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Practical Optical Resolution of Planar Chiral Pseudo-*ortho*-disubstituted [2.2]Paracyclophane

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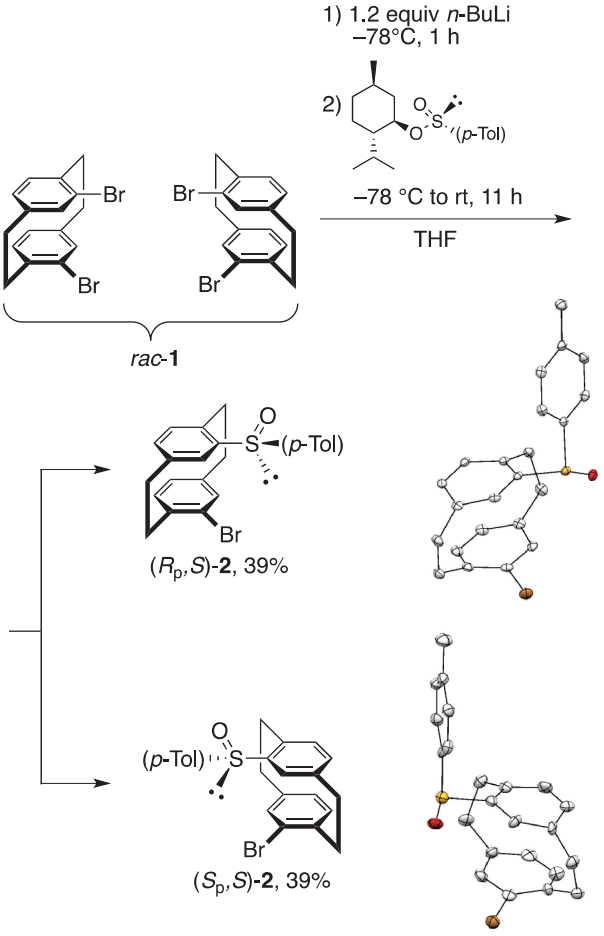
We describe the practical optical resolution of *rac*-pseudo-*ortho*-dibromo[2.2]paracyclophane to obtain the parent compound for a variety of cyclophane-based planar chiral compounds such as enantiopure chiral ligand [2.2]PHANEPHOS. In addition, the obtained enantiopure planar chiral (*R*)- and (*S*)-pseudo-*ortho*-disubstituted [2.2]paracyclophanes can be used as the building blocks for optically active carbon-rich compounds.

Planar chirality is one of the unique features of mono- and polysubstituted cyclophanes.[1] In contrast to conformationally flexible chiral molecules possessing an axis of rotation and a rotatable bond around a stereogenic center, cyclophanes have planar chirality, which suppresses the rotation of the aromatic rings and affords a conformationally stable chiral space. Therefore, the configuration and orientation of the functional groups in a cyclophane skeleton can be controlled precisely. Since the 1990's, various methods for the optical resolution of planar chiral [2.2]paracyclophanes have been developed,[1–6] and the optically active [2.2]paracyclophane derivatives have been mainly used as chiral auxiliaries in the field of organic and organometallic chemistry.[1b,5,6a,6b,7–9]

