JOM 23037

Oxidatively induced nucleophilic capture *vs.* degradation of cyclopentadienyl iron derivatives of simple carboxylic acids and of α-amino acids. A comparative study

C. Amiens, G. Balavoine and F. Guibé

Institut de Chimie Moléculaire d'Orsay, Laboratoire de Chimie Organique des Eléments de Transition, URA-CNRS 255, Université Paris-Sud, Bât. 420, 91405 Orsay Cedex (France)

(Received March 3, 1992)

Abstract

The electrochemical behaviour and the chemical oxidation of various cyclopentadienyl iron complexes of simple carboxylic acids and of amino-protected α-amino acids have been studied in relation to several factors including the nature of the ligands on the metal (Cp, Cp*, CO, PPh_3), the nature of the oxidizing agent (one-electron oxidants such as $Cu(OTf)_2$, FcOTf and CAN or a two-electron oxidant such as NBS) and the medium effects (especially the presence or absence of nucleophilic species). With simple carboxylic acid derivatives either homolytic dissociation (leading to alkyl radicals) or nucleophilic capture of the first-formed iron radical cations is observed, depending on the reaction conditions. With α-amino acid derivatives, an oxidative degradation to aldehyde is observed invariably, which is likely to proceed through the successive and transient formation of *N*-acyl α-amino radicals and *N*-acyl iminium ions.

1. Introduction

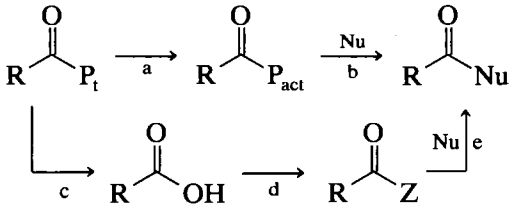
The concept of "dual function group" [1], Pt/Pact (or "activatable protecting group" [2,3]), *i.e.* of a group which is initially used to protect a given function (usually the carboxylic acid function) but may, at some appropriate time and through a specific chemical modification, be transformed into an activating entity of the same function, Pt → Pact, has found many applications in peptide chemistry [1,3]. By this strategy, direct coupling (Scheme 1, paths a, b) of a peptide fragment with various nucleophiles, including amino acid and peptide derivatives, is possible without the need of a preliminary deprotection step (Scheme 1, path c). Owing to the usually multifunctional character of peptide fragments, a convenient and specific method for this is not always available.

To the best of our knowledge, only organic fragments have been used as activatable protecting groups. It occurred to us that η^5-cyclopentadienyliron organometallic entities could serve the same purpose. Literature data show that Fp and Fp′ (Fp = $CpFe(CO)_2$, Fp′ = $CFe(PPh_3)(CO)$) derivatives of carboxylic acids are very stable in the presence of nucleophiles (a property which shows up in the low IR frequency of the acyl carbonyl vibration (about 1600 cm^{-1} for Fp′, about 1650 cm^{-1} for Fp derivatives)) and reasonably stable under acidic conditions [4]. In contrast, in the presence of various oxidizing agents, Fp′ acyl complexes are readily cleaved by nucleophilic species such as water, alcohols and amines, to give carboxylic acids, esters, and amides [4]. Although there is less information than for the Fp′ series, nucleophilic cleavage of

Correspondence to: Dr. F. Guibé.

The following abbreviations are used: Cp, cyclopentadienyl; Cp*, pentamethylcyclopentadienyl; Fp, $Cp(CO_2Fe$; Fp*, $Cp^*(CO)_2Fe$; Fp′, $Cp(CO)(PPh_3)Fe$; NBS, *N*-bromosuccinimide; CAN, ceric ammonium nitrate; $2(NH_4^+)\cdot[Ce(NO_3)_6]^{2-}$; FcOTf, ferricinium triflate; Boc, terbutyloxycarbonyl; Fmoc, 9-fluorenylmethyloxycarbonyl. The shorthand representation of iron acyl derivatives of amino acids follows that generally used in peptide chemistry and starts with the α-amino end of the amino acid or peptide fragments. Thus for instance H-Phe-Fp stands for H_2N–$CH(CH_2Ph)$–CO–$Fe(CO)_2Cp$, Boc-Phe-Fp stands for ^tBuO–CO–NH–$CH(CH_2Ph)$–CO–$Fe(CO)_2Cp$; Xxx represents an unspecified amino acid residue such as valine (Val), phenylalanine (Phe) and so on; P_t, protecting group; Pact, Z, activating groups; Nu, an unspecified nucleophilic species.

0022-328X/93/$6.00



P_t, protecting group; P_{act}, Z, activating groups; R, peptide fragment; Nu, nucleophilic species.

Scheme 1.

Fp acyl complexes under oxidative conditions has also been reported [5].

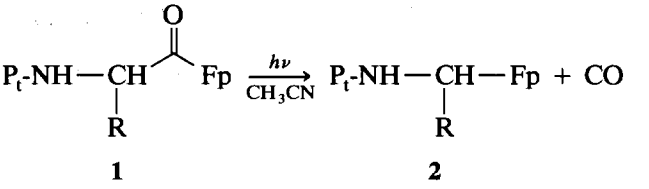
Fp acyl derivatives of α-amino acids have already been described by Hungate *et al.* [6]. These complexes are stable under the pseudoacidic conditions (trimethylsilyl iodide) used in the removal of the carbobenzyloxy amino-protecting group and under the basic conditions of peptide bond formation. We wished to investigate if such iron carboxy-protected derivatives of α-amino acids could be converted to activated acyl species and found that upon oxidation, iron α-amino acyl complexes undergo a rapid degradation process which unfortunately precludes any nucleophilic capture. Here we report the electrochemical and chemical oxidation of Fp, Fp′ and Fp* (Fp* = pentamethyl cyclopentadienyl iron dicarbonyl) derivatives of α-amino acids and dipeptides, the transformations of the oxidized species and our unsuccessful attempts to promote nucleophilic capture. For comparison, we have also studied the oxidation of some iron derivatives of simple carboxylic acids, especially of the Fp series for which few data are available.

2. Synthesis of iron acyl complexes

Fp acyl derivatives were obtained by condensing K^+Fp^- [7] with acyl chlorides in the case of simple carboxylic acids, and with the mixed carbonic anhydride derived from isobutyl chloroformate in the case of α-amino acids [6] (complexes **1**)]. Fp* acyl derivatives were obtained in a similar manner, starting from $K[FeCp^*(CO)_2]$. The dipeptide derivative Boc-Phe-Phe-Fp was synthesized by coupling the Fp derivative of phenylalanine, H-Phe-Fp, with *N*α-Boc-phenylalanine by the mixed carbonic anhydride method [6]. H-Phe-Fp itself was obtained by trifluoroacetolysis of Boc-Phe-Fp. The Fp moiety was found to be perfectly stable under these acidic conditions.

Fp′ derivatives of simple carboxylic acids, Fp′COR, were prepared by reaction of Fp alkyl complexes and triphenylphosphine in acetonitrile at reflux [8].

A similar insertion reaction was first tried for the synthesis of Fp′ derivatives of amino acids, starting from amino-protected Fp-aminoalkyl complexes **2**. Complexes **2** of the Boc series were obtained by photochemical decarbonylation [9,10] (eqn. (1)) of Fp derivatives of *N*α-Boc-aminoacids **1** (Boc-Xxx-Fp, Xxx = Gly or Phe). In the Fmoc series the same reaction leads only to decomposition products.

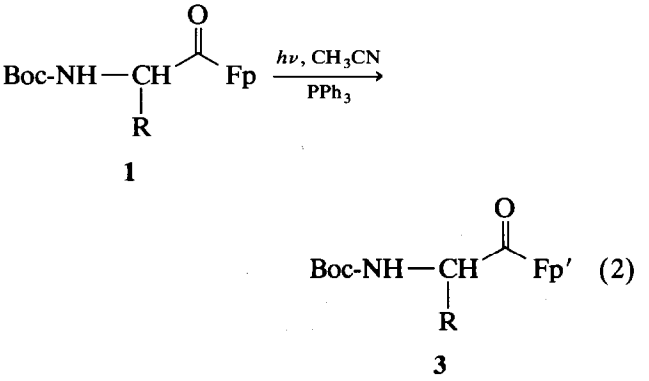


1 **2** (1)

R = H, CH_2Ph

P_t = Boc

Heating complexes **2** with triphenylphosphine in acetonitrile under reflux did not give the expected products Boc-Xxx-Fp′, which probably reflects a very low migrating aptitude of the α-carbalkoxyaminoalkyl group [11*]. Catalysis of the CO insertion reaction by Lewis acids [11a] was not attempted because of the sensitivity of the Boc group. We therefore attempted a photochemically induced ligand-exchange [12] on acyl complexes **1** (eqn. (2)).



1 **3** (2)

R = H, CH_2Ph

By this method, Fp′ acyl complexes **3** were indeed obtained, but as expected [13,14] competitive CO desinsertion processes could not be avoided, leading to Boc-NH-CH(R)-Fp and Boc-NH-CH(R)Fp′ complexes as side products. After chromatographic purification, Boc-Gly-Fp′ and Boc-Phe-Fp′ complexes were obtained (yields of 16% and 47% respectively). On the other hand, the photochemically induced ligand-exchange reaction, when tried on Boc-Xxx-Fp* com-

* Reference number with asterisk indicates a note in the list of references.

