Folded biomimetic oligomers for enantioselective catalysis

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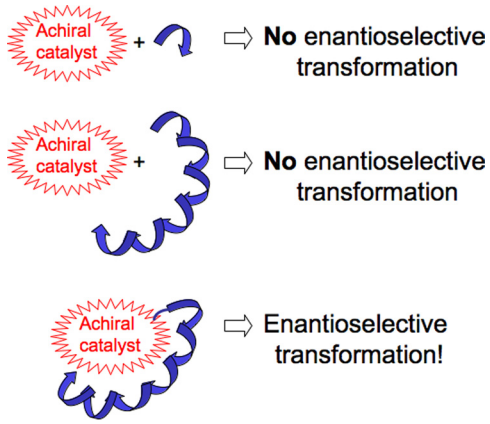
Many naturally occurring biopolymers (i.e., proteins, RNA, DNA) owe their unique properties to their well-defined three-dimensional structures. These attributes have inspired the design and synthesis of folded architectures with functions ranging from molecular recognition to asymmetric catalysis. Among these are synthetic oligomeric peptide (''foldamer'') mimics, which can display conformational ordering at short chain lengths. Foldamers, however, have not been explored as platforms for asymmetric catalysis. This report describes a library of synthetic helical ''peptoid'' oligomers that enable enantioselective transformations at an embedded achiral catalytic center, as illustrated by the oxidative kinetic resolution of 1-phenylethanol. In an investigation aimed at elucidating key structure–function relationships, we have discovered that the enantioselectivity of the catalytic peptoids depends on the handedness of the asymmetric environment derived from the helical scaffold, the position of the catalytic center along the peptoid backbone, and the degree of conformational ordering of the peptoid scaffold. The transfer of chiral information from a folded scaffold can enable the use of a diverse assortment of embedded achiral catalytic centers, promising a generation of synthetic foldamer catalysts for enantioselective transformations that can be performed under a broad range of reaction environments.

catalyst | foldamer | oxidative kinetic resolution | peptoid

The unique capabilities of biopolymers, which stem from their well-defined three-dimensional structures, have been a source of inspiration for the design and synthesis of functional chemical systems (1). A variety of strategies have been explored for de novo construction of modular catalysts that enable chemical selectivity, regioselectivity, or enantioselectivity as a consequence of their structural organization. For example, synthetic peptides equipped with catalytic artificial amino acid groups or transition metal sites have been demonstrated to be effective enantioselective catalysts due to the proximity of the catalytic sites to the asymmetric environment created by their backbone (2–4). Similarly, it has been reported that nucleic acids can be used as chiral scaffolds for asymmetric synthesis and catalysis (5, 6). A recent investigation of DNA-based asymmetric catalysis relies on the noncovalent association of an achiral metal catalyst at unspecified sites along a DNA backbone, creating a chiral environment about the catalytic center that results in enantioselective transformations (7, 8). Despite these advances, there remains a need for robust systems that permit rational design of versatile sequences and facile synthesis of libraries for high-throughput screening and optimization of catalytic performance.

In living systems, biopolymer catalysts have evolved to accelerate specific biologically relevant transformations. In contrast, synthetic catalysts must often be designed for nonbiological transformations to be performed in abiotic solvents, pH regimes, temperatures, and pressures that are incompatible with retention of biopolymer structure and activity. Proteins, however, rely on a limited repertoire of amino acid monomers and require substantial chain lengths to achieve significant structural organization. In this context, the monomer types and structural motifs available for the construction of polypeptide-based catalysts may prove limiting. This has inspired the design of ''foldamers''—unnatural oligomers that fold into well-defined secondary structures in solution (9–12), sometimes in a variety of solvents, even at short chain lengths. Substantial progress has been made in establishing foldamer architectures from various types of oligomers, [e.g., β-peptides, γ-peptides, oligo(phenylene ethynelene), oligoureas, peptoids] (10). Although foldamers have been explored for materials and biomedical applications, their potential as asymmetric catalysts has not been realized. Herein, we evaluate peptoids—oligomers of N-substituted glycine—as a synthetically tractable platform for the facile construction of enantioselective catalysts. These oligomers form unique, well-defined, and thermally stable helical architectures (13–16) that enable the covalent attachment of achiral catalytic centers at prescribed locations on a robust chiral peptoid scaffold for optimization of catalytic enantioselectivity and overall performance.



Scheme 1.

