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Article

New Strategy for the Synthesis of Some Valuable Chiral 1,3-Diols with High Enantiomeric Purity: New Organocatalyst, Asymmetric Aldol Reaction, and Reduction

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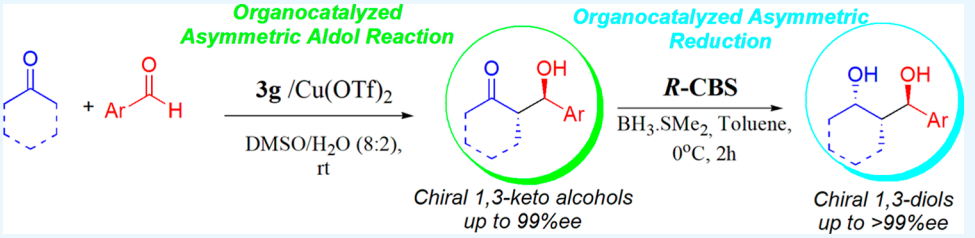

ABSTRACT: Chiral 1,3-diols are highly valuable molecules used in industries such as pharmaceuticals, cosmetics, and agriculture. Therefore, in this study, a new strategy was developed to synthesize enantiomerically pure (>99% *ee*) 1,3-diols. New chiral 1,3-diols (**5a−5q**) with high enantiomeric purity were synthesized from aldol products chiral 1,3-keto alcohols (**4a−4q**), which are aldol products with different structures. Chiral 1,3-keto alcohols (**4a−4q**) were synthesized by a new asymmetric aldol method in the first step. This method was developed using a new proline-derived organocatalyst (**3g**) and $Cu(OTf)_2$ as an additive in DMSO−H_2O for the first time. Almost >99% *ee* was obtained using our developed aldol procedure. In the second step, original chiral diols (**5a−5q**) of high enantiomeric purity were obtained by asymmetric reduction of chiral keto alcohols with chiral oxazaborolidine reagents. In this way, a two-step asymmetric reaction was developed for chiral 1,3-diol enantiomers with high enantiomeric purity. The structures of all the original chiral compounds obtained were elucidated by infrared and nuclear magnetic resonance spectroscopy, mass spectrometry, and elemental analysis methods. Their enantiomeric excesses were determined by the chiral high-performance liquid chromatography method. Both keto alcohols and their corresponding chiral diols synthesized can be used as chiral starting materials and chiral source materials or intermediates in the synthesis of many biologically active molecules, or they can be used as chiral ligands in asymmetric synthesis, serving as organocatalysts.

INTRODUCTION

Chiral diols, commonly found in various significant natural products, have proven to be valuable as chiral ligands and auxiliaries in stereoselective organic synthesis. Serving as crucial building blocks, chiral diols play a pivotal role in the preparation of diverse chiral chemicals (Figure 1).[1−3] Widely utilized in pharmaceuticals, cosmetics, and agriculture, particularly in the synthesis of natural and biologically active products, chiral diols and their derivatives find applications as starting or intermediate products.[4−7] Notably, natural products such as carbohydrates, with multiple hydroxy groups in their structure, predominantly exist as a single enantiomer. However, synthesizing a single enantiomer of alcohols with more than one hydroxy group is exceptionally challenging due to the prevalent formation of diastereoisomers and enantiomers in general synthesis methods.

Recent research has focused on the enantioselective synthesis of 1,3-diols containing two stereogenic centers. A key method for achieving this synthesis involves the enantioselective catalytic reduction of 1,3-hydroxy ketones, derived from corresponding dicarbonyl compounds. Various asymmetric reduction methods, including asymmetric heterogeneous and homogeneous hydrogenation, as well as diastereoselective induction, have been employed to obtain chiral diols.[8−14] Biochemical methods, such as enzymatic reduction of 1,3-diketones and enzymatic kinetic resolution, are also essential for synthesizing enantioselective diols.[15] Another important method of obtaining 1,3-diols is the reduction of aldol products. Especially, biocatalytic reduction of aldol products obtained by organocatalytic aldol reaction of an aldehyde and ketone is used very frequently and is among the most important methods.[16−19] Enzymatic reduction of 1,3-diketones[20−22] and enzymatic kinetic resolution[23−26] are also useful methods to synthesize enantioselective diols. Addition-

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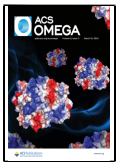

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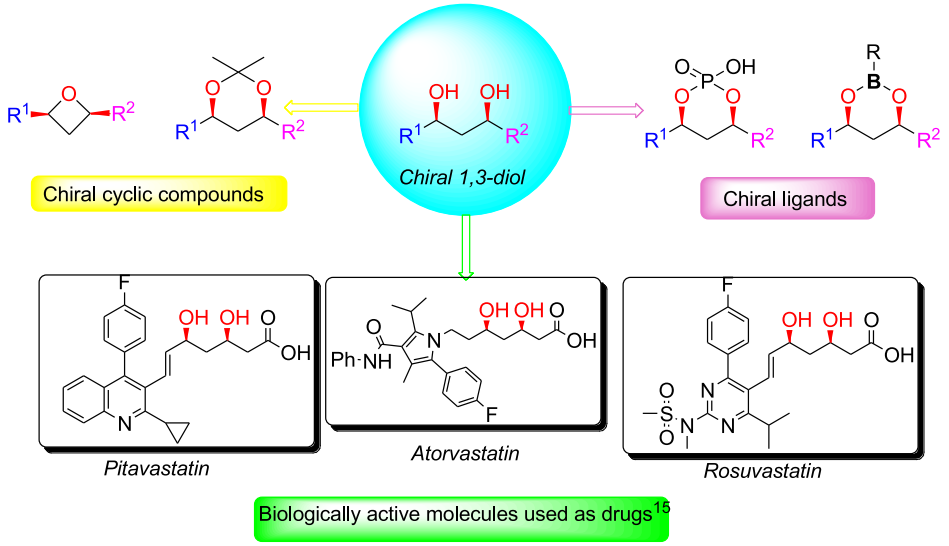

Figure 1. Some important applications of chiral 1,3-diols.

ally, chiral poly alcohols can be synthesized using stereoselective aldol-Tishchenko reactions.[27,28]

