

Synthesis of Urea Derivatives in Two Sequential Continuous-Flow Reactors

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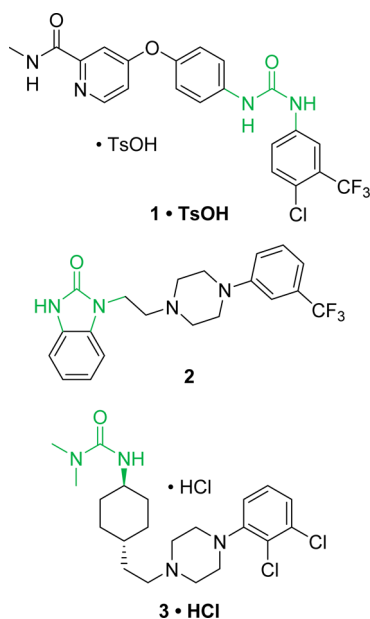
Supporting Information

ABSTRACT: A continuous-flow system consisting of two sequential microreactors was developed for the synthesis of nonsymmetrically substituted ureas starting from *tert*-butoxycarbonyl protected amines. Short reaction times could be achieved under mild conditions. In-line FT-IR analytical technique was used to monitor the reaction, including the formation of the isocyanate intermediate, thus allowing optimization of the reagent ratios. The mechanistic role of the applied base was also clarified. The setup was successfully utilized for the synthesis of several urea derivatives including the active pharmaceutical ingredient cariprazine.

1. INTRODUCTION

Substituted ureas are versatile moieties in bioactive compounds, such as agrochemicals and pharmaceuticals.¹ The kinase inhibitor sorafenib (**1** · TsOH, marketed as Nexavar),² flibanserine (**2**, marketed as Addyi) used for the treatment of female HSDD,³ and the antipsychotic drug cariprazine (**3** · HCl, marketed as Vraylar)⁴ are examples of recently developed active pharmaceutical ingredients (APIs) containing di- or trisubstituted ureas (Scheme 1).

Scheme 1. Active Pharmaceutical Ingredients Containing Substituted Urea Units^a



^aTsOH: *p*-toluenesulfonic acid.

Due to the significance of nonsymmetrically substituted ureas, a wide range of methods is available for the formation of this valuable functionality,^{1,5} predominantly utilizing isocyanate intermediates⁶ typically accessed via the reaction of amines and phosgene or its derivatives.⁷ Another possibility involves the rearrangement reactions of various starting materials.⁸ Direct conversion of protected amines is of particular interest,^{9–16} because omitting deprotection of synthetic intermediates leads to more streamlined approaches to complex molecules. Furthermore, it allows the synthesis of nonsymmetrical ureas by using two different amines, one of which is distinguished by the protecting group.

The reactivity^{17,18} of the ubiquitous *tert*-butoxycarbonyl protecting group has been recently exploited in the synthesis of ureas under mild conditions by Spyropoulos and Kokotos.¹⁹ The readily available *tert*-butoxycarbonyl protected amines (**4**) were treated with trifluoromethanesulfonic anhydride (Tf₂O) in the presence of 2-chloropyridine (2-ClPy) base to eliminate the *tert*-butoxy group, leading to an isocyanate intermediate (**5**). Addition of primary or secondary amines (**6**) in the second stage of the reaction sequence led to the desired urea derivatives (**7**) in high yields (Scheme 2). However, long reaction times were required, and reagents (especially the amine partner) had to be used in large (up to 9-fold) excess. Furthermore, the rather unusual base, 2-ClPy, was found to be necessary in order to reach good yields. The use of triethylamine (TEA), pyridine, 2-methylpyridine, and 4-(dimethylamino)pyridine gave poor results, while 2-fluoro-, 2-chloro-, and 2-bromopyridine were found to be effective. A subsequent study aiming for the synthesis of carbamates and thiocarbamates made similar observations regarding the base in the isocyanate formation step.²⁰ Unfortunately, this unusual specificity of the reaction remained unexplained.

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Scheme 2. Synthesis of Nonsymmetrical Ureas from Protected Amines^a

^aR: protected α -amino acid residues, substituted alkyl-, cyclohexyl-, phenyl-, benzyl-, and vinyl-groups. R¹-NH-R²: primary alkyl-, alkenyl-, cyclohexyl-, phenyl-, and benzyl amines, cyclic or acyclic secondary amines.

Rapid advances in flow chemical methods^{21–26} made continuous processing suitable for the synthesis of APIs and their intermediates.^{27–35} Multistep, end-to-end processes have also been developed on laboratory scale.^{36–51} Some of these endeavors were aided by in-line analysis, which is well-suited for the optimization of flow chemical processes,^{26,52–54} particularly when transient intermediates are present.^{55–57} Flow chemistry has been applied in the synthesis of ureas earlier,^{58,59} starting from carboxylic acids or acid chlorides through Curtius rearrangement of an intermediate azide, requiring harsh conditions.

In this study, we aimed to investigate the synthesis of nonsymmetrical urea derivatives under mild conditions in a laboratory scale continuous-flow process, which could be a key element in a multistep continuous-flow sequence leading to urea derivatives bearing medicinal chemical significance.

2. RESULTS AND DISCUSSION

Description of the Flow System. The flow chemistry implementation of the synthesis of urea derivatives in a mild, two-step sequence, based on the method described by Spyropoulos and Kokotos,¹⁹ was envisioned in a system consisting of two sequential microreactors. This way, the two steps of this transformation could be spatially separated, allowing the application of different conditions (Figure 1).

