Dicarba-*closo*-dodecaborane(12) derivatives of phosphonium salts: easy formation of *nido*-carborane phosphonium zwitterions†

Joseph A. Ioppolo,[a] Jack K. Clegg[b] and Louis M. Rendina*[a]

Received 16th January 2007, Accepted 20th February 2007
First published as an Advance Article on the web 14th March 2007
DOI: 10.1039/b700689f

The first examples of arylphosphonium salts containing a dicarba-*closo*-dodecaborane(12) (*closo*-carborane) are reported; in contrast to the 1,12-carborane derivative, the 1,2- and 1,7-isomers undergo a facile deboronation reaction in polar solvents to afford the corresponding *nido*-carborane phosphonium zwitterions.

Delocalised lipophilic cations (DLCs) can readily traverse the lipophilic mitochondrial membrane and accumulate in mitochondria.[1–8] The selection of DLCs for use as tumour imaging and anti-cancer agents has been based solely on their advantageous physical properties, lipophilicity and delocalised positive charge.[2,8] A high negative electrical potential that exists across the mitochondrial membrane enhances the uptake of DLCs into the mitochondria.[8] The potential difference across the membrane in normal, healthy cells has been determined to be −104 mV.[9] Mitochondria from human colon carcinoma cells, for example, have been shown to consistently exhibit elevated membrane potentials of −163 mV, sufficient to account for a ten-fold increase of DLC concentration in cancerous cells over healthy cells.[2]

Phosphonium salts represent a promising class of DLCs for use in tumour targeting and imaging. Tetraphenylphosphonium (TPP) salts, triphenylmethylphosphonium (TPMP) salts and related compounds based on these structures have demonstrated highly cancer-selective accumulation and cytotoxicity.[1,10–12] TPMP iodide, radio-labelled with the ^{11}C isotope, has been investigated for *in vitro* uptake and retention in canine brain tumour in the interest of imaging tumours using PET.[13] Not only was this compound rapidly taken up and retained in the tumour, but it was retained for a significant time (*ca.* 95 min) and achieved a tumour : healthy tissue ratio of 48 : 1. This ratio is also one order of magnitude greater than for other available glioma PET tracers and for clinical agents currently used in boron neutron capture therapy (BNCT).[13–16] TPMP is also known to suppress tumour growth.[17] Furthermore, animal studies have demonstrated that the expected toxic effects of TPMP may not prevent its use in humans.[13] In the context of BNCT, incorporation of boron into this compound would potentially result in the selective delivery of boron to the tumour site.

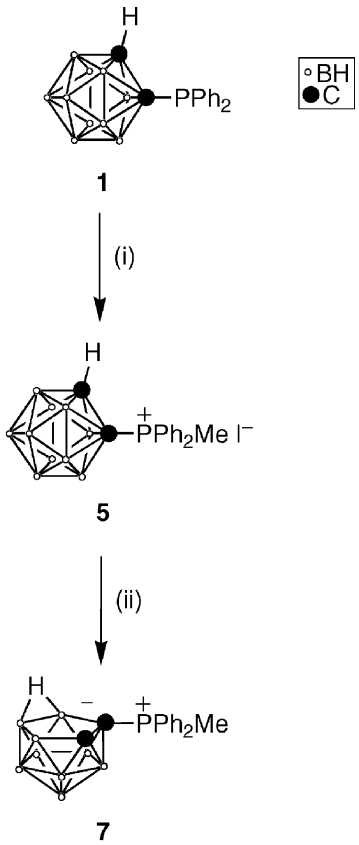
[a]*School of Chemistry, The University of Sydney, Sydney, NSW, 2006, Australia. E-mail: rendina@chem.usyd.edu.au; Fax: +61 2 9351 3329; Tel: +61 2 9351 4781*
[b]*Crystal Structure Analysis Facility, The University of Sydney, Sydney, NSW, 2006, Australia*
† Electronic supplementary information (ESI) available: Experimental details. See DOI: 10.1039/b700689f

Compounds that are selective toward certain cancers by targeting the mitochondria represent a new class of BNCT agents. To our knowledge, the only example of a carborane-containing DLC reported to date is the 1,12-carborane analogue of dequalinium, which was found to accumulate selectively in human epidermoid carcinoma of the oral cavity and rat glioma *in vitro*.[1] It also exhibited similar uptake and retention properties to Rhodamine 123, MKT-077 and TPP chloride, suggesting this and other boron-containing DLCs such as the phosphonium salts are worthy of investigation as potential BNCT agents. Herein we describe the synthesis and characterisation of novel carborane-containing phosphonium derivatives. The present study describes TPMP analogues that have one phenyl group replaced by either a *closo*-1,2-, 1,7- or 1,12-carborane. In two out of three cases, a deboronation reaction occurs in polar solvents to afford the corresponding *nido*-carborane phosphonium zwitterions.

