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Short communication

Biphenyl-oxazoline ligands derived from β-DDB: Their synthesis and application in asymmetric pinacol coupling reaction

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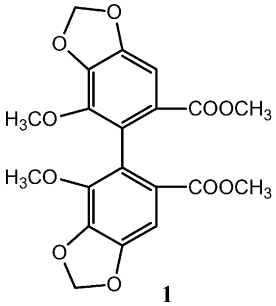
Abstract

Biphenyl-bisoxazoline ligands conveniently synthesized from β-DDB have been exploited in asymmetric pinacol coupling reaction for the first time. The pinacol products were obtained with good yields, high diastereoselectivities and good enantioselectivities (up to 83%e.e.). The stereochemistry of the diol products was dominated by the steric structure of the oxazoline component. Ligands bearing bulky groups in the chiral centre of the oxazolines showed more efficient for achieving both high diastereoselectivity and enantioselectivity.

Keywords: Bisoxazolines; Low-valent titanium; Pinacol coupling reaction; Asymmetric catalysis

1. Introduction

Optical pure 1,2-diols, an important kind of organic compounds in synthetic chemistry, have been widely used as chiral ligands [1], auxiliaries [2] and synthetic intermediates [3] in modern organic synthesis. Among the methods reported for chiral 1,2-diol preparations, asymmetric pinacol coupling seems to be the most direct and efficient way by formation of the functionalized carbon–carbon bond [4]. However, it has remained a great challenge to achieve high stereoselectivity, especially enantioselectivity. Still now, only a few catalytic systems have been successfully applied in asymmetric pinacol coupling reaction with both high diastereoselectivity and enantioselectivity, such as Schiff-base titanium complexes [5], Salen-titanium complex [6], and TBOxH–chromium complex [7]. Recently, chiral diol ligands with ferrocene backbone have been synthesized by asymmetric pinacol coupling with good diastereoselectivities [8]. To our knowledge, this is the first example of asymmetric pinacol coupling induced by oxazoline motif.



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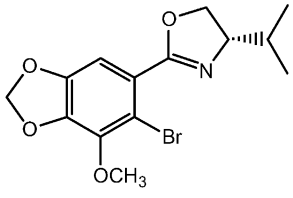
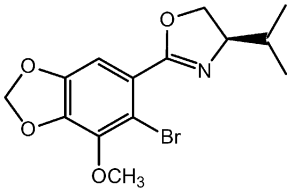


2a



2b

In our asymmetric total synthesis of β-DDB (**1**), a promising antiheptotoxic drug, the oxazoline intermediates (**2a** and **2b**) have been introduced to control the absolute configuration of the products. To our pleasure, these oxazoline compounds demonstrated not only good stability but also high asymmetric induced effects [9]. As a result, a series of bisoxazoline ligands were conveniently synthesized from racemic β-DDB and then applied in asymmetric pinacol coupling

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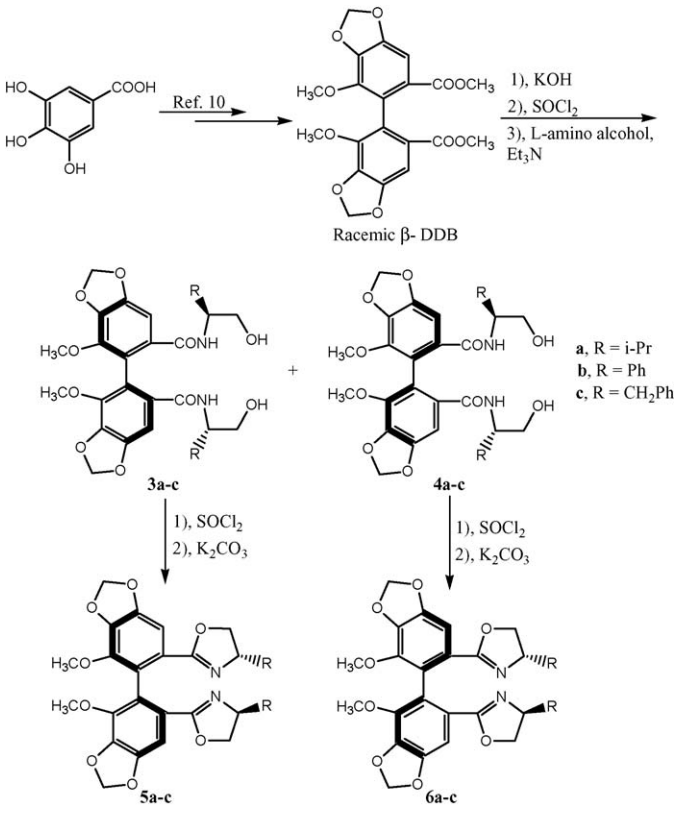


