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Binuclear versus mononuclear copper complexes as catalysts for asymmetric cyclopropanation of styrene

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Abstract

A number of (*S*)-(−)-2-amino-1,1-diaryl-1-propanol compounds have been synthesized. They were used to form the binuclear copper complexes through a spontaneous assembly of the individual components, the β-aminoalcohol, 2-hydroxy-5-methyl-1,3-benzenedialdehyde, and copper acetate monohydrate, in methanol. These binuclear complexes were examined as asymmetric catalysts for cyclopropanation of styrene by ethyl diazoacetate. Moderate improvement in enantioselectivity has been observed for the binuclear versus mononuclear copper complexes. The e.e. values up to 87% for *trans* and 93% for *cis* products and the ratio between *trans* and *cis* products up to 9:1 have been obtained.

1. Introduction

Most asymmetric catalysts studied to date are mononuclear metal complexes and metal aggregates, where synergistic effects among the transition metal centers rarely exist. Only recently has the synergistic cooperation among different metals and chiral templates been incorporated into the design of asymmetric catalysts.[1] The chiral compartmental complexes of a group of binuclear nickel complexes used for asymmetric O_2 oxidation of olefins into epoxides dated back to 1992. Unfortunately, no enantioselectivity was observed in that reaction.[2] This may somehow hinder the rapid development of this class of complexes as asymmetric catalysts. However, a growing number of binuclear complexes have been proposed as intermediates in numerous reactions such as the Sharpless epoxidation.[3] In our effort to develop chiral binuclear compartment complexes as asymmetric catalysts, we will select several mechanistically well understood reactions to demonstrate their advantages in the modulation of chiral transfers.

Cyclopropanation was selected as our model asymmetric reaction in this study. The reaction between diazo compounds and olefins is catalyzed by a variety of transition metal compounds.[4] This

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transformation is stereospecific and generally occurs with 'electron-rich' olefins, including substituted olefins, dienes, and vinyl ethers, but excluding α,β-unsaturated carbonyl compounds or nitriles.[5] Relative reactivities portray a highly electrophilic intermediate and an 'early' transition state for cyclopropanation reactions.[6] This may be reflected in the relative difficulty in controlling selectivity. For intermolecular reactions, the formation of geometrical isomers of regioisomers from reactions with dienes, and of enantiomers must all be taken into account. Currently, several available catalysts provide exceptional enantiocontrol in both inter- and intramolecular cyclopropanation reactions for certain types of olefins.[7] The most effective ligand systems are those introduced by Arantani,[8] Pfaltz,[9] Masamune,[10] Evans,[11] Doyle,[12] and Nishiyama.[13]

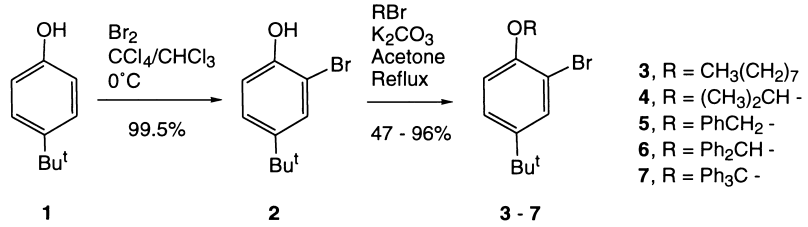
These catalysts either induce excellent stereoselectivities in intermolecular cyclopropanation reactions with olefins of low functionality such as styrene or 2,4-dimethyl-2,4-hexadiene, or give excellent results in intramolecular reactions. Functionalized olefins such as silyl enol ethers do not give satisfactory diastereomeric or enantiomeric selectivity.[14] The ligands and catalytic systems we have been developing differ from existing ones. First, two metal centers are involved to preorganize the carbene intermediate with one metal bound with the carbene and the other with carbonyl oxygen. This property may allow the modulation of both electronic and steric effects of the catalysts to fit a given class of substrates. Second, the chiral 'pocket' of the catalysts is spacious enough to allow the access of bulkier substrates other than monosubstituted or 1,1-disubstituted olefins, which gave much better enantioselectivity with the previously reported catalytic systems described above.

2. Results and discussion

Based on our understanding of the asymmetric cyclopropanation reactions, we are trying to build a module to optimize our binuclear metal complexes. We selected the Schiff base of salicylaldehyde as our ligand backbone. A generic structure for the catalyst is shown by **20**–**24** (Scheme 6). We have examined the dependence of the enantioselectivity on the steric bulk of the 2-alkoxide group of the aromatic substitutent.

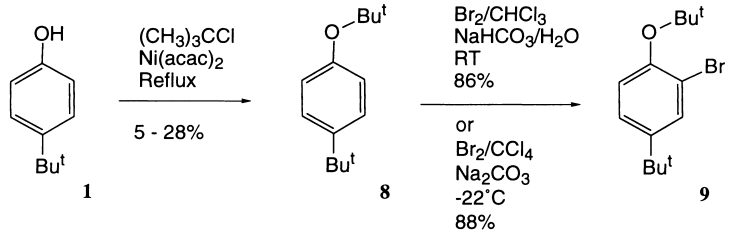
*2.1. Synthesis of 2-alkoxy-5-*t*-butyl-phenyl bromide*

Commercially available 4-*tert*-butyl-phenol **1** was brominated at the *ortho* position by bromine at 0°C in CCl_4 and $CHCl_3$ to give 4-*tert*-butyl-2-bromo-phenol (**2**) as the only product in almost quantitative yield (Scheme 1). Formation of phenyl ethers (**3**–**7**) was accomplished by alkylation of alkyl bromide under basic conditions. The reaction worked well for a variety of alkyl groups including primary bromide, secondary bromide, and triphenyl methyl chloride. However, neither tertiary bromide nor chloride worked under these conditions or any other conditions have we tried.



Scheme 1.

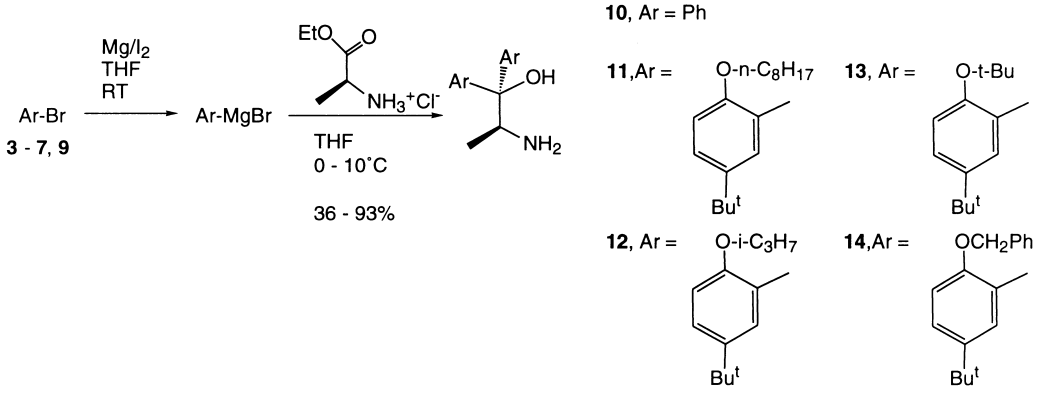
An alternative method for the synthesis of aryl *t*-alkyl ether **9** is the bromination of the ether **8** instead of the alkylation of **2** (Scheme 2). Aryl ether **8** was synthesized following an analogous procedure, found in the literature, in yields varying from 5 to 28%.[15] A reduced yield (about 5%) was obtained if *tert*-butyl bromide was used. From the rapid disappearance of the bromide, we believe that the elimination reaction to generate 2-methyl propene predominates under these conditions. Bromination of **8** was anything but straightforward. Under the conditions used for the bromination of aryl ethers, the only product observed was **2**. No trace of **9** was observed. We reasoned that the byproduct of the reaction, HBr, is responsible for the cleavage of the *tert*-butyl group. However, bromination under basic conditions such as with pyridine or 2,6-lutidine gave no product at all; only the starting material was recovered. It appears that successful bromination of **8** needs a delicate balance between the acid and base. After multiple trials, we found two procedures which gave satisfactory results (>80% isolated yields): (1) bromination with solid Na_2CO_3 at −22°C in CCl_4; (2) bromination with aqueous Na_2CO_3 solution in $CHCl_3$ at room temperature.



Scheme 2.

2.2. Synthesis of β-aminoalcohols

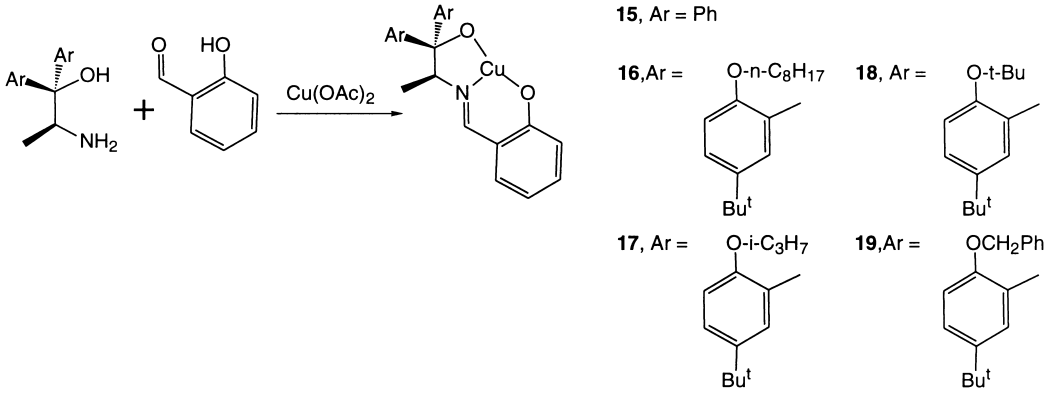
The β-aminoalcohols **10**–**14** were synthesized by the reaction of the Grignard reagent with the ester of alanine hydrochloride (Scheme 3).[16] Normally 5–10 equivalents of the Grignard reagent were used. The characteristic feature of the product in ^{1}H NMR spectrum is the unique quartet given by the CH attached to the amino group, with chemical shifts within the range of 4.0–4.5 ppm. All of the aminoalcohols we synthesized appeared as the last band eluted with pure ethyl acetate on a silica gel column. Multiple attempts to synthesize (*S*)-(−)-2-amino-1,1-di-(2′-diphenylmethyloxy-5′-*tert*-butyl-phenyl)-1-propanol and (*S*)-(−)-2-amino-1,1-di-(2′-triphenylmethyloxy-5′-*tert*-butyl-phenyl)-1-propanol failed. This may be due to the steric bulkiness of the *ortho*-substitutents.



