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

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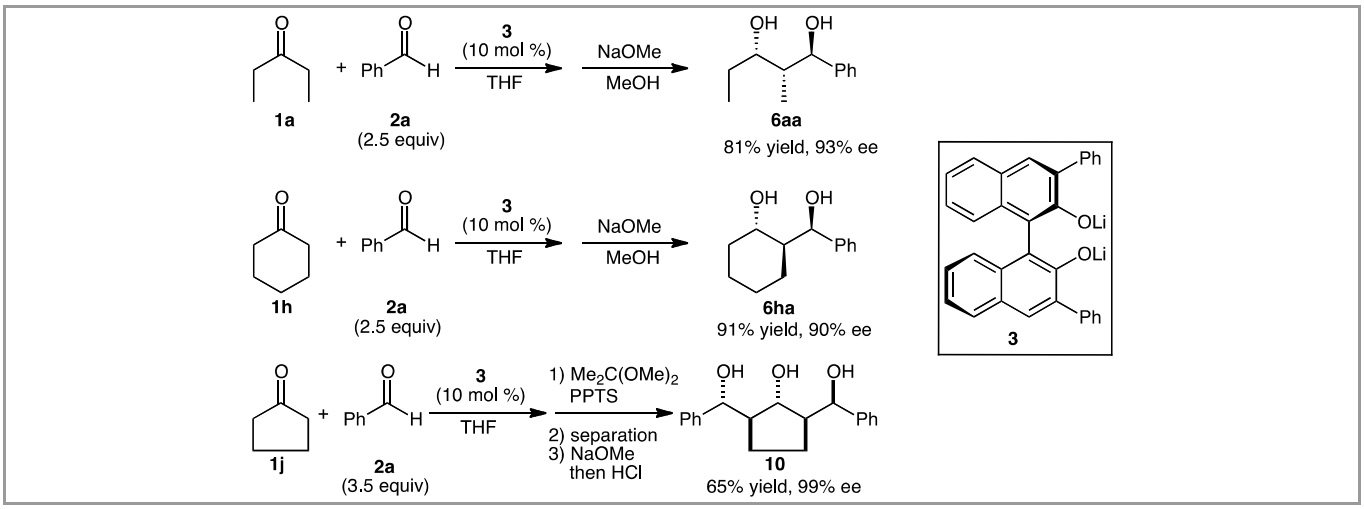
Abstract: 1,3-Diol derivatives with three contiguous stereocenters were efficiently prepared by an enantioselective direct aldol–Tishchenko reaction catalyzed by dilithium 3,3'-diphenylbinaphtholate. The reactions of acyclic ketones as aldol donors gave 1,2-*syn*-1,3-*anti* diol derivatives, whereas 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.

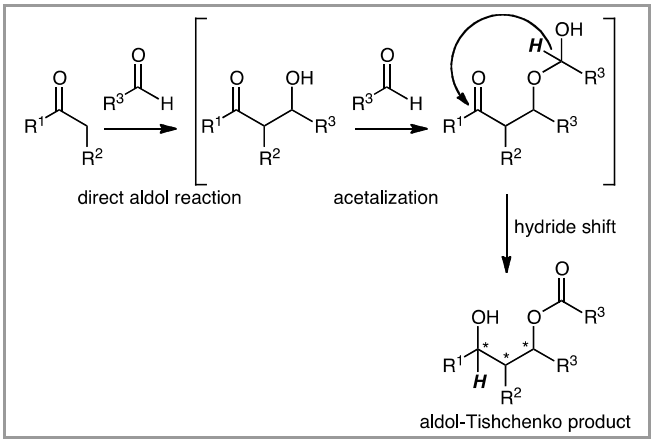
Key words: aldol reaction, asymmetric catalysis, enantioselectivity, stereoselectivity, tandem reaction.



Scheme 1

Introduction

The 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. The sequence of these conversions affords mono acyl-protected 1,3-diols with three contiguous asymmetric centers from two carbonyl compounds. The first enantioselective aldol–Tishchenko reaction was reported by Maeorg,[5] who used a monolithium salt of binaphthol; however, the observed enantioselectivities were low. Later, 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] Herein, we describe the efficient preparation of 1,3-diol derivatives with three contiguous stereocenters by an enantioselective direct aldol–Tishchenko reaction starting from two carbonyl compounds.

