Experimental Procedure

Diels–Alder reaction of methacrolein with cyclopentadiene catalyzed by **2d**: To a dry flask in an inert atmosphere dry box was added $CuBr_2$ (22 mg, 0.10 mmol), $AgSbF_6$ (69 mg, 0.20 mmol) and *tert*-butyl[pyridine-bis(oxazoline)] **2** (33 mg, 0.10 mmol). The flask was fitted with a serum cap, removed from the dry box and charged with 4 mL CH_2Cl_2. The resulting heterogenous mixture was allowed to stir for 6 h and then filtered through a plug of cotton to give a clear blue-green solution. This solution was then cooled to −40 °C and cyclopentadiene (2.4 mmol, 158 mg, 164 mL) was added followed by methacrolein (140 mg, 166 mL, 2.0 mmol). The reaction was monitored by taking a 100 μL aliquot and filtering through a small plug of silica gel eluting with 2 mL of diethyl ether. The solvent was removed in vacuo and the resulting oil dissolved in $CDCl_3$ and analyzed by ^1H NMR spectroscopy. The reaction mixture was monitored until the conversion was ≥95%. The crude reaction mixture was filtered through a plug of silica gel eluting with diethyl ether. The resulting solution was concentrated to give (1*R*,2*S*, 4*R*)-2-methylbicyclo-[2.2.1]hept-5-ene-2-carboxaldehyde as a clear colorless oil. $[\alpha]_D = +21.4$ ($c = 2.3$, EtOH); $R_f = 0.5$ (40% hexane/CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 9.69$ (s, 1H, CHO), 6.29 (dd, $J = 5.6$, 3.0 Hz, 1H, C(6)-H), 6.11 (dd, $J = 5.6$, 3.0 Hz, 1H C(5)-H), 2.89 (br s, 1H, C(1)-H), 2.82 (br s, 1H, C(4)-H), 2.25 (dd, $J = 11.9$, 3.8 Hz, 1H, C(3)HXH$_Y$), 1.39 (m, 2H, C(7)H$_2$), 1.01 (s, 3H, Me), 0.76 (d, $J = 11.9$ Hz, 1H, C(3)H$_X$HY); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 205.8$, 139.5, 133.1, 53.9, 48.5, 47.6, 43.2, 34.6, 20.0; IR (neat): $\tilde{\nu} = 2973$, 2870, 2705, 1720, 1448, 1333, 1119 cm^{-1}; Exact mass calcd for $C_9H_{12}O$ 136.0893; found 136.0888 (EI). At this point the *exo*:*endo* product ratio was ascertained by GLC: DB-1701, 110 °C, 5 psi, t_r(*exo*) = 5.40, t_r(*endo*) = 6.01. This aliquot was then derivatized and used for determination of the enantioselectivity of the reaction. The cycloaddition product (14 mg, 0.10 mmol) was diluted with CH_2Cl_2 (0.5 mL) and (−)-(2*R*,4*R*)-pentanediol (20 mg, 0.20 mmol) and a few crystals of *p*-TsOH were added. After stirring for 6 h at room temperature, tlc analysis indicated that acetalization was complete. The reaction mixture was eluted through a short plug of silica with ether and analysed by capillary GLC. In this way the enantiomeric excess of the *exo* cycloaddition product was determined. Using the enantiomer of the diol, (+)-(2*S*,4*S*)-pentanediol, gave the same numeric value for the *exo* enantiomeric excess (within ±2% ee) indicating that there was negligible kinetic resolution during the acetalization reaction. Purification by flash chromatography gave the pure (2(1*R*,2*S*, 4*R*),9*R*,11*R*)-4,6-dimethyl-2-(2-methylbicyclo[2.2.1]hept-5-ene-2-yl)-1,3-dioxane. R_f 0.42 (20% EtOAc/hexanes); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 6.13$–6.07 (m, 2H, C(5)-H, C(6)-H), 4.69 (s, 1H, C(8)-H), 4.32–4.28 (m, 1H, C(9)-H) 3.91–3.84 (m, 1H, C(11)-H) 2.73 (br s, 1H, C(1)-H), 2.65 (br s, 1H, C(4)-H), 1.76–1.55 (m, 3H, C(7)-CH$_2$, C(3)-H$_X$H$_Y$), 1.36 (d, $J = 7.0$ Hz, 3H, C(9)-CH$_3$), 1.28-1.33 (m, 2H, C(10)-CH$_2$), 1.20 (d, $J = 6.2$ Hz, 3H, C(11)-CH$_3$), 0.86 (s, 3H, C(2)-CH$_3$), 0.74 (dd, $J = 2.7$, 12.0 Hz, 1H, C(3)-H$_X$H$_Y$); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 137.2$, 135.7, 99.5, 67.9, 67.7, 47.9, 47.4, 45.5, 37.2, 36.9, 21.9, 18.8, 17.3; IR (neat): $\tilde{\nu} = 3058$, 2969, 1449, 1375, 1334, 1240, 1136, 1058, 1004 cm^{-1}; Exact mass calcd for $C_{14}H_{22}O_2$ 222.1625; found 222.1620 (EI); GLC, DB-1701, 110 °C, 5 psi, t_r(minor product) = 29.89, t_r (major product) = 30.63 min.

