Direct Synthesis of N-Protected Serine- and Threonine-Derived Weinreb Amides via Diboronic Acid Anhydride-Catalyzed Dehydrative Amidation: Application to the Concise Synthesis of Garner’s Aldehyde

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Direct Synthesis of Weinreb Amides

An efficient method for the direct synthesis of Weinreb amides, 1 are useful functional groups that can be easily protected serine-derived Weinreb amide is an important intermediate in the synthesis of Garner's aldehyde. 6, 7 Although Weinreb amides have been synthesized from simple products, 8 catalytic versions of the dehydrative amidation of Weinreb amides by means of organoboron catalysis has been developed. 19, 20

Recently, some condensation conditions using EDCI, HBTU, HATU, CDI, and T3P 13 as coupling reagents were applied to the synthesis of β-hydroxy-α-amino acid derived Weinreb amides. However, these conditions require stoichiometric amounts of reagents, resulting in cumbersome workup and purification procedures and poor atom economy. Therefore, the development of an environmentally benign catalytic version of the dehydrative amide condensation reaction is highly demanded (Scheme 1a). Starting with Yamamoto’s pioneering report on the catalytic dehydrative condensation of carboxylic acids with amines using electron-deficient aromatic boronic acids, 14 a variety of amidations and peptide synthesis utilizing organoboron catalysts, such as modified aromatic boronic acids, 15 18 diboron, 19 borate esters, 20 DATB, 21 and gem-diboronic acid, 22 have been developed. In this context, we disclosed that a diboronic acid anhydride possessing the B–O–B motif 23 is a highly efficient catalyst for the dehydrative amidation of α- or β-hydroxycarboxylic acids 24 a or β-hydroxy-α-amino acids. 24b More recently, we found that this hydroxy-directed amidation reaction could be also applied to the reaction of α- or β-hydroxycarboxylic acids with weakly nucleophilic N,O-dimethyhydroxylamine, demonstrating the first catalytic synthesis of Weinreb amides from carboxylic acids

N-Methoxy-N-methylamides, commonly called Weinreb amides, 1 are useful functional groups that can be easily converted into aldehydes or modified ketones in organic synthesis. 2 Especially, Weinreb amides derived from β-hydroxy-α-amino acids such as serine or threonine have been widely used as chiral building blocks for the synthesis of complex products. 3 Moreover, N-tert-butoxycarbonyl (Boc) protected serine-derived Weinreb amide is an important synthetic intermediate for Garner’s aldehyde, 4, 5 which is, in turn, a versatile chiral intermediate in the synthesis of natural products and biologically active chiral compounds. Figure 1. 6, 7 Although Weinreb amides have been synthesized from various precursors such as esters, amides, imides, aldehydes, alcohols, aryl halides, and acid chlorides, 2 the condensation reaction of carboxylic acids with N,O-dimethyldecarboxylamime is the most straightforward method. To this end, a number of coupling reagents have been developed. 8

Abstract

An efficient method for the direct synthesis of Weinreb amides derived from serine and threonine derivatives via diboronic acid anhydride-catalyzed hydroxy-directed amidation is described. This is the first successful example of the synthesis of serine- or threonine-derived Weinreb amides using catalytic dehydrative amidations. The methodology could be applied to the concise synthesis of Garner’s aldehyde.

Key words
dehydrative amidation, Weinreb amide, Garner’s aldehyde, organoboron catalysis, diboronic acid anhydride, hydroxy-directed reaction

Figure 1 Structures of Weinreb amides and Garner’s aldehyde
Herein, we report an efficient method for the direct preparation of N-protected serine- and threonine-derived Weinreb amides via diboronic acid anhydride-catalyzed dehydrative amidations (Scheme 1c). The synthetic utility of this catalytic system is demonstrated by its application to the concise synthesis of Garner’s aldehyde.

