Supramolecular double helical Cu(I) complexes for asymmetric cyclopropanation†

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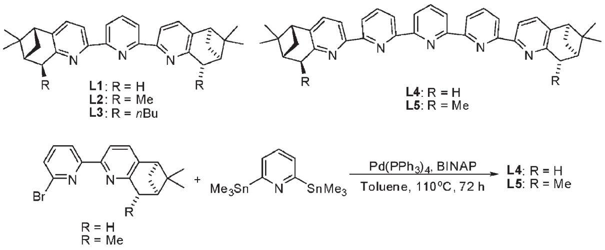
Chiral double-stranded helicates, formed between Cu(I) ion and C_2-symmetric oligopyridines, were used for catalytic asymmetric cyclopropanation of alkenes; low catalyst loadings (0.2 mol%), high TONs (up to 404) and short reaction times (30–60 min) were achieved with $[Cu_2L_2]OTf_2$ (L = chiral C_2-symmetric terpyridine).

Double-stranded helicates, a paradigmatic branch of supramolecular structures exhibiting helical topology, have received great attention over the past two decades and numerous examples have appeared.[1] Much research has been devoted to the understanding of the self-assembly process.[2] Potential applications in areas as varied as anticancer drugs,[3] DNA binding,[4] liquid crystalline materials,[5] supramolecular functional devices,[6] and host–guest interactions[7] have appeared. Although helicates are chiral, paradoxically, their use in asymmetric catalysis has not been explored.

Copper(I) ions form air-stable double-stranded dinuclear helicates with quaterpyridines[8,9] and terpyridines (tpy)[10–12] in various coordination modes. Stereoselective synthesis of Cu helicates could be achieved with the use of chiral ligands.[10,13] Trinuclear Cu(I) helicates of quinquepyridine have also been reported but are much less studied.[9a,14] Cu(I) complexes are well-known active catalysts in a number of important asymmetric reactions,[15] and herein we report several air-stable chiral double-stranded Cu(I) helicates with C_2-symmetric terpyridines **L1–3** and quinquepyridines **L4–5**, and their application in asymmetric cyclopropanation.

New ligands **L4–5** were synthesized by Pd-catalyzed Stille cross-coupling reactions (Scheme 1). Helicate formations with ligands **L1–3**[16] and **L4–5** were investigated with different Cu(I)X salts (X = PF_6^-, OTf^- and ClO_4^-).† The combination of elemental analysis and ESI-MS confirmed bimetallic complexes, of formula $[Cu_2L_2]X_2$, with **L1–3**; and trimetallic complexes, of formula $[Cu_3L_2]X_3$, with **L4**; although attempted isolation of trinuclear Cu(I) with **L5** only led to corresponding binuclear Cu helicate $[Cu_2\mathbf{L5}_2]^{2+}$. All double-stranded helicates are stable red solids which did not oxidize to Cu(II) even after prolonged storage in air.

NMR studies of crude $[Cu_2\mathbf{L1}_2]^{2+}$ showed two sets of resonances, which corresponded to *P*/*M* diastereomers of 29% de. Using more bulky methyl or *n*-butyl groups dramatically enhanced the selectivities to 89% and 95% de, respectively. The trinuclear helicates $[Cu_3\mathbf{L4}_2]^{3+}$ showed 79% de, but $[Cu_2\mathbf{L5}_2]^{2+}$ gave 30% de only. Since the enantiopurities of chiral helicates are important in preparing a chiral catalyst, all complexes were purified as a single diastereomer (⩾95%) upon repeated recrystallization. The helical structures of the Cu(I) helicates were further examined in solution by CD experiments. For example, the Cu(I) helicates of **L1**, **L4** and **L5** showed strong absorption (Cotton effect) in the region of 280–380 nm, indicating that the integrity is retained in solution (Fig. 1).



Scheme 1 Syntheses of **L4–5**.

The crystal structure of double helical $[Cu_2\mathbf{L3}_2]^{2+}$, together with a space-filling representation, is shown in Fig. 2.‡ The Cu(I) center adopts a distorted trigonal planar geometry and the complex exhibits almost a D_2-symmetry with a rare {3 + 3} coordination. The Cu···Cu distance is 2.536(1) Å, which is the shortest among reported tpy systems (2.57–2.63 Å).[10–12] In the case of $[Cu_2\mathbf{L5}_2]^{2+}$ (Fig. 3),‡ the geometries of the Cu(I) centers were perturbed by weak interactions of terminal pyridines at the axial positions, causing its structural parameters to be more like a pentacoordinate Cu(I) complex with *pseudo*-trigonal bipyramidal geometry. The Cu···Cu distance is 3.482(2) Å. The two methyl substituted groups of sterically demanding **L5** are in close proximity (C···C contacts: 3.81(1)–3.83(1) Å), which may render the coordination environment for the formation of trimetallic complexes unfavorable. The solid state structures of $[Cu_2\mathbf{L3}_2]^{2+}$ and $[Cu_2\mathbf{L5}_2]^{2+}$ both revealed stereoselective formation of *P*-helix.

