



HAL
open science

Highly Enantioselective Desymmetrization of Centrosymmetric pseudo - para -Diformyl[2.2]paracyclophane via Asymmetric Transfer Hydrogenation

Marie-Leonie Delcourt, Simon Felder, Erica Benedetti, Laurent Micouin

► **To cite this version:**

Marie-Leonie Delcourt, Simon Felder, Erica Benedetti, Laurent Micouin. Highly Enantioselective Desymmetrization of Centrosymmetric pseudo - para -Diformyl[2.2]paracyclophane via Asymmetric Transfer Hydrogenation. *ACS Catalysis*, 2018, 8 (7), pp.6612-6616. 10.1021/acscatal.8b01872 . hal-02113395

HAL Id: hal-02113395

<https://hal.science/hal-02113395>

Submitted on 17 Jul 2019

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Highly enantioselective desymmetrization of centrosymmetric *pseudo-para*-diformyl[2.2]paracyclophane via asymmetric transfer hydrogenation

Marie-Léonie Delcourt, Simon Felder, Erica Benedetti* and Laurent Micouin*

UMR 8601 CNRS, Université Paris Descartes, Sorbonne Paris Cité, UFR Biomédicale, 45 rue des Saints Pères, 75006 Paris (France).

[2.2]Paracyclophanes; planar chirality; centrosymmetric compounds; desymmetrization; asymmetric transfer hydrogenation

Supporting Information Placeholder

ABSTRACT: Herein we describe the desymmetrization of a centrosymmetric *pseudo-para*-diformyl[2.2]paracyclophane based on Noyori asymmetric transfer hydrogenations (ATH). The reduction proceeds smoothly in the presence of commercially available ruthenium complexes to afford a mono-hydroxymethylated product in good yields and excellent enantioselectivities (up to 74% isolated yield and 99% *ee*). Our approach is operationally simple and can be run in gram-scale without any significant loss in the reaction efficiency. This desymmetrization strategy allows an easy access to an enantiopure compound bearing on each aromatic ring of the pCp core different reactive groups suitable for regioselective orthogonal post-functionalization.

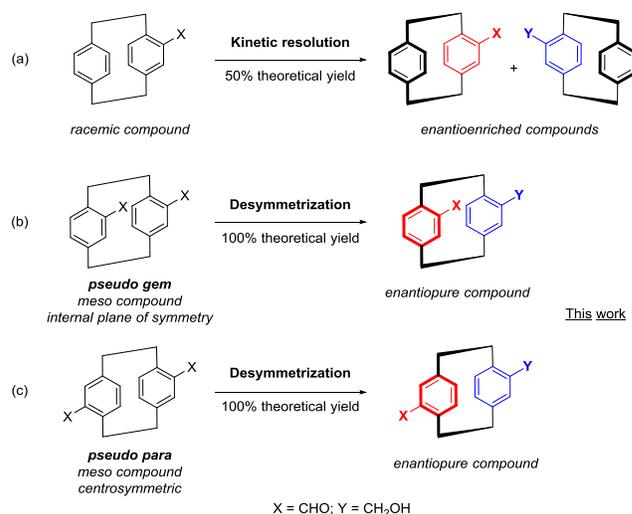
[2.2]Paracyclophane (pCp) and its derivatives constitute a well-known class of aromatic compounds characterized by an unusual three-dimensional framework and unique through-space interactions between their stacked aromatic subunits.¹ First discovered in the late 1940s,² these molecules find nowadays wide applications in material sciences for the development of through-space conjugated polymers³ and optoelectronic devices.⁴

Substituted paracyclophanes can show planar chirality due to their rigid structure which hinders the rotation of their two benzene rings.⁵ This characteristic recently proved to be particularly useful for the application of pCps as chiral inducers in asymmetric catalysis and stereoselective synthesis.^{1,6} Enantiopure paracyclophanes are also increasingly employed as building blocks for the development of circularly polarized light-emitting materials.⁷

Over the years, optically active paracyclophanes have mostly been prepared by classical stoichiometric resolution methods and/or chromatographic separation on chiral stationary phases.⁸ On the contrary, only few catalytic procedures for accessing enantioenriched pCps have been reported in the literature so far.⁹ The development of new catalytic

asymmetric processes allowing an efficient synthesis of planar-chiral paracyclophane derivatives is therefore highly desirable in order to expand the range of application of these molecules in different research areas.

