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A Practical Synthesis of (*S*)-2-Cyclohexyl-2-phenylglycolic Acid via Organocatalytic Asymmetric Construction of a Tetrasubstituted Carbon Center

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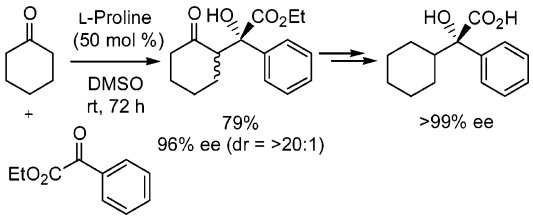
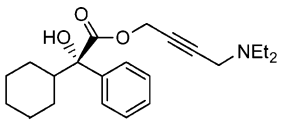
ABSTRACT

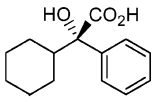


A concise and enantioselective synthesis of (*S*)-2-cyclohexyl-2-phenylglycolic acid as a key intermediate for (*S*)-oxybutynin is reported. The crucial asymmetric tetrasubstituted carbon center was constructed with excellent stereoselectivity through the proline-catalyzed direct asymmetric aldol reaction between cyclohexanone and ethyl phenylglyoxylate under mild conditions.

Racemic oxybutynin (ditropan) is a widely prescribed muscarinic receptor antagonist for the treatment of urinary frequency, urgency, and urge incontinence, but it causes side effects such as dry mouth, tachycardia, and mydriasis.[1] Since preliminary biological results suggested that (*S*)-oxybutynin (*S*)-**1** exhibits an improved therapeutic profile compared to the racemate, several groups have reported the asymmetric synthesis of (*S*)-2-cyclohexyl-2-phenylglycolic acid (*S*)-**2** as a key intermediate for the preparation of (*S*)-oxybutynin.[2,3] Some of these previous methods, however, require stoichiometric amounts of the chiral auxiliary, toxic reagents, or low-temperature reaction conditions. In this context, it would be a significant improvement to develop an alternative synthesis of (*S*)-**2** using an organocatalyst with the environmental advantages of mild and metal-free conditions in addition to the operational simplicity. Herein, we report a practical synthetic route to (*S*)-2-cyclohexyl-2-phenylglycolic acid (*S*)-**2** via a direct asymmetric aldol reaction catalyzed by L-proline.



(*S*)-Oxybutynin ((*S*)-**1**)



(*S*)-**2**

Our retrosynthetic analysis of (*S*)-**2** leads to the *β*-hydroxyketone **3** having a tetrasubstituted carbon center, which could

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(1) Thompson, I. M.; Lauvetz, R. *Urology* **1976**, *8*, 452.
(2) (a) Senanayake, C. H.; Fang, Q. K.; Grover, P.; Bakale, R. P.; Vandenbossche, C. P.; Wald, S. A. *Tetrahedron Lett.* **1999**, *40*, 819. (b) Grover, P. T.; Bhongle, N. N.; Wald, S. A.; Senanayake, C. H. *J. Org. Chem.* **2000**, *65*, 6283. (c) Bakale, R. P.; Lopez, J. L.; McConville, F. X.; Vandenbossche, C. P.; Senanayake, C. H. U.S. Patent 6140529.

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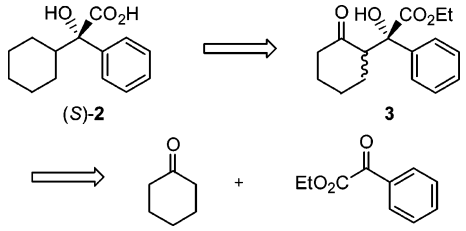
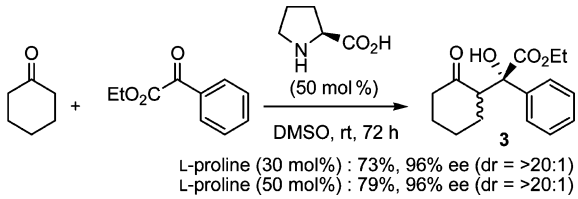
be constructed by organocatalytic direct asymmetric aldol reaction between cyclohexanone and phenylglyoxylate (Scheme 1).

Scheme 1. Retrosynthetic Analysis of (*S*)-**2**



To the best of our knowledge, however, such asymmetric transformation is unprecedented despite a number of recent reports on the development of the proline-catalyzed direct asymmetric aldol reactions based on pioneering works by Wiechert[4a] and Hajos[4b] in the early 1970s and by List and Barbas in 2000.[4c−m,5] Accordingly, we first focused on the development of the proline-catalyzed direct asymmetric aldol reaction between cyclohexanone and ethyl phenylglyoxylate. Gratifyingly, in preliminary studies on reaction conditions, we found that the reaction with a catalytic amount of L-proline (30 mol %) in DMSO at room temperature gave the desired aldol adduct **3** in good yield (73%) with excellent diastereo- and enantioselectivity (dr = >20:1, 96% ee). Furthermore, using 50 mol % of L-proline, the yield of **3** was improved to 79% without loss of stereoselectivity (Scheme 2).

