

# Enantioselective sulfonylation reactions mediated by a tetrapeptide catalyst

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**Nature excels at performing selective modifications of complex polyfunctional molecules by tailoring enzymes, but synthetic chemistry has lagged behind in this regard. In prior work, we have applied a biomimetic approach to this problem, developing small peptides to achieve various group transfer reactions on polyol substrates with high enantio- or regioselectivity. The use of sulfonates as synthetic building blocks and the scarcity of direct, selective methods for their preparation prompted our investigation into this area. In this article we report the development of a  $\pi$ -methyl histidine-based tetrameric peptide that effects the desymmetrization of *meso*-1,3-diols through enantioselective mono(sulfonylation). The catalyst exhibits structural similarities to another catalyst found to be effective in orthogonal group transfers, but results in modification of the enantiotopic alcohol. The practical and mechanistic implications of this discovery may extend beyond synthetic considerations and provide analogies to the diverse roles of histidine in enzyme active sites.**

Selective derivatization of single hydroxyl groups within frameworks containing several alcohols is a long-standing challenge in synthetic chemistry<sup>1</sup>. Work in our group has examined a variety of asymmetric group transfer reactions of alcohols (for example, acylation<sup>2,3</sup>, phosphorylation<sup>4</sup>, sulfonylation<sup>5</sup>, thiocarbonylation<sup>6</sup>) predicated on putative nucleophilic catalysis by histidine-containing peptides (Fig. 1). This concept has proven surprisingly general, furnishing additional powerful new methods and

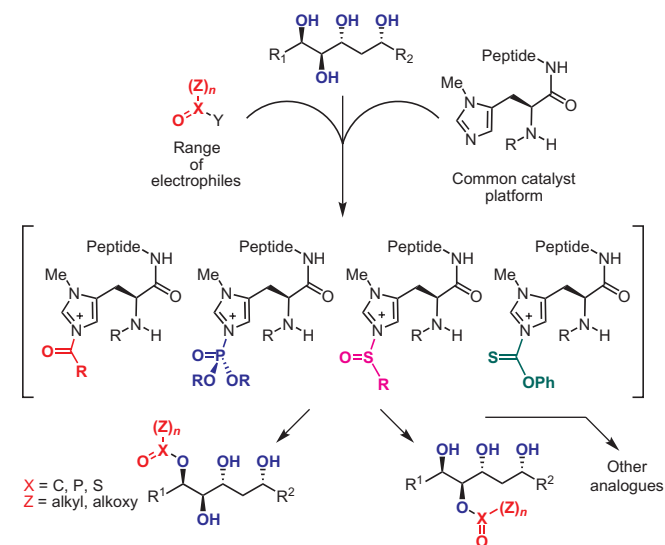
catalysts<sup>7,8</sup>. It is at the heart of one approach to the systematic modification of complex polyol structures, such as those found in complex antibiotics like erythromycin A. With this strategy, a unique type of catalyst library can be used, along with a range of electrophiles, to produce a set of natural product-derived analogues for biological evaluation<sup>9,10</sup>.

In order to expand the repertoire of analogues that can be accessed and to increase the general utility of these group transfer processes in organic synthesis, the addition of novel electrophiles is a consistent goal of this work. One underdeveloped subfield in this area is the asymmetric transfer of sulfur-based electrophiles. Asymmetric sulfonylation may be the best-studied subclass of sulfur-group transfer<sup>11,12</sup>. Yet, despite the widespread use of sulfonates in complex molecule synthesis, approaches to asymmetric catalytic sulfonate transfer are rare<sup>13–15</sup>.

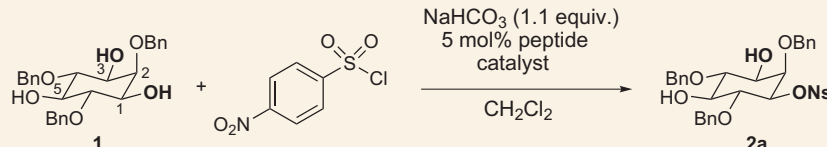
Herein, we report a tetrapeptide catalyst for the desymmetrization of select *meso*-1,3-diols through a direct enantioselective mono(sulfonylation) reaction. Notably, the lead catalyst bears strong stereochemical analogy to scaffolds previously found to be effective for orthogonal group transfer reactions. Yet, detailed studies of the stereochemical aspects of these two group transfer processes (sulfur-electrophile versus phosphorus-electrophile) reveal opposite enantioselectivities from a common catalyst scaffold for these processes<sup>16</sup>. Stereochemical divergence among related catalysts for orthogonal group transfers may reveal an as-yet underappreciated mechanistic nuance for histidine-dependent catalysts. Moreover, from the functional point of view, these observations expand the use of complementary group transfer processes, allowing access to complementary stereoisomeric products from a common catalyst scaffold.