TABLE 1. Electrochemical behaviour of the Fp series. Conditions: supporting electrolyte, $LiClO_4$ 0.1 mol dm^{-3}; working electrode, glassy carbon; concentration in complexes, 2 mmol dm^{-3} (Fp-COR derivatives) or 5 mmol dm^{-3} (Xxx-Fp derivatives)

Complex	E_a(V (SCE))	E_c(V (SCE))	Observations
[$FpCOCH_3$]	0.96		RT, acetone, ν: 0.1 V s^{-1} irreversible
[$FpCOCH_3$]	0.98	0.82	−40°C, ν: 1 V s^{-1}, acetone quasi-reversible
[$FpCOCH_2CH_3$]	1.26	1.12	−43° C, ν: 1 V s^{-1}, CH_3CN quasi-reversible
[$FpCOC_{11}H_{23}$]	1.10		RT, CH_3CN, ν: 0.1 V s^{-1} irreversible
[$FpCOC_{11}H_{23}$]	1.02	0.74	−40°C, ν: 1 V s^{-1}, acetone quasi-reversible
[$FpCOCH_2Bu^t$]	0.98	0.83	−40°C, ν: 1 V s^{-1}, acetone quasi-reversible
[$FpCOCH_2Bu^t$]	1.26	1.10	−43°C, ν: 1 V s^{-1}, CH_3CN quasi-reversible
[FpCOPh]	0.98	0.83	−40°C, ν: 1 V s^{-1}, acetone quasi-reversible
[FpCOPh]	1.26	1.10	−43°C, ν: 1 V s^{-1}, CH_3CN quasi-reversible
Boc-Gly-Fp	0.88		−40°C, acetone, ν: 0.1 V s^{-1} irreversible
Boc-Phe-Fp	0.80		−40°C, CH_3CN, ν: 1 V s^{-1} irreversible
Boc-Val-Fp	0.92		−40°C, CH_3CN, ν: 1 V s^{-1} irreversible
Boc-Glu(OBzl)-Fp	0.84		RT, acetonitrile, ν: 0.1 V s^{-1} irreversible
Fmoc-Phe-Fp	0.86		RT, acetonitrile, ν: 0.1 V s^{-1} irreversible
Boc-Phe-Phe-Fp	1.07		RT, acetone, ν: 1 V s^{-1}, irreversible
H-Phe-Phe-Fp	1.00		RT, acetone, ν: 1 V s^{-1} irreversible

TABLE 2. Electrochemical behaviour of the Fp* series. Conditions: 5 mmol dm^{-3}; supporting electrolyte, $LiClO_4$ 0.1 mol dm^{-3}; working electrode, glassy carbon

Complex	E_a(V(SCE))	E_c(V(SCE))	Observations
[Fp^*COCH_3]	0.80		RT, acetone, ν: 0.1 V s^{-1} irreversible
[Fp^*COCH_3]	0.85	0.72	−88°C, acetone, ν: 1 V s^{-1} quasi-reversible
Boc-Gly-Fp*	0.78		−40°C, acetone, ν: 0.1 V s^{-1} irreversible
Boc-Val-Fp*	0.80		−40°C, CH_3CN, ν: 1 V s^{-1} irreversible

TABLE 3. Electrochemical behaviour of the Fp′ series. Conditions: 5 mmol dm^{-3}; supporting electrolyte, $LiClO_4$ 0.1 mol dm^{-3}; working electrode, glassy carbon

Complex	E_a(V(SCE))	E_c(V(SCE))	Observations
[$Fp'COCH_3$]	0.72	0.66	RT, acetone, ν: 0.1 V s^{-1} reversible
[$Fp'COC_{11}H_{23}$]	0.64	0.56	RT, acetonitrile, ν: 0.1 V s^{-1} quasi-reversible
Boc-Gly-Fp′	0.65		−40°C, CH_3CN, ν: 0.1 V s^{-1} irreversible
Boc-Gly-Fp′	0.67		−40°C, CH_3CN, ν: 1 V s^{-1} irreversible

plexes, gave only the product of concomitant CO desinsertion Boc-NH-CH(R)-FeCp*(CO)(PPh_3); thus Boc-Xxx-FeCp*(CO)(PPh_3) complexes could not be prepared.

3. Electrochemical analysis of iron acyl complexes

Cyclic voltammetry studies of Fp, Fp* and Fp′ derivatives of simple carboxylic acids and of amino-protected α-amino acids were carried out in CH_3CN or CH_3COCH_3 ($LiClO_4$/0.1 mol dm^{-3} as the supporting electrolyte unless otherwise specified). The results are reported in Table 1 (Fp derivatives), Table 2 (Fp* derivatives) and Table 3 (Fp′ derivatives). Fp′ derivatives of simple carboxylic acids exhibit a reversible anodic wave (E_0 = 0.69 V (acetyl) and 0.60 V (dodecanoyl)) at a voltage sweep rate of 0.1 V s^{-1} and at room temperature. Under similar conditions, the oxidation process is irreversible for the corresponding Fp* and Fp derivatives, but it becomes quasi-reversible at a voltage sweep rate of 1 V s^{-1} and at low temperature with an E_0 value of 0.79 V ($E_a - E_c$ = 0.13 V) for Fp^*COCH_3 (−80°C in acetone), and an E_0 value of 0.90 V ($E_a - E_c$ = 0.15 V) for $FpCOCH_3$ and FpCOPh (−40°C in acetone). Magnuson *et al.* have reported an E_0 value of 0.94 V for $FpCOCH_3$ in acetonitrile [15]. The shift in E_0 values in the Fp, Fp*, Fp′ series may be related to the greater electron donor ability of Cp* (as compared with Cp) and of PPh_3 (as compared with CO) and is consistent with literature data [16*].

In contrast with the above observations, Fp, Fp* and Fp′ derivatives of amino acids all exhibit a non-reversible oxidation wave even at low temperature *. Never-

* The complexes $FpCOC_{11}H_{23}$ and Boc-Val-Fp were also studied at higher voltage sweep rates. As expected, a reversible couple was observed for $FpCOC_{11}H_{23}$ (E_0 = 1.0 V (SCE, standard calomel electrode); scan rate, 1050 V s^{-1}; solvent, CH_3CN; supporting electrolyte, (Bu_4N)(PF_6) but the oxidation wave is still irreversible for Boc-Val-Fp even at scan rates as high as 10,000 V s^{-1}.

TABLE 4. Oxidation of Fp, Fp* and Fp'$COC_{11}H_{23}$ complexes in a poorly nucleophilic medium

Complex	Products	Conditions
[$FpCOC_{11}H_{23}$]	RCO-OR, 75% (40 [a])	CH_3CN, RT [b], 2 equiv. CAN
[$Fp^*COC_{11}H_{23}$]	RCO-OR, 60%; $R\text{-}CO_2H$, 10%; R(-H), 1%	CH_3CN, 0°C [b], 2 equiv. CAN
[$Fp'COC_{11}H_{23}$]	$Fc(C_{11}H_{23})$, 23%; $Fc(C_{11}H_{23})_2$, 1%	CH_3CN, RT, 1 equiv. FcOTf

[a] Isolated. [b] Lowering the temperature to −40°C did not change significantly the proportions of products.

TABLE 5. Oxidation of Fp, Fp* and Fp'$COC_{11}H_{23}$ complexes in methanol

Complex	Products	Conditions
[$FpCOC_{11}H_{23}$]	$C_{11}H_{23}CO_2CH_3$, 25%; $C_{11}H_{23}CO_2C_{11}H_{23}$, 52%	CH_3OH, RT [a], 1.5 equiv. CAN
[$FpCOC_{11}H_{23}$]	$C_{11}H_{23}CO_2CH_3$, 80%	CH_3OH, 0°C, 1 equiv. NBS
[$Fp^*COC_{11}H_{23}$]	$C_{11}H_{23}CO_2CH_3$, 33%; $C_{11}H_{23}CO_2C_{11}H_{23}$, 15%	CH_3OH, RT [a], 1.5 equiv. CAN
[$Fp^*COC_{11}H_{23}$]	$C_{11}H_{23}CO_2CH_3$, 70%	CH_3OH, 0°C, 1 equiv. NBS
[$Fp'COC_{11}H_{23}$]	$C_{11}H_{23}CO_2CH_3$, 46%	CH_3OH, −78°C, 1.5 equiv. CAN
[$Fp'COC_{11}H_{23}$]	$C_{11}H_{23}CO_2,CH_3$, 51%	CH_3OH, 0°C, 1 equiv. NBS

[a] Lowering the temperature to −40°C did not change significantly the proportions of products.

theless, it should be noted that the E_a values are still dependent on the nature of the ligands on the metal. The trend in E_a values parallels the trend in E_0 observed on iron derivatives of simple carboxylic acid derivatives, Tables 1–3.

Finally, aside from the cyclic voltammetry studies, coulometric experiments were also attempted in the oxidation of iron acyl derivatives but were thwarted by electrode poisoning.

4. Chemical oxidation of iron acyl derivatives

The chemical oxidation of Fp and Fp* derivatives of amino-protected α-amino acids was carried out in non-nucleophilic solvents (acetonitrile nitrobenzene, dichloromethane) in the presence and absence of added nucleophiles. For comparison, a similar study was undertaken on the Fp, Fp* and Fp' derivatives of dodecanoic (lauric) acid ($C_{11}H_{23}CO_2H$) chosen as models of iron acyl derivatives of simple carboxylic acids. The oxidants used in these studies include one-electron oxidizing agents (copper(II) triflate, $Cu(OTf)_2$; ferricinium triflate, FcOTf; cerium ammonium nitrate, CAN) and the two-electron oxidizing agent, *N*-bromosuccinimide.

