Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 4341–4357

TETRAHEDRON: *ASYMMETRY*

Enantioselective catalytic cyclopropanation of styrenes by copper complexes with chiral pinene-[5,6]-bipyridine ligands

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Received 14 September 2000; accepted 6 October 2000

Abstract

Substituted mono- and bis-pinene-[5,6]-bipyridines are useful ligands in asymmetric copper-catalyzed cyclopropanation by styrenes. Copper complexes were prepared either in situ or prior to the reaction. The catalytic reaction of styrene with ethyl diazoacetate and **Cu–11b** yields ethyl *trans*-phenylcyclopropane carboxylate in >99% yield and 87% *e.e.* at 0°C. The corresponding *cis*-configured cyclopropane was produced with an *e.e.* of 90%. The *cis*/*trans* ratio is 22:78. Other ligands of this series are less effective. Various olefins were tested as substrates but *exo*-methylene olefins show the best results.

1. Introduction

In contrast to the earlier introduced catalytic systems containing phosphorus or oxygen donor ligands, such as hydrogenation catalysts, nitrogen donor ligands have been studied in detail only more recently.[1] They have a wide potential in enantioselective catalysis, especially in zinc-mediated alkylations, where N,O-donor ligands are favored, due to the relative hardness of the Zn^{2+} ion.[2–4]

The first example of an enantioselective catalytic cyclopropanation dates back to Nozaki in 1966, but shows only poor *e.e.*[5] The potential of N,N-donor ligands was evaluated by the groups of Evans and Pfaltz. Both published remarkable *e.e.* values in cyclopropanation reactions with copper complexes of bis-oxazolines **1**–**3**[6] (Scheme 1) or copper semicorrin complexes **4** and **5**[7] (Scheme 1). Similar work was done by the groups of Masamune[8] with bis-oxazolines **6** (Scheme 1) and Katsuki,[9,10] who used chiral bipyridine derivatives (molecules **7** and **8**) (Scheme 1). Synthesis of **7** and **8** requires preparative HPLC separation of a racemic mixture of an intermediate. Recently Kwong and Lee[11] reported successful enantioselective cyclopropana-

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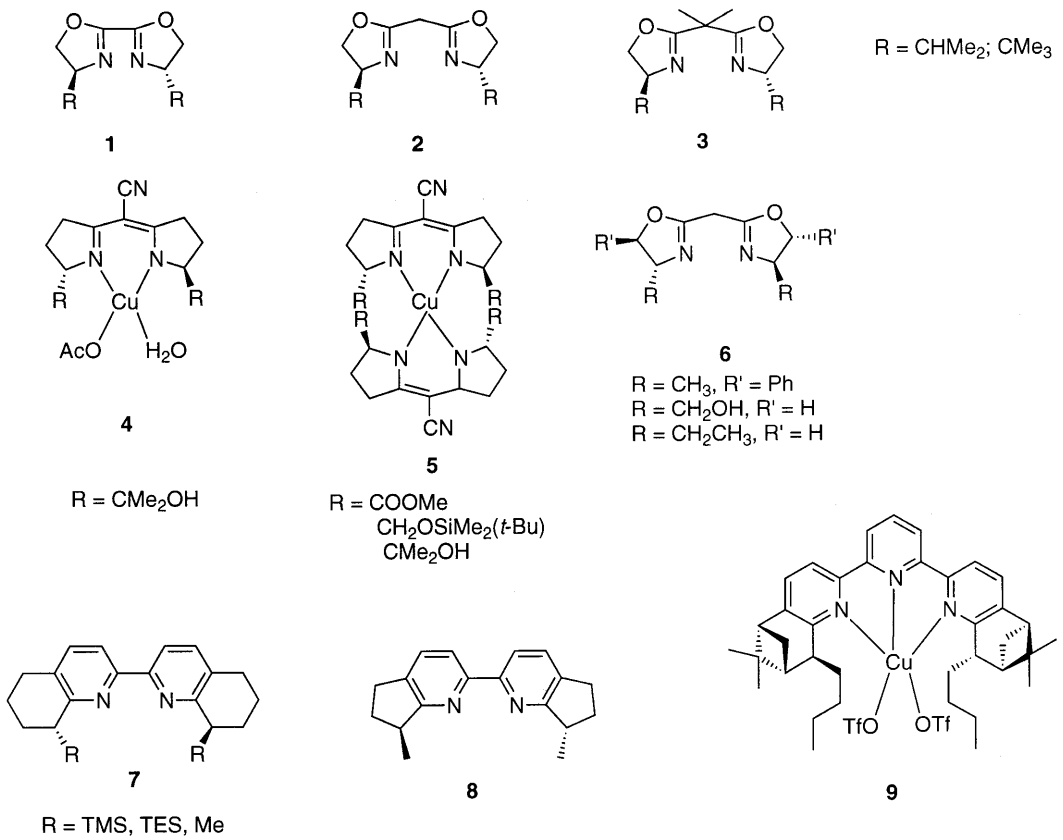
0957-4166/00/$ - see front matter
PII: S0957-4166(00)00401-8



Scheme 1. Ligands and complexes used for asymmetric cyclopropanations by other research groups

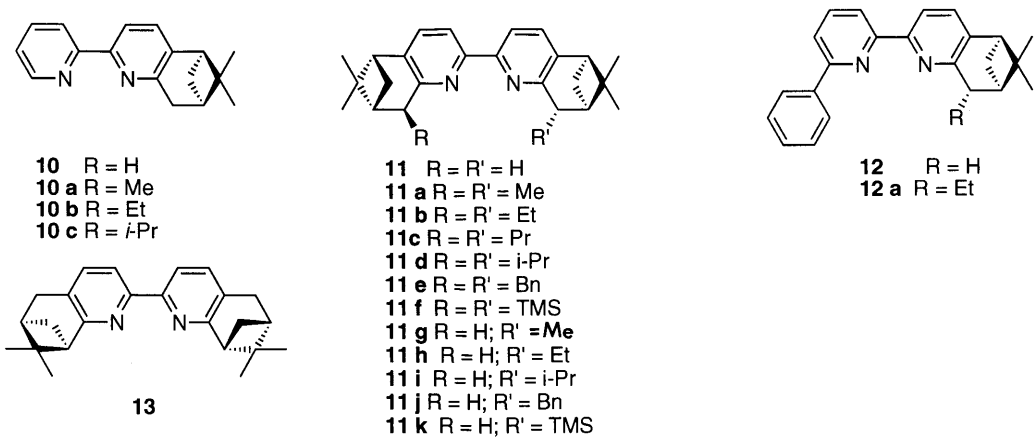
tions with chiral C_2-symmetric terpyridine ligands first synthesized in our laboratories.[12] In Kwong's work, the pinene moiety of the terpyridine was substituted with several alkyl groups. The best result for cyclopropanation of styrene with ethyl diazoacetate was shown by copper complex **9** (94% *e.e.*) (Scheme 1).

We present herein our results from copper-mediated enantioselective cyclopropanations with (−)-pinene-[5,6]-bipyridine ligands of the type **10**, **11**, **12** and **13** and their copper complexes (Scheme 2).

