Organocatalytic Desymmetrization Prompts Central-to-Planar Chirality Transfer to [2.2]Paracyclophanes

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Contributions

V.D. designed project and performed the synthesis of all compounds. F. K. performed selected NMR experiments. I. C. performed X-ray analysis. J. V. conceived the study and directed the project. V.D., and J.V. wrote the manuscript. All authors have approved the final version of the manuscript.

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Abstract

Planar chiral [2.2]paracyclophanes consist of two functionalized benzene rings connected by two ethylene bridges. These organic compounds have a wide range of applications in asymmetric synthesis, as both ligands and catalysts, and in materials science, as polymers, energy materials and dyes. However, these

molecules can only be accessed by enantiomer separation via a) time-consuming chiral separations and b) kinetic resolution approaches, often with a limited substrate scope, yielding both enantiomers. Here, we report a simple, efficient, metal-free protocol for organocatalytic desymmetrization of centrosymmetric diformyl[2.2]paracyclophanes. Our detailed experimental mechanistic study highlighted differences in the origin of enantiocontrol of *pseudo-para* and *pseudo-ipso* diformyl derivatives in NHC catalysed desymmetrizations based on whether a key Breslow intermediate is irreversibly or reversibly formed in this process. This gram-scale reaction enables a wide range of follow-up derivatizations of carbonyl groups, producing various enantiomerically pure planar chiral [2.2]paracyclophane derivatives, thereby underscoring the potential of this method.

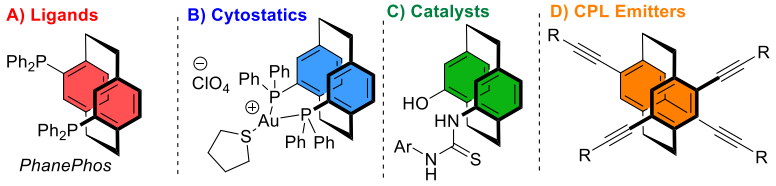
Introduction

Asymmetric organocatalysis uses small organic molecules as chiral catalysts to mimic biocatalytic processes, thereby expanding the chemical space.[1-4] Organocatalytic approaches are excellent tools for preparing enantiomerically pure compounds given the operational simplicity of their reactions, which frequently include water and air tolerance. In addition, organocatalysts are particularly stable, diverse and available in both enantiomeric forms, often derived from natural sources, such as amino acids and alkaloids.[5] Yet, despite the diversity of organocatalysts, organocatalytic approaches have been focused on the preparation of chiral molecules containing central and axial chirality. Consequently, asymmetric organocatalysis applications remain overlooked, especially in the production of planar chiral molecules, such as [2.2]paracyclophane derivatives.[6]

In [2.2]paracyclophanes, two benzene rings are covalently bound by two ethylene bridges at arene *para* positions. This molecular architecture suppresses the rotation of the benzene rings, providing [2.2]paracyclophanes with high configuration stability (up to 200 °C)[7] and planar chirality upon arene derivatization.[8] In fact, the first planar chiral derivative of these compounds was isolated by crystallization of brucine salts of 4 carboxy[2.2]paracyclophane[9] only six years after Brown and Farthing had pioneered the preparation of [2.2]paracyclophane.[10] Since then, considerable research efforts have

focused on the unique 3D structure of chiral [2.2]paracyclophanes for their unusual electronical[11,12] and photophysical properties.[13-19] Case in point, highly rigid planar chiral [2.2]paracyclophanes (Figure 1) have become a valuable toolbox for developing ligands[20-24] and organocatalysts.[25] Beyond synthetic chemistry, these scaffolds have also been applied in small-organic circularly polarized luminescence (CPL, Figure 1D)[26-28] and other phosphorescent emitters.[29]

Fig. 1: Selected examples of chiral [2.2]paracyclophanes.



Notwithstanding these applications, enantiopure [2.2]paracyclophanes lack general and efficient synthetic pathways, a major constraint that continues to stall progress in this research field. Currently available synthetic approaches rely on enantiomer separations or various resolutions, including chemical resolution through diastereomerization and kinetic resolution.[30] Kinetic resolution, in particular, involves metal[31-35] and enzyme-catalyzed processes[36-38] and organocatalytic methods[39-42] although the last approaches remain incipient. Regardless of the approach, though, kinetic resolution entails an inherent limitation, that is, the maximum product yield is only 50%. For a high-yielding and practical synthesis of chiral [2.2]paracyclophanes, desymmetrization or dynamic kinetic resolution can be used, but only one study has reported such an approach thus far, more specifically the desymmetrization of centrosymmetric diformyl[2.2]paracyclophanes by ruthenium-catalyzed asymmetric transfer hydrogenation.[43] Moreover, this method still has some limitations, not least of which a restricted substrate scope. Therefore, facilitating synthethic access to enantiopure [2.2]paracyclophanes requires developing high-yielding methods with a wide substrate scope.

Applicable to a broad scope of prochiral, *meso*-symmetric substrates, metal-free organocatalytic desymmetrization induced by chiral *N*-heterocyclic carbenes (NHCs) yields enantiomerically pure compounds.[44-47] Furthermore, NHC organocatalysis features versatile reactivity modes under mild

reaction conditions, broad functional-group tolerance, and bench-stable NHC precursors easily accessible from natural sources (such as amino acids).[48-50] For example, oxidative NHC catalysis was applied to the enantioselective desymmetrization of aromatic dialdehyde, producing axially chiral monoesters by central-to-axial chirality transfer.[46] However, central-to-planar chirality transfer from NHC to [2.2]paracyclophanes has never been attempted before. Nevertheless, a recent study has shown that NHC facilitates access to planar chiral ferrocenes via enantioselective desymmetrization.[51] Accordingly, we aimed at developing a method for preparing enantiomerically pure [2.2]paracyclophane derivates by central-to-planar chirality transfer using NHC catalysis.

