Fullerene Chemistry

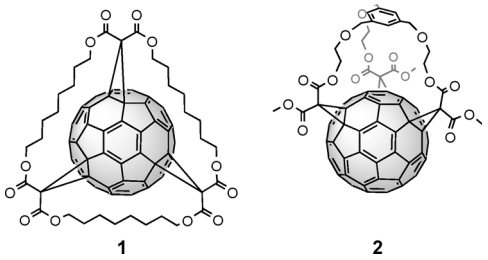
DOI: 10.1002/anie.201209981

Invertomers of Fullerenophosphates**

*Alexander Gmehling, Wolfgang Donaubauer, Frank Hampel, Frank W. Heinemann, and Andreas Hirsch**

The beauty of the carbon allotrope C_{60} lies in its highly symmetric icosahedral structure. However, the presence of 30 reactive [6,6]-double bonds still leaves regioselective multiadditions to the fullerene core to be a challenging task.[1] Stereoelectronic effects govern the product distribution of multiple additions. Unfortunately, subsequent attacks of segregated addends lead to a mixture of regioisomers, whose isolation requires tedious separation by HPLC.[2] Access to specific isomers, however, is very desirable, because it allows highly functional molecules to be developed in which the different building blocks are spatially arranged in a defined three-dimensional structure. This arrangement can lead to unprecedented properties such as the formation of shape-persistent micelles.[3] A possibility to overcome the low inherent regioselectivity of multiple additions is the "tether-directed remote functionalization" which was developed by Diederich and co-workers.[4] Following this approach tethers for all bisadduct regioisomers have been developed.[5] Attractive examples are bismalonates involving rigid porphyrin tethers allowing for the highly regioselective formation of bisdadducts with *trans-2* or *trans-1*-addition patterns.[6] Trisadducts of C_{60} involving a chiral C_3-symmetrical *e*,*e*,*e*-addition pattern represent another class of interesting target architectures.[7]

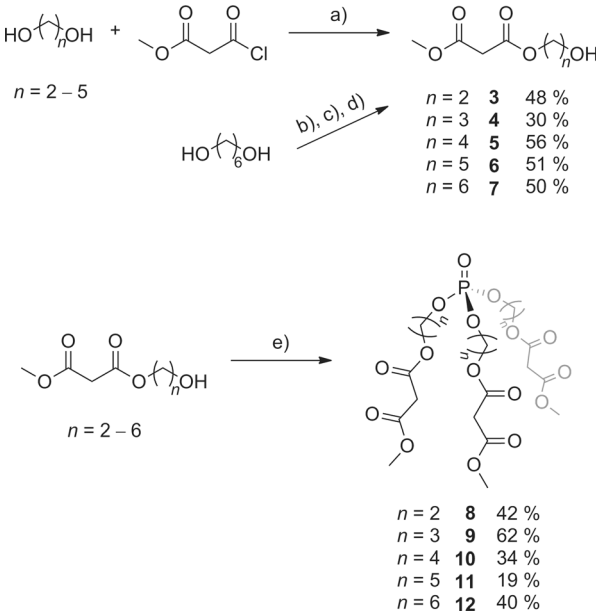
Suitable trisfunctional tether molecules encoding an *e*,*e*,*e*-addition pattern are, for example, cyclotriveratrylenes and cyclo[*n*]alkylmalonates or star-like addends with three malonates attached to a central benzene ring.[7c,8] Examples for corresponding trisadducts are compounds **1** and **2**. Adducts such as **2**, offer the additional opportunity of removing the aromatic template and leaving behind a fullerene triol that can be further functionalized at its periphery. However, the synthesis of such benzene-based tethers requires several steps with repeated chromatographic purification steps, making this approach still time-consuming and expensive.



1 **2**

Herein, we report a new tethered precursor for *e*,*e*,*e*-trisadducts, which is based on a central phosphate moiety. It is accessible in only two steps and allows for easy modulation of the constituent building blocks. The corresponding C_{60}–phosphate adducts were formed regioselectively as C_3-symmetric *e*,*e*,*e*-trisadducts. Remarkably, *in*- and *out*-isomerism was observed and the structures of both invertomers were unequivocally demonstrated by X-ray crystallography.

