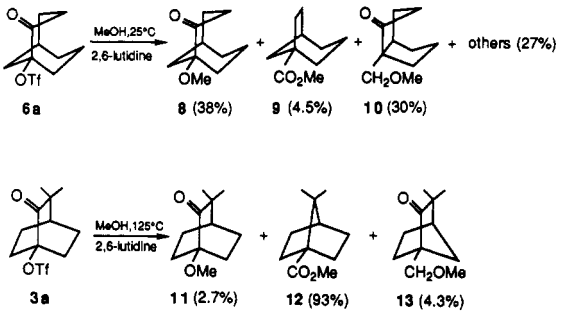
is that as much as 70–80% allylic conjugation is attained in the incipient carbocation from **6b**.

In contrast, the $k(X = O)/k(X = H_2)$ ratios are essentially constant with $10^{-8.7}$ to $10^{-8.2}$. It has been estimated that the full carbonyl π-conjugation in **1** would facilitate the rates of solvolysis of α-keto substrates by a factor of 10^4–10^5.[20] If this were the case, the **6b**/**6c** rate ratio would be 10^{-5} to 10^{-4} as a result of 70–80% carbonyl π-conjugation. A slight increase in the $k(X = O)/k(X = H_2)$ rate ratio in the manner $10^{-8.4}$ (**3a**/**3c**), $10^{-8.3}$ (**5a**/**5c**), and $10^{-8.2}$ (**6a**/**6c**) with the increase in the flexibility of the bicyclic ring system appears to be too small to positively support the π-conjugative effect.

AM1 calculations[21] conducted on the 2-methylene bicyclic bridgehead carbocations showed that with the increase in $k(X = CH_2)/k(X = H_2)$ the C(1)–C(2) bond order increases and the C=C bond order decreases (Table II). In the same sequence the net atomic charge on C(1) decreases and that on the olefinic methylene carbon increases. These results show that our approach is reasonable. Similar calculations on the α-keto bicyclic bridgehead carbocations indicated small decreases in the C=O bond order with increasing structural flexibility. However, the changes appear to be too small to evaluate the significance of the carbonyl π-conjugation. In addition, an inspection of net atomic charge reveals a decreasing trend of charge delocalization on the carbonyl oxygen with increasing ring flexibility, contrary to the expectation if carbonyl π-conjugation were important. More rigorous ab initio calculations on the 2-oxoethyl cation have been reported, and the results also indicate the unimportance of π-conjugation in **1**.[1d,22]

The products of solvolysis of **6a** and **7a** were studied in methanolysis in the presence of excess 2,6-lutidine at 25 °C. Although **7a** gave the corresponding bridgehead methyl ether exclusively, **6a** afforded a mixture of bridgehead methyl ether **8** (38%) and rearrangement poducts **9** (4.5%) and **10** (30%), accompanied by several unidentified products amounting to 27%.[23] Very recently, it has been suggested that the preferred formation of rearrangement products **12** (93%) and **13** (4.3%) from **3a**[3] might indicate σ-participation leading to a nonclassical ion in solvolysis.[1d] At the present stage the relative importance of σ-participation is difficult to assess. However, the exclusive bridgehead substitution in the solvolysis of **7a** suggests that the rearrangement is related to the skeletal structure of the first-formed, classical, bridgehead cation rather than the involvement of a nonclassical ion.



Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture, Japan, and a grant from the Asahi Glass Foundation.

Supplementary Material Available: ^{13}C NMR spectra of **6a**, **6b**, **7a**, **7b**, and their solvolysis products, and 2-oxo and 2-methylene bridgehead alcohols (19 pages). Ordering information is given on any current masthead page.

(20) Creary, X.; Geiger, C. C. *J. Am. Chem. Soc.* **1982**, *104*, 4151.
(21) *QCPE* 527.
(22) (a) Dixon, D. A.; Eades, R. A.; Frey, R.; Gassman, P. G.; Hendewerk, M. L.; Paddon-Row, M. N.; Houk, K. N. *J. Am. Chem. Soc.* **1984**, *106*, 3885. (b) Lien, M. H.; Hopkinson, A. C. *Ibid.* **1988**, *110*, 3788.

(23) The product distribution was determined by GLC (PEG 20M) for the reaction mixture after >10 half-lives and then each product separated by medium pressure column chromatography over silica gel. **9** (oil) was identified on the basis of the retention time in GLC, which agreed with that of an authentic sample. **8** (oil) was identified on the basis of the close resemblance of the ^{13}C NMR spectrum to that of the corresponding ketol. **10** (oil) was transformed to 1-(methoxymethyl)bicyclo[3.3.0]octane by Wolff-Kishner reduction, whose spectral and GLC data agreed with those of an authentic sample. The methanolysis product of **7a** was identified as 3-methoxyhomoadamantan-4-one (mp 56.0–56.5 °C) on the basis of spectroscopic and microanalytical data. **6b** and **7b** were solvolyzed in ethanol and 80% ethanol, respectively, to give only bridgehead substitution products, whose spectral data were consistent with proposed structures.

