CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200902141

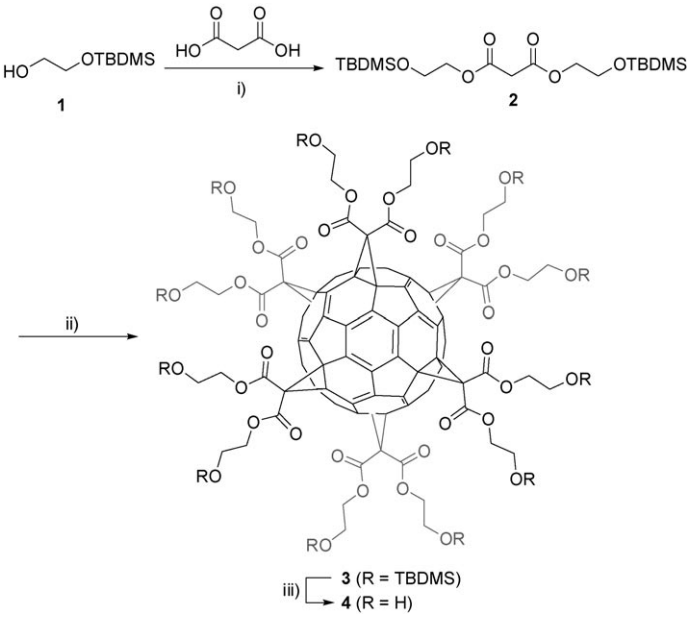
Di- and Dodeca-Mitsunobu Reactions on C_{60} Derivatives: Post-Functionalization of Fullerene Mono- and Hexakis-Adducts

Philippe Pierrat, Céline Réthoré, Thierry Muller,* and Stefan Bräse*[a]

The diverse addition patterns of fullerene adducts make them attractive molecules, generating widespread application.[1] Firstly, in terms of the latter, mono-adducts are extensively used in opto-electronic devices, owing to the fullerene core's capacity to accept up to six electrons.[2] A second important application involves the utilization of fullerene adducts as structural components in material sciences.[3] With their octahedral topology,[4] T_h-symmetric hexakis-adducts, are particularly intriguing. Amongst others, the latter have been used in C_{60}-based star polymers.[5] In the aforementioned contexts, the relatively stable methanofullerene adducts obtained through Bingel cyclopropanation reactions are of particular interest. However, this functionalization approach—primarily developed by A. Hirsch[6] and later optimized by Y.-P. Sun[7]—suffers from two critical weaknesses. One is its effectively exclusive limitation to malonates; only a few exceptions are known. The other is a structural concern. In fact, quite often only the use of fairly simple malonates leads to the desired fullerene adducts in reasonable yields without tedious purifications. In order to overcome these problems, several groups have developed post-functionalizations of methanofullerene adducts. For instance, J.-F. Nierengarten adapted the copper-mediated Huisgen 1,3-dipolar cycloaddition reaction and applied it to the preparation of complex hexasubstituted fullerenes.[8] A. Hirsch developed a selective deprotection–functionalization sequence of fullerene *e,e,e*-trisadducts.[9] Our own group derivatized hexakis methanofullerenes by using several organometallic cross-coupling reactions.[10]

This article outlines the use of the Mitsunobu reaction[11] as an efficient tool for the post-functionalization of fullerene mono- and hexakis-adducts. The mild, virtually neutral conditions under which this dehydrative coupling of an alcohol with a pronucleophile (generally an acid) proceeds, prompted our group to use this reaction for the derivatization of fullerene adducts. To this end, we have prepared a C_{60} mono-adduct bearing 2 hydroxyl groups and a hexakis-adduct with 12 hydroxyl functions. The preparation of hexakis compound **4** is depicted in Scheme 1.

Ethylene glycol was mono-protected as *tert*-butyldimethylsilyl ether according to a previously reported procedure.[12] Subsequent diesterification of malonic acid was performed in the presence of DCC in 97% yield. Hexakis-adduct **3** was then readily synthesized by using the optimized conditions



Scheme 1. i) DCC, MeCN, RT, 2 h (97%); ii) C_{60} (0.1 equiv), CBr_4 (10 equiv), DBU (2 equiv), *o*-dichlorobenzene, RT, 24 h; iii) HCl/MeOH, CH_2Cl_2, RT, 12 h (28% over 2 steps).

