An Efficient Diastereoselective Synthesis of Chiral Oxazolinylferrocene Compounds

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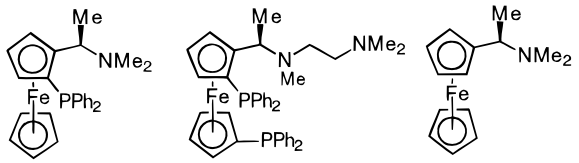
Chiral oxazolinylferrocenes **7** and **8** are synthesized from ethyl ferrocenecarboxylate and amino acid-derived amino alcohols in overall 81−85% yields, through trimethylaluminum-mediated transamidation followed by ring formation with *p*-toluenesulfonyl chloride and triethylamine. Lithiation of the oxazolinylferrocenes under various reaction conditions and subsequent coupling reactions with electrophiles such as $ClPPh_2$, $ClSnBu_3$, $ClSiMe_3$, PhSSPh, DMF, and CO_2 are described. Lithiated intermediates are found to have limited stability, depending on the solvent and the temperature. In THF, the lithiated intermediate rapidly decomposes at 25 °C: In Et_2O, it is quite stable at 0 °C but mostly decomposes at 25 °C within 6 h. Lithiation of the oxazolinylferrocenes is directed by the oxazoline moiety and is highly diastereoselective in the case of **8**. With *s*-BuLi in THF−cyclohexane, several ferrocene derivatives **11** are produced with diastereoselectivities of ≥96:4. *s*-BuLi and *n*-BuLi give better selectivities and yields than *t*-BuLi. With *s*-BuLi, generally better diastereoselectivities are obtained in THF−cyclohexane than in Et_2O−cyclohexanes. When $ClPPh_2$ is used as the electrophile, the *s*-BuLi in THF−cyclohexane system, however, gives variable yields depending on reaction temperature and time. With *n*-BuLi in Et_2O−hexanes at 25 °C, phosphino(oxazolinyl)ferrocene **11a** is consistently obtained in moderate yields with a 97:3 diastereoselectivity. Determination of the diastereoselectivity and characterization of new chiral ferrocene compounds including one X-ray crystal structure are described.

Introduction

Several ferrocene-derived chiral ligands have been successfully employed in organometallic catalysis for asymmetric synthesis. For example, aminoalkyl(ferrocenyl) phosphine **1**, initially developed by Kumada and co-workers, has been demonstrated to be an excellent ligand in the Ni- or Pd-catalyzed asymmetric Grignard coupling reaction.[1] A structural analog such as **2** has been used in the Au-catalyzed asymmetric aldol reaction and in the Pd-catalyzed asymmetric allylic substitution by Hayashi and others.[2] These chiral ferrocene derivatives are derived from (1-ferrocenylethyl)dimethylamine (**3**) through the diastereoselective ortho-lithiation developed by Ugi.[3]



1 **2** **3**

Recently, Kagan has reported an excellent method of the planar chirality control of ferrocene compounds, employing a chiral 1,3-dioxane moiety as the lithiation guide.[4] As part of our project directed toward the development of new N,P-chelates for chiral transition metal catalysts, we have studied the control of planar chirality of ferrocene employing chiral oxazolines as directing groups. Since oxazolines have been known to be good directing groups in the neighboring lithiation,[5] it was expected that certain chiral oxazolines would guide the diastereoselective lithiation of the ferrocene ring. Actually this approach was found to be efficient, and (diphenylphosphino)(oxazolinyl)ferrocene (DPOF) **11a** was synthesized with an excellent diastereoselectivity (Scheme 2). We demonstrated the utility of this new N,P-chelate in the Pd-catalyzed asymmetric allylic substitution, wherein up to 99% ee was realized.[6] Recently, the same conceptual approach to this oxazoline-directed diastereoselective lithiation of ferrocenes has been simultaneously reported by several authors, including us.[7] During the preparation of DPOF and other analogs, we have found that both diastereoselectivity and the yield of the lithiation and the subsequent reaction with several electrophiles were dependent on several factors such as the alkyllithium employed, the reaction temperature, and the solvent. Particularly, with $ClPPh_2$ as the electrophile, the coupling yield was variable and lower than those obtained with other electrophiles examined. In this

[⊗] Abstract published in *Advance ACS Abstracts,* June 15, 1996.

(1) (a) Hayashi, T.; Tajika, M.; Tamao, K.; Kumada, M. *J. Am. Chem. Soc.* **1976**, *98*, 3718. (b) Hayashi, T.; Konishi, M.; Fukushima, M.; Mise, T.; Kagotani, M.; Tajika, M.; Kumada, M. *J. Am. Chem. Soc.* **1982**, *104*, 180. (c) Hayashi, T.; Kumada, M. *Acc. Chem. Res.* **1982**, *15*, 395. (d) Hayashi, T.; Konishi, M.; Okamoto, Y.; Kabeta, K.; Kumada, M. *J. Org. Chem.* **1986**, *51*, 3772.

(2) (a) Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405. (b) Ito, Y.; Sawamura, M.; Hayashi, T. *Tetrahedron Lett.* **1986**, *28*, 6215. (c) Pastor, S. D.; Togni, A. *J. Am. Chem. Soc.* **1989**, *111*, 2333. (d) Hayashi, T. *Pure & Appl. Chem.* **1988**, *60*, 7 and references therein. (e) Sawamura, M.; Ito, Y.; Hayashi, T. *Tetrahedron Lett.* **1989**, *30*, 2247.

(3) Marquarding, D.; Klusacek, H.; Gokel, G.; Hoffmann, P.; Ugi, I. *J. Am. Chem. Soc.* **1970**, *92*, 5389.

(4) (a) Riant, O.; Samuel, O.; Kagan, H. B. *J. Am. Chem. Soc.* **1993**, *115*, 5835. (b) Using a chiral sulfoxide as the directing group, see: Rebière, F.; Riant, O.; Ricard, L.; Kagan, H. B. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 568.

(5) For recent reviews: (a) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356. (b) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.

(6) These results were presented at the 74th Annual Meeting of the Korean Chemical Society, Chungju, Chungbuk, Korea, October 1994; paper ORGN C17.

(7) (a) Sammakia, T.; Latham, H. A.; Schaad, D. R. *J. Org. Chem.* **1995**, *60*, 10. (b) Richards, C.; Damalidis, T.; Hibbs, D. E.; Hursthose, M. B. *Synlett* **1995**, 74. (c) Nishibashi, Y.; Uemura, S. *Synlett* **1995**, 79. (d) Park, J.; Lee, S.; Ahn, K. H.; Cho,C.-W. *Tetrahedron Lett.* **1995**, *36*, 7263.

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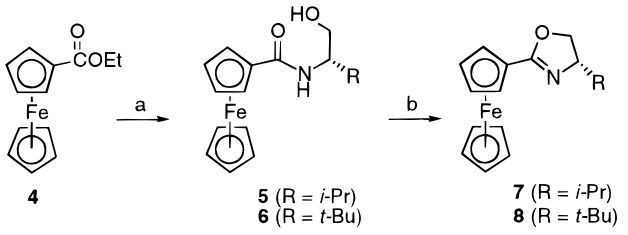
Scheme 1[a]



[a] (a) (*S*)-Valinol or (*S*)-*tert*-leucinol, Me_3Al, toluene, Δ, 8 h, 92−95%; (b) TsCl, Et_3N, CH_2Cl_2, 25 °C, 10 h, 88−89%.

paper, we wish to report the details of the diastereoselective lithiation of oxazolinylferrocenes and their subsequent reaction with several electrophiles. In addition, a new and efficient synthetic approach to the 2-oxazoline ring system is also described.

