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Three-Pot Synthesis of Chiral *Anti*-1,3-diols through Asymmetric Organocatalytic Aldol and Wittig Reactions Followed by Epoxidation and Reductive Opening of the Epoxide

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Cite This: *Org. Lett.* 2021, 23, 5896−5900 Read Online

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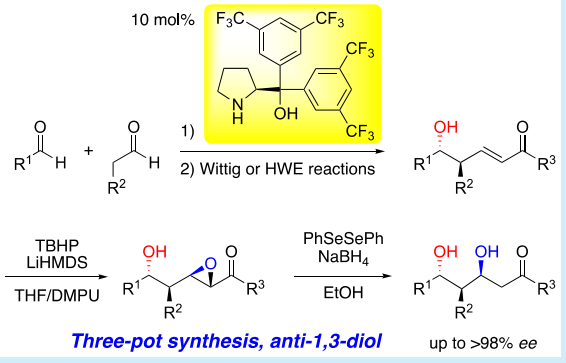
ABSTRACT: A three-pot asymmetric synthesis of the *anti*-1,3-diol unit was developed. In the first pot, enantioselective aldol reaction of aldehydes proceeds, catalyzed by organocatalyst, followed by either Wittig or Horner−Wadsworth−Emmons reactions to afford *δ*-hydroxy *α,β*-unsaturated carbonyls with excellent enantioselectivity. Diastereoselective hydroxy-directed *anti*-epoxidation proceeds in the next pot by the use of *tert*-BuOOH and LiHMDS. Reductive opening of the epoxide proceeds in a third pot to afford *anti-β,δ*-hydroxy carbonyl compounds with excellent diastereo- and enantioselectivity.

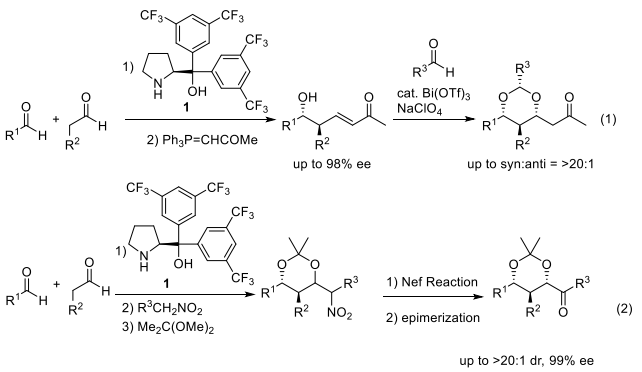


The *anti*-1,3-diol constitutes an important unit in organic chemistry because it is found in many natural products and medicines. The development of effective synthetic method of this unit is indispensable in synthetic organic chemistry. Several methods have been reported,[1] for instance, *anti*-selective reduction of *β*-hydroxy ketone using $Me_4NBH(OAc)_3$[2] or Tishchenko reduction catalyzed by SmI_2,[3] both of which were developed by Evans. Nucleophilic addition under chelation control[4] or reagent control[5] toward *β*-alkoxy or *β*-siloxy aldehyde is another widely used method.

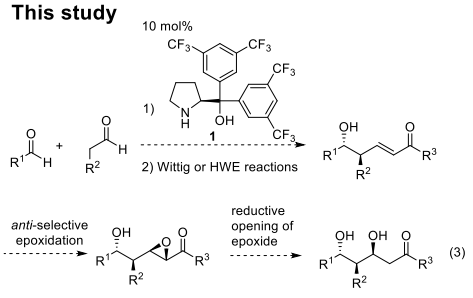
In thinking about the synthesis of chiral *anti*-1,3-diol unit, it is necessary to consider the availability of the starting materials. The total number of pots[6] from the starting materials to the 1,3-diols should also be considered. Namely, it is desired to devise an effective synthesis of chiral *anti*-1,3-diols with excellent enantioselectivity starting from the inexpensive starting materials with a small number of pots.

