Mini-ISES identifies promising carbafructopyranose-based salens for asymmetric catalysis: Tuning ligand shape via the anomeric effect

Kannan R. Karukurichi, Xiang Fei, Robert A. Swyka, Sylvain Broussy, Weijun Shen, Sangeeta Dey, Sanjip K. Roy, David B. Berkowitz*

This study introduces new methods of screening for and tuning chiral space and in so doing identifies a promising set of chiral ligands for asymmetric synthesis. The carbafructopyranosyl-1,2-diamine(s) and salens constructed therefrom are particularly compelling. It is shown that by removing the native anomeric effect in this ligand family, one can tune chiral ligand shape and improve chiral bias. This concept is demonstrated by a combination of (i) x-ray crystallographic structure determination, (ii) assessment of catalytic performance, and (iii) consideration of the anomeric effect and its underlying dipolar basis. The title ligands were identified by a new mini version of the in situ enzymatic screening (ISES) procedure through which catalyst-ligand combinations are screened in parallel, and information on relative rate and enantioselectivity is obtained in real time, without the need to quench reactions or draw aliquots. Mini-ISES brings the technique into the nanomole regime (200 to 350 nmol catalyst/20 μl organic volume) commensurate with emerging trends in reaction development/process chemistry. The best-performing β-o-carbafructopyranosyl-1,2-diamine–derived salen ligand discovered here outperforms the best known organometallic and enzymatic catalysts for the hydrolytic kinetic resolution of 3-phenylpropylene oxide, one of several substrates examined for which the ligand is “matched.” This ligand scaffold defines a new swath of chiral space, and anomeric effect tunability defines a new concept in shaping that chiral space. Both this ligand set and the anomeric shape-tuning concept are expected to find broad application, given the value of chiral 1,2-diamines and salens constructed from these in asymmetric catalysis.

INTRODUCTION

As part of a program directed at streamlining the process for discovering useful new reactivity and for identifying useful catalytic ligand-metal combinations, we have been laying the groundwork for an in situ enzymatic screening (ISES) approach to reaction screening. Although it is clear that reaction development requires a balance between screening and hypothesis-driven or computational (1, 2) approaches, in looking for fundamentally new reactivity, a broad initial screen can be of great use. This point is underscored through the recent successes of the groups of MacMillan (3) and Hartwig (4) in exploratory screens to “accelerate serendipity” yielding amine α-arylation, and Cu-mediated alkyne hydroamination transformations, respectively, and Chirik’s identification of an earth-abundant Co system for asymmetric alkene hydrogenation (5). Beyond this, recent advances in multicomponent reactions highlight the payoff attainable in systems with additional reactants (6–8) or catalytic entities (9–13). In such endeavors, once reactivity space is better defined, Sigman has shown that one may be able to tune the transformation, for example, by using empirical “sterimol” parameters (14).

The desire to interrogate catalyst structure/reactivity space broadly has spurred a parallel innovation in catalyst screening technology (15, 16). On-bead catalyst libraries have been exploited to enhance throughput with readouts including infrared thermography (17, 18) and gel-zone fluorescence (19, 20). More recently, microfluidic approaches have been invoked to address throughput (21–23). Optical sensing methods continue to be invoked and include fluorescence resonance energy transfer (24), indicator-displacement assays (16, 25), substrate chromophore induction (26), and optical rotatory dispersion (27). Mass spectrometric methods have proven invaluable to enhance throughput (4, 28) and provide information on reactivity (29) and stereoselectivity (30, 31). Perhaps inspired by the “combinatorial” path by which polypeptide catalysts evolve in nature, a number of successful “evolved” small-molecule catalysts feature peptidomimetic elements (32–40), perhaps none more strikingly than the catalyst suite developed by Miller and co-workers (41–44). Conversely, given both the inherent ability of enzymes to both differentiate stereoisomers and the opportunity to potentially leverage spectroscopic signals associated with a number of enzymatic transformations, we (45–51) and others (52–60) have developed protein-based sensing methods to facilitate the combinatorial catalysis enterprise.

Described herein is a miniaturized version of ISES (47) that is inspired by the recent disclosure from the Merck Process Group of a synthesis optimization platform that reduces volumes and quantities dramatically, down to the nanomole, for high-throughput chemistry development (61), by taking advantage of robotic instrumentation (62, 63). This report demonstrates proof of principle of mini-ISES, by using an ultraviolet (UV)/visible (vis) spectrophotometer outfitted with a quartz micromulticell for the biphasic catalyst screening method, thereby reducing the amount of catalyst needed per screen to the level of 200 to 350 nmol. This is done without specialized equipment, setting the stage for much higher-throughput, robotic versions of the technique, by demonstrating that catalysts can be effectively characterized from the reporting enzyme traces obtained on this nanomole scale, within minutes, and on the fly. The mini-ISES technique is applied here for the exploration of novel chiral space, with the goal of identifying fundamentally new scaffolds for asymmetric catalysis.

As one thinks about organizing chiral space for the design of asymmetric catalysts, the notion of symmetry often emerges. It has been argued, for example, that by building C2-symmetry into a ligand or catalyst,
one limits the number of chiral approaches available to substrate. In addition, although this can certainly be advantageous, as is illustrated in Fig. 1, “privileged chiral scaffolds” (64) for asymmetric catalysis are known that present chiral space in both C2-symmetric (A) and non-C2-symmetric senses (B). It is important to explore both topological domains in seeking to identify new chiral motifs of value (65). Among the chiral elements that have been invoked to carve out useful chiral space is axial chirality, from established ligands such as the BINAPs (Noyori) (66) to exploratory ligands being developed today around aniline systems with hindered rotation about C–N bonds (Curran) (67). Planar chirality is now an established chiral element, as highlighted by the success of the Phanephos (Pye) (68) and Josiphos ligands (Togni) (69), as well as related ferrocene-based scaffolds (70), including planar chiral “DMAP equivalents” (Fu) (71). Helical chirality is a chiral element still in its infancy for the chiral ligand design, with important recent contributions from Takenaka (72, 73).

That said, catalysts projecting central chirality in a non-C2-symmetric sense are of great importance in modern asymmetric synthesis, including those derived from chiral pool elements. These include proline-based oxazaborolidines (Itsuno, Corey) (74, 75) and proline-containing β-turn-based systems (Miller) (43, 76–79) in the domain of amino acids, not to mention proline itself, around which a plethora of organocatalytic transformations have been developed (80–87). The cinchona alkaloid-based systems are especially versatile, with proven efficacy in the asymmetric dihydroxylation of alkenes (Sharpless) (88), in asymmetric phase transfer alkylation (O’Donnell, Lygo, Corey) (89–91) and in asymmetric fluorination (Cahard) (92, 93). On the C2-symmetric side, tartrate esters (Sharpless) (94) and their derivative TADDOLates (Seebach) (95) also appear to be “privileged.”

This notion of “privileged” scaffolds has its origins in medicinal chemistry, harking back to the 1988 paper from Evans and the Merck med chem group, in which the term was used to describe benzodiazepine-type

---

**Fig. 1. “Privileged” chiral scaffolds.** (A) C2-symmetric scaffolds for asymmetric catalysis. Cinchona alkaloids (teal); trans-1,2-diaminocyclohexane systems (blue); TADDOLates (orange); Phanephos-planar chirality, helically chiral bipyridyl-type ligand (wine); BINAP systems (green). (B) Non-C2-symmetric scaffolds. Cinchona alkaloids (teal); trans-1,2-diaminocyclohexane-based Strecker catalyst (blue); proline-based systems-oxazaborolidine (red); Phanephos-planar chirality, helically chiral bipyridyl ligand (wine); planar chiral ferrocenyl phosphine systems (purple); CH-activated Ir-phosphoramidite catalyst (green). Arrows indicate the conversion of C2-symmetric systems into non-C2-symmetric systems.
structures for neuroactive ligands (96). The concept persists in medicinal chemistry circles and has been discussed more recently by Stockwell (97). In such discussions, ligands are presumed to have a particular propensity to bind to a range of protein targets and influence function. “Privileged chiral ligands,” on the other hand, it might be said, have a particular propensity to impart useful chiral bias to a catalytic center, usually upon ligating to a metal. This concept appears to have evolved from the medicinal chemistry concept and has been widely discussed in synthetic chemistry circles since the provocative piece in Science by Yoon and Jacobsen in 2003 (64).

Perhaps most interesting in this discussion of “privileged” chiral space and symmetry is the observation that depending on the system, advantage can be gained from both inducing $C_2$-symmetry where it is absent and breaking $C_2$-symmetry where it is present (see arrows depicting these “symmetry crossovers” in Fig. 1). Thus, Sharpless and co-workers generally improved upon the first-generation dihydroxylation ligands by constructing bidentate cinchona ligands into which a new $C_2$-axis is thereby built (98). On the other hand, while retaining the trans-1,2-diaminocyclohexane chiral scaffold from the “privileged” Jacobsen-type salen (64) and Trost-type bis-phosphines (99), Jacobsen and Sigman later found it advantageous to place this same chiral scaffold into a non-$C_2$-symmetric system, presumably to generate a more enzyme-like system, with dual catalytic roles, in building an asymmetric Strecker catalyst (40). Perhaps most interesting in this category is the fortuitous finding by Hartwig and associates that “privileged” $C_2$-symmetric phosphoramidite ligands pioneered by Feringa (100–102), at least in the context of Ir-catalyzed allylic amination, lead to a very effective iridiclyclic catalyst through a symmetry-breaking C–H activation event (103–105).

Our approach herein was to examine non-$C_2$-symmetric central chirality, and to investigate topologies not previously explored (106), with a particular focus on chiral 1,2-diamines and their derivative salens as chiral motifs with wide-ranging potential in asymmetric catalysis. Systems built around amino acid, terpenoid, and carbohydrate scaffolds were initially explored. A new set of interesting salen ligands built around the fructopyranosyl-4,5-acetonide emerged from these studies. We use mini-ISES to fingerprint the asymmetric profile of a focused array of ligands of this new class here. Key variables that have emerged include the ability to tune the shape of these ligands through the presence or absence of an anomic effect and the ability to pair such non-$C_2$-symmetric 1,2-diamines with nonsterically demanding salicylaldehyde equivalents, to produce the most selective salen ligands yet observed, particularly in cases of “matched” substrates.

