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Integrated Flow Synthesis of α-Amino Acids by *In Situ* Generation of Aldimines and Subsequent Electrochemical Carboxylation

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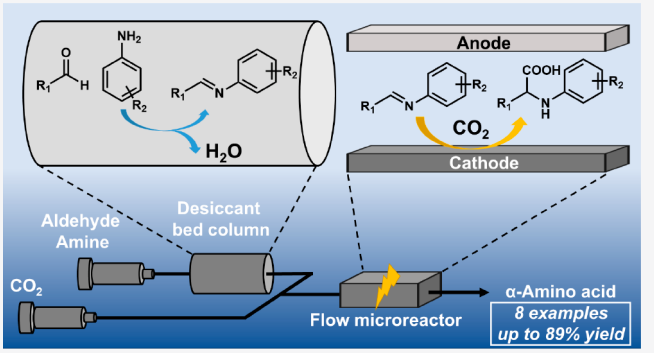
ABSTRACT: The synthesis of α-amino acids was carried out in a continuous flow system. In this system, aldimines were efficiently generated *in situ* via the dehydration−condensation of aldehydes with anilines in a desiccant bed column filled with 4 Å molecular sieves desiccant, followed by reaction with CO_2 in an electrochemical flow microreactor to afford the α-amino acids in high to moderate yields. The present system can provide α-amino acids without using stoichiometric amounts of metal reagents or highly toxic cyanide reagents.



INTRODUCTION

The organic synthesis of valuable products has thus far been based on reactions involving low-cost and readily available raw materials. However, in the multistep synthesis, the step-by-step synthetic method leads to some problems such as large amounts of organic solvent waste and time-consuming isolation procedures.[1] By contrast, a flow reactor enables simple reactions to be integrated with complete molecular transformations that comprise numerous steps without isolating intermediates.[2] Therefore, integrated synthesis in a single operation in a flow reactor system can minimize solvent waste and time consumption. Consequently, numerous conventional step-by-step syntheses have recently been replaced with integrated synthetic methods in a flow reactor.[3]

α-Amino acids are important and essential compounds in foods, drugs, cosmetics, and other products.[4] Therefore, the synthesis of α-amino acids has long been an important research topic. Some natural α-amino acids can be prepared on an industrial scale using a conventional fermentation process;[5] however, synthesizing unnatural α-amino acids using this process is difficult. Therefore, chemical synthetic routes to unnatural α-amino acids need to be developed. Although many chemical synthetic routes to α-amino acids have been developed, the α-carboxylation of amine derivatives with CO_2 is regarded as a reasonable and economical route because the carboxy unit can be derived directly from inexpensive and easily handled CO_2.[4c,6] For a carboxylation reaction with poorly reactive CO_2, the generation of highly reactive carbon nucleophiles from amine derivatives is necessary. Hence, stoichiometric quantities of basic organolithium reagents (Figure 1A)[6a−g] and difficult-to-handle metal reductants (Figure 1B)[6g] have been traditionally used; moreover, a large amount of reagent waste is usually generated after the reaction. In this context, electrochemical carboxylation represents an attractive alternative to conventional chemical carboxylation methods (Figure 1C).[7]

In electrochemical carboxylation, highly reactive carbon nucleophiles are readily generated at cathodes and then react with CO_2 immediately to provide the corresponding α-amino acids without handling sensitive, expensive, and toxic reagents. To date, several groups have demonstrated the synthesis of α-amino acids via the electrochemical carboxylation of aldimines.[7a−c] Moreover, in our previous work, we reported the electrochemical carboxylation of several aldimines in a flow microreactor to afford the corresponding α-amino acids in good to moderate yields.[8] However, numerous aldimines are moisture sensitive and not sufficiently stable for isolation.[9] In addition, some aldimines are readily tautomerized to the corresponding enamines. Therefore, the use of aldimines as substrates for electrochemical carboxylation appears to be less versatile, warranting the development of an alternative approach. To address this challenge, we developed an integrated synthesis in a single operation in a flow reactor system. We expected the integration of aldimine generation via condensation of the aldehyde and amine substrates and

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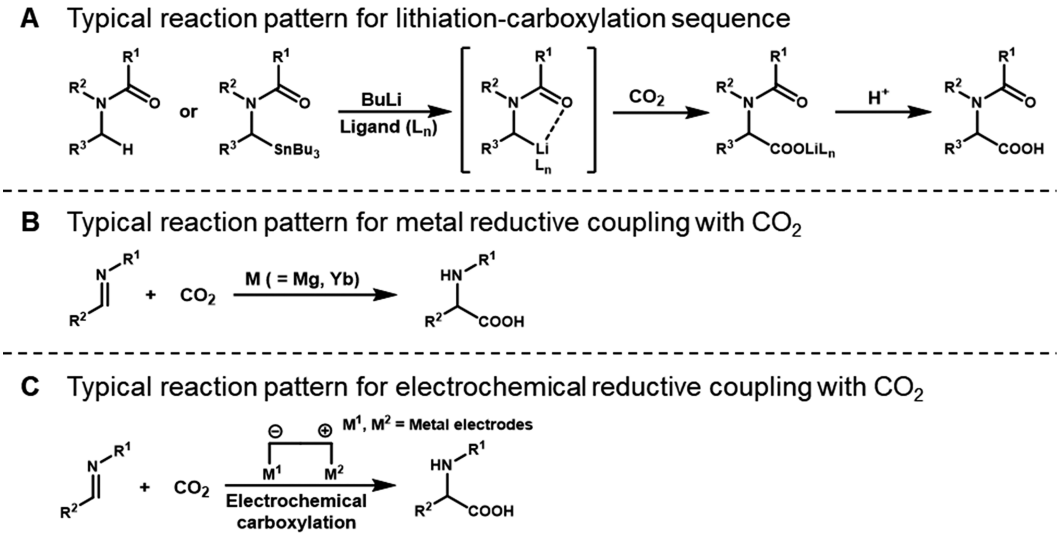

