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Asymmetric *syn*-Aldol Reaction of α-Hydroxy Ketones with Tertiary Amine Catalysts

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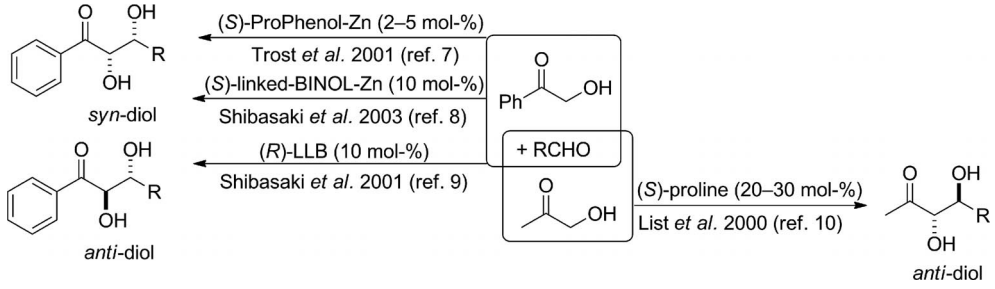
The tertiary amine-catalyzed direct asymmetric aldol reaction of 2-hydroxyacetophenones (2-hydroxy-1-arylethanones) with a variety of aliphatic aldehydes has been demonstrated. By using 20 mol-% of unmodified cinchonine as catalyst, the direct aldol reaction products were isolated in good yields and with remarkably high *syn* diastereocontrol and good asymmetric induction (40–78 % *ee*). This newly elaborated tertiary-amine-catalyzed direct asymmetric aldol reaction has extended the scope of organocatalytic processes to aromatic α-hydroxy ketones, which have hitherto been unreactive towards enamine catalysis.

Introduction

The asymmetric aldol reaction is undoubtedly one of the most powerful methods for the construction of carbon–carbon bonds under asymmetric control.[1] The recent rapid development in this area is related mainly to the direct catalytic aldol reaction which combines high selectivity with a requirement for catalytic amounts of chiral promoters.[2] Since the first reports of metal-complex-[3] and proline-catalysed direct asymmetric aldol reactions,[4] numerous catalysts have been designed that have further improved the catalyst reactivity, enantioselectivity and most importantly substrate scope of this reaction.[5]

Among the various substrate combinations, hydroxyketone-based aldol reactions are of considerable importance because they provide expedient access to the 1,2-diol unit that frequently occurs in natural products, such as in carbohydrates or polyhydroxylated molecules of significance in total synthesis.[6] Since 2000, few initial reports have addressed the direct aldol addition of hydroxy ketones to aldehydes by using both organometallic and proline catalysts (Scheme 1). In 2001, Trost et al. reported the use of the dinuclear zinc ProPhenol catalyst in the *syn*-selective synthesis of 1,2-diols from 2-hydroxyacetophenone.[7] The same *syn* selectivity for the reaction of 2-hydroxyacetophenone was achieved by Shibasaki and co-workers in the reaction promoted by a zinc-based catalyst with a BINOL ligand.[8] Interestingly, with a catalyst based on lanthanum ion with BINOL ligands (LLB), *anti*-configured diols have been predominantly formed, thus giving access to the remaining diastereoisomeric diols.[9]

Hydroxyacetone has also been activated by organocatalysts. At the very beginning of the renaissance of organocatalysis (2000), Notz and List showed that proline is a remarkably effective catalyst for the direct asymmetric



Scheme 1. Aldol reactions between hydroxy ketones and aldehydes.

aldol reaction of hydroxyacetone to various aldehydes with *ee* values of the *anti*-aldol products ranging from 67 to 99 %.[10] In spite of high catalyst (30 mol-%) and ketone (20 vol.-%) loadings, these authors demonstrated the first successful application of unprotected acetone as a donor in non-enzymatic asymmetric aldol reactions. Later, a number of organocatalysts were tested to control the difficult

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regio-[11] and stereoselective[12] addition of unprotected hydroxyacetone. Only recently, various amine-based organocatalysts have been successfully used for the selective formation of *syn* diols from the unprotected hydroxyacetone donor.[13] It was assumed that organocatalysts containing primary and secondary amine functions activated hydroxyacetone by forming a (*Z*)- or (*E*)-enamine intermediate, which attacked one face of the aldehyde stereoselectively.[14] It is striking that most organocatalysts have been applied to the reaction of hydroxyacetone and, in contrast to metalloorganic catalysts, not a single organocatalyst has been demonstrated to activate aromatic hydroxy ketones (i.e., 2-hydroxyacetophenone). This deficiency in organocatalysis is not only a methodological problem, but also a considerable limitation in the synthesis of natural products.[15] Therefore we planned to address this issue and develop organocatalysts for direct asymmetric aldol reactions of 2-hydroxyacetophenones. However, this task required significant effort and was successful only by using tertiary amine catalysts instead of secondary amine catalysts and catalytic enamine formation. Herein we report the application of unmodified cinchona alkaloid-type organocatalysts for use in enantioselective *syn*-selective direct aldol reactions.