The phosphate malonates **8**–**12** were straightforward to generate by the condensation of the alcohols **3**–**7** with $POBr_3$. We first synthesized the phosphate trismalonate **8** involving three ethano spacers in a two-step procedure (Scheme 1),



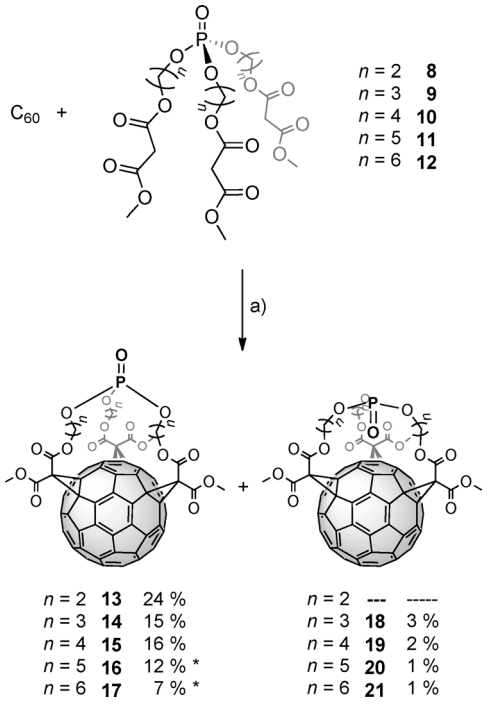
Scheme 1. Synthesis of phosphate trismalonates **8**–**12** with variable spacer length. a) pyridine or NEt_3, 0°C, THF; b) DHP, Dowex 50WX2, toluene; c) CH_3COCH_2COCl, NEt_3, 0°C, CH_2Cl_2; d) CH_2Cl_2, MeOH, HCl; e) $POBr_3$, pyridine, 0°C, toluene.

[*] A. Gmehling, W. Donaubauer, Dr. F. Hampel, Prof. Dr. A. Hirsch
Department of Chemistry & Pharmacy, Organic Chemistry & Interdisciplinary Center for Molecular Materials (ICMM)
Friedrich-Alexander-Universität Erlangen-Nürnberg
Henkestrasse 42, 91054 Erlangen (Germany)
E-mail: andreas.hirsch@chemie.uni-erlangen.de
Homepage: http://www.chemie.uni-erlangen.de/hirsch
Dr. F. W. Heinemann
Department of Chemistry & Pharmacy, Inorganic Chemistry
Friedrich-Alexander-Universität Erlangen-Nürnberg
Egerlandstrasse 1, 91058 Erlangen (Germany)

[**] We would like to thank the DFG (SFB 953—Synthetic Carbon Allotropes), the Fonds der Chemischen Industrie, and the Graduate School Molecular Science (GSMS) for financial support.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201209981.

which is considerably more efficient than that of benzene-based trismalonate tethers. Ethylene glycol was esterified with methyl malonyl chloride according to a literature procedure.[9] The corresponding methyl malonyl alkanol **3** was then converted into trismalonate **8**. It turned out, that the reaction proceeded much faster when $POBr_3$ was used instead of $POCl_3$ as the phosphorylating reagent. The final threefold cyclopropanation of C_{60} was conducted with DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) as a base and iodine for the in situ halogenation (Scheme 2).[10]



Scheme 2. Cyclopropanation of C_{60} with phosphate trismalonates yielding the P_{in}- and P_{out}-isomers for spacers longer than ethyl. a) DBU, I_2, toluene. * = obtained as mixture of isomers.

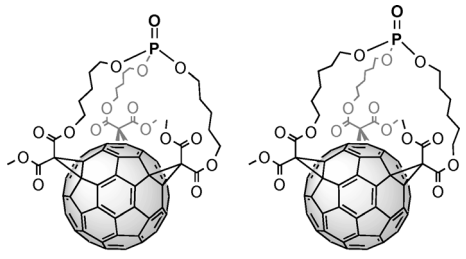
After a couple of hours product formation was detected by thin layer chromatography (TLC). Purification was accomplished by column chromatography. Trisadduct **13** was isolated in 24% yield. No other regioisomer was detected, demonstrating the high selectivity of this approach. The UV/Vis-spectrum of **13** displayed the characteristic absorptions for C_{60}-*e*,*e*,*e*-trisadducts.[11] The *e*,*e*,*e*-addition pattern of **13** was also confirmed by ^{13}C NMR spectroscopy.[2c]

The successful synthesis of the phosphate trisadduct **13** demonstrated, that the phosphate tether is capable of templating the formation of *e*,*e*,*e*-trisadducts. In a next step, the influence of the spacer length on the addition pattern was investigated. The corresponding malonate alkanols **4**–**6** with chain lengths between three and five carbon atoms were prepared in the same way as ethyl derivative **3**. Malonate **7** involving a hexyl chain was synthesized by a slightly different procedure, because the mono-THP-protection of 1,6-hexanediol proceeded exceptionally well, according to a literature procedure.[12] The preparation of the corresponding elongated phosphate trismalonates **9**–**12** was accomplished as for **8**.

