Reviews:

Roy, M.-N.; Lindsay, V. N. G.; Charette, A. B. *Stereoselective Synthesis: Reactions of Carbon–Carbon Double Bonds (Science of Synthesis)*; de Vries, J. G., Ed.; Thieme: Stuttgart, **2011**, *Vol 1.*; 731–817.
Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977–1050.
Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103,* 2861–2903.
Li, A-H.; Dai, L. X.; Aggarwal, V. K. *Chem. Rev.* **1997**, *97*, 2341–2372.

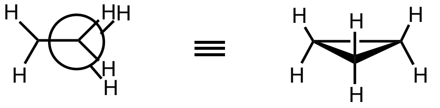
- Applications of Cyclopropanes in Synthesis

Carson, C. A.; Kerr, M. A. *Chem. Soc. Rev.* **2009**, *38*, 3051–3060.
Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103,* 1151–1196.
Gnad, F.; Reiser, O. *Chem. Rev.* **2003**, *103,* 1603–1624.

- Cyclopropane Biosynthesis

Thibodeaux, C. J.; Chang, W.-c.; Liu, H.-w. *Chem. Rev.* **2012**, *112,* 1681–1709.

Introduction



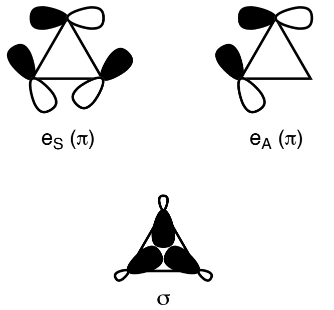
- Cyclopropanes are stable but highly strained compounds (ring strain ~29 kcal/mol).

- C–C bond angles = 60º (vs 109.5º for normal C_{sp3}–C_{sp3} bonds).

- Substituents on cyclopropanes are eclipsed. H–C–H angle is ~120º. As a result, the C–H bonds have higher s character compared to normal sp^3 bonds.

- Because of their inherent strain, the reactivity of cyclopropanes is more closely analogous to that of alkenes than that of alkanes.

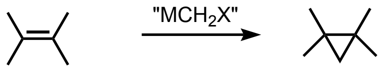
- Bonding Orbitals in Cyclopropane (Walsh Model):



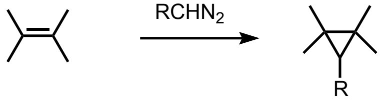
de Meijere, A. *Angew. Chem. Int. Ed.* **1979**, *18*, 809–886.

General Strategies for Cyclopropanation:

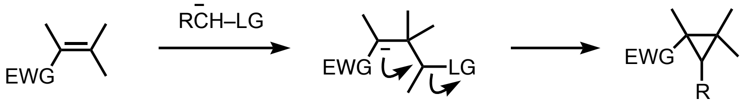
- via carbenoids

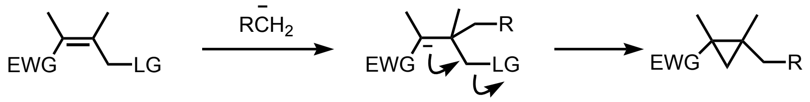


- via carbenes generated by decomposition of diazo compounds



- via Michael addition and ring closure



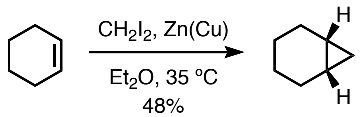


Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977–1050.

James Mousseau, Fan Liu

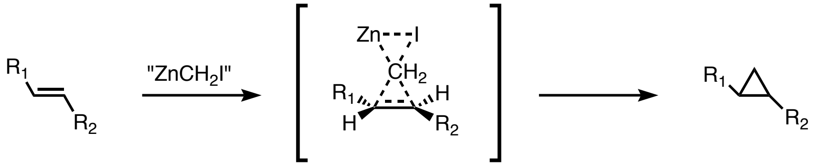
Simmons-Smith Reaction — Zinc Reagents in Cyclopropanation

- Original Report:



Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.* **1958**, *80*, 5323–5324.

- Reaction Overview:



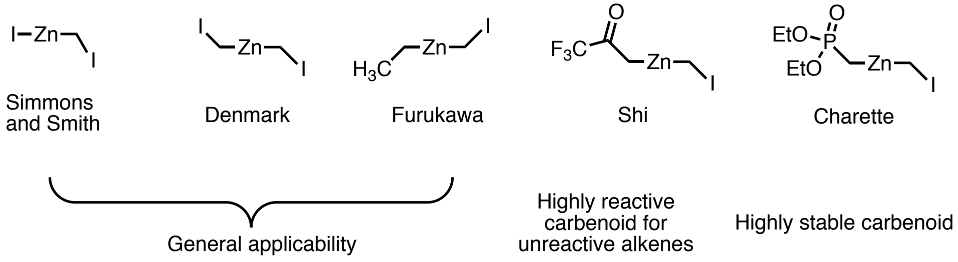
Butterfly transition state

- The reaction is proposed to proceed through a "butterfly" transition state.

Simmons, H. E. *Org. React.* **1973**, *20*, 1–133.

- Zinc cyclopropanating reagents can be generated in various ways. Both Zn metal and $ZnEt_2$ can be used.

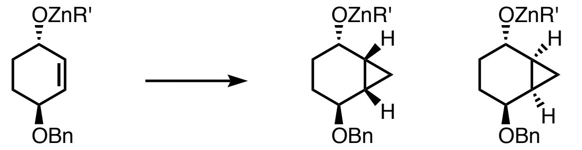
- Many zinc reagents for cyclopropanation have been developed:



- Diastereoselective cyclopropanation is possible in the presence of directing groups:

Dauben, W. G.; Berezin, G. H. *J. Am. Chem. Soc.* **1963**, *85*, 468–472.

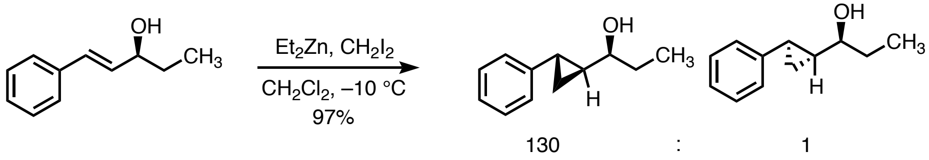
- Interestingly, excess carbenoid can reverse the directing effect of alcohols.



Zinc Reagent	*dr*	yield
$Zn(CH_2I)_2$ (1 equiv)	>25:1	>95%
$EtZnCH_2I$ (9 equiv)	1:>25	>95%

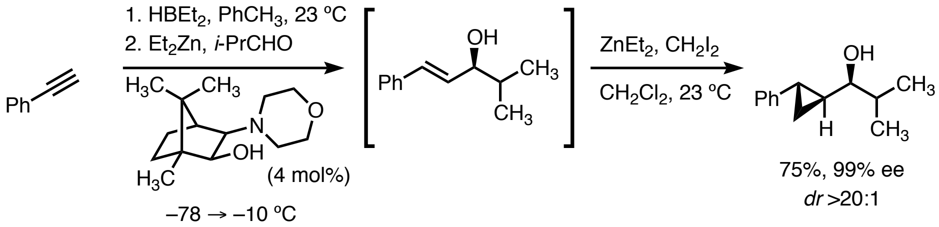
Charette, A. B.; Marcoux, J. F. *Synlett*, **1995**, 1197–1207.

- Directed cyclopropanation is also possible in acyclic systems:



Charette, A. B.; Lebel, H. *J. Org. Chem.* **1995**, *60*, 2966–1967.