## Results

To achieve catalytic enantioselective synthesis of sulfonate esters by sulfonyl transfer, we chose 2,4,6-tribenzyl-*myo*-inositol (**1**) as a test substrate and *p*-nitrobenzenesulfonyl chloride (*p*-NsCl) as the sulfonylating agent (Table 1). Derivatives of *myo*-inositol have proven valuable in earlier studies of enantioselective group transfer, in particular for analogous transfers of phosphorous(v)-based reagents such as diphenylphosphoryl chloride<sup>17</sup>. *myo*-Inositol



**Figure 1 |  $\pi$ -Methyl-histidine-containing peptides for group transfer chemistry.** Previous work from the Miller group has resulted in selective transfer of acyl, phosphoryl, sulfonyl and thiocarbonyl groups to alcohols using  $\pi$ -methyl-histidine-containing peptides. These reactions are thought to proceed through an *N*-methyl imidazolium intermediate generated by nucleophilic attack of the imidazole moiety on the electrophile. Careful design and optimization of the peptide catalysts can allow for the facile synthesis of a variety of analogues of complex polyols. Ph, phenyl; Me, methyl.

**Table 1 | Selected data from sulfonylation catalyst screen.**


Entry	Catalyst	Temperature	<i>i</i> + 1*	<i>i</i> + 2*	<i>i</i> + 3*	<i>i</i> + 4*	e.r. <sup>†</sup>
1	<b>3</b>	23 °C	Hyp(But)	Sp5	Tyr(But)	Phe	67.5:32.5
2	<b>4</b>	23 °C	Hyp(But)	Sp5	Leu	Phe	84.5:15.5
3	<b>5</b>	23 °C	Hyp(But)	Aib	Leu	Phe	83.5:16.5
4	<b>6</b>	23 °C	Pro	Aib	Leu	Phe	76.5:23.5
5	<b>4</b>	0 °C	Hyp(But)	Sp5	Leu	Phe	89.0:11.0
6	<b>5</b>	0 °C	Hyp(But)	Aib	Leu	Phe	87.0:13.0
7	<b>7</b>	0 °C	Hyp(But)	D-Val	Leu	Phe	92.5:7.5
8	<b>8</b>	0 °C	Hyp(But)	Val	Leu	Phe	60.0:40.0
9	<b>9</b>	0 °C	Hyp(But)	Sp5	Leu	D-Phe	91.5:8.5
10	<b>10</b>	0 °C	Hyp(But)	Sp5	Leu	---	97.0:3.0
11	<b>11</b>	0 °C	Hyp(But)	D-Val	Leu	---	95.5:4.5

Reactions were run with 1.0 equiv. 2,4,6-tribenzyl-*myo*-inositol (**1**) and 1.0 equiv. *p*-nitrobenzenesulfonyl chloride. Reactions were run under a common set of conditions, and conversions were found to be approximately 10%, with some variation. The issue of secondary kinetic resolution was addressed subsequently (see Fig. 3).

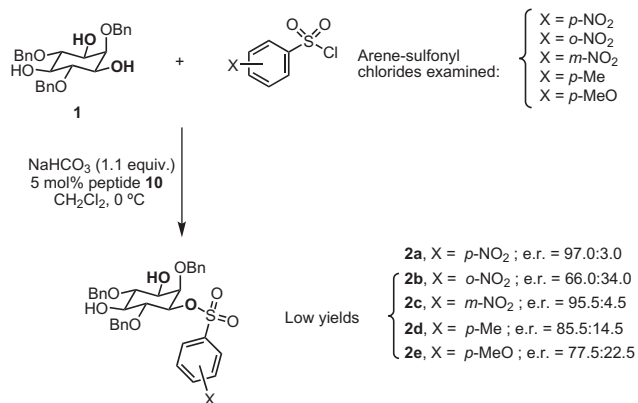
\*Tested catalysts incorporated a variety of amino acids in the peptide chain. *i* + 1 indicates the first amino acid attached to the catalyst platform shown in Fig. 1, *i* + 2 the second and so on.

