Synthesis and evaluation of new chiral nonracemic C_2-symmetric and unsymmetric 2,2′-bipyridyl ligands†

Michael P. A. Lyle,‡ Neil D. Draper‡ and Peter D. Wilson*

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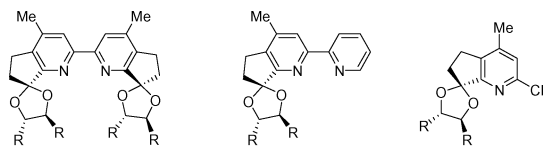
The synthesis of a series of chiral nonracemic and C_2-symmetric 2,2′-bipyridyl ligands (R = Me, *i*-Pr and Ph) as well as the syntheses of the corresponding unsymmetric 2,2′-bipyridyl ligands (R = Me and Ph) is described. These bipyridyl ligands were prepared, in a notably direct and modular fashion, from the readily available and corresponding 2-chloropyridine acetals (R = Me, *i*-Pr and Ph). The bipyridyl ligands were evaluated in copper(I)-catalyzed cyclopropanation reactions of styrene with the ethyl and *t*-butyl esters of diazoacetic acid. The stereoselectivities, as well as the yields of the cyclopropanation reactions, were dependant on the ratio of the bipyridyl ligands and copper triflate that was employed. The best result was obtained in the asymmetric cyclopropanation reaction of styrene and *tert*-butyl diazoacetate with the C_2-symmetric bipyridyl ligand (R = *i*-Pr). This afforded the corresponding *trans*-cyclopropane in good diastereoselectivity (4 : 1) and in moderate enantioselectivity (44% ee). The X-ray structure determination of a complex formed between the C_2-symmetric 2,2′-bipyridyl ligand (R = Ph) and copper(I) chloride showed that two bipyridyl ligands had coordinated to the copper(I) ion. This information, along with the results of a series of cyclopropanation reactions and NMR data, led to the conclusion that the 2,2′-bipyridyl ligands had the propensity to form catalytically inactive bis-ligated copper(I) species in solution that were in equilibrium with catalytically active copper(I) triflate and the desired mono-ligated copper(I) species. Moreover, it was observed that the complex of the bipyridyl ligand (R = Ph) and copper(I) chloride had a particularly large optical rotation (sodium *D*-line). The maximum positive optical rotation was subsequently found to be $+1.1 \times 10^4$ at 304 nm and the maximum negative optical rotation was -1.3×10^4 at 329 nm.

Introduction

We have recently established a new design concept for the efficient and modular construction of chiral nonracemic auxiliaries, ligands and catalysts for use in asymmetric synthesis.[1] These novel chiral directors can be prepared from functionalized indan-1-one derivatives (as well as their heterocyclic analogues) and a series of chiral nonracemic C_2-symmetric 1,2-diols by experimentally simple acid-catalyzed condensation reactions. In this paper, the synthesis of a series of chiral nonracemic and C_2-symmetric 2,2′-bipyridyl ligands **1a**–**c** (R = Me, *i*-Pr and Ph) as well as the syntheses of the corresponding unsymmetric 2,2′-bipyridyl ligands **2a**–**b** (R = Me and Ph) is described (Fig. 1).[2] The bipyridyl ligands were prepared from the corresponding 2-chloropyridine acetals **3a**–**c** (R = Me, *i*-Pr and Ph) and were evaluated in copper(I)-catalyzed asymmetric cyclopropanation reactions of styrene with the ethyl and *t*-butyl esters of diazoacetic acid. The observations and conclusions made in this detailed study are of significance for the future design, synthesis and application of new chiral nonracemic ligands in transition metal-catalyzed asymmetric processes.



1a, R = Me*
1b, R = *i*-Pr
1c, R = Ph

2a, R = Me*
2b, R = Ph

3a, R = Me*
3b, R = *i*-Pr
3c, R = Ph

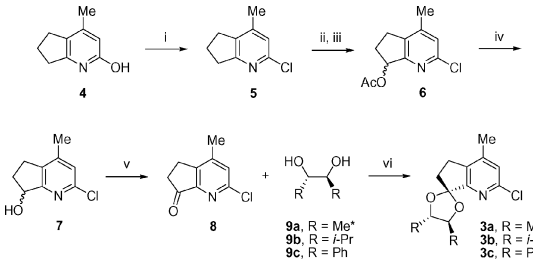
Fig. 1 Chiral nonracemic 2,2′-bipyridyl ligands **1a**–**c** (R = Me, *i*-Pr and Ph) and **2a**–**b** (R = Me and Ph). * The compound used in the following study was the enantiomer of that indicated in the figure.

We have previously reported the six-step synthesis of the precursors to the chiral nonracemic ligands described in this paper, the 2-chloropyridine acetals **3a**–**c** (R = Me, *i*-Pr and Ph), from the known 2-hydroxypyridine **4** (Scheme 1).[3,4] Thise 2-hydroxypyridine was readily prepared on a multi-gram scale (from cyclopentanone, ethyl acetoacetate and ammonium acetate) and converted to the 2-chloropyridine **5** on heating with phenylphosphonic dichloride. Subsequent oxidation with 30% aqueous hydrogen peroxide afforded the corresponding pyridine *N*-oxide that was converted to the acetate **6** on heating with acetic anhydride. Hydrolysis of the acetate **6** with lithium hydroxide

Department of Chemistry, Simon Fraser University, 8888 University Drive, Burnaby, British Columbia, Canada V5A 1S6. E-mail: pwilson@sfu.ca; Fax: 1 604 291-3765; Tel: 1 604 291-5654

† Electronic supplementary information (ESI) available: General experimental details, detailed experimental procedures and full product characterization data for all of the additional compounds synthesized. An experimental procedure for the preparation and crystallization of the bis-2,2′-bipyridyl ligand copper(I) chloride complex **18**. ^{1}H and ^{13}C NMR spectra for compounds **1a**–**c**, **2a**–**b** and **10**–**15** as well as for the complex **18**. See DOI: 10.1039/b513286j

‡ M. P. A. L. performed all of the synthetic work and obtained all of the compound characterization data described herein. N. D. D. determined the X-ray crystal structure of the bis-2,2′-bipyridyl ligand copper(I) chloride complex **18**.



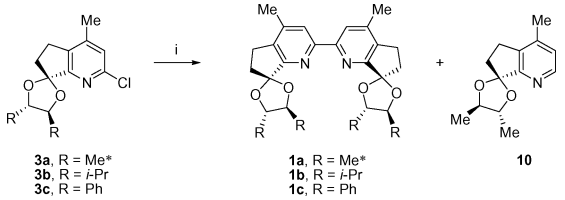
Scheme 1 Synthesis of the chiral nonracemic 2-chloropyridine acetals **3a**–**c** (R = Me, *i*-Pr and Ph). Reagents and conditions: (i) $PhP(O)Cl_2$, 160 °C, 16 h, 83%; (ii) H_2O_2, H_2O, AcOH, 80 °C, 16 h; (iii) Ac_2O, room temperature, 1 h then 100 °C, 4 h, 60% (over two steps); (iv) LiOH, THF, H_2O, room temperature, 16 h, 94%; (v) $(COCl)_2$, DMSO, CH_2Cl_2; NEt_3, −78 °C to room temperature, 90%; (vi) *p*-TsOH (cat.), benzene, reflux, 16 h, 85% (**3a**), 89% (**3b**), 79% (**3c**). * The compound used in this study was the enantiomer of that indicated in the scheme.

