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# Palladium-Catalyzed Cross-Coupling of Terminal Alkynes with 4-Trifloyloxazole: Studies toward the Construction of the C26–C31 Subunit of Phorboxazole A

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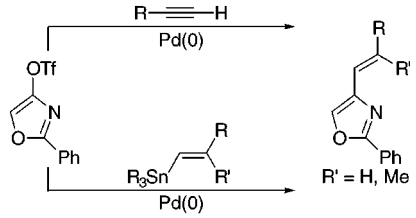
## ABSTRACT




**A strategy has been developed that successfully takes advantage of transition-metal-catalyzed coupling reactions for the synthesis of highly functionalized oxazoles. Trifloyloxazoles have been used as coupling partners with alkyne-derived vinylmetallic intermediates in Stille- and Negishi-type couplings to assemble the corresponding oxazoles in good isolated yield. The results obtained provide a close analogy and thus good precedent to employ this strategy in the synthesis of the oxazole subunits of phorboxazole A.**

Transition-metal-catalyzed cross-coupling reactions have had a significant influence on the area of organic chemistry. The ability to affect carbon−carbon bond formation has inspired a wide range of innovative applications. For instance, palladium(0)-catalyzed cross-coupling has emerged as an effective method for the union of two trigonal carbon systems, as recently demonstrated in the synthesis of complex natural products.[1]

In this letter we report the synthesis of oxazoles bearing di- and trisubstituted alkenes by transition-metal-catalyzed cross-couplings of trifloyloxazoles and alkynes. The application to the C16−C21 and C26−C31 subunits of phorboxazole A documents a new and useful demonstration of the versatility of this process. Since the target structure bears substitution on each of the two oxazoles to an $sp^2$ carbon, we chose to address the construction of the two oxazole moieties in our projected synthesis of phorboxazole A[2,3] (Scheme 1) by cross-coupling methods. A transition-metal-catalyzed $sp^2-sp^2$ carbon coupling strategy for the construction of the C18−C19 and C29−C28 $\sigma$-bonds of phorboxazole was envisioned as an efficient and direct route for their assembly. In doing so, we chose the oxazoles as the electrophilic coupling partner. In a consideration of synthetic approaches to appropriately functionalized systems that would participate in cross-coupling strategies, literature

(1) For illustrative examples see: (a) Nicolaou, K. C.; Chakraborty, T. K.; Piscopio, A. D.; Minowa, N.; Bertinato, P. *J. Am. Chem. Soc.* **1993**, *115*, 4419−4420. (b) Masters, J. J.; Link, J. T.; Snyder, L. B.; Young, W. B.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1723−1726. (c) Panek, J. S.; Jain, N. F. *J. Org. Chem.* **1998**, *63*, 4572−4573. (d) Evans, D. A.; Ng, H. P.; Rieger, D. L. *J. Am. Chem. Soc.* **1993**, *115*, 11446−11459. (e) White, J. D.; Porter, W. J.; Tillre, T. *Synlett* **1993**, 535−538. (f) Panek, J. S.; Hu, T. *J. Org. Chem.* **1999**, *64*, 4959−4961.

(2) For isolation and biological data see: (a) Searle, P. A.; Molinski, T. F. *J. Am. Chem. Soc.* **1995**, *117*, 8126−8131. (b) Searle, P. A.; Molinski, T. F. *J. Am. Chem. Soc.* **1996**, *118*, 9422−9423. (c) Molinski, T. F. *Tetrahedron Lett.* **1996**, *37*, 7879−7880.

(3) For previous synthesis see: Forsyth, C. J.; Ahmed, F.; Cink, R. D.; Lee, C. H. *J. Am. Chem. Soc.* **1998**, *120*, 5597−5598.

(4) (a) Whitney, S. E.; Rickborn, B. *J. Org. Chem.* **1991**, *56*, 3058−3063. (b) Vedejs, E.; Luchetta, L. M. *J. Org. Chem.* **1999**, *64*, 1011−1014.

(5) Ritter, K. *Synthesis* **1993**, 735−762.

(6) Barrett, A. G. M.; Khort, J. T. *Synlett* **1995**, 415−416.

(7) (a) White, J. D.; Holoboski, M. A.; Green, N. J. *Tetrahedron Lett.* **1997**, *38*, 7333−7336. For other propargylic systems in cross-coupling employing addition of higher order cuprates, see: (b) Craig, D.; Payne, A. H.; Warner, P. *Synlett* **1998**, *11*, 1264−1266. (c) Harris, L.; Jarowicki, K.; Kocienski, P.; Bell, R. *Synlett* **1996**, *9*, 903−905.

