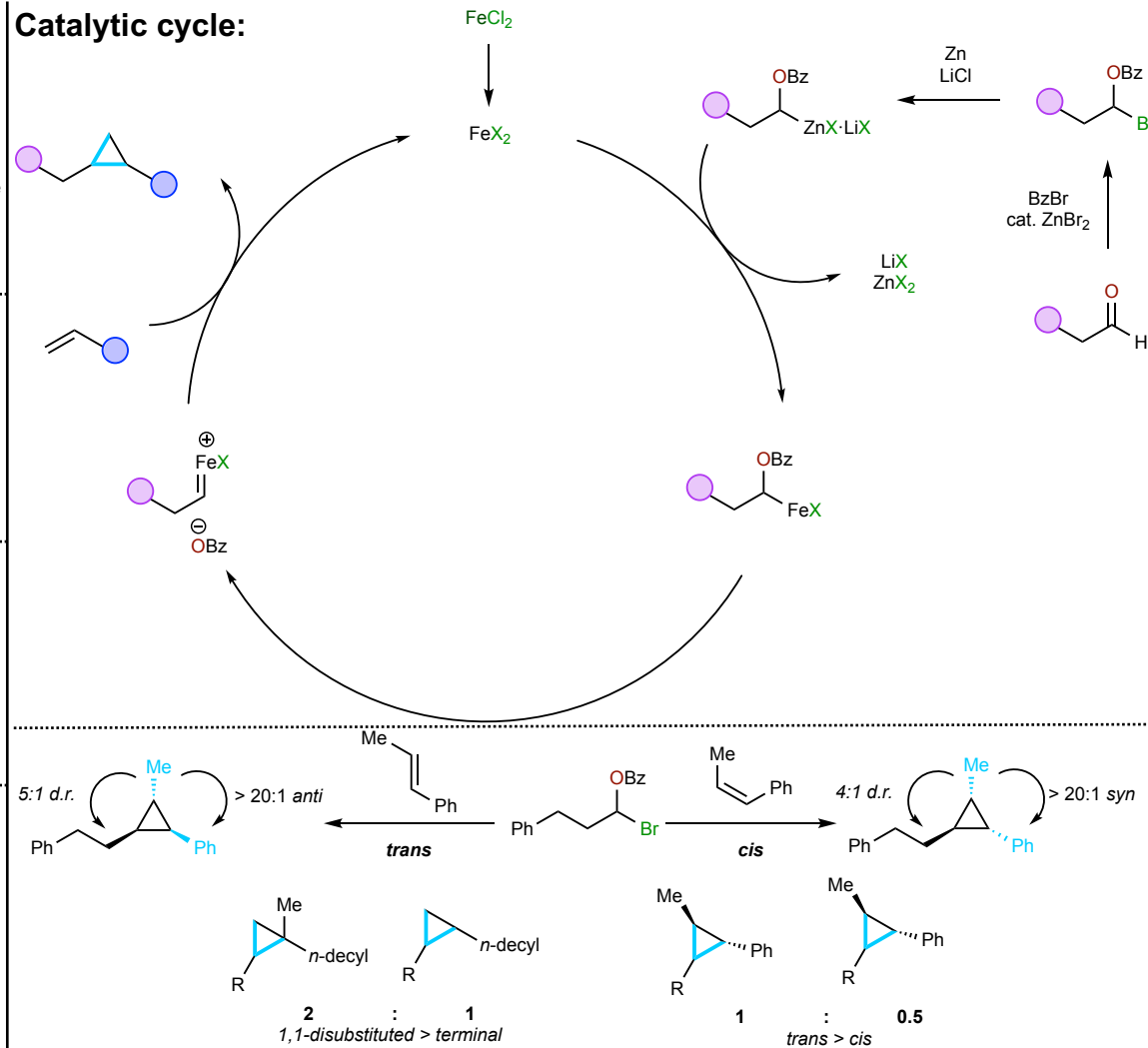
unactivated olefins



spirocycles



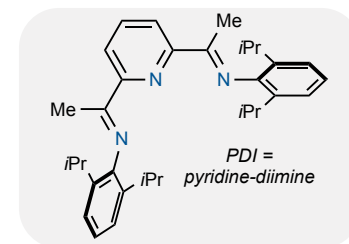
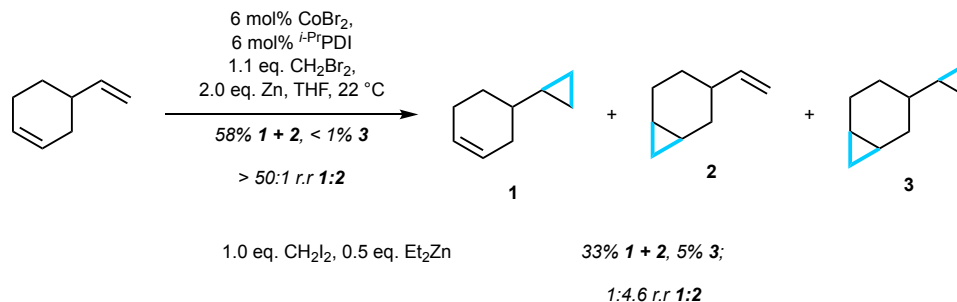
Catalytic cycle:



