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The Ferrocenylmethyl(Fem) Group as a Highly Lipophilic and Chromophoric Group for the Masking of Peptide Bonds**

By *Heiner Eckert** and *Christoph Seidel*

In the course of exploring a new strategy for the chemical synthesis of peptides,[1] which is characterized by the use of strongly lipophilic and chromophoric groups, we have developed a method for the masking of peptide bonds. The treatment of the chemically reactive functional groups is largely covered by the conventional protecting group methodology.[2] Peptide bonds, on the other hand, are particularly "physically reactive"—i.e., they exert a great effect on the secondary structure and solubility of a peptide. Such conformational effects often make the synthesis of peptides difficult. *Weygand* et al. have attempted to prevent[3] these effects by using the 2,4-dimethoxybenzyl group.[3a] *Ugi* et al. recognized the preparative value of the lipophilic and chromophoric ferrocenylalkyl group in stereospecific reagents.[3b] The *tert*-butoxycarbonylation of the peptide bond in a prolyl-glycine derivative was recently described by *Ragnarsson* et al.[3c]

The chromophoric (yellow) ferrocenylmethyl(Fem) group[4] makes possible an economically practical, regenerative masking of peptide bonds in order to suppress or manipulate the secondary structures of peptide derivatives and in order to solubilize them lipophilically. The Fem group can be introduced by facile catalytic reductive alkylation of amino acids or amino acid esters with commercially available ferrocenecarbaldehyde **1** and hydrogen. The highly selective palladium(II) phthalocyanine[5] may be used as hydrogenation catalyst. Whereas **1** is only reduced extremely slowly, the azomethine **2** obtained from **1** and the amino acid or the amino acid ester undergoes hydrogenation within a few hours. The Fem-amino acids, or their esters, are thereby formed in high yields without racemization (Table 1) and without undergoing further reduction. The racemization-free course of the reaction is exemplified by reaction of the amino acid phenylalanine, which is highly susceptible to racemization. After isolation and subsequent hydrogenation of ferrocenylmethylene-Phe-O*t*Bu, the ester Fem-Phe-O*t*Bu is deblocked using trifluoroacetic acid and the specific optical rotation of the free phenylalanine is measured to be $[\alpha]_D^{25}$ −32.7. This value is identical with that of the starting phenylalanine. Fem-amino acids are very stable; for example, Fem-Gly-OMe can be distilled (b.p. = 235 °C/0.1 torr) quantitatively

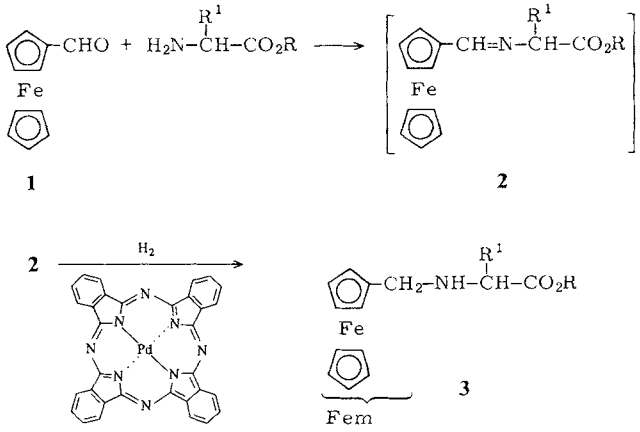

Table 1. Synthesis of Fem-amino acids and derivatives (**3**, R = H, Me, *t*Bu or Na).

	Fem–NH–CHR¹–CO₂R **3**	Yield [%]	M.p. [°C]	$[\alpha]^{25}$ (λ [nm])
3a	Fem–Gly–OH	73	198	—
3b	Fem–Gly–OMe	60	oil	—
3c	Fem–Ala–ONa	83	232	−38.3 (546)
3d	Fem–Ala–OMe	71	oil	−73.3(546); −53.4 (589)
3e	Fem–Phe–ONa	82	305	− 9.5(546)
3f	Fem–Phe–O*t*Bu	81	oil	−13.8 (589)
3g	Fem–Leu–O*t*Bu	85	oil	−26.7 (546)
3h	Fem–Val–O*t*Bu	89	oil	−34.0 (546); −23.5 (589)

without undergoing decomposition. In contrast, the corresponding "free" H-Gly-OMe ester undergoes quantitative decomposition within a few hours at room temperature to give 2,5-diketopiperazine.

