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Synthesis and Stereoselective Reactions of New Stable α-Ferrocenyllithium Derivatives. An Umpolung of the Ferrocene Reactivity**

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The design of new chiral ligands for asymmetric catalysis is an important synthetic goal. In particular, ferrocenyl ligands have attracted considerable attention and numerous synthetic methods for the preparation of new ferrocenyl derivatives have been developed.[1] Many useful ferrocenyl ligands can be prepared by the nucleophilic substitution of readily available α-ferrocenylcarbinol derivatives of type **1** (Scheme 1).[1, 2] According to Ugi[2b] these substitutions proceed with retention of configuration via a chiral cationic intermediate **2** and lead to products of type **3**. Herein we report the umpolung of this reactivity. It was possible to generate α-ferrocenyllithium derivatives[3] of type **4** and to react them stereoselectively with different electrophiles to give the new chiral ferrocenyl derivatives **5** with complete retention of configuration.

In preliminary experiments the ferrocenyl thioether **6a** (95% *ee*) was treated with lithium naphthalenide (3 equiv) at

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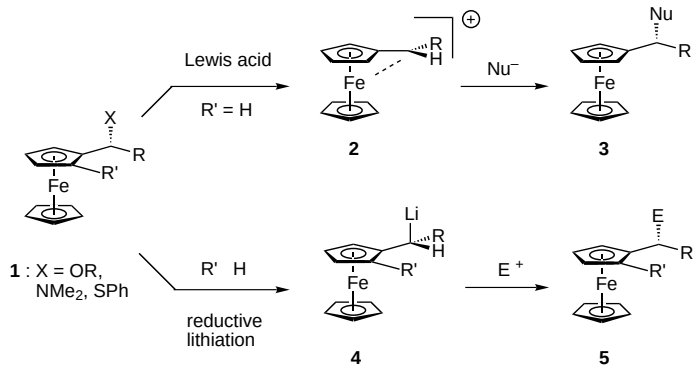
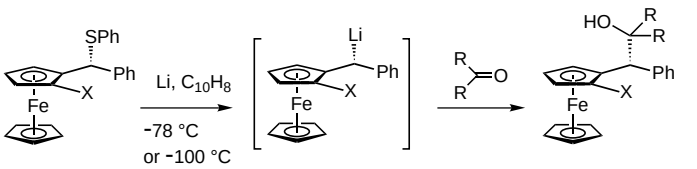


Scheme 1.

low temperature in the presence of 3-pentanone (2 equiv). The reductive lithiation[4] proceeded smoothly at $-78\,^{\circ}C$ (Scheme 2) to afford the desired tertiary alcohol **7a** in 80% yield and 36% *ee*, which showed that the intermediate benzylic lithium reagent has only a limited stability. The stability of the anionic intermediate configuration could be improved by lowering the temperature to $-100\,^{\circ}C$, and this afforded **7a** in 70% yield and 60% *ee*. However, a dramatic improvement of the stereoselectivity of the reaction was observed by introduction of a substituent at position 2 of the ferrocenyl ring. Thus, treatment of 2-trimethylsilyl substituted thioether **6b**[5] with lithium naphthalenide (2.2 equiv)[6] or an excess of lithium powder in the presence of a catalytic amount of naphthalene[7] afforded, after quenching with acetone, the desired alcohol **7b** with complete retention (93%; *de* > 96%; 95% *ee*).[8]



