Special topic paper

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Metathetic approach to new NORPHOS-related bisphosphanes: facile synthesis and application in asymmetric hydrogenation

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Abstract: A highly efficient synthesis of new chiral bisphosphanes derived from the renowned NORPHOS ligand is presented. The synthesis involves ring-opening metathesis of NORPHOS dioxide with an external olefin, followed by saturation of the new double bonds and adjustment of the oxidation level of phosphorus centers oxidation level. The synthesized bisphosphanes retain the configuration and enantiomeric purity of the starting NORPHOS. Their utility as ligands in asymmetric catalysis is exemplified using an *open*-NORPHOS ligand in some benchmark Rh-catalyzed hydrogenations of enamides where excellent chemical yields and enantiomeric purities of the products have been secured. The proposed protocol demonstrated the possibility of a straightforward synthesis of new chiral catalysts to be utilized in the asymmetric synthesis of pharmaceutically important compounds, such as amino acid derivatives.

Keywords: amino acids; asymmetric hydrogenation; C_2-symmetry; ChemRAWN; chiral phosphanes; NORPHOS; one-pot syntheses; ROM.

Introduction

About 50 % of all organic pharmaceutically active ingredients (API) of drugs (for human and animal cure) in the market and most newly developed ones possess the stereogenic elements; more than half of them were made synthetically. Many of those compounds were introduced to the clinical practice as racemates [1], since the synthesis and operations with the optically pure com-pounds are much more complicated. The term "stereophobia" was introduced to highlight the pharmaceutical companies' strive to produce racemic drugs [2]. The situation had changed after the thalidomide tragedy, which has a place in the late 60th [3] since the awareness of an influence of chirality on the pharmacological properties of drugs attracts more attention. The extensive studies carried out on that topic were obvious [4, 5]: the enantiomers of one API usually differ in its pharmacological and toxicological properties; for example, *d*-sotalol is a type 3 antiarrhythmic agent while *l*-sotalol is a *ß*-blocker; *l*-propranolol is a *ß*-blocker; *d*-propranolol is not. In 1992 FDA issued the policy statement for the development of

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new stereoisomeric drugs [6] according to which the priority in drug development should be given to the enantiomerically pure APIs. Moreover, the examination of both enantiomers' pharmacological and safety properties is required for the new racemic APIs. This complicates the process of developing the racemic drugs and initiates the era of a "racemic switch," which involves the development of a pure enantiomer of a drug that is already marketed as a racemate [7]. The list of tasks and questions that need to be addressed before a new drug is approved to come to market has also been prepared [8]. FDA guidance was promptly adopted by drug regulatory agencies worldwide. Nevertheless, the regulatory agencies are responsible for making decisions about drug approval which of two forms API will be developed (racemate versus a single enantiomer) basing on the rationale provided by the sponsor, based on the results of scientific complex analysis of the case provided. Aside from pharmacy, chiral non racemic compounds have also found a wide applications in cosmetics and perfumery [9, 10], agrochemistry [11–13], liquid crystals [14, 15] and other fields [16–19].

More than half of chiral non-racemic APIs are made synthetically, either by asymmetric synthesis, by separation of enantiomers, or by modifying the structures of naturally-occurring compounds from a chiral pool. In many cases, asymmetric synthesis is a method of choice. Especially attractive is asymmetric catalysis in which utilisation of a tiny amount of the well-designed catalysts effects in preparation of bulky amounts of desirable enantiomerically pure products [20–23] what is not only highly economically beneficial but also satisfies the concepts of Green Chemistry [24–26], and Sustainable Development [27]. Notably, from the perspective of efficiency, simplicity and atom economy [28], transition metal [29] complexes mediated asymmetric hydrogenation is one of the most desirable processes [30–32].

A successful ligand design is the key to an efficient catalyst [33]. The variation of ligands constitutes the most powerful tool for deriving new catalytic advantage of the prominent transition metal (TM) catalyzed reactions. It is important not only to synthesize ligands, which furnish highly active and selective TM catalysts but also to perform their synthesis in a fast, cost-affordable, and atom economy manner appropriate for creating a library of ligands of similar structure. Because there is not possible to design a universal catalyst that is good for every reaction, an efficient method for preparing a series of structurally modified chiral ligands of altered properties to achieve maximal efficiency in a given reaction is desirable. Our approach to properly constructed chiral hydrogenation catalysts has been focused on the systematic modification of a ligand known already for its high efficiency and readily availability on a practical scale. It should be robust and preferably possess functionality allowing for further straightforward structural modifications enabling precise tuning of its steric and electronic properties.

Considering this goal, we decided to prepare a series of optically active bisphosphane ligands derived from NORPHOS [34]. The (*R*,*R*)- and (*S*,*S*)-NORPHOS ligands (**1**) were at first discovered by Bruner and Pieronczyk in 1979 [35, 36] and its synthesis based on [4 + 2] cycloaddition reactions [37] was re-published with minimal modifications in 2008 [38]. NORPHOS (**1**) is one of the most frequently used ligands in enantioselective catalysis such as hydrogenation of alkenes [39–42], allylic alkylations [43, 44] and cross-coupling reactions [45–48]. Although, several variations of **1** structure were already published (Fig. 1), an unified approach to their synthesis has never been developed and each **1**-related ligand was obtained by its own synthetic route [49–51].

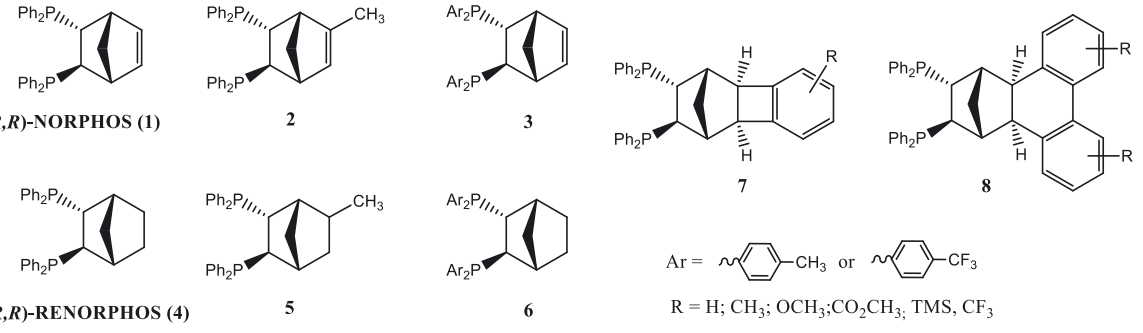


Fig. 1: NORPHOS and RENORPHOS derived chiral bisphosphanes.

Importantly, not only bicyclic and polycyclic norbornane-based phosphanes but also their less rigid monocyclic modifications such as ligands based on cyclopentane core were extensively studied. It has been amply demonstrated that enantioselectivity of asymmetric hydrogenations utilizing this class of bisphosphane ligands is always very high [52–54] (Fig. 2).

With this in mind, we develop a synthetic root to a library of chiral bisphosphane ligands based on cyclopentane skeleton derived from **1**. Operating with the powerful tools provided by contemporary alkene metathesis [55–58], we considered use of the double bond present in **1** for efficient and rapid modification of its structure. This paper proposes a series of facile transformations that furnish new chiral ligands and can be further subjected to polymerization or impregnation on stationary phase support ligand's precursors. Among the number of appropriate modifications available due to the presence of unsaturated function at the **1** core, the Ring-Opening Metathesis (ROM) approach was selected to create a series of new chiral 1,2-bisphosphane cyclopentanes substituted at positions 3 and 5.

Results

Recently, we demonstrated the possibilities to apply CM strategy in the synthesis of P-chiral phosphane oxides [59, 60]. That strategy was later adopted for the phosphane borane derivatives [61]. Applying the developed methodology of the cross-metathesis of phosphorus substituted olefins and well-defined methodology of Ring-Opening Metathesis Polymerisation (ROMP) of norbornenes [62] we designed a ring-opening metathesis (ROM) reaction between an alkene and double bond of norbornene backbone of **1**. The free NORPHOS ligand, due to its phosphane groups, was not compatible with ruthenium type catalysts used. Also, bis-borane adduct of **1** was not stable under ROM conditions. This difficulty was overcome by the utilization of NORPHOS dioxide (**1-O$_2$**) derivatives.

ROM ethenolysis of NORPHOS dioxide

Our synthetic strategy toward 1,2-bisphosphane cyclopentanes was based on the ROM reactions of the unsaturated ring system. For this purpose, chiral **1-O$_2$** was subjected to ethenolysis under mild 1 bar pressure of ethene with an application of only 5 mol% of the ruthenium catalysts: Grubbs I (**GI**), Grubbs II (**GII**), or Hoveyda-Grubbs I (**HGI**). The reactions resulted in complete substrate conversion over 16 h. To achieve completion of the reaction in a shorter time (8 h), ethylene pressure increased to 40 bar was applied (Scheme 1).

