Supporting Information

Facile Synthesis and Stereo-Resolution of Chiral 1,2,3-Triazole

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I. General Methods and Materials

General Information

All of the reactions dealing with air and/or moisture-sensitive reactions were carried out under an atmosphere of nitrogen using oven/flame-dried glassware and standard syringe/septum techniques. Unless otherwise noted, all commercial reagents and solvents were obtained from the commercial provider and used without further purification. $^1$H-NMR and $^{13}$C-NMR spectra were recorded on Varian 400 MHz spectrometers and Bruker 400 MHz spectrometers. Chemical shifts were reported relative to internal tetramethylsilane ($\delta$ 0.00 ppm) or CDCl$_3$ ($\delta$ 7.26 ppm), CD$_3$CD ($\delta$ 3.31 ppm) for $^1$H and CDCl$_3$ ($\delta$ 77.0 ppm), CD$_3$CD ($\delta$ 49.75 ppm) for $^{13}$C. Flash column chromatography was performed on 300-400 mesh silica gels. Analytical thin layer chromatography was performed with precoated glass baked plates (250µ) and visualized by fluorescence and by charring after treatment with potassium permanganate stain. Optical rotations were measured on a commercial automatic polarimeter (WZZ-1S digital, Shanghai Physical Optics Instrument Factory ) and reported as follows: $[\alpha]$$^D$ (c = g/100 mL, solvent). Melting points were measured on a X-4 digital microscopy apparatus and uncorrected. HRMS were recorded on LTQ-FTUHRA spectrometer and Bruker Apexll mass spectrometer. Anhydrous Toluene was purchased from Beijing Chemical Reagent Co. and distilled with sodium, immediately before use.

General procedure for the preparation of 5a/5b

4-(cyclohex-1-en-1-yl)-5-phenyl-2H-1,2,3-triazole (1b) was synthesized according the following literature:

4-(cyclohex-1-en-1-yl)-5-phenyl-2H-1,2,3-triazol-2-yl)methyl pivalate (1c). To the solution of compound 1b (30.0g, 0.13mol) in acetone (60 mL), chloromethylene pivalate (23.4g, 0.26mol) and K$_2$CO$_3$ (35.9g, 0.26mol) were added. The mixture was stirring at RT for 12h. The white solid was removed by filtrating. After removing the solvent under vacuum, the resulting crude product was purified by column chromatography on silica gel (petroleum ether: EtOAc= 10:1).
(4-(7-oxabicyclo[4.1.0]heptan-1-yl)-5-phenyl-2H-1,2,3-triazol-2-yl)methyl pivalate (1d). Compound 1c (35.0g, 0.11mol) was dissolved in 50ml dry DCM at 0 °C in ice-both under N₂ atmosphere. And then the solution of m-CPBA(26.9g, 0.17mol) in 20 ml dry DCM was added dropwise over 10 mins. The reaction mixture was stirred for 3 hours at RT and monitored by TLC. After the completing of starting material, the reaction mixture was filtrated to remove the white solid. The filtrate was then washed with 10% Na₂CO₃ solution and brine. The organic phase was dried with MgSO₄ and concentrated under vacuum. The crude product was purified by column chromatography on silica gel (petroleum ether: EtOAc= 8:1).

(4-(2-oxocyclohexyl)-5-phenyl-2H-1,2,3-triazol-2-yl)methyl pivalate (1e). The compound 1d (30.0g, 0.085mol) was added to an ice-cold 5 M LPDE solution (17 mL) under N₂ atmosphere and monitored by TLC. The mixture was quenched by 50 mL H₂O, and then extracted by 50 mL CH₂Cl₂ three times. The combined organic phase was washed by 50 mL brine twice, dried by MgSO₄. Solvent was removed under vacuum. The crude product was purified by column chromatography on silica gel (petroleum ether:EtOAc= 5:1)

4-(2-hydroxycyclohexyl)-5-phenyl-2H-1,2,3-triazol-2-yl)methyl pivalate (5a/5b) To the solution of compound 1e (2.0g, 5.6mmol) into 20 mL MeOH at 0 °C, NaBH₄ (0.43g, 11.2mmol) was added. After stirring at 0 °C for 3h, the mixture was quenched by 50 mL H₂O, extracted by 50 mL EtOAc three times. The combined organic layer was washed by 100 mL brine twice, dried by MgSO₄. Solvent was removed under vacuum. The crude product was purified by column chromatography on silica gel (petroleum ether: EtOAc= 5:1).
General Procedure for kinetic resolution of 5a and 5b with CalB.

