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Asymmetric Petasis Borono-Mannich Allylation Reactions Catalyzed by Chiral Biphenols

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Abstract

Chiral biphenols catalyze the asymmetric Petasis borono-Mannich allylation of aldehydes and amines through the use of a bench-stable allyldioxaborolane. The reaction proceeds via a two-step, one-pot process and requires 2 – 8 mol% of 3,3'-Ph₂-BINOL as the optimal catalyst. Under microwave heating the reaction affords chiral homoallylic amines in excellent yields (up to 99%) and high enantioselectivities (e.r. up to 99:1). The catalytic reaction is a true multicomponent condensation reaction whereas both the aldehyde and the amine can possess a wide range of structural and electronic properties. Use of crotyldioxaborolane in the reaction results in stereodivergent products with *anti*- and *syn*-diastereomers both in good diastereoselectivities and enantioselectivities from the corresponding *E*- and *Z*-borolane stereoisomers.

COMMUNICATION

Aldehydes and amines are assembled with allylboronates in one-pot two-step procedure to provide chiral homoallylic amines. The reaction is catalyzed by chiral biphenols to afford the products in high enantioselectivities.

Keywords

enantioselective synthesis; organocatalysis; boronate; multicomponent reactions; imine allylation

The Petasis borono-Mannich reaction is a multicomponent condensation reaction of aldehydes, amines, and boronic acid nucleophiles.^[1] The reaction products have proven useful as building blocks for synthesis in academic and industrial settings.^[2] A specific

subset of this reaction uses allyl boronates as nucleophiles. The corresponding chiral homoallylic amines are also valuable building blocks for the synthesis of biologically and pharmacologically active molecules.^[3,4] Considerable efforts have been devoted to the development of a direct enantioselective allylation of imines.^[5–14] In addition, we introduced the use of chiral biphenols as catalysts in the enantioselective allylboration of acyl imines.^[15] However, the reaction did not leverage the most attractive nature of the Petasis–Borono-Mannich reaction, the multicomponent condensation giving rise to chiral amines that have different functionality at the aldehyde and amine component. We sought to develop a more general approach in performing the asymmetric allyl-Mannich reaction using amines and aldehydes in the imine formation step then performing the asymmetric allylboration reaction [Eq. (1)]. Herein, we report a highly enantioselective Petasis borono-Mannich reaction catalyzed by chiral biphenols in a one-pot procedure using aldehydes, amines, and allylboronates.

The challenge in performing an asymmetric allylation of imines is identifying a set of conditions that enable the use of amines and aldehydes that possess a wide range of steric and electronic properties; thereby maximizing the potential utility of the method. Notable asymmetric imine allylation methodologies use nitrogen protecting groups that can be removed subsequent to allylation such as acyl,^[7] phosphinoyl,^[8] sulfonyl,^[9] and silyl^[10] groups. Developing a reaction that would be highly enantioselective and yet general enough to permit the use of amines possessing different structural and electronic properties in the imine formation step is a significant challenge. Progress towards this goal include two notable examples of a three-component asymmetric imine allylation reaction employing *in-situ* generated imines. The condensation of aldehydes, 2-hydroxyaniline, and allyl tin reagents catalyzed by chiral scandium complexes in excellent enantioselectivities was reported in 2008.^[16] In addition, List and co-workers used fluorenylmethyl carbamate, aldehydes, and allyl silane in a chiral acid catalyzed imine allylation achieving high enantioselectivities.^[17] We sought to develop a methodology that would utilize the multicomponent strategy of the Petasis Borono-Mannich reaction, leveraging the ability to activate boronates for nucleophilic additions using chiral diols and biphenols developed by us^[15,18] and others^[19]. We envisioned a general method that was highly enantioselective irrespective of the imine used in the reaction.

