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REVIEW

Enantioselective Allylic C–H Bond Oxidation of Olefins Using Copper Complexes of Chiral Oxazoline Based Ligands

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Abstract
This review article discusses historical and contemporary research studies of asymmetric allylic oxidation of olefins using homogeneous and heterogeneous copper complexes of various kinds of oxazoline-based ligands, until the end of 2021. It is revealed that this strategy is a powerful method to form a new stereogenic center bearing an oxygen substituent adjacent to an unchanged C=C bond. Enantioselectivities as well as chemical yields, and also the reactivity, are strongly dependent on the type of substrate, oxidant, the copper salt and its oxidation state, ligand structure, temperature, nature of the solvent, and additives such as phenylhydrazine and porous materials.

Keywords Asymmetric allylic C–H bond oxidation · Copper complexes of chiral oxazoline ligands · Olefin · Perester · Allylic ester

1 Introduction

In 1958, Kharasch and Sosnovsky [1–3] introduced non-stereoselective allylic oxidation of olefins using *tert*-butyl peroxybenzoate and catalytic amounts of copper (I) bromide in refluxing benzene. This process led to the formation of allylic esters with moderate-to-high yields (50–80%) and relatively good regioselectivity of the internal secondary ester over the terminal primary ester at a ratio of 9:1 (Scheme 1).

The asymmetric version of allylic C–H bond oxidation of olefins (known as enantioselective Kharasch–Sosnovsky reaction) giving access to chiral allylic esters and, after hydrolysis or reduction, chiral allylic alcohols, is a valuable asymmetric transformation for synthetic organic chemists, where, unlike the hydroxylation and epoxidation, the second functional group forms while the double bond remains unchanged. The resulting olefinic products can also be further

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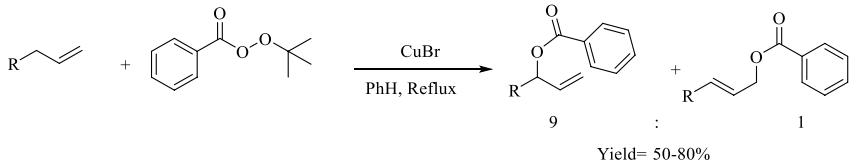
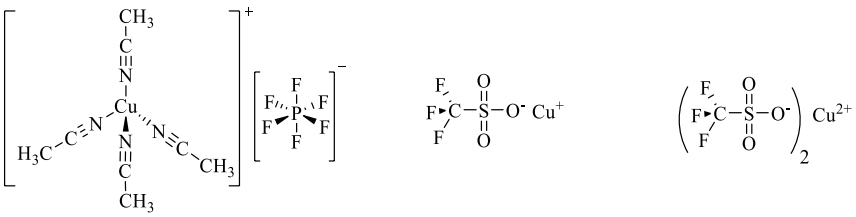


Scheme 1 Non-stereoselective allylic oxidation of olefins with *tert*-butyl perbenzoat in the presence of CuBr by Kharasch and Sosnovsky

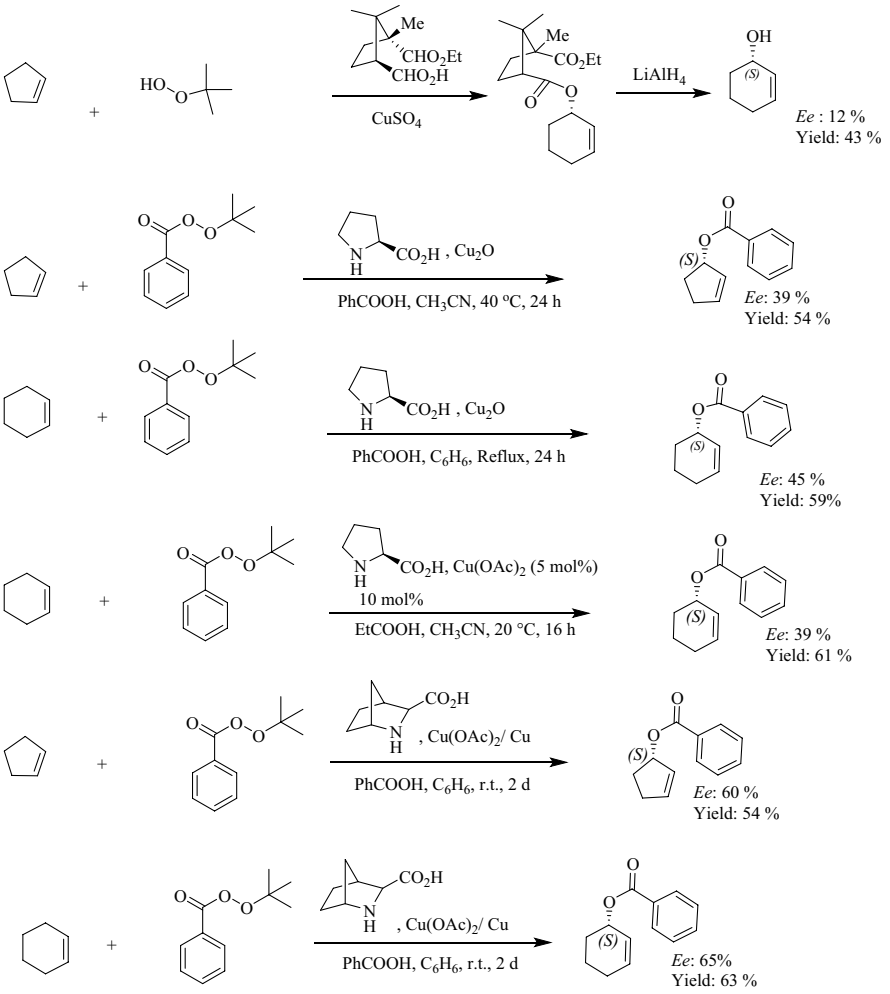
functionalized to afford a variety of desirable compounds. This enantioselective process is attractive, as it employs simple and inexpensive olefins. The reaction is carried out in the presence of a catalytic amount of various types of metal catalysts, particularly copper salts [4–9].

This enantioselective transformation is depends largely on the nature of the ligand, perester, type of metal and its oxidation state, counter anion, temperature, solvent, and additive. These factors affect the rate, enantioselectivity and also the yield of the reaction. There is a special focus on chiral copper catalysts because of their superior efficiency in terms of reactivity, yield, and selectivity. It worth mentioning that the active copper species involved in the allylic oxidation reactions is copper (I), so common copper salts that are used in this reaction are copper (I) salts. However, in some cases, copper (II) salts show satisfactory results. Furthermore, experimental results have shown that $Cu(CH_3CN)_4PF_6$, CuOTf and $Cu(OTf)_2$ are frequently used copper salts that are capable of complexing with the appropriate ligands for construction of efficient chiral catalysts [4–9] (Scheme 2).

Although this review focuses on oxazoline-based copper catalysts, it has to be mentioned that other various chiral copper complexes have been used as catalysts in the Kharasch–Sosnovsky reaction. Chiral carboxylic acids [10], proline [11–13] and bicyclic amino acids based on the proline skeleton [14, 15] have given modest enantioselectivities and yields. For instance, cyclohexene and cyclopentene in the presence of a copper-bicyclic proline complex using *t*-butyl perbenzoate at room temperature were oxidized to the corresponding



Scheme 2 Most efficient copper salts in the asymmetric allylic oxidation



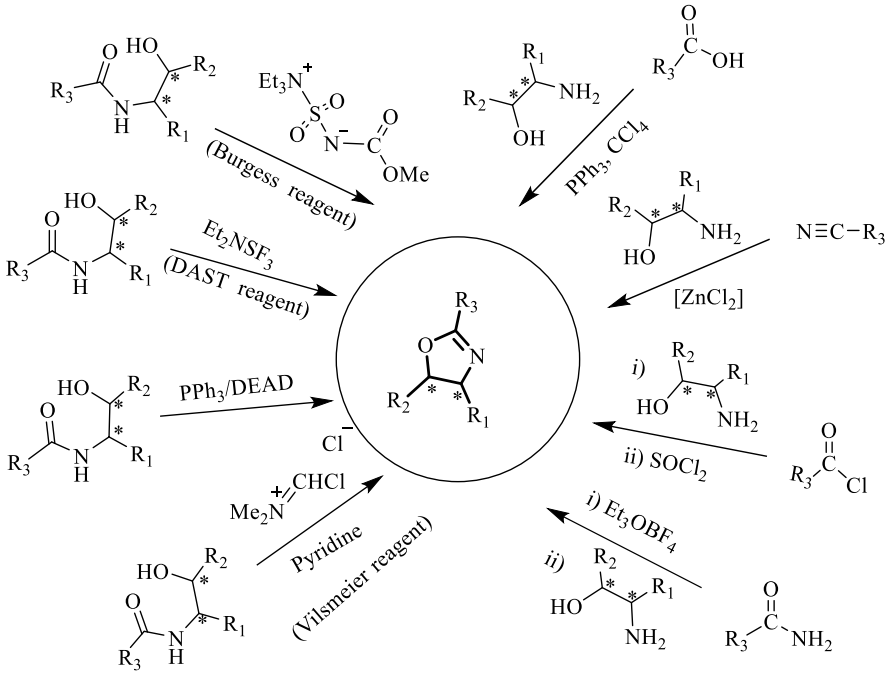
Scheme 3 Using chiral carboxylic acids, proline, and bicyclic amino acids ligands in the asymmetric allylic oxidation

(*S*)-benzoates in moderate yields with enantioselectivities of 60% and 65% *ee*, respectively (Scheme 3). It should be noted that this type of chiral ligands has been rarely studied in allylic oxidation, presumably because of the higher efficiency of oxazoline ligands.

Furthermore, in recent years, new non-oxazoline ligands like (iminophosphoranyl)ferrocenes [16], C_2-symmetric 1,10-phenanthrolines [17], C_1- and C_2-symmetric bipyridineligands [18], aza-arene cis-dihydrodiol-derived 2,2′-bipyridine ligands [19], aldimine ligands [20], C_1-pyridyl–thiazole ligands [21], *N*,*N*-bidentate and *N*,*N*,*N*-tridentate pyridine-based ligands [22], diamino alcohols [23], polyfluorous proline [24, 25] and proline [26, 27] have been employed, which,

in some cases, are able to provide chiral products with enantioselectivities and yields in almost the same ranges as oxazoline-based ligands. However, in general, oxazoline moieties have proved to be the chosen ligands due to their specific characteristics, which make them one of the most privileged chiral ligand classes in a wide range of enantioselective transformations. Their accessibility, as well as the potential to modify the structure, can be considered as remarkable aspects of oxazoline ligands, which allow fine-tuning of the ligand structure for a specific application. Besides, the presence of a stereocenter close to the donor nitrogen atom creates a well-ordered chiral environment at the catalytic site [28, 29]. Accordingly, oxazoline-based ligands have been applied frequently in asymmetric allylic oxidation and provided chiral allylic esters in excellent yields and enantioselectivities. These versatile ligands can be prepared easily from reaction of carboxylic acids or derivatives thereof and also nitriles with chiral β-amino alcohols, usually obtained from the reduction of natural amino acids, although different synthesis methods have been developed [30–42] (Scheme 4).

In the present review, we will summarize all the progress in asymmetric allylic oxidations of olefins catalyzed by chiral oxazoline-based homogeneous and heterogeneous Cu catalysts until the end of 2021, including all aspects of this valuable asymmetric transformation.



Scheme 4 Various synthetic routes for the preparation of chiral oxazoline ligands

2 The Mechanism of Allylic C–H Bond Oxidation of Olefins

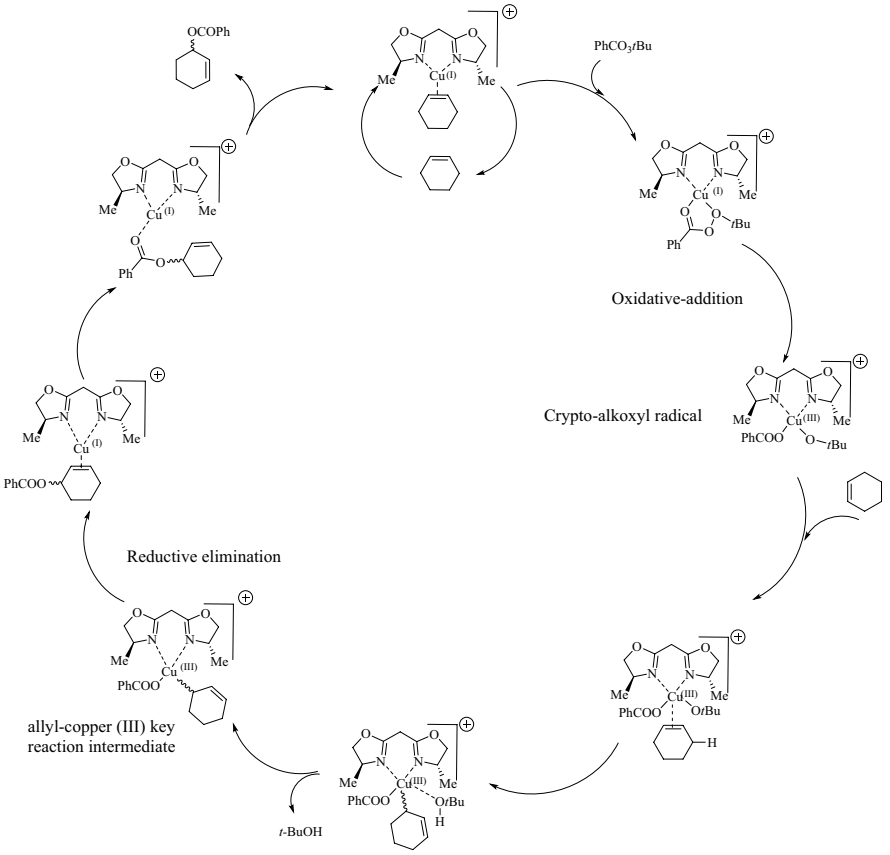
The mechanism of allylic C–H bond oxidation of olefins has been studied extensively by several research groups, e.g., Kochi [43–46], Walling [47, 48], Beckwith [49], Salvatella [50], Slough [51], and Bao [52]. In the beginning, a chiral catalyst would be formed by addition of copper salt to the chiral ligand, then a multi-step mechanism occurs upon addition of the required compounds through a catalytic cycle with chang in the oxidation state of the Cu atom. In a non-coordinating solvent, the copper (I)-alkene complex is the main component [50, 51, 53]. The catalytic cycle begins by replacing the alkene with perester, *tert*-butyl perbenzoate, which coordinates to the copper (I) through two of its oxygen atoms to generate a perester-copper (I) complex. In a subsequent step, the copper (I) is oxidized to copper (III) and a crypto-alkoxyl radical is formed through oxidative-addition of the oxygen–oxygen bond of the perester [50]. It should be noted that there is ample evidence in the literature suggesting that the reaction proceeds via a free radical intermediate, and most of the mechanisms rely upon the participation of a *tert*-butoxyl free radical [43–49]. Hereupon, alkene is again coordinated to the copper (III) complex and thereafter, in a limiting step, allylic hydrogen of the alkene is abstracted intramolecularly by a crypto-alkoxyl radical. As a result, the obtained complex can release *tert*-butyl alcohol to form a key allyl-copper (III) reaction intermediate. Subsequently, by a pericyclic rearrangement of the resulting allyl-copper (III) intermediate through a stereospecific reductive-elimination including the migration of a π-bond, a product–catalyst complex can be formed. Finally, the initial alkene–catalyst complex is regenerated by releasing the chiral allylic ester as the reaction product through exchanging it with alkene (Scheme 5).

3 Asymmetric Allylic Oxidation Using Chiral Oxazoline Based Catalysts

3.1 Homogeneous Catalysts

3.1.1 Comprehensive Studies

In 1995, the use of oxazoline ligands in asymmetric allylic oxidation of olefins was investigated independently by the research groups of Pfaltz [54] and Andrus [55]. These groups studied chiral Cu-bisoxazoline complexes in the allylic oxidation of cyclic and linear olefins in the presence of peresters, leading to the corresponding chiral allylic esters in good enantioselectivities and yields. Pfaltz and coworkers evaluated asymmetric allylic oxidation of some substrates such as cyclopentene, cyclohexene, and cycloheptene using malonyl bisoxazoline **1a–c** and pyridine bisoxazoline (Pybox) ligand **2a** in the presence of copper salts such as copper (I) triflate, copper (II) triflate, and copper (I) hexafluorophosphate

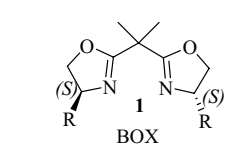


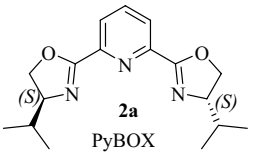
Scheme 5 Mechanism of allylic C–H bond oxidation

in polar solvents like acetone and acetonitrile at the temperature range of −20 to +50 °C [54]. The results revealed that conducting the reactions at low temperatures (Table 1, entries 4 and 8), especially in the presence of ligand **1c**, containing bulky *t*-butyl groups at the stereogenic centers, led to the improvement in enantioselectivity. It seems that, under these circumstances, the bulkier the groups, the higher the enantioselectivities. In terms of copper salts and solvents, the best enantioselectivities were achieved using copper (I) triflate in bi-solvent systems acetonitrile/chloroform (3:1) (Table 1, entry 4) and acetone/chloroform (3:1) (Table 1, entry 8). Almost the same results were achieved using copper (I) hexafluorophosphate or copper (I) triflate, while copper (II) triflate showed low activity and enantioselectivity. Generally, counter ions and oxidation states of copper not only have a great impact on the enantioselectivity but could also affect the reactivity of the catalyst and the yields of the chiral products.