Numerous organocatalytic enantioselective aldol reactions have successfully yielded chiral hydroxy ketones, utilizing small amino acids such as proline or its derivatives.[29−34] Organocatalytic asymmetric cross-aldol reactions remain widely employed as a crucial tool in carbon−carbon bond formation reactions.[35,36] In our previous studies, we reported the use of various lipase enzymes in aldol reactions between different ketone and aldehyde species, achieving antiproducts with enantioselectivity ranging from 80 to 99% *ee*. Additionally, we described the enzymatic kinetic resolution of racemic 1,3-keto alcohols and biocatalytic hydrolysis of racemic 1,3-keto acetates, obtaining (*S*)-*β*-hydroxy ketones with high enantioselectivities.[37−39] The results of these works lead us to develop a new two-step asymmetric synthesis by the combined use of organocatalytic aldol reaction and asymmetric reduction. Although many studies achieved in multistep synthetic methodologies, only a few works have been made by combining a two-step organocatalytic process in order to synthesize chiral 1,3-diols. For example, Sonoike et al. synthesized 1,3-diol enantiomers by one-pot chemoenzymatic reaction in a water/acetone system at room temperature by a combination of enzymatic aldol reactions.[17] In another study, using a combination of enantioselective chemo- and biocatalytic reactions, the structures of both stereogenic centers of 1,3-diols were obtained.[16]

In this study, we introduce a novel aldol reaction procedure utilizing a new amino acid-derived catalyst (**3g**) in the presence of copper triflate ($Cu(OTf)_2$) as an additive in a DMSO−water mixture. While previous studies employed L-proline with various Lewis acids as additives for aldol reactions, the $Cu(OTf)_2$ compound, yielding optimal results in our study, has not been utilized before.[40,41] In the subsequent step, we achieved the asymmetric reduction of the keto group to alcohol using organoborane catalysts. Unlike previous studies using conventional reduction reagents or biocatalysts for reduction, we employed CBS-oxazaborolidine complexes for the first time, introducing a new aspect to the reduction of chiral hydroxy ketones and the formation of a second stereogenic center.[13,16]

Oxazaborolidine catalysts, particularly CBS−oxazaborolidine complexes, are vital in asymmetric reduction, playing a crucial role in obtaining chiral alcohols and diols with high enantioselectivity.[42,43] Building on our prior work utilizing CBS−oxazaborolidine complexes for the synthesis of chiral alcohols and diols, we demonstrate their efficiency in achieving a single enantiomer of chiral diols by reducing chiral keto alcohols.[14,44] The rationale behind employing asymmetric reduction at this stage is to ensure the highly selective formation of the secondary stereogenic center, increasing the probability of obtaining a single enantiomer.

RESULTS AND DISCUSSION

We used cyclohexanone (**1a**) and *p*-nitrobenzaldehyde (**2a**) as a bench reaction in DMSO, the optimum solvent for the asymmetric aldol reaction. Various amino acid−based molecules were tried in the aldolization reaction as organocatalysts in this study. Among the catalysts used, only L-proline (**3a**), (*R*)-amino-phenyl-acetic acid (**3b**), and (*S*)-diphenyl-pyrrolidin-2-yl-methanol (**3c**) were purchased, while the others (**3c-3i**) were synthesized in our previous studies.[44,45] All amino

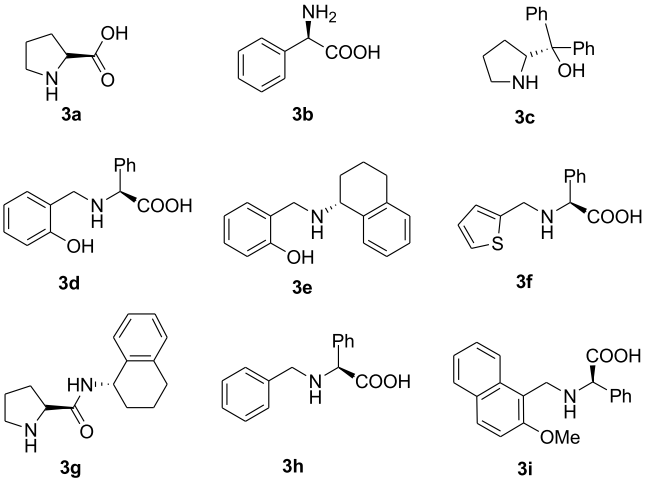

Figure 2. Organocatalysts used for the asymmetric aldol reactions.

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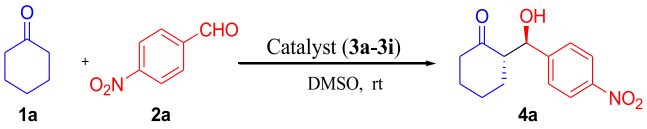
Table 1. Screening of Different Organocatalysts for the Asymmetric Aldol Reactions[a]

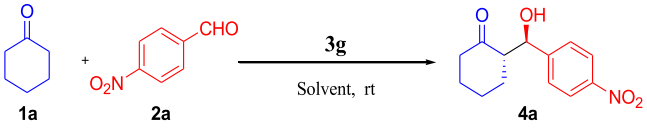


1a 2a 4a

entry	catalyst	yield (%)[b]	*dr* (*anti*/*syn*)[c]	*ee* (%)[c]
1	**3a**	83	78:22	71
2	**3b**	67	76:24	20
3	**3c**	59	63:37	26
4	**3d**	45	55:45	14
5	**3e**	63	68:32	63
6	**3f**	73	60:40	52
7	**3g**	**85**	78:22	**78**
8	**3h**	75	67:33	46
9	**3i**	64	61:39	15

[a]Conditions: Cyclohexanone (**1a**) (0.5 mmol), *p*-nitrobenzaldehyde (**2a**) (0.1 mmol), and catalyst (20% equiv) are stirred in DMSO (1 mL) at room temperature for 3 days. [b]Combined isolated yield of *anti*-**4a** and *syn*-**4a**. [c]*ee* and *dr* were determined by high-performance liquid chromatography (HPLC) analysis using a Chiralpac AD-H chiral column. The absolute configuration of **4a** was assigned by comparison of the retention times of known compounds.