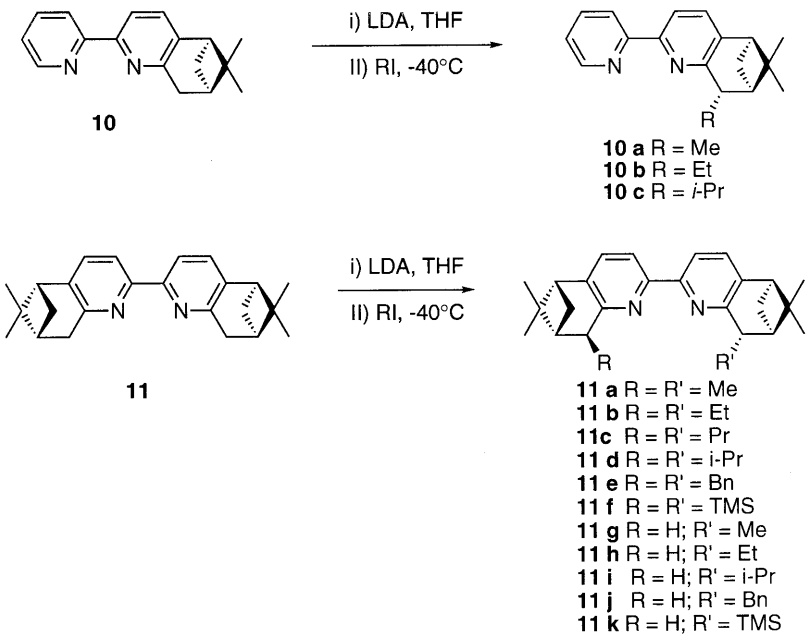
2. Results and discussion

2.1. Ligand syntheses

The synthesis of the ligand **10** (R = H) has been published earlier;[13] the synthesis of the alkylated species **10a–c** was achieved by lithiation of **10** and quenching with the proper alkyl iodide[14] (Scheme 3). Synthesis of the C_2-symmetric bipyridine **11** (R = R′ = H) was first carried out in our laboratories.[15] Alkylation of this ligand was done in a similar way using LDA and up to 3 equiv. of the appropriate alkyl iodide to yield either C_1- or C_2-symmetric bipyridines **11a–k** depending on the number of equivalents of LDA (Scheme 3). The synthesis of the



Scheme 2.

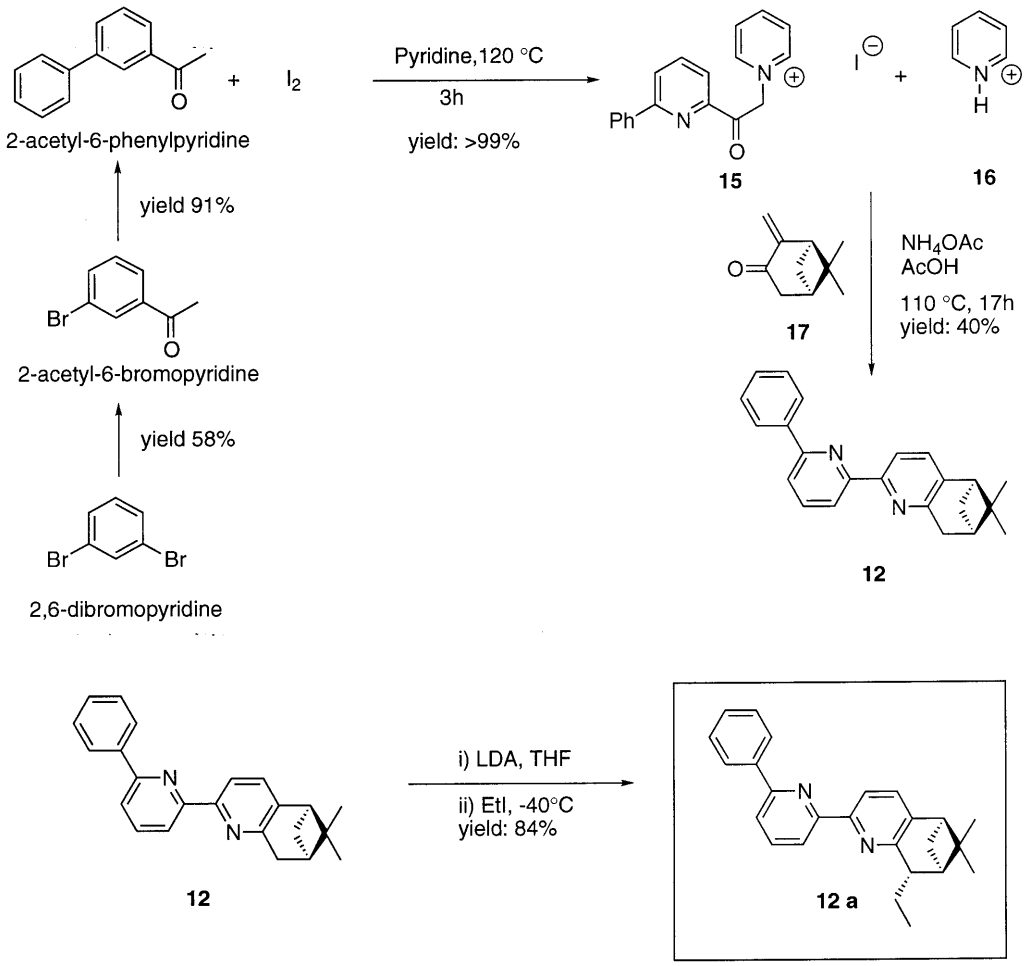


Scheme 3. Alkylation of bipyridines **10** and **11**

C_1-symmetric bipyridine **12** was carried out in the way shown in Scheme 4, starting from 2-acetyl-6-phenylpyridine **14**. Formation of the Kröhnke salt **15** using pyridine and iodine was almost quantitative, however the formation of pyridinium iodide **16** could not be inhibited. Annellation of the Kröhnke salt **15** with (+)-pinocarvone **17**[16] yielded the desired bipyridine **12** in 40% yield. Ligand **12a** was then synthesized in 84% yield by lithiation of **12** using LDA and ethyliodide as the alkylating agent.

Ligand **13** was prepared according to a published procedure of our laboratories, starting from (−)-β-pinene.[17]

There are two different possibilities for carrying out catalytic cyclopropanations. The first method is a one-pot synthesis using either copper(I) trifluoromethanesulfonate $CuOTf{\cdot}0.5C_6H_6$



Scheme 4. Synthesis of bipyridines **12** and **12a**

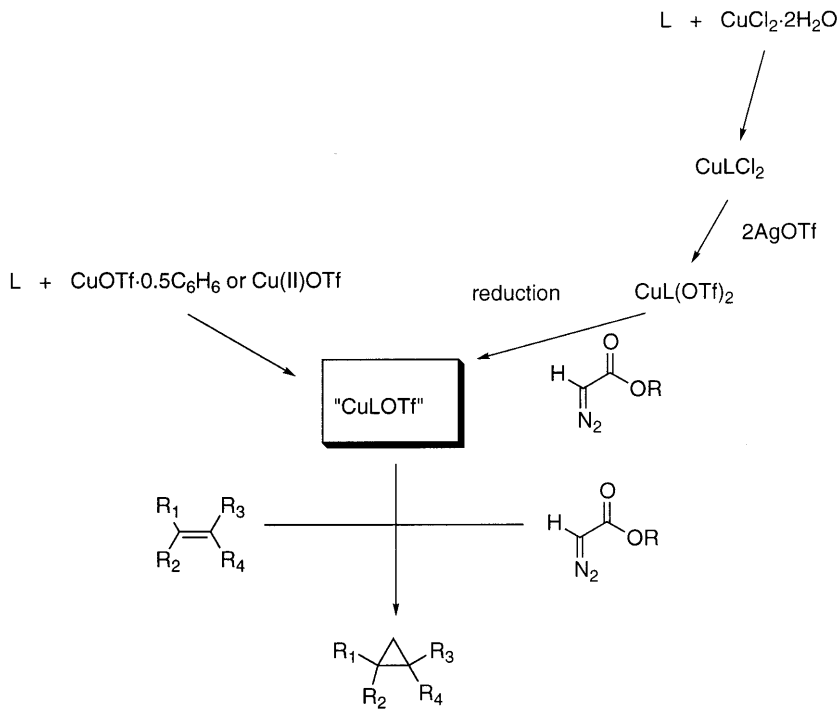
or Cu(II)OTf as the copper source. The active species is formed in situ by reduction. This method is reported in most of the publications wherein cyclopropanation reactions are studied. The second method is described by Kwong et al.[18] In this method, the copper(II)–dichloro complex is synthesized prior to the catalytic cyclopropanation reaction. This complex is then transferred into the ditriflate and reduced in situ by the cyclopropanation agent (Scheme 5).