Scheme 3.

2.3. Synthesis of mono-copper complexes

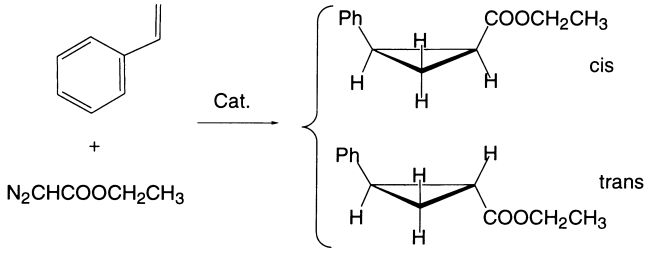
The catalyst **15** was synthesized by means of an one-pot reaction of β-aminoalcohol, **10**, salicylaldehyde, and copper acetate monohydrate in methanol (Scheme 4). However, no reactions were observed when analogous conditions were used in attempts to make **16**–**19**. In these cases the addition of solid NaOH was essential. The catalysts were soluble in a wide range of solvents with different polarity from pentane to methanol. The crystal structure of an analogous Cu(II) catalyst precursor [Ar=5-*tert*-butyl-2-(*n*-butyloxy)phenyl] was found to be a binuclear copper complex bridged by the phenolate,[8] although the actual catalyst was believed to be a mononuclear copper(I) complex.[7a]



Scheme 4.

2.4. Optimization of the chiral mono-copper(II) complexes

Aratani and associates pioneered the design of chiral salicylaldimine copper catalysts which gave high enantioselectivity for intermolecular cyclopropanations.[17] The 'Sumitomo process', which is employed for the construction of cilastatin, an in vivo stabilizer of the antibiotic imipenem, is based on this chemistry. While the mono-copper Schiff base complex **15** was used as the catalyst for cyclopropanation of styrene with ethyl diazoacetate (Scheme 5), the enantioselectivity significantly depended on the polarity of the solvents as shown in Table 1. CH_3CN is the best solvent for both reaction rate and enantioselectivity, and is the solvent of choice for subsequent investigation when we vary the substitutents on the aromatic group.



Scheme 5.

Although variation of the length of the alkoxide group at the 2-position of the aromatic group had been evaluated by Aratani and associates on the optimization of the enantioselectivity for the synthesis of cilastatin, this is the first study performed on branched alkoxide groups. We reasoned that these groups may have better steric shielding effects in the chiral transfer step. The results of the study are summarized

Table 1
Dependence of the e.e. values on solvents for catalyst precursor **15**[a]

Solvents	*Trans* : *Cis*[b]	*Trans* (e.e.)	*Cis* (e.e.)	Yield (%)
CH_3CN	85 : 15	67	63	50
CH_2Cl_2	84 : 16	41	37	35
$ClCH_2CH_2Cl$	79 : 21	29	32	39
Toluene	79 : 21	8	5	35

a: At 50°C. b: The ratio of the *trans* and *cis* product was determined by the integration from HPLC spectra.

Table 2
Dependence of the e.e. values on the substituents (R) on mononuclear copper catalysts[a]

Catalyst	*Trans* : *Cis*[b]	*Trans* (e.e.)	*Cis* (e.e.)	Yield (%)
15	85 : 15	67	63	50
16 (*n*-C_8H_{17})	74 : 26	83	88	30
17 (*iso*-C_3H_7)	71 : 29	86	82	37
18 (*tert*-C_4H_9)	74 : 26	74	53	33
19 ($CH_2C_6H_5$)	75 : 25	77	87	42

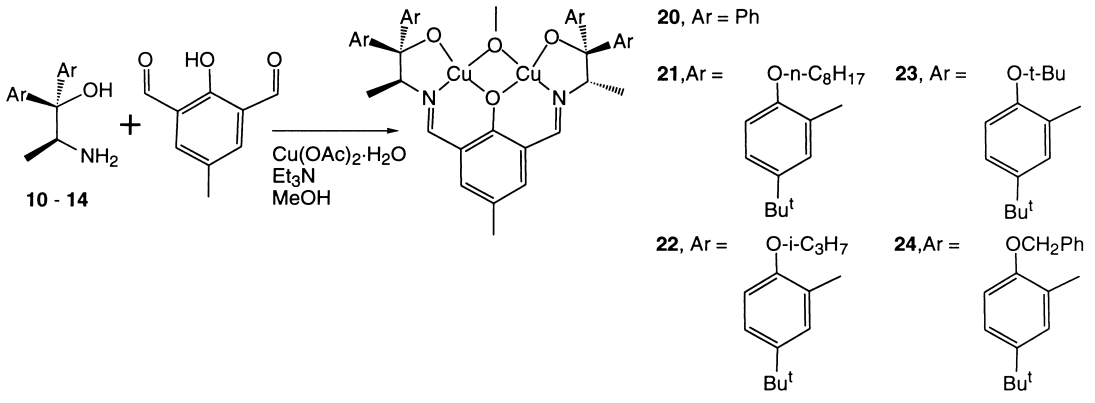
a: At 50°C in CH_3CN; b) The ratio of the *trans* and *cis* product was determined by the integration from HPLC spectra.

in Table 2. The best enantioselectivity for the *trans* isomer peaked at the isopropyloxy group, while that for the *cis* isomer peaked at the linear chain alkoxide. Further increase of branches of the alkoxide decreases the enantioselectivity slightly for the *trans* isomer, but substantially for the *cis* isomer.

2.5. Synthesis of binuclear copper complexes

The catalysts **20**–**24** were synthesized by means of a one-pot reaction of β-aminoalcohols **10**–**14**, 2-hydroxy-5-methyl-1,3-benzenedialdehyde, and copper acetate monohydrate in the presence of triethylamine, respectively (Scheme 6). Triethylamine is not necessary but was included to remove AcOH generated during the reaction. This is in sharp contrast to the synthesis of mononuclear copper complexes, where a strong base is necessary. Pure complexes **20**–**24** were obtained by washing with methanol. It is noteworthy that methanol is one of the reactants which has been demonstrated by an X-ray diffraction study as shown in Fig. 1. All of these complexes are green or dark gray in color, and are soluble in a variety of solvents such as benzene, ethyl acetate, CH_2Cl_2, $CHCl_3$, CH_3CN, acetone, DMF, and DMSO. The relative solubility was found to depend on the substituents.

The molecule of **20** in Fig. 1 has an overall C_2 symmetry, and the environments of the two copper centers are identical. Each copper center adopts a square pyramidal configuration. Among the five coordination sites, three are from the pentadentate ligand, one is from bridging methoxide, and the other is from a methanol molecule. The methyl group on the bridging methoxide is disordered and modeled between two positions. The copper centers, the imine groups, the central phenolate, and the oxygen atom of the bridging methoxide adopt a planar configuration. The most interesting part of the structure is the five-membered rings involving chiral centers. Overall the rings adopt a half-chair conformation with the tertiary carbon at the apex position, with one phenyl at the axial position and the other at the equatorial position. The methyl group at the chiral carbon occupies an axial position, instead of the equatorial position. Fig. 2 illustrates the conformational analysis along the C21–C22 single bond. Among



Scheme 6.

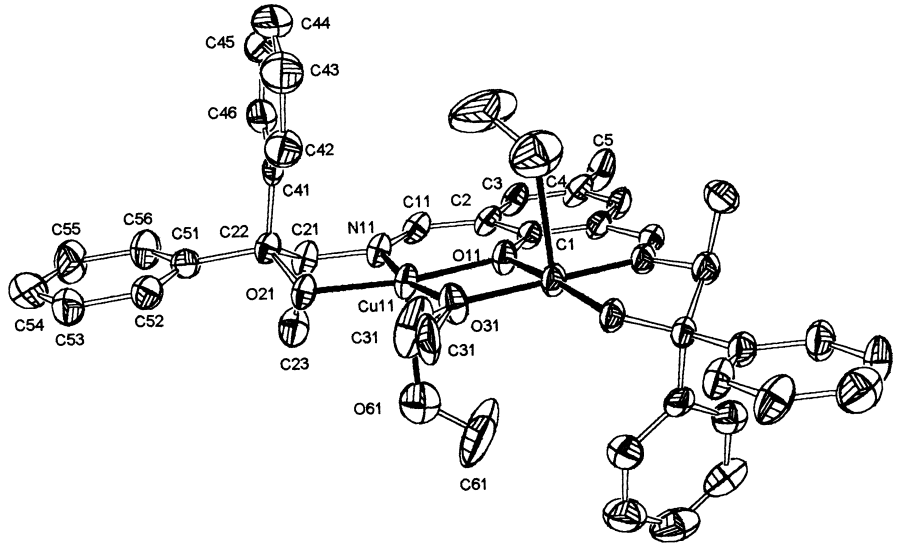


Figure 1. Molecular structure of complex **20** with atomic numbering (ORTEP, 50% probability ellipsoids, hydrogen atoms omitted for clarity). Selected bond distances (Å) and angles (°): Cu11–N11 1.924(4), Cu11–O11 1.970(3), Cu11–O21 1.916(3), Cu11–O31 1.913(3), Cu11–O61 2.493(4), Cu11· · ·Cu11 3.0103(7), N11–Cu11–O11 90.7(2), O11–Cu11–O31 78.29(9), O21–Cu11–O31 104.3(2), N11–Cu11–O21 86.15(14), O11–Cu11–061 94.5(1), N11–Cu11–O61 95.1(1), O21–Cu11–O61 93.1(1), O31–Cu11–O61 89.7(1), Cu11–O11–Cu11 99.6(2), Cu11–O31–Cu11 103.8(2)

the possible different steric interactions, it appears that the phenyl–methyl interaction predominates. This makes the methyl at the equatorial position less stable. The crystal structure of an analogous compound shows the same conformational preference.[8]

2.6. Optimization of the chiral binuclear copper(II) complexes

We examined the enantioselectivity of catalyst **20** in the asymmetric cyclopropanation reaction in different solvents as compared with the corresponding mononuclear copper complex **15** (Scheme 5). The results are summarized in Table 3. CH_3CN is still the best solvent for this class of catalysts. Although the best enantioselectivity did not increase from the mononuclear to binuclear copper catalyst, the binuclear complex showed much less dependence on solvent, especially for non-polar solvents like toluene (8 vs.

