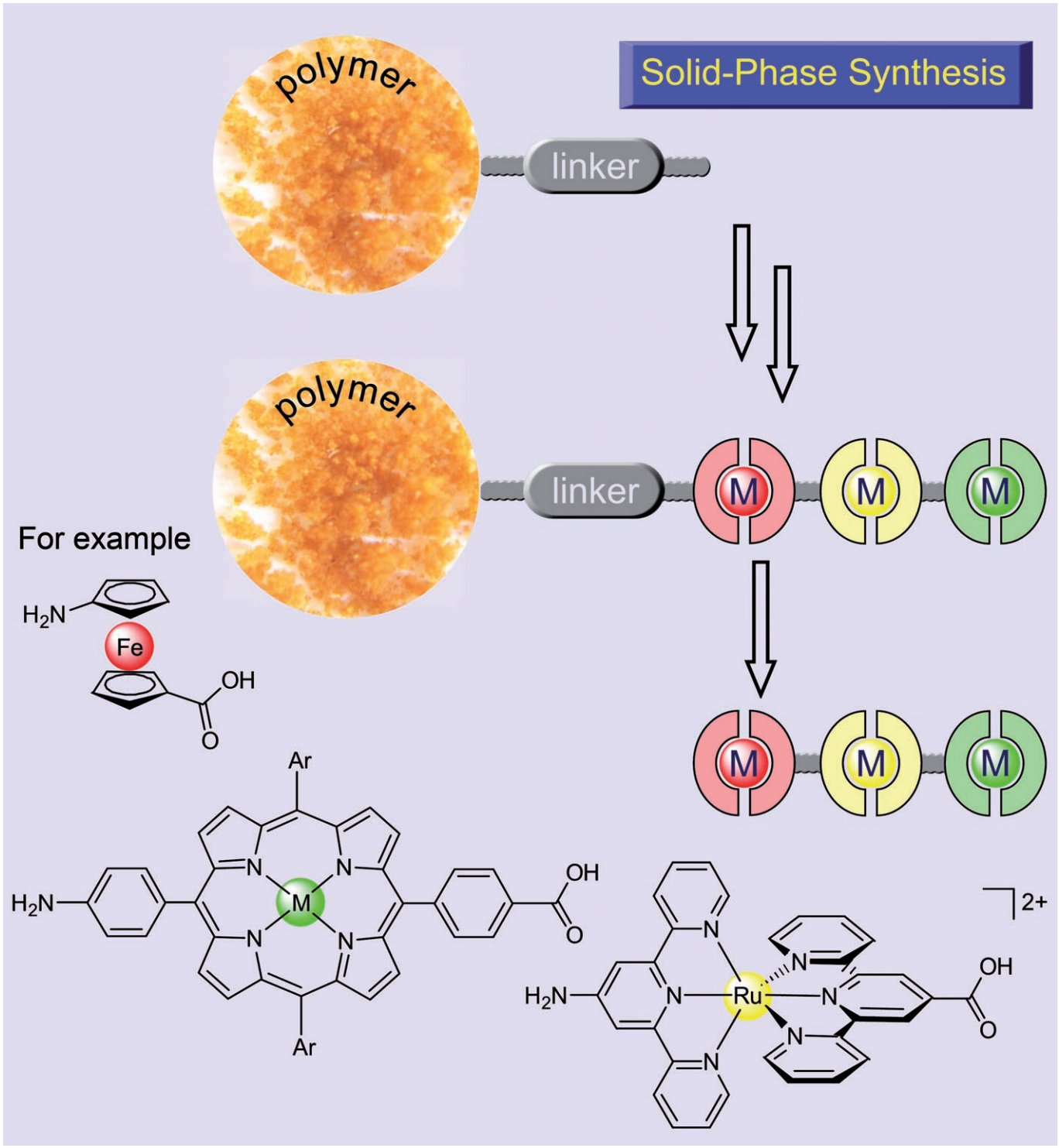
CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200800697

Solid-Phase Synthesis of Transition-Metal Complexes

Katja Heinze,* Manuela Beckmann, and Klaus Hempel[a]



Abstract: This overview highlights recent progress in the field of selective construction of linear, oligonuclear transition-metal complexes by using solid-phase synthesis procedures. Two general protocols have been identified: formation of coordinative bonds between metal centres and bridging ligands and formation of covalent bonds between preformed kinetically inert transition-metal-containing building blocks in the chain growth step. Currently available suitable building blocks for the second approach are based on ferrocene units, bis(terpyridine)–ruthenium(II) moieties or metal porphyrins.

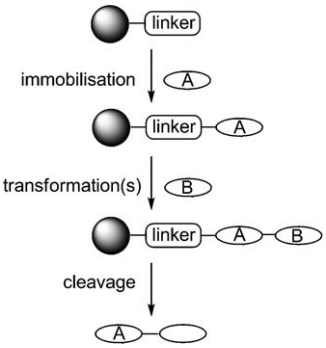
Keywords: heterometallic complexes · immobilization · polymer-bound complexes · solid-phase synthesis

Introduction

In the last decades solid-phase organic synthesis (SPOS) has become a powerful tool for synthetic organic and biological chemistry. Although already developed more than 40 years ago by Merrifield[1] for selective peptide synthesis (solid-phase peptide synthesis, SPPS) there has been a rapid growth in this research area in recent years so that solid-phase organic synthesis is nowadays widely employed in all kinds of organic syntheses.[2–6] The variety of available solid supports and linkers[6] allows many reaction conditions, so that solid-phase synthesis can be implemented for most organic synthesis protocols. Solid-phase synthesis is ideally suited to perform reactions in parallel, because it readily enables the (automated) performance of multistep synthetic sequences.

A general solid-phase synthesis (SPS) scheme is depicted in Scheme 1. A suitably functionalised solid support is simply shaken with a mixture of solvents and reactants for a given time; the mixture is then filtered and the support is washed with suitable solvents. The immobilised substrate A is then transformed, deprotected or coupled with reactant B. Finally the product A–B is cleaved from the support giving products of high purity.

Employing this stepwise synthesis, full control over sequence, chain length and end groups of the resulting oligomers is achieved and any possible sequence isomer can be prepared, paving the way for rapid parallel combinatorial syntheses. This contrasts with supramolecular approaches (self-assembly) which usually yield only one isomer or assembly, namely the thermodynamically most stable one under the applied conditions.



Scheme 1. General solid-phase synthesis (SPS).

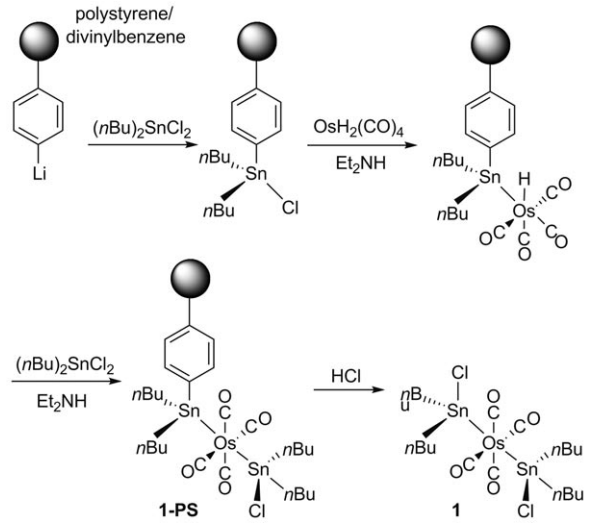
Despite the rapid development of solid-phase organic synthesis examples for the application of this strategy to the field of inorganic chemistry, that is, the synthesis and transformation of transition-metal complexes, are rare. The most important and common application of immobilised transition-metal complexes is catalysis.[7–10] For this purpose a well-defined molecular pre-catalyst is permanently bound to a solid support through adsorption, ionic or covalent bonding, or intercalation depending on the type of support (inorganic oxides, organic polymers or dendrimers).[11,12] Certainly, for efficient catalysis the active site should remain on the support during the whole catalytic process and leaching of the catalytic centre should be inhibited, so that the catalyst can be reused several times.

In contrast to catalytic applications of immobilised transition-metal complexes, the intermediates in SPOS are bound to the solid phase through suitable linkers that enable the easy attachment of the starting material to the support. They are also stable under a broad variety of reaction conditions, but allow selective cleavage at the end of the synthesis without damage of the product.

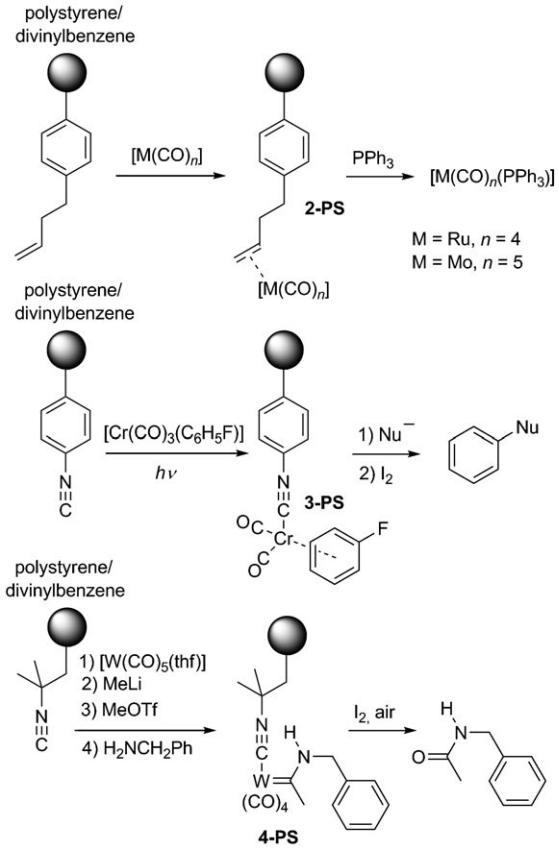
To our knowledge the very first application of a solid-phase synthesis protocol to construct an oligonuclear transition-metal complex was reported in 1975 by Burlitch and Winterton.[13] Di-*n*-butyltin-dichloride was coupled to lithiated styrene/20% divinylbenzene copolymer followed by coupling of tetracarbonyldihydridoosmium(II) with diethylamine as the coupling agent (Scheme 2). The second metal–metal bond was formed by using $(n\mathrm{Bu})_2\mathrm{SnCl}_2/\mathrm{Et}_2\mathrm{NH}$ giving the polymer-anchored trinuclear complex **1-PS**. Release of intact *trans*-bis(di-*n*-butylchlorotin)tetracarbonylosmium(II) (**1**) from the polymer was accomplished by acidic cleavage.