The efficient synthesis of peptoids uses primary amine synthons, enabling the incorporation of innumerable functional groups at specified N-positions along their spine. The handedness of peptoid helices can be enforced by defining the stereochemistry of bulky chiral pendant groups. For example, (*S*)- or (*R*)-phenylethyl N-substituents prompt the formation of helices provided that they constitute the majority of the substituents along the chain (15). Our design of enantioselective catalysts relies on attaching an achiral catalytic center to a helical peptoid scaffold, which provides an asymmetric environment (Scheme 1). The modular nature of the oligomer synthesis allows the

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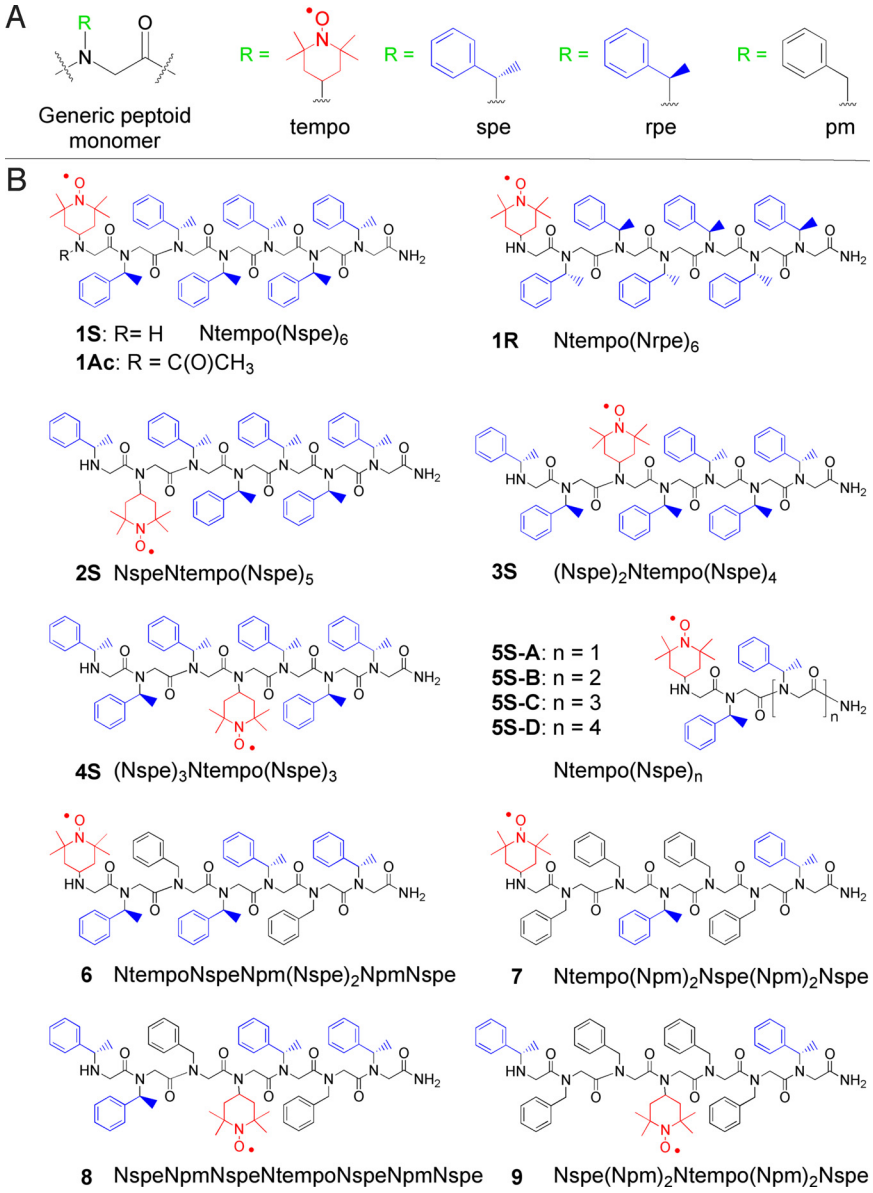


Fig. 1. A library of peptoid sequences evaluated for catalysis. (*A*) Monomeric units used in the design of catalytic peptoids. (*B*) Examples of catalytic peptoids and their sequence descriptors. Modular peptoid synthesis permits systematic control of the chain length, position of the TEMPO catalytic site (red), and the position and number of chiral (blue) and achiral (black) substituents.

