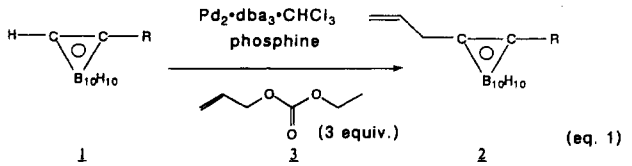
Table I. Palladium-Catalyzed Allylation of 1

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]



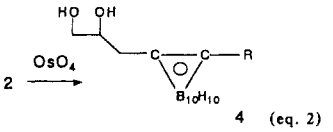
1 **3** **2**

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.

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(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.

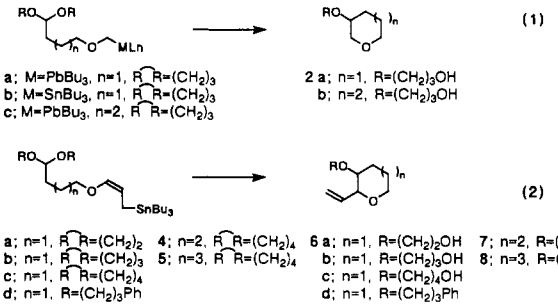
A New Approach to the Construction of β-Alkoxy-Substituted Cyclic Ethers via the Intramolecular Cyclization of ω-Trialkylplumbyl and ω-Trialkylstannyl Ether Acetals

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.

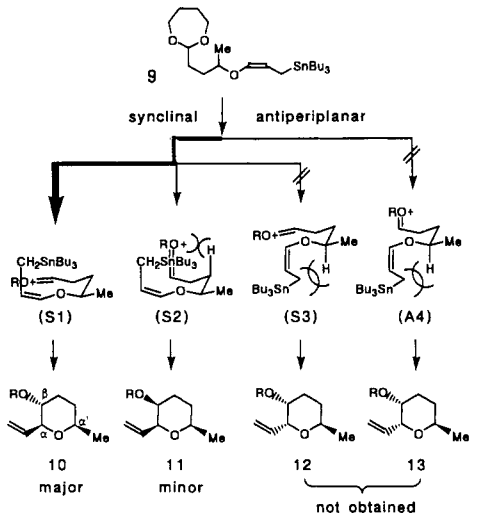
0022-3263/90/1955-6066$02.50/0

Natural products with a framework of β-alkoxy-substituted cyclic ethers are an important synthetic target.[1] Until recently, few methods existed for constructing such structural units, especially those incorporating medium-sized ring cyclic ethers.[2] We report that the intramolecular cyclization of ω-trialkylplumbyl and ω-trialkylstannyl ether acetals gives the desired cyclic ethers in good yield (eqs 1 and 2).

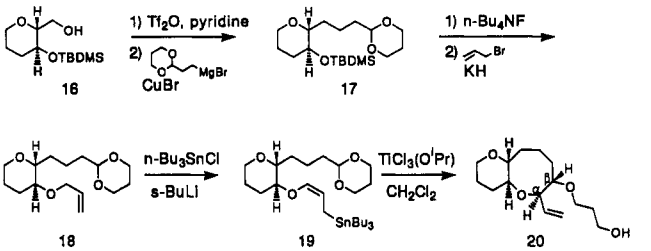


Thus treatment of the organolead compound **1a** in the presence of 2 equiv of $TiCl_4$ in CH_2Cl_2 at −78 °C gave **2a** in 60% isolated yield (eq 1).[4] The reaction itself was very clean, but the high water solubility of **2a** led to some product loss during workup.[3] The organotin compound **1b** or its lithium analogue did not give the desired product. The attempted preparation of **2b** from **1c** failed: only small amounts of **2b** were obtained. However, intramolecular cyclizations[5] of other trialkylstannyl ether acetals were successful (eq 2). The reaction of **3b** in the presence of 2 equiv of $TiCl_3$ (OiPr) in CH_2Cl_2 at −78 °C produced **6b** in 57% yield (trans:cis = 1.5:1.0). Other Lewis acids, such as $BF_3{\cdot}OEt_2$, $TiCl_4$, $TiCl_2$ $(OiPr)_2$, and $MgBr_2{\cdot}OEt_2$, were less effective catalysts. The effect of the acetal structure on the cyclization was next examined. Compound **3a** gave **6a** in 84% yield (trans:cis = 1.3:1.0), and **3c** afforded **6c** in 86% yield (trans:cis = 3.1:1.0). The acyclic acetal **3d** produced **6d** in 67% yield (trans:cis = 3.8:1.0). Therefore, the use of either a 5- or a 7-membered acetal seemed to be more effective than the use of acyclic acetals for promoting cyclization. Cyclization of ω-trialkylstannylaldehydes, instead of the corresponding of acetals gave lower yields.[10] The analogous trialkylsilyl and trialkylplumbyl ether acetals failed to give the desired cyclic ethers.

