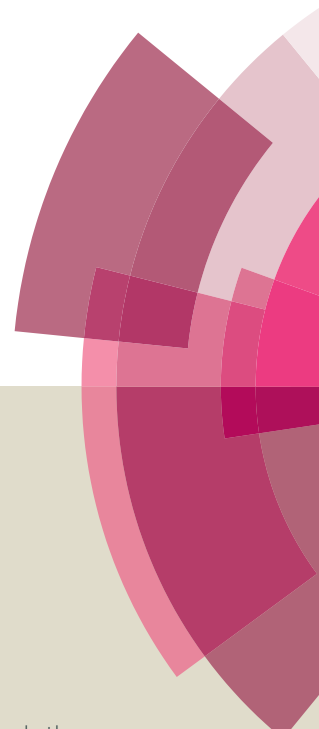
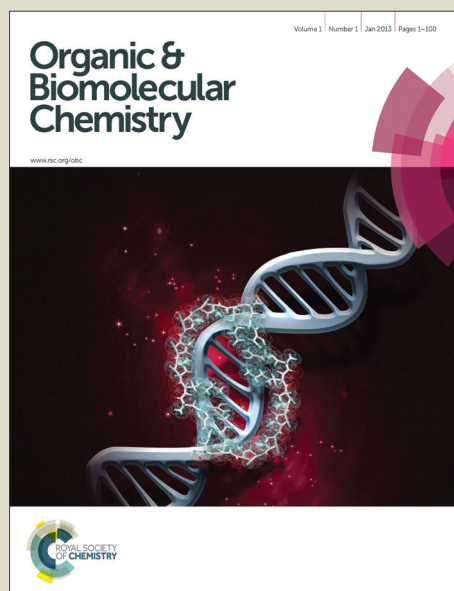


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Paper

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

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Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

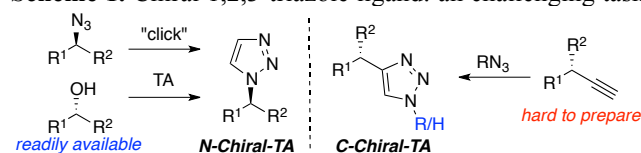
DOI: 10.1039/b000000x

We describe herein the first facile synthesis of chiral triazoles through side chain functionalization. Readily available C-vinyl triazoles were used as starting materials, followed by sequential epoxidation, rearrangement and reduction to give the corresponding hydroxyl-triazole. The CalB lipase catalyzed kinetic resolution gave enantiomerically pure, (>99% ee) chiral triazoles in excellent yield. This new chiral TAs were also successfully applied as ligands in asymmetric addition of diethylzinc towards aldehyde.

Introduction

Since the report of Cu-catalyzed azide-alkyne cycloaddition (often referred to "Click chemistry"), the 1,2,3-triazole (TA) has received tremendous attentions in chemical, material and biological research.¹ The recent development of triazole as a ligand to adjust transition metal reactivity has further extended its applications.² For this reason, more triazole based metal complexes were discovered with interesting new reactivity. However, there are few examples been reported as using triazole ligand in asymmetric catalysis, mainly due to the limited accesses to enantiomerically pure triazoles.

Scheme 1. Chiral 1,2,3-triazole ligand: an challenging task.



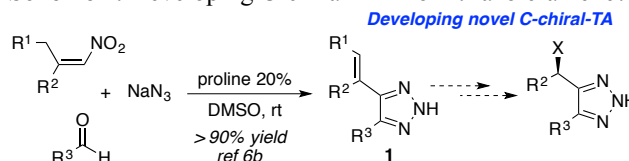
The chirality of triazole is derived from the substituent group, either on the carbon or nitrogen, therefore providing two basic categories of chiral triazole