Figure 1. Approaches for carboxylation of amine derivatives with CO_2.

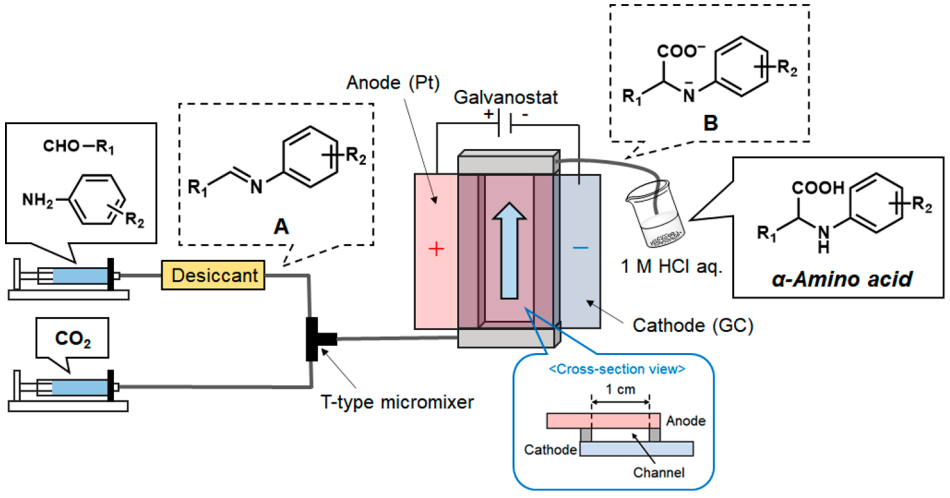

Figure 2. Schematic representation of the electrochemical carboxylation of *in situ* generated aldimines in a continuous flow system.

subsequent electrochemical carboxylation with CO_2 to represent an elegant solution to the aforementioned challenge.

Herein, we report the first *in situ* generation of aldimines and subsequent electrochemical carboxylation for the efficient synthesis of α-amino acids in a continuous flow system. Factors such as the desiccant material, supporting electrolyte, and current density were optimized to establish a highly efficient and green α-amino acid synthesis system.

RESULTS AND DISCUSSION

To realize our objective, as shown in Figure 2, we fabricated a flow microreactor for a model integrated synthetic reaction comprising three stages: the aldimine **A** formation stage involving the dehydration−condensation of aldehydes with anilines in a desiccant bed column, the electrochemical carboxylation stage for the generation of carboxylate ions **B** in an electrochemical flow microreactor, and the acidification stage for the rapid protonation of **B** with 1 M HCl aq. For electrochemical carboxylation to proceed in a conventional batch-type reactor, metal ions generated at sacrificial anodes (e.g., Mg and Al anodes) are generally required in order to stabilize the unstable carboxylate ions.[7b−d] However, from a green chemistry perspective, metal-ion contamination in the reaction mixture is a serious drawback. In sharp contrast, because of the rapid acidification of unstable carboxylate ions **B** in the flow operation, the electrochemical carboxylation would be completed without decomposition, even in the absence of a sacrificial anode.

Prior to demonstrating the integrated synthetic reaction, we examined the dehydration−condensation of benzaldehyde **1a** with aniline **2a** in two types of desiccant-bed columns with different dimensions to determine which column was better suited for the present reaction system. In these experiments, 4 Å molecular sieves (4 Å MS) were used as a desiccant and were filled into the columns (Table 1). As shown in entry 1, the use of a column 10 cm long and with a 1.5 cm inner diameter gave the desired aldimine **3a** in 87% yield. In this case, the corresponding amount of unreacted aldehyde **1a** and aniline **2a** were also recovered. By contrast, aldimine **3a** was obtained in 98% yield when a column 20 cm long and with a 1.0 cm inner diameter (entry 2) was used. Although the volumes of both columns were approximately the same and the amount of desiccant filled was also approximately the same, the reaction using the longer column proceeded more efficiently. In addition, such an excellent yield was maintained even when the concentration of the reaction substrates was increased by

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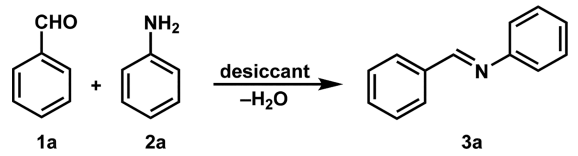
Table 1. Effect of Column Type and Concentration of Benzaldehyde (1a) on the Yield of Benzylideneaniline (3a) in the Dehydration−Condensation of 1a with Aniline (2a)[a]



entry	column length (cm)	diameter (cm)	concentration of **1a** (M)	yield of **3a** (%)[b]
1	10	1.5	0.12	87
2	20	1.0	0.12	98
3	20	1.0	0.18	95

[a]Experimental conditions: flow rate, 7.5 mL h^{-1}; flow solution, 0.14 M Bu_4NClO_4 in THF; substrate, benzaldehyde **1a** (1 equiv) and aniline **2a** (1.2 equiv); desiccant, 11 g 4 Å MS. [b]Determined by HPLC.

