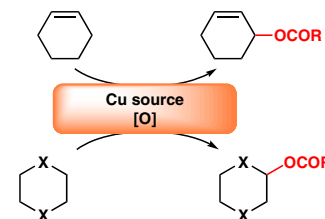


Copper-Catalyzed Oxidation of Alkenes and Heterocycles

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Abstract A variety of copper species catalyze the allylic oxidation of olefins and the introduction of an ester group at the α -position of a heterocycle. Both transformations are closely related in terms of reaction conditions and radical species involved. This short review highlights the progress made in these two types of oxidations, emphasizing work that has occurred within the last fifteen years.

- 1 Introduction
- 2 General Overview of the Copper-Catalyzed Allylic Oxidation of Olefins
- 3 Mechanistic Considerations
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- 5 Other Landmarks of the Copper-Catalyzed Oxidation of Olefins
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Key words allylic oxidation, α -acyloxylation, copper, Kharasch–Sosnovsky reaction, olefins, heterocycles

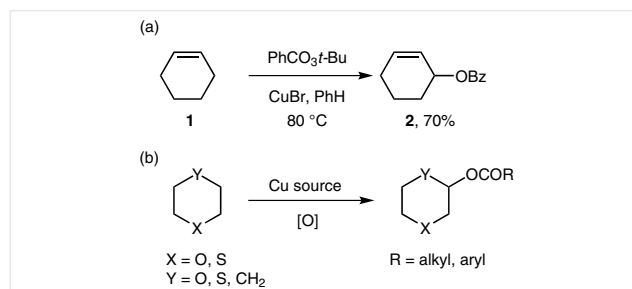
1 Introduction

The oxidation of C–H bonds is one of the more active fields in chemistry at the present time.¹ With the aim of converting the indolent C–H bond into a more manageable functional group, the synthetic community is making a great effort to overcome the main problems associated with this task: the inertness of the C–H bonds, the control of selectivity in molecules bearing different types of these bonds, and the overoxidation of the products. These factors have hampered the wider incorporation of C–H bonds into the pool of synthetically useful functional groups.

Although this kind of transformation is a complex problem, one can find, however, favorable scenarios. The presence of a double bond in a molecule is usually enough to

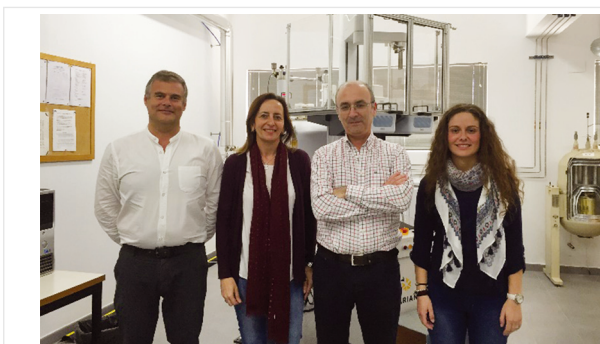
activate allylic hydrogen atoms towards oxidation. Likewise, C–H bonds located contiguous to heteroatoms are also activated and can be conveniently transformed into other functional groups under certain oxidative conditions. To help in this task, a useful ally has been found in the humblest of the coinage metals: copper.

In 1958, a very interesting group of Cu-catalyzed reactions was discovered by Kharasch and published posthumously by his students in a series of papers.² Basically, they discovered that traces of copper or cobalt altered the outcome of a reaction between an organic peroxide and an alkene. The reaction was thereafter known as the Kharasch–Sosnovsky oxidation and an example is the oxidation of cyclohexene (**1**) with *tert*-butyl peroxybenzoate ($\text{PhCO}_3t\text{-Bu}$) in the presence of CuBr (Scheme 1, a).



Scheme 1 (a) The Kharasch–Sosnovsky oxidation of cyclohexene (**1**). (b) α -Acyloxylation of O- and/or S-containing heterocycles.

Interest in this transformation has suffered its ups and downs. After its discovery, it went unnoticed for many years, until the early 1990s, when the first examples of enantioselective versions were described. Once it was found that there would not be a universal catalytic system and that each reaction should be optimized individually, interest somewhat waned. However, at present, there seems to



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be a renaissance, given the mentioned interest in the oxidation of C–H bonds.

Early on, some studies demonstrated that the same conditions employed for the copper-catalyzed allylic oxidation of olefins, could be applied to the α -oxidation of heterocycles. Notwithstanding its potential as a way to construct densely functionalized heterocycles, this transformation has received less attention, although some remarkable examples have been, indeed, reported (Scheme 1, b).

Two short reviews by Brunel, Buono, et al.³ and by Eames and Watkinson⁴ and a comprehensive one by Andrus and Lashley⁵ covered the Kharasch–Sosnovsky reaction until the beginning of the 2000s. More than a decade has passed and new information about the mechanism of these transformations has been obtained. New ligands and more efficient procedures have also been discovered. It seems, therefore, appropriate to update our view of the topic. In this short review, we will mainly highlight those key landmarks not covered by the previously mentioned reviews. However, to ease the reading, we will also include significant aspects that have already been mentioned in these works that are relevant to explain the current status of the subject.

2 General Overview of the Copper-Catalyzed Allylic Oxidation of Olefins

There are important reasons to explain why this reaction has not been fully incorporated into the pool of synthetically useful reactions. On one hand, it is common to find procedures requiring long reaction times, usually days. On the other hand, the reaction usually takes place using a large excess of the alkene, typically a five- to ten-fold excess, and the yields are given based upon the oxidant. Although this is not a problem when the substrate is a simple alkene such as cyclohexene (**1**), it can be a serious drawback in cases when the olefin is expensive or has to be synthesized by a laborious route.

The reaction proceeds well either with copper(I) or copper(II) sources and even other metals such as cobalt have been described to catalyze the reaction.^{2a} The copper sources are diverse, from cheap CuBr, CuCl, Cu₂O, or CuO to more sophisticated copper complexes.

The oxidant is usually a peroxyester, *tert*-butyl peroxybenzoate being the most frequent, although many examples of the use of *tert*-butyl peroxyacetate have been reported.⁵ Additionally, *tert*-butyl hydroperoxide (TBHP) in the presence of a carboxylic acid is an alternative oxidation system. Peroxyesters have been traditionally prepared from anhydrous *tert*-butyl hydroperoxide and carboxylic acid chlorides. Recently, Wan et al. have described a useful method for the preparation of *tert*-butyl peroxyesters from aldehydes that can be employed in these copper-catalyzed reactions.⁶

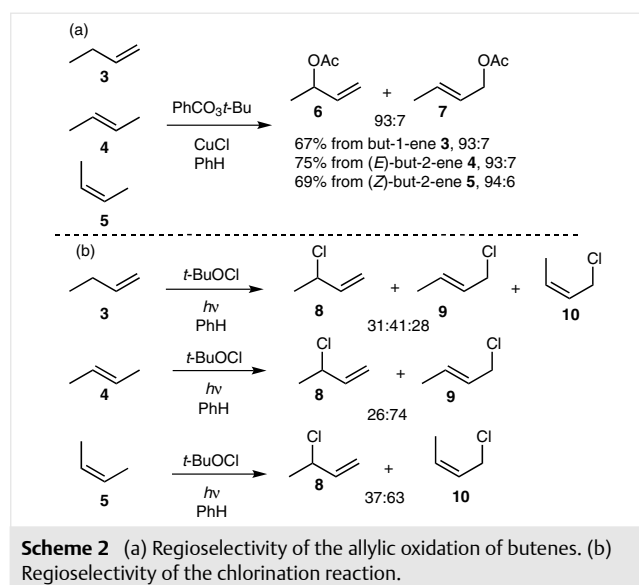
The substrate nature has been somewhat limited. Most of the work has been done with hydrocarbons, mainly cyclic alkenes or very simple linear alkenes. Cyclohexene (**1**) has been the substrate of choice in most studies, usually providing the highest yields among related olefins under a wide range of conditions. Cyclooctene also proceeds with moderate to good yields. In contrast, the behavior of cyclopentene and cycloheptene is less predictable. Benzylic sys-

tems can also be employed, although the reaction rate seems to be slower than in allylic systems.⁷

With regard to solvents, the reaction proceeds well in solvents such as acetonitrile or benzene. Rigorous exclusion of water is not necessary. In fact, it has been reported that a 70% aqueous solution of *tert*-butyl hydroperoxide can be used as the oxidant in the presence of the carboxylic acid to be incorporated. Obviously, solvents bearing active hydrogen atoms that can produce stable radicals are to be avoided.

The regiochemistry of the copper-catalyzed allylic oxidation of olefins has been an important issue, and it has provided fundamental insights into the mechanism. In a simple substrate such as 1-methylcyclohexene, its oxidation already provides three regioisomeric esters. The oxidation of allylic positions located in cycles is preferred over exocyclic ones. Such is the case of 4-vinylcyclohexene, where no oxidation is observed adjacent to the appended vinyl group.⁸

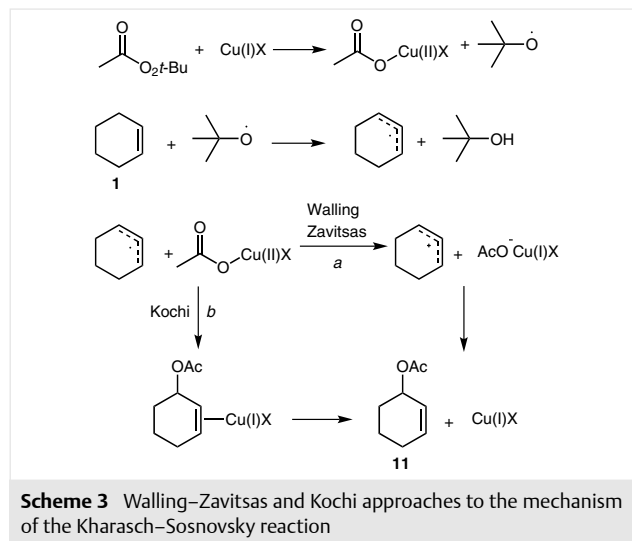
Beckwith and Zavitsas carried out a complete study of the copper-catalyzed allylic oxidation of terminal olefins.⁹ The regioselectivity was compared with that obtained by chlorination with *tert*-butyl hypochlorite of the same olefins, a well-known radical reaction (Scheme 2). In the case of allylic oxidation, there was a marked bias toward the formation of the secondary internal ester with the thermodynamically less stable alkene. It was also observed that but-1-ene (**3**), (*E*)-but-2-ene (**4**), and (*Z*)-but-2-ene (**5**) provided the same mixture of 3-acetylbut-2-ene (**6**) and (*E*)-1-acetylbut-2-ene (**7**). This different trend in both reactions seemed to point to a more complex mechanism for allylic oxidation than the formation and trapping of a discrete radical. With all these data, these authors proposed the generally accepted mechanism⁹ that has been revised recently by several groups.



3 Mechanistic Considerations

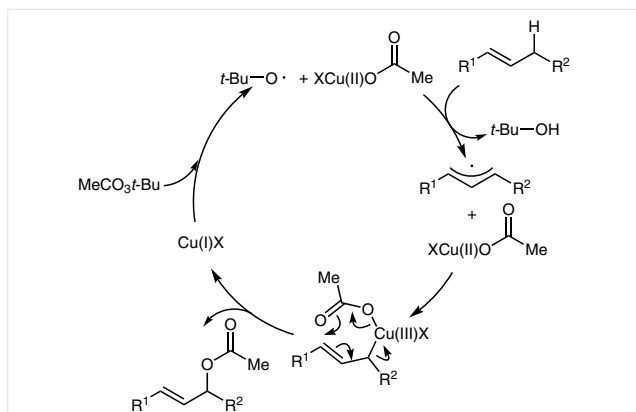
The mechanism of the reaction has been controversial. At first, it was assumed that the reaction between *tert*-butyl peracetate and the copper source generated a Cu(II) carboxylate and *tert*-butoxy radical. This latter species abstracts a hydrogen atom of cyclohexene (**1**), to give an allyl radical and *tert*-butyl alcohol.