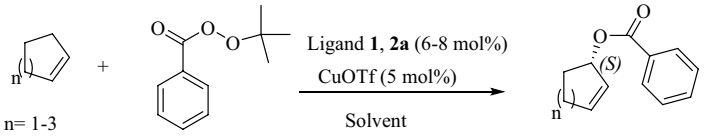
Employing 1-methyl cyclohexene as a substituted cycloolefine resulted in allylic esters with good enantiomeric excess, but low regioselectivity. It should

Table 1 Using bisoxazoline-CuOTf in asymmetric allylic oxidation





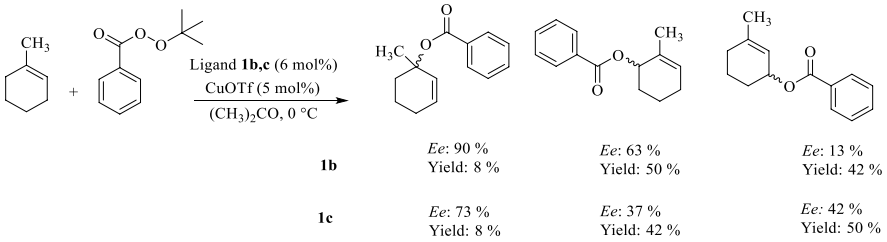
R = a: Ph, b: *i*-Pr, c: *t*-Bu



Entry	*n*	Ligand	Solvent	T (°C)	Time (d)	Yield (%)	*Ee* (%)
1	1	**1b**	$CH_3CN/CHCl_3$	23	4	74	74
2	1	**1b**	$CH_3CN/CHCl_3$	7	12	81	77
3	1	**1b**	$(CH_3)_2CO/CHCl_3$	0	14	76	75
4	1	**1b**	$(CH_3)_2CO/CHCl_3$	− 20	22	66	82
5	1	**1c**	$CH_3CN/CHCl_3$	23	4	68	74
6	1	**1c**	$CH_3CN/CHCl_3$	7	12	65	79
7	1	**1c**	$CH_3CN/CHCl_3$	0	12	64	80
8	1	**1c**	$CH_3CN/CHCl_3$	− 20	22	61	84
9	1	**1a**	$(CH_3)_2CO/CHCl_3$	23	5	84	71
10	2	**1b**	$(CH_3)_2CO/CHCl_3$	50	1	71	58
11	2	**1b**	$(CH_3)_2CO/CHCl_3$	23	3	69	64
12	2	**1b**	$CH_3CN/CHCl_3$	23	9	64	61
13	2	**1c**	$CH_3CN/CHCl_3$	50	1	44	51
14	2	**1c**	$CH_3CN/CHCl_3$	23	7	68	60
15	2	**1c**	$CH_3CN/CHCl_3$	7	15	64	77
16	2	**1a**	$(CH_3)_2CO/CHCl_3$	23	3	77	67
17	2	**2a**	$CH_3CN/CHCl_3$	23	3	80	71
18	3	**1b**	$CH_3CN/CHCl_3$	50	2	57	69
19	3	**1b**	$CH_3CN/CHCl_3$	23	3	75	74
20	3	**1b**	$CH_3CN/CHCl_3$	7	14	44	82

be noted that the chiral allylic esters that formed through oxidation of the methyl-substituted C atom were obtained in poor yield but high enantiomeric excess (Scheme 6).

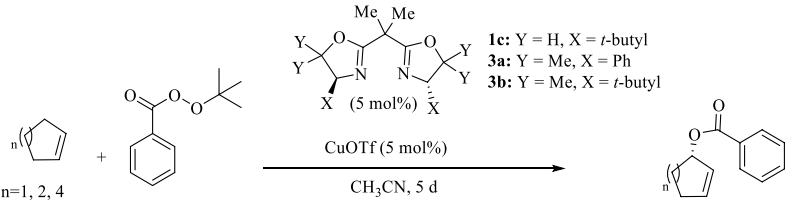
In a similar study by Andrus and colleagues [55], when the reaction was carried out in the presence of 5 mol% of bisoxazoline **1c**-CuOTf as catalyst at −20 °C in CH_3CN instead of a bi-solvent system, chiral allylic esters were obtained with moderate yields but in almost the same enantioselectivities reported by Pfaltz et al. [54].



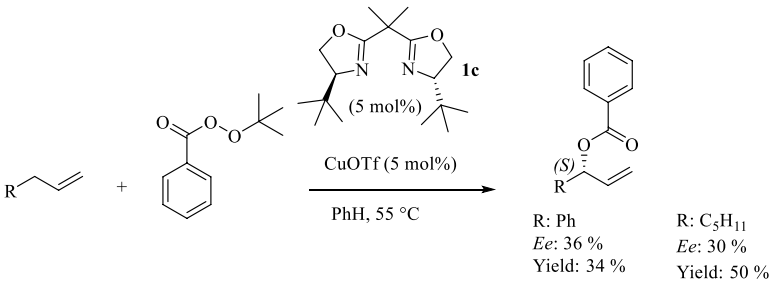
Scheme 6 Asymmetric allylic oxidation of 1-methyl cyclohexene using bisoxazoline **1b,c**-CuOTf

Besides, it is noteworthy that the reaction was completed in a shorter time. Further studies have revealed that the oxazoline ligand **1c** could not be recycled and reused, presumably due to its decomposition during the oxidation process. It had been assumed that, the CH_2 group in the oxazoline ring has the potential to be oxidized under reaction conditions, which can affect catalyst efficiency. To avoid this problem, Andrus designed bis-gem-dimethyl bisoxazolines **3a** and **3b**, which were stable ligands under reaction conditions, by replacing the both hydrogens with methyl groups (Table 2). In the presence of ligand **3a**, oxidation of cyclopentene proceeded with 81% enantiomeric excess, whereas this substrate with ligand **3b** was oxidized in much lower enantiomeric excess of 42% (Table 2, entries 2 and 3). In the case of cyclohexene, ligand **3b** showed much better efficiency than **3a**, but, in contrast

Table 2 Effect of CH_2 protected bisoxazolines on allylic oxidation



Entry	*n*	Ligand	*T* (° C)	Yield (%)	*Ee* (%)
1	1	**1c**	− 20	44	70
2	1	**3b**	− 20	41	42
3	1	**3a**	− 20	49	81
4	2	**1c**	5	62	67
5	2	**1c**	− 20	43	80
6	2	**3b**	− 20	49	67
7	2	**3a**	5	59	46
8	2	**3a**	− 20	44	47
9	4	**1c**	− 20	44	13
10	4	**3b**	− 20	43	0



Scheme 7 Acyclic chiral allylic ester formation catalyzed by bisoxazoline **1c**-CuOTf

to cyclopentene, the best enantioselectivity was obtained with **1c** (Table 2, entries 4–8). The enantioselectivities were even lower for cyclooctene (Table 2, entries 9 and 10). This drop in enantiomeric excess could be explained by the fact that the bigger ring systems might be too bulky to fit in the catalyst complex cavity, which is determined by two substituents on the bisoxazoline.

However, acyclic substrates such as allylbenzene and 1-octene did not give satisfactory results. Allylic oxidation of allylbenzene using ligand **1c**-copper (I) in acetonitrile at low temperature proceeded with 50% yield, and the corresponding chiral allylic ester was obtained in racemic form. Surprisingly, at higher temperatures (55 °C) in the non-polar solvent of benzene, the enantioselectivity increased to 36% and 30% for both allylbenzene and 1-octene, respectively (Scheme 7).

A selectivity model, proposed for the reactions of cyclohexene and acyclic substrates [55], is shown in Fig. 1. The Cu(III) intermediates adopt a distorted square planar coordination geometry. The rearrangement leading to the product delivers the benzoate to the internal position of the acyclic olefin or to the distal position of the cycloalkene. In the favored transition states, the benzoate and allyl groups are positioned in such a way that repulsive steric interactions with the adjacent *tert*-butyl groups of the bisoxazoline ligand are minimized. With cyclic alkenes, the reaction of the Cu(II) intermediate with the allyl radical can produce two diastereomeric allyl complexes. The enantioselectivity in this case may result from stereoselective

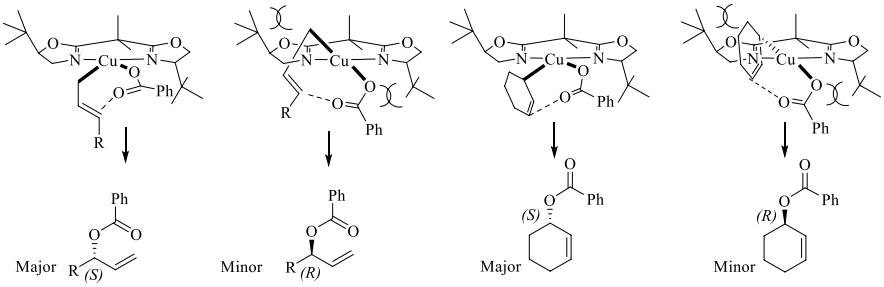
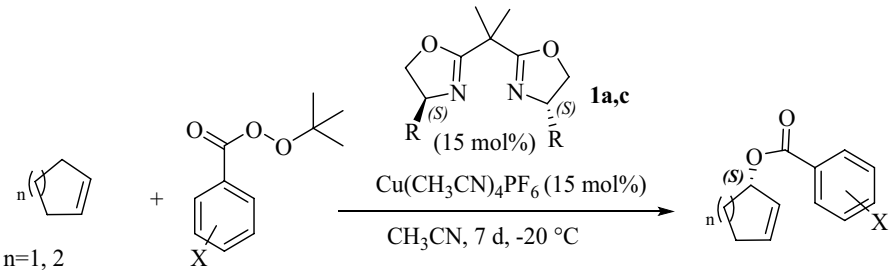


Figure 1 Proposed selectivity model for allylic oxidation of cyclic and acyclic olefins in the presence of **1c**

formation of the Cu(III)-allyl complex followed by a stereospecific rearrangement. Alternatively, if the two diastereomeric Cu(III) complexes equilibrate rapidly, the enantioselectivity may be induced by kinetic discrimination of the two possible rearrangement pathways leading to the major and minor product enantiomers. In the reaction of acyclic terminal olefins, only one allyl complex is formed. In this case, the rearrangement must be the enantioselective step. The lower enantioselectivity of acyclic olefins may be explained by their greater conformational flexibility, making both olefin faces easily accessible.

As it was observed, allylic oxidation of cycloolefins generally proceeds slowly. To solve this challenging issue, Andrus introduced a new category of peresters containing withdrawing substituents on the phenyl ring. It was supposed that withdrawing substitutions can weaken the oxygen–oxygen bond in the perester, causing acceleration of *tert*-butoxy radical formation, and consequently increasing the rate of reaction. In this case, reactivity was not increased; however, the yields and *ee*s were similar to those obtained using unsubstituted perester [54, 55] (Table 3 vs Tables 1, 2). It was also found that enantiomeric excesses will be simply enhanced when the mole percentage of the copper–ligand complex was raised. In the oxidation of cyclohexene with para-nitroperbenzoate, for example, the increasing amount of catalyst **1c** from 5 mol% to 15 mol% not only improved stereoselectivity from 63% to 76% but also enhanced the yield considerably (Table 3, entry 7 vs 9). Furthermore, the effect

Table 3 Effect of substituted peresters on allylic oxidation of cyclopentene and cyclohexene



Entry	Ligand	X	*n* = 1		*n* = 2	
			Yield (%)	*Ee* (%)	Yield (%)	*Ee* (%)
1	**1c**	*p*-Cl	76	57	73	75
2	**1a**	*p*-Cl	82	39	83	75
3	**1c**	*m*-Cl	67	51	46	72
4	**1a**	*m*-Cl	64	29	69	74
5	**1c**	*o*-Cl	76	66	67	73
6	**1a**	*o*-Cl	70	10	78	71
7	**1c**	*p*-NO_2	49	53	60	76
8	**1a**	*p*-NO_2	48	31	71	76
9[a]	**1c**	*p*-NO_2	–	–	34	63

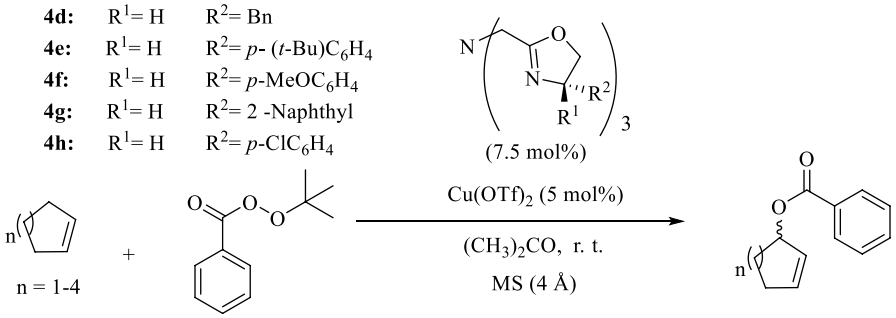
[a]In the presence of 5 mol% of catalyst

of counter anions of copper (I) salts on yield and enantioselectivity revealed that $Cu(CH_3CN)_4PF_6$ is preferred over other Cu salts. It would seem that, due to stronger interactions between more acidic copper salt and allyl radical, high stereoselectivity will be obtained. In optimum conditions at −20 °C and in acetonitrile solvent, the best results (66% *ee*, 76% yield) for cyclopentene were obtained when *o*-chloroperester and ligand **1c** were employed (Table 3, entry 5), whereas the combination of *p*-chloroperester and ligand **1a** was suitable for cyclohexene (75% *ee*, 83% yield) (Table 3, entry 2) [56].

In the same year, in addition to the Pfaltz [54] and Andrus [55] research groups, Katsuki was studying asymmetric allylic oxidation of olefins by applying Cu-oxazoline complexes. This group designed and synthesized a series of tetradentate tris-(oxazoline) ligands **4a–h** containing alkyl and aryl substituents with steric and electronic effects on the oxazoline moiety [57, 58]. Investigation of this kind of ligands under various reaction conditions resulted in desired chiral allylic esters in moderate-to-excellent enantioselectivities. Using a wide range of solvents from non-polar to polar indicated that, contrary to the previous studies, which have suggested acetonitrile as a promising solvent in terms of selectivity, performing the reaction in acetone could contribute to better results. However, the findings did not reveal any clear link between the polarity of the solvent and asymmetric induction. Enantioselectivity of cyclopentene, for example, in toluene and DMF was found in the same range (66% *ee* and 68% *ee*), and even higher than acetonitrile (18% *ee*). Interestingly, inconsistent with Pfaltz and Andrus' findings, Cu (II) gave higher asymmetric induction than Cu (I). It was observed that tris-(oxazoline) bearing aryl groups at the chiral center exhibits remarkable potential for higher *ee*s and yields than other ligands, presumably due to attractive interactions between the aryl substituents and the allyl radical intermediates. Steric and electronic effects also did not lead to better results, although the *p*-methoxy group showed a slight increase in *ee* but the allylic ester was obtained in lower yield (Table 4, entries 6–12). In a comparative study among three different oxidizing reagents, benzoyl peroxide, *t*-butyl hydroperoxide, and *t*-butyl perbenzoate, it was demonstrated that *t*-butyl perbenzoate is a more suitable candidate for achieving chiral allylic products with reasonable enantiomeric excess and yield, which is similar to previous reports. For instance, although *t*-butyl hydroperoxide resulted in (*S*)-cyclopent-2-en-1-yl benzoate, with an acceptable level of enantioselectivity (68%), the yield was poor (21%) and undesired compounds were produced too. In the case of benzoyl peroxide, enantioselectivity was inferior (13%) as well. The effect of temperature on the yield and enantioselectivity of the reaction was also in accordance with earlier studies [54, 55]. In other words, enantioselectivity increased as the reaction temperature decreased. The highest enantioselectivity of 88% at –20 °C was obtained when cyclopentene was used as the substrate, although the yield was very low (11%). In larger substrates like cyclooctene, the corresponding ester with moderate enantioselectivity of 54% in 18% yield was obtained at room temperature. Further studies have shown that longer reaction times have a slightly negative impact on enantiomeric excess [58]. Katsuki et al. reasoned that the Lewis acidity of Cu (II)-**4a** complex, probably makes a contribution to partial racemization in the allylic esters. It was expected that the addition of water could reduce the Lewis acidity of Cu (II) via coordination to copper ion. However,

Table 4 Effect of molecular sieves (MS) on allylic oxidation catalyzed by tetradentate tris-oxazoline-Cu complexes

4a: R^1= Ph R^2= H
4b: R^1= H R^2= *i*-Pr
4c: R^1= H R^2= *t*-Bu
4d: R^1= H R^2= Bn
4e: R^1= H R^2= *p*- (*t*-Bu)C_6H_4
4f: R^1= H R^2= *p*-$MeOC_6H_4$
4g: R^1= H R^2= 2 -Naphthyl
4h: R^1= H R^2= *p*-ClC_6H_4



Entry	Ligand	*n*	Time (h)	Yield (%)	*Ee* (%)	Configuration
1[a,b]	**4a**	1	40	67	66	*S*
2[b]	**4a**	1	40	68	74	*S*
3	**4a**	1	16	83	76	*S*
4[c]	**4a**	1	150	81	83	*S*
5[d]	**4a**	1	200	30	93	*S*
6[b]	**4b**	1	40	8	23	*S*
7[b]	**4c**	1	40	–	–	–
8[b]	**4d**	1	20	–	–	–
9[b]	**4e**	1	20	–	–	–
10	**4f**	1	15	31	81	*R*
11[c]	**4g**	1	50	38	50	*R*
12	**4h**	1	10	60	20	*R*
13	**4a**	2	20	19	42	*S*
14	**4a**	3	90	5	60	*S*
15	**4a**	4	50	11	64	*S*

[a]In the presence of CuOTf

[b]Without MS

[c]Reaction performed at 0 °C

[d]Reaction performed at −20 °C

the reaction in no way made progress in the presence of one equivalent of water to copper ion. Therefore, they deduced that if the process completes in a shorter time, racemization can diminish. To achive this aim, water was removed from the reaction mixture by adding 4 Å molecular sieves (MS). It was observed that MS have a remarkable effect on improving the enantioselectivity, yield and also reaction rate. For example, in the presence of MS, cyclopentene was oxidized in 16 h (compared

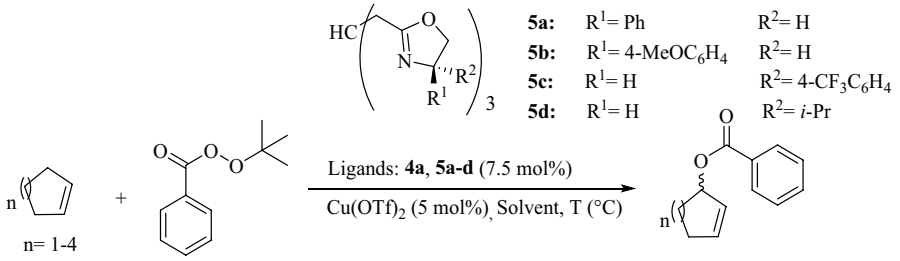
with 40 h in the absence of MS) and (*S*)-cyclopen-2-yl benzoate was afforded with enantiomeric excess of 76% and 83% yield (Table 4, entry 3). Enantioselectivity at the temprature of −20 °C was increased to excellent 93% *ee*, although the yield dropped to 30% and the reaction was prolonged to 200 h (Table 4, entry 5). The same pattern was observed in cycloolefins larger than cyclopentene. In the presence of MS at room temperature, the corresponding chiral allylic esters were achieved in good-to-moderate *ee*s, although the yields were very poor (Table 4, entries 13–15). Utilizing aryl substituents of peroxyesters had no impressive impact on reactivity and enantioselectivity. Apart from the *o*-methyl group, which slightly improved enantioselectivity, *o*-chloro resulted in lower *ee* and the *p*-nitro group decelerated the reaction rate. Oxidation of 1-methyl cyclopentene at 0 °C provided chiral regioisomeric esters with low to high enantiomeric excesses, closely similar to Pfaltz's studies [54]. Furthermore, based on Andrus' findings [55], acyclic olefin 1-octene gave allylic ester in both poor yield and *ee* at room temperature.