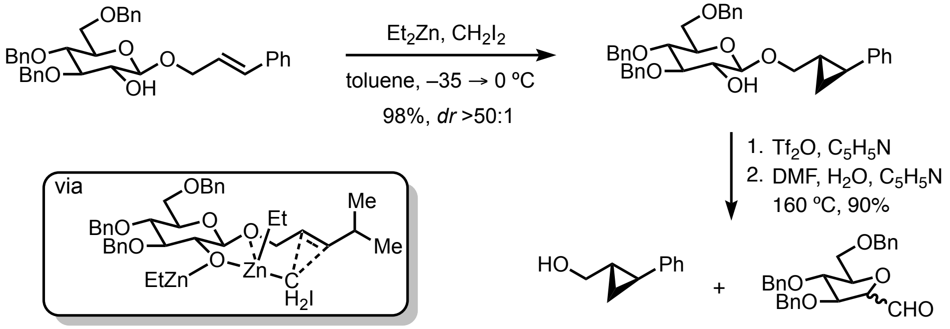
- Diastereoselective cyclopropanation has been used in tandem asymmetric organozinc additions:



Kim, H. Y.; Lurain, A. E.; Garcia-Garcia, P.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2005**, *127*, 13138–13139.

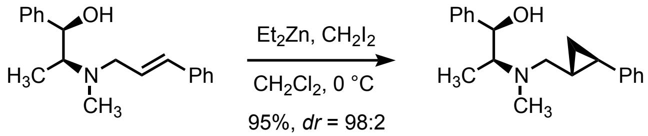
James Mousseau, Fan Liu

- **Asymmetric Simmons-Smith Reaction Using Chiral Auxiliaries**
- Allylic alcohols:



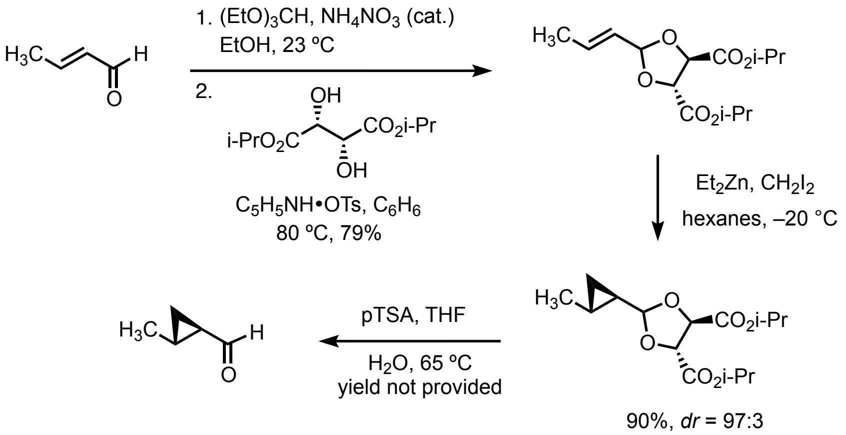
Charette, A. B.; Côté, B.; Marcoux, J.-F. *J. Am. Chem. Soc.* **1991**, *113*, 8166–8167.

- Allylic amines:



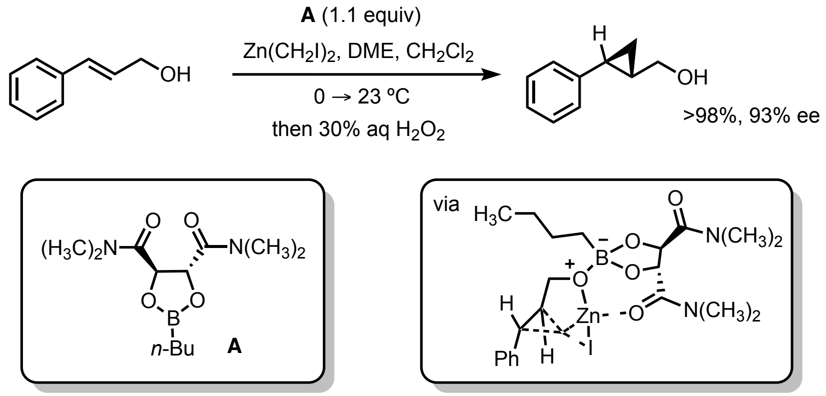
Aggarwal, V. K.; Fang, G. Y.; Meek, G. *Org. Lett.* **2003**, *5*, 4417–4420.

- α,β-Unsaturated carbonyls:



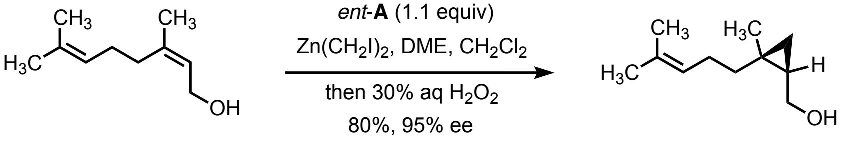
Mash, E. A.; Nelson, K. A. *J. Am. Chem. Soc.* **1985**, *107*, 8256–8258.
Mori, A.; Arai, I.; Yamamoto, H. *Tetrahedron* **1986**, *42*, 6447–6458.

- **Stoichiometric Promoter for Asymmetric Simmons-Smith Cyclopropanation**
- A chiral dioxaborolane auxiliary prepared from tetramethyltartramide and butylboronic acid has been shown to be effective in the asymmetric cyclopropanation of allylic alcohols.
- A hydrogen peroxide work-up is employed to remove boron side-products.



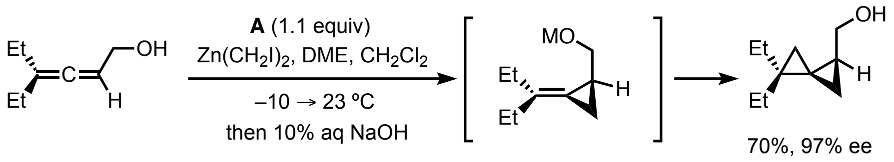
Charette, A. B.; Juteau, H.; Lebel, H.; Molinaro, C. *J. Am. Chem. Soc.* **1998**, *120*, 11943–11952.

- Allylic alcohols are cyclopropanated selectively:



Nicolaou, K. C.; Sasmal, P. K.; Rassais, G.; Reddy, M. V.; Altmann, K. H.; Wartmann, M.; O'Brate, A.; Giannakakou, P. *Angew. Chem. Int. Ed.* **2003**, *42*, 3515–3520.

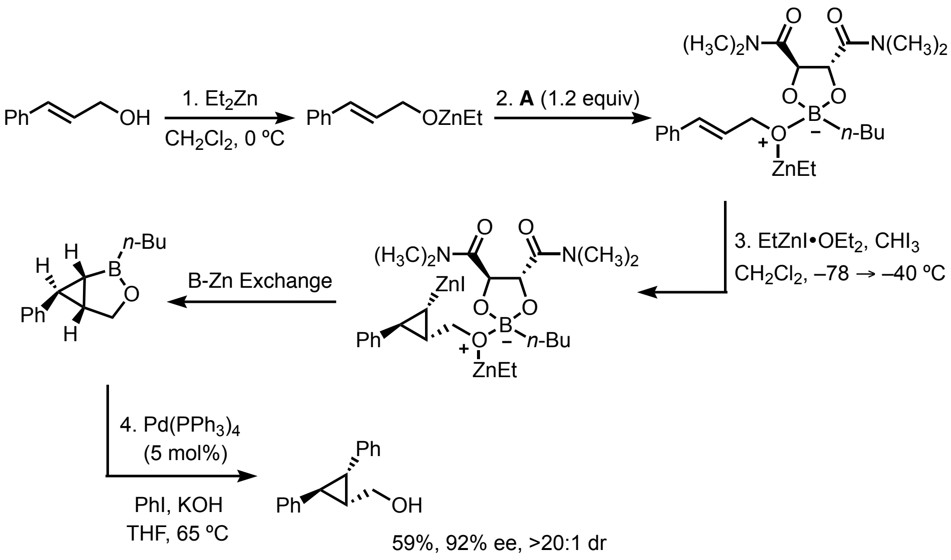
- The cyclopropanation of allenic alcohols affords spiropentane derivatives:



