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Arylid-OX and Arylid-BOX derived catalysts: applications in catalytic asymmetric cyclopropanation

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ABSTRACT

A novel family of chiral non-racemic monodentate oxazoline ligands known as Arylid-OXs **1a** and **1b** was prepared in good overall yields. These ligands were screened in bench-mark Cu(I)-catalyzed cyclopropanations and gave ees as high as 58%. Both ^{1}H NMR and computational studies using **1a** indicated that the active catalyst was most likely to be the di-coordinated complex, Cu(I)-**1a**$_2$(MeCN)$_2$. Two novel *ortho*-substituted Arylid-BOX ligands **2a** and **2b** were also synthesized in very good yields. These ligands were tested in the same reaction as for **1a** and **1b** and, although excellent yields could be obtained with **2b**, which is assumed to be due to an electron-donating effect from the *ortho*-methoxy group, a best ee of only 56% was obtained with **2a**. In fact, both the enantioselectivities and diastereoselectivities obtained with these *ortho*-substituted ligands were in line with those previously obtained with the *para*-substituted series.

1. Introduction

Chiral non-racemic C_2 symmetric bidentate bis-oxazoline (BOX) ligands first appeared in the literature about 18 years ago, and are used to form catalysts with appropriate metals, giving very good enantioselectivities in a number of catalytic asymmetric reactions.[1] Cu(I)-BOX catalysts have been shown to be very useful for accessing enantio-enriched chiral cyclopropanes. The synthesis of chiral cyclopropanes remains as a considerable challenge, especially since the cyclopropane unit is often found in a variety of natural products and biologically active compounds.[2] Over the last few years, we have developed and tested a number of novel Cu(I)-BOX catalysts based on a first generation novel BOX family known as IsBut-BOX[3] and a second generation family known as Arylid-BOX (Fig. 1).[4] The latter proved to be more effective and versatile in some bench-mark Cu(I) asymmetric cyclopropanation reactions and has been extensively studied. Despite the enormous propensity for functional diversity in this ligand system, until now only those ligands with a substituent in the *para*-position have been evaluated. It was thus of interest to synthesize derivatives with substituents in other positions, preferably at the *ortho*-position, principally because the relevant substituent will be closer to the metal centre. Despite the large application of bidentate chiral ligands in catalytic asymmetric synthesis, monodentate versions have rarely had the same impact, for the main reason that they fail to form compact catalytic manifolds that are pivotal for high asymmetric induction during the reaction. Monodentate ligands offer the advantage that they are in general less structurally complex than di- and multidentate ligands and thus the synthesis in principle is less demanding. Some monodentate systems are known which give very good results. For instance, Feringa used chiral phosphoramidite ligands for copper-catalyzed dialkylzinc additions and ees of up to 98% could be obtained.[5] Also, Luan et al. studied a series of monodentate N-heterocyclic carbene ligands in the asymmetric α-arylation of amides and obtained enantioselectivi-

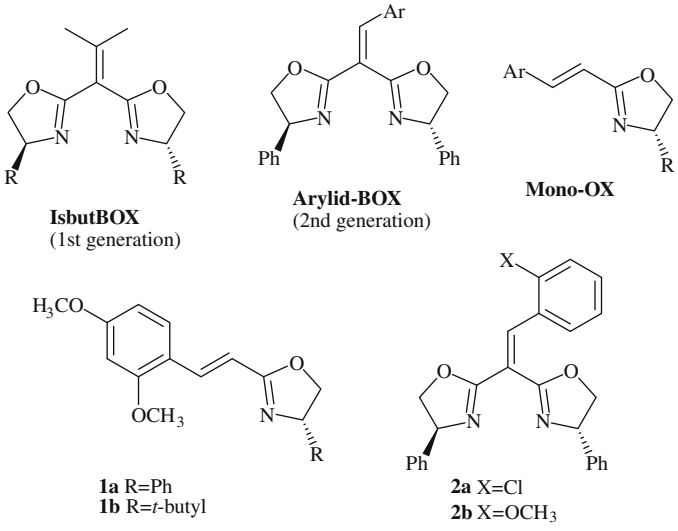

Figure 1. Mono-Arylid-OX and Arylid-BOX ligands.

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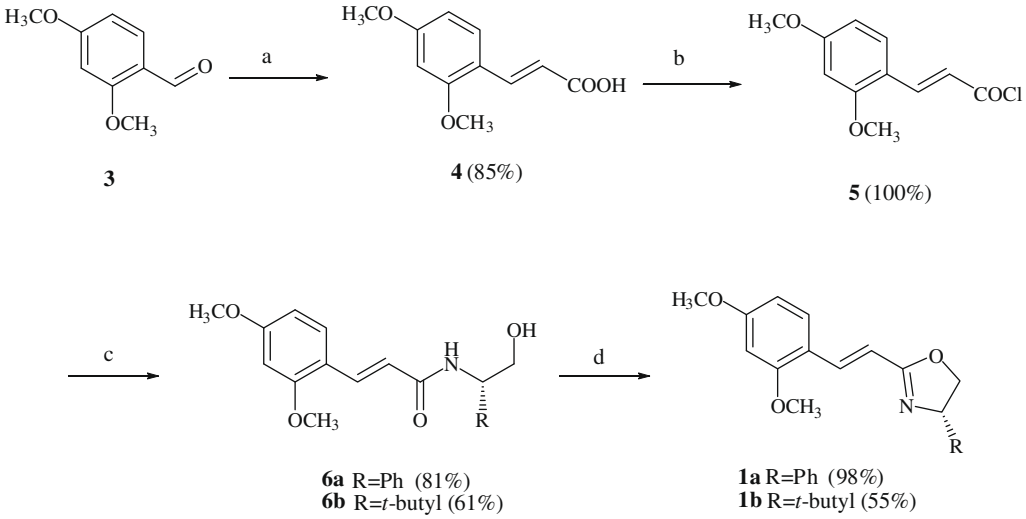


Scheme 1. Reagents and conditions: (a) malonic acid, 70 °C; (b) $(COCl)_2$, DMF, CH_2Cl_2, 0 °C; (c) (*S*)-(+)-phenylglycinol or (*S*)-*tert*-leucinol, NEt_3, CH_2Cl_2; (d) CH_3SO_2Cl, NEt_3, CH_2Cl_2.

ties of up to 98% ee.[6a] Ikeda et al.[6b] have used some chiral monooxazoline ligands with moderate success (a highest ee of 58% was obtained) in catalytic enantioselective [2+2+2] cycloadditions with Ni. We thus developed a monodentate version of Arylid-BOX known as Arylid-OX (Fig. 1) which gave unexpected results in some bench-mark cyclopropanation reactions. Herein we report the synthesis of the novel Arylid-OX ligands **1a** and **1b** (Fig. 1), the *ortho*-substituted Arylid-BOXs **2a** and **2b**, their application in a bench-mark cyclopropanation reaction and our investigations on the structure of the active catalyst in the reactions with Arylid-OX ligands.

