Asymmetric Synthesis

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Catalytic Enantioselective Functionalization of Unactivated Terminal Alkenes

*John R. Coombs and James P. Morken**

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Terminal alkenes are readily available functional groups which appear in α-olefins produced by the chemical industry, and they appear in the products of many contemporary synthetic reactions. While the organic transformations that apply to alkenes are amongst the most studied reactions in all of chemical synthesis, the number of reactions that apply to nonactivated terminal alkenes in a catalytic enantioselective fashion is small in number. This Minireview highlights the cases where stereocontrol in catalytic reactions of 1-alkenes is high enough to be useful for asymmetric synthesis.

1. Introduction

Catalytic asymmetric reactions of monosubstituted alkenes offer important opportunities for strategic chemical synthesis. These reactions can facilitate both hydrocarbon-chain extension and functional-group installation simultaneously, and in a stereoselective fashion. As substrates, terminal alkenes are amongst the most attractive of starting materials for chemical synthesis. They are readily available from large-scale industrial processes and they may be accessed on smaller scale by a number of efficient, catalytic, and highly selective processes. In addition to ready availability, the reactivity characteristics of alkenes render them ideal functional groups for strategic chemical synthesis. They are relatively nonpolar and hence inert to all but the strongest of bases. Moreover, their reluctance to engage with many common oxidants, reductants, and nucleophiles allows polar functionality (i.e. halides, alcohols, ketones, esters, etc.) to be manipulated in their presence. Coupled with this general inertness, however, is a crucial feature: under specialized reaction conditions, alkenes may be transformed, often with exquisite levels of chemoselectivity, into a range of functionalized products.

Considering the remarkable properties of terminal alkenes and the utility of their asymmetric transformations, it may seem surprising that so little progress has been charted in regards to their efficient catalytic asymmetric transformation. However, there are well-founded reasons that selective transformations, which apply to this functional group, have been slow to emerge. This Minireview surveys the challenges associated with stereocontrol in reactions of α-olefins and documents the techniques which are currently available to synthetic chemists for the asymmetric transformation of this substrate class in useful levels of selectivity (> ca. 80% *ee*). For reasons that will be delineated below, we restrict the discussion to transformations which apply to aliphatic alkenes and do not include the many reactions that apply only to electronically biased alkenes (i.e. styrenes, dienes, enynes, enones), or that require the presence of chelating groups, directing groups, or other auxiliary functionality.

Enantioselective transformations of unactivated alkenes are most often accomplished with transition-metal catalysts. For many of these reactions, quadrant diagrams can simplify stereochemical analysis and provide insight into the stereochemical outcome. In these diagrams, a chiral ligand attached to a reaction center provides a nonsymmetric environment where steric encumbrance (shaded quadrant) guides reaction of the substrate. In the example below, stereochemistry determining olefin insertion into an M−A bond is depicted as a prototypical elementary catalytic step which might control enantioselectivity (Scheme 1). As depicted, a significant obstacle to controlling the selectivity in some reactions of terminal alkenes can arise because in many olefin insertion reactions, bond formation occurs by 1,2-insertion of the alkene into the M−A bond. In this mode, in contrast to reactions of *cis*, *trans*, and trisubstituted alkenes, the steric bias provided by the ligand framework is remote from the prochiral carbon atom of the substrate and prospects for effective stereocontrol are diminished. In contrast, asymmetric reactions of functionalized terminal alkenes are often more successful, in part because the substrate functionality reverses the regioselectivity of insertion reactions thereby

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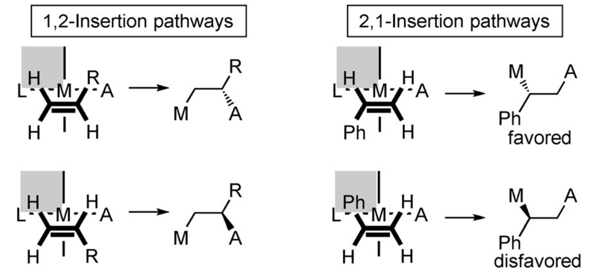
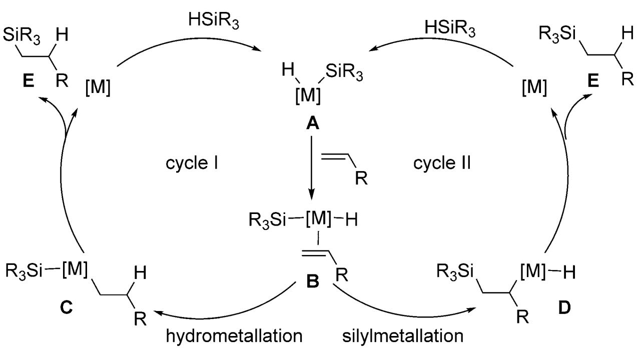
[*] J. R. Coombs, Prof. J. P. Morken
Department of Chemistry, Boston College, Merkert Research Labs
2609 Beacon St., Chesnut Hill, MA 02467 (USA)
E-mail: morken@bc.edu



Scheme 1. Quadrant diagrams describe pathways for migratory insertion of a prochiral substituted alkene into the M–A bond in a representative chiral transition-metal complex. The shaded quadrant indicates and area of steric encumbrance established by the ligand framework.



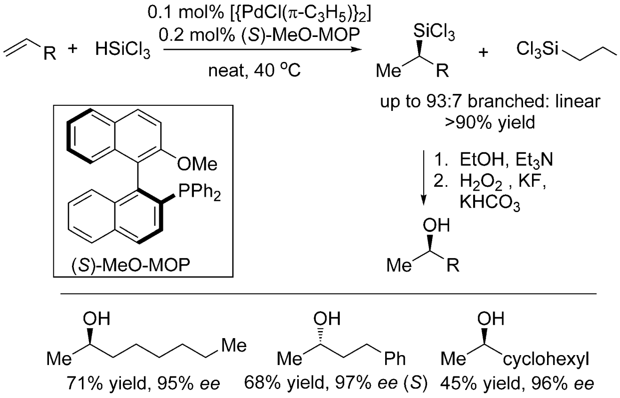
Scheme 2. Mechanisms for transition-metal-catalyzed hydrosilylation.

positioning the prochiral carbon atom of the alkene much closer to the chiral ligand (2,1-insertion). For example, π-benzyl and π-allyl stabilization of organometallics reverses the insertion regiochemistry of styrenes and dienes, and hence highly selective hydro- and difunctionalizations of these substrates are well developed. Similarly, chelation can reverse the regiochemistry of vinyl acetate and allyl alcohol insertions. The end result of these features is that the many excellent enantioselective reactions which apply to styrenes, dienes, and heteroatom-functionalized terminal alkenes, often give achiral linear products or are less selective with common aliphatic terminal olefins.

2. Hydrosilylation

The catalytic hydrosilylation of 1-alkenes is well-studied, and many transition metals have been utilized to date, including platinum, palladium, nickel, rhodium, and even a number of lanthanides.[1] In almost all cases, hydrosilylation of unactivated 1-alkenes proceeds with high anti-Markovnikov selectivity by a Chalk–Harrod-type mechanism (or closely related variants thereof) to provide achiral 1-silylalkanes (Scheme 2, cycle I).[2] In such a mechanism, oxidative addition with a hydrosilane furnishes the coordinatively unsaturated complex **A**, followed by coordination of an alkene substrate to generate the intermediate **B**. Subsequently, hydrometallation provides the alkyl–silyl complex **C** after a 1,2-insertion. Finally, reductive elimination delivers the 1-silylalkane **E** and regenerates the active catalyst. Alternatively, an alkene insertion into the M–Si bond (i.e. silylmetallation) has been suggested, most notably under Rh^{I} or Co^{III} catalyst systems (cycle II).[2b,3] In this variant, a 2,1-migratory insertion mode results in generation of the complex **D**, with subsequent reductive elimination to form the hydrosilylation product **E**.

