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Organocatalyzed Highly Enantioselective Direct Aldol Reactions of Aldehydes with Hydroxyacetone and Fluoroacetone in Aqueous Media: The Use of Water To Control Regioselectivity

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Abstract: An organocatalyst prepared from (2*R*,3*R*)-diethyl 2-amino-3-hydroxysuccinate and L-proline exhibited high regio- and enantioselectivities for the direct aldol reactions of hydroxyacetone and fluoroacetone with aldehydes in aqueous media. It was found that water could be used to control the regioselectivity. The presence of 20–30 mol% of the catalyst afforded the direct aldol reactions of a wide range of aldehydes with hydroxyacetone to give the otherwise disfavored products with excellent enantioselectivities, ranging from 91 to 99% *ee*, and high regioselectivities. Aldolizations of fluoroacetone with aldehydes mediated by 30 mol% of the organocatalyst in aqueous media preferentially occurred at the methyl group, yielding products with high enantioselectivities (up to 91% *ee*); however, these additions took place dominantly at the fluoromethyl group in THF. Optically active 3,5-disubstituted tetrahydrofurans and (2*S*,4*R*)-dihydroxy-4-biphenylbutyric acid were prepared by starting from the aldol reaction of hydroxyacetone. Theoretical studies on the role of water in controlling the regioselectivity revealed that the hydrogen bonds formed between the amide oxygen of proline amide, the hydroxy of hydroxyacetone, and water are responsible for the regioselectivity by microsolvation with explicit one water molecule as a hydrogen-bond donor and/or an acceptor.

Keywords: aldol reaction · green chemistry · organocatalysis · proline amides · regioselectivity

Introduction

The development of highly selective organic reactions for the formation of carbon–carbon bonds is an everlasting topic of organic chemistry. The aldol reaction is considered one of the most important carbon–carbon bond-forming reactions in organic synthesis. Its great usefulness for constructing natural products, in particular those with polyoxygenated subunits,[1] has promoted the rapid evolution of efficient chiral catalysts.[2] Aldol reactions that employ enol or enolate derivatives as donors have been well established.[2] As opposed to reactions involving preactivated donors, the direct aldol reaction is more atom efficient,[3] making it an attractive alternative for the synthesis of polyoxygenated compounds. Since the seminal studies on direct asymmetric aldol reactions were reported,[4,5] a large number of chiral catalysts, including transition-metal complexes[6] and organic molecules,[7–12] have been applied to these transformations. However, most of them were performed in organic solvents, with the exception of a limited number of direct aldol reactions which were attempted in ionic liquids[13] and in wa-

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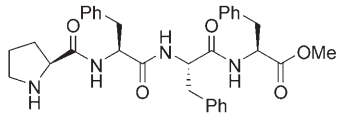
ter.[5d,8b,14] The discovery of a highly enantioselective organocatalyzed asymmetric aldolization in environmentally benign medias is therefore desirable.

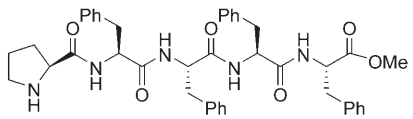
Water is absolutely the most environmentally benign solvent. Its use as a solvent not only makes the reaction environmentally amenable, but much safer to handle, as aqueous conditions principally avoid flammable organic solvents and the strictly anhydrous conditions. In addition, the performance of the organic reactions in aqueous conditions leads to certain unprecedented reactions as compared to those conducted in organic solvents.[15] Water has unique physical and chemical properties, such as a dielectric constant and high polarity. To develop a water-compatible organic reaction is a great challenge as water destroys moisture-sensitive transition states and breaks the hydrogen bond required for the activation of substrates. Despite these drawbacks, in recent years organic reactions in aqueous media have received a great deal of interest and important advances have been made on this area.[16] As for asymmetric catalysis, transition-metal-catalyzed asymmetric reactions in aqueous media have also been actively investigated.[15a,17] However, apart from the asymmetric phase-transfer catalyses[18] and chiral ketone-mediated asymmetric epoxidations,[19] few organocatalyzed asymmetric reactions in aqueous media have been reported[5d,8b,14,20] and most of them gave lower enantioselectivities than their counterparts in pure organic solvent.[14a–i]

In fact, water is essential for reactions in the biological system. Enzyme-catalyzed organic reactions are usually performed in water. Thus, studies on the organic reactions in aqueous media might also lead to a better understanding of enzyme catalysis. Proline and its derivatives catalyze direct aldol reactions by means of an enamine mechanism, similar to that which Class I aldolase enzymes[2e,21a] and aldolase catalytic antibodies use to catalyze similar reactions in water,[21b–d] indicating that such organic molecules would exhibit a catalytic ability similar to enzymes, and they may catalyze highly enantioselective organic reactions in aqueous media.[14k,j]

Recently, we reported that L-proline-based oligopeptides (**1**, **2**, and their analogues) catalyzed the direct aldol reaction

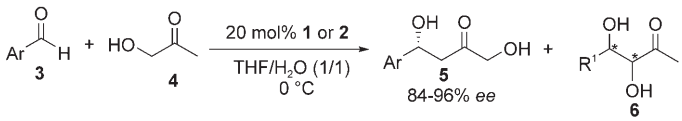


Pro-Phe-Phe-Phe-OMe (**1**)



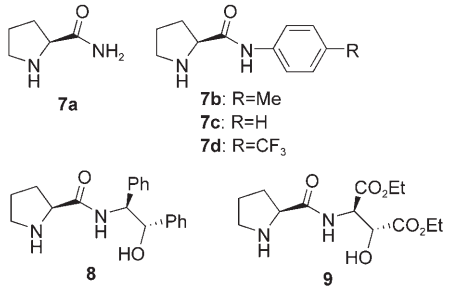
Pro-Phe-Phe-Phe-Phe-OMe (**2**)

of aldehydes **3** with hydroxyacetone **4** in aqueous media to provide 1,4-diols **5** with high enantioselectivities.[22] Interestingly, the regioselectivity to 1,4-diol **5** or 1,2-diol **6** was reversible upon performing the reaction in the presence or absence of water. More valuably, we found that the regio- and enantioselectivities altered as the peptide size varied. In general, the regioselectivity decreased and enantioselectivity increased as the peptide size increased. The peptides **1** and **2** were extended to catalyze aldol reactions of a limited number of electron-poor aromatic aldehydes with hydroxyacetone, providing enantioselectivities ranging from 84 to 96% *ee* (Scheme 1).



Scheme 1. Preparation of 1,4-diol **5** and 1,2-diol **6**.

However, there are some inherent drawbacks in this process, [22] which are as follows: 1) the regioselectivity (1,4-diol/1,2-diol, up to 4:1) continues to be unsatisfactory, 2) the process is limited to electron-deficient aryl aldehydes and gives excellent enantioselectivity (>90%) for a limited number of special cases, making it synthetically impractical, 3) oligopeptides **1** or **2** have much higher molecular weights than either the substrate or the product, so this reaction is not truly catalytic with respect to weight. To address these problems and the importance of asymmetric reactions in aqueous media, we herein report that a family of simple L-proline amides **7**–**9** catalyzed direct aldol reactions of aldehydes with hydroxyacetone and fluoroacetone in aqueous media with high enantioselectivities. Application of the optically active 1,4-diols to the syntheses of chiral 3,5-disubstituted tetrahydrofurans and a biologically active compound is also presented. Moreover, theoretical studies on the possible roles of water in the control of regioselectivity of the aldol reaction of hydroxyacetone with aldehydes are also discussed.



Results and Discussion

Direct aldol reaction of hydroxyacetone with aldehydes: The asymmetric direct aldol reaction of aldehydes with hydroxyketones provides a convenient entry to highly oxygen-

ated compounds. 2-Hydroxy-1-aryl ethanones serve as aldol donors to react with aldehydes in the presence of chiral transition-metal complexes, offering highly enantioselective 1,2-diols favoring the *anti* form.[4d–e,6a,c] In cases involving hydroxyacetone, biocatalysts, such as catalytic antibodies, were found to be efficient for this reaction, leading to the formation of *syn* diols as major products with extremely high enantioselectivity.[21d,23] Recent important advances with organocatalyzed direct aldol reactions revealed that L-proline had a great ability to catalyze the aldol reaction of hydroxyacetone producing *anti* diols with a high stereochemical outcome.[5d,e]

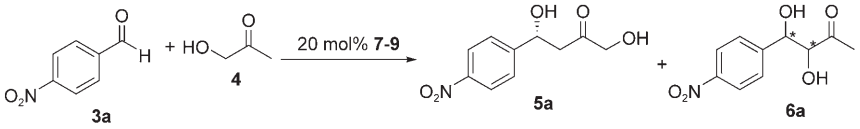
Direct aldol reactions of siloxy- and alkoxy-acetones with aldehydes mediated either by $TiCl_4/Et_3N$ or Bu_2BOTf take place regioselectively at the methyl group.[24] In these cases, an excess of a Lewis acid is required to obtain high yields. Antibody 84G3 preferentially catalyses the aldolization of methoxylacetone at the methyl group with excellent enantioselectivity, which only includes *4*-nitrobenzaldehyde as an acceptor.[25] However, these reactions all preclude the hydroxyacetone as a donor and can thus be considered indirect alternatives to access the 1,4-diols **5** by aldolization.

In our previous studies,[22] we have noticed that the regioselectivity in the aldol reaction of hydroxyacetone with aldehydes depends to some degree on the peptide size, and that regioselectivity generally decreases as the peptide size increases. These observations point out that the use of simple L-proline amides **7–9**, which can be regarded as short peptides, as catalysts would further enhance the regioselectivity. We were therefore encouraged to employ the L-proline amides **7–9** to catalyze the titled reaction in aqueous media.

