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Efficient and stereoselective synthesis of (*S*)-α-propargylglycine derivatives from allenylboronic acid

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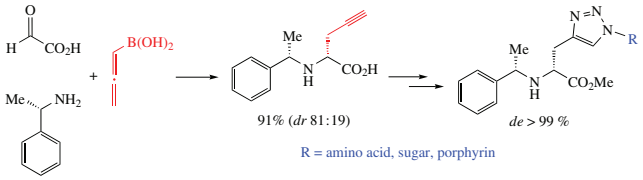
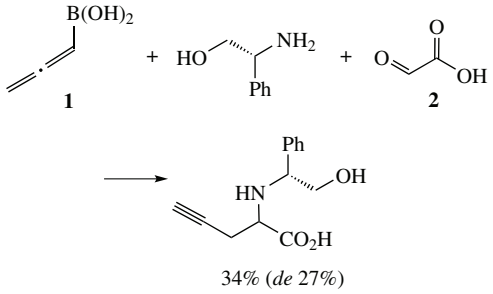
The Petasis–Mannich reaction of allenylboronic acid with glyoxylic acid and (*S*)-1-phenylethylamine diastereoselectively leads to N-substituted propargylglycine of high optical purity in good yield. This product can be further subjected to esterification followed by bioconjugate synthesis using Cu^{I}-catalyzed alkyne–azide 1,3-dipolar cycloaddition reaction ('click reaction').



Peptides modified with nonproteinogenic amino acids are useful building blocks for drug discovery. In particular, amino acids containing alkynyl moieties have been of interest since their incorporation into peptides opened up ample opportunities for the synthesis of large numbers of pharmaceutically relevant compounds.[1] The Petasis reaction is a powerful and atom-economical method for the construction of structurally diverse secondary or tertiary amine derivatives, and it has been widely employed as a key step in the synthesis of many bioactive molecules and complex natural products.[2–8] In general, the Petasis–Mannich reaction is performed between aldehyde, primary/secondary amine and organoboronic acid or boronate.[9–16]

Related reactions using allenylboronic acid or pinacol allenylboronate, however, have been less used. S. G. Pyne and coworkers reported the borono-Mannich reaction of salicylaldehyde, glycolaldehyde, and chiral α-hydroxy aldehydes with amines and commercially available pinacol allenylboronate.[17] Simultaneously, N. Petasis reported the reaction of allenylboronic acid **1** and its pinacol ester with glyoxylic acid **2** and amines,[18] where the ready access to α-propargyl amino acids or isomeric α-allenyl amino acids, depending on the regiochemistry of nucleophilic attack by allenylboronic acid, was described. Asymmetric synthesis of α-propargylglycine derivative was illustrated on a single example, however the product was obtained in a low yield and with poor diastereoselectivity (Scheme 1).

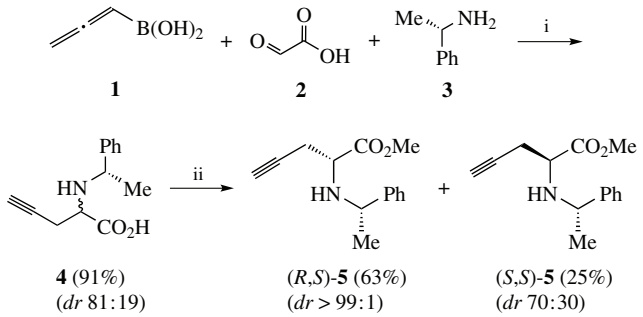


Scheme 1 See ref. 18.

The goal of our study was the Petasis–Mannich reaction-based synthesis of optically pure propargylglycine derivatives. α-Propargyl amino acids, especially enantiopure, are not readily accessible, while they can be substrates for the Cu^{I}-catalyzed 1,3-dipolar cycloaddition reaction with azides ('click reaction'), which should be valuable for the search for new bioactive molecules.[19–21]

We report here the results of our study of the borono-Mannich reaction of glyoxylic acid **2** with chiral (*S*)-α-phenylethylamine **3** and allenylboronic acid **1** (Scheme 2). The choice of amine was based on to the following reasons: (1) amine should induce stereoselective construction of the new chiral center, and (2) amino group of the product could be readily deprotected from chiral auxiliary *via* hydrogenation.

