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Asymmetric pinacol coupling reaction catalyzed by dipeptide-type Schiff bases

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Abstract

Several dipeptide Schiff bases and its mimics were conveniently synthesized from natural amino acids. Their titanium complexes were investigated in pinacol coupling reaction for the first time; good yields, high diastereoselectivity and moderate enantioselectivity were obtained.

Keywords: Peptide Schiff bases; Titanium complexes; Pinacol coupling

1. Introduction

Much attention has been focused on reductive coupling of carbonyl compounds, also namely pinacol coupling, which has been proved to be an efficient method for vicinal diol generation and carbon–carbon bond formation simultaneously [1]. Since the pioneering contributions in this field by Mukaiyama et al. [2] and McMurry [3], the catalytic pinacol coupling reaction has been accomplished in moderate to high diastereoselectivity using various metals including Na [4], Zn [5], Mg [6], Mn [7], Sn [8], Al [9], Ce [10], Sm [11], In [12], V [13], Ti [14] and Cr [15]. However, high enantioselectivity has remained elusive through stoichiometric as well as catalytic protocols. Recently, good to high enantioselectivity has been achieved using titanium-Schiff base complexes [7] and titanium-SALEN complexes [16] by different groups, respectively. Especially, chromium-TBOxH complex developed by Yamamoto and co-workers [17] represents the best result to date. Our group [18] has improved a new titanium-Schiff base complex for the pinacol coupling of aromatic aldehydes, excellent diastereoselectivities and high enantioseletivities have been obtained. Continuously, we have further prepared a series of peptide-Schiff bases and its mimics then used these ligands to catalyze the pinacol coupling reaction. Herein, we would like to report the corresponding results.

2. Experimental

2.1. General

All reactions were carried out under inert atmosphere. Commercial reagents were used without further purification. THF was dried and freshly distilled from sodium-benzophenone under an atmosphere of dry nitrogen. Dichloromethane and acetonitrile were distilled from P_2O_5 before use. Liquid aldehydes and trimethylchlorosilane were freshly distilled. Solid aldehydes were recrystallized before use. Melting points were measured by XT-4 apparatus and uncorrected. Optical rotations were determined by WZZ-1 rotation spectrometer. NMR spectra were measured on a Bruker av300 spectrometer (300 MHz) by using $CDCl_3$ as solvent and TMS as internal standard. IR spectra were recorded on a Bruker VECTOR-22 (KBr) spectrometer. Elemental analyses were performed on a Vari E spectrometer. HPLC analyses were carried out by AGILENT1100 SERIES spectrometer. The diastereomeric excesses were determined by HPLC or ^{1}HNMR and enantiomeric excesses were determined by HPLC with chiral columns.

2.2. Preparation of N-[(2-hydroxy-1-benzyl)methylene]-(S)-valyl-(S)-valine methyl ester (*1a*, Sal-S-Val-S-Val-OMe)

To a suspension of (*S*)-valine methyl ester hydrochloride (1.68 g, 10 mmol) in anhydrous THF (20 mL) was added triethylamine (1.39 mL, 10 mmol), and the mixture was stirred

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at room temperature for 1 h to afford the free amino acid methyl ester. To the vigorously stirred solution of carbobenzoxy-(*S*)-valine (2.51 g, 10 mmol) in THF (15 mL) was added triethylamine (1.39 mL, 10 mmol) and isobutyl chloroformate (1.31 mL, 10 mmol) at −10 °C. To this mixture, the suspension of (*S*)-valine methyl ester was added and stirred for 30 min then at room temperature overnight. After the solvent was evaporated, the residue was dissolved in a mixture of ethyl acetate (100 mL) and water (10 mL), the organic layer was separated and washed with saturated $NaHCO_3$ solution, 10% HCl and saturated abrine successively (50 mL each then dried over Na_2SO_4 and concentrated in vaccuo to give crude carbobenzoxy-(*S*)-valyl-(*S*)-valine methyl ester (3.51 g, 96%) which was directly used for the following reaction without further purification.