6a : X = H; 95 % *ee*

-78 °C : **7a** : X = H; R = Et; 80 %; 36 % *ee*

- 100 °C : **7a** : X = H; R = Et; 70 %; 60 % *ee*

6b : X = $SiMe_3$; 95 % *ee*

- 78 °C : **7b** : X = $SiMe_3$; R = Me; 93 %; *de* > 96 %; 95 % *ee*

Scheme 2. Reductive lithiation of α-ferrocenyl thioethers **6a** and **b.**

This behavior proved to be general and several electrophiles (ketones, benzaldehyde, benzyl bromide, or chlorodiphenylphosphane) reacted stereospecifically[9] under these conditions to give the ferrocene derivatives **7b–f** in excellent yields (Table 1). Especially interesting is the reaction of **6c** (X = PPh_2, 98.5% *ee*)[5] under our conditions, since after quenching with $ClPPh_2$ and protection with $BH_3 \cdot SMe_2$, the borane-protected, Josiphos-type diphosphane[10] **7g** (entry 6 of Table 1) was obtained in 56% yield (*de* > 96%). Alternatively, it was possible to generate the lithium intermediates of type **4** by treating the thioether **6b** directly with *n*BuLi (1.2 equiv) in THF ($-78\,^{\circ}C \rightarrow$RT, 0.5h at RT). After quenching with benzyl bromide the expected product **7f** was isolated in 95% yield as a single diastereoisomer.

In order to simplify the synthetic procedure we examined if the more readily available corresponding α-ferrocenyl ethers **9a,b** can be used for the reductive lithiation (Scheme 3). Reaction of **8**[11] with *t*BuLi (1.1 equiv) in diethyl ether at $-78\,^{\circ}C$ and then stirring at RT for 1 h followed by quenching with Me_3SiCl or $ClPPh_2$ afforded the ferrocenyl ethers **9a** (57% yield; d.r. = 95:5) and **9b** (71% yield; d.r. = 98:2), respectively. Treatment of the major diastereoisomer **9a,b** (isolated after chromatography) with lithium naphthalenide (2.2 equiv, $-78\,^{\circ}C$, 10 min) and quenching with benzyl bromide, $ClPPh_2$ (followed by $BH_3 \cdot SMe_2$), 2-chloromethylpyridine, or acetone provided the desired chiral ferrocene derivatives **7b** and **7f–i** in good to excellent yields with complete retention of the stereochemical information.

Finally, we extended this methodology to the generation of α-ferrocenylalkyllithium species (R = alkyl) starting from α-ferrocenylalkylamine derivatives **10a** and **b** (Scheme 4). These substrates are well suited for the generation of α-ferrocenyllithium reagents bearing alkyl substituents. Thus, treatment of the aminoferrocenes **10a**, **b** with ethyl chloroformate[12] (1.2 equiv, RT, 1 h)[13] followed by the addition of lithium naphthalenide (5 equiv, $-78\,^{\circ}C$, 10 min) afforded the desired lithium reagent, which was trapped successfully with acetone or benzyl bromide to yield the chiral ferrocene derivatives **11a–c** as single diastereoisomers.

The fact that all reactions proceed with complete retention of configuration would be difficult to explain if an epimeric mixture of organolithium intermediates of type **4** were present. We would then expect different stereoselectivities depending on the electrophile used.

The high stereoselectivity observed can be explained as a result of the presence of a sterically demanding substituent at

Table 1. Chiral ferrocenes **7b–g** obtained by the reductive lithiation of the α-ferrocenyl thioethers **6b,c** and quenching with an electrophile.

Entry	Thioether	X	Electrophile	Method[a]	Product	Yield[b] [%]	*de*[c] [%]	*ee*[d] [%]
1	**6b**	TMS	acetene	A	**7b**	93	> 96	95
2	**6b**	TMS	EtCOEt	A	**7c**	86	> 96	95
3	**6b**	TMS	PhCHO	A	**7d**	71	–[e]	–
4	**6b**	TMS	$ClPPh_2$[f]	B	**7e**	67	> 96	96
5	**6b**	TMS	$PhCH_2Br$	B	**7f**	90	> 96	95
6	**6c**	PPh_2	$ClPPh_2$[f]	B	**7g**	56	> 96	nd[g]

[a] Method A: Barbier type conditions with an excess of lithium powder and a catalytic amount of naphthalene. [b] Yield of isolated analytically pure products. [c] Determined by ^1H NMR spectroscopy (just one diastereoisomer detected). [d] Determined by HPLC on a chiral phase (Chiralcel OD, OJ, or AD columns; Daicel Chemical Industries). [e] The alcohol **7d** is a diastereoisomeric mixture of epimers (68:32). [f] The reaction mixture is treated with $BH_3 \cdot SMe_2$ before work-up to afford the borane–phosphane complex as the product. [g] The enantiomers could not be separated by HPLC analysis.

