Inherent Chirality

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Can Hetero-Polysubstituted Cyclodextrins be Considered as Inherently Chiral Concave Molecules?**

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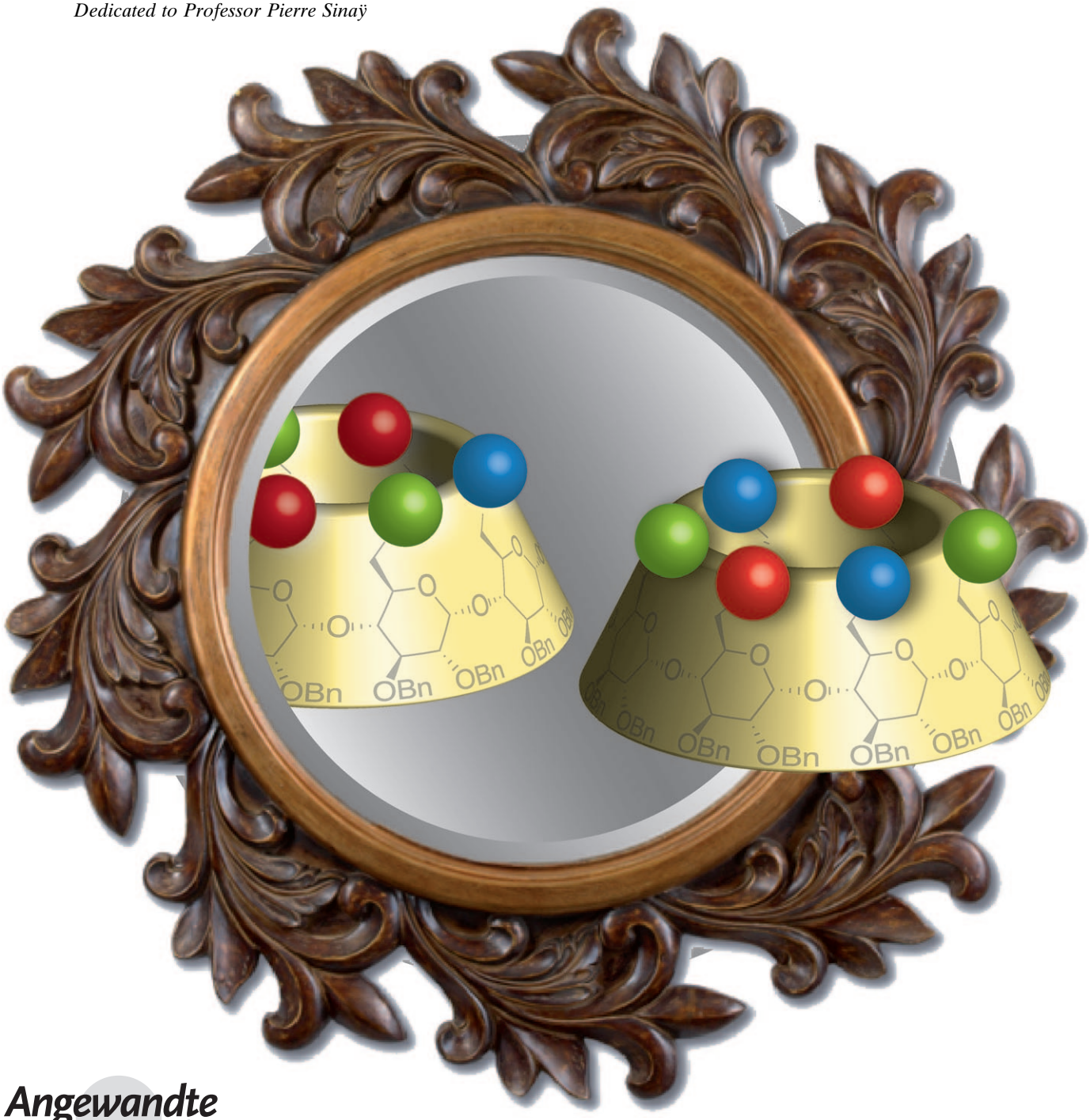
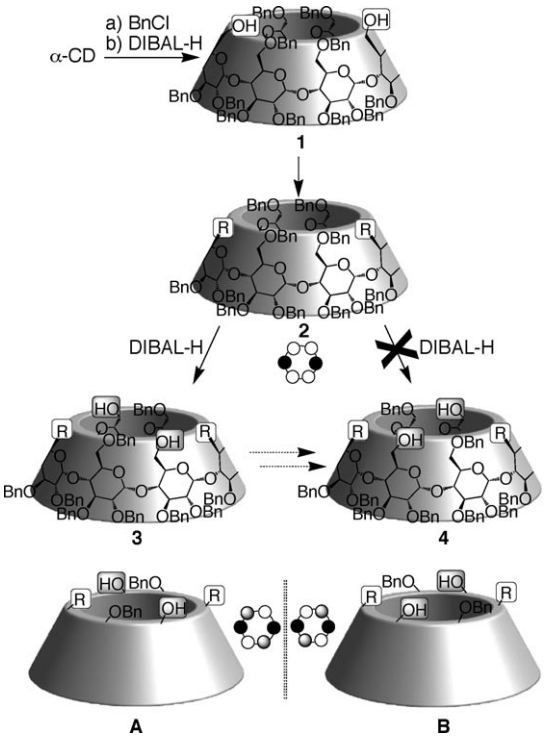
Dedicated to Professor Pierre Sinaÿ



