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Manipulating the Diastereoselectivity of Ortholithiation in Planar Chiral Ferrocenes

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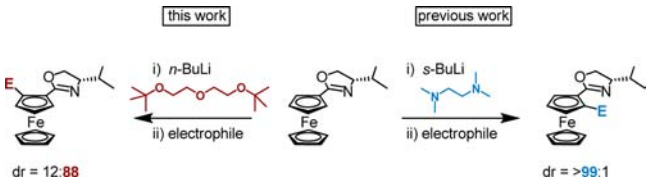
ABSTRACT



The sense of asymmetric ortholithiation directed by a chiral oxazoline may be inverted simply by the choice of achiral ligand. Comparison of results with a number of ferrocenyl oxazoline derivatives suggests that lithiation takes place by coordination to the oxazoline nitrogen irrespective of the ligand used.

Ferrocenes have been extensively studied and are the subject of much topical research, particularly since their use in material[1,2] and even medicinal chemistry[3] has been widespread. Significantly, the planar chiral aspect of ferrocene substitution has been an important feature of their success.[4] Control of the absolute planar chiral configuration of ferrocenyl systems has been achieved in a number of ways, typically involving asymmetric lithiation of the ferrocene through the use of chiral directing groups.[2a,5] One of the most common of these methods has been the use of chiral oxazolines, first described in 1995 simultaneously by the groups of Richards,[6] Uemura,[7] and Sammakia.[8] This method involves the use of an alkyllithium base directed by a chiral oxazoline to diastereoselectively deprotonate one of the ferrocenyl *ortho*-protons. By quenching the reaction with a wide range of electrophiles, diastereomer **2a** can be obtained, which can be further modified downstream for a multitude of purposes, for example the synthesis of the valuable ferrocenylphosphine (Fc-Phox)[1a,9] and organosilanol[10] ligands. Sammakia has developed the method of choice, showing that *sec*-butyllithium in conjunction with *N,N,N′,N′*-tetramethylethylenediamine

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(1) Selected review articles: (a) Sutcliffe, O. B.; Bryce, M. R. *Tetrahedron: Asymmetry* **2003**, *14*, 2297–2325. (b) Atkinson, R. C. J.; Gibson, V. C.; Long, N. J. *Chem. Soc. Rev.* **2004**, *33*, 313–328. (c) Arrayás, R. G.; Adrio, J.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 7674–7715. (d) Butler, I. R. *Eur. J. Inorg. Chem.* **2012**, 4387–4406.

(2) Selected books: (a) *Ferrocenes: Ligands, Materials and Biomolecules*; Stepnicka, P., Ed.; Wiley: Chichester, 2008. (b) *Chiral Ferrocenes in Asymmetric Catalysis: Synthesis and Applications*; Dai, L.-X., Hou, X. L., Eds.; Wiley-VCH: Weinheim, 2010. (c) *Ferrocenes: Compounds, Properties & Applications (Chemical Engineering Methods and Technology)*; Philips, E. S., Ed.; Nova Science Publishers: New York, 2011.

(3) Selected review articles: (a) Fouda, M. F. R.; Abd-Elzaher, M. M.; Abdelsamaia, R. A.; Labib, A. A. *Appl. Organomet. Chem.* **2007**, *21*, 613–625. (b) Hillard, E. A.; Jaouen, G. *Organometallics* **2011**, *30*, 20–27. (c) Roux, C.; Biot, C. *Future Med. Chem.* **2012**, *4*, 783–797.

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(7) (a) Nishibayashi, Y.; Uemura, S. *Synlett* **1995**, 79–81. (b) Nishibayashia, Y.; Segawaa, K.; Arikawaa, Y.; Ohea, K.; Hidaib, M.; Uemura, S. *J. Organomet. Chem.* **1997**, *545–546*, 381–398.

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(9) Geisler, F. M.; Helmchen, G. *J. Org. Chem.* **2006**, *71*, 2486–2492.

