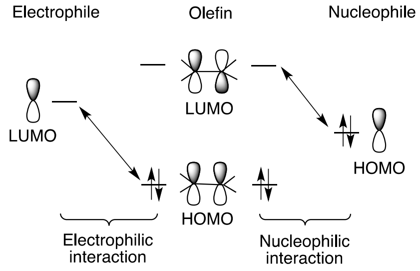
OLEFIN ADDITION REACTIONS

INTRODUCTION

Olefins are reactive functional groups because of their C=C π bond. They can be readily transformed to other functional groups by adding suitable reagents across the double bond. There are two general types of addition to olefins: electrophilic (mainly with electron rich double bonds) and nucleophilic (mainy electron poor double bonds e.g. enones).

Frontier molecular orbitals of transition structures in electrophilic and nucleophilic addition to olefins



Electrophilic addition to olefin: LUMO of electrophile + HOMO of olefin

Nucleophilic addition to olefin: LUMO of olefin + HOMO of nucleophile

Houk *Science* **1986**, *231*, 1108

In this chapter, enantioselective and regioselective olefin addition reactions will be discussed.

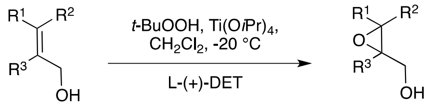
I ENANTIOSELECTIVE TRANSFORMATIONS

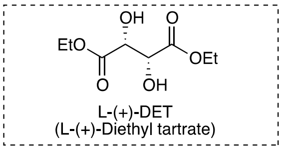
1.1 Epoxidation reactions

Enantioselective epoxidations have been well established, they can be performed with both electron poor and electron rich double bonds. As most of the reactions discussed in this chapter, they can additionally be divided into directed and non-directed reactions.

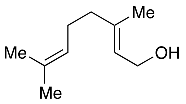
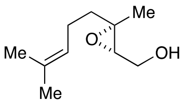
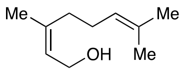
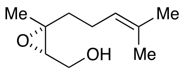
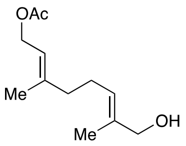
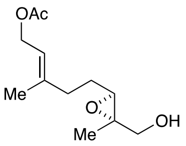
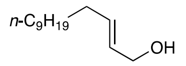
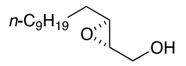
1.1.1 Sharpless epoxidation

Barry Sharpless was awarded the 2001 Nobel Prize for his contributions in stereoselective oxidations of olefins (epoxidation, dihydroxylation, aminohydroxylation).





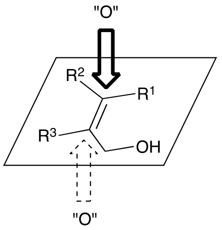
L-(+)-DET
(L-(+)-Diethyl tartrate)

Allylic alcohol	Product	Yield, %	*ee*, %
		77	95
		79	94
		70	>95
		79	>95

Stereoselectivity is dependent on configuration of the tartrate:

1. Place hydroxymethyl group at the lower right corner.
2. **(–)-diethyl tartrate**: epoxidation from the **top** face.
   (+)-diethyl tartrate: epoxidation from the **bottom** face.

D-(–)-diethyl tartrate (unnatural)



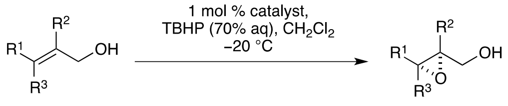
L-(+)-diethyl tartrate (natural)

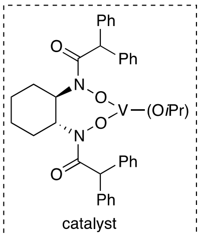
Sharpless *J. Am. Chem. Soc.* **1980**, *102*, 5974
Sharpless *J. Am. Chem. Soc.* **1987**, *109*, 5765

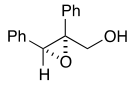
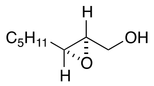
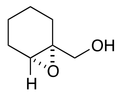
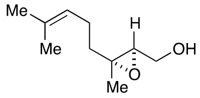
Sharpless epoxidation relies on alcohol as a directing group and works only with allylic alcohols. Other double bonds in the molecule are unreactive under these conditions. However this has been one of the most widely used reactions to install a stereocenter in the molecule.

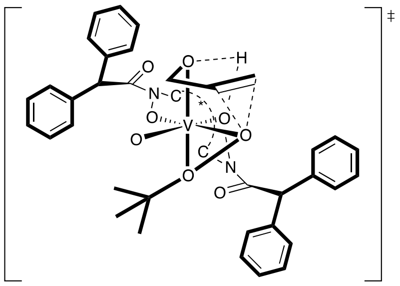
1.1.2 Yamamoto's vanadium-catalyzed enantioselective epoxidations

Epoxidations of allylic alcohols using vanadium and a bishydroxamic acid complex are highly enantioselective. Other great features include mild reaction conditions, 1 mol % or less catalyst loading is needed and aqueous *t*-BuOOH (TBHP) can be used as achiral oxidant.




catalyst

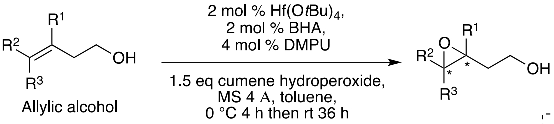
Product	Time, h	Yield, %	*ee*, %
	48	91	97
	72	51	95
	48	79	95
	48	68	95

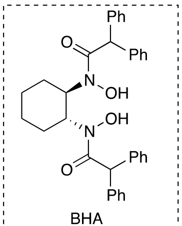

Proposed transition state

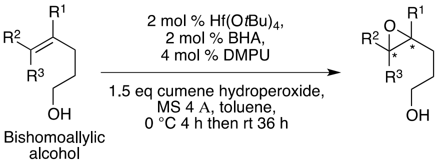
Yamamoto *Angew. Chem. Int. Ed.* **2005**, *44*, 4389

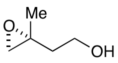
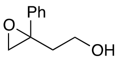
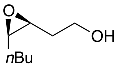
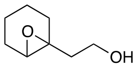
Recently, Yamamoto reported catalytic enantioselective epoxidation of homoallylic and bishomoallylic alcohols (more challenging substrates) using zirconium(IV) and hafnium(IV) in the presence of bishydroxamic acid (BHA).

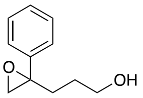
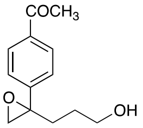
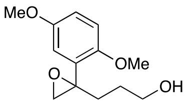
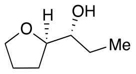
- Hafnium(IV)-catalyzed systems result in better yields and higher enantioselectivities
- Works very well with homoallylic alcohols
- Bishomoallylic alcohols show lower reactivities and therefore require higher catalyst loading (10 mol%).




BHA



Product	Yield, %	*ee*, %
	81	97
	69	98
	83	96
	81	89

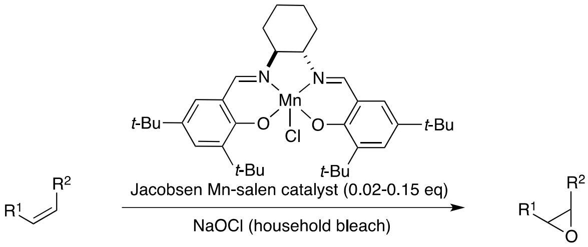
Product	Yield, %	*ee*, %
	75	99
	79	97
	25	97
	43	95

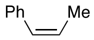
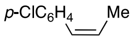
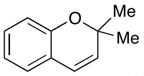
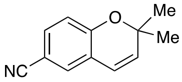
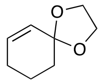
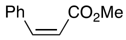
Yamamoto *J. Am. Chem. Soc.* **2010**, *132*, 7878
Yamamoto *J. Am. Chem. Soc.* **2013**, *135*, 3411

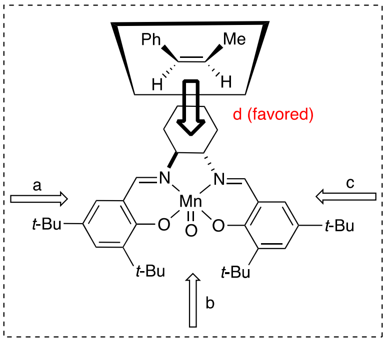
1.1.3 Jacobsen and Katsuki's Mn-salen complex-catalyzed epoxidations

- Unfunctionalized olefins that lack the specific directing group show lower selectivities towards epoxidation
- Due to the lack of efficient catalytic systems, enantioselective epoxidations of unfunctionalized olefins have been a long-standing goal
- The first breakthrough in the epoxidation of unfunctionalized olefins was made independently by Jacobsen and Katsuki in 1990 (Katsuki *Tetrahedron Lett.* **1990**, *31*, 7345–7348 and Jacobsen *J. Am. Chem. Soc.* **1990**, *112*, 2801–2803).

Chiral Mn-salen complexes provide a convenient and inexpensive procedure for efficient asymmetric epoxidation of unfunctionalized olefins. Cis-olefins works very well for this catalysis, however, trans-olefins tend to be poor substrates (low reactivity and enantioselectivity).