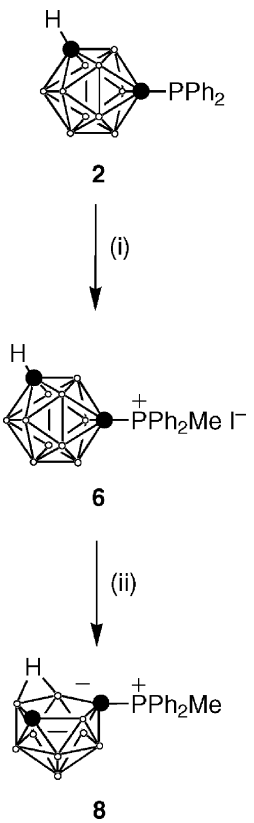
Syntheses of trisubstituted phosphines from the parent *closo*-carboranes were based upon the known preparation of the *closo*-1,2-carborane derivative **1**.[18] One equivalent of *n*-BuLi was treated with *closo*-1,2-, 1,7- or 1,12-carborane in DME at low temperatures to minimise disproportionation and hence disubstitution at the carbon atoms,[19] and chlorodiphenylphosphine was then added to afford the desired phosphine compounds **1–3**.[18,20–22] Small amounts of the disubstituted carborane derivative were also obtained in all three cases and could be separated readily from the monosubstituted species by means of flash column chromatography.

The synthesis of the phosphonium salts was achieved in all cases by a facile methylation reaction between **1–3** and MeI to afford the corresponding phosphonium iodides **4–6** (Schemes 1–3). An excess of MeI was used in the reaction as this step was generally not high-yielding, possibly because the carborane cage is somewhat electron-withdrawing thereby deactivating the phosphorus centre toward electrophiles. The characterisation of **4–6** was primarily achieved by means of mass spectrometry and NMR spectroscopy.‡ The Me group exhibited a downfield-shifted doublet in the ^{1}H NMR spectra, with $^2J_{PH}$ = 13–14 Hz. A single peak in the ^{31}P{^{1}H} NMR spectra at δ 24–30 was located downfield from the peak of the corresponding tertiary phosphine precursor.

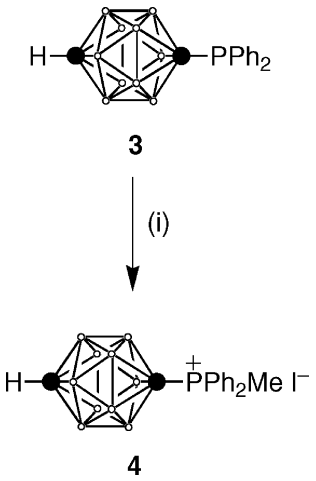
Compounds **5** and **6** were found to readily deboronate to afford the corresponding *nido*-carborane zwitterions **7** and **8**, respectively, in polar solvents such as DMSO and DMF. Alternatively, treatment of **5**, for example, with fluoride ion in EtOH solution resulted in the rapid formation of the zwitterionic product **7** with an optimised yield (Scheme 1).‡[23] The deboronation reaction was not observed for **4**, which contains *closo*-1,12-carborane and is therefore highly resistant to the deboronation reaction because



Scheme 1 *Reagents*: (i) MeI; (ii) CsF, EtOH.



Scheme 2 *Reagents*: (i) MeI; (ii) CsF, EtOH.



Scheme 3 *Reagent*: (i) MeI.

no boron atoms within the cluster are bonded to two adjacent and electronegative carbon atoms.[24] In contrast, the deboronation of *closo*-1,2-carborane under mild, non-basic conditions is known with alcohols, water and acids[25–27] and has also been observed when functional groups located *α* to the cage are electron-withdrawing and the compounds are exposed to polar solvents containing small amounts of H_2O or MeOH.[28,29] In our case, the deboronation reactions occur in polar solutions such as dry DMF and thus most likely proceed by nucleophilic attack of the iodide counter-ion on the most electrophilic boron atoms in the cage, *i.e.* B3 (or B6) for 1,2-carborane and B2 (or B3) for 1,7-carborane. To our knowledge, no other halides except fluoride[23,29–31] are known to deboronate *closo*-1,2- and 1,7-carborane.§

