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Enantioselective synthesis of planar chiral azaferrocenes via chiral ligand-mediated ring- and lateral-lithiations

Tsutomu Fukuda, Kengo Imazato and Masatomo Iwao*

Department of Applied Chemistry, Faculty of Engineering, Nagasaki University, 1-14 Bunkyo-machi, Nagasaki 852-8521, Japan

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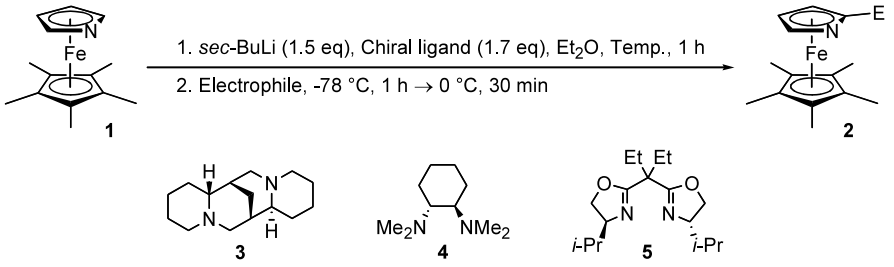
Abstract—Lithiation of 1′,2′,3′,4′,5′-pentamethylazaferrocene (**1**) with *sec*-BuLi/(−)-sparteine (**3**) in Et_2O at −78°C followed by quenching with electrophiles gave the ring-substituted products **2** in 74–81% ee. On the other hand, lithiation of 1′,2,2′,3′,4′,5,5′-heptamethylazaferrocene (**6**) with *sec*-BuLi in the presence of *S*-valine-derived bis(oxazoline) **5** in Et_2O at −55°C and subsequent reaction with electrophiles afforded the laterally functionalized products **7** in excellent enantioselectivity (96–99% ee).

Azaferrocene is a molecule in which pyrrolyl and cyclopentadienyl rings are π-bound to iron.[1] Azaferrocene derivatives having a substituent at the 2-position of the pyrrolyl ring are chiral. Compared to the parent ferrocenes,[2] utilization of such planar-chiral azaferrocenes in asymmetric synthesis has been overlooked for a long time. Recently, however, Fu and coworkers have demonstrated that the chiral azaferrocenes are highly useful in enantioselective acylation as the nucleophilic catalysts[3] and in transition metal-catalyzed asymmetric reactions as the chiral ligands.[4] The synthesis of chiral azaferrocenes has been achieved by traditional resolution techniques, such as crystallization of diastereomeric salts,[5] chromatographic separation of

Table 1. Enantioselective ring-lithiation of azaferrocene **1**



Entry	Chiral ligand	Temp. (°C)	Electrophile	E	Product	**2** (%)[a]	% ee[b]	Config.[c]
1	**3**	−55	$(CH_2O)_n$	CH_2OH	**2a**	77	69	S_p
2	**4**	−55	$(CH_2O)_n$	CH_2OH	**2a**	50	38	S_p
3	**5**	−55	$(CH_2O)_n$	CH_2OH	**2a**	58	38	R_p
4	**3**	−78	$(CH_2O)_n$	CH_2OH	**2a**	70	81	S_p
5	**3**	−78	I_2	I	**2b**	87	74	S_p
6	**3**	−78	Ph_2CO	$C(OH)Ph_2$	**2c**	87	79[d]	S_p

[a] Isolated yield.
[b] Enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak AD) unless otherwise mentioned.
[c] Absolute configuration was determined by chiroptical comparison of the reported data: see Ref. 6.
[d] Enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak AD-H).

* Corresponding author. Tel.: +81-95-819-2681; fax: +81-95-819-2681; e-mail: iwao@net.nagasaki-u.ac.jp

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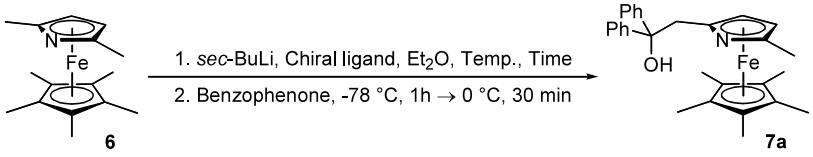
diastereomers,[3] and direct HPLC separation on a chiral stationary phase.[3] Recently, Johansen et al. have developed a more attractive method which allows the synthesis of a variety of chiral 2-substituted azaferrocenes by generation of the optically pure 2-azaferrocenyllithiums.[6] Unfortunately, however, this method requires the synthesis of optically pure 2-azaferrocenyl *p*-tolyl sulfoxides, and the auxiliary *p*-tolyl sulfoxide group is destroyed during the ligand exchange process to provide chiral 2-ferrocenyllithiums. Herein, we present another highly efficient approach to generate chiral lithium derivatives of azaferrocenes by using an external chiral ligand-mediated enantioselective lithiation technique.[7]