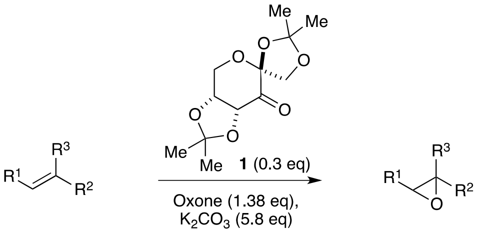
Substrate	Yield, %	ee, %
	84	92
	67	92
	72	98
	96	97
	63	94
	65	89

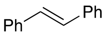
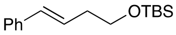
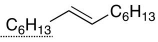


Jacobsen *J. Am. Chem. Soc.* **1991**, *113*, 7063

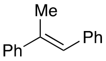
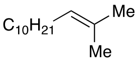
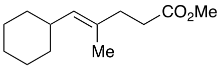
1.1.4 Shi's dioxirane-catalyzed epoxidation

- Complementary to Mn-salen-catalyzed asymmetric epoxidation of ***cis*-olefins**, Shi's fructose-derived chiral ketone enantioselectively epoxidizes ***trans*-olefins** in the presence of oxone
- Subsequent reaction optimizations showed that the efficiency of the ketone catalyst is increased at higher pH (10.5 compared to 7-8 previously). At higher pH, the competing ketone decomposition pathway via the Baeyer-Villiger reaction is suppressed since high pH favors the equilibrium of intermediate **2** and **3** (see proposed mechanism below)
- Great enantioselectivities can be obtained with ***trans*-olefins**. On the contrary, very low enantioselectivities are observed with ***cis*-olefins**

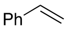
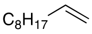
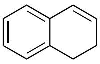


Substrate	Yield, %	*ee*, %
	78	99
	71	95
	89	95

trans-disubstituted olefins

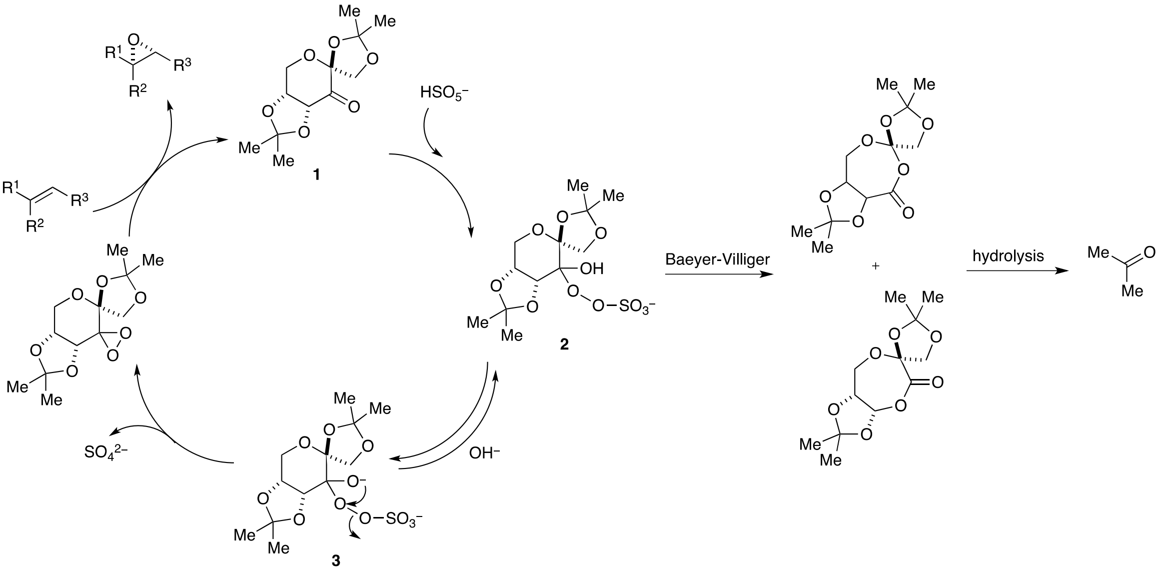
Substrate	Yield, %	*ee*, %
	89	96
	97	87
	89	94

trans-trisubstituted olefins

Substrate	Yield, %	*ee*, %
	90	24
	92	17
	92	12

terminal olefins and *cis*-olefins

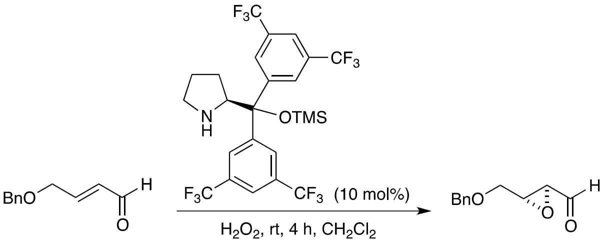
Proposed mechanism:



Shi *J. Am. Chem. Soc.* **1996**, *118*, 9806
Shi *J. Org. Chem.* **1997**, *62*, 2328
Shi *J. Am. Chem. Soc.* **1997**, *119*, 11224

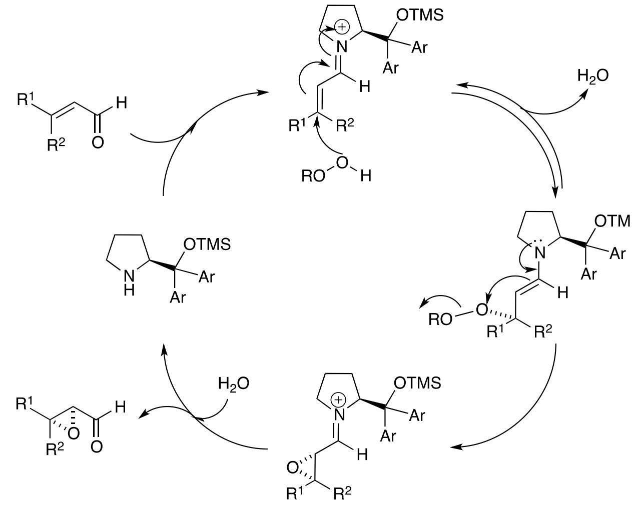
1.1.5 Jorgensen's chiral pyrrolidine catalysis of α,β-unsaturated aldehydes

- Electron poor alkenes can be readily epoxidized using pyrrolidine-derived catalysts popularized by Jorgensen
- The corresponding enone is converted into an iminium, thus lowering the LUMO of the system
- Hydrogen peroxide works as a stoichiometric oxidant



96% *ee*
dr = 96:4

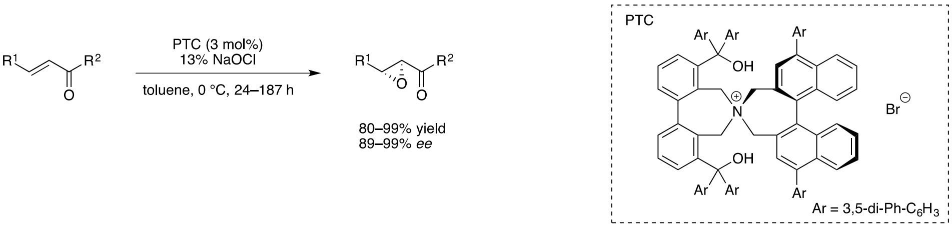
Mechanism:

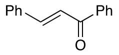
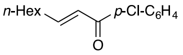
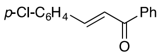
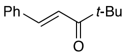
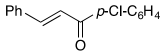
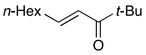


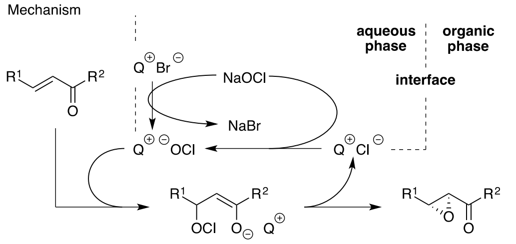
Jorgensen *J. Am. Chem. Soc.* **2005**, *127*, 6964

1.1.6 Maruoka's phase transfer catalysis (PTC) of α,β-unsaturated ketones

- Phase transfer catalysis also works for enantioselective alkene epoxidation of α,β-unsaturated ketones
- Ketone moiety should have bulky substituent such as phenyl or *tert*-butyl group
- Reaction proceeds through biphasic mechanism in which the quaternary ammonium salt serves to bring the nucleophilc oxidizing agent across the interface



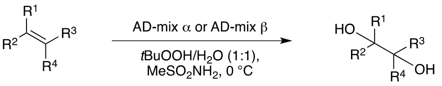
Substrate	Yield, %	*ee*, %	Substrate	Yield, %	*ee*, %
	99	97		99	96
	99	96		99	92
	99	96		80	91

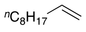
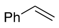
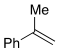
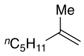
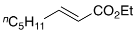
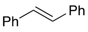
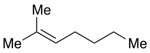
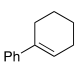


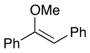
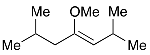
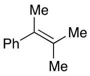
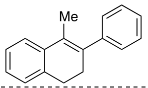
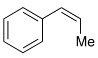
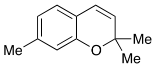
Maruoka *J. Am. Chem. Soc.* **2004**, *126*, 6844

2 ALKENE DIHYDROXYLATION

- Another contribution of Sharpless in the field of asymmetric catalysis is the asymmetric dihydroxylation
- In the case with $K_3Fe(CN)_6$ as the co-oxidant, the reaction is performed under biphasic conditions
- $K_2OsO_2(OH)_4$ is used as the osmium source because it's not volatile (OsO_4 is highly toxic)
- Premixes called "AD-mix" containing $K_2OsO_2(OH)_4$, $K_3Fe(CN)_6$ and chiral bidentate ligand have been formulated and are commercially available
- Dihydroxylation is applicable to almost all type of substitution pattern in alkene substrates (see substrate scope below)
- $MeSO_2NH_2$ was found to increase the rate and catalytic turnovers of dihydroxylation. It was added to all reactions, except in the case of terminal olefins

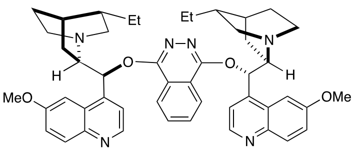


		AD-mix α (*ee*)	AD-mix β (*ee*)
Monosubstituted ($MeSO_2NH_2$ not used)		84	80
		97	97
1,2-Disubstituted ($MeSO_2NH_2$ not used)		94	93
		78	76
trans-Olefin		99	96
		99	>99
Trisubstituted		98	95
		99	97

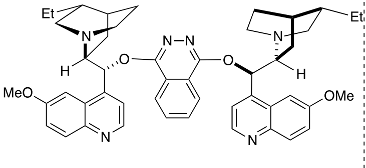
		AD-mix α (*ee*)	AD-mix β (*ee*)
Enol ethers (products are α-hydroxy ketones)		99	98
		91	93
Tetrasubstituted		39	
		83	85
		with DHQD-IND	with DHQ-IND
cis-Olefin		72	59
		32	67

AD-mix α: $(DHQ)_2PHAL + K_2OsO_2(OH)_4 + K_3Fe(CN)_6$

AD-mix β: $(DHQD)_2PHAL + K_2OsO_2(OH)_4 + K_3Fe(CN)_5$



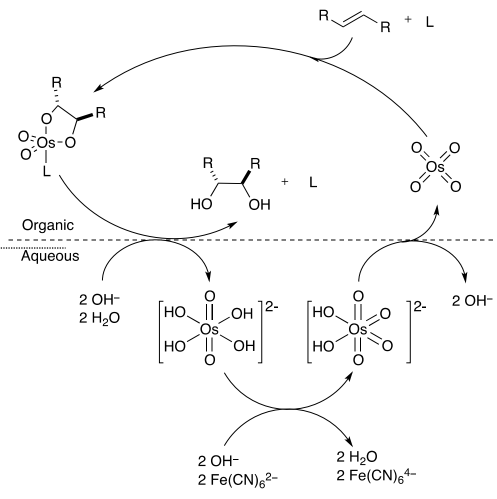
$(DHQD)_2PHAL$

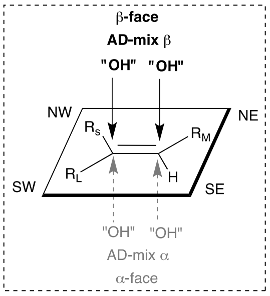


$(DHQ)_2PHAL$

Note: $(DHQD)_2PHAL$ and $(DHQ)_2PHAL$ are not enantiomers.