In this study, we report a highly efficient and versatile protocol for organocatalytic desymmetrization esterification of centrosymmetric diformyl[2.2]paracyclophanes through NHC catalysis under mild conditions. For this purpose, we used amino acid-derived precursors to induce enantiocontrol via central-to-planar chirality transfer. After optimizing the reaction conditions, we analysed the substrate scope and conducted mechanistic studies to understand differences in the origin of enantiocontrol of organocatalytic desymmetrization.

Results and Discussion

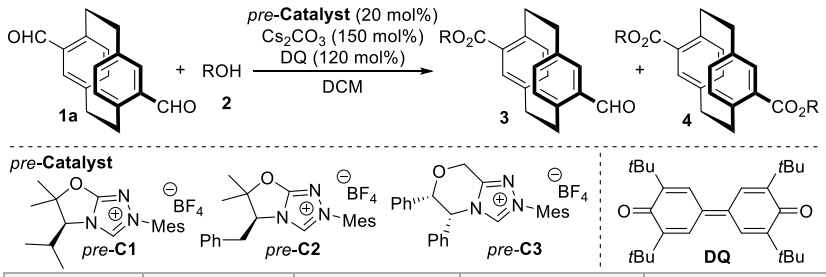
Optimization of Reaction conditions

From the outset of our study, we chose the *pseudo-para* derivative (**1a**) as a model substrate considering the accessibility of centrosymmetric diformyl[2.2]paracyclophanes. Simply mixing achiral paracyclophane **1a** with an excess of methanol and in the presence of an L-valine-derived NHC-precursor (*pre*-**C1**), an oxidant (Kharash reagent, 3,3'5,5'-tetra-*tert*-butyldiphenoquinone, DQ), and a base (cesium carbonate) produced planar chiral monoester **3a** in 51 % isolated yield with enantioselectivity 92:8 *er*, along with an easily separable diesterification by-product (Table 1, entry 1). Based on the results from this proof-of-concept experiment, we aimed at optimizing the efficiency and stereochemical outcomes by varying the reaction conditions. For this purpose, we tested different amino acid-derived and other NHC precursors, oxidants, bases, and solvents.

The isolated yield of **3a** significantly increased in the model reaction (entry 2) mediated by an L-phenylalanine-derived NHC precursor (*pre*-**C2**). Other precursors, such as morpholine-based *pre*-**C3**, failed to improve the efficiency of this reaction. In addition to these amino acid-derived NHC precursors, we also tested various other NHC precursors (for further information on the optimization survey, please refer to the Supplementary Information file), but the model reaction became less tolerant to bases and solvents. For instance, with triethylamine as a base or chloroform as a solvent, the model reaction displayed lower yield and enantiocontrol (entries 4, 5). The same outcome was found when replacing DQ by the single-electron oxidant TEMPO (entry 6). Conversely, electroredox oxidation using tetrabutylammonium iodide iodine (TBAI) as a promoter[52] produced the expected product **3a** in 47% yield, albeit slightly decreasing the enantiocontrol (entry 7). Nevertheless, this experiment validated electrochemical oxidation as a potentially greener and more suitable approach than other systems involving additional oxidants.

After further optimizing the reaction conditions, we found that increasing the amount of base (2.0 equiv., entry 8) slightly improved the stereocontrol of the model reaction. Under optimized reaction conditions, we tested the desymmetrization approach using ethanol instead of methanol, but the enantiocontrol decreased significantly (entry 9). This decrease led us to reexamine the catalyst for esterification using ethanol. Surprisingly, the reaction mediated by *pre*-**C1** produced nearly an enantiopure product with a good yield (entry 10). Moreover, this reaction proved equally effective with methanol, providing the desired product 3a in excellent yield and enantiocontrol (entry 11).

Table 1: Optimization studies of desymmetrization



Entry[a]	R	*pre*-Cat.	Time (h)	Yield[b] (3, %)	Yield[b] (4, %)	*er*[c] (3)
1	Me	*pre*-**C1**	15	51	6	92:8
2	Me	*pre*-**C2**	15	82	10	93:7
3	Me	*pre*-**C3**	15	44	15	9:91
4[d]	Me	*pre*-**C2**	15	41	37	85:15
5[e,f]	Me	*pre*-**C2**	72	65	25	84:16
6[g,f]	Me	*pre*-**C2**	72	21	traces	88:12
7[h,f]	Me	*pre*-**C2**	30	47	traces	83:17
8[i]	Me	*pre*-**C2**	15	72	22	96:4
9[i]	Et	*pre*-**C2**	15	55	11	64:36
10[i]	Et	*pre*-**C1**	15	69	9	99:1
11[i]	Me	*pre*-**C1**	15	87	6	99:1

[a] Reactions were conducted with **1a** (0.10 mmol), the corresponding alcohol **2** (0.5 mmol), Cs_2CO_3 (0.15 mmol), DQ (0.12 mmol), and *pre*-catalyst (20 mol%) in DCM (1.0 ml) at room temperature. [b] Isolated yield after column chromatography. [c] Determined by chiral HPLC analysis. [d] $CHCl_3$ was used as a solvent. [e] TEA was used as a base. [f] Full consumption of **1a** was not observed. [g] TEMPO was used as an oxidant. [h] Electrochemical oxidation (Pt cathode and anode, constant current: 1 mA, total charge: 5.44 F/mol) using TBAI (0.2 mmol) in IKA ElectraSyn 2.0 was applied instead of DQ. [i] 0.2 mmol of Cs_2CO_3 was used instead of 0.15 mmol.

