Efficient Preparation of 1,3-Diol Derivatives with Three Contiguous Stereocenters by an Enantioselective Direct Aldol–Tishchenko Reaction

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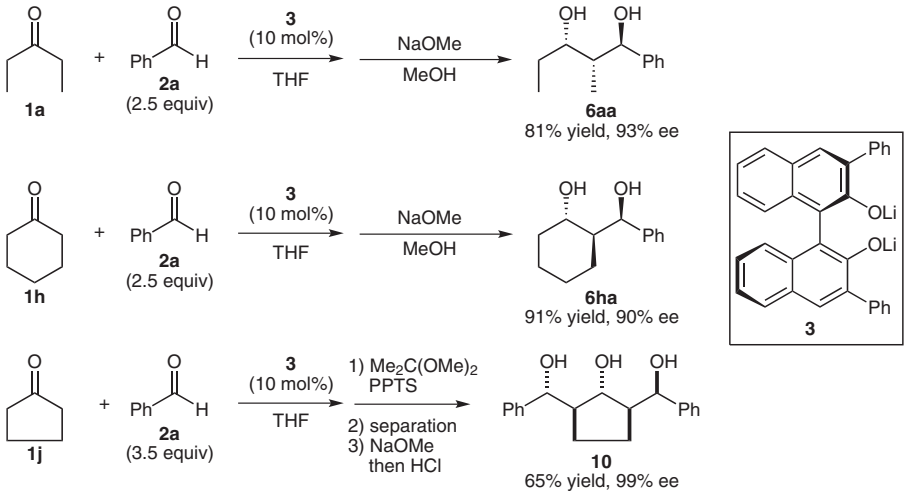
Received: 29.02.2012; Accepted: 21.03.2012

PSP No 234

Abstract: 1,3-Diol derivatives with three contiguous stereocenters were efficiently prepared by an enantioselective direct aldol–Tishchenko reaction catalyzed by dilithium 3,3′-diphenylbinaphtholate. The reactions of acyclic ketones as aldol donors gave 1,2-*syn*-1,3-*anti*-diol derivatives, whereas the reactions of cyclic ketones as aldol donors gave 1,2-*anti*-1,3-*anti*-diol derivatives. Sequential aldol–aldol–Tishchenko reactions gave a triol derivative with five consecutive chiral centers.

Key words: aldol reaction, asymmetric catalysis, enantioselectivity, stereoselectivity, tandem reaction



Scheme 1

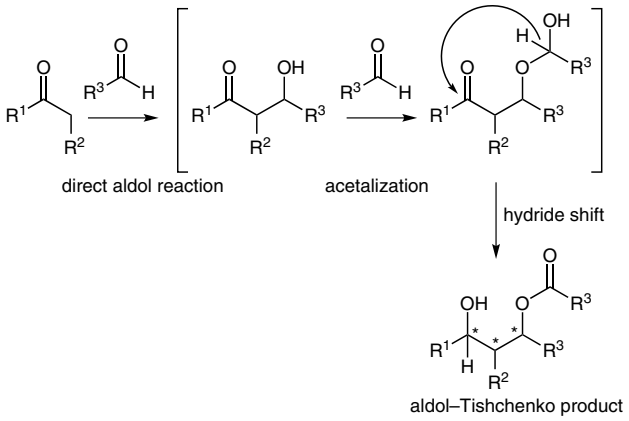
Introduction

The efficient preparation of 1,3-diol derivatives with three contiguous stereocenters by an enantioselective direct aldol–Tishchenko reaction starting from two carbonyl compounds is described (Scheme 1). The enantioselective synthesis of 1,3-diols is important in synthetic organic chemistry because numerous biologically active compounds include 1,3-diol units.[1] Direct aldol–Tishchenko reactions[2] are cascade reactions[3] consisting of a direct aldol process,[4] an acetalization, and a hydride shift (Scheme 2). The sequence of these conversions affords monoacyl-protected 1,3-diols with three contiguous asymmetric centers from two carbonyl compounds. The first enantioselective aldol–Tishchenko reaction was reported by Loog and Mäeorg,[5] who used a monolithium salt of binaphthol; however, the observed enantioselectivities were low. Later, the research groups of Morken,[6] Shibasaki,[7] Mlynarski,[8] and Mahrwald[9] developed a highly enantioselective aldol–Tishchenko reaction using, respectively, yttrium, lanthanum, ytterbium, and titanium complexes as catalysts. We previously reported that dilithium binaphtholate[10,11] catalyzes an enantioselective direct aldol reaction and the subsequent Tishchenko reaction.[12] Here, we present a practical synthetic procedure for the preparation of 1,3-diol derivatives with three contiguous stereocenters.

Scope and Limitations

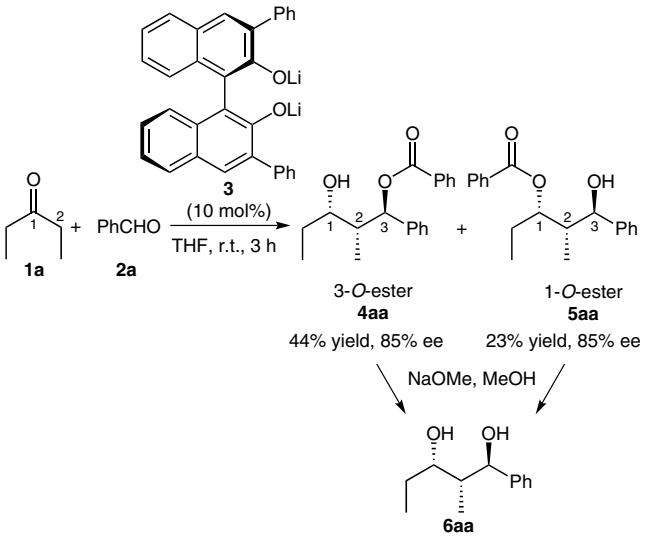
In the initial study, we investigated the aldol–Tishchenko reaction using pentan-3-one (**1a**) and benzaldehyde (**2a**) as substrates with dilithium 3,3′-diphenylbinaphtholate as a catalyst (Scheme 3). The reaction proceeded to afford the product as a mixture of 3-*O*-ester **4aa** and 1-*O*-ester **5aa** having the same sense and magnitude of absolute and relative configurations (1,2-*syn*-1,3-*anti*). As expected, the isolated 3-*O*-ester **4aa** and 1-*O*-ester **5aa** easily inter-