The Cu(I) complexes were tested in the asymmetric cyclopropanation of styrene with ethyl diazoacetate (EDA). Helicate $[Cu_2\mathbf{L2}_2](OTf)_2$ showed unusual reactivities in air (Table 1, entry 1), but a better result was achieved under nitrogen. Consistent with a previous report, the use of OTf^- salt gave the best yields and enantioselectivities.[17] By employing a more conventional slow addition method,[17] the reaction completed in 4 h and afforded a 92% isolated yield of cyclopropane (Table 1, entry 3). The trinuclear double helix is also active; under the same conditions, $[Cu_3\mathbf{L4}_2](OTf)_3$ gave good yield but required longer

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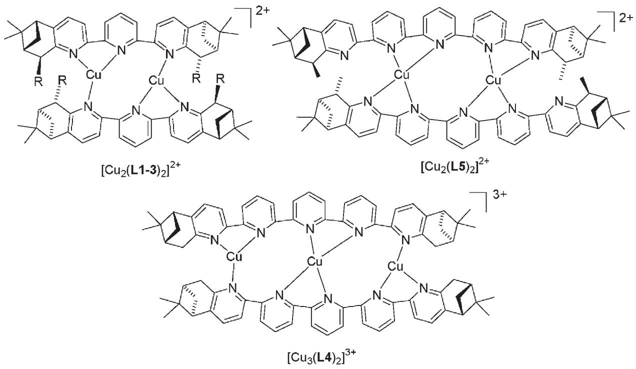
† Electronic supplementary information (ESI) available: Characterizations of $[Cu_2\mathbf{L5}_2](PF_6)_2$ and $[Cu_2\mathbf{L3}_2](ClO_4)_2$ and general procedure of catalytic cyclopropanation. See DOI: 10.1039/b713010d



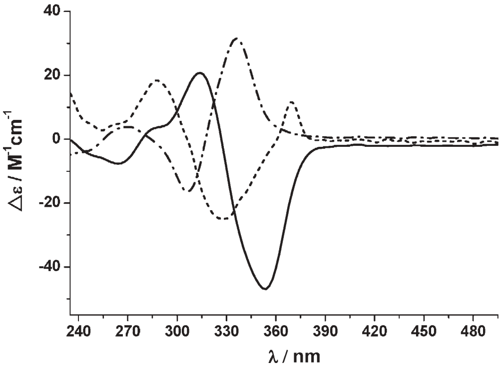


Fig. 1 CD spectra of $[Cu_2(\mathbf{L1})_2](ClO_4)_2$ (1.92×10^{-4} M) (---), $[Cu_3(\mathbf{L4})_2](ClO_4)_3$ (1.22×10^{-5} M) (—) and $[Cu_2(\mathbf{L5})_2](PF_6)_2$ (1.27×10^{-4} M) (-··-) in CH_2Cl_2.

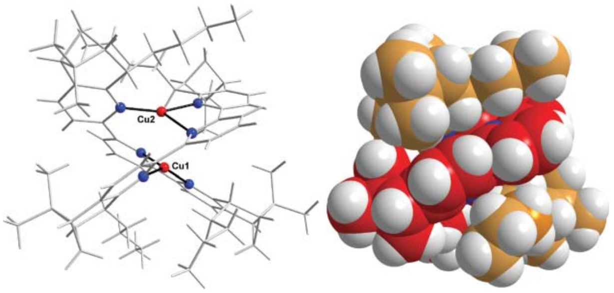


Fig. 2 Crystal structure and space-filling model of cationic double helicate $[Cu_2\mathbf{L3}_2]^{2+}$.

