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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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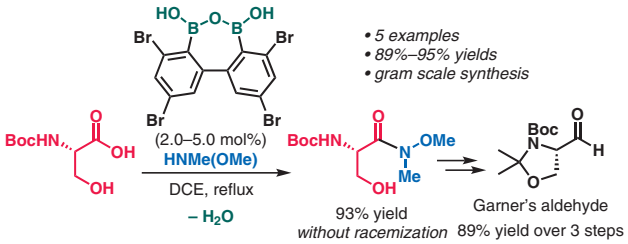

Catalytic synthesis of serine- and threonine-derived Weinreb amides

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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

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*-dimethylhydroxylamine is the most straightforward method. To this end, a number of coupling reagents have been developed.[8]

Recently, some condensation conditions using EDCI,[9] HBTU,[10] HATU,[11] CDI,[12] 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 amide 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[24a] 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*-dimethylhydroxylamine, demonstrating the first catalytic synthesis of Weinreb amides from carboxylic acids

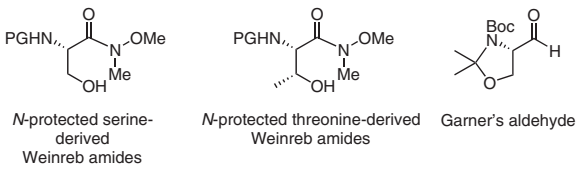

Figure 1 Structures of Weinreb amides and Garner's aldehyde

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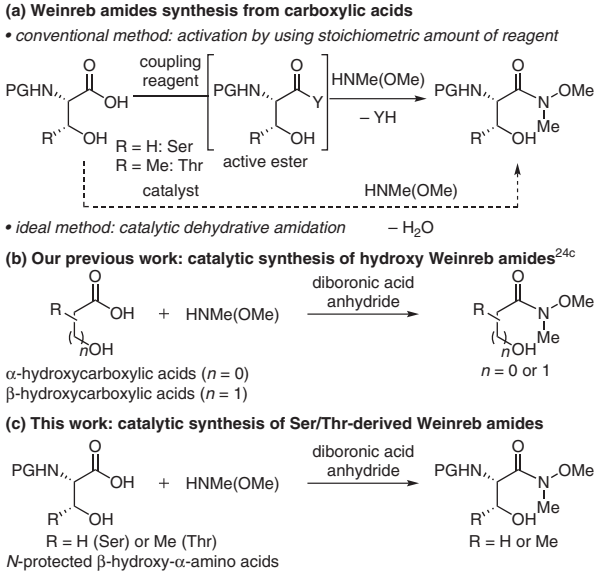
(Scheme 1b).[24c] Herein, we report an efficient method for the direct preparation of *N*-protected serine- and threonine-derived Weinreb amides via diboronic acid anhydride-catalyzed dehydrative amidations (Scheme 1c). The synthetic utility of this catalytic system is demonstrated by its application to the concise synthesis of Garner's aldehyde.



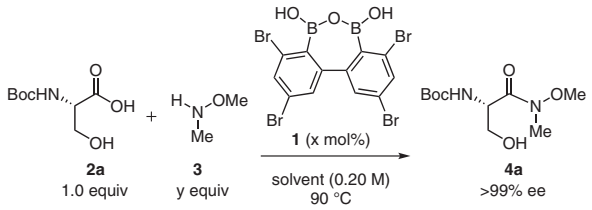
Scheme 1 Synthesis of Weinreb amides

On the basis of our previous work, we initially explored the dehydrative amidation of *N*-Boc-protected serine (**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).[25] 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.[26] 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

Table 1 Optimization of Dehydrative Amidation Conditions[a]



Entry	**1** (x mol%)	**3** (y equiv)	Solvent	Time (h)	Yield (%)[b]
1	2.0	3.0	toluene	4	60
2	2.0	3.0	C_6H_5Cl	4	70
3	2.0	3.0	$C_6H_5CF_3$	4	63
4	2.0	3.0	DCE	4	74
5	2.0	2.0	DCE	4	50
6	2.0	5.0	DCE	4	74
7	2.0	3.0	DCE	24	96 (93)
8[c]	2.0	3.0	DCE	24	(82)
9	1.0	3.0	DCE	24	84
10	0.5	3.0	DCE	24	70
11	–	3.0	DCE	24	3

[a] 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.
[b] Yields were determined by ^{1}H NMR of the crude reaction mixture of products using 1,1,2,2-tetrachloroethane as an internal standard. Isolated yields in parentheses.
[c] Performed at 1 g scale.

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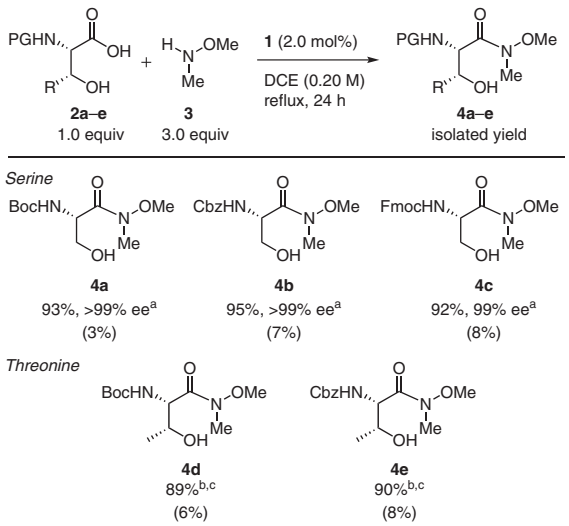
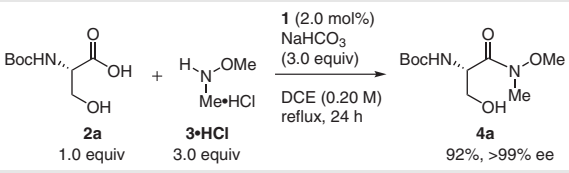