Apart from catalytic applications,[7–11] polymer-supported carbonyl complexes have been recently used in stoichiometric reactions (Scheme 3). Carbonyl–molybdenum(0) and –ruthenium(0) fragments were bound to polymers by coordination to double bonds (**2-PS**) and released by ligand displacement with PPh_3.[14] Polymer-anchored arene–tricarbonylchromium(0) complexes **3-PS** were employed as traceless

[a] Dr. K. Heinze, Dr. M. Beckmann, K. Hempel
Department of Inorganic Chemistry
University of Heidelberg, Im Neuenheimer Feld 270
69120 Heidelberg (Germany)
Fax: (+49) 6221-545707
E-mail: katja.heinze@urz.uni-heidelberg.de



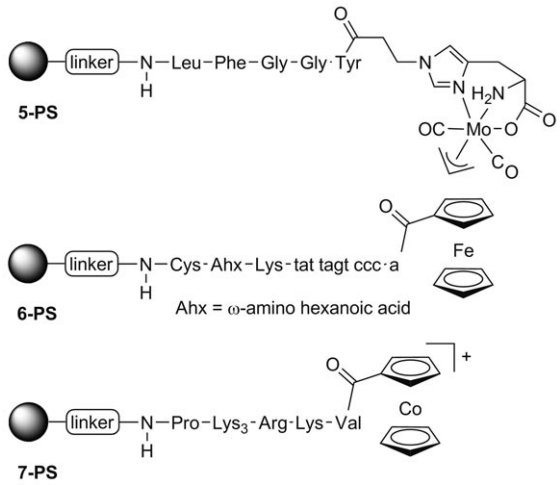
Scheme 2. SPS of *trans*-bis(di-*n*-butylchlorotin)tetracarbonylosmium(II).[13]



Scheme 3. Stoichiometric reactions with polymer-supported transition-metal–carbonyl complexes.

linkers for performing metal-activated, aromatic nucleophilic substitution reactions on a solid support.[15] Fischer carbene complexes were prepared on a polymer support. Amination with benzylamine to give amino–carbene **4-PS** and oxidative cleavage with I_2/air releases the oxygenated amino–carbene ligand.[16] In all the transformations depicted in Scheme 3 the polymer-bound complex is modified or destroyed during release from the resin, so these types of anchored transition-metal complexes are best described as supported reagents.

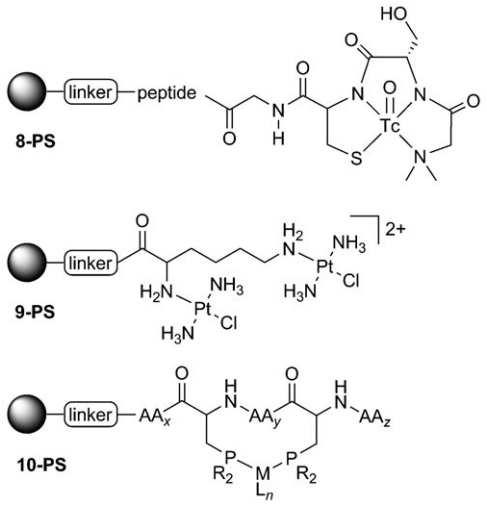
Solid-phase synthesis with transition metals as a part of the target product arose from biochemistry, medicinal chemistry, analytical chemistry and catalysis. As inorganic compounds possess specific properties that are not present in biomolecules, such as peptides or DNA, the labelling of biomolecules with transition-metal complexes has become an active area of research.[17] To be of use in these fields of chemistry the transition-metal complexes employed should be stable in water and air and compatible with typical coupling, deprotection and cleavage conditions. IR- and redox-active organometallic moieties have been appended to peptides or PNA by SPPS (Scheme 4; **5-PS**–**7-PS**), for example, for potential use in immunoassays or as an efficient mediator for enhanced cellular uptake.[17–20]



Scheme 4. Metal-labelled (bio)molecules prepared on a solid support.[16–20]

In drug development solid-phase library synthesis has become a major strategy that has recently also be applied to metal-containing drugs and pharmaceuticals. The peptide-^{99m}Tc–chelate conjugate **8-PS** has been prepared by SPPS as a potential radiopharmaceutical equipped with a targeting vector (Scheme 5).[21] Reedijk et al. reported the first example of a solid-phase synthesis of peptide-tethered dichloroplatinum(II) complexes,[22–24] and the automated synthesis of a family of 36 analogues[25] as well as the SPPS of dinuclear lysine-bridged platinum(II) complexes (Scheme 5; **9-PS**)[26] with the aim to discover new potent platinum anticancer agents. DNA-sequence selective hairpin polyamide platinum(II) complexes have also been prepared on solid supports.[27]

The discovery and optimisation of lead structures in catalysis research has also profited by solid-phase peptide synthesis techniques. Gilbertson and later Meldal and co-workers have introduced phosphino-containing amino acids into pep-

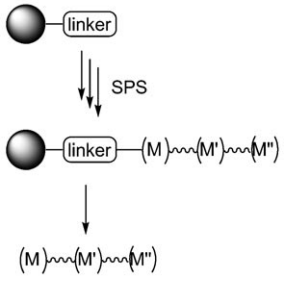


Scheme 5. Metal-functionalised (bio)molecules for drug discovery and asymmetric catalysis.

tides by means of SPPS (Scheme 5; **10-PS**). These peptides serve as chiral ligands for organometallic fragments, for example, {Rh(norbonadiene)} or {Pd(allyl)Cl} in asymmetric catalytic reactions.[28,29]

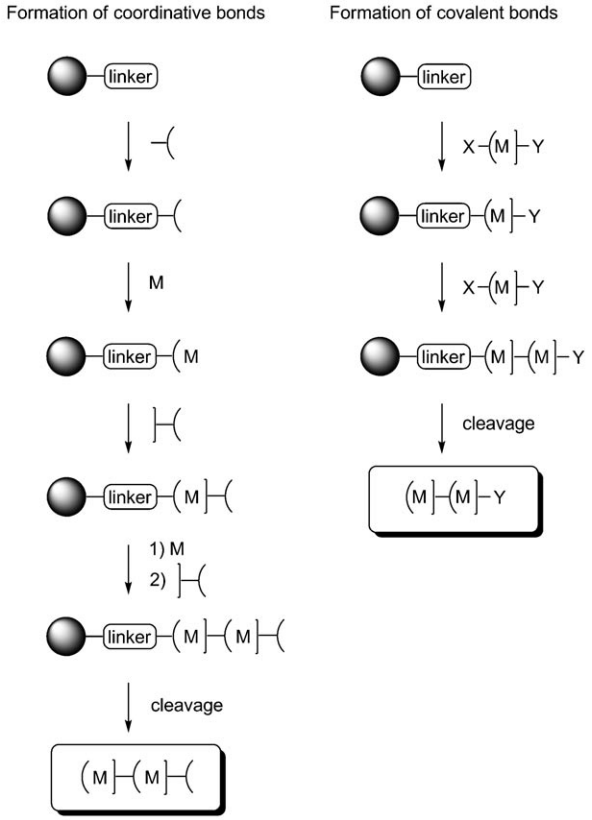
Metal-modified biomolecules prepared by SPS with one metal label attached to the terminus of the oligomer (see, for example, references [30–35]) as well as side-chain modifications of biooligomers (see, for example, references [36–39]) will not be considered further in this article. The preparation of metal-complex/peptide conjugates by solid-phase peptide synthesis has been recently summarised in microreviews and will not be covered in this article.[40]

Often metalation is the last step in the SPS so that the benefits of using solid-phase methodology are not immediately clear, as in this case metalation could also easily be performed after cleavage of the molecule from the solid support in homogeneous solution (on-resin labelling vs. post-SPS labelling). However, when combinatorial chemistry comes into play (e.g., solid-phase library synthesis[25] and solid-phase library screening[41]) the necessity of introducing the metal while the molecule is still bound to the support becomes evident. This is even mandatory when the transition metal constitutes an integral part of an oligomer backbone (Scheme 6).



Scheme 6. Polymer-anchored, oligonuclear transition-metal complexes.

Our approaches to selectively synthesise well-defined, multinuclear, transition-metal complexes by SPS are outlined in Scheme 7. The first approach relies on the formation of coordinative bonds between an asymmetric bridging ligand]–(and a metal centre in each chain-elongation step to build oligonuclear transition-metal complexes in a controlled stepwise fashion on solid support. In the second approach chain growth is achieved by formation of covalent bonds between ligands of suitably functionalised transition-metal complexes X-(M]-Y. Both strategies will be described in the following sections.



Scheme 7. SPS of oligonuclear transition-metal complexes.

