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Cu(I) catalysed cyclopropanation of olefins: Stereoselectivity studies with Arylid-Box and Isbut-Box ligands

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Abstract

In our quest to find new ligands for highly stereoselective reactions, we tested a variety of chiral non-racemic *pseudo*-C_2 symmetric bis-oxazolines derived from malonic acid containing an arylidene bridge unit (and appropriately termed Arylid-Box) in the catalytic asymmetric cyclopropanation (CAP) reaction of styrene and ethyl diazoacetate using between only 1–2 mol% of a Cu(I) pre-catalyst. Some very good e.e.s (up to 86%), were obtained. It was possible to isolate **10a**′-$[Cu(CH_3CN)_4]PF_6$ which existed as a bench stable solid that proved to be more efficient than the catalyst prepared *in situ*. Cu(I) pre-catalysts were used for the first time in the CAP reaction with the Isbut-Box ligands **13a** and **13b** and, although, the e.e.s were better for ligand **13a** using these pre-catalysts, in the case of ligand **11b** this was not the case. Spectroscopic studies (UV–Vis and ^1H NMR) were carried out to gain an insight into the nature of the catalytic species at work so that the conditions could be optimised giving better results. Some theoretical studies were conducted to try to explain the better enantioselectivities obtained using Evans' *tert*-Box–Cu(I) complex over our complex.

Keywords: Bis-oxazolines; Catalytic asymmetric synthesis; Cyclopropanation; Counter-ion effect

1. Introduction

Over the last 15 years chiral bis-oxazoline (Box) compounds have been shown to be very useful ligands for catalytic asymmetric synthesis demonstrating good to high enantioselectivities in a number of catalytic asymmetric reactions [1]. Despite the large number of Box ligands already known, only a handful have been shown to be highly stereoselective, and there is a need to develop new Box ligands with novel structures which have potential to meet the aforementioned requirement. For this purpose we recently introduced a new family of Box ligands called Isbut-Box (Fig. 1) [2]. These ligands showed some satisfactory e.e.s and d.e.s (up to 70% and 72%, respectively) for catalytic asymmetric olefin cyclopropanations. A second generation series of Boxs with an arylidine bridge between the rings (and termed Arylid-Box) was then developed (Fig. 1) and also tested in a number of benchmark catalytic asymmetric olefin cyclopropanations [3]. In this paper, we wish to report: (1) our full experimental results for the synthesis of our Arylid-Box ligands; (2) our findings on the effect of the counter-ion on the reaction selectivity; (3) our results for comparative studies on the stereoselectivity of the Isbut-Box system with the Arylid-Box system in this reaction (4) studies probing the structure of the catalytic species involved and (5) a comparative DFT study of a particular Arylid-Box–Cu(I) complex with Evans'

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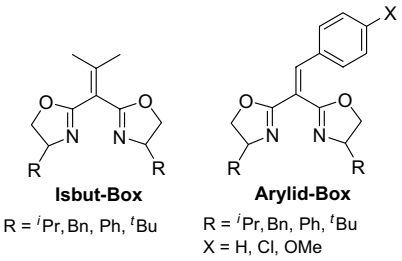


Fig. 1. Isbut-Box and Arylid-Box ligands.

tert-But-Box–Cu(I) complex and their corresponding metallocarbene complexes.

2. Results and discussion

The series of Arylid-Box ligands[1] **5a**, **5b**, **10a–f** and **10a′** were prepared in satisfactory yields using the synthetic pathways shown in Schemes 1 and 2. For the synthesis of the Arylid-Boxs **5a**, **5b**, **10a–f** and **10a′** (Schemes 1 and 2) the key starting material was the arylidene malonic acid obtained either by hydrolysis of the corresponding commercially available diethyl benzylidenemalonate ester [2] or the known dimethyl arylidene malonate esters [4] or via the procedure of Neustadt et al. [5] using a simple Knoevenagel condensation with malonic acid (both benzylidene malonic acid and its *para*-substituted methoxy analogue were prepared by this procedure).

A standard synthetic procedure was subsequently used to transform the acids to the corresponding Boxs via their acid chloride intermediates. It must be noted that all the acid chloride intermediates were not purified and used in the proceeding step like so, due to their unstable nature. Satisfactory yields could be obtained in all cases. To ascertain the stability of these Arylid-Box ligands in solution, a ^{1}H NMR spectrum was recorded for the Arylid-Box **10f** in $CDCl_3$ and after 8 days of standing in this solvent at room temperature there was no change in the ^{1}H NMR spectrum.

These ligands were subsequently used in a series of Cu(I) catalysed olefin cyclopropanations with ethyl diazoacetate [3] using the Cu(I) pre-catalyst, $[Cu(CH_3CN)_4]PF_6$ and the Cu(II) pre-catalyst, Cu(II)$(OTf)_2$ (Scheme 3) which was reduced *in situ* to Cu(I).

The highest e.e. recorded (89%) was obtained using ligand **10d** with $[Cu(CH_3CN)_4]PF_6$ in toluene [3], and the best d.e. (40%) using **10e** with Cu(II)$(OTf)_2$ in CH_2Cl_2. At the outset we expected some correlation between the type of substituted Arylid-Box ligand used and the reaction stereoselectivity, given that both inductive and resonance effects were expected, like for instance, decreased reactivity using *para*-methoxy substituted Arylid-Boxs **10e** and **10f** due to the expected reduction in the metallocarbene intermediate electrophilicity. Such trends were not observed [3] and we postulated that this was due to slight tilting of the arylidene phenyl unit out of the plane as suggested by a density functional theory (DFT) study conducted at a B3LYP level [6] that would prevent any significant ressonace effects in such complexes. The DFT study was conducted on the Cu(I)–Arylid-Box **10b** complex (for reasons of simplicity, in our model no other ligands were considered nor any counter-ions) by using the GAMESS-US [7] package with the 6-31G* basis-set for C, N, O and H and applying the Stuttgart RSC 1997 [8] effective core potential for Cu (some selected measurements appear in the caption for Fig. 2). Geometry was optimized without symmetry constraints and the stationary point was subsequently confirmed to be a minimum by frequency calculations carried out at that level.

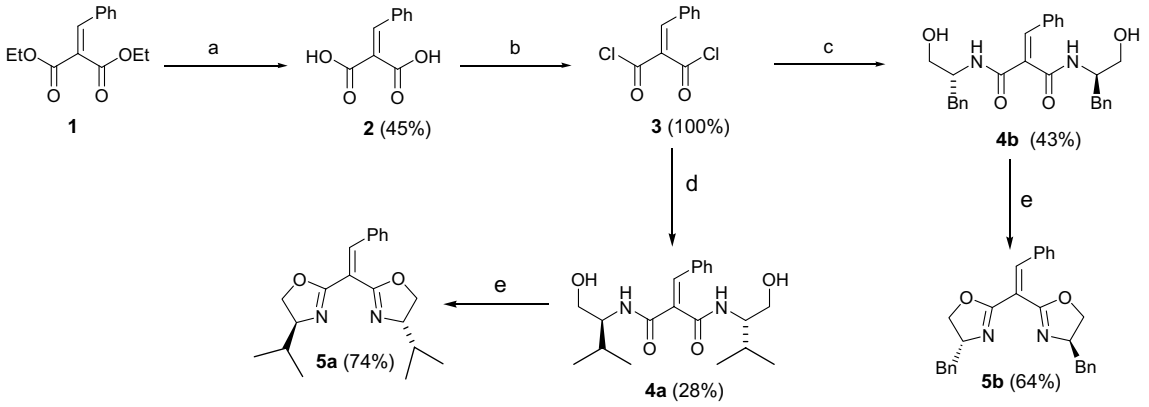
The two N–Cu bond lengths were equivalent (1.931 Å and 1.932 Å) and the N–Cu–N bite angle was calculated to be 107.5°. The calculated N–Cu bond lengths are close to the values of 1.90–1.91 Å reported by Rasmussen et al. [9] and compares well with the observed value of 1.88 Å for a N–Cu bond determined for an oxazoline–Cu(I) complex by X-ray crystallographic analysis by Evans et al. [10]. Also the calculated bite angle value is close to the value of 110° ± 2° calculated by Rasmussen et al. [9].

The torsion angle of 28.6° calculated for the C(3)–C(1)–C(2)–C(5) unit, showed the degree to which the phenyl ring was forced out of the plane. A comparative study was also carried out on the *gem*-dimethyl malonate derived ligand–Cu(I) complex of Evans [11], namely *tert*-But-Box–Cu(I) (see Supporting information) and bond lengths of 1.934 and 1.932 Å, respectively were calculated for both the N–Cu bonds and a slightly smaller bite angle of 107.0° was calculated. The fact that we were unable to obtain e.e.s as high as those reported by Evans using the *tert*-But-Box–Cu(I) complex led us to postulate that the slightly larger bite angle calculated for our complex should allow the carbenoid carbon of the intermediate metallocarbene–Cu(I) complex to move slightly away from the source of asymmetric induction than in Evans' complex. In fact, this hypothesis was later substantiated by some DFT calculations on some Cu(I) metallocarbene model complexes (vide infra).