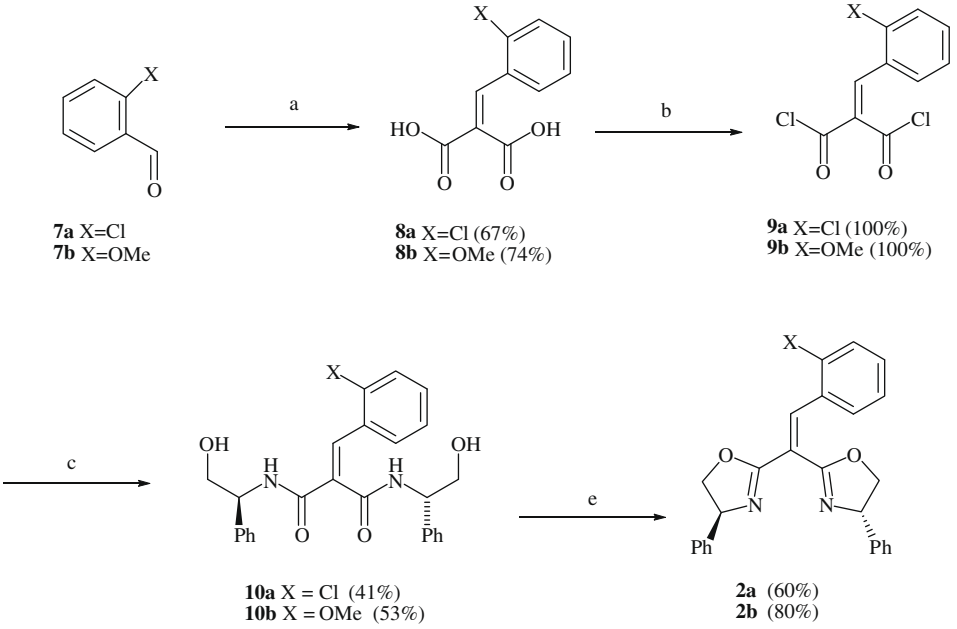
2. Results and discussion

The series of Arylid-OX ligands **1a** and **1b**, and Arylid-BOX ligands **2a** and **2b** was prepared in very good yields using the synthetic pathways shown in Schemes 1 and 2. For the synthesis of the Arylid-OXs **1a** and **1b**, and Arylid-BOXs **2a** and **2b** both *trans*-2,4-dimethoxycinnamic acid **4** (Scheme 1) and arylidene malonic acids **8a** and **8b** (Scheme 2) were used. These were obtained via the procedure reported by Neustadt et al.[7] using a simple Knoevenagel condensation with malonic acid and the respective aldehyde. Our standard synthetic procedure[3,4] was subsequently used to transform the acids to the corresponding ligands. Satisfactory yields could be obtained in all cases.

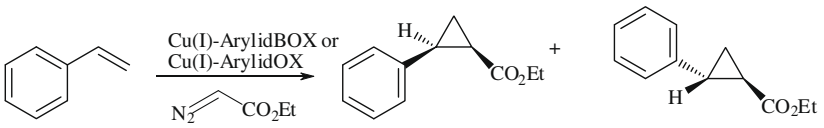
These ligands were subsequently used in a series of Cu(I)-catalyzed olefin cyclopropanations with ethyl diazoacetate using $[Cu(MeCN)_4]PF_6$ and Cu(I)(OTf) as pre-catalysts (Scheme 3).

2.1. Arylid-OX

Monodentate Arylid-OXs **1a** and **1b** were tested in some catalytic asymmetric cyclopropanations with Cu(I) (Table 1). An ee as high as 58% for the *trans*-product could be obtained using ligand



Scheme 2. Reagents and conditions: (a) malonic acid, 70 °C; (b) $(COCl)_2$, DMF, CH_2Cl_2, 0 °C; (c) (*S*)-(+)-phenylglycinol, NEt_3, CH_2Cl_2; (d) CH_3SO_2Cl, NEt_3, CH_2Cl_2.



Scheme 3. Asymmetric cyclopropanation of styrene—the bench-mark reaction.

Table 1
Catalytic asymmetric cyclopropanation of styrene[a]

Entry	Ligand (mol %)	Pre-catalyst (mol %)	Yield (%)	*cis*:*trans*[c]	*cis*[c,d] (ee%)	*trans*[c,d] (ee%)	Ratio Cyclopropanes:maleates[c]
1	**1a** (2.2)	Cu(I)OTf (1)	13[b]	32:68	3 (1*R*, 2*S*)	5 (1*R*,2*R*)	89:11
2	**1a** (2.2)	$CuPF_6$ (2)	18[b]	36:64	15 (1*R*, 2*S*)	20 (1*R*,2*R*)	84:16
3	**1b** (2.1)	$CuPF_6$ (2)	27[e]	33:67	29 (1*S*,2*R*)	26 (1*S*,2*S*)	91:9
4	**1a** (3.14)	Cu(I)OTf (1)	18[b]	38:62	13 (1*R*, 2*S*)	16 (1*R*,2*R*)	75:25
5	**1a** (3.14)	$CuPF_6$ (2)	26[b]	36:64	38 (1*R*, 2*S*)	32 (1*R*,2*R*)	92:8
6	**1a** (4.2)	Cu(I)OTf (1)	15[b]	35:65	19 (1*R*, 2*S*)	22 (1*R*,2*R*)	78:22
7	**1a** (4.2)	$CuPF_6$ (2)	17[b]	34:66	33 (1*R*, 2*S*)	32 (1*R*,2*R*)	86:14
8	**1b** (4.2)	Cu(I)OTf (1)	32[e]	39:61	6 (1*S*,2*R*)	7 (1*S*,2*S*)	72:28
9	**1b** (4.2)	$CuPF_6$ (2)	31[e]	40:60	43 (1*S*,2*R*)	45 (1*S*,2*S*)	82:18
10	**1b** (6.3)	$CuPF_6$ (2)	34[e]	31:69	51 (1*S*,2*R*)	58 (1*S*,2*S*)	86:14

