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Catalytic enantioselective cyclopropanation of olefins using *N*-salicylidene-4-amino[2.2]paracyclophane as an asymmetric ligand

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Abstract

The chiral ligand (±)-*N*-salicylidene-4-amino[2.2]paracyclophane (**1**) was synthesized and resolved. Resolved **1** was complexed to copper(II) for use as an asymmetric catalyst for the cyclopropanation of selected styrenes and stilbenes by diazoesters. Conversions of styrenes to cyclopropanes were high, typically > 90% but were less than 40% for the stilbenes. Enantioselectivity was observed for the cyclopropanation of all substrates used, ranging from 8% ee for 1,1-diphenylethylene with *t*-butyldiazoacetate to 41% for styrene with *t*-butyldiazoacetate. The origin of the differences in reactivity and enantioselectivity for this catalyst system with the different substrate/diazoester combinations is discussed with regard to a steric model.

Keywords: Chiral [2.2]paracyclophane derivatives; Chiral Schiff-base; *N*-Salicylidene copper(II) complexes; Asymmetric catalysis

1. Introduction

There has been an increasing interest in the use of chiral derivatives of [2.2]paracyclophane as chiral auxiliaries and ligands in asymmetric reactions [1–4]. The most noteworthy uses have been in the synthesis of β-hydroxy α-amino acids [2] and recently in the asymmetric hydrogenation of prochiral olefins [1]. In these examples moderate to high enantiomeric excesses were achieved showing that the chirality of disubstituted [2.2]paracyclophanes could be utilized to achieve enantioselectivity in reactions. To our knowledge the utilization of any monosubstituted [2.2]paracyclophane as an asymmetric ligand in catalytic cyclopropanation reactions has not been reported. Asymmetric cyclopropanation of prochiral olefins using chiral Schiff-base catalysts has received considerable attention [5,6] providing a useful system to test the use of *N*-salicylidene-4-amino[2.2]paracyclophane (**1**) as an asymmetric ligand. We report here on the synthesis, resolution [7], and utilization of **1** as an asymmetric ligand in the copper(II) catalyzed cyclopropanation of olefins with diazoesters.

2. Experimental

Benzene was distilled under nitrogen from CaH_2. Styrene and α-methylstyrene were ob-

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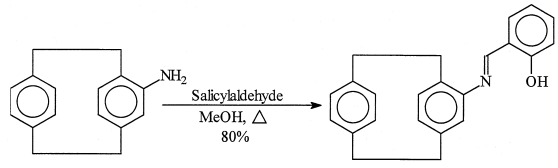
tained from Aldrich Chemical and filtered through neutral alumina prior to use. Triphenylethylene and *cis*-stilbene were obtained from Aldrich Chemical and used as received. *Trans*-4,4′-dimethylstilbene was prepared by a literature procedure [8]. ^{1}H NMR spectra were recorded on either a 300 or 400 MHZ Varian NMR spectrometer using chloroform as solvent, and referenced to residual solvent proton. Reaction conversions were determined by gas chromatography. Enantioselectivities were determined by HPLC using either a Chiracel AD or OJ column with 1:9 (vol/vol) *i*-PrOH/Hexanes as solvent. HPLC was performed using either a Shodex RI detector or a BioRad UV/Vis detector at 254 nm and an SSI pump. Melting points were determined using a Meltemp apparatus and are uncorrected. Optical rotations were determined using an Rudolph Research Autopol III polarimeter with methanol as solvent. Low-resolution mass spectra were obtained using a Hewlett Packard HP 5985 mass spectrometer. High resolution mass spectra (FAB) were obtained on a VG ZAB-E mass spectrometer using Xe atoms as the ionization source and 3-nitrobenzyl alcohol as the matrix. Ethyldiazoacetate (EDA) and *tert*-butyldiazoacetate (TBDA) were prepared by literature methods [9,10]. Cyclopropanation reactions were performed in dried glassware under an ultrahigh purity argon atmosphere.