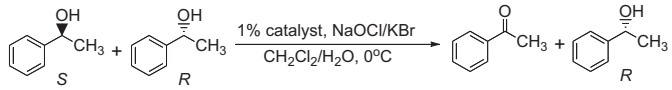
systematic modification of each component (catalytic center, recognition and chirality elements) to optimize reactivity and enantioselectivity, and to enable the investigation of structure–function relationships. This bifunctional strategy allows independent control of the asymmetric environment and the nature of the chemical transformation, promising extraordinary versatility for designing catalysts that can be tailored for a broad range of substrates and reaction environments.

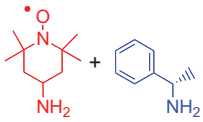
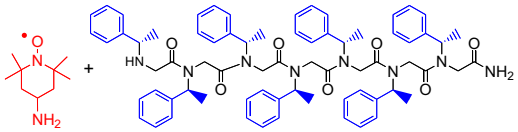
Our approach is illustrated by the attachment of TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl), a well-known catalyst for oxidative transformations (17–19), to various sites along the spine of peptoid oligomers, generating a small library of catalytic peptoids (Fig. 1). The asymmetric environment supplied by the helix can be expected to favor the transformation of one enantiomer in a racemic mixture of a chiral secondary alcohol (to its respective ketone), thus creating an excess of the other enantiomer, a process described as oxidative kinetic resolution (OKR). We evaluate a family of peptoid oligomers as catalysts for the OKR of racemic mixtures of chiral secondary alcohols (20–23), which often appear in natural products and are valuable as enantiopure synthetic intermediates for specialty chemicals, including pharmaceuticals and agrochemicals (24, 25). Specifically, we describe the OKR of 1-phenylethanol, which has been used as a benchmark for this transformation (26–28).

Results and Discussion

Synthesis and Characterization of Peptoids Incorporating TEMPO Side Chains. The library of catalytic peptoids in Fig. 1 was synthesized on solid support from (*S*)- or (*R*)-1-phenylethylamine (spe or rpe, respectively), benzylamine (pm), and 4-amino-TEMPO (tempo) as submonomer synthons in an efficient iterated two-step protocol (29). The modularity of this protocol permits the attachment of the catalytic center, achiral substituents, and chiral substituents at defined positions along the peptoid backbone, enabling systematic investigation of the role of primary sequence and secondary structure on enantioselective catalysis.

Table 1. Conversions, enantioselectivities, and enantiomeric excess for the catalytic oxidation of 1-phenylethanol by peptoids



Catalytic system*	Conversion†, %	Selectivity§, %	ee %	S¶
	22	None	None	1
	86	None	None	1
1S (right-handed helix)	84	60 (*S*)	>99 (*R*)	5.6
	48‡	75 (*S*)	46 (*R*)	4.6
1R (left-handed helix)	85	59 (*R*)	>99 (*S*)	5.4
	49‡	74 (*R*)	45 (*S*)	4.2
2S (right-handed helix)	26‡	None	None	1
3S (right-handed helix)	25‡	None	None	1
4S (right-handed helix)	56	≈52 (*R*)	≈5 (*S*)	1.1

*All reactions were performed with mole ratio of 1:100 catalyst 1-phenylethanol.
†Conversion values are based on 2 h of reaction time unless otherwise specified.
‡Conversion values at 30 min.
§Selectivity at the quoted conversion value is defined as (% preferred enantiomer / % conversion).
¶*S* is the selectivity coefficient, as defined by $S = \ln(1 - C)(1 - ee)/\ln[(1 - C)(1 + ee)]$.

The peptoid products were cleaved from the solid support and purified before use as catalysts for the OKR of 1-phenylethanol. CD spectra confirmed the existence of secondary structure, resembling a polyproline type I helix (13), in catalytic peptoids **1S**–**4S**. Peptoids **1S** and **1R** exhibited CD ellipticities (θ) of equal magnitude with opposite sign, indicating the formation of right- and left-handed helices, respectively, with an equivalent degree of helical character. In general, the degree of helical character increased with increasing values of n (the number of monomer units) in the series **5S-A** through **5S-D**. As expected, the introduction of achiral benzyl substituents in compounds **6**-**9** reduced the magnitude of θ commensurate with the number of achiral groups [see supporting information (SI) *Appendix*].

Peptoids as Catalysts for OKR. The OKR reactions were performed in a biphasic mixture consisting of the catalytic peptoid (1 mol % based on the 1-phenylethanol substrate) dissolved in dichloromethane, an aqueous solution of KBr (0.5 M), and 1-phenylethanol (typically 1×10^{-4} mol). The oxidation reaction commenced upon addition of an aqueous solution containing 0.5 M sodium hypochlorite (26) (see *Methods*).