SYNTHESIS 2012, 44, 3145–3151
Advanced online publication: 29.06.2012
DOI: 10.1055/s-0031-1291138; Art ID: SS-2012-Z0209-PSP



Scheme 2

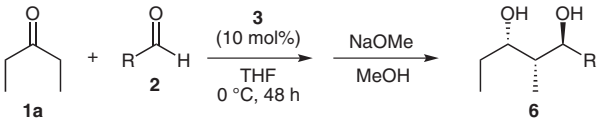
converted via isomerization under the reaction conditions, which suggested that 1-*O*-ester **5aa** formed via a transesterification from the 3-*O*-ester **4aa** after the Tishchenko process. Therefore, prior to isolating the product, we removed the benzoyl group to obtain the product as a single diastereomer for data collection.



Scheme 3

The results obtained in the aldol–Tishchenko reactions of pentan-3-one (**1a**) with various aldehydes at 0 °C are listed in Table 1. Although a slight decrease in the selectivity was observed in the reaction of *p*-bromobenzaldehyde (**2d**) (entry 4), both *p*-tolualdehyde (**2b**) and *p*-anisaldehyde (**2c**) gave a selectivity of 95% ee (entries 2 and 3), similar to that obtained from the reaction of benzaldehyde (**2a**). The reaction of cinnamaldehyde (**2e**) gave a slightly lower chemical yield, but with a high selectivity (entry 5). Hydrocinnamaldehyde (**2f**) did not give the corresponding adduct (entry 6), although the self-aldol–Tishchenko product **7** was obtained in 83% in racemic form (Figure 1). Sterically bulky pivalaldehyde (**2g**) did not react at all (entry 7).

Table 1 Aldol–Tishchenko Reaction of Pentan-3-one with Various Aldehydes



Entry	R	Product	Yield (%)	ee (%)
1	Ph (**2a**)	**6aa**	81	93
2	4-MeC_6H_4 (**2b**)	**6ab**	87	95
3	4-$MeOC_6H_4$ (**2c**)	**6ac**	81	95
4	4-BrC_6H_4 (**2d**)	**6ad**	80	88
5	PhCH=CH (**2e**)	**6ae**	61	94
6	$PhCH_2CH_2$ (**2f**)	**6af**	0	–
7	*t*-Bu (**2g**)	**6ag**	0	–

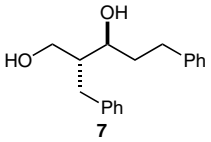
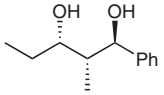
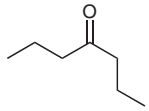
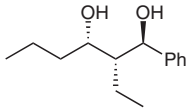
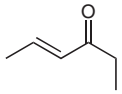
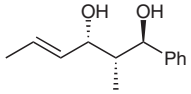
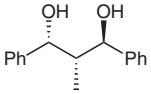
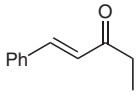
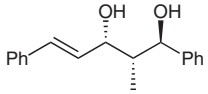
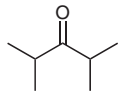
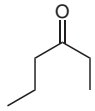
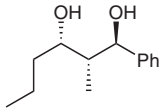
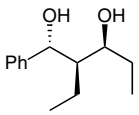
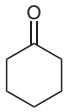
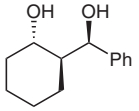
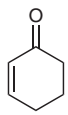
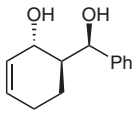


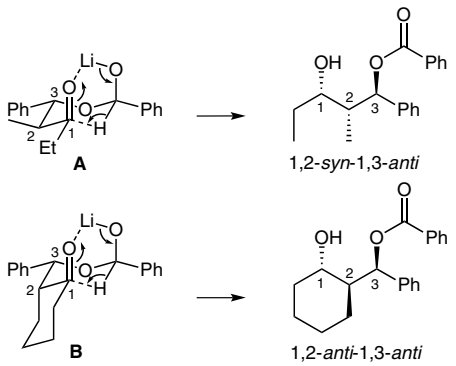
Figure 1

High enantioselectivities were obtained using other ketones as aldol donors (Table 2). In the reactions involving acyclic ketone aldol donors and benzaldehyde as the aldol acceptor, 1,2-*syn*-1,3-*anti*-diols were obtained as single diastereomers with high chemical and optical yields (entries 1–3). It should be noted that this is the highest level of enantioselectivity yet reported for an aldol–Tishchenko reaction using simple aliphatic ketones as aldol donors. Aromatic ketones were less reactive and gave the corresponding diols in high chemical yields at room temperature; the enantioselectivities, however, were slightly lower (entries 4 and 5) than those obtained from aliphatic ketones. The sterically congestesd ketone **1f** did not react at all (entry 6). In the reaction of hexan-3-one (**1g**), which includes two reactive sites, the diol **6ga** (upon reaction at the ethyl site) and the diol **8ga** (upon reaction at the propyl site) were obtained in a ratio of 4.4 to 1 (entry 7). It is interesting that the present reaction selectively distinguished between the ethyl and propyl groups, which do not differ significantly in bulk or reactivity.

The reactions of cyclic ketones as aldol donors, such as cyclohexanone (**1h**) and cyclohex-2-en-1-one (**1i**), afforded 1,2-*anti*-1,3-*anti*-diols as single diastereomers with high chemical and optical yields (Table 2, entries 8 and 9). Transition-state model A, proposed by early pioneers,[13] can explain the formation of the 1,2-*syn*-1,3-*anti*-isomer from an acyclic aldol donor, whereas the reaction of a cyclic ketone may proceed via a tricyclic transition state B, proposed by Fang and co-workers,[13f] to afford the 1,2-*anti*-1,3-*anti*-isomer (Scheme 4).

