Non-Kolbe electrolysis of *N*-protected-α-amino acids: a standardized method for the synthesis of *N*-protected (1-methoxyalkyl)amines†

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Here, we report a standardized method for the synthesis of *N*-protected (1-methoxyalkyl)amines by the electrochemical decarboxylative α-methoxylation of α-amino acid derivatives using the commercially available, easy-to-use, compact ElectraSyn 2.0 setup. The use of equipment with a standardized power source, electrodes, and other accessories allows this experimental procedure to be easily transferred to any laboratory in the world. A simple workup and chromatography-free purification produced the products in excellent yields above 90%.

Introduction

Synthetic organic electrochemistry is one of the most important alternatives to classical chemical approaches. It can be used to obtain structurally diverse compounds under mild and green conditions in high yields and, more importantly, good regio- and chemoselectivity.[1–6] Thus, it is no wonder that the number of articles describing the use of electrochemical synthetic methods has continually increased over the last decade.

Among the many electrochemical oxidation reactions, the reaction of compounds containing a carboxyl group deserves special attention.[7,8] Depending on the structure of the substrate and the conditions, reactions can occur *via* two pathways. The one-electron oxidation of carboxylate anions followed by decarboxylation and the formation of radicals that can easily dimerize is called Kolbe electrolysis, which is considered to be the oldest known electro-organic reaction.[9] A high current density increases the concentration of radicals on the anode surface, which promotes the formation of dimers; however, if the oxidation potential of the radical intermediates is low enough (due to their structure), a second electron may be detached, which generates stabilized carbocations. This process

is known as non-Kolbe electrolysis.[10] This route occurs for compounds with an electron-donating group in the α position to the carboxyl group, *e.g.*, *N*-protected α-amino acids. Electrolysis can be carried out in protic (nucleophilic) solvents, *e.g.*, MeOH, H₂O, or AcOH, in which newly-formed carbocations are quickly captured by solvent molecules. The first step in the decarboxylative α-methoxylation of *N*-protected α-amino acids **1** is the formation of highly reactive *N*-aciliminium-type cations, which easily subsequently react with nucleophilic MeOH to give *N*-protected (1-methoxyalkyl)amines **2** (Fig. 1).

N-Protected (1-methoxyalkyl)amines **2** are one of the most relevant α-amidoalkylating agents used for α-amidoalkylation reactions.[11] They can be easily transformed into reactive α-amido sulfones,[12] *N*-[1-(benzotriazol-1-yl)alkyl]amides,[13] or 1-(*N*-acylamino)alkyltriarylphosphonium salts,[14] which have recently been introduced to organic synthesis. All of the above mentioned compounds (including *N*-protected (1-alkoxyalkyl) amines) play an important role in the synthesis or modification
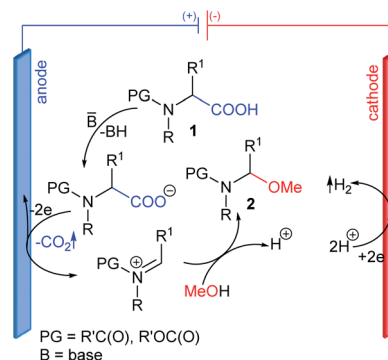
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† Electronic supplementary information (ESI) available: The experimental procedure for the preparation of *N*-pivaloylalanine **1a** and characterization data. Table with comparison of yields for both (previous and current) procedures. ¹H and ¹³C NMR spectra of products **2a–u.** ¹H and ¹³C NMR spectra of products **2** obtained in repeated syntheses. See DOI: 10.1039/d1ra08124a

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Fig. 1 Electrochemical decarboxylative α-methoxylation of *N*-protected α-amino acids.

of a wide range of organic compounds, including natural and/or bioactive products with particular importance in pharmaceutical chemistry.[11] The main reason for this is the ease of forming new C–C and C-heteroatom bonds (e.g., C–P, C–S, C–N) via both intermolecular α-amidoalkylation and intramolecular cyclization, leading to carbo- and heterocyclic compounds.[11,15–19]

Previous electrochemical methods

The most general and effective strategies for the synthesis of N-protected (1-alkoxyalkyl)amines are based on electrochemical reactions such as the decarboxylative α-alkoxylation of N-protected α-amino acids or the electrochemical oxidation of amides, lactams, or carbamates; however, among the above routes, the first one is of particular importance (Fig. 1).[11]

In 1951, Linstead et al. reported the decarboxylative α-alkoxylation of glycine and alanine derivatives in an alcoholic solution with the addition of metallic sodium to provide the corresponding N-(1-alkoxyalkyl)amides in good yields.[20] After this pioneering work, the electrochemical decarboxylative α-methoxylation of N-acylated α-amino acids was explored by several research groups. However, the described methods were initially limited to relatively simple N-acyl-α-amino acids, such as derivatives of glycine, alanine, valine, leucine, phenylalanine, or proline.[20–22] Next, the reaction was expanded to more complex compounds, such as oxazolidine-2-one-4-carboxylic acids derived from threonine,[23] 2,5-piperazinediones derived from aminomalonic acid,[24] and di-, tri-, or tetrapeptides.[25] From 2000–2003, the Matsumura and Onomura groups applied this electrochemical process for the stereoselective functionalization of N,O-acetals derived from serine.[26–28]

Electrochemical alkoxylation is usually carried out in MeOH in the presence of a base. Sodium methanolate (MeONa),[22,26–28] inorganic bases,[21,24] such as KOH, NaOAc, LiH, CsCO₃ or organic bases Et₃N or (i-Pr)₂EtN,[25] are typically used to generate carboxylate ions from the corresponding α-amino acids. Additionally, in 2007, Tajima et al. showed that the decarboxylative α-methoxylation of alanine and proline derivatives could be accomplished using solid-supported bases (e.g., 3-(1-piperidino)propyl-functionalized silica gel (SiO₂-Pip)).[29]