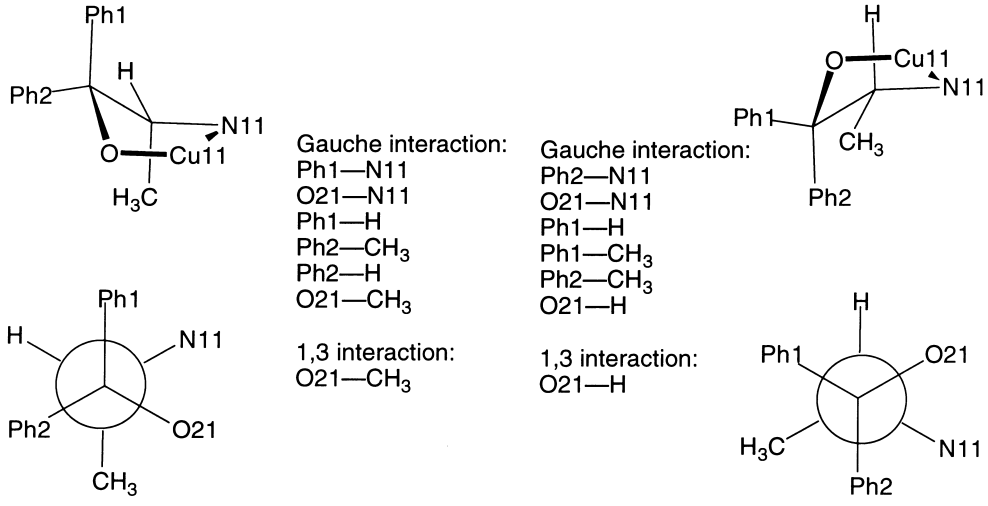


Figure 2. Conformational analysis of the complex **20**

Table 3
Dependence of the e.e. values on solvents for catalyst precursor **20**[a]

Solvents	*Trans* : *Cis*[b]	*Trans* (e.e.)	*Cis* (e.e.)	Yield (%)
CH_3CN	87 : 13	67	58	41
CH_2Cl_2	90 : 10	38	35	37
$ClCH_2CH_2Cl$	84 : 16	48	28	37
Toluene	88 : 12	54	50	35

a: At 50°C. b: The ratio of the *trans* and *cis* product was determined by the integration from HPLC spectra.

Table 4
Dependence of the e.e. values on the substituents (R) on binuclear copper catalysts[a]

Catalyst	*Trans* : *Cis*[b]	*Trans* (e.e.)	*Cis* (e.e.)	Yield (%)
20	87 : 13	67	58	41
21 (*n*-C_8H_{17})	71 : 29	81	92	65
22 (*iso*-C_3H_7)	73 : 27	86	92	55
23 (*tert*-C_4H_9)	73 : 27	87	93	64
24 ($CH_2C_6H_5$)	75 : 25	87	93	59

a: At 50°C in CH_3CN; b) The ratio of the *trans* and *cis* product was determined by the integration from HPLC spectra.

54% for *trans*, 5 vs. 50% for *cis*). The *trans* to *cis* ratio uniformly increased for all solvents tested, as compared with that of **15**.

Variation of the alkyl group on the alkoxide substantially changes the e.e. values (Table 4). When the alkyl group is benzyl, the e.e. values reach 87% and 93%, respectively, for the *trans* and *cis* isomers of the product, ethyl 2′-phenyl-1-cyclopropyl carboxylate. No mono-copper Schiff base complexes give such high e.e. values.

The enantioselectivity does not increase linearly with the bulkiness of the substitutent on the 2-position. The enantioselectivity reaches a plateau at groups larger than isopropyloxy for the *trans* isomer. The same

Table 5
Solvent dependence of the enantioselectivity based on catalyst **22**[a]

CH_2Cl_2	THF	CH_2ClCH_2Cl	CH_3CN	DMF
77	64[b]	83	88	85

a: The e.e. values are for the *trans* isomer only. b: The e.e. value drops as the reaction progresses.

pattern is observed for the *cis* isomer, but it appears that the selectivity levels off with a much smaller alkoxide group. This is different from the pattern observed for the mononuclear copper catalysts shown in Table 2. Efforts to synthesize diphenylmethyl and triphenylmethyl substituted β-aminoalcohols failed as described above. To our surprise, the effect of the benzyl group is comparable with that of the isopropyl group.

2.7. Solvent dependence of the enantioselectivity

Binuclear copper complex **22** was used to evaluate the solvent dependence. Non-polar to highly polar solvents were examined as shown in Table 5. The solvent which gives the highest e.e. values is still CH_3CN. It is interesting to note that the addition of 2,6-lutidine in this solvent dramatically reduces the rate of the reaction. The reaction in THF or DMF is also slow.

2.8. Temperature dependence of the cyclopropanation

Using catalyst **22** as an example, the reaction yield based on ethyl diazoacetate was 33% at rt, 55% at 50°C, and leveled off (about 60%) at higher temperatures. Temperature has no effect on the enantioselectivity (e.e. 88% for *trans* and 93% for *cis*) of the reaction, however, it does have a dramatic effect on the yield.

2.9. Mechanistic implications

Synthesis of the binuclear copper complexes utilizing different temperatures, solvents, and reaction times, does not affect the enantioselectivity significantly, probably the actual catalyst is the same at the catalytic conditions. After the catalyst precursors reacted with $PhNHNH_2$ at rt or 50°C for a few minutes, the color of the solution changed from green or dark gray to brown, which remained during the reaction. This supports the assumption that the copper(II) is reduced to copper(I) by $PhNHNH_2$ in situ. However, it is not clear at present whether both copper sites in the same molecule are reduced, or only one. The persistent brown color is consistent with the charge transfer band observed for other mixed valence binuclear copper complexes.[18]

2.10. Determination of the e.e. values of the products

The e.e. values for both *trans* and *cis* products were determined by GLC analysis of the corresponding L-menthyl esters.[9,10] Others used chiral HPLC to determine the e.e. of the *trans* product directly,[19] but not for the *cis* product. Evan and associates transformed the *cis* ester into the amide of (*S*)-(−)-α-methylbenzylamine, and determined the e.e. values of the amide.[11] In our case, the harsh conditions for this transformation prevented small scale operations. Instead, the *cis*-ester was reduced to the corresponding alcohol by LAH at rt, and the peak separations on Chiralcel OD column increased from 0.23 min to 0.46 min. The alcohol was then transformed into the (1*S*)-(−)-camphanic ester by

reacting with (1*S*)-(−)-camphanic chloride, which is commercially available. Well-resolved peaks for both enantiomers were observed under our conditions, as specified in the experimental section. This was confirmed when the racemic mixture was used as an internal control.

3. Conclusion

As compared with those of the mononuclear counterparts, the binuclear copper(II) catalytic systems have the following advantages: (1) they showed moderately increased enantioselectivity on the asymmetric cyclopropanation of styrene by ethyl diazoacetate; (2) their enantioselectivity is much less dependent on solvents; and (3) they are easier to assemble from the individual components. The binuclear nature of the complexes in the precursors is believed to be maintained during the catalytic conditions, since the pentadentate ligand system provides strong stabilization for such an arrangement. These designed binuclear complexes represent a new avenue for the assembly of catalysts to control the enantioselectivity in asymmetric catalysis.

4. Experimental

4.1. 4-tert-Butyl-2-bromophenol (2)[20]

4-*tert*-Butylphenol (70 g, 0.467 mol) was dissolved in 220 mL of $CHCl_3$:CCl_4 (1:1), and the solution was cooled to 0°C. Bromine (82 g, 0.513 mol) in 90 mL $CHCl_3$ was added dropwise into the well-stirred reaction mixture. The addition took about 1 h, and the mixture was then stirred for another hour. Dry dinitrogen was bubbled through the mixture to remove the HBr. Upon removal of the solvent, the product was distilled at reduced pressure (78–81°C/0.3 torr) to afford 109 g product. Yield 99.5%. ^{1}H NMR in $CDCl_3$, δ, 7.43 (d, $^4J_{HH}$=2.4 Hz, 1H, Ar–*H*); 7.24 (dd, $^3J_{HH}$=9.0 Hz, $^4J_{HH}$=2.5 Hz, 1H, Ar–*H*); 6.96 (d, $^3J_{HH}$=8.7 Hz, 1H, Ar–*H*); 5.34 (s, 1H, O*H*); 1.29 (s, 9H, CH_3). ^{13}C{^{1}H} NMR in $CDCl_3$, δ, 149.8 (*C*–O, 1C), 145.0 (*C*–C, 1C), 128.7 (*C*H, 1C), 126.1 (*C*H, 1C), 115.5 (*C*H, 1C), 109.8 (*C*–Br, 1C), 34.1 (*C*CH_3 1C), 31.3 (*C*H_3, 3C). MS, 230, 228 (25%, M^+), 215, 213 (100%, M−CH_3^+). High resolution MS for $C_{10}H_{13}OBr$, found: 228.014429; calcd: 228.014976.

4.2. 4-tert-Butyl-2-bromo-1-octyloxy-benzene (3)

4-*tert*-Butyl-2-bromophenol (43.5 g, 0.19 mol), octylbromide (40.3 g, 0.209 mol), and K_2CO_3 (26.2 g, 0.19 mol) were refluxed in dry acetone (100 mL) for 48 h or until the starting phenol almost disappeared. The solid was filtered off, and extracted with acetone. Upon removal of the solvent, octyl bromide was distilled off under vacuum. The residue was loaded onto a silica gel column, and the product was eluted with hexane to afford 45 g. Yield 70%. ^{1}H NMR in $CDCl_3$, δ, 7.53 (d, $^4J_{HH}$=1.3 Hz, 1H, Ar–*H*); 7.24 (dd, $^3J_{HH}$=8.9 Hz, $^4J_{HH}$=1.9 Hz, 1H, Ar–*H*); 6.81 (d, $^3J_{HH}$=8.8 Hz, 1H, Ar–*H*), 3.99 (t, $^3J_{HH}$=6.4 Hz, 2H, OCH_2); 1.82 (pent, $^3J_{HH}$=7.4 Hz, 2H, OCCH_2); 1.49 (pent, $^3J_{HH}$=7.7 Hz, 2H, OCCCH_2); 1.34–1.20 (m, 8H, CH_2); 1.28 (s, 9H, C(CH_3)$_3$); 0.886 (t, $^3J_{HH}$=6.7 Hz, 3H, CH_3). ^{13}C{^{1}H} NMR in $CDCl_3$, δ, 153.1 (*C*–O, 1C), 144.7 (*C*–C, 1C), 130.3 (*C*H, 1C), 125.0 (*C*H, 1C), 112.7 (*C*H, 1C), 111.8 (*C*–Br, 1C), 69.2 (O*C*H$_2$, 1C), 34.0 (*C*(CH$_3$)$_3$, 1C), 31.7 (*C*H$_2$, 1C), 31.3 (C(*C*H$_3$)$_3$, 3C), 29.2 (*C*H$_2$, 1C), 29.1 (*C*H$_2$, 1C), 29.0 (*C*H$_2$, 1C), 25.9 (*C*H$_2$, 1C), 22.6 (*C*H$_2$, 1C), 14.0 (*C*H$_3$, 1C). MS, 342, 340 (5%, M^+), 230,

228 (12%, M−octene$^+$), 215, 213 (100, M−octene−Me$^+$). High resolution MS for $C_{18}H_{29}OBr$, found: 340.139887; calcd: 340.140177.