Diels–Alder reaction of β-chloroimide **3c** with cyclopentadiene. A solution of catalyst **1d** (X = SbF_6) was prepared by mixing $CuCl_2$ (766 mg, 5.7 mmol), *tert*-butylbis(oxazoline) **1** (1.89 g, 6.3 mmol), and $AgSbF_6$ (3.92 g, 11.4 mmol) in CH_2Cl_2 (57 mL), stirring for 8 h at ambient temperature and filtering through celite. Imide **3c** (10.96 g, 62.4 mmol) was then added as a solution in CH_2Cl_2 (60 mL) by cannula (5 mL rinse of CH_2Cl_2). Immediately thereafter, cyclopentadiene (62 mL, 744 mmol) was added by syringe. The resulting solution was stirred at room temperature for 24 h. The reaction mixture was directly applied to a short column of silica gel (6 × 6 cm) and eluted with approximately 1 L of 1:1 ethyl acetate/hexane. Concentration afforded the unpurified product **4c** which was analyzed. ^1H NMR analysis indicated that the reaction had proceeded to >98% conversion. The unpurified reaction mixture was analyzed directly by chiral GLC, which showed the *endo*/*exo* ratio to be 87:13 (*endo* isomer 96% ee, chiraldex G-TA column; oven temperature = 150 °C, flow rate = 20 psi; t_r(*endo* major enantiomer) = 47.40, t_r (*endo* minor enantiomer) = 57.62, t_r(*exo* enantiomer 1) = 50.27, t_r(*exo* enantiomer 2) = 51.85). The product mixture was then purified by chromatography (8 × 32 cm silica gel, 30% ethyl acetate/hexane) to afford 14.45 g (59.8 mmol, 96%) of **4c** as a white solid. Recrystallization from ethyl acetate/hexane yielded enantiomerically pure **4c**: $[\alpha]_D = -113$ ($c = 1.10$, CH_2Cl_2); IR (CH_2Cl_2): $\tilde{\nu}$ 3000, 1781, 1699, 1480, 1387 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 6.23$ (dd, 1H, $J = 5.6$, 3.3 Hz, C*H*=CH), 5.90 (dd, 1H, $J = 5.6$, 2.7 Hz, CH=C*H*), 4.41 (t, 2H, $J = 7.8$ Hz, OCH$_2$), 4.24 (m, 1H, -CH-), 4.13 (m, 1H, -CH-), 4.05–3.87 (m, 2H, -NCH$_2$), 3.39 (br d, 1H, $J = 1.4$ Hz, bridgehead H), 3.06 (br s, 1H, bridgehead H), 2.10 (br d, 1H, $J = 9.1$ Hz, one of -CH$_2$-), 1.72 (dd, 1H, $J = 9.0$, 1.7 Hz, one of -CH$_2$-); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 172.0$, 153.2, 136.2, 134.4, 62.1, 58.8, 54.8, 52.4, 48.1, 46.9, 42.8; exact mass calcd for $C_{11}H_{12}N_1O_3Cl_1$ requires *m/z* 241.0506; found *m/z* 241.0494 (EI).

