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Preparation and Diastereoselective *Ortho*-Metalation of Chiral Ferrocenyl Imidazolines: Remarkable Influence of LDA as Metalation Additive

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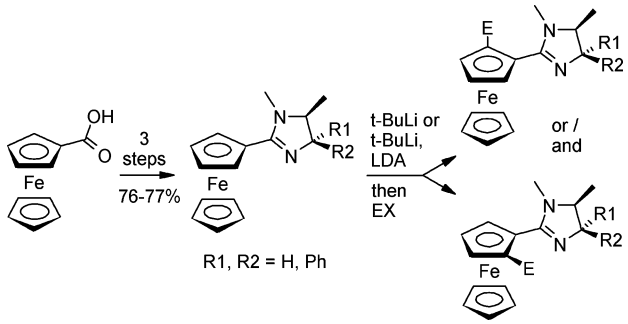
ABSTRACT



The preparation of optically pure ferrocenyl imidazolines starting from ferrocenecarboxylic acid and the application to diastereoselective *ortho*-metalations is described highlighting the remarkable influence of lithium dialkylamides, especially LDA, as metalation additives (in combination with *tert*-butyllithium) on the diastereoselectivity.

Chiral oxazolines[1] as well as planar chiral ferrocenes[2] are among the most successful ligand motifs in homogeneous asymmetric catalysis, and the combination of both concepts within planar chiral ferrocenyl oxazolines[3] **1** (Figure 1) has emerged as an excellent ligand system.[4]

Recently, several groups have disclosed their studies using chiral bidentate imidazoline ligands **2** in asymmetric catalysis.[5] Replacing an oxazoline oxygen atom by a group NR allows for the accurate adjustment of the electron density on the imino-type nitrogen atom by selecting either electron-withdrawing or -donating residues R.[6] This additional

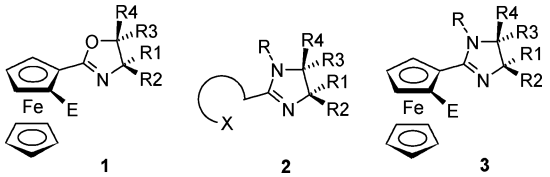


Figure 1. Imidazolines **3** complementing ligands **1** and **2**.

(1) (a) Ghosh, A. K.; Mathivanen, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1. (b) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336.

(2) (a) *Ferrocenes*; Hayashi, T., Togni, A., Eds.; VCH: Weinheim, Germany, 1995. (b) Richards, C. J.; Locke, A. J. *Tetrahedron: Asymmetry* **1998**, *9*, 2377.

(3) (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.

(4) Selected examples: (a) Sammakia, T.; Stangeland, E. L. *J. Org. Chem.* **1997**, *62*, 6104. (b) Bolm, C.; Muñiz Fernandez, K.; Seger, A.; Raabe, G.; Günther, K. *J. Org. Chem.* **1998**, *63*, 7860. (c) Arikawa, Y.; Ueoka, M.; Matoba, K.; Nishibayashi, Y.; Uemura, Y. *J. Organomet. Chem.* **1999**, *572*, 163. (d) Nishibayashi, Y.; Takei, I.; Uemura, S.; Hidai, M. *Organometallics* **1999**, *18*, 2291.

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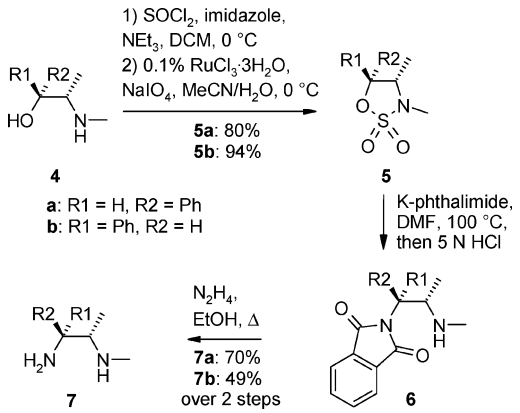
electronic tuning option thus leads to even more adaptable ligand systems as compared to oxazolines,[7] and the imidazoline derived catalyst systems were often superior to the corresponding oxazolines in terms of the enantioselectivity of the catalysis product.[5]

Our main interest in the preparation of ferrocenyl-substituted imidazolines **3** results from the anticipated enrichment of electron density at the imino nitrogen atom due to the strongly electron-donating properties of the ferrocenyl moiety in the 2-position of the heterocyclic system. The electron-rich amidine group[8] should thus be an even stronger σ-donor ligand, base, and nucleophile[9] than in conventional imidazolines. Herein, we present the first synthesis of optically active, chiral ferrocenylimidazolines[10] and their diastereoselective *ortho*-metalation giving rise to novel planar chiral systems.

