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Pd(0)-Catalyzed Cross-Coupling Reactions of Boron Derivatives with a Lactam-Derived *N*-Boc Enol Triflate

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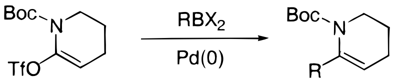
ABSTRACT

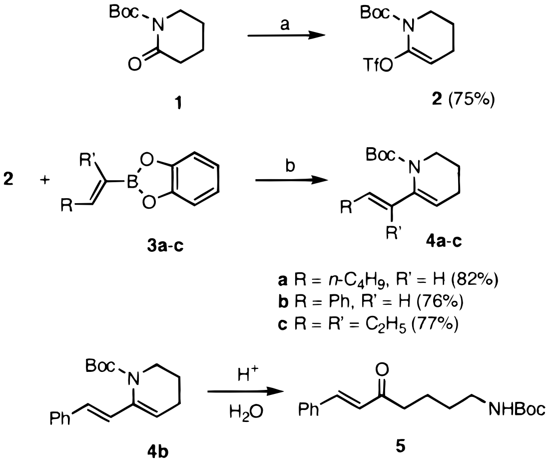


The cross-coupling reaction of 2-(1-alkenyl)-1,3,2-benzodioxaboroles, obtained from alkynes and catecholborane, and other boron derivatives with a lactam-derived *N*-Boc enol triflate occurred under very mild conditions in a THF–water medium employing $(Ph_3P)_2PdCl_2$ as a catalyst, providing the corresponding 6-substituted *N*-Boc 3,4-dihydro-2*H*-pyridines in high yields.

In recent years, lactam-derived enol triflates have gained importance as intermediates in the synthesis of heterocyclic compounds. Hiemstra and Speckamp[1] have shown that these compounds can undergo palladium-mediated displacement of the triflate group with nucleophiles such as organotin and organozinc derivatives, as well as methoxycarbonylation reactions. Comins[2] and other authors[3,4] have reported coupling reactions with organocuprates and organotin compounds, while Sonogashira-type cross-coupling reactions with monosubstituted acetylenes have been described by Isobe[5] and, more recently, by Cha.[6] Surprisingly, no examples of Suzuki-type reactions of lactam-derived enol triflates have been yet described, although the use of organoboron compounds as nucleophiles in Pd-catalyzed cross-coupling reactions with vinyl and aryl triflates or halides is a powerful methodology in organic synthesis.[7]

The possibility of forming new C−C bonds by Pd(0)-catalyzed coupling reactions of 2-(1-alkenyl)-1,3,2-benzodioxaboroles and other boron derivatives with six-membered enol triflates such as **2** (Scheme 1), bearing a *N*-Boc protecting group, would certainly extend the utility and scope of this class of compounds[8] in the preparation, and the further synthetic elaboration, of heterocyclic compounds.[1,2,9] Moreover, the *N*-Boc protection provides a possible alternative

Scheme 1



a: LiHMDS, HMPA, $PhNTf_2$, THF, -78 to 25 °C, 15 h.
b: $(Ph_3P)_2PdCl_2$, THF-H_2O, 2 M Na_2CO_3, 40 °C, 6-7 h.

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to other electron-withdrawing protecting groups such as *N*-tosyl,[1] *N*-Bz,[2,3] or *N*-Cbz,[2,9] since it is removable under different conditions.

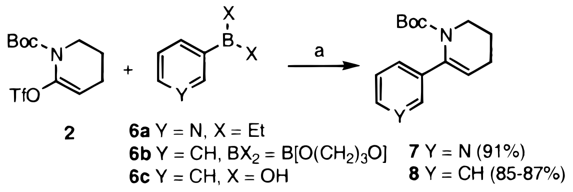
N-Boc enol triflate **2** was prepared in 75% yield by treatment of *N*-Boc lactam **1** with LiHMDS and *N*-phenyltriflimide, in the presence of HMPA.[3] The reaction of **2** with 2-[(*E*)-1-hexenyl]-1,3,2-benzodioxaborole **3a**[10] (Scheme 1) was first attempted under the classical conditions reported for the reaction of enol triflates with alkenylboronate, i.e., using $(Ph_3P)_4Pd$ catalyst in dioxane at 85 °C and K_3PO_4 as a base.[11] However, the reaction did not occur at all, recovering after 5 h the unreacted starting material **2**. Instead, when we used $(Ph_3P)_2PdCl_2$ as a catalyst (5% mol) in a THF−water mixture and in the presence of Na_2CO_3 as a base (Scheme 1), the reaction proceeded very fast at 80 °C, affording **4a**[12] after 2 h in 81% yield and with maintenance of the double bond geometry; the reaction rate was slightly slower at 40 °C (82% yield after 6 h), while at room temperature it reached completion (82% yield) after 16 h.