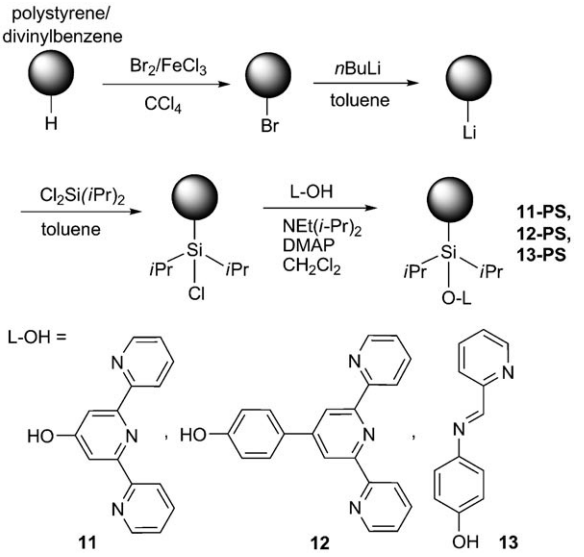
SPS of Transition-Metal Complexes: Formation of Coordinative Bonds

Suitable building units for this approach have to satisfy several conditions: to suppress ligand scrambling or chain rupture during the synthesis the metal-complex fragments employed need to be rather inert, preferably closed-shell transition-metal complexes. At the same time free coordination sites must be generated during the chain elongation step to accommodate the bridging ligand. Furthermore the cleavage conditions must be compatible with the stability of the coordination bonds in the backbone of the oligonuclear complex. Finally, on-resin analysis of solid-supported compounds at

intermediate stages is very advantageous in guiding the multistep synthesis. So the first part of this section briefly addresses suitable linkers, suitable on-resin analytical methods and stability of polymer-anchored, transition-metal complexes.

For rather sensitive organometallic complexes a silyl ether linker between the polymer and the first ligand has been successfully employed.[42–46] This linker type has been used in organic solid-phase synthesis of sensitive compounds, for example, oligosaccharides and prostaglandins.[47–49] The feasible and mild cleavage of silyl ethers by using fluoride ions was also attractive especially for sensitive organometallic complexes (low-valent, soft transition metals).

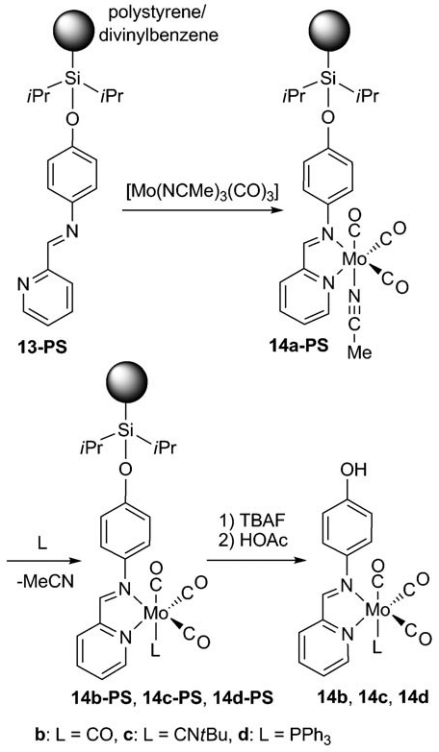
A silyl-functionalised resin (polystyrene/divinylbenzene copolymer) was prepared by bromination, lithiation and silylation according to the reaction sequence shown in Scheme 8.[42] A variety of hydroxyl-substituted ligands, such as tridentate 2,2′:6′,2″-terpyridines or bidentate Schiff bases (**11**, **12**, **13**), can be attached to the resin by DMAP-catalysed silyl ether formation (DMAP = 4-(dimethylamino)pyridine) giving the polymer–linker–ligand constructs **11-PS**, **12-PS** and **13-PS**, respectively.



Scheme 8. Immobilisation of ligands through a silyl ether linker on a polystyrene/divinylbenzene resin.

Selective breaking of the Si–O bond and thus release of the ligand from the polymer is accomplished by fluoridolysis with tetra-*n*-butylammonium fluoride (TBAF).[42] Single reaction steps on a solid support are easily monitored by IR spectroscopy, if significant changes occur in the IR spectra during the reaction.[50] The success of other reaction steps on resin can only be controlled by elemental analyses or by time- and material-consuming "cleave and analyse" procedures. Very useful progress in this respect was, therefore, the development of a mass spectrometric technique based on electron ionisation mass spectrometry.[42] This simple and widely available technique allows monitoring of all reaction steps on resin and thus facilitates a deeper insight in the reaction progress on solid support. In addition, resin loading can be easily estimated by this method. Intensities of observed peaks of the substituted polystyrene resin relative to a characteristic styrene peak as internal standard correlate with resin loading. This finding even enables the determination of rate constants for single reaction steps on the polymeric support. The fact that only a minimal amount of resin is required for analysis makes this method additionally attractive. However, the rather harsh conditions of the electron impact ionisation method impede its use for resin-bound transition-metal complexes. For organometallic complexes, especially carbonyl complexes, IR spectroscopy is the method of choice to monitor the reaction progress on the polymer support (highly sensitive IR detection of CO stretching vibrations in an otherwise empty spectral region).

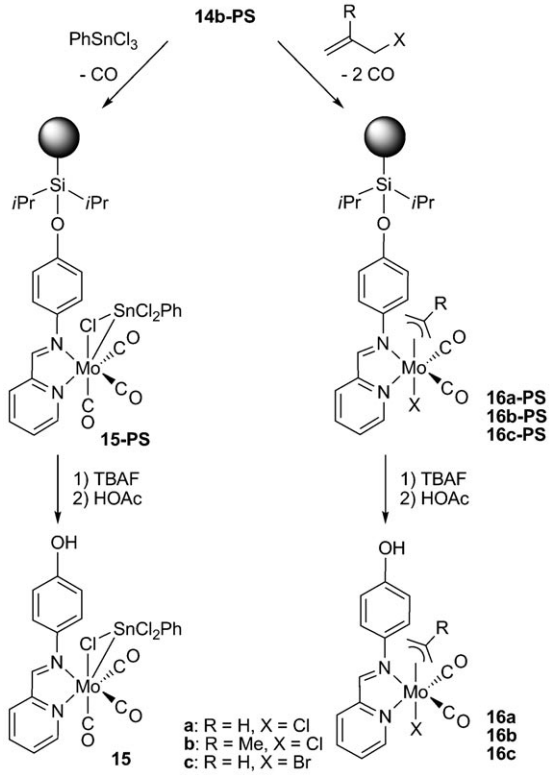
Polymer-supported carbonyl–molybdenum(0) complex **14a-PS** is selectively formed by adding the tricarbonylmolybdenum(0) source $[Mo(CH_3CN)_3(CO)_3]$ to **13-PS** (Scheme 9).[43] The labile acetonitrile ligand of **14a-PS** can easily be substituted by monodentate ligands, such as carbon monoxide, isonitriles or triphenyl phosphine, to yield the polymer-bound molybdenum(0) complexes **14b-PS**–**14d-PS** (Scheme 9). The intact mononuclear complexes **14b**–**14d** are retrieved from the resin by fluoridolysis and mild acidic workup.[43] By carefully optimising reaction conditions, such as cross-linking of the polymer, temperature and solvent, the chromium and tungsten analogues of **14b**–**14d** are accessible in a similar fashion.[51,52]



Scheme 9. Formation, transformation and release of molybdenum–carbonyl complexes.

The polymer-anchored carbonyl complexes **14b-PS**–**14d-PS** are immune to ligand scrambling under the reaction conditions (up to 60 °C) and cleavage conditions (fluoride ions, dilute acetic acid). Stability studies also prove the high thermal stability up to 200 °C, at which loss of carbon monoxide is observed.

Despite its thermal stability **14b-PS** undergoes oxidative addition reactions with phenyltin trichloride and allyl halides with concomitant loss of one and two equivalents of carbon monoxide, respectively (Scheme 10).[45] The former

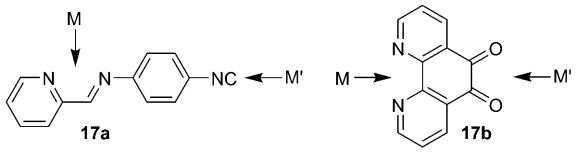


Scheme 10. Oxidative addition reactions performed on solid support.

reaction yields the seven-coordinate heterobimetallic molybdenum(II) complex **15-PS** and the latter allyl molybdenum(II) complexes **16a-PS**–**16c-PS**. All molybdenum(II) complexes can be released from the support without damage giving **15** and **16a**–**16c**, respectively. Thus mononuclear M^0 (M = Cr, Mo, W) and Mo^{II} complexes fulfil the conditions required for SPS of oligonuclear metal complexes and the SPS of oligonuclear complexes was addressed.[44,46]

For this approach the bifunctional diimine isonitrile ligand **17a** (for mixed-metal carbonyl complexes) and 1,10-phenanthroline-5,6-dione (**17b**; for platinum(II) complexes, vide infra) were employed (Scheme 11). Ligand **17a** is capable of coordinating two metal–carbonyl units, one through the isonitrile group and another one by the diimine chelate and is, therefore, an ideal directional bridging ligand.