To realize the preparation of imidazolines **3**, synthetic access to optically active 1,2-diamines **7** possessing a primary and a secondary amino group was a prerequisite.[11] We have thus developed a practical four-step sequence starting from (−)-ephedrine **4a** and (+)-pseudoephedrine **4b** (Scheme 1)

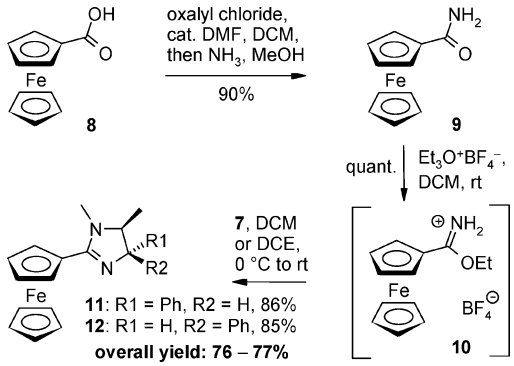
Scheme 1



avoiding any chromatographic purification.[12] The enantiomerically pure amino alcohols were converted into the corresponding sulfamidates **5** in high yield utilizing a modified literature procedure[13] using just 0.1 mol % of $RuCl_3$.[14] Sulfamidates **5** were then regio- and diastereoselectively ring opened by nucleophilic attack of potassium phthalimide using S_N2 type conditions. Deprotection of phthalimides **6** by hydrazinolysis revealed the free primary amino group. This synthetic sequence is amenable to multigram preparations.[15]

The synthesis of chiral ferrocenylimidazolines started from commercially available ferrocenyl carboxylic acid **8**, which was converted to primary amide **9** via a modified literature procedure (Scheme 2).[16] Compound **9** was then activated by

Scheme 2



O-alkylation with 1 equiv of $Et_3O^+BF_4^-$ generating iminium ether tetrafluoroborate salt **10**. The formation of the heterocyclic system by condensation of **10** with **7** was accomplished at room temperature without the need for isolating **10**. The resulting amidinium salt was converted to the free base with 1.0 N NaOH. When 0.1 N NaOH was employed, the heterocyclic moiety was still partly protonated indicating its highly basic character.[17]

The optically pure heterocyclic systems, which were prepared without the need for chromatographic purifications, were then investigated in diastereoselective *ortho*-lithiations[18]

(5) (a) Botteghi, C.; Schionato, A.; Chelucci, G.; Brunner, H.; Kürzinger, A.; Obermann, U. *J. Organomet. Chem.* **1989**, *370*, 17. (b) Morimoto, T.; Tachibana, K.; Achiwa, K. *Synlett* **1997**, 783. (c) Davenport, A. J.; Davies, D. L.; Fawcett, J.; Russell, D. R. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1500. (d) Menges, F.; Neuburger, M.; Pfaltz, A. *Org. Lett.* **2002**, *4*, 4713. (e) Busacca, C. A. U.S. Patent 6,316,620, 2001. (f) Busacca, C. A.; Grossbach, D.; So, R. C.; O'Brien, E. M.; Spinelli, E. M. *Org. Lett.* **2003**, *5*, 595. (g) Casey, M.; Smyth, M. P. *Synlett* **2003**, 102.

(6) Further selected examples: (a) Bastero, A.; Ruiz, A.; Claver, C.; Castillón, S. *Eur. J. Inorg. Chem.* **2001**, 3009. (b) Bastero, A.; Ruiz, A.; Claver, C.; Milani, B.; Zangrando, E. *Organometallics* **2002**, *21*, 5820. (c) Bastero, A.; Claver, C.; Ruiz, A.; Castillón, S.; Daura, E.; Bo, C.; Zangrando, E. *Chem. Eur. J.* **2004**, *10*, 3747.

(7) The N substituent also influences the ligand geometry due to steric interaction with the ligand backbone.

(8) Fernàndez, B.; Perillo, I.; Lamdan, S. *J. Chem. Soc., Perkin Trans. 2* **1973**, 1371.

