



## Communication

## Enantioselective pinacol coupling reaction of aromatic aldehydes catalyzed by chiral vanadium complexes

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## ABSTRACT

The asymmetric pinacol coupling of aromatic aldehydes by chiral salen–vanadium complexes as effective catalysts is reported. Chiral 1,2-diols were obtained with high diastereoselectivities (up to 90/10) and moderate to high enantioselectivities (up to 82% ee). The possible mechanism of the pinacol coupling reaction is also discussed.

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## 1. Introduction

Chiral diols are very useful chiral intermediates and auxiliaries in stereoselective organic synthesis [1]. Among various methods explored, the asymmetric pinacol coupling reaction provides a direct way by transforming the achiral aldehydes into chiral 1,2-diols. Although a variety of metals [2–15] had been exploited extensively in the pinacol coupling reaction, these utilizations were mainly focused on the diastereoselective way. Given the fact that both high diastereoselectivity and enantioselectivity should be considered for a successful asymmetric pinacol coupling reaction, this formidable challenge highlights the demand for an efficiently catalytic system. Nonetheless, asymmetric pinacol coupling reaction has been studied mostly in the use of chiral titanium complexes [16–24], however, those results are still far from satisfying. In 2004, Yamamoto developed a chiral chromium complex in this reaction with good diastereoselectivity and high enantioselectivity, which afforded a practical approach to prepare the optically active 1,2-diols [25].

Our recent studies demonstrated that chiral salen–Mo complexes were effective in enantioselective pinacol coupling reaction of aryl aldehydes [26]. The use of salen (reduced salen) ligand instead of salen was the key factor for achieving the high diastereoselectivities and enantioselectivities. Recent investigations showed that the type of salen ligands displayed superior asymmet-

ric induction over salen ligands in some reactions [27–31]. On the other hand, although the applications of vanadium compounds in pinacol coupling reaction had been well documented [7–10], to our knowledge, no chiral vanadium complexes have been used in the reaction in an enantioselective way. Herein we describe the highly asymmetric pinacol coupling of aromatic aldehydes catalyzed by chiral salen–VO(acac)<sub>2</sub> complexes.

## 2. Results and discussion

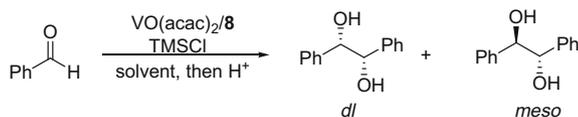
Following the protocol of the vanadium-catalyzed pinacol coupling reaction, in which Me<sub>3</sub>SiCl was used as a mediator and other metal agents were employed as a co-reducing reagent, the readily obtainable tetradentate salen ligand **3**, was chosen as the model ligand examined in the reaction. We initially utilized 5 mol% **3**–VO(acac)<sub>2</sub> complexes as catalyst and benzaldehyde as the substrate for the first investigation. The reactions were carried out in THF with 1.5 equivalent of Me<sub>3</sub>SiCl, 2 equivalent of activated Zn powder at 0 °C for 36 h. After that, the isolated silyl ethers were treated with aqueous HCl in THF to afford the 1,2-diphenylethane-1,2-diols.

The initial results suggested that the 1,2-diols were obtained with moderate diastereoselectivity and moderate enantioselectivity (Table 1, entry 1). Subsequent investigation on different solvents showed that THF was the best one of all four solvents examined. Further investigation revealed that Mg, Al and Mn, which usually had been utilized as co-reducing reagent in the pinacol coupling reaction, gave unsatisfactory results comparable to Zn under the same

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**Table 1**  
Asymmetric pinacol coupling reaction of benzaldehyde.<sup>a</sup>



Entry	M	Solvent	Yield(%) <sup>b</sup>	dl/meso <sup>c</sup>	Ee (%) <sup>d</sup>
1	Zn	THF	85	85/15	47
2	Zn	DME	92	74/26	36
3	Zn	Et <sub>2</sub> O	84	66/34	32
4	Zn	CH <sub>3</sub> CN	67	54/46	17
5	Mg	THF	35	57/43	<5
6	Al	THF	54	77/23	28
7	Mn	THF	62	53/47	<5
8 <sup>e</sup>	Zn	THF	86	86/14	56
9 <sup>f</sup>	Zn	THF	85	87/13	57

<sup>a</sup> Unless otherwise noted, all of reactions were conducted under such conditions: PhCHO/**8**-VO(acac)<sub>2</sub>/Zn/Me<sub>3</sub>SiCl = 1/0.05/2/1.5, 0 °C for 36 h.