In 2012, we conducted extensive research in the electrochemical decarboxylative α-methoxylation of N-protected α-amino acids. We developed an efficient method for transforming structurally diverse N-protected α-amino acids 1 to N-protected (1-methoxyalkyl)amines 2 in the presence of MeONa or SiO₂-Pip.[14] The latter approach (in the presence of SiO₂-Pip) was particularly useful since no aqueous workup was required to isolate the product. The electrolysis of N-protected α-amino acids 1 in MeOH was performed under stirring at a current density of 0.3 A dm⁻² at 10 °C until 2.4–3.75 F mol⁻¹ charge had passed (Fig. 2A). Then, the solid-supported base was filtered off, and pure N-protected (1-methoxyalkyl)amines 2 were obtained after evaporating volatiles.[14]

All of the above electro-organic methods produced N-protected (1-methoxyalkyl)amines in good to excellent yields and chemoselectivity, but they also have some limitations. When using bases such as MeONa or KOH, aqueous workup was necessary, which resulted in a lower reaction efficiency, especially for products derived from polar, hydrophilic amino acids. The application of more expensive, albeit reusable, solid-supported bases, such as SiO₂-Pip, simplified the workup procedure; however, as we observed, during electrolysis in the presence of SiO₂-Pip, platinum electrodes were mechanically degraded, which generated additional costs (see Note A). For non-"electro-curious" chemists, the collection or purchase of equipment and the subsequent construction of homemade electrochemical setups is often a great technical inconvenience; especially that even the detailed copying of self-made installations does not guarantee the reproducibility necessary to obtain the expected results. The necessity to optimize the reaction conditions each time makes electrochemical methods problematic from a synthetic point of view.

The ideal solution for electrochemical reactions seems to be the commercially available, easy-to-use, compact setup, like ElectraSyn 2.0 (designed by IKA®). A synthetic method performed on equipment with a standardized power source, electrodes, and other accessories would allow the successful transfer of an experimental procedure from one lab to another every time.

Herein, we report our results of the application of the ElectraSyn 2.0 setup for improving the electrochemical decarboxylative α-methoxylation of N-protected α-amino acids.

Results and discussion

In preliminary experiments, we screened various reaction conditions for the decarboxylative α-methoxylation of N-Piv-α-alanine 1a as a model N-acyl-α-amino acid (Table 1). An initial set of experiments was performed to evaluate the influence of the electrode material and the type of base on the reaction. All experiments were carried out in an electrochemical reactor (ElectraSyn 2.0) equipped with a glass vial (5 mL), a magnetic stirrer, and a set of electrodes (Fig. 2B). Reactions were performed in constant current mode on a 0.4 mmol scale, using 0.1 M N-Piv-α-alanine 1a in MeOH in the presence of 0.075 equiv. of base. In contrast to our previous method, electrochemical decarboxylative α-methoxylation was carried out at room temperature, not at 10 °C.

In the first experiment, we used Pt-plated electrodes (anode and cathode) and SiO₂-Pip as a base, similar to our previous method. Under these conditions, a constant current of only 10 mA was achieved, which was 15 times lower than the value obtained using our self-made setup. Electrolysis was conducted until 3.8 F mol⁻¹ charge had passed (Table 1, entry 1). After this time, the progress of the reaction was determined by ¹H NMR. Unfortunately, the reaction mixture contained mainly unreacted substrate 1a and only a small amount of the expected product 2a (Table 1, entry 1). Next, with Pt-plated electrodes, changing the base from SiO₂-Pip to Et₃N increased the conductivity of the electrolyte, which allowed the
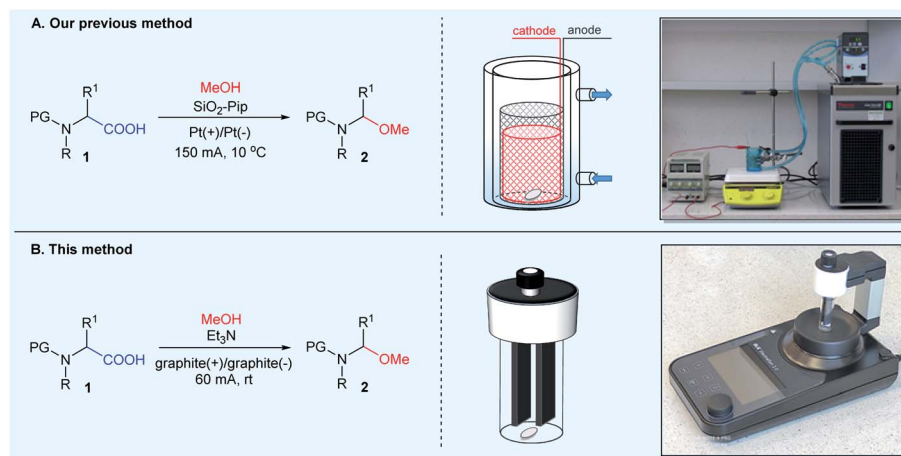
Fig. 2 Electrochemical methods for the synthesis of *N*-protected (1-methoxyalkylamines) **2**: (A) alkoxylations were conducted in an undivided cylindrical glass electrolyzer with a thermostatic jacket, equipped with a magnetic stirrer, and using a DC power supply. To overcome the high resistance of the electrolyte, a cylindrical mesh anode (Pt) and cathode (Pt) were arranged concentrically 2.5 ± 0.5 mm from each other; (B) methoxylations were carried out using commercially available, compact setup – IKA ElectraSyn 2.0.

