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Copper catalyzed allylic oxidation with peresters

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1. Introduction

Asymmetric transformations using catalytic metal complexes to produce functionalized intermediates continue to be indispensable in many areas.[1] The synthesis of natural products, pharmaceuticals, pesticides, herbicides, various materials applications, etc. are all benefited and indeed many of the key findings and advances in these fields are based on asymmetric catalysis. On a more fundamental level, metal complexes provide insights into non-covalent interactions, metal–ligand, solvent, and reagent energetics, reactivity, kinetic discrimination between closely related transition states, coordination geometry, and metalloprotein structure and function. Most notable are asymmetric dihydroxylation, epoxidation, and hydrogenation reactions, which have proven to be particularly successful with both theoretical and practical applications.[2] In contrast to epoxidation and dihydroxylation, allylic oxidation with copper catalysis and stoichiometric perester oxidant, often referred to as the Kharasch–Sosnovsky reaction, generates product with the olefin left intact (Fig. 1).[3] In this way, with the various transformations available for olefins, allylic oxidation has high potential for synthetic applications that complement epoxidation and dihydroxylation.

In 1958, Kharasch reported the allylic oxidation reaction

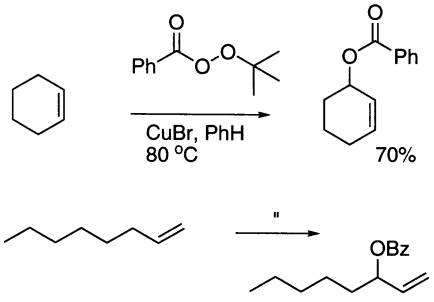

Figure 1. Allylic oxidation with *tert*-butyl perbenzoate and catalytic cuprous bromide in refluxing benzene.

Keywords: perester; allylic oxidation; metal complexes.
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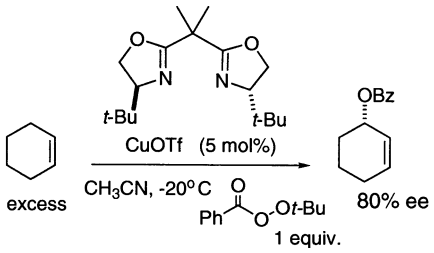


Figure 2. Asymmetric allylic oxidation using copper–bis-oxazoline catalysis.

using *t*-butyl perbenzoate and catalytic copper(I) in refluxing benzene.[4] Yields of allyl ester products are high with good regioselectivity giving the internal secondary ester over the terminal primary ester with 9:1 regioselectivity (Fig. 1). Early attempts by Denney and Muzart to develop asymmetric versions employed copper camphorate complexes and copper salts with added amino acids.[5] The selectivities were low, at best ~30% ee, determined using optical rotation. Independently, Pfaltz and co-workers[6] and our group discovered that copper(I)–bis-oxazoline complexes in acetonitrile at lower temperatures greatly increased the selectivity of the reaction up to 80% ee for cyclic olefins (Fig. 2).[7]

While the selectivities were greatly improved, the reaction rate and yields were only moderate or low. Most recently new perester oxidants, additives, and new ligands have improved the rates, yields, and selectivity of the reaction. An extensive review was published by Sosnovsky in 1972 detailing the substrates and reagents used to that point together with related processes using peroxide oxidants.[3] No reviews of the topic have appeared since then and none have been devoted solely to the topic.[8] Our purpose is to present the current findings concerning the development of a practical approach to the asymmetric version of the reaction. Earlier substrates and mechanistic work related will also be reviewed along with recent synthetic applications. The key allylic radical intermediate along with the nature of the copper(III) intermediate, the key step responsible for the stereoinduction, will be discussed. Particular attention will be paid to asymmetric control, both substrate control and the most current topic of enantiocontrol. Perester variants, additives, and solvents are also emphasized. As with other asymmetric metal-complex catalyzed reactions, selectivity for each specific substrate has been found to be highly dependent on the copper ligand. A single ligand that produces allyl esters in high selectivity

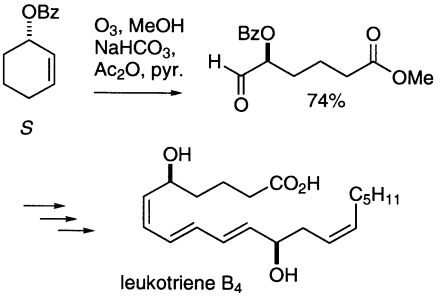


Figure 3. Utility of allylic oxidation shown by producing the key intermediate for leukotriene B_4 synthesis.

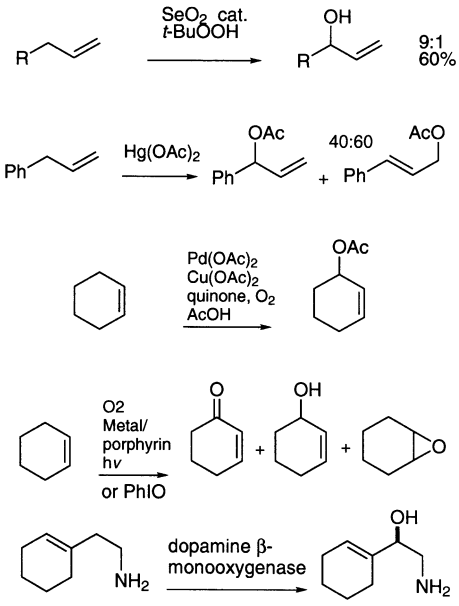


Figure 4. Other approaches to allylic oxidation.

with a wide range of substrates will most likely never be found. The metal–ligand combination will continue to be fine-tuned for each substrate for both reactivity and selectivity.

Potential applications of cycloalkenols derived from allylic oxidation are great. A particularly clear example is the conversion of (*S*)-cyclohexenyl benzoate to the key aldehyde–methyl ester intermediate for the synthesis of the inflammation mediator leukotriene B_4 (Fig. 3).

Using the selective ozonolysis conditions of Schreiber, Wallace accessed in a single step in high yield the key intermediate where other routes have required multiple steps from sugar based precursors.[9] Twelve routes to leukotriene B_4 have been published that use this intermediate. The most efficient route to this intermediate used six steps from 2-deoxy-D-ribose and the least efficient required 11 steps from D-xylose.[9] Now using asymmetric allylic oxidation, this intermediate can be accessed in *only two steps* from cyclohexene. Other potential applications are seen in recent applications of racemic copper catalyzed allylic oxidation to chrysanthemic acid,[10] brevetoxin,[11] and amyrin.[12] Numerous other uses of chiral 2-cycloalkenols also serve to point out the utility and potential of this reaction.[13]

2. Other methods

The Kharasch–Sosnovsky reaction will be placed in context to other allylic oxidation methods (Fig. 4). Selenium dioxide is a well-known reagent for the conversion of alkenes to allylic alcohols. Specifically, the catalytic version of Sharpless using *tert*-butyl hydrogen peroxide has been popular.[14] In general selenium dioxide is used in one of two ways for allylic oxidation. If SeO_2 is the reagent, peroxide is added to oxidize the $Se(OH)_2$, and if SeO_2 is present in catalytic amounts then *t*-butyl hyperoxide is used.

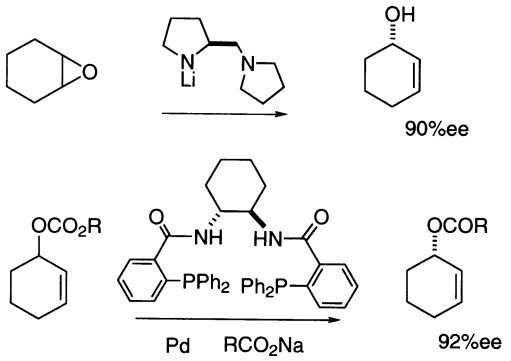


Figure 5. Other asymmetric routes to cyclic alkenols.

Even with the use of *t*-butyl hyperoxide, some modifications such as solid-state supports with microwave irradiation are still required.[15]

Although allylic rearrangements have been observed, there is considerable evidence that the reaction proceeds by an ene-reaction followed by a [2.3] sigmatropic shift.[16] This reaction also produces conjugated aldehydes under certain circumstances. The ene-reaction sigmatropic shift mechanism limits the versatility of the reaction, and the ligand based asymmetric versions have not been developed. The reaction is further limited in that certain substrates, in particular *endo*-cyclic olefins, are not useful.

Stoichiometric mercury acetate can transform olefins to allyl acetates in good yields.[17] The regioselectivity with terminal olefins is poor giving a mixture of primary and secondary ester products. Mixed metal allylic oxidations, processes developed to mimic cytochrome P-450 oxidations, have been reported. A particularly useful system, reported by McMurry and Kocovsky, employs both palladium and copper acetates with quinone and oxygen in acetic acid.[18] The presence of two metals renders asymmetric ligand development difficult in this case. Other systems, involving metal–porphyrin complexes, give products with poor chemoselectivity.[19] Most often enones, allylic alcohols, and epoxides are all formed in significant amounts. There are oxidative enzymes that can perform allylic oxidations, dopamine β-monooxygenase for example. Enzyme based approaches are usually substrate specific and usually do not perform well abiotically.[20]

The Kharasch–Sosnovsky reaction remains the most practical approach to direct allylic oxidation of olefins to give allyl esters with reliable regio and stereoselectivity. Other allylic oxidation catalysts that have been reported include chalcogenide-based transition metals in the presence of molecular oxygen and base-catalyzed sulfur dioxide-induced allylic oxidation.[21] Cobalt catalyzed oxidation of cyclic olefins with molecular oxygen can promote either the oxidation of the double bond to produce an epoxide, or allylic oxidation leading to allyl alcohols or enones. Oxidation of olefins by the combined use of molecular oxygen and 2-methylpropanol with a cobalt(II) complex derived from an imine favors epoxide formation.[22] Conversely, the same reaction with a neutral cobalt imine-based complex favors allylic oxidation. Presumably, the formation of various reactive oxygen species is strongly influenced by the local cobalt environment of the ligand complex. The ability of Co to adopt multiple oxidation states with small energy potentials between them also influences the reaction.

Allylic oxidation of cyclohexene and indene has also been accomplished with a *cis*-$[Ru(IV)(bpy)_2(py)(O)]^{2+}$ catalyst.[23] Kinetic studies in acetonitrile indicate that the reactions is first-order in $Ru^{IV}{=}O^{2+}$ and substrate. Heterogeneous oxidation of allylic alcohols to ketones catalyzed by magnesium–aluminum–ruthenium hydrotalcites in the presence of molecular oxygen gives product with yields ranging from 64 to 95%. Terpesti and co-workers reported base-catalyzed sulfur dioxide-induced allylic oxidation of cyclohexene in the presence of molecular oxygen yielding cyclohexenone with minor amounts of 1,2-cyclohexanediol diacetate.[25] Oxidation at the allylic position occurs only if the reaction is base catalyzed. The mechanism is an anion-radical involving the formation of SO_2 stabilized peroxide ions. Copper catalyzed perester based allylic oxidation should also be contrasted with the various forms of chromium based allylic oxidation to give vinyl ketones. Parish and co-workers have published variations that include pyridinium chlorochromate (PCC) used in excess.[24] This method was used for a prominent late stage A-ring oxidation in Nicolaou's synthesis of Taxol.[25] Catalytic chromium oxidations using *tert*-butyl hydroperoxide are also known.[26] The more recent work of Miller with catalytic ruthenium(III) chloride and *tert*-butyl hydroperoxide has been shown to be superior for various substrates including B-ring oxidations of Δ-5 steroids.[27]

Other routes to allyl alcohols and esters can also be mentioned at this point. Various methods to arrive at these targets are well known and usually involve oxygenated starting materials. Achiral cyclic epoxides can be opened with chiral, enantiopure bases, to give allylic alcohols with high enantioselectivity (Fig. 5).