4.3. 4-tert-Butyl-2-bromo-1-isopropyloxy-benzene (**4**)

This compound was synthesized by the same procedure as above except using isopropyl bromide instead of octyl bromide. Yield 95%. ^{1}H NMR in $CDCl_3$, δ, 7.53 (d, $^4J_{HH}$=2.1 Hz, 1H, Ar–*H*); 7.23 (dd, $^3J_{HH}$=8.7 Hz, $^4J_{HH}$=2.7 Hz, 1H, Ar–*H*); 6.85 (d, $^3J_{HH}$=8.7 Hz, 1H, Ar–*H*); 4.50 (hepta, $^3J_{HH}$=6.0 Hz, 1H, C*H*$(CH_3)_2$); 1.37 (d, $^3J_{HH}$=5.7 Hz, 6H, CCH(C*H*$_3)_2$); 1.28 (s, 9H, C(C*H*$_3)_3$). ^{13}C{^{1}H} NMR in $CDCl_3$, δ, 152.2 (*C*–O, 1C), 145.1 (*C*–C, 1C), 130.4 (*C*H, 1C), 125.0 (*C*H, 1C), 115.5 (*C*H, 1C), 113.4 (*C*–Br, 1C), 72.2 (*C*H, 1C), 34.1 (*C*$(CH_3)_3$, 1C), 31.3 (C(*C*$H_3)_3$, 1C), 22.1 (CH(*C*$H_3)_2$, 2C). MS, 272, 270 (16%, M$^+$), 230, 228 (12%, M−propene$^+$), 215, 213 (100, M−propene−Me$^+$). High resolution MS for $C_{13}H_{19}OBr$, found: 270.061441; calcd: 270.061926.

4.4. 4-tert-Butyl-2-bromo-1-benzyloxy-benzene (**5**)

This compound was synthesized by the same procedure as above except using benzyl bromide instead of octyl bromide. Yield 96%. ^{1}H NMR in CD_3OD, δ, 7.54 (d, $^4J_{HH}$=2.9 Hz, 1H, Ar–*H*); 7.48–7.25 (m, 6H, Ar–*H*); 6.98 (d, $^3J_{HH}$=8.7 Hz, 1H, Ar–*H*); 5.12 (s, 2H, OC*H*$_2$); 1.27 (s, 9H, C*H*$_3$). ^{13}C{^{1}H} NMR in $CDCl_3$, δ, 152.7 (*C*–O, 1C), 145.3 (*C*–C, 1C), 136.7 (*C*–C, 1C), 130.5 (*C*H, 1C), 128.5 (*C*H, 2C, Ph), 127.8 (*C*H, 1C), 126.9 (*C*H, 2C, Ph), 125.1 (*C*H, C), 113.4 (*C*H, 1C, Ph), 112.0 (*C*–Br, C), 70.8 (O*C*H$_2$, 1C), 34.1 (*C*CH$_3$, 1C), 31.3 (*C*H$_3$, 3C). MS, 318, 320 (M$^+$, <5%), 91 (100%, $C_6H_5CH_2^+$). High resolution MS for $C_{17}H_{19}OBr$, found: 318.062333; calcd: 318.061926.

4.5. 4-tert-Butyl-2-bromo-1-diphenylmethyloxy-benzene (**6**)

This compound was synthesized by the same procedure as above except using diphenylmethyl bromide instead of octyl bromide. Yield 72%. ^{1}H NMR in $CDCl_3$, δ, 7.54 (d, $^4J_{HH}$=2.0 Hz, 1H, Ar–*H*); 7.50 (d, $^3J_{HH}$=7.8 Hz, 4H, *o*-*H*); 7.34 (t, $^3J_{HH}$=7.6 Hz, 4H, *m*-*H*); 7.26 (t, $^3J_{HH}$=7.4 Hz, 2H, *p*-*H*); 7.09 (dd, $^3J_{HH}$=8.1 Hz, $^4J_{HH}$=2.7 Hz, 1H, Ar–*H*); 6.75 (d, $^3J_{HH}$=8.8 Hz, 1H, Ar–*H*); 6.23 (s, H, OC*H*); 1.24 (s, 9H, C*H*$_3$). ^{13}C{^{1}H} NMR in $CDCl_3$, δ, 151.8 (*C*–O, 1C), 145.1 (*C*–C, 1C), 141.1 (*C*H, 1C), 130.4 (*C*H, 1C), 128.5 (*C*H, 4C), 127.6 (*C*H, 4C), 126.6 (*C*H, 2C), 124.9 (*C*–Br, 2C), 114.6 (*C*H, 1C), 112.5 (*C*–C, 1C), 82.2 (O*C*H, 1C), 34.0 (*C*C, 1C), 31.2 (*C*H$_3$, 3C). EI MS, 167 (100%, $(C_6H_5)_2CH^+$). FAB MS, 393.0160 (3%, M$^+$), 315.1020 (4%, M−$C_6H_6^+$), 167.0841 (100%, Ph_2CH^+). High resolution FAB MS for $C_{23}H_{22}OBr$, found: 393.085200; calcd: 393.085402. Elemental analysis for $C_{23}H_{23}OBr$, found: C, 69.55; H, 5.84; Br, 20.19; calcd: C, 69.88; H, 5.86; Br, 20.21.

4.6. 4-tert-Butyl-2-bromo-1-triphenylmethyloxy-benzene (**7**)

This compound was synthesized by the same procedure as above except using triphenylmethyl chloride instead of octyl bromide. Yield 47%. ^{1}H NMR in $CDCl_3$, δ, 7.51 (d, $^3J_{HH}$=6.6 Hz, 4H, *o*-*H*); 7.40 (s, ^{1}H, Ar–*H*); 7.26 (brs, 6H, *m*-*H*, *p*-*H*); 6.77 (d, $^3J_{HH}$=8.5 Hz, 1H, Ar–*H*); 6.42 (d, $^3J_{HH}$=8.7 Hz, 1H, Ar–*H*); 1.16 (s, 9H, C*H*$_3$). ^{13}C{^{1}H} NMR in $CDCl_3$, δ, 150.2 (*C*–O, 1C), 145.3 (*C*–C, 1C), 143.8 (*C*H, 1C), 129.7 (*C*H, 1C), 128.8 (*C*H, 6C), 127.6 (*C*H, 6C), 127.1 (*C*H, 3C), 123.6 (*C*–Br, 3C), 120.5 (*C*H, 1C), 115.2 (*C*–C, 1C), 91.1 (O*C*H, 1C), 33.9 (*C*C, 1C), 31.1 (*C*H_3, 3C). MS, 243 (41%, Ph_3C^+), 228 (4%,

$(CH_3)_3CC_6H_3(OH)Br^+$), 215, 213 (8%, $(CH_3)_2CC_6H_3(OH)Br^+$), 165 (20%, $Ph_3C^+-C_6H_6$). Elemental analysis for $C_{29}H_{27}OBr$, found: C, 73.68; H, 5.80; Br, 17.14; calcd: C, 73.88; H, 5.77; Br, 16.95.

*4.7. 4-*tert*-Butyl-1-*tert*-butyloxy-benzene (**8**)*

4-*tert*-Butylphenol (15 g, 0.10 mol), $Ni(acac)_2$ (300 mg, 1.2 mmol), and $NaHCO_3$ (16.8 g, 0.2 mol) were suspended in 50 mL of *tert*-butyl chloride. The mixture was refluxed overnight. Ether (200 mL) was added, and the solution was filtered. Upon removal of the solvent, the crude solid was loaded onto a silica gel column. The product was eluted by hexane to afford 4.6 g product. Yield 23%. ^{1}H NMR in $CDCl_3$, δ, 7.24 (d, $^3J_{HH}$=9.0 Hz, 2H, *o-H*); 6.89 (d, $^3J_{HH}$=8.8 Hz, 2H, *m-H*); 1.32 (s, 9H, C*H*$_3$); 1.29 (s, 9H, C*H*$_3$). ^{13}C{^{1}H} NMR in $CDCl_3$, δ, 152.8 (*C*–O, 1C), 145.8 (*C*–C, 1C), 125.5 (*C*H, 2C), 123.4 (*C*H, 2C), 77.9 (*C*–O, 1C), 34.1 (*C*C, 1C), 31.4 (*C*H$_3$, 3C), 28.8 (*C*H$_3$, 3C). MS, 206 (M^+, 1%), 191 ($M-CH_3^+$, 1%), 150 ($M-CH_2=C(CH_3)_2^+$), 135 ($M-CH_2=C(CH_3)_2-CH_3^+$, 100%). High resolution MS $C_{14}H_{22}O$, found: 206.166370; calcd: 206.167066.

*4.8. 4-*tert*-Butyl-2-bromo-1-*tert*-butyloxy-benzene (**9**)*

Method 1. 4-*tert*-Butyl-1-*tert*-butyloxy-benzene (0.60 g, 2.9 mmol) and K_2CO_3 (5.0 g, 36 mmol) were suspended in 200 mL of CCl_4. The solution was then cooled to −23°C by dry ice/CCl_4 cooling bath. Bromine (0.69 g, 4.3 mmol) was added drop by drop within 24 h. After the reaction, the solid was removed by filtration, and the solvent was removed to give a viscous liquid which was extracted by ether. The ether solution was dried by anhydrous Na_2SO_4. Removal of the solvent gave the crude product, which was purified on a silica column using hexane as eluent to afford 0.73 g of pure product. Yield 88%.