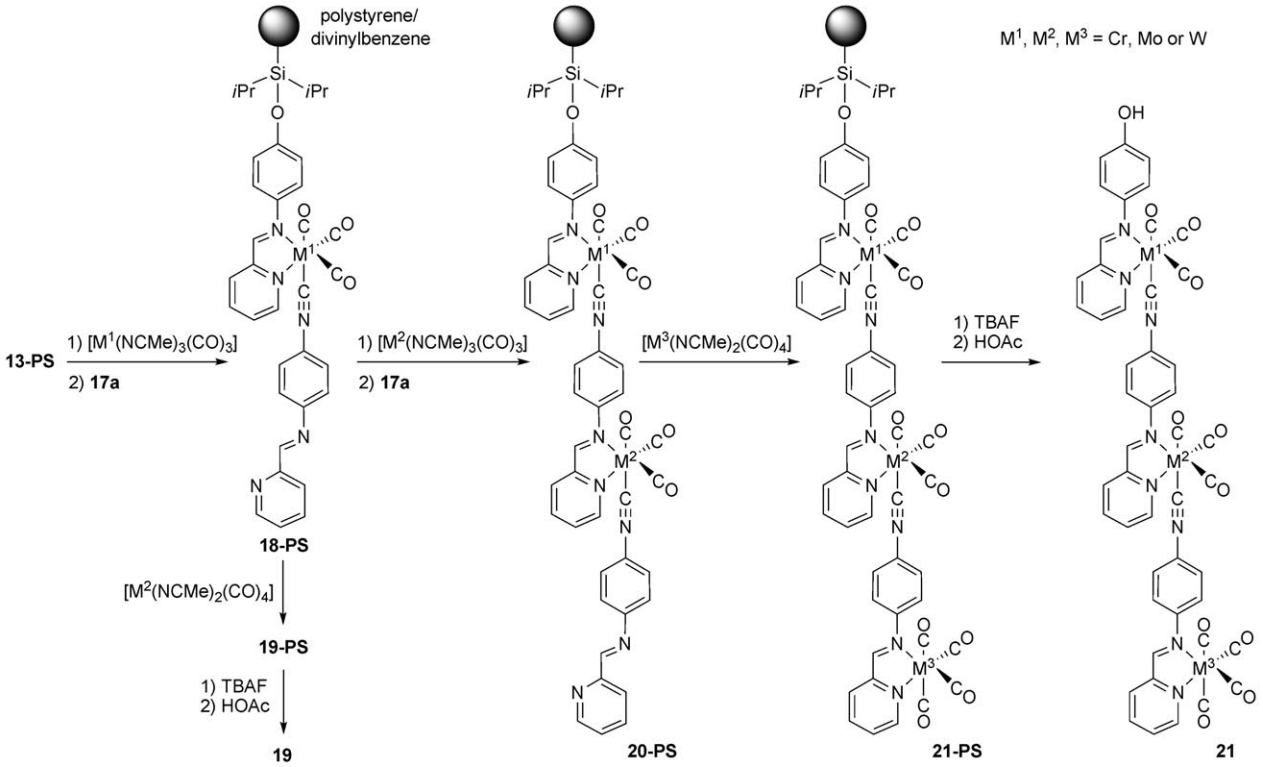
The SPS of bi- and trinuclear complexes by using ligand **17a** as the connecting unit is summarised in Scheme 12.[44,46]



Scheme 11. Directional bridging ligands **17a** and **17b**.

Coordination of a $M^1(CO)_3$ fragment (M^1 = Cr, Mo or W) to **13-PS** is followed by addition of the bridging ligand **17a**, which binds to M^1 in a monodentate fashion through its isonitrile functionality (Scheme 12, **18-PS**). Repeating this procedure employing a $M^2(CO)_3$ source (M^2 = Cr, Mo or W) furnishes the expandable dinuclear complex **20-PS**, while end-capping with a $M^2(CO)_4$ source yields the blocked dinuclear complex **19-PS**. Capping of **20-PS** with a $M^3(CO)_4$ fragment (M^3 = Cr, Mo or W) gives trinuclear **21-PS**. Up to four $M(CO)_n$ units can be precisely arranged in this manner; however, poor solubility of the products prohibits further chain elongation.[53] Libraries of di- and trinuclear complexes (**19-PS**, **21-PS**) were prepared by parallel SPS. In all cases the sequence of the $M(CO)_n$ units is defined by the synthetic protocol and is preserved during all synthetic steps; that is, no ligand scrambling or chain rupture is observed. Although the SPS protocol requires more reaction steps (immobilisation and cleavage) than a conventional synthesis in solution, the advantages of the SPS fully outweigh these additional steps. All reactions can be driven to completion by using excess building blocks and purification is simply achieved by filtration. In a homogenous phase the stoichiometry must be scrupulously adhered to as purification (chromatography, recrystallisation) is very tedious and inefficient.[53]

Conferring this resin/linker SPS strategy to the SPS of the mononuclear Pt^{II} complex **22** has been equally successful, as the mild cleavage conditions are fully compatible with the stability of platinum(II) complexes (Scheme 13).[54] A similar attempt to prepare 2,2′-bipyridinedichloroplatinum(II) complexes on a solid support with a Sasrin linker[6] was already reported in 1999.[55] However, under the cleavage conditions employed (trifluoroacetic acid), the proposed polymer-supported platinum(II) complexes were degraded; this result emphasises the need for transition-metal-complex compatible linkers. Platinum(II) complexes with aliphatic amines as ligands (**24**, Scheme 13) reported by Reedijk et al. are reasonably stable under acidic conditions and libraries of peptide–platinum(II) conjugates were prepared on solid phase (using a Rink amide linker[6]) and their anticancer activity was evaluated after cleavage from the support.[25] For resin-bound Pt^{II} complexes, gel-phase ^{195}Pt NMR spectroscopy was found to be a very useful analytical tool for monitoring the reaction.[23] The use of **22-PS** or **24-PS** as starting materials for the SPS of oligonuclear metal complexes with well-defined chain lengths and end groups awaits exploration. Chloride abstraction from **22-PS** or **24-PS** under salt formation is rather inconvenient, as salts are usually difficult to remove from organic resins. However, the SPS of the dinu-



Scheme 12. SPS of heterobi- and trinuclear transition-metal–carbonyl complexes.

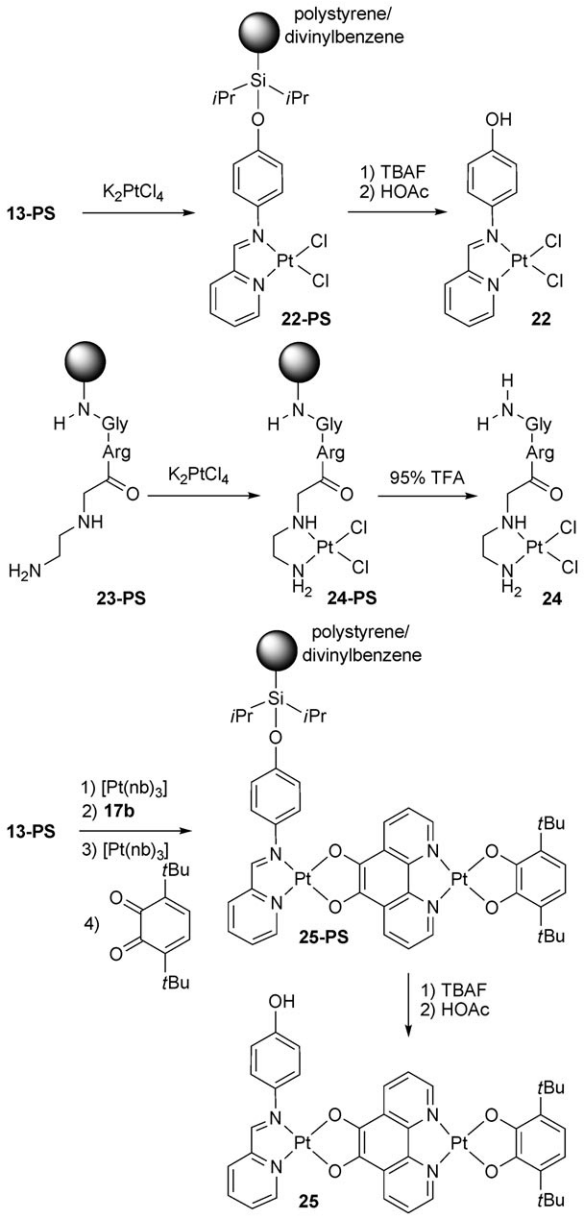
clear platinum(II) complex **25** with the metal in the main chain has been successful, starting from polymer-bound (diimine)platinum(0) species and oxidative addition of *ortho*-quinones, such as ligand **17b** (Scheme 11), to zero-valent platinum (Scheme 13).[56]

For the construction of heterodinuclear complexes Darensbourg et al. used the resin-bound tripeptide Cys-Gly-Cys-Ac **26-PS** (prepared on a TentaGel resin equipped with a Rink linker[6]) as a tetradentate N_2S_2 ligand for nickel(II) ions. This immobilised metalloligand can accommodate a second transition-metal fragment such as $[W(CO)_5]$ or $[Rh(CO)_2]^+$ (Scheme 14, **27-PS** and **28-PS**).[57] Again, IR spectroscopy proved to be valuable for on-resin analysis of the immobilised carbonyl complexes. However, no attempt to release the final dinuclear Ni–W or Ni–Rh complexes from the support was reported, although a Rink linker[6] has been employed. Chain elongation, starting from complexes of the type **26-PS**, to form oligonuclear complexes is conceivable by extending the peptide chain with more [Cys-Gly-Cys] units. This corresponds to a chain elongation approach with formation of covalent bonds. This approach is outlined in the following section by using metal-functionalised amino acids.

