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Synthesis of Chiral Cyclobutane Containing C_3-Symmetric Peptide Dendrimers†

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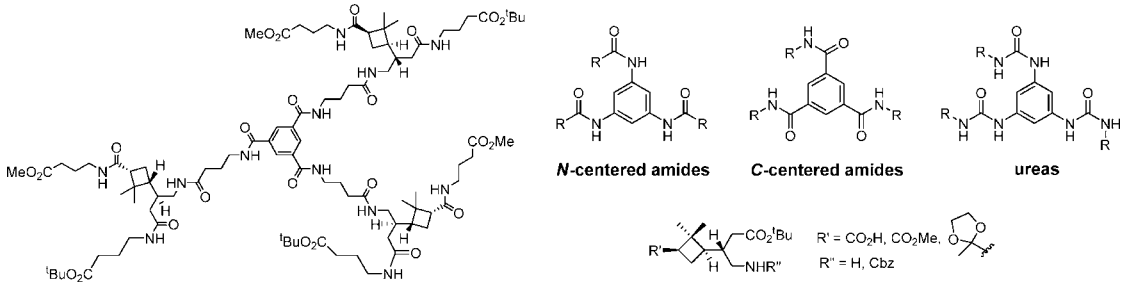
ABSTRACT



Five new highly functionalized cyclobutane containing C_3-symmetric peptide dendrimers have been synthesized through a convergent approach from 1,3,5-trisubstituted benzene and chiral γ,ε-amino diacid derivatives as well as a γ-tetrapeptide. The first example of the synthesis of N-centered amides by using 1,3,5-triaminobenzene and a carboxylic acid is reported.

C_3-Symmetric benzene-cored molecules are useful compounds with very different applications. Of special interest are those linked to the core through a urea, *C*-amide, or *N*-amide group. They have been described as good nucleation agents for polymers,[1] as new materials,[2] and especially as organogelators,[3] some of them with conducting[4] or photoresponsive properties,[5] and as ligands for metals.[6] Some also have interesting biological applications.[6a,7] Nevertheless, there are very scarce examples of benzene-cored dendrimers containing a peptide nature in their dendron structure.[2d,3c,7b,8]

In our laboratory, according to a research program on the synthesis, structural study, and applications of cyclobutane amino acids and oligomer derivatives,[9] we have prepared cyclobutane γ-amino acids and different γ-oligomers.[10]

In this paper, we describe new branched polyfunctional benzene-cored C_3-symmetric dendrimers that have been synthesized through a convergent approach. This synthetic strategy, which consists of the attachment of presynthesized dendrons to the core, leads to dendrimers of monodisperse molecular weight which are easy to purify. These dendrimers are highly functionalized and orthogonally protected, which could allow us to elongate their structures selectively. The different possible combinations of deprotected monomers and functionalized benzene cores have led to urea (**1**, **2**), N-centered amide (**3**), and C-centered amide derivatives (**4**, **5**) (Figure 1). It is worth mentioning that there are not as many examples of N-centered benzene triamides in the literature as there are of C-centered ones.

1,3,5-Trisubstituted benzenes were used as cores. Commercially available 1,3,5-benzenetricarboxylic acid (trimesic acid) and 1,3,5-benzenetricarbonyl trichloride were directly used in some cases, whereas 1,3,5-benzenetriisocyanate was

† Dedicated to Professor Pelayo Camps on the occasion of his 65th birthday.

(1) (a) Kristiansen, M.; Smith, P.; Chanzy, H.; Baerlocher, C.; Gramlich, V.; McCusker, L.; Weber, T.; Pattison, P.; Blomenhofer, M.; Schmidt, H.-W. *Cryst. Growth Des.* **2009**, *9*, 2556. (b) Mohmeyer, N.; Behrendt, N.; Zhang, X.; Smith, P.; Altstädt, V.; Sessler, G. M.; Schmidt, H.-W. *Polymer* **2007**, *48*, 1612. (c) Blomenhofer, M.; Ganzleben, S.; Hanft, D.; Schmidt, H.-W. *Macromolecules* **2005**, *38*, 3688.

