Chiral Metallocenes

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# Catalytic and Stereoselective *ortho*-Lithiation of a Ferrocene Derivative**

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*Dedicated to Professor Werner Uhl on the occasion of his 60th birthday*

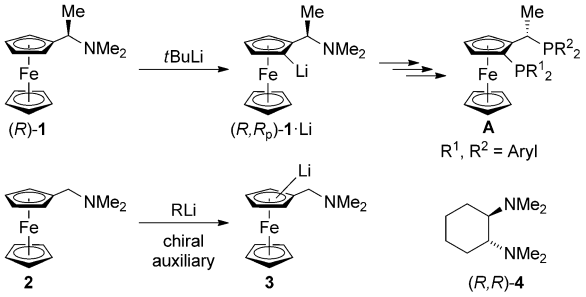
Planar chiral ferrocene derivatives are important ligands for a variety of catalysts in asymmetric synthesis.[1] Commonly, the stereoinformation is introduced into the ferrocene by a diastereo-differentiating lithiation in the *ortho*-position to a chiral directing group.[2] A large variety of heteroatom-based chiral directing groups have been evaluated in the past.[3] In contrast, achiral substituted ferrocenes that do not bear defined chiral information require the presence of an external chiral auxiliary in the lithiation step to achieve their stereoselective desymmetrization.[4]

(*R*)-*N*,*N*-Dimethyl-1-ferrocenylethylamine (**1**), or Ugi's amine, is certainly the best-known example of a ferrocene derivative with a chiral directing group, as its *ortho*-lithiation proceeds with high stereoselectivity.[5] Consequently, since the inception of its lithiation it has evolved into a crucial entry point for routes to important and efficient ferrocene-based chiral ligands (see Scheme 1).[6]

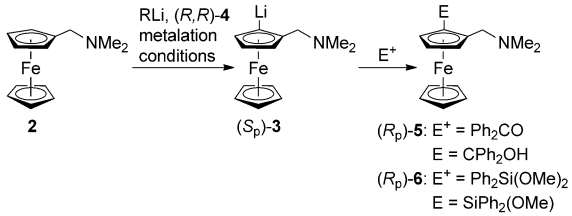
*N*,*N*-Dimethylferrocenylmethylamine (**2**) is an inexpensive, achiral analogue of Ugi's amine. Therefore, its desymmetrization by *ortho*-lithiation has to be mediated by chiral auxiliaries. Herein lies a principal problem that has limited its use as a prochiral building block to date: procedures for the asymmetric lithiation of **2** suffer from low conversion and/or stereoselectivities,[7] and even the racemic *ortho*-metalation of **2** has to rely on a bimetallic superbasic mix to achieve high yields.[8]

However, past investigations by Uemura and co-workers revealed that the diamine ligand (*R*,*R*)-tetramethyl-1,2-cyclohexanediamine (TMCDA, **4**)[9] shows some potential as a chiral additive in the desymmetrization of **2**.[7] As TMCDA is a readily available chiral auxiliary, this prompted us to reinvestigate its application in the asymmetric lithiation of the achiral aminomethylferrocene derivative **2**. Herein, our primary objective was to devise an efficient, one-pot desymmetrization route of **2** that combines high stereoselectivity and high yields.

Initially, we investigated the combination of TMCDA with different commercially available alkyl lithium reagents for the stereoselective *ortho*-lithiation of **2**. Benzophenone was selected as a suitable electrophile, as the racemic quenching product, carbinol **5**, is known.[10] Additional experiments were performed with dimethoxy(diphenyl)silane as an alternative electrophile (Scheme 2).




***Scheme 1.*** Above: *Ortho*-lithiation of chiral Ugi's amine (*R*)-**1** as an important route to chiral 1,2-functionalized ferrocenylphoshine catalysts.[5,6] Below: Alternative route starting from achiral analogue **2** in the presence of a chiral additive, such as (*R*,*R*)-TMCDA (**4**).[7]




***Scheme 2.*** TMCDA-mediated *ortho*-lithiation/quenching sequence of **2** with different metalation conditions and electrophiles (see Table 1).

