General Methods of Enantioselective Cyclopropanations

MacMillan Group Meeting

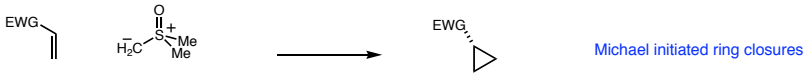
May 19, 2003

Roxanne Kunz

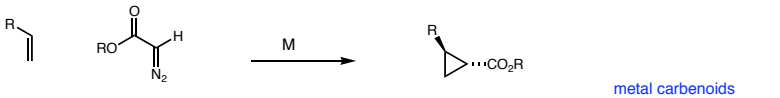
General Methods of Cyclopropanation

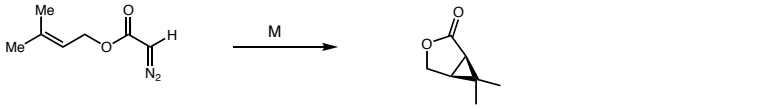
1. 

Simmons-Smith carbenoids

2. 

Michael initiated ring closures

3. 



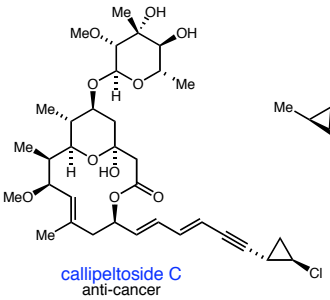
metal carbenoids
(M = Rh, Pd, Cu....)

4. 

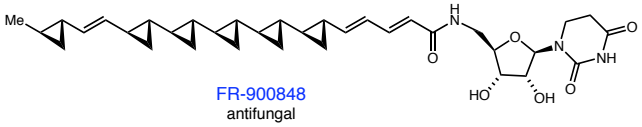
dihalocarbene

Charette, A.B. *Chem. Rev.* **2003**, *103*, 977.

Importance of Cyclopropanes in Nature and Drugs

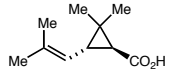


callipeltoside C
anti-cancer



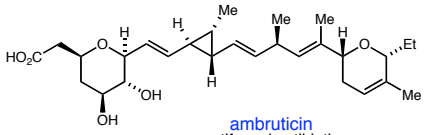
FR-900848
antifungal

U-106305
cholesterol esterase inhibitor



trans-chrysanthemic acid
anti-insecticide

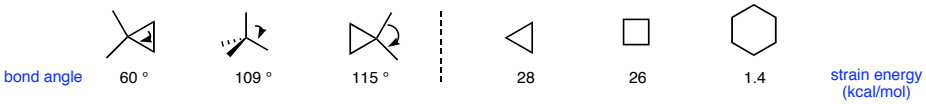
aminocarboxylic acids



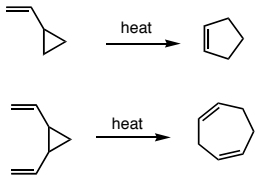
ambruticin
antifungal antibiotic

Synthetic Utility of Cyclopropanations

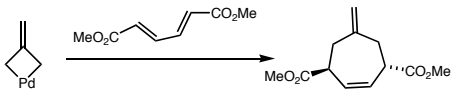
- cyclopropanes are reactive toward ring-opening and rearrangments due to special bonding properties

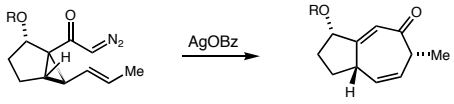


vinyl cyclopropane rearrangements

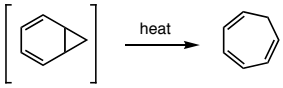


metal catalyzed cyclizations





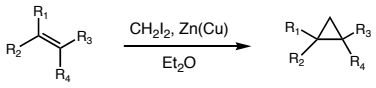
Buchner reaction



Enantioselective Simmons-Smith Cyclopropanations

general background

- First report by Simmons and Smith in 1958



reaction is stereospecific

cis → cis
and
trans → trans

- Plethora of contemporary methods for generating active reagent

reactants	active reagent
Et_2Zn, CH_2I_2	$EtZnCH_2I$ or $Zn(CH_2I)_2$
$EtZnI$, CH_2I_2	$IZnCH_2I$
TFA, Et_2Zn,CH_2I_2	$CF_3COOZnCH_2I$
Sm(Hg), CH_2I_2	$ISmCH_2I$
R_3Al, CH_2I_2	R_2AlCH_2I
ZnX_2, CH_2N_2	$Zn(CH_2I)_2$