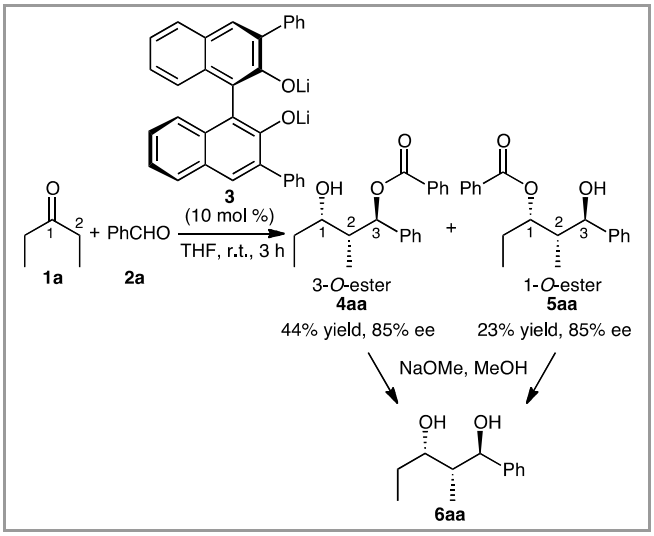


Scheme 2

Scope and Limitations

In the initial study, we investigated an aldol–Tishchenko reaction using diethyl ketone (**1a**) and benzaldehyde (**2a**) as substrates with dilithium 3,3'-

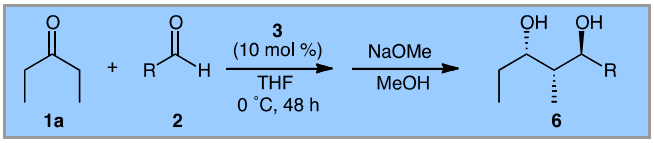
diphenylbinaphtholate as a catalyst. The reaction proceeded to afford the product as a mixture of 3-*O*-ester **4aa** and 1-*O*-ester **5aa** having the same sense and magnitude of absolute and relative configurations (1,2-*syn*-1,3-*anti*). As expected, the isolated 3-*O*-ester **4aa** and 1-*O*-ester **5aa** easily interconverted 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 a benzoyl group to obtain the product as a single diastereomer for data collection.



Scheme 3

The results obtained in the aldol–Tishchenko reactions of diethyl ketone (**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**), *p*-tolualdehyde (**2b**) and *p*-anisaldehyde (**2c**) gave selectivities 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-Tishcehenko reaction of 3-pentanone 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	-

Table 2 Aldol-Tishcehenko reactions of benzaldehyde with various ketones

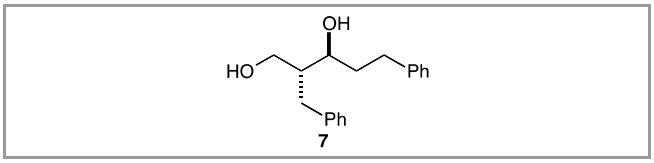
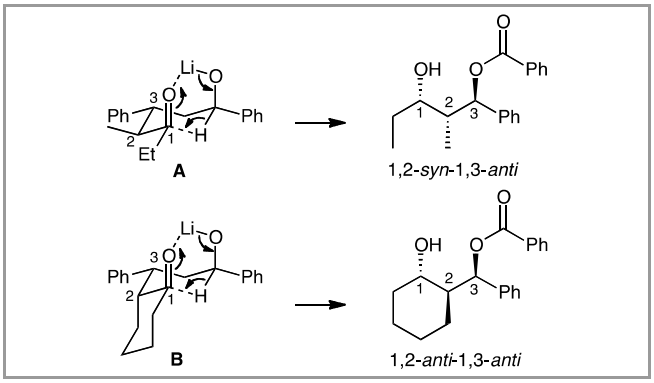