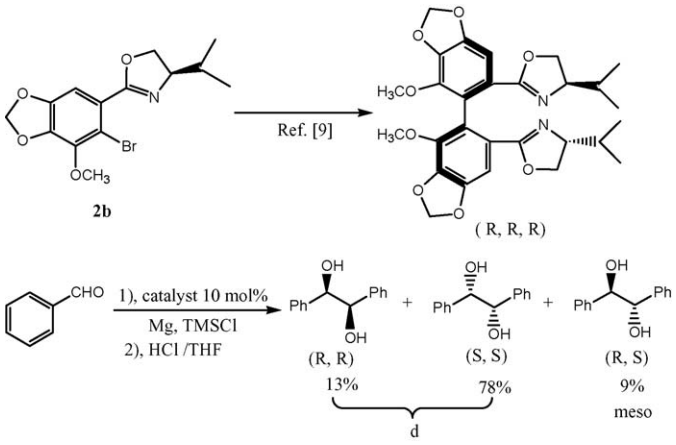
Scheme 1. Synthesis of biphenyl-oxazoline ligands from β-DDB.

reaction. Herein, we would like to report the corresponding results.

2. Results and discussions

To synthesize the desired bisoxazoline ligands (Scheme 1), racemic β-DDB was synthesized from gallic acid according to the literature [10], which was hydrolyzed to give corresponding acid. After treated with thionyl chloride, acyl chloride was produced and separated by distillation under reduced pressure, which was then reacted with L-amino alcohols to provide the amides **3a–c** and **4a–c**. Fortunately, the two isomers can be readily accessed by column chromatography or recrystallization. To obtain the desired bisoxazolines **5a–c** and **6a–c**, the amide isomers were reacted with thionyl chloride then treated with potassium carbonate successively. The absolute configuration of these bisoxazoline ligands was determined by transforming to corresponding optical pure β-DDB then checking their CD spectra [10].

Low-valent titanium, a useful reagent in organic synthesis, has been proved to be prominent in reductive coupling of carbonyl compounds [11]. In our previous reports [12], several types of chiral ligands have been investigated in catalytic asymmetric pinacol coupling reaction. However, it remains a long distance to achieve satisfactory results. Our efforts have ever been made to design and synthesize some more efficient ligands for asymmetric catalysis. To our pleasure, the biphenyl-bisoxazoline ligands in Scheme 1 have shown good asymmetric induced effects in asymmetric Kharasch–Sosnovosky reaction



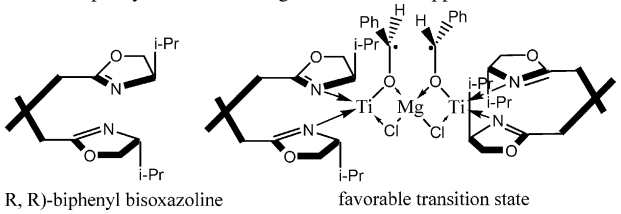
Scheme 2. Syntheses of (*R*,*R*,*R*)-isomer of **5a** [9] for asymmetric pinacol coupling.

[13]. This promoted us further to investigate their catalytic activities in low-valent titanium promoted pinacol coupling reaction.