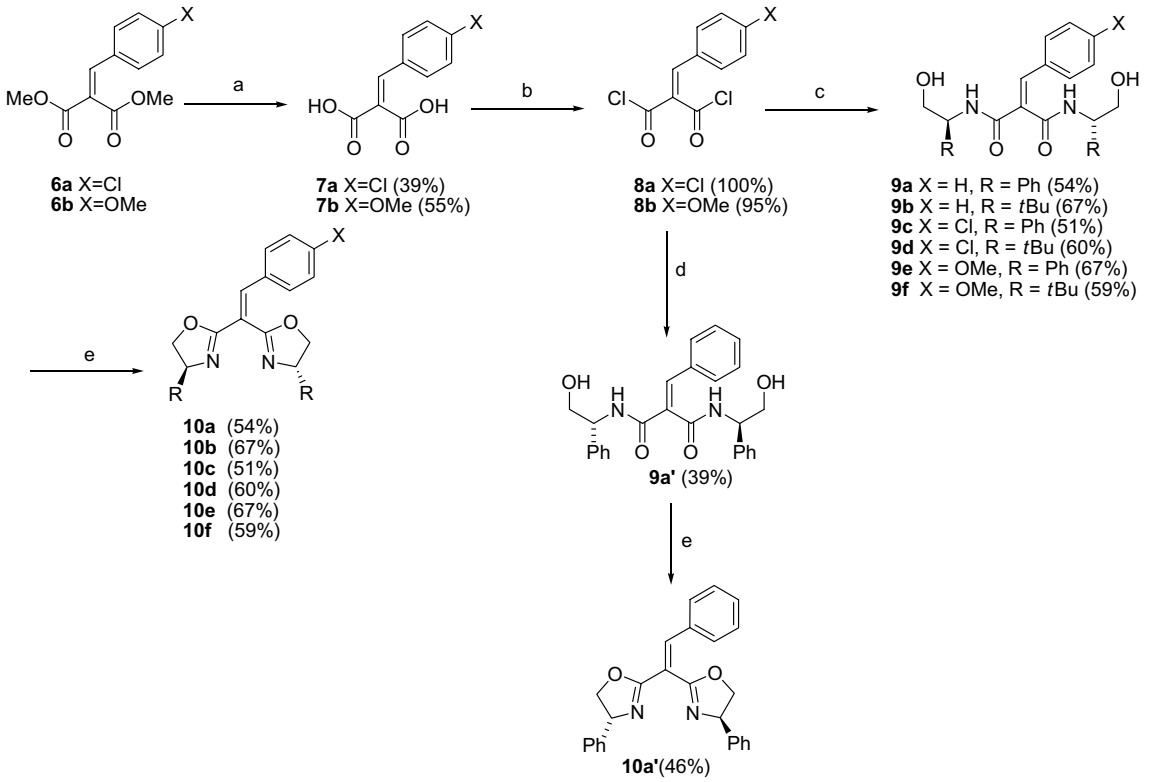
In order to determine the extent of electron delocalisation between the phenyl backbone and the oxazoline ring, Mayer bond orders were calculated for a number of key bonds and are presented in Table 1. Relatively weak electron delocalisation about the π-bonded framework was observed as implied by the magnitudes for the bond orders.

The bond order calculation predicts no uniform electron delocalisation between the back-bone phenyl ring and the oxazoline rings, because in some cases the bond order approximates to 1 (for example, C1–C3, C2–C4 and C2–C5), whilst in other cases it shows the typical bond order of a delocalised system (C1–C2 and C4–N13). The

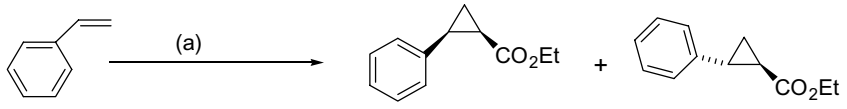
[1] It must be noted that in our previous two papers [2,3] (*R*)-(+)-phenylalaninol was inadvertently indicated and as a consequence the configurations of the corresponding amides and Box ligands were wrongly depicted in the relevant schemes.



Scheme 1. Reagents and conditions: (a) NaOH, EtOH; (b) $(COCl)_2$, DMF, CH_2Cl_2, 0 °C; (c) (*R*)-(+)-phenylalaninol (2 equiv.), NEt_3, CH_2Cl_2; (d) (*S*)-valinol (2 equiv.), NEt_3, CH_2Cl_2; (e) CH_3SO_2Cl (2.5 equiv.), NEt_3 (6 equiv.), CH_2Cl_2.



Scheme 2. Reagents and conditions: (a) NaOH, EtOH; (b) $(COCl)_2$, DMF, CH_2Cl_2, 0 °C; (c) (*S*)-(+)-phenylglycinol or (*S*)-*tert*-leucinol, NEt_3, CH_2Cl_2; (d) (*R*)-(−)-phenylglycinol, NEt_3, CH_2Cl_2; (e) CH_3SO_2Cl (2.5 equiv.), NEt_3 (6 equiv.), CH_2Cl_2.



Scheme 3. Reagents and conditions [3]: (a) ethyl diazoacetate, $[Cu(CH_3CN)_4]PF_6$ (1 or 2 mol%) or Cu(II)$(OTf)_2$ (1 or 2 mol%), Arylid-Box ligand (1.1 or 2.2 mol%), CH_2Cl_2 or toluene, r.t.

calculation also predicts a stable coordinate bond between N6, N13 and the metal (as the predicted bond orders of 0.475 and 0.463 show).

In our preliminary study [3], we used only two types of pre-catalyst, one containing Cu(I) ($[Cu(CH_3CN)_4]PF_6$) and the other contained Cu(II) [Cu(II)$(OTf)_2$]. It thus became

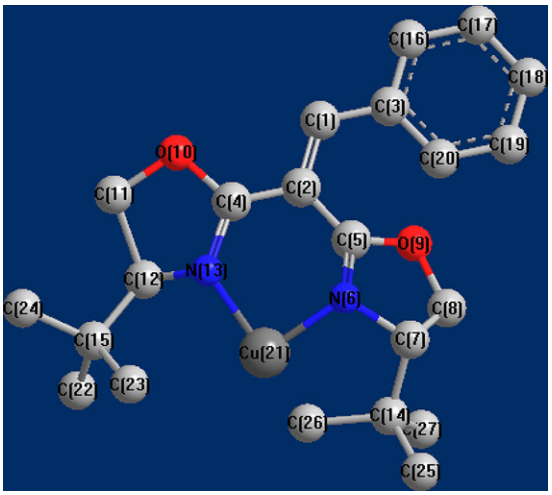


Fig. 2. Chem-3D representation of the Cu(I)–Arylid-Box **10b** model complex (Hs are omitted for clarity) whose optimised structure was determined using DFT. Selected bond lengths (Å) and bond angles (°): Cu–N13, 1.932; Cu–N6, 1.931; C1–C2, 1.372; N(13)–Cu(21), 1.932; C(4)–C(2)–C(5), 121.2; N(13)–Cu(21)–N(6), 107.5; C(3)–C(1)–C(2)–C(5), 28.6.

Table 1
Mayer bond orders derived from the DFT study

Bond	Bond order
C1–C3	1.120
C1–C2	1.574
C2–C4	1.086
C2–C5	1.046
C4–N13	1.404
C5–N6	1.427
Cu(21)–N6	0.475
Cu(21)–N13	0.463

of importance to look at other Cu(I) pre-catalysts and compare the results with those using $[Cu(CH_3CN)_4]PF_6$. For this reason, we decided to look at Cu(I)OTf, Cu(I)Cl and $Cu(I)SbF_6$. In the case of the latter, this pre-catalyst was generated *in situ* according to a modification of Evans' procedure [12]. These reactions were carried out using 1 and 2 mol% of pre-catalyst, respectively, and styrene as the olefin in all cases (Table 2).

It was obvious from this study that all the reactions using $[Cu(CH_3CN)_4]PF_6$ gave the highest e.e.s. $Cu(I)SbF_6$ gave e.e.s comparable with Cu(I)OTf. The best d.e.s were obtained using Cu(I)OTf, and in one case (Table 2, entry 6) a d.e. as high as 68% was obtained. CuCl was only used once (Table 2, entry 3) and it gave poor e.e.s. This was probably due to the poor coordinating ability of the counter-ion [11]. It would appear that the more coordinating trifluoromethanesulfonate (OTf) [13] leads to greater diastereoselection in this reaction. However, we are unsure why the reaction with ligand **10a′** and Cu(I)OTf (Table 2, entry 2) gives lower e.e.s than when PF_6^- or SbF_6^- are used as counter ions (Table 2, entry 1 and 4).