[a] Styrene (4 equiv), Chiral ligand, Cu(I) pre-catalyst, ethyl diazoacetate (1 equiv), CH_2Cl_2, rt, 24 h.
[b] Determined by gas chromatography using di-*n*-butylether as the internal standard.
[c] The diastereomeric ratio and the % ee was determined by GC.
[d] The major isomer is indicated in parentheses.
[e] Yield determined from the mass of isolated crude product isomers.

1b at a loading level of 6.3 mol % (Table 1, entry 10) with $[Cu(MeCN)_4]PF_6$ as the pre-catalyst. In all cases, the *trans*-isomer was the predominant isomer. The highest de obtained was 38% (Table 1, entry 10). Generally, ligand **1b** gave better ees than **1a** and this can be ascribed to the presence of a bulkier substituent.

The yields were only moderate and this was due to the formation of significant quantities of maleate products. In order to find optimized conditions, different ratios of ligand to Cu(I) were investigated. In the case of ligand **1a** using Cu(I)OTf (entries 1, 4 and 6), an increase in the ee was observed when the proportion of ligand was increased. The same was true with the other pre-catalyst, $[Cu(MeCN)_4]PF_6$, (entries 2, 5 and 7). The diastereoselectivities remained generally the same. In the case of ligand **1b** with $[Cu(MeCN)_4]PF_6$ (entries 3, 9 and 10), the ees increased on increasing the quantity of ligand.

2.1.1. NMR study

To gain an insight into the structure of the active catalyst involved in this reaction, both ^1H NMR and computational studies were carried out. Three types of complexation were conducted, using ligand **1a** and $[Cu(MeCN)_4]PF_6$, in the following ratios; 1:1, 2:1 and 3:1 ligand. (**1a** was mixed with the pre-catalyst in CH_2Cl_2 at rt for 30 min, the solvent was removed and the remaining solid was dried carefully). In all cases, the NMR spectra were clean and it was obvious that complexation had taken place, as the spectra were different from those of the free ligand. The observed chemical shifts of the principal signals are shown in Table 2. In the case of both 1:1 and 2:1 **1a**:pre-catalyst the difference in the chemical shifts was quite small. The fact that some solid precipitated when a 1:1 mixture of **1a** to pre-catalyst was used indicated the formation of a di-Arylid-OX-coordinated complex, that is, Cu(I)-**1a**$_2$(MeCN)$_2$. In the case of the system that comprises a 3:1 **1a**:pre-catalyst, the resolution was poorer than that in the previous cases, leading us to believe that an equilibrium was established between excess free ligand and the di-coordinated complex. The ^1H NMR studies indicate that the MeCN coordinates with the metal through vacant coordination sites on the metal.

Table 2
^1H NMR data for complex formation

1a:$[Cu(MeCN)_4]PF_6$	δ_H (ppm)				
	H_1	H_2	H_3	H_4	H_5
1:0	5.295	4.179	4.697	6.750	7.676
1:1	5.370	4.950	4.410	6.330	7.875
2:1	5.350	4.927	4.412	6.349	7.858
3:1	5.143	4.777	4.306	6.375	7.807

2.1.2. Computational study

A theoretical study was carried out to verify the observations obtained from ^1H NMR spectroscopy. The following four complexes were studied: $Cu(MeCN)_4$, Cu(I)-**1a**$(MeCN)_3$, Cu(I)-**1a**$_2$$(MeCN)_2$ and Cu(I)-**1a**$_3$(MeCN) to determine their relative energies in an attempt to establish the most viable catalytic complex involved in these catalytic reactions. Considering the number and size of these systems, a semi-empirical method proved to be the best choice for geometry optimization. The novel PM6 Hamiltonian[8] included in the recent version of MOPAC 2007[9] was employed in this study, followed by single point calculations at density functional theory (DFT) level.

The geometries were fully optimized in Cartesian coordinates and the stationary points obtained were further characterized by frequency calculations as minima.

Following the initial geometry optimization with the PM6 method, DFT calculations were carried out on all complexes. The DFT calculations were performed using the hybrid Becke exchange functional[10] and the correlation functional B3LYP[11] as contained in the Gamess package.[12] The Lanl2DZ effective core basis set was employed for the metal atom while the 6-31G** basis set was used for all the other atoms.

All the Cu(I) complexes studied were found to have a tetrahedral structure as illustrated in Figure 2 and in agreement to what is found experimentally for the majority of Cu(I) complexes.[13,14] The Cu(I)–N bond distances are depicted in Table 3. In the known tetrahedral complex $[CuI(MeCN)_4]$–ClO_4, Cu–N distances of 1.99 Å