In our preliminary investigation, reductive coupling of benzaldehyde was carried out in dichloromethane with 10 mol% catalyst which was generated by reacting with oxazoline ligand and $Ti(THF)_2Cl_4$ [14] in situ, a stoichiometric amount of TMSCl, and magnesium as reductant. As can be seen from the Table 1, all the reactions proceeded smoothly with good yields and good to high diastereoselectivities. Better results were obtained by the catalysts from the oxazolines bearing bulky *iso*-propyl group (entry **1** and **4**). However, absolute configurations of the diol products were not significantly affected by the axial chirality of the biphenyl part but the stereochemistry of the oxazoline component [15][1]. Oxazolines with *S*-configuration gave (*R*, *R*)-pinacols. To identify this opinion, the enantiomer of **5a** [9] was synthesized and exploited in this reaction. As expected, the enantiomeric excess of the product by HPLC showed that the (*S*, *S*) pinacol was obtained as major product (Scheme 2).

To further optimize the reaction conditions, our investigations were continued with different metals, solvents, and temperatures. Better results were obtained by magnesium and zinc as reductants in dichloromethane or acetonitrile. However, reaction carried out in THF showed poor diastereoselectivity and enantioselectivity, this may be due to the strong coordinating ability of THF itself which led to coordinating competition between oxazoline ligand and THF with centre ion. Lower temperature was obviously more favorable for achieving both high diastereoselectivity and enantioselectivity.

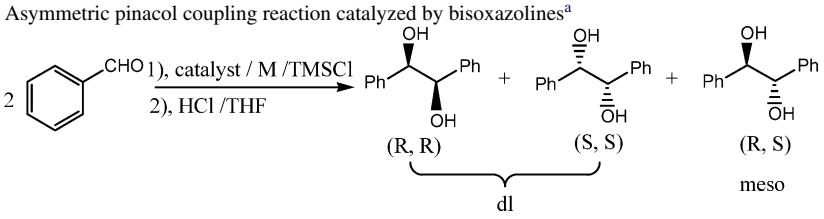
[1] According to the transition state suggested by Gansauer et al., a similar one based on our biphenyl bisoxazoline ligands has been supposed as follows:



(R, R, R)-biphenyl bisoxazoline favorable transition state

As can be seen from the figure, the chiral centre on the oxazoline component obviously showed greater importance for controlling the configuration of the pinacol products than the axial chirality of biphenyl part.

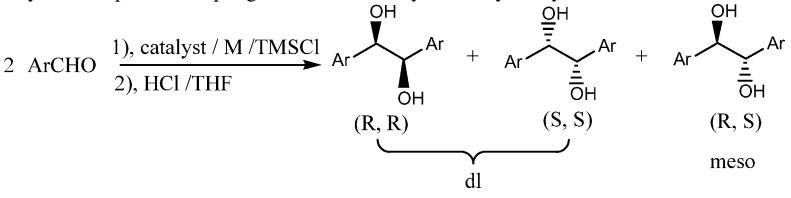
Table 1
Asymmetric pinacol coupling reaction catalyzed by bisoxazolines[a]



Entry	Ligand	Metal	Solvent	T (°C)	Yield[b] (%)	dl:meso[c]	e.e.[d] (%)
1	**5a**	Mg	CH_2Cl_2	20	89	96:4	66 (*R*,*R*)
2	**5b**	Mg	CH_2Cl_2	20	86	86:14	56 (*R*,*R*)
3	**5c**	Mg	CH_2Cl_2	20	84	68:32	44 (*R*,*R*)
4	**6a**	Mg	CH_2Cl_2	20	87	90:10	64 (*R*,*R*)
5	**6b**	Mg	CH_2Cl_2	20	90	88:12	49 (*R*,*R*)
6	**6c**	Mg	CH_2Cl_2	20	82	75:25	38 (*R*,*R*)
7	**5a**	Zn	CH_2Cl_2	20	92	85:15	62 (*R*,*R*)
8	**5a**	Mn	CH_2Cl_2	20	70	64:36	36 (*R*,*R*)
9	**5a**	Mg	THF	20	92	78:22	11 (*R*,*R*)
10	**5a**	Mg	CH_3CN	20	88	92:8	59 (*R*,*R*)
11	**5a**	Mg	CH_2Cl_2	0	85	95:5	73 (*R*,*R*)
12	**5a**	Mg	CH_2Cl_2	−20	81	>99:1	81 (*R*,*R*)

[a] All the reaction were performed with 10 mol% catalyst.
[b] Isolated yield.
[c] Determined by HPLC and ^{1}H NMR.
[d] Determined by HPLC with Daicel chiral OJ-H column, eluent: *n*-hexane/2-propanol = 90/10; flow: 1.0 mL/min; detect: UV254 nm. $t_r(S,S) = 12.1$ min, $t_r(R,R) = 13.6$ min, t_r(meso) = 17.8 min.