1.5 times (entry 3). This result is attributed to the larger theoretical plate number exhibited by the longer column.

The dehydration−condensation reaction of **1a** with **2a** was subsequently carried out using the longer column (20 cm long and 1.0 cm inner diameter) filled with different desiccants (Table 2). When the reaction was carried out with $MgSO_4$ as

Table 2. Effect of Desiccant Type on Yield of Benzylideneaniline (3a) in the Dehydration−Condensation of Benzaldehyde (1a) with Aniline (2a)[a]

entry	desiccant type	yield of **3a** (%)[b]
1	$MgSO_4$	19
2	Na_2SO_4	21
3	3 Å MS	83
4	4 Å MS	98

[a]Experimental conditions: flow rate, 7.5 mL h^{-1}; flow solution, 0.14 M Bu_4NClO_4 in THF; substrate, 0.12 M benzaldehyde (**1a**) and 0.144 M aniline (**2a**). [b]Determined by HPLC.

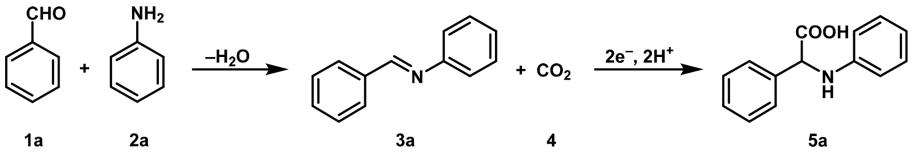
the desiccant, the desired aldimine **3a** was obtained in a 19% yield (entry 1). The use of Na_2SO_4 did not improve the yield of **3a** (entry 2). By contrast, the reaction proceeded smoothly with molecular sieves 3A (3 Å MS) to give **3a** in 83% yield (entry 3). As shown in the data from the investigation of column dimensions, the use of 4 Å MS, which has larger pores than 3 Å MS, further increased the yield of **3a** (98% yield, entry 4). Therefore, 4 Å MS appears to be a promising desiccant material for dehydration−condensation; 4 Å MS was selected as the desiccant for this reaction system and was used in the subsequent experiments.

We next investigated the model integrated synthetic reaction in the flow microreactor system illustrated in Figure 2. In this demonstration, the previous dehydration−condensation reaction of **1a** with **2a** was carried out using the longer column (20 cm length and 1.0 cm inner diameter) filled with 4 Å MS, and the subsequent electrochemical carboxylation of **3a** was conducted with Bu_4NClO_4 electrolyte in THF at different current densities (Table 3, entries 1−4). Since THF is a reduction-resistant solvent, it is expected not to interfere with the reduction of **3a**. On the other hand, it is relatively easy to be oxidized, so sacrificial anodic oxidation of THF is expected to prevent the oxidation of the product **5a**. The electrolysis at 6.3 mA cm^{-2} smoothly proceeded to afford the desired α-amino acid **5a** in 65% yield (entry 1). In this case, *N*-phenylbenzylamine was also obtained as a side product in ∼24% yield, and unreacted aldimine **3a** was recovered to some extent. The yield of **5a** reached 74% at 12.7 mA cm^{-2} (entry 2) but decreased at current densities greater than 19 mA cm^{-2} (entries 3 and 4). This decrease is attributed to a competing CO_2 reduction reaction in the electrochemical carboxylation step.

The rate of the nucleophilic reaction between the radical−anion intermediate generated reductively from aldimine **3a** and CO_2 can be accelerated by using a supporting electrolyte with larger cation because this leads to fewer ion-pair interactions with the radical−anion intermediate. To confirm this conjecture, we carried out electrochemical carboxylation using a different supporting electrolyte with larger cations: tetrahexylammonium (Hex_4N^+) (Table 3, entry 5). As expected, the use of Hex_4NClO_4 further increased the yield of the desired product **5a**.

Finally, to demonstrate the general applicability of the proposed continuous flow system, we investigated the use of various aldehydes and anilines as starting substrates (Table 4). In parallel with a demonstration of the integrated synthesis, the yield of nonenolizable and isolable aryl-substituted aldimine intermediates formed after the dehydration−condensation

Table 3. Effect of the Supporting Electrolyte and Current Density on the Yield of α-Amino Acid 5a in the Integrated Synthesis[a]



entry	supporting electrolyte	current density (mA cm^{-2})	yield of **3a** (%)[b]	yield of **5a** (%)[b]
1	Bu_4NClO_4	6.30	98	65
2	Bu_4NClO_4	12.7	98	74
3	Bu_4NClO_4	19.0	98	71
4	Bu_4NClO_4	25.0	98	62
5	Hex_4NClO_4	12.7	95	81

[a]Experimental conditions: cathode, glassy carbon plate; anode, Pt plate; charge passed, 8 F mol^{-1} (25 mA cm^{-2}), 6 F mol^{-1} (19 mA cm^{-2}), 4 F mol^{-1} (12.7 mA cm^{-2}), 2 F mol^{-1} (6.3 mA cm^{-2}); electrode distance, 20 μm, desiccant; 4 Å MS, 11 g. Inlet 1: solvent, THF; substrate, 0.12 M benzaldehyde and 0.144 M aniline; supporting electrolyte, 0.14 M; flow rate, 3.3 mL h^{-1}. Inlet 2: solution, THF saturated with CO_2; supporting electrolyte, 0.14 M; flow rate, 7.5 mL h^{-1}. [b]Determined by HPLC.