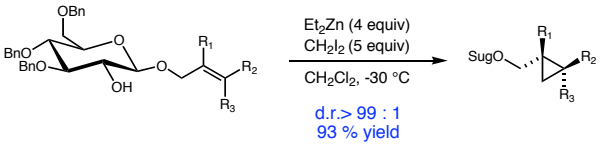
- In general, the most commonly used is Et_2Zn + CH_2I_2

J. Am. Chem. Soc. **1958,** *80,* 5323.

Enantioselective Simmons-Smith Cyclopropanations

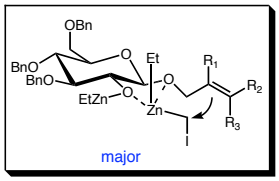
chiral auxiliary methods: allylic ethers

- Charette's 2-hydroxyglucopyranoside auxiliary



d.r.> 99 : 1
93 % yield

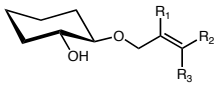
R_1	R_2	R_3
H	Me	H
H	Pr	H
H	Ph	H
H	Me	Me
H	H	Pr
H	H	CH_2OSiR_3
$-(CH_2)_4-$	$-(CH_2)_4-$	H



major

- coordination by second zinc activates CH_2I(ZnR) and enhances chelate structural rigidity
- auxiliary is cleaved in two steps (Tf_2O, pyr; DMF, pyr)

- Charette's simplified chiral diol auxiliary



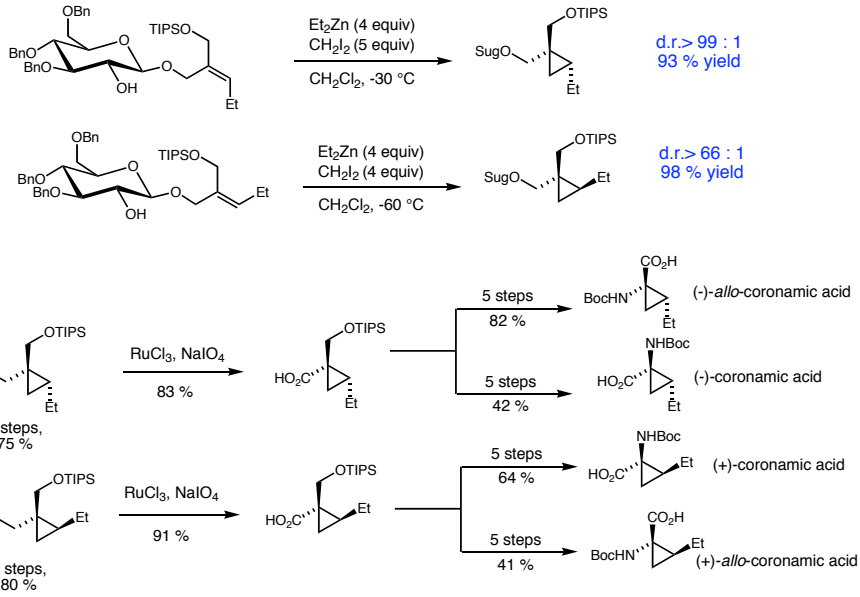
- similar substrate scope and d.r.'s
- available by enzymatic resolution

J. Am. Chem. Soc. **1991**, *113*, 8166.
Tet. Lett. **1993**, *34*, 7157.

Enantioselective Simmons-Smith Cyclopropanations

chiral auxiliary methods: synthesis of coronamic acids

- Switch of olefin geometry provides access to four isomers of coronamic acid

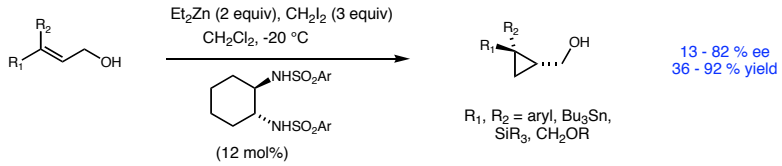


J. Am. Chem. Soc. **1995**, *117*, 12721.

Enantioselective Simmons-Smith Cyclopropanations

chiral controller ligands

- Kobayashi demonstrated the first catalytic asymmetric cyclopropanation



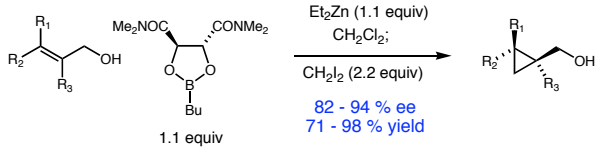
- low enantioselectivity attributed to background reaction catalyzed by ZnI_2
- works well for alkyl olefins, but less well for tri-and tetra-substituted olefins
- later studies by Denmark improved on the ee's by optimizing order of addition of reagents