Table 2
Asymmetric pinacol coupling of aromatic aldehydes catalyzed by 5a[a]



Entry	ArCHO	Yield[b]	dl:meso[c]	e.e. (%)
1	Benzaldehyde	81	>99: 1	81 (*R*,*R*)[d]
2	4-Tolualdehyde	84	dl only	83 (*R*,*R*)[d]
3	4-Methoxybenzaldehyde	86	>99: 1	79 (*R*,*R*)[e]
4	2-Chlorobenzaldehyde	83	89: 11	68 (*R*,*R*)[f]
5	4-Chlorobenzaldehyde	83	92: 8	71 (*R*,*R*)[f]
6	4-Bromobenzaldehyde	84	90: 10	73 (*R*,*R*)[e]
7	4-Fluorobenzaldehyde	82	93:7	71 (*R*,*R*)[e]
8	1 -Naphthaldehyde	86	>99: 1	78 (*R*,*R*)[e]

[a] Reactions conditions: 2.0 mmol of aldehyde, 10 mol% of catalyst, 2 equiv of metal, 1.5 equiv of TMSCl. under −20 °C for 24 h.
[b] Isolated yield.
[c] Determined by ^{1}H 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.

Under optimized conditions, asymmetric pinacol coupling reactions were carried out with some other aromatic aldehydes as substrates. The corresponding results were summarized in Table 2, from which we found that the electronic effects of the aldehydes did not significantly affect the enantiomeric excesses of the products as previous reports [5,6,12]. The steric effect of the oxazoline component showed greater importance for controlling the stereochemistry of the products.

3. Conclusion

In conclusion, a series of biphenyl-bisoxazoline ligands conveniently synthesized from β-DDB have been applied in asymmetric pinacol coupling reaction for the first time. The pinacol products were obtained with good yields, high diastereoselectivities and good enantioselectivities (up to 83%e.e.). The stereochemistry of the diol products was dominated by the steric struc-

ture of the oxazoline component. ligands bearing bulky groups in the chiral centre of the oxazolines showed more efficient for achieving both high diastereoselectivity and enantioselectivity.

4. Experimental

4.1. General

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) 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 AGILENT 1100 SERIES spectrometer. The diastereomeric excesses were determined by HPLC or ^{1}H NMR, and enantiomeric excesses were determined by HPLC with chiral columns.

All the 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. L- and D-Amino alcohols were synthesized from corresponding amino acids according to the reported procedure and identified by ^{1}H NMR, ^{13}C NMR and other physical parameters compared with literature [16].

4.2. General procedure for synthesis of **3a–c** and **4a–c**

Racemic β-DDB (10.0 g, 23.9 mmol) was suspended in a solution of 150 mL acetone and 150 mL 10% KOH. After heating to reflux for 10 h, a clear solution was obtained. Then, acetone was removed and the resulted solution was acidified by hydrochloric acid. The white precipitate formed was collected by filtration, washed with water, and dried at 100 °C. To the obtained diacid (3.90 g, 10 mmol) was added 50 mL $SOCl_2$ and the mixture was heated to reflux for 2 h until the system turned clear. After the excess $SOCl_2$ was removed, the resulted pale yellow solid was dissolved in 100 mL CH_2Cl_2 and added to the solution of L-amino alcohol (22.0 mmol) and 6.3 mL Et_3N (45.0 mmol) in 100 mL of CH_2Cl_2 cooled to −10 °C. The reaction mixture was stirred overnight, and then washed with 2N HCl, brine and dried over anhydrous Na_2SO_4. After removal of the solvent, a white solid was formed. TLC analysis of the product confirmed that two diastereomers 3 and 4 were produced, which were then separated by flash chromatography or recrystallization.