Results and Discussion

Synthesis of Oxazolinylferrocenes 7 and 8. The synthesis of the oxazolinylferrocenes **7** and **8** from ethyl ferrocenecarboxylate is shown in Scheme 1. Ethyl ferrocenecarboxylate (**4**) was obtained in 53% yield from ferrocene through lithiation with *t*-BuLi[8] and subsequent quenching with ethyl chloroformate. Conversion of the ester **4** to the hydroxy amide **5** with (*S*)-valinol was carried out in high yields according to a modified transamidation procedure, originally developed by Weinreb,[9] employing 2 mol equiv of trimethylaluminum. Employing an equimolar amount of trimethylaluminum led to incomplete reaction (ca. 80% conversion). The oxazoline ring formation (**5** → **7**), proceeded in high yield by treatment with *p*-toluenesulfonyl chloride (1.1 mol equiv) and triethylamine (2.2 mol equiv) in dichloromethane at room temperature.[10] Similarly, the oxazolinylferrocene **8** was obtained in high yield.[11]

Diastereoselective Synthesis of 9 and 11a. When the oxazolinylferrocene **7** was subjected to the lithiation with *n*-BuLi in Et_2O−hexanes (8:1, by volume, hexanes came from the alkyllithium) at 25 °C for 1−2 h and subsequent treatment with $ClPPh_2$, the DPOF **9** and **10** were obtained in a ratio of 68:32,[12] together with starting material (about 20%). The diastereoselectivity can be determined by ^{1}H NMR spectroscopy since the Cp ring proton adjacent to the oxazoline exhibited a different chemical shift for each isomer [$CDCl_3$, δ 4.95 (dd, J = 2.5, 1.3 Hz) for **9**; δ 4.93 (dd, J = 2.5, 1.3 Hz) for **10**]. The major isomer **9** can be purified to >98% de by recrystallization from ethanol. The absolute stereochemistry of

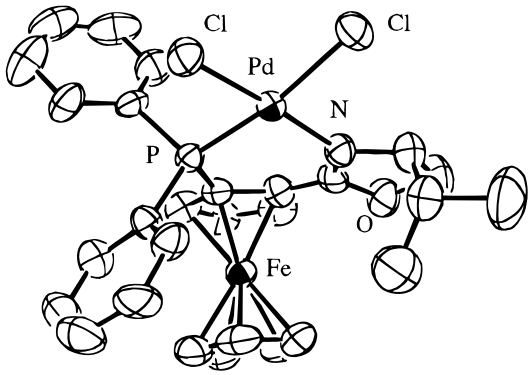
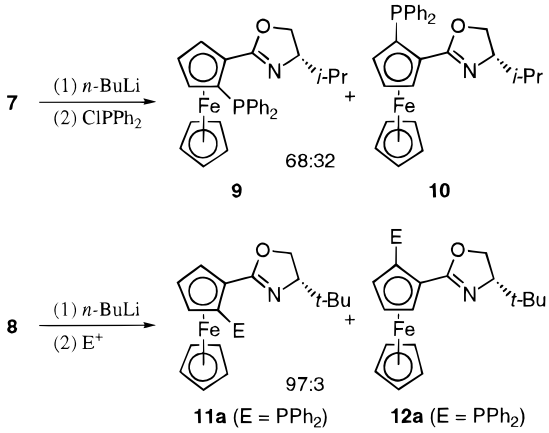


Figure 1. ORTEP drawing of (*S*,*S*)-**9**−$PdCl_2$ complex.

Scheme 2



9 was established as (*S*,*S*) by X-ray crystallography for the **9**−$PdCl_2$ complex, as shown in Figure 1.[13a,b] In contrast to the lower diastereoselectivity observed in the lithiation of **7**, the oxazolinylferrocene **8** gave a remarkable selectivity under the same conditions. Thus, the oxazoline **8** was transformed to **11a** with selectivity of 97:3 (**11a**:**12a**) (Scheme 2).[14] The diastereoselectivity of the formation of **11a** was unambiguously determined by ^{1}H NMR spectroscopy in comparison with its diastereomer **12a**, which was separately prepared according to Scheme 3. In this case, the chemical shift of *tert*-butyl protons was diagnostic ($CDCl_3$, δ 0.77 for **11a**; δ 0.62 for the **12a**). The absolute stereochemistry of **11a** was tentatively assigned as (*S*,*S*), based on the similar directed lithiation as for **7** and the same sense of enantioselectivity observed in the Pd-catalyzed allylic substitution using **9** and **11a** as chiral ligands.[6,15] These

(8) Rebiere, F.; Samuel, O.; Kagan, H. B. *Tetrahedron Lett.* **1990**, *31*, 3121.

(9) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, 4171.

(10) This mild protocol has been used by Meyers (Meyers, A. I.; Robichaud, A. J.; McKennon, M. J. *Tetrahedron Lett.* **1992**, *33*, 1181: see the footnote 10). Recently Sammakia has also used this method (see the supporting information of ref 7a).

(11) The described synthesis of oxazoline compounds from carboxylic acid esters is applicable to the synthesis of other oxazoline compounds such as (*S*)-(−)-2,2′-isopropylidenebis(4-isopropyl-2-oxazoline) (Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726) and 2-(2-bromophenyl)-4-isopropyl-2-oxazoline (Sprinz, J.; Helmchen, G. *Tetrahedron Lett.* **1993**, *34*, 1769) in greater than 90% yield. For an enolizable ester such as malonic acid dimethyl ester, the transamidation did not occur.

(12) Richards and Uemura synthesized these compounds, independently, but with a quite different selectivity (see references 7b and 7c). The selectivity obtained by us is similar to that obtained by Richards (2.5:1).

(13) (a) Crystal data for **9**−$PdCl_2$ complex: $C_{28}H_{28}NOCl_2PFePd\cdot 3CH_2Cl_2$, fw = 913.47, space group = triclinic, *P*1 (no. 1), a = 9.525(2) Å, b = 10.8666(9) Å, c = 10.9076(19) Å, α = 111.574(12)°, β = 98.786(16)°, γ = 109.115(13)°, vol = 4785.5(12) Å^3, Z = 8, temp = 23 °C, d(calcd) = 1.607 g/cm^3, λ (MoK_α) = 0.71073 Å, monochromator: graphite, linear abs coeff = 14.94 cm^{-1}, crystal size = 0.40 × 0.40 × 0.30 mm, crystal color: red, scan mode:$\omega/2\theta$, ω-scan width = (0.8 + 0.35 tan θ) deg, 2θ limits = 50°, no. of data collected = 3512, no. of unique data = 3512, no. of unique data with $I > 3\sigma(I)$ = 3085, no. of variables = 262, R = 0.048, R_w = 0.058, G.O.F. = 2.5; $R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$ $R_w = [\Sigma_w|F_o| - |F_c|)^2/\Sigma_w|F_o|^2]^{1/2}$; $w = 4F_o^2/\sigma^2(F_o)^2$; $\sigma(F_o^2) = [\sigma^2(I) + (pF_o^2)^2]^{1/2}$; p = 0.04. The X-ray crystal structure for **10**−$PdCl_2$ complex has been reported recently: Richards, C. J.; Hibbs, D. E.; Hursthouse, M. B. *Tetrahedron Lett.* **1995**, *36*, 3745. (b) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

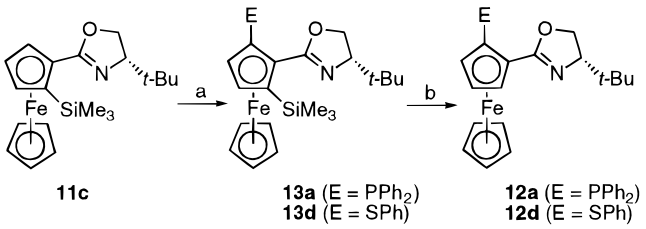
(14) Uemura and co-workers have also reported the synthesis of **11a**, with 84% de.[7c] The diastereoselectivity was determined by HPLC (Daicel Chiralcel OD) and ^{1}H NMR analysis for the crude products.