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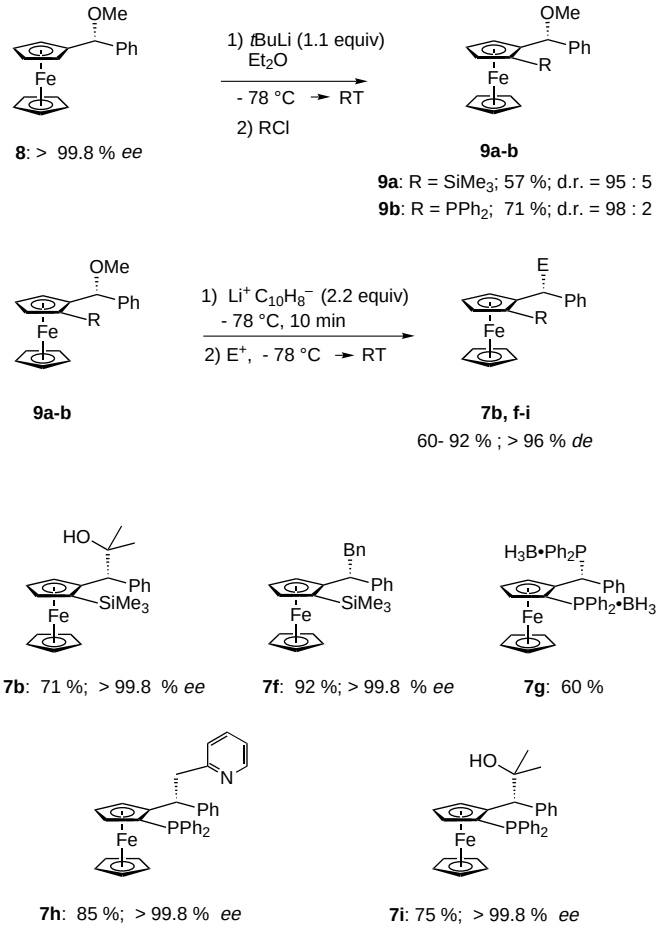


8: > 99.8 % *ee*

9a-b

9a: R = $SiMe_3$; 57 %; d.r. = 95 : 5
9b: R = PPh_2; 71 %; d.r. = 98 : 2

9a-b

7b, f-i
60- 92 % ; > 96 % *de*

7b: 71 %; > 99.8 % *ee*

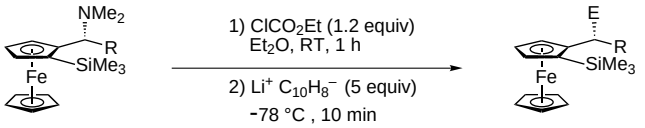
7f: 92 %; > 99.8 % *ee*

7g: 60 %

7h: 85 %; > 99.8 % *ee*

7i: 75 %; > 99.8 % *ee*

Scheme 3. Chiral ferrocene derivatives **7b** and **f-i** obtained by the reductive lithiation of the α-ferrocenyl ethers **9a**,**b** followed by the reaction with an electrophile.



10a : R = Me

10b : R = *i*Pr

11a : R = Me; E = $C(OH)Me_2$; 44 %; > 96 % *de*

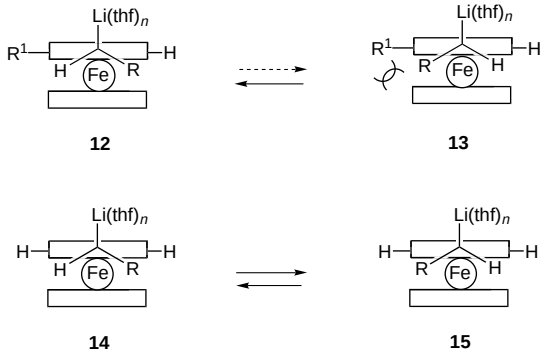
11b : R = Me; E = CH_2Ph ; 80 %; > 96 % *de*

11c : R = *i*Pr; E = CH_2Ph; 50 %; > 96 % *de*

Scheme 4.

the Cp ring (Scheme 5). In this case, the substituent R^1 (R^1 = PPh_2 or $SiMe_3$) does not allow the epimerization of the lithium reagent. Thus, the lithium intermediate **12** does not equilibrate with **13** even after warming up to room temperature. In the absence of this substituent the organolithium intermediate **14** is not configurationally stable and equilibrates with the enantiomeric species **15**, which results in a low enantioselectivity (see Scheme 2 and Scheme 5).

