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Chiral ligands with pyridine donors in transition metal catalyzed enantioselective cyclopropanation and hydrosilylation reactions

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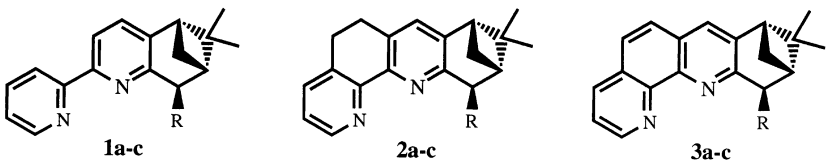
Abstract

Copper(I) and rhodium(I) complexes prepared in situ from $[Cu(OTf)(C_6H_6)_{0.5}]$ and $[Rh(cod)Cl]_2$ with a range of chiral 2,2′-bipyridines, 5,6-dihydro-1,10-phenanthrolines, 1,10-phenanthrolines and 2,2′:6′,2″-terpyridines were assessed as chiral catalysts for the enantioselective cyclopropanation of styrene with diazoacetates and for the hydrosilylation of acetophenone with diphenylsilane. Enantioselectivities up to 68% in the cyclopropanation and up to 32% in the hydrosilylation were obtained. © 2000 Published by Elsevier Science Ltd.

1. Introduction

Recently, we have evaluated the utility of a number of chiral ligands with nitrogen donors such as 2,2′-bipyridines **1**,[1] 5,6-dihydro-1,10-phenanthrolines **2**[2] and 1,10-phenanthrolines **3**[3] (Scheme 1) as chiral controllers in the enantioselective Pd-catalyzed allylic alkylation of 1,3-diphenylprop-2-enyl acetate. The differences in the catalytic activity and stereoselectivity



R= **a**: H; **b**: CH_3, **c**: CH_2-C_6H_5,

Scheme 1.

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observed with these ligands have been ascribed to the different conformational mobility induced in the catalyst by the heterocyclic template. The five-membered chelate ring resulting from the coordination of these ligands to the metal is most probably locked in a single conformation in the case of 1,10-phenanthroline derivatives, whereas a certain degree of conformational freedom is allowed in the case of 2,2′-bipyridine ligands, due to the inherently higher flexibility of this backbone. An intermediate situation is found in the 5,6-dihydrophenanthrolines **2** where the coplanarity of the two pyridine rings is not mandatory.

Pursuing our interest in this field, we have extended the application of ligands **1**–**3** to other metal-catalyzed asymmetric processes. In this paper we report the results obtained in the enantioselective Cu(I)-catalyzed cyclopropanation of styrene with diazoacetates and in the enantioselective Rh(I)-catalyzed hydrosilylation of acetophenone with diphenylsilane. For the sake of comparison with **1**–**3** and for a better understanding of the scope of chiral ligands with pyridine donors in the Rh(I)-catalyzed hydrosilylation, we have further pursued our study of this reaction to also include the ligands **9**–**13**, previously prepared in our laboratories. All these derivatives present the 2,2-dimethylnorpinan-2-yl unit as the unique chiral pendant. Ligands **9**, **12** and **13** have also previously been examined in the Cu(I)-catalyzed cyclopropanation of styrene with modest results.[4]

2. Results and discussion

2.1. Copper(I)-catalyzed asymmetric cyclopropanation

It has been repeatedly shown that C_2-symmetric 2,2′-bipyridines are capable of providing high *ee*s in the enantioselective cyclopropanation of olefins with diazoesters.[5] While there are no data on the use of C_2-symmetric 1,10-phenanthrolines in this reaction, a very low *ee* was obtained in the single isolated experiment where a C_1-symmetric 1,10-phenanthroline was used.[4]

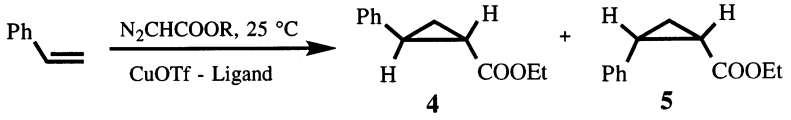
The reaction of styrene with ethyl diazoacetate, to give the *trans*- and *cis*-cyclopropanes **4** and **5**, was chosen as the model for the evaluation of the efficiency of ligands **1**–**3** in the copper(I)-catalyzed asymmetric cyclopropanation of olefins.[6] The reaction was carried out at rt by slow addition of ethyl diazoacetate to a solution of styrene in methylene chloride containing the copper(I)–ligand adduct. This was prepared in situ by adding the appropriate amount of ligand **1**–**3** to copper(I) trifluoromethanesulfonate–benzene complex [Cu(OTf)$(C_6H_6)_{0.5}$].

