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Amination **Hot Paper**

Continuous Synthesis of Aryl Amines from Phenols Utilizing Integrated Packed-Bed Flow Systems

Tomohiro Ichitsuka, Ikko Takahashi, Nagatoshi Koumura,* Kazuhiko Sato, and Shū Kobayashi**

Abstract: *Aryl amines are important pharmaceutical intermediates among other numerous applications. Herein, an environmentally benign route and novel approach to aryl amine synthesis using dehydrative amination of phenols with amines and styrene under continuous-flow conditions was developed. Inexpensive and readily available phenols were efficiently converted into the corresponding aryl amines, with small amounts of easily removable co-products (i.e., H_2O and alkanes), in multistep continuous-flow reactors in the presence of heterogeneous Pd catalysts. The high product selectivity and functional-group tolerance of this method allowed aryl amines with diverse functional groups to be selectively obtained in high yields over a continuous operation time of one week.*

Recently, considerable research effort has been directed at the development of synthetic routes to aryl amines, because these are important building blocks for pharmaceuticals, agrochemicals, organic dyes, functional polymers, etc.[1] Transition metal catalyzed C–N coupling reactions (e.g., Buchwald–Hartwig amination) are powerful methods for synthesizing diversely functionalized aryl amines (Figure 1 a), but pose the problem of high environmental loading, stoichiometric/excess amounts of strong bases, and require the use of expensive aryl (pseudo)halides, thus generating large amounts of by-products and featuring limited functional-group tolerance.[2–8] In contrast, Pd-catalyzed dehydrative amination of phenols has attracted attention as a new environmentally benign route to aryl amines (Figure 1 b).[9–12] In this reaction, cyclohexanones are formed by hydrogenation of phenols over a Pd catalyst and react with amines to give imines (Figure 1 c), which undergo dehydrogenative re-aromatization to afford aryl amines. The advantages of this route are i) generation of water as the only co-product, ii) easy removal of heterogeneous catalysts and H_2 or H_2 donors as additives after the reaction, and iii) low cost and availability of the phenols, which are produced from coal and lignocellulosic biomass and are a more attractive sources of aromatic rings.

Despite these advantages, the amination must be carried out at high temperatures and under high pressures in batch reactors, such as autoclaves.[9] Additionally, the highly practical reactions affording structurally more complex aryl amines have not yet been established. This is due to the incompatibility of this approach to thermally labile and easily reducible functional groups and the competitive generation of cyclohexylamines through the hydrogenation of imine intermediates, which greatly reduces product selectivity (Figure 1 c).[9,13] In 2015, Li and co-workers reported an improved method using Pd/C and trifluoroacetic acid as catalysts and

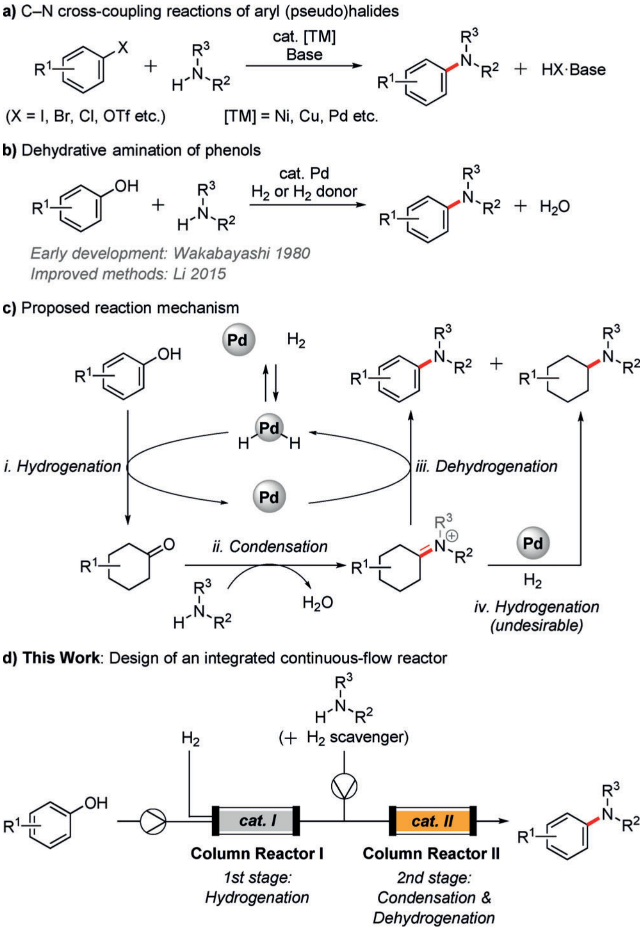

Figure 1. Summary of previous works and the present study. a) Modern transition metal catalyzed C–N cross-couplings of aryl (pseudo)halides with amines in the presence of a base. b) Pd-catalyzed dehydrative amination of phenols. c) Proposed mechanism of Pd-catalyzed dehydrative amination. d) Design of an integrated continuous-flow reactor for the dehydrative amination of phenols.