Method 2. 4-*tert*-Butyl-1-*tert*-butyloxy-benzene (1.0 g, 4.9 mmol) in 130 mL of $CHCl_3$ and $NaHCO_3$ (7.3 g, 87 mmol) in 18 mL of water were mixed at rt. Bromine (2.0 g, 12.5 mmol) in 25 mL of $CHCl_3$ was added dropwise overnight. After the reaction was completed as checked by TLC, the organic layer was separated and dried by anhydrous Na_2SO_4. The same procedure as above in method 1 was followed to obtain 1.2 g of the product. Yield 86%. ^{1}H NMR in $CDCl_3$, δ, 7.52 (d, $^4J_{HH}$=2.0 Hz, 1H, Ar–*H*); 7.20 (dd, $^3J_{HH}$=8.8 Hz, $^4J_{HH}$=2.0 Hz, 1H, Ar–*H*); 7.02 (d, $^3J_{HH}$=8.8 Hz, 1H, Ar–*H*), 1.42 (s, 9H, C*H*$_3$); 1.29 (s, 9H, C*H*$_3$). ^{13}C{^{1}H} NMR in $CDCl_3$, δ, 150.6 (*C*–O, 1C), 147.3 (*C*–C, 1C), 130.1 (*C*H, 1C), 124.7 (*C*H, 1C), 123.2 (*C*H, 1C), 118.6 (*C*–Br, 1C), 80.8 (C–O, 1C), 34.2 (*C*C, 1C), 31.2 (*C*H$_3$, 3C), 28.9 (*C*H$_3$, 3C). MS, 269, 271 ($M-CH_3^+$, 3%), 230 ($M-CH_2=C(CH_3)_2^+$, 25%), 213 ($M-CH_2=C(CH_3)_2-CH_3^+$, 100%), 135 ($M-CH_2=C(CH_3)_2-CH_3^+$, 100%). Elemental analysis for $C_{14}H_{21}OBr$, found: C, 58.92; H, 7.50; Br, 28.22; calcd: C, 58.95; H, 7.42; Br, 28.02.

*4.9. (S)-(−)-2-Amino-1,1-diphenyl-1-propanol (**10**)*

PhMgBr (350 mL of 1 M, 350 mmol) was added to a suspension of L-alanine methyl ester hydrochloride (6.0 g, 43 mmol) in THF at 0°C over a period of 1 h. The mixture was stirred overnight. Saturated aqueous NH_4Cl solution (300 mL) was then added, and the mixture was shaken vigorously until all white precipitate disappeared. The product was extracted into ether solution (3×200 mL). The combined ether solution was dried over Na_2SO_4. Upon removal of the solvent, the crude solid was loaded on a silica gel column, which was eluted with hexane first, then with hexane/ethyl acetate. The portion of ethyl acetate was increased gradually from 0.1 to 1. The product was then eluted with ethyl acetate. Removal of the solvent affords 4.23 g product. Yield 43%. ^{1}H NMR in CD_3OD, δ, 7.59 (d, $^3J_{HH}$=8.6 Hz, 2H, Ar–*H*);

7.50 (d, $^3J_{HH}$=8.7 Hz, 2H, Ar–*H*); 7.33 (t, $^3J_{HH}$=7.7 Hz, 2H, Ar–*H*); 7.28 (t, $^3J_{HH}$=7.7 Hz, 2H, Ar–*H*); 7.21 (t, $^3J_{HH}$=7.1 Hz, 1H, Ar–*H*); 7.16 (t, $^3J_{HH}$=7.5 Hz, 1H, Ar–*H*); 3.98 (q, $^3J_{HH}$=6.5 Hz, 1H, C*H*–N); 1.00 (d, $^3J_{HH}$=6.5 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR in CD_3OD, δ, 147.6 (*C*–C, 1C), 147.1 (*C*–C, 1C), 129.5 (*C*H, 2C, *o*-C), 129.1 (*C*H, 2C, *o*-C), 127.9 (*C*H, 1C, *p*-C), 127.6 (*C*H, 1C, *p*-C), 127.3 (*C*H, 2C, *m*-C), 127.0 (*C*H, 2C, *m*-C), 81.4 (*C*–O, 1C), 53.6 (*C*–N, 1C), 17.2 (*C*H_3–C–N). MS, 210 (1%, M−OH^+), 105 (30%, $PhCO^+$), 77 (48%, Ph^+), 44 (100, $CH_3CH{-}NH_2^+$). High resolution MS for $C_{15}H_{18}NO$, found: 228.138791; calcd: 228.138839.

*4.10. (S)-(−)-2-Amino-1,1-di-(2′-octyloxy-5′-*tert*-butyl-phenyl)-1-propanol (**11**)*

4-*tert*-Butyl-2-bromo-1-octyloxy-benzene (33 g, 96.7 mmol) and Mg (2.35 g, 97.9 mmol) were suspended in 100 mL of THF with slow stirring. I_2 (200 mg, 0.79 mmol) was added. A deep brown solution was formed. The color gradually faded. After the solution had been stirred overnight, or until no starting material was observed on a TLC plate, the residue Mg was removed by decantation. The reaction of this new Grignard reagent with L-alanine methyl ester hydrochloride was performed and purification as above afforded 5.5 g of product. Yield 93% based on the ester of the amino acid. ^1H NMR in $CDCl_3$, δ, 7.70 (s, 2H, Ar–*H*); 7.18 (dd, $^3J_{HH}$=8.9 Hz, $^4J_{HH}$=1.6 Hz, 1H, Ar–*H*); 7.15 (dd, $^3J_{HH}$=8.2 Hz, $^4J_{HH}$=1.5 Hz, 1H, Ar–*H*); 6.72 (d, $^3J_{HH}$=8.5 Hz, 1H, Ar–*H*); 6.66 (d, $^3J_{HH}$=8.6 Hz, 1H, Ar–*H*); 4.28 (q, $^3J_{HH}$=6.5 Hz, 1H, C*H*–N); 3.76–3.67 (m, 4H, OCH_2); 1.52 (m, 4H, OCCH_2); 1.34 (s, 9H, CH_3); 1.33 (s, 9H, CH_3); 1.29–1.20 (m, 10H, CH_2); 1.04 (d, $^3J_{HH}$=5.0 Hz, 3H, CH_3–C–N); 0.886 (t, $^3J_{HH}$=6.8 Hz, 6H, CH_3). $^{13}C\{^1H\}$ NMR in $CDCl_3$, δ, 154.0 (*C*–O, 1C), 153.3 (*C*–O, 1C), 142.1 (*C*–C, 1C), 141.8 (*C*–C, 1C), 132.7 (*C*–C, 1C), 132.0 (*C*–C, 1C), 125.5 (*C*H, 1C), 125.1 (*C*H, 1C), 124.4 (*C*H, 1C), 124.0 (*C*H, 1C), 112.1 (*C*H, 1C), 111.5 (*C*H, 1C), 80.2 (*C*–O, 1C), 68.3 (*C*H_2O, 1C), 68.1 (*C*H_2O, 1C), 49.6 (*C*H–N, 1C), 34.1 (*C*$(CH_3)_3$, 1C), 34.1 (C(*C*$H_3)_3$, 1C), 31.7 (C(*C*$H_3)_3$, 3C), 31.6 (C(*C*$H_3)_3$, 3C), 31.5 (*C*H_2, 1C), 31.4 (*C*H_2, 1C), 29.2 (*C*H_2, 2C), 29.1 (*C*H_2, 2C), 28.9 (*C*H_2, 2C), 25.8 (*C*H_2, 2C), 22.5 (*C*H_2, 2C), 17.8 (*C*H_3–C–N, 1C), 14.0 (*C*H_3–C, 2C). EI MS, 291 (9%), 179 (50%, $(CH_3)_3CC_6H_3(OH)C(OH)^+$), 151 (100%, $(CH_3)_3CC_6H_4(OH)^+$), 135 (32%), 57 (30%, $C_4H_9^+$). FAB MS, 596.4064 (14%, M^+), 578.3967 (100%, M−H_2O^+), 177.0929 (12%, $(CH_3)_3CC_6H_3(OH)–CO^+$). High resolution FAB MS for $C_{39}H_{66}NO_3$, found: 596.504400; calcd: 596.504271. Elemental analysis for $C_{39}H_{65}NO_3$, found: C, 81.23; H, 11.39; N, 2.98; calcd: C, 78.60; H, 10.99; N, 2.35.

*4.11. (S)-(−)-2-Amino-1,1-di-(2′-isopropyloxy-5′-*tert*-butyl-phenyl)-1-propanol (**12**)*

This compound was synthesized by the same procedure as above except using 4-*tert*-butyl-2-bromo-1-isopropyloxy-benzene instead of 4-*tert*-butyl-2-bromo-1-octyloxy-benzene to afford 3.1 g of product. Yield 59.3% based on the ester of the amino acid. ^1H NMR in CD_3OD, δ, 7.71 (d, $^4J_{HH}$=2.3 Hz, 1H, Ar–*H*); 7.69 (d, $^4J_{HH}$=2.4 Hz, 1H, Ar–*H*); 7.28 (dd, ^3J=8.7 Hz, $^4J_{HH}$=2.7 Hz, 1H, Ar–*H*); 7.22 (dd, ^3J=8.5 Hz, $^4J_{HH}$=2.5 Hz, 1H, Ar–*H*); 6.87 (d, $^3J_{HH}$=8.7 Hz, 1H, Ar–*H*); 6.78 (d, $^3J_{HH}$=8.6 Hz, 1H, Ar–*H*); 4.55 (hepta, $^3J_{HH}$=6.1 Hz, 1H, OC*H*$(CH_3)_2$); 4.51 (hepta, $^3J_{HH}$=6.0 Hz, 2H, OC*H*$(CH_3)_2$), 4.24 (q, $^3J_{HH}$=6.6 Hz, 1H, C*H*–N); 1.38 (s, 9H, C(C$H_3)_3$); 1.36 (s, 9H, C(C$H_3)_3$); 1.09 (d, $^3J_{HH}$=5.9 Hz, 3H, CH_3); 1.03 (d, $^3J_{HH}$=6.0 Hz, 3H, CH_3); 1.02 (d, $^3J_{HH}$=6.5 Hz, 3H, CH_3); 0.929 (d, $^3J_{HH}$=5.9 Hz, 3H, CH_3); 0.864 (d, $^3J_{HH}$=5.9 Hz, 3H, CH_3). ^1H NMR in $CDCl_3$, δ, 7.71 (s, 1H, Ar–*H*); 7.69 (s, 1H, Ar–*H*); 7.18 (dd, $^3J_{HH}$=8.7 Hz, $^4J_{HH}$=2.7 Hz, 1H, Ar–*H*); 7.14 (dd, $^3J_{HH}$=8.2 Hz, $^4J_{HH}$=2.0 Hz, 1H, Ar–*H*); 6.71 (d, $^3J_{HH}$=8.7 Hz, 1H, Ar–*H*); 6.65 (d, $^3J_{HH}$=8.6 Hz, 1H, Ar–*H*); 4.45 (penta, $^3J_{HH}$=6.0 Hz, 1H, OC*H*); 4.43 (penta, $^3J_{HH}$=6.0 Hz, 1H, OC*H*); 4.24 (q, $^3J_{HH}$=6.6 Hz, 1H, C*H*–N); 1.35 (s, 9H, C(C$H_3)_3$); 1.34 (s, 9H, C(C$H_3)_3$); 1.05 (brs, 3H, CH_3); 1.04 (brs, 3H, CH_3); 1.01 (brs, 3H, CH_3); 0.946 (brs, 3H,

