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N-(4-[2.2]paracyclophanyl)-2′-hydroxyacetophenone imine: An effective paracyclophane Schiff-base ligand for use in catalytic asymmetric cyclopropanation reactions

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ABSTRACT

The synthesis of planar chiral N-(4-[2.2]paracyclophanyl)-2′-hydroxyacetophenone imine (**5**) and its use as a ligand for the copper(II) catalyzed cyclopropanation of styrene and stilbene derivatives using diazoesters is presented. Catalyst loadings of 0.1 mol% gave conversions of >80% (turnover numbers approaching 1000) for styrene and its derivatives. When enantiomerically enriched (R)-**5** was used to form the catalyst for cyclopropanation of styrene using ethyldiazoacetate, the cyclopropane products were obtained in a *trans*/*cis* ratio of 1.9–1 and 75.8% and 60.5% ee (corrected), respectively. The use of *t*-butyldiazoacetate resulted in an increased *trans*/*cis* ratio of 4.6–1 and 88.2% and 77.9% ee, respectively. Enantioselectivities of up to 95% ee were observed. These are among the highest enantioselectivities observed for asymmetric reactions using catalysts where chirality is solely derived from the paracyclophanyl moiety. When compared to its non-methylated analog, the simple presence of a methyl group on the carbon of the imine moiety in **5** resulted in an average increase in enantioselectivity of ca. 60% ee for a variety of substrates. The origin of this dramatic improvement in selectivity is discussed.

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1. Introduction

Since the seminal work of Pye and co-workers on the use of chiral bisphosphino[2.2]paracyclophane ligands for the catalytic asymmetric hydrogenation of pro-chiral alkenes in high enantiomeric excess (ee) [1], there has been continual interest in the use of non-racemic [2.2]paracyclophane derivatives as sources of planar chirality in asymmetric transformations. Chiral catalysts have been constructed from asymmetric [2.2]paracyclophanes and used in a variety of different reactions [2–5], mainly for asymmetric 1,2- and 1,4-addition reactions to carbonyls [2,3,6,7] and asymmetric hydrogenations [1,8,9]. However, the vast majority of these [2.2]paracyclophane-based ligands incorporate a second, non-[2.2]paracyclophane-derived chiral center around the active catalytic site in the ligand construction in order to obtain high ee's. Aside from the bisphosphine-type [2.2]paracyclophane catalysts [1,8,9], and a few other notable exceptions [10,11], chiral [2.2]paracyclophane ligands have not generally achieved high ee's stemming from the planar chirality of the [2.2]paracyclophane moiety alone; most ee's in such cases being low to moderate. The development of highly effective [2.2]paracyclophane ligands where the catalytic asymmetric induction clearly arises solely from the cyclophane moiety, is therefore of considerable interest, both synthetically and from a ligand design perspective.

Attempts at constructing highly effective asymmetric cyclopropanation catalysts using [2.2]paracyclophane moieties as the sources of chirality have proven difficult. Vogtle et al. have published the synthesis and use of novel bipyridine ligands based on the [2.2]pyridinophane unit (**1**) and the [2.2]quinolinophane unit (**2**) (Fig. 1) [12,13]. However, ligands **1** and **2** required a lengthy construction of the chiral paracyclophane scaffold and the asymmetric induction of **1** and **2** with respect to the copper catalyzed cyclopropanation of styrene with ethyldiazoacetate was low (∼26% ee). Previous studies using N-salicylidene-4-amino[2.2]paracyclophane (**3**) as a chiral ligand in the copper(II) catalyzed cyclopropanation of styrene with diazoesters resulted in moderate enantioselectivities (40% ee for the *trans* isomer) [14]. Ligand **3** proved to be highly substrate and diazoester sensitive with respect to the % ee of the resulting cyclopropane products (for select results see Table 1B). Adding steric bulk in the form of *tert*-butyl groups to the salicylidene moiety improved the enantioselectivity of the cyclopropanation reactions [15]. Using N-(2′,4′-di-*tert*-butyl)salicylidene-4-amino[2.2]paracyclophane (**4**) as the

