

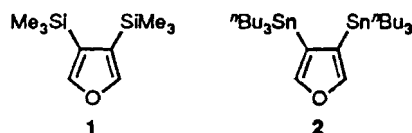
Regiospecific synthesis of 3,4-disubstituted furan†‡

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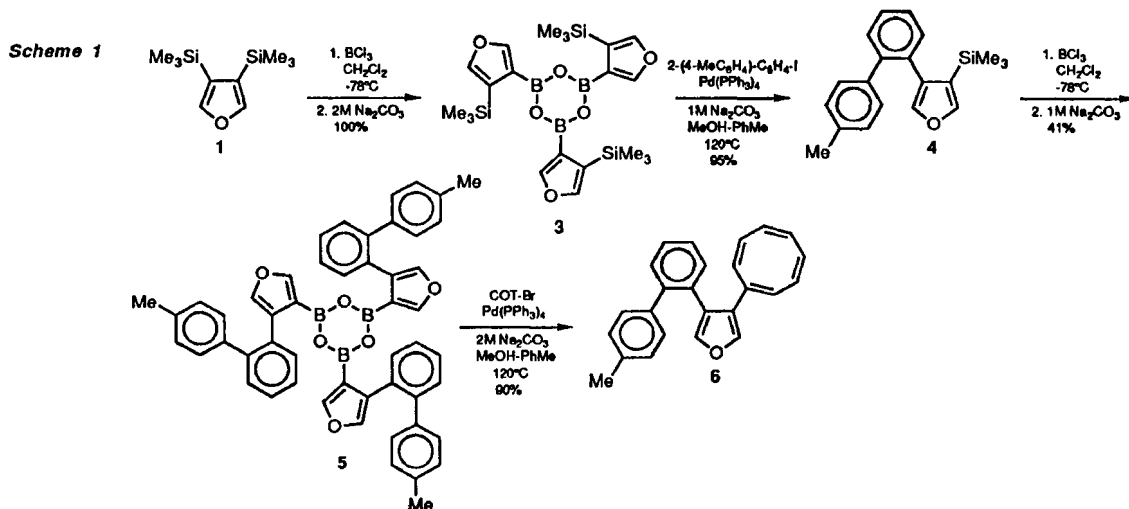
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Abstract : Tris[4-(substituted)furan-3-yl]boroxines, prepared from the corresponding 4-(substituted)-3-(trimethylsilyl)furan, were converted successfully through palladium-catalyzed cross-coupling reactions with tri-*n*-butylstannyl chloride to 4-(substituted)-3-(tri-*n*-butylstannyl)furans, which underwent further palladium-catalyzed reactions with organohalides to afford 3,4-disubstituted furans. Oxidation of tris[4-(substituted)furan-3-yl]boroxines generated the corresponding 4-substituted-3(2*H*)furanones.

In nature, a number of biologically interesting marine natural molecules having the skeleton of 3,4-disubstituted furans have recently been isolated and structurally elucidated.(1) 3,4-Disubstituted furans also played an important role as key precursors in organic synthesis.(2) We have recently reported that 3,4-bis(trimethylsilyl)furan (**1**)(3-7) and 3,4-bis(tri-*n*-butylstannyl)furan (**2**)(8-10) are exceedingly useful building blocks in the synthesis of 3,4-disubstituted furans. Our approach employed silyl groups and stannyl groups as potential *ipso*-directors. Well-known for their σ -donating character, silyl groups are able to stabilize a β -carbocation through the so-called (p - σ) $_{\pi}$ overlap, and as a result contribute to the *ipso*-substitution pattern.(11-13) By a similar argument, an even larger kinetic β -effect might be manifested by the stannyl groups.(14)



The role of **1** as a versatile precursor for 3,4-disubstituted furans is felicitously depicted in Scheme 1.(4,7) A regiospecific *ipso*-displacement (15,16) of one of the silyl groups of **1** with boron trichloride furnished presumably a dichloroborane, which was not isolated and was hydrolyzed directly with a dilute base to afford boroxine **3** in an almost quantitative yield. As can be exemplified in Scheme 1, Boroxine **3** were converted readily to **4** through the regular Suzuki reaction conditions.(17) The substitution of the remaining silyl group in **4** required more rigorous conditions, affording boroxine **5** in relatively inferior yields. Likewise, **5** was converted to a 3,4-disubstituted furan **6**.



† Dedicated to Prof. Peter J. Garratt, University College London, on the occasion of his 60th birthday.