Table 1 Screening of the reaction conditions[a]

Entry	Electrode	Base	I [mA]	Q [F mol^{-1}]	Conv.[b] [%]	2a[c] [%]
1	Pt (+/−)	SiO$_2$-Pip	10	3.8	13	—[d]
2	Pt (+/−)	Et$_3$N	60	3.8	50	—[d]
3	Pt (+/−)	Et$_3$N	60	7.6	>99	93
4	Graphite (+/−)	Et$_3$N	60	2.1	>99	95
5[e]	Graphite (+/−)	Et$_3$N	60	2.1	>99	95
6[f]	Graphite (+/−)	Et$_3$N	60	2.1	>99	97
7	Graphite (+/−)	SiO$_2$-Pip	10	2.1	>99	92

[a] Conditions: substrate **1a** (0.4 mmol), base (0.03 mmol, 0.075 equiv.), MeOH (4 mL), room temperature. Entries 1–4 and 7 were performed in a 5 mL vial on IKA Electrasyn 2.0. [b] Determined by integration of signals in the ^{1}H NMR spectrum. [c] Isolated yield. [d] Due to the low conversion of substrate **1a**, the product was not isolated. [e] The reaction on a scale of 0.75 mmol of **1a** in a 10 mL vial. [f] The reaction on a scale of 1.6 mmol of **1a** in a 20 mL vial.
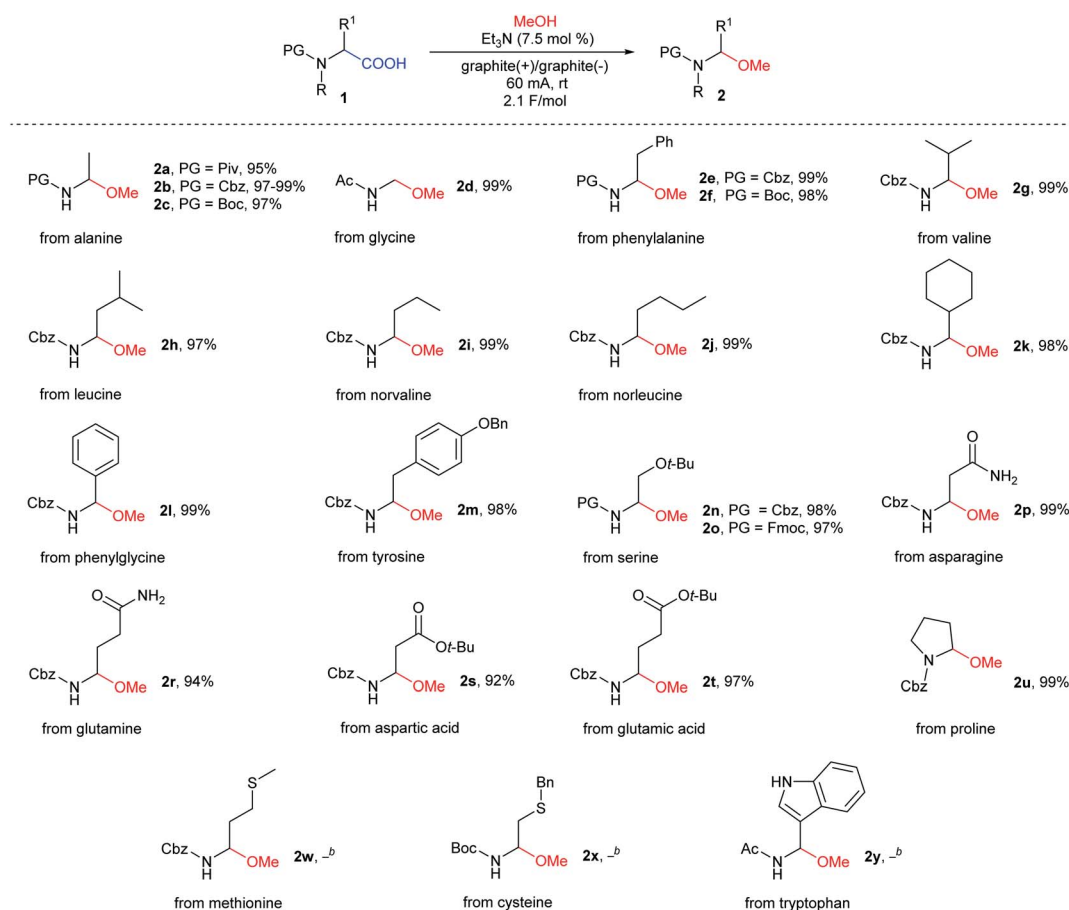
process to be carried out at a current of 60 mA. Upon a charge consumption of 3.8 F mol^{-1}, the substrate conversion was still unsatisfactory (Table 1, entry 2). Increasing the electric quantity from 3.8 F mol^{-1} to 7.6 F mol^{-1} produced the expected product **2a** with a high yield of 93% (Table 1, entry 2 *vs.* entry 3). However, the best results were achieved by replacing the Pt-plated electrodes with graphite ones (anode and cathode). In conjunction with Et$_3$N as the base and at a constant current of 60 mA, product **2a** was obtained in an excellent yield of 95%. A total charge of just 2.1 F mol^{-1} was necessary to perform this reaction (Table 1, entry 4). Next, the scalability of this process was explored by conducting the reaction using 0.75 mmol and 1.6 mmol of substrate **1a** (Table 1, entry 5 and 6). In both cases,

no decrease in the yield of product **2a** was observed. We also demonstrated that the decarboxylative α-methoxylation of *N*-Piv-alanine **1a** using graphite electrodes could be carried out effectively also in the presence of the solid-supported base, SiO$_2$-Pip (Table 1, entry 7). Similar to electrolysis with Pt-plated electrodes, the maximum current did not exceed 10 mA, which significantly affected the extension of the electrolysis time (Table 1, entry 1 *vs.* entry 7).

