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Catalytic enantioselective cyclopropanation of styrene derivatives using *N*-(2′,4′-di-*tert*-butyl) salicylidene-4-amino[2.2]paracyclophane as an asymmetric ligand

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Abstract

The synthesis and resolution of *N*-(2′,4′-di-*tert*-butyl)salicylidene-4-amino[2.2]paracyclophane and its utilization in the copper catalyzed enantioselective cyclopropanation of aromatic olefins is reported herein. Conversions of up to 90% and enantioselectivities of $>65\%$ have been achieved for selected olefins.

Keywords: [2.2]paracyclophane; Chiral Schiff-base; Asymmetric cyclopropanation; Copper catalyst

The use of chiral derivatives of [2.2]paracyclophane in asymmetric synthesis has recently received considerable attention [1–4]. Although there has been an increase in use of cyclophane ligands in general, few examples have been reported on their use as ligands for the asymmetric cyclopropanation reaction [5,6]. We have recently reported on the successful use of *N*-salicylidene-4-amino[2.2]paracyclophane (**1**), Fig. 1, as a chiral ligand in the copper catalyzed cyclopropanation of various aromatic olefins [7]. Enantioselectivities of up to 40% ee were obtained when **1** was used as the ligand in the copper-catalyzed cyclopropanation of styrene with *tert*-butyldiazoacetate. However, the fact that significant enantioselectivity was observed for all the olefins tested led us to believe that the use of modified chiral [2.2]paracyclophane derivatives would offer improved enantioselective copper-catalyzed cyclopropanation of olefins with diazoesters. The strategy of adding bulk around a metal center to improve enantioselectivity has proven successful in other metal-catalyzed asymmetric reactions [8]. In an attempt to improve enantioselectivity in the copper-catalyzed cyclopropanation of aromatic olefins with diazoesters using substituted [2.2]paracyclophanes as asymmetric ligands, we decided to add additional bulk around the copper center in hopes of creating a more effective "chiral pocket". Few highly effective salicylaldimine ligand-based cyclopropanation catalysts [9,10] have been reported since the historic

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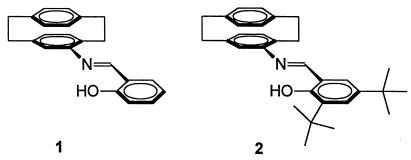
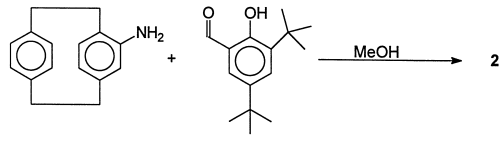


Fig. 1. Salicylaldimine ligands derived from 4-amino[2.2]paracyclophane. Ligands drawn with the (*S*) configuration.

results of Nozaki et al. [11]. Although Aratani et al. [12] reported the effective cyclopropanation of isobutylene and 2,5-dimethyl-2,4-hexadiene using modified salicylaldimine copper dimer catalysts, our interest in the cyclopropanation of aromatic olefins, such as styrene, and defining the chiral inductive ability of the [2.2]paracyclophane moiety prompted us to construct a ligand system more directly comparable to that of Nozaki et al. We wish to report here the results of the synthesis and use of *N*-(2′,4′-di-*tert*-butyl)salicylidene-4-amino[2.2]paracyclophane (**2**) as a chiral ligand in the copper-catalyzed enantioselective cyclopropanation of aromatic olefins.