Charette, A. B.; Jolicoeur, E.; Bydlinkski, G. A. S. *Org. Lett.* **2001**, *3*, 3293–3295

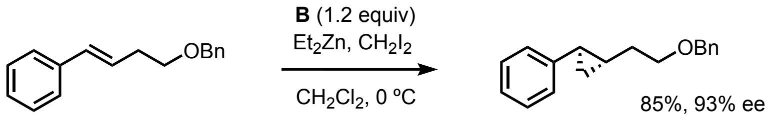
James Mousseau, Fan Liu

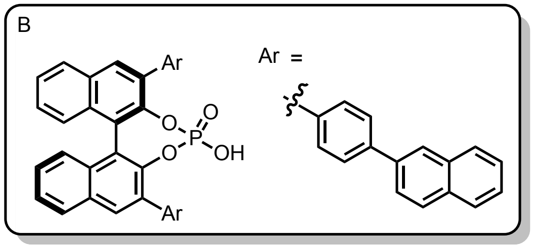
- The dioxaborolane promoter can be used to prepare 1,2,3-trisubstituted cyclopropanes.
- In the example shown, the intermediate borinate was used directly for Suzuki coupling:

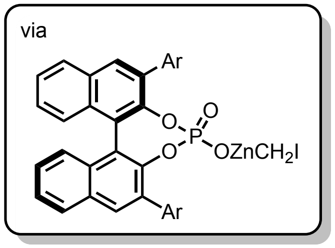


Zimmer, L. E.; Charette, A. B. *J. Am. Chem. Soc.* **2009**, *131*, 15624–15626.

- Homoallylic ethers can be cyclopropanated using a zinc phosphate, prepared *in situ* from a chiral phosphoric acid:

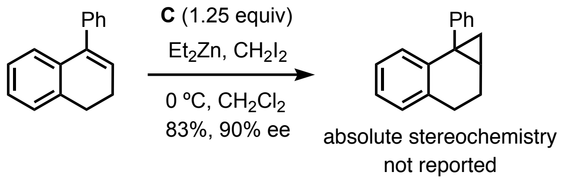


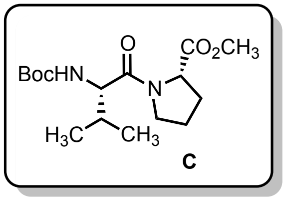




Lacasse, M.-C.; Poulard, C. Charette, A. B. *J. Am. Chem. Soc.* **2005**, *127*, 12440–12441.

- Unfunctionalized alkenes can undergo asymmetric Simmons–Smith cyclopropanation in presence of a valine/proline dipeptide.
- Selectivity is higher for trisubstituted alkenes than for disubstituted alkenes.

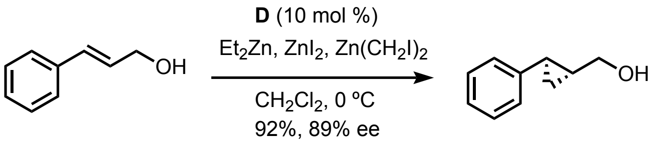


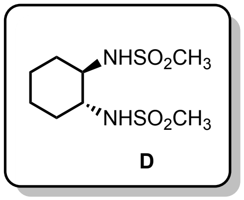


Long, J.; Yuan, Y.; Shi, Y. *J. Am. Chem. Soc.* **2003**, *125*, 13632–13633.

- **Catalytic Enantioselective Simmons-Smith Cyclopropanation Reactions**

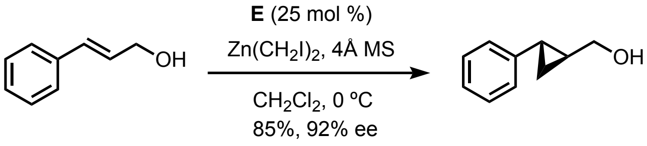
- Chiral bis-sulfonamides have been used to direct asymmetric Simmons–Smith reactions of allylic alcohols:

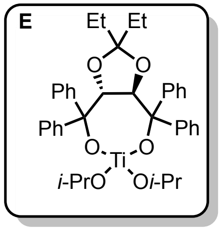




Denmark, S. E.; O'Connor, S. P. *J. Org. Chem.* **1997**, *62*, 584–594.

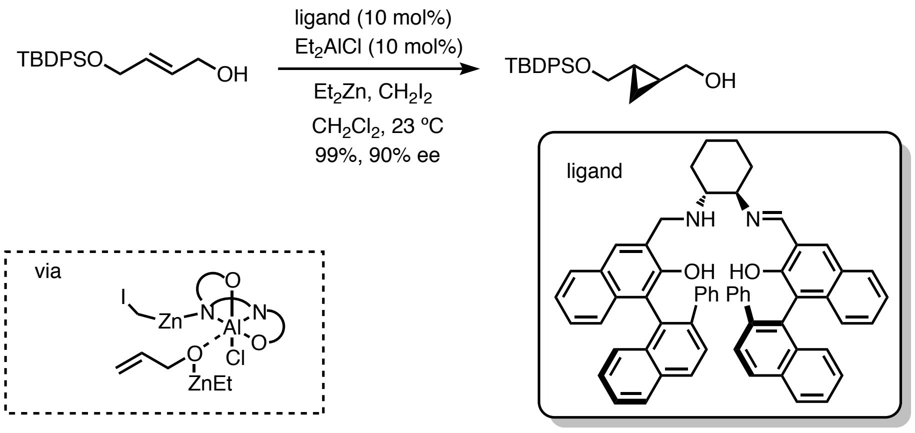
- "Taddolates" can also be used:





Charette, A. B.; Molinaro, C.; Brochu, C. *J. Am. Chem. Soc.* **2001**, *123*, 12168–12175.

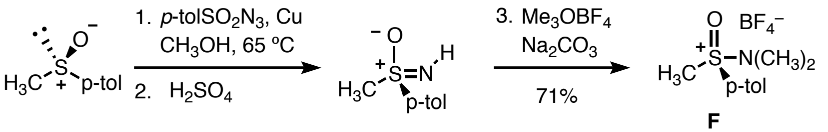
- A bifunctional Al-complex is an effective cyclopropanation catalyst and is believed to bind both the Zn and the allylic alcohol:



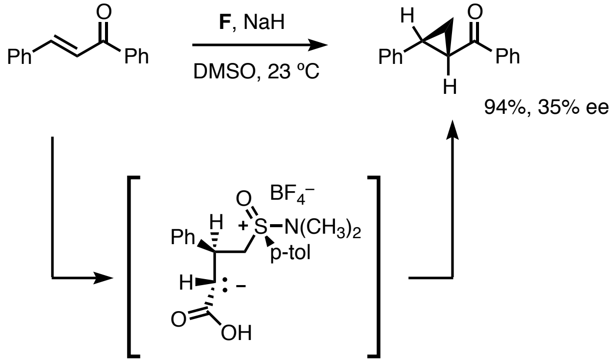
Shitama, H.; Katsuki, T. *Angew. Chem. Int. Ed.* **2008**, *47*, 2450–2453.

