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Remote Desymmetrization at Near-Nanometer Group Separation Catalyzed by a Miniaturized Enzyme Mimic

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Among the most challenging problems for enantioselective catalysis is that of remote asymmetric induction. For example, remote desymmetrizations of *meso* compounds require bond formation (or cleavage) at a site within a substrate that is distal from both a pro-stereogenic structural element and the competing enantiotopic functional group. Problems of this type are often handled through an intramolecular relay of chiral information through the substrate.[1,2] When *catalytic* bond formation is required, across a truly substantial distance, enzymes are often employed since their macromolecular architecture presents the potential for enantioselective recognition and functionalization over a substantial vector.[3,4] Selective C−H bond oxidations distal from functionality and stereogenic centers provide some of the most dramatic examples.[5,6] When small molecule catalysts are applied to desymmetrizations, oftentimes even striking cases involve relatively short distances between enantiotopic groups.[7]

During recent studies, it was of interest to obtain compounds related to **1**, a diphenyl methane derivative with two distinct para-oxygenated substituents, in optically pure form (Figure 1a). To obtain enantioenriched **1**, a desymmetrization of meso precursor **2** was envisioned. The unprecedented desymmetrization of bis(phenol) **2** presents a particularly challenging case since the desired site of functionalization is >5.7 Å from the prochiral stereogenic center of the substrate (Figure 1b); nearly a full nanometer spans the enantiotopic phenol oxygen atoms. We report herein a successful solution to this problem, using a simple, peptide-based catalyst for this unusual desymmetrization.

The initial approach to preparing **1** in a nonracemic fashion utilized lipase-catalyzed hydrolysis of bis(acetate) **3**. As shown in Scheme 1, the process requires the chemical synthesis of bis(acetate) **3** in a separate step as a prelude to enantioselective hydrolysis. Then, after extensive screening of over 450 enzymes for the enantioselective hydrolysis, we found that monoacetate **4** could be obtained with reasonable enantiomeric excess using several lipase catalysts. However, this approach has two drawbacks for practical implementation. First, high levels of conversion of the diacetate to **4** are difficult to achieve owing to the substrate's low solubility in the aqueous buffered media that the enzymatic reaction employs. Additionally, in order to obtain **4** in high ee, a large amount of material must be reverted to bisphenol **2**. The need for overhydrolysis of **4** to obtain high optical purity is a result of unremarkable enantiotopic group discrimination displayed by the enzyme. (i.e., **4** is produced with only 50−55% ee at low conversion). Indeed, monoacetate **4** is only obtained in high enantiomeric excess because of a subsequent kinetic resolution of **4** that serves to "correct" the desymmetrization through consumption of the minor enantiomer of **4**. Overconversion of **4** to starting material **2** greatly reduces the yield of the process.[8]

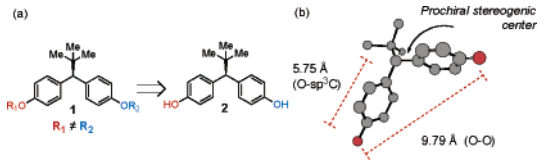
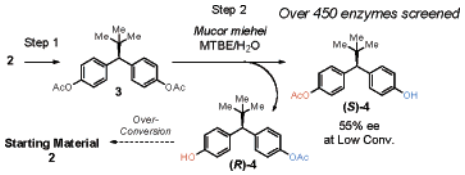


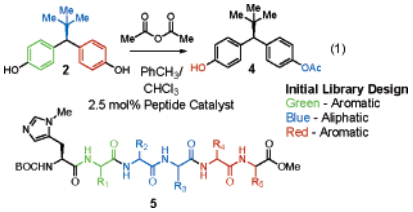
Figure 1. (a) Compound **1** and a potential meso precursor **2**; (b) substrate metrics for bis(phenol) **2**, defining a 5.7 Å distance between desired site of functionalization and prochiral stereogenic center (MM calculation). The span for the enantiotopic hydroxyl groups is 9.79 Å.

Scheme 1



While an aggressive pursuit of additional conditions might ultimately lead to an effective enzymatic solution,[9] the inherently low enantiotopic group recognition exhibited by the enzymes, as well as problems with low volumetric throughput,[10] stimulated the pursuit of an alternative strategy. In particular, we were intrigued by the possibility of employing peptide-based catalysts that are effective for a range of enantioselective group-transfer reactions.[11]

The initial objective became the identification of a suitable peptide catalyst for the direct desymmetrization of **2** to give **4** in a single step (eq 1). The study began with an examination of libraries of hexameric peptides terminated in a modified histidine residue (e.g., **5**), competent for catalytic transfer of a single acetate moiety to afford **4**. Residues were then introduced in a fashion that attempted to mirror the alternating aromatic/aliphatic/aromatic nature of substrate **2**.



Although the validation of catalyst−substrate interactions predicated upon aliphatic or aromatic group complementarity remains unproven, five rounds of library synthesis culminated in the identification of lead catalyst **6** (Figure 2a,b). The reaction catalyzed by peptide **6** results in 78% conversion to monoacetate **4** with a 90:10 enantiomeric ratio (80% ee). Notably, although a small amount of bis(acetate) **3** is also formed, independent control experiments also indicated that *no secondary kinetic resolution occurs* to improve product ee as monoacetate **4** reacts further. Thus,

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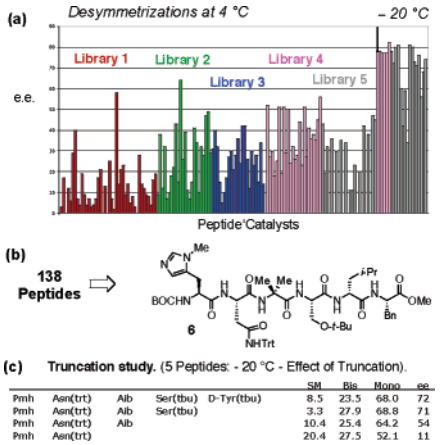
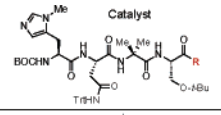


Figure 2. (a) Histogram of complete set of peptide catalysts that were screened (see SI for peptide sequences); (b) structure of catalyst **6** that emerged from the fifth-generation library; (c) sample of truncated peptides that were screened to probe catalyst SAR.