ligands, the N-chiral-TA and the C-chiral-TA (Scheme 1). Traditionally the N-chiral-TA can be prepared from chiral azides using Click Chemistry. More recently, we reported the stereospecific addition of NH-triazole toward chiral alcohol under Mitsunobu condition.³ This method allowed for the synthesis of N-chiral-TA from readily available enantiomerically enriched chiral alcohols, which greatly extended the scope of these types of chiral TA derivatives. When comparing with N-chiral-TA, the C-chiral-TA is potentially a more interesting ligand since it can serve as either neutral (L) or anionic (X) ligand. However, the challenges to access enantiomerically enriched alkynes limited its development. Currently, one successful reported strategy to prepare C-chiral-TA is the Click Chemistry of alkynes-functionalized BINOL motifs, which took many steps from expensive starting materials.⁴ Thus, a new synthesis of enantiomerically pure C-chiral-TA ligand from readily available starting materials is highly desirable. Herein, we report a highly efficient new route to reach triazole based N, O-bidentate ligands from the readily available vinyl-triazole derivatives. Through the successful resolution with CalB lipase, a new class of C-chiral-TA ligands was prepared in gram scale with excellent ee (> 99%).

Results and discussion

During the past several years, our successes on using triazole as ligand in new metal catalyst design has urged us to develop new methods for triazole synthesis and post-triazole functionalization.^{5,6} Among them, the L-proline catalyzed three-component condensation (nitroalkene, aldehyde and azide) is one interesting method for the synthesis of 4,5-disubstituted-NH triazole **1**.^{6b}

Scheme 2. Developing C-chiral-TA from triazole-alkene?



As shown in Scheme 2, this method allowed the synthesis of C4-vinyl triazole **1** in one step with good yield.

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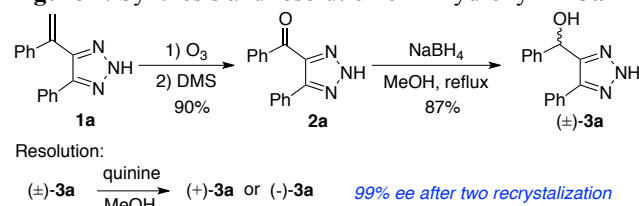
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† Electronic Supplementary Information (ESI) available: experimental details, and ¹HNMR, ¹³CNMR for all compounds. See http://dx.doi.org/10.1039/b000000x/

With the interest in extending triazole ligands into asymmetric catalysis, we turned our attention into developing new C-chiral-TA compounds through converting C4-vinyl group into functional groups containing stereogenic centers. Notably, this proposed strategy belongs to "post-triazole" functionalization and thus reactivity competition with the triazole ring, which is largely unknown in literature, will be the key issue of great interest for general triazole chemistry.

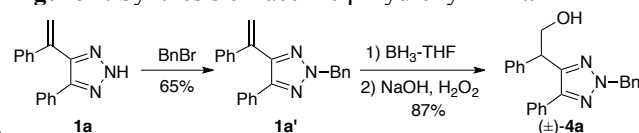
Oxidation of olefin to either ketone or diol will be one obvious to introduce the functionality. Considering the potential problems with metal catalyst coordination to NH-triazole (such as OsO₄ in dihydroxylation), we started exploring the oxidation of NH-triazole **1a** with ozone. Interestingly, a clean reaction was received with ketone NH-triazole **2a** obtained in 90% yield. Notably, no triazole N-oxide was observed, which indicated the low reactivity of triazole ring toward oxidation. Reduction of **2a** gave triazole alcohol **3a** in excellent yield.

Figure 1. Synthesis and resolution of α -hydroxy TA **3a**



After screening several resolution conditions, quinine was identified as the optimal reagent to resolve **3a** enantiomers. Recrystallization (twice) gave the enantiomerically pure (+)-**3a** (>99% ee). This method was exciting since it not only offered a new approach to access C-chiral-TA, but also confirmed the tolerability of the triazole ring towards certain oxidation and reduction conditions. However, one big drawback of this α -hydroxyl triazole **3a** was the stability of the benzylic stereogenic center. In fact, treating enantiomerically pure (+)-**3a** with Sc(OTf)₃ or Et₂Zn resulted in racemization over time (formation of racemic mixture after 24 hours, rt). To avoid racemization, we switched our effort to develop a synthetic route for β -hydroxy-triazole.