In 1991, Hayashi and co-workers reported the first and only catalytic asymmetric hydrosilylation of aliphatic terminal alkenes (Scheme 3).[4] With only 0.2 mol% of a palladium salt in conjunction with the chiral monodentate phosphine (*S*)-MeO-MOP, various terminal alkenes underwent hydrosilylation with trichlorosilane. These reactions provide 2-silylalkanes in high yields and greater than 80:20 regioselectivity in most cases (hindered terminal alkenes resulted in



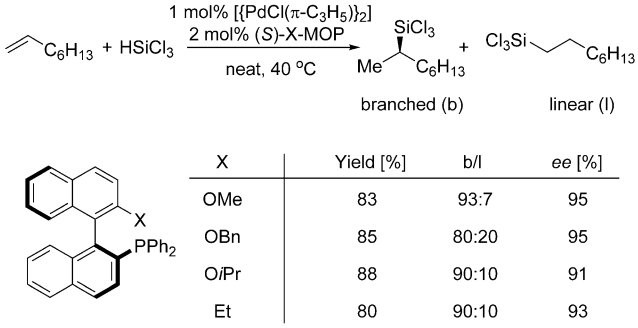
Scheme 3. Catalytic hydrosilylation of terminal alkenes developed by Uozumi and Hayashi.[4]

John Ryan Coombs earned his B.Sc. from Fordham University in 2010. Subsequently, he received his Ph.D. at Boston College as a LaMattina fellow under the guidance of Prof. James P. Morken, where he primarily studied the platinum-catalyzed asymmetric diboration of unsaturated hydrocarbons. He is currently a research investigator at Bristol-Myers Squibb in New Brunswick, New Jersey.

James P. Morken received his B.Sc. from the University of California at Santa Barbara, his Ph.D. from Boston College with Prof. Amir H. Hoveyda, and was a postdoctoral fellow with Prof. Stuart L. Schreiber at Harvard University. He began his independent career at UNC Chapel Hill in 1997 and moved to Boston College in 2006. He is currently the Louise and Jim Vanderslice and Family Professor of Chemistry. His research focuses on catalytic asymmetric organic synthesis.

lower regioisomeric ratios). The silylalkanes generated could be oxidized in situ under Tamao–Fleming oxidation[5] conditions (hydrogen peroxide in the presence of an anionic fluoride source) to generate 2-alkanols in greater than 94% *ee*.

While the authors do not speculate about the origin of the unusual regioselectivity, they suggest that the high reactivity arises because the monodentate ligand allows access to a 16-electron palladium(II) intermediate $[PdH(SiCl_3)L(CH_2{=}CHR)]$, bearing a coordination site for olefin binding and activation. Indeed, reactions conducted in the presence of chelating bis(phosphine) ligands such as BINAP did not provide hydrosilylation products even when conducted at elevated temperatures. Furthermore, the authors suggest that the MOP ligand accelerates reductive elimination relative to β-hydride elimination when compared to other monodentate ligands, such as triphenylphosphine or tri-*o*-tolylphosphine. This feature minimizes olefin isomerization during the course of the hydrosilylation. Lastly, it was found that the methoxy group at the 2′-position of the binaphthyl ligand framework is not imperative for high regioselectivity, since varying this group (Et-MOP, *i*PrO-MOP) provided similar levels of regio- and enantioselectivity (Scheme 4).[6] Consistent with these findings, a crystal structure of $[PdCl_2\{(R)\text{-MeO-MOP}\}_2]$ indicates that the substituent at the 2′-position does not interact with the palladium center (Figure 1).



X	Yield [%]	b/l	*ee* [%]
OMe	83	93:7	95
OBn	85	80:20	95
O*i*Pr	88	90:10	91
Et	80	90:10	93

Scheme 4. Comparison of substituted MOP ligands with varying substitution at the 2′-napthyl position.

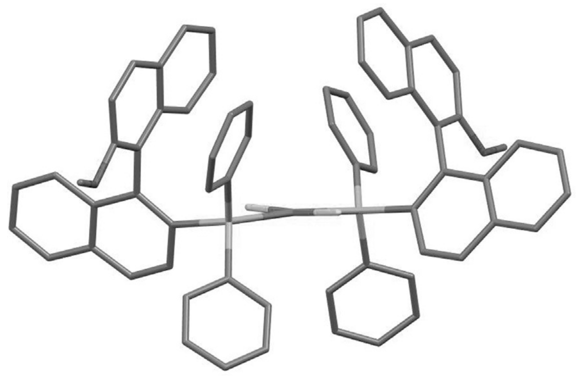
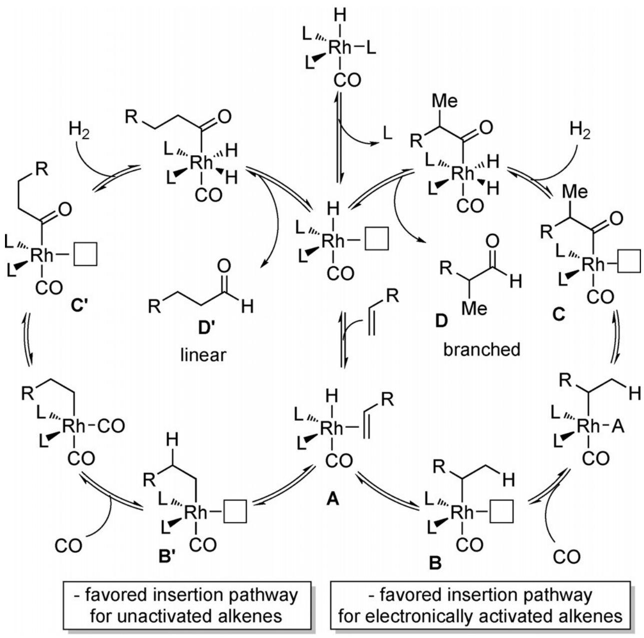


Figure 1. X-ray structure of $[PdCl_2\{(R)\text{-MeO-MOP}\}_2]$.

3. Hydroformylation

Given its superb atom economy, fast reaction rates, and high turnover numbers, transition-metal-catalyzed hydroformylation of alkenes has become one of the largest and most successful catalytic processes of commodity chemical manufacturing, thus producing millions of tons of achiral aldehydes annually.[7] Despite many decades of research to efficiently produce linear aldehydes from inexpensive petroleum feedstocks, methods of generating the chiral α-branched isomer with high regio- and enantioselectivity have not been well developed. Considering the abundance of biologically active compounds which may be derived from nonracemic chiral aldehydes, the ability to directly provide α-chiral aldehydes from terminal alkenes in an enantioselective manner would be an appealing transformation.

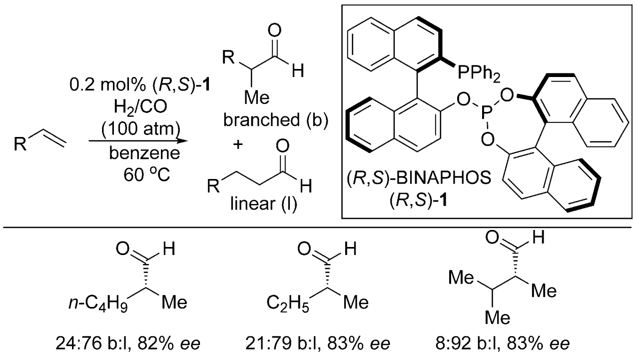
Highly successful asymmetric and branch-selective hydroformylations of electronically activated terminal olefins, or those containing chelating groups have been reported with a number of transition metals,[8] but most often with Rh^I.[9] As stated above, generation of the branched isomer from aliphatic terminal alkenes with similar catalyst systems has met with limited success, a result which can be explained by considering the mechanism for hydroformylation (Scheme 5).[10] During regioselectivity-determining olefin insertion, either the rhodium complex **B** or **B′** is generated from the precursor rhodium/alkene complex **A**. Coordination of CO and migratory insertion provides either the acyl complex **C** or **C′**. Finally, oxidative addition of H_2 followed by reductive elimination provides either the branched product **D** or linear product **D′** with concomitant regeneration of the rhodium catalyst. When **B** is stabilized by the substitution



Scheme 5. Catalytic cycle for rhodium-catalyzed olefin hydroformylation.

pattern on the alkene (for example, when R = Ph, a stable π-benzyl intermediate is formed), **D** is preferred and unfavorable steric interactions between the substrate and the metal center are overridden. However, with aliphatic alkenes, little to no stabilization effect exists and **B′** predominates. Thus, the linear product **D′** is favored so as to avoid steric interactions which are created in **B**.