C*H*$_3$); 0.888 (brs, 3H, C*H*$_3$). ^{13}C{^{1}H} NMR in $CDCl_3$, δ, 152.4 (*C*–O, 1C), 151.7 (*C*–O, 1C), 141.5 (*C*–C, 1C), 141.1 (*C*–C, 1C), 133.3 (*C*–C, 1C), 132.5 (*C*–C, 1C), 125.7 (*C*H, 1C), 125.3 (*C*H, 1C), 124.6 (*C*H, 1C), 124.1 (*C*H, 1C), 112.4 (*C*H, 1C), 111.6 (*C*H, 1C), 80.0 (*C*–O, 1C), 68.8 (*C*H–O, 1C), 68.4 (*C*H–O, 1C), 49.3 (*C*H–N, 1C), 34.1 (*C*(CH$_3$)$_3$, 1C), 34.1 (*C*(CH$_3$)$_3$, 1C), 31.6 (C(*C*H$_3$)$_3$, 3C), 31.4 (C(*C*H$_3$)$_3$, 3C), 21.7 (*C*H$_3$, 1C), 21.5 (*C*H$_3$, 1C), 21.4 (*C*H$_3$, 1C), 21.1 (*C*H$_3$, 1C), 18.0 (*C*H$_3$–C–N, 1C). MS, 411 (38%, M−CH$_3$CH(NH$_2$)$^+$), 327 (57%, M−CH$_3$CH(NH$_2$)−2×propene$^+$), 271 (10%), 219 (67%, (CH$_3$)$_3$CC$_6$H$_3$(O^{i}Pr)–CO$^+$), 177 (100%, (CH$_3$)$_3$CC$_6$H$_3$(OH)–CO$^+$), 161 (75%, (CH$_3$)$_3$CC$_6$H$_4$–CO$^+$), 44 (85%, CH$_3$CH–NH$_2^+$). Elemental analysis for $C_{29}H_{45}NO_3$, found: C, 77.92; H, 10.30; N, 3.08; calcd: C, 76.44; H, 9.95; N, 3.07.

4.12. (S)-(−)-2-Amino-1,1-di-(2′-tert-butyloxy-5′-tert-butyl-phenyl)-1-propanol (**13**)

This compound was synthesized by the same procedure as above except using 4-*tert*-butyl-2-bromo-1-*tert*-butyloxy-benzene instead of 4-*tert*-butyl-2-bromo-1-octyloxy-benzene to afford 1.1 g of product. Yield 51% based on the ester of the amino acid. ^{1}H NMR in $CDCl_3$, δ, 7.67 (s, 2H, Ar–*H*); 7.11 (dd, $^3J_{HH}$=8.8 Hz, $^4J_{HH}$=2.5 Hz, 1H, Ar–*H*); 7.08 (dd, $^3J_{HH}$=8.4 Hz, $^4J_{HH}$=2.0 Hz, 1H, Ar–*H*); 6.91 (d, $^3J_{HH}$=8.6 Hz, 1H, Ar–*H*); 6.86 (d, $^3J_{HH}$=8.7 Hz, 1H, Ar–*H*); 4.05 (q, $^3J_{HH}$=6.5 Hz, 1H, C*H*–N); 1.31 (s, 9H, C(C*H*$_3$)$_3$); 1.29 (s, 9H, C(C*H*$_3$)$_3$); 1.24 (s, 9H, C(C*H*$_3$)$_3$); 1.22 (s, 9H, C(C*H*$_3$)$_3$); 1.06 (d, $^3J_{HH}$=6.1 Hz, 3H, C*H*$_3$–C–N). ^{13}C{^{1}H} NMR in $CDCl_3$, δ, 151.7 (*C*–O, 1C), 151.2 (*C*–O, 1C), 141.7 (*C*–C, 1C), 141.3 (*C*–C, 1C), 134.6 (*C*–C, 1C), 134.4 (*C*–C, 1C), 125.8 (*C*H, 2C), 123.7 (*C*H, 2C), 123.4 (*C*H, 2C), 116.5 (*C*H, 1C), 115.9 (*C*H, 1C), 80.2 (*C*–O, 1C), 78.4 (*C*(CH$_3$)$_3$–O, 1C), 78.0 (*C*(CH$_3$)$_3$–O, 1C), 51.4 (*C*H–N, 1C), 34.1 (*C*(CH$_3$)$_3$, 1C), 34.0 (*C*(CH$_3$)$_3$, 1C), 31.5 (C(*C*H$_3$)$_3$, 6C), 29.2 (C(*C*H$_3$)$_3$, 6C), 18.0 (*C*H$_3$–C–N, 1C). EI MS, 439 (M−CH$_3$CH(NH$_2$)$^+$, 5%), 383 (M−CH$_3$CH(NH$_2$)–CH$_2$=C(CH$_3$)$_2^+$, 5%), 327 (M−CH$_3$CH(NH$_2$)–2CH$_2$=C(CH$_3$)$_2^+$, 100%). FAB MS, 484.2952 (98%, M$^+$), 466.2854 (67%, M−H$_2$O$^+$), 354.1643 (58%), 327.1135 (M−CH$_3$CH(NH$_2$)–2CH$_2$=C(CH$_3$)$_2^+$, 100%), 321.1085 (11%), 281.0839 (11%), 177.0851 (30%, (CH$_3$)$_3$CC$_6$H$_3$(OH)–CO$^+$), 161.0540 (13%). High resolution FAB MS for $C_{31}H_{50}NO_3$, found: 484.379000; calcd: 484.379070. Elemental analysis for $C_{31}H_{49}NO_3$, found: C, 76.79; H, 10.28; N, 2.92; calcd: C, 76.97; H, 10.21; N, 2.90.

4.13. (S)-(−)-2-Amino-1,1-di-(2′-benzyloxy-5′-tert-butyl-phenyl)-1-propanol (**14**)

This compound was synthesized by the same procedure as above except using 4-*tert*-butyl-2-bromo-1-benzyloxy-benzene instead of 4-*tert*-butyl-2-bromo-1-octyloxy-benzene to afford 0.27 g of product. Yield 36% based on the ester of the amino acid. ^{1}H NMR in $CDCl_3$, δ, 7.68 (d, $^3J_{HH}$=2.2 Hz, 1H, Ar–*H*); 7.68 (d, $^3J_{HH}$=2.4 Hz, 1H, Ar–*H*); 7.21–7.06 (m, 8H, *m* and *p* in Ph, Ar–*H*); 6.82 (d, $^3J_{HH}$=7.7 Hz, 2H, *o*-*H* in Ph); 6.79 (d, $^3J_{HH}$=7.3 Hz, 2H, *o*-*H* in Ph); 6.67 (d, $^3J_{HH}$=8.6 Hz, 1H, Ar–*H*); 6.59 (d, $^3J_{HH}$=8.6 Hz, 1H, Ar–*H*); 4.93–4.90 (m, 4H, OC*H*$_2$); 4.48 (q, $^3J_{HH}$=6.0 Hz, 1H, C*H*–N); 1.14 (s, 9H, CC*H*$_3$), 1.12 (d, $^3J_{HH}$=6.0 Hz, 3H, C*H*$_3$–C–N). ^{13}C{^{1}H} NMR in $CDCl_3$, δ, 153.6 (*C*–O, 1C), 152.9 (*C*–O, 1C), 142.9 (*C*–C, 1C), 142.6 (*C*–C, 1C), 137.2 (*C*–C, 1C), 136.9 (*C*–C, 1C), 132.6 (*C*–C, 1C), 131.9 (*C*–C, 1C), 128.7 (*C*H, 2C), 128.7 (*C*H, 2C), 127.8 (*C*H, 1C), 127.6 (*C*H, 1C), 126.9 (*C*H, 2C), 126.8 (*C*H, 2C), 126.2 (*C*H, 1C), 125.8 (*C*H, 1C), 124.6 (*C*H, 1C), 124.2 (*C*H, 1C), 112.7 (*C*H, 1C), 112.1 (*C*H, 1C), 80.6 (*C*–O, 1C), 69.9 (*C*H$_2$–O, 1C), 69.6 (*C*H$_2$–O, 1C), 49.3 (*C*H–N, 1C), 34.3 (*C*(CH$_3$)$_3$, 2C), 31.6 (*C*(CH$_3$)$_3$, 6C), 18.1 (*C*H$_3$–C–N, 1C). EI MS, 267 (8%, (CH$_3$)$_3$CC$_6$H$_3$(OCH$_2$Ph)CO$^+$), 243 (20%), 177 (24%, (CH$_3$)$_3$CC$_6$H$_3$(OH)–CO$^+$), 165 (15%), 91 (100, CH$_2$Ph), 59 (20%), 43 (50%, CH$_3$CH=NH$^+$). FAB MS, 552.2582 (82%, M$^+$), 534.2596 (100, M−H$_2$O$^+$), 177.0941 (30%, (CH$_3$)$_3$CC$_6$H$_3$(OH)–CO$^+$).

High resolution FAB MS for $C_{37}H_{46}NO_3$, found: 552.348000; calcd: 552.347770. Elemental analysis for $C_{37}H_{45}NO_3$, found: C, 79.51; H, 8.29; N, 2.60; calcd: C, 80.54; H, 8.22; N, 2.54.