Cobalt Catalysis

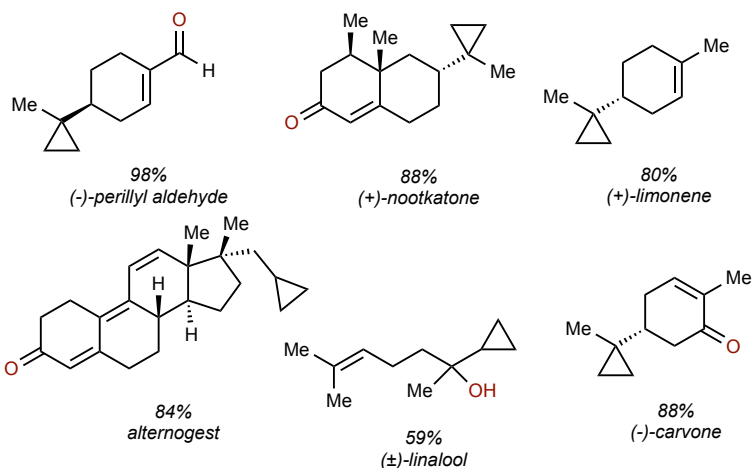
Uyeda (2018)

- Simmons-Smith often poor selectivity between multiple olefins with similar electronics
- Often results in mixtures of polycyclopropanated products
- Zn/Co bimetallic system helps discriminate between similar olefins by allowing for selectivity based on sterics

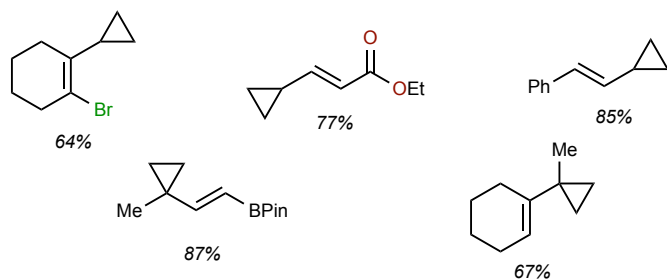


Substrate scope:

