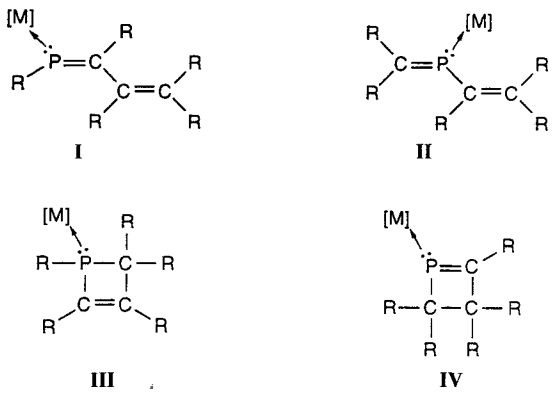
[13] a) A. Yamamoto, *Adv. Organomet. Chem.* **1992**, *34*, 111–147, and references therein; b) T. Yamamoto, J. Ishizu, A. Yamamoto, *J. Am. Chem. Soc.* **1981**, *103*, 6863–6869; c) *Bull. Chem. Soc. Jpn.* **1982**, *55*, 623–624.
[14] T. Kondo, S. Kajiya, S. Tantayanon, Y. Watanabe, *J. Organomet. Chem.* **1995**, *489*, 83–91.
[15] G. Jenner, A. Ben Taleb, *J. Mol. Catal.* **1994**, *91*, 31–43.
[16] a) D. L. Thorn, *Organometallics* **1982**, *1*, 197–204; b) D. Milstein, *J. Am. Chem. Soc.* **1986**, *108*, 3525–3526; c) C. Bianchini, M. Peruzzini, F. Vizza, F. Zanobini, *J. Organomet. Chem.* **1988**, *348*, C9–C11.
[17] Notably, an intermolecular association of mononuclear methoxycarbonyl ruthenium complexes has been recently reported, see G. Süss-Fink, J.-M. Soulié, G. Rheinwald, H. Stoeckli-Evans, Y. Sazaki, *Organometallics* **1996**, *15*, 3416–3422.
[18] a) Alternatively, loss of HCl [18b] from elusive hydrido intermediates may be the origin of the unsaturation, which allows further cleavage of the O–C($sp^3$) bond of the ester and condensation of the fragments; b) V. V. Grushin, *Acc. Chem. Res.* **1993**, *26*, 279–286.
[19] Small amounts of $CO_2$ and methane or ethane (depending on the alkyl formate source), but no traces of CO, were detected by GC in the gaseous phase of the reactor once the reaction was terminated.
[20] Note added in proof: In a continuatino of this work we have now found that the alkyl complex **2** can be generated (albeit less efficiently) from ethylene in the absence of alkyl formate with water as the only hydrogen source: C. Andres, S. Fabre, B. de Bonneval, G. Lavigne, P. Kalck, unpublished results.

# Stereoselective Synthesis and Isomerization of $\eta^1$-2-Phosphabutadiene Complexes to $\eta^1$-2,3-Dihydrophosphete Complexes**

Rainer Streubel,* Markus Hobbold, Jörg Jeske, and Peter G. Jones

*Dedicated to Professor Walter Siebert on the occasion of his 60th birthday*

Although various synthetic routes to $\eta^1$-1-phosphabutadiene complexes (**I**, Scheme 1)[1, 2] have been established, only one example is known of a "phospha-Wittig reaction" with isobutyraldehyde to form an $\eta^1$-2-phosphabutadiene complex (**II**).[3]