We developed diarylprolinol **1**, substituted with trifluoromethyl groups, as an effective organocatalyst for the asymmetric cross-aldol reaction of two different aldehydes.[7] The *β*-hydroxy aldehydes, which are generated with excellent enantioselectivity, are useful chiral building blocks. In fact, we recently reported a two-pot synthetic method for the synthesis of *syn*-1,3-diol units, through organocatalyst **1**-mediated aldol reaction, Wittig reaction, and acetalization, followed by $Bi(OTf)_3$-mediated oxy-Michael reaction (eq 1).[8] We also reported the three-pot synthesis of *syn-α,γ*-dihydroxycarbonyl units via organocatalyst **1**-mediated aldol reaction, Henry reaction, acetalization, Nef reaction, and epimerization (eq 2).[9] In these reactions, chiral *syn*-1,3-diol units are synthesized from

Our previous synthesis of *syn*-1,3-diol units



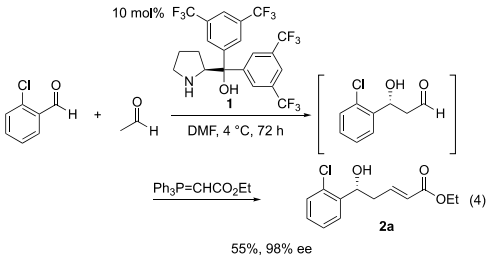
This study



Received: June 16, 2021
Published: July 27, 2021

readily available starting materials. As part of our continuing interest in the stereoselective synthesis of the 1,3-diol unit based on asymmetric aldol reaction, our next goal is the synthesis of the *anti*-1,3-diol unit. As *α,β*-epoxy carbonyl compounds can be converted into *β*-hydroxycarbonyl compounds through reductive opening of epoxide,[10] *anti*-1,3-diol units would be synthesized if the *anti*-selective epoxidation proceeds toward *δ*-hydroxy or *δ*-alkoxy *α,β*-unsaturated carbonyl compounds, which can be synthesized by our organocatalyst **1**-mediated cross-aldol reaction and Wittig reaction (eq 3). In this paper, we describe the successful realization of this scenario.

As a model substrate of the *δ*-hydroxy *α,β*-unsaturated carbonyl compounds, we selected (*R*)-ethyl 5-(*o*-chlorophenyl)-5-hydroxypent-2-enoate (**2a**), which is easily prepared by the asymmetric cross-aldol reaction of *o*-chlorobenzaldehyde and acetaldehyde catalyzed by diarylprolinol **1**,[7a] followed by Wittig reaction with ethyl (triphenylphosphoranylidene)-acetate in one-pot with excellent enantioselectivity (98% ee) (eq 4).



Diastereoselective epoxidation of **2a** was investigated (Table 1). Given that Rodriguez reported the stereoselective epoxidation of a *γ*-hydroxy *α,β*-unsaturated ester using *tert*-BuOOH (TBHP) and EtLi in THF and benzene as a solvent,[11] we first examined the use of these reaction conditions. Although the *anti*-isomer was obtained as the major product, the yield was low (entry 1). The use of MCPBA afforded both low yield and low selectivity.[12] When LiHMDS and TBHP were employed under dilute conditions in THF, good yield and high *anti*-selectivity were obtained (entry 3). In a mixture of THF and *N,N′*-dimethylpropyleneurea (DMPU), the reaction was fast and low concentration was not necessary (entries 4−7). At lower temperature (−40 °C), excellent yield and *anti*-selectivity were obtained (entry 7). NaHMDS and KHMDS were not effective (entries 8 and 9).