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[10] *exo*:*endo* Ratios determined by GLC analysis. (DB-1701, 110 °C, 5 psi) For acrolein: t_r(major product) = 5.32, t_r(minor product) = 5.92 min. For methacrolein: t_r(major product) = 5.40, t_r(minor product) = 6.01 min.; for bromoacrolein: t_r(starting aldehyde) = 2.33, t_r(major product) = 9.59, t_r(minor product) = 10.76 min. Enantiomeric excesses for acrolein and methacrolein adduct were determined by GLC analysis after conversion to the acetal of (*R*,*R*)-pentanediol (DB-1701, 110 °C, 5 psi) For the acrolein adduct-derived acetal: t_r(major product) = 28.15, t_r(minor product) = 28.91. For the methacrolein adduct-derived acetal: t_r(major product) = 29.89, t_r(minor product) = 30.55. For the bromoacrolein adduct, the enantiomeric excess was determined by GLC of the dimethyl acetal (GTA, 110 °C, 5 psi, t_r(minor product) = 62.95, t_r(major product) = 64.43 min and by ^{19}F NMR of the corresponding Mosher ester.

Aminocyclopentadienes, Aminoferrocenes, and Aminocobaltocenes**

Herbert Plenio* and Dirk Burth

More than forty years after the discovery of ferrocene, examples of aminocyclopentadienes and aminoferrocenes are still scarce.[1] Even what is probably the best synthesis (four steps starting from ferrocene) of the parent compound aminoferrocene $FcNH_2$ to date affords only small amounts;[2] alternate synthetic routes are equally demanding.[3] Several *N*,*N*-dialkylaminoferrocenes can, according to a paper by Boche et al., be prepared from *O*-tosylated *N*, *N*-dialkylhydroxylamines in good yields;[4] however, the number of hydroxyl derivatives[5] is limited and, in addition, the handling of these compounds poses certain risks,[6] which severely limits the possible applications of this reaction.

[*] Dr. H. Plenio, Dipl.-Chem. D. Burth
Institut für Anorganische und Analytische Chemie der Universität
Albertstrasse 21, D-79104 Freiburg (Germany)
Telefax: Int. code + (761)2035987
e-mail: plenio@sun8.ruf.uni-freiburg.de

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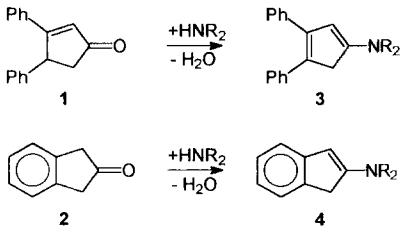
In the context of our own research in the area of redox-switchable ferrocene crown ethers,[7] we became interested in developing an efficient synthesis for aminocyclopentadienes, aminoferrocenes, and aminocobaltocenes.

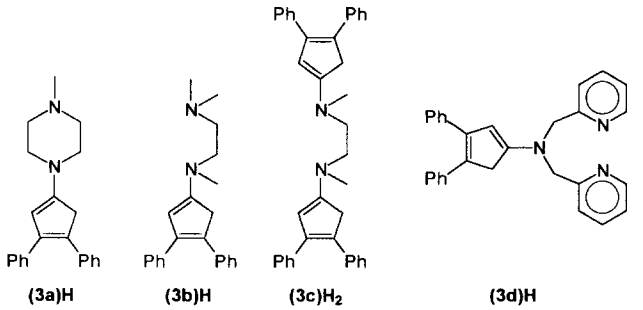
The reaction of ketones with secondary amines leads to enamines by the elimination of water.[8] Using cyclopentenones[9] as starting materials this reaction seemed ideally suited[7] for the preparation of *N,N*-dialkylaminocyclopentadienes, which could then be further reacted to yield the desired substituted ferrocenes and cobaltocenes.

Thus 3,4-diphenylcyclopent-2-enone (**1**)[10] and 2-indanone (**2**) were treated with secondary amines such as *N*-methylpiperazine (**a**), trimethylethylenediamine (**b**), *N,N'*-dimethylethylenediamine (**c**), and bis(2-picolyl)amine (**d**) (Scheme 1). In case of **1**, *N,N*-dialkylaminocyclopentadienes (**3a**)**H**, (**3b**)**H**, (**3c**)$\mathbf{H_2}$, and



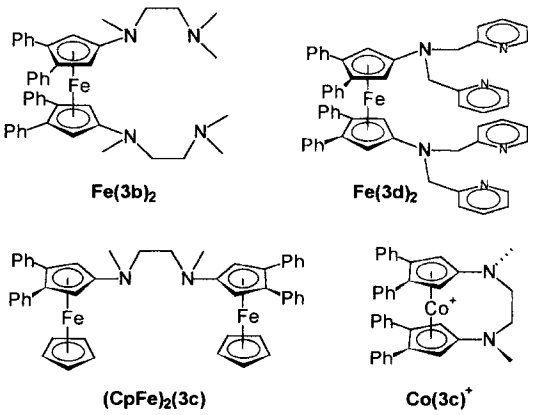
Scheme 1. Synthesis of *N,N*-dialkylaminocyclopentadienes **3** and -indenes **4**.

