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Asymmetric cyclopropanation of olefins catalysed by Cu(I) complexes of chiral pyridine-containing macrocyclic ligands (Pc-L*)†

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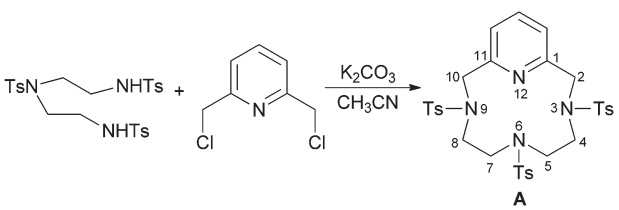
The synthesis and characterisation of copper(I) complexes of chiral pyridine-containing macrocyclic ligands (**Pc-L***) and their use as catalysts in asymmetric cyclopropanation reactions are reported. All ligands and metal complexes were fully characterised, including crystal structures of some species determined by X-ray diffraction on single crystals. This allowed characterising the very different conformations of the macrocycles which could be induced by different substituents or by metal complexation. The strategy adopted for the ligand synthesis is very flexible allowing several structural modifications. A small library of macrocyclic ligands possessing the same donor properties but with either C_1 or C_2 symmetry was synthesized. Cyclopropane products with both aromatic and aliphatic olefins were obtained in good yields and enantiomeric excesses up to 99%.

Introduction

Tetraazamacrocycles, such as cyclen (1,4,7,10-tetraazacyclododecane) or its derivatives bearing functional groups on the nitrogen atoms, have attracted much attention in recent years due to their ability to form stable complexes with a wide range of metal ions. In this context, complexes derived from substituted cyclen ligands and paramagnetic metal ions have been shown to be excellent probes for Magnetic Resonance Imaging (MRI).[1]

The macrocyclic framework can be adjusted by changing the nature of the donor atoms and the conformation flexibility of the ring system in order to obtain pre-organized ligands able to bind certain metal ions. In the field of MRI, some years ago, we reported the synthesis of tetraazamacrocycles containing the pyridine ring system with the aim of increasing the stereochemical rigidity of the resulting complexes, which could result in an increase of their thermodynamic stability.[2] The pyridine moiety may also provide a suitable site for a further functionalization which may facilitate the binding ability of the ligand itself.

The construction of the macrocyclic ring system is the crucial step and it is dependent on the ring size.[2] In the case of 12-membered ring systems, a 2 + 2 Richman–Atkins-type coupling[3] was adopted and modified in order to improve the chemical yields. By reacting 2,6-bis(chloromethyl)pyridine with 1,4,7-tritosyl-1,4,7-triazaheptane in anhydrous acetonitrile and in the presence of anhydrous potassium carbonate as heterogeneous base, conditions that approach a high dilution scenario, the yields of the cyclisation step were up to 94% (Scheme 1). Indeed, under the Richman–Atkins protocol (NaH/DMF as base/solvent system) the macrocycle **A** was isolated in less than 30% yield.



Scheme 1 Synthesis of the macrocyclic ring system and numbering scheme adopted.

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†Electronic supplementary information (ESI) available: Synthetic and analytical data for all new compounds, spectra illustrating sample purity; crystallographic tables and CIF files for compounds **4d**, **4f** and **5d**. CCDC 904090, 904091, 904092. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2dt32347h

In order to extend our method to the synthesis of chiral non racemic pyridine containing tetraazamacrocycles, we envisioned that *N*-tosyl aziridine[4] could be useful to prepare chiral 4-substituted 1,4,7-triazaheptanes by nucleophilic ring opening of 2 moles of *N*-tosyl aziridine with the appropriate enantiomerically pure amine.[5,6] The synthesized ligands were used to prepare the corresponding paramagnetic metal ion complexes, after introduction of the appropriate pendant arms on the nitrogen atoms.[5]

A few years ago, our group reported the synthesis and characterisation of copper(I) complexes of new pyridine containing tetraazamacrocyclic ligands[7] and preliminary results on their use as catalysts in asymmetric cyclopropanation reactions.[8] These ligands combine the advantages of macrocyclic polyamines and those of aminopyridine ligands.[9] Despite the evident potential of this class of C_1 symmetric ligands, their application in asymmetric catalysis has not been fully exploited.[10] Indeed, beside porphyrins and related ligands,[11–15] tetraazamacrocycles have found a limited use in metal complexes catalytically active in enantioselective reactions. Recently Allen and co-workers reported a new class of macrocyclic lanthanide complexes for the enantioselective Mukaiyama aldol reactions.[16,17]

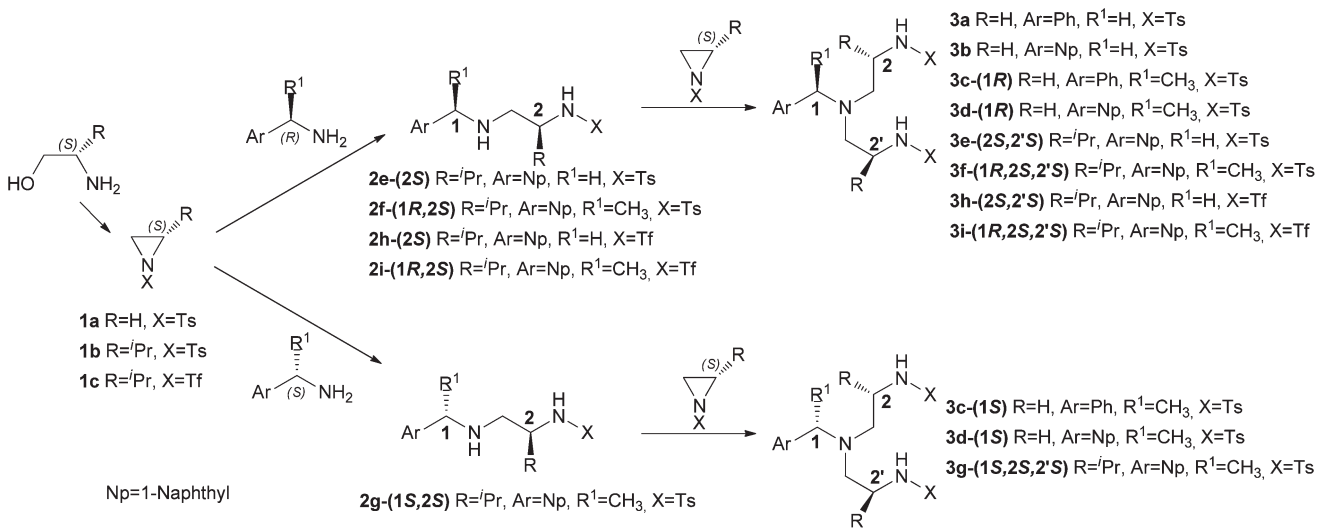
Transition metal-catalysed reactions of diazo compounds with alkenes have been widely used to prepare cyclopropanes. In particular the copper-catalysed enantioselective version of this reaction is now well established, and chiral C_2 symmetric bidentate ligands such as bisoxazolines are the most widely used.[18] Here we report our findings concerning the asymmetric cyclopropanation reaction of alkenes catalysed by copper(I) complexes derived from C_1 and C_2 symmetric pyridine containing 12-membered tetraazamacrocyclic ligands with two stereocenters on the ring skeleton and one stereocenter on the carbon atom bonded to *N*-6 nitrogen atom. The practical and efficient access to this class of compounds is relevant for the development of new synthetic methodologies in asymmetric catalysis.

