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Facile conversion of chromane-6-triflate to chromane-6-alanines under Palladium conditions

Daniel K. Miller^{a,b}

^aDepartment of Chemistry, University of Michigan, 930 N. University Avenue, Ann Arbor, Michigan, 48109

Abstract

Conversion of chromane-6-triflate **5** to chromane-6-dehydroalanine **9** or **10** via its Bpin-derivative **6** followed by Suzuki coupling with protected dehydroalanine bromides **7** or **8** were reported (86%). Alternatively, a palladium-catalyzed stannylation of **5** with Bu₆Sn₂ afforded the tributyltin derivative **11**, and iodination (**12**) followed by coupling with **13** gave chromane-6-alanine **15** (75%). Either approach constitutes a conversion from chromane-6-triflate to the corresponding protected chromane-6-alanine or its dehydro analog.

Keywords

Palladium-catalyzed coupling; Boronation; Stannylation; Aryl Triflate; Suzuki coupling

In connection with a synthetic project, we were interested in synthetic access to electron-rich phenylalanine derivative **4** or their potential dehydro precursors **3** from phenols **1** or triflates **2**. A structure-based search of electronic databases returned several options for relevant transformations starting from phenols, and interestingly literature also reported palladium-catalyzed coupling to build the key Ar-C bond. However, in each case, the outcome raised questions regarding overall yield or number of steps.^{1–4} On the other hand, most of these reports involved investigations where rapid access to the targets using reliable methods was probably the primary consideration. We were therefore encouraged to evaluate alternative routes from **1** to **3** or **4** that might improve overall efficiency, and that would provide a vehicle for expanding structure-based retrieval of the simple synthetic transform from **1** to **3** or **4** (Scheme 1).

The known triflate **5**⁵ was chosen as a precursor to demonstrate a Suzuki coupling approach⁶ via the corresponding pinacolboronate **6**, available in 96% yield from **5** using palladium-catalyzed boronation with bis(pinacolato)diboron, [pinB]₂, following literature analogies.^{7,8} Suzuki coupling of **6** with the known halogenated *N*-Boc dehydroamino acid derivative **7**⁹ or the derived *N*-bis-Boc analogue **8** was then conducted in the expectation that coupling efficiency would be high in the typically well-behaved sp²-sp² mode. Indeed, good yields of both **9** and **10** were obtained under these conditions (Scheme 1).⁶ The *Z*-geometry assigned to **9** was confirmed by a NOESY experiment, consistent with the previously established *Z*-

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Dkmiller2@bsu.edu; Phone: 765-620-0321, Fax: 765-285-6505.

^bPresent Address: Department of Chemistry, Ball State University Cooper Physical Science Building, room 305, Muncie, IN 47306.

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geometry of **7**.^{9a,c,10} In principle, enantioselective hydrogenation of **9** or **10** and analogous structures is possible using well known, high-yielding methods, and would provide access to either absolute configuration if desired.¹¹ The conversion from **5** to **9** or **10** constitutes a synthetic transform from triflates to dehydroamino acid derivatives.

An alternative version of the transform from chromane-6-triflate to a chromane-6-alanine was investigated via conversion to an intermediate aryl iodide (Scheme 2). First, the chromane-6-triflate **5** was reacted with hexabutylstannane in the presence of Pd(Ph₃P)₄/LiCl (dioxane, 90 °C, 12h) provided intermediate tributyltin derivative **11** according to NMR assay of the crude product.¹² Filtration over alumina and removal of unreacted hexabutylstannane under vacuum gave **11**, but material recovery was modest (46%) and attempted purification by chromatography over silica gel resulted in extensive protodestannylation due to the electron-rich aryl environment.¹³ Fortunately, this complication could be avoided by performing the iodination without isolating the intermediate **11**. Thus, reacting crude **11** with *N*-iodosuccinimide (NIS) in refluxing THF (4 days) gave the desired iodide **12** in 93% yield over the two steps from **5**.^{14,15} Coupling of chromane-6-iodide **12** with **13** (1.2 equiv) at RT (44 h) under the conditions developed by Jackson *et al.* in their initial studies¹⁷ proved relatively uneventful and gave the desired **15** in 47% yield. Using a re-optimized procedure the chromane-6-iodide **12** was used in the palladium-catalyzed Negishi coupling with the serine-derived organozinc reagent **13**¹⁶ together with SPhos (**14**) and Pd₂dba₃ as the Palladium source at room temperature resulting 75% yield of **15** and 70% yield from triflate **5**. Also, the literature procedure was slightly modified by using 2 equiv. of **13** to improve coupling efficiency with the relatively valuable iodide **12**, but the other variables were not changed.¹⁶ On the other hand, an attempt to use the same procedure starting from triflate **5** in place of the iodide gave only traces of **15** (<5%). The result was a 75% yield of **15** from iodide **12**¹⁸, or 70% from triflate **5** as shown in Scheme 2.

In summary, the desired conversion from triflate **5** to amino acid derivatives **9**, **10**, and **15** has been demonstrated. The sp²-sp² Suzuki coupling between the boronate **6** and alkenyl bromide **7** is somewhat higher yielding compared to the sp³-sp² Negishi coupling strategy (iodide **12** with **13**), but either approach offers improved efficiency compared to the literature alternatives¹⁻⁴ for analogous transformations. If the ultimate target is a protected amino ester, as represented by **15** in the current study, then either approach would involve three steps from the aryl triflate. The Suzuki coupling approach would require an enantioselective hydrogenation step¹¹ to access the chiral amino ester, but the other stages explicitly demonstrated in this report involve simple chemistry and provide the easiest access to the desired carbon framework.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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18. Procedure: Catalyst Pd₂dba₃ (22 mg, 0.025 mmol) and SPhos ligand (**14**; 21 mg, 0.05 mmol) were added in one portion to the solution of organozinc reagent **13** followed by syringe addition of iodide **12** (384 mg, 0.75 mmol) in DMF (0.5 mL). The mixture was stirred at room temperature overnight under a positive pressure of nitrogen. The crude reaction mixture was applied directly to a silica gel column and purified by flash column chromatography (9: 1 hexanes: ethyl acetate), to provide 331 mg (75%) of **15**

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