2.1. Synthesis of (±)-N-salicylidene-4-amino[2.2]paracyclophane (1)

A 50 ml round bottom flask was charged with 0.3977 g of (±) 4-amino[2.2]paracyclophane (**2**) [11] (1.560 mmol), 0.2247 g of salicylaldehyde (1.830 mmol), and 20 ml of methanol. The flask was fitted with a reflux condenser and the mixture was heated to reflux solvent for 15 min. Solvent was removed under reduced pressure and the resulting solid was dissolved in a minimum amount of methanol and placed in a freezer overnight. Crystals of **1** as yellow clusters were collected and rinsed with cold methanol to yield 0.4100 g (1.250 mmol) of isolated product (80%). Mp: 126–126.5°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.80 (1H, m), 3.04 (4H, m), 3.20 (2H, m), 3.62 (1H, m), 6.01 (1H, s), 6.36 (1H, dd 2 Hz, 8 Hz), 6.50 (4H, m), 6.82 (1H, dd 2 Hz, 8 Hz), 6.96 (1H, t 8 Hz), 7.10 (1H, d 8 Hz) 7.40 (2H, m), 8.32 (1H, s), 13.82 (1H, s D_2O exchangeable). ^{13}C NMR (100 MHz, $CDCl_3$): δ 32.57, 34.22, 34.94, 35.25, 117.16, 119.05, 119.58, 125.27, 129.11, 131.63, 131.78, 132.01, 132.94, 133.39, 134.70, 134.88, 138.92, 139.76, 139.80, 141.84, 146.66, 160.85, 161.10. MS (70 eV): m/z 327.1 (M +), 223.1, 104.0. HRMS (FAB) m/z calc for $C_{23}H_{22}NO$ ($M + H^+$) 328.1701 found 328.1713. Resolution of (±) **1** was achieved on a semi-preparative Chiralcel AD column (1:9 *i*-PrOH/hexanes at 3.00 ml/min), R_t: (−)6.5 min, (+)8.5 min. $[\alpha]_D$: -236.3 ± 14.9 and 248.6 ± 13.4.

2.2. Typical cyclopropanation

A dried 100 ml round bottom flask was charged with 3.08 g of styrene (29.0 mmol), 48 ml of freshly distilled benzene, and 0.1 mol% preformed copper catalyst. The copper catalyst was prepared by stirring 19.3 mg of **1** with an excess of copper(II) acetate in methanol for 3 h, removing the methanol under reduced pressure, precipitating excess copper(II) acetate with toluene, filtering the toluene solution through celite and removing solvent under reduced pressure. The catalyst was used immediately without further purification. The cyclopropanation flask was fitted with a reflux condenser connected to an argon inlet and a mineral oil bubbler. The solution was heated to reflux the



Scheme 1.

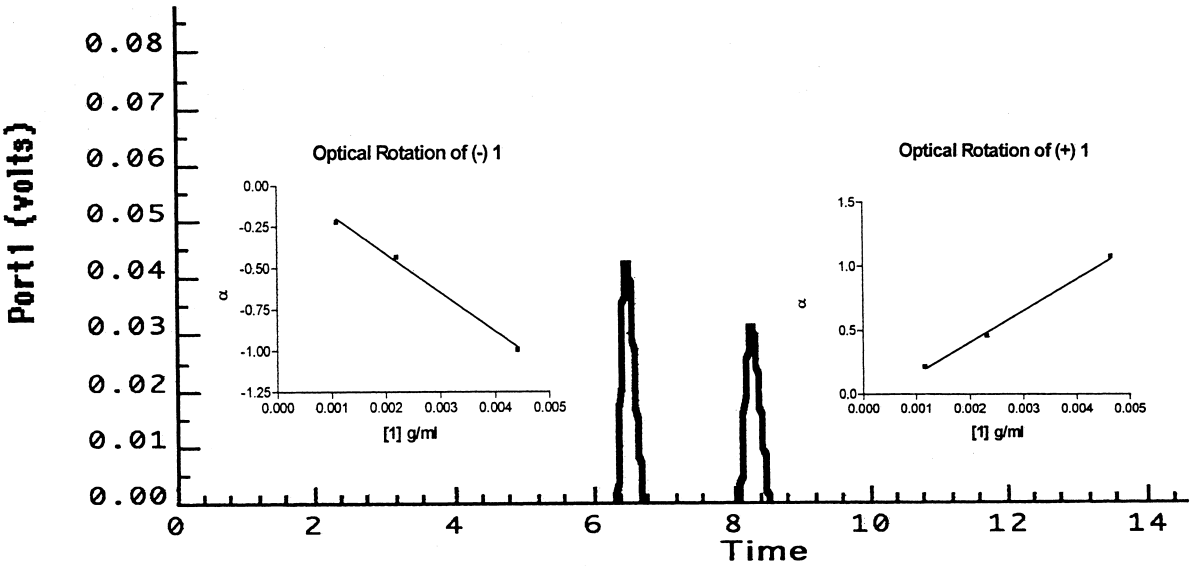


Fig. 1. HPLC chromatogram of (±) **1** and corresponding optical rotations.

solvent and 5.14 g (1.50 eq.) of ethyldiazoacetate (EDA), diluted to 20 ml with benzene, was added dropwise over a 5-h period using a syringe pump and stainless steel transfer needle. After the addition of EDA was complete, heating was continued an additional 30 min before the solution was cooled to room temperature. The resulting solution was filtered through a 6-in. neutral alumina column, using fresh benzene as eluent, to remove catalyst. All cyclopropane products were characterized by ^{1}H NMR, GC, GC/MS, and chiral HPLC.