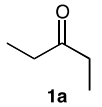
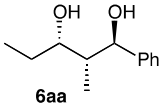
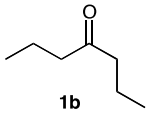
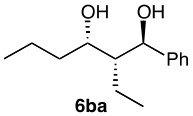
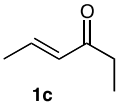
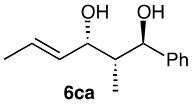
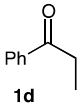
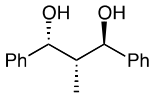
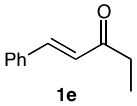
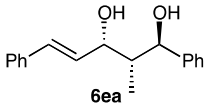
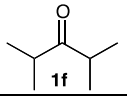
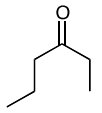
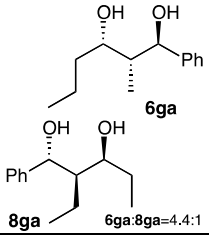
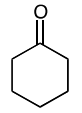
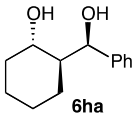
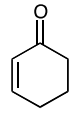
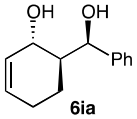
Figure 1

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 a single diastereomer 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 r.t.; the enantioselectivities, however, were slightly lower (entries 4 and 5) than those obtained from aliphatic ketones. The sterically congested ketone **1f** did not react at all (entry 6). In the reaction of ethyl propyl ketone (**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 bulkiness or reactivity.

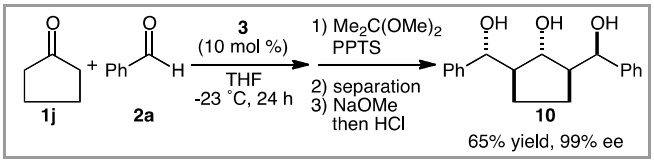
The reactions of cyclic ketones as aldol donors, such as cyclohexanone (**1h**) and cyclohex-2-en-1-one (**1i**), afforded 1,2-*anti*-1,3-*anti* diols as single diastereomers with high chemical and optical yields (entries 7 and 8). Transition-state model A, proposed by early pioneers,[13] can explain 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,[13f] to afford 1,2-*anti*-1,3-*anti* isomer (Scheme 4).



Scheme 4

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

In the reaction of cyclopentanone (**2j**), a highly enolizable aldol donor, the by-product derived from the sequential double aldol and Tishchenko reaction (aldol–aldol–Tishchenko reaction)[9,13d] was favored, even in the presence of 2.5 equiv benzaldehyde (**2a**) at –23°C. Therefore, we employed 3.5 equiv benzaldehyde (**2a**) as an 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). The relative configurations of the other isomers are not yet known, but the configuration of the major product **10** was determined by X-ray crystallographic analysis (CCDC 848047).



Scheme 5

In conclusion, we provide a new efficient method for preparing 1,3-diol derivatives with three contiguous stereocenters by an enantioselective direct aldol–Tishchenko reaction. The catalyst was 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 produced 1,2-*anti*-1,3-*anti* diol derivatives. In the case of cyclopentanone, a single manipulation controlled five successive chiral centers. The design of chiral catalysts to further enhance the reaction enantioselectivity, in addition to studies toward the

synthesis of biologically active compounds, are 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.

(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 solution 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**) (0.12mL, 1.18 mmol, 2.5 equiv) and 3-pentanone (**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 for 5 min at r.t. The aqueous layer was extracted with AcOEt and the combined organic layers were washed with brine (3 mL). After drying over Na_2SO_4 and concentration in vacuo, 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 AcOEt (20 mL), and washed with water (5 mL). The aqueous layer was extracted twice with AcOEt (10 mL × 2) and the combined organic layers were washed with brine (10 mL) and dried over Na_2SO_4. After concentration in vacuo, the residue was purified by column chromatography (SiO_2, hexane/AcOEt = 4/1) to give the diol **6aa** as a colorless oil (74 mg, 81%).

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

$[\alpha]_D^{29}$ +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, Hex/IPA = 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, Hex/IPA = 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*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 3-pentanone (**1a**) (41 mg, 0.47 mmol) gave diol **6ab** as a colorless oil (85 mg, 87%).
^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.81 (d, 3H, *J* = 7.3 Hz, CHC*H*$_3$), 0.89 (t, 3H, *J* = 7.3 Hz, CH_2CH_3), 1.35-1.58 (m, 2H, C*H*$_2$CH$_3$), 1.85-1.92 (m, 1H, C*H*CH$_3$), 2.33 (s, 3H, ArC*H*$_3$), 3.07 (brs, 1H, O*H*), 3.53 (brs, 1H, O*H*), 3.69 (ddd, 1H, *J* = 8.7, 4.6, 1.8 Hz, HOC*H*), 4.62 (d, *J* = 6.8 Hz, HOC*H*Ar), 7.13 (d, 2H, *J* = 7.8 Hz, Ar*H*), 7.20 (d, 2H, *J* = 7.8 Hz, Ar*H*).

