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Stereoretentive *N*-Arylation of Amino Acid Esters with Cyclohexanones Utilizing a Continuous-Flow System

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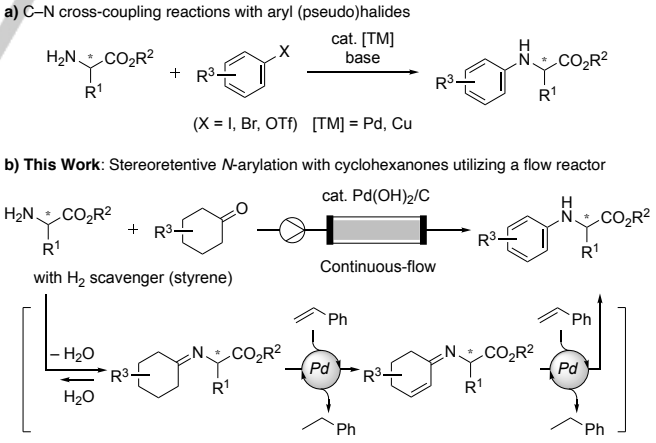
Abstract: The *N*-arylation of chiral amino acid esters with minimal racemization is a challenging transformation because of the sensitivity of the α-stereocenter. We developed a versatile synthetic method to prepare *N*-arylated amino acid esters using cyclohexanones as aryl sources under continuous-flow conditions. The designed flow system, which consists of a coil reactor and a packed-bed reactor containing a $Pd(OH)_2/C$ catalyst, efficiently afforded the desired *N*-arylated amino acids without significant racemization, accompanied by only small amounts of easily removable co-products (i.e., H_2O and alkanes). The efficiency and robustness of this method allowed for the continuous synthesis of the desired product in very high yield and enantiopurity with high space-time yield (74.1 g L^{-1} h^{-1}) and turnover frequency (5.9 h^{-1}) for at least 3 days.

Highly functionalized amino acid derivatives are important for the development of pharmaceuticals and agrochemicals.[1–3] The direct modification of chiral amino acids, which are easily available enantiopure feedstocks, is a straightforward and effective approach for the synthesis of desired amino acid derivatives.[4–6] However, the sensitivity of the α-stereocenter of the chiral amino acids to the reaction conditions typically results in reduced enantiopurity of the products.[7,8] Amino acid esters, a common form of amino acid reagents, are not always suitable for synthetic reactions because of side reactions such as the generation of oligopeptides by self-condensation.[9–11]

Stereoretentive *N*-arylation is a challenging transformation for amino acid esters.[12–16] Although transition metal-catalyzed *N*-arylation of amines with aryl halides is practical for synthesizing aryl amines,[17–19] it cannot be easily applied to stereoretentive reactions of amino acid esters (Scheme 1a); this *N*-arylation is limited by racemization and other side reactions from stoichiometric or excess amounts of strong base reagents.[13–16] In contrast, the catalytic *N*-arylation of amines with cyclohexanones is a promising method that can be applied to the synthesis of amino acid esters (Scheme 1b).[20–24] Unlike transition metal-catalyzed C–N couplings using aryl halides, this reaction proceeds under neutral conditions in the absence of base reagents and will, therefore, be compatible with base-sensitive amino acid compounds. Furthermore, this reaction, which consists of consecutive condensation and dehydrogenative aromatization, has several advantages over conventional C–N couplings: (i) small amounts of co-products such as H_2O are easily removable, (ii) cyclohexanones bearing various functional groups can be prepared using classical synthetic methodologies as halogen-free sources of aromatic rings, and (iii) the use of heterogeneous Pd catalysts can significantly reduce the costs associated with the catalysis and the purification process.