<sup>†</sup>All enantiomer ratios were measured using chiral HPLC. Bn, benzyl; Ns, *p*-nitrobenzenesulfonyl; Hyp(But), *t*-butylhydroxyproline; Pro, proline; Sp5, 1-amino-1-cyclopentane-carboxylic acid; Aib, 2-aminoisobutyric acid; Val, valine; Tyr(But), *t*-butyltyrosine; Leu, leucine; Phe, phenylalanine.

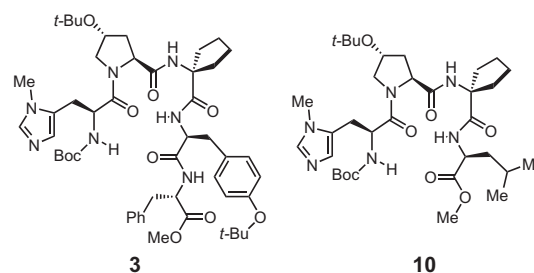
derivative **1** presents the challenge of desymmetrization of the enantiotopic hydroxyl groups at the 1- and 3-positions, as well as the free hydroxyl group at the 5-position, along the mirror plane of the substrate. As hindered amine bases are often sufficient to promote the sulfonylation of alcohols in the absence of any catalyst, insoluble inorganic bases were first evaluated as the stoichiometric base. Among the bases screened (including MgO, K<sub>2</sub>CO<sub>3</sub>, and Na<sub>2</sub>CO<sub>3</sub>), NaHCO<sub>3</sub> was identified as the optimal base, providing no observable sulfonate product in the absence of catalyst at 23 °C in 24 h, and good conversions in the presence of *N*-methyl imidazole or peptide catalyst.

With appropriate conditions established, a series of  $\pi$ -methyl-histidine-containing peptides were evaluated based on their ability to influence the enantioselectivity of the reaction (Table 1). Catalyst screening began with peptide **3** owing to its high

enantiocontrol in the phosphorylation of inositol substrate **1**<sup>4</sup>. Although the enantiomer ratio (e.r.) observed with peptide **3** was quite modest (67.5:32.5 e.r., entry 1), this result provided a starting point for catalyst optimization. Changing the amino acid three residues away from the Boc- $\pi$ -methyl-histidine residue (*i* + 3 position) from an aromatic residue to leucine dramatically increased the enantioselectivity to 84.5:15.5 e.r. (catalyst **4**, entry 2). The *tert*-butoxy group of the L-hydroxyproline residue was found to be important for high enantiomer ratios as replacement with L-proline resulted in a significant decrease in enantioselectivity (entry 3 versus 4). The impact of the *i* + 2 position on enantioselectivity was probed through the use of *gem*-disubstituted amino acids, L-valine, and D-valine (entries 5–8). The use of 2-aminoisobutyric acid resulted in a small decrease in enantioselectivity compared with the five-membered ring-containing residue. Incorporation of a D-amino acid improved the enantioselectivity (92.5:7.5 e.r., entry 7) whereas an L-amino acid led to reduced enantioselectivity (60.0:40.0 e.r., entry 8). It is possible that these changes influence  $\beta$ -turn stability<sup>18</sup>. The stereochemistry of the *i* + 4 position was also probed through the use of D-phenylalanine (catalyst **9**). This catalyst resulted in a more selective reaction than the analogous L-phenylalanine peptide (91.5:8.5 e.r. for catalyst **9**, and 89.0:11.0 e.r. for catalyst **4**). The small degree of influence, however, suggested that the peptide could be truncated and still retain its high enantioselectivity. In fact, tetrapeptide **10**, showed the highest enantioselectivity to date (97.0:3.0 e.r., entry 10).