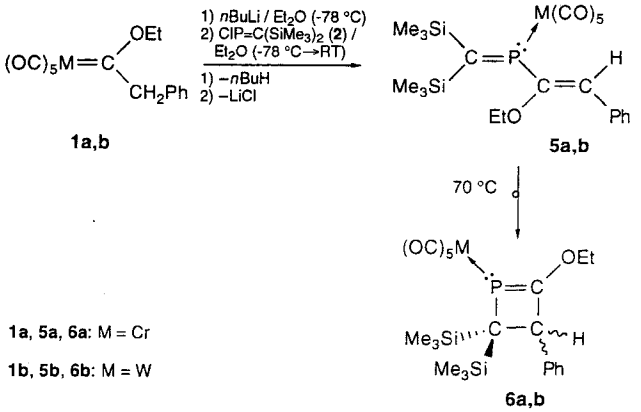

Scheme 1. $\eta^1$-1- (**I**) and $\eta^1$-2-phosphabutadiene complexes (**II**) and $\eta^1$-1,2- (**III**) and $\eta^1$-2,3-dihydrophosphete complexes (**IV**); [M] represents any metal complex fragment.

[*] Dr. R. Streubel, Dipl.-Chem. M. Hobbold, Dipl.-Chem. J. Jeske, Prof. Dr. P. G. Jones
Institut für Anorganische und Analytische Chemie der Technischen Universität
Postfach 3329, D-38023 Braunschweig (Germany)
Fax: Int. code +(531)391-5387
e-mail: streubel@mvs.anchem.nat.tu-bs.de

[**] Chemistry of Four-Membered Phosphorus Heterocycles, Part 2. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. Part 1: R. Streubel, L. Ernst, J. Jeske, P. G. Jones, *J. Chem. Soc. Chem. Commun.* **1995**, 2113.

1-Phosphabutadiene complexes and isomeric $\eta^1$-1,2-dihydrophosphete complexes (**III**) are well-known synthetic units in the heterocyclic chemistry of phosphorus. Compounds of type **I** are particularly notable for their Diels–Alder reactivity and are therefore of interest for the synthesis of six-membered heterocycles,[4] whereas compounds of type **III** have become important, for example, for the construction of five-membered heterocycles.[5] In complete contrast, little is known about the chemistry of $\eta^1$-2-phosphabutadiene complexes; for instance, it is remarkable that the isomerization of these compounds to $\eta^1$-2,3-dihydrophosphete complexes (**IV**) is unknown.

Here we report the synthesis of $\eta^1$-2-phosphabutadiene complexes by the reaction of chromium- or tungsten[benzyl(ethoxy)methylene] complex anions, generated in situ from **1**, with [bis(trimethylsilyl)methylene]chlorophosphane (**2**, Scheme 2).[6]




Scheme 2. RT = room temperature.

Thermal cyclization of the $\eta^1$-2-phosphabutadiene complexes provides metal complexes with the novel 2,3-dihydrophosphete ligand.[7]

Deprotonation of **1a,b**[8] with *n*-butyllithium at −78 °C followed by addition of **2** leads smoothly to the 2-phosphabutadiene metal complexes **5a,b**, which are isolated as yellow solids in moderate to good yields. Room-temperature $^{31}$P NMR spectra of the reaction solutions indicate that these P–C coupling reactions are stereoselective and form exclusively one isomer.

The proposed formulations of **5a,b** are based on the NMR spectra of their solutions (Table 1) and IR, MS, and analytical data (see Experimental Section). The $^{31}$P NMR signals are observed at low field (**5a**: $\delta$ = 341.6; **5b**: $\delta$ = 283.5), and **5b** displays a $^1J$(P,W) coupling constant (264.5 Hz) that corresponds roughly to that of {s-*trans*-[1-isopropyl-4-phenyl-2-phosphabutadiene-$\kappa P$-]pentacarbonyl-tungsten(0)} ($^1J$(P,W) = 254 Hz).[3] The $^{13}$C resonance signals of the butadiene carbon atoms in **5a,b** lie in the range of $sp^2$-hybridized carbon, which further supports the proposed formulations.[9]

The structure of **5a**, as determined by single crystal X-ray analysis,[10] shows many important features. The phenyl and ethoxy groups at the C6–C7 bond are *Z*-configurated, and the double bonds s-*trans* configured with $\eta^1$-coordination of the phosphorus atom at chromium (Figure 1). The C6–C7 and P–C16 bond lengths are 132.8(3) and 166.7(2) pm, respectively, and indicate localized double bonds.

