Pergamon

Tetrahedron Letters 39 (1998) 9027–9030

TETRAHEDRON
LETTERS

New Strategy for Convergent Synthesis of *trans*-Fused Polyether Frameworks Based on Palladium-Catalyzed Suzuki Cross-Coupling Reaction

Makoto Sasaki,* Haruhiko Fuwa, Masayuki Inoue, and Kazuo Tachibana*

Department of Chemistry, School of Science, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

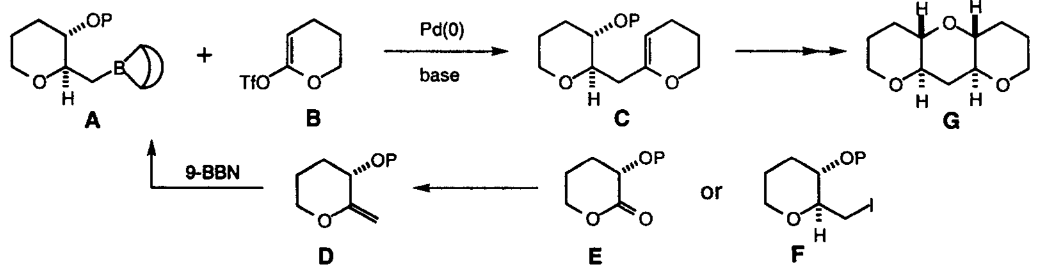
Received 31 August 1998; revised 14 September 1998; accepted 18 September 1998

Abstract: A new strategy for convergent synthesis of *trans*-fused polyethers based on palladium(0)-catalyzed Suzuki cross-coupling reaction of alkylboranes with cyclic enol triflates has been developed. The present method allows to construct polyether frameworks rapidly and efficiently.

Marine polyether toxins, exemplified by brevetoxins,[1,2] ciguatoxins,[3] and maitotoxin,[4] present formidable and challenging synthetic targets due to their structural complexity and exceptionally potent biological activities.[5] The most critical issue in the synthesis of these large polyether compounds is development of synthetic methods for convergent coupling of polyether fragments. In spite of recent advances in the synthesis of medium-sized cyclic ethers,[6] only a few methods for the convergent assembly of 6-membered polyether structure have been reported.[7] In this letter, we describe a new strategy for convergent synthesis of *trans*-fused polyether arrays based on palladium(0)-catalyzed cross-coupling reaction[8] of alkylboranes with enol triflates.

Palladium(0)-catalyzed Suzuki cross-coupling reaction of alkylboranes with aryl or alkenyl halides and triflates has been one of the most versatile carbon-carbon bond-forming reactions in organic synthesis[8] and the utility of this reaction was demonstrated in the synthesis of natural products and related compounds.[9] In the course of our synthetic studies on ciguatoxin and its simplified analogues,[10] we were interested in the possibility of assembling polyether structures in a convergent manner via Suzuki cross-coupling reaction of alkylborane **A** with cyclic enol triflate **B** to obtain enol ether **C** (Scheme 1). Alkylborane **A** should be generated from the precursor enol ether **D**, which can be easily prepared from lactone **E** using the Tebbe[11] or the Petasis reagents[12] or by base-treatment of iodide **F**. Elaboration of the coupling product **C** into the desired polyether system **G** should be feasible via stereoselective hydroboration and reductive hydroxy ketone cyclization.[7b,13]

Scheme 1



0040-4039/98/$ - see front matter © 1998 Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(98)02025-5

We chose to examine the cross-coupling reaction of alkylborane 3[9b] with enol triflate **4** as a model system to establish the reaction conditions (Scheme 2). Methylenation of lactone **1** with the Petasis reagent (Cp_2TiMe_2)[12] gave enol ether **2** in 89% yield. Hydroboration of **2** with 9-BBN provided the corresponding alkylborane **3**, which was in situ treated with an aqueous base and then enol triflate **4** in the presence of dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) [$PdCl_2$(dppf)] (0.1 equiv), potassium bromide (1.2 equiv), and ligand (Table 1). As seen from Table 1, the cross-coupling reaction was best carried out in the presence of cesium carbonate as a base and triphenylarsine[14] as a coligand in DMF at room temperature. Under these conditions, coupling product **5** was obtained in 63% yield.