In the first microreactor (R1) the premixed solution of the carbamate (4) and the 2-ClPy base comes into contact with the solution of Tf₂O, resulting in the formation of the isocyanate intermediate (5). In order to prevent its decomposition, this reactive intermediate is immediately transformed by addition of a secondary amine (6) to yield the desired urea (7) in the second microreactor (R2). The product stream exiting this unit is directed into an in-line flow cell (FC), for adequate *in situ* analysis (see Figure S1 in Supporting Information).

The selection of the microreactors and pumps were governed by corrosivity issues connected to the Tf₂O. This reagent (even in dilute solutions) rapidly degraded the plastic parts (also the highly resistant PEEK components) of reagent storage vessels, syringes, and tubing connectors (Figure S2(a)), only PTFE proved to be resistant. (In a related note, the caustic nature of trifluoromethanesulfonic acid and Tf₂O determined choice of reactor material in the flow synthesis of ibuprofen³⁶ and imatinib.⁹⁶) In order to avoid corrosion of the pumping mechanism, an infusion syringe pump (P2) was used with an all glass and PTFE syringe for the handling of the Tf₂O reagent. A custom-made stainless steel connector (Figure S2(b)) was employed to attach the syringe to the PTFE tubing.

Other reagents (the solution of the substrate premixed with the base (P1) and the solution of the secondary amine (P3)) were introduced via continuous syringe pumps. (Note: The use of HPLC pumps (Knauer AZURA P 2.1S) was also attempted, but harmful pulsation occurred, due to interference with the infusion syringe pump. Optimal selection of pumping mechanisms for certain tasks has been taken into account in the context of multistep flow processing.^{37,40,46})

A glass chip microreactor was used in the first step (R1), which was resistant to the corrosive reagent and provided excellent mixing. In the second step, a T-mixer (M1) provided sufficient mixing, followed by a PTFE coil reactor (R2) as a residence time unit in order to reach full conversion of the intermediate.

In-line Fourier transform infrared (FT-IR) spectroscopy was used to monitor the reaction mixture's composition, as each of the substrate, intermediate, and product gives distinguishable, characteristic vibrational bands in the mid-infrared region (Figure S4), which can be used for both qualitative and quantitative analysis. Although attenuated total reflection (ATR) probes are predominantly used for FT-IR applications in flow synthesis,^{55,60–66} the commonly used sensor materials (silicon sensors are prone to corrosion, while the more robust diamond sensors have a "blind spot", which overlaps with the characteristic vibration of the isocyanate group)^{55,62} were unsuitable for this study. These issues were avoided by employing the versatile (but previously neglected in continuous-flow synthesis) transmission flow cell (FC) using highly resistant ZnSe windows, providing wide spectral range.

In our experience, severe fluctuation (presumably caused by the mixing properties inside the flow cell) occurred in the composition of the product mixture after any major changes in reaction parameters (e.g., flow rate). This phenomenon gradually ceased as the system approached steady state. In order to obtain reproducible results, conversion was measured after reaching a steady state (after collecting 3 times the total reactor volume) in each case. Reproducibility was confirmed by the identical result of the repeated measurements.

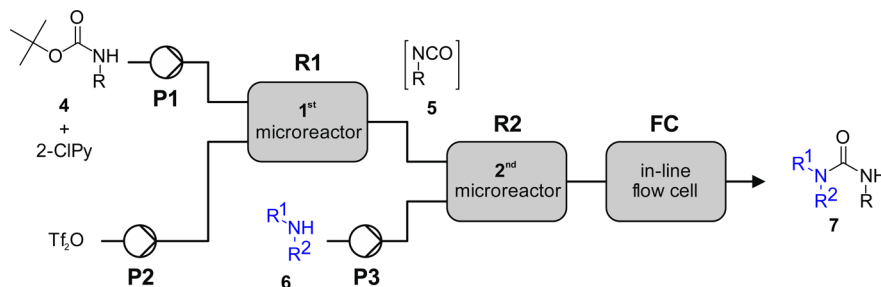
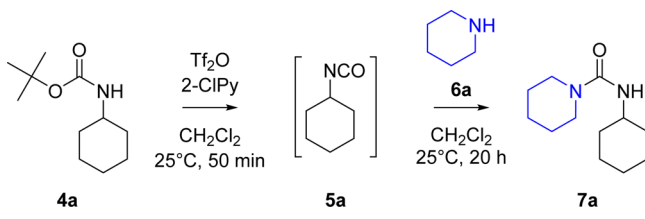


Figure 1. General schematic of the flow system consisting of two sequential microreactors.

Optimization of the Model Reaction. A simple model reaction was proposed (Scheme 3), in order to investigate the urea formation in the flow system. We chose *tert*-butyl cyclohexylcarbamate (**4a**) as starting material and piperidine (**6a**) as the amine partner.

Scheme 3. Model Reaction for the Investigation of the Flow Procedure



Preliminary experiments in the flow system (Figure 2) using the molar ratios reported in the literature (3 equiv of 2-ClPy, 1.5 equiv of TiF_2O , and 9 equiv of **6a**)¹⁹ and keeping reactors at room temperature revealed that the first reaction step was sufficiently fast to reach completion in a 250 μL reactor using convenient flow rate settings (0.5 mL/min at P1 and 22.5 $\mu\text{L}/\text{min}$ flow rate at P2). The somewhat slower second step required a 1000 μL internal volume reactor (0.5 mL/min flow rate at P3). These conditions correspond to low residence times in both steps ($t_{\text{R1}} = 32$ s, $t_{\text{R2}} = 68$ s), so raising the temperature was not necessary (also, higher temperatures could have led to the decomposition of isocyanate **5a**), and reducing temperature to 0 °C gave no considerable advantages.

