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A chiral phosphoric acid catalyst for asymmetric construction of 1,3-dioxanes

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A novel method of enantioselective 1,3-dioxane construction via a hemiacetalization/intramolecular oxy-Michael addition cascade by a chiral phosphoric acid catalyst was developed. The product was successfully transformed into an optically active 1,3-polyol motif, indicating that the proposed reaction can provide useful chiral building blocks for the *de novo* synthesis of polyketides.

The oxy-Michael addition is one of most important methods for the introduction of oxygen to the β -position of carbonyl compounds.¹ In particular, stereoselective construction of 1,3-dioxanes via a hemiacetalization/intramolecular oxy-Michael addition cascade is a well-designed approach to synthesize stereodefined 1,3-diols found in polyketides, which are promising candidates for therapeutics (Scheme 1 and Figure 1).^{2,3} Indeed, such transformations have been utilized in the synthesis of a number of pharmacologically important molecules.⁴ However, although several diastereoselective methods from chiral substrates under basic or acidic conditions have been reported,⁵ enantioselective methods have remained largely unexamined thus far due to the lack of a useful strategy for asymmetric induction in the intramolecular oxy-Michael addition reaction.

Scheme 1. 1,3-Dioxane construction via hemiacetalization/intramolecular oxy-Michael addition cascade.

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Figure 1. 1,3-Polyols in pharmaceutical compounds.

Recently, we have developed an efficient methodology for enantioselective intramolecular oxy-Michael addition reactions by utilizing multipoint recognition through hydrogen bonding with bifunctional organocatalysts.⁶⁻⁸ Intramolecular oxy-Michael additions from hemiacetal intermediates to afford 5-membered cyclic acetals, namely 1,3-dioxolanes, were conducted by using bifunctional aminothiurea catalysts. Such transformations, followed by deacetalization, proved efficient protocols for formal hydration to afford optically active polyols.^{6b,c,f} However, as the aminothiurea catalysts do not have a sufficient activity to effect the construction of 6-membered 1,3-dioxanes, we chose to focus on chiral phosphoric acids, because they have moderately higher acidity than thioureas and the following merits.⁹ Firstly, the phosphoric acid catalysts possess both acidic and basic sites, allowing for multipoint recognition of a substrate through hydrogen bonding in the oxycyclization. In addition, such dual functionality provides double activation of a substrate for cyclization, thus leading to sufficient catalytic activity even without particularly high acidity, which is unsuitable in this transformation since the hemiacetal intermediates or the acetal products will be decomposed through the formation of oxocarbenium ions. Finally, an appropriate choice of substituents at the 3- and 3'-positions of the catalysts enables their acidity and steric character to be finely tuned. Herein, we demonstrate novel asymmetric 1,3-dioxane

formation via a hemiacetalization/intramolecular oxy-Michael addition cascade using a chiral phosphoric acid catalyst.^{10,11}

Table 1. Optimization of conditions^a

Entry	Catalyst	R (2)	Solvent	Yield (%) ^{b,c}	ee (%)
1	4a	Cy (2a)	benzene	56	80
2	4b	Cy (2a)	benzene	59	17
3	4c	Cy (2a)	benzene	21	−43
4	4d	Cy (2a)	benzene	80	36
5	4e	Cy (2a)	benzene	52	5
6	4a	<i>i</i> -Pr (2b)	benzene	57	79
7	4a	<i>i</i> -Bu (2c)	benzene	64	71
8	4a	<i>t</i> -Bu (2d)	benzene	33	11
9	4a	Et (2e)	benzene	60	78
10	4a	<i>n</i> -C ₅ H ₁₁ (2f)	benzene	74	86
11	4a	<i>n</i> -C ₉ H ₁₉ (2g)	benzene	72	82
12	4a	PhCH ₂ CH ₂ (2h)	benzene	76	85
13	4a	Ph (2i)	benzene	<1	—
14	4a	<i>n</i> -C ₅ H ₁₁ (2f)	toluene	83	87
15	4a	<i>n</i> -C ₅ H ₁₁ (2f)	hexane	80	83
16	4a	<i>n</i> -C ₅ H ₁₁ (2f)	<i>c</i> -hexane	92	85
17	4a	<i>n</i> -C ₅ H ₁₁ (2f)	CH ₂ Cl ₂	76	68
18	4a	<i>n</i> -C ₅ H ₁₁ (2f)	Et ₂ O	40	82
19	4a	<i>n</i> -C ₅ H ₁₁ (2f)	CPME ^e	18	86
20	4a	<i>n</i> -C ₅ H ₁₁ (2f)	EtOAc	29	81
21	4a	<i>n</i> -C ₅ H ₁₁ (2f)	CH ₃ CN	<5	58
22 ^d	4a	<i>n</i> -C ₅ H ₁₁ (2f)	toluene	54	93
23 ^d	4a	<i>n</i> -C ₅ H ₁₁ (2f)	<i>c</i> -hexane	94	91

^aReactions were run using **1a** (0.1 mmol), **2** (0.12 mmol), and the catalyst (0.005 mmol) in the solvent (0.2 mL). ^bThe diastereomeric ratio was ≥20:1 in all cases. ^cIsolated yields. ^dReactions were run using **1a** (0.1 mmol), **2** (0.2 mmol), and the catalyst (0.005 mmol) in the solvent (2 mL) at 35 °C. ^eCPME = cyclopentyl methyl ether.