The introduction of asymmetry in cyclic concave molecules constituted of achiral repeating units can be achieved in various ways and leads to different types of chirality. This goal was first achieved through attachment of a chiral moiety to the cyclic scaffold; asymmetry is therefore due to the added stereogenic center located remotely from the cavity.[1] In contrast, hetero-polysubstitution of the repeating units afforded molecules that are qualified as inherently chiral species, as they are devoid of stereogenic atoms, and it is their cavity as a whole that is asymmetric.[2] More precisely, inherent chirality is defined as the association of a two-dimensional chiral pattern of functionalities with a curvature.[3] Consequently, racemization is operated by inside-out inversion of the curvature of the inherently chiral cycle, whereas opening of the cycle induces removal of the chirality. To date, asymmetrically substituted cavitands have been synthesized 1) as racemic mixtures,[4] which were resolved by HPLC on a chiral stationary phase,[5] 2) by introduction of a chiral auxiliary and resolution[6] or separation of the diastereoisomers,[7,8] or more recently 3) through crystallization of the inclusion complex between a racemic host and an enantiomerically pure guest.[9] Only very few reports of enantioselective syntheses of hetero-polysubstituted inherently chiral concave cycles have been reported, all of which present modest selectivities and/or yields.[10,11]

Within the general class of concave molecules, cyclodextrins (CDs) are an exception because they are rendered intrinsically chiral by their chiral sugar subunits. Consequently, as native CDs are already chiral, the hetero-functionalization of CDs does not induce chirality. Furthermore, the lack of efficient and regioselective methods to poly-heterofunctionalize CDs[12] has largely hampered developments in this direction.[13] However, we have devised a unique methodology to regioselectively functionalize the primary rim of CDs by using an iterative deprotection strategy.[14–17] An initial diisobutylaluminum hydride (DIBAL-H) induced deprotection of a perbenzylated α-CD affords diol **1**, which has diametrically opposed alcohol functions (face-to-face diol).[18] When the hydroxy groups of **1** are converted into R groups, and provided R is judiciously chosen to induce local steric decompression in CD **2**, a second deprotection of CD **2** with DIBAL-H exclusively delivers the face-to-face diol **3** as a single regioisomer, with no traces of the alternative regioisomer CD **4** (Scheme 1).[14,15]



Scheme 1. Twofold DIBAL-H deprotection regiospecifically affords **3**. The other regioisomer **4** has a mirror-image substitution arrangement. Bn = benzyl.

Both CDs **3** and **4** are chiral enantiopure molecules with C_2 symmetry. Compounds **3** and **4** do not share the same connectivity and are therefore constitutional isomers, however, they exhibit mirror-image functionalization patterns at their upper rims because of their opposing topologies (**A** and **B**, Scheme 1). Therefore, such upper-rim functionalization creates a new topological stereogenic unit, the layout of which is solely controlled by the chirality of the CD scaffold that undergoes the second DIBAL-H deprotection step. It should be noted, however, that the existence of the topological stereogenic unit is independent of the chirality of the starting scaffold and would persist if incorporated in an achiral scaffold (**A** and **B**, Scheme 1). As a consequence, we reasoned that **3** and **4** can be regarded, and possibly exploited, as topological equivalents of inherently chiral scaffolds, as the CD component provides the curvature, and the array of primary-rim substitution acts as a two-dimensional chiral pattern. The virtual inside-out inversion of the CD cone of **4** would lead to the same molecule **4** with the mirror-image orientation of the primary-rim substitution (Scheme 2). Therefore, although chirality of CDs **3** and **4** is theoretically provided by the CD component, these two CDs possess all the properties that confer inherent chirality to a curved macrocycle.