J. Am. Chem. Soc. **1998**, *120*, 11943.
ACIE. **1997**, *36*, 1090.

Enantioselective Simmons-Smith Cyclopropanations

chiral controller ligands

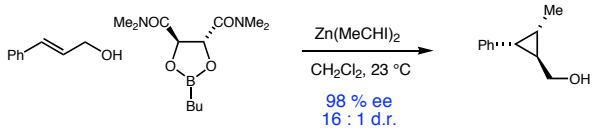
- Charette's chiral dioxaborolane ligand



R_1	R_2	R_3
H	H	H
Bu_3Sn	Bu_3Sn	Me
I	I	CH_2OR
Et	Pr	
CH_2OR	CH_2OR	
Me	Aryl	
	vinyl	

- on > 1 mmol scale, $Zn(CH_2I)_2$ prep is *explosive!*
- therefore, $Zn(CH_2I)_2 \bullet DME$ is used on > 1 mmol scale
- ligand prep is two steps from commercial starting materials

- 1,2,3-trisubstituted cyclopropanes



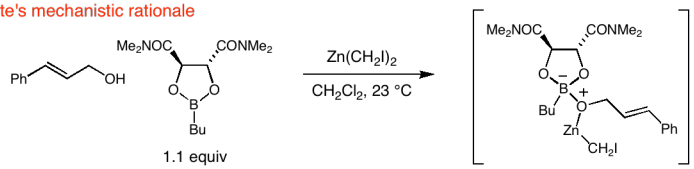
J. Am. Chem. Soc. **1998**, *120*, 11943.

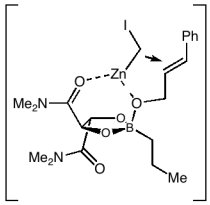
ACIEE. **1997**, *36*, 1090.

Enantioselective Simmons-Smith Cyclopropanations

Charette's dioxaborolane ligand

- Charette's mechanistic rationale





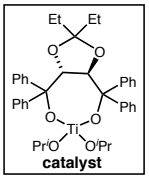
=

- cyclopropanation of the methyl or TIPS ether afforded racemic product
- ligand acts in a bidentate manner
- homoallylic alcohols give lower ee → proximity of the olefin is important

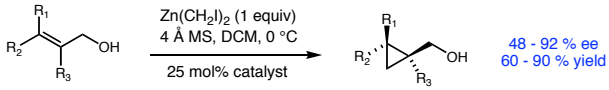
J. Am. Chem. Soc. **1998**, *120*, 11943.

Enantioselective Simmons-Smith Cyclopropanations

chiral lewis acid



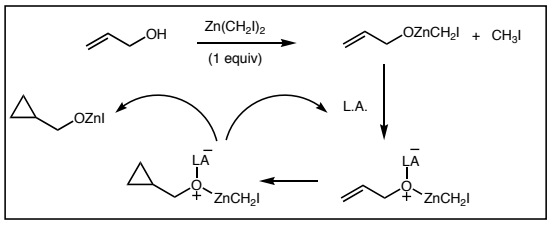
- Charette's Ti TADDOLate catalyzed cyclopropanations



48 - 92 % ee
60 - 90 % yield

R_1	R_2	R_3
H Ph Alk	H Alk aryl heteroaryl vinyl	H Me

- lower ee's were achieved for alkyl olefins
- best for aryl-substitued allylic alcohols

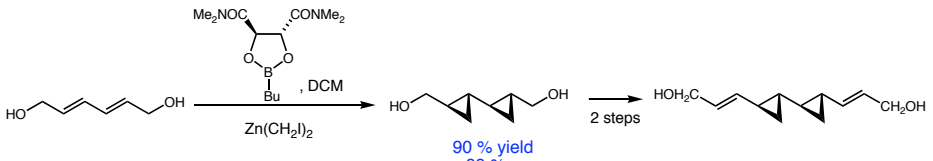


- bis(oxazoline), diethyl tartrate, binaphthol type catalysts all gave lower ee's

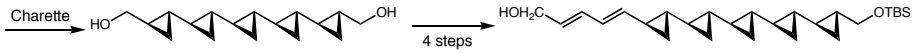
J. Am. Chem. Soc. **1995**, *117*, 11367.
J. Am. Chem. Soc. **2001**, *123*, 12168.