A mixture of the 4-amino-TEMPO catalyst and (*S*)-1-phenylethylamine was active for oxidation of 1-phenylethanol, but it did not produce enantioselective transformation (Table 1). A heptameric helical peptoid with (*S*)-1-phenylethylamine substituents exhibited greater activity for this reaction, but still did not produce enantioselective transformation. In contrast, the right-handed helical catalytic peptoid **1S**, with the catalytic TEMPO group covalently attached at the N terminus of the heptameric oligomer, displayed comparable activity but with enantioselectivity; the overall conversion after 2 h was 84% with 60% enantioselectivity for (*S*)-1-phenylethanol, resulting in 99% enantiomeric excess (ee) of the less-reactive *R*-enantiomer. At lower conversions, the apparent selectivity is larger and the percentage of ee is smaller, as expected for a transformation that is <100% enantioselective. This enantioselectivity also can be expressed in terms of a selectivity coefficient (*S*), which accounts for the dependence of the measured selectivity on overall conversion. Notably, peptoid **1R**, which adopts a left-handed helical configuration, exhibited identical catalytic activity and enantioselectivity, but for the opposite enantiomer, (*R*)-1-phenylethanol, producing an enantiomeric excess of the less reactive (*S*)-1-phenylethanol. Inserting the TEMPO group at interior positions along the oligomer chain results in substantially diminished enantioselectivity. For example, catalytic peptoids **2S** and **3S**, although active, did not display any enantioselectivity. Catalytic peptoid **4S** produced 56% conversion within 2 h but with only marginal enantioselectivity (≈52%) for the *R* enantiomer, affording ≈5% ee of the *S* enantiomer. Interestingly, the selectivity displayed by **4S** is opposite that of **1S**, even though the two compounds have the same helical handedness.

We sought to correlate the enantioselectivity of the oligomers to their structural organization. For small molecule catalysts, such correlations can prove opaque in the absence of detailed structural studies by X-ray diffraction or NMR techniques. For peptoids and some other foldamers, however, CD is a rapid, albeit low-resolution, spectroscopic tool for evaluating secondary structure content. Catalytic peptoids with the TEMPO group at the N terminus exhibited increasing enantioselectivity with increasing oligomer size (peptoids **5S-A** through **5S-D**), consistent with the increase of helical character with increasing chain length, as measured by CD. This behavior is not unlike that reported for peptide catalysts (30–32). The replacement of chiral phenylethyl substituents with achiral benzyl substituents produced catalytic peptoids **6**-**9**, with TEMPO located at either the terminus or the central position. Comparing peptoids **1S**, **6**, and **7**, with TEMPO at the terminus (Fig. 2), the enantioselectivity decreased upon incorporation of achiral substituents, in parallel with the decrease in the degree of helicity, as measured by CD. In contrast, an unexpected increase in enantioselectivity with

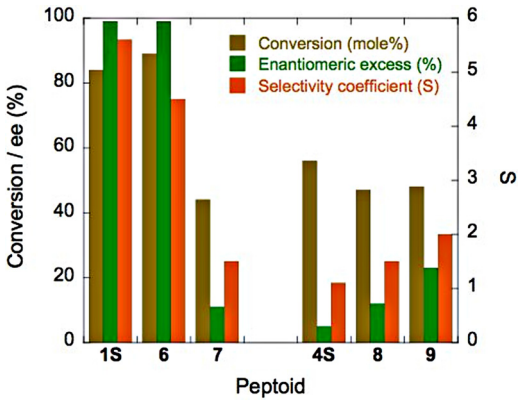


Fig. 2. Kinetic resolution of 1-phenylethanol catalyzed by peptoid oligomers. Reaction conditions were identical to those described in Table 1. The peptoids are grouped according to the location of TEMPO (**1S**, **6**, **7** at the N terminus; **4S**, **8**, **9** at the center).

decreasing helical character was detected for catalytic peptoids **4S**, **8**, and **9**, with TEMPO attached to the central residue (Fig. 2).