Next, with the optimal electrolysis conditions (with an optimal set of electrolysis parameters) in hand, a new procedure was tested on most of our previously reported *N*-protected α-amino acids (Fig. 2B, Table 2). Hydrophobic aliphatic and aromatic *N*-protected α-amino acids (alanine, valine, phenylalanine, norvaline, norleucine, cyclohexylglycine, phenylalanine, and phenylglycine), α-amino acids with functionalized side chains (tyrosine, serine, asparagine, glutamine, aspartic acid, and glutamic acid), and cyclic proline appeared to be suitable substrate. The expected *N*-protected (1-methoxyalkyl)amines **2a–u** were isolated in excellent yields (94–99%), which were comparable or higher than the yields obtained using our previous method. To verify the repeatability of this non-Kolbe electrolysis, the methoxylation of *N*-Cbz-α-alanine **1b** was carried out five times, obtaining the expected product **2b** in 99%, 99%, 97%, 98%, 99% yields, respectively. For a comparison of the yields obtained using both experimental procedures, see the ESI.†

Similar to previous studies, this reaction proved to be tolerant to various amine protecting groups. This time, however, the reaction workup only involved the evaporation of volatiles and drying of residues. In the case of methionine **2w**, cysteine **2x**, and tryptophan **2y** derivatives, the reaction proceeded with the formation of a complex mixture (Table 2). This was ascribed to the presence of easily oxidized fragments, *e.g.*, sulfide-type groups **2w–x** or sensitive nature of indole derivative **2y**.

Table 2 Reaction scope for the electrochemical transformation of *N*-protected α-amino acids **1** into (1-methoxyalkyl)amine derivatives **2**[a]

2a, PG = Piv, 95%
2b, PG = Cbz, 97-99%
2c, PG = Boc, 97%
from alanine

2d, 99%
from glycine

2e, PG = Cbz, 99%
2f, PG = Boc, 98%
from phenylalanine

2g, 99%
from valine

2h, 97%
from leucine

2i, 99%
from norvaline

2j, 99%
from norleucine

2k, 98%

2l, 99%
from phenylglycine

2m, 98%
from tyrosine

2n, PG = Cbz, 98%
2o, PG = Fmoc, 97%
from serine

2p, 99%
from asparagine

2r, 94%
from glutamine

2s, 92%
from aspartic acid

2t, 97%
from glutamic acid

2u, 99%
from proline

2w, –[b]
from methionine

2x, –[b]
from cysteine

2y, –[b]
from tryptophan

[a] Conditions: 0.4 mmol substrate **1**, 0.03 mmol Et$_3$N, MeOH (4 mL) in a 5 mL vial, at room temperature, constant current (60 mA), graphite SK-50 electrodes (anode and cathode), and charge 2.1 F mol^{-1}. Isolated yield. [b] A complex reaction mixture.

Procedure and characterization

General methods

Melting points were determined in capillaries, in a Stuart Scientific SMP3 melting point apparatus and were uncorrected. Infrared spectra (IR) were recorded on a Nicolet 6700 FT-IR spectrophotometer (ATR method). ^{1}H NMR spectra were acquired on either a Varian 600 or Agilent NMR Magnet-400 instrument, at 600 or 400 MHz, respectively. Data are recorded as follows: chemical shift (δ, ppm) with tetramethylsilane (TMS) as the internal standard, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet; qu = quintet; m = multiplet; br = broad), coupling constant (Hz), integration. ^{13}C NMR spectra were measured on either a Varian 600 or 400 MHz at, as appropriate, 150 or 100 MHz. Chemical shifts were reported in ppm from the solvent resonance employed as the internal standard. Data for ^{13}C NMR are reported in terms of chemical shift (δ, ppm). High resolution mass spectroscopy (HRMS) analyses were obtained using a commercial apparatus Waters Corporation Xevo G2 QTOF instrument (ESI source).

General procedure for the electrochemical synthesis of *N*-protected (1-methoxyalkyl)amines 2

(1) A 5 mL IKA ElectraSyn vial, equipped with a magnetic stir bar is charged sequentially with *N*-protected α-amino acid **1** (0.4 mmol, 1 equiv.), MeOH (4 mL), and Et$_3$N (4.2 μL, 0.03 mmol, 0.075 equiv.).

(2) The vial is then closed with a cap with two Graphite SK-50 electrodes attached, and the mixture is stirred at 500 rpm for 4 minutes (Note B).

(3) Next, the vial is put into the ElectraSyn set up, and electrolysis is carried out at room temperature. The mixture is stirred at 600 rpm in constant-current mode (60 mA) until 2.1 F mol^{-1} of charge is passed (time: 22 min 29 s).

(4) After completion of the reaction, the reaction mixture is quantitatively transferred to a round-bottom flask, and the

volatiles are removed under reduced pressure using rotary evaporator.

(5) Finally, the residue is dried under vacuum (10–15 mmHg) to yield desired product, N-protected (1-methoxyalkyl)amine **2**.

The original procedure was repeated for randomly selected N-protected α-amino acids (**2a, e, h, l, m, t**) by J. Adamek (at 0.4 mmol scale of appropriate substrate **1**).

N-(1-Methoxyethyl)pivaloylamide[14] (2a). White solid (60.6 mg, 95% yield): mp 74.0–75.5 °C (lit. 65.0–66.0 °C). ^{1}H NMR (600 MHz, CDCl$_3$) δ 5.74 (br s, 1H), 5.29 (dq, J_1 = 12.0 Hz, J_2 = 6.0 Hz, 1H), 3.31 (s, 3H), 1.33 (d, J = 6.0 Hz, 3H), 1.22 (s, 9H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 178.5, 77.7, 55.5, 38.8, 27.5, 21.6. IR (ATR) 3325, 2968, 2931, 1641, 1523, 1194, 1126, 1091 cm^{-1}.