Selective degradation of the *closo*-carborane cages in **5** and **6** to the corresponding *nido* derivatives was confirmed by the presence of an upfield broad peak at δ −2 in the $^1H\{^{11}B\}$ NMR spectra of **7** and **8** which is attributed to the bridging H-atom, as well as the significant upfield shifts of resonances in the $^{11}B\{^1H\}$ NMR spectra. In addition to the NMR studies, the structure of **7** was confirmed by X-ray crystallography.¶ An ORTEP[32] representation of **7** is presented in Fig. 1. The bond angles and lengths fall in the range of typical alkyltriarylphosphonium salts, *e.g.* $MePh_3P^+X^-$ ($X = ClO_4$, BF_4),[33] and are almost identical to those found in the phosphonium salt $MePh_3P^+(7,8\text{-}Et_2\text{-}7,8\text{-}nido\text{-}C_2B_9H_{10})^-$.[34] The central phosphorus atom is close to an ideal tetrahedral geometry with bond angles ranging from 112.87(6)° (C(2)–P(1)–C(4)) to 106.88(6)° (C(2)–P(1)–C(10)). The C(2)–P(1) bond length of **7** (1.7867(14) Å) is only marginally shorter than the C(10)–P(1) and C(4)–P(1) bond lengths (1.7982(13) and 1.7981(13) Å, respectively) indicating there is very little double-bond character between the phosphorus centre and the cage carbon atom.[34–36] Hence, a zwitterionic structure bearing separate but delocalised positive and negative charges at the $MePh_2P$ moiety and *nido*-carborane cage, respectively, is consistent with the X-ray data rather than a ylide-like structure in which there exists significant double-bond character and, consequently, a shortened phosphorus–carbon bond.* Such bond shortening has been observed in simple phosphorus ylide compounds, *e.g.* PPh_3CH_2 (1.661 Å)[37] and phosphorus–borane ylides such as *endo*-7-$[Ph_2(H)P]$-8-R-*hypho*-7,8-$C_2B_6H_{11}$, in which the P–C bond lengths were found to be 1.737(3) and 1.742(3) Å for R = H and Me, respectively.[38]

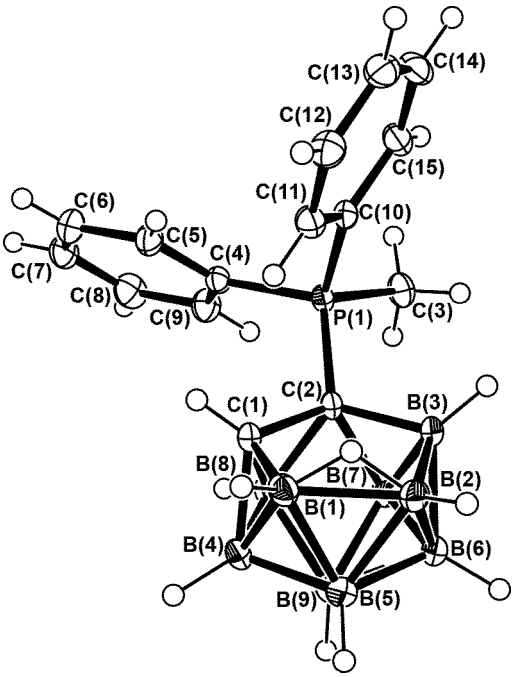


Fig. 1 An ORTEP representation and atomic numbering scheme of compound **7** shown with 50% probability ellipsoids. Selected bond distances (Å): C(1)–C(2) = 1.5680(17), C(2)–P(1) = 1.7867(14), C(3)–P(1) = 1.7957(14), C(4)–P(1) = 1.7981(13), C(10)–P(1) = 1.7982(13). Selected bond angles (°): C(1)–C(2)–P(1) = 116.46(9), C(5)–C(4)–P(1) = 120.96(10), C(9)–C(4)–P(1) = 119.20(10), C(15)–C(10)–P(1) = 119.80(10), C(11)–C(10)–P(1) = 120.64(10), C(2)–P(1)–C(3) = 109.76(6), C(2)–P(1)–C(4) = 112.87(6), C(3)–P(1)–C(4) = 108.23(6), C(2)–P(1)–C(10) = 106.88(6), C(3)–P(1)–C(10) = 109.27(6), C(4)–P(1)–C(10) = 109.79(6).

