Tetrahedron 67 (2011) 4640–4648

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Chiral monooxazolines as modular copper(I)-heterocomplex building blocks: investigations on the catalytic asymmetric cyclopropanation of alkenes

Elisabete P. Carreiro [a,b], J.P. Prates Ramalho [a,b], Anthony J. Burke [a,b,*]

[a] Centro de Química de Évora, Universidade de Évora, Rua Romão Ramalho, 59, 7000 Evora, Portugal
[b] Departamento de Química, Universidade de Évora, Rua Romão Ramalho, 59, 7000 Evora, Portugal

ARTICLE INFO

Article history:
Received 22 February 2011
Received in revised form 10 April 2011
Accepted 15 April 2011
Available online 21 April 2011

Keywords:
Mono(oxazoline)
Arylid-OX
Asymmetric catalysis
Cyclopropanation
Homocomplex
Heterocomplex
π–π interactions

ABSTRACT

Novel chiral monodentate oxazoline ligands have been synthesized in good yields. The catalytic activity of these monodentate oxazoline/Cu catalysts was evaluated in the catalytic asymmetric cyclopropanation of styrene and α-methylstyrene, giving moderate to good enantioselectivities (up to 74% ee for the *trans*-cyclopropane product) and full conversions (up to 100%). In an attempt to enhance the enantioselectivities of the cyclopropanations, heterocombinations of these ligands were used. Unfortunately, with the data set that was used in this study, no improvements were observed. However, to gain an insight into the nature of the active catalyst present under these circumstances, NMR, mass spectrometric and computational studies were carried out and indicated the presence of bidentate heterocomplexes in the equilibrium mixture. Analysis of the stereoselectivities (ees and des) did not prove very useful in pinpointing the identity of the active chiral catalyst and only afforded a very weak conclusion. In order to ascertain the importance of the π–π interactions, the monodentate oxazoline ligands **3a** and **3b** were synthesized and screened in these reactions, and the resulting stereoselectivities were compared to the results obtained using ligands **1a** and **1b**. There seemed to be very weak π–π interactions at work.

1. Introdution

Over the last number of years chiral monodentate ligands have proven their potential in numerous transition-metal-catalyzed asymmetric transformations. Although there is enormous 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, which 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 multi-dentate ligands, thus the synthesis in principle is less demanding. For example, Binol-based modular mono-phosphonites,[1] mono-phosphites[2] and mono-phosphoramidites[3] so far have been the principle monodentate ligand to be investigated, often leading to medium or high enantioselectivities in diverse asymmetric catalytic reactions when metals like Rh or Cu were used. Oxazoline ligands are superior to phosphine ligands in that they are stable to both hydrolysis and oxidative conditions, a considerable advantage when compared to the latter family, which are easily converted into phosphine oxides.[4] Monodentade oxazolines were applied successfully in catalytic asymmetric cyclopropanations,[5,6] in catalytic enantioselective [2+2+2] cycloadditions with Ni[7] and in enantioselective Diels–Alder reactions.[8,9] All of these reactions showed moderate stereoselectivity.

Chiral olefinic ligands have been shown to be useful in catalytic asymmetric synthesis and have been the subject of various reviews.[10a–c] In fact, recently, Glorius et al. introduced a new family of modular oxazolines, which are olefin/oxazolines (abreviated OlefOX).[10d] They were tested in Rh catalyzed conjugate additions of phenylboronic acid to cyclohexenone, and gave very good enantioselectivities. However, theses ligands are true bidentate ligands as the coordination to the Rh is via the oxazoline nitrogen and the olefinic bond. Monodentate ligands are very empowering as they allow for the creation of a large diversity of chiral catalysts, and are very amenable for application in combinatorial enantioselective catalysis using mixtures of such ligands. The first combinatorial homogeneous asymmetric catalysis using the concept of mixing chiral monodentate ligands was reported simultaneously by Reetz[11] and Feringa.[12] Using this concept in some catalytic asymmetric hydrogenations[11,12a] and in the conjugated addition of arylboronic acids[12b] it was possible to enhance the enantioselectivities, as well as the reaction rate, by simply mixing two known monodentate ligands. The heterocomplex formed was assumed to be the active catalyst.

In this paper, we introduce two families of olefinated monodentate oxazolines, designated Arylid-OX **2** and Propen-OX **3**, (Fig. 1). The design and synthesis of the Arylid-OX **1** family (Arylid-

* Corresponding author. Tel.: +351266745310; fax: +351266745303; e-mail address: ajb@dquim.uevora.pt (A.J. Burke).

0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.04.066

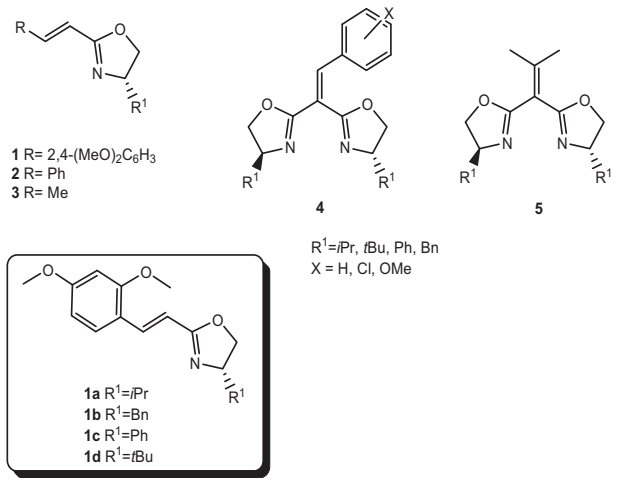
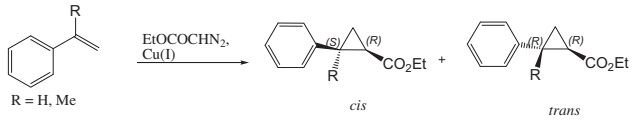


Fig. 1. Structures of monodentate oxazolines (**1**–**3**) and bis(oxazolines) (**4**,**5**).

OXs **1c** and **1d** have previously been reported for the catalytic asymmetric cyclopropanation reaction, CACP)[6] was inspired by the known Arylid-BOX **4**[13,14] and Isbut-BOX **5**[15] ligands developed by our research group. These ligands were tested in the catalytic asymmetric cyclopropanation of alkenes with ethyl diazoacetate (EDA) using $[Cu(MeCN)_4]PF_6$ and Cu(I)OTf as the pre-catalysts (Scheme 1).



Scheme 1. Asymmetric cyclopropanation of styrenes—the benchmark reaction for this study.

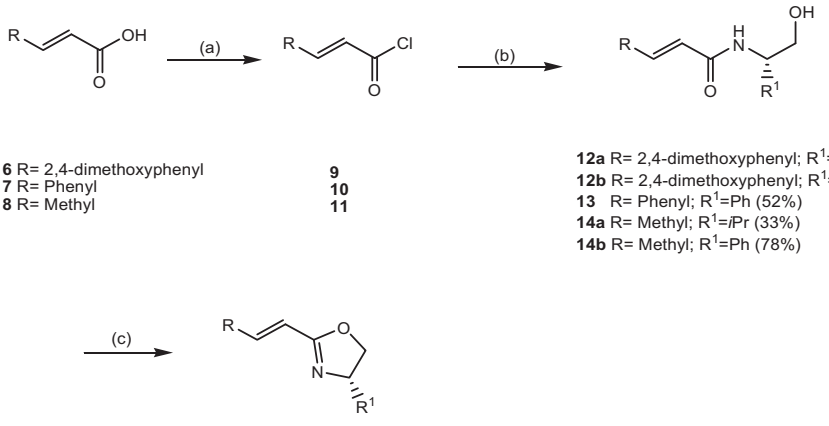
2. Results and discussion

The Arylid-OX families **1** and **2** and Propen-OX **3** were prepared in good yields using the synthetic pathway shown in Scheme 2. The carboxylic acid precursor was obtained via the procedure reported by Neustadt et al.[16] using a simple Knoevenagel condensation with malonic acid and the respective aldehyde. Our standard synthetic procedure was subsequently used to transform the acids to the corresponding ligands.[14,15]

