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Isbut-Box: A new chiral C_2 symmetric bis-oxazoline for catalytic enantioselective synthesis

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Abstract

A series of chiral non-racemic isobutylene bis-oxazoline (Isbut-Box) ligands have been synthesised in satisfactory overall yields. The utility of such ligands for catalytic asymmetric synthesis has been demonstrated using the Cu(I) catalysed enantioselective cyclopropanation of styrene and derivatives with ethyl diazoacetate as a test reaction. The Cu(I) moiety is generated in situ using ethyl diazoacetate prior to the addition of the olefin. In these preliminary studies, the aforementioned cyclopropanation reaction gave yields, enantioselectivities and diastereoselectivities of up to 69%, 70% ee and 72% de. The reaction results were shown to be solvent dependent, with dichloromethane demonstrating good yields and toluene showing good stereoselectivities. DFT studies and NMR spectroscopic studies were undertaken to probe the structure and behaviour of the Cu(I)-Isbut-Box ligands.

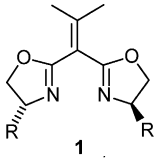
Keywords: Cyclopropanation; Enantioselective; Bis-oxazoline; Catalysis

1. Introduction

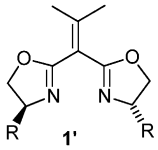
Over the last 14 years, chiral non-racemic C_2 symmetric bidentate bis-oxazoline compounds have been shown to be very useful ligands demonstrating good to high enantioselectivities in a number of catalytic asymmetric reactions [1], like: olefin cyclopropanations [2], aziridinations [2b,3], hydrosilylations [4], transfer hydrogenations [5], lewis acid catalysed cycloadditions [6], aldol reactions [7], carbonyl 1,4 [8] and 1,2 [9] additions and additions to imines [10], etc. Some of the ligands used in these reactions perform very well in a range of these reactions, but a universal bis-oxazoline system, which works well for the majority of these reactions, has still to be found.

Therefore, the design, synthesis and evaluation of new bis-oxazoline systems is a worthwhile endeavour.

In this preliminary paper, we report on a new family of structurally simple C_2 symmetric bis-oxazoline ligands **1a**, **1b**, **1′a** and **1′b** where the two oxazoline units are tethered geminally to an isobutylene unit.



1
a R = ^{i}Pr
b R = Bn



1'
a R = ^{t}Bu
b R = Ph

We envisioned these isobutylene-Box (Isbut-Box) ligand systems to show an improvement on other known bis-oxazolines for the following reasons: (1) possession of a relatively simple structure, (2) possession of a good bite-angle, (3) formation of a stable six-membered chelate

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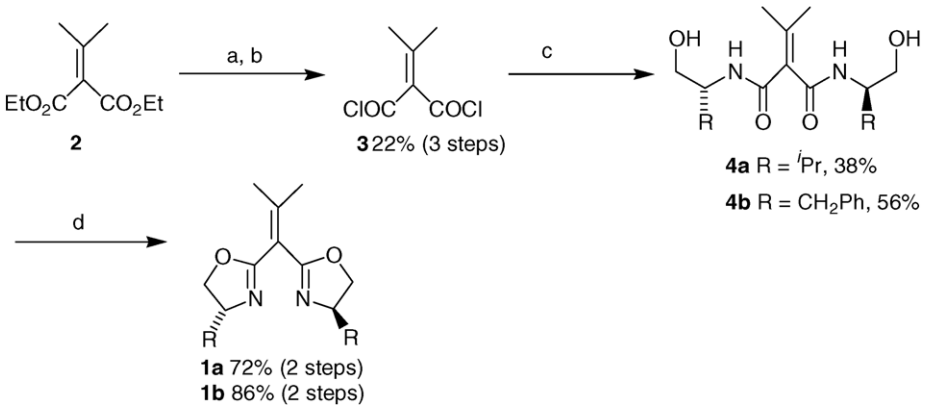


Scheme 1. (a) (i) NaOH, EtOH, 0 °C and (ii) HCl (conc.); (b) $(COCl)_2$, DMF, CH_2Cl_2, 0 °C; (c) (+)-phenylalaninol or (L)-valinol (2 equiv.), NEt_3, CH_2Cl_2; (d) CH_3SO_2Cl (2.5 equiv.), NEt_3 (6 equiv.), CH_2Cl_2.

complex, (4) possession of a rigid yet light back-bone, (5) straightforward preparation from readily available starting materials and (6) interesting electronic properties.

