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Proline-Mediated Enantioselective Construction of Tetrahydropyrans via a Domino Aldol/Acetalization Reaction

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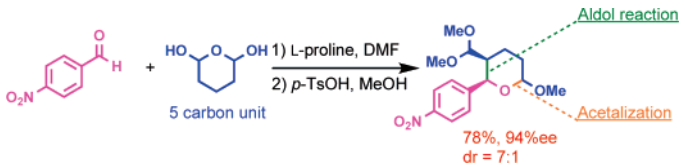
ABSTRACT



Highly enantioselective synthesis of tetrahydropyrans was accomplished via a domino proline-mediated aldol reaction/intramolecular acetal formation from an aldehyde and inexpensive aqueous tetrahydro-2*H*-pyran-2,6-diol as a five-carbon unit.

Tetrahydropyrans are found in many biologically active molecules and natural products.[1] Much effort has been devoted to the development of enantioselective syntheses of these heterocycles,[1] and several methods, including the Prins cyclization from optically active homoallylic alcohol,[2] an asymmetric catalytic hetero-Diels−Alder reaction,[3] and 1,5-cyclization,[4] have been reported. It is desirable to synthesize the tetrahydropyran moiety with high enantioselectivity in a minimum of steps from the readily available starting materials.

Organocatalysis is a rapidly expanding field in organic synthesis, and many organocatalyst-mediated reactions have been developed in recent years.[5] Domino reaction is a powerful method for the synthesis of complex molecules in a short sequence, and several enantioselective domino reactions have been developed.[6] Recently, organocatalysts have also been applied to the synthesis of complex molecules by domino reactions from simple starting materials.[7] We have reported the highly enantioselective synthesis of optically active cyclohexane derivatives by a domino Michael−Henry reaction of commercially available aqueous tetrahydro-2*H*-pyran-2,6-diol and nitroalkenes catalyzed by diphenylprolinolsilyl ether.[8] Because pentane-1,5-dial, a synthetically useful five-carbon unit, is generated under equilibrium conditions from inexpensive aqueous tetrahydro-2*H*-pyran-2,6-diol, this reagent would be successfully utilized for the formation of optically active tetrahydropyrans by the domino aldol[9]/acetal formation catalyzed by organocatalysis in the presence of water,[10] as shown in Scheme 1. That is,

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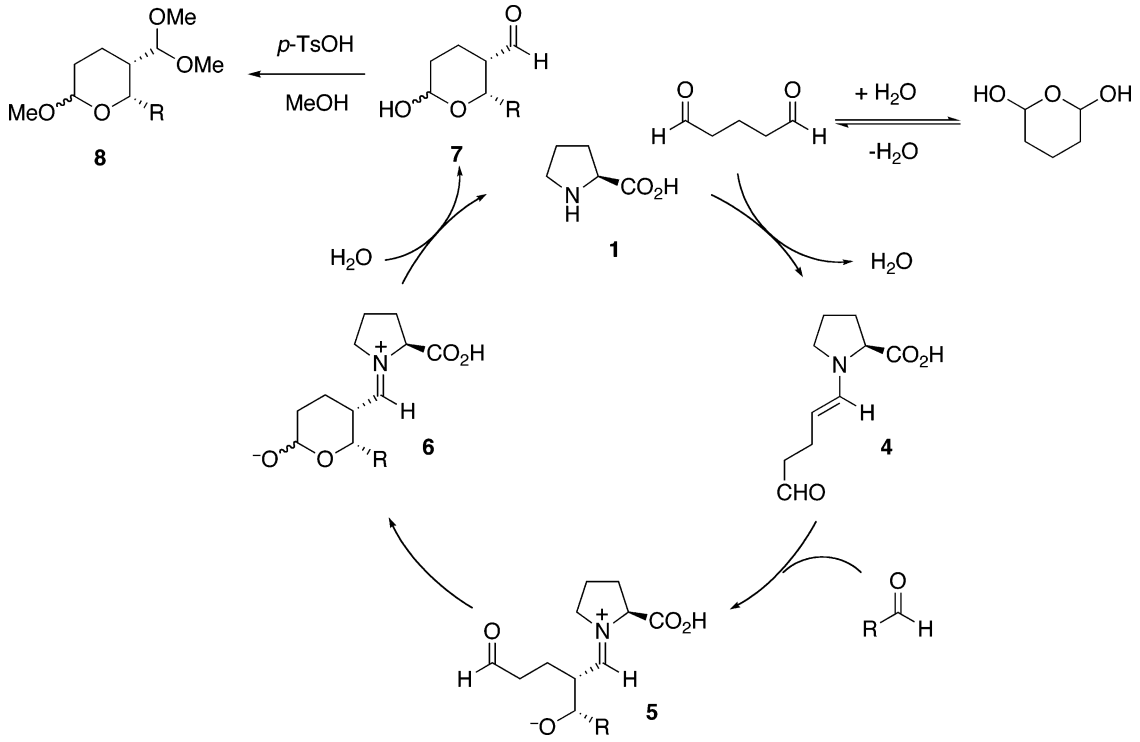
Scheme 1. Reaction Mechanism of Proline-Mediated Aldol, Followed by Acetal Formation