Developed by Takaya, Nozaki, and co-workers in 1993, the phosphine-phosphite-derived BINAPHOS **1** was the first ligand used for a highly enantioselective hydroformylation of aliphatic terminal alkenes (Scheme 6).[11] Although synthetically useful levels of enantioselectivity were achieved for 1-hexene (82 % *ee*) and 1-butene (83 % *ee*), the undesired linear isomer predominated (1:3 branched/linear), a problem that was compounded by the fact that similar chemical and physical properties of the two isomers render purification difficult. Through extensive theoretical studies, it was later determined that facial selectivity of the olefin addition is mainly dictated by the absolute configuration of the phosphine group (occupying the equatorial site), while the phosphite unit (apical site) has a significant impact on the degree of enantioselectivity that is observed.[7b,12,13] The favored conformation of the intermediate [RhH(CO)$_2$-{(*R*,*S*)-BINAPHOS}], along with quadrant representations of the two possible hydroformylation paths are provided in Figure 2. Calculations suggest that path II (Figure 2) is highly favored over path I since the catalyst conformation in path I does not have an unimpeded quadrant. Reaction through path II is highly selective with the alkene substituent placed in the unhindered site. It is concluded that for high stereoselectivity, rhodium/diphosphane catalysts require 1) equatorial-apical specific coordination containing chirality at the apical position to enhance diastereoisomeric ligand–substrate interactions, 2) two stereogenic centers which discriminate against competing equatorial-apical pathways, and 3) a rigid catalyst which enhances stereoinduction on the substrate.[12]



Scheme 6. Rhodium-catalyzed hydroformylation of alkenes developed by Takaya and co-workers.[11]

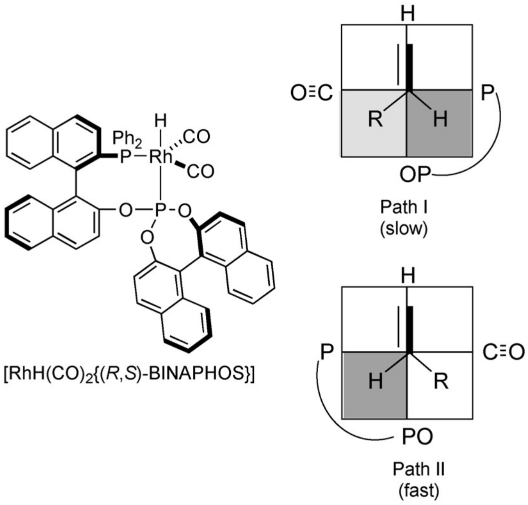
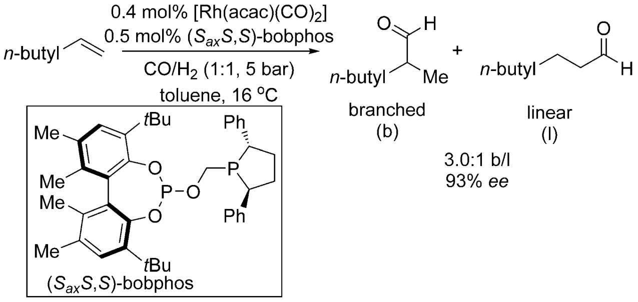


Figure 2. Favored catalyst conformation and quadrant diagrams showing preferred olefin binding modes.

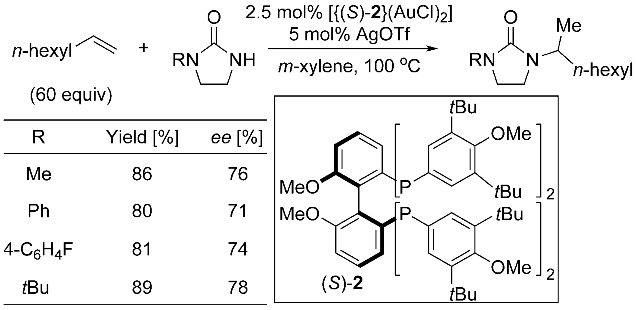
In 2012, Clarke and Cobley developed the first example of asymmetric hydroformylation in which electronically unbiased alkenes favored the branched isomer with high levels of enantioselectivity (Scheme 7).[14] For example, in the presence of bobphos and [Rh(acac)(CO)$_2$] as the precatalyst, 1-hexene underwent hydroformylation in 93 % *ee* and in a 3:1 branched/linear ratio. While low reaction temperatures resulted in low turnover numbers and incomplete conversion, even after long reaction times (21–66 h), the Clark system is a fundamentally important advance which is likely to lead to refined systems.



Scheme 7. Branched-selective rhodium-catalyzed hydroformylation of alkenes reported by Clarke, Cobley, and co-workers.[14] acac = acetylacetonate.

4. Hydroamination

Although asymmetric intramolecular hydroaminations of functionalized terminal alkenes have been well-studied, intermolecular variants that involve reaction of unactivated alkenes are lacking.[15] While iridium(I),[16] gold(I),[17] platinum(II),[18] and lanthanum[19] complexes are known to catalyze intermolecular Markovnikov hydroamination, the low reactivity of unactivated 1-alkenes necessitates use of high temperatures and often occurs with modest selectivity. Such limitations render asymmetric variants difficult to develop. Nonetheless, in 2009, Widenhoefer and co-workers reported an asymmetric gold(I)-catalyzed Markovnikov-selective intermolecular hydroamination of unactivated alkenes with imidazolidin-2-ones (Scheme 8).[20] The process em-



R	Yield [%]	ee [%]
Me	86	76
Ph	80	71
4-C_6H_4F	81	74
tBu	89	78

Note: Absolute configuration not determined.

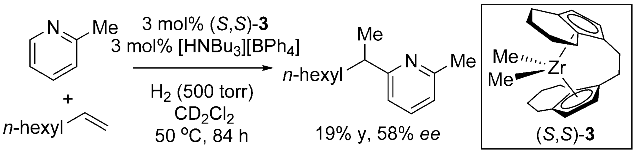
Scheme 8. Widenhoefer's gold(I)-catalyzed hydroamination of alkenes with cyclic ureas. Tf = trfluoromethanesulfonyl.

ployed a bis(gold) phosphine complex bearing the chiral bidentate ligand (*S*)-**2** in combination with a catalytic amount of AgOTf to provide good yields of the alkylated ureas in 71–78% *ee*. While superstoichiometric amounts of olefin were required for complete conversion, the inexpensive nature of many alkenes negates this problem. While the authors do not provide a mechanistic evaluation, enantioselective functionalizations of C=C π-bonds with chiral bis(gold)phosphine complexes have ample precedent.[21] Thus, the reaction may be expected to proceed by an outer-sphere nucleophilic attack of the external urea on gold-activated alkene, followed by internal proton transfer. Of note, critical control experiments were performed and excluded the possibility of silver- or acid-catalyzed pathways for olefin hydroamination.

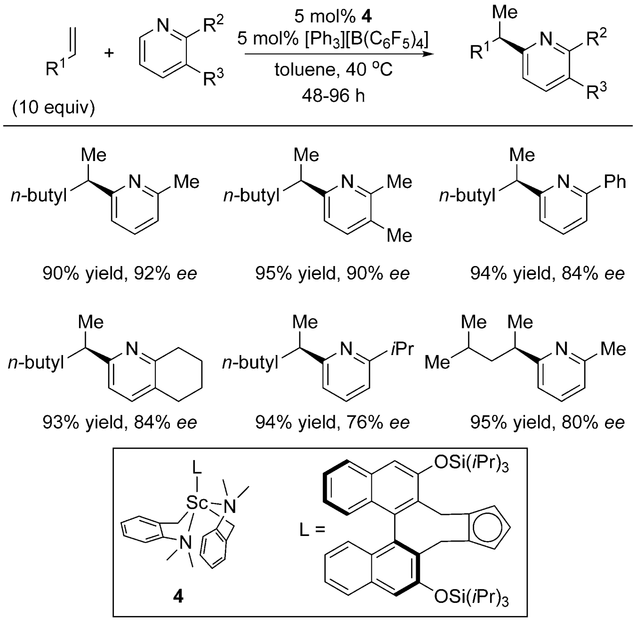
5. Addition of Pyridine C−H Bonds to Alkenes

The synthesis of chiral compounds containing pyridine moieties is of significant importance for synthetic chemists considering their prevalence in a wide array of natural products, pharmaceutically relevant and biologically active small molecules, and chiral ligands.[22] Asymmetric C−H additions of pyridines to alkenes remains underexplored despite a number of successful non-enantioselective variants.[23] In 1994, Rodewald and Jordan reported an enantioselective C−H alkylation of pyridines utilizing a chiral zirconocene-based catalyst (*S*,*S*)-**3** (Scheme 9).[24] However, low yields, resulting from poor catalyst turnover, and only moderate enantioselectivities were reported for unactivated monosubstituted alkenes.