Recently, we were able to demonstrate that catalytic kinetic resolutions of racemic pCps could be employed to efficiently access valuable synthetic intermediates in their enantiopure form (Scheme 1a).¹⁰ In order to overcome the limitation of 50% yield associated with the resolution strategy,¹¹ our efforts are currently directed towards the preparation of enantiopure pCp key intermediates through scalable desymmetrization reactions.

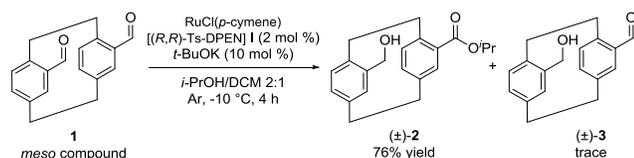


Scheme 1. Access to enantioenriched pCp derivatives

The classical desymmetrization approaches involve asymmetric transformations capable of differentiating the enantiotopic functional groups of *meso* compounds with internal mirror planes (Scheme 1b).¹² We therefore first focused our attention on the reduction of *pseudo-gem* diformyl-[2.2]paracyclophane **1** (Scheme 2) via asymmetric transfer

hydrogenation (ATH), this reaction being a particularly efficient tool for the kinetic resolution of monoformylated pCps.¹⁰

Compound **1** was synthesized starting from unsubstituted [2.2]paracyclophane following previously reported procedures.¹³ The *meso* bis-aldehyde was then submitted to a reaction in the presence of RuCl(*p*-cymene)[(R,R)-Ts-DPEN] (2 mol %) and *t*-BuOK (10 mol%), in a 1:1 mixture of *i*-PrOH and acetonitrile, at -10 °C under inert atmosphere. These conditions that were successfully employed in our laboratory to obtain enantiopure 4-formyl[2.2]paracyclophane by kinetic resolution¹⁰ led to the formation of racemic product **2** in 76% yield (Scheme 2). Compound **2**, which is characterized by both an hydroxymethyl group and an ester moiety, presumably arises from undesired intramolecular side reactions between the spatially close *pseudo-gem* reactive functions (Scheme 2).¹⁴



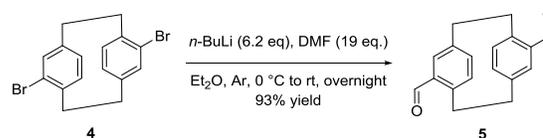
Scheme 2. Formation of the unexpected pCp **2**

In view of this result, we considered the possibility to follow a different approach and turned our attention to centrosymmetric compounds. Desymmetrization reactions can indeed also be applied to substrates showing an inversion center as their sole symmetry element. Although centrosymmetric fragments are often observed in natural products and biologically active molecules,¹⁵ this intriguing symmetry property has hardly been employed in stereoselective synthesis to access chiral compounds. Accordingly, only few desymmetrizations of centrosymmetric substrates have been reported so far.¹⁶ Promising examples of this technique include the direct enantioselective aldol reaction between an aliphatic dialdehyde and various ketone nucleophiles in the presence of zinc complexes¹⁷ or the asymmetric reduction of cyclic diketones promoted either by enzymes or CBS catalysts.¹⁸

The pCp molecule contains several symmetry elements whose combination can lead to centrosymmetric derivatives. Interestingly, centrosymmetric compounds can be preferentially obtained from unsubstituted [2.2]paracyclophane in simple transformations such as *pseudo-para* dibromination.¹⁹ To the best of our knowledge, no example of desymmetrization of centrosymmetric pCps have been described up to now. We therefore set out to study the desymmetrization of *pseudo-para*-diformyl[2.2]paracyclophane **5** (Scheme 3) via asymmetric transfer hydrogenation.

