

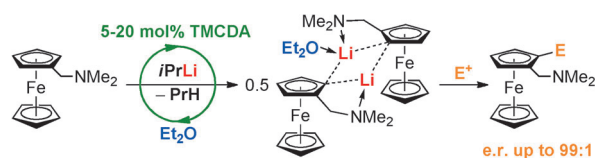
Communications



Chiral Metallocenes

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



***N,N*-Dimethylferrocenylmethylamine** can be lithiated stereoselectively by *i*PrLi in pentane/Et₂O using catalytic amounts of the chiral auxiliary (*R,R*)-TMCDA. In homogenous reactions, high e.r. values were obtained upon crystallization of the

lithiated species. The catalytic activity of TMCDA is made possible by its release from the stereomerically pure lithioferrocene as it dimerizes to a homochiral dimeric etherate.

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]

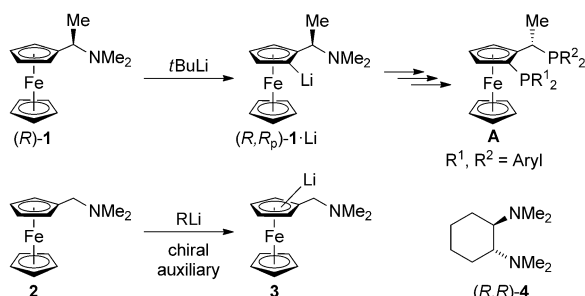
(*R*)-*N,N*-Dimethyl-1-ferrocenylethylamine (**1**), or Ugi's amine, is certainly the best-known example of a ferrocene derivative with a chiral directing group, as its *ortho*-lithiation proceeds with high stereoselectivity.^[5] Consequently, since the inception of its lithiation it has evolved into 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

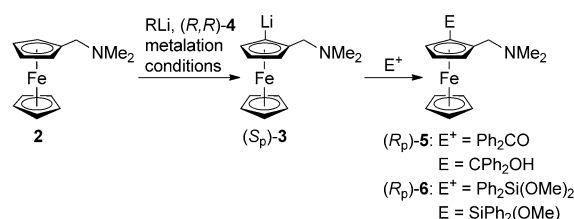
auxiliaries. Herein lies a principal problem that has limited its use as a prochiral building block to date: procedures for the asymmetric lithiation of **2** suffer from low conversion and/or stereoselectivities,^[7] and even the racemic *ortho*-metalation of **2** has to rely on a bimetallic superbasic 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 (TMCD, **4**)^[9] shows some potential as a chiral additive in the desymmetrization of **2**.^[7] As TMCD 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 TMCD 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 ferrocenylphosphine catalysts.^[5,6] Below: Alternative route starting from achiral analogue **2** in the presence of a chiral additive, such as (*R,R*)-TMCD (**4**).^[7]



Scheme 2. TMCD-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 TMCD in hydrocarbon/Et₂O 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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[**] We are grateful to the Deutsche Forschungsgemeinschaft and the European Research Area for financial support.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201303650>.

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

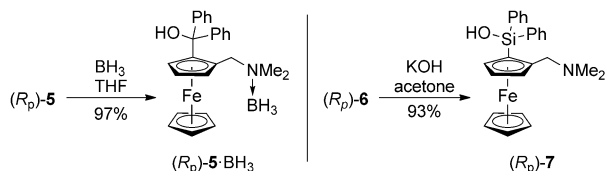
Entry	RLi	Equiv 4	Solvent	<i>t</i> [h]	<i>T</i> [°C]	% Yield ^[a]	e.r. ^[b]
1	<i>n</i> BuLi	2	hexane/Et ₂ O	6	−30	28	84:16
2	<i>t</i> BuLi	2	pentane/Et ₂ O	3	−30	77	53:47
3	<i>s</i> BuLi	2	cyclohexane/ Et ₂ O	6	−60	56	87:13
4	<i>i</i> PrLi	2	pentane/Et ₂ O	6	−60	90 ^[c]	95:5
5	<i>i</i> PrLi	2	pentane/THF	6	−60	90 ^[c]	50:50
6	<i>i</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 Et₂O, *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 TMCD (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 BH₃ 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 TMCD, but rather an ether-coordinated dimeric aggregate.