pentane-1,5-dial, generated from tetrahydro-2*H*-pyran-2,6-diol under equilibrium conditions, would react with an organocatalyst such as proline (**1**) to generate enamine **4**. Enamine **4** would react with an aldehyde to generate **5** via an aldol reaction, followed by acetal formation to provide tetrahydropyran **7** with regeneration of proline (**1**). Because tetrahydro-2*H*-pyran-2,6-diol is available as an aqueous solution,[11] these reactions have to be carried out in the presence of water or under aqueous conditions. We[12] and other groups[13,14] have shown that some of the aldol reactions proceed enantioselectively in the presence of water or under aqueous conditions. Thus, it is expected that aqueous tetrahydro-2*H*-pyran-2,6-diol would be employed directly in the domino aldol/acetal formation reaction. Successful realization of this scenario will be described in this paper.

First, we chose a reaction of *p*-nitrobenzaldehyde and aqueous tetrahydro-2*H*-pyran-2,6-diol as a model reaction, and L-proline (**1**) was employed as an organocatalyst. Because the adduct **7a** (R = 4-NO_2Ph) was found to be unstable and some degradation occurred during the purification by column chromatography, **7a** was converted to the stable methyl acetal **8a**, which was isolated. After completion of the aldol/cyclization reaction, an aqueous workup was carried out to remove the catalyst. Treatment of the crude mixture with MeOH in the presence of *p*-toluenesulfonic acid gave methyl acetal **8a**. Because four isomers (anti, syn aldol products and α and *β* anomers) are formed, α,*β*-methyl acetals of the major aldol product (anti isomer, vide infra) can be separated and their enantiomeric excesses can be determined. Both enantioselectivities of α and *β* anomers had the same value.

The activity of the organocatalyst was examined in detail. Siloxyproline **2**[12a,e] and surfactant−proline conjugated catalyst **3**[12b] (Figure 1), which promote highly enantioselective

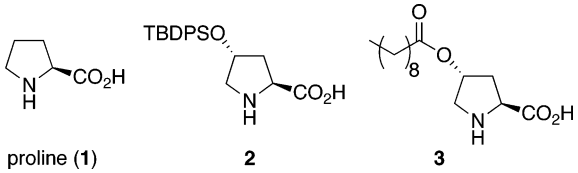


Figure 1. Organocatalysts examined in the present study.

aldol reaction in the presence of water, are found to be as effective as proline, producing slightly higher diastereo- and enantioselectivities (Table 1, entries 2 and 4). Because proline is inexpensive and both enantiomers are readily available,

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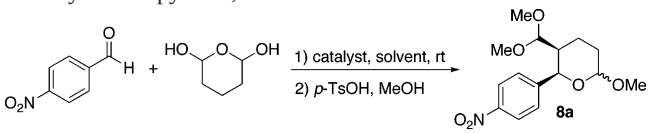
Table 1. Effect of Catalyst and Solvent in the Reaction of *p*-Nitrobenzaldehyde and Aqueous Tetrahydro-2*H*-pyran-2,6-diol[a]