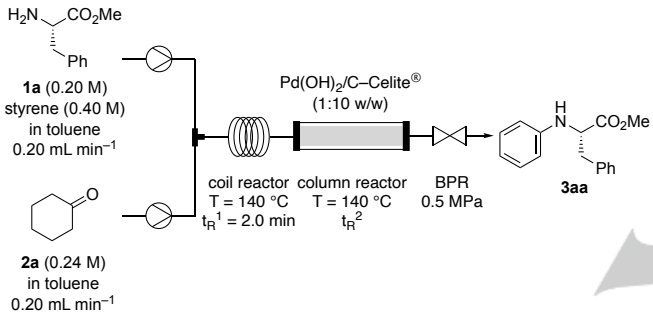


Scheme 1. Summary of previous work and the present study for the *N*-arylation of chiral amino acid esters. a) Modern transition metal-catalyzed C–N couplings with aryl (pseudo)halides in the presence of a base. b) Pd-catalyzed stereoretentive *N*-arylation with readily available cyclohexanones utilizing a packed-bed flow reactor.

Despite these advantages, this type of reaction has rarely been applied for the synthesis of amino acid compounds. Recently, we reported the continuous synthesis of aryl amines from cyclohexanones, which were prepared from the

hydrogenation of phenols, by utilizing an integrated packed-bed flow system.[25] In this protocol, amines and cyclohexanones, with styrene as a neutral hydrogen scavenger, were passed through a column reactor containing a heterogenous $Pd(OH)_2/C$ catalyst to afford the corresponding aryl amines in good to excellent yields. This flow method was applicable for the stereoretentive *N*-arylation of L-phenylalanine methyl ester. A similar method using 2-cyclohexen-1-ones as arylating reagents in batch methods was reported by Li and coworkers, but significant racemization was observed.[26] The flow method, which can complete the desired reaction under neutral reaction conditions within a short residence time, effectively suppresses racemization. Therefore, we herein describe a versatile synthetic method for preparing *N*-arylated amino acid esters with high enantiopurity utilizing stereoretentive *N*-arylation with cyclohexanones under continuous-flow conditions.

Table 1. Optimization of the *N*-arylation of **1a**.



entry	t_R^2 (min)	yield (%)[a]	ee (%)[b]	comment
1	1.4	61	99	–
2	2.7	92	98	–
3	6.5	94	98	–
4	14.0	91	97	–
5	6.7	59	98	w/o coil reactor

[a] Isolated yield. [b] Enantiomeric excess (ee) was determined by HPLC.

The *N*-phenylation of L-phenylalanine methyl ester (**1a**) with cyclohexanone (**2a**) was used to determine the optimum reaction conditions using a continuous-flow system in which a coil reactor and a packed-bed column reactor were connected in series (Table 1). In the designed flow system, the substrates would be rapidly converted to the desired product within a short residence time, and the resulting product could be continuously discharged out of the flow system. We hypothesized that this could minimize undesired racemization of the product. A toluene solution of enantiopure **1a** (0.20 M, 0.20 mL min^{-1}) containing styrene (0.40 M) was mixed with a toluene solution of **2a** (0.24 M, 0.20 mL min^{-1}) in a T-shaped mixer. The well-mixed solution was rapidly heated to 140 °C in a coil reactor (diameter = 1.0 mm, length = 100 cm, t_R^1 = 2.0 min) and continuously introduced into a column reactor (diameter = 5.0 mm, length = 50 mm) that was packed with a mixture of $Pd(OH)_2/C$ and Celite® (1:10 w/w, total 0.74 g). The reaction mixture was collected from the outlet of the back-pressure regulator that controlled the internal pressure (0.5 MPa) of the flow reactor.

This process gave the desired product in 61% yield even with a short residence time in the packed-bed column reactor (t_R^2 = 1.4 min; Table 1, entry 1). The enantiopurity of the product was 99% ee, indicating that racemization was not significant. This enantiopurity was surprisingly higher than that observed for batch method *N*-arylation reactions using 2-cyclohexene-1-one (57% ee)[26] or PhOTf (87% ee)[15]. We then sought the appropriate residence time to obtain both high product yield and excellent enantiopurity (Table 2, entries 1–4). When residence time t_R^2 was increased while changing the column volume, the yield improved significantly, and, fortunately, the decrease in enantiopurity was extremely gradual. The use of a larger column reactor (diameter = 10 mm, length = 5.0 mm, t_R^2 = 6.5 min) afforded the best result (94% yield, 98% ee) (Table 1, entry 3). Performing the flow reaction without a preheating coil reactor reduced the yield from 94% to 59% without loss of enantiopurity (98% ee; Table 1, entry 5). This indicates that rapid heating at the coil reactor contributes to completion of the dehydrative aromatization within a shorter residence time.

