Chinese Journal of Chemistry, **2004**, *22*, 512—514

Communication

Novel Chiral Ferrocenyl Aziridino Alcohol Catalysts Promoting Asymmetric Addition of Diethylzinc to Aldehydes

WANG, Min-Can(王敏灿) WANG, De-Kun*(王德坤) LOU, Jian-Ping(娄建平)
HUA, Yuan-Zhao(华远照)

Department of Chemistry, Zhengzhou University, Zhengzhou, Henan 450052, China

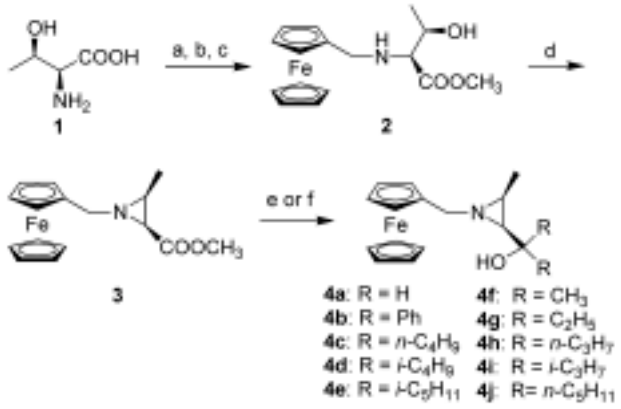
Optically active aziridino alcohols containing ferrocenyl groups were prepared from commercially available *L*-threonine in excellent yields and used as catalysts to promote the asymmetric addition of diethylzinc to aryaldehydes to afford 1-arylpropanol in up to 84% enantiomeric excesses with moderate to good yields.

Keywords ferrocenyl aziridino alcohol, catalyst, asymmetric addition

The catalytic asymmetric addition of diorganozincs to aldehydes is probably the most successful and still vigorously pursued area in asymmetric C—C bond formation.[1] During the development of various ligand structures and reaction conditions for the highly selective catalytic addition reactions, the chiral amino alcohols still remain an attractive choice of catalysts because of their easy availability and simple preparation conditions. At the meantime, diverse chiral ferrocenyl derivatives bearing either a central chirality in the side chain,[2] or a planar chirality on the substituted ferrocene moiety[3] or a combination of both,[4] have also proven to be highly enantioselective addition catalysts. Note that the chiral aziridino alcohols as another kind of amino alcohols which can be readily prepared from natural amino acids in asymmetric catalytic reactions have been limited to very few examples,[5] we report here the preparation of a new family of ferrocenyl-containing chiral aziridino alcohols and their use as chiral catalysts for asymmetric addition of diethylzinc to aryaldehydes.

The synthesis of ligands **4a**—**4j** is shown in Scheme 1. According to the literature procedure,[6] *L*-threonine **1** was first converted into its methyl ester hydrochloride, followed by reductive alkylation[7] giving the *N*-ferrocenyl amino ester **2** in 68% overall yield. **2** was then cyclized to the aziridino ester **3** in 87% yield by reaction with Ph_3P in the presence of CCl_4 in the solution of CH_3CN.[8] Reduction with $LiAlH_4$ led to the aziridino alcohol **4a** in 93% chemical yield after workup. Treatment of **3** with excess of PhMgBr, *n*-C_4H_9MgBr, *i*-C_4H_9MgBr, *i*-$C_5H_{11}MgBr$, CH_3MgI, C_2H_5MgBr, *n*-C_3H_7MgBr, *i*-C_3H_7MgBr or *n*-$C_5H_{11}MgBr$ afforded the ligands **4b** (88%), **4c** (80%), **4d** (71%), **4e** (66%), **4f** (57%), **4g** (62%), **4h** (68%), **4i** (66%) and **4j** (74%), respectively.[9]