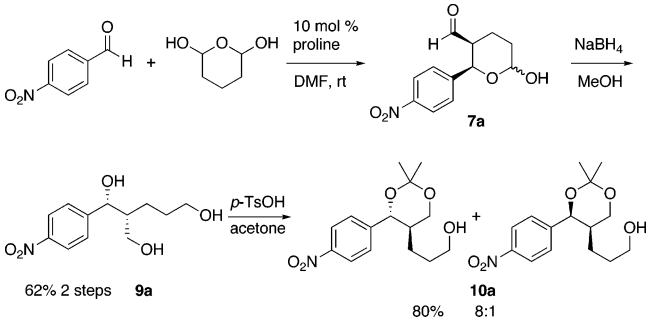
entry	cat.	solvent	time (h)	yield (%)[b]	de[c]	ee (%)[d]
1	**1**	DMF	12	78	7/1	94
2	**2**	DMF	12	74	10/1	98
3	**2**	*e*	20	<10		
4	**3**	DMF	20	70	9/1	96
5	**1**	DMSO	16	72	5/1	94
6	**1**	CH_2Cl_2	24	nr		
7	**1**	MeOH	20	27	2/1	79

[a] Conditions: *p*-nitrobenzaldehyde (1.0 mmol), aqueous tetrahydro-2*H*-pyran-2,6-diol (1.2 mmol), catalyst (0.1 mmol), solvent (1.0 mL), rt. [b] Isolated yield of four diastreomers. [c] Diastereoselectivity of the aldol reaction determined by ^{1}H NMR of the intermediate aldehyde before acetal protection by integration of aldehyde peaks. [d] The enantiomeric excess of the major isomer of the methyl acetal. [e] No organic solvent.

screening of the solvent was conducted using proline (**1**) as a catalyst, which showed that DMF is a good choice. The reaction was found to proceed in the presence of 10 mol % of proline in DMF, to produce methyl acetal **8a** in 78% yield with 94% enantiomeric excess after treatment of the aldol product with MeOH and *p*-TsOH (entry 1).

To determine the relative configuration of **8a**, the following transformation was performed as shown in Scheme 2.

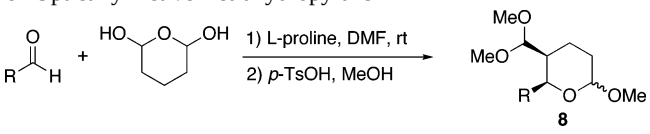
Scheme 2. Determination of Relative Configuration



After the first aldol reaction, inseparable anti and syn isomers **7a** were formed. The mixture was reduced with $NaBH_4$ in MeOH, producing the triol **9a** in 62% yield as a diastereomeric mixture. When triol **9a** was treated with acetone in the presence of *p*-TsOH, acetals **10a** were generated in 80% yield in an 8:1 ratio. The configuration of the major isomer was determined as an anti isomer by analysis of its NMR spectrum.

Because such good results were obtained with the model reaction, the generality of the reaction was investigated, with the results summarized in Table 2. A catalytic amount (10 mol %) of proline can promote the reaction efficiently in the cases of electron-deficient aldehydes such as *p*-, *m*-, and *o*-nitrobenzaldehydes and *p*-trifluoromethyl-, *p*-cyano-, and

Table 2. Organocatalytic Reaction of Aqueous Tetrahydro-2*H*-pyran-2,6-diol with Aldehydes for the Formation of Optically Active Tetrahydropyrans[a]



entry	R	conditions	time (h)	yield (%)[b]	de[c]	ratio α/β[d]	ee (%)[e]
1	4-$NO_2C_6H_4$	A	12	78	7/1	60/40	94
2	3-$NO_2C_6H_4$	A	14	60	4/1	65/35	99
3	2-$NO_2C_6H_4$	A	24	50	4/1	60/40	93
4	4-$CF_3C_6H_4$	A	16	71	7/1	65/35	97
5	4-CNC_6H_4	A	16	63	4/1	60/40	95
6	4-$TfOC_6H_4$	A	24	52	4/1	60/40	97
7	2-ClC_6H_4	B	48	67	4/1	65/35	99[f]
8	4-BrC_6H_4	B	48	59	4/1	60/40	95
9	Ph	B	48	42	4/1	60/40	97

[a] Condition A: 1.2 equiv of aqueous tetrahydro-2*H*-pyran-2,6-diol, 10 mol % proline. Condition B: 3 equiv aqueous tetrahydro-2*H*-pyran-2,6-diol, 30 mol % proline. [b] Isolated yield (after 2 steps). [c] Diastereoselectivity (anti:syn) of the aldol reaction. Calculated from crude ^{1}H NMR of first step. [d] Calculated from crude ^{1}H NMR after acetalization step. [e] Determined by chiral HPLC. [f] Determined after reduction of chloro by $LiAlH_4$.