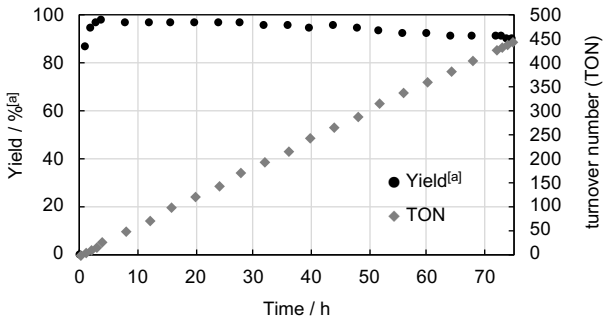


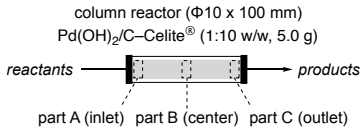
Figure 1. Synthesis of tens of grams of *N*-arylated amino acid ester **3aa** via scaled-up and long-term operation of the continuous-flow system. [a] GC yield calculated using *n*-dodecane as an internal standard.

The robustness and scalability of the continuous-flow system was verified by the long-term synthesis of **3aa** (Figure 1) in 95% isolated yield (41.9 g) with high enantiopurity (96% ee) over 72 h. The developed system showed a high space-time yield (STY) of 74.1 g L^{-1} h^{-1} and a high catalyst turnover number of 423 (turnover frequency = 5.9 h^{-1}). After approximately 48 h, a slight decrease in yield was observed while high enantioselectivity was maintained (Table S2). Inductively coupled plasma atomic emission spectroscopy analysis (ICP-AES) of the crude mixture revealed that Pd leaching was below the detection limit (<0.02% of the loaded Pd) even after 3 days of operation, suggesting that the catalyst deactivation cannot be attributed to metal leaching.

X-ray photoelectron spectroscopy (XPS) analysis of the fresh and used catalysts showed that the surface composition of the catalyst before and after the 72 h flow reactions differed significantly: the atomic concentration of Pd decreased while that of C and N increased (Table 2). This was particularly pronounced for the sample collected near the inlet of the packed-bed reactor. Therefore, catalyst deactivation by the adsorption of insoluble oligomers derived from **1a** or styrene was strongly suspected. The adsorption of peptides was further

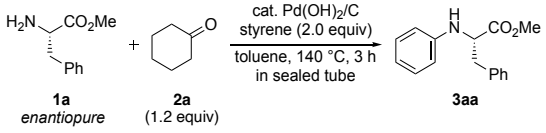
supported by direct analysis in real time mass spectrometry (DART-MS) measurement of the used catalysts (Figure S10).

Table 2. XPS analysis of the fresh and used catalysts.



catalyst	XPS-derived molar concentration (atom %)			
	Pd 3d	C 1s	N 1s	Others
fresh catalyst	1.0	10.7	n.d.	27.4
used catalyst (part A)	0.3	23.5	1.4	23.1
used catalyst (part B)	1.0	16.9	1.0	24.3
used catalyst (part C)	0.9	19.4	0.5	24.2

Table 3. *N*-Arylation of **1a** in a batch reactor.



entry	Pd loading (mol%)	yield (%)[a]	ee (%)[b]
1	2	69	84
2	5	74	80
3	10	76	74

[a] GC yield calculated using *n*-dodecane as an internal standard. [b] Enantiomeric excess (ee) was determined by HPLC.