<sup>b</sup> Isolated yields.

<sup>c</sup> Determined by <sup>1</sup>H NMR.

<sup>d</sup> Determined by HPLC with a Daicel Chiralcel OJ-H column.

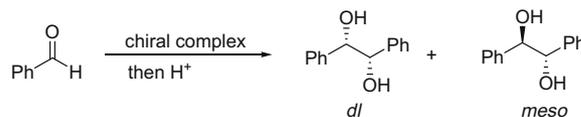
<sup>e</sup> 10 mol% of **3**-VO(acac)<sub>2</sub>.

<sup>f</sup> 15 mol% of **3**-VO(acac)<sub>2</sub>.

reaction conditions (entries 5–7). Changing the catalyst loading from 5 to 10 mol% resulted in a higher enantioselectivity (entry 8). Further increasing to 15 mol% did not enhance the enantioselectivity distinctively (entry 9).

Finally, screening a number of chiral ligands (Fig. 1) revealed that the combination of **8** with VO(acac)<sub>2</sub> gave the best results (72% ee) (Table 2, entry 10). However, the use of salen ligands **1**, **2** led to negligible enantioselectivity (entries 4 and 5). In addition, other vanadium compounds were investigated in the reaction when combined with ligand **3**. The results showed VOCl<sub>3</sub> gave the best yield and diastereoselectivity, whereas VCl<sub>3</sub> and VOSO<sub>4</sub> gave both low yield and selectivity (entries 1–3). Lowered the equivalent of Zn powder to 1.5 and 1.0 resulted in decreased yield and similar selectivity (entries 11 and 12). Given the above mentioned investigations, the combination of **8**-VO(acac)<sub>2</sub> (10 mol% loading), Zn and Me<sub>3</sub>SiCl in THF at 0 °C was selected as the optimal reaction condition.

**Table 2**  
Asymmetric pinacol coupling reaction of benzaldehyde.<sup>a</sup>



Entry	Ligand	V	Yield (%) <sup>b</sup>	dl/meso <sup>c</sup>	Ee (%) <sup>d</sup>
1	<b>3</b>	VCl <sub>3</sub>	57	65:35	12
2	<b>3</b>	VO(acac) <sub>2</sub>	43	72:28	15
3	<b>3</b>	VOCl <sub>3</sub>	88	89:11	34
4	<b>1</b>	VO(acac) <sub>2</sub>	61	76/24	<5
5	<b>2</b>	VO(acac) <sub>2</sub>	46	70/30	<5
6	<b>4</b>	VO(acac) <sub>2</sub>	76	80/20	37
7	<b>5</b>	VO(acac) <sub>2</sub>	74	76/24	26
8	<b>6</b>	VO(acac) <sub>2</sub>	79	81/19	19
9	<b>7</b>	VO(acac) <sub>2</sub>	87	86/14	44
10	<b>8</b>	VO(acac) <sub>2</sub>	88	89/11	72
11 <sup>e</sup>	<b>8</b>	VO(acac) <sub>2</sub>	76	90/10	70
12 <sup>f</sup>	<b>8</b>	VO(acac) <sub>2</sub>	62	84/16	66

<sup>a</sup> Unless otherwise noted, all of reactions were conducted under such conditions: PhCHO/catalyst/Zn/Me<sub>3</sub>SiCl = 1/0.1/2/1.5, 0 °C for 36 h, THF, catalyst loading is 10 mol%.

<sup>b</sup> Isolated yields.

<sup>c</sup> Determined by <sup>1</sup>H NMR.

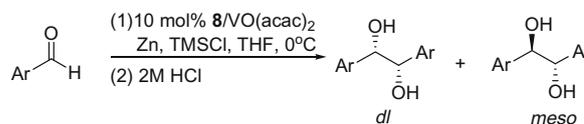
<sup>d</sup> Determined by HPLC with a Daicel Chiralcel OJ-H column.

<sup>e</sup> 1.5 equivalent of Zn.

<sup>f</sup> 1.0 equivalent of Zn.