The results obtained in these runs are summarized in Table 1. Ligands **1a**–**3a** (R = H) provide effective Cu(I)-catalysts, but negligible enantioselectivities. An *ee* in double figures (10% for the *cis*-cyclopropane) was obtained only in one case with **1a** as the ligand.

As a general trend, the introduction of an alkyl group onto the carbon adjacent to the heterocyclic ring of all the ligands **1**–**3** displays a positive effect on the enantioselectivity of the reaction. The *ee*s for both *trans*- and *cis*-isomers **4** and **5** increase substantially when the hydrogen of **1a**–**3a** was substituted by a methyl group leading to **1b**–**3b**. Increasing the steric bulk of the alkyl substituent from methyl to benzyl led to a sharp improvement in the *ee* in the case of ligands **1** and **2**, while in the case of ligand **3** it had no significant effect on the *trans*-isomer and it was even detrimental for the *cis*-isomer.

A further increase of the stereoselectivity was obtained when *t*-butyl diazoacetate was used in place of the ethyl ester. With this reagent, the *ee*s were in the range of 60–70% with all the ligands **1**–**3** and were basically identical for all the cyclopropanes, with the exception of the

Table 1
Enantioselective cyclopropanation of styrene with diazoacetates[a]



Ligand	Diazoacetate	Yield (%)[b]	*Trans*:*cis* ratio[c]	% *ee*[c]		Configuration[d]	
	R	**4**+**5**	**4**:**5**	**4**	**5**	**4**	**5**
1a	Et	74	70:30		10		1*R*, 2*S*
1b	Et	66	58:42	20	11	1*R*, 2*R*	1*S*, 2*R*
1c	Et	61	63:37	61	45	1*R*, 2*R*	1*S*, 2*R*
1c	^{t}Bu	55	77:23	64	68	1*R*, 2*R*	1*S*, 2*R*
2a	Et	65	64:36		3		1*R*, 2*S*
2b	Et	63	68:32	24	19	1*R*, 2*R*	1*S*, 2*R*
2c	Et	67	60:40	47	37	1*R*, 2*R*	1*S*, 2*R*
2c	^{t}Bu	61	70:30	65	64	1*R*, 2*R*	1*S*, 2*R*
3a	Et	64	68:32	3	2	1*S*, 2*S*	1*R*, 2*S*
3b	Et	57	64:36	30	22	1*R*, 2*R*	1*S*, 2*R*
3c	Et	51	60:40	32	12	1*R*, 2*R*	1*S*, 2*R*
3c	^{t}Bu	58	78:22	66	38	1*R*, 2*R*	1*S*, 2*R*

[a] The ligand (34 μmol) in CH_2Cl_2 (2.5 ml) was added to a suspension of $[Cu(OTf)(C_6H_6)_{0.5}]$ (8 mg, 32 μmol) in CH_2Cl_2 (2.5 ml). After 30 min, the mixture was filtered through packed adsorbent cotton under argon and, to the filtrate, was added styrene (1.59 ml, 13.87 mmol). Diazoacetate (2.5 μmol) in CH_2Cl_2 (2.5 ml) was added dropwise over a period of 1 h and then stirred for 24 h.

[b] Isolated yield, based on the diazoacetate, for the mixture of *trans*- and *cis*-cyclopropanes.

[c] Determined by GC analysis on a chiral column.

[d] Assignment according to Ref. 7.

cis-configured product arising from **3c** (38%). This (and the previous) dichotomic behaviour of the phenanthroline based ligands **3** is hard to rationalize.