To the solution of racemic alcohols 5a or 5b (1.07g, 3.0 mmol) in 30 mL of isooctane (HPLC grade), vinyl acetate (688 mg, 8.0 mmol) and lipase B (480 mg) were added. The mixture was then stirred in an orbital shaker (75 °C, 160 rpm) at 24-72h. The mixture was then filtered and the solvent evaporated. The residue was purified by silica gel column chromatography gel (Hexane: EtOAc=4:1) to give desired enantiopure alcohols. The stereochemistry assignment is based on rules for *Pseudomonas cepacia* lipases and *Candida rugosa* lipases (R. J. Kazlauskas, A. N. E. Weissfloch, A.T. Rappaport and L.A. Cuccia, *J. Org. Chem.*, 1991, 56, 2656-2665) thus, the stereochemical assignments are only tentative at this time. The crystal growing for the derivatives is undergoing in our lab, which will help for the conformation of stereochemical assignment.

Asymmetric additions of diethylzinc to aldehyes with Chiral β-hydroxyl TA ligand (5a’):

To a solution of Chiral β-hydroxyl TA ligand 5a’ (0.2 mmol) in toluene (1.0 ml) at 0 °C, 2.0 ml (1.0M, 2 mmol) diethylzinc in hexane was added. After stirring for 30 min, aldehyde (1 mmol in 1 mL toluene) was added slowly. The mixture was then stirred for 48 h at room temperature. The reaction was quenched with saturated ammoniumchloride solution (10 ml), and extracted with diethyl ether (20ml) twice. The combined organic extracts were washed with 30 mL brine twice, and dried by MgSO₄. Evaporate the solvent under vacuum. The residue was purified by chromatography on silica gel (Hexane: EtOAc= 5:1) to give the desired product (6a-6e).
II. Screening table for kinetic resolution of 5a and 5b with CalB.

To the solution of racemic alcohols 5a or 5b (89.2, 0.25 mmol) in 2 mL of isooctane (HPLC grade), vinyl acetate (57.3mg, 0.67 mmol) and lipase B (40 mg) were added. The mixture was then stirred in an orbital shaker (75 °C, 160 rpm) at 24-72h. The mixture was then filtered and the solvent evaporated. The mixture was used directly for HPLC analysis.

The conversion was calculated by:

\[ c = \frac{e_{es}}{e_{es}+e_{ep}} \]

where S for the substrate and P for the product.

The enatoselectivity, S was calculated by

\[ S = \frac{\ln [(1-c)(1-e_{es})]}{\ln [(1-c)(1+e_{ep})]} = \frac{\ln [1-c(1+e_{ep})]}{\ln [1-c(1-e_{es})]} \]

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* reuse for the first time ° reused for the second times ° reused for the three times

HPLC profile for entry 6
III. Compounds Characterization

4-(cyclohex-1-en-1-yl)-5-phenyl-2H-1,2,3-triazol-2-yl)methyl pivalate (1c)
The product was obtained as white solid 35.3g (85% yield). m.p. 76-78 °C. $^1$HNMR (400 MHz, CDCl3): δ 7.68-7.70 (d, J=7.2Hz, 2H), 7.36-7.48(m,3H), 6.26(s, 2H), 6.08(m, 1H), 2.32-2.38(m, 2H), 2.12-2.18(m, 2H), 1.66-1.80(m, 4H), 1.24(s,9H); 13C NMR(100 MHz, CDCl3): δ 177.0, 148.3, 145.7, 131.2, 130.2, 128.5, 128.5, 128.3, 128.2, 74.6, 38.9, 27.5, 27.0, 25.5, 22.6, 21.8. LC-MS(ESI) Calculated for [C$_{20}$H$_{25}$N$_3$O$_2$H]$^+$: 340.1947, Found: 340.1912.

(4-(7-oxabicyclo[4.1.0]heptan-1-yl)-5-phenyl-2H-1,2,3-triazol-2-yl)methyl pivalate (1d).
The product was obtained as white solid 31.2g (80% yield). m.p. 40-42°C. $^1$H NMR (400 MHz, CDCl3): δ 7.80-7.84 (d, J=7.2Hz, 2H), 7.39-7.49 (m, 3H), 6.23 (s, 2H), 3.48-3.51(m, 1H), 2.20-2.30(m, 1H), 1.91-2.20(m, 3H), 1.50-1.51(m, 2H), 1.30-1.42(m, 2H), 1.21(s, 9H); 13C NMR(100 MHz, CDCl3): δ 177.0, 147.1, 130.1, 128.9, 127.6, 128.1 74.4, 65.9, 58.4, 55.2, 38.9, 28.4, 24.2, 19.6, 19.1, 15.2. LC-MS(ESI) Calculated for [C$_{20}$H$_{25}$N$_3$O$_3$H]$^+$: 356.1896, Found: 356.1816.