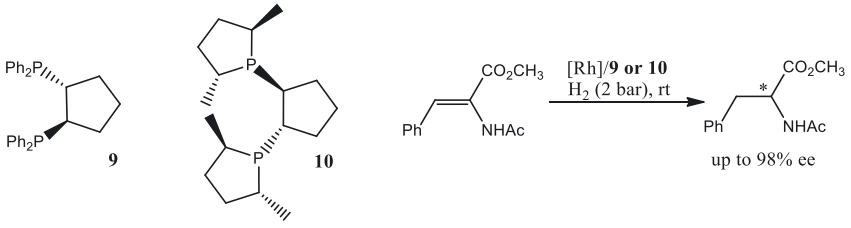
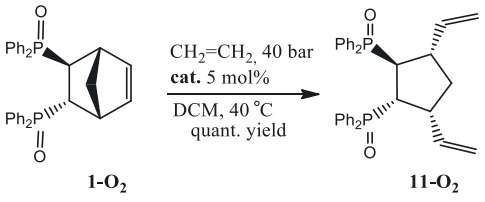


Fig. 2: Highly active bisphosphane ligand **9** and **10** with cyclopentane backbone.



Scheme 1: The ROM ethenolysis reaction of **1-O$_2$**.

It is worth to highlight, that the configuration of all stereogenic centers of substrate are maintained in the product formed.

It should be mentioned that chromatographically isolated off-white **11-O$_2$** has been typically contaminated by some insignificant traces of colored ruthenium complexes, but attempted repeated chromatographic purification always resulted in significant loss of the products (up to 20 %). Notably, not even traces of an oligomerization product of **11-O$_2$** or **1-O$_2$** could be detected in the reaction mixture.

Nevertheless, we decided to briefly test whether **1-O$_2$** could be oligomerized in the absence of ethylene under typical ROMP conditions. The attempted ROMP reactions of **1-O$_2$** were carried out in DCM in the presence of 10 mol% of **GII**, in sealed vials, at 40 and 100 °C, for 24 h. After 24 h reactions run no detectably amount of *oligo*-(NORPHOS dioxide) was formed, and almost all starting material was recovered. It seems that **1-O$_2$** does not undergo the homo-metathesis reaction. It required activation with another alkene and then underwent ROM.

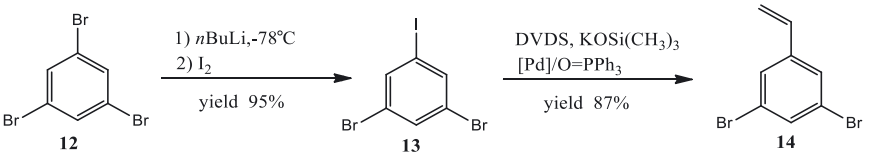
Then, we examined an alternative metathesis polycondensation approach utilizing the previously-obtained compound **11-O$_2$**. The reaction was run for 24 h in a sealed vial at 100 °C in DCM with 10 mol% of **GII**. The space available in the reactor allowed us to assume that ethene liberated during the reaction would predominantly stay in a gas phase, shifting the equilibrium towards products of the desired homo-metathesis of **11-O$_2$**. After passing the reaction mixture through a short pad of SiO_2, the crude product mixture was analyzed through MS and NMR spectroscopy. We were surprised to find that 30 % of **11-O$_2$** was converted back to the more strained **1-O$_2$**, and only less than 8 % was converted into dimers and trimers of **11-O$_2$**.

The CM reaction of **11-O$_2$** with several different terminal olefins such as styrene, equimolar mixture of E/Z 2-butenes, and 2-methyl-2-butene carried out in anhydrous DCM at 40 °C in the presence of 5–10 mol% of **GII** and 1.5–3.0 fold excess of olefins did not bring the expected products and only **11-O$_2$** was recovered after the reaction run. It seems that, according to Grubbs classification, **11-O$_2$** [63] belongs to the type-III of olefin reactivity and does not undergo homo-metathesis "dimerization" reaction but it reactivity towards the active olefins of type-I and II could be selective enough. It is worth mentioning that some internal alkenes (2-butene, and 2-methyl-2-butene) undergo the reactions with **1-O$_2$** leading to the formation of expected products in excellent yields when reactions catalyzed by 5 mol% of **GI** were performed in DCM at 40 °C.

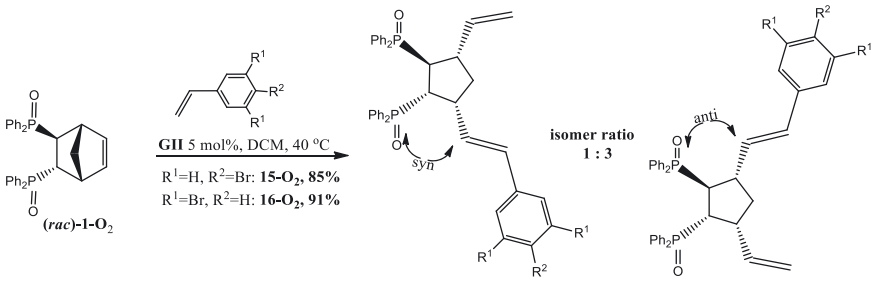
Approach to polymeric ligands. ROM of 1-O$_2$ with terminal olefins

Encouraged by the results of our ethenolyse reaction of **1-O$_2$**, we aim to prepare other NORPHOS derivatives, which could be used to synthesize useful ligands supported on the polymers. For this **1-O$_2$** was subjected to the ROM reactions with 4-bromostyrene and 3,5-dibromostyrene. The bromide functionality in the products could be used further to enable synthesis of the ligands supported on polymers or dendrimers by Suzuki or Heck type reactions.

While the 4-bromostyrene is a commercially available compound, the 3,5-dibromostyrene was synthesized using the reaction sequence shown in Scheme 2. The treatment of 1,3,5-tribromobenze with nBuLi followed by reaction with iodine gave us dibromoiodobenzene (**13**) in 95 % of yield [64]. To obtain 3,5-dibromostyrene (**14**), the methodology for palladium-catalyzed cross-coupling reaction presented by Denmark and Butler was applied [65]. We observed that dibromoiodobenzene (**13**) smoothly reacts at room temperature with vinyl precursor DVDS (divinyltetramethyldisiloxane) in the presence of a combination of $KOSiMe_3$ and π-allyl palladium complex in the presence of triphenylphosphane oxide. After flash column chromatography purification, the desired **14** was obtained in 87 % yield.



Scheme 2: Synthetic route to **14**.



Scheme 3: Synthetic route to **15-O$_2$** and **16-O$_2$**.

Initially, ROM reaction of **1-O$_2$** with 3- fold excess of 4-bromostyrene and 3,5-dibromostyrene were carried out in dry DCM at 40 °C and in the presence of 5 mol% of **GII** catalyst (Scheme 3). In both cases, after 12-h run, at full substrates conversions, the reactions afforded a ring-opened product as a pair of *syn* and *anti* diastereoisomers in a ≈ 1/3 ratio (*syn* and *anti* notation related to relative positions of neighboring styryl and phosphorus substituents). Purification of the reaction mixture by column chromatography and crystallization did not allow to separate the two diastereoisomeric products in neither case in reasonable yields. Thus, the products were isolated in the form of a mixture of diastereoisomers in 85 % in the case of 4-bromostyrene, and in 91 % in the case of 3,5-dibromostyrene. Some small amounts of pure isomers of products **15-O$_2$** and **16-O$_2$** were isolated from the mixtures chromatographically for the analytical purpose.

The isomer **16-O$_2$**-*anti*, crystallized form the mixture hexane/DCM forming the monocrystals suitable for X-ray diffraction experiment, and the molecular structure of the product **16-O$_2$**-*anti* has been finally confirmed (Fig. 3). The configuration of isomer **15-O$_2$**-*anti* was assigned by analogy.

To improve the isomer ratio of the ROM metathesis transformation, we decided to check the activity of other catalysts, such as Grubbs I (**GI**), Grubbs III (**GIII**), Hoveyda-Grubbs II (**HGII**), **nitro-Grela**, Umicore M2 catalyst (**M2**), and latent ruthenium complex (**Ru-latent**) [66]. The metathesis reactions were performed in DCM or toluene at 40 °C or 100 °C in the presence of 5 mol% of ruthenium catalyst and 1.1–3.0 fold excess of the olefin. The conversions and isomers ratios were determinate by ^{31}P NMR analysis. Table 1 summarizes the obtained results.

In the ROM reaction of **1-O$_2$** with 4-bromostyrene after 12 h, the full conversion was obtained with catalysts **GI**, **GII**, **HGII**, **M2** and **Ru-latent**. The best isomer ratio was reported with **GII**, and it was *syn*/*anti* 1/2 and 1/3 using 1.1 and 3.0 fold excess of 4-bromostyrene, respectively (Table 1, entry 2, entry 3). In turn, ROM reaction with 3,5-dibromostyrene proceeded smoothly using **GII**, **HGII**, **M2**, and latent catalyst. The reaction product was obtained as a mixture of *syn* and *anti* isomers in a ratio of ≈ 1:3 if **GII** or **M2** and 3.0 fold excess of 3,5-dibromostyrene was utilized.