The proposed reaction sequence for the formation of **5a,b** is shown in Scheme 3. An initial reaction of the metallaallyl anions **3a,b** with **2** that forms an M–P bond and leads to **4a,b** seems plausible, particularly since there is no evidence for prior decomposition and dissociation of **3a,b**. It cannot be unambigu-

Table 1. Selected NMR spectroscopic data [a] for **5a,b** and **6a,b**.

**5a**: $^1$H NMR: $\delta = 0.16$ (s, 9H, Si($CH_3$)$_3$), 0.36 (s, 9H, Si($CH_3$)$_3$), 1.33 (t, $^3J$(H,H) = 7.0 Hz, 3H, $OCH_2CH_3$), 3.99 (q, $^3J$(H,H) = 7.0 Hz, 2H, $OCH_2CH_3$), 5.94 (d, $^3J$(H,P) = 6.9 Hz, 1H, C*H*Ph), 7.18 ($m_c$, 3H, *o*/*p*-Ph), 7.55 (d, $^3J$(H,H) = 7.3 Hz, 2H, *m*-Ph). $^{13}$C{$^1$H} NMR: $\delta = 3.6$ (d, $^3J$(C,P) = 5.1 Hz, Si($CH_3$)$_3$), 3.9 (d, $^3J$(C,P) = 6.9 Hz, Si($CH_3$)$_3$), 15.6 (s, $OCH_2CH_3$), 67.8 (d, $^3J$(C,P) = 5.2 Hz, $OCH_2CH_3$), 121.8 (d, $^2J$(C,P) = 22.0 Hz, HPh*C*), 127.9 (s, *p*-Ph), 128.5 (s, *o*-Ph), 129.5 (s, *m*-Ph), 134.5 (d, $^3J$(C,P) = 9.1 Hz, *i*-Ph), 165.1 (d, $^1J$(C,P) = 2.9 Hz, C=*C*–P), 197.7 (d, $^1J$(C,P) = 24.4 Hz, P=*C*), 215.3 (d, $^2J$(C,P) = 16.0 Hz, *cis*-CO), 221.6 (d, $^2J$(C,P) = 4.2 Hz, *trans*-CO); $^{31}$P{$^1$H} NMR: $\delta = 341.6$ (s)

**5b**: $^1$H NMR: $\delta = 0.26$ (s, 9H, Si($CH_3$)$_3$), 0.50 (s, 9H, Si($CH_3$)$_3$), 1.14 (t, $^3J$(H,H) = 7.0 Hz, 3H, $OCH_2CH_3$), 3.93 (q, $^3J$(H,H) = 7.0 Hz, 2H, $OCH_2CH_3$), 6.19 (d, $^3J$(H,P) = 7.3 Hz, 1H, C*H*Ph), 7.13 ($m_c$, 3H, *o*/*p*-Ph), 7.22 (d, $^3J$(H,H) = 7.2 Hz, 2H, *m*-Ph). $^{13}$C{$^1$H} NMR: $\delta = 3.6$ (d, $^3J$(C,P) = 5.4 Hz, Si($CH_3$)$_3$), 4.0 (d, $^3J$(C,P) = 7.3 Hz, Si($CH_3$)$_3$), 15.6 (s, $OCH_2CH_3$), 68.1 (d, $^3J$(C,P) = 5.6 Hz, $OCH_2CH_3$), 123.4 (d, $^2J$(C,P) = 23.5 Hz, *C*=C–P), 128.4 (s, *p*-Ph), 129.0 (s, *o*-Ph), 130.0 (s, *m*-Ph), 134.6 (d, $^3J$(C,P) = 9.3 Hz, *i*-Ph), 165.9 (d, $^1J$(C,P) = 5.5 Hz, C=*C*–P), 190.2 (d, $^1J$(C,P) = 17.3 Hz, P=*C*), 196.8 (d, $^1J$(C,W) = 126.1 Hz, $^2J$(C,P) = 8.7 Hz, *cis*-CO), 198.9 (d, $^2J$(C,P) = 29.3 Hz, *trans*-CO); $^{31}$P{$^1$H} NMR: $\delta = 283.5$ (d, $^1J$(P,W) = 264.5 Hz)

