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Ligand Effects on the Stereochemistry of the Metalation of Chiral Ferrocenyloxazolines

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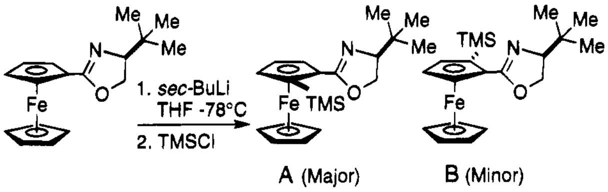
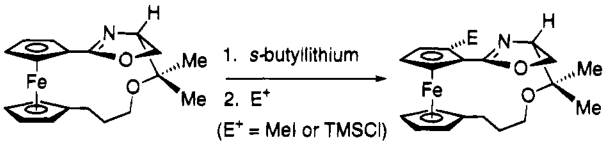
We recently described a method for the asymmetric synthesis of ferrocene complexes possessing planar chirality which relies on the diastereotopic group selective deprotonation of chiral ferrocenyloxazolines (eq 1).[1] In



(1)

this study, we saw a marked dependence of the magnitude of the asymmetric induction on the size of the alkyl group of the oxazoline, with more bulky groups providing higher selectivity. Because the sense of asymmetric induction was not consistent with our expectations, we undertook a study to determine whether the nitrogen or oxygen of the oxazoline is responsible for the directing effects of this functional group in ortho metalations. Our mechanistic studies relied on the outcome of the metalation and trapping of the conformationally constrained oxazoline shown in eq 2 and provided firm evidence that



(2)

the nitrogen of the oxazoline is directing the metalation.[2] The stereochemical outcome which we observe in the metalation of our unconstrained chiral oxazolines is therefore due to a nitrogen-directed reaction via the conformer shown in Figure 1, where the alkyl group of the oxazoline points toward the iron and the rest of the molecule. We reasoned that the predominance of this conformation is due to an interaction between the alkyl group of the oxazoline and the metalating agent. This interaction is present in the transition state leading to the minor diastereomer, but not the major diastereomer.[3-5] This paper describes a series of experiments designed to test this hypothesis that have led to conditions for the deprotonation of chiral ferrocenyloxazolines which provide diastereoselectivities in excess of 500:1.

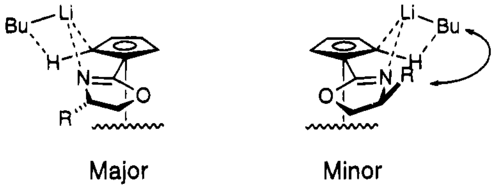


Figure 1.

If the interaction that dictates the diastereoselectivity is between the butyl group of the butyllithium and the alkyl group of the oxazoline, it is reasonable to expect that variations in the severity of this interaction will lead to variations in the rate and diastereoselectivity of the metalation. There are numerous factors that can influence the apparent "size" of alkyllithium reagents and consequently the severity of this interaction, including the size of the alkyl group of the alkyllithium, solvent, ligand, and aggregation-state effects.[6] We have therefore examined the metalation of chiral ferrocenyloxazolines under conditions that vary these factors. The results are consistent with our hypothesis and indicate that there is a dramatic effect on the yield and diastereoselectivity of the reaction depending upon the reagents and conditions used (Tables 2 and 3).

We first examined the difference in the rate of metalation of substituted and unsubstituted oxazolines. Competition experiments between the unsubstituted ferrocenyloxazoline (**1**) and the *tert*-butyl-substituted oxazoline **2** reveal a rate difference of 3.6:1 favoring **1** when *s*-BuLi is used as the base and $>$20:1 when *t*-BuLi is used (Table 1). This result is consistent with a nitrogen-directed reaction in which the increase in selectivity observed with *t*-BuLi is due to an increase in the steric interactions between the base and the alkyl group of the oxazoline.

We next examined the effect of solvent on the diastereoselectivity using the isopropyl-substituted oxazoline **3** and *n*-BuLi as the base. We found that THF and ether provide good yields and low to moderate diastereoselectivty (respectively), while hexanes provides very low yields and no selectivity (Table 2, entries 1–3). Interestingly, even *t*-BuLi provides low yields in hexanes (Table 2, entry 12). We then examined the selectivity observed in THF as a function of the metalating agent and found that the selectivity improves as the size of the alkyl group of the alkyllithium is increased (Table 2, entries 3–5). We next explored the effects of added ligands on the reaction in an attempt to increase the selectivity by varying the nature of the metalating agent. We reasoned that the binding of ligands to the alkyllithium reagent could influence the effective size of the metalating complex and provide greater selectivity. We initially examined the effects of stoichiometric amounts of TMEDA in THF using *n*-BuLi as the base and found little change in the selectivity (Table 2, entry 6). However, conducting the same reaction in ether or hexanes provides a highly diastereoselective reaction ($\approx$100:1) and

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[1] (a) Sammakia, T.; Latham, H. A.; Schaad, D. R. *J. Org. Chem.* **1995**, *60*, 10. For similar studies which appeared simultaneously, see: (b) Richards, C. J.; Damalidis, T.; Hibbs, D. E.; Hursthouse, M. B. *Synlett* **1995**, 74. (c) Nishibayashi, Y.; Uemura, S. *Synlett* **1995**, 79.