Ligand **2** was synthesized as shown in Scheme 1. A round-bottom flask was charged with 6.0 ml of methanol, 45.0 mg (2.02E − 4 mol) of 4-amino[2.2]paracyclophane (**3**) [13], and 44.0 mg of 2,4-di-*tert*-butylsalicylaldehyde (**4**) (prepared using 2,4-di-*tert*-butylphenol as outlined in Ref. [14]) and the resulting solution was heated to reflux solvent for 15 h. The resulting solution was cooled to room temperature and the solvent was removed under reduced pressure to obtain a yellow solid that was subsequently chromatographed on a silica gel column with low boiling petroleum ether as eluent (isolated yield 73%). Ligand **2** was characterized by ^{1}H and ^{13}C NMR and was efficiently resolved into its enantiomers by chiral HPLC chromatography on a semi-preparative Chiralcel AD column.[1] The absolute configuration of the enantiomers of **2** was determined by the condensation of (*R*)-4-amino[2.2]paracyclophane [15] with **4** followed by chiral HPLC analysis of the resulting (*R*)-**2**. Ligand **2** was complexed with copper(II) in situ as previously described [7]. The cyclopropanation reactions were performed at 0.1 mol% catalyst loading in refluxing benzene with slow diazoester addition under an argon atmosphere [7].

Ligand **2** was evaluated for the copper-catalyzed cyclopropanation reaction using a variety of styrene and stilbene derivatives as shown in Table 1. It is immediately apparent from Table 1 that the enantioselectivity for ligand **2** is an improvement over ligand **1** (the largest %ee value for **1** being 40%). The *cis*/*trans* selectivity, as presented in Table 1, is similar to the selectivity which was observed for **1** and other copper catalyzed cyclopropanations using Schiff base ligands [16]. When the more bulky TBDA was used as diazoester a significant increase in *trans* selectivity was observed as is expected [17]. Reaction conversions were moderate to excellent for the styrene derivatives when **2** was utilized as the chiral ligand. However, when *trans*-stilbene was utilized as the substrate no conversion to product was observed. The more reactive *cis*-stilbene also gave a low conversion to cyclopropane product. The stilbene derivatives suffer from steric congestion as shown in Fig. 2. Unlike the styrene derivatives, *trans*-stilbene is unable to adopt an orientation for which there is no steric interference between a phenyl ring of the stilbene and either the [2.2]paracyclophane moiety or the *tert*-butyl group located in the ortho position of the phenolic moiety of **2**. Like the *trans*-stilbene, *cis*-stilbene is also unable to adopt an orientation which relieves steric congestion on the [2.2]paracyclophane moiety or the ortho *tert*-butyl group resulting in reduced reactivity when **2** is utilized as the ligand. These observations of reactivity for the stilbene derivatives suggest that the added *tert*-butyl groups add significant steric interactions between the



Scheme 1. Synthesis of ligand **2**.

[1] ^{1}H NMR (300, $CDCl_3$): δ 1.34 (s, 9H), 1.54 (s, 9H), 2.80–3.70 (m, 8H), 6.0 (s, 1H), 6.35 (d, j = 7hz, 1H), 6.53 (m, 4H), 6.84 (d, j = 7hz, 1H), 7.20 (d, j = 3hz, 1H), 7.47 (d, j = 3hz, 1H), 8.33 (s, 1H), 14.01 (bs, D_2O exchangeable, 1H). ^{13}C NMR (75, CDC13): δ 29.55, 31.68, 32.77, 34.26, 34.30, 35.04, 35.28, 35.34, 118.60, 125.26, 126.49, 127.66, 128.99, 131.10, 131.71, 132.84, 133.34, 134.54, 134.69, 136.92, 138.80, 139.82, 140.37, 141.57, 146.82, 158.19, 161.82. Chiral HPLC (Chiralcel analytical column, 10% i-PrOH/hexanes at 1.0 ml/min): 4.50 min (*S*) enantiomer and 5.40 min (*R*) enantiomer. High resolution MS 439.2875 calcd, 439.2860 found.