Scheme I



Scheme II



Compounds **3** produced *trans*-**6** predominantly. However, this stereoselectivity did not tell whether a synclinal or antiperiplanar transition state was involved in the cyclization. To clarify this point, the cyclization of **9** was examined. The α,α′-trans products (**10** and **11**) were obtained in 85% yield, in a ratio of 1.4:1. The possible α,α′-trans products (**12** and **13**) were not detected. Because the methyl substitutent appears in the equatorial position of the 6-membered cyclic transition state, four possible transition-state geometries (S1, S2, S3, A4) can be drawn (Scheme I). It was clear from the experimental results that the synclinal transition states S1 and S2 were involved, with S1 predominant.[6] This was reasonable, since S1 is the less sterically crowded of the two. The production of α,α′-cis stereochemistry is very important, because this stereochemistry is found in most marine natural products with a cyclic ether framework.

Next, the synthesis of medium-sized rings was examined. Compound **4** gave **7**, as a single isomer with α,β-trans stereochemistry, in 59% yield. However, **5** produced **8** in

(1) For example, see: (a) Nicolaou, K. C.; Duggan, M. E.; Hwang, C. K. *J. Am. Chem. Soc.* **1989**, *111*, 6666. (b) *Ibid.* **1989**, *111*, 6676. (c) *Ibid.* **1989**, *111*, 6682. (d) Nicolaou, K. C.; McGarry, D. G.; Sommers, P. K. *J. Am. Chem. Soc.* **1990**, *112*, 3696. (e) Kozikowski, A. P.; Lee, J. *J. Org. Chem.* **1990**, *55*, 863. (f) Murata, M.; Legrand, A. M.; Ishibashi, Y.; Fukui, M.; Yasumoto, T. *J. Am. Chem. Soc.* **1990**, *112*, 4380. (g) Kanojia, R. M.; Wacher, M. P.; Levine, S. D.; Adams, R. E.; Chen, R.; Chin, E.; Cotter, M. L.; Hirsch, A. F.; Heuttemann, R.; Kane, V. V.; Ostrowski, P.; Shaw, C. J. *J. Org. Chem.* **1982**, *47*, 1310.

(2) For the synthesis of β-alkoxy-substituted cyclic ethers, see: (a) Nicolaou, K. C.; Prasad, C. V. C.; Hwang, C.-K.; Duggan, M. E.; Veale, C. A. *J. Am. Chem. Soc.* **1989**, *111*, 5321. (b) Nicolaou, K. C.; Hwang, C.-K.; Marron, B. E.; DeFrees, S. A.; Couladouros, E. A.; Abe, Y.; Carroll, P. J.; Snyder, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 3040. (c) Nicolaou, K. C.; Hwang, C.-K.; Nugiel, D. A. *J. Am. Chem. Soc.* **1989**, *111*, 4136. For a general synthesis of cyclic ethers, see: (d) Clark, J. S.; Holmes, A. B. *Tetrahedron Lett.* **1988**, *29*, 4333. (e) Tsushima, K.; Araki, K.; Murai, A. *Chem. Lett.* **1989**, 1313. (f) Schreiber, S. L.; Kelly, S. E.; Porco, J. A., Jr.; Sammakia, T.; Suh, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 6210. (g) Paquette, L. A.; Sweeney, T. J. *J. Org. Chem.* **1990**, *55*, 1703. (h) Blumenkopt, T. A.; Bratz, M.; Castañeda, A.; Look, G. C.; Overmann, L. E.; Rodriguez, D.; Thompson, A. S. *J. Am. Chem. Soc.* **1990**, *112*, 4386. (i) Moody, C. J.; Taylor, R. J. *J. Chem. Soc., Perkin Trans. 1* **1989**, 721. (j) Corey, E. J.; Shimoji, K. *J. Am. Chem. Soc.* **1983**, *105*, 1662. (k) Haseltine, J.; Visnick, M.; Smith, A. B., III. *J. Org. Chem.* **1988**, *53*, 6160. (l) Kotsuki, H.; Ushio, Y.; Kadota, I.; Ochi, M. *J. Org. Chem.* **1989**, *54*, 5153. (m) Nicolaou, K. C. McGarry, D. G.; Somers, P. K.; Veale, L. A.; Furst, G. T. *J. Am. Chem. Soc.* **1987**, *109*, 2504. (n) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5330. (o) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, L.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5335.