Upon reaction with C_{60} under modified cyclopropanation conditions, the *e*,*e*,*e*-fullerenophosphates **14**–**17** were obtained as the main products for all spacer lengths. The desired compounds were isolated by column chromatography. Increasing the spacer length is accompanied by a slightly decreasing polarity (TLC). The yields of isolated product and the selectivity for threefold *e*,*e*,*e*-addition decreased with increasing chain length from 16% to 7%. This change reflects the increasing flexibility of the elongated spacers, especially of the pentyl- and the hexyl chain. In addition to some by-product fractions, a second red but much less polar fraction was obtained for all the derivatives with an elongated spacer chain. These less-polar compounds **18**–**21** were isolated in yields of around 2%, with the yields also slightly decreasing with increasing chain length. Significantly, the color of these new adducts is characteristic for *e*,*e*,*e*-trisadducts. This remarkable discovery prompted us to look in more detail into the structural characterization of all the isolated trisadduct fractions.

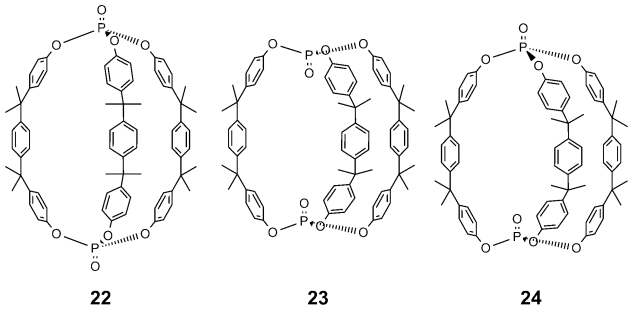
As already indicated by the color, the absorption spectra of the isolated trisadducts **13**–**21** are identical. Also the mass spectra (MALDI-TOF-MS and HiRes-ESI-MS) of each pair of a more polar and a less polar trisadduct are identical. The ^{13}C NMR spectra of each polar and the corresponding less-polar fraction were also almost identical and clearly reflect the depicted C_3-symmetry.

The only exceptions are the polar pentyl- and hexyl-spacer compounds **16** and **17** for which the ^{13}C NMR spectra displayed a second set of signals. The impurity could not be removed by automated flash chromatography or by HPLC. As the mass spectra indicated no additional compound, the UV/Vis spectra still resembled perfectly an *e*,*e*,*e*-addition pattern and as the polarity is so similar, the impurity is probably an *e*,*e*,*e*-isomer with one twisted malonate group. The pentyl- and hexyl-spacers are clearly flexible enough to allow the formation of the corresponding *out*,*out*,*in*-isomers **16a** and **17a**.[4b,13]



The ^{13}C NMR spectra of all the other, polar and nonpolar, *e*,*e*,*e*-trisadduct fractions suggested a single and pure component and were in perfect agreement with the expected structures.

Taking all these facts into account, the only possible difference between the two fractions had to be the orientation of the phosphate group. The double bonded oxygen atom can either point towards the fullerene surface or towards free space. This form of *in*/*out*-isomerism has been observed for macrobicyclic phosphates such as **22**–**24** (Figure 1).[14] In fact,



22 23 24

Figure 1. Literature examples of *in*- and *out*-isomerism in phosphate macrobicycles.[14]

it is a rather common structural feature of phosphorus containing macrocycles, which is also found for phosphites, phosphines, and phosphine oxides.[15]

Following the nomenclature of phosphate-capped cryptands and distinguishing it from the *in*/*out*-isomerism of malonates at fullerenes we denote our isolated isomers as P_{in}- and P_{out}-invertomers.[4b,14] The structural assignment was initially carried out by comparison with the properties of the ethyl-spacer derivative **13**. First, it has to be stated, that the ethyl chains are too short to promote P_{in}–P_{out} isomerism. As the polar invertomer **14** (R_f(**14**) = 0.16; CH_2Cl_2/THF = 95:5) has a similar polarity as the ethyl-spacer derivative **13** (R_f(**13**) = 0.06; CH_2Cl_2/THF = 95:5) it was concluded that it is the P_{out}-isomer. All the P_{in}-isomers are substantially less polar (e.g. R_f(**18**) = 0.90; CH_2Cl_2/THF = 95:5). The ^{31}P resonances can also be used to distinguish the two isomers. All P_{out}-isomers resonate at slightly negative values, between δ = −0.19 and −1.40 ppm, whereas the corresponding P_{in}-isomers resonate at more positive values in all cases.