Optimization was required in order to reduce the high excess of reagents in both steps. Initially, monitoring the conversion of carbamate (**4a**, $\nu(\text{CO}_{\text{carbamate}}) = 1706 \text{ cm}^{-1}$) to the isocyanate intermediate (**5a**, $\nu(\text{NCO}) = 2263 \text{ cm}^{-1}$) was attempted, by connecting the FT-IR cell directly to the output of the first microreactor (R1), without the incorporation of the second step (Figure S3). This way, low amounts (1 equiv) of 2-ClPy and TiF_2O seemed to be sufficient to reach full disappearance of the carbamate (**4a**) signal. Surprisingly, after the addition of **6a** to the stream exiting R1, both FT-IR and off-line analysis of the final product mixture formed in R2 showed considerable amounts of the starting material **4a**. We came to the realization that the apparent lack of the carbamate (**4a**) signal does not correspond to full conversion in the first step. Most likely, such intermediates are present that are not apparent using our FT-IR method and can be reversibly converted back to the substrate under the

conditions of the second step. Therefore, standalone optimization of the first step was not successful.

In order to overcome this problem, the optimization of the first step was realized by continuously in-line quenching its crude mixture using high excess (9 equiv) of amine **6a** in the second reactor (R2), and connecting the FT-IR flow cell thereafter, according to Figure 2. This way, intermediate **5a** is readily transformed to the urea (**7a**, $\nu(\text{CO}_{\text{urea}}) = 1640 \text{ cm}^{-1}$), and the ratio of signals of **4a** and **7a** reflects the conversion in the first step. First, the excess of 2-ClPy was investigated, while the amount of TiF_2O (1 equiv) was kept constant (Figure S5(a)). Although the use of equimolar base gave acceptable results, a 2-fold excess was found to be optimal. Next, the optimized amount of base was used, while molar ratio of TiF_2O was varied (Figure S5(b)). Even though slightly lower amounts were also satisfactory, we decided to use a minimal excess (1.1 equiv) to prevent instability due to traces of water.

Finally, we set out to reduce the high excess of piperidine (**6a**) in the second transformation (Figure S5(c)). While the first reactor was operated at optimal conditions, amount of **6a** was gradually decreased, and the FT-IR spectrum of the product mixture was monitored for the appearance of the strong absorption band of the isocyanate intermediate (**5a**), which indicates partial conversion in the second step. The excess of **6a** could be reduced to 4 equiv (Table 1, entry 1) without affecting

Table 1. Investigation of the Amount of Reagent and Base in the Second Step^a

entry	additional base	piperidine (6a) (equiv)	yield (%)
1	^b	4	97
2	TEA (1 equiv) ^b	3	92
3	TEA (2 equiv) ^b	2	96
4	basic ion-exchange resin ^c	1	84

^aConditions: **4a** (1 equiv), TiF_2O (1.1 equiv), 2-ClPy (2 equiv), additional base (optimized equivalents are shown), and **6a** (optimized equivalents are shown); both microreactors were kept at 25 °C; $t_{\text{R1}} = 33$ s, conversion was 100% in each case, isolated yields are shown.

^bSecond step was conducted in 1000 μL coil reactor, $t_{\text{R2}} = 94$ s.

^cSecond step was conducted in packed bed reactor, 1.6 mL free internal volume, $t_{\text{R2}} = 168$ s.

the reaction progress. This way, excellent isolated yield (97%) was obtained. Although relatively dilute solutions of the starting materials (0.03 M for the substrate) were used, reasonably high productivity of 182 mg/h was achieved. Owing to the low reactor volumes and optimal residence times ($t_{\text{R1}} = 33$ s, $t_{\text{R2}} = 94$ s), the

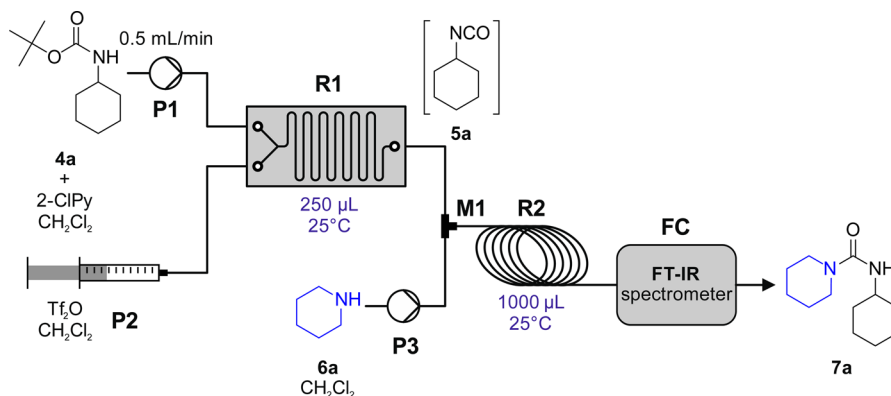


Figure 2. Flow system consisting of two microreactors and in-line FT-IR spectrometer.

system produced $0.696 \text{ mol L}_R^{-1} \text{ h}^{-1}$ of isolated product in terms of space–time yield (I_R = reaction volume in liters).

In order to reach even lower consumption of reagent **6a**, TEA was used as an additional base. These experiments (Table 1, entries 2–3) revealed that a part of the total amount of base (4 equiv) needed can be replaced by a cheaper base. This observation also emphasizes that **6a** acts not only as reactant, but as base too. Consequently, the total amount of base cannot be lowered further, even at higher temperatures, which justifies our initial decision to conduct the reaction at ambient temperature.