4.1. Oxidation of iron derivatives of dodecanoic acid (Tables 4–6)

$FpCOC_{11}H_{23}$ is oxidized by CAN but is inert towards the milder oxidizing agents FcOTf or $Cu(OTf)_2$. In acetonitrile, a poor nucleophile, at least 1.5 equivalents of CAN are necessary to ensure complete reaction. The only organic product of the reaction is the ester RCO_2R (75% yield, $R = C_{11}H_{23}$) (Table 4). The main organometallic products of the reaction are the cationic species $Fp(CO)^+$ (55%) (identified by ^1H NMR spectroscopy (one singlet at 5.6 ppm in CD_3CN) and IR ($\nu(CO) = 2125$, 2077 cm^{-1})) and $FpONO_2$ (about 15%). We have been able to confirm the formation of ester RCO_2R from the CAN oxidation of Fp acyl derivatives in other examples (with primary R groups such as ethyl or homoallyl) [17a]. A radical mechanism has been proposed [17a] for this reaction, in which the $[Fp\text{-}COR]^{+\cdot}$ radical cation acts both as a radical source and a radical trap (see Scheme 2).

In the presence of CCl_4 (Table 6) the CAN oxidation (1 to 1.5 equivalent) of $FpCOC_{11}H_{23}$ in acetonitrile leads to undecyl chloride. There is evidence for similar radical trapping processes with other Fp acyl derivatives [17a]. In the presence of $CHCl_3$, a less efficient trap than CCl_4, a mixture of undecane, undecyl chloride and ester RCO_2R was obtained. While the formation of undecane is best explained by direct abstraction by $R^\cdot$ of a hydrogen atom from $CHCl_3$, the formation of undecyl chloride probably involves chloride abstraction from an iron(III) chloride species present in the medium [18]. When the CAN oxidation (1 to 1.5 equivalent) was run in methanol (Table 5), both the product of nucleophilic cleavage RCO_2Me and the

TABLE 6. Oxidation of complexes Fp, Fp* and Fp'$COC_{11}H_{23}$ in the presence of a radical trap

Complex	Oxidation conditions	Product (%) (/FpCOR) [a]
[$FpCOC_{11}H_{23}$]	CH_3CN:CCl_4 (2:1) RT, 1.5 equiv. CAN	$C_{11}H_{23}$-Cl (83%)
[$FpCOC_{11}H_{23}$]	CH_3CN:$CHCl_3$ (2:1) RT, 1.5 equiv. CAN	$C_{11}H_{23}$-H (10%) $C_{11}H_{23}$-Cl (15%) $C_{11}H_{23}CO_2C_{11}H_{23}$ (5%)
[$FpCOC_{11}H_{23}$]	MeOH:CCl_4 (2:1) RT, 1.5 equiv. CAN	$C_{11}H_{23}$-Cl (18.5%) $C_{11}H_{23}$-CO_2Me (42%)
[$Fp^*COC_{11}H_{23}$]	CH_3CN:CCl_4 (2:1) RT, 1.5 equiv. CAN	$C_{11}H_{23}$-Cl (70%)
[$Fp^*COC_{11}H_{23}$]	MeOH:CCl_4 (2:1) RT, 1.5 equiv. CAN	$C_{11}H_{23}$-Cl (30%) $C_{11}H_{23}$-CO_2Me (12%)
[$Fp'COC_{11}H_{23}$]	CH_3CN:CCl_4 (2:1) RT, 1 equiv. $Cu(OTf)_2$	$C_{11}H_{23}$-Cl (17%)

[a] Yields determined by GC analysis or ^1H NMR.

ester RCO_2R were obtained. Finally, when the reaction was performed in the presence of both a radical (CCl_4) and a nucleophilic (MeOH) trap, a mixture of chloride RCl and of product of nucleophilic cleavage RCO_2Me was obtained (Table 6).

Inspection of Tables 4–6 shows that the chemical behaviour of $Fp^*COC_{11}H_{23}$ closely resembles that of the Fp derivative. In the CAN oxidation in methanol however (Table 5), the formation of the product of nucleophilic cleavage (methyl ester) as compared with formation of the ester RCO_2R seems to be more favourable with the Fp* complex.

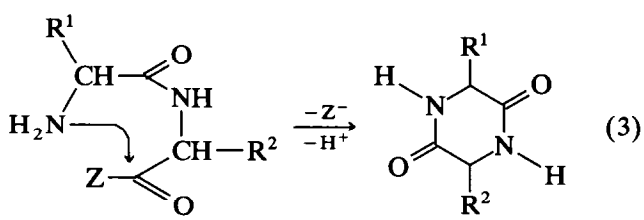
Rather different results were obtained with $Fp'COC_{11}H_{22}$. Unlike $FpCOC_{11}H_{23}$, $Fp'COC_{11}H_{23}$, with an E_0 value of about 0.3 V, less may be oxidized not only with CAN, but also with $Cu(OTf)_2$ or FcOTf. The oxidation of $Fp'COC_{11}H_{23}$ with $Cu(OTf)_2$ (one equivalent) in acetonitrile in the presence of CCl_4 leads to chloride RCl (albeit in rather low yield) (Table 6) while in methanol (CAN as the oxidizing agent, Table 5) the methyl ester is formed exclusively. In the absence of nucleophilic or radical trap, the CAN oxidation of $Fp'COC_{11}H_{23}$ leads to extensive decomposition of the iron complex. Under similar conditions but with FcOTf (one equivalent) instead of CAN as the oxidizing agent, undecyl- and diundecyl-ferrocene (yields of 23% and about 1% respectively) were characterized among other unidentified reaction products (Table 4). Under none of these conditions could the ester RCO_2R be detected.

When NBS (one equivalent) was used as the oxidizing agent in methanol (Table 5), the methyl ester $C_{11}H_{23}CO_2Me$ was obtained selectively regardless of the starting (Fp, Fp* or Fp') iron derivative. NBS-induced alcoholysis of Fp acyl [5] and Fp' acyl [4a] derivatives have precedents in the literature.

4.2. Oxidation of iron derivatives of amino-protected α-amino acids

The CAN oxidation of Fp derivatives of amino-protected α-amino acids was found to lead to extensive decomposition of starting material. However, and in contrast with what was observed previously with the Fp dodecanoyl derivative, we found that Fp amino acid derivatives could also be oxidized with the milder reagents $Cu(OTf)_2$ and FcOTf.

The $Cu(OTf)_2$ oxidation of Boc-Phe-Fp was first studied, in acetone and dichloromethane, and in the presence of water, methanol or benzylamine (Fc^+OTf^- which is decomposed rapidly by benzylamine could not be used as the oxidizing agent in this case). It was observed that only half of the starting Boc-Phe-Fp was consumed when one equivalent of copper(II) triflate was used. In no case could the products of nucleophilic capture (*i.e.* Boc-Phe-OH, Boc-Phe-OMe, Boc-Phe-NHBzl) be detected, even when the reaction was run in methanol. Instead, 2-phenylethanal was obtained as the only product of reaction. We have also investigated the oxidation of H-Phe-Phe-Fp. No diketopiperazine could be detected despite the fact that diketopiperazine formation in general (eqn. (3)) is a highly favoured reaction [19].



(3)

Z = leaving group

The oxidation of Fp acyl derivatives was investigated further in the absence of nucleophiles and in dichloro-

TABLE 7. Oxidation of complexes FpXxx and Fp*Xxx without nucleophile

Complex	Conditions	Product	Yield [a] (%)
Ac-Val-Fp	FcOTf (2 equiv.), RT, nitrobenzene or CH_2Cl_2	$(CH_3)_2CHCHO$	90
Boc-Val-Fp	FcOTf (2 equiv.), RT, nitrobenzene or CH_2Cl_2	$(CH_3)_2CHCHO$	98
Boc-Val-Fp	NBS (1 equiv.), RT, nitrobenzene or CH_2Cl_2	$(CH_3)_2CHCHO$	97
Boc-Phe-Fp	FcOTf (2 equiv.), RT, CH_3CN	$PhCH_2CHO$	75
Fmoc-Phe-Fp	FcOTf (1.5 equiv.), RT, CH_3CN	$Fp(CO)^+$; dibenzofulvene (Fmoc decomposition)	–
Boc-Glu(OBzl)-Fp	FcOTf (2 equiv.), RT, CH_3CN	$BzlOCO(CH_2)_2CHO$	95
Boc-Val-Fp*	FcOTf (2 equiv.), RT, nitrobenzene	$(CH_3)_2CHCHO$	97
		$Fp^*(CO)^+$	100
Boc-Val-Fp*	NBS (1 equiv.), RT, nitrobenzene	$(CH_3)_2CHCHO$	100
		Fp^*Br	80

[a] Determined by GC analysis.

methane, nitrobenzene or acetonitrile (Table 7). FcOTf was selected as the oxidizing agent. Total conversion of starting material was observed with two equivalents of FcOTf. 2-methylpropanal, from the valine derivatives Ac-Val-Fp and Boc-Val-Fp, and benzyl 4-oxobutanoate, from the glutamic acid derivative Boc-Glu(OBzl)-Fp, were obtained in close-to-quantitative yields. The more reactive 2-phenylethanal was obtained in slightly lower amounts (about 75%) from the complex Boc-Phe-Fp. Aside from ferrocene, the organometallic product of all the above reactions was the cationic complex $[Fp(CO)]^+$. Finally, the reaction of Fmoc-Phe-Fp with FcOTf gave a complex mixture of decomposition products, among which dibenzofulvene was identified.

When NBS replaced FcOTf in the oxidation of Boc-Val-Fp, 2-methylpropanal was again obtained, in close-to-quantitative yield.

Similar results were obtained in the FcOTf or NBS oxidation of Fp* derivatives of α-amino acids.