Under the above mentioned reaction conditions, we next investigated the coupling reaction of a variety of aromatic aldehydes catalyzed by **8**-VO(acac)<sub>2</sub>. The results, shown in Table 3, revealed that the substituted group of the aromatic aldehydes exhibited a crucial electronic effect on the enantioselectivity. The *ortho* and *para* methyl substituted benzaldehydes showed good reactivity, diastereoselectivity and enantioselectivity (Table 3, entries 2 and 3). However, the electron-withdrawing substituted aldehydes afforded both lower diastereoselectivity and enantioselectivity comparable to benzaldehyde (entries 4–6). It was noteworthy that 2-furyl aldehyde furnished the products in high diastereoselectivity but very low ee value (entry 8). In addition, 4-methoxy benzaldehyde gave the diols the best *dl* to *meso* ratio and high enantioselectivity (entry 7). The absolute configuration of the major isomers of the *dl* products was determined as (*S,S*).

**Table 3**  
Asymmetric pinacol coupling reaction of aromatic aldehydes.<sup>a</sup>



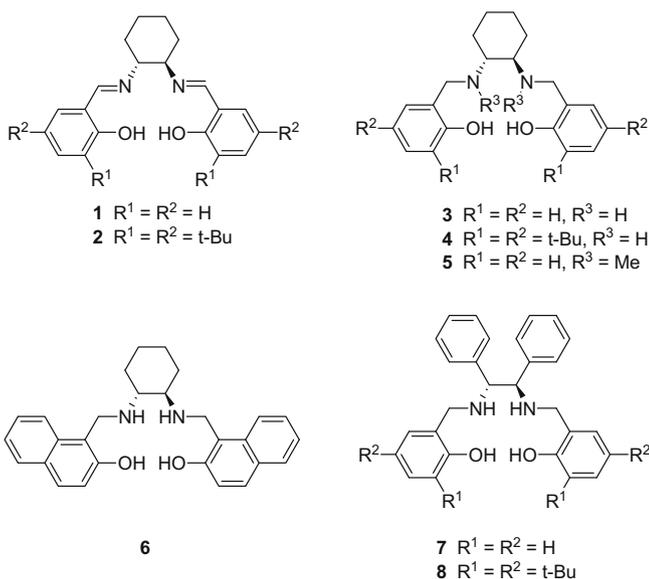
Entry	Aldehyde (Ar)	Yield (%) <sup>b</sup>	dl/meso <sup>c</sup>	Ee (%) <sup>d</sup>
1	Ph	88	89/11	72
2	<i>p</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	82	86/14	78
3	<i>o</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	84	81/19	82
4	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	83	79/21	68
5	<i>p</i> -BrC <sub>6</sub> H <sub>4</sub>	77	82/18	70
6	<i>p</i> -FC <sub>6</sub> H <sub>4</sub>	66	77/23	52
7	<i>p</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	84	90/10	81
8	2-Furyl	76	84/16	37

<sup>a</sup> Reaction conditions: ArCHO/**8**-VO(acac)<sub>2</sub>/Zn/Me<sub>3</sub>SiCl = 1/0.1/2/1.5, THF, 0 °C, 36 h.

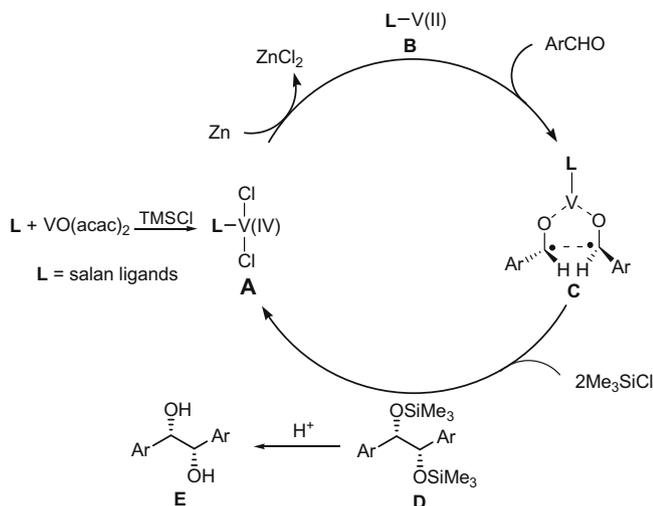
<sup>b</sup> Isolated yields.

<sup>c</sup> Determined by <sup>1</sup>H NMR.