Carbobenzoxy-(*S*)-valyl-(*S*)-valine methyl ester (1.10 g, 3 mmol) was dissolved in methanol (50 mL) and stirred at room temperature under a hydrogen atmosphere at the presence of 5% Pd/C for 9 h. Removing Pd/C by filtration to give a colorless solution, to which salicylaldehyde (0.47 mL, 3 mmol) was added. After stirring at room temperature overnight, the solution was evaporated under reduced pressure to give a yellow solid which was purified by column chromatography on silicon gel (petroleum ether–ethyl acetate, 4:1) to yield 0.76 g of **1a** (76%). mp: 97–98 °C; $[\alpha]_D^{20}$: +21° (c 1.0, EtOH); ^{1}H NMR: 12.5 (br s, 1H), 8.46 (s, 1H), 7.44–7.35 (m, 2H), 7.18–7.15 (m, 1H), 6.98–6.91 (m, 1H), 4.55–4.50 (m, 1H), 4.08 (m, 1H), 3.70 (s, 3H), 2.50–2.48 (m, 1H), 2.27–2.21 (m, 1H), 1.03–0.87 (m, 12H). ^{13}C NMR: 17.38, 17.84, 19.28, 19.75, 31.19, 32.21, 52.31, 57.08, 79.50, 117.32, 118.56, 119.37, 132.34, 133.39, 160.96, 168.13, 171.12, 172.16. IR (KBr): 3296, 1742, 1652, 1647. Anal. Calcd for $C_{18}H_{26}N_2O_4$: C 64.65, H 7.84, N 8.38. Found: C 64.58, H 7.79, N 8.27%.

*2.3. N-[(2-hydroxy-1-benzyl)methylene]-(S)-valyl-(S)-phenylalanine methyl ester (**1b**, Sal-S-Val-S-Phe-OMe)*

Prepared by the similar procedure as described above. Yield **1b** as a pale yellow solid 0.78 g (68%). mp: 98–100 °C; $[\alpha]_D^{20}$: −12.6° (c 1.0, EtOH); ^{1}H NMR: 12.36 (br s, 1H), 8.28 (s, 1H), 7.40–7.32 (m, 1H), 7.31–7.13 (m, 6H), 7.08–7.05 (d, J = 8.04 Hz, 1H), 7.07–6.93 (m, 1H), 6.50–6.42 (m, 1H), 4.88–4.85 (m, 1H), 3.69 (s, 3H), 3.23–3.16 (dd, J = 5.4 Hz, J = 5.34 Hz, 1H), 3.07–2.99 (dd, J = 7.74 Hz, J = 7.71 Hz, 1H), 2.39–2.36 (m, 1H), 0.85–0.82 (d, J = 6.9 Hz, 3H), 0.77–0.74 (d, J = 6.78 Hz, 3H). ^{13}C NMR: 17.08, 19.65, 31.98, 38.06, 52.48, 53.09, 79.37, 117.26, 118.53, 119.28, 127.33, 128.96, 129.18, 132.31, 133.35, 135.81, 160.91, 168.12, 170.78, 171.79. IR (KBr): 3304, 1740, 1657, 1650, 698. Anal. Calcd for $C_{22}H_{26}N_2O_4$: C 69.09, H 6.85, N 7.32. Found: C 69.01, H 6.79, N 7.26%.

*2.4. N-[(2-hydroxy-1-benzyl)methylene]-(S)-valyl-(S)-try-2ptophan methyl ester (**1c**, Sal-S-Val-S-Trp-OMe)*