[2] Sammakia, T.; Latham, H. A. Unpublished results.

[3] For a related transition structure proposal, see ref 1b.

[4] For a related transition structure hypothesis in an addition reaction, see: Kundig, E. P.; Ripa, A.; Liu, R.; Amurrio, D.; Bernardelli, G. *Organometallics* **1993**, *12*, 3737.

[5] For theoretical studies of heteroatom-directed metalations which suggest a similar transition structure geometry, see: Hommes, N. J. R. v. E.; Schleyer, P. v. R. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 755. Saa, J. M.; Deya, P. M.; Suner, G. A.; Frontera, A. *J. Am. Chem. Soc.* **1992**, *114*, 9093.

[6] The aggregation state of the metalating agent at the transition state has been studied and is known to be complex. Bauer and Schleyer speculate that ortho metalation of anisole proceeds via a dimer in toluene in the presence of TMEDA (see: Bauer, W.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1989**, *111*, 7191); however, Smith, Beak, and coworkers have performed kinetic measurements of the α′ lithiation of carboxamides and have concluded that the reaction can proceed by more that one pathway (see: Hay, D. R.; Song, Z.; Smith, S. G.; Beak, P. *J. Am. Chem. Soc.* **1988**, *110*, 8145). Consequently, it is difficult to extend the conclusions from one system to others. We therefore make the reasonable assumption that as the alkyl group of the metalating agent becomes larger, the "effective size" of the metalating agent also becomes larger. All our data and interpretations are consistent with this hypothesis.

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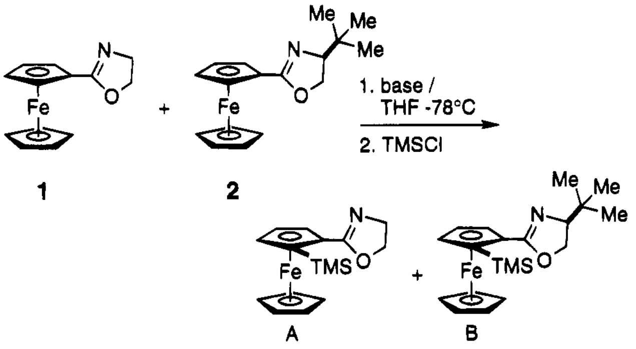
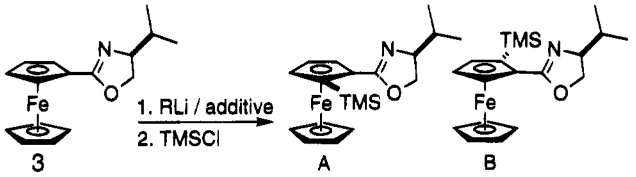
Table 1. Competition between Metation of *tert*-Butyl-Substituted and Unsubstituted Oxazoline[a]



base	ratio (A:B)	conversion (%)
s-BuLi	3.6:1	28
t-BuLi	>20:1	8

[a] Metalations were conducted at −78 °C for 2 h with 0.35 equiv of base and quenched with 0.5 equiv of TMSCl.

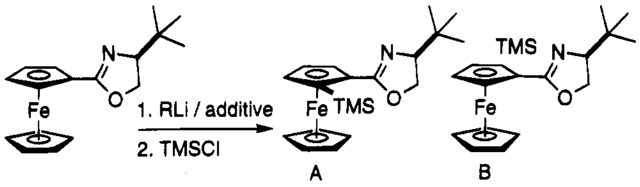
Table 2. Ligand, Solvent, and Base Effects on the Metalation of the Isopropyl-Substituted Oxazoline[a]



