Enantioselective Evans-Tishchenko Reduction of β-Hydroxyketone Catalyzed by Lithium Binaphtholate

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Received: 1 June 2011; in revised form: 10 June 2011 / Accepted: 15 June 2011 / Published: 17 June 2011

Abstract: Lithium diphenylbinaphtholate catalyzed the enantioselective Evans-Tishchenko reduction of achiral β-hydroxyketones to afford monoacyl-protected 1,3-diols with high stereoselectivities. In the reaction of racemic β-hydroxyketones, kinetic optical resolution occurred in a highly stereoselective manner.

Keywords: Evans-Tishchenko reduction; lithium binaphtholate; β-hydroxyketone; 1,3-diol; enantioselectivity

1. Introduction

Stereoselective synthesis of 1,3-diols is an important subject in synthetic organic chemistry because numerous biologically active compounds include such units [1,2]. One method to prepare chiral 1,3-diol is the reduction of β-hydroxyketones, and various metal hydride reagents have been applied to the syntheses of biologically active compounds using this method. Recently, acetalization of a β-hydroxy group with an aldehyde followed by a hydride shift to the carbonyl carbon, the so called Evans-Tishchenko reduction (Scheme 1) [3-5], has received much attention because it does not require the use of metal hydride reagents. Although the literature contains numerous examples using the Evans-Tishchenko reduction in the synthesis of biologically active compounds [6-13], the enantioselective Evans-Tishchenko reduction of an achiral β-hydroxyketone had not been reported prior to our preliminary study [14].
We have previously reported that an enantioselective aldol-Tishchenko reaction [14-21] catalyzed by lithium binaphtholate [22-30], affords 1,3-diol derivatives from a ketone and an aldehyde. Herein we report an enantioselective Evans-Tishchenko reduction, which yields optically active mono-acyl protected 1,3-diols from the reaction of achiral β-hydroxyketones with aldehydes catalyzed by lithium binaphtholate.

2. Results and Discussion

2.1. Optimization of Reaction Conditions

First we investigated the Evans-Tishchenko reduction of α,α-dimethyl-β-hydroxypropiophenone (2a) with benzaldehyde (3a) in THF at r.t. using lithium binaphtholate 1a, prepared in situ from binaphthol and BuLi, as a catalyst (Table 1, entry 1). The reaction gave the corresponding monobenzoyl 1,3-diol 4aa, but with low chemical yield (36%) and enantioselectivity (2% ee). Screening binaphthol derivatives revealed that introducing substituents to the 3,3′-positions of the catalyst dramatically increased both the chemical yield and enantioselectivity (entries 2–6). Among the various substituents surveyed, phenyl groups gave the best result (entry 4, 82% yield, 96% ee). Compared to THF, the use of ether or toluene as solvent gave unsatisfactory results (entries 7 and 8). Although lowering the reaction temperature increased the enantioselectivity (entry 9), the reaction did not proceed smoothly at −78 °C (entry 10).

Table 1. Evans-Tishchenko reduction of α,α-dimethyl-β-hydroxypropiophenone.

| Entry | Catalyst | Conditions | Solvent | Yield, % a | ee, % b |
|-------|----------|------------|---------|------------|---------|
| 1     | 1a (R = H) | rt, 24 h | THF     | 36         | 2       |
| 2     | 1b (R = Me) | rt, 24 h | THF     | 91         | 79      |
| 3     | 1c (R = Br) | rt, 24 h | THF     | 76         | 83      |
| 4     | 1d (R = Ph) | rt, 0.5 h | THF     | 82         | 96      |
| 5     | 1e (R = 4-MeC₆H₄) | rt, 0.5 h | THF     | 80         | 89      |
| 6     | 1f (R = 3,5-Me₂C₆H₃) | rt, 0.5 h | THF     | 84         | 20      |
| 7     | 1d (R = Ph) | rt, 0.5 h | Et₂O    | 73         | 56      |
| 8     | 1d (R = Ph) | rt, 0.5 h | toluene | 63         | 63      |
| 9     | 1d (R = Ph) | −40 °C, 0.5 h | THF      | 87         | 99      |
| 10    | 1d (R = Ph) | −78 °C, 48 h | THF      | 56         | 99      |

a Isolated yield; b Determined by HPLC analysis.
2.2. Evans-Tishchenko Reduction of Various Achiral β-Hydroxy ketones

With the optimum conditions in hand, we next examined the Evans-Tishchenko reduction of various β-hydroxyketones and aldehydes. The reaction of 2a with pivalaldehyde (3b) as a hydride source, which should afford pivaloyl ester, gave the corresponding product 4ab with the same absolute configuration as that with benzaldehyde in high yield at 0 °C, but was accompanied by the side product 5ab (5% yield), which was formed by transesterification of 4ab (Table 2, entry 2). The obtained enantioselectivity decreased to 90% ee, probably due to the higher reaction temperature (0 °C in entry 2 vs. −40 °C in entry 1). β-Hydroxyketone 2b, with cyclohexane at the α-position gave similar results as 2a with benzaldehyde (3a) or pivaldehyde (3b) (entries 3 and 4). Isopropyl ketone 2c gave the product 4ca in high enantioselectivity, but accompanied by 31% of the transesterification product 5ca (entry 5). Under the reaction conditions, either 4ca or 5ca was isomerized into a mixture of 4ca and 5ca ([4ca:5ca = 2:1]) without losing the enantioselectivity. The reaction of methyl ketone 2d and benzaldehyde (3a) gave excellent results, however, the products 4da and 5da ([4da:5da = 2:1]) were isolated as a single dibenzoyl ester 7da after benzyolation of the mixture of 4da and 5da (entry 6), because the monobenzoyl products 4da and 5da could not be separated.