Although these arguments are already convincing, unequivocal confirmation for the correct assignment of the structures was obtained from X-ray diffraction analysis (Figure 2). Single crystals of both isomers of the propyl-spacer derivatives **14** and **18** were obtained and their structures were determined.[16] They are the first crystal structures of *e*,*e*,*e*-trismalonate adducts of C_{60}. Recently, we reported the crystal structure of a pentakisadduct with an incomplete octahedral addition pattern and Chronakis and co-workers published the structure of a trisadduct with e_{edge},e_{face},*trans-1*-geometry.[17] An *e*,*e*,*e*-tris-dimethylanthracene adduct was the only other fullerene derivative with an *e*,*e*,*e*-addition pattern that was crystallized to date.[18] The single crystals of the P_{in}-isomer **18** were grown from hot [D_8]toluene solution. They belong to the chiral, orthorhombic space group $P2_12_12_1$. Fullerene trisadducts with an *e*,*e*,*e* addition pattern exist as two enantiomers depending on the orientation of the malonates towards each other.[11a] The measured crystal was enantiomerically pure and contained the ^{f}*C*-*e*,*e*,*e*-enantiomer with a clockwise orientation of the three malonates. The crystal structure (Figure 2 a,b) clearly confirmed the inward orientation of the P=O group as already concluded above. The molecule in the crystal is almost perfectly C_3 symmetric and the P=O group is tilted by only 2.5° from a perpendicular orientation to the hexagon below. The apical oxygen is 282.9 pm from this hexagon.

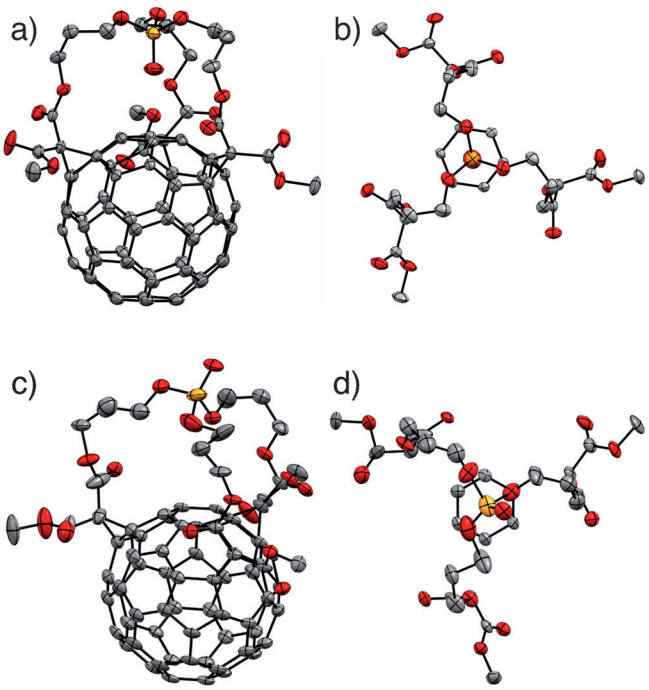


Figure 2. Single-crystal X-ray structures of **18** (top) and **14** (bottom): ORTEP representation with thermal ellipsoids set at 50% probability (C gray, O red, P orange; hydrogen atoms and solvent molecules are omitted for clarity). a), c) side view; b), d) top view of the addend part with the underlying hexagon of the C_{60} sphere.

Single crystals of the P_{out}-isomer **14** were grown by slow vapor diffusion of pentane into a benzene solution of the P_{out}-isomer **14**. It crystallized in the triclinic space group $P\bar{1}$ (Figure 2 c,d). The phosphate group, as well as one of the methoxy groups is disordered (not shown) and only geometric parameters of the major fraction (61.4% occupancy) will be discussed. The apical oxygen atom in this isomer is 615.4 pm from the hexagon below. The P=O group is strongly tilted by approximately 30° away from a perpendicular orientation and towards the underlying hexagon. This leads to substantially decreased symmetry of the arrangement of propyl chains and even the phosphate group itself is highly asymmetric. The angles between the P=O and the P–O bonds range from 104.9° to 120.1°.