Table 1

Substrate	Diazoester[a]	%Conversion[b]	*Cis / trans*[b]	%ee *Trans*[c]	%ee *Cis*[c]
Styrene	EDA	57	1:1.9	67.1	61.2
Styrene	TBDA	71	1:3.1	67.8	53.6
Styrene	DDM	75	–	"8.5" [d](*S*)[e]	
α-Methylstyrene	EDA	90	1:1.3	48.3	8.0
1,1-DPE[f]	EDA	70	–	"4.0" [d]	–
1,1-DPE	TBDA	70	–	"3.5" [d]	–
trans-Stilbene	EDA	NR	–	–	–
cis-Stilbene	EDA	19	1:7.4[g]	–	–

[a] EDA = ethyldiazoacetate,TBDA = *tert*-butyldiazoacetate,DDM = diethyldiazomalonate.
[b] Determined by gas chromatography.
[c] Determined by chiral HPLC (Chiralcel OJ column).
[d] The terms *cis* and *trans* are irrelevant.
[e] (*S*) configuration was obtained by cyclopropanation using the (*S*)-**2** ligand. The %ee and absolute configuration was determined by optical rotation of the dimethylester derivative.
[f] 1,1-Diphenylethylene.
[g] Refers to endo/exo ratio.

catalyst and substrate. It should be noted that the actual conformation(s) around the carbenoid center must allow for the *trans* cyclopropane products to form preferentially and that olefin approach can occur from both carbenoid faces.

In an attempt to better understand the origin of the enantioselective induction of ligand **2**, (*S*)-**2** was used as the ligand in the cyclopropanation of styrene with diethyldiazomalonate (DDM) (synthesized from diethyl malonate using a diazo transfer reaction) [18]. The cyclopropane product that was obtained was subjected to basic hydrolysis followed by treatment with diazomethane to yield the dimethyl ester derivative. The dimethyl ester derivative was subjected to polarimetry [19] that revealed a %ee of 8.5% and the major product had the (*S*) absolute configuration. Fig. 3 illustrates how the (*S*)-cyclopropane product results from the cyclopropanation of styrene with DDM when the (*S*)-**2** is utilized as the ligand. The (*S*) cyclopropane product can result from olefin approach from the less hindered "bottom" face of the putative catalytically active species [16]. The model shown in Fig. 3 is consistent with the putative catalytic species shown in Fig. 2.

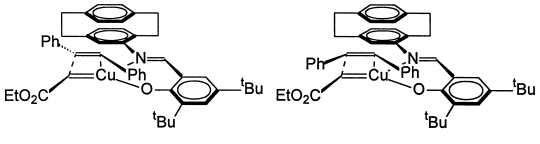


Fig. 2. Rationale for low reaction conversion of stilbene derivatives.

In conclusion, we have demonstrated that ligand **2** is an improvement over ligand **1** and Nozaki's original chiral Schiff-base ligand (%ee of $< 10\%$) [11] in the copper-catalyzed cyclopropanation of styrene derivatives with diazoesters. Interestingly, replacing the chiral phenethylamine unit of Nozaki's ligand with the more bulky 4-amino[2.2]paracyclophane unit dramatically increases the enantioselectivity of the resulting cyclopropane products showing that the [2.2]paracyclophane is more effective with regard to chirality transfer. The order of enantioselectivity for styrene derivatives is observed to be styrene > α-methylstyrene > 1,1-diphenylethylene, which suggests that enantioselectivity is decreased as the substituent bulk on the olefins becomes more symmetrical. The improvement in enantioselectivity could

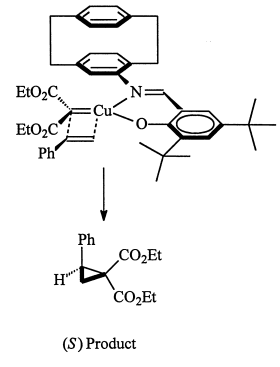


Fig. 3. Rationale for (*S*)-cyclopropane formation from (*S*)-catalyst.

potentially be due to the added steric bulk of the ortho *tert*-butyl group located on the phenolic moiety of ligand **2**, or the increased enantioselectivity could be due to the electronic effects of the ortho and para *tert*-butyl groups. The results as presented here suggest that cyclophane ligands can be constructed which give improved results over ligand **1**, and we will report in the future on other structural/electronic variants of **1** and **2** that will be used to determine the cause of the increased enantioselectivity of ligand **2**.[2]

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