afforded the corresponding alcohol **7** and subsequent Swern oxidation afforded the 2-chloroketone **8**.[5] The 2-chloropyridine acetals **3a**–**c** (R = Me, *i*-Pr and Ph) were then prepared in good yield on condensation of the 2-chloroketone **8** with the corresponding chiral nonracemic C_2-symmetric 1,2-diols **9a**–**c** (R = Me, *i*-Pr and Ph) by heating these reaction partners at reflux in benzene with a catalytic amount of *para*-toluenesulfonic acid.[6]

Results and discussion

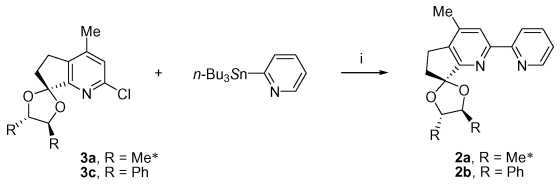
Synthesis of the 2,2′-bipyridyl ligands

The chiral nonracemic and C_2-symmetric 2,2′-bipyridyl ligands **1a**–**c** (R = Me, *i*-Pr and Ph) were prepared from the corresponding 2-chloropyridine acetals **3a**–**c** by a nickel(0)-mediated homocoupling reaction upon heating in tetrahydrofuran with dibromobis(triphenylphosphine)nickel(II), zinc dust and tetraethylammonium iodide (Scheme 2).[7] The reactions of the 2-chloropyridine acetals **3b**–**c** (R = *i*-Pr and Ph) both afforded the corresponding 2,2′-bipyridyl ligands **1b**–**c** in good yield (72 and 73%, respectively). However, in the case of the reaction of the 2-chloropyridine acetal **3a** (R = Me), a significant amount of the reductively dehalogenated product **10** (35% yield) was obtained along with the desired and corresponding 2,2′-bipyridyl ligand **1a** (41% yield).



Scheme 2 Synthesis of the chiral nonracemic and C_2-symmetric 2,2′-bipyridyl ligands **1a**–**c** (R = Me, *i*-Pr and Ph). Reagents and conditions: (i) $NiBr_2(PPh_3)_2$, Zn, Et_4NI, THF, 60 °C, 72 h, 41% (**1a**) and 35% (**10**), 72% (**1b**), 73% (**1c**). * The compound used in this study was the enantiomer of that indicated in the scheme.

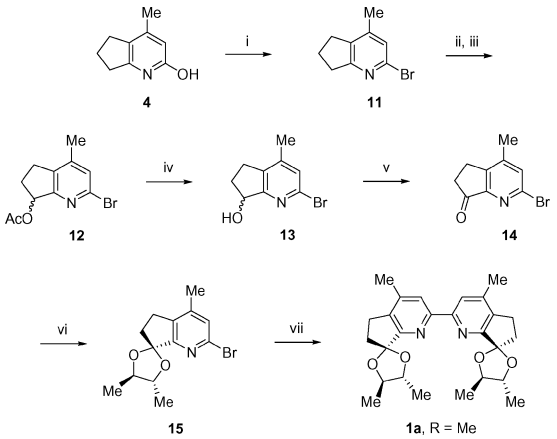
The chiral nonracemic and unsymmetric 2,2′-bipyridyl ligands **2a**–**b** (R = Me and Ph) were prepared from the corresponding 2-chloropyridine acetals **3a** and **3c** by palladium-catalyzed Stille coupling reactions with 2-(tri-*n*-butylstannyl)pyridine



Scheme 3 Synthesis of the chiral nonracemic and unsymmetric 2,2′-bipyridyl ligands **2a**–**b** (R = Me and Ph). Reagents and conditions: (i) 5 mol% Pd_2dba_3, 10 mol% P(*t*-Bu)$_3$, CsF, dioxane, reflux, 24 h, 72% (**2a**), 83% (**2b**). * The compound used in this study was the enantiomer of that indicated in the scheme.

(Scheme 3).[8,9] In the first instance, it was found that these 2-chloropyridine acetals reacted exceedingly slowly under standard Stille coupling reaction conditions, when tetrakis(triphenylphosphine)palladium(0) was employed as the catalyst on heating at reflux in benzene or toluene with potassium carbonate.[10] However, the coupling reactions proceeded smoothly on employment of the conditions recently reported by Fu and co-workers to afford the unsymmetric 2,2′-bipyridyl ligands **2a**–**b** in good yield (72 and 83%, respectively).[11] These reaction conditions involved heating a mixture of the 2-chloropyridine acetals **3a** and **3c** with 2-(tri-*n*-butylstannyl)pyridine and anhydrous cesium fluoride in dioxane at reflux in the presence of catalytic amounts of tris(dibenzylideneacetone)dipalladium(0) and tri-*t*-butyl phosphine.

The direct and modular synthesis of the C_2-symmetric 2,2′-bipyridyl ligands **1a**–**c** (R = Me, *i*-Pr and Ph) and the unsymmetric 2,2′-bipyridyl ligands **2a**–**b** (R = Me and Ph) further demonstrated the versatility of the corresponding 2-chloropyridine acetals **3a**–**c** as building blocks for the construction of new chiral ligands.[3] However, the formation of a significant quantity of the reductively dehalogenated product **10** in the nickel(0)-mediated homocoupling reaction of the 2-chloropyridine acetal **3a** (R = Me) was problematic because it occurred in the last step of the synthetic sequence, after the valuable chiral portion of the molecule had been installed. In order to circumvent this problem, it was decided to prepare the corresponding 2-bromopyridine acetal **15** (Scheme 4). In this case, it was considered that the higher reactivity of a pyridyl–bromide bond would lead to an improvement in the yield of the desired 2,2′-bipyridyl ligand **1a** (R = Me). The lower reactivity of aryl–chloride bonds relative to aryl–bromide bonds in metal-catalyzed coupling reactions is generally attributed to their reluctance to undergo oxidative addition to the metal catalyst.[12] This is in agreement with the bond dissociation energies of aryl halide bonds [at 298 K, Ph–Cl (96 kcal mol^{-1}) > Ph–Br (81 kcal mol^{-1})].[13] The mechanism by which reduction of the aryl–chloride bond occurred, in the case of the reaction of the 2-chloropyridine acetal **3a** (R = Me), is not obvious. However, if this coupling reaction proceeds *via* radical intermediates, the reaction solvent (tetrahydrofuran) or the reagent (tetraethylammonium iodide) could have acted as sources of the hydrogen atoms as this reaction was performed under strictly anhydrous conditions. The observation that the reduction process only occurred during the homocoupling reaction of the 2-chloropyridine acetal **3a** (R = Me) can be attributed to the fact that this is a less sterically encumbered molecule and so it is presumably more reactive than the 2-chloropyridine acetals **3b,c** (R = *i*-Pr and Ph).



Scheme 4 Synthesis of the C_2-symmetric 2,2′-bipyridyl ligand **1a** (R = Me) from the 2-bromopyridine acetal **15**. Reagents and conditions: (i) PBr_3, reflux, 12 h, 52%; (ii) H_2O_2, H_2O, AcOH, 80 °C, 16 h; (iii) Ac_2O, room temperature, 1 h then 100 °C, 4 h, 54% (over two steps); (iv) LiOH, THF, H_2O, room temperature, 16 h, 95%; (v) $(COCl)_2$, DMSO, CH_2Cl_2; NEt_3, −78 °C to room temperature, 90%; (vi) (2*R*,3*R*)-2,3-butanediol **9a**, *p*-TsOH (cat.), benzene, reflux, 20 h, 89%; (vii) $NiBr_2(PPh_3)_2$, Zn, Et_4NI, THF, 60 °C, 72 h, 83%.