The findings show that a combination of Cu (II)-**4a** complex and MS is only capable of inducing high enantiocontrol in allylic oxidation of cyclopentene. Hence, in a similar study Katsuki's group [59] synthesized a different type of tridentate C_3-symmetric tris-oxazoline ligands **5a-d** by replacement of the central N atom in ligand **4** with methyne (CH). As in their former studies [57, 58], ligands with aryl substitutients at the oxazoline ring were able to induce better stereocontrol than alkyl ones. Morever, ligand **5b** bearing an electron donating group (*p*-OMe) showed higher enentioselectivity (Table 5, entries 8, 13, 15 vs 16). It was found that, although ligands **4a** and **5a,b** have the same stereochemistry, the configuration of the resulting products was opposite, which presumably is due to different structures of the Cu(II) complexes with ligands of type **4a** and **5a,b** (Table 5, entries 1, 2 and 12). Interestingly, in contrast to tetradentate tris-oxazoline ligand **4a**, in the presence of ligands **5a**, MS exhibit an adverse effect on enantioselectivity (Table 5, entry 1 vs 3). Besides, using 1,2-dichloroethane as a non-polar solvent resulted in ralatively higher *ee* values in comparison with the previous findings in which acetonitrile or acetone exhibited promising results (Table 5, entries 3–7). However, non-polar aromatic solvents such as C_6H_6 and C_6H_5Cl have been found not to be effective for enantioselectivity (Table 5, entries 10, 11). In optimized conditions (Cu (II)-ligand **5b** at low temperature), Katsuki could upgrade the enantioselectivity of the larger cycloolefins such cycloheptene and cyclooctene to higher enantioselectivity than what was obtained in their previous works (Table 5, entries 18–20). However, the chemical yield at low temperatures (e.g., 0 °C) for cyclooctene was only 25%.

Under these conditions, desymmetrization of racemic olefin **6** through a meso intermediate led to regioisomeric chiral allylic esters with good-to-high *ee* values (58–85%). However, the yields were poor. It seems that low regioselectivity in the hydrogen abstraction step is responsible for the formation of undesired products (Scheme 8).

In 1996, Singh et al. [60] were working on a series of tridentate gem-diphenyl Pybox **7a–d** in which both hydrogens at C5 had been replaced with phenyl groups. Studying the effect of phenylhydrazine as a reductant agent for in situ generation of Cu (I) from Cu (II) may be considered as the leading characteristic of Singh's works. Besides, in accordance with the first study of Katsuki with ligand **4a** [58], it was

Table 5 Asymmetric allylic oxidation using of tetra and tridentate tris-oxazoline-Cu complexes

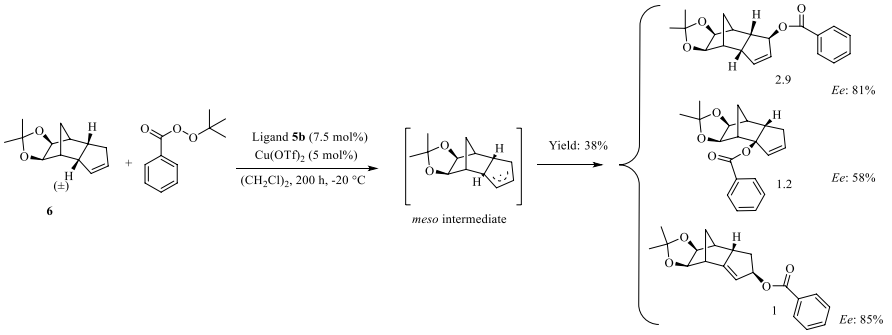


Entry	*n*	Ligand	Solvent	*T* (°C)	Time (h)	Yield (%)	*Ee* (%)	Configuration
1	1	**5a**	$(CH_3)_2CO$	r.t	10	46	65	*R*
2[a]	1	**4a**	$(CH_3)_2CO$	r.t	16	83	76	*S*
3[a]	1	**5a**	$(CH_3)_2CO$	r.t	46	77	31	*R*
4	1	**5a**	CH_3CN	r.t	21	69	63	*R*
5	1	**5a**	EtOAc	r.t	8	57	45	*R*
6	1	**5a**	CH_2Cl_2	r.t	7	77	74	*R*
7	1	**5a**	$(CH_2Cl)_2$	r.t	7	78	76	*R*
8	1	**5a**	$(CH_2Cl)_2$	0	48	80	83	*R*
9 [b]	1	**5a**	$(CH_2Cl)_2$	− 20	210	40	87	*R*
10	1	**5a**	C_6H_6	r.t	7	77	34	*R*
11	1	**5a**	C_6H_6Cl	r.t	8	71	56	*R*
12	1	**5b**	$(CH_2Cl)_2$	r.t	6	71	80	*R*
13	1	**5b**	$(CH_2Cl)_2$	0	48	73	85	*R*
14[b]	1	**5b**	$(CH_2Cl)_2$	− 20	200	46	89	*R*
15	1	**5c**	$(CH_2Cl)_2$	0	48	77	51	*S*
16	1	**5d**	$(CH_2Cl)_2$	r.t	11	43	2	*S*
17	2	**5b**	$(CH_2Cl)_2$	0	48	80	82	*R*
18	3	**5b**	$(CH_2Cl)_2$	0	48	64	88	*R*
19 [b]	3	**5b**	$(CH_2Cl)_2$	− 20	200	13	92	*R*
20 [b]	4	**5b**	$(CH_2Cl)_2$	0	200	25	85	*R*

[a]In the presence of MS (4 Å)

[b]Perester was not consumed completely

observed that 4 Å MS had a considerable impact on asymmetric induction, although the reaction was completed in longer time period. In further research [61], they focused their attempts on decreasing the reaction time and improving ee and also chemical yields. Although, various species of copper salts such as CuCN, Cu (II) triflate and Cu (I) triflate were capable of catalyzing the reaction, reasonable *ee* was obtained only with **7c**-Cu (I) triflate complex (Table 6, entries 1–5). Interestingly, it was observed that the procedure using Cu (I) formation has a significant effect on the rate of the reaction. In other words, the reaction in the presence of in situ generated Cu (I) from a combination of $Cu(OTf)_2$ and phenylhydrazine is much faster than

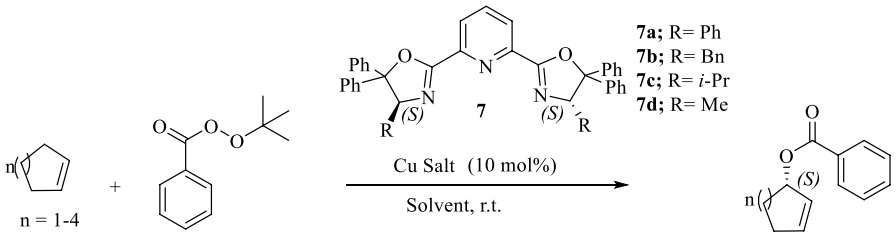


Scheme 8 Asymmetrization of racemic olefin by using tris-oxazoline **5b**

that of Cu (I) used directly from $(CuOTf)_2$.PhH (Table 6, entries 3 vs 5). Moreover, the use of phenylhydrazine and Cu (I) together dramatically reduced the reaction time from several days to a few hours. In case of cyclohexene, for instance, employing **7c**-$(CuOTf)_2$.PhH in conjunction with phenylhydrazine considerably accelerated the reaction rate, and the time of reaction diminished from 144 to 5 h without much adverse effect on *ee* (Table 6, entry 3 vs 7). Although adding 4 Å MS in the absence of phenylhydrazine increased enantiomeric excess, the reactivity was drastically decreased (Table 6, entry 11). It is noteworthy that simultaneous use of MS (4 Å) and phenylhydrazine was beneficial in particular for *ee*. It appears that, due to the use of phenylhydrazine the reactivity and *ee* were increased; however, some slight decrease in yield was observed (Table 6, entries 10, 12, 13 vs 14, 16, 17). This situation resulted in lower yield as well as *ee* for cyclohexene (Table 6, entry 11 vs 15). Furthermore, replacement of isopropyl group at ligand **7c** by different substitutents led to lower enantioselectivity (Table 6, entries 18–20).

It is worth noting that, in a reassessment investigation, some notably different results were observed by Singh and coworkers [62]. They found that recrystallization of gem-diphenyl Py-box ligand **7c** from diethyl ether would provide 91% *ee* as opposed to the 75% *ee* obtained in the previous study [61] in the case of cyclohexene; the reaction time was also drastically reduced from 24 h to only 1 h. Apparently, effective purification of chiral ligand **7c** is responsible for the improvement in catalytic activity. It was further found that, contrary to their later study [61], the beneficial effect of 4 Å MS was not observed and reconsideration of the results showed a decrease in enantioselectivity in the presence of MS. Interestingly, when the reaction was carried out in the presence of water (6 mol%) not only was no decline in enantioselectivity and yield observed, but the reaction time also increased from 1 h (67% yield, 91% *ee*) to 11 h (79% yield, 90% *ee*). These findings showed that, in this situation, the reaction is not moisture sensitive [62]. The experimental observations showed that allylic oxidation would be completed in a short time, providing that the Cu (I) species were prepared in situ by reduction of **7c**-$Cu(OTf)_2$ with phenylhydrazine in acetone. Besides, changing the solvent to acetonitrile increased the reaction time to several days from a few hours, and a drop in enantioselectivity (from 91 to 86% *ee* for cyclohexene) was

Table 6 Effect of phenylhydrazine and MS (4 Å) on enantioselectivity, reactivity and yield



Entry	*n*	Ligand	Cu salt	Solvent	Time (h)	Yield (%)	*Ee* (%)
1	2	**7c**	CuCN	CH_3CN	120	48	42
2	2	**7c**	CuI	CH_3CN	120	37	9
3	2	**7c**	$(CuOTf)_2$·PhH	$(CH_3)_2CO$	144	87	73
4	2	**7c**	$Cu(OTf)_2$	$(CH_3)_2CO$	28	44	26
5[a]	2	**7c**	$Cu(OTf)_2$	$(CH_3)_2CO$	24	65	71
6[a]	1	**7c**	$(CuOTf)_2$·PhH	$(CH_3)_2CO$	3	62	54
7[a]	2	**7c**	$(CuOTf)_2$·PhH	$(CH_3)_2CO$	5	78	70
8[a]	3	**7c**	$(CuOTf)_2$·PhH	$(CH_3)_2CO$	6	35	72
9[a]	4	**7c**	$(CuOTf)_2$·PhH	$(CH_3)_2CO$	24	26	81
10[b]	1	**7c**	$(CuOTf)_2$·PhH	$(CH_3)_2CO$	216	85	51
11[b]	2	**7c**	$(CuOTf)_2$·PhH	$(CH_3)_2CO$	504	88	86
12[b]	3	**7c**	$(CuOTf)_2$·PhH	$(CH_3)_2CO$	1440	47	66
13[b]	4	**7c**	$(CuOTf)_2$·PhH	$(CH_3)_2CO$	1800	20	70
14[a,b]	1	**7c**	$Cu(OTf)_2$	$(CH_3)_2CO$	4	80	60
15[a,b]	2	**7c**	$Cu(OTf)_2$	$(CH_3)_2CO$	24	73	75
16[a,b]	3	**7c**	$Cu(OTf)_2$	$(CH_3)_2CO$	24	42	82
17[a,b]	4	**7c**	$Cu(OTf)_2$	$(CH_3)_2CO$	72	28	81
18 [a,b]	2	**7a**	$Cu(OTf)_2$	$(CH_3)_2CO$	36	57	11
19 [a,b]	2	**7b**	$Cu(OTf)_2$	$(CH_3)_2CO$	24	79	62
20 [a,b]	2	**7d**	$Cu(OTf)_2$	$(CH_3)_2CO$	48	69	23

[a]In the presence of phenylhydrazine

[b]In the presence of MS

also observed. The use of electron paramagnetic resonance (EPR) spectroscopy elucidated that both phenylhydrazine and phenylhydrazone, which is generated in situ from condensation of acetone with phenylhydrazine, are able to reduce species of copper (II) to copper (I), and are responsible for the rate enhancement. However, the effect of phenylhydrazine is much stronger than that of phenylhydrazone. Moreover, a mechanism was proposed in which a π–π stacking interaction between the phenyl groups at the C-5 of the gem-diphenyl Py-box ligand **7c** and the incoming benzoate of perester in the transition state plays a key role in asymmetric induction [63, 64] (Fig. 2).

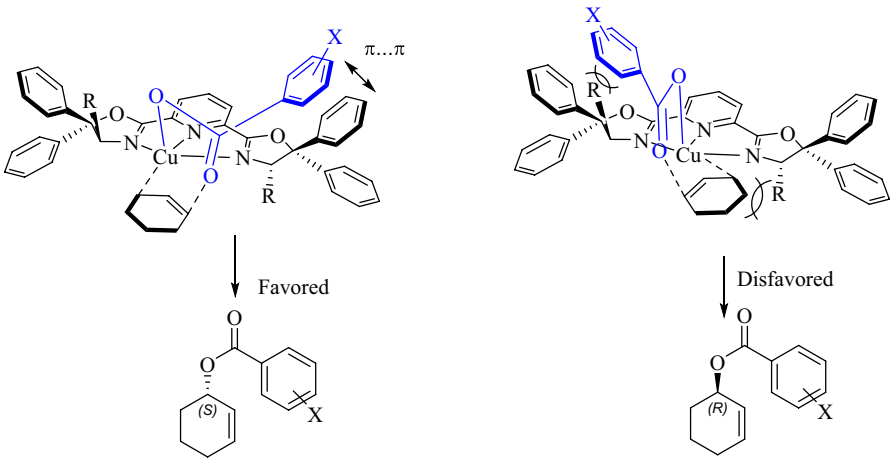
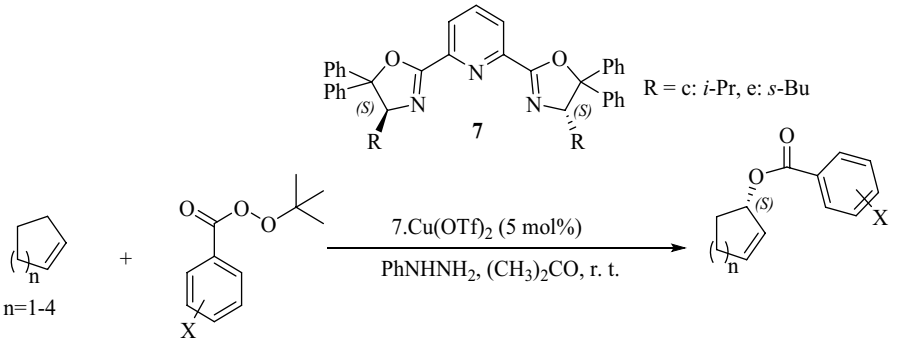


Figure 2 Proposed transition state models for enantioselective allylic oxidation by Singh and coworkers

Based on this proposed model, in the favored transition state, a π–π interaction would control the approach of the incoming benzoate from the less sterically hindered side. The olefin approaches Cu from the opposite side, due to disfavored interaction with the R group at C-4 of the oxazoline moiety. This transition state illustrates why the *S* product is formed as the major product. This model was supported by replacing phenyl groups at C-5 of ligand **7c** with hydrogen and benzyl groups. In these cases, due to lack of π–π interaction, asymmetric induction was declined. Consequently, it was expected that, because of stronger π–π stacking in the peresters containing electron-withdrawing substituents (such as NO_2), the chiral allylic esters would be formed with higher enantioselectivity. But, contrary to expectation, experimental observations have shown a decline in reactivity as well as selectivity. Instead, electron-donating groups (like methoxy and alkyl) provided the desired chiral allylic esters with excellent enantioselectivity. These findings indicated that, when the π–π interaction is stronger, steric repulsion with the R group of oxazoline at the sterogenic center does not play a significant role and, therefore, the reaction will proceed through both pathways. On the other hand, weaker stacking by electron-donating groups is not sufficient to overcome steric repulsion. Therefore, an optimal interaction is responsible for the highest asymmetric induction. The proposed model also explained the high level of enantioselectivity of the reaction with ligand **7e**, where R is *sec*-butyl [63, 64]. In this situation, oxidation using *tert*-butyl-*o*-methoxyperbenzoate provided the desired enantioenriched allylic esters in short reaction time with good-to-excellent enantioselectivities (Table 7) [63]. Cyclohexene, for example, gave (*S*)-cyclohex-2-en-1-yl 4-methoxybenzoate in excellent enantioselectivity (98% *ee*) and good yield (71%) in 2 h (Table 7, entry 8). In case of cycloheptene and cyclooctene *ee* values and yields were all high (Table 7, entries 9–16); however, cyclopentene was oxidized with good yield and *ee* (80%) (Table 7, entry 4).

