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Chiral Separation of Styrene Oxides Supported by Enantiomeric Tetrahedral Neutral Pd(II) Cages

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Supporting Information

ABSTRACT: The separation of enantiomers is of considerable importance in the preparation of the compounds of biological interests, catalysis, and drug development. Here, we report a novel enantioseparation of styrene epoxides (SOs) resolved in the presence of a pair of enantio-enriched tetrahedral cages. Chiral neutral cages of formula $[(Pd_3X^*)_4(C_6O_4Cl_2)_6]$ ($[X^*]^{3-}$ = RRR- or SSS-$[PO(N(^*CH(CH_3)Ph)_3]^{3-}$) are constructed from Pd_3 building units supported by tris(imido)phosphate trianions and chloranilate linkers. These cages exhibit considerable enantioselective separation capabilities toward a series of styrene epoxides via a crystallization inclusion method. A highest enantiomeric excess (ee) value of up to 80% is achieved for the (*R*)-4-fluorostyrene oxide.

Chiral separation is defined as the process of separating the individual enantiomers from their racemic pairs. Separation of enantiomers is essential, owing to their unique biochemical activities, as living systems are chiral in nature.[1] Chiral epoxides are important synthons in synthetic and pharmaceutical chemistry as the epoxy rings are very reactive toward nucleophiles and yield various chiral organic functionalities. Especially, styrene oxides act as excellent precursors for various biologically relevant compounds. (*S*)-styrene oxide (phenyl oxirane) is an important intermediate for the synthesis of nematocide,[2] Levamisole (anticancer agent),[3] and (−) hyperolactone C (anti-HIV agent).[4] The (*S*)-4-fluorostyrene oxide (2-(4-fluorophenyl) oxirane) is a useful starting material for the synthesis of several potential bioactive compounds.[5,6] A number of antiviral agents have been prepared from (*S*)-4-chlorostyrene oxide (2-(4-chlorophenyl) oxirane).[7] Among the methods available, a well-known protocol for the separation of epoxides is the hydrolytic or aminolytic kinetic resolution procedure (HKR) that was first shown to be assisted by Jacobsen's Co^{III}-(salen) type complexes, in which one of the enantiomers is converted into a chiral diol while the other one is retained as the epoxide.[8,9] Such HKR reactions have also been shown to be catalyzed by enzymes such as lipases and hydrolases.[10] However, for incorporating a variety of functional groups on the chiral backbone, it is highly desired that the epoxides are separated by other methods without altering them to diols. Hence, benign methods based on supramolecular systems like capsules, cavitands, metal−organic cages, and frameworks as host materials for the chiral recognition and separation of epoxides have been investigated.[11,12]

Recently, our group has reported the synthesis of an oxalate tethered enantiomeric pair of neutral tetrahedral cages **1**-R and **1**-S of formula $[(Pd_3X^*)_4(C_2O_4)_6]$ ($[X^*]^{3-}$ = RRR- or SSS-$[PO(N(^*CH(CH_3)Ph)_3]^{3-}$) that showed a direct separation of small organic compounds and epoxide such as (±)-epichlorohydrin via the crystallization inclusion method, albeit with low enantiomeric excess (ee) values.[13] Spurred by this, we set out to investigate the separation of biochemically important styrene oxides by utilizing tailor-made Pd(II) cages built on anilate bound tetrahedral cages. The cage assemblies **2**-$(R)_{all}$ and **2**-$(S)_{all}$ of formulas $[(Pd_3X^{RRR})_4(C_6O_4Cl_2)_6]$ and $[(Pd_3X^{SSS})_4(C_6O_4Cl_2)_6]$ were formally formed via the self-assembly of four chiral $Pd_3X^{RRRorSSS}$ units and six bis-bidentate chloranilate linkers. Further, we demonstrate the ability of these larger chiral cages for the efficient separation of racemic styrene derived epoxides by a crystallization inclusion method. A highest ee value of 80% was obtained for the R-4-fluorostyrene oxide (+F-SO), and reasonably good ee values as estimated by gas chromatography (GC) or high-pressure liquid chromatography (HPLC) were obtained for all the other investigated styrene epoxides.