The preparation of compound **5** was previously described starting from 1,2,4,5-hexatetraene and propiolic aldehyde through a [4+2] cycloaddition and consequent separation of the four dialdehyde isomers which form during the reaction.²⁰ An alternative approach consists in bromine-lithium exchange of commercially available 4,16-dibromo[2.2]paracyclophane **4** followed by formylation.²¹ A careful optimization of these reaction conditions led to the isolation of diformylated product **5** in 93% yield after recrystallization (Scheme 3). A precise control of reaction time was

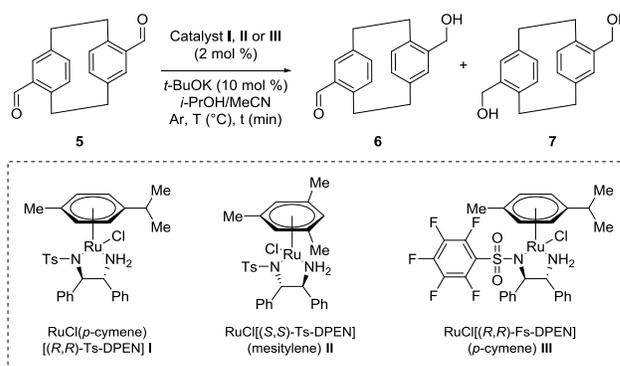
required to favour the formation of the dilithiated intermediate species and to ensure the reproducibility of this transformation in multi-gram scale.



Scheme 3. Synthesis of centrosymmetric pCp **5**

We next turned our attention to the ATH reaction. A first desymmetrization assay was performed using the conditions previously employed for the reduction of *pseudo-gem*-diformyl[2.2]paracyclophane **1**. To our delight, the reaction proceeded smoothly and the expected 4-formyl-16-hydroxymethyl[2.2]paracyclophane **6** could be isolated in 61% yield and 99% ee (Table 1, entry 1) together with 4,16-bishydroxymethyl[2.2]paracyclophane **7** (20% yield, Table 1 entry 1). Small amounts of unreacted precursor **5** could also be recovered after the reaction (9% yield, Table 1, entry 1).

Table 1. Desymmetrization of centrosymmetric pCp **5**



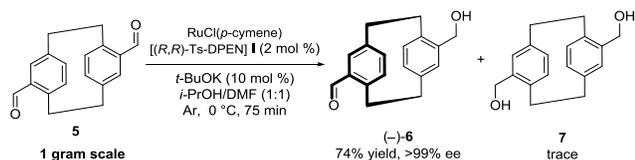
Entry	Cat.	T (°C)	t (min)	6 (%) ^{a,b}	7 (%) ^a	5 (%) ^a
1	I	-10	120	61 (99, -)	20	9
2	I	-10	30	25 (99, -)	0	65
3	II	-10	120	8 (98, +)	45	5
4	III	-10	120	61 (99, -)	28	6
5	I	-20	150	45 (99, -)	9	38
6	I	0	45	71 (99, -)	6	18
7	I	20	20	66 (99, -)	15	1
8	I	0	50	66 (99, -)	12	6
9	I	0	60	69 (99, -)	17	5
10 ^c	I	0	100	71 (99, -)	8	2
11 ^d	I	0	25	65 (99, -)	16	9
12 ^e	I	0	60	63 (99, -)	20	3
13 ^f	I	0	75	74 (99, -)	<1	3

^a Isolated yields. ^b In brackets: % ee, sign of optical rotation. ^c The reaction was carried out using 1 mol % of catalyst **I** and 5 mol % of *t*-BuOK. ^d The reaction was performed using 4 mol % of catalyst **I** and 20 mol % of *t*-BuOK. ^e DCM was used as co-solvent. ^f DMF was used as co-solvent.

Excellent enantioselectivities were observed in the early stages of the reduction (Table 1, entry 2), showing that the formation of *meso* diol **7** does not have a significant influence on the stereochemical outcome of this transformation by a subtractive Horeau-type amplification.