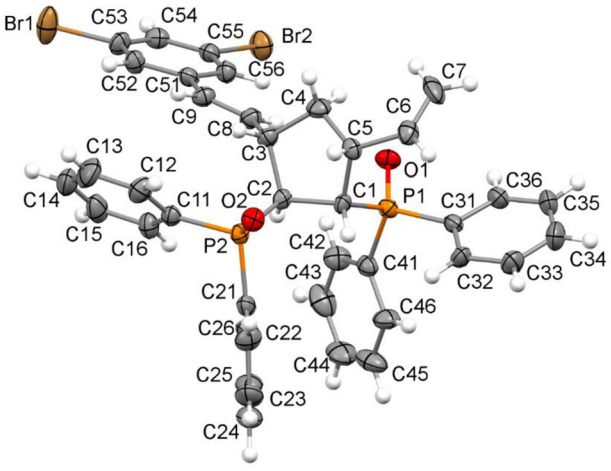


Fig. 3: Molecular structure and atom numbering scheme in **16-O$_2$**–*anti* (elipsoids drawn with 30 % probability).

Table 1: Reaction between **1-O$_2$** and 4-bromostyrene or 3,5-dibromostyrene in the presence of selected metathesis catalysts.

Entry	[Ru]	ROM with 4-bromostyrene		ROM with 3,5-dibromostyrene	
		Conv., %	*syn*/*anti*	Conv., %	*syn*/*anti*
1	GI	100	1.0/2.5	60	1.0/1.5
2	GII	100	1.0/2.0	100	1.0/2.5
3	GII	100	1.0/3.0*	100	1.0/3.0*
4	HGII	100	1.0/1.3	100	1.0/2.0
5	GIII	53	1.0/2.2	95	1.0/2.0
6	GIII	60	1.0/2.8	100	1.0/2.5*
7	M2	100	1.0/1.2	100	1.0/2.8
8	M2	100	1.0/2.0*	100	1.0/3.0*
9	*nitro*-Grela	82	1.0/1.0	80	1.0/2.5
10	Ru-latent	100	1.0/1.3**	100**	1.0/1.0

Conditions: **1-O$_2$** (0.2 mmol), [Ru] 5 mol%, olefin (0.22 mmol), DCM or toluene (4.0 ml) at 40 °C for 12 h. *0.6 mmol of the olefin was used; **reaction run at 100 °C in toluene.

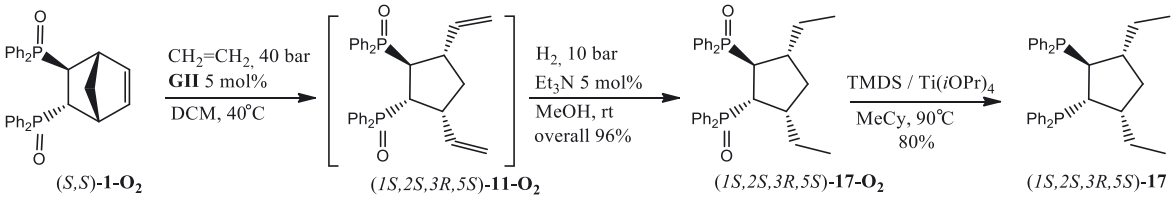
Synthesis and application of *(1S,2S,3R,5S)-open*-NORPHOS ligand (17)

To further illustrate the potential of the proposed methodology, we decided to demonstrate its use for preparation of a new ligand of cyclopentane skeleton, i.e., [(*1S,2S,3R,5S*)-3,5-diethylcyclopentane-1,2-diyl]bis(diphenylphosphane), *open*-NORPHOS ((*1S,2S,3R,5S*)-**17**) dubbed as *open*-NORPHOS. Toward this end, a sequence of reactions involving ROM reaction of *(S,S)*-**1-O$_2$** with ethylene, followed by one-pot hydrogenation of the resulting vinyl groups, and finally, deoxygenation of phosphane oxides was designed (Scheme 4). Since the designed transformations do not affect the stereogeneous centers of the parent NORPHOS core, it was expected that its configuration would be fully retained in the new ligand.

Applying the previously optimized conditions, an ethenolysis reaction of *(S,S)*-**1-O$_2$** was carried out in an autoclave in dry DCM under 40 bar pressure of ethylene and in the presence of 5 mol% of catalyst **GII**. After 12 h of reaction, ethylene was released, the reaction mixture was double diluted with methanol, and 5 mol% of Et_3N was added to convert metathesis catalyst into a catalyst active in the hydrogenation reaction. Remarkably, the hydrogenation reaction was carried out under 10 bar of hydrogen, for 12 h, at ambient temperature. This one-pot process proceeded with full substrate conversion and furnished, after chromatographic purification, the desired (*1S,2S,3R,5S*)-**17-O$_2$** in 96 % overall isolated yield (Scheme 4). An epimerization (which should lead to diastereomeric products) was not detected at any of those steps.

The X-ray diffraction experiment confirmed the molecular structure of the product (*1S,2S,3R,5S*)-**17-O$_2$** (Fig. 4).

In the final step, *open*-NORPHOS-O_2 was subjected to a deoxygenation reaction. The classical reduction protocols based on trichlorosilane [51], phenylsilane [44], and tri(trismethylsilyl)silane [44] did not allow to obtain bisphosphane in acceptable yield. To override this unfavorable reactivity of **17-O$_2$**, we applied an alternative reduction procedure which has been recommended for difficult-to-reduce phosphane oxides [47], [67]. Thus, treatment of **17-O$_2$** with a mixture of tetramethyldisiloxane (TMDS) and $(i\mathrm{PrO})_4\mathrm{Ti}$ in methylcyclohexane at 90 °C for 48 h led to its full conversion and formation of expected bis-phosphane product, which after chromatographic isolation gave *open*-NORPHOS (**17**) in 80 % yield. The potential of **17** as a new chiral biphosphane ligand was demonstrated in benchmark asymmetric hydrogenations of enamides, and its



Scheme 4: Synthesis of *open*-NORPHOS ligand **17**.

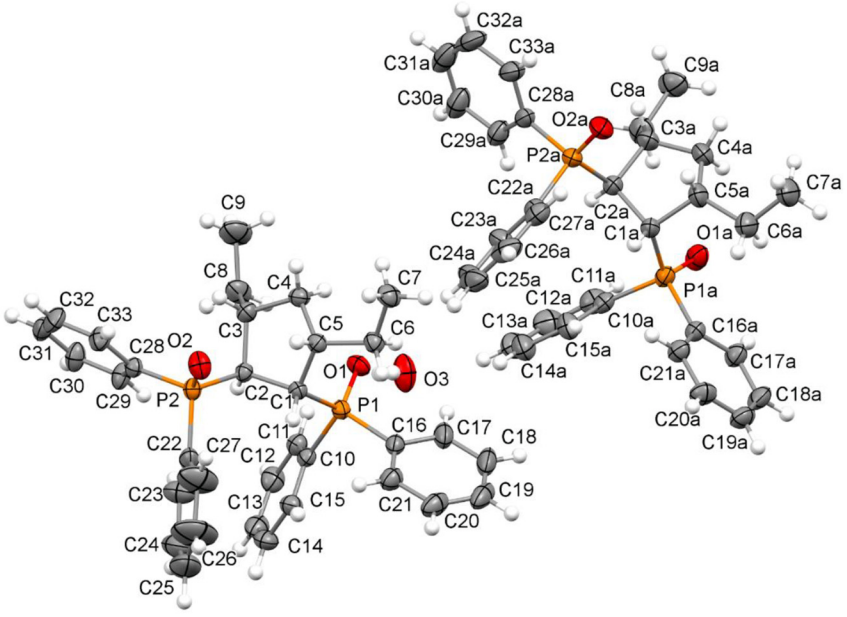
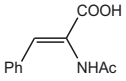
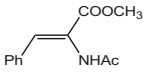
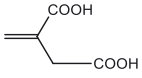
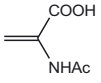


Fig. 4: Molecular structure and atom numbering scheme in two symmetrically independent molecules **17-O$_2$**-a (left) and **17-O$_2$**-b (right) in a crystal of (*1S,2S,3R,5S*)-**17-O$_2$** hydrate (elipsoids drawn with 30 % probability).

Table 2: Asymmetric hydrogenations catalyzed by [Rh]/(*1S,2S,3R,5S*)-**17** and [Rh]/(*S,S*)-**1** complexes.

Entry	Substrate	(*1S,2S,3R,5S*)-17			(*S,S*)-1		
		H_2 pressure, bar	conv.,%	ee, % (absolute configuration)[a]	H_2 pressure, bar	conv., %	ee, % (absolute configuration)[a]
1		20	100	93 (*R*)	20	100	87 (*R*)
2		5	100	95 (*R*)	5	100	95 (*R*)
3		20	100	76 (*R*)	20	100	65 (*R*)
4		5	100	81 (*R*)	5	100	83 (*R*)
5		20	100	62 (*S*)	20	100	51 (*S*)
6		20	100	90 (*R*)	20	100	33 (*R*)

Conditions: The reaction was run in ethanol under hydrogen pressure of 5 bar or 20 bar for 12 h. [Rh(cod)$_2$]BF$_4$ (2.0 mol%), phosphane ligand (2.2 mol %), olefin (100 mg), EtOH (4.0 ml). [a] Enantiomeric excess was determined by HPLC with chiral column or calculated from polarimetry by comparing the specific rotation of the product with literature values of an authentic sample.

efficacy was compared to the results obtained under the same conditions as those used in reactions with **1** (Table 2).