**Figure 2 | The influence of the arene-sulfonyl chloride on the enantioselectivity and yield.** The reactions were run using various substituted arene-sulfonyl chlorides. Yields were low for all reactions except when *p*-nitrobenzenesulfonyl chloride was used (product **2a**). Moving the nitro group to the *meta*-position had little effect on the enantiomer ratio (e.r.) of the product, whereas moving the nitro group in the *ortho*-position dramatically decreased the enantiomer ratio of the products. Additionally, a slight decrease in enantiomer ratio of the products was observed when electron-rich *para*-substituents were used (X = *p*-Me and *p*-MeO in **2d** and **2e**, respectively). Bn, benzyl.



In addition to *p*-NsCl, a variety of other sulfonylating agents were assayed using catalyst **10** and triol **1** as the substrate (Fig. 2). The use of *ortho*-nitrobenzenesulfonyl chloride led to reduced

**Table 2 | Substrate scope for sulfonylation of meso-1,3-diols.**

Entry	Substrate	Conditions*	Yield†	e.r.‡	Entry	Substrate	Conditions*	Yield†	e.r.‡
1		A	76%	97.0:3.0	6		A	75%	96.5:3.5
		B	66%	95.0:5.0			B	56%	95.5:4.5
2		A	75%	97.0:3.0	7		A	57%	88.0:12.0
		B	58%	95.0:5.0			B	42%	82.5:17.5
3		A	62%	95.5:4.5	8		A	12%	50.0:50.0
		B	60%	95.0:5.0			B	61%	50.0:50.0
4		A	58%	95.5:4.5	9		A	74%	89.0:11.0
		B	53%	91.5:8.5			B	65%	86.0:14.0
5		A	76%	96.0:4.0	10		A	16%	62.0:38.0
		B	76%	94.5:5.5			B	40%	69.0:31.0

All reactions were run with 5 mol% peptide **10**, 1.0 equiv. of substrate and 1.3 equiv. of *p*-nitrobenzenesulfonyl chloride, for 5–24 hours.

\*Condition A uses 0.2 ml saturated aqueous NaHCO<sub>3</sub> per 0.1 mmol of substrate; condition B uses 1.5 equiv. of 2,6-lutidine.

†Isolated yield of mono(sulfonate), an average of at least two trials.

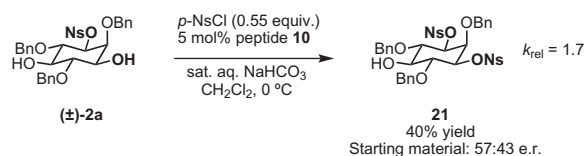
‡All enantiomer ratios were measured using chiral HPLC and are an average of at least two trials. Ns, *p*-nitrobenzenesulfonyl; Bn, benzyl; PMB, *p*-methoxybenzyl; TBS, *t*-butyldimethylsilyl; Me, methyl.

enantioselectivity (97.0:3.0 e.r. for **2a** versus 66.0:34.0 e.r. for **2b**) suggesting the reaction is sensitive to the steric effects. Nitro-substitution in the *meta*-position was less consequential (**2c**, 95.5:4.5 e.r.). Additionally, the enantiomer ratio of the reaction was found to be sensitive to the electronic properties of the arenanesulfonyl chloride, with electron donating groups having a detrimental effect on enantioselectivity (**2d** is formed with an 85.5:14.5 e.r.; **2e**, 77.5:22.5 e.r.).