Results and discussion

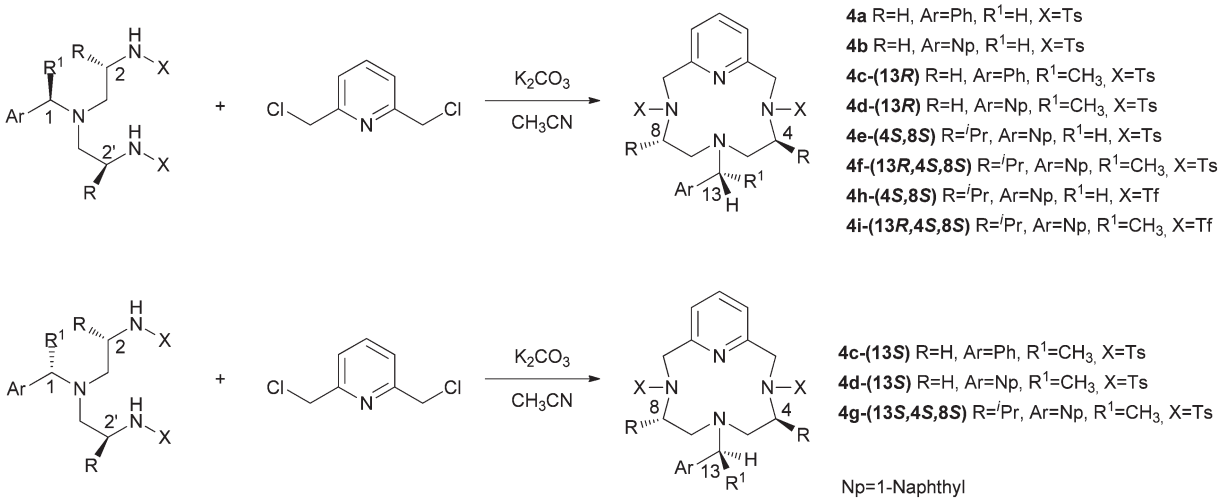
Design, synthesis and characterisation of complexes

The key step in the synthesis of the macrocyclic ligands, **Pc-L***, is the assembly of the pyridine unit from the reaction of 2,6-bis(chloromethyl)pyridine with an opportunely designed bis(sulfonamide) under heterogeneous reaction conditions. The synthetic approach employed to obtain the starting bis(sulfonamides) is reported in Scheme 2. There are two main steps involved in the synthesis. Firstly, ethanolamine or (L)-valinol was reacted with 2 equivalents of tosyl chloride in the presence of a weak base to afford aziridine derivatives **1a** and **1b**,[6] respectively. Use of triflic anhydride in the reaction with valinol in dichloromethane afforded the aziridine **1c**.[19] Since the aziridines carry electron-withdrawing groups on the nitrogen atom, they are expected to be susceptible to nucleophilic attack. Thus, reaction with commercially available primary aryl amines in refluxing toluene resulted in the formation of the desired bis(sulfonamides) **3a–i** in moderate to good yields (40–97%).

The nucleophilic attack of primary amines on 1-tosylaziridine **1a** occurs readily and use of two equivalents of aziridine afforded bis(sulfonamides) **3a–3d** directly, without isolation of intermediate **2**. When the chiral primary amines 1-benzylethylamine and 1-naphthylethylamine, were employed both enantiomers of the chiral sulfonamides **3c** and **3d** were synthesized and fully characterised. On the other hand, when bulkier (*S*)-2-isopropyl-*N*-tosylaziridine was used, the ring opening reaction was stopped after the addition of 1 equiv. of the aziridine and the mono adducts **2e–i** could be isolated, although in moderate yields (13–50%). It was interesting to note that in the present case, using naphthylalkylamines as nucleophiles, no large excess of amine was needed to obtain the mono adduct, contrary to that previously reported in the case of the ring opening of 2-isopropyl-*N*-(triflouromethylsulfonyl)aziridine with benzylamine.[20] These reactions are extremely slow, but



Scheme 2 Synthesis of mono(sulphonamides) **2e–i** and bis(sulphonamides) **3a–i**.



Scheme 3 Synthesis of the macrocyclic ligands (**Pc-L***) **4a–i**.

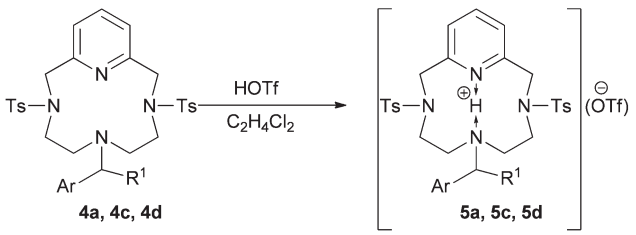
higher yields within shorter times were obtained by employing microwave irradiation. It was found that after 3 h at 150 °C in toluene, a 1.1 : 1 ratio of aziridine **1b** and amine afforded sulfonamides **2** in 70% yield. Extending the reaction time and using larger amounts of the aziridine relative to the amine did not significantly improve the yield of bis(sulphonamide) **3**. Thus a two-step strategy was followed for their synthesis. Firstly, the reaction was conducted at 150 °C under microwave heating. Then, an excess of the aziridine was added to the reaction mixture and the reaction was continued under conventional heating. Under these conditions, bis(sulfonamides) **3e–g** could be obtained in yields up to 74% after chromatographic purification.

As expected, (*S*)-2-isopropyl-*N*-(triflouromethylsulfonyl)aziridine **1c** is more reactive than the corresponding *N*-tosylaziridine analogue and the reaction requires milder conditions.

The attack at the terminal position of the aziridine is highly regioselective and we never observed a competing ring opening reaction at the substituted carbon which was reported in the case of 2-phenylaziridines.[21] This methodology allows extensive structural modifications, since a large number of primary amines can be used as nucleophiles in the ring opening reaction.

Once bis(sulfonamides) **3a–i** were obtained, the Richman–Atkins cyclisation with 2,6-bis(chloromethyl)pyridine was attempted. As already reported in the introduction, the macrocyclisation was run under heterogeneous conditions.[2] This synthetic methodology avoids high dilution techniques and the 12 membered macrocycles **4a–i** are obtained in 50–85% yields (Scheme 3).

Although the employed conditions allowed the synthesis of all the target macrocycles, in several cases (see ESI†), the time required was extremely long. In order to accelerate the reaction, we ran the synthesis in a microwave reactor. We initially focused on the synthesis of compound **4i**, that under conventional heating required 110 h of reflux to yield the desired macrocycle in 40% yield after purification. Maintaining the same stoichiometry and concentration of the reactants at 130 °C (see ESI†), 20% of macrocycle **4i** was observed after 2 h. When the temperature was raised to 150 °C, 50% yield was obtained in just 3 h. Nevertheless, upon prolonged reaction times under these conditions, no beneficial effect was observed to the reaction yield. Surprisingly, tosylsulfonamides **3a–g** failed to yield the macrocycles under microwave heating. Further studies will be needed to clarify this aspect, in order to shorten the reaction times needed for the macrocyclisation step and to improve the global yield. However, with the employed methodology, a small library of macrocyclic ligands possessing different symmetries, steric and electronic properties was easily obtained, starting from commercially available products in a few synthetic steps. In order to investigate the relative basicity of the four nitrogen atoms, we synthesized the protonated salts of some of the ligands, compounds **5a**, **5c** and **5d** (Scheme 4). The reaction was performed by treatment with triflic acid in dichloroethane.



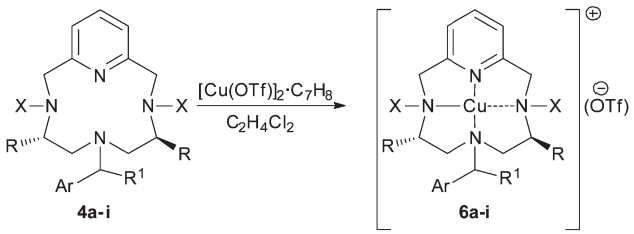
Scheme 4 Synthesis of the protonated salts **5a**, **5c** and **5d**.

Although the reaction was fast and quantitative as determined by ^{1}H NMR, the pure protonated salts were isolated only in modest yields (*ca.* 50%). The products were fully characterised, including X-ray structural determination in the case of the proton complex **5d** (see below). The proton, as expected for an ammonium salt, was located at high frequencies in the ^{1}H NMR spectra (11.82 ppm for **5a**, 11.24 ppm for **5c**, 10.66 ppm for **5d** in $CDCl_3$ at room temperature). Worthy

of note is the fact that for compound **5d** the ^{15}N NMR chemical shift for the pyridine nitrogen was observed at 282 ppm (solvent $CDCl_3$) instead of 312 ppm in the free ligand **4d**, and the resonance of *N*-6 (Scheme 1) was shifted from 39 to 52 ppm. This is consistent with a molecule where the proton is coordinated in a bridging position between these two nitrogen atoms (see Discussion of the X-ray data).

Metal complex formation with ligands **4a–i** was investigated with different copper salts (Scheme 5). Treating ligands **4a** and **4c** with $[Cu(OTf)]_2{\cdot}C_7H_8$ gave yellow Cu(I) complexes that undergo oxidation quite readily. These complexes have been isolated and fully characterised. Both complexes are readily formed by treating a suspension of the copper salt in 1,2-dichloroethane (DCE) at room temperature, yielding a light yellow solution. The addition of toluene to these solutions caused the precipitation of a white powder of complexes **6a** or **6c** in moderate yields. Both complexes were characterised by NMR spectroscopy. As previously reported by our group,[7] the ^{1}H NMR spectrum of complex **6a** in $CDCl_3$ displays a very low symmetry. Two sets of signals are observed for the sulfonamide moieties and this can be due to the fact that only one of the two nitrogen atoms bearing the tosyl substituent is truly coordinated to the metal ion (Scheme 5). The same low symmetry in solution is found also for complex **6c**. The effect of the copper complexation to the ligand was shown also by the ^{15}N NMR chemical shifts observed in $CDCl_3$ solution. For instance, the pyridine signal that resonates at 312 ppm in free ligand **4a**, is located at 248 ppm in complex **6a**. The nitrogen bearing the benzyl substituent is shifted from 32 ppm in the free ligand to 26 ppm upon complexation, whilst the less basic *N*-tosyl substituted nitrogen atoms are affected only to a lower extent, as expected.