Encouraged by these promising results, we next tried to optimize the ATH conditions. Different ruthenium complexes (**II** and **III**, Table 1) were screened and RuCl(*p*-cymene)[(*R,R*)-Ts-DPEN] **I** was confirmed to be the best catalyst to promote the desymmetrization (Table 1, entries 1, 3 and 4). The reduction was then performed at different temperatures. Cooling the solution to $-20\text{ }^{\circ}\text{C}$ had a detrimental impact on the reaction efficiency since both the product **6** and unreacted precursor **5** were isolated in moderate yields (45% and 38% yields respectively, Table 1, entry 5). On the contrary a higher 71% yield was observed for the formation of enantiopure compound **6** when the ATH was conducted at $0\text{ }^{\circ}\text{C}$ (Table 1, entry 6). Warming the mixture at $20\text{ }^{\circ}\text{C}$ had no beneficial effects on the reaction outcome as higher amounts of by-product **7** were isolated (15% yield, Table 1, entry 7). Based on these results, further optimization experiments were carried out at $0\text{ }^{\circ}\text{C}$. Longer reaction times slightly decreased the yield of derivative **6**, and favoured the formation of by-product **7** (Table 1, entries 8 and 9 vs entry 6). Decreasing the catalytic loading had little impact on the reduction yields and selectivity, but lower conversion rates were observed (Table 1, entry 10). On the other hand, the ATH was significantly accelerated when higher amounts of catalyst were employed and product **6** was isolated in a lower yield (65%, Table 1 entry 11). Different co-solvents, such as dichloromethane (DCM) and *N,N*-dimethylformamide (DMF), were finally employed. Whereas DCM seemed to favour the formation of by-product **7** (Table 1, entry 12), the reaction performed in a 1:1 mixture of *i*-PrOH and DMF delivered the desired enantiopure product **6** in 74% yield (Table 1, entry 13).

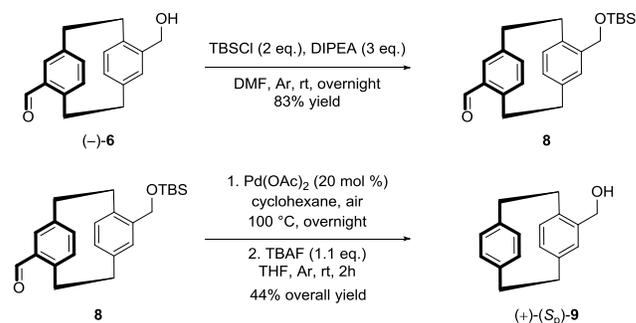
The desymmetrization of diformyl[2.2]paracyclophane **5** could be run on a 1 gram scale using our best ATH conditions (Table 1, entry 13) without any considerable loss in efficiency (Scheme 4).²² Both enantiomers of product **6** were easily accessible in their enantiopure form simply by switching from the (*R,R*)- to the (*S,S*)-Ru catalyst **I**.²³



Scheme 4. Scale-up of the desymmetrization reaction

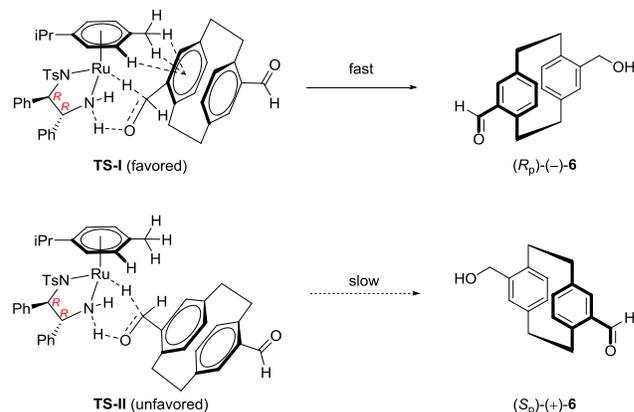
To determine the absolute configuration of product **6**, the enantiomer showing a negative rotation of plane-polarized light was converted into the known enantiopure 4-hydroxymethyl[2.2]paracyclophane^{10,24} via a three-step derivatization procedure involving a decarbonylation key step (Scheme 5). The hydroxyl function of compound **(-)-6** was first protected as *t*-butyl(dimethyl)silyl (TBS) ether (**8**) (Scheme 5). The decarbonylation of substrate **8** was then carried out in the presence of Pd(OAc)₂ (20 mol %) using previously described reaction conditions.²⁵ Removal of the TBS group finally afforded the decarbonylated product **(+)-(S_p)-9** in 44% overall yield (Scheme 5). The (*R_p*) absolute configura-

tion was therefore assigned to the levorotatory compound **(-)-6**.