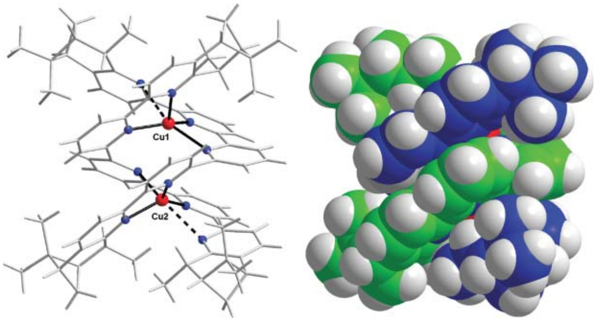
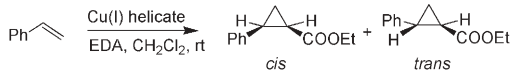


Fig. 3 Crystal structure and space-filling model of cationic double helicate $[Cu_2\mathbf{L5}_2]^{2+}$.

Table 1 Double helical Cu(I) helicates for asymmetric cyclopropanation



Entry	Helicate	Yield[a] (%)	Chemo-selectivity[b]	*cis* : *trans*[c]	% ee[d] *cis*	% ee[d] *trans*
1[e,f]	$[Cu_2\mathbf{L2}_2]^{2+}$	53	3.1 : 1	43 : 57	65	63
2[f]	$[Cu_2\mathbf{L2}_2]^{2+}$	66	3.6 : 1	43 : 57	73	71
3[g]	$[Cu_2\mathbf{L2}_2]^{2+}$	92	5.1 : 1	39 : 61	84	74
4[h]	$[Cu_2\mathbf{L2}_2]^{2+}$	93	12.1 : 1	43 : 57	83	76
5[h]	$[Cu_2\mathbf{L1}_2]^{2+}$	67	2.0 : 1	28 : 72	15	30
6[h]	$[Cu_2\mathbf{L3}_2]^{2+}$	45	1.8 : 1	45 : 55	23	52
7[g,i]	$[Cu_3\mathbf{L4}_2]^{3+}$	96	5.8 : 1	34 : 66	14	31

[a] Isolated yields based on the expected products. [b] Cyclopropanes : coupling products. [c] Determined by GC-FID. [d] Determined by chiral HPLC: *cis*-cyclopropane was (1*R*,2*S*), *trans*-cyclopropane was (1*R*,2*R*). [e] Result obtained in air. [f] One pot addition of EDA. [g] Slow addition of EDA for 4 h into the catalytic mixture. [h] Slow addition of EDA–styrene (1 : 4) for 0.5 h into the catalytic mixture. [i] Required 16 h for complete reaction.

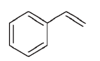
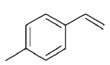
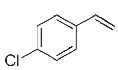
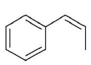
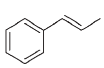
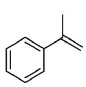
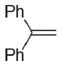
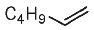
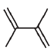
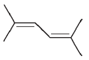
reaction time for completion (Table 1, entry 7). $[Cu_2\mathbf{L5}_2](OTf)_2$ afforded less than 5% yield of cyclopropanes.[18]

Since $[Cu_2\mathbf{L2}_2](OTf)_2$ gave the best result, conditions were modified to explore its catalytic behavior. In contrast to the prolonged EDA addition time (4 h) generally required to reduce the formation of coupling products in cyclopropanation, we found the helical complex to be very active: a loading of 0.2 mol% complex and one pot addition of EDA completely consumed all EDA and afforded cyclopropane/coupling product in 20 min. By adding EDA–styrene in a ratio of 1 : 4 to the solution of Cu helicates for 30 min, the coupling product was suppressed to 7% and the yield of cyclopropane improved to 93% (Table 1, entry 4). The turnover number (TON) reached 404 and good enantioselectivities for both *cis*- (83%) and *trans*-cyclopropanes (76%) were observed. Longer EDA addition time and higher EDA/styrene ratio yielded no further improvement. Dramatically, Cu(I) helicates of **L1** and **L3** gave much lower % yield and % ee (Table 1, entries 5 and 6).

Under optimum conditions, several alkenes were employed to determine the substrate scope of $[Cu_2\mathbf{L2}_2](OTf)_2$ (Table 2). At a catalyst : EDA : alkene ratio of 1 : 500 : 2000, the complex catalyzed a wide range of substrates with high TON and good enantioselectivities under nitrogen. Steric hindrance at the β-position of the styrene greatly affected the reactivities: both *cis*- and *trans*-β-methyl styrenes gave lower reaction yields, albeit that high levels of enantioselectivities were maintained. Most reactions finished in 30 min. Although generally less reactive towards cyclopropanation, with difficult substrates, such as 1-hexene and dienes, the catalytic reactions were completed within 1 h with high TON and moderate to good enantioselectivities.