(4-(2-oxocyclohexyl)-5-phenyl-2H-1,2,3-triazol-2-yl)methyl pivalate (1e).
The product was obtained as light white solid 18.6 g, with 68% yield. m. p. 83-85 °C. $^1$H NMR (400 MHz, CDCl3), δ 7.39-7.54 (m, 5H), 6.28 (s, 1H), 3.90 (t, J=8.5, 1H ), 3.90 (t, J=8.5, 1H ), 1.68-2.7 (m, 8H), 1.21 (s, 9H); 13C NMR (100 MHz, CDCl3) δ 208.57, 177.013, 148.11, 144.71, 130.39, 128.72, 128.67, 128.06, 74.46, 48.68, 41.86, 38.91, 32.76, 27.34, 24.67. LC-MS(ESI): calculated for C$_{20}$H$_{27}$N$_3$O$_3$ [C$_{20}$H$_{25}$N$_3$O$_3$H]$^+$: 356.1896, Found: 356.1812.

4-(2-hydroxycyclohexyl)-5-phenyl-2H-1,2,3-triazol-2-yl)methyl pivalate (5a/5b)
cis-5a was obtained as light yellow oil 1.0 g, with 52% yield. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.4-7.65 (m, 5H), 6.28 (s, 1H), 4.17 (m, 1H), 3.10 (m, 1H), 1.25-2.1 (m, 8H), 1.23 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 176.92, 150.14, 146.89, 130.33, 128.86, 128.71, 128.08, 74.23, 67.91, 39.16, 38.92, 32.16, 26.91, 26.89, 25.88, 19.50. LC-MS(ESI): calculated for [C$_{20}$H$_{27}$N$_3$O$_3$H]$^+$: 358.2052, Found: 358.2119.

trans-5b was obtained as light yellow oil 0.83 g, with 43% yield. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.4-7.65 (m, 5H), 6.28 (s, 1H), 4.15 (m, 1H), 2.98 (m, 1H), 1.25-2.1 (m, 8H), 1.23 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 177.02, 149.19, 147.85, 130.56, 128.73, 128.58, 128.02, 74.39, 73.44, 43.57, 38.91, 34.41, 31.86, 26.92, 25.66, 24.84. LC-MS(ESI): calculated for [C$_{20}$H$_{27}$N$_3$O$_3$H]$^+$: 358.2052, Found: 358.2119.

cis-(−)-5a was obtained as colorless liquid. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: (ppm) 7.4-7.65 (m, 5H), 6.28 (s, 2H), 4.17 (m, 1H), 3.10 (m, 1H), 1.25-2.1 (m, 8H), 1.23 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 176.92, 150.14, 146.89, 130.33, 128.86, 128.71, 128.08, 74.23, 67.91, 39.16, 38.92, 32.16, 26.91, 26.89, 25.88, 19.50. LC-MS(ESI): calculated for [C$_{22}$H$_{30}$N$_3$O$_4$H]$^+$: 358.2052, Found: 358.2119. Enantiomeric excess was determined by HPLC analysis with a Chiralcel OD-H column (hexane: 2-propanol = 97:3, 1.0 mL/min, 254 nm UV detector), t$_{\text{minor}}$ = 11.93 min and t$_{\text{major}}$ = 7.59 min. 99% $ee$. [$\alpha$]$_D$ = -33.9 (c=1.0, CHCl$_3$).

cis-(+)-5a' was obtained as yellow liquid. $^1$H NMR (400 MHz, CDCl$_3$); $\delta$ $\delta$ 7.57 (dt, $J$ = 8.1, 1.8 Hz, 2H), 7.47-7.37 (m, 3H), 6.24 (s, 2H), 5.21 (dd, $J$ = 4.8, 2.4 Hz, 1H), 3.24 (dt, $J$ = 10.8, 3.4 Hz, 1H), 2.17-2.10 (m, 1H), 2.06 (s, 3H), 2.00-1.88 (m, 5H), 1.79-1.53 (m, 5H), 1.44-1.36 (m, 2H), 1.22-1.18 (m, 9H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 176.7, 170.9, 170.1, 147.8, 147.2, 130.6, 128.58, 128.41, 128.1, 74.2, 70.5, 60.2, 38.7, 37.1, 29.7, 26.8, 26.5, 24.6, 20.98, 20.87, 20.7, 14.1. HRMS for [C$_{22}$H$_{30}$N$_3$O$_4$]$^+$: 400.2231, Found: 400.2233.
trans-\((+)-5b\) was obtained as colorless liquid. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: (ppm) 7.4-7.65 (m, 5H), 6.28 (s, 2H), 4.15 (m, 1H), 2.98 (m, 1H), 1.25-2.1 (m, 8H), 1.23 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: (ppm) 177.02, 149.19, 147.85, 130.56, 128.73, 128.58, 128.02, 74.39, 73.44, 43.57, 38.91, 34.41, 31.86, 26.92, 25.66, 24.84. LC-MS(ESI): calculated for [C$_{20}$H$_{27}$N$_3$O$_3$H]$^+$: 358.2052, Found: 358.2119. Enantiomeric excess was determined by HPLC analysis with a Chiralcel OD-H column (hexane: 2-propanol = 97:3, 1.0 mL/min, 254 nm UV detector), $t_{\text{minor}}$ = 9.41 min and $t_{\text{major}}$ = 9.88 min. 99% ee. $[\alpha]_{D}^{20} = +32.3$ (c 1.0, CHCl$_3$).

