

Short communication

# Asymmetric pinacol coupling catalyzed by TADDOL-titanium complexes

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## Abstract

Chiral diols **1–4** derived from tartaric acid have been exploited in asymmetry pinacol coupling reaction, good to excellent diastereoselectivities and moderate to good enantioselectivities were obtained.

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*Keywords:* Diols; Tartaric acid; Pinacol coupling

## 1. Introduction

The pinacol coupling of aldehydes or ketones to give diols is an important method for constructing vicinally functionalized carbon–carbon bonds [1], which have been reported to promote successfully by many low-valent metals, such as Ti [2], Cr [3], Nb [4] and so on. In addition, the introduction of chlorosilane prominently affects the pinacol coupling reactions in stoichiometric or catalytic version [5]. Recently, good to excellent diastereoselectivity and enantioselectivity have been achieved with low-valent titanium [6] and chromium complexes [7] by different groups, respectively. Our group [8] has applied a series of tartaric acid esters for the catalytic pinacol coupling reaction with high diastereoselectivities and moderate enantioselectivities. To the best of our knowledge, TADDOLs originated by Seebach [9] represented a versatile class of chiral auxiliaries or ligands in asymmetric syntheses. However, no example of pinacol coupling reaction has been reported using TADDOL as ligands up to date. Thus, we are interested in exploiting the usability of this ligand in asymmetric pinacol coupling reaction.

## 2. Experimental

### 2.1. General

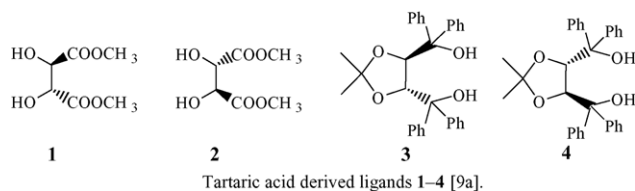
All reactions were carried out under inert atmosphere. Commercial reagents were used without further purification. THF

was dried and freshly distilled from sodium-benzophenone under an atmosphere of dry nitrogen. Dichloromethane was distilled from P<sub>2</sub>O<sub>5</sub> 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) using CDCl<sub>3</sub> 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 <sup>1</sup>H NMR and enantiomeric excesses were determined by HPLC using chiral column.

### 2.2. General procedure for pinacol coupling reaction

To a solution of TiCl<sub>4</sub> (0.2 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (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<sub>2</sub>Cl<sub>2</sub> (1 mL), stirring was continued for another 1 h and a red solution was obtained. After addition of 1.5 equiv. zinc powder, the catalyst solution was cooled to –10 °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, and 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

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Scheme 1.

temperature until the pinacol product had completely desilylated. The reaction was diluted with water and extracted with ethyl acetate ( $3 \times 15$  mL). The combined organic layers were dried over anhydrous  $\text{Na}_2\text{SO}_4$ , the solvent was removed under reduced pressure and the pinacol product was purified by silica gel chromatography or recrystallization.

### 3. Results and discussion

Chiral diols **1–4** derived from tartaric acid were synthesized according the literature [9a] with slight modification. Corresponding titanium complexes were generated in situ by an exchange reaction between ligands **1–4** and  $\text{TiCl}_4$  in  $\text{CH}_2\text{Cl}_2$  (Scheme 1).

The pinacol coupling reactions were carried out with different ligands, metals, the amounts of ligands and reaction temperatures. The results were listed in Table 1. As shown in the table, the pinacols were obtained with moderate to good diastereoselectivities and moderate enantioselectivities. TADDOLs (ligand **3** and **4**) offered much better results than diols **1** and **2** did. (*R,R*)-ligand gave (*S,S*)-pinacol. As most of the asymmetric reaction, lower temperature was favorable for both diastereoselectivity and enantioselectivity.