Enantioselective Simmons-Smith Cyclopropanations

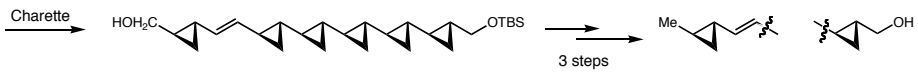
synopsis of Barrett's synthesis of FR - 900848



90 % yield
>99 % ee



93 % yield
single diastereomer



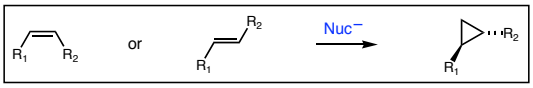
FR-900848
(20 steps)

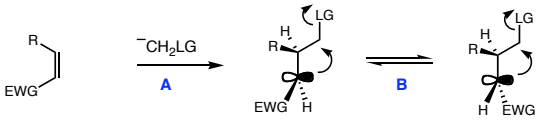
Chem. Comm. **1997,** 1693

Enantioselective Michael Initiated Ring Closures

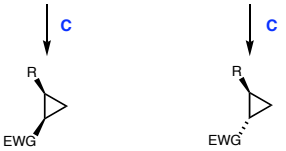
general background

- Michael initiated ring closures (MIRC) are not stereospecific, but may be highly stereoselective

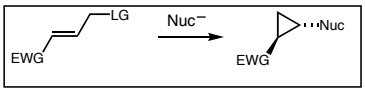




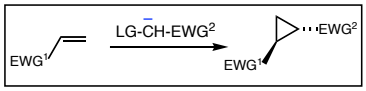
- usually, B >> C



- two categories of MIRC substrates



Class I

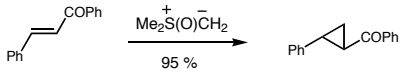


Class II

Enantioselective Michael Initiated Ring Closures

general background

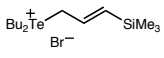
- Corey pioneered sulfoxonium ylides in 1960's



reagent	reactivity	
$Me_2\overset{+}{S}\text{-}\overset{-}{C}H_2$	esters & amides	ketones/ aldehydes → oxiranes
$Me_2\overset{+}{S}(O)\text{-}\overset{-}{C}H_2$	ketones	aldehydes → oxiranes
$Ph_2\overset{+}{S}\text{-}\overset{-}{C}Me_2$	ketones, esters amides	aldehydes → oxiranes
$Me_2\overset{+}{S}\text{-}\overset{-}{C}HCO_2R$	ketones, esters nitriles, **aldehydes**	

