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Chiral bisoxazoline ligands with a biphenyl backbone: development and application in catalytic asymmetric allylic oxidation of cycloolefins

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ABSTRACT

A simple and efficient method for the synthesis of chiral biphenylbisoxazoline ligands was developed. The bishydroxylamide precursors of ligands showed a dynamic atropselective resolution effect in the crystallization process. When biphenylbisoxazoline ligands were coordinated to tetrakis(acetonitrile)copper(I) hexafluorophosphate, it resulted in the formation of only a single diastereomer complex (*S*,a*S*,*S*), which behaved as a catalyst for the enantioselective allylic oxidation of cycloolefins. The enantioselectivity, yield, and rate of this reaction were optimized under different conditions, such as a change of solvents, temperature, and additives and also using various copper salts. The use of SBA-15 mesoporous silica as an additive played a crucial role in increasing the efficiency of the reaction.

1. Introduction

The enantioselective allylic oxidation of olefins using chiral copper complexes has been the subject of great interest over the last decade. This reaction provides access to chiral allylic alcohols, which are key intermediates in natural product synthesis.[1]

A literature survey shows that chiral C_2-symmetric bisoxazolines (box's) are one of the most effective and popular classes of chiral ligands studied for copper-catalyzed allylic oxidations, and their application has made a major breakthrough with drastic improvements in enantioselectivity and yield.[2] However, all of the reported allylic oxidations suffer from at least one disadvantage in terms of long reaction times, unsatisfactory yields, or enantioselectivities.[1f–n] Ikeda et al. in 2000 reported on a new class of atropisomeric chiral biphenylbisoxazoline ligands for the catalytic asymmetric cyclopropanation.[3] These ligands exist as a mixture of two diastereomers in equilibrium in solution. However, when these ligands were coordinated to a copper(I) ion, only one of the two possible complexes was formed. This feature of the biphenylbisoxazolines encouraged us to develop a new method for the synthesis of a series of them through an efficient, high yielding, and inexpensive procedure, and for the first time apply them to the catalytic enantioselective allylic oxidation of cycloolefins.

It is well known that additives are useful for achieving optimized conditions in allylic oxidation reactions.[1f,h,k] In this context, the effect of numerous additives in conjunction with the copper–biphenylbisoxazoline complexes on the asymmetric allylic oxidation of cycloolefins was examined. It is noteworthy to mention that in the presence of SBA-15 mesoporous silica, as the additive, only one enantiomer of the allylic benzoates was obtained with up to 95% ee and up to 99% yield in a reasonably short period of time.

Although two rotatory diastereomers of ligand **1** exist in equilibrium in solution, the dynamic atropselective resolution effect in biphenylbisoxazolines **1** was not confirmed. However, the bishydroxylamide precursor of ligands **5** showed this effect in the crystallization process.[4]

2. Results and discussion

The synthesis of chiral biphenyl bisoxazoline ligands **1** was accomplished in excellent yields and enantiomeric excess from the inexpensive starting material anthranilic acid **2** (Scheme 1). Diazotization of anthranilic acid **2** followed by homo-coupling of aryldiazonium salts in the presence of Cu(I) as the reducing agent led to symmetrical biphenyl diacid **3** with high yields.[5] Diacid **3** was exposed to oxalyl chloride in the presence of a catalytic amount of DMF and converted into the diacid chloride.[1l,m,2] Treatment of the diacid chloride with four individual (*S*)-amino alcohols **4a–d** resulted in the formation of (*S*,a*S*,*S*) and (*S*,a*R*,*S*)-bishydroxylamides **5a–d**.

In order to achieve the most efficient procedure for the synthesis of the desired ligand **1**, we were required to find a useful method for cyclization of the bishydroxylamide precursor **5**. To fulfill this requirement, three different activating agents were employed to promote this process (Scheme 1). The first method (a) consists of transforming bishydroxylamide **5** into its corresponding dichloride and further cyclization to the box under basic conditions.[2e,g,6] Treatment of bishydroxylamide precursor **5** with $Ph_3P/CCl_4/Et_3N$

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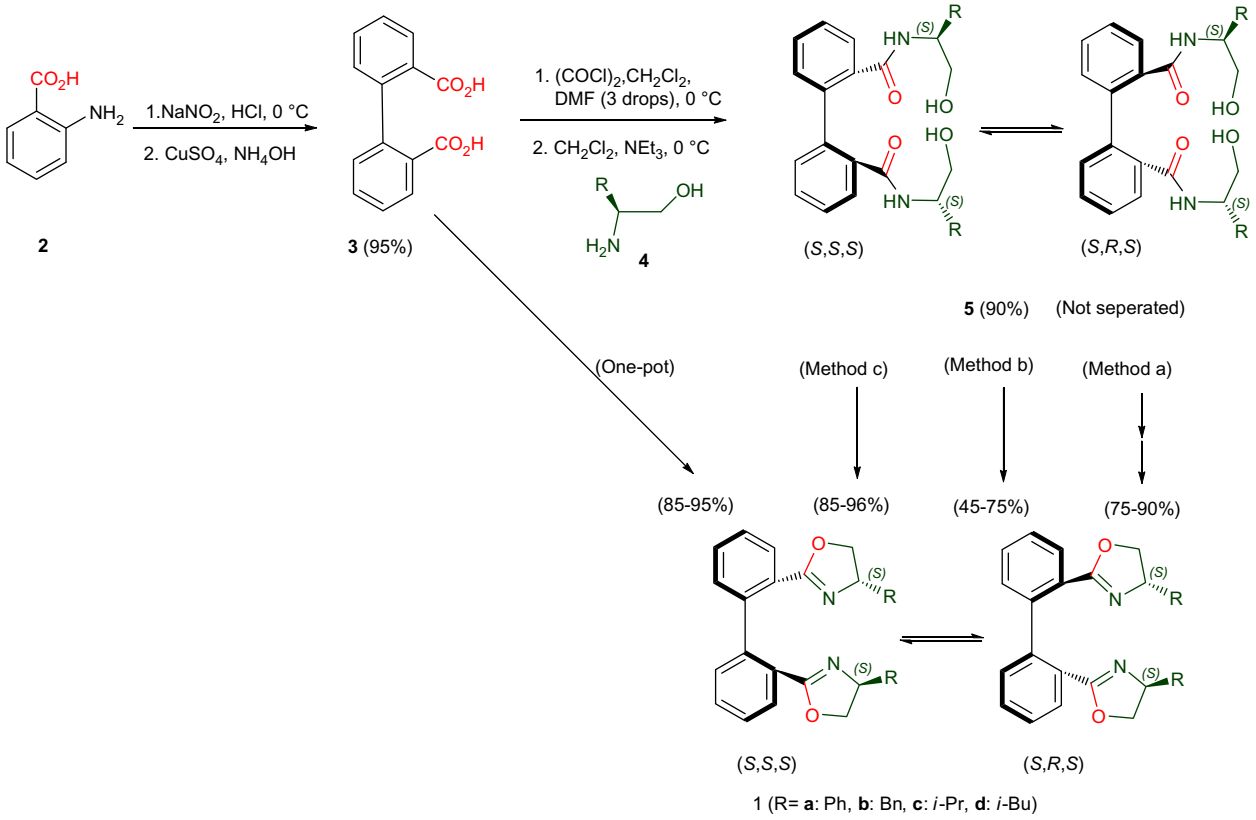


Scheme 1. Synthesis of chiral biphenyl bisoxazoline ligands **1a–d**.