Repeat: white solid (59.9 mg, 94% yield). ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.75 (br s, 1H), 5.29 (dq, J_1 = 12.0 Hz, J_2 = 6.0 Hz, 1H), 3.31 (s, 3H), 1.33 (d, J = 5.6 Hz, 3H), 1.22 (s, 9H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 178.4, 77.7, 55.6, 38.8, 27.5, 21.6.

Benzyl N-(1-methoxyethyl)carbamate[14] (2b). Orange oil (83.2 mg, 99% yield). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.37–7.32 (m, 5H), 5.13 and 5.11 (ABq, J_{AB} = 12.6 Hz, 2H), 5.07–4.91 (m, 2H), 3.34 (s, 3H), 1.34 (d, J = 5.6 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 155.8, 136.2, 128.5, 128.2, 128.1, 80.1, 66.8, 55.3, 21.7. IR (ATR) 3320, 2941, 1689, 1531, 1257, 1077 cm^{-1}.

tert-Butyl N-(1-methoxyethyl)carbamate[30] (2c). White crystals (67.9 mg, 97% yield): mp 67–68.5 °C. ^{1}H NMR (600 MHz, CDCl$_3$) δ 5.00–4.97 (m, 1H), 4.79 (br s, 1H), 3.33 (s, 3H), 1.46 (s, 9H), 1.32 (d, J = 6.0 Hz, 3H). ^{13}C NMR (150 MHz, CDCl$_3$) δ 155.2, 79.7, 79.4, 55.1, 28.3, 21.6. IR (ATR) 3322, 2980, 1685, 1523, 1364, 1250, 1151, 1068, 1044 cm^{-1}.

N-(Methoxymethyl)acetamide[14] (2d). Colorless oil (40.8 mg, 99% yield). ^{1}H NMR (600 MHz, CDCl$_3$) δ 6.47 (t ∼ br s, 1H), 4.66 (d, J = 7.2 Hz, 2H), 3.34 (s, 3H), 2.05 (s, 3H). ^{13}C NMR (150 MHz, CDCl$_3$) δ 170.9, 71.4, 55.9, 23.3. IR (ATR) 3309, 2934, 1667, 1541, 1369, 1281, 1128, 1063 cm^{-1}.

Benzyl N-(1-methoxy-2-phenylethyl)carbamate[14] (2e). White crystals (113.4 mg, 99% yield): mp 83.5–85.0 °C (lit. 85.0–86.0 °C). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.36–7.20 (m, 10H), 5.18–5.13 (m, 1H), 5.08 (s, 2H), 5.01 (br d, J = 9.6 Hz, 1H), 3.34 (s, 3H), 2.93 (d, J = 5.6 Hz, 2H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 155.9, 136.2, 135.8, 129.7, 128.5, 128.4, 128.2, 128.0, 126.7, 83.5, 66.8, 55.7, 41.6. IR (ATR) 3331, 2933, 1689, 1522, 1247, 1087, 1028 cm^{-1}.

Repeat: white solid (113.9 mg, 99% yield). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.36–7.21 (m, 10H), 5.18–5.13 (m, 1H), 5.08 (s, 2H), 5.00 (br d, J = 9.6 Hz, 1H), 3.34 (s, 3H), 2.93 (d, J = 6.0 Hz, 2H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 155.9, 136.2, 135.8, 129.7, 128.5, 128.4, 128.2, 128.0, 126.8, 83.5, 66.8, 55.7, 41.6.

tert-Butyl N-(1-methoxy-2-phenylethyl)carbamate[31] (2f). Creamy wax (98.8 mg, 98% yield). ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.32–7.22 (m, 5H), 5.11–5.07 (m, 1H), 4.79 (br d, J = 10.2 Hz, 1H), 3.32 (s, 3H), 2.91 (d, J = 5.4 Hz, 2H), 1.41 (s, 9H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 155.3, 136.2, 129.7, 128.3, 126.6, 82.9, 79.7, 55.5, 41.7, 28.2. IR (ATR) 3362, 2932, 1709, 1493, 1297, 1153, 1076 cm^{-1}.

Benzyl N-(1-methoxy-2-methylpropyl)carbamate[14] (2g). Colorless crystals (94.2 mg, 99% yield): mp 59.5–60.5 °C (lit. 97.0–99.0 °C). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.38–7.31 (m, 5H),

5.14 and 5.12 (ABq, J_{AB} = 12.0 Hz, 2H) 4.94 (br d, J = 10.0 Hz, 1H), 4.65 (dd, J_1 = 10.4 Hz, J_2 = 5.6 Hz, 1H), 3.35 (s, 3H), 1.88–1.76 (m, 1H), 0.94 (d, J = 6.8 Hz, 3H), 0.91 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 156.4, 136.3, 128.5, 128.2, 128.0, 87.8, 66.8, 55.8, 33.1, 17.7, 17.1. IR (ATR) 3295, 2962, 1688, 1534, 1244, 1090, 1031 cm^{-1}.

Benzyl N-(1-methoxy-3-methylbutyl)carbamate[14] (2h). Colorless oil (97.1 mg, 97% yield). ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.36–7.31 (m, 5H), 5.12 (s, 2H), 5.00–4.92 (m, 2H), 3.35 (s, 3H), 1.73–1.70 (m, 1H), 1.57–1.53 (m, 1H), 1.40–1.36 (m, 1H), 0.92 (d, J = 6.0 Hz, 3H), 0.91 (d, J = 6.6 Hz, 3H). ^{13}C NMR (150 MHz, CDCl$_3$) δ 156.0, 136.3, 128.5, 128.2, 128.1, 82.3, 66.8, 55.4, 44.6, 24.5, 22.6, 22.4. IR (ATR) 3314, 2956, 1700, 1522, 1225, 1087, 1046, 1026 cm^{-1}.