Results and Discussion

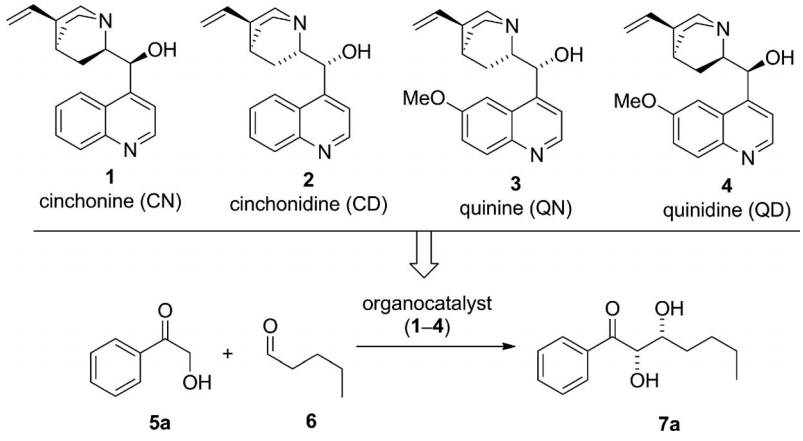
To select promising organocatalysts, we first examined the direct aldol reaction of 2-hydroxyacetophenone (**5a**) with pentanal (**6**), which was selected as a more demanding enolizable aldehyde partner. Interestingly, not one of the known enamine-containing organocatalysts described previously for the aldol reaction of hydroxyacetone[13] was able to deliver the desired product from **5a**.[16] However, our previous studies[17] have shown that the direct aldol reaction using a hydroxyacetone donor with various aldehydes catalysed by quinidine provided *syn*-selective aldol adducts albeit in moderate *ee* values. Following this discovery, we tested four native cinchona alkaloids **1**–**4** in the reaction of **5a** and **6** (Scheme 2).

The use of 20 mol-% of tertiary amine in THF at room temp. led to the preferential formation of *syn*-aldol **7a** in low yields ranging from only 14% for cinchinodine (**2**) to 31% for cinchonine (**1**) and quinidine (**4**) catalysts (Table 1, entries 1–4). However, the observed enantioselectivity encouraged us to continue this research. The most promising catalyst in terms of *ee* was cinchonine (**1**). Further careful optimization revealed that the reaction promoted by 20 mol-% of catalyst **1** in $CHCl_3$ at 0 °C resulted in the formation of aldol **7a** with remarkably high *syn* selectivity (94% *de*) and good enantioselectivity (61% *ee*; Table 1, entry 5). Although the reaction yield leaves much to be desired (ca. 35%), the selectivity was very good for commercial and inexpensive catalyst **1**. Note that the best reaction efficiency was observed for a 1:2 ratio of ketone to aldehyde, with no need to overload ketone as was the case previously.

Table 1. Screening for an efficient catalyst and conditions for the asymmetric aldol reaction of 2-hydroxyacetophenone with propanal.

Entry	Catalyst (amount [mol-%])	Solvent	Yield [%][a]	*syn*/*anti*	*ee* (*syn*)[b]
1[c]	**1** (20)	THF	31	86:14	35 (2*S*,3*R*)
2[c]	**2** (20)	THF	14	70:30	24 (2*R*,3*S*)
3[c]	**3** (20)	THF	16	74:26	19 (2*R*,3*S*)
4[c]	**4** (20)	THF	31	72:28	14 (2*S*,3*R*)
5[d]	**1** (20)	$CHCl_3$	34	97:3	61
6[d]	**2** (20)	$CHCl_3$	35	88:22	51
7[d]	**3** (20)	$CHCl_3$	18	95:5	41
8[d]	**4** (20)	$CHCl_3$	25	95:5	43
9[e]	**1** (5)	$CHCl_3$	n.d.	–	–
10[e]	**1** (10)	$CHCl_3$	8	–	–
11[e]	**1** (20)	$CHCl_3$	37	77:23	40
12[e]	**1** (30)	$CHCl_3$	59	86:14	40

[a] Isolated yield. [b] The enantiomeric excess was determined by HPLC analysis on a chiral phase column (Chiralpak AD-H). [c] Reagents and conditions: **5a** (1 mmol), **6** (2 mmol), catalyst (see table), THF (0.5 mL), room temp., 60 h. [d] Reagents and conditions: **5a** (1 mmol), **6** (2 mmol), catalyst (see table), $CHCl_3$ (2.5 mL), 0 °C, 60 h. [e] Reagents and conditions: **5** (1 mmol), **6** (2 mmol), catalyst (see table), $CHCl_3$ (2.5 mL), room temp., 60 h.

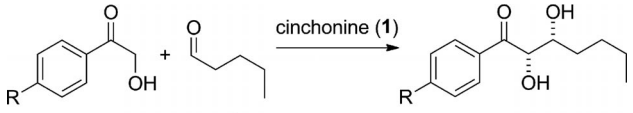


Scheme 2. Asymmetric reaction of 2-hydroxyacetophenone (**5a**) promoted by cinchona alkaloid catalysts **1**–**4**.

It was possible to considerably increase the reaction efficiency (59%, Table 1, entry 12) by using 30 mol-% of cinchona catalyst at room temp., but only at the expense of selectivity. Commenting on the correlation between the structure of the catalyst and the resulting aldol, application of **1**/**4** and pseudo-enantiomeric couple **2**/**3** delivers the expected enantiomeric aldol (Table 1, entries 1–4).

Because it is known that hydrogen bonds play an important role in the stabilization of the transition states of reactions involving cinchona catalysts,[18] we synthesized and tested various known modified derivatives of **1**. Unfortunately, unmodified catalyst **1** showed the best selectivity and for this reason was used for further studies.[19] The next step was to test our assumption that a change in the electronic structure of ketones can greatly affect the reactivity. We confirmed our suspicions by testing the reactions of *p*-chloro- and *p*-methoxy-substituted ketones. The reaction of 2-hydroxy-*p*-chloroacetophenone delivered the aldol in 74% yield, whereas the analogous ketone with an electron-releasing group was far less reactive under the same reaction conditions, even after a prolonged reaction time (Table 2, entries 1–3). Further examination of the reaction of 2-hydroxy-*p*-chloroacetophenone indicated that lowering the temperature is beneficial for enantioselectivity and that the use of 30 mol-% of the catalyst gave optimal results in terms of both the yield and selectivity (entry 5).