A first series of experiments carried out on the Fp' derivative of Boc-Phe-OH showed that 2-phenylethanal was still the only characterizable product of oxidation whatever the reaction conditions (NBS or FcOTf as the oxidizing agent, CH_2Cl_2 or methanol as the solvent). Owing to the difficulties encountered in the synthesis and purification of Fp' derivatives of amino acids (see above), the chemical oxidation of this latter class of compounds was not investigated further.

5. Discussion

In a previous study [17a], we have shown that the CAN oxidation of FpCOR complexes in poorly nucleophilic media involves a radical process which leads ultimately to the ester RCO_2R when R is a primary group. In the proposed mechanism, the first formed $[Fp\text{-}CO\text{-}R]^{+\cdot}$ radical cation acts both as an $R^\cdot$ source and an $R^\cdot$ acceptor (eqns. (4)–(6)). This process leads to the cationic iron Fischer carbene complex $[Fp=C(OR)R]^+$ which, in the presence of CAN and adventitious water, is further oxidized to the ester RCO_2R (eqn. (7)) [17*].

When $R^\cdot$ is a more oxidizable secondary or tertiary radical, the trapping reaction (eqn. (6)) is not observed. Instead $R^\cdot$ is oxidized by a second CAN equivalent to the corresponding R^+. R^+ is in turn trapped by a nitrate anion or by adventitious water to give the alkyl nitrate $RONO_2$ or the alcohol ROH (eqns. (8) and (9)).

$$R^\cdot \xrightarrow{CAN} R^+ \quad \text{(R secondary or tertiary)} \qquad (8)$$

$$R^+ + H_2O \text{ or } NO_3^- \longrightarrow ROH \text{ or } RONO_2 \qquad (9)$$

It has also been shown [17a] that in the presence of CCl_4, the CAN oxidation of FpCOR (R a primary group) leads to alkyl chlorides, RCl, instead of esters, RCO_2R. This had been explained by a rapid trapping by CCl_4 (eqn. (10)) of the $R^\cdot$ radical formed upon homolytic dissociation of the Fp-acyl radical cation (eqn. (5)).

$$R^\cdot + CCl_4 \longrightarrow R\text{-}Cl + CCl_3^\cdot \qquad (10)$$

The formation of undecyl chloride in the oxidation (CAN, $Cu(OTf)_2$) of $Fp^*COC_{11}H_{23}$ and $Fp'COC_{11}H_{23}$ in a CH_3CN–CCl_4 mixture as well as the formation of undecylferrocene in the oxidation of $Fp^*COC_{11}H_{23}$ with Fc^+OTf^-, which is best explained by the trapping of undecyl radicals by the radical cation $Fc^{+\cdot}$ [20] (eqn. (11)), show that, in all probability, the homolytic dissociation of iron acyl radical cations already observed with the Fp compounds (eqn. (5)) is in fact common to the Fp, Fp* and Fp' series (eqn. (12)*), see Table 6.

$$R^\cdot + Fc^{+\cdot} \longrightarrow R\text{-}Fc + H^+ \qquad (11)$$

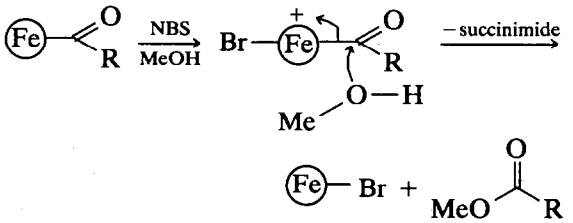
$$\left[\textcircled{Fe}\!-\!\overset{O}{\overset{\|}{C}}\!-\!R\right]^{+\cdot} \longrightarrow \left[\textcircled{Fe}(CO)\right]^+ + R^\cdot \qquad (12)$$

$\textcircled{Fe}$ = Fp, Fp* or Fp'

Scheme 2.

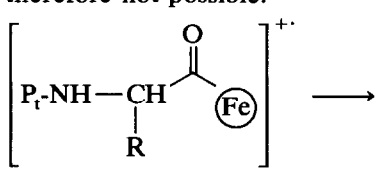
* On the other hand, unlike $(FpCOR)^{+\cdot}$ and $(Fp^*COR)^{+\cdot}$, the $(Fp'COR)^{+\cdot}$ radical cation is apparently not an efficient radical trap since under no conditions could the formation of ester RCO_2R be observed in the oxidation of $Fp'COC_{11}H_{23}$. At the present stage of our investigation, the fate of $R^\cdot$ when no radical trap is present has not been elucidated.

The non-reversibility of the anodic wave observed in the cyclic voltammograms at moderate scan rates for Fp (and Fp*) derivatives of simple carboxylic acids is in contrast with the reversibility of the oxidation of the corresponding Fp' derivatives. Therefore the homolytic dissociation of eqn. (12) must be markedly faster in the Fp and Fp* series than in the Fp' series. As a result, whereas the oxidatively induced ($Cu(OTf)_2$ see above, CAN [3b]) cleavage of Fp'COR in the presence of methanol leads to the product of nucleophilic capture of the iron acyl cation (*i.e.* the methyl ester RCO_2Me), under similar conditions, FpCOR complexes which are precursors of the short-lived $[FpCOR]^{+\cdot}$ radical cations undergo the competitive radical process of eqns. (4)–(7) leading to ester RCO_2R and the nucleophilic capture leading to RCO_2Me. In contrast the NBS-induced cleavage of iron acyl derivatives leads always to the methyl ester RCO_2Me, regardless of the ligands (Cp, Cp*, CO, PPh_3). We therefore favour electrophilic cleavage represented in eqn. (13) as already proposed by Liebeskind [4a].



(13)

Concerning iron acyl derivatives of α-amino acids, the non-reversibility of the cyclic voltammetry oxidation of Fp, Fp* and Fp' complexes (even at scan rates as high as 10,000 V s^{-1} for Fp complexes) suggests a very fast homolytic dissociation of the iron acyl radical cations **4** (eqn. (14)) whose nucleophilic capture is therefore not possible.



4

$$[(Fe)(CO)]^+ + P_t\text{-NH—}\dot{C}HR \quad (14)$$

5

P_t = Boc, acyl

The transient α-amino radical species **5** in all probability undergoes a second oxidation reaction (as secondary and tertiary radicals do in the presence of CAN; see eqn. (5)) leading to the *N*-acyliminium species **6**. Finally, trapping of **6** by adventitious water, either in the reaction mixture or upon work-up, would ultimately lead to the aldehydes RCHO (eqns. (15) and (16)).

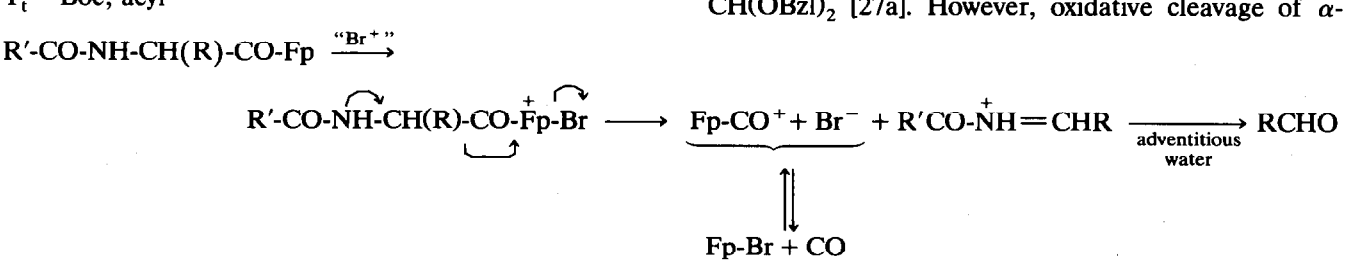
$$\underset{\mathbf{5}}{R\dot{C}H\text{—NH-}P_t} \xrightarrow{ox.} \underset{\mathbf{6}}{RCH{=}\overset{+}{N}H\text{-}P_t} \quad (15)$$

$$\underset{\mathbf{6}}{RCH{=}\overset{+}{N}H\text{-}P_t} \xrightarrow{H_2O} \underset{\mathbf{7}}{RCHO} \quad (16)$$

N-acyliminium ions are well recognized chemical species [21,22]. Some of them (bearing aromatic substituents on the carbon) have been fully characterized spectroscopically as their hexachloroantimonate salts [21]. Acyliminium ions are also postulated intermediates in the synthetically important amidoalkylation reactions [21,22] and in the anodic α-alkoxylation or α-acyloxylation of amides and carbamates [21,23]. Very recently *N*-acyliminium ions have been unambiguously characterized by ^1H and ^{13}C NMR spectroscopy in the reaction of α-alkoxycarbamates with Lewis acids [24]. However, a puzzling fact is our failure to detect α-methoxy amide or carbamate, which should have resulted from the trapping of the iminium cation **6** by methanol. A possibility is that α-methoxy carboxamido species are not stable under our reaction conditions. It should also be noted that the electrochemical oxidation of amides and carbamates in the presence of alcohols does not lead systematically to the α-alkoxy derivatives [21,23,25,26]. We plan to extend our investigation to other α-aminoacyl iron complexes, especially to compounds which should be prone to intramolecular trapping of the putative acyliminium intermediate [21].

Finally, for the NBS-induced cleavage of iron acyl derivatives of amino acids, we tentatively propose the electrophilic fragmentation mechanism described in Scheme 3.

This last reaction resembles the Br_2-induced cleavage of Fp'-α-benzyloxyacyl complexes Fp'COCH(OBzl)R in benzyl alcohol which leads to ketals R-CH$(OBzl)_2$ [27a]. However, oxidative cleavage of α-



Scheme 3.

benzyloxy Fp acyl derivatives at the iron–carbon bond recently has been found possible by use of chlorine in methanol, thus leading to α-benzyloxy methyl esters [27b].