During the initial screening of commercially available alkyl lithium using a two-fold excess of TMCDA in hydrocarbon/$Et_2O$ mixtures (Table 1, entries 1–4), we quickly found that *n*BuLi/**4** afforded some stereoselectivity (e.r. 84:16) but suffered from low conversion. In comparison, *t*BuLi/**4** proved the most reactive mixture but the *ortho*-lithiation proceeded with nearly no stereoselectivity (e.r. 53:47). *s*BuLi/**4** afforded a slightly improved stereoselectivity and a higher conversion at lower temperatures compared to *n*BuLi.[4b]

To our delight, switching from butyllithium reagents to *i*PrLi improved both the conversion and stereoselectivity

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***Table 1:*** Representative reaction conditions for the asymmetric, TMCDA-mediated lithiation of **2** and consecutive quenching with benzophenone to yield carbinol ($R_p$)-**5**.

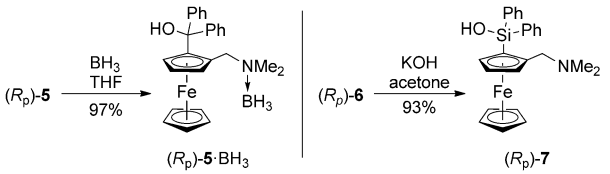
| Entry | RLi | Equiv **4** | Solvent | *t* [h] | *T* [°C] | % Yield[a] | e.r.[b] |
|---|---|---|---|---|---|---|---|
| 1 | *n*BuLi | 2 | hexane/$Et_2O$ | 6 | −30 | 28 | 84:16 |
| 2 | *t*BuLi | 2 | pentane/$Et_2O$ | 3 | −30 | 77 | 53:47 |
| 3 | *s*BuLi | 2 | cyclohexane/$Et_2O$ | 6 | −60 | 56 | 87:13 |
| 4 | *i*PrLi | 2 | pentane/$Et_2O$ | 6 | −60 | 90[c] | 95:5 |
| 5 | *i*PrLi | 2 | pentane/THF | 6 | −60 | 90[c] | 50:50 |
| 6 | *i*PrLi | 2 | pentane/toluene | 6 | −30 | –[d] | – |

[a] Isolated product. [b] Determined by chiral-phase HPLC. [c] Yield of crude product was more than 95% (determined by NMR spectroscopy). [d] Starting material recovered.

considerably. Using *i*PrLi/**4**, carbinol **5** was obtained in a stereomeric ratio of 95:5 and 90% yield after a lithiation time of 6 h at −60 °C.

If THF was used instead of $Et_2O$, *ortho*-lithiation occurred as well, albeit without any degree of stereodifferentiation. This can be attributed to the strongly coordinating properties of THF which suppress coordination of the chiral auxiliary.[11] Toluene did not promote *ortho*-lithiation of **2**, as it underwent benzylic lithiation in the presence of TMCDA (Table 1, entries 5 and 6).

The $R_p$ configuration of the 1,2-substituted quenching products was ascertained by reaction of aminocarbinol ($R_p$)-**5** with $BH_3$ and subsequent X-ray structural analysis of the resulting aminoborane derivative (Scheme 3). Switching from




***Scheme 3.*** Derivatization of the 1,2-disubstituted ferrocenes ($R_p$)-**5** and ($R_p$)-**6** and consecutive determination of the absolute configuration by X-ray structural analysis.

benzophenone to dimethoxydiphenylsilane as the electrophile afforded the corresponding silylated ferrocene ($R_p$)-**6** in excellent yields (92%) and identical stereoselectivities. The absolute configuration of ($R_p$)-**6** was confirmed by hydrolysis to and complete characterization of the resulting novel silanol ($R_p$)-**7**.[12]

The lithiated intermediate of the stereoselective *ortho*-metalation could be successfully crystallized. Storage of the reaction mixture at −78 °C for 3 d afforded a crop of bright red plates of the lithiated compound. To our surprise, the obtained aggregate was not the lithioferrocene ($S_p$)-**3** coordinated by TMCDA, but rather an ether-coordinated dimeric aggregate.