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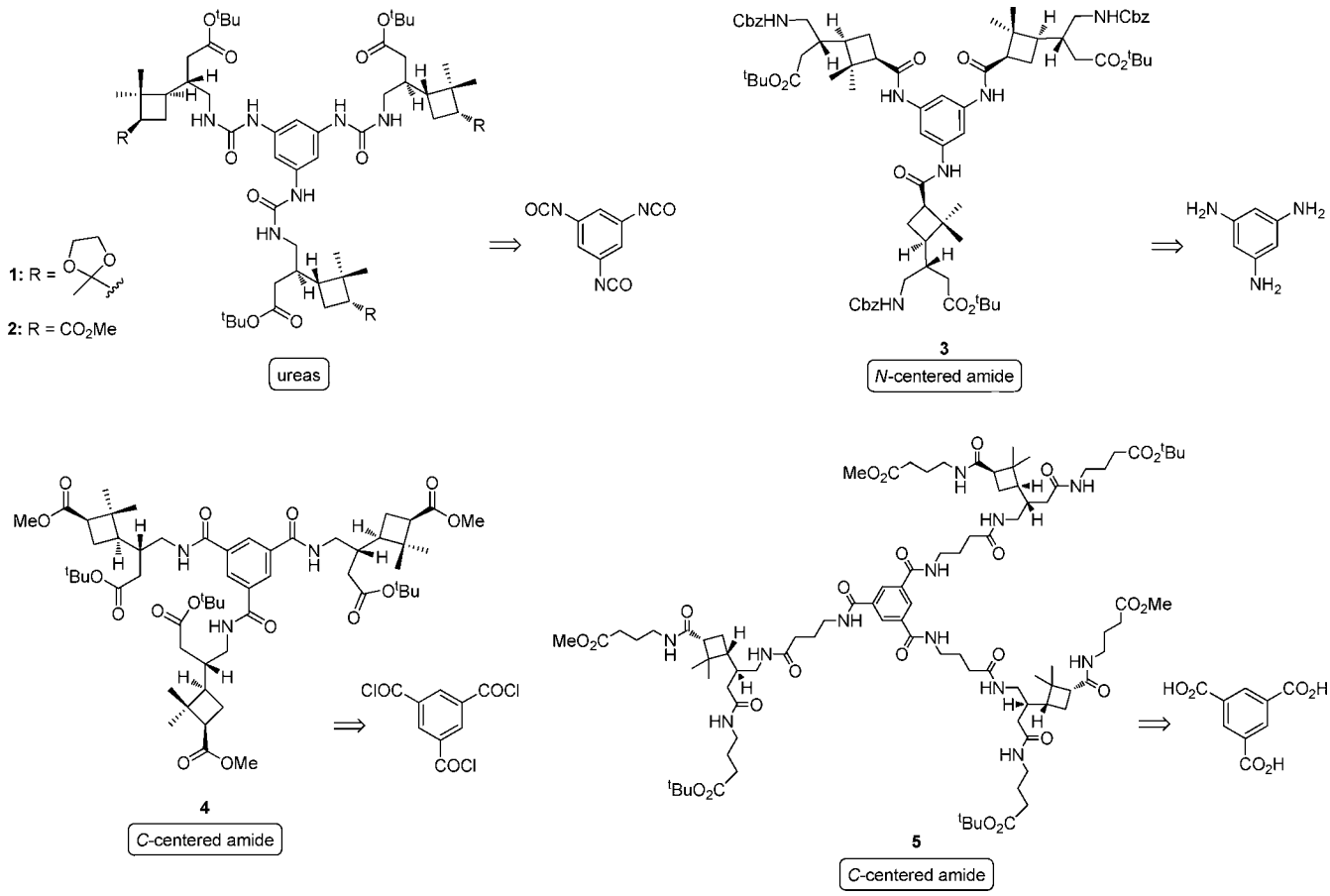