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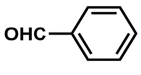
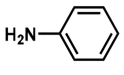
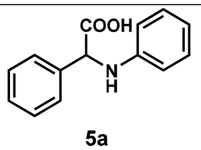
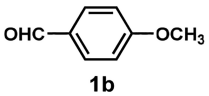
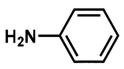
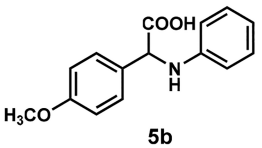
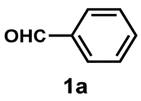
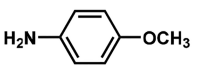
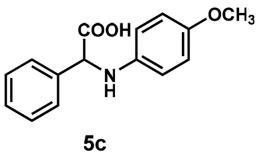
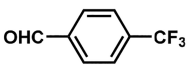
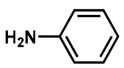
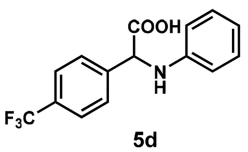
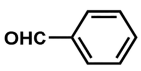
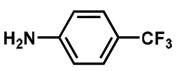
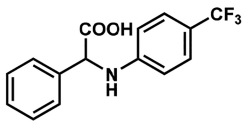
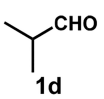
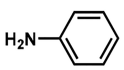
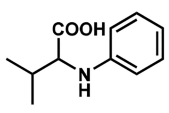
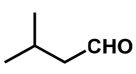
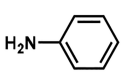
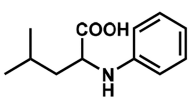
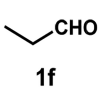
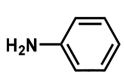
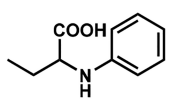
Table 4. Integrated Synthetic Reaction Using Aryl-Substituted Aldehydes with Anilines in a Continuous Flow System[a]

Entry	Aldehyde **1**	Amine **2**	α-Amino acid **5**	Yield of α-amino acid **5**[b] (%)
1	 **1a**	 **2a**	 **5a**	81
2	 **1b**	 **2a**	 **5b**	89
3	 **1a**	 **2b**	 **5c**	65
4	 **1c**	 **2a**	 **5d**	43
5	 **1a**	 **2c**	 **5e**	0
6	 **1d**	 **2a**	 **5f**	73
7	 **1e**	 **2a**	 **5g**	41
8	 **1f**	 **2a**	 **5h**	9

[a]Experimental conditions: cathode, glassy carbon plate; anode, Pt plate; charge passed, 4 F mol^{-1}; current density, 12.7 mA cm^{-2}; electrode distance, 20 μm; desiccant, 4 Å MS, 11 g. Inlet 1: solvent, THF; substrate, 0.12 M aldehyde (**1**) and 0.144 M aniline (**2**); supporting electrolyte, 0.14 M Hex_4NClO_4; flow rate, 3.3 mL h^{-1}. Inlet 2: solution, THF saturated with CO_2; supporting electrolyte, 0.14 M Hex_4NClO_4; flow rate, 7.5 mL h^{-1}. [b]Determined by HPLC.

reaction was also confirmed by collecting samples of the reaction solutions at the outlet of the desiccant column and analyzing them (Table 5). The reaction of benzaldehyde **1a** with aniline **2a** provided the desired α-amino acid **5a** in 81% yield (Table 4, entry 1) via the generation of aldimine **3a** in 98% yield (Table 5, entry 1). The dehydration−condensation of benzaldehyde bearing a methoxy group (**1b**) with aniline **2a** gave the corresponding aldimine **3b** in excellent yield (92%, Table 5, entry 2); the subsequent carboxylation of **3b** afforded the α-amino acid **5b** in 89% yield (Table 4, entry 2). In general, the increase in electron density on the carbon atom of the C═N bond enhances the nucleophilic reactivity of the

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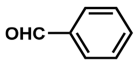
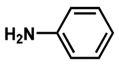
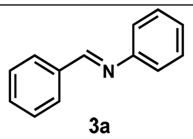
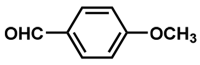
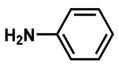
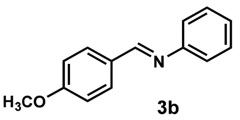
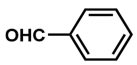
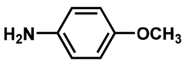
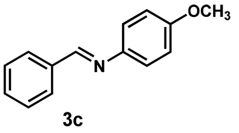
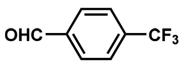
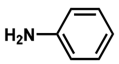
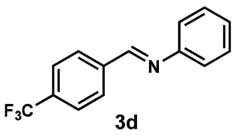
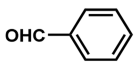
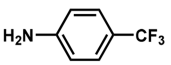
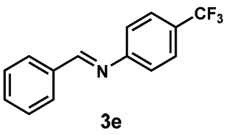
Table 5. Dehydration−Condensation of Various Benzaldehydes and Anilines in a Desiccant Bed Column Filled with 4 Å MS[a]