In conclusion, we have reported the first examples of arylphosphonium salts containing a *closo*-carborane. In contrast to the 1,12-carborane derivative **4**, the 1,2- and 1,7-isomers undergo a facile deboronation reaction in polar solvents to afford the corresponding zwitterionic *nido*-carborane phosphonium species. Preliminary *in vitro* cytotoxicity screening of **4** against the SF268 (human glioblastoma) cell line demonstrated a favourable GI_{50} > 40 μM compared with the control compound TPMP (GI_{50} = 12.5 μM). We are currently evaluating the detailed tumour cell uptake and biodistribution of **4** and the zwitterionic species **7** and **8**, and the results of this study will be published in due course.

We thank Dr Ian Luck (The University of Sydney) for assistance with the NMR studies and Dr Carleen Cullinane (Peter MacCallum Cancer Institute, Melbourne) for the cytotoxicity studies. We also thank the Australian Research Council for financial support.

Notes and references

‡ NMR spectroscopic and ESI-MS data for **4**: ^{1}H NMR (d_6-DMSO) δ 8.11 (m, 4H), 7.95 (m, 2H), 7.80 (m, 4H), 4.33 (br s, 1H, C_{cage}-H), 3.04 (d, $^2J_{P,H}$ = 13.42 Hz, 3H). ^{11}B{^{1}H} NMR (d_6-acetone) δ −12.5 (br, 10B). ^{31}P{^{1}H} NMR (d_6-DMSO) δ 27.1 (s). ^{13}C{^{1}H} NMR (d_6-DMSO) δ 135.96 (s, Ph), 133.81 (d, $J_{P,C}$ = 10.36 Hz, Ph), 129.98 (d, $J_{P,C}$ = 12.98 Hz, Ph), 116.22 (d, $J_{P,C}$ = 87.95 Hz, Ph), 70.48 (s, C_{cage}H), 6.90 (d, $J_{P,C}$ = 56.05 Hz), C_{cage}P not observed. MS: *m*/*z* 343.4 (M^+). NMR spectroscopic and ESI-MS data for **5**: ^{1}H NMR (d_6-acetone) δ 8.46 (m, 6H, Ph), 8.10 (m, 4H, Ph), 5.70 (br s, 1H, C_{cage}-H), 3.64 (d, $^2J_{P,H}$ = 13.12 Hz, 3H, CH_3). ^{11}B{^{1}H} NMR (d_6-acetone) δ −6.1 (br, 3B), −7.9 (br, 3B), −10.0 (br, 1B), −11.4 (br, 3B). ^{31}P{^{1}H} NMR (d_6-acetone) δ 30.0 (s). MS: *m*/*z* 344.3 (M^+). NMR spectroscopic and ESI-MS data for **6**: ^{1}H NMR (d_6-DMSO) δ 8.23 (m, 4H), 7.98 (m, 2H), 7.84 (m, 4H), 4.52 (br s, 1H, C_{cage}-H), 3.23 (d, $^2J_{P,H}$ = 13.49 Hz, 3H). ^{11}B{^{1}H} NMR (d_6-acetone) δ −1.3 (br, 1B), −3.4 (br, 1B), −7.8 (br, 3B), −10.0 (br, 3B), −13.4 (br, 2B). ^{31}P{^{1}H} NMR (d_6-acetone) δ 26.4 (s). MS: *m*/*z* 343.5 (M^+). NMR spectroscopic data for **7**: ^{1}H NMR (d_7-DMF) δ 7.91–7.76 (m, 10H, Ph), 3.48 (s, 1H, C_{cage}-H), 2.68 (d, $^2J_{P,H}$ = 13.61, 3H, CH_3). ^{11}B{^{1}H} NMR (d_6-acetone) δ −10.0 (br, 2B), −11.4 (br, 1B), −13.8 (br, 1B), −14.9 (br, 1B), −16.2 (br, 1B), −20.7 (br, 1B), −29.0 (br, 1B), −33.9 (br, 1B). ^{31}P{^{1}H} NMR (d_7-DMF) δ 29.9 (s). ^{13}C{^{1}H} NMR (d_7-DMF) δ 129.36 (s, Ph), 128.19 (d, $J_{P,C}$ = 10.06 Hz, Ph), 128.05 (d, $J_{P,C}$ = 10.06 Hz, Ph), 124.61 (d, $J_{P,C}$ = 12.07 Hz, Ph), 118.11 (d, $J_{P,C}$ = 92.16 Hz, Ph), 117.16 (d, $J_{P,C}$ = 86.93 Hz, Ph), 3.19 (d, $J_{P,C}$ = 57.94 Hz, CH_3), C_{cage}H and C_{cage}P were not observed.

