cis-(1*R*,2*S*)-2-ベンズアミドシクロヘキサンカルボン酸から誘導した1,3-アミノアルコールを用いた芳香族アルデヒドへの立体選択的アリール化反応における置換基による不斉制御

Chirality control in the enantioselective arylation of aromatic aldehydes catalyzed by *cis*-(1*R*,2*S*)-2-benzamidocyclohexanecarboxylic acid derived 1,3-aminoalcohols

廣瀬　卓司[1*]、王　祥波[1]、小玉　康一[1]、御前　仁美[2]、小松　拓磨[2]
Takuji Hirose[1], Xiangbo Wang[1], Koichi Kodama[1], Hitomi Misaki[2], Takuma Komatsu[2]

[1] 埼玉大学　大学院理工学研究科
Graduate School of Science and Engineering, Saitama University
[2] 株式会社インテリム
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Abstract

A series of chiral 1,3-aminoalcohols derived from *cis*-(1*R*,2*S*)-2-benzamidocyclohexanecarboxylic acid were synthesized and applied in the enantioselective arylation of aromatic aldehydes. The reactions exhibited good yields (up to 90%) and moderate to high enantioselectivities (up to 99%). Not only the enantioselectivity but also the stereochemistry of the product was controlled by the substituent effect of the chiral ligands.

Key Words: chirality control, 1,3-aminoalcohols, chiral ligand, aromatic aldehyde, enantioselective arylation, *cis*-(1*R*,2*S*)-2-benzamidocyclohexanecarboxylic acid

1. Introduction

Enantioselective addition of organozinc reagents to aldehydes is one of the most extensively investigated C-C bond formation reactions in the last few decades.[1] A large number of chiral ligands with various structures and reaction features have been developed to meet the demand.[2] Recently, the addition of arylzinc reagents to obtain enantiopure diarylmethanols has gained substantial attention, because they are key structures of pharmaceutically active compounds, such as (*R*)-neobenodine, (*R*)-orphenadrine, and (*S*)-carbinoxamine.[1d-1f,3] In most cases, the desired enantiomer of the product is available from one enantiomer of the ligand. However, it has also recently been reported that chirality inversion of the product can be achieved by a change of substituent with the same framework, that is, with the same ligand chirality.[4] For example, Szakonyi *et al.*[4b] obtained both enantiomers of the product in the

* 〒338-8570　さいたま市桜区下大久保 255
電話：048-858-3522; FAX：048-858-3522
Email：hirose@apc.saitama-u.ac.jp

asymmetric ethylation of aromatic aldehydes by applying their α-pinene derived 1,3-aminoalcohols. However there are as yet no reports on chirality inversion for the asymmetric arylation of aldehydes caused by the substituent effects of chiral ligands. Although both enantiomers of a target diarylmethanol can be obtained by interchanging two reactants, boronic acids and aldehydes, as shown by Bolm *et al.*,[5] it is of interest to determine if a similar chirality inversion is observed by changing the substituents of chiral ligands.

In our previous work on chiral *cis*-(1*R*,2*S*)-2-benzamidocyclohexanecarboxylic acid derived 1,3-aminoalcohols as ligands for the catalytic addition of Et_2Zn to arylaldehydes, we found that some ligands with the same configuration of the chiral centers effectively work to induce the opposite chirality in the product.[6] In this study, we investigated the substituent effect of chiral 1,3-aminoalcohol ligands to change the chirality of diarylmethanols obtained by the catalytic arylation of arylaldehydes. All optically active 1,3-aminoalcohols used in this study were prepared from the same chiral source, *cis*-(1*R*,2*S*)-2-benzamidocyclohexanecarboxylic acid.

2. Results and Discussion

All of the enantiopure 1,3-aminoalcohols in this study were prepared following our previous method.[6]

In order to examine the chiral induction abilities of 1,3-aminoalcohols, we chose the aryl transfer reaction to benzaldehyde using 4-chlorophenylboronic acid and diethylzinc as a model reaction. The reaction was conducted in the presence of 20 mol % of 1,3-aminoalcohols **1**–**7** and the results are summarized in Table 1.