2.1. Asymmetric catalytic cyclopropanation: homo- and heterocombinations of mono(oxazolines)

The novel monodentate mono(oxazolines) were evaluated in the Cu(I)-catalyzed asymmetric cyclopropanation of styrene and α-methylstyrene using ethyl diazoacetate (EDA) (Scheme 1). The catalyst was generated in situ by the addition of the pre-catalyst, $[Cu(MeCN)_4]PF_6$, and the relevant chiral mono(oxazoline) **1**–**3** in catalytic quantities, followed by the addition of excess alkene and then by the slow addition of EDA. This method had previously been established and optimized by our research group for the bisoxazolines **4**–**5**.[13–15] The reactions were conducted in both CH_2Cl_2 and toluene to determine the influence of both polar and apolar solvents. The reactions with toluene required heating for activation, but, unfortunately, heating probably destroyed or deactivated the catalyst, as the yield was poor. Given the distinct possibility of having π–π interactions at play, we focused on three types of Arylid-OX or Alkylid-OX ligands, namely, **1**, **2** and **3** (Scheme 2). The Arylid-OX ligands **1** contained a very electron-rich π-system. In fact, computational studies (vide infra) show that the aryl group is co-planar with the C=C. It was hoped that this extensive π-electron delocalization would promote significant π–π interactions, leading to more compact Cu-catalysts that would promote better asymmetric induction.[17] To test this hypothesis, the two ligand families, type **2**, with only a phenyl group in the back-bone, and thus expected to show less intense π–π interactions with lower reaction enantioselectivities expected, and type **3**, bereft of an aryl-backbone group, and thus expected to manifest even lower reaction enantioselectivities, were prepared and screened.

The homocombinations of Arylid-OXs **1a**/**1a** and **1b**/**1b** were tested in some catalytic asymmetric cyclopropanations with Cu(I) and styrene (Table 1). For comparative purposes, the Cu(I) catalyst was applied at two loading levels: 0.36 and 2 mol %, respectively. Unfortunately, the yields were low for all the reactions studied (6–37%). In the case of **1a**/**1a** the best enantioselectivity obtained was 48% ee for the *cis*-cyclopropane product using 6.3 mol % of ligand, on the other hand, with ligand **1b** the best enantioselectivity obtained was 45% ee for the *cis*-cyclopropane at a loading of only



Scheme 2. Reagents and Conditions: (a) $(COCl)_2$, DMF, CH_2Cl_2, 0 °C; (b) (*S*)-Phenylglycinol or (*S*)-Valinol or (*S*)-Phenylalaninol, NEt_3, CH_2Cl_2; (c) CH_3SO_2Cl, NEt_3, CH_2Cl_2.

Table 1
Catalytic asymmetric cyclopropanation of styrene.[a]

Entry	Oxazoline (mol %)	$Cu(MeCN)_4PF_6$ (mol %)	Yield (%)[c]	ee *cis* (%)[d]	ee *trans* (%)[d]	*cis*/*trans*[d]	Maleate/fumerate: cyclopropanes[d]
Homocombinations							
1	**1a**/**1a** (1.13)	0.36[b]	6	27	24	37:63	29:71
2	**1a**/**1a** (6.3)	2	12	48	37	39:61	3:97
3	**1b**/**1b** (1.13)	0.36[b]	4	45	35	38:62	26:74
4	**1b**/**1b** (6.3)	2	10	32	25	37:63	10:90
5	**1d**/**1d** (6.3)	2	34	51	58	31:69	14:86
6	**3b**/**3b** (6.3)	2	10	46	32	34:66	22:78
7	**3a**/**3a** (6.3)	2	17	42	33	44:56	16:84
Heterocombinations							
8	**1a**/**1b** (1.13)	0.36[b]	11	40	32	30:60	10:90
9	**1a**/**1d** (1.13)	0.36[b]	37	37	30	34:66	8:92

[a] Styrene (4 equiv), chiral ligand, Cu(I) pre-catalyst, ethyl diazoacetate (1 equiv), CH_2Cl_2, rt, 24 h.
[b] Styrene (0.7 equiv), chiral ligand, Cu(I) pre-catalyst, ethyl diazoacetate (1 equiv), CH_2Cl_2, rt, 24 h.
[c] Yield determined from the mass of isolated crude product isomers.
[d] Determined by chiral GC.

1.13 mol % of ligand. The formation of maleates at a loading of only 0.36 mol % of Cu(I) was considerably high with both ligands, this was evidently due to the presence of excess EDA under these conditions. The cis/trans ratio of the diastereomers did not change much. On comparing the homocombinations of **3a**/**3a** with **3b**/**3b**, it was **3a**/**3a** that gave the best enantioselectivity (46% ee for *cis*-cyclopropane) and the best diastereoselectivity (32% de), but the yield was lower and was due to the presence of a greater proportion of maleate/fumerate (Table 1, entry 6). Surprisingly, in all cases, the *cis*-cyclopropane gave a higher enantioselectivity than the *trans*-cyclopropane (the predominant isomer). On increasing the loading of pre-catalyst from 0.36 to 2 mol % there was a significant increase in the enantioselectivity for the homocombination **1a**/**1a** (Table 1, entries 1 and 2). The yield doubled as expected. In the case of **1b**/**1b** the enantioselectivity actually decreased. The yield also more than doubled. The lower yields obtained at the lower catalyst loading level, were most probably a consequence of the dimerization side-reaction, which was obviously enhanced by the presence of less styrene in the reaction mixture.

The formation of heterocomplexes was also investigated, by mixing two types of ligands. To this end, ligands **1a** and **1b** together with Cu(I), were combined in equimolar amounts. It was expected that the three catalyst types—i.e., $(\mathbf{1a})_2$Cu, $(\mathbf{1b})_2$Cu and (**1a1b**)Cu—would prevail in solution as a 1:1:2 mixture, having the heterocomplex (**1a1b**)Cu as the most active species based on literature precedent.[12b] Unfortunately, in the case of both heterocombinations using **1a**/**1b** and **1a**/**1d** (Table 1, entries 8–9), the enantioselectivities obtained were not as high as the two homocombinations of the respective ligands.

The catalytic asymmetric cyclopropanation of α-methylstyrene with all homocombinations of the mono(oxazoline) ligands were tested in the same proportion ((6.3:2) ligand: $Cu(I)(CH_3CN)_4PF_6$) (Table 2). Generally they gave very good conversions with this substrate, the *trans*-cyclopropane (the predominant isomer) gave the best enantioselectivity. The best enantioselectivity obtained was 74% ee with only 0.36 mol % of the homocombination **1d**/**1d** (Table 2, entry 6), this was undoubtedly due to the presence of the bulky *tert*-butyl group. In the case of **3a**/**3a** and **3b**/**3b**, the

Table 2
Catalytic asymmetric cyclopropanation of α-methylstyrene[a]