Table 2. Evans-Tishchenko reduction of various achiral β-hydroxy ketones.

| Entry | R1 | R2 | R3 | Conditions | Yield of 4 (5) % a | ee of 4 (5) % b |
|-------|----|----|----|------------|-------------------|----------------|
| 1     | 2a | 3a |    | −40 °C, 0.5 h | 87 (0)            | 99             |
| 2     | 2a | 3b |    | 0 °C, 1 h   | 93 (5)            | 90 (90)        |
| 3     | 2b | 3a |    | −40 °C, 0.5 h | 96 (0)            | 98             |
| 4     | 2b | 3b |    | 0 °C, 4 h   | 82 (13)           | 83             |
| 5     | 2c | 3a |    | rt, 4 h    | 64 (31)           | 93 (93)        |
| 6     | 2d | 3a |    | −40 °C, 6 h | 91 c              | 99 c           |

a Isolated yield; b Determined by HPLC analysis; c Isolated as dibenzoyl ester 7da. Ratio of 4da to 5da was calculated from the crude NMR before benzyolation.

2.3. Evans-Tishchenko Reduction of Chiral β-Hydroxypriophenone

Using chiral β-hydroxyketones under the above conditions, a kinetic optical resolution occurred in a highly enantioselective manner (Scheme 2). The reaction of racemic α-methyl-β-hydroxyketone 8 and
benzaldehyde (3a) at −45 °C for 24 h afforded monobenzoyl 1,3-diol 9 in 48% yield with 86% ee, and the unreacted starting material 8 was recovered in 42% yield with 88% ee. The stereochemistry of 9 was determined by the conversion to the stereochemically-known diol 10 [31] by debenzoylation with sodium methoxide in methanol. Scheme 3 explains the 1,2-syn stereochemistry using bicyclic transition model A for the reaction of 8 and benzaldehyde 3a. The α-methyl group preferred the equatorial position over the axial position, producing 1,2-syn product predominantly.

Scheme 2. Kinetic resolution of chiral β-hydroxyketone.

Scheme 3. Plausible reaction pathway.

2.4. Reaction of An α-Unsubstituted-β-Hydroxypropiophenone

In the reaction of α-unsubstituted-β-hydroxypropiophenone 11, the Evans-Tishchenko product was not observed, but rather the monobenzoyl triol 12 was obtained in high yield with a high enantioselectivity (Scheme 4). Compound 12 may be formed by the transesterification of the aldol-Tishchenko adduct 13. It is interesting that the Evans-Tishchenko reduction proceeded exclusively in methyl ketone 2d, while β-hydroxypropiophenone (11) gave predominantly the aldol-Tishchenko adduct, although both hydroxyketones have enolizable positions. This may be because the Li-coordinated cyclic structure promoted the enolate formation or the approach of the aldehyde, though the detail is not clear. The absolute configuration of 12 was determined by conversion to stereochemically-known triol 14 [32].
3. Experimental

3.1. General

$^1$H-NMR and $^{13}$C-NMR spectra were recorded using a JEOL JNM-ECX-400 ($^1$H, 400 MHz; $^{13}$C, 100 MHz) spectrometer. Chemical shift values are expressed in ppm relative to internal tetramethylsilane. Coupling constants ($J$) are reported in Hz. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Infrared spectra were recorded using a JASCO FT/IR-5300. HPLC was performed on a JASCO PU-1580 with a JASCO UV-1575 ($\lambda = 254$ nm), and chiral separations were performed using Daicel Chiralpak or Chiralcel columns ($\phi 0.46 \times 25$ cm) with mixtures of hexane/isopropyl alcohol (hex/IPA) as eluents. Optical rotations were obtained using a JASCO DIP-370 digital polarimeter. β-Hydroxyketones $2$, $6$ and $8$ were prepared according to the literature [33-36], as were the binaphthol derivatives [37].

3.2. Enantioselective Evans-Tishchenko Reduction of β-Hydroxyketones

3.2.1. (S)-2,2-Dimethyl-1-phenyl-1,3-propanediol 3-O-benzoate ($4\text{aa}$) [38]

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 (21 mg, 0.047 mmol, 10 mol %) in THF at $-45$ °C, and the mixture was stirred for 5 min. Then solutions of benzaldehyde ($3a$, 75 mg, 0.708 mmol, 1.5 equiv.) and 3-hydroxy-2,2-dimethyl-1-phenylpropan-1-one ($2a$, 84 mg, 0.472 mmol, 1.0 equiv.) were successively added to the above mixture. After 0.5 h, the reaction was quenched with sat. NH$_4$Cl aq. and the mixture was stirred for an additional 10 min at r.t. The aqueous layer was extracted with ethyl acetate and the combined organic layer was washed with brine. After drying over Na$_2$SO$_4$ and evaporating the solvent, the residue was purified by silica gel column chromatography (dichloromethane) to afford diol derivative $4\text{aa}$ (114 mg, 87% yield, 99% ee) as colorless prisms. Mp 73–74 °C. $^1$H-NMR (CDCl$_3$): $\delta$ 0.97 (s, 3H, CH$_3$), 1.04 (s, 3H, CH$_3$), 2.45 (brs, 1H, –OH), 4.02 (d, 1H, $J = 11.0$ Hz, OCH$_2$), 4.43 (d, 1H, $J = 11.0$ Hz, OCH$_2$), 4.69 (s, 1H, CHPh), 7.25–7.48 (m, 7H, ArH), 7.56–7.60 (m, 1H, ArH), 8.04–8.06 (m, 2H, ArH). HPLC (Daicel Chiralpak AD-H, hex/IPA = 9/1, 1.0 mL/min): $t_R$ 8.8 (S), 12.8 min (R). [α]$^{30}_D$ $-23.1$ (c 1.13, CHCl$_3$) for 99% ee.
Determination of the absolute configuration of 4aa.