*4.14. Synthesis of mononuclear copper complex, **15** (Ar=Ph)*

10 (26.8 mg, 0.118 mmol), $Cu(OAc)_2 \cdot H_2O$ (23 mg, 0.115 mmol), and salicylaldehyde (14 mg, 0.115 mmol) were suspended in 5 mL of methanol. The mixture was stirred at rt overnight, and the color of the solution changed to deep green. The solvent was removed, and the solid was washed with pentane and methanol. Removal of the solvent afforded 39 mg of product **15**. Yield 85%. The catalyst was used without further purification.

15, MS, ESI, 809.0 (40%), 787.1 (100%, $2M^+$), 515.7 (22%), 412.1 (25%). IR (cm^{-1}), 3057, 2935 (w, CH), 1633 (s, C_6H_5), 1602 (w, C_6H_5), 1537 (w), 1447 (m), 1405 (w), 1316 (w), 1195 (w), 1133 (w), 998 (w), 912 (w), 759 (m), 702 (m), 674 (w), 570 (w), 539 (w), 445 (w). UV–vis (nm), 372 (ε=3198), 365 (ε=3320), 358 (ε=2617), 271 (ε=7121), 246 (ε=10 652), 222 (ε=18 109), 200 (ε=30 993).

*4.15. Synthesis of mononuclear copper complexes, **16–19***

11 (44.6 mg, 0.078 mmol), $Cu(OAc)_2 \cdot H_2O$ (14.7 mg, 0.074 mmol), and salicylaldehyde (9.1 mg, 0.075 mmol) were suspended in 5 mL of methanol. After about 5 min, solid NaOH (120 mg, 3.0 mmol) was added, and the mixture was stirred at rt for 18 h, and the color of the solution changed to deep green. The solvent was removed, and the solid was extracted with pentane. Removal of the solvent afforded 36.6 mg of product **16**. Yield 65%. The catalyst was used without further purification. **17**, yield 100%; **18**, yield 95%; **19**, yield 95%.

16, MS, ESI, 1523.6 (100%, $2M^+$), 1479.1 (76%, $2M-C_3H_7^+$), 1435.1 (34%, $2M-2\times C_3H_7^+$), 761.4 (77%, M^+), 717.2 (64%, $M-C_3H_7^+$). IR (cm^{-1}), 2953, 2925, 2856 (s, CH), 1630, 1604 (m, C_6H_3), 1500 (m), 1456 (w), 1398 (w), 1264 (m), 1026 (w), 900 (w), 809 (m), 758 (w), 668 (w). UV–vis (nm), 374 (ε=1320), 276 (ε=4640), 246 (ε=4652), 218 (sh, ε=13 180), 208 (ε=19 267).

17, MS, ESI, 1288.7 (45%), 1243.3 (100%, $2M^+$), 1180.4 (15%, $2M-Cu^+$), 661.7 (17%, $M+CH_3CN^+$), 652.5 (26%, $M+CH_3OH$), 621.3 (42%, M^+), 603.4 (30%). IR (cm^{-1}), 2964, 2894, 2852 (s, CH), 1627, 1603 (s, C_6H_3), 1537 (w), 1498 (m), 1448 (w), 1395 (w), 1321 (w), 1252 (w), 1197 (w), 1147 (w), 1111 (s), 952 (w), 812 (w), 758 (w). UV–vis (nm), 374 (ε=4458), 274 (ε=13 045), 246 (ε=14 787), 226 (ε=30 845), 208 (ε=40 062).

18, MS, ESI, 1344.9 (100%), 1299.3 (96%, $2M^+$), 1237.4 (33%), 1172.3 (25%), 1132.6 (51%), 859.1 (24%), 680.6 (62%), 649.2 (44%, M^+), 588.2 (22%), 524.3 (27%), 519.3 (23%), 466.4 (16%). IR (cm^{-1}), 2965, 2933, 2909, 2872 (m, CH), 1627, 1604 (s, C_6H_3), 1515 (w), 1494 (s), 1447 (w), 1394 (m), 1366 (w), 1266 (w), 1174 (s), 906 (w), 817 (w), 757 (w), 671 (w). UV–vis (nm), 374 (ε=5552), 274 (ε=16 797), 246 (ε=18 426), 228 (ε=42 539), 208 (ε=60 884).

19, MS, ESI, 1435.2 (100%, $2M^+$), 782.3 (5%), 717.3 (9%, M^+). IR (cm^{-1}), 2951, 2902, 2870 (m, CH), 1629, 1603 (s, C_6H_3), 1504 (m), 1444 (w), 1394 (w), 1318 (w), 1267 (w), 1220 (w), 1149 (w), 1020 (w), 900 (w), 809 (w), 757 (w), 696 (w), 670 (w). UV–vis (nm), 374 (ε=2976), 274 (ε=8745), 244 (ε=11 211), 226 (ε=21 586), 212 (ε=26 967).

*4.16. Synthesis of binuclear copper complexes, **20–24***

The synthesis of catalyst **22** is used as an example. **12** (17 mg, 0.037 mmol), $Cu(OAc)_2 \cdot H_2O$ (7.3 mg, 0.037 mmol), and 2-hydroxy-5-methyl-1,3-benzenedialdehyde (3.0 mg, 0.018 mmol) were suspended in

5 mL of methanol. After about 5 min, triethylamine (5 equiv.) was added, and the mixture was stirred at rt for 2 h. The color of the solution changed to deep green. The solvent was removed, and the solid was washed with methanol. Drying the solid afforded 24 mg of product **22**. Yield 100%. The catalyst was used without further purification. Using this procedure, the yield for **20** was 46%; for **21**, 63%; for **23**, 97%; for **24**, 100%.

20, MS, ESI, 738.9 (100%, M^+), 555.0 (33%), 412.1 (51%), 370.1 (68%, M^{2+}), 238.9 (26%), 229.9 (20%). IR (cm^{-1}), 3409 (brs, OH), 1677 (w), 1626 (m, C_6H_5), 1535 (w), 1433 (w), 1400 (w), 1307 (w), 1229 (w), 973 (w), 887 (w), 836 (w), 766 (w), 686 (w), 652 (w), 533 (w). UV–vis (nm), 413 (ε=3582), 399 (ε=3503), 388 (ε=3574), 383 (ε=3573), 366 (ε=3665), 250 (ε=16 607), 237 (16 620), 198 (ε=19 621), 190 (ε=21 746).

The X-ray quality crystals were grown from methanol solution at rt. $C_{46}H_{62}Cu_2N_2O_{10}$; space group *C2*, *a*=18.0489(4) Å, *b*=13.3410(3) Å, *c*=10.55680(10) Å, β=117.2490(10)°, *V*=2259.88(7) $Å^3$, crystal dimensions 0.3×0.2×0.2 mm, *Z*=4, d_{calcd}=1.367 g/cm^3, *F(000)*=980 e, Siemens SMART/CCD diffractometer, Mo-*K*α=radiation (λ=0.71073 Å), *T*=−60°C. Data were corrected for Lorentz and polarization effects as well as absorption [empirical, absorption coefficient=0.999 mm^{-1}]. 7528 reflections measured, 4973 [*R*(int)=0.0245] unique reflections. Non-H atoms were refined with anisotropic displacement parameters. Hydrogen atoms were calculated in idealized geometry and included with isotropic contributions. Refined parameters (285) *wR2* [unique data]=0.0941, $R1[Fo \geq 2\sigma(Fo)] = 0.0417$, $wR2 = [\sum w(Fo^2 - Fc^2)^2] / \sum [w(Fo^2)^2]^{1/2}$, $R1 = \sum(||Fo| - |Fc||) / \sum |Fo|$, $w = q/2\sigma^2(Fo^2) + (ap)^2 + bp$, $p = (Fo^2 + 2Fc^2)/3$; $a = 0.0546$, $b = 0.0000$, $\rho_{final} = +0.367/-0.385$ e $Å^{-3}$. The structure was solved by direct methods and refined by full matrix least–square calculations (SHELX-93, Sheldrick, G. M. SHELXL-93, Göttingen, 1993).

21, MS, ESI, 1475.4 (100%, M^+), 834.8 (29%), 803.4 (21%), 738.4 (51%, M^{2+}), 622.5 (30%). IR (cm^{-1}), 2967, 2912 (S, CH), 1614 (S, C_6H_3), 1517 (m), 1404 (m), 1367 (m), 1265 (w), 1172 (m), 1107 (w), 898 (w), 818 (w), 679 (w). UV–vis (nm), 410 (ε=5662), 272 (ε=17 236), 252 (ε=17 774), 216 (sh, ε=53 593), 210 (ε=61 233).

22, MS, ESI, 1917 (22%), 1521.2 (33%), 1283.5 (62%), 1269.2 (71%), 1255.0 (47%), 1241.2 (40%), 1223.0 (79%), 1209.3 (92%), 1194.6 (100%, M^+), 813.3 (47%), 799.2 (52%), 771.3 (25%), 598.4 (32%, M^{2+}). IR (cm^{-1}), 2968, 2908, 2863 (m, CH), 1635, 1604 (m, C_6H_3), 1496 (m), 1451 (m), 1395 (m), 1332 (w), 1299 (w), 1266 (m), 1243 (m), 1141 (w), 1112 (m), 1054 (w), 950 (w), 837 (w), 812 (w), 687 (w), 618 (w). UV–vis (nm), 412 (ε=8314), 386 (ε=10 707), 278 (ε=37 069), 250 (ε=39 950), 222 (ε=90 780), 208 (ε=152 173).

23, MS, ESI, 1429.4 (25%), 1338.9 (39%), 1324 (26%), 1309.7 (27%), 1296.9 (9%), 1277.3 (43%), 1262.5 (20%), 1250.5 (100%, M^+), 1216.3 (24%), 1174.1 (10%), 838.9 (18%), 797.1 (20%), 715.6 (25%), 626.2 (36%, M^{2+}), 561.0 (18%), 524.1 (13%), 480 (9%). IR (cm^{-1}), 2954, 2857 (m, CH), 1614 (m, C_6H_3), 1493 (m), 1403 (m), 1367 (w), 1265 (w), 1172 (m), 1113(w), 898 (w), 818 (w), 677 (w), 621 (w). UV–vis (nm), 414 (ε=12 051), 390 (ε=15 408), 276 (ε=56 571), 254 (ε=54 750), 224 (ε=133 270), 212 (ε=179 533).