[a] Dr. P. Pierrat, Dr. C. Réthoré, Dr. T. Muller, Prof. Dr. S. Bräse
Institut für Organische Chemie and Center
for Functional Nanostructures (CFN)
Karlsruhe Institute of Technology (KIT)
Fritz-Haber-Weg 6, 76131 Karlsruhe (Germany)
Fax: (+49) 721 608 8581
E-mail: Stefan.Braese@kit.edu

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200902141.

described by Y.-P. Sun.[7] The resulting crude mixture was purified on silica-gel column to afford an inseparable mixture of pentakis- and hexakis-adduct. The mixture of both isomers was subjected to desilylation using an excess of hydrogen chloride as a methanolic solution. At this stage, pentakis and hexakis derivatives could be easily separated through a silica gel column chromatography using acetone/EtOH (90/10) as eluent. The chemical structure of compound **4** was confirmed by ^{1}H- and ^{13}C NMR analysis. As shown in Figure 1, the ^{13}C NMR spectrum of fullerene hexakis-adduct **4** is in complete agreement with its T_h-symmetrical structure and shows the three expected fullerene resonances ($\delta = 68.6$ ppm for the sp^3 C atoms; 140.5 and 144.9 ppm for the two different sp^2 C atoms), a signal for the bridgehead C atoms ($\delta = 45.3$ ppm), a signal for the carbonyl groups ($\delta = 162.7$ ppm), and two signals for the $(CH_2)_2$ linkers ($\delta = 58.5$ and 68.5 ppm). The corresponding mono-adduct **5** was obtained following the same strategy in an overall yield of 36% over 4 steps (see the Supporting Information).

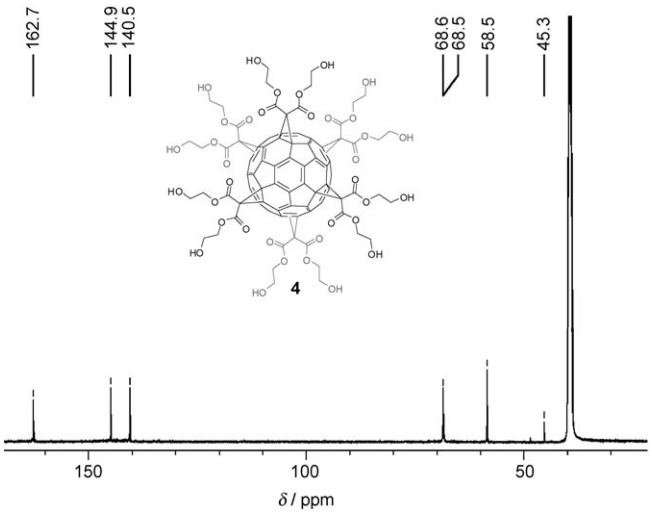
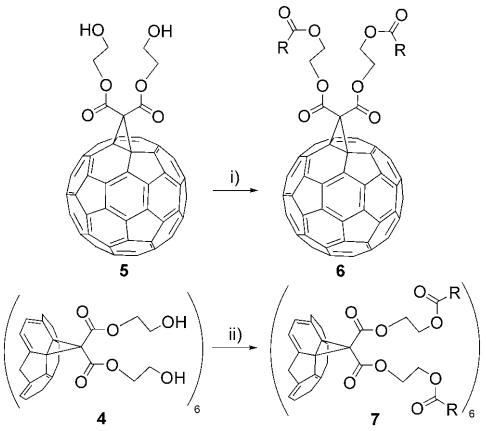


Figure 1. ^{13}C NMR spectra ([D$_6$]DMSO, 125 MHz) of dodeca alcohol **4**.

With polyalcohol **4** and diol **5** in hand, we started investigating the Mitsunobu reaction (Scheme 2, Table 1). We were pleased to note that the classic Mitsunobu conditions using a combination of diethyl azodicarboxylate (DEAD) as oxidizing azo reagent and triphenylphosphine (TPP) as reducing agent delivered the desired di- and dodeca-esters in moderate to good yields (Table 1, entries 1–5). Yields per alcohol function are however corresponding to yields previously reported in the literature. To the best of our knowledge, this is the first time that a twelvefold Mitsunobu reaction has been undertaken.

With activated Mitsunobu pronucleophiles ($pK_a \leq 11$, entries 1–4), the reaction proceeds properly. However, if inactivated substrates are used, the yields drop significantly for both fullerene adducts (entry 5). Better yields per alcohol function are consistently attained with hexakis fullerene derivative **4** than with mono-adduct **5** (entries 1–5). A possible explanation for this result involves unidentified side products generated through the reaction of the fullerene core of mono-adduct **5**. In contrast, for hexakis-adduct **4**, the core is completely shielded by the malonates and cannot react anymore. No reaction took place with known Mitsunobu substrates 4-methyl-*N*-(prop-2-ynyl)benzenesulfonamide and isoindoline-1,3-dione (entries 6, 7).



