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Aminoferrocene Lithiation by Boron Trifluoride Activation

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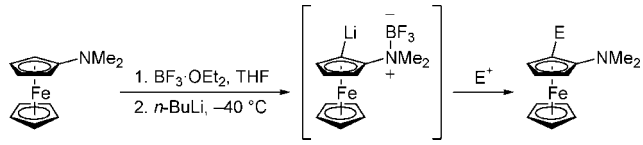
ABSTRACT



Lithiation of BF_3-complexed dimethylaminoferrocene occurs exclusively ortho to the dimethylamino group in the cyclopentadienyl ring providing structurally diverse products in 76−94% yield after electrophile quench. This method represents the first direct C2-lithiation of a monosubstituted aminoferrocene, offering rapid and complementary access to this class of compounds over procedures that utilize carbon- and sulfur-based directing groups and may serve as a prelude to an asymmetric process.

The lithiation of monosubstituted ferrocenes bearing chiral or achiral directing groups[1,2] is a key method for the preparation of planar chiral reagents with applications in catalysis[3] and materials science.[4] Carbon-based directing groups that have been developed for this purpose include (dialkylaminomethyl)ferrocenes[5] (e.g., **1**), oxazolines[6] (**2**), acetals[7] (**3**), hydrazones[8] (**4**), and carboxamides[9] (**5**), which impart planar chirality by diastereoselective or enantioselective deprotonation (Figure 1).[1,2,10] The most commonly employed heteroatom-based directing groups are chiral sulfoxides **6** (R = *p*-Tol, *t*-Bu)[11] and related sulfoximines,[12] derivatives of which have been applied in asymmetric synthesis.[3a] More recently, nonstereoselective lithiation of ferrocenyl benzimidazoles (**7**) has also been reported.[13]

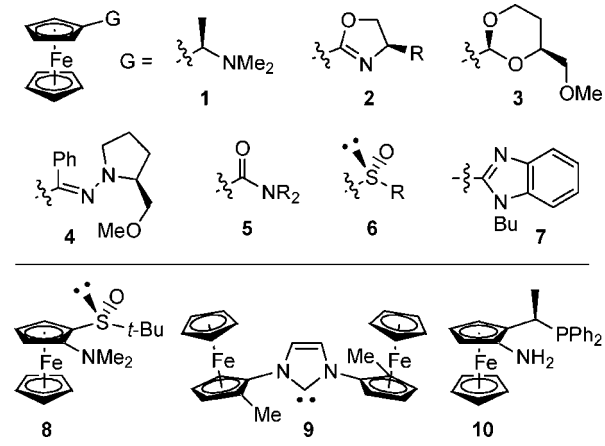


Figure 1. Carbon- and sulfur-based directing groups in ferrocenes and derived aminoferrocenes.

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(6) (a) Richards, C. J.; Damalidis, T.; Hibbs, D. E.; Hursthouse, M. B. *Synlett* **1995**, *n/a*, 74. (b) Uemura, S.; Nishibayashi, Y. *Synlett* **1995**, *n/a*, 79. (c) Sammakia, T.; Lathman, H. A.; Schad, D. R. *J. Org. Chem.* **1995**, *60*, 10.
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While most of the preceding starting materials contain nitrogen, none feature a carbon−nitrogen bond to the cyclopentadienyl (Cp) ring as would be present in an aminoferrocene. A rekindling of interest in aminoferrocenes in recent years has resulted in planar chiral ligands such as aminosulfoxide **8**, which is prepared by "N^+" electrophile quench of 2-lithio sulfoxide **6**.[14] In contrast, ferrocenyl *N*-heterocyclic carbenes[15] (**9**) and aminophosphines[16] (**10**) have been prepared by more circuitous routes involving Curtius rearrangement of ferrocene-2-carboxylic acids derived from **3** and **1**. Surprisingly, an alternate strategy involving C2-lithiation of tertiary aminoferrocenes, which already contain a carbon−nitrogen bond to the Cp ring, has not been explored. Realization of such a process may provide access to 2-substituted aminoferrocenes of greater structural diversity by eliminating the need to manipulate carbon or sulfur-based directing groups.