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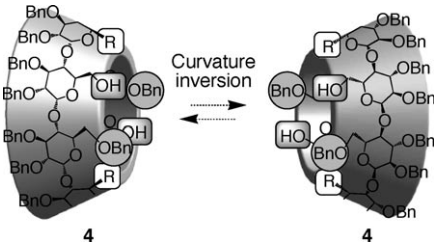
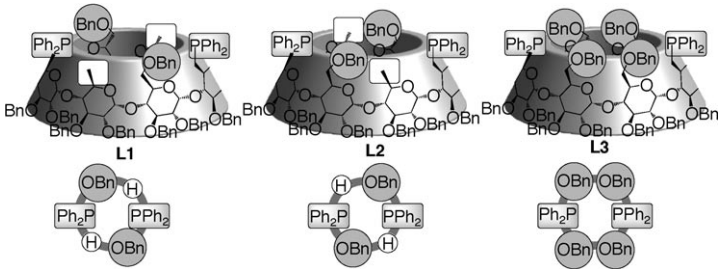


Scheme 2. Inside-out inversion of the curvature of **4** induces inversion of the substituent arrangement, as expected for an inherently chiral concave cycle.

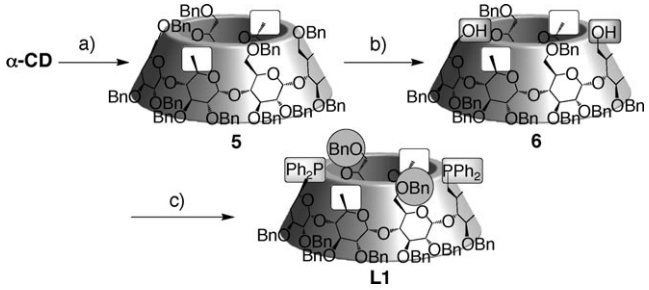
This fascinating apparent theoretical paradox prompted us to experimentally confirm the anticipated topological pseudoenantiomeric relationship between CDs **3** and **4**. RajanBabu et al. showed that enantioselectivity could depend only on the local chirality of a six-membered ring of two vicinal carbon atoms that bear chelating groups.[19] Furthermore, following the seminal work of Reetz and Waldvogel on phosphine-modified CDs,[20] Matt, Armspach, and co-workers elegantly demonstrated that a transition metal can be efficiently chelated above the cavity of a CD by two phosphine groups installed on the primary rim, thereby forming metallo-capped CDs.[21-25] We therefore designed three new CD-based diphosphines **L1**–**L3** in order to evaluate them as topological pseudoenantiomeric ligands,[26] the chirality of which stems from the regioisomery of their substitution patterns. Ligands **L1** and **L2** bear diametrically opposed phosphine, methyl, and benzyloxymethyl groups in a mutual mirror-image arrangement on the primary rim. The diphosphine **L3** has a symmetrical substitution pattern and can be used as pseudoachiral ligand (Scheme 3).[27]



Scheme 3. Structures of ligands **L1**–**L3**.

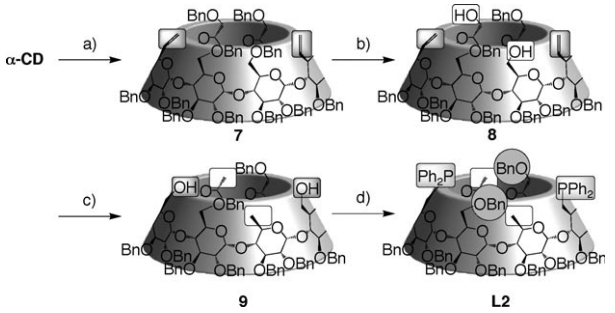
Based on our knowledge of regioselective deprotection of CDs, we synthesized the dideoxy CD **5** using the DIBAL-H deprotection method starting from α-CD (62% yield over four steps). Regioselective deprotection of **5** was driven by steric orienting effects to afford face-to-face diol **6**[15] in 75% yield. Diol **6** was then conveniently converted into the diphosphine CD **L1** in 68% yield, by using the methodology developed by Matt, Armspach, and co-workers,[24] in which mesylation followed by nucleophilic substitution by lithium diphenylphosphide was employed (Scheme 4).