Improving upon this work, Hou and co-workers recently reported a highly enantioselective C−H bond addition of pyridines to alkenes by employing the chiral half-sandwich dialkyl scandium precatalyst **4** (Scheme 10).[25] High yields and excellent branched selectivity were obtained in the enantioselective reaction between unactivated α-olefins and 2-substituted pyridines. The novel catalyst retains a monocyclopentadienyl ligand which bears a tethered chiral binaphthyl backbone. The chiral element serves to block one of the two possible olefin binding modes with the major complex, thus positioning the R group of the olefin away from the cyclopentadienyl ring, and results in facially selective 1,2-insertion of the scandium–pyridyl bond to the alkene (Figure 3). Unfortunately, reactions of unsubstituted pyridine and quinoline did not occur, most likely because of the enhanced coordination of unhindered pyridines to the metal center, which may poison the catalyst by inhibiting olefin coordination.



Scheme 9. Zirconium-catalyzed C−H addition of 2-picoline to 1-octene reported by Rodewald and Jordan.



Scheme 10. Work of Hou and co-workers on asymmetric C−H bond addition of pyridines to 1-alkenes.[25]

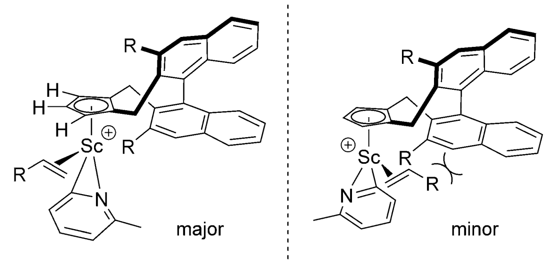
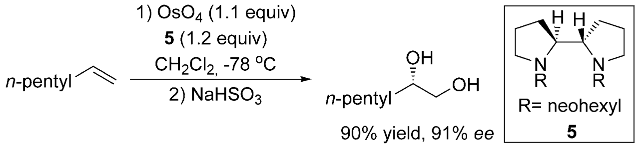


Figure 3. Proposed stereochemical model for olefin coordination in asymmetric C−H addition of pyridines to 1-alkenes.

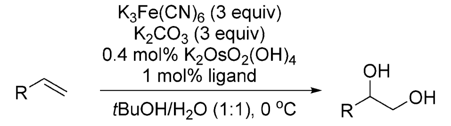
6. Dihydroxylation

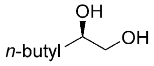
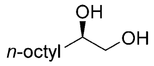
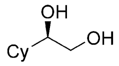
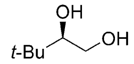
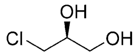
Developed in 1980, the Sharpless asymmetric dihydroxylation (SAD) is one of the most broadly used and well-studied olefin difunctionalizations in organic synthesis.[26] Early variants by Sharpless and co-workers necessitated stoichiometric amounts of both a chiral-quinuclidine-based ligand and expensive and toxic OsO_4. Furthermore, initial dihydroxylation conditions provided diminished enantioselectivities for unactivated terminal olefins. Building on early findings by Sharpless that chiral-quinuclidine- and chiral-amine-based ligands can both accelerate reaction rate and control facial selectivity during oxidation of the olefin,[27] Oishi and Hirama reported the first highly enantioselective dihydroxylation of unactivated terminal olefins by utilizing chiral *N*,*N'*-dineohexyl-2,2'-bypyrrolidine (**5**).[28] For example, 1-heptene could be dihydroxylated to generate the vicinal 1,2-diol in 90% yield and 91% *ee* (Scheme 11). However, the strongly binding bidentate nature of the ligand appeared to inhibit hydrolysis of the osmium(VI) glycolate product, thereby inhibiting ligand and osmium turnover. Thus, the Hirama example necessitates stoichiometric amounts of both OsO_4 and chiral ligand, in addition to an external oxidant.

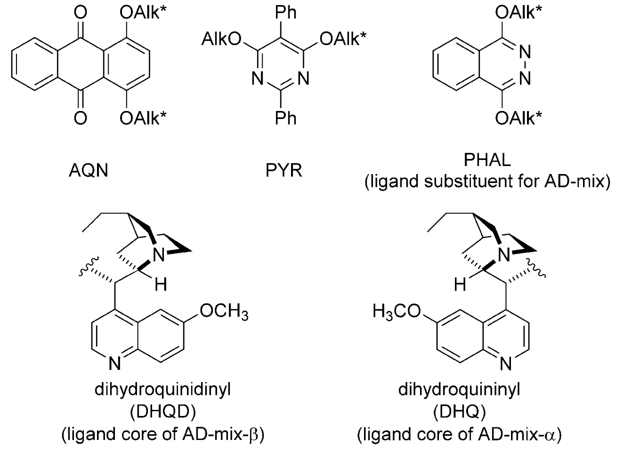


Scheme 11. Early examples of a highly enantioselective dihydroxylation of terminal alkenes reported by Oishi and Hirama.[28]

In 1988, Sharpless demonstrated catalytic enantioselective dihydroxylation of alkenes by employing *N*-methylmorpholine *N*-oxide as a co-oxidant.[29] In this process, lower enantioselectivities were observed compared to those of the stoichiometric variant because of a secondary competing and nonselective catalytic cycle.[30] This alternate mechanism could be avoided by performing the reaction with $K_3Fe(CN)_6$ as a stoichiometric reoxidant under biphasic conditions.[31] By 1996, with an effective and reliable catalytic system in hand, the group of Sharpless had tested over 500 different ligands, ultimately discovering that easily accessible dihydroquinidinyl- and dihydroquininyl-based ligands, $(DHQD)_2AQN$ and $(DHQ)_2AQN$, respectively, provided high enantioselectivities for a broad range of olefin substrates (Scheme 12). Importantly, terminal unactivated olefins were found to undergo dihydroxylation with moderate to good levels of enantioinduction.[32] A diphenylpyrimidine-based ligand, $[(DHQD)_2PYR]$, was also found to be highly selective with unactivated terminal alkenes, especially those with α-branching. Important to note, is that while AD-mix catalysts derived from phthalazine-based ligands $[(DHQD)_2PHAL$ or $(DHQ)_2PHAL]$ outperform most catalyst/ligand combinations for most alkene classes, AD-mix underperforms for unactivated terminal alkenes and the pyrazine catalysts are generally superior.



Entry	Diol	*ee* [%] [$(DHQD)_2AQN$]	[$(DHQD)_2PYR$]	AD-mix-β
1		87 (*R*)	87 (*R*)	80 (*R*)
2		92 (*R*)	89(*R*)	84 (*R*)
3		86 (*R*)	96 (*R*)	88 (*R*)
4		--	92 (*R*)	64 (*R*)
5		90 (*S*)	53 (*S*)	63 (*S*)

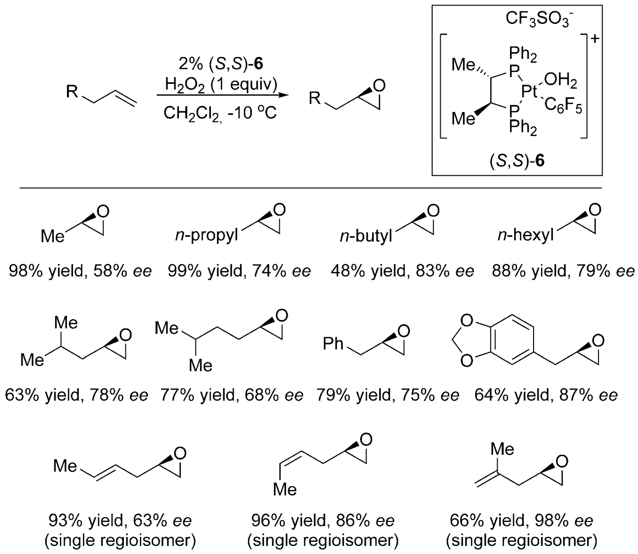


Scheme 12. Sharpless' asymmetric dihydroxylation applied to 1-alkenes.

7. Epoxidation

Although many highly stereoselective epoxidation methods have been developed, the majority of these require electronically-biased or functionalized substrates.[33] Selective epoxidation of unfunctionalized substrates are generally limited to alkenes which are di- and trisubstituted, with selective reactions of unfunctionalized terminal alkenes being quite scarce. In addition to the recurring challenge associated with poor facial selectivity with terminal olefins, the lower HOMO energy of monosubstitued alkenes relative to their more substituted counterparts often leads to diminished reactivity of 1-alkenes towards electrophilic oxidants. Without practical and scalable methodology in hand for this challenging substrate class, production processes for nonracemic terminal epoxides rely on nonselective olefin epoxidation followed by Co^{III}/salen-catalyzed hydrolytic kinetic resolution.[34] While this process is highly practical with inexpensive substrates, for more precious alkene starting materials resolution processes may be too costly.