afforded the desired ligands in only 45–60% yields (Method b).[1t,2e,g] In the third method (c), biphenyl bisoxazoline ligand **1** was prepared by stirring overnight the mixture of bishydroxylamide **5** in the presence of *p*-TsCl, DMAP, and Et_3N at room temperature. The convenience of this procedure and the high yield obtained (>85%) were important features of this cyclization method. By using activated agents for the cyclization in method c, we managed to prepare ligand **1** in a one-pot synthesis through the modification and combination of two final steps of the reaction (Scheme 1). In general, the reaction *via* this easy-to-handle method occurred slightly faster and gave products in higher yields than the other methods.[7]

As expected, the ^{1}H NMR spectrum of precursor **5** and ligand **1** clearly showed the presence of two rotatory diastereomers and the ratio of two sets of signals for each pair changed at different temperatures. However, the two atropisomers were not chromatographically separable but the interconversion of the two rotatory diastereomers was slow enough to be detected by NMR.[3,8]

The conformational equilibrium between atropisomers **5** and **1** was used to perform a dynamic atropselective resolution in order to obtain them as pure single crystalline compounds. It is noteworthy that crystallization of the precursor mixture **5** led to only one rotameric diastereoisomer without co-precipitation of the other diastereomer from the mother liquor. In order to confirm the dynamic atropselective resolution effect and to represent the conformational equilibrium between these atropisomers, the single-crystal X-ray analysis of various samples of **5d** was investigated. We observed that the absolute configuration of this precursor was (*S*,a*S*,*S*) in all cases and that all of the molecules in the unit cell have the same sense of chirality at the stereogenic aryl–aryl bond (Fig. 1). Since the crystallization was accomplished with higher than 95% yield, the process can be considered to be a crystallization-induced asymmetric transportation.[4] The shift of the equilibrium is most probably controlled by the (more) efficient hydrogen bonding of the molecules of the (*S*,a*S*,*S*)-isomer. Despite an intensive effort, the growth of suitable crystals of ligands **1** for single-crystal analysis was not successful to confirm the transformation effect in the ligands.

The copper complexation behavior of these ligands with $CuPF_6$ in chloroform-*d* was then examined. The ^{1}H NMR spectrum showed the formation of only one diastereomeric complex. For example, the ^{1}H NMR spectrum of **1b** consisted of two doublet of doublets at δ = 2.95–3.02 (J = 5.2 and 13.6 Hz) with an intensity ratio of 70:30 in the absence of the copper salt; but when this ligand was coordinated with copper(I) hexafluorophosphate only one of the diastereomeric complexes was formed with a doublet of doublets at δ = 2.76–2.83 (J = 13.6, 5.4 Hz).

The configuration of the complex generated was assigned as (*S*,a*S*,*S*), utilizing a Nuclear Overhauser Effect (NOE) similar to Ikeda's analysis procedure.[3]

Encouraged by this efficient protocol for the synthesis and copper complexation of ligands **1a–d** and in order to demonstrate the new potential of these ligands, their application was investigated in the copper-catalyzed allylic oxidations of cycloolefins (Scheme 2). In a typical experimental procedure, the reactions were carried out by using cyclohexene as the substrate in the presence of various ligands **1a–d** (10 mol %) and $[Cu(CH_3CN)_4]PF_6$ (10 mol %) as the catalyst at different temperatures in acetonitrile. The reactions were monitored by TLC for consumption of the perester and stopped at the given time. Our results are summarized in Table 1. The yields and enantiomeric ratios of the products showed the temperature dependence of this process. A decrease in the reaction temperature from −10 to −20 °C did not give a favorable ee% and greatly decreased the reaction yield; the enantioselectivity also dropped dramatically when the temperature was increased from −10 to 40 °C (entries 1–6).

It can also be seen in Table 1 and Figure 2 that the type of R group on the oxazoline substituent has a great effect on the

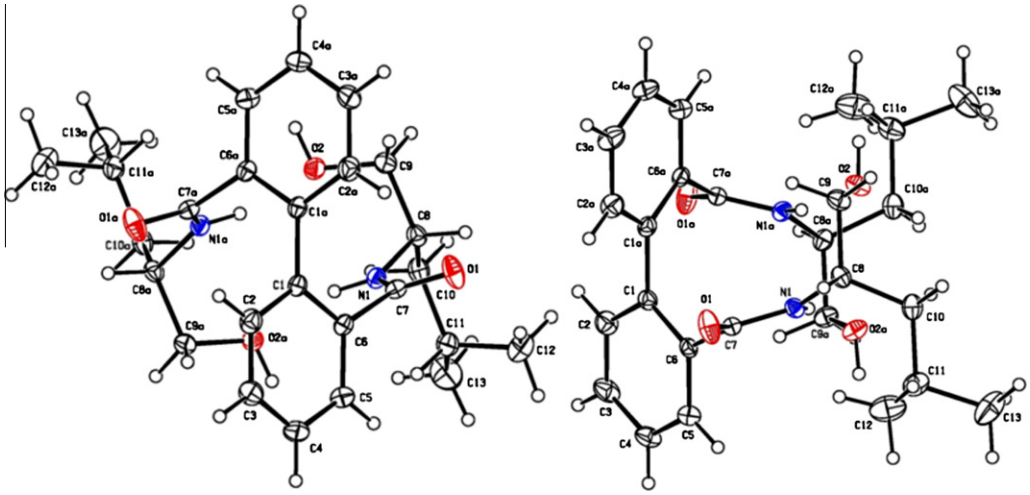
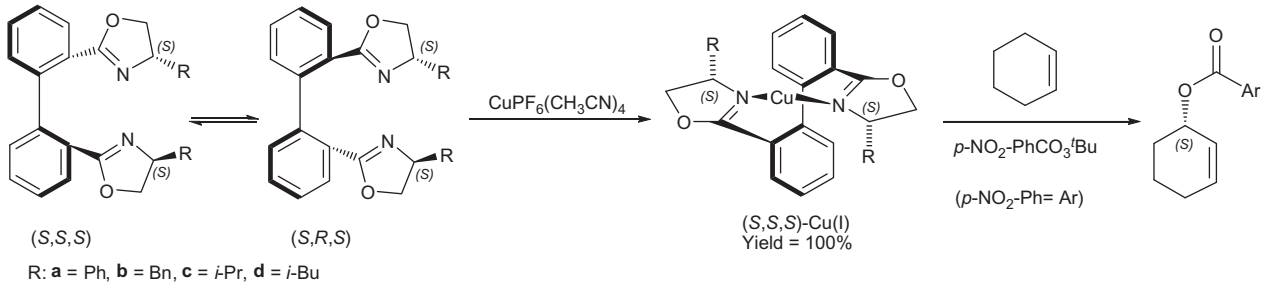
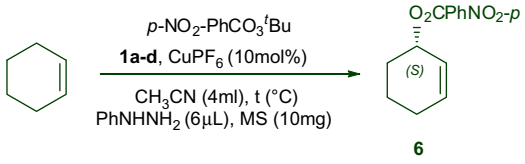


Figure 1. Two views of the ORTEP diagram of bishydroxylamide precursor **5d**. Thermal ellipsoids are at 30% probability level.



Scheme 2. Asymmetric allylic oxidation of cyclohexene with chiral ligands **1**.

Table 1
Effect of catalyst on the reaction at different temperatures



Entry	Catalyst	Temperature (°C)	Time (h)	Yield (%)	ee (%)
1	**1a**	40	1.5	85	35
2	**1a**	25	3.5	90	45
3	**1a**	10	24	88	51
4	**1a**	0	82	76	55
5	**1a**	−10	195	77	62
6	**1a**	−20	292	70	64
7	**1b**	−10	185	77	75
8	**1c**	−10	195	65	23
9	**1d**	−10	186	70	23

enantioselectivity of the process. The phenyl or benzyl substituted oxazolines **1a** and **1b** resulted in considerably higher enantioselectivities in comparison with the other two ligands **1c** and **1d** carrying alkyl substitutions (entries 6 and 10). The highest enantioselectivities and yields were achieved by employing ligand **1b** at −10 °C (entry 7).