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

HPLC (Daicel chiralpak AD-H, Hex/IPA = 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, Hex/IPA = 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*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 3-pentanone (**1a**) (41 mg, 0.47 mmol) gave diol **6ac** as a colorless oil (85 mg, 81%).
^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.79 (d, 3H, *J* = 7.4 Hz, CHC*H*$_3$), 0.90 (t, 3H, *J* = 7.3 Hz, CH_2CH_3), 1.38-1.58 (m, 2H, C*H*$_2$CH$_3$), 1.83-1.91 (m, 1H, C*H*CH$_3$), 3.12 (brs, 1H, O*H*), 3.62 (brs, 1H, O*H*), 3.69 (ddd, 1H, *J* = 8.2, 4.1, 1.8 Hz, HOC*H*), 3.78 (s, 3H, OC*H*$_3$), 4.60 (d, *J* = 7.3 Hz, HOC*H*Ar), 6.84-6.88 (m, 2H, Ar*H*), 7.21-7.25 (m, 2H, Ar*H*).

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

HPLC (Daicel chiralpak AD-H, Hex/IPA = 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, Hex/IPA = 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*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 3-pentanone (**1a**) (41 mg, 0.47 mmol) gave diol **6ad** as a colorless prism (103 mg, 80%); mp 96-97 °C.
^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.84-0.89 (m, 6H, CHC*H*$_3$, CH_2CH_3), 1.34-1.54 (m, 2H, C*H*$_2$CH$_3$), 1.80-1.87 (m, 1H, C*H*CH$_3$), 3.04 (brs, 1H, O*H*), 3.63 (ddd, 1H, *J* = 8.7, 5.0, 2.3 Hz, HOC*H*), 4.08 (brs, 1H, O*H*), 4.60 (d, 1H, *J* = 6.4 Hz, HOC*H*Ar), 7.15-7.19 (m, 2H, Ar*H*), 7.43-7.46 (m, 2H, Ar*H*).

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

HPLC (Daicel chiralpak AS-H, Hex/IPA = 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, Hex/IPA = 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*E*,3*S*,4*R*,5*S*)-4-Methyl-7-phenylhepta-6-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 3-pentanone (**1a**) (41 mg, 0.47 mmol) gave diol **6ae** as a colorless oil (63 mg, 61%).
IR (neat) ν 3552 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.92-0.98 (m, 6H, -CHC*H*$_3$, -CH_2CH_3), 1.49-1.61 (m, 2H, C*H*$_2$CH$_3$), 1.73-1.80 (m, 1H, C*H*CH$_3$), 2.85 (brs, 1H, O*H*), 3.29 (brs, 1H, O*H*), 3.84-3.88 (m, 1H, HOC*H*), 4.30 (t, 1H, *J* = 6.4 Hz, HOC*H*), 6.25 (dd, 1H, *J* = 16.0, 6.4 Hz, PhCH=C*H*), 6.62 (d, 1H, *J* = 15.6 Hz, PhC*H*=CH), 7.21-7.39 (m, 5H, Ar*H*).

^{13}C NMR ($CDCl_3$, 100 MHz) 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.

LR-FABMS ($CHCl_3$+NBA+NaI) 243 ($(M+Na)^+$), 241, 176 (bp), 145, 136, 55.

HR-FABMS calcd for $C_{14}H_{20}O_2Na$ ($(M+Na)^+$) 243.1361, found 243.1340.

$[\alpha]_D^{29}$ +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, Hex/IPA = 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*).

(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 4-heptanone (**1b**) (54 mg, 0.47 mmol) gave diol **6ba** as a colorless oil (74 mg, 71%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.82 (t, 3H, *J* = 6.9 Hz, $CHCH_2CH_3$), 0.91 (t, 3H, *J* = 7.3 Hz, $CH_2CH_2CH_3$), 1.16-1.63 (m, 7H, $CHCH_2CH_3$, $CH_2CH_2CH_3$), 3.32 (brs, 1H, O*H*), 3.74 (ddd, *J* = 9.2, 4.1, 1.8 Hz, HOC*H*), 3.89 (brs, 1H, O*H*), 4.85 (d, 1H, *J* = 5.5 Hz, OC*H*Ph)), 7.22-7.35 (m, 5H, Ar-*H*).