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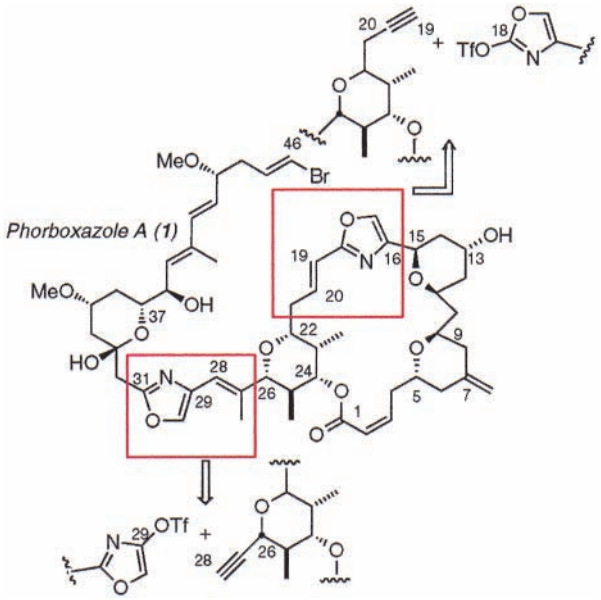
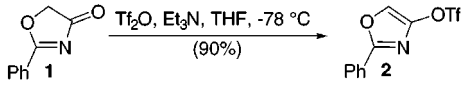
**Scheme 1.** Retrosynthetic Highlights



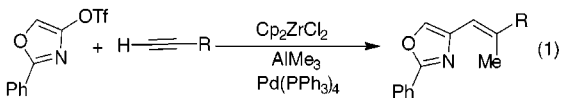

precedent indicated the difficulties associated with selective halogenation of oxazoles.[4] Our approach then focused on the selective formation of a trifloyloxazole from the oxazolone precursor (Scheme 1). We were encouraged that this approach would be successful by the recent advances in transition-metal-catalyzed coupling reactions and the advances in the transformation of carbonyls to enol enol triflates.[5]

The cross-coupling strategy was investigated by surveying known trifloyloxazoles. In that regard, trifloyloxazole **2** is not a known coupling partner but has been used to prepare the corresponding trimethylstannane from Pd(0) and hexamethylditin.[6] Optimization of the reported procedure yields trifloyloxazole **2** in 90% yield by treatment of oxazolone **1** with triflic anhydride and TEA in $CH_2Cl_2$ (Scheme 2).

**Scheme 2**

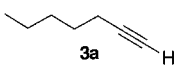
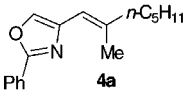
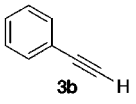
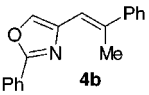
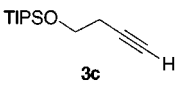
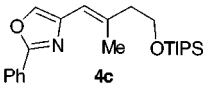
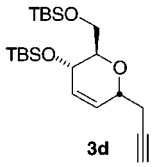
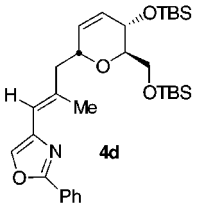



The carboalumination of 1-heptyne, followed by palladium-catalyzed coupling with **2**, yielded the 2-substituted oxazole **4a** with the desired *E* selectivity. This reaction provided, in one pot, a trisubstituted olefin bearing the correct olefin geometry similar to that of the C26−C31 subunit of phorboxazole.



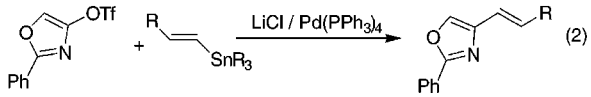

The optimal reaction conditions for the carboalumination were found to be catalytic $Cp_2ZrCl_2$ (10 mol %) and 1.2 equiv of $AlMe_3$. The coupling employed 1.0 equiv of the trifloyloxazole with 1 equiv of the alkyne and 10 mol % of $Pd(PPh_3)_4$. As illustrated in Table 1, aliphatic alkynes (entries 1 and 3), as well as an arene-containing alkyne (entry 2), were successfully coupled, affording the desired product in 70−75% isolated yield. In addition, the substituted dihydropyran **3d** was subjected to identical carboalumination conditions to afford the pyran-containing oxazole **4d** in 68% yield.

**Table 1.** Carbometalation of Terminal Alkynes and Coupling to Trifloyloxazole **2**

| entry | substrate | product[a] | isolated yield[b] |
|---|---|---|---|
| 1 |  **3a** |  **4a** | 75 % |
| 2 |  **3b** |  **4b** | 70% |
| 3 |  **3c** |  **4c** | 72% |
| 4 |  **3d** |  **4d** | 68% |

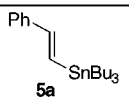
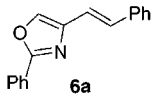
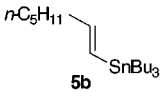
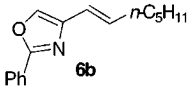
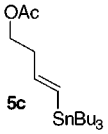
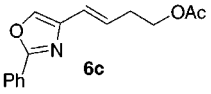
[a] Gave satisfactory $^1H$, $^{13}C$ NMR, IR, and HRMS data. [b] Based on pure material after purification by flash chromatography on $SiO_2$.