Similarly, high *ee* values up to 96% were obtained for cyclooctadiene substrates with *tert*-butyl-*p*-methoxy perbenzoate in the presence of ligand **7c**,

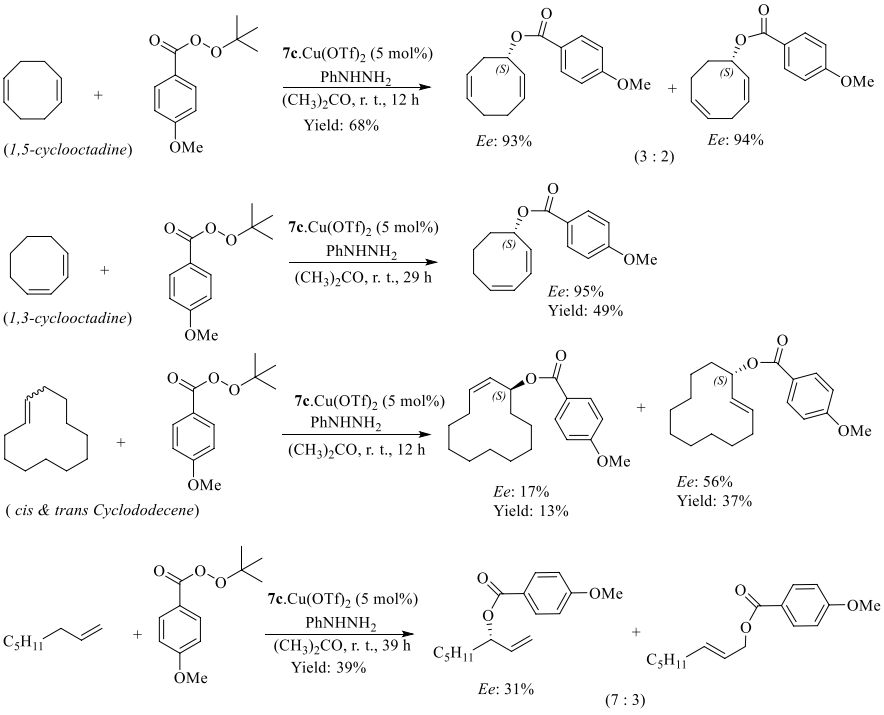
Table 7 Allylic oxidation of cycloolefins with *gem*-diphenyl pyridine bisoxazoline ligands



Entry	*n*	*X*	Time (h)		Yield (%)		*Ee* (%)	
			7c	**7e**	**7c**	**7e**	**7c**	**7e**
1	1	H	3	20	76	75	70	65
2	1	*p*-NO_2	13	6	47	42	62	58
3	1	*p*-OMe	3	3	55	57	77	72
4	1	*o*-OMe	4	4	71	74	80	80
5	2	H	1	8	67	57	91	91
6	2	*p*-NO_2	10	15	65	49	86	87
7	2	*p*-OMe	2	5	60	61	93	92
8	2	*o*-OMe	5	2	50	71	91	98
9	3	H	6	–	47	–	86	–
10	3	*p*-NO_2	64	72	36	40	85	90
11	3	*p*-OMe	96	18	45	45	91	94
12	3	*o*-OMe	13	16	42	39	91	87
13	4	H	6	24	34	34	94	95
14	4	*p*-NO_2	36	72	28	39	91	88
15	4	*p*-OMe	21	19	31	42	96	90
16	4	*o*-OMe	33	48	38	43	91	92

although 1,5-cyclooctadien gave a mixture of products with roughly the same *ee* values. Regarding the mixture of cis and trans cyclododecene, both enantioselectivity and yield were low to medium (Scheme 9) [63]. It should be noted that while high level of facial selectivity was obtained for most cycloolefines, the reaction was not effective for acyclic ones. Oxidation of 1-octene with *tert*-butyl-*p*-methoxy perbenzoate gave a mixture of allylic esters with poor enantioselectivity up to 31% (Scheme 9).

Continuing their investigations, Andrus et al. [65] developed and evaluated bis-tolyl bis-oxazoline ligands (*S, aS, S*)-**8** and (*S, aR, S*)-**9** in the asymmetric allylic oxidation. Evidence revealed that the axial chirality of the ligands has a significant effect on the stereoselectivity of the resulting ester; thus, (*S, aS, S*)-atropisomer **8**



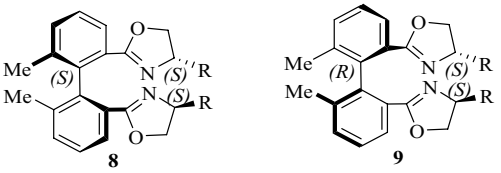
Scheme 9 Asymmetric allylic oxidation using tert-butyl-4-methoxy perbenzoate

resulted in allylic esters with higher enantioselectivity compared with (*S, aR, S*)-atropisomer **9** (Table 8). A detailed look at the geometry of ligands signifies that this discrepancy can be attributed to the steric control of the R groups in the stereoisomers. The R groups in the (*S, aS, S*)-isomer occupy a pseudo axial position, whereas in the (*S, aR, S*)-isomer they are in the equatorial position (Scheme 10). In the (*S, aR, S*)-ligands all four quadrants are almost equally congested, leading to products with lower *ee* values.

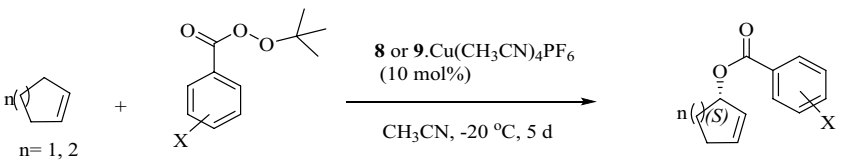
On the other hand, in contrast to the malonyl bisoxazolines [55] in which steric hindrance of the *tert*-butyl group led to great stereoselectivity, higher reactivity and also enantioselectivity were achieved by use of this type of ligands containing less hindered Ph and Bn substituents (Table 8). It seems that replacement of the less sterically demanding groups on the oxazoline by more sterically bulky *tert*-butyl contributes to a larger bite-angle and consequently both the reaction rate and enantioselectivity were decreased. Employing diffrent *t*-butyl perbenzoate derivatives showed that the best results can be obtained in the presence of *t*-butyl *p*-nitro-perbenzoate (Table 8).

In an another attempt, Andrus et al. [66] examined different atropisomeric ligands naphthyloxazolinyl quinazoline **10** and oxazolinyl isoquinoline **11**. Based on promising results in the previous study, the reaction was again carried out with *t*-butyl *p*-nitro-perbenzoate in the presence of Cu (I) at −20 °C in acetonitrile. Although the

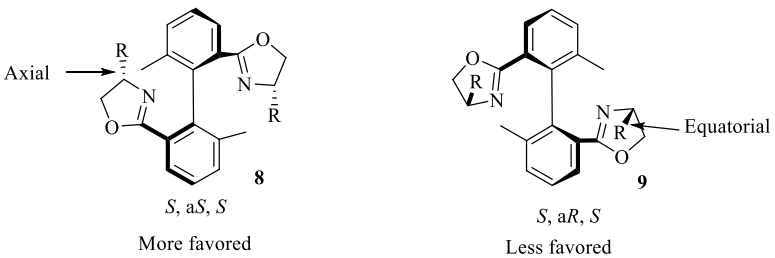
Table 8 Employing atropisomeric bisoxazolines **8** and **9** in allylic oxidation



R = a: Ph, b: Bn, c: *i*-Pr, d: *t*-Bu



Entry	Ligand	X	*n* = 1		*n* = 2	
			Yield (%)	*Ee* (%)	Yield (%)	*Ee* (%)
1	**8a**	*p*-NO_2	59	69	78	73
2	**9a**	*p*-NO_2	51	10	76	0
3	**8a**	*o*-I	55	65	63	71
4	**8a**	2,4,6-Cl_3	–	–	20	11
5	**8d**	*p*-NO_2	2	0	5	18
6	**9d**	*p*-NO_2	0	0	0	0
7	**8b**	*p*-NO_2	63	72	48	52
8	**9b**	*p*-NO_2	70	22	67	11
9	**8b**	*o*-I	61	18	68	70
10	**9b**	*o*-I	61	36	25	13
11	**8b**	2,4,6-Cl_3	–	–	21	15
12	**8c**	*p*-NO_2	22	45	25	66
13	**9c**	*p*-NO_2	–	–	29	16
14	**8c**	*o*-I	18	54	20	62

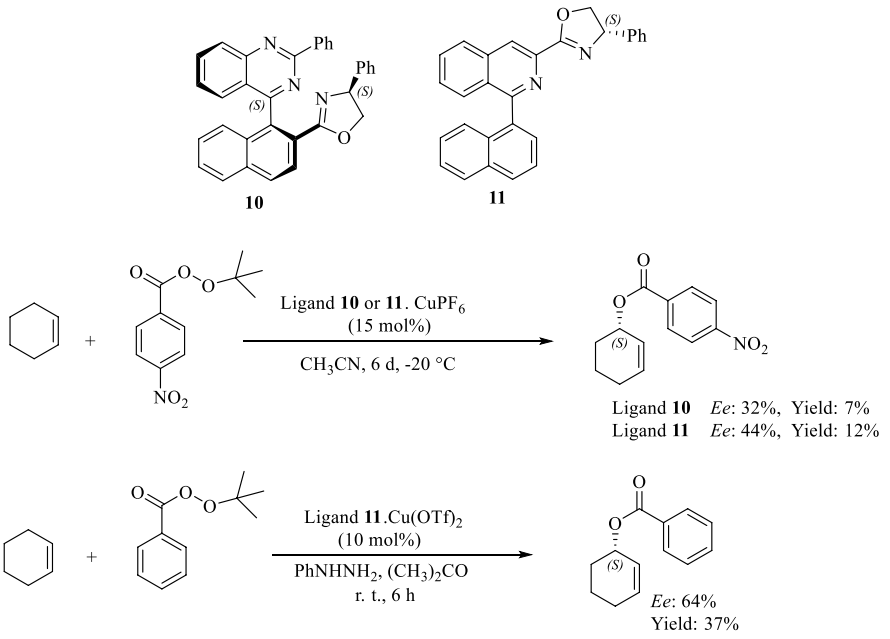


Scheme 10 Position of R groups in (*S, aS, S*) and (*S, aR, S*) atropisomers

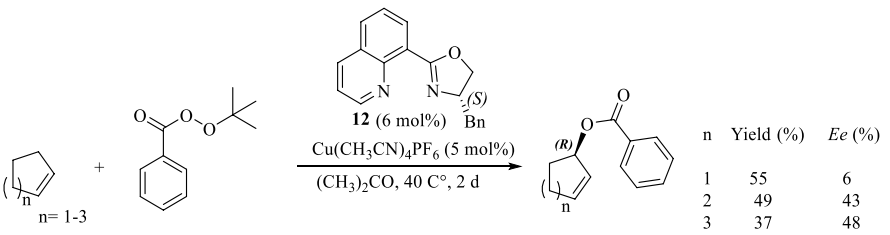
results were not acceptable, ligand **11** showed better outcomes compared with **10**. It can be proposed that the greater steric congestion of phenyl groups in ligand **10** is responsible for this discrepancy. Similar to Singh's findings [61] when the reaction was carried out in the presence of phenylhydrazine in conjunction with $Cu(OTf)_2$ in acetone, an improvement in enantioselectivity and yield was observed (64% and 37%, respectively). In such a situation, the reaction time was reduced dramatically from 6 days to 6 h at room temperature too (Scheme 11).

By applying quinolinyloxazoline **12**, which contains a structure similar to ligand **11** [66], Zhou et al. [67] obtained moderate enantioselectivities and yields with cyclohexene and cycloheptene but only with 6% *ee* for cyclopentene (Scheme 12).

In a notable study using malonyl-derived bisoxazolines, Andrus's group demonstrated that excellent enantiocontrol can be obtained when the reaction conditions



Scheme 11 Moderate enantioselectivities in the presence of ligands **10** and **11**



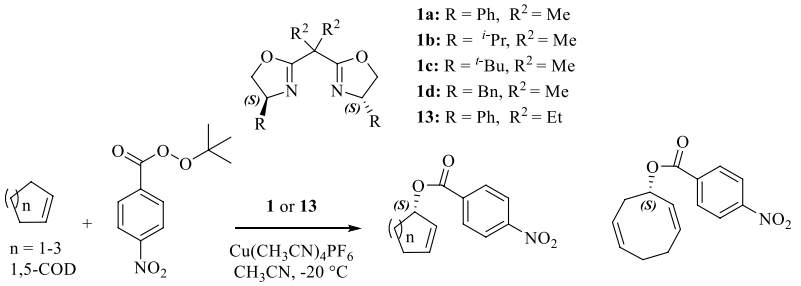
Scheme 12 Quinoline-oxazoline ligand **12** furnishes low-to-moderate enantioselectivity and chemical yields

and the ligand structure are finely tuned for each specific substrate [68]. They succeeded in achieving enantioenriched allylic esters with the highest *ee*, which had not been reported until then. For each cycloolefin in optimal condition, $Cu(CH_3CN)_4PF_6$ and *t*-butyl *p*-nitroperbenzoate in acetonitrile at −20 °C, the efficiency of different malonyl-derived bisoxazoline ligands were evaluated. In such circumstances, cyclohexenyl ester was produced in 96% *ee* by using gem-dimethyl diphenyl ligand **1a**, while gem-diethyl diphenyl ligand **13** was suitable for oxidation of cyclopentene with a remarkable 99% *ee* (Table 9, entries 5, 6). Oxidation of cycloheptene with gem-dimethyl di-*i*-Pr **1b** resulted in very high enantioselectivity (99%); 1,5-cyclooctadiene, in contrast, exhibited excellent enantioselectivity (94%) in the presence of gem-dimethyl di-*t*-butyl **1c** (Table 9, entries 12,18). It should be noted that, in all the cases, (*S*)-allylic esters were produced from the *S*, *S* ligands and, in contrast to the high levels of asymmetric induction, the yields were not satisfactory even in extended times. These observations can be interpreted in accordance with the geometry of bisoxazoline-Cu complexes. Different studies [69, 70] have shown that gem-dimethyl bisoxazoline Cu-complexes prefer a distorted square planer geometry. It was envisioned that both *t*-Bu in **1c** occupy pseudo-axial positions, whereas in **1a**, one of the phenyl groups tends to be in pseudo-axial and the other in more relaxed pseudo-equatorial position. Lower yields achieving by cyclopentene (49% vs 52%) and cyclohexene (44% vs 61%) in the presence of **1a** can be attributed to the disfavored interaction between phenyl at the pseudo-equatorial position and incoming benzoate. However, this interaction presumably is favored for higher degree of asymmetric induction in cyclopentene (82% vs 79%) and cyclohexene (96% vs 84%). Similarly, due to the stronger interaction of bulky *t*-Bu in **1c** with cycloheptene and cycloocadiene, the corresponding esters were obtained in high enantioselectivities (95% and 94%), but very poor yields (3% and 13%) (Table 9, entries 13 and 18).

Due to good stereocontrol for a range of substrates with the malonyl-derived bisoxazoline ligands bearing phenyl groups at the stereogenic centers, and also more flexibility in comparison with the corresponding *t*-butyl derivatives, Andrus supposed that by replacing phenyl groups with naphthyl, the yields would be enhanced without affecting enantioselectivities [71]. In this situation, (*S*)-cyclohex-2-en-1-yl 4-nitrobenzoate was obtained with 75% and 40% yields and 85% and 80% *ee* values in the presence of naphthyl-substituted malonyl-derived bisoxazolines **1e** and **1f**, prepared from naphthyl amino alcohols by the Sharpless aminohydroxylation of vinylnaphtalenes [72], respectively (Table 10, entries 1 and 2). It seems that the greater flexibility of ligand **1f** compared with ligand **1e**, is responsible for this difference. It was also found that, in contrast to earlier studies with ligands **1** and **13** [68], perester was totally consumed by using the copper complex of ligand **1e**. Besides, tridentate Pybox **2b** did not contribute to reasonable results (Table 10, entry 3). It is worth noting that the low solubility of employed ligands in the preferred acetonitrile solvent, which was inevitably replaced by chloroform and methylene chloride or a mixture of the two, could be responsible for a decrease in both reactivity and enantioselectivity (Table 10).