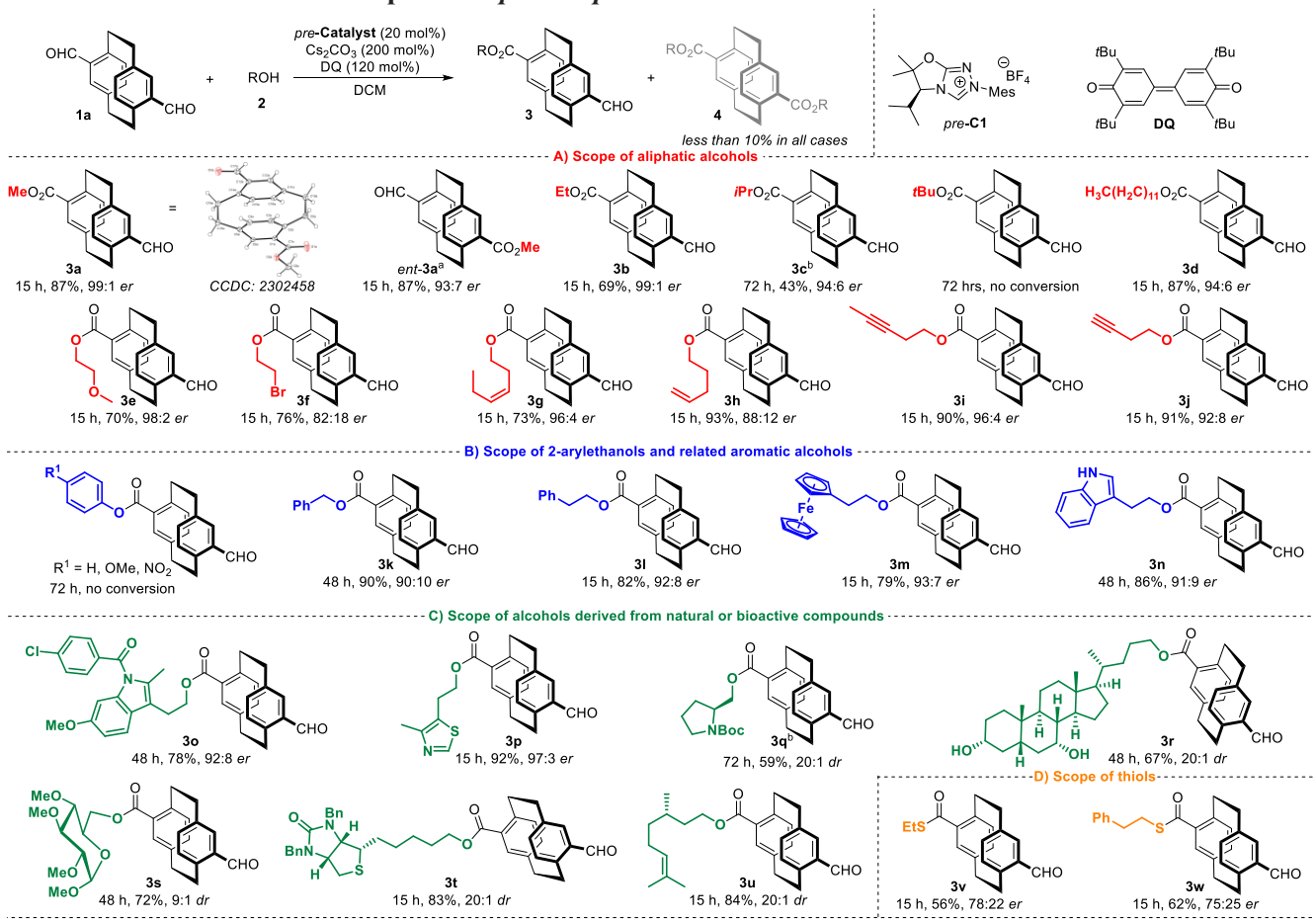
Substrate scope

After optimizing the reaction conditions, we began exploring the scope of the desymmetrization reaction of *pseudo-para* derivative **1a** (Scheme 1). When conducted with *ent-pre*-**C1** derived from unnatural D-valine, the desymmetrization reaction produced the expected opposite enantiomeric product (*ent*-**3a**) in high yield, albeit with slightly diminished enantiopurity. Then, we assessed the effect of the steric hindrance of selected aliphatic alcohols on the reaction rate and stereochemical outcome (Scheme 1A). Unsurprisingly, the reaction rate was significantly slower when using sterically hindered alcohols. Conversely, longer aliphatic alcohols, such as lauryl alcohol, produced the corresponding ester 3d in high yield (87%) and enantiopurity (94:6 *er*). Substituted aliphatic alcohols with halogen, methoxy, or internal and terminal alkenyl or alkynyl groups showed similar efficiency.

Subsequently, we explored the scope of this method using various aromatic alcohols (Scheme 1B). The results showed that this method was intolerant to phenols, including substituted phenols, but tolerated well benzyl alcohol and 2-phenylethanol. In addition, the expected products (**3m** and **3n**) were formed in high yields and enantiopurities when using 2-(ferrocenyl)ethanol or tryptophol. Such functional group tolerance encouraged us to apply the desymmetrization reaction of **1a** to the late-stage modification of structurally diverse alcohols derived from natural or bioactive molecules (Scheme 1C), including indometacin, proline, biotin, and chenodeoxycholic acid, or bioactive alcohols (sulfurol, citronellol, protected glucose derivative).

These desymmetrization reactions resulted in good-to-high yields of esters, with high levels of enantiopurity of the final product. For instance, the steroidal product **3r** was obtained in high yield (67%) as a single diastereomer (20:1 *dr*) in a reaction where the starting material contained three unprotected hydroxy groups. In this case, differences in the reaction rates of desymmetrization of secondary alcohols resulted in regioselectivity. Moreover, thiols also worked as esterification agents in this desymmetrization reaction (Scheme 1D), but their efficiency, in terms of yield and optical purities of thioesters **3v** and **3w**, was lower than that of the aforementioned esters.