In this paper, we report our preliminary results regarding a new method of preparing 2-substituted aminoferrocenes by direct C2-lithiation of Lewis acid activated tertiary aminoferrocenes. This approach was inspired by the work of Kessar,[17] Harmata,[18] Vedejs,[19] and Simpkins[20] who have demonstrated that BF_3- or BH_3-complexed tertiary amines such as pyrrolidines[17] (**11**, **12**), tetrahydroisoquinolines[17,20] (**13**), Troeger's base[18] (**14**), aziridines[19] (**15**), and isoindolines[21] (**16**) undergo facile deprotonation α to nitrogen (Figure 2).[22] The method may be amenable to development

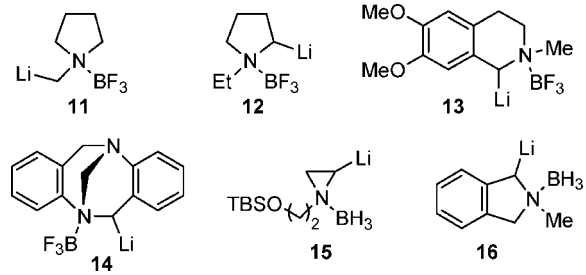

Figure 2. BF_3- and BH_3-activated lithiation α to nitrogen.

of an asymmetric synthesis of chiral aminoferrocenes by using chiral diamines to mediate deprotonation, since (−)-sparteine-mediated lithiation of **12**,[23] **15**,[24] and **16**[21] at −78 °C[25] provides products in appreciable enantiomeric purity (70−89% ee). While the above cases involve deprotonation of formally sp^3-hybridized carbon, the BF_3-activated[26] lithiation of aromatic sp^2-hydridized positions has until recently[27] been limited to pyridines.[28] To the best of our knowledge, the method has not been extended to aminoferrocenes with prochiral sp^2 positions.

To check the feasibility of this approach, dimethylaminoferrocene[29] (**17**) was prepared as a test substrate by reductive amination of aminoferrocene[30] with paraformaldehyde ($NaBH_3CN$/AcOH). A control experiment in which **17** was treated with 2 equiv of *n*-BuLi in THF at 0 °C for 2 h followed by addition of TMSCl resulted only in recovery of starting material. Similarly, precomplexation of **17** with an equimolar amount of BH_3·THF followed by sequential deprotonation and TMSCl quench afforded only a trace amount of the 2-trimethylsilyl adduct. Significantly better results were obtained when BF_3·OEt_2 was used. Addition of 1 equiv of BF_3·OEt_2 to a solution of **17** in THF at 0 °C resulted in a rapid color change from orange to yellow, presumably as a result of the formation of zwitterion **18** (Scheme 1). After the solution was cooled to −78 °C, 1 equiv of *n*-BuLi was added and the reaction mixture was warmed to −40 °C for 1 h. At this temperature, a distinct color change from yellow to orange-red was observed, indicating the formation of the putative 2-lithioferrocene. Addition of TMSCl at −78 °C provided 2-trimethylsilyl dimethylaminoferrocene **19a** in excellent yield after purification (93%).

By the same route, carbon electrophiles such as benzophenone, phenyl isocyanate, and dimethylformamide provided the corresponding alcohol **19b**, amide **19c**, and aldehyde **19d** in 87, 93, and 76% yields, respectively. Heteroatoms could also be also readily introduced. Thus, quench of the 2-lithioferrocene with triethylborate gave **19e** in 84% yield after transesterification with pinacol. Similarly, Ph_2PCl quench

(10) For a summary of these and other methods, see: (a) Perseghini, M.; Togni, A. In *Science of Synthesis*; Lautens, M., Ed.; Georg Thieme-Verlag KG: Stuttgart, Germany, 2001; Vol. 1, pp 889−929.