Scheme 2

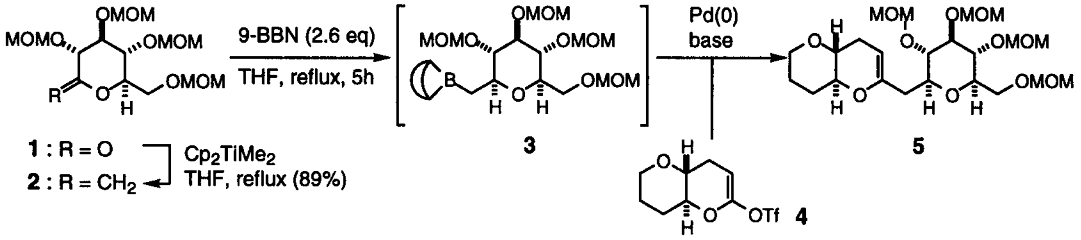


Table 1. Cross-coupling of alkylborane **3** with enol triflate **4** in the presence of Pd(0) catalyst and base.[a]

Entry	Base	Ligand	% Yield
1	3M aq. K_3PO_4 (1.5 equiv)	none	40%
2	3M aq. Cs_2CO_3 (1.5 equiv)	none	51%
3	3M aq. Cs_2CO_3 (1.5 equiv)	Ph_3As (0.4 equiv)	63%
4	3M aq. Cs_2CO_3 (3.0 equiv)	Ph_3As (0.4 equiv)	63%

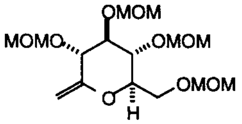
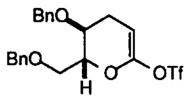
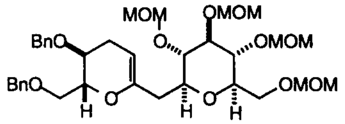
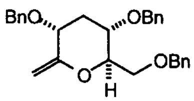
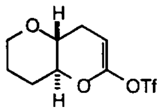
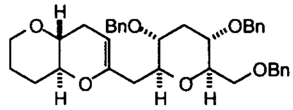
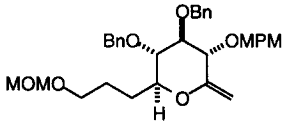
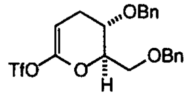
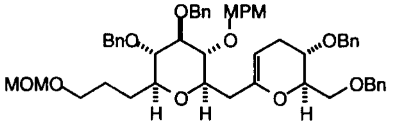
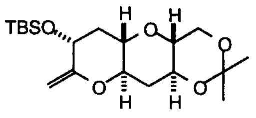
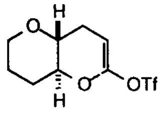
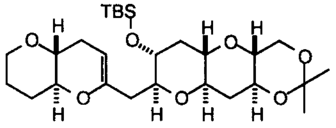
[a] Coupling reactions were carried out in the presence of $PdCl_2$(dppf) (0.1 equiv) and KBr (1.2 equiv) in DMF at room temperature for 20 h.

The generality of the present coupling method was next investigated by employing a variety of substrates. As illustrated in Table 2, the coupling method appeared to be quite general and efficient. Especially, the mild nature of this reaction is emphasized by the coupling of **4** with complex tricyclic alkylborane generated from **12**, leading to pentacyclic system **13** in 66% yield (entry 4).

The applicability of this coupling method to the convergent assembly of polyether frameworks was demonstrated by the synthesis of pentacyclic polyether system **16** (Scheme 3). Regio- and stereoselective hydroboration of enol ether **13** with thexylborane followed by oxidative workup and oxidation of the resultant secondary alcohol under Swern conditions afforded ketone **14** in 82% yield for the two steps. Acidic removal of the silyl and acetonide groups followed by acetylation provided hemiketal diacetate **15** in 94% yield for the two steps. Finally, exposure of **15** to triethylsilane and boron trifluoride etherate (CH_2Cl_2, -10 °C) furnished *trans*-fused pentacyclic polyether **16** in 83% yield based on recovered **15** (24%). Thus, pentacyclic **16** was constructed rapidly and efficiently in only six steps starting from **12** and **4**.