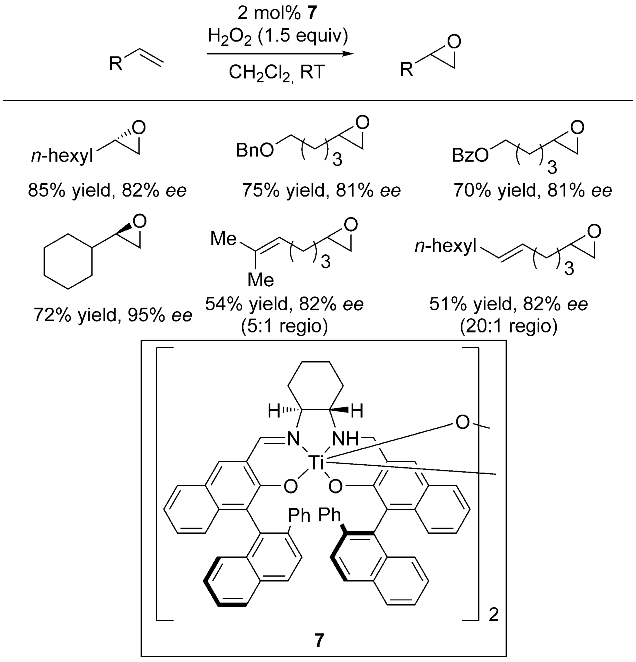
In 2006, Strukul and co-workers reported that use of 2 mol% of the platinum complex (*S*,*S*)-**6** along with environmentally benign hydrogen peroxide furnished enantiomerically enriched terminal epoxides in good yields and moderate levels of enantioselectivity (Scheme 13).[35] Reactions of 1,4-dienes resulted in complete regioselectivity for the terminal double bond with excellent enantioinduction, an important breakthrough considering most chiral metal-based catalysts favor epoxidation of the more electron-rich substituted double bond. Kinetic analysis[35b] shows the reaction rate is first-order in alkene concentration and independent of peroxide concentration. Further analysis of stoichiometric reactions of the platinum catalysts shows the process is complex and does not operate by either outer-sphere attack of peroxide on a platinum/alkene complex, or by oxo-transfer from a platinum-activated peroxide to the olefin. Instead, the authors propose hydrogen-bond-mediated association of H_2O_2 to the fluoroarene ligand, followed by reversible alkene association, and slow intramolecular oxo transfer. The molecular geometry involved in such a transformation is difficult to predict, but it was suggested that the C_6F_5 group may enhance steric interactions between the substrate and the rigid chiral ligand.[36]



Scheme 13. Platinum-catalyzed asymmetric epoxidation of alkenes developed by Strukul and co-workers.[35]

Prior to Strukul's report, Katsuki and co-workers realized some success with the di-μ-oxo titanium(salen) complex **7** and hydrogen peroxide as the oxidant.[37] While initial studies only surveyed a limited range of substrates, further examination found that a broad array of terminal olefins underwent asymmetric epoxidation with good to excellent enantioselectivity (Scheme 14).[38] Notably, α-branched terminal olefins, a substrate class which was not examined by Strukul, provided the highest levels of enantioenrichment. Lastly, use of competition experiments which employ 1,6-dienes showed that the terminal alkene is more reactive and generated the terminal epoxide in moderate to high regioselectivity.

Inspired by the Katsuki studies on epoxidation, Berkessel et al. recently examined simplified ligands which might also offer effective catalysts for titanium-catalyzed alkene epoxidation with H_2O_2.[39] In an important advance, it was found that nonsymmetric ligands derived from *meso*-1,2-diaminocyclohexane, in particular **8** (Scheme 15), offered outstanding reactivity and selectivity in the reaction. Interestingly, the ligand **9**, a hybrid of **8** and **7**, allowed the reaction to be conducted with very low catalyst loadings (0.1 mol%) while still maintaining outstanding selectivity. X-ray crystallographic analysis of complexes derived from the ligand frameworks **8** and **9**, suggests that the configuration of the amine-bearing carbon atom causes the complexes to provide chiral-at-metal titanium complexes with Δ-chirality, but the precise details of the mechanism for oxygen-atom transfer remain to be determined.



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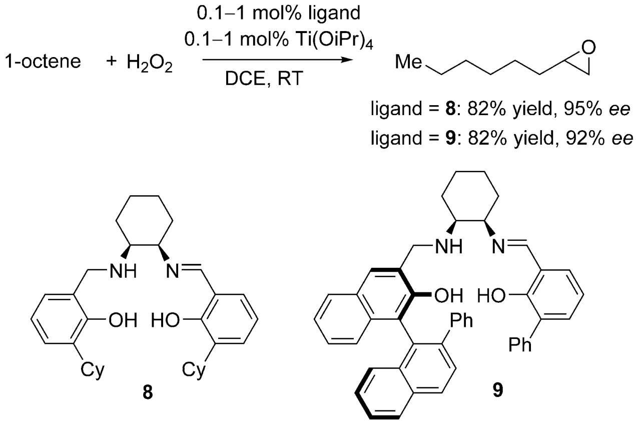
Scheme 14. Katsuki's [Ti(salen)]-catalyzed asymmetric epoxidation of terminal alkenes. DCE = 1,2-dichloroethane.

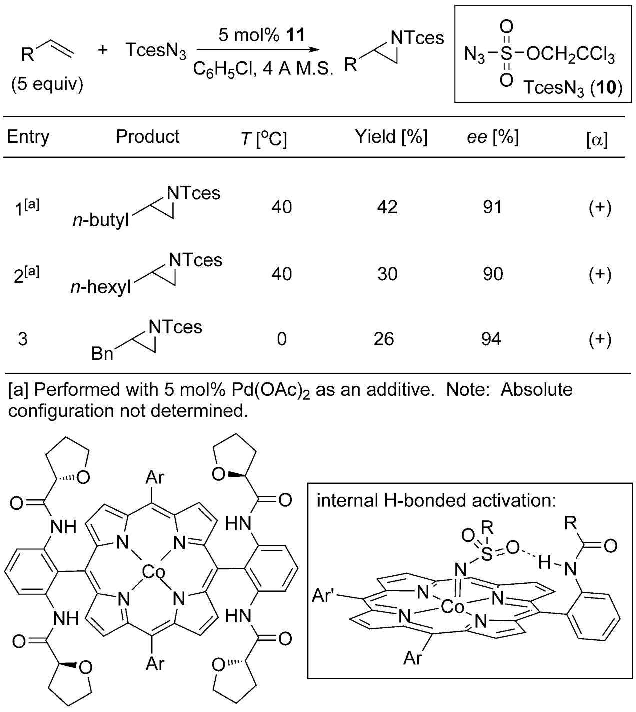


Scheme 15. [Ti(salen)]-catalyzed asymmetric epoxidation of terminal alkenes reported by Berkessel et al.[39]

8. Aziridination

The asymmetric aziridination of unactivated olefins is particularly difficult not only because of low reactivity of the substrate, but also because of the difficulty of finding highly reactive nitrene sources which are both accessible and easily deprotected.[40] Iminoiodane derivates such as PhI=NTs have proven useful for copper-catalyzed asymmetric aziridinations of electronically activated olefins or those bearing proximal polar functionality.[41] However, low reactivity with unfunctionalized terminal olefins suggests that a secondary binding interaction might be necessary to enhance reaction rates by induced intramolecularity.[42] Atom-economic azide derivatives were found by many to provide an alternate efficient route to metal nitrene intermediates.[43] Still, harsh reaction conditions are often needed for both azide decomposition and N-deprotection, thus hindering development of asymmetric variants.[44]

In 2009, Zhang et al. developed the cobalt(II)/porphyrin-based catalyst **11** which performed asymmetric aziridination of unactivated terminal alkenes under mild reaction temperatures (Scheme 16).[45] Two keys to the success of this system are notable: first, was use of trichloroethoxysulfonyl azide (TcesN$_3$) as a highly reactive and easily accessible nitrene source; second was the use of **11** where an internal hydrogen bond with the S=O (see inset, Scheme 16) provides organization and enhances both selectivity and reactivity. The report from Zhang et al. represents the first highly asymmetric aziridination of terminal alkenes.