	RLi	solvent	additive	A:B	yield (%)
1	*n*-BuLi	hexanes		1:1	3
2	*n*-BuLi	ether		6:1	
3	*n*-BuLi	THF		2:1	
4	*s*-BuLi	THF		8:1	
5	*t*-BuLi	THF		16:1	
6	*n*-BuLi	THF	TMEDA	3:1	
7	*n*-BuLi	ether	TMEDA	100:1	80
8	*n*-BuLi	hexanes	TMEDA	100:1	75
9	*n*-BuLi	hexanes	THF (3 eq)	3:1	70
10	*n*-BuLi	hexanes	DME (3 eq)	6:1	
11	*n*-BuLi	hexanes	3:1 THF:TMEDA	100:1	
12	*t*-BuLi	hexanes		5:1	35
13	*s*-BuLi	hexanes	TMEDA	>500:1	94
14	*t*-BuLi	hexanes	TMEDA	28:1	

[a] All metalations were conducted with 1.3 equiv of base at −78°C for 2 h followed by warming to 0 °C for 15 min and quenched with 2 equiv of TMSCl. In cases where TMEDA is indicated, 1.3 equiv was added. See the supporting information for details. All yields are greater than 75% unless otherwise noted.

Table 3. Ligand, Solvent, and Base Effects on the Metalation of the *t*-Butyl Substituted Oxazoline[a]



	RLi	solvent	additive	A:B	comments
1	*n*-BuLi	THF		6:1	
2	*s*-BuLi	THF		36:1	
3	*t*-BuLi	THF		6:1	
4	*n*-BuLi	hexanes		1:1	11% yield
5	*t*-BuLi	hexanes		1:1	4% yield + 12% bottom ring metalation
6	*n*-BuLi	hexanes	TMEDA	>500:1	
7	*s*-BuLi	hexanes	TMEDA	>500:1	
8	*t*-BuLi	hexanes	TMEDA	34:1	

[a] All metalations were conducted with 1.3 equiv of base at −78°C for 2 h followed by warming to 0 °C for 15 min and quenched with 2 equiv of TMSCl. In cases where TMEDA is indicated, 1.3 equiv was added. See supporting information for details. All yields are greater than 75% unless otherwise noted.

excellent yields in both solvents (Table 2, entries 7 and 8). These results are to be compared to the reaction in hexanes with no additives which provides no selectivity and essentially no reaction (Table 2, entry 1). We then examined the effects of other ligands on the metalation in hexanes and found that both THF and DME are capable of increasing the rate of the metalation but that these ligands do not provide good levels of stereoselectivity (Table 2, entries 9 and 10). Interestingly, in a competition between approximately equimolar amounts of THF and TMEDA as ligands in hexanes, we observe results consistent with TMEDA acceleration (Table 2, entry 11). This indicates that in stoichiometric quantities, TMEDA has a greater influence on the course of the reaction than THF, but that this effect is overwhelmed when THF is used as the solvent. Finally, we were able to further improve the selectivity by increasing the size of the metalating agent, up to a point. Accordingly, the use of *s*-BuLi in hexanes containing a stoichiometric amount of TMEDA provides a >500:1 ratio of diastereomers, but the use of *t*-BuLi under the same conditions provides only a 28:1 ratio (Table 2, entries 13 and 14). We suspect that the *t*-BuLi−TMEDA complex has reached the limits of steric crowding and that the loss of selectivity is either due to reaction via a non-TMEDA-complexed pathway or due to partial intervention of an oxygen-directed or a nondirected pathway.

We have also conducted a similar study using the *tert*-butyl-substituted oxazoline **2**. Steric interactions in the transition state are much more pronounced with this substrate as evidenced by the increase in selectivity using *s*-BuLi as compared to *n*-BuLi but *decrease* upon using *t*-BuLi (Table 3, entries 1−3). Furthermore, in hexanes, metalation with *t*-BuLi provides a 4% yield of products derived from metalation of the cyclopentadienyl ring bearing the oxazoline and a 12% yield of metalation of the unsubstituted cyclopentadienyl ring. Finally, metalations in hexanes containing 1 equiv of TMEDA also show a decrease in selectivity upon using *t*-BuLi as compared to *s*-BuLi. These results suggest that while increased steric crowding can increase the selectivity of the metalation, severe steric crowding has a detrimental effect on the stereoselectivity, perhaps because coordination to the nitrogen of the oxazoline is precluded.

In conclusion, we have provided further evidence that the metalation of chiral ferrocenyloxazolines proceeds by a transition structure in which the alkyl group of the oxazoline is directed toward the bulk of the ferrocene and away from the lithiating reagent. We have used this information to optimize the stereoselectivity of the metalation and found that in hexanes as solvent, and with TMEDA as an additive, *s*-BuLi provides selectivities greater than 500:1 in the metalation of both the valine- and *tert*-leucine-derived oxazolines. This represents a useful entry into ferrocene systems possessing planar chirality.

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Supporting Information Available: Experimental details for the optimized metalation using TMEDA and *s*-BuLi (1 page).

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