Under similar conditions to those used for peptide catalysis,[22] the L-proline amides **7–9** were examined for their ability to catalyze the direct aldol reaction of 4-nitrobenzaldehyde with hydroxyacetone. As the data in Table 1 indicate, both reactivity and enantioselectivity are highly dependent on the structure of the organocatalyst. The L-proline amides **7a–d**, which catalyzed the direct aldol reaction of acetone and 4-nitrobenzaldehyde with low enantioselectivities (≈45% *ee*),[10] also showed moderate enantioselectivities (≈52% *ee*) in this case, favoring the generation of **5a** with a regioselection of up to 5.7:1 (entries 1–4).[22] In the addition to the unsatisfactory regio- and enantioselectivities with these simple proline amides, the slow reactions had the drawback of taking several days to give reasonable yields (entries 1–4). The L-proline amides **8** and **9** derived from chiral amino alcohols not only have a higher ability to control the regio- and enantioselectivity, but also are more catalytically active than L-proline amides **7a–d**, which lack the terminal hydroxy group (entries 1–9). In particular, organocatalyst **9**, a much more efficient catalyst in the direct aldol reaction of acetone with aldehydes than **8**,[11] provided the highest degree of enantioselectivity (entries 8 and 9). These observations indicate that the hydroxy group may be involved in the catalysis and may exert an important influence on stereocontrol. Performance of the reaction at a decreased temperature (−15 °C) and alteration of the ratio of THF/H_2O led to further improvements in enantioselectivity (entries 7 and 9). Even higher regioselectivity with respect to 1,4-diol **5a** (>95: 5) and enantioselectivity (95% *ee*) than those observed with either **1** or **2** were obtained under the optimal conditions with organocatalyst **9** (entry 9).[22] In contrast, the 1,2-diol **6a** became dominant when the reaction was performed in THF (entry 10). These results confirmed that the presence of water is crucial in forcing the reaction to occur preferentially at the methyl group of hydroxyacetone. In contrast to the proline amides efficiently catalyzing the reaction in aqueous media, proline did not have any catalytic activity (entry 11).

The superior organocatalyst **9** was then extended to a broad scope of aldehydes, and the results are summarized in Table 2. Excellent enantioselectivities, with *ee* values ranging from 91 to 99% *ee*, were observed for all the aldehydes tested regardless of the sterical and electronic properties of the substitutent. Notably, the current process has much more general applicability for aldehydes than that reported previously.[22] Peptides **1** and **2** were unable to catalyze the aldol reaction of the *para*-chloro- and *para*-phenylbenzaldehydes (**3k** and **3n**) with hydroxyacetone,[22] but the organocatalyst **9** gave high and moderate yields for **3k** and **3n**, respectively, both with an excellent 95% *ee* (entries 11 and 14). Benzaldehyde, which was unreactive toward hydroxyacetone in aqueous media with peptides as the catalysts, also gave high enanantioselectivities of up to 97% *ee* with orga-

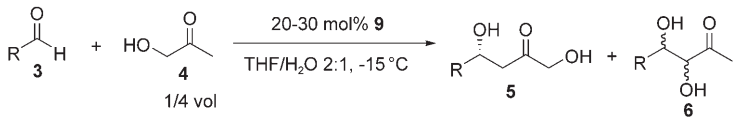
Table 1. Screening catalysts and optimizing reaction conditions.[a]



Entry	Cat.	Amount of THF/H_2O [mL]	Amount of **4** [mL]	T [°C]	t [d]	Yield of **5a** [%][b]	*ee* [%][c]	Yield of **6a** [%][b]
1	**7a**	1/1	0.4	0	5	73	46	25
2	**7b**	1/1	0.4	0	10	44	49	10
3	**7c**	1/1	0.4	0	10	47	51	13
4	**7d**	1/1	0.4	0	10	68	52	12
5	**8**	1/1	0.4	25	1	80	78	18
6	**8**	1/1	0.4	0	1.5	91	84	8
7	**8**	1/0.5	0.5	−15	2.5	87	87	12
8	**9**	1/1	0.4	0	3	92	90	7
9	**9**	1/0.5	0.5	−15	2.5	95	95	<5
10	**9**	THF	0.5	0	2.5	36	97	58
11	proline	1/1	0.4	0	5	0	–	0

[a] Unless otherwise specified, the concentration of aldehyde is 0.25 M. [b] Isolated yield based on aldehyde and the product. [c] The *ee* values were determined by HPLC.

Table 2. Direct aldol reaction of various aldehydes.[a]



Entry	Aldehyde (**3**)	Loading of **9** [%]	*t* [d]	Product **5**		Product **6**
				Yield [%][b]	*ee* [%][c]	Yield of **6** [%]
1	4-$NO_2C_6H_4$ (**3a**)	20	2.5	95 (76)	95 (87)	<5
2	2-ClC_6H_4 (**3b**)	20	3	84 (56)	93 (86)	9
3	4-$CF_3C_6H_4$ (**3c**)	20	3	90 (66)	96 (88)	8
4	2-$NO_2C_6H_4$ (**3d**)	20	3.5	77 (71)	91 (93)	5
5	3-$NO_2C_6H_4$ (**3e**)	20	2.5	89 (80)	95 (89)	7
6	3,5-$Br_2C_6H_3$ (**3f**)	20	3	85 (59)	96 (92)	7
7	4-CNC_6H_4 (**3g**)	20	3.5	90 (70)	94 (84)	8
8	3,5-$(CF_3)_2C_6H_3$ (**3h**)	20	2.5	79	96	12
9	2-BrC_6H_4 (**3i**)	20	3.5	84	93	8
10	4-BrC_6H_4 (**3j**)	30	5	69	93	12
11	4-ClC_6H_4 (**3k**)	30	5	70 (trace)	95 (–)	11
12	2-FC_6H_4 (**3l**)	30	3.5	80	93	10
13	2,6-$Cl_2C_6H_3$ (**3m**)	30	3	84 (73)	99 (96)	10
14	4-PhC_6H_4 (**3n**)	30	5	40 (trace)	95 (–)	11
15	1-$BrC_{10}H_6$ (**3o**)	30	5	77	99	9
16	Ph (**3p**)	30	5	44 (0)	97 (–)	trace
17	*c*-C_6H_{11} (**3q**)	30	5	28 (0)	98 (–)	trace

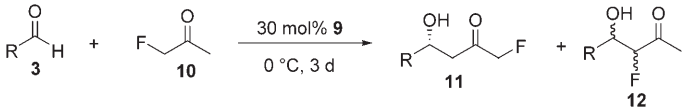
[a] Unless otherwise specified, the concentration of aldehyde is 0.25 M. [b] Isolated yield. The yields in parentheses are those obtained with peptide **2** (reference [22]). [c] Determined by HPLC. The *ee* values in parentheses are those obtained with peptide **2** (reference [22]).

nocatalyst **9** (entry 16). More importantly, an aliphatic aldehyde, such as cyclohexylformaldehyde, a very challenging substrate for direct aldol reactions in water,[14j,22] reacted with the hydroxyacetone in the presence of **9** with an excellent enantioselectivity (98% *ee*, entry 17). Apparently, the L-proline amide **9** is more enantioselective than either of peptides **1** or **2**, as indicated in the reactions that all of them catalyzed (entries 1–3, 5–7, and 13). The regioselectivities to 1,4-diols **5** were also significantly improved in comparison with those in the previous process.[22]

Aldolization of aldehydes with fluoroacetone: Fluorinated organic compounds play an important role in the preparation of pharmaceuticals.[26] A great number of studies have indicated that the α-fluoro carbonyl compounds are particularly useful in glycobiology research.[27] Asymmetric direct aldol reactions between aldehydes and fluoroacetone conveniently access the optically active α-fluoro carbonyl compounds, but it is a great challenge to control the reaction to selectively generate a single isomer as a mixture of at least six isomers is principally produced. Direct aldol reactions of fluoroacetone with aldehydes catalyzed by an amino alcohol preferentially gave *anti*-α-fluoro-β-hydroxy ketones **12** with good enantioselectivities and with an excellent regioselectvity of 94%.[28] The enzyme-catalyzed direct aldol reaction of fluoroacetone with an aldehyde favored the formation of **11** in a modest yield (40%).[29] The direct generation of **11** by aldolization activated by small chiral catalysts has not been realized yet and awaits further development.

In the presence of 30 mol% of organocatalyst **9**, the direct aldol reaction of aldehydes with fluoroacetone was attempted (Table 3). In an organic solvent, such as THF, the reaction dominantly afforded **12** in 94% yield with a regiomeric ratio of **11**/**12** 2:98 and an excellent enantioselectivity of 95% *ee* (entry 1). Interestingly, the regioselectivity was reversed when the reaction was conducted in an aqueous medium, demonstrating that the water plays an important role in the control of the otherwise disfavored regioselectivity. Compared with hydroxyacetone (Table 2), fluoroacetone is less reactive toward aldehydes in aqueous solution, with relatively lower isolated yields. Both the regioselectivity of **11**/**12** and the enantioselectivity of **11** varied as the substituents of the aldehyde changed. High enantioselectivities of up to 91% *ee* were observed.

Table 3. Direct aldol reaction of fluoroacetone with aldehydes.[a]



Entry	Aldehyde (**3**)	Solvent	Ratio of **11**/**12**[b]	Yield of **11** [%][c]	*ee* of **11** [%][d]
1	4-$NO_2C_6H_4$ (**3a**)	THF	2:98[e]	–	–
2	4-$NO_2C_6H_4$ (**3a**)	THF/H_2O 1:1	85:15	62	80
3	3,5-$Br_2C_6H_3$ (**3f**)	THF/H_2O 1:1	67:33	57	84
4	3-$NO_2C_6H_4$ (**3e**)	THF/H_2O 1:1	70:30	55	83
5	2,6-$Cl_2C_6H_3$ (**3m**)	THF/H_2O 1:1	87:13	65	91

[a] Unless otherwise specified, the concentration of aldehyde is 0.25 M. [b] The ratio was determined by ^{1}HNMR spectroscopic analysis of the crude product. [c] Isolated yield. [d] Determined by HPLC. [e] Isolated yield of **12** is 94%, the diastereomeric ratio of *anti*/*syn* is 2:1 on the basis of the ^{1}HNMR spectrum of the crude product, and the enantiomeric excess of the *anti* diastereomer is 95%.

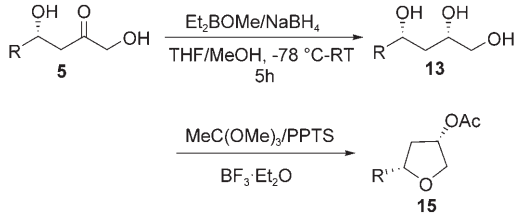
Preparation of optically active 1,2,4-triols and 3,5-disubstituted tetrahydrofurans: Optically active polyhydroxyl compounds are very useful intermediates in asymmetric organic syntheses.[1] The diastereoselective reduction of 1,4-diols 5 from the aldol reaction of hydroxyacetone and aldehydes generated a class of enantioenriched 1,2,4-triols. To optimize suitable conditions for the diastereoselective reduction of **5a**, the effect of different reducing reagents was examined.