Collectively, these observations demonstrate that enantioselectivity (*i*) requires attachment of the catalytic group to the helical peptoid scaffold; (*ii*) depends on the handedness of the asymmetric environment; (*iii*) depends on the position of the catalytic center along the peptoid backbone; and (*iv*) depends on the degree of conformational ordering of the scaffold. The results reveal that the selectivity is governed by the global structure of the catalyst and not solely from the local chirality at sites neighboring the catalytic center, a characteristic feature of enzymatic systems. In this context, it is interesting to note that the selectivity coefficient in the OKR of 1-phenylethanol is higher with peptoid **1S** as a catalyst than with peptides bearing a similar nitroxyl radical as the catalytic center (27).

Structural Origins of Enantioselectivity. A striking observation is the achievement of highest activity and enantioselectivity for catalytic peptoids with the TEMPO group positioned at the N terminus (peptoids **1S**, **1R**), indicating less-effective interaction of the substrate with the asymmetric environment when the TEMPO site is located in the center of the scaffold as in **4S**. The origins of enantioselectivity in the OKR of secondary benzylic alcohols are not well understood. We note, however, that the enantioselective acylation of (*R*)-1-phenylethanol from a racemic mixture by substituted pyridinium catalysts has been attributed to π–π interactions, electrostatic cation–π interactions, and steric repulsion in the likely transition states of the diastereomeric catalyst–substrate complexes (33). A model of the energy-minimized structure (see *SI Appendix*) of the catalytic peptoid **1S** (Fig. 3) reveals a sterically accessible reaction cleft–defined by the benzene ring of an spe group and the reactive nitroxyl center—that permits π–π interactions in the peptoid–substrate complex while the reactive alcohol group is positioned within 3 Å of the catalytic nitroxyl site at the opening of the cleft (Fig. 3*A*). Based on the average selectivity coefficient of S = 5.5 for **1S** and **1R**, the chiral discrimination reflects a difference of ≈0.8 kcal mol^{-1} between the transition states for the two diastereomeric catalyst–substrate complexes. The environment surrounding the catalytic TEMPO site in peptoid **4S**, however, is crowded (Fig. 3*B*), precluding π–π interactions with the substrate when its reactive end is in proximity with the nitroxyl group. These features provide a reasonable basis for the comparatively high enantioselectivity exhibited by catalytic peptoid **1S**.

The importance of steric accessibility (34) is further supported by our observation that peptoid **1Ac**, synthesized by acetylating the N terminus of **1S**, catalyzed the oxidation of 1-phenylethanol at the same rate as **1S** (83% conversion obtained in 2 h), but with no enantioselectivity. Inspection of the molecular model in Fig. 3*A*, reveals that the acetyl group in **1Ac** would protrude into the reaction cleft, thereby obstructing access of the substrate 1-phenylethanol to the asymmetric environment of the helical scaffold. Interestingly, steric crowding also is implicated by an increase in enantioselectivity upon the replacement of some of the chiral spe substituents in **4S** with achiral benzylamine substituents in peptoids **8** and **9**. The reduced degree of secondary structure in these compounds, as revealed by CD (see above), is anticipated to relieve the steric crowding about the catalytic site, allowing improved accessibility of the substrate to the asymmetric reaction environment, leading to an enantioselective transformation.

Conclusion

Synthetic foldamers have been found to exhibit well-defined conformational ordering (16, 35) and recent investigations have produced molecular architectures that emulate protein secondary and tertiary structures (36–38). Further advancement of foldamers will benefit from design strategies that enable sophisticated functions such as catalysis (39). In this respect, peptoids represent an outstanding opportunity, inasmuch as: (*i*) peptoids self-organize with chain lengths as short as five residues, simplifying synthesis; (*ii*) peptoid folding does not rely on hydrogen bonding, enabling use in solvents that otherwise would interfere with hydrogen bonds; (*iii*) peptoids are chemically inert toward