From this point onward, different alternatives have been presented. Walling and Zavitsas (Scheme 3, route *a*), proposed that the reaction between the allylic radical and the Cu(II) carboxylate produces an allylic cation that is trapped by the acetate group to provide the corresponding allylic acetate **11**.¹⁰ Alternatively, Kochi proposed that the reaction takes place through a Cu(II)- η^2 -olefin complex and subsequent ligand-controlled transfer of the acetate group to give the allylic ester (Scheme 3, route *b*).¹¹



In 1986, Beckwith and Zavitsas, in order to explain the selectivity of the allylic oxidation of *cis*-but-2-ene and *trans*-but-2-ene, proposed the formation of a Cu(III) intermediate that rearranges through a concerted process to yield the allylic acetate.⁹ This approach is consistent with the observed regioselectivity (Scheme 4).¹²

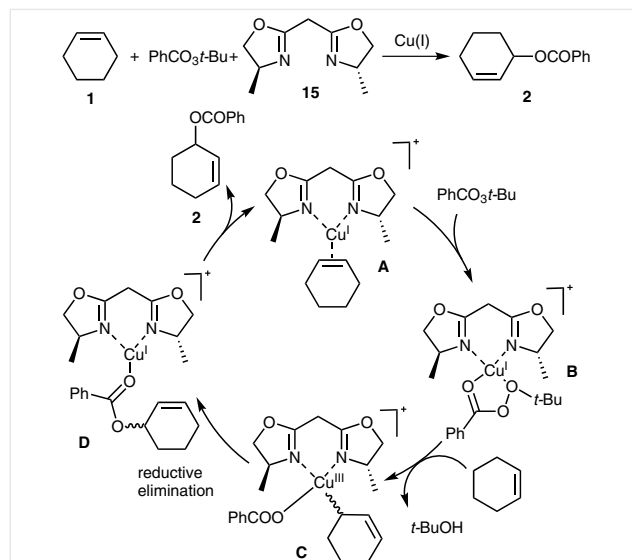
Slough et al., in a comparative study on allylic amination vs allylic oxidation, proposed that the C-H abstraction from cyclohexene (**1**) must occur on a copper-alkene complex, according to the mechanism shown in Scheme 5.¹³ Starting from the precatalyst **A**, the incorporation of a benzoic acid (**14**) molecule provides the complex **B**. Next, the incorporation of 3,3,6,6-tetradeuteriocyclohexene gives the 19-electron complex **C**, which evolves to an 18-electron Cu(III) intermediate **D**. Cleavage of the Cu-C bond in complex **D** would lead to the original catalyst and a cyclohexenyl radi-



Scheme 4 Proposal of mechanism by Beckwith and Zavitsas

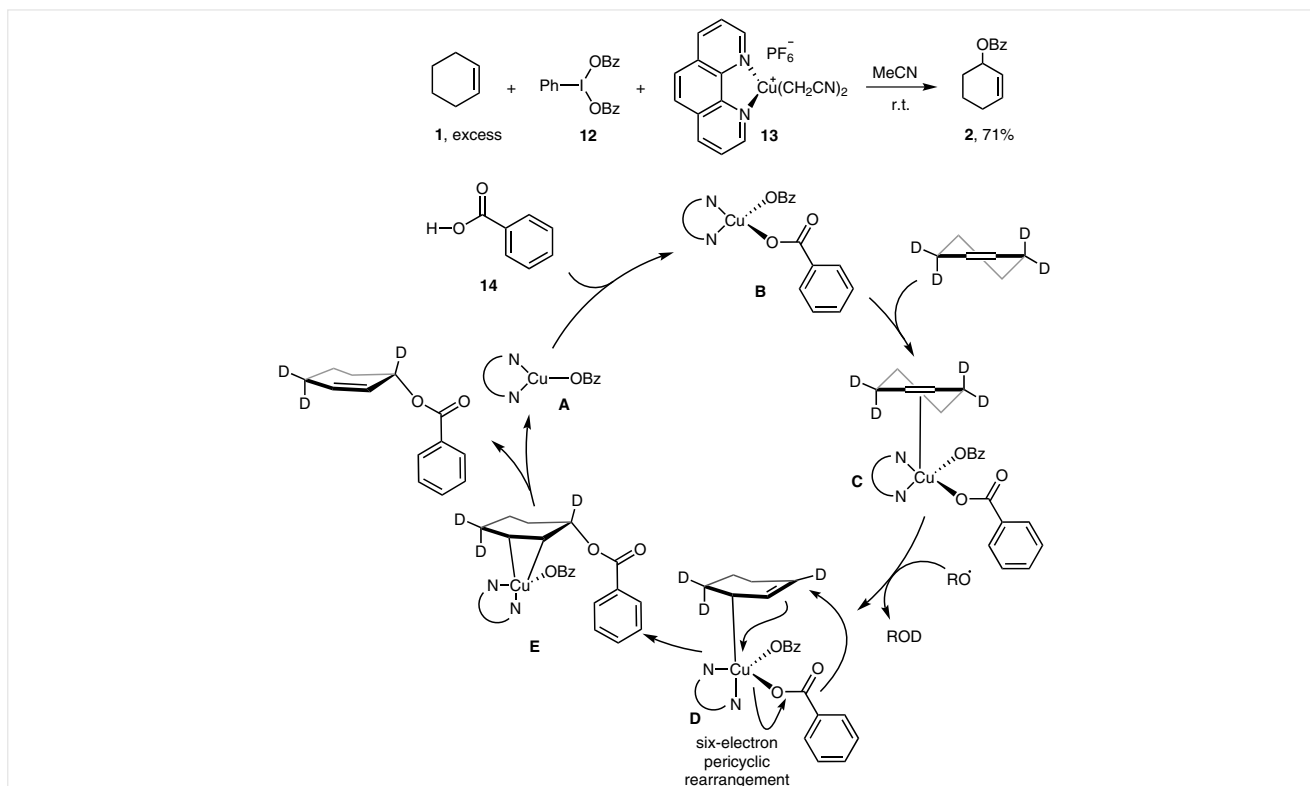
cal. A recombination of these two species with the opposite regiochemistry would lead to deuterium scrambling. A six-electron pericyclic rearrangement transfers the benzoate ligand to the allylic carbon atom, leading to the η^2 -complex **E**. Finally, dissociation of the alkene complex provides the allylic benzoate, with the double bond in the original position.

Finally, in 2008 the mechanism of the reaction was further investigated using theoretical calculations by Salvatella et al. and a more elaborated proposal has been presented.¹⁴



Scheme 6 Catalytic cycle for the allylic oxidation of cyclohexene (**1**) using *tert*-butyl peroxybenzoate as oxidant in the presence of mebox **15** as chiral ligand

The oxidation of cyclohexene (**1**) with $\text{PhCO}_3t\text{-Bu}$ in the presence of a methyl bisoxazoline (mebox) ligand **15** would follow the mechanism displayed in Scheme 6.



Scheme 5 Proposal of mechanism by Slough et al.

Starting from the Cu(I)–alkene complex **A**, easily formed in the presence of a large excess of the alkene, the first step of the catalytic cycle consists of the formation of the perester catalyst complex **B** by interchange of the cyclohexene (**1**) ligand with PhCO₂*t*-Bu. This complex reacts with cyclohexene (**1**) yielding the key intermediate benzoate(cyclohex-2-enyl)meboxCu(III) ion **C**. Reductive elimination of the copper yields the Cu(I) complex **D**, that by ligand interchange, gives cyclohex-2-enyl benzoate (**2**).

4 Enantioselective Version of the Allylic Oxidation of Olefins

The principal advantage offered by the Kharasch–Sosnovsky reaction relative to other approaches employed for the allylic oxidation, such as those based on selenium or chromium reagents, is the possibility of being carried out in an enantioselective manner. Since the pioneering works by Denney (α -ethyl camphorate),¹⁵ Muzart (*L*-proline),¹⁶ and Feringa (*L*-proline and propionic acid or anthraquinone)¹⁷ that resulted in modest enantiomeric excesses, a plethora of different chiral ligands have been developed, not always with satisfactory results. Symmetric cyclic alkenes usually provide acceptable enantiomeric excesses, although systematic screening is generally necessary to find the suitable catalyst for a given alkene.

In this section, we present those efforts oriented to develop enantioselective versions of the copper-catalyzed allylic oxidation of olefins. Frequently, the Kharasch–Sosnovsky reaction has served as a benchmark reaction for the evaluation of the catalytic properties of many ligands. We will focus on those ligands that have significant performance in terms of enantioselectivity, yield, or structural novelty.

4.1 Bisoxazoline-Type Ligands

The most popular ligands employed in the Kharasch–Sosnovsky oxidation are formed by two bisoxazoline (box) rings linked through different arrangements. Initial results based on the use of these C₂-symmetric ligands were published independently by the groups of Pfaltz (**16a**, **16c**, **16e**)¹⁸ and Andrus (**16a**, **16b**, **16d**),^{12,19} (**16f–j**)²⁰ (Figure 1). The highest enantiomeric excesses were observed for cyclopentene and cycloheptene (up to 84% at low temperatures), while cyclohexene (**1**) gave lower selectivities (60–77% ee). Acyclic substrates showed even lower yields and selectivities. Low temperature was critical to obtain high selectivity, leading to unduly long reaction times.

Further investigations have been carried out in an attempt to improve yields and enantiomeric selection and to shorten reaction times. Andrus et al. proved that the use of *tert*-butyl *p*-nitroperbenzoate and CuPF₆–bisoxazoline

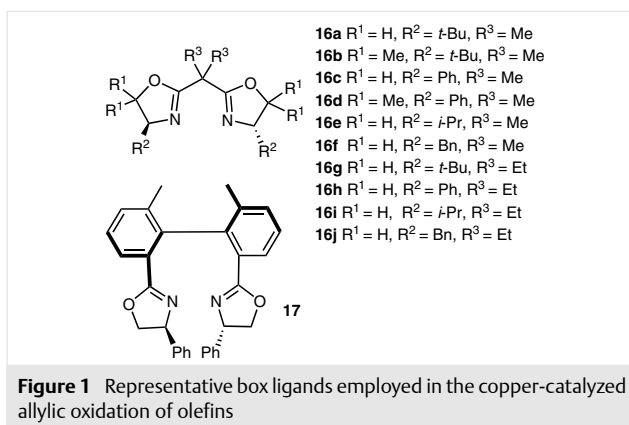


Figure 1 Representative box ligands employed in the copper-catalyzed allylic oxidation of olefins

complexes increased the enantioselectivity, although, yields were moderate for the isolated ester products. In addition, Andrus identified that some unique ligand–substrate combinations provided very high enantioselectivity. For instance, ligand **16c** proved to be the best, leading to 99% ee for cycloheptene, while ligand **16h** gave a remarkable 99% ee for cyclopentene, although the yields decreased significantly (Figure 1). Some models have been suggested to explain the selectivity of bisoxazoline-type ligands.^{12,21}

Andrus et al. have also synthesized a wide range of biaryl(bis(oxazoline) atropoisomers.²² Among them, ligand **17** (Figure 1) increased reactivity and improved selectivity, yielding 76% of (*S*)-cyclohex-2-enyl *p*-nitrobenzoate in 73% ee in 5 days. Nevertheless, the selectivity displayed by bisoxazolines with cyclohexene (**1**) was found to be widely divergent.

In recent work, the Jadidi group have studied the behavior of ligands **18** (Scheme 7).²³ Although these ligands exist as a mixture of two diastereomers in equilibrium in solution, when they coordinate to copper(I) ion only one of the two possible complexes **19** is formed. Ligand **18b** was found to be the best, leading to allylic benzoates with up to 95% ee and up to 99% yield in a reasonably short period of time, when SBA-15 mesoporous silica²⁴ was used as an additive.

Other authors have explored C₂-symmetric bisoxazolines bearing different core structures with meaningful results. Clark et al.²⁵ prepared a series of bidentate oxazoline ligands **20**, derived from (1*S*,2*R*)-1-aminoindan-2-ol, that were in general superior to those synthesized by Pfaltz¹⁸ under the same reaction conditions (24 h, 40 °C in MeCN) (Figure 2). Ligand **20d** afforded (*S*)-cyclohex-2-enyl benzoate [(*S*)-**2**] with 74% ee in 65% yield.