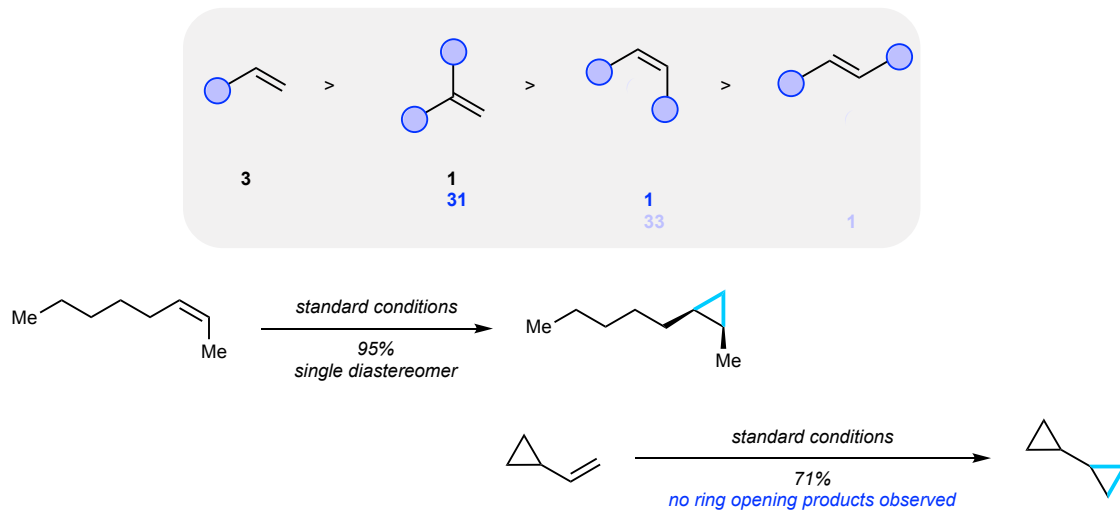
terpene natural products



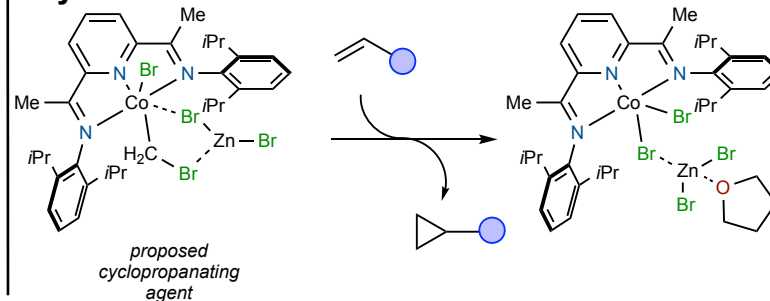
1,3 dienes



Stereospecificity and selectivity:



Key intermediates:

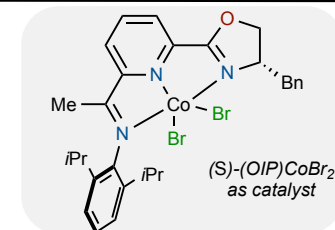
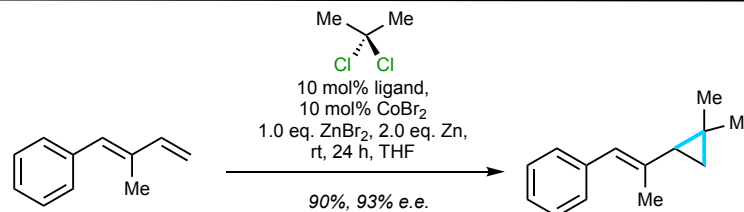


- Co(I)/Co(II) cycle
- Reaction without [Zn] displays much lower yields and r.r.
- Possible that [Zn] acts as a Lewis acid

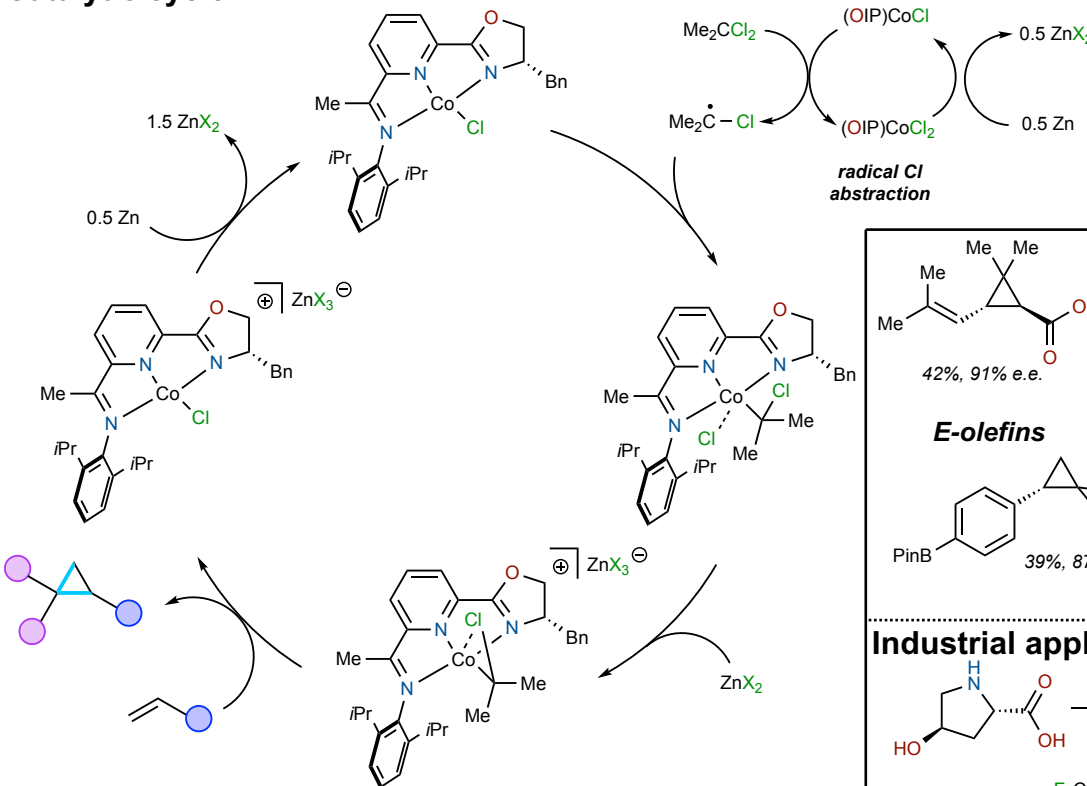
Asymmetric Cobalt Catalysis

Uyeda (2023)

