Asymmetric Pinacol Coupling of Aromatic Aldehydes Catalyzed by $TiCl_4(THF)_2$-Zn/Chiral Diamines

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Asymmetric pinacol coupling of aromatic aldehydes catalyzed by chiral diamines/low-valent titanium complexes gave corresponding pinacols in good yields with high diastereoselectivity and moderate enantioselectivities.

Keywords chiral diamine, pinacol, asymmetric coupling, enantioselectivity

Introduction

Formation of radical anions catalyzed by the transition metal is a challenging field in organic synthesis as it can lead to potential control of diastereoselectivity and enantioselectivity in a wide range of organic transformations.[1] The reductive coupling reaction of aldehydes is an important method of carbon-carbon bond formation. It is also the most direct and efficient method of synthesizing vicinal diols.[2,3] Various metals such as Mg,[4] Al,[5] Zn,[6] Ce,[7] Mn,[8] Sm,[9] Ti,[10] Sn[11] and Cr[12] have been shown to be efficient in pinacol coupling. Since the pioneering contributions in this field by Mukaiyama[13] and McMurry,[14] low valent titanium compounds are most prominent for this reaction of carbon-carbon bond formation. The low valent titanium compounds used in the reaction can be either a stable compound such as Cp_2TiCl and $TiCl_3$ or the species prepared *in situ* by the reaction of a readucing reagents such as Zn and Al with $TiCl_4$.[15-18]

Careful optimization of the reaction parameters can lead to high diastereoselectivities in intramolecular and intermolecular coupling of aromatic aldehydes.[18a,18b] The first example of a transition metal catalyzed enantioselective formation of vicinal diols was reported in 1999 by Gancäuer[19] in the asymmetric opening of meso epoxides mediated by an enantiopure titanocene catalyst. Recently, Enders and Ullrich[20] developed an enantioselective route of the pinacol coupling with titanium(II) chloride and enantiopure amine or hydrazine reagents as additives. Ahlem[21] reported enantioselective pinacol coupling of aromatic aldehydes catalyzed by chiral Schiff bases and $TiCl_4$. Li[22] indicated that $TiCl_4$-Zn/TMEDA reduced aromatic aldehydes to produce the vicinal diols in good yield and high diastereoselectivity, but no enantioselectivity. Herein, we modify this reaction into an asymmetric version using enantiopure diamines to displace TDEMA in the reaction system.

Results and discussion

The aromatic aldehydes **1** were treated with a solution of $TiCl_4(THF)_2$-Zn/chiral diamines in CH_2Cl_2. Hydrobenzoins were obtained in excellent yield (90%—97%), high diastereoselectivities and moderate enantiomeric excess. As shown in Table 1, the best result was achieved for substrate **1e** (97% yield, only *dl* isomers, and 65% enantiomeric excess). The enantioselectivities were significantly affected by the substituent of benzaldehyde, the bulkier substituent was favourable for getting higher enantiomeric excess (Entry 6). The electron withdrawing group in benzene ring was also favourable for achieving high yield and good enantioselectivity since the reaction intermediate was a radical anion. The results indicated that both bulkier and electron withdrawing groups were availed to produce high yield and good enantiomeric excess. Notably, the chiral diamines used in this reaction cound be recovered partly and reused without loss of enantioselectivity.

The aliphatic aldehydes were also tested in the pinacol coupling reaction as substrates, however, no corresponding pinacols were isolated.

According to the reports of Li,[22] Sobota[23] and Foling,[24] a plausible mechanism is suggested, which is shown in Fig. 1. First, the $TiCl_4(THF)_2$ is reduced by Zn to a binuclear complex $[Ti_2(\mu\text{-}Cl)_2Cl_4(THF)_4]$. Simultaneously, Zn is oxidized to $ZnCl_2$ which can form an ionic complex $[Ti_2Cl_4(THF)_3^+ \cdot ZnCl_3(THF)^-]$ with $[Ti_2(\mu\text{-}Cl)_2Cl_4(THF)_4]$. The binuclear complex $[Ti_2(\mu\text{-}Cl)_2Cl_4(THF)_4]$ is the active species which reduces the aromatic aldehydes to pinacol with high *dl*-selectivity, while the ionic complex $[Ti_2Cl_4(THF)_3^+ \cdot ZnCl_3(THF)^-]$ is inactive