(**3d**)**H**, respectively, were afforded as pale yellow solids (Scheme 2) in yields ranging from 45–70%. The analogous indenes (**4a**)**H**, (**4b**)**H**, (**4c**)$\mathbf{H_2}$, and (**4d**)**H** were obtained in yields of >80%.[11] As a general observation, reactions involving 2-indanones (**2**) proceed at a faster rate and under milder conditions than the analogous reactions with 3,4-diphenylcyclopent-2-enone (**1**). An important characteristic of the secondary amines HNR_2 employed in this study is the presence of donor units in the R group. This allows the formation of σ donor metal complexes with the amine nitrogen as binding site.[12]



Scheme 2. A selection of the new *N,N*-dialkylaminocyclopentadienes **3** (the corresponding 2-(*N,N*-dialkylamino)indenes **4** are not shown).

The derivatives (**3a**)**H**, (**3b**)**H**, and (**3c**)$\mathbf{H_2}$, as well as (**4a**)**H**, (**4b**)**H**, and (**4c**)$\mathbf{H_2}$ (not shown) are readily deprotonated with *n*BuLi to give the corresponding lithium compounds, which were found to be stable in a moisture- and oxygen-free atmosphere. The *N,N*-dialkylaminoferrocenes **Fe**(**3a**)$_2$, **Fe**(**3b**)$_2$, and **Fe**(**3c**) were obtained in 30–50% yield by treating the lithium salts of **3** with $FeCl_2$. The corresponding cobaltocenes **Co**(**3a**)$_2$, **Co**(**3b**)$_2$, and **Co**(**3c**) can be synthesized in yields of 40–60% in an analogous fashion by reacting the lithium salts of **3** with $CoBr_2 \cdot 3THF$ (the products were isolated as their cobaltocinium salts following oxidation) (Scheme 3). The lithium salts of **4** react in the same way. The derivative (**3d**)**H** decomposed rapidly upon attempted deprotonation; however, the *N,N*-dialkylaminoferrocene **Fe**(**3d**)$_2$ could be prepared by treating (**3d**)**H** with $Fe(NiPr_2)_2$ which had been generated in situ. (**CpFe**)$_2$(**3c**) is readily accessible by irradiating a mixture of **Li**$_2$(**3c**) and $[CpFeL]^+[PF_6]^-$ with UV light (L = *p*-xylene).



Scheme 3. A selection of the new aminoferrocenes and aminocobaltocenes.

Oxidation of these new aminoferrocenes and aminocobaltocenes ($E_{1/2}$ **Fe**(**3c**) −0.01 V, **Fe**(**3d**)$_2$ 0.00 V, **Co**(**4b**)$_2$ −1.15 V, **Co**(**4c**) −1.08 V) occurs at significantly more negative potential than reported for ferrocene ($E_{1/2}$ = + 0.40 V in CH_3CN vs. Ag/AgCl) and cobaltocene ($E_{1/2}$ = − 0.94 V in CH_3CN vs. Ag/AgCl). As a result of the weakly electron-withdrawing nature of the aryl groups both the aminoferrocenes and aminocobaltocenes are less sensitive to oxidation than 1,1'-bis(dimethylamino)ferrocene ($E_{1/2}$ = − 0.23 V in CH_3CN vs. SCE) and 1,1'-bis(dimethylamino)cobaltocene ($E_{1/2}$ = −1.35 V in CH_3CN vs. SCE).[4, 13]

According to X-ray diffraction analyses[14] the structures of the aminoferrocenes **Fe**(**3a**)$_2$[15] and **Fe**(**3d**)$_2$ [16] are very similar, despite the fact that the substituents at the amino groups vary considerably. Figure 1 depicts the structure of **Fe**(**3a**)$_2$ in the crystal as viewed along the axis centroid-Fe1-centroid. This projection shows that the six substituents of the ferrocene are arranged in such a manner that no unfavorable steric interactions result. The stacked phenyl rings are almost coplanar (12.4°); the distance between the two nitrogen atoms N1 and