Scheme 5. Determination of the absolute configuration of product **(-)-6**

Mechanistic models previously proposed for asymmetric transfer hydrogenation catalysis²⁶ may be used to rationalize the high degree of enantioselectivity observed in the desymmetrization process. Minimization of steric interactions between the bis-aldehyde **5** and the [Ru(*p*-cymene)] complex should lead to putative transition states **TS-I** and **TS-II** (Scheme 6). A stabilizing CH- π attractive interaction between the catalyst and the *p*Cp π -conjugated system should favor **TS-I** over **TS-II** and, in turn, induce the preferential formation of product (*R_p*)-**6**.



Scheme 6. Plausible transition states in the desymmetrization of *p*Cp **5** with RuCl(*p*-cymene)[(*R,R*)-Ts-DPEN]

In conclusion, we reported the first example of desymmetrization of a centrosymmetric *meso* diformyl[2.2]paracyclophane. Based on a highly enantioselective asymmetric transfer hydrogenation reaction, this route enables a practical access to an enantiopure molecule bearing on each aromatic ring of the *p*Cp core different reactive groups suitable for regioselective orthogonal post-functionalization. The desymmetrization of centrosymmetric derivatives thus seems to be a method of choice to synthesize enantiopure [2.2]paracyclophanes in an efficient way. We believe that our approach may be particularly useful in the future for the preparation of more complex planar chiral [2.2]paracyclophanes, which are not easily accessible in an enantiomerically pure form by using more conventional synthetic methods.

AUTHOR INFORMATION

Corresponding Author

laurent.micouin@parisdescartes.fr;
erica.benedetti@parisdescartes.fr.

Notes

The authors declare no competing financial interests.

SUPPORTING INFORMATION

Details of experimental procedures, ¹H NMR and ¹³C NMR spectra, HPLC chromatograms. This material is available free of charge via the Internet at <http://pubs.acs.org>.

ACKNOWLEDGMENT

We gratefully thank the CNRS, University Paris Descartes and the *Ministère de l'Enseignement Supérieur et de la Recherche* for financial support.