6. Conclusion

We have confirmed that, in the presence of nucleophilic species Nu (Nu = water, alcohol, amine), the electrophilic agent NBS or one-electron oxidants such as $Cu(OTf)_2$ or CAN induce the oxidative cleavage of the iron–C_{acyl} bond of Fp′ derivatives of simple carboxylic acids, leading to the product of nucleophilic capture R-CO-Nu. With the electron-poor FpCOR complexes, nucleophilic capture of the acyl moiety occurs specifically only with NBS. With the one-electron oxidant (CAN), the first-formed, short-lived $[Fp\text{-}CO\text{-}R]^{+\cdot}$ radical cation is engaged competitively in a radical process. This process, which in the absence of nucleophiles is exclusive, starts with the homolytic cleavage of the C_{acyl}–C_α bond of $[Fp\text{-}CO\text{-}R]^{+\cdot}$ and ends in the formation of the ester RCO_2R when no radical trap is present in the medium.

With Fp, Fp* and Fp′ derivatives of amino-protected α-amino acids, one-electron oxidants (FcOTf, $Cu(OTf)_2$) as well as NBS bring about a very fast oxidative degradation process to aldehyde RCHO with loss of both the amino and the acyl groups. The rapidity of this process is such that it precludes any attempt towards nucleophilic capture of the *N*-protected α-amino acyl moiety. With one-electron oxidants (FcOTf, $Cu(OTf)_2$), the reaction probably again involves homolytic C_{acyl}–C_α scission as the first step and is thought to proceed further through an acyliminium species, although direct evidence regarding this has not yet been obtained. If it occurs, the oxidative or electrophilic cleavage of an α-amino acyl iron complex could constitute a new way to the synthetically important acyliminium intermediates.

7. Experimental details

All reactions were carried out under argon of dinitrogen using vacuum line, syringe–septum and Schlenk tube techniques. THF and diethyl ether were distilled over sodium benzophenone ketyl; dichloromethane and acetonitrile were distilled from P_2O_5 and acetone was distilled from anhydrous potassium carbonate.

Infrared spectra were recorded on a Perkin–Elmer Model 880 instrument. ^1H NMR spectra were obtained at 250 MHz with a Bruker AM 250 or at 200 MHz with a Bruker AC 200 instrument. ^{13}C NMR spectra ($CDCl_3$) were recorded with a Bruker AC 200 instrument at 50.288 MHz. ^1H and ^{13}C chemical shifts are reported in ppm with reference to Me_4Si. GLC analysis was performed on a Fractovap 4130 Model equipped with an SE 54-coated 25 m glass capillary column (internal diameter 0.32 mm). GLC–MS analysis was carried out on a Nermag R-10-10 apparatus connected to a CPSIL quartz capillary column. Pre-coated silica gel plates Merck 60 F-254 or pre-coated neutral (type E) aluminium oxide plates Merck 60 F-254 were used for thin layer analytical chromatography.

Ultrasonic irradiations at 20 kHz were performed with a Vibra-cell Model VC 600 (600 W) instrument equipped with a titanium horn. Irradiation experiments were carried out with a mercury lamp Hanovia (200 W) equipped with a Pyrex filter ($\lambda > 280$ nm).

Most cyclic voltammetry studies were carried out on a PAR 273 Model using a one-compartment cell with a three-electrode configuration. A glassy carbon electrode was used as the working electrode. All potentials are reported *vs.* an aqueous SCE electrode with ferrocene set to 0.41 V as the standard. The experiments were conducted in acetone or acetonitrile solutions in concentrations of approximately 1 mmol dm^{-3} in complex and 0.1 mol dm^{-3} in lithium perchlorate (or tetrabutylammonium hexafluorophosphate). Cyclic voltammetry studies at high voltage sweep rates (10 to 10,000 V s^{-1}) were realized with a Tacussel GST-P4 signal generator equipped with a home-made potentiostat [28]; the current and potential values were recorded on a Nicolet 310 digital oscilloscope.

7.1. Starting materials

The acyl chlorides used in this study were freshly distilled over finely powdered calcium hydride. The *N*-protected α-amino acids, all with the L configuration, were used as purchased.

The dimer $[\{Cp(CO)_2Fe\}_2]$ was purchased from Strem Chemicals and used directly.

The dimer $[\{Cp^*(CO)_2Fe\}_2]$ was obtained by heating a solution of pentamethylcyclopentadiene and of iron pentacarbonyl in octane under reflux [29].

The potassium salts of $[Cp(CO)_2Fe]^-$ and $[Cp^*(CO)_2Fe]^-$ were prepared by sonochemically assisted reduction of the corresponding dimers with colloidal potassium metal in THF [7]. The solutions, calculated to be around 0.5 mol dm^{-3}, were used as such in further reactions.

7.2. General method for the preparation of [CpFe(CO)$_2$] (Fp) derivatives of simple carboxylic acids

To a stirred solution of $K[CpFe(CO)_2]$ (10 mmol) in THF (50 cm^3) at −78°C, the acyl chloride RCOCl (one equivalent) is added dropwise over a period of a few minutes. The solution is further stirred first during 20 min at −78°C and then while warming up to room

temperature over a period of 30 min. The solvent is then removed under reduced pressure and the oily residue taken up in hexane or chloroform, depending on the solubility of the Fp acyl complex. The precipitated potassium chloride is filtered off and the filtrate is evaporated under reduced pressure. The crude brown oil or solid residue is finally purified by column chromatography on neutral alumina, by sublimation or by recrystallization.

[$CpFe(CO)_2COPh$] [10]. Purified by recrystallization from hexane/chloroform at −20°C. Yellow solid, m.p. 62–65°C. IR (CCl_4): 2027(s), 1970(s), 1620(m) cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.4 (m, 5H), 4.9 (s, 5H). Anal. Found: C 58.82; H 3.37%. $C_{14}H_{10}FeO_3$ calc.: C 59.61; H 3.57%.

[$CpFe(CO)_2COCH_3$] [30]. Purified by sublimation at 52°C under 0.1 mmHg. Yield 48%. Orange solid, m.p. 52–59°C. IR ($CHCl_3$): 2023(s), 1966(s), 1645(m) cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.85 (s, 5H), 2.6 (s, 3H). Anal. Found C 49.03; H 3.78%. $C_9H_8FeO_3$ calc.: C 49.13; H 3.66%.

[$CpFe(CO)_2COCH_2CH_3$]. Purified by column chromatography on alumina. TLC alumina, $R_f = 0.6$ (AcOEt : cyclohexane 1 : 6). Yield 75%. Brown oil. IR ($CHCl_3$): 2016(s), 1957(s), 1652(m) cm^{-1}. ^1H (NMR($CDCl_3$): δ 4.86 (s, 5H), 2.9 (q, 2H, $J = 8$ Hz), 0.93 (t, 3H, $J = 8$ Hz).

[$CpFe(CO)_2COCH_2Bu^t$]. Purified by column chromatography on alumina. TLC alumina, $R_f = 0.85$ (AcOEt : cyclohexane 1 : 6). Yield 55%. Brown oil. IR ($CHCl_3$): 2018(s), 1963(s), 1665(m) cm^{-1}. ^1H NMR($CDCl_3$): δ 4.82(s, 5H), 2.9 (s, 2H), 0.94 (s, 9H). Anal. Found: C 57.54; H 5.94%. $C_{13}H_{16}FeO_3$ calc.: C 56.55; H 5.84%.

[$CpFe(CO)_2(COC_{11}H_{23})$]. Purified by column chromatography on alumina. TLC alumina $R_f = 0.7$ (AcOEt : cyclohexane 1 : 14). Yield 80%. Brown solid, m.p. 40–45°C. IR ($CHCl_3$): 2019(s), 1961(s), 1644(m) cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.85 (s, 5H), 2.9 (t, 2H, $J = 7.5$ Hz), 1.25 (m, 18H), 0.9 (t, 3H, $J = 7.5$ Hz). Anal. Found: C 64.06; H 8.03%. $C_{19}H_{28}FeO_3$ calc.: C 63.34; H 7.83%.

7.3. Preparation of $[Cp^*Fe(CO)_2COCH_3]$

To 10 cm^3 of a 0.2 mmol dm^{-3} THF solution of $K[Cp^*Fe(CO)_2]$ (prepared from 303 mg of $[\{Cp^*Fe(CO)_2\}_2]$ and 78 mg of colloidal potassium metal) cooled at −100°C, acetyl chloride (0.156 cm^3, 2.2 mmol) was added dropwise with stirring. Stirring was pursued at −100°C while the reaction was monitored by infrared analysis on aliquots. After one hour, the solvent was removed under reduced pressure and the residue was taken up in hexane. The precipitated potassium chloride was filtered off and the filtrate was concentrated under reduced pressure. The residue was chromatographed on Florisil. A first elution with hexane gave small amounts of $[Cp^*(CO)_2FeCH_3)]$ (IR (cyclohexane): 2030(s), 1986(s) cm^{-1}) and of the dimer $[\{Cp^*Fe(CO)_2\}_2]$. Further elution with CH_2Cl_2 : hexane (1 : 1) gave $[Cp^*(CO)_2FeCOCH_3]$ (45% yield) followed by $Cp^*(CO)_2FeCl$ (11% yield. IR (cyclohexane): 2030(s), 1986(s) cm^{-1}).