3. Results and discussion

1 was synthesized by the condensation of salicylaldehyde with **2** in 80% yield (Scheme 1).

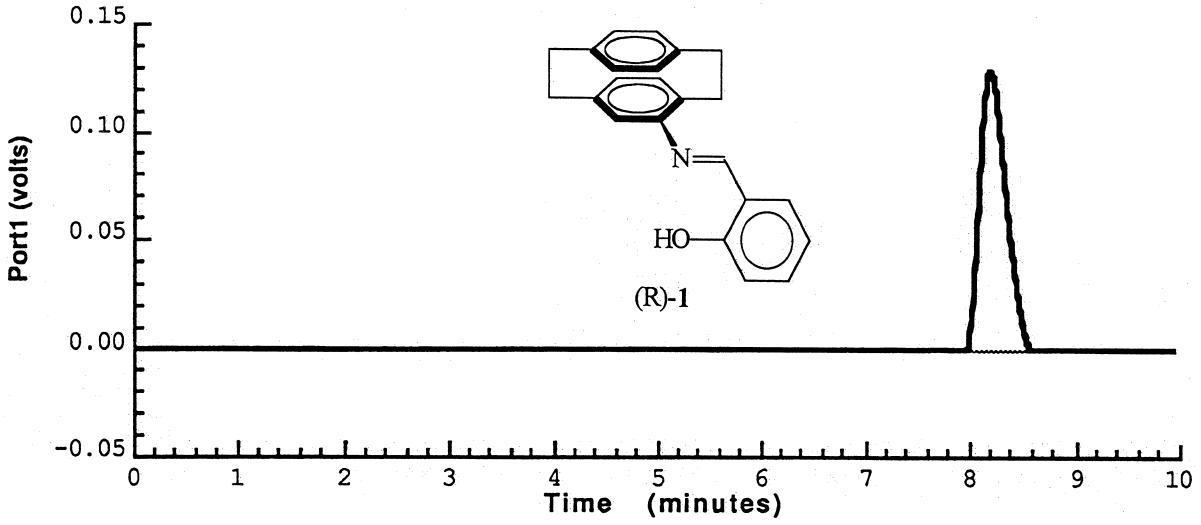
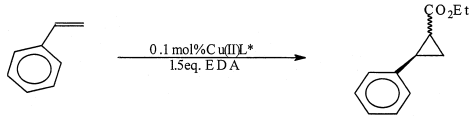


Fig. 2. (*R*)-1 and corresponding chiral HPLC chromatogram.



Scheme 2.

The enantiomers of **1** were cleanly resolved using chiral HPLC techniques (see Section 2) and their optical rotations were determined (see Fig. 1).

The absolute configuration of **1** was determined by preparing an authentic sample of (*R*)-4-amino[2.2]paracyclophane [12], condensing it with salicylaldehyde, and obtaining an HPLC chromatogram of (*R*)-**1**. Fig. 2 shows the resulting chromatogram illustrating that the (+) enantiomer of **1** is of the (*R*) configuration.

Compound **1** was complexed with copper(II) by stirring an appropriate amount of **1**, 0.2 mol% relative to substrate, with an excess of copper(II) acetate in methanol. The complex was worked up as described (see Section 2) to obtain a brown microcrystalline solid which was used without further purification.

Prior to using resolved **1** the cyclopropanation reaction conditions, such as catalyst loading, were optimized utilizing *N*-salicylidene-2,5-dimethylaniline (**3**) as an achiral model ligand [13]. The use of **3** gave racemic cyclopropane products which were utilized in screening chiral HPLC columns for resolution [14]. The optimum cyclopropanation conditions for styrene were determined to be as described for the typical cyclopropanation procedure (see Section 2). To the best of our knowledge the 0.1 mol% (based on copper(II)) catalyst loading is the smallest loading to date with a copper(II) Schiff-base catalyst system.

The copper(II) cyclopropanation catalyst derived from **1** was tested on two types of olefins; styrene derivatives and stilbene derivatives. A typical cyclopropanation is shown in Scheme 2.