The homochiral lithioferrocene crystallizes as the dimeric etherate [($S_p$)-**3**]$_2$·$Et_2O$ from pentane/$Et_2O$ in the monoclinic crystal system, space group $P2_1$.[22] The asymmetric unit contains one complete molecule of the aggregate. [($S_p$)-**3**]$_2$·$Et_2O$ exhibits a slightly skewed *cisoid* arrangement (angle between the two planes of the two substituted Cp rings 22.4°) of the two homochiral lithioferrocene units. Both aminomethyl side-arms display lithium coordination as can be expected for an *ortho*-directing, coordinating group.[13] Only one lithium center is four-coordinate owing to the contact to the oxygen of a $Et_2O$ donor. The other lithium center only has a coordination number of three as the two neighboring ferrocene ligands shield the fourth possible coordination site (Figure 1).[14]

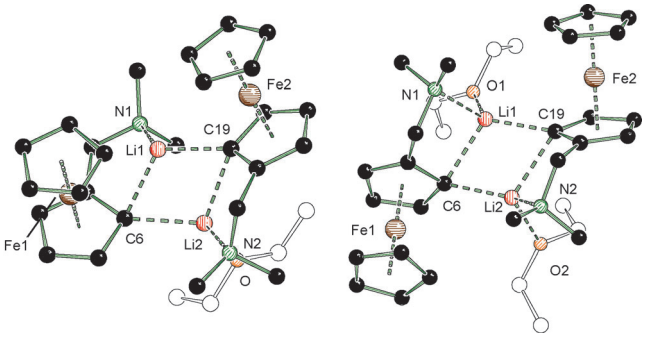



***Figure 1.*** Left: Monoetherate of the homochiral dimer [($S_p$)-**3**]$_2$·$Et_2O$. Right: Dietherate of the racemic analogue (*rac*-**3**·$Et_2O$)$_2$ (Heteroatoms and lithiated carbon centers are labeled, hydrogen atoms omitted for clarity). Selected bond lengths [Å] and angles [°]: [($S_p$)-**3**]$_2$·$Et_2O$ C6–Li2 2.089(3), C6–Li1 2.289(3), C19–Li2 2.174(3), C19–Li1 2.225(3), Li1–N1 2.132(4), Li2–N2 2.0373; Li2-C6-Li1 66.4(1), C19-Li1-C2 108.5(1), C6-Li2-C19 118.4(2). *rac*-(**5**·$Et_2O$)$_2$ C6–Li2 2.130(5), C6–Li1 2.272(5), C19–Li1 2.145(5), C19–Li2 2.366(5), Li1–N1 2.302(5), Li2–N2 2.236(5); Li2-C6-Li1 70.17(17), C15-Li1-C6 112.1(2).

For the purpose of comparison, the racemic lithiated intermediate was crystallized as well. Compound **2** was treated with *t*BuLi in $Et_2O$ at −30 °C. Storage of the reaction mixture at −78 °C for 3 d afforded lithiated species **5** as red crystalline blocks, which were identified as (*rac*-**3**·$Et_2O$)$_2$, the dietherate of dimeric **3**.