[$Cp^*Fe(CO)_2COCH_3$] [31]. Orange solid, m.p. 70–73°C. IR (cyclohexane): 2001(s), 1946(s), 1650(m) cm^{-1}, ^1H NMR (C_6D_6): δ 2.46 (s, 3H), 1.46 (s, 15H). Anal. Found: C 58.08; H 6.4%. $C_{14}H_{18}FeO_3$ calc.: C 57.96; H 6.25%.

7.4. Preparation of $[Cp^*Fe(CO)_2COC_{11}H_{23}]$

From $K[Cp^*Fe(CO)_2]$ and $C_{11}H_{23}COCl$ (0.8 equivalent). The experimental procedure was similar to the one used for the preparation of $[Cp^*Fe(CO)_2COCH_3]$ but at 0°C (instead of −100°C) and for 2 h. The product, $[Cp^*Fe(CO)_2COC_{11}H_{23}]$, was purified by column chromatography on alumina.

[$Cp^*Fe(CO)_2COC_{11}H_{23}$]. Yellow oil. Yield: 70%. TLC alumina, $R_f = 0.20$ (cyclohexane : dichloromethane 6 : 1). IR (CCl_4): 2001(s), 1941(s), 1643(m) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.80 (t, $J = 7.5$ Hz, 2H), 1.75 (s, 15H), 1.5 (m, 2H), 1.25 (s, 16H), 0.97 (t, $J = 7.5$ Hz, 3H). Anal. Found C 66.87; H 9.02%; $C_{24}H_{38}FeO_3$ calc.: C 66.97; H 8.90%.

7.5. Preparation of $[Cp(CO)_2FeCH_3]$ and $[Cp(CO)_2FeC_{11}H_{23}]$

[$Cp(CO)_2FeCH_3$] and [$Cp(CO)_2FeC_{11}H_{23}$] were prepared by alkylation of $K[CpFe(CO)_2]$ by methyl iodide (1.1 equivalent) and by undecyl bromide (one equivalent), respectively, using the experimental procedure described by Roger *et al.* [7] for the alkylation of $K[Cp^*Fe(CO)_2]$.

[$Cp(CO)_2FeCH_3$] [32]. Purified by sublimation at 50°C under 0.02 mmHg. Yield 90%. Waxy solid. IR ($CHCl_3$): 2009(s), 1950(s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.74 (s, 5H), 3.6 (s, 3H).

[$Cp(CO)_2FeC_{11}H_{23}$]. Purified by column chromatography on alumina (pentane as the eluant). Yield 70%. Yellow oil. IR ($CHCl_3$): 2003(s), 1943(s) cm^{-1}. ^1H NMR ($CDCl_3$: δ 4.75 (s, 5 H), 3.4 (t, 2H, $J = 7.5$ Hz), 1.25 (m, 18H), 0.9 (t, 3H, $J = 7.5$ Hz).

7.6. Preparation of $[CpFe(CO)(PPh_3)COCH_3]$ and $[CpFe(CO)(PPh_3)COC_{11}H_{23}]$

These complexes were obtained by heating the corresponding $Cp(CO)_2FeR$ complexes and triphenylphosphine in acetonitrile, under reflux [8].

[$Cp(CO)(PPh_3)FeCOCH_3$]. Yield 60% IR ($CHCl_3$): 1920(s), 1600(m). ^1H NMR ($CDCl_3$): δ 7.45 (m, 15H),

4.4 (s, 5H), 2.35 (s, 3H). Anal. Found: C 69.73, H 5.15%; $C_{26}H_{23}FeO_2P$ calc.: C 68.74, H 5.10%.

[Cp(CO)(PPh_3)$FeCOC_{11}H_{23}$]. Yield 80%. IR ($CHCl_3$): 1914(s), 1602(m). ^1H NMR ($CDCl_3$): δ 7.00 (m, 15H), 5.00 (s, 5H), 3.3 (t, 2H, $J = 7.5$ Hz), 1.8 (m, 18H), 1.5 (t, 3H, $J = 7.5$ Hz). Anal. Found: C 72.52, H 7.35%. $C_{36}H_{43}FeO_2P$ calc.: C 72.73; H 7.29%.

7.7. General procedure for the preparation of Xxx-Fe(CO)$_2$Cp (Xxx = BocNH–CH(R)–CO- or FmocNH–CH(R)–CO–) [6]

To a stirred solution of 1 mmol of *N*-protected α-amino acid in 10 cm^3 of THF at 0°C, 0.110 cm^3 (1 mmol) of *N*-methylmorpholine and 0.130 cm^3 (1 mmol) of *iso*butylchloroformate are added successively. A white precipitate forms. After stirring for 10 min, the solution is cooled at −78°C and the precipitate is filtered off under argon. To the filtrate maintained at −78°C, a THF solution of $K^+[CpFe(CO)_2]^-$ (1 mmol) is added dropwise. Stirring is pursued for 2 h at −78°C and then during warming to room temperature. The reaction mixture is neutralized with a small excess of a saturated and degassed aqueous ammonium chloride solution and the organic phase is transferred, for drying, over anhydrous $MgSO_4$. $MgSO_4$ is filtered off, the solvent is evaporated and the oily residue is purified by column chromatography on silica. Usually some ferrocene and dimer [{$CpFe(CO)_2$}$_2$] are first eluted. The FpXxx complex is then collected under argon.

Boc-Gly-Fe(CO)$_2$Cp. Eluent, hexane: AcOEt 4:1. TLC (silica) $R_f = 0.2$. Yield 70%. IR ($CHCl_3$): 2026(s), 1969(s), 1703 (s, carbamate), 1650(m) cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.15 (broad d, 1H, NH), 4.85 (s, 5H), 4.05 (d, $J = 2$ Hz, CH_2), 1.35 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 213.3 (CO), 155.4(CO carbamate), 95.4(CO acyl), 86.0(Cp), 79.1 (tertiary C), 55.2(CH_2), 28.1(CH_3). Anal. Found: C 49.99; H 5.2, N 3.92%. $C_{14}H_{17}FeNO_5$ calc.: C 50.17; H 5.11; N 4.18%.

Boc-Phe-Fe(CO)$_2$Cp. Eluent, hexane: AcOEt (4:1). TLC (silica) $R_f = 0.4$. Yield 47%. IR ($CHCl_3$): 2026(s), 1969(s), 1703(s, carbamate), 1650(m) cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.25 (m, 5H), 5.4 (broad d, 1H, NH), 4.85 (s, 5H), 4.7 (dt, $J = 4.5$ Hz and $J = 9.0$ Hz, αCH), 3.10 (m, 2H), 1.4 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 213 and 214(CO), 155.5(CO carbamate), 90(CO acyl), 86.3(Cp), 126.3, 128.2, 129.3 (phenyl), 79.3 (tertiary C), 75.3(CH_2), 35.8(CH), 28.1(CH_3). Anal. Found: C 59.44; H 5.44; N 3.12%. $C_{21}H_{23}FeNO_5$ calc.: C 59.31; H 5.45; N 3.29%.

Boc-Val-Fe(CO)$_2$Cp. Eluent, hexane: $CHCl_3$ (1:10). TLC (silica) $R_f = 0.6$. Yield 84%. IR($CHCl_3$): 2023(s), 1966(s), 1704(s, carbamate), 1637(m) cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.0 (broad d, 1H, NH), 4.85 (s, 5H), 4.4 (m, 1H), 2.31 (m, 1H), 1.0 (d, 3H, $J = 8$ Hz), 0.7 (d, 3H, $J = 8$ Hz), 1.45 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 213.5 and 214.3 (CO), 155.6 (CO carbamate), 88.3 (CO acyl), 86.3 (Cp), 79.2 (tertiary C), 75.3 (CH_2), 43.1 (CH), 28.2 (CH_3), 26.9 (CH), 20.0 and 16.0 (CH_3). Anal. Found: C 54.23; H 5.98; N 3.68%. $C_{17}H_{23}FeNO_5$ calc.: C 54.13; H 6.15; N 3.71%.

Boc-Glu(OBzl)-Fe(CO)$_2$Cp. Eluent, cyclohexane: CH_2Cl_2 (2:1). TLC (silica) $R_f = 0.33$. Yield 90%. IR ($CHCl_3$): 2027(s), 1972(s), 1730(s, ester) 1703, (s, carbamate), 1637(m) cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.35 (m, 5H), 5.15 (s, 2H), 5.1 (broad d, 1H, NH), 4.95 (s, 5H), 4.45 (td, 1H, $J = 2.5$ Hz and 10 Hz), 2.45 (t, 2H, $J = 7.5$ Hz), 2.25–1.5 (m, 2H), 1.4 (s, 9H). Anal. Found: C 58.55; H 5.23; N 2.88%. $C_{24}H_{27}FeNO_7$ calc.: C 58.84; H 5.53; N 2.74%.

Fmoc-Phe-Fe(CO)$_2$Cp. Eluent, cyclohexane: CH_2Cl_2 (2:1). TLC (silica) $R_f = 0.3$. Yield 65%. IR ($CHCl_3$): 2025(s), 1968(s), 1713(s, carbamate), 1638(m) cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.75–7.10 (m, 13H, aromatic), 5.2 (broad d, 1H, NH), 4.87(s, 5H), 4.75 (dt, 1H, $J = 5$ Hz and 8.7 Hz), 4.35–4.10 (m, 3H, CH–CH_2–O), 3.2 (dd, 1H, $^2J = 15$ Hz and $^3J = 5$ Hz, benzylic), 2.45 (dd, 1H, $^2J = 15$ Hz and $^3J = 10$ Hz, benzylic). Anal. Found: C 69.18; H 4.84; N 2.56%. $C_{31}H_{25}FeNO_5$ calc.: C 69.43; H 4.70; N 2.61%.