To a solution of 4aa (114 mg, 0.401 mmol, 1.0 equiv.) in MeOH (2 mL), NaOMe (0.05 mmol, 12 mol %) in MeOH (0.1 mL) was added and the resulting homogeneous mixture was stirred for 3 h. The mixture was diluted with ethyl acetate (20 mL), and washed with water (5 mL). The aqueous layer was extracted twice with ethyl acetate (10 mL x 2). The combined organic layers were washed with brine (10 mL) and dried over Na$_2$SO$_4$. After concentration in vacuo, the residue was purified by silica gel column chromatography (hexane/ethyl acetate = 4/1) to give diol 6a (70 mg, 96% yield, 99% ee) as colorless needles. The optical rotation data shows (+)-6a had an S -configuration, indicating (−)-4aa has an S-configuration. Mp 62–63 °C. 1H-NMR (CDCl$_3$) δ 0.79 (s, 3H, C$_3$H$_3$), 0.84 (s, 3H, C$_3$H$_3$), 3.43 (d, 1H, J = 10.6 Hz, OC$_2$H$_2$), 3.50–3.58 (m, 2H, OC$_2$H$_2$ and CH$_2$Ph), 3.77 (brs, 1H, OH), 4.57 (s, 1H, OH), 7.32–7.35 (m, 5H, ArH). [α]$_{30}^D$ +44.7 (c 1.00, CHCl$_3$) for 99% ee (S). [lit. 39: [α]$_{30}^D$ +21.7 (c 1.17, CHCl$_3$) for 55% ee (S)].

3.2.2. (S)-2,2-Dimethyl-1-phenyl-1,3-propanediol 3-O-pivaloate (4ab)

1H-NMR (CDCl$_3$): δ 0.87 (s, 3H, C(C$_3$H$_3$)$_2$), 0.95 (s, 3H, C(C$_3$H$_3$)$_2$), 1.26 (s, 9H, C(C$_3$H$_3$)$_3$), 2.39 (d, 1H, J = 3.2 Hz, OCH$_2$), 3.74 (d, 1H, J = 11 Hz, C$_2$H$_2$), 4.19 (d, 1H, J = 11 Hz, C$_2$H$_2$), 4.57 (d, 1H, J = 3.2 Hz, PhCH$_3$), 7.26–7.33 (m, 5H, ArH). 13C-NMR: δ 19.4, 21.3, 27.2, 39.0, 39.3, 70.5, 78.0, 127.5, 127.6, 127.7, 140.9, 178.6. IR (CHCl$_3$): 3480, 1715 cm$^{-1}$. MS (FAB): m/z 173, 287 ([M+Na]$^+$). HRMS: calcd for C$_{16}$H$_{24}$O$_3$Na 287.1623, found 287.1619. HPLC (Daicel Chiralcel OD-H, hex/IPA = 9/1, 1.0 mL/min) $t_R$: 5.1 (R), 6.7 (S) min. [α]$^{17_0}_D$ +51.4 (c 0.6, CHCl$_3$).

3.2.3. (S)-2,2-Dimethyl-1-phenyl-1,3-propanediol 1-O-pivaloate (5ab)

1H-NMR (CDCl$_3$): δ 0.87 (s, 3H, C(CH$_3$)$_2$), 0.95 (s, 3H, C(CH$_3$)$_2$), 1.26 (s, 9H, C(CH$_3$)$_3$), 2.34 (brs, 1H, OH), 3.24 (d, 1H, J = 11 Hz, CH$_2$), 3.42 (d, 1H, J = 11 Hz, CH$_2$), 5.77 (s, 1H, PhCH$_3$), 7.28–7.35 (m, 5H, ArH). 13C-NMR: δ 19.2, 21.6, 27.2, 39.0, 40.2, 69.1, 78.5, 127.66, 127.72, 127.8, 178.2. IR (neat): 3458, 1730 cm$^{-1}$. MS (FAB, NBA+NaI): m/z 287 ([M+Na]$^+$). HRMS: calcd for C$_{16}$H$_{24}$O$_3$Na 287.1623, found 287.1628. [α]$^{17_0}_D$ +51.4 (c 0.6, CHCl$_3$).

3.2.4. (−)-2,2-Pentamethylene-1-phenyl-1,3-propanediol 3-O-benzoate (4ba)

1H-NMR (CDCl$_3$): δ 1.17–1.26 (m, 1H, C(CH$_2$)$_2$C), 1.37–1.61 (m, 9H, C(CH$_2$)$_2$C), 2.50 (brs, 1H, OH), 4.21 (d, 1H, J = 11.4 Hz, OCH$_2$), 4.47 (d, 1H, J = 11.4 Hz, OCH$_2$), 4.74 (s, 1H, PhCH$_3$), 7.21–7.32 (m, 5H, ArH). 13C-NMR: δ 21.3, 21.4, 28.2, 28.3, 41.3, 65.2, 78.2, 127.3, 127.6, 127.7, 128.3, 129.5, 130.1, 132.9, 141.0, 166.4. IR (neat): 3502, 1716 cm$^{-1}$. MS (FAB, NBA+NaI): m/z 347 ([M+Na]$^+$). HRMS: calcd for C$_{21}$H$_{24}$O$_3$Na 347.1623, found 347.1643. HPLC (Daicel Chiralpak AD-H, hex/IPA = 49/1, 1 mL/min) $t_R$: 13.0 (major), 14.4 (minor) min. [α]$^{17_0}_D$ –11.4 (c 1.13, CHCl$_3$) for 98% ee.
3.2.5. (+)-2,2-Pentamethylene-1-phenyl-1,3-propanediol 3-O-pivaloate (4bb)