Entry	Oxazoline (mol %)	$Cu(MeCN)_4PF_6$ (mol %)	Conversion (%)[c]	ee *cis* (%)[c]	ee *trans* (%)[c]	*cis*/*trans*[c]	Maleates: cyclopropanes[c]
Homocombinations							
1	**1a**/**1a** (1.13)	0.36[b]	86	14	45	46:54	10:90
2	**1a**/**1a** (6.3)	2	94	22	42	45:55	2:98
3	**1b**/**1b** (6.3)	2	86	41	63	42:58	21:79
4	**1c**/**1c** (1.13)	0.36[b]	99	24	47	46:54	20:80
5	**1c**/**1c** (6.3)	2	100	34	44	46:54	4:96
6	**1d**/**1d** (1.13)	0.36[b]	100	42	74	43:57	9:91
7	**2**/**2** (1.13)	0.36[b]	98	22	29	46:54	10:90
8	**2**/**2** (6.3)	2	98	27	37	47:53	9:91
9	**3b**/**3b** (6.3)	2	92	35	39	47:53	12:88
10	**3b**/**3b** (6.3)	2[d]	98	12	24	46:54	12:88
11	**3a**/**3a** (6.3)	2	98	32	44	50:50	10:90
Heterocombinations							
12	**1a**/**1b** (6.3)	2	90	31	52	44:56	6:94
13	**1a**/**1c** (6.3)	2	80	24	46	44:56	57:43
14	**1b**/**1c** (6.3)	2	89	38	57	44:56	26:74
15	**1c**/**2** (6.3)	2	87	29	44	44:56	35:65
16	**1c**/**3b**(6.3)	2	94	38	44	45:55	18:82
17	**2**/**3b** (6.3)	2	100	37	44	45:55	7:93
18	**3a**/**3b** (6.3)	2	95	37	43	47:53	16:84

[a] α-Methylstyrene (4 equiv), chiral ligand, Cu(I) pre-catalyst, ethyl diazoacetate (1 equiv), CH_2Cl_2, rt, 24 h.
[b] α-Methylstyrene (0.7 equiv), chiral ligand, Cu(I) pre-catalyst, ethyl diazoacetate (1 equiv), CH_2Cl_2, rt, 24 h.
[c] Determined by chiral GC.
[d] Toluene, T=40 °C, t=48 h.

difference in the enantioselectivities obtained was small, ligand **3a** gave the best enantioselectivity for the *trans*-cyclopropane product (Table 2, entry 11, 44% ee), but there was no diastereoselectivity. Toluene was used with homocombination **3b**/**3b**, but the enantioselectivities for both isomers decreased approximately half, this was probably due to the higher reaction temperature leading to lower asymmetric induction with most likely, some catalyst decomposition. The highest diastereoselectivity achieved was 37% de using the homocomplex derived from **1d** and styrene (Table 1, entry 5).

A point needs to be made regarding the potential π–π interactions that were expected to enhance the reaction enantioselectivity and thus integrated into the ligand design. An analysis of the enantioselectivity and diastereoselectivity results (only for the homocombinations) for the cyclopropanation of both styrene and α-methylstyrene seemed to indicate very weak π–π interactions, as the differences in ees and des on changing the ligand were quite small. In the case of the cyclopropanation of styrene with **1a**, ees of 48% (*cis*) and 37% (*trans*) with a de of 22% were obtained (Table 1, entry 2), but for **3a** lower ees of 42% (*cis*) and 33% (*trans*), with a de of 12% (Table 1, entry 7) were obtained, clearly supporting the possibility of stronger π–π interactions being present in the case of the reaction with the former ligand system. However, in the case of α-methylstyrene, this was not so clear cut. For example, with **1a** ees of 22% (*cis*) and 42% (*trans*) with a de of 10% (Table 2, entry 2) were obtained, but for **3a**, ees of 32% (*cis*) and 44% (*trans*) were obtained with no diastereoselectivity (Table 2, entry 11). This was puzzling, if not contradicatory, as on the one hand the drop in diastereoselectivity on going from **1a** to **3a** might indicate weaker π–π interactions, but on the other hand, the increase in the ee of the cis-isomer with **3a** would seem to suggest otherwise. On comparing **1c** with **3b** (Table 2, entries 5 and 9) there was virtually no change in the stereoselectivities.

It was the homocomplexes that gave the highest enantioselectivities and diastereoselectivities.

In order to ascertain the catalyst stability during the catalytic reactions, two key reactions with α-methylstyrene as substrate were realized. These studies, which involved monitoring the variation of enantioselectivity over time (a 24 h period) were conducted with the homocomplex of **1c** and the heterocombination of **1b** and **1c**.[18] In the case of the homocomplex the enantioselectivity remained constant throughout. In the case of the heterocombination, the ee ascended to its maximum after about 1.5 h and remained there till the end.

2.2. NMR study

An insightful NMR study of the homocomplexes (**1a**)$_2$-Cu(I), (**1b**)$_2$-Cu(I) (as standards), and of the heterocombination of **1a**, **1b** and Cu(I) was also carried out. The complexes were prepared inside an NMR tube in dry $CDCl_3$ and the ligands were combined in equimolar amounts, together with 1 equiv of the Cu(I) pre-catalyst. The results are shown in Fig. 2 (the proposed signal attributions are shown in Table 3). The goal was to confirm exactly the types of complexes present in solution in order to gain an insight into the nature of the catalytic active species.

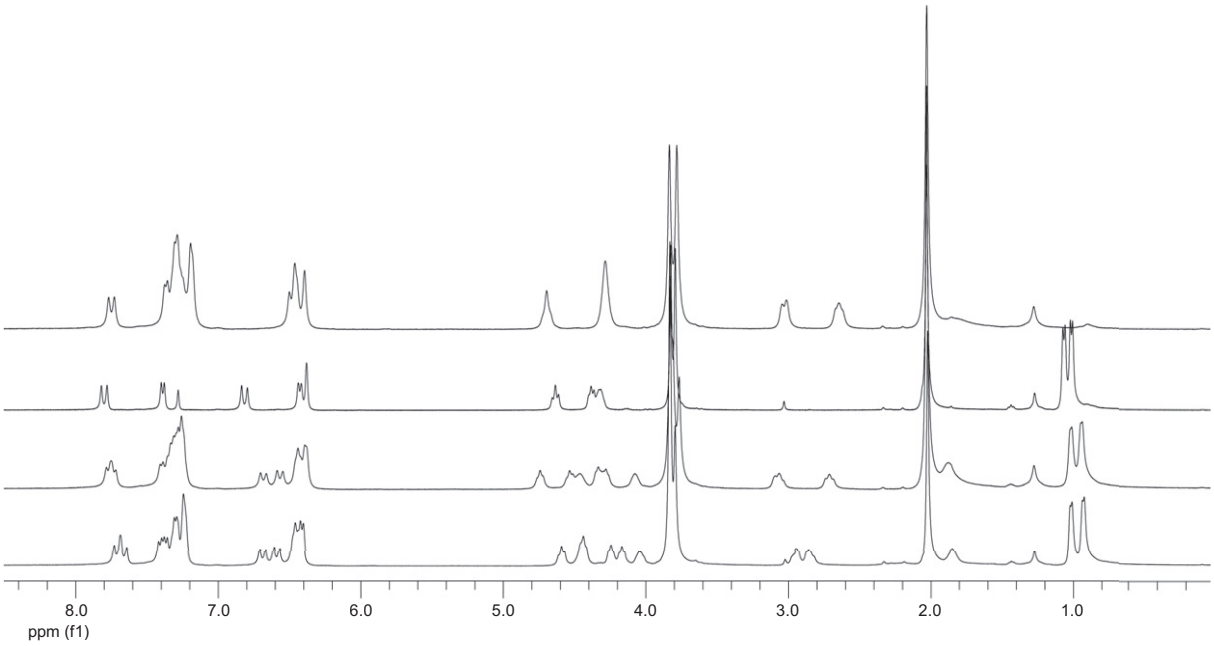


Fig. 2. ^{1}H NMR spectra of the homo- and heterocomplexes.

Table 3
Proposed attributions for the ^{1}H NMR spectra of the homo- and the putative heterocomplex ((**1a1b**)Cu(I))

Entry	Ligand/complex	δ (ppm)						
		H-1		H-2	H-2′	H-3		H-4
1	**1a**	4.32		4.00	[a]	6.66		7.54
2	**1b**	4.51		4.04	4.28	6.66		7.58
3	Cu(I)-(**1a**)$_2$	4.61		4.36		6.80		7.78
4	Cu(I)-(**1b**)$_2$	4.66		4.25		6.42		7.72
5	Cu(I)-(**1a1b**)[b]	4.74	4.07	4.51	4.31	6.69	6.57	7.75
6	Cu(I)-(**1a1b**)$_2$[b]	4.60	4.05	4.45	4.22	6.70	6.60	7.70

[a] Not observed, presumably hidden by the phenyl signal.
[b] This complex is believed to be the predominat complex in solution.