Moreover, the presence of a naphthyl substituent seems to confer a major stability to the copper(I) complexes and, although the synthesis is better performed under a protecting atmosphere, compounds **6b** and **6d–i** could be manipulated in air without decomposition. The reason of this major stability is due to the presence of the naphthyl group that can act as a further coordination site for the metal (Fig. 1). In these cases



Scheme 5 Synthesis of the copper(I) complexes **6a–i**.

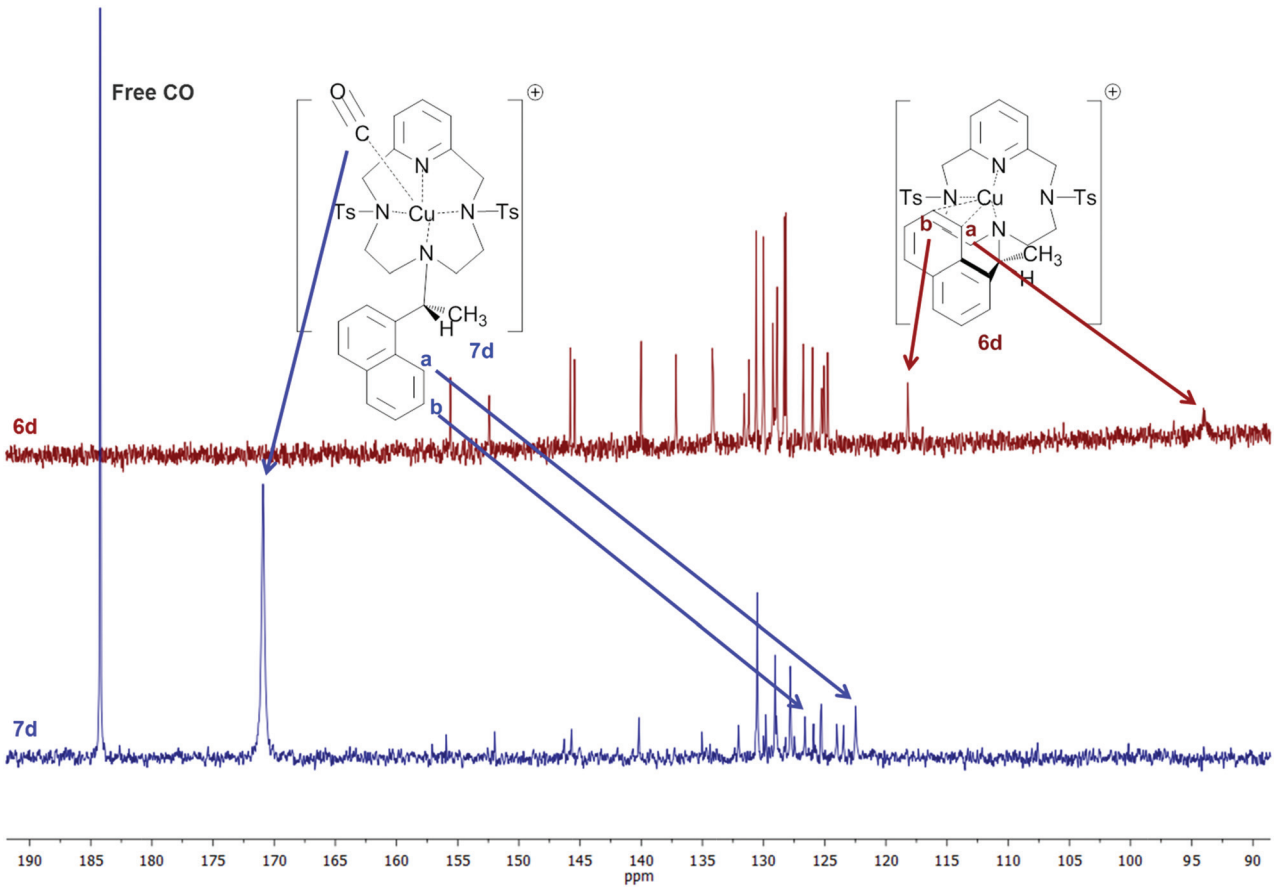


Fig. 1 ^{13}C NMR spectra of complexes **6d** (upper line) and **7d** (lower line) in $CDCl_3$.

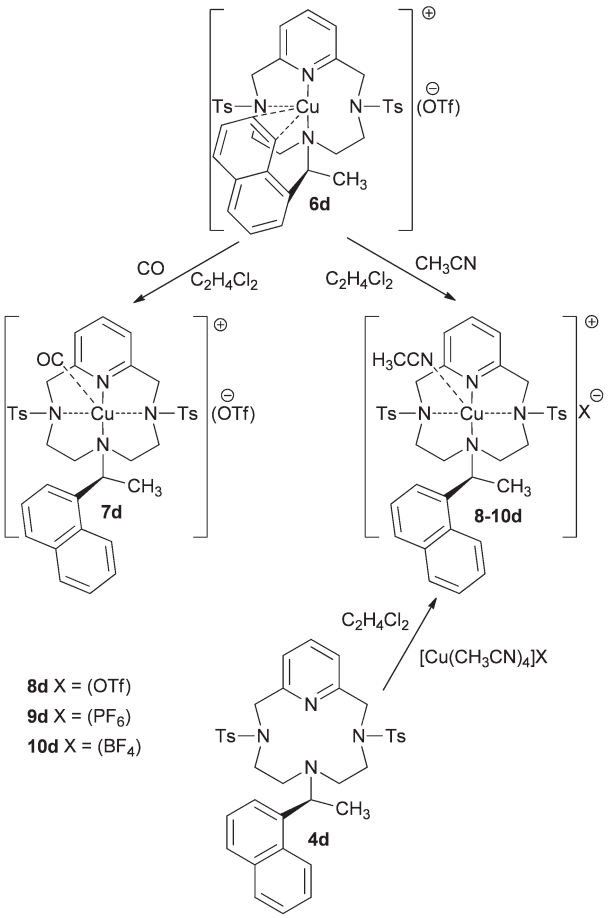
also, low symmetry is retained in solution, as shown by NMR studies. Again, the ^{15}N NMR spectrum shows a marked shift for the pyridinic nitrogen atom (from 313 to 245 ppm), while the *N*-6 atom (Scheme 1), bonded to the stereogenic carbon, is affected to a lower extent (from 39 to 51 ppm), similar to that previously reported for the ammonium salt **5d**. All these complexes were isolated in good yields and fully characterised.

The η^2 coordination mode of the naphthyl on copper(I) in solution has been observed by ^1H and ^{13}C NMR studies in $CDCl_3$ solution. In the case of complex **6d**, for example, a marked low frequency shift of the naphthylic carbon **a** involved in the η^2 bond with copper from 124.5 ppm in the free ligand, to 94.2 ppm in the complex (see Fig. 1 for labelling of the carbon atoms **a** and **b**). Carbon **b** is affected to a lower extent (low frequency shift from 124.6 to 118.2 ppm). A similar effect can be observed also in the ^1H NMR, with the proton directly bound to carbon **a** shifted to higher frequencies (from 8.16 to 8.93 ppm). The observed coupling constant ^1J (^{13}C, ^1H) of 149 Hz for carbon **a** provides hints of a partial re-hybridisation state from sp^2 to sp^3. Carbon **b**, instead, is less affected and a ^1J (^{13}C, ^1H) of 163 Hz is observed.[22] The copper(I)–arene coordinative interaction in a η^2 unsymmetrical fashion has been confirmed also by X-ray diffraction studies (*vide infra*) and the $Cu–C_1$ bond is significantly shorter than the $Cu–C_2$ bond. Although structurally characterised copper(I)–arene complexes remain quite rare and, to the best of our knowledge this is the first naphthyl complex reported, such a d–π interaction in copper(I) complexes has been already systematically investigated.[23]

In order to investigate the coordination behaviour of the naphthyl group in the presence of an added ligand, we decided to treat **6d** with CO in dichloroethane solution (Scheme 6). As revealed by IR in solution, a sharp band at 2111 cm^{-1} was present immediately after (5 min) exposure to CO at atmospheric pressure. The observed frequency of coordinated CO in complex **7d** is higher than those reported in the case of tetracoordinated copper(I) CO complexes of [bis(2-pyridylmethyl)amine],[24] probably due to the lower efficiency of aliphatic amines in transferring electron density to the metal centre compared to pyridine.

