Gram-Scale Electrosynthesis of Protected Dehydroamino Acids

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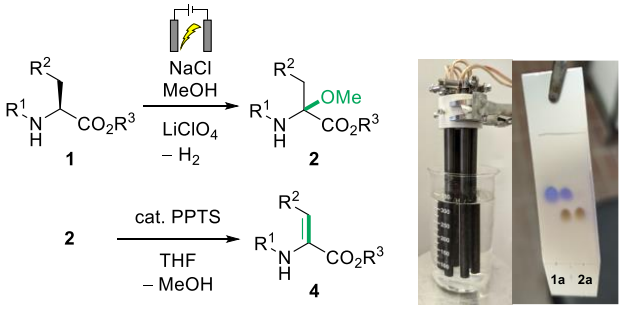
Supporting Information Placeholder



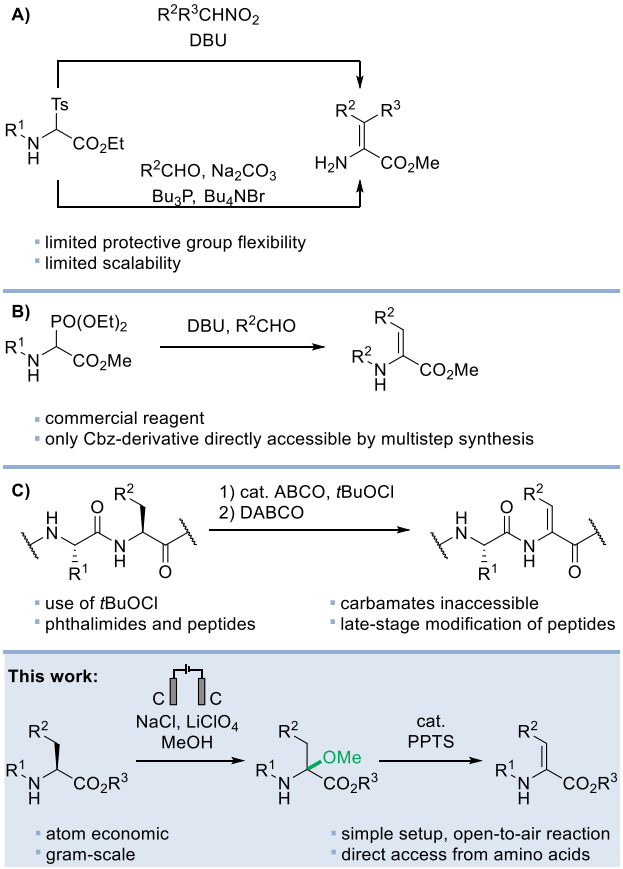
ABSTRACT: A NaCl-mediated electrochemical oxidation of amino acid carbamates (R^1 = Boc, Cbz) afforded α-methoxylated α-amino acids. Subsequent acid-catalyzed elimination delivered valuable dehydroamino acid derivatives. The simplicity of our open-to-air setup using simple graphite-electrodes submerged in a beaker was showcased producing *N*-Boc-ΔAla-OMe on decagram scale.

α,β-Dehydroamino acids (dhAAs) exhibit unique reactivity due to their combined electronic contributions of the nitrogen and carbonyl substituents and due to their pronounced somophilicity. Polar and radical additions have been exploited in the late-stage-functionalization of dhAA-containing peptides and natural products.[1] While dehydroalanine and dehydrobutyrine derivates are accessible from their respective serine, cysteine and threonine derivatives,[2] the synthesis of other dhAAs remains challenging.

Kinoshita reported two methods using *N*-Cbz-tosyl glycinates and nitro compounds[3] or aldehydes[4] in an alkylation/nitrite elimination-cascade or Wittig-type reaction, respectively (Scheme 1A). These approaches allow access to a variety of substituted dhAAs but are limited in the protective groups on the tosyl glycine derivative and the accessibility of their respective coupling partners. An alternative strategy utilizes the Schmidt reagent in Horner-Wadsworth-Emmons reactions (Scheme 1B).[5] The method was shown to be flexible, using the *N*-Cbz protected reagent accessible *via* a multistep synthesis. Other derivatives may be synthesized by modifications of the reagent.

Schmidt reported a direct synthesis of dhAAs from the corresponding amino acids using a *N*-chlorination, dehydrochlorination and rearrangement sequence.[6] Limitations include the use of reactive *t*BuOCl and challenging *N*-protection of the sensitive enamines. Nanjo and Takemoto applied a similar *N*-chlorination protocol to the selective late-stage desaturation of aliphatic peptides (Scheme 1C).[7] However, carbamate protected residues were not desaturated under these conditions.

