Experimental and theoretical investigation of the relationship between the stericstructure of Schiff bases and the diastereoselectivity of pinacol produced from benzaldehyde

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Abstract

After synthesis of a series of chiral Schiff bases from easily available amino-alcohol, pinacol coupling reaction of benzaldehyde catalyzed by a series of Schiff bases–Ti complexes afforded pinacol with high yield and different diastereoselectivity. The relationship between the stericstructure of these Schiff bases and the diastereoselectivity of pinacol was systemically studied and calculated by QSAR calculation method.
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1. Introduction

Pinacol coupling reaction of carbonyl compounds is an important organic reaction to form both the new C–C bond and pinacols [1,2], which has often been employed in total synthesis of many natural products [3,4]. The chiral pinacols are also the prominent auxiliaries in many asymmetric synthesis [5–7]. Since the first report of pinacol coupling reaction by Mukayama et al. [8], Considerable effort has been devoted to develop the reaction with high stereoselectivity and diastereoselectivity (DL/*meso* > 20). In recent years, various transition metal complexes derived from Ce [9], Ti [10–13], U [14], Sm [15], Cr [16], V [17] and Nb [18], have been used to catalyze pinacol coupling reaction with high yield and stereoselectivity.

A set of Schiff bases were synthesized from available amino-alcohols and natural L-amino acids, which were used to catalyze pinacol coupling reaction of benzaldehyde. The relationship between the diastereoselectivity of 1,2-dipheyl-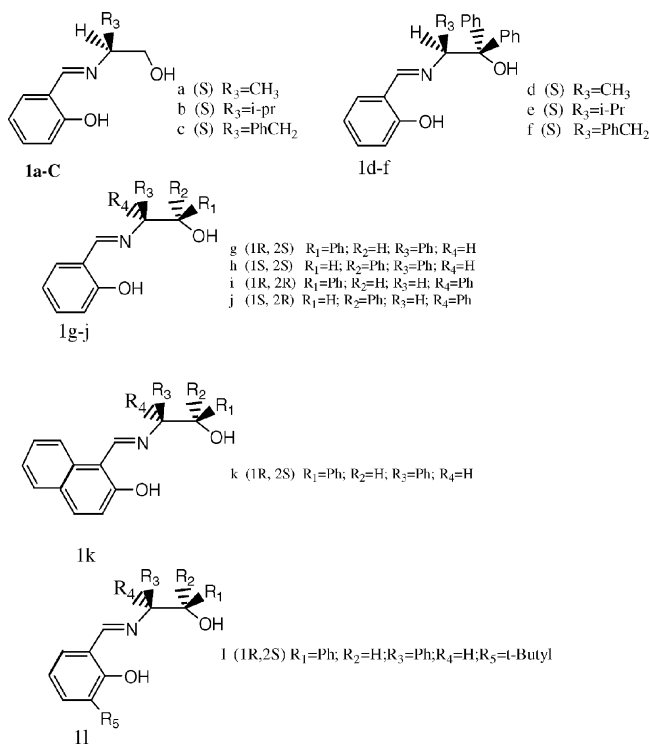1,2-ethanediol and the structure of the Schiff bases was found. Based on QSAR method with topological indices we proposed, the quantitative equation between the theoretical diastereoselectivity and the structure of Schiff bases was established. Our work may provide some useful information to the improvement of stereoselectivity of the reaction or design and synthesis of new catalyst.

Firstly, Schiff base **1a–l** (Scheme 1) was facilely prepared in high yield (85–95%) from salicylaldehyde and amino-alcohols according to the previously reported procedure [19].

Then, we set out to examine the steric effect of Schiff bases on pinacol coupling reaction of benzaldehyde. The results were listed in Table 1.