By employing (1*S*, 2*R*)-1-aminoindan-2-ol, Clark and co-workers [73] introduced a different series of C_2-symmetric bisoxazoline ligands **14–16**, which are capable of inducing acceptable *ee* values even at a temprature higher than the previous studies

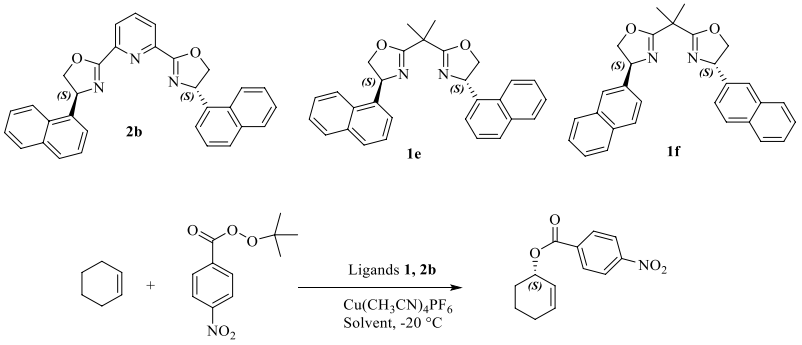
Table 9 Highest enantioselectivities achieved by tuning the reaction conditions in the presence of malonyl-derived bisoxazolines



Entry	Ligand	*n*	Time (h)	Yield (%)	*Ee* (%)
1	**1a**	1	240	49	82
2	**1b**	1	240	42	51
3	**1c**	1	240	52	79
4	**1d**	1	240	25	75
5	**13**	1	192	41	99
6	**1a**	2	408	44	96
7	**1b**	2	144	40	82
8	**1c**	2	168	61	84
9	**1d**	2	144	30	71
10	**13**	2	312	50	75
11	**1a**	3	240	23	56
12	**1b**	3	240	14	99
13	**1c**	3	240	3	95
14	**1d**	3	–	–	–
15	**13**	3	240	12	86
16	**1a**	1,5-COD	240	46	74
17	**1b**	1,5-COD	240	25	36
18	**1c**	1,5-COD	240	13	94
19	**1d**	1,5-COD	–	–	–
20	**13**	1,5-COD	240	34	59

(40 °C). Under these conditions, the yield and reactivity were increased and the reaction completed in almost 1 day. Cyclohexene, for example, was converted to the corresponding (*S*)-allylic ester after 24 h with 74% *ee* and 65% yield. As expected, lowering the reaction temperature to 0 °C improved the level of asymmetric induction and decreased both the yield and rate of reaction (21 days) (Table 11, entry 7). In the case of cyclopentene, BOX ligand **1a** showed higher enantioselectivity than ligands **14**. Moreover, using this type of ligand has not contributed to reasonable results for cyclooctene. Contrary to the above-mentioned studies by Katsuki [58] and Singh [60], enantioselectivity was not affected significantly in the presence of

Table 10 Effect of naphthyl substitution on efficiency of bisoxazoline ligands



Entry	Ligand	Solvent	Time (h)	Yield (%)	*Ee* (%)
1	**1e**	$CHCl_3/CH_2Cl_2$ (3:1)	5	75	85
2	**1f**	CH_3CN/CH_2Cl_2 (1:1)	7	40	80
3	**2b**	CH_2Cl_2	6	41	27

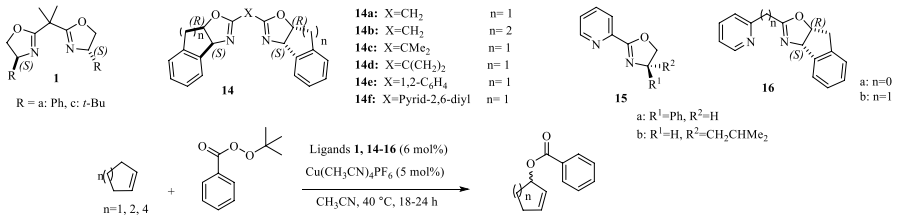
activated 4 Å MS, although an increase in yield was observed (Table 11, entry 6 vs 8). In contrast to Pfaltz's report [54], ligand BOX 1**a** showed better enantioselectivities than **1c**. It should be noted that, in the presence of ligands **15b** and **16**, the induced configuration of the resulting allylic esters is *R* (Table 11, entries 13–15).

When *exo*-methylene cycloolefins were employed as substrates, ligand **14c** showed the best results for methylenecyclohexane (26% *ee*), while the best outcomes in the case of methylenecyclopentane were obtained by ligand **14d** (43% *ee*). However, the absolute configuration of these products has not been reported (Scheme 13) [73].

In another study similar to Katsuki [59], Clark evaluated enantioselective symmetrizing–desymmetrizing allylic oxidation of a range of bridged bicyclic olefins **17a–d** using copper complexes of the bisoxazoline ligands as catalysts [74]. They succeed in obtaining the corresponding endo chiral allylic esters **21** through achiral meso allylic radicals in moderate-to-good yield and good selectivity (Table 12). Generally, derivatives of Pybox ligands **2c**, **18–20** provide better stereocontrol for substrate **17a** in comparison with malonyl bisoxazoline ligands **1a** and **1c**, although it was found that the enantioselectivities and the yields were not very influenced by the substituents at the ligands. In case of substrate **17b**, BOX ligand **1a** showed more preferable results. Under these conditions, substrates containing oxygen (**17c–d**) were unreacted and bicyclic diene **17e** was decomposed (Table 12). It is interesting to note that enhancement of enantioselectivity (up to 70% *ee*) and yield (up to 84%) was observed when the reaction was conducted under microwave irradiation or in a sealed tube at high temperature (60 °C).

In a different study, this group introduced peroxycarbamate as an efficient type of oxidant instead of peroxyester [75]. In comparison with peroxyesters under similar conditions, peroxycarbamates **22a–d** in conjunction with Cu-(*R*, *R*)-**1a**

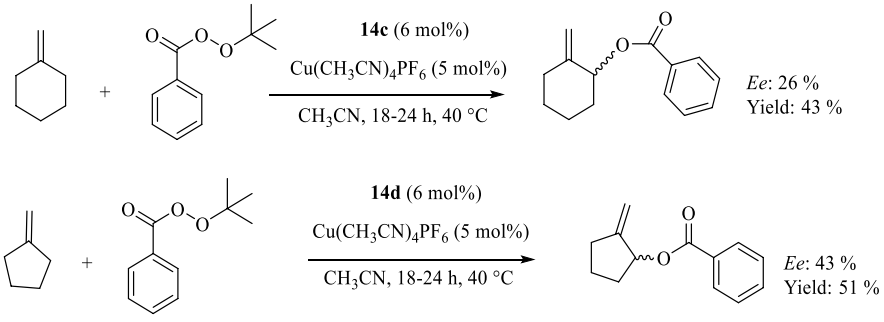
Table 11 Asymmetric allylic oxidation in the presence of oxazoline ligands derived from aminoindanol



Entry	*n*	Ligand	Yield (%)	*Ee* (%)	Configuration
1	1	**1a**	72	69	*S*
2	2	**1a**	71	59	*S*
3	2	**1c**	74	40	*S*
4	2	**14a**	62	45	*S*
5	2	**14b**	69	28	*S*
6	2	**14c**	65	69	*S*
7 [a]	2	**14c**	48	78	*S*
8 [b]	2	**14c**	76	71	*S*
9	2	**14d**	65	74	*S*
10	2	**14e**	59	21	*S*
11	2	**14f**	66	52	*S*
12	2	**15a**	56	17	*S*
13	2	**15b**	57	28	*R*
14	2	**16a**	63	37	*R*
15	2	**16b**	56	55	*R*
16	4	**14c**	31	10	*S*

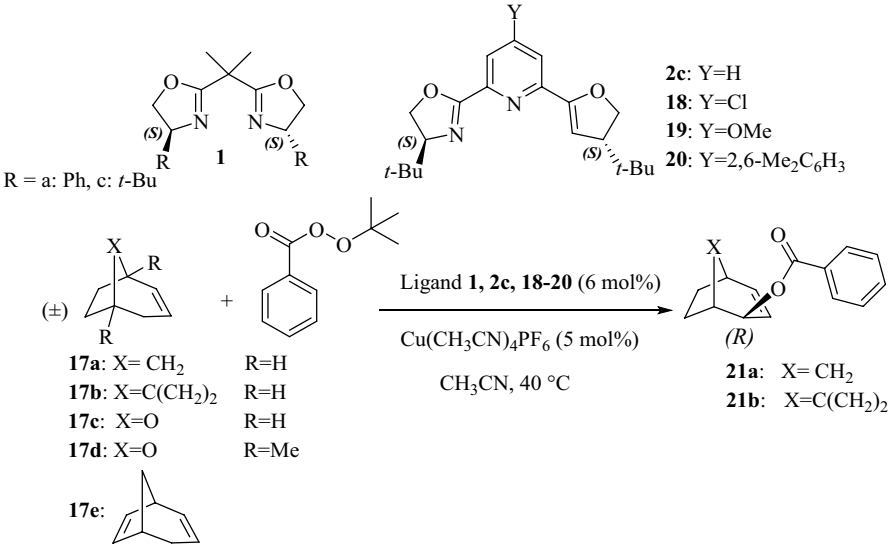
[a]Reaction performed over 21 days at 0 °C

[b]Activated 4 Å MS added to the reaction



Scheme 13 Allylic C–H bond oxidation of *exo*-methylene cyclohexane and cyclopentane

Table 12 Enantioselective symmetrizing–desymmetrizing allylic oxidation of *meso*-bicyclic olefins



Entry	Substrate	Ligand	Product	Time (day)	Yield (%)	*Ee* (%)
1	17a	**2c**	21a	10	70	5 8(−)
2	17a	**18**	21a	10	70	50 (−)
3	17a	**19**	21a	10	36	66 (−)
4	17a	**20**	21a	8	63	62 (−)
5	17b	**1a**	21b	6	48	60 (−)
6	17b	(*R*, *R*)-**1a**	*ent*-21b	5	38	54 (+)
7[a]	17a	**2c**	21a	2	80	66 (−)
8[b]	17a	**2c**	21a	0.42	84	70 (−)

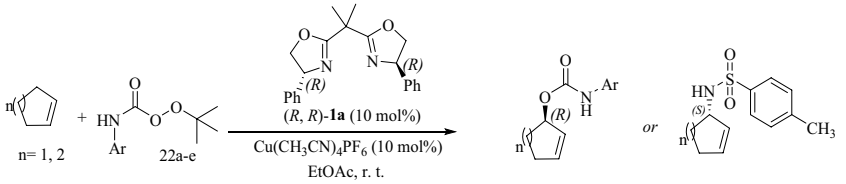
[a]Reaction performed in sealed tube at 60 °C

[b]Reaction performed under microwave irradiation at 60 °C

complex were capable of converting cyclohexene and cyclopentene into chiral esters with good enantioselectivity in a smooth process and in reasonable times (Table 13). Peroxycarbamate **22e**, containing a sulfonamide group, was able to direct the reaction towards allylic amination reaction instead of allylic oxidation, in moderate *ee* but low yield (Table 13, entries 9 and 10). More precisely, in the case of peroxycarbamate **22e**, the tendency to decarboxylation is more facile compared with peroxycarbamates **22a–d**. Such behavior indicates that, by adjusting the conditions, asymmetric allylic oxidation or amination reaction can occur.

Good enantioselectivities, yields and also high regioselectivities for cyclic and acyclic olefins under mild conditions as well as reasonable reaction time, without any additives, were obtained by Zhou [76, 77], who has introduced a new class of bisoxazolines **23** and **24** containing a chiral spiro bisindane backbone. In the case

Table 13 Employing peroxycarbamates in asymmetric allylic oxidation and allylic amination



Ar: a=Ph; b= *p*-BrPh; c= *m*-NO_2Ph; d= *p*-NO_2Ph; e= *p*-$MeC_6H_4SO_2$ Allylic oxidation product Allylic amination product

Entry	Oxidant	*n*	Allylic oxidation product		Allylic amination product	
			Yield (%)	*Ee* (%)	Yield (%)	*Ee* (%)
1	22a	1	34	76 (*R*)	–	–
2	22b	1	26	70 (*R*)	–	–
3	22c	1	40	81 (*R*)	–	–
4	22d	1	48	85 (*R*)	–	–
5	22a	2	37	61 (*R*)	–	–
6 [a]	22b	2	29	67 (*S*)	–	–
7	22c	2	57	65 (*R*)	–	–
8	22d	2	65	72 (*R*)	–	–
9[b]	22e	1	–	–	30	46 (*S*)
10[b]	22e	2	–	–	44	51 (*S*)

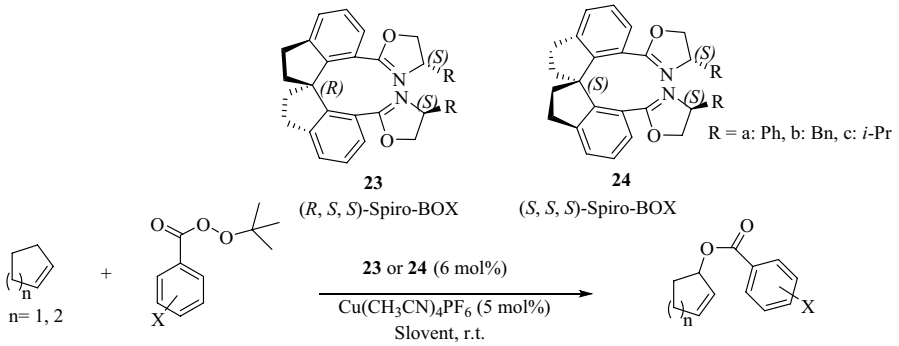
[a]Reaction performed with ligand (*S*, *S*)-**1a**

[b]Allylic amination in CH_2Cl_2

of cyclopentene and cyclohexene, room temperature was found to be the optimum temperature. Decreasing the reaction temperature to 0 °C or increasing it to 40 °C did not much affect the *ee* (Table 14, entries 7 and 8). Further studies have shown that the best results are achieved when the reaction is performed in the presence of 6 mol% of ligand **23b** and 5 mol% of $Cu(CH_3CN)_4PF_6$ in acetone. Additionally, in contrast to previous reports, substituents in the perester did not have a marked effect on the *ee*. Although the chemical yields were improved by *para* substituents, in the presence of *t*-butyl *o*-nitro-perbenzoate, the yield dropped to 16% (Table 14, entries 12–15 vs entry 3) [76].

As shown in the previous studies by Andrus [55] and Singh [63], allylic oxidation of acyclic olefins presents a major challenge, as enantioselectivities and regioselectivities are generally low. It was found that Cu (I)-ligand **23b** complex can be considered as a suitable catalyst for achieving satisfactory results [77]. With this catalyst, not only were the corresponding allylic esters obtained in good enantioselectivities (up to 67%) and yields (up to 64%), the regioselectivities (the ratio of branched **I** to linear esters **II**) were also improved (> 20:1 in most cases) (Table 15). Conducting the reaction at a temperature of 30 °C, in most cases produced almost exclusively branched allylic esters with good-to-moderate *ee* values

Table 14 Allylic oxidation using substituted peresters in the presence of spirobisoxazoline ligands



Entry	Ligand	*n*	*X*	Solvent	Time (h)	Yield (%)	*Ee* (%)
1	**23a**	2	H	$(CH_3)_2CO$	15	60	38
2	**24a**	2	H	$(CH_3)_2CO$	20	65	−15
3	**23b**	2	H	$(CH_3)_2CO$	48	58	70
4	**23c**	2	H	$(CH_3)_2CO$	25	59	2
5[a]	**23b**	2	H	$(CH_3)_2CO$	48	45	70
6[b]	**23b**	2	H	$(CH_3)_2CO$	48	43	68
7[c]	**23b**	2	H	$(CH_3)_2CO$	6	57	70
8[d]	**23b**	2	H	$(CH_3)_2CO$	288	45	69
9	**23b**	2	H	CH_3CN	48	69	58
10	**23b**	2	H	C_6H_6	48	57	14
11	**23b**	1	H	$(CH_3)_2CO$	48	58	70
12	**23b**	2	4-OMe	$(CH_3)_2CO$	48	67	67
13	**23b**	2	4-Me	$(CH_3)_2CO$	48	65	66
14	**23b**	2	4-NO_2	$(CH_3)_2CO$	48	80	67
15	**23b**	2	2-NO_2	$(CH_3)_2CO$	48	16	59

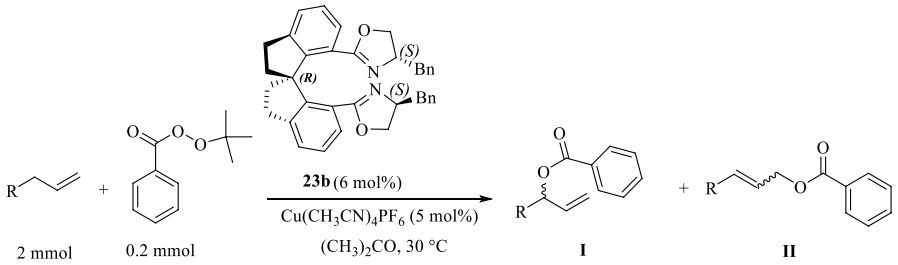
Reactions were performed in the presence of [a]$(CuOTf)_2$.PhH and [b]$Cu(OTf)_2$

Reactions were performed [c]at 40 °C and [d]at 0 °C

and yields; whereas changing the temperature led to a drop in the enantioselectivities and yields (Table 15, entries 1–3).