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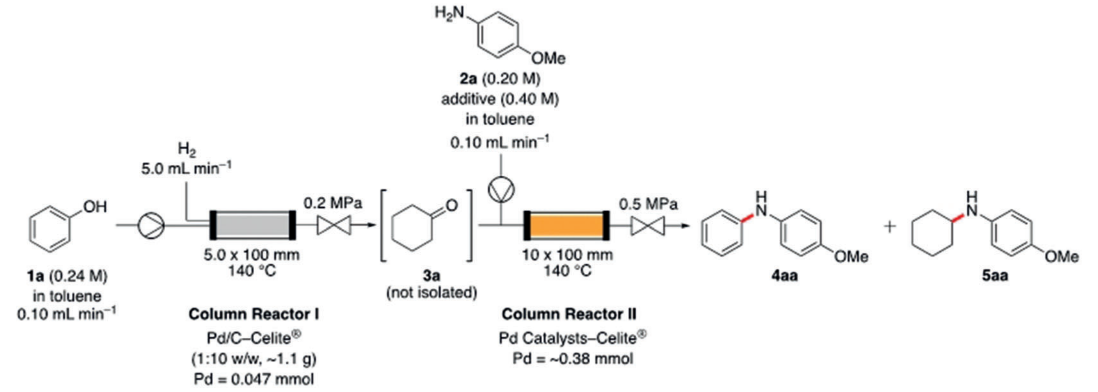
sodium formate as a hydrogen source to improve the product selectivity and conditions of the amination reaction at the expense of increased chemical waste generation.[10] Furthermore, the developed method remains inapplicable to some functional groups. For example, it is difficult to apply to amino acids or amines bearing olefin, nitrile, and halide groups, which are sensitive to reducing and high-temperature conditions.

To make the dehydrative amination of phenols compatible with fine-chemical synthesis, we relied on the use of a flow technique,[14] because it was thought that the problems of low functional-group tolerance and product selectivity were partially attributable to the conflict between hydrogenation and dehydrogenation reactions proceeding in the same reactor. Inspired by continuous-flow systems comprising multiple column reactors,[15–17] we designed a setup in which the first (hydrogenation)[18–20] and second (condensation- dehydrogenation)[21,22] steps were performed in separate reactors and then serially integrated (Figure 1 d). In the first column reactor, packed with a hydrogenation catalyst, phenols would be efficiently and continuously converted into the corresponding cyclohexanones, which were then mixed with amines and introduced into the next column reactor. Thus, consecutive condensation and dehydrogenation would proceed smoothly to afford the desired aryl amines without any by-products because of the absence of hydrogen. Furthermore, division of the flow reactors would enable the use of a hydrogen scavenger in the second stage[21–23] to more reliably control product selectivity. This segmentation and integration strategy could significantly improve the amine scope and product selectivity, while some features of flow reactors loaded with heterogeneous catalysts could not only increase reaction efficiency, but also allow reaction conditions milder than those used in the corresponding batch reactions to realize the continuous synthesis of various aryl amines.[24,25]

The dehydrative coupling of phenol (**1a**) with *p*-anisidine (**2a**) was chosen as a model reaction, which, consisted of hydrogenation (first stage) and consecutive condensation and dehydrogenation (second stage). Initially, we optimized a continuous-flow system for the hydrogenation of phenols over heterogeneous catalysts to produce the desired cyclohexanone derivatives (first stage, flow reactor I).[26] As shown in Figure 2 a, a toluene solution of **1a** (0.24 M, 0.10 mL min^{-1}) and hydrogen gas (5.0 mL min^{-1}) were passed through the column reactor (diameter = 5.0 mm, length = 10 cm) containing a heterogeneous Pd catalyst at 140 °C. The reaction mixture, collected from the outlet of the back-pressure regulator that controlled the internal pressure (0.2 MPa) of the flow reactor, was analyzed by gas chromatography. Catalyst screening revealed that Pd/C could fully convert **1a** into cyclohexanone (**3a**) with excellent selectivity (cyclohexanone/cyclohexanol = 99:1 mol mol^{-1}). The column reac-