Catalytic cycle with $K_3Fe(CN)_6$ as the cooxidant



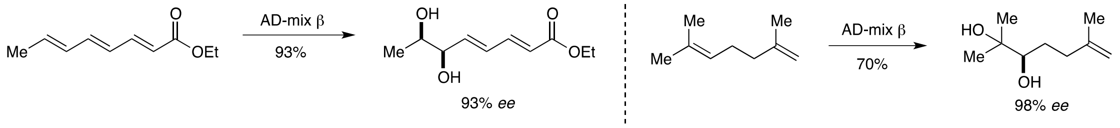


Mnemonic device for dihydroxylation using AD-mix α and AD-mix β:

1. Place R_L on the SW quadrant.
   R_L: "soft", large or flat (aromatic substituents)
2. AD-mix α approaches from bottom face.
   AD-mix β approaches from top face.

Sharpless *Chem. Rev.* **1994**, *94*, 2483

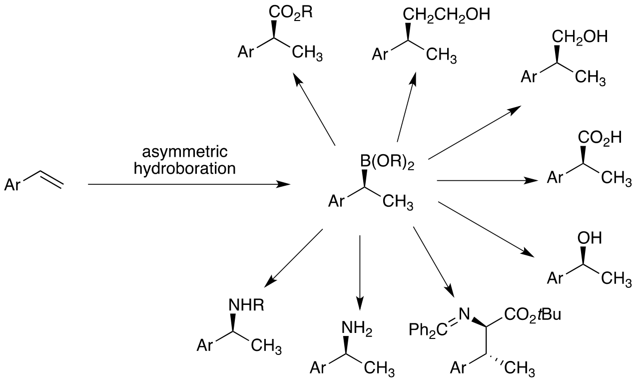
Chemoselectivity of asymmetric dihydroxylation:



Sharpless *J. Am. Chem. Soc.* **1992**, *114*, 7568
Sharpless *Science* **1993**, *259*, 64

3 ENANTIOSELECTIVE HYDROBORATION

Chiral boronate ester products of alkene hydrobration are useful synthetic intermediates. These substrates can be formed either using chiral reagents or asymmetric catalysis. Catalytic hydroboration and subsequent oxidation to the alcohol species remained as one of the most common reaction sequences. Transformation of the C-B bond into C-N and C-C bonds with retention of stereochemistry significantly expanded the synthetic utility of the catalytic enantioselective hydroboration reaction.

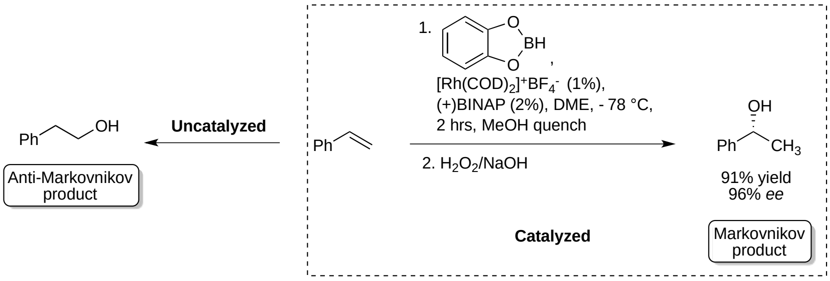


Transformations of the carbon-boron bond

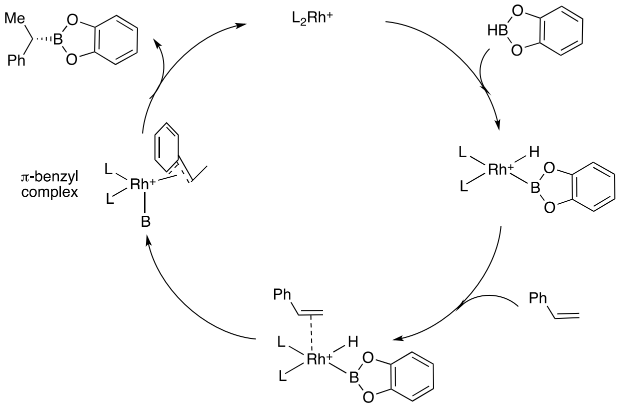
Crudden *J. Org. Chem.* **2003**, 4695

Rhodium-catalyzed enantioselective hydroboration with chiral bisphosphane ligands

- In 1991, Hayashi reported catalytic enantioselective hydroboration of styrenes in the presence of Rh(I) and BINAP.
- An intriguing feature of this reaction is the complete reversal of regioselectivity observed in the catalytic hydroboration relative to the uncatalyzed reaction.
- Importantly the catecholborane does not react with olefins, thus this reaction does not have a background rate
- The high regioselectivity observed in the rhodium-catalyzed hydroboration of styrenes was rationalized by the formation of a π-benzyl complex (see catalytic cycle below)



Crudden *J. Org. Chem.* **2003**, 4695



Hayashi *Tetrahedron: Asymmetry* **1991**, *2*, 601

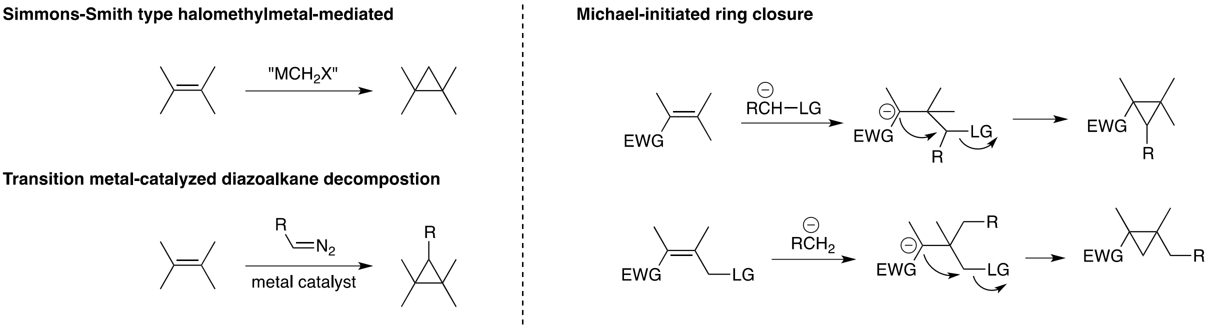
Other systems have been reported for asymmetric hydroboration, however this reaction in general works well, even though only for styrene and its derivatives (terminal olefins).

4 CYCLOPROPANATIONS

In comparison to epoxidations, the asymmetric cyclopropanation reactions have not been established to the same extent. Some methods are known, which mainly rely on the use of stoichiometric amount of catalysts, however they have not found broad application in synthetic chemistry yet.

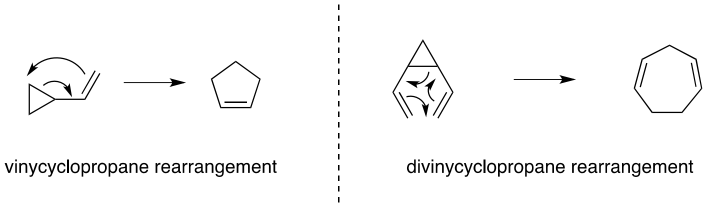
Reviews: Charette *Chem. Rev.* **2003**, *103*, 977 and Pellissier *Tetrahedron* **2008**, *64*, 7041

4.1 Classes of cyclopropanation reactions



The importance of cyclopropanes is exemplified in the following ways:

- The occurrence of cyclopropanes in natural and medicinally important compounds
- The function of cyclopropanes as a mechanistic probe
- The use of cyclopropanes in key synthetic transformations including vinylcyclopropane rearrangements and divinylcyclopropane Cope rearrangements



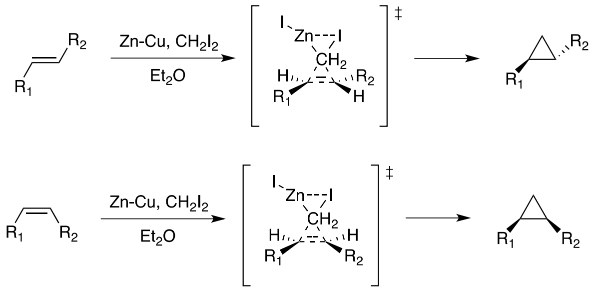
vinycyclopropane rearrangement

divinycyclopropane rearrangement

4.2 Simmons-Smith type cyclopropanations

4.2.1 Simmons-Smith reaction overview

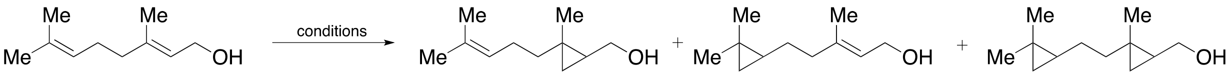
- Applicable to a wide range of olefins (simple, electron deficient, electron rich)
- Electron rich alkenes react faster (because of electrophilicity of zinc reagent)
- Stereospecific (*cis*-alkenes give *syn*-cyclopropanes and *trans*-alkenes give *anti*-cyclopropanes)
- Reactions proceed via a Butterfly-like transition state
- Typical conditions: Zn/Cu, CH_2I_2, Et_2O (In current procedures, Zn/Cu is often generated by the treatment of zinc powder with a $CuSO_4$ solution.)