Figure 2. Synthesis of racemic β -hydroxy TA **4a**



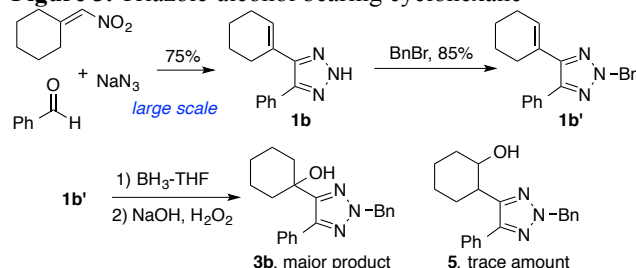
Reaction of NH-triazole **1a** with boranes (such as BH₃ and 9-BBN) failed to give hydroboration product. This is likely due to the formation of triazole borane complexes as we reported previously.⁷ Protecting NH-triazole to N2-benzyl triazole (**1a'**) avoided this problem, giving the desired *anti*-Markovnikov hydroxylation product **4a** (Figure 2). However, despite the effort, no good resolution methods were identified at this moment.

Nevertheless, the successful synthesis of **4a** confirmed the feasibility of developing β -hydroxy TA as a new type of C-chiral-TA.

The *trans*-1,2-disubstituted cyclohexane moiety is one well known framework in organic synthesis. The representative *trans*-1,2-cyclohexanyl diamine and its derivative salen have been widely applied into many asymmetric transformations.⁸ Encouraged by the results shown above, we put our attention to the β -hydroxy TA bearing cyclohexane ring.

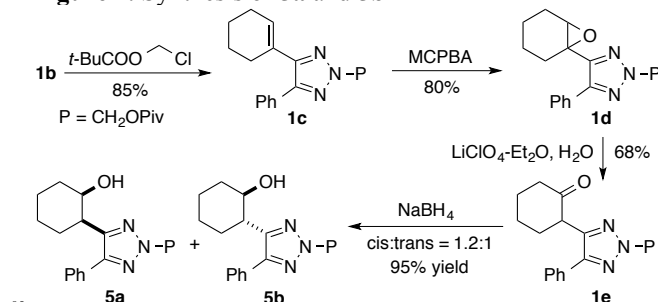
As shown in Figure 3, the cyclohexane-NH-TA **1b** could be readily prepared in a large scale using our previously reported method. However, the hydroboration-oxidation gave α -hydroxyl-TA **3b** as the dominant product with only trace amount of desired β -hydroxyl TA. Thus, to prepare the proposed cyclohexane-hydroxyl-triazole, a new synthetic route is necessary.

Figure 3. Triazole-alcohol bearing cyclohexane



An alternative route was proposed to reach β -hydroxyl-TA **5**. This new design included three steps: A) alkene epoxidation; B) rearrangement to ketone, and; C) ketone reduction to reach the desired β -hydroxyl-TA **5**. With this optimized route (Figure 4), the desired β -hydroxyl-TA was synthesized in good yields. Notably, the labile methylene pivalate protecting group survived these conditions, providing synthetic handle for further optimization on the triazole nitrogen position. Reduction of ketone **1e** gave mixture of *cis* (**5a**) and *trans* (**5b**) isomers, which could be easily isolated by column chromatography. Overall, this new route allowed facile synthesis of the desired β -hydroxyl-TA in a large scale.