When the *δ*-hydroxy group of **2a** was protected as its *tert*-butyldimethylsilyl ether or *p*-methoxybenzyl ether (PMB), the reaction was slow and gave a low yield using LiHMDS in THF and DMPU at −40 °C (conditions given in Table 1, entry 7). The *syn*-isomer was generated as the major isomer with low selectivity (Figure 1). Thus, the *δ*-hydroxy group is essential for achieving good yield and excellent *anti*-selectivity.[13]

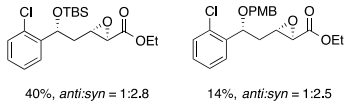
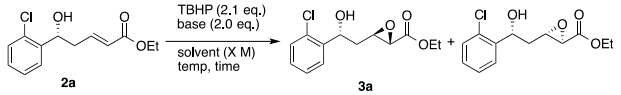


Figure 1. *δ*-Hydroxy protected substrates.

With the best reaction conditions determined (Table 1, entry 7), the generality of the reaction was investigated (Table 2). This is a two-pot reaction. The first pot reaction is an asymmetric aldol reaction, followed by Wittig reaction or Horner−Wadsworth−Emmons (HWE) reaction, and the second pot reaction is a stereoselective epoxidation reaction. As for the first cross-aldol reaction of acetaldehyde,[7a] aromatic aldehydes with electron-deficient aryl groups afforded the products with excellent enantioselectivity (entries 1−5). Alkynyl aldehyde was also a suitable electrophilic aldehyde,[7h] affording an *α,β*-unsaturated ester and ketone with excellent enantioselectivity (entries 6 and 7). The use of ethyl glyoxylate polymer also afforded the corresponding *α,β*-unsaturated ester with excellent enantioselectivity (entry 8).[7c] The second diastereoselective epoxidation proceeded with excellent *anti*-diastereoselectivity with substrates bearing *δ*-aryl substituents (entries 1−5). For substrates with an alkynyl group at the *δ*-position, diastereoselectivity was good to moderate, probably because of the reduced steric bulk of the alkynyl group (entries 6 and 7). In the case of substrates with an ester moiety at the *δ*-position, although the reaction was slow because of the electron-withdrawing ester moiety, good diastereoselectivity was obtained (entry 8). In all cases examined, the *anti*-isomer was generated predominantly. The optical purities of some of the epoxides were investigated. The enantiomeric excesses of **3a**, **3f**, and **3h** were 98, 95, and 87% ee, respectively, which are

Table 1. Effects of Solvent, Base, and Temperature in Epoxidation of 2a[a]

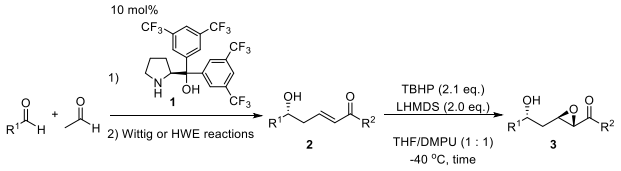


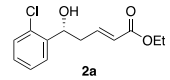
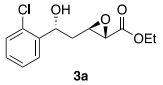
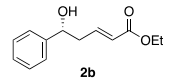
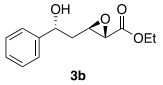
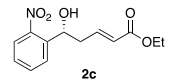
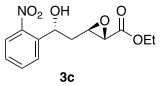
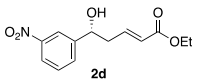
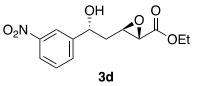
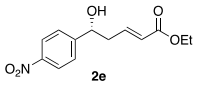
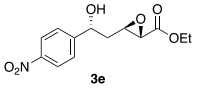
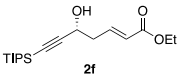
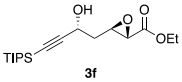
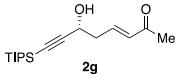
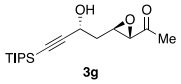
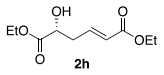
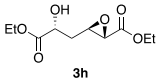
entry	base	solvent	conc. [M]	temp. [°C]	time [h]	yield [%][b]	*anti:syn*[c]
1[d]	EtLi	THF/benzene	0.20	−20	48	39	3.9:1
2	LiHMDS	THF	0.30	−20	20	44	4.8:1
3	LiHMDS	THF	0.01	−20	20	73	7.6:1
4	LiHMDS	THF/DMPU (5:1)	0.01	−20	4.5	76	13:1
5	LiHMDS	THF/DMPU (1:1)	0.01	−20	0.5	89	>20:1
6	LiHMDS	THF/DMPU (1:1)	0.08	−20	0.5	91	17:1
7	LiHMDS	THF/DMPU (1:1)	0.20	−40	2.5	84	20:1
8	NaHMDS	THF/DMPU (1:1)	0.20	−40	0.2	60	8.6:1
9	KHMDS	THF/DMPU (1:1)	0.20	−40	0.2	34	4.1:1