Enantioselective hydrogenation of the prochial enamides was performed with rhodium (I) complexes derived from (*1S,2S,3R,5S*)-**17** and (*S,S*)-**1**. Catalysts were prepared in situ by mixing [Rh(cod)$_2$]BF$_4$ and the respective phosphane. The enantiomeric excess of the hydrogenated product was determined by HPLC analysis or was calculated from a comparison of specific rotation of the product with the literature values of an authentic sample. In the case of 2-(*N*-acetylamino)cinnamic acid, the product formed was converted to the corresponding methyl ester, and its enantiomeric composition was analyzed by chiral HPLC.

Under 20 bar hydrogen, the asymmetric hydrogenation of (Z)-2-acetamido-3-arylacrylic acid gave the corresponding product with enantioselectivity of 93 % for [Rh]/**17** and 87 % for [Rh]/**1** complex (Table 2, Entry 1).

Lowering hydrogen pressure to 5 bar significantly improved ee's, and in the case of **17** it increased to 95 % (Table 2, Entry 2). Enantioselective hydrogenation of (Z)-2-acetamido-3-arylacrylic acid methyl ester catalyzed by [Rh]/**17** and [Rh]/**1** were also found to be very efficient. The desired 2-acetylalanine methyl ester with a purity of more than 81 % ee was obtained under 5 bar of H_2 with full conversion (Table 2, Entry 4). In turn, hydrogenation of itaconic acid and 2-acetamidoacrylic acid proceeded favorably with [Rh]/**17** system; the ee of the hydrogenated product was 62 and 90 %, respectively (Table 2, Entry 5 and 6).

The analysis of collected data allows us to conclude that the new **17** ligand rhodium complex is highly active and selective in enantioselectivities hydrogenation with certain superiority over commercial **1**. Moreover, the presented methodology gives straightforward access to other functionalized derivatives of cyclopentane-1,2-diylbisphosphane to be used in asymmetric catalysis.

Crystal structure of 16-O_2-*anti* and 17-O_2

Compounds **16-O_2**-*anti* and **17-O_2** crystallize in enantiomorphic space groups: **16-O_2**-*anti* in the orthorhombic $P2_12_12_1$ space group (Table 3, Fig. 3), whereas **17-O_2** forms crystals as a hydrate in the monoclinic $P2_1$ space group with two symmetrically independent molecules (**17-O_2**-a and **17-O_2**-b) and one water molecule per crystal unit (Fig. 4). Both molecules in **17-O_2** have similar geometry but have a different environment within the crystal net (Table 4).

Table 3: Crystal data and structure refinement for **16-O_2-*anti*** and **17-O_2**.

Identification code	16-O_2-*anti*	17-O_2
Empirical formula	$C_{39}H_{34}Br_2O_2P_2$	$C_{33}H_{37}O_{2.5}P_2$
Formula weight	756.42	535.61
Temperature/K	293	293
Crystal system	orthorhombic	monoclinic
Space group	$P2_12_12_1$	$P2_1$
a/Å	11.857(2)	11.70214(5)
b/Å	15.582(3)	14.83701(6)
c/Å	18.652(4)	17.14396(7)
α/°	90.00	90
β/°	90.00	92.2008(4)
γ/°	90.00	90
Volume/Å^3	3446.1(12)	2974.42(2)
Z; Z′	4; 1	4; 2
ρ_{calc} g/cm^3	1.458	1.1960
μ/mm^{-1}	4.120	1.548
F(000)	1536.0	1145.4
Crystal size/mm^3	0.32 × 0.20 × 0.15	0.25 × 0.25 × 0.25
Radiation	CuKα (λ = 1.54178)	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	7.4 to 150.32	7.56 to 135.36
Index ranges	$-14 \le h \le 14$, $0 \le k \le 19$, $0 \le l \le 22$	$-13 \le h \le 14$, $-17 \le k \le 17$, $-20 \le l \le 20$
Reflections collected	7298	60221
Independent reflections	6854 [R_{int} = 0.0327, R_{sigma} = 0.0772]	10775 [R_{int} = 0.0196, R_{sigma} = 0.0135]
Data/restraints/parameters	6854/0/407	10775/1/683
Goodness-of-fit on F^2	1.048	1.042
Final R indexes [$I \ge 2\sigma$ (I)]	R_1 = 0.0511, wR_2 = 0.1442	R_1 = 0.0332, wR_2 = 0.0917
Final R indexes [all data]	R_1 = 0.1252, wR_2 = 0.1748	R_1 = 0.0334, wR_2 = 0.0920
Largest diff. peak/hole/e Å^{-3}	0.49/−1.04	0.41/−0.27
Flack parameter	−0.01(3)	0.03(1)
CCDC No.	2045627	2045628

Table 4: Selected geometric parameters: bond lengths (Å) and torsion angles (°) of molecules in crystals of **16-O_2** and **17-O_2** (**17-O_2**-a and **17-O_2**-b are the two symmetrically independent molecules in **17-O_2**.

Bond lengths					
Bond	**16-O_2-*anti***	***Bond***	**17-O_2-a**	***Bond***	**17-O_2-b**
P1–O1	1.481(4)	P1–O1	1.485(2)	P1a–O1a	1.481(2)
P1–C41	1.800(7)	P1–C1	1.832(2)	P1a–C1a	1.828(2)
P1–C31	1.801(7)	P1–C10	1.817(2)	P1a–C10a	1.809(2)
P1–C1	1.830(6)	P1–C16	1.814(2)	P1a–C16a	1.816(2)
P2–O2	1.486(4)	P2–O2	1.488(2)	P2a–O2a	1.486(2)
P2–C21	1.799(7)	P2–C2	1.825(2)	P2a–C2a	1.822(2)
P2–C11	1.810(6)	P2–C22	1.806(2)	P2a–C22a	1.802(2)
P2–C2	1.825(6)	P2–C28	1.803(2)	P2a–C28a	1.813(2)
C1–C2	1.556(7)	C1–C2	1.556(2)	C1a–C2a	1.558(3)
C1–C5	1.582(8)	C1–C5	1.550(2)	C1a–C5a	1.566(3)
C2–C3	1.562(8)	C2–C3	1.559(3)	C2a–C3a	1.564(3)
C3–C4	1.519(9)	C3–C4	1.534(3)	C3a–C4a	1.518(3)
C3–C8	1.511(9)	C3–C8	1.521(3)	C3a–C8a	1.489(4)
C4–C5	1.529(9)	C4–C5	1.531(3)	C4a–C5a	1.527(4)
C5–C6	1.472(9)	C5–C6	1.524(3)	C5a–C6a	1.504(4)
C6–C7	1.326(13)	C6–C7	1.511(3)	C6a–C7a	1.489(4)
C8–C9	1.319(9)	C8–C9	1.528(4)	C8a–C9a	1.536(4)
C9–C51	1.463(9)				
C53–Br1	1.883(6)				
C55–Br2	1.883(7)				
Torsion angles					
Torsion	**16-O_2-*anti***	***Torsion***	**17-O_2**	***Torsion***	**17-O_2-*a***
C1–C2–C3–C4	–2.1(6)	C1–C2–C3–C4	–5.2(2)	C1a–C2a–C3a–C4a	–8.3(2)
C2–C3–C4–C5	–22.4(7)	C2–C3–C4–C5	–19.4(2)	C2a–C3a–C4a–C5a	–16.8(2)
C3–C4–C5–C1	37.8(7)	C3–C4–C5–C1	36.4(2)	C3a–C4a–C5a–C1a	35.0(2)
C4–C5–C1–C2	–37.8(6)	C4–C5–C1–C2	–38.6(2)	C4a–C5a–C1a–C2a	–38.6(2)
C5–C1–C2–C3	24.6(6)	C5–C1–C2–C3	27.2(2)	C5a–C1a–C2a–C3a	29.2(2)
C1–C5–C6–C7	113.4(9)	C1–C5–C6–C7	–177.9(2)	C1a–C5a–C6a–C7a	–171.8(2)
C4–C5–C6–C7	–7.1(11)	C4–C5–C6–C7	61.0(2)	C4a–C5a–C6a–C7a	66.0(3)
C2–C3–C8–C9	120.6(7)	C2–C3–C8–C9	174.2(2)	C2a–C3a–C8a–C9a	175.6(2)
C4–C3–C8–C9	–121.3(7)	C4–C3–C8–C9	–65.6(3)	C4a–C3a–C8a–C9a	–63.3(3)
C3–C8–C9–C51	178.0(6)	–	–	–	–
P1–C1–C2–P2	145.6(3)	P1–C1–C2–P2	146.42(9)	P1a–C1a–C2a–P2a	150.3(1)
P1–C1–C5–C4	82.6(5)	P1–C1–C5–C4	82.5(2)	P1a–C1a–C5a–C4a	82.2(2)
P2–C2–C3–C4	117.0(5)	P2–C2–C3–C4	114.3(1)	P2a–C2a–C3a–C4a	111.5(2)

The five-membered rings in **16-O_2**-*anti* and **17-O_2** have an envelope conformation (Figs. 3 and 4, Table 4). The planar aryl substituent in **16-O_2**-*anti* is almost perpendicular to the five-membered ring with an interplanar angle of 84(1)°. The ethylene group in 16 is coplanar with C4–C5 bond, whereas the ethyl substituents in molecules in **17-O_2** are coplanar with C2–C3 bond. The overlay of molecules **16-O_2**-*anti*, **17-O_2**, and **1** [38] shows only slight differences in the conformation along with the common molecular fragment (Fig. 5). The torsion along P–C–C–P bonds is higher (146–150°) in the reported here structures than in the **1** molecule (116). One of the P–C–C–C torsions along the five-membered ring is close to 82° (Table 4), while the other one is anticlinal in **16-O_2**-*anti* and **17-O_2** (111–117°), and antiperiplanar in **1** (161°).