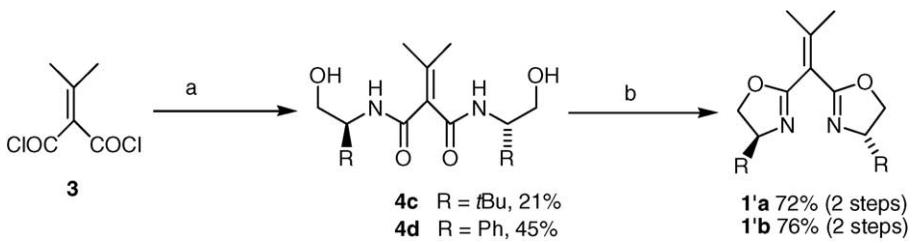
2. Results and discussion

We envisaged synthesising ligands **1a**, **1b**, **1′a** and **1′b** using commercially available diethyl isopropylidenemalonate **2** and a range of amino-alcohols (derived from cheap α-amino acids). Upon using these precursors and the synthetic pathways shown in Schemes 1 and 2, we successfully obtained all four ligands in reasonable overall yields (starting from **2**, five steps).

The procedure of Kim et al. [11] was used successfully for the conversion of the diamide to the bisoxazoline. However, prior to using this procedure we investigated the procedure of Moreno-Mañas and co-workers [12] in which the diamide **4b** was first treated with thionyl chloride to form the dichloride in situ and then treated with potassium carbonate to form the bis-oxazoline. This procedure failed to give the desired product.

We decided to evaluate the efficacy and selectivity of this new family of box ligands for catalytic asymmetric synthesis by screening them in the Cu(I) catalysed asymmetric cyclopropanation of olefins. However, we carried out a DFT quantum chemical calculation on the Cu(I)-*i*Pr-Isbut **1a** complex in order to determine its viability and obtain key structural information prior to commencing our evaluation of this new family of BOX ligands in these reactions. We consider this to be quite a realistic model of this complex owing to the weakly coordinative nature of the triflate anion in solution [13]. For comparison, we also conducted a DFT calculation on the Cu(I)-*i*PrBox complex of Evans [2b] making the same valid assumptions. For these DFT calculations, GAMESS-US [14] was used with the 6-31G* basis-set for C, N, O and H (or for the lightest atoms) and applying the Stuttgart RSC 1997 effective core potential for Cu (see Section 3). The calculations for our Cu(I)-*i*Pr-Isbut **1a** complex using this core potential resulted in a theoretically stable complex, this was compared with a calculation performed on the Cu(I)-*i*PrBox complex of Evans using this effective core potential. Fig. 1 shows the structures of both complexes and Table 1 some selected bond lengths and angles for both complexes.

It can be seen from the table that the calculated C1–C2–C3 and the N1–Cu–N2 bond angles for the two complexes are very similar. However, the Cu(I)-Isbut-Box **1a** complex is more asymmetric than the Cu(I)-*i*PrBox complex due to a difference of 0.018 Å in the Cu–N bond lengths. In the case of the other complex, this difference is negligible. What was of considerable interest was the observation that the calculation revealed that in the Cu(I)-Isbut-Box **1a** complex one of the oxazoline rings was slightly tilted out of the plane as can be seen from the difference in the Cu–N1–C5–C4 and the Cu–N2–C6–C7 dihedral angles (ca. 30°). In the case of the Cu(I)-*i*PrBox complex, this diference is only (ca. 2.4°). The reason for the twisting of this oxazoline ring is unknown.



Scheme 2. (a) (D)-Phenylglycinol or (L)-*tert*-leucinol (2 equiv.), NEt_3, CH_2Cl_2; (b) CH_3SO_2Cl (2.5 equiv.), NEt_3 (6 equivs.), CH_2Cl_2.

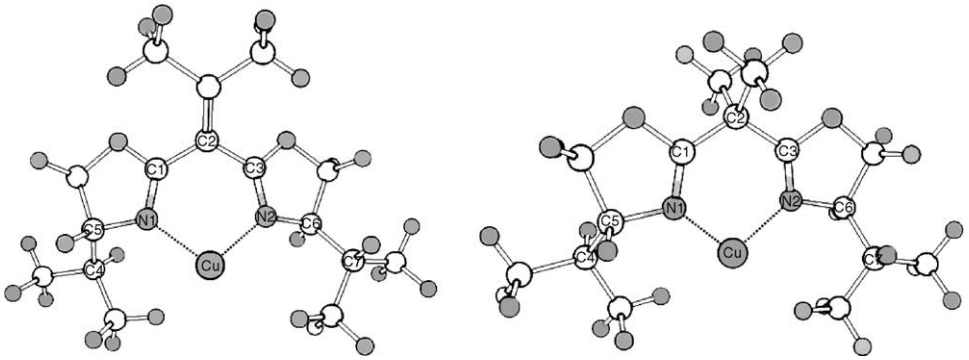


Fig. 1. Calculated structural features (DFT) for the Cu(I)-Isbut-Box **1a** (left) and Cu(I)-*i*PrBox (right).

