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Asymmetric pinacol coupling of aromatic aldehydes catalyzed by a new titanium–Schiff base complex

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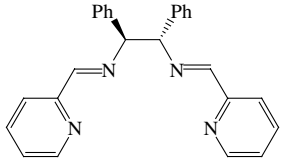
Abstract—A new Schiff-base with two stereogenic centers has been prepared and its titanium complex applied to catalyze the pinacol coupling of aldehydes, which afforded pinacols in high yield, excellent diastereoselectivities, and high enantioselectivities.

1. Introduction

Pinacol coupling of a carbonyl compound is one of the most effective routes for the formation of C–C bonds and the generation of vicinal diols in one step.[1] It has been employed in the key steps of several total syntheses of natural products.[2] Asymmetric pinacol coupling, which is one of the most promising methods for preparing chiral vicinal diols that are versatile chiral auxiliaries in various asymmetric reactions, has attracted increasing attention.[3] Since the first report by Mukayama of pinacol coupling reactions mediated with a titanium reagent in 1973,[4] a number of effective reductive systems have been developed to carry out this reaction.[5] Nevertheless, they all suffer from the principal drawback of having to be employed in stoichiometric amounts. Bandini et al.[6] achieved pinacol coupling of an aldehyde using a catalytic amount of a titanium–(Schiff-base) complex, while other groups[7] introduced various chiral ligands to conduct this reaction enantioselectively: however, only poor to moderate enantioselectivities were obtained. Bensari et al.[8] first developed a series of easily available chiral Schiff bases to improve the enantioselectivity. More recently, Joshi et al.[9] have enhanced the enantioselectivity with a tetradentate Schiff base. Based on Bensari's work, we have prepared a new chiral Schiff-base and applied it to the pinacol coupling of aldehydes; the corresponding pinacols were obtained in high yield, excellent diastereoselectivities, and high enantioselectivities under the mild condition.

2. Results and discussion

The chiral tetradentate Schiff-base **L** was prepared from (*S*,*S*)-(−)-1,2-diphenylethylenediamine and 2-pyridinecarboxaldehyde. Its chiral titanium complex was obtained by an exchange reaction between commercially $TiCl_4(THF)_2$ and the chiral Schiff-base in a ratio of 1:2.



L

Initially, the chiral Schiff-base with $TiCl_4(THF)_2$ was applied to catalyze the pinacol coupling of benzaldehyde under different conditions. The results are listed in Table 1.

In order to optimize the reaction conditions, the catalytic reaction with ligand **L** was investigated by varying solvent, reductant metal, reaction temperature, reaction time, and the amount of ligand **L**. The best results were achieved in CH_2CN at 0 °C for 12 h in the presence of 15% mol of ligand **L**, 1.5 equiv of Me_3SiCl, and 3 equiv of Mn power. The diastereoselectivity and enantioselectivity notably increased when the catalyst concentration was increased from 5 to 15 mol% (entries 5, 14, and 15); there was no significant improvement when the catalyst concentration was higher than 15% (entries 16 and 17).

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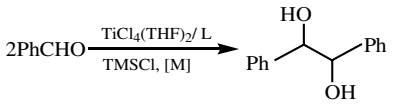
Table 1. Pinacol coupling of benzaldehyde under various conditions[a]



Entry	Cat. (mol%)	Solvent (reductant)	T (°C)	Yield (%)[b]	*Dl/meso*[c]	Ee (%)[c] (*S*,*S*)
1	15	CH_3CN(Mn)	50	56	85/15	39
2	15[d]	CH_3CN(Mn)	50	25	86/14	38
3	15	CH_3CN(Mn)	25	78	91/9	64
4	15[d]	CH_3CN(Mn)	25	41	91/9	63
5	15	CH_3CN(Mn)	0	95	93/7	88
6	15	CH_3CN(Mn)	−10	76	92/8	82
7	15[d]	CH_3CN(Mn)	−10	92	94/6	87
8	15	CH_3CN(Mn)	−25	65	90/10	78
9	15[d]	CH_3CN(Mn)	−25	89	93/7	86
10	15	CH_2Cl_2(Mn)	0	76	91/9	67
11	15	THF(Mn)	0	73	87/13	64
12	15	CH_3CN(Zn)	0	76	83/17	55
13	15	CH_3CN(Mg)	0	86	89/11	73
14	5	CH_3CN(Mn)	0	93	60/40	16
15	10	CH_3CN(Mn)	0	92	88/12	61
16	25	CH_3CN(Mn)	0	95	94/6	89
17	50	CH_3CN(Mn)	0	96	95/5	90