**6a**: $^1$H NMR: $\delta = 0.00$ (s, 9H, Si($CH_3$)$_3$), 0.31 (s, 9H, Si($CH_3$)$_3$), 1.02 (t, $^3J$(H,H) = 7.0 Hz, 3H, $OCH_2CH_3$), 4.09 ($m_c$, 2H, $OCH_2CH_3$), 4.66 (d, $^3J$(H,P) = 28.5 Hz, 1H, C*H*Ph), 7.06 ($m_c$, 5H, Ph). $^{13}$C{$^1$H} NMR: $\delta = 0.0$ (d, $^3J$(C,P) = 3.4 Hz, Si($CH_3$)$_3$), 1.5 (d, $^3J$(C,P) = 3.8 Hz, Si($CH_3$)$_3$), 14.0 (s, $OCH_2CH_3$), 31.0 (d, $J$(C,P) = 17.4 Hz, *C*Si$_2$), 64.3 (d, $^3J$(C,P) = 5.4 Hz, $OCH_2CH_3$), 67.7 (d, $J$(C,P) = 9.7 Hz, *C*HPh), 127.3 (s, *p*-Ph), 128.8 (s, *o*-Ph), 129.5 (s, *m*-Ph), 137.0 (d, $^3J$(C,P) = 12.2 Hz, *i*-Ph), 215.2 (d, $^2J$(C,P) = 14.6 Hz, *cis*-CO), 216.3 (d, $J$(C,P) = 23.1 Hz, P=*C*), 220.3 (d, $^2J$(C,P) = 4.4 Hz, *trans*-CO). $^{31}$P{$^1$H} NMR: $\delta = 171.4$ (s)

**6b**: $^1$H NMR: $\delta = -0.03$ (s, 9H, Si($CH_3$)$_3$), 0.28 (s, 9H, Si($CH_3$)$_3$), 1.04 (t, $^3J$(H,H) = 7.0 Hz, 3H, $OCH_2CH_3$), 4.15 ($m_c$, 2H, $OCH_2CH_3$), 4.67 (d, $^3J$(H,P) = 28.8 Hz, 1H, C*H*Ph), 7.03 ($m_c$, 5H, Ph). $^{13}$C{$^1$H} NMR: $\delta = 0.4$ (d, $^3J$(C,P) = 3.7 Hz, Si($CH_3$)$_3$), 2.1 (d, $^3J$(C,P) = 4.6 Hz, Si($CH_3$)$_3$), 14.5 (s, $OCH_2CH_3$), 29.9 (d, $J$(C,P) = 13.0 Hz, *C*Si$_2$), 64.5 (d, $^3J$(C,P) = 5.5 Hz, $OCH_2CH_3$), 68.0 (d, $J$(C,P) = 11.1 Hz, *C*HPh), 127.9 (s, *p*-Ph), 128.5 (s, *o*-Ph), 129.4 (s, *m*-Ph), 137.8 (d, $^3J$(C,P) = 13.0 Hz, *i*-Ph), 196.2 (d, $^2J$(C,P) = 8.3 Hz, *cis*-CO), 198.3 (d, $^2J$(C,P) = 21.2 Hz, *trans*-CO), 210.7 (d, $J$(C,P) = 27.8 Hz, P=*C*). $^{31}$P{$^1$H} NMR: $\delta = 114.2$ (d, $^1J$(P,W) = 223.9 Hz)

[a] All spectra of **5a** in $CDCl_3$, of **5b** and **6a,b** in $C_6D_6$, 25 °C; $^1$H NMR: 200.1 (**5a,b** and **6b**) or 300.1 MHz (**6a**), $^{13}$C NMR: 50.3 (**5a,b** and **6b**) or 75.5 MHz (**6a**), $^{31}$P NMR: 81.0 (**5a,b** and **6b**) or 121.5 MHz (**6a**); the deuterated solvents were used as internal standards and 85% $H_3PO_4$ as an external standard.