Seminal publications: Simmons and Smith *J. Am. Chem. Soc.* **1958**, *80*, 5323 and *J. Am. Chem. Soc.* **1959,** *81*, 4256

4.2.2 Directing effects and Modifications

- The Simmons-Smith reaction exhibits a strong directing effect and rate enhancement (with zinc when the alkene bears a heteroatom-containing functional group, and the methylene is delivered to the face of the alkene that is proximal to the heteroatom



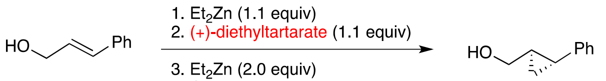
A **B** **C**

Conditions	A : B : C
Et_2Zn, CH_2I_2	74 : 2 : 3
i-Bu_3Al, CH_2I_2	1 : 76 : 4
Sm(Hg), ICH_2Cl	98 : 0 : 0
Et_2Zn; $IZnCH_2I$	91 : 2 : 3

Charette *J. Organomet. Chem.* **2001**, *617*, 702

4.2.3 Enantioselective Simmons-Smith reactions using stoichiometric chiral additives

First practical report of a stoichiometric chiral additive:

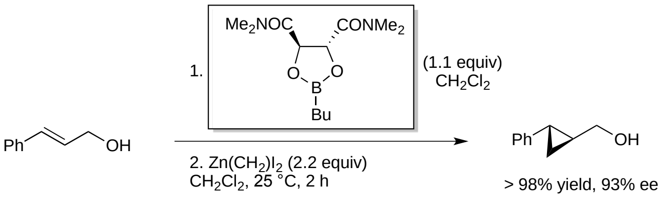


54% yield, 79% ee

Fujisawa *Chem. Lett.* **1992**, 61

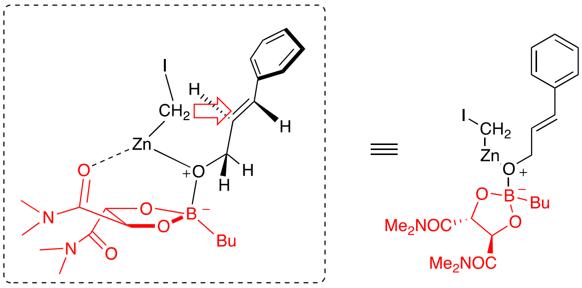
Charette's dioxaborolane

- Major breakthrough by Charette in 1994: Use of amphoteric, bifunctional ligands derived from (*R,R*)-(+)-*N,N,N',N'*-tetramethyltartartic acid diamide and butylboronic acid



> 98% yield, 93% ee

Charette *J. Am. Chem. Soc.* **1994**, *116*, 2651



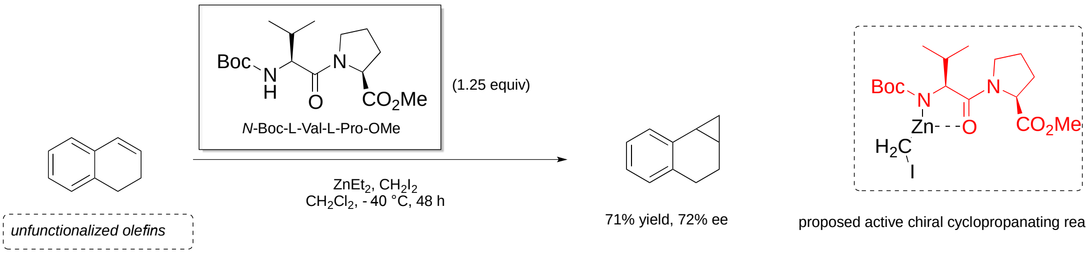
proposed transition state for enantioselective cyclopropanation of cinammyl alcohol using Charette's dioxaborolane

• The amphoteric dioxaborolane ligand coordinates both the allylic alcohol oxygen (through its acidic boron) and the zinc of the methylene transfer reagent (through its basic amide carbonyl).

- Reaction proceeds well with *cis*- and *trans*-disubstituted allylic alcohols and with tetra-substituted allylic alcohols but only with some tri-substituted allylic alcohols
- For > 1 mmol scale, DME complex, $Zn(CH_2I)_2$•DME, is used due to the exothermicity of $Zn(CH_2I)_2$ or zinc alkoxide formation (Charette *J. Org. Chem.* **1995**, *60*, 1081)
- Extended to the cyclopropanation of *homo*allylic alcohols (Charette *J. Am. Chem. Soc.* **1998**, *120*, 11943)

Shi's dipeptide

- In 2003, Shi reported the use of a chiral dipeptide that could be used stoichiometrically to enantioselectively cyclopropanate unfunctionalized (i.e., lacking a directing group) olefins (in 72–91% ee).

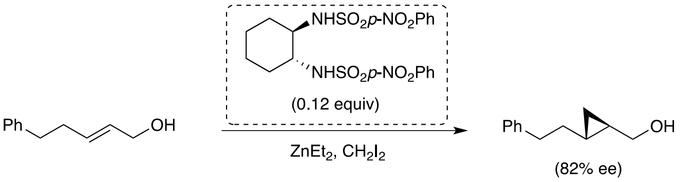


Shi *J. Am. Chem. Soc.* **2003** *125*, 13632

4.2.4 Catalytic enantioselective Simmons-Smith cyclopropanations

C_2-symmetric chiral disulfonamide ligands

- Kobayashi reported in 1992 that the Simmons-Smith cyclopropanation could be accelerated by addition of a chiral Lewis acid. Thus, they were able to use C_2-symmetric chiral disulfonamide ligands in catalytic amounts to achieve cyclopropanations in 13-82% ee.



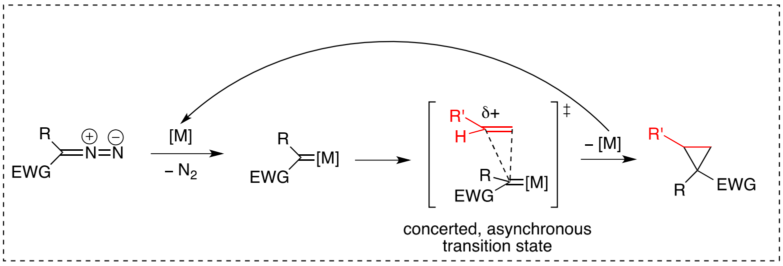
Kobayashi *Tetrahedron Lett.* **1992**, *33*, 2575
Kobayashi *Tetrahedron* **1995**, *51*, 12013

- Kobayashi et al. also showed that zinc may be replaced by aluminum in this reaction (Kobayashi *Chem. Lett.* **1994**, 23, 177)

4.3 Cyclopropanations using diazoalkane-generated carbenoids

4.3.1 General catalytic cycle

- Metal-carbenoid cyclopropanation is a concerted but asynchronous process, which involves a build-up of positive charge on one of the olefin carbons

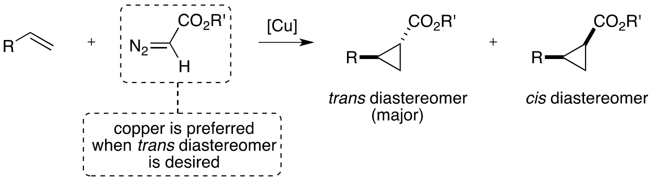


EWG = electron-withdrawing group
M = Rh(II), Cu(I), Ru, Os

Salvatella and García *J. Am. Chem. Soc.*, **2001**, *123*, 7616
Rasmussen *Chem. Eur. J.* **2002**, *8*, 177
Moser *J. Am. Chem. Soc.* **1969**, *91*, 1135

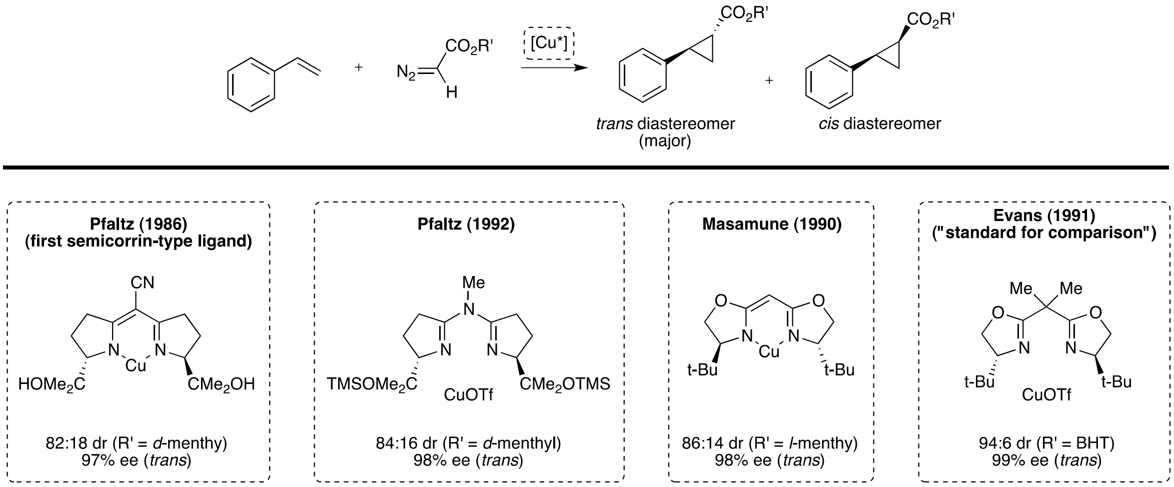
4.3.2 Copper: Intermolecular (and intramolecular) cyclopropanations using α-diazoesters

- Copper is the most effective and general metal for intermolecular cyclopropanations using α-diazoesters when the *trans* diastereomer is desired.
  - In general, a bulky ester is required to maximize the *trans*:*cis* ratio.



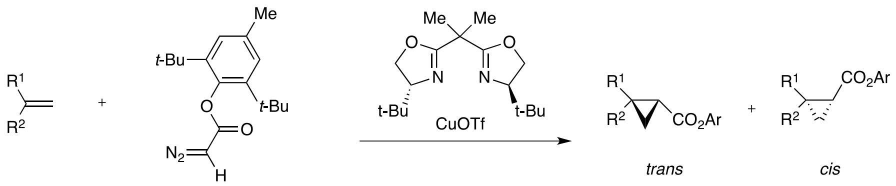
Nozaki *Tetrahedron Lett.* **1966**, *7*, 5239
Nazaki *Tetrahedron* **1968**, *24*, 3655

Chiral, C_2-symmetric bidentate bisoxazoline ligands are most widely used for enantioselective, copper-catalyzed cylopropanations



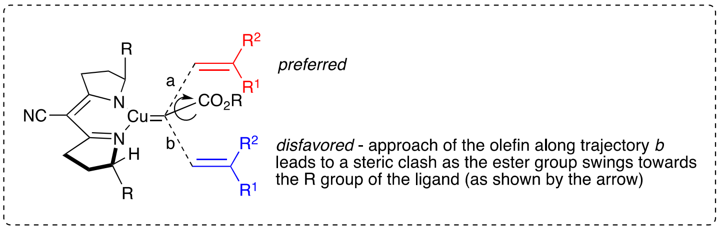
Pfaltz *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 1005
Pfaltz *Tetrahedron* **1992**, *48*, 2143
Masamune *Tetrahedron Lett.* **1990**, *31*, 6005
Evans *J. Am. Chem. Soc.* **1991**, *113*, 726

- Bisoxazoline ligands are very effective for the intermolecular copper-catalyzed cyclopropanation of mono- and 1,1-disubstituted alkenes
  - BHT (BHT = 2,6-di-*tert*-butyl-4-methylphenyl) esters can be cleaved to the corresponding primary alcohol by reduction with $LiAlH_4$