a) Flow setup



b) Optimization of the second stage

Entry	Pd catalyst[a]	additive	**4aa** (%)[b]	**5aa** (%)[b]
1	Pd/C	–	18	47
2	Pd/Al$_2$O$_3$	–	21	49
3	Pd/SiO$_2$	–	10	24
4	Pd/C (unreduced)	–	26	46
5	Pd(OH)$_2$/C	–	32	54
6	Pd(OH)$_2$/C	cyclohexene	13	74
7	Pd(OH)$_2$/C	1-octene	46	18
8	Pd(OH)$_2$/C	styrene	99	n.d.

[a] Pd catalyst (~0.38 mmol Pd) was diluted with Celite® at an appropriate ratio (see Supporting Information) and then packed into the column reactor II (inner diameter = 10 mm, length = 100 mm). [b] Gas chromatography yield calculated using *n*-tetradecane as an internal standard.

c) Long-term production of aryl amine **4aa**.

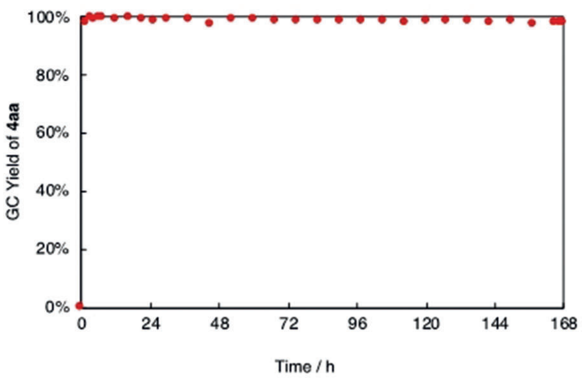


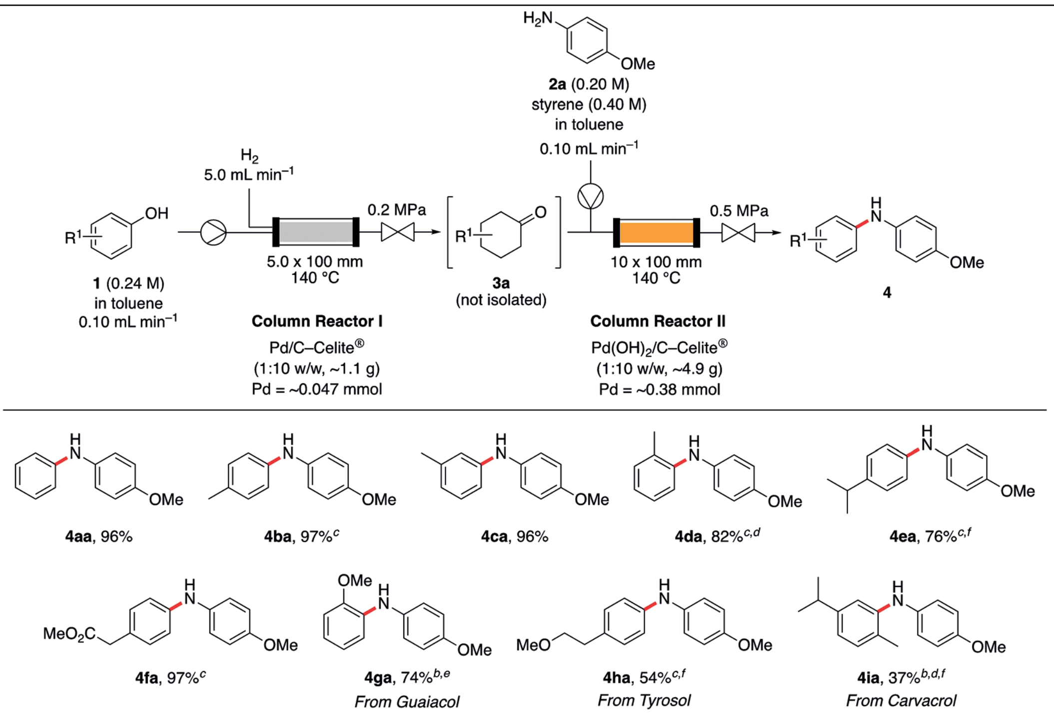
Figure 2. Application of an integrated continuous-flow reactor to dehydrative amination. a) Setup of the integrated continuous-flow reactor for the dehydrative amination of phenols. b) Optimization of reaction conditions for the second stage. c) Ten-gram-scale synthesis of aryl amine **4aa** by long-term operation of the integrated continuous-flow reactor.