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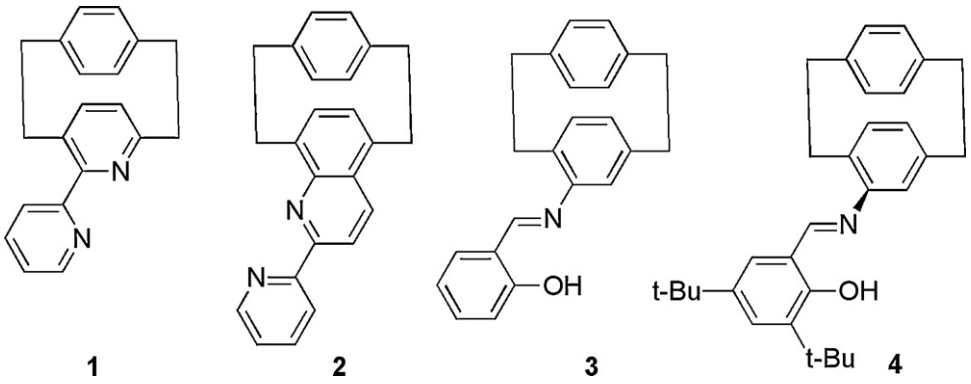


Fig. 1. Chiral cyclophanes used as ligands for catalytic cyclopropanation.

asymmetric ligand resulted in a 67% ee for the cyclopropanation of styrene (*trans* isomer) [15]. Although **4** proved to give better results than **3** in terms of the % ee of the products, **4** was also very substrate sensitive.

It was suspected that for the pyridineophane ligands **1** and **2** the low % ee's that were observed in the cyclopropane products were probably due to a relatively open, planar lower face resulting in cyclopropanation with little chiral discrimination. In ligands **3** and **4** the low to moderate % ee's observed were likely due primarily to rotation of the cyclophane unit about the aromatic-N bond resulting in conformations with relatively open reaction sites [14]. Molecular models suggested that replacing the imine hydrogen in ligand **3** with a methyl group would hinder rotation of the chiral cyclophane unit significantly and potentially increase enantioselectivity with respect to the cyclopropane products. Few highly enantioselective cyclopropanations have been performed using salen-type ligands [16,17] since the historic asymmetric cyclopropanation reaction of Nozaki et al. [18,19], which utilized a copper(II)-based salen-type catalyst system, and the related pioneering work of Aratani [20,21]. Herein we report the synthesis of the title compound (**5**), a salen ligand, which gave results directly comparable to those of Nozaki et al. (see Fig. 2), and its effective use as a ligand in the copper-catalyzed, asymmetric cyclopropanation of various substrates. The simple addition of a methyl group to the imine moiety in cyclophane ligand **3** resulted in a dramatic 2- to 7-fold increase in % ee's of the products, achieving high % ee's for most substrates. Ligand **5** is easily synthesized from the readily available [2.2]paracyclophane (**6**), thus alleviating any lengthy construction of the paracyclophane scaffold.

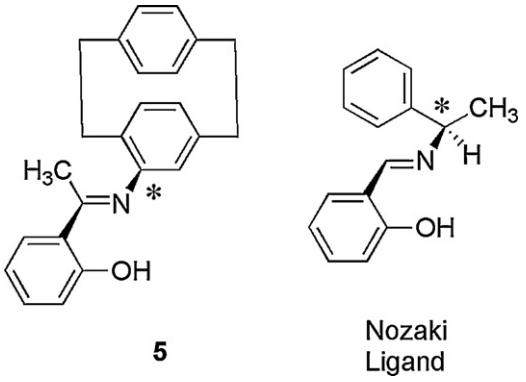


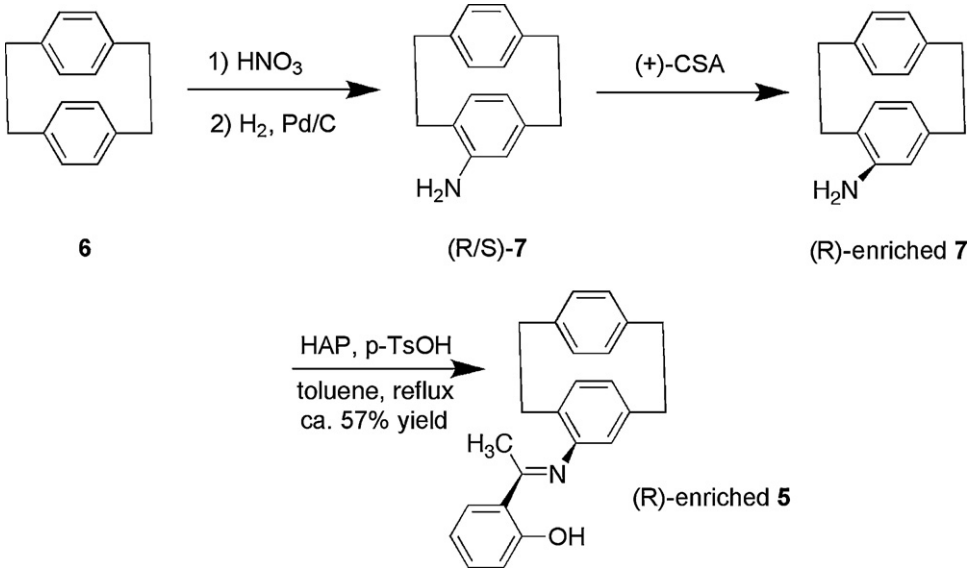
Fig. 2. Visual comparison of (R)-**5** with Nozaki's ligand.