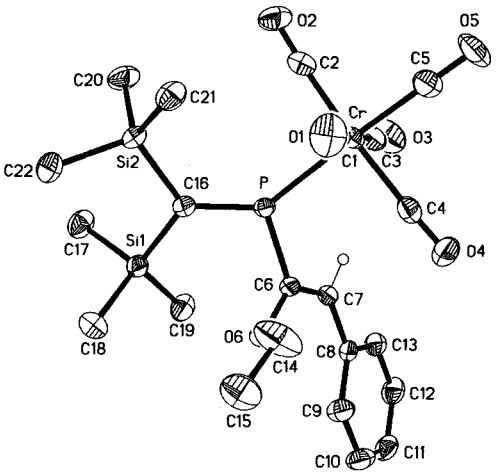
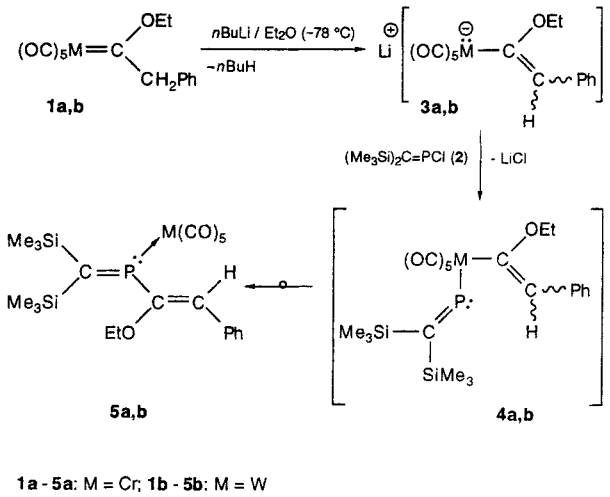



Figure 1. Molecular structure of **5a** in the crystal (ellipsoids represent 50% probability levels; all H atoms except H7 have been omitted for clarity). Selected bond lengths [pm] and angles [°]: P–W 235.09(6), P–C16 166.7(2), P–C6 182.9(2), C6–C7 132.8(3); C7-C6-P 121.08(14), C16-P-C6 107.80(9), C6-P-Cr 113.09(6), Cr-P-C16 139.09(7).

ously decided whether the configuration of the C–C double bond in **5a,b** is already determined in **3**, **4**, or during the **4** → **5** rearrangement (see ref. [11]). The final step of the reaction could represent a rare example of ligand coupling in the coordination sphere of a seven-coordinate d$^4$ metal (**4**) by reductive elimination, as discussed by R. Hoffmann and E. L. Muetterties.[12, 13]




**1a - 5a**: M = Cr; **1b - 5b**: M = W

Scheme 3. Postulated reaction sequence for the formation of **5a,b**.

Since there have been no reports on the isomerization of $\eta^1$-2-phosphabutadiene complexes, we were particularly interested in this aspect. When solutions of **5a,b** are warmed to 70 °C, formation of the $\eta^1$-2,3-dihydrophosphete complexes **6a,b** is complete after 2.5–3 h (Scheme 2). No intermediate formation of the *s-cis* isomers of **5a,b** could be detected by $^{31}$P NMR spectroscopy. The constitution of **6a,b** was deduced unambiguously from solution NMR spectroscopic (Table 1), IR, MS, and analytical data (see Experimental Section).