We have also successfully isolated a Cu(I)–Arylid-Box-**10a′** complex by mixing $[Cu(CH_3CN)_4]PF_6$ with Arylid-Box **10a′**. It existed as a bench stable metallic black powder, which was quite difficult to characterise (the ^1H NMR was very poorly resolved and furnished very little information), however, mass spectrometric analysis would appear to imply the existence of a di-coordinated complex. We failed to obtain crystals of this compound that would enable us obtain an X-ray crystal structure. It was used to catalyse a cyclopropanation reaction between styrene and ethyl diazoacetate giving a 43% yield of cyclopropane diastereomers, with a diastereoselectivity of 36% and e.e.s of 61% (*trans*-isomer) and 53% (*cis*-isomer) which was a somewhat better result than that obtained when the complex was generated *in situ*. The (1*S*,2*S*)-enantiomer was the major trans enantiomer whilst the (1*S*,2*R*)-enantiomer was the major *cis*-enantiomer.

In each of these reactions dimerisation of the intermediate Cu(I)–metallocarbene giving a mixture of diethyl fumarate and diethyl maleate occurred on a small scale (approx. 11% of the total product).

Table 2
Study to obtain the most effective pre-catalyst for the catalytic asymmetric cyclopropanation of styrene using Arylid-Box ligands **10a**, **10a′**, **10b**, **10d** and **10f**[a]

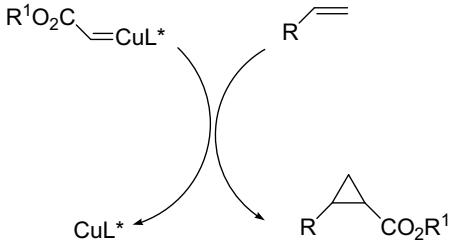
Entry	Pre-catalyst (mol%)	Ligand (mol%)	Yield (%)	*trans*:*cis*[b]	*trans* (% e.e.)[c,d]	*cis* (% e.e.)[c,d]
1	$[Cu(CH_3CN)_4]PF_6$ (2)	**10a** (2.2)	30	65:35	57(1R,2R)	45(1R,2S)
2	Cu(I)OTf (2)	**10a′** (2.2)	24	79:21	12(1S,2S)	7(1S,2R)
3	CuCl (2)	**10a′** (2.2)	12	64:36	13(1S,2S)	10(1S,2R)
4	$Cu(I)SbF_6$ (2)	**10a′** (2.2)	8	67:33	45(1S,2S)	57(1S,2R)
5	$[Cu(CH_3CN)_4]PF_6$ [3]	**10b** (1.1)	19	56:44	78(1R,2R)	69(1R,2S)
6	Cu(I)OTf (1)	**10b** (1.1)	18	84:16	74(1R,2R)	68(1R,2S)
7	$[Cu(CH_3CN)_4]PF_6$ (2)	**10d** (2.2)	20	61:39	86(1R,2R)	78(1R,2S)
8	Cu(I)OTf (2)	**10d** (2.2)	29	68:32	63(1R,2R)	48(1R,2S)
9	$Cu(I)SbF_6$ (2)	**10d** (2.2)	16	57:43	58(1R,2R)	52(1R,2S)
10	$[Cu(CH_3CN)_4]PF_6$ (2)	**10f** (2.2)	46	62:38	83(1R,2R)	75(1R,2S)
11	Cu(I)OTf (2)	**10f** (2.2)	28	66:34	77(1R,2R)	62(1R,2S)

[a] Ethyl diazoacetate, styrene, Cu(I) catalyst and Arylid-Box ligand, CH_2Cl_2, r.t.
[b] Determined by GC analysis.
[c] The % e.e. was determined by chiral GC analysis (on a cyclosil-B capillary column).
[d] The major isomer is indicated in parenthesis.

Although our primary interest was the acquisition of high enantio- and diastereoselection in this reaction, and this is where we focused our efforts, we later became conscious of the generally poor isolated yields that were obtained, no matter what reaction condition was used. This was hard to explain due to the fact that we obtained only cyclopropane isomers as the main products. However, careful examination of our experimental procedure revealed that as we used an excess of styrene (10 equiv. relative to EDA) the excess styrene at the end appeared to form a colloidal type layer that impeded the isolation of all the cyclopropane product at the pre-column purification stage (removal of the catalyst, see Experimental Part). To verify this, we carried out a cyclopropantion using 10 equiv. of styrene, with ligand **10a**′ (2.2 mol%) and $[Cu(CH_3CN)_4]PF_6$ (2 mol%) and at the end of the reaction the crude product was filtered to remove the catalyst, but this time instead of washing with just CH_2Cl_2 (as was always done before), both EtOAc and MeOH were used. Using this procedure, the cyclopropane products were isolated in a combined isolated yield of 64% after column chromatography. We also discovered that there was basically no change in the stereoselectivities from before (see Table 2, entry 1) as the *trans*-isomer was obtained with an e.e. of 62% (in favour of the 1*S*,2*S*-enantiomer) and the *cis*-isomer with an e.e. of 43% (in favour of the 1*S*,2*R*-enantiomer). The *trans*:*cis* ratio was also the same 62:38.

The proposed mechanism for the decomposition of the short-lived electrophilic copper–carbene intermediates derived from diazoacetates by olefins [9] (or the cyclopropanation step) is that shown in Scheme 4.

To obtain a better view of the nature of the catalytic species at work in this reaction and the kinetics for its formation, we conducted some spectroscopic studies on the $[Cu(CH_3CN)_4]PF_6$–**10a**′ complex. The ^{1}H NMR study on the $[Cu(CH_3CN)_4]PF_6$–**10a**′ complex was carried out to verify if in fact the complex was undergoing some structural re-organization in the early stage of this reaction. Unfortunately this study was inconclusive. We thus turned to UV–Vis spectroscopy for some insight. Soon after mixing the ligand **10a**′ with the $[Cu(CH_3CN)_4]PF_6$ complex an aliquot was removed at hourly intervals. The spectra were the same in all cases with absorption maxima of 231 and 330 nm, respectively. The ligand itself presented two absorption maxima of 231 and 285 nm, the first most probably a π–π^* transition was also observed in the complex. Interestingly, $[Cu(CH_3CN)_4]PF_6$ also presented an absorption maximum at 231 nm. Observation of the $[Cu(CH_3CN)_4]PF_6$–**10a**′ complex over a 3 h period, showed that there was in fact no change in the UV–Vis spectrum of the complex, thus ruling out the possibility of structural re-organization occurring. It has to be noted that if one considers the bathochromic shift from 285 to 330 nm, an indication of complexation, then complex formation was immediate. A study was then carried out to investigate the kinetics of decomposition of the EDA with the $[Cu(CH_3CN)_4]PF_6$–**10a**′ complex. The $[Cu(CH_3CN)_4]$-PF_6–**10a**′ complex was treated with 1 equivalent of ethyl diazoacetate (EDA). In this case, we observed a very slight bathochromic shift of 5 nm ($\lambda_{max} = 335$ nm). The spectrum remained more or less constant through out the duration of this study. The only difference was that the absorption maximum for the EDA ($\lambda_{max} = 245$ nm) disappeared after about 5 hours. This implies that it takes the complex about this time to decompose the EDA forming the transitory metallocarbene copper complex. We also attempted isolating the metallocarbene copper (I)-complex which results from the reaction of $[Cu(CH_3CN)_4]PF_6$–**10a**′ complex with EDA (by mixing $[Cu(CH_3CN)_4]PF_6$–**10a**′ complex with one equivalent of EDA) giving a green metallic solid. This was analysed by both variable temperature ^{1}H NMR and mass spectrometry. The variable temperature ^{1}H NMR study was uninformative, and there was very little difference between the spectrum at room temperature and that at −30 °C, in fact, the resolution deteriorated at the lower temperature. Likewise mass spectrometric analysis of this solid was also uninformative. The solid was also mixed with styrene in CH_2Cl_2 but no reaction was observed even after several days. All indications being that this solid was not the metallocarbene complex an assumption backed up by literature precedent [14,17] as these species are very elusive.



Scheme 4. Mechanism for the cyclopropanation step.