Prepared by the similar procedure as described above. Yield **1c** as a yellow solid 0.85 g (67%). mp: 109–111 °C; $[\alpha]_D^{20}$: −11.5° (c 1.0, EtOH); ^{1}H NMR: 12.53 (br s, 1H), 8.43 (s, 1H), 7.52–6.92 (m, 9H), 6.48 (m, 1H), 4.91–4.88 (m, 1H), 3.67 (s, 3H), 3.32–3.28 (m, 2H), 2.37–2.34 (m, 1H), 0.82–0.80 (d, J = 5.7 Hz, 3H), 0.71–0.69 (d, J = 6.78 Hz, 3H). ^{13}C NMR: 16.89, 19.45, 27.68, 30.89, 31.78, 52.33, 52.37, 79.03, 109.39, 111.38, 116.95, 117.51, 118.37, 118.41, 119.16, 119.51, 119.85, 122.12, 123.17, 127.07, 132.26, 133.14, 133.75, 136.35, 136.99, 160.66, 167.93, 170.89, 172.16. IR (KBr): 3329, 1740, 1650, 1630. Anal. Calcd for $C_{24}H_{27}N_3O_4$: C 68.39, H 6.46, N 9.97. Found: C 68.34, H 6.31, N 9.89%.

*2.5. N-(1-benzyl-2-hydroxy-2,2-diphenyl-ethyl)-2-[(2-hydroxy-benzylidene)-amino]-3-methyl-butyramide **2***

Prepared by the similar procedure as described above. Yield **2** as a yellow solid 0.96 g (63%). mp: 178–180 °C; $[\alpha]_D$: −18.0° (c 2.0, $CHCl_3$); ^{1}H NMR: 12.20 (br s, 1H), 7.94 (s, 1H), 7.64–7.61 (d, J = 7.35 Hz, 2H), 7.52–7.49 (d, J = 7.23 Hz, 2H), 7.32–7.04 (m, 15H), 6.21 (m, 1H), 5.2 (m, 1H), 4.89–4.86 (m, 1H), 3.35–3.33 (d, J = 5.04 Hz, 1H), 3.05–2.96 (dd, J = 11.01 Hz, J = 10.92 Hz, 1H), 2.88–2.82 (dd, J = 3.09 Hz, J = 3.0 Hz, 1H), 2.06–1.99 (m, 1H), 0.58–0.56 (d, J = 6.87 Hz, 3H), 0.44–0.41 (d, J = 6.75 Hz, 3H). ^{13}C NMR: 17.17, 19.30, 30.45, 31.85, 34.94, 60.59, 79.91, 80.42, 117.09, 118.46, 119.21, 125.76, 126.48, 126.82, 127.12, 128.14, 128.35, 128.47, 128.55, 128.64, 129.12, 129.44, 132.18, 133.22, 138.78, 144.73, 145.68, 160.68, 167.43, 171.85. IR (KBr): 3328, 1739, 1652, 1643, 698. Anal. Calcd for $C_{33}H_{34}N_2O_3$: C 78.23, H 6.76, N 5.53. Found: C 78.19, H 6.71, N 5.47%.

*2.6. N-butyl-2-[(2-hydroxy-benzylidene)-amino]-3-methyl-butyramide **3a***

Prepared by the similar procedure as described above. Yield **3a** as a yellow crystal 0.44 g (53%). mp: 80–81 °C; $[\alpha]_D^{20}$: +28.0° (c 2.0, $CHCl_3$); ^{1}H NMR: 12.61 (br s, 1H), 8.32 (s, 1H), 7.40–7.32 (m, 2H), 7.04–6.95 (m, 2H), 3.72–3.70 (d, J = 3.96 Hz, 1H), 3.39–3.34 (m, 1H), 3.23–3.18 (m, 1H), 2.58–2.42 (m, 1H), 1.52–1.46 (m, 2H), 1.36–1.29 (m, 2H), 0.99–0.88 (m, 9H). ^{13}C NMR: 13.84, 17.25, 19.81, 20.18, 31.79, 32.17, 39.25, 79.74, 117.19, 118.59, 119.44, 132.24, 133.36, 160.79, 167.70, 171.06. IR (KBr): 3297, 1647. Anal. Calcd for $C_{16}H_{24}N_2O_2$: C 69.53, H 8.75, N 10.14. Found: C 69.46, H 8.69, N 10.08%.