This reaction, pioneered by Whitesell and Asami, can be performed with either stoichiometric or now with catalytic chiral diamine bases with excess LDA.[28] Trost and co-workers have reported the use of palladium catalysts for the substitution of racemic allylic carbonates with high selectivity.[29] The bis-amide bis(diphenylphosphine) ligand has proven to be especially useful with cyclic substrates. Stoichiometric non-racemic pinene based hydroboration of cyclic dienes also gives allylic alcohols in high selectivity.[30] Other well-known methods fail to produce enantioenriched cyclic alkenols. These include hydrolyse[31] and titanium-tartrate epoxidation Sharpless resolution[32] and CBS enone reduction.[33]

3. Conditions

As mentioned, allylic oxidation using copper catalysis and perester oxidants is highly dependant on the nature of the ligand, perester, and reaction conditions. The copper oxidation state, counter ion, and solvent can affect the regioselectivity. Perester substitution can affect the rate and yield. These issues have important consequences for the

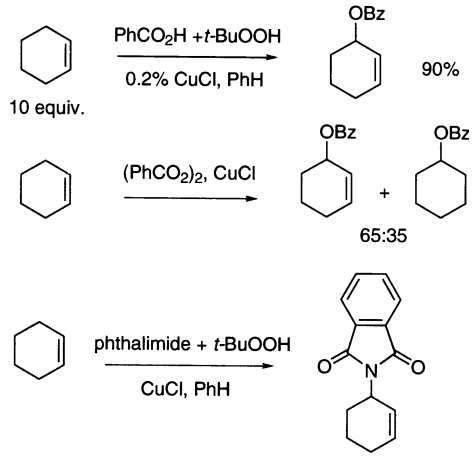


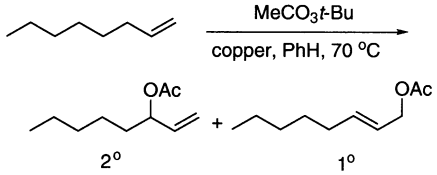
Figure 6. Other reagents for allylic oxidation.

successful development of the copper ligated asymmetric version.

3.1. Reagents

Kharasch and Sosnovsky reported the production of cyclohexenyl benzoate in 70% yield using *tert*-butyl perbenzoate and cuprous bromide (Fig. 1). Excess olefin, 5–10 equiv., is typically used and the yield is based on the perester oxidant, which is used as 1 equiv. The oxidation of 1-octene was reported to give exclusively the internal 3-substituted benzoate in the initial report. This process grew out of early efforts to develop new free radical initiation strategies for polymerization. Peresters are not good initiating agents, in contrast to benzoyl peroxides which have suitable half lives at lower temperatures. However, in the presence of trace amounts of transition metals, the reactivity of peresters was shown to be greatly enhanced. While perester polymer initiation use remained limited, success with C–H bond activation–oxidation was shown to be quite general. It is important to note here that peresters are stable, inexpensive, and commercially available compounds. They are easily made by reacting anhydrous *tert*-butyl hydrogen peroxide with carboxylic acid chlorides. Unlike peracids, there appears to be little detonation hazard, however, appropriate precaution should still be taken. Use of Teflon tubing, coated spatulas, a blast shield, and small initial scales are considered prudent.

Table 1. Effect of copper and solvent on selectivity



Entry	Copper	2°/1°
1	CuCl	86:14
2	$Cu(OAc)_2$	89:11
3	$Cu(OAc)_2$/pyr	70:30

Kharasch and Fono showed that various reagents had a profound effect on the course of the reaction (Fig. 6).[34]

One equivalent of benzoic acid and *tert*-butyl hydrogen peroxide used with catalytic cuprous chloride in refluxing benzene gave the same allyl benzoate product in high yield 90%. Asymmetric versions using this combination, in place of a perester, have been developed and will be discussed later. It was also reported that the rate of the reaction and the yield were comparable in other solvents, such as *tert*-butyl alcohol and nitrobenzene. Use of benzoyl peroxide with copper(I) chloride gave a 65:35 mixture of allyl benzoate and cyclohexyl benzoate. This is due to the higher tendency of benzoyl radical to add to olefins instead of abstracting an allyl hydrogen as is the case with the more reactive *tert*-butoxy radical, a key intermediate in perester-based oxidation. Alternative reagents include phthalimide with *tert*-butyl hydrogen peroxide to give the allylic phthalimide product shown. Surprisingly, no follow up to this work has been reported.

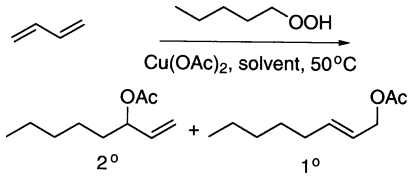
3.2. Copper

The initial report by Kharasch that claimed exclusive internal 3-substitution turned out to be inaccurate. Due to analytical limitations, the minor 1-allyl ester product was not observed. Follow up work by Walling[35] and Kochi[36] and co-workers found significant amounts of the thermodynamically more stable 1-substituted esters. This was a key factor in these studies, in that other reactive intermediates, formed via free radical chlorination and allylic cation trapping, give a much greater proportion of 1-substituted product. Examples of these results are shown below. In general copper catalyzed perester oxidation of acyclic olefins gives the internal product 10:1 over the terminal ester. This can vary greatly depending on the nature of copper. Walling reported the formation of a 86:14 mixture of 2°, internal ester to 1° ester using peracetate and copper(I) chloride (Table 1).[26] Copper(II) acetate also gave high internal selectivity at 89:11. Copper acetate complexed to pyridine on the other hand reduced the regioselectivity to 70:30. Copper complexes are unlike other transition metals in many regards, including a strong tendency for square planar coordination, enhanced sensitivity to the nature of ligands, and other electronic and spectral properties.[37] Other metals however have been shown to catalyze the reaction, including palladium(0), rhodium(I), and iron(II) complexes.[38] The efficiency of these metals compared to copper is very low. Other complexes of metals such as silver, nickel, and zinc show no reactivity.

3.3. Solvent

The reaction does not have a high dependency on the nature of the solvent. Once the materials are in solution, the polarity of the solvent has little effect on the rate. The rate-limiting step involves the formation of a neutral free radical. Early on Kochi found a significant solvent effect on regio-selectivity. In a related process using *n*-pentyl hydrogen peroxide and butadiene with copper(II) acetate, the regioselectivity of secondary to primary products and the nature of the substituting group varied greatly with the nature of the solvent (Table 2).[39]

Table 2. Effect of solvent on selectivity



Entry	Solvent	ε	2°/1°
1	EtOAc/AcOH	6.02	86:14
2	CH_3CN/AcOH	36.7	80:20
3	HCO_2H	58	80:20[a]
4	H_2O/AcOH	78.5	78:22[b]
5	AcOH/pyr	12.3	66:34

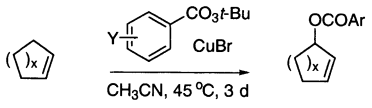
[a] Formate esters are formed.
[b] Alcohols formed.

The mechanism involves fragmentation of *n*-pentoxy radical to give *n*-butyl radical, which adds to butadiene, and formaldehyde. The allylic radical generated then undergoes oxidation with the copper–ligand complex to give allylic ester. The last step is the same as allylic oxidation with perester. The solvents shown are in order of increasing dielectric constant except for entry 5 with 5% pyridine–acetic acid. The least polar ethyl acetate mixture gives the highest internal selectivity at 86:14. The other more polar systems only slightly eroded the selectivity giving more terminal product. The pyridine mixture shows a dramatic reduction in selectivity to 66:34 most likely due to pyridine's ability to strongly coordinate copper. It should also be noted that stronger nucleophiles can exchange with ligands on copper and become incorporated into the product, as with formic acid (entry 3) to give formate ester products and water (entry 4) to give allylic alcohols.

3.4. Perester

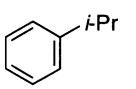
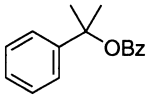
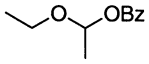
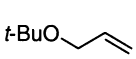
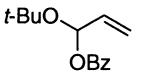
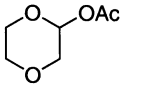
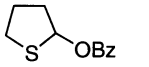
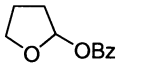
Various peresters can be used in the process including *tert*-butyl perbenzoate and acetate along with cumyl peresters.[26–28] *tert*-Amyl peracetate in the presence of copper salts decomposes rapidly to give ethylene, acetone, and acetic acid. *n*-Alkyl and other hydrogen peroxides can be used in the presence of carboxylic acids to give ester products. Various substituents can also be introduced on *tert*-butyl perbenzoate but using substituted acid chlorides. Effects on the selectivity and reactivity have been observed (Table 3).[40] Improved yields using *m*- and *o*-chloro peresters

Table 3. Effect of perester on cyclic alkene yield



X	Y	Yield (%)
1	*p*-Cl	65
1	*m*-Cl	81
1	*o*-Cl	89
1	*p*-NO_2	54
2	*p*-Cl	59
2	*m*-Cl	77
2	*o*-Cl	83
2	*p*-NO_2	57

Table 4. Other substrates for copper catalyzed peroxy oxidation

Substrate	Conditions	Product	Yield (%)
	*t*-BuOOH, BzOH, CuCl		40
Et_2O	$PhCO_3t$-Bu, CuBr, PhH		82
	$PhCO_3t$-Bu, CuBr, PhH		74
	CH_3CO_3t-Bu, CuBr, PhH		73
	$PhCO_3t$-Bu, CuBr, PhH		69
	CH_3CO_3t-Bu, $Cu(O_2CR)_2$, PhH, $h\nu$		75

were obtained with cyclopentene and hexene. *p*-Nitro showed lowered reactivity when compared to the unsubstituted perbenzoate with copper(I) bromide. This is not the case with the asymmetric versions as discussed below where the ligated version appears to be enhanced.

4. Substrates

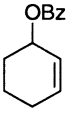
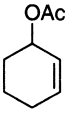
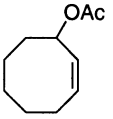
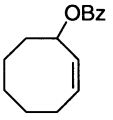
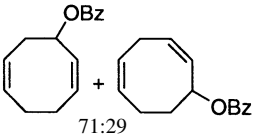
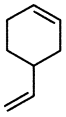
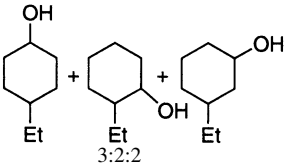
Before the olefin classes are covered, it is important to note that the reaction conditions are general and can be used to transform various functional groups.[3] Early on Sosnovsky demonstrated that other substrates underwent efficient oxidation under the perester copper reaction conditions to give in some cases useful products.[41] A representative collection of the substrates are shown (Table 4). Benzylic oxidation, while occurring at a lower rate than allylic oxidation, can be performed. Cumene, with a tertiary radical intermediate, is best with a 40% yield. Oxidation adjacent to electron rich heteroatoms is also common. The benzoate acetal of diethyl ether is produced in 82% yield under the perester conditions. THF is a much poorer substrate giving only a trace amounts of product under thermal conditions. Dioxane in contrast gives acetal product in good yield.

Tetrahydrothiophene also gives a moderate yield of mixed acetal product. THF can be functionalized under more forcing photochemical conditions in 75% yield. This list should be kept in mind when considering new solvents, substrates, and ligands. Any solvent with active, extractable hydrogen that will result in a stable radical at an electron rich position must be avoided. In addition, ligand design is limited to functionality that will not be reactive to electron deficient *t*-butoxy radical. Ligands and solvents with hydrogens adjacent to electron withdrawing functionality, as with acetonitrile, are unreactive.