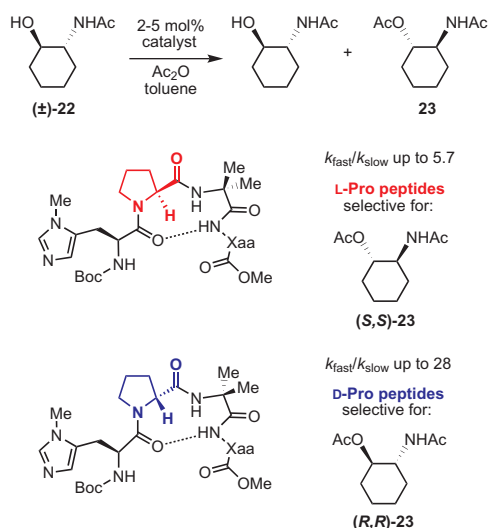
Concurrent with catalyst and sulfonylation agent optimization, other reaction parameters were explored to maximize rate and enantioselectivity. A variety of solvents were evaluated, but none proved superior to CH<sub>2</sub>Cl<sub>2</sub>. To further increase rates, catalyst **10** was evaluated at 23 °C. Indeed, faster rates were observed, but the enantiomer ratio was smaller (92.0:8.0). Although high enantioselectivity was consistently observed when solid NaHCO<sub>3</sub> was used as the base, the reaction rates were slow and inconsistent yields (25–75%) were recorded. As a result, two new sets of conditions were identified that produce consistently good yields of **2a** in shorter reaction times: condition A uses a biphasic system of saturated aqueous NaHCO<sub>3</sub>/CH<sub>2</sub>Cl<sub>2</sub> (1:2 v/v) to produce mono(sulfonate) **2a** in 76% yield and 97.0:3.0 e.r. (for a Schotten-Baumann-type sulfonylation method using *N*-alkylimidazole catalysts, see ref. 19); condition B uses 2,6-lutidine in CH<sub>2</sub>Cl<sub>2</sub> to give **2a** in 66% yield and 95.0:5.0 e.r. (Table 2, entry 1).

The rapid identification of a catalyst for the desymmetrization of **1** bodes extremely well for the identification of highly effective catalysts for enantioselective sulfonylation of broad and diverse structural types<sup>20,21</sup>. Moreover, the above results establish simple tetrapeptide catalysts as fertile ground for the study of a variety of stereochemical

arrays. For studies of polyol modification, catalyst ‘generality’ is much less significant than catalyst library ‘diversity’. Nevertheless, given the simplicity of catalyst **10**, and the highly practical nature of conditions A and B, we considered whether or not the processes identified for substrate **1** might be applicable to others. Notably, both conditions A and B enable desymmetrization of a number of other 1,3-diols (Table 2). In general, the biphasic conditions (A) provide higher yields and enantioselectivities. For example, the benzyl protecting groups can be exchanged for *p*-methoxybenzyl groups without loss of enantioselectivity (entry 2). Additionally, the reaction is tolerant of quite dramatic modifications of the 5-position of inositol (entries 3–6).

**Figure 3 | Kinetic resolution of racemic mono(sulfonate) **2a**.**

Mono(sulfonate) **2a** was prepared in racemic form and subjected to the reaction conditions. After 40% conversion to the bis(nosylate) **21**, the starting material was recovered with 57:43 e.r., corresponding to a relative rate constant ratio of the fast enantiomer to the slow enantiomer ( $k_{rel}$ ) of 1.7. This low  $k_{rel}$  indicates that the high enantioselectivity observed for the desymmetrization of inositol-based 1,3-diols is primarily the result of enantiotopic group selection rather than kinetic resolution of the monofunctionalized product. Ns, *p*-nitrobenzenesulfonyl; Bn, benzyl.



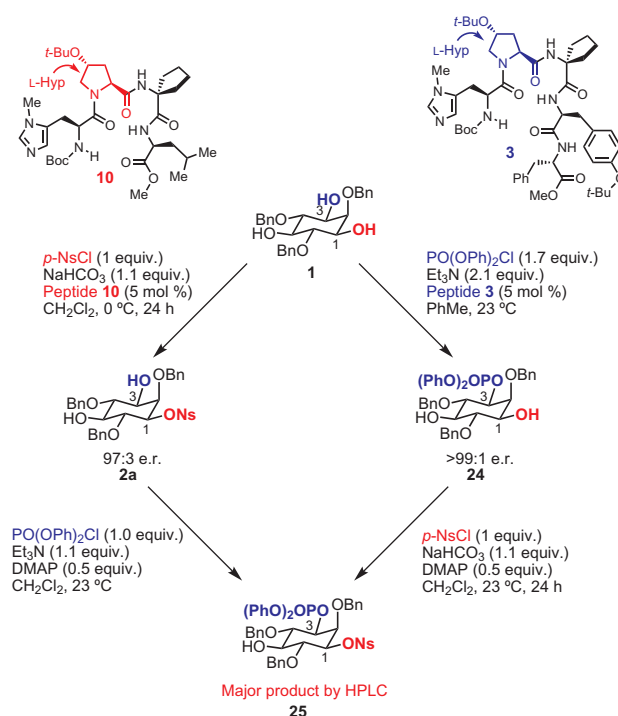
**Figure 4 | Chirality of proline determines the absolute sense of asymmetric induction.** In previous work in the Miller group<sup>23</sup>, the enantioselectivity of acylation reactions mediated by diastereomeric peptides was strongly dependent on whether the  $\beta$ -turn of the peptide catalyst was nucleated by a D-proline residue or an L-proline residue. Ac, acetyl; Boc, *t*-butoxycarbonyl; Me, methyl.