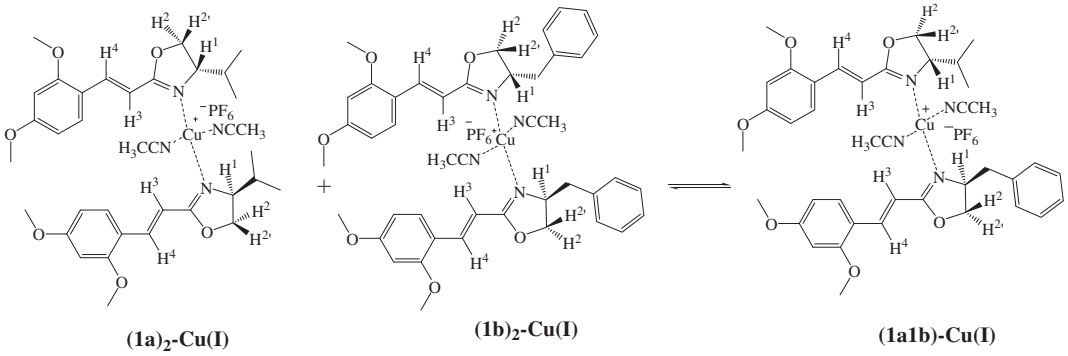
Analysis of the ^{1}H NMR spectra obtained for the (2:1) mono (oxazoline)/Cu(I) mixture, suggested the presence of the (**1a1b**)-Cu(I) complex, as two well defined doublets for the H_3 protons with coupling constants of 15 Hz (δ=6.69 ppm) and 16.8 Hz (δ=6.57 ppm) were observed. The signal corresponding to these protons in the spectrum for the (**1b**)$_2$-Cu(I) complex appears to be overlapped with the aromatic peaks. The signals for H-1 in the

spectra of the homocomplexes (**1a**)$_2$-Cu(I) and (**1b**)$_2$-Cu(I) appeared at 4.61 and 4.66 ppm, respectively, and these hydrogens in the spectrum of the heterocomplex **1a**/**1b**-Cu(I) appeared at 4.74 and 4.07 ppm, respectively. The purported equilibrium is shown in Scheme 3. Coordination of the ligands with Cu is expected to increase the chemical shifts of the H-1 signals due to electron donation from the oxazoline group. The H-1 signals for both ligands in the putative heterocomplex show a greater separation. When the ratio of the ligands to Cu was doubled, the chemical shifts decreased in the case of the putative H-1, H-2 and H-2′ protons (see Table 3, entry 6), indicating an equilibrium with the free ligand. Low temperature experiments were also conducted (down to −25 °C) in an effort to try and calculate the equilibrium constant for this process, but unfortunately, they were inconclusive.

presence of the two ligands, as well as both homocomplexes Cu(I)-(**1a**)$_2$ and Cu(I)-(**1b**)$_2$ and the heterocomplex Cu(I)-(**1a1b**) (in all cases without any coordinated MeCN ligands and having one methoxyl group cleaved off). These were the principle peaks in the spectrum.

2.3. Computational study

A quantum chemical theoretical study was carried out to verify if the heterocomplex is more likely to be the predominant complex in the equilibrium mixture in solution. Considering the number and size of these systems a semi-empirical method was considered the best choice for geometry optimization. The geometries were fully optimized in Cartesian coordinates by employing the novel PM6 Hamiltonian[19] included in the recent version of MOPAC 2007



Scheme 3. Postulated equilibrium between the homocomplexes ((**1a**)$_2$Cu(I) and (**1b**)$_2$Cu(I)) and the putative heterocomplex ((**1a1b**)Cu(I)).

In the case of the heterocombination (Table 3, entry 5) some comments need to be made regarding the increase in the chemical shift for one of the H-1 signals (to 4.74 ppm), and the decrease in the chemical shift in the case of the other H-1 signal (to 4.07 ppm). This is most probably due to some deshielding/shielding effect. Analysis of the calculated structure for Cu(I)-(**1a1b**) showed that the H-1 of **1a** appears to be close to the C=C bond of the other ligand, and perhaps sits in the deshielding zone of the latter. This is quite likely as the distance calculated between H-1 and H-3 (other ligand) was only 2.662 Å. In the case of the second H-1, analysis of the same model, seems to indicate that it lies in the shielding zone of one of the nitrile ligands.

(Fig. 3).[20] The same method has already been successfully employed in a previous study of Cu(I) complexes by us[14] and others[21] whose results (in our case) showed good agreement with the X-ray crystallographic data.[14] Frequency calculations further performed indicated that the stationary points obtained were minima. Following the initial geometry optimization with the PM6 method, Density Functional Theory (DFT) calculations were carried out on all complexes. These calculations were performed using the B3LYP[22,23] functional as included in the Gamess package.[24] 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. The binding energy for each heterocomplex was obtained by calculating the

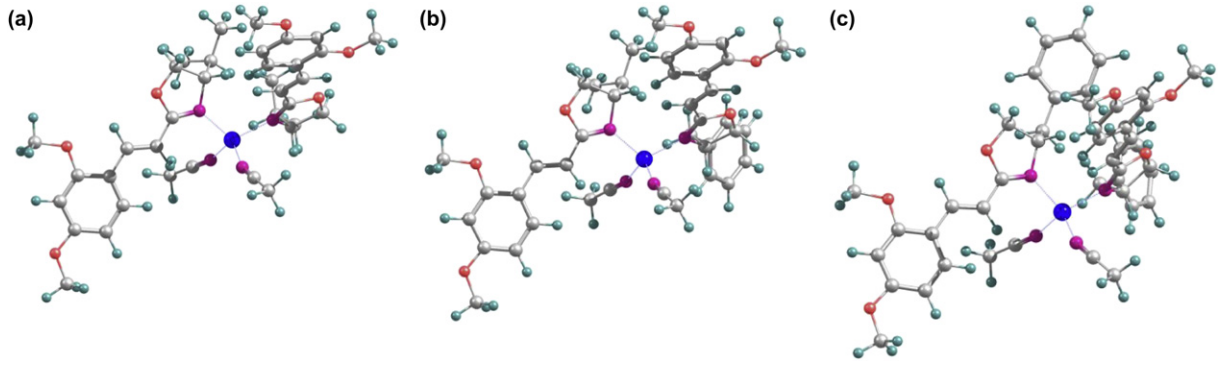


Fig. 3. Calculated structure for the Cu(I) complexes: (a) Cu(I)-**1a**$_2$(MeCNCu(I)-**1a**$_2$), (b) Cu(I)-**1b**$_2$(MeCN$_2$), and Cu(I)-**1a1b**$_2$(MeCN$_2$).

An insightful mass spectrometric study was also conducted that corroborates the observations obtained with the NMR study. Ligands **1a** and **1b** were mixed with [Cu(MeCN)$_4$]PF$_6$ in a ratio of 3:3:2 in dichloromethane at room temperature and after 2 h the solvent was removed and the remaining mixture was analyzed by ESI-TOF mass spectrometry.[18] Analysis of the resulting spectrum showed the

energy difference 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/Lanl2DZ, 6-31G*//PM6 method are depicted in Table 4. The calculations show that it is the heterocomplex—Cu(I)-**1a1b**(MeCN)$_2$—which has the lowest ΔE value indicating a higher stability for this complex.

