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Effects of Solvent and Lithiating Agent on Stereoselectivity in Lithiation of Chiral 1,1'-Bis(oxazolinyl)ferrocenes

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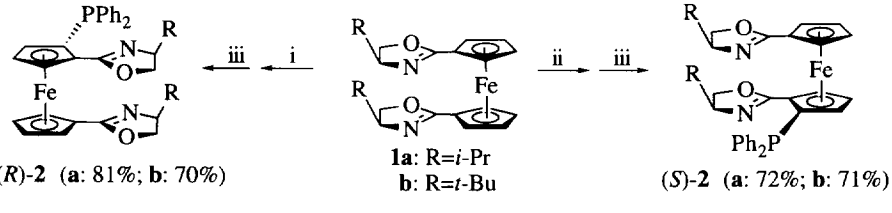
Abstract: The analysis of phosphorylation products was carried out to investigate the stereoselectivity change in lithiation of 1,1'-bis[(*S*)-2-(4-R-oxazolinyl)]ferrocene (**1**) with varying reaction conditions such as solvents, lithiating agents, and temperatures. Monolithiation with butyllithiums in Et_2O led to the configuration corresponding to (*R*)-**2**, while use of THF favors (*S*)-**2**. Dilithiation with *sec*-BuLi or *t*-BuLi in Et_2O led to the configuration corresponding to (*R,S*)-**3**. However, the step-by-step lithiation at different temperatures with *sec*-BuLi in Et_2O provided the dilithiated species corresponding to (*R,R*)-**3**. *sec*-BuLi in THF was special to give (*S,S*)-**3** as the major product.

Many chemists are interested in synthesis of chiral ferrocene derivatives.[1] One of their important applications is using as chiral ligands in catalytic asymmetric reactions.[2] Chiral oxazolinyl substituent has been shown as a good guiding group for diastereoselective derivatization through lithiation and subsequent reaction with various electrophiles.[3] Recently we reported the synthesis of 1,1'-bis(oxazolinyl)ferrocenes **1** and their phosphorylation via diastereoselective *ortho*-lithiation.[4]

We here wish to report the remarkable solvent effect that leads to almost complete reversal of the stereoselectivity in the lithiation of **1**. The stereoselectivity can be controlled simply by changing temperatures, solvents and/or lithiating agents, and all possible stereoisomers in *o*-phosphorylation and *o,o'*-diphosphorylation can be obtained as major products.



(*R*)-**2** (**a**: 81%; **b**: 70%)

1a: R=*i*-Pr
b: R=*t*-Bu

(*S*)-**2** (**a**: 72%; **b**: 71%)

Scheme 1 i: *s*-BuLi (1.2 equiv) / Et_2O ii: *s*-BuLi (1.2 equiv) / THF iii: $ClPPh_2$

As shown in Scheme 1, two similar reaction conditions except the solvent led to almost opposite diastereoselections in the *o*-phosphorylation of **1**. The absolute stereochemistry of (*R*)-**2b** was determined by X-ray diffraction analysis (Figure1):[5,6] An interesting feature of the molecular structure is that the diphenylphosphino group and two oxazolinyl groups come together in one side with the *t*-butyl substituents

pointing outside.

Lithiations of **1a** were carried out with varying solvents and butyllithiums and the stereochemistry was analyzed after phosphorylation of the resulting lithiated species (Table 1): The stereoselectivity of monolithiation seems to be affected mainly by the solvent. In Et_2O the lithiation favors the configuration corresponding to (*R*)-**2a**, while use of THF leads favorably to (*S*)-**2a**.[7] The best result for (*R*)-**2a** is given by the use of *s*-BuLi in Et_2O and that for (*S*)-**2a** is obtained by the use of *s*-BuLi in THF.