Most studies have indicated that, in addition to oxazoline backbones, the use of additives such as 4 Å MS and phenylhydrazine has a major effect on both enantioselectivity and yield. In 2013, our research group developed the synthesis of bistolyl bisoxazoline ligands (*S, aS, S*)-**8** and (*S, aR, S*)-**9** in gram scale from inexpensive and commercially available 3-methyl benzoic acid along with introducing a range of additives in asymmetric allylic oxidation [30] (Scheme 14). Similar to Andrus' report [65], it was found that higher asymmetric induction can be obtained by applying a (*S, aS, S*)-**8a** bisoxazoline-bearing phenyl group at stereogenic centers in conjunction with $Cu(CH_3CN)_4PF_6$. However, as expected, the effect of the additives

Table 15 Regioselective and enantioselective allylic oxidation of acyclic olefins using spiro bisoxazoline **23b**

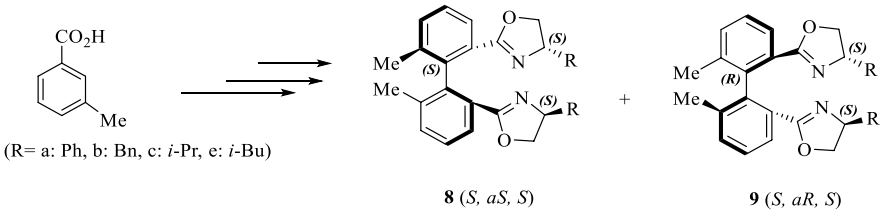


Entry	R	I:II	Yield (%)	*Ee* (%)
1	C_7H_{15}	> 20:1	52	54(*R*)
2[a]	C_7H_{15}	> 10:1	40	38(*R*)
3[b]	C_7H_{15}	> 10:1	25	11(*R*)
4	C_3H_7	13:1	50	34(*R*)
5	Cy	3:1	33	24(*S*)
6	C_6H_5	> 20:1	64	40(*S*)
7	4-$MeOC_6H_4$	7:1	55	17
8[c]	4-$CF_3C_6H_4$	> 20:1	37	67(S)
9	$TBSOC_3H_6$	> 20:1	57	46(R)
10	$BzOC_3H_6$	20:1	55	48
11	$TBSOCH_2$	19:1	35	40
12	$BzOCH_2$	18:1	43	45
13	CH_3COCH_2	> 20:1	36	27
14	AcOH	> 20:1	23	10
15	TMS	> 20:1	55	13

[a]Reaction conducted at 10 °C

[b]Reaction conducted at 60 °C

[c]The oxidant cannot be fully consumed at 30 °C in 3 days

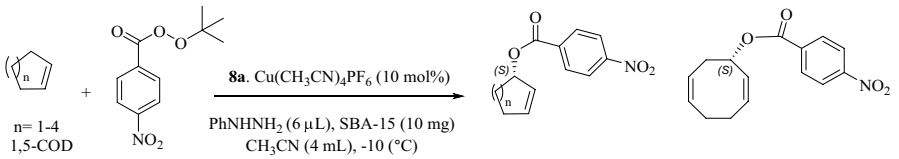


Scheme 14 Synthesis of chiral bistolyl bisoxazoline ligands **8** and **9** from 3-methyl benzoic acid

on yields and enantioselectivity was noticeable. In the case of cyclohexene, for instance, at −10 °C in conjunction with 4 Å MS and phenylhydrazine, cyclohexyl benzoate was obtained with 80% *ee* and 85% yield, versus 73% *ee* and 78% yield reported by Andrus. Lowering the temperature to more than −10 °C had no significant effect on the *ee*. However, evaluation of a range of additives such as activated silica gel, mesoporous silica SBA-15 and MCM-41, nanocrystalline MgO, CuO, and TiO_2, for the first time, has shown that in the presence of SBA-15 mesoporous silica both yields and enantioselectivities can be increased to 96% and 93%, respectively, in a shorter time (36 h vs 120 h, compared with Andrus's results). This upward trend was also observed with cyclopentene (90%, 81% *ee*) and seven-, and eight-membered cycloalkenes (Table 16). It should be noted that in contrast to Singh reports [62–64], oxidation of 1,5-cyclooctadiene led to only one regioisomer with higher yield (up to 95%) and *ee* (up to 97%). This behavior can be attributed to the catalyst complex cavity, which can be fitted to a twist-boat conformation of 1,5-cyclooctadiene determined by the substituents on the bisoxazoline ligand [78–80].

Although this type of ligand can be effective for achieving excellent yields and *ee*, only the (*S, aS, S*)-stereoisomer is able to induce high enantioselectivity. Moreover, due to similar polarity of both atropisomers, separation of diastereomeric ligands **8** and **9** is a tedious and time-consuming process. These limitations have been ingeniously solved by employing ligands **24**. It has been demonstrated that if both methyl groups are replaced with hydrogen atoms, rotation around the biphenyl axis will be possible, resulting in an equilibrium between atropisomers at ambient temperature [81–83]. In this case, by a chelation-induced process [84], a metal complex of only one diastereomer can be formed. Accordingly, a series of bisoxazoline ligands **24** with an axis-unfixed biphenyl backbone were synthesized from inexpensive and available starting material 2-amino benzoic acid [31]. As expected, both diastereomeric atropisomers were in equilibrium in the solution phase. Notably, complexation of the equilibrium mixture with $Cu(CH_3CN)_4PF_6$ led to the formation of only (*S*, *aS*, *S*) diastereomer (Scheme 15). This complex produced chiral allylic esters

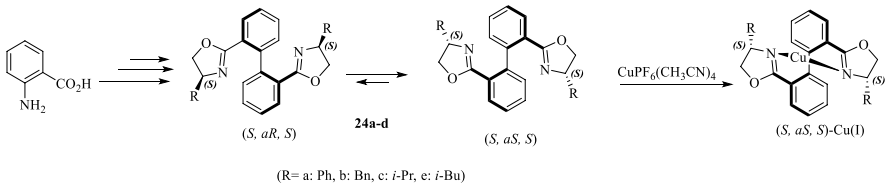
Table 16 SBA-15 mesoporous silica as a significant factor in asymmetric induction



Entry	*n*	Time (h)	Yield (%)	*Ee* (%)
1	1	100	90	81
2	2	36	96	93
3	3	80	94	93
4	4	150	84	70
5	1,5-COD	46	95	97

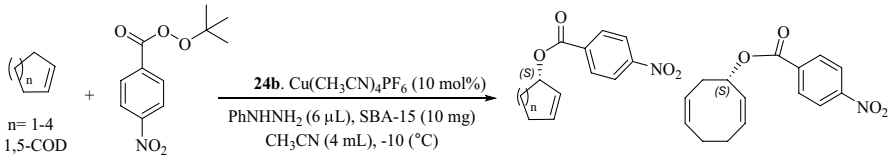
with high enantioselectivities and yields, similar to our former study [30]. Moreover, a study on the effect of the above-mentioned additives [30], especially SBA-15 silica, again led to improved results. The best results were obtained in the presence of bisoxazoline containing benzyl groups **24b** at the stereogenic centers at −10 °C in CH_3CN. 1,5-Cyclooctadiene was also oxidized in the highest yield (up to 99%) and up to 95% *ee*, as in the previous study [30] (Table 17). It is noteworthy that in both studies, similar to Andrus' results [65], the synergistic effect between configurations of the oxazoline rings and the backbone can enhance asymmetric induction.

Although both types of ligands **8** and **24** present high yields and very satisfactory levels of asymmetric induction, their preparation and separation suffer from laborious procedures. Thus, we attempted to design and synthesis a simple and efficient class of chiral amido-oxazolines **26a-d** from aminooxazolines **25**, which are generated from various amino alcohols and cyanogen bromide, and para-substituted benzoic acids such as OMe, NH_2, Br, and NO_2 [85]. It was observed that two equivalents of these ligands can coordinate with one equivalent of copper to form a C_2-symmetric complex as a catalyst (Scheme 16). Use of these ligands in allylic oxidation showed that the best results can be obtained by using **26a**-CuOTf complex in acetone at 0 °C (Table 18, entries 1 and 5). Under these conditions good *ee* values and yields were also observed for large cycloalkenes (Table 18, entries 9 and 13), although in the case of 1,5-cyclooctadiene, ligand **26b** bearing a benzyl

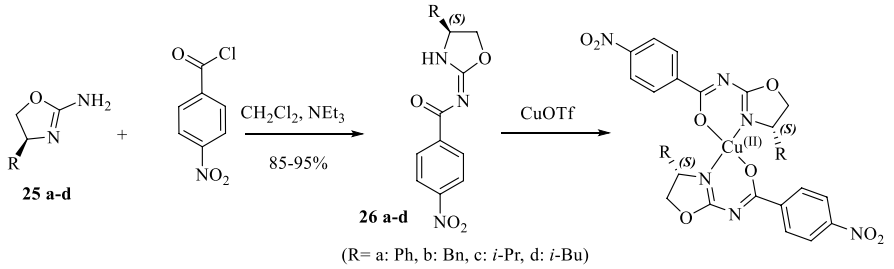


Scheme 15 Preparation of (*S*, *aS*, *S*)-Cu(I)-bisoxazoline complex by chelation-induced process

Table 17 Biphenyl bisoxazoline ligand **24b** in the presence of SBA-15 in asymmetric allylic oxidation

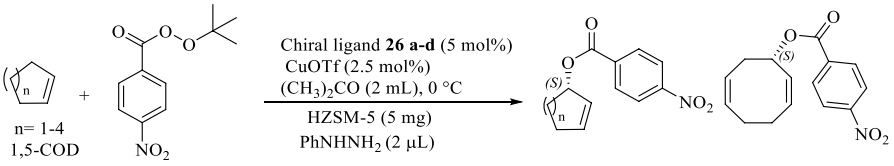


Entry	*n*	Time (h)	Yield (%)	*Ee* (%)
1	1	80	99	75
2	2	70	99	81
3	3	92	87	70
4	4	109	85	72
5	1,5-COD	70	99	95



Scheme 16 Synthesis of Cu-amido-oxazoline complex

Table 18 Excellent stereocontrol by using oxazoline ligands **26a-d** in the presence of HZSM-5



Entry	Ligand	*n*	Time (h)	Yield (%)	*Ee* (%)
1	**26a**	1	50	80	84
2	**26b**	1	70	90	77
3	**26c**	1	65	75	32
4	**26d**	1	81	82	25
5	**26a**	2	45	95	85
6	**26b**	2	50	88	75
7	**26c**	2	75	75	37
8	**26d**	2	70	65	24
9	**26a**	3	58	85	71
10	**26b**	3	77	80	63
11	**26c**	3	60	85	18
12	**26d**	3	50	74	23
13	**26a**	4	60	80	74
14	**26b**	4	73	59	77
15	**26c**	4	57	75	12
16	**26d**	4	75	80	20
17	**26a**	1,5-COD	30	85	90
18	**26b**	1,5-COD	76	90	94
19	**26c**	1,5-COD	58	90	33
20	**26d**	1,5-COD	71	80	20

group gave better enantioselectivity and yield than others (Table 18, entry 18). Consistent with the previous observation, use of *t*-butyl *p*-nitro-perbenzoate resulted in enantioenriched allylic esters with higher stereoselectivites and yields in a shorter

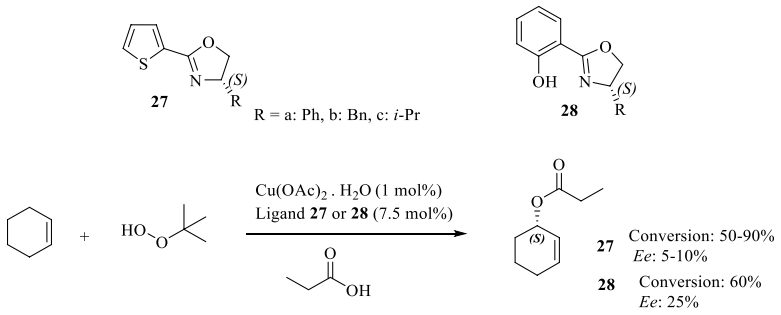
time than other *p*-substituted peresters. In addition, as expected, inorganic additives such as MS (4 Å), MCM-41, SBA-15, and HZSM-5 showed an increase in yields and enantioselectivities and also accelerated the reaction rate. However, HZSM-5 exhibited superior results compared with the other porous additives (Table 18). A key feature of this study, compared with other publications, was the decrease in the ratio of olefin to perester from 5–10:1 to 3:1 without affecting the obtained results. It should be noted that this protocol can be considered as an efficient procedure in the asymmetric allylic oxidation of cyclooefins, which gave chiral esters with high enantioselectivities (up to 94%) and yields (up to 95%).

3.1.2 Other Studies

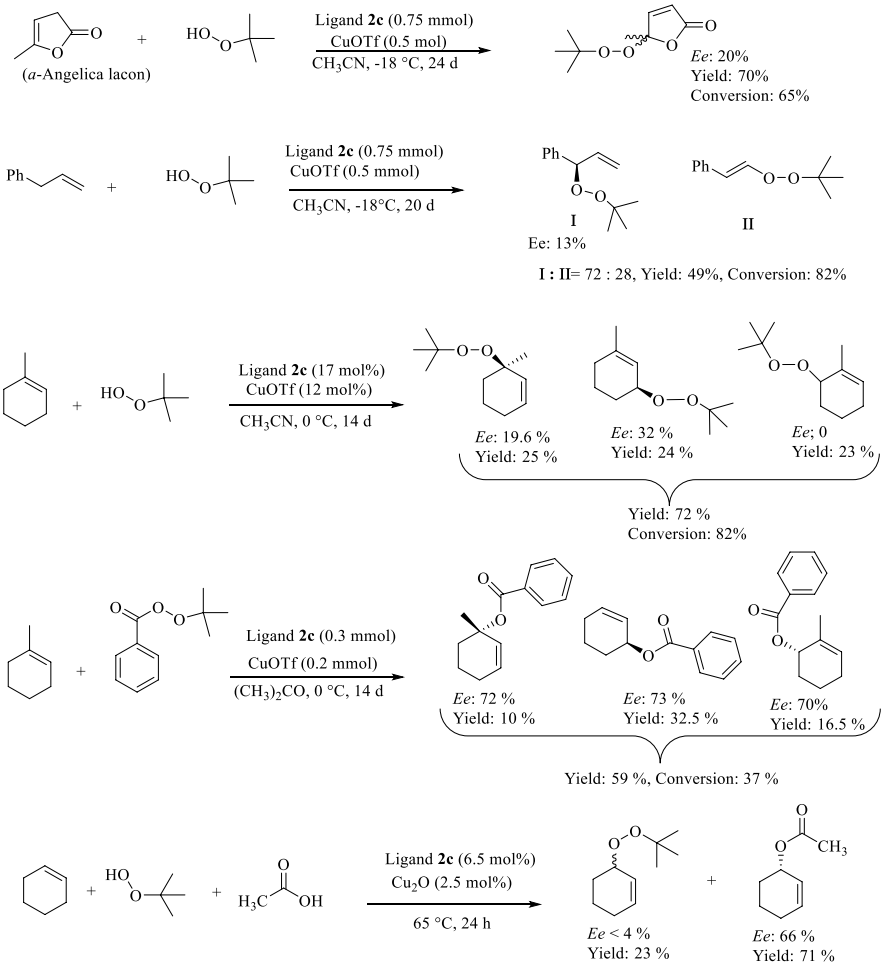
In addition to the above-mentioned comprehensive researches, some short investigations have been reported, describing a number of notable oxazoline ligands.

In most allylic oxidations, perester is added directly to the reaction mixture, but in a different strategy by Feringa and Zondervan [86], perester was generated in situ from a mixture of propionic acid and *t*-butyl hydroperoxide. However, the enantioselectivities with thiophenic and phenolic oxazoline ligands **27** and **28**, which were used in their study, were very low (Scheme 17).

A diverse range of compounds containing allylic and benzylic C–H bond has been studied by Schulz et al. with different oxidizing agents like perester, *t*-BuOOH, and *t*-BuOOH/acetic acid in the presence of Pybox **2c**-Cu(I)OTf complex [87]. The corresponding allylic esters and peroxides were obtained with poor-to-moderate selectivities and yields. The asymmetric peroxidation of methyl cyclohexene, for example, led to chiral regioisomeric allylic peroxides with enantioselectivities in the range of 0–32%. It was also observed that diminishing the amount of catalyst from 17 mol% to around 1.5 mol% led to a drastic decrease in the level of asymmetric induction. However, this drop in selectivity was almost compensated for when MS were added. It seems that deactivation of the catalyst by water, generated from decomposition of *tert*-butyl hydroperoxide, is responsible for this drop. A similar phenomenon was observed in Katsuki's studies with tetradentated tris-oxazoline ligands **4** [58, 59]. Additionally, allylic oxidation of the substituted cyclohexenes,



Scheme 17 Using in situ prepared perester in the presence of thiophenic and phenolic oxazoline ligands in asymmetric allylic oxidation of cyclohexene

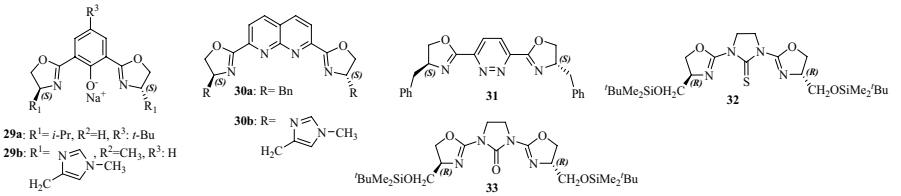


Scheme 18 Asymmetric allylic oxidation and peroxidation of alkenes with Pybox ligand **2c**

especially 1-methyl cyclohexene, by using Pybox **2c**-Cu(I), resulted in all three isomeric esters with higher enantioselectivities than those reported for BOX ligands [54], but with poor conversion. Besides, employing cyclohexene under conditions reported by Feringa and Zondervan [86] (a mixture of *t*-BuOOH/acetic acid), revealed competition between allylic acetoxylation and peroxidation (Scheme 18).