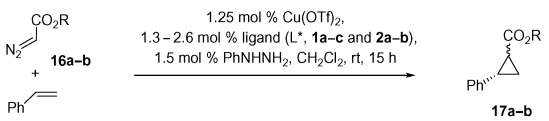
The 2-bromopyridine acetal **15** was prepared in a similar manner as to that used in the preparation of the corresponding 2-chloropyridine acetal **3a** (R = Me). This involved conversion of the 2-hydroxypyridine **4** to the 2-bromopyridine **11**, in reasonable yield, on heating with phosphorus tribromide. Subsequent treatment of the 2-bromopyridine **11** with 30% aqueous hydrogen peroxide in glacial acetic acid at 80 °C for 16 h afforded the corresponding pyridine *N*-oxide. This compound was then heated in acetic anhydride to afford the acetate **12** in good overall yield (54%, over two steps). Hydrolysis of the acetate **12** with lithium hydroxide afforded the corresponding alcohol **13** that was efficiently oxidized under Swern conditions to afford the 2-bromoketone **14**. Condensation of this 2-bromoketone with (2*R*,3*R*)-2,3-butanediol **9a** (R = Me) in the presence of a catalytic amount of *p*-toluenesulfonic acid monohydrate in benzene at reflux afforded the 2-bromopyridine acetal **15** in high yield (89%). This acetal was then subjected to the nickel(0)-mediated homocoupling reaction to afford the 2,2′-bipyridyl ligand **1a** (R = Me) in good yield (83%). In this case, and as anticipated, none of the reductively dehalogenated product **10** was detected.

Evaluation of the bipyridyl ligands

With a series of three chiral nonracemic and C_2-symmetric 2,2′-bipyridyl ligands **1a**–**c** (R = Me, *i*-Pr and Ph) as well as two unsymmetric 2,2′-bipyridyl ligands **2a**–**b** (R = Me and Ph) in hand, the evaluation of these ligands in copper(I)-catalyzed asymmetric cyclopropanation reactions of styrene with the ethyl and *t*-butyl esters of diazoacetic acid **16a**–**b** (R = Et and *t*-Bu) was undertaken (Table 1). These catalytic reactions were performed under a standard set of reaction conditions.[14] Of note, the study of copper(I)-catalyzed asymmetric cyclopropanation reactions of styrene and diazoacetates constitutes a standard ("benchmark") method for the evaluation of new chiral nonracemic 2,2′-bipyridyl ligands.[2,14]

The active copper catalysts in these reactions were generated by reduction of the complexes formed between 1.25 mol% of copper(II) triflate and 1.3 or 2.6 mol% of the 2,2′-bipyridyl ligands **1a**–**c** and **2a**–**b** with phenylhydrazine.[15] In all cases, the solutions of the copper(II) complexes formed between copper(II) triflate and the bipyridyl ligands were light green in colour that turned deep red

Table 1 Asymmetric copper(I)-catalyzed cyclopropanation reactions of styrene with the ethyl and *t*-butyl esters of diazoacetic acid **16a**–**b** (R = Et and *t*-Bu)



Entry	L*	R	L* : Cu Ratio	Product[a]	*trans* : *cis* Ratio[b]	Yield (%)[c]	Ee (%)[d]
1	**1a**	Et	1 : 1	*ent*-**17a**	3 : 2	55	9
2	**1a**	*t*-Bu	1 : 1	*ent*-**17b**	4 : 1	67	7
3	**1a**	Et	2 : 1	*ent*-**17a**	1 : 1	48	24
4	**1a**	*t*-Bu	2 : 1	*ent*-**17b**	7 : 3	47	38
5	**1b**	Et	1 : 1	**17a**	7 : 3	62	25
6	**1b**	*t*-Bu	1 : 1	**17b**	4 : 1	59	44
7	**1b**	Et	2 : 1	**17a**	7 : 3	53	34
8	**1b**	*t*-Bu	2 : 1	**17b**	3 : 1	57	42
9	**1c**	Et	1 : 1	(±)-**17a**	3 : 2	58	0
10	**1c**	Et	2 : 1	—	—	0	—
11	**2a**	Et	1 : 1	*ent*-**17a**	3 : 2	75	2
12	**2b**	Et	1 : 1	**17a**	3 : 2	74	3

[a] The absolute stereochemistry of the *trans*- and *cis*-diastereoisomers of cyclopropane reaction products were determined by comparison of the optical rotations with literature values.[17] [b] The ratios of the *trans*- and *cis*-diastereoisomers of the cyclopropane reaction products were determined by analysis of the ^1H NMR spectra (400 MHz, $CDCl_3$) of the crude reaction mixtures. [c] Combined yields of the chromatographically separated *trans*- and *cis*-cyclopropane reaction products. [d] The enantioselectivities were determined by analytical chiral HPLC (Daicel Chiralcel OD column) following reduction of the *trans*-cyclopropane reaction products to the corresponding primary alcohol with lithium aluminum hydride.

instantaneously when phenylhydrazine was added to the reaction mixture. This indicated that reduction to the copper(I) complexes had occurred. The asymmetric cyclopropanation reactions were carried out at room temperature in dichloromethane and involved the slow addition (over *ca.* 3 h) of the ethyl and *t*-butyl esters of diazoacetic acid **16a**–**b** (R = Et and *t*-Bu) to a solution of 2.2 equivalents of styrene and the preformed catalyst. It was found that both the yields and stereoselectivities of the cyclopropanation reactions were highly dependant on which bipyridyl ligand was employed as well as on the ratio of the ligand and copper(II) triflate.

The reaction of styrene with ethyl diazoacetate **16a** (R = Et) using a 1 : 1 ratio of the bipyridyl ligand **1a** (R = Me), that was derived from (2*R*,3*R*)-2,3-butanediol **9a**, and copper(II) triflate afforded the cyclopropane *ent*-**17a** in a *trans* : *cis* ratio of 3 : 2 and in low enantioselectivity (9% ee) (Table 1, entry 1).[16] Employment of the larger reaction substrate, *t*-butyl diazoacetate **16b** (R = *t*-Bu) (under identical reaction conditions), afforded the cyclopropane *ent*-**17b** in an improved *trans* : *cis* ratio (4 : 1). However, the enantioselectivity of the reaction remained low (7% ee) (Table 1, entry 2). The absolute stereochemistry of the major *trans*-cyclopropane reaction products *ent*-**17a**–**b** (R = Et and *t*-Bu) were determined to be (1*R*,2*R*) and the corresponding minor *cis*-cyclopropane reaction products *ent*-**17a**–**b** were determined to be (1*S*,2*R*) by comparison of the optical rotations with literature values.[17] These initial results led to the consideration that the bipyridyl ligand **1a** was not completely bound to the copper(I) salt (or that a bis-ligated copper(I) species had formed which would imply that copper(I) triflate was present in the reaction mixtures).[18] Thus, to attempt to improve the stereoselectivities of these initial experiments, the above reactions were repeated using a 2 : 1 ratio of the bipyridyl ligand **1a** and copper(II) triflate. It was found that the reactions, with ethyl and *t*-butyl diazoacetate **16a**–**b**, afforded the corresponding cyclopropanes *ent*-**17a**–**b** in improved enantioselectivities (24 and 38% ee, respectively) (Table 1, entries 3 and 4). Similar trends were observed on evaluation of the *pseudo*-enantiomeric bipyridyl ligand **1b** (R = *i*-Pr) that was derived from (1*S*,2*S*)-1,2-diisopropyl-1,2-ethanediol **9b**. The use of a 1 : 1 ratio of the bipyridyl ligand **1b** and copper(II) triflate, in the cyclopropanation reaction of styrene with ethyl and *t*-butyl diazoacetate **16a**–**b**, afforded the corresponding cyclopropanes **17a**–**b** in higher enantioselectivities (25 and 44% ee, respectively) (Table 1, entries 5 and 6). Of note, and as was expected for these latter reactions with this *pseudo*-enantiomeric bipyridyl ligand, the major *trans*-cyclopropanes **17a**–**b** (R = Et and *t*-Bu) had (1*S*,2*S*) stereochemistry and the corresponding minor *cis*-cyclopropanes **17a**–**b** had (1*R*,2*S*) stereochemistry.[17] The use of a 2 : 1 ratio of the bipyridyl ligand **1b** and copper(II) triflate with ethyl diazoacetate **16a** resulted in a further improvement in the enantioselectivity of the reaction (34% ee) (entry 7). However, the enantioselectivity of the reaction remained essentially the same (42% ee) when *t*-butyl diazoacetate **16b** was employed as the reaction substrate (Table 1, entry 8). This is in contrast to what was found for the bipyridyl ligand **1a** (R = Me) when the latter set of reaction conditions was employed.