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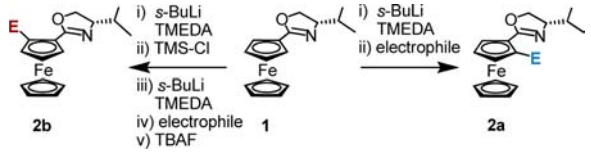
(TMEDA) and a noncoordinating solvent gave a superb diastereomeric ratio (*dr*) of >99:1 (Scheme 1).[8b] The mechanism has been proposed to be controlled by *N*-coordination of the oxazoline, but the wide range of diastereoselectivities reported under different conditions[11] suggests a much more complicated process in fine balance between four factors: (1) the group attached to the chiral center of the oxazoline, (2) the alkyllithium used, (3) the choice of solvent, and (4) the choice of ligand (although in the case of ferrocenes only TMEDA and glyme have been examined).[8b]

Although the so-called 'minor' diastereomer (**2b**) is accessible via a stepwise protection/deprotection method using a trimethylsilyl group (Scheme 1),[6b,12] we wondered whether the diastereoselectivity of the lithiation itself might be perturbed in such a way as to favor the direct formation of **2b**.[13] Herein we report our results, which show that this is indeed possible. They also allow us to contribute significant observations to the topical discussion of this mechanism.[14]

It is thought that the reason TMEDA successfully improves the diastereoselectivity of the ortholithiation of chiral ferrocenes resides in its ability to chelate and break down the alkyllithium complexes that exist in solution.[15] That said, it seemed surprising that other ligands which are known to do the same thing had not been explored in this system, particularly given that different ligands have been shown to have a profound effect in the diastereoselective ortholithiation of a calixarene oxazoline.[13c] Thus a selection of chelating ligands **3**–**8** was examined for their ability to influence the diastereoselectivity of the ortholithiation of ferrocenyl oxazoline **1** (Figure 1).

Scheme 1. Current Methods for Obtaining Both Diastereomers of Oxazoline Ferrocenes



Preliminary exploratory work found that pentane was not a suitable general solvent, particularly when using the other ligands. Toluene was found to be a compatible noncoordinating solvent and returned a better *dr* to that

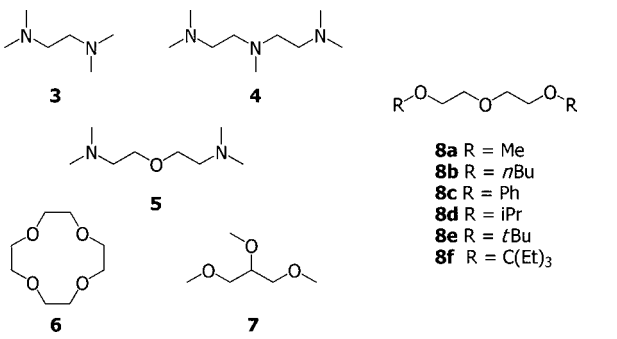
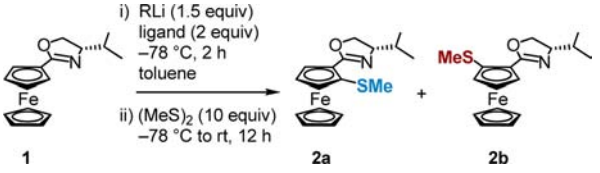


Figure 1. Ligands examined in this work.

Table 1. Ortholithiation Results with Oxazoline Ferrocene **1** with Various Ligands



entry	RLi	ligand	conv[a] (%)	dr[a] 2a:2b
1	*n*BuLi	TMEDA (**3**)	58	165:1
2	*n*BuLi	PMDTA (**4**)	96	25:1
3	*n*BuLi	DMAEE (**5**)	95	2:1
4	*n*BuLi	12-Crown-4 (**6**)	30	22:1
5	*n*BuLi	Trimethoxy glycerol (**7**)[c]	34	5:1
6	*n*BuLi	DGME (**8a**)	98	1:2
7	*s*BuLi	DGME (**8a**)	96	3:1
8	*t*BuLi	DGME (**8a**)	78	15:1
9	*n*BuLi	$(n\text{Bu})_2$-DGME (**8b**)	56	1:2
10	*n*BuLi	$(\text{Ph})_2$-DGME (**8c**)	9	1:1
11	*n*BuLi	$(i\text{Pr})_2$-DGME (**8d**)	88	1:4
12	*n*BuLi	$(t\text{Bu})_2$-DGME (**8e**)	85	1:6
13	*n*BuLi	$(\text{CEt}_3)_2$-DGME (**8f**)	18	2:1
14	*n*BuLi	$(t\text{Bu})_2$-DGME[b] (**8e**)	85	1:7

[a] Quantified using HPLC traces; conversion is relative to starting material. [b] At −86 °C with 2.5 equiv of ligand. [c] Synthesized via a reported method.[16]

reported when *n*-butyllithium and TMEDA (**3**) were used (Table 1, entry 1).[17] This established a baseline *dr* value for comparison with the other ligands.