4.1. Cycloalkenes

Cyclohexene has consistently given high yields under various reaction conditions and reagent combinations

Table 5. Cyclic alkene substrates for allylic oxidation

Substrate	Conditions	Product	Yield (%)
	$PhCO_3t$-Bu, CuBr, PhH		80
	AcOH, *t*-BuOOH, CuCl		88
	CH_3CO_3t-Bu, CuBr, PhH		38
	$PhCO_3t$-Bu, Cu–Na-HSZ-320 zeolite		68
	$PhCO_3t$-Bu, $Cu(O_2CR)_2$	 71:29	96
	$PhCO_3t$-Bu, Cu–Na-HSZ-320 zeolite	98:2	82
	(1) $PhCO_3t$-Bu, CuBr, PhH; (2) H_2, Pd/C; (3) NaOH	 3:2:2	36

(Table 5). Both perester at 80% yield[42] and the acid–*tert*-butyl hydroperoxide combination at 88% give efficient yields of allyl ester product.[26] Olefins are used in excess (5–10 equiv.) and the yields are based on the perester oxidant. Cyclopentene and heptene were not substrates reported in earlier studies. Cyclooctene gives product in much lower yields at 38%.[3] This is most likely due to an inability of the medium-sized ring to accommodate the flattened conformation needed for the intermediate allyl radical.

Recently, a moderate 68% yield of cyclooctene ester has been obtained using the Cu–Na-HAS-320 zeolite with heating for 20 h.[43] 1,5-Cyclooctadiene, in contrast, has been a good substrate giving a 96% yield under the standard conditions.[26] The flattened allyl radical is better accommodated, however, the regioselectivity is a 71:29 mixture of isomers. The zeolite conditions give an 82% isolated yield with greatly improved 98% selectivity in this case. This transformation was recently used by Martin as a starting point in a brevetoxin study using Walling's conditions.[11] 4-Vinylcyclohexene points out the group selectivity potential of the process.[44] Following hydrogenation and hydrolysis, the mixture of alcohol isomers showed that exclusive oxidation occurred in the ring with no reaction adjacent to the appended vinyl group. Proper electronic overlap between the allylic C–H bond and the olefin leading directly to the allylic radical is the probable explanation. Conformational freedom of the vinyl group precludes proper conjugation upon abstraction of the tertiary hydrogen at this α-position on the ring. This result contrasts with selenium dioxide oxidation of limonene that occurs exclusively by reacting with the appended vinyl group and not the ring olefin.[45]

4.2. Acyclic alkenes

Simple terminal olefins were discussed previously.[26,27] Typical selectivities are 80–90% for the internal secondary ester product over the primary terminal ester. 2-Alkenes offer the opportunity to access secondary esters with disubstituted olefins present in the product (Table 6). A

Table 6. Comparison of allylic oxidation and chlorination of 2-pentene

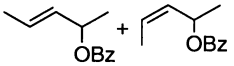
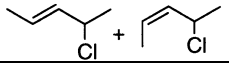
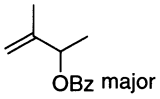
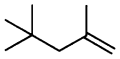
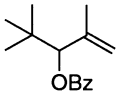
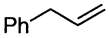
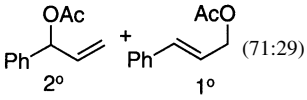
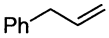
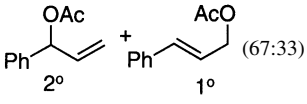
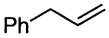
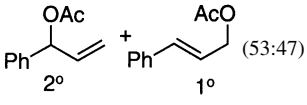
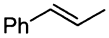
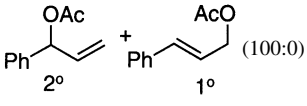
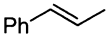
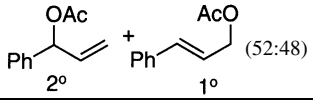
Substrate	Conditions	Products	Ratio
2-Pentene (*E*/*Z* 75:25)	$PhCO_3t$-Bu, CuCl, PhH		96:4
2-Pentene (*E*/*Z* 75:25)	*t*-BuOCl, PhH, $h\nu$, 70°C		76:24

Table 7. Acyclic alkene substrates for allylic oxidation

Substrate	Conditions	Product	Yield (%)
	$PhCO_3t$-Bu, $Cu(O_2CR)_2$, PhH, 70°C	 OBz major	71
	$PhCO_3t$-Bu, $Cu(O_2CR)_2$, PhH, 70°C	 OBz	78
	$PhCO_3t$-Bu, CuBr, PhH	 OBz	37
	CH_3CO_3t-Bu, CuCl, 70°C	 OAc, AcO, 2°, 1°	(71:29)
	$Cu(OAc)_2$	 OAc, AcO, 2°, 1°	(67:33)
	*t*-BuOOH, AcOH, CuCl	 OAc, AcO, 2°, 1°	(53:47)
	CH_3CO_3t-Bu, CuCl, 70°C	 OAc, AcO, 2°, 1°	(100:0)
	*t*-BuOOH, AcOH, CuCl	 OAc, AcO, 2°, 1°	(52:48)

75:25 *E*/*Z* mixture of 2-pentene gives allyl benzoates in 70% yield.[46]

The major products formed in 70% yield are secondary esters where 96% of the product olefin geometry is *E*. Only 4% of the product geometry is *Z*. The starting geometry of the 2-pentene was 25% *Z*. This example illustrates the unique nature of copper-based allylic oxidation. In contrast, the related free radical and cationic routes to allylic substitution have opposite regioselectivity. These differences are further highlighted below. Free radical chlorination using *tert*-butyl hypochlorite is shown reacted with this same 2-pentene mixture. Unlike the copper–perester reaction, the allylic chlorides reflect almost exactly the geometry of the starting materials giving a 76:24 *E*/*Z* ratio of isomers. These results are consistent with the allylic copper(III) intermediate proposed by Beckwith and Zavitsas. The allylic copper intermediate allows for σ-bond rotation to access more of the thermodynamically stable *E* isomer. Free radical chlorination goes through a free allylic radical that is trapped with chlorine from *tert*-butyl hypochlorite. The high energy of the allylic radical resonance energy (~24 kcal/mol)[47] does not allow for free rotation in this case and the olefin geometry is maintained in the product.

Other acyclic olefin substrates are compiled in Table 7. All classes of olefins perform well as substrates including trisubstituted, tetra-, and 1,1-disubstituted cases. 2-Methylbutene gives as the major internal secondary ester product in 71% yield.[48] 2,3-Dimethyl butene gives tertiary ester product in 78% yield.[37] 2,4,4-Trimethyl-1-pentene is an interesting case where again the internal product is favored.[4] Other examples of simpler 1,1-substituted starting materials have not been reported. Allyl benzene reacts with the usual selectivity producing secondary product 71:29 under standard conditions with copper(I) chloride according to Walling.[26]

Copper(II) erodes the selectivity to 2:1 while use of acetic acid and *tert*-butyl hydrogen peroxide give both secondary and primary products in essentially a 1:1 ratio. Remarkably the isomeric substrate, 2-methylstyrene, gives complete 100% selectivity for the secondary ester using copper(I) and *tert*-butyl peracetate. Hydrogen peroxide conditions produce the same poor 1:1 mixture of products with this substrate. The mechanistic implications of these results are discussed below.

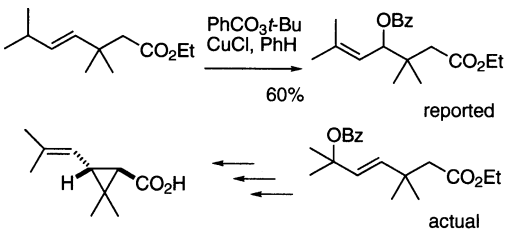


Figure 7. Kharasch reaction route to chrysanthemic acid.

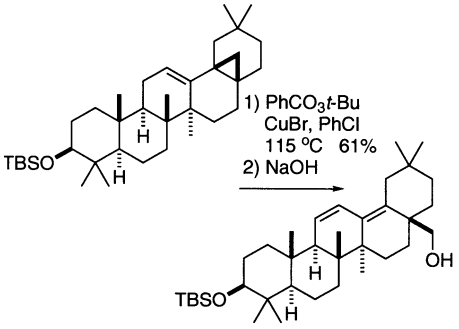


Figure 8. Route to pentacyclic triterpenes via vinyl-cyclopropane cleavage.

4.3. Applications

Finici and d'Angelo reacted the *gem*-dimethyl ester shown to reportedly give a secondary benzoate ester in 60% yield leading to racemic chrysanthemic acid (Fig. 7).[10]

This regioselectivity is not consistent with previous examples where the more substituted, in this case the tertiary ester, should predominate. Intrigued by the report, our lab repeated the experiment with copper(I) catalysis in refluxing benzene and found that the actual product obtained in 60% yield is indeed the expected tertiary product.[49] Two sets of *gem*-dimethyl groups were seen as identical signals and a pair of olefin proton signals are present. No indication of diastereotopic methyls are seen using high field ^{1}H NMR. The result is now in accord with other acyclic olefin substrates (Table 7). In this case, regardless of the regioselectivity, either product would lead to the final target.

Corey and Lee reported a closely related, unprecedented process involving the transformation of a steroid based vinylcyclopropane to an angular methylhydroxy diene product (Fig. 8). This compound was used as a common intermediate for the synthesis of four pentacyclic oleandric triterpene steroids, amyrin, erythrodiol, oleanolic acid, and aegiceradienol.[12] The primary benzoate product was hydrolyzed to the alcohol shown. The allylic radical intermediate initially formed fragments to give a diene methyl radical that was then oxidized by copper benzoate to provide the ester product. Only the example shown was reported. Surprisingly no other efforts to further develop this potentially useful process have been disclosed.

5. Mechanism

Prior to discussing the mechanism of the process, it is important to consider in more detail the regioselectivity of the reaction with butene. In particular, the geometry of the minor primary benzoate product and its comparison to free radical chlorination provide key mechanistic insights. Recently, Beckwith and Zavitsas have carefully analyzed the geometry of the minor isomer obtained using the isomeric butenes and have found it to be uniformly *E* (Table 8).[35] 1-Butene, *E*-2-butene, and *Z*-2-butene all give a 93:7 mixture of secondary and primary esters in moderate yield under the standard reaction conditions at 70°C. In each case, the minor primary ester product possesses nearly exclusive *E*-configuration. The *Z* conformation in the allyl radical intermediate in the last case from *Z*-2-butene is not retained. Less than one percent of *Z*-primary acetate was seen by GC. The products are stable to the reaction conditions. Appropriate controls were performed ensuring that isomerization or decomposition is not operative during the

Table 8. Allylic oxidation and butene

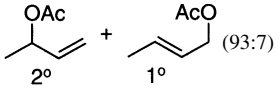
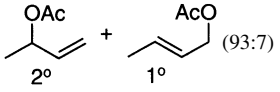
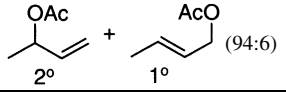
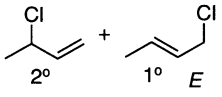
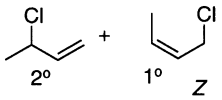
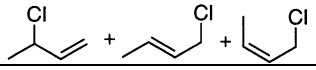
Substrate	Conditions	Products	Yield (%)
	CH_3CO_3t-Bu, CuCl, PhH	 (93:7)	67
	CH_3CO_3t-Bu, CuCl, PhH	 (93:7)	75
	CH_3CO_3t-Bu, CuCl, PhH	 (94:6)	69

Table 9. Allylic chlorination of butene with hypochlorite

Substrate	Conditions	Products	Ratio
	*t*-BuOCl, PhH, *hν*, 70°C		26:74
	*t*-BuOCl, PhH, *hν*, 70°C		37:63
	*t*-BuOCl, PhH, *hν*, 70°C		31:41:28

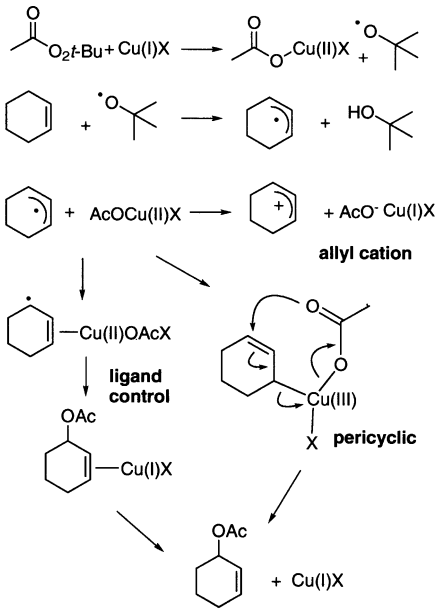


Figure 9. Mechanism of allylic oxidation with cyclic olefins.

reaction conditions and that the observed geometries were a consequence of the primary reactivity.