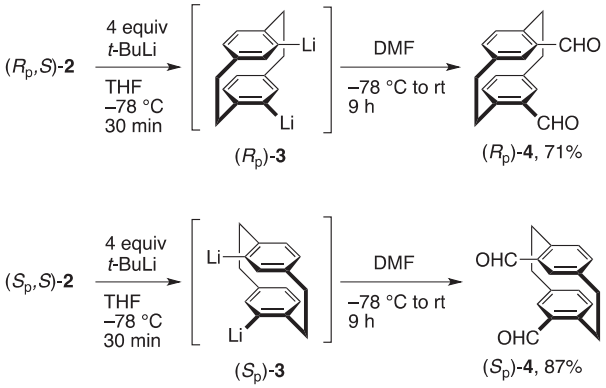
Optical resolutions of mono-substituted [2.2]paracyclophanes are well-established, and various enantiopure *ortho*-, pseudo-*geminal*-, and *syn-latero*-disubstituted [2.2]paracyclophanes have been synthesized.[3–5] With respect to pseudo-*ortho*-disubstituted [2.2]paracyclophanes, several optical resolution methods have been reported.[6] Optical resolution of *rac*-pseudo-*ortho*-bis(diarylphosphino)[2.2]paracyclophane (*rac*-[2.2]PHANEPHOS) by cocrystallization with a tartaric acid derivative is a successful example from the view point of application;[6a] planar chiral (S_p)- and (R_p)-[2.2]PHANEPHOS are commercially available and widely used as chiral ligands for transition-metal-catalyzed asymmetric reactions. [$Pd_2(dba)_3$]/[2.2]PHANEPHOS-catalyzed amination of *rac*-pseudo-*ortho*-dibromo[2.2]paracyclophane enables its kinetic resolution,[6b] and the obtained enantioenriched pseudo-*ortho*-dibromo[2.2]paracyclophane is the parent compound for planar chiral [2.2]paracyclophanes. Optical resolution of *rac*-4-bromo-12-hydroxy-[2.2]paracyclophane,[6c] *rac*-pseudo-*ortho*-dihydroxy[2.2]paracyclophane (*rac*-PHANOL),[6d] and *rac*-pseudo-*ortho*-dihydroxymethyl[2.2]paracyclophane[6e] was achieved by converting them to camphanic acid esters using chiral camphanic acid chlorides. The enzyme-catalyzed kinetic resolutions of *rac*-pseudo-*ortho*-disubstituted [2.2]paracyclophanes have also been reported.[6f–6h]

The potential applications of [2.2]paracyclophane derivatives in other fields such as polymer chemistry and material chemistry[10,11] necessitate the need for the further development and modification of practical resolution methods for pseudo-*ortho*-disubstituted [2.2]paracyclophanes. We believe that a facile method for the optical resolution of *rac*-pseudo-*ortho*-disubstituted [2.2]paracyclophanes is separation of the diastereomers. We have attempted to use a combination of pseudo-*ortho*-disubstituted [2.2]paracyclophanes and chiral resolving reagents to obtain the parent compound for a variety of cyclophane-based planar chiral compounds and materials. Herein, we report the optical resolution of *rac*-pseudo-*ortho*-dibromo[2.2]paracyclophane; the obtained enantiopure compound is the parent compound for the synthesis of various planar chiral pseudo-*ortho*-disubstituted [2.2]paracyclophane compounds.

Optical resolution of commercially available *rac*-pseudo-*ortho*-dibromo[2.2]paracyclophane (*rac*-**1**)[12] was carried out as shown in Scheme 1.[13] Treatment of *rac*-**1** with 1.1 equivalent of *n*-BuLi and (1*R*,2*S*,5*R*)-(−)-menthyl (*S*)-*p*-toluenesulfinate[14] caused conversion of one of the bromo groups into a sulfinyl



Scheme 1. Optical resolution of *rac*-**1**. For clarity, all hydrogen atoms are omitted (ellipsoids are drawn at 30% probability).



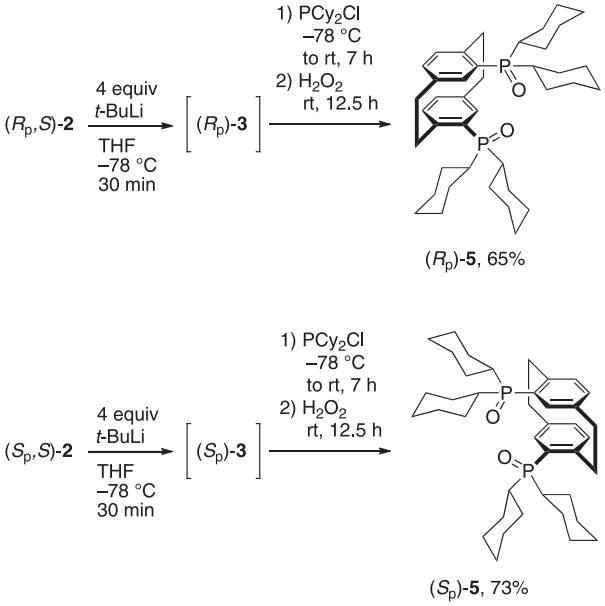
Scheme 2. Lithiation of (R_p,*S*)-**2** and (S_p,*S*)-**2**, and subsequent reaction with electrophile.