The First Alkylation of *o*-Carboranes under Essentially Neutral Conditions. Application to the Synthesis of ^{10}B Carriers

Hisao Nemoto, FengGuang Rong, and Yoshinori Yamamoto*
Department of Chemistry, Faculty of Science, Tohoku University, Sendai 980, Japan
Received August 13, 1990

Summary: The palladium-catalyzed reaction of 1,2-dicarbora-*closo*-dodecaboranes (*o*-carboranes) (**1**) with allyl ethyl carbonate (**3**) gave 2-allylated *o*-carboranes (**2**) in good to excellent yields. Compounds **2** could be converted to the corresponding diols (**4**), which were soluble in water and thus could be utilized as carriers for ^{10}B neutron capture therapy.

Development of a new synthetic method for ^{10}B carriers[1] with a relatively large number of ^{10}B atoms in the molecule is required in order to deliver a sufficient quantity of ^{10}B atoms to tumor cells. *o*-Carborane (**1**), one of the most stable boron clusters, is an appropriate candidate for use in such a method.[2] One of the most convenient methods for the alkylation of *o*-carboranes is the reaction of electrophiles with carborane carbanions.[3] However, the generation of the carbanion usually requires the use of strong bases, such as butyllithium and alkali metal amides,[4]

(1) Previous studies for the synthesis of ^{10}B carriers: (a) Yamamoto, Y.; Seko, T.; Nemoto, H. *J. Org. Chem.* **1989**, *54*, 4734. (b) Yamamoto, Y.; Seko, T.; Rong, F.; Nemoto, H. *Tetrahedron Lett.* **1989**, *30*, 7191.
(2) Miura, M.; Gabel, D.; Oenbrick, G.; Fairchild, R. G. *Tetrahedron Lett.* **1990**, *31*, 2247.
(3) Maurer, J. L.; Berchier, F.; Serino, A. J.; Knobler, C. B.; Hawthorne, M. F. *J. Org. Chem.* **1990**, *55*, 838 and the references cited therein.
(4) Niedenzu, K.; Buschbeck, K. C. *Gmelin Handbuch der Anorganischen Chemie*; Bowerbindungen, Springer-Verlag: Berlin, 1978; Vol. 11, p 81.

0022-3263/90/1955-6065$02.50/0

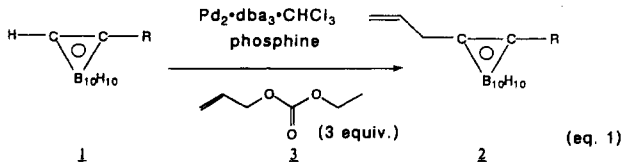
Table I. Palladium-Catalyzed Allylation of 1

entry	substrate	ligand[a]	temp	time (h)	yield of 2 (%)	recovery of 1 (%)
1	1a	DPPE	ambient	2.0	80	0
2		DPPP	ambient	25.0	53	15
3		DPPB	ambient	17.0	53	43
4		PPh_3	ambient	48.0	10	80
5		DPPE	reflux	3.5	58	0
6		DPPP	reflux	4.5	48	0
7		DPPB	reflux	6.5	100	0
8	1b	DPPE	ambient	45.0	86	0
9		DPPE	reflux	6.0	100	0
10	1c	DPPE	ambient	13.0	97	0
11	1d	DPPE	ambient	17.0	95	0
12	1e	DPPE	ambient	2.0	75	0
13		DPPB	reflux	5.0	90	0

[a] Molar ratio PPh_3:Pd = 4:1. Molar ratio bidentate phosphine: Pd = 2:1. THF was used as solvent.

because the pK_a values of carboranes are between 18 and 22.[5] However, for the synthesis of ^{10}B carriers bearing biologically active moieties, it would be desirable to carry out the alkylation under very mild conditions, under neutral conditions, if possible.

We report that the palladium-catalyzed reaction[6] of *o*-carboranes (**1**) with allyl ethyl carbonate (**3**) meets the requirement given above (eq 1). Alkylation takes place under essentially neutral conditions and thus permits the presence of base-sensitive functional groups, such as aldehyde. The latter feature is very important, since a carbon–carbon connection to biologically active moieties can be made by using the functionality.[1b]



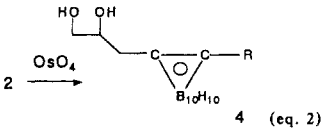
1 **3** **2**

a: R = -C_6H_4-m-CHO, b: R = -C_6H_4-m-CO_2Me, c: R = -C_6H_4-p-CO_2Me
d: R = -CO_2Me, e: R = -CH_2OCOCH_3 f: R = -CH_2OH