Recently, Norrby and co-workers [15] conducted DFT calculations using Gaussian 98 with the BP functional in ADF on some 2,2′-methylenebisoxazoline complexes to gain an insight into the mechanism of the copper(I)-catalysed cyclopropanation reaction. In this paper, they reported an N–Cu–N angle of $110^\circ \pm 2^\circ$ which is relatively close to our value using GAMESS-US. They also gave a Cu–N distance of 1.90–1.91Å, relatively close to the value reported by us (1.942–1.945 Å) for the Cu(I)-*i*PrBox complex. Fraile et al. [16] conducted a DFT calculation at the B3LYP/6-31G(d) theoretical level on a 2,2′-methylenebis[(4*S*)-methyl-2-oxazoline]-carbene complex and obtained Cu–N distances of 1.934 and 1.926Å. However, these authors did not report studying the simpler bi-dentate bis-oxazoline-Cu(I) complex.

Recently, Kwong and Lee [17] showed that highly stereoselective catalytic enantioselective cyclopropanations of alkenes with alkyl diazoacetates could be achieved using Cu(I) generated in situ from Cu(II) by adding a few equivalents of alkyl diazoacetates to reduce Cu(II) to Cu(I). These workers used C_2-symmetric 2,2′:6′,2″-terpyridines as the chiral ligands. We decided to conduct these catalytic asymmetric cyclopropanation reactions using our Isbut-Box ligands according to the procedure of Kwong and Lee for reasons of operational simplicity. As far as we are aware, this is the first example of a Cu(I)-BOX catalysed asymmetric cyclopropanation where the Cu(I) is generated in situ from Cu(II) without requiring phenylhydrazine [2a].

Table 1
Selected calculated bond lengths (Å), bond angles (°) and dihedral angles (°) for the two complexes using the Stuttgart RSC 1997 effective core potential for Cu

Cu(I)-Isbut-Box **1a**		Cu(I)-*i*PrBox	
Bond lengths		Bond lengths	
Cu–N1	1.953	Cu–N1	1.942
Cu–N2	1.935	Cu–N2	1.945
Cu–C4	3.523	Cu–C4	3.558
Cu–C7	3.746	Cu–C7	3.511
Bond angles		Bond angles	
C1–C2–C3	117.7	C1–C2–C3	117.1
N1–Cu–N2	105.5	N1–Cu–N2	104.2
Cu–N1–C5–C4	32.1	Cu–N1–C5–C4	42.3
Cu–N2–C6–C7	64.1	Cu–N2–C6–C7	39.5

We, then evaluated all four Isbut-Box ligands **1a**, **1b**, **1′a** and **1′b** using ethyl diazoacetate with styrene and derivatives.

These reactions show a number of interesting features. It is apparent from the table that the enantioselectivities are solvent dependent. For instance, ligand **1′a** gives the greatest enantioselectivity over the range of substrates studied when toluene is used as solvent; an ee of 70% was achieved for *trans*-ethyl 2-methyl-2-phenylcyclopropylcarboxylate. Much lower ees were obtained when CH_2Cl_2 is used and the best ligand in most cases was ligand **1′a**. The greatest diastereoselectivity obtained was when **1′b** was used in toluene for the cyclopropanation of 4-methylstyrene (de = 72%) (entry 20). However, the most efficient reactions were conducted in CH_2Cl_2 where the highest yield (71%) was obtained. The lower yields observed in toluene may be attributable to catalyst deactivation or decomposition as heating is necessary to initiate and maintain the reaction. For instance, in the case of the cyclopropanation of styrene using ligand **1′b** no reaction was observed between room temperature and 40 °C, the reaction commenced only at a temperature of 50 °C. The fact that higher ees can be obtained in toluene may be linked to the selective precipitation of non-complexed, non-asymmetric inducing Cu(I) when using this solvent system (some precipitate was observed in the bottom of the flask which very likely was non-complexed copper) thus, requiring more of the chiral Cu(I)-ligand complex to catalyse the reaction. The fact that the yield drops on changing the solvent to toluene would seem to support this postulate.