The enantiomeric excess of the obtained diarylmethanol increased with an increase in the number and size of *N*-substituents for primary alcohols **1**–**4** except for **2**, which holds larger *N*-substituents but shows lower enantioselectivity than tertiary amine **1**. With a 5-membered rigid cyclic structure, **1** showed the best chiral induction ability (71.5% ee) than any other ligand studied.

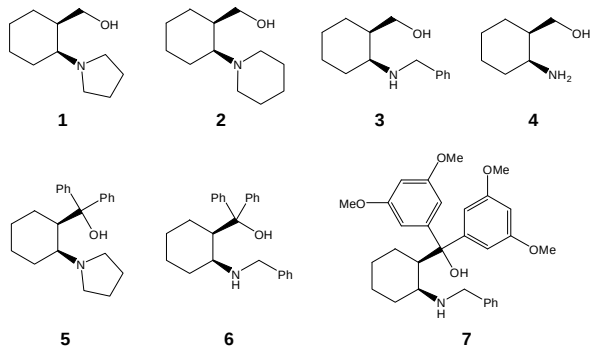
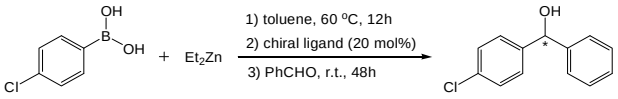


Figure 1. Chiral ligands studied.

Table 1. Asymmetric arylation of benzaldehyde with 4-chlorophenylboronic acid in the presence of **1**–**7**[a]



Entry	Chiral ligand	Yield (%)[b]	ee (%)[c]	Config.[d]
1	**1**	80.5	71.5	*S*
2	**2**	72.6	51.8	*S*
3	**3**	59.8	16.6	*S*
4	**4**	29.9	7.3	*S*
5	**5**	75.2	5.4	*R*
6	**6**	79.6	41.7	*R*
7	**7**	22.9	53.5	*R*

[a]Molar ratio: benzaldehyde/4-$ClC_6H_4B(OH)_2$/Et_2Zn/chiral ligand = 1:2:6:0.2.
[b]Isolated yield.
[c]Determined by HPLC analysis using a chiral column (Chiralpak AD-H; 2-PrOH/*n*-hexane = 10/90; 0.5 mL/min).
[d]Absolute configuration was determined by comparison of the HPLC elution order with the literature data.[7]

The introduction of two phenyl groups to the vicinity of the hydroxyl group of secondary amine **3** improved both the enantioselectivity (41.7% ee) and the chemical yield (Entries 3 vs. 6). The introduction of two 3,5-dimethoxyphenyl groups further improved the enantioselectivity (53.5% ee) for **7**, but decreased the chemical yield dramatically compared with **3** and **6** (Entries 3 and 6 vs. 7).

This is probably due to increased steric hindrance around the catalytic center. However, in the case of cyclic tertiary amine **5**, the introduction of two phenyl groups largely decreased the enantioselectivity (Entries 1 vs. 5).

In addition, the results summarized in Tab z le 1 clearly show the most interesting feature of the present system: both enantiomers of the product were obtained by changing the 1,3-aminoalcohol ligands, despite having the same chirality. Primary alcohols **1**–**4** gave (*S*)-isomers, while tertiary alcohols **5**–**7** afforded (*R*)-isomers. Previously, we reported that the substituent effect induces opposite chirality in the product of asymmetric ethylation reactions to aldeydes in the presence of 1,3-aminoalcohols **1** and **3**–**6**. Although such phenomena have been observed by several studies, to our knowledge there are still no reports on chirality inversion caused by ligands with the same chirality in the study of asymmetric arylation reactions.