7.8. Preparation of Xxx-Fe(CO)$_2$Cp complexes (Xxx = Boc-Gly, Boc-Val)*

These complexes were obtained by following the method already described for their Cp analogues.

Boc-Gly-Fe(CO)$_2$Cp*. Eluent, cyclohexane: CH_2Cl_2 (1:1). Yield 15%. IR($CHCl_3$): 2007(s), 1950(s), 1703(s, carbamate), 1626(m) cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.04 (broad d, 1H, NH), 3.85 (d, 2H, $J = 7.5$ Hz), 1.73 (s, 15H), 1.37 (s, 9H).

Boc-Val-Fe(CO)$_2$Cp*. Eluent, cyclohexane: CH_2Cl_2 (2:1). Yield 65%. IR ($CHCl_3$): 2001(s), 1943(s), 1700(s, carbamate), 1618(m) cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.15 (broad d, 1H, NH), 4.4 (d, 1H, $J = 7.5$ Hz), 2.3 (m, 1H), 1.75 (s, 15H), 0.96 (d, 3H, $J = 7.5$ Hz), 0.62 (d, 3H, $J = 7.5$ Hz), 1.39 (s, 9H). Anal. Found: C 58.96; H 7.63; N 3.18%. $C_{22}H_{33}FeNO_5$ calc.: C 59.07; H 7.44; N 3.13%.

7.9. Preparation of Xxx-Fe(CO)(PPh$_3$)Cp (Xxx = Boc-Gly, Boc-Phe) by photochemically induced ligand exchange on Xxx-Fe(CO)$_2$Cp complexes

In a typical experiment, 100 cm^3 of a 20 mmol dm^{-3} solution of Boc-Phe-Fe(CO)$_2$Cp (850 mg) in hexane containing seven equivalents of triphenylphosphine (3.675 g) were placed in a Pyrex vessel, cooled to 0°C in an ice bath and irradiated with a Hanovia lamp. The reaction was monitored by infrared analysis on aliquots. After 2.5 h, the irradiation was stopped, the reaction

mixture was concentrated under reduced pressure and the residue was column-chromatographed on neutral alumina. PPh_3 in excess was first eliminated by elution with pentane. Further elution with hexane : AcOEt 5 : 1 allowed the successive isolation of desinsertion and ligand exchange products Boc-NH-CH(CH_2Ph)-Fe(CO)$_2$Cp, Boc-NH-CH(CH_2Ph)-Fe(PPh_3)(CO)Cp and of the complex Box-NH-CH(CH_2Ph)CO-Fe(PPh_3)(CO)Cp.

BocNH-CH(CH_2Ph)-CO-Fe(CO)(PPh_3)Cp (*i.e.* Boc-Phe-Fp', yield 45%) IR ($CHCl_3$): 1918(s), 1710(s) cm^{-1}.

BocNH-CH(CH_2Ph)-Fe(CO)(PPh_3)Cp. IR ($CHCl_3$): 1926(s), 1704(s), 1604(m) cm^{-1}.

Boc-NH-CH_2-CO-Fe(CO)(PPh_3)Cp (*i.e.* Boc-Gly-Fp', yield 16%) and BocNH-CH_2-Fe(CO)(PPh_3)Cp were similarly obtained.

Boc-NH-CH_2-CO-Fe(CO)(PPh_3)Cp. IR ($CHCl_3$): 1925(s), 1704(s), 1603(m) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.5–7.25 (m, 15H), 5.05 (broad s, 1H), 4.45 (s, 5H), 4.25 (dd, 1H, $^2J = 18$ Hz and $^3J = 6$ Hz), 3.7 (broad d, 1H, $J = 18$ Hz), 1.35 (s, 9H).

Boc-NH-CH_2-Fe(CO)(PPh_3)Cp. IR ($CHCl_3$): 1907(s), 1688(s) cm^{-1}.

7.10. Deprotection of Boc-Phe-Fe(CO)$_2$Cp to H-Phe-Fe(CO)$_2$Cp

850 mg (2 mmol) of Boc-Phe-Fe(CO)$_2$Cp were stirred at room temperature for 3 h in 50 cm^3 of 1/1 v/v dichloromethane and trifluoroacetic acid. The solvent was then evaporated and the oily residue was kept under vacuum (0.5 mmHg) for several hours in order to eliminate the excess trifluoroacetic acid. The crude product was dissolved in THF and neutralized with one equivalent of triethylamine. The THF was then evaporated and the residue was purified by chromagraphy on a short column of alumina. Less polar impurities were first eluted with cyclohexane–AcOEt 6 : 1 and the desired complex H-Phe-Fe(CO)$_2$Cp, which is very sensitive to air, was collected under argon upon elution with ethyl acetate. Yield 90%.

H-Phe-Fe(CO)$_2$Cp. IR ($CHCl_3$): 2021(s), 1953(s), 1638(m) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.3 (m, 5H), 5.2 (d, 2H), 4.85 (s, Cp), 4.7 (m, 1H), 3.1 (m, 2H).

7.11. Preparation of the dipeptide complex Boc-Phe-Phe-Fe(CO)$_2$Cp

To a solution of 0.139 cm^3 (1 mmol) of triethylamine and 0.130 cm^3 (1 mmol) of *iso*butylchloroformate in 5 cm^3 of THF at −15°C, 265 mg (1 mmol) of Boc-Phe-OH was added with stirring. A heavy white precipitate formed almost immediately. After 2 min, a solution of 325 mg of H-Phe-Fe(CO)$_2$Cp (1 mmol) in 5 cm^3 of THF was added to the heterogeneous mixture. The reaction mixture was then allowed to warm up to room temperature over a period of about 30 min. The solvent was then evaporated and the residue purified by column chromagraphy on alumina. TLC alumina, R_f(H-Phe-Fp) = 0.15, R_f(Boc-Phe-Phe-Fp) = 0.3 (cyclohexane–AcOEt 3 : 1).

Boc-Phe-Phe-Fe(CO)$_2$Cp. Yield 40%. IR ($CHCl_3$): 2025(s), 1986(s), 1703(s, CO Boc), 1660(s, CO amide), 1640(m) cm^{-1}. ^{1}H NMR (CD_3CN): δ 7.25 (m, 10H), 5.95 (broad d, 1H, $J = 7.5$ Hz) and 5.85 (broad d, 1H, $J = 8.5$ Hz) (NH), 5.05 (s, 5H, Cp), 5.0 (m, 1H, α-CH of *N*-terminal Phe) and 4.3 (m, 1H, FpCO-α-CH), 3.15–2.35 (m, 4H benzylic CH_2), 1.3 (s, 9H, tBu).

7.12. Deprotection of Boc-Phe-Phe-Fe(CO)$_2$Cp to H-Phe-Phe-Fe(CO)$_2$Cp

A solution of 170 mg of Boc-Phe-Phe-Fe(CO)$_2$Cp (0.35 mmol) in a mixture of 10 cm^3 of trifluoroacetic acid and 20 cm^3 of dichloromethane was stirred for 4 h at room temperature. The solvents were evaporated under reduced pressure and the oily residue was kept under vacuum (0.5 mmHg) for several hours. The crude product was dissolved in THF and neutralized with one equivalent of diisopropylethylamine. THF was evaporated and the residue was purified by column chromatography on alumina. Less polar impurities were first eluted with ethyl acetate. The H-Phe-Phe-Fe(CO)$_2$Cp complex was then eluted with AcOEt : MeOH 1 : 1 and collected under argon.

H-Phe-Phe-Fe(CO)$_2$Cp. IR($CHCl_3$): 2025(s), 1968(s), 1660(s, CO amide), 1640(m, CO acyl) cm^{-1}. ^{1}H NMR ($CDCl_3$–DMSO-d_6 (1 : 1)): δ 7.3–7.0 (m, 10H), 6.05 (s, 5H), 4.8 (dt, 1H, $J = 4.5$ Hz and 9.0 Hz, FpCOα-CH), 3.95 (m, 1H, α-CH of *N*-terminal Phe), 3.5–2.8 (m, 2H, benzylic H), 2.65–2.35 (m, 2H, benzylic H).

7.13. Chemical oxidation of Fp and Fp derivatives of simple carboxylic acids and of N-protected α-amino acids*

The oxidizing agent (FcOTf, Cu(OTf)$_2$, NBS, two equivalent) was added in one portion to approximately 20 mmol dm^{-3} solution of the iron complex in the desired solvent (dichloromethane, nitrobenzene, acetonitrile) and in the absence or presence of nucleophilic species (water, methanol or benzylamine) used as cosolvent (1/1 v/v mixture). The reactions were conveniently followed by infrared spectroscopy in the 2100–1600 cm^{-1} range or by TLC analysis on aliquots. Analytical yields of aldehyde (and other products) were measured either by ^{1}H NMR spectroscopy (in this case, the reaction was most conveniently run directly in an NMR tube and in deuterated solvent) or by GC analysis after filtration of the reaction mixture through

a short column of silica gel (tridecane was used as an internal standard).

The chemical oxidation of Fp and Fp* derivatives of simple carboxylic acids (FpCOR and Fp*COR) by CAN (1.8 equivalent) in acetonitrile or by CAN (1.5 equivalent) in methanol was studied in a similar manner (internal standard: ferrocene).