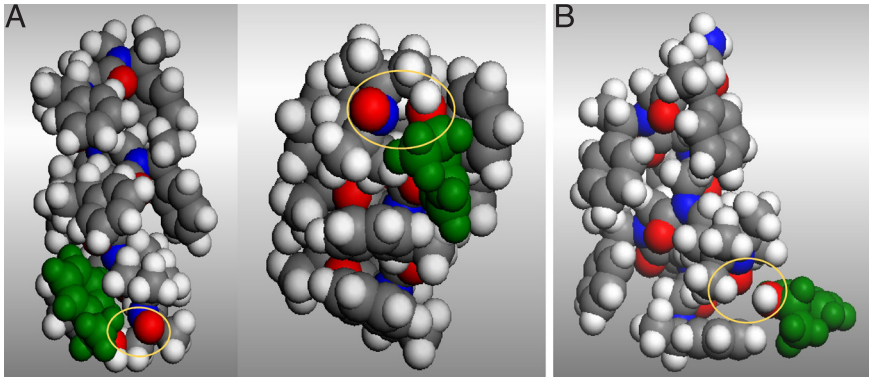


Fig. 3. Models of substrate–catalyst interaction. (*A*) Energy-minimized structure of substrate 1-phenylethanol docked in the cleft of peptoid **1S** as viewed perpendicular to the helix axis (*Left*) and down the helix axis with the N terminus projecting forward (*Right*). (*B*) The substrate 1-phenylethanol approaching the catalytic TEMPO site of the sterically encumbered scaffold of peptoid 4S. The ovals represent the reaction site comprising the substrate hydroxyl group and TEMPO nitroxyl radical. Color key: hydrogen, white; oxygen, red; nitrogen, blue; 1-phenylethanol (substrate), green.

many catalytic transformations and therefore represent a highly versatile scaffold; (*iv*) the number of chiral centers, the helical secondary structure content, and other physicochemical attributes can be tuned in a precise manner through introduction of different side chains at various positions, thus permitting systematic exploration of sequence–structure–function relationships and optimization of catalytic performance; (*v*) peptoids may be capable of accessing conformations and three-dimensional architectures that enable functions not readily accessible by biopolymer systems.

The ease of peptoid library synthesis permits rapid screening of catalytic activity for a wide range of structural attributes, which in turn will reveal pathways for optimization of catalysis while facilitating detailed mechanistic studies. Moreover, the inherent modularity of peptoids permits various chemical transformations simply by introducing different types of catalytic centers (e.g., catalysts suitable for hydrogenation, oxidation, acylation). Catalytic activity and selectivity can be adjusted and optimized systematically by simply altering the placement of catalytic sites and chiral recognition sites on the oligomeric scaffold. Finally, the transfer of chiral information from a folded scaffold (40) to an embedded achiral reactive center should prove applicable to synthetic foldamers in general.

Methods

Preparation of Peptoid Oligomers. Peptoid oligomers were synthesized manually on Rink amide resin by using the submonomer approach (29). All peptoid oligomers were synthesized at room temperature. Typically, 100 mg of resin was swollen in DCM for 20 min before Fmoc deprotection of the resin. Multiple washing steps using DMF were performed between each step described below. Fmoc was cleaved from the resin by 20% piperidine in DMF, followed by bromoacetylation, in which ≈20 eq of bromoacetic acid (1.2 M in DMF, 8.5 mL g^{-1} of resin) and 24 eq of diisopropylcarbodiimide (2 mL g^{-1} of resin) were added; this reaction was allowed to shake for 20 min. After the reaction, the bromoacetylation reagents were washed from the resin by using DMF (10 mL g^{-1} of resin) (3 × 1 min), and then 20 equivalents of a primary amine (1.0 M in DMF, 10 mL g^{-1} of resin) were added. The amine displacement reaction was allowed to shake for 20 min and was followed by multiple washing steps (DMF, 10 mL g^{-1} of resin) (3 × 1 min). The bromoacetylations and amine displacement steps were repeated until peptoid oligomers of desired sequence were obtained. To cleave the peptoid oligomers from solid support for purification, 100 mg of resin was treated with 95% TFA in water (40 mL g^{-1} of resin) for 10 min at room temperature. The cleavage mixture was evaporated, resuspended in 2 mL of HPLC solvent, frozen, and lyophilized. To regenerate the TEMPO radical species, the compound was dissolved in 9:1 ammonia (7 N solution in methanol)/water (4 mL per 100 mg of resin) and stirred for 6 h at 25 °C. The solvent was then evaporated, and the compound was resuspended in 2 mL of HPLC solvent, frozen, and lyophilized (see *SI Appendix*).

Structural Characterization by CD Spectroscopy. Solutions (10 mM in methanol) of lyophilized peptoid powders were prepared immediately before CD measurements. The final concentration of each measured sample was 100 μM in methanol/water 2.5:4 solution. CD scans were performed at 25 °C. Spectra were obtained by averaging six scans per sample in a fused quartz cell (path length = 0.1 cm; Starna Inc.). Scans were performed over the 300- to 190-nm region at a step of 0.5 nm (scan rate = 1 s per step).