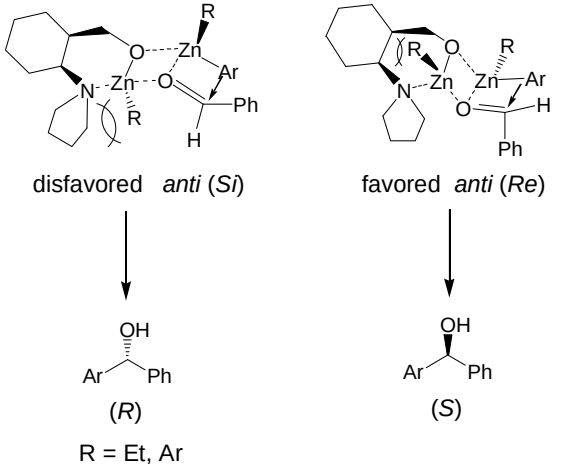


Figure 2. Proposed transition states for arylation of benzaldehyde using **1** as a chiral ligand

Based on the well-known transition state models proposed by some researchers,[8] the tentative 6/4/4 tricyclo transition states for the asymmetric arylation of aldehydes are shown in Figs. 2, 3 and 4 for **1**, **6** and **5**, respectively. In the reaction using **1** as a chiral ligand, the *anti*-(*Re*) transition state, which leads to the formation of the (*S*)-product, is favored over *anti*-(*Si*) because of the steric repulsion difference. In the *anti*-(*Si*) form, large steric repulsion is expected between the R group on Zn atom and the rigid and adjacent bulky cyclic structure of the tertiary amino group in the six-membered Zn-chelate ring, while the *anti*-(*Re*) form has smaller steric repulsion between the cyclohexane ring and the R group on Zn atom in the 1,3-relationship (Fig. 2). The three primary alcohols, **2**, **3** and **4** also showed (*S*)-selectivity but lower enantioselectivity because of the smaller or more flexible *N*-substituents.

Both improved enantioselectivity and the chirality inversion of **6** can be similarly explained by the substituent effect in the proposed transition states. It is obvious that the *anti*-(*Re*) form should have much larger steric repulsion with the R group on Zn atom in the 1,3-relationship compared with the transition states of **1**, while the *anti*-(*Si*) form avoids such repulsion to afford the (*R*)-product (Fig. 3).

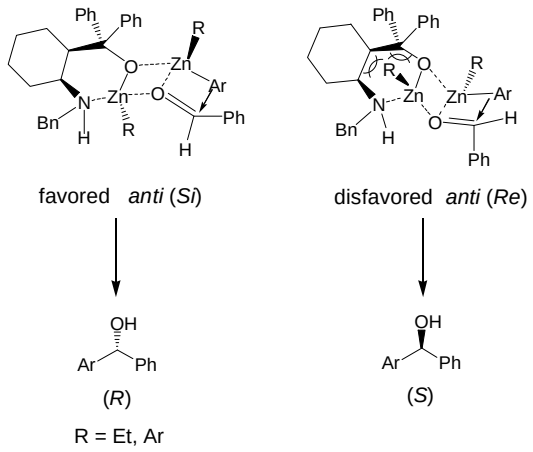
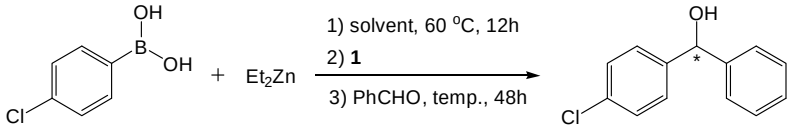


Figure 3. Proposed transition states for the arylation of benzaldehyde using **6** as a chiral ligand.

The additional 1,3-repulsion between the bulky phenyl groups and the R group on Zn atom make the *anti*-(*Re*) form of tertiary alcohol **6** less favored than that of primary alcohol **3**. Therefore, the introduction of substituents to the vicinity of the hydroxyl group can substantially alter the enantioselectivity.

Table 2. Optimization of the arylation of benzaldehyde with 4-chlorophenylboronic acid using **1**[a]



Entry	Chiral ligand loading (mol %)	Solvent (Toluene / *n*-hexane)	Temp. (°C)	Yield (%)[b]	ee (%)[c]	Config.[d]
1	20	1:0	0	71.3	67.9	*S*
2	20	1:0	r.t.	80.5	71.5	*S*
3	20	1:0	45	85.5	12.8	*S*
4	20	1:1	r.t.	75.9	68.7	*S*
5	20	0:1	r.t.	55.5	59.3	*S*
6	10	1:0	r.t.	73.8	54.9	*S*
7	30	1:0	r.t.	84.6	75.8	*S*
8[e]	20	1:0	r.t.	82.9	71.1	*S*
9[f]	20	1:0	r.t.	37.8	44.3	*S*
10[g]	20	1:0	r.t.	51.8	63.3	*S*

