

# Multigram-Scale Kinetic Resolution of 4-Acetyl[2.2]Paracyclophane *via* Ru-Catalyzed Enantioselective Hydrogenation: Accessing [2.2]Paracyclophanes with Planar and Central Chirality

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*Dedicated to Professor Henri Kagan on the occasion of his 90<sup>th</sup> birthday.*



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**Abstract:** [2.2]Paracyclophane (PCP) derivatives have been promising platforms to study the element of planar chirality and through-space electronic communications in  $\pi$ -stacked molecular systems. To access enantiomerically pure derivatives thereof, a kinetic resolution of 4-acetyl[2.2]-PCP employing a ruthenium-catalyzed enantioselective hydrogenation process was developed. This method can be performed on a multigram-scale and gives access to enantiomerically pure derivatives with planar and central chirality of (*R<sub>p</sub>*)-4-acetyl-PCP ( $\geq 97\%$  *ee*, 43%) and (*S<sub>p</sub>*)-PCP derivatives ( $\geq 97\%$  *ee*, 46%), which are useful intermediates for the synthesis of sterically demanding PCP-based ligand/catalyst systems and chiral synthons for engineering cyclophane-based chiroptical materials.

**Keywords:** Kinetic Resolution; Asymmetric Hydrogenation; Planar Chirality; [2.2]Paracyclophane

PCP is a co-facially stacked prevalent carbocyclic scaffold, exhibits distinct stereochemical features

(planar chirality) on regioselective functionalization,<sup>[1]</sup> for which it has been studied as a potential planar chiral ligand or chiral catalyst in stereo-controlled and enantioselective transformations of prochiral and racemic substances.<sup>[2]</sup> Beyond ligand or catalyst design, optically active PCPs have been largely utilized in materials dealing with chirality and through-space electronic communication e. g., in  $\pi$ -stacked conjugated polymers<sup>[3]</sup> and organic chiroptical materials.<sup>[4]</sup> One of the main focuses of cyclophane research centers on the molecular engineering of parylene-derived materials *via* chemical vapor deposition (CVD) polymerization that finds vast applications in biology and materials science.<sup>[5]</sup>

To access enantiomerically pure PCP derivatives, regioselective functionalization and chiral resolution strategies pose certain synthetic challenges due to the unusual reactivity of PCP which is a result of transannular effects (the short distance between the two co-facially stacked strongly interacting benzene rings causes abnormalities). This can be a tedious endeavor, especially when larger quantities of enantiomerically pure PCPs are needed.<sup>[6]</sup>

Classical chiral resolution of PCP derivatives is mainly achieved by the formation of diastereomers,

followed by separation – either *via* fractional crystallization or chromatography. These classical resolution techniques are well established for a variety of key compounds but require stoichiometric amounts of enantiopure derivatizing agents or chiral auxiliaries, are a tedious process, and often give moderate yields.<sup>[8]</sup> Hence, developing efficient and scalable routes towards enantiopure PCP scaffolds are highly desirable to diversify modern cyclophane chemistry. Herein, we report a kinetic resolution method *via* ruthenium-catalyzed enantioselective hydrogenation that offers significant practical advantages, comparing to the previously reported classic resolution strategies, for tailoring the PCP scaffold with efficient enantioselective control on a multi-gram scale (Scheme 1, bottom). The resulting products can be readily transformed into a wide variety of other enantiopure PCP synthons to showcase their utility in developing planar chiral ligands and engineering chiral materials such as chiral thin films and surface coatings.