Access to **L2** is not as straightforward as **L1**, owing to the unidirectionality of the DIBAL-H-induced debenzylation



Scheme 4. Synthesis of **L1**. a) 1. BnCl; 2. DIBAL-H; 3. MsCl, 4. $LiAlH_4$, 62% (4 steps); b) DIBAL-H, 75%; c) 1. MsCl, pyridine, 73%; 2. Ph_2PH, *n*BuLi, 93%. Ms = mesyl.

reaction. Accordingly, the divinyl CD **7** was first synthesized from α-CD (57% over four steps) and then deprotected with DIBAL-H (90% yield) to give the face-to-face diol **8**.[15] This compound was then converted into the dideoxy CD **9** through mesylation, subsequent hydride reduction (80% yield), and reductive ozonolysis (93% yield). Diol **9** is the topological regioisomer of the face-to-face diol **6** produced by the direct DIBAL-H deprotection of **5**. Diphosphine **L2** was obtained from **9** using the same methodology as for **L1** (Scheme 5). Finally, diphosphine **L3** was obtained in 56% yield from diol **1**.[15,18]



Scheme 5. Synthesis of **L2**. a) 1. BnCl; 2. DIBAL-H; 3. $(COCl)_2$, DMSO then Et_3N; 4. Ph_3PCH_3Br, *n*BuLi, 57% (4 steps); b) DIBAL-H; c) 1. MsCl, pyridine, 99%; 2. $LiAlH_4$, 80%, c) 1. MsCl, pyridine, 99%; 2. $LiAlH_4$, 80%, $O_3/NaBH_4$, 93%; d) 1. MsCl, pyridine, 84%; 2. Ph_2PH, *n*BuLi, 60%.

To validate our concept and probe the anticipated topological pseudoenantiomeric relationship between **L1** and **L2**, the popular Tsuji–Trost Pd^0-catalyzed substitution of 1,3-diphenylallyl acetate with the dimethylmalonate anion[28] was selected as a benchmark reaction. Classical conditions were used to test ligands **L1**–**L3** (10 mol%), using dimeric allyl palladium chloride as the Pd^0 precursor (10 mol%) and the couple BSA (3 equiv)/AcOK (3 mol%) as the enolizing system. While use of **L3** afforded the desired allylated product in modest yield of 19%, the use of **L1** and **L2** led to satisfactory yields of 77% and 87%, respectively. Quantification of the enantiomeric excesses by HPLC analysis[29] and ^1H NMR spectroscopy in the presence of chiral europium salts,[30] showed clear opposite enantioselectivities (30%) arising from the use of regioisomeric pseudo-

enantiomeric ligands **L1** and **L2**. Moreover, the pseudoachiral ligand **L3** did not induce any enantioselectivity, thus ruling out the role of the sugar chirality in this asymmetric induction (Figure 1).