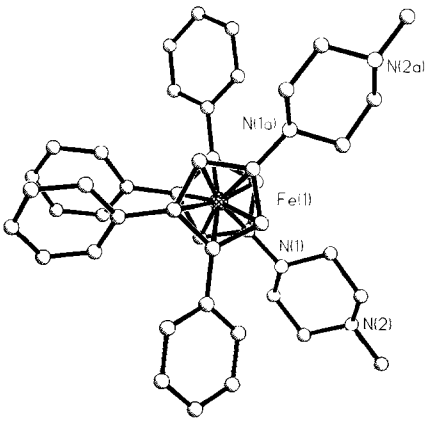


Fig. 1. Structure of **Fe**(**3a**)$_2$ in the crystal as viewed along the axis centroid-Fe1-centroid. For clarity, the hydrogen atoms have been omitted.

N1a is only 508.9 pm and thus they are already well preorganized for the chelating complexation of a metal ion. The substituents of the ferrocene are arranged in a similar way in the solid state for **Fe(3d)**$_2$ (Fig. 2). The distance N1–N2 is also rather small (503.8 pm), and the planes of two stacked phenyl rings are only slightly tilted (24.1°). The bond lengths and angles in **Fe(3a)**$_2$ and **Fe(3d)**$_2$ are unremarkable.

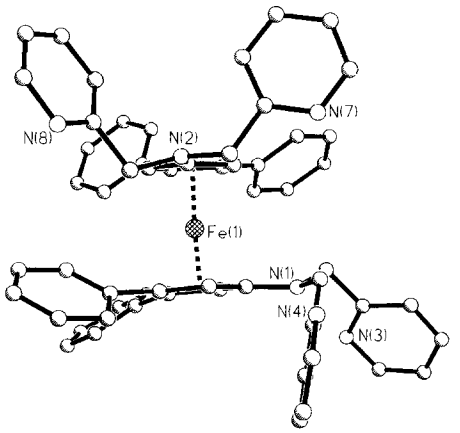


Fig. 2. Structure of **Fe(3d)**$_2$ in the crystal as viewed along the plane of the cyclopentadienyl rings. For clarity, the hydrogen atoms have been omitted.

The nitrogen atoms contained in the side chains of the aminoferrocenes can be used for the formation of σ donor complexes. For instance, the isolation of a stable complex between two $LiClO_4$ and **Fe(3b)**$_2$ demonstrates the relationship of the latter to TMEDA (tetramethylethylenediamine).

In summary, the reaction of 3,4-dimethylcyclopent-2-enone (**1**) and 2-indanone (**2**) with secondary amines provides a convenient entry to an almost unlimited number of *N*,*N*-dialkylaminocyclopentadienes **3** and -indenes **4**, respectively. Further reaction of compounds **3** and **4** has been shown to afford the corresponding aminoferrocenes and aminocobaltocenes. We are currently investigating the reactions of **3** and **4** with other metal salts and the complexation behavior of the donor atoms in the side chain.

Experimental Procedure

The following compounds were synthesized and fully characterized: *N*,*N*-dialkylaminocyclopentadienes, **(3a)H**, **(3b)H**, **(3c)H**, and **(3d)H**; 2-(*N*,*N*-dialkylamino)-indenes, **(4a)H**, **(4b)H**, **(4c)H**, and **(4d)H**; ferrocenes, **Fe(3a)**$_2$, **Fe(3b)**$_2$, **Fe(3c)**, **(CpFe)**$_2$**(3c)**, **Fe(3d)**$_2$; cobaltocenes, **Co(3a)**$_2$, **Co(3b)**$_2$, **Co(3c)**, **Co(4a)**$_2$, **Co(4b)**$_2$, **Co(4c)**, and **Co(4d)**$_2$. Only a representative selection of experimental procedures and NMR data is given here.

(3d)H: A mixture of **1** (5.85 g, 25 mmol), bis(2-picolyl)amine (**d**) (5.0 g, 25 mmol), and *p*-toluenesulfonic acid (0.05 g) in benzene (100 mL) was heated to reflux for 48 h under N_2 in a water separator. After the solvent had been removed by vacuum destillation, the residue was recrystallized from toluene/hexane to afford **(3d)H** as a yellow powder. Yield: 6.0 g (58%). ^{1}H NMR ($CDCl_3$): δ = 3.64 (s, 2H, CpH), 4.66 (s, 4H, CH_2-Py), 5.26 (s, 1H, CpH), 6.97–7.34 (m, 14H, ArH + PyH), 7.63 (dt, J = 1.8, 7.7 Hz, 2H, PyH), 8.55 (d, J = 4.34 Hz, 2H, PyH).