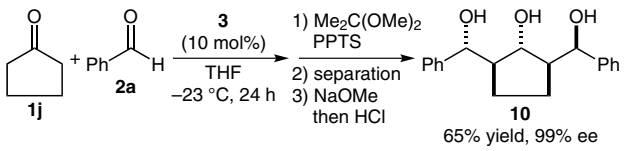
Table 2 Aldol–Tishchenko Reaction of Benzaldehyde with Various Ketones

Entry	Ketone	Conditions	Product	Yield (%)	ee (%)
1	 **1a**	0 °C, 48 h	 **6aa**	81	93
2	 **1b**	0 °C, 48 h	 **6ba**	71	91
3	 **1c**	0 °C, 48 h	 **6ca**	80	87
4	 **1d**	r.t., 48 h	 **6da**	80	72
5	 **1e**	r.t., 48 h	 **6ea**	91	70
6	 **1f**	r.t., 48 h	–	0	–
7	 **1g**	–10 °C, 48 h	 **6ga**  **8ga** **6ga**/**8ga** = 4.4:1	70 (**6ga**) 16 (**8ga**)	94 (**6ga**) 97 (**8ga**)
8	 **1h**	0 °C, 24 h	 **6ha**	91	90
9	 **1i**	–23 °C, 24 h	 **6ia**	88	85



Scheme 4

In the reaction of cyclopentanone (**1j**), a highly enolizable aldol donor, the byproduct derived from the sequential double aldol and Tishchenko reaction (aldol–aldol–Tishchenko reaction)[9,13d] was favored, even in the presence of 2.5 equivalents of benzaldehyde (**2a**) at –23 °C. Therefore, we employed 3.5 equivalents of benzaldehyde (**2a**) as aldol acceptor to afford a mixture of two inseparable diastereomers (3:1). As the isomers could not be separated, we converted the isomers into acetonides, which could be separated by silica gel chromatography. The sequential deprotection of benzoyl and acetonide groups afforded a triol **10** with five consecutive chiral centers with extremely high enantioselectivity (Scheme 5). Although the relative configurations of the other isomers are not yet known, the configuration of the major product **10** was determined by X-ray crystallographic analysis (CCDC 848047).



Scheme 5

In conclusion, we have provided a new, efficient method for preparing 1,3-diol derivatives with three contiguous stereocenters by an enantioselective direct aldol–Tishchenko reaction. The catalyst is easily prepared from common reagents and does not contain rare metals. The reactions of acyclic ketones as aldol donors produced 1,2-*syn*-1,3-*anti*-diol derivatives, whereas the reactions of cyclic ketones as aldol donors produced 1,2-*anti*-1,3-*anti*-diol derivatives. In the case of cyclopentanone, a single manipulation controlled five consecutive chiral centers. The design of chiral catalysts to further enhance the reaction enantioselectivity, in addition to studies toward the synthesis of biologically active compounds, is currently in progress.

All reactions were carried out under an argon atmosphere using dried glassware. All starting materials were purchased from commercial suppliers and were used without purification, unless otherwise stated. 3,3′-Diphenylbinaphthol was prepared according to the method described in the literature.[14] Yields refer to isolated compounds estimated to be >95% pure, as determined by ^{1}H NMR spectroscopy. IR spectra were recorded on a JEOL JIR 6500-W spectrophotometer. ^{1}H and ^{13}C NMR spectra were determined for solutions in $CDCl_3$ with Me_4Si as internal standard on a JEOL JNM-ECX 400 instrument. HRMS data were measured on a JEOL JMS-DX303HF mass spectrometer. Optical rotations were recorded on a JASCO P-1010.

(1*R*,2*R*,3*S*)-2-Methyl-1-phenylpentane-1,3-diol (6aa);[8d] Typical Procedure for the Aldol–Tishchenko Reaction

Under an argon atmosphere, *n*-BuLi (0.094 mmol, 20 mol%) in hexane (0.17 M, 0.55 mL) was added to a soln of (*R*)-3,3′-diphenylbinaphthol (20.7 mg, 0.047 mmol, 10 mol%) in THF (1 mL) at 0 °C, and the mixture was stirred for 5 min. Benzaldehyde (**2a**) (0.12 mL, 1.18 mmol, 2.5 equiv) and pentan-3-one (**1a**) (41 mg, 0.47 mmol) in THF (0.5 mL) were successively added to the above mixture, and the mixture was stirred for 48 h. The reaction was quenched with sat. NH_4Cl (2 mL) and the mixture was stirred at r.t. for 5 min. The aqueous layer was extracted with EtOAc (3 × 10 mL) and the combined organic layers were washed with brine (3 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was dissolved in MeOH (2 mL) and treated with NaOMe (0.05 mmol, 11 mol%) in MeOH (0.5 M, 0.1 mL). After 3 h, the mixture was diluted with EtOAc (20 mL), and washed with H_2O (5 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL) and the combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane–EtOAc, 4:1) to give diol **6aa** as a colorless oil; yield: 74 mg (81%).

$[\alpha]_D^{29}$ +45.4 (*c* 1.22, $CHCl_3$; 93% ee), $[\alpha]_D^{29}$ +43.6 (*c* 1.01, CH_2Cl_2; 93% ee) [Lit.[8d] $[\alpha]_D$ –36.2 (*c* 0.60, CH_2Cl_2; 75% ee (1*S*,2*S*,3*R*))].

HPLC (Daicel Chiralpak AD-H, hexane–*i*-PrOH (19:1), 1.0 mL/min): t_R (min) = 14.7 (major, 1*R*,2*R*,3*S*), 20.3 (minor, 1*S*,2*S*,3*R*) [Lit.[8d] AD-H, hexane–*i*-PrOH (9:1), 1.0 mL/min: t_R (min) = 7.8 (1*R*,2*R*,3*S*), 10.1 (1*S*,2*S*,3*R*)].

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.85 (d, *J* = 6.8 Hz, 3 H, CHC*H*$_3$), 0.89 (t, *J* = 7.3 Hz, 3 H, CH_2CH_3), 1.36–1.56 (m, 2 H, C*H*$_2$CH$_3$), 1.88–1.95 (m, 1 H, C*H*CH$_3$), 2.91 (br s, 1 H, O*H*), 3.54 (br s, 1 H, O*H*), 3.70 (ddd, *J* = 8.7, 4.6, 2.3 Hz, 1 H, HOC*H*), 4.67 (d, *J* = 6.9 Hz, 1 H, HOC*H*Ph), 7.22–7.36 (m, 5 H, Ar*H*).