The chiral tetrahedral cages, **2**-$(R)_{all}$ and **2**-$(S)_{all}$ (henceforth shortly referred as **2**-R and **2**-S),[14] were isolated as brownish red solids from the reaction of the respective chiral phosphoramides, $X^{RRR}H_3$ and $X^{SSS}H_3$, with $Pd(OAc)_2$ in the presence of chloranilic acid (LH_2) in methanol (Scheme 1). The MALDI-TOF mass spectrum of both **2**-R and **2**-S in chloroform gave peaks centered at 4159 and 4278 corresponding to the $[M + Na]^+$ and $[M + CHCl_3 + Na]^+$ species, respectively (Figure S1, Supporting Information). The ^1H NMR spectrum gave well resolved signals due to the peripheral imido-P(V) trianions, presenting chemical shifts due to the α-methyl benzylamino group. The ^{13}C NMR gave peaks corresponding to the chloranilate linkers at 141.46, 180.59, and 181.03 ppm, in addition to the peaks due to the imido

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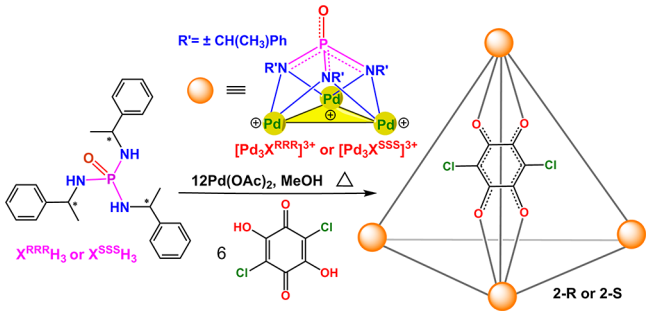
Scheme 1. Synthesis of Chiral Neutral Cages 2-R or 2-S from the Enantiopure $X^{RRR}H_3$ or $X^{SSS}H_3$ Ligands[a]



[a]Only one out of the six chloranilate linkers along the edges of the tetrahedron is shown for clarity.

ligands (Figures S2−S6, Supporting Information). The thermogravimetric analysis (TGA) data revealed that the cages were stable up to 250 °C (Figure S7, Supporting Information).

The circular dichroism (CD) spectra confirm the enantio-enrichment of **2**-R and **2**-S in solution. Thus, both **2**-R and **2**-S gave mirror image peaks at 249, 341, and 396 nm, with the respective positive and negative Cotton effects. While the first peak is due the ligand centric $\pi-\pi^*$ transitions, the second and third ones are due to metal to ligand charge transfer (MLCT) transitions (Figure 1). The absolute configurations ($[\alpha]^2D$) of

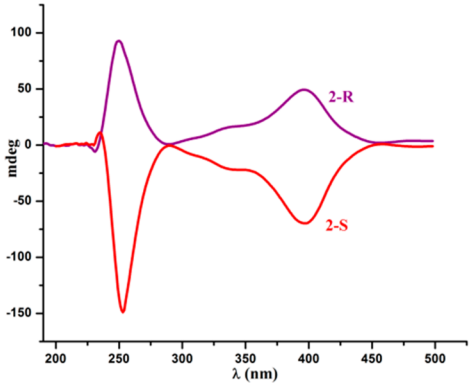


Figure 1. Circular dichroism spectra of the chiral cages **2**-R and **2**-S.

2-R and **2**-S were determined by optical rotation measurements in 0.1 M solution of $CHCl_3$. The observed $[\alpha]^2D$ values of **2**-R (1322°) and **2**-S (−1340°) were higher than the corresponding phosphoramide ligands X^RH_3 (+23) and X^SH_3 (−25).

Further, the enantiopure structures of these cages were confirmed by their structural determination. Crystals of **2**-R and **2**-S suitable for single crystal X-ray diffraction (SCXRD) analysis were grown from slow evaporation of their corresponding DCM solutions. Both the cages were crystallized in chiral cubic space group *I*23 signifying the T-symmetry of these cages (Figure 2). The asymmetric unit consists of one-twelfth of the cage molecule. Each corner of the tetrahedron consists of the trigonal Pd_3X^* chiral units that are built via the *cis*-coordination of the tridentate tris(imido)phosphate trianions. The edges of the tetrahedron consist of chloranilate linkers which offer a pair of wide-angle O,O- chelation to the 90° cisoidal sites at each Pd(II) center.