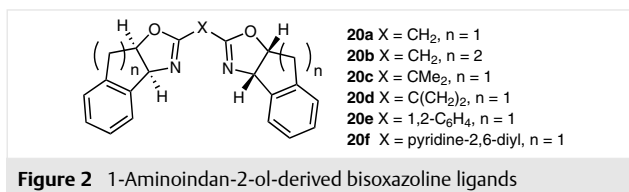
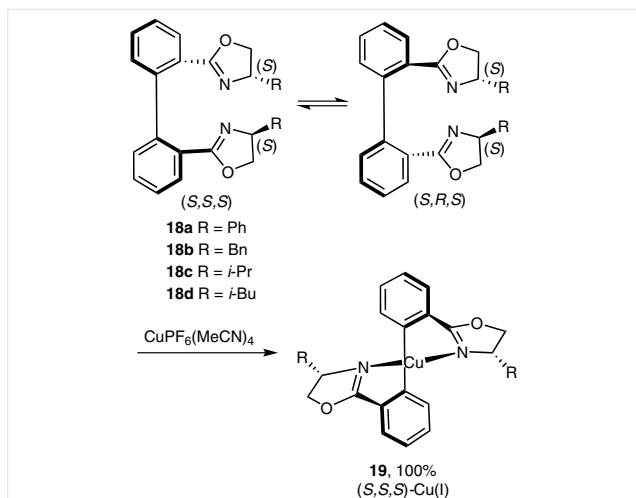


Figure 2 1-Aminoindan-2-ol-derived bisoxazoline ligands



Scheme 7 Interconversion of atropoisomers in ligands **18** and locking enforced by the copper atom

The typical behavior for most ligands developed is an increase in enantioselectivity at the expense of the activity of the catalyst when the temperature is lowered, which sometimes leads to excessively long reaction times. A compromise is usually accepted and the reactions are carried out at 0 °C or at room temperature. At higher temperatures, enantioselectivities decrease dramatically. This problem has been partially solved by Zhou et al., who developed a series of ligands bearing a chiral spirobiindane scaffold (SpiroBox) (Figure 3).²⁶ Ligand **21b** provides cycloalkenyl benzoates in moderate enantioselectivities but allows the temperature to be raised to 40 °C without loss of ee, substantially shortening the reaction time.

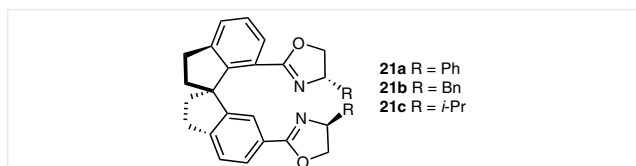


Figure 3 Spirobox ligands

Interesting results were reported by Desimoni et al.²⁷ with 4,5-diphenyl-substituted box ligands **22a,b** which afforded similar yields and enantioselectivities to those reported by other box ligands (Figure 4). The difference is that they produced the *R*-enantiomer instead of the *S*-enantiomer usually obtained with other ligands. The stereochemistry bearing on carbons C-4 seems to be fundamental, although there is no influence of the stereogenic center at C-5 on the enantioselectivity of the reaction.

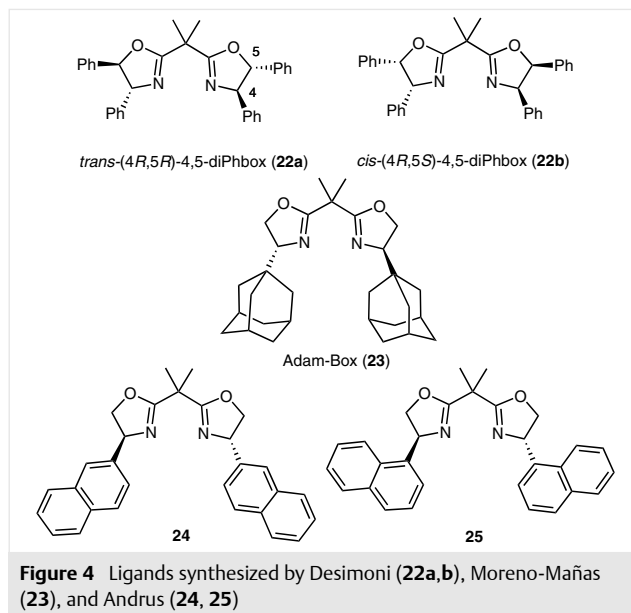


Figure 4 Ligands synthesized by Desimoni (**22a,b**), Moreno-Mañas (**23**), and Andrus (**24, 25**)

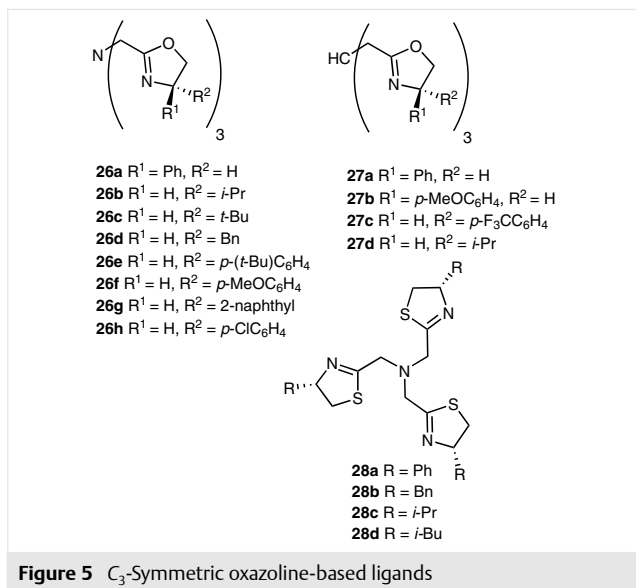
Similar behavior has been reported by Moreno-Mañas et al. with the (*R,R*)-Adam-Box ligand **23** which gave the *R*-enantiomer of cyclopent-2-enyl benzoate in 82% ee (Figure 4).²⁸

Recently, Andrus et al.²⁹ have prepared a malonyl-derived bisoxazoline **25** substituted with a 1-naphthyl moiety that gives the ligand a stiff structure that provides, at low temperature, the allylic ester of cyclohexene (**1**), in good yield preserving a high enantioselectivity (85% ee, 75% yield) (Figure 4). Interestingly, the less constrained 2-naphthyl substituted ligand **24** produces the allylic oxidation product in 80% ee with a remarkable lower yield (40%).

4.2 Trisoxazoline-Type Ligands

Similar behavior has been observed with the C₃-symmetric tris(oxazoline) ligands **26**, developed by Katsuki et al. (Figure 5).³⁰ Katsuki found that tetradentate tris(oxazoline) ligand **26a** showed high enantioselectivity (93% ee) but low yield (30%) in the oxidation of cyclopentene. Cyclohexene (**1**), cycloheptene, and cyclooctene yielded allylic benzoates with moderate enantioselectivity at room temperature. As usual, lower temperatures increased enantioselectivity, but decreased yield. Although most of them exhibited poor catalytic activity, it is worth noting that the sense of the asymmetric induction by Cu(II)-**26b** was opposite to that found with the Cu(II)-**26a** complex, suggesting the existence of some attractive interaction between the aryl substituent and the intermediary allyl radical.

Katsuki also observed this difference in the sense of the asymmetric induction in ligands **27** (Figure 5), synthesized from methanetricetic acid and optically pure β-amino alcohols.³¹ The reaction of cyclopentene as starting material

Figure 5 C₃-Symmetric oxazoline-based ligands

with ligand **27a** was slower and the enantioselectivity was lower than when **26a** was employed as the catalyst. Interestingly, the sense of the enantioselection was opposite, despite the fact that the oxazoline units in both ligands were the same. This fact suggests that the geometry of both copper complexes was different. In addition, ligand **27b** showed wide applicability, proceeding with high enantioselectivity (82–88%) at 0 °C (48 h) with good yields with cyclopentene, cyclohexene (**1**), and cycloheptene, although the oxidation of cyclooctene was slow. It is also interesting to note that the absolute configuration of the allylic benzoates obtained with ligand **27b** was *R*, opposite to that usually found with most chiral ligands.

Fu et al. explored the tris(thiazolines) **28a–d** with modest results (Figure 5).³² Ligand **28a** proved to be the best, although it showed only moderate asymmetric catalytic activity and enantioselectivity. Nevertheless, as in the case of **27b**, the *R*-enantiomer of the allylic ester was obtained.

4.3 Pyridine Bisoxazoline-Type Ligands (Pybox)

The Singh group has studied the use of pybox ligands in copper-catalyzed allylic oxidation (Figure 6).^{21,33} Their study commenced with the Cu(II) complex bearing the pyridine bis(oxazoline) ligand **29a**, which had been previously employed for asymmetric cyclopropanations.³⁴ This catalytic system led to 81% ee and 58% yield for cyclohexene (**1**), although the enantioselection for other olefins was low.

Ligand **29a** displayed higher enantioselectivities and the presence of the nitrogen in the pyridine core was essential for the asymmetric induction to occur. A significant improvement in the rate of the reaction was introduced with this ligand when phenylhydrazine was added with acetone

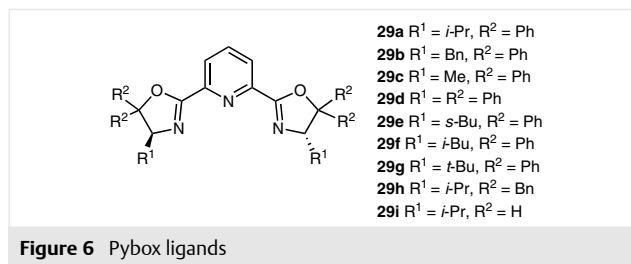


Figure 6 Pybox ligands

as solvent. The purity of ligand **29a** was critical for the conversion of cycloolefins into *S*-allylic benzoates with up to 94% ee in good yields in only 1–5 hours.

An exhaustive study, changing appendages in pybox ligands **29**, peresters, and reaction conditions, found that very high enantioselectivity in the allylic oxidation of cyclic olefins could be obtained by choosing a unique combination of a chiral ligand and a perester at room temperature.

Desimoni et al. prepared *trans*- and *cis*-4,5-diphenylpybox **30a** and **30b** (Figure 7).²⁷ These ligands gave modest ee, although as in the case of **22a** and **22b**, the *R*-enantiomer was obtained.

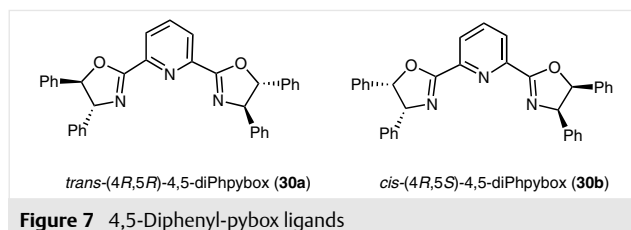


Figure 7 4,5-Diphenyl-pybox ligands

4.4 2,2'-Bipyridine-Type Ligands

Most of the ligands reported exhibiting high enantioselectivities required excessively long reaction times to achieve moderate conversions. Chiral C₂-symmetrical bipyridines developed by Kočovský et al.³⁵ formed an active catalytic system that shortened reaction times considerably (Figure 8). Thus, ligand PINDY (**31**),³⁶ derived from (–)-β-pinene, gave the allylic oxidation of cyclohexene (**1**) in 96% yield and 62% ee, in less than 30 minutes at room temperature. As usual, lower temperatures improve enantioselectivity, although involving longer reaction times.

Molecular modelling carried out on PINDY (**31**) prompted the authors to prepare a family of ligands based on several chiral terpenes.³⁷ Most of them gave poor enantioselectivity or even racemic products. The menthol-derived ligand, MINDY (**32**), although exhibiting moderate ee in cyclopropanation reactions, gave very low reactivity and enantioselectivity in the allylic oxidation of cycloalkenes. The best ligand of the series proved to be CANDY (**33**), which afforded the allylic oxidation of cyclohexene (**1**) in 98% yield and 66% ee, at 20 °C in a short reaction time. It is noteworthy that unlike most ligands, CANDY (**33**) generates

the *R*-enantiomer of cyclohex-2-enyl benzoate (**2**). Illustratively, the relative ligand Me-CANDY (**34**) gives the *S*-enantiomer, although with lower enantiomeric excess (Figure 8).

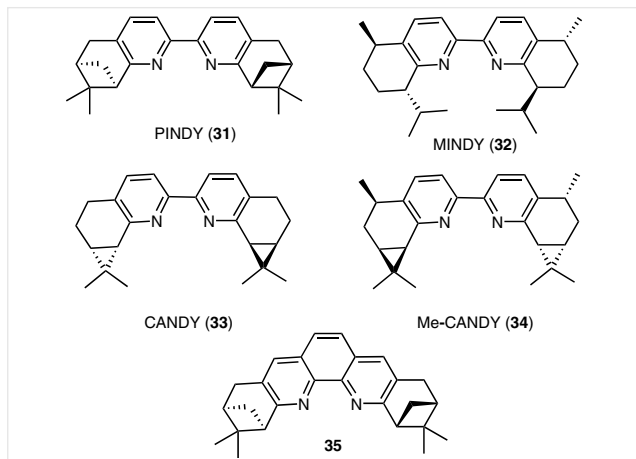


Figure 8 Kočovský (**31–34**) and Chelucci (**35**) bipyridine ligands

A chiral 1,10-phenanthroline **35**, related to PINDY (**31**), has been prepared by Chelucci et al. (Figure 8).³⁸ Although the structures of these ligands are similar, they display different coordinating properties. The coordination of the metal in **35** is locked in a single conformation, while the flexibility of the backbone of **31** should allow certain degree of conformational mobility. Despite the differences, the catalytic activity of both structures is similar.