General Procedure for Oxidation Catalysis. A glass vial (8-mL volume) was charged with 1×10^{-4} mol of peptoid catalyst, 0.25 mL of CH_2Cl_2, 0.125 mL of 0.5 M KBr in water, and 1×10^{-6} mol of substrate (alcohol), placed in an ice bath and cooled to 0 °C under stirring. The reaction was initiated with the addition of 0.31 mL of freshly made 0.5 M NaOCl solution (10–13% Cl).

Analysis of the Catalysis Products. Gas chromatograph (GC) analysis was performed on a HP 6890 instrument, by using a 30-m Astec chiraldex B-PM column with an inner diameter of 0.25 μm and 0.25 mm thickness. The reaction was quenched by an addition of 1 mL of CH_2Cl_2, followed by extraction of the aqueous layer. Then, a sample from the CH_2Cl_2 layer (typically 1 μL) was injected to the GC at initial temperature of 100 °C. In these conditions, acetophenone is eluted at a retention time of 5.8 min, (*R*)-1-phenylethanol is eluted at a retention time of 8.7 min, and (*S*)-1-phenylethanol is eluted at a retention time of 8.9 min.

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1. Breslow R (1995) Biomimetic chemistry and artificial enzymes: Catalysis by design. *Acc Chem Res* 28:146–153.
2. Davie EAC, Mennen SM, Xu Y, Miller SJ (2007) Asymmetric catalysis mediated by synthetic peptides. *Chem Rev* 107:5759–5812.
3. Miller SJ (2004) In search of peptide-based catalysts for asymmetric organic synthesis. *Acc Chem Res* 37:601–610.
4. Wiesner M, Revell JD, Wennemers H (2008) Tripeptides as efficient asymmetric catalysts for 1,4-addition reactions of aldehydes to nitroolefins—a rational approach. *Angew Chem Int Ed* 47:1871–1874.
5. Joyce GF, et al. (1984) Chiral selection in poly (C)-directed synthesis of oligo (G). *Nature* 310:602–604.
6. Stuhlmann F, Jäschke A (2002) Characterization of an RNA active site: Interactions between a diels-alderase ribozyme and its substrates and products. *J Am Chem Soc* 124:3238–3244.
7. Coquiere D, Feringa BL, Roelfes G (2007) DNA-based catalytic enantioselective Michael reactions in water. *Angew Chem Int Ed* 46:9308–9311.
8. Boersma AJ, Klijin JE, Feringa BL, Roelfes G (2008) DNA-based asymmetric catalysis: Sequence-dependent rate acceleration and enantioselectivity. *J Am Chem Soc* 130:11783–11790.
9. Gellman SH (1998) Foldamers: A manifesto. *Acc Chem Res* 31:173–180.
10. Hill DJ, Mio MJ, Prince RB, Hughes TS, Moore JS (2001) A field guide to foldamers. *Chem Rev* 101:3893–4011.
11. Hecht S, Huc I, eds (2007) *Foldamers: Structure, Properties, and Applications* (Wiley-VCH, Weinheim, Germany).
12. Seebach D, Cardiner J (2008) β-Peptidic peptidomimetics. *Acc Chem Res* 41:1366–1375.
13. Kirshenbaum K, et al. (1998) Sequence-specific polypeptoids: A diverse family of heteropolymers with stable secondary structure. *Proc Natl Acad Sci USA* 95:4303–4308.
14. Wu CW, Sanborn TJ, Huang K, Zuckermann RN, Barron AE (2001) Peptoid oligomers with R-chiral, aromatic side chains: Sequence requirements for the formation of stable peptoid helices. *J Am Chem Soc* 123:6778–6784.
15. Wu CW, et al. (2003) Structural and spectroscopic studies of peptoid oligomers with alpha-chiral aliphatic side chains. *J Am Chem Soc* 125:13525–13530.
16. Yoo B, Kirshenbaum K (2008) Peptoid architectures: Elaboration, actuation and application. *Curr Opin Chem Bio* 12:714–721.
17. Sheldon RA, Arends IWCE, Brink G-JT, Dijksman A (2002) A green, catalytic oxidation of alcohols. *Acc Chem Res* 35:774–781.
18. Sheldon RA, Arends IWCE (2004) Organocatalytic oxidations mediated by nitroxyl radicals. *Adv Synth Catal* 346:1051–1071.
19. Malkov AV, Kocovsky P (2007) Chiral *N*-oxides in asymmetric catalysis. *Eur J Org Chem* 1:29–36.
20. Adam W, Saha-Möller CR, Ganeshpure PA (2001) Synthetic applications of nonmetal catalysts for homogeneous oxidations. *Chem Rev* 101:3499–3548.
21. Wei S, Hongwang W, Chungu X, Jingwei L, Peiqing Z (2003) Chiral-Mn(salen) complex catalyzed kinetic resolution of secondary alcohols in water. *Angew Chem Int Ed* 42:1042–1044.
22. Trend RM, Stoltz BM (2008) Structural features and reactivity of (sparteine)$PdCl_2$: A model for selectivity in the oxidative kinetic resolution of secondary alcohols. *J Am Chem Soc* 130:15957–15966.
23. Sigman MS, Jensen DR (2006) Ligand-modulated palladium-catalyzed aerobic alcohol oxidations. *Acc Chem Res* 39:221–229.
24. Mohr JT, Krout MR, Stoltz BM (2008) Natural products as inspiration for the development of asymmetric catalysis. *Nature* 455:323–332.
25. Laumen K, Breitgoff D, Schneider MP (1988) Enzymic preparation of enantiomerically pure secondary alcohols. Ester synthesis by irreversible acyl transfer using a highly selective ester hydrolase from *Pseudomonas* sp: An attractive alternative to ester hydrolysis. *Chem Commun*, 1459–1461.
26. Anelli PL, Biffi C, Montanari F, Quici S (1987) Fast and selective oxidation of alcohols to aldehydes or to carboxylic acids and secondary alcohols to ketones mediated by oxoammonium salts under two-phase conditions. *J Org Chem* 52:2559–2562.
27. Formaggio F, et al. (2002) Nitroxyl peptides as catalysts of enantioselective oxidations. *Chem Eur J* 8:84–93.
28. Ebner DC, et al. (2008) Palladium-catalyzed enantioselective oxidation of chiral secondary alcohols: Access to both enantiomeric series. *Angew Chem Int Ed* 47:6367–6370.
29. Fafarman AT, Borbat PP, Freed JH, Kirshenbaum K (2006) Characterizing the structure and dynamics of folded oligomers: Pulsed ESR studies of peptoid helices. *Chem Commun*, 377–379.
30. Takagi R, Shiraki A, Manabe T, Kojima S, Ohkata K (2000) The Julia–Colonna type asymmetric epoxidation reaction catalyzed by soluble oligo-L-leucines containing an α-aminoisobutyric acid residue: Importance of helical structure of the catalyst on asymmetric induction. *Chem Lett* 29:366–367.