*2.7. N-butyl-2-[(2-hydroxy-benzylidene)-amino]-3-phenyl-propionamide **3b***

Prepared by the similar procedure as described above. Yield **3b** as a pale yellow crystal 0.67 g (69%). mp: 100–102 °C; $[\alpha]_D^{20}$: −82.0° (c 2.0, $CHCl_3$); ^{1}H NMR: 12.34 (br s, 1H), 7.93 (s, 1H), 7.26–7.11 (m, 8H), 7.02–6.99 (d, J = 8.25 Hz, 1H), 6.89–6.87 (m, 1H), 4.12–4.09 (m, 1H), 3.39–3.11 (m, 4H), 1.46–1.41 (m, 2H), 1.30–1.23 (m, 2H), 0.91–0.86 (m, 3H). ^{13}C NMR: 13.87, 20.15, 31.68, 39.39, 41.19, 75.63, 117.16, 119.41, 126.93, 128.58, 129.90, 132.25, 133.35, 137.14, 160.63, 167.64, 170.73. IR (KBr): 3356, 1652, 698. Anal. Calcd for $C_{20}H_{24}N_2O_2$: C 74.04, H 7.46, N 8.64. Found: C 74.01, H 7.41, N 8.58%.

2.8. 2-[(2-Hydroxy-benzylidene)-amino]-3-methyl-1-piperidin-1-yl-butan-1-one **4a**

Prepared by the similar procedure as described above. Yield **3b** as a yellow crystal 0.63 g (73%). mp: 120–122 °C; $[\alpha]_D^{20}$: +28.0° (c 2.0, $CHCl_3$); ^{1}H NMR: 13.16 (br s, 1H), 8.38 (s, 1H), 7.55–7.27 (m, 2H), 6.98–6.86 (m, 2H), 4.01–3.98 (d, J = 8.97 Hz), 3.61–3.57 (m, 4H), 2.37–2.33 (m, 1H), 1.67–1.53 (m, 6H), 1.03–1.01 (d, J = 6.63 Hz, 3H), 0.97–0.94 (d, J = 6.63 Hz). ^{13}C NMR: 19.19, 19.38, 20.10, 24.59, 25.79, 26.66, 31.41, 43.57, 46.75, 77.59, 117.09, 117.64, 118.73, 118.79, 119.92, 120.72, 131.89, 132.73, 133.79, 137.06, 161.11, 161.66, 166.01, 168.60. IR (KBr): 3329, 1647. Anal. Calcd for $C_{17}H_{24}N_2O_2$: C 70.80, H 8.39, N 9.71. Found: C 70.71, H 8.33, N 9.64%.

2.9. 2-[(2-Hydroxy-benzylidene)-amino]-3-phenyl-1-piperidin-1-yl-propan-1-one **4b**

Prepared by the similar procedure as described above. Yield **4b** as a yellow crystal 0.78 g (77%). mp: 126–128 °C; $[\alpha]_D^{20}$: −121.3° (c 2.0, $CHCl_3$); ^{1}H NMR: 12.99 (br s, 1H), 7.29–7.13 (m, 7H), 6.97 (d, 1H), 6.86–6.85 (m, 1H), 4.68–4.65 (m, 1H), 3.59–3.57 (m, 2H), 3.42–3.35 (m, 3H), 3.11–3.06 (m, 1H), 1.59–1.49 (m, 6H). ^{13}C NMR: 24.45, 25.60, 26.37, 39.81, 43.52, 46.72, 68.78, 117.10, 118.66, 118.76, 126.73, 128.53, 129.69, 131.85, 132.72, 137.69, 160.95, 166.17, 168.13. IR (KBr): 3358, 1652. Anal. Calcd for $C_{21}H_{24}N_2O_2$: C 74.97, H 7.19, N 8.33. Found: C 74.89, H 7.13, N 8.26%.