(1*R*,2*R*,3*S*)-2-Methyl-1-(4-methylphenyl)pentane-1,3-diol (6ab)[8d]

Following the typical procedure, the reaction of *p*-tolualdehyde (**2b**) (0.14 mL, 1.18 mmol, 2.5 equiv) and pentan-3-one (**1a**) (41 mg, 0.47 mmol) gave diol **6ab** as a colorless oil; yield: 85 mg (87%).

$[\alpha]_D^{29}$ +41.0 (*c* 1.05, $CHCl_3$; 95% ee).

HPLC (Daicel Chiralpak AD-H, hexane–*i*-PrOH (29:1), 1.0 mL/min): t_R (min) = 24.6 (major, 1*R*,2*R*,3*S*), 29.4 (minor, 1*S*,2*S*,3*R*) [Lit.[8d] AD-H, hexane–*i*-PrOH (9:1), 1.0 mL/min: t_R (min) = 8.4 (1*R*,2*R*,3*S*), 9.1 (1*S*,2*S*,3*R*)].

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.81 (d, *J* = 7.3 Hz, 3 H, CHC*H*$_3$), 0.89 (t, *J* = 7.3 Hz, 3 H, CH_2CH_3), 1.35–1.58 (m, 2 H, C*H*$_2$CH$_3$), 1.85–1.92 (m, 1 H, C*H*CH$_3$), 2.33 (s, 3 H, ArC*H*$_3$), 3.07 (br s, 1 H, O*H*), 3.53 (br s, 1 H, O*H*), 3.69 (ddd, *J* = 8.7, 4.6, 1.8 Hz, 1 H, HOC*H*), 4.62 (d, *J* = 6.8 Hz, 1 H, HOC*H*Ar), 7.13 (d, *J* = 7.8 Hz, 2 H, Ar*H*), 7.20 (d, *J* = 7.8 Hz, 2 H, Ar*H*).

(1*R*,2*R*,3*S*)-1-(4-Methoxyphenyl)-2-methylpentane-1,3-diol (6ac)[8d]

Following the typical procedure, the reaction of *p*-anisaldehyde (**2c**) (0.14 mL, 1.18 mmol, 2.5 equiv) and pentan-3-one (**1a**) (41 mg, 0.47 mmol) gave diol **6ac** as a colorless oil; yield: 85 mg (81%).

$[\alpha]_D^{29}$ +41.8 (*c* 0.75, $CHCl_3$; 95% ee).

HPLC (Daicel Chiralpak AD-H, hexane–*i*-PrOH (9:1), 1.0 mL/min): t_R (min) = 11.0 (major, 1*R*,2*R*,3*S*), 12.4 (minor, 1*S*,2*S*,3*R*)

[Lit.[8d] AD-H, hexane–*i*-PrOH (9:1), 1.0 mL/min: t_R (min) = 11.3 (1*R*,2*R*,3*S*), 12.7 (1*S*,2*S*,3*R*)].

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.79 (d, *J* = 7.4 Hz, 3 H, CHC*H*$_3$), 0.90 (t, *J* = 7.3 Hz, 3 H, CH$_2$C*H*$_3$), 1.38–1.58 (m, 2 H, C*H*$_2$CH$_3$), 1.83–1.91 (m, 1 H, C*H*CH$_3$), 3.12 (br s, 1 H, O*H*), 3.62 (br s, 1 H, O*H*), 3.69 (ddd, *J* = 8.2, 4.1, 1.8 Hz, 1 H, HOC*H*), 3.78 (s, 3 H, OC*H*$_3$), 4.60 (d, *J* = 7.3 Hz, 1 H, HOC*H*Ar), 6.84–6.88 (m, 2 H, Ar*H*), 7.21–7.25 (m, 2 H, Ar*H*).

(1*R*,2*R*,3*S*)-1-(4-Bromophenyl)-2-methylpentane-1,3-diol (6ad)[8d]

Following the typical procedure, the reaction of *p*-bromobenzaldehyde (**2d**) (212 mg, 1.18 mmol, 2.5 equiv) and pentan-3-one (**1a**) (41 mg, 0.47 mmol) gave diol **6ad** as colorless prisms; yield: 103 mg (80%); mp 96–97 °C.

$[\alpha]_D^{29}$ +34.5 (*c* 1.05, $CHCl_3$; 88% ee).

HPLC (Daicel Chiralpak AS-H, hexane–*i*-PrOH (9:1), 1.0 mL/min): t_R (min) = 7.2 (major, 1*R*,2*R*,3*S*), 10.2 (minor, 1*S*,2*S*,3*R*) [Lit.[8d] AS-H, hexane–*i*-PrOH (9:1), 1.0 mL/min: t_R (min) = 6.3 (1*R*,2*R*,3*S*), 10.1 (1*S*,2*S*,3*R*)].

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.84–0.89 (m, 6 H, CHC*H*$_3$, CH$_2$C*H*$_3$), 1.34–1.54 (m, 2 H, C*H*$_2$CH$_3$), 1.80–1.87 (m, 1 H, C*H*CH$_3$), 3.04 (br s, 1 H, O*H*), 3.63 (ddd, *J* = 8.7, 5.0, 2.3 Hz, 1 H, HOC*H*), 4.08 (br s, 1 H, O*H*), 4.60 (d, *J* = 6.4 Hz, 1 H, HOC*H*Ar), 7.15–7.19 (m, 2 H, Ar*H*), 7.43–7.46 (m, 2 H, Ar*H*).

(1*E*,3*S*,4*R*,5*S*)-4-Methyl-1-phenylhept-1-ene-3,5-diol (6ae)

Following the typical procedure, the reaction of *trans*-cinnamaldehyde (**2e**) (0.15 mL, 1.18 mmol, 2.5 equiv) and pentan-3-one (**1a**) (41 mg, 0.47 mmol) gave diol **6ae** as a colorless oil; yield: 63 mg (61%).

$[\alpha]_D^{29}$ +6.9 (*c* 1.27, $CHCl_3$; 94% ee), $[\alpha]_D^{31}$ +15.4 (*c* 1.14, benzene; 94% ee).

HPLC (Daicel Chiralpak AD-H, hexane–*i*-PrOH (19:1), 1.0 mL/min): t_R (min) = 18.5 (major, 3*S*,4*R*,5*S*), 21.2 (minor, 3*R*,4*S*,5*R*).