tor packed with a mixture of Pd/C and Celite (1:10 w/w, ≈1.1 g) allowed us to continuously produce **3a** with excellent yield at least for 24 hours. The Pd turnover frequency reached 32 h^{-1}, while the space-time yield was as high as 1.70 kg day^{-1} L^{-1}. The high productivity and selectivity were attributed to the higher mixing efficiency and shorter residence times compared to those of batch methods, which motivated us to design a sequential process with an integrated flow reactor. Hence, column reactor I was connected with column reactor II to perform the condensation of **2a** with **3a**, followed by dehydrogenation, which was the second stage of the desired dehydrative amination (Figure 2a). At the second stage, a toluene solution of **3a** (0.24 M, 0.10 mL min^{-1}) from the first-stage column reactor was separated from unreacted H_2 and mixed with a toluene solution of **2a** (0.20 M, 0.10 mL min^{-1}) with a T-shaped mixer. The mixture was preheated to 140 °C in a coil reactor (diameter = 1.0 mm, length = 100 cm), and continuously introduced into the second-stage column reactor filled with a heterogeneous Pd catalyst and Celite. Catalyst screening (Figure 2b, entries 1–5) showed that although the highest conversion was observed for Pd(OH)$_2$/C, both the desired diaryl amine (**4aa**) and the undesired cyclohexylamine (**5aa**) were obtained in a molar ratio of about 1:2. This result indicated that the side product **5aa** was generated through hydrogen transfer, that is, the imine intermediate was reduced by the Pd–H species formed through the dehydrogenation of another imine.[10,13] It was hypothesized that this problem could be mitigated through the use of oxidants or hydrogen scavengers,[21–23] and the corresponding screening (Figure 2b, entries 6–8) revealed that styrene (2 equiv) acted as a good hydrogen scavenger to achieve excellent product selectivity. Under optimal reaction conditions [column reactor diameter = 10 mm, length = 10 cm; catalyst = mixture of Pd(OH)$_2$/C and Celite® (1:10 w/w, ≈4.9 g)], the desired diaryl amine **4aa** could be continuously produced as the sole product in excellent yield for at least 24 hours (Figure 2b, entry 8).

The robustness of the integrated flow reactor was tested by the long-term synthesis of **4aa** (Figure 2c), over the course of one week a 96 % yield (38.6 g) of **4aa** was produced. The developed system showed a high space-time yield of 0.31 kg L^{-1} day^{-1} and a high catalyst turnover number in each column reactor (5372 for hydrogenation and 267 for consecutive condensation and dehydrogenation). Inductivity coupled plasma atomic emission spectroscopy analysis revealed that after a one-week operation, only 53 µg of Pd (0.06 % of loaded Pd) was present in **4aa** before purification, therefore the extent of Pd leaching was negligible.