1H-NMR (CDCl3): δ 1.22 (s, 9H, C(CH3)3), 1.34-1.58 (m, 10H, CCH2C), 2.54 (brs, 1H, OH), 3.94 (d, 1H, J = 11.4 Hz, OCH2), 4.21 (d, 1H, J = 11.4 Hz, OCH2), 4.62 (s, 1H, PhCH), 7.25–7.32 (m, 5H, ArH). 13C-NMR: δ 21.2, 21.4, 25.8, 27.2, 28.2, 28.3, 38.9, 41.1, 64.9, 78.5, 127.3, 127.6, 127.7, 140.9, 178.3. IR (KBr): 3498, 1711 cm\(^{-1}\). MS (FAB, NBA+Na\(^{+}\)): m/z 287, 327 ([M+Na\(^{+}\)]. HRMS: calcld for C\(_{19}\)H\(_{28}\)O\(_3\)Na 327.1936, found 327.1929. HPLC (Daicel Chiralpak AD-H, hex/IPA = 49/1, 1 mL/min) \(t\)_R: 28.1 (minor), 33.0 (major) min. \([\alpha]^{17}\)\(_D\) +6.0 (c 1.36, CHCl3) for 83% ee.

3.2.6. (+)-2,2-Pentamethylene-1-phenyl-1,3-propanediol 1-O-pivaloate (5bb)

1H-NMR (CDCl3): δ 1.12-1.59 (m, 9H, CCH2C), 1.24 (s, 9H, C(CH3)3), 1.69–1.72 (m, 1H, CCH2C), 2.07 (brs, 1H, OH), 3.49 (d, 1H, J = 11.9 Hz, OCH2), 3.63 (s, 1H, J = 11.9 Hz, OCH2), 5.78 (s, 1H, PhCH), 7.26–7.33 (m, 5H, ArH). 13C-NMR: δ 21.1, 21.3, 25.9, 27.2, 28.2, 28.4, 39.0, 41.9, 62.9, 79.8, 127.7, 127.8, 127.9, 137.3, 177.6. IR (neat): 3513, 1732 cm\(^{-1}\). MS (FAB, NBA+Na\(^{+}\)): m/z 57, 91, 305 ([M+H\(^{+}\)]. HRMS: calcd for C\(_{19}\)H\(_{29}\)O\(_3\) 305.2117, found 305.2128. \([\alpha]^{17}\)\(_D\) +23.3 (c 1.47, CHCl3).

3.2.7. (S)-2,2,4-Trimethyl-1,3-pentanediol 1-O-benzoate (4ca)

1H-NMR (CDCl3): δ 0.97 (d, 3H, J = 6.9 Hz, CH(CH3)2), 1.02 (d, 3H, J = 6.9 Hz, CH(CH3)2), 1.05 (s, 3H, C(CH3)3), 1.07 (s, 3H, C(CH3)3), 1.97–2.00 (m, 2H, OH, CH(CH3)2), 3.38 (s, 1H, CH(OH), 4.02 (d, 1H, J = 11 Hz, CH2), 4.38 (d, 1H, J = 11 Hz, CH2), 7.43–7.47 (m, 2H, ArH), 7.55–7.59 (m, 1H, ArH), 8.03–8.05 (m, 2H, ArH). 13C-NMR: δ 17.9, 19.7, 22.3, 23.0, 28.6, 40.3, 70.0, 80.3, 128.5, 129.8, 129.9, 133.2, 167.6. IR (KBr): 3340, 1724 cm\(^{-1}\). MS (FAB, NBA+Na\(^{+}\)): m/z 77, 105, 273 ([M+Na\(^{+}\)]. HRMS calcd for C\(_{15}\)H\(_{22}\)O\(_3\)Na 273.1467, found 273.1458. HPLC (Daicel Chiralpak AD-H, hex/IPA = 39/1, 1.0 mL/min) \(t\)_R: 14.4 (S), 15.7 (R) min. \([\alpha]^{17}\)\(_D\) +9.5 (c 2.14, benzene) for 93% ee, (S). The absolute configuration of 4ca was determined by conversion to diol 6a. \([\alpha]^{29}\)\(_D\) –11.3 (c 1.54, CH\(_2\)Cl\(_2\)) for 93% ee. [lit. 40: \([\alpha]^{30}\)\(_D\) –9.5 (c 1.0, CH\(_2\)Cl\(_2\)) for 75% ee, (S)].