2.2. Complex syntheses

Copper(II) complexes were synthesized using $CuCl_2 \cdot 2H_2O$ and the corresponding ligands.

$$CuCl_2 \cdot 2H_2O + L \xrightarrow[\text{rt, reflux}]{CH_2Cl_2/EtOH} CuLCl_2 + 2H_2O$$

The chiral bipyridine ligands **11**, **11a**–**c**, and **13** used for this purpose form complexes, soluble in dichloromethane, which were isolated as brown to red solids in good yields. The results of these complex syntheses are shown in Table 1.



Scheme 5. Two different ways to carry out catalytic cyclopropanations

Crystals suitable for X-ray diffraction could be obtained for complexes **Cu–11**, **Cu–11a**, and **Cu–13** from dichloromethane/diethyl ether solution. The molecular structure and crystallographic numbering scheme is illustrated in the PLATON[20] drawings. (Figs. 1–3).

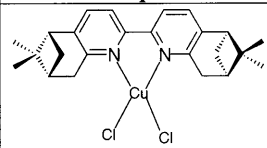
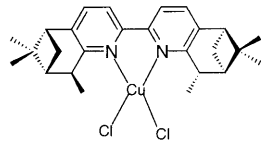
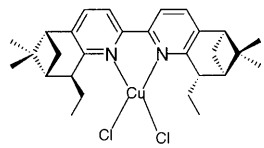
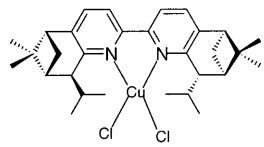
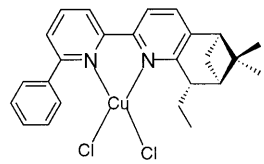
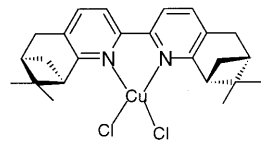
The copper center is coordinated in a distorted tetrahedral environment. Table 2 summarizes the structural parameters and Table 3 shows selected bond angles and torsion angles for the complexes. In the solid state, all of these complexes are C_1-symmetric. A remarkable property of complex **Cu–13** is seen in Fig. 2. The two chloride ligands attached to the copper(II) ion are pointing towards the bulky methyl groups of the pinene moiety (carbons C12/C13 and C32/C33), while in complex **Cu–11**, this is not the case. Here, the chlorides of the copper ion are going in the opposite direction to the bulky methyl groups.

2.3. Enantioselective cyclopropanations

The chloride complexes mentioned above are not active catalysts in cyclopropanation. However, the corresponding triflate complexes, formed by treating the chloride complexes with silver triflate and reduction in situ with ethyl diazoacetate, were active. The potential of these ligands and copper complexes was tested with styrene as substrate using both methods for the catalytic reaction (Scheme 6). The reaction of ethyl diazoacetate leads to the formation of all four possible cyclopropanes **18**. The results are shown in Tables 4 and 5.

The results of the catalytic cyclopropanations with copper complexes of ligands **10a–c** show increasing *e.e.* values with increasing steric demand of the alkyl group. With R = *iso*-propyl an *e.e.* of 58% for the *trans*-cyclopropane was achieved. The best results with up to 84% *e.e.* for the C_2-symmetrical ligands **11a–f** were obtained with small substituents such as methyl **11a** and ethyl

Table 1
Synthesis of Cu(II) complexes

Ligand	yield [%]	complex
11	93	 **Cu-11a**
11a	92	 **Cu-11b**
11b	64	 **Cu-11c**
11d	65	 **Cu-11d**
12a	72	 **Cu-12a**
13	78	 **Cu-13**

11b. However, more bulky substituents reduce the *e.e.* significantly or show no *e.e.* at all (**11d**), but still give up to 80% yield. Either there is no complexation of copper(II) triflate by the ligands **11c** and **11d** or the two pyridine rings complex the copper cation differently, e.g. in an intermolecular way. This differs from the results published by Katsuki,[9] who shows that ligand systems **7** and **8** (Scheme 1) produce the best results with rather bulky triethylsilyl groups. In our case, the trimethylsilyl substituted ligand **11f** shows already reduced *e.e.* values compared to ligand **11b**. The diastereoselectivity ranges from 45:55 to 27:73. The best result was also achieved with ligand **11b**.

The mono-alkylated bis-pinene-[5,6]-bipyridines **11g–k** show similar results. The most efficient ligand is the mono-ethylated ligand **11h** with an *e.e.* of 71% for *trans*-cyclopropane. The other

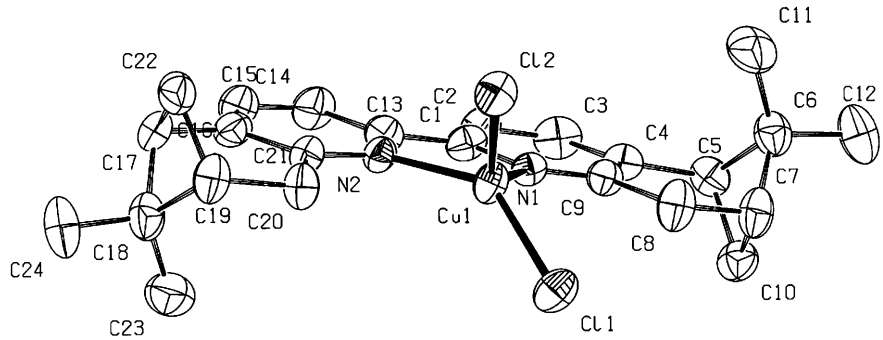


Figure 1. ORTEP plot of **Cu–11**

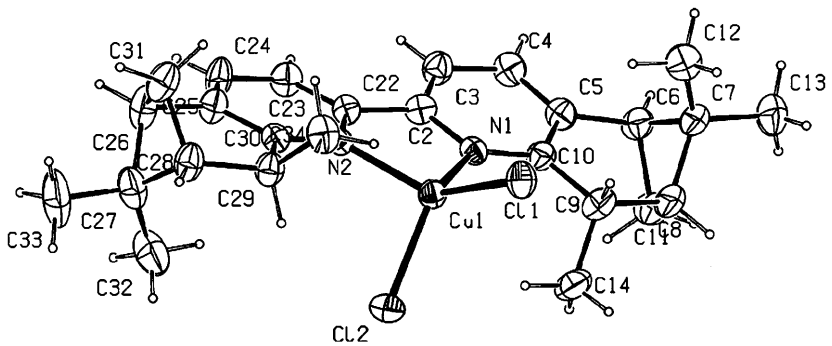


Figure 2. ORTEP plot of **Cu–11a**

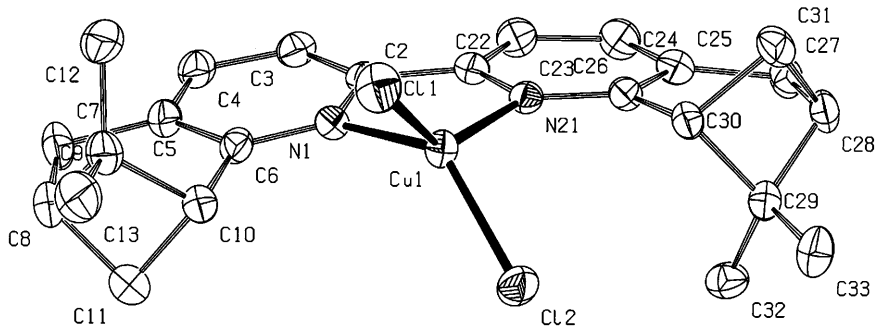


Figure 3. ORTEP plot of **Cu–13**

derivatives show lower *e.e.* values between 40 and 60%. It seems that the lower spatial requirements of the mono-alkylated ligands compared to the bis-alkylated ligands allow the formation of the copper complex. However, the substrates can bind more flexibly to the catalytic center, thus lowering the enantioselectivity and diastereoselectivity (Table 6). The unsubstituted ligands **10** and **13** induce almost no *e.e.* in the catalytic reaction. This shows clearly that the formation of a stereogenic center on C(7) and/or C(7′) is crucial for the induction of chirality to the cyclopropanes. The reactions of ligand **11b** with different olefins are shown in Table 7. The ligand system works best on cyclopropanation of *exo*-methylene double bonds. *Cis*-substituted