We investigated this reaction using a batch method to understand the key features of the reaction process. Upon treatment of **1a** with **2a** in the presence of $Pd(OH)_2/C$ (2 mol%) and styrene (2.0 equiv) in toluene at 140 °C for 3 h, the desired *N*-phenylated product (**3aa**) was obtained in 69% yield (Table 3, entry 1). Although the reaction proceeded in the absence of a base, the enantiopurity of **3aa** was only 84% ee. Moreover, when Pd loading was increased from 2 to 5 and 10 mol%, the product yield gradually improved from 69% to 74% and 76%, while the enantiopurity decreased from 84% to 70% and 74% ee (Table 3, entries 2 and 3). This unexpectedly suggests that the Pd catalyst contributes to partial racemization of the amino acid compounds. There are three plausible racemization pathways that can proceed from different amino acid derivatives: amino acid esters **1** (Figure 2a, path A), imine intermediates **4** (path B), and *N*-arylated amino acid esters **3** (path C).

To determine the racemization mechanism, starting materials **1a** (>99% ee) and **3aa** (98% ee) were each treated at 140 °C in the presence of $Pd(OH)_2/C$ under batch and flow conditions (Figure 2b and 2c). In both methods, **3aa** maintained high enantiopurity (98% ee) without any racemization. In contrast, slight racemization of **1a** was observed in both methods, with the flow conditions resulting in lower enantiopurity (92% ee) than the batch conditions (99% ee). We therefore propose that the racemization process occurs though the consecutive dehydrogenation and re-hydrogenation of **1a** over the $Pd(OH)_2/C$ catalyst (Figure 2a, path A).[27,28] The flow method may have resulted in a lower enantiopurity of **1a** owing to a high local concentration of Pd catalyst in the reactor. This is inconsistent with the higher enantiopurity obtained by the flow method in the *N*-arylation reaction. These contradictory results indicate the existence of another racemization pathway, namely path **B** involving imine intermediate **4** bearing a more acidic proton on an α-stereocenter.[29] We propose that features of the flow method such as rapid preheating and a high local concentration of catalyst in the column reactor contribute to a dramatic increase in the *N*-arylation reaction rate, allowing it to be completed in a short period of time and minimizing the contact time of both substrate **1** and intermediary **4** with the Pd catalyst, thus suppressing racemization.