(3c)H$_2$: ^{1}H NMR ($CDCl_3$): δ = 2.92 (s, 6H, CH_3), 3.43 (s, 4H), 3.54 (s, 4H), 5.19 (s, 2H, CpH), 7.0–7.40 (m, 20H, ArH). ^{13}C NMR ($CDCl_3$): δ = 38.70, 42.66, 50.34, 102.20, 123.30, 124.52, 126.78, 126.84, 128.02, 128.31, 128.37, 137.64, 138.51, 143.58, 155.93.

(4b)H: Trimethylethylenediamine (**b**) (155 mg, 1.52 mmol) was added to a solution of **2** (200 mg, 1.52 mmol) in methanol (5 mL) and heated to reflux for 2 h. After the methanol had been removed by vacuum destillation, the product **(4b)H** was obtained as a brown oil. ^{1}H NMR ($CDCl_3$): δ = 2.25 (s, 6H, CH_3), 2.44 (t, J = 7.6 Hz, 2H, NCH_2), 2.86 (s, 3H, CH_3), 3.28 (t, J = 7.6 Hz, 2H, NCH_2), 3.36 (s, 2H, NC-CH_2), 5.29 (s, 1H, NC=CH), 6.77–7.18 (m, 4H, ArH). ^{13}C NMR ($CDCl_3$): δ = 36.75, 37.58, 45.21, 50.56, 55.77, 95.80, 116.02, 119.04, 122.02, 126.06, 136.00, 147.46, 156.29.

Fe(3d)$_2$: **(3d)H** (414 mg, 1 mmol) was added to a solution of $FeCl_2$ (63.5 mg, 0.5 mmol) and $LiN(i\text{-}C_3H_7)_2$ (107 mg, 1 mmol) in THF (15 mL) at −78 °C. The reaction mixture was allowed to slowly warm to room temperature. After 2 h the solvent was removed by vacuum destillation and the residue was purified by chromatography using cyclohexane/ ethyl acetate/ Et_2NH (5:5:1) as eluant. Further purification was accomplished by recrystallization from toluene/hexane to give **Fe(3d)**$_2$ as a deep red powder; yield: 154 mg (35%). ^{1}H NMR ($CDCl_3$): δ = 4.19 (s, 4H, CpH), 4.23 (s, 8H, CH_2-Py), 7.11 (ddd, J = 1.4, 4.8, 7.4 Hz, 4H, PyH), 6.59–6.79 (m, 20H, PyH + ArH), 7.17–7.23 (m, 8H, PyH + ArH), 8.10 (ddd, J = 0.9, 1.8, 4.8 Hz, 4H, PyH). ^{13}C NMR (C_6D_6): δ = 59.06, 60.81, 82.03, 116.61, 121.73, 122.40, 125.88, 127.90, 130.20, 135.92, 139.17, 149.51, 159.95. $C_{58}H_{48}FeN_6$ (884.9), calcd. (found): C 78.72 (78.25), H 5.47 (5.50), N 9.50 (9.78).

Fe(3c): ^{1}H NMR (C_6D_6): δ = 2.60 (s, 6H, CH_3), 2.95 (s, 4H, CH_2), 4.60 (s, 4H, FcH), 6.92–7.03 (m, 12H, ArH), 7.34–7.39 (m, 8H, ArH). ^{13}C NMR (C_6D_6): δ = 38.49, 48.86, 57.68, 82.99, 111.42, 125.96, 127.78, 129.71, 138.78.

(CpFe)$_2$**(3c)**: ^{1}H NMR (C_6D_6): δ = 2.47 (s, 6H, CH_3), 3.01 (s, 4H, CH_2), 4.10 (s, 10H, C_5H_5), 7.06–7.10 (m, 12H, ArH), 7.50–7.55 (m, 8H, ArH). ^{13}C NMR ([D_6]acetone): δ = 39.84, 52.96, 57.50, 71.28, 81.85, 115.7, 126.57, 128.35, 130.40, 140.11. $C_{48}H_{22}Fe_2N_2$ (760.58), calcd. (found): C 75.80 (76.12), H 5.83 (5.58), N 3.68 (3.92).