Table 2. Solvent Effect in Asymmetric Aldol Reaction[a]



1a 2a 4a

entry	solvent	yield (%)[b]	*dr* (*anti*/*syn*)[c]	*ee* (%)[c]
1	DMSO	85	78:22	78
2	EtOH	48	65:34	45
3	MeOH	86	76:24	75
4	hexane	12	57:43	18
5	THF	23	59:41	19
6	toluene	15	61:39	21
7	DMF	75	75:25	74
8	cyclohexanone	84	74:26	73
9	MeCN	15	55:44	16
10	**DMSO−H_2O (8:2)**	**92**	91:9	**85**
11	H_2O	10	50:50	0

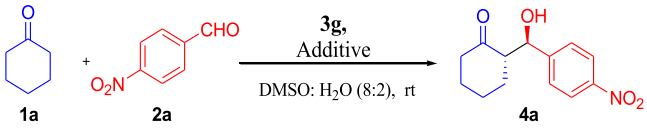
[a]Conditions: Cyclohexanone (**1a**) (0.5 mmol), *p*-nitrobenzaldehyde (**2a**) (0.1 mmol), and catalyst **3g** (20% eq.) are stirred in solvent (1 mL) at room temperature for 3 days. [b]Combined isolated yield of *anti*-**4a** and *syn*-**4a**. [c]*ee* and *dr* were determined by HPLC analysis using a Chiralpac AD-H chiral column. The absolute configuration of **4a** was assigned by comparison of the retention times of known compounds.

acid-derived organocatalysts, except for L-proline, were used for the first time in an aldol reaction. These organocatalysts used are given in Figure 2, and the results obtained from these catalysts are shown in Table 1.

As can be seen from Table 1, it was determined that the best catalyst was our newly synthesized proline-derived catalyst **3g**. As expected, proline gave a good result, while, interestingly, catalyst **3g** showed slightly a better result than proline (entry 7). Other catalysts tested were observed to show moderate or low *ee* and *dr* results.

An additional screening was performed to increase the *ee* values by testing some organic solvents in equal reaction

Table 3. Effect of Lewis Acids and Organic Acids Used as Additives on the Reaction[a]



1a 2a 4a

entry	additive (10%)	yield (%)[b]	*dr* (*anti*/*syn*)[c]	*ee* (%)[c]
1	no	92	91:9	85
2	**$Cu(OTf)_2$**	**99**	97:3	**98**
3	$FeCl_3$	95	92:8	95
4	$MnCl_2$	64	78:22	76
5	$CoCl_2$	90	90:10	88
6	$ZnCl_2$	93	85:25	94
7	$Al(OIPA)_3$	61	87:13	24
8	benzoic acid	75	84:16	78
9	acetic acid	59	76:24	65
10	$Cu(OAc)_2{\cdot}H_2O$	81	90:10	88
11	$Cu(OTf)_2$ (5%)	90	96:4	96

[a]Conditions: Cyclohexanone (**1a**) (0.5 mmol), *p*-nitrobenzaldehyde (**2a**) (0.1 mmol), catalyst **3g** (20% equiv), and additive (10% equiv) are stirred in DMSO/H_2O (8:2) (1 mL) at room temperature for 3 days. [b]Combined isolated yield of *anti*-**4a** and *syn*-**4a**. [c]*ee* and *dr* were determined by HPLC analysis using a Chiralpac AD-H chiral column. The absolute configuration of **4a** was assigned by comparison of the retention times of known compounds.

conditions and the same substrates (Table 2). Many apolar, polar protic, and aprotic solvents were tested as solvents. According to the results given in Table 2, methanol from polar protic solvents gave a good yield, ethanol gave a medium yield, and water gave a low yield. Very low yields were obtained with hexane and toluene from apolar solvents and acetonitrile and tetrahydrofuran from polar aprotic solvents. The best yield was obtained with an 8:2 mixture of DMSO, a polar aporotic solvent, and water, a polar protic solvent. Gratifyingly, we found that the reaction of **1a** with **2a** was accomplished with an improved yield (92%) and selectivity (*anti*/*syn* 91:9; 85% *ee*) in DMSO−H_2O (8:2) (Table 2, entry 10). Especially in asymmetric aldol reactions, it is preferred together with DMSO and some water, and it has been used in many previous studies.[46−49] Moreover, the reports prepared by the U.S. Environmental Protection Agency have mentioned that DMSO is a nontoxic solvent that does not harm human health.[50]

In our next experiments, we tested some Lewis acids and organic acids as an additive to increase the enantiomeric excess by forming a catalyst complex, and we monitored the results in Table 3.

Looking at Table 3, entry 2, it is seen that the best yield and ee were obtained by using $Cu(OTf)_2$ as an additive. It was observed that the yield and *ee* values decreased when a lower equivalent amount of $Cu(OTf)_2$ (5% equiv) was used. As a result of these trials, a new proline derivative catalyst and the $Cu(OTf)_2$ binary catalyst system was used for the first time, and a very high yield (99%), enantiomeric excess (98%), and diastereomeric ratio (97:3) was obtained.

We made a possible prediction for the aldol reaction mechanism of cyclohexanone and aromatic aldehydes in the presence of **3g** catalyst and $Cu(OTf)_2$ (Figure 3). According to this mechanism, the oxygen side of the catalyst forms a symmetric complex with copper. The basic nitrogen in the pyrroline ring then attacks the carbonyl of cyclohexanone and