The beneficial effect of the *t*-butyl substitution was modest in the case of ligand **1**, but was significant for ligand **3** where a doubling of the *ee* of the *trans*-cyclopropane occurred.

The presence of larger groups, both in the ligand and in the diazoester, also affects the *trans–cis* diastereoselectivity which improves moderately with the steric bulk of the substituents, approaching the limiting value of 60% *de*.

Notably, the presence of an alkyl substituent in the structures of **1**–**3** caused a chiral switch of the configuration of both cyclopropanes to those obtained from the unsubstituted ligands **1a**–**3a**: this suggests that the stereochemistry of the reaction is basically dictated by the new stereocentre originating from the introduction of the alkyl substituent onto the basic structure **a** and that this stereocentre has a mismatching stereotopic relationship with those preexisting on the bridge.

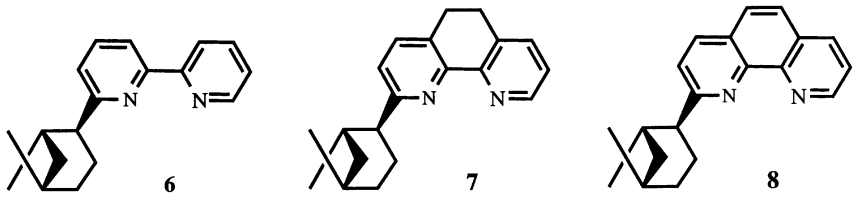
The dependence of the stereoselectivity on the rigidity of the ligand was not at all consistent. In the case of the methyl substituted ligands **b**, an increase of the rigidity was met by a modest, but definite increase in the *ee* for both the cyclopropane esters. The benzyl substituted derivatives **c** performed exactly opposite. Due to these contrasting trends, no meaningful conclusion could be drawn at this point for the structure–activity relationship.

2.2. Rhodium(I)-catalyzed asymmetric hydrosilylation

Several years ago we reported the use of a range of 2,2′-bipyridines[8] and 1,10-phenanthrolines, including one 5,6-dihydro derivative,[9] as ligands in the Rh(I)-catalyzed hydrosilylation of acetophenone with diphenylsilane.

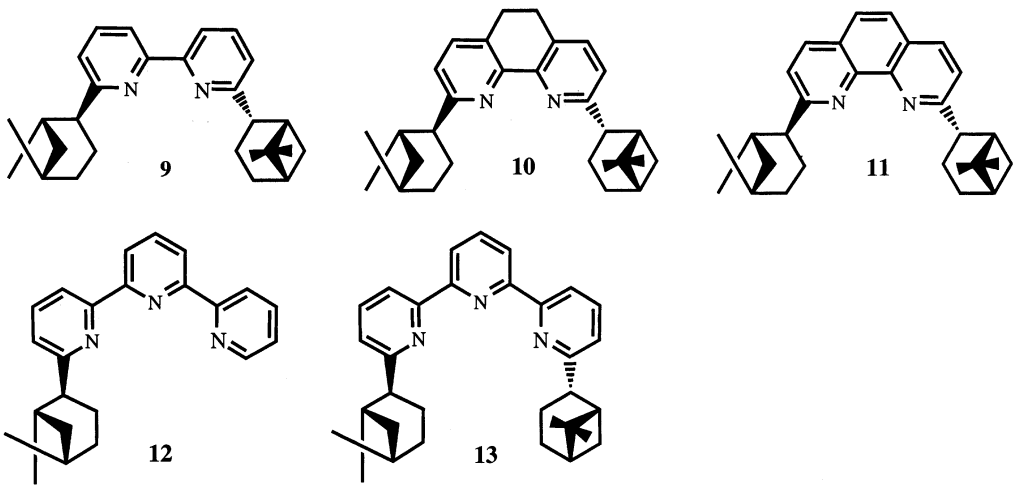
In the course of those investigations, it was pointed out that these chiral controllers could provide catalysts of high efficiency in the hydrosilylation of acetophenone and that the best *ee*s were consistently obtained with the ligands bearing the chiral substituent as close as possible to the reactive site of the catalyst. We concluded that the coordination of these ligands to the metal was not inhibited by the presence of rather bulky substituents on the carbon adjacent to the nitrogen.