2.10. General procedure for pinacol coupling

To a solution of $TiCl_4$ (0.2 mmol) in CH_2Cl_2 (2 mL) was added THF (0.2 mmol) at 0 °C under argon. The mixture was stirred for 30 min, and then a yellow suspension was obtained. To this suspension was added a solution of ligand (0.2 mmol) in CH_2Cl_2 (1 mL), stirring was continued for another 1 h and a red solution was obtained. After addition of 1.5 equiv. magnesium powder the catalyst solution was cooled to −10 °C then treated with aldehyde followed by addition of trimethylchlorosilane (TMSCl) dropwise. The reaction was stirred for 24 h and then quenched with 10% sodium bicarbonate solution, and with ethyl acetate (3× 15 mL). The combined organic solution was evaporated under reduced pressure. The resulted oil was dissolved in THF solution of 1 M HCl and stirred at room temperature until the pinacol product had completely desilylated. The reaction was diluted with water and extracted with ethyl acetate (3× 15 mL). The organic layers were combined and dried over anhydrous Na_2SO_4, the solvent was removed under reduced pressure and the pinacol product was purified by silica gel chromatography or recrystallization.

2.11. (S,S)-(−)-1,2-diphenyl-ethane-1,2-diol

Colorless crystals; mp: 142–144 °C; $[\alpha]_D$: −59.6° (c 1.0, ethanol), 63% ee. [Ref. [16], $[\alpha]_D$: −94.5° (c 1.0, ethanol) for 100% ee *S*,*S*-enantiomer]; ^{1}H NMR and HPLC shows a DL/meso ratio of 99:1; enantiomeric excess was determined by HPLC with chiral OJ-H column (hexane:2-propanol, 90:10; flow rate, 1.0 mL/min), t_r (*S*,*S*) = 12.7 min, t_r (*R*,*R*) = 14.4 min, t_r (meso) = 18.2 min.

2.12. (S,S)-(−)-1,2-di(4-methylphenyl)ethane-1,2-diol

Colorless crystals; mp: 102–104 °C; $[\alpha]_D$: −72.8° (c 1.0, ethanol), 71% ee. [Ref. [16], $[\alpha]_D$: −102.5° (c 1.0, ethanol) for 100% ee *S*,*S*-enantiomer]; ^{1}H NMR shows only DL pinacol product; enantiomeric excess was determined by HPLC with chiral OJ-H column (hexane:2-propanol, 90:10; flow rate, 1.0 mL/min), t_r (*S*,*S*) = 10.97 min, t_r (*R*,*R*) = 12.97 min.

2.13. (S,S)-(−)-1,2-di(4-methoxylphenyl)ethane-1,2-diol

Colorless crystals; mp: 130–132 °C; $[\alpha]_D$: −75.7° (c 1.0, ethanol), 66% ee. [Ref. [16], $[\alpha]_D$: −118.3° (c 1.0, ethanol) for 100% ee *S*,*S*-enantiomer]; ^{1}H NMR shows a DL/meso ratio of 99:1; enantiomeric excess was determined by HPLC with chiral AD column (hexane:2-propanol, 95:5; flow rate, 1.0 mL/min), t_r (*S*,*S*) = 9.28 min, t_r (*R*,*R*) = 11.06 min, t_r (meso) = 14.92 min.

2.14. (S,S)-(−)-1,2-di(2-chlorophenyl)ethane-1,2-diol

Colorless crystals; mp: 130–132 °C; $[\alpha]_D$: −22.8° (c 1.0, $CHCl_3$), 41% ee. [Ref. [18], $[\alpha]_D$: −38° (c 1.0, $CHCl_3$) for 60% ee *S*,*S*-enantiomer]; ^{1}H NMR shows a DL/meso ratio of 83:17; enantiomeric excess was determined by HPLC with chiral WH column (hexane:2-propanol, 90:10; flow rate, 1.0 mL/min), t_r (*S*,*S*) = 9.57 min, t_r (*R*,*R*) = 11.24 min, t_r (meso) = 15.12 min.