Entry	Aldehyde **1**	Amine **2**	Aldimine **3**	Yield of aldimine **3** (%)
1	 **1a**	 **2a**	 **3a**	98 [b]
2	 **1b**	 **2a**	 **3b**	92 [b]
3	 **1a**	 **2b**	 **3c**	>99 [c]
4	 **1c**	 **2a**	 **3d**	76 [b]
5	 **1a**	 **2c**	 **3e**	9 [b]

[a]Experimental conditions: flow rate, 7.5 mL h^{-1}; flow solution, 0.14 M Hex_4NClO_4 in THF; substrate, 0.12 M aldehyde (**1**) and 0.144 M aniline (**2**). [b]Determined by HPLC. [c]Determined by GC.

radical−anion intermediates. Therefore, the carboxylation of **3b** bearing an electron-donating group (CH_3O group) would proceed very smoothly. The aniline bearing a methoxy group (**2b**) was also a good substrate for the formation of amino acid **5c** as a final product (65%, Table 4, entry 3). In our previous work, we carried out the electrochemical carboxylation of **3c** as a single reaction.[8] At that time, almost no product **5c** was obtained. However, in the present work, before the integrated reaction, the supporting electrolyte was sufficiently dried to prevent the deactivation of the radical−anion intermediate by a small amount of water dissolved in the medium. In addition, because the desiccant column in the former process not only drives the dehydration−condensation reaction but also further dehydrates the reaction medium, it positively affects the latter carboxylation reaction. The dehydration−condensation of benzaldehyde bearing a CF_3 group (**1c**) with aniline **2a** provided the corresponding aldimine **3d** in good yield (76%, Table 5, entry 3). However, the subsequent carboxylation of **3c** resulted in a lower yield of the corresponding amino acid **5d** (43%, Table 4, entry 3). This lower yield is attributed to a decrease in electron density on the carbon atom of the C═N bond, which diminished the nucleophilic reactivity of the radical−anion intermediate toward CO_2. When the reaction was carried out with aniline bearing a CF_3 functionality (**2c**), the corresponding amino acid **5e** was not obtained at all (Table 4, entry 5). In this case, aldimine **3e** formed from the former dehydration−condensation of benzaldehyde **1a** with aniline **2c** was hardly obtained (9%, Table 5, entry 5).

In the aforementioned investigations, nonenolizable and isolable aryl-substituted aldimine intermediates were involved in the integrated synthesis reactions. However, in the case of entries 6−8, we carried out integrated synthesis reactions that involve more demanding alkyl-substituted aldimine intermediates derived from alkyl-substituted aldehydes. Alkyl-substituted aldimines are a class of intermediates known to not be readily isolated and purified and are typically prone to decomposition.[10] Therefore, these investigations are also important to confirm the versatility of the integrated synthesis system. The reaction of alkyl-substituted aldehyde **1d** with aniline **2a** provided the desired α-amino acid **5f** in 73% yield (Table 4, entry 6). Similarly, the integrated reaction of alkyl-substituted aldehyde **1e** with aniline **2a** proceeded to afford the desired α-amino acid **5g** in reasonable yield (41%) (Table 4, entry 7). However, when the alkyl-substituted aldehyde **1f** was used as the starting substrate, the corresponding α-amino acid **5h** was obtained in low yield (9%) (Table 4, entry 8). This result is ascribed to poor reactivity in the dehydration−condensation because a large amount of unreacted aldehyde **1f** and aniline **2a** were recovered from the solution that passed through the desiccant bed column.

These generality experiments show that this integrated synthesis system is extremely useful in controlling reactions involving unstable aldimines and their rapid use in subsequent

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electrochemical carboxylation, although there are a few exceptions.

CONCLUSIONS

We demonstrated the synthesis of α-amino acids in a continuous flow system. In the present system, aldimines were generated *in situ* from the dehydration−condensation of aldehydes with anilines in a desiccant bed column filled with a desiccant and subsequently reacted with CO_2 in an electrochemical flow microreactor to afford the α-amino acids. By examining various desiccant materials, 4 Å molecular sieves (4 Å MS) were found to be the most efficient in providing aldimines. In addition, the structure of a desiccant bed column was also optimized. For the electrochemical carboxylation step, a supporting electrolyte with a large cation such as Hex_4N^+ was also found to be effective. From the generality experiments, it was also found that this integrated synthesis system was extremely useful in controlling reactions involving *in situ* generated aldimines and their rapid use in subsequent electrochemical carboxylation, although there are a few exceptions. This process does not require the handling of stoichiometric amounts of metal reagents or highly toxic cyanide reagents. Therefore, in order to further improve this reaction system, we will continue to optimize the structure of the electrochemical flow microreactor. In addition, we plan to investigate ortho/meta-substituents and electrophiles other than CO_2 in order to expand the scope of the reaction.