- phosphorus, tellerium, and arsonium ylides are known, but less commonly used

$Ph_3P{=}CH_2$ $Ph_3P{=}CMe_2$ $Ph_3As{=}CHCOPh$

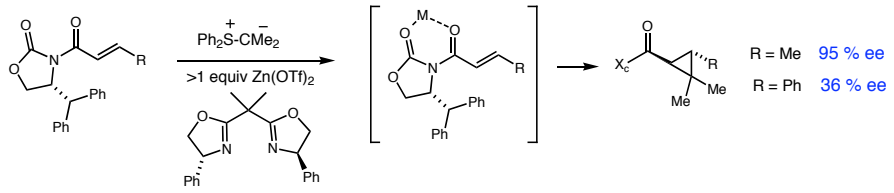


J. Am. Chem. Soc. **1962**, *84*, 866.

Enantioselective Michael Initiated Ring Closures

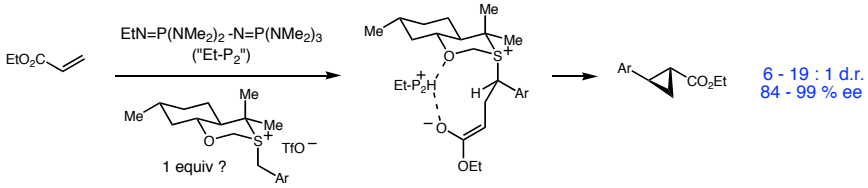
chiral auxiliaries

- Evans' oxazolidinone strikes again, but with limited substrate scope



- non-selective reaction catalyzed by $LiBF_4$ is competitive

- a chiral sulfide auxiliary finds more success



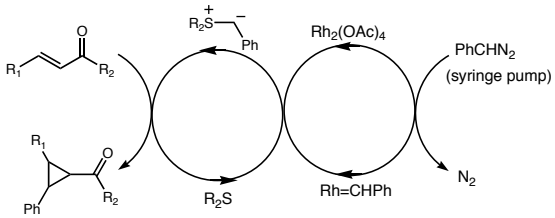
- ylide generated *in situ*, but not catalytically
- the oxirane is formed with α,β-unsaturated aldehyes

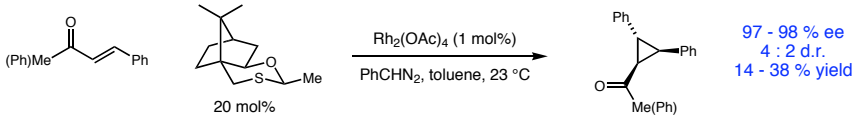
ACIEE **1998**, *37*, 1689.
Tet. Lett. **2000**, *41*, 9009.

Enantioselective Michael Initiated Ring Closures

Aggarwal's methodology

- Aggarwal combined the sulfonium ylide concept with diazo carbenes





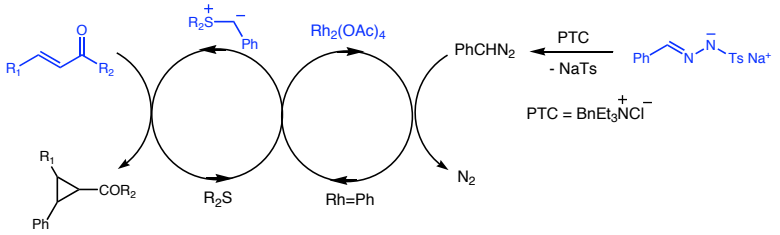
- yields increased when stoichiometric amount of sulfide was used
- enantioselectivity reduction over the reaction course wasn't seen in the catalytic examples
- sulfide available in two steps from camphorsulfonyl chloride

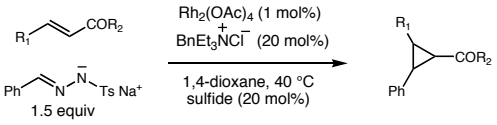
Chem. Comm. **1997**, *1*, 1785.

Enantioselective Michael Initiated Ring Closures

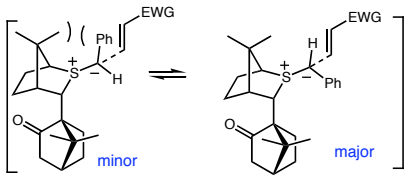
Aggarwal's improved methodology--a truly catalytic reaction

- generation of carbene in situ from tosyl hydrazones





alkene	% yield	d.r.	% ee
Ph, COPh	73	4:1	91
Me, COPh	50	4:1	90
Ph, COMe	12	--	--
CO_2Me	10	7:1	--

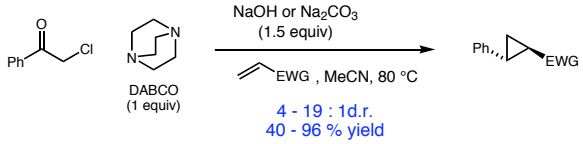


ACIEE **2001**, *40*, 1433.

