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Tandem Stille/Suzuki–Miyaura Coupling of a Hetero-Bis-metalated Diene. Rapid, One-Pot Assembly of Polyene Systems

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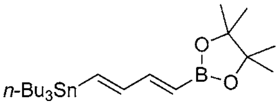
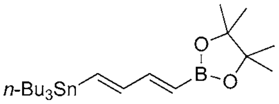
ABSTRACT



The synthesis of a hetero-bis-metallo 1,3-butadiene is reported, and its use as an orthogonal Stille and Suzuki–Miyaura coupling partner is detailed. The tin/boron diene participated successfully in a one-pot, sequential Stille and Suzuki–Miyaura coupling protocol, and its utility was demonstrated in the two-step construction of the pentaene side chain of the *Fusarium* metabolite lucilactaene.

Palladium-catalyzed cross-coupling reactions are a tremendously effectual tool in organic chemistry; it is difficult to imagine the design and execution of complex molecule syntheses in their absence. The Stille[1] and Suzuki−Miyaura[2] reactions are preeminent due to their compatibility with a diverse range of functional groups and because of the ease with which boron and tin can be incorporated into organic molecules.

Expanding the range of coupling partners for these reactions is an important undertaking, and we report the synthesis of hetero-bis-metalated 1,3-butadiene **1** (Figure 1) and demonstrate its utility in the rapid, one-pot construction of archetypal polyene systems.



1

Figure 1. Hetero-bis-metalated butadiene.

The synthesis of conjugated polyenes is of great interest because of their wide occurrence in natural[3] and unnatural products.[4] As part of an interest in the efficient and stereodefined production of polyene systems,[5] we have developed a novel lynchpin system useful for construction of biologically relevant polyenes. The easily prepared tin/boron 1,4-bis-metallo-1,3-butadiene **1** was designed as a differentially and orthogonally functionalized coupling partner, which would permit stepwise and bidirectional elaboration based on the intrinsic differential reactivity of the two carbon−metal bonds. This reagent represents a prototypical orthogonal Stille/Suzuki−Miyaura system.

Other reported hetero-bis-metalated systems include a well-known tin/silicon alkene[6] and a single report of a vinylic boron/tin system.[7] Several homo-bis-metalated olefins are well-known, including those of tin[8] and boron.[9]

Herein, we report orthogonal coupling conditions that allow selective coupling at the differentially metalated termini

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[1] (a) Stille, J. K.; Milstein, D. *J. Am. Chem. Soc.* **1978**, *100*, 3636. (b) Stille, J. K. *Angew. Chem., Int. Ed Engl.* **1986**, *25*, 508. (c) Farina, V. *Pure Appl. Chem.* **1996**, *68*, 73. (d) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1.

[2] (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263. (c) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147.

[3] Thirsk, C.; Whiting, A. *J. Chem. Soc., Perkin Trans. 1* **2002**, *8*, 999.

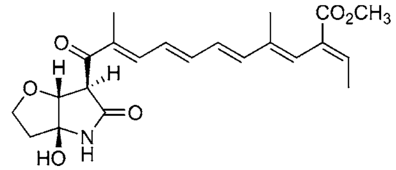
[4] Krasnaya, Zn. A.; Tatikolov, A. S. *Russ. Chem. Bull., Int. Ed.* **2003**, *52*, 1641.

[5] (a) Coleman, R. S.; Garg, R. *Org. Lett.* **2001**, *3*, 3487. (b) Coleman, R. S.; Liu, P.-H. *Org. Lett.* **2004**, *6*, 577.

[6] Murakami, M.; Matsuda, T.; Itami, K.; Ashida, S.; Terayama, M. *Synthesis* **2004**, 1522.

10.1021/ol050768u CCC: $30.25

of **1**. In addition, we report a one-pot sequential Stille/Suzuki–Miyaura coupling sequence[10] as a valuable attribute of **1**. Application of this methodology to biologically relevant systems is illustrated by the rapid construction of the side chain of lucilactaene (Figure 2).[11]

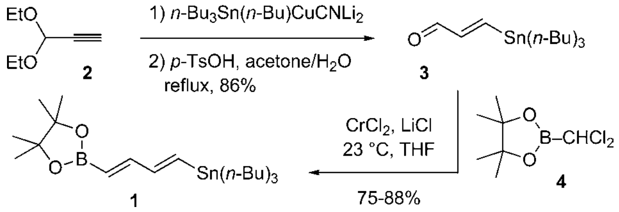


lucilactaene

Figure 2. Structure of *Fusarium* metabolite lucilactaene.