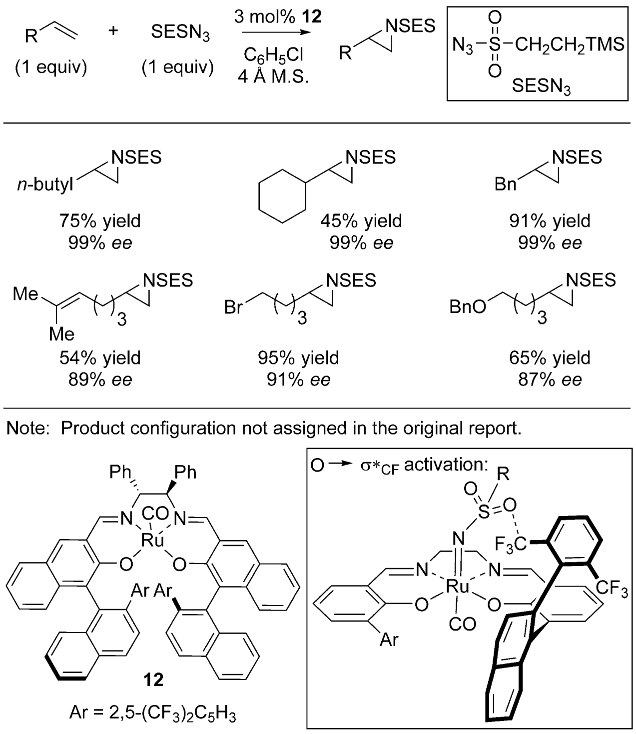
Entry	Product	T [°C]	Yield [%]	*ee* [%]	[α]
1[a]	NTces *n*-butyl	40	42	91	(+)
2[a]	NTces *n*-hexyl	40	30	90	(+)
3	NTces Bn	0	26	94	(+)

[a] Performed with 5 mol% Pd(OAc)$_2$ as an additive. Note: Absolute configuration not determined.

11: Ar = 3,5-di-*tert*-butylphenyl

Scheme 16. Asymmetric aziridination of 1-alkenes with TcesN$_3$ as reported by Zhang and co-workers. Ms = methanesulfonyl, M.S. = molecular sieves.

Building on the precedent from Zhang et al., the group of Katsuki reported a mild [Ru(CO)(salen)]-catalyzed asymmetric aziridination of unactivated terminal olefins utilizing 2-(trimethylsilyl)ethanesulfonyl azide (SESN$_3$) as a nitrene source (Scheme 17).[46] Employing 3 mol% of the complex **12** and equimolar amounts of azide and alkene provided high yields and excellent enantioselectivities for a variety of terminal alkenes. Importantly, the report by Katsuki provided an expanded substrate scope which included nonconjugated dienes, bromide- and ether-containing alkenes, as well as α-branched olefins. Of note, the aziridine protecting group was easily removed through use of tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF). Similar to the system reported by Zhang et al. (Scheme 16), it is proposed that **12** provides internal activation of the nitrene, and in this case is by overlap between the sulfonyl oxygen atom and a low-lying σ* C–F orbital (see inset, Scheme 17). Thus, in both the Zhang and Katuski systems, the catalysts likely benefit from organization which limits the number of competing transition states, thereby offering excellent selectivity.



Note: Product configuration not assigned in the original report.

12

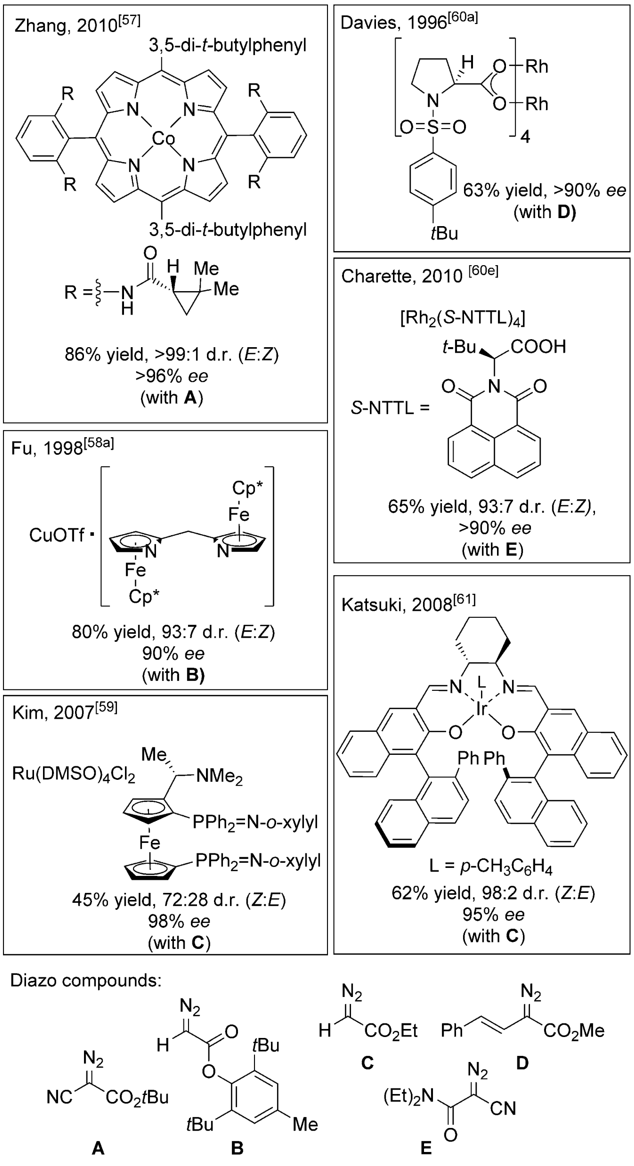
Ar = 2,5-(CF$_3$)$_2$C$_5$H$_3$

Scheme 17. Katsuki's [Ru(salalen)]-catalyzed aziridination of terminal alkenes.

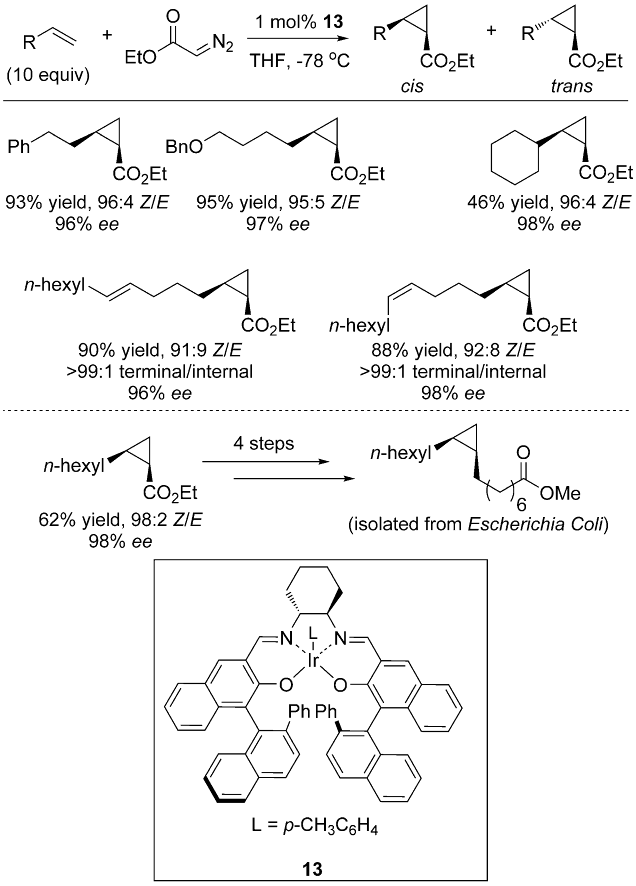
9. Cyclopropanation

The catalytic asymmetric cyclopropanation of alkenes represents one of the most general methods of accessing chiral cyclopropane units, a motif which is present in a number of natural or synthetic pharmaceutically relevant compounds.[47] Since the seminal report by Nozaki, Noyori, and co-workers[48] many reliable asymmetric transition-metal-catalyzed processes have been developed for cyclopropane synthesis.[49] Impressively, unactivated terminal alkenes have been found to undergo selective transition-metal-catalyzed cyclopropanation with many stabilized diazo compounds. Effective catalysts have been developed and are based on Co$^{\text{II}}$,[50] Cu$^{\text{I}}$,[51] Ru$^{\text{II}}$,[52] Rh$^{\text{II}}$,[53] and Ir$^{\text{III}}$[54] complexes (major contributions are summarized in Scheme 18). The body of work in this field is large compared to that of other asymmetric transformations of terminal alkenes, and thus only a few key examples will be discussed in detail.