Using a series of chiral dinuclear bisoxazoline complexes, Fahrni [88] has shown that variation of the copper: ligand ratio strongly affects asymmetric induction, presumably due to changes in the structure of active catalyst species. However, the results obtained with this class of ligands were disappointing. For instance, under optimum conditions, cyclohexenyl benzoate was obtained around 38% *ee* and moderate yield (Table 19, entry 9). It is worth noting that analysis of the side products of the reaction in the presence of ligands **30** revealed formation

Table 19 Low selectivity in the presence of chiral dinclear bisoxazoline ligands



Entry	Ligand (mol%)	Time (h)	Conversion (%)	Ester	Imide	Ester	Imide
				Yield (%)		*Ee* (%)	
1	**29a** (5)	65	98	77	0	6.6*(R)*	–
2	**29a** (10)	65	43	38	0	14.7*(R)*	–
3	**29a** (20)	65	4	< 1	0	49.3*(R)*	–
4	**29b** (5)	60	55	52	0	4.9*(R)*	–
5	**30a** (5)	90	86	36	2	22.5*(S)*	0.6*(R)*
6	**30a** (10)	90	76	32	25	30.2*(S)*	5.4*(S)*
7	**30a** (20)	90	19	2	8	13.2*(S)*	10.8*(S)*
8	**30b** (5)	60	91	56	0	6.3*(S)*	–
9	**30b**	(10)60	46	36	0	37.7*(S)*	–
10	**30b** (20)	60	10	5	0	10.4*(S)*	–
11	**31** (5)	65	> 99	72	0	5.3*(R)*	–
12	**31** (10)	65	99	73	3	0.7*(S)*	–
13	**31** (20)	65	> 99	70	8	5.9*(S)*	– 1.7*(R)*
14	**32** (5)	65	17	15	0	4.2*(R)*	–
15	**32** (10)	65	83	69	0	4.5*(R)*	–
16	**33** (5)	65	86	82	0	16.8*(R)*	–
17	**33** (10)	65	> 99	97	0	8.3*(R)*	–
18	**33** (20)	65	93	92	0	11.8*(R)*	–

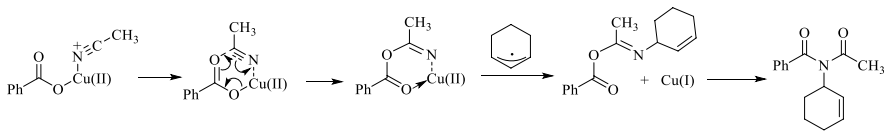
[a]Reaction performed over 21 days

[b]Activated 4 Å MS added to the reaction

of an imide product in low yield and enantioselectivity, which is formed through a sequence involving reaction of acetonitrile as solvent with the intermediate Cu(II)-benzoate complex (Scheme 19, Table 19, entries 5–7).

The extra ratio of olefin to perester 5–10 to 1 equivalent can be considered as a major drawback of allylic oxidation. This limitation has been partially solved by Christ and Sorokin [89]. Stepwise addition of *t*-butyl peroxybenzoate to the reaction mixture at a 1:1 molar ratio of cyclohexene to perester led to (*S*)-cyclohex-2-en-1-yl benzoate with good *ee* (68%) and excellent yield (99%) (Scheme 20).

Manas [90] tried to increase enantioselectivity by employing malonyl *gem*-dimethyl bisoxazoline **1g** copper (I) complex bearing bulky and rigid adamantyl moiety,

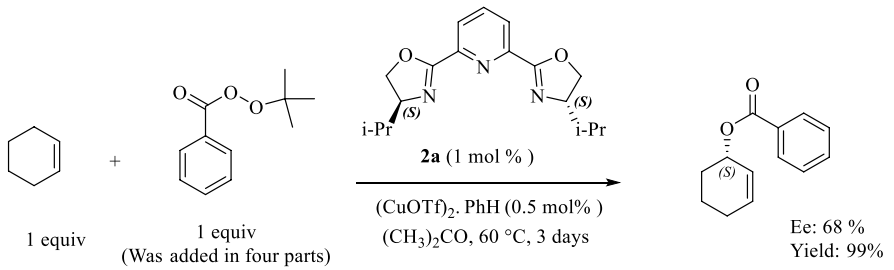


Scheme 19 Proposed mechanism for side product (allylic imide) formation

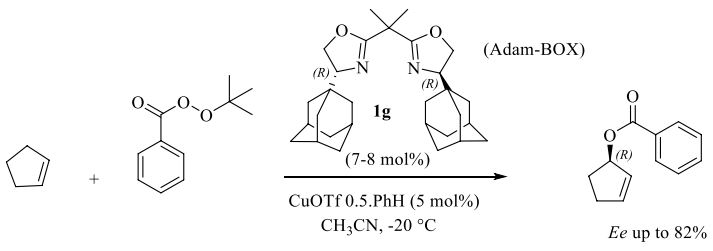
but this strategy was not so successful in comparison with the standard *t*-Bu-BOX (**1c**) [54]. The *ee* obtained in case of cyclopentene was up to 82% (Scheme 21).

Desimoni and Sinou [91] have evaluated the effect of introducing a further sterogenic center at C-5 of the oxazoline rings of malonyl gem-dimethyl and pyridine bisoxazoline ligands **34–37**. It was observed that the malonyl ligands showed better yields and selectivity than the Pybox ligands. Oxidation of five- to seven-membered cycloalkenes in the presence of Cu (I)-complexes of these type of ligands led to allylic esters up to 84% *ee* and 80% yield, i.e., no better than the simple and more accessible standard BOX ligands **1** [54] (Table 20). It should be noted that the sense of the asymmetric induction is determined by the absolute configuration at C-4, while the additional stereogenic centers at C-5 induce a small-to-modest match/mismatch effect.

Additional steric congestion has been introduced by attaching various groups to the bridging carbon of the bisoxazolines. Gade and his colleagues have reported a series of bisxazoline-derivatives with one or two sidearms attached to the bridge carbon atoms [92]. Under optimum conditions in the presence of 5 mol% of Cu

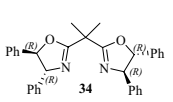


Scheme 20 Asymmetric allylic oxidation by stepwise addition of perester at a 1:1 molar ratio of cyclohexene to perester

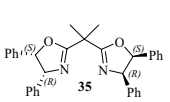


Scheme 21 Application of Adam-BOX in asymmetric allylic oxidation of cyclopentene

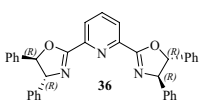
Table 20 Asymmetric allylic oxidation of cycloolefins by using diPhPyBOX and diPhBOX



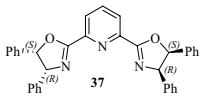
trans-(4R,5R)-4,5-diPhBox



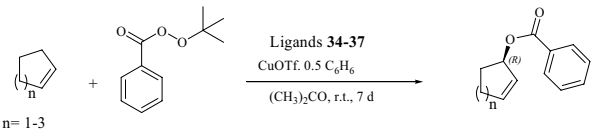
cis-(4R,5S)-4,5-diPhBox



trans-(4R,5R)-4,5-diPhPyBox



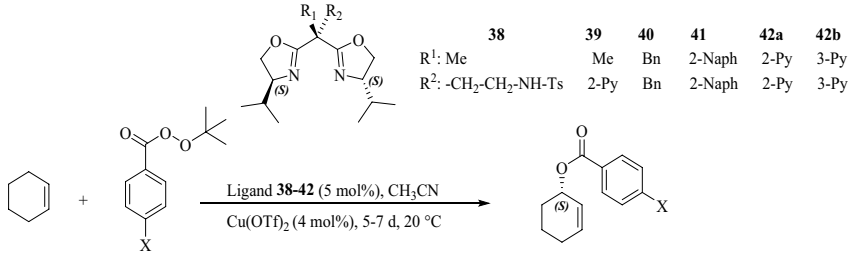
cis-(4R,5S)-4,5-diPhpyBox



Entry	*n*	Ligand	Yield (%)	*Ee* (%)
1	1	**34**	80	84
2	1	**35**	70	80
3	1	**36**	26	3
4	1	**37**	37	15
5	2	**34**	70	64
6	2	**35**	78	61
7	2	**36**	66	28
8	2	**37**	60	36
9	3	**34**	50	62
10	3	**35**	50	80
11	3	**36**	28	26
12	3	**37**	42	48

(II)-ligands **38–42** in combination with *tert*-butyl *p*-nitroperbenzoate at 20 °C, cyclohex-2-en-1-yl 4-nitrobenzoate was obtained with respectable levels of asymmetric induction (*ee* up to 85%) and moderate yield (52%) (Table 21, entry 8). It was shown that the *ee* is increased considerably by introducing two sidearms on the bisoxazolines. It seems that, as a result of coordination of 2-pyridyl groups to the Cu at the bridging C-atom of ligand **42a**, the level of asymmetric induction and yield are better than ligand **42b** with 3-pyridyl groups (Table 21, entries 5 vs 6 and 10 vs 11).

Table 21 Role of sidearm(s) in asymmetric induction

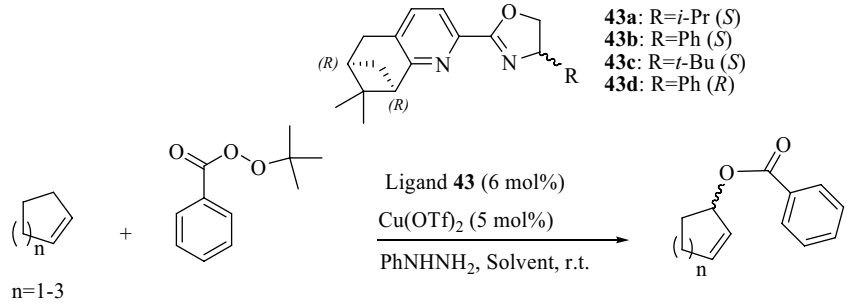


Entry	Ligand	*X*	Yield (%)	*Ee* (%)
1	**38**	H	70	60
2	**39**	H	44	61
3	**40**	H	55	80
4	**41**	H	52	77
5	**42a**	H	61	79
6	**42b**	H	54	55
7	**38**	NO_2	87	77
8	**40**	NO_2	52	85
9	**41**	NO_2	42	84
10	**42a**	NO_2	60	82
11	**42b**	NO_2	49	65

Malkov and Kocovsky [93] introduced pinene-derived pyridyl oxazolines **43**, containing additional chiral elements in the pinene backbone, for allylic oxidation of five- to seven-membered cycloolefins. The use of this type of ligand in conjunction with copper (II) and phenyl hydrazine resulted in the corresponding chiral allylic esters in modest enantioselectivities and yields. In the best case, up to 67% *ee* was obtained in the oxidation of cycloheptene employing chiral ligand **43a** in acetone at room temperature. It should be noted that changes in the stereochemistry of the ligand at the oxazoline moiety did change the configuration of the chiral allylic esters (Table 22, entries 12–14), reflecting the fact that enantiodiscrimination is influenced mainly by the chirality of the oxazoline ring rather than by the pinene unit.

In general, a drop in asymmetric induction is observed when the reaction temperature is raised. Pfaltz and coworkers [94] could partially overcome this drawback by designing boron-bridged bisoxazolines (Borabox) **44** prepared from chiral oxzolines and haloboranes. Higher electron density at the metal center of Borabox complexes, and a larger bite angle due to the longer bond between the boron atom and

Table 22 Allylic oxidation of cycloolefins with pinene-derived 2-pyridyl oxazoline ligands **43**

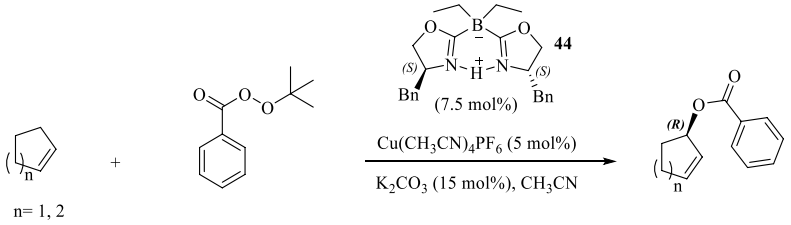


Entry	Ligand	*n*	Solvent	Time (h)	Yield (%)	*Ee* (%)
1	**43a**	2	$(CH_3)_2CO$	0.5	67	44 (*S*)
2	**43a**	2	CH_3CN	72	15	60 (*S*)
3	**43a**	2	$CH_3COOC_2H_5$	72	15	20 (*S*)
4[a]	**43a**	2	$(CH_3)_2CO$	72	45	45 (*S*)
5	**43a**	3	$(CH_3)_2CO$	6	62	67 (*S*)
6	**43b**	1	$(CH_3)_2CO$	16	39	0
7	**43b**	2	$(CH_3)_2CO$	16	62	22 (*S*)
8	**43b**	3	$(CH_3)_2CO$	16	50	23 (*S*)
9	**43c**	1	$(CH_3)_2CO$	3	43	14 (*S*)
10	**43c**	2	$(CH_3)_2CO$	0.5	62	7 (*S*)
11	**43c**	3	$(CH_3)_2CO$	1.5	48	42 (*S*)
12	**43d**	2	$(CH_3)_2CO$	0.5	76	19 (*R*)
13	**43d**	2	$CHCl_3$	72	43	14 (*R*)
14	**43d**	3	$(CH_3)_2CO$	5	72	30 (*R*)

[a]Reaction carried out at 0 °C

the oxazoline rings, are the main features of this type of ligand. It was observed that both enantioselectivity and yield were affected only moderately by the reaction temperature, and good-to-high enantiomeric excesses were obtained within a temperature range from –15 to + 80 °C (Table 23). Cyclopentene showed lower temperature dependence of the asymmetric induction compared with cyclohexene. At high temperature (+80 °C), cyclopentene and cyclohexene were oxidized with 76% and 65% enantioselectivities and good yields in 1 h and 11 h, respectively (Table 23, entries 6 and 9).

Table 23 Lower temperature dependence of Borabox in allylic oxidation of cyclopentene and cyclohexene



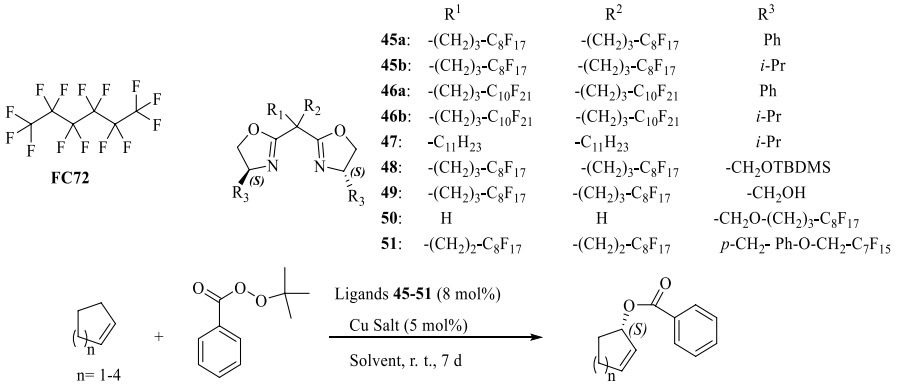
Entry	*n*	T (°C)	Time (h)	Yield (%)	*Ee* (%)
1	1	−15	360	30	86
2	1	5	141	80	82
3	1	25	48	79	82
4	1	40	8	78	81
5	1	60	2	70	78
6	1	80	1	69	76
7	2	25	219	69	79
8	2	60	86	72	68
9	2	80	11	61	65

3.2 Heterogeneous catalysts

Due to potential benefits of heterogeneous over homogeneous catalyst systems such as easy handling as well as simple separation and also combination of these features with several reused cycles without considerable loss of catalyst activity, some attempts have been made to prepare chiral heterogeneous oxazoline-based catalysts during the last two decades [32, 33, 95–97]. Although only a small number of such heterogeneous catalysts have been applied in asymmetric allylic oxidation to date, remarkable results have been obtained and in some cases these catalysts can compete with homogeneous analogs.

The first study with heterogeneous catalyst was carried out in 2004 by Sinou and Bayardon [98], who prepared fluorous bis(oxazolines) with fluorine content between 52.7 and 58.7% by alkylation of the methylene bridge of bis(oxazolines) **45–51**. Allylic oxidation of cycloalkenes at room temperature catalyzed by Cu (I)-ligand **45** and **46** complexes under biphasic conditions (FC72/CH_3CN) gave the corresponding allylic benzoates in enantioselectivities of up to 77% *ee* and yields of up to 86% after 7 days (Table 24). These results were quite close to those obtained with analogous non-flourous bis(oxazolines) under similar conditions (Table 24, entry 7). Although the recycling of $CuPF_6$-ligands **45** and **46** was unsatisfactory (Table 24, entries 9 and 14), allylic oxidation at 50 °C in a mixture of $CHCl_3$/CH_3CN allowed easy separation of the catalyst system. It should be noted that reusing the heterogeneous catalyst in another reaction, resulted in a considerable decrease in the enantioselectivity (Table 24, entry 4 vs 5). Increasing the fluorine content to 56.9% and 59.3% by

Table 24 Use of heterogeneous fluorous bis(oxazolines) ligands in enantioselective allylic oxidation



Entry	*n*	Ligand	Cu salt	Solvent	Yield (%)	*Ee* (%)
1	2	**45a**	CuOTf. 0.5 PhH	$CHCl_3/CH_3CN$	51	73
2	2	**45a**	CuOTf. 0.5 PhH	$FC72/CH_3CN$	61	69
3	2	**45b**	CuOTf. 0.5 PhH	$CHCl_3/CH_3CN$	48	62
4[a]	2	**45b**	CuOTf. 0.5 PhH	$CHCl_3/CH_3CN$	51	57
5[b,c]	2	**45b**	CuOTf. 0.5 PhH	$CHCl_3/CH_3CN$	53	37
6	2	**45b**	CuOTf. 0.5 PhH	$FC72/CH_3CN$	66	60
7[d]	2	**47**	CuOTf. 0.5 PhH	$CHCl_3/CH_3CN$	64	61
8	2	**45b**	$Cu(CH_3CN)_4PF_6$	$FC72/CH_3CN$	67	61
9[e]	2	**45b**	$Cu(CH_3CN)_4PF_6$	$FC72/CH_3CN$	< 10	–
10	2	**46a**	CuOTf. 0.5 PhH	$FC72/CH_3CN$	51	71
11	2	**46b**	CuOTf. 0.5 PhH	$FC72/CH_3CN$	48	60
12	2	**46b**	$Cu(CH_3CN)_4PF_6$	$FC72/CH_3CN$	39	60
13[a]	2	**46b**	$Cu(CH_3CN)_4PF_6$	$FC72/CH_3CN$	49	52
14[e]	2	**46b**	$Cu(CH_3CN)_4PF_6$	$FC72/CH_3CN$	< 10	–
15	2	**48**	CuOTf. 0.5 PhH	$CHCl_3/CH_3CN$	37	71
16	2	**49**	CuOTf. 0.5 PhH	$CHCl_3/CH_3CN$	9	–
17	1	**45a**	CuOTf. 0.5 PhH	$FC72/CH_3CN$	86	77
18	3	**45a**	CuOTf. 0.5 PhH	$FC72/CH_3CN$	58	49
19	4	**45a**	CuOTf. 0.5 PhH	$FC72/CH_3CN$	32	10
20[f]	2	**50**	CuOTf. 0.5 PhH	$CHCl_3/CH_3CN$	76	43
21[f]	2	**51**	CuOTf. 0.5 PhH	$CHCl_3/CH_3CN$	49	50
22[f,g]	2	**51**	CuOTf. 0.5 PhH	$CHCl_3/CH_3CN$	43	50
23[f]	2	**51**	$Cu(CH_3CN)_4PF_6$	$FC72/CH_3CN$	12	–