Following the report of Moreno-Mañas and co-workers [12] we carried out a reaction in the presence of molecular sieves (entry 3) and observed that although the yield increased by 15% the enantioselectivity for both the *cis* and *trans*-isomers dropped slightly, indicating that water perhaps appears to have some minor role in stabilizing the transition states in this reaction. A study directed at determining if the stereoselectivities were temperature dependent revealed in the case of the cyclopropanation of α-methylstyrene at

0 °C using **1a** (entry 10) that there was a slight increase in the enantioselectivities for both the *cis* and *trans*-isomers, but the diastereoselectivity remained constant. The yield had also improved by 14%. In order to establish if cyclopropanation of the ligand occurred during the reaction, we carried out a control cyclopropanation reaction using ligand **1′b**, ethyl diazoacetate and $Cu(OTf)_2$ and achieved a good percentage recovery of the ligand at the end of the reaction, thus indicating that this side reaction did not occur [19]. Besides, such a reaction is very unlikely due to the electrodeficiency of the ligand C=C double bond.

It is interesting to note that our ligand **1a** matches the Isp-BOX ligand of Evans et al. [2b] in both efficiency and stereoselectivity for the cyclopropanation of styrene. However, surprisingly, it was found that for the same reaction our Cu(I)-**1′a** system gave inferior stereoselectivities to that of the Evan's Cu(I)-*t*Bu-Box system [1b]. To gain an insight into the lower enantioselectivities afforded by our ligand **1′a** we decided to study our Cu(II)-**1′a** complex by ^{1}H NMR spectroscopy. To facilitate this study we chose to investigate the Cu(II)-**1′a** complex instead of the Cu(I)-**1′a** complex due to the greater air stability of $Cu(OTf)_2$ over Cu(OTf). The Cu(II)-**1′a** complex was formed in $CDCl_3$ by mixing 1 equiv. of $Cu(OTf)_2$ to the ligand and it was monitored over a 24 h period [20]. What we appeared to observe was a very fast dynamic coordinative equilibrium between the ligand and the complex during the course of the experiment. This point of view was supported by the report by Evans et al. [13] who observed rapid ligand redistribution when their Cu(I)-*t*Bu-Box polymeric solid was dissolved in $CDCl_3$ and analysed by ^{1}H NMR. We also appeared to observe other peaks in the spectrum suggesting the existence of perhaps a tetracoordinated complex of the type Cu(II)-(**1′a**)$_2$ [20].

3. Experimental

3.1. General methods

All reactions requiring dry conditions were conducted under a nitrogen atmosphere and using oven-dried glassware. Dry solvents were obtained using common drying procedures [21]. Microdistillations were carried out using a standard laboratory apparatus.

Normal 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 Kiselgel 60 F_{254} plates (Merck). Plates were visualised either by UV light or phosphomolybdic acid in ethanol.

Gas chromatographic (GC) analyses of the products obtained from the cyclopropanation reactions were performed on a Hewlett Packard (HP) 6890 instrument equipped with a flame ionization detector (FID). The chromatograph was fitted with a cyclodex-B capillary column (30 m, 250 μm, 0.25 μm) (Agilent 112-2532).

A KDS 200 infusion syringe pump was used to add the ethyl diazoacetate in the cyclopropanation reactions. Melting points were recorded on a leica Galen III apparatus and they are uncorrected. The ^{1}H NMR and ^{13}C NMR spectra were recorded on either a Bruker AMX300 (^{1}H: 300 MHz and ^{13}C: 75 MHz) or a Bruker Avance (^{1}H: 400 MHz and ^{13}C: 100 MHz) or a Bruker Avance 500 (^{1}H: 500 MHz and ^{13}C: 125 MHz) instrument using $CDCl_3$ as solvent and TMS as internal standard (for measurements made with the Bruker AMX300 instrument) and the signal from residual $CHCl_3$ as an internal standard (for the measurements made with the Bruker Avance instrument). ^{13}C NMR spectra were obtained with 135° DEPT editing to identify methylene groups. Mass spectra were recorded on a VG Autospec M spectrometer using the FAB technique. Infra-red spectra were recorded using a Perkin-Elmer Paragon 1000 instrument. Optical rotations were measured with a Perkin-Elmer 241 polarimeter and a Rudolph Autopol IV Addendum using a 10 cm cell and the concentrations are quoted in g/100 ml.

3.2. Computational methods

Quantum chemical DFT calculations were performed using the GAMESS-US program where Becke's three-parameter hybrid functional [22] with the LYP correlation functional [23] (B3LYP) was employed. The standard 6-31G* set for C, N, O and H and the Stuttgart RSC 1997 [24–26] effective core potentials for Cu were chosen to perform the DFT study. Geometries were optimized at this level of theory without any symmetry constraints.