As shown in Table 4, the diastereoselectivity varied with respect to reductive reagents. Sodium boronhydride ($NaBH_4$) gives very low diastereoselectivity (2:1) favoring the *syn*-4-(4′-nitrophenyl)butane-1,2,4-triol (**13a**) (entry 1). The combined reagent of Et_3B[30] and $NaBH_4$, reduced **5a** to **13a** with an improved diastereomeric ratio of 82:18 (entry 2). The diastereoselectivity was further increased from 82:18 to 86:14 by the replacement of Et_3B with Et_2BOMe[31] (entry 3). K-selectride also provided a good diastereomeric ratio of 84:16 (entry 4).[32] The use of $NaBH(OAc)_3$[33] to reduce **5a** favored the *anti*-4-(4′-nitrophenyl)butane-1,2,4-triol (**14a**) in a diastereomeric ratio of 16:84 (entry 5). $Me_4NBH(OAc)_3$[34] reduced **5a** to give mainly **13a** with a diastereomeric ratio of 75:25. Thus, the combined reagent of Et_2BOMe and $NaBH_4$ is best for the generation of **13a** by reduction of **5a**.

Substituted tetrahydrofurans are very important synthetic building blocks for the construction of many natural products. Recently, Borhan and co-workers discovered an efficient one-pot stereoselective cyclization reaction of 1,2-*n*-triols to give substituted tetrahydrofurans with high stereoselectivity.[35] Triols **13a** and **14a**, readily obtained from the diastereoselective reduction of compounds **5a**, were treated with a combined reagent of $MeC(OMe)_3$, PPTS (PPTS = pyridinium *p*-toluenesulphonate), and $BF_3{\cdot}Et_2O$, respectively, to give the (3*S*,5*S*)- and (3*R*,5*S*)-acetic acid 5-(4-nitrophenyl)tetrahydrofuran-3-yl esters (**15a** and **16a**) in high yields, maintaining the enantiomeric excesses. Interestingly, the absolute configuration of the chirality at C4 reversed from *R* to *S*, and no diastereomers (**17a** of **15a** or **18a** of **16a**) were detected (Scheme 2).

The diastereoselective reduction with the combined reagent of Et_2BOMe and $NaBH_4$ and cyclization reactions were then extended to the chiral 1,4-diols **5a**, **5f**, **5g**, and **5m** for the syntheses of the optically active 3,5-disubstituted tetrafurans **15**. Table 5 summarizes the results. The diastereoselectivity of the reduction reaction was highly dependent on the substituent of the 1,4-diols **5** and it tended to increase as the bulkiness of the substituent increased. For example, **5f** and **5m** provided much higher diastereomeric ratios (91:9 and >99:1, respectively) than did **5a** and **5g** (86:14 and 85:15, respectively) with the combined reductive reagent of $Et_2BOMe/NaBH_4$. Following treatment with $MeC(OMe)_3$, PPTS, and $BF_3{\cdot}Et_2O$, **13a–d** underwent cyclization smoothly to give the 3,5-disubstituted tetrafurans **15a–d** in good yields; the diastereomers of **15a–d** were not observed.

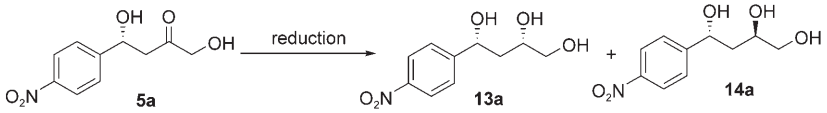
Table 5. Diastereoselective reduction of **5** and the preparation of **15**.[a]



Entry	R (**5**)	*dr* (*syn*:*anti*)[b]	Product **13**	Yield [%][c]	Product **15**	Yield [%][d]
1	4-$NO_2C_6H_4$ (**5a**)	86:14	**13a**	71	**15a**	71
2	3,5-$Br_2C_6H_3$ (**5f**)	91:9	**13b**	84	**15b**	81
3	4-CNC_6H_4 (**5g**)	85:15	**13c**	75	**15c**	74
4	2,6-$Cl_2C_6H_3$ (**5m**)	>99:1	**13d**	78	**15d**	65

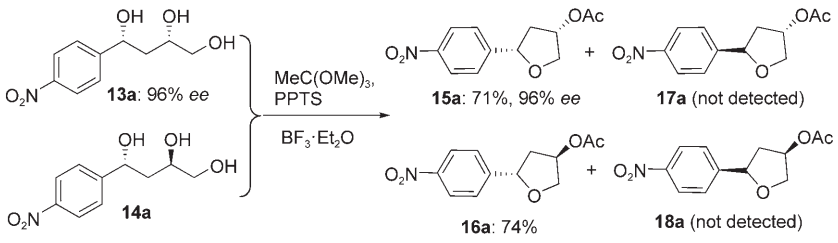
[a] The reaction was carried out on a 0.5 mmol scale. [b] Determined by ^1H NMR spectroscopy. [c] Isolated yield of **13**. [d] Isolated yield based on analytically pure **15** and **13**.

Table 4. Optimization of the conditions for the diastereoselective reduction of **5a**.



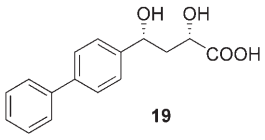
Entry	Reagent	Solvent	*T* [°C]	*t* [h]	*dr* (**13a**: **14a**)[a]	Yield [%] (**13a**+**14a**)[b]
1	$NaBH_4$	MeOH	0	1	2:1	75
2	$Et_3B/NaBH_4$	THF	−78–RT	5	82:18	87
3	$Et_2BOMe/NaBH_4$	THF/MeOH	−78–RT	5	86:14	90
4	K-selectride	THF	−78–RT	5	84:16	89
5	$NaBH(OAc)_3$	AcOH/THF	−78–RT	3	16:84	96
6	$Me_4BH(OAc)_3$	AcOH/CH_3CN	−40	24	75:25	95

[a] Determined by ^1H NMR spectroscopic analysis of the crude product. [b] Isolated yield.



Scheme 2. Synthesis of esters **15a** and **16a**.

Synthesis of (2*S*,4*R*)-dihydroxy-4-biphenylbutyric acid: (2*S*,4*R*)-Dihydroxy-4-biphenylbutyric acid (**19**) and its structural analogues have shown anti-inflammatory and antiplatelet aggregation activity.[36] (2*S*,4*R*)-Dihydroxy-4-biphenylbutyric acid (**19**) was originally obtained from the urinary excretion of guinea pigs that



were dosed with 3-(4-biphenylylcarbonyl)propionic acid, a biological transformation precursor to both threo- and erythro-2,4-dihydroxy-4-biphenylbutyric acids.[36]

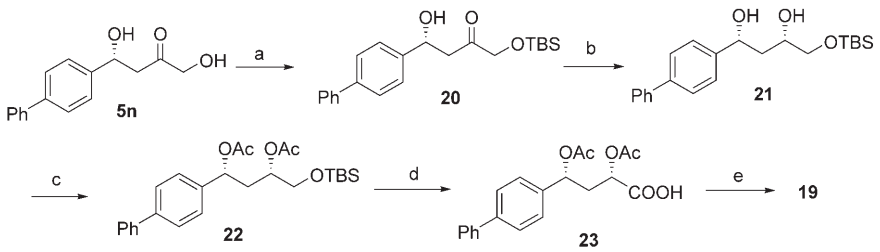
The organocatalyzed asymmetric direct aldol reaction presented here was the basis for the preparation of optically pure 2*S*,4*R*-dihydroxy-4-biphenylbutyric acid (**19**), as illustrated in Scheme 3. (*R*)-1,4-Dihydroxy-4-biphenyl-butan-2-one (**5n**), which was obtained from the direct aldol reaction of 4-phenylbenzaldehyde with hydroxyacetone with 95% *ee*, was treated with *tert*-butyldimethylsilylchloride (TBSCl) and triethylamine to give compound **20**. Diastereoselective reduction of **20** with a combined reagent of $Et_2BOMe/NaBH_4$ afforded **21** in 97% yield with a diastereomeric ratio of 97:3 in favor of the *syn* diastereomer. Compound **21** then underwent an esterification reaction by using acetic anhydride in pyridine with a catalytic amount of dimethylaminopyridine (DMAP), generating compound **22** in 95% yield. Compound **22** then underwent Jones oxidation to give **23** in 71% yield. Finally, removal of the acyl groups in compound **23** with lithium hydroxide (LiOH) gave the target molecule **19** in 90% yield.

Theoretical studies on the role of water in controlling regioselectivity: The quantum mechanics calculation has been carried out previously on the direct aldol reactions catalyzed by proline[37] and proline amide derivatives.[10] These studies revealed that the formation of a hydrogen bond between the carboxylic acid of proline or amide group of proline amide derivatives and the carbonyl group of aldehyde in the process of the addition of the enamine intermediate, formed from the condensation of acetone with proline or proline amide derivatives, to aldehyde is crucial in controlling the stereochemistry. To further understand the factors of controlling the distinct regioselectivity in water from that in organic solvent, such as THF, we have studied the two kinds of different intermediate, enamine model **I** and enol-enamine model **II**, and the corresponding transition structures of the two intermediates with benzaldehyde by theoretical calculations with the Gaussian 03 program.[38] Geometries were fully optimized and characterized by frequency analysis using the HF/6-31+G* method, and each transition structure was validated with one imaginary frequency related to the C–C-bond formation. Based on the fully-optimized structures, the energy of each structure was further evaluated by using hybrid density functional theory (B3LYP) and the 6-31++G** basis set as implemented in Gaussian 03, and corrected by calculated zero-point energies from the frequency analysis using the HF/6-31+G* method. Solvation was modeled by microsolvation with explicit solvent molecule water as the donor and/or acceptor in the formation of a hydrogen bond with the hydroxyl group of either the intermediates or transition-state structures.

As shown in Figure 1, the intermediate enamine 01 was predicted to be a little more favorable than the enol-enamine with a slightly lower enthalpy of about 0.5 kcal mol^{-1} in the gas phase for the best two different intermediates (enamine 01 and enol-enamine 02), although there are various orientations for the hydroxyl group. The difference is so little that the reversible transformation between these two isomers results in the competitive formation of products 1,2-diols and 1,4-diols, which should be controlled by the addition reaction of either the enamine or enol-enamine to benzaldehyde. The transition structures were located for the reaction as shown also in Figure 1. The hydroxyl group can adopt two conformations in both intermediates, enamine and enol-enamine, and corresponding transition structures were located as TS-1,2 and TS-1,4 (TS = transition state), respectively. The best transition structures for the aldolization of hydroxylacetone with benzaldehyde are similar to those for the aldol reaction of acetone with benzaldehyde in the presence of a proline amide,[10] except that the hydroxyl group functions differently in two isomers, TS-1,2 and TS-1,4. It was predicted that TS-1,2-01, which leads to the formation of the major product observed experimentally in polar aprotic solvents, such as THF, is much more stable than TS-1,4 with a much lower enthalpy of about 6 kcal mol^{-1} and a lower reaction barrier of about 4 kcal mol^{-1}, due to the promotion of electron density from the hydroxyl group conjugated to the carbon–carbon double bond of enol-enamine in TS-1,2.