24, MS, ESI, 1713.2 (19%), 1611.3 (10%), 1445.1 (16%), 1387.3 (100%, M^+), 1330.5 (10%), 1293.5 (5%), 1231.7 (12%), 885.2 (15%), 847.3 (7%), 759.2 (13%), 694.3 (15%, M^{2+}). IR (cm^{-1}), 2954, 2862 (m, CH), 1639, 1582 (m, C_6H_3), 1552 (w), 1456 (m), 1371 (w), 1319 (w), 1266 (w), 1227 (m), 1114 (w), 1020 (m), 808 (w), 734 (w), 697 (w), 613 (w). UV–vis (nm), 528 (ε=272), 412 (ε=8 849), 386 (ε=14 376), 366 (ε=13 550), 266 (ε=49 270), 216 (ε=115 868), 192 (ε=12 893).

4.17. Asymmetric cyclopropanation

In a glovebox, the catalyst **22** (25 mg, 0.020 mmol) was dissolved in 3.0 mL of CH_3CN. $PhNHNH_2$ (2.4 equiv.) in CH_3CN was added in one portion. Ethyl diazoacetate (236 mg, 2.1 mmol) in 3.0 mL of CH_3CN was placed in an addition funnel. The green color of the catalyst remained after the mixture was taken out of the glovebox. A few drops of $N_2CHCOOC_2H_5$ solution were added, and the reaction mixture was heated to 50°C until the color of the solution changed to brown (about 2 minutes). Styrene (1 mL, 8.74 mmol) was added in one portion. After 5 minutes, the solution of $N_2CHCOOC_2H_5$ was added and the reaction stirred overnight. After the reaction, the solvent was removed and the product was purified using the TLC plate.

4.18. Determination of the e.e. values for the trans product

The e.e. value of the *trans* isomer was determined directly by a Chiralcel OD column with the eluent hexane:isopropanol=95:5. The retention times were 10.4 and 13.7 minutes, respectively.

4.19. Determination of the e.e. values for the cis product

4.19.1. Reduction of the cis ester to the cis alcohol

In a typical example, the *cis* ester (58 mg, 0.31 mmol) was dissolved in 5.0 mL of THF, and $LiAlH_4$ (11.6 mg, 0.31 mmol) was added in one portion. After 0.5 h, 1 mL of water was added to quench the excess $LiAlH_4$. The product was extracted by ether, and the ether solution was dried by Na_2SO_4. Purification of the product by silica gel column or TLC plate (ethyl acetate:hexane=30:70) afforded 36 mg of product. Yield 78%.

4.19.2. Synthesis of (1S)-(−)-camphanic ester

The *cis* alcohol (20 mg, 0.14 mmol) and (1*S*)-(−)-camphanic chloride (45 mg, 0.21 mmol) were dissolved in 4 mL of CH_2Cl_2:$(C_2H_5)_3N$ (1:1). DMAP (5 mg, 0.041 mmol) was added in one portion. After 3 h, or when no starting alcohol was detectable on TLC, the solvent was removed, and the product was purified by TLC plate to afford 40 mg of the ester. Yield 87%. The e.e. values were determined as above, with the retention times, 24.2 and 25.4 minutes, respectively.

References

1. (a) Shibasaki, M.; Sasai, H.; Arai, T. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 1236–1256. (b) Kless, A.; Lefeber, C.; Spannenberg, A.; Kempe, R.; Baumann, W.; Holz, J.; Börner, A. *Tetrahedron* **1996**, *52*, 14599–14606. (c) Sawamura, M.; Sudoh, M.; Ito, Y. *J. Am. Chem. Soc*. **1996**, *118*, 3309–3310. (d) Süss-Fink, G. *Angew. Chem., Int. Ed. Engl*. **1994**, *33*, 1, 67–69. (e) Konsler, R. G.; Karl, J.; Jacobsen, E. N. *J. Am. Chem. Soc*. **1998**, *120* (41), 10780–10781.
2. Oda, T.; Irie, R.; Katsuki, T.; Okawa, H. *Synlett* **1992**, 641–643.
3. (a) Williams, I. D.; Pedersen, S. F.; Sharpless, K. B.; Lippard, S. J. *J. Am. Chem. Soc*. **1984**, *106*, 6430–6431. (b) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley & Sons: New York, 1994; p. 264. (c) Girard, C.; Kagan, H. B. *Angew. Chem., Int. Ed. Engl*. **1998**, *37*, 2922–2959.
4. (a) Tamblyn, W. H.; Hoffman, S. R.; Doyle, M. P. *J. Organomet. Chem*. **1981**, *216*, C64–C68. (b) Hanks, T. W.; Jennings, P. W. *J. Am. Chem. Soc*. **1987**, *109*, 5023–5025. (c) Tomilov, Y. V.; Kostitsyn, A. B.; Shulishov, E. V.; Nefedov, O. M. *Synthesis* **1990**, 246–248.
5. (a) Adams, J.; Spero, D. M. *Tetrahedron* **1991**, *47*, 1765–1808. (b) Maas, G. *Top. Curr. Chem*. **1987**, *137*, 75–253. (c) Doyle, M. P. *Chem. Rev*. **1986**, *86*, 919–939. (d) Doyle, M. P. *Acc. Chem. Res*. **1986**, *19*, 348–356.

6. (a) Anciaux, A. J.; Hubert, A. J.; Noels, A. F.; Petiniot, N.; Teyssié, P. H. *J. Org. Chem*. **1980**, *45*, 695–702. (b) Doyle, M. P.; Griffin, J. H.; Bagheri, V.; Dorow, R. L. *Organometallics* **1984**, *3*, 53–61.
7. (a) Doyle, M. P. *Asymmetric Cyclopropanation* in *Catalytic Asymmetric Synthesis*; Ojima, I., Ed. VCH: New York, 1993; pp 63–99. (b) Singh, V. K.; Datta Gupta, A.; Sekar, G. *Synthesis* **1997**, 137–149. (c) Doyle, M. P.; McKervey, M. A. *J. Chem. Soc., Chem. Commun*. **1997**, 983–989. (d) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley & Sons: New York, 1994; pp. 199–207.
8. Aratani, T. *Pure Appl. Chem*. **1985**, *57*, 1839–1844.
9. Fritschi, H.; Leutenegger, U.; Pfaltz, A. *Helv. Chim. Acta* **1988**, *71*, 1553–1565.
10. (a) Lowenthal, R. E.; Abiko, A.; Masamune, S. *Tetrahedron Lett*. **1990**, *31*, 6005–6008. (b) Lowenthal, R. E.; Masamune, S. *Tetrahedron Lett*. **1991**, *32*, 7373–7376. (c) Masamune, S.; Lowenthal, R. E. U.S. Patent 5298623, **1994**. [*Chem. Abstr*. **1994**, *121*, 205742 g.]
11. (a) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc*. **1991**, *113*, 726–728. (b) Evans, D. A.; Woerpel, K. A.; Scott, M. J. *Angew. Chem., Int. Ed. Engl*. **1992**, *31*, 430–432.
12. (a) Doyle, M. P.; Protopopova, M. N.; Brandes, B. D.; Davies, H. M. L.; Huby, N. J. S.; Whitesell, J. K. *Synlett* **1993**, 151–153. (b) Doyle, M. P.; Winchester, W. R.; Protopopova, M. N.; Müller, P.; Bernadinelli, G.; Ene, D.; Motallebi, S. *Helv. Chim. Acta* **1993**, *76*, 2227–2235. (c) Müller, P.; Baud, C.; Ené, D.; Motallebi, Doyle, M. P.; Brandes, B. D.; Dyatkin, A. B.; See, M. M. *Helv. Chim. Acta* **1995**, *78*, 459–470.
13. (a) Nishiyama, H.; Itoh, Y.; Matsumoto, H.; Park, S. -B.; Itoh, K. *J. Am. Chem. Soc*. **1994**, *116*, 2223–2224. (b) Nishiyama, H.; Itoh, Y.; Sugawara, Y.; Matsumoto, H.; Aoki, K.; Itoh, K. *Bull. Chem. Soc. Jpn*. **1995**, *68*, 1247–1262. (c) Park, S.-B.; Murata, K.; Matsumoto, H.; Nishiyama, H. *Tetrahedron: Asymmetry* **1995**, *6*, 2487–2494. (d) Park, S.-B.; Sakata, N.; Nishiyama, H. *Chem. Eur. J*. **1996**, *2*, 303–306.
14. Schumacher, R.; Dammast, F.; Reibig, H.-U. *Chem. Eur. J*. **1997**, *3*, 614–619.
15. Camps, F.; Coll, J.; Moretó, J. M. *Synthesis* **1982**, 186–188.
16. For examples of related derivatives: (a) Itsuno, S.; Nakano, M.; Miyazaki, K.; Masuda, H.; Ito, K. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2039–2044. (b) Wey, S.; O'Connor, K. J.; Burrows, C. J. *Tetrahedron Lett*. **1993**, *34*, 1905–1908.
17. Doyle, M. P. *Asymmetric Cyclopropanation in Catalytic Asymmetric Synthesis*; Ojima I, Ed. VCH: New York, 1993; pp. 63–99.
18. (a) Mahroof-Tahir, M.; Karlin, K. D. *J. Am. Chem. Soc*. **1992**, *114*, 7599–7601. (b) Harding, C.; McKee, V.; Nelson, J. *J. Am. Chem. Soc*. **1991**, *113*, 9684–9685. (c) Long, R. C.; Hendrickson, D. N. *J. Am. Chem. Soc*. **1983**, *105*, 1513–1521. (d) Hendrickson, D. N.; Long, R. C.; Hwang, Y. T.; Chang, H. R. In *Biological and Inorganic Copper Chemistry*; Karlin, K. D.; Zubieta, J., Eds. Adenine Press: Guilderland, New York, 1985. (e) Gagné, R. R.; Koval, C. A.; Smith, T. J.; Comolino, M. C. *J. Am. Chem. Soc*. **1979**, *101*, 4571–4580. (f) Gagné, R. R.; Henling, L. M.; Kistenmacher, T. J. *Inorg. Chem*. **1980**, *19*, 1226–1230. (g) Gagné, R. R.; Koval, C. A.; Smith, T. J. *J. Am. Chem. Soc*. **1977**, *99*, 8367–8368.
19. Kanemasa, S.; Hamura, S.; Harada, E.; Yamamoto, H. *Tetrahedron Lett*. **1994**, *43*, 7985–7988.
20. Jones, B. *J. Chem. Soc*. **1941**, 358–364.