Table 4
Calculated energies for complexes: Cu(I)-**1a**$_2$(MeCN)$_2$, Cu(I)-**1b**$_2$(MeCN)$_2$ and Cu(I)-**1a1b**(MeCN)$_2$ at the B3LYP/Lanl2DZ, 6-31G*//PM6 level

Chemical species	Total energy (au)	ΔE (kcal/mol)	ΔE_{rel} (kcal/mol)
Cu(I)-(**1a**)$_2$	−2265.7216795	−157.370	0.000
Cu(I)-(**1a1b**)	−2418.0626597	−161.709	−4.339
Cu(I)-(**1b**)$_2$	−2570.3924010	−158.996	−1.626
1a	−902.1820275	—	—
1b	−1054.5160923	—	—
MeCN	−132.6734221	—	—
Cu(I)	−195.7599954	—	—

These results support the conclusions obtained from both ^{1}H NMR spectroscopy and mass spectrometric experiments. Although these calculations indicate a slightly greater stability for the heterocomplex (Cu(I)-**1a1b**(MeCN)$_2$), this does not mean that this complex is the most active chiral catalyst present.[25]

2.4. The active chiral catalyst in the heterocombination case

From the previous studies (Sections 2.2 and 2.3) there is strong evidence that only three types of complex are present in the heterocombination case; i.e., two homocomplexes and one heterocomplex. Given the impossibility of isolating the heterocomplexes, attempts were made at trying to identify patterns in this data, which would indicate the active chiral catalyst under these conditions. However, this proved to be a very non-trivial exercise, as there was very little variation in the enantioselectivities and diastereoselectivities for the various systems studied (13 and 16% maximum for the enantioselectivity and diastereoselectivity, respectively). Only the results obtained with α-methylstyrene were considered, as the yields obtained with styrene were very poor and no meaningful conclusions could be drawn under these circumstances. However, the following key observations were made with α-methylstyrene leading to some weak conclusions. It was observed that in some cases the enantioselectivities for the cis and trans isomers were an average of those values obtained for the homocomplex cases. For example, in the case of the heterocombination of **1a**/**1b** ees of 31% (*cis*) and 52% (*trans*) with a de of 12% (Table 2 entry 12) were obtained, whereas for the homocombination cases, ees of 22% (*cis*) and 42% (*trans*) with a de of 10% were obtained for **1a** (Table 2, entry 2) and 41% (*cis*) and 63% (*trans*) with a de of 16% for **1b** (Table 2, entry 3). This situation could arise from two scenarios: (1) the two homocomplexes are equally active and the observed values, are in fact, the average for these two predominate catalytic cycles or (2) the heterocomplex is the most active catalyst, but it gives stereoselectivities that are the average of that achieved with the two homocomplexes. However, in most other cases the enantioselectivities approached only the values obtained for one of the homocomplexes. For example, in the same cyclopropanation reaction with the heterocombination **1b**/**1c** the results were 38% ee (cis) and 57%ee (trans) with a de of 12% (Table 2, entry 14), and this result approximates the results obtained with the homocomplex derived from **1b** (Table 2, entry 3). In the case of the heterocombination **1c**/**2** (Table 2, entry 15), there was again an alignment towards the homocomplex formed from **1c** (Table 2, entry 5), which was again observed with the heterocombination **3a**/**3b** (Table 2, entry 18) where there was an alignment towards the homocomplex **3b** (Table 2, entry 9, when both the ees and des are taken into consideration).

This pattern was again repeated for **1a**/**1c** (Table 2, entry 13) where there was an alignment towards the homocomplex formed from **1c** (Table 2, entry 5). These latter results seem to indicate that one of the homocomplexes is the most active catalyst with certain combinations of ligands!

3. Conclusions

In an attempt to understand if π–π interactions are important for maintaining catalyst integrity in such systems—an interaction previously believed to be operational and important in such systems[5,6]—the analogous ligand system, Propen-OX **3**, was prepared and studied. A careful analysis of the results obtained appeared to indicate that these interactions were very weak indeed, and thus appear to be less important for achieving significant stereoselectivities. It seems that other factors (like the type of substituent at the stereogenic centre, etc.) are more influential.

Whilst computational studies suggested the existence of the heterocomplexes in the heterocombination cases, NMR and mass spectrometric studies on the heterocombination **1a**/**1b**, in fact, proved the existence of the (**1a1b**)Cu(I) heterocomplex, which is expected to exist in all cases.

In the case of the heterocombination of ligands, attempts were made via a variety of chemical and analytical techniques to identify the nature of the active chiral catalyst. These studies showed that only three types of complex were present, two homocomplexes and one heterocomplex. A careful analysis of the stereoselectivities failed to allow firm conclusions to be made about the nature of the active chiral catalyst at work in these reactions, but there is an indication—albeit very slight—that in fact, one of the homocomplexes is the active catalyst in a number of instances.

The potential of the Arylid-OX **1**–**2** family for catalytic asymmetric synthesis was probed using the standard benchmark catalytic asymmetric cyclopropanation of alkenes. A highest enantioselectivity of 74% ee was obtained, demonstrating their potential. The use of mixtures of these modular mono-oxazoline ligands is a powerful approach for creating enormous chemical diversity.

4. Experimental

4.1. General remarks

trans-2,4-Dimethoxycinnamic acid **6** was obtained using the literature method.[16] 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 F_{254} plates (Merck). Plates were visualised either by UV light or 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 point was recorded on a Barnstead Electrothermal 9100 apparatus and was uncorrected. The ^{1}H NMR spectra were recorded on either a Bruker AMX300 (^{1}H: 300.13 MHz and ^{13}C: 75 MHz) or a Bruker Avance III instrument (^{1}H: 400 MHz and ^{13}C: 100 MHz) using $CDCl_3$ as solvent and TMS as internal standard. Mass spectra were recorded on a VG Autospec M(Waters-Micromass) spectrometer using the FAB technique, Waters-Micromass GC-TOF and MicroTOF Focus (Bruker Daltonics) using the TOF technique and electron spray ionization (ESI) mass spectra were performed on a Brucker Daltonics Apex-Qe instrument at 300.0. Infra-red spectra were measured with a Perkin–Elmer Paragon 1000 model. Specific rotations were measured on a Perkin–Elmer 241 polarimeter.

4.2. Synthesis of Arylid-OX 1

*4.2.1. General procedure for the synthesis of cinnamamides (**12a**, **12b**).* A dry two-necked round bottom flask (50 mL) equipped with

a magnetic stir bar was charged with *trans*-2,4-dimethoxycinnamic acid **6** (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 **9** 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 bottom flask (50 mL) fitted with a magnetic stirring bar was charged with a solution of (*S*)-valinol (0.796 g, 7.72 mmol) and dry CH_2Cl_2 (15 mL) and the solution was cooled to 0 °C using an ice bath. Dry triethylamine (1.08 mL, 7.72 mmol) was added via syringe. A solution of *trans*-2,4-dimethoxycinnamoyl chloride **9** (1.00 g, 4.41 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*-(1-hydroxy-3-methylbutan-2-yl)-2,4-dimethoxycinnamamide **12a** as a yellow solid. The crude product was purified by recrystallization (EtOAc/hexane) to afford amide **12a** as a white solid. Yield: 0.492 g (81%); mp 140.4–141.8 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.81 (d, 1H *J*=15.6 Hz, RC*H*=CRH), 7.39 (d, 1H *J*=8.4 Hz, C*H*(Ar)), 6.52–6.45 (m, 3H, RCH=C*H*R, C*H*(Ar)), 5.81 (d, 1H *J*=8.1 Hz, N*H*), 3.86–3.83 (m, 1H, C*H*), 3.86 (s, 3H, −OCH_3), 3.83 (s, 3H, −OCH_3), 3.77–3.69 (m, 2H, CH_2), 1.99–1.93(m, 1H, C*H*), 1.02(s, 3H, −(CH_3)*2*), 1.00(s, 3H, −(CH_3)$_2$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=168.0, 162.1, 159.8, 136.6, 130.4, 119.7, 116.8, 105.0, 98.3, 63.9, 57.0, 55.3, 29.2, 19.5, 19.0 ppm. IR (KBr): ν_{max} 3371, 3311, 2960, 2864, 1643, 1603, 1568, 1531, 1460, 1417, 1355, 1304, 1260, 1216, 1163, 1138, 1075, 1042, 977, 934, 847, 800, 680, 639, 600 cm^{-1}. $[\alpha]^{22}_D$ −85.22 (*c* 0.67, $CHCl_3$). FAB-MS *m*/*z*: 294.17 [M+H].

