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Organocatalytic α-hydroxymethylation of cyclopentanone with aqueous formaldehyde: Easy access to chiral δ-lactones

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ABSTRACT

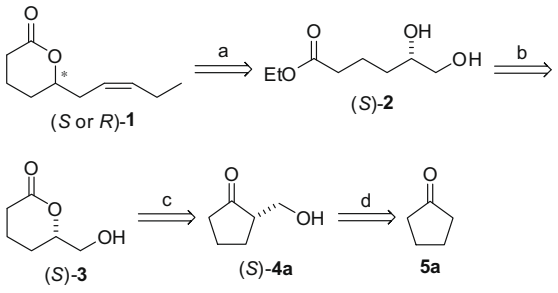
Optically active lactones are important synthons in perfume and aroma manufacturing. Therefore, developments of efficient asymmetric syntheses are desired. Organocatalytic asymmetric α-hydroxymethylations of cyclopentanone with aqueous formaldehyde have been developed, to furnish the corresponding α-(hydroxymethyl)cyclopentanone with high enantioselectivity. Further chemical transformation of α-(hydroxymethyl)cyclopentanone gave the key intermediate for jasmine lactone, which is widely found in fruits and flowers.

Chiral δ-lactones as represented by jasmine lactone (**1**) are widely found in fruits and flowers. Enantiomers of fragrances generally show characteristic differences in odor, therefore, the enantiomeric composition is an important property of all living organisms. Both enantiomers of the lactone **1** are found in nature. Interestingly (*R*)-lactone **1** is extracted from *Jasminum* flowers,[1] whereas only (*S*)-enantiomer is biosynthesized in the *Tuberose* species.[2] Here we report the formal synthesis[3] of both enantiomers of **1** through organocatalytic α-hydroxymethylation of cyclopentanone with aqueous formaldehyde.

The retrosynthesis of **1** is depicted in Scheme 1. Both enantiomers of **1** are available from the diol (*S*)-**2**.[3a] The diol is generated from the δ-hydroxymethyl lactone (*S*)-**3** by employing a ring-opening reaction. The chiral lactone (*S*)-**3** is obtained by Baeyer–Villiger oxidation of the chiral α-(hydroxymethyl)cyclopentanone (*S*)-**4a** prepared from cyclopentanone (**5a**). Although the final intermediate (*S*)-**2** is synthesized in only three steps from cyclopentanone, enantioselective α-hydroxymethylation of **5a** is the most challenging transformation. Prior to this Letter Baeyer–Villiger oxidations of racemic α-(hydroxymethyl)cyclopentanone **4a** catalyzed by engineered microorganisms were employed, but the chiral ketone **4a** was isolated in low enantiomeric excess (<12% ee).[4]

Recently, catalytic asymmetric α-hydroxymethylation in an aqueous solution of formaldehyde was intensively investigated. Water-compatible transition metal-complexes catalyzed the α-hydroxymethylation of silicon enolates with aqueous formaldehyde, achieving excellent enantiofacial selectivity.[5] Organocatalysis is another useful tool for performing the direct α-hydroxymethylation of ketones with aqueous formaldehyde, in which over 90% enantiomeric excess is achieved.[6,10] To the best of our knowledge, this pioneering work is a practical method for the preparation of chiral α-(hydroxymethyl)cyclohexanone, but has not yet been investigated for the synthesis of chiral cyclopentanone derivatives such as **4a**. Our recent research focuses on organocatalytic aqueous reactions,[7] therefore we carefully reinvestigated the α-hydroxymethylation of cyclopentanone (**5a**).

L-Proline (**7**), which is one of the most effective organocatalytic reagents when employing a cyclohexanone donor,[6,10] catalyzed the α-hydroxymethylation of **5a**. However, low yield and enantioselectivities were observed with **5a** in nonpolar solvent such as CH_2Cl_2 (y. 23%, 24% ee), $CHCl_3$ (y. 20%, 7% ee), and THF (y. 15%, 22% ee). On



Scheme 1. Retrosynthesis of (*S*)-jasmine lactone ((*S*)-**1**) from cyclopentanone (**5a**): (a) see Ref. 3a; (b) ring-opening reaction; (c) Baeyer–Villiger oxidation; (d) α-hydroxymethylation.