3.2.8. (S)-2,2,4-Trimethyl-1,3-pentanediol 3-O-benzoate (5ca)

1H-NMR (CDCl3): δ 0.95 (s, 3H, C(CH3)3), 1.01 (d, 3H, J = 6.9 Hz, CH(CH3)2), 1.09 (d, 3H, J = 6.9 Hz, CH(CH3)2), 1.10 (s, 3H, C(CH3)3), 2.17–2.21 (m, 1H, CH(CH3)2), 2.79 (brs, 1H, OH), 3.09 (d, 1H, J = 11.9 Hz, CH2), 3.34 (d, 1H, J = 11.9 Hz, CH2), 5.04 (d, 1H, J = 2.8 Hz, OCH), 7.45–7.49 (m, 2H, ArH), 7.58–7.61 (m, 1H, ArH), 8.08–8.10 (d, 2H, J = 7.3 Hz, ArH). 13C-NMR: δ 17.9, 19.7, 22.3, 23.0, 28.6, 40.3, 70.0, 80.3, 128.5, 129.8, 129.9, 133.2, 167.6. IR (neat): 3493, 1720 cm\(^{-1}\). MS (FAB, NBA+Na\(^{+}\)): m/z 105, 273 ([M+Na\(^{+}\)]. HRMS: calcd for C\(_{15}\)H\(_{22}\)O\(_3\)Na 273.1476, found 273.1447. HPLC (Daicel Chiralpak AD-H, hex/IPA = 39/1, 1 mL/min) \(t\)_R: 13.5 (S), 14.8 (R) min. \([\alpha]^{17}\)\(_D\) –15.4 (c 1.15, CHCl3) for 93% ee, (S).

Treatment of 4ca (93% ee) with 10 mol % of 1d for 3 h at rt afforded 5ca (32% yield, 92% ee) with unreacted 4ca (63% yield, 93% ee). Treatment of 5ca (93% ee) with 10 mol % of 1d for 3 h at r.t. afforded 4ca (58% yield, 93% ee) with unreacted 5ca (32% yield, 93% ee).
3.2.9. (+)-2,2-Dimethyl-1,3-butanediol dibenzoate (7da)

Starting from 2d (0.057 mL, 0.470 mmol, 1.0 equiv.) and 3a (75 mg, 0.708 mmol, 1.5 equiv.), a mixture of 4da and 5da was obtained by the above method. To the solution of the mixture in dichloromethane (2 mL), benzoyl chloride (0.820 mL, 0.710 mmol, 1.5 equiv.), Et3N (0.147 mL, 1.41 mmol, 3.0 equiv.) and DMAP (11.5 mg, 0.094 mmol, 10 mol %) were added successively. After being stirred for 12 h at r.t., the reaction mixture was quenched by diethylamine (0.1 mL) and was diluted with ethyl acetate. The organic layer were washed with HCl aq., NaHCO3 aq. and brine (10 mL) successively, and dried over Na2SO4. After concentration in vacuo, the residue was purified by silica gel column chromatography (hexane/dichloromethane = 1/1) to give dibenzoate 7da (141 mg, 92% yield, 99% ee) as a oil. 1H-NMR (CDCl3) δ 1.13 (s, 3H, CH3), 1.17 (s, 3H, CH3), 1.37 (d, 3H, J = 6.4 Hz, CH3), 4.22 (d, 1H, J = 11.5 Hz, CH2), 4.26 (d, 1H, J = 11.5 Hz, CH2), 5.28 (q, 1H, J = 6.4 Hz, CH), 7.39–7.44 (m, 4H, ArH), 7.51–7.55 (m, 2H, ArH), 8.03–8.06 (m, 4H, ArH). 13C-NMR (CDCl3) δ 14.70, 20.38, 21.33, 38.07, 70.02, 74.50, 128.24, 128.28, 129.39, 129.45, 130.02, 130.42, 132.76, 132.83, 165.66, 166.28. IR (neat): 1720 cm⁻¹. MS (FAB, NBA+NaI) m/z 327 ((M+H)+), 205, 154, 137, 105, 83, 77. HRMS (FAB) calcd for C20H23O4 ((M+H)+) 327.1602, found 327.1597. [α]29D +66.6 (c 1.47, CHCl3) for 99% ee. HPLC (Daicel Chiralpak AD-H, hex/IPA = 200/1, 1.0 mL/min): tR: 19.3 (minor), 20.7 (major) min.

3.3. Kinetic Optical Resolution of 3-Hydroxy-2-methyl-1-phenylpropan-1-one (8)

Under an argon atmosphere, n-BuLi (0.094 mmol, 20 mol %) in hexane (0.19 M, 0.49 mL) was added to a solution of (R)-3,3'-diphenylbinaphthol (21 mg, 0.047 mmol, 10 mol %) in THF at −45 °C, and the mixture was stirred for 5 min. Then solutions of benzaldehyde (3a, 50 mg, 0.470 mmol, 1.0 equiv.) and racemic 3-hydroxy-2-methyl-1-phenylpropan-1-one (8, 77 mg, 0.470 mmol, 1.0 equiv.) were successively added to the above mixture. After 24 h, the reaction was quenched with sat. NH4Cl aq. and the mixture was stirred for 20 min at r.t. The aqueous layer was extracted twice with dichloromethane and the combined organic layers were washed with brine. After drying over Na2SO4 and evaporating the solvent, the residue was purified by silica gel column chromatography (hexane/ethyl acetate = 6/1 ~ 2/1) to afford the diol derivative 9 (61 mg, 48% yield, 86% ee) and unreacted starting material 8 (32 mg, 42%, 88% ee).