(9) Basic/nucleophilic planar chiral ferrocenes: Mermerian, A. H.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 5604 and references therein.

(10) Only one achiral ferrocenyl imidazoline (**3** with R, R1−4, E = H) has been described so far: Nametkin, N. S.; Shvekhgeimer, G. A.; Tyurin, V. D.; Tutubalina, A. I.; Kosheleva, T. N. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1971**, 1567.

(11) Our attempts to prepare **3** directly from amino alcohols failed.

(12) For previous syntheses, see: (a) Gust, R.; Gelbcke, M.; Angermeier, B.; Bachmann, H.; Krauser, R.; Schönenberger, H. *Inorg. Chim. Acta* **1997**, *264*, 145. (b) Tytgat, D.; Gelbcke, M.; Smith, D. F. *Pharmazie* **1990**, *45*, 835.

(13) Williams, A. J.; Chakthong, S.; Gray, D.; Lawrence, R. M.; Gallagher, T. *Org. Lett.* **2003**, *5*, 811.

(14) Review about the synthesis and reactivity of sulfamidates: Meléndez, R. E.; Lubell, W. D. *Tetrahedron* **2003**, *59*, 2581.

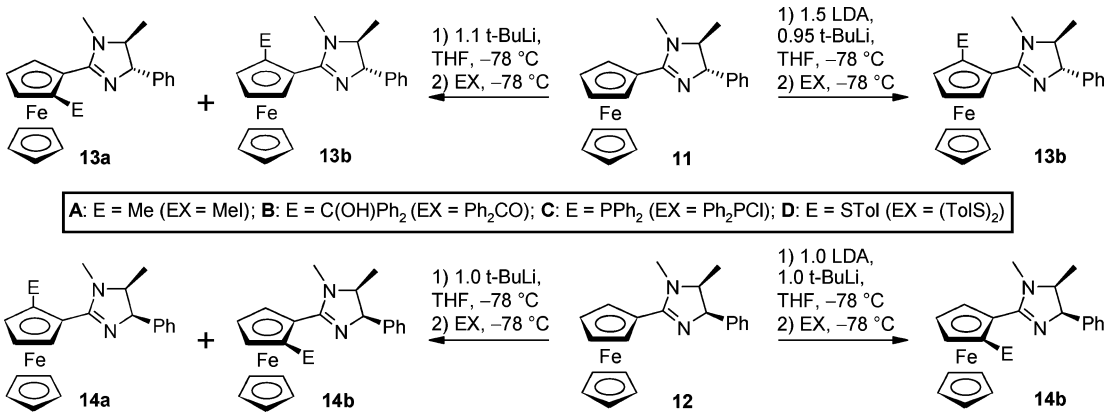
(15) This new route for the preparation of optically active diamines is not restricted to ephedrines. The full scope will be presented separately.

(16) Arimoto, F. S.; Haven, A. C., Jr. *J. Am. Chem. Soc.* **1955**, *77*, 6295.

(17) The basicity is thus markedly increased by the ferrocenyl moiety in comparison to conventional imidazolines (typical pK_{HA} values are 6−10, see ref 8).

(18) For previous stereoselective *ortho* metalations of ferrocene derivatives, see ref 3 and: (a) Marquarding, D.; Klusacek, H.; Gokel, G.; Hoffmann, P.; Ugi, I. *J. Am. Chem. Soc.* **1970**, *92*, 5389. (b) Riant, O.; Samuel, O.; Flessner, T.; Taudien, S.; Kagan, H. B. *J. Org. Chem.* **1997**, *62*, 6733. (c) Ganter, C.; Wagner, T. *Chem. Ber.* **1995**, *128*, 1157. (d) Riant, O.; Argouarch, G.; Guillaneux, D.; Samuel, O.; Kagan, H. B. *J. Org. Chem.* **1998**, *63*, 3511. (e) Tsukazaki, M.; Tinkl, M.; Roglans, A.; Taylor, N. J.; Snieckus, V. *J. Am. Chem. Soc.* **1996**, *118*, 685. (f) Enders, D.; Peters, R.; Lochtman, R.; Runsink, J. *Eur. J. Org. Chem.* **2000**, 2839.