In an attempt to produce a more rigid framework than that present in the bipyridine-based ligands **32–34**, Chelucci et al. carried out the preparation of ligands **36–47** (Figure 9). They discovered that simple ligands such as **36** and **37** showed no activity;³⁹ the presence of a substituent close to the heterocyclic nitrogen atom is necessary. Moreover, the existence of C_2 -symmetry was not essential. The substitution pattern was determinant: while 2-substituted ligand **38** completed the reaction in 30 minutes, 3-substituted ligand **39** was unreactive. The same pattern was observed in the rigid phenanthroline-derived ligands **40** and **41**. Mono-terpene- and steroid-derived ligands **42–47** were prepared and evaluated. Whilst yields were good, enantioselectivity was very low and only a moderate 36% ee was obtained with ligand **45** (Figure 9).

4.5 (Iminophosphoranyl)ferrocene-Type Ligands

Chiral (iminophosphoranyl)ferrocenes **48**, **49**, and **50** have been reported by Kim et al. (Figure 10).⁴⁰ Unlike other type of ligands, the enantiomeric excesses obtained with them seem to be virtually independent of the nature of both the olefin and the ligand. Additionally, the high enantioselectivity observed (up to 98% ee), was not accompa-

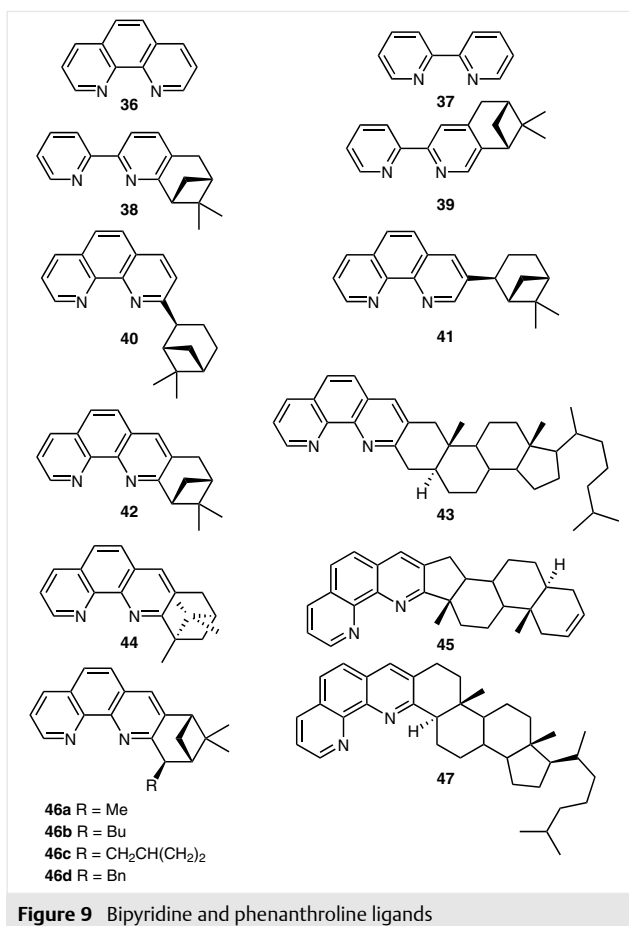


Figure 9 Bipyridine and phenanthroline ligands

nied by a loss in reactivity. The allylic oxidation of the less reactive substrate, cycloocta-1,5-diene was also notable since, regardless of the ligands, perfect enantioselectivity (>99% ee) and complete conversion (>99%) were obtained. Only ligand **49a**, with no reasonable explanation, showed low ee, which seems to be an exception.

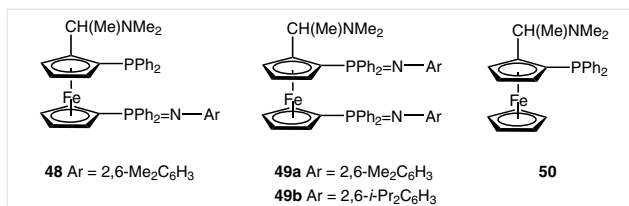


Figure 10 Chiral (iminophosphoranyl)ferrocenes

4.6 Pyox Ligands

Kočovský et al. have synthesized the pinene-derived pyridyl oxazolines **51** (Figure 11), that bear chiral elements in both the oxazoline and the pyridine units.⁴¹ Ligand **51a** catalyzed the asymmetric allylic oxidation of simple olefins

with good conversion rate but modest enantioselectivity (<67% ee). Ligands **51a**, **51b**, and **51c** provided *S*-enantiomers, while **51d** gave *R*-enantiomers.

Ward et al.⁴² have carried out the allylic oxidation of cyclohexene (**1**) using chiral pyridine-derived ligands such as **52** (Figure 11). The results obtained were very low both in conversion and enantioselectivity. A detailed study of the reaction process established that ligand **52** was prone to hydrolysis in the coordination sphere of copper, affording pyridine-2-carboxylate ligands. Therefore, the stability of these ligands during catalysis should be taken into account in their design.

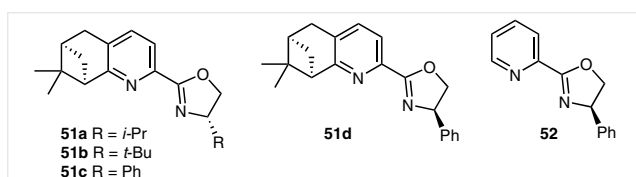


Figure 11 Pyridine-linked oxazolines

5 Other Landmarks of the Copper-Catalyzed Allylic Oxidation of Olefins

5.1 Use of Additives

The use of additives that accelerate the rate of the reaction in the Kharasch–Sosnovsky reaction has been a constant. One of the most important additives used in these reactions is phenylhydrazine. Singh and Ginotra have studied the use of phenylhydrazine as a reducing agent of Cu(II) species to Cu(I).⁴³ They studied the oxidation of cyclohexene (**1**) in the presence of ligand **29a**, employing different copper sources and solvents. For instance, treatment of cyclohexene (**1**) with **29a**–Cu(OTf) complex took 39 hours to completion, giving the corresponding benzoate **2** in 91% ee. In the presence of phenylhydrazine, the same reaction was complete in only 9 hours without affecting the enantioselectivity. If the Cu(I) species was prepared in situ by reduction of **29a**–Cu(OTf)₂ with phenylhydrazine in acetone, the reaction was complete in 1 hour with 91% ee. After some experimentation it was concluded that the Cu(I) species prepared by reduction of **29a**–Cu(OTf)₂ in acetone is more efficient than the use of a Cu(I) salt directly (Table 1).

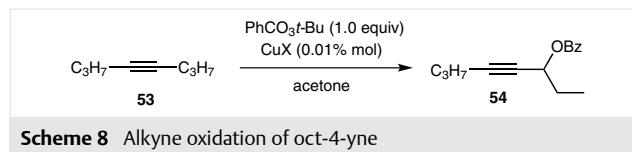
In 2002, Le Bras and Muzart, in a study oriented at lowering the excess of olefin to stoichiometric amounts, reported the necessity to employ amines such as DBU, DBN, or DMAP when cyclopentene or cycloheptene were used as substrates.⁴⁴ We have confirmed the beneficial effect of the use of DBU in the oxidation of several alkenes in a work aimed at optimizing reaction yields by a statistical multivariate optimization method.⁴⁵

Table 1 Use of Phenylhydrazine as a Reducing Agent

Entry	PhNHNH ₂	Cu source	Time (h)	Yield (%)	ee (%)
1	yes	CuOTf·PhH	9	73	91
2	no	CuOTf·PhH	39	67	91
3	yes	[Cu(MeCN) ₄]PF ₆	11	62	92
4	no	[Cu(MeCN) ₄]PF ₆	43	90	91
5	yes	Cu(OTf) ₂	1	67	91

5.2 Oxidation of Other Unsaturated Compounds

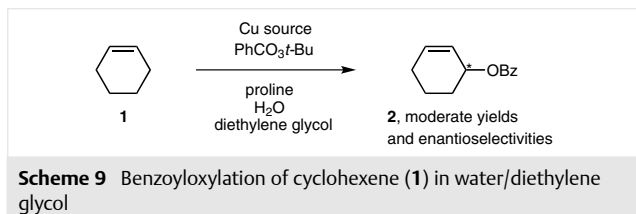
Christ, Sorokin, et al. reported a procedure for allylic or propargylic oxidation catalyzed by copper–bisoxazoline employing copper complexes Cu(MeCN)₄PF₆, (CuOTf)₂·PhH, and Cu(OTf)₂ in acetonitrile or acetone as the solvents.⁴⁶ The use of symmetric alkynes was studied. Comparatively, these substrates were less reactive than alkenes. Thus, oct-4-yne (**53**) was converted into the corresponding benzoate **54** in 140 hours in acetone at room temperature. The reactions were cleaner and the use of a large excess of either substrate or oxidant was not necessary (Scheme 8).



5.3 Water as a Solvent

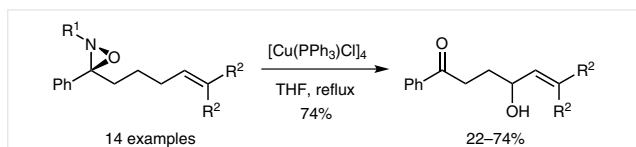
As a way to find valuable alternatives that diminish the environmental impact, Le Bras and Muzart studied the possibility of performing the Kharasch–Sosnovsky reaction in water.⁴⁷ They found that the oxidation of cyclohexene (**1**) could be accomplished in a mixture of water and diethylene glycol employing diverse copper sources, PhCO₃*t*-Bu as the oxidant, and proline as a chiral ligand. The enantioselectivity ranged from low to moderate, showing a remarkable dependence on the reaction conditions. When a Cu(II) source was employed, the reaction displayed an induction period of 5 days, after which time, the reaction proceeded normally, finishing after 8 days. This induction period could be suppressed by heating the catalyst in water/diethylene glycol in the presence of a catalytic amount of PhCO₃*t*-Bu for 30 minutes prior to the addition of cyclohexene (**1**) and the bulk of the oxidant. When the substrate and catalyst are in separate layers, auto-association of copper species in the

water is possible, leading to a loss of the catalytic activity. The addition of diethylene glycol inhibits this process by coordination to the copper species or by forming a third phase enriched in the catalyst. Cyclopentene reacted faster than cyclohexene (**1**), but cyclooctene failed to provide the corresponding allylic ester. When the experiments were carried out under an argon atmosphere, the catalysts could be recycled, showing even a slight increase in the catalytic activity of the catalyst (Scheme 9).



5.4 Unusual Oxidants

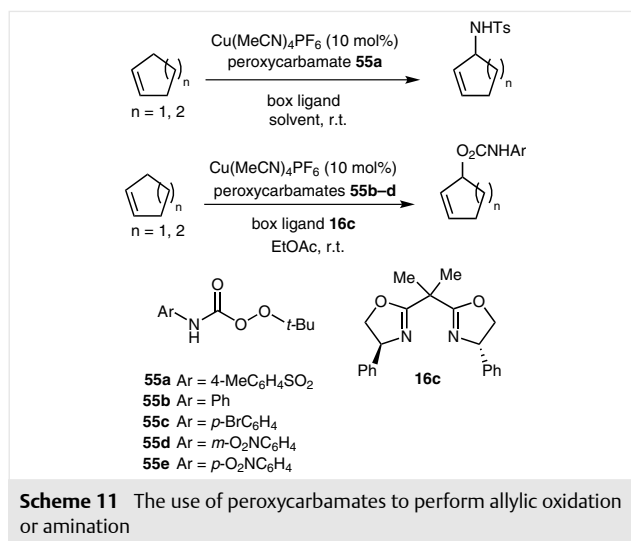
In 2013, Aubé et al. reported an ingenious way to install a hydroxyl group at the allylic position of an olefin.⁴⁸ They achieved the intramolecular delivery of the oxygen atom of an oxaziridine to the allylic position of the olefin. The starting oxaziridine is formed from the corresponding ketone, by condensation with a primary amine and subsequent treatment by *m*-CPBA. A mixture of *Z*- and *E*-oxaziridines was obtained, but the ratio was irrelevant since the starting carbonyl group was recovered. The yields were in the range of 22–74%. An example is displayed in Scheme 10.