EXPERIMENTAL SECTION

General Methods. Commercial reagents and solvents were used without further purification. Benzylideneaniline (**3a**) and *N*-(4-methoxybenzylidene)aniline (**3b**) were purchased from Tokyo Chemical Industry. A silicon oil bath was used as a heat source for the reactions. High-performance liquid chromatography (HPLC) analyses of **3a**, **3b**, **3d**, and **3e** were performed on an apparatus with a liquid chromatography (LC) pump (LC-20AD, Shimadzu), a UV detector (SPD-10A, Shimadzu), and a column (Mightysil RP-18 GP Aqua 250−4.6 (5 μm), Kanto Kagaku) using a mixture of *n*-hexane/isopropyl alcohol/diethylamine as a mobile phase. Gas chromatography (GC) analysis of **3c** was performed using a Shimadzu gas chromatograph (GC2014) equipped with a capillary column (0.50 μm, 30.0 m, 0.25 mm ID (CP-Sil 8 CB for amines, Agilent Technologies)). HPLC analyses for **5a**, **5b**, **5c**, **5d**, and **5e** were performed with a column (Inertsil ODS-4, GL Sciences) using a mixture of H_2O/MeCN/H_3PO_4 as a mobile phase. HPLC analyses of **5f**, **5g**, and **5h** were performed with a column (Inertsil ODS-4, GL Sciences) using a mixture of H_2O/tetrahydrofuran (THF)/H_3PO_4 as a mobile phase. All chromatograms were recorded using an LC or GC workstation (LabSolutions DB, Shimadzu). Infrared (IR) spectra were recorded using an IRAffinity-1 (Shimadzu). ^{1}H NMR spectra were recorded on a Bruker DRX-500 (500 MHz) spectrometer using tetramethylsilane (TMS) as an internal standard with the solvent resonance ($CDCl_3$: δ 7.26, DMSO: δ 2.50). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants, integration. ^{13}C NMR spectra were recorded on a Bruker DRX-500 (126 MHz) spectrometer with complete proton decoupling. Chemical shifts were reported in ppm from the TMS internal standard with the solvent resonance (DMSO: δ 39.5). ^{19}F NMR spectra were recorded on a JEOL Resonance ECA-500 (471 MHz) spectrometer with complete proton decoupling. Chemical shifts were reported in ppm from a fluorobenzene internal standard (δ −113.15) in dimethyl sulfoxide (DMSO).

Electrochemical Flow Microreactor. The reactor was constructed from an anode plate (Pt, 30 mm width, 30 mm length) and a cathode plate (glassy carbon (GC), 30 mm width, 30 mm length) (Figure S1). A spacer (20 μm thickness double-faced adhesive type) was used to leave a rectangular channel exposed, and the two electrodes were simply sandwiched together (area of the two electrodes: 10 × 30 mm^2). After Teflon tubing was connected to the inlets and outlet, the reactor was sealed with epoxy resin (Figure S2).

Continuous-Flow Microreactor System. The continuous-flow microreactor system for the model integrated synthetic reaction was fabricated as illustrated in Figure 2. Dehydration−condensation of aldehydes with anilines was performed with two types of desiccant bed columns with different dimensions (glass column 178170 (20 cm long with 1.0 cm inner diameter) and glass column 129450 (10 cm long with 1.5 cm inner diameter), EYELA Glass). The dehydration−condensation reaction was carried out by introducing a solution (0.14 M Bu_4NClO_4 or Hex_4NClO_4 in THF) containing aldehydes and anilines into the column via a syringe pump (KdScientific KDS100, Muromachi Kikai). Electrolyte (Bu_4NClO_4 or Hex_4NClO_4) was also added to the THF solution in advance for subsequent electrochemical carboxylation. CO_2 solution was prepared by bubbling analytical grade CO_2 in 0.14 M Bu_4NClO_4 or Hex_4NClO_4 in THF for 30 min. As a micromixer in which the aldimines **A** formed by the dehydration−condensation reaction and CO_2 solution were mixed, a T-type micromixer (SUS316L ⌀1.0) manufactured by Sankoh Seiki Co. was used. Thus, a solution of aldimines **A** and a solution of CO_2 were introduced into the T-type micromixer via a syringe pumping technique (the KDS100 syringe pump was also used to flow CO_2 solution). The solution mixture was then introduced into the electrochemical flow microreactor, where the electrochemical carboxylation of aldimines **A** was carried out. The electrochemical carboxylation was conducted in constant-current mode using a galvanostat (HABF-501A, Hokuto Denko).

General Procedure for the Synthesis of Aldimines (3c−e) as Authentic Samples for HPLC Analysis. Aldimines (**3c−e**) were synthesized according to a method reported in the literature.[11] To a solution of the corresponding aromatic aldehyde (5.0 mmol, 1.0 equiv) in dry toluene (5.0 mL) and 4 Å MS (1.0 g) was added the corresponding aromatic amine (5.0 mmol, 1.0 equiv). The reaction mixture was heated at reflux for 24 h, cooled to room temperature (rt), and filtered through Celite. The solvent was removed under reduced pressure. The residue was purified by column chromatography using silica gel (hexane/Et_2O 50:1) to afford the products (**3c−e**).

