# *Notes*

## New Ferrocenyloxazoline for the Preparation of Ferrocenes with Planar Chirality

Eric Manoury, John S. Fossey, Hassan Aït-Haddou,*,† Jean-Claude Daran, and Gilbert G. A. Balavoine*

*Laboratoire de Chimie de Coordination, CNRS-UPR 8241, 205 Route de Narbonne, F-31004 Toulouse, France*

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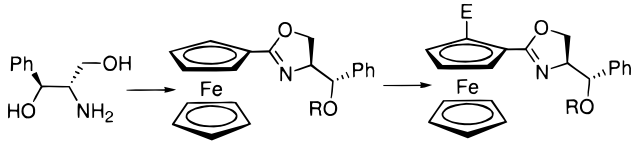
*Summary: New ferrocenyloxazolines with two stereogenic centers were prepared with excellent yields starting from the (1S,2S)-(+)-2-amino-3-phenyl-1,3-propanediol. They can then be used for the preparation of ferrocenes with planar chirality with very high diastereoselectivities (>99:1%) by a lithiation/electrophile-trapping sequence. The syntheses of chiral (phosphinoferrocenyl)oxazoline and (phenylthioferrocenyl)oxazoline and their use as ligands in conjunction with bis[(π-allyl)palladium chloride] in the enantioselective allylic alkylation of rac-1,3-diphenylprop-2-enyl acetate was investigated.*



Ferrocene derivatives have attracted tremendous interest during recent years.[1] Among them, those that exhibit planar chirality are especially important because of their involvement in asymmetric catalysis and materials chemistry. Since the pioneering work of Ugi,[2] activity has been stimulated in the design and synthesis of new chiral-planar ferrocene derivatives.[3] Recently the syntheses of chiral-planar ferrocenes containing an oxazoline fragment[4] were initiated independently by Sammakia, Richards, and Uemura by diastereoselective lithiation of parent ferrocenyloxazolines with great success. These oxazolines are potential ligands for transition metals and have been successfully used for asymmetric catalysis.[5]

In connection with our recent work concerning the syntheses of new bis(oxazoline) ligands with four stereogenic centers and their application in the asymmetric catalysis,[6] we were interested in investigating the oxazoline fragment which contains two stereogenic centers, with one of them located on the side chain, as an *ortho*-directing group for the preparation of ferrocenes with planar chirality. We describe here the synthesis of newly designed ferrocenyloxazoline compounds **1** from the (1*S*,2*S*)-(+)-2-amino-3-phenyl-1,3-propanediol, **3**, and their use in the diastereoselective metalation for the synthesis of ferrocenyloxazolines **2** (Scheme 1) with controlled planar chirality. The preliminary results using two of these new ferrocenyloxazolines **2** as ligands for palladium-catalyzed asymmetric allylic alkylation are presented.

**Scheme 1. New Ferrocenyloxazolines for the Preparation of Ferrocenes with Planar Chirality**




**3** **1** **2**

Ferrocenyloxazoline **1** was prepared easily in a large scale (Scheme 2). The ferrocenoyl chloride generated in situ from the ferrocenecarboxylic acid and oxalyl chloride was reacted with a small excess of (1*S*,2*S*)-2-amino-3-phenyl-1,3-propanediol, **3**, to give the dihydroxyamide **4** in quasi-quantitative yields (98%). Conversion of **4**[7] to oxazoline **1** was achieved by selective activation of

† Current address: Department of Chemistry and Biochemistry, University of Texas at Austin, Austin, TX 78712-167. Fax: (001) 512-471-7791. E-mail: ahhassan@mail.utexas.edu.