[a] The reaction was carried out in acetonitrile at 0 °C with 15% mol of chiral Schiff-base, 1.5 equiv of Me_3SiCl, and 3 equiv of Mn power (99.9%, 50 mesh) for 12 h.
[b] Isolated yield.
[c] Measured by chiral HPLC column: chiralcel-OJ-H; hexane/2-propanol = 9:1, flow rate = 0.5 mL/min, t_r (*S*,*S*)=27.3, t_r (*R*,*R*)=30.2, t_r (*meso*)=37.5.
[d] The reaction was carried out for 24 h.

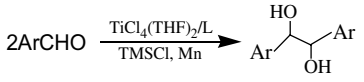
Under the optimized conditions, pinacol couplings of various aldehydes were investigated with the results summarized in Table 2. It seems an electron-donating group at the *para*-position of –CHO group slightly improves the diastereoselectivity and enantioselectivity (entries 3 and 4), while an electron-withdrawing group had the opposite effect (entries 5, 6, and 7). The diol resulting from the coupling of 2-thiophenecarboxaldehyde only showed a moderate enantioselectivity (entry 8). For isobutyraldehyde (entry 9), no diol could be obtained.

The mechanism of the previous reports[7,9] may be invoked to explain the results we obtained.

3. Conclusion

In conclusion, the titanium complex of ligand **L** is an effective catalyst for the asymmetric pinacol coupling of aromatic aldehydes. These results provide useful information for designing more efficient catalyst systems for

Table 2. Pinacol coupling of aromatic aldehydes in the presence of **L**[a]



1a-h **2a-h**

Entry	**1** ArCHO(Ar)	**2** Yield[b] (%)	*Dl/meso*[c]	Ee[c] (%) (*S*,*S*)
1	Phenyl	95 (**a**)	93/7	88
2	1-Naphthaldehyde	82 (**b**)	95/5	80
3	4-Methoxybenzaldehyde	92 (**c**)	98/2	91
4	4-Tolualdehyde	90 (**d**)	95/5	90
5	2-Chlorobenzaldehyde	86 (**e**)	92/8	60
6	4-Chlorobenzaldehyde	84 (**f**)	87/13	68
7	2,4-Dichlorobenzaldehyde	87 (**g**)	93/7	74
8	2-Thiophenecarboxaldehyde	80 (**h**)	89/11	53
9	Isobutyraldehyde	0	—	—

[a] The reaction was carried out in acetonitrile at 0 °C with 15% mol of chiral Schiff-base, 1.5 equiv of Me_3SiCl, and 3 equiv of Mn power (99.9%, 50 mesh) for 12 h.
[b] Isolated yield.
[c] Measured by chiral-HPLC column.[10,7b]

enantioselective pinacol coupling reactions of aldehydes, ketones or imines.

4. Experimental

4.1. General

All reactions were carried out under argon atmosphere. Commercial reagents were used without further purification. All solvents were dried using standard methods and were freshly distilled before use. Melting points were determined using hot-stage apparatus and are uncorrected. Optical rotations were measured on a WZZ-1 rotation spectrometer. NMR spectra were measured on a Bruker av300 spectrometer (300 Hz) by using a $CDCl_3$ as solvent and TMS as internal standard. IR spectra were recorded on a Bruker VECTOR-22 (KBr) spectrometer. Element analyses were performed on a Vari E spectrometer. HPLC analyses were performed using AGILENT1100 SERIES spectrometer. The diastereomeric excesses (*dl*/*meso*) and the enantiomeric excesses were determined by HPLC using chiral stationary phases or ^{1}H NMR analysis.