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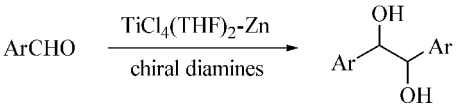
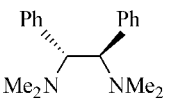
to the pinacol coupling of aromatic aldehydes. When a Lewis base such as TMEDA or *N*,*N*,*N*′,*N*′-tetramethyl-1,2-diphenylethylenediamine is added, the ligand will coordinate with $[Ti_2(\mu\text{-}Cl)_2Cl_4(THF)_4]$ and the ionization of $[Ti_2(\mu\text{-}Cl)_2Cl_4(THF)_4]$ can be suppressed because the activity of $ZnCl_2$ is decreased. Meanwhile, such coordination can improve the *dl*-selectivity because of steric interaction. If a chiral diamines (**3** or **4**) is employed, the binuclear titanium complex can coordinate with the chiral diamines to form a binuclear complex **I** which reduces two molecules of aromatic aldehyde to give a diradical intermediate **II**. Finally, the diradical intermediate **II** undergoes radical coupling to form carbon-carbon bond and then produces the cooresponding pinacol via hydrolyzation. The phenyl groups in the chiral diamines interacting with aromatic groups of aldehydes produce sterically crowded environment, which obviously improved the diastereoselectivities and enantioselecivities of the reaction. Meanwhile, a competing formation of the corresponding alcohol is a side reaction since the binuclear complex can be decomposed to the mononuclear complex. The yield of alcohol gradually increases when the reaction time lasted longer than 20 min (Table 2).

Table 1 Enantioselective pinacol coupling reaction of aromatic aldehydes catalyzed by $TiCl_4(THF)_2$-Zn/chiral diamines

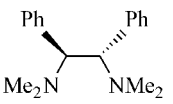


1a–1e **2a–2e**

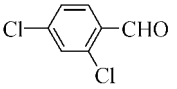
Diamines:



N,*N*,*N*′,*N*′-tetramethyl-(1*R*,2*R*)-(+)-1,2-diphenylethylenediamine **3**



N,*N*,*N*′,*N*′-tetramethyl-(1*S*,2*S*)-(−)-1,2-diphenylethylenediamine **4**

Entry	Aldehyde	Diamines	**2**	Yield[a] (%)	*dl*/*meso*[b]	*ee*[c] (%)
1	PhCHO (**a**)	**3**	**a**	95	*dl* only	52 (*S*,*S*)
2	PhCHO (**a**)	**4**	**a**	95	*dl* only	53 (*R*,*R*)
3	*p*-ClC_6H_4CHO (**b**)	**3**	**b**	97	*dl* only	46 (*S*,*S*)
4	*m*-ClC_6H_4CHO (**c**)	**3**	**c**	91	*dl* only	34 (*S*,*S*)
5	*p*-$CH_3C_6H_4CHO$ (**d**)	**3**	**d**	92	*dl* only	56 (*S*,*S*)
6	 (**e**)	**3**	**e**	97	*dl* only	65 (*S*,*S*)

[a] Pinacol isolated yield; [b] determined by ^1H NMR (300 Hz) or GC; [c] determined by HPLC analysis using Chiralcel column.[20]

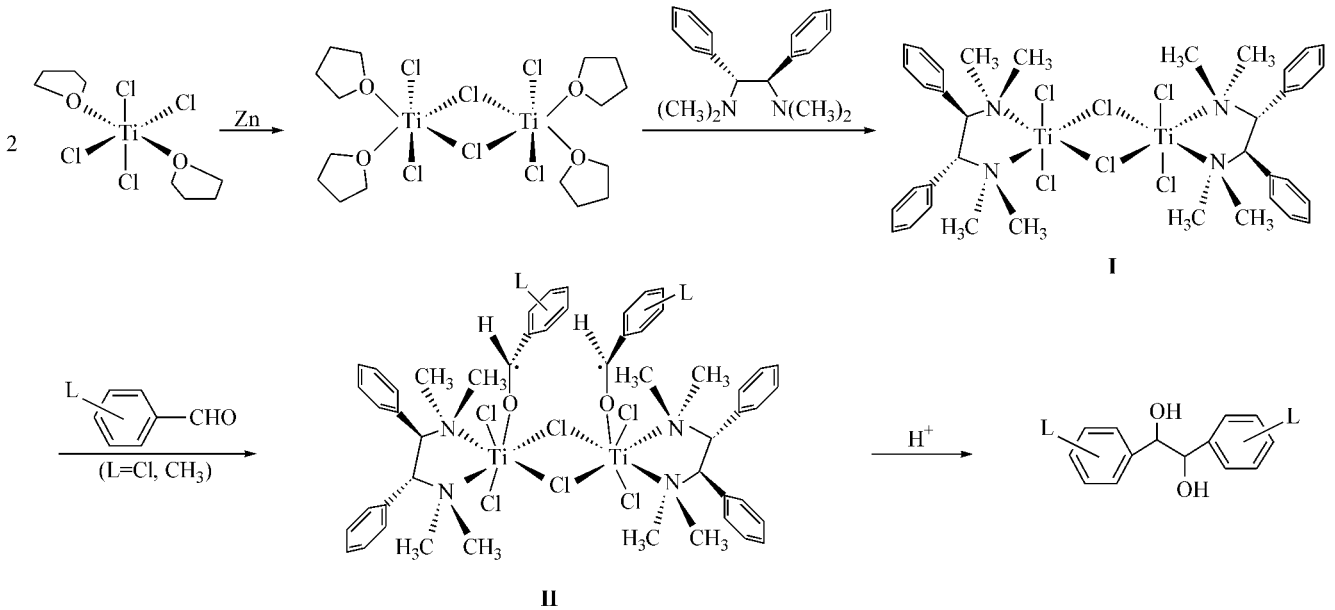
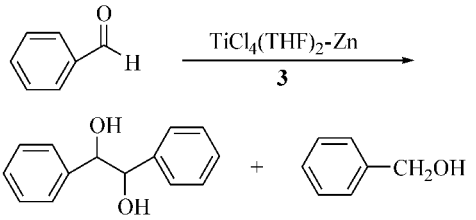