Important information about the structure is provided by the $^{31}$P NMR signals of the 2,3-dihydrophosphete ring atoms (**6a**: $\delta = 171.4$, **6b**: $\delta = 114.2$), which are shifted significantly to high field relative to those of the precursors, and the low-field $^{13}$C NMR signals of the sp$^2$ (**6a**: $\delta = 216.3$, **6b**: $\delta = 210.7$) and sp$^3$ carbon atoms (**6a**: $\delta = 31.0$ (*C*[SiMe$_3$]$_2$), 67.7 (*C*HPh); **6b**: $\delta = 29.9$ (*C*[SiMe$_3$]$_2$), 68.0 (*C*HPh)); further data are presented in Table 1. The conclusion that **6a,b** contain planar rings seems justified, since otherwise the formation of diastereomers would be expected (due to ring folding and concomitant exo/endo positions of the substituents on the CHPh ring moiety).

## *Experimental Section*

**5a,b**: **1a** (1.97 g, 5.78 mmol) or **1b** (3.42 g, 7.24 mmol) was dissolved in diethyl ether (55 or 72 mL) with stirring, and *n*-BuLi (1.6 M, 3.61 or 4.53 mL, 5.78 or 7.24 mmol) added at −78 °C. After the solution was stirred for 45 min, additional diethyl ether (55 or 70 mL) was added, and, after a further 20 min, **2** (1.30 g, 5.78 mmol or 1.63 g, 7.24 mmol) in diethyl ether (6 or 10 mL). The reaction mixture was allowed to warm up to RT over 2 h, stirred for 3 h, and the solvent removed in vacuo (0.1 mbar). The residue was taken up in *n*-hexane (140 or 160 mL) and filtered through celite after 30 min. After removal of the solvent, the remaining solids were washed at −50 °C with *n*-pentane (10 mL) twice and dried in vacuo (0.1 mbar). Crystallization from *n*-pentane at −30 °C gave yellow single crystals of **5a**.

**5a**: Yellow powder, yield 1.51 g (2.86 mmol, 49%), m.p. = 90 °C (decomp); MS (CI ($NH_3$), $^{52}$Cr): $m/z = 529$ ([$M$+H]$^+$); IR (KBr, $\nu_{C=O}$): $\tilde{\nu} = 2064.8$ (vs), 1998.9 (s), 1971.8 (vs), 1937.2 (vs) cm$^{-1}$; correct C,H analyses.

**5b**: Yellow powder, yield 3.62 g (5.48 mmol, 76%), m.p. = 104 °C (decomp); MS (EI, 70 eV, $^{184}$W): $m/z = 660$ ([$M$]$^+$); IR (KBr, $\nu_{C=O}$): $\tilde{\nu} = 2072.9$ (s), 1997.6 (m), 1967.9 (s), 1929.9 (vs) cm$^{-1}$; correct C,H analyses.

**6a,b**: A solution of **5a** (0.73 g, 1.38 mmol) in toluene (30 mL) or **5b** (0.64 g, 5.78 mmol) in *n*-hexane (70 mL) was warmed to 70 °C for 2.5 h or 3 h. The solvent was then removed in vacuo (0.1 mbar). The residue was washed at −60 °C with *n*-pentane (three times with 5 mL or two times with 4 mL) and then dried in vacuo.

**6a**: Pale yellow powder, yield 0.54 g (1.02 mmol, 74%), m.p. = 83 °C (decomp); MS (EI, 70 eV, $^{52}$Cr): $m/z = 528$ ([$M$]$^+$); IR ($CH_2Cl_2$, $\nu_{C=O}$): $\tilde{\nu} = 2068.0$ (m), 1953.0 (vs), 1948.0 (vs), 1942.0 (vs) cm$^{-1}$; correct C,H analyses.