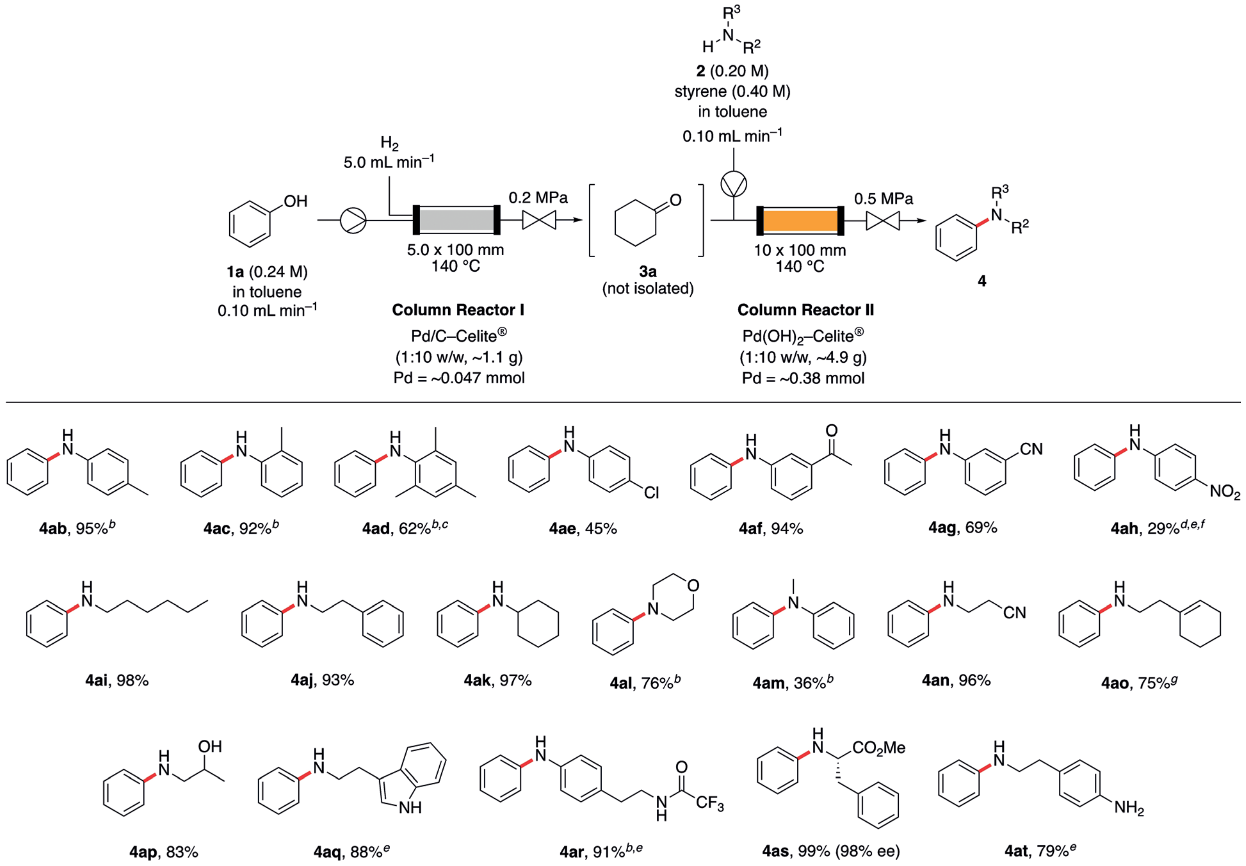
The developed flow reactor was then used to prepare various aryl amines (Table 1). When the scope with respect to the phenol was examined using **2a** as a coupling partner under optimized reaction conditions, alkyl-group-bearing phenols (**1b—e**) reacted smoothly to afford the desired diaryl amines **4ba–ea** in good to excellent yields. Among these phenols,

Table 1: Scope with respect to the phenols.[a]



[a] Yields of isolated products. [b] Column reactor I (inner diameter = 10 mm, length = 50 mm) packed with Pd/C-Celite® (1:10 w/w, ≈2.2 g) was used at 150 °C for the first stage. [c] Column reactor II (inner diameter = 10 mm, length = 200 mm) packed with Pd(OH)$_2$/C-Celite® (1:10 w/w, ≈9.8 g) was used at 140 °C for the second stage. [d] Column reactor II (inner diameter = 10 mm, length = 200 mm) packed with Pd(OH)$_2$/C-Celite® (1:10 w/w, ≈9.8 g) was used at 150 °C for the second stage. [e] Column reactor II (inner diameter = 10 mm, length = 200 mm) packed with Pd(OH)$_2$/C-Celite® (1:10 w/w, ≈9.8 g) was used at 160 °C for the second stage. [f] Co-products generated by excess dehydrogenation of the methylene chain of **4** were obtained (see the Supporting Information).