There is a gap of efficiency between these two types of ligands with regard to the ee% of this reaction as illustrated in Figure 2.

Considering ligand **1b** as the best ligand, we next focused our attention on the effects of solvent, copper salts, phenylhydrazine,[1j] and molecular sieves (MS) in order to achieve the best reaction conditions for the asymmetric allylic oxidation of cyclohexene. A series of results are presented in Table 2. It was observed that the reaction rate, yield, and ee of the products were generally improved when molecular sieves were used as an additive (entry 2 versus entry1). When using phenyl hydrazine as an additive, the enantioselectivity and yield only slightly increased but the reaction rate improved remarkably (entry 3 versus entry 1). Encouraged by these results, we performed the reaction in the presence of phenyl hydrazine and MS simultaneously, and the reaction rate, yield, and ee values of the products **6** were markedly improved (entry 4). In order to determine the influence of other peresters on the efficiency of this reaction, phenyl *tert*-butyl and *p*-methoxyphenyl *tert*-butyl peresters were also used. However, the isolated yield and ee% in comparison to *p*-nitrophenyl *tert*-butyl perester decreased (entry 4 vs 5–6).

The effect of Cu salts was also investigated. In all cases, $CuPF_6$ proved to be the best copper source while other Cu salts such as $Cu(OTf)_2$, $Cu(OAc)_2$, CuCl, and CuI led to a decrease in the ee by 12–38% and longer reaction times (entry 4 vs 7–11).

The application of phenylhydrazine was necessary when $Cu(OTf)_2$ was used in the reaction because in this case, the Cu(I) complex that formed in situ, accelerates the oxidation reaction (compare entry 5 and entry 10). It should be noted that when CuOTf was used as the Cu(I) source, it resulted in better values in isolated yield, reactivity, and ee% than the combination of $Cu(OTf)_2$ and phenylhydrazine under similar conditions (compare entry 7 and entry 13).

Three different solvents were examined under various conditions and the best results were obtained in MeCN (entry 4 vs entries 14–15).

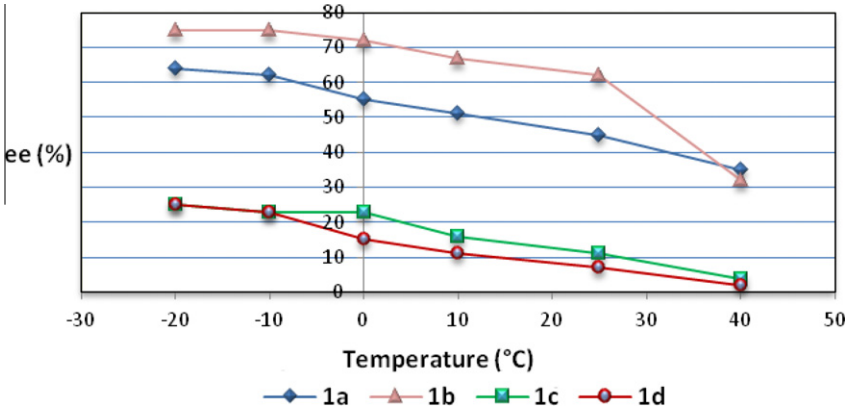
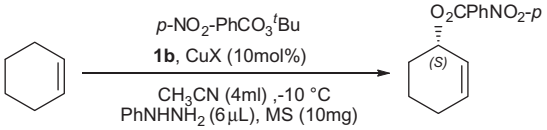


Figure 2. Dependency of ee values on ligand structure at different temperatures.

Table 2
Effect of solvents, additives, and counter anions on the reaction



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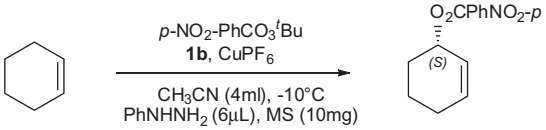
Entry	Cu salt (10 mol %)	Solvent	Time (h)	Yield (%)	ee (%)
1[a]	$CuPF_6$	CH_3CN	370	60	40
2[b]	$CuPF_6$	CH_3CN	340	74	55
3[c]	$CuPF_6$	CH_3CN	210	65	45
4	$CuPF_6$	CH_3CN	185	77	75
5[d]	$CuPF_6$	CH_3CN	172	52	59
6[e]	$CuPF_6$	CH_3CN	165	45	56
7	$Cu(OTf)_2$	CH_3CN	390	60	38
8	CuOTf	CH_3CN	215	85	62
9	$Cu(OAc)_2$	CH_3CN	370	65	28
10	CuCl	CH_3CN	440	48	19
11	CuI	CH_3CN	215	54	21
12[b]	$Cu(OTf)_2$	CH_3CN	425	45	24
13[b]	CuOTf	CH_3CN	350	69	48
14	$CuPF_6$	Acetone	240	80	61
15	$CuPF_6$	CH_2Cl_2	450	52	33

[a] In the absence of any additives.
[b] In the presence of MS only.
[c] In the presence of $PhNHNH_2$ only.
[d] With phenyl *tert*-butyl perester.
[e] With *p*-methoxyphenyl *tert*-butyl perester.

Table 3
Effects of catalyst loading on the reaction



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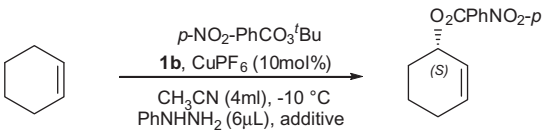
Entry	Catalyst (mol %)	Time (h)	Yield (%)	ee (%)
1	1	500	25	20
2	2.5	335	36	24
3	5	295	50	38
4	10	185	77	75
5	15	250	54	62
6	20	210	45	56

Table 4
Effects of additive on the reaction



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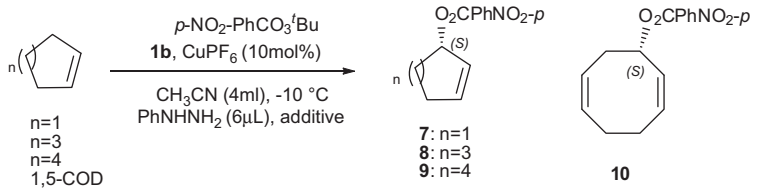
Entry	Additive	Time (h)	Yield (%)	ee (%)
1	MS (10 mg)	185	77	75
2	Activated silica gel (10 mg)	225	60	55
3	SBA-15 (10 mg)	70	99	81
4	SBA-15 (5 mg)	89	95	79
5	SBA-15 (2.5 mg)	92	90	60
6	MCM-41(10 mg)	115	85	60
7	MgO (10 mg)	82	85	65
8	TiO_2 (10 mg)	85	80	71
9	CuO (10 mg)	68	90	71

The effects of catalyst loading were also investigated. The results which described in Table 3 indicated that the enantioselectivity, the reactivity, and the yield were influenced by the amount of catalyst. The best results were obtained when 10% catalyst loading was used. Lowering the catalyst loading to less than 10 mol % or increasing it to 20 mol % led to a sharp decrease in the results (Table 3).