IR (neat): 3552 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92–0.98 (m, 6 H, CHC*H*$_3$, CH$_2$C*H*$_3$), 1.49–1.61 (m, 2 H, C*H*$_2$CH$_3$), 1.73–1.80 (m, 1 H, C*H*CH$_3$), 2.85 (br s, 1 H, O*H*), 3.29 (br s, 1 H, O*H*), 3.84–3.88 (m, 1 H, HOC*H*), 4.30 (t, *J* = 6.4 Hz, 1 H, HOC*H*), 6.25 (dd, *J* = 16.0, 6.4 Hz, 1 H, PhCH=C*H*), 6.62 (d, *J* = 15.6 Hz, 1 H, PhC*H*=CH), 7.21–7.39 (m, 5 H, Ar*H*).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.63, 11.02, 26.71, 41.78, 74.10, 76.61, 126.41, 127.52, 128.50, 130.74, 131.60, 136.68.

LRMS–FAB ($CHCl_3$ + NBA + NaI): *m*/*z* = 243 $[M + Na]^+$, 241, 176 (100), 145, 136, 55.

HRMS–FAB: *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{20}O_2Na$: 243.1361; found: 243.1340.

(1*R*,2*R*,3*S*)-2-Ethyl-1-phenylhexane-1,3-diol (6ba)[8d]

Following the typical procedure, the reaction of benzaldehyde (**2a**) (0.12 mL, 1.18 mmol, 2.5 equiv) and heptan-4-one (**1b**) (54 mg, 0.47 mmol) gave diol **6ba** as a colorless oil; yield: 74 mg (71%).

$[\alpha]_D^{28}$ +37.6 (*c* 0.99, $CHCl_3$; 91% ee).

HPLC (Daicel Chiralpak AS-H, hexane–*i*-PrOH (19:1), 1.0 mL/min): t_R (min) = 8.6 (major, 1*R*,2*R*,3*S*), 11.4 (minor, 1*S*,2*S*,3*R*) [Lit.[8d] Daicel Chiralpak AS-H, hexane–*i*-PrOH (9:1), 1.0 mL/min: t_R (min) = 5.1 (1*R*,2*R*,3*S*), 5.7 (1*S*,2*S*,3*R*)].

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.82 (t, *J* = 6.9 Hz, 3 H, CHCH$_2$C*H*$_3$), 0.91 (t, *J* = 7.3 Hz, 3 H, CH$_2$CH$_2$C*H*$_3$), 1.16–1.63 (m, 7 H, C*H*CH$_2$CH$_3$, C*H*$_2$CH$_2$CH$_3$), 3.32 (br s, 1 H, O*H*), 3.74 (ddd, *J* = 9.2, 4.1, 1.8 Hz, 1 H, HOC*H*), 3.89 (br s, 1 H, O*H*), 4.85 (d, *J* = 5.5 Hz, 1 H, HOC*H*Ph), 7.22–7.35 (m, 5 H, Ar*H*).

(1*R*,2*R*,3*S*,4*E*)-2-Methyl-1-phenylhex-4-ene-1,3-diol (6ca)

Following the typical procedure, the reaction of benzaldehyde (**2a**) (0.12 mL, 1.18 mmol, 2.5 equiv) and hex-4-en-3-one (**1c**) (46 mg, 0.47 mmol) gave diol **6ca** as a colorless oil; yield: 78 mg (80%).

$[\alpha]_D^{28}$ +5.7 (*c* 1.34, $CHCl_3$; 87% ee).

HPLC (Daicel Chiralcel OD-H, hexane–*i*-PrOH (19:1), 1.0 mL/min): t_R (min) = 11.1 (minor, 1*S*,2*S*,3*R*), 12.2 (major, 1*R*,2*R*,3*S*).

IR (neat): 3354 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.69 (d, *J* = 7.3 Hz, 3 H, CHC*H*$_3$), 1.72 (d, *J* = 5.5 Hz, 3 H, CH=CHC*H*$_3$), 1.96–2.04 (m, 1 H, C*H*CH$_3$), 3.42 (br s, 1 H, O*H*), 3.87 (br s, 1 H, O*H*), 4.20–4.23 (m, 1 H, HOC*H*), 4.57 (d, *J* = 8.3 Hz, 1 H, HOC*H*Ph), 5.56–5.89 (m, 2 H, C*H*=C*H*), 7.23–7.34 (m, 5 H, Ar*H*).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.5, 17.8, 44.2, 75.0, 77.9, 126.6, 127.5, 127.7, 128.3, 130.7, 143.6.

LRMS–FAB ($CHCl_3$ + NBA + NaI): *m*/*z* = 229 (100) $[M + Na]^+$, 173, 149, 107, 55.

HRMS–FAB: *m*/*z* $[M + Na]^+$ calcd for $C_{13}H_{18}O_2Na$: 229.1204; found: 229.1200.

(1*R*,3*R*)-2-Methyl-1,3-diphenylpropane-1,3-diol (6da)[8d]

Following the typical procedure, the reaction of benzaldehyde (**2a**) (0.12 mL, 1.18 mmol, 2.5 equiv) and propiophenone (**1d**) (63 mg, 0.47 mmol) gave diol **6ba** as a colorless oil; yield: 91 mg (80%).

$[\alpha]_D^{17}$ +15.1 (*c* 1.20, $CHCl_3$; 72% ee), $[\alpha]_D^{17}$ +13.8 (*c* 1.20, CH_2Cl_2; 72% ee) [Lit.[8d] $[\alpha]_D^{28}$ −13.0 (c 0.60, CH_2Cl_2; 75% ee (1*S*, 3*S*)].

HPLC (Daicel Chiralpak AD-H, hexane–*i*-PrOH (9:1), 1.0 mL/min): t_R (min) = 11.6 (major, 1*R*,3*R*), 14.4 (minor, 1*S*,3*S*) [Lit.[8d] hexane–*i*-PrOH (9:1), 1.0 mL/min: t_R (min) = 11.4 (1*R*,3*R*), 14.5 (1*S*,3*S*)].