Table 2: Scope with respect to the amines.[a]



4ab, 95%^{b} **4ac**, 92%^{b} **4ad**, 62%^{b,c} **4ae**, 45% **4af**, 94% **4ag**, 69% **4ah**, 29%^{d,e,f}

4ai, 98% **4aj**, 93% **4ak**, 97% **4al**, 76%^{b} **4am**, 36%^{b} **4an**, 96% **4ao**, 75%^{g}

4ap, 83% **4aq**, 88%^{e} **4ar**, 91%^{b,e} **4as**, 99% (98% ee) **4at**, 79%^{e}

[a] Yield of the isolated product. [b] Column reactor II (inner diameter = 10 mm, length = 200 mm) packed with $Pd(OH)_2$/C-Celite® (1:10 w/w, ≈9.8 g) was used for the second stage. [c] The second-stage reaction was performed at 160 °C. [d] The second-stage reaction was performed at 150 °C. [e] 1,4-Dioxane was used as a solvent for the amines **2** instead of toluene. [f] **4′ah** was obtained in 6% yield via the undesired hydrogenation of a nitro group (see the Supporting Information). [g] **4aj** was also produced in 11% yield by the unfavorable dehydrogenation from a cyclohexene moiety.

sterically hindered *o*-cresol (**1d**) was converted into the corresponding product (**4da**) in 82% yield under modified conditions. Notably, the ester-group-bearing **4fa** was obtained in 97% yield without any undesirable reactions of the ester moiety such as reduction and ester–amide exchange. Moreover, naturally abundant phenols and their derivatives were successfully converted into the corresponding aryl amines, that is, lignin pyrolysis-produced guaiacol (**1g**) was converted into **4ga** in 74% yield, while tyrosol methyl ether (**1h**) afforded **4ha** in moderate yield, and carvacrol (**1i**), a monoterpene derivative found in the essential oil of oregano, was converted into the desired amine **4ia** in 37% yield.

Next, we investigated the scope with respect to the amines using **1a** as a coupling partner (Table 2). The anilines **2b–e** were converted into the corresponding diaryl amines **4ab–ae**, and even sterically hindered 2,4,6-trimethylaniline (**2d**) reacted to give **4ad** in 62% yield. Additionally, the reaction of **2e**, bearing a hydrogenation-sensitive chloro substituent, proceeded to afford the corresponding diaryl amine **4ae** in 42% yield without loss of the chloro group. Even **4af** and **4ag**, bearing acetyl and cyano groups, respectively, which are also sensitive to hydrogenation, were successfully synthesized in the corresponding yields of 94% and 69% without the undesirable reduction of these functional groups. Furthermore, the use of 4-nitroaniline (**2h**) gave the desired aryl amine **4ah** in 29% yield, while the undesired *N*,*N*′-diphenylbenzene-1,4-diamine (**4′ah**) was produced as a byproduct in 6% yield by the consecutive hydrogenation and phenylation of a nitro moiety.

The transformation was applied not only to anilines but also to aliphatic amines; primary alkylamines including sterically hindered cyclohexylamine (**2k**) were converted into the desired *N*-alkylated anilines **4ai–ak** in high yields. In addition, morpholine (**2l**) and *N*-methylaniline (**2m**), which are secondary amines, also reacted to give the tertiary anilines **4al** and **4am**, respectively, in the corresponding yields of 76% and 36%. Notably, the developed method showed a high functional-group tolerance, as the aryl amines **4an** and **4ao** were successfully synthesized in good to excellent yields without the undesirable hydrogenation of their nitrile and alkene moieties. Furthermore, unprotected hydroxy and NH indolyl groups were also tolerated, and the corresponding products **4ap** and **4aq** were obtained in high yields. In contrast to transition metal catalyzed C–N couplings using aryl halides, our flow process proceeded under neutral conditions and was therefore compatible with base-sensitive functional groups.[5] For instance, trifluoroacetamides, which are viewed as representative protected amines, easily decompose under basic conditions. Herein, the reaction of **2r** proceeded to afford the desired product **4ar** in 91 % yield with complete retention of the trifluoroacetamide moiety.

Considering this aspect, we investigated the *N*-arylation of amino acid derivatives, and this reaction is typically hindered by racemization in the presence of bases.[27,28] The L-phenylalanine methyl ester **2s** was selected as a model substrate and subjected to dehydrative amination in the continuous-flow system to enantioselectively obtain the *N*-phenylated product **4as** (98 % *ee*), whereas the application of a batch method to the same reaction afforded the desired product in lower yield and with lower enantioselectivity (67 %, 66 % *ee*; see Scheme S4 in the Supporting Information). The suppression of racemization in the former case was ascribed to the neutral reaction conditions and short residence time, in contrast to batch method conditions. Considering the generation of an imine intermediate, we envisioned a selective reaction of diamines.[29] The diamine **2t** bearing both aliphatic and aryl amines afforded the diamine **4at** arylated only at the aliphatic amine in 79 % yield and with quantitative selectivity, whereas lower yield and selectivity were observed under batch conditions (see Scheme S5). The high chemoselectivity observed in the former case was attributed to the high mixing efficiency of our flow method.