3.3.1. (1R,2S)-2-Methyl-1-phenyl-1,3-propanediol 3-O-benzoate (9)

1H-NMR (CDCl3): δ 1.03 (d, 3H, J = 6.9 Hz, CH3), 2.16 (dd, 1H, J = 1.4, 3.6 Hz, OH), 2.28–2.36 (m, 1H, CHCH3), 4.14 (dd, 1H, J = 6.0, 11 Hz, CH2), 4.43 (dd, 1H, J = 6.7, 11 Hz, CH2), 4.84–4.86 (m, 1H, PhCH), 7.26–2.29 (m, 1H, ArH), 7.34–7.36 (m, 4H, ArH), 7.43–7.47 (m, 2H, ArH), 7.56–7.59 (m, 1H, ArH), 8.01–8.03 (m, 2H, ArH). 13C-NMR: δ 11.2, 40.1, 67.1, 74.3, 126.0, 127.4, 128.3, 128.4, 130.0, 130.1, 133.0, 142.7, 166.7. IR (neat): 3492, 1722 cm⁻¹. MS (FAB, NBA+NaI): m/z 77, 105, 154, 271 ([M+H]+). HRMS: calcd for C17H19O3 (M+H)+ 271.1334 found 271.1356. HPLC (Daicel Chiralpak AD-H, hex/IPA = 9/1, 1.0 mL/min): tR: 9.8 (1R,2S), 11.2 (1S,2R) min. [α]18D −17.4 (c 1.45, CHCl3) for 88% ee, (1R,2S). The relative and absolute configuration of 9 were determined by conversion to diol 10. [α]21D +39.2 (c 0.88, CHCl3) for 88% ee (1R,2S). [lit. 31: [α]27D +56.1 (c 0.75, CHCl3) for >99% ee, (1R,2S)].
3.3.2. (S)-3-Hydroxy-2-methyl-1-phenylpropan-1-one (8)

HPLC (Daicel Chiralpak AD-H, hex/IPA = 19/1, 1 mL/min) t<sub>R</sub>: 17.6 (R), 19.7 (S) min. [α]<sup>29</sup> <sub>D</sub> −37.9 (c 0.86, EtOH) for 86% ee (S). [lit. 41: [α]<sup>23</sup> <sub>D</sub> +41.2 (c 0.90, EtOH) for 91% ee, (R)].

3.4. The Aldol-Tishchenko Reaction of An α-Unsubstituted-β-Hydroxypropiophenone

(1R,3R)-2-Benzoyloxymethyl-1,3-diphenyl-1,3-propanediol (12)

Under an argon atmosphere, n-BuLi (0.094 mmol, 20 mol %) in hexane (0.19 M, 0.49 mL) was added to a solution of (R)-3,3’-diphenylbinaphthol (21 mg, 0.047 mmol, 10 mol %) in THF at −45 °C, and the mixture was stirred for 5 min. Then solutions of benzaldehyde (3a, 76 mg, 0.716 mmol, 1.5 equiv.) and 3-hydroxy-1-phenylpropan-1-one (11, 70 mg, 0.470 mmol, 1.0 equiv.) were successively added to the above mixture. After 24 h, the reaction was quenched with sat. NH<sub>4</sub>Cl aq. and the mixture was stirred for 20 min at r.t. The aqueous layer was extracted twice with dichloromethane and the combined organic layers were washed with brine. After drying over Na<sub>2</sub>SO<sub>4</sub> and evaporating the solvent, the residue was purified by silica gel column chromatography (hexane/ethyl acetate = 1/1 then dichloromethane) to afford the diol derivative 12 (158 mg, 93% yield, 90% ee) as colorless needles. Mp 119–120 °C. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 2.45–2.50 (m, 1H, CC<sub>H</sub>C), 3.89 (d, 1H, J = 6.7 Hz, O<sub>H</sub>), 3.90 (d, 1H, J = 4.6 Hz, O<sub>H</sub>), 4.20 (dd, 1H, J = 5.5, 11.5 Hz, BzOCH<sub>2</sub>), 4.65 (dd, 1H, J = 8.3, 11.5 Hz, BzOCH<sub>2</sub>), 5.33–5.57 (m, 1H, HOC<sub>H</sub>), 5.11 (dd, 1H, J = 4.6, 4.6 Hz, HOCH), 7.16–7.20 (m, 3H, Ar<sub>H</sub>), 7.24–7.30 (m, 3H, Ar<sub>H</sub>), 7.35–7.43 (m, 6H, Ar<sub>H</sub>), 7.50–7.54 (m, 1H, Ar<sub>H</sub>), 7.80–7.83 (m, 2H, Ar<sub>H</sub>). <sup>13</sup>C-NMR: δ 50.7, 61.7, 71.6, 73.5, 125.4, 125.7, 127.0, 127.6, 128.2, 128.6, 129.5, 129.7, 133.0, 141.9, 142.2, 166.8. IR (neat): 3477, 1713 cm<sup>−1</sup>. MS (FAB, NBA+NaI) 385 ((M+Na)<sup>+</sup>), 326, 323, 242, 176, 173, 92, 77. HRMS (FAB) calcd for C<sub>23</sub>H<sub>22</sub>O<sub>4</sub>Na ((M+Na)<sup>+</sup>) 385.1420, found 385.1416. HPLC (Daicel Chiralpak AD-H, hex/IPA = 9/1, 1.0 mL/min) t<sub>R</sub>: 19.3 (S,S), 25.1 (R,R) min. [α]<sup>29</sup> <sub>D</sub> +44.1 (c 1.04, CHCl<sub>3</sub>) for 92% ee, (S,S).