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

HPLC (Daicel chiralpak AS-H, Hex/IPA = 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: Hex/IPA = 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*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 (78 mg, 80%).

IR (neat) ν 3354 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.69 (d, 3H, *J* = 7.3 Hz, $CHCH_3$), 1.72 (d, 3H, *J* = 5.5 Hz, $CH{=}CHCH_3$), 1.96-2.04 (m, 1H, $CHCH_3$), 3.42 (brs, 1H, O*H*), 3.87 (brs, 1H, O*H*), 4.20-4.23 (m, 1H, HOC*H*), 4.57 (d, 1H, *J* = 8.3 Hz, OC*H*Ph), 5.56-5.89 (m, 2H, C*H*=C*H*), 7.23-7.34 (m, 5H, Ar*H*).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.5, 17,.8, 44.2, 75.0, 77.9, 126.6, 127.5, 127.7, 128.3, 130.7, 143.6.

LR-FABMS ($CHCl_3$+NBA+NaI) 229 ($(M+Na)^+$, bp), 173, 149, 107, 55.

HR-FABMS calcd for $C_{13}H_{18}O_2Na$ ($(M+Na)^+$) 229.1204, found 229.1200.

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

HPLC (Daicel chiralcel OD-H, Hex/IPA = 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*).

(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 (91 mg, 80%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.71 (d, 3H, *J* = 7.1 Hz, CH_3), 2.14 (m, 1H), 3.05 (d, 1H, *J* = 3.4 Hz, O*H*), 3.15 (d, 1H, *J* = 3.4 Hz, O*H*), 4.64 (dd, *J* = 3.6, 6.6 Hz, OC*H*Ph), 4.96 (t, *J* = 3.1 Hz, OC*H*Ph), 7.20-7.40 (m, 10H, Ar-*H*).

$[\alpha]_D^{17}$ +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, Hex/IPA = 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: Hex/IPA = 9/1, 1.0 mL/min, t_R (min) 11.4 (1*R*,3*R*), 14.5 (1*S*,3*S*)].

(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-phenyl-1-pentene-3-one (**1e**) (75 mg, 0.47 mmol) gave diol **6ea** (115 mg, 90% yield, 70% ee) as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.77 (d, 3H, *J* = 7.3 Hz, CH_3), 2.08-2.16 (m, 1H, $CHCH_3$), 4.48 (d, 1H, *J* = 5.5 Hz, HOC*H*), 4.65 (d, 1H, *J* = 7.8 Hz, HOC*H*), 6.30 (dd, 1H, *J* = 5.9, 15.6 Hz, C=C*H*), 6.58 (d, 1H, *J* = 15.6 Hz, C=C*H*), 7.18-7.42 (m, 10H, Ar*H*).

^{13}C NMR ($CDCl_3$, 100 MHz) 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.

IR ($CHCl_3$) ν 3604, 3477 cm^{-1}.

LR-FABMS ($CHCl_3$+NBA+NaI) 291 $(M+Na)^+$, 73 (bp).

HR-FABMS calcd for $C_{18}H_{20}O_2Na$ ($(M+Na)^+$) 291.1361, found 291.1355.

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

HPLC (Daicel chiralcel OD-H, Hex/IPA = 9/1, 1.0 mL/min): t_R (min) 17.4 (major), 24.9 (minor).

(1*R*,2*R*,3*S*)-2-Methyl-1-phenylhexane-1,3-diol (6ga)[16] **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 3-hexanone (**1g**) (47 mg, 0.47 mmol) gave diol **6ga** (69 mg, 70%) and **8ga** (16 mg, 16%) as colorless oil.

6ga: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.82 (d, 3H, *J* = 7.3 Hz, $CHCH_3$), 0.87 (t, 3H, CH_2CH_3), 1.19-1.61 (m, 4H, CH_2), 1.84-1.92 (m, 1H, $CHCH_3$), 3.06 (brs, 1H, O*H*), 3.71-3.73 (m, 1 H, HOCH), 3.75 (br s, 1 H, OH), 4.65 (d, 1H, *J* = 6.9 Hz, HOC*H*), 7.20-7.36 (m, 5H, Ar*H*).

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

IR ($CHCl_3$) ν 3608, 3446 cm^{-1}.

LR-FABMS ($CHCl_3$+NBA+NaI) 231 ($(M+Na)^+$, bp), 119, 23.