<sup>d</sup> The ee values were determined by HPLC with Daicel Chiralcel OJ-H or AD-H columns. Absolute configuration (*S,S*) was assigned by comparison of optical rotation with literature values.



**Fig. 1.** Chiral ligands examined for asymmetric pinacol coupling reaction.



**Fig. 2.** Proposed mechanism for vanadium-catalyzed asymmetric pinacol coupling reaction.

### 3. Mechanism study

The proposed mechanism for the **8**-VO(acac)<sub>2</sub> catalyzed enantioselective pinacol coupling reaction was shown in Fig. 2. Reaction of chiral oxovanadium (IV) complex with Me<sub>3</sub>SiCl affords the ligand exchange dichloro intermediate **A**. Following reduction with Zn generates a low valent V(II) species **B**. Subsequently addition of aldehyde results in the formation of V–O bond between the metal atom and the oxygen atoms of the aldehydes. This diketyl radical intermediate **C** is thought as the plausible transition state structure. The electrons transfer from the vanadium atom to two carbonyl substrates results in the formation of the new C–C bond and the oxidation state of vanadium is changed from +2 to +4. Cleavage of V–O bonds with Me<sub>3</sub>SiCl affords the diol silyl ether **D** and the intermediate **A** is regenerated. The whole catalytic circulation is finished.

### 4. Conclusion

In summary, we have developed a highly enantioselective pinacol coupling reaction of aromatic aldehydes catalyzed by a chiral salan–vanadium complex in the presence of Zn and Me<sub>3</sub>SiCl. The 1,2-diols were obtained in high diastereoselectivities (up to 90/10) and moderate to high enantioselectivities (up to 82% ee). The mechanism of the reaction has also been discussed. To our knowledge, this approach provides the first example of asymmetric pinacol coupling catalyzed by a chiral vanadium complex.

### 5. Experimental

#### 5.1. General

All reactions were carried out under an argon atmosphere using standard Schlenk techniques. Unless otherwise indicated, all materials were obtained from commercial sources and were used without further purification. THF and ethyl ether were distilled from sodium/benzophenone. Dichloroethane was distilled from CaH<sub>2</sub>. Acetonitrile was distilled from P<sub>2</sub>O<sub>5</sub> before use. Liquid aldehydes and trimethylchlorosilane were freshly distilled. Elemental analyses were carried out on a Perkin–Elmer 240 C elemental analyzer. NMR data were recorded on a Bruker AMX-300 spectrometer with chemical shifts referenced to SiMe<sub>4</sub> as internal standard. Infrared spectra were measured in cm<sup>-1</sup>, using a 5DX-FT-2 spectrometer. Electro spray ionization mass spectrums were recorded on Finnigan

LCQ Electro spray Mass Spectrometer. Normal mass spectra were taken using HP 5989A mass spectrometer. Optical rotations were recorded on a Perkin Elmer 241 Polarimeter. Ee values were determined by a Perkin–Elmer 200 HPLC on a chiral Chiralcel OJ-H or AD-H column. The diastereomeric excesses were determined by HPLC and <sup>1</sup>H NMR.

#### 5.2. General Procedure for pinacol coupling reaction

To a mixture of **8** (0.10 mmol) and VO(acac)<sub>2</sub> (0.10 mmol) was added anhydrous THF (2 mL) under argon. The deep blue mixture was stirred for 10 min at room temperature, and then Zn powder (2 mmol) was added. After stirred for another 10 min, the mixture was cooled to 0 °C and the freshly distilled Me<sub>3</sub>SiCl (1.5 mmol) was added. After 30 min, aldehyde (1 mmol) was added and the mixture was stirred at 0 °C for 36 h. The suspension was filtered through a glass funnel, and the filtrate was treated with 2 M HCl (5 mL) and stirred for 1 h. Then the mixture was extracted with EtOAc (3 × 10 mL) and the organic layer was washed with a saturated NaHCO<sub>3</sub> solution (2 × 10 mL). After dried over anhydrous sodium sulfate and removal of solvent under reduced pressure, the crude products were purified by flash chromatography on silica gel (petroleum ether/EtOAc = 5:1) to remove the impurities. The ratio of *dl* to *meso* of the diols was measured by <sup>1</sup>H NMR analysis. The ee values of the *dl* diols were determined by chiral HPLC using a Daicel Chiralcel OJ-H or AD-H column.

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