Although the use of molecular sieves gave cyclohex-2-enyl benzoate **6** in good yield and enantioselectivity, a longer reaction time was required (entry 1, Table 4). Therefore, further optimization of the reaction conditions could be achieved by exploring the effect of numerous additives on this reaction. For this purpose, we prepared and examined the activated silica gel,[9] mesoporous MCM-41[10] and SBA-15[11] silica, nanocrystalline MgO,[12] CuO,[13] and TiO_2[14] as additives in the asymmetric allylic oxidation of cycloolefins in which some of them (MgO and CuO) have been successfully used in other asymmetric transformations.[15] The results are shown in Table 4 and it can be seen that the reaction in the presence of these nanoparticles is generally faster than in the case of molecular sieves (entries 3–9). When we performed the reaction in the presence of SBA-15 as an additive (10 mg/mmol), the enantioselectivity of the reaction improved up to 81% and the reaction was complete in only 70 h and provided chiral allylic ester **6** in quantitative yield (entry 3). Lowering the amount of this mesoporous to 2.5 mg/mmol slightly reduced the yield and reactivity but greatly decreased the ee to 60% (compare entry 5 with entry 3). However, a further increase in the amount of SBA-15 did not lead to any observable changes in the results of the reaction.

Table 5
Additive effect on other cycloolefins



Entry	Additive (mg)	7			8			9			10		
		Time (h)	Yield (%)	ee (%)	Time (h)	Yield (%)	ee (%)	Time (h)	Yield (%)	ee (%)	Time (h)	Yield (%)	ee (%)
1	SBA-15 (10)	80	99	75	92	87	70	109	85	72	70	99	95
2	Activated silica gel (10)	200	64	52	221	67	52	265	54	44	194	62	58
3	MCM-41 (10)	115	80	63	123	87	60	140	60	68	95	95	85
4	MgO (2.5)	90	85	70	86	82	67	103	55	54	76	99	78
5	TiO_2 (10)	90	80	71	97	76	68	123	45	60	82	99	71
6	CuO (10)	79	80	64	76	75	63	84	74	64	66	99	78

Mesoporous MCM-41 silica exhibited higher yields and reactivity, yet the enantioselectivity dropped considerably in contrast to MS (compare entry 6 with entry 1). It was also found that utilizing metal oxides as additives, resulted in comparable enantioselectivity with higher rates and better yields in comparison with MS (entries 7–9).

The effect of these additives on the allylic oxidation of cyclohexene encouraged us to examine this effect on other substrates. We extended the reaction to several cycloolefins and in all cases, allylic esters **7–10** were also obtained in high yields and ees; the best results were achieved in the presence of SBA-15 (10 mg) (Table 5).

In the case of 1,5-cyclooctadiene in the presence of this mesoporous silica, the reaction proceeded at a much higher rate in quantitative yield and highest enantiomeric excess (95%) compared with other cycloolefins.

The SBA-15 was reused in all cases at least three times without a significant loss of efficiency. The XRD, SEM, and IR results clearly demonstrated that the mesoporous structure of SBA-15 was preserved after reuse for the three times. In order to evaluate the importance of the nanoparticle systems, we carried out the reaction with activated silica gel (amorphous system) under the similar conditions. As the results show in Tables 4 and 5, a drastic decrease in values was observed in terms of yields and enantioselectivities and reactivities.

These results showed that nanoparticles most probably have a participatory role in the reaction; it is most likely that the hydroxyl groups on the surface of the nanoparticles coordinate to the metal center of the copper(I)-biphenyl bisoxazoline catalyst in general and SBA-15 in particular. These experimental results demonstrate the important aspect of nanoparticles in asymmetric chemistry. However, further experimental study is required in order to examine the effect of particle size and type of additive on the results of the reaction, and also computational calculations for proposing a proper mechanism for the reaction is needed. These investigations are currently in progress in our laboratory.

3. Conclusion

In conclusion, we have developed an efficient and simple method for the preparation of chiral biphenyl bisoxazoline ligands **1a–d** from an inexpensive starting material, anthranilic acid **2**. The catalytic potential of these ligands for the copper-catalyzed allylic oxidations of cycloolefins was investigated utilizing numerous nanosized additives. With the optimization of the reaction conditions in the presence of SBA-15 and with ligand **1b**, the reaction took place in a reasonably short period of time and one enantiomer of the allylic benzoates was obtained with up to 95% ee and up to 99% yield. A new and very important aspect of SBA-15 mesoporous silica with regard to improving the yields, ees, and rates of the reaction was discovered. Further efforts to extend the utility of the nanoparticles in conjunction with the chiral bisoxazoline ligands in other enantioselective reactions are currently underway in our laboratory.

4. Experimental

4.1. General

Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer 341 polarimeter at 589 nm. ^1H and ^{13}C NMR spectra were recorded on a BRUKER DRX-300 AVANCE spectrometer at 300.13 and 75.47 MHz, 100 MHz in $CDCl_3$, and DMSO-d_6 using TMS ($\delta = 0.0$ ppm) as internal standard. IR spectra were recorded on a Bomen FT-IR-MB-series instrument. Enantiomeric excess (ee) of the allylic esters **6–10** were determined by HPLC analysis using an EC 250/4.6 Nucleocel Alpha S column. All reactions were performed under an atmosphere of dry, oxygen-free nitrogen. All reagents and starting materials were purchased from Aldrich, Merck, and Fluka. Olefins were distilled from calcium hydride before use. All solvents were of reagent grade and were dried and distilled immediately before use as follows: acetonitrile and acetone from P_2O_5, methylene chloride from calcium hydride. Column chromatography was performed using silica gel 60 (230–400 mesh) eluting with ethyl acetate/*n*-hexane. TLC was performed using silica gel 60 F_{256} plates with visualization by UV.

4.1.1. [1,1′-Biphenyl]-2,2′-dicarboxylic acid 3[5]

Light yellow powder; (95%); mp 220–224 °C; ^1H NMR (300 MHz, DMSO-d_6) δ_H(ppm) = 7.13–7.15 (m, 2H), 7.42–7.44 (m, 2H), 7.51–7.53 (m, 2H), 7.86–7.89 (m, 2H), 12.21–12.43 (br s OH, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C(ppm) = 127.2, 127.8, 130.9, 133.3, 136.5, 141.1, 168.7; IR (KBr, cm^{-1}): 1688, 3071.

4.1.2. Typical procedure for the synthesis of bishydroxylamide 5a–d

To a solution of diacid **3** (0.73 g, 3.0 mmol) in dichloromethane (10 mL) were added oxalyl chloride (1.25 mL, 12 mmol) and a catalytic amount of DMF (3 drops) at 0 °C. After stirring for 4 h at room temperature under nitrogen, the solvent was removed under reduced pressure to afford the acid chloride as a light yellow solid (0.84 g, 99%). This solid residue was then dissolved in

dichloromethane (10 mL) and slowly added to a stirred solution of (*S*)-phenyl glycinol **4a** (0.9 g, 6.5 mmol) and Et_3N, (1 mL) in dichloromethane (10 mL) at 0 °C over 30 min. The reaction mixture was allowed to warm to room temperature slowly and stirred overnight under nitrogen. The formation of two new compounds (*S*,a*S*,*S*)- and (*S*,a*R*,*S*)-**5a** and consumption of acid chloride was confirmed by TLC (90:10 EtOAc/*n*-hexane). After completion of the reaction, brine (10 ml) was added and the aqueous layer was extracted with ethyl acetate (3 × 15 ml) and dried over magnesium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography (eluent: EtOAc/*n*-hexane; 80–100: 20–0); to afford a white solid in 95%. The total yield for other compounds **5b**, **5c**, and **5d** were 90%, 99%, and 99%, respectively.