Ligands **4**–**7** (entries 2–5) were all less effective than TMEDA in promoting high *dr* values, confirming the singularly unique and fascinating relationship TMEDA has had with alkyllithiums. Interestingly the diglyme (DGME) ligand (**8a**) showed a promising, albeit small, preference for the opposite diastereomer **2b** (entry 6). Attempting the same reaction but with *sec*- or *tert*-butyllithium switched the selectivity back toward the conventional diastereomer **2a** (entries 7 and 8), leading us to suspect that the reversal in diastereoselectivity may be intimately tied to the steric environment of the

(11) Some examples for isopropyl ferrocenyl oxazoline: *n*-BuLi/THF (2:1);[8b] *n*-BuLi/ether (6:1);[8b] *s*-BuLi/ether (39:1);[7b] *s*-BuLi/hexanes/TMEDA (>99:1);[8b] *t*-BuLi/hexanes/TMEDA (28:1).[8b]

(12) Ahn, K. H.; Cho, C.-W.; Baek, H.-H.; Park, J.; Lee, S. *J. Org. Chem.* **1996**, *61*, 4937–4943.

(13) Very few examples of reagent-induced reversal of diastereoselectivity in ortholithiation reactions exist. In a chromium arene, see: (a) Overman, L. E.; Owen, C. E.; Zipp, G. G. *Angew. Chem., Int. Ed.* **2002**, *41*, 3884–3887. In a 1,1′-bis-oxazoline ferrocene, see: (b) Park, J.; Lee, S.; Ahn, K. H.; Cho, C.-W. *Tetrahedron Lett.* **1996**, *37*, 6137–6140. In a calixarene, see: (c) Herbert, S. A.; Arnott, G. E. *Org. Lett.* **2010**, *12*, 4600–4603.

(14) Chadwick, S. T.; Ramirez, A.; Gupta, L.; Collum, D. B. *J. Am. Chem. Soc.* **2007**, *129*, 2259–2268.

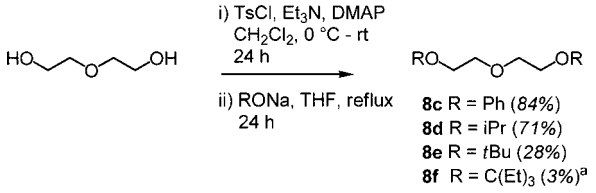
(15) Saá, J. *Helv. Chim. Acta* **2002**, *85*, 814–840.

(16) García, J. I.; García-Marín, H.; Mayoral, J. A.; Pérez, P. *Green Chem.* **2010**, *12*, 426–434.

(17) *n*BuLi/TMEDA in either diethyl ether or hexanes has been reported to give a 100:1 (**2a**:**2b**) diastereomeric ratio.[8b]

alkyllithium–ligand complex. We therefore targeted symmetrical derivatives of DGME (**8b**–**f**) to perturb the steric environment of the lithiating complex and investigate their influence on the reaction. Ligand **8b** was commercially available, while ligands **8c**–**f** could be synthesized using a Williamson ether synthesis on the bis-tosylate of diethylene glycol (Scheme 2).[18]

Scheme 2. Synthesis of DGME-Based Ligands



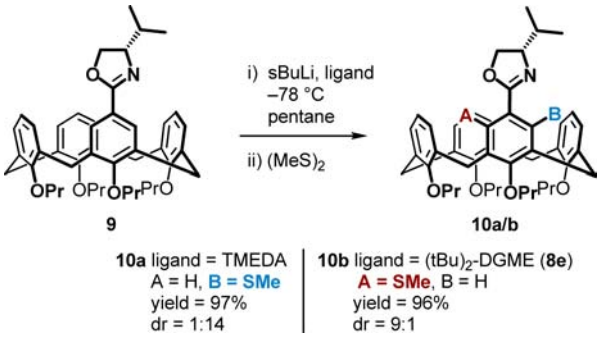
[a] **8f** synthesized from bis-mesylate.