Cyclopropanation via Michael Addition and Ring Closure — Asymmetric Cyclopropanation Through Chiral Ylides

- In an early report, optically enriched oxosulfonium **F** was prepared in 3 steps, which stereoselectively cyclopropanates Michael-acceptors:

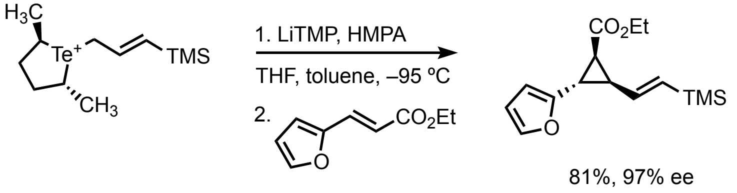


F



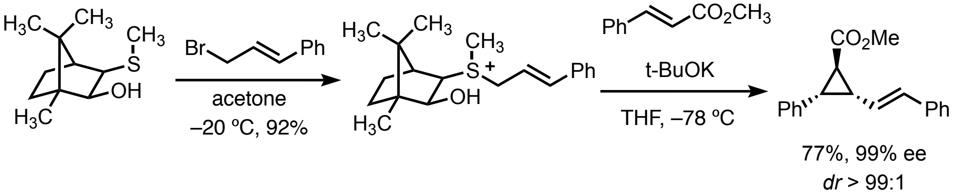
Johnson, C. R.; Schroeck, C. W. *J. Am. Chem. Soc.* **1968**, *90*, 6852–6854.

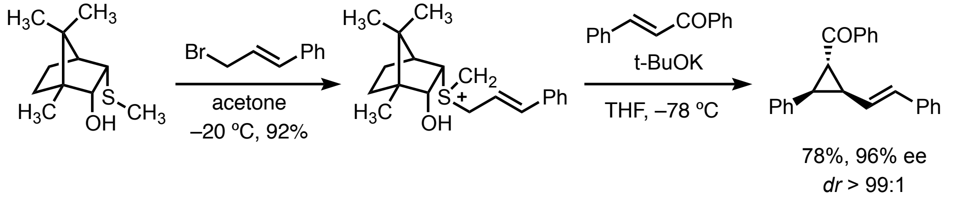
- Telluronium ylides can also be used:



Liao, W.-W.; Li, K. Tang, Y. *J. Am. Chem. Soc.* **2003**, *125*, 13030–13031.

- Camphor-derived sulfur ylides can be employed for stereoselective cyclopropanations of Michael-acceptor olefins:

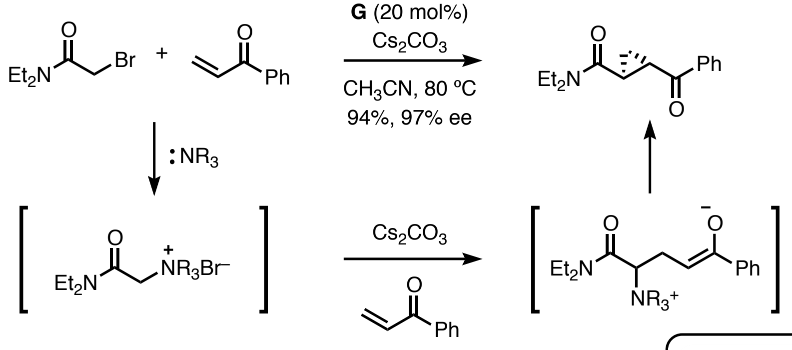


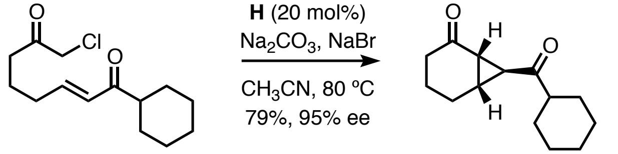


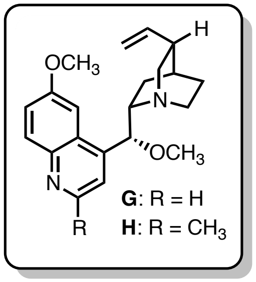
Deng, X.-M.; Cai, P.; Ye, S.; Sun, X.-L.; Liao, W.-W,; Li, K.; Tang, Y.; Wu, Y.-D.; Dai, L.-X. *J. Am. Chem. Soc.* **2006**, *128*, 9730–9740.

James Mousseau, Fan Liu

- **Catalytic Enantioselective Ylide Cyclopropanations**
- Cinchona alkaloids have been employed to generate chiral ammonium ylides, which stereoselectively cyclopropanates Michael-acceptors:



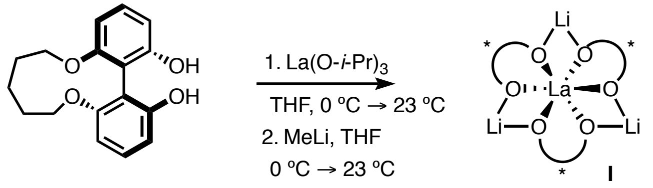


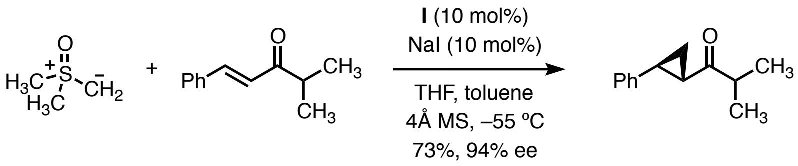


Papageorgiou, C. D.; Cubillo de Dios, M. A.; Ley, S. V.; Gaunt, M. J. *Angew. Chem. Int. Ed.* **2004**, *43*, 4641–4644.

Johansson, C. C. C.; Bremeyer, N.; Ley, S. V.; Owen, D. R.; Smith, S. C.; Gaunt, M. J. *Angew. Chem. Int. Ed.* **2006**, *45*, 6024–6028.

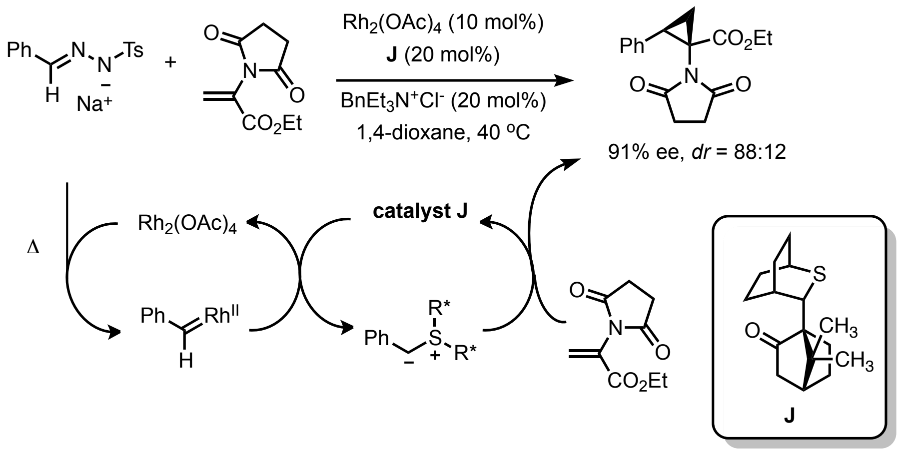
- Lanthanum complexes were also found to be effective:





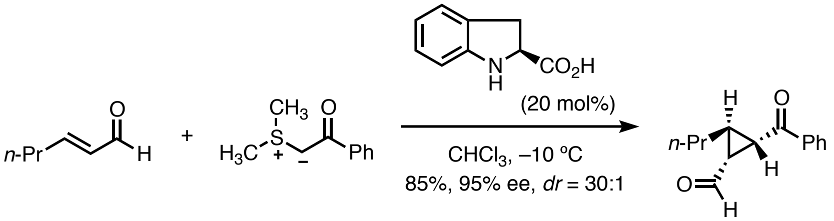
Kakei, H.; Sone, T.; Sohtome, Y.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 13410–13411.

- Chiral sulfoxonium intermediates can be generated *in situ* by trapping of a rhodium carbenoid:



Aggarwal, V. K.; Alonso, E.; Fang, G.; Ferrara, M.; Hynd, G.; Porcelloni, M. *Angew. Chem. Int. Ed.* **2001**, *40*, 1433–1436.