RESULTS

In the cassette ISES approach, multiple candidate catalytic combinations are screened in an information-rich parallel format. The experimentalist gains data on relative rate, sense and magnitude of enantioselectivity, and substrate generality for the catalyst candidates being evaluated. The process is truly in situ, obviating the need to take aliquots or quench the reaction to obtain readouts on reaction progress. The hydrolytic kinetic resolution (HKR) serves as a very useful platform for both the investigation of new catalyst screening modalities and the development of new salen ligands, with the picture of a stereochemistry-determining transition state involving bimolecular metal-salen participation (vide infra) emerging (107–110).

Mini-ISES

The experimental configuration developed for mini-ISES is illustrated in Fig. 2 for the screening of Co(III)-salen catalysts for the HKR of epoxides, using both (+)-propylene oxide and (+)-hexene oxide as test substrates. The product 1,2-diols diffuse from the lower organic layer (20 µl) into an upper aqueous buffer layer (90 µl) containing reporting enzymes that oxidize the product, resulting in the conversion of NAD$^+$ (nicotinamide adenine dinucleotide) to NADH (reduced form of NAD$^+$) with a concomitant increase in the Abs$^{340}$ observable by UV/vis spectroscopy. The experimental setup used herein uses 4 of 16 available 110-µl wells in a single quartz micromulticell per catalyst candidate and substrate pair, significantly streamlining the process. Additionally, as is described in detail below, three new KRED (ketoreductase; Codexis naming system) reporting enzymes have been identified, also serving to facilitate implementation of this information-rich, in situ screening methodology. Specifically, KRED 23 was found to be a complement to TBADH (Thermoanaerobium brockii alcohol dehydrogenase) for following the HKR of propylene oxide. The former is selective for (S)-1,2-propanediol and the latter for the (R)-antipode (see the Supplementary Materials for detailed kinetic analysis and data). For the HKR of hexene oxide, KRED 119 was identified as an (R)-selective reporting enzyme and KRED 107 as a highly (S)-selective enzyme.

After considerable experimentation with these reporting enzymes and the quartz micromulticell platform, it was found that the aqueous reporting layer could be reduced from 500 µl (cuvette-ISES) to 90 µl. The organic layer volume could be reduced from 300 to 20 µl in the micromulticell well, allowing for a significant reduction in the amount of catalyst/substrate needed for screening. Even under these mini-ISES conditions, reliable UV/vis spectroscopic traces were obtained from the reporting enzyme window. In terms of loading for mini-ISES, it was found that under optimal conditions, one can obtain useful ISES traces using only 200 to 350 nmol of active Co(III)-salen catalyst (0.25 mol %) within minutes (Fig. 2B). The salen ligand stereopreference profiles obtained are presented below, following a discussion of the design of this focused salen array and the synthesis of this new ligand class.

Design of the salen array

The original salen array that we assembled for double cuvette-ISES (48) was composed of 1,2-diamines derived from the chiral pool. Terpenoid, amino acid, and carbohydrate scaffolds were all fashioned into 1,2-diamines that were combined with variously substituted salicylaldehyde or α-hydroxy aryl aldehyde partners to generate the salen/pseudosalen array. Two particularly intriguing new salen motifs emerged from those early studies. On the one hand, a salen derived from the β-pinene–derived 1,2-diamine and α-hydroxynaphthaldehyde showed high $E$ values for the HKR of matched terminal epoxides. This chiral diamine was new to asymmetric synthesis and was inspired by the success Midland (111) and Brown (112) had enjoyed in building chiral organoboron reagents from the α-pinenoind scaffold, most notably Alpine-borane and DIP-chloride. Indeed, this terpenoid β-pinene–derived pseudosalen ligand served as the source of all chirality in the rapid asymmetry assembly of the antipodal oxabicyclo[4.3.1]dodecyl cores of the sesquiterpene lactone natural products zaluzanin A and linearifolin in these laboratories (45).

α-Carbofructopyranose–based 1,2-diamines

The more provocative ISES lead was generated by exploring the fructopyranose scaffold as a new chiral scaffold around which to build...
1,2-diamines. Prior to our work, D-fructose–based chirality had been used in both the furanose form (diphosphite ligands for Ni-mediated alkene hydrocyanation) (113) and the pyranose form in the seminal work of Shi (114,115), in which the 3-position of the sugar supports a chiral dioxirane moiety for alkene epoxidation. Against that backdrop, we chose to explore the D-fructopyranose-4,5-acetonide scaffold as a bicyclic chiral 1,2-diamine backbone. This appears to be the first example of the use of fructose-based chirality in 1,2-diamine ligand design. Figure 3 illustrates how the α- (5) and β-D-fructopyranosyl-1,2-diamines (6) can be readily assembled in six steps from D-fructose itself. Because of promise seen in the D-fructopyranose–based 1,2-diamines as new chiral motifs for asymmetric catalysis and the desire to prevent anomerization, it was decided to explore the corresponding carbocyclic system.

![Image](https://example.com/image.png)

**Fig. 2.** Depiction of the mini-ISES format for information-rich catalyst screening (ee, relative rate, and substrate scope). (A) Quartz micromulticell in the background; reporting wells for catalyst derived from salen 16a in the foreground featuring both (S)- and (R)-selective dehydrogenase reporting enzymes for both propylene oxide (KRED 23 and TBADH, respectively) and hexene oxide (KRED 107 and KRED 119, respectively). The protein structure shown is the actual structure of TBADH (PDB 1YKF). (B) Actual ISES data for the HKR of the respective epoxides mediated by the Co(III)-salen catalyst derived from 16a in the lower organic layer (20 μl); spectral data reflect the conversion of NAD(P)⁺ to NAD(P)H upon diol oxidation by the respective reporting enzyme, with the concomitant increase in A_{540} nm versus t (min).

Our initial entry into the projected D-carbafructosyl-1,2-diamine scaffold emanates from (−)-quinic acid, as outlined in Fig. 4. The selective capture of the quinate carboxylic acid functionality as the 1,3-diaxially disposed lactone is based on the elegant work of Shing (116). This permits for the simultaneous blocking of the remaining vicinal diol via a cyclohexanone-derived ketal. Lactone cleavage then releases a single secondary alcohol allowing for site-selective oxidation. Pyridinium chlorochromate (PCC)–mediated oxidation then proceeds smoothly with concomitant elimination of the tertiary alcohol into the α,β-unsaturated ketone 8. Sodium borohydride–mediated carbonyl reduction from the convex face followed by trankeletalization leads to α,β-unsaturated ester 9. Barton deoxygenation is followed by bis-Grignard addition into the methyl ester, giving triol 10. The triol was selectively O-methylated at the lone secondary alcohol in the triol followed by
oxidative cleavage of the vic-tert-diol with Pb(OAc)$_4$ to yield stereo-defined ketone 12. Subsequent Wittig methylation produced the desired carbofructose-leading olefin 13 in 80% yield. Next, the key step, diazidation of the exocyclic alkene, was realized, adopting a procedure developed by Snider and co-workers (117). Namely, Mn(OAc)$_3$-mediated alkene diazidation delivered the $\delta$-carbofructopyranosyl-1,2-diazide as a mixture of the anticipated $\alpha$- (14) and $\beta$-pseudo-anomers (15). After chromatographic separation, these diastereomeric diazides were hydrogrogenated to give the respective diamines, 16 and 17, as desired, in quantitative yield.

**Assembly and screening of focused carbofructopyranose-based Co(III)-salen array**

With both the oxac- and carbacyclic fructopyranosyl-1,2-diamines in hand, we next constructed a focused library of Co(III)-salen catalysts as depicted in Table 1. The $\alpha$- and $\beta$-diastereomers of both the oxacyclic (5, 6) and carbacyclic $\delta$-fructopyranosyl-1,2-diamines (16, 17) were paired with salicylaldehydes bearing varied 3',5'-substitution patterns [di- (a) or mono-$t$-butyl (b), diodo (c)], as well as with the $\alpha$-hydroxy-$\beta$-naphthaldehyde (d). Each salen was converted to the Co(II)-salen (precipitates out) by incubation with Co(OAc)$_2$ in MeOH. Immediately before performing HKR runs, the Co(II)-salen was converted to the Co(III)-salen(DNB) complex, by air oxidation in the presence of 3,5-dinitrobenzoic acid.

The newly developed mini-ISES was used for a rapid screening. As discussed, on the basis of dial oxidation efficiency and stereoselectivity, KRED 107 and KRED 119 were selected as reporting enzymes for the HKR of (±)-hexene oxide, whereas KRED 23 and TBADH were used to screen the HKR of (±)-propylene oxide. Then, by using a standard UV/vis apparatus, outfitted with the quartz micromulticell, the focused salen library could be expeditiously screened across both test substrates (see the Supplementary Materials for detailed characterization).

ISES-estimated ee values were compared with the measured ee values under typical flask conditions. Three-dimensional (3D) bar graph representations of these results are depicted in Fig. 5. The ISES screen involves biphasic organic (CHCl$_3$, epoxide)/aqueous conditions, wherein one sample diol product diffuses into the aqueous layer at early times and with minimal catalyst loading (0.25 mol %). On the other hand, the “flask conditions” here involve incubation of Co(III)-salen catalyst in neat epoxide, with 0.55 eq. water, at longer times (3 hours) and somewhat higher catalyst loading (0.5 to 1 mol %). The goal is to explore how well a rapid early screen serves to predict kinetic resolution efficiency.

As can be seen in the 3D bar graph patterns for ISES estimations of product ee at early times (Fig. 5, left side, blue/green bars) versus the high-performance liquid chromatography (HPLC) determinations of product diol ee under flask conditions (right side, pink, aqua bars), ISES serves as a useful, predictive screening tool here. In particular, one notes the clear (S)-selectivity of both Co(III)-5c-DNB and Co(III)-17c-DNB from the paired positively oriented bars, representing the two test substrates across both bar graphs. These catalysts, particularly those derived from the novel $\beta$-$\delta$-carbofructopyranosyl-1,2-diamine, 17c, emerged from this focused screen as worthy of much greater study here. From a catalyst screening point of view, these initial studies demonstrate proof of principle for the ability to obtain reliable ISES data in this new micromulticell format, that is, mini-ISES. Recall that these data were obtained with the 20-µl organic layer/90-µl aqueous reporting layer volumes described and required nanomolar levels of catalyst per micromulticell well.