4.1.3. N^2,$N^{2'}$-Bis((*S*)-2-hydroxy-1-phenylethyl)-[1,1′-biphenyl]-2,2′-dicarboxamide (*S,S,S*)- and (*S,R,S*)-5a

The ^{1}H NMR and ^{13}C NMR of **5a** showed two sets of signals, major/minor (52:48). Mp: 85–92 °C; R_f = 0.38, 0.47 (100% EtOAc); Major (*S,S,S*): ^{1}H NMR (300 MHz, $CDCl_3$): δ_H(ppm) = 3.57–3.79 (m, 4H), 4.99–5.02 (m, 2H), 6.91–7.60 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C(ppm) = 59.9, 65.2, 126.7–134.4 (8C), 137.9, 138.4, 139.2, 139.4, 170.4. Minor (*S,R,S*): ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm) = 3.57–3.79 (m, 4H), 4.91–4.92 (m, 2H), 6.91–7.60 (m, 20 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) = 59.1, 65.6, 126.6–134.6 (8C), 137.6, 138.9, 140.1, 170.1; IR (KBr, cm^{-1}): 1540, 1640, 3078.

4.1.4. N^2,$N^{2'}$-Bis((*S*)-1-hydroxy-3-phenylpropan-2-yl)-[1,1′-biphenyl]-2,2′-dicarboxamide (*S,S,S*)- and (*S,R,S*)-5b

The ^{1}H NMR and ^{13}C NMR of **5b** also showed two sets of signals, major/minor (73:27). Mp: 70–78 °C; R_f = 0.43, 0.57 (100% EtOAc); Major (*S,S,S*): ^{1}H NMR (300 MHz, $CDCl_3$): δ_H(ppm) = 2.50–2.54 (m, 2H), 2.75–2.78 (m, 2H), 3.55 (m, 4H), 4.07(m, 2H) 7.08–7.57 (m, 20H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ_C(ppm) = 37.3, 57.9, 63.5, 125.9–131.2 (8 C), 138.1, 138.7, 169.6;) Minor (*S,R,S*): ^{1}H NMR (300 MHz, $CDCl_3$): δ_H(ppm) = 2.50–2.54 (m, 2H), 2.75–2.78 (m, 2H), 3.59 (m, 4H), 4.07(m, 2H) 7.08–7.57 (m, 20H); ^{13}C NMR (62.5 MHz MHz, $CDCl_3$): δ_C(ppm) = 38.6, 57.3, 64.8, 125.9–131.2 (8 C), 138.4, 138.5, 168.9; IR (KBr, cm^{-1}): 1547, 1640, 3270.

4.1.5. N^2,$N^{2'}$-Bis((*S*)-1-hydroxy-3-methylbutan-2-yl)-[1,1′-biphenyl]-2,2′-dicarboxamide (*S,S,S*)- and (*S,R,S*)-5c

The ^{1}H NMR and ^{13}C NMR of **5c** showed two sets of signals, major/minor (54:46). Mp: 93–99 °C; R_f = 0.24, 0.30 (100% EtOAc); Major (*S,S,S*): ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm) = 0.63–0.69 (m, 6H), 0.77–0.83 (m, 6H),1.69–1.78 (m, 2H), 3.27–3.29 (m, 2H), 3.33–3.43 (m, 2H), 3.57 (m, 2H), 7.04–7.10 (m, 2H), 7.32–7.60 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C(ppm) = 18.9, 19.3, 28.7, 57.6, 63.2, 126.9–129.9 (4C), 136.5, 138.6, 170.7; Minor (*S,R,S*): ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm) = 0.63–0.69 (m, 6H),0.77–0.83 (m, 6H),1.58–1.69 (m, 2H), 3.27–3.29 (m, 2H), 3.33–3.43 (m, 2H), 3.57 (m, 2H), 7.04–7.10 (m, 2H), 7.32–7.60 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C(ppm) = 18.5, 19.2, 28.8, 57.4, 63.0, 126.9–129.9(4C), 136.0, 138.8, 170.4; IR (KBr, cm^{-1}): 1547, 1633, 1732, 3280.

4.1.6. N^2,$N^{2'}$-Bis((*S*)-1-hydroxy-4-methylpentan-2-yl)-[1,1′-biphenyl]-2,2′-dicarboxamide (*S,S,S*)- and (*S,R,S*)-5d

The ^{1}H NMR and ^{13}C NMR of **5d** showed two sets of signals, major/minor (77:33), Mp:135–144 °C; R_f = 0.27, 0.34 (100% EtOAc); Major (*S,S,S*): ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm) = 0.71–0.75 (m, 12H), 1.04–1.07 (m, 4H), 1.18–1.25 (m, 2H), 3.14–3.22 (m, 2H), 3.28–3.40 (m, 2H), 3.83 (m, 2H), 6.92–6.96. (m, 2H), 7.27–7.66 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C(ppm) = 21.9, 23.2, 24.4, 39.6, 50.3, 65.5, 129.6–126.7(4C), 135.9, 138.8, 170.5; Minor (*S,R,S*): ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm) = 0.78–0.80 (m, 12H), 1.04–1.07 (m, 4H), 1.18–1.25 (m, 2H), 3.14–3.22 (m, 2H), 3.28–3.40 (m, 2H), 3.83 (m, 2H), 6.92–6.96. (m, 2H), 7.27–7.66 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C(ppm) = 22.0, 23.1, 24.6, 39.5, 50.1, 65.2, 129.6–126.7(4C), 136.5, 138.5, 170.4; IR (KBr, cm^{-1}): 1553, 1640, 3264.

4.2. Typical procedure for the synthesis of ligands 1a–d

Method a: Cyclization procedures of bishydroxylamides **5a–d** were performed according to the Andrus procedure.[1m]

Method b: A solution of bishydroxylamide **5a** (234 mg, 0.5 mmol), triphenylphosphine (0.14, 5.2 mmol), triethylamine (69 μL, 0.44 mmol), and tetrachloromethane (50 μL, 0.44 mmol) in dry acetonitrile (3 ml) was stirred overnight. After being concentrated in vacuo, the residue was dissolved with CH_2Cl_2, washed with water, dried over anhydrous magnesium sulfate, and then concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent: *n*-hexane/EtOAc; 90:10); to afford a pure light yellow **1a** in 89% yield. Compounds **1b, 1c**, and **1d** were obtained in a similar manner as light yellow products in 45%, 60%, and 50% total yield, respectively.[1t]

Method c: A flame-dried 25 mL Schlenk flask equipped with a stirrer bar was charged with bishydroxylamide **5a** (1 mmol, 0.48 g, 1 equiv), 4-(dimethylamino) pyridine (0.01 g, 0.1 mmol, 0.1 equiv), and dichloromethane (10 mL) under nitrogen. The flask was placed in ice and triethylamine (0.6, 4.4 mmol, 4.4 equiv) and a solution of *p*-toluenesulfonyl chloride (0.38 g, 2 mmol, 2 equiv) in dichloromethane (4 mL) were added to the reaction mixture. After stirring at room temperature for 18 h, the mixture was washed with saturated aqueous NH_4Cl (10 mL) and the aqueous layer was extracted again with dichloromethane (3 × 10 ml). The extracted organic layers were combined and washed with saturated aqueous $NaHCO_3$ (10 mL), dried over Na_2SO_4 and concentrated. The light yellow oil **1a** obtained was purified by column chromatography (*n*-hexane/EtOAc; 90:10); to afford pure light yellow **1a** in 95% yield. Other ligands **1b, 1c**, and **1d** were synthesized via a similar method in 85%, 96%, and 90% total yield, respectively.