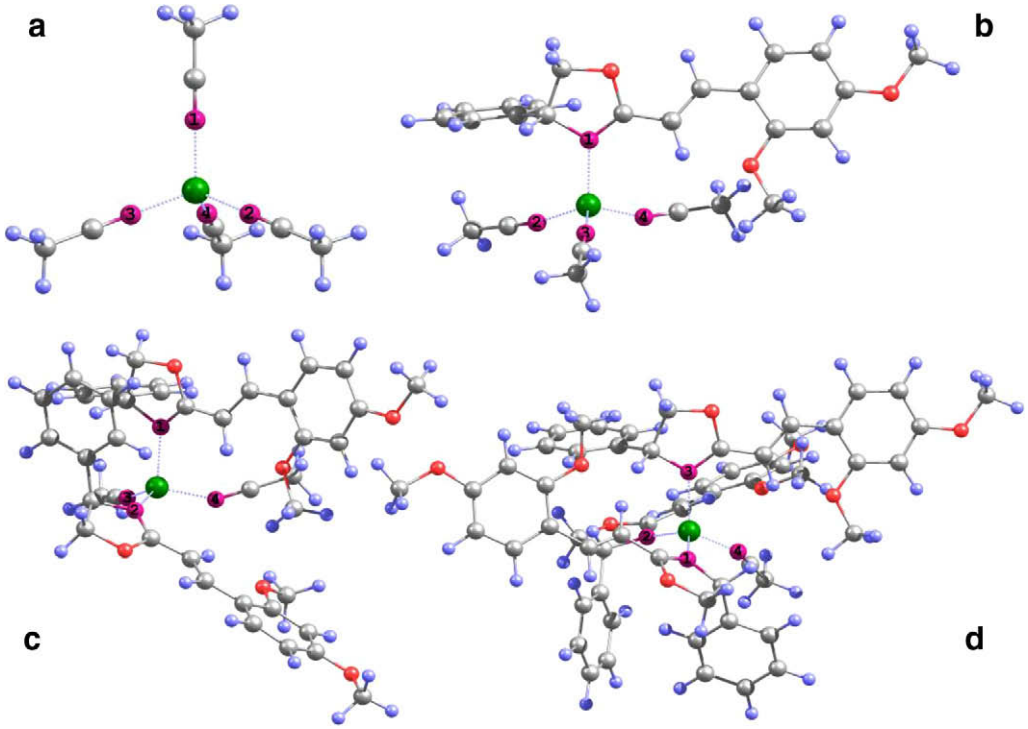


Figure 2. Calculated structures for the Cu(I) complexes (a) Cu(I)(MeCN)$_4$, (b) Cu(I)-**1a**(MeCN)$_3$, (c) Cu(I)-**1a**$_2$(MeCN)$_2$ and (d) Cu(I)-**1a**$_3$(MeCN).

Table 3
Selected bond lengths (Å) for complexes Cu(I)(MeCN)$_4$, Cu(I)-**1a**(MeCN)$_3$, Cu(I)-**1a**$_2$(MeCN)$_2$ and Cu(I)-**1a**$_3$(MeCN)

	Cu(I)(MeCN)$_4$	Cu(I)-**1a**(MeCN)$_3$	Cu(I)-**1a**$_2$(MeCN)$_2$	Cu(I)-**1a**$_3$(MeCN)
Cu–N$_1$	1.971	2.044[a]	2.050[a]	2.024[a]
Cu–N$_2$	1.971	1.964	2.023[a]	2.033[a]
Cu–N$_3$	1.971	1.961	1.955	2.043[a]
Cu–N$_4$	1.971	1.968	1.969	1.965

[a] Nitrogen atom belonging to the **1a** moiety.

were experimentally observed[15] and should be compared with the Cu–N distances in the first column of Table 3. The close agreement observed here supports the suitability of the PM6 method to determine the molecular geometries of these complexes. The calculated Cu–N(oxazoline) distances are slightly longer than the calculated Cu–N(MeCN) distances for all oxazoline-containing complexes. The binding energy for each complex was obtained by calculating the difference in energy between the optimized structure for each complex and the sum of the energies of the optimized isolated moieties. Selected energy values calculated with the B3LYP/6-31G**//PM6 method are depicted in Table 4. This study clearly shows that it is the di-oxazoline-coordinated complex—Cu(I)-**1a**$_2$(MeCN)$_2$—which has the lowest ΔE value indicating a higher stability for this complex. This result strongly supports our previous postulate based on ^{1}H NMR spectroscopy.

Table 4
Calculated energies for complexes Cu(I)(MeCN)$_4$, Cu(I)-**1a**(MeCN)$_3$, Cu(I)-**1a**$_2$(MeCN)$_2$ and Cu(I)-**1a**$_3$(MeCN) at the B3LYP/G-31G*//PM6 level

Chemical unit	Total energy (a.u.)	ΔE (kcal/mol)	ΔE_{rel} (kcal/mol)
Cu(I)	−195.7599954	—	—
1a	−1015.2558668	—	—
MeCN	−132.6776021	—	—
Cu(I)(MeCN)$_4$	−726.7069097	−148.410	0.000
Cu(I)-**1a**(MeCN)$_3$	−1609.2982735	−156.629	−8.220
Cu(I)-**1a**$_2$(MeCN)$_2$	−2491.8870626	−163.234	−14.820
Cu(I)-**1a**$_3$(MeCN)	−3374.4607609	−160.368	−11.960

2.2. Cu(I)-bis-Arylid-BOX catalysis

Bis-Arylid-BOXs **2a** and **2b** were tested in catalytic asymmetric cyclopropanations with Cu(I) (Table 5). This study demonstrated that on using both [Cu(MeCN)$_4$]PF$_6$ and Cu(I)OTf with **2a** and **2b** the ees were better with the former pre-catalyst. Ligand **2a** gave the highest ee using [Cu(MeCN)$_4$]PF$_6$ as the pre-catalyst (Table 5, entry 2, 56% *trans*-isomer), but it was the catalyst formed from **2b** which gave the better yields. This is most likely due to the presence of the electron-donating group in the ortho position. The des were only moderate, a maximum of 40% being obtained with both **2a** and **2b**. We tested ligand **2b** with toluene, using [Cu(MeCN)$_4$]PF$_6$ (Table 5, entry 5), but there was only a slight increase in ee for both isomers. The chemical yield had greatly decreased in relation to using CH_2Cl_2 (24% as opposed to 100% with CH_2Cl_2. On comparing the results obtained using both **2a** and **2b** with those found for their *para*-substituted counterparts[4a] ([Cu(MeCN)$_4$]PF$_6$ as the pre-catalyst) it can be seen that the ees are similar (53% and 61% for both the *cis* and *trans* isomers—*para*-chloro-substituted ligand, and 41% and 48%—*para*-methoxy-substituted ligand). The des obtained with **2a** and **2b** were slightly higher than those of their *para*-substituted counterparts, which were about 30%. However, the yields using the ortho-substituted ligands were better.

In most cases, the quantity of maleate side product was less than that encountered with the Arylid-OX-based Cu(I) catalysts.