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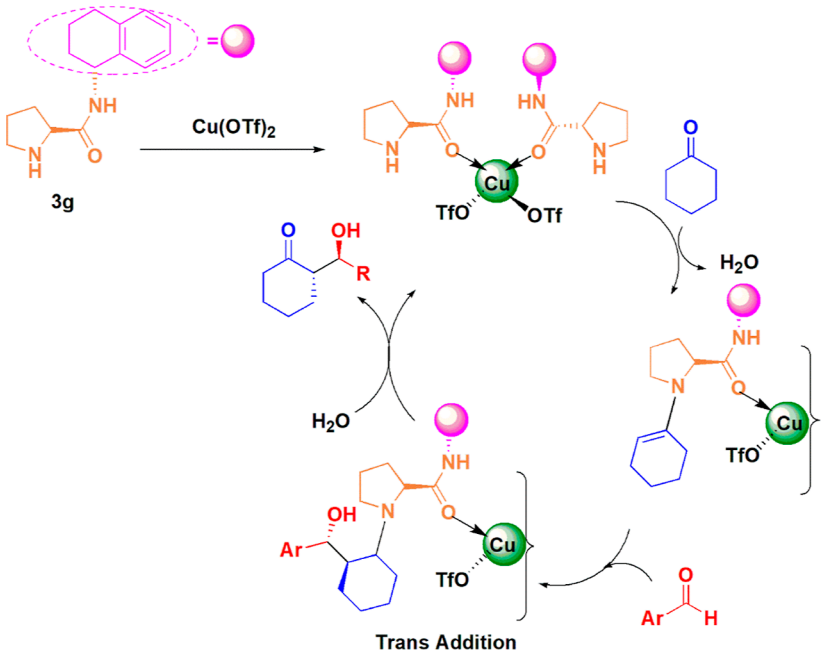
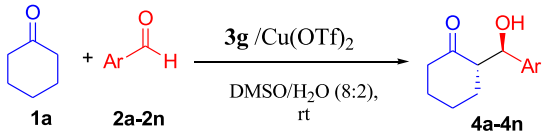


Figure 3. Postulated mechanism of the new aldol method.

Table 4. Synthesized Cyclohexanone Derivative Chiral 1,3-Keto Alcohols and Their Yields[a]



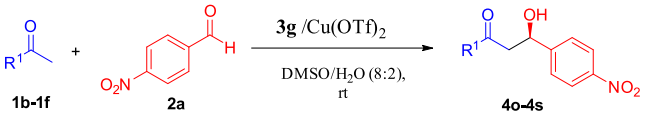
entry	product	Ar	yield(%)[b]	*dr* (*anti*/*syn*)[c]	*ee* (%)[c]
1	**4a**	4-$NO_2C_6H_4$	99	97:3	98
2	**4b**	Ph	97	93:7	96
3	**4c**	3-$CH_3C_6H_4$	93	95:5	91
4	**4d**	2-furyl	86	70:30	87
5	**4e**	2-naphthyl	94	95:5	99
6	**4f**	2-$CH_3OC_6H_4$	90	86:14	98
7	**4g**	4-$CH_3OC_6H_4$	92	98:2	96
8	**4h**	2-FC_6H_4	89	88:12	99
9	**4i**	2-BrC_6H_4	85	82:18	99
10	**4j**	2-thienyl	87	91:9	97
11	**4k**	2-$PhOC_6H_4$	80	96:4	99
12	**4L**	2-(4-FC_6H_4)OC_6H_4	84	83:17	99
13	**4m**	2-(4-CH_3)SC_6H_4	56	99:1	97
14	**4n**	2-(4-FC_6H_4)SC_6H_4	67	83:17	99

[a]Conditions: Cyclohexanone (**1a**) (0.5 mmol), aldehyde (**2a**−**2n**) (0.1 mmol), catalyst **3g** (20% eq), and $Cu(OTf)_2$ (10% eq) are stirred in DMSO/H_2O (8:2) (1 mL) at room temperature for 3 days. [b]Combined isolated yield of *anti*- and *syn*-isomers. [c]*ee* and *dr* were determined by HPLC analysis using a chiral column. The absolute configuration of **4a**−**4n** was assigned by comparison of the retention times of known compounds.

an enamine structure is formed. Afterward, the aldehyde adds this enamine from only one surface.

With this developed new method, a total of 14 chiral 1,3-keto alcohols were synthesized using different aldehydes and cyclohexanone. Benzaldehyde derivatives containing electron withdrawing and donating groups and hetero aromatic aldehydes were used as aldehyde derivatives. Four of them

Table 5. Synthesized Different Ketone Derivative Chiral 1,3-Keto Alcohols and Their Yields[a]



entry	product	R^1	yield(%)[b]	*dr* (*anti*/*syn*)[c]	*ee* (%)[c]
1	**4o**	methyl	52		68
2	**4p**	−$(CH_2)_5$−	83	75:15	73
3	**4q**	benzyl	46		64
4	**4r**	phenyl	0		
5	**4s**	pentyl	0		

[a]Conditions: Ketone (**1b**−**1f**) (0.5 mmol), aldehyde (**2a**) (0.1 mmol), catalyst **3g** (20% eq), and $Cu(OTf)_2$ (10% eq) are stirred in DMSO/H_2O (8:2) (1 mL) at room temperature for 3 days. [b]Combined isolated yield of *anti*- and *syn*-isomer. [c]*ee* and *dr* were determined by HPLC analysis using a chiral column. The absolute configuration of **4o**−**4q** was assigned by comparison of the retention times of known compounds.

are original (**4k**, **4l**, **4m**, and **4n**), and all synthesized chiral keto alcohols, their % yields, and *ee* values are given below (Table 4).

As can be seen from Table 4, the *anti*-diastereoisomer of keto alcohols was obtained with a higher percentage in all products. The configurations of keto alcohols were determined by comparing the HPLC retention times of the enantiomers in previous studies under the same conditions.[19,51,52] *Anti*-diastereoisomer was separated from *syn*-diastereoisomer by column chromatography, using hexane and increasing amounts of ethyl acetate as eluents.

Then we examined the effect of different ketones in the reaction by using different ketones instead of cyclohexanone (**1a**). Acetone (**1b**), cycloheptanone (**1c**), benzyl methyl ketone (**1d**), acetophenone (**1e**), and 2-heptanone (**1f**) were used as ketones, and the reaction results are shown in Table 5.