The one-pot procedure: To a solution of diacid **3** (0.73 g, 3.0 mmol) in dichloromethane (10 mL) were slowly added oxalyl chloride (1.25 mL, 12 mmol) and then three drops of DMF at 0 °C. The reaction mixture was stirred for 4 h at room temperature under nitrogen. The solvent was evaporated under reduced pressure to afford the acid chloride as a light yellow solid (0.84 g, 99%). This solid material was then dissolved in dichloromethane (10 mL) and a solution of (*S*)-phenyl glycinol **4a** (0.9 g, 6.5 mmol) and Et_3N (1 mL) in dichloromethane (10 mL) was added to the reaction flask at 0 °C over 30 min. The resulting solution was allowed to warm slowly to room temperature with stirring overnight. The formation of bishydroxylamide **5a** was monitored by TLC; R_f = 0.38, 0.47 (100% EtOAc). Next, methanesulfonyl chloride (0.51 mL, 6.6 mmol) was added at 0 °C, and the mixture was stirred at room temperature for 6 h. After completion, the reaction mixture was diluted with dichloromethane (10 ml) and washed with saturated aqueous NH_4Cl (10 ml). The aqueous layer was extracted again with dichloromethane (2 × 10 ml) and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (10 ml) and dried over Na_2SO_4. The solvent was removed under reduced pressure to afford a light yellow oil, which was chromatographed (*n*-hexane/EtOAc; 90:10) over silica gel to provide pure light yellow products **1a** in 90% total yield. Compounds **1b, 1c**, and **1d** were synthesized in a similar manner in 85%, 85%, and 95% total yield, respectively.[7]

4.2.1. 2,2′-Bis((*S*)-4-phenyl-4,5-dihydrooxazol-2-yl)-1,1′-biphenyl (*S,S,S*)- and (*S,R,S*)-1a

The ^{1}H NMR of **1a** showed two sets of signals, major/minor (61:39). R_f = 0.35, 0.55 (*n*-hexane/EtOAc; 40:60); Major (*S,S,S*): ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm) = 3.83–3.93 (m, 2H), 4.39–4.55

(m, 2H), 5.12–5.27 (m, 2H), 7.16–7.59 (m, 16H) 7.97–8.03 (m 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) = 69.9, 75.2, 126.7–130.4 (8C), 141.4, 142.4, 166.1; Minor (*S,R,S*): ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm) = 3.99–4.03 (m, 2H), 4.39–4.55 (m, 2H), 5.12–5.27 (m, 2H), 7.16–7.59 (m, 16H) 7.97–8.03(m. 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) = 69.7, 74.6, 126.7–130.4 (8C), 141.9, 142.5, 165.4; IR (KBr, cm^{-1}): 1447, 1646, 2886, 3018, 3065; $[\alpha]_D^{26} = -179.9$ (*c* 0.50, $CHCl_3$); MS m/z (%): 444 (8, M^+), 367(12), 298 (100), 226 (31), 77(42).

4.2.2. 2,2′-Bis((S)-4-benzyl-4,5-dihydrooxazol-2-yl)-1,1′-biphenyl (*S,S,S*)- and (*S,R,S*)-1b

The ^{1}H NMR of 1**b** showed two sets of signals: major/minor (70:30). R_f = 0.15, 0.33 (*n*-hexane/EtOAc; 40:60); Major (*S,S,S*): ^{1}H NMR (300 MHz, $CDCl_3$): δ_H(ppm) = 2.54–2.68 (m, 2H), 2.95–3.02 (dd, 2H, *J* 5.2, 13.6 Hz), 3.80–3.90 (m, 2H), 3.97–3.4.03 (t, 2H, *J* 8.8 Hz), 4.36–4,41 (m, 2H), 7.11–7.53 (m, 16H), 7.81–7.84(d, 2H, *J* 7.4 Hz);^{13}C NMR (75 MHz, $CDCl_3$): δ_C(ppm) = 41.3, 67.9, 71.9, 126.3–130.2 (8C), 138.2, 141.4, 164.6; Minor (*S,R,S*): ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm) = 2.54–2.68 (m, 2H), 2.06–3.12 (dd, 2H, *J* 4.34, 13.6 Hz), 3.80–3.90 (m, 2H), 4.10–4.15 (t, 2H, *J* 8.8 Hz), 4.36–4,41 (m, 2H), 7.11–7.53 (m, 16H), 7.88–7.90 (d, 2H, *J* 7.3 Hz);^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) = 41.5, 67.9, 72.0, 126.3–130.2 (8 C), 138.2, 141.6, 164.5; IR (KBr, cm^{-1}): 1501, 1653, 1726, 2913, 3065; MS *m/z* (%): 472 (11, M^+), 382(19), 313 (100), 238 (27), 93(54); $[\alpha]_D^{26} = -193.6$ (*c* 0.50, $CHCl_3$).

4.2.3. 2,2′-Bis((S)-4-isopropyl-4,5-dihydrooxazol-2-yl)-1,1′-biphenyl (*S,S,S*)- and (*S,R,S*)-1c

The ^{1}H NMR of 1c showed two sets of signals, major/minor (80:20); R_f = 0.18, 0.5 (*n*-hexane/EtOAc; 40: 60); Major (*S,S,S*): ^{1}H NMR (300 MHz, $CDCl_3$): δ_H(ppm) = 0.80–0.82 (m, 12H), 1.65–1.74 (m, 2H), 3.74 (t, 2H, *J* 7.9 Hz), 3.82–3.90 (m, 2H), 4.14 (t, 2H, *J* 8.7 Hz), 7.22–7.50 (m, 6H), 7.81 (d, 2H, *J* 7.6 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ_C(ppm) = 18.7, 19.4, 33.3, 69.4, 72.5, 125.8, 127.1, 128.2, 132.3, 136.1, 140.5, 165.4; Minor (*S,R,S*): ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm) = 0.86–0.88(d, 12H, *J* 6.7 Hz), 1.65–1.74 (m, 2H), 3.74 (t, 2H, *J* 7.9 Hz), 3.82–3.90 (m, 2H), 4.14 (t, 2H, *J* 8.7 Hz), 7.22–7.50 (m, 6H), 7.86 (d, 2H, *J* 7.3 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ_C (ppm) = 18.5, 19.0, 33.0, 70.2, 72.7, 126.2, 127.7, 128.1, 132.1, 136.9, 140.2, 165.1; IR (KBr, cm^{-1}): 1467, 1646, 2873, 2959; MS *m/z* (%): 376 (10, M^+), 334(21), 265 (100), 191 (26), 43(46); $[\alpha]_D^{26} = -157.5$ (*c* 0.50, $CHCl_3$).

4.2.4. 2,2′-Bis((S)-4-isobutyl-4,5-dihydrooxazol-2-yl)-1,1′-biphenyl ((*S,S,S*)- and (*S,R,S*)-1d

The ^{1}H NMR of **1d** showed two sets of signals: major/minor (63:38). R_f = 0.4, 0.53 (*n*-hexane/EtOAc; 50:50); Major (*S,S,S*): ^{1}H NMR (300 MHz, $CDCl_3$): δ_H(ppm) = 0.85–0.90 (m, 12H), 1.11–1.30(m, 2H), 1.42–1.64 (m, 4H), 3.59–3.65 (m, 2H), 4.05–4.23 (m, 4H), 7.23–7.48 (m, 6H), 7.75–7.77 (d, *J* 7.9, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ_C(ppm) = 19.9, 20.3, 33.7, 43.5, 68.1, 76.1, 126.6, 127.1, 128.1, 131.9, 136.5, 139.7, 164.1; Minor (*S,R,S*): ^{1}H NMR (300 MHz, $CDCl_3$): δ_H(ppm) = 0.85–.90 (m, 12H), 1.11–1.30 (m, 2H), 1.42–1.64 (m, 4H), 3.59–3.65 (m, 2H), 4.05–4.23 (m, 4H), 7.23–7.48 (m, 6H), 7.82–7.85 (d, *J* 7.4, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ_C(ppm) = 20.1, 20.5, 33.2, 43.6, 67.8, 76.2, 126.1, 126.9, 127.7, 131.6, 136.6, 140.2, 163.5; IR (KBr, cm^{-1}): 1461, 1666, 1726, 2926, 2952. MS *m/z* (%): 404 (4, M^+), 347(9), 278 (100), 206 (24), 91(47), 55(37); $[\alpha]_D^{26} = -121.4$ (*c* 0.50, $CHCl_3$).