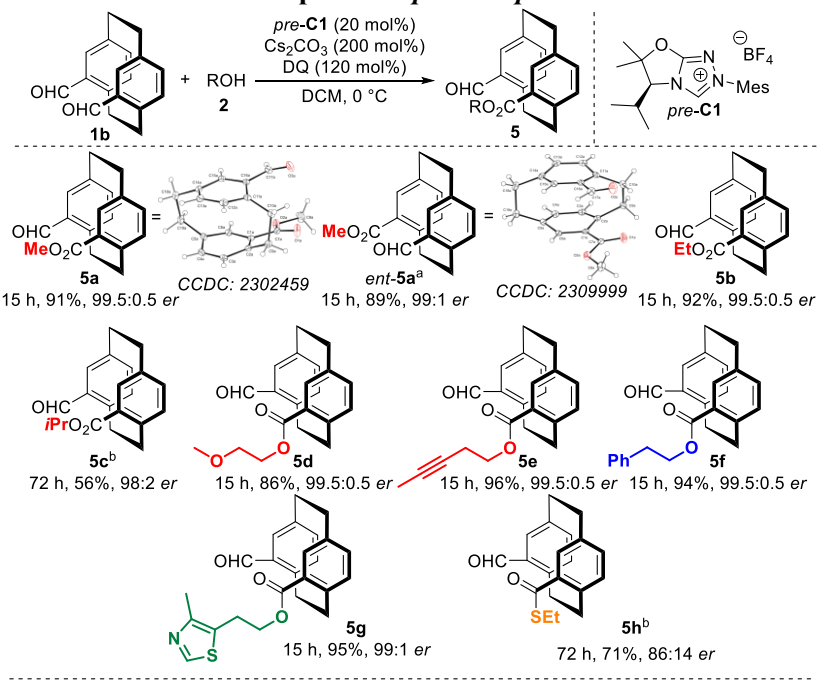
Scheme 1: Substrate scope of the *pseudo-para* derivative



[a] *Ent-pre*-**C1** was used. [b] Full consumption of **1a** was not observed.

To assess our method (Scheme 2), we introduced another centrosymmetric [2.2]paracyclophane, namely *pseudo-ipso*-diformylparacyclophane (**1b**). We began by optimizing the reaction conditions (for more details, please refer to the Supplementary Information file). After lowering the reaction temperature, we noted that the expected product **5a** was formed in excellent yield and enantiomeric purity (91%, 99.5/0.5 *er*) without the diester byproduct. In turn, by using the opposite enantiomeric form (*ent-pre*-**C1**), we gained access to the opposite enantiomer (*ent*-**5a**), obtaining the expected product in excellent yield and stereochemical outcomes. With sterically hindered alcohols, the reaction rate decreased, unsurprisingly, albeit without significantly affecting the enantiocontrol. Moreover, introducing different alcohols improved the yield and stereocontrol of the desymmetrization process.

Scheme 2: Substrate scope of the *pseudo-ipso* derivative



[a] *Ent-pre*-**C1** was used. [b] Full consumption of **1b** was not observed.

Mechanistic studies

To elucidate the reaction mechanism and origin of stereocontrol, we conducted control experiments were with both substrates 1 (Scheme 3). First, treating **1a** (*pseudo-para*) with deuterated methanol-d_4 (Scheme 3A, left) under optimized conditions provided **3a**-d_3 with deuterated aldehyde (~40%, validated by ^{2}H NMR), indicating the reversible formation of the Breslow intermediate. Subsequently, we studied the parallel kinetic isotopic effect (Scheme 3B, left) using **1a** and **1a**-d_2 in a desymmetrization reaction with methanol under optimized reaction conditions for 1 hour. The results showed a KIE value of 2.8, implying that proton transfer in the formation of the Breslow intermediate is the rate-limiting step.

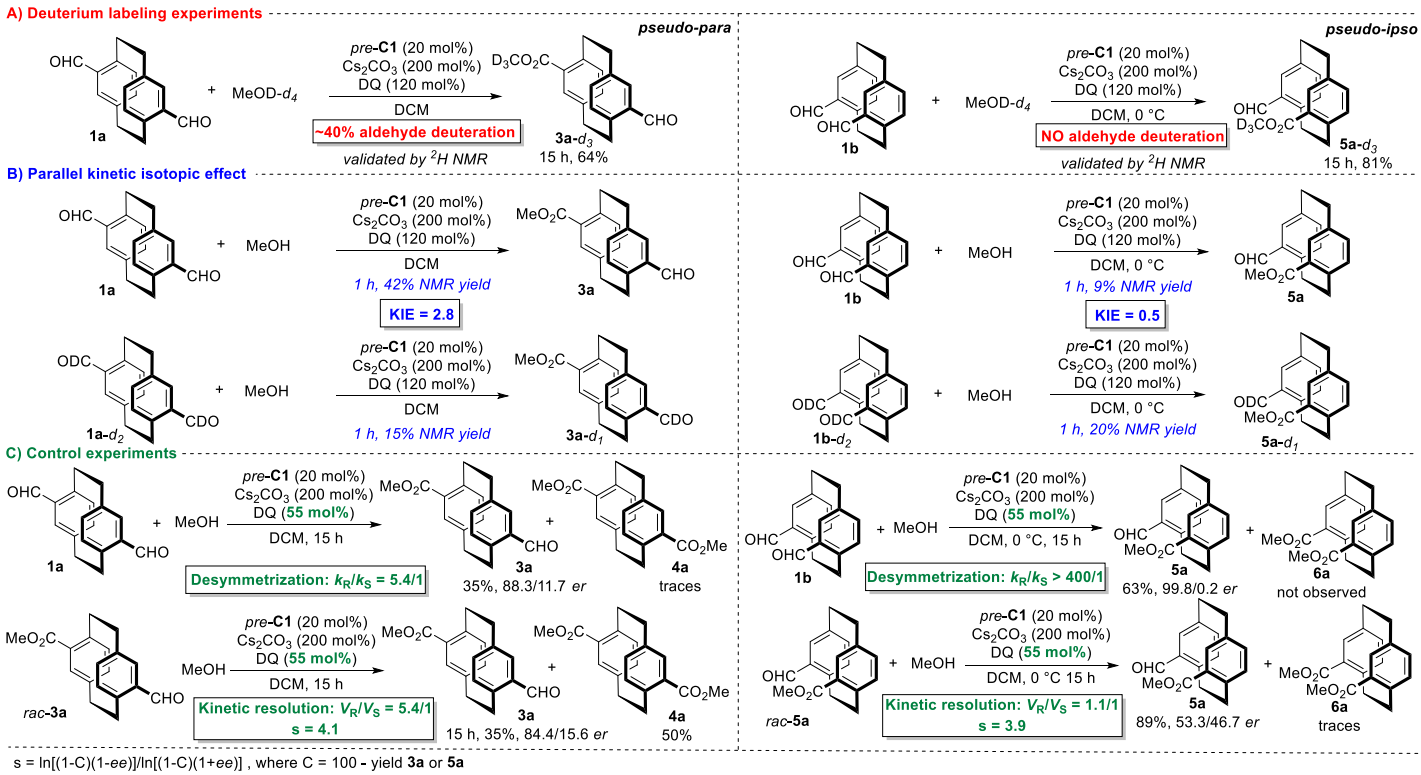
To investigate the origin of enantiocontrol, we conducted a series of control experiments (Scheme 3C, left). The model reaction with a lowered amount of oxidant (55 mol%) produced **3a** in 88:12 *er* with traces of the diesterification product, suggesting that desymmetrization is an enantiodivergent process and that an additional enantiocontrol mechanism could be kinetic resolution reaction. To confirm this hypothesis, we conducted a kinetic resolution reaction of *rac*-**3a** under optimized reaction conditions with