- Asymmetric cyclopropanation through a chiral iminium intermediate:



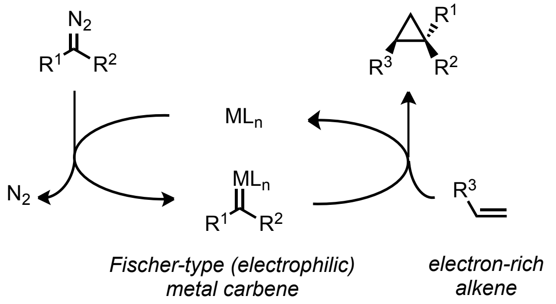
Kunz, R. K.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 3240–3241.

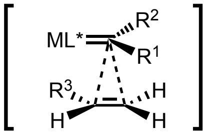
David W. Lin, Fan Liu

Asymmetric Cyclopropanation using Metal Carbenes

- Transition metals catalyze the cyclopropanation of electron-rich olefins via carbenoids formed from electron-deficient diazo compounds.

- The catalytic cycle proceeds via a Fischer-type (electrophilic) metal carbene formed from diazo precursors:



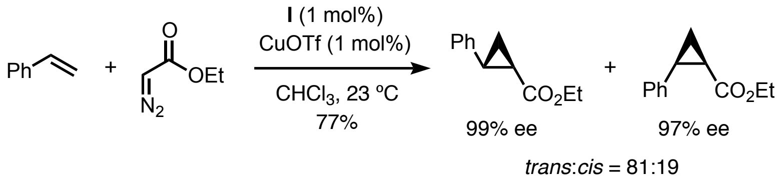


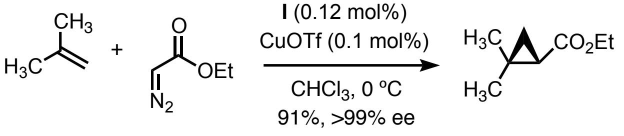
transition state

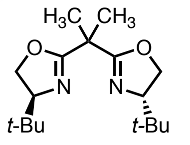
- This methodology is most effective for three classes of diazo substrates:
  - Diazo substrates with one electron-withdrawing group
  - Diazo substrates with two electron-withdrawing groups
  - Diazo substrates with one electron-withdrawing group and one electron-donating group

- **Diazo Substrates with One Electron-Withdrawing Group**

- The use of C_2-symmetric Cu(I) oxazoline complexes for cyclopropanation was first reported by Evans:



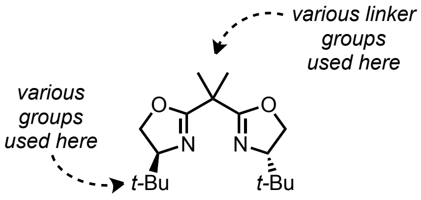




I

Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726–728.

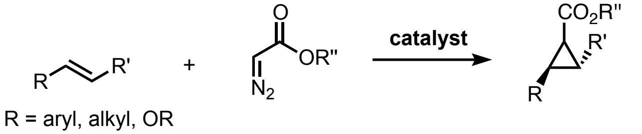
- Since the initial report, extensive research has been done to develop other C_2-symmetric Cu(I) and Ru(II) oxazoline complexes.



catalyst

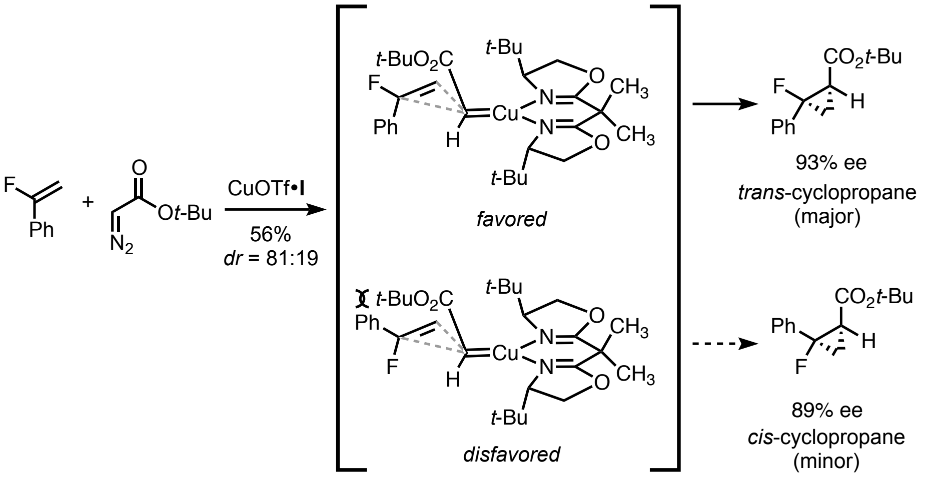
- Many alkenes can be used, with styrenes and enol ethers being the most common.

- The reaction proceeds with retention of the olefin geometry:



- Up to three stereocenters can be formed.

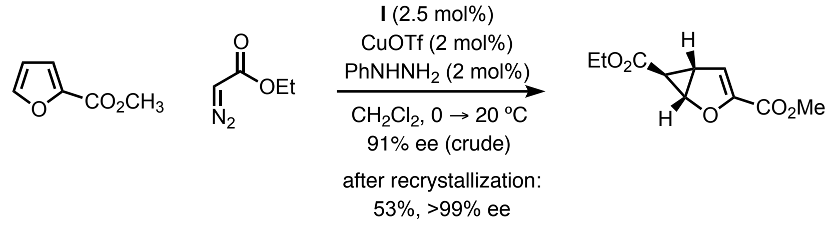
- Cu(I) and Ru(II) oxazoline complexes typically give *trans*-1,2-cyclopropanes selectively:



Haufe, G.; Rosen, T. C.; Meyer, O. G. J.; Fröhlich, R.; Rissanen, K. *J. Fluorine Chem.* **2002**, *114*, 189–198.

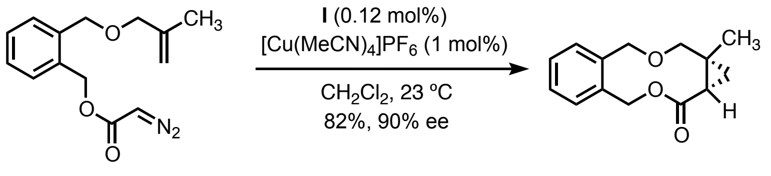
David W. Lin, Fan Liu

- Examples of Cu(I)- and Ru(II)-catalyzed enantioselective cyclopropanations:

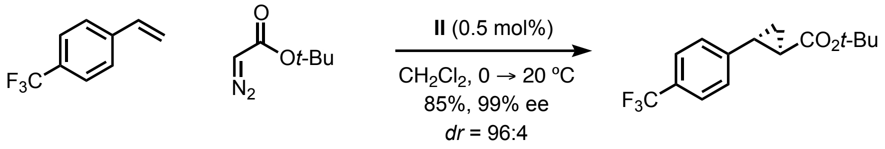


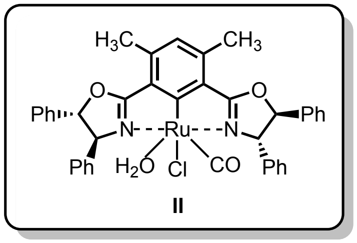
Böhm, C.; Reiser, O. *Org. Lett.* **2001**, *3*, 1315–1318.

- Intramolecular reactions can also proceed with high enantioselectivities:



Doyle, M. P.; Peterson, C. S.; Parker Jr., D. L. *Angew. Chem. Int. Ed.* **1996**, *35*, 1334–1336..