When studies with different ketones were examined, it was observed that while new aldol products (**4o**, **4p**, and **4q**) were

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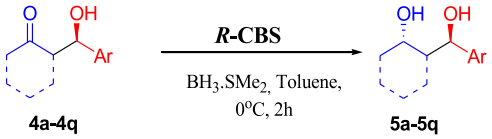
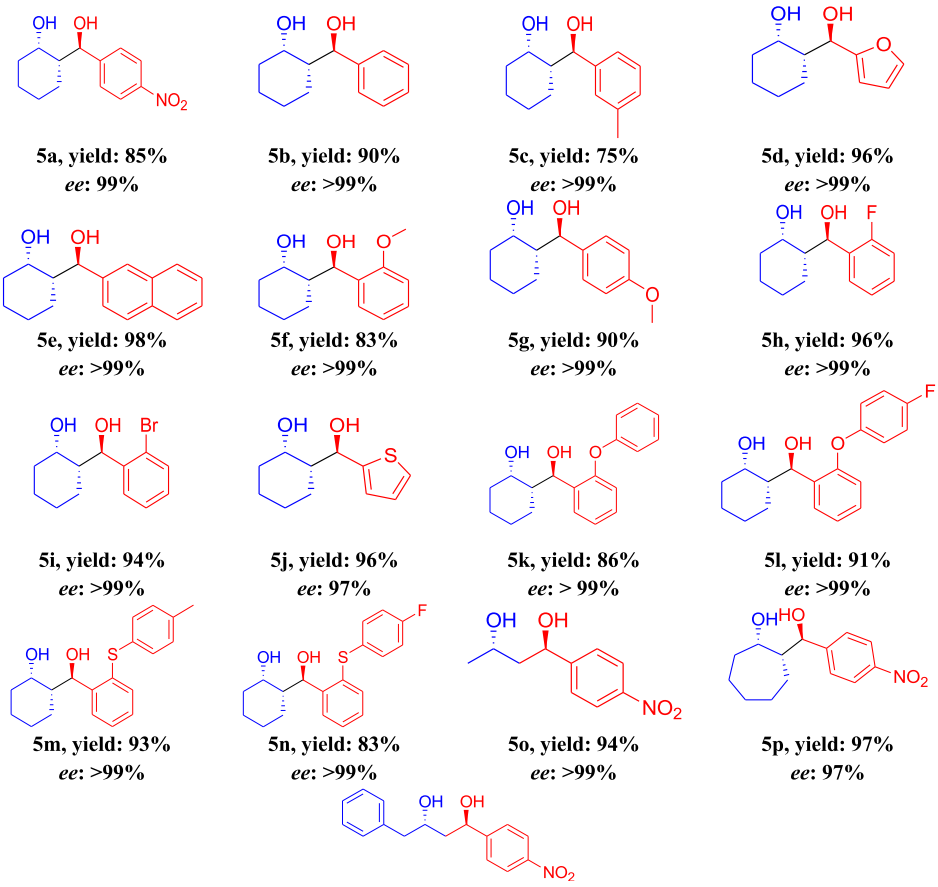
Table 6. Synthesized Chiral 1,3-Diols and Their Yields[a]





[a]Conditions: To a mix of 1 M CBS catalyst [0.1 mmol (0.1 mL) solution in toluene] and 1.5 mmol 2 M BH_3−SMe_2 in toluene, 1 mmol of keto alcohol is added in 5 mL of dry toluene at 0 °C under a N_2 atmosphere, and the mixture is stirred for 2h. Isolated yield of products. *ee* values were determined by HPLC analysis using chiral columns. The absolute configuration of **5a**−**5q** was assigned by comparison of the retention times of known compounds.

formed with acetone, cycloheptanone, and benzyl methyl ketone, no aldol products (**4r** and **4s**) were formed with the other two ketones.

Finally, all the synthesized chiral keto alcohols were reduced asymmetrically with the *R*-CBS−oxazaborolidine complex. The chiral 1,3-diols structures were obtained as a result of asymmetric reduction, and their results are given in Table 6. When chiral keto alcohols were reduced with *R*-CBS, a single enantiomer of diols was obtained. The synthesized chiral diols, except for **5b** and **5o**, are original and have been newly introduced into the literature. The configurations of the new chiral alcohols were determined based on the HPLC retention times of **5b** synthesized in a previous study.[19]

CONCLUSIONS

In this study, we synthesized 17 novel chiral 1,3-diols (**5a**−**5q**) with high enantiomeric excess from chiral 1,3-keto alcohols (**4a**−**4q**) via organocatalyzed asymmetric aldol reaction and asymmetric reduction. We developed a two-step asymmetric synthesis method to obtain a single enantiomer of 1,3-diols with two stereogenic centers. First, a new organocatalyzed asymmetric aldol reaction was improved using a proline-derived catalyst and $Cu(OTf)_2$ as an additive in DMSO−H_2O. Chiral 1,3-keto alcohols are obtained as starting compounds with ee up to 99%. Then, they were reduced asymmetrically using the *R*-CBS−oxazaborolidine complex. Thus, a single enantiomer of the 1,3-diols was obtained in an excellent way.

These molecules are important intermediates that can be used in the synthesis of drugs and chiral ligands because of their molecular motifs. In particular, 1,3-diol compounds can form chiral ligands or organometallic complexes, as well as are found in various pharmaceuticals. It is also possible to synthesize various heterocyclic compounds that have important biological activities using 1,3-diols with two stereogenic centers.

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EXPERIMENTAL SECTION

The chemicals were commercially purchased from Aldrich, Acros, or Merck and were used without any purification. All the obtained new compounds were purified by column chromatography and defined by infrared (IR), ^{1}H nuclear magnetic resonance (NMR), and ^{13}C NMR spectroscopic methods, elemental analysis, and gas chromatography−mass spectrometry (GC−MS). Reactions were monitored by thin-layer chromatography (TLC) using silica gel plates, and the products were purified by flash column chromatography on silica gel (230−400 mesh). NMR spectroscopy was conducted at 500 MHz for ^{1}H and 125 MHz for ^{13}C using Me_4Si as an internal standard in $CDCl_3$. GC−MS spectra were recorded on a Shimadzu/QP2010 Plus spectrometer. IR spectra were recorded on a Bruker Vertex 70 IR spectrometer. Melting points were determined with the Buchi Melting Point B-540 and were not corrected. To determine the values, HPLC was performed on a Shimadzu/DGU-20 A5 HPLC apparatus equipped with 25 cm Chiralcel OD, Chiralcel OD-H, Chiralcel OJ-H, and Chiralpac AD-H chiral columns. Optical rotations were measured with an Optical Activity AA-55 digital polarimeter at room temperature.