2.15. (S,S)-(−)-1,2-di(4-chlorophenyl)ethane-1,2-diol

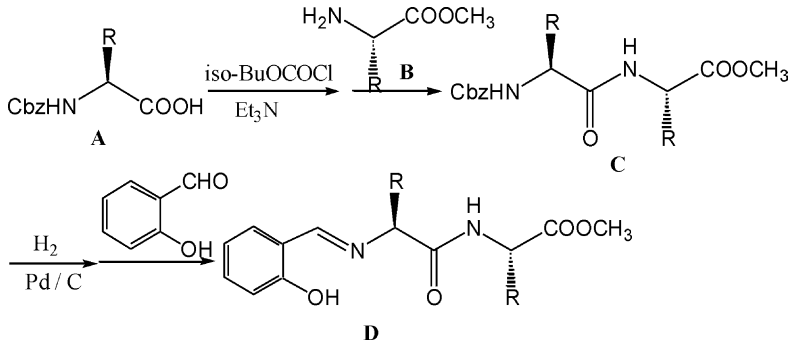
Colorless crystals; mp: 129–131 °C; $[\alpha]_D$: −41.0° (c 1.0, ethanol), 46% ee. [Ref. [16], $[\alpha]_D$: +93° (c 1.0, $CHCl_3$) for 100% ee *R*,*R*-enantiomer]; ^{1}H NMR shows a DL/meso ratio of 89:11; enantiomeric excess was determined by HPLC with chiral WH column (hexane:2-propanol, 95:5; flow rate, 1.0 mL/min), t_r (*S*,*S*) = 7.24 min, t_r (*R*,*R*) = 9.12 min, t_r (meso) = 12.62 min.

2.16. (S,S)-(−)-1,2-di(2,4-dichlorophenyl)ethane-1,2-diol

Colorless crystals; mp: 135–137 °C; $[\alpha]_D$: −22.8° (c 1.0, $CHCl_3$), 21% ee. [Ref. [18], $[\alpha]_D$: −58° (c 1.0, $CHCl_3$) for 74% ee *S*,*S*-enantiomer]; ^{1}H NMR shows a DL/meso ratio of 64:36; enantiomeric excess was determined by HPLC with chiral WH column (hexane:2-propanol, 90:10; flow rate, 1.0 mL/min), t_r (*S*,*S*) = 13.79 min, t_r (*R*,*R*) = 16.27 min, t_r (meso) = 20.15 min.

2.17. (S,S)-(−)-1,2-di(1′-naphthyl)ethane-1,2-diol

Colorless crystals; mp: 174–175 °C; $[\alpha]_D$: −40.0° (c 1.0, THF), 58% ee. [Ref. [16], $[\alpha]_D$: +68° (c 0.86, THF) for 100% ee *R*,*R*-enantiomer]; ^{1}H NMR shows a DL/meso ratio of >99:1; enantiomeric excess was determined by HPLC with chiral AD



Scheme 1. Synthesis of dipeptide-type ligands [19].

column (hexane:2-propanol, 85:15; flow rate, 1.0 mL/min), t_r (*S*,*S*) = 21.88 min, t_r (*R*,*R*) = 23.76 min, t_r (meso) = 25.42 min.

2.18. 1,2-Dicyclohexyl-ethane-1,2-diol

Colorless crystals; ^{1}H NMR shows a DL/meso ratio of 75:25.

3. Results and discussion

The dipeptide Schiff bases were prepared by the method shown in Scheme 1. Coupling of N-protected amino acids **A** with amino acid ester **B** afforded the corresponding dipeptides **C**, which was hydrogenolyzed with Pd/C for deprotection of amino group followed by condensation with salicylaldehyde to yield the desired ligands **D**.

All of the ligands were summarized in Fig. 1.

Considering that the low-valent titanium complexes are most prominent for pinacol coupling reaction, titanium complexes of all the Salycylal-type ligands were used as catalysts to investigate the pinacol coupling reaction of benzaldehyde with different reductive metals, solvents and different reaction temperatures. The results were summarized in Table 1. As shown in the table, all the reactions were proceeded with good to high yield and diastereoselectivity. Relatively good enantioselectivities (36, 52, 44% ee) were obtained with ligands **1a**, **2** and **3a** under room temperature in dichloromethane and magnesium as reductant. Magnesium seems more favorable than zinc and manganese as reductant in this reaction. Excellent yield was obtained in THF, however, only moderate diastereoselectivity and poor enantioselectivity was achieved. Relative low temperature favors the diastereoselectivity and enantioselectivity remarkably though lowers the yield slightly.