Scheme 1 Synthesis of aziridino alcohols containing ferrocenyl groups

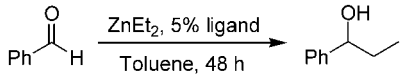


Reagents and conditions: (a) dry MeOH, $SOCl_2$, −15 ℃ to rt, 11 h; *L*-threonine, reflux; (b) Et_3N, FcCHO, MeOH, −10 to 0 ℃; (c) $NaBH_4$; (d) PPh_3, CCl_4, Et_3N, MeCN, rt; (e) $LiAlH_4$, THF, 0 ℃ to rt (for compound **4a**); (f) RMgBr, THF, −20 ℃ to rt (for compounds **4b**, **4c**, **4d**, **4e**, **4f**, **4g**, **4h**, **4i**, and **4j**)

The synthesized chiral ferrocenyl aziridino alcohols (**4a**—**4j**) were then used as catalysts in the addition of diethylzinc to benzaldehyde to check their asymmetric induction efficiency. The chemical yields of 1-phenylpropanol were good to excellent (70%—99%) with enantiomeric excesses from 3% to 69%. The results are summarized in Table 1. It was shown that the enantioselectivity of the reaction was very sensitive to the structure of the chiral catalyst. For example, when the ligands **4a**, **4b**, **4e**, **4f**, **4g** and **4j** were employed, *(S)*-1-phenylpropanol was obtained in low *ee* values (3%—23% *ee*, Table 1, Entries 1, 2, 5, 8, 9, 12), while **4c**, **4d**, **4h** and **4i** not only showed high catalytic activity,

* E-mail: wangd@zzu.edu.cn
Received October 28, 2003; revised December 15, 2003; accepted March 30, 2004.
Project supported by the National Natural Science Foundation of China (No. 20172047), Henan Outstanding Youth Program 2001, and the Education Department of Henan Province.

Table 1 Addition of diethylzinc to benzaldehyde catalyzed by ligands 4 [a]



Entry	Ligand	Temp./℃	Yield [b]/%	*ee* [c]/%	Config.[d]
1	**4a**	rt	70	3	*S*
2	**4b**	rt	88	8	*S*
3	**4c**	rt	99	68	*S*
4	**4d**	rt	97	58	*S*
5	**4e**	rt	75	11	*S*
6	**4c**	0	96	69	*S*
7	**4c**	−20	76	69	*S*
8	**4f**	rt	85	9	*S*
9	**4g**	rt	82	23	*S*
10	**4h**	rt	78	50	*S*
11	**4i**	rt	90	52	*S*
12	**4j**	rt	77	9	*S*

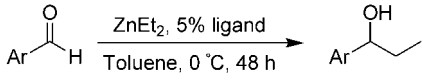
[a] The molar ratio of ligand/Et_2Zn/aldehyde was 0.05/2/1. [b] Isolated yields. [c] Determined by HPLC using a chiral OD column. [d] Absolute configuration assigned by comparison with known elution order from a Chiralcel OD column according to the literature.[10]

but also gave the product with moderate *ee* values (50%—69% *ee*, Table 1, Entries 3, 4, 6, 7, 10, 11). The low *ee* values achieved with **4a**, **4b**, **4e**, **4f**, **4g** and **4j** might arise from the mismatching of the stereochemistry between the substrates and the catalysts or from the steric effects of the less bulky Ph and *i*-C_5H_{11} group. Temperature has little effect on the optical yields (Table 1, Entries 3, 6, 7).

The chiral ligand **4c** was then examined for the asymmetric addition of diethylzinc to a series of aromatic aldehydes under the optimized conditions. The results are summarized in Table 2. As can be seen, **4c** afforded 1-phenylpropanol with moderate *ee* values (56%—76% *ee*, Table 2, Entries 1—7) for various aromatic aldehydes, including *ortho*-, *para*-, and *meta*- substituted benzaldehydes. More interestingly, we found that the higher asymmetric induction (84% *ee*, Table 2, Entry 8) was obtained by using ferrocenyl aldehyde as substrate. As expected, addition of diethylzinc to ferrocenyl aldehyde in the presence of chiral ligand **4d** also gave the product with 80% *ee* (Table 2, Entry 9). This might be rationalized by the stereochemical matching of the structure of formylferrocene with the chiral ferrocenyl aziridino alcohol. Indeed, the addition of diethylzinc to ferrocenyl aldehyde led to the higher *ee* of 1-ferrocenylpropanol (Table 3) than that of 1-phenylpropanol (Table 1).