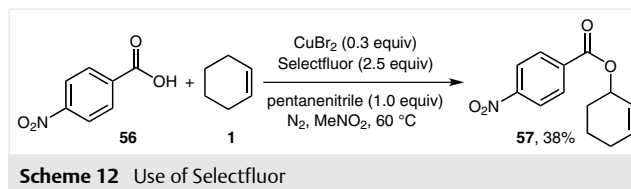
Clark and Roche reported the enantioselective reaction of an alkene with a peroxycarbamate in the presence of a copper-bisoxazoline complex.⁴⁹ The outcome could be tuned to give either allylic amination or oxidation depending on the conditions employed. For instance, whilst the use of peroxycarbamate **55a** gave the amination product, the employment of carbamates **55b–d** led to the oxidation products. The yields and the level of asymmetric induction found were higher for the oxidation process (Scheme 11).

5.5 Use of Fluorinated Ligands and Recovery of Catalysts

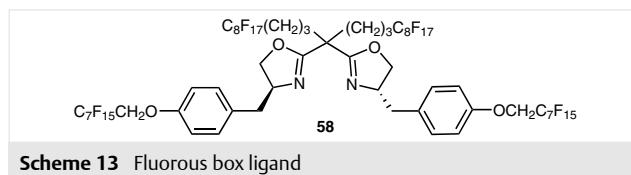
In a work aimed at the oxidation of unactivated C(sp³)-H bonds employing Selectfluor and CuBr₂, Zhou et al.⁵⁰ carried out the oxidative coupling of cyclohexene (**1**) and *p*-ni-



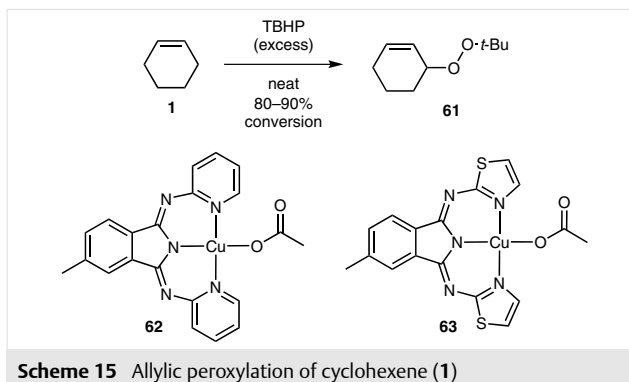
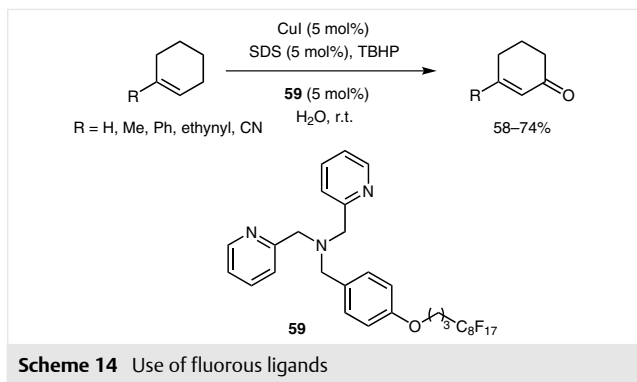
trobenzoic acid (**56**), providing the corresponding ether **57** in 38% yield. The same conditions were employed for the activation of the C(sp³)-H bond adjacent to an oxygen atom with negative results (Scheme 12).



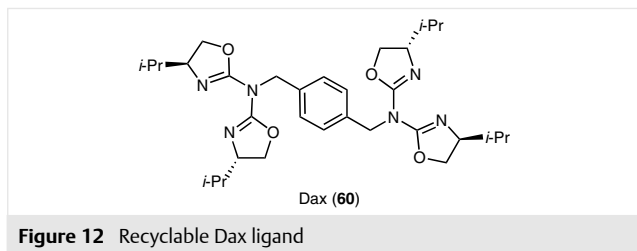
The Sinou group has reported the use of a bisoxazoline modified with fluorous ponytails (Scheme 13). These fluorous box analogues displayed enantioselectivities comparable to those reported for the traditional box ligands. The ligands could be recovered without loss of selectivity.⁵¹



In 2015, Lam and Ang reported the oxidation of allylic and benzylic sp³ C-H bonds by aqueous TBHP in water using recyclable ligands with C₈F₁₇ tags (Scheme 14).⁵² Several cyclohexene derivatives were employed as substrates, leading always to the corresponding unsaturated ketone. The reaction was more effective in the presence of a surfactant such as sodium dodecyl sulfate (SDS). The ligand **59** could be recovered by fluorous solid-phase extraction. Using 1-phenylcyclohex-1-ene, the reaction could be carried out on a gram-scale in 71% yield.



A different strategy has been conducted by García, Reiser, et al.⁵³ using a ditopic azabis(oxazoline) ligand Dax **60** capable of being immobilized as an insoluble linear coordination polymer with copper salts when non-coordinating solvents are used (Figure 12). The catalytic reaction takes place in a homogenous phase with solvents such as acetonitrile, allowing the recovery of the catalytic system with solvents such as hexane. The recycled catalysts provided good yields in further runs, although enantioselectivity gradually diminished, due to the probable loss of chiral ligand during recovery.



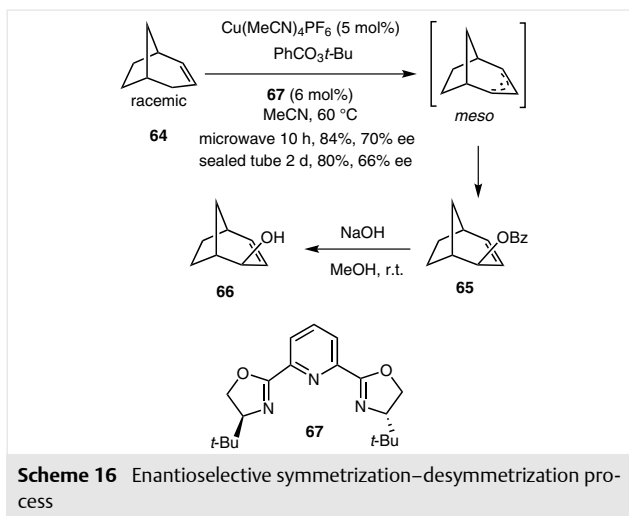
5.6 Allylic Peroxylation

Much less popular than allylic acyloxylation is an alternative reaction, allylic peroxylation. In 2004, Meder and Gade, prepared the copper complexes [Cu(4-MeBPI)(OAc)] **62**, and [Cu(4-MeBTI)(OAc)] **63** [BPI = 1,3-bis(2-pyridylimino)isoindole, BTI = 1,3-bis(thiazol-2-ylimino)isoindole] (Scheme 15).⁵⁴ These complexes catalyzed the allylic peroxylation of cyclohexene (**1**) with TBHP (70% aqueous solution) leading to *tert*-butyl cyclohex-2-enyl peroxide (**61**) with 86% conversion for **62** and 80% conversion for **63**.

5.7 Desymmetrization Processes

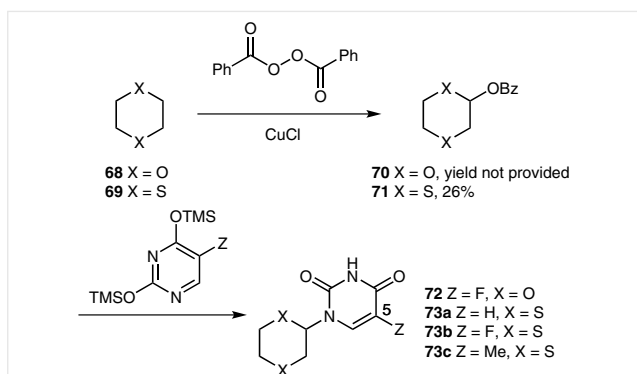
The enantioselective version of the Kharasch-Sosnovsky reaction has been cleverly employed by Clark et al.⁵⁵ They carried out an enantioselective symmetrizing-desymmetrizing process of a bicyclic alkene en route to the synthesis of highly functionalized five- and six-membered

heterocycles. Treatment of racemic **64** with Cu(MeCN)₄PF₆ and PhCO₃*t*-Bu as the oxidant in the presence of a chiral pybox ligand **67**, provided enantiopure benzoate **65**, via a *meso* radical. The absolute stereochemistry of **65** was confirmed after its hydrolysis by comparison with literature data (Scheme 16).

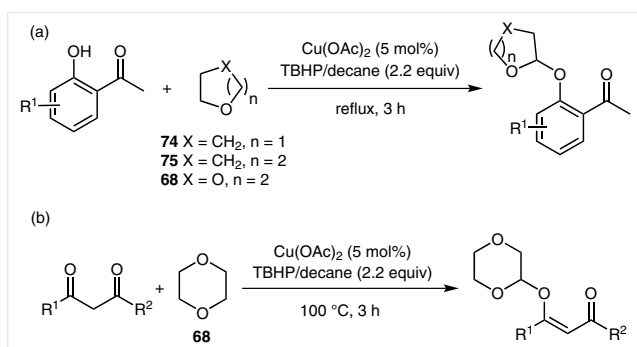


6 α -Oxidation of Heterocycles

Early on, Sosnovsky and Yang demonstrated that 1,4-dioxane **68** reacted sluggishly with benzoyl peroxide and that the addition of CuCl significantly improved the process, resulting in the smooth oxidation of the heterocycle.⁷ Since then, no significant progress has been made in the oxidation at the α -position of oxygen- or sulfur-containing heterocycles. In 1982, Hronowski and Szarek⁵⁶ reported the preparation of 2-(benzoyloxy)-1,4-dioxane (**70**) and 2-(benzoyloxy)-1,4-dithiane (**71**) following the Sosnovsky and Yang procedure. These two heterocycles were coupled with several 2,4-bis(trimethylsilyloxy)pyrimidines in the search for surrogates of 5-fluorouracil (Scheme 17).

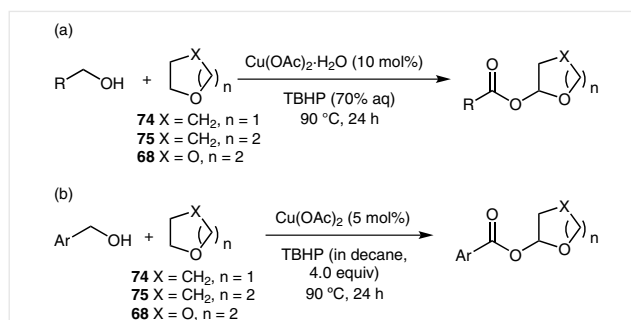
Scheme 17 α -Acyloxylation of heterocycles

Reddy, Kappe, et al. have presented the construction of C–O bonds via α -C–H bond activation of ethers using $\text{Cu}(\text{OAc})_2$ and a TBHP solution in decane as the stoichiometric oxidant (Scheme 18, a).⁵⁷ The reaction can be carried out in a continuous flow regime, avoiding the use of large volumes of ether and peroxide. The reaction was further extended to β -keto esters (Scheme 18, b).

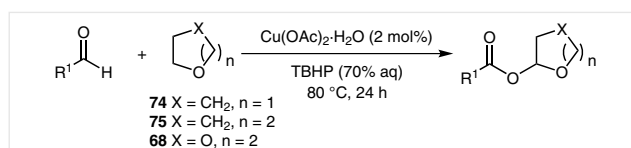
Scheme 18 (a) α -Acyloxylation of tetrahydrofuran (**74**), tetrahydropyran (**75**), and 1,4-dioxane (**68**). (b) α -Acyloxylation of 1,4-dioxane (**68**) with 1,3-dicarbonyl compounds.