2. Experimental

Cyclopropanation reactions were performed as previously described [14]. Enantiomerically enriched (R)-4-amino[2.2]paracyclophane was prepared as described in the literature [22]. 2-Hydroxyacetophenone was obtained from Aldrich Chemical Company, Inc. and used as received. ^{1}H NMR spectra were recorded on a Varian Unity 400 MHz spectrometer, ^{13}C NMR spectra were recorded on a Varian XL300 spectrometer and the spectra were referenced to internal solvent resonances. The enantiomeric purity of (R)-**5** and cyclopropane products was determined using a Chiralcel OJ HPLC column with either a BioRad UV/Vis detector at 254 nm and SSI pump system or an HPLC APCI MS system.

2.1. Synthesis of (R)-5

A 50 mL pear shaped flask was charged with 0.378 g (1.69 E^{-3} mol) of enriched (R)-4-amino[2.2]paracyclophane, ca. 20 mg of p-TsOH, 20 mL of toluene, and a stir bar. The flask was fitted with a Hickman still and a reflux condensor and the resulting solution was heated to reflux solvent. After all the water was removed azeotropically from the reaction vessel, fresh toluene was added to bring the volume to 20 mL. The solution was again heated to reflux solvent and 0.249 g (1.83 E^{-3} mol) of 2-hydroxyacetophenone was added by syringe over a 30 min period. The resulting solution was heated to reflux solvent overnight. The Hickman still was removed and activated 4 A molecular sieves were added and the solution was heated to reflux solvent an additional 24 h. The resulting yellow mixture was filtered through a 1 in. pad of neutral alumina which was subsequently washed with fresh toluene. The solvent was removed under reduced pressure to obtain 0.3295 g (9.650 E^{-4} mol) of crude (R)-**5** (~57% yield). The crude (R)-**5** was dissolved in 10 mL of boiling methanol, cooled to room temperature, and hexanes were added until the solution became cloudy. This cloudy mixture was placed in a freezer for 48 h and the solid (R)-**5** microcrystals were collected and rinsed with cold hexanes. The % ee of (R)-**5** was determined using an analytical Chiralcel OJ column (1:9 i-PrOH/hexanes at 1.00 mL/min; (*S*)-**5** 18 min, (*R*)-**5** 23 min). The % ee was determined to be 86.3% by HPLC. MP (racemic): 178–179.5 °C. ^{1}H NMR (400, $CDCl_3$): δ 2.18 (3H,s), 2.93–2.99 (1H, m), 3.06–3.23 (8H, m with 1 D_2O exchangeable proton), 5.76 (1H, s), 6.44–6.53 (4H, m), 6.60–6.62 (1H, dd 2 Hz, 8 Hz), 6.90 (1H, t, 7 Hz), 7.10 (2H, d 8 Hz), 7.41 (1H, t, 7 Hz), 7.60 (1H, d 8 Hz). ^{13}C NMR (75 MHz, $CDCL_3$): δ 17.46, 32.33, 34.25, 35.08, 35.41, 118.09, 118.21, 119.67, 127.68, 128.80, 128.99, 130.07, 132.06, 132.27, 132.79, 133.10, 133.30, 134.90, 138.97, 139.58, 140.84, 143.98, 162.21,



Scheme 1. Synthesis of (R)-5 from [2.2]paracyclophane (**6**). CSA, HAP, and p-TsOH stand for 10-camphorsulfonic acid, 2-hydroxyacetophenone, and *para*-toluenesulfonic acid, respectively.

169.95. HRMS (FAB): *m*/*z* calcd for $C_{24}H_{24}NO$ ($M+H^+$) 342.1858 found 342.1873.

Due to its low solubility, completely resolved (R)-**5** was not readily available. Nonetheless, several milligrams of (R)-**5** were resolved further on a semi-preparative Chiralcel OJ column (1:9 i-PrOH) in a lengthy process. The sample was determined by Chiral HPLC to be >99% R. This sample was used to perform a cyclopropanation (see Table 1) as a check of the validity of correction method for calculating reaction ee's (vide infra).