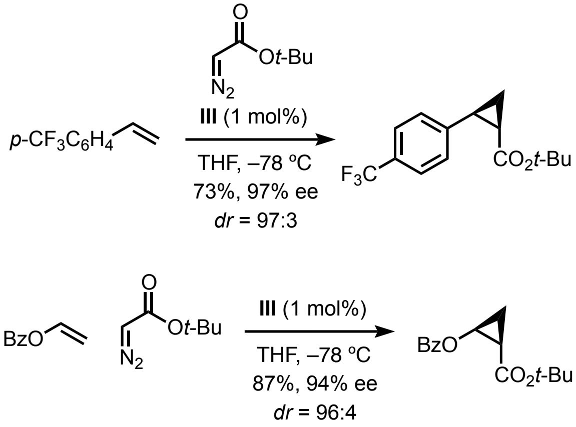


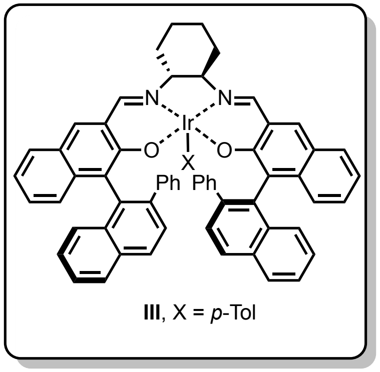


II

Ito, J.-i.; Ujiie, S.; Nishiyama, H., *Chem.–Eur. J.* **2010**, *16*, 4986–4990.

- Chiral Ir(III)-salen complexes afford *cis*-1,2-cyclopropanes with high enantioselectivities:

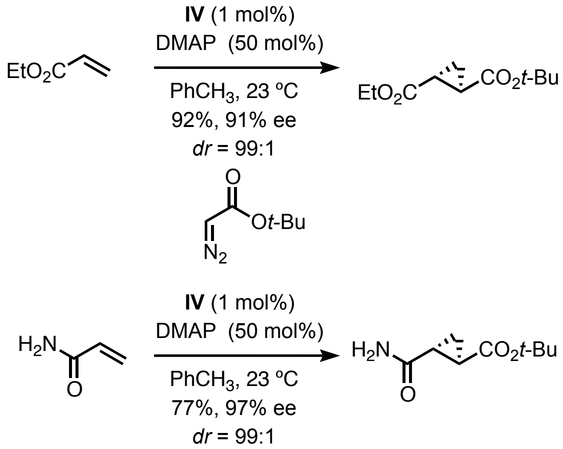


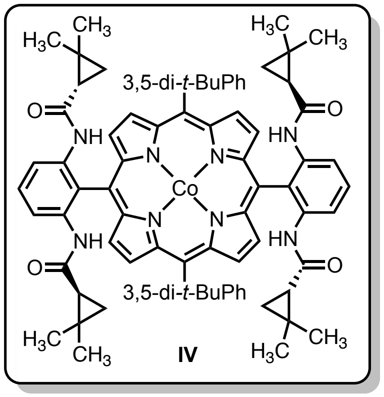


III, X = *p*-Tol

Suematsu, H.; Kanchiku, S.; Uchida, T.; Katsuki, T. *J. Am. Chem. Soc.* **2008**, *130*, 10327–10337.

- Co(II)-porphyrin complexes can cyclopropanate electron-deficient alkenes enantioselectively:



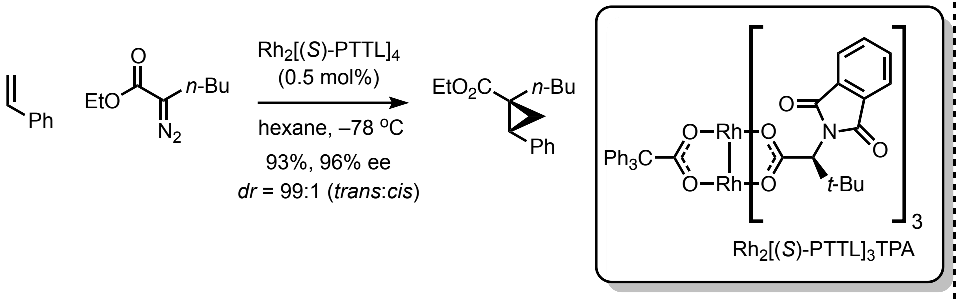


IV

Chen, Y.; Ruppel, J. V.; Zhang, X. P. *J. Am. Chem. Soc.* **2007**, *129*, 12074–12075.

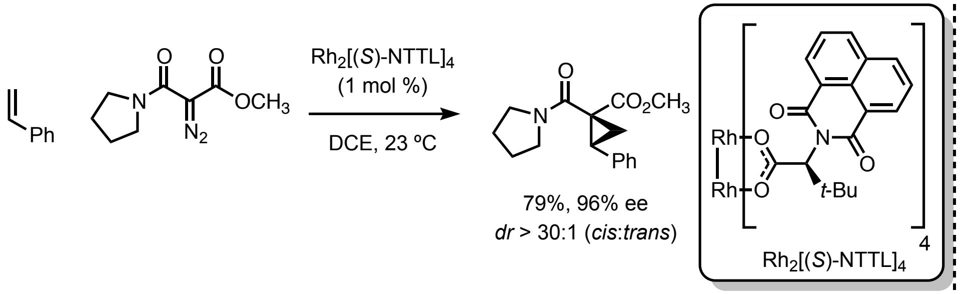
David W. Lin

- At low temperatures, rhodium(III) catalysts are compatible with higher α-alkyl-α-diazoesters, which otherwise often undergo undesired β-hydride elimination upon metal carbene formation:



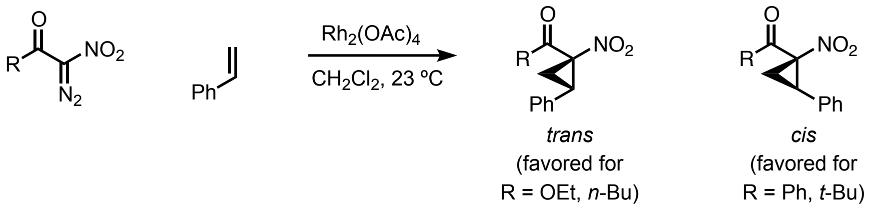
Boruta, D. T.; Dmitrenko, O.; Yap, G. P. A.; Fox, J. M. *Chem. Sci.* **2012**, *3*, 1589–1593.

- **Diazo Substrates with Two Electron-Withdrawing Groups**
- While symmetrical diazomalonates give poor selectivities, unsymmetrical diazomalonates are excellent substrates:



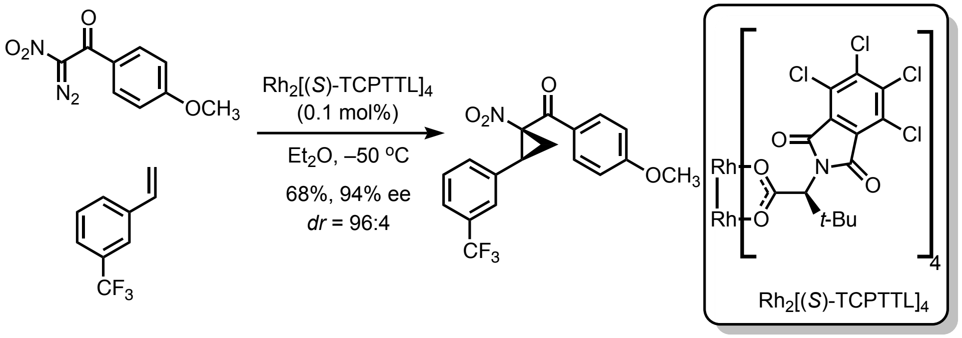
Marcoux, D.; Charette, A. B. *Angew. Chem. Int. Ed.* **2008**, *47*, 10155–10158.