The coupling of *N*-protected amino acids with Fem-amino acid derivatives **3** to give peptides **4**, which have Fem-masked peptide bonds, can be carried out conveniently according to the DCCI method[2a,6] within a few hours (Table 2). The yields are generally high. Even the coupling of Tcboc-Val-OH[6] with Fem-Val-O*t*Bu **3h**, which is a sterically highly hindered reaction, affords **4f** in 50% yield. The investigation of the racemization[2a] during the coupling of Boc-Gly-Fem-Ala-OH with H-Leu-O*t*Bu using DCCI showed that the Izumiya test peptide derivative Boc-Gly-Fem-Ala-Leu-O*t*Bu (92% yield) contained 27% D-alanine and 73% L-alanine. The comparable reaction without the Fem group under the same conditions afforded the test peptide derivative (84% yield) with 12% D-alanine and 88% L-alanine. This observation must be taken into consideration in fragment condensations, which are subject to racemization. In contrast, the coupling of Tcboc-Fem-Ala-OH with H-Leu-O*t*Bu (85% yield) gives a product with <0.02% D-alanine. This means that no racemization occurs in the coupling of *N*-urethaneprotected Fem-amino acids, which makes a stepwise peptide synthesis relatively easy.

Intermediates that contain the Fem group can be purified by column chromatography on inexpensive silica gel with hexane-containing solvent systems (high resolution). This is due to their extremely high lipophilicity[7] and their strong yellow color. The Fem group may be cleaved with trifluoroacetic acid/β-thionaphthalene in dichloromethane

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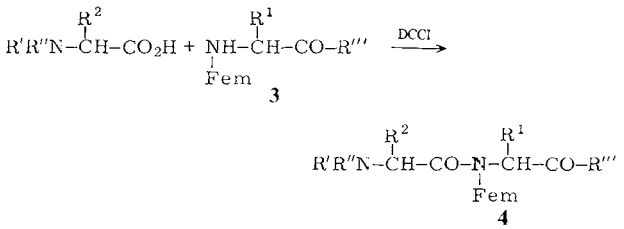

Table 2. Coupling reactions with Fem-amino acid derivatives **3** to give peptides **4** containing Fem-protected peptide bonds [6].

Starting materials	Products	Yield [%]
Z–Ala–OH + Fem–Phe–O*t*Bu **3f**	Z–Ala–Phe–O*t*Bu (Fem) **4a**	83
Boc–Gly–OH + Fem–Ala–OMe **3d**	Boc–Gly–Ala–OMe (Fem) **4b**	91
Boc–Gly–OH + Fem–Ala–Leu–O*t*Bu	Boc–Gly–Ala–Leu–O*t*Bu (Fem) **4c**	75
Tcboc–Phe–OH + Fem–Leu–O*t*Bu **3g**	Tcboc–Phe–Leu–O*t*Bu (Fem) **4d**	93
Tcboc–Fem–Gly–OH + Fem–Gly–OMe **3b**	Tcboc–Fem–Gly–Gly–OMe (Fem) **4e**	80
Tcboc–Val–OH + Fem–Val–O*t*Bu **3h**	Tcboc–Val–Val–O*t*Bu (Fem) **4f**	50

within 2–4 h at the same rate as that observed for cleavage of the Boc or O*t*Bu groups.

Experimental Procedure

Fem-amino acid esters 3 (R = alkyl): A mixture consisting to the amino acid amino acid (10 mmol), **1** (2.14 g, 10 mmol), anhydrous Na_2CO_3 (2.12 g, 20 mmol), and palladium(II) phthalocyanine (0.06 g, 0.1 mmol)/[5] in 40 mL of methanol was saturated with H_2 and then vigorously stirred under H_2 (from a gas burette) for several hours, until gas absorption stopped. The suspension was filtered through a 4-cm thick layer of Na_2SO_4, which is then washed with methanol, and the filtrate is concentrated to 10–20 mL. Addition of ether results in precipitation of the sodium salt of the Fem-amino acid. This is recrystallized from water or methanol/water, affording yellow crystals.