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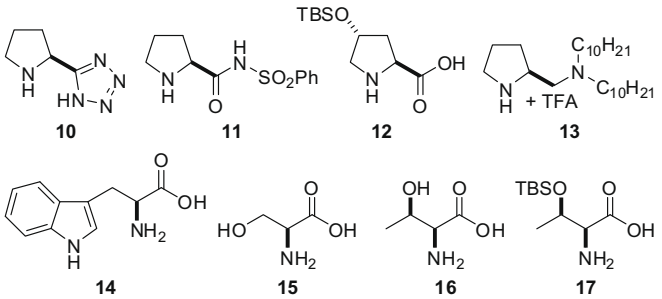
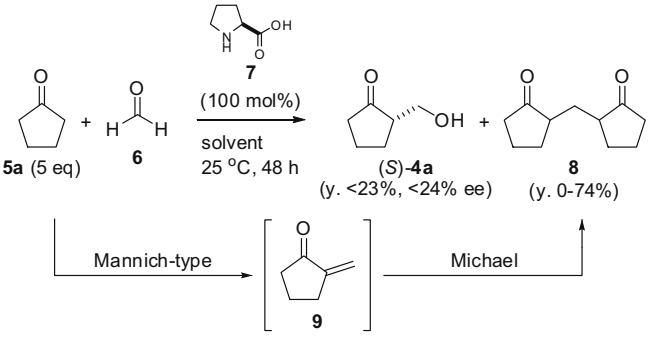


Figure 1. Small amine molecules as organocatalyst.

the other hand, in polar solvent such as DMSO, DMF, MeOH, EtOH, and 2-PrOH the diketone **8**, derived through Mannich-type/Michael domino reaction, was obtained as a sole product with no diastereoselectivity (Scheme 2).

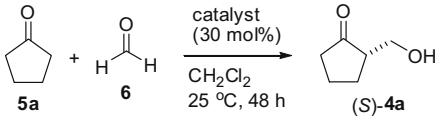
Therefore, small amine molecules were screened as an organocatalyst as shown in Fig. 1 and Table 1. Well-known secondary amine molecules **10**[8] and **11**,[9] which show high yields and enantiomeric excess in organocatalytic aldol reactions, were ineffective in aqueous α-hydroxymethylations (Table 1, entries 2 and 3). Due to the importance of efficient water-compatible organocatalytic reactions special catalysts such as L-siloxyproline **12**,[10] diamine/TFA combination catalyst **13**,[7] and tryptophan **14**[11] have been developed and emerged in aqueous direct aldol reactions without the addition of any organic solvents. Aqueous α-hydroxymethylations using these water-compatible catalysts were subsequently examined. The siloxyproline **12** and the diamine/TFA combination catalyst **13** bearing long alkyl groups catalyzed the reaction to give the aldol product **4** with slightly better yields (entries 4 and 5). Although yield is very low, the simple primary amino acid tryptophan **14** showed better enantioselectivity than the secondary amino acid proline **7** (entry 1 vs entry 6). Thus, we screened natural primary amino acids in the α-hydroxymethylation reaction of cyclopentanone (**5a**). We found that β-hydroxy amino acids such as L-serine (**15**) and L-threonine (**16**) afforded high enantioselectivity (entries 7 and 8). In particular, L-threonine (**16**) improved the enantioselectivity as well as chemical yield (42% yield, 75% ee).

Using L-threonine (**16**) as the primary catalyst, a series of different solvent systems were evaluated as shown in Table 2. Alcohols, DMF, and DMSO were inferior solvents in terms of product yield (entries 1, 4, and 6–8). Hexane, toluene, and diethyl ether were also poor solvents, probably due to low solubility of the catalyst **16** in these solvents (entries 2, 3, and 5). The reaction in cyclopentanone (**5a**) without addition of any conventional organic co-solvent resulted in good enantiomeric excess but low chemical yield (entry 9). Halogenated solvent, acetonitrile, and THF afforded good ee in moderate yield (entries 10–13). 1,4-Dioxane afforded the highest



Scheme 2. L-Proline (**7**) catalyzed α-hydroxymethylation of cyclopentanone (**5a**).

Table 1
α-Hydroxymethylation of cyclopentanone (**5a**) with aqueous formaldehyde (**6**) by use of various organocatalysts[a]



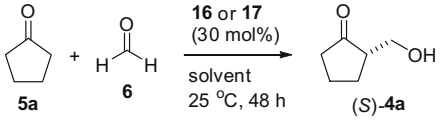
Entry	Catalyst	Yield[b] (%)	ee[c,d] (%)
1	**7**	14	22
2	**10**	3	ND
3	**11**	2	ND
4	**12**	12	ND
5[e]	**13**	10	ND
6	**14**	5	45
7	**15**	6	58
8	**16**	42	75