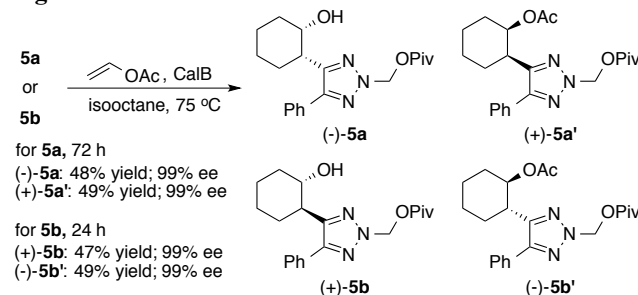
Figure 4. Synthesis of **5a** and **5b**



Attempts to resolve **5a** or **5b** using tartaric acid and quinine were unsuccessful. We then turned our attention to a kinetic resolution. Compared with chemical resolution (such as Lewis base catalyzed asymmetric esterification),

enzyme promoted biocatalysis has some unique advantages, including mild conditions, high efficiency and overall lower cost. *Candida antarctica* lipase B (CalB) is a thermostable lipase that has been widely used as an enantioselective biocatalyst for effective kinetic resolution of secondary alcohol and primary amines.⁹ After brief screening, isooctane was identified as the optimal solvents and excellent *ee* was obtained from both *cis* and *trans* isomers (see detailed condition screening in SI).¹⁰

Figure 5. Kinetic resolution of **5a** and **5b** with CalB



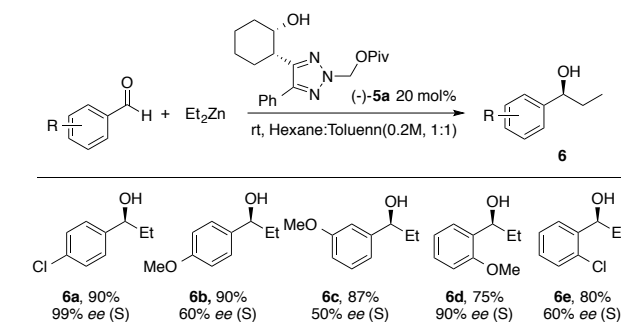
As shown in **Figure 5**, under the optimal conditions, the desired *trans*-esterification reaction was achieved for both *cis*-**5a** and *trans*-**5b** isomer with excellent selectivity with *S* > 200 obtained for both **5a** and **5b**. It is important to notice here that CalB could be recycled, giving almost identical reactivity after being reused for three times and slightly lower selectivity after that. The recyclability greatly reduced the cost of this synthesis and made it very practical.

Overall, the synthesis of enantiomerically pure TA is an exciting development, and the development of **5a/5b** into N-N and N-P type ligands is certainly reasonable and is currently being investigated in our group. To demonstrate the reactivity of this new N-O type ligand, the asymmetric Et₂Zn addition to an aldehyde was explored.¹¹ As shown in **Figure 6**, under the optimal conditions, modest to excellent stereoselectivity was obtained. These results confirmed the viability of the using these chiral hydroxyl-triazole compounds in asymmetric catalysis. Broader investigations on the reactivity and selectivity of these new class ligands are currently underway in our group and will be reported in due course.

Conclusions

Herein, we describe the synthesis and resolution of chiral hydroxyl-triazoles. The synthesis used simple and low cost starting materials. The overall procedure was efficient and the products were prepared in excellent overall yields. Considering the great interest in searching for novel chiral ligand for asymmetric synthesis and the recent advance in the synthesis and application of 1,2,3-triazole as a ligand, this chiral ligand will be of great interest for catalytic approaches enlisting asymmetric catalysts.

Figure 6. Hydroxyl-TA promoted asymmetric addition of diethylzinc to aldehyde.



Experimental

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. ¹H-NMR and ¹³C-NMR spectra were recorded on Varian 400 MHz spectrometers and Bruker 400 MHz spectrometers. Chemical shifts were reported relative to internal tetramethylsilane (δ 0.00 ppm) or CDCl₃ (δ 7.26 ppm), CD₃CD₂ (δ 3.31 ppm) for ¹H and CDCl₃ (δ 77.0 ppm), CD₃CD₂ (δ 49.75 ppm) for ¹³C. 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: [α]_D²⁰ (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 ApexII mass spectrometer. Anhydrous Toluene was purchased from Beijing Chemical Reagent Co. and distilled with sodium, immediately before use.