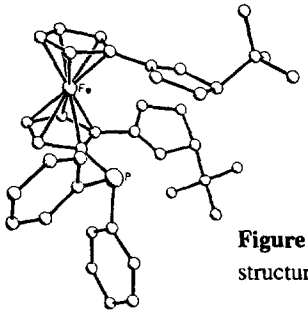
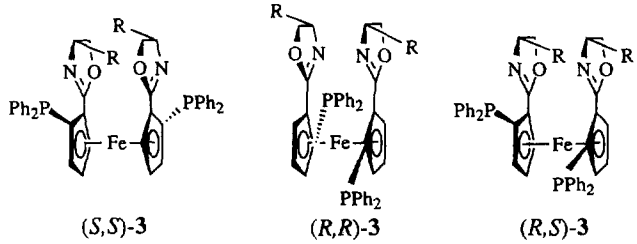


Figure 1. The Molecular structure of (*R*)-**2b**

Table 1. Monophosphorylation of **1a** under Various Conditions

entry	Lithiation Condition	Products (% yield)[a,b]				
	BuLi (equiv) / Solvent	(*R*)-**2a**	(*S*)-**2a**	(*R,R*)-**3a**	(*S,S*)-**3a**	(*R,S*)-**3a**
1	*n*-BuLi (1.2) / Et_2O[c]	58	4	15		
2	*s*-BuLi (1.2) / Et_2O	81	3	9		6
3	*t*-BuLi (1.2) / Et_2O	46	6	3		16
4	*n*-BuLi (1.2) / THF	12	38			
5	*s*-BuLi (1.2) / THF	6	72	1	6	7
6	*t*-BuLi (1.2) / THF	8	54	1	7	16

[a] The yields of products were estimated by chromatographic separation of mono- and diphosphorylated products and by the analysis of their ^{1}H-NMR spectra. [b] The yield of the major product is underlined. [c] Lithiation was completed at 25 °C, while 0 °C was enough for other cases.



(*S,S*)-**3** (*R,R*)-**3** (*R,S*)-**3**

Table 2. Diphosphorylation of **1a** under Various Conditions

entry	Lithiation Condition	Products (% yield)[a,b]				
	BuLi (equiv) / Solvent	(*R*)-**2a**	(*S*)-**2a**	(*R,R*)-**3a**	(*S,S*)-**3a**	(*R,S*)-**3a**
1	*n*-BuLi (2.2) / Et_2O[c]	57		15		
2	*s*-BuLi (2.2) / Et_2O			7		63
3	*s*-BuLi (2.2) / Et_2O[d]			27		26
4	*t*-BuLi (2.2) / Et_2O					60
5	*n*-BuLi (2.2) / THF	9	2	11	10	35
6	*s*-BuLi (2.2) / THF			5	56	19
7	*t*-BuLi (2.2) / THF	2	7	6	17	51

[a] The yields of products were estimated by chromatographic separation of mono- and diphosphorylated products and by the analysis of their ^{1}H-NMR spectra. [b] The yield of the major product is underlined. [c] Lithiation was completed at 25 °C, while 0 °C was enough for other cases. [d] A step-by-step lithiation was applied.[8]

Solvent was a crucial factor in the stereoselective dilithiation of **1a**. Lithiating agents also varied selectivities and yields. Table 2 shows the results from the phosphorylation of the lithiated species formed in reactions with two equivalents of butyllithiums: *n*-BuLi in Et_2O seems not to be strong enough for dilithiation even at room temperature. An interesting aspect of this case is that only (*R,R*)-**3a** is provided out of three possible *o,o'*-diphosphorylated stereoisomers. *s*-BuLi and *t*-BuLi in Et_2O lead to (*R,S*)-**3a** as the major product. However, (*R,R*)-**3a** is obtained in almost same yield as that of (*R,S*)-**3a** by the step-by-step litiation at different temperatures with *s*-BuLi in Et_2O.[8] The use of THF increases the yield of (*S,S*)-**3a**. In particular *s*-BuLi in THF provides (*S,S*)-**3a** as the major product.[9]

Based on the results from the phosphorylation of **1a**, a number of reaction conditions were selected for the *t*-butyl analog **1b** (Table 3): In monophosphorylation the trend of reactions with **1b** is similar to that with **1a**. (*R*)-Configuration is favored in Et_2O but the use of THF reverses the selectivity. Tetramethylethylenediamine (TMEDA) provides the effect similar to that of THF. The selectivities for *o,o'*-diphosphorylated products are also dependent on solvent and TMEDA. In Et_2O (*R,S*)-**3b** is the major product but (*S,S*)-**3b** is the major one in THF or Et_2O/TMEDA. Noticeably (*R,R*)-**3b** is obtained as the major product by application of the step-by-step dilitiation with *s*-BuLi in Et_2O.[8] However, (*R,S*)-**3b** is the major one again when 1.2 equiv of TMEDA is added at the second lithiation stage.