The experiment was then repeated but exposing a $CDCl_3$ solution of complex **6d** in an NMR tube to ^{13}C doped carbon monoxide atmosphere. As reported in Fig. 1, a sharp signal at 171.3 ppm was observed, in a typical range for CO coordinated to copper(I).[25] On the other hand, signals relative to carbon **a** and **b** were located at 122.9 and 127.0 ppm respectively, thus clearly indicating that the naphthyl group is no longer coordinated to the copper atom after the CO uptake. This result is of particular relevance to catalysis, since it is reasonable to assume that the naphthyl moiety can stabilise the coordination sphere of the copper atom, but can be easily displaced by incoming substrates.

The reactivity of complex **6d** was also tested with acetonitrile (Scheme 6). We first accomplished this by stirring a dichloroethane solution of **6d** in the presence of excess of acetonitrile (5 equivalents). The ^1H NMR spectrum shows a



Scheme 6 Reaction of complex **6d** with CO and CH_3CN. Syntheses of complexes **7–10d**.

marked shift of all the signals, especially in the aliphatic region. The ^{15}N NMR spectrum shows that the position of the pyridine nitrogen signal is unaffected while the sp^3 nitrogen atom bonded to the stereogenic carbon is located at 38 ppm. The excess of acetonitrile can be easily removed under reduced pressure to yield $[Cu(CH_3CN)\mathbf{4d}]\cdot(OTf)$, **8d**, containing only one coordinated acetonitrile molecule (ν_{CN} = 2250 cm^{-1}), as shown by integration of the CH_3CN signal in the ^1H NMR spectrum. The same product, with different counter anions, can also be synthesized by treating the free ligand **4d** with $[Cu(CH_3CN)_4]\cdot(PF_6)$ or $[Cu(CH_3CN)_4]\cdot(BF_4)$, to yield complexes **9d** and **10d**, respectively. Both complexes show the same chemical shifts as **8d** for the cation in the ^1H NMR spectra, indicating that the counter anion does not affect the symmetry of the product in solution.

X-ray diffraction studies

The crystal structures of some of the species **4–10** have been determined through X-ray diffraction on single crystal samples (see Fig. 2–7 for the molecular geometries). This allowed characterising the very different conformations of the cycles, which could be induced by the substituents R, R^1 and Ar or by the complexation to the metal. In Table 1, we report a summary of

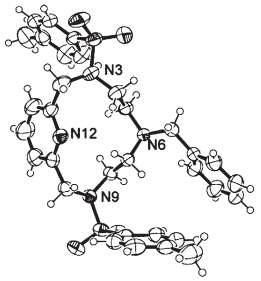


Fig. 2 Structure of compound **4a** (thermal ellipsoids are shown at 50% probability level). To give an idea of the size available for coordination inside the cycle, the distances N6···N12 and N3···N9 are 3.935(5) Å and 5.741(6) Å, respectively.[7]

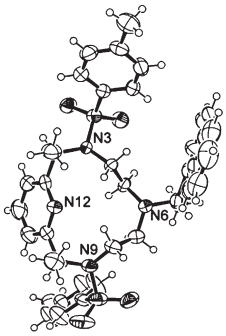


Fig. 3 Structure of compound **4d(13*S*)** (thermal ellipsoids are shown at 50% probability level). Distances within the coordination pocket are: N6···N12 4.122(5) Å and N3···N9 5.363(6) Å.

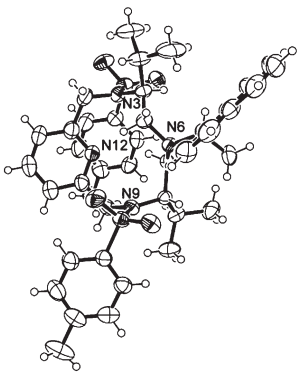


Fig. 4 Structure of compound **4f** (thermal ellipsoids are shown at 50% probability level). Distances within the coordination pocket are: N6···N12 3.629(5) Å and N3···N9 4.910(6) Å.

the conformations about each bond of the cycle. Apart from the rigid conformations induced by the pyridine ring at the 12–1 and 11–12 bonds, all others show a fairly large flexibility, so that only small similarities are found among the six species studied in this work. In particular, it is obvious that complexation to Cu atom induces severe conformational changes to the ring because the four nitrogen atoms must approach the metal for coordination (though, in **6d** one nitrogen is not really bound to Cu, in spite of the favourable conformation, see Fig. 6).

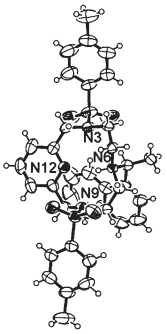


Fig. 5 Structure of compound **5d** (thermal ellipsoids are shown at 50% probability level; the $[CF_3SO_3]^-$ counter ion is omitted for clarity). Selected bond distances (Å) and angle (°): N6–H2 is fixed at 0.91, N6–H2–N12 153. For sake of comparison with **4d**, N6···N12 is 2.916(5) and N3···N9 5.090(5).

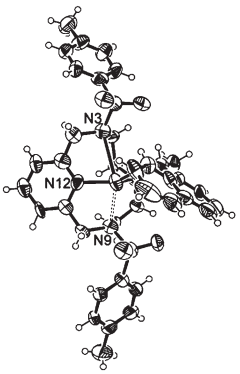


Fig. 6 Structure of compound **6d** (thermal ellipsoids are shown at 50% probability level; the $[CF_3SO_3]^-$ counter ion is omitted for clarity). Selected bond distances (Å) and angle (°): Cu–N12 1.980(7), Cu–N6 2.151(6), Cu–N3 2.346(7), Cu–N9 2.820(9), Cu–C1 2.017(8), Cu–C2 2.428(10), N3–Cu–N9 140.1(3).[8] For sake of comparison with **4d** and **5d**, N6···N12 is 3.151(6) and N3···N9 is 4.902(6).

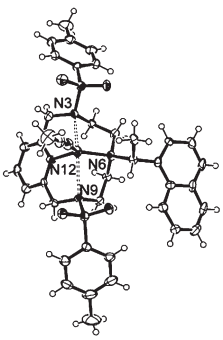


Fig. 7 Structure of compound **10d** (thermal ellipsoids are shown at 50% probability level; the $[CF_3SO_3]^-$ counter ion is omitted for clarity). Selected bond distances (Å) and angle (°): Cu–N12 2.058(4), Cu–N6 2.111(5), Cu–N3 2.567(4), Cu–N9 2.549(5), Cu–N(CH_3CN) 1.898(5), N3–Cu–N9 139.1(1).[8] For sake of comparison with **4d**, **5d** and **6d**, N6···N12 is 3.306(5) and N3···N9 is 4.793(6).

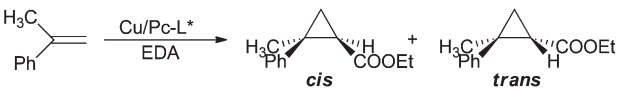
In the free ligands, the conformation of the cycle brings the tosyl bonded nitrogens *antiparallel* and the aromatic rings (the two tolyls and the phenyl or naphthyl) oriented far from each other. In **4f** and **5d**, one tosyl or the naphthyl is directed

Table 1 Summary of the conformational features of the cyclic structures with (**6** and **10**) or without (**4** and **5**) Cu complexation, as determined from X-ray diffraction on single crystal samples[a]

	12–1	1–2	2–3	3–4	4–5	5–6	6–7	7–8	8–9	9–10	10–11	11–12
4a	−ap	+sc	−sc	+ac	−ap	+sc	+sc	−ap	+sc	+sc	−ac	+ap
4d	−ap	+sc	−sc	+ac	−ap	+ac	−sc	+ac	−ac	+sc	−sc	+ap
4f	+ap	+sc	−ac	+sc	+sc	−ac	−sc	+ac	+sc	−ac	+sc	+ap
5d	+ap	+sc	−ac	+ac	−sc	+ac	+ap	+sc	+sc	−ac	+sc	+ap
6d	+ap	−sc	−sc	+ac	−sc	−sc	−ap	−sc	−sc	+sc	+sc	−ap
10d	+ap	+sp	+sc	−ac	−sc	+ap	−sc	−sc	+ac	−sc	−sc	−ap

[a] Legend: sp = syn-periplanar; sc = syn-clinal; ac = anti-clinal; ap = anti-periplanar. +/− indicate the rotation.