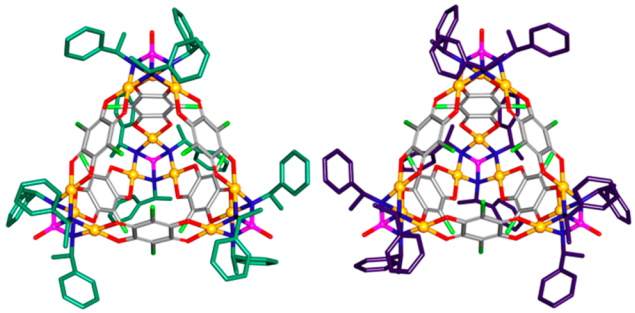


Figure 2. SCRXD structures of **2**-R (left) and **2**-S (right). Color code: Pd, orange; $C_{anilate}$, gray; N, blue; O, red; Cl, green; P, magenta. The carbon atoms of the chiral substituents are represented as dark green and violet colored atoms.

The cages exhibit additional rotational chirality as observed by the clockwise (in **2**-R) or anticlockwise (in **2**-S) orientation of the methyl groups attached to the stereogenic carbon centers. Their packing structures indicate solvent accessible voids of volume 3000 Å^3 which amounts to 33% of the total unit cell volume (Figures S8 and S9, Supporting Information). Notably, both **2**-R and **2**-S exhibit a tighter packing than the previously reported **1**-R and **1**-S (13051 Å^3; 51% of the unit cell volume), though the intrinsic void volumes of these new cages are higher at 224 Å^3 per cage.[15,16] A closer analysis of the void structures in **2**-R and **2**-S indicates that they exhibit a remarkable 3D-net of Sodalite topology for channels running along the exterior cavities of the cages, which are in turn connected to the intrinsic cavities of the individual cages (Figure S10, Supporting Information).

Inspired by the host−guest capabilities of the earlier reported cages based on such imido-Pd_3 motifs, we examined the preliminary guest encapsulation studies of these chiral cages for CCl_4 and toluene. Thus, the CCl_4 and toluene treated samples of **2**-S gave the respective peaks at m/z = 4310 and 4256 corresponding to the $[CCl_4\subset\mathbf{2}\text{-S}]^+$ and $[C_7H_8\subset\mathbf{2}\text{-S}]^+$ ions (Figures S12 and S13, Supporting Information). A similar set of experiments yielded the same results for **2**-R as well. Furthermore, due to the charge neutral nature of these chiral cages as well as due to the presence of quinoid linkers, we investigated the suitability of these cages for the chiral separation of racemic styrene oxides (SOs). A family of styrene oxides, phenyl oxirane (SO), 2-(4-fluorophenyl)-oxirane (F-SO), 2-(4-chlorophenyl)oxirane (Cl-SO), and 2-(4-bromophenyl)oxirane (Br-SO), were probed for the enantioselective adsorption experiments with **2**-R and **2**-S. For the separation experiments, the chloroform solutions of the host cages were mixed with the racemic mixture of the styrene oxides in excess and left for evaporation at 298 K. The obtained solids were washed with cold *n*-pentane in order to remove the remaining guest molecules. The resultant solids were soaked in *n*-hexane to remove the enantio-enriched styrene oxides, and the filtrates were subsequently injected for the HPLC analysis.