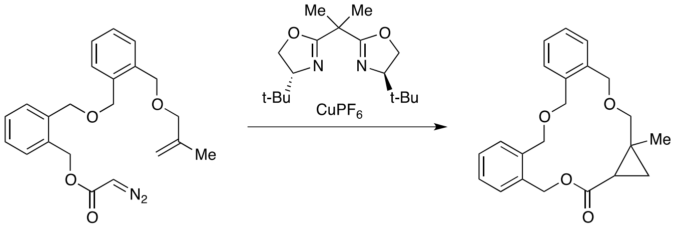
R^1	R^2	yield (%)	*trans:cis*	ee *trans* (%)
Ph	H	85	94:6	99
$PhCH_2$	H		93:7	>99
Ph	Ph	70		>99
Me	Me	91		>99

- Preferred approach of olefin for cyclopropanation using Pfaltz ligands:



disfavored - approach of the olefin along trajectory *b* leads to a steric clash as the ester group swings towards the R group of the ligand (as shown by the arrow)

- Macrocyclic cyclization cyclopropanations typically work well using $CuPF_6$ in combination with Evans' bisoxazoline ligand

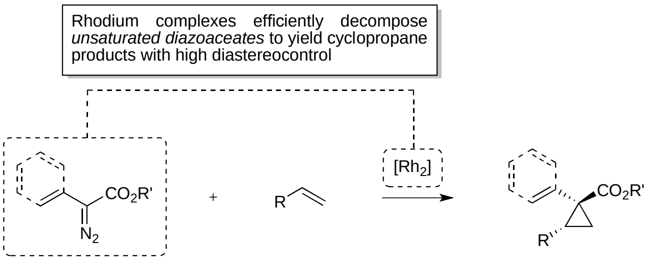


cis:trans 69:31
trans: 85% *ee*

Doyle *J. Am. Chem. Soc.* **2000**, *122*, 5718

4.3.3 Rhodium

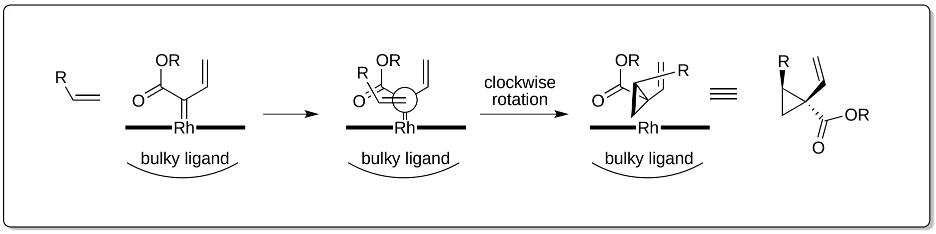
- For *intermolecular* cyclopropanation reactions using *vinyl and aryl diazoesters*, rhodium catalysts are generally preferred



Rhodium complexes efficiently decompose *unsaturated diazoaceates* to yield cyclopropane products with high diastereocontrol

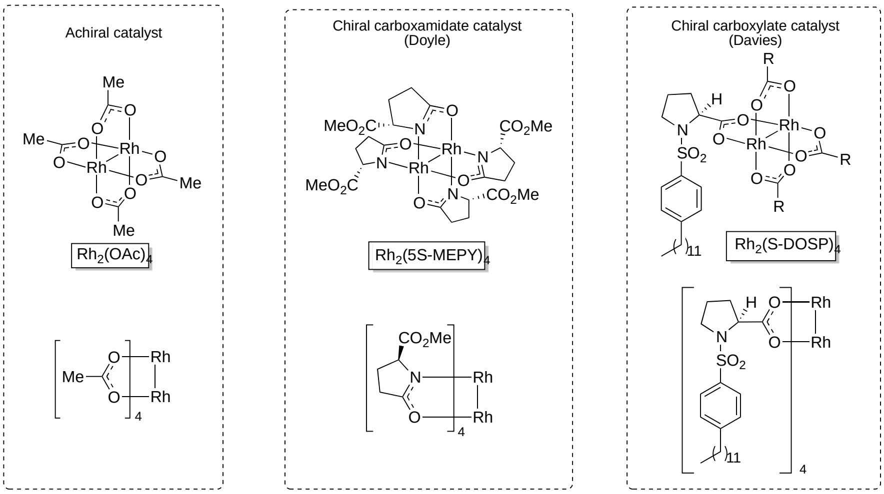
Model for diastereoselectivity in rhodium-catalyzed cyclopropanations

- The presence of an electron-withdrawing substituent (ester) and electron-donating substituent (vinyl group) is important for high diastereoselectivities. Alkene approaches from the side of the ester. The developing positive charge on the more substituted alkene carbon is likely to be stabilized by the carbonyl oxygen

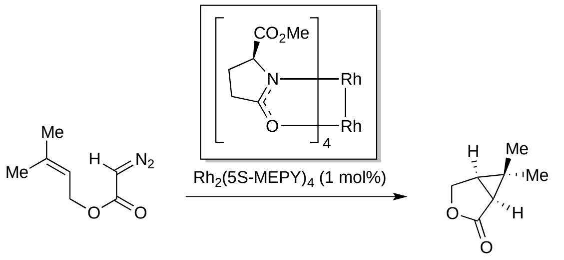


- For diazo compounds of the type (H)(EWG)C=N_2, diastereocontrol is generally inferior to that obtained with copper, ruthenium, and cobalt carbenes

Representative rhodium(II) catalysts: (“paddle-wheel”/”Schaufelrad” structure)



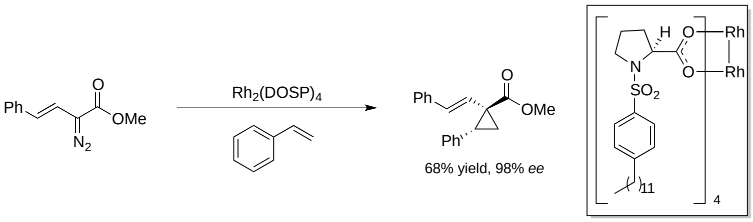
- Doyle pioneered the use of chiral dirhodium(II) (specifically, using carboxamidate ligands) catalysts with α-diazo carbonyl compounds to generate reactive rhodium carbenoids capable of efficient asymmetric cyclopropanation



82% yield, 99% *ee*

Doyle *J. Am. Chem. Soc.* **1991**, *113*, 1423

- Davies has developed a series of chiral dirhodium(II) carboxylate catalysts that efficiently decompose unsaturated diazoacetates to the corresponding rhodium carbenoids, which then participate in enantioselective cyclopropanation reactions



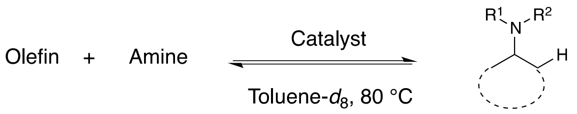
68% yield, 98% *ee*

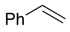
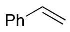
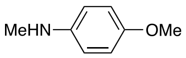
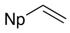
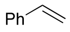
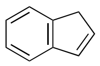
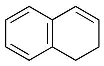
Davies *J. Am. Chem. Soc.* **1996**, *118*, 6897

5 **HYDROAMINATION** [Review: Schulz *Chem. Eur. J.* **2013**, *19*, 4972]

- The hydroamination reaction is the addition of an amine to an unsaturated C-C bond.
- It has great synthetic potential because it not only reduces the formation of waste (increased atom economy), but it also utilizes very simple starting materials.
- This transformation, thermodynamically feasible under normal conditions, suffers from a high activation barrier due to electrostatic repulsions between the lone pair of the nucleophilic nitrogen atom and the π-orbital of the electron-rich double bond.
- Reviews have stated that the hydroamination of olefins is thermodynamically favored. However, experimental equilibrium constants, enthalpies, and entropies for olefin hydroamination in solution are lacking. In 2006, Hartwig reported direct measurements of the equilibrium constants for addition of aromatic amines with varied steric and electronic properties to several types of vinyl arenes.

Thermodymanics of Hydroamination



Entry	Olefin	Amine	Catalyst[a]	K (M^{-1})	ΔG (kcal/mol)
1		HNMePh	A	1.5±0.1	–0.28±0.05
2			A	2.4±0.1	–0.61±0.03
3		HNMePh	A	1.30±0.01	–0.18±0.01
4		*m*-anisidine	A	155±1	–3.54±0.01
5		*m*-anisidine	B	0.69±0.05	0.26±0.05
6		*m*-anisidine	C	0.16±0.04	1.31±0.18

[a] Catalyst composition:

(**A**) *Forward*: 2 mol% *t*-BuXantphosPd(OTf)$_2$. *Backward*: 2 mol% CpPd(η^3 -allyl)/*t*-BuXantphos/HOTf.

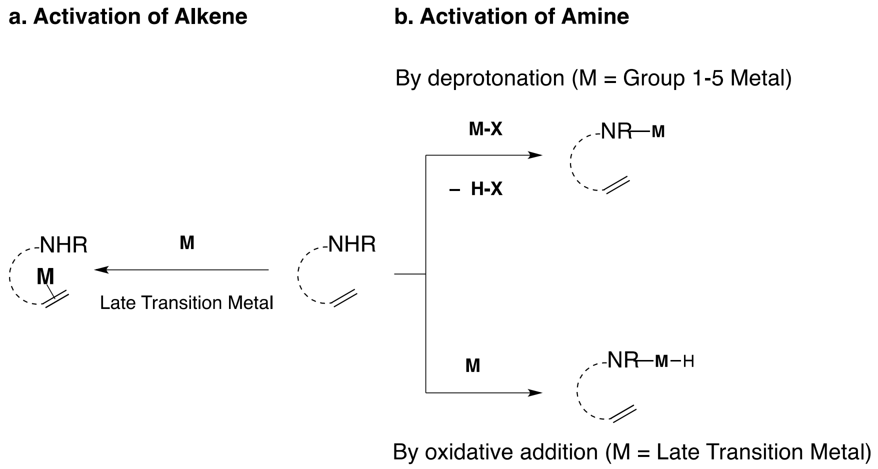
(**B**) *Forward*: 10 mol% Pd(TFA)$_2$/DPPF/HOTf. *Backward*: 10 mol% CpPd(η^3 -allyl)/DPPF/HOTf.

