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Article

Enantioselective Pinacol Coupling of Aromatic Aldehydes Mediated by $TiCl_4(THF)_2$/Zn with Tartaric Ester†

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Asymmetric pinacol coupling of aromatic aldehydes mediated by low valent titanium complexes of chiral ligands derived from natural tartaric acid provided corresponding pinacols in good yields with excellent diastereoselectivities and moderate enantioselectivities.

Keywords pinacol, asymmetric coupling, enantioselectivity, tartaric acid

Introduction

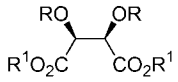
Reductive coupling of carbonyl compounds which leads to vicinal diols is one of the most important reactions for the formation of carbon-carbon bond.[1] Its mechanism and applications have been intensively studied for many years.[2] Recently the reductive coupling of carbonyl compounds has been used in the synthesis of HIV-protease inhibitors[3] and some natural products such as taxol.[4]

Since the pioneering contributions in this field by Mukaiyama[5] and McMurry[6], various metals including Na,[7] Zn,[8] Mg,[9] Mn,[10] Sn,[11] Ti,[12] Sm,[13] Al,[14] Ce,[15] Te,[16] U,[17] Cr[18] and V[19] have been shown to efficiently mediate or catalyze pinacol coupling reaction. Several chiral ligands have been introduced to conduct this reaction in enantioselective versions. However, only poor or moderate enantioselectivties were obtained[20] when catalytic amount of chiral ligands was used. Bensari[21] remarkably improved the enantioselectivity by using a titanium complex of Schiff-base ligand with single chiral center. More recently, Joshi[22] further enhanced the enantioselectivity with a titanium complex of the tetradentate Schiff base. We had indicated that $TiCl_4$-Zn/chiral diamines could reduce aromatic aldehydes to give the vicinal diols in good yields, *dl*-diastereoselectivities and moderate enantioselectivities.[23] Here, we would like to report the results of our continued study on this reaction using tartaric esters.

Results and discussion

The chiral bidentate ligands **1**—**4** (Scheme 1) were derived from the natural tartaric acid. Their chiral titanium complexes were obtained by an exchange reaction between chiral ligands **1**—**4** and $TiCl_4(THF)_2$ in a ratio of 2∶1.

Scheme 1



1 R = H, R^1 = Et
2 R = Me, R^1 = Et
3 R = H, R^1 = $PhCH_2$
4 R = Me, R^1 = $PhCH_2$

To optimize the reaction condition, the coupling reactions were investigated with different ligands, metals, reaction temperatures and the amounts of ligands (Table 1). The best results were achieved in CH_2Cl_2 at 20 ℃ for 20 min in the presence of stoichiometric amount ligand **4** and Zn as the reductant (Entries 1—4). The diastereoselectivity and enantioselectivity were remarkably decreased when the catalyst loading was decreased from the stoichiometric amount to 25 mol% (Entries 4, 8 and 9). The higher temperature was unfavorable to the yield, diastereoselectivity and enantioselectivity (Entry 5). Further lowering of the temperature seemed to be able to slightly increase the enantioselectivity (Entries 6 and 7). Simultaneously, the bulky ester groups could obviously improve the enantioselectivities (Entries 3, 4 vs. 1, 2).

Under the optimized conditions, pinacol coupling of various aldehydes was investigated and the results are summarized in Table 2. The aromatic aldehydes possessing an electron-donating group are more favorable to improve the diastereoselectivity and enantioselectivity (Entries 3 and 4) than the substrates with an electron-withdrawing group (Entries 5 and 6). The isobutyraldehyde was also tested in the pinacol coupling reaction as substrate. However, no corresponding pinacol was isolated (Entry 7).