Repeat: colorless oil (100.0 mg, 99% yield). ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.36–7.31 (m, 5H), 5.12 (s, 2H), 4.99–4.92 (m, 2H), 3.35 (s, 3H), 1.75–1.69 (m, 1H), 1.58–1.53 (m, 1H), 1.40–1.36 (m, 1H), 0.92 (d, J = 6.6 Hz, 3H), 0.91 (d, J = 6.6 Hz, 3H). ^{13}C NMR (150 MHz, CDCl$_3$) δ 156.0, 136.3, 128.5, 128.2, 128.1, 82.3, 66.8, 55.4, 44.6, 24.5, 22.6, 22.4.

Benzyl N-(1-methoxybutyl)carbamate[32] (2i). White crystals (94.3 mg, 99% yield): mp 68.0–70.0 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.37–7.31 (m, 5H), 5.12 (s, 2H), 5.03 (br d, J = 9.6 Hz, 1H), 4.91–4.86 (m, 1H), 3.35 (s, 3H), 1.67–1.62 (m, 1H), 1.53–1.48 (m, 1H), 1.42–1.36 (m, 2H), 0.92 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 156.1, 136.2, 128.5, 128.2, 128.0, 83.4, 66.8, 55.5, 37.6, 18.1, 13.7. IR (ATR) 3305, 2938, 1686, 1530, 1256, 1091,1059, 959 cm^{-1}. HRMS (ESI) m/z: calcd for C$_{13}$H$_{19}$NO$_3$Na [M + Na]$^+$ 260.1263, found 260.1269.

Benzyl N-(1-methoxypentyl)carbamate[32] (2j). Creamy wax (99.7 mg, 99% yield). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.36–7.26 (m, 5H), 5.12 (s, 2H), 5.00 (br d, J = 10.0 Hz, 1H), 4.89–4.84 (m, 1H), 3.35 (s, 3H), 1.71–1.62 (m, 1H), 1.57–1.48 (m, 1H), 1.33 (br s, 4H), 0.89 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 156.1, 136.3, 128.5, 128.2, 128.0, 83.6, 66.8, 55.5, 35.3, 26.9, 22.3, 13.9. IR (ATR) 3293, 2943, 1690, 1534, 1259, 1240, 1098, 1047, 962 cm^{-1}. HRMS (ESI) m/z: calcd for C$_{14}$H$_{21}$NO$_3$Na [M + Na]$^+$ 274.1419, found 274.1421.

Benzyl N-[cyclohexyl(methoxy)methyl]carbamate[32] (2k). White crystals (90.1 mg, 98% yield): mp 102.0–103.0 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.39–7.30 (m, 5H), 5.12 (s, 2H), 4.98 (br d, J = 10.0 Hz, 1H), 4.64 (dd, J_1 = 10.4 Hz, J_2 = 6.0 Hz, 1H), 3.34 (s, 3H), 1.83–1.61 (m, 5H), 1.52–1.43 (m, 1H), 1.26–0.97 (m, 5H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 156.3, 136.3, 128.5, 128.2, 128.0, 87.2, 66.8, 55.8, 42.8, 28.2, 27.7, 26.3, 25.8, 25.7. IR (ATR) 3277, 2912, 1687, 1538, 1260, 1226, 1079, 1046, 973 cm^{-1}. HRMS (ESI) m/z: calcd for C$_{16}$H$_{23}$NO$_3$Na [M + Na]$^+$ 300.1576, found 300.1581.

Benzyl N-(1-methoxy-1-phenylmethyl)carbamate[14] (2l). White crystals (107.4 mg, 99% yield): mp 81.0–82.0 °C (lit. 77.0–79.0 °C). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.41–7.32 (m, 10H), 5.89 (d, J = 9.6 Hz, 1H), 5.35 (br d, J = 10.2 Hz, 1H), 5.15 (s, 2H), 3.46 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 155.9, 139.0, 136.1, 128.59, 128.56, 128.54, 128.2, 128.1, 125.8, 84.0, 67.1, 55.7. IR (ATR) 3291, 1691, 1529, 1248, 1087, 1046 cm^{-1}.

Repeat: white crystals (106.8 mg, 98% yield). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.42–7.32 (m, 10H), 5.89 (d, J = 10.0 Hz, 1H), 5.35

(br d, J = 11.2 Hz, 1H), 5.17 (s, 2H), 3.47 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 155.9, 139.1, 136.1, 128.6, 128.56, 128.55, 128.2, 128.1, 125.8, 84.0, 67.1, 55.7.

Benzyl N-[1-methoxy-2-(4-benzyloxyphenyl)ethyl]carbamate[14] **(2m).** White crystals (155.1 mg, 98% yield): mp 103.5–105.0 °C (lit. 105–107 °C). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.43–7.31 (m, 14H), 5.13–5.05 (m, 1H), 5.08 (s, 2H), 5.03 (s, 2H), 4.98 (br d, J = 9.6 Hz, 1H), 3.34 (s, 3H), 2.87 (d, J = 5.6 Hz 2H), ^{13}C NMR (100 MHz, CDCl$_3$) δ 157.7, 155.9, 137.1, 136.2, 130.7, 128.6, 128.5, 128.2, 128.1, 128.0, 127.9, 127.4, 114.8, 83.5, 70.0, 66.8, 55.7, 40.7. IR (ATR) 3307, 1696, 1532, 1509, 1258, 1235, 1046, 1023 cm^{-1}.

Repeat: white crystals (155.0 mg, 98% yield) ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.43–7.6.89 (m, 14H), 5.11–5.08 (m, 1H), 5.09 (s, 2H), 5.03 (s, 2H), 4.98 (br d, J = 10 Hz, 1H), 3.33 (s, 3H), 2.86 (d, J = 5.6 Hz 2H), ^{13}C NMR (150 MHz, CDCl$_3$) δ 157.7, 155.9, 137.0, 136.2, 130.7, 128.54, 128.51, 128.2, 128.0, 127.9, 127.4, 114.8, 83.5, 70.0, 66.8, 55.7, 40.7.