3. Conclusions

The two chiral monodentate ligands **1a** and **1b** were screened in a bench-mark cyclopropanation reaction with styrene and ethyl diazoacetate using two different Cu(I) sources. Although satisfactory ees could be obtained (up to 58%) the yields were only moderate. Surprisingly, ees as high as those obtained using the Arylid-BOX

Table 5
Catalytic asymmetric cyclopropanation of styrene using Cu(I)-**2a** and Cu(I)-**2b**[a]

Entry	Ligand (mol %)	Pre-catalyst (mol %)	Yield[b] (%)	*cis*:*trans*[c]	*cis*[c,d] (ee%) (1*R*,2*S*)	*trans*[c,d] (ee%) (1*R*,2*R*)	Ratio Cyclopropanes:maleates[c]
1	**2a** (2.2)	Cu(I)OTf(2)	19	32:68	38	49	81:19
2	**2a** (2.2)	$CuPF_6$(2)	60	30:70	50	56	95:5
3	**2b** (2.2)	Cu(I)OTf(2)	100	34:66	10	10	99.5:0.5
4	**2b** (2.2)	$CuPF_6$(2)	100	31:69	41	50	95:5
5[e]	**2b** (2.2)	$CuPF_6$(2)	24	30:70	48	35	97:3

[a] Styrene (4 equiv), Chiral ligand, Cu(I) pre-catalyst, ethyl diazoacetate (1 equiv), CH_2Cl_2, rt, 24 h.
[b] Determined by gas chromatography using di-*n*-butylether as the internal standard.
[c] The diastereomeric ratio and the % ee was determined by GC.
[d] The major isomer is indicated in parentheses.
[e] Solvent was toluene, 40 °C.

ligands **2a** and **2b** were obtained. Mechanistic studies using NMR spectroscopy and computational calculations indicate that the active catalyst is most likely to be; Cu(I)-**1a**$_2$(MeCN)$_2$. On screening the *ortho*-substituted Arylid-BOX ligands **2a** and **2b** in the same test reaction, despite obtaining some excellent yields a highest ee of 56% (*trans*-isomer) was obtained. The ees were the same as those obtained for the *para*-substituted phenyl-Arylid-BOX series.

We are currently investigating ligands **1a** and **1b** and other derivatives in other catalytic asymmetric reactions, including using such ligands to form hetero-Cu(I) complexes for screening in the asymmetric cyclopropanation reaction.

4. Experimental

4.1. General remarks

trans-2,4-Dimethoxycinnamic acid **4**, 2-(2-chlorobenzylidene)malonic acid **8a**, and 2-(2-methoxybenzylidene)malonic acid **8b**, were prepared as reported previously.[7] All reagents were obtained from Aldrich, Fluka, Alfa Aesar or Acros. Solvents were dried using common laboratory methods. Column chromatography was carried out on silica gel (sds, 70–200 μm) and flash column chromatography (Merck, 40–63 μm and sds, 40-63 μm). TLC was carried out on aluminium-backed Kisel-gel 60 F254 plates (Merck). Plates were visualized either by UV light or by phosphomolybdic acid in ethanol. Gas chromatographic (GC) analyses of the products were performed on a Hewlett Packard (HP) 6890 series instrument equipped with a flame ionization detector (FID). The chromatograph was fitted with a cyclosil-B capillary column (30 m, 250 μm, 0.25 μm) (Agilent 112-2532). The melting points were recorded on a Barnstead Electrothermal 9100 apparatus and was uncorrected. The NMR spectra were recorded on either a Bruker AMX300 or a Bruker Avance 400 instrument. Mass spectra were recorded on a VG Autospec M(Waters-Micromass) spectrometer using the FAB technique and Waters-Micromass GC-TOF and MicroTOF Focus (Bruker Daltonics) using the TOF technique. Infra-red spectra were measured with a Perkin Elmer Paragon 1000 model.

4.2. Ligand synthesis

4.2.1. General procedure for the synthesis of cinnamamides 6a and 6b

A dry two-necked round-bottomed flask (50 mL) equipped with a magnetic stirrer bar was charged with *trans*-2,4-dimethoxycinnamic acid **4** (2.0 g, 9.61 mmol), dimethylformamide (0.08 mL, 1.03 mmol) and CH_2Cl_2 (20 mL). The solution was cooled to 0 °C, and oxalyl chloride (1.73 mL, 1.98 mmol) was added dropwise over a 30-min period and the solution was stirred at room temperature until the evolution of gas ended. The solvent was evaporated in vacuo to give *trans*-2,4-dimethoxycinnamoyl chloride **5** as a dark green solid (due to the unstable nature of this compound it was stored in the freezer at −10 °C). Yield: 2.17 g (100%). A two-necked round-bottomed flask (50 mL) fitted with a magnetic stirring bar was charged with a solution of (*S*)-phenylglycinol (1.25 g, 9.12 mmol) and dry CH_2Cl_2 (20 mL) and the solution was cooled to 0 °C using an ice bath. Dry triethylamine (1.27 mL, 9.12 mmol) was added via syringe. A solution of *trans*-3-(2,4-dimethoxyphenyl)acryloyl chloride **5** (1.06 g, 4.68 mmol) in CH_2Cl_2 (5 mL) was slowly added via syringe to the vigorously stirred reaction mixture over 30 min. The ice bath was removed, and the reaction mixture was stirred at room temperature for a further 4 h. The reaction mixture was washed with 2 M HCl (12 mL), saturated aqueous $NaHCO_3$ (15 mL) and the aqueous layer was back-extracted with CH_2Cl_2 (15 mL). The combined organic extracts were washed with brine (15 mL), and the aqueous layer was back-extracted with CH_2Cl_2 (15 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to give (*S*)-*trans*-*N*-(2-hydroxy-1-phenylethyl)-2,4-dimethoxycinnamamide **6a** as an orange solid. The crude product was purified by column chromatography (silica gel, EtOAc) to afford amide **6a** as a white solid. Yield: 1.23 g (81%); mp 152.2–153.3 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.8 (d, 1H, J = 15.7 Hz, RC*H*=CRH), 7.35–7.25 (m, 6H, C*H*(Ar), 6.54–6.41 (m, 4H, N*H*, RCH=C*H*R, C*H*(Ar)), 5.18–5.14 (m, 1H, C*H*), 3.95–3.82 (m, 2H, CH_2), 3.80 (s, 3H, –OCH_3), 3.79 (s, 3H, –OCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.67, 162.20, 159.75, 139.16, 137.37, 130.78, 128.82, 127.78, 126.81, 118.44, 116.74, 105.03, 92.42, 66.80, 56.41, 55.38, 55.35 ppm. IR (KBr) ν_{max}: 3291, 3064.24, 3031.16, 2960.27, 2939.23, 2873.67, 2839.95, 1652.38, 1616.66, 1575.96, 1544.47, 1502.36, 1455.85, 1420, 1351.75, 1318.22, 1290.59, 1212.07, 1161.54, 1118.42, 1037.96, 975.72, 836.85, 798.59, 751.29, 698.05, 523.39 cm^{-1}. $[\alpha]_D^{22} = +13.7$ (c 1.22, $CHCl_3$). FAB-MS m/z: 328.16 $[M+H]^+$.