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.71 (d, *J* = 7.1 Hz, 3 H, C*H*$_3$), 2.14 (m, 1 H), 3.05 (d, *J* = 3.4 Hz, 1 H, O*H*), 3.15 (d, *J* = 3.4 Hz, 1 H, O*H*), 4.64 (dd, *J* = 3.6, 6.6 Hz, 1 H, HOC*H*Ph), 4.96 (t, *J* = 3.1 Hz, 1 H, HOC*H*Ph), 7.20–7.40 (m, 10 H, Ar*H*).

(1*R*,2*R*,3*S*,4*E*)-2-Methyl-1,5-diphenylpent-4-ene-1,3-diol (6ea)

Following the typical procedure, the reaction of benzaldehyde (**2a**) (0.12 mL, 1.18 mmol, 2.5 equiv) and 1-phenylpent-1-en-3-one (**1e**) (75 mg, 0.47 mmol) gave diol **6ea** as a colorless oil; yield: 115 mg (91%).

$[\alpha]_D^{18}$ –23.4 (*c* 0.42, $CHCl_3$; 70% ee).

HPLC (Daicel Chiralcel OD-H, hexane–*i*-PrOH (9:1), 1.0 mL/min): t_R (min) = 17.4 (major, 1*R*,2*R*,3*S*), 24.9 (minor, 1*S*,2*S*,3*R*).

IR ($CHCl_3$): 3604, 3477 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.77 (d, *J* = 7.3 Hz, 3 H, C*H*$_3$), 2.08–2.16 (m, 1 H, C*H*CH$_3$), 4.48 (d, *J* = 5.5 Hz, 1 H, HOC*H*), 4.65 (d, *J* = 7.8 Hz, 1 H, HOC*H*), 6.30 (dd, *J* = 5.9, 15.6 Hz, 1 H, CH=C*H*), 6.58 (d, *J* = 15.6 Hz, 1 H, C*H*=CH), 7.18–7.42 (m, 10 H, Ar*H*).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.6, 44.5, 74.7, 78.1, 126.4, 126.5, 127.5, 127.7, 128.4, 128.5, 129.4, 130.9, 136.7, 143.3.

LRMS–FAB ($CHCl_3$ + NBA + NaI): *m*/*z* = 291 $[M + Na]^+$, 73 (100).

HRMS–FAB: *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{20}O_2Na$: 291.1361; found: 291.1355.

(1*R*,2*R*,3*S*)-2-Methyl-1-phenylhexane-1,3-diol (6ga)[15] and (1*R*,2*R*,3*S*)-2-Ethyl-1-phenylpentane-1,3-diol (8ga)

Following the typical procedure, the reaction of benzaldehyde (**2a**) (0.12 mL, 1.18 mmol, 2.5 equiv) and hexan-3-one (**1g**) (47 mg, 0.47 mmol) gave diols **6ga** [yield: 69 mg (70%)] and **8ga** [yield: 16 mg (16%)] as colorless oils.

6ga

$[\alpha]_D^{14}$ +35.3 (*c* 0.91, $CHCl_3$; 94% ee).

HPLC (Daicel Chiralpak AD-H, hexane–*i*-PrOH (9:1), 1.0 mL/min): t_R (min) = 7.8 (major, 1*R*,2*R*,3*S*), 9.1 (minor, 1*S*,2*S*,3*R*).

IR ($CHCl_3$): 3608, 3446 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.82 (d, *J* = 7.3 Hz, 3 H, CHC*H*$_3$), 0.87 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 1.19–1.61 (m, 4 H, C*H*$_2$CH$_2$), 1.84–1.92 (m, 1 H, C*H*CH$_3$), 3.06 (br s, 1 H, O*H*), 3.71–3.73 (m, 1 H, HOC*H*), 3.75 (br s, 1 H, O*H*), 4.65 (d, *J* = 6.9 Hz, 1 H, HOC*H*), 7.20–7.36 (m, 5 H, Ar*H*).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.5, 14.0, 19.4, 35.7, 43.5, 72.4, 78.2, 126.2, 127.3, 128.3, 143.8.

LRMS–FAB ($CHCl_3$ + NBA + NaI): *m*/*z* = 231 (100) $[M + Na]^+$, 119, 23.

HRMS–FAB: *m*/*z* $[M + Na]^+$ calcd for $C_{13}H_{20}O_2Na$: 231.1361; found: 231.1359.

8ga

$[\alpha]_D^{14}$ +51.9 (*c* 0.52, $CHCl_3$; 97% ee).

HPLC (Daicel Chiralpak AD-H, hexane–*i*-PrOH (9:1), 1.0 mL/min): t_R (min) = 7.2 (major, 1*R*,2*R*,3*S*), 10.2 (minor, 1*S*,2*S*,3*R*).

IR ($CHCl_3$): 3608, 3481 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 7.4 Hz, 3 H, CH_2CH_3), 0.95 (t, *J* = 7.3 Hz, 3 H, CH_2CH_3), 1.36–1.67 (m, 5 H, 2 × C*H*$_2$ + C*H*), 2.90 (br s, 1 H, O*H*), 3.51 (br s, 1 H, O*H*), 3.63–3.68 (m, 1 H, HOC*H*), 4.91 (d, *J* = 3.6 Hz, 1 H, HOC*H*Ph), 7.24–7.39 (m, 5 H, Ar*H*).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.7, 12.5, 18.2, 26.4, 50.0, 73.6, 75.6, 126.1, 127.2, 128.3, 144.0.

LRMS–FAB ($CHCl_3$ + NBA + NaI): *m*/*z* = 231 $[M + Na]^+$, 83, 55 (100), 41.

HRMS–FAB: *m*/*z* $[M + Na]^+$ calcd for $C_{13}H_{20}O_2Na$: 231.1361; found: 231.1353.

(α*R*)-α-[(1*S*,2*S*)-2-Hydroxycyclohexyl]benzenemethanol (6ha)[16]

Following the typical procedure, the reaction of benzaldehyde (**2a**) (0.12 mL, 1.18 mmol, 2.5 equiv) and cyclohexanone (**1h**) (46 mg, 0.47 mmol) in THF (3 mL) gave diol **6ha** as colorless needles; yield: 88 mg (91%); mp 122–124 °C.

$[\alpha]_D^{27}$ +27.6 (*c* 1.02, $CHCl_3$; 90% ee) [Lit.[16] $[\alpha]_D$ +32 (*c* 0.95, $CHCl_3$; 99% ee (1*S*,2*S*,α*R*))].