General Procedure for the resolution of α-hydroxyl TA

3a: To a solution of **2a** (2.35 g, 9.36 mmol, 1 eq.) in dry MeOH (40 mL), Quinine (1.82 g, 5.61 mmol, 0.6 eq.) in 10 mL MeOH was added dropwise. Keep stirring for another 2 h under reflux and then allow the mixture cool to rt. The reaction mixture was allowed to cool to 0 °C in ice bath for another 10 min. The resulting white solid was collected through filtration and diluted with 100 mL ether acetate. The mixture was then washed with diluted HCl and brine three times, dried by MgSO₄. After removing the solvent, the residue was recrystallized with Toluene/ MeOH twice to give corresponding (+)-**3a** as white solid.

Phenyl(5-phenyl-2H-1,2,3-triazol-4-yl)methanol (+)-**3a**

¹H-NMR (400 MHz; CD₃OD): δ 6.03-6.00 (m, 2H), 5.81-

5.73 (m, 5H), 5.70-5.66 (m, 2H), 5.64-5.61 (m, 1H), 2.97 (s, 1H). ^{13}C -NMR (100 MHz; CD_3OD): δ 142.5, 128.93, 128.77, 128.65, 128.46, 128.0, 127.0, 67.9. Enantiomeric excess was determined by HPLC on Chiralpak OD-H column (n-hexane-isopropanol 85:15 V/V, flow rate 0.5 mL/min, 254 nm), major enantiomer t_R = 18.9 min, minor enantiomer t_S = 14.3 min, 99 % ee. LC-MS(ESI) Calculated for $[\text{C}_{15}\text{H}_{13}\text{N}_3\text{OH}]^+$: 252.1131, Found: 252.1131.

General Procedure for synthesis of compound 5a and 5b:

(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_2CO_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). The product was obtained as white solid 35.3g (85% yield). m.p. 76-78 °C. ^1H NMR (400 MHz, CDCl_3): 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); ^{13}C NMR(100 MHz, CDCl_3): 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 $[\text{C}_{20}\text{H}_{25}\text{N}_3\text{O}_2\text{H}]^+$: 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). Compound 1c (35.0g, 0.11mol) was dissolved in 50ml dry DCM at 0 °C in ice-bath under N_2 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% Na_2CO_3 solution and brine. The organic phase was dried with MgSO_4 and concentrated under vacuum. The crude product was purified by column chromatography on silica gel (petroleum ether: EtOAc= 8:1). The product was obtained as white solid 31.2g (80% yield). m.p. 40-42°C. ^1H NMR (400 MHz, CDCl_3): 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); ^{13}C NMR(100 MHz, CDCl_3): 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 $[\text{C}_{20}\text{H}_{25}\text{N}_3\text{O}_3\text{H}]^+$: 356.1896, Found: 356.1816.

(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 N_2 atmosphere and monitored by TLC. The mixture was quenched by 50 mL H_2O , and then extracted by 50 mL CH_2Cl_2 three times. The combined organic phase was washed by 50 mL brine twice, dried by MgSO_4 . Solvent was removed under vacuum. The crude product

was purified by column chromatography on silica gel (petroleum ether:EtOAc= 5:1) and was obtained as light white solid 18.6 g, with 68% yield. m.p. 83-85 °C. ^1H NMR (400 MHz, CDCl_3), 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); ^{13}C NMR (100 MHz, CDCl_3) 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 $\text{C}_{20}\text{H}_{27}\text{N}_3\text{O}_3$ $[\text{C}_{20}\text{H}_{25}\text{N}_3\text{O}_3\text{H}]^+$: 356.1896, Found: 356.1812.