Regioselective C-2 lithiation of 1′,2′,3′,4′,5′-pentamethylazaferrocene (**1**) has been conducted by *n*-BuLi in THF at 0°C.[6] It is obvious, however, that the enantioselective lithiation must be carried out in a solvent of less coordinating ability and at lower temperatures.[7] Thus, we initially performed the lithiation of **1** in Et_2O at −55°C using *sec*-BuLi as a base and (−)-sparteine (**3**) as an approved chiral ligand.[7,8] The lithio species thus generated was trapped with paraformaldehyde to give 2-hydroxymethylazaferrocene **2a** in 77% chemical yield with 69% enantiomeric excess (ee) after chromatographic purification (Table 1, entry 1). Other common chiral ligands such as *N*,*N*,*N*′,*N*′-tetramethyl-(1*R*,2*R*)-1,2-diaminocyclohexane (**4**)[9] and *S*-valine-derived bis(oxazoline) **5**[10] were found to be less effective than (−)-sparteine (**3**) (entries 2 and 3). The enantioselective lithiation of **1** with *sec*-BuLi/**3** can be carried out at −78°C to give **2a** in much improved 81% ee without significant loss of the chemical yield (entry 4). The reactions with other electrophiles such as iodine and benzophenone produced the corresponding 2-substituted products **2b** and **2c** in good yields with slightly lower ee (entries 5 and 6). The configurations of **2a**–**c** prepared under *sec*-BuLi/(−)-sparteine conditions were found to be S_p by chiroptical comparisons with the reported data.[6]

Next, we turned our attention to the enantioselective lateral lithiation[11] of 1′,2,2′,3′,4′,5,5′-heptamethylazaferrocene (**6**). Since the lateral lithiation of azaferrocenes has not been reported, we initially tested the feasibility of this reaction under achiral conditions. Treatment of azaferrocene **6** with *sec*-BuLi (1.5 equiv.) in Et_2O at −55°C for 1 h followed by quenching with benzophenone produced racemic **7a** in 10% yield (Table 2, entry 1). The yield of **7a** was improved to 64% by using TMEDA as an additive (entry 2). Although the lateral lithiation of **6** is somewhat sluggish compared with ring-lithiation of **1**, the reaction is completely regioselective at the methyl groups adjacent to the pyrrolyl nitrogen.

The lithiation of **6** with *sec*-BuLi in the presence of chiral ligands **3**, **4**, and **5** at −55°C was examined next (entries 3–5). As shown in entry 5, when bis(oxazoline) **5** was used, **7a** was isolated in 31% yield with excellent optical purity (99% ee). Other ligands were not as effective as **5** for the chiral induction. In order to gain insight into this highly enantioselective reaction, we investigated the effects of temperature and time on yield and optical purity of the product. At −40°C, the

Table 2. Enantioselective lateral lithiation of azaferrocene **6**

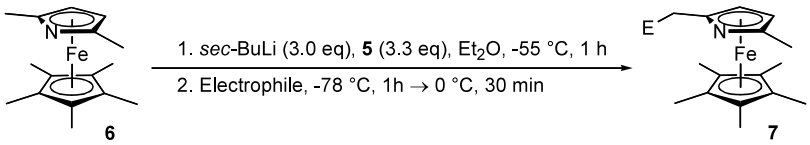


6 **7a**

Entry	BuLi (equiv.)	Chiral ligand (equiv.)	Temp. (°C)	Time (h)	**7a** (%)[a]	% ee[b]
1	*sec*- (1.5)	None	−55	1	10	–
2	*sec*- (1.5)	TMEDA (1.7)	−55	1	64	–
3	*sec*- (1.5)	**3** (1.7)	−55	1	16	57
4	*sec*- (1.5)	**4** (1.7)	−55	1	57	40
5	*sec*- (1.5)	**5** (1.7)	−55	1	31	99
6	*sec*- (1.5)	**5** (1.7)	−40	1	28	99
7	*sec*- (1.5)	**5** (1.7)	−78	1	12	65
8	*sec*- (1.5)	**5** (1.7)	−55	0.5	35	97
9	*sec*- (1.5)	**5** (1.7)	−55	2	26	>99
10	*n*- (1.5)	**5** (1.7)	−55	1	0	–
11	*tert*- (1.5)	**5** (1.7)	−55	1	7	96
12	*sec*- (1.0)	**5** (1.1)	−55	1	20	99
13	*sec*- (2.0)	**5** (2.2)	−55	1	44	99
14	*sec*- (2.5)	**5** (2.8)	−55	1	49	99
15	*sec*- (3.0)	**5** (3.3)	−55	1	57	99
16	*sec*- (3.5)	**5** (3.9)	−55	1	52	>99
17	*sec*- (2.0)	**5** (1.0)	−55	1	47	93