The phosphoryl oxygen atoms accept hydrogen bonding from the acidic aromatic C–H groups in **16-O_2**-*anti* and **17-O_2** (Table 5). Additionally, in **17-O_2**, the water molecule forms O–H…O hydrogen bonds with the same acceptor. Despite the presence of aromatic rings, there are no π-stacking interactions in **16-O_2**-*anti* and **17-O_2.**

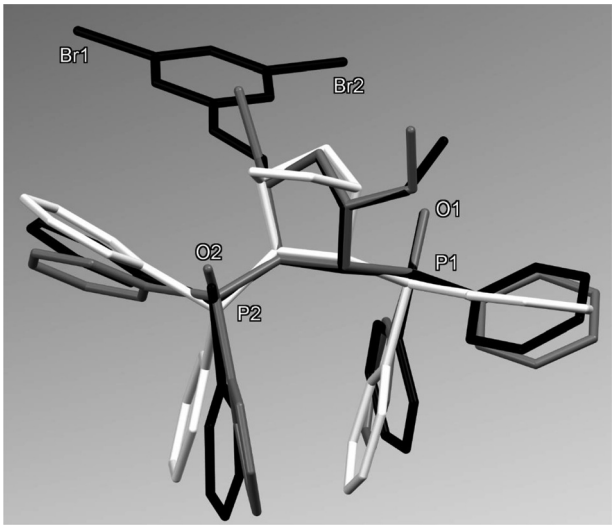


Fig. 5: Overlay of molecules **16-O_2** (black), **17-O_2** (grey) and **1** (white, Refcode PIVXOI [38]. Hydrogen atoms were omitted for clarity.

Table 5: Hydrogen bonds in **16-O_2**-*anti* and **17-O_2**.

D–H…A	D–H	H…A	D…A	∠ DHA	Symmetry operation
16-O_2					
C14–H14…O1	0.93	2.34	2.25(1)	166	$1/2 - x$, $1 - y$, $1/2 + z$
C35–H35…O2	0.93	2.52	3.43(1)	167	$3/2 - x$, $1 - y$, $1/2 + z$
C25–H25…O2	0.93	2.60	3.35(1)	138	$3/2 - x$, $1 - y$, $-1/2 + z$
17-O_2					
O3–H3c…O1	0.85	1.97	2.818(3)	173	–
O3–H3b…O2	0.85	2.04	2.872(3)	166	–
C11–H11…O2	0.93	2.65	3.410(3)	140	$-x$, $-1/2 + y$, $1 - z$
C27a–H27a…O1a	0.93	2.85	3.547(3)	133	$1 - x$, $1/2 + y$, $-z$
C14–H14…O2a	0.93	2.65	3.526(3)	158	x, y, $1 + z$

The Hirshfeld surface analysis [68, 69] was performed to show the differences in the crystal packing (Figs. 6 and 7). The presence of Br atoms in 16 has a meaningful impact (12.1 %) on the contribution of these atoms in the intermolecular contacts, but the amount of contacts formed by O and C atoms remains at a similar level in comparison to **17-O_2**. A difference between two symmetrically independent molecules in **17-O_2** is observed for contacts formed by O atoms (5.9 vs. 7.2 %). The fingerprint plots for molecules **16-O_2**-*anti*, **17-O_2**-a, and **17-O_2**-b are presented in Fig. 8.

Materials and methods

General Information

Unless noted otherwise, all starting materials and solvents were used as obtained from commercial suppliers without further purification. Organic solvents used in this study were dried over appropriate drying agents and distilled before use. Thin-layer chromatography was carried out using Merck silica gel 60 F_{254} plates

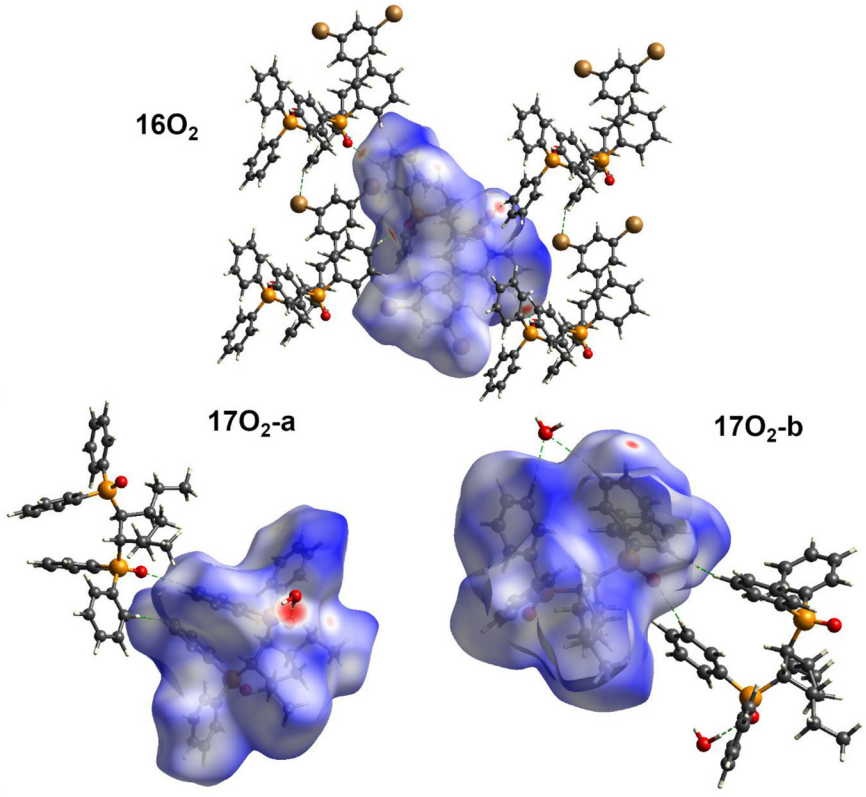


Fig. 6: Hirshfeld surfaces of molecules **16-O_2**-*anti*, **17-O_2**-a, and **17-O_2**-b plotted over d_{norm}.

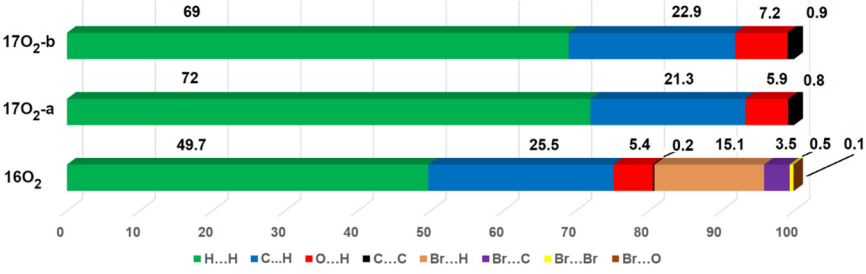


Fig. 7: Percentage contribution of various intermolecular contacts formed by molecules **16-O_2**-*anti*, **17-O_2**-a, and **17-O_2**-b.

(Merck, Kenilworth, NJ, USA) eluted with hexanes/ethyl acetates/methanol mixtures in appropriate for the substance being considered ratios, the retardation factor (R_f) was calculated as the distance traveled by the substance being considered divided by the total distance traveled by the mobile phase. Visualization of TLC plates was performed by UV light either $KMnO_4$ or I_2 stains. NMR spectra were recorded on Bruker Avance 500 MHz spectrometer, and chemical shifts are reported in ppm, and calibrated to residual solvent peaks at 7.27 and 77.00 ppm for ^1H and ^{13}C in $CDCl_3$ or internal reference compounds. The following abbreviations are used in reporting NMR data: *s* (singlet), *d* (doublet), *t* (triplet), *q* (quartet), *m* (multiplet), *br* (broad). Coupling constants (J) are in Hz. Spectra are reported as follows: chemical shift (δ, ppm), multiplicity, integration, coupling constants (Hz). IR spectra were recorded on the Nicolet 8700A FTIR-ATR spectrometer: wave numbers are in cm^{-1}. Products were purified by flash chromatography on silica gel 60 (230–400 mesh). The X-ray diffraction intensities were collected on SuperNova X-ray diffractometer equipped with Atlas S2 CCD detector using mirror-monochromatized Cu *K*α radiation (λ = 1.54184 Å). Low- and high-resolution mass spectra were obtained with Shimadzu LC-MS (Kinetex® 2.6 µm Biphenyl 100 Å 50 × 2.1 mm LC-column, acetonitrile/water with HCO_2H additive mobile phase) IT-TOF spectrometer. Not available commercially substrates were obtained by known literature procedures.

