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Electrophilic Substitution of Dibromoparacyclophane: A Route to Novel Paracyclophane Phosphine Ligands

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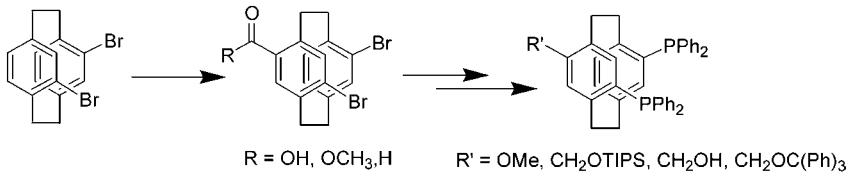
ABSTRACT



The regioselective functionalization of 4,12-dibromoparacyclophane via electrophilic aromatic substitution is reported for the first time. The functionalization of the paracyclophane backbone allows the development of a new family of paracyclophane-based phosphines (named ParaPhos) that opens the possibility of improved catalyst development and tuning while retaining all the catalysis potential of the PhanePhos family of ligands.

The [2.2]paracyclophane backbone offers a number of interesting opportunities to synthetic chemists in their quest for ever new and more efficient ligands for asymmetric catalysis.[1] The general reactivity of [2.2]paracyclophanes was extensively studied by Cram et al. in the late 1960s,[2] but it has only been in the last 10 years that paracyclophane-based ligands have been prepared and applied in asymmetric catalysis. The planar chiral diphosphine PhanePhos (**1**) (Figure 1) provides the most impressive success story in this area.[3]

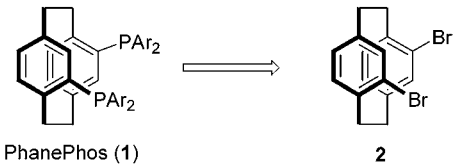


Figure 1. PhanePhos ligand.

The synthesis of PhanePhos (**1**) was originally reported by Rossen and Pye in 1997, and since then the ligand has proven its efficacy in rhodium-catalyzed hydrogenation of dehydroamino acids,[3] allylic acids,[4] palladium-catalyzed amination,[5] ruthenium-catalyzed hydrogenation of β-ketoesters,[6] enantioselective hydroboration of cyclopropenes,[7] and more recently the "Noyori-type" ruthenium-catalyzed hydrogenation of unfunctionalized ketones.[8,9]

The common precursor of all PhanePhos derivatives is 4,12-dibromo[2.2]paracyclophane (**2**) (Figure 1). Formation of the Grignard reagent and reaction with diphenylphosphinyl chloride yields the phosphine oxide that is subsequently resolved with dibenzoyl tartaric acid to give PhanePhos (**1**).[3] The potential for industrial use shown by this class of ligands

(1) Gibson, S. E.; Knight, J. D. *Org. Biomol. Chem.* **2003**, *1*, 1256.
(2) (a) Reich, H. J.; Cram, D. J. *J. Am. Chem. Soc.* **1969**, *91*, 3505. (b) Reich, H. J.; Cram, D. J. *J. Am. Chem. Soc.* **1969**, *91*, 3517. (c) Reich, H. J.; Cram, D. J. *J. Am. Chem. Soc.* **1969**, *91*, 3527.
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(4) Boulton, L. T.; Lennon, I. C.; McCague, R. *Org. Biomol. Chem.* **2003**, *1*, 1094.
(5) Rossen, K.; Pye, P. J.; Maliakal, A.; Volante, R. P. *J. Org. Chem.* **1997**, *62*, 6462.
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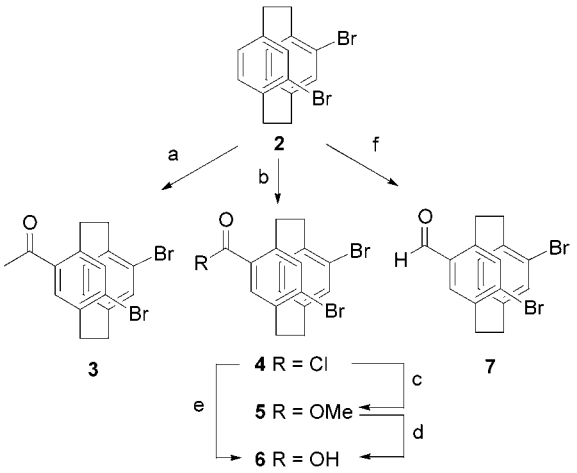
prompted us to undertake an investigation of the reactivity of 4,12-dibromo[2.2]paracyclophane (**2**) toward electrophilic substitution. Our research had the following aims: (i) Improving the efficiency of the synthesis of the paracyclophane-based phosphines by the introduction of an early stage resolution step. By doing so, we would gain the advantage of obtaining all the phosphine derivatives from an enantiomerically pure common precursor. (ii) Expanding the range of the available phosphines by the introduction of substituents with different electronic properties on the paracyclophane backbone, possibly breaking the C_2 symmetry of the ligand.