Although the mechanism of the catalytic cyclopropanation is still unclear at this stage, however, preliminary experiments looking at the reaction of $[Cu_2\mathbf{L2}_2](OTf)_2$ with cyclohexyl isocyanides gave a solid that showed positive ions at *m*/*z* 1282 ($[Cu_2\mathbf{L2}_2(CNC_6H_{11})OTf]^{1+}$) in ESI-MS and strong absorptions in its CD spectrum. Similar results were also found for $[Cu_3\mathbf{L4}_2](OTf)_3$. These observations suggest that these Cu(I) helicates contained at least one vacant site for catalysis.

Table 2 Asymmetric cyclopropanation of alkenes by $[Cu_2\mathbf{L2}_2](OTf)_2$[a]

Entry	Alkene	% Yield (TON)[b]	Chemo-selectivity[c]	*cis* : *trans*[d]	% ee[e] *cis*	% ee[e] *trans*
1		93 (404)	12.1 : 1	43 : 57	83	76
2		91 (406)	16 : 1	38 : 62	78	76
3		93 (365)	6.8 : 1	36 : 64	77	80
4[f]		86 (240)	2.2 : 1	18 : 82	83	57
5[f]		73 (130)	0.8 : 1	29 : 71	83	19
6		86 (394)	9.3 : 1	47 : 53	88	76
7		87 (365)	9.3 : 1	—	74	
8[f]		83 (212)	1.7 : 1	47 : 53	68	19
9[f]		86 (316)	4.7 : 1	49 : 51	68	33
10[f]		72 (172)	1.3 : 1	39 : 61	66	31

[a] Conditions: 0.2 mol% cat (6.25 mM) in CH_2Cl_2 at rt, slow addition of 1 : 4 of EDA and olefin mixture over 30 min. [b] Isolated cyclopropanes based on expected products. [c] Cyclopropanes : coupling products. [d] Determined by GC-FID. [e] Determined by chiral HPLC:[19] for entries 1–3 and 6, *cis*-cyclopropanes were (1*R*,2*S*), *trans*-cyclopropanes were (1*R*,2*R*); entry 7, the absolute configuration was (1*R*). Others were not determined. [f] Required 60 min for complete reaction.

In conclusion, we have prepared several new double-helical Cu(I) helicates with chiral oligopyridines **L1–5** and applied some of them in asymmetric cyclopropanation. This represents the first application of double-stranded helicate in asymmetric catalysis. The nature of the active intermediates and the utilities of helical systems in other asymmetric reactions are under active investigation in our group.

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Notes and references

‡ *Crystal data*: $(Cu_2\mathbf{L3}_2)(ClO_4)_2(H_2O)$: $C_{74}H_{96}Cl_2Cu_2N_6O_9$, $M = 1411.55$, monoclinic, space group $P2_1$, $a = 14.961(9)$ Å, $b = 14.001(9)$ Å, $c = 18.179(11)$ Å, $\beta = 95.0730(10)^\circ$, $V = 3793.07(40)$ Å^3, $Z = 2$, $D_{calc} = 1.236$ g cm^{-3}, $\mu(MoK\alpha) = 0.687$ cm^{-1}. 18953 reflections measured, 12119 unique, $R_{int} = 0.1380$, $R_1 = 0.0654$ ($I_o > 2\sigma(I_o)$) and 0.1456 (for all data), w$R_2 = 0.1432$ ($I_o > 2\sigma(I_o)$) and 0.1760 (for all data). Flack parameter = 0.007(18). CCDC 651264. *Crystal data*: $(Cu_2\mathbf{L5}_2)(PF_6)_2$: $C_{82}H_{82}Cu_2F_{12}N_{10}P_2$, $M = 1624.60$, monoclinic, space group $P12_11$, $a = 15.5877(8)$ Å, $b = 13.2827(7)$ Å, $c = 19.0425(10)$ Å, $\beta = 101.6540(10)^\circ$, $V = 3861.41(30)$ Å^3, $Z = 2$, $D_{calc} = 1.397$ g cm^{-3}, $\mu(MoK\alpha) = 0.673$ cm^{-1}. 19386 reflections measured, 13289 unique, $R_{int} = 0.0782$, $R_1 = 0.0535$ ($I_o > 2\sigma(I_o)$) and 0.0819 (for all data), w$R_2 = 0.1354$ ($I_o > 2\sigma(I_o)$) and 0.1535 (for all data). Flack parameter = −0.002(12). CCDC 651265. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b713010d

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