(**C**) *Forward*: 5 mol% Pd(TFA)$_2$/DPPF/HOTf. *Backward*: 5 mol% CpPd(η^3 -allyl)/DPPF/HOTf

Hartwig *J. Am. Chem. Soc.* **2006**, *128*, 9306; *J. Am. Chem. Soc.* **2000**, *122*, 9546

- Overall, the reactions are exothermic but nearly ergoneutral. The electronic effect on this reaction is almost purely a result of kinetics, not thermodynamics. Factors, as the equilibrium constants, for these additions are similar (entries 2 *vs.* 1, 3 *vs.* 1). In contrast, steric properties of the amine significantly affected the equilibrium constant. The addition of aniline to styrene occurred at a much higher conversion than the addition of *N*-methylaniline under equilibrium conditions (entries 4 *vs.* 1-2). Because disubstituted olefins are more stable than mono-substituted olefins, the reactions of aniline to indene and 1,2-dihydronaphthalene (entries 5-6) were limited by thermodynamics. These precise measurements of the thermodynamic parameters for the reactions between amines and olefins of varied structures established benchmark values that can be used to predict, which types of hydroaminations will be favorable and which will be unfavorable.
- The development of novel catalyst systems for hydroamination has seen significant progress in the last two decades but the intermolecular hydroamination of unactivated alkenes with simple amines remains very challenging. It is not surprising that asymmetric hydroamination reactions have been studied predominantly in intramolecular reactions. Intermolecular reactions have been reported only sporadically and all of these studies were limited to the reaction between aniline derivatives and activated alkenes, such as vinyl arenes, 1,3-dienes and strained bicyclic alkenes.

5.1 Metal-catalyzed Hydroamination



Activation of the Amine:

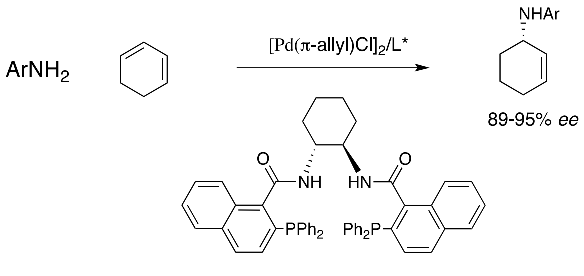
- Group 1–5 metal-based catalysts have been proposed to proceed by activation of the amine through a rapid protonolysis, leading to the formation of a metal-amido (or imido) complex that will further react through an insertive, non-insertive, or [2π + 2π] mechanism to generate the hydroamination product. On the other hand, oxidative addition of the N-H bond on a late transition metal in low oxidation state may occur to form a metal-hydride complex. Subsequent insertion of the C-C double bond into the metal-hydride complex and reductive elimination reaction will afford the hydroamination product.

Activation of the Alkene:

- π-Activation of the alkene by a Lewis-acidic, late transition metal may lead to the nucleophilic attack of the lone electron pair of the nitrogen to the coordinated alkene. The cleavage of the carbon–metal bond by protonolysis will then liberate the hydroamination product

5.1.1 Palladium

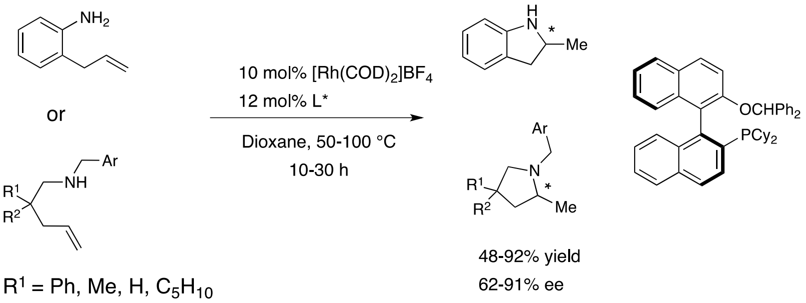
- Significant studies have been published by the group of Hartwig devoted to the Pd-catalyzed intermolecular hydroamination, allowing the fine-tuning of phosphine-based ligands for the enantioselective hydroamination with enantiomeric excesses of up to 95 %.



Hartwig *J. Am. Chem. Soc.* **2001**, *123,* 4366

5.1.2 Rhodium

- Buchwald reported the first examples of late transition-metal-catalyzed enantioselective intramolecular hydroamination of unactivated olefins. By using $[Rh(COD)_2]BF_4$ in the presence of binaphthyl-based electron-rich phosphines, they successfully cyclized *N*-benzyl protected aminoolefins to the corresponding pyrrolidine derivatives under mild conditions in dioxane in high yield and with up to 91 % *ee*. This reaction could also be performed with substrates lacking gem-substitutions.

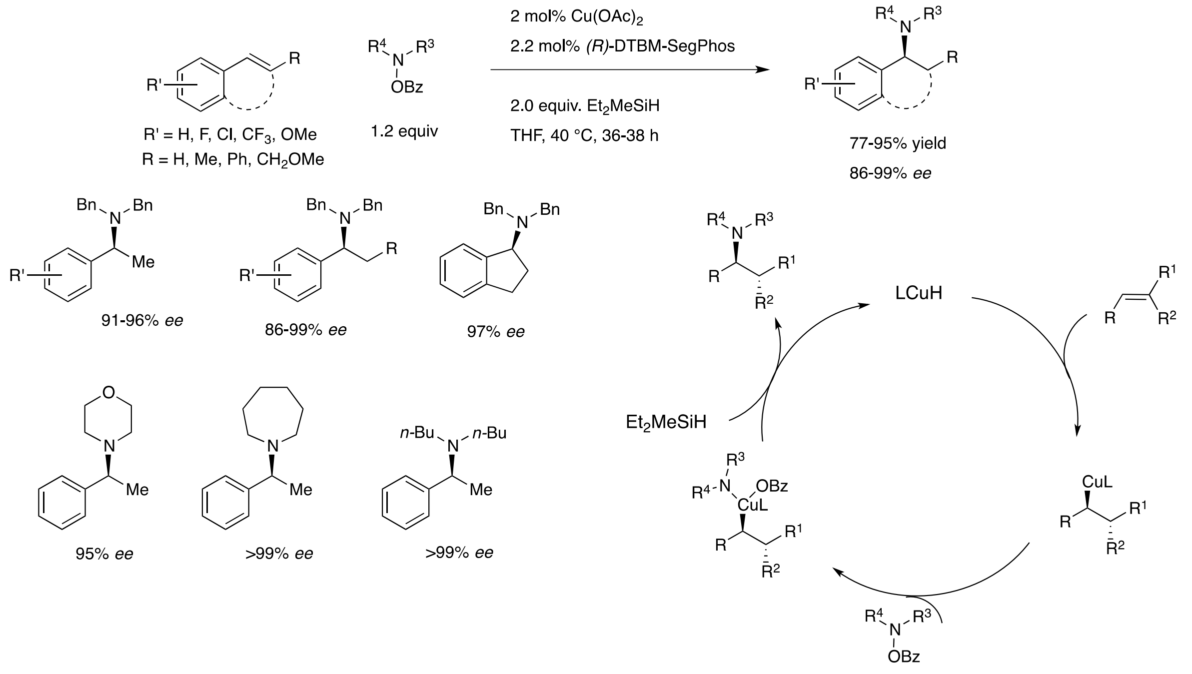


R^1 = Ph, Me, H, C_5H_{10}
R^2 = Ph, H
Ar = Ph, *o*-Me-C_6H_4, *p*-Cl-C_6H_4, *p*-OMe-C_6H_4, *p*-CO_2Me-C_6H_4

Buchwald *Angew. Chem. Int. Ed.* **2010**, *49*, 564

5.1.3 Copper

- Copper has been recently used as a potential inexpensive catalyst
- Cu(II) triflate and acetate were demonstrated to promote the intermolecular hydroamination of alkenes
- Buchwald has reported a copper-catalyzed hydroamination for synthesizing chiral tertiary amines with high enantioselectivities. They proposed that the insertion of an alkene into a chiral ligand-bound LCu(I)H-species would form an alkyl-copper complex (see mechanism below). Subsequent oxidative addition of an electrophilic hydroxylamine source followed by reductive elimination would form the C−N bond enantioselectively. The resulting copper(I)-species would further undergo transmetalation with an external hydride-transfer reagent to regenerate the LCu(I)H species.

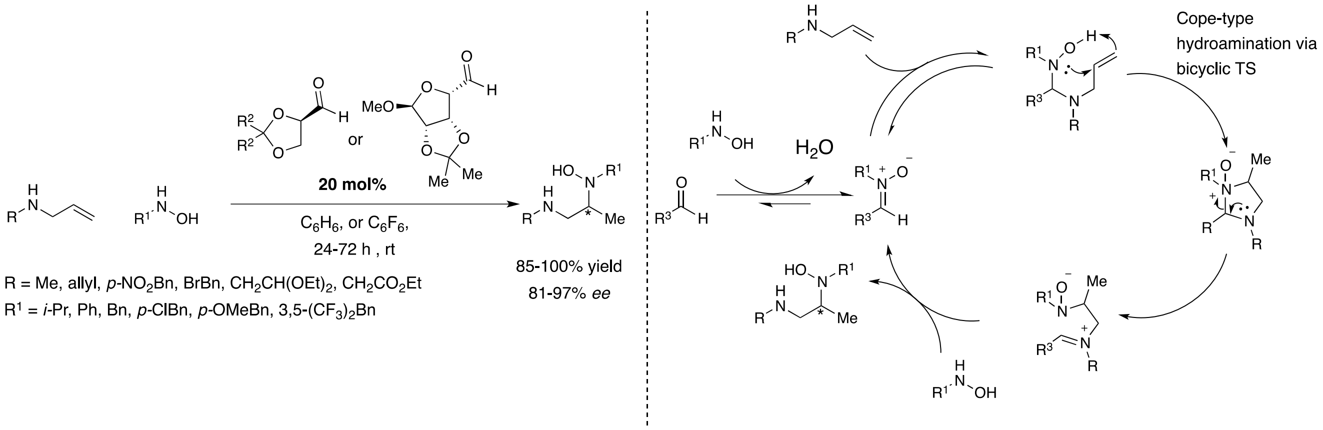


Buchwald *J. Am. Chem. Soc.* **2013**, *135*, 15746

- Substitution occurs in a regioselective manner to generate the new C−N bond at the α-position of styrene derivatives
- This method has been shown to be compatible with various substituted styrene derivatives, also styrenes with β-substitution
- Additionally, this method allows the development of copper-catalyzed anti-Markovnikov hydroaminations of terminal aliphatic alkenes

5.2 Metal-free Enantioselective Hydroamination

- In 2011, Beauchemin described a metal-free catalytic tethered strategy to promote an enantioselective intermolecular hydroamination reaction. The rate of such entropically unfavored transformation could be enhanced by the use of a catalytic organic species, appropriately designed as tether in order to temporarily bringing together both reaction partners to react intramolecularly through a Cope-type rearrangement. Acetaldehyde derivatives were used as catalyst for the intermolecular Cope-type hydroamination of allylic amines and hydroxylamine, high yields and *ee* values of up to 97% at room temperature could be afforded.