The homochiral lithioferrocene crystallizes as the dimeric etherate [(S_p)-**3**]₂·Et₂O from pentane/Et₂O in the monoclinic crystal system, space group *P*2₁.^[22] The asymmetric unit

contains one complete molecule of the aggregate. [(S_p)-**3**]₂·Et₂O 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 amino-methyl 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 Et₂O 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]

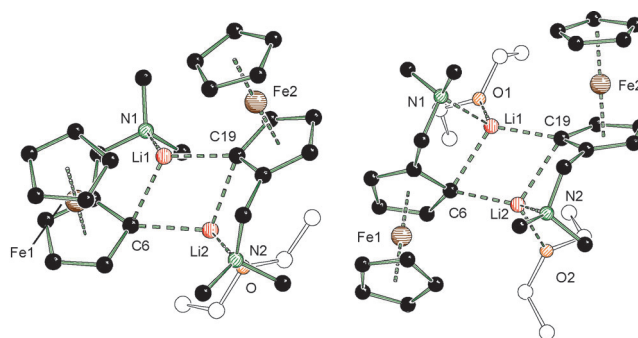


Figure 1. Left: Monoetherate of the homochiral dimer [(S_p)-**3**]₂·Et₂O. Right: Dietherate of the racemic analogue (*rac*-**3**·Et₂O)₂ (Heteroatoms and lithiated carbon centers are labeled, hydrogen atoms omitted for clarity). Selected bond lengths [Å] and angles [°]: [(S_p)-**3**]₂·Et₂O C6–Li2 2.089(3), C6–Li1 2.289(3), C19–Li2 2.174(3), C19–Li1 2.225(3), Li1–N1 2.132(4), Li2–N2 2.037(3), Li2–C6–Li1 66.4(1), C19–Li1–C2 108.5(1), C6–Li2–C19 118.4(2). *rac*-(**3**·Et₂O)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 Et₂O 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**·Et₂O)₂, the dietherate of dimeric **3**.

The racemic dimer (*rac*-**3**·Et₂O)₂ crystallizes from pentane/Et₂O 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 Et₂O 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·Et₂O. Thus, the two ferrocenyl moieties are able to evade the spatial demand of their respective counterpart to accommodate for a second coordinating Et₂O 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 $[(S_p)\text{-}3]_2\text{Et}_2\text{O}$ 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 stereo-differentiating transition states were computed in the pre-lithiation complex $[2\cdot\text{TMCDa}\cdot i\text{PrLi}]$.^[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 $[2\cdot\text{TMCDa}\cdot\text{RLi}]$, *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]

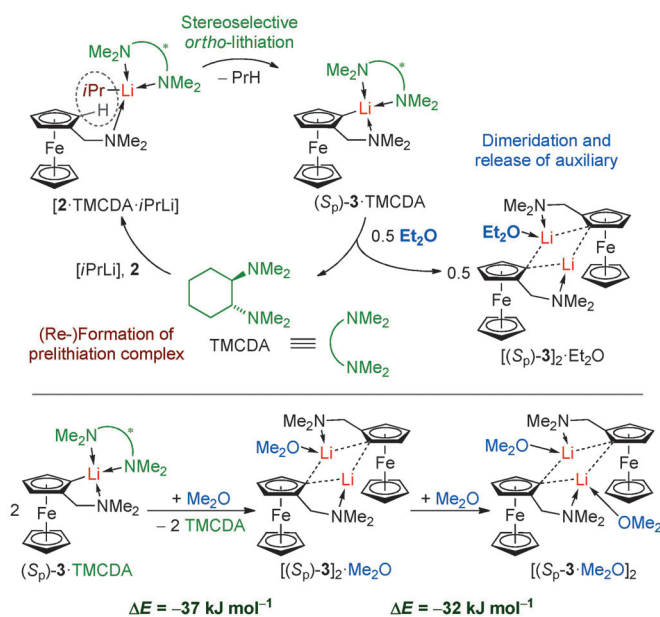
For TMCDa to be catalytically active, it has to be released from the enantiomerically enriched *ortho*-lithiated species (*S_p*)-**3**·TMCDa to be available for the formation of further pre-lithiation complexes with unreacted starting material and *i*PrLi. From complex $[2\cdot\text{TMCDa}\cdot i\text{PrLi}]$, 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>i</i> PrLi	0.2	pentane/ Et_2O (1:1)	96	-78	86 ^[c]	81:19
2	<i>i</i> PrLi	0.1	pentane/ Et_2O (1:1)	96	-78	82 ^[c]	78:22
3	<i>i</i> PrLi	0.05	pentane/ Et_2O (1:1)	96	-78	83 ^[c]	71:29
4	<i>i</i> PrLi	0.2	pentane	96	-78	17 ^[d]	82:18
5	<i>i</i> PrLi	0.2	pentane/ Et_2O (12:1)	96	-78	93 ^[c]	86:14
6	<i>i</i> PrLi	0.2	pentane/ Et_2O (12:1)	2	-78 ^[e]	94 ^[c]	85:15
7	<i>i</i> PrLi	0.2	pentane/ Et_2O (1:1)	192	-78	68 ^[f]	> 99:1
8	<i>i</i> PrLi	0.2	pentane/MTBE (1:1)	2	-78 ^[e]	87 ^[c]	67:33
9	<i>s</i> BuLi	0.2	cyclohexane/ Et_2O (1:1)	96	-78	41	80:20
10	<i>s</i> 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.



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

Received: April 29, 2013

Published online: ■■ ■■, ■■■■

Keywords: carbanions · lithiation · metallocenes · stereoselective catalysis · structure elucidation

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