Particularly interesting and surprising results were obtained when the (1*S*,2*S*)-1,2-diphenyl-1,2-ethanediol **9c** derived bipyridyl ligand **1c** (R = Ph) was employed in these cyclopropanation reactions. Employment of a 1 : 1 ratio of the bipyridyl ligand **1c** and copper(II) triflate in the reaction of styrene with ethyl diazoacetate **16a** resulted in the isolation of the cyclopropane (±)-**17a** in racemic form (Table 1, entry 9). This was a surprising result in that it was expected that the ligand **1c** (R = Ph) would be the most efficient chiral director in view of the relatively large size of the cyclic acetal moiety. Moreover and remarkably, no reaction occurred when the above reaction was repeated with a 2 : 1 ratio of the bipyridyl ligand **1c** and copper(II) triflate (Table 1, entry 10).

The unsymmetric 2,2′-bipyridyl ligands **2a**–**b** (R = Me and Ph) were also evaluated in the cyclopropanation reaction of styrene with ethyl diazoacetate **16a**. In these instances, on employment of a 1 : 1 ratio of the bipyridyl ligands **2a**–**b** and copper(II) triflate, the cyclopropanes *ent*-**17a** and **17a** were isolated in good yield but in very low enantiomeric excess (2 and 3%, respectively) (Table 1, entries 11 and 12). The low enantioselectivities obtained here are presumably due to the lack of sufficient steric bulk on one side of these ligands and so no further experiments were conducted.

Crystallographic studies of the bis-2,2′-bipyridyl ligand copper(I) chloride complex (18)

In order to probe the structure of the species involved in the asymmetric cyclopropanation reactions with the C_2-symmetric 2,2′-bipyridyl ligands **1a**–**c** (R = Me, *i*-Pr and Ph), a crystallographic study was undertaken.§ The bipyridyl ligand **1c** (R = Ph) was selected for this study in light of the interesting results that had been obtained in this case. Due to the air and moisture sensitivity of copper(I) triflate complexes, the corresponding copper(I) chloride complex of the bipyridyl ligand **1c** was prepared. This involved the reaction of equimolar quantities of the ligand **1c** and anhydrous copper(I) chloride in a mixture of ethanol and dichloromethane (1 : 1). Bright red X-ray quality crystals of the resultant complex **18**, which was formed quantitatively, were obtained by recrystallization from a mixture of ether and dichloromethane (1 : 1) on slow evaporation of the solvent. Analysis of the X-ray data revealed that two bipyridyl ligands were coordinated, in a geometry that was somewhat distorted from tetrahedral, to the copper(I) centre. In addition, the chloride counterion that had been displaced from the coordination sphere of the complex had combined with the remaining copper(I) chloride to form a copper(I) dichloride counterion ($CuCl_2^-$).[19] An ORTEP representation of complex **18** is shown below (Fig. 2). Around the copper(I) centre, the following bond angles were determined: N1–Cu1–N2 = 82.2° and N2–Cu1–N1* = 131.2°. The N1–Cu1 bond length was 2.057 Å and the N2–Cu1 bond length was 2.052 Å.[20]

Mechanistic aspects of the cyclopropanation reactions

Based on the above structure determination, the results of the cyclopropanation reactions (*i.e.* the dependence of the enantioselectivity of reaction as a function of the ratio of the bipyridyl ligand and copper reagent employed in the process) can be rationalized. It is proposed that the bipyridyl ligands **1a**–**c** (R = Me, *i*-Pr and Ph) have the propensity to form bis-ligated copper(I) complexes in solution and that an equilibrium is established between copper(I) triflate, the mono-ligated copper(I) triflate complexes **19**, and the bis-ligated copper(I) triflate complexes **20** (Fig. 3). The latter bis-ligated complexes **20** are presumably

§ CCDC reference number 293622. For crystallographic data in CIF format see DOI: 10.1039/b513286j

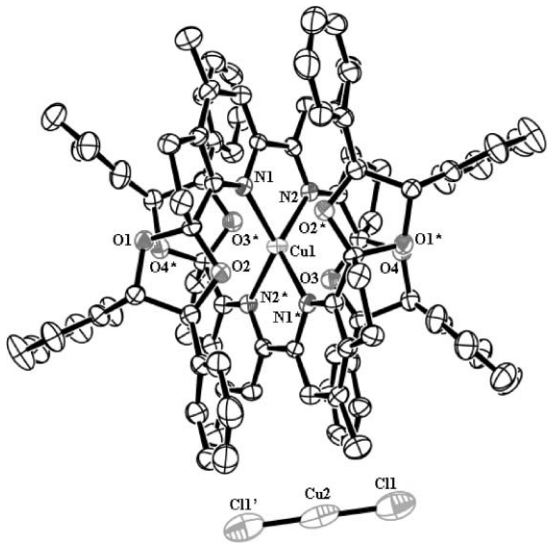


Fig. 2 ORTEP representation of the bis-2,2′-bipyridyl ligand copper(I) chloride complex **18**. The thermal ellipsoids are drawn at a 25% probability level and the atoms of the incorporated solvent molecule (dichloromethane) as well as the hydrogen atoms have been removed for clarity.

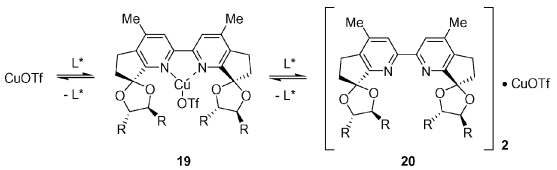


Fig. 3 Proposed equilibrium established in solution between copper(I) triflate and the C_2-symmetric 2,2′-bipyridyl ligands (L*).

inactive cyclopropanation catalysts since all coordination sites on the copper centre are blocked. However, copper(I) triflate and the mono-ligated copper(I) triflate complexes **19** would be active catalysts and so the enantioselectivities observed in the cyclopropanation reactions are a result of the relative rates of catalysis by these two species.[21] It is also possible that the desired mono-ligated copper(I) triflate complexes **19** [derived from the C_2-symmetric 2,2′-bipyridyl ligands **1a**–**b** (R = Me and *i*-Pr)] could be very effective chiral directors in asymmetric cyclopropanation reactions. However, in the cases that were studied, the free copper(I) triflate in solution had compromised the overall enantioselectivity of the reactions. In the case of the bipyridyl ligand **1c** (R = Ph), the results of the cyclopropanation reactions suggested that the corresponding bis-ligated complex was the major complex in solution. This conclusion is further supported by the fact that the ^{1}H and ^{13}C NMR spectra of the bis-2,2′-bipyridyl ligand copper(I) chloride complex **18** in deuterated chloroform were well-resolved and no free ligand was observed. Thus, when a 1 : 1 ratio of the ligand **1c** and copper(II) triflate was employed in the cyclopropanation reaction, the two species in solution would have been catalytically active copper(I) triflate and the corresponding catalytically inactive bis-ligated complex **20**. This would account for the fact that the cyclopropane reaction product (±)-**17a** was isolated in racemic form. When the cyclopropanation reaction was performed with a 2 : 1 ratio of the ligand **1c** and copper(II) triflate, the copper ions would have been entirely sequestered as the corresponding bis-ligated complex **20**. This would account for the additional fact that the cyclopropanation reaction was completely shut down in this instance. The relative kinetic and thermodynamic stability of this particular complex could be the result of favourable π–π interactions (between one of the phenyl rings of each of the four chiral acetal moieties and both aromatic rings of the two bipyridyl moieties) or that the two bipyridyl ligands are rigidly interlocked once they are positioned around the copper ion (see Fig. 2).