3. Results and discussion

The title compound (R)-**5** was constructed as shown in Scheme 1. The key step of Scheme 1 is the previously reported treatment of racemic 4-amino[2.2]paracyclophane (**7**) with (+)-10-camphorsulfonic acid (CSA) to obtain enantiomerically enriched (R)-7 [22]. Enriched (R)-**7** was condensed with 2-hydroxyacetophenone (**8**) in the presence of p-TsOH to produce the title compound (R)-**5**. After recrystallization, (R)-**5** was subjected to chiral HPLC analysis which revealed a 86.3% enantiomeric purity. The solubility of **5** in solvents appropriate for further chiral HPLC resolution was very low. However, since the title compound (R)-**5**, produces a putative single site catalyst upon complexation with copper(II), it was decided to use the ligand without further resolution and to correct the % ee of the cyclopropane products for the %ee of the ligand (R)-**5** [23]. A small amount of highly resolved (R)-**5** was isolated and used for one cyclopropanation reaction to confirm that use of this correction provided valid results. In principal, enantiomerically pure **5** could be obtained by using completely resolved **7**. The synthetic route shown in Scheme 1 has the advantage that the construction of the [2.2]paracyclophane moiety is unnecessary, which gives rise to a simple and rapid construction of salen-type ligand **5**.

It was initially suspected that **5** would be more structurally rigid with respect to the metal center to the cyclophane moiety than ligands **3** and **4**. Molecular modeling suggested that rotation about the cyclophane–nitrogen bond would be restricted due to interactions of the methyl group in **5** with the ethano bridges of the cyclophane moiety (Fig. 3), causing it to rotate in an *exo* fashion to the exterior of the cyclophane. Further *exo* rotation of the methyl group eventually brings the methyl group into close proximity with the aromatic hydrogens in the *ortho*, *pseudo-ortho*, and *pseudo-gem* positions relative to the imine nitrogen on the paracyclophane moiety. It is therefore likely that the global minimum energy conformation of **5** is one in which the methyl group is *exo*, causing the 2′-hydroxyacetophenone imine functionality involved in complexation to favor an *endo* conformation, and resulting in the catalytic metal center residing in a more sterically demanding environment. Although a similar qualitative analysis can be made for the corresponding ligand **3**, the expected amplification of the conformational effects by replacing the hydrogen on the imine carbon with a methyl group suggested that enantioselectivities for cyclopropanations using ligand **5** to form the copper catalyst would improve relatively.

Enriched (R)-**5** was complexed with copper(II) and used in the copper catalyzed cyclopropanation reaction of various substrates with both ethyldiazoacetate (EDA) and *tert*-butyldiazoacetate (TBDA). The results of the cyclopropanation reactions using enriched (R)-**5** are presented in Table 1A and the % ee's are corrected for the % ee of ligand (R)-**5** [23]. Included for comparison in Table 1B are selected cyclopropanation results using ligand **3** [14].

When styrene (**9**) was used as the substrate (Table 1A, entry 1), and (R)-**5** as the ligand, an ee of 75.8% was obtained for the *trans* isomer and a 60.5% ee was obtained for the *cis* isomer. This is a dramatic improvement over ligand **3** as shown in Table 1B, entry 7. When the non-methylated ligand **3** was used as the ligand in the cyclopropanation of styrene with EDA an ee of 27.4% was obtained for the *trans* product and the *cis* product showed an ee of 12.7%. The cyclopropanation of α-methylstyrene (**10**) with EDA using ligand (R)-**5** gave an ee of 84.3% for the *trans* product and a 95.0% ee for the *cis* product. When methyl substituted (R)-**5** was used in the cyclopropanation

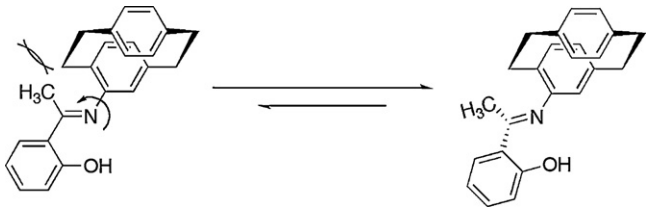


Fig. 3. Steric interaction of the imine methyl group with an ethano paracyclophane bridge in ligand **5**.

Table 1A
Cyclopropanations using ligand **5**.