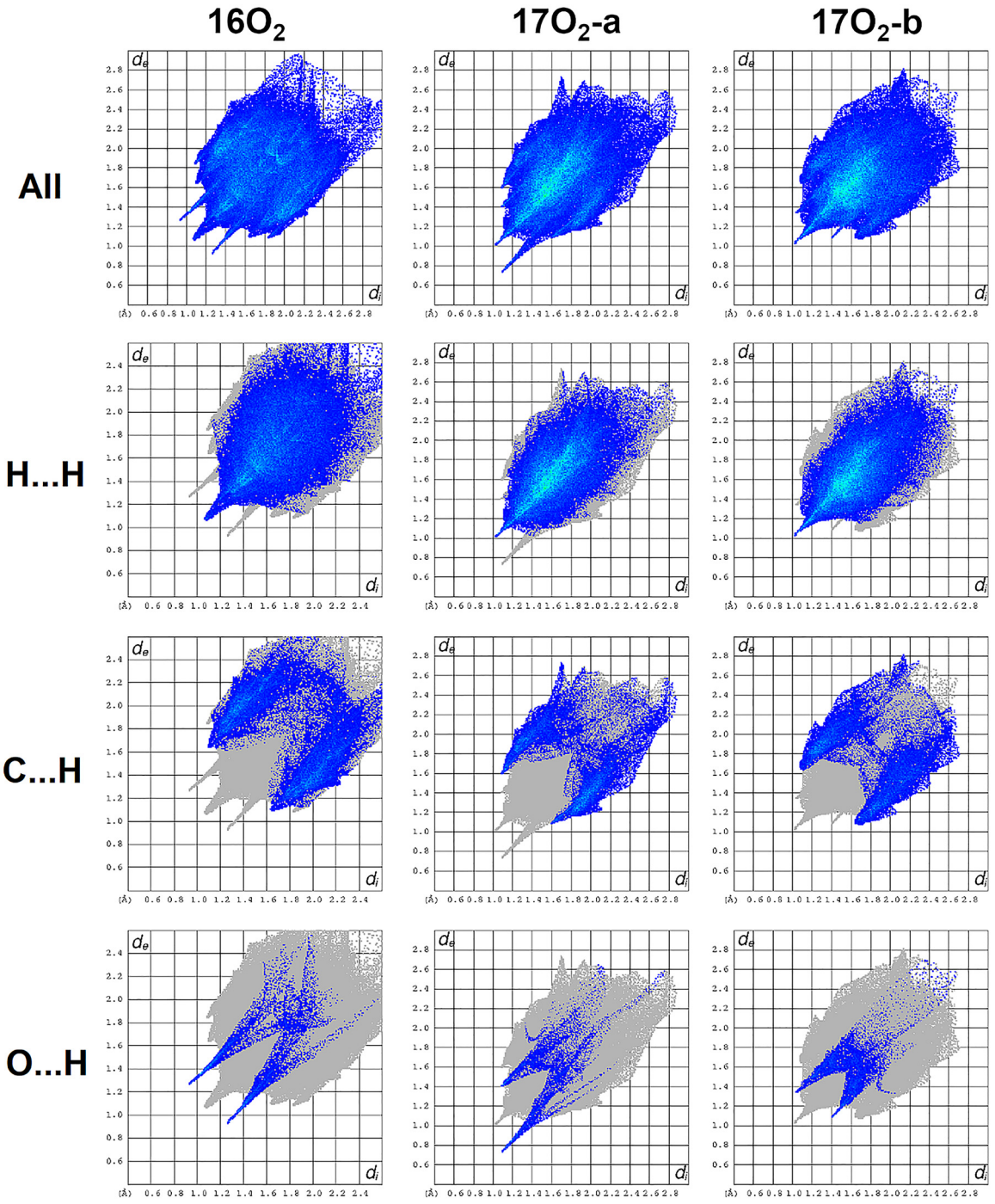


Fig. 8: Fingerprint plots for various solid-state interactions of molecules **16-O_2**-*anti*, **17-O_2**-a, and **17-O_2**-b.

Synthesis and Spectral data

Synthesis of [(*1S,2S,3R,5S*)-3,5-diethenylcyclopentane-1,2-diyl]bis(diphenylphosphane) dioxide ((*1S,2S,3R,5S*)-11-O_2)

Into an pressure tube equipped with magnetic stirbar were added 500 mg of (*S,S*)-**1-O_2** (1.0 mmol), ruthenium complex (**GI**, **HGI**, **GII**, 5.0 mol%) and dry DCM (10 ml) under argon. The vessel was pressurized to 40 bar of ethylene (CP grade, 99.5 %) under rapid stirring. The reaction was stirred at 40 °C for 10 h. Then, pressure was released and the solvent was removed in vacuum to afford a dark brown oil that was purified by flash chromatography (with ethyl acetate) to give **11-O_2** as a white solid with final yield 85–96 %, *mp*: 130.5–130.9 °C, $[\alpha]_D$ = −83 (*c* 0.5, $CHCl_3$), analytical TLC: R_f 0.60 (ethyl acetate). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.97–2.02 (*m*, 1H, CH), 2.41–2.48 (*m*, 1H, CH), 2.86 (*d*, *J* = 20.0, 1H, CH), 2.99–3.07 (*m*, 1H, CH), 3.30 (*dd*, *J* = 5.0, 20.0, 1H, CH), 3.49–3.59 (*m*, 1H, CH), 4.28 (*d*, *J* = 15.0, 1H, CH), 4.50 (*d*, *J* = 10.0, 1H, CH), 4.75 (*d*, *J* = 10.0, 1H, CH), 4.98 (*d*, *J* = 20.0, 1H, CH), 5.62 (*dd*, *J* = 10.0, 20.0, 1H, CH), 6.17 (*dd*, *J* = 10.0, 15.0, 1H, CH), 7.19–7.50 (*m*, 16H, Ar-H), 7.64–7.70 (*m*, 4H, Ar-H). ^{13}C NMR (125 MHz, CDCl3): δ = 39.6 (*d*, *J* = 3.7), 42.7(*d*, *J* = 70.0), 43.3, 43.7 (*d*, *J* = 70.0), 49.2 (*d*, *J* = 5.0), 114.5, 115.7, 128.2, 128.2, 128.3, 128.3, 128.6, 128.7, 128.7, 128.8, 130.7, 130.7, 130.9, 130.9, 131.0, 131.2 (*d*, *J* = 2.5), 131.4, 131.4 (*d*, *J* = 2.5), 131.6, 131.7, 131.8 (*d*, *J* = 2.5), 132.1, 132.4, 133.1, 133.9, 137.7 (*d*, *J* = 5.0), 141.4 (*d*, *J* = 7.5). ^{31}P NMR (202 MHz, $CDCl_3$): δ = 33.2 (*d*, *J* = 40.4), 36.7 (*d*, *J* = 40.4). IR (CH_2Cl_2 film) 431, 455, 448, 510, 526, 555, 694, 729, 771, 758, 855, 879, 909, 918, 997, 1041, 1071, 1101, 1115, 1160, 1181, 1223, 1311, 1436, 1590, 1639, 2896, 3075, 3474 cm^{-1}. HRMS (ESI+) calcd. for $[C_{33}H_{32}NaO_2P_2 + Na]^+$ = 545.1766 Da, found 545.1770 Da (diff. −0.4 ppm).

Synthesis of 1,3-dibromo-5-iodobenzene (13)

The 1,3,5-tribromobenzene **12** (3.0 g, 9.5 mmol) was dissolved in dry Et_2O (30 ml) and the obtained solution was cooled to −78 °C. The solution of *n*BuLi (2.0 M in cyclohexane, 14.2 mmol) was next added over 30 min, and the reaction mixture was stirred for an additional 1 h at −78 °C. Then, the solution of I_2 (4.8 g, 18.0 mmol) in 30 ml of dry Et_2O was added slowly. After stirring for 30 min at −78 °C the solution was warmed to room temperature and saturated $Na_2S_2O_3$ was added until colorless. The organic phase was separated and washed with water (2 × 60 ml) and brine (2 × 60 ml). The solution was dried over $MgSO_4$ and after filtration the solvent was removed. The desired product was crystallized form EtOH at −10 °C to yield 3.28 g (95 %) as a white solid. An analysis of spectra of the product confirms it corresponds to the literature data [70]. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.66 (*t*, *J* = 5.0, 1H, Ar-H), 7.82 (*d*, *J* = 5.0 Hz, 2H, Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 123.4, 133.6 138.5.

Synthesis of 1,3-dibromo-5-ethenylbenzene (14)

In the Schenk tube, 3.0 g of 1,3-dibromo-5-ethenylbenzene 13 (8.3 mmol), π-allyl palladium dimer (2.5 mol%), PPh_3 = O (5.0 mol%), DVDS (3.7 g, 20.0 mmol) and $KOSiMe_3$ (4.2 g, 33.2 mmol) were combined in dry DMF (20 ml). The reaction was stirred under argon for 10 h at rt. Then water was added (50 ml) and aqueous layer was extracted with hexane (3 × 30 ml). The organic layer was washed sequentially with water. The organic phase was dried with Na_2SO_4, filtered and concentrated. Purification of the crude product by column chromatography with hexane gave 1.89 g (87 %) a clear, colorless oil. The analysis of spectra of the product confirms that it corresponds to the literature data [71]. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.37 (*d*, *J* = 10.0, 1H, CH), 5.76 (*d*, *J* = 20.0, 1H, CH), 6.77 (*dd*, *J* = 10.0, 15.0, 1H, CH), 7.47 (*d*, *J* = 1.7, 1H, Ar-H), 7.55 (*t*, *J* = 5.0, 1H Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 116.8, 123.1, 127.9, 133.0, 134.3, 141.0.