We tested also the more hindered $(o\text{-tol}_3P)_2PdCl_2$ for the reaction of **2** with **3a**, but the reaction was slower, furnishing **4a** in 16% yield after 48 h at room temperature.

Two other alkenylboronates, **3b**,**c**, prepared from the corresponding alkynes and catecholborane as reported,[10] were used as nucleophiles (Scheme 1). The reactions, always carried out with $(Ph_3P)_2PdCl_2$, were successful in providing the corresponding products **4b**,**c**. After 6 h at 40 °C, the conversion was complete in both cases. Compound **4b**, obtained in 76% yield, maintained the *E* geometry of the double bond. This compound in particular was quite acid sensitive, and even when left in $CDCl_3$ solution it underwent ring opening to give **5** in a 6:1 ratio with **4b** after 48 h (Scheme 1).

For the introduction of an aryl group, we found convenient the use of aryldiethylboranes, 2-aryl-1,3,2-dioxaborinanes, and arylboronic acids, such as commercially available compounds **6a**−**c** (Scheme 2). Diethyl(3-pyridyl)borane **6a** reacted fast with **2** under the usual conditions at 80 °C, providing **7** in 91% yield after 2 h. The reaction of boron derivative **6b** with **2** was complete after 3 h at 40 °C, affording 6-phenyl-substituted *N*-Boc 3,4-dihydro-2*H*-pyridine **8** in 85% yield. The same compound was obtained in 87% yield after 2 h at 40 °C using phenylboronic acid **6c**. In this case, we increased the volume of the aqueous 2 M Na_2CO_3 solution to avoid a possible ring opening of the product, which we observed when performing the reaction under the usual conditions.

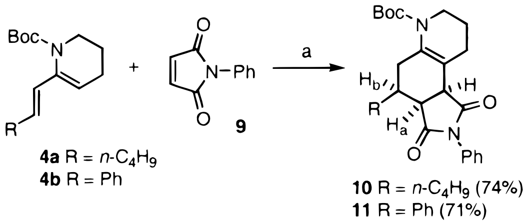
Scheme 2



a: $(Ph_3P)_2PdCl_2$, THF-H_2O, 2 M Na_2CO_3, 40-80 °C, 2-3 h

N-Boc-protected compounds **4a**−**c** are potential dienes for Diels−Alder reactions, as reported for closely related compounds in which the N atom bore a tosyl[1a] or a Cbz group.[9] We carried out the cycloaddition between **4a** and **4b** and *N*-phenylmaleimide **9** (2.5 equiv) (Scheme 3) in refluxing benzene obtaining, after 2 h, *endo*-cycloadducts **10** (74%) and **11** (71%) in which migration of the double bond to the more substituted position occurred.[9] The *endo* stereochemistry, easily assignable by the ^1H NMR coupling constant value of about 4.0 Hz between protons H_a and H_b (in cis relationship), is in accordance with the results obtained by Cha in the cycloaddition of *N*-phenylmaleimide with a similar *N*-Cbz-protected substrate.[9]

Scheme 3



a: PhH, reflux, 2 h

In conclusion, we have shown that the coupling reaction of alkenylboronates and other boron derivatives with six-membered lactam-derived *N*-Boc enol triflates is feasible under very mild conditions in THF−water employing $(Ph_3P)_2PdCl_2$ as a catalyst, which provides in high yields the corresponding 6-(1-alkenyl)- and 6-aryl-substituted *N*-Boc 3,4-dihydro-2*H*-pyridines. The former are useful dienes for Diels−Alder reactions in the construction of more complex heterocyclic structures.

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Supporting Information Available: Experimental procedures and characterization of compounds **4a**−**c**, **7**−**8**, **10**, and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[8] The extension of the methodology to five-membered enol triflates from *N*-acylpyrrolidin-2-ones is not immediate due to the high instability and difficulty in the isolation of these compounds (see refs 1a,b and 2).

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[12] All new compounds were fully characterized and gave satisfactory elemental analysis.