HPLC (Daicel Chiralcel OD-H, hexane–*i*-PrOH (9:1), 1.0 mL/min): t_R (min) = 7.3 (minor, 1*R*,2*R*,α*S*), 8.7 (major, 1*S*,2*S*,α*R*).

^1H NMR (400 MHz, $CDCl_3$): δ = 0.78–0.92 (m, 1 H, C*H*$_2$), 1.02–1.15 (m, 2 H, C*H*$_2$), 1.25–1.35 (m, 1 H, C*H*$_2$), 1.50–1.65 (m, 3 H, C*H*$_2$), 1.74–1.81 (m, 1 H, C*H*$_2$), 1.89–1.93 (m, 1 H, C*H*), 3.23 (br s, 1 H, O*H*), 3.49 (dt, *J* = 10.5, 4.6 Hz, 1 H, CH$_2$C*H*OH), 3.70 (br s, 1 H, O*H*), 4.92 (s, 1 H, PhC*H*), 7.24–7.36 (m, 5 H, Ar*H*).

(α*R*)-α-[(1*S*,2*S*)-2-Hydroxycyclohex-3-en-1-yl]benzenemethanol (6ia)

Following the typical procedure, the reaction of benzaldehyde (**2a**) (0.12 mL, 1.18 mmol, 2.5 equiv) and cyclohex-2-en-1-one (**1i**) (45 mg, 0.47 mmol) in THF (3 mL) at –23 °C gave diol **6ia** as colorless needles; yield: 84 mg (88%); mp 135–137 °C. The absolute and relative configurations of **6ia** were determined by ^1H NMR spectroscopy and from the specific rotation after the conversion into **6ha** by hydrogenation.

$[\alpha]_D^{27}$ –11.4 (*c* 0.99, $CHCl_3$; 85% ee).

HPLC (Daicel Chiralcel OD-H, hexane–*i*-PrOH (9:1), 1.0 mL/min): t_R (min) = 8.8 (minor, 1*R*,2*R*,α*S*), 11.3 (major, 1*S*,2*S*,α*R*).

IR (KBr): 3313 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.15–1.24 (m, 1 H, C*H*$_2$), 1.62–1.67 (m, 1 H, C*H*$_2$), 1.93–2.09 (m, 3 H, C*H* + C*H*$_2$), 2.71 (br s, 1 H, O*H*), 3.12 (br s, 1 H, O*H*), 4.24 (d, *J* = 8.7 Hz, 1 H, =CHC*H*OH), 4.98 (s, 1 H, PhC*H*), 5.56–5.60 (m, 1 H, CH=C*H*), 5.70–5.72 (m, 1 H, C*H*=CH), 7.26–7.38 (m, 5 H, Ar*H*).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.2, 25.0, 47.4, 68.1, 76.2, 126.5, 127.4, 128.1, 128.8, 130.3, 142.0.

LRMS–FAB ($CHCl_3$ + NBA + NaI): *m*/*z* = 227 (100) $[M + Na]^+$, 173, 149, 107, 77.

HRMS–FAB: *m*/*z* $[M + Na]^+$ calcd for $C_{13}H_{16}O_2Na$: 227.1048; found: 227.1030.

(+)-*rel*-(α^1*R*,α^3*R*,1*R*,3*S*)-2-Hydroxy-α,α′-diphenyl-1,3-cyclopentanedimethanol (10)

Under an argon atmosphere, *n*-BuLi (0.094 mmol, 20 mol%) in hexane (0.17 M, 0.55 mL) was added to a soln of (*R*)-3,3′-diphenylbinaphthol (20.7 mg, 0.047 mmol, 10 mol%) in THF (3 mL) at –23 °C, and the mixture was stirred for 5 min. Then, benzaldehyde (**2a**) (0.17 mL, 1.65 mmol, 3.5 equiv) and cyclopentanone (**1j**) (40 mg, 0.47 mmol) in THF (0.3 mL) were added to the above mixture. After 24 h, the reaction was quenched with sat. NH_4Cl (2 mL) and the mixture was stirred at r.t. for 5 min. The aqueous layer was extracted with EtOAc (3 × 10 mL) and the combined organic layers were washed with brine (3 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2) to give an inseparable mixture of triol monoesters as a colorless oil.

To the solution of the monoesters, PPTS (12 mg, 0.047 mmol, 10 mol%) and 2,2-dimethoxypropane (0.09 mL, 0.71 mmol, 1.5 equiv) were added, and the mixture was stirred for 12 h, then diluted with EtOAc (20 mL). The mixture was washed with H_2O (3 × 5 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane–toluene, 1:1) to give acetonide **9** [yield: 137 mg (66%, 2 steps), $[\alpha]_D^{27}$ –8.2 (*c* 1.01, $CHCl_3$; 99% ee), HPLC (Daicel Chiralpak AD-H, hexane–*i*-PrOH (99:1), 1.0 mL/min): t_R (min) = 14.4 (major), 17.4 (minor)] as colorless needles and its diastereomer **9′** [yield: 46 mg (22%, 2 steps)] as colorless needles.

To a soln of **9** in MeOH (2 mL), NaOMe (0.05 mmol, 11 mol%) in MeOH (0.5 M, 0.1 mL) was added, and the resulting homogeneous mixture was stirred for 12 h. The reaction was quenched with concd aq HCl (5 mL) and the mixture was stirred at r.t. for 1 h. The mixture was diluted with EtOAc (20 mL), and washed with H_2O (5 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL) and the combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane–EtOAc, 3:2) to give triol **10** as colorless prisms; yield: 88 mg [65%, from cyclopentanone (**1j**)]; mp 136–137 °C.

$[\alpha]_D^{30}$ +55.5 (*c* 1.01, $CHCl_3$).