Butadiene **1** was effectively synthesized from propargaldehyde diethyl acetal (**2**) by stannylcupration[12] followed directly by acetal hydrolysis to afford β–stannylacrolein **3**.[13] Takai olefination with dichloromethylborinate **4** afforded butadiene **1** in yields routinely above 75% (Scheme 1).

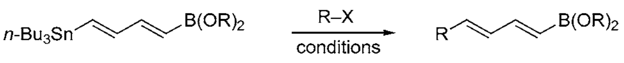
Scheme 1. Preparation of Butadiene **1**

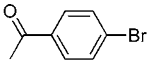
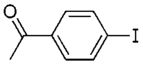
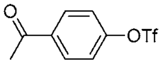
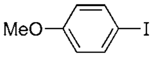
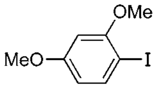
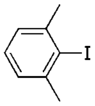
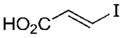
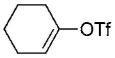


Selective Stille coupling at the tin-bearing terminus of **1** was possible because of the need for basic reaction conditions to effect transmetalation at the boron-bearing end. Bromides, iodides, and triflates all effectively participated in Stille coupling reactions with **1** (Table 1).

There was little difference in yield between electron-deficient aryl bromide **5** (entry 1) and iodide **7** (entry 2), although aryl triflate **8** (entry 3) provided modest yields of coupled product **6**. Electron-rich aryl iodides **9** (entry 4) and **11** (entry 5), and sterically crowded 2,6-dimethyl substituted

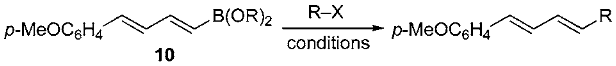
Table 1. Stille Coupling Reactions of 1

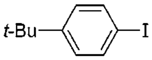
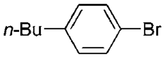
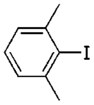
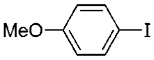
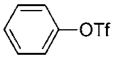
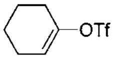


entry	coupling partner (R–X)		product	conditions[a]	yield (%)[b]
1	**5**		**6**	A	84
2	**7**		**6**	A	90
3	**8**		**6**	A, LiCl	55
4	**9**		**10**	A	90
5	**11**		**12**	A	87
6	**13**		**14**	A	95
7	**15**		**16**	B	90
8	(E)-**17** (Z)-**17**	n-BuCH=CH–I	(E)-**18** (Z)-**18**	B B	75 68
9	**19**		**20**	B	91

[a] Key: (A) Pd_2dba_3 (1.5 mol %), P(furyl)$_3$ (3.5 mol %), NMP, 23–50 °C; (B) $PdCl_2(CH_3CN)_2$ (5 mol %), DMF, 25 °C. [b] Isolated yield (average of two runs).

Table 2. Suzuki–Miyaura Coupling Reactions of **10**



entry	coupling partner (R–X)		product	conditions[a]	yield (%)[b]
1	**21**		**22**	C	94
2	**23**		**24**	C	60
3	**13**		**25**	D	71
4	**9**		**26**	C	81
5	**27**		**28**	E	74
6	**19**		**29**	C	24
7	(E)-**17** (Z)-**17**	n-BuCH=CH–I	(E)-**30** (Z)-**30**	C C	67 67

[a] Key: (C) $(Ph_3P)_4Pd$ (5 mol %), 2 M aq K_2CO_3, toluene/EtOH, 23–60 °C; (D) Pd_2dba_3 (1.5 mol %), P(furyl)$_3$ (3.5 mol %), CsF, NMP, 23 °C; (E) $(Ph_3P)_4Pd$ (5 mol %), K_3PO_4, dioxane, 85 °C. [b] Isolated yield (average of two runs).

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(7) Lhermitte, F.; Carboni, B. *Synlett* **1996**, 377.

(8) Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1988**, *110*, 1557. Renaldo, A. F.; Labadie, J. W.; Stille, J. K. *Org. Synth.* **1989**, *67*, 86.

(9) Ishiyama, T.; Matsuda, N.; Miyaura, N.; Suzuki, A. *J. Am. Chem. Soc.* **1993**, *115*, 11018.

(10) (a) Ogima, M.; Hyuga, S.; Hara, S.; Suzuki, A. *Chem. Lett.* **1988**, 809. (b) Ogima, M.; Hyuga, S.; Hara, S.; Suzuki, A. *Chem. Lett.* **1989**, 1959. (c) Meijere, A.; Zezschwitz, P.; Nüske, H.; Stulgies, B. *J. Organomet. Chem.* **2002**, *653*, 129.

(11) Kakeya, H.; Kageyama, S.-I.; Nie, L.; Onose, R.; Okada, G.; Beppu, T.; Norbury, C. J.; Osada, H. *J. Antibiot.* **2001**, *54*, 850.