The racemic dimer (*rac*-**3**·$Et_2O$)$_2$ crystallizes from pentane/$Et_2O$ in the monoclinic crystal system, space group *C*2/*c*. The asymmetric unit contains one complete molecule of the dimeric species and one half of a co-crystallized $Et_2O$ solvent molecule. The central structural motif of the pseudo-$C_2$-symmetric dimer is a four-membered C–Li ring comprised of the two lithium centers and the two carbanionic centers of the substituted cyclopentadienyl moiety. With an angle of 123.8° between the planes of the two substituent-bearing Cp rings of the ferrocenyl moieties, the two halves of the dimer adopt a substantially more tilted, *trans*-like arrangement in relation to the central C–Li ring as compared to [($S_p$)-**3**]$_2$·$Et_2O$. Thus, the two ferrocenyl moieties are able to evade the spatial demand of their respective counterpart to accommodate for a second coordinating $Et_2O$ molecule, resulting in a coordination number of four for both lithium centers.[15]

As the presence of a ligand-centered or intramolecular center of defined chirality is an important feature to induce one preferred configuration in stereomerically enriched organolithium species,[11] we were surprised to note that the

lithiated intermediate $[(S_p)\text{-}\mathbf{3}]_2{\cdot}Et_2O$ does not feature coordination of the lithium centers by the chiral additive that had been used in its synthesis. Thus, despite its role in the asymmetric *ortho*-lithiation step, TMCDA apparently does not play a role for the aggregation of the resulting lithiated species.

This prompted us to investigate the stereoselectivity of the *ortho*-metalation of **2** using sub-stoichiometric amounts of TMCDA. While the use of catalytic amounts of chiral lithium amides in stereoselective deprotonation reactions has attracted considerable attention,[16] similar examples for workable deprotonation reactions involving organolithium reagents with substoichiometric amounts of chiral ligands are still comparatively scarce:[17] To the best of our knowledge, only one example of a stereoselective catalytic deprotonation reaction utilizing alkyl lithium bases has been previously reported. O'Brien and co-workers developed a (−)-sparteine/bispidine-based asymmetric catalytic lithiation of *N*-Boc pyrrolidine or phosphinoboranes, albeit in the presence of stoichiometric amounts of an achiral auxiliary bispidine, which supplants sparteine from the lithiated substrate.[18]

Thus, we investigated the catalytic stereoselective *ortho*-lithiation of **2** (Table 2). We found that 0.2 equiv TMCDA and 1.3 equiv *i*PrLi at −78 °C in a mixture of pentane/$Et_2O$ resulted in a near-quantitative conversion of **2** after 96 h, and upon quenching with benzophenone, in an e.r. of 81:19. If only 0.05 equiv TMCDA was used, the e.r. decreased to 71:29 while the conversion remained nearly quantitative (Table 2, entries 1 and 3). This indicates that at low temperatures in $Et_2O$, *i*PrLi is capable of slowly metalating **2** even in the absence of the coordinating diamine.

This non-stereoselective background reaction obviously competes with the stereoselective metalation mediated by sub-stoichiometric amounts of the chiral auxiliary. Interestingly, the reaction did not proceed quantitatively with catalytic amounts of TMCDA if no $Et_2O$ was added to the reaction mixture, but only to the mole fraction of the additive (Table 2, entry 4). $Et_2O$ is obviously essential for the promotion of the catalytic activity of TMCDA. Consequently, the stereoselectivity of the reaction could be improved by lowering the amount of $Et_2O$ in the reaction solvent: Performing the lithiation in a 12:1 pentane/$Et_2O$ mixture with 0.2 equiv TMCDA afforded an e.r. of 85:15 coupled with nearly quantitative conversion and a short reaction time (entry 6). Interestingly, the substitution of $Et_2O$ for MTBE under identical conditions resulted in a decrease of stereoselectivity (e.r. = 67:33; Table 2, entry 8).

If the reaction mixture was stored for longer periods at −78 °C, crystallization of the stereomerically enriched aggregate occurred. This could be proven by separation of the crystals from the mother liquor. Quenching them afforded the highly stereomerically enriched product $(R_p)$-**6** (e.r. > 99:1) in an yield of 68 % (entry 7).[19] The combination of *s*BuLi and catalytic amounts of TMCDA resulted in a decrease of conversion and a slightly lower stereoselectivity comparable to the respective stoichiometric runs described above (entries 9, 10).

