New Enantiopure *N*-Ferrocenylmethyl Azetidin-2-yl(diphenyl)methanol and Its Application in Catalytic Asymmetric Ethylation and Arylation of Arylaldehydes

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Abstract: A novel, facile and practical approach to preparation of new enantiopure *N*-ferrocenylmethyl azetidin-2-yl(diphenyl)methanol has been developed. In the presence of a catalytic amount of the chiral *N*-ferrocenylmethyl azetidin-2-yl(diphenyl)methanol, the enantioselective ethylation and arylation of arylaldehydes afforded addition products with enantioselectivities of up to 98.4% ee and 95.7% ee, respectively.

Key words: asymmetric addition, diethylzinc, aryl boronic acids, ethylation, arylation

Since the initial report of Oguni and Omi on the reaction of diethylzinc with benzaldehyde in the presence of a catalytic amount of (*S*)-leucinol producing an addition product with moderate enantioselectivity (49% ee) in 1984,[1] great progress has been made in the catalytic asymmetric addition of organozinc reagents to aldehydes using chiral amino alcohols as ligands, and products with excellent enantiomeric excesses have been achieved with all types of substrates.[2] In addition, the reaction of diethylzinc with aldehydes has also become a classical test in the design of new ligands for catalytic enantioselective synthesis. Recently, the enantioselective arylation of aldehydes has received a special attention in the presence of catalytic amounts of chiral ligands because the arylation products of this reaction are chiral diarylmethanols,[3–15] some of which are key intermediates for the preparation of pharmacologically and biologically important compounds.[16] In this context, the asymmetric arylation of aldehydes using aryl boronic acids as aryl resources,[9–15] instead of Ph_2Zn or Ph_2Zn–Et_2Zn as aryl resources,[4–8,10c] becomes an attractive method for the preparation of diarylmethanols in high enantioselectivity. This new protocol allows the easy preparation of several substituted arylzinc reagents and therefore the synthesis of a wide range of substituted chiral diarylmethanols. In addition, phenylboronic acids offer a cheaper alternative to the expensive diphenyl zinc and the background reaction generated by use of Ph_2Zn itself as aryl resource is avoided. Unfortunately, ligands that effectively catalyze the asymmetric arylation of aldehydes using aryl boronic acids as aryl resource with high ee values are relatively rare. So, the development of new, easily prepared and effective chiral ligands is an important challenge for the practical applications of arylation reactions.

More recently, we reported the synthesis of a series of chiral ferrocenyl aziridino alcohols **1**[17] and pyrrolidino alcohols **2**[18] and their application in the catalytic asymmetric addition of Et_2Zn to aldehydes. Moreover, it was discovered that the replacement of the phenyl group on the nitrogen atom of heterocycle-based skeleton with a ferrocenyl unit led to a dramatic improvement in the enantioselectivity when used as the catalyst in the addition of diethylzinc to benzaldehyde in the presence of five mol% of chiral ligands (Figure 1). In order to examine the generality of this finding, in this article, we present our preliminary results on the synthesis of enantiopure *N*-ferrocenylmethyl azetidin-2-yl(diphenyl)methanol (**6**) and its application in catalytic asymmetric ethylation and arylation of arylaldehydes.

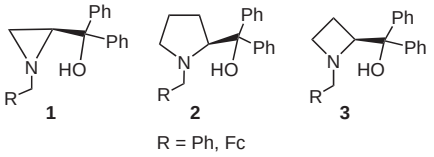
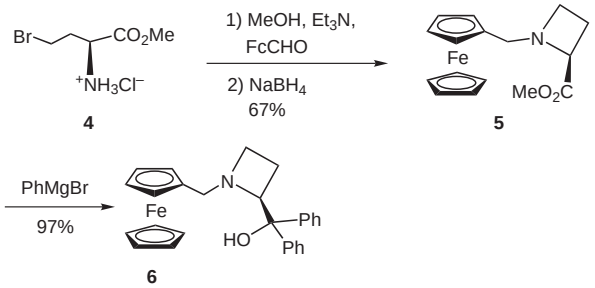


Figure 1

The preparation of azetidino alcohol **6** is shown in Scheme 1. The starting material **4** for the synthesis of enantiopure compound **5** was prepared readily from commercially available L-2-amino-4-bromobutanoic acid. Treatment of L-2-amino-4-bromobutanoic acid with methanol saturated with anhydrous hydrogen chloride afforded methyl L-2-amino-4-bromobutanoate (**4**) in 89% yields.