Finally, to demonstrate the utility of the integrated flow system, we conducted a formal continuous synthesis of phentolamine, a nonselective α-adrenergic antagonist[30] (Figure 3) currently produced by the C–N coupling of 3-aminophenol (**2u**) with 4-bromotoluene in the presence of bases to generate stoichiometric amounts of inorganic salts as chemical waste.[31] Advantageously, our flow method allowed 4-bromotoluene to be replaced with *p*-cresol (**1b**) as a coupling partner and thus avoid chemical waste generation. As shown in Figure 3, **1b** and **2u** were continuously processed in the integrated flow reactor to continuously produce the key intermediate, 3-(*p*-tolylamino)phenol (**4bu**), at a rate of 4.6 g day^{-1}.

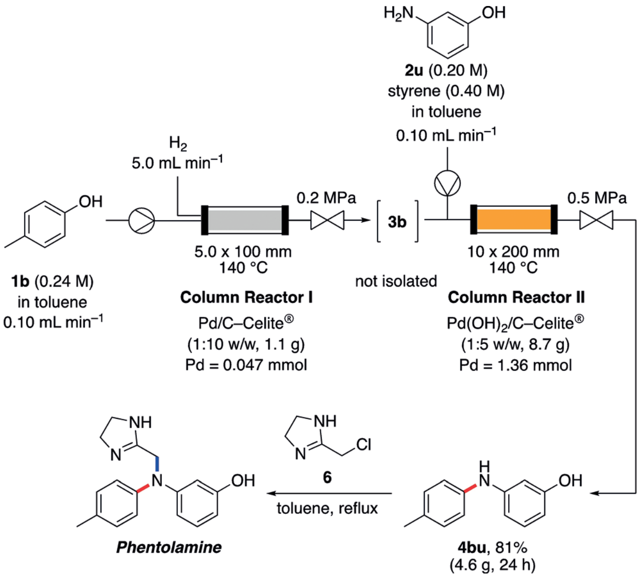


Figure 3. Formal continuous-flow synthesis of phentolamine.

Herein, we developed a method for the dehydrative amination of phenols using an integrated flow system and heterogeneous Pd catalysts. The adopted protocol allowed inexpensive and readily available phenols to be efficiently reacted with amines in the presence of styrene to give the corresponding aryl amines and only small amounts of easily removable co-products (i.e., H_2O and ethylbenzene). Furthermore, the use of multistep continuous-flow methods with heterogeneous catalysts and the use of a suitable hydrogen scavenger significantly increased product selectivity and functional-group tolerance. For instance, the developed flow method was suitable for the synthesis of aryl amines having various functional groups sensitive to hydrogenation and bases. Moreover, the above method was superior to the corresponding batch method in terms of side-reaction suppression and selectivity control because of the high mixing efficiency and short residence time of the former technique. Thus, our method is a powerful and environmentally benign route to aryl amines as an alternative to the current C–N coupling reactions using aryl halides and realizes continuous synthesis of aryl amines.

Conflict of interest

The authors declare no conflict of interest.

Keywords: amines · continuous-flow synthesis · heterogeneous catalysis · palladium · phenols

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Communications

Amination

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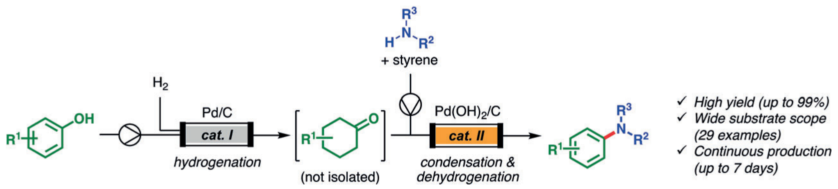
K. Sato, S. Kobayashi* ______ ■■■■–■■■■

Continuous Synthesis of Aryl Amines from Phenols Utilizing Integrated Packed-Bed Flow Systems



Flow with it: Dehydrative amination of phenols under continuous-flow conditions has been developed. In an integrated packed-bed flow system containing heterogeneous Pd catalysts, phenols reacted with amines to obtain aryl amines and small amounts of easily removable co-products. The method has high product selectivity and excellent functional-group tolerance, so that variously substituted aryl amines can be selectively prepared in high yields.