In addition to providing the primary terminal allylic chloride as the major product, allylic chlorination also shows near complete retention of the alkene starting material geometry (Table 9).[35] These reactions were also performed at 70°C temperature for comparison purposes. The major product from *E*-2-butene is primary chloride formed with complete *E* geometry and the major product from *Z*-2-butene is *Z* primary chloride. 1-Butene gives a mixture of primary allylic chlorides whose geometry reflects the conformational preference of the starting material upon hydrogen abstraction. In addition, solvolysis

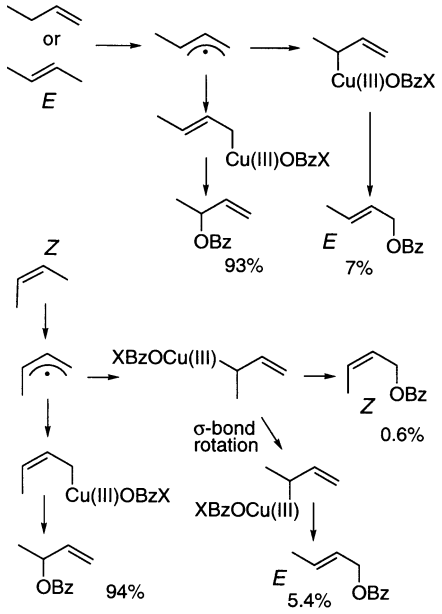


Figure 10. Mechanism with acyclic olefins with Cu(III) intermediate bond rotation giving *E* minor products.

of isomerically pure 1-chlorobutenes in water also shows a strong preference for retention of olefin geometry as seen in the product alcohols.[50] These results are consistent with an allylic copper(III) intermediate for allylic oxidation.

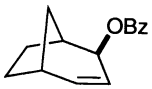
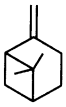
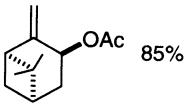
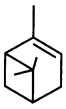
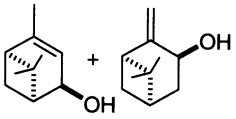
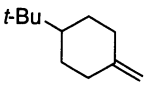
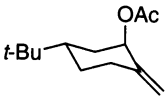
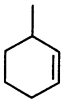
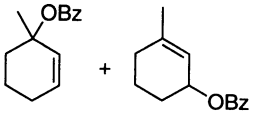
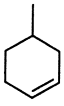
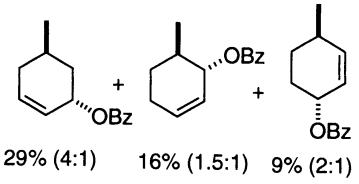
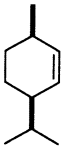
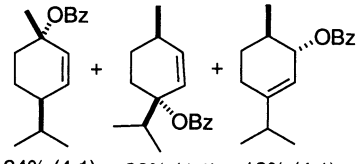
From the work of Kochi,[51] Walling[26] and Beckwith and Zavitsas[35] a mechanism emerges that involves homolysis of the pester oxygen–oxygen bond to give copper(II) carboxylate and *tert*-butoxy radical (Fig. 9). Only the main path to allyl ester is shown using cyclohexene for clarity. Other steps operative including chain terminating radical–radical coupling, atom abstraction from solvent, perester thermolysis, etc. are not shown. The next step is hydrogen atom abstraction from the allylic position by *tert*-butoxy radical to give an allylic radical and *tert*-butyl alcohol. While no detailed measurement of the rate of each elementary step has been made, the first two steps are known to be very fast, nearly diffusion controlled, by analogy to other observed rates.[40] The oxidation step leading to product from this point on has been controversial. In some manner, the allylic radical combines with copper carboxylate to give allyl ester product. Three proposals have been made: an 'essentially free' allyl cation type process involving initial electron transfer to copper to give copper(I) and carboxylate followed by ion combination to give product as proposed by Walling, a ligand-control type process where a copper(II)-η^2 olefin complex is initially formed followed by carboxy radical transfer to give product as proposed by Kochi, and finally copper(III) formation followed by a percyclic rearrangement that directly gives product as proposed by Beckwith.

All three routes account for regeneration of the copper(I) catalyst, but only the Beckwith route is consistent both with the observed regioselectivity and olefin isomerization found in acyclic cases. Neither the route of Walling, where the cation is only partially free and rapidly trapped, nor the ligand control route of Kochi accounts for the geometry of the minor isomer from acyclic olefins. Both the allyl cation and the allyl radical pathways, having barriers to isomerization with relatively high resonance energy, require retention of olefin geometry. This is clearly not the case as shown by the Beckwith–Zavitsas study discussed above. The central idea of this work is shown more clearly in Fig. 10. Both 1-butene and *E*-2-butene give the same allyl radical. Trapping at the less hindered C-1 position gives the primary Cu(III) intermediate, which rearranges to the major secondary product in 93% selectivity.

Alternatively, trapping at less favored internal C-3 position gives a secondary Cu(III) intermediate that, in an *anti* methyl-vinyl conformation shown, produces the minor *E*-primary ester in 7% selectivity. From *Z*-2-butene, the radical intermediate is formed with a *cis* conformation due to resonance. The barrier for conversion to the more stable *trans* conformation is relatively high at 24 kcal/mol.[36] Trapping at C-1 followed by rearrangement again gives the major secondary ester product with high selectivity.

In order to account for the *E*-configuration of the minor isomer from this intermediate, an isomerization event must occur prior to ester formation. Trapping at C-3

Table 10. Cyclic alkene substrate stereocontrol

Substrate	Conditions	Product	Yield (%)
 $[\alpha]_D$ -80°	$PhCO_3t$-Bu, CuBr, PhH	 $[\alpha]_D$ 0°	85
	CH_3CO_3t-Bu, CuBr, PhH	 85%	90, *trans*
	CH_3CO_3t-Bu, CuBr, PhH/NaOH		50, 30
	CH_3CO_3t-Bu, CuBr, PhH/NaOH		26
	$PhCO_3t$-Bu, $Cu(O_2CR)$, PhH		28, 29
	$PhCO_3t$-Bu, $Cu(O_2CR)$, PhH	 29% (4:1) 16% (1.5:1) 9% (2:1)	
	$PhCO_3t$-Bu, $Cu(O_2CR)$, PhH	 34% (4:1) 26% (4:1) 13% (4:1)	

gives the Cu(III) intermediate with an initial eclipsed methyl–vinyl conformation. Rearrangement at this point would give the *Z*-1-ester minor product. However, this product is only formed in trace amount with 0.6% selectivity. The majority of the primary product being formed with an *E* configuration is accounted for by invoking a simple sigma bond rotation to give the more stable *anti* methyl–vinyl conformation. This intermediate then rearranges to form the *E* primary minor isomer as shown. Modifications to the cation and ligand control routes that account for these findings are problematic. The Cu(III) pathway can also account for the higher selectivity of methylstyrene versus allyl benzene reported by Walling. Incipient allyl radical from methyl styrene forms at the terminal C-3 position in close proximity to copper(II). Attack at this less encumbered C-1 position then leads to exclusive internal secondary product following rearrangement. Allyl benzene on the other hand begins with an internal secondary incipient radical at C-1. Close proximity with copper then leads to more trapping at the internal position, which leads to more primary minor product upon rearrangement.

While other issues remain to be resolved, including explanations for reduced selectivity with Cu(II) catalysts and more polar solvents, as seen with *tert*-butyl hydrogen peroxide in acetic acid, only the Cu(III) mechanism adequately addresses both the selectivity and the minor isomer configuration to this point. Clearly more detailed kinetic and theoretical work needs to be done. Early preliminary work reported the reaction to be first order in peroxide[52] and pseudo-first order in perester.[26] Regardless, all data points to an interaction between copper and the substrate upon formation of the new carbon–oxygen bond. This assured that appropriate conditions were possible for the development of asymmetric versions.

6. Stereocontrol

An issue of primary concern has been the development of substrates and conditions to control the stereochemistry of the C–O ester bond. Facial selectivity of the copper complex attack prior to carboxylate delivery and the regioselectivity of the attack are then key factors. The development of diastereo- and regioselectivity via substrate stereocontrol are now addressed followed by the progressive development of chiral non-racemic ligands for enantioselection.

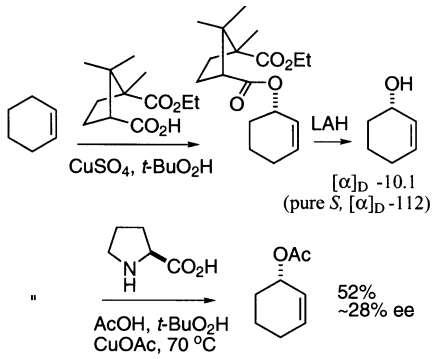


Figure 11. Stereocontrol via chiral acid.

6.1. Substrate

The effect of pre-existing stereocenters on the selectivity of allylic oxidation was investigated early on with various cyclic chiral olefins. In general, a high level of selectivity can be achieved when one face of the olefin is sufficiently hindered. A key issue is the regioselectivity of hydrogen atom abstraction and the attack of the copper complex. Unlike acyclic olefin regioselectivity, poor selectivity is often seen with cyclic chiral olefins. Selected early examples are shown along with more recent examples (Table 10). Goering and Mayer reacted enantiomerically enriched [3.1.2]bicyclo-1-octene and obtained racemic allyl benzoate product.[53] Complete *exo*-selectivity was obtained, however the symmetric nature of the allylic radical intermediate prevented retention of alkene stereochemistry. The copper complex attacked the ends of the symmetrical allyl radical with equal rates. Attack on the *exo* face, on the side of the methylene bridge away from the larger ethylene, occurs exclusively. A similar effect was observed by Denney using an optically active menthene substrate.[54] *exo*-Methylene β-pinene was transformed to the secondary ester in 85% yield with 90% *trans* selectivity.[55] The *gem*-dimethyl methylene provides sufficient hindrance to force ester delivery to the opposite face. In this example, the primary ester product is not observed. α-Pinene on the other hand gives two isomeric products both with *anti* selectivity.[31] Abstraction of the secondary hydrogen occurs at a faster rate giving 3-hydroxy β-pinene as the major product after hydrolysis. The explanation for no tertiary product is unclear in this case.