In his original reports of macrorings, Cram described the transannular directive influences in electrophilic substitution of monosubstituted [2.2]paracyclophanes.[2] Very little has been reported, however, on the reactivity of 4,12-dibromo-[2.2]paracyclophane (**2**), except for being involved in the tetrabromination[10] and tetrabromomethylation[11] of paracyclophane, both requiring long reaction times and leading to mixtures of regioisomers. It might be expected that **2** would be deactivated toward Lewis acid electrophilic substitution. To test this, we subjected **2** to a range of Lewis acid-catalyzed electrophilic substitution reactions.[12]

In our initial experiment, acetyl chloride was added to a solution of **2** and $AlCl_3$ at −45 °C and allowed to warm to room temperature (Scheme 1). This led to smooth conversion

Scheme 1 [a]



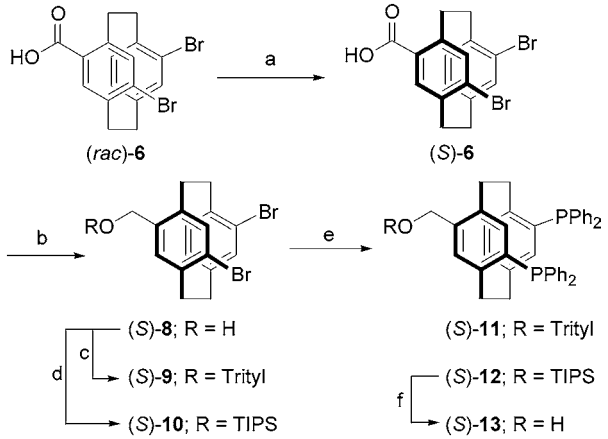
[a] Reagents and conditions: (a) $AlCl_3$, CH_3COCl, CH_2Cl_2, −45 °C to rt, 70%; (b) $AlCl_3$, oxalyl chloride, CH_2Cl_2, −10 °C to rt; (c) MeOH, 0 °C to rt, 79% from **2**; (d) LiOH, MeOH, H_2O, 100 °C, 95%; (e) H_2O, THF, 80% from **2**; (f) $TiCl_4$, Cl_2CHOCH_3, CH_2Cl_2, 0 °C to rt, 85%.

to the monoacetyl dibromide paracyclophane **3** in high yield. To our surprise, the reaction produced substitution exclusively in the position para to one of the bromine atoms. No disubstitution was detected even in the presence of excess Lewis acid. This result was tentatively explained by considering the inductive effect of the further deactivated aromatic ring on the second aromatic ring.

