Medicinal chemistry relies on the efficient generation of analogs of lead compounds. Natural products represent a special class of leads since they have survived eons of natural selection and generally evolved to perform a specific function.[1] Yet, natural products are difficult to modify efficiently.

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by chemical methods because of their complexity and multi-functional nature.[5] Enzymatic catalysts have been applied in this context.[6] However, the specificities they exhibit, often lead to a limited set of natural-product analogs. Using peptide-based catalysts, we report herein unique examples of small-molecule, chiral catalyst-dependent, site-selective modifications of a natural product polyol, erythromycin A.

The selective derivatization of polyols is a special challenge to asymmetric catalysis. Unlike enantioselective catalysis, wherein competing reaction pathways present equivalent activation barriers in the absence of a chiral catalyst (e.g., desymmetrization as shown in Scheme 1a),

![Scheme 1](image1)

**Scheme 1.** a) Reaction coordinate for the enantioselective desymmetrization of a meso substrate. With an achiral catalyst, the two hydroxy groups react at equal rates. A chiral catalyst may accelerate one pathway leading to enantioselectivity. b) In a site-selective reaction, the two hydroxy groups are of unequal reactivity. Achiral catalysts lead to a product distribution that reflects the inherent reactivity of the two sites ($\Delta G^\circ$); $1$ is the major product). To form the product of functionalization at the least reactive site ($2$), $\Delta G^\circ$ must be large to overcome the lower reactivity, and further favor the formation of the “minor” product.

... enhance inherent reactivity in a “matched” sense.[4] Alternatively, in the case of a desired reversal of innate selectivity, one wishes to find powerful catalysts that are “mismatched,” in order to fully overcome the native kinetic preference.

As a prototype polyol for study of site-selective catalysis, we began with erythromycin A ($3$), an antibiotic with a storied history in both medicinal and synthetic chemistry.[5] We then chose to explore the fundamental process of alcohol acylation, a typical “group transfer” process that could lead to classes of analogs wherein hydroxy groups are converted to unique esters. We have reported that low molecular weight peptide-based catalysts are effective enantioselective catalysts for various group transfers, including acylation,[9] phosphorylation,[7] and sulfenylation.[8] The common chiral catalyst scaffold for group transfer is exemplified by nucleophilic, histidine-based catalysts as shown in Scheme 2.

![Scheme 2](image2)

**Scheme 2.**

We initially demonstrated that indeed, the hydroxy group array of $3$ provides a range of relative reactivities. The reactivity hierarchy was initially established in the seminal report of Abbott Laboratories, employing pyridine as solvent and catalyst.[9] In our own studies, we found the Abbott results to be entirely reproducible. Furthermore, we established that the achiral catalyst N-methylimidazole (NMI) afforded similar results. Indeed, the C2'-hydroxy group undergoes acylation first, due in part to the autocatalytic vicinal tertiary amine, to give the 2'-monoacetate $4$ as the major product when a limiting quantity of acetic anhydride (Ac$_2$O) is used (Equation (1) in Scheme 3). Indeed, this site undergoes acylation even in the absence of a catalyst. The next most reactive position is the C4''-hydroxy, as evidenced by preferential formation of the C2'-,C4''-diacetate when NMI is used with additional Ac$_2$O; this diacetate is converted to C4''-monoacetate $5$ when the reaction is quenched with MeOH, which autocatalytically cleaves the C2'-acetate group (Equation (2) in Scheme 3). Finally, the least reactive secondary site, the C11-OH, acylates such that an EryA-triacetate (not shown) forms, but only after prolonged reaction time. The tertiary alcohols of $3$ are substantially less reactive under these conditions. Under catalysis by NMI (10 mol%), or when pyridine is employed as solvent, the inherent selectivity for 5/6...
We estimate by 1H NMR integration that catalyst clearly the C11-derivative turn-like structures are employed (e.g., b).

However, when peptides disposed toward the adoption of libraries. Shown in Scheme 3 are typical 1H NMR spectra catalyst candidates, chosen at random from our catalyst examined exhibit NMI or pyridine-like behavior, favoring the C4+-monoacetate 5, after MeOH quench (Scheme 3b).

When peptides disposed toward the adoption of ß-turn-like structures are employed (e.g., 7), a reversal of inherent selectivity is observed. In addition, the peptide-catalyzed reactions are generally significantly faster than those promoted by pyridine or NMI. The major product formed under catalysis by propionyl transfer with achiral catalysts leads to modest selectivity for the inherently favored 9c (2:1), whereas catalyst 7 favors formation of 9d (1:3.5, Table 1, entry 4). Notably, in all cases peptide 7 is a far more active catalyst than the achiral catalysts, leading to isolation of C11-derivatized material. While chromatographic separations of compounds at the diester stages are difficult and can limit yields of isolated 9, in all cases methanolysis of the C2-derivatized esters leads to C11-monoesters with excellent purity.