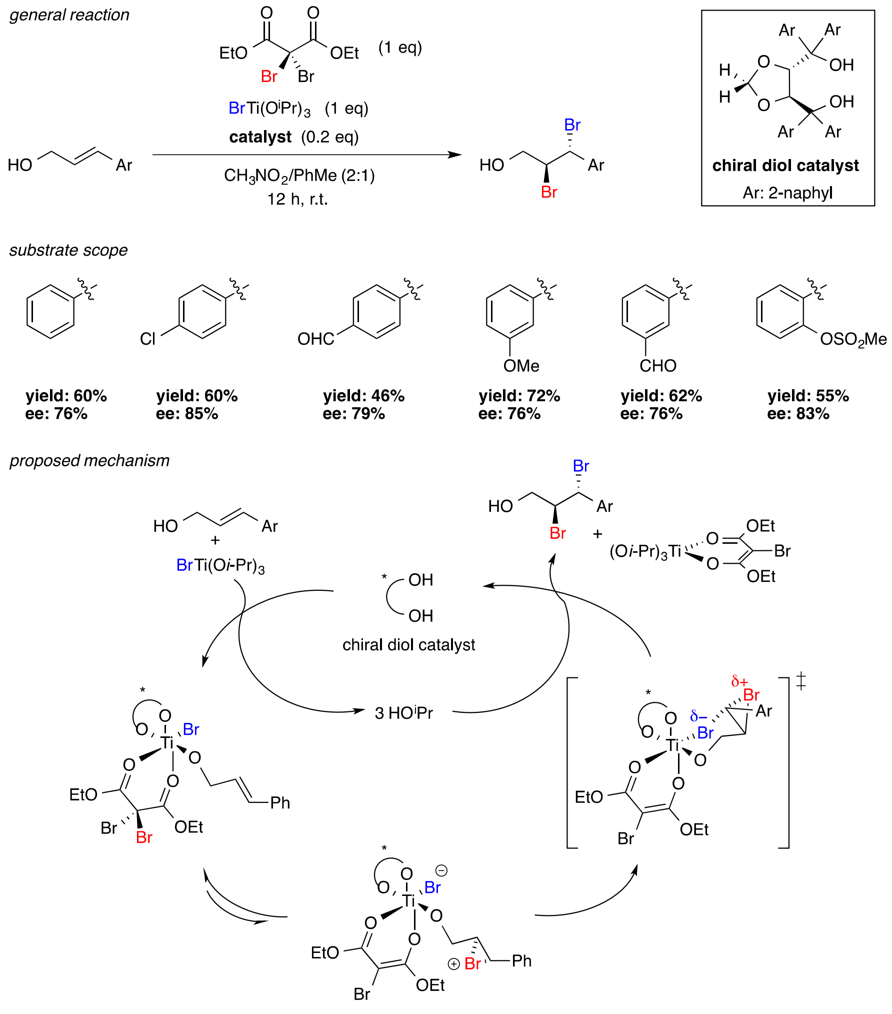
Beauchemin *J. Am. Chem. Soc.* **2011**, *133*, 20100

Beauchemin *Chem. Eur. J.* **2013**, *19*, 2597

6 DIBROMINATION

Alkene dibromination is one of the oldest and most fundamental olefin reactions. Only recently it has been rendered enantioselective.

- There are two major difficulties in controlling the absolute stereochemical outcome of alkene dibromination. First, common dibrominating reagents (also bromine) react rapidly with alkenes and therefore nonselective background bromination is often faster than the desired catalytic pathway. Furthermore, the enantioenriched bromonium-cation intermediate can rapidly racemize.
- The group of Burns reported a directed catalytic dibromination of allylic alcohols using an unusual malonate-derived species as the bromonium source (reactive only in the presence of a Lewis acid) and a titanium bromide species (Lewis acid) as bromide source. Enantiocontrol was achieved by using a chiral TADDOL-derived ligand, which also accelerates the reaction.

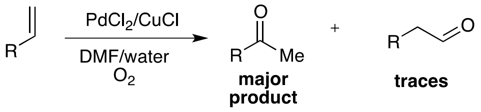


Burns *J. Am. Chem. Soc.* **2013**, *135*,12960

II REGIOSELECTIVE TRANSFORMATIONS

Regioselectivity in olefins can be achieved in several different ways. It can either be substrate-controlled (most often Markovnikov selectivity); catalyst or reagent-controlled or the reaction can also be directed. A lot of effort has been (and still is today) devoted to identify new catalysts and systems, which can override the inherent (Markovnikov) reactivity.

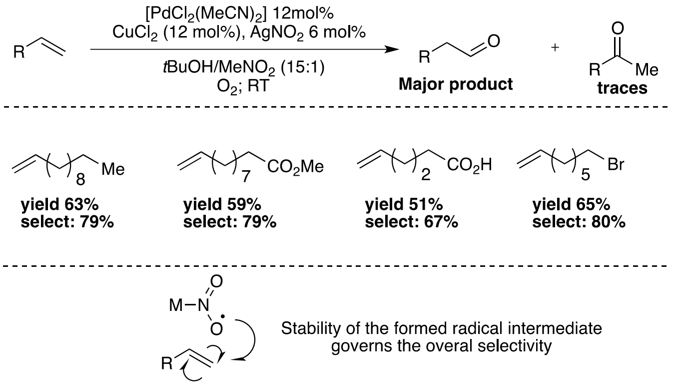
1 Wacker oxidation



Typical selectivity in Wacker oxidation

Wacker oxidation is a classical example of conversion of olefins to the corresponding carbonyl compounds. Various functional groups are tolerated and the reaction is very atom efficient. The selectivity of this reaction is highly substrate-controlled (Markovnikov selectivity), thus terminal olefins predominantly afford methyl ketones. Careful substrate design can offer biased alkenes, which circumvent Markovnikov's rule and yield aldehydes as products. However, this approach is limited to only certain classes of olefins (see Feringa *Angew. Chem. Int. Ed.* **2013**, *52*, 5561).

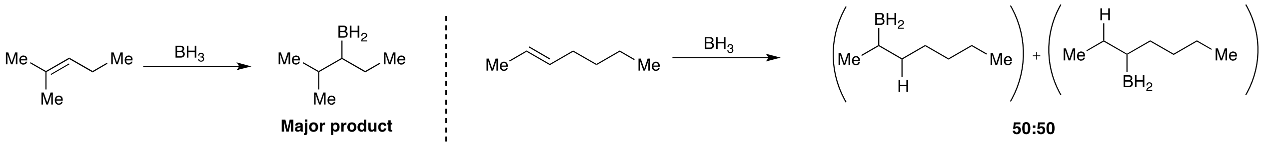
Recently the group of Grubbs reported a catalytic system, which predominantly yields aldehydes as products. Mechanistic studies suggest involvement of the NO_2 radical that upon addition to the double bond would offer a more stable radical intermediate thus overriding the inherent selectivity.



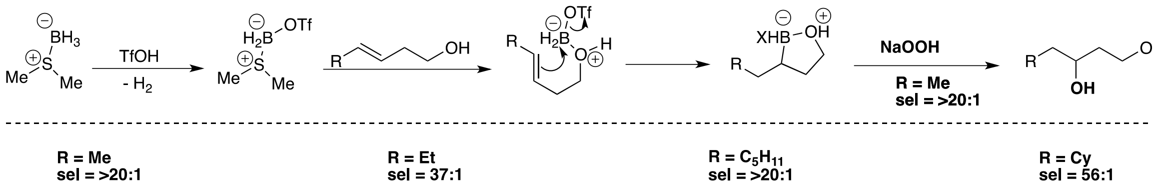
Grubbs *Angew. Chem. Int. Ed.* **2013**, *52*, 11257

2 Hydroboration

The regioselectivity in hydroboration reactions is also highly dependent on the substrate and is mainly affected by steric factors. However, linear internal olefins show no or insignificant regioselectivity for hydroboration with borane (BH_3) or even with larger derivatives (9-BBN).



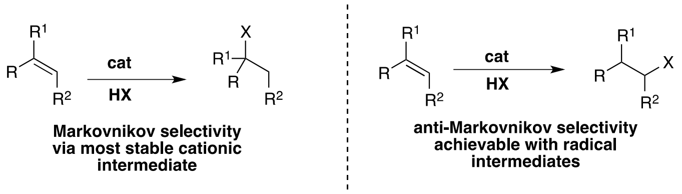
Vedejs and coworkers have introduced a system relying on alcohols or amines as directing groups. The method is based on creating a leaving group on the boron, which can be displaced by nucleophilic attack of the olefin.



Vedejs *J. Am. Chem. Soc.* **2008**, *130*, 9182
Vedejs *J. Am. Chem. Soc.* **2008**, *130*, 8669 (for amines)

3 Catalytic anti-Markovnikov additions

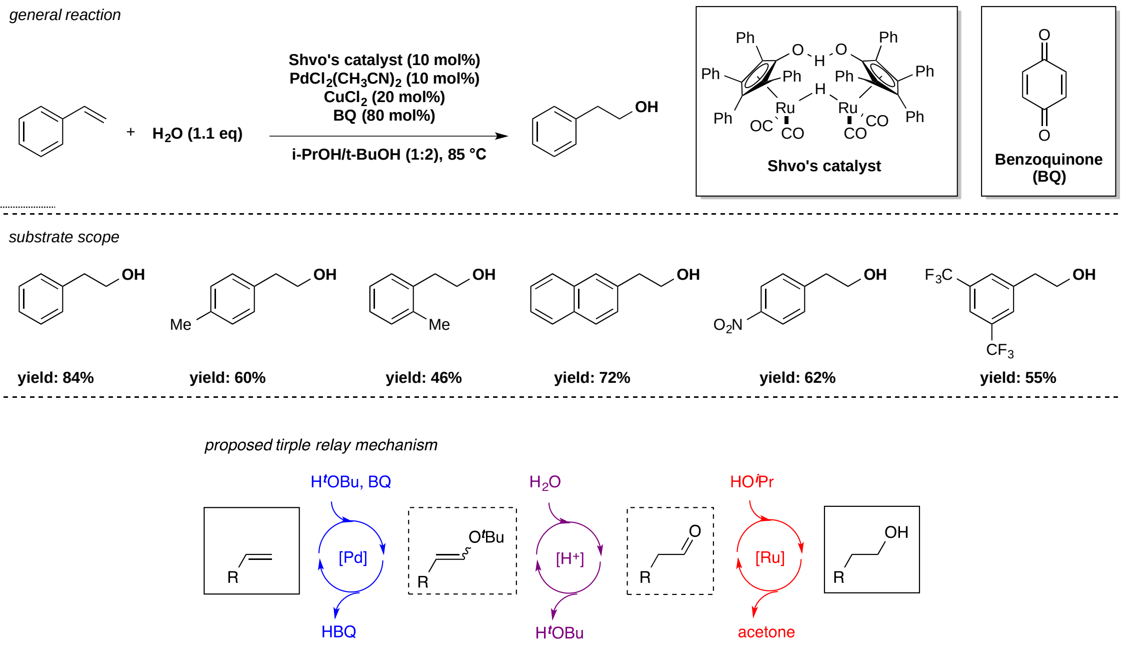
3.1 General principal of anti-Markovnikov addition