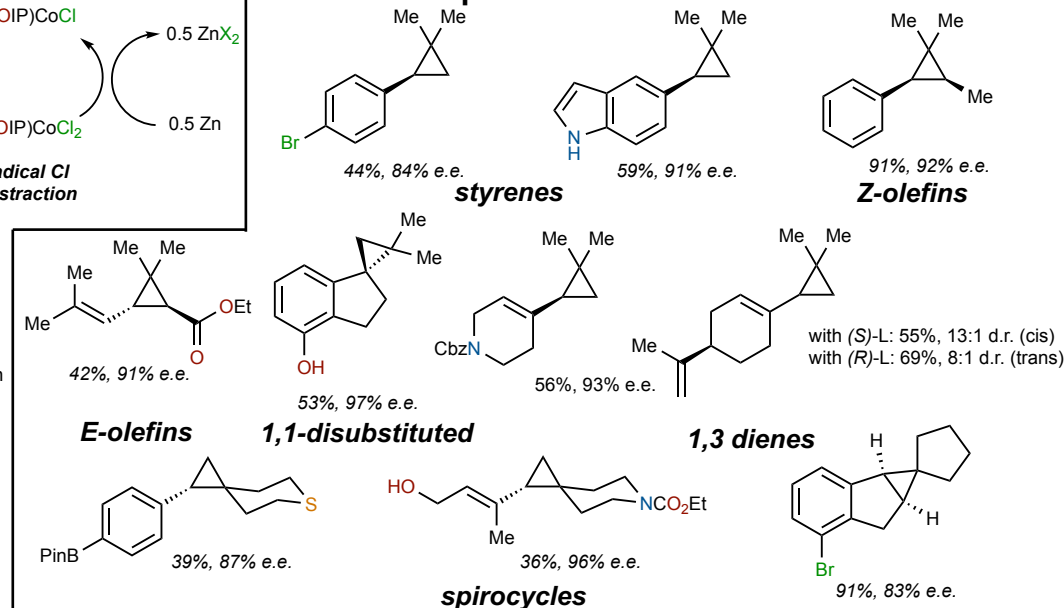
- Enantioselective Simmons-Smith reactions generally work best with allylic alcohols and are based on chiral Lewis acids
- Transfer of alkyl-substituted carbenes in reductive cyclopropanation remains challenging



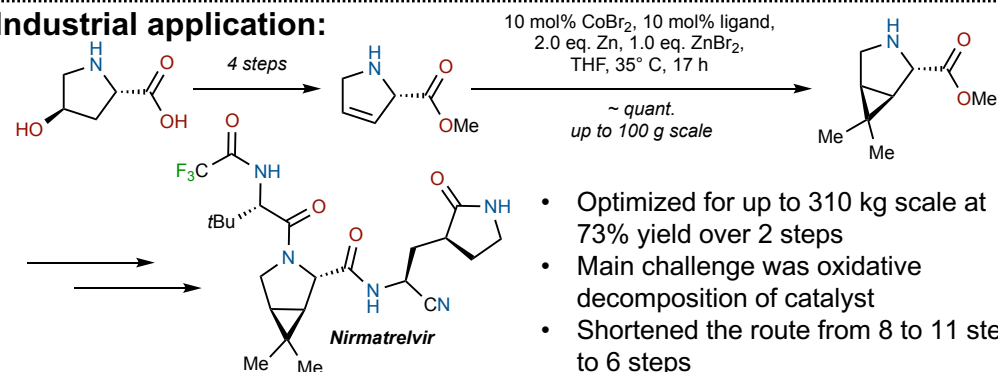
Catalytic cycle:



Substrate scope:



Industrial application:

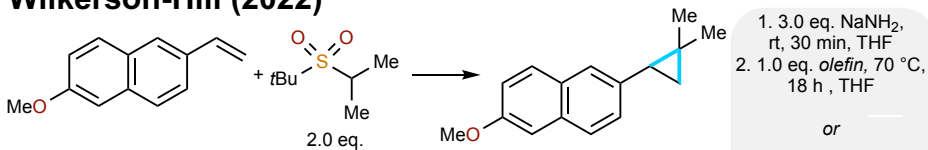


- Stoichiometric studies in ZnBr₂ gave 60% yield; with ZnX₂ additive result was 0% yield
- Branching required for good enantioselectivity
- Pro-R transition state places carbene away from Bn group and olefin substituents away from aryl group