Replacement of acetyl chloride with oxalyl chloride led to the synthetically more useful acyl chloride **4**. The acyl chloride **4** was hydrolyzed in water/THF to give the acid **6** or reacted with methanol to give ester **5**. The purification of the methyl ester **5** was somewhat easier, and the compound could be readily converted to the free acid **6** by ester hydrolysis. The formyl derivative **7** was obtained by reaction of **2** with $TiCl_4$ and α,α-dichloromethyl methyl ether in again excellent yield and with completely regioselective substitution at the para position (Scheme 1).[13] These reactions were carried out on racemic dibromide **2**, but we have found that they can also be performed on the chiral dibromide[5] without any racemization.

When the electrophilic substitution is carried out on racemic **2**, the introduction of the carboxylic functional group lends itself to the potential of a classical resolution of the monoacid dibromide **6**. As indicated earlier this would dramatically improve the efficiency of the synthesis of paracyclophane-based ligands. To test this hypothesis, compound **6** was subjected to a number of chiral bases. In the presence of (−)-cinchonidine, classical resolution of acid **6** was achieved to give 52% yield of the (*S*)-enantiomer in >97% ee after two recrystallizations (Scheme 2).[14] The lower

Scheme 2 [a]



[a] Reagents and conditions: (a) (i) (−)-Cinchonidine, EtOH, 90 °C; (ii) recrystallization from EtOH; (iii) 10% aqueous HCl, CH_2Cl_2, 52%, ee > 97%. (b) $BH_3{\cdot}SMe_2$, THF, 45 °C, 96%. (c) Trityl chloride, DBU, CH_2Cl_2, 91%. (d) TIPSOTf, lutidine, CH_2Cl_2, 94%. (e) *t*BuLi, Ph_2PCl, Et_2O or THF, −78 °C to room temperature, 80% for **11**, 66% for **12**. (f) TBAF, THF, 70%.

ee batches were combined and recycled to provide further amounts of enantiopure (*S*)-**6**. The crystallization in the

(8) (a) Noyori, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 2008. (b) Noyori, R.; Ohkuma, T. *Angew Chem., Int. Ed.* **2001**, *40*, 40.

(9) Burk, M. J.; Hems, W. P.; Herzburg, D.; Malan, C.; Zanotti-Gerosa, A. *Org. Lett.* **2000**, *2*, 4173.

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(12) During the course of our work, an example of dinitration of 4,12-dibromo[2.2]paracyclophane (**2**) was published: Braddock, D. C.; MacGilp, I. D.; Perry, B. G. *Synlett* **2003**, 1121.

presence of quinine of the enantiomerically enriched (*R*)-acid obtained from the mother liquors yielded the (*R*)-enantiomer in >97% ee.[15] X-ray analysis of the salt allowed us to confirm both the absolute stereochemistry of compound **6** and the regiochemistry of the electrophilic substitution (Figure 2).

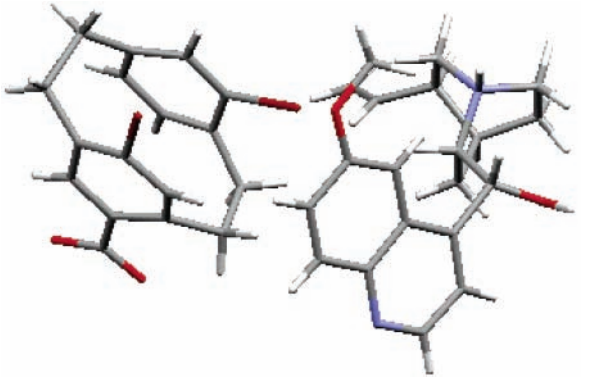
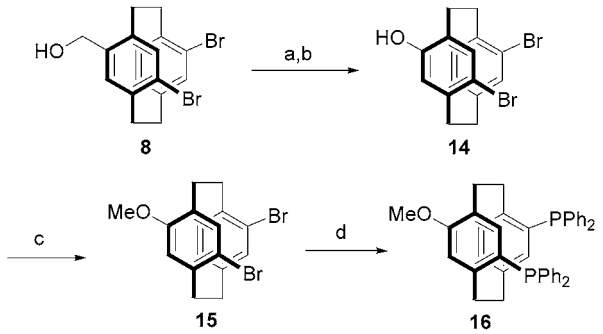


Figure 2. Crystal structure of the quinine salt of (*R*)-**6**.