§ Interestingly, the deboronation reaction is not reported for *boron*-substituted alkylphosphonium bromide salts of *closo*-1,2-carborane in which the cationic centre is separated from the carborane cage by at least four bonds.[39]

¶ Colourless prismatic crystals were grown from the slow diffusion of diethyl ether into a DMF solution containing **7** over several days. X-Ray data: Formula $C_{15}H_{24}B_9P$, *M* 332.60, monoclinic, space group *P*21/*c* (#14), *a* = 11.4316(14), *b* = 9.4232(10), *c* = 17.547(2) Å, *β* = 102.805(6)°, *V* = 1843.2(4) Å^3, *Dc* = 1.199 g cm^{-3}, *Z* = 4, crystal size = 0.314 × 0.290 × 0.157 mm, colourless prism, temperature = 150(2) K, *λ*(MoK*α*) = 0.71073 Å, *μ*(MoK*α*) = 0.143 mm^{-1}, *T*(SADABS)min,max = 0.750, 0.98, 2*θ*max = 61.28, *hkl* range = −16 to 16, −13 to 13, −25 to 25, *N* = 37976, N_{ind} = 5637 (R_{merge} 0.0635), N_{obs} = 4587 ($I > 2\sigma(I)$), N_{var} = 242, residuals $R1 = \sum||F_o| - |F_c||/\sum|F_o|$ for $F_o > 2\sigma(F_o)$; $wR2 = (\sum w(F_o^2 - F_c^2)^2/\sum(wF_c^2)^2)^{1/2}$ all reflections $w = 1/[\sigma^2(F_o^2) + (0.0632P)^2 + 0.8298P]$, where $P = (F_o^2 + 2F_c^2)/3$. $R1(F) = 0.0444$, $wR2(F^2) = 0.1318$, GoF(all) = 1.085, $\Delta\rho_{min,max}$ = −0.584, 0.499 e Å^{-3}. CCDC reference number 629314. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b700689f

* The X-ray structure of **7** also reveals a number of ring-stacking interactions present throughout the crystal lattice. The zwitterionic molecules pack together forming infinite one-dimensional chains through offset face-to-face interactions which are illustrated by C(7)···C(12) [at (*x*, 1/2 − *y*, 1/2 + *z*)] = 3.446(2) Å. These chains pack closely together with adjacent chains forming a two-dimensional sheet-like motif, which propagates in the *bc*-plane and is held together by π–BH interactions between the delocalised carborane cages and the phenyl rings of adjacent molecules. Indicative BH···ring centroid distances are the B(5)H···ring centroid of the C(12)-containing ring = 3.25 Å and B(4)H···ring centroid of the C(8)-containing ring = 3.41 Å.

1 D. M. Adams, W. Ji, R. F. Barth and W. Tjarks, *Anticancer Res.*, 2000, **20**, 3395.
2 J. S. Modica-Napolitano and J. R. Aprille, *Adv. Drug Delivery Rev.*, 2001, **49**, 63.
3 T. C. Rowe, V. Weissig and J. W. Lawrence, *Adv. Drug Delivery Rev.*, 2001, **49**, 175.
4 K. Takasu, T. Shimogama, C. Saiin, H. Kim, Y. Wataya, R. Brun and M. Ihara, *Chem. Pharm. Bull.*, 2005, **53**, 653.
5 J. S. Modica-Napolitano, R. Nalbandian, M. E. Kidd, A. Nalbandian and C. C. Nguyen, *Cancer Lett.*, 2003, **198**, 59.
6 E. Galeano, E. Nieto, A. I. Garcia-Perez, M. D. Delgado, M. Pinilla and P. Sancho, *Leuk. Res.*, 2005, **29**, 1201.
7 M. J. McKeage, L. Maharaj and S. J. Berners-Price, *Coord. Chem. Rev.*, 2002, **232**, 127.
8 V. R. Fantin and P. Leder, *Oncogene*, 2006, **25**, 4787.
9 J. S. Modica-Napolitano and J. R. Aprille, *Cancer Res.*, 1987, **47**, 4361.
10 J. D. Steichen, M. J. Weiss, D. R. Elmaleh and R. L. Martuza, *J. Neurosurg.*, 1991, **74**, 116.
11 S. Davis, M. J. Weiss, J. R. Wong, T. J. Lampidis and L. B. Chen, *J. Biol. Chem.*, 1985, **260**, 13844.
12 J.-J. Min, S. Biswal, C. Deroose and S. S. Gambhir, *J. Nucl. Med.*, 2004, **45**, 636.
13 I. Madar, J. H. Anderson, Z. Szabo, U. Scheffel, P. Kao, H. T. Ravert and R. F. Dannals, *J. Nucl. Med.*, 1999, **40**, 1180.
14 K. Yokoyama, S. Miyatake, Y. Kajimoto, S. Kawabata, A. Doi, T. Yoshida, T. Asano, M. Kirihata, K. Ono and T. Kuroiwa, *J. Neuro–Oncol.*, 2006, **78**, 227.
15 R. F. Barth, J. A. Coderre, M. G. H. Vicente and T. E. Blue, *Clin. Cancer Res.*, 2005, **11**, 3987.