Table 2
Crystallographic data for complexes **Cu–11**, **Cu–11a**, and **Cu–13**

	Cu–11a	**Cu–11b**	**Cu–13**
Empirical formula	$C_{24}H_{28}Cl_2CuN_2 \cdot CH_2Cl_2$	$C_{26}H_{32}Cl_2CuN_2 \cdot 0.4(CH_2Cl_2)$	$C_{24}H_{28}Cl_2CuN_2 \cdot CH_2Cl_2$
Formula weight (g mol^{-1})	563.85	540.95	563.85
Crystal color, habit	Red, block	Purple, plate	Red, block
Crystal size (mm)	$0.34 \times 0.34 \times 0.19$	$0.50 \times 0.30 \times 0.15$	$0.40 \times 0.25 \times 0.20$
Crystal system	Monoclinic	Orthorhombic	Orthorhombic
Space group	$P2_1$	$P2_12_12_1$	$P2_12_12_1$
a (Å)	8.6296(5)	12.2293(7)	10.3549(7)
b (Å)	15.4946(12)	14.048(7)	13.6271(9)
c (Å)	10.4406(7)	16.5056(13)	17.9559(14)
α (°)	90	90	90
β (°)	109.470(10)	90	90
γ (°)	90	90	90
V (Å^3)	1316.20(15)	2835.5(14)	2533.7(3)
Z	2	4	4
D_{calc} (g cm^{-3})	1.423	1.267	1.478
Absorption coefficient (mm^{-1})	1.252	1.050	1.300
F (000)	582	1127	1164
θ min. and max. (°)	2.07–25.49	2.07–25.91	2.27–26.03
Reflections collected/unique	5102/2551	13867/5284	19903/4924
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Final R indices [$I>2\sigma(I)$]	$R_1=0.0468$, $wR_2=0.0931$	$R_1=0.0576$, $wR_2=0.1679$	$R_1=0.0357$, $wR_2=0.0856$
R indices all data	$R_1=0.0696$, $wR_2=0.1037$	$R_1=0.0662$, $wR_2=0.1767$	$R_1=0.0450$, $wR_2=0.0889$
Absolute structure parameter	0.00(3)	0.01(2)	0.000(14)
Largest difference peak and hole (e Å^{-3})	0.345 and −0.424	1.823 and −0.471	1.176 and −0.709

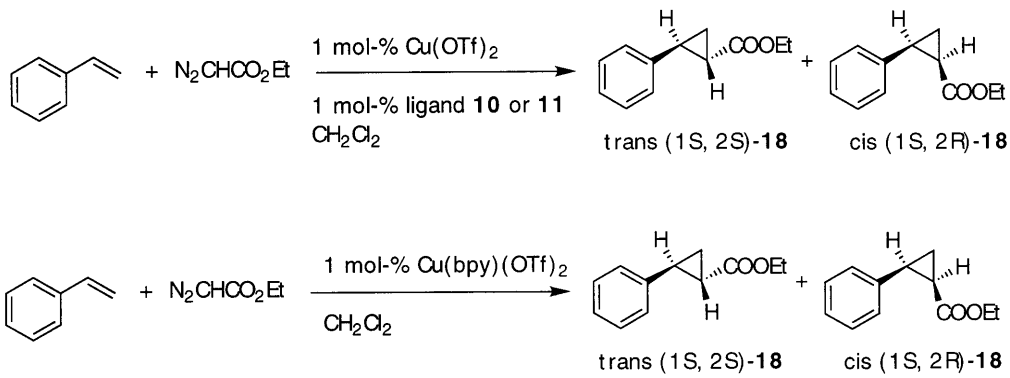
alkenes show moderate *e.e.* values, while in *trans*-configured alkenes the enantioselectivity is further reduced.

If we compare the catalytic reactions of the one-pot synthesis (method 1) with method 2 where the pre-catalysts are formed prior to the reaction, one can see, that method 2 gave slightly better results in enantioselectivity and in diastereoselectivity. This could be explained by the fact, that the copper–nitrogen bonds—necessary for the formation of the active species—are already formed. Decrease of the reaction temperature to 0°C has only a slight influence on enantio- and diastereoselectivity for cyclopropanation.

Based on the absolute configuration of the products obtained, the sense of asymmetric induction observed here can be explained by the model shown in Scheme 7 and first proposed by Pfaltz et al.[7] In the proposed mechanism, the metal carbenoid attacks the olefinic double bond according to the pathways **a** and **b**. In the case of pathway **a**, repulsive steric interaction is built up between the ester group and the adjacent bulky alkyl group at C(7) of the ligand. In the case of pathway **b**, no such steric interaction, leading to the *cis*-(1*R*)- or to the *trans*-(1*R*)-cyclopropyl esters, is consistent with the experimental results. Therefore, pathway **a** is more

Table 3
Selected bond lengths (Å), angles (°), and torsion angles (°) for **Cu–11**, **Cu–11a**, and **Cu–13**

Cu–11a		**Cu–11b**		**Cu–13**	
Cu(1)–N(2)	2.002(5)	Cu(1)–N(1)	2.002(3)	Cu(1)–N(2)	2.006(4)
Cu(1)–N(1)	2.036(5)	Cu(1)–N(21)	2.023(3)	Cu(1)–N(1	2.036(4)
Cu(1)–Cl(1)	2.197(2)	Cu(1)–Cl(1)	2.2220(10)	Cu(1)–Cl(1)	2.2110(15)
Cu(1)–Cl(2)	2.245(2)	Cu(1)–Cl(2)	2.2271(9)	Cu(1)–Cl(2)	2.2492(15)
N(2)–Cu(1)–N(1)	82.7(2)	N(1)–Cu(1)–N(21)	82.35(12)	N(2)–Cu(1)–N(1)	84.09(17)
N(2)–Cu(1)–Cl(1)	139.03(18)	N(1)–Cu(1)–Cl(1)	101.76(9)	N(2)–Cu(1)–Cl(1)	137.74(12)
N(1)–Cu(1)–Cl(1)	107.70(15)	N(21)–Cu(1)–Cl(1)	136.40(9)	N(1)–Cu(1)–Cl(1)	104.98(13)
N(2)–Cu(1)–Cl(2)	100.81(17)	N(1)–Cu(1)–Cl(2)	133.03(8)	N(2)–Cu(1)–Cl(2)	100.00(14)
N(1)–Cu(1)–Cl(2)	130.44(17)	N(21)–Cu(1)–Cl(2)	104.12(8)	N(1)–Cu(1)–Cl(2)	128.90(13)
Cl(1)–Cu(1)–Cl(2)	101.22(8)	Cl(1)–Cu(1)–Cl(2)	103.82(4)	Cl(1)–Cu(1)–Cl(2)	104.94(6)
N(2)–Cu(1)–N(1)–C(9)	−179.7(6)	N(21)–Cu(1)–N(1)–C(6)	174.0(3)	N(2)–Cu(1)–N(1)–C(10)	178.0(5)
Cl(1)–Cu(1)–N(1)–C(9)	−40.4(6)	Cl(1)–Cu(1)–N(1)–C(6)	−50.1(3)	Cl(1)–Cu(1)–N(1)–C(10)	40.0(5)
Cl(2)–Cu(1)–N(1)–C(9)	82.3(6)	Cl(2)–Cu(1)–N(1)–C(6)	71.8(3)	Cl(2)–Cu(1)–N(1)–C(10)	−83.9(5)
N(2)–Cu(1)–N(1)–C(1)	4.5(5)	N(21)–Cu(1)–N(1)–C(2)	−5.6(2)	N(2)–Cu(1)–N(1)–C(2)	0.7(3)
Cl(1)–Cu(1)–N(1)–C(1)	143.8(4)	Cl(1)–Cu(1)–N(1)–C(2)	130.3(2)	Cl(1)–Cu(1)–N(1)–C(2)	−137.3(3)
Cl(2)–Cu(1)–N(1)–C(1)	−93.5(5)	Cl(2)–Cu(1)–N(1)–C(2)	−107.8(2)	Cl(2)–Cu(1)–N(1)–C(2)	98.7(3)
N(1)–Cu(1)–N(2)–C(21)	174.2(6)	Cu(1)–N(1)–C(2)–C(3)	−176.3(3)	N(1)–Cu(1)–N(2)–C(30)	−177.6(4)
Cl(1)–Cu(1)–N(2)–C(21)	65.6(7)	Cu(1)–N(1)–C(6)–C(5)	176.4(3)	Cl(1)–Cu(1)–N(2)–C(30)	−71.8(5)
Cl(2)–Cu(1)–N(2)–C(21)	−55.9(6)	Cu(1)–N(1)–C(6)–C(10)	−5.7(5)	Cl(2)–Cu(1)–N(2)–C(30)	53.9(4)
N(1)–Cu(1)–N(2)–C(13)	−5.2(5)	N(1)–Cu(1)–N(21)–C(26)	−174.7(3)	N(1)–Cu(1)–N(2)–C(22)	4.7(3)
Cl(1)–Cu(1)–N(2)–C(13)	−113.9(5)	Cl(1)–Cu(1)–N(21)–C(26)	86.2(3)	Cl(1)–Cu(1)–N(2)–C(22)	110.5(3)
Cl(2)–Cu(1)–N(2)–C(13)	124.7(5)	Cl(2)–Cu(1)–N(21)–C(26)	−42.2(3)	Cl(2)–Cu(1)–N(2)–C(22)	−123.8(3)