However, the hydroxyl group in both enol-enamine and enamine can act as a hydrogen-bond donor and/or acceptor in aqueous media and it is just possible to be a donor in THF. The regioselectivity of the reaction would vary as the reaction solvent changes from an organic solvent to the aqueous one. It is reasonable to explore the situations in aqueous solution by considering the formation of a hydrogen bond between the solvent molecule and the intermediate. To investigate the special function of the solvent molecule water in this reaction, the character of the complexes of the water molecule with intermediates enamine and enol-enamine was also studied by theoretical calculations.

Of all complexes of intermediates, enol-enamine and



Scheme 3. Preparation of (2*S*,4*R*)-dihydroxy-4-biphenylbutyric acid. a) TBSCl, Et_3N, DMAP (5 mol%), CH_2Cl_2, 0°C–RT, 18 h, 81%; b) $Et_2BOMe/NaBH_4$, THF/MeOH, −78°C–RT, 5 h, 97%, *dr* = 97:3; c) $(AcO)_2O$, pyridine, DMAP (5 mol%), 0°C, 3 h, 95%; d) Jones oxidation, 71%; e) $LiOH{\cdot}H_2O$, $THF/H_2O/MeOH$ 2:1:2, RT, 5 h, 90%.

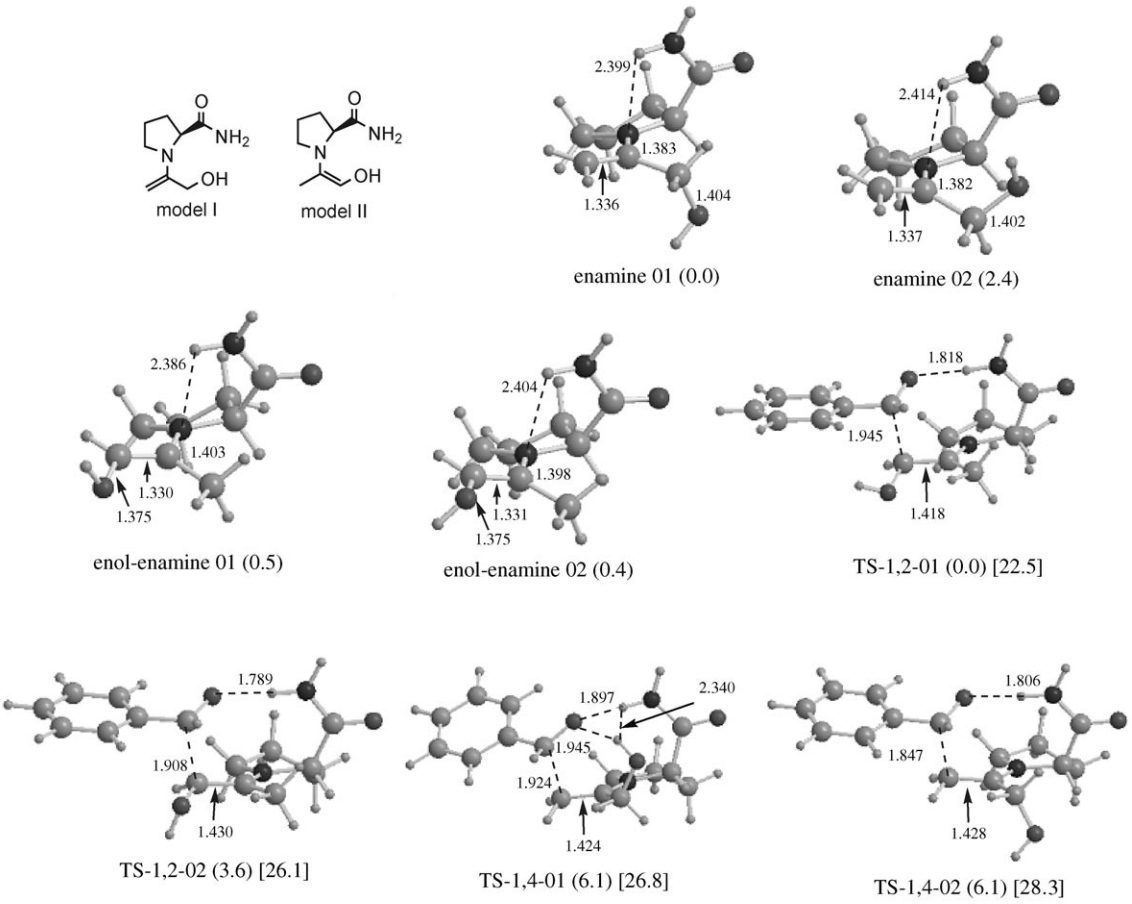


Figure 1. Model intermediates and TS structures in the gas phase with optimized geometries, partial structural parameters, and relative energies (kcal mol^{-1}): enthalpy in () and activation free energy in [].

enamine, with water (Figure 2), although there was a good H-bond for each case, as indicated by the shorter hydrogen bond as shown in complexes **I** and **II**, theoretical calculations predicted that the best complex for the formation of hydrogen bonds between two intermediates and solvent molecules H_2O was complex **II** with a higher stability of ≈ 6.6 kcal mol^{-1}. The explanation for this is that the water molecule acts like a bridge to form a hydrogen bond with the proton of the hydroxy group in the enamine moiety and the amide oxygen, respectively. Such a strong solvation effect made the formation of the enamine (complex **II**) much more favorable than the enol-enamine (complex **I**) in the aqueous

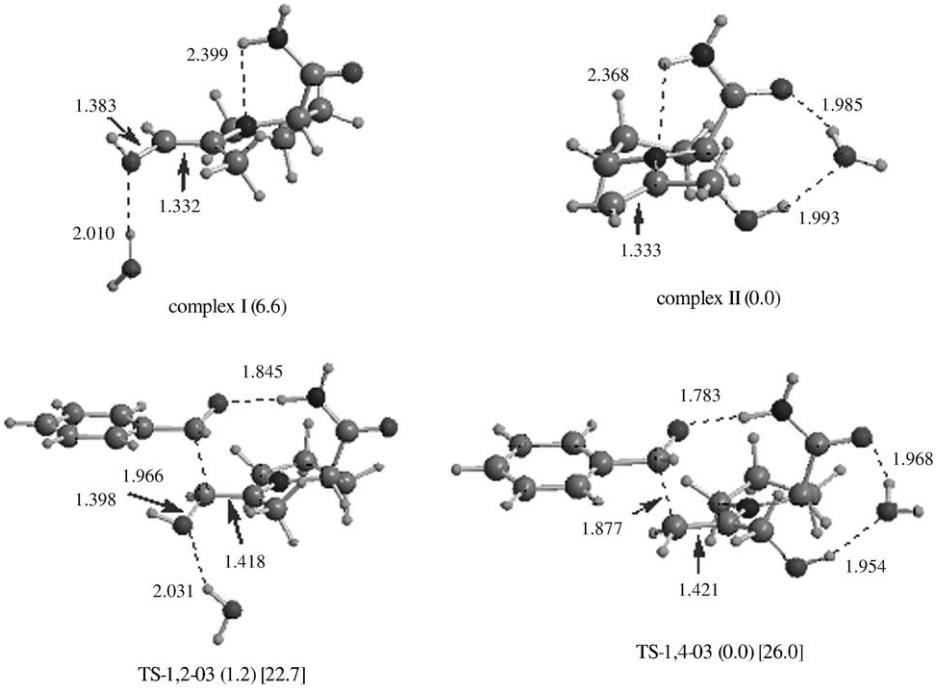


Figure 2. Optimized geometries of H_2O-solvated intermediates and TS structures, partial structural parameters and relative energies (kcal mol^{-1}): enthalpy in () and activation free energy in [].

media. This hydrogen-bonding network should exist in the whole reaction process. As indicated by the located transition-state structures, TS-1,2-03 was an early TS compared to TS-1,4-03, the distance of the C–C bond being formed in TS-1,2-03 is longer than that in TS-1,4-03 by about 0.1 Å. However, the later is favored with a lower enthalpy of about 1.2 kcal mol^{-1} due to stabilization by the two hydrogen bonds formed between water and both the hydroxyl group and amide oxygen. The solvation interactions stabilized the late TS of TS-1,4-03 and reduced the activation energy highly. Although the lower stability of the intermediate enol-enamine reduced the activation energy of TS-1,2-03 substantially, the barrier of TS-1,2-03 is slightly lower than TS-1,4-04 by about 3.3 kcal mol^{-1}. Considering the evaluated total barrier reaching to 23–26 kcal mol^{-1}, the selectivity to generate either of the 1,2- or 1,4-diols should not only depend on the activation barrier, but also on the stability of the two intermediates, complexes **I** and **II**. The favorable formation of the excellent H-bonding bridge in complex **II** in aqueous media was beneficial to the regioselective formation of 1,4-diol, which was the major product observed experimentally in the aqueous solution. While in pure THF, it was impossible to form such a bridged H-bond to stabilize both intermediate and TS, therefore the formation of the 1,2-diol became a dominant product.

Conclusions

L-Proline amides derived from simple amines and optically pure β-amino alcohols have been evaluated for their ability at catalyzing the direct aldol reaction of hydroxyacetone with 4-nitrobenzaldehyde in aqueous media, demonstrating that the organocatalyst prepared from (2*R*,3*R*)-diethyl 2-amino-3-hydroxysuccinate and L-proline shows superior stereo- and regiocontrol for the reaction. In the presence of 20–30 mol% of the catalyst, excellent enantioselectivities ranging from 91 to 99% *ee* and high regioselectivities were observed for the otherwise disfavored products from direct aldol reactions of hydroxyacetone with a broad scope of aldehydes. Aldolizations of fluoacetone with aldehydes mediated by 30 mol% of the organocatalyst in aqueous media preferentially occurred at the methyl group with good regioselectivities (up to 7:1) and high enantioselectivities (up to 91% *ee*). The aldol adducts from the reaction of hydroxyacetone have been used for the preparation of chiral 3,5-disubstituted tetrafurans in high optical purity and a biologically active compound, (2*S*,4*R*)-dihydroxy-4-biphenylbutyric acid. Theoretical studies on the transition states by using a microsolvation model revealed that the role of water in controlling the regioselectivity arises from the hydrogen bonds formed between water and the amide oxygen of the proline amide and hydroxy of hydroxyacetone.

Experimental Section

General data: NMR spectra were recorded on a Brucker 300 MHz spectrometer. Optical rotations were measured on a Perkin–Elmer 241 Polarimeter at $\lambda = 589$ nm. FTICR-MS spectra were recorded on P-SIMS-Gly of Bruker Daltonics. IR spectra were recorded on a Nicolet MX-1E FTIR spectromter. HPLC analysis was performed on Waters-Breeze (2487 Dual λ Absorbance Detector and 1525 Binary HPLC Pump). Chiralpak AS, AD, OD, and OJ columns were purchased from Daicel Chemical Industries. Hexane and ethyl acetate for column chromatography were distilled before use.