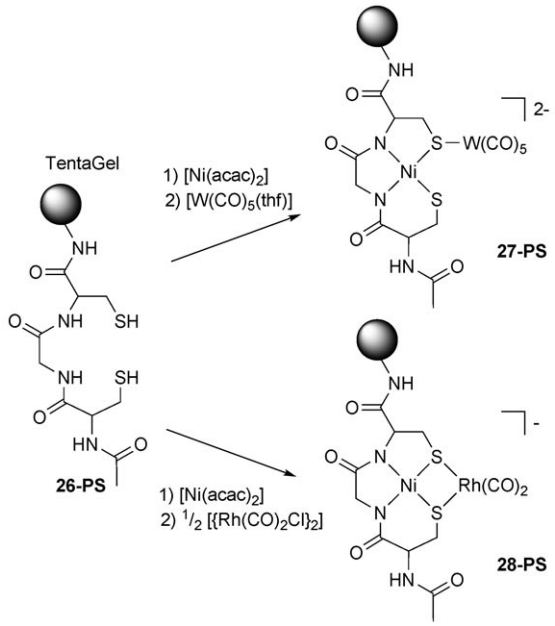
SPS of Transition-Metal-Containing Peptides: Formation of Covalent Bonds

Nature uses a stock of 20 α-amino acids to synthesise a large variety of peptides and proteins in vivo. For a synthetic chemist the most powerful tool for peptide synthesis in vitro is the solid-phase peptide synthesis (SPPS) developed by Merrifield.[1] SPPS is not restricted to natural amino acids. Applying this methodology, non-natural amino acids and even metal-containing building blocks can be incorporated into a peptide. Conjugating a metal complex to a peptide can confer new properties to the peptide and therefore enables new applications; for example, the use as specific label or as tool for electron-transfer studies in peptides.[17,58] To allow incorporation of a transition-metal complex at any position within a peptide the transition-metal building block requires both an amino functionality and a carboxylic acid group. To this end a variety of side-chain modified amino acids has been designed (**29**–**38**, Scheme 15).[39,59–66] Recently, a stable α-amino acid derivative incorporating a ferrocene unit at the α-position has been reported.[97]

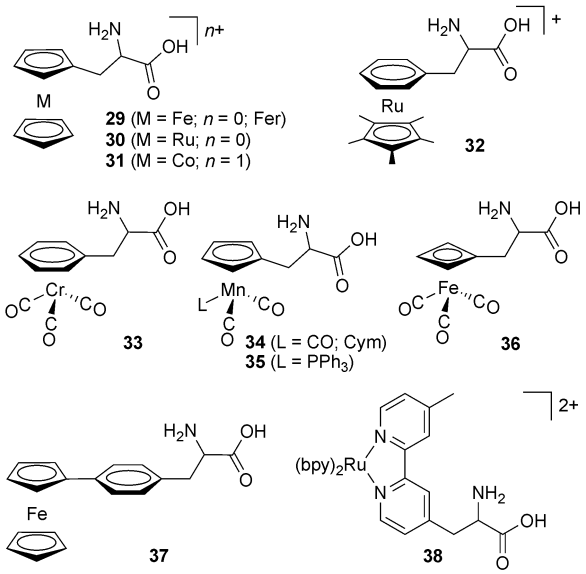
Some of these metalloamino acids are sufficiently stable under aqueous and ambient conditions and can be employed in SPPS.[67–71] For example, ferrocenylalanine (Scheme 15; **29**, Fer) and cymantrenylalanine (Scheme 15; **34**, Cym) were incorporated in the pentapeptide [Leu^5]–enkephalin by SPPS replacing phenylalanine to give [Fer^4,Leu^5]–enkephalin **39a** and [Cym^4,Leu^5]–enkephalin **39b**, respectively (Scheme 16).[67–69] Two Fer amino acids were coupled to a Glu_4 tetrapeptide (Scheme 16, **40**).[70] As expected, considering the large Fe–Fe distance, the two ferrocene units in **40** are electrochemically insulated from each other.[70] The tris(2,2′-bipyridyl)ruthenium(II) amino acid **38** was introduced into a 22 amino acid, alanine-based peptide (**41**) by SPPS by using Boc/benzyl chemistry (Boc = *tert*-butyloxycar-



Scheme 13. SPS of platinum(II) complexes (nb = norbonene).



Scheme 14. Ni–W and Ni–Rh complexes prepared on resin.

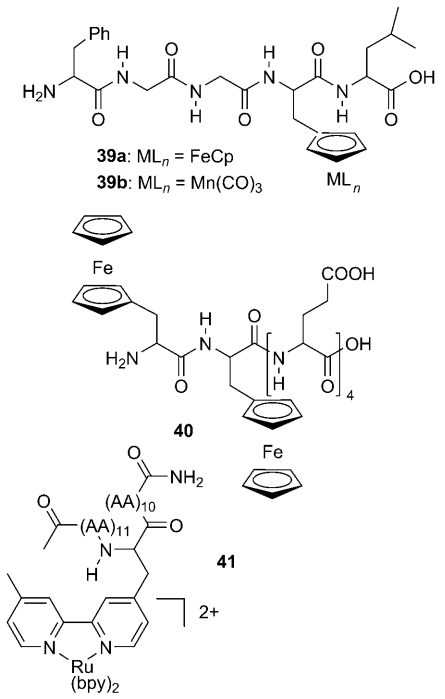


Scheme 15. Side-chain modified amino acids (bpy = 2,2′-bipyridine).

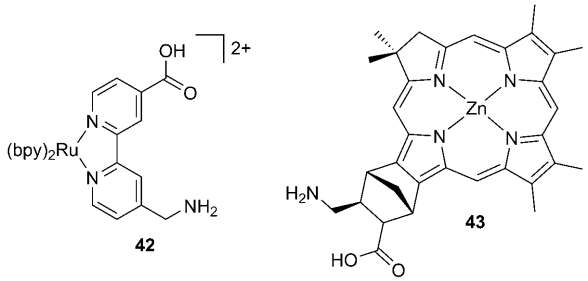
bonyl) on a MBHA resin (Scheme 16).[39] Potential applications of these α-amino acid derivatives include peptide labelling, such as IR-sensitive labelling (piano-stool amino acids **33**–**36**) or radiolabelling (**30**, **32**), and electron transfer studies (**29**, **31** or **38**).[17,58,70,72]

All metal-functionalised amino acids **29**–**38** (Scheme 15) are conceptually similar as the transition-metal complex is located in the side-chain of an α-amino acid. Placing the metal-coordinating moiety (Scheme 17, tris(2,2′-bipyridine)-ruthenium complex **42**,[73] chlorine–zinc(II) complex **43**[74]) or the transition-metal fragment itself (Scheme 18, ferrocene derivatives **44a**[75–77] and **44b**,[78] bis(2,2′:6′,2″-terpyridine)ruthenium(II) derivatives **45a**–**45d**[79,80] and porphyrin derivatives **46a**–**46d**[81]) between the carboxy and the amino substituent should give transition-metal-containing building blocks with significantly different properties as compared to side-chain modified α-amino acids (Scheme 15).

Incorporating building blocks **42**–**46** into peptide-like structures should have a large impact on electrochemical, photochemical and dynamical properties of the resulting pseudo-peptides (electronic communication and/or cooperative effects such as folding or guest recognition). Furthermore the use of peptide coupling techniques should allow the construction of oligonuclear, directional, metal complexes with well-defined building-block sequences (Schemes 6 and 7). The tris(2,2′-bipyridine)ruthenium complex **42** can be protected with Boc or Fmoc protecting



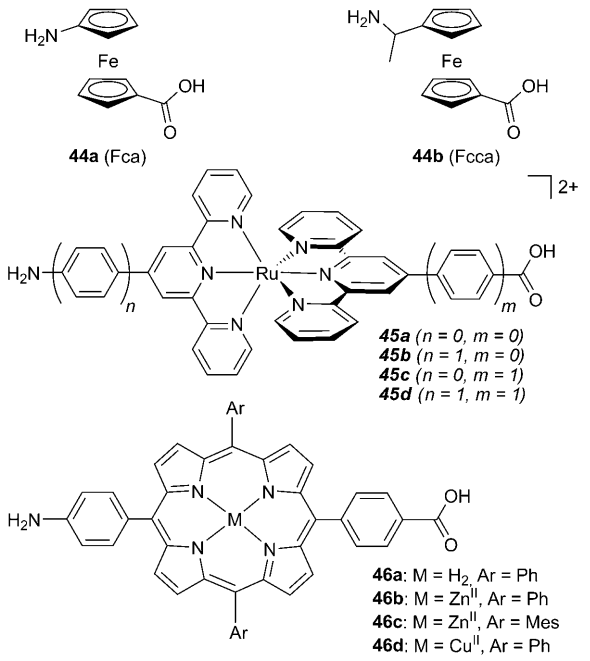
Scheme 16. Peptides incorporating transition-metal-functionalised amino acids prepared by SPPS.



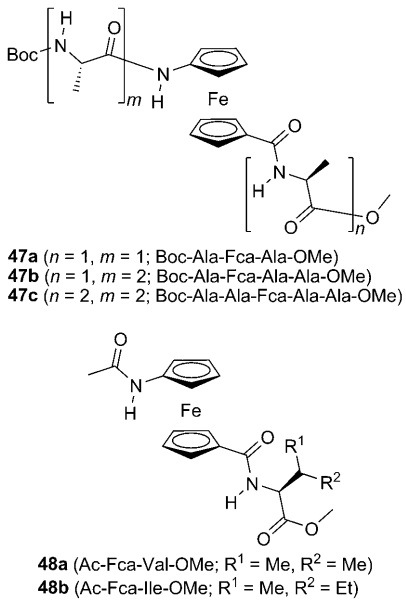
Scheme 17. Transition-metal-containing amino acids with the metal-coordinating moiety between COOH and NH_2.

groups (Fmoc = fluoren-9-ylmethoxycarbonyl); however, integration of this building block in peptides has not yet been published.[73] A chlorine–chlorin dyad has been prepared from suitable precursor analogues of **43** as a mimic of the photosynthetic reaction centre and the preferred conformation of the dyad has been elucidated.[74]

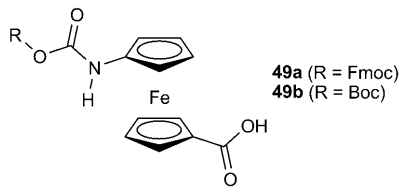
A single ferrocene amino acid (**44a**, Fca) has been incorporated in peptides built from alanine, valine or isoleucine (Scheme 19; **47a**–**47c**, **48a**, **48b**) by standard peptide-coupling techniques in solution by using the DCC/HOBt or EDC/HOBt protocols (DCC = 1,3-dicyclohexylcarbodiimide, EDC = *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide, HOBt = 1-hydroxybenzotriazole).[82–84] Fca can also be protected with the common Fmoc and Boc N-protecting groups and is stable towards the respective deprotection procedures (Scheme 20; **49a**,[77] **49b**[76]), which is mandatory for the selective synthesis of oligomers. The conformations of the



Scheme 18. Transition-metal-containing amino acids with the metal-complex fragment between COOH and NH_2.