The result indicates that 1,2-dipheyl-1,2-ethanediol was obtained in high yield, the diastereoselectivity varied regularly with the substituent of Schiff bases. The presence of bulkier group R_3 at β-amino attached carbon leads to better diastereoselectivity(entry **1**–**3**). This conclusion can also be obtained from the results of entries **4**–**6**. On the other hand, the groups at α-hydroxy attached carbon also play a very important role for the diastereoselectiviy of the reaction. When two groups change from H to phenyl, the diastereoselectivity enhances dramatically (entry **4** versus **1**, **5** versus **2**, **6** versus **3**). It is interesting to note that when two

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1a-C

a (S) R_3=CH$_3$
b (S) R_3=i-pr
c (S) R_3=PhCH$_2$

1d-f

d (S) R_3=CH$_3$
e (S) R_3=i-Pr
f (S) R_3=PhCH$_2$

1g-j

g (1R, 2S) R_1=Ph; R_2=H; R_3=Ph; R_4=H
h (1S, 2S) R_1=H; R_2=Ph; R_3=Ph; R_4=H
i (1R, 2R) R_1=Ph; R_2=H; R_3=H; R_4=Ph
j (1S, 2R) R_1=H; R_2=Ph; R_3=H; R_4=Ph

1k

k (1R, 2S) R_1=Ph; R_2=H; R_3=Ph; R_4=H

1l

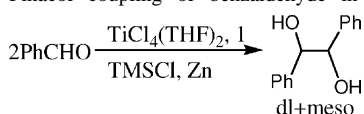l (1R,2S) R_1=Ph; R_2=H;R_3=Ph;R_4=H;R_5=t-Butyl

Scheme 1.

bulky groups at α-carbon and β-carbon are anti, the better diastereoselectivity (entry **4–6**, **8**, **9**) are obtained. The entries **7**, **10** in the catalysis of **1g**, **1j** respectively with two phenyl groups are *syn*, result in lower diastereoselectivity. Various aromatic group at β-amino nitrogen has no influence on diastereoselectivity (entry **11**, **12**).

Table 1
Pinacol coupling of benzaldehyde in the presence of Schiff bases

$$2PhCHO \xrightarrow[\text{TMSCl, Zn}]{\text{TiCl}_4\text{(THF)}_2, \text{1}} \begin{array}{c} HO \quad Ph \\ Ph \quad OH \end{array}$$
dl+meso

Entry	Ligand	Yield[a]	DL/*meso*[b] experimental	DL/*meso* calculated
1	**1a**	89	53/47	59/41
2	**1b**	92	65/35	63/37
3	**1c**	96	83/17	74/26
4	**1d**	95	90/10	85/15[c]
5	**1e**	91	97/3	90/10
6	**1f**	99	99/1	100/0
7	**1g**	93	66/34	71/29
8	**1h**	97	96/4	100/0
9	**1i**	92	99/1	99/1
10	**1j**	88	73/27	73/27
11	**1k**	89	65/35	–
12	**1l**	97	66/34	–

The reaction was carried out in acetonitrile at room temperature with 5 mmol% of Schiff base–Ti complexes, 1.1 equivalent of TMSCl and 3 equivalent of Zn power.
[a] Isolated yield.
[b] Measured by ^{1}H NMR.
[c] Internal validation case in calculation.
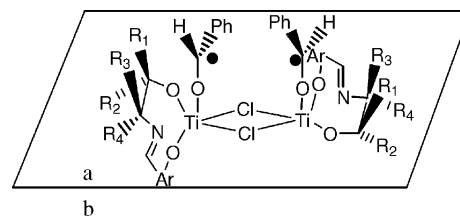
Scheme 2.

No pinacol is obtained when the substrates are aliphatic aldehydes. More work is now required to study the relationship between the Schiff bases and other aromatic aldehydes.

Based on our experiment results and related mechanism suggested by Wang [20]. It seems plausible that benzaldehyde attacks titanium(III) complex from a or b face forming the active species–binuclear titanium(IV) complex binding both ketyl radicals, in which various steric hindrance induces different diastereoselectivity. When two bulky groups at α-carbon and β-carbon are *syn*, benzaldehyde attacks titanium atom from the face whose steric hindrance is smaller.