Scheme 6. Catalytic cyclopropanation of styrene with ethyl diazoacetate

favored than pathway **b**. This explains the enantioselectivity. The diastereoselectivity could also be explained in a similar way (Scheme 8). If the mechanism follows pathway **c**, that means a cisoid position of the R_1 group on the olefin according to the ester group, the steric hindrance between these two groups is very high. Therefore the approach shown in pathway **d** will be preferred. This is again consistent with our experimental results.

Table 4
Cyclopropanation of styrene with ethyl diazoacetate and Cu(I) catalysts of (−)-mono-pinene-[5,6]-bipyridine (one-pot method)[a]

Catalyst	Yield (%)	*D.e.* (*cis*/*trans*)	*E.e* (*cis*) (%)	*E.e.* (*trans*) (%)
10a R = Methyl	73	36:64	20	31
10b R = Ethyl	83	37:63	45	55
10c R = *i*-Propyl	39	37:63	51	58

[a] Reaction conditions: 1 mol% catalyst; 3 equiv. styrene; methylene chloride at rt for 7 h. All *d.e.* and *e.e.* values were determined via chiral GC. Ligands **10a–c** all 92% (*e.e.*).

Table 5
Cyclopropanation of styrene with ethyl diazoacetate and Cu(I) catalyst of (−)-bis-pinene-[5,6]-bipyridine (one-pot method)[a]

Catalyst	Yield (%)	*D.e.* (*cis*/*trans*)	*E.e.* (*cis*) (%)	*E.e.* (*trans*) (%)
11: R = R′ = H	80	33:67	3	4
11g: R = H; R′ = Me	78	40:60	48	54
11h: R = H; R′ = Et	78	33:67	64	71
11i: R = H; R′ = *i*-Pr	91	40:60	43	42
11j: R = H; R′ = Bn	77	42:58	50	60
11k: R = H; R′ = TMS	85	36:64	42	55
11a: R = R′ = Me	93	38:62	78	79
11b: R = R′ = Et	94	27:73	83	84
11c: R = R′ = Pr	80	43:57	1[c]	16[c]
11d: R = R′ = I–Pr	78	37:63	<1	<2
11e: R = R′ = Bn	79	45:55	40	18
11g: R = R′ = TMS	71	42:58	31	41
13	74[b]	36:64	5.5	8

[a] Reaction conditions: 1 mol% catalyst; 3 equiv. styrene; methylene chloride at rt for 7 h; all *d.e.* and *e.e.* values were determined via chiral GC; *d.e.* values of ligands **11a–k**: 98% (**11b**, **11c**, **11d**, **11e**, **11h**, **11i**, **11j**); 92% (**11a**, **11g**), 84% (**11f**, **11k**).

[b] Not isolated.

[c] Other enantiomer was formed; absolute configuration: *trans*-(1*S*,2*S*)-1-phenylcyclopropane carboxylate, *cis*-(1*S*,2*R*)-phenylcyclopropane carboxylate.

3. Conclusions

The ligand systems and the complexes derived from enantiopure natural compounds, which are described in this paper are able to produce cyclopropanes with moderate to good enantioselectivities and diastereoselectivities. The ligand **11b** and especially complex **Cu–11b** shows by far the best results with respect to enantioselectivity and diastereoselectivity. Further investigations in this subject are in progress.

Table 6
Cyclopropanantion of styrene with ethyl diazoacetate and copper complexes **Cu–11**, **Cu–11a**, **Cu–11b**, **Cu–12a**, and **Cu–13**[a]

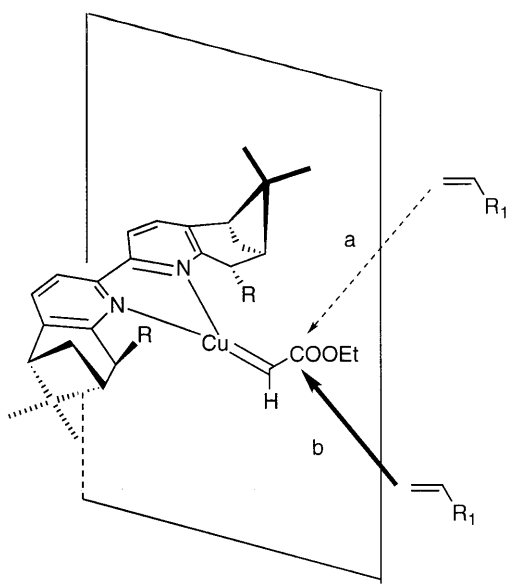
Catalyst	Yield (%)	*D.e.* (*cis*/*trans*)	*E.e.* (*cis*) (%)	*E.e.* (*trans*) (%)
Cu–11	52[b]	34:66	3	3
Cu–11a at rt	72[b]	37:63	85	81
Cu–11a at 0°C	77[b]	39:61	88	87
Cu–11b at rt	77[b]	23:77	85	84
Cu–11b at 0°C	>99[b]	22:78	90	87
Cu–12a	86[b]	37:63	9	17
Cu–13	72[b]	39:61	5.5	8

[a] Reaction conditions are according to Kwong et al.: 2 equiv. of AgOTf according to the complex (1 mol%), styrene 4 equiv. according to ethyl diazoacetate.
[b] Not isolated.

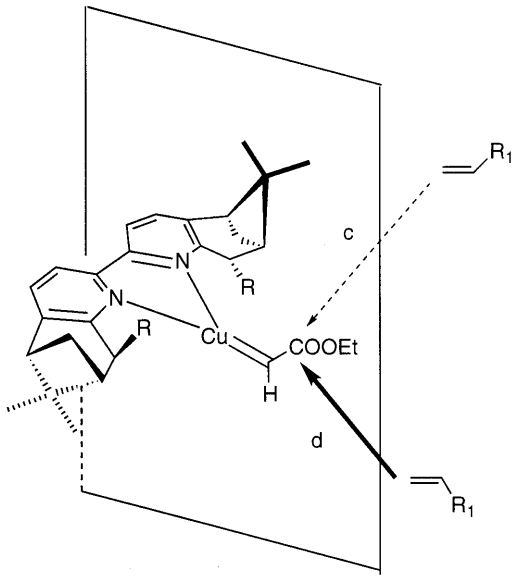
Table 7
Cyclopropanation of different olefins with ethyl diazoacetate and Cu(I) catalyst **11b** (one-pot method)

Substrate	Yield (%)	*D.e.* (*cis*/*trans*)	*E.e.* (*cis*) (%)	*E.e.* (*trans*) (%)
Styrene	94	37:63	83	84
α-Methyl styrene	64	34:66	75[a]	79[a]
β-Methyl styrene	75	45:55	46[a]	11[a]
Dihydronaphthalene	91		52[a]	

[a] Absolute configuration not determined.