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(2) (a) Marquarding, D.; Klusaceck, H.; Gokel, G.; Hoffmann, P.; Ugi, I. *J. Am. Chem. Soc.* **1970**, *92*, 5389. (b) Battelle, L. F.; Bau, R.; Gokel, G. W.; Ugi, I. K. *J. Am. Chem. Soc.* **1973,** *95*, 482.
(3) For recent reviews see ref 1 and: (a) Richards, C. J.; Locke, A. J. *Tetrahedron: Asymmetry* **1998**, *9*, 2377. (b) Balavoine, G. G. A.; Daran, J.-C.; Iftime, G.; Manoury, E.; Moreau-Bossuet, C. *J. Organomet. Chem.* **1998**, *567*, 191. (c) Wagner, G.; Herrmann, R. In *Ferrocenes*; Togni, A., Hayashi, T., Eds.; VCH: Weinheim, 1995; p 173.
(4) (a) Sammakia, T.; Latham, H. A.; Schaad, D. R. *J. Org. Chem.* **1995**, *60*, 10. (b) Richards, C. J.; Damalidis, T.; Hibbs, D. E.; Hursthouse, M. B. *Synlett* **1995** 74. (c) Nishibayashi, Y.; Uemura, S. *Synlett* **1995**, 79. (d) Sammakia, T.; Latham, H. A. *J. Org. Chem.* **1995**, *60*, 6002. (e) Sammakia, T.; Latham, H. A. *J. Org. Chem.* **1996**, *61*, 1629. (f) Richards, C.; Mulvaney, A. W. *Tetrahedron Lett.* **1996**, *7*, 1419. (g) Ahn, K. H.; Cho, C.-W.; Baek, J.; Lee, S. *J. Org. Chem.* **1996**, *61*, 1, 4937. (h) Nishibayashi, Y.; Segawa, K.; Arikawa; Y.; Ohe, K.; Hidai, M.; Uemura, S. *J. Organomet. Chem.* **1997**, *545*, 381.
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(6) (a) Hoarau, O.; Aït-Haddou, H.; Castro, M.; Balavoine, G. G. A. *Tetrahedron: Asymmetry* **1997**, *8*, 3755. (b) Hoarau, O.; Aït-Haddou, H.; Daran, J.-C.; Cramailère, D.; Balavoine, G. G. A. *Organometallics* **1999**, *18*, 2718.
(7) The use of the method described by Helmchen and co-workers gave **1**, which was isolated in 66% yield and 30% of **4** was recovered; see: Peer, M.; De Jong, J. C.; Kiefer, M.; Langer, T.; Rieck, H.; Schell, H.; Sennhenn, P.; Sprinz, J.; Steinhagen, H.; Wiese, B.; Helmchen, G. *Tetrahedron* **1996**, *52*, 7547.

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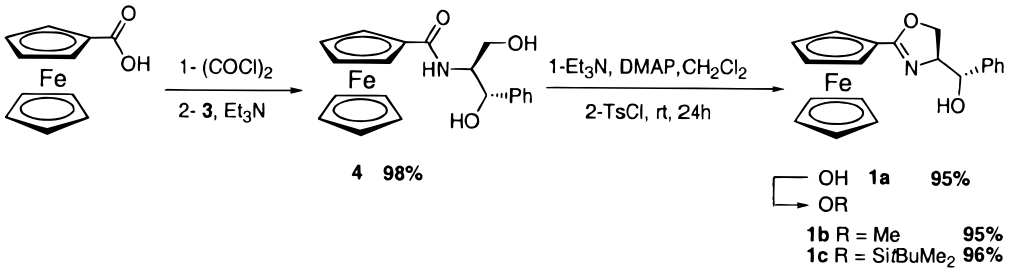
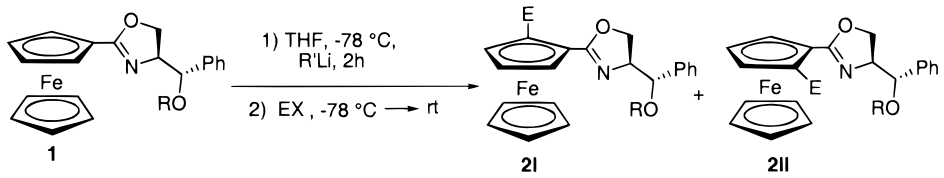
**Scheme 2. Synthesis of the Ferrocenyloxazolines 1**