Scheme 1. Synthetic approaches towards dhAAs.

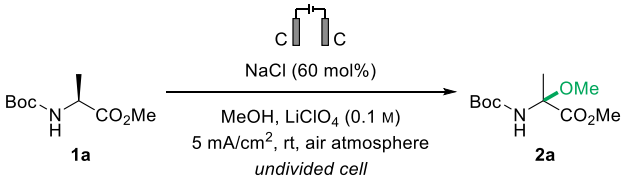


The Shono oxidation is a powerful electrochemical C-H functionalization reaction that has been extensively studied for the alkoxylation of various amino compounds.[8] Recently, Shono-type processes have been applied to the late-stage functionalization of drug-like molecules and peptides.[9] Aiming to develop a preparative-scale method for the desaturation of carbamate protected amino acids into the corresponding dehydroamino acids, we devised a strategy that couples an electrochemical α-methoxylation with a subsequent elimination of methanol (Scheme 1D).

While α-methoxylations of electron-deficient α-amino acid carbamates have been reported by the Shono group, the scope has been limited to sterically less demanding methyl carbamates.[10] To render more versatile protecting groups, e.g. benzyl and *tert*-butyl carbamates, accessible, we started to explore conditions tolerant thereof. In addition, we aimed at developing a mild elimination protocol to afford dhAAs.

We initiated our investigation of the anodic oxidation with Boc-Ala-OMe (**1a**) as the model system for exploring suitable conditions for the Shono-type oxidation. Reaction optimization revealed the α-methoxylation to proceeded virtually quantitative using NaCl (60 mol%) as a mediator, $LiClO_4$ as electrolyte and MeOH (0.3 mol/L) as the solvent (Table 1, entry 1, see Supporting Information for full table). The reaction did not proceed in the absence of NaCl (entry 2) and the faradaic efficiency dropped significantly at lower substrate concentrations (entries 3-4). Without $LiClO_4$, the product **2a** was obtained in a significantly lower yield of 83% (entry 5).

Table 2. Optimization of the anodic oxidation.[a]



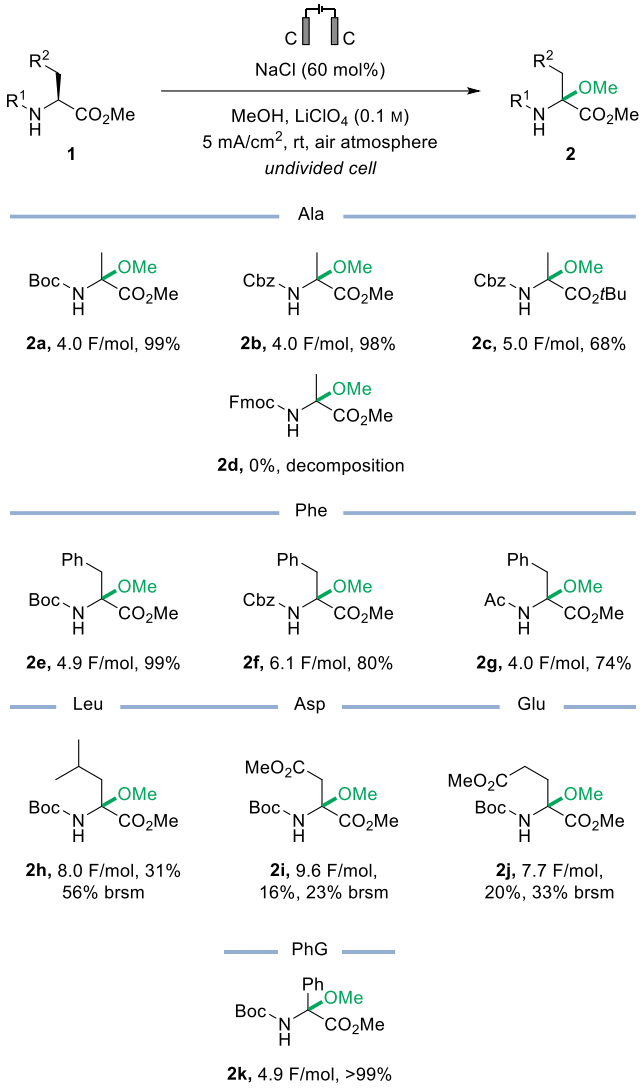
entry	variation from standard conditions	F/mol	Conversion (yield)
1	None	4	Full (99%)
2	no NaCl	4	Trace
3	0.05 M substrate	10	25%
4	0.1 M substrate	4	77%
5	No $LiClO_4$	4	Full (83%)

[a]Reaction conditions: **1a** (1.0 eq., 0.3 M), NaCl (0.6 eq.), $LiClO_4$ (0.1 M), 8.2 mm graphite electrodes, J = 5 mA/cm^2, 4 F/mol, rt, air atmosphere.