[a]Molar ratio: benzaldehyde/4-$ClC_6H_4B(OH)_2$/Et_2Zn = 1:2:6.
[b]Isolated yield.
[c]Determined by HPLC analysis using a chiral column (Chiralpak AD-H; 2-PrOH/*n*-hexane = 10/90; 0.5 mL/min).
[d]Absolute configuration was determined by comparison of the HPLC elution order with data from reports in the literature.[7,12b]
[e]MPEG (mw = 2000 g/mol 10 mol %) was added.
[f]Et_3N (10 mol %) was added.
[g]DMAP (10 mol %) was added.

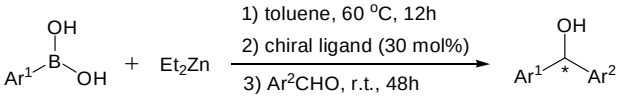
In order to optimize the reaction conditions, tertiary amine **1** was used in the model reaction and the results are summarized in Table 2. It was shown that reaction temperature has a large effect on the enantioselectivity, and the best result was obtained at room temperature (71.5% ee; Entry 2). However, only a small effect on conversion was observed (Entries 1–3); therefore, the following reactions were performed at room temperature.

In accordance with reports in the literatures,[3,5-8b,11-17] toluene and *n*-hexane were chosen and the effects on enantioselectivity and conversion were studied (Entries 2, 4 and 5). Toluene afforded a better chemical yield and enantioselectivity than the less polar toluene/*n*-hexane mixture and *n*-hexane, perhaps due to the higher solubility of boronic acid in toluene.

The investigation of ligand loading showed that enantioselectivity and chemical yield were gradually improved by increasing the amount of **1** (Entries 2, 6 and 7). Ligand loading less than 20 mol % greatly decreased the enantioselectivity of asymmetric arylation reactions (Entries 2 vs. 6).

It has been reported that enantioselectivity is improved by the addition of a catalytic amount of DiMPEG or MPEG.[5,9] However, the addition of MPEG to the present system led to similar enantioselectivity and chemical yield (Entries 2 vs. 8). The addition of Et_3N and DMAP showed that the basic additives could not improve either enantioselectivity or chemical yield (Entries 2, 9 and 10). Possible coordination of the nitrogen atoms of the additives to Zn atoms has a negative effect on the transition states.[10]

Table 3. Asymmetric arylation of aldehydes in the presence of **1** and **6**[a]



Entry	Chiral ligand	Ar^1	Ar^2	Yield (%)[b]	ee (%)[c]	Config.[d]
1	**1**	4-ClPh	Ph	84.6	75.8	*S*
2	**1**	4-ClPh	4-MePh	78.6	63.5	*S*
3	**1**	4-ClPh	3-MePh	70.9	59.4	-[e]
4	**1**	4-ClPh	2-MePh	60.9	68.5	*R*
5	**1**	4-ClPh	4-MeOPh	78.6	53.2	*S*
6	**1**	4-ClPh	4-BrPh	90.0	>99	*R*
7	**1**	4-ClPh	2-thienyl	56.4	5.2	-[e]
8	**1**	2-MePh	4-MePh	60.3	84.5	*S*
9	**1**	4-MePh	2-MePh	59.0	80.6	*R*
10	**1**	4-MePh	4-MeOPh	38.5	57.1	*R*
11	**1**	4-MePh	4-ClPh	68.8	60.1	*R*
12	**1**	Ph	4-MePh	44.5	49.5	*R*
13	**1**	Ph	4-ClPh	83.5	61.2	*R*
14	**6**	4-ClPh	Ph	74.1	50.2	*R*
15	**6**	4-ClPh	4-MePh	78.8	57.2	*R*
16	**6**	4-ClPh	4-BrPh	82.7	74.5	*S*
17	**6**	4-MePh	2-MePh	27.6	53.5	*S*
18	**6**	4-MePh	4-MeOPh	52.0	34.4	*S*
19	**6**	4-MePh	4-ClPh	67.6	51.4	*S*
20	**6**	Ph	4-ClPh	75.9	46.3	*S*

[a]Molar ratio: $Ar^2CHO/Ar^1B(OH)_2/Et_2Zn$/chiral ligand = 1:2:6:0.3.
[b]Isolated yield.
[c]Based on HPLC analysis.
[d]Absolute configuration assigned by comparison of the known elution order with data from reports in the literature.[5,7,8b,11,12b,15,17]
[e]Not determined.