- Optimized for up to 310 kg scale at 73% yield over 2 steps
- Main challenge was oxidative decomposition of catalyst
- Shortened the route from 8 to 11 steps to 6 steps

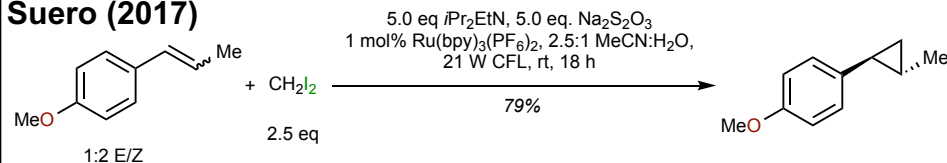
Cyclopropanation of Styrenes

Wilkerson-Hill (2022)



- Known previously with Ni(0) catalysis to transfer methylene units
- Allows for transfer of dialkyl groups larger than methyl

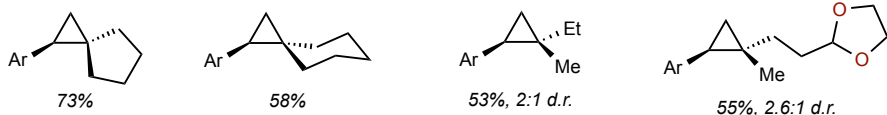
Suero (2017)



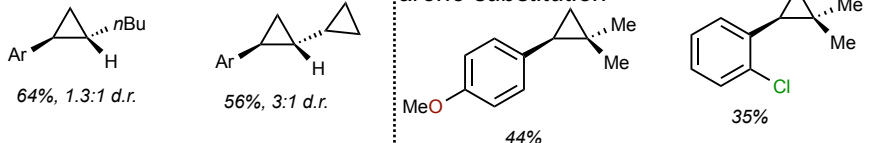
- Stereoconvergent cyclopropanation of styrenes allows for mixtures of olefin isomers to be utilized, as intermediates leading to *trans* isomer reacts faster

Substrate scope:

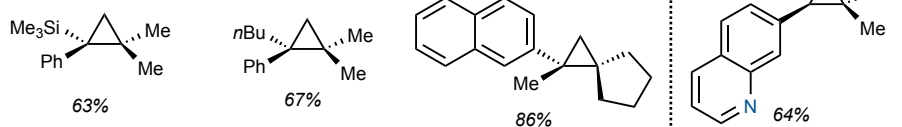
sulfones



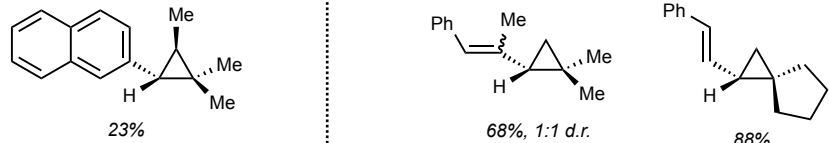
arene substitution



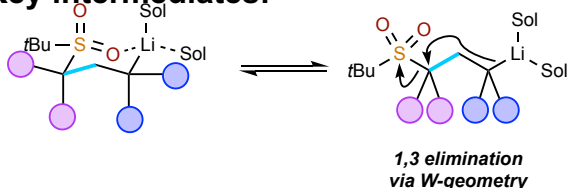
olefin substitution



dienes



Key intermediates:

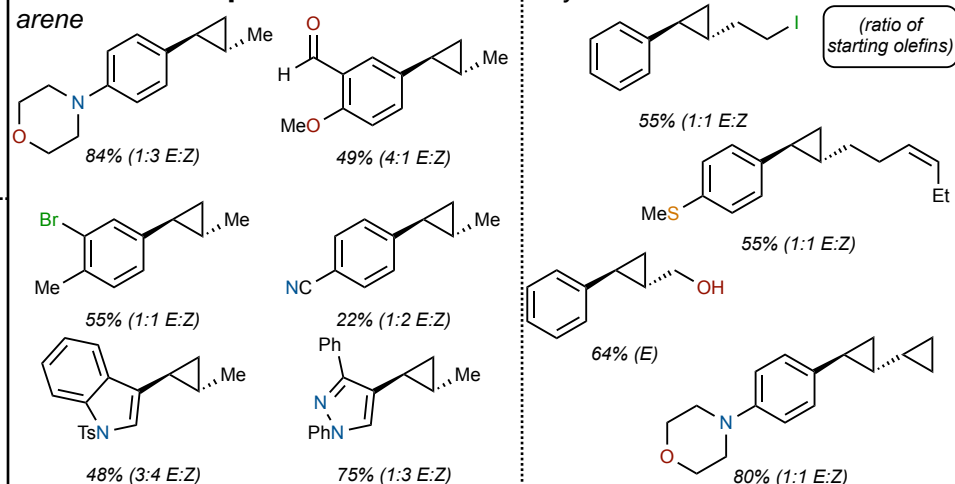


Solvent choice and $t\text{Bu}$ as sulfone substitution prevent unwanted anionic polymerization reactions