The results are summarized in Table I. First attempted were reactions of the carboranyl aldehyde **1a** with allyl ethyl carbonate (**3**). The allylated product **2a** was obtained in excellent yield with tris(dibenzylideneacetone)dipalladium·chloroform/1,2-bis(diphenylphosphino)ethane (Pd_2DBA_3·$CHCl_3$/DPPE) in tetrahydrofuran (THF) (entry 1). When 1,3-bis(diphenylphosphino)propane (DPPP), 1,4-bis(diphenylphosphino)butane (DPPB), or triphenylphosphine were used as ligands at room temperature, the starting material **1a** was not completely consumed (entries 2, 3, and 4). However, the use of DPPB at reflux gave the best results among the three phosphine ligands (entry 7 compared to entries 5 and 6). In entry 5, polar polymeric materials were obtained as byproducts under reflux conditions. In contrast, ester **1b** was converted to the desired compound **2b** in high yield under essentially the same conditions (entry 9). It seems that the palladium complex with DPPE, a strong cis-bidentate ligand, is very reactive, and thus an undesired reaction with the aldehyde group occurred[7] (entry 5). The complex of palladium and DPPB, a weaker ligand than DPPE, apparently is less reactive toward the aldehyde group, although the desired allylation reaction thus required higher temperature.

The carboranes **1b**, **1c**, **1d**, and **1e** were converted to **2b**, **2c**, **2d**, and **2e**, respectively, in excellent yield (entries 8–13). It is known that carbon acids, such as malonic esters (pK_a = 13[8]), react with π-allylpalladium.[6b] However, attempted allylation of acetophenone (pK_a = 19[9]) under the same reaction conditions as entry 9 failed. The pK_a values of the proton of carboranes are between 18 and 22.[5] Consequently, it is noteworthy that carboranes react with the π-allylpalladium generated from allyl carbonate.

The allyl group of **2** could be converted to a 1,2-dihydroxyl group upon treatment with OsO_4,[10] thereby giving the carborane hydrophilicity. For example, osmylation of **2e**, followed by deacetylation during workup, gave water-soluble **4f** in 80% yield (eq 2).



In conclusion, a new alkylation reaction of *o*-carboranes under essentially neutral conditions was realized by Pd-catalyzed allylation. We are now in a position to prepare water-soluble ^{10}B carriers with a carborane structure, via the newly developed allylation/osmylation procedure.

Supplementary Material Available: Full characterization data for **1a–e**, **2a–e**, and **4f**, along with detailed synthetic procedures (6 pages). Ordering information is given on any current masthead page.

(5) Niedenzu, K. *Gmelin Handbook of Inorganic Chemistry*; Bowerbindungen, Springer-Verlag: Berlin, 1981; Vol. 20, p 1.
(6) (a) Tsuji, J.; Shimizu, I.; Minami, I.; Ohashi, Y. *Tetrahedron Lett.* **1982**, *23*, 4809. (b) Tsuji, J. *Pure Appl. Chem.* **1989**, *61*, 1673.
(7) Nokami, J.; Mandai, T.; Watanabe, H.; Ohyama, H.; Tsuji, J. *J. Am. Chem. Soc.* **1989**, *111*, 4126.
(8) House, H. O. *Modern Synthetic Reactions*; Benjamin-Cummings: Menlo Park, CA, 1972; p 492.
(9) Dessey, R. E.; Okuzumi, Y.; Chen, A. *J. Am. Chem. Soc.* **1962**, *84*, 2899.
(10) Wai, J. S. M.; Markó, I.; Svendsen, J. S.; Finn, M. G.; Jacobson, E. N.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 1123.

A New Approach to the Construction of β-Alkoxy-Substituted Cyclic Ethers via the Intramolecular Cyclization of ω-Trialkylplumbyl and ω-Trialkylstannyl Ether Acetals

Jun-ichi Yamada, Tetsuya Asano, Isao Kadota, and Yoshinori Yamamoto*
Department of Chemistry, Faculty of Science, Tohoku University, Sendai 980, Japan
Received September 4, 1990

Summary: The ω-trialkylplumbyl ether acetal (**1a**) gave the β-alkoxy cyclic ether (**2a**) upon treatment with 2 equiv of $TiCl_4$ in CH_2Cl_2. The reaction of the ω-trialkylstannyl ether acetals **3**, **4**, and **5** in the presence of 2 equiv of $TiCl_3$(OiPr) in CH_2Cl_2 produced the corresponding β-alkoxy-α-vinyl cyclic ethers **6**, **7**, and **8**, respectively. This new procedure permitted the chiral synthesis of a fundamental structural unit (**20**) of cyclic ether natural products.

0022-3263/90/1955-6066$02.50/0