(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, NaBH_4 (0.43g, 11.2mmol) was added. After stirring at 0 °C for 3h, the mixture was quenched by 50 mL H_2O , extracted by 50 mL EtOAc three times. The combined organic layer was washed by 100 mL brine twice, dried by MgSO_4 . Solvent was removed under vacuum. The crude product was purified by column chromatography on silica gel (petroleum ether: EtOAc= 5:1).

cis-5a was obtained as light yellow oil 1.0 g (52% yield) ^1H NMR (400 MHz, CDCl_3) δ 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) δ 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 $[\text{C}_{20}\text{H}_{27}\text{N}_3\text{O}_3\text{H}]^+$: 358.2052, Found: 358.2119.

trans-5b was obtained as light yellow oil 0.83g (43 % yield). ^1H NMR (400 MHz, CDCl_3) δ 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) δ 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 $[\text{C}_{20}\text{H}_{27}\text{N}_3\text{O}_3\text{H}]^+$: 358.2052, Found: 358.2119.

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 (-)-5a and (+)-5b.

Asymmetric additions of diethylzinc to aldehydes 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 under N_2 , 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 phase

was washed with 30 mL brine twice, and dried by MgSO_4 . 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**).

Acknowledgements

We thank the NSF (CHE-1362057 and CHE-1228336) and NSFC (21228204) for financial support.

Notes and references

- (a) H. C. Kolb, M. G. Finn and K. B. Sharpless, *Angew. Chem. Int. Ed.*, 2001, **40**, 2004; (b) H. C. Kolb and K. B. Sharpless, *Drug Discovery Today*, 2003, **8**, 1128-1137; (c) W. H. Binder and R. Sachsenhofer, *Macromol. Rapid Commun.*, 2007, **28**, 15-54; (d) J. E. Moses and A. D. Moorhouse, *Chem. Soc. Rev.*, 2007, **36**, 1249-1262; (e) G. C. Tron, T. Pirali, R. A. Billington, P. L. Canonico, G. Sorba and A. A. Genazzani, *Med. Res. Rev.*, 2008, **28**, 278-308; (f) C. R. Becer, R. Hoogenboom and U. S. Schubert, *Angew. Chem. Int. Ed.*, 2009, **48**, 4900-4908; (g) R. K. Iha, K. L. Wooley, A. M. Nystrom, D. J. Burke, M. J. Kade and C. J. Hawker, *Chem. Rev.*, 2009, **109**, 5620-5686.
- D. Huang, P. Zhao and D. Astruc, *Coord. Chem. Rev.*, 2014, **272**, 145-165.
- W. Yan, T. Liao, O. Tuguldur, C. Zhong, J. L. Petersen and X. Shi, *Chem. Asian J.*, 2011, **6**, 2720-2724.
- (a) S. Beckendorf and O. G. Mancheno, *Synthesis*, 2012, **44**, 2162-2172; (b) A. J. Neel, J. P. Hehn, P. F. Tripet and F. D. Toste, *J. Am. Chem. Soc.*, 2013, **135**, 14044-14047.
- (a) H. Duan, S. Sengupta, J. L. Petersen, N. G. Akhmedov and X. Shi, *J. Am. Chem. Soc.*, 2009, **131**, 12100; (b) H. Duan, S. Sengupta, J. L. Petersen and X. Shi, *Organometallics*, 2009, **28**, 2352-2355; (c) W. Liao, Y. Chen, Y. Liu, H. Duan, J. L. Petersen and X. Shi, *Chem. Commun.*, 2009, 6436-6438; (d) W. Yan, Q. Wang, Y. Chen, J. L. Petersen and X. Shi, *Org. Lett.*, 2010, **12**, 3308-3311; (e) W. Yan, X. Ye, N. G. Akhmedov, J. L. Petersen and X. Shi, *Org. Lett.*, 2012, **14**, 2358-2361; (f) X. Ye, Z. He, T. Ahmed, K. Weise, N. G. Akhmedov, J. L. Petersen and X. Shi, *Chem. Sci.*, 2013, **4**, 3712-3716; (g) R. Cai, D. Wang, Y. Chen, W. Yan, N. R. Geise, S. Sharma, H. Li, J. L. Petersen, M. Li and X. Shi, *Chem. Commun.*, 2014, **50**, 7303-7305; (h) Q. Wang, S. E. Motika, N. G. Akhmedov, J. L. Petersen and X. Shi, *Angew. Chem. Int. Ed.*, 2014, **53**, 5418-5422; (i) Y. Xi, B. Dong, E. J. McClain, Q. Wang, T. L. Gregg, N. G. Akhmedov, J. L. Petersen and X. Shi, *Angew. Chem. Int. Ed.*, 2014, **53**, 4657-4661; (j) Y. Xi, D. Wang, X. Ye, N. G. Akhmedov, J. L. Petersen and X. Shi, *Org. Lett.*, 2014, **16**, 306-309; (k) X. Ye and X. Shi, *Org. Lett.*, 2014, **16**, 4448-4451.
- (a) Y. Chen, Y. Liu, J. L. Petersen and X. Shi, *Chem. Commun.*, 2008, 3254-3256; (b) S. Sengupta, H. Duan, W. Lu, J. L. Petersen and X. Shi, *Org. Lett.*, 2008, **10**, 1493-1496.
- W. Liao, Y. Chen, Y. Liu, H. Duan, J. L. Petersen and X. Shi, *Chem. Commun.*, 2009, 6436-6438.
- (a) T. Katsuki, *Coord. Chem. Rev.*, 1995, **140**, 189-214; (b) L. Canali and D. C. Sherrington, *Chem. Soc. Rev.*, 1999, **28**, 85-93; (c) T. Katsuki, *Chem. Soc. Rev.*, 2004, **33**, 437-444.
- (a) E. M. Anderson, M. Karin and O. Kirk, *Biocatal. Biotransform.*, 1998, **16**, 181-204; (b) B. A. Persson, A. L. E. Larsson, M. Le Ray and J. E. Backvall, *J. Am. Chem. Soc.*, 1999, **121**, 1645-1650; (c) J. Gonzalez-Sabin, V. Gotor and F. Rebollo, *Tetrahedron: Asymmetry*, 2004, **15**, 481-488; (d) O. Pamies and J. E. Backvall, *Trends Biotechnol.*, 2004, **22**, 130-135; (e) A.-B. L. Fransson, Y. Xu, K. Leijondahl and J.-E. Baekvall, *J. Org. Chem.*, 2006, **71**, 6309-6316; (f) V. Gotor-Fernandez, E. Busto and V. Gotor, *Adv. Synth. Catal.*, 2006, **348**, 797-812; (g) A. Bajaj, P. Lohan, P. N. Jha and R. Mehrotra, *J. Mol. Catal. B: Enzym.*, 2010, **62**, 9-14.