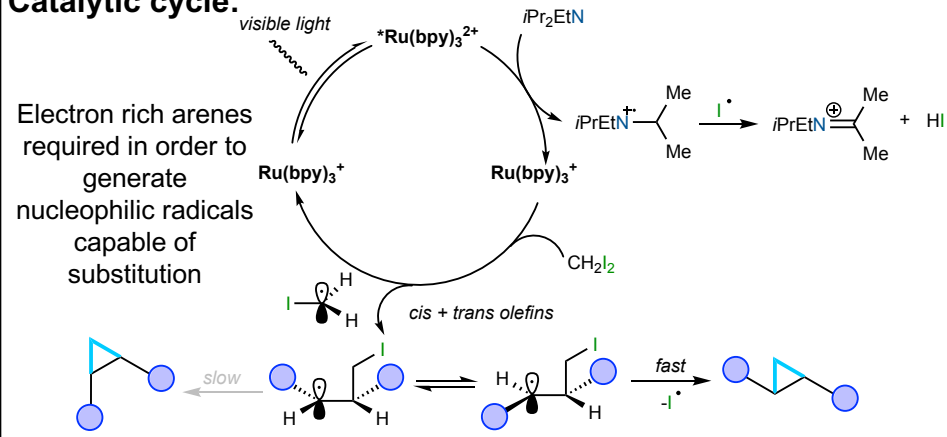
J. Am. Chem. Soc. **2022**, 144, 14471–14476 <https://doi.org/10.1021/jacs.2c07063>

Substrate scope:

arene



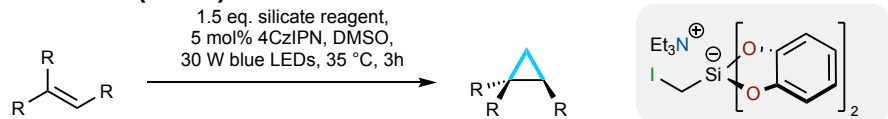
Catalytic cycle:



Angew. Chem. Int. Ed. **2017**, 56, 1610–1613 <https://doi.org/10.1002/anie.201610924>

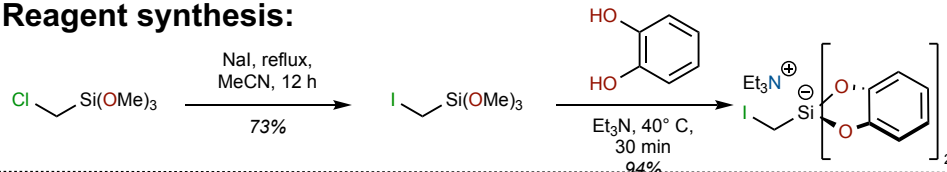
Cyclopropanation of Styrenes

Molander (2018)



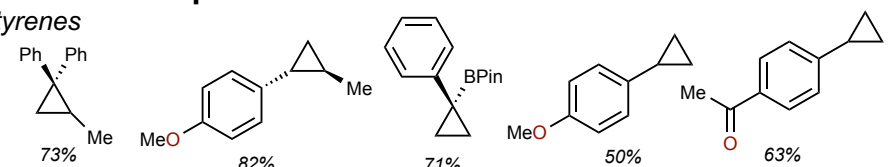
- Halo-methyl silicate reagent as methylene equivalent via Giese-type addition to styrenes
- Stereoconvergence observed for 1,2 disubstituted and trisubstituted olefins

Reagent synthesis:

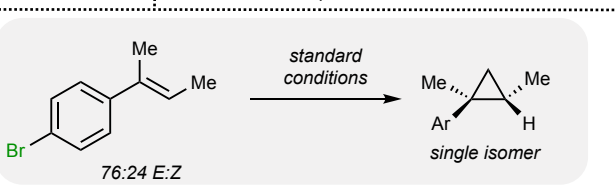
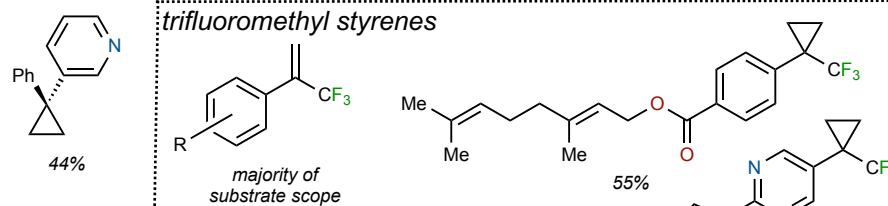