However, small changes at the 2-position of inositol lead to some decrease in enantioselectivity (88.0:12.0 e.r., entry 7). Additionally, further simplification of the substrate to *cis*-1,3-cyclohexane diol resulted in good reactivity but no enantioselectivity. We believe that condition A gives a low yield of product owing to the high water solubility of the starting material. Interestingly, the acyclic 1,3-diol derived from adonitol (**19**) shows high enantioselectivity (89.0:11.0 e.r.) and good reactivity (entry 9), whereas all-*syn* stereoisomer **20** reacts slowly and with depreciated enantioselectivity (62.0:38.0 e.r.; entry 10).

From a mechanistic point of view, the observed desymmetrizations appear to be a result of enantiotopic group selection, rather than secondary kinetic resolution of the monofunctionalized product<sup>22</sup>. As shown in Fig. 3, when peptide **10** was evaluated for kinetic resolution of racemic ( $\pm$ )-**2a**, the starting material was recovered (60% mass recovery) with only 57.0:43.0 e.r. ( $k_{\text{rel}} = 1.7$ ).

These initial mechanistic studies set the stage for a rather remarkable observation. The determination of the absolute configuration of the products derived from the mono(sulfonylation) reveals a stark contrast between peptide-catalysed asymmetric sulfonylations and the equivalent peptide-catalysed phosphorylations. We have shown on a number of occasions a strong correlation between the secondary structure of a given enantioselective histidine-based catalyst and the absolute sense of chirality transfer for various electrophiles. For example, the enantioselectivity of acylation reactions mediated by diastereomeric peptides was strongly dependent on the type of  $\beta$ -turn nucleated by either a D-proline residue or an L-proline residue in the catalyst (Fig. 4)<sup>18,23</sup>.

Analogous observations consistently appear throughout our studies of asymmetric phosphorylation<sup>17</sup>. However, we have not previously systematically compared the absolute sense of induction provided by related peptide-based catalysts when challenged with different electrophiles. In fact, naively, we had often assumed that although the mechanisms of acyl transfer, phosphoryl transfer and other group transfers were clearly nuanced and different, the details of catalyst-substrate recognition could likely be analogous, and the absolute senses of asymmetric induction would also be the same in most cases. Thus, in order to evaluate this issue, we synthesized the mono(nosylated), mono(phosphorylated) inositol **25** through two independent methods (Fig. 5) and compared their



**Figure 5 | Determination of absolute configuration of sulfonates by comparison to phosphorylation.** Mono(nosylated), mono(phosphorylated) inositol **25** was prepared through two independent methods, and the products were compared by high-performance liquid chromatography retention times. From previous work<sup>4</sup>, it was known that peptide **3** selectively phosphorylates inositol **1** at the *meta*-position to give diol **24**. Sulfonylation of **24** using an achiral catalyst produces compound **25**. Surprisingly, phosphorylation of mono(sulfonate) **2a** obtained through nosylation mediated by peptide **10** also yielded **25**. Therefore, despite the similarity between peptides **3** and **10**, they act at enantiotopic alcohols for phosphorylation and sulfonylation, respectively. *t*-Bu, *tert*-butyl.