The results from the cyclopropanation reactions are listed in Table 1.

It was observed that the styrene derivatives exhibited nearly quantitative reaction conversions, whereas the *cis*- and *trans*-stilbene derivatives had much lower conversion to product. The lower conversion for the *trans*-stilbene has been observed for other copper catalysts [16]. The lower yield for the stilbenes can be explained by a steric model similar to one previously reported [17] (see Fig. 3).

It was observed that the order of enantioselectivity, utilizing EDA, is as follows: styrene > α-methylstyrene > 1,1-diphenylethylene sug-

Table 1

Substrate	Diazoester[a]	Conversion (%)	*Cis*/*Trans*	*Trans*[b,c] (% ee)	*Cis* (% ee)
Styrene	EDA	96	1:2.4	27.4	12.7
α-Methylstyrene	EDA	91	1:1.8	18.2	13.5
1,1-Diphenylethylene	EDA	93	–	9.5[d]	–
1,1-Diphenylethylene	TBDA	70[e]	–	8.3[d]	–
Styrene	TBDA	96[e]	1:5.9	40.5	12.7
Cis-stilbene	EDA	37	1:4.9	–	–
Trans-stilbene	EDA	39	–	11.8[f]	–
Trans-4,4′-dimethylstilbene	EDA	32[g]	–	30[f,h]	–
Triphenylethylene	EDA	NR			

[a] EDA = ethyldiazoacetate, TBDA = *t*-butyldiazoacetate.
[b] Both *cis* and *trans* % ee was determined on a Chiracel OJ HPLC column.
[c] All reaction products were identified by ^{1}H NMR [15] and GC-MS.
[d] 2,2-Diphenylcyclopropanecarboxylate.
[e] Reaction conversion was determined by NMR.
[f] *Trans* configuration with respect to the phenyl rings.
[g] Reaction was performed using 10 mol% catalyst.
[h] % ee was determined on a Chiralcel AD HPLC column.

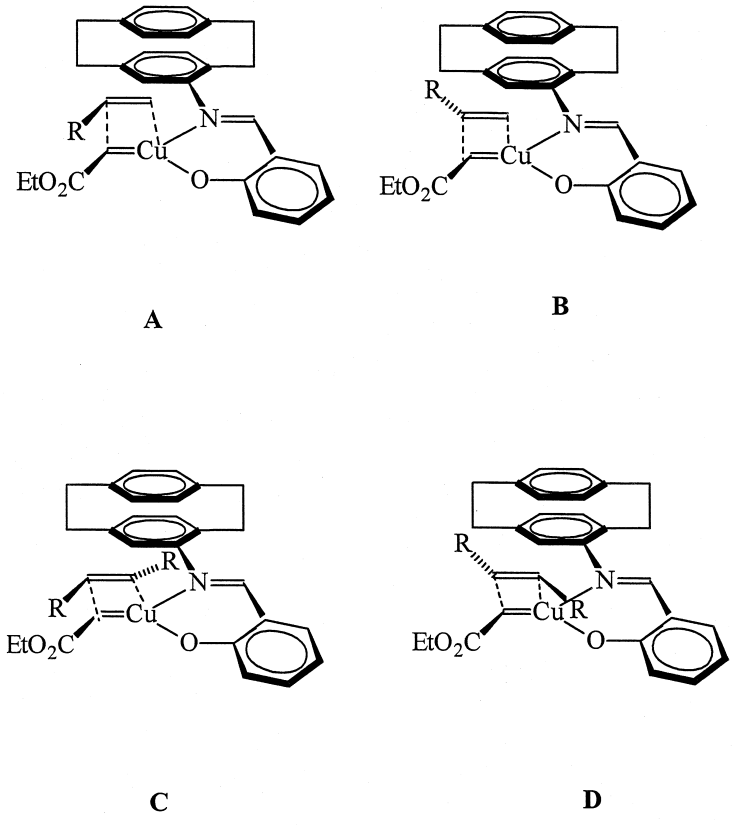


Fig. 3. Steric rationale for conversion and enantioselectivity.