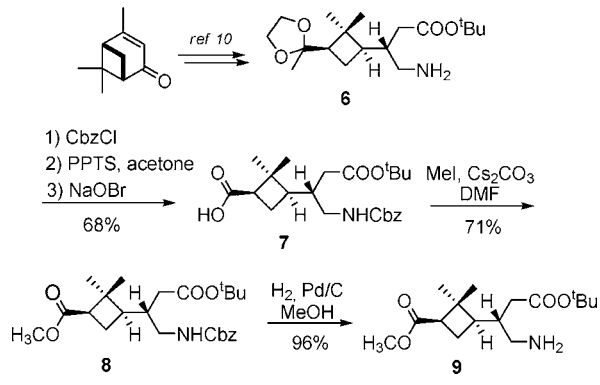
Figure 1. Target dendrimers and retrosynthetic analysis.

prepared from the same acid after activation as a mixed anhydride. 1,3,5-Triaminobenzene was synthesized by hydrogenation of 3,5-dinitroaniline as previously reported.[11] For the synthesis of dendrons, we used optically pure polyfunctional orthogonally protected cyclobutane γ-amino ester **6**[10a] and some convenient derivatives, as well as tetrapeptide **16** (Schemes 1 and 2). All of the dendrons deriving from **6** contain a cyclobutane ring which confers rigidity and provides functional groups that can be selectively manipulated. The dendron deriving from tetrapeptide **16** is based on a cyclobutane and three pending γ-aminobutyric acid (GABA) segments that tune up the flexibility to the molecule. This dendron is also interesting because it is known that oligomers derived from γ- amino acids tend to adopt defined structures.[12] Moreover, in our laboratory, we have observed that the presence of GABA-derived residues in related structures, such as ureas and peptides, makes it easier for this kind of molecule to gelify.

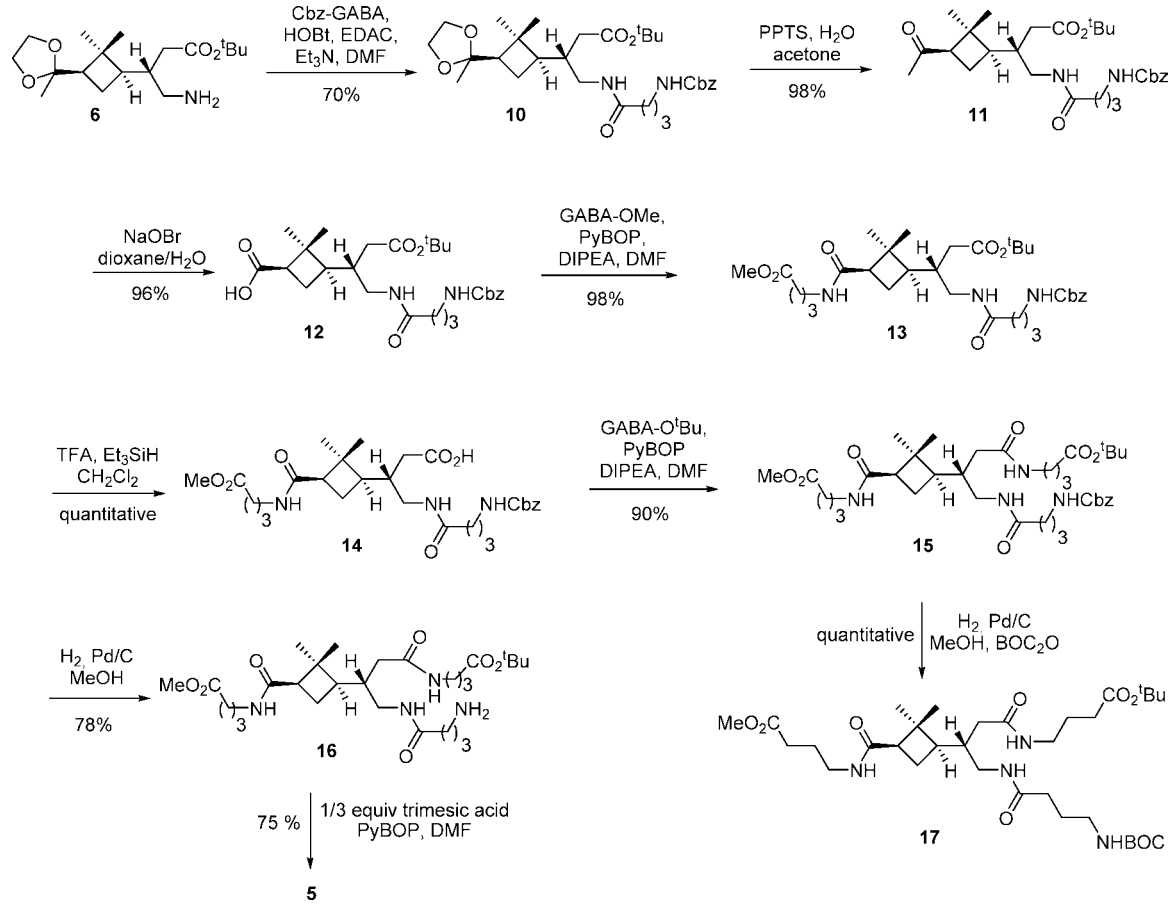
Monomers derived from amino ester **6** were prepared starting from (−)-verbenone according to Scheme 1. After amine protection, ketal removal, and Lieben degradation, it was derived into acid **7**. Methylation of the acid with methyl iodide and cesium carbonate followed by hydrogenolysis of the benzyl carbamate led to amine **9**.