4. Catalytic reactions

4.1. General procedure for the Cu(I) catalysed asymmetric cyclopropanations of styrene and derivatives with chiral ligands *1a*, *1b*, *1′a*, and *1′b*

$Cu(OTf)_2$ (0.010 g, 0.0276 mmol) was added to a two-neck round-bottomed flask containing the ligand (0.0304 mmol) in CH_2Cl_2 (2 ml) or toluene (2 ml) and the solution was stirred at room temperature for 2h under an nitrogen atmosphere. Alkene (5.54 mmol) and ethyl diazoacetate (0.032 g, 0.277 mmol) were then added and the mixture was stirred at room temperature for a further 30 min. A solution of ethyl diazoacetate (0.157 g, 1.38 mmol) in CH_2Cl_2 (1 ml) or toluene (1 ml) was then added to the reaction mixture over a period of 4 h using a syringe pump. After the addition of ethyl diazoacetate, the mixture was stirred for 16 h. The mixture was then worked up by removing the solvent and the crude product mixture obtained was purified by column chromatography (hexane/EtOAc 10:1). All cyclopropane products were obtained as a mixture of *cis* and *trans* diastereomers. Reaction temperatures, isolated total yields, diastereoselectivities, and enantioselectives are given in Table 2.

Table 2
Catalytic asymmetric cyclopropanation of styrene substrates[a]

Entry	Substrate	Ligand	Solvent	Temperature (°C)	Yield[b] (%)	*trans*:*cis*[b]	*trans* (%ee)[c]	*cis* (%ee)[c]
1	Styrene	**1a**	CH_2Cl_2	r.t.	63	64:36	46[d]	43[d]
2	Styrene	**1b**	CH_2Cl_2	r.t.	54	68:32	47[d]	22[d]
3	Styrene[e]	**1b**	CH_2Cl_2	r.t.	69	62:38	44[d]	19[d]
4	Styrene	**1′a**	CH_2Cl_2	r.t.	61	58:42	46[d]	42[d]
5	Styrene	**1′b**	CH_2Cl_2	r.t.	38	62:38	34[d]	27[d]
6	Styrene	**1′b**	CH_2Cl_2	40	32	67:33	38[d]	25[d]
7	Styrene	**1′a**	Toluene	50	19	63:37	64[d]	56[d]
8	Styrene	**1′b**	Toluene	50	21	66:33	46[d]	34[d]
9	α-Methylstyrene	**1a**	CH_2Cl_2	r.t.	32	56:44	10	11
10	α-Methylstyrene	**1a**	CH_2Cl_2	0	46	56:44	14	15
11	α-Methylstyrene	**1b**	CH_2Cl_2	r.t.	71	50:50	45	38
12	α-Methylstyrene	**1′a**	CH_2Cl_2	r.t.	66	49:51	29	25
13	α-Methylstyrene	**1′b**	CH_2Cl_2	r.t.	64	50:50	24	21
14	α-Methylstyrene	**1′a**	Toluene	r.t.	15	60:40	70	66
15	α-Methylstyrene	**1′b**	Toluene	50	nd	49:51	26	22
16	4-Methylstyrene	**1b**	CH_2Cl_2	r.t.	40	62:38	nd	14
17	4-Methylstyrene	**1′a**	CH_2Cl_2	r.t.	40	59:41	nd	54
18	4-Methylstyrene	**1′b**	CH_2Cl_2	r.t.	42	66:34	nd	23
19	4-Methylstyrene	**1′a**	Toluene	50	26	62:38	nd	55
20	4-Methylstyrene	**1′b**	Toluene	50	36	86:14	nd	29

[a] Ethyl diazoacetate (1.66 mmol), olefin (5.54 mmol), $Cu(OTf)_2$ (0.0276 mmol, 1.7 mol%), ligand (0.03 mmol, 1.8 mol%), CH_2Cl_2, r.t.
[b] After removal of the chiral complex by silica gel chromatography the yield and the ratio of *cis* and *trans*-isomers were determined by GC analysis of the styrene—product mixture.
[c] The %ee was determined by chiral GC analysis.
[d] Compounds (1*R*,2*R*) and (1*R*,2*S*) were the major enantiomers based on a comparison of our chromatograms with those given in the literature [18].
[e] Molecular sieves 4A were present during the reaction. nd = not determined.