Co(4b)$_2^+$**[CF_3SO_3]**$^-$: ^{1}H NMR (CD_3CN): δ = 2.33 (s, 12H, CH_3), 2.49 (t, J = 6 Hz, 4H, NCH_2), 2.97 (s, 6H, CH_3), 3.31 (br, 4H, NCH_2), 5.72 (s, 4H, CpH), 7.08–7.12 (m, 4H, ArH), 7.28–7.33 (m, 4H, ArH). $C_{29}H_{38}CoF_3N_4O_3S \cdot CH_3OH$ (670.68), calcd. (found): C 53.73 (53.53), H 6.31 (6.21), N 8.35 (8.10).

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[15] a) X-ray structure analysis of **Fe(3a)**$_2 \cdot 0.5\,H_2O$ ($C_{44}H_{46}FeN_4 \cdot 0.5\,H_2O$): crystal dimensions: 0.5 × 0.4 × 0.4 mm^3, cubic, space group *Fd*-3, Z = 48, a = 36.905(4) Å, V = 50264(9) Å^3, ρ_{calcd} = 1.246 g cm^{-3}, θ = 2.4–23°, T = 293(2) K, 9144 reflections measured, 2953 of which are independent, empirical absorption correction, $\mu(Mo_{K\alpha})$ = 0.47 mm^{-1}, data/ parameters = 2003/ 231,

full-matrix least-squares refinement on F^2. H atom riding model, R values $[I > 4\sigma(I)]$: $R1 = 0.0635$, $wR2 = 0.171$. GOOF = 1.03, residual electron density = +0.41, −0.42 e Å^{-3}. The relatively poor quality of single crystals of **Fe(3a)$_2$** limited the data collection to $\theta = 23°$. This explains the large number of unobserved reflections and the moderate R values. b) Further details of the crystal structure investigations may be obtained from the Fachinformationszentrum Karlsruhe, D-76344 Eggenstein-Leopoldshafen (Germany), on quoting the depository numbers CSD-401290 (**Fe(3a)$_2$**·0.5 H$_2$O) and CSD-401324 **Fe(3d)$_2$**·H$_2$O.

[16] X-ray structure analysis of **Fe(3d)$_2$**·H$_2$O ($C_{58}H_{48}FeN_6$)·H$_2$O: crystal dimensions: 0.5 × 0.4 × 0.2 mm^3, triclinic, space group $P\bar{1}$, $Z = 2$, $a = 11.031(2)$, $b = 11.042(2)$, $c = 20.607(4)$ Å, $\alpha = 83.74(3)$, $\beta = 76.96$, $\delta = 79.47(3)°$, $V = 2398.1(8)$ Å^3, $\rho_{calcd} = 1.25$ g cm^{-3}, $\theta = 2.8$–$26°$, $T = 293(2)$ K, 9943 reflections measured, 9427 of which are independent reflections, empirical absorption correction, $\mu(Mo_{K\alpha}) = 0.36$ mm^{-1}, data/ parameters = 7209/ 588, full-matrix least-squares refinement on F^2, H atom riding model, R values $[I > 4\sigma(I)]$: $R1 = 0.0610$, $wR2 = 0.153$. GOOF = 1.09, residual electron density = +0.50, −0.40 e Å^{-3} [15b].

A Novel Allylic Anchor for Solid-Phase Synthesis—Synthesis of Protected and Unprotected O-Glycosylated Mucin-Type Glycopeptides**

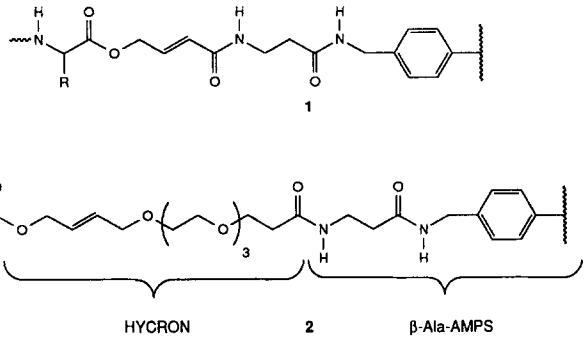
Oliver Seitz and Horst Kunz*

Dedicated to Professor Hans Jeschkeit on the occasion of his 65th birthday

Solid-phase synthesis provides rapid access to biologically relevant peptides.[1] The anchor group used between the target peptide and the polymeric support plays a very significant role. For glycopeptides as well as phosphopeptides or peptides containing acid- and base-sensitive protecting groups, which are to be employed in fragment condensations, the anchor group has to meet specific requirements. The same applies to the area of combinatorial chemistry for the preparation of peptide[2] and structure libraries.[3]