[a] Conditions: small amine (30 mol %), **5a** (5 equiv), and **6** (1.0 mmol) in CH_2Cl_2 (1.0 mL).
[b] Determined by GC (TC-17) of the crude product.
[c] Determined by chiral-phase HPLC analysis of its benzoate. HPLC (Daicel CHIRALCEL AD-H, hexane/2-PrOH = 97:3, flow rate 0.5 mL/min, λ = 254 nm); t_R = 32.06 (*R*), 38.13 (*S*) min.
[d] ND = not determined.
[e] The reaction was carried out using **5a** (1 equiv), **6** (10 equiv), and **13** (10 mol %) in solvent-free condition.

ee and chemical yield of the solvents tested. Therefore, we chose 1,4-dioxane as a solvent for further study (entry 14). Prolonged reaction time improved chemical yield of **4a** up to 60% (entry 15). Both enantiomers of threonine (**16**) are readily commercially available, and they are generally less expensive than proline (**7**). Under the same conditions, D-threonine furnished the opposite enantiomer (*R*)-**4a** in 48% yield with 85% ee (entry 16).

Water molecules are essential in aldolase-catalyzed reactions through proton relay,[12] furthermore, in primary organocatalysis

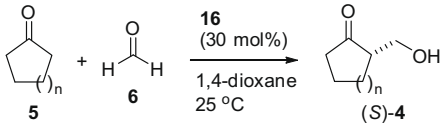
Table 2
α-Hydroxymethylation of cyclopentanone (**5a**) with aqueous formaldehyde (**6**) by use of L-threonine derivatives[a]



Entry	Catalyst	Solvent	Yield[b] (%)	ee[c,d] (%)
1	**16**	MeOH	2	ND
2	**16**	Hexane	5	ND
3	**16**	Toluene	7	ND
4	**16**	DMF	7	ND
5	**16**	Et_2O	8	ND
6	**16**	EtOH	8	ND
7	**16**	DMSO	12	ND
8	**16**	2-PrOH	14	ND
9	**16**	None	24	75
10	**16**	$CHCl_3$	36	73
11	**16**	CH_2Cl_2	42	75
12	**16**	MeCN	42	71
13	**16**	THF	43	76
14	**16**	1,4-Dioxane	50	82
15[e]	**16**	1,4-Dioxane	60	76
16	*ent*-**16**	1,4-Dioxane	48	−85
17[f]	**16**	1,4-Dioxane	36	66
18	**17**	CH_2Cl_2	46	20
19	**17**	1,4-Dioxane	26	9

[a,b,c,d] See Table 1.
[e] The reaction was carried out for 144 h.
[f] The reaction was carried out using dry formaldehyde gas (excess) instead of aqueous formaldehyde.

Table 3
α-Hydroxymethylation of cycloalkanones (**5**) with aqueous formaldehyde (**6**) by use of L-threonine (**16**)[a]



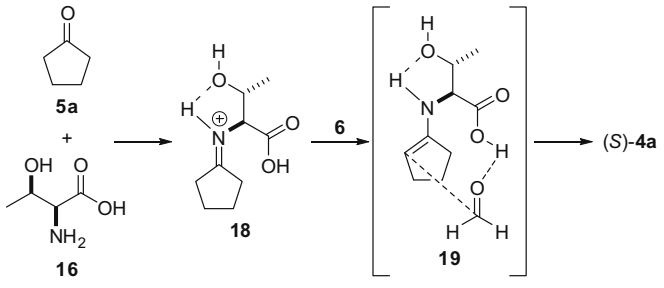
Entry	*n*	Time (h)	Yield[b] (%)	ee[c] (%)
1	1	48	50	82
2	2	48	63	93
3	3	96	31	97
4	4	96	47	93

[a,b,c] See Table 1.

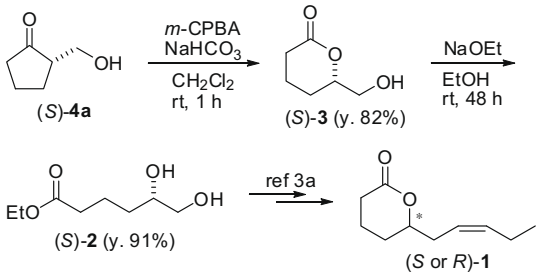
water significantly accelerated the aldol reaction.[13] Aqueous formaldehyde is apparently more reactive and stereoselective than dry formaldehyde gas (entry 17). To evaluate the influence of the hydroxy moiety, *tert*-butyldimethylsilyl protected L-threonine **17** was investigated in α-hydroxymethylation. Chemical yields were slightly low, but the enantioselectivity diminished (entries 18 and 19). This result suggested that a hydrogen bond is a key to enhancing the reactivity as well as enantioselectivity.