Substrate scope:

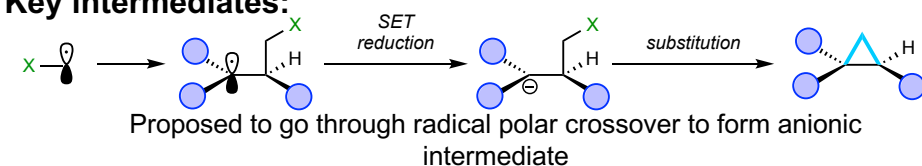
styrenes



trifluoromethyl styrenes

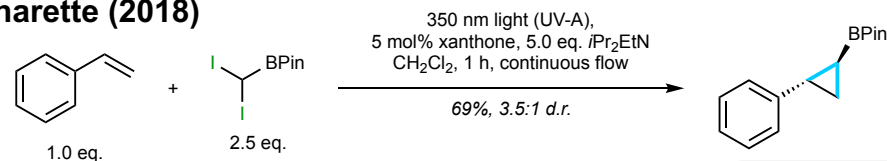


Key intermediates:

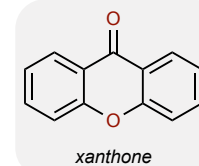


J. Am. Chem. Soc. **2018**, *140*, 8037–8047 <https://doi.org/10.1021/jacs.8b05243>

Charette (2018)

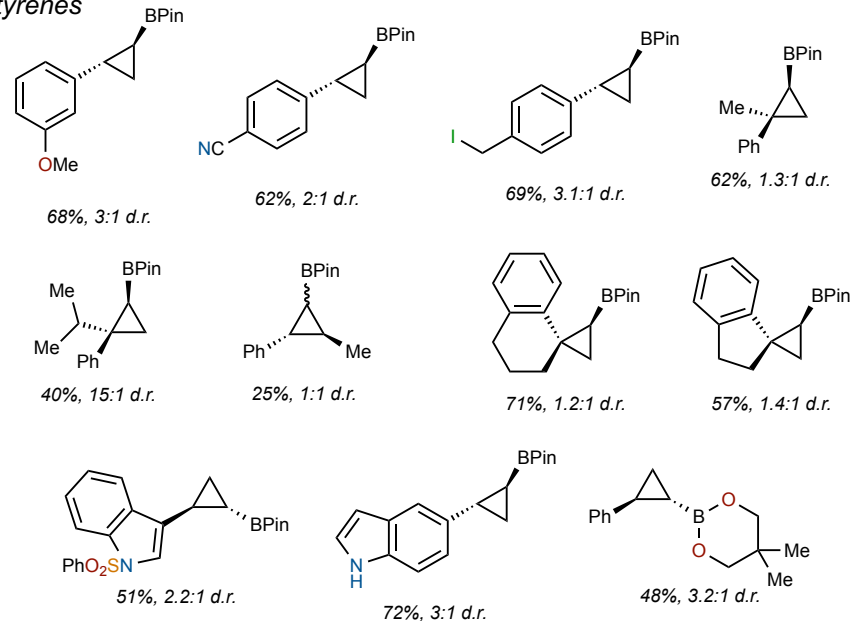


- Common alternative approaches include Simmons-Smith or via diazo compounds on vinyl boronates, hydroboration of cyclopropenes, or lithium/halogen exchange on halogenated cyclopropane followed by trialkylborate trapping



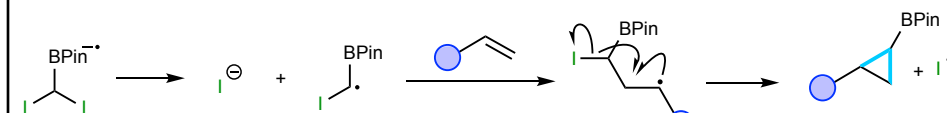
Substrate scope:

styrenes



Key intermediates:

Xanthone radical anion transfers an electron to form fragmentation precursor

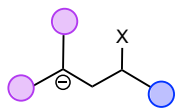
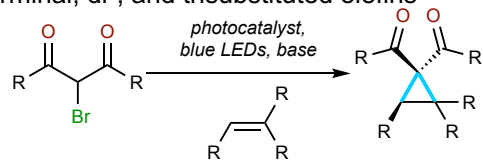