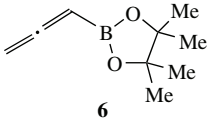
We carried out the synthesis of allenylboronic acid according to the published procedure.[22] In our hands, the three-component reaction between reactants **2**, **3** and freshly prepared allenylboronic acid **1** afforded desired amino acid **4** in high yield and with good diastereselectivity. Reaction occurred in dichloromethane at room temperature; the resulting α-propargylglycine derivative **4** was obtained in 91% yield and possessed 81 : 19 *dr* (see Scheme 2). Esterification of enantiomerically enriched derivative **4** (*dr* 62%) with methanol was performed routinely. The major and minor diastereomers of the resulting amino ester **5** were separated



Scheme 2 *Reagents and conditions:* i, CH_2Cl_2, room temperature; ii, MeOH, $SOCl_2$, then column chromatography.

by silica gel chromatography. The pure major isomer (*R,S*)-**5** was obtained in 63% yield (see Scheme 2).

The similar attempted three-component Petasis reaction comprising amine **3** and more stable pinacol allenylboronate **6** failed. Although various reaction conditions were tried (a range of solvents and temperature variation), the desired product **4** was not obtained. Probably, a combination of the bulky boronate ester with a branched amine was an obstacle for the reaction to occur.

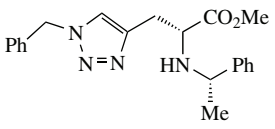


6

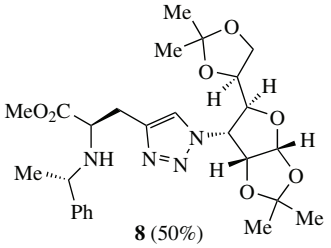
Taking into account the similarity of allenylboronic acid **1** and allylboronic acid we suggest identical Petasis–Mannich reaction mechanism for both reagents as well as absolute configuration of the main isomer of the synthesized products. The absolute configuration assignment of *N*-[(*S*)-1-phenylethyl]-substituted allylglycine methyl ester was made previously,[23] the (*R*)-configuration at α-carbon was deduced for the main diastereomer. So we can assume that (*R,S*)-configured amino ester **5** was predominantly obtained in the present work.

The application of (*R,S*)-**5** for the synthesis of triazole-linked conjugates from readily available azides *via* the Cu^{I}-catalyzed 1,3-dipolar cycloaddition reaction was further demonstrated. Benzyl azide was chosen for preliminary experiments for optimization of reaction conditions to ensure a high yield of the desired triazole **7**. Two catalytic systems could be equally applied: (1) $CuSO_4$ and sodium ascorbate and (2) CuI and DIPEA/DMF. For further studies, CuI/DIPEA/DMF system was selected.

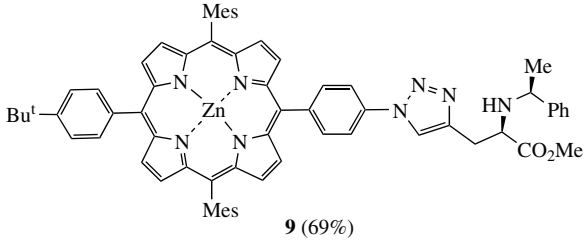
To examine the functional group tolerance of the 'click' protocol, the three biological objects (amino acid, sugar and porphyrin) were used for [3+2] cycloaddition with (*R,S*)-**5**. In this way, the expected bioconjugates **8**–**10** were obtained in good yields.



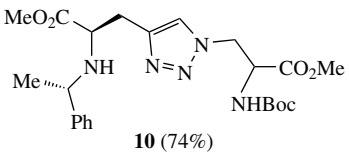
7 (87%)



8 (50%)



9 (69%)



10 (74%)

In summary, the reaction of allenylboronic acid **1** with glyoxylic acid and (*S*)-1-phenylethylamine is regiospecific and highly stereoselective, providing easy access to α-propargylglycine derivative **4**. Its further processing should ensure the preparation of a variety of promising new non-racemic bioconjugates.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.09.006.

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