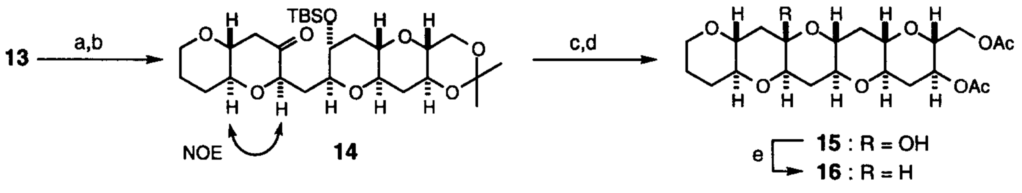
In conclusion, we demonstrated that palladium(0)-catalyzed Suzuki cross-coupling of alkylboranes with cyclic enol triflates provided a highly convergent and efficient method for the construction of *trans*-fused polyether frameworks. Application of the present strategy to synthesis of marine natural products and their simplified analogues is currently underway in our laboratory.

Table 2. Pd(0)-catalyzed cross-coupling of alkylboranes and enol triflates.[a]

Entry	Olefin	Enol triflate[b]	Coupling product	% Yield
1	 **2**	 **6**	 **7**	61
2	 **8**[c]	 **4**	 **9**	66
3	 **10**[d]	 **6**	 **11**	76
4	 **12**[c]	 **4**	 **13**	66

[a] Conditions: 9-BBN (2.6 equiv), THF, reflux, 5 h, then aq. Cs_2CO_3 (3 equiv), $PdCl_2(dppf)$ (0.1 equiv), KBr (1.2 equiv), Ph_3As (0.4 equiv), DMF, r.t., 20 h. [b] Prepared from the corresponding lactone by standard method (1.2 equiv of KHMDS, 1.5 equiv of HMPA, THF, -78 °C; 1.2 equiv of $PhNTf_2$, -78 to 0 °C). [c] Prepared from the corresponding lactone with Tebbe reagent (2.2 equiv) in THF-toluene-pyridine at -40 °C (72-76%). [d] Prepared from the corresponding iodide by base-treatment (*t*-BuOK, THF, 0 °C, 92%).

Scheme 3



Reagents and conditions: (a) $ThexylBH_2$, THF, 0 °C; H_2O_2, NaOH, r.t.; (b) Swern oxidation, 82% (2 steps); (c) CSA, CH_2Cl_2-MeOH, r.t.; (d) Ac_2O, Pyr, r.t., 94% (2 steps); (e) Et_3SiH, BF_3·OEt_2, CH_2Cl_2, -10 °C, 83%.

Acknowledgment: This work was financially supported by the Grant-in-Aid for Scientific Research on Priority Area No. 08245103 from the Ministry of Education, Science, Sports and Culture, of Japanese Government and by a fellowship from the Japan Society for the Promotion of Science for Young Scientists to M.I.