Benzyl N-(2-tert-butoxy-1-methoxyethyl)carbamate[14] **(2n).** 98% yield (109.9 mg). White crystals; mp 42.0–43.0 °C (lit. 36.0–38.0 °C). ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.37–7.32 (m, 5H), 5.61 (br d, J = 9.0 Hz, 1H), 5.15 and 5.13 (ABq, J_{AB} = 12.9 Hz, 2H), 5.00–4.98 (m, 1H), 3.54 (dd, J_1 = 9.6 Hz, J_2 = 3.0 Hz, 1H), 3.43 (dd, J_1 = 9.6 Hz, J_2 = 3.6 Hz, 1H), 3.39 (s, 3H), 1.19 (s, 9H). ^{13}C NMR (150 MHz, CDCl$_3$) δ 156.2, 136.3, 128.5, 128.2, 128.1, 81.9, 73.5, 66.9, 63.4, 55.9, 27.3. IR (ATR) 3345, 2972, 1694, 1537, 1265, 1197, 1099, 1052 cm^{-1}.

Fluorenylmethyl N-(2-tert-butoxy-1-methoxyethyl)carbamate (2o). Cream-colored crystals (143.8 mg, 97% yield): mp 84.9–86.5 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.77–7.30 (m, 8H), 5.59 (br d, J = 9.2 Hz, 1H), 4.99 (d, J = 9.6 Hz, 1H), 4.49 (dd, J_1 = 10.4 Hz, J_2 = 7.2 Hz, 1H), 4.38 (dd, J_1 = 10.8 Hz, J_2 = 7.2 Hz, 1H), 4.25 (t, J = 6.8 Hz, 1H), 3.55 (dd, J_1 = 10.0 Hz, J_2 = 2.8 Hz, 1H), 3.45 (dd, J_1 = 9.8 Hz, J_2 = 3.8 Hz, 1H), 3.36 (s, 3H), 1.21 (s, 9H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 156.2, 143.8, 143.7, 141.3, 127.7, 127.03, 127.01, 125.05, 125.00, 120.0, 81.9, 73.6, 66.8, 63.5, 55.8, 47.2, 27.4. IR (ATR) 3308, 2975, 1698, 1533, 1260, 1194, 1193, 1101, 1048 cm^{-1}. HRMS (ESI) m/z: calcd for C$_{22}$H$_{27}$NO$_4$Na [M + Na]$^+$ 392.1838, found 392.1836.

Benzyl N-(2-carbamoyl-1-methoxyethyl)carbamate[14] **(2p).** White crystals (101.5 mg, 99% yield): mp 153.5–155.0 °C (lit. 154–155 °C). ^{1}H NMR (400 MHz, DMSO) δ 7.86 (d, J = 9.2 Hz, 1H), 7.40–7.30 (m, 6H), 6.85 (s, 1H), 5.12–5.02 (m, 3H), 3.17 (s, 3H), 2.47 (dd, J_1 = 14.4 Hz, J_2 = 7.2 Hz, 1H), 2.32 (dd, J_1 = 14.4 Hz, J_2 = 5.6 Hz, 1H). ^{13}C NMR (100 MHz, DMSO) δ 171.2, 156.1, 137.1, 128.7, 128.1, 128.0, 80.9, 65.7, 54.7, 41.0. IR (ATR) 3384, 3327, 3189, 1687, 1654, 1529, 1278, 1219, 1101, 1042, 1016 cm^{-1}.

Benzyl N-(3-carbamoyl-1-methoxypropyl)carbamate[14] **(2r).** Colorless crystals (100.6 mg, 94% yield): 130–131 °C (lit. 132–133 °C). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.37–7.29 (m, 5H), 5.66 (br s, 2H), 5.57 (d, J = 10.0 Hz, 1H), 5.11 (s, 2H), 4.93–4.87 (m, 1H), 3.34 (s, 3H), 2.38–2.20 (m, 2H), 1.96 (q, J = 6.8 Hz, 2H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 174.8, 156.2, 136.2, 128.5, 128.2, 128.1, 82.9, 66.8, 55.5, 30.8, 30.5. IR (ATR) 3391, 3308, 1689, 1525, 1255, 1046 cm^{-1}.

Benzyl N-(2-tert-butoxycarbonyl-1-methoxyethyl)carbamate[14] **(2s).** Colorless crystals (113.9 mg, 92% yield): mp 49.5–51.0 °C (lit. 48–50 °C). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.38–7.30 (m, 5H), 5.94 (br d, J = 10.8 Hz, 1H), 5.22–5.17 (m, 1H), 5.12 (s, 2H), 3.35 (s, 3H), 2.60 (dd, J_1 = 15.8 Hz, J_2 = 5.4 Hz, 1H), 2.55 (dd, J_1 = 15.2 Hz, J_2 = 5.2 Hz, 1H), 1.44 (s, 9H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 169.2, 155.9, 136.2, 128.5, 128.2, 128.1, 81.4, 80.2, 66.8, 55.7, 41.1, 28.0. IR (ATR) 334, 1717, 1532, 1316, 1208, 1156, 1009 cm^{-1}.

Benzyl N-(3-tert-butoxycarbonyl-1-methoxypropyl) carbamate[14] **(2t).** Colorless oil (125.1 mg, 97% yield). ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.37–7.33 (m, 5H), 5.23 (br d, J = 9.6 Hz, 1H), 5.11 (s, 2H), 4.92–4.88 (m, 1H), 3.34 (s, 3H), 2.38–2.32 (m, 1H), 2.30–2.25 (m, 1H), 1.95–1.85 (m, 2H), 1.43 (s, 9H). ^{13}C NMR (150 MHz, CDCl$_3$) δ 172.3, 156.0, 136.2, 128.5, 128.2, 128.0, 82.9, 80.5, 66.8, 55.6, 30.9, 30.4, 28.0. IR (ATR) 3324, 2977, 1704, 1522, 1250, 1151, 1046 cm^{-1}.