Optical rotary dispersion spectrum of the bis-2,2′-bipyridyl ligand copper(I) chloride complex (18)

In the process of obtaining full spectroscopic data for the bis-2,2′-bipyridyl ligand copper(I) chloride complex **18**, it was noted that this compound had a particularly large specific rotation ($[\alpha]_D^{20}$ −1300 [*c* 0.0030, chloroform]). Pfaltz and co-workers have reported a similar optical rotation ($[\alpha]_{436}^{20}$ −1574 [*c* 0.01, ethanol]) for a bis-ligated copper(II) semicorrin complex.[18] This result led us to record an optical rotary dispersion spectrum on a dilute solution of the complex **18** (1.9×10^{-5} M) in chloroform (Fig. 4). Remarkably, the maximum positive specific optical rotation was $+1.1 \times 10^4$ at a wavelength of 304 nm and the maximum negative specific rotation was -1.3×10^4 at 329 nm. To put these values in context, the classic hydrocarbons—the helicenes—have extraordinarily high specific rotations ($[\alpha]_D$) that range from 3640 for [6]-helicene to 9620 for [13]-helicene.[22] A UV-vis spectrum of the complex **18** was also recorded. Strong absorptions at 287 nm ($\varepsilon = 3.8 \times 10^4$ M^{-1} cm^{-1}), 309 ($\varepsilon = 3.9 \times 10^4$ M^{-1} cm^{-1}) and 472 nm ($\varepsilon = 6.2 \times 10^3$ M^{-1} cm^{-1}) were observed. The absorbance at 472 nm is in the blue-visible region of the electromagnetic spectrum which accounts for the intense red colour of the complex.

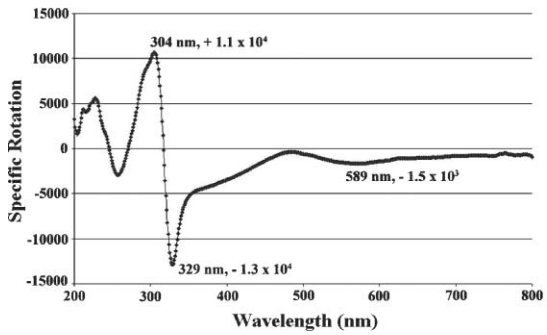


Fig. 4 Optical rotary dispersion spectrum of the bis-2,2′-bipyridyl ligand copper(I) chloride complex **18**. The spectrum was recorded at 20 °C in chloroform [*c* 0.0030 (g per 100 mL)].

Stereochemical interpretation of the asymmetric cyclopropanation reactions

The stereochemical outcome of the asymmetric cyclopropanation reactions of the copper(I) complexes of the C_2-symmetric 2,2′-bipyridyl ligands **1a**–**b** (R = Me and *i*-Pr) can be rationalized in terms of the minimization of steric interactions between the reacting species. A schematic representation, that depicts the proposed low and high energy modes for the reaction of styrene with the copper–carbenoid intermediates [for the bipyridyl ligand **1a** (R = Me) and the diazoacetates **16a**–**b** (R = Et and *t*-Bu)]

that would lead to the four possible stereoisomeric cyclopropane reaction products, is shown below (Fig. 5).

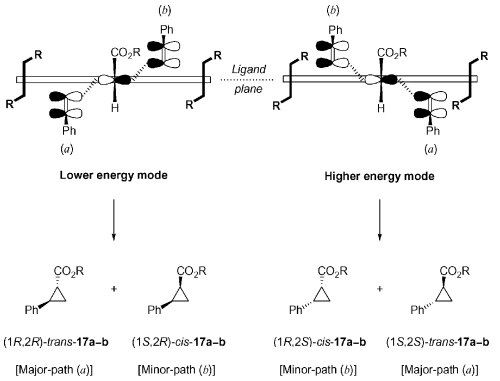


Fig. 5 Rationalization of the stereochemical outcome of the asymmetric cyclopropanation reactions of styrene and the diazoacetates **16a**–**b** (R = Et and *t*-Bu) with the C_2-symmetric 2,2′-bipyridyl ligand **1a** (R = Me).

The lower energy mode would result from minimization of steric interactions between the substituents (R) of the chiral acetal moieties and styrene. In addition, the favoured approach of styrene (from the accessible front face of the complex, as drawn) along reaction pathway (*a*) would lead to the major *trans*-cyclopropane reaction products (1*R*,2*R*)-**17a**–**b** (due to minimization of additional interactions with the ester moiety). Conversely, approach along reaction pathway (*b*) (again from the front face of the complex) would lead to the minor *cis*-cyclopropane reaction products (1*S*,2*R*)-**17a**–**b**. Approach from the front face of the complex along reaction pathways (*a*) and (*b*) in the higher energy mode would lead to the enantiomeric major *trans*-cyclopropane reaction products (1*S*,2*S*)-**17a**–**b** and the minor *cis*-cyclopropane reaction products (1*R*,2*S*)-**17a**–**b**. In this mode, the steric interactions between the substituents (R) of the chiral acetal moieties and styrene are more severe. Moreover, from this schematic representation, the relationship of the observed diastereoselectivity of the reaction to the size of the ester moiety can also be realized.

Conclusions

The direct and modular synthesis of a series of chiral nonracemic and C_2-symmetric 2,2′-bipyridyl ligands **1a**–**c** (R = Me, *i*-Pr and Ph) as well as the syntheses of the corresponding unsymmetric 2,2′-bipyridyl ligands **2a**–**b** (R = Me and Ph) from the 2-chloropyridine acetals **3a**–**c** (R = Me, *i*-Pr and Ph) have been developed. These bipyridyl ligands were evaluated for use in asymmetric synthesis in copper(I)-catalyzed cyclopropanation reactions of styrene with the ethyl and *t*-butyl esters of diazoacetic acid **16a**–**b** (R = Et and *t*-Bu). The catalytic species in these reactions were generated by reduction of the complexes formed between 1.25 mol% of copper(II) triflate and 1.3 or 2.6 mol% of the bipyridyl ligands with phenylhydrazine in dichloromethane. It was found that the stereoselectivities, as well as the yields of the reactions, were dependant on the ratio of the bipyridyl ligands and copper(II) triflate employed. The best result was obtained in the asymmetric cyclopropanation reaction of styrene with *t*-butyl diazoacetate **16b** (R = *t*-Bu) when the C_2-symmetric bipyridyl ligand **1b** (R = *i*-Pr) was employed. This afforded the corresponding *trans*-cyclopropane reaction product **17b** (R = *t*-Bu) in good diastereoselectivity (4 : 1) and in moderate enantioselectivity (44% ee). An X-ray structure determination of the complex **18** formed between the C_2-symmetric 2,2′-bipyridyl ligand **1c** (R = Ph) and copper(I) chloride showed that two bipyridyl ligands had coordinated to the copper(I) ion. This information, along with the results from the cyclopropanation reactions and NMR data, led to the conclusion that the 2,2′-bipyridyl ligands **1a**–**c** (R = Me, *i*-Pr and Ph) had the propensity to form catalytically inactive bis-ligated copper(I) species in solution that were in equilibrium with catalytically active copper(I) triflate and the desired mono-ligated copper(I) species. It was also inferred that the mono-ligated copper(I) species could possibly be very selective in the asymmetric cyclopropanation reactions and that the observed enantioselectivities were significantly eroded by free copper(I) triflate in solution. For this reason, future studies with these ligands will involve their application in asymmetric reactions which are catalyzed by copper(II) species or by transition metals other than copper. The bis-2,2′-bipyridyl ligand copper(I) chloride complex **18** was found to have a particularly large optical rotation (sodium *D*-line). Moreover, the maximum positive optical rotation was $+1.1 \times 10^4$ at 304 nm and the maximum negative optical rotation was -1.3×10^4 at 329 nm. In view of these exceptionally high values, a future study will involve the use of the bipyridyl ligand **1c** (R = Ph) for the detection of trace quantities of metal ions by optical rotation measurements. To further demonstrate the versatility of the design concept employed in the synthesis of these bipyridyl ligands, the 2-chloropyridine acetals **3a**–**c** (R = Me, *i*-Pr and Ph) will also be used to construct additional chiral nonracemic ligands and catalysts for evaluation in asymmetric synthesis.