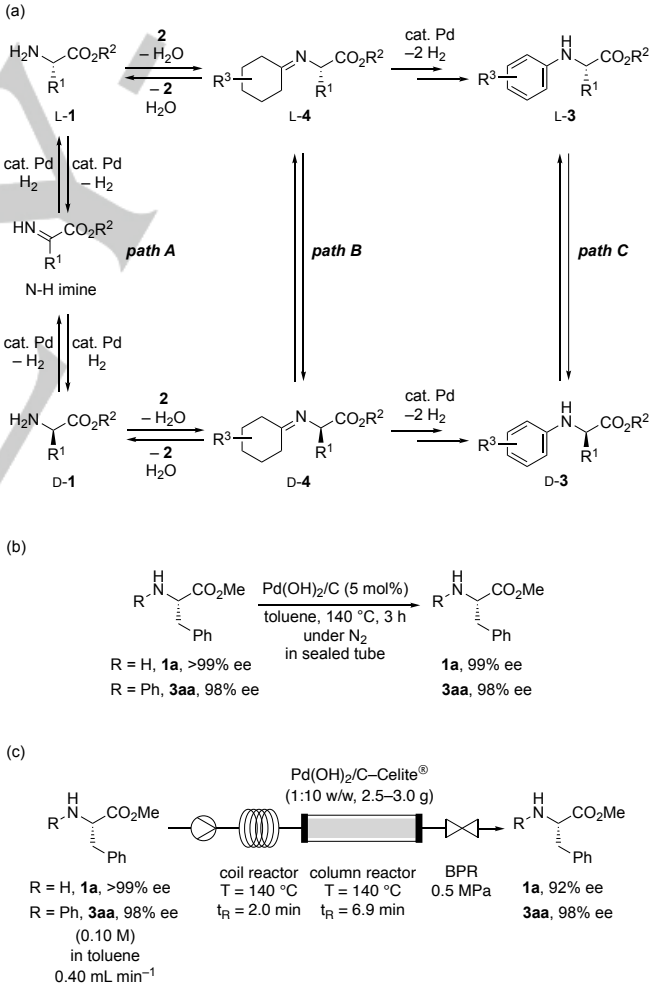
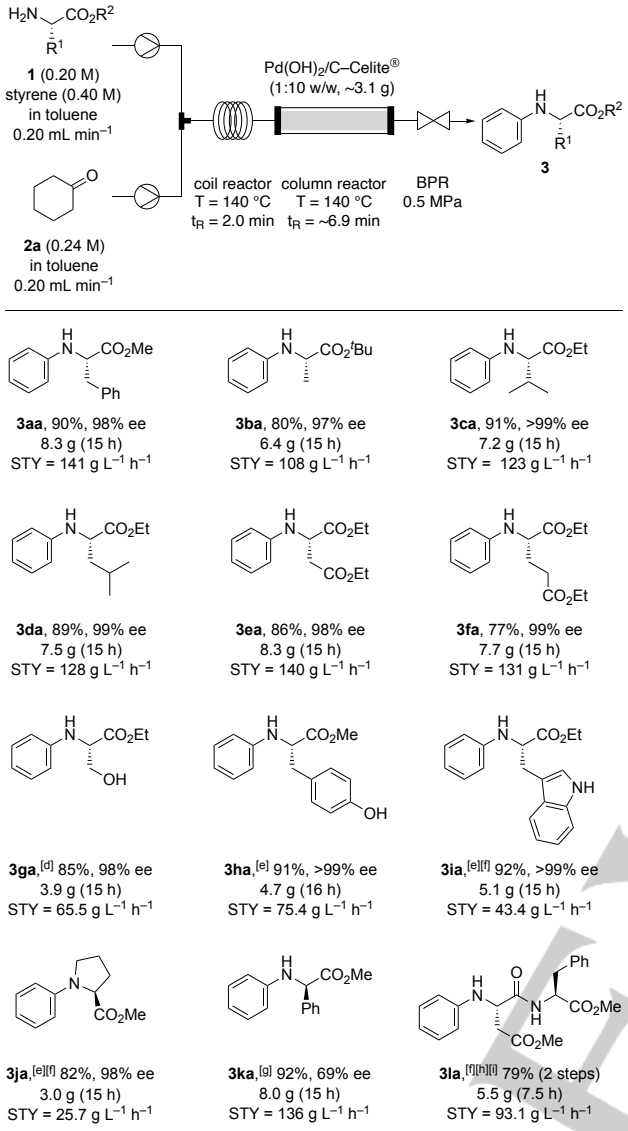
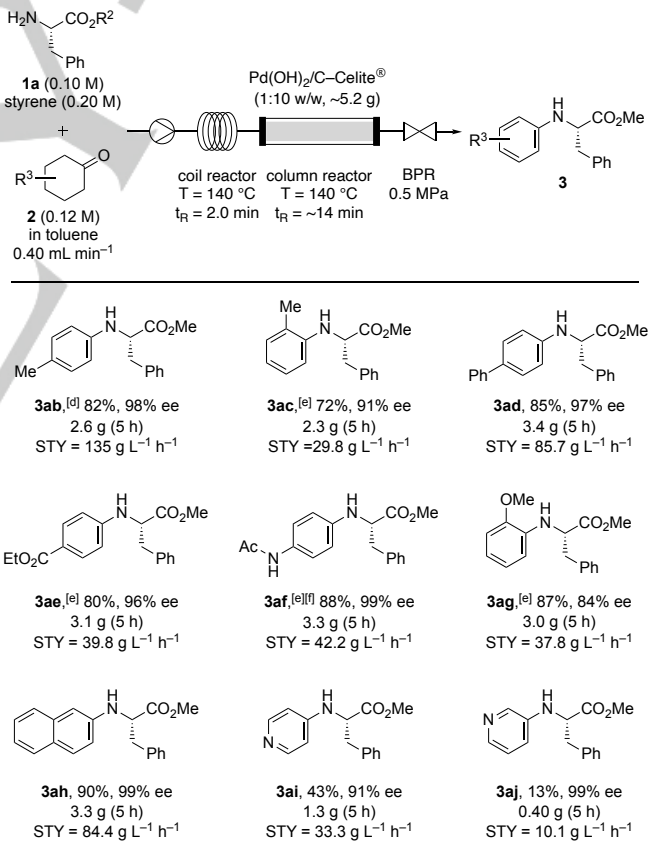


Figure 2. a) Plausible racemization pathways. b, c) Experimental investigations of the racemization of amino acid esters **1** and **3** using the batch and flow methods.