4.2.1. (S,S,S)-6,6′-dimethoxy-4,5,4′,5′-dimethylenedioxy-biphenyl-2,2′-dicarboxylic acid bis[(2-hydroxy-1-iso-propyl-ethyl)-amide] (**3a**)

Yield: 47%; R_f = 0.56 (100% EtOAc); m.p. 223–224 °C; $[\alpha]_D^{20} = -52.5$ (0.5, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.75 (d, J = 6.76 Hz, 6H), 0.84 (s, J = 6.76, 6H), 1.73–1.80 (m, 2H), 2.58 (s, br, 2H), 3.45–3.47 (m, 4H), 3.58–3.71 (m, 2H), 3.88 (s, 6H), 5.98 (s, 2H), 6.01 (s, 2H), 6.71 (s, 2H), 6.76 (s, br, 2H). ^{13}C NMR (300 MHz, $CDCl_3$): 18.8, 19.4, 29.1, 57.5, 60.1, 63.7, 101.8, 102.0, 120.2, 132.4, 138.0, 141.6, 149.3, 170.3. IR (KBr, cm^{-1}): 3420, 2924,1642. Anal. Calcd. for $C_{28}H_{36}N_2O_{10}$: C, 59.99; H, 6.47; N, 5.00; Found: C, 59.92; H, 6.42; N, 5.03.

4.2.2. (S,S,S)-6,6′-dimethoxy-4,5,4′,5′-dimethylenedioxy-biphenyl-2,2′-dicarboxylic acid bis[(2-hydroxy-1-phenyl-ethyl)-amide] (**3b**)

Yield: 46%; R_f = 0.63 (100% EtOAc); m.p. 109–111 °C; $[\alpha]_D^{20} = -11.4$ (0.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.98 (s, br, 2H), 3.58–3.65 (m, 4H), 3.87 (s, 6H), 4.90–4.92 (m, 2H), 5.97 (s, 2H), 5.99 (s, 2H), 6.69 (s, 2H), 6.90 (s, br, 2H), 7.02–7.05 (m, 4H), 7.22–7.28 (m, 6H). ^{13}C NMR (300 MHz, $CDCl_3$): 56.1, 60.0, 60.5, 65.8, 101.8, 102.2, 120.1, 126.8, 127.6, 128.6, 138.1, 138.9, 141.4, 149.4, 169.5. IR (KBr, cm^{-1}): 3445, 2942, 1646, 1602, 1452. Anal. Calcd. for $C_{34}H_{32}N_2O_{10}$: C, 94.96; H, 5.13; N, 4.46; Found: C, 94.92; H, 5.11; N, 4.51.

4.2.3. (S,S,S)-6,6′-dimethoxy-4,5,4′,5′-dimethylenedioxy-biphenyl-2,2′-dicarboxylic acid bis[(2-hydroxy-1-benzyl-ethyl)-amide] (**3c**)

Yield: 41%; R_f = 0.60 (100% EtOH); m.p. 213–215 °C; $[\alpha]_D^{20} = -79.4$ (1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.61–2.76 (m, 4H), 3.35–3.45 (m, 4H), 3.85 (s, 6H), 4.08–4.10 (m, 2H), 5.95 (s, 2H), 5.97 (s, 2H), 6.54 (s, 2H), 6.68–6.82 (s, br, 2H), 7.16–7.29 (m, 10H). ^{13}C NMR (300 MHz, $CDCl_3$): 36.6, 53.0, 60.1, 63.4, 101.8, 101.9, 120.1, 126.6, 128.6, 129.2, 132.2, 137.9, 138.0, 141.5, 149.3, 169.6. IR (KBr, cm^{-1}): 3418, 2924, 1632, 1538, 1471. Anal. Calcd. for $C_{36}H_{36}N_2O_{10}$: C, 65.84; H, 5.53; N, 4.27; Found: C, 65.71; H, 5.48; N, 4.25.