trans-\((-)-5b^*\) was obtained as yellow liquid $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.72-7.69 (m, 2H), 7.49-7.39 (m, 3H), 6.24 (d, $J$ = 0.2 Hz, 2H), 5.29 (s, 2H), 5.08 (td, $J$ = 10.6, 4.3 Hz, 1H), 3.12 (ddd, $J$ = 11.9, 10.5, 3.9 Hz, 1H), 2.21-2.17 (m, 1H), 2.03 (d, $J$ = 3.5 Hz, 1H), 1.99-1.94 (m, 1H), 1.86-1.74 (m, 5H), 1.53-1.25 (m, 5H), 1.24-1.19 (m, 8H). 13-C NMR (101 MHz; dcdl3): $\delta$ 176.7, 170.9, 169.6, 161.5, 148.3, 147.4, 130.6, 128.59, 128.55, 128.51, 128.36, 128.23, 128.20, 128.05, 127.99, 76.4, 74.2, 60.2, 53.3, 39.7, 38.7, 32.0, 31.8, 26.7, 25.2, 24.2, 20.8, 14.1. HRMS for [C$_{22}$H$_{30}$N$_3$O$_4$]$^+$: 400.2231, Found: 400.2233.

**(S)-1-(4-Chlorophenyl)-1-propanol**

6a was obtained as light yellow oil. 90% yield. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.29 (d, $J$ = 8.4 Hz, 2H), 7.24(d, $J$ = 8.4 Hz, 2H), 4.57 (t, $J$ = 6.8 Hz, 1H), 2.12 (s, 1H), 1.82-1.66 (m, 2H), 0.90 (t, $J$ = 7.2 Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 143.0, 133.0, 128.4, 127.3, 75.2, 31.9, 9.9. Enantiomeric excess was determined by HPLC analysis with a Chiralcel OD-H column (hexane: 2-propanol = 97:3, 1.0 mL/min, 254 nm UV detector), $t_S$ = 27.10 min for \((S)\) and $t_R$ = 31.10 min for \((R)\), 99% ee \((S)\).

**(S)-1-(4-Methoxyphenyl)-1-propanol (6b)**
**6b** was obtained as light yellow oil. 90% yield. $^1$H NMR (400 MHz, CDCl$_3$): δ 7.36–7.25 (m, 2H), 6.90–6.86 (m, 2H), 4.54 (t, J = 6.7 Hz, 1H), 3.80 (s, 3H), 1.84–1.69 (m, 3H), 0.89 (t, J = 7.2 Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 158.8, 136.9, 127.2, 113.7, 75.4, 55.2, 31.7, 10.1. Enantiomeric excess was determined by HPLC analysis with a Daicel Chiralcel OD-H column, (hexane: 2-propanol = 97:3, 1.0 mL/min, 254 nm UV detector), $t_S = 18.38$ min for (S) and $t_R = 15.79$ min for (R), 60% ee (S)

![Image of 6c](image1.png)

**(S)-1-(3-Methoxyphenyl)-1-propanol (6c)**

**6c** was obtained as yellow oil. 87% yield. $^1$H NMR (400 MHz, CDCl$_3$): δ 7.26 (t, J = 8.0 Hz, 2H), 6.91 (d, $J = 6.8$ Hz, 2H), 6.83–6.80 (m, 1H), 4.57 (t, $J = 6.5$ Hz, 1H), 3.81 (s, 3H), 1.85–1.71 (m, 2H), 0.92 (t, $J = 7.4$ Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 158.8, 136.9, 127.2, 113.7, 75.4, 55.2, 31.7, 10.1. Enantiomeric excess was determined by HPLC analysis with a Daicel Chiralcel OD-H column, (hexane: 2-propanol = 97:3, 1.0 mL/min, 254 nm UV detector), $t_S = 23.21$ min for (S) and $t_R = 21.95$ min for (R), 90% ee (S)