GENERAL PROCEDURE FOR THE SYNTHESIS OF THE RACEMIC 1,3-KETO ALCOHOLS (PROCEDURE I)[49]

The synthesis of racemic 1,3-keto alcohols was carried out by applying the new modified method previously developed by us, by aldol condensation in the presence of a suitable ketone and aldehyde.[49] 10 mmol ketone, 7.5 mmol aromatic aldehyde, 10% eq of K_2CO_3 (0.1 g), and 15 mL of DMSO/H_2O (8:2) were placed in a reaction vessel. It was stirred at room temperature for 1 day. The completion of the reaction was checked by TLC. The reaction was taken into a separatory funnel and extracted by DCM. Then the combined extracts were washed with saturated brine and dried over anhydrous Na_2SO_4, and the solvents were removed under reduced pressure. For purification, flash chromatography was performed on silica gel (Merck; 230−400 mesh) with hexane−ethyl acetate (v/v 9:1) as the mobile phase.

GENERAL PROCEDURE FOR THE SYNTHESIS OF THE CHIRAL 1,3-KETO ALCOHOLS (PROCEDURE II)

5 mmol ketone, 1 mmol aromatic aldehyde, 20% equiv of **3g**, 10% equiv of Cu(OTf)$_2$, and 3 mL of DMSO/H_2O (8:2) were placed in a reaction tube. It was stirred at room temperature for 1−3 days. The completion of the reaction was checked by TLC. The reaction was taken into a separatory funnel and extracted by DCM. Then the combined extracts were washed with saturated brine and dried over anhydrous Na_2SO_4, and the solvents were removed under reduced pressure. For the purification, flash chromatography was performed on silica gel (Merck; 230−400 mesh) with *n*-hexane−ethyl acetate (v/v 3:2) as the mobile phase.

GENERAL PROCEDURE FOR THE SYNTHESIS OF THE RACEMIC 1,3-DIOLS (PROCEDURE III)

Racemic diols were synthesized by racemic reduction of all synthesized racemic keto alcohols. Keto alcohol (1 mmol) was dissolved in methanol and cooled to 0 °C under a nitrogen atmosphere. $NaBH_4$ (1.5 mmol) was added to the solution in portions. The reaction was stirred until complete, controlled by TLC. Then it was extracted with DCM and dried with Na_2SO_4 and the solvent was evaporated.

GENERAL PROCEDURE FOR THE SYNTHESIS OF CHIRAL 1,3-DIOLS (PROCEDURE IV)[14,53]

To a solution (*R*)-Me-CBS (0.1 mmol, 0.1 mL of 1 M solution in toluene) was added BH_3·Me_2S (2 M in toluene, 1.5 mmol, 0.75 mL) and the mixture were stirred under a nitrogen atmosphere and then cooled to −10 °C. After 10 min of stirring, the solution of keto alcohol (1 mmol) in 5 mL of toluene was simultaneously added within 40 min at −10 °C until the keto alcohol disappeared based on TLC (0.5−2 h). The reaction mixture was quenched with cold (0 °C) MeOH (1 mL) carefully and the cooling bath was removed and stirring continued for 1 h. Then it was extracted with DCM, dried with Na_2SO_4 and the solvent was evaporated. Removal of solvents in vacuo and purification of the residue by column chromatography (*n*-hexane−EtOAc 7:3) yielded the diol product.[14]

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c07948.

Experimental details, general procedures, experimental characterization data (IR, NMR, MS, HPLC, and elemental analysis), and ^{1}H and ^{13}C NMR spectra of all products (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) *Pharmaceutical Substances: Syntheses, Patents Applications*, 4th ed.; Kleeman, A.; Engels, J.; Kutscher, B.; Reichert, D., Eds.; Georg