a lowered amount of oxidant (55 mol%), thereby forming enantioenriched product **3a** and confirming the existence of an additional source of enantiocontrol. Based on our findings, we propose that **1a** enantioselective desymmetrization is followed by kinetic resolution, resulting in a high level of enantiocontrol (for details, please see the Supplementary Information file), in line with the slightly decreased enantiocontrol in the preparation of *ent*-**3a**.

We also performed another series of control experiments involving the desymmetrization of *pseudo-ipso* derivative **1b**. We noticed striking differences from the desymmetrization of **1a**. For example, we did not detect deuterium incorporation in the control reaction conducted with methanol-d_4 (Scheme 3A, right), indicating that the formation of the Breslow intermediate is an irreversible process. In the desymmetrization of **1b**, the KIE was significantly lower (approximately 0.5). Accordingly, the initial carbene nucleophilic attack of **1b** is most likely the rate-limiting step (Scheme 3B, right).

The origin of enantiocontrol was clear (Scheme 3C, right) because we observed nearly enantiopure product formation (99.8:0.2 *er*) in a control reaction of **1b** with a lowered amount of oxidant (55 mol%) under optimized conditions. Additionally, the kinetic resolution of *rac*-**5a** was ineffective, indicating that enantioselective desymmetrization is crucial for enantiocontrol in this process (for details, please refer to the Supplementary Information file). Based on these findings, *pseudo-ipso*[2.2]paracyclophanes, not limited to dialdehydes, stand out as candidates for further elaboration in desymmetrization processes.

Scheme 3: Mechanistic studies



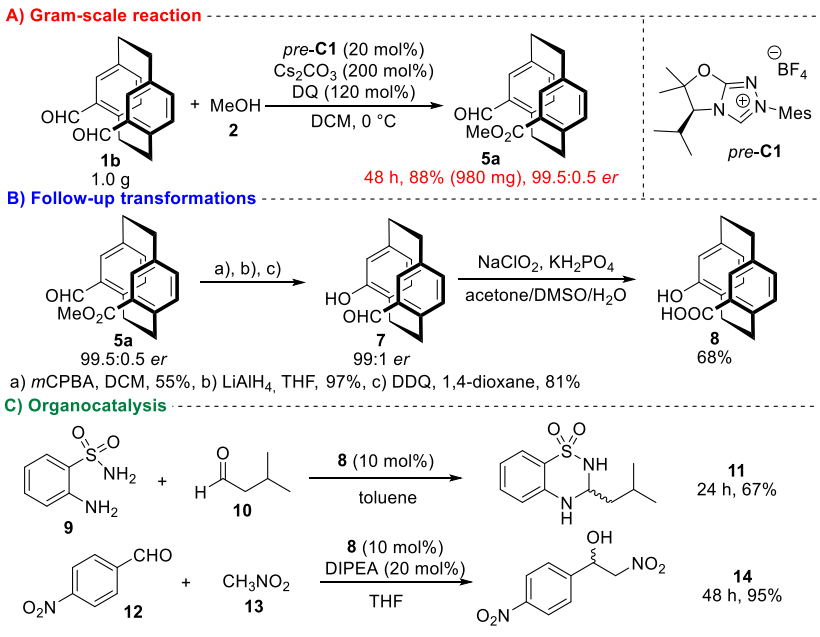
s = ln[(1-C)(1-*ee*)]/ln[(1-C)(1+*ee*)] , where C = 100 - yield **3a** or **5a**

Synthetic utilization of the chiral product

To showcase the practicality of this method, we performed a gram-scale desymmetrization of **1b** under optimized conditions (Scheme 4A). This gram-scale reaction provided us with access to a highly enantioenriched product **5a** in a high yield of 88% with 99.5/0.5 *er*. The follow-up reactions of the planar chiral product **5a** highlighted the usefulness and modulation of both carbonyl groups (Scheme 4B), as shown by conducting Bayer-Villiger oxidation followed by reduction and oxidation steps.[53] These steps yielded product **7** without significantly affecting the enantiomeric excess of the product. We then conducted Pinnick oxidation of aldehyde to obtain carboxylic acid **8** because this compound has been proposed as a bifunctional organocatalyst. To test its catalytic activity, we conducted selected reactions, such as aminalization[54] and the Henry reaction[55] (Scheme 4C). In both examples, we observed the formation of the desired products in high isolated yields without significant enantiocontrol. Furthermore,

the planar chiral derivatives 7 and 8 are considered potential key intermediates for preparing [2.2]paracyclophane-based ligands.[56-58]

Scheme 4: Gram-scale desymmetrization and synthetic utility demonstration.