Table 1. Lithiation of Oxazolinylferrocene 8 under Various Reaction Conditions

Entry	RLi[a]	Solvent[b]	Lithiation temp	Electrophile[d]	%Yield[e]
1	*s*-BuLi	THF-cyclohexane (5:1, v/v)	-78 °C, 2 h	*n*-Bu_3SnCl	94
2	*s*-BuLi	THF-cyclohexane (5:1, v/v)	15 min[c] → -78 °C, 2 h → 0 °C	*n*-Bu_3SnCl	92
3	*s*-BuLi	Et_2O-cyclohexane (5:1, v/v)	-78 °C, 2 h	*n*-Bu_3SnCl	71 (7)[f]
4	*n*-BuLi	Et_2O-hexanes (8:1, v/v)	0 °C, 2 h	*n*-Bu_3SnCl	15 (50)
5	*n*-BuLi	Et_2O-hexanes (8:1, v/v)	25 °C, 1-2 h	*n*-Bu_3SnCl	79[f]
6	*t*-BuLi	Et_2O-pentane (8:1, v/v)	2 h → -78 °C, 15 min → 25 °C	*n*-Bu_3SnCl	52 (16)[g]
7	*n*-BuLi	THF-hexanes (8:1, v/v)	-30 °C, 2 h	*n*-Bu_3SnCl	66 (≤10)
8	*s*-BuLi	THF-cyclohexane (5:1, v/v)	40 min → -78 °C, 2 h → 25 °C	Me_3SiCl	≤5
9	*s*-BuLi	Et_2O-cyclohexane (7:1, v/v)	0 °C, 2 h	$ClPPh_2$	8 (≤5)
10	*n*-BuLi	Et_2O-hexanes (8:1, v/v)	25 °C, 6 h	$ClPPh_2$	9 (19)[f]

[a] 1.1-1.2 equiv of RLi are used. [b] Cyclohexane, hexanes, or pentane is the solvent of alkyllithiums used. [c] The time elapsed after exchange of a dry ice-acetone bath (-78 °C) to an ice-water one (0 °C). [d] 1.2 equiv except for $ClPPh_2$ (2 equiv). [e] The yield after SiO_2 column chromatography: Values in parentheses denote recovered starting materials. [f] A significant amount of unknowns is also obtained. [g] 2,5-Disubstituted product is also obtained (ca 15%).

Scheme 3[a]

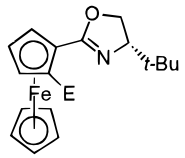


11c **13a** (E = PPh_2) **13d** (E = SPh) **12a** (E = PPh_2) **12d** (E = SPh)

[a] (a) *n*-BuLi, Et_2O−hexane, 25 °C, 1 h; and then $ClPPh_2$ (46%) or PhSSPh (60%); (b) TBAF, wet THF, reflux, 2 h, 82−85%.

results are very promising for the synthesis of other chiral ferrocene compounds, since the oxazolinylferrocene can be readily prepared from the corresponding amino alcohol and also it can be readily converted to other useful functional groups.[16]

When we changed the base system from the *n*-BuLi in Et_2O−hexanes (8:1) to *s*-BuLi in THF−cyclohexane (5:1), the coupling yield of **11a** was variable (25−60%), depending on the reaction conditions. This result is in contrast to the same coupling reaction with other electrophiles such as Me_3SiCl, *n*-Bu_3SnCl, DMF, PhSSPh, and CO_2, for which higher yields are consistently obtained with the latter base system.



11a: E = PPh_2
11b: E = $SnBu_3$
11c: E = $SiMe_3$
11d: E = SPh
11e: E = CHO
11f: E = CO_2H

To find out the controlling factors in the coupling reactions, a detailed study was undertaken for the lithiation of **8** and subsequent reaction with an electrophile.

Lithiation of the Oxazolinylferrocene 8. Lithiation conditions for different alkyllithiums are listed in Table 1. Several entries provide information about the stability of the lithium intermediate. The degree of the lithiation can be easily measured using *n*-Bu_3SnCl as the electrophile, since the coupling reaction was fast even at −78 °C (less than 10 min). With *s*-BuLi in THF−cyclohexane (5:1), the lithiation of **8** at −78 °C was complete within 2 h (entry 1). In Et_2O−cyclohexane (5:1), starting material (7%) remained under otherwise the same conditions (entry 3); therefore, it was necessary to raise the lithiation temperature briefly before treating with an electrophile (see Table 2). With *n*-BuLi in Et_2O−hexanes (8:1), a higher lithiation temperature (25 °C) was required to get good coupling yields (entry 4 vs 5). As also noted by others,[7a] *t*-BuLi gave inferior results compared to those with *s*-BuLi and *n*-BuLi, apparently due to its strong basicity, producing a significant amount of the 2,5-disubstituted product (entry 6).[17] We have found that *the lithiated oxazolinylferrocene undergoes decomposition depending on the solvent and the temperature.* Decomposition was significant, particularly in THF.[18] For example, when the lithiated intermediate derived from **8** was warmed to 25 °C, it did not give any appreciable coupling yield (entry 8). In Et_2O at 0 °C, the lithiated intermediate was relatively stable, but at 25 °C the decomposition was significant. With *n*-BuLi in Et_2O-hexanes at 25 °C, the lithiation competed with the decomposition of the lithium intermediate; thus, a prolonged lithiation was detrimental to the coupling yield (entry 5 vs 10).

(15) A full manuscript is in preparation.
(16) Meyers, A. I.; Shimano, M. *Tetrahedron Lett.* **1993**, *34*, 4893.
(17) For a recent study on the stability of *t*-BuLi in THF and related references, see: Stanetty, P.; Koller, H.; Mihovilovic, M. *J. Org. Chem.* **1992**, *57*, 6833.
(18) The instability of lithiated ferrocene itself in THF is reported during our study: Guillaneux, D.; Kagan, H. B. *J. Org. Chem.* **1995**, *60*, 2502.