These findings illustrate the potential of chiral catalyst-dependent, site-selective modification of polyol natural products. In addition, the discovery of catalyst-dependent modifications that reorganize natural product architecture may be of additional utility in the science of natural product analog generation. The mechanistic basis of these transformations is a frontier area of chiral catalysis, and studies of catalyst interactions with polyfunctional substrates are underway.

Catalyst 7 appears general for additional group transfers. For example, a dramatic reversal is observed with octanoyl anhydride, setting the stage for site-selective “lipidation” of natural products (Table 1, entry 1). Whereas reaction with pyridine delivers 8a/9a with greater than 10:1 selectivity, catalyst 7 strongly reverses the selectivity such that 9a is the major product with selectivity of 1:9. Transfer of the ß-alanyl moiety via the mixed anhydride also provides a strong reversal (Table 1, entry 2). Achiral catalysts favor 8b (5:1 over 9b), while catalyst 7 delivers high selectivity for 9b (1:10). The transfer of functionalized reagents implies the potential for selective labeling of natural products at specific sites. Selective transfer of an alkenyl group is illustrated in entry 3, wherein catalyst 7 reverses the inherent selectivity such that 9c is the preferred product (5:1 selectivity, 9c/8c).

Notably, peptide 7 provides not only a catalyst-dependent derivatization of a unique, inherently less reactive hydroxy. In addition, C11-monoacetate 6 exists almost exclusively as its hemiketal tautomer. Everett and co-workers have rationalized hemiketalization of C11-acetate derivatives of erythromycin as a consequence of the loss of a macrolide-stabilizing hydrogen bond between the C11-OH and the C9-carbonyl in native erythromycin. Independent of the structural basis of the tautomerization, the site-selective catalysis results in skeletal reorganization of the natural product. Such reactions, wherein a chiral catalyst not only modifies a unique, inherently disfavored site, but also reorganizes the natural product structure, may be of particular value to the generation of diverse, natural product-derived compounds.
Table 1: Site-selective reactions of erythromycin A with achiral catalyst versus 7.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Protonation</th>
<th>Cat.</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R= (CH$_2$)$_2$CH$_3$</td>
<td>&gt;10:1</td>
<td>2:1</td>
<td>1:9 (58%)</td>
</tr>
<tr>
<td>2</td>
<td>R= (CH$_2$)$_2$NHBoc</td>
<td>1:3.5</td>
<td>2:1</td>
<td>1:3.5 (28%)</td>
</tr>
<tr>
<td>3</td>
<td>R= (CH$_2$)$_2$CH=CH$_2$</td>
<td>1:5</td>
<td>2:1</td>
<td>1:5 (56%)</td>
</tr>
<tr>
<td>4</td>
<td>R= Et</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[a] Reaction catalyzed by pyridine as solvent. Reactions catalyzed by NMI provide similar ratios. [b] Reactions with pyridine or NMI are generally sluggish and not preparatively useful. Consistent with the reports of Abbott Laboratories, the yields of 8 (R=Me) under conditions promoted by pyridine is about 70% after 3 days reaction time. Yields of 9 under catalysis by pyridine are extremely low and difficult to quantify. Thus, peptide 7 provides unique access to 9. [c] Yields are determined from isolated material after chromatography. In cases where co-elution with minor components occurs, conversion into the corresponding C11-monooester following methanolysis of the C2'-OH-ester delivers pure compounds for full characterization. See Supporting Information for details.

Experimental Section

General procedure for the acylation of erythromycin A: Erythromycin A (3, 100 mg, 0.136 mmol) was dissolved in CHCl$_3$ (100 mL, 1.36 mL) in a flame-dried vial. Triethylamine (5 equiv, 93.0 µL, 0.681 mmol) and the catalyst (5 mol%, 20.0 mmol in CHCl$_3$, 0.340 mL, 0.61 µmol) were then added sequentially. For less reactive anhydrides, 10 mol% catalyst is employed (see Supporting Information for details.). Acetic anhydride (10 equiv, 128 µL, 1.36 mmol) was added and the reaction was allowed to stir at 25°C. Reaction progress was monitored by $^1$H NMR (400 MHz) by removing 100 µL aliquots followed by a methanol quench. The resulting solutions were passed through a silica gel plug eluting with a CHCl$_3$/MeOH (95:5 v/v) solvent system and concentrated under high vacuum. After an appropriate time interval, the full reaction mixture was quenched by addition of methanol and passed through a silica gel plug and concentrated to dryness. If complete cleavage of the labile 2'-acetyl was desired, the unpurified reaction mixture was redissolved in MeOH and allowed to stir for 72 h. After concentration of the reaction mixture, reaction selectivity was analyzed by $^1$H NMR (400 MHz). Individual products were isolated by silica gel column chromatography (CHCl$_3$/MeOH/NH$_3$/OH, 14:1; 95:5/1 v/v/v) and/or semipreparative HPLC techniques.

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[11] A table of the catalysts that were screened, reflecting their diverse performance, may be found in the Supporting Information.
[12] The ratios are supported by both NMR analysis and yields of isolated products; see Supporting Information.