Using the established procedure, we next explored the substrate scope (Scheme 2). *tert*-Butyl and benzyl carbamates gave clean conversions with little influence on the faradaic efficiency. Fmoc-protection was not tolerated and decomposition of the substrate with formation of 9-methylidene-9H-fluorene was observed. We speculate that *in situ* formed methoxide ions might effect base-induced deprotection. The sterically demanding *tert*-butyl ester (**2c**) showed a minor decrease in faradaic efficiency and the yield dropped from 98% to 68% compared to the methyl ester (**2b**).

While alanine and phenylalanine derivatives showed good faradaic efficiencies, leucine (**1h**), asparagine (**1i**) and glutamine (**1j**) carbamates showed a lowered faradaic efficiency of <25%. Critically for those substrates (**1h-1j**), the reactions stopped before complete conversion. It is worth mentioning that electrolysis of Boc-Glu-OMe (**1j**) afforded methyl 4-(*N*-Boc)-4-methoxybutanoate **3j** as the byproduct in 8% yield (see Supporting Information). Its formation can be rationalized by decarboxylation in a Hofer-Moest-type process.[11] No conversion was achieved with β-branched amino acid derivatives, e.g. valine.

Scheme 2. Scope of the NaCl-mediated Shono-type oxidation.[a]

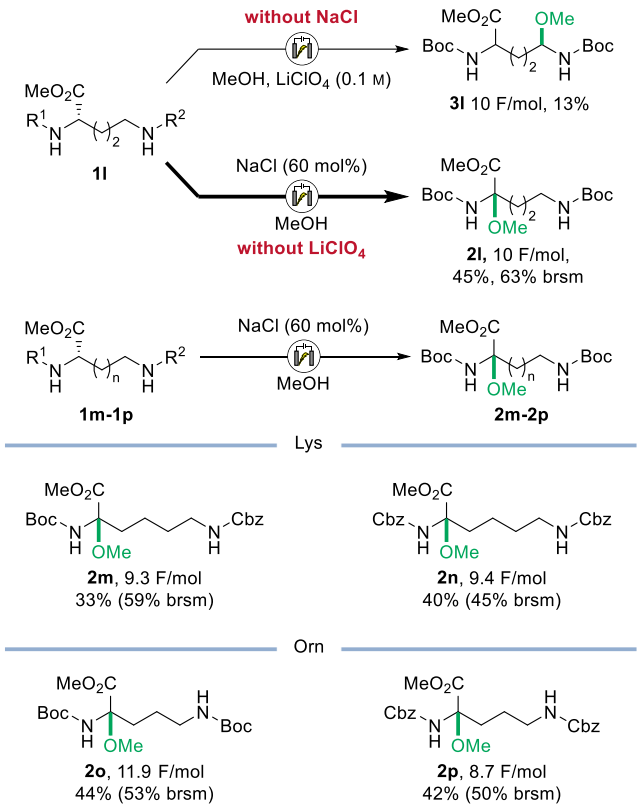


[a]Reaction conditions: substrate **1a-k** (4 mmol, 1 equiv), 60 mol% NaCl, MeOH (0.3 M), 0.1 M $LiClO_4$, 5 mA/cm^2 constant current, graphite anode and cathode.

Dehydroalanine has received attention as monomer in the synthesis of polydehydroalanines[12] and as starting material for the synthesis of non-canonical amino acids.[13] To render our process viable for large-scale preparation (17 g scale), we demonstrated the applicability using a setup with six graphite rods instead of two (see Supporting Information for a graphical guide). The reaction proceeded cleanly to afford spectroscopically pure product in 86% yield without further purification. When the conversion stopped at 86% at ~3 F/mol, a simple switch of the electrode polarities resulted in full conversion at 7.6 F/mol, suggesting product adsorption at the electrode surface.

To evaluate the regioselectivity of the reaction, we continued our investigation with protected ornithine and lysine derivatives bearing two carbamate groups (Scheme 3). Direct anodic oxidation of Boc-Lys(Boc)-OMe (**1l**) without NaCl as mediator gave ε-methoxylated lysine **3l** selectively. Methoxylation of the α-position was not observed. The faradaic efficiency and yield of this process were low. Application of our optimized conditions resulted in low faradaic efficiency and limited regioselectivity leading to an inseparable mixture of α-, ε-, and dimethoxylated products. Fortunately, running the reaction without $LiClO_4$ as additional conducting salt showed high selectivity for the α-position. As previously discussed, the conversion stalled after 10 F/mol, probably due to passivation of the anode surface.