Table 2. Effect of donor substituents on the asymmetric aldol reaction of 2-hydroxyacetophenones with propanal catalyzed by **1**.



5 **6** **7a–c**

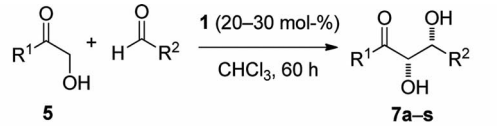
Entry	R	Temp.	Yield [%][a]	*syn*/*anti*	*ee* (*syn*)[b]
1	H (**7a**)	r.t.	37	77:23	40
2	Cl (**7b**)	r.t.	74	81:19	28
3[c]	OMe (**7c**)	r.t.	12	91:9	45
4	Cl (**7b**)	0 °C	17	92:8	65
5[d]	Cl (**7b**)	0 °C	55	95:5	72

[a] Isolated yield. Reagents and conditions: ketone (1 mmol), **6** (2 mmol), **1** (20 mol-%), $CHCl_3$ (2.5 mL), room temp. or 0 °C, 60 h. [b] The enantiomeric excess was determined by HPLC analysis on a chiral phase column (Chiralpak AD-H, AS-H). [c] Reaction time: 72 h. [d] 30 mol-% of catalyst was used.

Finally, to explore the scope and limitation of the elaborated methodology in depth, the reactions of various ketones and aldehydes were investigated with **1** as the catalyst (Table 3). The reactions were performed with 20 or 30 mol-% of cinchonine under the standard reaction conditions for 60 h. Entries 1–6 in Table 3 show the results for less reactive ketones, whereas entries 7–16 present the data for synthetically useful ketones with electron-withdrawing substituents.

In accord with previous observations, the reaction of 2-hydroxyacetophenone resulted in the selective formation of *syn*-aldols in low-to-good yields (Table 2 and Table 3, entries 1–4). Interestingly, the reaction of 2-hydroxyaceto-

Table 3. Substrate scope of direct catalytic asymmetric aldol reactions catalyzed by **1** (20–30 mol-%).



5 **7a–s**

Entry	Aldol	Yield (%)[a]	*syn*/*anti*	*ee* (*syn*)[b]
1	**7d**	48	86/14	41[c]
2	**7e**	14[d]	97/3	66[c]
3	**7f**	28[d]	89/11	42
4	**7g**	60	99/1	rac.
5	**7h**	35	94/6	54[c]
6	**7i**	84	88/12	31
7	**7j**	67	93/7	42
8	**7k**	91	93/7	41
9	**7l**	56	78/12	54
10	**7m**	57	92/8	52
11	**7n**	45	99/1	56
12	**7o**	57	99/1	67

Table 3. *(Continued)*

Entry	Aldol	Yield (%)[a]	*syn/anti*	*ee* (*syn*)[b]
13	**7p**	47	90/10	71
14	**7q**	59	93/3	57
15	**7r**	54	97/4	62
16	**7s**	50	97/3	78

[a] Yield refers to the combined yield of isolated diastereomers. Reagents and conditions: ketone (1 mmol), aldehyde (2 mmol), **1** (20–30 mol-%), $CHCl_3$ (2.5 mL), room temp. or 0 °C, 60 h. [b] The enantiomeric excess was determined by HPLC analysis on a chiral phase column (Chiralpak AD-H, OD-H). [c] In this reaction the catalyst seems to lead to the selective formation of the 2*S*,3*R* product. The stereochemistry of the resulting aldols was determined based on a comparison of the optical rotation and HPLC analysis of authentic samples with previously published data.[8,15] [d] Reaction time: 12 h.

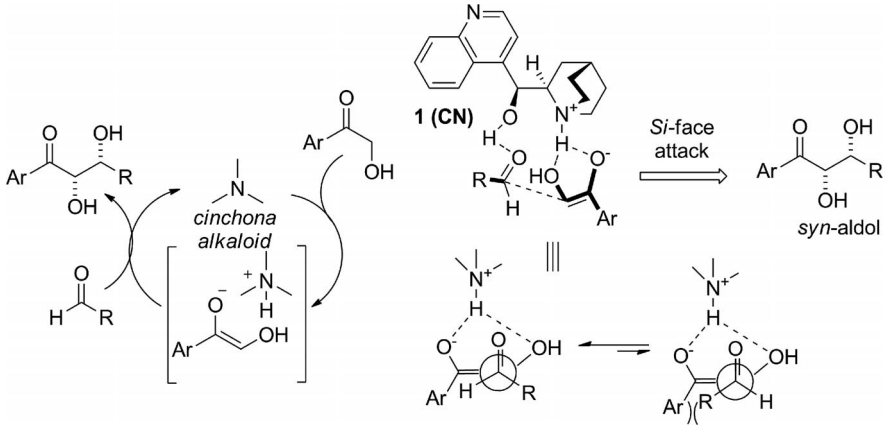
phenone with α-branched 2-methylpropanal led to a low yield but relatively high enantioselectivity (66% *ee*, Table 3, entry 2). In the cases of 2-methylpropanal (entry 2) and benzyloxyacetaldehyde (entry 3), it is likely that substrate self-condensation affected the yield, the best reaction efficiency being observed in a shorter reaction time. Unfortunately, a remarkably efficient reaction with chloral delivered the corresponding racemic aldol (entry 4). The reaction also worked well when 2-acetylfuran was used as donor (entries 5 and 6), but the observed *ee* of aldol **7i** was lower, reaching only 31% (entry 6). The absolute configurations of the *syn*-aldol products **7d**, **7e** and **7h** were determined to be 2*S*,3*R* by comparison of the optical rotation values and HPLC analysis with the known compounds prepared by asymmetric Sharpless dihydroxylation.[8,15]