Applying these ligands to the ortholithiation of oxazoline ferrocene **1** showed what initially appeared to be a trend of increasing selectivity for diastereomer **2b** as the R-group on the DGME ligand increased in steric size (entries 9–12). However bis(tri(3-ethylpentyl))-DGME (**8f**) failed to effect further improvement in the *dr* (entry 13), leading us to suggest that the reaction had reached the limits of the steric strain imposed on the system.[19] However, by optimizing the number of equivalents of ligand **8e** and lowering the temperature of the reaction to −86 °C, we were able to demonstrate an optimized 1:7 (= 12:88) ratio in favor of diastereomer **2b** (entry 14).[20] Although this ratio is a far cry from the >99:1 diastereoselectivity when using *sec*-butyllithium–TMEDA, it is remarkable that the diastereoselectivity can be manipulated this far. Synthetically the switch from >99:1 to 12:88 allows either diastereoisomer of a functionalized ferrocene product to be made in up to 87% yield by just a change of an achiral ligand.

The effect is potentially general for other diastereoselective oxazoline-directed metalations. For example, switching TMEDA to **8e** in the lithiation of an oxazoline substituted calixarene (Scheme 3) led to an inversion of the diastereoselectivity from 1:14[13c] to 9:1, again demonstrating a remarkable reversal of selectivity based solely on the choice of achiral ligand.

In principle the oxazoline may direct the ortholithiation of the ferrocene via either the N- or O-atom.[14] However,

Scheme 3. Reversal of Diastereoselectivity in a Oxazoline Calix[4]arene System



Sammakia and Latham have used a conformationally restricted ferrocenyl oxazoline to show that only an N-coordination mode occurs during ortholithiation,[8c] even though computationally the difference between the two mechanisms is small.[14] The results reported here prompt the question as to whether the DGME ligands are promoting a switch to an O-coordination mechanism, which may account for the reversal of diastereoselectivity.[13c] Information regarding N- vs O-coordination was obtained by looking at differently substituted chiral oxazolines, i.e. by studying the effect of increasing and decreasing the size of the R-group on the chiral center, and shifting its position from next to the N-atom to next to the O-atom.[21] To this end five ferrocenyl oxazolines were synthesized (**11**–**15**, Scheme 4) in excellent yields, except *cis*-diphenyl-oxazoline ferrocene **15** which appeared to be prone to decomposition. These were then treated with *n*-butyllithium and THF, TMEDA (**3**), or di-*tert*-butyl-DGME (**8e**) as ligands (Table 2).

The results paint an intriguing picture. Decreasing the R′-group's steric bulk from *tert*-butyl, to isopropyl, to methyl (entries 1–3, Table 2) shows a correlation with decreased *dr* only when THF is used. With both TMEDA and di-*tert*-butyl-DGME (**8e**) no simple relationship between selectivity and steric bulk was observed. Curiously, with di-*tert*-butyl-DGME (**8e**) the change from ferrocenyl *tert*-butyl oxazoline **11** to isopropyl oxazoline **1** results in a significant change in *dr*, but what should amount to a significant reduction of steric strain with methyl oxazoline **12** has no effect whatsoever on the *dr*. The yields of the reactions with di-*tert*-butyl-DGME (**8e**) are also instructive, showing that decreasing the steric bulk on the oxazoline increases the rate of the reaction, this being consistent with an N-coordination mechanism.[22] Furthermore, it would be expected that moving the methyl group from being α to the N-atom (**12**) to being α to the O-atom (**13**)

(18) Low yields of the di-*tert*-butyl-DGME (**8e**) and bis(tri(3-ethylpentyl))-DGME (**8f**) ligands were obtained due to a competing elimination reaction giving the monovinyl ether. Whilst the divinyl ether was presumed to have been formed, it was undetected owing to its very low boiling point of 28 °C. Attempts to improve the yield by conducting the reaction in diethyl ether or toluene failed, returning similar results to those performed in THF.

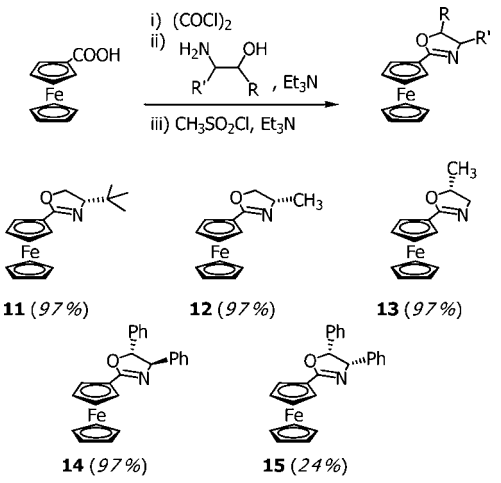
(19) Attempting to correlate a linear free energy relationship with the steric bulk of the R-groups on the diglyme ligands was also unsuccessful, even when applying recent developments in this area; see: Harper, K. C.; Bess, E. N.; Sigman, M. S. *Nat. Chem.* **2012**, *4*, 366–374.