Experimental

4,4′-Dimethyl-6,6′,7,7′-tetrahydro-5*H*,5′*H*-2,2′-bi([1]pyridinyl)-7,7′-dione-(1*S*,2*S*)-1,2-diphenyl-1,2-ethanediolbisacetal (1c). Representative procedure for the preparation of the 2,2′-bipyridyl ligands (1a–c) from the 2-chloropyridine acetals (3a–c)

To a stirred solution of dibromobis(triphenylphosphine)nickel(II) (743 mg, 1.00 mmol) in degassed tetrahydrofuran (15 mL) were added zinc dust (<10 μm, 197 mg, 3.02 mmol) and tetraethylammonium iodide (517 mg, 2.01 mmol). The reaction mixture was stirred at room temperature for 30 min and then a solution of the 2-chloropyridine acetal **3c**[23] (760 mg, 2.01 mmol) in degassed tetrahydrofuran (12 mL) was added *via* a cannula. The resultant mixture was heated at 60 °C for 72 h and then was allowed to cool to room temperature. The reaction mixture was then poured into an aqueous solution of ammonium hydroxide (10% *w*/*w*, 300 mL) and was extracted with ether (3 × 50 mL). The combined organic extracts were washed with water (2 × 20 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo* to afford the crude product. Flash chromatography using hexanes–ether (6 : 1) as the eluant afforded the title compound **1c** (502 mg, 73%) as a white crystalline solid. Mp 214–215 °C, hexanes–ether; $[a]_D^{20}$ +250 (*c* 1.00, chloroform); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39 (6H, s, ArCH_3), 2.70–2.84 (4H, m, ArCH_2CH_2), 2.97–3.07 (4H, m, ArCH_2), 4.95 (2H, d, J = 8.5 Hz, CH), 5.79 (2H, d, J = 8.5 Hz, CH), 7.28–7.45 (16H, m, ArH), 7.65–7.78 (4H, m, ArH),

8.39 (2H, s, Ar*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 18.7, 24.3, 36.1, 86.0, 86.5, 115.7, 122.5, 127.0, 128.0, 128.4, 128.5, 136.0, 136.6, 137.8, 145.0, 156.7, 161.0; IR (KBr) ν_{max} 2366, 2341, 1594, 1498, 1436, 1422, 1326, 1195, 1159, 1141, 1099, 1023, 938, 916, 761, 700 cm^{-1}; MS (MALDI-TOF) *m/z* 686 (M + H); Anal. calcd for $C_{46}H_{40}N_2O_4$: C, 80.68; H, 5.89; N, 4.09. Found: C, 80.50; H, 5.77; N, 4.06.

4-Methyl-2-(2′-pyridyl)-6,7-dihydro-5*H*-[1]pyridin-7-one-(1*S*,2*S*)-1,2-diphenyl-1,2-ethanediol acetal (2b). Representative procedure for the preparation of the unsymmetric 2,2′-bipyridyl ligands (2a–b) from the 2-chloropyridine acetals (3a and 3c)

To a stirred solution of the 2-chloropyridine acetal **3c**[23] (261 mg, 0.690 mmol) and 2-(tri-*n*-butylstannyl)pyridine[8a] (472 mg, 0.759 mmol) in anhydrous, degassed dioxane (5 mL) at room temperature were added tris(dibenzylideneacetone)dipalladium(0) (16 mg, 17 μmol), a solution of tri-*t*-butylphosphine in tetrahydrofuran (0.10 M, 0.69 mL, 69 μmol) and anhydrous cesium fluoride (231 mg, 1.52 mmol). The resultant solution was heated at reflux for 24 h and then was allowed to cool to room temperature. The reaction mixture was filtered through a pad of silica gel using ethyl acetate as the eluant and the filtrate was then concentrated *in vacuo* to afford the crude product. Flash chromatography using hexanes–ether (4 : 1) as the eluant afforded the title compound **2b** (242 mg, 83%) as a white crystalline solid. Mp 120–121 °C, hexanes–ether; $[a]_D^{20}$ −98.4 (*c* 1.00, chloroform); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.40 (3H, s, ArCH_3), 2.68–2.82 (2H, m, ArCH$_2$CH_2), 2.96–3.03 (2H, m, ArCH_2), 4.92 (1H, d, J = 8.5 Hz, C*H*), 5.77 (1H, d, J = 8.5 Hz, C*H*), 7.29–7.37 (9H, m, Ar*H*), 7.61–7.66 (2H, m, Ar*H*), 7.80–7.86 (1H, m, Ar*H*), 8.30 (1H, s, Ar*H*), 8.52–8.56 (1H, m, Ar*H*), 8.67–8.71 (1H, m, Ar*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 18.5, 24.3, 36.1, 86.1, 86.5, 115.6, 121.4, 122.2, 123.6, 126.9, 127.9, 128.4, 128.5, 128.5, 136.5, 137.1, 137.5, 145.4, 149.0, 156.7, 161.2; IR (KBr) ν_{max} 1586, 1564, 1492, 1441, 1381, 1351, 1320, 1289, 1253, 1210, 1185, 1164, 1103, 1056, 1021, 936, 920, 796, 761, 751, 700 cm^{-1}; MS (CI) *m/z* (rel. intensity) 421 (M + H, 90), 314 (2), 225 (100); Anal. calcd for $C_{28}H_{24}N_2O_2$: C, 79.98; H, 5.75; N, 6.66. Found: C, 79.64; H, 6.02; N, 6.30.

2-Bromo-4-methyl-6,7-dihydro-5*H*-[1]pyridine (11)

A solution of the 2-hydroxypyridine **4**[4,15a] (3.00 g, 20.1 mmol) in phosphorus tribromide (4.5 mL, 47 mmol) was heated at reflux for 12 h. The reaction mixture was then allowed to cool to room temperature and was poured into an ice-cold aqueous solution of sodium hydroxide (2 M, 300 mL). The resultant mixture was extracted (gentle agitation to avoid emulsification) with ethyl acetate (3 × 200 mL). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated *in vacuo* to afford the crude product. Flash chromatography using chloroform as the eluant afforded the title compound **11** (2.20 g, 52%) as a colourless oil which crystallized upon standing. Mp 35–36 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.04–2.16 (2H, m, ArCH$_2$CH_2), 2.21 (3H, s, ArCH_3), 2.80 (2H, apparent t, J = 7.5 Hz, ArCH_2), 2.99 (2H, apparent t, J = 7.8 Hz, ArCH_2), 7.05 (1H, s, Ar*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 18.7, 25.9, 32.31, 74.9, 127.7, 135.3, 141.1, 147.4, 165.2; IR (KBr) ν_{max} 2356, 2337, 1733, 1717, 1700, 1684, 1653, 1558, 1507, 1458, 1419, 1375, 1305, 1261, 1186, 1090, 865 cm^{-1}; MS (CI) *m/z* (rel. intensity) 213 [M(^{81}Br) + H, 97], 211 [M(^{79}Br) + H, 100]; Anal. calcd for $C_9H_{10}NBr$: C, 50.97; H, 4.75; N, 6.60. Found: C, 50.66; H, 4.73; N, 6.39.