To show the synthetic potential of the developed method, selected reactive ketones were prepared and used as donor in the *syn*-selective aldol reaction with various aldehydes. 2-Hydroxyacetophenones equipped with 4-chloro- (entry 7), 4-trifluoromethyl- (entry 8–10) and 3,5-bis(trifluoromethyl) substituents (entry 11) were converted into the expected *syn*-aldols in good yields (45–91%) and with good enantioselectivity (up to 56% *ee*). The tetrafluoro-substituted 2-hydroxyacetophenones are better substrates in terms of reactivity and selectivity (entries 12–16); for this donor substrate *syn*-aldols were isolated in *ee* values of up to 78%.

To explain the stereochemistry of the reaction, we assumed that the tertiary amine catalyst acts through the formation of a tight ion pair with the ketone enolate followed by stereocontrolled aldehyde addition (Scheme 3). Although the reaction of the ketone involves an initial deprotonation by the cinchona catalyst **1** and subsequent attack on the aldehyde, the catalyst also provides an asymmetric environment for the reaction centre through a network of hydrogen bonds. The high *syn* selectivity can be explained by (*Z*)-enol formation from the hydroxy ketone, which then attacks the *Si* face of the aldehyde. Reaction at the *Re* face of the aldehyde is more difficult due to steric repulsion between the two larger substituents.

Conclusions

We have found a class of tertiary amine catalysts that are effective as highly *syn*-selective catalysts in the direct asymmetric aldol reaction of aromatic hydroxy ketones. Simple commercial and unmodified cinchona alkaloids were found to efficiently promote the direct aldol reaction of hydroxy ketones with various aldehydes in good yields and with good enantioselectivities of up to 78%. This is a



Scheme 3. Potential mechanism for the asymmetric aldol reaction catalyzed by chiral cinchona amine and a possible structure of the transition state.

valuable synthetic strategy not only because of the ready availability of the catalysts, but also because of the lack of other organocatalysts activating 2-hydroxyacetophenone derivatives. Moreover, the reaction protocol developed may be useful for the synthesis of fluoro- and trifluoromethyl-derived chiral diols, which may be desired targets because of their pharmacological properties.[20] As a result of the simplicity of the concept presented, we believe that this procedure will influence the development of asymmetric synthesis and lead to the discovery of more selective organocatalysts.

Experimental Section

General: Unless otherwise stated, all reagents were purchased from commercial sources and used as received. IR spectra were recorded with a FTIR spectrometer. ^{1}H NMR spectra were recorded at 300 MHz in $CDCl_3$. Data are reported as follows: chemical shifts in parts per million (ppm) from tetramethylsilane as an internal standard, integration, multiplicity (s singlet, d doublet, t triplet, q quartet, dd double doublet, m multiplet, br broad), coupling constants (in Hz) and assignment. ^{13}C NMR spectra were recorded at 100 MHz with complete proton decoupling. Chemical shifts are reported in ppm relative to the residual solvent as an internal standard. HRMS were recorded with an electrospray ionization time-of-flight (ESI-TOF) mass spectrometer. Optical rotations were measured with a digital polarimeter at room temperature. The reactions were monitored by using TLC on silica [alu-plates (0.2 mm)]. All reagents and solvents were purified and dried according to common methods. All organic solutions were dried with anhydrous magnesium sulfate. Reaction products were purified by flash chromatography using silica gel 60 (240–400 mesh). HPLC analysis was performed with an HPLC system equipped with chiral stationary phase columns (detection at 254 nm).

2-Hydroxy Ketones: The 2-hydroxy ketones were prepared according to a previously described procedure.[21] Iodobenzene diacetate (11.3 g, 35 mmol, 1.1 equiv.) was added during 15 min to a stirred solution of the corresponding methyl ketone (32 mmol, 1 equiv.) and powdered potassium hydroxide (10 g, 180 mmol, 5.5 equiv.) in methanol (20 mL) at 0 °C. The mixture was warmed to room temperature, stirred for 3 h, and then evaporated to dryness under reduced pressure. The residue was shaken with water (20 mL) and diethyl ether (20 mL). The ether solution was separated, dried with magnesium sulfate and the solvents evaporated to dryness. The residue was dissolved in a mixture of methanol (20 mL) and aqueous hydrochloric acid (2 M, 20 mL) and then stirred overnight at room temp. and then filtered. The solid product was recrystallized from methanol or light petroleum ether.

General Procedures for the Aldol Reaction: Aldehyde (2 equiv.) was added to a solution of catalyst (20–30 mol-%) and ketone (1 equiv.) in $CHCl_3$ (2.5 mL) at room temp. or 0 °C for 60 h (see Table 3). The reaction mixture was stirred until TLC control showed disappearance of the substrates (hexane/MTBE/dichloromethane 2:1:5) and then the reaction mixture was dissolved in AcOEt (25 mL), washed with water, saturated $NaHSO_3$ (2× 10 mL), water again and brine, dried with $MgSO_4$ and the solvents evaporated to dryness. Standard purification method by column chromatography on silica gel with hexane/MTBE/dichloromethane (2:1:5) as eluent afforded the desired aldol product.