Materials: All starting materials were purchased from Acros or Aldrich and used directly

General procedure for the aldol reaction: Hydroxyacetone (0.5 mL) was added to a solution of the aldehyde (0.5 mmol) and catalyst (20–30 mol%) in a solvent mixture of H_2O (0.5 mL) and THF (1.0 mL). After the reaction mixture had been stirred at −15 °C for 2.5–5 days, the reaction was quenched with saturated aqueous ammonium chloride solution and the layers were separated. The aqueous layer was extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. After removal of solvent, the residue was purified by flash-column chromatography on silica gel (CH_2Cl_2/AcOEt 6:1) to give the pure adducts.

1,4-Dihydroxy-4-(4-nitrophenyl)butan-2-one (5a): Table 2, entry 1; Yield: 95%; white solid; m.p. 80–82 °C; $[\alpha]_D^{25} = +51.6$ ($c = 0.31$ in EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.75$–2.92 (m, 2H), 2.95–2.99 (t, $J = 5.0$ Hz, 1H), 3.14 (d, $J = 3.5$ Hz, 1H), 4.3 (d, $J = 4.9$ Hz, 2H), 5.3 (m, 1H), 7.6 (d, $J = 8.8$ Hz, 2H), 8.23 ppm (d, $J = 8.8$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 46.9$, 68.2, 68.5, 123.0, 126.4, 147.5, 151.9, 208.2 ppm; IR (KBr): $\tilde{\nu} = 3382$, 2898, 1735, 1604, 1516, 1344, 1081, 1052, 858 cm^{-1}; 95% *ee*, determined by HPLC (Daicel Chiralpak AS-H, *i*PrOH/hexane 30:70), detection method = UV spectroscopy ($\lambda = 254$ nm), flow rate = 1.0 mL min^{-1}, *R* isomer: $t_R = 12.8$ min, *S* isomer: $t_R = 16.8$ min.

4-(2-Chlorophenyl)-1,4-dihydroxybutan-2-one (5b): Table 2, entry 2; Yield: 84%; colorless oil; $[\alpha]_D^{25} = +73.9$ ($c = 0.41$ in EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.34$–2.92 (m, 2H), 3.47 (m, 1H), 4.29 (dd, $J = 19.2$, 23.4 Hz, 2H), 5.57 (m, 1H), 7.22–7.34 (m, 3H), 7.60 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 45.3$, 66.6, 68.8, 126.8, 127.3, 128.8, 129.4, 139.8, 209.2 ppm; IR (KBr): $\tilde{\nu} = 3334$, 2904, 1721, 1594, 1489, 1088, 1056 cm^{-1}; 93% *ee*, determined by HPLC (Daicel Chiralpak AS-H, *i*PrOH/hexane 30:70), detection method = UV spectroscopy ($\lambda = 254$ nm), flow rate = 1.0 mL min^{-1}, *R* isomer: $t_R = 7.6$ min, *S* isomer: $t_R = 6.5$ min.

1,4-Dihydroxy-4-(4-trifluoromethylphenyl)butan-2-one (5c): Table 2, entry 3; Yield: 90%; white solid; m.p. 104–105 °C; $[\alpha]_D^{25} = +52.3$ ($c = 0.30$ in EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.71$–2.92 (m, 2H), 4.26 (s, 2H), 5.29 (m, 1H), 7.48 (d, $J = 8.1$ Hz, 2H), 8.24 ppm (d, $J = 8.1$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 47.2$, 69.1, 69.5, 124.1 (q, $J = 270$ Hz), 125.8 (q, $J = 3.8$ Hz), 126.0, 130.3 (q, $J = 32$ Hz), 146.5, 209.0 ppm; IR (KBr): $\tilde{\nu} = 3392$, 2907, 1722, 1618, 1304, 1110, 1068, 842 cm^{-1}; 96% *ee*, determined by HPLC (Daicel Chiralpak AS-H, *i*PrOH/hexane 15:85), detection method = UV spectroscopy ($\lambda = 254$ nm), flow rate = 1.0 mL min^{-1}; *R* isomer: $t_R = 16.0$ min, *S* isomer: $t_R = 19.0$ min.

1,4-Dihydroxy-4-(2-nitrophenyl)butan-2-one (5d): Table 2, entry 4; Yield: 82%; white solid; m.p. 108–110 °C; $[\alpha]_D^{28} = -105.9$ ($c = 0.32$ in EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.84$ (m, 2H), 4.29 (s, 2H), 5.67 (m, 1H), 7.48 (m, 1H), 7.71 (m, 1H), 7.91 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 47.9$, 66.0, 69.3, 125.1, 129.2, 129.3, 134.4, 141.1, 148.8, 209.3 ppm; IR (KBr): $\tilde{\nu} = 3361$, 2941, 1715, 1608, 1577, 1523, 1514, 1089, 1019, 741 cm^{-1}; 92% *ee*, determined by HPLC (Daicel Chiralpak AS-H, *i*PrOH/hexane = 30:70), detection method = UV spectroscopy ($\lambda = 254$ nm), flow rate = 1.0 mL min^{-1}, *R* isomer: $t_R = 12.6$ min, *S* isomer: $t_R = 10.2$ min.

1,4-Dihydroxy-4-(3-nitrophenyl)butan-2-one (5e): Table 2, entry 5; Yield: 89%; white solid; m.p. 132–134 °C; $[\alpha]_D^{25} = +24.4$ ($c = 0.32$ in EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.16$–2.94 (m, 2H), 4.24 (dd, $J = 18.7$, 23.2 Hz, 2H), 5.27 (m, 1H), 7.58 (t, $J = 8.0$ Hz, 1H), 7.79 (d, $J = 7.7$ Hz, 1H), 8.13 (m, 1H), 8.30 ppm (d, $J = 1.7$ Hz, 1H); ^{13}C NMR (75 MHz,

$CDCl_3$): δ = 47.0, 68.2, 68.4, 120.3, 121.8, 129.2, 131.8, 146.8, 148.4, 208.3 ppm; IR (KBr): $\tilde{\nu}$ = 3482, 3379, 2909, 1716, 1599, 1508, 1344, 1081, 1058, 810, 741 cm^{-1}; 95% *ee*, determined by HPLC (Daicel Chiralpak AS-H, *i*PrOH/hexane 20:80), detection method = UV spectroscopy (λ = 254 nm), flow rate = 1.0 mL min^{-1}, *R* isomer: t_R = 24.3 min, *S* isomer: t_R = 28.6 min.

4-(3,5-Dibromophenyl)-1,4-dihydroxybutan-2-one (5f): Table 2, entry 6; Yield: 85%; white solid; m.p. 91–93 °C; $[\alpha]_D^{25}$ = +38.2 (*c* = 0.51 in EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.34–2.94 (m, 2H), 4.28 (s, 2H), 5.16 (m, 1H), 7.44 (d, *J* = 1.4 Hz, 1H), 7.58 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 46.9, 68.6, 68.9, 123.2, 127.4, 133.5, 146.4, 208.7 ppm; IR (KBr): $\tilde{\nu}$ = 3432, 2882, 1719, 1583, 1554, 1122, 1035, 850, 741 cm^{-1}; 96% *ee*, determined by HPLC (Daicel Chiralpak AS-H, *i*PrOH/Hexane 20:80), detection method detection method = UV spectroscopy (λ = 254 nm), flow rate = 1.0 mL min^{-1}; *R* isomer: t_R = 8.6 min, *S* isomer: t_R = 10.8 min.

1,4-Dihydroxy-4-(4-cyanophenyl)butan-2-one (5g): Table 2, entry 7; Yield: 90%; colorless oil; $[\alpha]_D^{25}$ = +24.4 (*c* = 0.32 in EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.71–3.26 (m, 2H), 4.27 (s, 2H), 5.29 (m, 1H), 7.49 (d, *J* = 8.2 Hz, 2H), 7.65 ppm (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 46.9, 68.9, 69.1, 111.7, 118.5, 126.2, 132.4, 147.7, 208.7 ppm; IR (KBr): $\tilde{\nu}$ = 3411, 2922, 2229, 1720, 1609, 1559, 1504, 1409, 1110, 1072, 842, 681 cm^{-1}; 94% *ee*, determined by HPLC (Daicel Chiralpak AS-H, *i*PrOH/hexane 30:70), detection method = UV spectroscopy (λ = 254 nm), flow rate = 1.0 mL min^{-1}, *R* isomer: t_R = 13.4 min, *S* isomer: t_R = 21.0 min.

4-(3,5-Bis-trifluoromethylphenyl)-1,4-dihydroxybutan-2-one (5h): Table 2, entry 8; Yield: 79%; white solid; m.p. 119–121 °C; $[\alpha]_D^{25}$ = +39.7 (*c* = 0.30 in EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.77–2.94 (m, 2H), 3.29 (d, *J* = 3.0 Hz, 1H), 4.33 (d, *J* = 3.0 Hz, 2H), 5.39 (d, *J* = 4.5 Hz, 1H), 7.82 (s, 1H), 7.9 ppm (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 46.9, 68.6, 68.9, 121.9, 124.9, 125.9, 131.8, 144.9, 208.7 ppm; IR (KBr): $\tilde{\nu}$ = 3424, 2919, 1719, 1623, 1279, 1132, 1074, 842, 681 cm^{-1}; 96% *ee*, determined by HPLC (Daicel Chiralpak AS-H, *i*PrOH/hexane 5:95), detection method = UV spectroscopy (λ = 254 nm), flow rate = 1.0 mL min^{-1}, *R* isomer: t_R = 11.1 min, *S* isomer: t_R = 13.6 min; HRMS (FTICR-MS): *m*/*z*: calcd for $C_{12}H_9F_6O_3$: 315.0450 $[M]^+$; found: 315.0460.

1,4-Dihydroxy-4-(2-bromophenyl)butan-2-one (5i): Table 2, entry 9; Yield: 84%; white solid; m.p. 72.5–73.5 °C; $[\alpha]_D^{25}$ = +63.1 (*c* = 0.71 in EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.64–2.94 (m, 2H), 3.19 (brs, 2H), 4.31 (s, 2H), 5.52 (m, 1H), 7.17 (m, 1H), 7.36 (m, 1H), 7.52 (m, 1H); 7.61 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 45.5, 68.7, 68.8, 121.1, 127.1, 127.9, 129.2, 132.7, 141.4, 209.1 ppm; IR (KBr): $\tilde{\nu}$ = 3394, 2909, 1718, 1566, 1466, 1071, 1056, 758 cm^{-1}; 93% *ee*, determined by HPLC (Daicel Chiralpak AS-H, *i*PrOH/hexane 15:85), detection method = UV spectroscopy (λ = 254 nm), flow rate = 1.0 mL min^{-1}, *R* isomer: t_R = 14.9 min, *S* isomer: t_R = 13.2 min; HRMS (FTICR-MS) *m*/*z*: calcd for $C_{10}H_{11}BrO_3$+Na^+: 280.9784; found: 280.9774.