7.14. Chemical oxidation of [Fp'$COC_{11}H_{23}$]

(1) By ferricinium triflate: a degassed solution of 204 mg (0.345 mmol) of [Fp'$COC_{11}H_{23}$] in 10 cm^3 of acetonitrile was added dropwise over a period of 10 min to a heterogeneous and vigorously stirred mixture of 115 mg (0.345 mmol) of ferricinium triflate in 10 cm^3 of acetonitrile at room temperature. At the end of the addition, the deep green colour of the reaction mixture was completely discharged. After 10 min of further stirring, the reaction mixture was evaporated under reduced pressure. The residue was dissolved in pentane. Analytical yields of mono- and di-undecylferrocene were measured by reference to an internal standard (tetrahydroacridine) by GC analysis after filtration of the crude reaction mixture through a short column of celite.

(2) By $Cu(OTf)_2$ or CAN in dry methanol: 1.1 equivalent of the oxidizing agent in solution in 2 cm^3 of dry methanol was added to a degassed solution of 26 mg (0.044 mmol) of [Fp'$COC_{11}H_{23}$] in 2 cm^3 of dry methanol. A green colour rapidly developed which subsequently vanished within 1 h. The reaction mixture was then evaporated under reduced pressure. The residue was dissolved in pentane and analysed by GC and ^1H NMR; analytical yields of $C_{11}H_{23}CO_2CH_3$ were determined by reference to an internal standard (ferrocene).

7.15. Chemical oxidations of Fp, Fp and Fp' derivatives of $C_{11}H_{23}CO_2H$ in the presence of a radical trap ($CHCl_3$ or CCl_4)*

The oxidizing agent (CAN, 1.8 equivalent) was added in one portion to approximately 20 mmol dm^{-3} solution of the iron complex in the desired solvent: 2:1 mixture of acetonitrile: radical trap or 2:1 mixture of methanol: radical trap. The reactions were followed in the 2100–1600 cm^{-1} range or by TLC analysis on aliquots. At the end of the reaction the solvent was evaporated under reduced pressure, the residue dissolved in pentane and filtrated through a short column of celite. Analytical yields in methyl ester and alkane or alkyl chloride were measured by reference to an internal standard (ferrocene), either by ^1H NMR spectroscopy or by GC analysis.

7.16. Preparation of authentic samples of mono- and di-undecylferrocene

Mono- and di-undecylferrocene were obtained by alkylation (THF, room temperature, two days) of lithioferrocene (from ferrocene and t-butyl lithium) with 1-bromoundecane, according to the procedure of Rebiere *et al.* [33]. Equimolecular amounts of t-butyllithium, ferrocene and bromoundecane were used in this reaction. After two days at room temperature the reaction mixture was quenched with H_2O–NH_4Cl and extracted several times with diethylether. GC–MS of the etheral extract showed that it contained a mixture of ferrocene, 1-bromoundecane and of mono- and di-undecylferrocene. Diethylether was evaporated; the residue was taken up in pentane and part of the ferrocene was eliminated by selective precipitation at −20°C. Pure samples of mono- and di-undecylferrocene were finally obtained by preparative TLC (silica, hexane as the eluent; di-undecylferrocene $R_f = 0.61$, mono-undecylferrocene $R_f = 0.54$, ferrocene $R_f = 0.46$).

Acknowledgments

We thank Dr. A. Gref for useful discussions. We are very grateful to Dr. C. Amatore and Dr. C. Lefrou for helpful discussions and for performing cyclic voltammetry measurements at high voltage sweep rates (10 to 10,000 V s^{-1}).

References and notes

1 B. J. Johnson, Dual function groups, in E. Gross and J. Meienhofer (eds.), *The Peptides, Analysis, Synthesis, Biology*, Academic Press, New York, 1981.
2 K. Narasaka, T. Hirosi, T. Uchimaru and T. Mukaiyama, *Chem. Lett.* (1982) 991.
3 A. Rieker, R. Beisswenger and K. Regier, *Tetrahedron, 47* (1991) 645.
4 (a) L. S. Liebeskind, M. E. Welker and R. W. Fengl, *J. Am. Chem. Soc., 108* (1986) 6328, and references cited therein. (b) K. Broadley and S. G. Davies, *Tetrahedron Lett., 25* (1984) 1743; (c) S. G. Davies and J. C. Walker, *J. Chem. Soc., Chem. Commun.* (1985) 209; (d) G. Bashiardes and S. G. Davies, *Tetrahedron Lett., 28* (1987) 5563; (e) G. Bashiardes and S. G. Davies, *Tetrahedron Lett., 29* (1988) 6509; (f) R. P. Beckett and S. G. Davies, *J. Chem. Soc., Chem. Commun.*, (1988) 160.
5 J. W. Herdon and W. Chao, *Tetrahedron Lett., 30* (1989) 5745. See also ref. 27(b).
6 R. W. Hungate, F. Miller and M. S. Goodman, *Tetrahedron Lett., 29* (1988) 4273.
7 C. Roger, M. J. Tudoret, V. Guerchais and C. Lapinte, *J. Organomet. Chem., 365* (1989) 347.
8 M. Green and D. J. Westlake, *J. Chem. Soc., A*, (1971) 368.
9 A. Wojcicki, *Adv. Organomet. Chem., 11* (1973) 87.
10 R. B. King and M. B. Bisnette, *J. Organomet. Chem., 2* (1964) 15.
11 In that context, the very low migratory aptitude of the structurally related alkoxymethyl group is worth mentioning; see (a) A. R.

Cutler, P. K. Hanna and J. C. Vites, *Chem. Rev., 88* (1988) 1363, and references cited therein; (b) T. Bodner, G. Coman, S. La Croce, C. Lambert, K. Menard and A. Cutler, *J. Am. Chem. Soc., 130* (1981) 2471.
12 S. T. Belt, D. W. Ryba and D. C. Ford, *J. Am. Chem. Soc., 113* (1991) 9524.
13 M. D. Johnson, Mononuclear iron compounds with η^1-hydrocarbon ligands, in G. Wilkinson (ed.), *Comprehensive Organometallic Chemistry, Vol. 4*, Pergamon Press, Oxford, 1982, pp. 355–361.
14 J. J. Alexander, *J. Am. Chem. Soc., 97* (1975) 1730.
15 R. H. Magnuson, S. Zulu, T'sai Win Ming and W. P. Giering, *J. Am. Chem. Soc., 102* (1980) 6887.
16 Effects of ligands (CO *vs.* phosphorus ligands) and of alkyl substitution of the Cp ring on redox potentials of iron alkyl or acyl derivatives, see (a) Md. M. Rahman, L. Hong-Ye, K. Eriks, A. Prock and W. P. Giering, *Organometallics, 8* (1989) 1; (b) M. Moran, C. Paswal, I. Cuachado, J. R. Masaguer and J. Losada, *J. Organomet. Chem., 363* (1989) 157.
17 (a) C. Amiens, G. Balavoine and F. Guibé, *J. Chem. Soc., Chem. Commun.*, (1991) 1458; (b) In a related area, the oxidation of chromium or tungsten Fischer carbene complexes by CAN in aqueous medium is a well documented reaction; see A. Satoshi, T. Fujimura and E. Nakamura; *J. Am. Chem. Soc., 114* (1992) 2985, and references cited therein; (c) The difficulty of thoroughly eliminating water molecules from CH_3CN–CAN mixtures is well known. A recent illustration of this fact is provided by a study of Snider *et al.* on the CAN-induced formation of the radical cation from silylenol ethers. Such reactions are conveniently carried out with t-butyldimethylsilyl enol ethers but not with trimethylsilyl enol ethers which are readily hydrolysed to ketones. C. B. N. Snider and T. Kwon, *J. Org. Chem., 57* (1992) 2399.
18 (a) B. Giese, *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*, Pergamon, Oxford, 1986, p. 76; (b) F. Minisci, *Acc. Chem. Res., 8* (1975) 185.
19 J. Jones, *The Chemical Synthesis of Peptides*, Clarendon, Oxford, 1991.
20 Ferricinium cation as a radical trap: (a) W. F. Little, K. N. Lynn and R. Williams, *J. Am. Chem. Soc., 85* (1963) 3055; (b) A. L. J. Beckwith and R. J. Leydon, *J. Am. Chem. Soc., 96* (1964) 952.
21 W. N. Speckamp and H. Hiemstra, *Tetrahedron, 41* (1985) 4367, and references cited therein.
22 A. R. Katutzki, I. Takahashi, F. Wei-Xiang and J. Pernak, *Synthesis* (1991) 1147, and references cited therein.
23 T. Shono, *Tetrahedron, 40* (1984) 811.
24 V. Yamamoto, T. Nakada and H. Nemoto, *J. Am. Chem. Soc., 114* (1992) 121.
25 Z. Blum and K. Nyberg, *Acta. Chem. Scand., B, 36* (1982) 165.
26 T. Shono, H. Hamaguchi and Y. Matsumura, *J. Am. Chem. Soc., 97* (1975) 4264.
27 (a) S. G. Davies, D. Middlemiss, A. Naylor and M. Wills, *J. Chem. Soc., Chem. Commun.*, (1990) 797; (b) F. Stolz, P. Strazenski, C. Tamm, M. Neuburger and M. Zehnder, *Ang. Chem. Int. Ed. Engl., 31* (1992) 193.
28 C. Amatore, C. Lefrou and F. Pfluger, *J. Electroanal. Chem., 207* (1989) 43.
29 R. B. King and M. B. Bisnette, *J. Organomet. Chem., 8* (1967) 287–297.
30 R. B. King, *J. Am. Chem. Soc., 85* (1918) 1963.
31 R. B. King, W. M. Douglas and A. J. Efraty, *J. Organomet. Chem., 69* (1974) 131.
32 R. B. King, *Organomet. Synth., 1* (1965) 145.
33 F. Rebiere, O. Samuel and H. B. Kagan, *Tetrahedron Lett., 31* (1990) 3121.