(2*S*,3*R*)-2,3-Dihydroxy-1-phenylheptan-1-one (7a):[22] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.92–7.86 (m, 2 H), 7.67–7.59 (m, 1 H), 7.55–7.47 (m, 2 H), 5.00 (d, J = 3.3 Hz, 1 H), 4.00–3.87 (m, 2 H), 1.78–1.66 (m, 5 H), 1.58–1.30 (m, 3 H), 0.93 (t, J = 7.1 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.5, 134.1, 129.1, 128.6, 75.6, 73.1, 34.6, 28.1, 22.8, 14.1 ppm. HPLC (Chiralpak AD-H, hexane/*i*PrOH = 80:20, flow rate: 1.0 mL/min, λ = 254 nm): t_R = 8.3 (*anti*), 9.5 (*anti*), 11.7 (*syn*, major), 13.7 min (*syn*, minor).

(2*S*,3*R*)-1-(4-Chlorophenyl)-2,3-dihydroxyheptan-1-one (7b):[22] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.87–7.78 (m, 2 H), 7.52–7.45 (m, 2 H), 4.95 (d, J = 1.6 Hz, 1 H), 3.89 (td, J = 7.1, 1.5 Hz, 1 H), 1.77–1.64 (m, 2 H), 1.58–1.29 (m, 4 H), 0.92 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.4, 140.7, 132.3, 130.1, 129.4, 75.7, 73.0, 34.4, 28.1, 22.8, 14.12 ppm. HPLC (Chiralpak AD-H, hexane/*i*PrOH = 80:20, flow rate: 1.0 mL/min, λ = 254 nm): t_R = 6.7 (*anti*), 8.1 (*anti*), 10.5 (*syn*, minor), 11.7 min (*syn*, major).

(2*S*,3*R*)-1-(4-Methoxyphenyl)-2,3-dihydroxyheptan-1-one (7c):[22] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.97–7.80 (m, 2 H), 7.03–6.93 (m, 2 H), 4.94 (dd, J = 5.7, 1.7 Hz, 1 H), 3.98 (d, J = 5.7 Hz, 1 H), 3.89 (s, 3 H), 1.89 (d, J = 9.4 Hz, 1 H), 1.77–1.62 (m, 2 H), 1.58–1.29 (m, 4 H), 0.93 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.6, 164.4, 131.1, 126.6, 114.3, 75.1, 73.4, 55.7, 34.6, 28.2, 22.8, 14.2 ppm. HPLC (Chiralpak AS-H, hexane/*i*PrOH = 80:20, flow rate: 0.5 mL/min, λ = 278 nm): t_R = 19.6 (*anti*), 25.1 (*anti*), 29.8 (*syn*, major), 33.8 min (*syn*, minor).

(2*S*,3*R*)-2,3-Dihydroxy-1,5-diphenylpentan-1-one (7d):[7,8,9] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.81–7.72 (m, 2 H), 7.66–7.55 (m, 1 H), 7.52–7.40 (m, 2 H), 7.37–7.16 (m, 5 H), 4.98 (s, 1 H), 4.07–3.92 (m, 2 H), 2.90–2.75 (m, 2 H), 2.19–1.99 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.2, 141.4, 134.5, 134.2, 133.7, 129.2, 129.0, 128.7, 128.6, 128.4, 126.49, 126.2, 75.5, 72.3, 36.1, 32.1 ppm. HPLC (Chiralpak AD-H, hexane/*i*PrOH = 80:20, flow rate: 1.0 mL/min, λ = 254 nm): t_R = 12.1 (*anti*), 14.2 (*anti*), 17.9 (*syn*, major), 22.6 min (*syn*, minor).

(2*S*,3*R*)-2,3-Dihydroxy-4-methyl-1-phenylpentan-1-one (7e):[7,9,22] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.92–7.84 (m, 2 H), 7.67–7.58 (m, 1 H), 7.57–7.47 (m, 2 H), 5.20 (dd, J = 5.0, 1.2 Hz, 1 H), 3.96 (d, J = 5.1 Hz, 1 H), 2.08–1.90 (m, 1 H), 1.13 (d, J = 6.7 Hz, 3 H), 1.04 (d, J = 6.7 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.8, 134.1, 133.8, 129.1, 128.6, 78.2, 73.8, 32.4, 19.4, 19.2 ppm. HPLC (Chiralpak AD-H, hexane/*i*PrOH = 80:20, flow rate: 1.0 mL/min, λ = 254 nm): t_R = 9.7 (*anti*), 11.4 (*anti*), 17.6 (*syn*, minor), 18.6 min (*syn*, major).

(2*S*,3*R*)-4-(Benzyloxy)-2,3-dihydroxy-1-phenylbutan-1-one (7f): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.97–7.89 (m, 2 H), 7.65–7.56 (m, 1 H), 7.52–7.42 (m, 2 H), 7.40–7.22 (m, 5 H), 5.24 (s, 1 H), 4.58 (s, 2 H), 4.16 (dd, J = 9.2, 3.8 Hz, 1 H), 3.68 (dd, J = 9.2, 6.9 Hz, 1 H), 3.62 (dd, J = 9.2, 6.1 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.9, 137.9, 134.2, 133.7, 128.9, 128.9, 128.8, 128.6, 128.5, 127.9, 127.9, 127.8, 73.7, 73.2, 71.4, 71.0 ppm. HPLC (Chiralpak AD-H, hexane/*i*PrOH = 80:20, flow rate: 1.0 mL/min, λ = 254 nm): t_R = 13.4 (*anti*), 14.0 (*anti*), 16.2 (*syn*, major), 20.4 min (*syn*, minor).