In an attempt to gain an insight into the lower e.e.s that were obtained for our *tert*-butyl substituted ligands compared to those obtained with Evans' gem-dimethyl malonate derived ligand, we conducted some DFT calculations (at the same level of theory as previously [6–8,15–18]), on the model Cu(I)–metallocarbene complexes **11** and **12** (Fig. 3) which are basically approximations of the Cu(I)–metallocarbene species derived from our Cu(I)–Arylid-Box ligands and Evans' gem-dimethyl malonate derived ligands. It was observed that for both Cu(I)–metallocarbene complexes **11** and **12** the Cu–N bond lengths were longer than in the Cu(I)–Arylid-Box **10b**, meaning that coordination with the metal was weaker in the metallocarbene complexes. There was also a greater difference in the Cu–N bond lengths for either metallocarbene complex, for example in the case of Cu(I)–Arylid-Box **10b**, the difference was only 0.001 Å, but in the case of **11** and **12** it was 0.023 Å and 0.009 Å, respectively. These bond lengths, particularly those for **11** are close to the values calculated by Fraile et al. [18] for the Cu(I) metallocarbene derived from 2,2′-methylenebis[(4*S*)-methyl-2-oxazoline] and methyl diazoacetate. The fact that the calculated Cu–N

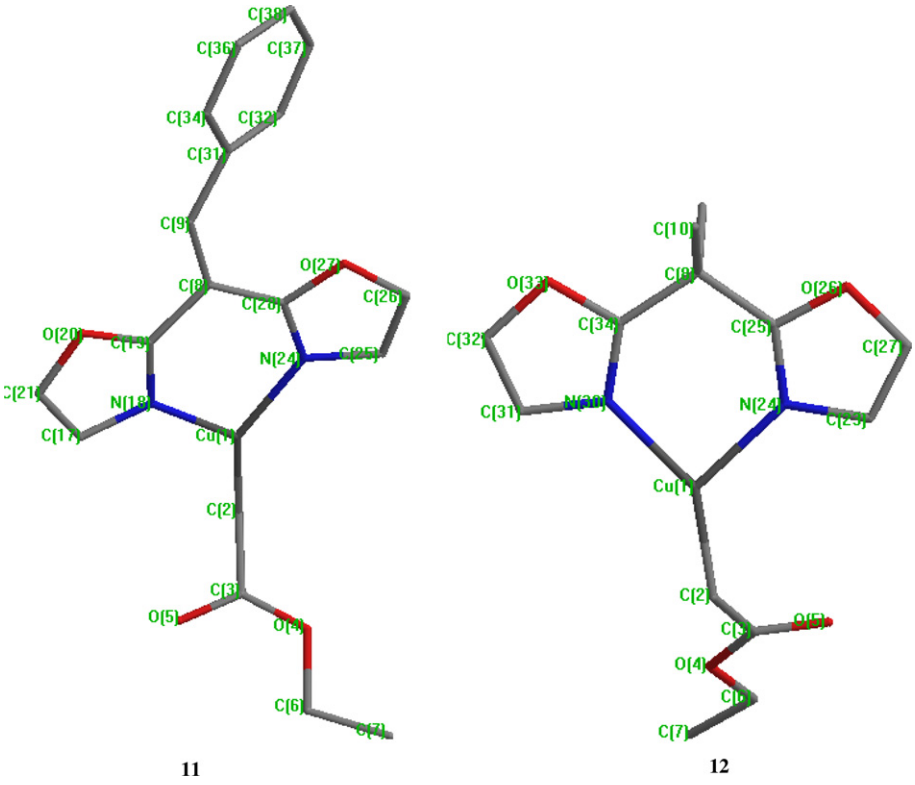


Fig. 3. Chem-3D representations (with the Hs omitted for clarity) of the Cu(I)–metallocarbene complexes **11** and **12** model complexes whose optimised structure was determined using DFT. Selected bond lengths (Å) and bond angles (°): For complex **11**: Cu–N18, 2.005; Cu–N24, 1.982; Cu–C2, 1.813; C19–C8–C28, 116.3, N18–Cu–C2, 128.7; N24–Cu–C2, 140.5; N18–Cu–N24, 90.8; N18–Cu–C2–C3, 74.2. For complex **12**: Cu–N30, 2.000; Cu–N24, 2.009; Cu–C2, 1.818; C32–C8–C25, 112.0; N30–Cu–C2, 144; N24–Cu–C2, 124.3; N30–Cu–N24, 91.6; N24–Cu1–C2–C3, 67.9.

bond lengths for **11** were shorter than for **12** would seem to indicate the former has the greater inherent stability, which is reinforced by the observation that the calculated Cu–C bond length for **11** was just slightly shorter than that for **12**. The bite angles calculated for **11** and **12** were very close, but somewhat smaller than that calculated in the Cu(I) metallocarbene studied by Fraile et al. [18] (95°). The carbonyl group for both **11** and **12** was calculated to be roughly perpendicular with the Cu–C bond, with **11** having the greater dihedral angle of 74.2° as opposed to 67.9° for **12**. An angle of 65.8° was reported by by Fraile et al. for their system [18]. In our case, this would imply that the carbenoid carbon of **11** should be the harder acid centre. On the basis of Pearson's HSAB theory [19] if one considers styrene a soft base then metallocarbene **12** should be the more reactive of the two. What was most interesting was the finding that there were significant differences between the N–Cu–C angles for both **11** (128.7° and 140.5°) and **12** (124.3° and 144°) meaning that the Cu–carbenoid carbon bond deviates away from the symmetry axis of the metallocarbene complex (this asymmetry was also observed in the system studied by Fraile et al. [18]) and it has important stereochemical implications as pointed out by Fraile et al. [18]. This calculation suggests that when one ignores electronic effects, complex **12** probably gives higher ees in the cyclopropanation reaction due to the closer proximity of the carbenoid carbon to one of the stereogenic centres.

Although we have shown that when Cu(II)$(OTf)_2$ is used as pre-catalyst with the Arylid-Box ligand system generally the enantioselectivities are better than with our first generation Isbut-Box ligand system [3], we became curious to know: (1) would there be a similar trend if a Cu(I) pre-catalyst was used and (2) would a Cu(I) pre-catalyst improve the enantioselectivities when Isbut-Box ligands were used. We thus carried out a number of cyclopropanations with the Isbut-Box ligands **13a** [2] and **13b** [2] (Fig. 4) and both ($[Cu(CH_3CN)_4]PF_6$) and Cu(I)OTf as the pre-catalysts (Table 3, the results obtained for the equivalent Arylid-Box ligands are included for comparative purposes as are the results for the Isbut-Box **13a** with Cu(II)$(OTf)_2^2$).

This study demonstrated that on using both Cu(I)OTf and $[Cu(CH_3CN)_4]PF_6$ with **13a** the e.e.s were much better than when Cu(II) $(OTf)_2$ was used (compare entry 1 with entries 2 and 3). Ligand **10b** gave slightly better e.e.s than **13a** when $[Cu(CH_3CN)_4]PF_6$ was used. In the case of ligand **13b** using Cu(II)$(OTf)_2$ (entry 6) the best e.e. was

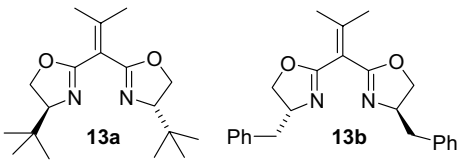


Fig. 4. Isbut-Box ligands used for cyclopropanations with Cu(I) pre-catalysts (Table 3).

Table 3
Study to compare the efficiency and stereoselectivity of Isbut-Box **13a** and **13b** with the Arylid-Box ligand **10b** using Cu(I) pre-catalysts[a]

Entry	Pre-catalyst	Ligand	Yield (%)	*trans*:*cis*[b]	*trans* (% e.e.)[c,d]	*cis* (% ee)[c,d]
1	Cu(II) $(OTf)_2^e$ [2]	**13a**[f]	61	58:42	46(1R,2R)	42(1R,2S)
2	Cu(I)OTf	**13a**	61	59:41	79(1R,2R)	73(1R,2S)
3	$[Cu(CH_3CN)_4]PF_6$	**13a**	38	56:44	67(1R,2R)	63(1R,2S)
4	Cu(I)OTf	**10b**	18	84:16	74(1R,2R)	78(1R,2S)
5	$[Cu(CH_3CN)_4]PF_6$ [3]	**10b**	19	56:44	78(1R,2R)	69(1R,2S)
6	Cu(II) $(OTf)_2^e$ [2]	**13b**	54	68:32	47(1R,2R)	22(1R,2S)
7	Cu(I)OTf	**13b**	20	62:38	38(1R,2R)	22(1R,2S)
8	$[Cu(CH_3CN)_4]PF_6$	**13b**	22	54:46	25(1R,2R)	7(1R,2S)

[a] Styrene, ethyl diazoacetate, Cu(I) catalyst (1 mol%) and ligand (1.1 mol%), CH_2Cl_2, r.t.
[b] Determined by GC analysis.
[c] The % e.e. was determined by chiral GC analysis (on a cyclosil-B capillary column).
[d] The major isomer is indicated in parenthesis.
[e] 1.7 mol% pre-catalyst was used.
[f] 1.8 mol% of **13a** was used.

obtained for the trans cyclopropane product. Overall, ligand **13a** seemed to give the better stereoselectivities.

3. Conclusions

In summary, we have carried out a number of detailed experiments to determine the most suitable Cu(I) pre-catalyst for the catalytic asymmetric cyclopropanation of styrene with ethyl diazoacetate using our Arylid-Box ligands. Our results indicate that it is $[Cu(CH_3CN)_4]PF_6$ which gives the best e.e.s, whilst Cu(I)OTf gives the best d.e.s. When the Isbut-Box ligands **13a** and **13b** were tested with Cu(I) pre-catalysts, it was ligand **13a** which gave the best results as it gave e.e.s close to those obtained with the equivalent Arylid-Box ligand **10b**. A DFT study at a B3LYP level [6] predicts a great similarity between our ligand system and the Evans ligand system, when a comparative study was made between Cu(I)–Arylid-Box **10b** and Evans' *tert*-But-Box–Cu(I) complex. The UV–Vis spectroscopy study seems to indicate that the EDA decomposed relatively slowly. The DFT study of a model Cu(I)–metallocarbene complex of the Cu(I)–metallocarbene complex which we suspect to be active in our reactions and that of the Cu(I)–metallocarbene complex suspected to be present when Evans' *tert*-But-Box–Cu(I) complex is used showed that the carbenoid carbon in the latter veers more to one of the oxazoline ring stereogenic centres implying greater enantiofacial discrimination. We are currently evaluating these ligands and other analogues in this reaction and other transition metal promoted catalytic asymmetric reactions and at immobilising these ligand systems to appropriate solid supports.