Repeat: colorless oil (126.0 mg, 97% yield). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.37–7.30 (m, 5H), 5.20 (br d, J = 9.6 Hz, 1H), 5.12 (s, 2H), 4.93–4.87 (m, 1H), 3.34 (s, 3H), 2.37–2.26 (m, 1H), 1.95–1.85 (m, 2H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 172.3, 156.0, 136.2, 128.5, 128.2, 128.1, 82.9, 80.6, 66.8, 55.6, 30.9, 30.4, 28.0.

N-(Benzyloxycarbonyl)-2-methoxypyrrolidine[14] **(2u).** Colorless oil (93.2 mg, 99% yield). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.39–7.28 (m, 5H), 5.24–5.10^b (m, 3H), 3.54–3.50^c and 3.47–3.34^b (m, 2H), 3.39^c and 3.26^c (s, 3H), 2.14–1.69^b (m, 4H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 155.8^c and 154.9^c, 136.6^c and 136.5^c, 128.4^b, 128.0^b, 127.8^b, 89.1^c and 88.5^c, 67.1^c and 66.8^c, 55.9^c and 55.3^c, 45.9^c and 45.7^c, 32.5^c and 31.9^c, 22.6^c and 21.7^c. IR (ATR) 2944, 1702, 1402, 1356, 1079 cm^{-1}. ^{a}Two diastereomers with stereogenic centers at C$_\alpha$ and N. ^{b}Overlapping signals of both diastereomers. ^{c}Separate signals from both diastereomers.

Reagents and solvents

- *N*-Cbz-*O*-benzyl-L-tyrosine (**1m**) (Sigma-Aldrich, CAS Registry No. 16677-29-5, ≥98.0% purity).
- Cbz-*O*-*tert*-butyl-L-serine (**1n**) (Sigma-Aldrich, CAS Registry No. 1676-75-1, ≥98% purity).
- Fmoc-*O*-*tert*-butyl-L-serine (**1o**) (Sigma-Aldrich, CAS Registry No. 71989-33-8, ≥98% purity).
- Cbz-L-asparagine (**1p**) (Acros Organics, CAS Registry No. 2304-96-3, 98% purity).
- *N*-Cbz-L-glutamine (**1r**) (Fluka, CAS Registry No. 2650-64-8, ≥99.0% purity).
- *N*-Cbz-L-aspartic acid 4-*tert*-butyl ester (**1s**) (Fluka Analytical, CAS Registry No. 5545-52-8, ≥98% purity).
- *N*-Cbz-L-glutamic acid 5-*tert*-butyl ester (**1t**) (Acros Organics, CAS Registry No. 3886-08-6, ≥98% purity).
- *N*-Cbz-L-proline (**1u**) (Acros Organics, CAS Registry No. 1148-11-4, 99% purity).
- *N*-Cbz-D,L-methionine (**1w**) (Fluka, CAS Registry No. 4434-61-1, ≥98% purity).
- *N*-Boc-*S*-benzyl-L-cysteine (**1x**) (Acros Organics, CAS Registry No. 5068-28-0, ≥98% purity).
- *N*-Ac-D,L-tryptophan (**1y**) (Sigma-Aldrich, CAS Registry No. 87-31-1, 98% purity).
- Triethylamine (Alfa-Aesar, CAS Registry No. 121-44-8, 99% purity).
- Methanol, p.a. ACS, ISO, Ph. Eur (S.WITKO CHS, Chemsolve, CAS Registry No. 67-56-1, 99.8% purity)

Reagent setup

- *N*-Piv-D,L-alanine **1a** was synthesized by described protocol[33] (see ESI†).
- The reagents **1b–y**, Et₃N and MeOH, purchased from commercial suppliers were used without further purification.

Equipment
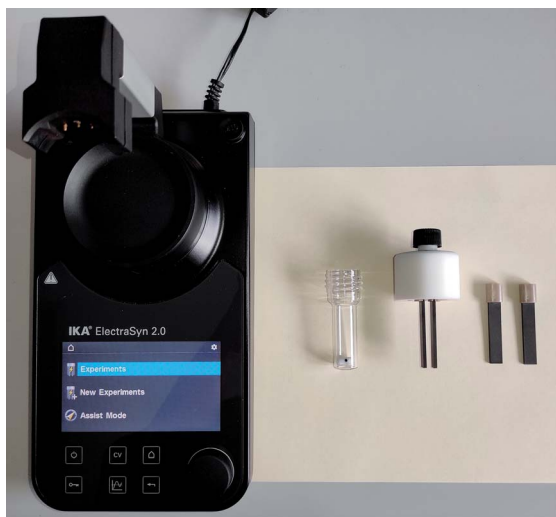
- ElectraSyn 2.0 with 5 mL vial and two graphite SK-50 electrodes (IKA®).

Notes

Note A: a photo of the degraded platinum electrodes.

Note B: good mixing of the reagents ensures rapidly achieving stable electrolysis parameters. Only in the case of Cbz-L-asparagine (**1p**), the electrolysis was carried out for the suspension, which disappeared during the reaction progress.

Conclusions

Herein, we have described an improved method for the non-Kolbe electrolysis of *N*-protected-α-amino acids using an ElectraSyn 2.0 setup. As we have demonstrated, this easy-to-use and compact apparatus allows us to conduct electrochemical decarboxylative methoxylation under mild conditions in excellent yields. The necessity of building a homemade electrochemical setup is no longer a limitation of this transformation. Moreover, the use of standardized equipment ensures the repeatability of the reactions performed in laboratories all over the world. Besides, a simple, low-waste workup procedure and the possibility of using clean electricity are in line with the trends of developing sustainable and "green" organic synthesis procedures.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

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