On the basis of our previous work, we initially explored the dehydrative amidation of N-Boc-protected serine-derivative Weinreb amides (2a) with 3.0 equivalents of N,O-dimethylhydroxylamine (3) in the presence of 2.0 mol% of diboronic acid anhydride 1 (Table 1). The reaction in toluene proceeded smoothly at 90 °C to give serine-derived Weinreb amide 4a in 60% yield (entry 1). A survey of solvents revealed that 1,2-dichloroethane (DCE) was the optimal solvent for this transformation (entries 2–4). We also performed a screening of the amount of amine 3, finding that a reduction to 2.0 equivalents dropped the yield to 50% (entry 5), whereas an increase to 5.0 equivalents did not change the yield (entry 6). Moreover, prolonging the reaction time resulted in an improved yield of Weinreb amide 4a to 93% isolated yield (entry 7). It is significant that 4a was obtained without any racemization at the α-position of the amino acid, which was confirmed by chiral high-performance liquid chromatography (HPLC) analysis. By using 1 as a catalyst, Weinreb amide 4a was also successfully synthesized in a gram scale (entry 8). A high product yield of 84% was maintained even when reducing the catalyst loading to 1.0 mol% (entry 9), whereas a slight decrease in the yield (70%) was observed with 0.5 mol% of catalyst 1 (entry 10). In the absence of catalyst 1, the reaction hardly proceeded, affording a low 3% yield (entry 11). These results demonstrate the usefulness of diboronic anhydride 1 for the preparation of N-Boc-protected serine-derived Weinreb amide. To the best of our knowledge, this is the first example of a catalytic synthesis of Weinreb amides derived from amino acids.

By using diboronic acid anhydride 1 as a catalyst, we then explored the dehydrative amidation of several serine-derivatives possessing different N-protected groups (Scheme 2). High product yields with minimum racemization were consistently observed with either N-Cbz-serine (2b) or N-Fmoc-serine (2c), giving the corresponding Weinreb amides 4b and 4c in 95% and 92% yields, respectively. We next turned our attention to the reaction of threonine derivatives, a residue that bears an additional methyl group at the β-position. Gratifyingly, N-Boc-threonine (2d) and N-Cbz-threonine (2e) were applicable as substrates, and the corresponding Weinreb amides 4d and 4e were obtained in 89% and 90%, respectively; however, in this case, an increased catalyst loading of 5.0 mol% was necessary to obtain satisfactory product yields.

In this catalytic reaction, the desired Weinreb amide 4a was obtained in 92% yield even when using a commercially available N,O-dimethylhydroxylamine hydrochloride.

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**Table 1** Optimization of Dehydrative Amidation Conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>1 (x mol%)</th>
<th>3 (y equiv)</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>2.0</td>
<td>3.0</td>
<td>toluene</td>
<td>4</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>2.0</td>
<td>3.0</td>
<td>C6H5Cl</td>
<td>4</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>2.0</td>
<td>3.0</td>
<td>C6H6CF3</td>
<td>4</td>
<td>63</td>
</tr>
<tr>
<td>4</td>
<td>2.0</td>
<td>3.0</td>
<td>DCE</td>
<td>4</td>
<td>74</td>
</tr>
<tr>
<td>5</td>
<td>2.0</td>
<td>2.0</td>
<td>DCE</td>
<td>4</td>
<td>50</td>
</tr>
<tr>
<td>6</td>
<td>2.0</td>
<td>5.0</td>
<td>DCE</td>
<td>4</td>
<td>74</td>
</tr>
<tr>
<td>7</td>
<td>2.0</td>
<td>3.0</td>
<td>DCE</td>
<td>24</td>
<td>96 (93)</td>
</tr>
<tr>
<td>8</td>
<td>2.0</td>
<td>3.0</td>
<td>DCE</td>
<td>24</td>
<td>82</td>
</tr>
<tr>
<td>9</td>
<td>1.0</td>
<td>3.0</td>
<td>DCE</td>
<td>24</td>
<td>84</td>
</tr>
<tr>
<td>10</td>
<td>0.5</td>
<td>3.0</td>
<td>DCE</td>
<td>24</td>
<td>70</td>
</tr>
<tr>
<td>11</td>
<td>–</td>
<td>3.0</td>
<td>DCE</td>
<td>24</td>
<td>3</td>
</tr>
</tbody>
</table>