5. Preparation of ligands

*5.1. (−)-Bis[(R)-4-isopropyloxazolin-2yl]-2-methylpropene **1a***

A solution of diethyl isopropylidenemalonate **2** (2.0 g, 0.01 mol) in ethanol (25 ml) was added to a solution of NaOH (0.8g, 0.02 mol) in ethanol (25 ml) and the solution was stirred for 15 h at room temperature. The ethanol was removed under reduced pressure and the residue was dissolved in H_2O (20 ml), cooled, and cautiously acidified with conc. HCl to a pH of 7.0. The solution was extracted with CH_2Cl_2 (2 × 15 ml) to remove unreacted ester. The acidification was continued to a pH of 3, and the acid was extracted with EtOAc (4 × 30 ml). The organic layers were dried ($MgSO_4$), filtered and concentrated to afford isopropylidenemalonic acid (0.815 g, 57%) as white crystals, mp = 175–177 °C, ^{1}H NMR (300 MHz, MeOD) 2.12 (s, 6H).

A dry two-necked round bottom flask (25 ml) equipped with a magnetic stir bar was charged with isopropylidenemalonic acid (2.00 g, 13.80 mmol), dimethylformamide (0.13 g, 0.12 ml, 1.85 mmol, 0.13 equiv.) and CH_2Cl_2 (15 ml). The solution was cooled to 0 °C, and oxalyl chloride (5.26 g, 41.62 mmol, 3.61 ml, 3 equiv.) was added dropwise over 1.5 h and then the solution was stirred overnight at room temperature. The solution was concentrated in vacuo to give a dark brown liquid that was distilled by microdistillation to give isopropylidenemalonyl chloride **3** (1 g, 39%) as a yellow liquid, ^{1}H NMR (300 MHz, $CDCl_3$) 2.19 (s, 6H).

A two necked round bottom flask (50 ml) fitted with a magnetic stirring bar was charged with a solution of L-valinol (1.80 g, 17.4 mmol, 2 equiv.) and dry CH_2Cl_2 (15 ml) and the solution was cooled to 0 °C using an ice bath. Dry triethylamine (2.63 g, 3.64 ml, 26.10 mmol, 3 equiv.) was added via syringe. A solution of isopropylidenemalonyl chloride **3** (1.57 g, 8.70 mmol) in CH_2Cl_2 (5 ml) was slowly added via syringe to the vigorously stirred reaction mixture over 20 min. The ice bath was removed, and the white suspension was stirred at room temperature for 2 h. CH_2Cl_2 (10 ml) was added, dissolving most of the white solid. The reaction mixture was washed with 2 M HCl (8 ml), saturated aqueous $NaHCO_3$ (10 ml) and the aqueous layer was back-extracted with CH_2Cl_2 (10 ml). The combined organic extracts were washed with brine (10 ml), and the aqueous layer was back-extracted with CH_2Cl_2 (10 ml). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to give (*R*,*R*)-*N*,*N*′-bis-(1-hydroxymethyl-2-methyl-propyl)-2-isopropylidene-malonamide **4a** as a white solid. The crude product was purified by column chromatography (silica gel, EtOAc) to afford diamide (1.64 g, 38%) as white crystals; mp = 105–106 °C; $[\alpha]_D^{21}$ +42.5 (*c* = 0.28, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) 7.64 (s, 1H), 7.46 (d, 1H, *J* = 2.1 Hz), 7.44 (d, 1H, *J* = 3.6 Hz), 7.38–6.65 (m, 5H), 3.91–3.34 (m, 6H), 0.94 (d, 3H, *J* = 6 Hz), 0.92 (d, 3H, *J* = 6 Hz), 0.85 (d,

3H, $J = 6$ Hz), 0.78 (d, 3H, $J = 6$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.23, 165.11, 138.51, 133.52, 131.84, 129.67, 129.43, 128.65, 63.51, 63.16, 57.72, 57.32, 29.44, 28.90, 19.52, 19.43, 18.92, 18.56; IR (KBr) ν_{max} 3455, 3304, 1619, 1523, 1076 cm^{-1}; FAB-MS *m/z*: 363.27 $[M + H]^+$.

A solution of methanesulfonyl chloride (0.50 g, 4.37 mmol, 2.5 equiv.) in dry dichloromethane (1 ml) was added dropwise over 20 min to a solution of diamide **4a** (0.55 g, 1.74 mmol) and dry triethylamine (1.05 g, 1.45 ml, 10.44 mmol, 6 equiv.) in dry dichloromethane (5 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 2 days. The reaction mixture was then poured into a saturated aqueous NH_4Cl solution (5 ml). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 3 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**)** giving the *title bisoxazoline* **1a** as a brown viscous oil (0.35 g, 72%), $[\alpha]_D^{21}$ −70.88 ($c = 0.4$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) 4.29–4.22 (m, 2H), 4.03–3.98 (m, 4H), 2.06 (s, 6H), 1.82–1.75 (m, 2H), 0.97 (d, 6H, $J = 5.2$ Hz), 0.90 (d, 6H, $J = 5.2$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 161.78, 151.85, 72.43, 69.61, 32.66, 23.41, 18.88, 18.25); IR (KBr) ν_{max} 3261, 3068, 2958, 1715, 1638, 1551, 1466, 1076 cm^{-1}; FAB-MS *m/z*: 279.19 $[M + H]^+$; HRMS (FAB) found, 279.2079; $C_{16}H_{27}N_2O_2$ requires 279.2073.