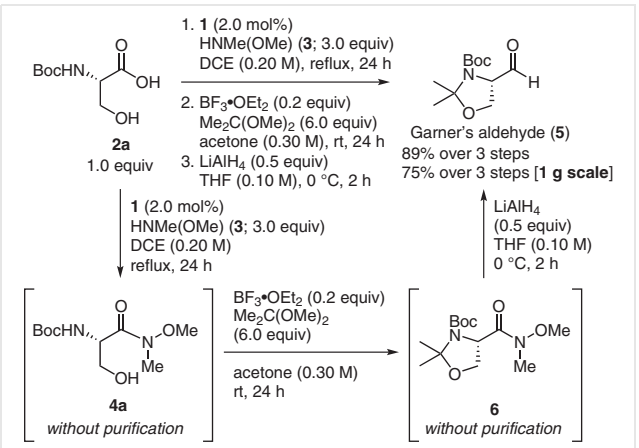
Scheme 2 Catalytic synthesis of β-hydroxy-α-amino acid derived Weinreb amides.*Reagents and conditions*: The reactions were conducted in the presence of *N*-protected β-hydroxy-α-amino acid **2** (0.10 mmol, 1.0 equiv), HNMe(OMe) (**3**, 0.30 mmol, 3.0 equiv), and catalyst **1** (2.0 mol%) in DCE (0.20 M, 0.50 mL) under reflux (bath temp, 90 °C). Percentages in parentheses are the yields in the absence of catalyst **1** determined by ^{1}H NMR analysis of the crude reaction mixture of products using 1,1,2,2-tetrachloroethane as an internal standard. [a] Determined by chiral HPLC analysis. [b] Performed with 5.0 mol% of catalyst **1**. [c] The significant epimerization was not observed by ^{1}H NMR analysis.

(**3**·HCl) in the presence of sodium hydrogen carbonate (Scheme 3). This could be an operational advantage, since the prerelease of the free amine is not required. It is also noteworthy that racemization was completely suppressed, and **4a** was obtained with an excellent optical purity of >99% ee.



Scheme 3 Catalytic synthesis of Weinreb amide using HNMe(OMe)·HCl salt

Finally, to demonstrate the synthetic utility of the dehydrative amidation catalyzed by diboronic acid anhydride **1**, we conducted the concise synthesis of Garner's aldehyde (**5**, Scheme 4).[27] Commercially available *N*-Boc-serine (**2a**) and amine **3** were treated with catalyst **1** under the optimized conditions, and the resulting crude Weinreb amide **4a** was converted into oxazoline **6** without purification. The latter was then reduced with $LiAlH_4$[6] to furnish aldehyde **5** in 89% yield over three steps. This result indicates that our method is practical and efficient, enabling the preparation 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.[28]



Scheme 4 Concise synthesis of Garner's aldehyde (**5**) via diboronic acid anhydride catalyzed dehydrative amidation

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.

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Supporting Information

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

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(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 $CHCl_3$) to give *tert*-butyl (*S*)-(3-hydroxy-1-[methoxy(methyl)amino]-1-oxopropan-2-yl)carbamate (**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
R_f = 0.35 ($CHCl_3$/MeOH = 19:1); $[\alpha]_D^{25}$ 14.2 (*c* 1.0, MeOH); mp 116–117 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 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). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0, 155.7, 79.8, 63.2, 61.5, 52.4, 32.0, 28.2. IR (KBr): ν = 3473, 3357, 2978, 1060, 1704, 1537, 1363, 1297, 1181, 980, cm^{-1}. HRMS (ESI): *m/z* calcd for $C_{10}H_{20}N_2NaO_5$ [M + Na]$^+$: 271.1270; found: 292.1266. HPLC (CHIRALPAK IC?, hexane/*i*-PrOH = 80:20, 230 nm, flow rate 1.0 mL/min): t_R = 14.4 min (minor), 26.4 min (major).

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(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. $BF_3{\cdot}OEt_2$ (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, Et_3N (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 $NaHCO_3$ aq (30 mL), water (30 mL), and brine (30 mL) successively and dried over Na_2SO_4. Filtration and concentration under reduced pressure furnished the crude product, which was subjected to the next step without further purification. $LiAlH_4$ (2.50 mL, 1.0 M in THF, 2.50 mmol, 0.50 equiv) was added dropwise to a solution of the crude mixture in THF (50 mL, 0.1 M) at 0 °C. After stirring for 1 h at 0 °C under N_2 atmosphere, saturated $KHSO_4$ aq (5 mL) was added carefully. The mixture was diluted with Et_2O (120 mL) and washed by water (30 mL) and brine (30 mL) successively and dried over Na_2SO_4. 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).[28]

Analytical Data for Compound 5

Pale yellow oil; R_f = 0.33 (*n*-hexane/EtOAc = 1:1.5); $[\alpha]_D^{25}$ –93.1 (*c* = 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, 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). ^{13}C NMR (100 MHz, $CDCl_3$, 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 $C_{14}H_{20}N_2NaO_5$ $[M + Na]^+$: 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).

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