(12) Lipshutz, B. H.; Lindsley, C. *J. Am. Chem. Soc.* **1997**, *119*, 4555. Lipshutz, B. H.; Ullman, B.; Lindsley, C.; Pecchi, S.; Buzard, D. J.; Dickson, D. *J. Org. Chem.* **1998**, *63*, 6092.

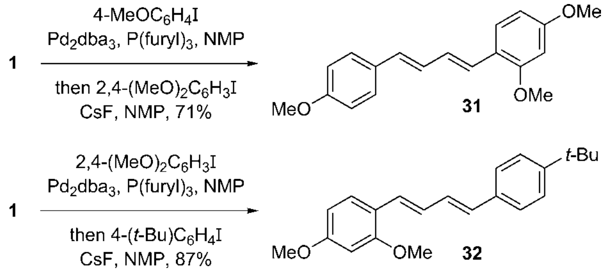
(13) A route to **3** involving hydrostannylation of propargyl alcohol was less reproducible because a poor and variable *E*/*Z* ratio was obtained.

iodide **13** (entry 6) both provided excellent yields of products **10**, **12**, and **14**, respectively. Iodoacrylic acid (**15**, entry 7) was an effective partner, as were *cis*- and *trans*-1-iodo-1-hexene (entry 8). In comparison to aryl triflate **8** (entry 3), enol triflate **19** (entry 9) could be coupled with **1** in excellent yield.[14] Reactions generally proceeded quantitatively, with no evidence of competing reaction of the vinyl borinate.

Subsequential Suzuki–Miyaura coupling the borinate **10** was effectively achieved with various partners (Table 2). Aryl iodide **21** provided the highest yield of coupled product (entry 1), significantly higher than the comparable bromide **23** (entry 2). Yields were also lower for sterically crowded iodide **13** (entry 3) and electron rich system **9** (entry 4). Phenyl triflate (**27**) coupled effectively (entry 5), but enol triflate **19** was not an effective partner (entry 6). Stereoisomeric vinyl iodides **17** participated effectively (entry 7).

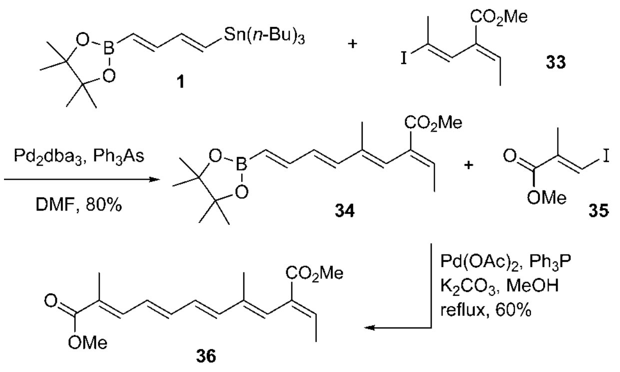
Tandem coupling of **1** was implemented in a sequential one-pot sequence, performing the Stille coupling with one partner followed by direct addition of CsF and the second coupling partner to the reaction flask to effect Suzuki–Miyaura coupling. This one-pot, sequential Stille/Suzuki–Miyaura coupling could be achieved in excellent overall yield in the formation of **31** and **32** (Scheme 2).

Scheme 2. One-pot Sequential Stille/Suzuki–Miyaura Coupling with Butadiene **1**



Use of **1** in the synthesis of the pentaene side chain of lucilactaene clearly demonstrates the potential for orthogonal, tandem coupling protocols. Dienyl iodide **33**[15] was coupled with **1** under Stille conditions to afford tetraene **34**. Subsequent Suzuki–Miyaura coupling with β-iodoacrylate **35** afforded the lucilactaene pentaene fragment **36** in nearly 50% overall yield for the two sequential coupling reactions (Scheme 3).

Scheme 3. Assembly of Lucilactaene Pentaene Side Chain



The one-pot, two-directional coupling by sequential Stille and Suzuki–Miyaura couplings clearly shows the potential of this reagent and strategy. The utility of **1** as a lynchpin reagent was demonstrated in an efficient two-step coupling to form the pentaene side chain of the *Fusarium* metabolite lucilactaene. This novel reagent system demonstrates the potential of orthogonal Stille and Suzuki–Miyaura coupling protocols in synthesis.

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Supporting Information Available: Experimental procedures and characterization of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[14] Isolated yields were lowered because of the difficulty of purifying vinyl boronates. Chromatography with Florosil gave higher yields than with silica.

[15] Coleman, R. S.; Walczak, M. C. Unpublished studies.