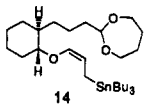
(3) Consequently, some of the products were isolated as the less soluble acetates.

(4) For the intermolecular reaction, see: Yamada, J.; Abe, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **1990**, *112*, 6118.

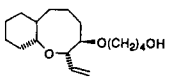
(5) For the intermolecular reaction, see: (a) Yamamoto, Y.; Schmid, M. *J. Chem. Soc., Chem. Commun.* **1989**, 1310. (b) Koreeda, M.; Tanaka, Y. *Tetrahedron Lett.* **1987**, *28*, 143. (c) Keck, G. E.; Abbott, D. E.; Wiley, M. R. *Tetrahedron Lett.* **1987**, *28*, 139. For allylic tin condensation reactions, see: (d) Yamamoto, Y. *Aldrichim. Acta* **1987**, *20*, 45; *Acc. Chem. Res.* **1987**, *20*, 243.

(6) For the transition state geometry for the intramolecular allylic tin cyclization, see: (a) Denmark, S. E.; Willson, T. M. *J. Am. Chem. Soc.* **1989**, *111*, 3475. (b) Denmark, S. E.; Weber, E. J.; Wilson, T. M. *Tetrahedron* **1989**, *45*, 1053. For the intramolecular allylic silane cyclization, see: (c) Yamamoto, Y.; Furuta, T. *J. Org. Chem.* **1990**, *55*, 3971. (d) Shinzer, D. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 308. (e) Tokoroyama, T.; Tsukamoto, M.; Iio, H. *Tetrahedron Lett.* **1984**, *25*, 5067.

only 8% yield. The low yield was presumably due to the flexibility of the carbon chain.[7] Incorporation of a cyclohexane ring into the chain enhanced the chemical yield. Thus, **14** gave **15**, as a single isomer, in 36% yield. It is noteworthy that the relative stereochemistry at the α,α' and β carbons of **15** corresponds to that of brevetoxin and related compounds.



14



15

The most attractive aspect of the procedure is its potential for iterative ring construction (Scheme II). The triflate of optically active **16** (100% ee)[2b] was converted to **17** in 64% yield by copper-mediated coupling to a Grignard reagent.[8] Allylation of **17** gave **18** in 93% yield with 100% ee. Compound **18** was converted to the allyltin **19** in 80% yield. The cyclization of **19** gave a 11:1 mixture of α,β-*trans*-**20** and α,β-*cis*-**20** in 30% yield. Starting with 6-8 bicyclic **20** it should be possible to construct a 6-8-6 tricyclic system.[9] We are actively pursuing such a possibility.

Supplementary Material Available: Synthetic methods and spectra for **1–20** (18 pages). Ordering information is given on any current masthead page.

(7) Incorporation of a cis-double bond or a carbocycle into the carbon chain is required for an efficient synthesis of medium-sized ring systems.[2a]

(8) Kotsuki, H.; Kadota, I.; Ochi, M. *Tetrahedron Lett.* **1989**, *30*, 1281.

(9) Selective hydroboration of the exocyclic carbon-carbon double bond with 9-BBN, followed by oxidation, should give the corresponding hydroxyethyl derivative. Oxidation of the alcohol to an aldehyde and subsequent conversion to an acetal, followed by removal of the hydroxypropyl group, should produce the hydroxy acetal. Then, allylation, stannylation, and cyclization should give the 6-8-6 system.