31. Jarvo ER, Copeland GT, Papaioannou N, Bonitatebus PJ, Jr, Miller SJ (1999) A biomimetic approach to asymmetric acyl transfer catalysis. *J Am Chem Soc* 121:11638–11643.
32. Dziedzic P, Zou W, Háfren J, Córdova A (2006) The small peptide-catalyzed direct asymmetric aldol reaction in water. *Org Biomol Chem* 4:38–40.
33. Li X, Liu P, Houk KN, Birman VB (2008) Origin of enantioselectivity in CF_3–PIP-catalyzed kinetic resolution of secondary benzylic alcohols. *J Am Chem Soc* 130:13836–13837.
34. Fierman MB, O'Leary DJ, Steinmetz WE, Miller SJ (2004) Structure–selectivity relationships and structure for a peptide-based enantioselective acylation catalyst. *J Am Chem Soc* 126:6967–6971.
35. Goodman CM, Choi S, Shandler S, DeGrado WF (2007) Foldamers as versatile frameworks for the design and evolution of function. *Nat Chem Biol* 3:252–262.
36. Lee B-C, Zuckermann RN, Dill KA (2005) Folding a nonbiological polymer into a compact multihelical structure. *J Am Chem Soc* 127:10999–11009.
37. Lee B-C, Chu TK, Dill KA, Zuckermann RN (2008) Biomimetic nanostructures: Creating a high-affinity zinc-binding site in a folded nonbiological polymer. *J Am Chem Soc* 130:8847–8855.
38. Daniels DS, Petresson EJ, Qiu JX, Schepartz A (2007) High-resolution structure of a beta-peptide bundle. *J Am Chem Soc* 129:1532–1533.
39. Müller MM, Windsor MA, Pomerantz WC, Gellman SH, Hilvert D (2009) A rationally designed aldolase foldamer. *Angew Chem Int Ed* 48:922–925.
40. Maayan G, Ward MD, Kirshenbaum K (2009) Metallopeptoids. *Chem Commun*, 56–58.