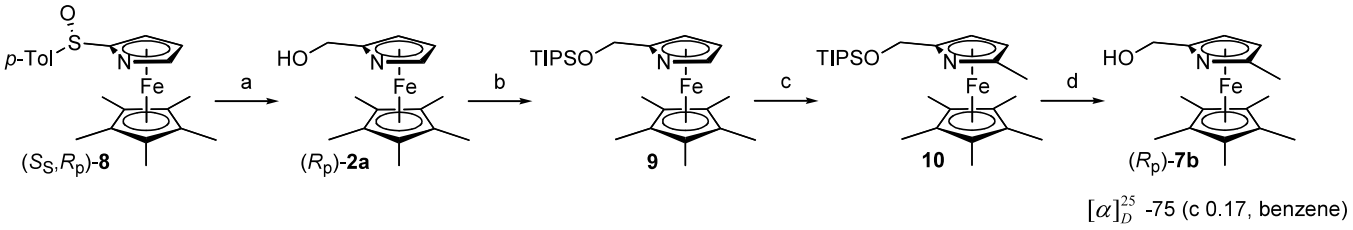
[a] Isolated yield.
[b] Enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak AD).

Table 3. Enantioselective synthesis of planar chiral azaferrocenes **7**



Entry	Electrophile	E	Product	**7** (%)[a]	% ee[b]	$[\alpha]_D$ (benzene)
1	Ph_2CO	$C(OH)Ph_2$	**7a**	57	99	$[\alpha]_D^{26}=-169$ (*c* 0.24)
2	$(TMSO)_2$	OH	**7b**	17	99 (R_p)[c]	$[\alpha]_D^{25}=-69$ (*c* 0.28)
3	$(PhS)_2$	SPh	**7c**	46	99	$[\alpha]_D^{26}=-94$ (*c* 0.32)
4	$TMSCH_2N_3$	NH_2	**7d**	46	96	$[\alpha]_D^{26}=-29$ (*c* 0.28)

[a] Isolated yield.
[b] Enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak AD).
[c] Absolute configuration was determined by an unequivocal synthesis.



Scheme 1. *Reagents and conditions*: (a) (i) *tert*-BuLi, THF, −78°C, 10 min; (ii) paraformaldehyde, −78°C, 10 min→0°C (59%). (b) TIPS-Cl, imidazole, DMF, rt, 2 h (52%). (c) (i) *sec*-BuLi, TMEDA, Et_2O, −78°C, 1 h; (ii) MeI, −78°C, 1 h→0°C, 30 min (52%). (d) TBAF, THF, rt, 30 min (quant., 94% ee).

yield of **7a** was slightly decreased without depression of the high optical purity (entry 6). To our surprise, when the lithiation was carried out at −78°C, not only the chemical yield but also the ee value were decreased considerably (65% ee) (entry 7). Shorter reaction time (0.5 h) at −55°C increased the yield (35%) but lowered the optical purity (97% ee) (entry 8). Longer reaction time (2 h) decreased the yield (26%) but increased the optical purity (>99% ee) (entry 9). These results may be rationalized by assuming that the complexes Li·**6**/**5** are rather unstable under the reaction conditions and the minor complex decomposed much faster than the major one at −55°C or higher temperatures. This decomposition may be suppressed at −78°C. Dynamic thermodynamic resolution[7a] may be ruled out in view of the configurational stability of the planar chiral lithiated species.

The lithiation conditions were explored further to improve the chemical yield of **7a**. *n*-BuLi and *tert*-BuLi were useless as the lithiating agents (entries 10 and 11). The yield of **7a** was increased gradually in proportion to the amount of *sec*-BuLi/**5** employed without reduction of 99% ee. The best yield (57%) was achieved by using 3.0 equiv. of *sec*-BuLi and 3.3 equiv. of **5** (entry 15). It is noteworthy that even in 2:1 ratio of *sec*-BuLi/**5**, **7a** was obtained in 47% yield with 93% ee (entry 17).