Table 1. Optimization of Tetramer C-Terminal Functionality[a]



Entry	Catalyst	Ee[b] (Conv. to 4)[c]
1	**7**, R = OMe	62 (65)
2	**8**, R = Bn-NH	61 (68)
3	**9**, R = (*R*)-α(Me)Bn-NH	60 (70)
4	**10**, R = (*S*)-α(Me)Bn-NH	68 (69)
5	**11**, R = (*R*)-α(Me)-2-Np-NH	76 (67)
6	**12**, R = (*S*)-α(Me)-2-Np-NH	71 (79)
7	**13**, R = *i*Pr-NH	74 (58)
8	**14**, R = 	89 (84)
9	**15**, R = 	82 (64)

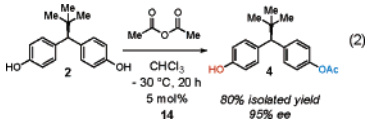
[a] All reactions were run at −30 °C in the presence of 2.5 mol % catalyst. Reactions were run 0.1 M in $CHCl_3$ with trace THF to assist in solublization of **2**. [b] All enantiomeric excesses were measured using chiral HPLC. The major enantiomer was found to be (*R*). [c] Isolated yields are defined in the optimized reaction procedure in the Supporting Information.

the selectivity that is observed is *dominated by enantiotopic group discrimination*, rather than through secondary kinetic resolution. The fact that peptide **6** affords substantial selectivity without a secondary kinetic resolution stands in sharp contrast to the enzymatic catalysis, which only delivers comparable enantioselectivity via consumption of the desired product, reducing overall yield.

Hexapeptide **6** is orders of magnitude less complex than *Mucor miehei* in terms of molecular weight. Even so, we performed a study with truncated versions of peptide **6** to determine the minimal nature of the peptide catalyst (Figure 2c). Both a pentamer and a tetramer lead to optically enriched **4**, each with 71−72% ee (67−68% conversion to **4**). Even a tripeptide gave results comparable to the best of the enzymes that were screened.

The truncation study stimulated examination of a focused library of tetramers (Table 1). Notably, methyl ester **7** and benzyl amide derivative **8** afford essentially the same level of enantioselectivity for the desymmetrization (62% ee and 61% ee respectively; entries 1 and 2). The introduction of a stereogenic center in the amide moiety leads to a slight change in selectivity. For example, (*R*)-α-Me-benzylamide **9** results in **4** with 60% ee; (*S*)-α-Me-benzylamide **10** delivers **4** with 68% ee (entries 3 and 4). The trend is reversed with the corresponding naphthalene derivatives. Whereas the (*R*)-derivative **11** gives **4** with 76% ee, the (*S*)-derivative **12** now yields **4** with a slightly lower 71% ee (entries 5 and 6). A simple isopropyl amide derivate (**13**) provides comparable ee (74%, entry 7). A significant enantioselectivity boost is observed with catalyst **14**, functionalized with an (*S*,*S*)-*N*-tosyl diamine amide tail. In this case, monoacetate **4** is isolated with 89% ee, at 84% conversion (entry 8). The diastereomeric catalyst **15** is somewhat less selective, delivering **4** with 82% ee (entry 9).

At this stage, we optimized reaction conditions with peptide **14** as the lead catalyst. Variations in solvent composition and substrate concentration culminated in a process shown in eq 2. When substrate **2** is dissolved in chloroform, exposure to Ac_2O (2.1 equiv) and 5 mol % **14** delivers **4** with 95% ee in 80% isolated yield after silica gel chromatography.



The exploration of the fundamental mechanism associated with this remote asymmetric induction is complex. On the one hand, these catalysts present substantial conformational mobility that is often uncharacteristic of either small molecule asymmetric catalysts, or enzymes.[12] On the other, a striking effect occurs when substrate **2** is exposed to catalyst **14** in solution (Figure 3). In the absence of catalyst, bis(phenol) **2** presents in the ^{1}H NMR spectrum as a symmetrical meso compound, with only two unique ^{1}H resonances associated with the aromatic region. As peptide **14** is introduced into the solution, the proton resonances for substrate **2** lose their degeneracy. Thus, it may be that unobvious molecular recognition interactions are at the heart of the desymmetrization. Whether these effects are manifest through differential stabilization of competing ground states or transition states is a persistent question throughout the various fields of asymmetric catalysis. The detailed study of this extreme case of remote asymmetric induction is ongoing in our laboratories.

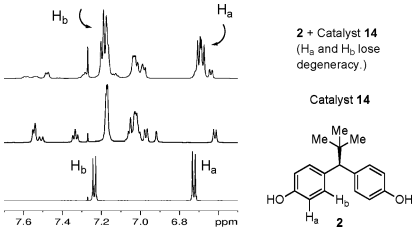


Figure 3. ^{1}H NMR spectra illustrating the association of catalyst **14** with **2** that breaks the degeneracy of the phenol moieites.

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Supporting Information Available: Experimental procedures and data. This material is available free of charge via the Internet at http://pubs.acs.org.

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