Application of immobilized base was also attempted. The coil microreactor (**R2**) was replaced by a column (**R2'**), packed with an ion-exchange resin (Amberlyst A21) containing moderately basic tertiary amine functionalities (Figure S6 in Supporting Information). Full conversion was observed using equimolar amount of **6a** (Table 1, entry 4), explained by the effective base catalysis provided by the high local excess of the resin's basic functionalities. However, rapid decline in the activity was witnessed, which can be interpreted by the fact that the basic functionalities of the resin were not only of a catalytic role. The stream from the first step contained the trifluoromethanesulfonate salt of the weakly basic 2-ClPy, which was liberated by the more basic tertiary amine groups of the resin. During this process the resin was converted to its protonated form and lost its activity as base catalyst. The need for regeneration of the exhausted resin made this setup impractical for continuous-flow synthesis.

Investigation of the Mechanistic Role of the Applied Base. As shown in the Introduction, Spyropoulos and Kokotos conducted screening experiments to find the most appropriate base for the first step of the reaction sequence. Poor reactivity was demonstrated for the usually employed organic bases, while 2-halopyridines (especially 2-ClPy) led to effective transformations.¹⁹ It could be speculated that either the weak basicity of 2-ClPy is necessary for the reaction, or alternatively it plays a pivotal role in the reaction mechanism. The latter scenario would involve the cleavage of the C–Cl bond, thus consuming the 2-ClPy and generating aromatic side products (Scheme S1).

This assumption could be tested by subjecting the reaction mixture to ¹H NMR analysis at the end of the reaction time (chloroform-*d* was used as solvent instead of dichloromethane). Two sets of batch experiments were conducted using different amounts (1 or 3 equiv) of 2-ClPy, with blind runs (omitting the Tf₂O reagent) in both cases (for details see Supporting Information). Based on the ¹H NMR spectra of the crude mixtures, no aromatic side products were observed (Figure S8), and 94–100% of the initial quantity of 2-ClPy remained unchanged in the mixture (Table S1). Therefore, mechanisms affecting the C–Cl bond should be deemed insignificant.

In order to further elaborate the role of the base in the first reaction, an extensive study of bases was conducted. A slightly modified flow system was used to allow the rapid screening (Figure S9 in Supporting Information). Reagents were used in excess and the conversion of the first step was determined after in-line quenching of the formed isocyanate (after directly checking its formation) using piperidine (**6a**). In this setup, 20 different bases were investigated in total (Table 2), although in some cases clogging impeded conversion measurement (Table 2, entries 10, 11, 12, 17, and 20). Amines possessing a wide range of basicities ($\text{p}K_{\text{BH}^+}$) from weak bases to some of the most basic ones were evaluated. Surprisingly, no clear connection was found between base strength and reactivity, which led us to realize that

Table 2. Conversion of the First Step Using Various Bases^a

entry	base	$\text{p}K_{\text{BH}^+}$	conversion (%)
1	2,6-dichloropyridine ^b	−2.86 ^c	35
2	1-methyl-2-pyridone	0.32 ^c	0
3	quinoxaline ^b	0.56 ^c	48
4	2-ClPy	0.72 ^c	100
5	2-hydroxypyridine ^b	0.75 ^c	47
6	<i>N,N</i> -dimethylaniline	2.51 ^d	19
7	pyridine	3.45 ^d	5
8	2-methylpyridine	4.01 ^d	13
9	2,6-dimethylpyridine	4.46 ^d	90
10	4-methylmorpholine	7.40 ^c	^e
11	Proton-sponge ^b	7.47 ^d	^e
12	DMAP ^b	7.86 ^d	^e
13	DIPEA	8.90 ^d	93
14	TEA	9.00 ^d	26
15	TBD ^b	11.22 ^c	72
16	TMP	11.24 ^c	65
17	PMP	11.25 ^c	^e
18	TMG	13.20 ^d	70
19	DBU	13.90 ^d	61
20	Verkade's base ^b	26.80 ^d	^e

^aConditions: **4a** (1 equiv), Tf₂O (1.5 equiv), base (3 equiv), **6a** (9 equiv); both microreactors were kept at 25 °C (DMAP: 4-(dimethylamino)pyridine; TBD: 1,5,7-triazabicyclo[4.4.0]dec-5-ene; TMP: 2,2,6,6-tetramethylpiperidine; PMP: 1,2,2,6,6-pentamethylpiperidine; TMG: 1,1,3,3-tetramethylguanidine; DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene; Verkade's base: 2,8,9-trimethyl-2,5,8,9-tetraaza-1-phosphabicyclo[3.3.3]undecane). ^bSolid reagents were used as concentrated solution in dichloromethane. ^cDissociation constant of the conjugated acid, literature data (H₂O).^{67–70} ^dDissociation constant of the conjugated acid, literature data (DMSO).^{71–76} ^eClogging occurred.

nucleophilicity determines the conversion, instead of base strength.

In fact, 2-ClPy can be classified as a non-nucleophilic base, because of the electron withdrawing and steric shielding effect of the chlorine atom. Additionally, the commonly used non-nucleophilic strong bases (Table 2, entries 9, 13, 15, 16, 18, and 19) gave good results.

The effect of subtle changes in nucleophilicity connected to steric hindrance is also noteworthy. While pyridine and its 2-methyl derivative (Table 2, entries 7 and 8) showed no considerable reaction, the use of the bulky 2,6-dimethylpyridine led to nearly full conversion (Table 2, entry 9). Similar dramatic difference in reactivity can be observed in the relation of TEA and *N,N*-diisopropylethylamine (DIPEA) (Table 2, entries 13 and 14), even though their basicities are nearly identical.

In our interpretation, bases of nucleophilic character react with the highly electrophilic Tf₂O, while being transformed to a quaternary ammonium salt. Not only the Tf₂O reagent, but 1 equiv of base is also consumed in this process, which prevents the progress of the desired reaction.