The best enantioselectivities were recorded with ligands **6** (72% *ee*), **7** (70% *ee*) and **8** (76% *ee*) having the 2,2-dimethylnorpinan-2-yl group as the common chiral substituent (Scheme 2). As the same chiral unit is present in ligands **1**–**3** in the form of a cycloalkeno-condensed substituent, we became interested in checking the behaviour of these derivatives also in this Rh(I)-catalyzed reaction.



Scheme 2.

In addition to the ligands **1**–**3**, we have also assessed compounds **9**–**11**[10] in the hydrosilylation (Scheme 3), which are the C_2-symmetric compounds corresponding to **6**–**8**, and the two 2,2′:6′,2″-terpyridines **12** and **13**,[11] with C_1- and C_2-symmetrical structures, respectively. Terdentate nitrogen ligands of similar design, but with two oxazolines in place of the two pyridines (Pybox), have shown remarkable activity and enantioselectivity in the hydrosilylation of ketones with Rh(I)-catalysts.[12]



Scheme 3.

The results obtained in the Rh(I)-catalyzed hydrosilylation[13] of acetophenone with diphenylsilane in the presence of ligands **1**–**3** and **9**–**11** are reported in Table 2. The degree of hydrosilylation (conversion of acetophenone) and the relative amounts of the silyl enol ether **16** and of the silylalkyl ether **15** were determined by ^{1}H NMR,[14] while the *ee* was determined by GC analysis on a chiral column of the carbinol **17** obtained after acid hydrolysis (Scheme 4).

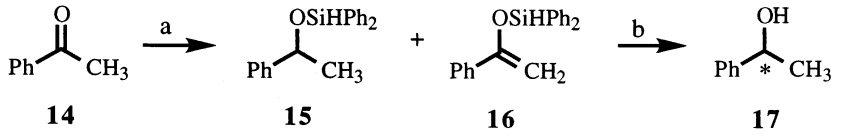
Table 2
Enantioselective hydrosilylation of acetophenone with diphenylsilane [a]

Ligand	Enolether (%) [b]	Conversion (%) [b]	Yield (%) [b]	% *ee* [c]	Configuration
1a	2	90	88	32	*R*
1b	25	85	63	2	*S*
1c	26	83	61	3	*S*
2a	36	82	56	21	*R*
2b	27	85	61	1	*S*
2c	32	72	49	0	*S*
3a	19	94	73	10	*S*
3b	22	77	55	0	
3c	25	79	61	1	*R*
9	30	100	70	1	*S*
10	27	93	69	2	*S*
11	33	94	63	1	*S*

[a] Ligand (0.2 mmol), $[Rh(cod)Cl]_2$ (10 mg, 0.02 mol) and acetophenone (1 ml, 8.5 mmol) in CCl_4 (2 ml) were stirred at 25°C for 30 min. Diphenylsilane (1.6 ml, 8.6 mmol) was added at 0°C and then the mixture slowly warmed to 25°C and stirred for 24 h.

[b] Determined by ^{1}H NMR spectroscopy according to Ref. 14.

[c] Determined by chiral GC.



14 **15** **16** **17**

a: $[Rh(cod)Cl]_2$, ligand, H_2SiPh_2; b: *p*-TsOH, CH_3OH

Scheme 4.

High levels of conversion and satisfactory yields were obtained with all the ligands after 24 h at rt. Much to our surprise, however, in most cases the reaction was completely devoid of enantioselectivity. Only with the unsubstituted cycloalkeno-condensed derivatives **1a**–**3a**, a modest but definite *ee* was obtained and this showed a decreasing trend in going from bipyridines **1** to phenanthrolines **3**. These last derivatives also induced a chiral switch in the reaction product as compared to ligands **1** and **2**.

We were particularly disappointed by the results obtained with the substituted ligands **1b**–**3b** and **1c**–**3c**, where an enantioselectivity higher than the one observed with the unsubstituted counterparts **1a**–**3a** was confidently expected in view of the close proximity of one chirogenic element of the ligand to the metal centre.