Table 2 Cu(I)/**4a** catalysed cyclopropanation of α-methylstyrene[a]



Entry	Copper source	*T*	Solvent	Yield[b] (%)	*cis* : *trans*[c]
1	$[Cu(OTf)]_2{\cdot}C_6H_6$	r.t.	$C_2H_4Cl_2$	31	42 : 58
2	$[Cu(OTf)]_2{\cdot}C_7H_8$	r.t.	$C_2H_4Cl_2$	33	42 : 58
3	CuI	r.t.	$C_2H_4Cl_2$	32	42 : 58
4[d]	$[Cu(OTf)]_2{\cdot}C_6H_6$	0 °C	$C_2H_4Cl_2$	89	43 : 57
5[d]	$[Cu(CH_3CN)_4]{\cdot}BF_4$	0 °C	$C_2H_4Cl_2$	45	43 : 57
6[d]	$Cu(OTf)_2$	0 °C	$C_2H_4Cl_2$	89	43 : 57
7[d]	$CuCl_2$	0 °C	$C_2H_4Cl_2$	10	44 : 56
8[d]	$Cu(OAc)_2{\cdot}H_2O$	0 °C	$C_2H_4Cl_2$	16	45 : 55
9[d,e]	$[Cu(OTf)]_2{\cdot}C_6H_6$	0 °C	$C_2H_4Cl_2$	32	44 : 56
10[d,f]	$[Cu(OTf)]_2{\cdot}C_6H_6$	0 °C	$C_2H_4Cl_2$	43	45 : 55
11[d,g]	$[Cu(OTf)]_2{\cdot}C_6H_6$	0 °C	$C_2H_4Cl_2$	88	43 : 57
12[d]	$[Cu(OTf)]_2{\cdot}C_6H_6$	0 °C	CH_2Cl_2	44	64 : 36
13[d]	$[Cu(OTf)]_2{\cdot}C_6H_6$	0 °C	CH_3CN	10	50 : 50
14[d]	$[Cu(OTf)]_2{\cdot}C_6H_6$	0 °C	Toluene	50	77 : 23
15[d]	$[Cu(OTf)]_2{\cdot}C_6H_6$	0 °C	Chlorobenzene	47	72 : 28
16[d]	$[Cu(OTf)]_2{\cdot}C_6H_6$	0 °C	THF	19	66 : 34
17[d]	$[Cu(OTf)]_2{\cdot}C_6H_6$	0 °C	$C_2H_4Cl_2$[h]	37	40 : 60

[a] Reactions were performed with equimolar amounts of Cu salt (3.0×10^{-2} mmol) and **4a** in solvent. Cu–**4a**–EDA–α-mehylstyrene 1 : 1 : 35 : 170. [b] Isolated yields based on EDA. [c] Determined by GC-MS. [d] Slow addition of EDA over 100 min. [e] In the presence of molecular sieves. [f] Cu–**4a** ratio = 1 : 2. [g] Synthesized according to ref. 41. [h] Not distilled.

toward the centre of the cycle as it also occurs in the Cu complex **6d** (whereas it is not possible in **10d**, because of the acetonitrile ligand). In **4f** and **5d** the bonds C2–N3 and C10–N9 are associated with *anti-clinal* conformations, that makes the pyridine ring lying on the average plane of the cycle, instead of being significantly tilted as in **4a** and **4d** and in the Cu complexes. This conformation is less prompt for coordination to Cu, but likely a re-arrangement about C2–N3 and C10–N9 is relatively easy.

In general, the intermolecular packing is not very tight, in the absence of strong hydrogen bonding or other intermolecular interactions. However, we cannot exclude that the observed conformations could also be affected by packing effects. A full investigation of the conformations of the ligands in isolation is currently underway by means of theoretical gas phase quantum chemical calculations.

The presence of S atoms, and the coordination to Cu, allows a correct evaluation of the absolute configuration of the species **4d**, **4f**, **5d**, **6d** and **10d**, which is in agreement with expectation.

Cyclopropanation reactions

The catalytic activity of copper complexes with ligand **4a** in cyclopropanation reactions was investigated. As a model reaction we chose the cyclopropanation of α-methyl styrene with EDA (EDA = ethyl diazoacetate). Catalytic reactions were run by adding EDA to a solution containing the olefin, the ligand and the Cu salt (Cu–**4a**–EDA–olefin ratio 1 : 1 : 35 : 170), following by IR spectroscopy the disappearance of the band due to the stretching of the N_2 moiety (ν = 2114 cm^{-1}). We first tested the reaction by changing the copper salt, the solvent, the temperature and the modality of addition of the EDA solution. The results are summarised in Table 2. All reported yields were isolated and based on EDA. In all cases cyclopropanes were obtained as major products. However, the high volatility of the products requires a careful isolation from the eluates. Fumarate and maleate, the homo-coupling product of EDA, were the only detected side products.

As can be seen from the data reported in Table 2, the best results in terms of yield were obtained at 0 °C by slow addition

of EDA with a syringe pump employing $[Cu(OTf)]_2{\cdot}C_6H_6$ as the copper source (the same results were obtained with the more expensive toluene complex) in 1,2-dichloroethane (Table 2, entry 4). Lower yields were observed when using copper(II) sources such as $CuCl_2$ or $Cu(OAc)_2$ (Table 2, entries 7 and 8). Better results were obtained when employing copper(II) triflate instead (Table 2, entry 6). It is reasonable to assume, anyway, that copper must be reduced to oxidation state I by EDA under the reaction conditions and that the active species is again a cationic copper(I) complex of the ligand having an outersphere non coordinating triflate anion.[26] In preliminary experiments, freshly distilled solvents were employed. However, the use of molecular sieves during the reaction was found to be detrimental while yields were not severely affected by the use of not distilled solvents (Table 2, entries 9 and 17, respectively). Good yields were obtained in other chlorinated solvents such as dichloromethane and chlorobenzene and in toluene, while by using acetonitrile, lower yields were observed. In this case acetonitrile competes with the ligand and the substrates for coordination to the copper atom (see later). A different explanation instead should be given for the low yield of cyclopropanes formed when using THF. In this case the product derived from the C–H insertion into the α-CH bond of the solvent was also observed (Table 2, entry 16).[27]

We next studied the effect of the different ligands under the optimised conditions in $C_2H_4Cl_2$ as solvent. The preformed complexes **6d**, **8d**, **9d** and **10d** were also tested. Results are reported in Table 3. All the reported yields in this case were determined by GC with the addition of 2,4-dinitrotoluene as internal standard, confirmed by quantitative ^1H NMR analysis of the reaction mixture. In all cases cyclopropanes were obtained in good to excellent yields; again fumarate and maleate were the only detected side products and accounted for the missing mass balance of the reactions. The presence of the naphthyl group, although conferring a better stability to the copper complex, does not alter the reaction course and ligand **4b** essentially gave the same results compared to **4a** (Table 3, entry 1). In the case of chiral ligands, the presence of a naphthyl substituent seems to be beneficial and the enantioselectivities obtained with ligand **4d** are slightly better than those with ligand **4c** (Table 3, compare entries 8 and 9 with entries 3 and 4). Further decreasing the temperature did not improve the selectivity of the reaction (Table 3, entry 5). Identical results were obtained whether preformed **6d** or **4d**/$[Cu(OTf)]_2{\cdot}C_6H_6$ were used (Table 3, entries 16 and 8). The presence of acetonitrile in the reaction mixture slightly decreased the yields, without affecting to a major extent the observed stereoselectivities (Table 3, entries 6–7 and 17–19). This result suggests that the coordinated acetonitrile molecule dissociates in solution before the activation of the EDA, and that the precatalyst is **4d** whilst **6d**, **7d** and **8d** are inactive. The inhibiting effect was observed also upon addition of external acetonitrile (Table 3, entry 20).