Table 3. Phosphorylation of **1b** under Various Conditions

entry	Lithiation Condition	Products (% yield)[a,b]				
	BuLi (equiv) / Solvent	(*R*)-**2b**	(*S*)-**2b**	(*R,R*)-**3b**	(*S,S*)-**3b**	(*R,S*)-**3b**
1	*n*-BuLi (1.2) / Et_2O[c]	86		5		
2	*s*-BuLi (1.2) / Et_2O	70	12			
3	*s*-BuLi (1.2) / THF	4	71			
4	*s*-BuLi-TMEDA (1.2) / Et_2O	9	63			
5	*t*-BuLi (1.2) / Et_2O	63		2		8
6	*s*-BuLi (2.2) / Et_2O			26		53
7	*s*-BuLi-TMEDA (2.2) / Et_2O				59	20
8	*s*-BuLi (2.2) / Et_2O[d]			47		20
9	*s*-BuLi (2.2) / TMEDA (1.2) / Et_2O[e]			12	10	59
10	*s*-BuLi (2.2) / THF				81	9

[a] The yields of products were estimated by chromatographic separation of mono- and diphosphorylated products and by the analysis of their ^{1}H-NMR spectra. [b] The yield of the major product is underlined. [c] Lithiation was completed at 25 °C. [d] Step-by-step lithiation was applied. [e] TMEDA was added at the second lithiation stage.

The steric hindrance between the alkyl substituent of the oxazolinyl unit and aggregated butyllithiums has been suggested for the major factor to point the alkyl substituent toward the other cyclopentadienyl ring in the lithiation of mono(oxazolinyl)ferrocenes.[10] And the nitrogen-directed lithiation followed by phosphorylation results in the (*S*)-configuration.[11] This stereoselective formation of (*S*)-**2** in THF can be explained similarly. However, in Et_2O, participation of both oxazolinyl groups would be considered in the monolithiation of **1**, which leads to (*R*)-**2**.

The dilithiated species corresponding to (*R,S*)-**3** is formed by the second lithiation of the monolithiated species at the other cyclopentadienyl ring with the opposite configuration. The cooperative coordination of lithium with the oxazolinyl groups is also probable in the monolithiated species in Et_2O, although the mode is not clear yet. The cooperative coordination can be inferred by the observations that the formation of (*R,R*)-**3** is increased by elevating temperature at the second lithiation stage and that (*S,S*)-**3** is formed as the major product by the addition of TMEDA into Et_2O. Considering the competitive coordinating abilities of

THF and TMEDA, their stereochemical effects, which favor (*S*)-**2** and (*S,S*)-**3**, are consistent with above explanations.