Table 2. Diastereoselective Synthesis of 11 from 8 under Various Reaction Conditions

Entry	RLi[a]	Solvent[b]	Lithiation temp	Electrophile[d]	11:12	%Yield[g]
1	*s*-BuLi	THF-cyclohexane (5:1, v/v)	-78 °C, 2 h	*n*-Bu_3SnCl	97:3	94
2	*s*-BuLi	Et_2O-cyclohexane (5:1, v/v)	-78 °C, 2 h	*n*-Bu_3SnCl	88:12	71 (7)[h]
3	*n*-BuLi	Et_2O-hexanes (8:1, v/v)	25 °C, 2 h	*n*-Bu_3SnCl	90:10	79[h]
4	*n*-BuLi	TMEDA-hexanes	15 min[c] → -78°C, 2 h → 0 °C	*n*-Bu_3SnCl	>99:1	99
5	*s*-BuLi	THF-cyclohexane (5:1, v/v)	-78 °C, 2 h	Me_3SiCl[e]	>96:4	78
6	*s*-BuLi	Et_2O-cyclohexane (8:1, v/v)	15 min[c] → -78°C, 2 h → 0 °C	Me_3SiCl[e]	>95:5	74
7	*n*-BuLi	THF-hexanes (8:1, v/v)	15 min[c] → -78°C, 2 h → 0 °C	Me_3SiCl[e]	80:20	-
8	*n*-BuLi	Et_2O-hexanes (8:1, v/v)	25 °C, 2 h	Me_3SiCl	94:6	64
9	*s*-BuLi	THF-cyclohexane (5:1, v/v)	15 min[c] → -78°C, 2 h → 0 °C	PhSSPh[e]	97:3	81
10	*s*-BuLi	THF-cyclohexane (5:1, v/v)	15 min[c] → -78°C, 2 h → 0 °C	DMF[e]	-	73
11	*n*-BuLi	Et_2O-hexanes (8:1, v/v)	25 °C, 2 h	CO_2[e,f]	-	83
12	*s*-BuLi	THF-cyclohexane (5:1, v/v)	-78 °C, 2 h	$ClPPh_2$	>99:1	31[i] (≤5)
13	*s*-BuLi	Et_2O-cyclohexane (7:1, v/v)	15 min[c] → -78°C, 2 h → 0 °C	$ClPPh_2$	93:7	65 (≤5)
14	*n*-BuLi	Et_2O-hexanes (8:1, v/v)	25 °C, 2 h	$ClPPh_2$	97:3	47 (20)[j]
15	*n*-BuLi	TMEDA-hexanes	15 min[c] → -78°C, 2 h → 0 °C	$ClPPh_2$	>99:1	28 (6)

[a] 1.1-1.2 equiv of RLi are used. [b] Cyclohexane, hexanes, or pentane is the solvent of alkyllithiums used. [c] The time elapsed after exchange of a dry ice-acetone bath (-78 °C) to an ice-water one (0 °C). [d] 1.2 equiv except for $ClPPh_2$ (2 equiv). [e] The reaction mixture is allowed to warm to 25 °C. [f] The coupling reaction is started at -78 °C. [g] The yield after SiO_2 column chromatography: Values in parentheses denote recovered starting materials. [h] A significant amount of unknowns is also obtained. [i] The yield is variable depending on the coupling temperature (25-60%). [j] 2,5-Disubstituted product is obtained together (ca 15%).

Diastereoselective Synthesis of 11 under Various Conditions. We have studied the diastereoselective synthesis of several other ferrocene derivatives (**11a**−**f**) under various reaction conditions. The results are summarized in Table 2. The diastereoselectivities can be determined by either using separately prepared authentic minor diastereomers (**12a** and **12d**, Scheme 3) or an isolated minor diastereomer (**12b**: E = $SnBu_3$). In the case of **12c** (E = $SiMe_3$) which cannot be easily prepared and also difficult to separate from **11c**, the minor peaks in the ^1H NMR spectrum of the reaction mixture were assumed to come from **12c**. As also noted by Sammakia and co-workers, the diastereoselectivity of the lithiation of **11** is dependent on the alkyllithium and the solvent used. With *s*-BuLi, an excellent diastereoselectivity of ≥96:4 was generally obtained in THF−cyclohexane (entries 1, 5, 9, 12). A better selectivity is observed in THF−cyclohexane than in Et_2O−cyclohexane (entry 1 vs 2, entry 12 vs 13), which corresponds to the results of Sammakia. Interestingly, in the case of $ClSnBu_3$ and $ClPPh_2$, the base system of *n*-BuLi in Et_2O−hexanes at 25 °C produced similar or better diastereoselectivities than that of *s*-BuLi in Et_2O−cyclohexane at −78 °C (entry 3 vs 2, entry 14 vs 13). Also, somewhat different diastereoselectivities were obtained for different electrophiles with the same base system except for the different coupling temperature. The reason for these variances is not clear. As mentioned before, the coupling with $ClPPh_2$ resulted in a lower yield compared to other electrophiles, particularly in THF. In the case of $ClPPh_2$, unknown complexes of low R_f were always observed as side products.[19] An attempt to characterize these products was fruitless. After the completion of this work, Sammakia and co-workers reported a dramatic effect of additives on the diastereoselectivity in the lithiation of the oxazolinylferrocenes:[20] With an equimolar amount of TMEDA, ca. >500:1 diastereoselectivity was obtained with *n*-BuLi in hexanes for **11c**. We briefly tested this condition for the synthesis of **11b** and could confirm the effectiveness of the method (entry 4). However, the low coupling yield obtained in the case of $ClPPh_2$ could not be improved, albeit with excellent diastereoselection.

In summary, we have synthesized several chiral ferrocene compounds through an efficient synthesis of oxazolinylferrocenes and subsequent highly diastereoselective lithiation directed by the oxazoline moiety. It has

(19) Also if purification of the extracts by SiO_2 chromatography is delayed for overnight at 5 °C, a lower yield is obtained, possibly owing to the oxidation of the phosphine compound.

(20) Sammakia, T.; Latham, H. A. *J. Org. Chem.* **1995**, *60*, 6002: Discussion about the directed lithiation mechanism with related references and an excellent demonstration for the *N*-directed lithiation are included in this paper.

been found that the lithiated intermediate has limited stability in THF at 0 °C and in Et_2O at 25 °C. When *s*-BuLi is used in THF−cyclohexane, the diastereoselective lithiation of oxazolinylferrocenes must be carried out at low temperature, preferably at −78 °C. When Et_2O is used as the solvent, the lithiation with *s*-BuLi should be preferably begun at −78 °C, and then the reaction temperature can be briefly raised to 0 °C before treating with an electrophile. When *n*-BuLi is used for the lithiation in Et_2O at 25 °C, decomposition of the lithiated species competes with lithiation; however, a good coupling yield is obtained if the lithiation time is limited to 1−2 h. In the case of the coupling reaction with $ClPPh_2$ as an electrophile, Et_2O is preferred to THF, because in the latter solvent unidentified side reactions occur. For couplings employing other electrophiles, the use of *s*-BuLi in THF at −78 °C lead to consistently higher coupling yields with excellent diastereoselectivities.

Experimental Section

All reactions were run under an atmosphere of nitrogen. THF and Et_2O were distilled from sodium−benzophenone ketyl. Alkyllithiums were purchased from Aldrich and titrated with diphenylacetic acid.[21] Melting points (mp) are not corrected. Elemental analyses were performed by the Galbraith Laboratories, Inc. Column (flash) chromatography was performed by the method of Still.[22] Chemical shifts of ^1H and ^{13}C NMR spectra are reported in ppm (δ): multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad), and app t (apparent triplet). In the carbon spectra all peaks for which a coupling constant is reported are doublets due to phosphorus coupling. IR spectra were taken for the thin film of samples on a NaCl cell.