Triurea **1** was synthesized from freshly prepared 1,3,5-benzenetriisocyanate and aminoester **6** in anhydrous toluene at room temperature overnight (80% yield). Triurea **1** contains a ketal-protected methyl ketone and a *tert*-butyl ester as side groups that can be selectively deprotected for further functionalization. We were interested in testing whether it was possible to manipulate triurea **1** to synthesize triurea **2**. Deprotection of the methyl ketones worked satisfactorily, but attempts to convert it to the triacid through a Lieben degradation were unsuccessful. Transformations on the dendron amino ester **6** to prepare amine **9**, which could be

Scheme 1. Synthesis of Monomers **6** and **9**



Scheme 2. Synthesis of Tetrapeptide **16**



then coupled to 1,3,5-benzenetriisocyanate, proved to be a much better strategy to obtain triurea **2** (70% yield).

The same amine **9** was used to prepare C-centered amide **4** by reaction with 1,3,5-benzenetricarbonyl trichloride in the presence of triethylamine in dichloromethane for 21 h at room temperature. In this way, **4** was obtained in 58% yield. This molecule contains methyl ester and *tert*-butyl ester protecting groups, which can also be selectively removed if desired.

As an example of a third type of dendrimer, N-centered triamide **3** was synthesized starting from acid **7**. Previous model reactions carried out in our laboratory had shown that 1,3,5-triaminobenzene reacts better with a carboxylic acid in the presence of a coupling agent than in the presence of an isocyanate. This fact led us to use acid **7** in this reaction with 1,3,5-triaminobenzene in the presence of HATU as coupling agent and DIPEA in anhydrous acetonitrile. After reflux for 48 h, triamide **3** was obtained in a moderate yield (28%), probably due to the intrinsic instability of the 1,3,5-triaminobenzene. This product contains three orthogonally protected γ-amino acids and is very attractive for further transformations. This convergent approach to triamide **3** is the first example in the synthesis of N-centered amides starting from a carboxylic acid and 1,3,5-triaminobenzene.

A larger and longer branched C-centered triamide, **5**, was prepared from tetrapeptide **16** using some other coupling conditions due to the low stability of 1,3,5-benzenetricarbonyl trichloride (Scheme 2). In this case, 1,3,5-benzenetricarboxylic acid was used as starting material and PyBOP as coupling agent in the presence of DIPEA in anhydrous DMF. After 2 h at room temperature, triamide **5** was obtained in 75% yield in high purity.

In turn, the synthesis of tetrapeptide **16** was accomplished starting from amino ester **6**. Coupling of the latter with 4-(benzyloxycarbonylamino)butanoic acid (Cbz-GABA)[13] under standard conditions (HOBt, EDAC) afforded γ-dipeptide **10** in 70% yield. Deprotection of the methyl ketone under mild conditions (PPTS, acetone) afforded **11** in a nearly quantitative yield and without epimerization. Lieben degradation furnished acid **12** in 96% yield. Tripeptide **13** was obtained in 94% yield by reacting **12** with methyl 4-aminobutanoate (GABA-OMe)[14] using PyBOP as a coupling agent.