A more elegant and practical, but less common way to separate the enantiomers of PCP, is a kinetic resolution that relies on the different reaction rates of the enantiomers with a chiral catalyst. Asymmetric hydrogenation pioneered by Noyori and Knowles, followed by considerable advances in recent years, gave access to highly stereo-controlled and enantioselective processes.<sup>[9]</sup> Benedetti, Micouin, and coworkers have demonstrated a ruthenium-based asymmetric transfer hydrogenation protocol for the kinetic resolution of 4-formyl [2.2]paracyclophane (**1**) on 1 g scale (Scheme 1, top).<sup>[7b]</sup> Apart from the enantiopure 4-formyl[2.2]paracyclophane (**1**) and PCP-derived enan-

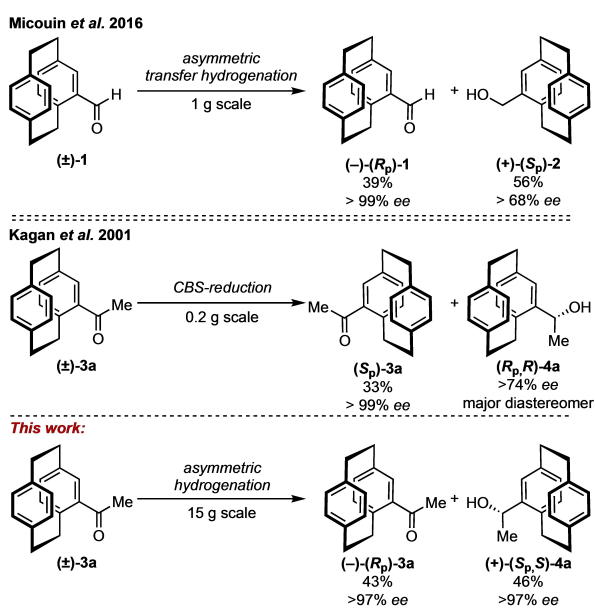
tiopure alcohol **2**, this method could also be used in the kinetic resolution and desymmetrization of difunctionalized PCP derivatives bearing an aldehyde functionality.<sup>[10]</sup> The resolution of 4-acetyl[2.2]paracyclophane (**3a**) previously has been reported by Kagan *et al.* by borane reduction in the presence of a Corey-Bakshi-Shibata (CBS) catalyst. (Scheme 1, middle).<sup>[7a]</sup>

In our pursuit of a scalable and efficient kinetic resolution method, we employed molecular hydrogen for the reduction of 4-acetyl[2.2]paracyclophane (**3a**), as a model platform because of the significant application perspectives of the conceivable resulting PCP-products. The starting material **3a** is easily accessible *via* Friedel-Crafts acylation on a multigram scale in good yield (240 mmol PCP, 60% yield).<sup>[11]</sup> For the asymmetric reduction of **3a** to the corresponding PCP-derived alcohol **4**, conditions for both hydrogenation (Table 1, entries 1–2) and asymmetric transfer hydrogenation (Table 1, entries 3–4) were initially examined. In asymmetric transfer hydrogenation, RuCl(arene)(*N*-sulfonylated diamine) complexes are commonly used and display great efficiency in both reactivity and enantioselectivity. Therefore, various commonly used Ru-based catalysts in combination with formic acid/triethylamine azeotrope (5:2) as hydrogen source were examined (Table 1, entries 3–4). Neither the ruthenium catalyst based on TsDPEN (**III**, entry 3, Table 1) nor the often more reactive oxotethered version (**IV**, entry 4, Table 1) led to any conversion to the corresponding alcohol **4a**.

However, ruthenium diphosphine diamine complexes, which are used in asymmetric hydrogenation reactions, afforded high enantioselectivities albeit having the disadvantage of requiring a pressure reactor. The conventional DAIPEN-based catalyst (**I**, entry 1, Table 1) failed to give any conversion, whereas with the ruthenacycle catalyst (*S*)-RUCY<sup>®</sup>-XylBINAP (**II**, entry 2, Table 1) at 50 bar H<sub>2</sub>-pressure, 44% of the alcohol **4a** was isolated and 46% of the starting material **3a** was recovered. Both compounds **3a** and **4a** were obtained in excellent enantiopurity of *ee* ≥ 97%.