![Image of 6d](image2.png)

**(S)-1-(2-Methoxyphenyl)-1-propionanolic acid (6d)**

**6d** was obtained as yellow oil. 75% yield. $^1$H NMR (400 MHz, CDCl$_3$): δ 7.30–7.23 (m, 1H), 6.95–6.86 (m, 2H), 4.60 (t, $J = 6.4$ Hz, 1H), 3.84 (s, 3H), 1.77–1.86 (m and s overlap, 3H), 0.95 (t, $J = 7.2$ Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 159.7, 146.3, 129.4, 118.3, 112.9, 111.4, 75.9, 55.2, 31.9, 10.1. Enantiomeric excess was determined by HPLC analysis with a Daicel Chiralcel OD-H column (hexane: ethanol = 97:3, 0.5 mL/min, 254 nm UV detector), $t_S = 16.55$ min for (S) and $t_R = 18.41$ min for (R), 90% ee (S)

![Image of 6e](image3.png)

**(S)-1-(2-Chlorophenyl)-1-propanol (6e)**

**6e** was obtained as yellow oil. 90% yield. $^1$H NMR (400 MHz, CDCl$_3$): δ 7.55 (dd, $J = 1.6$ Hz, $J = 7.6$ Hz, 1H), 7.36–7.25 (m, 2H), 7.25–7.16 (m, 1H), 5.10–5.05 (dd, $J = 4.8$ Hz, $J = 7.6$ Hz, 1H), 2.14 (s, 1H), 1.90–1.71 (m, 2H), 1.01 (t, $J = 7.2$ Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 141.9, 131.9, 129.3, 128.3, 127.1, 127.0, 71.9, 30.4, 10.1. Enantiomeric excess was determined by HPLC analysis with a Daicel Chiralcel OD-H column (hexane: ethanol = 97:3, 0.5 mL/min, 254 nm UV detector), $t_S = 19.00$ min for (S) and $t_R = 20.45$ min for (R), 90% ee (S)
2-propanol = 97:3, 1.0 mL/min, 254 nm UV detector), $t_S = 8.68$ min for (S) and $t_R = 10.19$ min for (R). 60% ee (S)
HPLC Profile
\[ \text{Detector A (254 nm)} \]

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\[ \text{Totals} \]

|               |            | 100.000  |         |         | 100.000  |

\[ \text{Detector A (254 nm)} \]

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\[ \text{Totals} \]

|               |            | 39298066 | 100.000 | 2351280 | 100.000  |
6b
59% ee (S)

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VI. NMR spectra data
(+)-3a $^1$HNMR
400 MHz, CD$_3$OD
(+)-3a $^{13}$CNMR
100 MHz, CD$_3$OD
$^{1}$H NMR
$400 \text{ MHz, CDCl}_3$
$1^3$C NMR
100 MHz, CDCl$_3$
**1d** $^1$H NMR
400 MHz, CDCl$_3$
$^{13}$C NMR
100 MHz, CDCl$_3$

1d
1e $^1$HNMR
400 MHz, CDCl$_3$
Ph

1e $^{13}C$NMR
100 MHz, CDCl$_3$
5a $^1$HNMR
400 MHz, CDCl$_3$
$^{13}$C NMR
100 MHz, CDCl$_3$
$^{1}HNMR$

$400$ MHz, CDCl$_3$
$\text{Ph}$ $5b \text{CNMR}$

100 MHz, CDCl$_3$
(+)-5a \textsuperscript{1}HNMR
400 MHz, CDCl\textsubscript{3}
(+)-5a' $^{13}$C NMR
100 MHz, CDCl$_3$
(-)-5b' $^1$HNMR
400 MHz, CDCl$_3$
6a $^1$HNMR
400 MHz, CDCl$_3$
$^{13}$C NMR
100 MHz, CDCl$_3$
$6b$ $^1$HNMR
400 MHz, CDCl$_3$
$\text{MeO}$

$\text{Et}$

$\text{OH}$

$\text{6b}$ $^{13}\text{CNMR}$

100 MHz, CDCl$_3$
6c $^1$HNMR
400 MHz, CDCl$_3$
$^{13}$C NMR
100 MHz, CDCl$_3$
6d $^1$HNMR
400 MHz, CDCl$_3$
6d $^{13}$CNMR
100 MHz, CDCl$_3$
$^{13}$C NMR, 100 MHz, CDCl$_3$