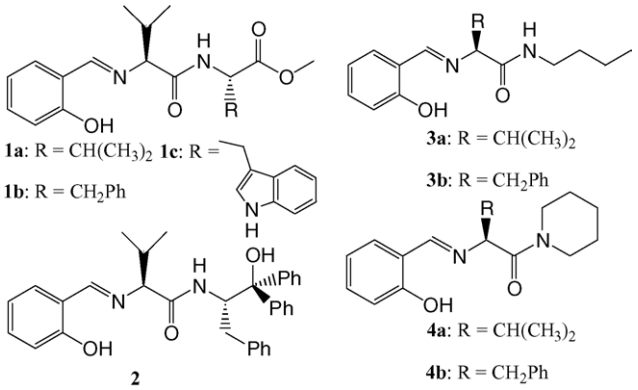
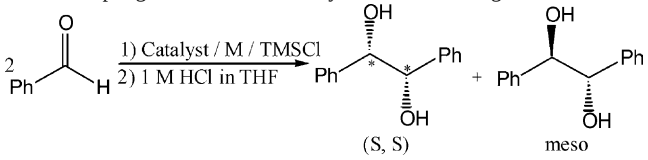


Fig. 1. Dipeptide-type ligands.

Under optimized conditions, the pinacol coupling reaction was further carried out with different aldehydes. The results were summarized in Table 2, from which we could find that aromatic aldehydes generally demonstrate better yield and higher diastereoselectivity than aliphatic aldehyde. Obvious electronic effect was observed: electron-donating groups in the benzene ring were favorable for achieving higher diastereoselectivity and enantioselectivity (entries 2 and 3); however, electron-withdrawing substituents showed negative effect in pinacol coupling reaction (entries 4–6). Especially, when 4-nitrobenzaldehyde was used as substrate in this reaction (entry 7), no pinacol was obtained. The probable reason was that 4-nitrobenzaldehyde itself could capture the radical electron

Table 1
Pinacol coupling reaction of benzaldehyde with different ligands and conditions[a]



Entry	Ligand	Reductant	Solvent	*T* (°C)	Yield (%)[b]	DL:meso[c]	ee (%)[d]
1	**1a**	Mg	CH_2Cl_2	25	90	86:14	36
2	**1b**	Mg	CH_2Cl_2	25	98	82:18	24
3	**1c**	Mg	CH_2Cl_2	25	86	83:17	12
4	**2**	Mg	CH_2Cl_2	25	91	85:15	52
5	**3a**	Mg	CH_2Cl_2	25	82	82:18	44
6	**3b**	Mg	CH_2Cl_2	25	76	93:7	10
7	**4a**	Mg	CH_2Cl_2	25	62	88:12	32
8	**4b**	Mg	CH_2Cl_2	25	87	92:8	12
9	**2**	Zn	CH_2Cl_2	25	83	77:23	3
10	**2**	Mn	CH_2Cl_2	25	58	58:42	0.3
11	**2**	Mg	CH_3CN	25	72	60:40	8
12	**2**	Mg	THF	25	99	79:21	29
13	**2**	Mg	CH_2Cl_2	0	88	89:11	56
14	**2**	Mg	CH_2Cl_2	−10	86	99:1	63

[a] All the reactions were carried out with 10 mol% ligand for 24 h.
[b] Isolated yield.
[c] Determined by ^{1}H NMR and HPLC.
[d] Determined by HPLC with chiral OJ-H column.