Scheme 7. Explanation of the enantioselectivity



Scheme 8. Explanation of the diastereoselectivity

4. Experimental

4.1. Products

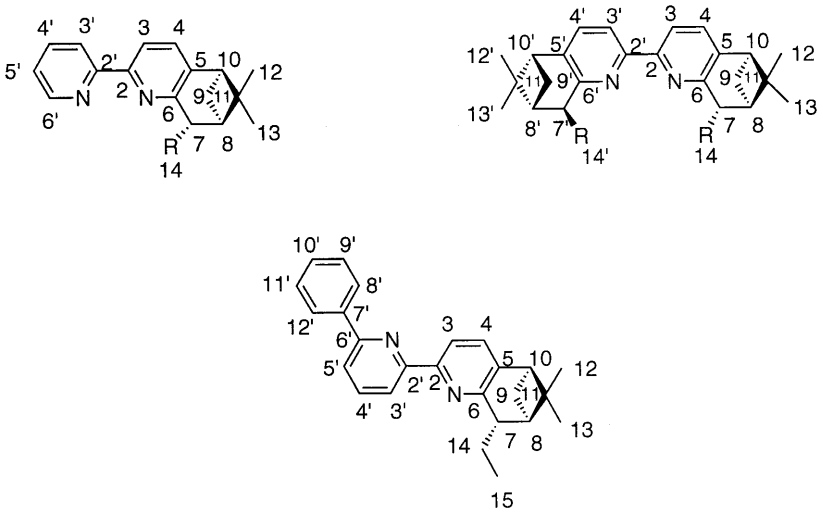
Solvents and reagents were purchased from Fluka or Aldrich. Iodine was sublimed before utilization. Pyridine was dried over KOH and freshly distilled prior to use. Ammonium acetate was dried for 5–6 h before use in a vacuum oven at 40°C. Diethyl ether was distilled from sodium/benzophenone prior to use. Dichloromethane was dried over CaH_2 and distilled prior to use.

4.2. Measurements

NMR spectra were recorded on a 'Varian Gemini 300' (300.075 MHz) or on a 'Bruker Avance DRX500' (500.13 MHz) spectrometer, chemical shifts are given in ppm using TMS or the solvent itself as internal standards, coupling constants J are given in hertz. Attribution of the ^{1}H and ^{13}C signals was performed by COSY, DEPT, and HECTOR techniques. Diastereotopic protons are labeled as H_a for the *endo* oriented protons and H_b for the *exo* oriented protons. The *exo* methyl groups of the pinene moieties are assigned as 12 and 12′, the *endo* oriented ones as 13 and 13′, respectively. The numbering scheme for the ligands is shown in Scheme 9.

UV–vis spectra were measured on a Perkin–Elmer Lambda 40 spectrometer. Mass spectral data were acquired on 'VG Instrument 7070E' equipped with a FAB inlet system. Elemental analysis were obtained from EIF (Ecole d'ingénieurs de Fribourg, Switzerland). CD spectra were measured on a 'Jasco J-715' spectropolarimeter.

X-Ray diffraction: Intensity data were collected at room temperature on a Stoe AED2 4-circle diffractometer using Mo Kα graphite-monochromated radiation ($\lambda = 0.71073$ Å) with ω–2Θ scans in the 2Θ range 4–51°. The structure was solved by direct methods using the program



Scheme 9. Numbering scheme for the ligands

SHELXS-97.[19] The refinement and all further calculations were carried out using SHELXL-97. H atoms were included in calculated positions and treated as riding atoms using SHELXL-97 default parameters. The non-H atoms were refined anisotropically, using weighted full-matrix least-squares on F^2. The coordinates correspond to the absolute structure of the molecule in the crystals.

Chiral GC: Hewlett–Packard 5890 Series II gas chromatograph and Supelco Beta-Dex 110 column. $T_{oven} = 120°C$; (1*S*,2*R*)-**18**: t_R 46.4 min, (1*R*,2*S*)-**18**: t_R 47.7 min, (1*R*,2*R*)-**18**: t_R 55.3 min, (1*S*,2*S*)-**18**: t_R 56.2 min.

4.3. Synthesis of the ligands

The synthesis of the ligand **10** (R = H) has been published earlier.[13] The synthesis of the alkylated species **10a–c** was achieved by lithiation of **10** followed by quenching with the respective alkyl iodide.[14] Synthesis of the C_2-symmetric bipyridine **11** (R = R′ = H) was first carried out in our laboratories.[15] Alkylation of this ligand was done in a similar way using LDA and up to 3 equiv. of the appropriate alkyl iodide to yield either C_1- or C_2-symmetric bipyridines **11a–m** depending on the number of equivalents of LDA and alkylating agent. Synthesis of ligand **12** started from 2,6-dibromopyridine, which is commercially available.

4.3.1. 2-Acetyl-6-bromopyridine

23.69 g (0.1 mol, 1.0 equiv.) of 2,6-dibromopyridine were solubilized in 300 ml of dry diethyl ether. At −60°C, 77 ml (0.1 mol, 1.0 equiv.) of *n*-BuLi (1.3 M in hexane) were added within 30 min. The resulting yellow solution was stirred for 30 min at −40°C and 13.9 ml of dimethylacetamide (freshly distilled from BaO) were added at −60°C. The solution was stirred and heated to room temperature. The resulting yellow mixture was hydrolyzed by 100 ml of saturated NH_4Cl. Extraction of the aqueous solution by diethyl ether, drying over Na_2SO_4, and evaporation of the solvent gave 37.67 g of a yellow to brown solid. Recrystallization in diethyl ether/pentane afforded 11.60 g of a yellow solid (yield 58%). ^1H NMR (300 MHz, $CDCl_3$): δ

7.95 (dd, $^3J=6.9$ and 6.8 Hz, 1H); 7.65 (2d, $^3J=6.9$ and 7.0 Hz, 2H); 2.69 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.6 (C), 154.3 (C, 1C), 141.4 (C, 1C), 139.2 (CH, 1C), 131.8 (CH, 1C), 120.5 (CH, 1C), 25.8 (CH_3, 1C). MS-EI: 201 (31), 199 (30), 173 (36), 78 (88), 76 (100).

4.3.2. 2-Acetyl-6-phenylpyridine

7.75 g (38.74 mmol, 1.0 equiv.) of 2-acetyl-6-bromopyridine were dissolved in dry xylene (75 ml). Phenylboronic acid (7.09 g, 58.11 mmol, 1.5 equiv.) was added and the resulting suspension was degassed three times. Tetrakis(trisphenylphosphine)palladium (5% mol, freshly purified) and potassium carbonate (10.71 g, 77.48 mmol, 2.0 equiv.) were added. The solution was degassed again three times and stirred for 2 h at room temperature. Water (500 ml) was added and the mixture was extracted by dichloromethane (500 ml). The resulting organic phases were dried over sodium sulfate and solvents were evaporated to afford after recrystallization in hexane/ethyl acetate 6.95 of the desired compound (91% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.03 (dd, 2H), 7.91–7.8 (m, 3H), 7.44–7.38 (m, 3H), 2.75 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.9 (C, 1C), 156.9 (C, 1C), 153.8 (C, 1C), 138.8 (C, 1C), 138.0 (C, 1C), 129.8 (C, 1C), 129.2 (CH, 2C), 127.3 (CH, 2C), 123.8 (CH, C), 120.2 (CH, 1C), 26.1 (CH_3), 1C). MS-EI: 197 (100), 154 (80), 127 (25), 77 (15).