Ethyl Ferrocenecarboxylate (4). To a THF (23 mL) solution of ferrocene (5 g, 26.9 mmol) at 0 °C (ice−water bath) was added *t*-BuLi (19.0 mL, 1.18 M in pentane) under an argon atmosphere. The resulting mixture was stirred at 0 °C for additional 15 min, the ice−water bath was removed, and it was further stirred for additional 10 min before recooling to −78 °C. Ethyl chloroformate (3.86 mL, 40.4 mmol) was added dropwise to the lithiated ferrocene at −78 °C, and then the resulting mixture was allowed to warm to 0 °C for 1.5 h. The reaction mixture was treated with saturated aqueous NH_4Cl solution and was extracted with diethyl ether twice. The organic layer was dried over anhydrous $MgSO_4$ and concentrated to give the crude product. Purification of the crude product by column chromatography (eluant: EtOAc/hex = 5/95, v/v) gave **5** (3.4 g, 59% yield based on used *t*-BuLi): mp 63−64 °C; IR (NaCl, cm^{-1}) 3099, 2980, 1711, 1461, 1375, 1276, 1136, 1036, 1005; ^1H NMR (300 MHz, $CDCl_3$) δ 4.79 (app t, 2 H, J = 1.9 Hz), 4.36 (app t, 2 H, J = 1.9 Hz), 4.26 (q, 2 H, J = 6.8 Hz), 4.18 (s, 5 H), 1.34 (t, 3 H, J = 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.20, 72.18, 71.76, 70.72, 70.33, 60.68, 15.24; MS (EI) m/z (rel intensity) 258 (M^+, 76), 229 (73), 186 (67), 137 (70), 121 (77), 93 (83), 81 (100), 73 (74), 64 (77).

***N*-[(1(*S*)-(Hydroxymethyl)-2-methylpropyl]ferrocenecarboxamide (5).** To a toluene (29 mL) solution of L-valinol (1.42 g, 13.76 mmol) at 0 °C was added dropwise Me_3Al (12.79 mL, 2.0 M in toluene, 25.58 mmol). The resulting mixture was allowed to warm to 25 °C and further stirred for 45 min. To this aluminum complex was added a toluene (29 mL) solution of ethyl ferrocenecarboxylate (3.0 g, 11.63 mmol) via a cannula at 25 °C. The resulting mixture was heated at reflux for 8 h. After cooling to room temperature, 20% aqueous solution of Rochelle salt was added to the reaction mixture, and the resulting mixture was vigorously stirred for several hours until clear phase separation was obtained. The organic layer was separated, and the resulting aqueous layer was extracted with EtOAc. The organic layers were combined, washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to give the crude product. Purification by column chromatography (eluant: EtOAc/hex = 70/30, v/v) gave **5** (3.4 g, 95%): mp 105−106 °C; $[\alpha]^{20}_D$ −10.1 (*c* 0.99, EtOH); IR (NaCl, cm^{-1}) 3352, 2955, 1628, 1533, 1381, 1106; ^1H NMR (300 MHz, $CDCl_3$) δ 5.96 (d, 1 H, J = 7.5 Hz), 4.68 (dd, 2 H, J = 8.1, 1.9 Hz), 4.34 (app t, 2 H, J = 1.9 Hz), 4.20 (s, 5 H), 3.91−3.83 (m, 1 H), 3.75 (d, 2 H, J = 6.2 Hz), 3.06 (s, 1 H), 2.05−1.94 (m, 1 H), 1.05 (d, 3 H, J = 2.5 Hz), 1.02 (d, 3 H, J = 2.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.00, 76.73, 71.14, 71.10, 70.42, 69.07, 68.61, 64.58, 57.71, 29.71, 20.34, 19.68; MS (EI) m/z (rel intensity) 315 (M^+, 50), 297 (91), 254 (59), 229 (16), 211 (66), 185 (24), 129 (39), 121 (100), 83 (25), 55 (60); Anal. Calcd for $C_{16}H_{20}NO_2Fe$: C, 60.97; H, 6.72; N, 4.44. Found: C, 60.95; H, 6.84; N, 4.48.

***N*-[1(*S*)-(Hydroxymethyl)-2,2-dimethylpropyl]ferrocenecarboxamide (6).** A similar procedure as for **5** gave **6** in 92% yield (4.0 g scale): mp 177−178 °C; $[\alpha]^{20}_D$ +8.5 (*c* 1.07, EtOH); IR (NaCl, cm^{-1}) 3252, 2958, 1613, 1554, 1368, 1308, 1105, 1055, 1019; ^1H NMR (300 MHz, $CDCl_3$) δ 5.95 (d, 1 H, J = 8.7 Hz), 4.68 (dd, 2 H, J = 6.2, 1.3 Hz), 4.35 (d, 2 H, J = 1.3 Hz), 4.22 (s, 5 H), 4.00−3.88 (m, 2 H), 3.66−3.63 (m, 1 H), 3.05 (t, 1 H, J = 5.0 Hz), 1.04 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.68, 76.07, 70.48, 70.42, 69.73, 68.41, 67.82, 63.38, 59.47, 33.55, 30.82, 27.08; MS (EI) m/z (rel intensity) 329 (M^+, 67), 311 (34), 254 (46), 213 (100), 211 (31), 185 (33), 129 (41), 121 (51), 56 (30). Anal. Calcd for $C_{17}H_{23}NO_2Fe$: C, 62.02; H, 7.04; N, 4.25. Found: C, 62.25; H, 7.21; N, 4.27.

[4(*S*)-Isopropyl-2-oxazolin-2-yl]ferrocene (7). To a CH_2Cl_2 (37 mL) solution of the hydroxy amide **5** (3.5 g, 11.1 mmol) at 0 °C were added Et_3N (2.0 mL, 14.35 mmol) and TsCl (2.75 g, 14.42 mmol) sequentially. The reaction mixture was allowed to warm to 25 °C and stirred for 10 h. The reaction mixture was treated with saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2. Drying over anhydrous $MgSO_4$, filtration, and concentration *in vacuo* gave the crude product. Purification by column chromatography gave **7** (2.95 g, 89%): mp 73−74 °C; $[\alpha]^{21}_D$ −135.2 (*c* 1.07, EtOH); IR (NaCl, cm^{-1}) 3097, 2958, 1656, 1476, 1380, 1109, 1020; ^1H NMR (300 MHz, $CDCl_3$) δ 4.74 (dd, 2 H J = 10.6, 1.9 Hz), 4.31 (d, 2 H, J = 1.9 Hz), 4.26 (dd, 1 H, J = 7.5, 1.8 Hz), 4.18 (s, 5 H), 4.05 (dd, 1 H, J = 8.1, 7.5 Hz), 4.01−3.94 (m, 1 H), 1.88−1.82 (m, 1 H), 1.00 (d, 3 H, J = 6.8 Hz), 0.93 (d, 3 H, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.17, 72.91, 71.24, 70.66, 70.63, 70.11, 69.90, 69.57, 69.54, 32.89, 19.48, 18.41; MS (EI) m/z (rel intensity) 297 (M^+, 100), 254 (63), 226 (15), 211 (50), 129 (12), 121 (58), 56 (22); Anal. Calcd for $C_{16}H_{18}NOFe$: C, 64.67; H, 6.44; N, 4.71. Found: C, 64.56; H, 6.46; N, 4.73.