4. Experimental

4.1. General remarks

Dimethyl *p*-chlorobenzylidienemalonate **6a**, dimethyl *p*-metoxybenzylidienemalonate **6b**, benzylidenemalonic acid **2**, 2-(4-chlorobenzylidene)malonic acid **7a**, 2-(4-methoxybenzylidene)malonic acid **7b** were prepared as reported previously [3–5,20,21].

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 points were recorded on a Barnstead Electothermal 9100 apparatus and are uncorrected. The ^1H NMR spectra were recorded on either a Bruker AMX300, Bruker Avance 400 or a Bruker Avance 500 instrument using $CDCl_3$ as solvent and TMS as internal standard. In some cases, the signals for the NH and OH protons could be observed, but in other cases they were not observed possibly due to overlap with other peaks. Mass spectra were recorded on a VG Autospec M (Waters-Micromass) spectrometer using the FAB technique. Infra-red spectra were measured with a Perkin–Elmer Paragon 1000 model.

4.2. Ligand synthesis

General procedure for the synthesis of acid chlorides (3, 8a and 8b): A dry two-necked round bottom flask (50 mL) equipped with a magnetic stir bar was charged with benzylidenemalonic acid (1.86 g, 9.6 mmol), dimethylformamide (0.1 mL, 1.25 mmol) and CH_2Cl_2 (25 mL). The solution was cooled to 0 °C, and oxalyl chloride (2.5 mL, 29 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 benzy-

lidenemalonyl chloride **3** as an orange oil (Due to the unstable nature of this compound it was stored in the freezer at −10 °C). Yield: 2.00 g (100%). ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 7.96$ (s, 1H, ArHC=C), 7.60–7.56 (m, 2H, Har), 7.52–7.46 (m, 3H, Har) ppm.

8a: Using the same procedure as described previously 2-(4-chlorobenzylidene)malonic acid **7a** (4.0 g, 9.6 mmol) was reacted with dimethylformamide (0.17 mL, 1.25 mmol) and oxalyl chloride (3.8 mL, 44 mmol) to give 2-(4-chlorobenzylidene)malonyl chloride **8a** as an orange oil. Yield: 4.80 g (100%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.89$ (s, 1H, ArHC=C), 7.54–7.42 (m, 4H, Har) ppm.

8b: Using the same procedure as described preveliously 2-(4-methoxybenzylidene)malonic acid **7b** (0.8 g, 3.6 mmol) was reacted with dimethylformamide (34.2 mg, 0.47 mmol) and oxalyl chloride (0.94 mL, 10.8 mmol) to give 2-(4-methoxybenzylidene)malonyl chloride **8b** as a yellow oil. Yield: 0.89 g (95%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.86$ (s, 1H, ArHC=C), 7.58 (d, $J = 9$ Hz, 2H, Har), 6.99 (d, $J = 8.7$ Hz, 2H, Har), 3.90 (s, 3H, –OCH_3) ppm.

General Procedure for the synthesis of malonamides (4a, 4b, 9a–f and 9a′): A two necked round bottom flask (50 mL) fitted with a magnetic stirring bar was charged with a solution of (*S*)-valinol (0.90 g, 8.7 mmol) and dry CH_2Cl_2 (10 mL) and the solution was cooled to 0 °C using an ice bath. Dry triethylamine (1.83 mL, 13.0 mmol) was added via syringe. A solution of benzylidenemalonyl chloride **3** (1.2 g, 5.2 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 (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 (*S*,*S*)-*N*,*N*′-bis-(1-hydroxymethyl-2-methylpropyl)-2-benzylidenemalonamide **4a** as an orange solid. The crude product was purified by column chromatography (silica gel, EtOAc) to afford the diamide **4a** as a white solid. Yield: 0.44 g (28%); m.p.: 129.5–130.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.54$ (s, 1H, ArHC=C), 7.43 (d, $J = 1.6$ Hz, 2H, Har), 7.42–7.27 (m, 4H, Har and N–H), 6.95 (d, 1H, $J = 8.8$ Hz, N–H), 3.90–3.82 (m, 2H, CH_2OH), 3.73–3.68 (m, 2H, CH_2OH), 3.54–3.45 (m, 2H, CH), 1.81–1.76 (m, 1H, CH(CH_3)$_2$), 1.73–1.68 (m, 1H, CH(CH_3)$_2$), 0.90 (d, $J = 6.8$ Hz, 3H, CH(CH_3)$_2$), 0.88 (d, $J = 6.8$ Hz, 3H, CH(CH_3)$_2$), 0.84 (d, $J = 6.8$ Hz, 3H, CH(CH_3)$_2$), 0.77 (d, $J = 6.8$ Hz, 3H, CH(CH_3)$_2$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 169.23$, 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 ppm. IR (KBr) υ_{max}: 3319.04, 3258.48, 3060.09, 2957.40, 2874.08, 1736.58, 1651.97, 1640.28, 1616.31, 1547.04, 1465.44, 1289.53, 1071.85, 749.37, 689.55 cm^{-1}. $[\alpha]_D^{22} = -16.64$ ($c = 0.3$, $CHCl_3$). FAB-MS *m*/*z*: 363.27 $[M+H]^+$.

4b: The same procedure as described previously was used in the reaction of benzylidenemalonyl chloride **3** (0.89 g, 3.89 mmol) with (*R*)-(+)-phenylalaninol (1.18 g, 7.78 mmol) and dry triethylamine (1.63 mL, 11.7 mmol) to give (*R*,*R*)-*N*,*N*′-bis-(1-benzyl-2-hydroxyethyl)-2-benzylidenemalonamide **4b** as a white solid after purification by column chromatography (silica gel, EtOAc); Yield: 0.77 g (43%). m.p.: 167.2–168.1 °C; ^{1}H NMR (500 MHz, CD_3OD): $\delta = 7.45$ (s, 1H, ArHC=C), 7.33–7.16 (m, 15H, Har), 4.47–4.42 (m, 1H, CH), 4.28–4.23 (m, 1H, CH), 3.69 (dd, $J = 11.5$, 4.3 Hz, 1H, CHHOH), 3.61 (dd, $J = 11.5$, 5 Hz, 1H, CHHOH), 3.57 (dd, $J = 11$, 6 Hz, 1H CHHOH), 3.44 (dd, $J = 11$, 8 Hz, 1H, CHHOH), 2.89 (dd, $J = 14$, 6.5 Hz, 1H, CHHAr), 2.82 (dd, $J = 14$, 6.5 Hz, 1H, CHHAr), 2.77 (dd, $J = 14$, 8.5 Hz, 1H, CHHAr), 2.66 (dd, $J =$ 14, 8.5 Hz, 1H, CHHAr). ^{13}C NMR (100 MHz, CD_3OD): $\delta = 170.09$, 166.05, 139.69, 139.44, 139.06, 134.75, 132.67–127.62, 127.43, 64.99, 64.00, 55.02, 54.48, 38.02, 37.39 ppm. IR (KBr) υ_{max}: 3257.77, 3058.18, 2920.82, 1736.40, 1643.81, 1611.29, 1538.60, 1449.51, 1288.84, 1068.52, 745.65, 695.68 cm^{-1}. $[\alpha]_D^{22} = -71.70$ ($c = 0.22$, acetone). FAB-MS *m*/*z*: 459.28 $[M+H]^+$.

9a: The same procedure as described previously was used in the reaction of benzylidenemalonyl chloride **3** (1.0 g, 4.37 mmol) with (*S*)-(+)phenylglycinol (1.2 g, 8.74 mmol) and dry triethylamine (1.82 mL, 13 mmol) to give (*S*,*S*)-*N*,*N*′-bis(2-hydroxy-1-phenylethyl)-2-benzylidenemalonamide **9a** as a white solid after purification by column chromatography (silica gel, EtOAc); Yield: 0.77 g (41%). m.p.: 74.6–75.2 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.00$ (d, 1H, $J = 8$ Hz, N–H), 7.66 (s, 1H, ArHC=H), 7.49 (d, 1H, $J = 8$ Hz, N–H), 7.38–7.24 (m, 10H, Ar), 7.16–7.12 (m, 5H, Ar), 5.29–5.25 (m, 1H, CH), 5.24–5.20 (m, 1H, CH), 3.90 (dd, 1H, $J = 4.3$, 12.3 Hz, CHHOH), 3.83–3.75 (m, 3H, CH_2OH and CHHOH), 2.18 (s, 2H, CH_2OH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 168.38$, 164.86, 139.58, 138.38, 137.54, 132.83, 130.75–126.73, 126.55, 65.74, 65.44, 56.16, 55.99 ppm. IR (KBr) υ_{max}: 3269.24, 3059.14, 2874.53, 1736.39, 1659,84, 1612.97, 1529.28, 1451.82, 1055.29, 757.13, 697.47 cm^{-1}. $[\alpha]_D^{22} = +73.46$ ($c = 0.26$, $CHCl_3$). FAB-MS *m*/*z*: 431.24 $[M+H]^+$.