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p-trifluoromethanesulfonylbenzaldehydes, to produce the corresponding tetrahydropyran derivatives with excellent enantioselectivity (entries 1−6, conditions A).

In the reaction of arylaldehydes without strong electron-withdrawing substituents, such as *o*-chlorobenzaldehyde, *p*-bromobenzaldehyde, and benzaldehyde, the reaction proceeds in the presence of 30 mol % of the catalyst using three equivalents of aqueous tetrahydro-2*H*-pyran-2,6-diol to produce the tetrahydropyran derivatives with excellent enantioselectivity (entries 7−9, conditions B).

The absolute configuration was determined by X-ray crystallographic analysis of the β-methyl acetal **8a** derived from *p*-nitrobenzaldehyde (Figure 2).[15] This absolute configuration is in accordance with that expected from the L-proline-mediated aldol reaction.[16]

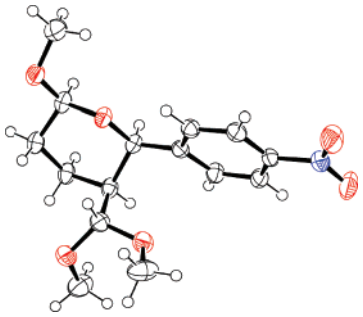
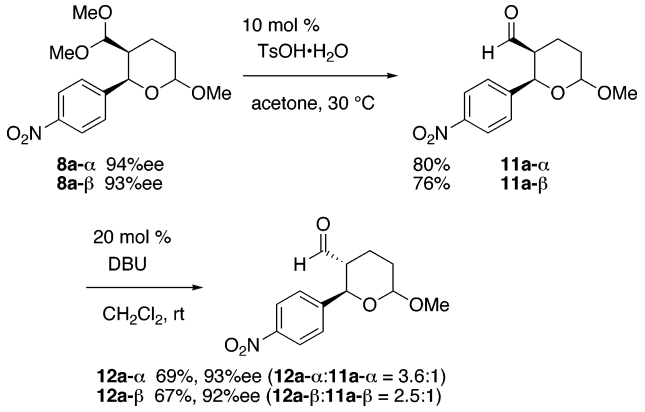


Figure 2. ORTEP drawing of **8a**-β. Displacement ellipsoids are drawn at the 50% probability level.

Tetrahydropyrans **8** have two dialkyl acetal moieties. One is the dimethyl acetal and the other is the monomethyl acetal. From a synthetic point of view, selective discrimination of these two moieties has to be achieved. The dimethyl acetal moiety of both α and β anomers **8a** (R = 4-NO_2Ph) is deprotected selectively to the corresponding monomethyl acetal **11** by treatment with *p*-toluenesulfonic acid in acetone at 30 °C in good yield. When **11** was treated with base (DBU) in CH_2Cl_2 at room temperature, isomerization occurred to produce the trans isomer predominantly, starting from both α,β-cis anomers without compromising the enantioselectivity. Thus, by a combination of the present domino reaction and a successive isomerization reaction, both trans- and cis-substituted tetrahydropyran derivatives are obtained with excellent optical purities.

Scheme 3. Isomerization of Tetrahydropyran **8a**



In summary, we have developed an enantioselective synthetic method for substituted tetrahydropyrans via a domino proline-mediated aldol reaction/acetal cyclization reaction. Pentane-1,5-dial, a useful five-carbon unit, is generated from inexpensive aqueous tetrahydro-2*H*-pyran-2,6-diol under equilibrium conditions. It is a noteworthy advantage of the organocatalyst that the reaction proceeds efficiently with excellent enantioselectivity under aqueous conditions. Because the obtained cis-substituted tetrahydropyran derivative can be transformed into the trans isomer without compromising the enantioselectivity, the present method would be an effective method for the preparation of substituted chiral tetrahydropyran derivatives.

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Supporting Information Available: Detailed experimental procedures, full characterization, and copies of ^{1}H and ^{13}C NMR and IR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) A CIF file for **8a**-β was deposited to the Cambridge Crystallographic Data Centre with the deposition number CCDC 678278. Copies of the data can be obtained free of charge via http://www.ccdc.cam.ac.uk or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax +44(1223)336033; deposit@ccdccam.ac.uk.

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