Compound **6b**: The same procedure as described previously was used in the reaction of *trans*-2,4-dimethoxycinnamoyl chloride **4** (1.12 g, 4.96 mmol) with (*S*)-*tert*-leucinol (0.64 g, 5.45 mmol) and dry triethylamine (1.06 mL, 7.44 mmol) to give (*S*)-*trans*-*N*-(1-hydroxy-3,3-dimethylbutan-2-yl)-(2,4-dimethoxycinnamamide **6b** as a white solid after purification by column chromatography (silica gel, EtOAc); Yield: 0.92 g (61%). mp 64–65 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.83 (d, 1H, J = 15 Hz, RC*H*=CHR), 7.36 (d, 1H, J = 9 Hz, C*H*(Ar)), 6.53 (d, 1H, J = 16 Hz, RCH=C*H*R), 6.39 (t, 2H, J = 6.6 Hz, C*H*(Ar)), 6.15 (d, 1H, J = 9 Hz, N–*H*), 4.03–3.88 (m, 2H, C*H*, C*H*H), 3.80 (s, 3H, –OCH_3), 3.79 (s, 6H, –OCH_3), 3.65–3.58 (m, 1H, CH*H*), 0.99 (s, 9H, (CH_3)$_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.39, 162.04, 159.57, 136.81, 130.43, 118.79, 116.81, 104.95, 98.31, 63.01, 59.66, 55.35, 33.75, 26.97 ppm. IR (KBr) ν_{max}: 3290.35, 3075.35, 2961.10, 2837.86, 1651.53, 1605.25, 1545.18, 1545.18, 1504.74, 1419.70, 1355.60, 1298.89, 1268.05, 1211.12, 1160.20, 1138.74, 1033.08, 985.76, 833.11, 798.31, 731.20, 634.75 598.38 cm^{-1}. $[\alpha]_D^{21} = -3.3$ (c 1.17, $CHCl_3$). TOF-MS m/z:

308.19 $[M+H]^+$ HRMS (TOF) found, 308.18563; $C_{17}H_{26}N_1O_4$ requires 307.17836.

4.2.2. General procedure for the synthesis of Arylid-OXs (1a and 1b)

A solution of methanesulfonyl chloride (0.21 g, 1.8 mmol) in dry CH_2Cl_2 (1 mL) was added dropwise over 20 min to a solution of cinnamamide **6a** (0.3 g, 6.12 mmol) and dry triethylamine (0.51 mL, 3.67 mmol) in dry CH_2Cl_2 (15 mL) and the solution was stirred between −5 and −10 °C. The reaction mixture was allowed to warm to room temperature and stirring was continued for 3 days. The reaction mixture was then poured into a saturated aqueous NH_4Cl solution (15 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated to afford the crude product. The crude product was purified by column chromatography (silica gel, EtOAc/Hex (1:1)) giving the (+)-(*S*)-*trans*-2-(2,4-dimethoxyphenyl)-(4-phenyloxazoline-2-yl)ethene **1a** as a white semi-solid. Yield: 0.278 g (98%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.64 (d, 1H, *J* = 16.4 Hz, RC*H*═CHR), 7.41 (d, 1H, *J* = 8.6 Hz, C*H*(Ar)), 7.33–7.29 (m, 2H, C*H*(Ar)), 7.26–7.21 (m, 3H, C*H*(Ar)), 6.71 (d, 1H, *J* = 16 Hz, RCH═C*H*R), 6.48 (dd, 1H, *J* = 8.5 and 2.3 Hz, C*H*(Ar)), 6.42 (d, 1H, *J* = 2.3 Hz, C*H*(Ar), 5.26 (dd, 1H, *J* = 10 and 8 Hz, CH*H*), 4.66 (dd, 1H, *J* = 10 and 8 Hz, C*H*H), 4.14 (t, 1H, *J* = 8.2 Hz, C*H*), 3.81 (d, 3H, *J* = 6 Hz, –OCH_3), 3.78 (d, 3H, *J* = 6 Hz, –OCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.30, 162.08, 159.22, 142.51, 135.69, 129.50, 128.96, 128.64, 127.43, 126.63, 117.21, 112.94, 105.13, 98.38, 74.24, 69.82, 55.37 ppm. IR (NaCl, $CHCl_3$): ν_{max} 3035.14, 3025.48, 3016.37, 2962.79, 1646.10, 1607.91, 1576.04, 1504.34, 1465.94, 1421.05, 1363.97, 1269.68, 1161.88, 1033.79, 994.42, 839.88, 790.23, 776.47, 700.94, 665.69 cm^{-1}. $[\alpha]_D^{22}$ = +7.7 (*c* 0.57, $CHCl_3$). FAB-MS *m*/*z*: 310.17 $[M+H]^+$.