It is known that less bulky, more nucleophilic bases, such as pyridine,^{77–79} 2-methylpyridine,⁸⁰ and TEA⁸¹ (Table 2, entries 7, 8, and 14), are highly reactive toward Tf₂O and give rise to *N*-sulfonyl derivatives. On the other hand, this kind of reaction could not be demonstrated in the case of the electron-deficient 2-ClPy,⁷⁹ and it has not been observed in the case of DIPEA either (Table 2, entries 4 and 13). Nevertheless, the formation of the *N*-triflate derivative of 2,6-dimethylpyridine was hypothesized to explain impurities forming in reactions involving Tf₂O and this

base.⁸² The good conversion in our case (Table 2, entry 9) can be the consequence of the more rapid reaction with the carbamate substrate than with the hindered base.

Implementation of DIPEA as Base in the First Reaction

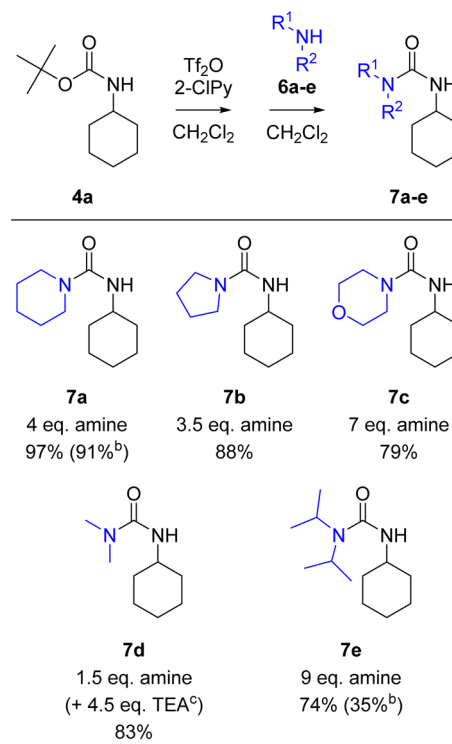
Step. To exploit these findings, we implemented DIPEA into our flow system for the realization of the model reaction (Scheme 3). Slightly lower reactivity was observed; consequently, higher excess of Ti_2O (1.5 equiv) was required, and a modified system (Figure S10) was employed to allow higher residence time ($t_{\text{R}1} = 115$ s) in the first microreactor (for details see Supporting Information). Additionally, a higher excess (4 equiv) of DIPEA had to be used, compared to 2-ClPy (2 equiv), in order to reach full conversion in the first step. Nevertheless, we expected that the higher base strength of DIPEA would allow it to be an effective base catalyst in the addition of piperidine (6a) to the isocyanate intermediate (5a). The excess of 6a could be indeed lowered (2 equiv), while maintaining complete conversion in the second step, and giving rise to 7a in good yield.

However, despite the ability to apply the same base in both reaction steps and to reduce the excess of the secondary amine, the total amount of amine reagents remained unaffected. Thus, the use of DIPEA was not justified, as it did not have a clear advantage over 2-ClPy, either chemically or price-wise. (Note: Molar price of DIPEA and 2-ClPy is 48.7 USD/mol and 22.9 USD/mol, respectively; for ca. 500 g packages of $\geq 99\%$ purity reagents, Sigma-Aldrich, accessed Jan 5 2017.)

Synthesis of Urea Derivatives of *tert*-Butyl Cyclohexylcarbamate (7a–e). In order to explore the scope of the method, further urea derivatives were synthesized using the developed flow system (Figure 2). First, the reaction of *tert*-butyl cyclohexylcarbamate (4a) with cyclic and acyclic secondary amines (6a–e), leading to ureas 7a–e, was investigated (Table 3). The parameters of the first step were identical to the model reaction, while the second step was optimized according to the reactivity of the secondary amine. In the case of pyrrolidine (6b), a slight decrease of the amine excess was possible compared to piperidine (6a), without affecting the conversion. On the other hand, a larger excess of morpholine (6c) was necessary to reach full conversion. Dimethylamine was available as its hydrochloride salt (6d · HCl); thus a triple molar amount of TEA was used to prepare its solution. Optimum conversion was reached using 1.5 equiv of dimethylamine together with 4.5 equiv of TEA, 1.5 equiv of which was consumed to liberate the amine; therefore, the effective total amount of base (4.5 equiv) was comparable to the amount of other secondary amines. The sterically hindered diisopropylamine (6e) necessitated high excess of the amine (9 equiv) to reach completion upon identical conditions. The optimized system gave good to excellent yields in each case, with 126–156 mg/h productivity. The higher amine consumption and lower yields of the nonoptimized batch reactions (in case of 7a and 7e; Table 3) clearly show the benefits of the immediate transformation of the instable isocyanate intermediate, as well as the advantages of rapid optimization in this flow system.

Synthesis of Urea Derivatives of Ethyl 2-(*trans*-4-Aminocyclohexyl)acetate (7f–j). Next, urea derivatives of a more complex substrate were synthesized in the flow system. Ethyl 2-(*trans*-4-((*tert*-butoxycarbonyl)amino)cyclohexyl)acetate (4b) was chosen as starting material, which is a known intermediate^{83,84} of the active pharmaceutical ingredient cariprazine (3). The presence of the ester group made the FT-IR analysis of the reaction mixture challenging, since the ester ($\nu(\text{CO}_{\text{ester}}) = 1723 \text{ cm}^{-1}$) and the carbamate ($\nu(\text{CO}_{\text{carbamate}}) = 1706 \text{ cm}^{-1}$) carbonyl bands were overlapping. Consequently,

Table 3. Synthesis of Urea Derivatives of Cyclohexylamine Using the Flow System^a