Under optimized conditions, asymmetric arylation reactions of other aromatic aldehydes with arylboronic acids were conducted to further investigate the ligand effect on chiral induction using 30 mol % of **1** and **6**. As seen in Table 3, all substrates afforded the corresponding diarylmethanols. As is widely known,[5] both enantiomers of the desired products are obtained using the same catalyst by the reverse combination of arylboronic acid and aromatic aldehyde. For example, the reaction of 4-chlorophenylboronic acid with benzaldehyde gave (*S*)-(4-chlorophenyl)phenylmethanol (75.8% ee, Entry 1), while that of phenylboronic acid and 4-chlorobenzaldehyde gave corresponding (*R*)-isomer (61.2% ee, Entry 13). Unfortunately, the present system was not effective for the heteroaromatic aldehyde (Entry 7), as the enantioselectivity was very low in contrast to the systems by Bolm *et al.*[11] As commented by

Noyori *et al.*,[1d] the possible heteroatom coordination to the Zn atom disturbed the transition states of the present ligands.

The substituent effect on chirality inversion (Table 1) was reconfirmed for all the other aromatic aldehydes studied; when **1** and **6** were used in asymmetric arylation, the opposite enantiomers of each target product were obtained, respectively (e.g., Entries 1 vs. 14, 2 vs. 15, 6 vs. 16, 9-11 vs. 17-19). The use of the substituent effect to switch the product chirality is important for chiral ligand design from certain natural chiral sources.

For the reaction of *p*-substituted benzaldehydes with (4-chlorophenyl)boronic acid, the enantioselectivities decreased in the order of Br > H > Me > OMe for the *para*-substituents of benzaldehyde (Entries 1, 2, 5 and 6). This result suggests that introduction of stronger electron-donating group to benzaldehyde lowers the enantioselectivity. In addition, when comparing the enantioselectivities of the products from *p*-substituted phenylboronic acids and arylaldehydes, (4-chlorophenyl)boronic acid afforded better results than phenylboronic acid and (4-methylphenyl)boronic acid (e.g., Entries 2 vs. 12, 5 vs. 10). The improved enantioselectivity is attributed to the enhanced reactivity of the arylboronic acid by the electron-withdrawing substituent. In fact, the reaction of (4-chlorophenyl)boronic acid and 4-bromobenzaldehyde afforded excellent chemical yield and selectivity (>99% ee, Entry 6).

From the slightly higher enantioselectivity observed for the reaction of 2-methylbenzaldehyde (Entry 4) compared with those of 3- and 4-methylbenzaldehydes (Entries 2 and 3), a positional effect of the substituent was suggested for ligand **1**. Considering the *anti*-6/4/4 tricyclo transition states, the *ortho*-substituent will directly lead to an increase in steric repulsion with the alkyl group on Zn atom for the *anti*-(*Si*) form compared with the *anti*-(*Re*) form (Fig. 2). The high enantioselectivity of Entry 9 (80.6% ee) appears to come from the same substituent effect of the *ortho*-methyl group, despite its electron-donating property.

3. Conclusion

The enantioselective arylation of aromatic aldehydes was explored in the presence of optically active 1,3-aminoalcohols derived from *cis*-(1*R*,2*S*)-2-benzamidocyclohexanecarboxylic acid. The results demonstrated that substituents in the vicinity of the hydroxyl group give a crucial effect on chirality control. Both enantiomers of the product could be obtained using the same chirality ligands with different substituents. The chirality inversion ability of the substituent effect of 1,3-aminoalcohols was confirmed for all aromatic aldehydes studied. The present study will help to design new chiral ligands derived from natural sources, such as amino acids.

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