HR-FABMS calcd for $C_{13}H_{20}O_2Na$ ($(M+Na)^+$) 231.1361, found 231.1359.

$[\alpha]_D^{14}$ +35.3 (*c* 0.91, $CHCl_3$, 94% ee, (1*R*,2*R*,3*S*)).

HPLC (Daicel chiralpak AD-H, Hex/IPA = 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*).

8ga: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.86 (t, 3H, *J* = 7.4 Hz), 0.95 (t, 3H, *J* = 7.3 Hz, CH_2CH_3), 1.36-1.67 (m, 5H, CH_2&C*H*), 2.90 (brs, 1H, O*H*), 3.51 (brs, 1H, O*H*), 3.63-3.68 (m, 1H, HOC*H*), 4.91 (d, 1H, *J* = 3.6 Hz, HOC*H*Ph), 7.24-7.39 (m, 5H, Ar*H*).

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

IR ($CHCl_3$) ν 3608, 3481 cm^{-1}.

LR-FABMS ($CHCl_3$+NBA+NaI) 231 ($(M+Na)^+$), 83, 55 (bp), 41.

HR-FABMS calcd for $C_{13}H_{20}O_2Na$ ($(M+Na)^+$) 231.1361, found 231.1353.

$[\alpha]_D^{14}$ +51 9 (*c* 0.52, $CHCl_3$, 97% ee, 1*R*,2*R*,3*S*).

HPLC (Daicel chiralpak AD-H, Hex/IPA = 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*).

(1*S*,2*S*,α*R*)-α-(2-Hydroxycyclohexyl)-benzenemethanol (6ha)[15]

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 (88 mg, 87%); mp 122-124 °C.
^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.78-0.92 (m, 1H, CH_2), 1.02-1.15 (m, 2H, CH_2), 1.25-1.35 (m, 1H, CH_2), 1.50-1.65 (m, 3H, CH_2), 1.74-1.81 (m, 1H, CH_2), 1.89-1.93 (m, 1H, C*H*), 3.23 (brs, 1H, O*H*), 3.49 (dt, 1H, *J* = 10.5, 4.6 Hz, CH_2CHO), 3.70 (brs, 1H, O*H*), 4.92 (s, 1H, PhC*H*), 7.24-7.36 (m, 5H, Ar*H*).

$[\alpha]_D^{27}$ +27.6 (*c* 1.02, $CHCl_3$, 90% ee), [lit. 15: $[\alpha]_D$ +32 (*c* 0.95, $CHCl_3$, 99% ee, 1*S*,2*S*,α*R*)]

HPLC (Daicel chiralcel OD-H, Hex/IPA = 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*).

(1*S*,2*S*,α*R*)-α-(2-Hydroxycyclohex-3-enyl)-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 (3mL) at -23 °C gave diol **6ia** as colorless needles (84 mg, 88%), mp 135-137 °C.
IR (KBr) ν 3313cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.15-1.24 (m, 1H, CH_2), 1.62-1.67 (m, 1H, CH_2), 1.93-2.09 (m, 3H, C*H*&CH_2), 2.71 (brs, 1H, O*H*), 3.12 (brs, 1H, O*H*), 4.24 (d, 1H, *J* = 8.7 Hz, CH_2CHO), 4.98 (s, 1H, PhC*H*), 5.56-5.60 (m, 1H, C=C*H*), 5.70-5.72 (m, 1H, C=C*H*), 7.26-7.38 (m, 5H, Ar*H*).

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

LR-FABMS ($CHCl_3$+NBA+NaI) 227 ($(M+Na)^+$, bp), 173, 149, 107, 77.

HR-FABMS calcd for $C_{13}H_{16}O_2Na$ ($(M+Na)^+$) 227.1048, found 227.1030.

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

HPLC (Daicel chiralcel OD-H, Hex/IPA = 9/1, 1.0 mL/min): t_R (min) 8.8 (minor, 1*R*,6*R*,α*S*), 11.3 (major, 1*S*,6*S*,α*R*).

The absolute and relative configurations of **6ia** were determined by ^{1}H NMR and $[\alpha]_D$ after the conversion to **6ha** by hydrogenation.