[4(*S*)-*tert*-Butyl-2-oxazolin-2-yl]ferrocene (8). A similar procedure as for **7** gave **8** in 88% yield (3.6 g scale): mp 143−144 °C; $[\alpha]^{21}_D$ −169.1 (*c* 1.02, EtOH); IR (NaCl, cm^{-1}) 2954, 1661, 1482, 1358, 1268, 1115, 1017; ^1H NMR (300 MHz, $CDCl_3$) δ 4.73 (dd, 2 H J = 19.7, 1.3 Hz), 4.29 (d, 2 H, J = 1.3 Hz), 4.25−4.10 (m, 1 H), 4.18 (s, 5 H), 3.87 (dd, 1 H, J = 9.8, 7.9 Hz), 0.95 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.01, 76.65, 71.41, 70.56, 70.50, 69.99, 69.54, 69.48, 68.77, 34.07, 26.49; MS (EI) m/z (rel intensity) 311 (M^+, 86), 254 (100), 226 (17), 211 (58), 129 (11), 121 (49), 56 (13). Anal. Calcd for $C_{17}H_{21}NOFe$: C, 65.61; H, 6.80; N, 4.50. Found: C, 65.48; H, 6.47; N, 4.54.

1-[4(*S*)-*tert*-Butyl-2-oxazolin-2-yl]-2(*S*)-(diphenylphosphino)ferrocene (11a). To an ethereal solution (Et_2O, 65 mL) of the oxazolinylferrocene **8** (3.69 mg, 11.85 mmol) at 25 °C was added *n*-BuLi (8.9 mL, 1.6 M in hexanes) dropwise. The reaction mixture was stirred for 1−2 h at 25 °C and then treated with $ClPPh_2$ (4.3 mL, 23.7 mmol). After being stirred for 30 min, the reaction mixture was diluted with Et_2O and quenched with saturated aqueous $NaHCO_3$ solution. The organic layer was separated and the aqueous layer was extracted twice with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to give the crude product. The ratio of **11a**:**12a** was 97.5:2.5, determined by ^1H NMR spectroscopy and also by HPLC analysis using a chiral column (Chiralcel OD, 25 cm × 0.46 cm, *i*-PrOH:hexanes = 96:4, flow rate = 1.5 mL/min, t_R = 2.85, 6.16 min, respectively). The crude product was subsequently purified by column

(21) Kofron, W. G.; Baclawski, L. M.; Ronald, R. C. *J. Org. Chem.* **1976**, *41*, 1879.
(22) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

chromatography (Et_2O/hexanes = 1/4) to give **11a** (2.75g, 47%) (If the crude product was purified after keeping it in a refrigerator at 5 °C overnight, the yield decreased.): mp 128−129 °C (EtOH); $[\alpha]^{24}_D$ −26 (*c* 1.0, EtOH); IR (NaCl, cm^{-1}) 2954, 1660, 1478, 1432, 1139; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45−7.51 (m, 2H), 7.34−7.37 (m, 3 H), 7.20−7.27 (m, 5H), 4.95 (dd, 1 H, *J* = 2.5, 1.2 Hz), 4.35 (app t, 1 H, *J* = 2.5 Hz), 4.20 (s, 5 H), 4.19 (dd, 1 H, *J* = 10.0, 8.7 Hz), 3.86 (app t, 1 H, *J* = 8.1 Hz), 3.73 (dd, 1 H, *J* = 10.0, 8.1 Hz), 3.60 (d, 1 H, *J* = 1.9 Hz), 0.78 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.10, 140.46 (d, *J* = 12.4 Hz), 139.21 (d, *J* = 13.6 Hz), 135.58 (d, *J* = 21.5 Hz), 133.14 (d, *J* = 19.2 Hz), 129.48, 128.75 (d, *J* = 6.8 Hz), 128.57 (d, *J* = 7.9 Hz), 128.40, 79.37 (d, *J* = 14.7 Hz), 76.74, 76.31 (d, *J* = 17.4 Hz), 74.48 (d, *J* = 4.5 Hz), 72.83, 71.36, 71.20, 69.06, 34.18, 26.39; MS (EI) *m*/*z* (rel intensity) 495 (M^+, 100), 438 (12), 418 (19), 410 (22), 253 (20), 183 (13), 121 (33). Anal. Calcd for $C_{29}H_{30}NOPFe$: C, 70.31; H, 6.10; N, 2.83. Found: C, 70.56; H, 5.76; N, 2.95.

1-[4(*S*)-Isopropyl-2-oxazolin-2-yl]-2(*S*)-(diphenylphosphino)ferrocene (9). A similar procedure as for **11b** afforded a mixture of **9** and **10** in 45−49% yields. The ratio of **9**:**10** was 68:32, determined by ^1H NMR spectroscopy (see the text for the diagnostic protons). The diastereoselectivity was also determined by HPLC using a chiral column (Chiralcel OD, 25 cm × 0.46 cm, *i*-PrOH:hexane = 96:4, flow rate = 0.9 mL/min, t_R = 5.04, 10.72 min, respectively). The major isomer **9** was purified to >98% de by three crystallizations from ethanol: mp 160−161 °C; $[\alpha]^{24}_D$ +68.8 (*c* 1.0, EtOH); IR (NaCl, cm^{-1}) 2956, 1656, 1433, 1135; ^1H NMR (300 MHz, $CDCl_3$) δ 7.46−7.52 (m, 2H), 7.34−7.36 (m, 3 H), 7.20−7.21 (m, 5H), 4.97 (dd, 1 H, *J* = 2.5, 1.2 Hz), 4.35 (app t, 1 H, *J* = 2.5 Hz), 4.24 (dd, 1 H, *J* = 9.4, 8.1 Hz), 4.21 (s, 5 H), 3.84 (m, 1 H), 3.68 (app t, 1 H, *J* = 8.1 Hz), 3.62 (app t, 1 H, *J* = 2.5 Hz), 1.66 (m, 1 H), 0.84 (d, 3 H, *J* = 6.2 Hz), 0.71 (d, 3 H, *J* = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.69, 140.32 (d, *J* = 14.5 Hz), 138.99 (d, *J* = 13.5 Hz), 135.58 (d, *J* = 21.3 Hz), 133.08 (d, *J* = 19.1 Hz), 129.55, 128.79 (d, *J* = 7.9 Hz), 128.61 (d, *J* = 6.7 Hz), 128.46, 79.27 (d, *J* = 14.6 Hz), 76.11 (d, *J* = 15.7 Hz), 74.48 (d, *J* = 4.5 Hz), 72.85, 72.82, 72.79, 71.39, 70.24, 32.77, 19.27, 18.26; MS (EI) *m*/*z* (rel intensity) 481 (M^+, 100), 410 (43), 404 (29), 318 (14), 253 (13), 183 (14), 170 (18), 121 (41), 56 (12). Anal. Calcd for $C_{28}H_{28}NOPFe$: C, 69.87; H, 5.86; N, 2.91. Found: C, 69.81; H, 5.85; N, 2.93.