(10) With certain Lewis acids, the cyclization gave high yields, and the result will be reported shortly.

Armed/Disarmed Effects[1] in Glycosyl Donors: Rationalization and Sidetracking[2]

Bert Fraser-Reid,* Zufan Wu, Uko E. Udodong, and Håkan Ottosson

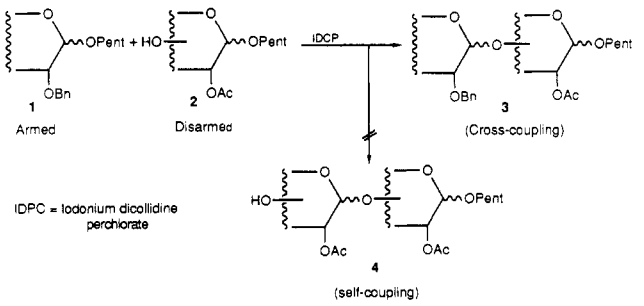
Department of Chemistry, Paul M. Gross Chemical Laboratory, Duke University, Durham, North Carolina 27706

Received August 20, 1990

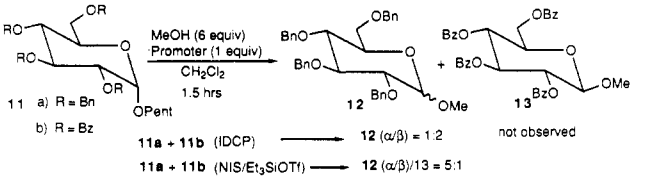
Summary: A general rationalization for armed/disarmed effects, first recognized in *n*-pentenyl glycosides but recently extended to a variety of other glycosyl donors, is postulated. Reaction of a glycosyl donor with an appropriate electrophile gives a positively charged intermediate which is less favorable when there is an adjacent electron-withdrawing group (for example OCOR, as in a disarmed donor) than when there is an adjacent alkoxy group (as in the armed counterpart). The latter therefore reacts faster and if, in the reaction medium, there is a disarmed species carrying a free hydroxyl group, a pathway based on Le Chatelier's principle can be envisaged that leads to products of cross-coupling with (virtually) none of the self-coupled analogue. In *n*-pentenyl glycosides activation of the anomeric center involves two preequilibrium steps, the second of which can be sidetracked to afford a vicinal dibromo derivative. The ability to prepare such derivatives in near quantitative yields allows the normal armed/disarmed protocol for saccharide assembly to be reversed.

In the course of investigating the chemistry of *n*-pentenyl glycosides (NPGs) we noted that the rate of oxidative hydrolysis was substantially affected by the nature of the C2 protecting group,[3] and this observation subsequentially led us to demonstrate that glycosyl donors could be "armed" or "disarmed" by a C2 ether or C2 ester group, **1** and **2**, respectively.[4] This observation was developed into a procedure for selective coupling to give **3** (Scheme I), and our report[4] was followed by accounts of similar effects with other glycosyl donors,[5-7] thereby suggesting that the armed/disarmed protocol of oligosaccharide assembly could have general applicability. We have therefore sought to obtain a fuller understanding of the phenomenon, and in this paper we disclose some recent results which show, inter alia, how the effect can be sidetracked in the case of NPGs.

Scheme I



Scheme II



(1) The terms "armed" and "disarmed" are used[3] instead of activated and deactivated since a disarmed donor can, in fact, be readily activated.[11]

(2) This work was supported grants from the National Science Foundation (CHE 8920033), the National Institutes of Health (GM 41071), and Glycomed, Hayward, CA.

(3) Mootoo, D. R.; Date, V.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1988**, *110*, 2662.

(4) Mootoo, D. R.; Konradsson, P.; Udodong, U.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1988**, *110*, 5583.

(5) Friesen, R. W.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6656.

(6) Mereyala, H. N.; Reddy, G. V. *17th IUPAC International Symposium on the Chemistry of Natural Products*, New Delhi, India, February 4–9, 1990.

(7) Veeneman, G. H.; van Leeuwen, S. H.; van Boom, J. H. *Tetrahedron Lett.* **1990**, *31*, 1331. Veeneman, G. H.; Van Boom, J. H. *Tetrahedron Lett.* **1990**, *31*, 275.

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