Fu, Yuan, et al. recently disclosed the copper-catalyzed formation of C–O bonds by oxidative coupling of benzylic alcohols with ethers employing a 70% aqueous TBHP solution as the oxidant in air.⁵⁸ Other oxidants, such as DDQ, NaClO, H₂O₂, O₂, *m*-chloroperbenzoic acid, did not show any activity. The molar ratio of reagents was very important, and an excess of the TBHP (6.0 equiv) and the ether (60 equiv) had to be employed (Scheme 19, a). Simultaneously, the same reaction was studied by Nagaiah et al. leading to a very similar oxidation system (Scheme 19, b).⁵⁹

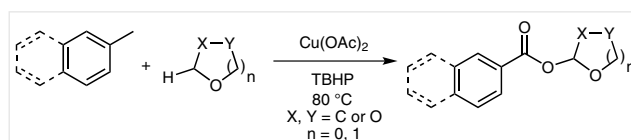
Fu, Yuan, et al. also reported the oxidative cross-coupling reaction of aldehydes and ethers.⁶⁰ The use of Cu(II) was crucial, since the employment of Cu(I) salts, such as CuBr or CuCl, did not lead to any product. The ether again

Scheme 19 α -Acyloxylation reaction of heterocycles

had to be used in a large excess (40 mmol) and the copper source was used in 2 mol%. A larger amount of catalyst resulted in solubility problems and lower yields (Scheme 20).

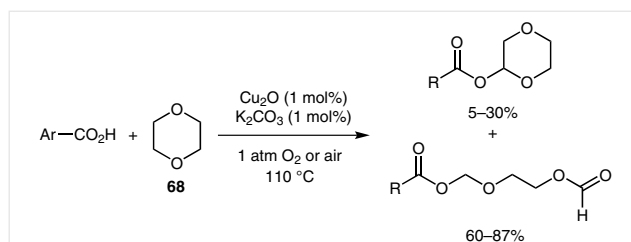
Scheme 20 Acyloxylation of tetrahydrofuran (**74**), tetrahydropyran (**75**), and 1,4-dioxane (**68**)

Patel et al. described the esterification of alkylbenzenes with cyclic ethers. A competing self-coupling of toluene was avoided by a careful choice of the reaction conditions. The transformation was accomplished by employing $\text{Cu}(\text{OAc})_2$ and TBHP (Scheme 21).⁶¹

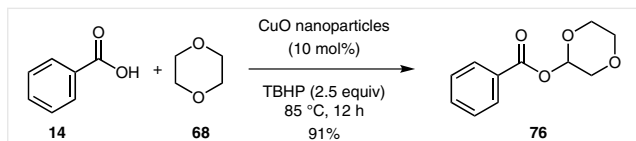


Scheme 21 Esterification of alkylbenzenes

In 2012, Liu et al. reported the secondary production of α -acyloxy ethers by treatment of an aromatic carboxylic acid with Cu_2O in the presence of K_2CO_3 using O₂ as the oxidant.⁶² Nevertheless, in these reactions the major product was that resulting from cleavage of the heterocycle (Scheme 22).

Scheme 22 Dehydrogenative cross-coupling between aromatic acids and 1,4-dioxane (**68**) with concomitant heterocycle ring opening

The use of CuO nanoparticles as a catalyst for the dehydrogenative cross-coupling of benzoic acid (**14**) and 1,4-dioxane (**68**) has been reported by Kantam et al. (Scheme 23).⁶³



Scheme 23 Use of CuO nanoparticles as a catalyst for the dehydrogenative cross-coupling between benzoic acid (**14**) and 1,4-dioxane (**68**)

7 Reactions in Heterogeneous Phase

Over the last few decades, synthetic chemists have focused their attention on heterogeneous catalysis in an attempt to overcome the limitations of the homogeneous approach. Easier handling, the possibility of reuse in several cycles without loss of activity, the ease of separation of the catalyst, and a simpler isolation of the products are the main advantages of this approach.

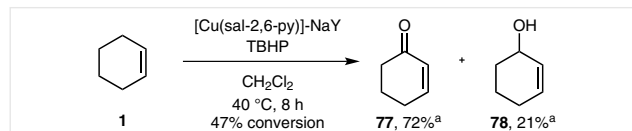
The examples of efficient heterogeneous versions of reactions described here are part of a field that has yet to be fully developed, and the examples described in the literature are scarce and they present some limitations. For instance, it is common in these reports to provide conversions instead of isolated yields; the latter would provide a more accurate idea of the potential of the methodology. Most of them are applied mainly to cyclohexene (**1**) as a model substrate, and epoxidation remains a persistent competitor of allylic oxidations.

7.1 Use of Zeolites

One of the most important challenges in synthesis in heterogeneous phase is the design of materials that can be used without loss of activity. In this sense, research on the synthesis of porous materials such as the zeolites has helped to understand the relationship between the catalytic properties and the number of the active sites on the material surface. Factors that make zeolites particularly appreciated in comparison with other catalysts are their high superficial area, adsorption capacity, and thermal and hydrothermal stability. In recent years, a substantial number of articles have been published dealing with the preparation of copper complexes of Schiff base ligands encapsulated in the cavities of zeolites, and their application to the allylic oxidation of simple alkenes.

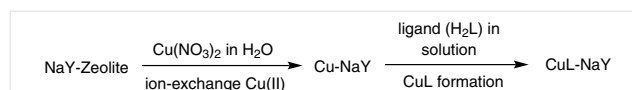
In 2008, Shaterian et al. reported a Cu(II) complex with a pentadentate Schiff base ligand entrapped in the nanocavity of a Na-Y zeolite ([Cu(sal-2,6-py)]-NaY).⁶⁴ This host-guest nanocomposite material (HGNM) catalyzes the allylic oxidation of cyclohexene (**1**) in the presence of TBHP with

47% conversion and selectivities of 72% and 21% for the formation of cyclohex-2-en-1-one (**77**) and cyclohex-2-en-1-ol (**78**), respectively (Scheme 24).



Scheme 24 Oxidation of cyclohexene (**1**) with TBHP catalyzed by nanodimensional pores of zeolite-Y encapsulated copper(II) complex. ^a Selectivity.

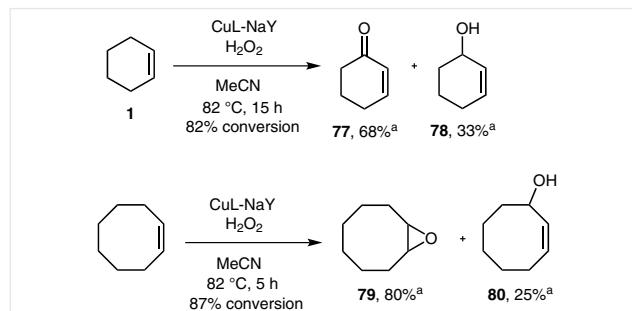
Lashanizadegan and Zareian published the preparation of a copper-exchanged Y-zeolite for the oxidation of cyclohexene (**1**) using TBHP as an oxidant in good yield.⁶⁵ For this purpose, copper(II) was incorporated into a Na-Y zeolite. Then, an azo-linked Schiff-base ligand (H₂L), prepared by the reaction of 4-(phenylazo)salicylaldehyde with propane-1,2-diamine, was encapsulated in the zeolite (Scheme 25).



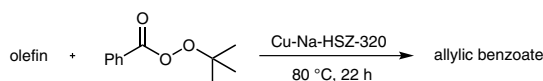
Scheme 25 Preparation of the encapsulated Cu(II) complex (CuL-NaY)

The encapsulated Cu(II) complex in the Na-Y zeolite (CuL-NaY) was employed for the allylic oxidation of cyclohexene (**1**) in acetonitrile at reflux, affording 100% conversion of the starting material, with a selectivity of 83% for cyclohex-2-en-1-one (**77**).

In 2011, Rayati et al. reported the allylic oxidation of cyclohexene (**1**) and cyclooctene catalyzed by a copper(II) complex of N₄ Schiff base ligand encapsulated within the nanopores of a Y-zeolite (CuL-NaY).⁶⁶ The oxidation of cyclohexene (**1**) was carried out successfully in the presence of H₂O₂ or TBHP to afford cyclohex-2-en-1-one (**77**) and cyclohex-2-en-1-ol (**78**) as the major products. Treatment of cyclooctene under the same conditions produced the epoxide **79** as the major oxidation product and the corresponding alcohol **80** as a minor compound (Scheme 26).



Scheme 26 Oxidation products distribution in oxidation of cyclohexene (**1**) and cyclooctene in the presence of CuL-NaY and H₂O₂. ^a Selectivity.

Table 2 Scope of the Kharasch–Sosnovsky Reaction Catalyzed by Cu-Na-HSZ Zeolite

Entry	Olefin	Product	Yield (%)
1	cyclopentene	cyclopent-2-enyl benzoate	60
2	cyclohexene	cyclohex-2-enyl benzoate	70
3	cyclooctene	cyclooct-2-enyl benzoate	68
4	cycloocta-1,4-diene	cycloocta-2,6-dienyl benzoate	82
5	dec-1-ene	dec-1-en-3-yl benzoate	32
6	oct-1-ene	oct-1-en-3-yl benzoate	38

Similar work by Prasad et al. presented a comparative study of homogeneous and heterogeneous catalysis in the oxidation of cyclohexene (**1**) to afford cyclohex-2-en-1-one (**77**) and cyclohex-2-en-1-ol (**78**) as major oxidation products.⁶⁷ This group reported the oxidation of cyclohexene (**1**) employing a Schiff base copper(II) complex of ligands 4-(2-aminoethylimino)pent-2-en-2-ol (HL¹) and 4-[2-(3-hydroxy-1-methylbut-2-enylideneamino)ethylimino]pent-2-en-2-ol (H₂L²) in homogeneous and heterogeneous phase. The insertion of the ligands into the cavities of a Cu-Y-zeolite allowed the synthesis of encapsulated copper(II) complexes. Although the oxidation reaction in homogeneous media reached higher conversion efficiency and shorter reaction times than the encapsulated complexes, the copper(II) complexes within zeolite can be recovered and reused without loss of activity.

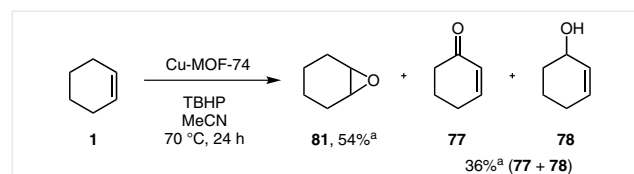
An interesting heterogeneous system was proposed by the Sartori group, who studied the Kharasch–Sosnovsky oxidation of olefins catalyzed by copper-exchanged zeolites.⁶⁸ They prepared Cu-Na-HSZ-320 catalyst from the commercially available zeolite Na-HSZ-320 and an aqueous solution of Cu(NO₃)₂ by the traditional ion-exchange method. The allylic oxidation of different olefins was carried out employing the catalyst and PhCO₂t-Bu at 80 °C for 22 hours. The yields of the allylic oxidation products and the scope of the reaction, including both cyclic and linear olefins, are displayed in Table 2. Moreover, the Cu-Na-HSZ-320 zeolite could be reused almost 10 times in the benchmark reaction with cyclohexene (**1**).

Notwithstanding their qualities, one of the limitations of zeolites is the pore size. In some cases, it is possible to restrict the pore size limitation, but then its crystallinity and henceforth the capacity to control and design the active sites is usually lost. As a result, there is a growing interest in synthesizing new materials that can serve as zeolite surrogates.

7.2 Use of Metal–Organic Frameworks (MOFs)

In recent years, metal–organic frameworks (MOFs) have been studied as zeolite replacements. MOFs are crystalline materials that are formed from metal ions connected through multidentate organic linkers. Unlike zeolites, MOFs do not need activation or regeneration at high temperatures and they are less dense and present higher surface areas.

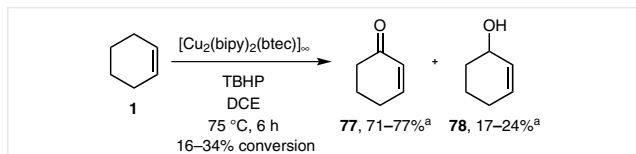
Once more, the studies with MOFs usually employ the oxidation of cyclohexene (**1**) as a benchmark reaction. Such is the case of the Sánchez-Sánchez group, who reported the preparation of nanocrystalline Cu-MOF-74 as a heterogeneous catalyst for the oxidation of cyclohexene (**1**) using TBHP as the oxidant in acetonitrile.⁶⁹ The results showed 90% overall oxidation yield with epoxide **81** as the major product (Scheme 27).



Scheme 27 Oxidation of cyclohexene (**1**) with TBHP and catalyzed by Cu-MOF-74. ^a Selectivity.