Scheme 3. Regioselectivity of the anodic oxidation of lysine and ornithine derivatives.

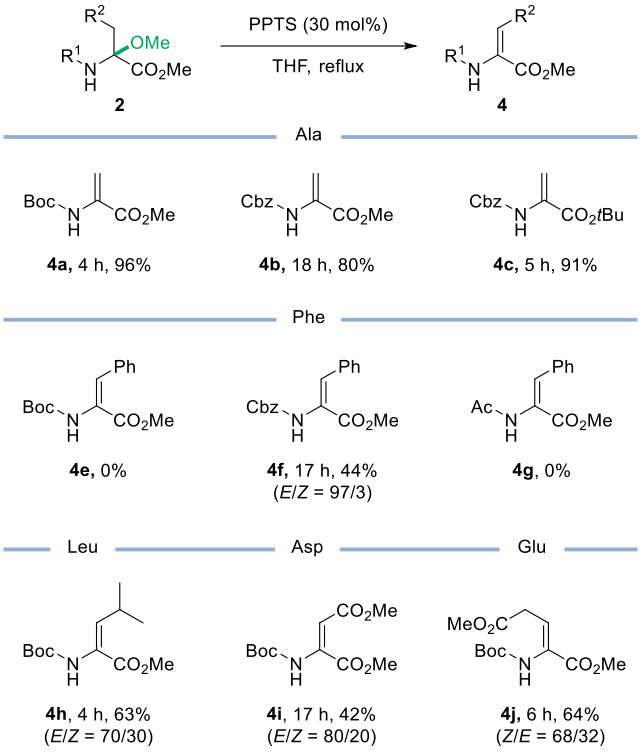


The regioselectivity was not affected in orthogonally protected Boc-Lys(Cbz)-OMe (**1m**), albeit a slight decrease in yield was observed (**2l**: 45% and **2m**: 33%) due to incomplete conversion. Bis(benzylcarbamate) protected lysine **1n** gave comparable yields (**2n**: 40%). The shorter hydrocarbon chain of ornithine carbamates had little influence on the reaction. Faradaic efficiency, yield and regioselectivity were comparable to lysine derivatives.

With α-methoxylated amino acid derivatives in hand, we next focused on the synthesis of dhAA derivatives *via* elimination of the methoxy group. To access *N*-Boc-protected dhAAs, we tested different Brønsted-acid catalysts. For less sensitive enecarbamates, elimination can be catalyzed by NH_4Cl (17 mol%) at 100-160 °C under solvent-free conditions.[9] Due to the susceptibility of dhAA derivatives to polymerize,[12] we aimed at suppressing this path using a solution of **2**. Molecular sieves, NH_4Cl and AcOH showed no conversion of **2a** upon refluxing in THF. The use of Amberlyst 15® or 1 M HCl resulted in polymerization at room temperature while Lewis-acids $Ti(OiPr)_4$ or $AlMe_3$ gave a complex product mixture. Base-induced elimination using KO*t*Bu or DBU was successful but resulted in incomplete conversion even with 3 equiv. of DBU.

Finally, we discovered pyridinium para-toluenesulfonate (PPTS) to be a superior catalyst for the elimination, giving a clean reaction with virtually no side-products in the case of methoxylated alanines **2a-2c (**Scheme 4**)**. The reactions proceeded in excellent yield without the need for chromatographic purification. A 70 mmol-scale elimination of **2a** afforded **4a** with virtually quantitative yield (see Supporting Information). It is important to note that on scale, PPTS precipitated upon cooling and could be easily recovered by filtration.

Scheme 4. PPTS-catalyzed elimination reaction towards dehydroamino acid derivatives.