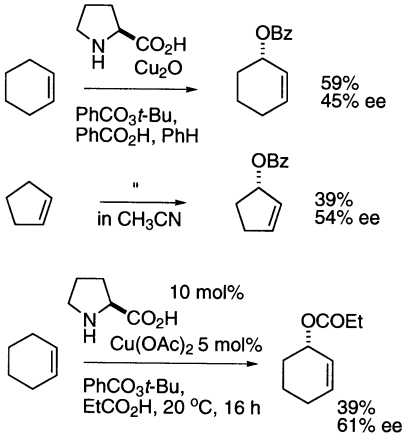


Figure 12. Stereocontrol with proline–copper complexes.

Hydrogen abstraction gives 2-hydroxy α-pinene. *exo*-Methylene-4-*tert*-butylcyclohexane gives secondary acetate product with *trans* selectivity in low yield.[56] Beckwith and Phillipou investigated a series of chiral cyclic olefins that again showed low selectivity.[57]

3-Methylcyclohexene gives a 1:1 mixture of tertiary and secondary ester products where abstraction of the tertiary allylic hydrogen is highly favored. The catalyst in this case is a copper(II) carboxylate reacted at 80°C. 4-Methylcyclohexene produces three regioisomeric products, all of which have the *trans* stereoisomer dominant. Conformational control appears to be operative with a clear preference for abstraction of axial allylic hydrogen. Proper overlap between the olefin and the allylic C–H σ-bond is only found through an axial conformation. 3-Isopropyl-6-methylcyclohexene, with only tertiary hydrogens available, also gives multiple products again with the *trans* products dominant. There is a slight preference for removal of the axial hydrogen at the C-1 position giving both the favored tertiary ester as well as minor secondary products. The major tertiary product arises from hydrogen atom abstraction at the methyl bearing C-6 position followed by attack at C-2 adjacent to the isopropyl group. The reaction has also been performed on a variety of unsaturated $\Delta^{5,6}$ steroid substrates giving B-ring allylic esters as mixtures of α- and β-isomers.[58] After an initial flurry of activity, the investigation of chiral olefin substrates has come to a halt.

6.2. Enantiocontrol

Present work in the area focuses almost exclusively on the development of enantioselective versions with simple cyclic olefins. Key developments include new chiral ligands, peresters, and additives to increase reaction rates and selectivities. Surprisingly, stoichiometric chiral auxiliaries with copper coordinating functionality attached either on an olefin substrate or on a perester have not been successfully developed. In this regard, the reaction has not followed the usual progression of asymmetric strategy development, i.e. substrate to reagent to auxiliary to catalysis-control, as with more common reactions, for example the alkylation and aldol reactions.

Initially, asymmetric Kharasch strategies involved the use of chiral carboxylic acids (Fig. 11). Denney in 1965 reported the use of non-racemic α-ethyl comphorate together with *tert*-butyl hydrogen peroxide.[59] The resultant ester was hydrolyzed and the cyclohexenol was found to have a specific rotation of −10.1. Pure *S*-cyclohexenol has a rotation of −112.[60] Other olefin substrates were also reported giving product with little or no optical rotation. It is difficult to tell in these cases whether the stereoinduction resulted from the allylic oxidation or from crystallization of the solid ester intermediate. The stage was now set for further work, but it was not until 1991 that the next advance was reported. Muzart used catalytic amounts of L-proline together with *tert*-butyl hydrogen peroxide in acetic acid with copper(I) catalysis to provide ester product.[61] The enantiomeric excess was estimated to be 28% calculated

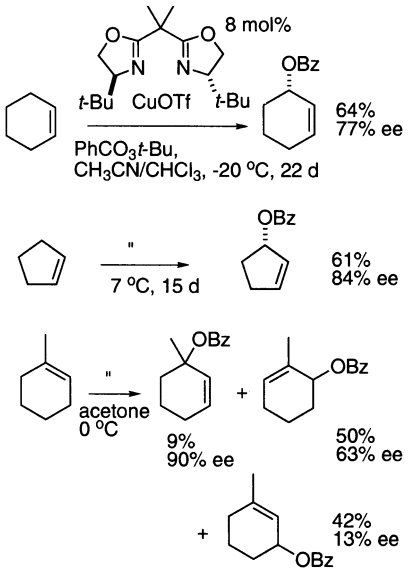


Figure 13. Stereocontrol with bis-oxazoline–copper complexes according to Pfaltz.

from the optical rotation. Other amino acids investigated gave inferior results.

An extensive follow up to the initial report was published. The use of perester was found to be superior in the catalytic L-proline–copper(I) system (Fig. 12).[62] A sequential simplex method,[63] varying the equivalents, concentration, and time, was used to optimize the reaction. The optimal proline to copper ratio was two for the best selectivities shown. The optimal ratio of olefin to peroxide was also investigated and shown to be in the 20–30 equiv. range. Lower yields and selectivities were found at other ratios of substrate to oxidant. For cyclohexene, 5 mol% bis-proline–copper oxide catalyst with perester and benzoic acid in refluxing benzene gave 49% yield with 45% ee determined using a chiral shift reagent. Acetonitrile was shown to be the optimal solvent for cyclopentene. In a later study by Muzart the bis-proline–copper complex formed from copper(II) carbonate was formed and monitored by UV/vis spectroscopy. Its absorption at 572 nm persisted indicating that it was stable throughout the duration of the reaction. No other intermediates or products were observed during the reaction.[64]

Feringa reported that the selectivity could be improved using a proline–copper acetate complex and propionic acid and a lower temperature.[65] A trade off between yield and selectivity was noticed. An improved yield of 70% was obtained using 20 mol% catalyst but the selectivity dropped to 57% ee.

Enantioselectivities in this case were determined by chiral GC analysis. Subsequent to this work, a study on the linearity of the proline process was reported by Feringa.[66] A slightly negative non-linear effect was shown between the ee of the proline catalyst and the ee of the resulting cyclohexenyl benzoate. This effect in the presence of anthraquinone, an oxidant additive used commonly in palladium systems,[16] was reversed to give a more commonly observed,[67] more pronounced, positive non-linear effect. It is difficult to draw conclusions on these results in that the selectivities, yields, and magnitudes of non-linearity are small and the best selectivities in both cases were found using 100% ee proline. A variety of control experiments were performed including addition of enantiomerically enriched product and use of $Pd(CH_3CN)_2Cl_2$ as catalyst. At 50°C, the ee of recovered material was eroded from 57 to 51%. The duration of the reaction in this case was not reported. Palladium, in contrast, added with the copper–proline catalyst resulted in a slight increase of the selectivity to 63% ee.

A major breakthrough with dramatic improvement in allylic oxidation enantioselectivity was found with the C_2-symmetric bis-oxazolines. These ligands are conveniently derived from amino acids and have been successfully applied to cyclopropanations[68] and aziridinations.[69] They have become the ligand of choice with various metals for a variety of catalytic transformations including allylic displacement,[70] imine addition,[71] Diels–Alder,[72] aldol,[73] 1,3-dipolar cycloaddition,[74] reduction,[75] and the ene reaction.[76] Cyclopropanation and aziridination reactions in particular are analogous in that copper adopts various oxidation states throughout the catalytic cycle.[77] Copper acts as a Lewis acid in most of the other transformations. With the successes achieved with these transformations, the decision was made to employ bis-oxazoline–copper complexes in the Kharasch reaction. Both the Pfaltz group[6] and our group,[7] knowing of each others efforts, published our initial results in 1995. Pfaltz previously focused on the use of semicorrin–copper complexes, a system shown to be very successful with copper catalyzed cyclopropanations.[78] Enantiomeric excesses proved to be encouraging in the 65–75% range under stoichiometric conditions in this case, but the selectivity was greatly reduced in catalytic versions. With copper(I) triflate *S*,*S*-di-*tert*-butyl bis-oxazoline catalyst at 8 mol%, cyclohexene was transformed to the *S*-ester in 64% yield with 77% ee, determined using chiral HPLC (Fig. 13). The reaction was performed in a 3:1 acetonitrile–chloroform mixture at −20°C for 22 days. Cyclopentene at 7°C for 15 days gave product with even higher selectivity at 84% ee. Acetone was shown to give product in slightly higher yields but with somewhat reduced selectivities. A linear response to temperature was also noted with higher temperatures giving reduced selectivity. 1-Methylcyclohexene was also explored with limited success. As shown previously, the regioselectivity of the reaction is often poor.

Interestingly, the ee of the minor tertiary ester formed in 9% yield was very high at 90%. The major secondary esters products were formed with lower enantioselectivity. Mention was made of the use of the more stable copper(I) source $Cu(CH_3CN)_4PF_6$ used in place of the extremely sensitive triflate with equal success.[79] The more stable copper(II) triflate was found to be distinctly less reactive and selective in these cases. The diisopropyl 2,6-pyridyl bis-oxazoline of Nishiyama[80] was also reported to be effective.

Our work also included *S*,*S*-di-*tert*-butyl bis-oxazoline with copper(I) triflate at 5 mol% to give *S*-cyclohexenyl benzoate in high, 80% ee, selectivity.[7] Low temperature was critical

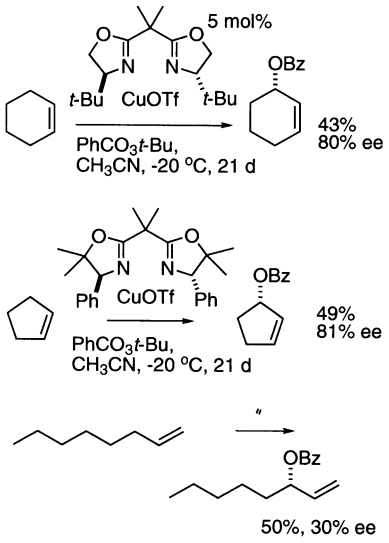


Figure 14. Stereocontrol with bis-oxazoline–copper complexes with cyclic and acyclic substrates.

for high selectivity and acetonitrile was found to be the most effective solvent. Again extended reaction times were needed to achieve moderate yields with high selectivity. As before, excess olefin at 5 equiv., was used and the yields were based on the perester. Cyclopentene was transformed to the benzoate ester by use of the bis-*gem*-dimethyl bis-oxazoline, where the positions adjacent to oxygen in the heterocycle are blocked. The Kharasch conditions, copper(I) with perester, are known to promote the con-

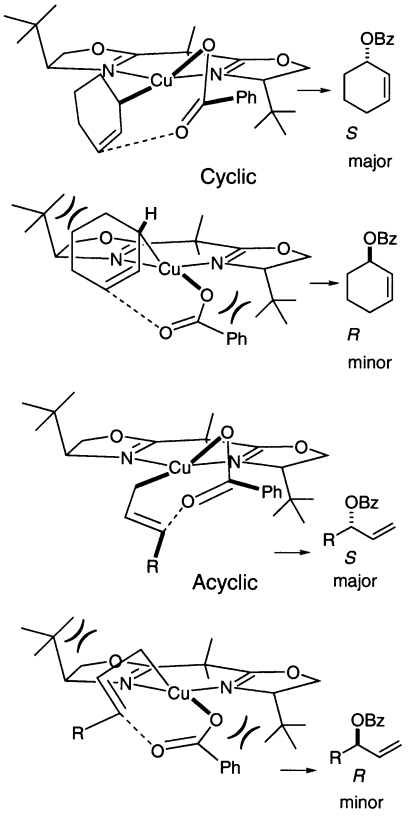
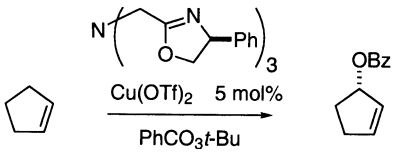


Figure 15. Transition state model of the stereo-induction leading to the major and minor products.