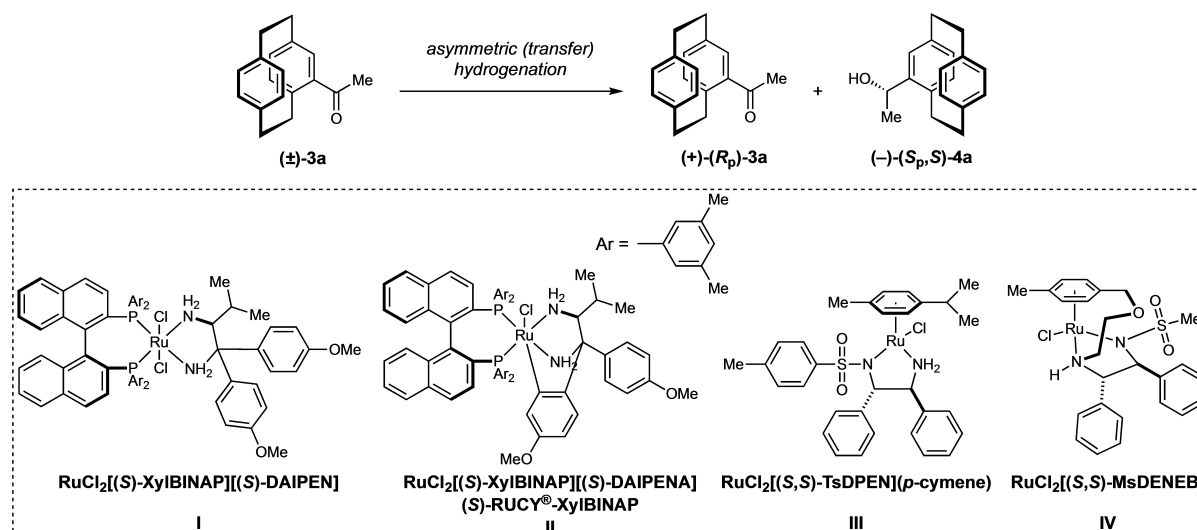
The efficiency of the kinetic resolution was evaluated by calculation of the selectivity factor.<sup>[12]</sup> The resolution was found to be efficient with *s* > 200.

The absolute stereochemistry of the products was assigned by specific rotation and found to be [ $\alpha$ ]<sub>D</sub> = +64 for the recovered 4-acetyl [2.2]paracyclophane (**3a**), which is in good agreement with literature values for (+)-(*S*<sub>p</sub>)-**3a**. Oxidation of the alcohol to **3a** and specific rotation measurements confirmed the absolute stereochemistry to be (–)-(*R*<sub>p</sub>)-**3a** ([ $\alpha$ ]<sub>D</sub> = –65).<sup>[7a,13]</sup> The relative stereochemistry of the obtained alcohol **4a** was assigned by NMR comparison with literature and proved it to be (–)-(*R*<sub>p</sub>,*R*)-**4a**.<sup>[7a]</sup>



**Scheme 1.** Overview of kinetic resolution methods of racemic PCP derivatives.<sup>[7]</sup>

**Table 1.** Ru-catalysts screening for the kinetic resolution of 4-acetyl[2.2]paracyclophane ((±)-**3a**).<sup>[a]</sup>



Entry	catalyst	solvent <sup>[b]</sup>	T (°C)	p <sub>H<sub>2</sub></sub> (bar)	S/C <sup>[c]</sup>	yield (%) <sup>[d]</sup>	ee (%)
1 <sup>[e]</sup>	I	CH <sub>2</sub> Cl <sub>2</sub>	20	50	500	—	—
2 <sup>[e]</sup>	II	CH <sub>2</sub> Cl <sub>2</sub>	20	50	1000	90	97/97
3	III	F/T, THF (3:2)	60	—	200	—	—
4	IV	F/T, DMF (1:1)	60	—	1000	—	—

<sup>[a]</sup> (±)-**3a** (4.00 mmol, 1.0 M), 24 h reaction time.

<sup>[b]</sup> F/T = formic acid/triethylamine azeotrope (5:2).

<sup>[c]</sup> substrate to catalyst ratio.

<sup>[d]</sup> isolated yield.