Scheme 3



(Scheme 3, Table 1, and Supporting Information). In contrast to the related oxazolines **1** (E = H), deprotonations using simple alkyllithium bases in ethereal solvents at low temperature did not induce high diastereoselectivities (Table 1, entries 1 and 10). For that reason, several metalation additives were screened. Enders, Peters, et al. had previously shown that $LiClO_4$ in THF has a positive influence on *ortho*-lithiations of optically pure ferrocenoyl hydrazones regarding yield and regioselectivity.[19] In the case of **11** and **12**, however, $LiClO_4$ had in most cases a detrimental influence on diastereoselectivity and conversion. While lithium tetramethylpiperidide (LTMP) effected *ortho*-deprotonation with low stereoselectivity, other lithium amides such as lithium diisopropylamide (LDA, Table 1, entry 2) were not basic enough. The dialkylamides were, however, found to have a major influence on the diastereoselectivity when combined with alkyllithium bases: the configuration of the major isomer with regard to the planar chirality could thus be reversed for **11** (Table 1, entries 3, 4, 8, and 9) or at least significantly increased for **12** (Table 1, entry 11).

Table 1. Screening of the Effect of Lithium Amides as Metalation Additives on the Diastereoselective *Ortho*-Metalations of **11** and **12**

entry	product	*t*-BuLi (equiv)	amide (equiv)	conv[a] (%)	dr[a]
1	**13aA**	1.10		72	5:1
2			LDA (1.10)	0	n.a.
3	**13bA**	1.00	LDA (1.05)	76	1:9
4	**13bA**	0.95	LDA (1.50)	79	1:12
5	**13aA**	1.50	LDA (1.05)	92	3:1
6	**13aA**	2.10	LDA (2.10)	93	2:1
7	**13bA**	1.10	LTMP (1.10)	95	1:2
8	**13bA**	1.10	$LiNCy_2$ (1.10)	26	1:4
9	**13bA**	1.05	$LiNEt_2$ (1.10)	55	1:5
10	**14bA**	1.00		43	1:3
11	**14bA**	1.00	LDA (1.00)	80	1:31
12	**14A**	2.20	LDA (2.00)	80	1:1

[a] Based on ^{1}H NMR of the crude reaction mixture.

The most selective base/additive combination in our case consists of 0.95−1.00 equiv of *t*-BuLi and 1.00−1.50 equiv of LDA in THF at −78 °C (Table 1, entries 4 and 11) giving access to planar chiral imidazolines **13** or **14** with diastereoselectivities ranging from 12:1 to 31:1 (Table 2). To the best of our knowledge, this is the first reported example for the remarkable influence of lithium dialkylamide additives on the diastereoselective generation of planar chiral systems.[20] The influence of lithium amides (and also of lithium alkoxides and other lithium salts) on the reactivity and selectivity of organolithium species usually results from the formation of hetero-aggregates $[(RLi)_x(R'_2NLi)_y]$, which are more stable than the homo-aggregate species $(RLi)_n$ and

Table 2. Diastereoselective *Ortho*-Metalations of **11** and **12**

entry	product	*t*-BuLi (equiv)	LDA (equiv)	EX	dr[a] **a/b**	yield[b] (%)	dr[c]
1	**13aA**	1.10		MeI	5:1	61	20:1[d]
2	**13bA**	**0.95**	**1.50**	**MeI**	**1:12**	**66**	**1:>99**[d]
3	**13aB**	1.10		Ph_2CO	4:1	34	19:1[e]
4	**13bB**	**0.95**	**1.50**	**Ph_2CO**	**1:12**	**50**	**1:>99**[e]
5	**13bC**	**0.95**	**1.50**	**Ph_2PCl**	**1:7**	**50**	**1:8**[d]
6	**13bD**	**0.95**	**1.50**	**$(TolS)_2$**	**1:17**	**53**	**1:10**[d]
7	**14bA**	1.00		MeI	1:3	nd	
8	**14bA**	**1.00**	**1.00**	**MeI**	**1:31**	**41**	**1:150**[e]
9	**14bB**	1.00		Ph_2CO	1:2	nd	
10	**14bB**	**1.00**	**1.00**	**Ph_2CO**	**1:21**	**41**	**1:>99**[e]

[a] Based on ^{1}H NMR of the crude reaction mixture. [b] Yield of isolated product after column chromatography or trituration. [c] Based on ^{1}H NMR of the isolated product purified by column chromatography or trituration. [d] Diastereomeric ratio after column chromatography. [e] Diastereomeric ratio after trituration.