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References and Notes

1. Hayashi, T.; Konishi, M.; Fukushima, M.; Mise, T.; Kagotani, M.; Tajika, M.; Kumada, M. *J. Am. Chem. Soc.* **1982**, *104*, 180-186 and references therein.
2. For leading references, see: *Ferrocenes*; Togni, A.; Hayashi, T., Eds.; VCH: Weinheim, 1995.
3. Sammakia, T.; Latham, H. A.; Schaad, D. R. *J. Org. Chem.* **1995**, *60*, 10-11 and references therein.
4. Park, J.; Lee, S.; Ahn, K. H.; Cho, C. W. *Tetrahedron Lett.* **1995**, *36*, 7263-7265.
5. The configurations of (*R*)-**2** and (*R,R*)-**3** have been assigned to the opposite direction in the previous paper: See ref. 4.
6. X-ray analysis of (*R*)-**2b**: $C_{36}H_{41}N_2O_2PFe$. M_r=620.53 g/mol. Orange crystals: crystal size 0.55 x 0.50 x 0.30 mm, orthorhombic, a=10.5884(7), b=14.6191(8), c=20.878(6) Å, space group $P2_12_12_1$ (No. 19), V=3232.8(9) Å^3, Z=4, T=293(2) K, d_{cal} = 1.275 g/cm^3, linear abs. coeff.=5.50 cm^{-1}. Enraf-Nonius CAD4 diffractometer, λ=0.71073 Å, scan mode=ω (ω-scan width: 1.70 to 23.95°). 2850 reflections were measured, giving 2431 unique data with $I > 2\sigma(I)$. R = 0.042, R_w = 0.045, G.O.F. = 0.48. Atomic coordinates, bond lengths, angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Center.
7. (*S*)-**2a**: ^{1}H NMR ($CDCl_3$): δ 7.53 - 7.15 (m, 10H), 5.00 (d, J = 0.72 Hz, 1H), 4.87 (d, J = 1.20 Hz, 1H), 4.67 (d, J = 1.10 Hz, 1H), 4.43 (m, 2H), 4.34 (dd, J = 2.49 Hz, 1H), 4.25 (m, 2H), 4.00 (m, 1H), 3.91 (m, 1H), 3.81 (m, 1H), 3.69 (s, 1H), 3.59 (t, J = 8.28 Hz, 1H), 1.80 (m, 1H), 1.63 (m, 1H), 0.96 (d, J = 6.75 Hz, 3H), 0.87 (d, J = 6.81 Hz, 3H), 0.81 (d, J = 6.81 Hz, 3H), 0.64 (d, J = 6.75 Hz, 3H) ^{13}C NMR ($CDCl_3$): δ 165.0, 164.9, 139.9, 139.8, 138.4, 135.6, 135.4, 133.2, 132.9, 129.6, 128.9, 128.6, 81.1, 80.9, 75.3, 74.7, 74.4, 74.1, 73.4, 73.1, 73.0, 72.8, 71.9, 71.5, 70.2, 70.1, 32.9, 32.6, 19.6, 19.4, 18.5, 18.2.
(*S*)-**2b**: ^{1}H NMR ($CDCl_3$): δ 7.52 - 7.16 (m, 10H), 4.99 (d, J = 0.63 Hz, 1H), 4.83 (d, J = 1.20 Hz, 1H), 4.66 (s, 1H), 4.42 (d, J = 1.38 Hz, 2H), 4.31 (t, J = 2.52 Hz, 1H), 4.21 - 4.05 (m, 3H), 3.86 - 3.70 (m, 3H), 3.67 (d, J = 0.63 Hz, 1H), 0.88 (s, 9H), 0.76 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 164.8, 164.4, 140.2, 140.0, 138.7, 138.5, 135.7, 135.5, 133.2, 133.0, 129.6, 128.9, 128.8, 128.7, 128.6, 128.5, 81.0, 80.9, 76.8, 75.4, 74.8, 74.5, 74.3, 73.4, 73.1, 71.9, 71.4, 69.1, 69.0, 34.1 34.0, 26.6, 26.4.
8. At -78 °C 1.0 equiv of *s*-BuLi was added. The reaction mixture was stirred for 2 h at -78 °C and was warmed up slowly to 25 °C over 1 h. Then additional 1.2 equiv of *s*-BuLi was added dropwise.
9. Ikeda group has reported the diastereoselective preparation of (*S,S*)-**3** by use of *s*-BuLi (2.6 equiv) in THF, see: Zhang, W.; Adachi, Y.; Hirao, T.; Ikeda, I. *Tetrahedron: Asymmetry*, **1996**, *7*, 451-460.
10. a) Damalidis, T.; Hibbs, D. E.; Hursthouse, M. B. *Synlett* **1995**, 74-76. b) Nishibashi, Y.; Uemura, S. *Synlett* **1995**, 79-81.
11. a) Sammakia, T.; Latham, H. A. *J. Org. Chem.* **1996**, *61*, 1629-1635. b) Sammakia, T.; Latham, H. A. *J. Org. Chem.* **1995**, *60*, 6002-6003.

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