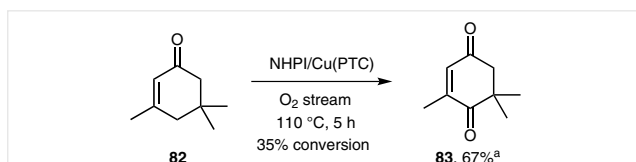
In 2014, the Spodine group published a heterogeneous alternative based on the use of a copper MOF for the allylic oxidation of cyclohexene (**1**).⁷⁰ They reported that the oxidation of cyclohexene (**1**) can be undertaken by using the MOF [Cu₂(bipy)₂(btec)]_∞ as the heterogeneous catalyst and aqueous TBHP as the oxidant in dichloroethane at 75 °C for 6 hours. The catalyst activity was retained during four catalytic cycles. The outcome of the reaction employing different molar ratios of substrate/TBHP/catalyst was studied. In all cases, the total conversion of cyclohexene (**1**) oxidation displayed values between 16 and 34%. The reaction carried out with the optimal conditions showed selectivities of 72%

and 24% for cyclohex-2-en-1-one (**77**) and cyclohex-2-en-1-ol (**78**), respectively. Under these conditions, the cyclohexene epoxide **81** was not observed (Scheme 28).



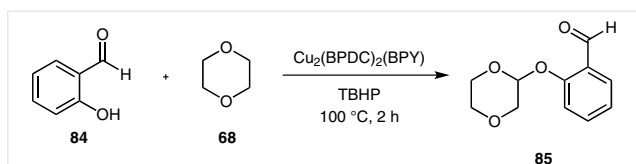
Scheme 28 Allylic oxidation of cyclohexene (**1**) catalyzed by the MOF $[\text{Cu}_2(\text{bipy})_2(\text{btec})]_\infty$. ^a Selectivity.

Tang et al. reported the preparation of three metal organic frameworks with Cu(II) and different carboxylate ligands: H_3PTC (pyridine-2,4,6-tricarboxylate), H_3BTC (benzene-1,3,5-tricarboxylic acid), and H_2PDA (pyridine-2,6-dicarboxylic acid).⁷¹ They examined their efficiency in the allylic oxidation of α -isophorone (**82**) with molecular oxygen as the oxidant. The heterogeneous catalytic system was formed by adsorbing *N*-hydroxyphthalimide (NHPI) into the synthesized copper MOFs. Their advantages include a simpler reaction procedure by filtration, easier product purification, and the reusability of the catalyst. The reaction, which was carried out employing NHPI/Cu(PTC) as the catalyst with oxygen as primary terminal oxidant under solvent-free conditions, afforded ketoisophorone **83** as the sole product with 35% conversion (Scheme 29).



Scheme 29 Allylic oxidation of α -isophorone (**82**) catalyzed by NHPI/Cu(PTC) catalyst system and a stream of molecular oxygen. ^a Selectivity.

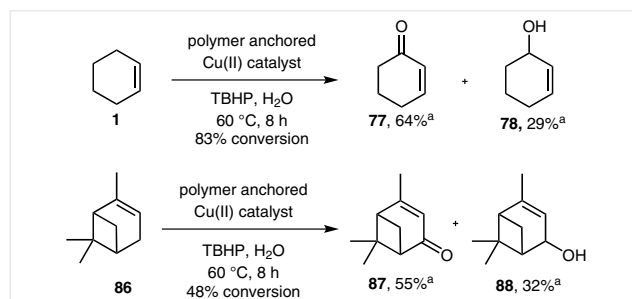
The Nguyen group has recently reported the preparation and use of a copper MOF, $\text{Cu}_2(\text{BPDC})_2(\text{BPY})$, as a heterogeneous catalyst for the cross-dehydrogenative coupling reaction of ethers with salicylaldehydes.⁷² When the cross-coupling reaction was carried out using 2-hydroxybenzaldehyde (**84**) and 1,4-dioxane (**68**), with TBHP as the oxidant, the conversion was 100% after 2 hours (Scheme 30).



Scheme 30 Cross-dehydrogenative coupling reaction of 2-hydroxybenzaldehyde (**84**) and 1,4-dioxane (**68**) using $\text{Cu}_2(\text{BPDC})_2(\text{BPY})$ as a solid catalyst

7.3 Polymer-Based Supports

As mentioned earlier, other mesoporous materials such as polymers can be used as solid supports in copper-catalyzed oxidation reactions. These supported materials can be obtained as complexes with copper and Schiff base ligands by heterogenization process. The application of a polymer-anchored copper(II) catalyst to the allylic oxidation of cyclohexene (**1**) and α -pinene (**86**) with TBHP in aqueous media has been reported by the Salam group.⁷³ This catalyst can be easily recovered by filtration and is recyclable up to five times without significant loss of its catalytic activity. When tested in the oxidation of cyclohexene (**1**) and α -pinene (**86**), the catalytic system showed good results. In both cases, the major oxidation products were the corresponding enone and the allylic alcohol. For cyclohexene (**1**), 83% conversion with 64% selectivity for cyclohex-2-en-1-one (**77**) and 29% for cyclohex-2-en-1-ol (**78**) was obtained. In the case of the α -pinene (**86**), 48% conversion led to verbenone (**87**) and verbenol (**88**) as major compounds (Scheme 31).



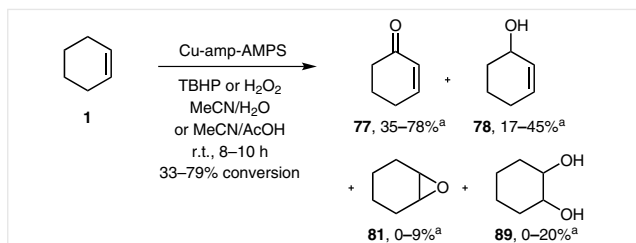
Scheme 31 Allylic oxidation of cyclohexene (**1**) and α -pinene (**86**) using a polymer-anchored copper(II) catalyst and TBHP in aqueous media. ^a Selectivity.

7.4 Silica-Based Supports

Silica has also served as a support for the heterogeneous catalysis of the allylic oxidation of olefins. In 2006, the Bhaumik group reported the allylic oxidation of cyclohexene (**1**) using a Schiff base copper complex immobilized over a modified silica surface (Cu-amp-AMPS) either in acetonitrile/acetic acid or acetonitrile/water using H_2O_2 or TPHP as the oxidant.⁷⁴ In this work, cyclohex-2-en-1-one (**77**) was obtained as the major allylic product (Scheme 32).

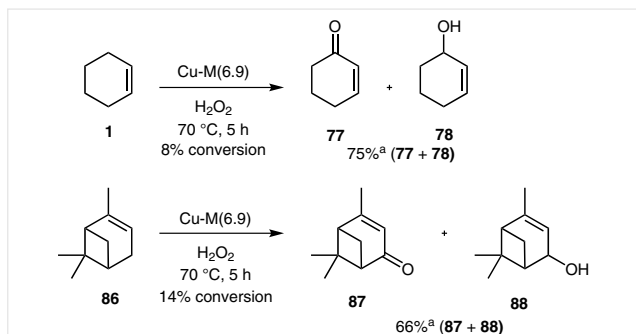
7.5 Molecular Sieves

The allylic oxidation of cyclohexene (**1**) and α -pinene (**86**) has also been studied by using mesoporous molecular sieves modified with copper $[\text{Cu-M}(6.9)]$ by the template ion-exchange method.⁷⁵ The heterogeneous catalyst can be



Scheme 32 Allylic oxidation of cyclohexene (**1**) catalyzed by Cu-amp-AMPS. ^a Selectivity.

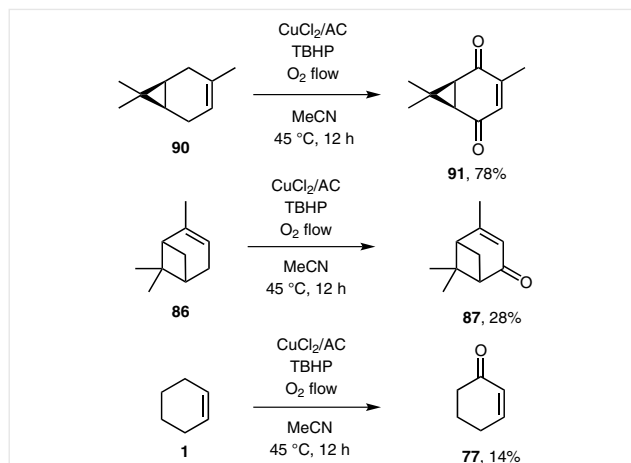
recovered and reused several times without loss of activity. The oxidation was carried out using H_2O_2 as the oxidant at 70°C for 5 hours, producing cyclohex-2-en-1-one (**77**) and cyclohex-2-en-1-ol (**78**) or verbenone (**87**) and verbenol (**88**) as the major products, respectively (Scheme 33).



Scheme 33 Allylic oxidation of cyclohexene (**1**) and α -pinene (**86**) employing mesoporous molecular sieves modified with copper [Cu-M(6.9)]. ^a Selectivity.

7.6 Carbon-Based Catalysts

There are several advantages that the use of activated carbon offers as a solid support: its remarkable mechanical strength, large surface area, thermal stability and inertness. For these reasons, some authors have employed it as a support for metal catalysis in heterogeneous phase. For example, the Xu group has recently reported the allylic oxidation of (+)-3-carene (**90**), α -pinene (**86**), and cyclohexene (**1**) to afford their corresponding ketones.⁷⁶ The reaction is carried out in acetonitrile employing TBHP under a flow of oxygen. The reaction is catalyzed by activated carbon-supported CuCl_2 (CuCl_2/AC), which is prepared by the impregnation method. Under the optimal conditions, (-)-3-carene-2,5-dione (**91**) was produced in 78% yield. Verbenone (**87**) (28% yield) and cyclohex-2-en-1-one (**77**) (14% yield) were also synthesized via allylic oxidation of α -pinene (**86**) and cyclohexene (**1**), respectively, under the same conditions (Scheme 34).

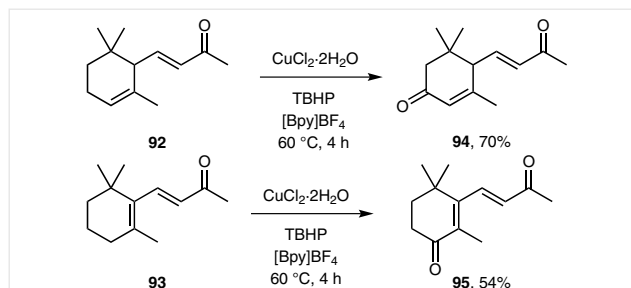


Scheme 34 Allylic oxidation of (+)-3-carene (**90**), α -pinene (**86**), and cyclohexene (**1**) using CuCl_2/AC catalyst with O_2 -TBHP

Recently, our group has employed a carbon integral honeycomb monolith prepared from a natural coal as support for copper catalysts. Good to excellent yields (60–100% as function of the carboxylic acid employed) were obtained in the oxidation of cyclohexene (**1**). The monolith can be reused up to five reaction cycles without significant loss of activity.⁷⁷

7.7 Nanoparticle-Based Systems

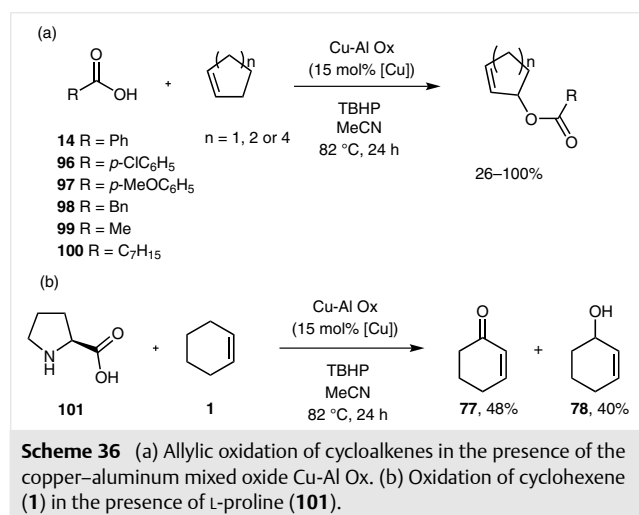
An emerging approach is based on the use of transition-metal nanoparticles formed and stabilized in pyridinium ionic liquids.⁷⁸ This catalytic system, which offers advantages of homogeneous-like reaction and heterogeneous separation (it can be reused for the next cycle), was employed for the allylic oxidation of α -ionone (**92**) and β -ionone (**93**). The reactions were carried out using $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ as the catalyst and TBHP as the oxidant. The best results were obtained when $[\text{Bpy}]\text{BF}_4$ was used as the solvent (Scheme 35).