[a]Unless otherwise shown, the reaction was performed by employing **2a** (0.4 mmol), TBHP (0.84 mmol), and base (0.80 mmol, 1.0 M in THF). See the Supporting Information for details. [b]Isolated yield of a diastereomer mixture of *anti* and *syn* isomers. [c]Ratio of the diastereomers was determined by ^{1}H NMR. [d]TBHP (0.60 mmol), EtLi (0.44 mmol, 0.5 M in benzene), and THF (1.1 mL) were used.

https://doi.org/10.1021/acs.orglett.1c01986
Org. Lett. 2021, 23, 5896−5900

Table 2. Generality of Asymmetric Aldol and Epoxidation for Synthesis of δ-Hydroxy α,β-Epoxy Carbonyls[a]



	2			3			
entry		yield [%][b]	ee [%][c]	time [h]	yield [%][b]	*anti:syn*[d]	ee [%][c]
1[e]	 2a	55	98	 3a	2.5	84	20:1	98
2	 2b	23	>98	 3b	2.5	66	>20:1	
3	 2c	50	>98	 3c	2.5	65	>20:1	
4	 2d	59	94	 3d	3.0	76	>20:1	
5	 2e	56	>98	 3e	2.5	62	>20:1	
6[f]	 2f	68	95	 3f	21	67	7.5:1	95
7[f,g]	 2g	66	94	 3g	5	64	3.1:1	
8[h]	 2h	60	87	 3h	34	51	10:1	87

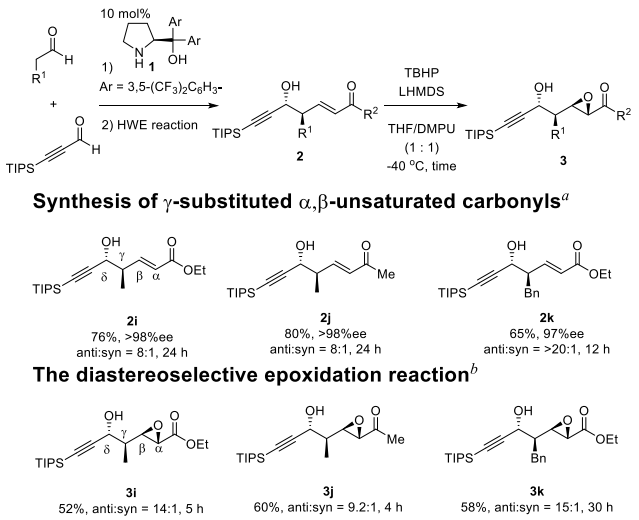
[a]Unless otherwise shown, the first reaction was performed by employing an electrophilic aldehyde (2.0 mmol), acetaldehyde (10.0 mmol), and diarylprolinol **1** (0.2 mmol) in DMF (2.0 mL) at room temperature. After the reaction, Wittig reagent (6.0 mmol) was added. The second epoxidation reaction was performed using **2** (0.4 mmol), TBHP (0.84 mmol), LiHMDS (0.80 mmol, 1.0 M in THF) in THF (0.2 mL) and DMPU (0.98 mL). See the Supporting Information for details. [b]Isolated yield. [c]Determined by HPLC analysis on a chiral column material. [d]Ratio was determined by ^{1}H NMR. [e]Aldol reaction was performed at 4 °C. [f]In the first aldol reaction, solvent was 1,4-dioxane (2.0 mL). Acetaldehyde (6.0 mmol) was used, and water (6.0 mmol) was added. Instead of the Wittig reaction, HWE reaction was used. See the Supporting Information for details. [g]Epoxidation was performed at −60 °C. [h]In the first aldol reaction, solvent was acetonitrile (2.0 mL). Acetaldehyde (4.0 mmol) was used, and water (6.0 mmol) was added.