**Scheme 3. Diastereofunctionalization of 1b and 1c**




**a** : R = Me; E = Me
**b** : R = $SiMe_2tBu$; E = Me
**c** : R = $SiMe_2tBu$; E = $SiMe_3$
**d** : R = $SiMe_2tBu$; E = I
**e** : R = $SiMe_2tBu$; E = $PPh_2$
**f** : R = $SiMe_2tBu$; E = SPh

the primary alcohol via the tosylate followed by in situ cyclization to the oxazoline in excellent yield (95%).[8]

To investigate the effectiveness of this oxazoline fragment in the diastereoselective *ortho*-functionalization of the ferrocene, **1a** was transformed to its corresponding methyl ether **1b** (95% yield) and silyl ether **1c** (96% yield). The lithiation of these new ferrocenyloxazolines **1b** and **1c** was carried out with various alkyllithium bases and studied after quenching by methyl iodide as electrophile. The deprotonation reactions were carried out with 1.3 equiv of RLi at −78 °C in tetrahydrofuran (THF) over 2 h and were followed by addition of methyl iodide at the same temperature.[9] The reaction mixture was then allowed to warm to room temperature to produce methyl-substituted ferrocenes (see Scheme 3). After filtration on silica gel, the **2I**:**2II** ratio was determined by proton NMR of the crude product. The results of the functionalization of **2b** and **2c** are summarized in Table 1.

From these results some interesting factors are apparent: (i) *n*-BuLi seems to be the appropriate base system for these ferrocenyloxazolines (entries 1 and 4). On the other hand, the reaction seems to be led predominantly by steric effects; as the protecting group on the hydroxyl becomes larger, the selectivity increases (compare **2b** with **2c**), with a *tert*-butyl dimethylsilyl group providing the highest level of diastereoselectivity and excellent yield (entry 4). These results are consistent with a nitrogen-directed lithiation in which the selectivities observed with RLi are due to steric interactions between the base and the side chain of the oxazoline.[10] We are currently investigating the effect of both the stereogenic center and the oxygen atom located on the side chain. Modest to good selectivities were obtained with *t*-BuLi (entries 3 and 6) and *sec*-BuLi (entries 2 and 5). We suppose that the limits of steric crowding were reached with these base systems and that the decrease in the selectivity is probably due to partial intervention of the oxygen-directed pathway.

**Table 1. Lithiation of the Ferrocenyloxazolines 1b and 1c[a]**

| entry | FcOx | R′Li | EX | product | **2I**:**2II**[b] | yield[c] |
|---|---|---|---|---|---|---|
| 1 | **1b** | *n*BuLi | MeI | **2a** | 97:3 | 83% |
| 2 | **1b** | *sec*BuLi | MeI | **2a** | 93:7 | 68% |
| 3 | **1b** | *t*BuLi | MeI | **2a** | 89:11 | 75% |
| 4 | **1c** | *n*BuLi | MeI | **2b** | >99:1 | 95% |
| 5 | **1c** | *sec*BuLi | MeI | **2b** | 93:7 | 65% |
| 6 | **1c** | *t*BuLi | MeI | **2b** | 95:5 | 85% |
| 7 | **1c** | *n*BuLi | $Me_3SiCl$ | **2c** | >99:1 | 85% |
| 8 | **1c** | *n*BuLi | $(ICH_2)_2$ | **2d** | >99:1 | 48% |
| 9 | **1c** | *n*BuLi | $CH_2I_2$ | **2e** | >99:1 | 66% |
| 10 | **1c** | *n*BuLi | $Ph_2PCl$ | **2f** | >99:1 | 68% |
| 11 | **1c** | *n*BuLi | $(PhS)_2$ | **2g** | >99:1 | 82% |

[a] FcOx = starting ferrocenyloxazoline; THF at −78 °C; 1.3 equiv of RLi, 2 h; 2 equiv of EX, −78 °C to room temperature. [b] Determined by proton NMR on the crude product. [c] Yields are given after purification and are based on the initial FcOx.