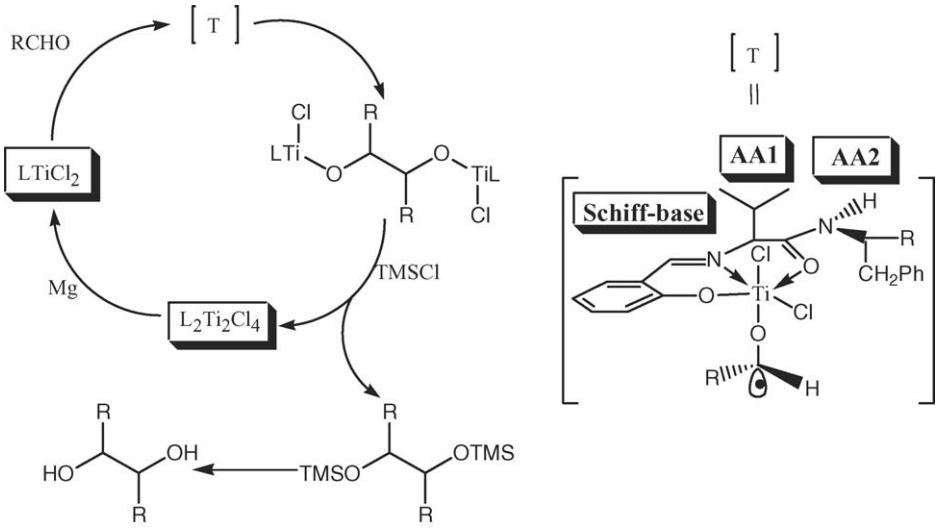
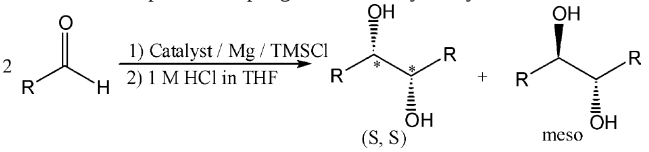


Fig. 2. Plausible reaction mechanism.

generated by low-valent titanium [20]. Cyclohexanecarboxaldehyde as a representative aliphatic example was also tested, however, only moderate yield and diastereoselectivity were observed.

As for the reaction mechanism, the plausible pathway is the dimerization of aldehyde radicals generated by the single electron transmission (SET) process [1a,16]. Reduction of Ti(IV) complex with metal generates a Ti(III) species, which reacts with aldehyde to generate a carbon radical [T] as shown in Fig. 2, the steric structure of **AA1** part in dipeptide Schiff base ligand favors the two R groups orienting trans to each other to form DL pinacol product, while the absolute configuration of pinacol is controlled by stereochemistry of **AA2** part of the ligand.

Table 2
Enantioselective pinacol coupling reaction catalyzed by 2[a]



Entry	RCHO	Yield[b]	DL:meso[c]	ee (%)
1	Benzaldehyde	86	99:1	63[d]
2	4-Tolualdehyde	87	100:0	71[d]
3	4-Methoxybenzaldehyde	86	99:1	66[e]
4	2-Chlorobenzaldehyde	72	83:17	41[f]
5	4-Chlorobenzaldehyde	76	89:11	46[f]
6	2,4-Dichlorobenzaldehyde	51	64:36	21[f]
7	4-Nitrobenzaldehyde	0	–	–
8	1-Naphthaldehyde	78	>99:1	58[e]
9	Cyclohexanecarboxaldehyde	65	75:25	Nd[g]

[a] Reactions were carried out with 10 mol% of ligand **2** in CH_2Cl_2 at −10 °C for 24 h.
[b] Isolated and purified product.
[c] Determined by ^1H NMR and HPLC.
[d] Determined by HPLC with chiral OJ-H column.
[e] Determined by HPLC with chiral AD column.
[f] Determined by HPLC with chiral WH column.
[g] Not detected.

4. Conclusion

In summery, several dipeptide Schiff bases and its mimics were synthesized conveniently from natural amino acids. Their titanium complexes were investigated in pinacol coupling reaction for the first time; good yields, high diastereoselectivity and moderate enantioselectivity were obtained. And plausible mechanism was suggested.

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