*5.2. (−)-Bis[(R)-4-benzyloxazolin-2yl]-2-methylpropene **1b***

The same procedure as described previously was used in the reaction of isopropylidenemalonyl chloride **3** (0.5 g, 2.76 mmol) with (*R*)-(+)-phenylalaninol (0.83 g, 5.4 mmol, 2 equiv.) and dry triethylamine (0.83 g, 1.15 ml, 8.28 mmol, 3 equiv.) to give (*R*,*R*)-*N*,*N*′-bis-(1-benzyl-2-hydroxy-ethyl)-2-isopropylidene-malonamide **4b** (0.63 g, 56 %) as white crystals after purification by column chromatography (silica gel, EtOAc); mp 154–155 °C (recr. from EtOAc); $[\alpha]_D^{21}$ +12.1 ($c = 0.28$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) 7.27–7.17 (m, 10H); 7.04 (s, 1H), 7.02 (s, 1H), 4.35–4.28 (m, 2H), 3.97 (br s, 2H), 3.78-3.71 (m, 2H), 3.51-3.43 (m, 2H), 2.80 (dd, 2H, $J = 13.7$, 6.5 Hz), 2.69 (dd, 2H, $J = 13.7$, 6.5 Hz), 2.69 (dd, 2H, $J = 13.7$, 9.0 Hz), 1.57 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.57, 146.11, 137.59, 129.68, 129.18, 128.51, 126.58, 64.46, 52.88, 37.04, 22.05; IR(KBr) ν_{max} 3364, 3269, 1635, 1534, 1081, 744, 699 cm^{-1}; FAB-MS *m/z*: 411.26 $[M + H]^+$.

Using the same procedure as described previously malonamide **4b** (0.30 g, 0.75 mmol) was reacted with methanesulfonyl chloride (0.21 g, 1.88 mmol, 2.5 equiv.) and dry triethylamine (0.63 ml, 0.45 g, 4.53 mmol, 6 equiv.) to give the *title bis-oxazoline* **1b** (0.236 g, 86%) as a yellow gum after purification by column chromatography (silica gel, EtOAc); $[\alpha]_D^{21}$ −33.94 ($c = 0.2$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) 7.31–7.20 (m, 10H), 4.55–4.49 (m, 2H), 4.23 (dd, 2H, $J = 9$, 8.5 Hz), 4.03 (dd, 2H, $J = 9$,7.5 Hz), 3.17 (dd, 2H, $J = 13.5$, 5 Hz), 2.70 (dd, 2H, $J = 13.5$, 8.5 Hz), 2.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) 152.75, 138.05, 129.27, 128.51, 126.43, 71.40, 67.72, 41.63, 23.51; IR (KBr) ν_{max} 3292, 2916, 1712, 1668, 1643, 1217, 734, 701 cm^{-1}; FAB-MS *m/z*: 375.18 $[M + H]^+$; HRMS (FAB) found, 375.2074; $C_{24}H_{27}N_2O_2$ requires 375.2073.

*5.3. (−)-Bis[(S)-4-tert-butyloxazolin-2yl]-2-methylpropene **1′a***

The same procedure as described previously was used in the reaction of isopropylidenemalonyl chloride **3** (0.842 g, 4.65 mmol) with (*S*)-(−)-*tert*-leucinol (1.089 g, 9.3 mmol) and dry triethylamine (1.41 g, 1.95 ml, 14.0 mmol, 3 equiv.) to give (*S*,*S*)-*N*,*N*′-bis-(1-hydroxymethyl-2,2-dimethyl-propyl)-2-isopropylidene-malonamide **4c** (0.335 g, 21%) as white crystals after purification by column chromatography (silica gel, EtOAc); mp 150–152 °C; $[\alpha]_D^{22}$ +93.7 ($c = 0.3$, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) 7.11 (br s, 1H); 7.08 (br s, 1H); 3.92–3.79 (m, 4H), 3.52–3.45 (m, 2H), 1.97 (s, 6H), 0.93 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) 168.37, 144.49, 130.81, 61.62, 59.94, 33.38, 26.86, 22.50; IR (KBr) ν_{max} 3278, 2961, 1630, 1541, 1475, 1367, 1050, 730 cm^{-1}.