Synthesis of (3-(4-bromostyryl)-5-vinylcyclopentane-1,2-diyl)bis(diphenylphosphane dioxide) (15-O_2): Typical Procedure

In a Schlenk tube under argon atmosphere the solution of racemic **1-O_2** (100 mg, 0.2 mmol) and ruthenium complex **GII** were dissolved in dry DCM or dry toluene (4.0 ml) and then 4-bromostyrene (0.22 mmol or 0.6 mmol) was added. The reaction was stirred for 12 h at 40 °C or at 100 °C. The conversion of the ROM reaction and isomers ratio was determinate by ^{31}P NMR analysis. The reaction mixture was purified by chromatography column with hexane/ethyl acetate/MeOH (15:5:0.5) to give a mixture of the isomers in ratio from 3/1 to 2/1 and in overall yield 85 % (116 mg). Pure isomer **15-O_2**-*anti* could be isolated by fractional crystallization of the obtained mixture from diethyl ether or hexane/DCM mixture in small yields. **15-O_2**-*syn* ^{31}P NMR (202 MHz, $CDCl_3$): δ = 36.83 (*d*, *J* = 40), 33.02 (*d*, *J* = 40). **15-O_2**-*anti* ^{31}P NMR (202 MHz, $CDCl_3$): δ = 36.2 (*d*, *J* = 40), 33.2 (*d*, *J* = 40). **15-O_2**-*anti* ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.1 (*m*, 1H, CH), 2.63 (*m*, 1H, CH_2), 2.94 (*dm*, *J* = 19.8, 1H, CH), 3.20 (*m*, 1H, CH_2), 3.34 (*dd*, *J* = 18.5, 7.1, 1H, CH), 3.79 (*m*, 1H, CH), 5.35 (*d*, *J* = 15.7, 1H, CH), 5.94 (*dd*, *J* = 15.7. 9.0, 1H, CH), 6.3 (*d*, *J* = 15.9, 1H, CH), 6.56 (*d*, *J* = 8.4, 2H, 2xCH), 6.64 (*dd*, *J* = 15.6, 9.4, 1H, CH), 7.12 (*d*, *J* = 8.4, 2H, Ar-H), 7.62 (*m*, 22H, Ar-H). IR (CH_2Cl_2 film) 3053, 1638, 1589, 1486, 1436, 1182, 1113, 1100, 1070, 1007, 997, 917, 857, 806, 730, 719, 692, 547, 521 cm^{-1}. HRMS (ESI$^+$) calcd. for $[C_{39}H_{35}NaO_2P_2Br + Na]^+$ = 699.1199 Da, found 699.1188 Da (diff. 1.1 ppm).

Synthesis of (3-(3,5-dibromostyryl)-5-vinylcyclopentane-1,2-diyl)bis(diphenylphosphane dioxide) (16-O_2): Typical Procedure

In a Schlenk tube under argon atmosphere the solution of racemic **1-O_2** (100 mg, 0.2 mmol) and ruthenium complex **GII** were dissolved in dry DCM or dry toluene (4.0 ml) and then 1,3-dibromo-5-ethenylbenzene **14** (0.22 mmol or 0.6 mmol) was added. The reaction was stirred for 12 h at 40 °C or at 100 °C. The conversion of the ROM reaction and isomers ratio was determinate by ^{31}P NMR analysis. The reaction mixture was purified by chromatography column with hexane/ethyl acetate/MeOH (15:5:0.5) to give a mixture of the isomers in ratio ~ 3/1 and in overall yield 91 % (137 mg). Some small amounts of pure isomers **16-O_2** could be obtained by column chromatography on silica eluting the fractions with mixture of hexane/methanol/ethyl acetate = 50/2/30. The isomer *anti* was next crystallized from hexane/DCM mixture to form the material for X-ray characterization. **16-O_2**-*syn* ^{31}P NMR (202 MHz, $CDCl_3$): δ = 36.76 (*d*, *J* = 40.1), 32.74 (*d*, *J* = 40.1). **16-O_2**-*syn* ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.04 (*m*, 1H, CH), 2.56 (*td*, *J* = 12.3, 12.3, 9.3, 1H, CH_2), 2.89 (*dm*, *J* = 19.4, 1H, CH), 3.08 (*m*, 1H, CH_2), 3.32 (*dd*, *J* = 18.3, 7.3, 1H, CH), 3.73 (*m*, 1H, CH), 4.30 (*dd*, *J* = 17.0, 1.3, 1H, CH), 4.78 (*dd*, *J* = 9.9, 1.5, 1H, CH), 5.99 (*m*, 1H, CH), 6.21 (*m*, 2H, 2xCH), 6.72 (*d*, *J* = 1.8, 2H, Ar-H), 7.36 (*m*, 17H, Ar-H), 7.68 (*m*, 4H, Ar-H). **16-O_2**-*syn* ^{13}C NMR (125 MHz, $CDCl_3$): δ = 39.88 (*d*, *J* = 2.9), 43.53 (*d*, *J* = 5,7), 43.97, 44.42 (*d*, *J* = 3.4), 48.63 (*d*, *J* = 4.0), 115.09, 122.86, 127.93, 128.32, 128.66, 128.82, 129.08, 129.17, 129.23, 129.32, 130.95, 131.03, 131.05, 131.15, 131.28, 131.40, 131.47 (*d*, *J* = 2.3), 131.68 (*d*, *J* = 2.9), 131.93 (*d*, *J* = 2.9), 132.01, 132.14, 132.34, 132.87, 133.60, 134.56 (*d*, *J* = 5.7), 141.01, 141.82 (*d*, *J* = 6.3). **16-O_2**-*anti* ^{31}P NMR (202 MHz, $CDCl_3$): δ = 33.22 (*d*, *J* = 39.0), 35.89 (*d*, *J* = 39.5). **16-O_2**-*anti* ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.01 (*m*, 1H, CH), 2.54 (*td*, *J* = 12.5, 12.5, 9.5, 1H, CH), 2.90 (*dm*, *J* = 19.8, 2H, CH, CH_2), 3.14 (*m*, 1H, CH), 3.29 (*dd*, *J* = 18.5, 7.0, 1H, CH), 3.63 (*d*, 1H, CH), 4.50 (*dd*, *J* = 10.2, 1.6, 1H, CH), 4.99 (*dm*, *J* = 17.0, 1H, CH), 5.23 (*d*, *J* = 15.7, 1H, CH), 5.58 (*ddd*, *J* = 17.0, 10.0, 8.7, 1H, CH), 6.52 (*dd*, *J* = 15.7, 8.5, 2H, Ar-H), 7.38 (*m*, 17H, Ar-H), 7.67 (*m*, 4H, Ar-H). IR (CH_2Cl_2 film) 3420, 3055, 2927, 1579, 1544, 1181, 1113, 1100, 1070, 997, 910, 851, 773, 719, 692, 531, 519 cm^{-1}. HRMS (ESI$^+$) calcd. for $[C_{39}H_{34}NaO_2P_2Br_2 + Na]^+$ = 777.0283 Da, found 777.0293 Da (diff. –1.0 ppm).

One pot synthesis of [(*1S,2S,3R,5S*)-3,5-diethylcyclopentane-1,2-diyl]bis(diphenylphosphane) dioxide ((*1S,2S,3R,5S*)-17-O_2)

Into a pressure vessel equipped with a magnetic stirring bar were added 500 mg of (*S,S*)-**1-O_2** (1.0 mmol), **GII** (5.0 mol%) and dry DCM (10 ml) under argon. The vessel was pressurized to 40 bar of ethylene (CP grade, 99.5 %) under rapid stirring. The reaction mixture was stirred at 40 °C for 12 h. Then, pressure was released and

Et_3N (5.0 mol%) and MeOH (10 ml) were added. The vessel was again pressurized to 10 bar of hydrogen and the resulting reaction mixture was stirred at room temperature for 12 h. After this time hydrogen was released and the mixture was concentrated. The product was purified by flash chromatography (ethyl acetate) to give *open*-NORPHOS-O_2 (**17-O$_2$**) in 96 % yield as a white solid. Mp: 169–170 °C, $[\alpha]_D$ = –124 (*c* 0.5, $CHCl_3$), analytical TLC: R_f 0.63 (ethyl acetate). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.65 (*t*, *J* = 10.0, 10.0, 3H, CH_3), 0.71 (*t*, *J* = 5.0, 10.0, 3H, CH_3), 1.12–1.37 (*m*, 3H, CH, CH_2), 1.17–1.90 (*m*, 2H, CH, CH_2), 2.18 (*dd*, *J* = 10.0, 15.0, 1H, CH), 2.24–2.33 (*m*, 1H, CH), 2.60–2.66 (*m*, 1H, CH), 2.70–2.80 (*m*, 1H, CH), 3.10 (*dd*, *J* = 5.0, 20.0, 1H, CH), 7.26–7.37 (*m*, 8H, Ar-H), 7.42–7.50 (*m*, 8H, Ar-H), 7.61–7.71 (*m*, 4H, Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.6, 13.7, 25.3 (*d*, *J* = 3.7), 29.8 (*d*, *J* = 6.2), 37.2 (*d*, *J* = 3.7), 39.9, 42.0 (*d*, *J* = 66.2), 44.7 (*d*, *J* = 66.2), 47.3 (*d*, *J* = 3.7), 128.3, 128.4, 128.5, 128.5, 128.6, 128.6, 128.6, 128.7, 130.5, 130.6, 130.8, 130.9 (*d*, *J* = 2.5), 131.1, 131.1, 131.1, 131.2, 131.2, 131.2, 131.3, 131.5, 131.7 (*d*, *J* = 2.5) 131.4 (*d*, *J* = 95.0), 131.9 (*d*, *J* = 93.7), 133.6 (*d*, *J* = 116.2), 134.1 (*d*, *J* = 113.7). ^{31}P NMR (202 MHz, $CDCl_3$): δ = 33.3 (*d*, *J* = 42.4), 36.0 (*d*, *J* = 46.4). IR (CH_2Cl_2 film) 3056, 2959, 2220, 1680, 14636, 1184, 1112, 1027, 926, 726, 699, 586, 551, 531, 513 cm^{-1}. HRMS (ESI$^+$) calcd. for $[C_{33}H_{36}P_2O_2 + Na]^+$ 549.2087 Da, found 549.2083 Da (diff. 0.4 ppm).