In summary, we have developed a synthesis of α-ferrocenyllithium reagents that react with complete retention of configuration with various electrophiles. This new methodology represents an umpolung of the usual reactivity at the α position of ferrocenes and allows an entry to new types of chiral ferrocenyl ligands.



12 **13**

14 **15**

Scheme 5.

Experimental Section

Method A:[4, 7] A solution of **6b** (150 mg, 0.33 mmol) and acetone (0.05 mL, 0.66 mmol) in dry THF (2 mL) was added dropwise at $-78\,^{\circ}C$ under an argon atmosphere to a solution of lithium powder (60 mg, 8.6 mmol) and naphthalene (10 mg, 0.078 mmol) in dry THF (3 mL). The mixture was stirred for 10 min and then carefully quenched with MeOH. After usual work-up and flash chromatography **7b** was isolated in 93 % yield (124 mg, orange oil).

Method B:[6] To a solution of **6b** (150 mg, 0.33 mmol) in dry THF (2 mL) was added dropwise under an argon atmosphere, 0.8 mL (0.72 mmol, 2.2 equiv) of a lithium naphthalenide solution (0.9 M in THF). The dark red mixture was stirred for 10 min at $-78\,^{\circ}C$ before benzyl bromide (0.08 mL, 0.67 mmol, 2 equiv) was added dropwise. The reaction was stirred for a further 10 min and then allowed to warm up to RT, and quenched with water. After usual work-up and flash chromatography **7f** was isolated in 90 % yield (130 mg, orange oil).

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[8] Efforts are in progress to determine the exact structure of ferrocenyllithium derivatives of type **4**.

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[9] Removal of the TMS group in **7f** leads to the (*R*)-(α-benzylphenylmethyl)ferrocene (95% *ee* determined by HPLC on a chiral phase (Chiracel OD column)). The same enantiomer was obtained by a nucleophilic substitution of the (*R*)-(α-acetoxyphenylmethyl)ferrocene with benzylzinc bromide,[2d] which proved the retention of configuration in the former reaction.
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[11] Synthesis of **8**: a) see reference [5a]; b) see reference [5b]; c) MeOH, AcOH (cat.), 100%, 97% *ee*; d) Recrystallization in MeOH, 83%, *ee* > 99.8%.
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Nucleotide Platination Induced by Visible Light**

Nicole A. Kratochwil, John A. Parkinson, Patrick J. Bednarski, and Peter J. Sadler*

There is increasing interest in the development of photoactive metal complexes as luminescent markers and photocleaving agents for DNA,[1] and in the design of photosensitisers for photodynamic therapy.[2, 3] Photosensitisers catalyze the production of reactive singlet oxygen and therefore rely on the presence of oxygen in the target tissue. An advantage of photo-chemotherapeutic agents is that they can be activated selectively at the target site, thereby minimizing the side-effects of chemotherapy. We are investigating the design of oxygen-independent photoactivated metallodrugs, in particular photoactive analogues of the anticancer drug cisplatin, *cis*-$[PtCl_2(NH_3)_2]$. Iodo complexes of Pt^{IV} are promising in this respect because their cytotoxicity against tumor cells is potentiated by visible light.[4] We show here that stereospecific reactions between a diiododiamine–Pt^{IV} complex and the nucleotide guanosine 5′-monophosphate (5′-GMP) can be induced by visible light, and that photoactivation can be controlled by the axial ligands, which will allow fine-tuning of the photoreactivity of this class of complexes. This appears to be the first report of nucleotide platination induced solely by visible light.