(*rel*-1*R*,3*S*,1α*R*,2α*R*)-(+)-2-Hydroxy-α1,α3-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 solution 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**) (0.17mL, 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 for 5 min at rt. The aqueous layer was extracted with AcOEt and the combined organic layers were successively washed with brine (3 mL). Drying over Na_2SO_4 and concentration in vacuo, the residue was purified by column chromatography (SiO_2, CH_2Cl_2) to give an inseparable mixture of triol mono esters as a colorless oil. To the solution of the mono ethers, pyridinium *p*-toluenesulfonate (12 mg, 0.047 mmol, 10 mol %) and 2,2-dimethoxypropane (0.09 mL, 0.71 mmol, 1.5 equiv) was added and the mixture was stirred for 12 h. After diluted with AcOEt (20 mL), the mixture was washed with water (5 mL × 3) and brine (10 mL) and dried over Na_2SO_4. After concentration in vacuo, the residue was purified by column chromatography (SiO_2, hexane/toluene = 1/1) to give **9** (137 mg, 66%, $[\alpha]_D^{27}$ -8.2 (*c* 1.01, $CHCl_3$, 99% ee), HPLC (Daicel chiralpak AD-H, Hex/IPA = 99/1, 1.0 mL/min): t_R (min) 14.4 (major), 17.4 (minor)) as colorless needles and its diastereomer **9'** (46 mg, 22 %, 2 steps) as colorless needles.

To the solution 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 conc. HCl aq. (5 mL) and the mixture was stirred for 1 h at rt. The mixture was diluted with AcOEt (20 mL), and washed with water (5 mL). The aqueous layer was extracted twice with AcOEt (10 mL × 2) and the combined organic layers were washed with brine (10 mL) and dried over Na_2SO_4. After concentration in vacuo, the residue was purified by column chromatography (SiO_2, hexane/AcOEt = 3/2) to give triol **10** as colorless prisms (88 mg, 65%, from cyclopentanone (**1j**)); mp 136-137 °C.

IR (KBr) ν 3302 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.04-1.14 (m, 1H, CH_2), 1.23-1.32 (m, 1H, CH_2), 1.45-1.61 (m, 2H, CH_2), 2.09-2.18 (m, 1H, C*H*), 2.30 (ddd, *J* = 18.8, 9.2, 5.0 Hz, C*H*), 2.61 (d, 1H, *J* = 3.6 Hz, O*H*), 3.05 (s, 1H, O*H*), 3.10 (s, 1H, O*H*), 4.01 (t, 1H, *J* = 9.2 Hz, CHC*H*O), 4.48 (d, 1H, *J* = 9.6 Hz, PhC*H*), 4.86-4.88 (m, 1H, PhC*H*), 7.24-7.37 (m, 10H, Ar*H*).

^{13}C NMR ($CDCl_3$, 100 MHz) 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.

LR-FABMS ($CHCl_3$+NBA+NaI) 321 ($(M+Na)^+$), 263, 245, 176, 154 (bp), 136, 107, 69.

HR-FABMS calcd for $C_{19}H_{22}O_3Na$ ($(M+Na)^+$) 321.1467, found 321.1475.

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

References

(1) (a) Oishi, T.; Nakata, T. *Synthesis* **1990**, 635-645. (b) Bode, S.E.; Wolberg, M.; Müller, M. *Synthesis* **2006**, 557-588.

(2) Reviews on aldol-Tishchenko rections: (a) Mahrwald, R. *Curr. Org. Chem*. **2003**, *7*, 1713-1723. (b) Mlynarski, J. *Eur. J. Org. Chem.* **2006**, 4779-4786.

(3) Reviews on cascade reactions: (a) K. C. Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem. Int. Ed*. **2006**, *45*, 7134-7186. (b) Grondal, C.; Jeanty, M.; Enders, D. *Nature Chemistry* **2010**, *2*, 167-178.

(4) Reviews on direct aldol reactions: (a) Groger, H.; Vogl, E. M.; Shibasaki, M. *Chem. Eur. J.* **1998**, 4, 1137-1141. (b) Trost, B. M.; Brindle, C. S. *Chem. Soc. Rev*. **2010**, *39*, 1600-1632.

(5) Loog, O.; Mäeorg, U. *Tetrahedron: Asymmetry* **1999**, *10*, 2411-2415.

(6) Mascarenhas, C. M.; Miller, S. P.; White, P. S.; Morken, J. P.; *Angew. Chem. Int. Ed.* **2001**, *40*, 601-603.