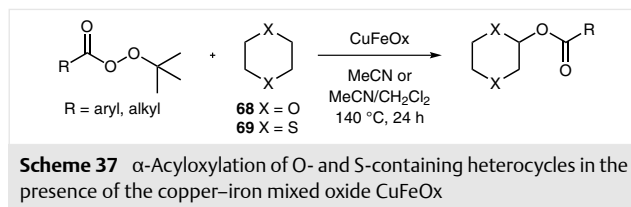
Scheme 35 Allylic oxidation of α -ionone (**92**) and β -ionone (**93**) by copper salt nanoparticles catalyst formed and stabilized in pyridinium liquids

7.8 Mixed Oxides

An alternative in which our group has been interested is the employment of mixed oxides of copper and another metal (Al or Fe). Recently, we prepared a copper–aluminum mixed oxide (Cu–Al Ox) and used it to perform the allylic oxidation of a series of olefins.⁷⁹ Thus, treatment of the olefin with a carboxylic acid, employing TBHP as the oxidant in the presence of Cu–Al Ox produced the corresponding allylic ester in good yields (Scheme 36, a). The reaction performed well not only with simple alkenes but also with monoterpenes and sesquiterpenes. Incorporation to the reaction of L-proline (**101**) instead of the carboxylic acid resulted in the formation of the allylic alcohol or enone (Scheme 36, b).



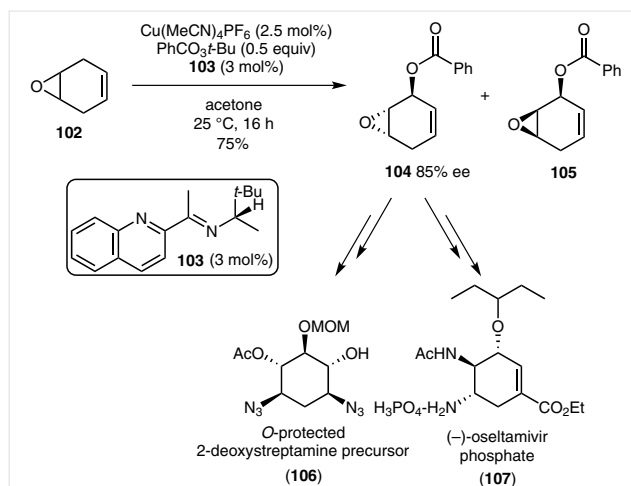
We have followed a similar approach for the synthesis of α -substituted dioxanes and dithianes employing a copper–iron mixed oxide (CuFeOx) to prepare α -substituted dioxanes and dithianes.⁸⁰ The peroxyester partners were prepared by Wan's method⁶ that is sufficiently versatile to provide a variety of ester groups that can be appended to the heterocycle. Although acyloxylation of dioxanes has been relatively well described in the literature, only the Hronowski and Szarek⁵⁶ precedent had been reported prior to our study regarding the use of sulfur-containing heterocycles as substrates. The presence of sulfur atoms in a molecule usually imposes significant constraints on the use of copper-based catalysts due to catalyst poisoning. The use of this mixed oxide surmounts this problem and displays a beneficial synergic effect of two different metal centers over the substrate (Scheme 37).

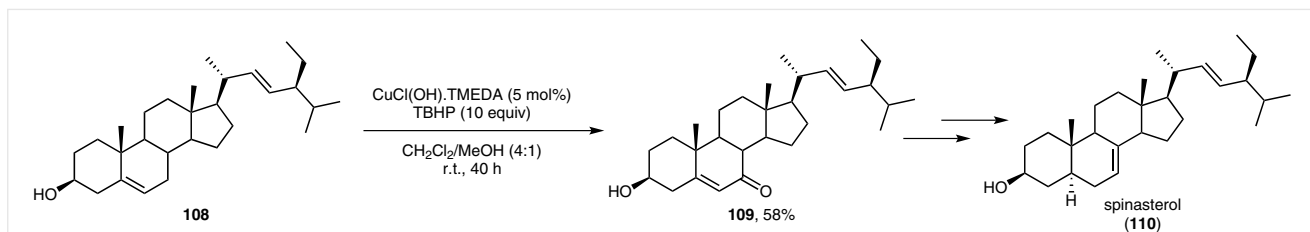


8 Applications

Although there may be perceived risks in relying on this type of transformation for the key step in the synthesis of complex molecules, its potential in terms of setting new functionality in an enantioselective manner, has aroused the interest and produced motivating examples. In this section, we present cases found in the literature that employ the copper-catalyzed allylic oxidation of an olefin as the key step in the synthesis of products and pharmaceuticals. Some of the examples have been previously collected in a review on allylic oxidation reactions in natural products synthesis by Nakamura and Nakada.⁸¹

In 2009, the Hayashi and Tan group published the enantioselective preparation of an *O*-protected 2-deoxystreptamine precursor **106**, an amino-glycoside antibiotic.⁸² Its synthesis involves the asymmetric desymmetrization of 4,5-epoxycyclohex-1-ene (**102**) by Kharasch–Sosnovsky reaction as the key step. The enantioselective allylic oxidation was carried out using Cu(MeCN)₄PF₆ as the copper source, combined with a chiral *N,N*-bidentate ligand **103**, and PhCO₃*t*-Bu in acetone at room temperature. The authors obtained *trans*-3-(benzoyloxy)-4,5-epoxycyclohex-1-ene (**104**) as the major isomer in 75% yield and 85% ee, respectively. The *trans*-isomer allowed the synthesis of the *O*-protected 2-deoxystreptamine precursor **106** after seven



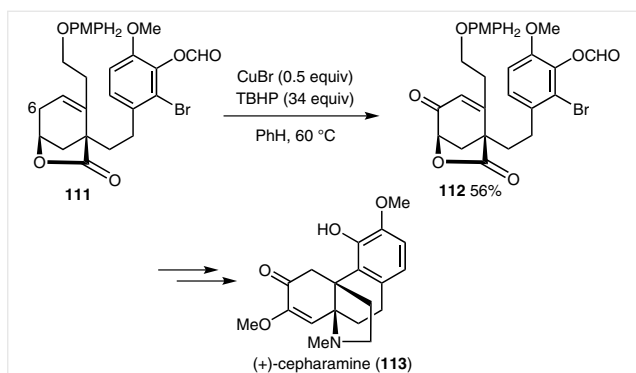


Scheme 39 Synthesis of spinasterol (110)

reaction steps (Scheme 38). The same group later employed the same copper-catalyzed asymmetric desymmetrization procedure for the preparation of a chiral intermediate in the total synthesis of (–)-oseltamivir phosphate (107, Tamiflu)⁸³ reported previously by Shibasaki et al.⁸⁴

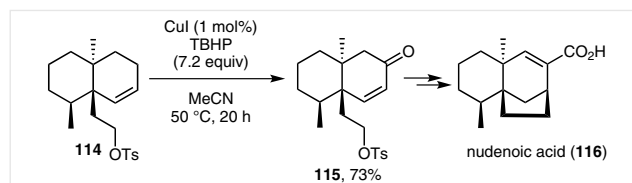
The synthesis of steroids is one field where copper-catalyzed allylic oxidation has been more successful. The relatively inert steroid framework usually yields the corresponding enone instead the allylic alcohol. Samadi et al.⁸⁵ have recently reported the synthesis in four steps reactions of spinasterol (110) from stigmasterol (108). For this purpose, the unprotected steroids were treated with CuCl(OH)·TMEDA as the catalyst and TBHP as the oxidant, in CH₂Cl₂/MeOH mixture of solvents to afford the corresponding enone 109 in 58% yield (Scheme 39). These types of phytosterol could have applications in medicine because of their anti-inflammatory properties and their ability to modulate mitochondrial activity. Several more examples of Kharasch–Sosnovsky reactions applied to the synthesis of steroids can be found in the literature.⁸⁶

In 1998, Schultz and Wang published the enantioselective total synthesis of the hasubanan alkaloid (+)-cepharamine (113), the unnatural enantiomer, very interesting from a pharmacological perspective in as much as it has a structure similar to that of morphine.⁸⁷ Kharasch–Sosnovsky conditions were employed to introduce a carbonyl group at C-6 in compound 111 by treatment with 0.5 equivalents of CuBr and a large excess of TBHP in benzene at 60 °C providing the intermediate enone 112 in 56% yield (Scheme 40).



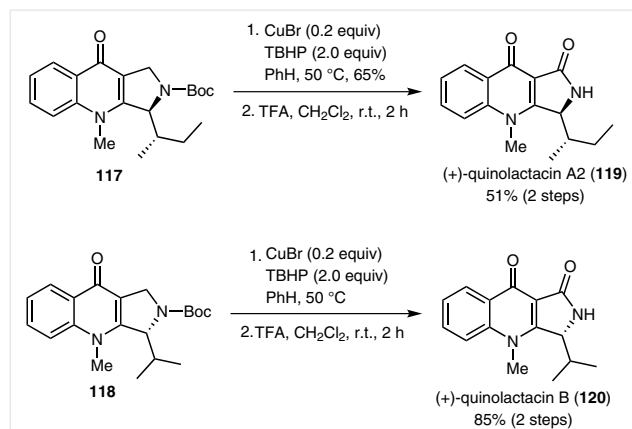
Scheme 40 Asymmetric total synthesis of (+)-cepharamine (113)

Ho and Su reported the total synthesis of the sesquiterpene (±)-nudenol acid (116), a tricyclic sesquiterpene isolated from the liverwort *Mylia nuda*.⁸⁸ The introduction of a carbonyl group into the allylic position of the double bond in the octalin system 114 was carried out using CuI as the catalyst and TBHP as the oxidant, in acetonitrile at 50 °C for 20 hours. The obtained enone tosylate 115 (73%) proved to be unstable, thus it was necessary to purify it at ice temperature (Scheme 41).



Scheme 41 Total synthesis of (±)-nudenol acid (116) by Ho and Su

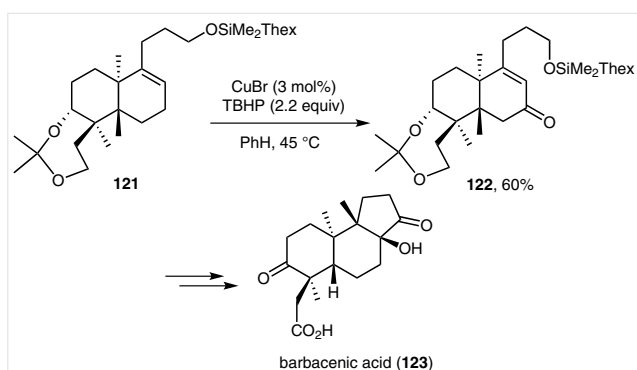
In 2003, Zhang et al. described the enantioselective syntheses of quinolactacins A2 (119) and B (120).⁸⁹ The value resides in their potential antibiotic activity and their exceptional structure (a quinolone skeleton conjugated with a γ -lactam ring). The reported asymmetric syntheses include an allylic oxidation reaction as one of the critical steps. In



Scheme 42 Total enantioselective synthesis of (+)-quinolactacins A2 (119) and B (120)

both cases, methylated quinolones **117** and **118** were subjected to treatment with CuBr and TBHP in benzene at 50 °C for 2 hours. After the successful oxidation step, deprotection of the Boc group with TFA in dichloromethane led to the corresponding quinolactacins **119** and **120** in good yields (Scheme 42).

Barbacenic acid (**123**), a novel bisnorditerpene isolated from *Barbacenia flava*, was synthesized by a highly stereocontrolled route.⁹⁰ In this synthesis Kanazawa et al. performed the allylic oxidation on the silyl ether intermediate **121** using TBHP in the presence of CuBr in benzene at 45 °C. Under these conditions the desired enone **122** was obtained in 60% yield (Scheme 43).



Scheme 43 Stereocontrolled synthesis of barbacenic acid (**123**)

9 Summary

In this review, we examined the potential of the allylic oxidation of olefins and the α -oxidation of heterocycles catalyzed by copper. Although the history of these reactions dates back to the late 1950s, they have not been fully incorporated into the arsenal of reactions commonly used in organic synthesis. The early versions of these reactions were slow and their use was limited to simple substrates. Additionally, they present a mechanism that displays a complexity higher than those found in common radical reactions. A universal catalytic system is yet to be found and currently, every process has to be individually optimized. However, the efforts made over the recent years have led to significant progress. On one hand, unique substrate–catalytic system combinations providing high enantiomeric excesses in good yields and reasonable reaction times have been reported. On the other hand, the use of copper, a low-risk metal in terms of supply and toxicity, is an asset that stimulates investigations in this field.

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