REFERENCES

- 1 *Modern Cyclophane Chemistry*; Gleiter, R., Hopf H., Eds.; Wiley-VCH: Weinheim, 2004.
- 2 Brown, C. J.; Farthing, A. C. Preparation and Structure of Di-p-Xylylene. *Nature* **1949**, *164*, 915-916.
- 3 a) Morusaki, Y.; Chujo, Y. Through-space conjugated polymers consisting of [2.2]paracyclophane. *Polym. Chem.* **2011**, *2*, 1249-1257. b) Morusaki, Y.; Chujo, Y. in *Through-Space Conjugated Polymers*; Chujo, R. Y., Ed.; Wiley-VCH: Weinheim, 2010. c) Hopf, H. [2.2]Paracyclophanes in Polymer Chemistry and Materials Science. *Angew. Chem., Int. Ed.* **2008**, *47*, 9808-9812. d) Morusaki, Y.; Chujo, Y. Synthesis and Properties of a Novel Through-Space Conjugated Polymer with [2.2]Paracyclophane and Ferrocene in the Main Chain. *Macromolecules* **2003**, *36*, 9319-9324.
- 4 a) Buchwald, S. L.; Huang, W. Patent No: US 20160359118, **2016**. b) Chen, J. P.; Ueno, K.; Suzuki, K. Patent No: US 6869698, **2005**. c) Bartholomew, G. P.; Ledoux, I.; Mukamel, S.; Bazan, G. C.; Zyss, J. Three-Dimensional Nonlinear Optical Chromophores Based on Through-Space Delocalization. *J. Am. Chem. Soc.* **2002**, *124*, 13480-13485. d) Bartholomew, G. P.; Bazan, G. C. Bichromophoric Paracyclophanes: Models for Interchromophore Delocalization. *Acc. Chem. Res.* **2001**, *34*, 30-39. e) Zyss, J.; Ledoux, I.; Volkov, S.; Chernyak, V.; Mukamel, S.; Bartholomew, G. P.; Bazan, G. C. Through-Space Charge Transfer and Nonlinear Optical Properties of Substituted Paracyclophane. *J. Am. Chem. Soc.* **2000**, *122*, 11956-11962.
- 5 Cram, D. J.; Allinger, N. L. Macro Rings. XII. Stereochemical Consequences of Steric Compression in the Smallest Paracyclophane. *J. Am. Chem. Soc.* **1955**, *77*, 6289-6294.
- 6 For selected reviews, see a) David, O. R. P. Syntheses and applications of disubstituted [2.2]paracyclophanes. *Tetrahedron* **2012**, *68*, 8977-8993. b) Gibson, S. E.; Knight, J. D. [2.2]Paracyclophane derivatives in asymmetric catalysis. *Org. Biomol. Chem.* **2003**, *1*, 1256-1269.
- 7 a) Gon, M.; Morisaki, Y.; Chujo Y. Optically Active Phenylethene Dimers Based on Planar Chiral Tetrasubstituted [2.2]Paracyclophane. *Chem. Eur. J.* **2017**, *23*, 6323-6329. b) Gon, M.; Sawada, R.; Morisaki, Y.; Chujo Y. Enhancement and Controlling the Signal of Circularly Polarized Luminescence Based on a Planar Chiral Tetrasubstituted [2.2]Paracyclophane Framework in Aggregation System. *Macromolecules* **2017**, *50*, 1790-1802. c) Gon, M.; Kozuka, H.; Morisaki, Y.; Chujo Y. Optically Active Cyclic Compounds Based on Planar Chiral [2.2]Paracyclophane with Naphthalene Units. *Asian J. Org. Chem.* **2016**, *5*, 353-359. d) Gon, M.; Morisaki, Y.; Chujo Y. Highly Emissive Optically Active Conjugated Dimers Consisting of a Planar Chiral [2.2]Paracyclophane Showing Circularly Polarized Luminescence. *Eur. J. Org. Chem.* **2015**, 7756-7762. e) 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* **2015**, *3*, 521-529. f) Morisaki, Y.; Inoshita, K.; Chujo Y. Planar-Chiral Through-Space Conjugated Oligomers: Synthesis and Characterization of Chiroptical Properties. *Chem. Eur. J.* **2014**, *20*, 8386-8390.