Table 11. Tris-oxazoline–copper complexes of Katsuki

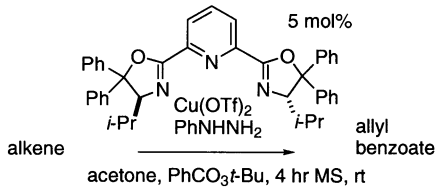


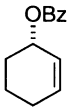
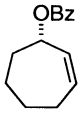
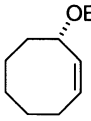
Solvent	*T* (°C)	Time (day)	Yield (%)	% ee
Acetone	Rt	2	68	74
Acetone	0	4	44	84
Acetone	−20	5	11	88
+4 MS	−20	10	30	93
CH_3CN	Rt	2	15	18

version of oxazolines to oxazoles.[81] Initially it was thought that the *gem*-dimethyls at the α- to oxygen-positions would be needed to create a ligand that would be stable to the reaction conditions. In these cases however, di-*tert*-butyl bis-oxazoline and the bis-*gem*-dimethyl bis-oxazoline ligand can be recovered from the reaction mixture by chromatography in approximately 80% yield and can be recycled (Fig. 14). Recovery and reuse of more recent ligands has also been performed as noted below. The oxazolines are not converted to the oxazole in this case presumably due to the steric effect of the side chair R groups. The *gem*-dimethyl ligand provided ester in 81% ee with cyclopentene. Cyclooctene gave product with much lower selectivity, 13% ee, and yield. Acyclic olefins were also reported including allyl benzene and 1-octene. Interestingly, the best selectivities in these cases, 30% ee, were obtained at higher temperature at 55°C in benzene. Low selectivities were obtained at low temperatures in acetonitrile.

A model was proposed to account for the selectivity.[7] The favored transition states are depicted with the allyl and benzoate ligands positioned to minimize interaction with the flanking *tert*-butyl groups of the oxazolines (Fig. 15). Ligated copper attacks the pro-chiral allyl radical to give the Cu(III) intermediate shown. The seven-membered rearrangement with the allyl portion of the cyclohexenyl group and the benzoate in the less encumbered quadrants then occurs to provide the *S*-ester major product. Distorted square-planar copper coordination geometry has been observed in various bis-oxazoline complexes, most recently those reported by Evans and co-workers.[82] Other groups have reported both copper(II) and (III) complexes with similar geometries.[83] Attack on the opposite pro-chiral end of the allyl radical generates a Cu(III) intermediate that places the cyclohexenyl and benzoate groups in the sterically encumbered quadrants occupied by the *tert*-butyl groups of the ligand. This higher energy arrangement leads to the minor *R* enantiomer. Many issues concerning the model remain to be addressed including the rates of formation of the diastereomeric Cu(III) intermediates, reversibility of this step, and the relative rates of product formation from these intermediates. It is most likely that the radical addition step is the enantio-differentiating step giving the Cu(III) intermediate that irreversibly leads to product. In the acyclic case, the same issues apply only now there are more degrees of freedom. Additional flexibility gives transition state arrangements that are closer in energy leading to lower selectivities.

Table 12. Pyridyl-bis-oxazoline–copper complexes with phenylhydrazine additive by Singh



Alkene	Time (h)	Ester	Yield (%)	% ee
	4		80	60
	24		73	75
	24		42	82
	72		28	81

In the same year of the initial bis-oxazoline reports, Katsuki and co-workers reported the use of the analogous tris-oxazolines, C_3-tripodal ligands (Table 11).[84] The connecting group is a tertiary amine in the backbone and the side chain group was phenyl in the ligand with the highest selectivity. Katsuki and co-workers explored the geometry of the tris-oxazoline ligand by preparing a bis-oxazoline ligand that contained an *N*-substituent in place of one of the chelating oxazolines. It showed poor asymmetric induction (<10% ee) in the oxidation of cyclopentene, in contrast to the tris-oxazoline ligand that showed high selectivity. Therefore it is likely that the tris-oxazoline ligand forms a three point chelate and the geometry of the copper–tris-oxazoline complex is twisted trigonal bypyramid or tetrahedral. Copper(II) triflate was used in acetone to give product from cyclopentene with high selectivity 88% ee. In this best case however, the yield was very low at 11%. Selectivities with cyclohexene as substrate or using the *iso*-propyl ligand were lower. Interestingly, use of acetonitrile as solvent also led to a dramatic lowering of the selectivity. A follow-up investigation using the tripodal ligand system showed that 4 Å molecular sieves further improved both the selectivity to 93% ee and the yield somewhat to 30% with cyclopentene.[85] Other solvents found to give good reactivities included ethyl acetate and methylene chloride. Acetonitrile, dimethyl formamide and toluene gave poor reactivity. Added water was shown to stop the reaction completely. Previous work with unligated copper catalysis showed that water did not adversely effect the reactivity but gave allyl alcohols instead.[28] It was also noted by Katsuki that extended reaction times at room temperature lead to significant racemization of the product. Cyclopentyl benzoate initially at 75% ee decreased to 65% ee following 60 h at room temperature in the presence of the copper–ligand catalyst. Various substituted peresters were also explored. *ortho*-Methyl perbenzoate gave product in 91% ee but the yield was again very low at only 5%. Other peresters offered no advantage in this tripodal system.

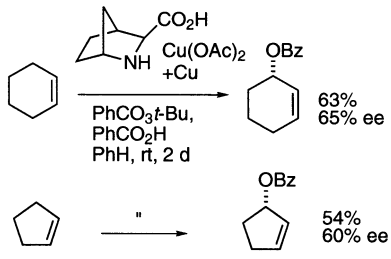
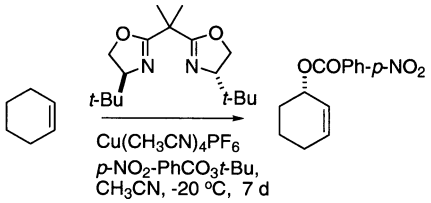


Figure 16. Stereocontrol with bicyclic amino-acid copper complex.

Table 13. Dependence on catalyst stoichiometry with bis-oxazoline–copper hexfluorophosphate and nitroperester

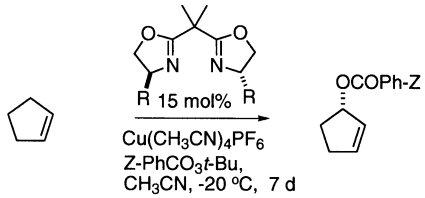


mol% cat.	Yield (%)	% ee
5	34	63
15	60	76

Singh reported a bis-*gem*-diphenyl variation on Nishiyama's catalyst with *iso*-propyl side chains (Table 12).[86] The best selectivity for cyclohexene was 81% ee. Other olefins were much lower in selectivity. A significant advance came when Singh and co-workers used the reducing additive phenylhydrazine in a catalytic amount along with copper(II) triflate and ligand in acetone.[87] Use of reducing additives had been previously employed with success in copper catalyzed cyclopropanations.[88] Kochi noted early on the effects of zinc powder, zinc–copper couple, and hydroxylamine as additives for the reduction of copper(II) back to the active copper(I) form.[28] With hydrazine in acetone, the phenyl hydrazone generated can donate an electron to the copper(II) species to generate copper(I). During the catalytic cycle, the slight excess of hydrazine relative to copper is able to keep more of the copper in the reduced state. Molecular sieves were also found to be advantageous. Remarkably, the reaction times were dramatically reduced to 4 h in the case of cyclopentene. Somewhat surprisingly, the best selectivities were now found with cycloheptene and -octene. Hydrazine additive gave reduced selectivities in the cases of cyclopentene and -hexene. Even with the greatly enhanced reactivity, a trade off was still noted between reactivity and selectivity.

Bicyclic amino acid analogs of proline were made by Andersson and used following the precedent of Muzart.[89] The best case reported involved the aza-norbornane acid shown added in excess compared to the metal. Catalytic copper(II) acetate and copper bronze gave ester products with moderate selectivities (Fig. 16). Compared to L-proline in previous work, this ligand is superior in both reactivity and selectivity. This result indicates that there may be

Table 14. Cyclopentene oxidation with chloroperesters and with bis-oxazoline–copper hexfluorophosphate complexes



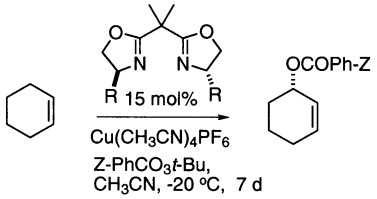
Ligand, R	Perester, Z	Yield (%)	% ee
t-Bu	*p*-Cl	76	57
Ph	*p*-Cl	82	39
t-Bu	*m*-Cl	67	51
Ph	*m*-Cl	64	29
t-Bu	*o*-Cl	76	66
Ph	*o*-Cl	70	10

additional room for improvement using an amino acid based strategy. Since this report, no further examples of amino acid ligands have appeared.

As a follow up to our work with methylene linked bis-oxazoline ligands, a number of other variations were attempted.[90] A significant dependence on catalyst stoichiometry was noted (Table 13). When 5 mol% copper and ligand were used together with *p*-nitroperester, the isolated yield was only 34% and the selectivity was 63% ee with cyclohexene. At 15 mol% catalyst, the yield nearly doubled to 60% and the selectivity improved to 76% ee. The reaction was also performed using chloro-substituted perbenzoate ester oxidants in acetonitrile at −20°C. Cyclopentene gave the highest selectivity with di-*tert*-butyl bis-oxazoline at 66% ee with *o*-chloro perester (Table 14). The diphenyl ligand was always much lower in these cases. The yields reported were for isolated, chromatographed materials again based on the perester and the ees were determined by chiral HPLC with comparisons to racemic ester product. Cyclohexene consistently gave moderate selectivity at 75% ee regardless of the ligand or the perester used (Table 15). The best yield in this case was obtained using *p*-chloro perester. Again the time of reaction was held constant for 7 days for comparison purposes.