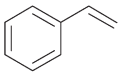
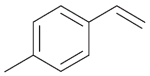
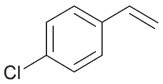
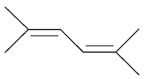
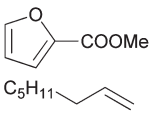
Best results in terms of enantioselectivities for both *cis* (88%) and *trans* (99%) isomers were obtained with the more sterically hindered ligand **4f** (Table 3, entry 11). Ligand **4f** has a matching configuration of all the stereocenters and as a result the observed enantioselection was significantly higher than in the case of ligands **4d** and **4e** (Table 3, compare entries 8 and 10 with entry 13). On the other hand, a mismatching

Table 3 Cu(I)/**Pc-L*** complexes for asymmetric cyclopropanation of α-methylstyrene[a]

					ee[d] (%)	
Entry	**Pc-L***/Cu	*T*	Yield[b] (%)	*cis* : *trans*[c]	*cis*	*trans*
1	**4b**/$[Cu(OTf)]_2{\cdot}C_6H_6$	0 °C	86	43 : 57	—	—
2[e]	**4c-(13*S*)**/$[Cu(OTf)]_2{\cdot}C_6H_6$	r.t.	75(53)	55 : 45	−44	−35
3[e]	**4c-(13*S*)**/$[Cu(OTf)]_2{\cdot}C_6H_6$	0 °C	90(70)	65 : 35	−50	−38
4	**4c-(13*R*)**/$[Cu(OTf)]_2{\cdot}C_6H_6$	0 °C	91(72)	65 : 35	50	38
5	**4c-(13*R*)**/$[Cu(OTf)]_2{\cdot}C_6H_6$	−20 °C	80(59)	64 : 36	53	38
6	**4c-(13*R*)**/$[Cu(CH_3CN)_4]{\cdot}BF_4$	0 °C	78(65)	57 : 43	33	36
7	**4d-(13*R*)**/$[Cu(CH_3CN)_4]{\cdot}BF_4$	0 °C	70(56)	55 : 45	45	44
8	**4d-(13*R*)**/$[Cu(OTf)]_2{\cdot}C_6H_6$	0 °C	99(83)	60 : 40	53	65
9[e]	**4d-(13*S*)**/$[Cu(OTf)]_2{\cdot}C_6H_6$	0 °C	99(83)	60 : 40	−53	−65
10	**4e**/$[Cu(OTf)]_2{\cdot}C_6H_6$	0 °C	99(88)	33 : 67	30	50
11	**4f**/$[Cu(OTf)]_2{\cdot}C_6H_6$	0 °C	98(57)	50 : 50	88	99
12	**4f**/$Cu(OTf)_2$	0 °C	96	52 : 48	70	77
13	**4g**/$[Cu(OTf)]_2{\cdot}C_6H_6$	0 °C	66	35 : 65	57	52
14[e]	**4h**/$[Cu(OTf)]_2{\cdot}C_6H_6$	0 °C	91	52 : 48	−21	−16
15	**4i**/$[Cu(OTf)]_2{\cdot}C_6H_6$	0 °C	95	42 : 58	23	59
16	**6d**	0 °C	98(82)	57 : 43	55	66
17	**8d**	0 °C	80(72)	58 : 42	49	63
18	**9d**	0 °C	75(65)	57 : 43	45	62
19	**10d**	0 °C	85(73)	55 : 45	54	62
20[f]	**4d-(13*R*)**/$[Cu(OTf)]_2{\cdot}C_6H_6$	0 °C	79(65)	59 : 41	53	65

[a] Reactions were performed with equimolar amounts of Cu(I) salt (3.0×10^{-2} mmol) and **Pc-L*** with a *S* configuration in dichloroethane (5 mL). Cu–**4**–EDA–α-mehylstyrene 1 : 1 : 35 : 170. [b] Yields based on EDA determined by GC (isolated yield). [c] Determined by GC. [d] Determined by chiral HPLC; absolute configurations: *cis*-cyclopropanes were (1*S*,2*R*), *trans*-cyclopropanes were (1*S*,2*S*). [e] Absolute configurations: *cis*-cyclopropanes were (1*R*,2*S*), *trans*-cyclopropanes were (1*R*,2*R*). [f] In the presence of added acetonitrile (5 equiv.).

Table 4 Asymmetric cyclopropanation of alkenes by Cu(I)/**Pc-L***[a]

Entry	Pc-L*	Alkene	Yield[b] (%)	*cis* : *trans*[c]	ee[d] (%) *cis*	ee[d] (%) *trans*
1	**4d-(13*R*)**		72(51)	50 : 50	33	50
2	**4f**		97	38 : 62	99	87
3	**4d-(13*R*)**		66(45)	53 : 47	34	45
4	**4e**		79	25 : 75	33	40
5	**4d-(13*R*)**		88(68)	47 : 53	36	50
6	**4e**		88	19 :81	42	53
7	**4f**		86	42 : 58	66	78
8	**4d-(13*R*)**		64(56)	—	50	
9	**4e**		85	—	62	
10	**4f**		45	—	88	
11[e]	**4d-(13*R*)**		81(54)	67 : 33	30	15
12	**4d-(13*R*)**		54(45)	>1 : 99	n.d.	57
13	**4e**		55	>1 : 99	n.d.	28
14	**4f**		74	>1 : 99	n.d.	76
15	**4f**		73	38 : 62	75	55

[a] Reactions were performed with slow addition of EDA over 100 min to a solution of $[Cu(OTf)]_2 \cdot C_6H_6$ and **Pc-L*** (3.0×10^{-2} mmol) in dichloroethane (5 mL) at 0 °C. [b] Yields based on EDA determined by GC (isolated yield). [c] Determined by GC-MS. [d] Determined by chiral HPLC; absolute configurations:[28–30] for entries 1–7 *cis*-cyclopropanes were (1*S*,2*R*), *trans*-cyclopropanes were (1*R*,2*R*); entries 8–10: the absolute configuration was (1*S*). For entries 11 and 15 the absolute configurations were not determined; for entries 12–14 *trans*-cyclopropane was (1*R*,5*R*,6*R*). [e] Cu(I)–**4d**–EDA–olefin = 1 : 1 : 35 : 1750.

diastereoselection is observed: ligand **4d** gave preferentially the *cis* isomer, while ligand **4e** the *trans* and, in the case of ligand **4f**, equal amounts of both isomers were obtained. Noticeably, the reaction with $Cu(OTf)_2$ still gave very good yields, but a significant drop in the enantioselection (Table 3, entry 12).

The two diastereoisomers **4g** and **4f** afforded the same enantiomer albeit in different enantiomeric excess (Table 3, entry 13). The experimental results show that better enantiomeric excesses were obtained if a stereogenic carbon is present in position 13 (Scheme 3). On the other hand, the diastereoselection in favour of the *cis*-isomer is influenced by the presence of bulky substituents on the macrocycle. The presence of the *i*-propyl moieties, in fact, confine the macrocycle in a more rigid environment (Fig. 4).

Surprisingly, when employing ligand **4h** we obtained the opposite enantiomer (Table 3, entry 14). The stereocenters of this molecule are exactly in the same configuration as those of **4e**. It is reasonable to assume that trifyl moieties induces a different conformation of the macrocyclic ring system.

When employing the bulkier *tert*-butyl diazoacetate, ^{t}BuDA, (condition as in the caption to Table 2, **4d**/$[Cu(OTf)]_2 \cdot C_6H_6$ as catalyst) both lower yields (28%) and a decrease of enantioselectivity (ee *cis* 12%, *trans* 46%) were observed with an inversion of the diastereoselectivity (*cis* : *trans* = 27 : 73). Similar effects on increasing the size of the diazoacetate are not unprecedented and have been explained in terms of overcrowding of the transition state.[31]

Under optimal conditions, other alkenes were employed to determine the substrate scope of the cyclopropanation reaction catalysed by the **Pc-L***/$[Cu(OTf)]_2 \cdot C_6H_6$ system in dichloroethane (Table 4). At a Cu(I)–EDA–alkene ratio of 1 : 35 : 170, the formed complex catalysed the reaction of all the tested substrates yielding the cyclopropanes in good yields and enantioselectivities. The absence of α-substituents on the styrene affected the diastereoselectivity of the reaction (Table 4, entries 1–7) yielding preferentially to the *trans* isomer (up to a 4 fold excess in the case of 4-Cl-styrene, entry 6). Steric hindrance at the α position does not hamper the reaction and good yields were obtained with 1,1-diphenyl ethylene (Table 4, entries 8–10).

The catalytic activity is not confined to styrenic double bonds. With 2,5-dimethyl-2,4-hexadiene, an important precursor to the chrysanthemic acid synthesis,[32] the catalytic reaction yielded the desired cyclopropanes (cyclopropanation of only one double bond was observed)[33] and with reasonable diastereoselectivities, if a large excess of the olefin is employed (Table 4, entry 11).

Good yields (attack only at the non-substituted double bond) and excellent diastereoselectivities in favour of the *trans* isomer (>99%) were obtained with 2-methylfuroate, (Table 4, entries 12–14).[34] From this precursor, some years ago Reiser reported a very elegant synthesis of roccellaric acid.[35]

Non-activated aliphatic alkenes are known to be less reactive in comparison with aromatic or activated alkenes towards copper mediated cyclopropanations.[36] Chiral catalysts for the

enantioselective cyclopropanation of aliphatic 1-alkenes are very often *trans* selective,[37,38] although more recent examples of highly *cis* selective catalysts have been reported.[39,40] When 1-octene was reacted with EDA in the presence of Cu(I)/**4f** the corresponding cyclopropane derivative was obtained in 73% yield, thus extending the scope of **Pc-L*** copper(I) complexes in asymmetric synthesis (Table 4, entry 15).