1-[4(*S*)-*tert*-Butyl-2-oxazolin-2-yl]-2(*R*)-(diphenylphosphino)ferrocene (12a). To an ethereal solution (13.4 mL of Et_2O) of **11c** (822 mg, 2.14 mmol) at 25 °C was added *n*-BuLi (1.61 mL, 1.6 M in hexanes). The reaction mixture was stirred at the same temperature for 1 h before treating with $ClPPh_2$ (0.77 mL, 3.91 mmol). An extractive workup and purification by column chromatography gave 1-[4(*S*)-*tert*-butyl-2-oxazolin-2-yl]-2(*R*)-(diphenylphosphino)-5(*S*)-(trimethylsilyl)ferrocene (**13a**) in 46% yield (556 mg) which was subjected to the next desilylation reaction. To this silyl compound (556 mg, 0.98 mmol) in THF (5 mL, not dried) at 25 °C was added tetrabutylammonium fluoride (2.94 mL, 1 M in THF). Then the resulting reaction mixture was heated to reflux for 2 h. An extractive workup and column chromatography gave **12a** in 82% yield (398 mg): mp 143−144 °C (EtOH); $[\alpha]^{21}_D$ +7.5 (*c* 1.2, EtOH); IR (NaCl, cm^{-1}) 3060, 2955, 1655, 1479, 1433, 1361, 1141; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50−7.53 (m, 2H), 7.36−7.38 (m, 3 H), 7.22−7.30 (m, 5H), 4.96 (d, 1 H, *J* = 1.1 Hz), 4.37 (s, 1 H), 4.25 (s, 5 H), 4.01−4.12 (m, 2 H), 3.85 (dd, 1 H, *J* = 9.1, 7.3 Hz), 3.63 (d, 1 H, *J* = 0.9 Hz), 0.64 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.83 (d, *J* = 3.4 Hz), 139.83 (d, *J* = 11.4 Hz), 138.87 (d, *J* = 13.2 Hz), 135.41(d, *J* = 21.1 Hz), 132.83 (d, *J* = 19.1 Hz), 129.28, 128.55 (d, *J* = 6.8 Hz), 128.34 (d, *J* = 6.6 Hz), 128.15, 78.50 (d, *J* = 13.3 Hz), 76.39, 75.50 (d, *J* = 15.9 Hz), 74.56 (d, *J* = 4.2 Hz), 72.85, 71.06, 70.77, 68.57, 34.03, 25.90; MS (FAB) *m*/*z* (rel intensity) 496 (M + 1, 100), 418 (20), 362 (45), 346 (42), 312 (36), 253 (40), 217 (66), 201 (78), 183 (58), 170 (29); HRMS (FAB) $C_{29}H_{30}NOPFe$ ($[MH]^+$) cald 495.1414, obsd 495.1415.

A General Experimental Procedure for the Coupling of an Electrophile with *s*-BuLi in THF−Cyclohexane. To a THF (3.1 mL) solution of the oxazolinylferrocene **8** (1.0 mmol) at −78 °C (with a dry ice−acetone bath) was added *s*-BuLi (1.1 equiv) in cyclohexane dropwise. The reaction mixture was stirred at −78 °C for 2 h and then quenched with a reactive electrophile (1.2 equiv) such as *n*-Bu_3SnCl: In the case of less reactive electrophiles such as TMSCl, PhSSPh, and DMF, the bath was exchanged with an ice−water bath and further stirred for ≤15 min before treating with an electrophile, and then the reaction mixture was warmed to 25 °C. After the reaction was complete as judged by TLC, the reaction mixture was diluted with Et_2O and treated with saturated aqueous $NaHCO_3$ solution. The organic layer was collected, and the aqueous layer was further extracted with Et_2O twice. The combined organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to give the crude product, which can be purified by column chromatography. The diastereoselectivity can be determined by ^1H NMR spectroscopy [The diagnostic proton for **11**/**12** is the α-proton to the oxazoline ring: **11b**, δ 4.91 (dd, *J* = 2.4, 1.2 Hz); **12b**, δ 4.89 (dd, *J* = 2.5, 1.3 Hz); **11c**, δ 4.89 (dd, *J* = 2.3, 1.3 Hz); **12c**, δ 4.92 (dd, *J* = 2.3, 1.3 Hz); **11d**, δ 4.85 (dd, *J* = 2.6, 1.6 Hz); **12d**, δ 4.96 (dd, *J* = 2.7, 1.6 Hz)].

1-[4(S)-*tert*-Butyl-2-oxazolin-2-yl]-2(*S*)-(tri-*n*-butylstannyl)ferrocene (11b). Compound **11b** can be separated from its diastereomer **12b** by a careful column chromatography as a yellow oil (R_f: **11b** = 0.35; **12b** = 0.40 in Et_2O/hexanes = 1/10). $[\alpha]^{29}_D$ +143.3 (*c* 1.02, EtOH); IR (NaCl, cm^{-1}) 3094, 2954, 2921, 2866, 1654, 1458, 1132; ^1H NMR (300 MHz, $CDCl_3$) δ 4.91(dd, 1 H, *J* = 2.4, 1.2 Hz), 4.45 (dd, 1 H, *J* = 2.4, 1.8 Hz), 4.20 (dd, 1 H, *J* = 9.9, 8.7 Hz), 4.19 (m, 1 H), 4.14 (s, 5H), 4.05 (app t, 1H, *J* = 8.1 Hz), 3.84 (dd, 1H, *J* = 9.9, 8.1 Hz), 1.46−1.62 (m, 6 H), 1.28−1.41 (m, 6 H), 1.00−1.16 (m, 6 H), 0.95 (s, 9 H), 0.91 (t, 9 H, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.89, 77.70, 77.12, 76.13, 73.30, 72.92, 72.07, 69.88, 68.68, 34.18, 29.98, 28.19, 26.69, 14.42, 11.83; MS (FAB) *m*/*z* (rel intensity) 600 (M^+, 16), 544 (100), 428 (57), 329 (35), 235 (24), 179 (72), 120 (43). Anal. Calcd for $C_{29}H_{47}NOSnFe$: C, 58.03; H, 7.89; N, 2.33. Found: C, 57.93; H, 7.67; N, 2.28.

1-[4(S)-*tert*-Butyl-2-oxazolin-2-yl]-2(*R*)-(tri-*n*-butylstannyl)ferrocene (12b). This compound was obtained as an oil by a careful column chromatography as above from the diastereomeric mixture obtained by employing the *s*-BuLi−Et_2O system (entry 2 in Table 2): $[\alpha]^{19}_D$ −147.1 (*c* 1.00, EtOH); IR (NaCl, cm^{-1}) 3096, 2954, 2922, 2870, 1654, 1456, 1134; ^1H NMR (300 MHz, $CDCl_3$) δ 4.89 (dd, 1 H, *J* = 2.4, 1.2 Hz), 4.47 (app t, 1 H, *J* = 2.3 Hz), 4.23 (dd, 1 H, *J* = 9.6, 8.7 Hz), 4.19 (d, 1 H, *J* = 1.1 Hz), 4.13 (s, 5 H), 4.05 (app t, 1 H, *J* = 8.4 Hz), 3.84 (dd, 1H, *J* = 9.5, 8.4 Hz), 1.50−1.59 (m, 6 H), 1.31−1.38 (m, 6 H), 0.97−1.09 (m, 6 H), 0.88−0.94 (m, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.75, 77.70, 77.02, 76.61, 72.99, 72.73, 72.18, 69.89, 68.94, 34.21, 30.02, 28.21, 26.76, 14.44, 11.98; MS (FAB) *m*/*z* (rel intensity) 601 (M + 1, 8), 544 (74), 430 (36), 330 (20), 235 (17), 210 (22), 179 (100).