Scheme 2. Amino acid ester scope.[a–c] [a] Substrate **1** (36 mmol) was treated over the course of 15 h in the packed-bed flow reactor. [b] Yield of isolated products. [c] Enantiomeric excess (ee) was determined by HPLC. [d] A 1,4-dioxane solution of **1g** (0.060 M) and **2a** (0.072 M) containing styrene (0.12 M) was pumped into the flow reactor (0.40 mL min^{-1}). [e] A 1,4-dioxane solution of **1** (0.10 M) with styrene (0.20 M) and a 1,4-dioxane solution of **2a** (0.12 M) were used instead of toluene solutions. [f] A column reactor (inner diameter = 10 mm, length = 100 mm) packed with $Pd(OH)_2$/C–Celite® (1:10 w/w, ~5.3 g) was used. [g] D-substrate was used. [h] 1,4-dioxane was used instead of toluene solvent. [i] Yield after two steps consisting of dehydrochlorination and *N*-arylation (see SI).

The developed continuous-flow system was then used for the multigram synthesis of various *N*-arylated amino acid esters (Schemes 2 and 3). The scope of the amino acid esters was examined using **2a** as a coupling partner under the optimized conditions (Scheme 2). The hydrophobic alanine, valine, and leucine amino acid esters (**1b**–**1d**) reacted smoothly to afford the desired products **3ba**–**3da** in high yields and excellent enantiopurity. *N*-Phenylation of the diester-type substrates aspartic and glutamic acid esters **1e** and **1f** afforded the products **3ea** and **3fa**, respectively, in good yields and excellent enantiopurity without any undesirable reactions of the ester moiety such as ester–amide exchange.[30] Notably, the developed method tolerated unprotected polar amino acids; products **3ga**–**3ia** bearing unprotected hydroxyl and *N*-H indolyl groups on side chains were obtained in high yields with negligible levels of racemization. Even proline ester **1j**, a secondary amino acid ester that suffered from low yield and significant racemization in a previous C–N couplings,[15] was tolerated; the reaction gave the corresponding product (**4ja**) in 85% yield with excellent enantioselectivity. The method was also applicable to D-phenylglycine ester (**1k**), a non-natural amino acid that is known to be easily racemized. The desired **3ka** was obtained in 92% yield with a moderate enantiopurity of 69% ee, which is a significant improvement over that of the conventional method (1% ee).[13,31] Methionine and histidine esters were also tested, but were not applicable to this method. It is noteworthy that this protocol was also applied to peptides that can undergo not only epimerization, but also intramolecular cyclization under basic conditions.[32] *N*-Arylation of aspartame ester (**1l**) proceeded smoothly to afford **3la** in 79% yield as a single diastereomer. Gratifyingly, the developed system afforded high yields (77–91%) and excellent enantiopurity (69–99% ee), in addition to a turnover frequency (TOF) of up to 10.8 h^{-1} and an STY of up to 141 g L^{-1} h^{-1}. The development of the reaction for more structurally complex peptides is under investigation.



Scheme 3. Cyclohexanone scope. [a–c] [a] Substrate **1** (12 mmol) was treated over 5 h in the packed-bed flow reactor. [b] Yield of isolated products. [c] Enantiomeric excess (ee) was determined by HPLC. [d] A column reactor (inner diameter = 10 mm, length = 50 mm) packed with $Pd(OH)_2$/C–Celite® (1:10 w/w, 2.6 g) was used. [e] A column reactor (inner diameter = 10 mm, length = 200 mm) packed with $Pd(OH)_2$/C–Celite® (1:10 w/w, ~11.0 g) was used. [f] 1,4-Dioxane was used as a solvent instead of toluene.