The third GABA residue was incorporated after quantitative deprotection of the *tert*-butyl ester using trifluoroacetic acid and triethylsilane and subsequent coupling with *tert*-butyl 4-aminobutanoate (GABA-O^{t}Bu)[15] furnishing tetrapeptide **15** in 90% yield.

Product **15** is very interesting due to its orthogonal protection, which could allow synthesis of varied products by peptide elongation through selective deprotection of its functional groups. Moreover, we realized that self-assembling

properties of these types of compounds are influenced by the nature of the protecting groups.[16] Thus, benzyl carbamate exchange in **15** for *tert*-butyl carbamate led quantitatively to tetrapeptide **17** by hydrogenation with Pd/C in MeOH in the presence of di-*tert*-butyl dicarbonate. Tetrapeptide **17** gelified readily (12 mM) in chloroform, whereas **15** did not. Finally, hydrogenolysis of benzyl carbamate under standard conditions (H_2, Pd/C, MeOH) led to tetrapeptide **16** in 78% yield.

In summary, we have presented a very versatile synthesis of highly functionalized enantiopure peptide dendrimers with C_3-symmetry. The influence of the nature and length of the spacer from the aromatic core and the cyclobutane ring on the properties of these compounds is currently under study. The understanding of these factors and the possibility of further elongation and functionalization of these dendrimers should allow us to establish a rational synthetic design of unique molecules for future applications in the field of new chiral materials.

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Supporting Information Available: Experimental procedures and full characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(2) (a) Kreger, K.; Wolfer, P.; Audorff, H.; Kador, L.; Stingelin-Stutzmann, N.; Smith, P.; Schmidt, H.-W. *J. Am. Chem. Soc.* **2010**, *132*, 509. (b) Smulders, M. M. J.; Filot, I. A. W.; Leenders, J. M. A.; van der Schoot, P.; Palmans, A. R. A.; Schenning, A. P. H. J.; Meijer, E. W. *J. Am. Chem. Soc.* **2010**, *132*, 611. (c) Smulders, M. M. J.; Stals, P. J. M.; Mes, T.; Paffen, T. F. E.; Schenning, A. P. H. J.; Palmans, A. R. A.; Meijer, E. W. *J. Am. Chem. Soc.* **2010**, *132*, 620. (d) Matsuura, K.; Matsuyama, H.; Fukuda, T.; Teramoto, T.; Watanabe, K.; Murasato, K.; Kimizuka, N. *Soft Matter* **2009**, *5*, 2463. (e) Huang, Y.; Cong, Y.; Li, J.; Wang, D.; Zhang, J.; Xu, L.; Li, W.; Li, L.; Pan, G.; Yang, C. *Chem. Commun.* **2009**, 7560. (f) van Gorp, J. J.; Vekemans, J. A. J. M.; Meijer, E. W. *Mol. Cryst. Liq. Cryst.* **2003**, *397*, 191. (g) Lightfood, M. P.; Mair, F. S.; Pritchard, R. G.; Warren, J. E. *Chem. Commun.* **1999**, 1945.

(3) (a) Zhou, Y.; Xu, M.; Li, T.; Guo, Y.; Yi, T.; Xiao, S.; Li, F.; Huang, C. *J. Colloid Interface Sci.* **2008**, *321*, 205. (b) Pichon, B. P.; Wong Chi Man, M.; Dieudonné, P.; Bantignies, J.-L.; Bied, C.; Sauvajol, J.-L.; Moreau, J. J. E. *Adv. Funct. Mater.* **2007**, *17*, 2349. (c) de Loos, M.; van Esch, J. H.; Kellogg, R. M.; Feringa, B. L. *Tetrahedron* **2007**, *63*, 7285. (d) van Gorp, J. J.; Vekemans, J. A. J. M.; Meijer, E. W. *J. Am. Chem. Soc.* **2002**, *124*, 14759. (e) Yasuda, Y.; Iishi, E.; Inada, H.; Shirota, Y. *Chem. Lett.* **1996**, 575.

(4) Danila, I.; Riobé, F.; Puigmartí-Luis, J.; Pérez del Pino, A.; Wallis, J. D.; Amabilino, D. B.; Avarvari, N. *J. Mater. Chem.* **2009**, *19*, 4495.