(1)

The reaction of benzaldehyde **1a** with *p*-anisidine **2a** was first evaluated as the aldehyde and amine component in the Petasis reaction. Performing a screen of chiral biphenol catalysts with the pure imine identified 3,3'- Ph_2 -BINOL catalyst **4** as the optimal catalyst (see

Supporting Information for details); consistent to what was observed in the asymmetric allylboration of acyl imines.^[15] Using on 2 mole % of the catalyst was enabled by the addition of *t*-BuOH as an additive to the neat reaction, an observation we made in the asymmetric allylboration of ketones.^[18f] A one-pot procedure was subsequently developed. A mixture of benzaldehyde **1a** and *p*-anisidine **2a** in the presence of 3Å molecular sieves was stirred in dichloromethane at room temperature; after concentration, to the crude aldimine was added *t*-BuOH, 3,3'-Ph₂-BINOL catalyst **4** and cyclic allyldioxaborolane **3**. The reaction was then subjected to microwave irradiation conditions, 10 Watts achieving 50 °C, affording the allylation product amine **5a** in 90% isolated yield and 97:3 enantiomeric ratio (e.r., Scheme 1). The observed enantioselectivity was consistent with the reaction of allyldioxaborolane with acyl imines.^[15]

We examined the scope of the Petasis allylation reaction using *p*-anisidine as the amine with the objective of identifying the structural and electronic parameters of the aldehyde component that resulted in good yields and selectivities. In general, electron-deficient aromatic aldehydes produced excellent yields and enantioselectivities (Scheme 1, **5b–5g**). Electron-rich aromatic aldehydes were less reactive under the optimized conditions; however, better yields were obtained when higher catalyst loadings (4 mol%) and conventional heating for an extended period of time (**5h–5i**). Heteroaromatic aldehydes were also determined to be good substrates for the reaction (**5k** and **5l**) as was 2-naphthaldehyde (**5j**). The general reaction conditions were also effective for aliphatic aldehydes.^[20] Cyclohexane-carboxaldehyde afforded the homoallylic product **5p** in excellent yield and enantioselectivity (93% yield, 99:1 e.r.). Notably, ethyl glyoxylate could be employed as an substrate, affording the chiral alpha-amino ester **5s** in 70% yield and 97:3 e.r.^[21,22] Branched aliphatic aldehydes isovaleraldehyde and pivaldehyde, while challenging substrates for other methods, were also excellent substrates, affording the products **3t** and **3u** in great enantioselectivities (>97:3 e.r.) and good yields (70 and 57% isolated yield respectively).

We next performed experiments to assess the use of amines possessing different electronic and steric properties in the multicomponent condensation reaction (Scheme 2). Cyclohexane carboxaldehyde was chosen as a representative aliphatic aldehyde and aryl amines were first evaluated. Substitution at the *para*-position with both electron-donating and electron-withdrawing groups resulted in similar yields and enantioselectivities (98:2 e.r., Scheme 2, **6a–6d**). Substitution at the *meta*-position led to similar results in enantioselectivity (**6e** and **6f**), and 2-bromoaniline afforded *ortho*-substituted homoallyl amine **6h** in excellent enantiomeric purity (99:1 e.r.), demonstrating tolerance for substituents at the *ortho* positions. 2-Naphthylamine also proved to be an excellent substrate in the Petasis allylation reaction (**6g**). However, 2-amino pyridine afforded the desired product **6i** in lower yield, even when conventional heating reaction conditions were employed, attributed to the coordinating ability of the pyridine nitrogen. However, the product was still isolated in 50% yield and 96:4 e.r.

Petasis condensation products of fluorinated and oxygenated anilines exhibit utility in the synthesis of anti-bacterials and antifungals.^[23] Bearing this in mind condensation products **6j** and **6k** were obtained with excellent yields and selectivities (98:2 e.r.). We then evaluated

the use of aliphatic amines in the Petasis borono-Mannich reaction. Chiral homoallylic amine products derived from aliphatic amine Mannich allylation reactions are challenging to achieve in high enantio-selectivities,^[14] although important for natural product and bioactive molecule synthesis.^[24] Higher biphenol catalyst concentrations enabled the use of *p*-methoxy-benzylamine and allylamine in the Petasis allylation reaction, affording **6l** and **6m** in excellent yields and enantioselectivities (>95:5). Products such as the di-olefin **6m** serve as precursors for ring closing metathesis, utilized as building blocks in synthesis.^[25] Furthermore, aliphatic aldehydes were also successfully used with benzylamine (**6n** and **6o**) further demonstrating the scope of the asymmetric Petasis borono-Mannich allylation reaction.