Fig. 1 Suggested mechanism for the asymmetric pinacol coupling of aromatic aldehydes catalyzed by $TiCl_4(THF)_2$-Zn/chiral diamines.

Table 2 Influence of reaction time on the yield of side product, benzylalcohol



Entry	Reaction time (min)	Pinacol yield[a] (%)	Benzyl alcohol[b] (%)
1	5	20	0
2	10	57	1
3	15	83	3
4	20	95	4
5	25	82	15
6	30	68	27
7	35	61	34
8	40	50	46
9	45	42	54
10	50	26	69
11	55	5	93
12	60	0	95

[a,b] Isolated yield.

Moreover, the failure of obtaining pinacol from a corresponding aliphatic aldehyde may be attributed to the unstablity of their corresponding radical anions.

In conclusion, the chiral diamines were effective for control of diastereoselectivities and enantioselecivities of asymmetric pinacol coupling of aromatic aldehydes. This method might provide useful information for designing more efficient catalyst systems for enantioselective pinacol coupling reactions.

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 were freshly distilled before use. Melting points were determined using hot-stage apparatus and were uncorrected. NMR spectra were measured on a Bruker av300 analyzer (300 Hz) by using $CDCl_3$ as solvent and TMS as internal standard. Mass spectra (EI) were determined on a TRACE-MS analyzer. IR spectra were recorded on a Bruker VECTOR-22 (KBr) spectrometer. Element analyses were performed on a Vari E Ⅲ analyzer. GC-MS and HPLC analyses were performed using TRACE/GC-MS analyzer and AGILENT1100 SERIES analyzer, respectively. The diastereomeric excesses (*dl*/*meso*) were determined by ^1H NMR and GC analysis, the enantiomeric excesses were determined by HLPC using chiral stationary phases. Chiral diamines **3** and **4** were prepared from (1*R*, 2*R*)- and (1*S*, 2*S*)-1,2-diphenyethylenediamine.[25]

The optimized procedure 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 diamines (4.0 mmoL) in CH_2Cl_2 (1 mL) was added dropwise at room temperature. 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 aldehydes (4.0 mmol) in CH_2Cl_2 (1 mL) was introduced to the reaction mixture. After further stirring 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 on silica gel chromatographic column to give pure hydrobenzoin. The chiral diamines can be recovered from the organic phase (51%—68%). The authenticity of the product was established by their NMR, IR and Mass spectra.

2a *dl*-1,2-Diphenyl-1,2-ethanediol (*d*/*l* = 24/76) Colorless crystals; m.p. 122—124 ℃ (lit.[26] 122—123 ℃); $[\alpha]_D^{20}$ − 4.1 (*c* 0.10, $CHCl_3$); ^1H NMR δ: 2.03 (s, 2H, OH), 4.72 (s, 2H, PhCH), 7.12—7.30 (m, 10H, Ph); IR (KBr) ν_{max}: 3400—3480 cm^{-1}; MS *m*/*z* (%): 214 (1), 180 (7.6), 167 (12.5), 149 (6), 107 (93.8), 79 (100), 77 (73.8). Anal. calcd for $C_{14}H_{14}O_2$: C 77.96, H 6.61; found C 78.51, H 6.54; Enantiomeric excess analysis by HPLC: Chiralcel-OJ (hexane:2-propanol = 85:15, flow rate = 1.0 mL/min), t_r (*S*, *S*) = 10.66 min, t_r (*R*, *R*) = 12.93 min.