Compound **1b:** Using the same procedure as described previously, cinnamamide **6b** (0.40 g, 1.3 mmol) was reacted with methanesulfonyl chloride (0.22 g, 1.95 mmol) and dry triethylamine (0.55 mL, 3.91 mmol) to give the (*S*)-*trans*-2-(2,4-dimethoxyphenyl)-(4-*tert*-butyloxazoline-2-yl)ethene **1b** as a yellow semi-solid after purification by column chromatography (silica gel, EtOAc:Hex (1:2)). Yield: 0.21 g (55%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.54 (d, 1H, *J* = 16.4 Hz, RC*H*═CHR), 7.42 (d, 1H, *J* = 8.5 Hz, C*H*(Ar)), 6.68 (d, 1H, *J* = 16.4 Hz, CRH═C*H*R), 6.5 (dd, 1H, *J* = 7.5 and 3 Hz, C*H*(Ar)), 6.44 (d, 1H, *J* = 2.3 Hz, C*H*(Ar)), 4.30–4.23 (m, 1H, C*H*), 4.13 (t, 1H, *J* = 9 Hz, C*H*H), 3.97 (dd, 1H, *J* = 8 and 9 Hz, CH*H*), 3.85 (s, 3H, –OCH_3), 3.83 (s, 3H, –OCH_3), 0.93 (s, 9H, C(CH_3)$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.01, 161.90, 159.04, 134.84, 129.22, 113.13, 105.02, 98.26, 75.83, 68.13, 55.22, 33.72, 25.75 ppm. IR (NaCl, $CHCl_3$): ν_{max} 3030.34, 3019.90, 2967.63, 1640.46, 1601.90, 1505.25, 1458.14, 1301.40, 1277.66, 1206.28, 1163.33, 1121.82, 1033.77, 931.21, 841.06, 780.98, 663.41 cm^{-1}. $[\alpha]_D^{21}$ = −38.3 (*c* 1.44, $CHCl_3$). TOF-MS *m*/*z*: 290.18 $[M+H]^+$. HRMS (TOF) found 290.17507 $C_{17}H_{24}N_1O_3$ requires 289.16779.

4.2.3. General procedure for the synthesis of malonamides 10a and 10b

A dry two-necked round-bottomed flask (50 mL) equipped with a magnetic stir bar was charged with 2-(2-chlorobenzylidene)malonic acid **8a** (4.8 g, 21.0 mmol), dimethylformamide (0.23 mL, 2.94 mmol) and CH_2Cl_2 (30 mL). The solution was cooled to 0 °C, and oxalyl chloride (4.6 mL, 53 mmol) was added dropwise over 30 min and the solution was stirred at room temperature until the evolution of gas ended. The solution was evaporated in vacuo to give 2-(2-chlorobenzylidene)malonyl chloride **9a** as a yellow semi-solid (due to the unstable nature of this compound it was stored in the freezer at –10 °C). Yield: 5.14 g (100%). A two-necked round-bottomed flask (50 mL) fitted with a magnetic stirring bar was charged with a solution of (*S*)-phenylglycinol (1.0 g, 7.30 mmol) and dry CH_2Cl_2 (20 mL) and the solution was cooled to 0 °C using an ice bath. Dry triethylamine (1.27 mL, 9.13 mmol) was added via syringe. A solution of 2-(2-chlorobenzylidene)malonyl chloride **9a** (0.96 g, 3.6 mmol) in CH_2Cl_2 (5 mL) was slowly added via syringe to the vigorously stirred reaction mixture over 30 min. The ice bath was removed, and the reaction mixture was stirred at room temperature for 4 h. The reaction mixture was washed with 2 M HCl (12 mL), saturated aqueous $NaHCO_3$ (15 mL) and the aqueous layer was back-extracted with CH_2Cl_2 (10 mL). The combined organic extracts were washed with brine (15 mL), and the aqueous layer was back-extracted with CH_2Cl_2 (15 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated in *vacuo* to give (*S*,*S*)-*N*,*N*′-bis(2-hydroxy-1-phenylethyl)-2-(2-chlorobenzylidene)malonamide **10a** as a yellow solid. The crude product was purified by column chromatography (silica gel, EtOAc) to afford the amide **11a** as a white solid. Yield: 0.69 g (41%); mp 79–80 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.12 (d, 1H, *J* = 8.1 Hz, N*H*), 7.88 (s, 1H, RC*H*═CR_2), 7.41 (d, 1H, *J* = 8.1 Hz, N*H*), 7.32–7.12 (m, 10H, C*H*(Ar)), 7.02–7.00 (m, 3H, C*H*(Ar)), 6.90–6.85 (m, 2H, C*H*(Ar)), 5.22–5.12 (m, 2H, C*H*), 3.93–3.62 (m, 4H, CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.66, 164.43, 138.39, 137.59, 136.57, 134.35, 133.10, 131.78, 130.49, 129.83, 129.50, 128.80, 128.68, 128.56, 127.80, 127.70, 126.88, 126.72, 66.03, 66.43, 56.42, 55.98 ppm. IR (KBr) ν_{max}: 3270.75, 3061.11, 3031.37, 2928.83, 2875.23, 1664.61, 1529.25, 1454.52, 1373.48, 1262.64, 1205.16, 1053.98, 1035.17, 950.65, 910.67, 839.09, 804.63, 756.08, 699.96, 636.69, 531.42 cm^{-1}. $[\alpha]_D^{20}$ = +62.2 (*c* 1.03, $CHCl_3$). TOF-MS *m*/*z*: 465.16 $[M+H]^+$; HRMS (TOF) found 465.15756, $C_{26}H_{26}N_2O_4Cl_1$ requires 464.15029.

Compound **10b**: The same procedure as described previously was used in the reaction of 2-(2-methoxy-benzylidene)malonyl chloride **9b** (0.95 g, 3.65 mmol) with (*S*)-phenylglycinol (1.0 g, 7.3 mmol) and dry triethylamine (1.27 mL, 9.13 mmol) to give (*S*,*S*)-*N*,*N*′-bis(2-hydroxy-1-phenylethyl)-2-(2-methoxybenzylidene)malonamide **10b** as a white solid after purification by column chromatography (silica gel, EtOAc); Yield: 0.884 g (53%). mp 130.2–131.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.4 (d, 1H, *J* = 7.8 Hz, N*H*), 7.95 (s, 1H, RC*H*═CR_2), 7.32–7.17 (m, 11H, C*H*(Ar)), 7.03–7.01 (m, 2H, N*H*, C*H*(Ar)), 6.72–6.66 (m, 2H, C*H*(Ar)), 5.20–5.13 (m, 2H, C*H*), 3.87–3.63 (m, 4H, CH_2), 3.55 (s, 3H, –OCH_3), 3.32 (sb, 1H, –O*H*), 2.06 (sb, 1H, –O*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.50, 164.77, 157.47, 138.65, 137.92, 136.51, 131.04, 130.70, 129.88, 128.65, 127.69, 127.63, 126.88, 126.71, 122.42, 120.50, 110.68, 66.46, 65.61, 56.37, 55.88, 55.14 ppm. IR (KBr) ν_{max}: 3333.23, 3247.66, 3061.21, 2939.26, 2939.26, 2878.50, 2837.51, 1656.85, 1601.89, 1534.53, 1489.62, 1462.37, 1436.63, 1373.17, 1283.52, 1247.93, 1196.21, 1127.67, 1050.56, 1027.27, 901.51, 850.75, 753.43, 700.98, 637.15, 526.94 cm^{-1}. $[\alpha]_D^{22}$ = +62.2 (*c* 0.85, $CHCl_3$). FAB-MS *m*/*z*: 416.27 $[M+H]^+$.