4.3. General procedure for the synthesis of the 1-Cu complex

To a solution of ligand **1** (0.02 mmol) in chloroform-*d* was added 1 equiv of $Cu(I)PF_6(CH_3CN)_4$ (0.018 mmol, 6.6 mg,) under nitrogen atmosphere. The resulting light yellow solution was stirred at room temperature for 3 h. After completion of the reaction as indicated by TLC, only a single new spot (R_f = 0.0 in 50% EtOAc/*n*-hexane) was observed.

4.3.1. (*S*)-2,2′-Bis((S)-4-phenyl-4,5-dihydrooxazol-2-yl)-1,1′-biphenyl copper(I) hexafluoro phosphate complex (*S*,a*S,S*)-1a-$CuPF_6$

^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm) = 3.75–3.80 (t, *J* = 8.4, 2H), 4.40–4.45 (t, *J* = 10.0, 2H), 5.13–5.19 (t, *J* = 9.9, 2H), 6.91–7.77 (m, 18H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) = 69.8, 74.6, 125.9–128.4 (6C), 132.2, 136.9, 140.0, 142.7, 169.6; IR (KBr, cm^{-1}): 561, 841, 1086, 1514, 1642, 1688, 2302, 2919, 3740;MS *m/z* (%): 507 (1, $[M-PF_6]^+$), 444 (18, M+), 326 (22), 298 (100), 206 (73), 77(31); $[\alpha]_D^{26} = +23.4$ (*c* 1, $CHCl_3$).

4.3.2. (*S*)-2,2′-Bis((*S*)-4-benzyl-4,5-dihydrooxazol-2-yl)-1,1′-biphenyl copper(I) hexafluoro phosphate complex (*S*,a*S,S*)-1b-$CuPF_6$

^{1}H NMR (300 MHz, $CDCl_3$): δ_H(ppm) = 2.30–2.37 (dd, *J* = 13.6, 8.8, 2H), 2.76–2.83 (dd, 2H, *J* = 13.6, 5.4 Hz), 3.69–3.74 (t, *J* = 7.3, 2H), 3.93–3.99 (t, *J* = 8.8, 2H), 4.26–4.31 (m, 2H), 7.07–7.65 (m, 18H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) = 35.9, 65.6, 73.8, 124.6, 125.8, 126.8, 127.9, 128.7, 129.2, 130.1, 132.1, 136.4, 137.0, 170.0; IR (KBr, cm^{-1}): 552, 837, 1082, 1546, 1653, 1692, 2316, 2912, 3748;MS *m/z* (%): 535 (0.7, $[M-PF_6]^+$), 472 (20, M^+), 381(69), 312 (100), 247 (53), 91(62); $[\alpha]_D^{26} = +70.8$ (*c* 1, $CHCl_3$).

4.3.3. (*S*)-2,2′-Bis((S)-4-isopropyl-4,5-dihydrooxazol-2-yl)-1,1′-biphenyl copper(I) hexafluoro phosphate complex (*S*,a*S,S*)-1c-$CuPF_6$

^{1}H NMR (300 MHz, $CDCl_3$): δ_H(ppm) = 0.66–0.84 (m, 12H), 1.60–1.90 (m, 2H), 4.31 (br s, 4H), 4.36–4.58 (m, 2H), 7.15–7.42 (m, 6H), 7.61 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C(ppm) = 18.1, 18.6, 32.6, 70.0, 72.4, 126.6, 126.8, 129.9, 131.4, 137.3, 139.7, 167.1; IR (KBr, cm^{-1}): 552, 771, 843, 1089, 1381,1474, 1638, 1725, 2269, 2965, 3423; MS *m/z* (%): 439 (0.5, $[M-PF_6]^+$), 376 (41, M^+), 403 (35), 292 (71), 264 (100), 206 (54), 91(34); $[\alpha]_D^{26} = +9.2$ (*c* 1, $CHCl_3$).

4.3.4. (*S*)-2,2′-Bis((*S*)-4-isobutyl-4,5-dihydrooxazol-2-yl)-1,1′-biphenyl copper(I) hexafluoro phosphate complex (*S*,a*S,S*)-1d-$CuPF_6$

^{1}H NMR (300 MHz, $CDCl_3$): 0.95–1.12 (m, 12H), 1.32–1.55 (m, 4H), 1.70–1.71 (m, 2H), 4.23–4.48 (br s, 4H), 4.96 (m, 2H), 7.56 (m, 6H), 7.80–7.83 (d, *J* = 8.2, 2H).; ^{13}C NMR (75 MHz, $CDCl_3$): δ_C(ppm) = 20.8, 22.6, 25.6, 45.8, 65.3, 73.2, 126.8, 127.6, 128.5, 131.7, 137.5, 141.0, 168; IR (KBr, cm^{-1}): 559, 842, 1089, 1381,1467, 1637, 1719, 2276, 2959, 3409; MS *m/z* (%): 467 (0.5, $[M-PF_6]^+$), 403(11, M^+), 347(23), 278 (100), 206 (45), 91(37), 55(56); $[\alpha]_D^{26} = +62.9$ (*c* 1, $CHCl_3$).

4.4. Synthesis of *tert*-butyl 4-nitrobenzoperoxoate[1n]

p-Nitrobenzoyl chloride (3.2 g, 17.2 mmol) was dissolved in a 100 mL round bottom flask containing CH_2Cl_2 (35 mL). The solution was cooled to −20 °C and stirred under nitrogen for 15 min. Pyridine (1.7 mL, 20.0 mmol) was then added and the reaction mixture was stirred for 10 min. Next, *tert*-butyl hydroperoxide (3.5 mL, 20.0 mmol) was added dropwise to the reaction at −20 °C, and stirred for 4 h. Then the reaction solution was then diluted with CH_2Cl_2 (20 mL), and washed with water. The organic layer was separated, dried over $MgSO_4$, and evaporated to obtain a crude yellow solid product. Purification using flash chromatography (*n*-hexane/EtOAc; 90:10) afforded a light yellow solid product. (3.9 g, 98% yield); Mp 75–78 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H(ppm) = 1.45 (9H, s, Me), 8.14–8.35 (4H, m, Ar).

4.5. General procedure for the enantioselective allylic oxidation of cycloolefins using *tert*-butyl 4-nitrobenzoperoxoate

To a flame-dried round bottom flask (25 mL), a light yellow solution of the bisoxazoline ligand **1** (0.065 mmol) and copper salt (0.55 mmol) were stirred in CH_3CN (4 mL) and stirred for 3 h at ambient temperature. In this case, TLC analysis indicated the formation of a single spot (R_f = 0.0 in 50% EtOAc/ hexanes). After the addition of phenyl hydrazine (6 μl, 0.06 mmol), the color of the solution changed from blue green to red. Next, 10 mg of 4 Å molecular sieves and MCM-41 or SBA-15 (or other nanoparticles) were added. After a few min, cycloolefin (5 mmol) was added. The reaction mixture was cooled to −10 °C and then *tert*-butyl 4-nitrobenzoperoxoate (0.203 g, 0.85 mmol) was added dropwise to the reaction solution under a nitrogen atmosphere. The mixture was kept at −10 °C until TLC showed the complete disappearance of perester. The reaction mixture was dissolved in 10% NH_4OH, extracted with EtOAc and dried over $MgSO_4$. Removal of solvent in vacuo afforded a yellow residue that was chromatographed over silica gel to provide the pure white solid product (yield up to 99%), and recovered bisoxazoline ligand in 80–95%yield.