4.2.4. (S,R,S)-6,6′-dimethoxy-4,5,4′,5′-dimethylenedioxy-biphenyl-2,2′-dicarboxylic acid bis[(2-hydroxy-1-iso-propyl-ethyl)-amide] (**4a**)

Crystallized twice from EtOAc; yield: 45%, R_f = 0.42 (EtOAc); m.p. 198–199 °C; $[\alpha]_D^{20} = -62.4$ (0.5, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.71 (d, J = 6.75 Hz, 6H), 0.78 (d, J = 6.75 Hz, 6H), 1.67–1.78 (m, 2H), 1.5 (s, br, 2H), 3.48–3.49 (m, 4H), 3.58–3.62 (m, 2H), 3.82 (s, 6H), 6.01 (s, 2H), 6.03 (s, 2H), 6.75 (s, br, 2H), 6.90 (s, 2H). ^{13}C NMR (300 MHz, $CDCl_3$): 18.8, 19.5, 57.8, 61.1, 64.5, 103.2, 103.5, 120.2, 123.5, 138.0, 142.0, 150.1, 171.2. IR (KBr, cm^{-1}): 3418, 2920, 1640. Anal. Calcd. for $C_{28}H_{36}N_2O_{10}$: C, 59.99; H, 6.47; N, 5.00; Found: C, 59.92; H, 6.51; N, 5.02.

4.2.5. (S,R,S)-6,6′-dimethoxy-4,5,4′,5′-dimethylenedioxy-biphenyl-2,2′-dicarboxylic acid bis[(2-hydroxy-1-phenyl-ethyl)-amide] (**4b**)

Yield: 42%; R_f = 0.47 (100% EtOAc); m.p. 112–113 °C; $[\alpha]_D^{20} = -23.9$ (0.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.68 (s, br, 2H), 3.55–3.70 (m, 4H), 3.66 (s, 6H), 4.90–4.96 (m, 2H), 5.99 (s, 4H), 6.70 (s, 2H), 7.03–7.06 (m, 4H), 7.21–7.25 (m, 6H), 7.40 (s, br, 2H). ^{13}C NMR (300 MHz, $CDCl_3$): 56.2, 60.2, 60.5, 66.0, 101.9, 103.1, 120.2, 126.8, 126.9, 127.7, 128.6,

128.7, 131.6, 138.7, 140.9, 149.2, 169.1. IR (KBr, cm^{-1}): 3440, 2942, 1645, 1602, 1450. Anal. Calcd. for $C_{34}H_{32}N_2O_{10}$: C, 94.96; H, 5.13; N, 4.46; Found: C, 94.90; H, 5.15; N, 4.42.

*4.2.6. (S,R,S)-6,6′-dimethoxy-4,5,4′,5′-dimethylenedioxy-biphenyl-2,2′-dicarboxylic acid bis [(2-hydroxy-1-benzyl-ethyl)-amide] (**4c**)*

Yield: 45%; $R_f = 0.45$ (100% EtOAc); m.p. 95–97 °C; $[\alpha]_D^{20} = -52.0$ (0.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.25 (s, br, 2H), 2.64 (d, $J = 7.34$ Hz), 3.31–3.35 (m, 4H), 3.77 (s, 6H), 4.06–4.10 (m, 2H), 5.98 (s, 2H), 6.01 (s, 2H), 6.75 (s, 2H), 6.80 (s, br, 2H), 7.14–7.30 (m, 10H). ^{13}C NMR (300 MHz, $CDCl_3$): 36.5, 53.2, 60.3, 63.4, 102.0, 103.0, 119.9, 126.6, 128.6, 129.2, 137.8, 138.5, 140.8, 149.4, 169.0. IR (KBr, cm^{-1}): 3418, 2922, 1630, 1539, 1471. Anal. Calcd. for $C_{36}H_{36}N_2O_{10}$: C, 65.84; H, 5.53; N, 4.27; Found: C, 65.81; H, 5.53; N, 4.29.