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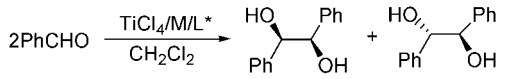
Table 1 Pinacol coupling of benzaldehyde under various conditions[a]

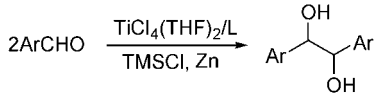


dl *meso*

Entry	Ligand/ mmol%	Temp./ ℃	Yield[b]/ %	*dl*/*meso*[c]	*ee*[c]/% (*S*,*S*)
1	1 (100)	20	91	*dl* only	44
2	2 (100)	20	87	*dl* only	45
3	3 (100)	20	93	*dl* only	64
4	4 (100)	20	95	*dl* only	67
5	4 (100)	50	64	91∶9	25
6	4 (100)	0	94	*dl* only	69
7	4 (100)	−20	97	*dl* only	70
8	4 (50)	20	47	87∶13	33
9	4 (25)	20	43	84∶16	18.6
10[d]	4 (100)	20	82	*dl* only	56
11[e]	4 (100)	20	79	*dl* only	48

[a] The reaction was carried out in CH_2Cl_2 at 20 ℃ with chiral ligands, Zn as reductant for 20 min. [b] Isolated yield. [c] Measured by HPLC on chiralcel-OJ-H column; Hexane∶2-propanol=9∶1, flow rate=0.5 mL/min, t_r(*S*,*S*) =27.3 min, t_r(*R*,*R*)=30.2 min, t_r(*meso*)=37.5 min. [d] Mn as reductant. [e] Mg as reductant.

Table 2 Pinacol coupling of aromatic aldehydes in the presence of **4**[a]



1a −1h **2a − 2h**

Entry	Aldehyde **1**	Yield[b]/% of **2**	*dl*/*meso*[c]	*ee*[c]/% (*S*,*S*)
1	Benzaldehyde (**a**)	95 (**a**)	*dl* only	67
2	1-Naphthaldehyde (**b**)	92 (**b**)	*dl* only	65
3	4-Methoxybenzaldehyde (**c**)	95 (**c**)	*dl* only	68
4	4-Tolualdehyde (**d**)	96 (**d**)	*dl* only	70
5	2-Chlorobenzaldehyde (**e**)	85 (**e**)	*dl* only	49
6	4-Chlorobenzaldehyde (**f**)	83 (**f**)	*dl* only	47
7	Isobutyraldehyde	0	—	—

[a] The reactions were carried out in CH_2Cl_2 at 20 ℃ with a stoichiometric amount of chiral ligand **4**, Zn as reductant for 20 min. [b] Isolated yields. [c] Measured by HPLC on chiral column.[23,24]

Experimental

General

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

Chiral ligands were prepared according to the literature procedures[25] with slight modification. **1:** m.p. 17 ℃, $[\alpha]_D^{20}$ +7.5 (neat) [lit.[25b] m.p. 17 ℃; $[\alpha]_D^{20}$ +7.9 (neat)]. **2:** $[\alpha]_D^{20}$ +88 (*c* 1.0, C_2H_5OH) [lit.[28a] $[\alpha]_D^{20}$ +89.9 (*c* 1.0, C_2H_5OH)]. **3**: m.p. 49—51 ℃, $[\alpha]_D^{20}$ +18.5 (*c* 1.0, C_2H_5OH) [lit.[25b], m.p. 50 ℃; $[\alpha]_D^{15}$ +19.3 (*c* 1.0, C_2H_5OH)]. **4** m.p. 81—83 ℃, $[\alpha]_D^{20}$ +112.5 (*c* 1.0, C_2H_5OH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.11 (s, 3H, OCH_3), 4.60 (s, H, CH), 4.53 (s, 2H, CH_2), 7.33—7.35 (m, 5H, Ph).

The optimized procedure of pinacol coupling is as follows: to a 50 mL three neck flask, a solution of $TiCl_4$ (4.0 mmol) in a mixed solvent of CH_2Cl_2 (8 mL) and THF (8.0 mmol) was added carefully and stirred for 3 min, then the chiral ligands (4.0 mmol) in CH_2Cl_2 (1 mL) was added dropwise at 20 ℃. After stirring for 5 min, zinc powder (4.0 mmol) was added in one portion. The color of the reaction mixture changed to green immediately. After stirring for additional 3 min, a solution of aromatic aldehyde (4.0 mmol) in CH_2Cl_2 (1 mL) was introduced to the reaction mixture. After further being stirred for 20 min, the reaction mixture was quenched with a saturated solution of $NaHCO_3$ (5 mL). The stirring was continued for 20 min, and the solution was diluted with ethyl acetate. The mixture was filtered through sintered glass funnel. The aqueous phase was separated and extracted with ethyl acetate (2×10 mL). The organic phase was washed with saturated solution of NaCl (2×10 mL), and dried over Na_2SO_4. The product was purified by silica gel chromatographic column to give pure hydrobenzoin. The chiral ligands could be recovered from the organic phase (43%—56%). The authenticity of the product was established by their ^{1}H-NMR, IR and Mass spectra.