Thieme Verlag: Stuttgart, 2001; Vol. 2. p 2521, 599 Euros. ISBN: 3-13-558404-6. Org. Process Res. Dev. 2002, 6(5), 739−740.
(2) Wu, X.; Liu, N.; He, Y.; Chen, Y. Cloning, Expression, and Characterization of a Novel Diketoreductase from Acinetobacter Baylyi. *Acta Biochim. Biophys. Sin.* **2009**, *41* (2), 163−170.
(3) Sit, S. Y.; Parker, R. A.; Motoc, I.; Han, W.; Balasubramanian, N.; Catt, J. D.; Brown, P. J.; Harte, W. E.; Thompson, M. D.; Wright, J. J. Synthesis, Biological Profile, and Quantitative Structure-Activity Relationship of a Series of Novel 3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase Inhibitors. *J. Med. Chem.* **1990**, *33* (11), 2982−2999.
(4) Superchi, S.; Contursi, M.; Rosini, C. Monobenzylether of (R,R)-1,2-Diphenylethane-1,2-Diol as Chiral Auxiliary in the Diastereoselective Reduction of α-Ketoesters. *Tetrahedron* **1998**, *54* (37), 11247−11254.
(5) Konopelski, J. P.; Boehler, M. A. Enantiomerically Pure Vinylketene Acetals as Dienes in the Diels-Alder Reaction. *J. Am. Chem. Soc.* **1989**, *111* (12), 4515−4517.
(6) Prasad, K. R. K.; Joshi, N. N. C2-Symmetric Chiral Zinc Alkoxides as Catalysts for the Enantioselective Addition of Diethylzinc to Aryl Aldehydes. *Tetrahedron: Asymmetry* **1996**, *7* (7), 1957−1960.
(7) Başpınar Küçük, H.; Yaşa, H.; Yıldız, T.; Yusufoğlu, A. S. Detailed Studies on the Reduction of Aliphatic 3-4-6-and 13-Oximino Esters: Synthesis of Novel Isomeric Amino Esters, Oximino Alcohols, and Amino Alcohols. *Synth. Commun.* **2017**, *47* (22), 2070−2077.
(8) Bode, S. E.; Wolberg, M.; Müller, M. Stereoselective Synthesis of 1,3-Diols. *Synthesis* **2006**, *2006*, 557−588.
(9) Nagoya, R. Asymmetric Catalysis In Organic Synthesis. *Molecules* **2001**, *6* (12), 1012.
(10) Ojima, I. *Catalytic Asymmetric Synthesis: Third Edition*; John Wiley & Sons, Inc., 2010..
(11) Hayashi, Y.; Aratake, S.; Okano, T.; Takahashi, J.; Sumiya, T.; Shoji, M. Combined Proline-Surfactant Organocatalyst for the Highly Diastereo- and Enantioselective Aqueous Direct Cross-Aldol Reaction of Aldehydes. *Angew. Chem., Int. Ed.* **2006**, *45* (33), 5527−5529.
(12) Davis, T. A.; Chopade, P. R.; Hilmersson, G.; Flowers, R. A. Reduction of β-Hydroxyketones by $SmI_2/H_2O/Et_3N$. *Org. Lett.* **2005**, *7* (1), 119−122.
(13) Evans, D. A.; Chapman, K. T.; Carreira, E. M. Directed reduction of .beta.-hydroxy ketones employing tetramethylammonium triacetoxyborohydride. *J. Am. Chem. Soc.* **1988**, *110* (11), 3560−3578.
(14) Yildiz, T.; Yusufoğlu, A. Asymmetric Synthesis of New Chiral 1,2- and 1,3-Diols. *Monatsh. Chem.* **2013**, *144* (2), 183−190.
(15) Gupta, P.; Mahajan, N.; Taneja, S. C. Recent Advances in the Stereoselective Synthesis of 1,3-Diols Using Biocatalysts. *Catal.: Sci. Technol.* **2013**, *3*, 2462−2480.
(16) Baer, K.; Kraußer, M.; Burda, E.; Hummel, W.; Berkessel, A.; Gröger, H. Sequential and Modular Synthesis of Chiral 1,3-Diols with Two Stereogenic Centers: Access to All Four Stereoisomers by Combination of Organo- and Biocatalysis. *Angew. Chem., Int. Ed.* **2009**, *48* (49), 9355−9358.
(17) Sonoike, S.; Itakura, T.; Kitamura, M.; Aoki, S. One-Pot Chemoenzymatic Synthesis of Chiral 1,3-Diols Using an Enantioselective Aldol Reaction with Chiral Zn 2+ Complex Catalysts and Enzymatic Reduction Using Oxidoreductases with Cofactor Regeneration. *Chem. - Asian J.* **2012**, *7* (1), 64−74.
(18) Andreu, C.; Del Olmo, M. Exploring the Potential of Some Yeast Strains in the Stereoselective Synthesis of Aldol Reaction Products and Its Reduced 1,3-Dialcohol Derivatives. *J. Mol. Catal. B: Enzym.* **2013**, *92*, 57−61.
(19) Acetti, D.; Brenna, E.; Fuganti, C.; Gatti, F. G.; Serra, S. Baker's Yeast Reduction of β-Hydroxy Ketones. *Eur. J. Org Chem.* **2010**, *2010* (1), 142−151.
(20) Ahmad, K.; Koul, S.; Taneja, S. C.; Singh, A. P.; Kapoor, M.; Riyaz-ul-Hassan; Verma, V.; Qazi, G. N. Enzyme Directed Diastereoselectivity in Chemical Reductions: Studies towards the Preparation of All Four Isomers of 1-Phenyl-1,3-Butanediol. *Tetrahedron: Asymmetry* **2004**, *15* (11), 1685−1692.
(21) Berti, F.; Bincoletto, S.; Donati, I.; Fontanive, G.; Fregonese, M.; Benedetti, F. Albumin-directed stereoselective reduction of 1,3-diketones and β-hydroxyketones to anti diols. *Org. Biomol. Chem.* **2011**, *9* (6), 1987−1999.
(22) Vitale, P.; Perna, F. M.; Agrimi, G.; Scilimati, A.; Salomone, A.; Cardellicchio, C.; Capriati, V. Asymmetric Chemoenzymatic Synthesis of 1,3-Diols and 2,4-Disubstituted Aryloxetanes by Using Whole Cell Biocatalysts. *Org. Biomol. Chem.* **2016**, *14* (48), 11438−11445.
(23) Levayer, F.; Rabiller, C.; Tellier, C. Enzyme Catalysed Resolution of 1,3-Diarylpropan-1,3-Diols. *Tetrahedron: Asymmetry* **1995**, *6* (7), 1675−1682.
(24) Ward, D. E.; Liu, Y.; How, D. Preparation of Desymmetrized Meso Derivatives by Kinetic Resolution of Meso/Dl Stereoisomeric Mixtures. *J. Am. Chem. Soc.* **1996**, *118* (12), 3025−3026.
(25) Jakob, F.; Schneider, C. Enzyme-Catalyzed Kinetic Resolution of 1,3-Anti-Diol Monoesters - Efficient Preparation of Enantiomerically Highly Enriched and Unsymmetrically Substituted 1,3-Anti-Diols. *Eur. J. Org Chem.* **2007**, *2007* (18), 2958−2963.
(26) Kłossowski, S.; Redzej, A.; Szymkuć, S.; Ostaszewski, R. Studies towards Enzymatic Kinetic Resolutions of 1,3-Diol Peptidomimetics Obtained via the Ugi Reaction. *Arkivoc* **2013**, *2013* (4), 134−143.
(27) Ichibakase, T.; Nakajima, M. Direct Enantioselective Aldol-Tishchenko Reaction Catalyzed by Chiral Lithium Diphenylbinaphtholate. *Org. Lett.* **2011**, *13* (7), 1579−1581.
(28) Ralston, K. J.; Hulme, A. N. The Evans-Tishchenko Reaction: Scope and Applications. *Synthesis* **2012**, *44*, 2310−2324.
(29) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. Asymmetric Enamine Catalysis. *Chem. Rev.* **2007**, *107*, 5471−5569.
(30) Zlotin, S. G.; Kucherenko, A. S.; Beletskaya, I. P. Organocatalysis of Asymmetric Aldol Reaction. Catalysts and Reagents. *Russ. Chem. Rev.* **2009**, *78* (8), 737−784.
(31) Kucherenko, A. S.; Siyutkin, D. E.; Maltsev, O. V.; Kochetkov, S. V.; Zlotin, S. G. Asymmetric Organocatalysis: From Proline to Highly Efficient Immobilized Organocatalysts. *Russ. Chem. Bull.* **2012**, *61*, 1313−1320.
(32) Dalko, P. I. *Enantioselective Organocatalysis: Reactions and Experimental Procedures*; John Wiley & Sons, Inc., 2007, p 559.
(33) Kucuk, H. B.; Kanturk, G.; Yerlikaya, S.; Yildiz, T.; Senturk, A. M.; Guzel, M. Novel β-hydroxy ketones: Synthesis, spectroscopic characterization, molecular docking, and anticancer activity studies. *J. Mol. Struct.* **2022**, *1250*, 131772.
(34) Yadav, G. D.; Deepa; Singh, S. Prolinamide-Catalysed Asymmetric Organic Transformations. *ChemistrySelect.* **2019**, *4*, 5591−5618.
(35) Mhaldar, S. N.; Tilve, S. G. An Approach towards (+)-Allokainic Acid via Diphenylprolinol-Catalyzed Direct Cross-Aldol Reaction. *Org. Biomol. Chem.* **2023**, *21*, 5469−5474.
(36) Wang, W.; Qin, Z.; Tan, Z.; Yang, W. Organocatalytic Enantioselective Cross-Aldol Reaction of Aryl Ketones with Heteroaromatic Trifluoromethyl Ketone Hydrates for the Synthesis of α-Trifluoromethyl Tertiary Alcohols. *Org. Biomol. Chem.* **2023**, *21* (25), 5234−5239.
(37) Yıldız, T.; Yaşa, H.; Hasdemir, B.; Yusufoğlu, A. S. Different Bio/Lewis Acid-Catalyzed Stereoselective Aldol Reactions in Various Mediums. *Monatsh. Chem.* **2017**, *148* (8), 1445−1452.
(38) Can, H.; Yıldız, T.; Onar, H. C.¸. Synthesis of Chiral 1,3-Keto-Acetates through Enzymatic Kinetic Resolution with Amano Lipase from Pseudomonas Fluorescens. *ChemistrySelect* **2020**, *5* (25), 7543−7547.
(39) Yıldız, T. An Enzymatic and Environmentally Friendly Route for the Synthesis of Chiral β-Hydroxy Ketones. *ChemistrySelect* **2019**, *4* (27), 7927−7931.
(40) Penhoat, M.; Barbry, D.; Rolando, C. Direct Asymmetric Aldol Reaction Co-Catalyzed by l-Proline and Group 12 Elements Lewis Acids in the Presence of Water. *Tetrahedron Lett.* **2011**, *52* (1), 159−162.