(2*S*,3*R*)-4,4,4-Trichloro-2,3-dihydroxy-1-phenylbutan-1-one (7g): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.08–7.99 (m, 2 H), 7.74–7.65 (m, 1 H), 7.61–7.51 (m, 2 H), 5.73 (s, 1 H), 4.51–4.28 (m, 2 H), 3.73 (d, J = 10.5 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.9, 134.9, 132.3, 129.4, 129.1, 101.7, 80.7, 71.3 ppm. IR (neat): $\tilde{\nu}$ = 3384, 3361, 3063, 2967, 2939, 2847, 1689, 1598, 1580, 1448, 1410, 1322, 1308, 1277, 1125, 981, 939, 898, 822, 771, 722, 693, 675, 667 cm^{-1}. HPLC (Chiralpak AD-H, hexane/*i*PrOH = 80:20, flow rate: 1.0 mL/min, λ = 254 nm): t_R = 10.7 (*anti*), 11.8 (*anti*), 12.8 (*syn*), 21.7 min (*syn*). HRMS (ESI): calcd. for $C_{10}H_9Cl_3O_3$ [M + Na]$^+$ 304.9515; found 304.9500.

(2*S*,3*R*)-1-(Furan-2-yl)-2,3-dihydroxyheptan-1-one (7h):[15] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.66 (dd, J = 1.7, 0.8 Hz, 1 H), 7.38 (dd, J = 3.7, 0.8 Hz, 1 H), 6.62 (dd, J = 3.6, 1.7 Hz, 1 H), 4.78 (s, 1 H), 4.11 (t, J = 6.0 Hz, 1 H), 3.78 (d, J = 4.5 Hz, 1 H), 2.37 (s, 1 H), 1.80–1.68 (m, 2 H), 1.62–1.33 (m, 4 H), 0.96 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 188.7, 150.6, 147.2, 119.4, 112.9, 76.0, 72.9, 34.4, 28.1, 22.8, 14.2 ppm. HPLC (Chiralpak AD-H, hexane/*i*PrOH = 80:20, flow rate: 1.0 mL/min, λ = 254 nm): t_R = 10.2 (*anti*), 11.2 (*anti*), 13.3 (*syn*, major), 15.9 min (*syn*, minor).

(2*S*,3*R*)-4-(Benzyloxy)-1-(furan-2-yl)-2,3-dihydroxybutan-1-one (7i): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.65 (dd, J = 1.7, 0.5 Hz, 1 H), 7.47–7.29 (m, 6 H), 6.60 (dd, J = 3.6, 1.7 Hz, 1 H), 4.95 (d, J = 1.9 Hz, 1 H), 4.62 (s, 2 H), 4.35 (td, J = 6.2, 1.9 Hz, 1 H), 3.81–3.65 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 187.9, 150.4, 147.4, 137.9, 128.6, 128.5, 127.9, 127.9, 127.4, 119.8, 112.8, 73.9, 73.7, 71.4, 71.2 ppm. IR (neat): $\tilde{\nu}$ = 3297, 3126, 3032, 2935, 2886, 2859, 1704, 1670, 1570, 1490, 1468, 1417, 1392, 1318, 1236, 1138, 1118, 1080, 1033, 985, 885, 860, 772, 758, 734, 696 cm^{-1}. HPLC (Chiralpak AD-H, hexane/*i*PrOH = 80:20, flow rate: 1.0 mL/min, λ = 254 nm): t_R = 15.6 (*anti*), 16.9 (*anti*), 19.1 (*syn*, major), 23.5 min (*syn*, minor). HRMS (ESI): calcd. for $C_{15}H_{16}O_5$ [M + Na]$^+$ 299.0895; found 299.0873.

(2*S*,3*R*)-4-(Benzyloxy)-1-(4-chlorophenyl)-2,3-dihydroxybutan-1-one (7j): ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.89–7.84 (m, 2 H), 7.46–7.41 (m, 2 H), 7.39–7.28 (m, 5 H), 5.19 (s, 1 H), 4.62–4.54 (m, 2 H), 4.16–4.10 (m, 1 H), 3.91 (s, 1 H), 3.66 (dd, J = 9.2, 6.9 Hz, 1 H), 3.62 (dd, J = 9.2, 5.8 Hz, 1 H), 2.32 (s, 1 H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 198.9, 140.7, 137.8, 132.1, 130.3, 129.4, 128.7, 128.1, 127.9, 73.7, 73.2, 71.4, 70.8 ppm. IR (neat): $\tilde{\nu}$ = 3297, 3089, 3060, 3032, 2935, 2882, 1701, 1591, 1490, 1455, 1400, 1317, 1255, 1214, 1134, 1096, 1029, 1014, 996, 983, 876, 867, 815, 740, 698 cm^{-1}. HPLC (Chiralpak AD-H, hexane/*i*PrOH = 80:20, flow rate: 1.0 mL/min, λ = 254 nm): t_R = 13.9 (*anti*), 14.6 (*anti*), 15.4 (*syn*, major), 16.3 min (*syn*, minor). HRMS (ESI): calcd. for $C_{17}H_{17}ClO_4$ [M + Na]$^+$ 243.0713; found 243.0710.