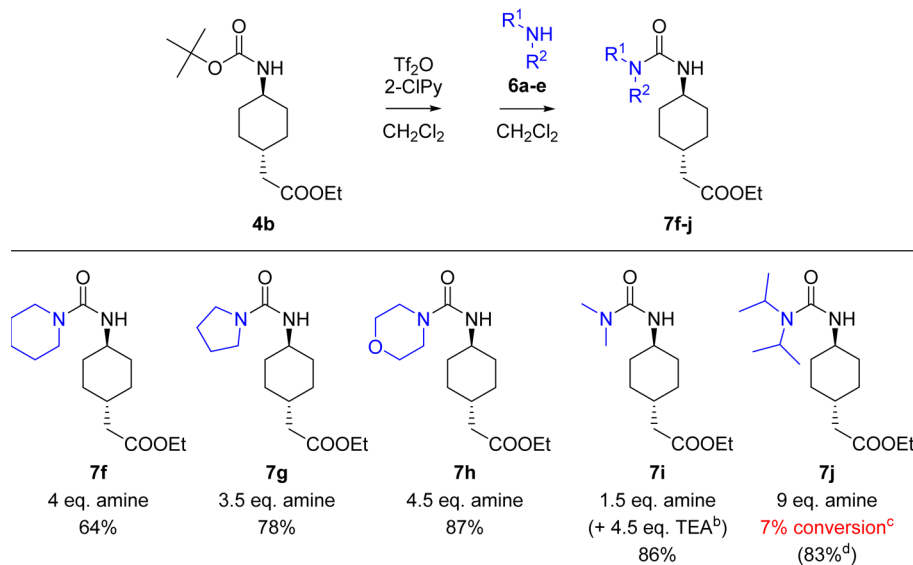
^aConditions: 4a (1 equiv), Ti_2O (1.1 equiv), 2-ClPy (2 equiv), amine (optimized equivalents are shown for each product); both microreactors were kept at 25 °C; $t_{\text{R}1} = 33$ s, $t_{\text{R}2} = 68$ –97 s; conversion was 100% in each case; isolated yields are shown. ^bYield of the batch reactions. General conditions: 4a (1 equiv), Ti_2O (1.5 equiv), 2-ClPy (3 equiv), amine (9 equiv); 25 °C; 50 min, then 20 h; isolated yields are shown. ^cTEA was used to liberate the dimethylamine base.

conversion of the first reaction was not quantitatively monitored. The optimum conditions of the model reaction were used, which to our delight led to complete conversion, as confirmed by the off-line thin-layer chromatography (TLC) analysis of the product mixture.

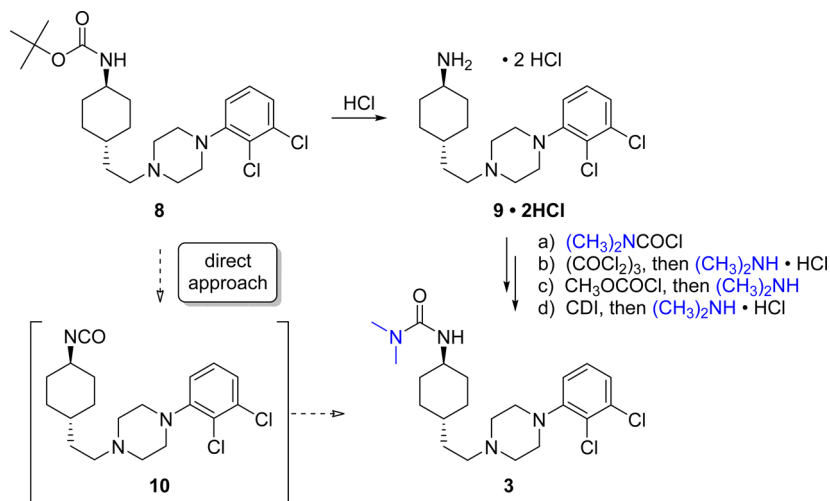
Optimal amounts of the secondary amines were similar in the case of piperidine, pyrrolidine, morpholine, and dimethylamine (6a–d; leading to 7f, 7g, 7h, and 7i, respectively; Table 4). The rather bulky diisopropylamine (6e) led to incomplete conversions in the continuous flow microreactor, even at high excess (9 equiv). Therefore, the product (7j) of the flow procedure was not isolated. Longer reaction time using batch processing was required to obtain the product with reasonable yield, while slight precipitation was observed in the reaction mixture, emphasizing the inapplicability of flow conditions in this exceptional case.

Apart from the last one, good yields could be obtained in each case, with 170–233 mg/h productivity. These experiments also showed the tolerance of ester functional group. Additionally, no loss of relative stereochemistry was observed, which reinforces the conclusions of the original report.

Synthesis of Cariprazine (3). Our ultimate goal was to apply the urea formation for the synthesis of cariprazine (3) directly from its *tert*-butoxycarbonyl protected intermediate (8). This transformation was previously described in a multistep sequence (Scheme 4): deprotection of 8 yielded the primary amine intermediate as dihydrochloride salt (9 · 2HCl), which was converted to the urea containing final product (3) using various

Table 4. Synthesis of Urea Derivatives of Ethyl 2-(*trans*-4-Aminocyclohexyl)acetate Using the Flow System^a

^aConditions: **4b** (1 equiv), TiF_2O (1.1 equiv), 2-ClPy (2 equiv), amine (optimized equivalents are shown for each product); both microreactors were kept at 25 °C; $t_{\text{R1}} = 33$ s, $t_{\text{R2}} = 90\text{--}97$ s; conversion was 100%, except where noted; isolated yields are shown. ^bTEA was used to liberate the dimethylamine base. ^cIsolation of product was not attempted after the flow process. ^dYield of the batch reaction. Conditions: **4b** (1 equiv), TiF_2O (1.5 equiv), 2-ClPy (3 equiv), **6e** (9 equiv); 25 °C; 50 min, then 20 h; isolated yield is shown.