- For α-nitro-α-diazo carbonyls, the diastereoselectivity is sensitive to the nature of the carbonyl substituent:



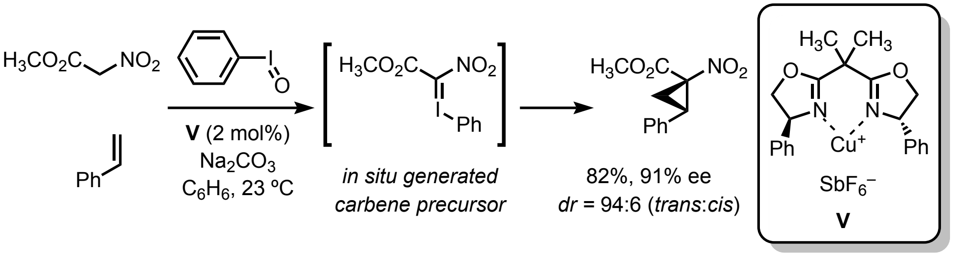
Charette, A. B.; Wurz, R. P.; Ollevier, T. *Helv. Chim. Acta* **2002**, *85*, 4468–4484.

- α-nitro-α-diazo aryl ketones give *cis* cyclopropanes selectively:



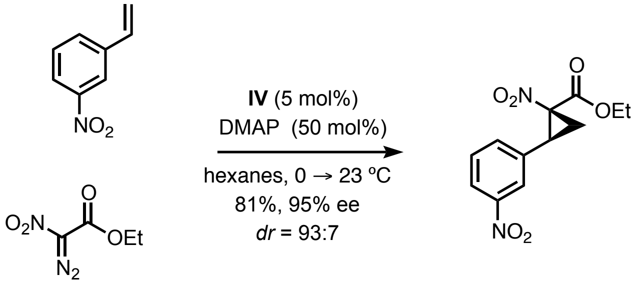
Lindsay, V. N. G.; Lin, W.; Charette, A. B. *J. Am. Chem. Soc.* **2009**, *131*, 16383–16385.

- α-nitro-α-diazo esters give *trans* cyclopropanes selectively. In the example below, the oxidant iodosobenzene can be used to form the carbene precursor from α-nitro esters *in situ*:



Moreau, B.; Charette, A. B. *J. Am. Chem. Soc.* **2005**, *127*, 18014–18015.

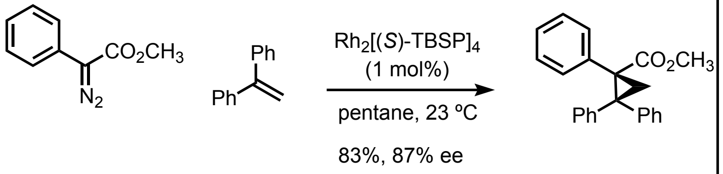
- Alternatively, α-nitro-α-diazo acetates give *cis* cyclopropanes with cobalt(II)-porphyrin catalysts:

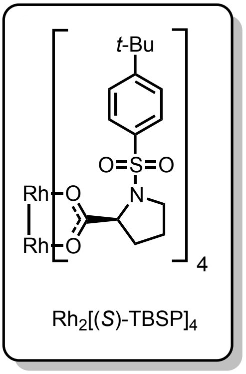


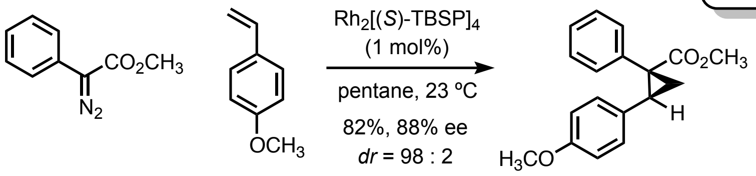
Zhu, S.; Perman, J. A.; Zhang, X. P. *Angew. Chem. Int. Ed.* **2008**, *47*, 8460–8463.

David W. Lin

- **Diazo Substrates with One Electron-Withdrawing Group and One Electron-Donating Group**
- Metal carbenes with adjacent electron-donating and electron-withdrawing groups ("push-pull" systems) are relatively stable and reactive.
- Rhodium(II) complexes using chiral ligands derived from proline have often been employed:

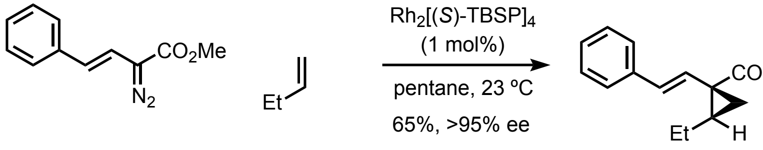






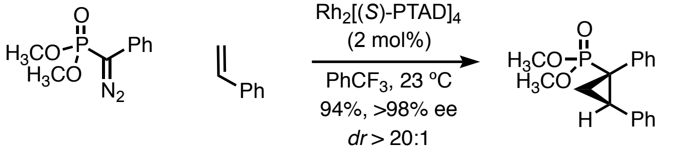
Doyle, M. P.; Zhou, Q.-L.; Charnsangavej, C.; Longoria, M. A.; McKervey, M. A.; GarcÌa, C. F. *Tetrahedron Lett.* **1996**, *37*, 4129–4132.
Davies, H. M. L.; Bruzinski, P. R.; Fall, M. J. *Tetrahedron Lett.* **1996**, *37*, 4133–4136.

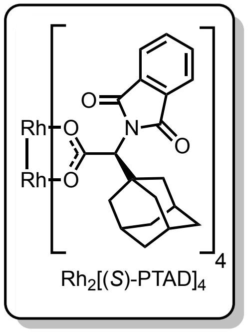
- Styrenes can also be considered as electron-donating groups on the diazo substrate:



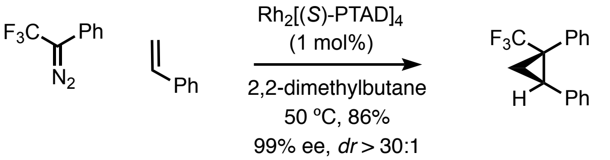
Davies, H. M. L.; Bruzinski, P. R.; Lake, D. H.; Kong, N.; Fall, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 6897–6907.

- A wide range of electron-withdrawing groups within the diazo substrate are tolerated:

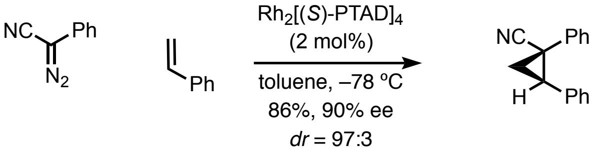




Reddy, R. P.; Lee, G. H.; Davies, H. M. L. *Org. Lett.* **2006**, *8*, 3437–3440.

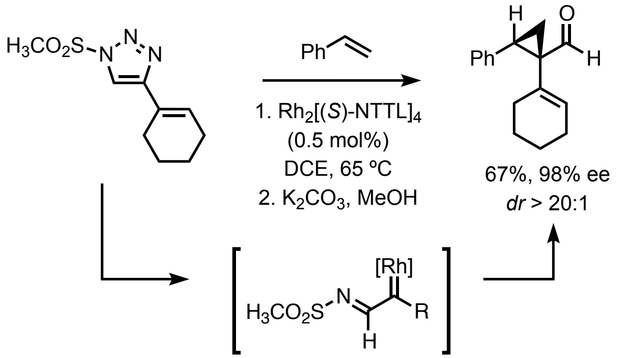


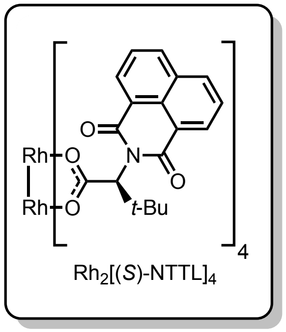
Denton, J. R.; Sukumaran, D.; Davies, H. M. L. *Org. Lett.* **2007**, *9*, 2625–2628.



Denton, J. R.; Cheng, K.; Davies, H. M. L. *Chem. Commun.* **2008**, 1238–1240.