high-performance liquid chromatography retention times. From previous work, it is known that peptide **3** phosphorylates **1** with high levels of enantioselectivity (>99:1 e.r.) at the 3-position of inositol to provide **24**<sup>17</sup>. Upon mono(sulfonylation) with an achiral catalyst, **25** was then obtained. However, mono(sulfonate) **2a**, obtained from reaction with peptide **10** (97.0:3.0 e.r.), was then subjected to phosphorylation and surprisingly also gave compound **25**. It should be noted that neither **24** nor **2a** racemize under the sulfonylation or phosphorylation conditions. In contrast, selective phosphorylation at the 1-position of **1** (ref. 4) followed by nosylation gives the opposite enantiomer. Thus, peptides **3** and **10**, which possess superficially similar peptide sequences, catalyse bond-forming reactions at enantiotopic hydroxyl groups when subjected to either phosphorylation or sulfonylation conditions. These results suggest disparate details of catalyst-substrate recognition in the respective group transfer reactions, depending on conditions and the nature of the electrophile. The mechanistic basis of these enantio-divergent reactions at present is elusive, and a myriad of mechanistic scenarios must be considered. Changes in mechanism as drastic as the difference between nucleophilic and general base catalysis represent but one possibility under consideration. Likewise, the differences in the nature of the charge distributions exhibited by various activated Lewis basic catalytic intermediates may have fundamentally different consequences for activated catalyst conformations<sup>24</sup>. Elucidation of these mechanistic nuances requires extensive physical organic studies, and these are underway in our laboratory.

The significance of these observations is both methodological and fundamental. On the one hand, these results expand the scope of

asymmetric peptide-catalysed group transfer reactions to include an important class of sulfur-based electrophiles. The substrate scope exhibited by even a single catalyst is encouraging as expanded catalyst libraries may now be applied to more complex substrates with the goal of achieving disparate sites of reaction for the realization of analogues. In addition, our new findings point to intriguing mechanistic nuances when different electrophiles are used. The notion that a unique amino acid side chain may exhibit distinct and unusual roles is well predated in enzymes, in particular when diverse reactions are carried out by different enzymes. For example, the active site histidine in various histidine-dependent kinases is often demonstrated to serve as a catalytic nucleophile<sup>25</sup>. In lipases and proteases, however, the active site histidines more often serve the role of a general base<sup>26</sup>. Although our experiments in no way imply so drastic a change in mechanism, the reversal of enantioselectivity in two superficially similar reactions support very different transition states for the two enantiomer determining steps. Highly selective catalysts that bear structural similarity, but exhibit their catalytic prowess by different mechanisms have been viewed by some as a hallmark of privileged catalysts in nature<sup>27</sup>, or the laboratory<sup>28</sup>. We hope to learn more about these issues as we pursue methodological goals with this intriguing family of peptide-based catalysts in parallel.

## Methods

**General procedure for sulfonylation using condition A (Table 2).** To an oven-dried 1-dram vial equipped with a magnetic stir bar was added diol substrate (0.10 mmol) and CH<sub>2</sub>Cl<sub>2</sub> (0.4 ml). The peptide catalyst **10** (3.4 mg, 0.005 mmol) was then added and the reaction was cooled to 0 °C. *p*-Nitrobenzenesulfonyl chloride (28.8 mg, 0.13 mmol) was added followed by 0.2 ml of saturated aqueous NaHCO<sub>3</sub> solution. The reaction was monitored by thin layer chromatography for the disappearance of the sulfonyl chloride and allowed to stir at 0 °C for 5–48 h. The biphasic reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (2 ml) and saturated aqueous NaHCO<sub>3</sub>, and the layers were separated. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 2 ml). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The resulting yellow oil was purified by silica gel flash chromatography.

**General procedure for sulfonylation using condition B (Table 2).** To an oven-dried 1-dram vial equipped with a magnetic stir bar was added diol substrate (0.10 mmol) and CH<sub>2</sub>Cl<sub>2</sub> (0.4 ml). The peptide catalyst **10** (3.4 mg, 0.005 mmol) was then added and the reaction was cooled to 0 °C. *p*-Nitrobenzenesulfonyl chloride (28.8 mg, 0.13 mmol) was added followed by 2,6-lutidine (17.5 μl, 0.15 mmol). The reaction was monitored by thin layer chromatography for the disappearance of the sulfonyl chloride and allowed to stir at 0 °C for 5–48 h. The reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (2 ml), and 1 M HCl (0.5 ml) was added. The layers were separated, and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 2 ml). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The resulting yellow oil was purified by silica gel flash chromatography.

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## Author contributions

All authors conceived and designed the experiments and analysed the data. K.W.F. and A.L.A.P. performed the experiments, K.W.F. and S.J.M. wrote the paper jointly, and all authors edited and commented on the manuscript.

## Additional information

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