1,2-Diphenyl-1,2-ethanediol (**2a**): m.p. 147—149 ℃ [lit.[26] m.p. 148—150 ℃]; $[\alpha]_D^{20}$ −60.5 (*c* 1.0, EtOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.03 (s, 2H, OH), 4.72 (s, 2H, PhCH), 7.12—7.30 (m, 10H, Ph). Enantiomeric excess was determined by HPLC on chiralcel-OJ column (Hexane∶2-propanol=90∶10, flow rate=0.5 mL/min): t_r(*S*,*S*)=27.3 min, t_r(*R*,*R*)=30.2 min.

1,2-Di(1-naphthyl)-1,2-ethanediol (**2b**): m.p. 122～124 ℃; $[\alpha]_D^{20}$ −54.5 (*c* 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.71 (s, 2H, OH), 5.79 (s, 2H, CH for *dl*), 5.81 (s, 2H, CH for *meso*), 7.96—7.26 (m, 14H, Ar). Enantiomeric excess was determined by HPLC on chiralcel-AD column (Hexane∶2-propanol=85∶15, flow rate=1.0 mL/min): t_r(*S*,*S*)=20.8 min, t_r(*R*,*R*)=

23.4 min.

1,2-Di(4-mthoxylphenyl)-1,2-ethanediol (**2c**): m.p. 130—132 ℃ [lit.[26] m.p. 132—134 ℃] $[\alpha]_D^{20}$ −70.5 (*c* 1.0, C_2H_5OH); ^1H NMR ($CDCl_3$, 300 MHz) δ: 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 was determined by HPLC on chiralcel-AD column (Hexane∶2-propanol=95∶5, flow rate=1.0 mL/min): $t_r(S,S)$=8.9 min, $t_r(R,R)$=10.9 min.

1,2-Di(4-methylphenyl)-1,2-ethanediol (**2d**): m.p. 104—105 ℃ (lit.[26] 105—107 ℃); $[\alpha]_D^{20}$ −72.0 (*c* 1.0, EtOH); ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.76 (s, 2H, OH), 2.43 (s, 6H, CH_3), 4.77 (s, 2H, ArCH), 7.28—8.01 (m, 8H, Ar). Enantiomeric excess was determined by HPLC on chiralcel-WH column (Hexane∶2-propanol=9∶1, flow rate=1.0 mL/min): $t_r(S,S)$=10.9 min, $t_r(R,R)$=12.8 min.

1,2-Di(2-chlorophenyl)-1,2-ethanediol (**2e**): m.p. 130—131 ℃ (lit.[26] 132—133 ℃); $[\alpha]_D^{20}$ −27.0 (*c* 0.10, EtOH); ^1H NMR ($CDCl_3$, 300 MHz) δ: 3.17 (s, 2H, OH), 5.39 (s, 2H, ArCH), 7.18—7.68 (m, 8H, Ar). Enantiomeric excess was determined by HPLC on chiralcel-WH column (Hexane∶2-propanol=9∶1, flow rate =0.8 mL/min): $t_r(S,S)$=8.0 min, $t_r(R,R)$=10.0 min.

1,2-Di(4-chlorophenyl)-1,2-ethanediol (**2f**): Colorless crystals; m.p. 119—120 ℃ (lit.[26] 121 ℃); $[\alpha]_D^{20}$ −32.0 (*c* 0.1, C_2H_5OH); ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.88 (s, 2H, OH), 4.63 (s, 2H, ArCH), 7.01—7.28 (m, 8H, Ar). Enantiomeric excess was determined by HPLC on chiralcel-WH column (Hexane∶2-propanol=95∶5, flow rate=1.0 mL/min): $t_r(S,S)$=7.3 min, $t_r(R,R)$=9.1 min.

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