same as those of the products of the first pot reaction (**2a**, **2f**, and **2h**). These results confirm that no reduction in enantiomeric integrity occurred in the epoxidation step.

Propargylic alcohols are useful synthetic intermediates because the alkyne moiety can be converted into many functional groups. Thus, we next examined the synthesis of more substituted 1,3-diols with an alkynyl moiety. In the first aldol reaction, alkynyl aldehyde[7h] was used as an electrophilic aldehyde, and propanal and 3-phenylpropanal were used as a nucleophilic aldehyde. In this case, two chiral centers would be generated in the first aldol reaction and three continuous chiral centers would be generated in the epoxidation step (Scheme 1). The first aldol reaction of alkynyl aldehyde proceeded with good *anti*-selectivity and excellent enantioselectivity. When a mixture of *anti*- and *syn*-γ-alkyl-δ-hydroxy-substituted carbonyls **2** was used in the second epoxidation reaction, *anti*-γ,δ-disubstituted isomer **2** reacted smoothly to afford the *anti*-β,δ-substituted epoxide **3** with excellent selectivity, while the epoxidation did not proceed with *syn*-γ,δ-disubstituted isomer **2**, which was recovered unchanged. This phenomenon is synthetically useful because the diastereomers generated in the first aldol reaction can be separated easily after the epoxidation reaction. Four possible diastereomers **3** would be generated according to the three chiral centers in the epoxidation reaction, but only two diastereomers with chiral centers at the β- and δ-positions were observed. γ-Substituents such as methyl and benzyl gave similarly excellent diastereoselectivity in the epoxidation reaction (**3i**, **3k**). In addition to α,β-unsaturated esters **2i** and **2k**, α,β-unsaturated ketone **2j** was also a suitable substrate, affording the epoxide **3j** with excellent

https://doi.org/10.1021/acs.orglett.1c01986
Org. Lett. 2021, 23, 5896−5900

Scheme 1. Generality of Asymmetric Aldol and Epoxidation of δ-Alkynyl γ-Substituted α,β-Epoxy Carbonyls

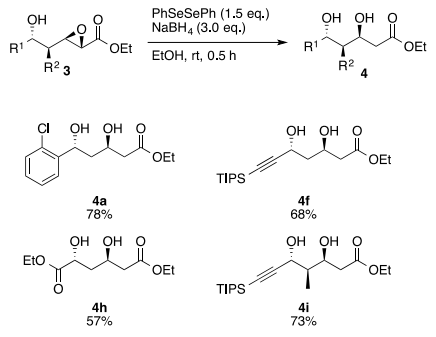


[a]First reaction was performed by employing alkynyl aldehyde (2.0 mmol), propanal or 3-phenylpropanal (4.0 mmol), water (6.0 mmol), and diarylprolinol **1** (0.2 mmol) in 1,4-dioxane (2.0 mL) at room temperature for the indicated time. After the reaction, Horner–Wadsworth–Emmons (HWE) reaction was conducted with HWE reagent (6.0 mmol) and NaH (60% in oil) (2.5 mmol) in THF (3.6 mL) and DMF (3.6 mL) at room temperature for 30 min. Yield is an isolated yield of a mixture of *anti* and *syn* isomers. *Anti:syn* ratio was determined by ^{1}H NMR. [b]Second epoxidation reaction was performed by **2** (0.4 mmol), TBHP (0.84 mmol), LiHMDS (0.80 mmol, 1.0 M in THF) in THF (0.2 mL) and DMPU (0.98 mL) at −40 °C for the indicated time. Yield is an isolated yield. See the Supporting Information for details. Diastereomeric ratio about relative configuration at β and δ-positions was determined by ^{1}H NMR.

diastereoselectivity. Compared to the results obtained with substrates **2f** and **2g**, without a substituent at the γ-position (Table 2, entries 6 and 7), higher diastereoselectivity was obtained in the case of γ-methyl-substituted substrates **2i** and **2j**.