Scheme 1 Synthesis of **6**

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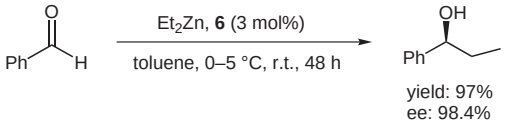
Construction of the four-membered ring heterocycle from acyclic compound is a key step in this synthesis. Ferrocenecarboxaldehyde was first condensed with the compound **4** in methanol in the presence of triethylamine, and then reduced by sodium borohydride. Incidentally, the cyclization reaction also took place during the condensation reaction to give the desired methyl (*S*)-*N*-ferrocenylmethyl azetidine-2-carboxylate (**5**). The reaction of **5** with excess phenylmagnesium bromide furnished the corresponding β-amino alcohol ligand **6** (97%).[19]

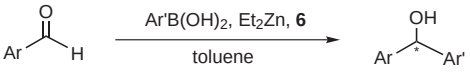
As described above, the reaction of diethylzinc with benzaldehyde has become a typical reaction to examine whether or not the designed chiral ligands induce high enantioselectivities. With the new chiral ligand **6** in hand, we first examined the enantioselective addition of diethylzinc to benzaldehyde in the presence of 3 mol% of the chiral ligands **6** in toluene at 0 °C to room temperature (Equation 1).[20] The reactions using **6** as catalyst afforded 1-phenylpropanol (*S* configuration) in excellent yield (97%) with outstanding enantiomeric excess (98.4% ee).



Scheme 2 Asymmetric ethylation of benzaldehyde

Recently, Zwanenburg et al. reported a similar type of chiral ligand **3** (R = Ph) for the addition of diethylzinc to benzaldehyde with good enantioselectivities (88% ee) in the presence of 20% mol of **3**.[21] A comparison of our results (98.4% ee, 3% mol **6**) with those (88% ee, 20% mol **3**) of Zwanenburg et al. demonstrated that the replacement of the phenyl group on the nitrogen atom of azetidine-based skeleton with a ferrocenyl unit led to a remarkable improvement in the enantioselectivity when used as the catalyst in the addition of diethylzinc to benzaldehyde. These results also suggested that the steric hindrance pro-

Table 1 Asymmetric Arylation of Arylaldehydes Catalyzed by **6**[a]



Entry	Ar	Ar′	**6** (mol%)	Temp (°C)	Yield (%)[b]	ee (%)[c]	Config.[d]
1	*p*-MeC_6H_4	Ph	10	0	96	89.0	*S*
2	*p*-MeC_6H_4	Ph	10	–20	95	92.0	*S*
3	*p*-MeC_6H_4	Ph	10	–40	71	88.5	*S*
4	*p*-MeC_6H_4	Ph	5	–20	88	84.0	*S*
5	*p*-MeC_6H_4	Ph	15	–20	96	92.1	*S*
6	*o*-$MeOC_6H_4$	Ph	10	–20	86	83.9	*S*
7	*m*-$MeOC_6H_4$	Ph	10	–20	99	87.1	*S*
8	*p*-$MeOC_6H_4$	Ph	10	–20	95	83.3	*S*
9	*m*-$PhOC_6H_4$	Ph	10	–20	94	93.9	*S*
10	*o*-ClC_6H_4	Ph	10	–20	94	83.4	*S*
11	*m*-ClC_6H_4	Ph	10	–20	98	90.0	*S*
12	*p*-ClC_6H_4	Ph	10	–20	80	83.1	*S*
13	*m*-BrC_6H_4	Ph	10	–20	97	85.7	*S*
14	*o*-$CF_3C_6H_4$	Ph	10	–20	92	91.1	*S*
15	3,4-$OCH_2OC_6H_3$	Ph	10	–20	99	88.2	*S*
16	Ferrocenyl	Ph	10	–20	84	95.5	*S*
17	Ph	*o*-MeC_6H_4	10	–20	88	95.7	*R*
18	Ph	Naph	10	–20	79	70.0	*R*

[a] The molar ratio of Ar′$B(OH)_2$–Et_2Zn–aldehyde was1:3:1.
[b] Isolated yields.
[c] Determined by HPLC using a chiral column: Chiralcel OD, Chiralcel OB or Chiralpak AD.
[d] Absolute configuration was assigned by comparison with the known elution order from a Chiralcel OD, OB and AD columns according to the literature.[10–14]

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vided by the ferrocenyl group, compared to a phenyl group, played an important role in the enantioselectivities. The outstanding enantioselectivity of the new chiral ligand **6**, as compared with **3** (R = Ph), gave further support to the generality of the advantage of the replacement of the phenyl group on the nitrogen atom of heterocycle-based skeleton with a ferrocenyl unit.

This exciting result encouraged us to examine the efficiency of the asymmetric arylation of arylaldehyde in the presence of the chiral ligand **6** using aryl boronic acids as aryl resources.[22] The results are summarized in Table 1.

The asymmetric phenylation of 4-tolualdehyde was tested (Table 1, entries 1–5). The phenylzinc reagent was prepared in situ by heating a mixture of diethylzinc and phenylboronic acid in hexanes to 60 °C for 12 hours. We first investigated the effect of reaction temperature on the enantioselectivity in the presence of ten mol% of the chiral ligand **6**. Decreasing the reaction temperature from 0 °C to –20 °C led to an increase in the enantioselectivity from 89.0% to 92.0% (Table 1, entries 1 and 2). We attempted to further decrease the reaction temperature in order to have a better enantioselectivity, but a substantial decrease in both the yield and the enantioselectivity was observed when the reaction was performed at –40 °C (Table 1, entry 3). We then examined the effects of the chiral ligand loading on the enantioselectivity. Lowering the ligand amount from 10% to 5% led to a decrease in both the yield and the enantioselectivity at –20 °C (Table 1, entries 4 vs. 1). Increasing the ligand loading from 10% to 15% did not result in the improvement of yield and enantioselectivity (Table 1, entries 2 and 5).