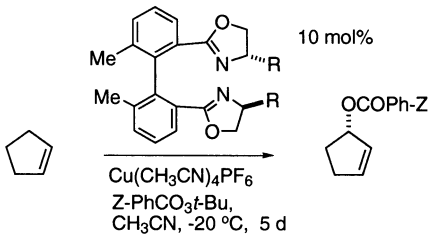
A recent investigation from our laboratory concerned the

Table 15. Cyclohexene oxidation with chloroperesters and with bis-oxazoline–copper hexfluorophosphate complexes



Ligand, R	Perester, Z	Yield (%)	% ee
t-Bu	*p*-Cl	73	75
Ph	*p*-Cl	83	75
t-Bu	*m*-Cl	46	72
Ph	*m*-Cl	69	74
t-Bu	*o*-Cl	67	73
Ph	*o*-Cl	78	71

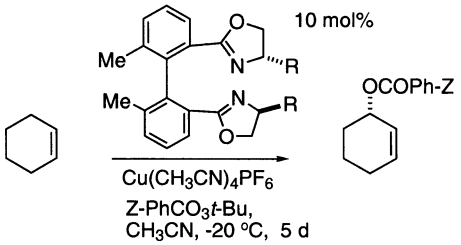
Table 16. Cyclopenetene oxidation with bi-*o*-tolyl-bis-oxazoline–copper complexes



Ligand, R	Perester, Z	Yield (%)	% ee
Ph, *S*,*S*,*S*	*p*-NO_2	59	69
Ph, *S*,*R*,*S*	*p*-NO_2	51	10
Ph, *S*,*S*,*S*	*o*-I	55	65
t-Bu, *S*,*S*,*S*	*p*-NO_2	2	0
t-Bu, *S*,*R*,*S*	*p*-NO_2	0	0
Bn, *S*,*S*,*S*	*p*-NO_2	63	72
Bn, *S*,*R*,*S*	*p*-NO_2	70	22
Bn, *S*,*S*,*S*	*o*-I	61	18
Bn, *S*,*R*,*S*	*o*-I	61	36

synthesis and use of biaryl bis-oxazolines as ligands for the reaction. While the vast majority of bis-oxazoline ligands are methylene and pyridyl linked, Corey first reported a biaryl bis-*o*-tolyl ligand for a highly selective intramolecular cyclopropanation leading to (−)-sirenin.[91] We developed two asymmetric Ullman coupling routes to both the binaphthyl and bi-tolyl ligands variants as convenient alternatives to preparative chiral HPLC that was required previously.[92] The non-equilibrating atropisomeric biaryl bond adds another stereochemical element. In addition the longer tether connecting the two oxazolines creates a smaller, more narrow metal bite angle upon coordination.[93] This effect is intended to crowd the reacting allyl and benzoate groups and create a higher difference in energy between the two transition states leading to product. While the end result turned out not to be a further improvement in selectivity, much was learned concerning the relationship between the ligand and the perester. Both atropisomeric series of ligands were made using a range of side chain groups including phenyl, *tert*-butyl, benzyl, and *iso*-propyl. Copper(I) and the ligand were used at

Table 17. Cyclohexene oxidation with bi-*o*-tolyl-bis-oxazoline–copper complexes



Ligand, R	Perester, Z	Yield (%)	% ee
Ph, *S*,*S*,*S*	*p*-NO_2	78	73
Ph, *S*,*R*,*S*	*p*-NO_2	76	0
Ph, *S*,*S*,*S*	*o*-I	63	71
Ph, *S*,*S*,*S*	2,4,6-Cl_3	20	11
t-Bu, *S*,*S*,*S*	*p*-NO_2	5	18
t-Bu, *S*,*R*,*S*	*p*-NO_2	0	0

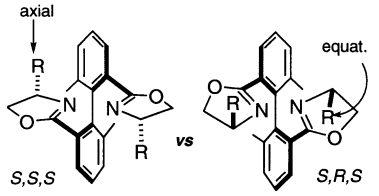
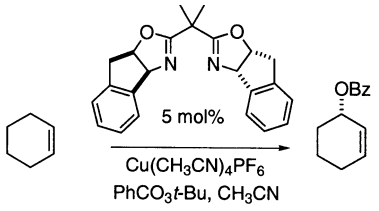


Figure 17. Comparison of biaryl-bis-oxazoline atropisomeric ligands.

10 mol% in acetonitrile at −20°C. The reactions were performed for 5 days. The *S*,*S*,*S*-diphenyl ligand with cyclopentene gave moderate 69 and 65% ee with *p*-nitro and *o*-iodoperesters (Table 16).[94] In contrast, the atropisomeric *S*,*R*,*S*-ligand gave lower selectivity at 10% ee. Both atropisomeric di-*tert*-butyl ligands gave very low reactivity and selectivity. The dibenzyl case is interesting in that now the *S*,*R*,*S*-ligand was best using *o*-iodoperester.

The selectivity with cyclohexene using the biaryl bis-oxazolines is even more widely divergent (Table 17). Diphenyl *S*,*S*,*S*-ligand with *p*-nitroperester gave a high yield of ester product with good 73% ee selectivity. The *S*,*R*,*S*-ligand in this case also gave a high yield but the product was racemic. Chloroperesters were shown to be very effective previously, but now 2,4,6-trichloroperester has poor reactivity and selectivity with the *S*,*S*,*S*-diphenyl ligand. Again both isomers of the *tert*-butyl ligand are poor in reactivity and selectivity. The lower reactivity of the *S*,*R*,*S*-ligands can be rationalized by considering the complex conformations

Table 18. Cyclohexene oxidation with perbenzoate and aminoindanol derived bis-oxazoline–copper complex



T (°C)	Time (day)	Yield (%)	% ee
40	1	65	69
40, +4 MS	1	76	71
0	21	48	78

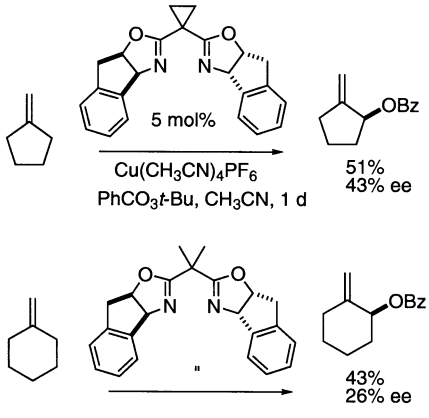


Figure 18. *Exo*-methylene oxidation with aminoindanol derived bis-oxazolines.

(Fig. 17). The *S*,*S*,*S*-isomer, with metal complexed, has the side chain groups R arrayed in pseudo-axial positions, parallel to the biaryl σ-bond. This C_2-arrangement creates distinct binding quadrants for the allyl and benzoate groups where two opposing quadrants are sterically encumbered by the R groups and two quadrants that are unencumbered. Placement of the allyl and benzoate groups in the quadrants away from the R groups leads to the *S*-ester product as before. The *S*,*R*,*S*-ligand conformation places the R groups in equatorial positions. This creates two equally encumbered hemispheric regions where there is now little or no difference between the transition states leading to product. The narrow bite angle in both cases, with *tert*-butyl as the side chain, creates a very crowded metal coordinating environment leading to poor reactivity and selectivity.

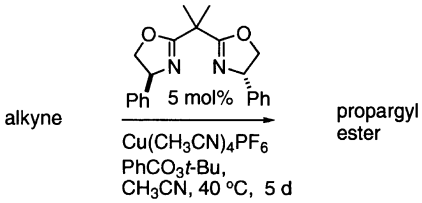
Clark and co-workers recently explored various aminoindanol-derived bis-oxazolines using copper(I) hexafluorophosphate–acetonitrile conditions (Table 18, Fig. 18).[95] The best linking group was the malonyl *gem*-dimethyl functionality shown. When the reaction was performed at 40°C for 1 day, cyclohexene was converted to ester with good selectivity, 69% ee. Molecular sieves gave slight improvement, while lower temperature for an extended time gave product with 78% ee.

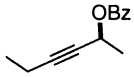
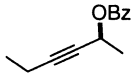
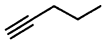
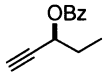
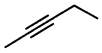
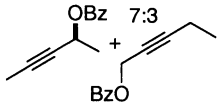
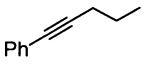
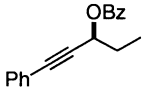
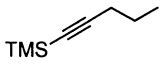
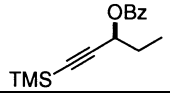
Other linking groups, methylene, 1,1-cyclopropyl, 1,2-phenyl, and 2,6-pyridyl gave lower selectivities. Asymmetric allylic oxidation was also performed for the first time with cyclic *exo*-methylene substrates in this study. The major product maintains the *exo*-cyclic olefin. Cyclopropyl linked aminoindanol bis-oxazoline was found to be best with *exo*-methylene cyclopentane at 43% ee, while the *gem*-dimethyl ligand used before was optimal for *exo*-methylene cyclohexane. Improvements in selectivity are eagerly anticipated with this class of substrates due to the high synthetic potential they promise.

Asymmetric propargyl oxidation of alkynes was also reported by Clark and co-workers (Table 19).[96] Kropf and co-workers previously reported the first general study of propargyl oxidation using the Kharasch conditions and unligated copper salts.[97] Various ligands including the above mentioned aminoindanol derived bis-oxazolines were explored by Clark. The best conditions found employed biphenyl bis-oxazoline with copper(I) at 40°C in acetonitrile. 3-Hexyne reacted in excess to give propargyl benzoate product in high yield, 80%, but with low selectivity 20% ee. 1-Pentyne, reacted with the perester in excess, again gave product with low selectivity. The unsymmetrical substrate 2-pentyne produced a 7:3 mixture of regioisomeric products with the secondary, internal ester dominant. Again the selectivity was low at 15% ee. 1-Phenyl and 1-trimethylsilyl-1-pentyne, with perester used in excess, gave product in high yield and with moderate selectivity, 51 and 46% ee. The synthetic potential of these products will lead to the investigation of other ligands and conditions.

An interesting follow-up to the work from the Pfaltz lab is a recent paper by Fahrni describing the use of various dinuclear copper complexes.[98] Few dinuclear complexes have been explored in the context of asymmetric catalytic

Table 19. Alkyne oxidation with perester and bis-oxazoline–copper catalyst



Substrate	Sub/perester	Ester	Yield (%)	% ee
	5:1		80	21
	1:1		38	21
	1:4		43[a]	20
	5:1		73	15
	1:4		95[a]	51
	1:4		92[a]	46

[a] Yield based on alkyne.

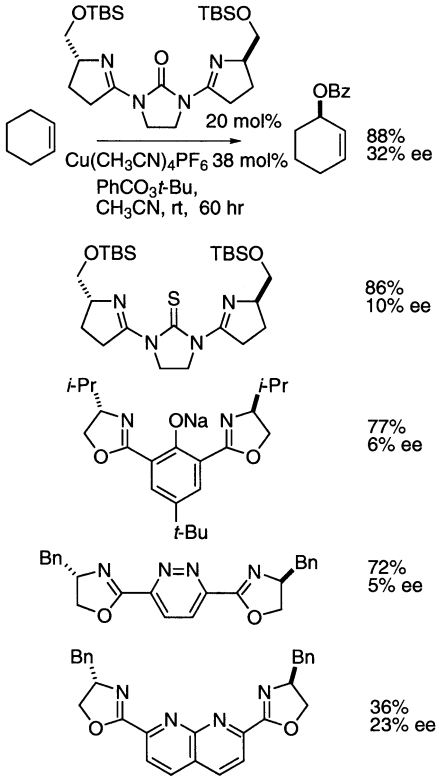


Figure 19. Cyclohexene oxidation with dinuclear copper complexes.

olefin oxidation. Known enzymatic based processes include methane monoxygenase that consists of a dinuclear iron complex in the active site and an iron(III)-peroxocomplex that has been used for hydrocarbon oxidation.[99] The best results were obtained when 38 mol% copper(I) was added to 20 mol% ligand (Fig. 19). The imidazolidone gave the highest selectivity at 32% ee while all others were lower. Reactivity remained high except for the diazanaphthalene ligand. When copper and ligand were used at 1:1 stoichiometry both the yields and selectivities were significantly decreased supporting the idea that the most active catalyst in this case is a dinuclear metal complex.