We began by investigating the reaction between (*E*)-5-hydroxy-1-phenylpent-2-en-1-one (**1a**) and cyclohexanecarbaldehyde (**2a**) (Table 1) in the presence of 5 mol% of chiral phosphoric acid catalysts **4** (Figure 2) in benzene at 25 °C. As expected, the 1,3-dioxane product **3** was obtained enantioselectively as a single diastereomer (Table 1, entries 1–5), with (*S*)-TRIP (**4a**) proving the most promising among the various catalysts investigated (Table 1, entry 1). Using **4a** as a catalyst, reactions with other aldehydes **2** were also investigated (Table 1, entries 6–13). While the use of pivalaldehyde (**2d**) resulted in poor enantioselectivity, unbranched aliphatic aldehydes were shown to be efficient, with **2f** exhibiting the highest enantioselectivity (Table 1, entry 10). The use of benzaldehyde (**2i**) was also investigated, but failed to afford the desired reaction product (Table 1, entry 13).¹² Subsequently, a range of reaction solvents were investigated (Table 1, entries 14–21), and it was found that less polar solvents gave improved yields and higher enantioselectivities (Table 1, entries 14–16). The enantioselectivity of the reaction was further improved by carrying out the reaction at lower concentrations in toluene at 35 °C (Table 1,

entry 22).¹³ In addition, the use of cyclohexane as a solvent also resulted in an enhanced yield, and only a slight loss of enantioselectivity was observed (Table 1, entry 23).

Figure 2. Chiral phosphoric acid catalysts.

With the optimal conditions for the transformation established, we explored the substrate scope for the reaction (Table 2). It was found that both electron-rich and electron-deficient enones gave high enantioselectivities (**3bf** and **3cf**). Substrates bearing 4-methylphenyl, 2-naphthyl, and 4-bromophenyl groups were also suitable, and afforded the corresponding 1,3-dioxanes in high yields and enantioselectivities (**3df**, **3ef**, and **3ff**). In addition, although the use of an aliphatic enone resulted in moderate enantioselectivity under the current conditions (**3gf**), better enantioselectivity was attained in the reaction of an alkenyl ketone (**3hf**), allowing further modifications such as a regioselective hydration to approach higher polyols. Furthermore, although no desired product could be obtained in the reaction from an α,β-unsaturated ester substrate, product **3bf** could be transformed into the corresponding ester **5** by means of a Baeyer–Villiger oxidation using *m*-CPBA and TFA, without loss of optical purity (Scheme 2). This modification allows for further extension of this compound for the synthesis of longer polyketide structures through iterative manipulations of an established route,^{4j,k,s} consisting of the reduction to formyl group followed by allylation, olefin metathesis with acrylates, and another diastereoselective acetalization.^{5a,b} Our product can therefore be regarded as a useful chiral building block for polyketide synthesis. The absolute configuration of **3ef** was determined by X-ray crystallography (see the SI for details), and the configurations of all other products were assigned analogously.

Table 2. Substrate scope^a

^aReactions were run using **1** (0.1 mmol), **2f** (0.2 mmol), and the catalyst **4a** (0.005 mmol) in cyclohexane (2 mL). Yields represent material isolated after silica gel column chromatography. The diastereomeric ratio was $\geq 20:1$ in all cases.

Scheme 2. Baeyer–Villiger oxidation of **3bf**.

The use of our product in the asymmetric synthesis of a chiral 1,3,5-triol was then demonstrated. Reduction of **3af** with lithium borohydride in the presence of europium chloride afforded the corresponding alcohols in a 12:1 diastereomeric ratio, in which *syn*-isomer **6** was the major product.¹⁴ Subsequent de-acetalization of the diastereomer mixture, followed by isolation of the major diastereomer using flash silica gel column chromatography, gave chiral 1,3,5-triol **7** with high optical purity (Scheme 3).

Scheme 3. Synthesis of chiral 1,3,5-triol **7**.

In summary, we have presented a novel enantioselective hemiacetalization/intramolecular oxy-Michael addition cascade for the construction of 1,3-dioxanes, mediated by a chiral phosphoric acid catalyst. In addition, the utility of the products for the construction of stereodefined 1,3-polyol motifs was also demonstrated. These results indicate that the proposed methodology utilizing the dual functional organocatalyst opens a new avenue for the *de novo* synthesis of optically active polyketides. Investigation into the further sophistication of this synthetic method and its application to the asymmetric synthesis of attractive 1,3-polyol substructures from bioactive agents are currently underway, and the results will be reported in due course.

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