4.2. Preparation of (*S*,*S*)-1,2-diphenylethylenediamine

(1*S*,2*S*)-1,2-Diphenylethylenediamine was prepared according to the literature[11] with slight modification. Mp 83–84 °C, $[\alpha]_D^{20} = -106.5$ (*c* 1.0, CH_3OH); {lit.[11], mp 82–84 °C; $[\alpha]_D^{20} = -105.2$ (*c* 1.0, CH_3OH)}.

4.3. Preparation of (1*S*,2*S*)-*N*,*N*′-Bis(pyridylmethene)-1,2-diphenylethylenediimine

(1*S*,2*S*)-1,2-Diphenylethylenediamine (0.416 g, 2 mmol) and 2-pyridincarboxaldehyde (0.214 g, 1 mmol) were dissolved in 30 mL dry benzene. The mixture was gently refluxed under an inert atmosphere of argon. The water from the reaction was released by a Dean–Stark trap. After approximately 2 h, all of the water had been separated. The mixture was cooled to room temperature and concentrated under reduced pressure. The Schiff base was then obtained as a yellow solid in quantitative yield. Mp 164–166 °C; $[\alpha]_D^{20} = -12.7$ (*c* 1.0, C_2H_5OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 4.73 (s, 2H, CH), 6.77 (d, 2H, Ar), 6.92 (d, 2H, ArH), 7.13–7.96 (m, 12H, Ar), 8.30 (s, 2H, N=CH), 8.81 (d, 2H, Ar); ^{13}C NMR δ (ppm): 81.08, 117.02, 118.76, 127.73, 127.87, 128.28, 131.25, 132.48, 139.45, 161.11, 162.02. IR (KBr) ν (cm^{-1}): 1350, 1650; Anal. Calcd for $C_{26}H_{22}N_4$: C 80.78, H 5.95, N 14.08. Found: C 80.62, H 5.63, N 14.35.

4.4. Typical procedure for the pinacol coupling of aldehydes catalyzed by Schiff base

To a solution of **L** (0.3 mmol) in CH_3CN (2 mL), $TiCl_4(THF)_2$ (0.15 mmol) was added under argon. The resulting red solution was stirred for 30 min at room temperature then cooled to 0 °C. The Mn power (6 mmol) was added followed by the addition of Me_3SiCl (0.28 mL, 3 mmol) with the suspension turning green-blue. After a few minutes, the benzaldehyde (2 mmol) was added and the suspension stirred at 0 °C for 12 h. The suspension was quenched with a solution of 10% Na_2CO_3 and extracted with EtOAc. The organic solvent was evaporated under reduced pressure. The resulting brown-red oil was dissolved in THF solution of 1 M HCl (5 mL) and stirred at room temperature until the pinacol product had completely desilylated. The reaction was diluted with water and extracted twice with EtOAc. The organic phases were collected and dried over Na_2SO_4 and the residue purified by chromatography.

Compound **2a**, 1,2-diphenylethane-1,2-diol: Colorless crystals; mp 142–144 °C; $[\alpha]_D^{20} = -82.5$ (*c* 1.0, $CHCl_3$); ^{1}H NMR: δ (ppm) 2.03 (s, 2H, OH), 4.73 (s, H, *dl*), 4.83 (s, H, *meso*), 7.12–7.30 (m, 10H, Ph); enantiomeric excess by HPLC: chiralcel-OJ-H (hexane/2-propanol = 90:10, flow rate = 0.5 mL/min): t_r (*S*,*S*)=27.3 min, t_r (*R*,*R*)=31.1 min, t_r (*meso*)=38.8 min.

Compound **2b**, 1,2-di(1-naphthyl)ethane-1,2-diol: Colorless crystals; mp 122–124 °C; $[\alpha]_D^{20} = -41.0$ (*c* 1.0, C_2H_5OH); ^{1}H NMR: δ (ppm) 1.71 (s, 2H, OH), 5.79 (s, 2H, *dl*), 5.81 (s, 2H, *meso*), 7.58–7.02 (m, 6H, Ph), 7.96–7.60 (m, 8H); enantiomeric excess by HPLC: chiralcel-AD (hexane/2-propanol = 85:15, flow rate = 1.0 mL/min): t_r (*S*,*S*)=21.2 min, t_r (*R*,*R*)=22.4 min, t_r (*meso*) = 25.2 min.