Quantum-chemical calculations were performed to elucidate the proposed selectivity and catalytic activity of TMCDA during the *ortho*-lithiation cycle. For the abstraction of the two prochiral *ortho*-hydrogen atoms, the respective stereodifferentiating transition states were computed in the pre-lithiation complex [**2**·TMCDA·*i*PrLi].[20] In fact, the deprotonation leading to $(S_p)$-configuration in the lithiated intermediate is favored by 7 kJ mol$^{-1}$ in comparison to the other transition state. This difference in energies corresponds satisfactorily to the enantiomeric ratios observed in the products after quenching of metalation runs with stoichiometric amounts of TMCDA (e.r. = 86:14).

In the possible prelithiation complex [**2**·TMCDA·RLi], *i*PrLi seems to provide the ideal combination of sterical demand and reactivity to necessitate a highly stereoselective *ortho*-lithiation. In comparison, primary alkyl lithium *n*BuLi seems to be too small and *t*BuLi too bulky to induce the high selectivities that are observed when using *i*PrLi.[20]

For TMCDA to be catalytically active, it has to be released from the enantiomerically enriched *ortho*-lithiated species $(S_p)$-**3**·TMCDA to be available for the formation of further pre-lithiation complexes with unreacted starting material and *i*PrLi. From complex [**2**·TMCDA·*i*PrLi], another stereo-differentiating lithiation step can occur. The molecular structure of the lithiated intermediate suggests a possible mechanism for the release of TMCDA: Obviously, upon aggregation of the lithioferrocene **3** to a more stable dimer, a bidentate amine such as TMCDA is unsuitable to coordinate the lithium centers in the dimer owing to its increased steric demand in comparison to monodentate ether donors. In contrast, as soon as the formation of an etherate or dietherate is considered, the dimerization becomes highly favorable. This releases the chiral catalyst TMCDA from the lithiated intermediate and its further activity in the catalytic cycle (Scheme 4).

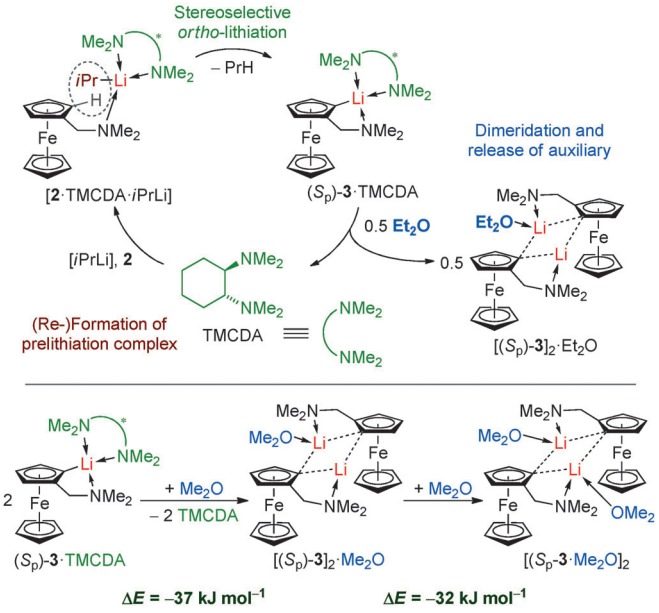
The solvent-mediated propensity of the lithiated substrate for dimerization constitutes the driving force behind the release of the

***Table 2:*** Catalytic asymmetric, TMCDA-mediated lithiation of **2** and consecutive quenching with benzophenone to yield carbinol $(R_p)$-**5**.