**Structure/enantioselectivity relationships**

In examining the patterns seen in this focused salen library screen, two interesting observations emerge, both unexpected and both useful in thinking about ligand structure/enantioselectivity relationships. First, in both the carbacyclic and oxacyclic series, an “enantioswitch” is...
observed based on the substituent on the salicylaldehyde and not the chiral element, that is, the d-fructopyranose-based 1,2-diamine. Specifically, when evaluated for the HKR of propylene oxide and hexene oxide, the Co(III)-salen catalyst derived from the pairing of the \(b\)-D-carbafructopyranose-1,2-diamine (17) with 3,5-di-tert-butylsalicylaldehyde (a) gives rise to the (R)-diol products, whereas the catalyst derived from pairing of this same chiral diamine (17) with 3,5-diiodosalicylaldehyde (c) gives the corresponding (S)-diol products. This is the same pattern that is seen in the oxacylic (native fructose-derived) series with the true \(b\)-D-fructopyranosyl-1,2-diamine (that is, 6a versus 6c). However, given that 6 and the corresponding \(\alpha\)-anomer 5 can interconvert via an anomerization mechanism, one could always hypothesize that in the oxacyclic series, an undetected anomerization might somehow underlie this apparent “enantioswitch” in catalyst preference. The result with the carbacyclic system (that is, 17a versus 17c) now seems to firmly rule out this “undetected anomerization” mechanism for change of enantipreference in the oxa-fructopyranose series. The overall result here is important. Namely, within the context of these new carba- and oxacyclic \(b\)-D-fructopyranosyl-1,2-diamine chiral scaffolds, one can alter the sense of enantiopreference and improve the magnitude of enantioselection by moving from the more sterically encumbering 3,5-di-tert-butyl substitution pattern on the salen to the less sterically encumbering 3,5-diiodo substitution pattern.

However, probably the most interesting and informative observation made here is the notable enantioselectivity improvement from the oxafructopyranose-based ligand 6c to the carbafructopyranose-based

---

Fig. 4. Synthesis of \(\alpha\)- and \(\beta\)-d-carbafructopyranosyl-1,2-diamines from quinic acid.
ligand 17c. Replacing the ring oxygen with a methylene confers a significantly higher (S)-selectivity upon the resulting Co(III)-salen complex, with an about three- to fourfold increase in $E$ value—from 13 to 44 and from 28 to 104 for the HKR of the propylene and hexene oxides, respectively. This experimental observation prompted us to examine the underlying structural basis of such a dramatic change in chiral bias by single atom replacement. Of course, it had not escaped our attention that this particular single-atom replacement could have important structural consequences, as one would be effectively removing a ground state anomeric effect, such as it is, in such a diamino-sugar system. For these reasons, complete crystallographic characterization of these Co-salens was undertaken and provides important insight in this regard, as is discussed in detail below.

**Benchmarking performance for the carbofructopyranosyl-1,2-diamine–derived salen-17c**

To assess the potential of the most promising ISES hit for asymmetric catalysis, the top mini-ISES hit, catalyst Co(III)-(17c)-DNB, was next taken well beyond the screening set and examined for its HKR performance across a range of differentially structured and substituted epoxide substrates. The results are collected in Table 2. Given the difficulty in obtaining accurate values for the selectivity factor for any kinetic resolution, we find it useful to measure yield and ee values. The ISES-estimated % ee values of the produced diols are presented in brackets, followed by the observed % ee values (chiral HPLC) and calculated $E$ values.

| Table 1. HKR screening of focused oxa/carbafructopyranose-derived salen array. Each box provides the HKR data of propylene oxide (black) and hexene oxide (blue) under the catalysis of the corresponding Co(III)-salen 3,5-dinitrobenzoate. The ISES-estimated % ee values of the produced diols are presented in brackets, followed by the observed % ee values (chiral HPLC) and calculated $E$ values. |
|---|---|---|---|
| 5 | [77(+)] | [64(+)] | [70(+)] | [67(+)] | [42(+)] | [40(+)] |
| 69(+) | 45(+) | 2.6(+), 2.4(+), 1.7(+) |
| 4.7(−), 4.2(−) | [33(−)] | [64(−)] | # | 2.5(−), 2.4(−), 13(+) | 28(+) |
| 6(−), 52(−) | [28(−)] | [31(−)] | [85(+)] | [77(+)] | [85(+)] |
| 40(−), 36(−) | 83(+) | 85(+) |
| 16 | [53(−)] | [23(−)] | [76(−)] | [40(−)] | [91(−)] | [42(−)] | 17(−), 5.0(−), 4.3(−), 3.8(−) |
| 37(−), 29(−) | 75(−), 45(−) | 85(−), 63(−) | 61(−), 55(−) |
| 2.3(−), 2.0(−) | 8.2(−), 3.5(−) | 17(−) |
| 17c | [39(−)] | [67(−)] | [50(−)] | [94(+)] | [77(+)] |
| 28(−), 30(−) | 48(−), 53(−) | 93(+) | 92(+) |
| 1.9(−), 2.1(−) | 3.4(−), 3.4(−), 2.2(−) | 44(+), 104(+), # |
| 17 | # | 34(−) |
| § | § |

†Difficulty was encountered in synthesizing appreciable quantities of this salen. #These catalysts gave negligible ISES rates. §These catalysts gave a conversion < 2% after 72 hours.
On the enzymatic side, Reetz and co-workers have carried out two separate directed evolution studies, both emanating from native Aspergillus niger epoxide hydrolase (ANEH) and both directed at developing enzymatic catalysts optimized for the HKR of O-phenylglycidol. In the first case, 20,000 clones were generated in a five-step process resulting in an evolved ANEH with nine point mutations and an $E$ value of 115 (119). A more recent study, in which ePCR was first used, expression levels led to a new ANEH variant with seven point mutations, plus a 13-mer peptide insertion (apparently an unintended consequence of the QuikChange protocol for site-directed mutagenesis) (120). This new directed evolution mutant shows an $E$ value of 160 for the HKR of O-phenylglycidol. Thus, Co(III)-17c shows a chiral bias ($E = 95 ± 2$ at $51\%$ conversion) comparable to the best-known chiral Co-salen catalyst ($E = 90 ± 30$ at 18 to $54\%$ conversion) but somewhat lower than the best-evolved enzymes for this reaction ($E = 115; 160$). For the HKR of 3-phenylpropylene oxide, (2a) the trans-1,2-diaminocyclohexane–based Co(III)-salen due to Jacobsen is the most selective metal-organic catalyst previously reported, with $E = 96$ ($20\%$ conversion) (110). (2b) In the enzymatic realm, in this case, the Widersten group recently described the directed evolution of a plant enzyme, Solanum tuberosum epoxide hydrolase (STEHI), targeted at the HKR of this substrate. Through four cycles of directed evolution, the best variant featured five point mutations and displayed $E = 14$ (121). Then, the Co(III)-17c catalyst introduced here shows a chiral bias ($E = 106 ± 13$ at $51\%$ conversion) that is at least equivalent to the best-known chiral salen catalyst ($E = 96$ at $20\%$ conversion) and superior to the best enzymatic catalyst ($E = 14$) yet described.

**X-ray crystallographic analysis: Tuning ligand shape via the anomeric effect**

To gain further insight into the chiral space mapped out by these new chiral ligands and into the structural basis of the enantiopreferences displayed by the most promising catalyst, we next set out to obtain diffractible crystals. We report here the x-ray crystal structures of three Co(II)-salen complexes, namely, those derived from salens 6a, 6c, and 17c. The 3D structures of each of these three new d-fructopyranose–derived salen scaffolds are displayed in Fig. 6. One sees very clearly that whereas both oxacycles assume a distorted 3,6β boat-like structure for the pyranose ring, the carbacycle displays a 5C2 chair-like geometry. The information gleaned here suggests that the shape of these ligands can be "tuned" by the anomeric effect (122). Thus, in the absence of an anomeric effect, in the carbacycle, the steric of the Co(salen) system are apparently such as to favor a 5C2 conformation for the cyclohexyl ring as is revealed by the structure of Co(II)-17c (Fig. 6C). Introduction of the ring oxygen into this system would produce a 3C2 conformation for the cyclohexyl ring depicted in Fig. 6A for the Co(II)-6c complex. As can be seen, this would introduce an unfavorable reinforcing dipole-dipole interaction between the anomeric C–N bond and the ring dipole (123). Distortion of the amino sugar core from a 5C2 conformation to a 3βB conformer (Fig. 6B) serves to relieve this dipolar strain, thereby changing the shape
of the ligand, the chiral space that it maps out, and the chiral bias that it manifests in the HKR reaction.

There is good precedent for the anomeric effect playing an important role in the pyranose forms of the parent sugars for all four of the diastereomeric ketohexoses. Thus, both β-D-fructopyranose (124) and β-D-psicopyranose (125) are known to assume the 2C5 chair, whereas both α-D-tagatose (126) and α-L-sorbose (127) exist predominantly in the 5C2 chair as pyranoses. In all such cases, the anomeric C–O bond is oriented so as to partially oppose the ring dipole. The amino sugar salens being investigated here differ from the parent sugar pyranoses, both in having an unusual anomeric C–N bond and in having both the C1- and the C2-nitrogens engaged in a rigid Co-salen ring system. We believe that this has the effect of distorting the normally favored chair conformer into a boat-like conformer that nonetheless displays a favorable anomeric effect (partially opposing dipoles) as is seen the structures for both Co(II)-6c and Co(II)-6a (Fig. 7, B and D, respectively). The removal of the ring oxygen in these systems not only locks out anomerization but also reshapes the ligand, by removing this boat-enforcing anomeric effect, generating an even more enantiodiscriminating chiral scaffold.