Our laboratory has suggested a QSAR calculation method for catalytic asymmetric reactions with topological indices [21]. We applied this method to this set of experiement data of ligands **1a–j** (including an internal validation case). Those ligands have the same fixed framework as shown in Scheme 2. The following equation was achieved:

$$dl/\text{meso}\,(\%) = 57.8 + 0.76 A_{x_1}^{R_1} + 0.90 A_{x1} - 14.0C$$
$$r^2 = 0.911, \quad F = 10.278, \quad N = 9, \quad s = 7.387$$

r^2 is the squared correlation coefficient, F is the Fisher significance radio, N is the number of cases used in analysis, s is the standard error of the estimates. $A_{x_1}^{R_1}$, $A_{x_1}^{R_2}$, $A_{x_1}^{R_3}$ are the A_{x_1} topological indices [22] for substituent R_1, R_2, R_3 as shown in the Scheme 2. The indicator variable C identifies whether R_3 is at the same side of the coordinate plane with the larger substituent of R_1/R_2. In **1a–f**, as $R_1 = R_2$, we set $C = 0$. In **1g–j**, $R_1 \neq R_2$, $C = 1$ when at the same side and $C = -1$ on the contrary. The results drawn by the equation are shown in Table 1 and Scheme 3 which are quite consistent to the experiment data as well as the internal validation case.

From the equation, we may discover that the contributions to DL/*meso* ratio of R_1, R_2, R_3 are similar, as the coeffients varied not too much. The bulkier substituents lead to the higher diastereoselectivity. The relative distribution of the larger substituents at α-carbon and β-carbon influence the diastereoselectivity a lot. The QSAR calculation supports our primary supposition.
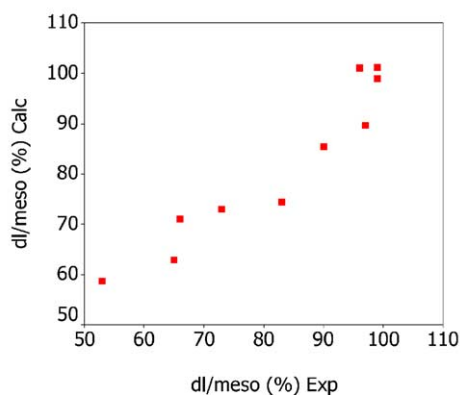
2. Typical experimental procedure for the pinacol coupling

To a solution of **1a** 0.034 g (0.1 mmol) in CH$_3$CN 2 ml, TiCl$_4$(THF)$_2$ 0.023 g (0.1 mmol) was added under argon.
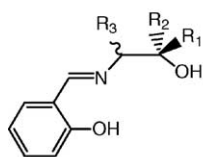
a (S) R_1=H; R_2=H; R_3=CH$_3$
b (S) R_1=H; R_2=H; R_3=i-pr
c (S) R_1=H; R_2=H; R_3=PhCH$_2$
d (S) R_1=Ph; R_2=Ph; R_3=CH$_3$
e (S) R_1=Ph; R_2=Ph; R_3=i-Pr
f (S) R_1=Ph; R_2=Ph; R_3=PhCH$_2$
g (1R, 2S) R_1=Ph; R_2=H; R_3=Ph; C=1
h (1S, 2S) R_1=H; R_2=Ph; R_3=Ph; C=-1
i (1R, 2R) R_1=Ph; R_2=H; R_3=Ph; C=-1
j (1S, 2R) R_1=H; R_2=Ph; R_3=Ph; C=1

1 a-j

Scheme 3.

The resulting red solution was stirred 30 m at room temperature then cooled to 0 °C. The Zn power 0.33 g (6 mmol) was added followed by the addition of Me$_3$SiCl 0.28 ml (2.2 mmol). The suspension became green-blue. After few minutes, the benzaldehyde 0.2 ml (2 mmol) was added and the suspension was stirred at room temperature for 5 h. The suspension was quenched with a solution of 10% Na$_2$CO$_3$ and extracted with EtOAc and 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 was completely desilylated. The reaction was diluted with water and extracted twice with EtOAc. The organic phases were collected and dried over Na$_2$SO$_4$, concentrated in vacro and the residue was purified by chromatography.

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