We then turned our attention to the asymmetric Petasis crotylation reaction of imines. Crotylboration is expected to proceed through a Zimmerman-Traxler transition state (TS), resulting in high diastereoselectivities.^[6,26] However, the stereochemical outcome of imine crotylboration can be complicated by factors: 1) whether a boat TS^[15] or a chair TS is involved in the reaction and 2) spontaneous *E/Z* isomerization of the imines^[27] prior to crotylboration.^[26] As anticipated, (*E*)-crotylboronate **7** resulted in the formation of the *anti*-diastereomer **9a** in high diastereo- and enantioselectivity. Conversely, (*Z*)-crotylboronate **8** afforded the *syn*-diastereomer **10a** predominantly in low e.r. yield and d.r. (9:1, Scheme 3).

The observed enantioselectivity and diastereoselectivity was consistent with the reaction of (*E*)-crotyl boronate with acyl imines.^[15] In contrast, the (*Z*)-crotyl boronate afforded the anticipated *syn* product in the present study.^[26] The observed enantioselectivity but lower diastereoselectivity and yield for (*Z*)-crotylboration can be attributed to a pseudo-diaxial interaction between the crotyl-methyl group on the boronate and the aryl substituent of *in situ* isomerized *Z*-imine.^[26] The benzyl amine imine was also evaluated in the crotylation reaction. The (*E*)- and (*Z*)-crotylboronate afforded the corresponding *anti*- and *syn*-diastereomers in excellent diastereoselectivities and enantioselectivities (Scheme 3). The *syn*-diastereomer **10b** was achieved in a higher diastereoselectivity in comparison to **10a**; attributed to the free rotation introduced by the additional methylene of the benzyl group reducing the steric interaction in the transition state between the (*Z*)-crotylmethyl group and the *N*-benzyl substituent.

In summary, we have developed an asymmetric Petasis borono-Mannich allylation reaction that affords chiral homoallylic amines using chiral biphenol catalysts. The enantioselective reaction is tolerant of aldehydes and amines possessing a range of electronic and steric properties. The reaction is operationally straightforward; a one-pot, two-step procedure affording the chiral amine products in excellent yields and enantioselectivities. Furthermore, the crotylboration reactions provide access to both *syn*- and *anti*-diastereomers which bear two vicinal stereogenic centers. The generality of the imine condensation step indicates a broader utility of the allylation products than has been previously observed for enantioselective allylation reactions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Scheme 1.

Aldehyde substrate scope.^[a] [a] Unless noted otherwise, all reactions were run in the following conditions: aldehyde (0.4 mmol), *p*-anisidine (0.8 mmol) and 3 Å molecular sieves (350 mg) were mixed in CH₂Cl₂ (1 mL) at room temperature for 2 h then concentrated in vacuo by rotary evaporation and high vacuum; then allylboronate (0.6 mmol), catalyst (0.012 mmol), *t*-BuOH (1.2 mmol) were added and submitted to the microwave reactor held at 10 W for 1 h. [b] Conventional heating at 50 °C for 24 h. [c] 4 mol% catalyst.

Scheme 2.

Amine substrate scope.^[a] [a] Unless noted otherwise, all reactions were run in the following conditions: aldehyde (0.4 mmol), amine (0.8 mmol) and 3 Å molecular sieves (350 mg) were mixed in CH₂Cl₂ (1 mL) at room temperature for 2 h then concentrated in vacuo by rotary evaporation and high vacuum; then allylboronate (0.6 mmol), catalyst (0.012 mmol), *t*-BuOH (1.2 mmol) were added and submitted to the microwave reactor held at 10 W for 1 h. [b] Conventional heating at 50 °C for 24 h. [c] 4 mol% catalyst. [d] 0.4 mmol (1 equiv) amine. [e] 8 mol% catalyst.

83% y, 98:2 er, >20:1 dr

35% y, 96:4 er, 9:1 dr

89% y, 95:5 er, >20:1 dr

61% y, 99:1 er, >20:1 dr

Scheme 3.

Asymmetric crotylation. [a] 2 mol% catalyst. [b] 4 mol% catalyst. [b] 8 mol% catalyst.