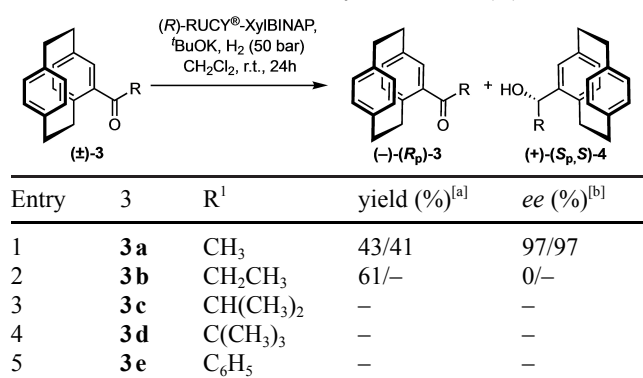
<sup>[e]</sup> <sup>t</sup>BuOK (0.4 mmol) as base.

With the opposite stereochemistry of the catalyst (*R*)-RUCY<sup>®</sup>-XylBINAP, (−)-(*R<sub>p</sub>*)-**3a**, (+)-(*S<sub>p</sub>,S*)-**4a** were obtained in slightly better enantioselectivity (*ee* ≥ 99%) and the same good yield. Scale-up of the reaction to 60 mmol starting material (15 g of **3a**) was easily achieved with the same high selectivity and yield and was only limited by the volume of the pressure reactor.

Following optimization and scale-up of the kinetic resolution of **3a**, different PCP acyl derivatives were examined. Compounds with a longer and branched alkyl chain as well as an aryl substituent were synthesized *via* Friedel-Crafts acylation and tested in the kinetic resolution (Table 2). Under the established hydrogenation conditions, neither the branched alkyl chains (entry 3 and 4) nor the aryl-substituted derivative (entry 5) showed any considerable conversion, which is probably a result of the increased steric demand of the substrates. In the case of ethyl-substituted derivative (entry 2) under these conditions, starting material was re-isolated as racemate in 61% yield.

Product **3a** was found to be an excellent substrate for the quick and high yielding transformation into valuable building blocks (Scheme 2). The 4-acetyl[2.2]

**Table 2.** Kinetic resolution of acyl derivatives (±)-**3**.<sup>[a]</sup>

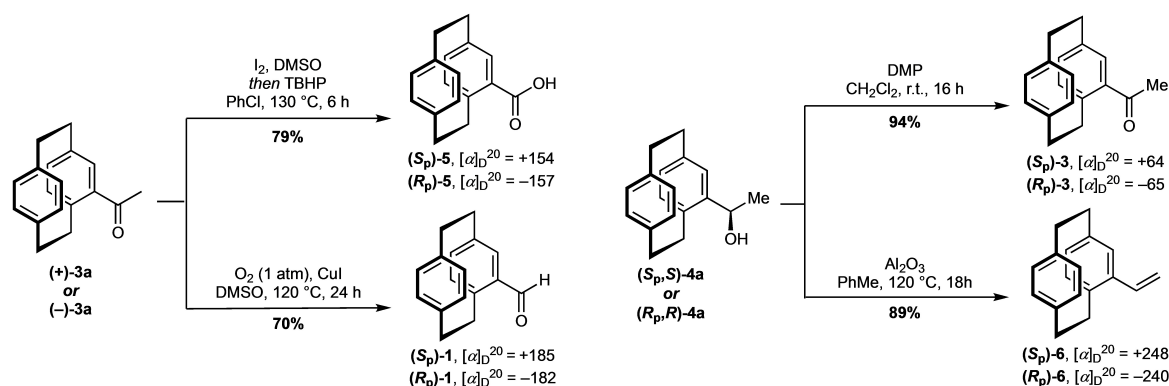


<sup>[a]</sup> **3** (4.00 mmol, 1.0 M), <sup>t</sup>BuOK (0.40 mmol), 24 h reaction time.

<sup>[b]</sup> isolated yield.