(2*S*,3*R*)-4-(Benzyloxy)-2,3-dihydroxy-1-(4-trifluoromethylphenyl)-butan-1-one (7k): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.07–7.98 (m, 2 H), 7.79–7.69 (m, 2 H), 7.45–7.27 (m, 5 H), 5.23 (d, J = 1.9 Hz, 1 H), 4.57 (s, 2 H), 4.17–4.07 (m, 1 H), 3.75–3.58 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.9, 138.2, 137.3, 129.7, 129.3, 129.2, 128.7, 128.6, 128.5, 128.4, 126.5, 126.5, 74.3, 74.2, 71.7, 71.2 ppm. IR (neat): $\tilde{\nu}$ = 3331, 3063, 3032, 2929, 2874, 1708, 1615, 1579, 1490, 1455, 1410, 1330, 1254, 1212, 1171, 1132, 1069, 1017, 989, 874, 745, 699 cm^{-1}. HPLC (Chiralpak AD-H, hexane/*i*PrOH = 80:20, flow rate: 1.0 mL/min, λ = 254 nm): t_R = 9.9 (unseparated *anti*), 11.5 (*syn*, major), 12.3 min (*syn*, minor). HRMS (ESI): calcd. for $C_{18}H_{17}F_3O_4$ [M + Na]$^+$ 377.0977; found 377.0939.

(2*S*,3*R*)-2,3-Dihydroxy-1-(4-trifluoromethylphenyl)butan-1-one (7l): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.12–7.97 (m, 2 H), 7.83–7.74 (m, 2 H), 4.91 (d, J = 2.4 Hz, 1 H), 4.13 (m, 1 H), 1.39 (d, J = 6.5 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.5, 136.9, 129.0, 128.9, 125.9, 69.2, 68.8, 20.5 ppm. IR (neat): $\tilde{\nu}$ = 3436, 2978, 2929, 1694, 1515, 1413, 1332 1269, 1173, 1137, 1069, 1011, 984, 863, 847, 823 cm^{-1}. HPLC (Chiralpak OD-H, hexane/*i*PrOH = 80:20, flow rate: 0.5 mL/min, λ = 254 nm): t_R = 11.8 (*syn*, major), 12.9 (*syn*, minor), 15.1 min (unseparated *anti*). HRMS (ESI): calcd. for $C_{11}H_{11}F_3O_3$ [M + Na]$^+$ 271.0558; found 271.0493.

(2*S*,3*R*)-2,3-Dihydroxy-4-phenyl-1-(4-trifluoromethylphenyl)butan-1-one (7m): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75–7.62 (m, 4 H), 7.45–7.26 (m, 5 H), 4.92 (s, 1 H), 4.19–4.08 (m, 1 H), 3.12–2.95 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.4, 137.2, 136.3, 135.3, 134.9, 129.5, 128.9, 128.8, 128.1, 127.4, 127.1, 125.9, 125.8, 121.5, 73.8, 73.8, 40.9 ppm. IR (neat): $\tilde{\nu}$ = 3453, 3063, 3023, 2928, 2850, 1695, 1496, 1455, 1413, 1329, 1261, 1173, 1135, 1069, 1017, 986, 871, 755, 743, 705 cm^{-1}. HPLC (Chiralpak AD-H, hexane/*i*PrOH = 80:20, flow rate: 1.0 mL/min, λ = 254 nm): t_R = 11.7 (*syn*, minor), 12.3 (*syn*, major), 17.3 (*anti*), 18.7 min (*anti*). HRMS (ESI): calcd. for $C_{17}H_{15}F_3O_3$ [M + Na]$^+$ 347.0871; found 347.0810.

(2*S*,3*R*)-1-[3,5-Bis(trifluoromethyl)phenyl]-2,3-dihydroxy-4-phenylbutan-1-one (7n): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.07 (s, 2 H), 7.47–7.20 (m, 6 H), 4.90 (d, J = 1.3 Hz, 1 H), 4.17 (ddd, J = 8.7, 6.4, 1.3 Hz, 1 H), 3.12–2.95 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.9, 136.8, 135.1, 132.8, 132.4, 129.2, 129.2, 128.6, 127.2, 126.9, 124.4, 120.8, 73.8, 73.73, 40.6 ppm. IR (neat): $\tilde{\nu}$ = 3492, 3360, 3093, 3066, 3029, 2927, 2855, 1695, 1614, 1497, 1456, 1406, 1376, 1288, 1258, 1191, 1145, 1060, 914, 946, 783, 752, 701, 682 cm^{-1}. HPLC (Chiralpak OD-H, hexane/*i*PrOH = 96:4, flow rate: 0.5 mL/min, λ = 206 nm): t_R = 11.7 (*anti*), 15.8 (*anti*), 30.5 (*syn*, minor), 34.1 min (*syn*, major). HRMS (ESI): calcd. for $C_{18}H_{14}F_6O_3$ [M + Na]$^+$ 415.0745; found 415.0658.

(2*S*,3*R*)-2,3-Dihydroxy-1-(2,3,5,6-tetrafluoro-4-methoxyphenyl)-heptan-1-one (7o): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.71 (dd, J = 3.9, 2.0 Hz, 1 H), 4.21 (t, J = 1.9 Hz, 3 H), 4.17–4.07 (m, 2 H), 3.92–3.83 (m, 1 H), 1.75–1.65 (m, 2 H), 1.50–1.29 (m, 5 H), 0.94 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 195.4, 79.6, 72.3, 62.0, 34.0, 27.8, 22.5, 13.9 ppm. IR (neat): $\tilde{\nu}$ = 3331, 2955, 2872, 1706, 1648, 1510, 1487, 1440, 1408, 1330, 1309, 1202, 1161, 1092, 1003, 944, 915, 861, 811, 775, 689, 659 cm^{-1}. HPLC (Chiralpak AD-H, hexane/*i*PrOH = 80:20, flow rate: 1.0 mL/min, λ = 254 nm): t_R = 5.4 (*anti*), 5.7 (*anti*), 7.8 (*syn*, major), 8.3 min (*syn*, minor). HRMS (ESI): calcd. for $C_{14}H_{16}F_4O_4$ [M + Na]$^+$ 347.0882; found 347.0885.