In summary, our metal-free methodology for NHC-catalyzed enantioselective desymmetrization of diformyl[2.2]paracyclophanes provides efficient access to highly enantioenriched planar chiral compounds. This operationally simple and effective strategy has a wide substrate scope involving natural and bioactive starting materials. Moreover, the feasibility of the gram-scale desymmetrization reaction and the potential for diverse follow-up transformations underscore the value of this method. And as shown in our comprehensive experimental mechanistic studies, differences in the origin of enantiocontrol of *pseudo-para* and *pseudo-ipso* diformyl derivatives in NHC-catalysed desymmetrizations identified *pseudo-ipso* diformyl[2.2]paracyclophanes as valuable synthons for future elaborations. Accordingly, ongoing research into the synthesis of planar chiral molecules organocatalytic reactions and their applications in organocatalysis or novel ligand synthesis will continue in our laboratories.

Methods

Representative procedure

The vial (4 ml) was charged with **1** (0.1 mmol), *pre*-**C1** (0.02 mmol), DQ (0.12 mmol), and Cs_2CO_3 (0.2 mmol), followed by DCM (1.0 ml), and the corresponding alcohol (0.5 mmol) at the corresponding temperature. At this temperature, the reaction mixture was stirred for the indicated time (TLC control). After completing the reaction, the solvent was evaporated. The crude product was purified by column chromatography (eluting by hexane/EtOAc mixtures).

Data Availability

The authors declare that the data supporting the findings of this study are available within the article and the Supplementary Information file. Other detailed data are available from the corresponding author upon request. The X-ray crystallographic coordinates for structures reported in this study have been deposited at the Cambridge Crystallographic Data Centre (CCDC), under deposition numbers CCDC 2302458, 2302459 and 2309999. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif, or by emailing da-ta_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

References

1. MacMillan, D. W. C. The advent and development of organocatalysis. *Nature* **455**, 304-308 (2008).
2. List, B. & Yang, J. W. The Organic Approach to Asymmetric Catalysis. *Science* **313**, 1584-1586 (2006).
3. Xiang, S.-H. & Tan, B. Advances in asymmetric organocatalysis over the last 10 years. *Nat. Commun.* **11**, 3786 (2020)
4. Lassaletta, J. M. Spotting trends in organocatalysis for the next decade. *Nat. Commun.* **11**, 3787 (2020)

5. Han, B., He, X.-H., Liu, Y.-Q., He, G., Peng, C. & Li, J.-L. Asymmetric organocatalysis: an enabling technology for medicinal chemistry. *Chem. Soc. Rev.* **50**, 1522-1586 (2021).
6. López, R. & Palomo, C. Planar Chirality: A Mine for Catalysis and Structure Discovery. *Angew. Chem. Int. Ed.* **61**, e202113504 (2022).
7. *Modern Cyclophane Chemistry*. *Modern Cyclophane Chemistry* (Wiley, 2004).
8. David, O. R. P. Syntheses and applications of disubstituted [2.2]paracyclophanes. *Tetrahedron* **68** 8977-8993 (2012).
9. Cram, D. J. & Allinger, N. L. Macro Rings. XII. Stereochemical Consequences of Steric Compression in the Smallest Paracyclophane. *J. Am. Chem. Soc.* **77**, 6289-6294 (1955).
10. Brown, C. & Farthing, A. Preparation and structure of Di-*p*-*xylylene*. *Nature* **164**, 915-916 (1949).
11. Majerz, I. & Dziembowska, T. Aromaticity and Through-Space Interaction between Aromatic Rings in [2.2]Paracyclophanes. *J. Phys. Chem. A* **120**, 8138-8147 (2016).
12. Miyazaki, T., Shibahara, M., Fujishige, J., Watanabe, M., Goto, K. & Shinmyozu, T. Synthesis and electronic and photophysical properties of [2.2]- and [3.3]paracyclophane-based donor-donor′-acceptor triads. *J. Org. Chem.* **79**, 11440-11453 (2014).
13. Felder, S., Delcourt, M.-L., Contant, D., Rodríguez, R., Favereau, L., Crassous, J., Micoun, L. & Benedetti, E. Compact CPL emitters based on a [2.2]paracyclophane scaffold: recent developments and future perspectives. *J. Mat. Chem. C* **11**, 2053-2062 (2023).
14. Roy, I., David, A. H. G., Das, P. J., Pe, D. J. & Stoddart, J. F. Fluorescent cyclophanes and their applications. *Chem. Soc. Rev.* **51**, 5557-5605 (2022).
15. Teng, J.-M., Zhang, D.-W. & Chen, C.-F. Recent Progress in Circularly Polarized Luminescence of [2.2]Paracyclophane Derivatives. *ChemPhotoChem* **6**, e202100228 (2022).
16. Hassan, Z., Spuling, E., Knoll, D. M. & Bräse, S. Regioselective Functionalization of [2.2]Paracyclophanes: Recent Synthetic Progress and Perspectives. *Angew. Chem. Int. Ed.* **59**, 2156-2170 (2020).