Table 1  
Pinacol coupling reaction of benzaldehyde with different ligands and conditions<sup>a</sup>

Entry	Ligand	Metal	<i>T</i> (°C)	Yield <sup>b</sup> (%)	dl:meso <sup>c</sup>	ee (%) <sup>d</sup> (configuration)
1	<b>1</b>	Zn	25	76	66:34	13 ( <i>S,S</i> )
2	<b>2</b>	Zn	25	74	62:38	11 ( <i>R,R</i> )
3	<b>3</b>	Zn	25	93	87:13	64 ( <i>S,S</i> )
4	<b>4</b>	Zn	25	90	82:18	56 ( <i>R,R</i> )
5	<b>3</b>	Mg	25	91	81:19	61 ( <i>S,S</i> )
6	<b>3</b>	Mn	25	67	55:45	46 ( <i>S,S</i> )
7	<b>3</b>	Zn	0	89	89:11	67 ( <i>S,S</i> )
8	<b>3</b>	Zn	−10	88	99:1	71 ( <i>S,S</i> )
9 <sup>e</sup>	<b>3</b>	Zn	25	95	82:18	66 ( <i>S,S</i> )
10 <sup>f</sup>	<b>3</b>	Zn	25	99	83:17	67 ( <i>S,S</i> )

<sup>a</sup> Reaction conditions: 2.0 mmol of benzaldehyde, 0.1 equiv. catalyst, 2 equiv. metal, 1.5 equiv. TMSCl for 24 h.

<sup>b</sup> Isolated yield.

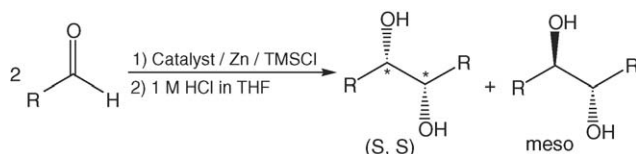
<sup>c</sup> Determined by  $^1\text{H}$  NMR and HPLC.

<sup>d</sup> Determined by HPLC with chiral OJ-H column.

<sup>e</sup> 0.2 equiv. of catalyst.

<sup>f</sup> 0.5 equiv. of catalyst.

Table 2  
Enantioselective pinacol coupling reaction catalyzed by **3**<sup>a</sup>



Entry	RCHO	Yield <sup>b</sup>	dl:meso <sup>c</sup>	ee (%)
1	Benzaldehyde	88	99:1	71 <sup>d</sup> ( <i>S,S</i> )
2	4-Tolualdehyde	93	100:0	74 <sup>d</sup> ( <i>S,S</i> )
3	4-Methoxybenzaldehyde	92	99:1	73 <sup>e</sup> ( <i>S,S</i> )
4	2-Chlorobenzaldehyde	82	83:17	49 <sup>f</sup> ( <i>S,S</i> )
5	4-Chlorobenzaldehyde	86	89:11	58 <sup>f</sup> ( <i>S,S</i> )
6	2,4-Dichlorobenzaldehyde	76	64:36	51 <sup>f</sup> ( <i>S,S</i> )
7	1-Naphthaldehyde	89	98:2	68 <sup>d</sup> ( <i>S,S</i> )
8	Cyclohexanecarboxaldehyde	86	77:23	Nd <sup>g</sup>

<sup>a</sup> Reaction conditions: 2.0 mmol of aldehyde, 0.2 equiv. catalyst, 2 equiv. metal, 1.5 equiv. TMSCl under  $-10^\circ\text{C}$  for 24 h.

<sup>b</sup> Isolated yield.

<sup>c</sup> Determined by  $^1\text{H}$  NMR and HPLC.

<sup>d</sup> Determined by HPLC with chiral OJ-H column.

<sup>e</sup> Determined by HPLC with chiral AD column.

<sup>f</sup> Determined by HPLC with chiral WH column.

<sup>g</sup> Not detected.

Under the optimized conditions, pinacol coupling of various aldehydes was further investigated, the results were summarized in Table 2. From the table, we could find that aromatic aldehydes substituted with electron-donating groups in the benzene ring were more favorable for achieving higher diastereoselectivity and enantioselectivity (entries 2, 3). Cyclohexanecarboxaldehyde as a representative example of aliphatic aldehyde was also tested in pinacol coupling reaction, good yield and moderate diastereoselectivity were obtained.

### 4. Conclusion

In conclusion, tartaric acid-derived ligands **1–4** were conveniently synthesized. Their titanium complexes were investigated in asymmetric pinacol coupling reaction. Excellent diastereoselectivities and moderate to good enantioselectivities were obtained.

### Acknowledgment

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