4-(4-Bromophenyl)-1,4-dihydroxybutan-2-one (5j): Table 2, entry 10; Yield: 69%; white solid; m.p. 110–112 °C; $[\alpha]_D^{25}$ = +54.1 (*c* = 0.32 in EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.68–2.91 (m, 2H), 2.93 (d, *J* = 3.0 Hz, 1H), 3.04 (t, *J* = 4.9 Hz, 1H), 4.27 (d, *J* = 3.1 Hz, 2H), 5.19 (m, 1H), 7.23 (d, *J* = 6.6 Hz, 2H), 7.48 ppm (d, *J* = 6.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 47.1, 68.9, 69.4, 121.9, 127.2, 131.8, 141.5, 208.9 ppm; IR (KBr): $\tilde{\nu}$ = 3318, 2902, 1721, 1589, 1484, 1397, 1077, 1054, 825 cm^{-1}; 93% *ee*, determined by HPLC (Daicel Chiralpak AS-H, *i*PrOH/hexane 15:85), detection method = UV spectroscopy (λ = 254 nm), flow rate = 1.0 mL min^{-1}, *R* isomer: t_R = 16.9 min, *S* isomer: t_R = 20.1 min; HRMS (FTICR-MS): *m*/*z*: calcd for $C_{10}H_{11}BrO_3$+Na^+: 280.9784; found: 280.9777.

4-(4-Chlorophenyl)-1,4-dihydroxybutan-2-one (5k): Table 2, entry 11; Yield: 70%; white solid; m.p. 103–105 °C; $[\alpha]_D^{30}$ = +45.0 (*c* = 0.30 in EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.68–2.91 (m, 2H), 2.88 (s, 1H), 3.01 (s, 1H), 4.28 (s, 2H), 5.21 (m, 1H), 7.30 (d, *J* = 6.2 Hz, 2H), 7.34 ppm (d, *J* = 6.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 47.2, 69.0, 69.4, 126.9, 128.8, 133.7, 141.0, 209.0 ppm; IR (KBr): $\tilde{\nu}$ = 3434, 3329, 2921, 1729, 1623, 1470, 1109, 1078 cm^{-1}; 95% *ee*, determined by HPLC (Daicel Chiralpak AS-H, *i*PrOH/hexane 15:85); detection method = UV spectroscopy (λ = 254 nm); flow rate = 1.0 mL min^{-1}, *R* isomer: t_R = 17.1 min, *S* isomer: t_R = 19.5 min; HRMS (FTICR-MS): *m*/*z*: calcd for $C_{10}H_{11}ClO_3$+Na^+: 237.0289; found: 237.0294.

1,4-Dihydroxy-4-(2-fluorophenyl)butan-2-one (5l): Table 2, entry 12; Yield: 80%; white solid; m.p. 67–69 °C; $[\alpha]_D^{25}$ = +70.5 (*c* = 0.60 in EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.81–2.94 (m, 2H), 3.07 (s, 2H), 4.23 (s, 2H), 5.50 (m, 1H), 7.03 (m, 1H), 7.18 (m, 1H), 7.27 (m, 1H); 7.52 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 45.7, 64.3, 68.7 (d, *J* = 12.2 Hz), 115.4 (d, *J* = 21 Hz), 124.5, 127.1 (d, *J* = 3.5 Hz), 129.4 (d, *J* = 8.3 Hz), 157.7, 161.0, 209.2 ppm; IR (KBr): $\tilde{\nu}$ = 3356, 2922, 1716, 1615, 1586, 1490, 1454, 1075, 1051, 765 cm^{-1}; 93% *ee*, determined by HPLC (Daicel Chiralpak AS-H, *i*PrOH/hexane 15:85), detection method = UV spectroscopy (λ = 254 nm), flow rate = mL min^{-1}, *R* isomer: t_R = 14.4 min, *S* isomer: t_R = 13.4 min; HRMS (FTICR-MS): *m*/*z*: calcd for $C_{10}H_{11}FO_3$+Na^+: 221.0584; found: 221.0578.

4-(2,6-Dichlorophenyl)-1,4-dihydroxybutan-2-one (5m): Table 2, entry 13; Yield: 82%; white solid; m.p. 94–96 °C; $[\alpha]_D^{25}$ = −10.0 (*c* = 0.34 in EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.74 (m, 1H), 3.47 (m, 1H), 4.35 (m, 2H), 6.01 (m, 1H), 7.17 (m, 1H), 7.32 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 43.4, 67.5, 129.4, 129.6, 134.5, 135.9, 207.8 ppm; IR (KBr): $\tilde{\nu}$ = 3400, 2986, 1729, 1576, 1558, 1433, 1074, 1062, 790, 766 cm^{-1}; 99% *ee*, determined by HPLC (Daicel Chiralpak OJ-H, *i*PrOH/hexane 10:90), detection method = UV spectroscopy (λ = 254 nm), flow rate = 1.0 mL min^{-1}, *R* isomer: t_R = 27.0 min, *S* isomer: t_R = 25.1 min.

4-Biphenyl-4-yl-1,4-dihydroxybutan-2-one (5n): Table 2, entry 14; Yield: 40%; white solid; m.p. 123–134 °C; $[\alpha]_D^{30}$ = +43.3 (*c* = 0.40 in EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.73–2.99 (m, 2H), 3.10 (brs, 1H), 4.29 (d, *J* = 3.7 Hz, 2H), 5.27 (m, 2H), 7.41 (m, 5H), 7.59 ppm (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 47.2, 69.0, 69.9, 126.0, 127.0, 127.4, 128.8, 140.5, 141.0, 141.5, 209.1 ppm; IR (KBr): $\tilde{\nu}$ = 3409, 3330, 2868, 1712, 1608, 1566, 1486, 1406, 1077, 1050, 843 cm^{-1}; 95% *ee*, determined by HPLC (Daicel Chiralpak AS-H, *i*PrOH/Hexane 10:90), detection method = UV spectroscopy (λ = 254 nm), flow rate = 1.0 mL min^{-1}, *R* isomer: t_R = 24.5 min, *S* isomer: t_R = 29.9 min; HRMS (FTICR-MS): *m*/*z*: calcd for $C_{16}H_{16}O_3$+Na^+: 279.0992; found: 279.0982.

4-(1-Bromonaphthalen-2-yl)-1,4-dihydroxybutan-2-one (5o): Table 2, entry 15; Yield: 77%; white solid; m.p. 103–105 °C; $[\alpha]_D^{30}$ = +59.8 (*c* = 0.61 in EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.76–3.00 (m, 2H), 3.08 (brs, 1H), 3.15 (brs, 1H), 4.35 (s, 2H), 5.90 (d, *J* = 9.6 Hz, 1H), 7.57 (m, 2H), 7.74 (d, *J* = 8.6 Hz, 1H), 7.85 (m, 2H), 8.31 ppm (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 45.5, 68.8, 69.8, 121.0, 123.8, 126.8, 127.2, 127.7, 128.2, 128.4, 132.0, 134.2, 139.3, 209.1 ppm; IR (KBr): $\tilde{\nu}$ = 3401, 2915, 1715, 1630, 1498, 1086, 1054, 1013, 821, 744 cm^{-1}; 99% *ee*, determined by HPLC (Daicel Chiralpak AS-H, *i*PrOH/hexane 30:70), detection method = UV spectroscopy (λ = 254 nm), flow rate = 1.0 mL min^{-1}, *R* isomer: t_R = 8.0 min, *S* isomer: t_R = 6.9 min; HRMS (FTICR-MS): *m*/*z*: calcd for $C_{14}H_{13}BrO_3$+Na^+: 330.9940; found: 330.9933.

1,4-Dihydroxy-4-phenylbutan-2-one (5p): Table 2, entry 16; Yield: 44%; white solid; m.p. 119–122 °C; $[\alpha]_D^{30}$ = +43.6 (*c* = 0.25 in EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.71–2.96 (m, 2H), 2.82 (brs, 1H), 3.07 (brs, 1H), 4.27 (s, 2H), 2.21–5.24 (m, 1H), 7.26–7.36 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 47.3, 69.0, 70.2, 125.5, 128.1, 128.7, 142.5, 209.1 ppm; IR (KBr): $\tilde{\nu}$ = 3526, 3312, 2921, 1716, 1499, 1452, 1390, 1075, 1050, 765, 709 cm^{-1}; 97% *ee*, determined by HPLC (Daicel Chiralpak AS-H, *i*PrOH/hexane 15:85), detection method = UV spectroscopy (λ = 222 nm), flow rate = 1.0 mL min^{-1}, *R* isomer: t_R = 16.0 min, *S* isomer, t_R = 17.4 min; HRMS (FTICR-MS): *m*/*z*: calcd for $C_{10}H_{12}O_3$+Na^+: 203.0679; found: 203.0686.

1,4-Dihydroxy-4-(cyclohexyl)butan-2-one (5q): Table 2, entry 17; Yield: 28%; colorless oil; m.p. 103–105 °C; $[\alpha]_D^{25}$ = +10.2 (*c* = 0.46 in EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.96–1.40 (m, 6H), 1.63–1.84 (m, 5H), 2.53 (brs, 1H), 2.54–2.62 (m, 2H), 3.16 (brs, 1H), 3.84–3.90 (m, 1H), 4.28 ppm (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.9, 26.0, 26.3, 28.1, 28.7, 42.4, 43.3, 68.9, 71.9, 210.6 ppm; IR (neat): $\tilde{\nu}$ = 3359, 2924, 2851, 1720, 1672, 1447, 1093, 1059 cm^{-1}; 98% *ee*, determined by HPLC (Daicel Chiralpak AD-H, *i*PrOH/hexane 30:70), detection method = UV spectroscopy (λ = 254 nm), flow rate = 1.0 mL min^{-1}, *R* isomer: t_R = 20.7 min, *S*

isomer: $t_R = 24.1$ min; HRMS (FTICR-MS): m/z: calcd for $C_{10}H_{18}O_3+Na^+$: 209.1148; found: 209.1140.

General procedure for the aldol reaction of aldehydes and fluoroacetone: Fluoroacetone (0.3 mL) was added to a solution of the aldehyde (0.25 mol) and catalyst (30 mol%) in a solvent mixture of H_2O (0.5 mL) and THF (0.5 mL). After the reaction mixture had been stirred at −15 °C for 2–3 days, the reaction was quenched with saturated aqueous ammonium chloride solution and the layers were separated. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. After removal of solvent, the residue was purified by flash-column chromatography on silica gel (hexane/ethyl acetate 4:1) to give the pure adducts.