* The reactions were performed in the presence of N-Boc serine (2a, 0.10 mmol, 1.0 equiv), HNMe(Ome) (3), and catalyst 1 in a certain solvent (0.20 M, 1.0 mL) at 90 °C (bath temp). The optical purity of amide 4a was determined by chiral HPLC analysis.

a Yields were determined by 1H NMR of the crude reaction mixture of products using t,1,2,2-tetrachloroethane as an internal standard. Isolated yields are in parentheses.

b Determined at 1 g scale.
was then reduced with LiAlH₄ converted into oxazoline amine conditions, and the resulting crude Weinreb amide administratively amidation catalyzed by diboronic acid anhydride (Scheme 4).²⁷ Commercially available we conducted the concise synthesis of Garner’s aldehyde (4a) in 89% yield over three steps without any loss of optical purity.

Finally, to demonstrate the synthetic utility of the dehydration amidation catalyzed by diboronic acid anhydride 1, we conducted the concise synthesis of Garner’s aldehyde (5) in three steps with a single purification. Furthermore, the present protocol could be adapted easily to a gram-scale synthesis, which afforded 5 in 75% yield over three steps without any loss of optical purity.

In conclusion, we have successfully developed a catalytic synthesis of Weinreb amides derived from β-hydroxy-α-amino acids using diboronic anhydride 1 as the catalyst. This hydroxy-directed amidation reaction provides N-protected serine- or threonine-derived Weinreb amides with high optical purity, while the racemization at the α-position of the carbonyl groups is suppressed. Furthermore, the practical utility of this method is demonstrated by conducting the concise synthesis of Garner’s aldehyde (5), which is widely used as a chiral building block.

Conflict of Interest
The authors declare no conflict of interest.

Funding Information
JSPS KAKENHI Grant Number 19K07000 to N.S. for Scientific Research (C).

Acknowledgment
We thank Dr. K. Nagai and Ms. N. Sato at Kitasato University for instrumental analyses.

Supporting Information
Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610773.


(25) Procedure for the Catalytic Synthesis of Weinreb Amide 4a

Table 1, Entry 8, 1 g Scale

N-O-Dimethylhydroxylamine (3, 25.0 mL, 0.60 M in DCE, 15.0 mmol, 3.0 equiv) was added dropwise over 1 h to a suspension of diboronic acid anhydride 1 (54.0 mg, 0.100 mmol, 2.0 mol%) and Boc-Ser-Oh (2a, 1.03 g, 5.00 mmol, 1.0 equiv) in DCE (8.3 mL, total 0.15 M) under reflux (bath temp, 90 °C). After stirring for 24 h under reflux, the reaction mixture was cooled to room temperature. Concentration under reduced pressure furnished the crude product, which was purified by silica gel column chromatography (5% MeOH in CHCl₃) to give tert-butyl (S)-(3-hydroxy-1-{[methoxy[methyl]amino]-1-oxopropan-2-yl]carboxylate (4a, 1.02 g, 4.08 mmol, 82%). The optical purity of 4a was determined to be >99% ee by chiral HPLC analysis.