4.2.4. General procedure for the synthesis of Arylid-Box 2a and 2b

A solution of methanesulfonyl chloride (0.15 g, 1.3 mmol) in dry dichloromethane (1 mL) was added dropwise over 20 min to a solution of malonamide **10a** (0.2 g, 0.43 mmol) and dry triethylamine (0.36 mL, 2.58 mmol) in dry dichloromethane (10 mL) and the solution was stirred between −5 and −10 °C. The reaction mixture was allowed to warm to room temperature and stirring was continued for 3 days. The reaction mixture was then poured into a saturated aqueous NH_4Cl solution (10 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated to afford the crude product. The crude product was purified by column chromatography

(silica gel, EtOAc:Hex (1:2)) giving the (+)-bis[(*S*)-4-phenyloxazoline-2-yl]-2-(2-chlorophenyl)ethene **2a** as a white semi-solid. Yield: 0.11 g (60%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.99 (s, 1H, $R_2C{=}CHR$), 7.65 (d, J = 7.2 Hz, C*H*(Ar)), 7.45–7.18 (m, 12H, C*H*(Ar)), 5.47 (t, 1H, J = 9.3 Hz, C*H*), 5.35–5.29 (m, 1H, C*H*), 4.84–4.69 (m, 2H, CH_2), 4.27–4.18 (m, 2H, CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.02, 161.36, 141.97, 141.70, 138.80, 132.83, 128.68, 128.54, 126.91, 126.73, 126.66, 120.82, 74.92, 70.33 ppm. IR (NaCl, $CHCl_3$): ν_{max} 3030.55, 3016.64, 3011.29, 1671.60, 1639.05, 1494.09, 1473.40, 1454.80, 1409.44, 1355.76, 1261.55, 1230.10, 1209.92, 1182.48, 1021.59, 935.88, 790.36, 755.96, 665.58 cm^{-1}. $[\alpha]_D^{20} = +50.3$ (c 1.89, $CHCl_3$). TOF-MS m/z: 428.13 $[M+H]^+$; HRMS (TOF) found 429.2073; $C_{26}H_{22}N_2O_2Cl_1$ requires 428.12916.

Compound **2b**: Using the same procedure as described previously, malonamide **10b** (0.40 g, 8.69 mmol) was reacted with methanesulfonyl chloride (0.25 g, 2.17 mmol) and dry triethylamine (0.73 mL, 5.21 mmol) to give the (+)-bis[(*S*)-4-phenyloxazoline-2-yl]-2-(2-methoxyphenyl)ethene **2b** as a white solid after crystallization with CH_2Cl_2/EtOAc/Hex. Yield: 0.29 g (80%); mp 167.0–168.0 °C ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.05 (s, 1H, $R_2C{=}CHR$), 7.60 (d, 1H, J = 6.6 Hz, C*H*(Ar)), 7.36–7.27 (m, 8H, C*H*(Ar)), 7.25–7.22 (m, 3H, C*H*(Ar)), 6.89 (t, 2H, J = 6.9 Hz, C*H*(Ar)), 5.48–5.32 (m, 2H, C*H*), 4.81–4.72 (m, 2H, CH_2), 4.26–4.18 (m, 2H, CH_2), 3.85 (s, 3H, $-OCH_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.63, 162.22, 156.81, 142.29, 142.00, 137.72, 129.41, 128.61, 128.49, 126.98, 126.74, 123.30, 120.35, 118.17, 110.68, 74.84, 74.81, 70.20, 70.10, 55.49 ppm. IR (KBr) ν_{max}: 3057.47, 3024.99, 3002.36, 2972.93, 2941.31m 2908.30, 2852.81, 2605.41, 2496.44, 1676.68, 1633.40, 1597.21, 1576.55, 1489.23, 1467.47, 1450.61, 1403.22, 1355.34, 1318.32, 1299.83, 1250.74, 1200.81, 1176.47, 1113.87, 1018.05, 962.11, 936.94, 910.55, 756.63, 701.76, 641.56, 596.73, 526.34 cm^{-1}. $[\alpha]_D^{20} = +137.8$ (c 0.94, $CHCl_3$). TOF-MS m/z: 425.18 $[M+H]^+$. HRMS (TOF) found, 425.18597; $C_{27}H_{25}N_2O_3$ requires 424.17869.

4.3. Cyclopropanations using $[Cu(OTf)]_2{\cdot}(C_6H_6)$ and $[Cu(MeCN)_4]PF_6$ pre-catalysts

Pre-catalyst (0.014 mmol, 1 mol %) or (0.028 mmol, 2 mol %) was added to a two-necked round-bottomed flask containing the chiral ligand (2.1–6.3 mol %) in CH_2Cl_2 (1 ml) and the solution was stirred at room temperature for 15 min under a nitrogen atmosphere. Alkene (14 mmol) and a solution of ethyl diazoacetate (0.159 g, 1.4 mmol) in CH_2Cl_2 (1 ml) or toluene (1 ml) were then added to the reaction mixture over a period of 16 h using a syringe pump. After the addition of ethyl diazoacetate, the mixture was stirred for 16 h. The reaction mixture was firstly passed through a short pad of silica gel (washed with CH_2Cl_2) to remove the catalyst complex, the products were then isolated by column chromatography (hexane/EtOAc 9:1). All cyclopropane products were obtained as a mixture of *cis* and *trans* diastereomers, and the ratio was determined using GC analysis. Isolated yields, diastereoselectivities and enantioselectivities are given in Tables 1 and 5.

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