| Entry | RLi | Equiv **4** | Solvent | *t* [h] | *T* [°C] | % yield[a] | e.r.[b] |
|---|---|---|---|---|---|---|---|
| 1 | *i*PrLi | 0.2 | pentane/$Et_2O$ (1:1) | 96 | −78 | 86[c] | 81:19 |
| 2 | *i*PrLi | 0.1 | pentane/$Et_2O$ (1:1) | 96 | −78 | 82[c] | 78:22 |
| 3 | *i*PrLi | 0.05 | pentane/$Et_2O$ (1:1) | 96 | −78 | 83[c] | 71:29 |
| 4 | *i*PrLi | 0.2 | pentane | 96 | −78 | 17[d] | 82:18 |
| 5 | *i*PrLi | 0.2 | pentane/$Et_2O$ (12:1) | 96 | −78 | 93[c] | 86:14 |
| 6 | *i*PrLi | 0.2 | pentane/$Et_2O$ (12:1) | 2 | −78[e] | 94[c] | 85:15 |
| 7 | *i*PrLi | 0.2 | pentane/$Et_2O$ (1:1) | 192 | −78 | 68[f] | > 99:1 |
| 8 | *i*PrLi | 0.2 | pentane/MTBE (1:1) | 2 | −78[e] | 87[c] | 67:33 |
| 9 | *s*BuLi | 0.2 | cyclohexane/$Et_2O$ (1:1) | 96 | −78 | 41 | 80:20 |
| 10 | *s*BuLi | 0.2 | cyclohexane/$Et_2O$ (1:1) | 2 | −78[e] | 87 | 67:33 |

[a] Isolated product. [b] Determined by chiral-phase HPLC. [c] Yield in crude product was more than 95 % (determined by NMR spectroscopy). [d] Yield of crude product was about 20 %. [e] Intermediary warming to RT. [f] Obtained upon separation of crystals from mother liquor.




***Scheme 4.*** Above: Postulated catalytic cycle for the stereoselective *ortho*-lithiation involving dimerization of the lithiated substrate [($S_p$)-**3**] to the etherate [($S_p$)-**3**]$_2$·Et$_2$O under release of the chiral auxiliary TMCDA. Below: Computed energies for ligand exchange/dimerization processes of ($S_p$)-**3** under release of TMCDA [M052X/6-31+G(d)].[20,21]

chiral catalyst and as such constitutes another example for the importance of the structure–reactivity relationship in organolithium chemistry.

Herein, we presented an approach for the efficient and highly stereoselective desymmetrization of *N*,*N*-dimethylferrocenylmethylamine (**2**) by *ortho*-lithiation as a feasible alternative to the established lithiation of its chiral derivative, namely Ugi's amine. Furthermore, we could demonstrate that this reaction is possible in the presence of substoichiometric amounts of chiral auxiliary, marking this reaction as a new and promising example for a catalytic and stereoselective deprotonation reaction in organolithium chemistry. Ferrocene **2** can be efficiently lithiated by secondary alkyl lithium species in the presence of substoichiometric amounts of the chiral auxiliary (*R*,*R*)-TMCDA. The reaction proceeds with stereoselectivities between 85:15 (0.2 equiv TMCDA) and 71:29 (0.05 equiv TMCDA) in homogenous runs but can be boosted to more than 99:1 by separation of the enantiomerically enriched lithiated species by crystallization. The catalytic cycle is made possible by the release of the chiral promoter from the lithiated species upon its dimerization.

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[21] For a recent benchmark on computational methods in organolithium chemistry, see: V. H. Gessner, S. G. Koller, C. Strohmann, A.-M. L. Hogan, D. F. O'Shea, *Chem. Eur. J.* **2011**, *17*, 2996 – 3004. For computational purposes only, $Et_2O$ was substituted for the smaller analogue $Me_2O$ to minimize the size of the aggregates.

[22] CCDC 930668 ($[(S_p)$-**3**$]_2 \cdot Et_2O$) and CCDC 930666 ((*rac*-**3**$\cdot Et_2O)_2$) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

  