*N-Benzylidene-4-methoxyaniline (**3c**).*[12] Yellow solid, 0.99 g, 79% yield. ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.49 (s, 1H), 7.89 (dt, *J* = 3.94, 2.92 Hz, 2H), 7.48−7.45 (m, 3H), 7.23−7.26 (m, 2H), 6.96−6.92 (m, 2H), 3.84 (s, 3H).

*N-(4-(Trifluoromethyl)benzylidene)aniline (**3d**).*[13] Yellow solid, 0.85 g, 81% yield. ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.52 (s, 1H), 8.03 (d, *J* = 7.88 Hz, 2H), 7.74 (d, *J* = 7.88 Hz, 2H), 7.44−7.40 (m, 2H), 7.29−7.20 (m, 1H).

*N-Benzylidene-4-trifluoromethylaniline (**3e**).*[12] Yellow solid, 0.73 g, 59% yield. ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.43 (s, 1H), 7.93−7.90 (m, 2H), 7.65 (dd, *J* = 8.83, 0.63 Hz, 2H), 7.53−7.48 (m, 3H), 7.25 (s, 2H).

General Procedure for the Synthesis of α-Amino Acids (5a, 5b, 5d, 5e) as Authentic Samples for HPLC Analysis. α-Amino acids (**5a**, **5b**, **5d**, and **5e**) were synthesized according to a method reported in the literature.[14] A solution of the corresponding aromatic aldehyde (5.0 mmol, 1.0 equiv) and aromatic amine (5.0 mmol, 1.0 equiv) in MeOH (20 mL) was stirred for 10 min at rt. After the reaction, a mixture of pyruvic acid (5.0 mmol, 1.0 equiv) and cyclohexyl isocyanide (5.0 mmol, 1.0 equiv) was added, and the resultant mixture was stirred at rt for 48 h. The reaction mixture was then treated with a solution of KOH (6.0 mmol, 1.2 equiv) in MeOH (4.0 mL). After the mixture was stirred for 2 h at room temperature, the solvent was removed under reduced pressure, and the residue was partitioned between H_2O (30 mL) and $CHCl_3$ (30 mL). The layers were separated, and the aqueous phase was acidified to pH 4 by the addition of formic acid. The resultant suspension was filtered, and the

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collected solid product was washed with water and dried to give the α-amino acids (**5a**, **5b**, **5d**, and **5e**).

*α-(Phenylamino)benzeneacetic Acid (**5a**).*[14] Yellow solid, 0.30 g, 26% yield. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.50 (d, J = 7.30 Hz, 2H), 7.35 (t, J = 7.41 Hz, 2H), 7.31−7.26 (m, 1H), 6.64 (d, J = 7.57 Hz, 2H), 6.53 (t, J = 7.02 Hz, 1 H), 5.06 (s, 1 H).

*4-Methoxy-α-(phenylamino)benzeneacetic Acid (**5b**).*[14] Yellow solid, 0.18 g, 14% yield. ^{1}H NMR (500 MHz; DMSO-d_6): δ 6.91 (d, J = 8.51 Hz, 2H), 6.63 (d, J = 8.20 Hz, 2H), 6.53 (t, J = 7.09 Hz, 1H), 4.99 (s, 1H), 3.76−3.70 (m, 3H).

*α-(Phenylamino)-4-(trifluoromethyl)benzeneacetic Acid (**5d**).* Yellow solid, 0.33 g, 22% yield. ^{1}H NMR (500 MHz; DMSO-d_6): δ 7.77−7.72 (m, 4H), 7.72−7.63 (m, 1H), 7.04 (t, J = 8.04 Hz, 2H), 6.66 (d, J = 7.88 Hz, 2H), 6.56 (t, J = 7.25 Hz, 1H), 5.26 (s, 1H). ^{13}C{^{1}H} NMR (126 MHz; DMSO-d_6): δ 172.0, 146.6, 128.7, 128.2 (q, J = 31.46 Hz), 128.2, 125.2 (q, J = 3.94 Hz), 124.2 (q, J = 271.9 Hz), 116.7, 113.1, 72.1, 59.42; ^{19}F NMR (471 MHz; DMSO-d_6): δ −61.1 (s, 3F). IR (KBr): 2934, 1717, 1589, 1496, 1420, 1379, 1328, 1259, 1167, 1126, 1070, 760 cm^{-1}. HRMS (ESI): m/z calcd for $C_{15}H_{13}NO_2F_3$ [M + H]$^+$, 296.0893; found, 296.0917.

*α-[(4-Trifluoromethylphenyl)amino]benzeneacetic Acid (**5e**).* Yellow solid, 0.65 g, 44% yield. ^{1}H NMR (500 MHz; DMSO-d_6): δ 7.51 (d, J = 7.88 Hz, 2H), 7.41−7.30 (m, 6H), 6.98 (d, J = 6.62 Hz, 1H), 6.79 (d, J = 8.20 Hz, 2H), 5.20 (d, J = 6.94 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz; DMSO-d_6): δ 172.3, 150.0, 137.8, 128.5, 127.9, 127.4, 126.0 (q, J = 270.02 Hz), 125.1 (q, J = 3.97 Hz), 116.3 (q, J = 32.07 Hz), 112.4, 59.3; ^{19}F NMR (471 MHz; DMSO-d_6): δ −59.4 (s, 3F). IR (KBr): 3422, 3273, 1719, 1618, 1533, 1329, 1267, 1219, 1182, 1125, 1067 cm^{-1}. HRMS (ESI): m/z calcd for $C_{15}H_{13}NO_2F_3$ [M + H]$^+$, 296.0893; found, 296.0898.