Conclusions

In conclusion, we have prepared and fully characterised a new family of Cu(I) complexes with chiral pyridine containing macrocyclic ligands (**Pc-L***). The strategy adopted for the synthesis of these macrocyclic ligands is very flexible and allows for structural modification. A small library of ligands possessing the same donor properties but with either C_1 or C_2 symmetry was synthesized. Their use in catalytic asymmetric cyclopropanation reactions was investigated. Our group is currently investigating the nature of the active intermediates and the utility of pyridine containing macrocyclic ligands in other asymmetric reactions. The structural features of these ligands allow further modifications in order to modulate the properties of the corresponding complexes. Furthermore, since mono adducts **2e–i** could be isolated in good yields and purity, the synthesis of unsymmetrical bis(sulfonamides) can be envisaged and this will be the subject of forthcoming work from our group.

Experimental section

General information

NMR spectra were recorded on Bruker Avance 300-DRX or Avance 400-DRX spectrometers. Chemical shifts (ppm) are reported relative to TMS. The ^{1}H NMR signals of the compounds described in the following have been attributed by COSY and NOESY techniques. Assignments of the resonance in ^{13}C NMR were made using the APT pulse sequence and HSQC and HMBC techniques. The ^{15}N NMR signals of the compound described have been attributed by HMBC technique. Infrared spectra were recorded on a BIO-RAD FTS-7 spectrophotometer. Elemental analyses and mass spectra were recorded in the analytical laboratories of Milan University. GC-MS analysis were performed on a Shimadzu GCMS-QP5050A instrument. Optical rotation were measured on a Perkin Elmer instruments model 343 plus; $[\alpha]_D$ values are given in 10^{-1} ° cm^2 g^{-1}. Microwave assisted reactions were performed with a MILESTONE® microSYNT multimode labstation, using 12 mL sealed glass vessels. The internal temperature was detected with a fiber optic sensor. Unless otherwise specified, all the reactions were carried out in a dinitrogen atmosphere employing standard Schlenk techniques and magnetic stirring. Solvents were dried prior to use by standard procedures and stored under dinitrogen. α-Methylstyrene was distilled over CaH_2 and stored under dinitrogen. Copper(I) triflate benzene complex, copper(I) tetrakis–acetonitrile esafluorophosphate complex and copper(I) tetrakis–acetonitrile tetrafluoroborate complex were synthesized following literature methods.[41] All other starting materials were commercial products and were used as received.

X-ray structure determination

Data collections for the crystal structure determinations were carried out using a Bruker Apex II difractometer (**4a**, **5d**, **6d** and **10d**) or an Agilent SuperNova Mo microsource, Al filtered[42] and working at 50 kV and 0.8 mA (compounds **4d** and **4f**). All crystal structures were solved by direct methods using SHELXS97 and refined with SHELX97,[43] within the WINGX suite of programs.[44] H atoms were rigidly modelled on the riding C or N atoms.

Details of the crystal structures and data collections of **4a**,[7] **6d** and **10d**[8] have been already reported. Crystallographic information files and Tables with crystallographic data for **4d**, **4f** and **5d** are reported as ESI.† Here we report only the major features of each crystal structure.

4a. Crystals suitable for an X-ray structural determination were obtained by crystallization of **4a** from a dichloromethane/toluene solution (Fig. 2). In the absence of chirality, this compound crystallize in centrosymmetric $P\bar{1}$.

4d(13*S*). Crystals suitable for an X-ray structural determination were obtained by crystallization from a ethyl acetate/*n*-hexane solution (Fig. 3). The species crystallizes in chiral $P2_12_12_1$. As reported in Table 1, the conformation of **4d** is not so dissimilar from **4a**, albeit not identical. The absolute configuration is confirmed (Flack parameter −0.07(10)).

4f(13*R*4*S*8*S*). Crystals suitable for X-ray diffraction were obtained from $CDCl_3$. The samples were stable in air, and a data collection was run at ambient conditions. The compound crystallizes in $P2_12_12_1$ space group, which is as expected a chiral space group (see Fig. 4). The presence of S atoms allows the determination of the absolute configuration, with sufficient accuracy (Flack parameter 0.01(6)).

5d(13*R*). Crystals suitable for an X-ray structural determination were obtained by crystallization of **5d** from a dichloroethane solution (Fig. 5). The species crystallizes as a salt of $[CF_3SO_3]^-$ in chiral $P2_12_12_1$. As described above, **5d** and **4f** have some similarities in the conformation of the cycle, but overall they are quite different (see Table 1), mainly because of the intra-molecular N–H···N hydrogen bond (d_{N-N} 2.916 Å) occurring between the protonated N6 and the pyridine N12. The larger perturbation at N6 is in keeping with the assigned position of the H atom, which was also tentatively refined (resulting in d_{N6-H6} 0.7 Å). As this refinement was somewhat unstable, in the final model it was constrained into the stereochemically predicted position. The absolute configuration is confirmed by the X-ray analysis (Flack parameter −0.02(10)).

6d(13*S*). Crystals suitable for an X-ray structural determination were obtained by layering with benzene a dichloroethane solution from a ethyl acetate/*n*-hexane solution (Fig. 6). The space group is $P2_12_12_1$ and the absolute configuration could be confirmed with sufficient precision (Flack

parameter 0.04(3)). The main feature of this complex is the loose coordination of N9 to the Cu complex (2.820(9) Å), which implies a tetra-coordination, instead of a penta-coordination.

10d(13*S*). Crystals suitable for an X-ray structural determination were obtained by crystallisation from dichloroethane/*n*-hexane. The structure of complex **10d**, (Fig. 7) shows the copper atom placed in the middle of the macrocyclic cavity, again in a fivefold coordination site produced by the four ligand nitrogens and the acetonitrile. At variance from **6d**, in **10d** Cu is therefore truly pentacoordinated in a strongly distorted trigonal bipyramidal geometry. N3 and N9 occupy particularly elongated axial sites (Cu–N ~ 2.5 Å), whereas N6, N12 and the acetonitrile are in equatorial positions. As expected, the naphthyl group has been displaced from the coordination sphere of the metal by the incoming acetonitrile molecule. The complex crystallizes in $P2_1$, and the absolute configuration is well established (Flack parameter −0.003(16)).

Synthesis of 1,7-ditosyl-2,6-[(*S*,*S*)-iso-propyl]-4-[(*R*)-1-naphthylethyl]-1,4,7-triazaheptane, 3f-(1*R*,2*S*,2′*S*). A solution of (*S*)-2-isopropyl-1-tosylaziridine **1b** (0.781 g, 3.21 mmol) and (*R*)-1-(1-naphthyl)ethyl amine (0.514 g, 3.0 mmol) in toluene (21 mL) was added in a microwave tube. The solution was stirred and heated by microwave irradiation for 3 h at 150 °C. The resulting mixture, without any purification, was added to a solution of (*S*)-2-isopropyl-1-tosylaziridine **1b** (0.785 g, 3.28 mmol) in distilled toluene (4 mL) and was stirred and heated under reflux for 45 h. The mixture was dried and purified by silica gel chromatography using *n*-hexane–ethyl acetate = 7 : 3 as eluent, obtaining a light yellow solid **3f-(1*R*,2*S*,2′*S*)** (0.785 g, 1.21 mmol, 40%). ^{1}H NMR (400 MHz; $CDCl_3$; T = 300 K) δ 7.94 (1H, m, Ar*H*) 7.79 (4H, d, J = 8.0 Hz, Ar*H*) overlapping with 7.79 (1H, m, Ar*H*), 7.73 (1H, dd, J = 5.8 Hz, J = 3.4 Hz, Ar*H*), 7.45–7.42 (2H, m, Ar*H*), 7.40–7.39 (2H, m, Ar*H*), 7.29 (4H, d, J = 8.0 Hz, Ar*H*), 4.66 (2H, d, J = 7.9 Hz, N*H*), 4.59 (1H, q, J = 6.6 Hz, C*H*), 3.26 (1H, m, C*H*), 2.46 (2H, dd, J = 13.4 Hz, J = 5.1 Hz, CH_2), 2.41 (6H, s, CH_3), 1.55 (2H, m, C*H*), 1.20 (3H, d, J = 6.6 Hz, CH_3) 0.56 (6H, d, J = 6.9 Hz, CH_3), 0.19 (6H, d, J = 6.8 Hz, CH_3). ^{13}C NMR (75 MHz; $CDCl_3$; T = 300 K) δ 143.4 (*C*), 138.2 (*C*), 138.0 (*C*), 134.1 (*C*), 132.1 (*C*), 129.7 (*C*H), 128.8 (*C*H), 128.2 (*C*H), 127.3 (*C*H), 125.6 (*C*H), 125.5 (*C*H), 125.1 (*C*H), 125.0 (*C*H), 123.9 (*C*H), 56.6 (*C*H), 53.6 (*C*H), 52.3 (CH_2), 27.6 (*C*H), 21.6 (CH_3), 19.3 (CH_3), 14.8 (CH_3), 12.4 (CH_3). ^{15}N NMR (40 MHz; $CDCl_3$; T = 300 K) δ 94.0 (*N*HTs), 38.3 (*N*HC). The signal relative to *N*-Ts was not detected. Elemental Analysis: Found: C, 66.6; H, 7.6; N, 6.5%. Calc. for $C_{36}H_{47}N_3O_4S_2$: C, 66.5; H, 7.3; N, 6.5%. $[\alpha]_D^{20}$ = −47.22 (*c* 1.37 in $CHCl_3$).