Given our preliminary results, it was thought that the carboalumination/palladium-catalyzed coupling strategy would successfully install the C27−C29 olefin of phorboxazole. Alkyne **7** was prepared and subjected to the identical coupling conditions that were found to be optimal for the previous substrates. However, no desired product was obtained from this reaction. A set of conditions could not be found that would successfully afford the desired product. In support of this notion, there have been documented examples of propargylic ether substrates yielding a complex mixture of products from the methylalumination conditions.[7] This led us to reconsider the route to the desired alkenylmetal reagent. In an attempt to define another route to (*E*)-olefin-substituted oxazoles, the Stille coupling (eq 2) of ((*E*)-alkenyl)stannanes was investigated (Table 2).




The Stille coupling was effected using 4 mol % of $Pd(PPh_3)_4$ and 3.1 equiv of LiCl in DMF at 60 °C for 1.5 h.

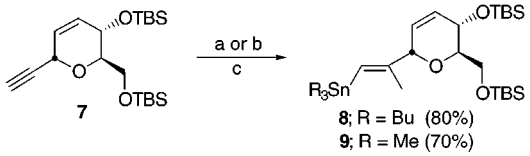
**Table 2.** Stille Coupling with Trifloyloxazole **2**

| entry | substrate | product[a] | isolated yield[b] |
|---|---|---|---|
| 1 |  **5a** |  **6a** | 75 % |
| 2 |  **5b** |  **6b** | 80% |
| 3 |  **5c** |  **6c** | 84% |

[a] Gave satisfactory $^1$H, $^{13}$C NMR, IR, and HRMS data. [b] Based on pure material after purification by flash chromatography on $SiO_2$.

In all cases, the desired product could be isolated in >70% yield. Given the success of the Stille coupling procedure, the corresponding (*E*)-alkenyl stannane of pyran **7** was synthesized. Addition of the (tributylstannyl)butylcuprate reagent (*n*-$Bu_3Sn$)Cu(Bu)$CNLi_2$[8] to pyran **7** followed by trapping of the intermediate alkenylcuprate with MeI afforded vinylstannane **8** in 80% yield (Scheme 3, method a).

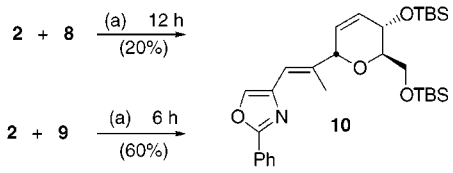
**Scheme 3**




(a) ($nBu_3Sn$)Cu(Bu)$CNLi_2$, THF, -78 °C.
(b) ($Me_3Sn$)$_2$CuCN$Li_2$, THF, -78 °C.
(c) MeI, DMPU -78 °C → rt

In our initial experiments, the synthesis of oxazole **10** by the coupling of pyran **8** with trifloyloxazole **2** could only be achieved in 20% yield (6 mol % $Pd_2(dba)_3$/12 mol % P*t*$Bu_3$/LiCl/NMP) (Scheme 4). Since stannane **8** could be recovered from the reaction, it is possible that the transmetalation of the stannane reagent is the rate-limiting step. It was postulated that the relative rate of transmetalation would be enhanced if the size of the tin reagent was reduced. The vinylogous trimethylstannane reagent **9** was synthesized in 70% yield by the addition of the bis(trimethylstannyl)cuprate species ($Me_3Sn$)$_2$Cu(CN)$Li_2$[9] to pyran **7** followed by trapping of the intermediate alkenylcuprate with MeI (Scheme 3, method b). Employing the conditions which had provided the best result with tributylstannane **9**, we obtained the desired coupling product in 60% isolated yield (Scheme 4). The successful Stille coupling of trifloyloxazole **2** and trimethylstannane **9** in good yield affords a 4-substituted oxazole which closely resembles the C26−C31 subunit of phorboxazole A.

**Scheme 4**




(a) 6 mol% $Pd_2(dba)_3$•$CHCl_3$ , 12 mol% P($^t$Bu)$_3$, LiCl, NMP, 60 °C

In summary, we have developed a strategy that successfully takes advantage of palladium(0)-catalyzed coupling reactions for the synthesis of highly substituted oxazoles. The ease of synthesis of the oxazole coupling partner and functional group tolerance associated with palladium-catalyzed cross-coupling suggest that other transition metals such as nickel may also be effective. In that regard, this constitutes an attractive method for the synthesis of substituted oxazoles.

**Acknowledgment.** We are grateful to Drs. Tao Hu and Scott E. Schaus (Harvard University) for helpful discussions. We also thank Ms. Bobbianna J. Neubert for technical support. Financial support was obtained from the NIH/NCI (Grant No. R01CA56304).

**Supporting Information Available:** Experimental details and compound characterization. This materail is available free of charge via the Internet at http://pubs.acs.org.

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(8) For the preparation of $SnBu_3Cu(Bu)CNLi_2$ and other higher order cuprates see: *Organocopper Reagents: A Practical Approach*, Taylor, R. J. K., Ed.; Oxford University Press: Oxford, U.K., 1994; Chapter 12, p 279.

(9) For procedures concerning the preparation of ($Me_3Sn$)$_2$Cu(CN)$Li_2$, see the Supporting Information.