Analytical Data for Compound 4a

\[ \text{R}_t = 0.35 \text{ (CHCl₃}/\text{MeOH} = 19:1) ; [\alpha]_D^{24} = 14.2 (c 1.0, MeOH); \text{ mp} = 110–115 °C \text{ NMR (400 MHz, CDCl₃): } \delta = 5.58 (br s, 1 H), 4.80 (br s, 1 H), 3.83–3.81 (m, 2 H), 3.78 (s, 3 H), 3.23 (s, 3 H), 1.45 (s, 9 H); \text{ ¹³C NMR (100 MHz, CDCl₃): } \delta = 171.0, 155.7, 79.8, 63.2, 61.5, 52.4, 32.0, 28.2, \text{ IR (KBr): } \nu = 3471, 3357, 2978, 1060, 1704, 1537, 1363, 1297, 1181, 980, \text{ cm}^{-1} \text{ HRMS (ESI): } [{\text{M} + Na}^{+}] = 271.1270; \text{ found: 292.1266. HPLC (CHIRALPAK IC), hexane/ProOH = 80:20, 230 nm, flow rate 1.0 mL/min: } \text{ tᵢ = 14.4 min (minor), 26.4 min (major).} \]
(26) In order to compare the catalytic efficiency with 1, we examined the reaction using several organoboron and metal catalysts. As a result, it was shown that 1 exhibits higher catalytic activity compared to previous catalysts under the same conditions. See SI-Table 1 in the Supporting Information for details.

(27) Procedure for the Synthesis of Garner's Aldehyde (5, Scheme 4, 1 g Scale)

N,O-Dimethylhydroxylamine (3, 25.0 mL, 0.60 M in DCE, 15.0 mmol, 3.0 equiv) was added dropwise over 1 h to a suspension of diboronic acid anhydride 1 (54.0 mg, 0.100 mmol, 2.0 mol%) and Boc-Ser-OH (2a, 1.03 g, 5.00 mmol, 1.0 equiv) in DCE (8.3 mL, total 0.15 M) under reflux (bath temp 90°C). After stirring for 24 h under reflux (bath temp 90°C), the reaction mixture was cooled to room temperature. Concentration under reduced pressure furnished the crude product, which was subjected to the next step without further purification. BF₃·OEt₂ (125 μL, 1.00 mmol, 0.2 equiv) was added to a solution of the crude mixture and 2,2-dimethoxy propane (3.68 mL, 30.0 mmol, 6.0 equiv) in acetone (16.6 mL, 0.3 M). After stirring for 24 h at room temperature, Et₃N (1.0 mL) was added, and the solvent was removed under reduced pressure to give a brown oil, which was dissolved in EtOAc (120 mL). The resulting organic layer was washed with saturated NaHCO₃ aq (30 mL), water (30 mL), and brine (30 mL) successively and dried over Na₂SO₄. Filtration and concentration under reduced pressure furnished the crude product, which was purified by silica gel column chromatography (20% EtOAc in n-hexane) to give Garner's aldehyde (5, 860 mg, 3.74 mmol, 75% over 3 steps) as a pale yellow oil of rotamer mixture (major/minor = 59:41).

Analytical Data for Compound 5

Pale yellow oil; Rf = 0.33 (n-hexane/EtOAc = 1:1.5); [α]D₂⁵ -93.1 (c = 1.0, CHCl₃). 1H NMR (400 MHz, CDCl₃, rotamer*): δ = 9.61* (br, 0.41 H), 9.55 (br, 0.59 H), 4.34* (br, 0.41 H), 4.20 (br, 0.59 H), 4.12–4.07 (m, 2 H), 1.66–1.44 (m, 15 H). 13C NMR (100 MHz, CDCl₃, rotamer*): δ = 199.3, 152.5*, 151.3, 95.0, 94.3*, 81.3*, 81.0, 64.6, 63.8, 63.4*, 28.2, 26.6*, 25.7, 24.6*, 23.7. IR (neat): ν = 2980, 1709, 1367, 1266, 1171, 1095, 1062, cm⁻¹. HRMS (ESI): m/z calcd for C₁₄H₂₀N₂NaO₅ [M + Na]⁺: 252.1212; found: 252.1210.

(28) The optical purity of 5 was determined to be >99% ee by chiral HPLC analysis after conversion into the corresponding benzoate (for details see the Supporting Information).