(7*R*,*S*)-7-Acetoxy-2-bromo-4-methyl-6,7-dihydro-5*H*-[1]pyridine (12)

To a stirred solution of the 2-bromopyridine **11** (2.20 g, 10.4 mmol) in glacial acetic acid (20 mL) was added an aqueous solution of hydrogen peroxide (30% *w/w*, 5.0 mL, 49 mmol). The resultant solution was heated at 80 °C for 20 h and then was allowed to cool to room temperature. The reaction mixture was concentrated *in vacuo* and the residue was taken up in water (100 mL). The resultant slightly acidic mixture was neutralized by the careful addition of solid potassium carbonate which was then extracted with chloroform (3 × 50 mL). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated *in vacuo* to afford the pyridine *N*-oxide (2.35 g, 99%) as a white crystalline solid. This material was taken up in acetic anhydride (20 mL) and the reaction mixture was heated slowly to 100 °C over 2 h. The resultant mixture was heated at 100 °C for 2 h and then allowed to cool to room temperature. The reaction mixture was then concentrated *in vacuo* and purified by flash chromatography using hexanes–ether (1 : 1) as the eluant to afford the title compound **12** (1.50 g, 54% over two steps) as a light orange oil which crystallized upon standing. Mp 68–69 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.00–2.11 (4H, m, ArCH$_2$C*H*H and CH_3CO), 2.26 (3H, s, ArCH_3), 2.68–2.69 (1H, m, ArCH$_2$CH*H*), 2.69–2.80 (1H, m, ArC*H*H), 2.87–2.98 (1H, m, ArCH*H*), 5.98–6.02 (1H, m, C*H*OAc), 7.22 (1H, s, Ar*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 18.7, 21.5, 26.3, 30.6, 122.9, 136.9, 141.5, 147.2, 160.8, 170.8; IR (KBr) ν_{max} 2363, 2337, 1734, 1653, 1635, 1559, 1541, 1507, 1370, 1337, 1235, 1094, 1036, 856 cm^{-1}; MS (CI) *m/z* (rel. intensity) 272 [M(^{81}Br) + H, 97], 270 [M(^{79}Br) + H, 100], 212 (30), 101 (35); Anal. calcd for $C_{11}H_{12}NO_2Br$: C, 48.91; H, 4.48; N, 5.19. Found: C, 48.63; H, 4.43; N, 5.32.

(7*R*,*S*)-2-Bromo-4-methyl-6,7-dihydro-5*H*-[1]pyridin-7-ol (13)

A stirred solution of the acetate **12** (1.50 g, 5.55 mmol) and lithium hydroxide monohydrate (932 mg, 22.2 mmol) in tetrahydrofuran (15 mL) and water (5 mL) was stirred at room temperature for 5 h. The reaction mixture was then diluted with water (25 mL) and extracted with chloroform (3 × 25 mL). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated *in vacuo* to afford the crude product. Flash chromatography using hexanes–ether (1 : 1) as the eluant afforded the title compound **13** (1.20 g, 95%) as a white crystalline solid. Mp 110–111 °C, hexanes–ether; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.99–2.12 (1H, m, ArCH$_2$C*H*H), 2.26 (3H, s, ArCH_3), 2.48–2.59 (1H, m, ArCH$_2$CH*H*), 2.63–2.75 (1H, m, ArC*H*H), 2.87–2.97 (1H, m, ArCH*H*), 5.18 (1H, apparent t, J = 7.2 Hz, C*H*OH), 7.19 (1H, s, Ar*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 18.6, 25.8, 32.2, 74.8, 127.6, 135.2, 141.0, 147.3, 165.1; IR (KBr) ν_{max} 3258, 2361, 1733, 1717, 1700, 1684, 1653, 1636, 1559, 1541, 1507, 1187, 1090, 863 cm^{-1}; MS (CI) *m/z* (rel. intensity) 230 [M(^{81}Br) + H, 22], 228 [M(^{79}Br) + H, 22], 201 (100), 173 (25), 118 (18), 91 (53), 77 (36), 65 (36), 51 (33), 39 (42); Anal. calcd for $C_9H_{10}NOBr$: C, 47.39; H, 4.42; N, 6.14. Found: C, 47.61; H, 4.45; N, 5.98.

2-Bromo-4-methyl-6,7-dihydro-5*H*-[1]pyridin-7-one (14)

To a stirred solution of oxalylchloride (415 μL, 4.76 mmol) in dichloromethane (40 mL) at −78 °C was added dimethylsulfoxide (1.10 mL, 14.2 mmol) dropwise over *ca.* 5 min. The resultant solution was stirred for 10 min and then a solution of the alcohol **13** (900 mg, 3.95 mmol) in anhydrous dichloromethane (15 mL) was added *via* a cannula. After an additional 10 min, triethylamine (2.80 mL, 20.1 mmol) was added and the reaction mixture was then allowed to warm to room temperature. The resultant mixture was diluted with dichloromethane (50 mL) and was washed with brine (20 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo* to afford the crude product. Flash chromatography using dichloromethane as the eluant afforded the 2-bromoketone **14** (804 mg, 90%) as a white crystalline solid. Mp 188–189 °C, dichloromethane; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39 (3H, s, ArCH_3), 2.74–2.80 (2H, m, ArCH$_2$CH_2), 2.97–3.02 (2H, m, ArCH_2), 7.46 (1H, s, ArH)]; ^{13}C NMR (101 MHz, $CDCl_3$) δ 17.5, 21.9, 34.7, 132.0, 143.9, 148.9, 149.0, 154.2, 203.5; IR (KBr) ν_{max} 2360, 1719, 1684, 1653, 1559, 1540, 1521, 1094 cm^{-1}; MS (CI) *m*/*z* (rel. intensity) 228 [M(^{81}Br) + H, 100], 226 [M(^{79}Br) + H, 100]; Anal. calcd for C_9H_8NOBr: C, 47.82; H, 3.57; N, 6.20. Found: C, 47.71; H, 3.48; N, 6.22.