1-Fluoro-4-hydroxy-4-(4-nitrophenyl)butan-2-one (11a): Table 3, entry 2: Yield: 62%; white solid; m.p. 76–78 °C; $[\alpha]_D^{25} = +41.0$ ($c = 0.30$ in EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.91$–3.06 (m, 2H), 3.23 (br s, 1H), 4.71 (d, $J = 47.4$ Hz, 2H), 5.33–5.37 (m, 1H), 7.6 (d, $J = 8.9$ Hz, 2H), 8.22 ppm (d, $J = 8.8$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 46.9$, 68.3, 85.0 (d, $J = 184.0$ Hz), 123.9, 126.4, 147.4, 149.6, 206.3 ppm (d, $J = 20.1$ Hz); IR (KBr): $\tilde{\nu} = 3446$, 2922, 1733, 1606, 1518, 1347, 1108, 1052, 857 cm^{-1}; 80% *ee*, determined by HPLC (Daicel Chiralpak AS-H, *i*PrOH/hexane 30:70), detection method = UV spectroscopy ($\lambda = 254$ nm), flow rate = 1.0 mL min^{-1}, *R* isomer: $t_R = 13.6$ min, *S* isomer: $t_R = 20.1$ min; HRMS (FTICR-MS): m/z: calcd for $C_{10}H_{10}FNO_4+Na^+$: 250.0486; found: 250.0490.

4-(3,5-Dibromophenyl)-1-fluoro-4-hydroxybutan-2-one (11f): Table 3, entry 3; Yield: 57%; white solid; m.p. 82–84 °C; $[\alpha]_D^{25} = +40.3$ ($c = 0.34$ in EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.90$–3.02 (m, 2H), 3.07 (br s, 1H), 4.84 (d, $J = 47.4$ Hz, 2H), 5.16–5.20 (m, 1H), 7.45 (s, 2H), 7.57 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 46.9$, 51.5, 85.0 (d, $J = 184.2$ Hz), 123.2, 127.5, 133.1, 133.4, 206.3 ppm (d, $J = 20.2$ Hz); IR (KBr): $\tilde{\nu} = 3432$, 2924, 1729, 1586, 1557, 1424, 1109, 1054, 741 cm^{-1}; 84% *ee*, determined by HPLC (Daicel Chiralpak AD-H, *i*PrOH/hexane 10:90), detection method = UV spectroscopy ($\lambda = 254$ nm), flow rate = 1.0 mL min^{-1}; *R* isomer: $t_R = 15.4$ min, *S* isomer: $t_R = 17.5$ min; HRMS (FTICR-MS): m/z: calcd for $C_{10}H_9Br_2FO_2+Na^+$: 360.8846; found: 360.8845.

1-Fluoro-4-hydroxy-4-(3-nitrophenyl)butan-2-one (11e): Table 3, entry 4; Yield: 55%; white solid; m.p. 88–90 °C; $[\alpha]_D^{25} = +47.5$ ($c = 0.20$ in EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.92$–3.10 (m, 2H), 3.21 (br s, 1H), 4.87 (d, $J = 47.5$ Hz, 2H), 5.34–5.38 (m, 1H), 7.55 (t, $J = 7.9$ Hz, 1H), 7.73 (d, $J = 7.7$ Hz, 1H), 8.16 (m, 1H), 8.27 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 47.0$, 68.2, 85.0 (d, $J = 184.2$ Hz), 120.7, 122.8, 129.6, 131.7, 144.5, 206.2 ppm (d, $J = 20.1$ Hz); IR (KBr): $\tilde{\nu} = 3550$, 2937, 1729, 1582, 1529, 1071, 1026, 810, 717 cm^{-1}; 83% *ee*, determined by HPLC (Daicel Chiralpak OJ-H, *i*PrOH/hexane 30:70), detection method = UV spectroscopy ($\lambda = 254$ nm), flow rate = 1.0 mL min^{-1}; *R* isomer: $t_R = 13.8$ min, *S* isomer: $t_R = 16.5$ min; HRMS (FTICR-MS): m/z: calcd for $C_{10}H_{10}FNO_4+Na^+$: 250.0486; found: 250.0490.

4-(2,6-Dichlorophenyl)-1-fluoro-4-hydroxybutan-2-one (11m): Table 3, entry 5; Yield: 65%; colorless oil; $[\alpha]_D^{25} = -12.5$ ($c = 0.52$ in EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.83$–2.90 (m, 1H), 3.13 (br s, 1H), 3.60–3.69 (m, 1H), 4.89 (d, $J = 47.5$ Hz, 2H), 6.02–6.06 (m, 1H), 7.15–7.20 (m, 1H), 7.29–7.34 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 43.2$, 66.9, 85.2 (d, $J = 184.1$ Hz), 129.5, 134.4, 135.8, 205.3 ppm (d, $J = 20.2$ Hz); IR (neat): $\tilde{\nu} = 3455$, 2928, 1719, 1580, 1561, 1437, 1089, 1049, 768, 732 cm^{-1}; 91% *ee*, determined by HPLC (Daicel Chiralpak OD-H, *i*PrOH/hexane 5:95), detection method = UV spectroscopy ($\lambda = 254$ nm), flow rate = 1.0 mL min^{-1}; *R* isomer: $t_R = 21.1$ min, *S* isomer: $t_R = 17.8$ min; HRMS (FTICR-MS): m/z: calcd for $C_{10}H_9Cl_2FO_2+Na^+$: 272.9856; found: 272.9860.

General procedure for the syntheses of *syn* 1,2,4-triols: Alkoxydialkylborane (1.1 mmol, 1.1 mL) was added dropwise to a solution of 1,4-diols (1.0 mmol) in anhydrous THF (8 mL) and MeOH (2 mL) at −78 °C. After the resulting mixture had been stirred for 15 min, sodium borohydride (42 mg, 1.1 mmol) was added and the mixture was stirred for 3–5 h depending on the substrate used. When the reaction was completed, the addition of AcOH (1 mL) quenched the reaction and the mixture was diluted with AcOEt (30 mL). The organic solution was washed with aqueous sodium bicarbonate and dried over anhydrous Na_2SO_4. After removal of solvent, the residue was azeotroped a few times with methanol until the hydrolysis of boronate was complete. The crude product was purified by flash-column chromatography on silica gel (CH_2Cl_2/MeOH 40:1).

General procedure for the syntheses of *anti* 1,2,4-triols: Acetic acid (1.5 mL) was added to a suspension of $NaBH(OAc)_3$ (3.0 mmol) in THF (3 mL) at −78 °C under argon. After 10 min, a solution of 1,4-diols (1.0 mmol) in THF (2 mL) was added. The reaction mixture was stirred at this temperature for 3 h, and then it was warmed to room temperature. The reaction was quenched with water (2 mL). After being neutralized with 20% aqueous NaOH solution, the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. After removal of solvent, the residue was purified by flash-column chromatography on silica gel (CH_2Cl_2/MeOH 40:1) to give the pure product.

General procedure for the cyclization of 1,2,4-triols: Trimethylorthoacetate (0.6 mmol) and a catalytic amount of PPTS (0.01 mmol) were added to a solution of triols (0.5 mmol) in anhydrous CH_2Cl_2 (10 mL). The reaction mixture was stirred at room temperature for 30 min, and then cooled down to 0 °C. Boron trifluoroetherate (0.05 mmol) was added and the reaction mixture was stirred at 0 °C for 2 h, and then it was gradually warmed to room temperature. The reaction was quenched with saturated aqueous sodium bicarbonate. The resultant aqueous solution was diluted with water (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine and dried over sodium sulfate. After the solvent had been removed under reduced pressure, the residue was purified by column chromatography (hexane/ethyl acetate 4:1) on silica gel to give the pure product

(3*S*,5*S*)-acetic acid 5-(4-nitrophenyl)tetrahydrofuran-3-yl ester (15a): Table 5, entry 1; Yield: 71%; white solid; m.p. 108–110 °C; $[\alpha]_D^{30} = -3.6$ ($c = 0.14$ in EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.92$–2.02(m, 1H), 2.12 (s, 3H), 2.47–2.53 (m, 1H), 3.97–4.01 (m, 1H), 4.33–4.38 (m, 1H), 5.14–5.19 (m, 1H), 5.42 (m, 1H), 7.50 (m, 2H), 8.20 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.1$, 41.3, 73.9, 75.0, 78.8, 123.8, 126.3, 147.4, 149.1, 170.6 ppm; IR (KBr): $\tilde{\nu} = 2986$, 2853, 1722, 1605, 1514, 1344, 1248, 1084, 859 cm^{-1}; 96% *ee*, determined by HPLC (Daicel Chiralpak AS-H, *i*PrOH/Hexane 30:70), detection method = UV spectroscopy ($\lambda =$ 254 nm), flow rate = 1.0 mL min^{-1}; (*R,R)* isomer: $t_R = 14.4$ min, (*S,S)* isomer: $t_R = 20.1$ min; HRMS (FTICR-MS): calcd for $C_{12}H_{13}NO_5+Na^+$: m/z: 275.0686; found: 274.0696.

(3*R*,5*S*)-acetic acid 5-(4-nitrophenyl)tetrahydrofuran-3-yl ester (16a): Yield: 74%; white solid; m.p. 81.5–83; $[\alpha]_D^{30} = +13.5$ ($c = 0.23$ in EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.94$–2.00 (m, 4H), 2.75–2.85 (m, 1H), 3.99–4.04 (m, 1H), 4.16–4.20 (m, 1H), 4.99–5.04 (m, 1H), 5.35 (m, 1H), 7.53 (m, 2H), 8.21 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 20.9$, 40.7, 73.7, 74.8, 79.1, 123.6, 126.5, 147.3, 149.7, 170.6 ppm; IR (KBr): $\tilde{\nu} =$ 2919, 2862, 1739, 1605, 1514, 1347, 1246, 1094, 854 cm^{-1}; HRMS (FTICR-MS) calcd for $C_{12}H_{13}NO_5+Na^+$: m/z: 275.0686; found: 274.0678.