(20) From a practical point of view it was also found that the ligand could be isolated from the reaction mixture by protonating the ferrocene products with 3 M HCl and extracting the ligand into diethyl ether. The recovered ligand could then be distilled and reused.

(21) Whilst the tethered approach of Sammakia would seem ideal to examine this, it suffers from a 13-step, low yielding (4%) synthetic process, making it undesirable for multiple experiments. We were also concerned with whether restricting the rotation of the oxazoline would impede subtle conformational aspects that only manifest with free rotation.

(22) It has been shown that the increased steric bulk of the group α to the nitrogen atom reduces the reaction rate; see refs 8b and 23.

Scheme 4. Chiral Ferrocenyl Oxazolines Synthesized for a Mechanistic Probe

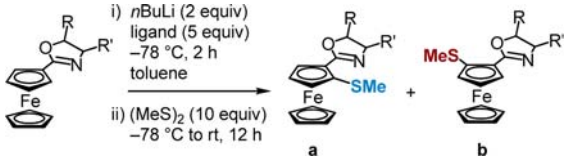


would improve the *dr* if an O-coordination mechanism was important. Entry 4 (Table 2) shows the converse, with the diastereoselectivity of the reaction being effectively shut down in all cases. Lastly, ferrocenyl oxazolines **14** (Ph,Ph *trans*) and **15** (Ph,Ph *cis*) have the same configuration α to the N-atom but opposite configurations α to the O-atom. They might therefore be expected to give very different outcomes in the ortholithiation reaction should O-coordination be important. It was however found that the *dr* values were essentially the same (entries 5 and 6), supporting an N-coordination mechanism.

These results have shed some light on the mechanistic aspects of this reaction. The strong evidence for the absence of an O-coordination mechanism suggests that the role of the DGME ligands is not to change to coordination site of the organolithium base. Rather, they must exert their influence in another way: i.e., either (1) the initial DGME·*n*BuLi[23] species coordinates to the N-atom of the oxazoline and forms a prelithiation complex which then finds a lowest energy pathway for deprotonation that is different (effectively opposite) from that when TMEDA

(23) No data exists regarding the nature of this species, but it is more than likely monomeric in solution. For DGME·LiHMDS monomer data, see: Lucht, B. L.; Bernstein, M. P.; Remenar, J. F.; Collum, D. B. *J. Am. Chem. Soc.* **1996**, *118*, 10707–10718.

Table 2. Results of Mechanistic Probe Reactions



		THF[b]		TMEDA (**3**)		$(tBu)_2$-DGME (**8e**)	
entry[a]	ferrocene (R,R')	conv (%)	dr a:b	conv (%)	dr a:b	conv (%)	dr a:b
1	**11** (H,*t*Bu)	87	7:1	95	81:1	26	1:1
2	**1** (H,iPr)	75[c]	2:1	58	170:1	70	1:6
3	**12** (H, Me)	98	1:2	93	38:1	94	1:6
4	**13** (Me, H)	78	1:1	83	1:1	51	1:1
5	**14** (Ph,Ph *trans*)	98	4:1	97	75:1	96	1:4
6	**15** (Ph,Ph *cis*)	56	6:1	94	41:1	91	1:4

[a] Conversion and *dr* quantified using HPLC traces; conversion is relative to starting material. [b] Reactions were conducted in THF as solvent. [c] Reaction reported in literature.[8b]

is used; or (2) that the DGME·*n*BuLi complex acts as a bulky Lewis acid coordinating to the oxazoline nitrogen, blocking rather than allowing deprotonation. The ortho-hydrogen next to the oxazoline oxygen would then be free for deprotonation.

In conclusion we have reported on a new ligand for alkyllithium chemistry that in the case of oxazoline directed asymmetric ortholithiation shows a remarkable ability to manipulate the diastereoselectivity from conventionally accepted values. We have also lent further experimental support to the N-coordination theory for these types of reactions.

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Supporting Information Available. Experimental procedures and characterization data are included. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.