Further work from the Katsuki lab includes an intriguing study with cyclopentadiene dimer type substrates.[100] The racemic acetonide protected cyclopentadiene diol was reacted with 5 mol% tripodal ligand–copper complex to give a mixture of three products (Fig. 20). Secondary ester from the achiral allyl radical intermediate was formed in 36% yield with 80% ee selectivity. Tertiary ester product from the chiral radical also formed in 36% yield but with much lower 12% ee selectivity. A small amount, 6%, of the secondary product from this intermediate was also formed with moderate selectivity. Only *exo* products were observed as seen previously with the above-mentioned pinene substrates. Cyclopentadiene dimer also reacted giving secondary ester with good selectivity along with racemic tertiary ester. While there is not much preference for the formation of the allyl radical intermediates in this case, the selectivities of the ester products differ greatly. The usual preference for tertiary hydrogen atom abstraction is thwarted in this case by the close proximity of the tertiary

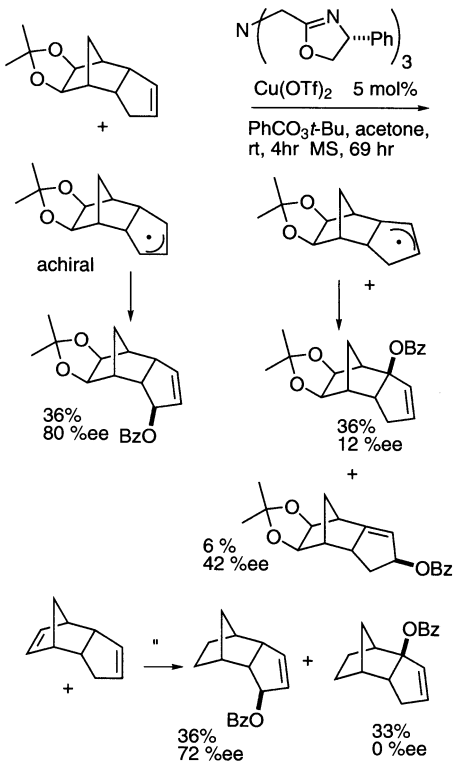


Figure 20. Cyclopentadiene dimer oxidation with trisoxazoline copper catalyst.

allylic hydrogen to the hindered bridgehead position. Oxidation of the achiral radical is highly selective while the oxidation of the more substituted racemic allyl radical occurs with low selectivity. This is most likely due to the fact that attack of the chiral radical occurs at a position adjacent to the ring fusion position while attack of the racemic radical is two carbons removed from this position. By being proximal to the substrate stereocenters, the copper(II) complex can differentiate between the two ends of the radical to a greater degree.

Katsuki and Kohmura have also recently improved the tripodal ligand by producing the carbon analog of the trisoxazoline (Fig. 21).[101] The methine linked ligand, unlike the previous tertiary amine tripodal ligand, produces product

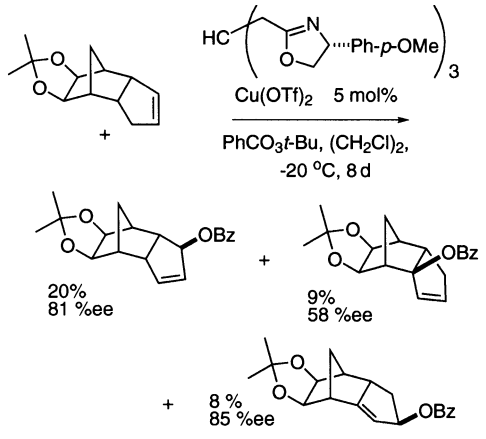
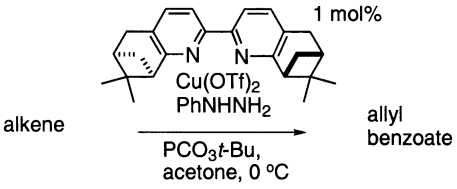
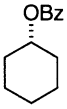
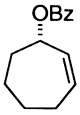


Figure 21. Cyclopentadiene dimer oxidation with methine-linked trisoxazoline copper catalyst.

Table 20. PINDY–copper complexes with phenylhydrazine additive



Alkene	Time (h)	Ester	Yield (%)	% ee
	12		80	59
	0.5		96	49
	0.5		88	62

with a range of olefins with high selectivity. Although the yields are low, 13 and 25%, both cycloheptene and octene now give high selectivities at 92 and 85% ee. D-amino acids were used for the oxazolines leading to *R*-ester products in this case. Again the metal was copper(II) triflate reacted in 1,2-dichloroethane at −20°C for 8 days. Racemic cyclopentadiene was also oxidized and products were obtained with a higher preference for the secondary ester from the racemic allyl radical. The use of phenyl hydrazine in acetone proved detrimental to the reaction in these cases.

Kocovsky and co-workers have recently developed an interesting bipyridine ligand derived from (−)-β-pinene.[102] Allylic oxidations have been performed using copper(II) triflate and phenyl hydrazine following the method of Singh in acetone at 0°C (Table 20).[75] Short reaction times were again found and ester products were produced in excellent yields, however the selectivities were only modest.[103] Undoubtedly, other variations will be attempted in an effort to improve the selectivity with this highly reactive new system.

Biaryl oxazoline ligands have been developed recently that include a naphthylquinazoline and an isoquinoline (Fig. 22).[104] The design principle was to maintain two-point binding together with a biaryl 'fence' and a single oxazoline. The naphthylquinazoline oxazoline was made in two isolable atropisomeric forms. The *S*,*S*-ligand shown gave a low yield of product with cyclohexene and low selectivity. Bidentate complexation with copper with this ligand involves a 7-ring chelate. The two phenyl groups in this case may lead to excessive crowding accounting for the low reactivity. The naphthyl isoquinoline oxazoline, which exists as an inseparable freely rotating compound, gave product with only slight improvement. The 5-ring chelate in this case is far less encumbered giving enhanced reactivity. Both the yield and selectivity were dramatically improved in this case when phenylhydrazine in acetone were used giving 37% product with 64% ee selectivity and the time of reaction was greatly reduced to 6 h at room temperature. In previous cases using the biaryl

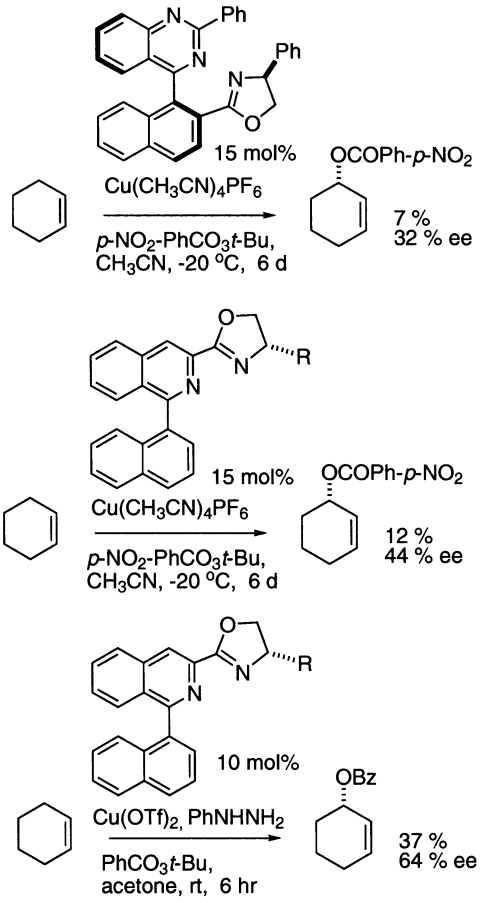


Figure 22. Use of new biaryl ligands, quinazoline–oxazoline and naphthyl-isoquinoline oxazoline.

bis-oxazolines, the hydrazine–acetone conditions were not advantageous. Only the phenyl side chain ligands have been attempted to this point with these new ligands. Other quinazoline and isoquinoline oxazolines may prove to be more reactive and selective. Other recent studies with new ligands include a bipyridine ligand[105] and a quinoline–oxazoline ligand[106] that give product with moderate selectivity.

Recently, our group has reinvestigated the *gem*-dimethyl linked bis-oxazolines with a wider array of substitutions, both at the side chain R group, and at the malonyl central carbon, together with various peresters (Fig. 23).[107] While new ligands have offered certain advantages, overall, the most effective ligands have been the *gem*-dimethyl linked bis-oxazolines. We hoped to uncover more selective ligand–perester combinations. Very favorable preliminary results include use of the previous diphenyl *gem*-dimethyl ligand reacting with *p*-nitro perester in acetonitrile for 17 days to give cyclohexene benzoate in 96% ee. This is the highest reported selectivity in this case. The yield, again based on the perester, was moderate at 44% using excess olefin. The previous high selectivity obtained above 90% ee was obtained with only very poor yields. The best combination for cyclopentene is now 98% ee obtained using the previously unexplored *gem*-diethyl diphenyl ligand with a moderate yield of 54%. Other combinations and experimental details, will appear shortly.

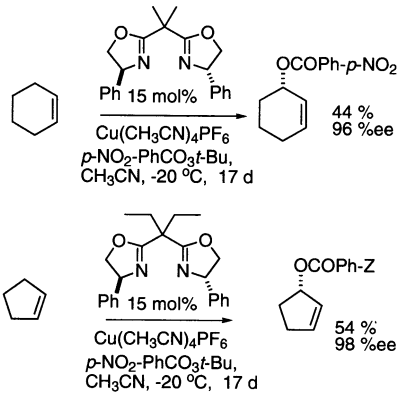


Figure 23. Favorable enantioselectivities with malonyl bis-oxazolines and nitroperestrer.

The asymmetric copper catalyzed Kharasch reaction using peresters to transform simple olefins into useful allylic esters has now reached a high degree of development. The most successful ligands to date are bis-oxazolines that produce selectivities in the excellent range with many substrates. There is no universal ligand, and there probably never will be a single ligand, that gives high selectivity with a wide range of substrates. Each substrate has to be fine tuned for the ligand and conditions. Additives have been identified that can increase the rate of reaction and maintain good selectivities. Innovations to solve key problems include improving catalyst turnover, lowering the catalyst loading with more stable and reactive ligands, finding ligands that are highly selective and specific to individual substrates, and simplifying the recovery and recycling of the ligand.

Mechanistic work that needs to be done includes the identification of the step responsible for controlling the ester stereocenter and the nature of the seven membered rearrangement step. Theoretical work also remains including the determination of the coordination states of the intermediate complexes, together with the copper oxidation states, geometries, and their viability in the catalytic cycle. As these issues are successfully addressed, asymmetric allylic oxidation may take its place along side epoxidation and dihydroxylation as a preparatively useful standard transformation.

Acknowledgements

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Biographical sketch

Merritt B. Andrus is a native of Burbank, California. His older brother Alex, now at Applied BioSystems, Foster City, CA, inspired him to become a chemist at an early age. He received a BS degree in chemistry from Brigham Young University in 1986 doing undergraduate work with Professor Jerald S. Bradshaw. In 1991, he received PhD in organic chemistry from the University of Utah with Professor Gary E. Keck working with asymmetric allyl stananne additions. From 1991 to 1993, he was an NIH sponsored postdoctoral fellow in the laboratory of Professor Stuart L. Schreiber at Harvard University working on the design and synthesis of FK506-like compounds. In 1993, he became an assistant professor in the Department of Chemistry at Purdue University in West Lafayette, IN. In 1997, he and his group moved back to Provo, Utah, where he is now an associate professor in the Department of Chemistry and Biochemistry at Brigham Young University. Areas of research continue to be synthetic methodology, natural product synthesis, and combinatorial chemistry and figuring out how best to raise his five kids. The work in his lab has been supported by the NIH, NSF, The American Chemical Society, The American Cancer Society, and Procter and Gamble.

Jason C. Lashley received a BS degree in chemistry and mathematics from College of the Ozarks in 1994 doing undergraduate work in organofluorine chemistry with Professor Jerry Easdon. He joined the Andrus research group at Purdue University and received a PhD in physical chemistry from the Brigham Young University with Professor Brian Woodfield, Professor Merritt Andrus, and Dr James L. Smith working with the preparation of organic superconductors and the low-temperature specific heat of actinide single crystals. He is a staff member of the structure and properties relations group where he continues to study the low-temperature thermodynamics of actinides, martensitic transformations, and heavy fermion materials. For his work, he was awarded the 1999 Distinguished Performance Award at Los Alamos.