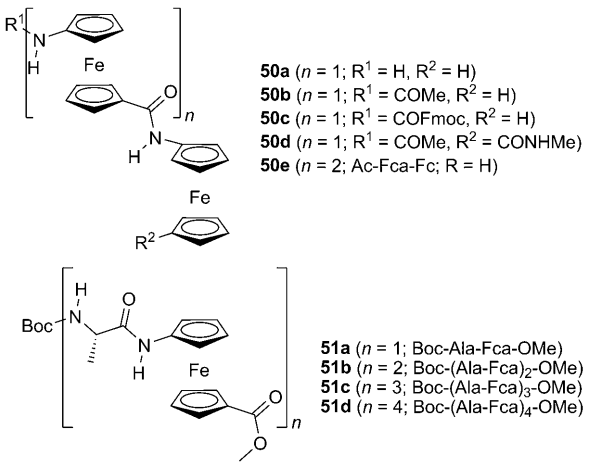
Scheme 19. Oligoamides incorporating a single Fca moiety.



Scheme 20. N-Protected Fca derivatives Fmoc-Fca-H (**49a**) and Boc-Fca-H (**49b**).

Fca-containing peptides have been determined by using a combination of spectroscopic and theoretical techniques.[82–84] The chiral ferrocene amino acid (Scheme 18; **44b**; Fcca) has only recently been reported and awaits incorporation into peptides.[78]

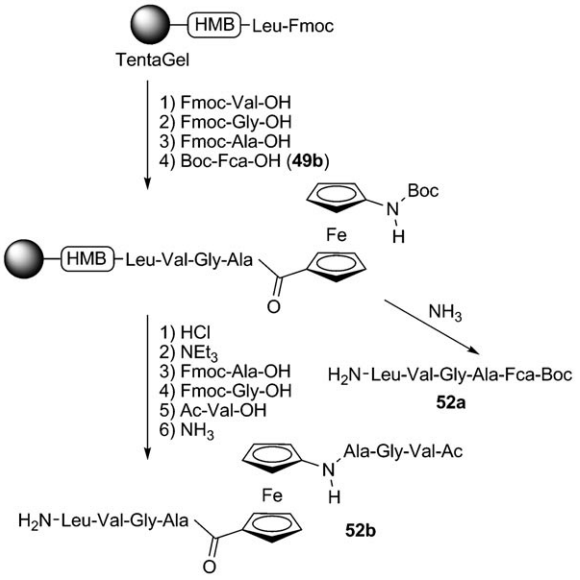
Incorporation of more than one Fca unit with a direct amide link between two ferrocene units has been realised in diferrocenes **50a–50d** and triferrocene **50e** (Scheme 21).[75,77,85,86] Acid activation with acid fluorides



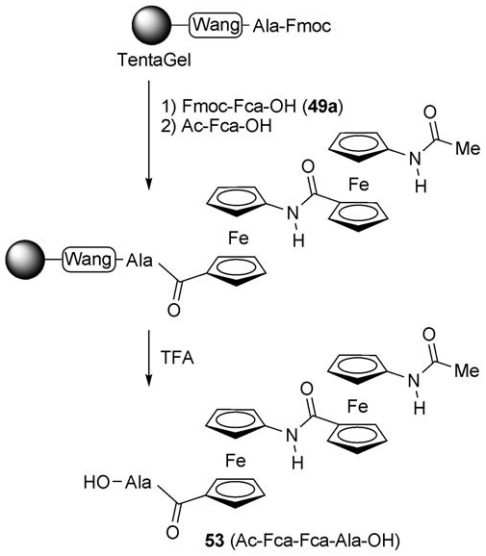
Scheme 21. Oligoamides incorporating more than a single Fca moiety.

instead of benzotriazole esters proved advantageous in the amide coupling of ferrocenes.[86] The conformations of the oligoferrocenes have been investigated in solution by using spectroscopic and theoretical methods. Electrochemical investigations indicate a moderate electronic communication between the redox-active ferrocene units in **50a–50e**.[75,77,85,86] Organometallic peptide conjugate foldamers with alternating Ala and Fca moieties **51a–51d** have been prepared and their ordered structures determined.[87] A strong electronic communication between ferrocene units in **51a–51d**, however, seems quite unlikely due to the electronically insulating alanine units.

Conferring amide coupling reactions involving Fca to SPPS protocols was successful. One Fca unit has been appended to a tetrapeptide to give the pentapeptide Boc-Fca-Ala-Gly-Val-Leu-NH_2 (**52a**) and incorporated internally into the octapeptide Ac-Val-Gly-Ala-Fca-Ala-Gly-Val-Leu-NH_2 (**52b**) by using Fmoc-protected α-amino acids, Boc-Fca-H (**49b**) and a TentaGel resin with a base-labile HMB linker[6] (Scheme 22; HMB = hydroxymethylbenzoyl).[88] Two ferrocene units have been linked together on solid support (TentaGel resin with an acid-labile Wang linker[6]) by using Fmoc-protected α-amino acids and Fmoc-Fca-H (**49a**) giving the tripeptide Ac-Fca-Fca-Ala-OH (Scheme 23, **53**).[89] In a fully analogous fashion the tripeptides with one internal Fca unit Ac-Ala-Fca-Gly-OH (**54a**), Ac-Ala-Fca-Ala-OH (**54b**) and Ac-Gly-Fca-Phe-OH (**54c**) were pre-



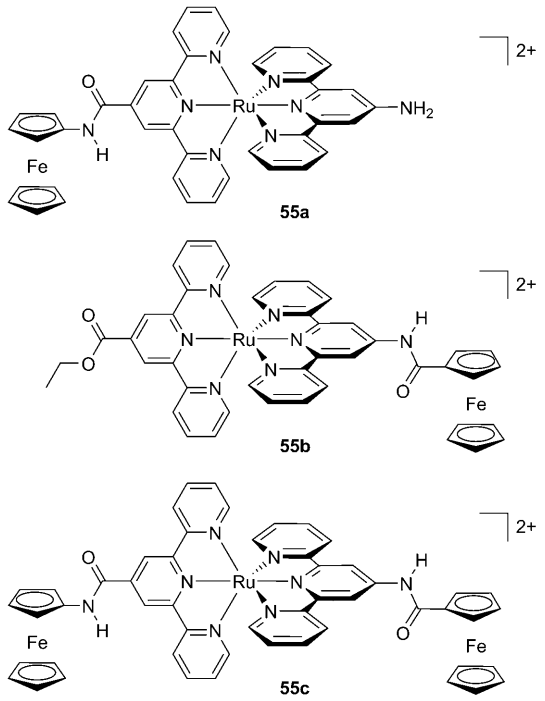
Scheme 22. SPPS of peptides containing one ferrocene unit.



Scheme 23. SPPS of peptides containing two ferrocene units.

pared by using Fmoc protecting groups on TentaGel-Wang resin.[89,90]

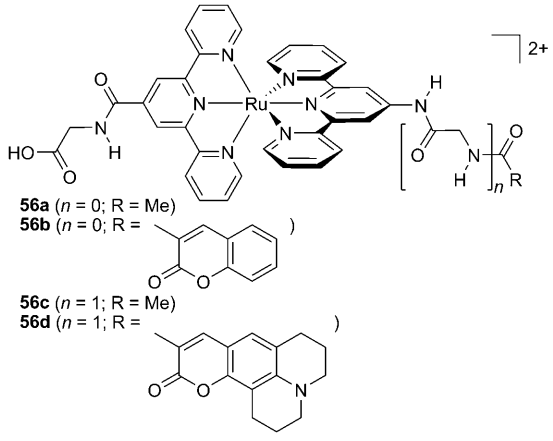
The bis(2,2′:6′,2″-terpyridine)ruthenium(II) amino acid **45a** (Scheme 18) has been coupled to ferrocene units in solution by using HOBt activation of the acid and deprotonation of the unreactive amine with the Schwesinger phosphazene base P_1tBu (P_1tBu = *tert*-butylimino-tris(dimethylamino)phosphorane) giving ferrocene- and ruthenium(II)-containing amides **55a–55c** (Scheme 24).[79] Cyclic voltammetry indicates that the two ferrocene units in **55c** are electronically uncoupled. However, in **55a** and **55c** the ferrocene moiety quenches the ruthenium-based MLCT excited state by photoelectron transfer.[79]



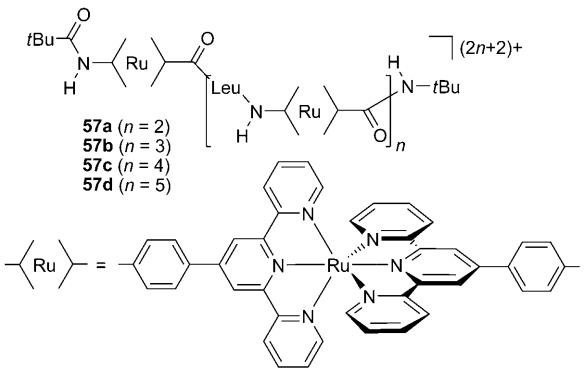
Scheme 24. Amides containing **45a** and ferrocene units.