Contrary to our expectations, the introduction of an alkyl substituent onto the carbon adjacent to the heterocyclic ring resulted in the reduction both of the chemical yield and of the stereoselectivity of the reaction. During the preparation of the Rh(I)–ligand adducts in situ, we observed that the colour of the solution changed from yellow to orange with ligands **1a**–**3a**, while with the substituted ligands, the solution remained yellow with no variation noticed. This observation seems to indicate that the substituted ligands do not bind readily to rhodium.

The catalysts originating from ligands **9**–**11** were reasonably active, but also provided a racemic product. It could not be ascertained if this should be ascribed to the C_2-symmetry or to a failure in the binding determined by the presence of two encumbering substituents in the close proximity of the donor centres.

Table 3 summarizes the results obtained in the Rh(I)-catalyzed hydrosilylation of acetophenone with diphenylsilane in the presence of the 2,2′:6′,2″-terpyridine ligands **12** and **13**. These tridentate ligands led to lower conversions and lower rates. This drawback was not counterbalanced by an increase in the *ee* which remained very poor and exceeded 10% in only one case. A change in the solvent from methylene chloride to tetrachloromethane led to an increase in the amount of the enol ether **16** and addition of silver fluoroborate had the same effect.

Table 3
Enantioselective hydrosilylation of acetophenone with diphenylsilane [a]

Run	Ligand	Solvent	Reaction time (h)	Enolether (%) [b]	Conversion (%) [b]	Yield (%) [b]	*ee* (%)[c]	Conf.
1	**12**	CH_2Cl_2	20	31	78	51	6	*S*
2	**12** [d]	CH_2Cl_2	40	26	82	54	6	*S*
3	**12**	CCl_4	44	81	41	8	n.d.	
4	**12** [e]	CCl_4	67	100	36	0		
5	**13**	CH_2Cl_2	20	36	94	53	1	*S*
6	**13**	CCl_4	20	35	88	55	2	*S*
7	**13** [e]	CCl_4	20	49	74	37	14	*S*

[a] Ligand (0.2 mmol), $[Rh(cod)Cl]_2$ (10 mg, 0.02 mol) and acetophenone (1 ml, 8.5 mmol) in the appropriate solvent (2 ml) were stirred at 25°C for 30 min (if $AgBF_4$ was added, stirring was continued for another 30 min). Diphenylsilane (1.6 ml, 8.6 mmol) was added at 0°C and then the mixture slowly warmed to 25°C and stirred for the appropriate time.

[b] Determined by ^1H NMR spectroscopy according to Ref. 14.

[c] Determined by chiral GC.

[d] In this case **12** and $[Rh(cod)Cl]_2$ were stirred at 25°C for 72 h.

[e] Eccess of $AgBF_4$ was added.

Taken overall, the results assembled in Tables 1–3 show that the ligands with pyridine donors used throughout this work are poorly suited chiral controllers in the Rh(I)-catalyzed hydrosilylation of acetophenone, while they seem to warrant attention for their possible applications in the field of Cu(I)-catalyzed cyclopropanation. Further studies on this subject are currently in progress in our laboratory.

3. Experimental

3.1. General

Gas chromatographic analyses were performed with a HP 5900 chromatograph using He (60 kPa) as the carrier gas. Copper(I) trifluoromethanesulfonate benzene complex $[Cu(OTf)(C_6H_6)_{0.5}]$, $[Rh(cod)Cl]_2$, ethyl and *t*-butyl diazoacetate were purchased from Aldrich. The ligands were prepared according to reported procedures: 5,7-methano-6,6-dimethyl-2-(2-pyridinyl)-5,6,7,8-tetrahydroquinoline **1a**[1] and the corresponding 8-methyl **1b**[1] and 8-benzyl derivatives **1c**,[1] 8,10-methano-9,9-dimethyl-8,9,10,11-tetrahydrobenzo[*b*][1,10]phenanthroline **2a**[2] and the corresponding 11-methyl **2b**[2] and 11-benzyl derivatives **2c**,[2] 8,10-methano-9,9-dimethyl-5,6,8,9,10,11-hexahydrobenzo[*b*][1,10]phenanthroline **3a**[3] and the corresponding 11-methyl **3b**[3] and 11-benzyl derivatives **3c**,[3] 6,6′-bis[6,6-dimethylnorpinan-2-yl]-2,2′-bipyridine **9**,[10] 2,9-bis[6,6-dimethylnorpinan-2-yl]-5,6-dihydro-1,10-phenanthroline **10**,[10] 2,9-bis[6,6-dimethylnorpinan-2-yl]-1,10-phenanthroline **11**,[10] 6-[6,6-dimethylnorpinan-2-yl]-2,2′:6′,2″-terpyridine **12**[11] and 6,6″-bis[6,6-dimethylnorpinan-2-yl]-2,2′:6′,2″-terpyridine **13**.[11]