While many methods are available for the generation of thermodynamically stable *trans*-disubstituted[51] and trisubstituted cyclopropanes,[50,53] synthesis of *cis*-disubstituted cyclopropane derivatives in high diastereo- and enantioselectivity is still challenging. In 2008, Katsuki and co-workers reported an asymmetric iridium-catalyzed *cis*-selective cyclopropanation of nonconjugated olefins (Scheme 19).[54] Employing 1 mol% of the aryliridium/salen complex **13** in the presence of ethyl α-diazoacetate and a large excess of olefin furnished *cis*-disubstituted cyclopropanes in high yields and excellent enantioselectivities. Of note, subsequent manipulation of the pendant ester moiety provides a straightforward method for chain extension or functional-group installation.



Scheme 18. Selected examples of asymmetric transition-metal-catalyzed cyclopropanation of 1-hexene.



Scheme 19. Katsuki's iridium-catalyzed asymmetric cyclopropanation of alkenes. THF = tetrahydrofuran.

Although the authors state that a detailed mechanism of the stereochemical control is unclear, they do provide a stereochemical model based on crystal structures of the catalyst, and with the help of density functional theory calculations. It is suggested that the diazo precursor replaces a weakly bound methanol at the apical position to provide the corresponding iridium–carbenoid intermediate displayed in Figure 4. With the C$_{\text{carbene}}$–C$_{\text{ester}}$ bond bisecting two Ir–N vectors, an incoming olefin is favored to attack the carbenoid carbon atom from the least hindered side over one of the naphthalene rings by a perpendicular, side-on approach. Subsequently, a counterclockwise rotation of the olefin positions the substituent away from the ester moiety of the carbenoid, thus leading to formation of the major isomer. Note that a clockwise rotation is unfavored because of the development of steric repulsion between the olefin substituent and the basal salen ligand.

In 2010, the Zhang group reported on a highly versatile chiral cobalt(II) porphyrin complex (**14**) which was found to catalyze the asymmetric cyclopropanation of a variety of

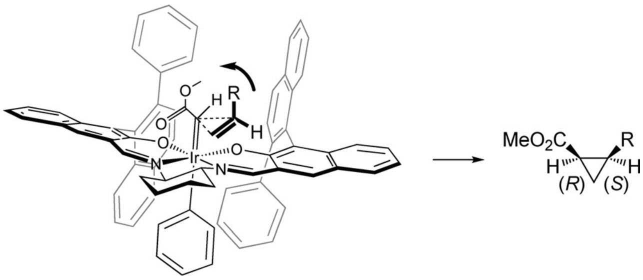
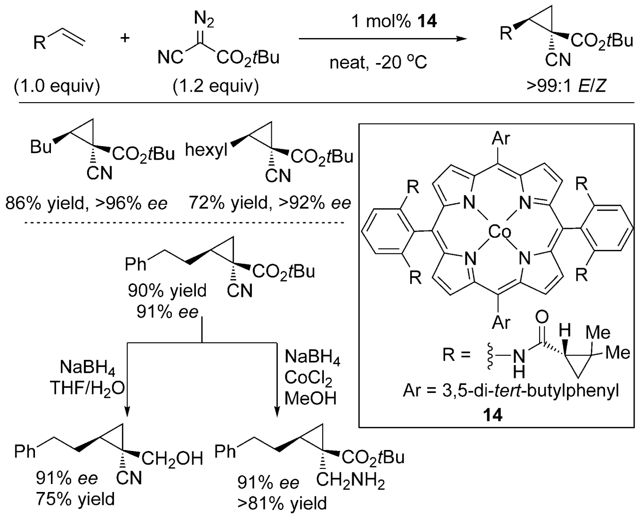


Figure 4. Stereochemical model for the iridium/salen catalyzed cyclopropanation of terminal alkenes.

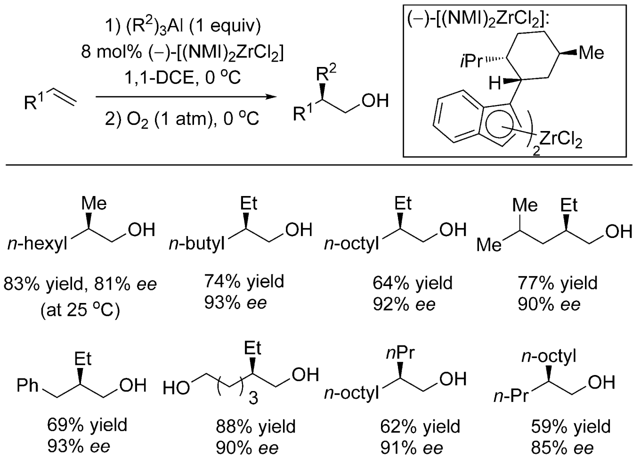
activated and unactivated alkenes with *tert*-butyl α-cyanodiazoacetate as the carbene source (Scheme 20).[50] High enantioinduction and *E* selectivity was achieved for all substrates.[55] Unlike most metal-catalyzed carbene-transfer methods, the reaction proceeded efficiently with olefin as the limiting reagent. Furthermore, the reaction is performed under solvent-free conditions and does not require slow addition of the diazoacetate.[56] Through appropriate reagent choice, either the ester group or the cyano group could be reduced chemoselectively with complete preservation of stereochemistry.



Scheme 20. Cobalt-catalyzed asymmetric terminal alkene cyclopropanation followed by chemoselective reduction as reported by Zhang and co-worekers.[50]

10. Carboalumination

In 1995, Negishi and co-workers described a zirconium-catalyzed asymmetric carboalumination (ZACA) of monosubstituted alkenes, thus adding to the list of stereoselective C−C bond-forming reactions available for this challenging substrate class.[57] Subsequent to treatment of the olefin starting material with 8 mol% of (−)-[(NMI)$_2$ZrCl$_2$] and equimolar amounts of trimethylaluminum, the carboaluminated products could be oxidized in situ to provide β-methyl primary alcohols in good yield and moderate enantioselectivity. Initially, extending the methodology to include other trialkylaluminum reagents resulted in low enantioselectivity. However, upon further evaluation, a dramatic solvent effect was observed and high enantioinduction was eventually obtained when using 1,1-dichloroethane in place of 1,2-dichloroethane for other trialkylaluminum reagents (Scheme 21).[58] While the authors do not offer a mechanistic rationale for this useful result, they have noted that use of more polar solvents suppresses carbometallation pathways involving metallacycles, which are observed with reactions performed in hexanes. Through the principle of statistical enantiomeric amplification,[59] asymmetric carboalumination has been utilized for the syntheses of highly enantioenriched deoxypolypropionates by a one-pot tandem ZACA/palladium-catalyzed vinylation process.[60]



Scheme 21. Zirconium-catalyzed carboalumination (ZACA) of terminal alkenes reported by Kondakov and Negishi.[58]

Negishi and co-workers have proposed a stereochemical model for the asymmetric methylalumination of alkenes (Figure 5).[61] It has been suggested that a stereoselective methylzirconation is operative, in which the C_2-symmetric cationic zirconium intermediate **15** interacts with the *re*-face of the olefin. Alternatively, an associated complex, in which the zirconium intermediate **16** is the active complex, is also plausible. In both scenarios, the alkyl substituent of the alkene occupies the least hindered quadrant of the metal, with the neomenthyl unit controlling the orientation of the alkene.

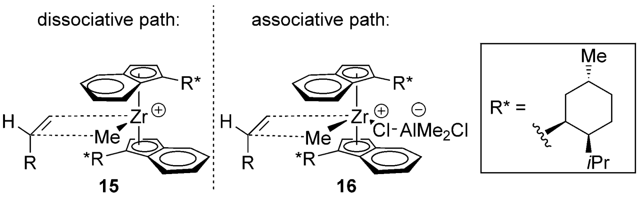
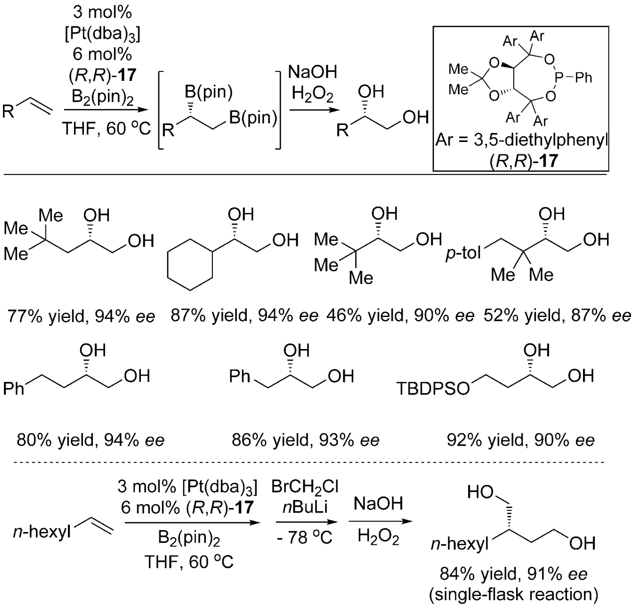


Figure 5. Proposed stereochemical model for the zirconium-catalyzed methylalumination of 1-alkenes.