17. Hassan, Z., Spuling, E., Knoll, D. M., Lahann, J. & Bräse, S. Planar chiral [2.2]paracyclophanes: from synthetic curiosity to applications in asymmetric synthesis and materials. *Chem. Soc. Rev.* **47**, 6947-6963 (2018).
18. Paradies, J. [2.2]Paracyclophane Derivatives: Synthesis and application in catalysis. *Synthesis* 3749-3766 (2011).
19. Hopf, H. [2.2]Paracyclophanes in Polymer Chemistry and Materials Science. *Angew. Chem. Int. Ed.* **47**, 9808-9812 (2008).
20. Liang, H., Guo, W., Li, J., Jiang, J. & Wang, J. Chiral Arene Ligand as Stereocontroller for Asymmetric C−H Activation. *Angew. Chem. Int. Ed.* **61**, e202204926 (2022).
21. Kumar, S. V. & Guiry, P. J. Zinc-Catalyzed Enantioselective [3+2] Cycloaddition of Azomethine Ylides Using Planar Chiral [2.2]Paracyclophane-Imidazoline N,O-ligands. *Angew. Chem. Int. Ed.* **61**, e202205516 (2022).
22. Zippel, C., Hassan, Z., Nieger, M. & Bräse, S. Design and Synthesis of a [2.2]Paracyclophane-based Planar Chiral Dirhodium Catalyst and its Applications in Cyclopropanation Reaction of Vinylarenes with α-Methyl-α-Diazo Esters. *Adv. Synth. Catal.* **362**, 3431-3436 (2020).
23. Knoll, D. M., Hu, Y., Hassan, Z., Nieger, M. & Bräse, S. Planar chiral [2.2]paracyclophane-based bisoxazoline ligands and their applications in Cu-Mediated N-H insertion reaction. *Molecules* **24**, 4122 (2019).
24. Bestgen, S., Seidl, C., Wiesner, T., Zimmer, A., Köberle, B., Austeri, M., Paradies, J., Bräse, S., Schepers, U. & Roesky, P. W. Double-Strand DNA Breaks Induced by Paracyclophane Gold(I) Complexes. *Chem. Eur. J.* **23**, 6315-6322 (2017).
25. Schneider, J. F., Fröhlich, R. & Paradies, J. Paracyclophane-derived planar-chiral hydrogen-bond receptors. *Isr. J. Chem.* **52**, 76-91 (2012).
26. Chen, C.-H. & Zheng, W.-H. Planar Chiral B-N Heteroarenes Based on [2.2]Paracyclophane as Circularly Polarized Luminescence Emitters. *Org. Lett.* **23**, 5554-5558 (2021).

27. Gon, M., Morisaki, Y. & Chujo, Y. Optically active cyclic compounds based on planar chiral [2.2]paracyclophane: extension of the conjugated systems and chiroptical properties. *J. Mater. Chem. C* **3**, 521-529 (2015).
28. Morisaki, Y., Gon, M., Sasamori, T., Tokitoh, N. & Chujo, Y. Planar Chiral Tetrasubstituted [2.2]Paracyclophane: Optical Resolution and Functionalization. *J. Am. Chem. Soc.* **136**, 3350-3353 (2014).
29. Sharma, N., Spuling, E., Mattern, C. M., Li, W., Fuhr, O., Tsuchiya, Y., Adachi, C., Bräse, S., Samuel, I. D. W. & Zysman-Colman, E. Turn on of sky-blue thermally activated delayed fluorescence and circularly polarized luminescence (CPL): *via* increased torsion by a bulky carbazolophane donor. *Chem. Sci.* **10**, 6689-6696 (2019).
30. Felder, S., Wu, S., Brom, J., Micouin, L. & Benedetti, E. Enantiopure planar chiral [2.2]paracyclophanes: Synthesis and applications in asymmetric organocatalysis. *Chirality* **33**, 506–527 (2021).
31. Zhao, Y., Ding, Y.-X., Wu, B. & Zhou, Y.-G. Nickel-Catalyzed Asymmetric Hydrogenation for Kinetic Resolution of [2.2]Paracyclophane-Derived Cyclic N-Sulfonylimines. *J. Org. Chem.* **86**, 10788-10798 (2021).
32. Zhao, Y., Wang, X.-Q., Yu, Y.-J. & Zhou, Y.-G. Kinetic Resolution of [2.2]Paracyclophane-Derived Cyclic *N*-Sulfonylimines via Palladium-Catalyzed Addition of Arylboronic Acids. *J. Org. Chem.* **86**, 1262-1272 (2021).
33. Zippel, C., Hassan, Z., Parsa, A. Q., Hohmann, J. & Bräse, S. Multigram-Scale Kinetic Resolution of 4-Acetyl[2.2]Paracyclophane *via* Ru-Catalyzed Enantioselective Hydrogenation: Accessing [2.2]Paracyclophanes with Planar and Central Chirality. *Adv. Synth. Catal.* **363**, 2861-2865 (2021).
34. Zhao, Y., Wang, H., Wu, B. & Zhou, Y.-G. Synthesis of paracyclophanes with planar and central chirality: Kinetic resolution of [2.2]paracyclophane aldimines *via* palladium-catalyzed addition of arylboronic acids. *Org. Chem. Front.* **6**, 3956-3960 (2019).