3.2. Asymmetric cyclopropanation of styrene: typical procedure

A solution of the ligand (34 μmol) in CH_2Cl_2 (2.5 ml) was added to a suspension of $[Cu(OTf)(C_6H_6)_{0.5}]$ (8 mg, 32 μmol) in CH_2Cl_2 (2.5 ml). After 30 min, the mixture was filtered through packed adsorbent cotton under argon and, to the filtrate, styrene (1.59 ml, 13.87 mmol) was added. Then a solution of the diazoacetate ester (2.5 μmol) in CH_2Cl_2 (2.5 ml) was added dropwise over a period of 1 h. The mixture was stirred for 24 h at rt and then concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 15/1) to afford a mixture of ethyl *trans*- and *cis*-2-phenyl-cyclopropane-1-carboxylates as a colurless oil. The *trans*/*cis* ratio and the *ee* were determined by GC analysis on a diethyl-*t*-butylsilyl β-cyclodextrin capillary column 25×0.25 mm operated at 60°C for 5 min, then programmed at 3°C min^{-1} to 160°C. [Retention times: 33.2 (1*S*,2*S*) and 33.5 (1*R*,2*R*) min for *trans* **4**; retention times: 31.4 (1*R*,2*S*) and 31.8 (1*S*,2*R*) min for *cis*-**5**].

3.3. Asymmetric hydrosilylation of acetophenone: typical procedure

The catalyst was prepared by dissolving the precursor $[Rh(cod)Cl]_2$ (10 mg, 0.02 mol) and the ligand (0.2 mmol) in acetophenone (1 ml, 8.5 mmol) under argon. Then the proper solvent (2 ml) was added and stirring was continued for 30 min (if $AgBF_4$ was added, the stirring time was 60 min). The mixture was cooled at 0°C and after 30 min diphenylsilane (1.6 ml, 8.6 mmol) was added. The solution was slowly warmed up to rt and then stirred for 24 h (Table 2) or for an appropriate length of time (Table 3). A sample was then taken (0.2 ml), diluted with $CDCl_3$ (0.4 ml) and a ^1H NMR (300 MHz) was recorded to determine the amount of silylenol ether (**16**/**15**+**16**), the degree of hydrosilylation (conversion of acetophenone, **15**+**16**/**14**+**15**+**16**) and the chemical yield of silylalkyl ether (**15**/**14**+**15**+**16**).[14] The following integrals were used for the analysis: $\delta = 5.70$ ppm (s, Si-H, silylenol ether **16**), $\delta = 5.40$ ppm (s, Si-H, silylalkyl ether **15**) and $\delta = 2.50$ ppm (s, CH_3, acetophenone **14**).

The mixture was diluted with methanol (10 ml) and treated with a few crystals of *p*-TsOH. After stirring at rt for 30 min the solvent was evaporated and the residue was distilled in a

Kugelrohr apparatus at 130°C/2 Torr. The enantiomeric excess (*ee*) was determined by GC analysis on a diethyl-*t*-butylsilyl β-cyclodextrin column operated at 60°C for 5 min, then programmed at 3°C min^{-1} to 150°C. Retention times: 23.75 min [(*R*)-1-phenylethanol] and 24.20 min [(*S*)-1-phenylethanol].

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