<sup>[c]</sup> determined *via* chiral HPLC – Chiralpak<sup>®</sup> OD-H, 1.0 mL/min <sup>n</sup>Hex/*i*PrOH, 90:10.

paracyclophane (**3a**) can be readily oxidized<sup>[14]</sup> to access enantiomerically pure PCP 4-carboxylic acid **5**, which has found application in the synthesis of planar chiral ligands and catalysts.<sup>[15]</sup> Oxidative C–C bond



**Scheme 2.** Synthetic transformations of the PCP as a model platform for accessing structurally diverse enantiopure cyclophanyl scaffolds for developing planar chiral ligands and engineering cyclophane-based chiral materials.

cleavage as reported by Liao *et al.*<sup>[16]</sup> gives direct access to enantiopure aldehyde **1**.

Re-oxidation of enantiopure alcohol **4a** to compound **3** with Dess-Martin periodinane (DMP) is possible in 94% yield and gives access to the carboxylic acid **5** and aldehyde **1** of opposite stereochemistry as described above. By elimination of the alcohol group, 4-vinyl[2.2]paracyclophane (**6**) is accessible in 89% yield.

In conclusion, a highly efficient kinetic resolution protocol of racemic 4-acetyl[2.2]paracyclophane using ruthenium-catalyzed asymmetric hydrogenation was developed. By using this method, both enantiomers of PCP with planar and central chirality of (*R<sub>p</sub>*)-4-acetyl-PCP ( $\geq 97\%$  *ee*, 43%) and (*S<sub>p</sub>,S*)-PCP derivatives ( $\geq 97\%$  *ee*, 46%) are easily accessible on a multigram-scale. Other commonly used valuable planar chiral PCP intermediates such as the corresponding carboxylic acid, aldehyde, and vinyl derivatives can be obtained *via* this PCP building block to broaden its implementation and synthetic scope.

## Experimental Section

**Enantioselective hydrogenation of racemic 4-acetyl-PCP **3a** using (*S*)-RUCY<sup>®</sup>-XylBINAP:** Inside an argon-filled glovebox, a pressure reactor was charged with (*rac*)-4-acetyl[2.2]paracyclophane (1.00 g, 4.00 mmol, 1.00 equiv.), (*S*)-RUCY<sup>®</sup>-XylBINAP (4.73 mg, 4.00  $\mu$ mol, 0.10 mol%), potassium *tert*-butoxide (44.9 mg, 0.40 mmol, 10.0 mol%) and dry, degassed dichloromethane (4.0 mL). Hydrogen was initially introduced into the autoclave at a pressure of 10 atm, before being reduced to 1 atm by carefully releasing the stop valve. This procedure was repeated three times, and the vessel was pressurized to 50 bar. The mixture was vigorously stirred (750 rpm) at room temperature for 24 h. The autoclave was carefully vented, and the solvent was removed under reduced pressure. The crude solid was purified by flash column chromatography (silica, *n*-pentane/EtOAc/CH<sub>2</sub>Cl<sub>2</sub>, 7:1:1 to 2:1:1) to obtain (*S<sub>p</sub>*)-4-acetyl[2.2]paracyclophane (455 mg, 1.82 mmol, 46%) and (*R<sub>p</sub>,R*)-1-

(4-[2.2]paracyclophanyl) ethanol (440 mg, 1.74 mmol, 44%) as colorless solids with  $> 97\%$  *ee*.

The reaction was also conducted using (*rac*)-4-acetyl[2.2]paracyclophane (15.0 g, 60.0 mmol) and (*R*)-RUCY<sup>®</sup>-XylBINAP. (*R<sub>p</sub>*)-4-acetyl[2.2]paracyclophane (6.50 g, 26.0 mmol, 46%) and (*S<sub>p</sub>,S*)-1-(4-[2.2]paracyclophanyl) ethanol (6.21 g, 24.6 mmol, 41%) were isolated as colorless solids with  $> 97\%$  *ee*.

Analytical Chiral HPLC (Chiralcel<sup>®</sup> OD-H, 250  $\times$  4.6 mm, *n*-hexane/*i*-PrOH, 90:10, 1.0 mL/min,  $\lambda = 256/218$  nm):  $t_{R(Sp-acetyl)}$  = 10.0 min,  $t_{R(Rp-acetyl)}$  = 11.4 min,  $t_{R(Sp,S-OH)}$  = 9.6 min,  $t_{R(Rp,R-OH)}$  = 13.7 min.

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