1-[4(*S*)-*tert*-Butyl-2-oxazolin-2-yl]-2(*S*)-(trimethylsilyl)ferrocene (11c): mp 64−65 °C (hexanes); $[\alpha]^{29}_D$ +172.7 (*c* 0.99, EtOH); IR (NaCl, cm^{-1}) 3097, 2955, 2900, 1656, 1241, 1143; ^1H NMR (300 MHz, $CDCl_3$) δ 4.89 (app t, 1 H, *J* = 2.4 Hz), 4.43 (app t, 1 H, *J* = 2.4 Hz), 4.27 (app t, 1 H, *J* = 2.4 Hz), 4.20−4.26 (m, 1 H), 4.18 (s, 5 H), 4.09 (app t, 1 H, *J* = 8.1 Hz), 3.89 (dd, 1 H, *J* = 10.0, 8.1 Hz), 0.96 (s, 9 H), 0.33 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.28, 77.84, 77.47, 76.02, 74.00, 73.82, 72.09, 70.10, 68.54, 34.28, 26.74, 1.25; MS (FAB) *m*/*z* (rel intensity) 383 (M^+, 35), 368 (4), 326 (18), 285 (6), 268 (14), 204 (4), 120 (8), 103 (5), 90 (35), 83 (7), 73 (100). Anal. Calcd for $C_{20}H_{29}NOSiFe$: C, 62.66; H, 7.62; N, 3.65. Found: C, 62.68; H, 7.61; N, 3.57.

1-[4(*S*)-*tert*-Butyl-2-oxazolin-2-yl]-2(*S*)-(phenylthio)ferrocene (11d): mp 96−97 °C (hexanes); $[\alpha]^{29}_D$ +97.8 (*c* 1.01, EtOH); IR (NaCl, cm^{-1}) 3075, 2955, 1658, 1478, 1142; ^1H NMR (300 MHz, $CDCl_3$) δ 7.09−7.28 (m, 5 H), 4.85 (dd, 1 H, *J* = 2.6, 1.7 Hz), 4.38 (d, 2 H, *J* = 2.5 Hz), 4.28 (s, 5 H), 4.25 (dd, 1 H, *J* = 10.0, 8.7 Hz), 4.10 (dd, 1 H, *J* = 8.7, 7.5 Hz), 3.89 (dd, 1H, *J* = 10.0, 7.5 Hz), 0.90 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.58, 139.32, 129.20, 129.16, 126.32, 81.16, 76.67, 76.20, 74.26, 71.78, 71.63, 70.33, 69.01, 34.25, 26.26; MS (FAB) *m*/*z* (rel intensity) 419 (M^+, 100), 362 (13), 321 (16), 298 (23), 254 (39), 227 (16), 211 (42), 165 (21), 121 (68), 90 (18), 77 (33).

Anal. Calcd for $C_{23}H_{25}NOSFe$: C, 65.87; H, 6.01; N, 3.34. Found: C, 66.10; H, 5.89; N, 3.35.

1-[4(*S*)-*tert*-Butyl-2-oxazolin-2-yl]-2(*R*)-(phenylthio)ferrocene (12d). Prepared from **11c** in overall 51% yield employing the same procedure as for the synthesis of **12a**, except using PhSSPh as the electrophile instead of $ClPPh_2$: mp 97−98 °C (hexanes); $[\alpha]^{21}_D$ −354.6 (*c* 0.99, EtOH); IR (NaCl, cm^{-1}) 3074, 2954, 1654, 1478, 1142; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.03−7.19 (m, 5 H), 4.96 (dd, 1 H, J = 2.7, 1.6 Hz), 4.49 (dd, 1 H, J = 2.2, 1.7 Hz), 4.46 (app t, 1 H, J = 2.6 Hz), 4.31 (s, 5 H), 4.10−4.22 (m, 2 H), 3.85 (dd, 1 H, J = 9.5, 7.1 Hz), 0.85 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.62, 140.15, 128.92, 127.28, 125.45, 78.36, 77.76, 76.03, 74.45, 72.12, 71.56, 70.66, 68.81, 34.18, 26.08; MS (FAB) *m*/*z* (rel intensity) 420 (M + 1, 100), 362 (9), 320 (12), 254 (33), 227 (12), 211 (32), 177 (13); HRMS (FAB) $C_{23}H_{25}NOSFe$ ($[MH]^+$) calcd 419.1006, obsd 419.1007.

1-[4(*S*)-*tert*-Butyl-2-oxazolin-2-yl]-2(*S*)-formylferrocene (11e): mp 121−122 °C (Et_2O−hexanes); $[\alpha]^{29}_D$ −913.0 (*c* 0.99, EtOH); IR (NaCl, cm^{-1}) 3100, 2955, 1664, 1427, 1215; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.74 (s, 1 H), 5.08 (dd, 1 H, J = 2.4, 1.2 Hz), 4.99 (dd, 1 H, J = 2.4, 1.8 Hz), 4.72 (dd, 1 H, J = 1.8, 1.2 Hz), 4.29 (s, 5 H) 4.27 (dd, 1 H, J = 9.9, 8.7 Hz), 4.19 (overlapped dd, 1 H, J = 8.7, 7.5 Hz), 3.95 (dd, 1 H, J = 9.9, 7.5 Hz), 0.98 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.71, 164.14, 79.21, 76.89, 75.40, 74.27, 73.64, 71.72, 70.66, 68.75, 34.19, 26.49; MS (FAB) *m*/*z* (rel intensity) 340 (M + 1, 100), 274 (9), 240 (32), 212 (20), 173 (19), 129 (5), 121 (34); Anal. Calcd for $C_{18}H_{21}NO_2Fe$: C, 63.74; H, 6.24; N, 4.13. Found: C, 63.76; H, 6.07; N, 4.05.

1-[4(*S*)-*tert*-Butyl-2-oxazolin-2-yl]-2(*S*)-carboxyferrocene (11f). This compound was synthesized under similar conditions as in the synthesis of **11a**, except for the quenching temperature with CO_2. In this case the lithiation intermediate, precooled to −78 °C, was treated with an excess amount of powdered dry ice, and then the reaction mixture was allowed to warm to 25 °C. An acidic workup and purification by column chromatography gave **11f** in 83% yield: mp 150−151 °C (Et_2O−hexanes); $[\alpha]^{29}_D$ −516.5 (*c* 1.00, EtOH); IR (NaCl cm^{-1}) 3528, 3106, 2956, 1696, 1654, 1472, 1372, 1293, 1000; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.04 (s, 1H), 5.34 (dd, 1 H, J = 2.4, 1.8 Hz), 4.87 (dd, 1 H, J = 2.4, 1.8 Hz), 4.63 (dd, 1 H, J = 3.0, 2.4 Hz), 4.46 (overlapped dd, 1 H, J = 9.9, 8.7 Hz), 4.34 (overlapped dd, 1 H, J = 8.7, 8.1 Hz), 4.30 (s, 5H), 4.03 (dd, 1 H, J = 9.9, 8.1 Hz), 1.07 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.69, 170.69, 77.77, 74.67, 74.12, 73.46, 72.89, 72.44, 72.29, 70.73, 33.86, 26.47; MS (FAB) *m*/*z* (rel intensity) 365 (M + 1, 19), 311 (9), 254 (9), 218 (15), 162 (14), 150 (11), 119 (16), 100 (22), 90 (66), 77 (100), 72 (88). Anal. Calcd for $C_{18}H_{21}NO_3Fe$: C, 60.86; H, 5.96; N, 3.94. Found: C, 60.38; H, 5.68; N, 3.70.

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