(5) Zhou, Y.; Xu, M.; Yi, T.; Xiao, S.; Zhou, Z.; Li, F.; Huang, C. *Langmuir* **2007**, *23*, 202.

(6) (a) Jia, T.; Zhao, Y.; Xing, F.; Shao, M.; Zhu, S.; Li, M. *J. Mol. Struct.* **2009**, *920*, 18. (b) Birkmann, B.; Fröhlich, R.; Hahn, F. E. *Chem.—Eur. J.* **2009**, *15*, 9325. (c) Caulder, D. L.; Brückner, C.; Powers, R. E.; König, S.; Parac, T. N.; Leary, J. A.; Raymond, K. N. *J. Am. Chem. Soc.* **2001**, *123*, 8923.

(7) (a) Müller, M. K.; Brunsveld, L. *Angew. Chem., Int. Ed.* **2009**, *48*, 2921. (b) Trouche, N.; Wieckowski, S.; Sun, W.; Chaloin, O.; Hoebeke, J.; Fournel, S.; Guichard, G. *J. Am. Chem. Soc.* **2007**, *129*, 13480.

(8) (a) Kotha, S.; Shah, V. R. *Amino Acids* **2008**, *35*, 83. (b) van den Hout, K. P.; Martín-Rapún, R.; Vekemans, J. A. J. M.; Meijer, E. W. *Chem.—Eur. J.* **2007**, *13*, 8111. (c) Matsuura, K.; Murasato, K.; Kimizuka, N. *J. Am. Chem. Soc.* **2005**, *127*, 10148. (d) Tor, Y.; Libman, S.; Shanzer, A.; Felder, C. E.; Lifson, S. *J. Am. Chem. Soc.* **1992**, *114*, 6653.

(9) See, for example: (a) Torres, E.; Gorrea, E.; Burusco, K. K.; Da Silva, E.; Nolis, P.; Rúa, F.; Boussert, S.; Díez-Pérez, I.; Dannenberg, S.; Izquierdo, S.; Giralt, E.; Jaime, C.; Branchadell, V.; Ortuño, R. M. *Org. Biomol. Chem.* **2010**, *8*, 564. (b) Torres, E.; Gorrea, E.; Da Silva, E.; Nolis, P.; Branchadell, E.; Ortuño, R. M. *Org. Lett.* **2009**, *11*, 2301. (c) Rúa, F.; Boussert, S.; Diez-Pérez, I.; Branchadell, V.; Giralt, E.; Ortuño, R. M. *Org. Lett.* **2007**, *9*, 3643.

(10) (a) Aguilera, J.; Gutiérrez-Abad, R.; Mor, A.; Moglioni, A. G.; Moltrasio, G. Y.; Ortuño, R. M. *Tetrahedron: Asymmetry* **2008**, *19*, 2864. (b) Aguilera, J.; Moglioni, A. G.; Moltrasio, G. Y.; Ortuño, R. M. *Tetrahedron: Asymmetry* **2008**, *19*, 302.

(11) Jeong, M. J.; Park, J. H.; Lee, C.; Chang, J. Y. *Org. Lett.* **2006**, *8*, 2221.

(12) (a) Seebach, D.; Hook, D. F.; Glättli, A. *Biopolymers* **2006**, *84*, 23. (b) Hintermann, T.; Gademann, K.; Jaun, B.; Seebach, D. *Helv. Chim. Acta* **1998**, *81*, 983.

(13) Tegoni, M.; Ferretti, L.; Sansone, F.; Remelli, M.; Bertolasi, V.; Dallavalle, F. *Chem.—Eur. J.* **2007**, *13*, 1300.

(14) García-Álvarez, I.; Garrido, L.; Fernández-Mayoralas, A. *ChemMedChem* **2007**, *2*, 496.

(15) Lee, K.; Kim, D.-K. *J. Korean Chem. Soc.* **2004**, *48*, 161.

(16) For some recent applications, see: Hirst, A. R.; Escuder, B.; Miravet, J. F.; Smith, D. K. *Angew. Chem., Int. Ed.* **2008**, *47*, 8002, and references therein. See also: Ghosh, S.; Reches, S.; Gazit, E.; Verma, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 2002.