Next, we investigated the scope of the cyclohexanones using **1a** as a coupling partner (Scheme 3). Cyclohexanones bearing a methyl or phenyl group gave **3ab**–**3ad** bearing the corresponding aryl group in good to high yields. Polar functional groups were also tolerated; *N*-arylated amino acid esters **3ae**–**3ag** bearing an ester, amide, or ether moiety were successfully synthesized in high yields. These cyclohexanones, except 2-methylcyclohexanone (**2c**) and 2-methoxycyclohexanone (**2g**), which are sterically hindered around the carbonyl group, showed extremely high enantiopurity (96–99% ee). While the steric hindrance of the bulky cyclohexanones inhibited the desired dehydrogenation step, it likely did not affect the competing racemization reactions from the unreacted **1** or the intermediary **4** (Figure 2a), resulting in a decrease in the enantiopurity of **3**.

It is noteworthy that the developed flow method could also supply fused aryl and heteroaryl groups to the amino acid esters. 2-Tetralone reacted to afford the desired *N*-naphthyl product (**3ah**) in high yield with 99% ee. Furthermore, *N*-benzylated 4- and 3-piperidones **2i** and **2j** produced the 4- and 3-pyridine derivatives **3ai** and **3aj**, respectively.[14] In this interesting transformation, it is assumed that the *N*-pyridyl group is introduced via consecutive condensation and dehydrogenative aromatization involving *N*-debenzylation by the Pd catalyst. Almost all the examples afforded a high yield of up to 90%, good to excellent enantiopurity of 84–99% ee, a TOF of up to 9.7 h^{-1}, and an STY of up to 135 g L^{-1} h^{-1}.

Herein, we reported a synthetic method for obtaining *N*-arylated amino acid esters with excellent enantiopurity utilizing a continuous-flow system. The designed flow system consisted of a coil reactor and a packed-bed reactor containing a $Pd(OH)_2/C$ catalyst, and allowed various amino acid esters to efficiently react with cyclohexanones in the presence of styrene as a H_2 scavenger to give the desired *N*-arylated products with only small amounts of easily removable co-products (i.e., H_2O and alkanes). The flow method furnished the desired products within a short residence time, dramatically minimizing racemization and other side reactions that are difficult to eliminate using a batch method. Even with the same catalyst system, the flow method resulted in much higher product yield, enantiopurity, and selectivity than the batch method. Moreover, halogen-free cyclohexanones and their analogs, which can be prepared using classical synthetic methodologies for carbonyl compounds, can be used as aryl and heteroaryl sources to facilitate the versatile synthesis of *N*-arylated amino acid compounds. Our developed method is an attractive and promising approach for the continuous synthesis of functionalized amino acid compounds and an alternative to the current C–N cross coupling reactions that suffer from racemization.

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Keywords: amino acids • *N*-arylation • continuous-flow synthesis • cyclohexanones • heterogeneous catalysis

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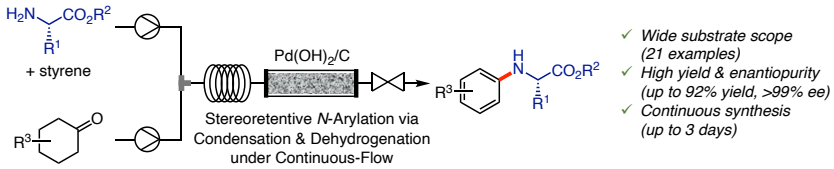

Stereoretentive *N*-arylation of chiral amino acid esters with cyclohexanones as halogen-free aryl sources was performed under continuous-flow conditions. The designed flow system, comprising a coil reactor and a packed-bed reactor containing a $Pd(OH)_2/C$ catalyst, efficiently afforded the desired *N*-arylated amino acid products without significant racemization, accompanied by only small amounts of easily removable co-products. This method allowed for the continuous synthesis of the desired product in very high yield and enantiopurity for at least 3 days.