Since we established the best conditions for the enantioselective lateral lithiation of **6**, we next carried out functionalization of **6** with some other electrophiles. The results are summarized in Table 3. In general, laterally substituted products **7** were isolated in about 50% yields with excellent optical purity (>96% ee). The low yield of **7b** may be attributable to the poor reactivity of $(TMSO)_2$ to the labile, laterally lithiated **6**.

Finally, the absolute configuration of product **7b** was determined by chemical transformation from the known (S_s,R_p)-1′,2′,3′,4′,5′-pentamethy-2-(*p*-toluenesulfinyl)azaferrocene (**8**)[6] (Scheme 1). The lithiation of **8** with *tert*-BuLi in THF at −78°C followed by quenching with paraformaldehyde produced (R_p)-2-hydroxymethyl-1′,2′,3′,4′,5′-pentamethylazaferrocene (**2a**) in 59% yield. The hydroxyl group of **2a** was protected by TIPS ether to give **9**. The ring lithiation of **9** followed by quenching with MeI gave the product **10** in 52% yield. Deprotection of the TIPS group using tetra-*n*-butylammonium fluoride (TBAF) gave (R_p)-**7b**. Since the specific rotation and chiral HPLC profile of this sample are essentially the same as those of **7b** prepared by the enantioselective lithiation/functionalization of **6**, the absolute configuration of **7b** thus synthesized was determined to be R_p. We suspect the absolute configurations of other products **7a**, **7c** and **7d** may also be R_p, because of the configurational stability of the lithiated species.

In conclusion, we have developed an enantioselective synthesis of planar chiral azaferrocenes via a chiral ligand mediated lithiation technique. The ring lithiation of **1** with *sec*-BuLi/**3** proceeded smoothly to give the

2-functionalized products **2a**–**c** in good yields with 74–81% ee.[12] Although the lateral lithiation of **6** with *sec*-BuLi/**5** is sluggish compared with the ring lithiation, the ee values of the products **7a**–**d** are remarkably high (96–99% ee).[13] Since both enantiomers of the ligand **5** are readily available, the latter lateral lithiation technique is especially useful to produce planar chiral azaferrocenes of high optical purity.

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12. *Typical procedure (synthesis of **2a**)*: 1′,2′,3′,4′,5′-pentamethylazaferrocene (**1**) (90.2 mg, 0.351 mmol) and **3** (140 mg, 0.597 mmol) were dissolved in dry Et_2O (5.0 mL) under an argon atmosphere and the solution was cooled to −78°C. A solution of *sec*-BuLi in hexane–cyclohexane (0.980 M, 540 μL, 0.526 mmol) was added dropwise to this solution at the same temperature. After being stirred for 1 h, a mixture of paraformaldehyde (105 mg, 3.51 mmol) in dry Et_2O (2.0 mL) was added. The reaction mixture was stirred for 1 h at −78°C, warmed to 0°C, and stirred for 30 min. The mixture was quenched with water and extracted with Et_2O. The extract was washed successively with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was subjected to flash chromatography (SiO_2, ethyl acetate) to give 2-hydroxymethyl-1′,2′,3′,4′,5′-pentamethylazaferrocene (**2a**) (70.0 mg, 70%). Enantiomeric excess of the product **2a** was determined to be 81% ee by HPLC analysis (Daicel Chiralpak AD, hexane-*i*-PrOH = 9:1).
13. *Typical procedure (synthesis of **7a**)*: 1′,2,2′,3′,4′,5,5′-heptamethylazaferrocene (**6**) (100 mg, 0.351 mmol) and **5** (341 mg, 1.16 mmol) were dissolved in dry Et_2O (5.0 mL) under an argon atmosphere and the solution was cooled to −55°C. A solution of *sec*-BuLi in hexane–cyclohexane (0.994 M, 1.06 mL, 1.06 mmol) was added dropwise to this solution at the same temperature. After being stirred for 1 h, the reaction mixture was cooled to −78°C and a solution of benzophenone (256 mg, 1.40 mmol) in dry Et_2O (1.0 mL) was added. The reaction mixture was stirred for 1 h at −78°C, warmed to 0°C, and stirred for 30 min. The mixture was quenched with water and extracted with Et_2O. The extract was washed successively with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was subjected to flash chromatography (SiO_2, hexane–ethyl acetate = 5:1 to 3:1) to give 2-(2,2-diphenyl-2-hydroxyethyl)-1′,2′,3′,4′,5,5′-hexamethylazaferrocene (**7a**) (93.0 mg, 57%). Enantiomeric excess of the product **7a** was determined to be 99% ee by HPLC analysis (Daicel Chiralpak AD, hexane–*i*-PrOH = 19:1).