In summary, the new chiral ferrocenyl aziridino alcohols have been readily synthesized with high yields. When the new family of amino alcohols was applied as catalysts in the addition of diethylzinc to aromatic aldehydes, they provided the corresponding alcohol with moderate to high *ee*. These new chiral ligands are currently evaluated to other reactions in our laboratory.

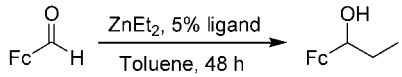
Table 2 Asymmetric addition of diethylzinc to aldehydes using ligands **4c** [a]



Entry	ArCHO	Yield [b]/%	*ee* [c]/%	Config.[d]
1	C_6H_5CHO	99	69	S
2	*p*-$MeOC_6H_4CHO$	65	60	S
3	*o*-$MeOC_6H_4CHO$	90	56	S
4	Heliotripine	99	76	ND
5	*p*-ClC_6H_4CHO	40	61	S
6	*m*-ClC_6H_4CHO	25	58	S
7	*m*-BrC_6H_4CHO	57	68	S
8	Ferronenyl aldehyde	100	84	S
9	Ferronenyl aldehyde	99	80	S

[a] The molar ratio of **4c**/Et_2Zn/aldehyde was 0.05/2/1. [b] Isolated yields. [c] Determined by HPLC using a chiral OD column. [d] Absolute configuration assigned by comparison with the sign of optical rotation of known compound and known elution order from a Chiralcel OD column.[10,11]

Table 3 Addition of diethylzinc to ferronenyl aldehyde catalyzed by ligands **4** [a]



Entry	Ligand	Temp./℃	Yield [b]/%	*ee* [c]/%	Config.[d]
1	**4a**	0	79	16	*S*
2	**4b**	0	81	12	*S*
3	**4e**	0	85	65	*S*
4	**4f**	0	83	40	*S*
5	**4g**	0	91	77	*S*
6	**4h**	0	89	76	*S*
7	**4i**	0	95	82	*S*
8	**4j**	0	85	63	*S*

[a] The molar ratio of **4**/Et_2Zn/aldehyde was 0.05/2/1. [b] Isolated yields. [c] Determined by HPLC using a chiral OD column. [d] Absolute configuration assigned by comparison with the sign of optical rotation of known compound and known elution order from a Chiralcel OD column.[10]