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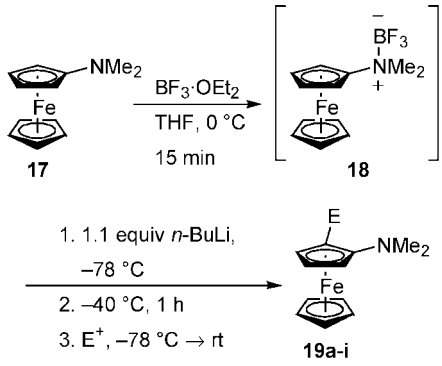
Scheme 1

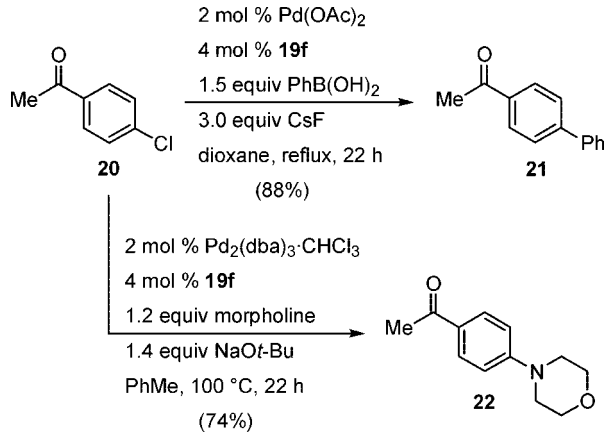


E^+	E	Product	yield, %
TMSCl	TMS	**19a**	93
Ph_2CO	Ph_2COH	**19b**	87
PhNCO	PhNHCO	**19c**	93
DMF	CHO	**19d**	76
$B(OEt)_3$	Bpin	**19e**	84
Ph_2PCl	Ph_2P	**19f**	77
$(PhS)_2$	PhS	**19g**	82
Me_3SnCl	Me_3Sn	**19h**	91
$(ICH_2)_2$	I	**19i**	94

provided **19f** (77% yield), a rare example of a 1,2-substituted ferrocenyl aminophosphine.[31] The corresponding phenyl sulfide (**19g**), stannane (**19h**), and iodide (**19i**) were also prepared in yields ranging from 82 to 94%.

Preliminary experiments have indicated that aminophosphine **19f** is an effective ligand for promoting Suzuki−Miyaura and aryl amination reactions of aryl chlorides. Cross-coupling of 4-chloroacetophenone (**20**) with phenylboronic acid in the presence of 2 mol % $Pd(OAc)_2$ and 4 mol % **19f** gave the corresponding biaryl **21** in 88% isolated yield (Scheme 2). Likewise, amination of **20** with morpholine was catalyzed

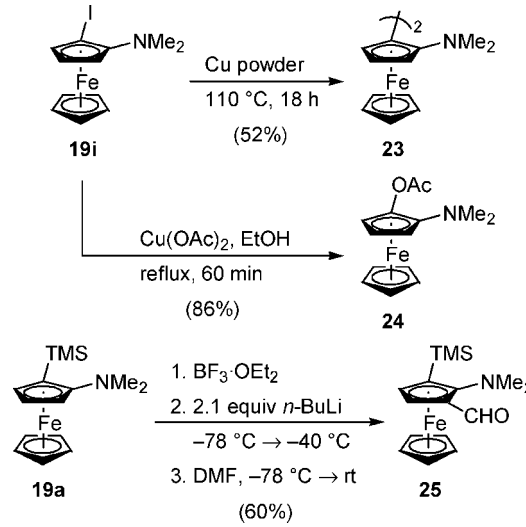
Scheme 2



by 2 mol % of $Pd_2(dba)_3$·$CHCl_3$ and 4 mol % of **19f** to afford amine **22** in 74% yield. In comparison, 4-bromoacetophenone gave **21** and **22** in 92% and 77% yields, respectively. These yields compare favorably to those reported by Buchwald and co-workers using a biaryl aminophosphine ligand in similar transformations.[32]

Ullmann homocoupling[33] of iodide **19i** with copper powder at 110 °C gave 1,1″-diaminobiferrocene **23** in 52% yield as a 1:1 mixture of separable *rac* and *meso* stereoisomers (Scheme 3). Notably, *rac*-**23** is an unprecedented[34]

Scheme 3



planar chiral ferrocenyl analogue of the axial chiral *N*,*N*,*N*′,*N*′-tetramethyl-2,2′-diamino-l,l′-binaphthyl ligand.[35] A related $Cu(OAc)_2$-assisted substitution[36] reaction of **19i** gave the 2-acetoxy aminoferrocene **24** in 86% yield, an unusual 1,2-*N*,*O*-substituted ferrocene. In addition, it was found that subjection of the 2-TMS derivative **19a** to another BF_3-activated lithiation sequence (2 equiv of *n*-BuLi, THF, −78 °C) followed by DMF quench afforded the contiguously 1,2,3-substituted formyl animoferrocene **25** in 60% yield (Scheme 3). This result may have future implications for the preparation of antipodes of enantiomerically enriched products **19b**−**i** by desilylation of congeners of **25**.[37]