4.5.1. (*S*)-Cyclopent-2-en-1-yl 4-nitrobenzoate 7[1n]

Mp: 77–79 °C; R_f = 0.57 (90: 10, *n*-hexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H(ppm) = 1.97–2.04 (1H m), 2.38–2.50 (2H, m), 2.59–2.63 (1H, m), 5.98 (2H, m), 6.22 (1H, m), 8.20 (d, 2H, *J* 8.5 Hz), 8.28 (d, 2H, *J* 8.5 Hz); IR (KBr, cm^{-1}) 1109, 1268, 1520, 1706, 2846; $[\alpha]_D^{20} = -159.3$ (*c* 1.0, $CHCl_3$); The enantiomeric excess was determined by chiral HPLC (EC 250/4.6 Nucleocel Alpha S column, *iso*-propyl alcohol/hexanes; 99.5:0.5; flow rate 0.4 ml/min; t_R = 35.1 min (*R*), 36.7 min (*S*)) (maximum ee = 80% (*S*)).

4.5.2. (*S*)-Cyclohex-2-en-1-yl 4-nitrobenzoate 6[1n]

Mp: 68–71 °C; R_f = 0.64 (*n*-hexane/EtOAc; 90:10, ^{1}H NMR (300 MHz, $CDCl_3$): δ_H(ppm) = 1.76–2.14 (6H m), 5.54 (1H m), 5.84 (1H d, *J* 9.8 Hz), 6.04 (1H d, *J* 9.8 Hz), 8.21–8.31(4H m); ^{13}C NMR (300 MHz, $CDCl_3$): δ_C(ppm) = 18.8, 25.0, 28.2, 69.8, 123.4, 125.0, 130.7, 133.6, 136.2; IR (KBr, cm^{-1}): 1107, 1278, 1525, 1713, 2928. $[\alpha]_D^{20} = -125.2$ (*c* 1.0, $CHCl_3$). The enantiomeric excess was determined by chiral HPLC (EC 250/4.6 Nucleocel Alpha S column, *iso*-propyl alcohol/hexanes; 99.5:0.5; flow rate 0.5 ml/min; t_R = 34.8 min (*R*), 37.1 min (*S*)) (maximum ee = 81% (*S*)).

4.5.3. (*S*)-Cyclohept-2-en-1-yl 4-nitrobenzoate 8[1n]

Mp: 72–75 °C; R_f = 0.57 (*n*-Hexane/EtOAc; 90:10); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H(ppm) = 1.66–1.72 (m, 4H), 2.02–2.12(m, 2H), 2.07–2.40 (m, 2H), 5.58–5.64 (m, 1H), 5.75–5.82 (m, 1H), 5.92–5.98 (m, 1H), 8.22–8.28 (m, 4H); IR (KBr, cm^{-1}): 1106, 1273, 1528, 1709, 28930; $[\alpha]_D^{20} = -68.7$ (*c* 1.0, $CHCl_3$). The enantiomeric excess was determined by chiral HPLC (EC 250/4.6 Nucleocel Alpha S column, *iso*-propyl alcohol/hexanes; 99.5:0.5; flow rate 0.4 ml/min; t_R = 26.6 min (*R*), 28.5 min (*S*)) (maximum ee = 78% (*S*)).

4.5.4. (*S*)-Cyclooct-2-en-1-yl 4-nitrobenzoate 9[1n]

Mp: 71–74 °C; R_f = 0.67 (*n*-Hexane/EtOAc; 90:10); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H(ppm) = 1.46–1.72 (m, 7H), 2.07–2.40 (m, 3H), 5.60–5.66 (m, 1H), 5.73–5.82 (m, 1H), 5.92–5.96 (m, 1H), 8.22–8.32 (m, 4H); IR (KBr, cm^{-1}): 1108, 1281, 1527, 1718, 2853; $[\alpha]_D^{20} = -39.4$ (*c* 1.0, $CHCl_3$). The enantiomeric excess was determined by chiral HPLC (EC 250/4.6 Nucleocel Alpha S column, *iso*-propyl alcohol/hexanes; 99.5:0.5; flow rate 0.4 ml/min; t_R = 24.4 min (*R*), 27.0 min (*S*)) (maximum ee = 75% (*S*)).

4.5.5. (*S*)-Cycloocta-2,6-dien-1-yl 4-nitrobenzoate 10[1n]

Mp: 74–76 °C; R_f = 0.62 (*n*-Hexane/EtOAc; 90:10); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H(ppm) = 5.57–5.84 (m, 4H), 2.21–2.41 (m, 2H), 2.54–2.68 (m, 2H), 2.85–2.95 (m, 2H), 5.57–5.84 (m, 4H), 6.17–6.26 (m, 1H), 8.23(d, 2H, *J* 8.5 Hz),)8.30 (d, 2H, *J* 8.4 Hz); IR (KBr, cm^{-1}): 1106, 1281, 1523, 1719, 2906; $[\alpha]_D^{20} = -26.5$ (*c* 1.0, $CHCl_3$). The enantiomeric excess was determined by chiral HPLC (EC 250/4.6 Nucleocel Alpha S column, *iso*-propyl alcohol/hexanes, 99.5:0.5; flow rate 0.4 ml/min; t_R = 38.2 min (*R*), 40.5 min (*S*)) (maximum ee = 95% (S)).

4.6. Crystal structure determination and refinement of 5d

The X-ray diffraction measurement was made on a STOE IPDS-II diffractometer with graphite monochromated Mo-Kα radiation. For **5d**, a block colorless crystal was chosen using a polarizing microscope and was mounted on a glass fiber which was used for data collection. Cell constants and orientation matrices for data collection were obtained by least-squares refinement of diffraction data from 3677 unique reflections. Data were collected to a maximum 2θ value of 58.38° in a series of ω scans in 1° oscillations and integrated using the Stoe X-AREA[16] software package. The data were corrected for Lorentz and Polarizing effects. The structure was solved by direct methods[17] and subsequent difference Fourier maps and then refined on F^2 by a full-matrix least-squares procedure using anisotropic displacement parameters.[18] All hydrogen atoms attached to the carbon were added in idealized positions. Hydrogen atoms of N–H and O–H were found in difference Fourier maps. The atomic factors were taken from the International Tables for X-ray crystallography.[19] All refinements were performed using the X-STEP32 crystallographic software package.[20] CCDC No. 895781 contains crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Center via http://www.ccdc.cam.ac.uk/data_request/cif.

Crystal data for **5d**; $C_{26}H_{36}N_2O_4$, M = 440.57, colorless block, crystal dimensions: 0.4 × 0.32 × 0.20 mm^3; tetragonal, space group $P4_12_12$; a = 13.0262(18), b = 13.0262(18), c = 16.027(3) Å; V = 2719.5(9) Å^3; T = 120(2) K; Z = 4; D_{calc} = 1.076 g cm^{-3}; μ = 0.072 mm^{-1} (for Mo Kα, λ = 0.71073 Å); F(000) = 952; reflections collected = 31313; reflections independent = 3677 [R_{int} = 0.1783]; θ range 2.21 to 29.19; h, k, l range: $-17 \leqslant h \leqslant 15$, $-17 \leqslant k \leqslant 17$, $-21 \leqslant l \leqslant 21$; full-matrix least-squares on F^2; parameters = 154; restraints = 0; R_1 = 0.0932; wR_2 = 0.1338 [$I > 2$sigma(I)]; Goo$F$ = S = 1.200; largest difference in peak and hole, $\Delta\rho_{max}$ and $\Delta\rho_{min}$ = 0.198 and −0.189 e Å^3.

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