[a]Reactions performed at 50 °C for 2 days

[b]The precipitated catalyst from entry 4 was reused

[c]Experiment performed at 50 °C for 3 days

[d]Experiment performed at 50 °C for 9 days

[e]Recycling experiment

[f]Reactions were performed at 50 °C in 168, 48, 48, 72 h, respectively

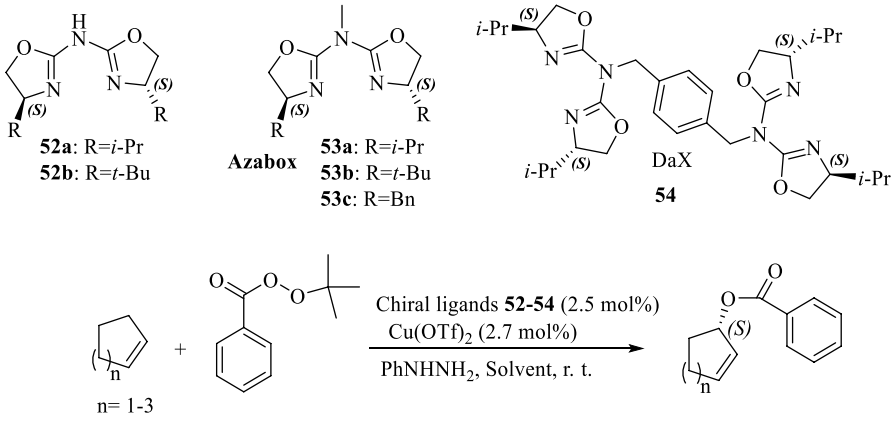
[g]Using recycled catalyst from entry 21

using bis (oxazolines) **50** and **51** derived from amino acids (*S*)-serine and (*S*)-tyrosine gave (*S*)-cyclohex-2-en-1-yl benzoate in lower yield and enantioselectivity [99]. It was found that conducting the reaction in a mono-phasic solvent system ($CHCl_3$/CH_3CN) provided better results compared with the biphasic system FC72/CH_3CN (Table 24, entries 23 vs 20–21). In fact, in comparison with ligand **50**, when the reaction was carried out with ligand **51** at 50 °C, the rate was accelerated (2 days vs 7 days) and a slight increase in the *ee* and a drop in yield was observed (Table 24, entry 20 vs 21). Moreover, recovery and reuse of the catalyst did not show any change in enantioselectivy, while the yield was diminished slightly (Table 24, entry 22).

In an interesting approach, Reiser and Garcia [100] introduced a recoverable and reusable catalyst based on ditopic aza-bisoxazoline ligand (DaX **54**) and Cu salts. This ligand is capable of coordinating with two copper ions, leading to the formation of linear polymers, where each Cu salt is linked to two bisoxazoline units. In contrast with conventional heterogeneous catalysts, these coordination polymers are disassembled by coordinating solvents such as acetone and acetonitrile and then converted to soluble homogeneous aza-bisoxazoline-copper complexes. However, the initial insoluble solid coordination polymer could be reassembled if the solvent was replaced with a non-coordinating solvent like *n*-hexane. Evaluation of this ingenious catalytic system in allylic oxidation of five- to seven-membered cycloolefins in the presence of copper (II) and phenylhydrazine at room temperature gave the chiral allylic products in good-to-high yield (up to 92%) and enantioselectivity (up to 90%) with outperforming analogous homogeneous catalysts derived from bis(oxazolines) and aza-bis(oxazolines) **52** and **53** (Table 25). *N*-methylated azabis(oxazoline) **53a** showed better results than the corresponding unsubstituted ligand **52a** (Table 25, entries 1–7). Besides, in agreement with most studies, the use of phenylhydrazine, as a reducing agent, for reducing Cu (II) to catalytically active Cu (I) is crucial (Table 25, entries 4, 5). The bulky *tert*-butyl substituted ligand **53b** did not result in reasonable enantiomeric excess (Entry 6). Another notable feature of the self-supported ligand **54-**Cu catalytic system is that it can be recycled easily by filtration and reused several times without considerable loss of reactivity and enantioselectivity. It was also observed that recharging the reaction with a small amount of the chiral ligand (0.5 mol %) after each recovery, maintained both the yield and the enantioselectivity relatively constant, whereas recharging with 0.5 mol % $Cu(OTf)_2$ contributed to an increase in the yield and a small decrease in *ee*.

In continuation of our studies with mesoporous additives that had a notable effect on the enantioselectivity, our research group designed and synthesized a series of chiral 4-oxazolinylaniline ligands **55** on a gram scale from 4-amino benzoic acid in four steps and then covalently grafted them on ordered silica

Table 25 Ditopic aza-bisoxazoline ligand **54** as an efficient recoverable and reusable catalyst

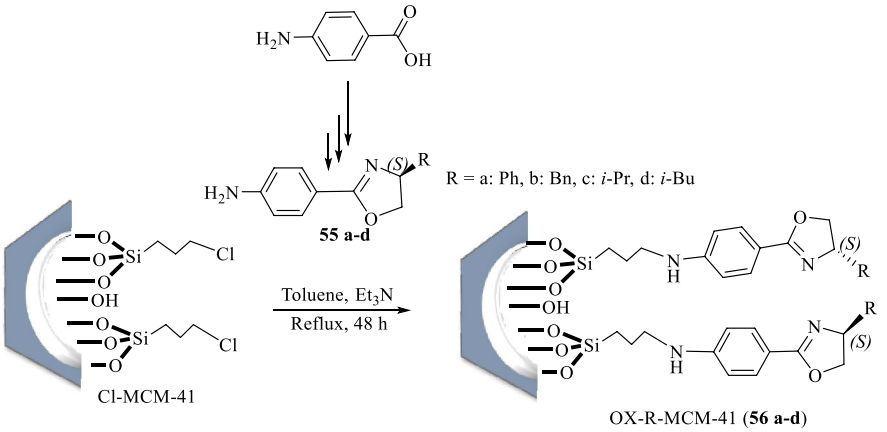


Entry	*n*	Ligand	Solvent	Time (h)	Conversion (%)	*Ee* (%)
1	2	**52a**	$(CH_3)_2CO$	1	67	55
2[a]	2	**52a**	$(CH_3)_2CO$	16	64	66
3	2	**52b**	$(CH_3)_2CO$	2	74	75
4	2	**53a**	CH_3CN	36	93	85
5[b]	2	**53a**	CH_3CN	36	38	74
6	2	**53b**	CH_3CN	36	68	40
7	2	**53c**	$(CH_3)_2CO$	16	54	78
8	2	**53a**	CH_3CN	36	78	85
9	2	**54**	CH_3CN	36	88	84
10	1	**53a**	CH_3CN	36	80	87
11	1	**54**	CH_3CN	36	89	85
12	3	**53a**	CH_3CN	36	82	85
13	3	**54**	CH_3CN	36	92	90

[a]Reaction was carried out at 0 °C

[b]In the absence of phenylhydrazine

mesoporous MCM-41 (Scheme 22). Evaluating these heterogeneous catalysts showed that the most promising results were obtained with catalyst **56a** in conjunction with $Cu(CH_3CN)_4PF_6$ in acetonitrile at −10 °C and in the presence of phenylhydrazine (Table 26, entries 1, 5, 9, 13, 17). Although only a slight

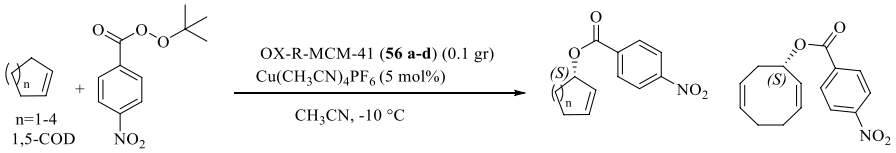


Scheme 22 Immobilization of oxazolinylanilines on mesoporous MCM-41

decrease in the enantioselectivity and yield was observed in the absence of phenylhydrazine, the reactivity was diminished significantly. The corresponding chiral allylic esters were obtained in moderate-to-good enantioselectivities (up to 80%) and high yields (up to 95%). 1,5-Cyclooctadiene was also oxidized with the highest enantioselectivity and yield (Table 26, entry 17), in line with our previous studies. Importantly, the catalyst could be recovered easily and reused five times without notable decrease in enantioselectivity, yield, and reactivity [32].

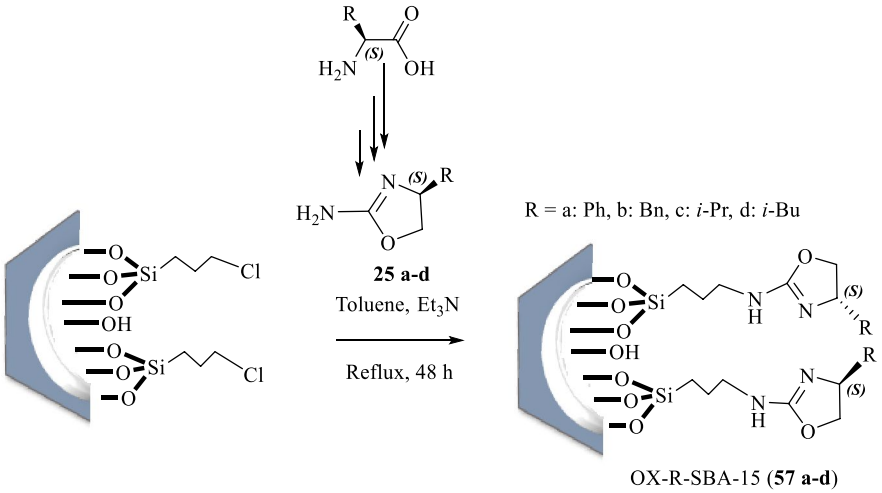
In our most recent study, amino oxazoline ligands **25** were immobilized covalently on mesoporous SBA-15 (Scheme 23) [101]. Consistent with our previous studies and the findings of Katsuki [58], the best results were achieved with phenyl- or benzyl-substituted oxazolines (**57a** or **57b**), which can be attributed to the interaction between allyl radical intermediates and aryl substituents in the transition state. In contrast to most catalyst systems, reactions at room temperature provided remarkably high enantioselectivities. Although lowering the temperature led to a small increase in *ee*, both the reactivity and yield were markedly diminished (Table 27, entries 1 vs 6 and 7). Allylic oxidation by using *t*-butyl *p*-nitroperbenzoate and *t*-butyl *o*-iodoperbenzoate in conjunction with $Cu(CH_3CN)_4PF_6$ in

Table 26 Using chiral 4-oxazolinylaniline ligands grafted on MCM-41 mesoporous silica in allylic oxidation



Entry	*n*	Ligand	Time (h)	Yield (%)	*Ee* (%)
1	1	**56a**	150	70	53
2	1	**56b**	185	62	48
3	1	**56c**	250	65	22
4	1	**56d**	235	60	15
5	2	**56a**	195	82	70
6	2	**56b**	185	82	60
7	2	**56c**	195	70	33
8	2	**56d**	186	75	33
9	3	**56a**	175	75	50
10	3	**56b**	215	55	57
11	3	**56c**	225	50	28
12	3	**56d**	225	55	20
13	4	**56a**	250	59	53
14	4	**56b**	255	59	50
15	4	**56c**	280	55	18
16	4	**56d**	300	45	10
17	1,5-COD	**56a**	140	95	80
18	1,5-COD	**56b**	180	85	68
19	1,5-COD	**56c**	210	75	32
20	1,5-COD	**56d**	225	80	23

acetonitrile led to almost the same *ee* values and yields, which were higher than those obtained with other peroxybenzoates containing electron-donating or -withdrawing substituents at the ortho or para position (Table 27, entries 1 vs 8–13). This catalyst system gave higher yields (up to 95%) and enantioselectivities (up



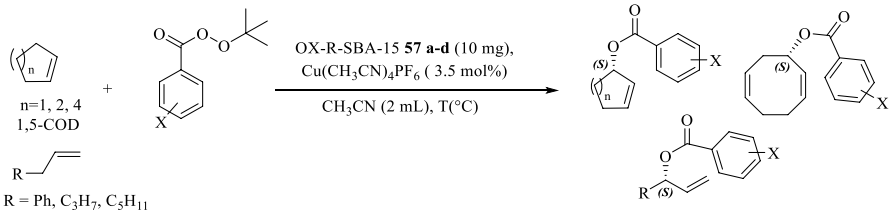
Scheme 23 Immobilization of amino oxazolines on mesoporous SBA-15

to 96%) for cyclic alkenes in comparison with the other reported heterogeneous catalysts (Table 27, entries 1 and 13–19). In the case of acyclic substrates such as 1-hexene, 1-octene, and allyl benzene, the reaction proceeded with poor yields of up to 23% and enantioselectivities of up to 18% (Table 27, entries 20–22). Moreover, the results have shown that the homogeneous *N*-Me-amino oxazoline (*N*-Me-**25b**) can induce chirality better than amino oxazoline **25b**. Nevertheless, the enantioselectivity of heterogeneous catalysts **57b** was higher than that of homogeneous analogues (Table 27, entries 1 vs 23, 24). This heterogeneous catalyst system can be recovered easily and applied to several consecutive catalytic runs without affecting the results significantly.

4 Conclusions

This review focused on the development of asymmetric allylic oxidation of olefins in the presence of copper-oxazoline complexes. Although accomplished studies have been limited so far mostly to simple substrates, some general conclusions can be drawn. In the case of unsubstituted cyclic olefins, although accessible standard BOX at low temperature (−20 °C) functions as an effective ligand, the yields are only moderate and the rate of the reaction is slow. Use of $Cu(CH_3CN)_4PF_6$ and CuOTf, and sometimes $Cu(OTf)_2$, in acetonitrile and acetone was found to give the best results. Excellent enantioselectivity can be obtained using *t*-butyl *p*-nitroperbenzoate as an oxidant. Addition of a small amount of phenylhydrazine as a reducing agent, in most cases, leads to the

Table 27 Immobilized amino oxazoline on mesoporous SBA-15 as a most efficient heterogeneous catalyst



Entry	*n*	Ligand	*X*	*T* (°C)	Time (h)	Yield (%)	*Ee* (%)
1	2	**57b**	*o*-I	r.t	24	90	90
2	2	*ent*-**57b**	*o*-I	r.t	32	85	− 80
3	2	**57a**	o-I	r.t	28	95	81
4	2	**57c**	*o*-I	r.t	45	87	41
5	2	**57d**	*o*-I	r.t	49	82	46
6	2	**57b**	*o*-I	0	72	68	93
7	2	**57b**	*o*-I	− 10	102	54	95
8	2	**57b**	*o*-Br	r.t	50	83	77
9	2	**57b**	*o*-Cl	r.t	36	84	74
10	2	**57b**	*p*-Cl	r.t	30	75	76
11	2	**57b**	*p*-Me	r.t	64	60	45
12	2	**57b**	H	r.t	53	70	61
13	2	**57b**	*p*-NO_2	r.t	40	95	90
14	1	**57b**	*o*-I	r.t	40	85	87
15	1	**57b**	*p*-NO_2	r.t	38	90	86
16	4	**57b**	*o*-I	r.t	56	79	85
17	4	**57b**	*p*-NO_2	r.t	40	77	72
18	1,5-COD	**57b**	*o*-I	r.t	24	95	88
19	1,5-COD	**57b**	*p*-NO_2	r.t	27	90	90
20	1-Hexene	**57b**	*o*-I	r.t	96	17	10
21	1-Octene	**57b**	*o*-I	r.t	84	20	15
22	Allyl benzene	**57b**	*o*-I	r.t	70	23	18
23	2	**25b**	*o*-I	r.t	72	30	15
24	2	*N*-Me-**25b**	*o*-I	r.t	45	70	50

acceleration of this slow reaction. Moreover, porous additives such as MS, SBA-15, and HZSM-5 have a beneficial effect on the enantioselectivities, yields and also on the rate of reaction. The high ratio of olefin to perester is a drawback that can be reduced from 10–5:1 to 3:1 by employing homogeneous **26**-CuOTf catalysts. Only a few studies on heterogeneous ligands have been reported to date, but the results have been very promising. Simple aminooxazolines immobilized on SBA-15 (ligand **57**) gave the corresponding enantioenriched allylic esters in high *ee*s and yields at room temperature in shorter times than analogous homogeneous

catalysts. It is noteworthy that this heterogeneous system can be recovered and reused easily without significant loss of catalytic activity. Despite considerable progress in this field, low regioselectivity remains as a major challenge for unsymmetric cyclic substrates and acyclic olefins. Moderate enantioselectivity and yield with high regioselectivity have been obtained for acyclic olefins only by spiro ligand **24**. So far, there is still a lack of a reliable mechanistic model that could serve as a basis for the design of new catalysts. Thus, further studies will be needed to emphasize mechanistic aspects in order to obtain a clearer picture of the catalyst-substrate interactions and other factors that play a role in the reaction, such as additives, solvent, etc.

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Declarations

Conflict of Interest The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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