2-Bromo-4-methyl-6,7-dihydro-5*H*-[1]pyridin-7-one-(2*R*,3*R*)-2,3-butanediol acetal (15)

A solution of the 2-bromoketone **14** (650 mg, 2.87 mmol), (2*R*,3*R*)-2,3-butanediol **9a** (0.33 mL, 3.6 mmol) and *p*-toluenesulfonic acid monohydrate (82 mg, 0.43 mmol) in anhydrous benzene (15 mL) was heated at reflux in a Dean–Stark trap for 20 h. The reaction mixture was then allowed to cool to room temperature and potassium carbonate (200 mg) was added. After 10 min, the reaction mixture was filtered and concentrated *in vacuo* to afford the crude product. Flash chromatography using hexanes–ethyl acetate (2 : 1) as the eluant afforded the title compound **15** (760 mg, 89%) as a white crystalline solid. Mp 128–129 °C, hexanes–ethyl acetate; $[\alpha]_D^{20}$ − 25.8 (*c* 1.07, chloroform); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (3H, d, J = 6.1 Hz, CHCH_3), 1.41 (3H, d, J = 6.1 Hz, CHCH_3), 2.22 (3H, s, ArCH_3), 2.35–2.40 (2H, m, ArCH$_2$CH_2), 2.72–2.78 (2H, m, ArCH_2), 3.72–3.90 (1H, m, CHCH$_3$), 4.35–4.43 (1H, m, CHCH$_3$), 7.19 (1H, s, ArH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.6, 17.1, 18.1, 23.9, 35.9, 79.2, 79.7, 113.6, 128.4, 135.0, 141.8, 147.1, 162.4; IR (KBr) ν_{max} 2985, 2933, 2361, 2331, 1588, 1441, 1376, 1314, 1263, 1204, 1107, 1077, 931, 865 cm^{-1}; MS (CI) *m*/*z* (rel. intensity) 300 [M(^{81}Br) + H, 97], 298 [M(^{79}Br) + H, 100], 226 (21), 115 (53); Anal. calcd for $C_{13}H_{16}NO_2Br$: C, 52.36; H, 5.41; N, 4.70. Found: C, 52.25; H, 5.47; N, 4.61.

Preparation of 4,4′-dimethyl-6,6′,7,7′-tetrahydro-5*H*,5′*H*-2,2′-bi([1]pyridinyl)-7,7′-dione-(2*R*,3*R*)-butanediolbisacetal (1a) from the 2-bromopyridine acetal (15)

To a stirred solution of dibromobis(triphenylphosphine)nickel(II) (224 mg, 0.302 mmol) in degassed tetrahydrofuran (15 mL) were added zinc dust (<10 μm, 197 mg, 3.02 mmol) and tetraethylammonium iodide (517 mg, 2.01 mmol). The resultant mixture was stirred at room temperature for 30 min and then a solution of the 2-bromopyridine acetal **15** (600 mg, 2.01 mmol) in degassed tetrahydrofuran (6 mL) was added *via* a cannula. The reaction mixture was then heated at 60 °C for 72 h. The resultant mixture was allowed to cool to room temperature and was then poured into an aqueous solution of ammonium hydroxide (10% *w*/*w*, 150 mL). The resultant mixture was extracted with a mixture of ether and benzene (1 : 1, 3 × 100 mL). The combined organic extracts were washed with water (2 × 20 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo* to afford the crude product. Flash chromatography using chloroform as the eluant afforded the title compound **1a** (364 mg, 83%) as a white crystalline solid. The spectroscopic data for this compound were in agreement with that recorded for the material prepared from the 2-chloropyridine acetal **3a** (refer to the electronic supplementary information).

General procedure for the copper(I)-catalyzed enantioselective cyclopropanation reactions of styrene with the ethyl and *t*-butyl esters of diazoacetic acid (16a–b)

To a stirred solution of copper(II) triflate (9.0 mg, 25 μmol) in dichloromethane (4 mL) was added the 2,2′-bipyridyl ligand **1a**–**c** or the unsymmetrical 2,2′-bipyridyl ligand **2a**–**b** (26 μmol *or* 52 μmol) and the resultant solution was stirred at room temperature for 30 min. Phenylhydrazine (3.0 μL, 30 μmol) and styrene (0.50 mL, 4.4 mmol) were then added. A solution of the ethyl or *t*-butyl ester of diazoacetic acid **16a**–**b** (2.00 mmol) in dichloromethane (3 mL) was then added over *ca.* 3 h *via* syringe pump. After the addition was complete, the reaction mixture was stirred for an additional 12 h and then was concentrated *in vacuo* to afford the crude product. The ratios of the *trans*- and *cis*-isomers of the cyclopropane reaction products **17a**–**b** were then determined by ^{1}H NMR spectroscopy. Flash chromatography using petroleum ether–ethyl acetate (96 : 4) as the eluant afforded the pure *trans*-cyclopropanes **17a**–**b** and the corresponding *cis*-cyclopropanes. The enantiomeric purities of the major *trans*-isomers of the cyclopropane reaction products were determined following reduction with lithium aluminum hydride.

***trans*-2-Phenyl-cyclopropane-1-carboxylic acid ethyl ester (17a).** ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25–1.34 (4H, m, CH_3 and CHH), 1.56–1.63 (1H, m, CHH), 1.87–1.93 (1H, m, CHCO$_2$Et), 2.52 (1H, ddd, J = 10.2, 6.4, 4.1 Hz, CHPh), 4.17 (2H, q, J = 7.2 Hz, CH_2CH$_3$), 7.07–7.14 (2H, m, ArH), 7.17–7.23 (1H, m, ArH), 7.24–7.32 (2H, m, ArH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.4, 17.2, 24.3, 26.3, 60.8, 126.3, 126.6, 128.6, 140.3, 173.5; IR (neat) ν_{max} 2988, 1721, 1603, 1496, 1411, 1189, 1040, 1019, 847, 761, 722, 701 cm^{-1}; MS (CI) *m*/*z* (rel. intensity) 191 (M + H, 100). Analytical chiral HPLC analysis of the corresponding primary alcohol using a Daicel Chiralcel OD column [hexanes–isopropanol (90 : 10), flow rate at 0.5 mL min^{-1}, detection at λ = 220 nm, t_1 = 15.4 min, t_2 = 25.2 min].

***trans*-2-Phenyl-cyclopropane-1-carboxylic acid *t*-butyl ester (17b).** ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (1H, m, CHH), 1.47 (9H, s, *t*-Bu), 1.50–1.56 (1H, m, CHH), 1.84 (1H, m, CHCO$_2$*t*-Bu), 2.44 (1H, m, CHPh), 7.06–7.12 (2H, m, ArH), 7.16–7.22 (1H, m, ArH), 7.24–7.31 (2H, m, ArH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 17.4, 25.6, 26.1, 28.5, 80.9, 126.4, 126.7, 128.7, 140.9, 172.9; IR (neat) ν_{max} 2977, 1715, 1606, 1498, 1403, 1367, 1343, 1222, 1152, 936, 844, 783, 761, 744 cm^{-1}; MS (CI) *m*/*z* (rel. intensity) 219 (M + H, 18), 163 (100). Analytical chiral HPLC analysis of

the corresponding primary alcohol using a Daicel Chiralcel OD column [hexanes–isopropanol (90 : 10), flow rate at 0.5 mL min^{-1}, detection at $\lambda = 220$ nm, $t_1 = 15.4$ min, $t_2 = 25.2$ min].

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20 Empirical formula, $C_{93}H_{82}Cl_4Cu_2N_4O_8$; FW (g mol^{-1}), 1648.35; temperature (K), 293; wavelength (Cu Kα, Å), 1.54180; crystal system, orthorhombic; space group, $P2_12_12$; a (Å), 14.7325(4); b (Å), 15.2366(2); c (Å), 19.0213(3); α (deg), 90; β (deg), 90; γ (deg), 90; Z, 2; U ($Å^3$), 4269.77(15); D_{calc} (g cm^{-3}), 1.285; 2θ limits (deg), 4.65–144.25; reflections collected, 28285; independent reflections, 6828; reflections observed [$I = 2.5\sigma(I)$], 4566; goodness-of-fit on F, 0.601; R_1 and R_w [$I = 2.5\sigma(I)$], 0.0532 and 0.750.
21 Of note, when a 2 : 1 ratio of ligands **1a**–**b** and copper(II) triflate were employed in the cyclopropanation reactions the isolated yields of products were lower. This indicated that less of the two catalytically active species [copper(I) triflate and the mono-ligated copper(I) complexes] were present in these instances and that more of the catalytically inactive bis-ligated copper(I) complexes were formed.
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