16 A. H. Soloway, W. Tjarks, B. A. Barnum, F.-G. Rong, R. F. Barth, I. M. Codogni and J. G. Wilson, *Chem. Rev.*, 1998, **98**, 1515.
17 J. Patel, D. Rideout, M. R. McCarthy, T. Calogeropoulou, K. S. Wadwa and A. R. Oseroff, *Anticancer Res.*, 1994, **14**, 21.
18 C. Viñas, R. Benakki, F. Teixidor and J. Casabo, *Inorg. Chem.*, 1995, **34**, 3844.
19 J. F. Valliant, K. J. Guenther, A. S. King, P. Morel, P. Schaffer, O. O. Sogbein and K. A. Stephenson, *Coord. Chem. Rev.*, 2002, **232**, 173.
20 W. E. Hill and L. M. Silva-Trivino, *Inorg. Chem.*, 1979, **18**, 361.
21 R. Kivekas, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.*, 1994, **C50**, 2027.
22 N. N. Godovikov, V. P. Balema and E. G. Rys, *Russ. Chem. Rev. (Engl. Transl.)*, 1997, **66**, 1017.
23 J. Yoo, J.-W. Hwang and Y. Do, *Inorg. Chem.*, 2001, **40**, 568.
24 D. C. Busby and M. F. Hawthorne, *Inorg. Chem.*, 1982, **21**, 4101.
25 E. Svantesson, J. Pettersson, Å. Olin, K. Markides and S. Sjöberg, *Acta Chem. Scand.*, 1999, **53**, 731.
26 V. A. Ol'shevskaya, R. Ayuob, Z. G. Brechko, P. V. Petrovskii, E. G. Kononova, G. L. Levit, V. P. Krasnov, V. N. Charushin, O. N. Chupakhin and V. N. Kalinin, *J. Organomet. Chem.*, 2005, **690**, 2761.
27 Y.-J. Lee, J.-D. Lee, J. Ko, S.-H. Kim and S. O. Kang, *Chem. Commun.*, 2003, 1364.
28 J. J. Schaeck and S. B. Kahl, *Inorg. Chem.*, 1999, **38**, 204.
29 M. A. Fox, W. R. Gill, P. L. Herbertson, J. A. H. MacBride and K. Wade, *Polyhedron*, 1996, **15**, 565.
30 Y. Byun and W. Tjarks, *Tetrahedron Lett.*, 2006, **47**, 5649.
31 H. Tomita, H. Luu and T. Onak, *Inorg. Chem.*, 1991, **30**, 812.
32 L. J. Farrugia, *J. Appl. Crystallogr.*, 1999, **30**, 565.
33 T. Wiest, H. Eickmeier, H. Reuter and R. Blachnik, *Z. Kristallogr.*, 2000, **215**, 52.
34 R. Sillanpää, J. Pedrajas, C. Viñas, F. Teixidor and R. Kivekäs, *Acta Crystallogr., Sect. C*, 1999, **55**, 1008.
35 F. Teixidor, R. Núñez, C. Viñas, R. Sillanpää and R. Kivekäs, *Inorg. Chem.*, 2001, **40**, 2587.
36 K. Su, P. J. Fazen, P. J. Carroll and L. G. Sneddon, *Organometallics*, 1992, **11**, 2715.
37 J. C. J. Bart, *J. Chem. Soc. B*, 1969, 350.
38 D. Hong, P. J. Carroll and L. G. Sneddon, *Organometallics*, 2004, **23**, 711.
39 W. Chen, M. Diaz, J. J. Rockwell, C. B. Knobler and M. F. Hawthorn, *C. R. Acad. Sci., Ser. IIc: Chim.*, 2000, **3**, 223.