- The stereochemistry assignment is based on rules for *Pseudomonas cepacia* lipases and *Candida rugosa* lipases, 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. See: (a) H. Honig and P. S. Wessertal, *J. Chem. Soc. Perkin Trans.* 1989, **1**, 2341-2345. (b) R. J. Kazlauskas, A. N. E. Weissfloch, A. T. Rappaport and L. A. Cuccia, *J. Org. Chem.*, 1991, **56**, 2656-2665; (c) A. Ghanem and H. Y. Abou-Enein, *Tetrahedron: Asymmetry*, 2004, **15**, 3331-3351.
- (a) J. C. Anderson and M. Harding, *Chem. Commun.*, 1998, 393-394; (b) Y. J. Wu, H. Y. Yun, Y. S. Wu, K. L. Ding and Y. Zhou, *Tetrahedron: Asymmetry*, 2000, **11**, 3543-3552; (c) D. Steiner, S. G. Sethofer, C. T. Goralski and B. Singaram, *Tetrahedron: Asymmetry*, 2002, **13**, 1477-1483; (d) Q. S. Guo, B. Liu, Y. N. Lu, F. Y. Jiang, H. B. Song and J. S. Li, *Tetrahedron: Asymmetry*, 2005, **16**, 3667-3671; (e) R. Dave and N. A. Sasaki, *Tetrahedron: Asymmetry*, 2006, **17**, 388-401.