11. Diboration

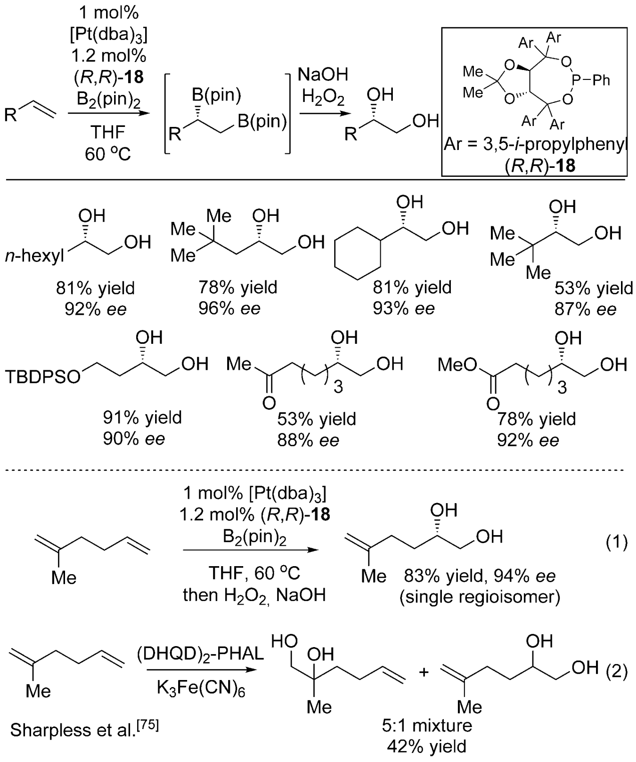
Organoboronates are useful reagents in organic synthesis because of their high chemical stability and accessibility. Also of note, a wide array of stereospecific transformations can be performed on organoboronates, thus making them versatile intermediates for transformation into other useful products. Thus, the asymmetric construction of adjacent borylated centers by diboration of an alkene represents a versatile strategy for alkene difunctionalization, thereby connecting simple alkene starting materials to a broad array of chiral building blocks.

In 2009, our lab reported the first highly enantioselective diboration of simple terminal alkenes.[62] Utilizing 3 mol% [Pt(dba)$_3$] and 6 mol% of the TADDOL-derived phosphonite (*R*,*R*)-**17** with bis(pinacolato)diboron (B$_2$pin$_2$), terminal 1,2-diols could be obtained in high yields and excellent enantioselectivity (Scheme 22) after an oxidative work-up. Furthermore, it was found that a single-flask diboration/homologation/oxidation sequence could generate 1,4-diols without loss of stereoselection. Later, additional optimization of catalyst structure, ligand/catalyst ratio, catalyst loading, and an expansion of the substrate scope was performed (Scheme 23).[63] With the commercially available TADDOL-derived phosphonite (*R*,*R*)-**18**, catalyst loading could be reduced to 0.5 mol% platinum, or even as low as 0.2 mol% platinum without diminishing enantiomeric ratios. Of note, di- or trisubstituted alkenes remained completely unreactive under the reaction conditions, and thus diboration provides a regiocomplementary strategy for vicinal diol construction relative to Sharpless asymmetric dihydroxylation [Scheme 23, Eqs. (1) and (2)].[64]

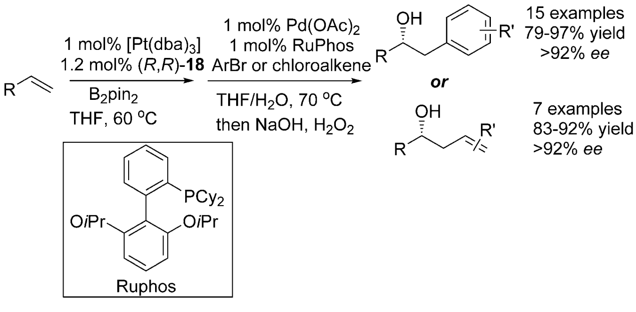


Scheme 22. Platinum-catalyzed enantioselective diboration of terminal alkenes reported in 2009. dba = dibenzylidene acetone, pin = pinacol.

Subsequent to optimization of diboration conditions, a one-pot diboration/cross-coupling (DCC) cascade sequence was developed by our group (Scheme 24).[65] In this strategy, subsequent to diboration, addition of 1 mol% Pd(OAc)$_2$ and 1 mol% RuPhos allowed efficient regioselective cross-coupling of the terminal boronate with both aryl and vinyl electrophiles. Notably, the internal boronate of the diboration product was not reactive in cross-coupling, thus the DCC sequence provides a method of differentiating the two boronates in complexity-generating reaction sequences.



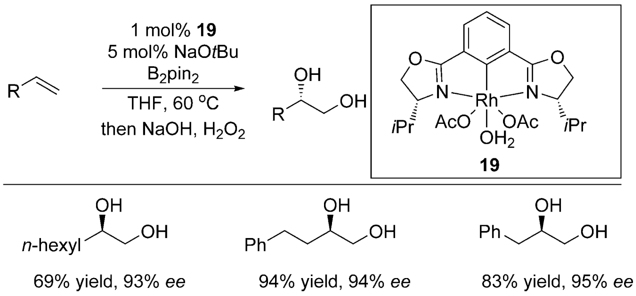
Scheme 23. Optimized platinum-catalyzed asymmetric alkene diboration. TBDPS = *tert*-butyldiphenylsilyl.



Scheme 24. Single-flask asymmetric diboration/cross-coupling (DCC) applied to terminal alkenes.

Extensive experimental and computational studies have been performed on the platinum-catalyzed asymmetric diboration reaction. Through kinetic analysis and natural abundance ^{12}C/^{13}C kinetic isotope effect experiments, it was found that addition of a Pt–B bond across the alkene is irreversible, turnover-limiting, and therefore the stereochemistry-controlling step of the catalytic cycle. Additional study of the insertion reaction with probe substrates suggested that a 2,1-insertion mode was operative, in which an internal C−Pt bond is furnished rather than a terminal C−Pt bond. Thus, it is proposed that the insertion mode positions the prochiral carbon atom of the olefin in close proximity to the chiral ligand, thus enhancing stereoinduction. To some extent, this uncommon insertion mode also explains why similar selectivities are observed for aliphatic olefins and for styrenic olefins which benefit from π-benzyl stabilization.

Lastly, an impressive advance was recorded by Toribatake and Nishiyama who described a [Rh(Phebox)] catalyst capable of diborating a variety of activated and unactivated terminal alkenes in good yields and high enantiomeric excess (Scheme 25).[66] Use of 1 mol% **19** and 5 mol% NaO*t*Bu efficiently catalyzed the addition of B_2pin_2 across an olefin, thus providing enantiomercially enriched vicinal 1,2-diols upon oxidation with $NaBO_3$. Given the fact that the reaction is base-promoted, the authors conclude that either σ-bond metathesis or transmetallation is involved in forming a Rh^{III}−boryl species from a Rh^{III}−O*t*Bu intermediate, followed by Rh−B bond alkene insertion.



Scheme 25. The [Rh(Phebox)]-catalyzed diboration/oxidation of terminal alkenes reported by Toribatake and Nishiyama.[66]

12. Summary and Outlook

Simple α-olefins are abundant and accessible from both large-scale industrial and smaller-scale synthetic processes, thus making them ideal substrates for asymmetric catalysis. Despite recent advances in catalytic olefin functionalization, highly enantioselective transformations of terminal aliphatic olefins are still uncommon. Additional progress in catalyst design and reaction engineering which allows both high facial selectivity and control of regioselection is critical to developing practical catalytic enantioselective processes. Nonetheless, recent approaches have led to the development of unique and highly versatile catalysts which promote selective reactions for both activated and unactivated olefins alike, thus bringing new hope for the discovery of more strategic and concise methods for chemical synthesis.

Note added in proof: The peer-reviewed version of this manuscript included a section on asymmetric chlorohydroxylation and dibromination of 1-alkenes reported by Henry et al.[67] However, during typesetting of this Minireview, a report by Denmark et al. appeared that determined that the Henry results are incorrect with all reactions affording racemic products.[68] Accordingly, this section was removed.

Acknowledgements

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