Enantioselective Michael Initiated Ring Closures

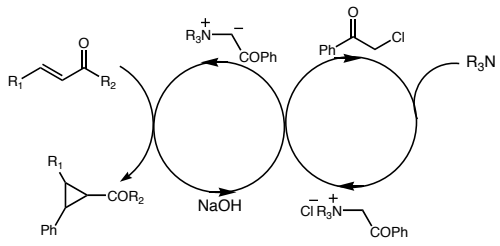
ammonium ylide mediated cyclopropanations

- Gaunt and Ley's intermolecular ammonium ylide methodology

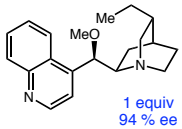


4 - 19 : 1d.r.
40 - 96 % yield

EWG	
CO_2tBu	SO_2Ph
C(O)Me	CN
$C(O)NMe_2$	**CHO (40 %)**



- one enantioselective example was reported using cinchona alkaloid



1 equiv
94 % ee
58 % yield

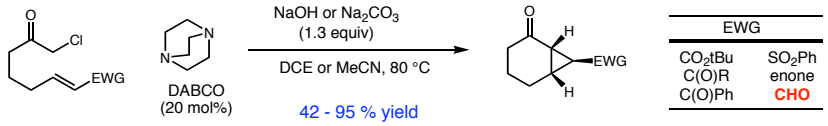
- catalytic asymmetric examples were not reported
- base + heat will erode ee over time

ACIEE. **2003**,*42*, 828.

Enantioselective Michael Initiated Ring Closures

ammonium ylide mediated cyclopropanations

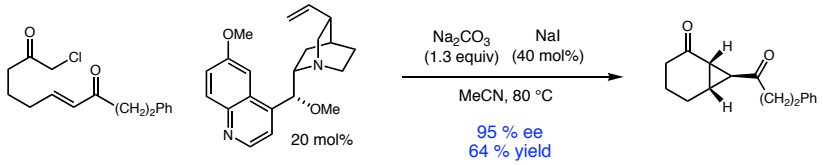
- extension of Gaunt and Ley's methodology to intramolecular systems



EWG	
CO_2tBu	SO_2Ph
C(O)R	enone
C(O)Ph	**CHO**

- products isolated as single diastereomers

- one asymmetric example using cinchona alkaloids

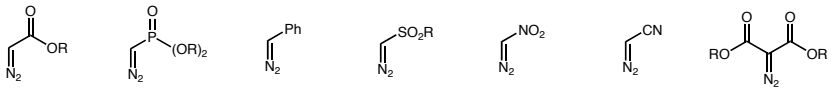


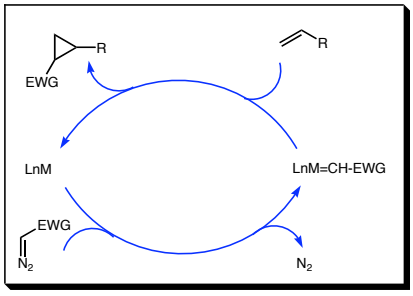
- sodium iodide facilitates formation of the ammonium salt

ACIEE. **2004**, *43*, 2681.

Enantioselective Metal-Carbenoid Cyclopropanations

- examples of the most commonly used α-substituted carbenoid precursors

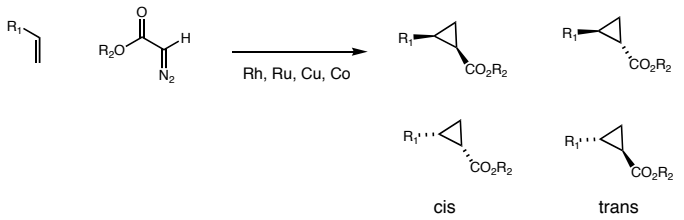




- diazoalkanes (i.e. diazomethane) and aryl, alkenyl, and alkynyldiazo compounds are potentially explosive
- variety of metal salts catalyze diazo reagent decomposition (Rh, Ru, Cu, Pd, Pt..)
- electron-rich olefins are optimal substrates for cyclopropanation

Intermolecular Enantioselective Metal Carbenoid Cyclopropanations

some "general" trends



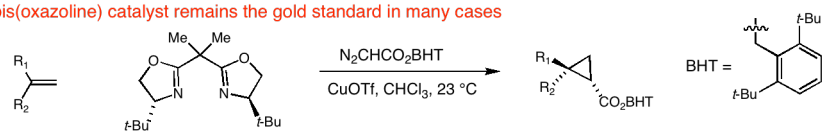
- in general, copper catalysts are more selective for *trans*-cyclopropanes and have widest scope
- rhuthenium catalysts are very effective, but have limited substrate scope
- rhodium catalysts produce lower ee's and d.r.'s
- cobalt catalysts are more selective for *cis*-cyclopropanes but ligands are hard to prepare
- most methodologies apply only to mono and 1,1-disubstituted olefins