Entry	Substrate	Diazoester[a]	% Conv.[b]	Turnover #[c]	*Trans*/*Cis*	% ee *Trans*[d]	% ee *Cis*[d]
1	Styrene	EDA	93	929	1.9:1	75.8	60.5
2	Styrene	TBDA	81	807	4.6:1	88.2	77.9
3	α-Methylstyrene	EDA	86	858	3.3:1	84.3	95.0
4	α-Phenylstyrene	EDA	85	847	–	74.4[e]	–
5	Trans-stilbene	EDA	20	202	–	23.4[e] 23.8[e,f]	–
6	Cis-stilbene	EDA	22	220	16.8:1[g]	–	–

[a] EDA, ethyldiazoacetate; TBDA, *tert*-butyldiazoacetate.
[b] Determined by gas chromatography.
[c] Calculated using the following equation: (mole olefin × % conversion)/mole catalyst.
[d] Determined using a Chiralcel OJ HPLC analytical column and the % ee was corrected for the % ee of the ligand using the following equation: (observed ee/ligand ee) × 100.
[e] The terms *cis* and *trans* are irrelevant.
[f] Run using >99% (R)-**5** to check validity of *d*.
[g] Refers to exo/endo ratio.

Table 1B
Results using ligand **3** [14].

Entry	Substrate	Diazoester	% Conv.	Turnover#	*Trans*/*cis*	% ee *Trans*	% ee *Cis*
7	Styrene	EDA	96	960	2.4:1	27.4	12.7
8	Styrene	TBDA	96	960	5.9:1	40.5	12.7
9	α-Methylstyrene	EDA	91	910	1.8:1	18.2	13.5
10	α-Phenyl styrene	EDA	93	930	–	9.5[a]	–
11	Trans-stilbene	EDA	39	390	–	11.8[a]	–

[a] The terms *cis* and *trans* are irrelevant.

reaction of α-phenylstyrene (Table 1A, entry 4), an ee of 74.4% was obtained. When α-phenylstyrene was used as the substrate in the catalytic cyclopropanation reaction using non-methylated ligand **3**, the resulting cyclopropane product was obtained in less than 10% ee. It is clear from the results presented in Table 1A that the ability of **5** to induce enantioselectivity in the cyclopropane products is a substantial improvement over ligands **1**–**4**. It is possible that the improved enantioselectivity in the cyclopropanation reaction using ligand **5** could be due in part to the electronic effects of the electron donating methyl substituent. However, the improved enantiomeric induction of **5** is largely attributable to restricted rotation about the cyclophane–nitrogen bond as discussed earlier. Restricted rotation prevents the bulky chiral cyclophane unit from orienting itself away from the catalytic copper center, allowing it to efficiently transfer its chiral information to the resulting cyclopropane products.It is also worth noting that the conversions of substrate to product were quite good when (R)-**5** was used as the ligand. Table 1A illustrates that conversions were typically >80% for the styrene derivatives, with turnover numbers approaching 1000 (catalyst loading 0.1 mol%). The advantage of low catalyst loadings is that unwanted diazo coupling products are not detected in these reactions. To the best of our knowledge this is the lowest catalyst loading used for a salen-type ligand. Substituting the chiral phenethylamine unit in Nozaki's original ligand with the more bulky chiral 4-amino[2.2]cyclophane has a dramatic effect on the % ee of the resulting cyclopropane products (Fig. 2). The cyclopropanation of styrene with EDA in the presence of Nozaki's ligand resulted in ee's less than 10% for both the *cis* and *trans* cyclopropane products [18], whereas salen ligands **3** and **5** resulted in much improved enantioselectivities (Tables 1A, entry 1 and 1B, entry 7). This shows that the simple chiral [2.2]paracyclophanyl moiety can be much more effective in chiral induction compared to the chiral phenethylamine unit of Nozaki's ligand and is indicative of the potential for the sterically demanding [2.2]paracyclophanyl unit to construct highly effective chiral ligands for asymmetric catalysis.

4. Conclusion

It has been demonstrated that **5** can be readily constructed from commercially available [2.2]paracyclophane and 2-hydroxyacetophenone and that **5** can be used as a ligand for copper-catalyzed asymmetric cyclopropanation of styrene derivatives. The simple substitution of a methyl group for the imine hydrogen of **3** makes the cyclophane ligands much more effective for asymmetric induction. Cyclopropanations of styrenes run using **5** as a ligand showed a dramatic average increase of 60% ee (2- to 8-fold increases in % ee) compared to those run with ligand **3**. Ligand **5** was also less substrate sensitive with respect to enantioselectivity while maintaining a good catalytic turnover. We have grown crystals of ligands **3** and **5** and are currently carrying out X-ray crystal structure analysis to obtain exact atom coordinates for computational studies of the conformation differences between **3** and **5**. These studies, together with spectroscopic studies of **3** and **5** in solution to elucidate the exact nature of the factors behind the dramatic increase in asymmetric induction with ligand **5**, are ongoing.

Acknowledgments

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