The highest ee value of 80% is recorded for the R-isomer of F-SO resolved by cage **2**-R. A similarly high ee value of 78% is again obtained for the +F-SO desorbed from **2**-S as well. For SO, the ee values of 7 and 39% for the R-isomer as resolved by **2**-R and **2**-S, respectively, were obtained from HPLC analysis. The HPLC resolved ee values were found to be intermediate at 57 and 56% for the R- isomer of Cl-SO using the cages **2**-R and **2**-S, respectively (Table 1). The obtained ee values were

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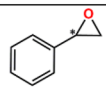
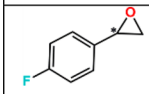
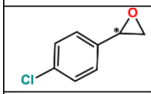
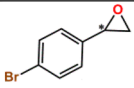
Table 1. Racemic Epoxides Employed in the Chiral Separation Studies Resolved by 2-R and 2-S along with Their HPLC-Determined Separation Results

Compound	% *ee* resolved by 2-R (excess enantiomer)	% *ee* resolved by 2-S (excess enantiomer)
	7 (R)	39 (R)
	80 (R)	78 (R)
	57 (R)	56 (R)
	cannot resolve	cannot resolve

consistently reproducible for three independent separation experiments (Tables S3 and Figures S14–S22, Supporting Information). Remarkably, the host cages can be regenerated after each separation cycle by crystallizing them from DCM. From the above observations, the obtained enantioselectivities fall in the order of F-SO > Cl-SO > SO with respect to the cages **2**-R and **2**-S. The Br-SO did not show any selectivity at all, probably due to its larger size being incompatible with the guest binding sites at the external cavities of the cages. Control experiments showed that the ligands X^RH_3 and X^SH_3 alone could not resolve the above mentioned styrene oxides under identical conditions. The previously reported cages **1**-R and **1**-S did not show any selectivity as well. This indicates that the tight association of the present cages, containing planar metal-coordinated electron deficient chloranilate dianion surfaces, with the oxirane guests plays a vital role in their enantioselective separation.

To track the nature of interaction of these racemic styrene oxides with the chiral cages, ^{1}H NMR and MALDI-TOF mass spectral analyses were performed on the host–guest mixtures in solution. Since the size of ±SO is similar to that of toluene, we presumed that it might exhibit encapsulation within the intrinsic cavities of the cage. However, the MALDI-TOF mass spectrometry and ^{1}H and ^{1}H-2D-DOSY NMR of the ±SO did not show any encapsulation at the intrinsic cavities (Figures S23–S28, Supporting Information). Also, no encapsulation and enantioselective separation were observed for the other oxiranes such as *p*-cyano and *p*-nitro styrene oxides and other chiral molecules such as 2-butanol and 1-phenyl ethanol.

Furthermore, we obtained crystals of both **2**-R and **2**-S when treated with either ±SO or ±F-SO. However, higher quality data sets from these crystals did not show the presence of these guest molecules in their structures, albeit these cages were found to crystallize in the rhombohedral space group of *R*3. Formation of these new polymorphs could presumably be driven by the template effects of the guest molecules which resulted in the efficient packing of the cages in the *R*3 phase compared to that in the *I*23 phase. These observations suggest that the guest molecules would seemingly be recognized at the chiral centers located at the exteriors of the cages via any one of the possible C–H···N_{imido}, C–H···$O_{epoxide}$, and π_{ligand}···$\pi_{epoxide}$ interactions. This inference is in line with our earlier report where the X-ray derived structure of an isostructural cage exhibited prominent encapsulation of the guest molecules at their external cavities.[13] Similar transformations involving cubic *P*23 to rhombohedral *R*3 have been observed in the family of chiral tetrahedral organic cages reported by Cooper and co-workers.[17]

In summary, this work illustrates a reasonably good enantioseparation of styrene epoxides by a crystallization inclusion method using supramolecular ensembles. The tetrahedral cages **2**-R and **2**-S were built in a facile strategy by using trinuclear Pd(II) clusters containing chiral tris(imido)phosphate trianions and chloranilate linkers. A highest enantioseparation of 80% has been observed for the +F-SO compound using the **2**-R cage. For the other SOs, the ee values were found to range from 7 to 78%, indicating the variations in the noncovalent interactions between the host and guest molecules play a crucial role in the enantioseparation process. These findings pave the way for the search of novel supramolecular systems that can facilitate the efficient separation of epoxides and other sensitive organic racemates.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.inorgchem.9b02389.

NMR and additional figures pertaining to crystal structures, tables of bond lengths and bond angles, TGA (PDF)

Accession Codes

CCDC 1898032–1898033 and 1957460–1957461 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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