The sense of the diastereoselectivity for both **1b** and **1c** was determined by X-ray crystal diffraction of the corresponding major diastereoisomer obtained (**2a**) and the only diastereoisomer obtained (**2b**). Indeed crystals of **2a** and **2b** suitable for X-ray diffraction were obtained by slow diffusion of hexane into a dichloromethane solution of the ferrocenyloxazoline. Molecular views for **2a** and **2b** using CAMERON[11] are disclosed respectively

(8) Molecular structure of **1** was established by NMR spectroscopy compared to the ferrocenyloxazoline obtained by cyclization involving the secondary hydroxyl group of **3** and confirmed by X-ray crystallography. Aït-Haddou, H.; Tissot, O.; Manoury, E.; Daran, J.-C. and Balavoine, G. G. A. Manuscript in preparation.

(9) Solvents' and additives' effects are currently under investigation. We note that the solvents' and additives' effects on the diastereoselective *ortho*-lithiation of chiral ferrocenyloxazolines are reported,; see refs 4d and 4g.

(10) Sammakia and co-workers have reported highly diastereoselective lithiation of the constrained ferrocenyloxazoline containing a linking oxazolinyl moiety to the other Cp ring, where the lithiation clearly proceeded via lithium−nitrogen chelation; see ref 4e.

(11) Watkins, D. J.; Prout C. K., Pearce L. J. *CAMERON*; Chemical Crystallography Laboratory: University of Oxford, Oxford, 1996.

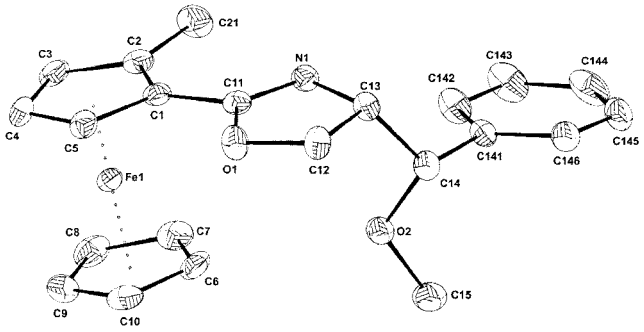



**Figure 1.** Molecular view of complex **2a** with atom-labeling scheme. Ellipsoids are drawn at 30% probability.

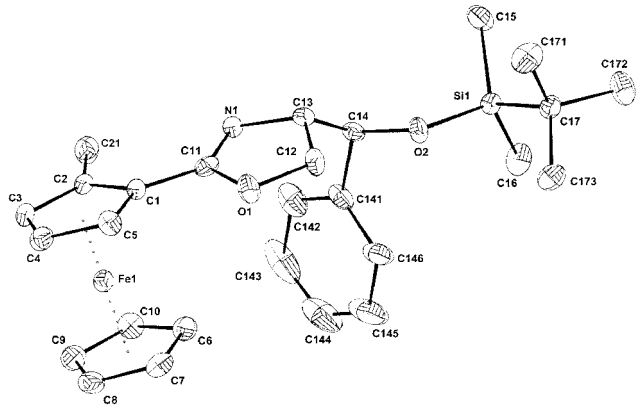



**Figure 2.** Molecular view of complex **2b** with atom-labeling scheme. Ellipsoids are drawn at 30% probability.

**Table 2. Enantioselective Allylic Alkylation of *rac*-5 with Ligands 2e and 2f[a]**

| entry | base | L | *t* (h) | ee[c] | abs config[d] | yield[e] |
|---|---|---|---|---|---|---|
| 1 | NaH | **2e** | 48 | 82% | *R* | 97% |
| 2 | BSA/KOAc[b] | **2e** | 24 | 79% | *R* | 95% |
| 3 | NaH | **2f** | 24 | 92% | *R* | 98% |
| 4 | BSA/KOAc | **2f** | 24 | 95% | *R* | 98% |