(3*S*,5*S*)-acetic acid 5-(3,5-dibromophenyl)tetrahydrofuran-3-yl ester (15b): Table 5, entry 2; Yield: 81%; colorless oil; $[\alpha]_D^{30} = -4.8$ ($c = 0.40$ in EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.89$–2.01 (m, 1H), 2.10 (s, 3H), 2.39–2.46 (m, 1H), 3.93–3.96 (m, 1H), 4.29–4.34 (m, 1H), 4.98–5.03 (m, 1H), 5.37–5.40 (m, 1H), 7.41 (s, 2H), 7.57 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.1$, 41.3, 73.8, 75.0, 78.3, 123.0, 127.4, 133.1, 145.7, 170.6 ppm; IR (neat): $\tilde{\nu} = 2936$, 2875, 1738, 1587, 1557, 1242, 1221, 1081, 855, 740 cm^{-1}; HRMS (FTICR-MS): m/z: calcd for $C_{12}H_{12}Br_2O_3+Na^+$: 384.9045; found: 384.9048.

(3*S*,5*S*)-acetic acid 5-(4-cyanophenyl)tetrahydrofuran-3-yl ester (15c): Table 5, entry 3; Yield: 74%; colorless oil; $[\alpha]_D^{30} = -2.2$ ($c = 0.27$ in EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.92$–2.00 (m, 1H), 2.10 (s, 3H), 2.43–2.50 (m, 1H), 3.94–3.99 (m, 1H), 4.31–4.36 (m, 1H), 5.08–5.13 (m, 1H), 5.39 (m, 1H), 7.44 (d, $J = 8.1$ Hz, 2H), 7.63 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 20.0$, 41.3, 73.9, 75.0, 78.9, 111.4, 118.7, 126.2, 132.3, 147.1, 170.6 ppm; IR (neat): $\tilde{\nu} = 2941$, 2879, 2228, 1738, 1609, 1505, 1374, 1245, 1087, 837 cm^{-1}; HRMS (FTICR-MS): m/z: calcd for $C_{13}H_{13}NO_3+Na^+$: 254.0788; found, 254.0794.

(3*S*,5*S*)-acetic acid 5-(2,6-dichlorophenyl)tetrahydrofuran-3-yl (15d): Table 5, entry 4; Yield: 65%; colorless oil; $[\alpha]_D^{30} = -29.0$ ($c = 0.40$ in EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.13$ (s, 3H), 2.25–2.31 (m,

1H), 2.45–2.60 (m, 1H), 3.98–4.02 (m, 1H), 4.42–4.47 (m, 1H), 5.50–5.53 (m, 1H), 5.87–5.92 (m, 1H), 7.14 (m, 1H), 7.29 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.2, 36.4, 73.6, 75.9, 79.4, 129.4, 129.8, 134.6, 135.0, 170.7 ppm; IR (neat): $\tilde{\nu}$ = 2955, 2878, 1740, 1581, 1562, 1438, 1243, 1098, 769, 724 cm^{-1}; HRMS (FTICR-MS): *m*/*z*: calcd for $C_{12}H_{12}Cl_2O_3$+Na$^+$: 297.0056; found: 297.0047.

4-Biphenyl-4-yl-1-(*tert*-butyldimethylsilanyloxy)-4-hydroxybutan-2-one (20): DMAP (0.174 mmol, 40 mg) and Et_3N (3.82 mmol, 0.53 mL) were added to a solution of diol **5n** (3.47 mmol, 890 mg) in CH_2Cl_2 (5 mL) and CH_3CN (5 mL) at RT. The resulting mixture was stirred for 30 min at 0 °C, and then TBSCl (1.2 equiv, 4.17 mmol, 628 mg) in CH_2Cl_2 was added dropwise over 1 h. The reaction mixture was stirred at 0 °C for another 2 h, and then at room temperature for 18 h. After the solvent had been removed, AcOEt was added to dissolve the residue. The organic solution was washed with KH_2PO_4 (1 M, 10 mL × 2), and the aqueous phase was extracted with AcOEt (10 mL × 3). The combined organic layers were dried over anhydrous $MgSO_4$. After removal of solvent, the residue was purified by flash-column chromatography on silica gel (hexane/ethyl acetate 10:1) to give the pure product. Yield: 81% (1.039 g); white solid; m.p. 62–63.5 °C; $[\alpha]_D^{30}$ = +36.5 (*c* = 0.20 in EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.09 (s, 6H), 0.93 (s, 9H), 2.91–3.05 (m, 2H), 3.29 (br s, 1H), 4.21 (s, 2H), 5.21–5.25 (m, 1H), 7.36 (m, 1H), 7.44 (m, 4H), 7.60 ppm (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = −5.5, 18.3, 25.7, 45.9, 69.6, 69.7, 126.1, 127.0, 127.3, 128.7, 140.6, 140.7, 141.9, 210.0 ppm; IR (KBr): $\tilde{\nu}$ = 3397, 2928, 2856, 1729, 1640, 1597, 1483, 1260, 1253, 1090, 1050, 837, 767, 698 cm^{-1}; HRMS (FTICR-MS): calcd for $C_{22}H_{30}O_3Si$+Na$^+$: 393.1856; found: 393.1865.

1-Biphenyl-4-yl-4-(*tert*-butyldimethylsilanyloxy)butane-1,3-diol (21): The procedure described for the synthesis of *syn* 1,3-diol was same as that for the syntheses of *syn* 1,2,4-triols. Yield 97% (*syn*/*anti* 97:3); colorless oil; $[\alpha]_D^{30}$ = +12.4 (*c* = 0.21 in EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.08 (s, 6H), 0.91 (s, 9H), 1.82–1.90 (m, 2H), 3.03 (br s, 1H), 4.21 (s, 2H), 3.45–3.64 (m, 2H), 3.75 (br s, 1H), 3.98 (m, 2H), 5.01–5.05 (m, 1H), 7.41 (m, 1H), 7.46 (m, 4H), 7.59 ppm (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = −5.4, 18.3, 25.9, 41.6, 67.1, 72.4, 73.9, 125.9, 126.2, 127.1, 127.2, 128.7, 140.4, 140.9, 143.4 ppm; IR (neat): $\tilde{\nu}$ = 3387, 3029, 2953, 2856, 1599, 1486, 1471, 1462, 1256, 1124, 1076, 837, 765, 696 cm^{-1}; HRMS (FTICR-MS): *m*/*z*: calcd for $C_{22}H_{32}O_3Si$+Na$^+$: 395.2013; found: 395.2020.

Acetic acid 3-acetoxy-3-biphenyl-4-yl-1-(*tert*-butyldimethylsilanyloxymethyl)propyl ester (22): DMAP (0.079 mmol, 18 mg) and acetic anhydride (2 mL) at 0 °C were added to a solution of diol **21** (1.57 mmol, 600 mg) in pyridine (8 mL), and the mixture was stirred at room temperature for 3 h. After removal of pyridine, AcOEt (20 mL) was added and the organic solution was washed with aqueous KH_2PO_4 (1 M, 2 × 10 mL). The aqueous solution was extracted with AcOEt (3 × 10 mL) and the combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. After removal of solvent, the residue was purified by flash-column chromatography on silica gel (hexane/ethyl acetate 20:1) to give the pure product. Yield: 95% (TBS ether 677 mg); colorless oil; $[\alpha]_D^{30}$ = +31.5 (*c* = 0.31 in EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.04 (s, 6H), 0.88 (s, 9H), 2.01 (s, 3H), 2.09 (s, 3H), 2.22–2.28 (m, 2H), 3.62–3.68 (m, 2H), 4.81–4.85, 1H), 5.84–5.88 (m, 1H), 7.37 (m, 5H), 7.56 ppm (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$); δ = −5.5, 18.2, 21.1, 21.3, 25.8, 36.9, 63.7, 71.4, 73.0, 126.9, 127.1, 127.3, 128.7, 138.9, 140.7, 141.0, 170.1, 170.4 ppm; IR (neat): $\tilde{\nu}$ = 2955, 2929, 2857, 1741, 1600, 1487, 1471, 1371, 1235, 836, 767, 697 cm^{-1}; HRMS (FTICR-MS): *m*/*z*: calcd for $C_{26}H_{36}O_5Si$+Na$^+$: 479.2224; found: 479.2244.

2,4-Diacetoxy-4-biphenyl-4-ylbutyric acid (23): To a solution of Jones reagent (4.4 mmol) at 0 °C in acetone (15 mL) was added dropwise a solution of **22** (500 mg, 1.1 mmol) in acetone (15 mL). The brown mixture was stirred for 4 h at room temperature, and then 2-propanol was added dropwise until the reaction mixture became blue. After filtration and removal of the solvent, water (10 mL) was added. The aqueous phase was extracted with ethyl acetate (6 × 10 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by flash chromatography (hexane/ethyl acetate 2:1→1:1), to give **23**. Yield 71% (276 mg); white solid; m.p. 125–127 °C; $[\alpha]_D^{25}$ = +44.1 (*c* = 0.17 in EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.05 (s, 3H), 2.14 (s, 3H), 2.36–2.65 (m, 2H), 5.03–5.07 (m, 1H), 5.30 (br s, 2H), 5.97–6.92 (m, 1H), 7.42 (m, 5H), 7.58 ppm (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.4, 21.0, 37.0, 68.6, 71.7, 126.9, 127.1, 127.5, 128.8, 137.9, 140.5, 141.5, 170.1, 170.2, 174.5 ppm; IR (KBr): $\tilde{\nu}$ = 3416, 3303, 2855, 1739, 1695, 1600, 1488, 1244, 1066, 847, 769, 698 cm^{-1}; HRMS (FTICR-MS): *m*/*z*: calcd for $C_{20}H_{20}O_6$+Na$^+$ 379.1152; found: 379.1155.

4-Biphenyl-4-yl-2,4-dihydroxybutyric acid (19): LiOH·H_2O (1.2 mmol, 50.4 mg) was added to a solution of **23** (106.2 mg, 0.3 mmol) in a solvent mixture of THF/H_2O/CH_3OH (2:1:2, 10 mL). After the reaction mixture had been stirred at room temperature for 5 h, the organic solvent was removed, then aqueous HCl solution (1.0 M) was added slowly to adjust the pH to pH 4. The material was recrystallized from water to give **19**. Yield: 90% (73 mg); white solid; m.p. 144–146 °C; $[\alpha]_D^{30}$ = +26.3 (*c* = 0.27 in MeOH); ^{1}H NMR (300 MHz, DMSO): δ = 1.94–1.99 (m, 2H), 3.77–3.79 (m, 1H), 4.74–4.78 (m, 1H), 7.42 (m, 5H), 7.64 ppm (m, 4H); ^{13}C NMR (75 MHz, DMSO): δ = 43.6, 67.6, 69.4, 126.5, 126.6, 126.7, 127.3, 128.9, 138.9, 140.1, 144.6, 175.7 ppm; IR (KBr): $\tilde{\nu}$ = 3446, 2923, 1710, 1647, 1484, 1098, 837, 762, 726 cm^{-1}; HRMS (FTICR-MS): *m*/*z*: calcd for $C_{16}H_{15}O_4$: 271.0965 [*M*]$^+$; found: 271.0959.

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