Angew. Chem. Int. Ed. **2018**, *57*, 13514–13518 <https://doi.org/10.1002/anie.201807347>

Summary

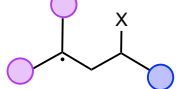
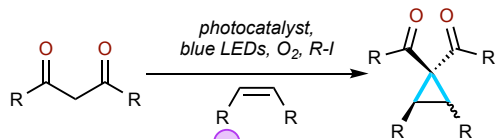
Carreira (2023)

- transfer of 2 electron-withdrawing R groups
- terminal, di-, and trisubstituted olefins



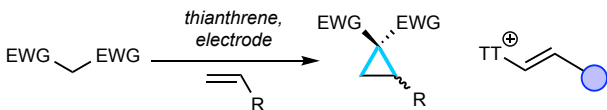
Giri (2023)

- transfer of 2 electron-withdrawing R groups
- terminal, and 1,2 disubstituted olefins



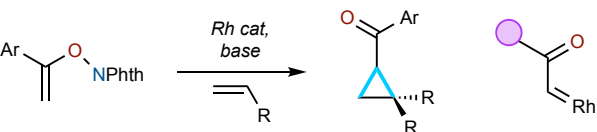
Wickens (2023)

- transfer of 2 electron-withdrawing R groups
- terminal olefins



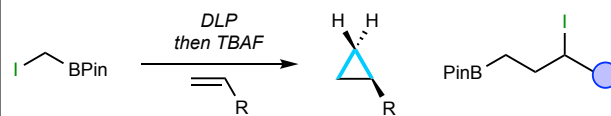
Rovis (2019)

- transfer of 1 electron-withdrawing R group
- 1,1 disubstituted olefins



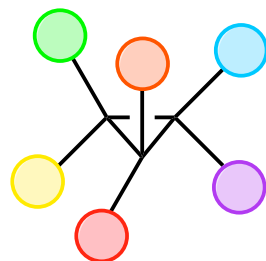
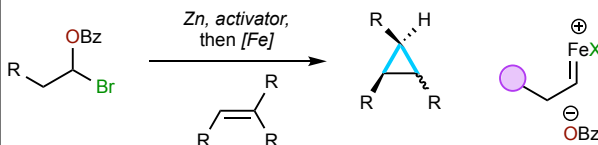
Renaud (2019)

- transfer of methylene group
- terminal olefins



Nagib (2024)

- transfer of 1 alkyl R group
- terminal, 1,1-, and 1,2 disubstituted olefins



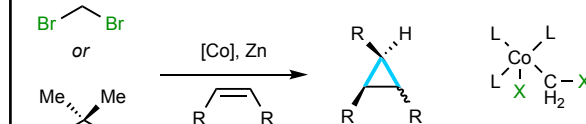
Mechanisms other than free or stabilized carbenes/carbenoids allow for different disconnections, transfer of a variety of substituents, and do not require activated or pre-functionalized substrates

Challenges:

- Transfer of 2 alkyl R groups, especially 2 different R groups
- Synthesis of cyclopropanes with 5-6 substituents
- Achieving high diastereoselectivities

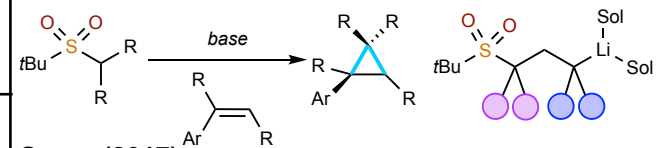
Uyeda (2023)

- transfer of methylene or 2 methyl groups
- terminal, 1,1- and 1,2 disubstituted olefins
- enantioselective



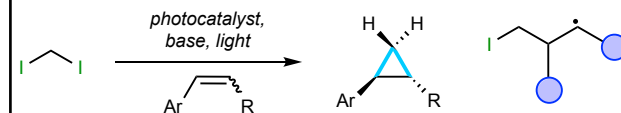
Wilkerson-Hill (2023)

- transfer of 2 alkyl R groups
- mono-, and unsubstituted styrenes



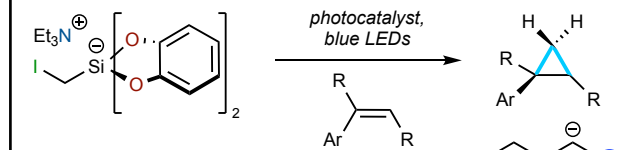
Suero (2017)

- transfer of methylene group
- monosubstituted styrenes



Molander (2018)

- transfer of methylene group
- mono- di-, and unsubstituted styrenes



Charette (2018)

- transfer of 1 boronic ester
- mono-, di-, and unsubstituted styrenes