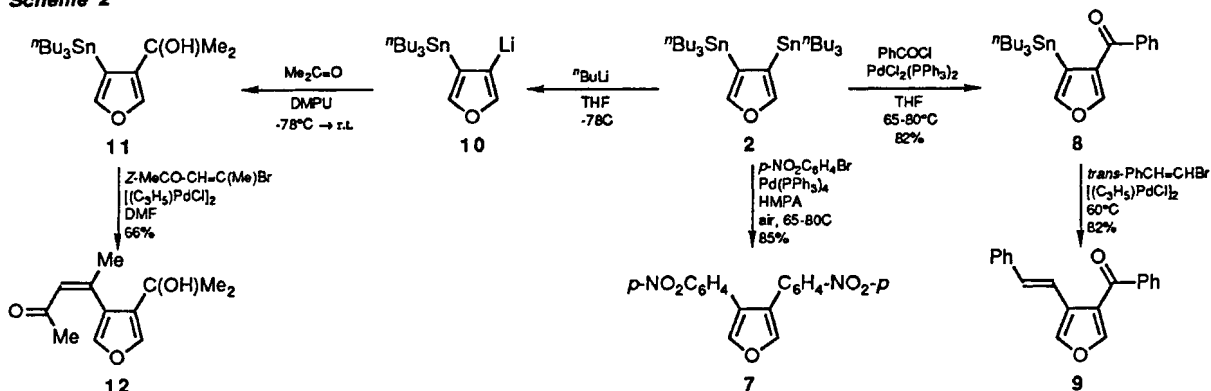
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The palladium-catalyzed cross-coupling of **2** with aryl bromides gave only symmetrical diarylfurans **7** (Scheme 2).^(8,10) On the other hand, similar reaction between **2** and benzoyl chloride yielded **8**. This partial acylation therefore provided a direct entry to unsymmetrical 3,4-disubstituted furans, as can be befittingly demonstrated by the conversion of **8** to **9**.^(8,10)

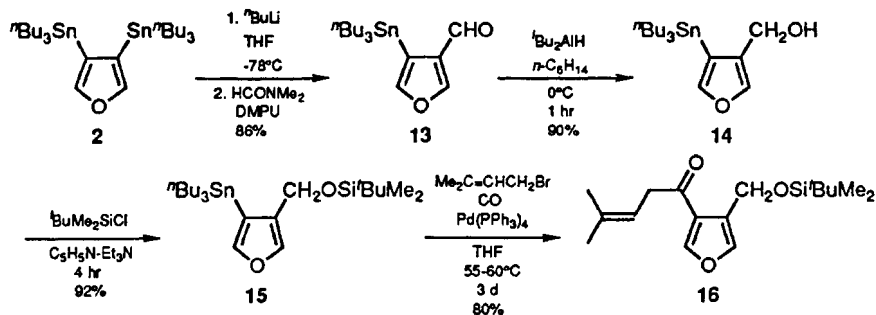
Another route from which unsymmetrical 3,4-disubstituted furans could be obtained was by utilizing a tin-lithium exchange pathway,⁽¹⁸⁾ as outlined in Scheme 2.^(9,10) To achieve a complete exchange of one stannyl group in **2**, generating **10**, 2.2 equivalents of *n*-butyllithium were needed. One of the transformations of **10** was effected with acetone, which furnished alcohol **11**. The reaction yield was improved significantly when acetone was added together with 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU). Again, a palladium-catalyzed cross-coupling reaction converted **11** to **12**.^(9,10)

Scheme 2



The conciseness and effectiveness of the combined use of a lithiation reaction plus a palladium-catalyzed coupling reaction are demonstrated by the synthesis of a 3,4-disubstituted furan **16** as shown in Scheme 3.^(9,10) Thus, furan **2** was converted in a usual manner to aldehyde **13**, which was reduced by DIBAL to give a good yield of **14**. The hydroxy group was protected to provide a silyl ether **15**. The palladium-catalyzed carbonylation⁽¹⁰⁾ of **15** afforded the target molecule **16**.