9a′: The same procedure as described previously was used in the reaction of benzylidenemalonyl chloride **3** (1.1 g, 4.8 mmol) with (*R*)-(−)-phenylglycinol (1.04 g, 7.6 mmol) and dry triethylamine (1.3 mL, 9.5 mmol) to give (*R*,*R*)-*N*,*N*′-bis(2-hydroxy-1-phenylethyl)-2-benzylidenemalonamide **9a′** as a white solid after purification by column chromatography (silica gel, EtOAc); Yield: 0.64 g (39%). m.p.: 74.3–75.4 °C; $[\alpha]_D^{22} = -95.82$ ($c = 0.91$, $CHCl_3$).

9b: The same procedure as described previously was used in the reaction of benzylidenemalonyl chloride **3** (1.12 g, 4.9 mmol) with (*S*)-*tert*-leucinol (1.148 g,

9.8 mmol) and dry triethylamine (2.05 mL, 14.7 mmol) to give (*S*,*S*)-*N*,*N*′-bis-(1-hydroxymethy-2,2-dimethylpropyl)-2-benzylidenemalonamide **9b** as white crystals after purification by column chromatography (silica gel, EtOAc); Yield: 0.96 g (50%); m.p.: 144.3–145.7 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.61$ (s, 1H, ArHC=C), 7.46–7.39 (m, 3H, N–H and Har), 7.32–7.30 (m, 3H, Har), 6.81 (d, $J = 9$ Hz, 1H, N–H), 4.01–3.90 (m, 2H, C*H*), 3.88–3.80 (m, 2H, CH_2OH), 3.53–3.45 (m, 2H, CH_2OH), 0.94 (s, 9H, C(CH_3)$_3$), 0.84 (s, 9H, C(CH_3)$_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 169.74$, 165.61, 138.0, 138.04, 133.58, 132.24, 129.44, 128.58, 62.10, 61.74, 60.28, 59.99, 33.87, 33.30, 26.97, 26.72 ppm. IR (KBr) υ_{max}: 3271.95, 3064.49, 2962.35, 1737.25, 1651.76, 1616.35, 1540.15, 1473.16, 1273.08, 1051.11, 756.71, 693.89 cm^{-1}. $[\alpha]_D^{19} = -16.33$ ($c = 0.98$, $CHCl_3$). FAB-MS *m*/*z*: 391.17 $[M+H]^+$.

9c: The same procedure as described previously was used in the reaction of 2-(4-chlorobenzylidene)malonyl chloride **8a** (1.28 g, 4.84 mmol) with (*S*)-phenylglycinol (1.04 g, 7.59 mmol) and dry triethylamine (1.6 mL, 11 mmol) to give (*S*,*S*)-*N*,*N*′-bis(2-hydroxy-1-phenylethyl)-2-(4-chlorobenzylidene)malonamide **9c** as white crystals after purification by column chromatography (silica gel, EtOAc). Yield: 0.80 g (46%); m.p.: 153.8–155.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.97$ (d, $J = 8.5$ Hz, 1H, N–H), 7.91 (d, $J = 8.5$ Hz, 1H, N–H), 7.42 (s, 1H, ArHC=C), 7.38–7.23 (m, 10H, H_{ar}), 7.18–7.14 (m, 2H, Har), 7.05 (d, $J = 8.5$ Hz, 1H, Har), 6.96 (d, $J = 8.5$ Hz, 1H, Har), 5.32–5.26 (m, 1H, CH), 5.22–5.17 (m, 1H, CH), 3.88–3.69 (m, 4H, CH_2OH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 168.01$, 164.69, 138.21, 138.16, 137.42, 135.71, 131.42, 131.31, 130.69, 128.97, 128.82, 128.78, 128.75, 128.31, 128.02, 127.85, 127.05, 126.72, 126.56, 65.96, 65.50, 56.21, 56.01 ppm. IR (KBr) υ_{max}: 3395.91, 3243.14, 1739.26, 1651.71, 1613.84, 1541.79, 1472.30. 1265.57, 1058.75, 744.28, 699.27 cm^{-1}; $[\alpha]_D^{19} = 38.6$ ($c = 0.59$, $CHCl_3$). FAB-MS *m*/*z*: 465.10 $[M+H]^+$.

9d: The same procedure as described previously was used in the reaction of 2-(4-chlorobenzylidene)malonyl chloride **8a** (1.23 g, 5.33 mmol) with (*S*)-*tert*-leucinol (1.00 g, 8.53 mmol) and dry triethylamine (1.78 mL, 12.7 mmol) to give (*S*,*S*)-*N*,*N*′-bis(1-hydroxymethyl-2,2-dimethylpropyl)-2-(4-chlorobenzylidene)malonamide **9d** as an orange solid. The crude product was purified by column chromatography (silica gel, EtOAc) to afford the diamide **9d** as a white solid. Yield: 0.69 g (33%). m.p.: 171.1–171.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.46$ (d, $J = 10$ Hz, N–H), 7.33 (d, $J = 5.4$ Hz, 2H, Har) 7.30 (s, 1H, ArHC=C), 7.21–7.18 (m, 3H, Har and N–H), 4.05 (td, $J = 10$, 3.5 Hz, 1H, CH), 3.91–3.79 (m, 3H, C*H* and CH_2OH), 3.55–3.42 (m, 2H, CH_2OH), 0.89 (s, 9H, C(CH_3))$_3$, 0.88 (s, 9H, C(CH_3)$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 169.41$, 165.79, 136.25, 135.62, 132.61, 131.82, 130.81, 128.82, 62.23, 61.57, 60.41, 60.21, 33.94, 33.31, 26.86, 26.71 ppm. IR (KBr) υ_{max}: 3333.61, 3067.45, 2962.86, 1738.34, 1658.74, 1642.28, 1616.21, 1536.19, 1489.12, 1273.44, 1098.18, 1017.94, 821.28 cm^{-1}. $[\alpha]_D^{20} = -8.30$ ($c = 0.47$, $CHCl_3$). FAB-MS *m*/*z*: 425.10 $[M+H]^+$.

9e: The same procedure as described previously was used in the reaction of 2-(4-methoxybenzylidene)malonyl chloride **8b** (1.06 g, 4.1 mmol) with (*R*)-phenylglycinol (0.9 g, 6.56 mmol) and dry triethylamine (1.36 ml, 9.8 mmol) to give (*R*,*R*)-*N*,*N*′-bis(2-hydroxy-1-phenylethyl)-2-(4-methoxybenzylidene)malonamide **9e** as an orange solid. The crude product was purified by column chromatography (silica gel, EtOAc) to afford diamide as a white solid. Yield: 0.72 g (38%); m.p.: 69.5–70.2 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.04$–8.01 (m, 1H, N–H), 7.85 (d, $J = 8.4$ Hz, 1H, N–H), 7.45 (s, 1H, ArHC=C), 7.28–7.24 (m, 10H, Har), 7.12 (d, J= 8.7 Hz, 2H, Har), 6.53 (d, $J = 8.7$ Hz, 2H, Har), 5.37–5.34 (m, 1H, CH), 5.25–5.18 (m, 1H, CH), 3.91–3.85 (m, 4H, CH_2OH), 3.73 (s, 3H, –OCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 166.87$, 160.99, 141.47, 138.98, 129.45, 129.33, 128.87, 128.78, 127.85, 127.33, 126.92, 126.81, 126.75, 126.64, 117.75, 114.23, 66.63, 66.43, 56.26, 55.96, 55.24 ppm. IR (KBr) υ_{max}: 3292.24, 1736.65, 1654.84, 1603.58, 1513.26, 1253.19, 1177.72, 1028.10, 759.04, 699.78 cm^{-1}. $[\alpha]_D^{21} = -16.2$ ($c = 0.58$, $CHCl_3$). FAB-MS *m*/*z*: 461.16 $[M+H]^+$.