[a] S = substrate (1 equiv), $H_2C(CO_2Me)_2$ (3 equiv), NaH (3 equiv), [{$Pd(C_3H_5)Cl$}$_2$] (1% mol), L = ligand (2% mol), $CH_2Cl_2$, 36 °C. [b] Substrate (1 equiv), $H_2C(CO_2Me)_2$ (2 equiv), [{$Pd(C_3H_5)Cl$}$_2$] (1% mol), ligand (2% mol), BSA = *N*,*O*-bis(trimethylsilyl)acetamide (2 equiv) and catalytic amount of potassium acetate, $CH_2Cl_2$, 36 °C. [c] The ee values were determined by HPLC using a chiral column (Pharmacir 7C, flow rate 0.7 mL min$^{-1}$, *n*-BuOH/*n*-hexane 1:9). [d] The absolute stereochemistry of the product was determined by comparison of the optical rotation with the literature values.[15] [e] Yields refer to purified product after column chromatography.

in Figures 1 and 2 with their atom-labeling schemes (Table 2).[12] For both compounds, the Cp rings are almost parallel and the oxazoline ring is only slightly twisted with respect to the Cp plane (by 6.29° for **2a** and by 12.09° in **2b**). In both structures, the C(13) and C(14) atoms have the *S* configuration; however the oxazoline substituents display different conformations, as shown in the Newman projections along the C(13)−C(14) bond presented in Figure 3. In **2b**, owing to the bulky $SiMe_2CMe_3$ group, the ether fragment has rotated around the C(13)−C(14) bond to minimize steric hindrance and the $OSiMe_2CMe_3$ group points away from the ferrocene moiety, whereas in **2a** the OMe group points toward the ferrocene.

Having found excellent reaction conditions (*n*-BuLi, THF, −78 °C) for the diastereoselective *ortho*-functionalization of the ferrocenyloxazoline **1c** using methyl iodide as an electrophile, we have turned our attention to testing the applicability of these conditions to other electrophiles. The generality of this process is demonstrated by successful extension to various electrophiles (Table 1, entries 7−11). In all cases, only one isomer was detected by NMR, indicating that the metalation proceeds with a very high level of diastereoselectivity (>99:1). Two sources of iodine were used for the preparation of iodo compound **2d**: the classical 1,2-diiodoethane and the diiodomethane (entries 8 and 9). The diiodomethane appears to be preferable as an iodine source. The preparation of the two hybrid ligands N-P **2e** and N-S **2f** is of particular interest to us because of their very efficient synthesis (good yields and high selectivities) and their possible usefulness in asymmetric catalysis.

The ferrocenyloxazolines **2e** and **2f** were examined as chiral ligands in palladium-catalyzed allylic alkylation of *rac*-1,3-diphenylprop-2-enyl acetate, **5**, with dimethyl

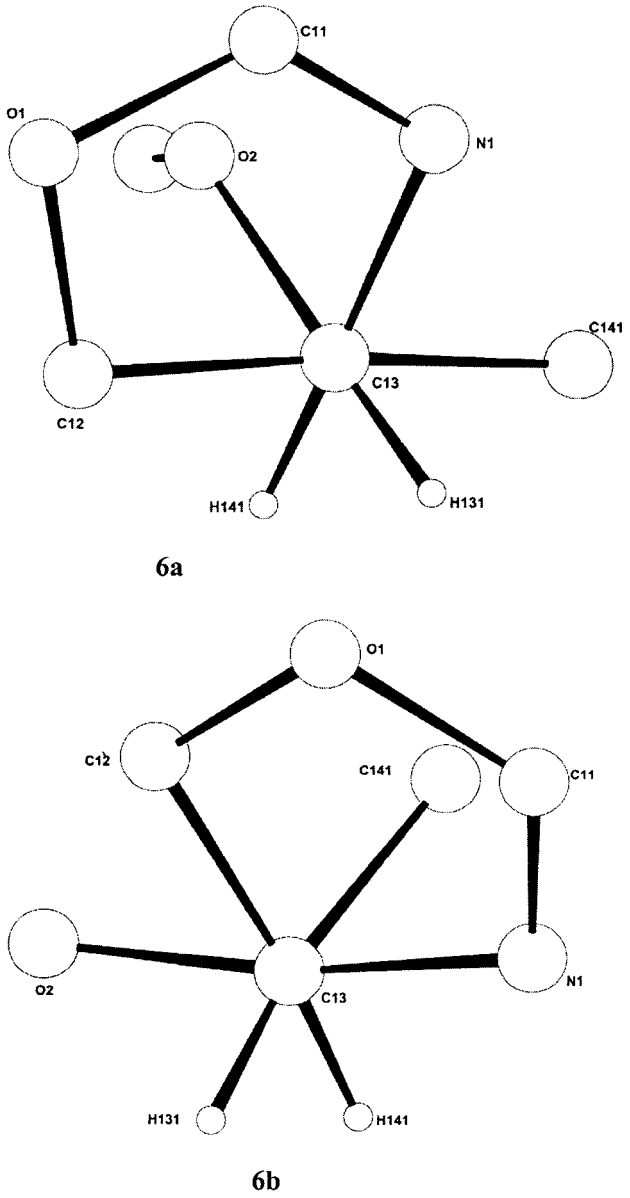
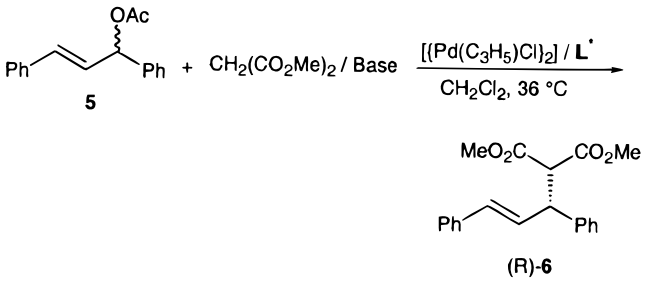