- *N*-sulfonyl-1,2,3-triazoles serve as alternatives to diazo compounds as carbene precursors:



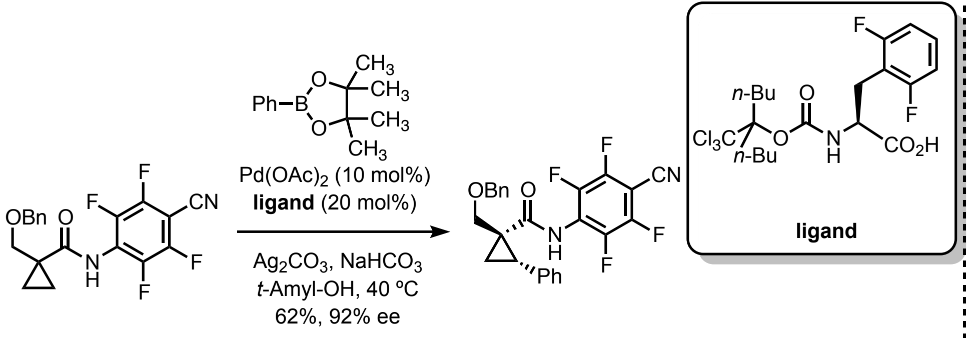


Chuprakov, S.; Kwok, S. W.; Zhang, L.; Lercher, L.; Fokin, V. V. *J. Am. Chem. Soc.* **2009**, *131*, 18034.
Grimster, N.; Zhang, L.; Fokin, V. V. *J. Am. Chem. Soc.* **2010**, *132*, 2510.

David W. Lin

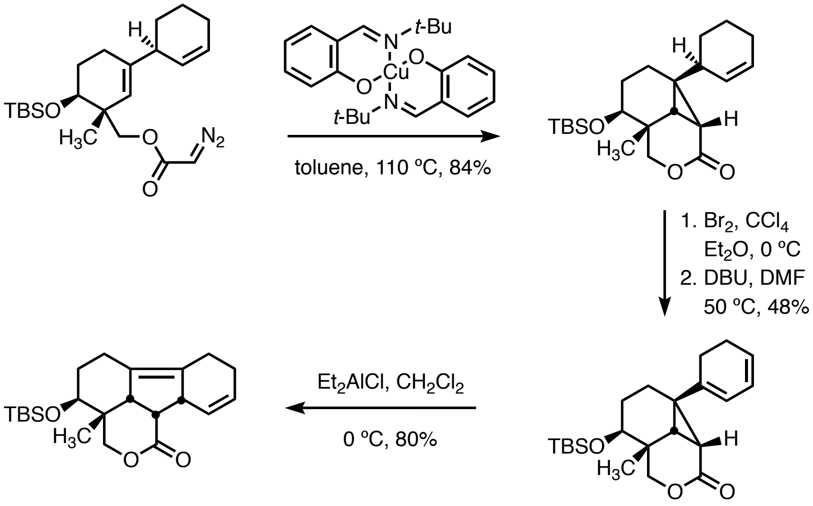
Selected Transformations of Cyclopropanes

- Cyclopropanes can undergo direct C-H functionalization enantioselectively by Pd(II) complexes with chiral amino acid ligands.
- A special directing group is required on the cyclopropane substrate to coordinate the Pd(II) complex and direct insertion into the adjacent *cis* C-H bond.
- The directing group is readily available and can be hydrolyzed to give the corresponding acid:



Wasa, Y.; Engle, K. M.; Lin, D. W.; Yoo, E.-J.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 19598–19601.

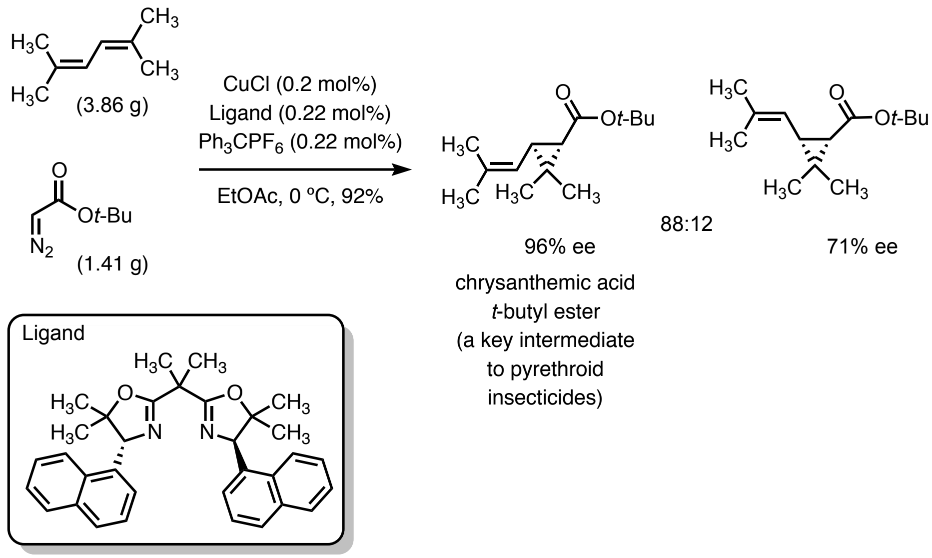
- Cyclopropanes can undergo vinylcyclopropane-cyclopentene rearrangements:



Corey, E. J.; Myers, A. G. *J. Am. Chem. Soc.* **1985**, *107*, 5574–5576.
Corey, E. J.; Myers, A. G. *Tetrahedron Lett.* **1984**, *25*, 3559–3562.

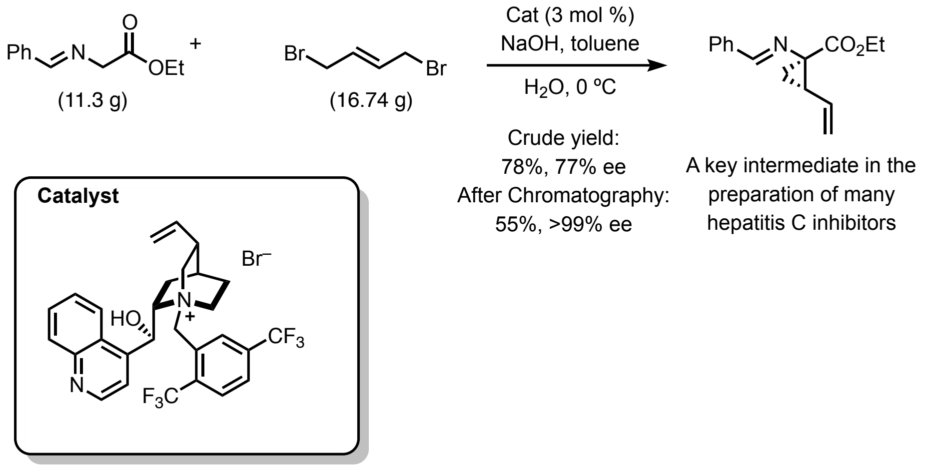
Selected Industrial Examples

- A copper-catalyzed diazo decomposition led to the asymmetric cyclopropanation of 2,5-dimethyl-2,4-hexadiene in good yield and high enantioselectivities:



Itagaki, M.; Masumoto, K.; Suenobu, K.; Yamamoto, Y. *Org. Proc. Res. Dev.* **2006**, *10*, 245–250.

- Cinchona alkaloids were applied to the synthesis of (1*R*,2*S*)-1-amino-2-vinylcyclopropanecarboxylic acid ethyl esters in good yield and modest ee's.



Belyk, K. M.; Xiang, B.; Bulger, P. G.; Leonard, W. R.; Balsells, J.; Yin, J.; chen, C.-y. *Org. Proc. Res. Dev.* **2010**, *14*, 692–700.

James Mousseau, David W. Lin, Fan Liu