Compound **2c**, 1,2-di(4-methoxylphenyl)ethane-1,2-diol: Colorless crystals; mp 130–132 °C; $[\alpha]_D^{20} = -105.0$ (*c* 1.0, C_2H_5OH); ^{1}H NMR: δ (ppm) 1.68 (s, 2H), 3.75 (s, 6H), 4.63 (s, H, *dl*), 4.74 (s, H, *meso*), 6.74–7.22 (m, 10H); enantiomeric excess by HPLC: chiralcel-AD (hexane/2-propanol = 95:5, flow rate = 1.0 mL/min): t_r (*S*,*S*)=9.3 min, t_r (*R*,*R*)=11.1 min, t_r (*meso*) = 15.4 min.

Compound **2d**, 1,2-di(4-methylphenyl)ethane-1,2-diol: Colorless crystals; mp 109–111 °C; $[\alpha]_D^{20} = -91.5$ (*c* 1.0, C_2H_5OH); ^{1}H NMR: δ (ppm) 2.30 (s, 6H), 2.75 (s, 2H, OH), 4.67 (s, H, *dl*), 4.74 (s, H, *meso*), 7.04–7.23 (m, 8H); enantiomeric excess by HPLC chiralcel-WH (hexane/2-propanol = 9:1, flow rate = 1.0 mL/min): t_r (*S*,*S*)= 11.2 min, t_r (*R*,*R*)=12.4 min, t_r (*meso*)=15.2 min.

Compound **2e**, 1,2-di(2-chlorophenyl)ethane-1,2-diol: Colorless crystals; mp 130–132 °C; $[\alpha]_D^{20} = -38$ (*c* 0.5, $CHCl_3$); ^{1}H NMR: δ (ppm) 1.64 (s, 2H), 5.32 (s, H, *dl*), 5.45 (s, H, *meso*), 7.25–7.32 (m, 8H, Ar); nantiomeric excess by HPLC: chiralcel-WH (hexane/2-propanol = 9:1, flow rate = 0.8 mL/min): t_r (*S*,*S*)=8.6 min, t_r (*R*,*R*)=10.2 min, t_r (*meso*)=14.1 min.

Compound **2f**, 1,2-di(4-chlorophenyl)ethane-1,2-diol: Colorless crystals; mp 189–191 °C; $[\alpha]_D^{20} = -42.5$ (*c* 0.5, $CHCl_3$); ^{1}H NMR: δ (ppm) 2.53 (s, 2H), 5.36 (s, H, *dl*), 5.60 (s, H, *meso*), 7.14–7.65 (m, 8H); enantiomeric excess by HPLC: chiralcel-WH (hexane/2-propanol = 95:5,

flow rate = 1.0 mL/min): t_r (*S*,*S*)=7.4 min, t_r (*R*,*R*)= 9.1 min, t_r (*meso*)=12.3 min.

Compound **2g**, 1,2-di(2,4-dichlorophenyl)ethane-1,2-diol: Colorless crystals; mp 135–137 °C; $[\alpha]_D^{20} = -58.0$ (*c* 1.0, $CHCl_3$); ^1H NMR: δ (ppm) 1.57 (s, 2H), 5.43 (s, H, *dl*), 5.55 (s, H, *meso*), 7.13–7.32 (m, 6H); enantiomeric excess by HPLC: chiralcel-WH (hexane/2-propanol = 9:1, flow rate = 0.8 mL/min): t_r (*S*,*S*)=15.1 min, t_r (*R*,*R*)=17.2 min, t_r (*meso*)=21.1 min.

Compound **2h**, 1,2-di(2-thiophenyl)ethane-1,2-diol: Colorless crystals; mp 102–104 °C; $[\alpha]_D^{20} = -26.0$ (*c* 1.0, C_2H_5OH); ^1H NMR: δ (ppm) 3.74 (s, 2H), 5.22 (s, H, *dl*), 5.37 (s, H, *meso*), 6.68–7.22 (m, 6H); enantiomeric excess by HPLC: chiralcel-OB (hexane/2-propanol = 85:15, flow rate = 0.5 mL/min): t_r (*S*,*S*)=10.5 min, t_r (*R*,*R*)=11.5 min, t_r (*meso*)=14.1 min.

Acknowledgements

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