**Figure 3.** Newman projection along the C(13)−C(14) bond showing the different conformations for molecules **2a** and **2b**.

(12) The crystallographic data (atomic coordinates and bonding parameters) have been placed in the Supporting Information.

**Scheme 4. Enantioselective Allylic Alkylation of *rac*-5 Using 2e and 2f**




malonate anion.[6b,13] Allylic substitutions of *rac*-**5** were performed in $CH_2Cl_2$ at 36 °C in the presence of the palladium(II) complex generated in situ from bis[($\pi$-allyl)palladium chloride] and the appropriate ligand (Scheme 4). The results of catalytic reactions are summarized in Table **2**. From these preliminary results it appears that the ligands **2e** and **2f** exhibited high efficiency for the palladium-catalyzed allylic substitution reactions. The N-S ligand **2f** gave very high enantioselectivities (92−95% ee) with almost quantitative chemical yields.[14] Furthermore the enantioselectivities with **2e** and **2f** depend only slightly on the methods for the generation of the malonate anion nucleophiles (entry 4 vs 3). The two ligands **2e** and **2f** gave the preferred (*R*)-**6** probably due to their similar behavior in this transformation.

In summary, we have prepared a new class of chiral ferrocenyloxazolines from the (1*S*,2*S*)-(+)-2-amino-3-phenyl-1,3-propanediol. These oxazolines were successfully used in the syntheses of ferrocene systems possessing planar chirality. Two hybrid ligands (P-N and S-N) were prepared with good yields and very high diastereoselectivies. Preliminary results in asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate with sodium dimethyl malonate demonstrate the potential of these novel types of ligands. Efforts to extend the application of these ligands to other enantioselective metal-catalyzed reactions are in progress.

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**Supporting Information Available:** Text giving full experimental details and spectroscopic analytical data for compounds **1a**−**c**, **4**, and **2a**−**f**, experimental details for the palladium-catalyzed asymmetric allylic alkylation using **2e**,**f**, and tables of X-ray structural data, including data collection parameters, positional and thermal parameters, and bond distances and angles for compounds **2a** and **2b**. This material is available free of charge via the Internet at http://pubs.acs.org.

OM000016Y

(13) (a) Hayashi, T. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; Vol. 1, p 325. (b) Reiser, O. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 547. (c) Frost, C. G.; Howarth, J.; Williams, J. M. J. *Tetrahedron Lett.* **1992**, *3*, 1089. (d) Trost, B. M.; van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395.

(14) For the use of other N-S chiral ligands in this transformation see: Allen, J. V.; Coote, S. J.; Dawson, G. J.; Frost, C. G.; Williams, J. M. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2065, and references therein.