Compound **12b**: The same procedure as described previously was used in the reaction of *trans*-2,4-dimethoxycinnamoyl chloride **9** (1.0 g, 4.41 mmol) with (*S*)-phenylalalinol (1.167 g, 7.72 mmol) and dry triethylamine (1.08 mL, 7.72 mmol) to give (*S*)-*trans*-*N*-(1-hydroxy-3-propan-2-yl)-2,4-dimethoxycinnamamide **12b** as a white solid after purification by recrystallization (EtOAc/hexane); Yield: 0.702 g (47%); mp 145.0–146.7 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.78 (d, 1H, *J*=15.6 Hz, RC*H*=CHR), 7.36 (d, 1H, *J*=8.4 Hz, C*H*(Ar)), 7.31–7.21 (m, 5H,C*H*(Ar)), 6.48–6.36 (m, 3H, RCH=C*H*R, C*H*(Ar)), 5.91 (d, 1H, *J*=7.5 Hz, N*H*), 4.28 (m(br s), 1H, C*H*), 3.83 (s, 3H, −OCH_3), 3.82 (s, 3H, −OCH_3), 3.78–3.63 (m, 2H, CH_2), 2.95 (d, 2H *J*=7.2 Hz, CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$/MeOD): δ=167.8, 162.0, 159.4, 137.8, 136.2, 129.9, 129.0, 128.2, 126.1, 118.3, 116.5, 104.9, 98.1, 62.8, 55.1, 52.5, 36.6 ppm. IR (KBr): ν_{max} 3399, 3017, 2955, 2859, 1637, 1591, 1534, 1504, 1439, 1300, 1280, 1048, 980, 827, 759, 646, 596 cm^{-1}. $[\alpha]^{22}_D$ −63.37 (*c* 0.98, $CHCl_3$). ESI-MS *m*/*z*: 342.1698 [M+H].

*4.2.2. General procedure for the synthesis of Arylid-OX (**1a**, **1b**).* A solution of methanesulfonyl chloride (0.234 g, 2.04 mmol) in dry CH_2Cl_2 (1 mL) was added dropwise over 20 min to a solution of cinnamamide **12a** (0.4 g, 1.36 mmol) and dry triethylamine (0.57 mL, 4.08 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-isopropyloxazoline-2-yl)ethene **1a** as a yellow oil. Yield: 0.374 g (70%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.55 (d, 1H, *J*=16.4 Hz, RC*H*=CHR), 7.41 (d, 1H, *J*=8.7 Hz, C*H*(Ar)), 6.66 (d, 1H *J*=16.4 Hz, RCH=C*H*R), 6.51–6.43 (m, 2H, C*H*(Ar)), 4.33 (m, 1H, C*H*), 4.02–4.00 (m, 2H, CH_2), 3.84 (s, 3H, −OCH_3), 2.92 (s, 3H, −OCH_3), 1.7–1.8 (m, 1H, C*H*), 1.01 (d, 1H *J*=6.7 Hz, −(CH_3)$_2$), 0.913 (d, 1H *J*=6.7 Hz, −(CH_3)$_2$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=163.9, 161.8, 159.0, 134.7, 129.2, 117.3, 114.0, 105.0, 98.3, 72.4, 69.7, 55.0, 32.8, 18.9, 18.2 ppm. IR (NaCl, CH_2Cl_2): ν_{max} 3055, 2969, 1743, 1604, 1505, 1465, 1301, 1214, 1162, 1033, 777, 669 cm^{-1}. $[\alpha]^{22}_D$ −51.56 (*c* 1.44, $CHCl_3$). FAB-MS *m*/*z*: 276.16 [M+H].

Compound **1b**: Using the same procedure as described previously, cinnamamide **12b** (0.40 g, 1.17 mmol) was reacted with methanesulfonyl chloride (0.20 g, 1.76 mmol) and dry triethylamine (0.49 mL, 3.51 mmol) to give the (*S*)-*trans*-2-(2,4-dimethoxyphenyl)-(4-benzyloxazoline-2-yl)ethene **1b** as a yellow oil after purification by column chromatography (silica gel, EtOAc/Hex (1:1)). Yield: 0.339 g (90%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.56 (d, 1H, *J*=16.4 Hz, RC*H*=CHR), 7.42 (d, 1H, *J*=8.5 Hz, C*H*(Ar)), 7.34–7.22 (m, 5H, C*H*(Ar)), 6.65 (d, 1H, *J*=16.4 Hz, CRH=C*H*R), 6.52–6.44 (M, 2H, C*H*(Ar)), 4.55–4.44 (m, 1H, C*H*), 4.03 (t, 1H, *J*=8 Hz, C*H*H), 4.26 (t, 1H, *J*=8 Hz, CH*H*), 3.85 (s, 3H, −OCH_3), 3.83 (s, 3H, −OCH_3), 3.21–3.13 (m, 1H, CH*H*), 2.69 (dd, 1H *J*=8.7 and 13.7 Hz, C*H*H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=164.6, 161.9, 159.0, 138.2, 135.2, 129.4, 129.2, 128.6, 126.4, 117.3, 113.3, 105.1, 98.4, 71.4, 67.7, 55.4, 41.9 ppm. IR (NaCl, CH_2Cl_2): ν_{max} 3055, 2955, 1714, 1640, 1603, 1506, 1460, 1248, 1214, 1031, 939, 842, 775, 693 cm^{-1}. $[\alpha]^{22}_D$ +159.0 (*c* 0.52, $CHCl_3$). ESI-MS *m*/*z*: 324.16 [M+H].

4.3. Synthesis of Arylid-OX 2

A dry two-necked round bottom flask (25 mL) equipped with a magnetic stirring bar was charged with *trans*-cinnamic acid **7** (1.5 g, 10 mmol), dimethylformamide (0.1 mL, 1.3 mmol) and CH_2Cl_2 (15 mL). The solution was cooled to 0 °C, and oxalyl chloride (1.1 mL, 12.7 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*-cinnamoyl chloride **10** as a dark green solid (due to the unstable nature of this compound it was stored in the freezer at −10 °C). A two-necked round bottom flask (25 mL) fitted with a magnetic stirring bar was charged with a solution of (*S*)-phenylglycinol (2.06 g, 15 mmol) and dry CH_2Cl_2 (15 mL) and the solution was cooled to 0 °C using an ice bath. Dry triethylamine (2.01 mL, 15 mmol) was added via syringe. A solution of *trans*-cinnamoyl chloride **10** (all quantity, 10 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 (15 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)-cinnamamide **13** as a yellow solid. The crude product was purified by recrystallization (EtOAc/hexane) to afford amide **13** as a white solid (1.389 g, 52%); mp 190.1–191.1 °C. ^{1}H NMR (400 MHz, CD_3OD): δ=7.54–7.24 (m, 12H, C*H*(Ar), N*H*, RC*H*=CRH), 6.73 (d, 1H *J*=15.7 Hz, RCH=C*H*R), 5.11 (br s, 1H, C*H*), 3.81–3.77 (m, 2H, CH_2) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ=168.5, 142.1, 141.3, 136.4, 130.8, 129.9, 129.6, 128.9, 128.5, 128.1, 122.0, 66.3, 57.3 ppm. IR (KBr): ν_{max} 3304, 3062, 3028, 3062, 2953, 2859, 1654, 1623, 1547, 1494, 1450, 1355, 13,345, 1233, 1215, 1160, 1074, 1058, 972, 863, 700, 528 cm^{-1}. $[\alpha]^{21}_D$ −20.12 (*c* 0.815, MeOH).