Scheme 4. Known and Proposed Approaches to the Synthesis of Cariprazine (**3**) from Its Boc-Protected Intermediate (**8**)^a

^aCDI: 1,1'-carbonyldiimidazole.

reagent systems in one or two steps.^{85–89} The direct approach would not require the isolation of the primary amine (**9**) and provide a shorter route to this API.

The method for urea formation was adapted to the synthesis of cariprazine (**3**) in the flow system (Figure 2). When the carbamate (**8**) was subjected to the conditions that were found optimal in the model reaction, incomplete conversion to the corresponding isocyanate (**10**) was observed in the first step. The reduced reactivity can be explained by partial decomposition of the TiF_2O reagent caused by the nucleophilic amino moiety of the starting material (**8**).

Consequently, higher excess of both TiF_2O and 2-ClPy had to be used (1.8 and 3 equiv, respectively) to reach total conversion in the first step. In the second stage, dimethylamine hydrochloride (**6d** • HCl) was dissolved together with TEA (triple molar amount of **6d**), in order to liberate **6d**, similarly to the

preparation of the simple dimethylamino ureas (**7d** and **7i**). After optimization, low excess (2 equiv of **6d** • HCl + 6 equiv TEA) was found to be sufficient to form the product (**3**) in full conversion with 76% isolated yield (Figure 3a).

However, in our early experiments, isolation and purification of the basic product (**3**) from the TEA containing crude mixture was problematic. To our delight, TEA could be omitted, and solid potassium phosphate could be used instead. The basicity of the trivalent phosphate ions was enough to shift the equilibrium to full liberation of dimethylamine base (**6d**), and both the phosphate and the formed hydrogen phosphate salts were insoluble in dichloromethane. This allowed conveniently letting the solid salts settle in the feed storage flask after the dimethylamine hydrochloride was dissolved, and the clear solution could be transferred by pump P3 through an inlet filter. Reoptimization of the second stage led to using a

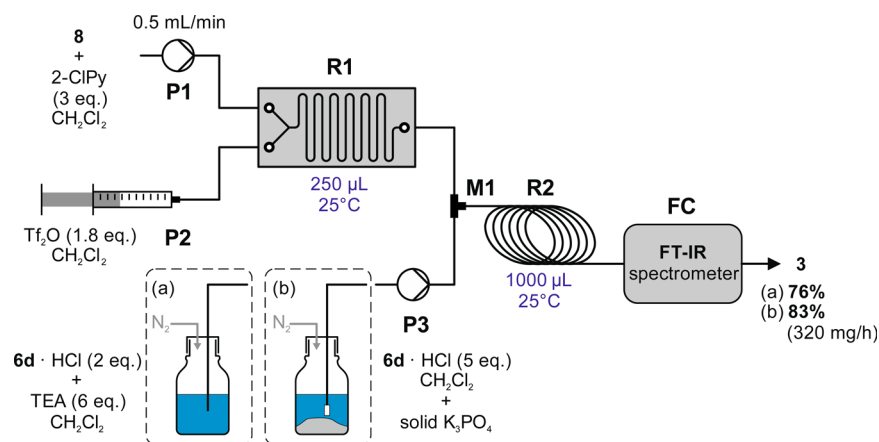


Figure 3. Flow system for the synthesis of cariprazine (**3**), optimal settings, and isolated yields are shown. (a) TEA is used to solubilize dimethylamine (**6d**); $t_{R1} = 31$ s, $t_{R2} = 81$ s. (b) Solid K_3PO_4 is used to solubilize dimethylamine (**6d**); $t_{R1} = 31$ s, $t_{R2} = 87$ s.

moderately higher amount of dimethylamine hydrochloride (5 equiv), the product could be isolated in 83% yield, which corresponds to 320 mg/h productivity (Figure 3b).

3. CONCLUSION

A small footprint continuous-flow system was developed for the synthesis of nonsymmetrically substituted ureas under mild conditions. By taking advantage of continuous processing and the in-line transmission FT-IR analytical technique, the drawbacks of the previous literature method could be addressed. This way, rapid reactions and lowered reagent amounts were allowed. Furthermore, the mechanistic role of the unusual 2-chloropyridine base was clarified, and application of a rationally selected alternative was attempted.

The setup consisting of two sequential microreactors was applied for the synthesis of several urea derivatives including cariprazine.

4. EXPERIMENTAL SECTION

General. All solvents and reagents were purchased from commercial vendors and were used without additional purification. Substrates *tert*-butyl cyclohexylcarbamate (**4a**), ethyl 2-(*trans*-4-((*tert*-butoxycarbonyl)amino)cyclohexyl)acetate (**4b**), and *tert*-butyl (*trans*-4-(2-(4-(2,3-dichlorophenyl)piperazin-1-yl)ethyl)cyclohexyl)carbamate (**8**) were prepared according to literature descriptions.^{83,90} Flash chromatography purifications were conducted using Teledyne Isco CombiFlash Rf 150 device equipped with ELS detector.

Melting points were determined using EZ-Melt MPA120 (Stanford Research Systems, Sunnyvale, CA, USA) apparatus.

FT-IR spectra of the purified products were measured using Bruker ALPHA FT-IR spectrometer (Bruker Optik GmbH, Ettlingen, Germany) equipped with Harrick TFC-S13–3 flow cell (Harrick Scientific Products Inc., Pleasantville, NY, USA) using 100 μ m optical path and ZnSe windows. The samples were introduced as a dichloromethane solution, 16 scans were recorded, and the background of the pure solvent was subtracted.