(19) (a) Enders, D.; Peters, R.; Lochtman, R.; Raabe, G. *Angew Chem., Int. Ed.* **1999**, *38*, 2421. (b) Enders, D.; Peters, R.; Lochtman, R.; Raabe, G.; Runsink, J.; Bats, J. W. *Eur. J. Org. Chem.* **2000**, 3399.

(20) We are currently investigating if this a general effect for the generation of planar chiral ferrocenes and if it is also valid for ferrocenyloxazolines and Ugi-type amines.

$(LiX)_n$.[21] We have reason to assume that the mixed aggregate formation of LDA and *t*-BuLi is probably not the only rationalization in the present studies, since, e.g., the selectivity dropped significantly, when 2 equiv of *t*-BuLi and the same amount of LDA were used (Table 1, entries 6 and 12). Here, the same mixed aggregate should have been formed as with 1 equiv of each component (Table 1, entries 3 and 11). This could indicate that the generated lithiated ferrocene derivatives are also primarily involved in the aggregation process, thus influencing the configurational outcome. It is important to note the reproducibly high diastereoselectivities were only obtained, when the freshly prepared LDA solutions were aged for several hours (2−48 h) at 0 °C prior to use.

Silica gel column chromatography or trituration allowed in most cases to further improve the dr (Table 2, entries 1−5, 8, and 10). The absolute configuration could be determined by X-ray analyses for **13bB**[22] and **14bB** (Figure 2).[23] Since

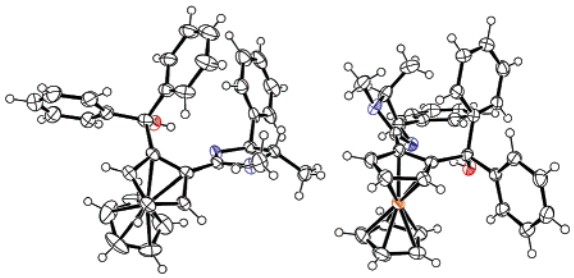


Figure 2. Crystal structures of **13bB** (left) and **14bB** (right).

the diastereoselective formation of the *ortho*-lithiated intermediate is responsible for the configuration of the planar chiral product, the absolute configuration for all compounds can be assigned.[24]

(21) (a) Gossage, R. A.; Jastrzebski, J. T. B. H.; van Koten, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 1448. (b) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624.

In conclusion, we have presented the preparation of the first optically active ferrocenyl imidazolines starting from commercially available ferrocenyl carboxylic acid via a high yielding operationally simple three-step procedure. To realize this task, we have developed a practical four-step sequence to optically active 1,2-diamines possessing a primary and a secondary amino group. Investigation of diastereoselective *ortho*-lithiations has revealed that LDA, as a metalation additive in combination with *t*-BuLi, has a significant influence on the configuration of the reaction product with regard to the planar chirality. This method provides access to a novel class of chiral ligands, bases, and nucleophiles for further study.

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Supporting Information Available: Experimental procedures, full characterization data for all new products, and further results of the metalation screening. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) X-ray data for **13bB** (crystal size: plate 0.16 × 0.14 × 0.04 mm): $C_{34}H_{32}FeN_2O$; M_r = 540.490; monoclinic, $P2_1$; a = 7.2470(2) Å, b = 20.1918(7) Å, c = 9.7910(4) Å; α = 90.00°, β = 104.179(2)°, γ = 90.00°; V = 1389.07(8) Å^3; Z = 2; D_x = 1.292 g cm^{-3}; Mo Kα radiation λ = 0.71073; 172 K. Structure refinement with SHELXL-97; H atoms are calculated; R(all) = 0.0786; 4442 observed reflections.

(23) X-ray data for **14bB** (crystal size: plate 0.40 × 0.40 × 0.38 mm): $C_{34}H_{32}FeN_2O$; M_r = 540.490; orthorhombic, $P2_12_12_1$; a = 9.8803(2) Å, b = 13.2759(2) Å, c = 20.8422(4) Å; α = 90.00°, β = 90.00°, γ = 90.00°; V = 2733.87(9) Å^3; Z = 4; D_x = 1.313 g cm^{-3}; Mo Kα radiation λ = 0.71073; 173.2 K. Structure refinement with SHELXL-97; H atoms are calculated; R(all) = 0.0535; 7049 observed reflections.

(24) However, we have found that the diastereoselectivity also depends on the electrophile to some degree (see Table 2).