group. The resulting compound was readily purified by conventional silica gel column chromatography to obtain diastereomers (R_p,*S*)-**2** and (S_p,*S*)-**2** (each in 39% isolated yield). The molecular structures and absolute configurations of (R_p,*S*)-**2** and (S_p,*S*)-**2** were confirmed by X-ray crystallography (Scheme 1).

The main reason for introducing the sulfinyl group into the cyclophane skeleton is to ensure that the sulfinyl–lithium exchange reaction readily proceeds upon treatment with alkyllithium reagents, as demonstrated by Rowlands and co-workers.[4,15,16] The reaction of (R_p,*S*)-**2** with 4 equiv *t*-BuLi afforded the (R_p)-pseudo-*ortho*-dilithio[2.2]paracyclophane intermediate (R_p)-**3**, which could react with various electrophiles. Thus, it was apparent that (R_p,*S*)-**2** and (S_p,*S*)-**2** are the parent compounds for planar chiral (R_p)- and (S_p)-pseudo-*ortho*-disubstituted [2.2]paracyclophanes, respectively. For example, (R_p)-**3** was allowed to react with DMF, an electrophile, to obtain (R_p)-pseudo-*ortho*-diformyl[2.2]paracyclophane (R_p)-**4** in 71% isolated yield (Scheme 2). The enantiomer (S_p)-**4** was also obtained in 87% isolated yield by the same procedure from (S_p,*S*)-**2**.

Another synthetic application of the present optical resolution and transformation is demonstrated by the following reaction. Treatment of (R_p)-**3** (obtained from (R_p,*S*)-**2**) with chloro(dicyclohexyl)phosphine and subsequent oxidation with H_2O_2 afforded the enantiopure (R_p)-4,12-bis(dicyclohexylphosphino)[2.2]paracyclophane (cyclohexyl–PHANEPHOS) dioxide (R_p)-**5** in 65% isolated yield, and (S_p)-**5** was obtained in 73% isolated yield from (S_p,*S*)-**2** (Scheme 3). In this study, the phosphorus atoms of cyclohexyl–[2.2]PHANEPHOS were oxidized in situ with H_2O_2 for easy handling. As mentioned above, chiral ligand [2.2]PHANEPHOS has been prepared by cocrystallization with a tartaric acid derivative; therefore, despite its usefulness in organic as well as organometallic chemistry, only two kinds of [2.2]PHANEPHOS, phenyl–PHANEPHOS[6a] and xylyl–PHANEPHOS,[17] have prevailed.[18] Thus, the present method provides a new route to enantiopure [2.2]-PHANEPHOSs[6a,17–19] via simple nucleophilic substitutions, even if diastereomeric cocrystallization with a tartaric acid derivative is unsuccessful.

In summary, we developed a method for the optical resolution of commercially available *rac*-pseudo-*ortho*-dibromo[2.2]paracyclophane.[20] The resulting enantiopure compound could be the parent compound for the synthesis of various planar chiral pseudo-*ortho*-disubstituted [2.2]paracyclophane com-



Scheme 3. Synthesis of (R_p)- and (S_p)-cyclohexyl[2.2]-PHANEPHOS.

pounds such as pseudo-*ortho*-diformyl[2.2]paracyclophane and [2.2]PHANEPHOS via simple nucleophilic substitution. Pseudo-*ortho*-diformyl[2.2]paracyclophanes can be converted and used as the chiral building blocks for optically active three-dimensional conjugated carbon-rich compounds.

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