By using a SPPS approach (TentaGel resin; Wang linker; acid chlorides as coupling reagents) **45a** has been successfully connected to the amino acid glycine and several coumarin-based chromophores to give dyads **56b** and **56d** and chromophore-free reference compounds **56a** and **56c**. For this multistep synthesis the SPPS approach is clearly highly advantageous as purification of intermediates reduces to simple washing and filtration steps. The coumarin conjugates **56b** and **56d** display energy transfer from the chromophore to the bis(2,2′:6′,2″-terpyridine)ruthenium(II) unit in the excited state (Scheme 25).[91]

The expanded bis(2,2′:6′,2″-terpyridine)ruthenium(II) amino acid **45d** (Scheme 18) has been incorporated into leucine-based peptides by means of alternate complexation and ligand coupling reactions in solution to give **57a**–**57d** (Scheme 26); this method is a combination of formation of coordinative and covalent bonds during the multistep solution synthesis (Scheme 7). Oligomers **57a**–**57d** display right-handed helical structures in solution according to spectroscopic measurements.[92]

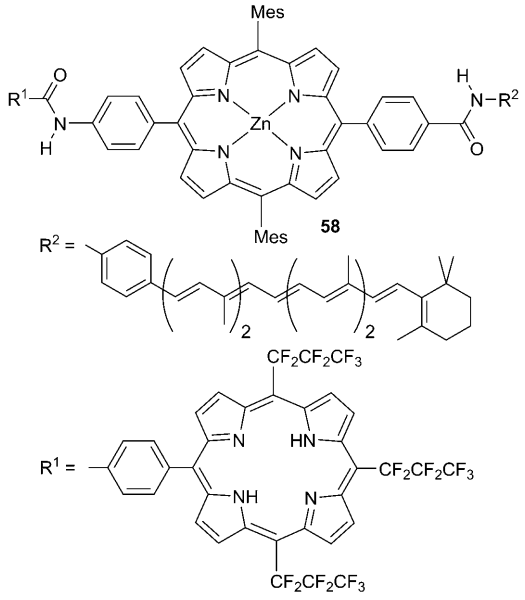


Scheme 25. Oligoamides containing **45a** and chromophore units prepared by SPPS.



Scheme 26. Expanded oligo(leucines) containing bis(2,2′:6′,2″-terpyridine)ruthenium(II) moieties.

Porphyrinato–zinc(II) amino acid **46c** has been incorporated into triad **58** with a carotenoid as electron donor and a tris(heptafluoropropyl)porphyrin as electron acceptor, displaying characteristics of an artificial photosynthetic reaction centre (Scheme 27).[93] Metal-free porphyrin amino acid derivatives have been conjugated to switchable organic chromophores and the resulting conjugates have been shown to act as logic gates and molecular switches.[94–96]



Scheme 27. Triad **58** as artificial photosynthetic reaction centre.

Conclusion

The next logical step in the field of SPS with transition-metal complexes is the extension of the method to the synthesis of hetero-oligometallic (peptidic) oligomers in a combinatorial fashion. Such well-defined hetero-oligomers could find useful applications as receptors, sensors, sensitisers, molecular wires, devices and switches, see for example, references [79, 85, 89, 94–96].

In summary, the strategy of the solid-phase synthesis provides access to the synthesis of transition-metal oligomers and transition-metal-functionalised peptidic architectures that are difficult to obtain by solution-synthesis methods. A main advantage of the solid-phase approach is that reagents can be used in an excess and thus reactions can be driven to completion. The very simple purification procedure on resin is also a great benefit and even allows for automation and parallel library synthesis. Therefore SPS is a valuable method—not only for the synthetic organic chemist, but also in the field of coordination and organometallic chemistry. Future developments will show if SPS of transition-metal complexes will make a similar impact on transition-metal chemistry as has conventional SPPS in peptide chemistry.

Acknowledgements

The authors thank the Deutsche Forschungsgemeinschaft for financial support and for a Heisenberg fellowship (to K.H.) and all the co-workers, whose names appear in the references for their contribution.

[1] R. B. Merrifield, *J. Am. Chem. Soc.* **1963**, *85*, 2149–2154.
[2] J. S. Früchtel, G. Jung, *Angew. Chem.* **1996**, *108*, 19–46; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 17–42.
[3] P. H. H. Hermkens, H. C. J. Ottenheijm, D. Rees, *Tetrahedron* **1996**, *52*, 4527–4554.
[4] P. H. H. Hermkens, H. C. J. Ottenheijm, D. C. Rees, *Tetrahedron* **1997**, *53*, 5643–5678.
[5] F. Zaragoza Dörwald, *Organic Synthesis on Solid Phase*, Wiley-VCH, Weinheim, **2000**.
[6] F. Guillier, D. Orain, M. Bradley, *Chem. Rev.* **2000**, *100*, 2091–2157.
[7] D. C. Bailey, S. H. Langer, *Chem. Rev.* **1981**, *81*, 109–148.
[8] *Chiral Catalyst Imobilization and Recycling* (Eds.: D. E. De Vos, I. F. J. Vankelecom, P. A. Jacobs), Wiley-VCH, Weinheim, **2000**.
[9] N. E. Leadbeater, M. Marco, *Chem. Rev.* **2002**, *102*, 3217–3274.
[10] M. Heitbaum, F. Glorius, I. Escher, *Angew. Chem.* **2006**, *118*, 4850–4881; *Angew. Chem. Int. Ed.* **2006**, *45*, 4732–4762.
[11] J. M. Thomas, R. Raja, D. W. Lewis, *Angew. Chem.* **2005**, *117*, 6614–6641; *Angew. Chem. Int. Ed.* **2005**, *44*, 6456–6482.
[12] E. Lindner, T. Schneller, F. Auer, H. A. Mayer, *Angew. Chem.* **1999**, *111*, 2288–2309; *Angew. Chem. Int. Ed.* **1999**, *38*, 2154–2174.
[13] J. M. Burlitch, R. C. Winterton, *J. Am. Chem. Soc.* **1975**, *97*, 5605–5606.
[14] N. E. Leadbeater, E. L. Sharp, *Organometallics* **2003**, *22*, 4167–4169.
[15] C. Baldoli, S. Maiorana, E. Licandro, L. Casiraghi, G. Zinzalla, P. Seneci, E. De Magistris, A. Paio, C. Marchioro, *J. Comb. Chem.* **2003**, *5*, 809–813.
[16] J. Barluenga, A. de Prado, J. Santamaria, M. Tomas, *Organometallics* **2005**, *24*, 3614–3617.
[17] *Bioorganometallics* (Ed.: G. Jaouen), Wiley-VCH, Weinheim, **2006**.
[18] D. R. van Staveren, N. Metzler-Nolte, *Chem. Commun.* **2002**, 1406–1407.
[19] A. Maurer, H.-B. Kraatz, N. Metzler-Nolte, *Eur. J. Inorg. Chem.* **2005**, 3207–3210.
[20] F. Noor, A. Wuestholz, R. Kinscherf, N. Metzler-Nolte, *Angew. Chem.* **2005**, *117*, 2481–2485; *Angew. Chem. Int. Ed.* **2005**, *44*, 2429–2432.
[21] J. F. Valliant, R. W. Riddoch, D. W. Hughes, D. G. Roe, T. K. Fauconnier, J. R. Thornback, *Inorg. Chim. Acta* **2001**, *325*, 155–163.
[22] M. S. Robillard, A. R. P. M. Valentijn, N. J. Meeuwenoord, G. A. van der Marel, J. H. van Boom, J. Reedijk, *Angew. Chem.* **2000**, *112*, 3226–3229; *Angew. Chem. Int. Ed.* **2000**, *39*, 3096–3099.
[23] M. S. Robillard, J. S. Leith, G. A. van der Marel, J. H. van Boom, J. Reedijk, *Eur. J. Inorg. Chem.* **2003**, 1529–1532.
[24] M. S. Robillard, S. van Alphen, N. J. Meeuwenoord, B. A. J. Jansen, G. A. van der Marel, J. H. van Boom, J. Reedijk, *New J. Chem.* **2005**, *29*, 220–225.
[25] M. S. Robillard, M. Bacac, H. van den Elst, A. Flamigni, G. A. van der Marel, J. H. van Boom, J. Reedijk, *J. Comb. Chem.* **2003**, *5*, 821–825.
[26] S. van Zutphen, M. S. Robillard, G. A. van der Marel, H. S. Overkleeft, H. den Dulk, J. Brouwer, J. Reedijk, *Chem. Commun.* **2003**, 634–635.
[27] R. I. Taleb, D. Jaramillo, N. J. Wheate, J. R. Aldrich-Wright, *Chem. Eur. J.* **2007**, *13*, 3177–3186.
[28] S. R. Gilbertson, X. Wang, G. S. Hoge, C. A. Klug, J. Schaefer, *Organometallics*, **1996**, *15*, 4678–4680.
[29] C. A. Christensen, M. Meldal, *Chem. Eur. J.* **2005**, *11*, 4121–4131.
[30] S. I. Khan, A. E. Beilstein, M. Sykora, G. D. Smith, X. Hu, M. W. Grinstaff, *Inorg. Chem.* **1999**, *38*, 3922–3925.
[31] C. A. Hastings, J. K. Barton, *Biochemistry* **1999**, *38*, 10042–10051.
[32] K. S. Schmidt, D. V. Filippov, N. J. Meeuwenoord, G. van der Marel, J. H. van Boom, B. Lippert, J. Reedijk, *Angew. Chem.* **2000**, *112*, 383–385; *Angew. Chem. Int. Ed.* **2000**, *39*, 375–377.
[33] a) J. C. Verheijen, G. A. van der Marel, J. H. van Boom, N. Metzler-Nolte, *Bioconjugate Chem.* **2000**, *11*, 741–743; b) K. S. Schmidt, M. Boudvillain, A. Schwartz, G. A. van der Marel, J. H. van Boom, J. Reedijk, B. Lippert, *Chem. Eur. J.* **2002**, *8*, 5566–5570.
[34] M. C. Kuchta, A. Gross, A. Pinto, N. Metzler-Nolte, *Inorg. Chem.* **2007**, *46*, 9400–9404.
[35] J. T. Chantson, M. V. V. Falzacappa, S. Crovella, N. Metzler-Nolte, *ChemMedChem* **2006**, *1*, 1268–1274.
[36] a) S. I. Khan, A. E. Beilstein, M. W. Grinstaff, *Inorg. Chem.* **1999**, *38*, 418–419; b) A. E. Beilstein, M. W. Grinstaff, *Chem. Commun.* **2000**, 509–510.
[37] J. Caddy, U. Hoffmann, N. Metzler-Nolte, *Z. Naturforsch. B* **2007**, *62*, 460–466.
[38] I. Vargas-Baca, D. Mitra, H. J. Zulyniak, J. Banerjee, H. F. Sleiman, *Angew. Chem.* **2001**, *113*, 4765–4768; *Angew. Chem. Int. Ed.* **2001**, *40*, 4629–4632.
[39] K. J. Kise, B. E. Bowler, *Inorg. Chem.* **2002**, *41*, 379–386.
[40] a) G. Dirscherl, B. König, *Eur. J. Org. Chem.* **2008**, 597–634; b) N. Metzler-Nolte, *Chimia* **2007**, *61*, 736–741.
[41] N.-M. Hsu, W.-R. Li, *Angew. Chem.* **2006**, *118*, 4244–4248; *Angew. Chem. Int. Ed.* **2006**, *45*, 4138–4142.
[42] K. Heinze, U. Winterhalter, T. Jannack, *Chem. Eur. J.* **2000**, *6*, 4203–4210.
[43] K. Heinze, *Chem. Eur. J.* **2001**, *7*, 2922–2932.
[44] K. Heinze, J. B. Toro, *Angew. Chem.* **2003**, *115*, 4671–4674; *Angew. Chem. Int. Ed.* **2003**, *42*, 4533–4536.
[45] K. Heinze, V. Jacob, C. Feige, *Eur. J. Inorg. Chem.* **2004**, 2053–2061.
[46] K. Heinze, J. D. B. Toro, *Eur. J. Inorg. Chem.* **2004**, 3498–3507.
[47] S. J. Danishefsky, K. F. McClure, J. T. Randolph, R. B. Ruggeri, *Science* **1993**, *260*, 1307–1309.
[48] J. T. Randolph, S. J. Danishefsky, *J. Am. Chem. Soc.* **1995**, *117*, 5693–5700.
[49] L. A. Thompson, F. L. Moore, Y.-C. Moon, J. A. Ellman, *J. Org. Chem.* **1998**, *63*, 2066–2067.
[50] B. Yan, *Acc. Chem. Res.* **1998**, *31*, 621–630.
[51] K. Heinze, *J. Chem. Soc. Dalton Trans.* **2002**, 540–547.
[52] K. Heinze, V. Jacob, *J. Chem. Soc. Dalton Trans.* **2002**, 2379–2385.