### Table 2. Overview of HKR performance of the Co(III)-dinitrobenzoate catalyst derived from salen 17c. rt, room temperature.

| Entry | Epoxide educt (±) | Catalyst loading (mol%) | Conditionsa | Conversionb | Isolated epoxidec | Isolated diold |
|-------|------------------|-------------------------|-------------|-------------|------------------|----------------|
| 1     | ![Me](H2O)       | 0.14                    | Neat, 0°C, 15 hours | 45          | 50, −74, 44      | 46, 88, 34    |
| 2     | ![Ph](O)        | 0.5                     | DCM, rt, 20 hours  | 51          | 47, −96, 97      | 46, 92, 93   |
| 3     | ![H3C](O)       | 0.5                     | Neat, 0°C, 30 hours | 52          | 45, −99, 104     | 48, 91, 116  |
| 4     | ![Ph](O)       | 0.5                     | Neat, 0°C, 23 hours | 51          | 48, −97, 119     | 49, 92, 93  |
| 5     | ![tBuO](O)     | 1.0                     | THF, rt, 35 hours  | 44          | 55, −72, 49      | 40, 92, 52  |
| 6     | ![Ph](O)       | 0.5                     | Neat, rt, 30 hours  | 54          | 40, −99, 61      | 48, 82, 40  |
| 7     | ![Ph](O)       | 0.5                     | DCM, rt, 20 hours  | 32          | 68, −39, 16      | 26, 86, 20  |
| 8     | ![Ph](O)       | 1.0                     | THF, rt, 50 hours  | 28          | 63, −33, 17      | 28, 90, 27  |

aCatalyst (0.2 to 1 mol %) was added to a solution of epoxide in THF or DCM or neat condition. The mixture was cooled to 0°C or kept at room temperature and 0.5 equivalent water was added to initiate the reaction. The reaction was stirred at 0°C or room temperature until completion. bConversion of the reaction was determined by 1H NMR. cThe purified yield (black), % ee (red), and calculated E value (blue) are listed consecutively. Note: All diol products are presumed to be (S)-configured but, for entry 2, due to a change in Cahn-Ingold-Prelog prioritization. A negative sign as prefix for the % ee designates that the epoxide is (S)-configured.

### Considering bimolecularity in the HKR transition state

In seeking to model the favorable chiral bias (Table 2) exhibited by the Co(III)-17c-salen catalyst, we began from the crystal structure coordinates of the corresponding Co(II)-17c complex. Modeling was guided by three key observations from the Co(III)-salen HKR literature. (i) First, careful kinetic studies by Blackmond and Jacobsen indicate that two molecules of Co(III)-salen are involved in the HKR mechanism (109), one to deliver the hydroxide nucleophile to the epoxide and the other [likely bearing a DNB counterion (108); a second molecule of Co(III)-salen–OH is used here for the model] as a Lewis acid. Density functional theory (DFT) studies agree with these experimental observations, finding that a cooperative, bimolecular SN2-like pathway for Co-salen–mediated epoxide hydrolysis is favored over unimolecular alternatives (128). (ii) The Chin crystal of an aziridine Co(III)-salen complex was used to guide both the coordination distance and
coordination angle of the Co-salen–bound epoxide \((\text{129})\). (iii) A recent DFT computational study by Jacobsen and co-workers posits that key stereoelectronic control elements are at play in such Co-salen–mediated epoxide openings. Their studies project that the \(\text{O-Co-O} \) dihedral angle \((\theta)\) is critical, with the energy well for productive coordination complexes displaying a shallow minimum, suggesting that dihedral angles approximately in the 20 to 60° range are optimal \((\text{107})\).

As noted above, x-ray crystallography reveals a chair-like carbasugar ring in the Co(II)-17c structure. The Co(III)-17c-OH complex was built from these crystallographic coordinates, followed by docking of a typical terminal epoxide substrate, taking care to minimize unfavorable van der Waals interactions in so doing. The model obtained is presented in Fig. 8. \((\text{S})\)-hexene oxide is coordinated to the Co(III) center at 1.99 Å, close to the Co–N distance in the Chin crystal structure (1.95 Å). In addition, the oxirane ring approaches the Co center at an angle \((122 \pm 18°)\) modeled after that of the bound aziridine \((123 \pm 3°)\) in this structure. The dihedral angle is 24°, close to the O–Co–N–C angle observed in the Chin structure \((33°)\) within the domain of the shallow minimum identified by the Jacobsen group. Adhering to these constraints, the \((\text{S})\)-hexene oxide substrate is well positioned underneath the \(\pi\) face of HO-Co-salen moiety, a face that is particularly accommodating with diodo substitution. Finally, Jacobsen also puts forth the notion that enantioselection in such biomolecular salen-epoxide complexes may be governed by the overall stepped conformation of the Co-salen complex \((\text{107})\). To investigate this in the context of the new Co-salen complexes described here, the step heights for each of the three Co-salen crystal structures were estimated (see the Supplementary Materials for details) with the observation that the Co(II)-17c complex also displays the largest step height of the set at 0.76 Å. That the fructopyranose-based Co-salen complexes being investigated here by both crystallography and chiral bias display a similar structure/enantioselectivity relationship to that seen by Jacobsen and co-workers lends support to the notion that these systems proceed through similar mechanisms (for example, as modeled in the bimolecular transition state envisioned in Fig. 7).

Streamlined synthesis of \(\beta\)-D-carbafructopyranosyl-1,2-diamine
Given the promise shown by this previously undescribed \(\beta\)-D-carbafructosyl-1,2-diamine chiral scaffold, we have now also developed a streamlined, second-generation entry into this system beginning from a cheap, readily available starting material, \(\alpha\)-methyl-D-mannopyranoside (Fig. 8). Thus, an Appel reaction efficiently transforms the 6-hydroxyl into the 6-iodide. The requisite acetonide may then be selectively installed across the cis-configured vicinal 2,3-diol through exposure to dimethoxypropane/aceton with catalytic p-TsOH. C-4-O-methylation and dehydrohalogenation can then be achieved in a single step, in nearly quantitative yield, giving enol ether \textbf{19}. For the key type II Ferrier rearrangement, several divalent, late-transition metal catalysts [HgCl\(_2\), Pd(OAc)\(_2\), and PdCl\(_2\)] were examined, with...
variation of solvent and temperature. The optimal conditions identified use 10 mol % Pd(OAc)$_2$ in a mixture of acetone, dioxane, and water (40:40:20) at 0°C, providing rearranged product 20 in 85% yield. The temperature proved to be critical, with warming the reaction to room temperature resulting in unwanted side products. To remove the resultant hydroxyl group in 20, Barton deoxygenation was initially envisioned. However, the projected phenyl thionocarbonate ester proved to be unstable and tended to be eliminated upon exposure to silica gel. This observation led us to modify the route, adding an O-mesylation step to facilitate in situ β elimination to the α,β-unsaturated ketone intermediate in 80% yield. Hydrogenation then gives 12, the key intermediate in the synthesis of 17c, in quantitative yield. The newly developed synthesis saves six steps, raises the overall yield more than fivefold compared to the first-generation route from (−)-quinic acid, and also begins from a more economical starting material, namely, D-mannopyranose.

**DISCUSSION**

Inspired by recent developments in leading process chemistry groups to reduce the scale for reaction development and catalyst optimization down to the nanomolar regime (61), we report here a mini-ISES screen that exploits a quartz micromulticell for parallel screening of catalysts in 20-μl organic volumes at 200 to 350 nmol of catalyst loading. The technique is used to probe for diamine ligands and their derivative salens that map out new and potential useful chiral space for asymmetric catalysis. Out of these efforts emerged a new chiral motif built around the non-C$_2$-symmetric β-D-fructopyranosyl-1,2-diamine and its cognate carbacycle, particularly when combined when the sterically unencumbered 3′,5′-diiodosalicylaldehyde, to build salen ligands with promise for asymmetric catalysis. In pairing a non-C$_2$-symmetric diamine with a sterically unencumbered salicylaldehyde partner, this approach parts from conventional wisdom in metal-salen catalyst design and yet the swath of chiral space that results is clearly of value (see Fig. 9 for a schematic representation of the catalyst discovery and analysis pathway taken in this study).

From the point of view of chiral ligand development, there are two principal concepts that emerged from these studies. On the one hand, the β-D-carbafructopyranosyl-1,2-diamine scaffold is a potentially ‘privileged’ scaffold for the construction of chiral reagents and catalysts (64), although any such designation certainly must await much more extensive characterization of this new chiral framework across a greater breadth of salen-asymmetric and non-salen-asymmetric synthesis space. Thus, to our knowledge, the carbacyclic diamine, when incorporated into the Co(III)-17c catalyst, displays a chiral bias for the HKR of 3-phenylpropylene oxide ($E=106 \pm 13$ at 51% conversion) comparable to or better than that of the best catalysts reported heretofore, including the best such metal-salen catalyst ($E=96$ at 20% conversion) (110) and the best such evolved enzyme ($E=14$) (121). For the HKR of O-phenylglycidol, this metal-salen appears to be equivalent ($E=95 \pm 2$ at 51% conversion) to the best known such catalyst ($E=90 \pm 30$ at 18 to 54% conversion) (118), and both of these metal-salens fall just short of the best-evolved enzymes ($E=115; 160$) (107, 119, 120). These experimental observations attest to the potential of this new chiral scaffold for asymmetric catalysis.

The second interesting conceptual finding here relates to the tunability of these ligands, beyond the stereochemistry, substituent distribution, and bicyclic nature of the ring system in this non-C$_2$-symmetric chiral-1,2-diamine, and beyond its matched or mismatched pairing with

---

Fig. 7. Chin structure versus transition-state model for the HKR of hexene oxide with catalyst Co(III)-17c. (A) Chin’s Co(III)-salen-aziridine complex (second aziridine ligand omitted for clarity). (B) TS model for the HKR of hexene oxide with catalyst Co(III)-17c. Note: The catalyst structure was built from the x-ray coordinates of the Co(II)-17c structure (Fig. 6C) using the Chin structure as a guide in Spartan. The preferred substrate enantiomer, (S)-hexene oxide, was docked (Accelrys) at a Co–O coordination bond length of 1.99 Å, similar to the Co-N distance in the Chin structure. The O–Co–O–C dihedral angle $\theta$ in the TS model is at $24^\circ$, within the preferred range described by Jacobsen and co-workers.
Fig. 8. Streamlined access into the key intermediate toward the β-carbafructopyranosyl-1,2-diamines from D-mannose.