These reaction conditions were tested on other arylaldehydes in the presence of the ligand **6** (Table 1, entries 6–16). As can be seen from Table 1, good to excellent enantioselectivities could be achieved for various aromatic aldehydes containing *ortho*-, *para*- and *meta*-substituents on the benzene ring. The presence of electron-donating or electron-withdrawing substituents on the aromatic ring also furnished the corresponding products in good to outstanding levels of enantioselectivity. The best asymmetric induction (with as high as 95.5% ee) was found by using a ferrocenyl aldehyde as the substrate (Table 1, entry 16).

In order to examine if different aryl groups could be transferred to aldehydes with the same levels of enantioselectivity, the aryl transfer reaction of some substituted phenylboronic acids with benzaldehyde was investigated (Table 1, entries 17 and 18). Excellent enantioselectivity of up to 95.7% ee was obtained when *ortho*-methyl phenylboronic acid was used as the aryl transfer reagent.

In conclusion, we have developed a novel, facile and practical approach to asymmetric preparation of new enantiopure *N*-ferrocenylmethyl azetidin-2-ylmethanol. In the key cyclization step, a three-step, one-pot protocol for the construction of the chiral azetidine ring was developed. The enantioselective ethylation and arylation of arylaldehyde gave the enantioselectivity of up to 98.4% ee and 95.7% ee, respectively, in the presence of a catalytic amount of the new chiral ligand **6**. Further applications of chiral compound **6** for asymmetric synthesis are under investigation in our laboratory.

Acknowledgment

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(19) Compound **6**: mp 122.7–123.9 °C; $[\alpha]_D^{20}$ –27.2 (*c* = 0.32, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.87–2.09 (m, 1 H), 1.92–2.03 (m, 1 H), 2.81, 2.87 (dd, *J* = 13.2 Hz, 2 H), 2.89–2.93 (m, 1 H), 3.18 (t, *J* = 6.0 Hz, 1 H), 3.83–4.05 (m, 9 H), 4.27 (t, *J* = 7.2 Hz, 1 H), 5.20 (s, 1 H), 7.18–7.61 (m, 10 H). MS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{27}H_{27}FeNO$: 438; found: 438.

(20) **Enantioselective Addition of Diethylzinc to Benzaldehyde**: A solution of diethylzinc (1 M in *n*-hexane, 1.1 mL) was added to a solution of a chiral catalyst **6** (0.015 mmol, 3 mol%) in anhyd toluene under a nitrogen atmosphere. The mixture was cooled to 0 °C, and stirred for 30 min. Freshly distilled benzaldehyde (0.05 mL, 0.5 mmol) was added to the mixture. The resulting mixture was stirred for 10 h at 0–5 °C and was allowed to warm to the r.t., and stirring was continued for another 38 h at the same temperature. The reaction was quenched by the addition of sat. aq NH_4Cl (4 mL). The mixture was extracted with Et_2O (3 × 8 mL). The combined organic layers were washed with brine, dried over anhyd Na_2SO_4 and evaporated under reduced pressure. Purification of the residue by the preparative silica gel TLC plate (hexane–EtOAc = 4:1) afforded the (*S*)-1-phenyl-1-propanol. The ee was determined by HPLC analyses using a chiral column (a Chiralcel OD); hexane–*i*-PrOH = 100:2, flow rate: 0.6 mL/min, $t_R(R)$ = 19.6 min, $t_R(S)$ = 23.8 min.

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(22) **Asymmetric Arylation of Arylaldehydes Catalyzed by 6; General Procedure**: A dried Schlenk tube containing toluene (2 mL), aryl boronic acid (122 mg, 1 mmol), and diethylzinc (3 mmol, 1.0 M solution in hexanes) was heated at 60 °C for 12 h. After the mixture was cooled to r.t., the chiral amino alcohol ligand **6** (43.7 mg, 0.1 mmol) was added. The mixture was stirred for another 15 min. It was cooled to –20 °C, and the aldehyde (1 mmol) was subsequently added under nitrogen atmosphere. After 48 h at –20 °C, the reaction was quenched by the addition of sat. aq NH_4Cl (8 mL). The mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine, dried over anhyd Na_2SO_4 and evaporated under reduced pressure. Purification of the residue by the preparative silica gel TLC plate (hexane–EtOAc) afforded the pure diarylmethanol. The ee was determined by HPLC analyses using a chiral column: Chiralcel OB, Chiralcel OD or Chiralpak AD.

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