Encouraged by these results, we further examined the scope of this class of aldol reactions by utilizing a series of cycloalkanone donors **5** with L-threonine catalyst **16** under the same reaction conditions (Table 3).[14] Cyclohexanone (**5b**) was a good donor: the reaction provided the α-(hydroxymethyl)ketone (*S*)-**4b** in 63% yield with 93% ee (entry 2). When cycloheptanone (**5c**) was used as a donor, the expected α-(hydroxymethyl)ketone **4c** was obtained with excellent enantioselectivity but low chemical yield (entry 3). The reaction of cyclooctanone (**5d**) donor afforded α-(hydroxymethyl)ketone **4d** in moderate chemical yield with high enantiomeric excess (entry 4). Chemical yields of the desired products **4** are not as high as desired, however; these are first examples of preparing chiral five-, seven-, and eight-membered α-(hydroxymethyl)cycloalkanones,[15] which are potential chiral synthons in natural product synthesis.

The major α-(hydroxymethyl)ketone **4a** was determined to have (*S*)-configuration by comparison with the reported optical rotation value of δ-lactone **3** and the diol (*S*)-**2** derived from **4a** via Bayer–Villiger oxidation as described below.[16] Therefore, L-threonine catalyzed a *re*-facial attack on the enamine intermediate **19** (Scheme 3). This result is in accord with previously proposed L-proline-based aldol transition states.[6,17,10] We propose that L-threonine catalyzed the aldol reaction with the following mechanism, although the exact reason for stabilization is not clear.[18] The iminium intermediate **18** derived from nucleophilic addition of the catalyst **16** to the ketone **5a** is stabilized by intramolecular hydrogen bonding. The stabilized iminium intermediate **18** is tautomerized to the enamine intermediate, which reacts with formaldehyde **6** through the transition state **19**.



Scheme 3. Proposed enamine mechanism and transition state.



Scheme 4. Formal synthesis of chiral jasmine lactone (**1**).

Finally, we examined a formal synthesis of jasmine lactone (**1**) as shown in Scheme 4. The ketone **4a** (82% ee) was stereoselectively oxidized with *m*-chloroperbenzoic acid to obtain the corresponding δ-lactone (*S*)-**3** in 82% yield.[19] The δ-lactone (*S*)-**3** was treated with sodium ethoxide in ethanol to afford the corresponding diol (*S*)-**2** in 91% yield, which is a precursor for both enantiomers of chiral jasmine lactone (**1**) via reported transformations.[3a]

In summary, L-threonine demonstrated good reactivity and enantioselectivity in this class of direct α-hydroxymethylation of cycloalkanones with aqueous formaldehyde. This method provides direct access to chiral α-(hydroxymethyl)cycloalkanone, which are versatile precursors for chiral lactones.

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14. *Typical procedure for* Table 3, *entry 1*: To the solution of cyclopentanone (**5**, 463 μL, 5 mmol) in dichloromethane (1.0 mL) L-threonine (**16**, 36 mg, 0.3 mmol) was added. After stirring for 1 h at 25 °C, 37% aq formaldehyde solution (**6**, 75 μL, 1 mmol) was added. The reaction mixture was stirred for

48 h, then purified by flash silica gel column chromatography without further workup to provide aldol product (**4a**, 57 mg, 0.5 mmol, 50% yield).
15. Reactions of cyclododecanone (12-membered) and/or cyclopentadecanone (15-membered) with aqueous formaldehyde in the presence of L-threonine resulted in no reaction.
16. Compound (*S*)-**3**: $[\alpha]_D^{19}$ +28.0 (*c* 0.6, $CHCl_3$), (lit. $[\alpha]_D^{20}$ +34.5 (*c* 0.6, $CHCl_3$, 98% ee); Compound (*S*)-**2**: $[\alpha]_D^{22}$ −14.7 (*c* 2.0, EtOH), (lit. $[\alpha]_D^{20}$ −14.1 (*c* 2.0, EtOH). Liu, Z.-Y.; Ji, J.-X.; Li, B.-G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3519.
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18. It has long been thought that a secondary enamine is better stabilized by hyperconjugation, whereas a primary amine gives the predominant imine form. However, recent advance on organocatalysis using primary amine, effective tautomerization of the iminium form to the enamine form proceeded, to construct carbon–carbon bond between the enamine and an acceptor progressed in a stereoselective fashion. See: Xu, L.-W.; Lu, Y. *Org. Biomol. Chem.* **2008**, *6*, 2047.
19. The δ-lactone (*S*)-**3** is a highly versatile intermediate, for example, in Corey's synthesis of leukotriene B. See: Corey, E. J.; Pyne, S. G.; Su, W. G. *Tetrahedron Lett.* **1983**, *24*, 4883.