**6b**: Pale yellow powder, yield 0.51 g (0.77 mmol, 76%), m.p. = 84 °C (decomp); MS (EI, 70 eV, $^{184}W$): $m/z = 660$ ($[M^+]$); IR (KBr, $\nu_{C=O}$): $\tilde{\nu} = 2074.4$ (s), 1992.2 (m), 1950.5 (vs), 1917.5 (vs) $cm^{-1}$; correct C,H analyses.

Received: November 22, 1996 [Z9803IE]
German version: *Angew. Chem.* **1997**, *109*, 1131–1133

**Keywords:** carbene complexes · phosphorus heterocycles · valence isomerization

[1] B. A. Boyd, R. J. Thoma, W. H. Watson, R. A. Neilson, *Organometallics* **1988**, *7*, 572.
[2] A. Marinetti, L. Ricard, F. Mathey, *Organometallics* **1990**, *9*, 788.
[3] A. Marinetti, S. Bauer, L. Ricard, F. Mathey, *J. Chem. Soc. Dalton Trans.* **1991**, 597.
[4] a) N. H. Tran Huy, F. Mathey, *Tetrahedron Lett.* **1988**, *29*, 3077; b) H. Trauner, E. de la Cuesta, A. Marinetti, F. Mathey, *Bull. Soc. Chim. Fr.* **1995**, *132*, 384.
[5] a) N. Maigrot, L. Ricard, C. Charrier, F. Mathey, *Angew. Chem.* **1990**, *102*, 575; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 534; b) N. Maigrot, M. Sierra, C. Charrier, F. Mathey, *Bull. Soc. Chim. Fr.* **1994**, *131*, 397.
[6] R. Appel, A. Westerhaus, *Tetrahedron Lett.* **1981**, *22*, 2159.
[7] Until now the 2,3-dihydrophosphete ring was only known as a subunit of 2-Dewar-phosphinines: J. Fink, W. Rösch, U.-J. Vogelbacher, M. Regitz, *Angew. Chem.* **1986**, *98*, 265; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 280.
[8] D. J. Darensbourg, M. Y. Darensbourg, *Inorg. Chim. Acta* **1971**, *5*, 247.
[9] A. Appel, *Phosphaalkenes* in *Multiple Bonds and Low Coordination in Phosphorus Chemistry* (Eds.: M. Regitz, O. J. Scherer), Thieme, Stuttgart, **1990**, p. 157 ff. and references therein.
[10] Crystal structure analysis of **5a**: $C_{22}H_{29}CrO_6PSi_2$, monoclinic, space group $P2_1/n$: $a = 773.10(6)$, $b = 2139.3(2)$, $c = 1651.7(2)$ pm, $\beta = 100.575(10)°$; $V = 2.6853(4)$ $nm^3$; $Z = 4$; $\rho_{calcd} = 1.307$ $Mg\,m^{-3}$; $\lambda = 0.71073$ pm, $T = 143$ K. A crystal ($0.75 \times 0.4 \times 0.4$ mm) was mounted in perfluoropolyether oil at $-130$ °C on a Stoe STADI-4 diffractometer. A total of 4779 reflections (4738 independent) were registered to $2\theta = 50°$. The structure was solved with direct methods (SHELXS86) and refined by full-matrix least-squares on $F^2$ (SHELXL93). Methyl hydrogen atoms were refined as rigid groups, and all other H atoms with a riding model. Final values: $wR = 0.0809$ based on $F^2$ for all data, conventional $R(F)$ value $R1 = 0.0317$, 296 parameters, max. $\Delta\rho = 362$ $e\,nm^{-3}$. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-100026. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: int. code +(1223)336-033; e-mail: deposit@chemcrys.cam.ac.uk).
[11] It has been assumed that the configuration at the C–C double bond is determined at the stage of the metallaallyl anion or vinylmetallate: C. P. Casey, W. R. Brunsvold, *Inorg. Chem.* **1977**, *16*, 391.
[12] Theoretical studies of the structure and reductive elimination of complexes with seven-coordinate metal centers: R. Hoffmann, B. F. Beier, E. L. Muetterties, A. R. Rossi, *Inorg. Chem.* **1977**, *16*, 511.
[13] Reductive ligand–ligand coupling reactions at seven-coordinate $Mo^{II}$ centers: a) C. T. Lam, P. W. R. Corfield, S. J. Lippard, *J. Am. Chem. Soc.* **1977**, *99*, 617; b) J. C. Dewan, C. M. Giandomenico, S. J. Lippard, *J. Am. Chem. Soc.* **1981**, *20*, 4069.