The reductive opening of the epoxides was then examined. Four representative substrates, **3a**, **3f**, **3h**, and **3i**, were investigated. The *anti*-1,3-diols were successfully obtained by treatment of the epoxide with PeSeSePh and $NaBH_4$ by using the procedure reported by Miyashita (Scheme 2).[10] 1,3-Diol

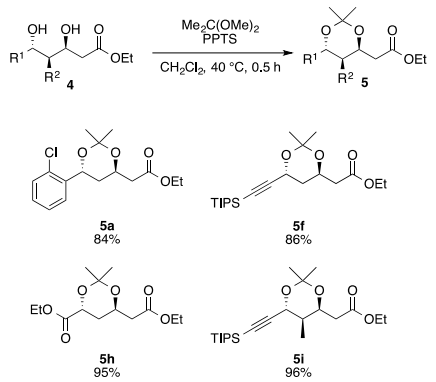
Scheme 2. Reductive Opening of Epoxide 3[a]



[a]Reaction was performed using **3** (2.0 mmol), $NaBH_4$ (0.94 mmol), and PhSeSePh (0.47 mmol) in EtOH (3.0 mL) at room temperature for 30 min. Yield is an isolated yield. See the Supporting Information for details.

units possessing aryl, ester, and alkynyl moieties were synthesized in moderate to good yields. The four diols, **4a**, **4f**, **4h**, and **4i**, were treated with acetone dimethyl acetal in the presence of PPTS to afford the corresponding acetonides in good yield (Scheme 3); the relative configuration of these acetonides was determined by analysis of ^{1}H and ^{13}C NMR spectra.[14] Thus, *anti*-β,δ-isomers were confirmed to be generated selectively.

Scheme 3. Acetalization of Diol 4[a]



[a]Reaction was performed using **4** (0.077 mmol), PPTS (0.023 mmol), and acetone dimethyl acetal (0.3 mL) in CH_2Cl_2 at 40 °C for 30 min. Yield is an isolated yield. See the Supporting Information for details.

In summary, we have established a three-pot synthesis of *anti*-β,δ-dihydroxy carbonyl units. The first pot is a synthesis of δ-hydroxy α,β-unsaturated carbonyl units via diarylprolinol **1**-mediated cross-aldol reaction and either Wittig or HWE reactions. The second pot is a hydroxy-directed diastereoselective epoxidation. The reductive opening of the epoxide is a third pot reaction. In the second epoxidation reaction, only *anti*-γ-alkyl-δ-hydroxy α,β-unsaturated carbonyls reacted to afford epoxides, with recovery of *syn*-γ-alkyl-δ-hydroxy α,β-unsaturated carbonyls, which were easily separated. Given that the first cross-aldol reaction proceeds with excellent enantioselectivity with a wide variety of substrates,[7] the final 1,3-diols were obtained with excellent enantioselectivity. Given that we previously reported the synthesis of β,δ-*syn*-dihydroxy carbonyls based on an asymmetric cross-aldol reaction as one of the key steps (eq 1),[8] both *anti*- and *syn*-β,δ-dihydroxy carbonyl units can be prepared by using the same aldol reaction.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01986.

Experimental procedures and analytical data (PDF)

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https://doi.org/10.1021/acs.orglett.1c01986
Org. Lett. 2021, 23, 5896−5900

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by JSPS KAKENHI Grant No. JP20H04801 in Hybrid Catalysis for Enabling Molecular Synthesis on Demand, and JP19H05630.

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