35. Delcourt, M.-L., Felder, S., Turcaud, S., Pollok, C. H., Merten, C., Miccouin, L. & Benedetti, E. Highly Enantioselective Asymmetric Transfer Hydrogenation: A Practical and Scalable Method to Efficiently Access Planar Chiral [2.2]Paracyclophanes. *J. Org. Chem.* **84**, 5369-5382 (2019).
36. Braddock, D. C., MacGilp, I. D. & Perry, B. G. Improved synthesis of (±)-4,12-dihydroxy[2.2]paracyclophane and Its enantiomeric resolution by enzymatic methods: Planar chiral (*R*)- and (*S*)-phanol. *J. Org. Chem.* **67**, 8679-8681 (2002).
37. Pamperin, D., Hopf, H., Syldatk, C. & Pietzsch, M. Synthesis of planar chiral [2.2]paracyclophanes by biotransformations: Kinetic resolution of 4-formyl-[2.2]paracyclophane by asymmetric reduction. *Tetrahedron Asymetry* **8**, 319-325 (1997).
38. Cipiciani, A., Fringuelli, F., Mancini, V., Piermatti, O., Scappini, A. M. & Ruzziconi, R. Enzymatic kinetic resolution of (±)-4-acetoxy[2.2] paracyclophane by *Candida cylindracea* lipase. An efficient route for the preparation of (+)-R-4-Hydroxy- and (+)-S-4-acetoxy[2.2)paracyclophane. *Tetrahedron* **53**, 11853-11858 (1997).
39. Yu, S., Bao, H., Zhang, D. & Yang, X. Kinetic resolution of substituted amido[2.2]paracyclophanes via asymmetric electrophilic amination. *Nat. Commun.* **14**, 5239 (2023).
40. Weinzierl, D. & Waser, M. Synthesis of [2.2]Paracyclophane-Based Glycidic Amides Using Chiral Ammonium Ylides. *Helv. Chim. Acta* **104**, e2100073 (2021).
41. Weinzierl, D. & Waser, M. Chiral isothiourea-catalyzed kinetic resolution of 4-hydroxy[2.2]paracyclophane. *Beilstein J. Org. Chem.* **17**, 800-804 (2021).
42. Akagawa, K., Nishi, N., Yoshikawa, I. & Kudo, K. Kinetic Resolution of a Planar-Chiral [2.2]Paracyclophane Derivative by Helical-Peptide-Catalyzed Michael Addition of Nitromethane. *Eur. J. Org. Chem.* **2015**, 5055-5059 (2015).
43. Delcourt, M.-L., Felder, S., Benedetti, E. & Micouin, L. Highly Enantioselective Desymmetrization of Centrosymmetric *pseudo-para*-Diformyl[2.2]paracyclophane via Asymmetric Transfer Hydrogenation. *ACS Catal.* **8**, 6612-6616 (2018).

44. Nájera, C., Foubelo, F., Sansano, J. M. & Yus, M. Enantioselective desymmetrization reactions in asymmetric catalysis. *Tetrahedron* **106-107**, 132629 (2022).
45. Di Iorio, N., Crotti, S. & Bencivenni, G. Organocatalytic Desymmetrization Reactions for the Synthesis of Axially Chiral Compounds. *Chem. Rec.* **19**, 2095-2104 (2019).
46. Borissov, A., Davies, T. Q., Ellis, S. R., Fleming, T. A., Richardson, M. S. W. & Dixon, D. J. Organocatalytic enantioselective desymmetrisation. *Chem. Soc. Rev.* **45**, 5474-5540 (2016).
47. Xu, Y., Zhai, T.-Y., Xu, Z. & Ye, L.-W. Recent advances towards organocatalytic enantioselective desymmetrizing reactions. *Trends Chem.* **4**, 191-205 (2022).
48. Song, R., Xie, Y., Jin, Z. & Chi, Y. R. Carbene-Catalyzed Asymmetric Construction of Atropisomers. *Angew. Chem. Int. Ed.* **60**, 26026-26037 (2021).
49. Wang, Z., Pan, D., Li, T. & Jin, Z. *N*-Heterocyclic Carbene (NHC)-Organocatalyzed Kinetic Resolutions, Dynamic Kinetic Resolutions, and Desymmetrizations. *Chem. Asian J.* **13**, 2149-2163 (2018).
50. Wu, Y., Li, M., Sun, J., Zheng, G. & Zhang, Q. Synthesis of Axially Chiral Aldehydes by N-Heterocyclic-Carbene-Catalyzed Desymmetrization Followed by Kinetic Resolution. *Angew. Chem. Int. Ed.* **61**, e202117340 (2022).
51. Lv, X., Xu, J., Sun, C., Su, F., Cai, Y., Jin, Z. & Chi, Y. R. Access to Planar Chiral Ferrocenes via N-Heterocyclic Carbene-Catalyzed Enantioselective Desymmetrization Reactions. *ACS Catal.* **12**, 2706-2713 (2022).
52. Zhou, P., Li, W., Lan, J. & Zhu, T. Electroredox carbene organocatalysis with iodide as promoter. *Nat. Commun.* **13**, 3827 (2022).
53. Rozenberg, V. I., Antonov, D. Y., Sergeeva, E. V., Vorontsov, E. V., Starikova, Z. A., Fedyanin, I. V., Schlultz, C. & Hopf, H. Enantiomerically pure (*R*)- and (*S*)-15-Hydroxy[2.2]paracyclophane-4-carbaldehyde (*iso*-FHPC): A Novel Parent Compound for Planar Chiral Ligands. *Eur. J. Org. Chem.* **2003**, 2056-2061 (2003).

54. Sui, Y., Cui, P., Liu, S., Zhou, Y., Du, P., Zhou, H. Highly Enantioselective Synthesis of Cyclic Aminals with a Cyclopentadiene-Based Chiral Carboxylic Acid. *Eur. J. Org. Chem.* **2018**, 215-218 (2018).
55. Kitagaki, S., Ueda, T. & Mukai, C. Planar chiral [2.2]paracyclophane-based bis(thiourea) catalyst: Application to asymmetric Henry reaction. *Chem. Commun.* **49**, 4030-4032 (2013).
56. Bolm, C. & Whelligan, D. K. The synthesis of pseudo-geminal, pseudo-ortho and ortho hydroxy-oxazolinyl[2.2]paracyclophanes for use as ligands in asymmetric catalysis. *Adv. Synth. Catal.* **348**, 2093-2100 (2006).
57. Bolm, C. & Whelligan, D. K. Synthesis of pseudo-*geminal*-, pseudo-*ortho*-Phosphinyl-oxazolinyl-[2.2]paracyclophanes for Use as Ligands in Asymmetric Catalysis. *J. Org. Chem.* **71**, 4609-4618 (2006).
58. Wu, X.-W., Zhang, T.-Z., Yuan, K. & Hou, X.-L. Regulation of the flexibility of planar chiral [2.2]paracyclophane ligands and its significant impact on enantioselectivity in asymmetric reactions of diethylzinc with carbonyl compounds. *Tetrahedron Asymmetry* **15**, 2357-2365 (2004).

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Ethics declarations

Competing interests

The authors declare no competing interests.