*4.3. General procedure for synthesis of **5a–c** and **6a–c***

Thionyl chloride (5.94 g, 50.0 mmol) in 50 mL CH_2Cl_2 was added dropwise to the solution of **3a–c** or **4a–c** (5.0 mmol) in 100 mL CH_2Cl_2 cooled to −10 °C under nitrogen atmosphere. The solution was stirred overnight then quenched by adding water and neutralized by saturated K_2CO_3 solution. The organic layer was separated, dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and to the residue was added CH_3CN (65 mL), H_2O (10 mL) and K_2CO_3 (2.0 g) then heated to reflux for 3 h. After cooling, CH_3CN was evaporated and the mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined CH_2Cl_2 layers were washed with brine and water successively, then dried over anhydrous Na_2SO_4. Removal of CH_2Cl_2 gave a white solid which can be further purified by flash chromatography (silical gel, petroleum ether:ethyl acetate = 3:1).

*4.3.1. (S,S,S)-6,6′-dimethoxy-4,4′,5,5′-dimethylenedioxy-2,2′-bis(4-iso-propyl-4,5-dihydro-oxazole) (**5a**)*

Yield: 76%; $R_f = 0.58$ (PE:EA = 1:1); m.p. 120–121 °C; $[\alpha]_D^{20} = -85.0$ (0.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.75 (d, $J = 6.64$ Hz, 6H), 0.85 (d, $J = 6.64$ Hz, 6H), 1.57–1.60 (m, 2H), 3.66–3.75 (m, 4H), 3.80 (s, 6H), 4.04–4.07 (m, 2H), 6.00 (s, 4H), 7.10 (s, 2H). ^{13}C NMR (300 MHz, $CDCl_3$): 18.5, 19.2, 33.0, 59.8, 70.4, 72.7, 101.5, 104.3, 122.5, 125.4, 138.8, 141.5, 148.2, 163.2. IR (KBr, cm^{-1}): 1645(C=N). Anal. Calcd. for $C_{28}H_{32}N_2O_8$: C, 64.11; H, 6.15; N, 5.34; Found: C, 64.15; H, 6.10; N, 5.32.

*4.3.2. (S,S,S)-6,6′-dimethoxy-4,4′,5,5′-dimethylenedioxy-2,2′-bis(4-phenyl-4,5-dihydro-oxazole) (**5b**)*

Yield: 78%; $R_f = 0.60$ (PE:EA = 1:1); m.p.81–83 °C; $[\alpha]_D^{20} = -6.5$ (1.2, $CHC1_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.81 (s, 6H), 3.82–3.91 (m, 4H), 4.44–4.50 (m, 2H), 5.10–5.17 (m, 2H), 5.99 (s, 2H), 6.02 (s, 2H), 7.09–7.22 (m, 12H). ^{13}C NMR (300 MHz, $CDCl_3$): 59.9, 70.1, 74.5, 101.7, 104.4, 122.3, 126.9, 127.1, 128.5, 139.2, 142.6, 148.5, 164.7. IR (KBr, cm^{-1}): 1640(C=N). Anal. Calcd. for $C_{34}H_{28}N_2O_8$: C, 68.91; H, 4.76; N, 4.73; Found: C, 68.88; H, 4.74; N, 4.78.

*4.3.3. (S,S,S)-6,6′-dimethoxy-4,4′,5,5′-dimethylenedioxy-2,2′-bis(4-benzyl-4,5-dihydro-oxazole) (**5c**)*

Yield: 78%; $R_f = 0.52$ (PE:EA = 1:1); m.p. 152–153 °C; $[\alpha]_D^{20} = -69.0$ (0.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.49–2.57 (m, 2H), 3.05–3.11 (m, 2H), 3.71 (t, $J = 8.2$ Hz, 2H), 3.81 (s, 6H), 4.04 (t, $J = 8.2$ Hz), 4.26–4.31 (m, 2H), 5.99 (s, 2H), 6.01 (s, 2H), 7.09 (s, 2H), 7.13–7.28 (m, 10H). ^{13}C NMR (300 MHz, $CDCl_3$): 41.7, 59.9, 67.9, 72.2, 101.6, 104.2, 122.4, 125.1, 126.3, 128.5, 129.2, 138.6, 139.0, 141.4, 148.4, 164.1. IR (KBr, cm^{-1}): 1640(C=N). Anal. Calcd. for $C_{36}H_{32}N_2O_8$: C, 69.67; H, 5.20; N, 4.51; Found: C, 69.75; H, 5.15; N, 4.47.