Anchoring through allyl esters[4] not only allows peptide derivatives to be detached without affecting acid- and base-labile structural elements, but also provides orthogonal stability relative to the temporary protecting groups commonly used in solid-phase peptide synthesis.[5] Thus, the *tert*-butyloxycarbonyl (Boc) group and the fluorenylmethoxycarbonyl (Fmoc) group can be used as N-terminal protecting groups. The cleavage of the allyl ester can be achieved by a palladium(0)-catalyzed transfer of the allyl group to a scavenger nucleophile like morpholine or *N*-methylaniline, which traps the allyl moiety irreversibly.[6] As a result, stabilized, long-lived cations are not generated as is the case with the frequently employed acid-labile anchors based on alkoxybenzyl, benzhydryl, or trityl esters.[7] This also avoids alkylation of nucleophilic structural elements[8] of the peptide and does not endanger acid-labile structural elements.

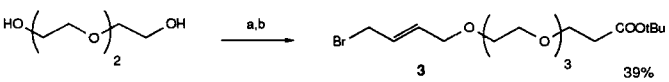
Derivatives of hydroxycrotonic acid were initially used to functionalize the polymeric support, aminomethylpolystyrene (AMPS), with allylic anchor groups.[5a] Insertion of a standard amino acid, for instance β-alanine, between the anchor and the polymer creates a spacer effect and allows the determination of the peptide loading independent of the degree of dryness.[9] Complex glycopeptides have been synthesized successfully according to this principle (β-HYCRAM **1**, Scheme 1).[10]



Scheme 1. Segments of peptide-loaded β-Ala-aminomethylpolystyrene (β-Ala-AMPS) with allylic anchor groups: β-HYCRAM **1** and novel anchor group HYCRON in **2**.

While the glycopeptides could be detached from the resin in high yields when the Boc strategy was used, reduced yields were observed when the Fmoc group was used as the temporary amino protection group. β-HYCRAM-bound glycine was used as a low molecular weight model. Upon exposure to morpholine/DMF (1:1) for 3 d, 12% of the allyl ester was aminolyzed.[11] As in many solid-phase syntheses, however, losses can occur at the dipeptide stage (formation of diketopiperazine) and, due to steric hindrance, during the cleavage process itself. Therefore a new anchor of the allyl ester type should incorporate a flexible, polar spacer in order to reduce steric hindrance and associations with the polystyrene matrix.[4] The achievements in solid-phase synthesis with graft copolymers made of polyethyleneglycol and polystyrene demonstrate the beneficial properties of polar spacers.[12] Moreover, the α,β-unsaturated carbonyl structure should be replaced to increase the stability against nucleophilic attack.

Structure **2** contains an allylic anchor (HYCRON) that meets the requirements outlined above. The precursor **3** of the allyl anchor, which allows the linkage to both the starting amino acid and the polymeric support, is synthesized by a sodium glycolate catalyzed Michael addition of triethgleneglycol to *tert*-butyl acrylate (Scheme 2) and subsequent reaction of the Michael adduct with 1,4-dibromo-2-butene under phase-transfer conditions.



Scheme 2. a) H$_2$C=CH-COO*t*Bu, THF, sodium glycolate (1 mol%); b) BrCH$_2$-CH=CH-CH$_2$Br, NaOH, Bu$_4$NHSO$_4$, H$_2$O, CH$_2$Cl$_2$.

To load the polymer with the starting amino acid, the amino acid–anchor adduct **4** is prepared. Adduct **4** is obtained by reaction of the protected amino acid with allyl bromide **3** under phase-transfer conditions and subsequent cleavage of the carboxyl protecting group R′ (Scheme 3). The nucleophilic esterification avoids racemization of the starting amino acid, for example, the anchored threonine **5**.

The applicability of the new anchor (HYCRON) was tested in the solid-phase synthesis of the O-glycosylated tetrapeptide **6**. Peptide **6** is a partial structure of peptide T, a threonine-rich segment of the HIV-envelope protein gp120.[13]

[*] Prof. Dr. H. Kunz, Dipl.-Chem. O. Seitz
Institut für Organische Chemie der Universität Mainz
J.-J. Becher-Weg 18-20, D-55099 Mainz (Germany)
Telefax: Int. code + (6131)39-4786

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