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9 Compound **4a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.14 (d, J=5.4 Hz, 3H, CH_3), 1.70—1.76 [m, 2H, $(CH)_2N$], 3.21, 3.44 (d, J=12.8 Hz, each 1H, CHH'N), 3.45, 3.68 (dd, J_1=6.4, J_2=4.4 Hz, 2H, CHH'OH), 4.09—4.22 (m, 9H, FcH). Compound **4b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.02 (d, J=2.8 Hz, 3H, CH_3), 1.85—1.95 (m, 1H, CH_3C**H**), 2.34 (d, H, J=6.8 Hz, CH_3CHC**H**), 3.44, 3.48 (d, J=12.6 Hz, each 1H, CHH'N), 3.9—4.1 (m, 9H, FcH), 4.61 (s, 1H, OH), 7.17—7.48 (m, 10H, PhH). Compound **4c**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.9 (t, J=6.7 Hz, 6H, 2×CH_2C**H**$_3$), 1.28 (d, J=2.9 Hz, 3H, CH_3), 1.29—1.48 (m, 13H, 2×$(CH_2)_3$, NCH), 1.59—1.65 (m, 1H, CH_3C**H**), 2.96 (br s, 1H, OH), 3.32, 3.47 (d, J=12.8 Hz, each 1H, CHH'N), 4.12—4.22 (m, 9H, FcH). Compound **4d**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.93—0.96 (m, 12H, 4×CH_3), 1.35 (d, J=5.3 Hz, 3H, CHC**H**$_3$), 1.27—1.47 (m, 5H, 2×CH_2, NCH), 1.56—1.63 (m, 1H, CH_3C**H**), 1.72—1.84 (m, 2H, 2×CH), 3.02 (s, 1H, OH), 3.14, 4.21 (d, J=13 Hz, each 1H, CHH'N), 4.12 (s, 7H, FcH), 4.17 (d, J=12 Hz, 2H, FcH). Compound **4e**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.88—0.95 (m, 12H, 4×CH_3), 1.31 (d, J=6 Hz, 3H, CHC**H**$_3$), 1.15—1.50 (m, 11H, 2×CH_2CH_2CH, NCH), 1.58—1.64 (m, 1H, CH_3C**H**), 2.93 (s, 1H, OH), 3.31, 3.40 (d, J=12.8 Hz, each 1H, CHH'N), 4.10—4.21 (m, 9H, FcH). Compound **4f**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.10 (s, 3H, CH_3), 1.17 (s, 3H, CH_3), 1.32 (d, J=6 Hz, 3H, CHC**H**$_3$), 1.37 (d, J=6.8 Hz, 1H, NCH), 1.62—1.64 (m, 1H, CH_3C**H**), 2.92 (s, 1H, OH), 3.20, 3.54 (d, J=12.4 Hz, each 1H, CHH'N), 4.10—4.21 (m, 9H, FcH). Compound **4g**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.86—0.92 (m, 6H, 2×CH_2C**H**$_3$), 1.32 (d, J=6 Hz, 3H, CHC**H**$_3$), 1.40—1.57 (m, 5H, 2×C**H**$_2$$CH_3$, NCH), 1.59—1.65 (m, 1H, CH_3C**H**), 2.94 (s, 1H, OH), 3.23, 3.54 (d, J=12.4 Hz, each 1H, CHH'N), 4.10—4.21 (m, 9H, FcH). Compound **4h**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.87—0.92 (m, 6H, 2×CH_2C**H**$_3$), 1.31 (d, J=6.8 Hz, 3H, CHC**H**$_3$), 1.32—1.45 (m, 9H, 2×C**H**$_2$$CH_3$, NCH), 1.55—1.63 (m, 1H, CH_3C**H**), 2.92 (s, 1H, OH), 3.23, 3.47 (d, J=12.4 Hz, each 1H, CHH'N), 4.10—4.21 (m, 9H, FcH). Compound **4i**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.98—1.01 (m, 12H, 4×CH_2C**H**$_3$), 1.29 (d, J=6 Hz, 3H, CHC**H**$_3$), 1.46 (d, J=6.4 Hz, 1H, NCH), 1.51—1.57 (m, 1H, CH_3C**H**), 1.90—2.91 (m, 2H, 2×C**H**$(CH_3)_2$), 2.87 (s, 1H, OH), 2.81, 3.98 (d, J=13.2 Hz, each 1H, CHH'N), 4.10—4.21 (m, 9H, FcH). Compound **4j**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.87—0.92 (m, 6H, 2×CH_2C**H**$_3$), 1.21—1.48 (m, 20H, 2×$(CH_2)_4$, CHC**H**$_3$, NCH), 1.58—1.65 (m, 1H, CH_3C**H**), 2.94 (br s, 1H, OH), 3.27, 3.45 (d, J=12.8 Hz, each 1H, CHH'N), 4.12—4.22 (m, 9H, FcH).

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(E0310282 PAN, B. F.)