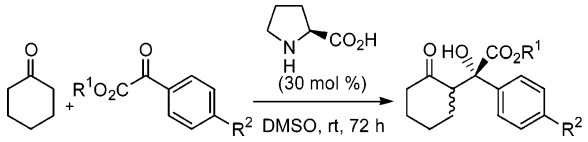
Scheme 2. Proline-Catalyzed Aldol Reaction for the Construction of a Tetrasubstituted Carbon Center



Similar proline-catalyzed direct asymmetric aldol reactions between cyclohexanone and phenylglyoxylate derivatives are also investigated as shown in Table 1. Use of methyl phenylglyoxylate showed excellent diastereo- and enantioselectivity (entry 1). Ethyl phenylglyoxylates possessing electron-withdrawing groups at the para position were also suitable substrates for the present reaction (entries 2 and 3). In addition, a substrate with an electron-donating substituent on the aromatic ring exhibited a virtually complete stereoselectivity at the expense of chemical yield (entry 4).

(3) (a) Masumoto, S.; Suzuki, M.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2002**, *43*, 8647. (b) Gupta, P.; Fernandes, R. A.; Kumar, P. *Tetrahedron Lett.* **2003**, *44*, 4231. (c) Masumoto, S.; Suzuki, M.; Kanai, M.; Shibasaki, M. *Tetrahedron* **2004**, *60*, 10497.

Table 1. Proline-Catalyzed Asymmetric Aldol Reaction between Cyclohexanone and Phenylglyoxylate Derivatives[a]

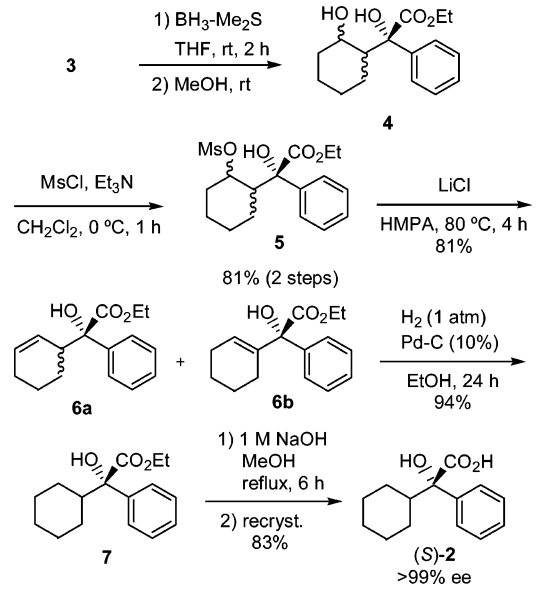


entry	R^1	R^2	yield[b] (%)	dr[c]	% ee[d]
1	Me	H	89	>20/1	98
2	Et	CF_3	>99	>20/1	97
3	Et	Cl	95	>20/1	96
4	Et	Me	45	>20/1	>99

[a] The reaction of phenylglyoxylate (0.25 mmol) with cyclohexanone (0.25 mL, 2.4 mmol) in DMSO (0.25 mL) was carried out in the presence of 30 mol % of L-proline at room temperature. [b] Isolated yield after silica gel chromatography. [c] Determined by ^{1}H NMR. [d] The ee of major isomer was determined by HPLC on a Chiralpak AD-H column with hexane/2-propanol (90/10).

With this information in hand, we studied the conversion of aldol product **3** to (*S*)-2-cyclohexyl-2-phenylglycolic acid (*S*)-**2** (Scheme 3). First, attempted reduction of the ketone carbonyl group of **3** to methylene under Wolff−Kishner conditions was unsuccessful. In addition, reduction of **3** with $NaBH_4$ to the diol **4** gave the undesired enone resulting from the β-hydroxy elimination. On the other hand, the treatment of **3** with BH_3−Me_2S in THF at room temperature and subsequent addition of methanol gave **4** cleanly, which was reacted with methanesulfonyl chloride and triethylamine at room temperature to furnish the mesylate **5** in 81% yield from **3**. Unfortunately, however, the reduction of **5** with Ph_3SiH under radical condition gave a complex mixture. We then turned our attention to induce the olefin formation by the elimination of methanesulfonic acid from **5**. Unexpectedly, the elimination of methanesulfonic acid using DBU or

Scheme 3. Synthesis Route of (*S*)-**2**



KO*t*-Bu resulted in formation of a mixture of **6a** and **6b** accompanied by large amounts of unknown byproducts. In contrast, substitution of the methanesulfonyloxy group in **5** with NaI or LiBr with concomitant elimination afforded **6a** and **6b** in moderate yields (44−54%). Furthermore, the elimination reaction using LiCl in HMPA proceeded smoothly to give **6a** and **6b** in good yield (81%). The resulting olefins **6a** and **6b** were hydrogenated to **7** at ambient temperature under hydrogen atmosphere (1 atm) with 10% Pd−C in ethanol. Hydrolysis of **7** in a mixture of methanol and 1 M NaOH (3:1, v/v) afforded crude (*S*)-2-cyclohexyl-2-phenylglycolic acid (*S*)-**2**. A single recrystallization from hexane/CH_2Cl_2 yielded optically pure (*S*)-**2** in good yield (83%, >99% ee). The absolute stereochemistry of (*S*)-**2** was determined by comparison of the optical rotation and the HPLC retention time with literature values.[2a,b]

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Supporting Information Available: Detailed experimental procedure as well as spectroscopic characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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