9f: The same procedure as described previously was used in the reaction of 2-(4-methoxy-benzylidene)malonyl chloride **8b** (1.0 g, 3.85 mmol) with (*S*)-*tert*-leucinol (0.91 g, 7.7 mmol) and dry triethylamine (1.62 ml, 12.0 mmol) to give (*S*,*S*)-*N*,*N*′-bis(1-hydroxymethyl-2,2-dimethylpropyl)-2-(4-methoxybenzylidene)malonamide **9f** as an orange solid. The crude product was purified by column chromatography (silica gel, EtOAc) to afford diamide as a white solid. Yield: 0.65 g (40%); m.p.: 161.1–161.8 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.55$ (s, 1H, ArHC=C), 7.43 (d, $J = 8.7$ Hz, 2H, Har), 7.34 (d, $J = 9.5$ Hz, 1H, N–H), 6.82 (d, $J = 8.7$ Hz, 2H, Har), 6.71 (d, $J = 9.5$ Hz, 1H, N–H), 4.04–3.98 (m, 1H, C*H*HOH), 3.94–3.86 (m, 3H, CH_2OH and CH*H*OH), 3.81 (s, 3H, –OCH_3), 3.55–3.48 (m, 2H, CH), 0.94 (s, 9H, C(CH_3)$_3$), 0.88 (s, 9H, C(CH_3)$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 170.13$, 166.14, 160.63, 137.50, 131.50, 129.61, 125.85, 113.90, 62.20, 61.65, 60.18, 60.06, 55.22, 33.94, 33.27, 26.85, 26.71 ppm. IR (KBr) υ_{max}: 3332.96, 3062.63, 2961.16, 1736.50, 1642.58, 1605.79, 1529.58, 1469.67, 1256.75, 1178.30, 1032.38, 827.35 cm^{-1}. $[\alpha]_D^{20} = -5.87$ ($c = 0.46$, $CHCl_3$). FAB-MS *m*/*z*: 421.17 $[M+H]^+$.

General procedure for the synthesis of Bis-oxazolines (5a, 5b, 10a–10f and 10a′): A solution of methanesulfonyl chloride (0.24 g, 2.07 mmol) in dry dichloromethane (1 mL) was added dropwise over 20 min to a solution of diamide **4a** (0.3 g, 0.83 mmol) and dry triethylamine (0.69 mL, 4.97 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) giving the (−)-bis[(*S*)-4-isopropyloxazoline-2-yl]-2-phenylethene **5a** as a white semi-solid. Yield: 0.20 g (74%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.57$ (s, 1H, ArHC=C), 7.49–7.45 (m, 2H, Har), 7.35–7.32 (m, 3H, Har), 4.4–4.29 (m, 2H, CH), 4.14–4.06 (m, 4H, CH_2), 1.90–1.77 (m, 2H, C*H*$(CH_3)_2$), 0.99 (s, 3H, CH(C*H*$_3)_2$), 0.97 (s, 3H, CH(C*H*$_3)_2$), 0.94 (s, 3H, CH(C*H*$_3)_2$), 0.89 (s, 3H, CH(C*H*$_3)_2$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 161.76$, 160.41, 140.75, 134.11, 129.46, 129.34, 128.36, 118.94, 72.83, 72.80, 70.26, 70.15, 32.88, 32.36, 18.96, 18.77, 18.46, 18.21 ppm. IR (NaCl): υ_{max}: 3343.37, 2964.15, 2930.98, 2875.81, 1662.37, 1568.96, 1466.28, 1364.46, 1176.97, 774.47, 734.28, 669.74 cm^{-1}. $[\alpha]_D^{19} = -12.46$ ($c = 0.35$, $CHCl_3$). FAB-MS *m*/*z*: 327.13 $[M+H]^+$; HRMS (FAB) found, 326.2072; $C_{20}H_{27}N_2O_2$ requires 327.2073.

5b: Using the same procedure as described previously, malonamide **4b** (0.45 g, 0.98 mmol) was reacted with methanesulfonyl chloride (0.28 g, 2.45 mmol) and dry triethylamine (0.85 mL, 5.89 mmol) to give the (−)-bis[(*R*)-4-benzyloxazoline-2-yl]-2-phenylethene **5b** as a yellow semi-solid after purification by column chromatography (silica gel, EtOAc). Yield: 0.27 g (64%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.60$ (s, 1H, ArHC=C), 7.43–7.41 (m, 2H, Har), 7.34–7.32 (m, 3H, Har), 7.29–7.19 (m, 10H, Har), 4.62–4.55 (m, 1H, C*H*HCH), 4.40–4.14 (m, 2H, C*H*$_2$CH), 4.11–4.06 (m, 1H, C*H*HCH), 3.21–3.15 (m, 2H, CH_2Ar), 2.78–2.67 (m, 2H, CH_2Ar). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 162.25$, 160.83, 141.49, 137.74, 137.68, 133.93, 129.57–126.35, 118.44, 71.98, 71.61, 68.06, 68.00, 41.41, 40.93 ppm. IR (NaCl): υ_{max}: 3337.78, 3065.18, 3025.61, 3008.22, 2962.12, 2932.84, 1667.93, 1638.42, 1496.59, 1452.14, 1357.16, 1182.32, 1011.28, 962.91, 771.63, 701.76 cm^{-1}. $[\alpha]_D^{20} = -10.79$ ($c = 0.38$, $CHCl_3$). FAB-MS *m*/*z*: 423.07 $[M+H]^+$. HRMS (FAB) found, 423.2066; $C_{28}H_{27}N_2O_2$ requires 423.2073.

10a: Using the same procedure as described previously, malonamide **9a** (0.40 g, 0.93 mmol) was reacted with methanesulfonyl chloride (0.27 g, 2.32 mmol) and dry triethylamine (0.8 mL, 5.57 mmol) to give the (+)-bis[(*S*)-4-phenyloxazoline-2-yl]-2-phenylethene **10a** as a yellow semi-solid after purification by column chromatography (silica gel, EtOAc). Yield: 0.2 g (54%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.76$ (s, 1H, ArHC=C), 7.54–7.53 (m, 2H, Har), 7.37–7.28 (m, 10H, Har), 7.25–7.23 (m, 3H, Har), 5.48–5.37 (m, 2H, CHAr), 4.83–4.75 (m, 2H, CH_2), 4.32–4.19 (m, 2H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 163.40$, 161.84, 142.10, 141.84, 141.81, 134.00, 129.79, 129.45, 129.20, 128.76, 128.64, 128.58, 128.53, 127.79, 127.50, 127.43, 126.94, 126.82, 126.69, 118.50, 74.89, 74.88, 70.23, 70.12, 53.39, 37.51, 30.89 ppm. IR (NaCl): υ_{max}: 3340.47, 3065.00, 3011.92, 2968.06, 2927.78, 1654.97, 1565.50, 1453.84, 1210.95, 1029.02, 763.75, 737.37, 669.76 cm^{-1}. $[\alpha]_D^{19} = +90.7$ ($c = 0.9$, $CHCl_3$). FAB-MS *m*/*z*: 395.06 $[M+H]^+$, HRMS (FAB) found, 395.1760; $C_{26}H_{23}N_2O_2$ requires 395.1757.

10a′: Using the same procedure as described previously, malonamide **9a′** (0.40 g, 0.93 mmol) was reacted with methanesulfonyl chloride (0.27 g, 2.32 mmol) and dry triethylamine (0.8 mL, 5.57 mmol) to give the (−)-bis[(*R*)-4-phenyloxazoline-2-yl]-2-phenylethene **10a′** as a yellow semi-solid after purification by column chromatography (silica gel, EtOAc). Yield: 0.17 g (46%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.76$ (s, 1H, ArHC=C), 7.54–7.53 (m, 2H, Har), 7.37–7.23 (m, 13H, Har), 5.45–5.4 (m, 2H, CHAr), 4.82–4.77 (m, 2H, CH_2), 4.32–4.22 (m, 2H, CH_2) ppm. $[\alpha]_D^{19} = -115$ ($c = 0.92$, $CHCl_3$).

10b: Using the same procedure as described previously, malonamide **9b** (0.40 g, 1.02 mmol) was reacted with methanesulfonyl chloride (0.29 g, 2.55 mmol) and dry triethylamine (0.86 mL, 6.14 mmol) to give the (+)-bis[(*S*)-4-*tert*-butyloxazoline-2-yl]-2-phenylethene **10b** as a white semi-solid after purification by column chromatography (silica gel, EtOAc). Yield: 0.27 g (67%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.53$ (s, 1H, ArHC=C), 7.48–7.45 (m, 2H, Har), 7.34–7.31 (m, 3H, Har), 4.37–4.13 (m, 4H, CH_2), 4.07–3.99 (m, 2H, CH), 0.97 (s, 9H, C$(CH_3)_3$), 0.91 (s, 9H, C$(CH_3)_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 161.76$, 160.45, 140.41, 134.15, 129.44, 129.40, 128.38, 118.99, 68.84, 68.53, 34.04, 33.89, 26.130, 25.8 ppm. IR (NaCl): υ_{max}: 3350.01, 2959.32, 2874.08, 1658.37, 1570.50, 1473.35, 1362.03, 1244.89, 1193.47, 1083.22, 770.77, 733.94, 669.67 cm^{-1}. $[\alpha]_D^{20} = 22.1$ ($c = 1$, $CHCl_3$). FAB-MS *m*/*z*: 355.13 $[M+H]^+$, HRMS (FAB) found, 355.2389; $C_{22}H_{31}N_2O_2$ requires 355.2386.