Scheme 2. i) RCO_2H (or NuH) (3 equiv), DEAD (3 equiv), PPh_3 (3 equiv), THF, RT, 15–18 h; ii) RCO_2H (or NuH) (20 equiv), DEAD (20 equiv), PPh_3 (20 equiv), THF, RT, 15–18 h.

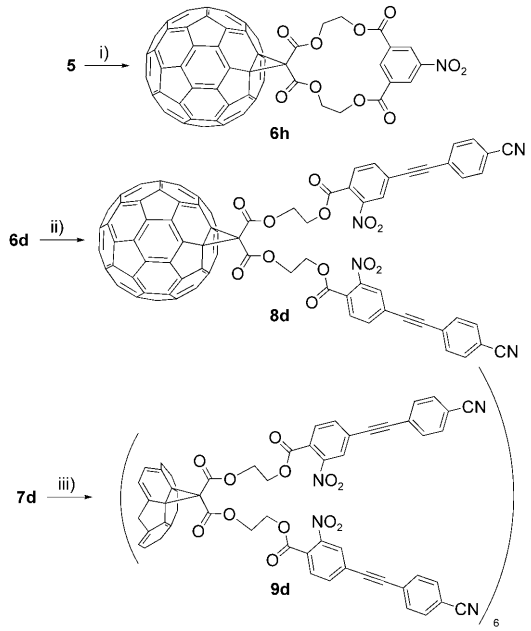
Table 1. Pronucleophiles used in the Mitsunobu reaction.

Entry	RCO_2H (or NuH)	Product **6** [yield in %][a]	Product **7** [yield in %][a]
1	4-nitrobenzoic acid	**6a** [53 (73)]	**7a** [70 (97)]
2	4-cyanobenzoic acid	**6b** [69 (83)]	**7b** [21 (88)]
3	1-phenyl-1*H*-tetrazole -5-thiol[b]	**6c** [52 (72)]	**7c** [70 (97)]
4	4-iodo-2-nitrobenzoic acid	**6d** [62 (79)]	**7d** [21 (88)]
5	4-iodobenzoic acid	**6e** [3 (17)]	**7e** [10 (83)]
6	4-methyl-*N*-(prop-2-ynyl) benzenesulfonamide[b]	**6f** [0]	**7f** [0]
7	isoindoline-1,3-dione[b]	**6g** [0]	**7g** [0]

[a] In parentheses: Calculated yield per alcohol function. [b] Pronucleophile NuH containing an acidic hydrogen atom.

Even the use of 1,1′-(azodicarbonyl)dipiperidine (ADDP) and tributylphosphine (TBP)—an alternative redox system specifically developed for inactivated pronucleophiles having a pKa higher than 11[13]—did not generate better results (data not shown).

Subsequently, we explored some of the possible applications of our Mitsunobu approach. Two particularly promising results are shown in Scheme 3. The first involves a cyclization by a twofold Mitsunobu reaction using 5-nitroisophthalic acid and diol **5** opening up the road to novel fullerene-cyclic malonate derivatives. The second example demonstrates that the Mitsunobu products of both mono- and hexakis-adducts can be further functionalized by means of Sonogashira cross coupling reactions in good yield for **9d** (52%, 95% per iodide). Although the yield of mono-adduct



Scheme 3. i) 5-Nitroisophthalic acid (1.1 equiv), DEAD (3 equiv), PPh_3 (3 equiv), THF, RT, 18 h (29%); ii) 4-ethynylbenzonitrile (4 equiv), $PdCl_2(PPh_3)_2$ (0.2 equiv), CuI (0.4 equiv), $THF/CH_2Cl_2/Et_3N$ (15:15:2), RT, 24 h (34%); iii) 4-ethynylbenzonitrile (24 equiv), $PdCl_2(PPh_3)_2$ (1.2 equiv), CuI (2.4 equiv), $THF/CH_2Cl_2/Et_3N$ (15:15:2), RT, 24 h (51%).

8d seems quite moderate (34%, 58% per iodide), this is actually a rare example in which an organometallic cross coupling product from a lower fullerene adduct was isolated. Palladium-mediated cross couplings on lower fullerene adducts are indeed known to cause problems, because the fullerene core may act as ligand for the metal, either poisoning the catalyst or leading to side reactions.

In conclusion the Mitsunobu condensation between alcohols and acids has been successfully applied to the derivatization of methanofullerene mono- and hexakis-adducts. Although results obtained thus far suggest that this approach is limited to activated Mitsunobu substrates, further investigations are being undertaken to enable the use of a larger substrate spectrum. This approach enables for third generation derivatization of the fullerene substrates, which, if combined with existing methods, is a very interesting route yet to be explored. Within our group, efforts are currently being made to determine the scope and limitations of this approach.