The P atoms in macrobicyclic compounds can exhibit different chemical behaviors. Phosphates **22**–**24** were prepared by oxidation from the corresponding phosphites.[14] In that case, it was shown, that the P_{in}-phosphites are protected by the macrocycle and thus are less reactive than the P_{out}-phosphites.

In the case of our fullerenophosphates, we targeted the removal of the phosphate moiety to obtain the corresponding open-chain bromides as valuable building blocks for the construction of functional materials. Preliminary results showed that the P_{in}-isomers are much more inert against the deprotection conditions (trimethylsilyl bromide, DBU, $CHCl_3$, reflux), than the P_{out}-isomers, because the P_{in} phosphate groups are shielded both by the alkyl chains and the fullerene sphere. This situation is especially evident in the

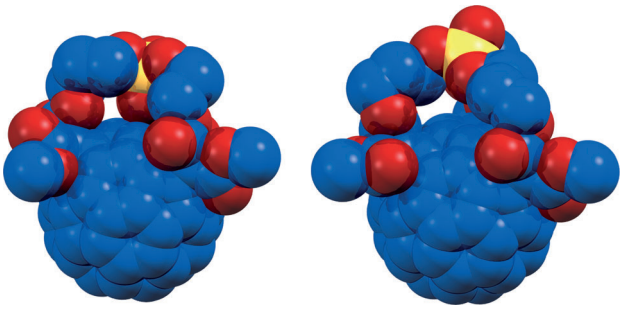


Figure 3. The space-filling representations of the X-ray crystal structures of **18** (left) and **14** (right) illustrate the protection of the internal P=O-group.

space-filling representation of the X-ray structure of **18** compared with that of **14** (Figure 3).

In conclusion, we have regioselectively synthesized and isolated a family of fullerenophosphate trisadducts. We were able to obtain for the first time, crystal structures of C_{60}–trismalonates with a C_3-symmetrical *e*,*e*,*e*-trisaddition pattern. We have discovered P_{in}–P_{out} isomerism with respect to the orientation of the P=O group relative to the fullerene core. Altogether four P_{in}-isomers were isolated with spacers from propyl to hexyl. The corresponding P_{out}-isomers were obtained in pure form with ethyl, propyl, and butyl spacers, whereas those with pentyl and hexyl spacers were obtained as *out*,*out*,*out*/*out*,*out*,*in*-isomeric mixtures because of the increased flexibility of the spacers. We showed that the P_{in}- and the corresponding P_{out}-isomers have different chemical properties. Further investigations on the removal of the phosphate group are currently underway and will be reported in due course.

Received: December 13, 2012
Published online: February 12, 2013

Keywords: fullerenes · *in*/*out*-isomerism · phosphorus · structure elucidation · trisadducts