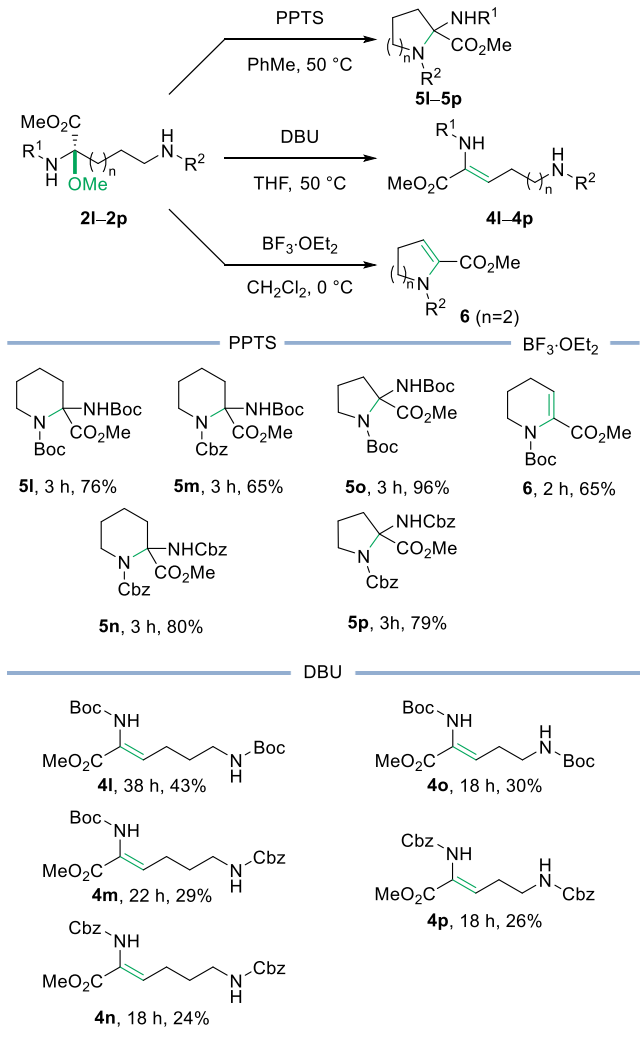


We then investigated this elimination for the β-substituted methoxylated products **2e-2j**. Stereoisomers could be separated by chromatography and configurations were determined by ^1H NOESY (see Supporting Information). Aliphatic derivatives like Boc-ΔLeu-OMe **4h** and Boc-ΔGlu-OMe **4j** could be synthesized in good yield but moderate *E*/*Z*-selectivity. Whereas formation of the (*E*)-isomer of **4h** was preferred due to the bulky isopropyl residue, Glu derivative **4j** showed moderate (*Z*)-selectivity. In contrast, conjugated products like Cbz-ΔPhe-OMe (**4f**) and Boc-ΔAsp-OMe (**4i**) were accessed with high (*E*)-selectivity. In case of Boc-ΔPhe-OMe rapid polymerization was observed, probably due to deprotection of the conjugated enamine. Even milder acids like $HNEt_3Cl$ resulted in polymerization. Base-mediated elimination using DBU resulted in product decomposition starting at about 56% conversion (GC-MS analysis) thus demonstrating the lability of the substrate.

To our surprise, application of PPTS as catalyst to methoxylated lysine or ornithine derivatives **2l-2p** showed a different reactivity (Scheme 5). Cyclization of the sidechain afforded new 2-aminoproline- and 2-aminopipecolic acid derivatives **5m-5p**.

We also investigated solvent effects in the elimination of **2l** and did not observe any formation of **4l** even in protic solvents like HFIP. Instead, cyclization and subsequent elimination of the α-carbamate function to form 2-dehydropipecolic acid **6** was observed. The reaction in THF and toluene gave pipecolic acid **5l** in 65% and 76%, respectively. To access the dehydrolysine **4l**, we revisited the base-induced elimination. Using DBU in THF at 50 °C, we obtained the (*Z*)-isomer selectively in 43% yield. A major side product of the base-mediated elimination of methanol, we observed partial exchange of the α-carbamate groups (Boc, Cbz) to their methyl analogs. Interestingly, treatment of **4n** with PPTS protocol did not result in the formation of **5n**, suggesting that **4n** is not an intermediate in the PPTS-catalyzed cyclization.

Scheme 5: Diversification of α-methoxylated ornithine and lysine derivatives.



In conclusion, we have developed a direct synthesis of dhAAs from amino acid carbamates. The method proved reliable on the gram-scale for the synthesis of a variety of carbamate protected dhAAs. The simplicity of the setup using inexpensive, reusable graphite-rods and NaCl as mediator render this protocol an economic alternative to previous approaches. In case of alanine derivatives, no chromatography is required in both steps. The synthesis of Boc-ΔAla-OMe (**4a**) was demonstrated on a decagram-scale and opens the door for follow-up transformations. In addition, stereoselective access to dehydrolysines and ornithines was achieved using a base-induced elimination of methanol. Brønsted acid catalyzed cyclization of the same substrate afforded valuable 2-aminoproline and 2-aminopipecolic acid derivatives.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, characterization data, ^{1}H, ^{13}C and ge-NOESY spectra of synthesized compounds (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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