The new functionalized dibromides were then transformed into the corresponding phosphines (Scheme 2). The enantiomerically pure acid **6**, obtained either by classical resolution or by electrophilic aromatic substitution on enantiomerically pure dibromide **2**, was reduced to the benzylic alcohol **8** via a high-yielding borane reduction. To avoid unwanted side reactions during the following step, involving reaction with *t*BuLi, the free alcohol was protected with the trityl group (compound **9**) or the triisopropyl silyl group (TIPS, **10**). Both substrates **9** and **10** could be cleanly lithiated with *t*BuLi and reacted with chlorodiphenylphosphine to produce ligands **11** and **12**. While the direct synthesis of the phosphine ligand **13** from the benzylic alcohol proved to be more challenging, the same ligand was readily obtained from deprotection of the TIPS derivative **12** with tetrabutylammonium fluoride (TBAF).

A parallel synthetic pathway was also developed with the formyl derivative **7** (Scheme 3). This compound was obtained by electrophilic substitution (Scheme 1) or, alternatively, by the high-yielding oxidation of the benzylic alcohol **8**. Compound **7**, in its enantiomerically pure form, was subjected to a Baeyer−Villiger oxidation using *meta*-chloroperbenzoic acid (mCPBA) to give an intermediate formate derivative that was subsequently hydrolyzed in situ to

Scheme 3 [a]

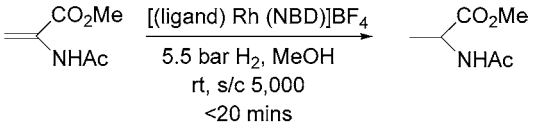


[a] Reagents and conditions: (a) MnO_2, CH_2Cl_2, 96%; (b) mCPBA, CH_2Cl_2, 75%; (c) NaH, MeI, THF, 88%; (d) *t*BuLi, Ph_2PCl, THF, −78 °C to room temperature, 86%.

produce the phenolic derivative **14**. Methylation to **15** was achieved by treatment with sodium hydride and methyl iodide. The derived phosphine ligand **16** was then obtained by our standard synthetic procedure in good yield. This new ligand was designed to increase the electronic differential between the rings of the paracyclophane backbone.

With the synthesis of these novel paracyclophane phosphines in hand, we sought to begin a preliminary investigation of their performance in homogeneous asymmetric hydrogenation. To this end, the rhodium catalysts were prepared by reaction of the free ligands with $[Rh(NBD)_2]$-BF_4 (NBD = 2,5-norbornadiene) and tested against a standard substrate, methyl *N*-acetamido acrylate, at a molar substrate-to-catalyst ratio (s/c) of 5000 (Table 1). All the

Table 1. Asymmetric Hydrogenation of Methyl Acetamido Acrylate Using Rhodium Catalysts



entry	precatalyst	conversion (%)[a]	ee (%)[a]
1	[(*S*)-**1** Rh NBD]BF_4	100	96.7 (*S*)[b]
2	[(*R*)-**1** Rh NBD]BF_4	100	96.4 (*R*)[b]
3	[(*S*)-**11** Rh NBD]BF_4	100	97.0 (*S*)
4	[(*S*)-**12** Rh NBD]BF_4	100	95.0 (*S*)
5	[(*R*)-**13** Rh NBD]BF_4	100	96.8 (*R*)
6	[(*S*)-**16** Rh NBD]BF_4	100	96.0 (*S*)

[a] Determined by GC analysis on Chirasil Dex-CB. [b] Ee > 99% reported in ref 3 was obtained at s/c 100 under atmospheric pressure of hydrogen.

reactions were very fast, and the results underlined the substantial equivalence of the new class of phosphines in terms of catalytic efficacy with the ligand PhanePhos (**1**).