TOF-MS *m*/*z*: 268.14 $[M+H]^+$. A solution of methanesulfonyl chloride (0.411 g, 3.59 mmol) in dry CH_2Cl_2 (1 mL) was added dropwise over 20 min to a solution of cinnamamide **13** (0.64 g, 2.39 mmol) and dry triethylamine (1 mL, 7.17 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 flash column chromatography (silica, EtOAc/Hex (1:9)) giving the (+)-(*S*)-*trans*-2-phenyl-(4-phenyloxazoline-2-yl)ethene **2** as a white solid (0.455 g, 76%); mp: 59–60 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.53–7.49 (m, 3H, C*H*(Ar) and RC*H*=CHR), 7.45–7.33 (m, 5H, C*H*(Ar)), 7.31–7.27 (m, 3H, C*H*(Ar)), 6.75 (d, 1H *J*=16.3 Hz, RCH=C*H*R), 5.33 (dd, 1H *J*=8.4, 10 Hz, C*H*H), 4.72 (dd, 1H *J*=8.4, 10 Hz, CH*H*), 4.2 (t, 1H *J*=8.2 Hz, C*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=164.4, 142.2, 140.4, 135.1, 129.5, 128.8, 128.7, 127.5, 127.5, 126.6, 115.0, 74.3, 70.0 ppm. IR (KBr): ν_{max} 3057, 3030, 2955, 2889, 1650, 1605, 1492, 1474, 1450, 1361, 1244, 1201, 1074, 997, 981, 851, 760, 698, 536 cm^{-1}. $[\alpha]^{20}_D$ −12.12 (*c* 0.99, $CHCl_3$). TOF-MS *m*/*z*: 250.13 [M+H].

4.4. Synthesis of Propen-OX 3

*4.4.1. General procedure for the synthesis of amides (**14a**, **14b**).* A dry two-necked round bottom flask (25 mL) equipped with a magnetic stir bar was charged with *trans*-but-2-enoic acid **8** (1.0 g, 12 mmol), dimethylformamide (0.15 mL, 1.95 mmol) and CH_2Cl_2 (15 mL). The solution was cooled to 0 °C, and oxalyl chloride (1.27 mL, 15 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*-but-2-enoyl chloride **11** as a green oil (due to the unstable nature of this compound it was stored in the freezer at −10 °C). A two-necked round bottom flask (25 mL) fitted with a magnetic stirring bar was charged with a solution of (*S*)-phenylglycinol (2.06 g, 15 mmol) and dry CH_2Cl_2 (15 mL) and the solution was cooled to 0 °C using an ice bath. Dry triethylamine (2.1 mL, 15 mmol) was added via syringe. A solution of *trans*-but-2-enoyl chloride **11** (12 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)- but-2-enamide **14b** as a yellow solid. The crude product was purified by column chromatography (silica flash, EtOAc/Hex (7:2) and AcOEt) to afford amide **14b** as a white solid. Yield: 1.924 g (78%); mp 95.5–96.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.35–7.22 (m, 5H, H(Ar)), 6.81 (dq, 1H *J*=6.8, 15 Hz, MeC*H*=CHR), 6.61 (d, 1H *J*=6.8 Hz, N*H*), 5.83 (dd, 1H *J*=1.5, 15 Hz, MeCH=C*H*R), 5.06 (q, 1H *J*=5.4, 6 Hz, C*H*), 4.07–3.77 (m, 2H, C*H*2), 1.83 (dd, 3H *J*=6.8, 20.2 Hz, Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=166.5, 140.7, 139.1, 128.7, 127.9, 127.7, 126.7, 124.7, 66.2, 55.9, 17.7 ppm. IR (KBr): ν_{max} 3292, 3080, 3030, 2918, 1671, 1631, 1545, 1494, 1448, 1359, 1333, 1283, 1235, 1120, 1074, 1051, 968, 917, 850, 7550, 7000, 666, 524 cm^{-1}. $[\alpha]_{D^{22}}$ +68.01 (*c* 0.965, $CHCl_3$). TOF-MS *m*/*z*: 206.12 [M+H].

Compound **14a**: The same procedure as described previously was used in the reaction of *trans*-but-2-enoyl chloride **11** (8.6 mmol) with (*S*)-valinol (1.14 g, 11 mmol) and dry triethylamine (1.54 mL, 11 mmol) to give (*S*)-*trans*-*N*-(1-hydroxy-3,3-methylbutan-2-yl)-but-2-enamide **14a** as a white solid after purification by flash column chromatography (silica, EtOAc); Yield: 0.49 g (33%); mp 92.3–93.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.78 (dq, 1H *J*=6.8, 15.2 Hz, MeC*H*=CHR), 6.23 (d, 1H *J*=9.6 Hz, N*H*), 5.84 (dd, 1H *J*=1.6, 15.2 Hz, MeCH=C*H*R), 3.76–3.70 (m, 1H, C*H*), 3.67–3.59 (m, 2H, CH_2), 1.82–1.90 (m, 1H, C*H*), 1.8 (dd, 3H *J*=1.5, 6.9 Hz, Me), 0.92 (d, 3H *J*=6.8 Hz, CH(CH_3)2), 0.89 (d, 3H *J*=6.8 Hz, CH(CH_3)$_2$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=167.0, 140.0, 125.1, 63.4, 56.9, 28.8, 18.8, 17.6 ppm. IR (KBr): ν_{max} 3433, 3296, 3064, 3028, 2953, 2872, 1670, 1620, 1597, 1542, 1464, 1445, 1391, 1375, 1357, 1226, 1066, 975, 921, 839, 728, 685, 653, 523 cm^{-1}. $[\alpha]^{22}_D$ −44.56 (*c* 0.86, $CHCl_3$). TOF-MS *m*/*z*: 172.13 [M+H].

*4.4.2. General procedure for the synthesis of Propen-OX (**3a**, **3b**).* A solution of methanesulfonyl chloride (0.42 g, 3.65 mmol) in dry CH_2Cl_2 (1 mL) was added dropwise over 20 min to a solution of amide **14b** (0.5 g, 2.44 mmol) and dry triethylamine (1 mL, 7.32 mmol) in dry CH_2Cl_2 (20 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 flash column chromatography (silica, EtOAc/Hex (1:9)) giving the (*S*)-*trans*-(4-phenyloxazoline-2-yl)prop-2-ene **3b** as a colourless oil. Yield: 0.33 g (72%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.35–7.26 (m, 5H, *H*(Ar)), 7.25–7.23 (m, 5H, *H*(Ar)), 6.69 (dq, 1H *J*=6.9, 13.7 Hz, MeC*H*=CHR), 6.1 (dd, 1H *J*=6.9, 13.7 Hz, MeCH=C*H*R), 5.22 (t, 1H *J*=9 Hz, C*H*H), 4.62 (dd, 1H *J*=8.4, 10 Hz, CH*H*), 4.1 (t, 1H *J*=8.2 Hz, C*H*), 1.9 (dd, 3H *J*=1.7, 6.8 Hz, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=163.9, 142.4, 139.8, 128.4, 127.5, 126.6, 126.3, 126.2, 118.9, 74.2, 69.7, 18.4 ppm. IR (NaCl): ν_{max} 3272, 3061, 3030, 2968, 2912, 1732, 1676, 1644, 1612, 1585, 1494, 1474, 1454, 1360, 1178, 997, 968, 903, 761, 734, 701, 667, 542 cm^{-1}; $[\alpha]^{22}_D$ −113.80 (*c* 1.28, $CHCl_3$). TOF-MS *m*/*z*: 188.11 [M+H].