(2*S*,3*R*)-2,3-Dihydroxy-4-methyl-1-(2,3,5,6-tetrafluoro-4-methoxyphenyl)pentan-1-one (7p): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.88 (d, J = 1.6 Hz, 1 H), 4.19 (t, J = 1.9 Hz, 3 H), 4.15–4.05 (m, 2 H), 3.41 (dd, J = 8.9, 1.6 Hz, 1 H), 2.01–1.85 (m, 1 H), 1.03 (d, J = 6.7 Hz, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 78.7, 78.5, 62.7, 32.4, 19.7, 19.5 ppm. IR (neat): $\tilde{\nu}$ = 3471, 2965, 2941, 2868, 1708, 1650, 1511, 1491, 1440, 1412, 1314, 1203, 1141, 1097, 1068, 994, 802 cm^{-1}. HPLC (Chiralpak AD-H, hexane/*i*PrOH = 80:20, flow rate: 1.0 mL/min, λ = 254 nm): t_R = 7.6 (*anti*), 9.2 (*anti*), 9.8 (*syn*, minor), 11.3 min (*syn*, major). HRMS (ESI): calcd. for $C_{13}H_{14}F_4O_4$ [M + Na]$^+$ 333.0726; found 333.0714.

(2*S*,3*R*)-2,3-Dihydroxy-4,4-diphenyl-1-(2,3,5,6-tetrafluoro-4-methoxyphenyl)lbutan-1-one (7q): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.44–7.14 (m, 10 H), 4.68–4.57 (m, 1 H), 4.54 (d, J = 4.0 Hz, 1 H), 4.35 (d, J = 10.7 Hz, 1 H), 4.20 (t, J = 1.9 Hz, 3 H), 3.72 (d, J = 5.7 Hz, 1 H), 1.89 (d, J = 6.3 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 195.4, 140.8, 140.5, 129.3, 129.1, 129.1, 128.6, 128.4, 127.4, 127.3, 77.7, 74.5, 62.2, 55.1 ppm. IR (neat): $\tilde{\nu}$ = 3482, 3084, 3062, 3030, 2959, 2928, 2850, 1709, 1648, 1598, 1511, 1491, 1453, 1438, 1409, 1313, 1204, 1165 1124, 993, 812, 749, 707 cm^{-1}. HPLC (Chiralpak AD-H, hexane/*i*PrOH = 80:20, flow rate: 1.0 mL/min, λ = 254 nm): t_R = 8.4 (*syn*, major), 15.7 (*syn*, minor), 17.5 (*anti*), 18.6 min (*anti*). HRMS (ESI): calcd. for $C_{23}H_{18}F_4O_4$ [M + Na]$^+$ 457.1039; found 457.1020.

(2*S*,3*R*)-2,3-Dihydroxy-5-phenyl-1-(2,3,5,6-tetrafluoro-4-methoxyphenyl)pentan-1-one (7r): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.08 (m, 5 H), 4.67 (s, 1 H), 4.21 (t, J = 2.1 Hz, 3 H), 3.94–3.82 (m, 1 H), 3.78 (s, 1 H), 3.32 (s, 1 H), 2.88–2.65 (m, 2 H), 2.11–1.95 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 195.3, 141.2, 128.6, 128.5, 126.2, 79.7, 71.7, 69.9, 62.2, 35.9, 32.0 ppm. IR (neat): $\tilde{\nu}$ = 3452, 3028, 2959, 2856, 1711, 1648, 1512, 1488, 1456, 1439,

1406, 1313, 1204, 1163, 1120, 1061, 1004, 749, 703 cm^{-1}. HPLC (Chiralpak AD-H, hexane/*i*PrOH = 80:20, flow rate: 1.0 mL/min, λ = 254 nm): t_R = 9.8 (*syn*, major), 11.2 (*syn*, minor), 17.3 (*anti*), 18.1 min (*anti*). HRMS (ESI): calcd. for $C_{18}H_{16}F_4O_4$ $[M + Na]^+$ 395.0882; found 395.0879.

(2*S*,3*R*)-4-(Benzyloxy)-2,3-dihydroxy-1-(2,3,5,6-tetrafluoro-4-methoxyphenyl)butan-1-one (7s): ^1H NMR (600 MHz, $CDCl_3$): δ = 7.38–7.29 (m, 5 H), 5.66 (s, 1 H), 4.55–4.45 (m, 2 H), 4.18 (dt, *J* = 3.0, 1.6 Hz, 1 H), 4.09–4.05 (m, 3 H), 3.70–3.61 (m, 2 H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 128.8, 128.7, 128.7, 128.0, 127.9, 74.2, 73.9, 70.7, 67.9, 62.2 ppm. IR (neat): $\tilde{\nu}$ = 3437, 3031, 2917, 2870, 1729, 1651, 1496, 1455, 1418, 1312, 1201, 1137, 1028, 992, 748, 700 cm^{-1}. HPLC (Chiralpak AD-H, hexane/*i*PrOH = 80:20, flow rate: 1.0 mL/min, λ = 254 nm): t_R = 8.6 (*anti*), 10.4 (*anti*), 9.9 (*syn*, minor), 12.9 min (*syn*, major). HRMS (ESI): calcd. for $C_{18}H_{16}F_4O_5$ $[M + Na]^+$ 411.0832; found 411.0830.

Supporting Information (see footnote on the first page of this article): Detailed experimental procedures and copies of the HPLC data as well as ^1H NMR and ^{13}C NMR spectra of all aldol products.

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