Enantioselective Metal-Carbenoid Cyclopropanations

a sampling of catalysts

Enantioselective Intermolecular Metal Carbenoid Cyclopropanations

- Evans' bis(oxazoline) catalyst remains the gold standard in many cases



R_1	R_2	% yield	d.r.	% ee
Ph	H	85	16:1	99
$PhCH_2$	H	--	13:1	>99
Ph	Ph	70	--	>99
Me	Me	91	--	>99

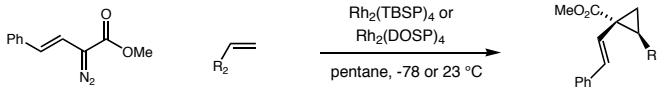
- BHT ester resistant to hydrolysis; LAH cleavage
- only mono and 1,1-disubstituted olefins
- extended later to furans, enol silanes, allylic alcohols

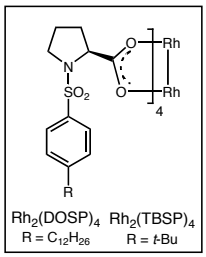
J. Am. Chem. Soc. **2001**, *123*, 7616.
J. Am. Chem. Soc. **1991**, *113*, 726.

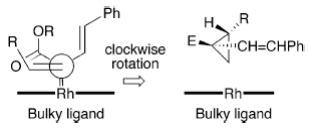
Intermolecular Enantioselective Metal Carbenoid Cyclopropanations

Davies' rhodium catalyzed methodology

- enantioselective synthesis of vinylcyclopropanes using dirhodium(II) carboxylates

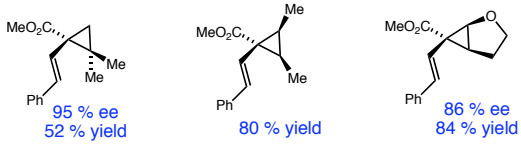






R_1	% yield	% ee
Ph	68	98
AcO	26	95
EtO	65	93
Bu	63	>90
Et	65	>95
i-Pr	58	95

- extension to other substrate types

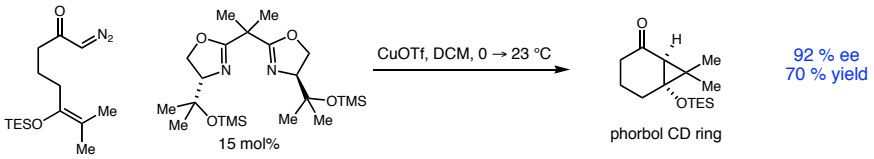


J. Am. Chem. Soc. **1996**, *118*, 6897.

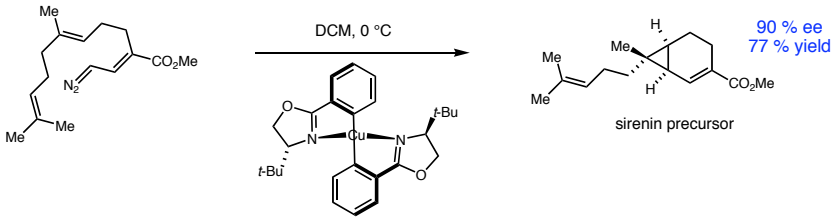
Intramolecular Enantioselective Metal Carbenoid Cyclopropanations

some notable examples

- cyclopropanation of a silylenol ether with Evans' derived catalyst



- Corey pushes the envelope with γ-diazocarbonyl carbenoid



Tet. Lett. **1996**, *37*, 2449.
Tet. Lett. **1995**, *36*, 8745.

General Methods of Enantioselective Cyclopropanations

conclusions

- Charette's Simmons-Smith methodology has widest substrate scope, but ee's and d.r.'s are very dependent upon reaction conditions
- Metal carbenoid cyclopropanations are powerful, but deleterious side reactions often result due to indiscriminate reactivity of metal carbenes
- Metal carbenoid cyclopropanations often require exhaustive catalyst screening to achieve good selectivities
- Substrate scope of metal carbenoid reactions is limited, mostly 1,1,-disubstituted and mono-substituted olefins
- Both Simmons-Smith and metal carbenoid reactions are air and water sensitive
- No general catalytic enantioselective MIRC methodology has been reported (YET)