References and Footnotes

1. Structures: (a) Lin, Y.-Y.; Risk, M.; Ray, S. M.; Van Engen, D.; Clardy, J.; Golik, J.; James, J. C.; Nakanishi, K. *J. Am. Chem. Soc.* **1981**, *103*, 6773-6775. (b) Shimizu, Y.; Chou, H.-N.; Van Duyne, G.; Clardy, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 514-515. (c) Lee, M. S.; Repeta, D. J.; Nakanishi, K.; Zagorski, M. G. *J. Am. Chem. Soc.* **1986**, *108*, 7855-7856.
2. Total synthesis of brevetoxin B: Nicolaou, K. C.; Rutjes, F. P. J. T.; Theodorakis, E. A.; Tiebes, J.; Sato, M.; Untersteller, E. *J. Am. Chem. Soc.* **1995**, *117*, 10252-10263 and references cited therein. Total synthesis of brevetoxin A: Nicolaou, K. C.; Yang, Z.; Shi, G.-q.; Gunzner, J. L.; Agrios, K. A.; Gartner, P. *Nature,* **1998**, *392*, 264-269.
3. (a) Murata, M.; Legrand, A.-M.; Ishibashi, Y.; Fukui, M.; Yasumoto, T. *J. Am. Chem. Soc.* **1990**, *112*, 4380-4386. (b) Satake, M.; Murata, M.; Yasumoto, T. *Tetrahedron Lett.* **1993**, *34*, 1975-1976. (c) Satake, M.; Ishibashi, Y.; Legrand, A.-M.; Yasumoto, T. *Biosci. Biochem. Biotech.* **1996**, *60*, 2103-2105. (d) Satake, M.; Morohashi, A.; Oguri, H.; Oishi, T.; Hirama, M.; Harada, N.; Yasumoto, T. *J. Am. Chem. Soc.* **1997**, *119*, 11325-11326. (e) Satake, M.; Fukui, M.; Legrand, A.-M.; Cruchet, P.; Yasumoto, T. *Tetrahedron Lett.* **1998**, *39*, 1197-1198.
4. (a) Murata, M.; Naoki, H.; Matsunaga, S.; Satake, M.; Yasumoto, T. *J. Am. Chem. Soc.* **1994**, *116*, 7098-7107. (b) Nonomura, T.; Sasaki, M.; Matsumori, N.; Murata, M.; Tachibana, K. Yasumoto, T. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1675-1678 and references cited therein. (c) Zheng, W.; DeMattei, J. A.; Wu, J.-P.; Duan, J. J.-W.; Cook, L. R. Oinuma, H.; Kishi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 7946-7968. (d) Cook, L. R.; Oinuma, H.; Semones, M. A.; Kishi, Y. *ibid.* **1997**, *119*, 7928-7937.
5. For a recent review on marine toxins, see: Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897-1909.
6. For a recent review on polyether synthesis, see: E. Alvarez, E.; Candenas, M.-L.; Pérez, R.; Ravelo, J. L.; Martín, J. D. *Chem. Rev.* **1995**, *95*, 1953-1980.
7. Nicolaou, K. C.; Postema, M. H. D.; Claiborne, C. F. *J. Am. Chem. Soc.* **1996**, *118*, 1565-1566.
8. (a) Miyaura, N.; Ishiyama, T.; Sasaki, T.; Ishikama, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc.* **1984**, *111*, 314-321. (b) Oh-e, T.; Miyaura, N.; Suzuki, A. *J. Org. Chem.* **1993**, *58*, 2201-2208. (c) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457-2483.
9. (a) Johnson, C. R.; Braun, M. P. *J. Am. Chem. Soc.* **1993**, *115*, 11014-11015. (b) Johns, B. A.; Pan, Y. T.; Elbein, A. D.; Johnson, C. R. *J. Am. Chem. Soc.* **1997**, *119*, 4856-4865. (c) Meng, D.; Bertinato, P.; Balog, A.; Su, D.-S.; Kamenecka, T.; Sorensen, E. J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1997**, *119*, 10073-10092.
10. (a) Inoue, M.; Sasaki, M.; Tachibana, K. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 965-969. (b) Sasaki, M.; Inoue, M.; Noguchi, T.; Takeichi, A.; Tachibana, K. *Tetrahedron Lett.* **1998**, *39*, 2783-2786.
11. (a) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611-3613. (b) Pine, S. H.; Zahler, R.; Evans, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **1980**, *102*, 3270-3274.
12. Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392-6394.
13. Alvarez, E.; Pérez, R.; Rico, M.; Rodriguez, R. M.; Martín, J. D. *J. Org. Chem.* **1996**, *61*, 3003-3016.
14. The use of Ph_3As as a coligand had a significant positive effect on palladium(0)-catalyzed cross-coupling reaction, see: (a) Farina, V.; Krishman, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585-9595. (b) Kojima, A.; Honzawa, S.; Boden, C. D. J.; Shibasaki, M. *Tetrahedron Lett.* **1997**, *38*, 3455-3458.