[53] J. D. Bueno Toro, Ph.D. thesis, Ruprecht Karls Universität Heidelberg **2005**.
[54] S. Reinhardt, K. Heinze, *Z. Anorg. Allg. Chem.* **2006**, *632*, 1465–1470.
[55] S. Tadesse, A. Bhandari, M. A. Gallop, *J. Comb. Chem.* **1999**, *1*, 184–187.
[56] K. Heinze, S. Reinhardt, unpublished results.
[57] K. N. Green, S. P. Jeffery, J. H. Reibenspies, M. Y. Darensbourg, *J. Am. Chem. Soc.* **2006**, *128*, 6493–6498.
[58] Y.-T. Long, E. Abu-Irhayem, H.-B. Kraatz, *Chem. Eur. J.* **2005**, *11*, 5186–5194.
[59] K. Schloegel, *Monatsh. Chem.* **1957**, *88*, 601–621.
[60] J. M. Osgerby, P. L. Pauson, *J. Chem. Soc.* **1958**, 656–660.
[61] H. Brunner, W. Koenig, B. Nuber, *Tetrahedron: Asymmetry* **1993**, *4*, 699–707.
[62] R. F. W. Jackson, D. Turner, M. H. Block, *Synlett* **1996**, 862–864.
[63] W. H. Soine, C. E. Guyer, F. F. Knapp, Jr., *J. Med. Chem.* **1984**, *27*, 803–806.
[64] A. J. Gleichmann, J. M. Wolff, W. S. Sheldrick, *J. Chem. Soc. Dalton Trans.* **1995**, 1549–1554.
[65] C. Sergheraert, J.-C. Brunet, A. Tartar, *J. Chem. Soc. Chem. Commun.* **1982**, 1417–1418.
[66] J. C. Brunet, E. Cuingnet, H. Gras, P. Marcincal, A. Mocz, C. Sergheraert, A. Tartar, *J. Organomet. Chem.* **1981**, *216*, 73–77.
[67] E. Cuingnet, C. Sergheraert, A. Tartar, M. Dautrevaux, *J. Organomet. Chem.* **1980**, *195*, 325–329.
[68] R. Epton, G. Marr, G. A. Willmore, D. Hudson, P. H. Snell, C. R. Snell, *Int. J. Biol. Macromol.* **1981**, *3*, 395–396.
[69] E. Cuingnet, M. Dautrevaux, C. Sergheraert, A. Tartar, B. Attali, J. Cros, *Eur. J. Med. Chem.* **1982**, *17*, 203–206.
[70] M. Kira, T. Matsubara, H. Shinohara, M. Sisido, *Chem. Lett.* **1997**, 89–90.
[71] J. Pospisek, S. Toma, I. Fric, K. Blaha, *Collect. Czech. Chem. Commun.* **1980**, *45*, 435–441.
[72] K. A. Mahmoud, H.-B. Kraatz in *Transition-Metal-Containing Polymers* (Eds.: A. S. Abd-El-Aziz, I. Manners), Wiley, **2007**.
[73] B. M. Bishop, D. G. McCafferty, B. W. Erickson, *Tetrahedron* **2000**, *56*, 4629–4638.
[74] T. Könekamp, A. Ruiz, J. Duwenhorst, W. Schmidt, T. Borrmann, W.-D. Stohrer, F.-P. Montforts, *Chem. Eur. J.* **2007**, *13*, 6595–6604.
[75] T. Okamura, K. Sakauye, N. Ueyama, A. Nakamura, *Inorg. Chem.* **1998**, *37*, 6731–6736.
[76] L. Barišić, V. Rapić, V. Kovac, *Croat. Chem. Acta* **2002**, *75*, 199–210.
[77] K. Heinze, M. Schlenker, *Eur. J. Inorg. Chem.* **2004**, 2974–2988.
[78] M. C. Semenčić, M. Dropučić, L. Barišić, V. Rapić, *Croat. Chem. Acta* **2006**, *79*, 599–612.
[79] K. Heinze, K. Hempel, M. Beckmann, *Eur. J. Inorg. Chem.* **2006**, 2040–2050.
[80] K. Hempel, Dissertation, University of Heidelberg **2008**.
[81] K. Heinze, A. Reinhart, *Dalton Trans.* **2008**, 469–480.
[82] L. Barišić, M. Dropučić, V. Rapić, H. Pritzkow, S. I. Kirin, N. Metzler-Nolte, *Chem. Commun.* **2004**, 2004–2005.
[83] K. Heinze, M. Beckmann, *Eur. J. Inorg. Chem.* **2005**, 3450–3457.
[84] L. Barišić, M. Čakić, K. A. Mahmoud, Y. Liu, H.-B. Kraatz, H. Pritzkow, S. I. Kirin, N. Metzler-Nolte, V. Rapić, *Chem. Eur. J.* **2006**, *12*, 4965–4980.
[85] K. Heinze, M. Schlenker, *Eur. J. Inorg. Chem.* **2005**, 66–71.
[86] K. Heinze, D. Siebler, *Z. Anorg. Allg. Chem.* **2007**, *633*, 2223–2233.
[87] S. Chowdhury, G. Schatte, H.-B. Kraatz, *Angew. Chem.* **2006**, *118*, 7036–7038; *Angew. Chem. Int. Ed.* **2006**, *45*, 6882–6884.
[88] L. Barišić, V. Rapić, N. Metzler-Nolte, *Eur. J. Inorg. Chem.* **2006**, 4019–4021.
[89] K. Heinze, U. Wild, M. Beckmann, *Eur. J. Inorg. Chem.* **2007**, 617–623.
[90] *Fmoc Solid-Phase Peptide Synthesis* (Eds.: W. C. Chan, P. D. White), Oxford University Press, Oxford, **2000**.
[91] K. Heinze, K. Hempel, unpublished results.
[92] T. Okamura, T. Iwamura, S. Seno, H. Yamamoto, N. Ueyama, *J. Am. Chem. Soc.* **2004**, *126*, 15972–15973.
[93] S. L. Gould, G. Kodis, R. E. Palacios, L. de la Garza, A. Brune, D. Gust, T. A. Moore, A. L. Moore, *J. Phys. Chem. B* **2004**, *108*, 10566–10580.
[94] S. D. Straight, J. Andréasson, G. Kodis, S. Bandyopadhyay, R. H. Mitchell, T. A. Moore, A. L. Moore, D. Gust, *J. Am. Chem. Soc.* **2005**, *127*, 9403–9409.
[95] D. Gust, T. A. Moore, A. L. Moore, *Chem. Commun.* **2006**, 1169–1178.
[96] J. Andréasson, S. D. Straight, S. Bandyopadhyay, R. H. Mitchell, T. A. Moore, A. L. Moore, D. Gust, *Angew. Chem.* **2007**, *119*, 976–979; *Angew. Chem. Int. Ed.* **2007**, *46*, 958–961.
[97] R. M. Moreno, M. Catasús, C. López, A. Moyano, *Eur. J. Org. Chem.* **2008**, 2388–2396.

Published online: July 9, 2008