The absolute configuration of 12 was determined by the conversion to triol 14. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 1.91 (brs, 1H, O<sub>H</sub>), 3.25 (brs, 1H, J = 10.6 Hz, CH<sub>2</sub>), 3.65 (dd, 1H, J = 5.48, 11.44 Hz, CH<sub>H</sub>), 4.18 (brs, 1H, O<sub>H</sub>), 4.43 (d, 1H, J = 4.12 Hz, CH<sub>2</sub>), 7.16–7.19 (m, 3H, Ar<sub>H</sub>), 7.22–7.25 (m, 3H, Ar<sub>H</sub>), 7.27–7.33 (m, 3H, Ar<sub>H</sub>). [α]<sup>18</sup> <sub>D</sub> −35.0 (c 2.16, CH<sub>2</sub>Cl<sub>2</sub>) for 92% ee [lit. 32: [α]<sup>20</sup> <sub>D</sub> −39 (c 0.97, CH<sub>2</sub>Cl<sub>2</sub>) for >99% ee, (R,R)].

4. Conclusions

We have demonstrated that lithium diphenylbinaphtholate catalyzes the enantioselective Evans-Tishchenko reduction of β-hydroxyketones, affording monoacyl-protected 1,3-diols in high stereoselectivities. In the reaction of racemic β-hydroxyketone, kinetic optical resolution occurs in a highly stereoselective manner. Further investigations to expand the substrate scope and to explore the reaction mechanism are currently underway.
References

1. Oishi, T.; Nakata, T. New aspects of stereoselective synthesis of 1,3-polyols. *Synthesis* **1990**, 635-645.
2. Bode, S.E.; Wolberg, M.; Müller, M. Stereoselective synthesis of 1,3-diols. *Synthesis* **2006**, 557-588.
3. Evans, D.A.; Hoveyda, A.H. Samarium-catalyzed intramolecular Tishchenko reduction of β-hydroxy ketones. A stereoselective approach to the synthesis of differentiated anti 1,3-diol monoesters. *J. Am. Chem. Soc.* **1990**, 112, 6447-6449.
4. Umekawa, Y.; Sakaguchi, S.; Nishiyama, Y.; Ishii, Y. Stereoselective reduction of β-hydroxy ketones with aldehydes via Tishchenko reactions catalyzed by zirconocene complexes. *J. Org. Chem.* **1997**, 62, 3409-3412.
5. Gillespie, K.M.; Munslow, I.J.; Scott, P. Stereoselective catalytic Tishchenko reduction of β-hydroxyketones using scandium triflate. *Tetrahedron Lett.* **1999**, 40, 9371-9374.
6. Romo, D.; Meyer, S.D.; Johnson, D.D.; Schreiber, S.L. Total synthesis of (−)-rapamycin using an Evans-Tishchenko fragment coupling. *J. Am. Chem. Soc.* **1993**, 115, 7906-7907.
7. Schöning, K.-U.; Hayashi, R.K.; Powell, D.R.; Kirschning, A. Synthetic studies toward ansatrienines: Application of the Evans-Tishchenko reaction to chiral enones. *Tetrahedron: Asymmetry* **1999**, 10, 817-820.
8. Shotwell, J.B.; Krygowski, E.S.; Hines, J.; Koh, B.; Huntsman, E.W.D.; Choi, H.W.; Schneekloth, J.S.; Wood, J.L.; Crews, C.M. Total synthesis of luminacin D. *Org. Lett.* **2002**, 4, 3087-3089.
9. Jiang, Y.; Hong, J.; Burke, S.D. Stereoselective total synthesis of antitumor macrolide (+)-rhizoxin D. *Org. Lett.* **2004**, 6, 1445-1448.
10. Aird, J.I.; Hulme, A.N.; White, J.W. An Evans-Tishchenko-ring-closing metathesis approach to medium-ring lactones. *Org. Lett.* **2007**, 9, 631-634.
11. Smith, A.B., III; Lee, D. Total synthesis of (+)-tedanolide. *J. Am. Chem. Soc.* **2007**, 129, 10957-10962.
12. Youngsaye, W.; Lowe, J.T.; Pohlki, F.; Ralifo, P.; Panek, J.S. Total synthesis and stereoochemical reassignment of (+)-neopeltolide. *Angew. Chem. Int. Ed.* **2007**, 46, 9211-9214.
13. Slavov, N.; Cvegros, J.; Neudörf, J.-M.; Schmalz, H.-G. Total synthesis of the marine antibiotics pestalone and its surprisingly facile conversion into pestalalactone and pestalachloride A. *Angew. Chem. Int. Ed.* **2010**, 49, 7588-7591.
14. Ichibakase, T.; Nakajima, M. Direct enantioselective aldol-Tishchenko reaction catalyzed by chiral lithium diphenylbinaphtholate. *Org. Lett.* **2011**, 13, 1579-1581.
15. Mahrwald, R. The aldol-Tishchenko reaction: A tool in stereoselective synthesis. *Curr. Org. Chem.* **2003**, 7, 1713-1723.
16. Mlynarski, J. Direct asymmetric aldol-Tishchenko reaction. *Eur. J. Org. Chem.* **2006**, 4779-4786.
17. Mascarenhas, C.M.; Miller, S.P.; White, P.S.; Morken, J.P. First catalytic asymmetric aldol-Tishchenko reaction-insight into the catalyst structure and reaction mechanism. *Angew. Chem. Int. Ed.* **2001**, 40, 601-603.
18. Schneider, C.; Hansch, M. First catalytic, enantioselective aldol-Tishchenko reaction with ketone aldols as enol equivalents. *Synlett* **2003**, 837-840.
19. Gnanadesikan, V.; Horiuchi, Y.; Ohshima, T.; Shibasaki, M. Direct catalytic asymmetric aldol-Tishchenko reaction. *J. Am. Chem. Soc.* **2004**, 126, 7782-7783.
20. Mlynarski, J.; Mitura, M. The first example of a catalytic asymmetric aldol-Tishchenko reaction of aldehydes and aliphatic ketones. *Tetrahedron Lett.* **2004**, *45*, 7549-7552.