- 8 a) Morisaki, Y.; Gon, M.; Sasamori, T.; Tokitoh, N.; Chujo, Y. Planar Chiral Tetrasubstituted [2.2]Paracyclophane: Optical Resolution and Functionalization. *J. Am. Chem. Soc.* **2014**, *136*, 3350-3353. b) Meyer-Eppler, G.; Vogelsang, E.; Benkhäuser, C.; Schneider, A.; Schnakenburg, G.; Lützen, A. Synthesis, Chiral Resolution, and Absolute Configuration of Dissymmetric 4,12-Difunctionalized [2.2]Paracyclophanes. *Eur. J. Org. Chem.* **2013**, 4523-4532. c) Schneider, J. F.; Fröhlich, R.; Paradies J. [2.2]Paracyclophane-Derived Planar-Chiral Hydrogen-Bond Receptors. *Isr. J. Chem.* **2012**, *52*, 76-91. d) Enders, D.; Noll, S.; Raabe, G.; Runsink, J. Synthesis of All Possible Stereoisomers of α -Branched [2.2]paracyclophanylalkylamines. *Synthesis* **2008**, *8*, 1288-1296. e) Enders, D.; Noll, S.; Bats, J. Efficient Entry to Diastereo- and Enantiomerically Pure α -Branched [2.2]Paracyclophanyl-alkylamines. *Synlett* **2005**, 2679-2681. f) Jiang, B.; Zhao, W.-L. A simple and efficient resolution of (\pm)-4,12-dihydroxy[2.2]paracyclophane. *Tetrahedron: Asymm.* **2004**, *15*, 1141-1143. g) Minuti, L.; Taticchi, A.; Marrocchi, A. An improved synthesis of (S)-(+)- and (R)-(-)-4-ethenyl[2.2]paracyclophane. *Tetrahedron: Asymm.* **2000**, *11*, 4221-4225. h) Hopf, H.; Grahn, W.; Barrett, D. G.; Gerdes, A.; Hilmer, J.; Hucker, J.; Okamoto, Y.; Kaida, Y. Optical Resolution of [2.2]Paracyclophanes by High-Performance Liquid Chromatography on Tris(3,5-dimethylphenylcarbamates) of Cellulose and Amylose. *Chem. Ber.* **1990**, *123*, 841-845.
- 9 a) 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. b) Braddock, D. C.; MacGilp, I. D.; Perry B. G. Improved Synthesis of (\pm)-4,12-Dihydroxy[2.2]paracyclophane and Its Enantiomeric Resolution by Enzymatic Methods: Planar Chiral (R)- and (S)-Phanol. *J. Org. Chem.* **2002**, *67*, 8679-8681. c) Rossen, K.; Pye, P. J.; Maliakal, A.; Volante R. P. Kinetic Resolution of rac-4,12-Dibromo[2.2]paracyclophane in a Palladium [2.2]PHANEPHOS Catalyzed Amination. *J. Org. Chem.* **1997**, *62*, 6462-6463.
- 10 Delcourt, M.-L.; Turcaud, S.; Benedetti, E.; Micouin, L. Efficient and Scalable Kinetic Resolution of Racemic 4-Formyl-[2.2]paracyclophane via Asymmetric Transfer Hydrogenation. *Adv. Synth. Catal.* **2016**, *358*, 1213-1218.
- 11 Keith, J. M.; Larrow, J. F.; Jacobsen E. N. Practical Considerations in Kinetic Resolution Reactions. *Adv. Synth. Catal.* **2001**, *343*, 5-26.
- 12 For a recent review, see: Merad, J.; Candy, M.; Pons, J.-M.; Bressy, C. Catalytic Enantioselective Desymmetrization of *Meso* Compounds in Total Synthesis of Natural Products: Towards an Economy of Chiral Reagents. *Synthesis* **2017**, *49*, 1938-1954.
- 13 a) Sergeeva, E. V.; Rozenberg, V. I.; Antonov, D. Y.; Vorontsov, E. V.; Starikova, Z. A.; Fedyanin, I. V.; Hopf, H. Novel Multichiral Diols and Diamines by Highly Stereoselective Pinacol Coupling of Planar Chiral [2.2]Paracyclophane Derivatives. *Chem. Eur. J.* **2005**, *11*, 6944-6961. b) Hopf, H.; Greiving, H.; Beck, C.; Dix, I.; Jones, P. G.; Desvergne, J.-P.; Bouas-Laurent, H. One-Pot Preparation of [n]Ladderanes by $2\pi + 2\pi$ Photocycloaddition. *Eur. J. Org. Chem.* **2005**, 567-581. For more details on the experimental procedures, see the ESI.
- 14 Traces of racemic mono-reduced derivative **3** could be isolated by column chromatography of the crude reaction product. See the ESI for more details.
- 15 a) Faulkner, D. J. Highlights of marine natural products chemistry (1972-1999). *Nat. Prod. Rep.* **2000**, *17*, 1-6. b) Holland, J. M.; Lewis, M.; Nelson A. First Desymmetrization of a Centrosymmetric Molecule in Natural Product Synthesis: Preparation of a Key Fragment in the Synthesis of Hemibrevetoxin B. *Angew. Chem. Int. Ed.* **2001**, *40*, 4082-4084.
- 16 For a review, see: Anstiss, M.; Holland, J. M.; Nelson, A.; Titchmarsh J. R. Beyond Breaking the Mirror Plane: The Desymmetrisation of Centro-symmetric Molecules as an Efficient Strategy for Asymmetric Synthesis. *Synlett* **2003**, *8*, 1213-1220.
- 17 Dodd, K.; Morton, D.; Worden, S.; Narquizian, R.; Nelson, A. Desymmetrisation of a Centrosymmetric Molecule by Carbon-