https://doi.org/10.1021/acsomega.3c07948
ACS Omega 2024, 9, 12657−12664

(41) Karmakar, A.; Maji, T.; Wittmann, S.; Reiser, O. L-Proline/CoCl2-Catalyzed Highly Diastereo- and Enantioselective Direct Aldol Reactions. *Chem. - Eur. J.* **2011**, *17* (39), 11024−11029.
(42) Corey, E. J.; Helal, C. J. Reduction of Carbonyl Compounds with Chiral Oxazaborolidine Catalysts: A New Paradigm for Enantioselective Catalysis and a Powerful New Synthetic Method. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986−2012.
(43) Corey, E. J.; Bakshi, R. K.; Shibata, S. Highly Enantioselective Borane Reduction of Ketones Catalyzed by Chiral Oxazaborolidines. Mechanism and Synthetic Implications. *J. Am. Chem. Soc.* **1987**, *109* (18), 5551−5553.
(44) Yildiz, T.; Yusufoğlu, A. Asymmetric Synthesis of New Chiral Long Chain Alcohols. *Tetrahedron: Asymmetry* **2010**, *21* (24), 2981−2987.
(45) Hasdemir, B.; Yaşa, H.; Yıldız, T.; Küçük, H. B.; Onar, H. C.,. Asymmetric Synthesis of Chiral γ- and δ-Amino Esters Using Trichlorosilane Activated with a Lewis Base Catalyst. *ChemistrySelect* **2020**, *5* (20), 6035−6039.
(46) Edin, M.; Bäckvall, J. E.; Córdova, A. Tandem Enantioselective Organo- and Biocatalysis: A Direct Entry for the Synthesis of Enantiomerically Pure Aldols. *Tetrahedron Lett.* **2004**, *45* (41), 7697−7701.
(47) Córdova, A.; Zou, W.; Dziedzic, P.; Ibrahem, I.; Reyes, E.; Xu, Y. Direct Asymmetric Intermolecular Aldol Reactions Catalyzed by Amino Acids and Small Peptides. *Chem. - Eur. J.* **2006**, *12* (20), 5383−5397.
(48) Hayashi, Y.; Itoh, T.; Nagae, N.; Ohkubo, M.; Ishikawa, H. The Effectiveness of Proteinogenic Amino Acids in the Asymmetric Aldol Reaction in DMSO and Aqueous DMSO. *Synlett* **2008**, *2008* (10), 1565−1570.
(49) Yıldız, T.; Can, H.; Yusufoğlu, A. S. An Effective and Environmentally Friendly Synthesis of 1,3-Keto-Alcohols. *Org. Prep. Proced. Int.* **2020**, *52* (1), 9−21.
(50) *Dimethyl Sulfoxide Producer Association US Environmental Protection Agency IUCLID Data Set*; Leesburg, VA, September 8, 2003, Report Number 201-14721A.
(51) Song, X.; Liu, A. X.; Liu, S. S.; Gao, W. C.; Wang, M. C.; Chang, J. Enantiopure Azetidine-2-Carboxamides as Organocatalysts for Direct Asymmetric Aldol Reactions in Aqueous and Organic Media. *Tetrahedron* **2014**, *70* (7), 1464−1470.
(52) Martínez, R.; Berbegal, L.; Guillena, G.; Ramón, D. J. Bio-Renewable Enantioselective Aldol Reaction in Natural Deep Eutectic Solvents. *Green Chem.* **2016**, *18* (6), 1724−1730.
(53) Yildiz, T. An Oxazaborolidine-Based Catalytic Method for the Asymmetric Synthesis of Chiral Allylic Alcohols. *Tetrahedron: Asymmetry* **2015**, *26* (8−9), 497−504.

https://doi.org/10.1021/acsomega.3c07948
ACS Omega 2024, 9, 12657−12664