2b *dl*-1,2-Di (4-chlorophenyl)-1,2-ethanediol (*d*/*l* = 27/73) Colorless crystals; m.p. 120—123 ℃ (lit.[27] 121 ℃); $[\alpha]_D^{20}$ + 4.2 (*c* 0.15, $CHCl_3$); ^1H NMR δ: 2.88 (s, 2H, OH), 4.63 (s, 2H, ArCH), 7.01—7.28 (m, 8H, Ar); IR (KBr) ν_{max}: 3380—3420 cm^{-1}; MS *m*/*z* (%): 282 (1), 235 (12), 165 (5.5), 141 (100), 107 (19), 77 (10). Anal. calcd for $C_{14}H_{12}Cl_2O_2$: C 59.11, H 4.02; found C 59.36, H 4.24; Enantiomeric excess analysis by HPLC: Chiralcel-WH (hexane:2-propanol = 95:5, flow rate = 1.0 mL/min), t_r (*S*, *S*) = 8.15 min, t_r (*R*, *R*) = 9.68 min.

2c *dl*-1,2-Di (2-chlorophenyl)-1,2-ethanediol (*d*/*l* = 33/67) Colorless crystals; m.p. 132—134 ℃ (lit.[27] 132—133 ℃); $[\alpha]_D^{20}$ + 2.3 (*c* 0.10, EtOH); ^1H NMR δ: 3.17 (s, 2H, OH), 5.39 (s, 2H, ArCH), 7.18—7.68 (m, 8H, Ar); IR (KBr) ν_{max}: 3265—3320 cm^{-1}; MS *m*/*z* (%): 263 (1.5), 251 (2), 178 (4.5), 141 (100), 113 (23.8), 77 (71). Anal. calcd for C_{14}-

$H_{12}Cl_2O_2$: C 59.13, H 4.04; found C 59.36, H 4.24; Enantiomeric excess analysis by HPLC: Chiralcel-WH (hexane:2-propanol = 9:1, flow rate = 0.8 mL/min), t_r (*S*, *S*) = 8.52 min, t_r(*R*, *R*) = 10.21 min.

2d *dl*-1,2-Di(4-methylphenyl)-1,2-ethanediol (*d*/*l* = 22/78) Colorless crystals; m.p. 125—127 ℃ (lit.[27] 125—126 ℃); $[\alpha]_D^{20}$ − 2.6 (*c* 1.50, EtOH); ^{1}H NMR δ: 1.76 (s, 2H, OH), 2.43 (s, 6H, CH_3), 4.77 (s, 2H, ArCH), 7.28—8.01 (m, 8H, Ar); IR (KBr) ν_{max}: 3280—3450 cm^{-1}; MS *m*/*z* (%): 242 (1.1), 195 (6), 121 (100), 107 (12), 93 (19), 77 (13). Anal. calcd for $C_{16}H_{18}O_2$: C 81.20, H 5.11; found C 81.36, H 5.08; Enantiomeric excess analysis by HPLC Chiralcel-WH (hexane:2-propanol = 9:1, flow rate = 1.0 mL/min), t_r(*S*, *S*) = 9.08 min, t_r(*R*, *R*) = 13.14 min.

2e *dl*-1,2-Di(2,4-dichlorophenyl)-1,2-ethanediol (*d*/*l* = 16/84) Colorless crystals; m.p. 140—142 ℃ (lit.[27] 140—141 ℃); $[\alpha]_D^{20}$ + 6.4 (*c* 0.10, EtOH); ^{1}H NMR δ: 2.04 (s, 2H, OH), 5.25 (s, 2H, ArCH), 7.24—7.63 (m, 6H, Ar); IR (KBr) ν_{max}: 3320—3400 cm^{-1}; MS *m*/*z* (%): 352 (1), 305 (1.4), 233 (10), 175 (100), 145 (10), 111 (25). Anal. calcd for $C_{14}H_{10}Cl_4O_2$: C 47.05, H 2.73; found C 47.73, H 2.84; Enantiomeric excess analysis by HPLC: Chiralcel-WH (hexane:2-propanol = 9:1, flow rate = 0.8 mL/min), t_r(*S*, *S*) = 17.63 min, t_r(*R*, *R*) = 22.00 min.

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