Carbon Bond Formation: Asymmetric Aldol Reactions of a Centrosymmetric Dialdehyde. *Chem. Eur. J.*, **2007**, *13*, 5857-5861.

18 a) Spivey, A. C.; Andrews, B. I.; Brown, A. D.; Frampton, C. S. First asymmetric desymmetrisation of a centrosymmetric molecule: CBS reduction of a 2-pyridone [4 + 4]-photodimer derivative. *Chem. Commun.* **1999**, 2523-2524. b) Dodds, D. R.; Jones, J. B. Enzymes in organic synthesis. 38. Preparations of enantiomerically pure chiral hydroxydecalones via stereospecific horse liver alcohol dehydrogenase catalyzed reductions of decalindiones. *J. Am. Chem. Soc.* **1988**, *110*, 577-583. c) Baumann, P.; Prelog, V. Reaktionen mit Mikroorganismen. 6. Mitteilung. Die stereospezifische Reduktion von stereoisomeren Dekalindionen-(1,5). *Helv. Chim. Acta*, **1958**, *7*, 2379-2386.

19 Pye, P. J.; Rossen, K.; Reamer, R. A.; Tsou, N. N.; Volante, R. P.; Reider, P. J. A New Planar Chiral Bisphosphine Ligand for Asymmetric Catalysis: Highly Enantioselective Hydrogenations under Mild Conditions. *J. Am. Chem. Soc.* **1997**, *119*, 6207-6208.

20 Dix, I.; Hopf, H.; Satyanarayana, T. B. N.; Ernst L. Preparation and NMR spectra of four isomeric diformyl[2.2]paracyclophanes (cyclophanes 66). *Beilstein J. Org. Chem.* **2010**, *6*, 932-937.

21 a) Wielopolski, M.; Molina-Ontoria, A.; Schubert, C.; Margraf, J. T.; Krokos, E.; Kirschner, J.; Gouloumis, A.; Clark, T.; Guldi, D. M.; Martin, N. Blending Through-Space and Through-Bond π - π -Coupling in [2.2]-Paracyclophane-oligophenylenevinylene Molecular Wires. *J. Am. Chem. Soc.* **2013**, *135*, 10372-10381. b) Bier, A. K.; Bogwitzki, M.; Schmidt, A.; Greiner A. Synthesis, Properties, and Processing of New Siloxane-Substituted Poly(p-xylylene) via CVD. *Macromolecules* **2012**, *45*, 633-639. For references on the synthesis of regioisomers of compound **5** by using this approach, see: c) Meyer-Eppler, G.; Vogelsang, E.; Benkhaeuser, C.; Schneider, A.; Schnakenburg, G.; Luetzen, A. Synthesis, Chiral Resolution, and Absolute Configuration of Dissymmetric 4,15-Difunctionalized [2.2]Paracyclophanes. *J. Org. Chem.* **2014**, *79*, 6679-6687. d) Bondarenko, L.; Dix, I.; Hinrichs, H.; Hopf, H. Cyclophanes. Part LII: Ethynyl[2.2]paracyclophanes - New Building Blocks for Molecular Scaffolding. *Synthesis* **2004**, *16*, 2751-2759.

22 As an alternative to the ATH approach, a Corey-Bakshi-Shibata reduction was also employed to perform the desymmetrization of compound **5**. In this case, however, product **6** was isolated in low yield and poor enantiomeric excess. See the ESI for more details.

23 See the ESI for more details.

24 The optical rotation of compound **6** was reported in the literature, see: Banfi, S.; Manfredi, A.; Montanari, F.; Pozzi, G.; Quici, S. Synthesis of chiral Mn(III)-meso-tetrakis-[2.2]-p-cyclophanyl-porphyrin: a new catalyst for enantioselective epoxidation. *J. Mol. Catal. A: Chem.* **1996**, *113*, 77-86.

25 Modak, A.; Deb, A.; Patra, T.; Rana, S.; Maity, S.; Maiti, D. A general and efficient aldehyde decarbonylation reaction by using a palladium catalyst. *Chem. Commun.* **2012**, *48*, 4253-4255.

26 a) Sandoval, C. A.; Ohkuma, T.; Utsumi, N.; Tsutsumi, K.; Murata, K.; Noyori, R. Mechanism of Asymmetric Hydrogenation of Acetophenone Catalyzed by Chiral η^6 -Arene-*N*-Tosylethylenediamine-Ruthenium(II) Complexes. *Chem. Asian J.* **2006**, *1*, 102-110; b) Noyori, R.; Yamakawa, M.; Hashiguchi, S. Metal-Ligand Bifunctional Catalysis: A Nonclassical Mechanism for Asymmetric Hydrogen Transfer between Alcohols and Carbonyl Compounds. *J. Org. Chem.* **2001**, *66*, 7931-7944.

Table of Contents (TOC):