Fig. 9. Overview of the application of mini-ISES to the screening and identification of new chiral scaffolds for asymmetric catalysis. A focused salen array is screening in parallel by UV/vis spectrophotometry using a micromulticell (20-μl organic layer) so as to bring catalyst loading down to the nanomolar level. Reporting enzyme output can then be processed to give an in situ readout on sense and magnitude of enantioselectivity. Out of this study, the cobalt-17c salen complex emerged as a particularly promising catalyst, indeed the best catalyst reported to date for the HKR of 3-phenyl propylene oxide.
substituted salicylaldehydes. There is an important additional control element built into this diamine ligand scaffold, namely, the ability to modulate ligand shape significantly by introducing or removing an anomic effect. Operationally, this amounts to a single heteroatom change, and to illustrate the underlying principle here, it is probably of advantage to run the thought experiment in the reverse direction to the actual experiment here. Thus, crystallographic studies demonstrate that the carbocyclic diamino-salen, Co(II)-17c, adopts a $d_2 C_2$ chair-like structure at its core (Fig. 6C). This confers a shape and overall step height that is commensurate with a highly enantioselective catalyst, at least for the HKR chemistry explored here. However, introduction of the sugar ring oxygen into Co(II)-6c would generate Co(II)-6c in a $d_2 C_2$ conformation that suffers from a significant ring dipole-anomeric change, and to illustrate the underlying principle here, it is probably an anomeric effect. Operationally, this amounts to a single heteroatom element built into this diamine ligand scaffold, namely, the ability to reinforce dipole reinforcement interaction, that is, an unfavorable anomeric effect (Fig. 6A). Distortion of the amino sugar core from a $d_2 C_2$ conformation to a $d_0 B$ conformation would relieve this dipolar strain, thereby changing the shape of ligand from chair- to boat-like at its core. This, in turn, fundamentally alters the chiral space that the ligand maps out, and the step height of the Co-salen complex, ultimately resulting in a changed chiral bias in the HKR reaction. We believe that this third degree of modularity of these ligands, grounded in the anomic effect, adds an important dimension to their versatility as building blocks for the construction of salen ligands, as well as other chiral catalyst or reagent frameworks. In the future, other subtle modifications, such as fluorination, that could have large effects on dipole-dipole interactions (123) may be strategically employable to modulate such anomic effect tuning approaches.

From a much broader catalyst evolution perspective, that substitution of a CH$_2$ for the ring oxygen boosts catalyst selectivity to the same approximate levels as two different highly evolved (directed evolution) epoxide hydrolase enzymes (119, 121) attests to the validity of this approach to chiral ligand/catalyst discovery. It is worth noting here that whereas this type of “isostere” replacement approach is common in medicinal chemistry, it is much less common in other fields, although elegant and revealing examples in both chemical biology (for example, replacement of a native protein β turn with a synthetic prosthetic) (130, 131) and in asymmetric catalyst design (for example, replacement of key amide bond with an alkene isostere) (132, 133) have appeared in recent years. As for the notion that this “tunable” carbafructopyranosyl-1,2-diamine–derived ligand scaffold is “privileged,” this will best be assessed through its further exploration across other metal-salen or chiral 1,2-diamine–mediated transformations both in these laboratories and beyond.

The ability to miniaturize the ISES method, using an uncomplicated commercially available micromicell, should make this method accessible to broader application in chiral catalyst development and continue to move this methodology further into the nanomolar regime, in keeping with the trend in catalytic and process chemistry (61). Truly high-throughput embodiments of mini-ISES will likely require the development of appropriate robotic platforms and automation, for example, building around the proof-of-principle experiments demonstrated herein with the UV micromicell. Future studies on the screening side will be directed at developing related platforms for an even more diverse array of chemical transformations. For, in the end, as Yoon and Jacobsen put it, “the identification of new ‘privileged’ ligands and catalysts remains enormously difficult and often requires a degree of serendipity (64).” It is hoped that the advances in both screening technology and ligand development described here will facilitate this enterprise.

### MATERIALS AND METHODS

**Experimental design**

ISES is used here to provide useful estimates of relative reaction rate, substrate specificity, and % ee of an array of catalyst candidates in parallel. To obtain these data, the assay is performed in a biphasic system. The upper aqueous enzymatic reporting layer is positioned above the organic layer, and a UV/vis spectrophotometer is used to monitor the conversion of NAD to NADH in a semicontinuous fashion across multiple parallel cuvettes or wells, in using the micromicell. The method requires that one identify a pair of screening enzymes that display distinct enantioselectivities for the chiral product being generated (1,2-propanediol and 1,2-hexanediol here). Toward this end, an array of KREDS (from Codexis, Sigma, Almac, or expressed in our laboratory) were screened, and four were selected as appropriate reporting enzymes for the screen. The enantioselectivity of these enzymes is described below. The miniaturized ISES procedure used for this work is outlined in detail after the enzyme characterization section. Finally, the second-generation synthesis of the carbafructopyranose diamine is reported, along with procedures to generate our best salen for this HKR and methods for its crystallization. This section concludes highlighting the HKR of O-phenylglyceraldehyde and 3-phenylpropylene oxide using this catalyst. Further synthetic detail for all compounds can be found in the Supplementary Materials.

**KRED characterization**

The enantioselectivity of each reporting enzyme was estimated by comparing the initial velocities of the oxidation for each (R) versus (S) product diols that would be obtained from the HKR of interest across a set of diol concentrations. Details can be found in the Supplementary Materials.

During earlier HKR-ISES experiments, we estimated the aqueous layer diol concentration to be in the range of 2.5 to 70 mM under screening conditions. Selectivity parameters appropriate for ISES screening are chosen on the basis of enantioselectivities observed in this concentration range. For KRED 119, a selectivity factor of 6.5 in favor of the (R)-1,2-hexanediol was used for ISES determinations. This corresponds to the selectivity observed in the standard assay cuvette at about 40 mM diol concentration. KRED 107 proved to be the most difficult reporting enzyme to parameterize, owing to its very high preference for the (S) enantiopole of 1,2-hexanediol. In the end, iterative analysis of candidate fitting factors led us to assign a selectivity factor of 59 for this reporting enzyme (corresponds approximately to the selectivity of this reporting enzyme on the lower end of the aforementioned concentration window). Selectivity factors of 8.4 ($v_S/v_R$) for TBADH (48) and 6.5 ($v_S/v_R$) for KRED 23 were used for 1,2-propanediol reporting. The complete set of enantiomeric diol screening data (rate versus concentration) for each of the selected KRED screening enzymes is provided in the Supplementary Materials.

**Procedure of the miniaturized ISES screen**

**Enzyme standardization.**

**Stock solutions:** The following stock solutions were made for enzyme standardization: 40 mM β-NAD$^+$ (nicotinamide adenine dinucleotide phosphate), 130 mM β-NAD$^+$. TBADH (0.016 mg/μl), KRED 23 (0.016 mg/μl), KRED 107 (0.002 mg/μl), and KRED 119 (0.002 mg/μl) in 25 mM sodium phosphate buffer (pH 7.0), 2 M (R)-1,2-propanediol in water. Enzyme units were calculated by measuring the rate of formation of NADPH (reduced form of NADP$^+$) or NADH at 340 nm
Were used in all previous ISES experiments. Here, we describe a gen-

The organic layer in wells A and B had the following composition:

oxide, well A contains TBADH and well B contains KRED 23. For hex-

Every catalyst, a four-well

length. This was indicative of 0.028 U/μl for the TBADH stock solu-

tion for the oxidation of (R)-1,2-propanediol.

Standardization of KRED 23: The assay cuvette contained the fol-

owing components: 7.2 mM (5 M) sodium pyrophosphate buffer (pH 8.8), and 200 mM (9 μl of 2 M stock) (R)-1,2-propanediol.

The reaction was initiated by the addition of the (R)-1,2-propanediol, which typically gave a rate of 0.540 abs/min at 25°C at 340-nm wavelength. This is indicative of 0.00398 U/μl for the KRED 23 stock solution for the oxidation of (R)-1,2-propanediol.

Standardization of KRED 107: The assay cuvette contained the fol-

owing components: 2.2 mM (5 μl of 40 mM stock solution) β-NADP⁺, 5 μl of KRED 107 stock solution, 81 μl of 50 mM sodium pyrophosphate buffer (pH 8.8), and 200 mM (9 μl of 2 M stock) (R)-1,2-hexanediol.

The reaction was initiated by the addition of the (R)-1,2-hexanediol, which typically gave a rate of 0.124 abs/min at 25°C at 340-nm wavelength. This is indicative of 0.00938 U/μl for the KRED 107 stock solution for the oxidation of (R)-1,2-hexanediol.

Step-by-step protocol. It was found to be practical to load the aqueous layers first. Routinely, 90-μl aqueous layers were loaded into individuate wells of 16-well quartz micromulticell either with a micro-
syringe or with a multichannel pipetter. The quartz cell was gently tapped to keep the layers evenly distributed in the solid quartz appa-
ratus, and then cooled on ice. Then, the organic layers were prepared by briefly vortexing the catalyst stock in CHCl₃ with (±)-propylene oxide or (±)-hexene oxide in iced microcentrifuge tubes. The low-volume (20 μl) organic layer was then loaded to each well, most easily by rapidly syringing below the aqueous layer. For an example of the primary spectrophotometric data obtained, see the traces in Fig. 2 of the text (vide supra).

Synthesis of the β-δ-carbafructopyranosyl-1,2-diamine

6-(lodomethyl)-4-methoxy-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-7-ol (21). Methyl-β-δ-mannopyranose (9 g, 46.3 mmol) was suspended in 200 ml of toluene at 80°C, and from that suspension, triphenylphosphine (13.9 g, 53.3 mmol) and imidazole (10.88 g, 160 mmol) were added, stirring continuously for 10 min at that temperature. Then, iodine (17.2 g, 66.7 mmol) was added in portions over 0.5 h. The resulting suspension was vigorously stirred at 80°C for 2 hours, and solution became dark brown. The solution was cooled, the product was extracted into H₂O (3 × 200 ml), and the aqueous layer was washed with 200 ml of toluene and concentrated under vacuum. The crude was purified by column chromatography with pure ethyl acetate (Rᵣ = 0.45 in 50% ethylacetate in acetone), and pure product (11.3 g, 80%) was obtained as white solid. [α]D +64.3 (c 1.1, EtOH); 1H NMR (400 MHz, D₂O) δ 3.37 (dd, J = 10.9, 7.1 Hz, 1H), 3.49 (dd, J = 9.4, 7.1, 2.2 Hz, 1H), 3.57 (app t, J = 9.5, 9.4 Hz, 1H), 3.63 (dd, J = 10.9, 2.2 Hz, 1H), 3.76 (dd, J = 9.5, 3.5 Hz, 1H), 3.93 (dd, J = 3.4, 1.7 Hz, 1H), 4.73 (d, J = 1.4 Hz, 1H); 13C NMR (100 MHz, D₂O) δ 51.1, 55.9, 69.8, 70.05, 70.6, 71.5, 101.1; HRMS (FAB) calcd for C₉H₁₃O₂Li (M + Li)⁺ 310.9961, obsd 310.9961.