(7) (a) Gnanadesikan, V.; Horiuchi, Y.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc*. **2004**, *126*, 7782-7783. (b) Horiuchi, Y.; Gnanadesikan, V.; Ohshima, T.; Masu, H. Katagiri, K.; Sei, Y.; Yamaguchi, K.; Shibasaki, M. *Chem. Eur. J.* **2005**, *11*, 5195-5204.

(8) Mlynarski, J.; Mitura, M.; *Tetrahedron Lett.* **2004**, *45*, 7549-7552. (b) Mlynarski, J.; Jankowska, J.; Rakiel, B. *Chem. Commun*. **2005**, 4854-4856. (c) Mlynarski, J.; Jankowska, J.; Rakiel, B. *Tetrahedron: Asymmetry* **2005**, *16*, 1521-1526. (d) Mlynarski, J.; Rakiel. B.; Stodulski, M.; Suszczynska, A.; Frelek, J. *Chem. Eur. J.* **2006**, *12*, 8158-8167.

(9) Rohr, K.; Herre, R.; Mahrwald, R. *Org. Lett.* **2005**, *7*, 4499-4501. (b) Rohr, K.; Herre, R.; Mahrwald, R. *J. Org. Chem.* **2009**, *74*, 3744-3749.

(10) (a) Nakajima, M.; Orito, Y.; Ishizuka, T.: Hashimoto, S. *Org. Lett*. **2004**, *6*, 3763-3765. (b) Orito, Y.; Hashimoto, S.; Ishizuka, T.; Nakajima, M. *Tetrahedron* **2006**, *62*, 390-400. (c) Ichibakase, T.; Orito, Y.; Nakajima, M. *Tetrahedron Lett.* **2008**, *49*, 4427-4429. (d) Tanaka, K.; Ueda, T.; Ichibakase, T.; Nakajima, M. *Tetrahedron Lett.* **2010**, *51*, 2168-2169.

(11) Recent examples of using lithium binaphtholate as a catalyst: (a) Schiffers, R.; Kagan, H. B. *Synlett* **1997**, 1175-1178. (b) Holmes, I. P.; Kagan, H. B. *Tetrahedron Lett*. **2000**, *41*, 7453-7456. (c) Hatano, M.; Ikeno, T.; Miyamoto, T.; Ishihara, K. *J. Am. Chem. Soc*. **2005**, *127*, 10776-10777. (d) Hatano, M.; Ikeno, T.; Matsumura, T.; Torii, S.; Ishihara, K. *Adv. Synth. Catal*. **2008**, *350*, 1776-1780. (e) Hatano, M.; Horibe, T.; Ishihara, K. *J. Am. Chem. Soc*. **2010**, *132*, 56-57.

(12) Ichibakase, T.; Nakajima, M. *Org. Lett.* **2011**, *13*, 1579-1581.

(13) Mechanistic studies of aldol-Tishchenko reaction: (a) Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc*. **1990**, *112*, 6447-6449. (b) Burkhardt, E. R.; Bergman, R. G.; Heathcock, C. H. *Organometallics*, **1990**, *9*, 30-44. (c) Mahrwald, R.; Costisella, B. *Synthesis* **1996**, 1087-1089. (d) Bodnar, P. M.; Shaw, J. T.; Woerpel, K. A. *J. Org. Chem*. **1997**, *62*, 5674-5675. (e) Abu-Hasanayn, F.; Streitwieser, A. *J. Org. Chem*. **1998**, *63*, 2954-2960. (f) Lu, L.; Chang, H.-Y.; Fang, J.-M. *J. Org. Chem*. **1999**, *64*, 843-853. (g) Mascarenhas, C. M.; Duffey, M. O.; Liu, S.-Y.; Morken, J. P. *Org. Lett*. **1999**, *1*, 1427-1429. (h) Markert, M.; Mahrwald, R. *Synthesis* **2004**, 1429-1433.

(14) Wu, T. R.; Shen, L.; Chong, J. M. *Org. Lett*. **2004**, *6*, 2701-2704.

(15) Acetti, D.; Brenna, E.; Fuganti, C.; Gatti, F. G.; Serra, S. *Eur. J. Org. Chem.* **2010**, 142-151.

(16) Ishihara, T.; Yamaguchi, K.; Kuroboshi, M.; Utimoto, K. *Tetrahedron Lett*. **1994**, *35*, 5263-5266.

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