gesting that olefin steric bulk and enantioselectivity are related. As the steric bulk of the olefin becomes more symmetrical the observed enantioselectivity decreases. The enantioselectivities that were observed in this series ranged from moderate to low. The cyclopropanation of styrene resulted in a *trans* percent ee of 27.4% and a *cis* percent ee of 12.7%, and the cyclopropanation of α-methylstryrene resulted in a *trans* percent ee of 18.2% and a *cis* percent ee of 13.5%. The best result was found to be the reaction of styrene with *tert*-butyldiazoacetate which resulted in a 40% ee for the *trans* isomer and a 12.7% ee for the *cis* isomer. This is a considerable improvement over the 27% ee obtained when EDA was used as the diazoester. The higher enantioselectivities that are observed for the *trans* isomers relative to the *cis* isomers is in agreement with previous reports [17,19] although the origin of this effect is uncertain. This increase in enantioselectivity is in agreement with other literature reports of increased percent ee with bulkier diazo compounds [19]. In the case of the styrene derivatives all observed diasteromeric ratios were similar to those reported in the literature for other copper(II) Schiff-base catalyst systems [5]. With regard to the model shown in Fig. 3, it should be noted that the actual conformation(s) available to the active catalyst must allow for *trans*-cyclopropane products to form preferentially.

From the steric interactions shown in Fig. 3, it is hypothesized that the styrene derivatives are able to orient themselves in such a manner

as to minimize steric congestion with the cyclophane moiety. Molecular mechanics calculations [18] suggest that the cyclophane moiety can rotate easily about the cyclophane–nitrogen bond giving rise to a number of possible conformations. Taking the orientations as shown in Fig. 3 as being representative of the chiral environment, A is lower in energy than B since A places the phenyl group away from the bulky cyclophane moiety. The *trans*-stilbene derivatives cannot adopt such an orientation with respect to the cyclophane. C and D illustrate that both possible orientations for *trans*-stilbene have similar steric interactions, both of which place a phenyl group in close proximity to the cyclophane moiety. This is believed to be the reason why the *trans*-stilbene derivatives experience a lower conversion to product, relative to the styrene derivatives, under identical reaction conditions. The low reactivity of the *cis*-stilbene is more difficult to explain. Based on the model depicted in Fig. 3, the low reactivity of the *cis*-stilbene suggests that the aromatic ring of the ligands salicylidene moiety has some steric interaction with the phenyl ring of the non-planar *cis*-stilbene which is comparable to the interaction of one of the phenyl rings in the *trans*-stilbene with the ligand cyclophane moiety. Cyclopropanations using cyclophane ligands with substituted salicylidene groups will help clarify this situation.

The cyclopropanation of *trans*-stilbene with EDA resulted in a percent ee of 11.8%. This low enantioselectivity is in agreement with the proposed model in Fig. 3. The possible orientations for *trans*-stilbene, C and D, are of similar energy. With C and D being of similar energy, there is no significant preference for one orientation over the other which results in reduced enantioselectivity. A moderate enantioselectivity of 30% was observed for the cyclopropanation of *trans*-4,4′-dimethylstilbene (at 10 mol% catalyst). The methyl groups of *trans*-4,4′-dimethylstilbene introduce an additional steric interaction with the bridging methylenes of the cyclophane resulting in an increased enantioselectivity relative to *trans*-stilbene. It was observed that the *trans* configuration was maintained in the cyclopropanation reaction of *trans*-stilbene, and the *cis* configuration was maintained in the cyclopropanation of *cis*-stilbene. This retention of configuration suggests that the reaction is a non radical process, as is expected from previous studies of the cyclopropanation mechanism [20].

The low to moderate enantioselectivities may be attributed to a non-rigid framework of **1**. Given that the molecular mechanics calculations suggest that rotation of the cyclophane moiety in **1** can take place easily [18], it is likely that a fixed conformation of the catalyst does not exist. The cyclophane may rotate in such a way as to minimize steric interactions with the olefin resulting in an overall reduction in enantioselectivity.

4. Conclusions

In conclusion it has been shown that 4-amino[2.2]paracyclophane **2** can be easily transformed into a Schiff-base ligand by condensing with salicylaldehyde. It has been demonstrated that **1** can be cleanly resolved using chiral HPLC techniques in quantitative recovery, and that the $(+)$ enantiomer is of the (R) configuration. We have shown that the copper(II) complex of **1** does induce enantioselectivity in the cyclopropanation reaction of all olefins tested. Even though the enantioselectivities that were observed are moderate, it was nonetheless a vast improvement relative to those of other copper(II) Schiff-base systems [5]. This improvement in enantioselectivity seems to suggest that monosubstituted cyclophane ligands similar to **1** can be engineered to show enhanced enantioselectivity. We will report in the near future on attempts to improve the enantioselectivity in these systems by restricting the number of possible conformations that the cyclophane moiety can adopt.

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