6-(lodomethyl)-4-methoxy-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-7-ol (18). To a solution of 21 (7.5 g, 24.6 mmol, 1 equivalent) in 120 ml of acetone at 0°C was added p-toluenesulfonic acid (936 mg, 4.92 mmol, 20%), followed by dropwise addition of dimethoxypropane (9.1 ml, 73.8 mmol, 3 equivalent) via syringe pump. The resulting solution was continuously stirred for 3 hours, upon which time all the starting materials disappeared. The reaction was quenched by Et₃N (1.37 ml, 9.84 mmol, 40%), and organic solvent was evaporated under reduced pressure. The resulting residues were resuspended in 60 ml of water and extracted with EtOAc (3 × 60 ml). The organic layer was washed with brine and dried under Na₂SO₄, filtered and evaporated, and resulted in a pale yellowish liquid as clean product (8.5 g, 95%) without the need for further purification. [α]D +33.4 (c 1.1, CHCl₃); 1H NMR (400 MHz, CDCl₃) δ 1.34 (s, 3H), 1.51 (s, 3H), 3.30 (dd, J = 10.5, 7.1 Hz, 1H), 3.4d (dd, J = 9.2, 7.1, 2.4 Hz, 1H), 3.46 (s, 3H), 3.49 (ddd, J = 9.4, 6.9, 3.4 Hz 1H), 3.58(dd, J = 10.6, 2.5 Hz, 1H), 4.10 to 4.12 (m, 2H), 4.91 (s, 1H); 13C NMR (100 MHz, CDCl₃) δ 6.81, 26.06, 27.97, 55.55, 68.95, 73.06, 75.69, 78.35, 98.33, 109.78; HRMS (FAB) calcd for C₉H₁₃O₂Li (M + Li)⁺ 345.0121, obsd 345.0204.

Karakurichi et al. Sci. Adv. 2015;1:e1500066
14 of 20
10 July 2015
6-(Iodomethyl)-4,7-dimethoxy-2,2-dimethyltetrahydro-3H-[1,3]dioxolo[4,5-c]pyran (22). To a solution of 18 (160 mg, 0.47 mmol) in 3 ml of THF at 0°C, imidazole (0.76 mmol, 20%) and 272 mg of NaH (11.3 mmol, washed with hexane to remove mineral oil) was dissolved in 40 ml of DMF, cooled to 0°C, and 0.47 ml MeI (7.56 mmol) was added, followed by slow addition of MeI (62 μl, 1 mmol). The resulting solution was continuously stirred at 0°C for 3 hours, and the reaction mixture was added 60 ml of EtOAc and 30 ml of saturated NaHCO3 solution. The layers were separated, and the organic layer was washed with water (3 × 60 ml) and then with brine. The resulting organic phase was dried with Na2SO4 and evaporated under reduced pressure to give a colorless oil (480 mg, 76% yield). [α]20D −84.4 (c 0.65, CHCl3); 1H NMR (400 MHz, CDCl3) δ 1.35 (d, J = 4.26 Hz, 3H), 1.40 (d, J = 4.38 Hz, 3H), 3.45 (d, J = 4.5 Hz, 3H), 3.82 (app t, J = 4.4, 5.2 Hz, 1H), 4.47 (m, 1H), 4.73 (m, 1H), 5.99 (dd, J = 10.25, 4.53 Hz, 1H), 6.64 to 6.69 (m, 1H); 13C NMR (100 MHz, CDCl3) δ 26.29, 27.82, 59.17, 71.12, 76.68, 81.07, 110.96, 128.08, 143.32, 194.96; HRMS FAB calcd for C10H17O4 (M + H)+ 205.1052, obsd 205.1046.

(3aR,4S,7aR)-7-Hydroxy-4-methoxy-2,2-dimethyltetrahydrobenzo[d][1,3]dioxolo-5(6H)-one (19). Two-step procedure from 18: To 150 mg of 22 (0.42 mmol) in 5 ml of DMF, 0.7 ml DBU (0.46 mmol) was added at room temperature. The resulting mixture was stirred at 80°C overnight. The reaction mixture was cooled down, and 60 ml of EtOAc and 30 ml of saturated NaHCO3 solution were added. The layers were separated, and the organic layer was washed with water (3 × 60 ml) and then with brine. The resulting organic phase was dried with Na2SO4 and evaporated under reduced pressure to give the product 60% yield: [α]19D +49.1 (c 1.1, CHCl3); 1H NMR (400 MHz, CDCl3) δ 1.33 (s, 3H), 1.48 (s, 3H), 3.46 (d, J = 0.7 Hz, 3H), 3.49 (d, J = 0.7 Hz, 3H), 3.81 (dd, J = 0.8, 4.6 Hz, 1H), 4.16 (d, J = 7.2, 3.8 Hz, 1H), 4.26 (dd, J = 7.1, 6.0 Hz, 1H), 4.43 (d, J = 0.8 Hz, 1H), 4.64 (d, J = 0.8 Hz, 1H), 4.86 (s, 1H); 13C NMR (100 MHz, CDCl3) δ 24.74, 26.89, 56.25, 57.91, 74.58, 75.86, 77.97, 93.22, 100.23, 109.80, 151.94; HRMS (FAB) calcd for C11H18O3Na (M + Na)+ 381.0175, obsd 381.0164.

To a solution of 19 (180 mg, 0.47 mmol) in 2:2:1 volume ratio of acetone, 2.27 (m, 1H), 3.30 (d, J = 6.8 Hz, 3H); 13C NMR (100 MHz, CDCl3) δ 26.29, 27.82, 59.17, 71.12, 76.68, 81.07, 110.96, 128.08, 143.32, 194.96; HRMS FAB calcd for C10H17O4 (M + H)+ 205.1052, obsd 205.1046.

(3aR,4S,7aR)-7-Hydroxy-4-methoxy-2,2-dimethyltetrahydrobenzo[d][1,3]dioxolo-5(6H)-one (12). To a solution of 23 (200 mg, 1.0 mmol) in EtOAc (10 ml) was added 20% Pd(OH)2/C (20 wt%, 40 mg). The resulting mixture was hydrogenated at 20 psi for 1 hour, and the catalyst was then filtered off a pad of Celite and washed with EtOAc. The filtrate was evaporated to give the ketone 12 as a colorless oil (202 mg, 100% yield). [α]19D −69.6 (c 1.1, CHCl3); 1H NMR (400 MHz, CDCl3) δ 1.33 (s, 3H), 1.43 (s, 3H), 2.09 to 2.14 (m, 1H), 2.21 to 2.30 (m, 2H), 2.46 to 2.55 (m, 1H), 3.41(s, 3H); 13C NMR (100 MHz, CDCl3) δ 26.29, 27.82, 59.17, 71.12, 76.68, 81.07, 110.96, 128.08, 143.32, 194.96; HRMS (CL) calcd for C10H17O4 (M + H)+ 199.1334, obsd 199.1338.

(3aR,4S,7aR)-7-Azido-5-(azidomethyl)-4-methoxy-2,2-dimethyltetrahydrobenzo[d][1,3]dioxole (15). A dry flask was charged with Na2S (442 mg, 6.8 mmol, 5 equivalent), Mn (OAc)2·2H2O (1.1 g, 4.1 mmol, 3 equivalent), and CH3CN (7 ml) and nitrogen gas were bubbled through the mixture. Then, the reaction mixture was cooled down to −20°C, and 13 (270 mg, 1.36 mmol, 1.41 (s, 3H), 2.42 (dd, J = 18.3, 6.2 Hz, 1H), 2.75 (dd, J = 18.3, 5.0 Hz, 1H), 3.45 (s, 3H), 3.56 to 3.63 (m, 1H), 3.70 (d, J = 5.2 Hz, 1H), 4.27 (app t, J = 6.9, 5.4 Hz, 1H), 4.39 (ddd, J = 7.0, 5.3 Hz, 1H), 5.51 to 5.55 (m, 2H); 13C NMR (100 MHz, CDCl3) δ 24.26, 26.73, 41.86, 59.00, 67.50, 76.71, 77.04, 83.89, 109.77, 204.70; HRMS FAB calcd for C10H17O3N2 (M + H)+ 217.1076, obsd 217.1073.
1H), 4.28 (br s, 1H), 7.48 (d, J = 7.5, 5.4 Hz, 1H), 1.92 (m, 2H), 2.25 (d, J = 7.3 Hz, 1H), 3.53 (s, 3H), 3.55 (d, J = 1.2 Hz, 1H), 3.62 (d, J = 1.2 Hz, 1H), 4.13 (dd, J = 7.2, 5.4 Hz, 1H), 4.25 (m, 1H); 13C NMR (100 MHz, CDCl3) δ 21.8, 26.2, 26.3, 28.4, 55.3, 60.2, 65.8, 73.9, 79.7, 82.5, 108.5; HRMS (FAB) calcd for C13H19N6O3 (M + H)+ 283.1519, obsd 283.1530. Fraction 2 yielded 55.3, 60.2, 65.8, 73.9, 79.7, 82.5, 108.5; HRMS (FAB) calcd for C13H19N6O3 (M + H)+ 283.1519, obsd 283.1530. Fraction 2 yielded the α-diazide as a clear oil (221 mg, 58%); [α]19D = −61.3 (c 1.0, CHCl3); 1H NMR (400 MHz, CDCl3) δ 1.30 (br s, 3H), 1.34 (s, 3H), 1.48 (s, 3H), 1.54 (dt, J = 13.6, 4.6 Hz, 2H), 1.57 (d, J = 1.2 Hz, 1H), 2.04 (tt, J = 13.3, 4.7 Hz, 1H), 2.6 (d, J = 12.7 Hz, 1H), 2.63 (d, J = 12.7 Hz, 1H), 3.08 (d, J = 12.7 Hz, 1H), 3.51 (s, 3H), 4.16 (app t, J = 6.8 Hz, 1H), 4.26 (m, 1H); 13C NMR (100 MHz, CDCl3) δ 21.9, 26.4, 27.7, 28.4, 51.7, 56.0, 60.0, 74.4, 80.2, 84.1, 107.7; HRMS (FAB) calcd for C13H19N6O3 (M + H)+ 231.1709, obsd 231.1700.