Synthesis of [(*1S,2S,3R,5S*)-3,5-diethylcyclopentane-1,2-diyl]bis(diphenylphosphane), *open*-NORPHOS ((*1S,2S,3R,5S*)-17)

The bisphosphane dioxide (*1S,2S,3R,5S*)-**17-O$_2$** (500 mg, 0.95 mmol), Na_2SO_4 (13 mg, 10 mol%), and methylcyclohexane (5 mL) were placed the in the sealed tube under argon. Then, TMDS (0.84 mL, 4.75 mmol) and Ti(O*i*-Pr)$_4$ (0.52 mL, 1.9 mmol) were added to the reaction vessel. The heterogeneous mixture was stirred at 90 °C. After 48 h, ^{31}P NMR analyses showed the complete conversion of the starting reagent. The mixture was filtered through a thin pad of Celite and the solvent was distilled off. The bisphosphane product was purified by flash chromatography with hexane/ethyl acetate (10:1) to give free phosphine 17 as a colorless oil (foam) with final yield 80 %, $[\alpha]_D$ = +174 (*c* 0.5, EtOH), analytical TLC: R_f 0.7 (hexane/ethyl acetate 5:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.66 (*t*, *J* = 5.0, 10.0, 3H, CH_3), 0.70 (*t*, *J* = 5.0, 10.0, 3H, CH_3), 1.10–1.17 (*m*, 1H, CH, CH_2), 1.24–1.38 (*m*, 2H, CH, CH_2), 1.75–1.88 (*m*, 2H, CH, CH_2), 2.18 (*m*, 1H, CH), 2.20–2.30 (*m*, 1H, CH), 2.58–2.64 (*m*, 1H, CH), 2.67–2.78 (*m*, 1H, CH), 3.08 (*dd*, *J* = 5.0, 15.0, 1H, CH), 7.24–7.48 (*m*, 16H, Ar-H), 7.60–7.70 (*m*, 4H, Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.6, 14.7, 24.3 28.8 (*d*, *J* = 6.2), 37.2, 39.9, 42.0 (*d*, *J* = 66.2), 44.0 (*d*, *J* = 65.0), 45.7 (*d*, *J* = 4.0), 128.0, 128.3, 128.3, 128.4, 128.5, 128.6, 128.6, 128.6, 130.4, 130.5, 130.7, 130.9 (*d*, *J* = 2.5), 131.1, 131.1, 131.2, 131.2, 131.3, 131.4, 131.7, 131.4 (*d*, *J* = 94.0), 131.8 (*d*, *J* = 94.7), 133.6, 134.0 (*d*, *J* = 114.0). ^{31}P NMR (202 MHz, $CDCl_3$): δ = –2.8 (*d*, *J* = 10.1), –16.4 (*d*, *J* = 10.1). HRMS (ESI$^+$) calcd. for $[C_{33}H_{36}P_2O_2 + H]^+$ = 527.2252 Da, found 527.2266 Da (diff. –1.0 ppm): an extremely dilutes sample of phosphane underwent a spontaneous oxidation to form corresponding dioxide.

Asymmetric hydrogenation

General procedure for asymmetric hydrogenation reaction

In a 5.0 ml glass vial catalyst precursor $[Rh(cod)_2]BF_4$ (2.0 mol%), *open*-NORPHOS ligand (2.2 mol %) (17) and 2.0 mL of dry EtOH were stirred for 30 min under argon atmosphere. Then olefin dissolved in EtOH (100 mg olefin in 2.0 ml) was added and the vessel was placed in an autoclave which was then charged with 5 or 20 bar of H_2 and stirred at 20–25 °C for 12 h. The pressure was then released and the solvent was removed. The hydrogenated product was purified by chromatography on silica gel eluting with ethyl acetate/MeOH (30:1). The enantiomeric composition and absolute configuration of the product of model asymmetric reaction were determined by the peak integration and an elution order from chiral HPLC Chiralcel OD-H column or was calculated from polarimetry by comparison of the specific rotation of the product with literature values of the authentic sample.

(*R*)-*N*-acetyl phenylalanine

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.78 (*s*, 3H, CH_3), 2.84 (*dd*, *J* = 5.0, 10.0, 1H, CH_2), 3.04 (*dd*, *J* = 5.0, 10.0, 1H, CH_2), 4.37–4.42 (*m*, 1H, CH), 7.16–7.35 (*m*, 5H, Ar-H), 8.20 (*d*, *J* = 10.0, 1H, NH), 12.68 (*br. s*, 1H, OH). The analysis of spectra of the product confirms that it corresponds to the literature data [72]. The product was converted to the corresponding methyl ester (with use MeOH/$SOCl_2$ at 0 °C) and it enantiomeric compositions was analyzed next by chiral HPLC. HPLC analysis (Chiralcel OD-H, hexane/*iso*-PrOH, 95:5, 0.6 mL/min, 254 nm): *tr*(minor) = 26.1 min, *tr*(major) = 24.5 min.

(*R*)-*N*-acetyl phenylalanine methyl ester

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.01 (*s*, 3H, CH_3), 3.10–3.19 (*m*, 2H, CH_2), 3.75 (*s*, 3H, OCH_3), 4.89–4.93 (*m*, 1H, CH), 7.10–7.32 (*m*, 2H, Ar-H), 7.33–7.35 (*m*, 3H, Ar-H). The analysis of spectra of the product confirms that it corresponds to the literature data [72]. The product was analyzed by chiral HPLC. HPLC analysis (Chiralcel OD-H, hexane/*iso*-PrOH, 95:5, 0.6 mL/min, 254 nm): *tr*(minor) = 26.1 min, *tr*(major) = 24.5 min.

2-(*S*)-methylsuccinic acid

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.10 (*d*, *J* = 10.0, 3H CH_3), 2.28 (*dd*, *J* = 5.0, 15.0, 1H, CH), 2.47–2.53 (*m*, 1H, CH), 2.64–2.68 (*m*, 1H, CH), 12.18 (*br. s*, 2H, OH). The analysis of spectra of the product confirms that it corresponds to the literature data [73]. Enantiomeric excess was calculated from polarimetry by comparison of the specific rotation of the product with literature values of an authentic sample. For *2-(R)*-methylsuccinic acid $[\alpha]_D$ = +16.88 (*c* 2.0, EtOH) [74]. For *ee* 61 (*S*)% was found $[\alpha]_D$ = –10.6 (*c* 2.0, EtOH).

(*R*)-*N*-Acetyl-alanine

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.24 (*d*, *J* = 10.0, 3H CH_3), 1.83 (*s*, 3H, CH_3), 4.16 (*dq*, *J* = 10.0, 15.0, 1H, CH), 8.15 (*d*, *J* = 5.0, 1H, NH). The analysis of spectra of the product confirms that it corresponds to the literature data [75]. Enantiomeric excess was calculated from polarimetry by comparison of the specific rotation of the product with literature values of an authentic sample. For *N*-Acetyl-(*R*)-alanine $[\alpha]_D$ = +66 (*c* 2.0, H_2O) [74]. For *ee* 90 (*R*)% was found $[\alpha]_D$ = +58.5 (*c* 2.5, H_2O).

Conclusions

Usage of well-characterized and known for its essential applicability ligands in the synthesis of their new modification is proven to be reasonable even when only a single altering functional group, as simple as a double bond, is present in the parent ligand structure. In this way, the unnecessary risk of creating an ineffective catalytic system could be minimized since obtained derivatives by-design adopt the optimal configuration beneficial in the asymmetric process of interest. Moreover, minor structural modification, introduced during ligand design and creation, could positively affect the catalysts' general efficiency since ligands tailored for a given process are developed. This straightforward and cost-efficient approach was demonstrated with a case of NORPHOS ligand modification introduced of a tandem one pot ROM/hydrogenation reactions (*both mediated by the once applied ruthenium catalyst*) followed by catalytic deoxygenation what furnish new enantiomericaly pure *open*-NORPHOS ligand in high yield. The *open*-NORPHOS ligand-based rhodium catalysts appear to be more efficient than the parent NORPHOS in benchmark asymmetric hydrogenations furnishing important compounds of interest to the pharmaceutical industry. The approach to other ligands by post functionalization of halogen-substituted *open*-NORPHOS derivatives has also been proposed. Also the observation that **11-O$_2$** can be metatheticaly reverted back to **1-O$_2$**, despite the apparent raise in strain, deserves an especial notice.

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