IR (KBr): 3302 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.04–1.14 (m, 1 H, C*H*$_2$), 1.23–1.32 (m, 1 H, C*H*$_2$), 1.45–1.61 (m, 2 H, C*H*$_2$), 2.09–2.18 (m, 1 H, C*H*), 2.30 (ddd, *J* = 18.8, 9.2, 5.0 Hz, 1 H, C*H*), 2.61 (d, *J* = 3.6 Hz, 1 H, O*H*), 3.05 (s, 1 H, O*H*), 3.10 (s, 1 H, O*H*), 4.01 (t, *J* = 9.2 Hz, 1 H, CHC*H*OH), 4.48 (d, *J* = 9.6 Hz, 1 H, PhC*H*), 4.86–4.88 (m, 1 H, PhC*H*), 7.24–7.37 (m, 10 H, Ar*H*).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.68, 23.85, 52.51, 52.71, 74.44, 79.14, 80.49, 126.30, 126.42, 127.52, 127.91, 128.37, 128.45, 142.95, 143.30.

LRMS–FAB ($CHCl_3$ + NBA + NaI): *m*/*z* = 321 $[M + Na]^+$, 263, 245, 176, 154 (100), 136, 107, 69.

HRMS–FAB: *m*/*z* $[M + Na]^+$ calcd for $C_{19}H_{22}O_3Na$: 321.1467; found: 321.1475.

References

(1) (a) Oishi, T.; Nakata, T. *Synthesis* **1990**, 635. (b) Bode, S. E.; Wolberg, M.; Müller, M. *Synthesis* **2006**, 557.

(2) For reviews on aldol–Tishchenko reactions, see: (a) Mahrwald, R. *Curr. Org. Chem.* **2003**, *7*, 1713. (b) Mlynarski, J. *Eur. J. Org. Chem.* **2006**, 4779.

(3) For reviews on cascade reactions, see: (a) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem. Int. Ed.* **2006**, *45*, 7134. (b) Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem.* **2010**, *2*, 167.

(4) For reviews on direct aldol reactions, see: (a) Groger, H.; Vogl, E. M.; Shibasaki, M. *Chem.–Eur. J.* **1998**, *4*, 1137. (b) Trost, B. M.; Brindle, C. S. *Chem. Soc. Rev.* **2010**, *39*, 1600.

(5) Loog, O.; Mäeorg, U. *Tetrahedron: Asymmetry* **1999**, *10*, 2411.

(6) Mascarenhas, C. M.; Miller, S. P.; White, P. S.; Morken, J. P. *Angew. Chem. Int. Ed.* **2001**, *40*, 601.

(7) (a) Gnanadesikan, V.; Horiuchi, Y.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 7782. (b) Horiuchi, Y.; Gnanadesikan, V.; Ohshima, T.; Masu, H.; Katagiri, K.; Sei, Y.; Yamaguchi, K.; Shibasaki, M. *Chem.–Eur. J.* **2005**, *11*, 5195.

(8) (a) Mlynarski, J.; Mitura, M. *Tetrahedron Lett.* **2004**, *45*, 7549. (b) Mlynarski, J.; Jankowska, J.; Rakiel, B. *Chem. Commun.* **2005**, 4854. (c) Mlynarski, J.; Jankowska, J.; Rakiel, B. *Tetrahedron: Asymmetry* **2005**, *16*, 1521. (d) Mlynarski, J.; Rakiel, B.; Stodulski, M.; Suszczynska, A.; Frelek, J. *Chem.–Eur. J.* **2006**, *12*, 8158.

(9) (a) Rohr, K.; Herre, R.; Mahrwald, R. *Org. Lett.* **2005**, *7*, 4499. (b) Rohr, K.; Herre, R.; Mahrwald, R. *J. Org. Chem.* **2009**, *74*, 3744.

(10) (a) Nakajima, M.; Orito, Y.; Ishizuka, T.; Hashimoto, S. *Org. Lett.* **2004**, *6*, 3763. (b) Orito, Y.; Hashimoto, S.; Ishizuka, T.; Nakajima, M. *Tetrahedron* **2006**, *62*, 390. (c) Ichibakase, T.; Orito, Y.; Nakajima, M. *Tetrahedron Lett.* **2008**, *49*, 4427. (d) Tanaka, K.; Ueda, T.; Ichibakase, T.; Nakajima, M. *Tetrahedron Lett.* **2010**, *51*, 2168.

(11) For recent examples of the use of dilithium binaphtholate as a catalyst, see: (a) Schiffers, R.; Kagan, H. B. *Synlett* **1997**, 1175. (b) Holmes, I. P.; Kagan, H. B. *Tetrahedron Lett.* **2000**, *41*, 7453. (c) Hatano, M.; Ikeno, T.; Miyamoto, T.; Ishihara, K. *J. Am. Chem. Soc.* **2005**, *127*, 10776. (d) Hatano, M.; Ikeno, T.; Matsumura, T.; Torii, S.; Ishihara, K. *Adv. Synth. Catal.* **2008**, *350*, 1776. (e) Hatano, M.; Horibe, T.; Ishihara, K. *J. Am. Chem. Soc.* **2010**, *132*, 56.

(12) Ichibakase, T.; Nakajima, M. *Org. Lett.* **2011**, *13*, 1579.

(13) For mechanistic studies of aldol–Tishchenko reactions, see: (a) Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447. (b) Burkhardt, E. R.; Bergman, R. G.; Heathcock, C. H. *Organometallics* **1990**, *9*, 30. (c) Mahrwald, R.; Costisella, B. *Synthesis* **1996**, 1087. (d) Bodnar, P. M.; Shaw, J. T.; Woerpel, K. A. *J. Org. Chem.* **1997**, *62*, 5674. (e) Abu-Hasanayn, F.; Streitwieser, A. *J. Org. Chem.* **1998**, *63*, 2954. (f) Lu, L.; Chang, H.-Y.; Fang, J.-M. *J. Org. Chem.* **1999**, *64*, 843. (g) Mascarenhas, C. M.; Duffey, M. O.; Liu, S.-Y.; Morken, J. P. *Org. Lett.* **1999**, *1*, 1427. (h) Markert, M.; Mahrwald, R. *Synthesis* **2004**, 1429.

(14) Wu, T. R.; Shen, L.; Chong, J. M. *Org. Lett.* **2004**, *6*, 2701.

(15) Ishihara, T.; Yamaguchi, K.; Kuroboshi, M.; Utimoto, K. *Tetrahedron Lett.* **1994**, *35*, 5263.

(16) Acetti, D.; Brenna, E.; Fuganti, C.; Gatti, F. G.; Serra, S. *Eur. J. Org. Chem.* **2010**, 142.