It is worth noting that for all lithiations of **17**·BF_3 and **19a**·BF_3 electrophile quench occurred exclusively *ortho* to

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(32) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722.
(33) Fanta, P. E. *Synthesis* **1974**, *n/a*, 9.
(34) SciFinder erroneously returns the following paper as containing an example of a 1,1″-diaminobiferrocene: (a) Meleshonkova, N. N.; Moiseev, S. K.; Postnov, V. N.; Klimova, E. I. *Metalloorg. Khim.* **1991**, *4*, 111.
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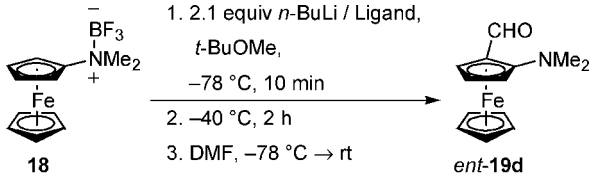
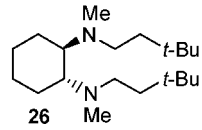
(37) Metallinos, C.; Szillat, H.; Taylor, N. J.; Snieckus, V. *Adv. Synth. Catal.* **2003**, *345*, 370.

the dimethylamino group. This regioselectivity implies an organized transition state involving complexation[38] of the alkyllithium to the BF_3 moiety during deprotonation. If this is true, the above substrates should be amenable to asymmetric lithiation mediated by chiral diamine additives. To this end, (−)-sparteine,[9] (*S*,*S*)-*N*,*N*,*N*′,*N*′-tetramethylcyclohexane-1,2-diamine (TMCDA),[39] and (*R*,*R*)-**26**[40] (Scheme 4) were evaluated for their ability to deprotonate **18** asymmetrically at low temperature. For the first two ligands, the formyl derivative *ent*-**19d** was obtained in moderate yield (43% or 64%), but only low enantiomeric purity (12% and 10% ee, respectively). The bulkier TMCDA derivative (*R*,*R*)-**26**, a (+)-sparteine surrogate, gave *ent*-**19d** in 71% yield and 22% ee.[41]

Scheme 4



Ligand	yield, %, *ent*-**19d**	er, *ent*-**19d**
(–)-sparteine	43	56:44 (12% ee)
(*S*,*S*)-TMCDA	64	55:45 (10% ee)
 **26**	71	39:61 (22% ee)

In conclusion, it has been shown that tertiary aminoferrocenes undergo regioselective lithiation upon activation with BF_3•OEt_2. Electrophile quench with nine different carbon and heteroatom-based electrophiles gives products in 76−94% yield, several of which may be of interest for applications in catalysis and materials science. Structurally more diverse products may be obtained by simple copper-catalyzed coupling of iodide **19i** to give unprecedented diaminobiferrocenes (**23**) and unusual heteroatom substitution patterns (**24**). The process also allows the preparation of contiguously 1,2,3-substituted products by a subsequent activation−lithiation−quench sequence (**25**). In addition, the electron-rich aminophosphine **19f** is effective for promoting Pd-catalyzed cross-coupling reactions of 4-chloroacetophenone with phenylboronic acid and morpholine, which bodes well for the continuing development of this underexplored class of ligands. Finally, asymmetric synthesis of products **19** is possible in principle, although the current enantiomeric ratios are low. An increase in enantioselectivity and expansion of the scope of this method to additional aminoferrocenes will be investigated and reported in due course.

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Supporting Information Available: Experimental procedures and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(40) For improved TMCDA derivatives such as **26** in asymmetric organolithium chemistry, see: (a) Stead, D.; O'Brien, P.; Sanderson, A. *Org. Lett.* **2008**, *10*, 1409. (b) Cabello, N.; Kizirian, J.-C.; Gille, S.; Alexakis, A.; Bernardinelli, G.; Pinchard, L.; Caille, J.-C. *Eur. J. Org. Chem.* **2005**, *n/a*, 4835.

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