Compound **3a**: Using the same procedure as described previously, amide **14a** (0.35 g, 2.04 mmol) was reacted with methanesulfonyl chloride (0.35 g, 3.07 mmol) and dry triethylamine (0.86 mL, 6.13 mmol) to give the (*S*)-*trans*-(4-isopropyloxazoline-2-yl)prop-2-ene **3a** as a colourless oil after purification by flash column chromatography (EtOAc/Hex (1:5)). Yield: 0.193 g (62%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.54 (dq, 1H *J*=6.9, 13.7 Hz, MeC*H*=CHR), 5.96 (d, 1H *J*=15.8 Hz, MeCH=C*H*R), 4.28–4.18 (m, 1H, C*H*), 3.94–3.89 (m, 2H, CH_2), 1.82 (d, 3H *J*=6.9 Hz, Me), 1.75–1.70 (m, 1H, C*H*(CH_2)$_2$), 0.94 (d, 3H *J*=6.8 Hz, CH(CH_2)$_2$), 0.89 (d, 3H *J*=6.8 Hz, CH(CH_2)$_2$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=162.7, 138.8, 119.1, 72.2, 69.6, 32.7, 18.8, 18.2, 18.2 ppm. IR (NaCl): ν_{max} 3272, 2961, 2912, 2874, 1722, 1679, 1648, 1614, 1468, 1446, 1357, 1309, 1250, 1192, 1178, 1103, 995, 970, 911, 815, 795, 733, 668, 529 cm^{-1}. $[\alpha]^{22}_D$ −69.06 (*c* 0.96, $CHCl_3$). TOF-MS *m*/*z*: 154.13 [M+H].

4.5. Representative cyclopropanation using $Cu(MeCN)_4]PF_6$ pre-catalyst

$[Cu(MeCN)_4]PF_6$ (0.36 mol % or 2 mol %) was added to a two-neck round-bottomed flask containing the chiral oxazoline (1.13–6.3 mol %) in CH_2Cl_2 (1 mL) and the solution was stirred at room temperature for 15 min under a nitrogen atmosphere. Alkene (2.66 mmol) and a solution of ethyl diazoacetate (7.45 mmol) or (0.665 mmol) in CH_2Cl_2 (1 mL) was then added to the reaction mixture over a period of 8 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* diastereoisomers, the ratio was determined using GC analysis. Isolated yields, diastereoselectivities and enantioselectivities are given in Tables 1 and 2.

Acknowledgements

We are grateful for financial support from the Fundação para a Ciência e a Tecnologia (FCT) (project; PPCDT/QUI/55779/2004) through POCI 2010, supported by the European community fund, FEDER. FCT is also acknowledged for the award of a Ph.D. grant to EPC (SFRH/BD/277688/2006). We acknowledge LabRMN at FCT-UNL for the acquisition of NMR spectra, the NMR spectrometers are part of the National NMR Network and were purchased in the framework of the National Programme for Scientific Re-equipment, contract REDE/1517/RMN/2005, with funds from POCI 2010 (FEDER) and FCT.

References and notes

1. (a) Reetz, M. T.; Sell, T. *Tetrahedron Lett.* **2000**, *41*, 6333; (b) Claver, C.; Fernandez, E.; Gillon, A.; Heslop, K.; Hylett, D. J.; Martorell, A.; Orpen, A. G.; Pringle, P. G. *Chem. Commun.* **2000**, 961.
2. Reetz, M. T.; Mehler, G. *Angew. Chem., Int. Ed.* **2000**, *39*, 3889.
3. (a) Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346; (b) Yoon, T. P.; Jacobsen, E. N. *Science* **2003**, *299*, 1691; (c) Hulst, R.; de Vries, N. K.; Feringa, B. L. *Tetrahedron: Asymmetry* **1994**, *5*, 699; (d) van den Berg, M.; Minnaard, A. J.; Schudde, E. P.; van Esch, J.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L. *J. Am. Chem. Soc.* **2000**, *122*, 11539; (e) Teichert, J. F.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2010**, *49*, 2486.
4. Braunstein, P.; Naud, F. *Angew. Chem., Int. Ed.* **2001**, *40*, 680.
5. Dakovic, S.; Liscic-Tumir, L.; Kirin, S. I.; Vinkovic, V.; Raza, Z.; Suste, A.; Sunjic, V. *J. Mol. Catal. A: Chem.* **1997**, *118*, 27.
6. Carreiro, E. P.; Ramalho, J. P. P.; Rodrigues, A. I.; Burke, A. J. *Tetrahedron: Asymmetry* **2009**, *20*, 1272.
7. Ikeda, S.; Kondo, H.; Arii, T.; Odashima, K. *Chem. Commun.* **2002**, 2422.
8. Bonini, B. F.; Capitó, E.; Comes-Franchini, M.; Ricci, A.; Bottoni, A.; Bernardi, F.; Miscione, G. P.; Giordano, L.; Cowley, A. R. *Eur. J. Org. Chem.* **2004**, 4442.
9. Chuzel, O.; Magnier-Bouvier, C.; Schulz, E. *Tetrahedron: Asymmetry* **2008**, *19*, 1010.
10. (a) Glorius, F. *Angew. Chem., Int. Ed.* **2004**, *43*, 3364; (b) Johnson, J. B.; Rovis, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 840; (c) Defeiber, C.; Grützmacher, H.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4482; (d) Hahn, B. T.; Tewes, F.; Fröhlich, R.; Glorius, F. *Angew. Chem., Int. Ed.* **2009**, *48*, 1.
11. (a) Reetz, M. T.; Sell, T.; Meiswinkel, A.; Mehler, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 790; (b) Reetz, M. T.; Li, X. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 2959; (c) Reetz, M. T.; Fu, Y.; Meiswinkel, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1412.
12. (a) Peña, D.; Minnaard, A. J.; Boogers, J. A. F.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L. *Org. Biomol. Chem.* **2003**, *1*, 1087; (b) Duursma, A.; Hoen, R.; Schuppan, J.; Hulst, R.; Minnaard, A.; Feringa, B. L. *Org. Lett.* **2003**, *5*, 3111.
13. Carreiro, E. P.; Chercheja, S.; Moura, N. M. M.; Gertrudes, S. C.; Burke, A. J. *Inorg. Chem. Commun.* **2006**, *9*, 823.
14. Burke, A. J.; Carreiro, E. P.; Chercheja, S.; Moura, N. M. M.; Ramalho, J. P. P.; Rodrigues, A. I.; Santos, C. I. M. *J. Organomet. Chem.* **2007**, *692*, 4863.
15. Carreiro, E. P.; Chercheja, S.; Burke, A. J.; Ramalho, J. P. P.; Rodrigues, A. I. *J. Mol. Catal. A: Chem.* **2005**, *236*, 38.
16. Neustadt, B. R.; Smith, E. M.; Nechuta, T. L.; Bronnenkant, A. A.; Haslanger, M.; Watkins, R. W.; Foster, C. J.; Sybertz, E. J. *J. Med. Chem.* **1994**, *37*, 2461.
17. Headen, T. F.; Howard, C. A.; Skipper, N. T.; Wilkinson, M. A.; Bowron, D. T.; Soper, A. K. *J. Am. Chem. Soc.* **2010**, *132*, 5735.
18. Burke, A. J.; Carreiro, E. P. unpublished results.
19. Stewart, J. J. P. *J. Mol. Model.* **2007**, *13*, 1173.
20. Stewart, J.J.P. MOPAC2007, Computational Chemistry, Version 7.319L web: http://openmopac.net/.
21. Meng, Q.; Li, M.; Tang, D.; Shen, W.; Zhang, J. *J. Mol. Struct.: THEOCHEM* **2004**, *711*, 193.
22. Beck, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.
23. Lee, C.; Yang, W.; Parr, R. G. *Physiol. Rev.* **1988**, *37*, 785.
24. Schmidt, M. W.; Baldridge, K. K.; Boatz, J. A.; Elbert, S. T.; Gordon, M. S.; Jensen, J. H.; Koseki, S.; Matsunga, N.; Nguyen, K. A.; Su, S. J.; Windus, T. L.; Dupuis, M.; Montgomery, J. A. *J. Comput. Chem.* **1993**, *14*, 1347.
25. Wassenaar, J.; Jansen, E.; van Zeist, W.-J.; Bickelhaupt, F. M.; Siegler, M. A.; Speck, A. L.; Reek, J. N. H. *Nat. Chem.* **2010**, *2*, 417.