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Photoreactions of the ^{15}N-labelled diiodo–Pt^{IV} complexes ^{15}N-**1** and ^{15}N-**2** in the presence of 5′-GMP were followed by 1D ^1H, 2D [^1H,^{15}N] HSQC and 2D [^1H,^{15}N] HSQC-TOCSY NMR spectroscopy. Photo-irradiation was carried out using an argon ion laser equipped with a fibre optic link designed to deliver light directly into the sample within the magnet of the NMR spectrometer. No reactions between these Pt complexes and 5′-GMP occurred within 30 h in the dark.

trans,cis-$[Pt(OCOCH_3)_2I_2(^{15}N\text{-en})]$ ^{15}N-**1**

trans,cis-$[Pt(OH)_2I_2(^{15}N\text{-en})]$ ^{15}N-**2**

The time-course of the photoreaction of the acetato complex **1** ($\varepsilon_{457.9} = 327\,M^{-1}cm^{-1}$) with 1 equivalent of 5′-GMP (200 μM in water, 298 K, pH 6.2)[5] was observed by 1D ^1H NMR spectroscopy (Figure 1; for the structures and numbering of the complexes see Scheme 1A). After irradiation with low-power visible light ($\lambda_{irr} = 457.9$ nm, $12.2 \times 10^{-3}\,J\,s^{-1}$), the signals for **1** (CH_2: $\delta = 2.7$; CH_3: $\delta = 2.05$) decreased in intensity, and two new multiplets in the en(CH_2) region of the spectrum at $\delta = 3.01$ (***3a***) and $\delta = 2.60$ (***3b***), and a singlet at $\delta = 3.08$ (***4***) appeared. Two new singlets that could be assigned to coordinated acetate ($\delta = 2.09$; ***3***) and to released acetate ($\delta = 1.99$) were detected in the methyl region. During later stages of the photoreaction a new singlet was observed at $\delta = 8.52$, which was assigned to H8 of Pt-bound 5′-GMP (free 5′-GMP: $\delta = 8.10$). A high frequency shift such as this for the H8 resonance of 5′-GMP is typical of metal coordination to N7 of 5′-GMP.[6]

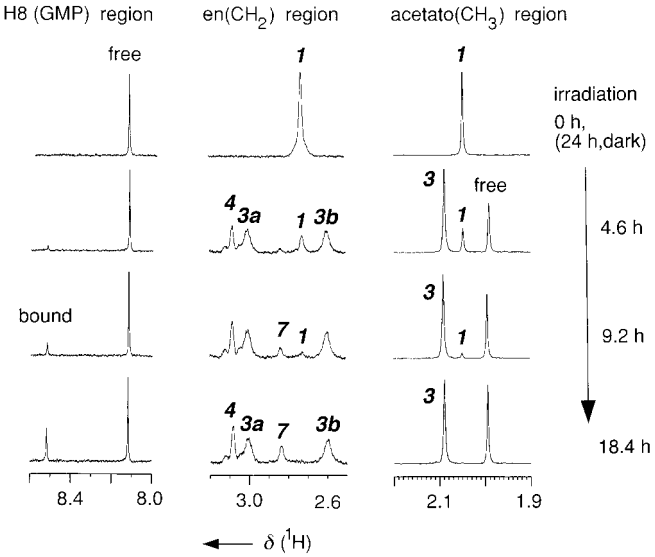

Figure 1. Selected regions of 500 MHz 1D ^1H NMR spectra acquired during the photoreaction ($\lambda_{irr} = 457.9$ nm) of **1** in the presence of 5′-GMP at irradiation times of 0, 4.6, 9.2, and 18.4 h (and 24 h in the dark), pH 6.2, 298 K. Binding of 5′-GMP is preceded by initial light-induced ligand exchange of **1** to give **3**.

The pathway of the photoinduced reaction of ^{15}N-**1** with 5′-GMP was further elucidated by 2D [^1H,^{15}N] HSQC and HSQC-TOCSY NMR spectroscopy (Figure 2). After 1 h irradiation (Figure 2A) the cross peak for **1** with a chemical

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