The application of the new ligands to ruthenium-catalyzed hydrogenation of aromatic ketones turned out to be as successful as for the related ligand PhanePhos (**1**). The

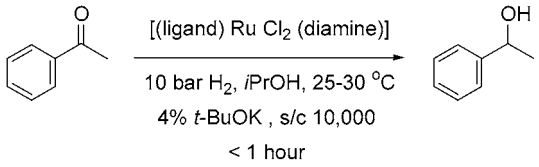
(13) Rozenberg, V. I.; Antonov, D. Y.; Sergeeva, E. V.; Vorontsov, E. V.; Starikova, Z. A.; Fedyanin, I. V.; Schulz, C.; Hopf, H. *Eur. J. Org. Chem.* **2003**, 2056.

(14) Stereochemistry assigned as in ref 1 and: Pye, P. J.; Rossen, K. *Tetrahedron*: *Asymmetry* **1998**, *9*, 539.

(15) Treatment of racemic **6** with quinine in refluxing EtOH, followed by recrystallization of the obtained salt, allowed the separation of enantiopure (*R*)-**6** (>97% ee). However, in our hands, the chiral resolution of acid **6**, when done in multigram scale, worked more effectively following the procedure described in the text. The mother liquors of each recrystallization were combined, concentrated, and recrystallized to minimize the loss of material (see Supporting Information for full details).

ruthenium catalysts of the type [(ligand)$RuCl_2$(DPEN)] (DPEN = 1,2-diphenylethylenediamine) were prepared according to standard procedures.[9] As reported in Table 2, the

Table 2. Asymmetric Hydrogenation of Acetophenone Using Ruthenium Catalysts



entry	precatalyst	conversion (%)[a]	ee (%)[a]
1	(*R*)-**11** Ru Cl_2 (*S*,*S*)DPEN	100	99.2 (*R*)
2	(*R*)-**12** Ru Cl_2 (*S*,*S*)DPEN	100	98.5 (*R*)
3	(*R*)-**13** Ru Cl_2 (*S*,*S*)DPEN	100	99.3 (*R*)
4	(*S*)-**16** Ru Cl_2 (*R*,*R*)DPEN	100	98.6 (*S*)

[a] Determined by GC analysis on Chirasil DEX-CB

hydrogenation of acetophenone proceeded at s/c 10 000 displaying excellent selectivity and activity comparable to those obtained with the PhanePhos ligands.

At the beginning of this research we sought to extend the range and availability of paracyclophane-based phosphines having in mind the possibility of differentiating the two aromatic rings of the paracyclophane backbone and/or introducing a tool for further modification of the properties of the ligands. We have achieved this goal via regioselective Lewis acid-catalyzed electrophilic substitution of 4,12-dibromo[2.2]paracyclophane (**2**). All the steps involved in the synthetic pathways here described are high-yielding and require minimal purification of the crude products, therefore making this chemistry a promising starting point for the industrial use of the derived phosphine ligands. The new ParaPhos ligands display, as expected, an excellent degree of activity and selectivity in the hydrogenation of standard test substrates such as methyl *N*-acetamidoacrylate and acetophenone. Work is ongoing to explore the new possibilities opened by the functionalization of the paracyclophane backbone in terms of ligand stereoelectronic tuning.

Acknowledgment. We thank Fred Hancock for much encouragement in this venture, Dr. John E. Davies (University of Cambridge) for the X-ray analysis of compound **6**, and Dr. Laure Guy (Ecole Normale Supérieure de Lyon) for help in the crystallization study.

Supporting Information Available: Crystallographic details of **6**, experimental procedures and NMR characterization data for all new compounds described in the text. This material is available free of charge via the Internet at http://pubs.acs.org.

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