Acknowledgements

We gratefully acknowledge the financial support of the Alexander von Humboldt foundation (grants to P.P. and C.R.) and of the DFG Center for Functional Nanostructures (CFN, Project C5.2).

Keywords: condensation reaction · fullerenes · Mitsunobu reaction · post-functionalization · synthetic methods

[1] a) A. Hirsch, M. Brettreich, *Fullerenes: Chemistry and Reactions*, Wiley-VCH, Weinheim, **2005**; b) *Fullerenes Principles and Applications* (Eds.: F. Langa, J.-F. Nierengarten), RCS, Cambridge, **2007**; c) F. Diederich, C. Thilgen, *Science* **1996**, *271*, 317–323; d) F. Diederich, *Pure Appl. Chem.* **1997**, *69*, 395–400; e) U. Reuther, T. Brandmüller, W. Donaubauer, F. Hampel, A. Hirsch, *Chem. Eur. J.* **2002**, *8*, 2261–2273; f) C. Thilgen, F. Diederich, *Chem. Rev.* **2006**, *106*, 5049–5135.

[2] a) D. M. Guldi, *Chem. Commun.* **2000**, 321–327; b) R. Deschenaux, B. Donnio, D. Guillon, *New J. Chem.* **2007**, *31*, 1064–1073; c) L. Pérez, J. Lenoble, J. Barberá, P. de La Cruz, R. Deschenaux, F. Langa, *Chem. Commun.* **2008**, 4590–4592; d) M. Urbani, J. Iehl, I. Osinska, R. Louis, M. Holler, J.-F. Nierengarten, *Eur. J. Org. Chem.* **2009**, 3715–3725; e) P. Witte, F. Hörmann, A. Hirsch, *Chem. Eur. J.* **2009**, *15*, 7423–7433.

[3] a) D. Sun, F. S. Tham, C. A. Reed, L. Chaker, P. D. W. Boyd, *J. Am. Chem. Soc.* **2002**, *124*, 6604–6612; b) S. Zhang, O. Lukoyanova, L. Echegoyen, *Chem. Eur. J.* **2006**, *12*, 2846–2853; c) U. Hahn, A. Gégout, C. Duhayon, Y. Coppel, A. Saquet, J.-F. Nierengarten, *Chem. Commun.* **2007**, 516–518; d) P. Pierrat, C. Réthoré, T. Muller, S. Bräse, *Synlett* **2008**, 1706–1710.

[4] I. Lamparth, A. Herzog, A. Hirsch, *Tetrahedron* **1996**, *52*, 5065–5075.

[5] a) B. Schmaltz, C. Mathis, M. Brinkmann, *Polymer* **2009**, *50*, 966–972; b) A. J. Inglis, P. Pierrat, T. Muller, S. Bräse, C. Barner-Kowollik, unpublished results.

[6] A. Hirsch, I. Lamparth, T. Grösser, H. R. Karfunkel, *J. Am. Chem. Soc.* **1994**, *116*, 9385–9386.

[7] H. Li, A. Kitaygorodskiy, R. A. Carino, Y.-P. Sun, *Org. Lett.* **2005**, *7*, 859–861.

[8] a) J. Iehl, R. Pereira de Freitas, B. Delavaux-Nicot, J.-F. Nierengarten, *Chem. Commun.* **2008**, 2450–2452; b) J. Iehl, J.-F. Nierengarten, *Chem. Eur. J.* **2009**, *15*, 7306–7309.

[9] F. Beuerle, A. Hirsch, *Chem. Eur. J.* **2009**, *15*, 7434–7446.

[10] P. Pierrat, S. Vanderheiden, T. Muller, S. Bräse, *Chem. Commun.* **2009**, 1748–1750.

[11] a) T. Y. S. But, P. H. Toy, *Chem. Asian J.* **2007**, *2*, 1340–1355; b) K. C. K. Swamy, N. N. B. Kumar, E. Balaraman, K. V. P. P. Kumar, *Chem. Rev.* **2009**, *109*, 2551–2651.

[12] I. Azumaya, D. Uchida, T. Kato, A. Yokoyama, A. Tanatani, H. Takayanagi, T. Yokozawa, *Angew. Chem.* **2004**, *116*, 1384–1387; *Angew. Chem. Int. Ed.* **2004**, *43*, 1360–1363.

[13] T. Tsunoda, Y. Yamamiya, S. Itô, *Tetrahedron Lett.* **1993**, *34*, 1639–1642.

Received: August 1, 2009
Published online: October 9, 2009