Scheme 3



In the silicon-boron protocol (Scheme 1), it is perhaps less evident that acid halides cannot be employed for a coupling purpose in the Suzuki reaction because of the alkaline conditions used. On the other hand, tri-*n*-butylstannylfurans have been successfully converted to acyl-substituted products (Scheme 2). In view of the limitation of boroxines in acyl-coupling reactions, we sought to displace the C-B bond of boroxines with a tin functionality.⁽¹⁹⁾ This avenue was first explored in attempts to displace directly the boroxine unit of **17**^(4-7,19) via palladium-catalyzed Suzuki coupling with tri-*n*-butylstannyl chloride. Tetrakis(triphenylphosphine)palladium (10 mol%) was found effective in furnishing tri-*n*-butylstannyl-substituted furans **18** (Scheme 4 and Table 1).⁽¹⁹⁾ Furans **18** were transformed into unsymmetrical 3,4-disubstituted furans **19** via palladium-catalyzed coupling reactions and the results are listed in Table 1.⁽¹⁹⁾

Scheme 4

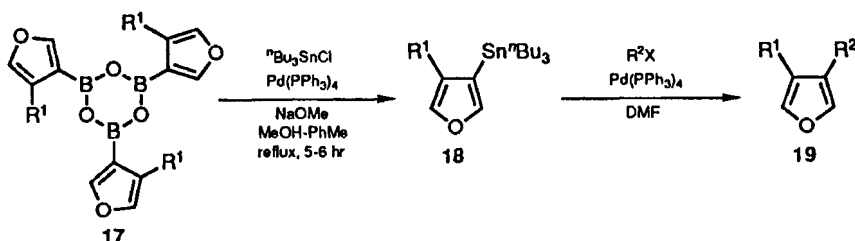




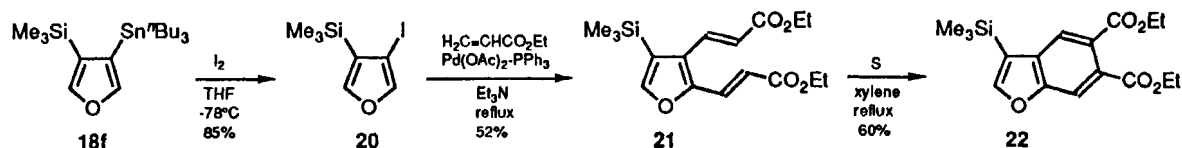
TABLE 1. Palladium-catalyzed cross-coupling reaction of boroxines **17** with tri-*n*-butylstannyl chloride and regiospecific synthesis of 3,4-disubstituted furans **19**

entry	17	R ¹	18 (Yield %) ^a	R ² X	19	R ²	Yield % ^a
1	17a	Me	18a (65)	<i>trans</i> -C ₄ H ₉ -CH=CH-I	19a	CH=CH- <i>trans</i> -C ₄ H ₉	75
2	17b	ⁿ Bu	18b (63)	Me ₂ C=CH-Br	19b	CH=CMe ₂	78
3	17c	CH ₂ C ₆ H ₄ - <i>p</i> -CO ₂ Me	18c (64)	<i>trans</i> -C ₄ H ₉ -CH=CH-I	19c	CH=CH- <i>trans</i> -C ₄ H ₉	70
4	17d	CH ₂ C ₆ H ₄ - <i>p</i> -NO ₂	18d (63)	9-bromophenanthrene	19d	phenanthren-9-yl	40
5	17e	CH ₂ C ₆ H ₂ -3,4,5-(OMe) ₃	18e (63)	<i>o</i> -Me-C ₆ H ₄ -I	19e	C ₆ H ₄ - <i>o</i> -Me	45
6	17e	CH ₂ C ₆ H ₂ -3,4,5-(OMe) ₃	18e (63)		19e'		45 ^c
7	17f	SiMe ₃	18f (70)	<i>p</i> -Me-C ₆ H ₄ -Br	19f	C ₆ H ₄ - <i>p</i> -Me	60
8	17f	SiMe ₃	18f (70)	EtO ₂ C-Cl ^b	19f'	CO ₂ Et	30

^a Isolated yields.^b The reaction was catalyzed with PdCl₂(PPh₃)₂ in PhMe-HMPA at 120 °C.^c Unpublished experiment.

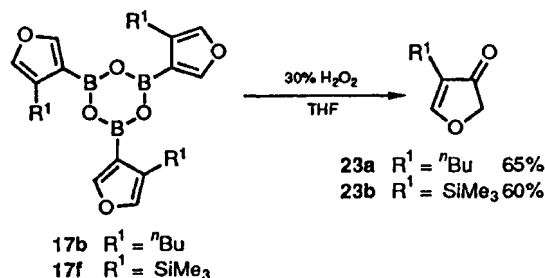
Although furan bears a pronounced aromatic disposition, it still behaves as a conjugated diene or as an enol ether.⁽²⁰⁾ In order to examine whether the Heck reaction⁽²¹⁾ of furan as an enol ether occurred, 4-iodo-3-(trimethylsilyl)furan (**20**), obtainable also from **18f**,⁽¹⁹⁾ was reacted with excess ethyl acrylate (≥ 3.5 molar equivalents) under Heck conditions to lead to formation of 2,3-bis(*trans*-ethoxycarbonylvinyl)-4-(trimethylsilyl)furan (**21**) (Scheme 5).^(5,19,22) The thermal 6 π -electrocyclic reaction⁽²³⁾ of **21** in the presence of sulfur resulted in formation of a benzoannulated product, 3-(trimethylsilyl)-5,6-bis(ethoxycarbonyl)benzo[2,3-*b*]furan (**22**), presumably through an additional dehydrogenation.⁽²³⁾

