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Stereoselective Synthesis of Dioxolanes and Oxazolidines via a Desymmetrization Acetalization/Michael Cascade

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Abstract

The desymmetrization of *p*-quinols using a Brønsted acid catalyzed acetalization/Michael cascade was achieved in high yields and diastereoselectivities for aldehydes and imines. Use of a chiral Brønsted acid allowed for the synthesis of 1,3-dioxolane and 1,3-oxazolidine products in modest enantioselectivity.

Graphical abstract

Keywords

acetals; desymmetrization; Michael addition; stereoselective synthesis; cascade catalysis

Acetals and amins are important structural motifs which are found in sugars, alkaloids and pharmaceuticals.¹ The catalytic asymmetric synthesis of *O,O*-acetals and *N,O*-amins is a challenging problem due to the inherent reversibility. Most enantioenriched acetals are prepared using chiral starting materials or stoichiometric chiral reagents but recent development in chiral hydrogen bond catalysts has opened the door for success in this area.^{2–5} The synthesis of cyclic acetals can be achieved via a acetalization/oxa-Michael cascade involving aldehydes and α,β -unsaturated carbonyl compounds. Although 1,2-dioxanes can be synthesized in high diastereoselectivity through this method, the analogous 1,3-dioxolanes have been more challenging.^{6–7} Matsubara recently synthesized 1,3-dioxolanes using a quinidine-derived bifunctional thiourea catalyst, proceeding in excellent enantioselectivity but modest to low diastereoselectivity.⁸

We previously reported that a chiral SPINOL derived phosphoric acid catalyst could catalyze the synthesis of 1,2,3-trioxanes in high enantioselectivity and diastereoselectivity

via a dynamic kinetic resolution of the peroxyhemiacetal intermediate (Scheme 1).⁸ We envisioned a similar approach to the stereoselective synthesis of 1,3-dioxolanes.

We initiated our investigation by exploring the racemic reaction of *p*-methylquinol¹⁰ **1** with isobutyraldehyde. A screen of Brønsted acid catalysts demonstrated that Amberlyst-15, *p*-toluene sulfonic acid (TsOH), (+)-camphorsulfonic acid (CSA), CF₃SO₃H, H₃PO₄, and HCl_{aq} all afford desired dioxolane **2/2'** in modest to good yield but poor diastereoselectivity ranging from 1:1 to 2.2:1 (Table 1, entries 1–6). Both trifluoroacetic acid (TFA) and dimethylphosphinic acid improved the selectivity to 14:1. Switching to a bulkier catalyst, phenylphosphonic acid, further improved the selectivity to 17:1 but the catalyst's low solubility diminished the yield. Implementing the larger and more soluble catalyst diphenylphosphinic acid improved both the yield and the diastereoselectivity to >20:1 favoring **3aa** (entry 10).¹¹ By increasing the temperature to 45 °C and using dichloroethane (DCE) as a solvent, we were able to decrease the reaction time and reduce the catalyst loading to 5 mol % while still maintaining excellent diastereoselectivity (entry 11). When excess water is added to the reaction while using diphenylphosphinic acid, the diastereoselectivity decreased to 17:1 (entry 12). This indicates that moderately dry conditions are preferred to prevent epimerization.

Our optimized reaction conditions were applied to a variety of aldehydes (Scheme 2).¹² Paraformaldehyde as well as sterically hindered aliphatic aldehydes all provided the 1,3-dioxolane products in good yields and high diastereoselectivity. Alkenes, alkynes, thioethers and protected alcohols are tolerated under the reaction conditions. Aryl aldehydes and acetone participate in the reaction but lower yields are obtained. The lower yields for the aromatic aldehydes, and acetone can be attributed to the less thermodynamically favorable hemiacetal/hemiketal formation.¹³

The high diastereoselectivity was tolerant to substitution on the quinol including ethers and multiple tetrasubstituted stereocenters (Scheme 3).

In addition to aldehydes and ketones, imines were found to be competent partners for the formal [3+2] cycloaddition. *N*-alkyl and *N*-aryl imines afforded the desired 1,3-oxazolidine products in good yields and high diastereoselectivity (Scheme 4).

In order to better understand the reaction we subjected single diastereomer **3aa** to the conditions with Amberlyst-15 (Table 2). The 1,2-dioxolane was slowly epimerized to a 4:1 ratio over two days using Amberlyst-15. Both the 1:1 mixture of diastereomers and the major diastereomer were not changed when they were individually subjected to diphenylphosphinic acid. This suggests that the diastereoselectivities observed with diphenylphosphinic acid are a product of kinetic control in the acetalization/cyclization.

After improving the diastereoselectivity, expanding the scope and exploring the reaction mechanism, we hoped to render the reaction asymmetric with the use of a chiral Brønsted acid. Isobutyraldehyde and quinol **1a** were screened with a variety of chiral catalysts (Table 3). Using the TRIP phosphoric acid catalyst **A** the product could be obtained in 35% ee at - 78 °C.