4.3.3. 1-(2-Acetyl-6-phenylpyridine)pyridinium iodide ***15***

Under an argon atmosphere, in 25 ml one-necked round-bottomed flask, equipped with a magnetic stirring bar and reflux condenser, 3.0 ml of pyridine (distilled over KOH, 14.6 equiv.) was added to 634 mg of iodine (2.53 mmol, 1.0 equiv.) and 500 mg of 2-acetyl-6-phenylpyridine (2.53 mmol, 1.0 equiv.). The resulting dark solution was kept at 130°C for 3 h and at 0°C for 20 h. The pyridine was then removed by distillation in vacuo to afford a black solid. After addition of dry ether, stirring, filtration under an argon atmosphere, and drying, 1.45 g of a black solid was obtained. ^{1}H NMR determination of the two most shifted doublet signals gave a ratio of 2:1 between the desired product **15** and pyridinium iodide **16** (100% yield). This crude material was stored at 20°C under an argon atmosphere and used without further purification in the next step.

4.3.4. 6′-Phenyl-5,6-pinene-2,2′-bipyridine ***12***

Accessible from (+)-pinocarvone and 1*S*-(−)-α-pinene. In a 25 ml two-necked-bottomed flask, a solution of 1.45 g (2.53 mmol, 1.0 equiv.) of crude product **15**, 380 mg of (+)-pinocarvone (obtained in one step from (−)-α-pinene, 2.53 mmol, 1.0 equiv.) and 3.2 ml of glacial acetic acid was heated to 55°C for 15 min. Ammonium acetate (1.70 g) as a solid (22.0 mmol, 1.0 equiv.) was added in portions and the reaction mixture was heated to 110°C for 16 h. After cooling to room temperature, 15 ml of water were added to the reaction mixture and the aqueous phase was extracted with 5×50 ml of CH_2Cl_2. The organic layers were combined and washed with 2×50 ml of water (pH 5). After drying over $MgSO_4$ and filtration the organic phase was treated with active charcoal (1 h, 25°C). Filtration over Celite gave a pale yellow solution which was evaporated in vacuo to yield 836 mg of a yellow solid. Recrystallization from acetone (7.0 ml) gave 407 mg of the pure desired bipyridine **12** (55% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.37 (d, $^3J_{2',3'}=8.0$ Hz, 1H, H–C(3′)); 8.31 (d, $^3J_{3,4}=8.0$ Hz, 1H, H–C(3)); 8.13 (dd, $^3J_{8',9'}=8.0$ Hz, $^4J_{8',10'}=2.1$ Hz, 2H, H–C(8′,12′)); 7.85 (dd, $^3J=7.4$ Hz, 2H, H–C(4′)); 7.72 (dd, $^3J=7.8$ Hz, $^4J=0.8$ Hz, 1H, H–C(5′)); 7.48 (dd, $^3J=7.4$ Hz, 2H, H–C(9′,11′)); 7.42 (dd, $^3J=7.9$ Hz, 1H, H–C(10′)); 7.37 (d, $^3J=8.0$ Hz, 1H, H–C(4)); 3.22 (m, 2H, H–C(7)); 2.83 (dd, $^3J=6.0$ and 5.6

Hz, 1H, H–C(10)); 2.71 (ddd, 1H, H–C(9b)); 2.40 (sept, $^3J=3.2$ Hz, 1H, H–C(8)); 1.42 (s, 3H, H–C(12)); 1.32 (d, $^3J_{9a,9b}=9.5$ Hz, 1H, H–C(9a)); 0.68 (s, 3H, H–C(13)). ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.6 (C, 1C); 156.5 (C, 1C), 154.0 (C, 1C); 142.5 (C, 1C); 139.8; 137.8 (CH, 1C); 134.0 (CH, 1C); 129.1 (CH, 1C); 128.9 (CH, 1C), 127.2 (CH, 1C), 119.9 (CH, 1C); 119.3 (CH, 1C), 118.4 (CH, 1C), 46.8 (CH, 1C), 40.6 (CH, 1C); 39.8 (C or CH_2; 1C); 37.0 (C or CH_2, 1C); 32.2 (C or CH_2, 1C), 26.4 (CH_3, 1C); 21.6 (CH_3, 1C). UV–vis ($CHCl_3$, 8.94×10^{-6} M): λ_{max} (ε) 304.0; 253.5 (29000). EI-MS: 326 (100, M^+), 311 (50, $M-CH_3^+$); 297 (36, $M-C_2H_5^+$); 283 (93, $M-C_3H_7^+$); 246 (10); 231 (2), 205 (7); 154 (15, $C_{11}H_8N^+$); 128 (35); 77 (20, $C_6H_5^+$); 51 (9). Elemental analysis: calculated for $C_{23}H_{22}N_2$: C 84.63, H 6.79, N 8.58%; found C 83.16, H 6.89, N 8.19.

4.3.5. Bipyridine ***12a***

To a 25 ml Schlenk flask 15 ml of dry THF (distilled over Na/benzophenone) and 0.29 ml (2.083 mmol, 1.7 equiv.) of dry diisopropylamine (distilled over KOH) were added. This mixture was then cooled down to –40°C and 1.3 ml of *n*-BuLi (1.6 M in hexane, 1.96 mmol, 1.6 equiv.) was added via a syringe. The weakly yellow colored solution was allowed to warm up to 0°C using an ice bath. After having stirred this solution for 30 min, it was cooled down again to –40°C and ligand **12** (400 mg, 1.225 mmol, 1 equiv.) dissolved in 5 ml of dry THF was added using a syringe pump within 1 h. After addition of one drop of this ligand solution, the reaction mixture became immediately blue. After this addition, the resulting dark blue solution was stirred at –40°C for 2 h. Then a solution of ethyliodide in 5 ml of dry THF was added using a syringe pump during 1 h. This resulting reaction mixture was allowed to warm up to room temperature overnight, and was quenched with 1 ml of water. THF was removed under reduced pressure and the residue was taken up with 50 ml of CH_2Cl_2. More water was added and the water phase was extracted with four 20 ml portions of CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered, and evaporated to yield a brown solid, which was then purified by column chromatography (SiO_2, hexane/ether/triethylamine = 10:1:0.1). A pale yellow solid could be isolated (yield 84%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.37 (d, $^3J_{3'4'}=8.0$ Hz, 1H, H–C(3′)); 8.31 (d, $^3J_{3,4}=8.0$ Hz, 1H, H–C(3)); 8.13 (dd, $^3J_{8',9'}=8.0$ Hz, $^4J_{8',10'}=2.1$ Hz, 2H, H–C(8′,12′)); 7.85 (dd, $^3J=7.4$ Hz, 2H, H–C(4′)); 7.72 (dd, $^3J=7.8$ Hz, $^4J=0.8$ Hz, 1H, H–C(5′)); 7.48 (dd, $^3J=7.4$ Hz, 2H, H–C(9′,11′)); 7.42 (dd, $^3J=7.9$ Hz, 1H, H–C(10′)); 7.37 (d, $^3J=8.0$ Hz, 1H, H–C(4)); 3.22 (m, 1H, H–C(9a)); 2.83 (dd, $^3J=6.0$ and 5.6 Hz, 1H, H–C(10)); 2.71 (ddd, 1H, H–C(9b)); 2.51 (m, 1H, 14b); 2.40 (sept, $^3J=3.2$ Hz, 1H, H–C(8)); 1.55 (m, 1H, H–C(14a); 1.42 (s, 3H, H–C(12)); 1.32 (d, $^3J_{9a,9b}=9.5$ Hz, 1H, H–C(9a)); 1.23 (t, $^3J=7.45$ Hz, 3H, H–C(15); 0.68 (s, 3H, H–C(13)). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.5 (C, 1C); 156.27 (C, 1C), 154.0 (C, 1C); 139.5 (C, 1C); 137.6 (CH, 1C); 134.0 (CH, 1C); 128.9 (CH, 1C); 128.7 (CH, 1C), 126.9 (CH, 1C), 119.8 (CH, 1C); 119.4 (CH, 1C), 118.4 (CH, 1C), 46.9 (CH, 1C), 45.7 (CH_2 1C); 42.8 (CH, 1C); 41.1 (C or CH_2; 1C); 28.41 (C or CH_2, 1C), 26.4 (CH_3, 1C); 25.65 (CH_2, 1C); 20.98 (CH_3, 1C). Elemental analysis: calculated for $C_{25}H_{26}N_2$: C 84.70, H, 7.39, N 7.90; found C 84.24, H 7.66, N 7.93. MS-FAB: 355.3 m/z (100, M^++H), 325.2 (18, $M-C_2H_5$), 297.2 (12), 283.2 (18), 147.1 (15).