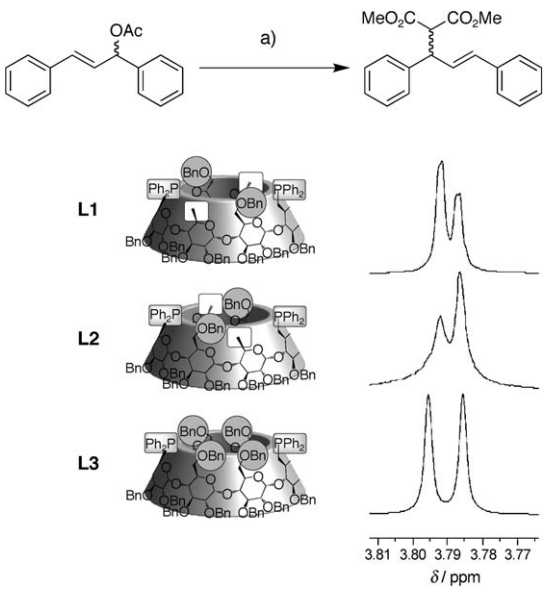


Figure 1. CDs **L1** and **L2** induce opposite enantioselectivities in a Tsuji–Trost reaction, whereas **L3** gives a racemic mixture, as shown by the ^{1}H NMR spectra of the products (methyl ester hydrogen atom signals in the presence of the chiral resolution reagent [Eu(hfc)$_3$]). a) [{Pd(η^3-C_3H_5)Pd(μ-Cl)}$_2$], ligand **L1**–**L3**, $CH_2(CO_2Me)_2$, BSA, AcOK, CH_2Cl_2, RT. BSA = *N*,*O*-bis(trimethylsilyl)acetamide.

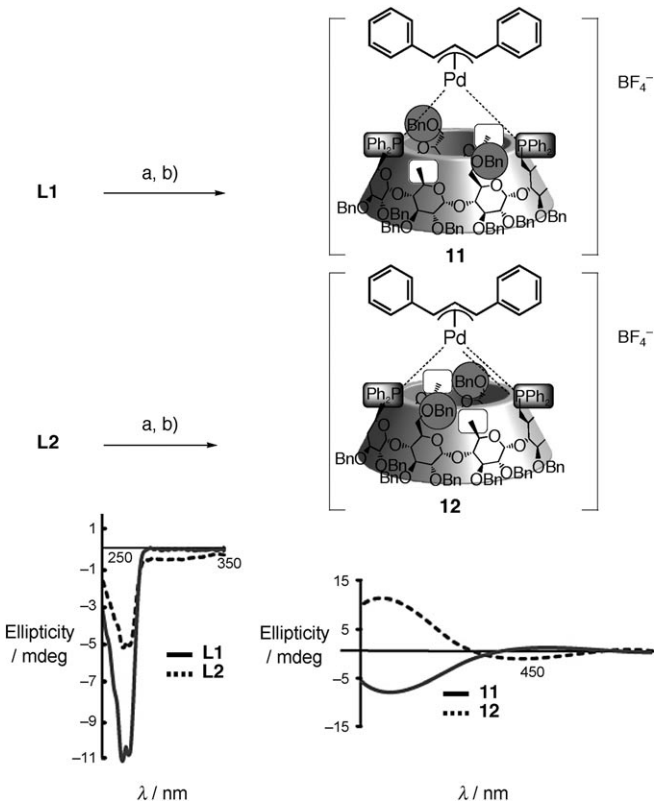


Figure 2. Synthesis of complexes **11** and **12**, and circular dichroism spectra of **L1**, **L2**, **11**, and **12**. a) [{Pd(η^3-PhC_3H_3Ph)(μ-Cl)}$_2$]; b) $NaBF_4$.

The opposite enantioselectivities observed for **L1** and **L2** imply that the environments around the metal in the corresponding η^3-allyl complexes are enantiomeric. We therefore recorded the circular dichroism spectra of the two ligands **L1** and **L2** as well as the two corresponding [Pd(η^3-PhC_3H_3Ph)(L)]$^+$ complexes **11** and **12,** which were synthesized by following a reported procedure.[31] As expected, both uncomplexed ligands displayed a negative Cotton effect in the low-wavelength region (250–300 nm); this feature is characteristic of the chirality of the sugar units, which is the same in both species. For the complexes **11** and **12**, the situation is strikingly different. In the region above 350 nm, which is the characteristic region for the d–d transitions of the metal,[32] two opposite Cotton effects can be seen (380 and 450 nm). These effects therefore unequivocally demonstrate the enantiomeric environments of the Pd atoms in complexes **11** and **12** (Figure 2).

We have synthesized two ligands **L1** and **L2** based on regiospecific hetero-trifunctionalized CD platforms. The inherent chirality imposed by their substitution pattern makes them behave as enantiomers. This feature is demonstrated by their propensity to induce opposite enantioselectivities in a Tsuji–Trost reaction, and confirmed by the circular dichroism spectra of their respective complexes. These results support the concept in which our twofold regioselective deprotection of CDs can serve as an enantioselective synthesis of inherently chiral cyclic surrogates, hence opening a vast range of possible applications where an easily accessible pure chiral concave structure is required.

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