3.2 Anti-Markovnikov Hydration

- Grubbs has reported a formal, catalytic anti-Markovnikov hydration reaction for terminal styrenes
- The process involves 3 catalytic cascade reactions and is therefore named triple relay catalysis.
- The transformation relies on a Wacker-type oxidation of the styrene to the corresponding vinylether (Pd and Cu catalysis) followed by hydrolysis with water (formal oxygen source). Finally the catalytic transfer hydrogenation using the ruthenium based Shvo-catalyst affords the primary alcohol (see proposed mechanism)

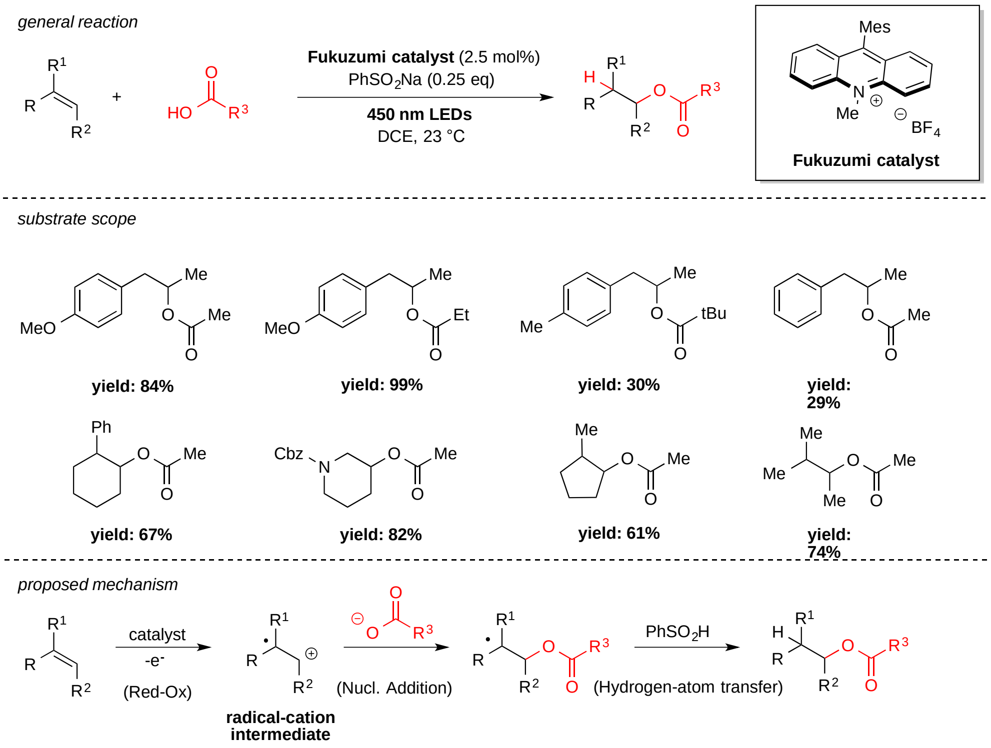
- Note: the same products can be prepared using a two-step hydroboration-oxidation strategy



Grubbs *Science* **2011**, *333*, 1609

3.3 Anti-Markovnikov hydroacetoxylation

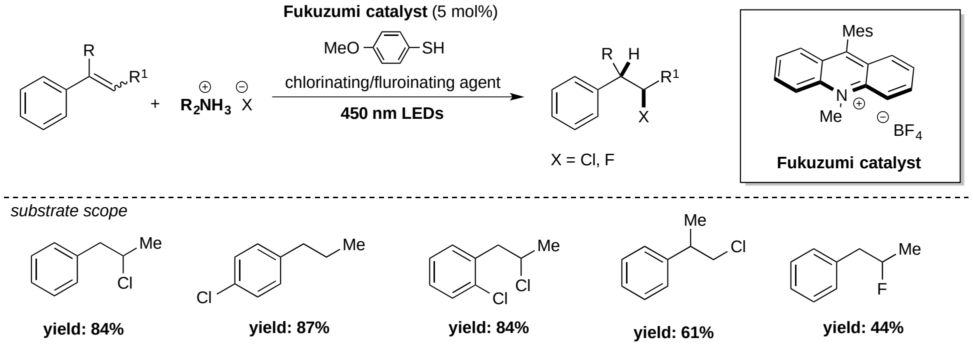
- A catalytic anti-Markovnikov hydroacetoxylation reaction using a photochemical approach was reported by Nicewicz (photoredox catalysis)
- Oxidation of the alkene by photo-excited Fukuzumi catalyst affords a radical-cation intermediate, which upon nucleophilic addition of the corresponding carboxylate (generated via the carboxylic acid/sodium benzosulphinate acid-base equilibrium) and subsequent proton transfer leads to carboxylic ester products.



Nicewicz *J. Am. Chem. Soc.* **2013**, *135*, 10334

3.4 Anti-Markovnikov hydrohalogenation

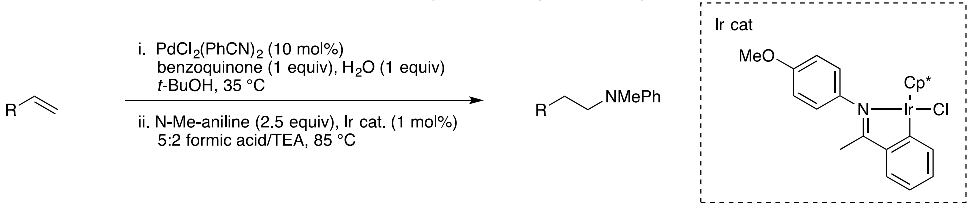
Recently, the same group reported anti-Markovnikov additions of various mineral acids to styrenes. Reaction conditions were optimized for the different mineral acids used in the reaction, however the methodology is quite general. The reaction mechanism is similar and proceeds via similar intermediates as in the hydroacetoxylation described in the previous chapter.

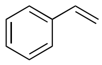
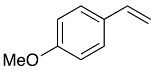
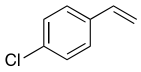
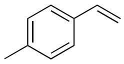
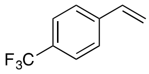
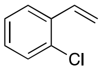
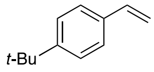
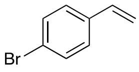
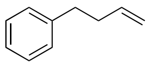


Nicewicz *Nature Chem.* **2014**, *6*, 720

3.5 Anti-Markovnikov hydroamination

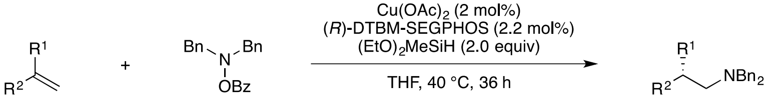
A catalytic anti-Markovnikov hydroamination has been still challenging. Although several approaches were developed, all of them have limitations such as harsh conditions, the requirement of a directing group, and limited substrate scopes. Recently, Grubbs reported the formal hydroamination transformation under the conditions, which are similar to anti-Markovnikov hydration (See, 3.2).

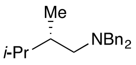
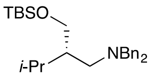
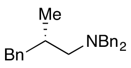
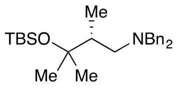
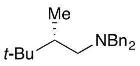
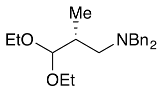


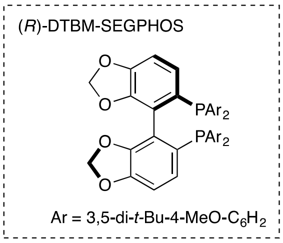
Substrate	Yield, %	Substrate	Yield, %	Substrate	Yield, %
	55		65		57
	61		50		43
	55		52		24

Grubbs *Chem. Sci.* **2014**, *5*, 101

Also, enantioselective anti-Markovnikov hydroamination has been reported by Buchwald.



Product	Yield, %	*ee*, %	Product	Yield, %	*ee*, %
	90	83		92	91
	88	60		99	92
	86	92		78	92

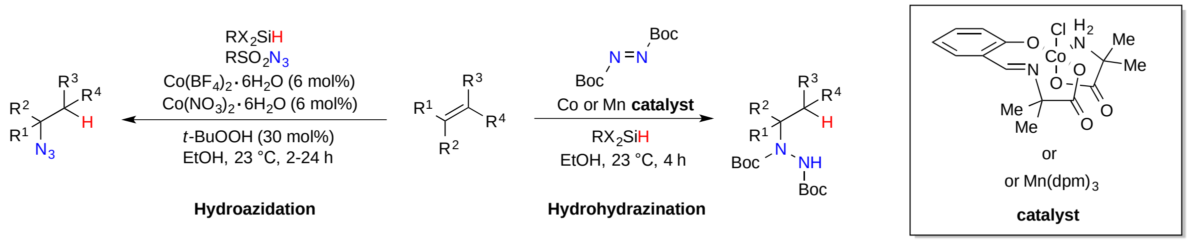


Buchwald *J. Am. Chem. Soc.* **2014**, *136*, 15913

4 Hydroazidation/Hydrohydrazination

The general method for azide preparation is the substitution of organic halides with sodium azide. This approach, however, requires the prior synthesis of the corresponding halides. Recently, Carreira and Jiang have developed new synthetic strategies towards direct azide formation from olefins avoiding the use of halides.

- Carreira and coworkers developed a metal-catalyzed synthesis for the direct hydroazidation and hydrohydrazination of olefins
- Most substrates are tolerated for both types of reactions (mono-, di-, tri-substituted olefins, heterocycles)
- High Markovnikov selectivities with nearly exclusive formation of the secondary hydrazine/azide product can be observed
- Phenyl groups show a strong activating and α-directing effect
- Mechanistic studies suggest hydrocobaltation (rate limiting step) of the alkene followed by the amination reaction



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