10c: Using the same procedure as described previously, malonamide **9c** (0.3 g, 0.64 mmol) was reacted with methanesulfonyl chloride (0.18 g, 1.6 mmol) and dry triethylamine (0.54 mL, 3.87 mmol) to give the (+)-bis[(*S*)-4-phenyloxazoline-2-yl]-2-(4-chlorophenyl)ethene **10c** as a white semi-solid after purification by column chromatography (silica gel, hexane:EtOAc (1:1)). Yield: 0.14 g (51%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.70$ (s, 1H, ArHC=C), 7.47 (d, $J = 8.7$ Hz, 2H, Har), 7.39–7.25 (m, 12H, HAr), 5.48–5.36 (m, 2H, CH_2), 4.82–4.75 (m, 2H, CH_2), 4.30 (t, $J = 8.4$ Hz, 1H, CH), 4.22 (t, $J = 8.3$ Hz, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 163.17$, 161.51, 141.96, 141.59, 140.44, 135.81, 132.47, 130.68, 128.88, 128.68, 128.59, 127.57, 126.88, 126.68, 119.13, 74.94, 74.91, 70.25, 70.08 ppm; IR ($CHCl_3$) υ_{max}: 2976.57, 1671.34, 1636.87, 1520.87, 1492.31, 1356.21, 1244.89, 1044.89, 929.19, 848.57, 626.00 cm^{-1} $[\alpha]_D^{21} = 16.2$ ($c = 0.58$, $CHCl_3$). FAB-MS *m*/*z*: 429.07 $[M+H]^+$. HRMS (FAB) found, 429.1370; $C_{26}H_{22}N_2O_2Cl$ requires 429.1384.

10d: Using the same procedure as described previously, malonamide **9d** (0.2 g, 0.47 mmol) was reacted with methanesulfonyl chloride (0.13 g, 21.17 mmol) and dry tri-

ethylamine (0.4 mL, 2.82 mmol) to give the (+)-bis[(*S*)-4-*tert*-butyloxazoline-2-yl]-2-(4-chlorophenyl)ethene **10d** as a white semi-solid after purification by column chromatography (silica gel, hexane:EtOAc (1:1)). Yield: 0.109 g (60%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.45$ (s, 1H, ArHC=C), 7.39 (d, $J = 8.7$ Hz, 2H, Har), 7.28 (d, $J = 8.8$ Hz, 2H, Har), 4.31 (dd, $J = 10.4$, 8.6 Hz, 1H, CH), 4.26–4.19 (m, 2H, CH_2), 4.13 (t, $J = 8.1$ Hz, 1H, CH), 4.03–3.98 (m, 2H, CH_2), 0.95 (s, 9H, $C(CH_3)_3$), 0.88 (s, 9H, $C(CH_3)_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 161.57$, 160.15, 138.96, 135.39, 132.62, 130.63, 128.68, 119.70, 76.56, 76.49, 68.92, 68.62, 34.04, 33.90, 26.12, 25.80 ppm. IR (NaCl): υ_{max}: 3329.61, 2963.04, 2909.13, 1736.84, 1673.79, 1633.30, 1483.82, 1402.05, 1364.06, 1249.46, 1190.29, 1092.14, 1016.36, 823.07, 775.96, 669.16 cm^{-1}. $[\alpha]_D^{20} = 45.75$ ($c = 0.37$, $CHCl_3$). FAB-MS *m*/*z*: 389.12 $[M+H]^+$. HRMS (FAB) found, 389.1996; $C_{22}H_{30}N_2O_2Cl$ requires 389.1996.

10e: Using the same procedure as described previously, malonamide **9e** (0.45 g, 0.98 mmol) was reacted with methanesulfonyl chloride (0.28 g, 2.44 mmol) and dry triethylamine (1.36 ml, 5.86 mmol) to give the (−)-bis[(*S*)-4-phenyloxazoline-2-yl]-2-(4-methoxyphenyl)ethene **10e** as a white semi-solid after purification by column chromatography (silica gel, hexane:EtOAc (1:1)). Yield: 0.28 g (67%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.70$ (s, 1H, ArHC=C), 7.52 (d, $J = 8.7$ Hz, 2H, Har), 7.41–7.26 (m, 10H, Har), 6.87 (d, $J = 8.7$ Hz, 2H, Har), 5.47–5.41 (m, 2H, CH_2), 4.86–4.75 (m, 2H, CH_2), 4.33 (t, $J = 8.4$ Hz, 1H, CH), 4.21 (t, $J = 8.2$ Hz, 1H, CH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 164.63$, 160.75, 142.36, 140.00, 128.96, 128.65, 127.86, 127.46, 126.58, 114.24, 112.53, 74.26, 69.90, 55.26 ppm. IR ($CHCl_3$): υ_{max}: 2975.91, 2927.43, 1667.12, 1608.51, 1516.87, 1424.21, 1043.45, 928.38, 626.58 cm^{-1}. $[\alpha]_D^{23} = -4.7$ ($c = 0.51$, $CHCl_3$). FAB-MS *m*/*z*: 425.13 $[M+H]^+$. HRMS (FAB) found, 425.1865; $C_{27}H_{25}N_2O_3$ requires 425.1883.

10f: Using the same procedure as described previously, malonamide **9f** (0.40 g, 1.02 mmol) was reacted with methanesulfonyl chloride (0.20 g, 1.78 mmol) and dry triethylamine (0.3 g, 0.71 mmol) to give the (+)-bis[(*S*)-4-*tert*-butyloxazoline-2-yl]-2-(4-methoxyphenyl)ethene **10f** as a white semi-solid after purification by column chromatography (silica gel, hexane:EtOAc (1:1)). Yield: 0.16 g (59%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.44$ (s, 1H, ArHC=C), 7.40 (d, $J = 8.8$ Hz, 2H, Har), 6.83 (d, $J = 8.8$ Hz, 2H, Har), 4.33 (dd, $J = 10$, 8 Hz, 2H, CH_2), 4.22 (t, $J = 9$ Hz, 1H, CH), 4.11 (t, $J = 8$ Hz, 1H, CH), 4.06–3.96 (m, 2H, CH_2), 3.78 (s, 3H, –OCH_3), 0.96 (s, 9H, $C(CH_3)_3$), 0.88 (s, 9H, $C(CH_3)_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 162.01$, 160.78, 160.62, 139.92, 131.25, 126.71, 116.43, 113.88, 76.48, 76.38, 68.76, 68.43, 55.20, 34.02, 33.89, 26.14, 25.78 ppm. IR (NaCl): υ_{max}: 3339.29, 2962.33, 2911.21, 1637.63, 1511.62, 1471.64, 1357.68, 1254.29, 1182.30, 1022.12, 830.30, 751.34, 668.48 cm^{-1}. $[\alpha]_D^{20} = 63.0$ ($c = 0.50$, $CHCl_3$). FAB-MS *m*/*z*: 385.17 $[M+H]^+$. HRMS (FAB) found, 385.2491; $C_{23}H_{33}N_2O_3$ requires 385.2490.

4.3. Formation of a $[Cu(CH_3CN)_4][PF_6]$–Box-10a′ complex

$[Cu(CH_3CN)_4][PF_6]$ (47 mg, 0.126 mmol) was added to a two-neck round-bottomed flask containing the ligand **10a**′ (50 mg, 0.126 mmol) in CH_2Cl_2 (5 ml), the mixture was stirred for 6 h at room temperature. The solvent was removed under *vacuo* giving a dark blue solid. Yield: 0.043 g (75%); IR (KBr) υ_{max}: 3417.46, 3031.57, 2924.21, 2362.18, 1647.04, 1592.19, 1489.38, 1453.39, 1386.53, 1238.81, 1063.68, 944.98, 839.45, 755.35, 697.48, 554.94 cm^{-1}. FAB-MS *m*/*z*: 474.94 (M+1).

4.4. Cyclopropanation reactions

4.4.1. Cyclopropanations using $[Cu(OTf)]_2(C_6H_6)$ and $[Cu(CH_3CN)_4]PF_6$ pre-catalysts

Catalyst (0.014 mmol, 1 mol%) or (0.028 mmol, 2 mol%) was added to a two-neck round-bottomed flask containing the chiral ligand (0.015 mmol, 1.1 mol%) or (0.030 mmol, 2.2 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) was 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. Isolated yields, diastereoselectivities, and enantioselectives are given in Tables 2 and 3.

4.4.2. Cyclopropanations using $Cu(I)SbF_6$ generated in situ

CuCl (4 mg, 0.04 mmol) was added to a two-neck round-bottomed flask containing the ligand **10a**′or **10d** (0.044 mmol) in CH_2Cl_2, the mixture was stirred for 1.5 h at room temperature. $AgSbF_6$ (27.7 mg, 0.08 mmol) was added to the mixture and stirred for 3 h without light. The mixture was transferred by cannula to another flask containing CH_2Cl_2 (1 ml), and was added styrene (1.91 g, 18.4 mmol) and stirred for 0.5 h. A solution of ethyl diazoacetate (0.210 g, 1.84 mmol) in CH_2Cl_2 (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 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. Reaction temperatures,

isolated total yields, diastereoselectivities, and enantioselectives are given in Table 2.

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Appendix A. Supplementary material

Tables of total energy and cartesian coordinates for the DFT-optimized geometries of the complexes discussed in the text. Spectra and information related to the uv-vis spectroscopic study of **10a**′–$Cu(CH_3CN)_6PF_6$ and for the kinetics of EDA decomposition using this complex. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jorganchem.2007.06.068.

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