Scheme 5



4-*n*-Butyl-3(2*H*)furanone (**23a**) and 4-trimethylsilyl-3(2*H*)furanone (**23b**) were obtained respectively in acceptable yields from reactions of tris(4-*n*-butylfuran-3-yl)boroxine (**17b**) and tris(4-trimethylsilylfuran-3-yl)boroxine (**17f**) with hydrogen peroxide (Scheme 6).^(19,24) Peroxide oxidation of trimethylsilyl-substituted furans generally produced the corresponding ketones with concomitant cleavage of the silicon-carbon bond. However, our own experience with **17f** demonstrated that the reactivity of the C-B bond towards oxidation was more rapid than that of the C-Si bond.

Scheme 6



ACKNOWLEDGMENT

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REFERENCES

1. Z.J. Pang, F. Bocchio and O. Sterner *Tetrahedron Lett.* **33**, 6863 (1992). R. Davis and R.J. Capon *Aust. J. Chem.* **46**, 1295 (1993).
2. *Inter alia*, see R.E. Danso-Danquah, A.I. Scott and D. Becker *Tetrahedron* **49**, 8195 (1993). W. Eberbach, N. Laber, J. Bussenius, H. Fritz and G. Rihs *Chem. Ber.* **126**, 975 (1993).
3. M.S. Ho and H.N.C. Wong *J. Chem. Soc., Chem. Commun.* 1238 (1989).
4. Z.Z. Song, Z.Y. Zhou, T.C.W. Mak and H.N.C. Wong *Angew. Chem. Int. Ed. Engl.* **32**, 432 (1993).
5. Z.Z. Song and H.N.C. Wong *Liebigs Ann. Chem.* **29** (1994).
6. Z.Z. Song and H.N.C. Wong *J. Org. Chem.* **59**, 33 (1994).
7. Z.Z. Song, M.S. Ho and H.N.C. Wong *J. Org. Chem.* **59**, 3917 (1994).
8. Y. Yang and H.N.C. Wong *J. Chem. Soc., Chem. Commun.* 656 (1992).
9. Y. Yang and H.N.C. Wong *J. Chem. Soc., Chem. Commun.* 1723 (1992).
10. Y. Yang and H.N.C. Wong *Tetrahedron* **50**, 9583 (1994).
11. S.N. Ushakov and A.M. Itenberg *Zh. Obshch. Khim.* **7**, 2495 (1937).
12. T.H. Chan and I. Fleming *Synthesis* 761 (1979).
13. S.E. Thomas, *Organic Synthesis. The Role of Boron and Silicon*, pp 47-50, Oxford University Press, Oxford (1992).
14. J.B. Lambert, G.T. Wang and D.H. Teramura *J. Org. Chem.* **53**, 5422 (1988).
15. F. Effenberger and D. Häbich *Liebigs Ann. Chem.* 842 (1979).
16. J.B. Lambert *Tetrahedron* **46**, 2677 (1990).
17. A. Suzuki *Pure Appl. Chem.* **63**, 419 (1991).
18. I. Fleming and M. Taddei *Synthesis* 898 (1985).
19. Z.Z. Song and H.N.C. Wong *J. Chin. Chem. Soc.* in press.
20. R. Asano, I. Moritani, Y. Fujiwara and S. Teranishi *Bull. Chem. Soc. Jpn.* **46**, 663 (1973).
21. R.F. Heck, *Palladium Reagents in Organic Synthesis*, Academic Press, New York (1985).
22. L.A. Jacob, B.-L. Chen and D. Stec *Synthesis* 611 (1993).
23. O. Reiser, B. König, K. Meerholz, J. Heinze, T. Wellaur, F. Gerson, R. Frim, M. Rabinovitz and A. de Meijere *J. Am. Chem. Soc.* **115**, 3511 (1993).
24. R.P. Dickinson and B. Iddon *J. Chem. Soc. (C)* 1926 (1970).