4.3.6. Typical procedure for the synthesis of mono- and bis-substituted bipyridines ***10a–c*** *and* ***11a–m*** *(for details see Refs. 14 and 15)*

A Schlenk flask was charged with 15 ml of dry THF and diisopropylamine and cooled down to –40°C. Then *n*-BuLi (1.6 M in hexane) was added. This mixture was stirred for 30 min at 0°C, and cooled again to –40°C. The corresponding bipyridine was dissolved in 5 ml of dry

THF and added to the LDA solution by a syringe pump within 1 h. This deep blue solution was then stirred for 2 h, followed by slow addition (during 1 h) of the respective alkyl halide (chloride, bromide or iodide) by a syringe pump. This reaction mixture was then allowed to warm up slowly to room temperature. After quenching with water and evaporating, more water was added and the water phase was extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$ or Na_2SO_4, filtered, and evaporated to dryness. The crude product was then purified by column chromatography to yield the desired alkylated bipyridine.

4.3.7. Complex syntheses

In a typical procedure $CuCl_2{\cdot}2H_2O$ was dissolved in 5 ml EtOH, and the corresponding bipyridine was added as a solution in CH_2Cl_2. The green solution turned red-brown immediately. The reaction mixture was stirred for 4 h. The reaction was controlled by TLC. The solution was then evaporated to dryness and to the residue was added diethyl ether in order to form a suspension. The solid was then filtered off and dried in high vacuo to yield the desired complex.

Cu–11: yield 93%. Elemental analysis: calculated for $C_{24}H_{28}Cl_2CuN_2{\cdot}CH_2Cl_2$: C 61.2, H 6.16, 5.71; found C 60.2, H 6.15, N 5.03. UV–vis (CH_2Cl_2, 5.0234×10^{-4} M): λ_{max} (ε) 379 (1110); 341 (1861); 328 (20666); 274 (14750). FAB-MS: 407.1 (100, M^+–2Cl), 351 (20), 309.0 (12), 257.0 (10), 204.1 (10), 142.0 (7).

Cu–11a: yield 92%. Elemental analysis: calculated for $C_{26}H_{32}Cl_2CuN_2{\cdot}0.4(CH_2Cl_2)$: C 58.6, H 6.1, N 5.18; found C 59.9, H 6.43, N 5.23. UV–vis (CH_2Cl_2, 6.1410510^{-5} M): λ_{max} (ε) 882 (127), 392 (1345), 327 (18777), 274 (15519), 230 (11888). FAB-MS: 435.2 (100, M^+–2Cl), 387.2 (68), 373.2 (96, L+1), 311.1 (14), 297.1 (12), 271.1 (11), 154.0 (12), 128.0 (11).

Cu–11b: yield 64%. Elemental analysis: calculated for $C_{28}H_{36}Cl_2CuN_2{\cdot}0.4CH_2Cl_2$: C 59.95, H 6.52, N 4.92; found C 60.38, H 6.59, N 4.69. UV–vis (CH_2Cl_2, 4.34514×10^{-5} M): λ_{max} (ε) 886 (158), 393 (1388), 329 (19957), 273 (16144), 227 (14049). FAB-MS: 498.0 (14, M^+–Cl), 463.1 (67, M^+–2Cl), 401.2 (100, L^++1), 154.1 (28).

Cu–11c: yield 65%. Elemental analysis: calculated for $C_{30}H_{40}Cl_2CuN_2{\cdot}CH_2Cl_2$: C 57.46, H 6.53, N 4.32; found C 59.51, H 6.59, 4.42. UV–vis (CH_2Cl_2, 5.17905×10^{-5} M): λ_{max} (ε) 847 (250), 458 (903), 327 (17576), 274 (16069), 227 (15251). FAB-MS: 526.1 (8, M^++2–Cl), 491.1 (12, M^++2–2Cl), 463.1 (8), 429.2 (100, L^++1).

Cu–12a: yield 72%. Elemental analysis: calculated for $C_{25}H_{26}Cl_2CuN_2$: C 61.41, H 5.28, N 5.30; found C 59.86, H 5.28, N 5.30. UV–vis (CH_2Cl_2, $3.7763{\cdot}10^{-5}$ M): λ_{max} (ε) 922 (174), 331 (18152), 260 (17739). FAB-MS: 417.0 (100, M^+–2Cl), 355.1 (38, L), 332.9 (8), 271.0 (6), 218.0 (4), 154.1 (7).

Cu–13: yield 68%. Elemental analysis: calculated for $C_{24}H_{28}Cl_2CuN_2{\cdot}CH_2Cl_2$: C 53.3, H 5.36, N 4.97; found C 55.83, H 5.83, N 5.30. UV–vis (CH_2Cl_2, $4.84804{\cdot}10^{-4}$M): λ_{max} (ε) 832 (228.3397), 377 (1858), 339 (17328), 328 (18587), 270 (11170), 267 (11283). FAB-MS: 751.3 (98, CuL_2–H), 442.1 (10, M^+–Cl), 407.2 (100, M^+–2Cl), 363.2 (19), 309.2 (9), 217.2 (6), 154.1 (12), 136.1 (14).

4.3.8. Cyclopropanation of styrene—method 1 (one-pot)

In a typical catalytic reaction, 10.9 mg (0.030 mmol) of Cu(II) triflate and 0.033 mmol of the (–)-ligand were dried in vacuo for 20 minutes, set under an inert gas atmosphere and dissolved in 4 ml of dry CH_2Cl_2. Upon addition of 937 mg (9.0 mmol) of styrene the slightly green solution turned yellow-brown. Ethyl diazoacetate (368 mg of a commercially available solution

in CH_2Cl_2; 3.0 mmol) dissolved in about 3 ml of CH_2Cl_2 was added using a syringe pump over a period of 7 h. First the diazoacetate reduces the Cu(II) species to a Cu(I) species, forming the active catalyst.[21] After addition the reaction mixture was stirred for an additional 2 hours. The solvent was removed and the liquid residue, mainly excess styrene, 2-phenylcyclopropane-1-carboxylates **18** and catalyst, was purified on silica gel (20 g SiO_2 100 ml of hexane/ethyl ether 20:1, then 100 ml of ether).

4.3.9. Cyclopropanation of styrene—method 2 (using the corresponding Cu(II) complex)

To a two-necked round-bottomed flask were added the corresponding Cu(II) complexes (0.048 mmol) and silver(I) triflate (0.096 mmol) under argon. Dry CH_2Cl_2 was added (3 ml) and the solution was stirred at room temperature for 2 h. The precipitated AgCl was filtered through a packed filter paper to a solution of the alkene (4.8 mmol) in CH_2Cl_2 (5 ml) in a 15 ml Schlenk flask. This solution was then degassed by the pump-and-freeze technique. A degassed solution of ethyl diazoacetate (1.185 mmol) in 5 ml of dry CH_2Cl_2 was then added via a syringe pump within 4 h. The reaction mixture was then stirred at room temperature or at 0°C for 16 h. Enantiomeric excess determination was carried out by chiral column chromatography without working up the reaction mixture. Yields were determined in the same way.

Acknowledgements

We thank Dr. Catherine Goujon-Ginglinger for the synthesis of ligand **12**. This work was supported by the Swiss National Science Foundation.

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