# C-Terminally Modified Peptides and Peptide Libraries—Another End to Peptide Synthesis**

Michael Davies and Mark Bradley*

Peptides modified at the C-terminus have been used for many years in a variety of applications, notably as substrates and inhibitors for a variety of proteolytic enzymes. In addition, many biologically important peptides and proteins are modified at the C-terminus.

C-terminal peptide amides have been accessible for some time by utilizing a number of specifically designed linkers[1] for solid-phase peptide synthesis. Very few other C-terminal modifications are directly accessible with traditional solid-phase techniques, although the recent work of Burdick et. al.[2] has demonstrated the solid-phase synthesis of a range of *para*-nitroanilides using an aminoanilide linker followed by oxidation of the resultant *para*-aminoanilide after cleavage of the peptide from the resin. To date, specific solution-phase approaches to individual compounds, which require considerable synthetic manipulation and expertise, have been necessary. Additionally, these methods are not adaptable to combinatorial methodologies in an area where the generation of diversity would be extremely desirable.

One potential solution to this problem is to synthesize peptides in a nontraditional manner (that is, from the N- to the C-terminus).[3] One major drawback with this approach is that it risks epimerization[4] at all coupling stages due to repeated resin-bound carboxyl activation. An alternative approach would be to invert the peptide following conventional (C → N) synthesis and then modify the C-terminus. Examples of inverting resin-bound peptides are known;[5] however, no method has been reported that allows inversion, C-terminal modification, and release of the modified peptide into solution. Such a method would allow an inverted peptide library to be C-terminally modified with pharmacophores such as chloro- and acyloxymethyl ketones.[6]

We now report the methodology for the general solid-phase synthesis of C-terminally modified peptides ready for a variety of solution screening applications and a method for retaining an Edman-sequencable coding strand for resin-screening purposes. The process was analyzed by cleavage of intermediates from the resin and subsequent HPLC, MS (Electrospray and FAB), amino acid analysis, and by our recently described technique of solid-phase reaction monitoring (MALDI-TOF SPIMS).[7]

The synthetic procedure is outlined in Scheme 1. Thus Fmoc-Lys(Boc)-OH was attached to either polystyrene aminomethyl resin (0.33 $mmol\,g^{-1}$) or to TentaGel S-$NH_2$ (130 $\mu$m beads, 0.29 $mmol\,g^{-1}$). The Fmoc group was removed with 20% piperidine in DMF, and the α-amine reprotected with an Aloc group by means of diallylpyrocarbonate.[8] The Boc group was removed, and the highly acid-labile linker (4-(4-hydroxymethyl-3-methoxyphenoxy)butanoic acid (HMPB)[9] coupled to the

[*] Dr. M. Bradley, Dr. M. Davies
Department of Chemistry
University of Southampton
Southampton, SO17 1BJ (UK)
Fax: Int. code +(1703)593781
e-mail: mb14@soton.ac.uk

[**] This work was supported by a BBSRC/EPSRC [BMS] project grant (no. B04846). We would like to acknowledge the Royal Society for a University Research Fellowship to M. B. We also thank Bryan Egner, Marianne Cardno, and Helen Smith for preliminary studies, John Horton of the Ferring Institute, Southampton for the amino acid analysis, and Lawrence Hunt for the peptide sequencing.