Procedure for the Synthesis of α-Amino Acid (5c) as Authentic Samples for HPLC Analysis. α-Amino acid **5c** was synthesized according to a method reported in the literature.[15] α-Bromophenylacetic acid (1.1 g, 5.0 mmol), $NaHCO_3$ (0.42 g, 5.0 mmol), and *p*-anisidine (0.74 g, 6.0 mmol) in ethanol (5.0 mL) were added to a solution of NaOH (0.20 g, 5.0 mmol) in water (20 mL) at 0 °C. After the mixture was heated at 90 °C for 12 h, the solution was concentrated, and 1 M hydrochloric acid was added at 0 °C until the pH was 4. The precipitate was filtered off, dried *in vacuo*, and recrystallized (Et_2O/hexane = 1:9) to afford the α-amino acid **5c**.

*α-[(4-Methoxyphenyl)amino]benzeneacetic Acid (**5c**).*[16] Yellow solid, 0.15 g, 12% yield. ^{1}H NMR (500 MHz; DMSO-d_6): δ 7.48 (d, J = 7.57 Hz, 2H), 7.35−7.29 (m, 1H), 7.28−7.23 (m, 1H), 6.67−6.63 (m, 2H), 6.59−6.55 (m, 2H), 4.89 (s, 1H).

General Procedure for the Synthesis of α-Amino Acids (5f) as an Authentic Sample for HPLC Analysis. α-Amino acid **5f** was synthesized according to a method reported in the literature.[15] 2-Bromopropionic acid (1.8 g, 10 mmol), $NaHCO_3$ (0.84 g, 10 mmol), and a solution of aniline (1.1 mL, 12 mmol) in ethanol (5.0 mL) were sequentially added with cooling to a solution of NaOH (0.4 g, 10 mmol) in water (20 mL). The resultant mixture was heated for 24 h, the solution was concentrated to a volume of 150 mL, dilute hydrochloric acid was added until the pH was 4−5, and the solution was then cooled to 0 °C. The precipitate was filtered, dried in the air, and recrystallized from absolute ethanol to afford α-amino acid **5f**.

*N-Phenylvaline (**5f**).*[15] Brown solid, 0.36 g, 19% yield. (500 MHz; DMSO-d_6): δ 7.06 (t, J = 7.17 Hz, 2H), 6.62 (d, J = 7.68 Hz, 2H), 6.54 (t, J = 7.52 Hz, 1H), 3.62 (d, J = 6.62 Hz, 1H), 2.05 (dq, J = 13.56 Hz, 1H), 1.07−0.93 (m, 6H).

General Procedure for the Synthesis of α-Amino Acids (5g and 5h) as Authentic Samples for HPLC Analysis. α-Amino acids (**5g** and **5h**) were synthesized according to a method reported in the literature.[15] Iodobenzene (1.1 mL, 10 mmol), CuI (190 mg, 1.0 mmol, 10 mol %), an aliphatic amino acid (15 mmol), potassium phosphate monohydrate (6.4 g, 30 mmol), decanol (3.0 mL), and water (10 mL) were added to a 50 mL round-bottom flask. The air was evacuated, and the flask was filled with N_2. The reaction mixture was vigorously stirred at 90 °C for 48 h. The reaction was cooled, and the reaction mixture was poured onto ice. Hydrochloric acid was added dropwise with stirring until precipitation was observed, and the pH was adjusted to 6−7. The acidified solution was extracted with EtOAc. The organic layer was separated, and the aqueous layer was acidified with hydrochloric acid to adjust the pH to 5−6. The aqueous layer was extracted with EtOAc again. The organic layer was separated, and the aqueous layer was adjusted to a pH of 4−5. The aqueous layer was extracted with EtOAc again. The combined organic layers were washed with brine and water, and the solvent was removed by evaporation. The crude product was purified by column chromatography (hexane/EtOAc = 5:1 to 1:1) to give the α-amino acids (**5g** and **5h**).

*N-Phenylleucine (**5g**).*[17] Brown solid, 0.68 g, 22% yield. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.06 (t, J = 7.15 Hz, 2H), 6.58−6.50 (q, 3H), 3.84 (dd, J = 8.67, 5.52 Hz, 1H), 1.85−1.73 (m, 1H), 1.66−1.53 (m, 2H), 0.95 (d, J = 6.62 Hz, 3H), 0.88 (d, J = 6.62 Hz, 3H).

*2-(Phenylamino)butyric Acid (**5h**).*[15] Brown solid, 1.9 g, 69% yield. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.06 (t, J = 7.41, 2H), 6.59−6.52 (m, 3H), 3.79 (t, J = 6.62 Hz, 1 H), 1.83−1.68 (m, 2 H), 0.97 (t, J = 7.25 Hz, 3H).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00821.

Schematic of the electrochemical flow microreactor, schematic of the construction procedure for the electrochemical flow microreactor, and ^{1}H, ^{13}C, and ^{19}F NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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