*4.3.4. (S,R,S)-6,6′-dimethoxy-4,4′,5,5′-dimethylenedioxy-2,2′-bis(4-iso-propyl-4,5-dihydro-oxazole) (**6a**)*

Yield: 80%; $R_f = 0.75$ (PE:EA = 1:1); m.p. 178–180 °C; $[\alpha]_D^{20} = -2.0$ (1.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.75 (d, $J = 6.76$, 6H), 0.78 (d, $J = 6.76$, 6H), 1.51–1.58 (m, 2H), 3.74–3.82 (m, 4H), 3.86 (s, 6H), 3.98–4.03 (m, 2H), 6.01 (s, 4H), 7.01 (s, 2H). ^{13}C NMR (300 MHz, $CDCl_3$): 18.3, 18.8, 32.8, 59.8, 70.2, 72.5, 101.5, 103.9, 122.5, 125.2, 138.8, 141.9, 148.3, 163.2. IR (KBr, cm^{-1}): 2904, 1643(C=N), 1612, 1477, 1377. Anal. Calcd. for $C_{28}H_{32}N_2O_8$: C, 64.11; H, 6.15; N, 5.34; Found: C, 64.10; H, 6.12; N, 5.38.

*4.3.5. (S,R,S)-6,6′-dimethoxy-4,4′,5,5′-dimethylenedioxy-2,2′-bis(4-phenyl-4,5-dihydro-oxazole) (**6b**)*

Yield: 82%; $R_f = 0.78$ (PE:EA = 1:1); m.p. 175–177 °C; $[\alpha]_D^{20} = +56.5$ (0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.87 (s, 6H), 3.87–3.93 (m, 2H), 4.38–4.44 (m, 2H), 5.12–5.18 (m, 2H), 6.01 (s, 2H), 6.03 (s, 2H), 7.06–7.27 (m, 12H). ^{13}C NMR (300 MHz, $CDCl_3$): 60.0, 69.6, 75.1, 101.7, 104.2, 122.4, 124.9, 126.7, 127.3, 128.5, 139.1, 141.8, 142.7, 148.6, 165.2. IR (KBr, cm^{-1}): 1640(C=N). Anal. Calcd. for $C_{34}H_{28}N_2O_8$: C, 68.91; H, 4.76; N, 4.73; Found: C, 68.82; H, 4.81; N, 4.71.

*4.3.6. (S,R,S)-6,6′-dimethoxy-4,4′,5,5′-dimethylenedioxy-2,2′-bis(4-benzyl-4,5-dihydro-oxazole) (**6c**)*

Yield: 81%; $R_f = 0.65$ (PE:EA = 1:1); m.p. 61–62 °C; $[\alpha]_D^{20} = -19.2$ (1.5, $CHC1_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.45–2.52 (m, 2H), 2.81–2.88 (m, 2H), 3.79–3.99 (m, 4H), 3.84 (s, 6H), 4.23–4.33 (m, 2H), 5.98 (s, 2H), 6.00 (s, 2H), 6.98 (s, 2H), 7.11–7.27 (m, 10H). ^{13}C NMR (300 MHz, $CDCl_3$): 41.4, 59.9, 67.6, 71.9, 101.6, 104.0, 122.4, 125.1, 126.3, 128.4, 128.5, 129.2, 129.3, 138.6, 139.9, 141.7, 148.5, 163.8. IR (KBr, cm^{-1}): 1645(C=N). Anal. Calcd. for $C_{36}H_{32}N_2O_8$: C, 69.67; H, 5.20; N, 4.51; Found: C, 69.71; H, 5.22; N, 4.45.

4.4. General procedure for asymmetric pinacol coupling reaction

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 1h and a red solution was obtained. After addition of 1.5 equiv magnesium powder the catalyst solution was cooled to −20 °C then treated with aldehyde followed by addition of trimethylchlorosilane (TMSCl) dropwise. The reaction mixture was stirred for 24 h and then quenched with 10% sodium bicarbonate solution. After removing off the solid by filtration the filtrates were extracted 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 combined organic layers were dried over anhydrous Na_2SO_4, the solvent was removed under reduced pressure and the pinacol product was purified by silical gel chromatography or recrystallization.

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