[1] A. Hirsch, M. Brettreich, *Fullerenes—Chemistry and Reactions*, Wiley-VCH, Weinheim, **2005**.
[2] a) F. Djojo, A. Herzog, I. Lamparth, F. Hampel, A. Hirsch, *Chem. Eur. J.* **1996**, *2*, 1537–1547; b) A. Hirsch, I. Lamparth, T. Groesser, H. R. Karfunkel, *J. Am. Chem. Soc.* **1994**, *116*, 9385–9386; c) A. Hirsch, I. Lamparth, H. R. Karfunkel, *Angew. Chem.* **1994**, *106*, 453–455; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 437–438.
[3] S. Burghardt, A. Hirsch, B. Schade, K. Ludwig, C. Boettcher, *Angew. Chem.* **2005**, *117*, 3036–3039; *Angew. Chem. Int. Ed.* **2005**, *44*, 2976–2979.
[4] a) L. Isaacs, R. F. Haldimann, F. Diederich, *Angew. Chem.* **1994**, *106*, 2434–2437; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2339–2342; b) J. F. Nierengarten, T. Habicher, R. Kessinger, F. Cardullo, F. Diederich, V. Gramlich, J. P. Gisselbrecht, C. Boudon, M. Gross, *Helv. Chim. Acta* **1997**, *80*, 2238–2276.
[5] F. Diederich, R. Kessinger, *Acc. Chem. Res.* **1999**, *32*, 537–545.
[6] a) J. Dannhäuser, W. Donaubauer, F. Hampel, M. Reiher, B. Le Guennic, B. Corzilius, K.-P. Dinse, A. Hirsch, *Angew. Chem.* **2006**, *118*, 3446–3450; *Angew. Chem. Int. Ed.* **2006**, *45*, 3368–3372; b) N. Armaroli, G. Marconi, L. Echegoyen, J.-P. Bourgeois, F. Diederich, *Chem. Eur. J.* **2000**, *6*, 1629–1645; c) J.-P. Bourgeois, F. Diederich, L. Echegoyen, J.-F. Nierengarten, *Helv. Chim. Acta* **1998**, *81*, 1835–1844; d) E. Dietel, A. Hirsch, E. Eichhorn, A. Rieker, S. Hackbarth, B. Röder, *Chem. Commun.* **1998**, 1981–1982.
[7] a) F. Beuerle, A. Hirsch, *Chem. Eur. J.* **2009**, *15*, 7447–7455; b) M. Braun, U. Hartnagel, E. Ravanelli, B. Schade, C. Boettcher, O. Vostrowsky, A. Hirsch, *Eur. J. Org. Chem.* **2004**, 1983–2001; c) U. Reuther, T. Brandmüller, W. Donaubauer, F. Hampel, A. Hirsch, *Chem. Eur. J.* **2002**, *8*, 2261–2273.
[8] a) G. Rapenne, J. Crassous, L. E. Echegoyen, L. Echegoyen, E. Flapan, F. Diederich, *Helv. Chim. Acta* **2000**, *83*, 1209–1223; b) F. Beuerle, N. Chronakis, A. Hirsch, *Chem. Commun.* **2005**, 3676–3678; c) F. Beuerle, A. Hirsch, *Chem. Eur. J.* **2009**, *15*, 7434–7446.
[9] E. Adams, M. Hiegemann, H. Duddeck, P. Welzel, *Tetrahedron* **1990**, *46*, 5975–5992.
[10] J.-F. Nierengarten, V. Gramlich, F. Cardullo, F. Diederich, *Angew. Chem.* **1996**, *108*, 2242–2244; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2101–2103.
[11] a) F. Djojo, A. Hirsch, S. Grimme, *Eur. J. Org. Chem.* **1999**, 3027–3039; b) G. Rapenne, F. Diederich, J. Crassous, A. Collet, L. Echegoyen, *Chem. Commun.* **1999**, 1121–1122.
[12] T. Nishiguchi, M. Kuroda, M. Saitoh, A. Nishida, S. Fujisaki, *J. Chem. Soc. Chem. Commun.* **1995**, 2491–2492.
[13] In ongoing attempts to remove the phosphate group, we were able to separate and characterize the corresponding isomers after the deprotection reaction. These results will be reported elsewhere.
[14] I. Bauer, O. Rademacher, M. Gruner, W. D. Habicher, *Chem. Eur. J.* **2000**, *6*, 3043–3051.
[15] a) I. Bauer, R. Fröhlich, A. Y. Ziganshina, A. V. Prosvirkin, M. Gruner, E. K. Kazakova, W. D. Habicher, *Chem. Eur. J.* **2002**, *8*, 5622–5629; b) B. P. Friedrichsen, D. R. Powell, H. W. Whitlock, *J. Am. Chem. Soc.* **1990**, *112*, 8931–8941; c) M. Stollenz, M. Barbasiewicz, A. J. Nawara-Hultzsch, T. Fiedler, R. M. Ladduwaw, N. Bhuvanesh, J. A. Gladysz, *Angew. Chem.* **2011**, *123*, 6777–6781; *Angew. Chem. Int. Ed.* **2011**, *50*, 6647–6651.
[16] CCDC 915467 (**14**) and 915455 (**18**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
[17] a) F. Hörmann, M. Brettreich, W. Donaubauer, F. Hampel, A. Hirsch, *Chem. Eur. J.* **2013**, DOI: 10.1002/chem.201203863; b) M. Riala, M. S. Markoulides, E. E. Moushi, N. Chronakis, *Chem. Commun.* **2011**, *47*, 11948–11950.
[18] A. Duarte-Ruiz, K. Wurst, B. Kräutler, *Helv. Chim. Acta* **2008**, *91*, 1401–1408.