While the 9-anthracenyl catalyst **B** showed very little enantioselectivity, the triphenyl silyl substituted catalyst gave a small improvement to 41% ee. The SPINOL derived phosphoric acid **D** gave a promising 45% ee at room temperature but unfortunately the reaction was very slow at - 78 °C. Chiral thiourea catalyst **E** and squaramide catalyst **F** showed no improvement over the phosphoric acid catalysts.

The enantioselective synthesis of a 1,3-oxazolidine was also investigated using quinol **1a** (Scheme 5). The best result came with catalyst **A** which gave the product 32% yield and 53% ee. The more hindered catalyst **D** only produced a trace amount of desired oxazolidine **6c**.

In summary, we have developed a diastereoselective synthesis of 1,3-dioxolanes and 1,3-oxazolidines via a diphenyl phosphonic acid catalyzed acetalization/oxa- Michael cascade. The reaction tolerates a variety of aliphatic and aryl aldehydes as well as imines. Employing chiral phosphoric acids allows for the synthesis of 1,3-dioxolane and 1,3-oxazolidine products in modest enantioselectivity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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11. The stereochemistry of the 1,3-dioxolane was confirmed using nuclear Overhauser effect (NOE) experiments on the minor diastereomer.
12. A 1.5 dram vial was charged with a magnetic stir bar, 4-methyl-4-hydroxycyclohexa-2,5-dienone **1** (0.25 mmol, 1.0 equiv), diphenylphosphinic acid (18 mg, 0.025 mmol, 0.1 equiv), aldehyde/imine (0.31 mmol, 1.25 equiv), and 1,2-dichloroethane or dichloromethane (1.0 mL, 0.25M). The vial was then sealed and stirred at room temperature until the starting material disappeared by TLC (6–48h). In some cases the reaction was heated to 45 °C. The reaction was concentrated in vacuo. Flash column chromatography 10–20% (hexanes:ethyl acetate) of the resulting clear or yellow residue gave the analytically pure product in high diastereoselectivity as a white solid or clear oil. Some products decompose slowly upon treatment with SiO₂ (via acetal hydrolysis) so fast column chromatography is optimal.
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• *Previous Work (Rovis⁸):*

• *This Work:*

Scheme 1.
Acetalization/Oxa-Michael Cascade

Scheme 2.

Aldehyde substrate scope (dr indicates stereochemistry at acetal wrt to ring juncture; dr at ring juncture is >20:1 cis)

Scheme 3.

Quinol substrate scope (dr indicates stereochemistry at acetal wrt to ring juncture; dr at ring juncture is >20:1 cis)

Scheme 4.

Imine substrate scope (dr indicates stereochemistry at acetal wrt to ring juncture; dr at ring juncture is >20:1 cis)

Scheme 5.
Enantioselective synthesis of 1,3-oxazolidine **5c**

Table 1Optimization of Reaction Conditions^a

Entry	Catalyst	Yield(%)	dr ^b
1	Amberlyst-15	93	1:1
2	TsOH	88	1.6:1
3	F ₃ CSO ₃ H	50	1.6:1
4	H ₃ PO ₄	85	1.9:1
5	(+)-CSA	90	2.2:1
6	HCl _{aq}	67	2.2:1
7	TFA	77	14:1
8	Me ₂ PO ₂ H	90	14:1
9	PhPO ₃ H	71	17:1
10	Ph ₂ PO ₂ H	92	>20:1
11 ^c	Ph ₂ PO ₂ H	91	>20:1
12 ^d	Ph ₂ PO ₂ H	85	17:1

^a Conditions: quinol **1** (1 equiv), *i*-PrCHO (1.25 equiv), 0.25M.^b Diastereoselectivity determined by ¹H NMR of unpurified reaction mixture.^c Ph₂PO₂H (5 mol %) in dichloroethane (DCE) at 45 °C.^d 10 mol % Ph₂PO₂H with 10 eq H₂O.

Table 2

Mechanistic Studies

Entry	Initial dr of 3aa	Catalyst	Product dr
1	20:1	Amberlyst-15	4:1
2	1:1	$\text{Ph}_2\text{PO}_2\text{H}$	1:1
3	20:1	$\text{Ph}_2\text{PO}_2\text{H}$	20:1

Table 3

Enantioselective Acetalization/Oxa-Michael Cascade

Entry	Catalyst	Temp. (°C)	Yield (%)	dr	ee (%)
1	A	23	89	9:1	10
2	A	-78	69	>20:1	35
3	B	-78	71	>20:1	11
4	C	-78	63	>20:1	41
5	D	23	26	>20:1	45
6	D	-78	<5	-	-
7	E	23	44	8:1	38
8	F	23	36	15:1	10