Synthesis of 6-[(*R*)-1-naphthylethyl]-3,9-ditosyl-3,8-[(*S*,*S*)-iso-propyl]-3,6,9,15-tetraazabicyclo[9,3,1]pentadeca-1(15),11,13-triene, 4f-(13*R*,4*S*,8*S*). A solution of amine **3f-(1*R*,2*S*,2′*S*)** (0.715 g, 1.10 mmol), 2,6-bis(chloromethyl)pyridine (0.194 g, 1.10 mmol) and micronized anhydrous potassium carbonate (0.608 g, 4.40 mmol) in distilled acetonitrile (37 mL) was stirred and heated under reflux for 116 h. The resulting mixture was washed with water end extracted with ethyl acetate, dried and purified by silica gel chromatography using *n*-hexane–ethyl acetate = 6 : 4 as eluent, obtaining a white solid **4f-(13*R*,4*S*,8*S*)** (0.471 g, 0.626 mmol, 57%). ^{1}H NMR (300 MHz; $CDCl_3$; T = 300 K) δ 8.58 (1H, d, J = 8.1 Hz, Ar*H*), 7.89 (1H, m, Ar*H*), 7.83 (1H, d, J = 8.1 Hz, Ar*H*), 7.69 (1H, d, J = 8.1 Hz, Ar*H*), 7.64–7.42 (8H, m, Ar*H*), 7.12 (4H, d, J = 7.8 Hz, Ar*H*), 7.05 (2H, m, Ar*H*), 5.18 (1H, m, H^{13}), 4.72 (2H, m, H^2), 3.94–3.82 (6H, m, *H*), 2.63–2.60 (2H, m, *H*), 2.40 (2H, m, *H*) overlapping with 2.33 (6H, s, CH_3), 1.57 (3H, d, J = 6.5 Hz, CH_3), 0.44 (12H, m, CH_3). ^{13}C NMR (75 MHz; $CDCl_3$; T = 300 K) δ 156.5 (*C*), 142.5 (*C*), 142.2 (*C*), 138.9 (*C*), 137.0 (*C*H), 134.2 (*C*), 131.7 (*C*), 129.2 (*C*H), 128.9 (*C*H), 127.8 (*C*H), 127.0 (*C*H), 126.0 (*C*H), 125.9 (*C*H), 125.8 (*C*H), 125.2 (*C*H), 124.0 (*C*H), 120.7 (*C*H), 66.5 (*C*H), 50.8 (CH_2), 49.5 (CH_2), 30.0 (*C*H), 23.8 (CH_3), 21.5 (CH_3), 21.1 (CH_3). A signal relative to a CH was not detected. ^{15}N NMR (40 MHz; $CDCl_3$; T = 300 K) δ 33.2 (*N*C). The signal relative to *N*-Ts and N^{12} were not detected. Elemental Analysis: Found: C, 68.4; H, 7.4; N, 7.1%. Calc. for $C_{43}H_{52}N_4O_4S_2$: C, 68.6; H, 7.0; N, 7.4%. *m*/*z* 753 (M + 1).

Synthesis of 6f. Copper(I) triflate benzene complex (0.0298 g, 0.0591 mmol) was added to a solution of macrocycle **4f-(13*R*,4*S*,8*S*)** (0.0891 g, 0.118 mmol) in dichloroethane (10 mL). The solution was stirred at room temperature for one hour, concentrated to 5 mL and then 10 mL of *n*-hexane were layered. Then the solid was filtered and dried *in vacuo* under nitrogen, obtaining complex **6f** as a white solid (0.111 g, 0.115 mmol, 97%). ^{1}H NMR (300 MHz; $CDCl_3$; T = 300 K) δ 8.68 (1H, d, J = 8.7 Hz, Ar*H*), 7.93 (1H, d, J = 8.0 Hz, Ar*H*), 7.87 (4H, d, J = 8.1 Hz, Ar*H*), 7.80–7.69 (3H, m, Ar*H*), 7.62–7.40 (7H, m, Ar*H*), 7.23–7.16 (2H, m, Ar*H*), 5.95 (1H, q, J = 6.6 Hz, C*H*), 5.25 (1H, d, J = 20 Hz, CH_2), 4.79 (1H, d, J = 12.7 Hz, CH_2), 4.71 (1H, d, J = 14.6 Hz, CH_2), 4.62 (1H, d, J = 20 Hz, CH_2), overlapping with 4.61 (1H, m, C*H*), 4.01 (1H, d, J = 14.6 Hz, CH_2), 2.78 (1H, d, J = 12.7 Hz, CH_2), 2.57 (3H, s, CH_3), overlapping with 2.57 (1H, m, C*H*), 2.52 (3H, s, CH_3), 2.42–2.37 (1H, m, CH_2), 2.30–2.15 (2H, m, CH_2 and C*H*), 2.10 (3H, d, J = 6.8 Hz, CH_3), 1.59 (1H, m, C*H*), 0.90 (3H, d, J = 6.7 Hz, CH_3), 0.68 (3H, d, J = 6.2 Hz, CH_3), 0.29 (3H, d, J = 6.5 Hz, CH_3), −0.49 (3H, d, J = 6.2 Hz, CH_3). ^{13}C NMR (75 MHz; $CDCl_3$; T = 300 K) δ 155.7 (*C*), 151.2 (*C*), 145.6 (*C*), 145.3 (*C*), 140.4 (*C*H), 134.8 (*C*), 134.5 (*C*), 133.9 (*C*), 132.1 (*C*), 131.5 (*C*H), 130.4 (*C*), 129.8 (*C*H), 129.3 (*C*H), 128.9 (*C*H), 127.7 (*C*H), 127.3 (*C*H), 126.4 (*C*H), 125.2 (*C*H), 124.8 (*C*H), 124.5 (*C*H), 123.9 (*C*H), 122.8 (*C*), 64.7 (*C*H), 62.0 (*C*H), 57.4 (CH_2), 57.1 (CH_2), 56.4 (*C*H), 55.5 (CH_2), 46.8 (CH_2), 29.9 (*C*H), 27.1 (*C*H), 24.5 (CH_3), 22.4 (CH_3), 21.9 (CH_3), 21.3 (CH_3), 20.3 (CH_3), 18.5 (CH_3). ^{19}F NMR (282 MHz; $CDCl_3$; T = 300 K) δ −78.58 (s). Elemental Analysis: Found: C, 54.7; H, 5.2; N, 5.7%. Calc. for $C_{44}H_{52}CuF_3N_4O_7S_3$: C, 54.7; H, 5.4; N, 5.8%.

General procedure for the catalytic cyclopropanation reactions

In a typical experiment, $[Cu(OTf)]_2{\cdot}(C_6H_6)$ (0.0075 g, 0.015 mmol), the ligand (0.020 g (**4d**), 0.030 mmol) and α-methyl styrene (0.650 mL, 5.0 mmol) were dissolved in distilled dichloroethane (5 mL) and the solution stirred for one hour at 0 °C. Then a dichloroethane solution (1 mL) of EDA (0.114 g, 0.105 mL, 1 mmol) was slowly added by a syringe

pump over 100 min. The reaction was monitored by IR, following the disappearance of the band due to the stretching of N_2 moiety at 2114 cm^{-1}. The reaction was considered to be finished when the absorbance of the EDA was below 0.03 (by using a 0.1 mm thick cell). 2,4-Dinitrotoluene was added as internal standard and the solution was analysed by GC. The solution was then evaporated to dryness *in vacuo* and analysed by ^1H NMR. The residue purified by silica gel chromatography (eluent ethyl acetate–*n*-hexane = 0.3 : 10).

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