Using the same procedure as described previously malonamide **4c** (0.296 g, 0.86 mmol) was reacted with methanesulfonyl chloride (0.247 g, 2.16 mmol, 2.5 equiv.) and dry triethylamine (0.72 ml, 0.524 g, 5.18 mmol, 6 equiv.) to give the *title bis-oxazoline* **1′a** (0.190 g, 72%) as a colourless oil after purification by column chromatography (silica gel, EtOAc); $[\alpha]_D^{21}$ −15.07 ($c = 0.69$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) 4.21 (dd, 2H, $J = 10.2$, 8.1 Hz), 4.08 (t, 2H, $J = 8.1$Hz), 3.97 (dd, 2H, $J = 10.2$,8.1 Hz), 2.08 (s, 6H), 0.92 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) 161.89, 151.72, 115.58, 76,15, 68.23, 33.86, 26.02, 23.51; IR (NaCl) ν_{max} 3280, 2957, 1653, 1475, 1364, 1215, 1014, 799 cm^{-1}; FAB-MS *m/z*: 307.17 $[M + H]^+$, HRMS (FAB) found, 307.2397; $C_{18}H_{31}N_2O_2$ requires 307.2386.

*5.4. (−)-Bis[(S)-4-phenyloxazolin-2yl]-2-methylpropene **1′b***

The same procedure as described previously was used in the reaction of isopropylidenemalonyl chloride **3** (1.50 g, 8.2 mmol) with (*S*)-phenylglycinol (2.25 g, 16.40 mmol, 2 equiv.) and dry triethylamine (2.48 g, 3.43 ml, 24.60 mmol, 3 equiv.) to give (*S*,*S*)-*N*,*N*′-bis-(2-hydroxy-1-phenyl-ethyl)-2-isopropylidene-malonamide **4d** (1.43 g, 45%) as white crystals after purification by column chromatography (silica gel, EtOAc), mp 144–145 °C, $[\alpha]_D^{22}$ +30.4 ($c = 0.3$, acetone), ^{1}H NMR (400 MHz, acetone-d_6) 7.80 (br s, 1H), 7.78 (br s., 1H), 7.32–7.19 (m, 10H), 5.12–5.08 (m, 2H), 3.83–3.79 (m, 2H), 3.89–3.70 (m, 2H), 1.91 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) 177.31, 167.25, 129.08, 127.77, 66.29, 56.38, 22.46;

IR (KBr) ν_{max} 3300, 1699, 1667, 1535, 1074, 763, 703 cm^{-1}; FAB-MS *m/z*: 383.17 $[M+H]^+$.

Using the same procedure as described previously malonamide **4d** (0.30 g, 0.78 mmol) was reacted with methanesulfonyl chloride (0.224 g, 1.96 mmol, 2.5 equiv.) and dry triethylamine (0.475 g, 0.65 ml, 4.70 mmol, 6 equiv.) to give the *title bis-oxazoline* **1′b** (0.205 g, 76%) as a colourless gum after purification by column chromatography (silica gel, EtOAc), $[\alpha]_D^{21}$ −68.07 ($c = 0.22$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) 7.31–7.26 (m, 10H), 5.34 (dd, 2H, $J = 8$, 6.8 Hz), 4.70 (dd, 2H, $J = 8$, 6.8 Hz), 4.17 (dd, 2H, $J = 6.8$, 6.8 Hz), 2.17 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) 153.43, 142.40, 128.64, 127.46, 126.82, 74.46, 69.97, 23.75; IR (Film on NaCl) ν_{max} 3291, 2927, 1738, 1661, 1634, 1537, 759, 700 cm^{-1}; FAB-MS *m/z*: 347.10 $[M+H]^+$; HRMS (FAB) found, 347.1747; $C_{22}H_{23}N_2O_2$ requires 347.1760.

6. Conclusion

In terms of efficiency, diastereoselectivity and enantioselectivity our results are encouraging. Solvent effects were observed in these reactions, with CH_2Cl_2 giving the best yields and toluene the best stereoselectivities.

It was also shown that ligand **1a** compares very well with the corresponding Evans ligand for the cyclopropanation of styrene. We are currently evaluating the Isbut-Box system in a number of other catalytic asymmetric reactions and at synthesising a family of Isbut-Box ligand analogues with greater modular structural diversity for catalytic asymmetric synthesis.

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