Fem-amino acid esters 3, (R = alkyl): A mixture consisting of the amino acid ester or its hydrochloride (10 mmol), **1** (2.14 g, 10 mmol), and palladium(II) phthalocyanine (0.06 g, 0.1 mmol) [5] in 10 mL of methanol and 20 mL of ethyl acetate (triethylamine (0.8 mL, 11 mmol) added in the case of the amino acid ester hydrochlorides) was saturated with H_2 and vigorously stirred under H_2 (from a gas burette) for several hours, until gas absorption stopped. The reaction mixture was then filtered through a 4-cm thick layer of Na_2SO_4, which was washed with ethyl acetate, and the filtrate was concentrated. The residue was chromatographed on silica gel with hexane/ethyl acetate (ca. 3 : 1). A deep orange oil was obtained.

Coupling reaction to give 4: The *N*-urethane-protected amino acid (10 mmol) and the Fem-amino acid ester **3** (10 mmol), R = alkyl, were cooled to −20 °C in 40 mL of dichloromethane. A solution of DCCI (2.27 g, 11 mmol) in 10 mL of dichloromethane was added over 5 min and the cold bath was then removed. After 12 h, the dicyclohexylurea was filtered off and the filtrate was concentrated. The residue was chromatographed on silica gel with hexane/ethyl acetate (ca. 3 : 1) [7]. A yellow solid was obtained.

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[4] We propose Fem as an abbreviation for ferrocenylmethyl.

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[6] Boc = *tert*-butoxycarbonyl, DCCI = dicyclohexylcarbodiimide, Tcboc = 2,2,2-trichloro-*tert*-butoxycarbonyl [2b], Z = benzyloxycarbonyl.

[7] The peptide derivatives **4** in Table 2 have R_F values in hexane/ethyl acetate (3 : 1) of 0.35 to 0.7 (Kieselgel 60 TLC plates).

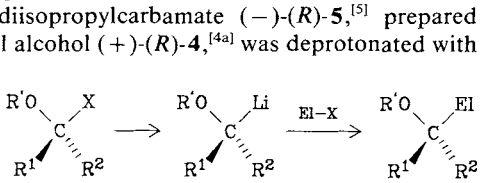
α-Deprotonation of an α-Chiral 2-Alkenylcarbamate with Retention and Lithium-Titanium Exchange with Inversion—the Homoaldol Reaction with 1,3-Chirality Transfer**

By *Dieter Hoppe** and *Thomas Krämer*

Dedicated to Professor Hans Musso on the occasion of his 60th birthday

Chiral 1-oxy alkyllithium compounds **2** (R^1, R^2 = alkyl, H) are configurationally stable,[1] and their substitution reactions with electrophiles to give **3** proceed with retention. The tin-lithium exchange[1] of stannanes **1a** has proved useful for the synthesis of **2**. In contrast, the reductive cleavage of monothioketals or monothioacetals[2] **1b** to give **2** is accompanied by racemization or epimerization, since radicals having low barriers to inversion are formed as intermediates. The simplest conceivable route—the stereospecific deprotonation of **1c** (R^1, R^2 = alkyl)—is not promising owing to the insufficient kinetic acidity of **1c**. Although resonance-stabilizing groups (e.g., R^1 = phenyl or vinyl) increase the carbon acidity of **1c**, they also increase the danger of racemization of **2** since they favor planarity and dissociation into ion pairs. We have now investigated the α-deprotonation of the optically active, α-chiral 2-alkenylcarbamate **5**[3] as well as the subsequent lithium-titanium exchange and the carbonyl addition, and report here our surprising results.

The *N*,*N*-diisopropylcarbamate (−)-(*R*)-**5**,[5] prepared from the allyl alcohol (+)-(*R*)-**4**,[4a] was deprotonated with



1a, X = $SnBu_3$
1b, X = SPh
1c, X = H

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