α-Diazide (16). α-Diazide 14 (168 mg, 0.6 mmol) was dissolved in EtOH (5 ml), and 20 mg of 10% Pd/C was added. The resulting suspension was hydrogenated at 52 psi for 12 hours, resulting total reduction to give α-diazide 17 (135 mg, 100%). [α]19D = −74.5 (c 0.35, CHCl3); 1H NMR (400 MHz, CDCl3) δ 1.30 (br s, 3 H), 1.37 to 1.47 (m, 4 H), 1.48 (s, 3 H), 1.54 (dt, J = 13.6, 4 Hz, 1H), 1.60 to 1.70 (m, 1 H), 1.92 (qt, J = 4, 15.6 Hz, 1H), 2.42 (d, J = 13.2 Hz, 1H), 2.67 (d, J = 13.2 Hz, 1H), 3.14 (d, J = 7.2 Hz, 1H), 3.51 (s, 3 H), 3.96 (dd, J = 5.6, 7.6 Hz, 1H), 4.20 to 4.24 (m, 1 H); HRMS (ESI) calcd for C13H19N6O3 (M + H)+ 231.1709, obsd 231.1706.

General procedure for HKR reactions using the Co(II)-17c catalyst

The Co(II)-17c complex was taken up in CH2Cl2 (2 ml) and stirred with 3,5-dinitrobenzoic acid (1 equivalent) in open air. The oxidation could be followed by TLC (formation of a greenish-brown spot of lower Rf (Co-III) complex) from the visibly red, higher Rf spot characteristic of the Co(II)-17c salen). When TLC indicated the completion of the reaction, the solvent was evaporated, and the Co(III)-17c-3,5-DNB complex was further dried in vacuo. The Co(III)-17c catalyst was used directly for HKR experiments under ISES (biphasic) conditions or under typical neat or one-phase flask conditions.

Two different general procedures were adapted on the basis of the ease of handling of the epoxides (see the Supplementary Materials for a complete set of examples and characterization data). Representative examples are provided hereunder.

**Procedure A: 3-Phenoxy-1,2-epoxypropane (O-phenylglycidol)—HCl**

Catalyst Co(III)-17c-3,5-DNB (5 mg, 0.005 mmol, 0.5 mol % loading) was mixed with 3-phenoxyl-1,2-epoxypropane (150 mg, 1 mmol) and 300 μl of CH2Cl2. The mixture was cooled to 0°C, and the reaction was initiated by adding 9 μl (0.5 equivalent) of water, and stirring was continued for 20 hours at room temperature. After the reaction, silica gel column chromatography provided the unresolved 3-phenoxyl-1,2-epoxypropane (71 mg, 47%, eluting with 50% ether/pentane) and 3-phenoxyl-1,2-propanediol (O-phenylglycidol; 77 mg, 46%, further eluting with 10% methanol/ether).

**3-Phenoxy-1,2-epoxypropane.** 1H NMR (400 MHz, CDCl3) δ 2.73 to 2.79 (m, 1H), 2.89 to 2.91 (t, J = 4.8 Hz, 1H), 3.33 to 3.37 (m, 1H), 3.94 to 4.04 (m, 1H), 4.19 to 4.25 (m, 1H), 6.88 to 7.00 (m, 3H), 7.23 to 7.33 (m, 2H); [α]19D = +22.3 (for 96% ee of S); [α]19D = +23.0, calcd (c = 1.4, CHCl3). The enantiomers of this epoxide were resolved via HPLC (Chiralcel OD column). For the epoxide (hexanes/i-PrOH 87:13, flow rate 1 ml/min), minor isomer, tR = 8.2 min (R) and major isomer, tR = 12.4 min (S).

**3-Phenoxy-1,2-propanediol.** 1H NMR (400 MHz, CDCl3) δ 2.54 (br s, 1H), 3.03 (br s, 1H), 3.71 to 3.84 (m, 2H), 4.01 to 4.11 (m, 3H), 6.88 to 6.98 (m, 3H), 7.23 to 7.30 (m, 2H); [α]19D = −9.1 (for 92% ee

Karukurichi et al. Sci. Adv. 2015;1:e1500066 10 July 2015
starting from epoxy-3-phenylpropane (315 mg, 2.3 mmol), treatment with selenide, leading to direct epoxide ring opening with phenyl selenide anion. After workup and SiO₂ column chromatography, both the seleno-alcohol (329 mg, 48%, 0→50% ether in pentane) and 3-phenyl-1,2-propanediol (175 mg, 49%, 50→0% ether in EtOAc) were obtained.

1-(Phenylseleno)-3-phenyl-2-propanol. 1H NMR (400 MHz, CDCl₃) δ 2.36 (d, J = 3.6 Hz, 1H), 2.86 to 2.88 (m, 2H), 2.91 to 2.96 (m, 1H), 3.10 to 3.14 (m, 1H), 3.92 to 3.96 (m, 1H), 4.07 to 4.09 (m, 1H), 4.24 (t, J = 2.3 Hz, 1H), 4.32 (t, J = 2.3 Hz, 1H), 4.85 (d, J = 13 Hz, 1H), 5.02 (s, 1H), 5.53 (s, 1H), 6.86 (d, J = 8 Hz, 2H), 7.34 (d, J = 8 Hz, 2H), 7.48 to 7.50 (m, 2H), 7.57 to 7.60 (m, 1H).

The enantiopurity of the diol was also resolved using a Chiralcel OD column. For the diol (hexanes/EtOH 95:5, flow rate 1 ml/min), minor isomer, tₘᵣₐᵣₑᵦ = 13.2 min (R) and minor isomer, tₘᵣᵦᵦᵦ = 20.4 min (S).
30. C. Eber, C. A. Mülller, C. Markert, A. Pfälz, Determining the enantioselectivity of chiral catalysts by mass spectrometric screening of their racemic forms. J. Am. Chem. Soc. 133, 4710–4713 (2011).
31. C. A. Mueller, A. Pfälz, Mass spectrometric screening of chiral catalysts by monitoring the back reaction of quasi-enantionic products: Palladium-catalyzed allylic substitution. Angew. Chem. Int. Ed. 47, 3363–3366 (2008).
32. F. Bächle, J. Duschmalé, C. Eber, A. Pfälz, H. Wennemers, Organocatalytic asymmetric conjugate addition of aldehydes to nitroalkenes: Identification of catalytic intermediates and the stereoselectivity-determining step by ES-MS. Angew. Chem. Int. Ed. 52, 12619–12623 (2013).
33. C. Mayer, D. Hilvert, A genetically encodable ligand for transfer hydrogenation. Eur. J. Org. Chem. 2013, 3427–3430 (2013).
34. S. J. Zuend, M. P. Coughlin, M. P. Lalonde, E. N. Jacobsen, Scaleable catalytic asymmetric strecker synthesies of unnatural α-amino acids. Nature 461, 968–970 (2009).
35. M. M. Müller, M. A. Windsor, W. C. Pomerantz, S. H. Gellman, D. Hilvert, A rationally designed aldolase foldamer. Angew. Chem. Int. Ed. 48, 922–925 (2009).
36. N. Maillard, A. Clouet, T. Darbe, J.-L. Reymond, Combinatorial libraries of peptide dendrimers: Design, synthesis, on-bead high-throughput screening, bead decoding and characterization. Nat. Protoc. 4, 132–142 (2009).
37. Y. Zhao, J. Rodrigo, A. H. Hoveyda, M. L. Snapper, Enantioselective silyl protection of alcohols catalyzed by an amino-acid-based small molecule. Nature 443, 67–70 (2006).
38. G. Xu, S. R. Gilbertson, Development of building blocks for the synthesis of N-heterocyclic carbene ligands. Org. Lett. 7, 4605–4608 (2005).
39. A. Berkesse, F. Cleemann, S. Mukherjee, Kinetic resolution of oxazinones: An organocatalytic approach to enantioselectively pure β-amino acids. Angew. Chem. Int. Ed. 44, 7466–7469 (2005).
40. M. S. Sigman, E. N. Jacobsen, Schiff base catalysts for the asymmetric Strecker reaction of alcohols catalyzed by an amino-acid-based small molecule. Nature 443, 67–70 (2006).
41. A. Buitrago Santanilla, E. L. Regalado, T. Pereira, M. Shevlin, K. Bateman, L.-C. Campeau, J. Schneeweis, S. Berritt, Z.-C. Shi, P. Nantermet, Y. Liu, R. Helmy, C. J. Welch, P. Vachal, I. W. Davies, T. Cernak, S. D. Dreher, Nanomole-scale high-throughput chemistry for the synthesis of complex molecules. Science 347, 49–53 (2013).
42. K. T. Barrett, A. J. Metrano, P. R. Rablen, S. J. Miller, Spontaneous transfer of chirality in an enantioselective catalytic reaction. Angew. Chem. Int. Ed. 41, 124–127 (2002).
43. J. Quinton, L. Charruault, M. C. Nevers, H. Volland, J. P. Dognon, C. Créminon, F. Taran, Communications: High-throughput screening of enantioselective catalysts by immunoassay. Angew. Chem. Int. Ed. 41, 124–127 (2002).
44. P. Abato, C. T. Seto, EMDee: An enzymatic method for determining enantiomeric excess. J. Am. Chem. Soc. 123, 9206–9207 (2001).
45. D. B. Berkowitz, G. Maiti, Following an ISES lead: The first examples of asymmetric Ni(0)-mediated asymmetric intramolecular allylic amination. Org. Lett. 9, 7009–7012 (2007).
46. D. B. Guthrie, D. P. Curran, Asymmetric radical and anionic cyclizations of axially chiral carbamates. Org. Lett. 11, 249–251 (2008).
47. P. J. Pye, K. Rossen, R. A. Reamer, N. N. Tsou, R. P. Volante, P. J. Reider, A new planar chiral bisphosphine ligand for asymmetric catalysis: Highly enantioselective hydrogenations under mild conditions. J. Am. Chem. Soc. 119, 6207–6208 (1997).
48. A. Togni, C. Breutel, A. Schnyder, F. Spindler, H. Landert, A. Tijani, A novel easily accessible chiral ferrocenylidiphosphine for highly enantioselective hydrogenation, alkylation, and hydroboration reactions. J. Am. Chem. Soc. 116, 4062–4066 (1994).
49. G. C. Fu, Applications of planar-chiral heterocycles as ligands in asymmetric catalysis. Acc. Chem. Res. 39, 853–860 (2006).
50. G. C. Fu, Enantioselective nucleophilic catalysis with “planar-chiral” heterocycles. Acc. Chem. Res. 33, 412–420 (2000).
51. N. Takenaka, J. Chen, B. Captain, R. S. Sarangthem, A. Chandrakumar, Helical chiral 2-aminoptyridinium ions: A new class of hydrogen bond donor catalysts. J. Am. Chem. Soc. 132, 4536–4537 (2010).
52. M. J. Narcis, N. Takenaka, Helical-chiral small molecules in asymmetric catalysis. Eur. J. Org. Chem. 2014, 31–34 (2014).
53. T. Inoue, D. Sato, K. Komura, S. Itsuno, Enantioselectically pure 2-piperazinemethanols as novel chiral ligands of oxazaborolidine catalysts in enantioselective borane reductions. Tetrahedron Lett. 40, 5379–5382 (1999).
54. E. J. Corey, J. C. Helal, Reduction of carbonyl compounds with chiral oxazaborolidine catalysts: A new paradigm for enantioselective catalysis and a powerful new synthetic method. Angew. Chem. Int. Ed. 37, 1986–1987 (1998).
55. T. P. Pathak, S. J. Miller, Chemical tailoring of teicoplanin with site-selective reactions. J. Am. Chem. Soc. 135, 8415–8422 (2013).
56. A. Hamberg, S. Lundgren, M. Penhoat, C. Moborg, X. Hult, High-throughput enzymatic method for enantiomeric excess determination of O-acetylated cyanohydrins. J. Am. Chem. Soc. 128, 2234–2235 (2006).
57. H. Matsuura, N. Yamamoto, M. M. Meijer, P. Wirsching, R. A. Lerner, M. Matsuoka, K. D. Janda, Chiral sensing using a blue fluorescent antibody. Mol. Biosyst. 1, 303–306 (2005).
58. C. M. Sprout, C. T. Seto, Using enzyme inhibition as a high through method to measure the enantiomeric excess of a chiral sulfoxide. Org. Lett. 7, 5099–5102 (2005).
59. F. Taran, C. Gauget, B. Mohar, S. Meunier, A. Valles, P. Yves Renard, C. Créminon, J. Grassi, A. Wagner, C. Mioskowski, Communications: High-throughput screening of enantioselective catalysts by immunoassay. Angew. Chem. Int. Ed. 41, 124–127 (2002).
60. J. Quinton, L. Charruault, M. C. Nevers, H. Volland, J. P. Dognon, C. Créminon, F. Taran, Toward the limits of sandwich immunoassay of very low molecular weight alkaloids. Anal. Chem. 82, 2536–2540 (2010).
61. E. W. Debler, G. F. Kaufmann, M. M. Meijer, A. Heine, J. M. Gee, G. Pljevaljic, A. J. Di Bilbo, P. G. Schultz, D. P. Millar, K. D. Janda, I. A. Wilson, H. B. Gray, R. A. Lerner, Deeply inverted electron-hole recombination in a luminescent antibody-stibinene complex. Science 319, 1232–1235 (2008).
organocatalyzed stereoselective ring opening of cyclopropanes. J. Am. Chem. Soc. 129, 10886–10894 (2007).