21. Rohr, K.; Herre, R.; Mahrwald, R. Enantioselective direct aldol-Tishchenko reaction: Access to chiral stereopentads. *Org. Lett.* **2005**, *7*, 4499-4501.

22. Schiffers, R.; Kagan, H.B. Asymmetric catalytic reduction of ketones with hypervalent trialkoxysilanes. *Synlett* **1997**, 1175-1178.

23. Holmes, I.P.; Kagan, H.B. The asymmetric addition of trimethylsilyl cyanide to aldehydes catalysed by anionic chiral nucleophiles. *Tetrahedron Lett.* **2000**, *41*, 7453-7456.

24. Hatano, M.; Ikeno, T.; Miyamoto, T.; Ishihara, K. Chiral lithium binaphtholate aqua complex as a highly effective asymmetric catalyst for cyanohydrin synthesis. *J. Am. Chem. Soc.* **2005**, *127*, 10776-10777.

25. Hatano, M.; Ikeno, T.; Matsumura, T.; Torii, S.; Ishihara, K. Chiral lithium salts of phosphoric acids as Lewis acid-base conjugate catalysts for the enantioselective cyanosilylation of ketones. *Adv. Synth. Catal.* **2008**, *350*, 1776-1780.

26. Hatano, M.; Horibe, T.; Ishihara, K. Chiral lithium(I) binaphtholate salts for the enantioselective direct Mannich-type reaction with a change of syn/anti and absolute stereochemistry. *J. Am. Chem. Soc.* **2010**, *132*, 56-57.

27. Nakajima, M.; Orito, Y.; Ishizuka, T.; Hashimoto, S. The enantioselective aldol reaction of trimethoxysilyl enol ether catalyzed by lithium binaphtholate. *Org. Lett.* **2004**, *6*, 3763-3765.

28. Ichibakase, T.; Orito, Y.; Nakajima, M. Enantioselective construction of quaternary asymmetric carbon centers using an aldol reaction of trimethoxysilyl enol ethers catalyzed by lithium binaphtholate. *Tetrahedron Lett.* **2008**, *49*, 4427-4429.

29. Tanaka, K.; Ueda, T.; Ichibakase, T.; Nakajima, M. Enantioselective alkynylation of ketones with trimethoxysilylalkynes using lithium binaphtholate as a catalyst. *Tetrahedron Lett.* **2010**, *51*, 2168-2169.

30. Tanaka, K.; Kukita, K.; Ichibakase, T.; Kotani, S.; Nakajima, M. Lithium acetylides as alkynylating reagents for the enantioselective alkynylation of ketones catalyzed by lithium binaphtholate. *Chem. Commun.* **2011**, *47*, 5614-5616.

31. Yakura, T.; Yoshimoto, Y.; Ishida, C.; Mabuchi, S. Synthesis of an immunomodulator (+)-conagenin and its analogs. *Tetrahedron* **2007**, *63*, 4429-4438.

32. Steif, F.; Wibbeling, B.; Meyer, O.; Hoppe, D. Enantio- and diastereoselective synthesis of (protected) 2-formyl- and 2-(hydroxymethyl)-1-phenylalkane-1,3-diols from chiral 2-methoxy-3-tosyl-1,3-oxazolidines by subsequent asymmetric formylation and aldolization. *Synthesis* **2000**, 743-753.

33. Sulmon, P.; De Kimpe, N.; Schamp, N. Preparation of α,α-dialkyl-β-haloketones. *Org. Prep. Proc. Int.* **1989**, *21*, 91-104.

34. Donnelly, J.A.; Hoey, J.G.; O'Donnell, R. Rearrangement of an oxetan-3-one and related alcohols by Grignard reagents. *J. Chem. Soc. Perkin Trans. 1* **1974**, 1218-1220.

35. Curzu, M.M.; Pinna, G.A. Hydroxymethylation of propiophenones in aqueous medium: A new route to 1-aryl-2-methyl-2-propen-1-ones. *Synthesis* **1984**, 339-342.

36. O'Neil, G.W.; Miller, M.M.; Carter, K.P. Direct conversion of β-hydroxyketones to cyclic disiloxanes. *Org. Lett.* **2010**, *12*, 5350-5353.
37. Wu, T.R.; Shen, L.; Chong, J.M. Asymmetric allylboration of aldehydes and ketones using 3,3'-disubstitutedbinaphthol-modified boronates. *Org. Lett.* **2004**, *6*, 2701-2704.
38. Markert, M.; Mahrwald, R. LiClO₄-amine mediated direct aldol process. *Synthesis* **2004**, *1429*-1433.
39. Kotani, S.; Shimoda, Y.; Sugiura, M.; Nakajima, M. Novel enantioselective direct aldol-type reaction promoted by a chiral phosphine oxide as an organocatalyst. *Tetrahedron Lett.* **2009**, *50*, 4602-4605.
40. Seifert, A.; Scheffler, U.; Markert, M.; Mahrwald, R. Asymmetric acid-catalyzed Meerwein-Ponndorf-Verley-aldol reactions of enolizable aldehydes. *Org. Lett.* **2010**, *12*, 1660-1663.
41. Kokubo, N.; Ogawa, C.; Kobayashi, S. Lewis acid catalysis in water with a hydrophilie substrate: Scandium-catalyzed hydroxymethylation with aqueous formaldehyde in water. *Angew. Chem. Int. Ed.* **2008**, *47*, 6909-6911.

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