84. K. K. Farnanás-Mastral, S. V. Ley, Asymmetric organocatalytic conjugate addition of malonates to enones using a proline tetrazole catalyst. Chem. Commun., 66–68 (2006).

85. D. D. Steiner, N. Mase, C. F. Barbas III, Direct asymmetric α-fluorination of aldehydes. Angew. Chem. Int. Ed. 44, 3706–3710 (2005).

86. D. Ender, C. Grondal, M. Vrettou, G. Raabe, Asymmetric synthesis of selectively protected amino sugars and derivatives by a direct organo-catalytic Mannich reaction. Angew. Chem. Int. Ed. 44, 4079–4083 (2005).

87. S. S. Brown, M. R. Brochu, C. J. Sinz, D. W. C. MacMillan, The direct and enantioselective organocatalytic α-oxidation of aldehydes. J. Am. Chem. Soc. 125, 10808–10809 (2003).

88. K. B. Sharpless, Searching for new reactivity (Nobel lecture). Angew. Chem. Int. Ed. 41, 2024–2032 (2002).

89. M. J. O’Donnell, The enantioselective synthesis of α-amino acids by phase-transfer catalysis with achiral Schiff base esters. Acc. Chem. Res. 37, 506–517 (2004).

90. B. Lygo, B. I. Andrews, Asymmetric phase-transfer catalysis utilizing chiral quaternary amine-catalysts with achiral auxiliaries.

91. Y.-H. Lam, K. N. Houk, How cinchona alkaloid-derived primary amines control asymmetric epoxidation of olefins with achiral Schiff base esters.

92. J. P. Springer, J. Hirshfield, Methods for drug discovery: Development of potent, selective, orally effective cholecystokinin antagonists.

93. D. F. Veber, P. S. Anderson, R. S. Chang, V. J. Lotti, D. J. Cerino, T. B. Chen, P. J. Kling, K. A. Kunkel, Angew. Chem. Int. Ed.

94. M. J. O’Donnell, The enantioselective synthesis of α-amino acids by phase-transfer catalysis with achiral Schiff base esters. Acc. Chem. Res. 37, 506–517 (2004).

95. B. E. Evans, K. E. Rittle, M. G. Bock, R. M. DiPardo, R. M. Freidinger, W. L. Whitter, G. F. Lundell, B. Lygo, B. I. Andrews, Asymmetric phase-transfer catalysis utilizing chiral quaternary amine-catalysts with achiral auxiliaries.

96. Y.-H. Lam, K. N. Houk, How cinchona alkaloid-derived primary amines control asymmetric epoxidation of olefins with achiral Schiff base esters.

97. J. P. Springer, J. Hirshfield, Methods for drug discovery: Development of potent, selective, orally effective cholecystokinin antagonists.

98. J. Am. Chem. Soc., 1922

99. J. Am. Chem. Soc., 8136–8147 (2012).

100. J. Am. Chem. Soc., 748 (1990).

101. J. Am. Chem. Soc., 9556–9559 (2014).

102. J. Am. Chem. Soc., 2756–2768 (1992).

103. J. Am. Chem. Soc., 7637 (2012).

104. J. Org. Chem., 11224–11235 (1997).

105. J. Am. Chem. Soc., 748 (1990).

106. J. Org. Chem., 1317, 7334 (2009).

107. J. Am. Chem. Soc., 15595–15608 (2013).

108. J. Org. Chem., 125, 14272–14273 (2003).

109. J. Am. Chem. Soc., 124, 4544–4545 (2002).

110. J. Org. Chem., 126, 1360–1362 (2004).

111. J. Am. Chem. Soc., 3673–3684 (2004).

112. J. Org. Chem., 748 (1990).

113. J. Am. Chem. Soc., 125, 2024–2032 (2003).

114. J. Am. Chem. Soc., 11215 (1997).

115. J. Am. Chem. Soc., 517 (2004).

116. J. Am. Chem. Soc., 115, 1837–1838 (2013).

117. J. Am. Chem. Soc., 116, 12257–12260 (2014).

118. J. Am. Chem. Soc., 131, 1529–1534 (2009).

119. J. Am. Chem. Soc., 124, 4544–4545 (2002).

120. J. Org. Chem., 126, 1360–1362 (2004).

121. J. Am. Chem. Soc., 128, 5968–5976 (2000).

122. J. Am. Chem. Soc., 129, 11680–11681 (2007).

123. J. Am. Chem. Soc., 125, 14272–14273 (2003).

124. J. Am. Chem. Soc., 125, 14272–14273 (2003).

125. J. Am. Chem. Soc., 125, 14272–14273 (2003).

126. J. Org. Chem., 126, 1360–1362 (2004).
135. M. Kapur, A. Khartulyari, M. E. Maier, Stereoselective synthesis of protected 1,2-diols and 1,2,3-triols by a tandem hydroboration–coupling sequence. Org. Lett. 8, 1629–1632 (2006).

136. D. B. Ramachary, C. F. Barbas III, Direct amino acid-catalyzed asymmetric desymmetrization of meso-compounds: Tandem aminooxidation/O–N bond heterolysis reactions. Org. Lett. 7, 1577–1580 (2005).

137. I. Ibrahim, G.-L. Zhao, H. Sundén, A. Córdova, A route to 1,2-diols by enantioselective organocatalytic α-oxidation with molecular oxygen. Tetrahedron Lett. 47, 4659–4663 (2006).

Acknowledgments: We thank D. R. Powell (University of Oklahoma) for x-ray crystal structure determination. This research was facilitated by the IR/D (Individual Research and Development) program associated with D.B.B.’s appointment at the NSF. Funding: The authors thank the NSF (DMR-1214019) for support of this research and the NIH (SIG-1-510-RR-06307) and NSF (CHE-0091975, MRI-0079750) for NMR instrumentation support and the NIH (RR016544) for facilities renovation. Author contributions: K.R.K., X.F., R.A.S., S.B., W.S., S.D., and S.K.R. performed the experiments. This team, along with D.B.B., designed the experiments and interpreted the results. D.B.B., X.F., and R.A.S. wrote the manuscript. Competing interests: The authors declare that they have no competing interests. Data and materials availability: Coordinates for crystal structures of the following Co-salen complexes—Co(II)-6a, Co(II)-6c, and Co(III)-17c—will be deposited in the Cambridge Crystallographic Database.

Submitted 18 January 2015
Accepted 11 May 2015
Published 10 July 2015
10.1126/sciadv.1500066

Citation: K. R. Karukurichi, X. Fei, R. A. Swyka, S. Broussy, W. Shen, S. Dey, S. K. Roy, D. B. Berkowitz, Mini-ISES identifies promising (Carba)fructopyranose-based salens for asymmetric catalysis: Tuning ligand shape via the anomeric effect. Sci. Adv. 1, e1500066 (2015).