NMR spectra were recorded at 25 °C on an Agilent (Varian) NMRS-500 spectrometer at 500 MHz for 1H and 126 MHz for ^{13}C using DMSO- d_6 as solvent. The chemical shifts (δ) were referenced to tetramethylsilane (TMS). Electrospray high-resolution MS measurements (ESI-HRMS) were performed on a Thermo LTQ FT Ultra spectrometer (Thermo Fisher Scientific, Bremen, Germany). The ionization method was ESI

and operated in positive ion mode; the ion transfer capillary temperature was set at 280 °C. Samples were infused into the ESI source MeOH solutions at a flow rate of 10 μ L/min. Resolving power of 50 000 (fwhm) at m/z 400 was used. Data acquisition and analysis were accomplished with Xcalibur software v 2.1 (Thermo Fisher Scientific Inc.). Electron impact high-resolution MS measurements (EI-HRMS) were performed on a Finnigan MAT 95XP mass spectrometer (Finnigan, Bremen, Germany). The ion source temperature was set at 220 °C; the applied ionization energy was 70 eV. Data acquisition and analysis were accomplished with Xcalibur software v 2.0 (Thermo Fisher Scientific Inc.).

Procedure for the Batch Syntheses of Cyclohexyl Ureas **7a, **7e**, and **7j**.** In a 50 mL round-bottom flask, 60 mg (0.3 mmol) of *tert*-butyl cyclohexylcarbamate (**4a**) or 86 mg (0.3 mmol) of ethyl 2-(*trans*-4-((*tert*-butoxycarbonyl)amino)cyclohexyl)acetate (**4b**) was dissolved in 10 mL of dichloromethane under nitrogen atmosphere, followed by addition of 90 μ L (0.9 mmol; 3 equiv) of 2-ClPy and 0.45 mL (0.45 mmol; 1.5 equiv) of 1 M solution of Tf_2O in dichloromethane. After stirring for 50 min at room temperature, 270 μ L (2.7 mmol; 9 equiv) of piperidine (**6a**) or 380 μ L (2.7 mmol; 9 equiv) diisopropylamine (**6e**) was added, and stirring was continued for 20 h at room temperature under nitrogen atmosphere.

The resulting mixture was concentrated under reduced pressure and subjected to flash chromatography using cyclohexane and 20% $\rightarrow$ 80% ethyl acetate eluent.

***N*-Cyclohexylpiperidine-1-carboxamide (**7a**).** This was accomplished utilizing piperidine (**6a**): white crystalline solid, 30 mg, 48% yield. Physical and spectral data (see Supporting Information) were consistent with the literature.^{11,91}

3-Cyclohexyl-1,1-diisopropylurea (7e**).** This was accomplished utilizing diisopropylamine (**6e**): white crystalline solid, 22 mg, 32% yield. Physical and spectral data (see Supporting Information) were consistent with the literature.⁹¹

Ethyl 2-(*trans*-4-(3,3-Diisopropylureido)cyclohexyl)acetate (7j**).** This was accomplished utilizing ethyl 2-(*trans*-4-((*tert*-butoxycarbonyl)amino)cyclohexyl)acetate (**4b**) and diisopropylamine (**6e**), white crystalline solid, 78 mg, 83% yield; mp. 96.7–98.0 °C. IR (9 mg/mL): ν_{max} 3481 (ν_{NH}), 2981 (ν_{CH_2}), 2933 (ν_{CH_2}), 2853 (ν_{CH_2}), 1727 ($\nu_{C=O}$ ester), 1632 ($\nu_{C=O}$ urea), 1507 (δ_{NH}) cm^{-1} ; 1H NMR: δ 5.46 (d, $J = 7.8$ Hz, 1H, NH), 4.05 (q, $J = 7.1$ Hz, 2H, OCH_2CH_3), 3.66 (hept, $J = 6.7$ Hz, 2H, $NCH(CH_3)_2$), 3.39–3.31 (m, 1H, C4–H), 2.17 (d, $J = 7.0$

H_z, 2H, C1-CH₂), 1.78–1.70 (m, 2H, C3-H_e), 1.70–1.64 (m, 2H, C2-H_e), 1.63–1.53 (m, 1H, C1-H), 1.24–1.16 (m, 2H, C3-H_a), 1.17 (t, *J* = 7.1 Hz, 3H, OCH₂CH₃), 1.14 (d, *J* = 6.7 Hz, 12H, NCH(CH₃)₂), 1.05–0.93 (m, 2H, C2-H_a) ppm; ¹³C NMR: δ 172.0 (ester CO), 155.6 (urea CO), 59.5 (OCH₂CH₃), 48.6 (C4), 44.5 (NCH(CH₃)₂), 40.8 (C1-CH₂), 33.9 (C1), 32.6 (C3), 31.4 (C2), 21.2 (NCH(CH₃)₂), 14.1 (OCH₂CH₃) ppm; ESI-HRMS: calcd for C₁₇H₃₃O₃N₂ [M + H]⁺: 313.24857; found: 313.24841; δ = −0.5 ppm.

Flow System and In-Line Analytics. Feed solutions of the carbamate substrates (**4a–b**) and the secondary amines (**6a–e**) were kept under 1 bar N₂ atmosphere in the Asia Pressurized Input Store (Syrris Ltd., Royston, UK) and transferred by the Asia Syringe Pump system (**P1** and **P3**, respectively; Syrris Ltd., Royston, UK).

Commercially available 1 M solution of Tf₂O was introduced into a Hamilton Gastight 1002 (2.5 mL volume) syringe (Hamilton Bonaduz AG, Bonaduz, Switzerland) injected by a Cole-Parmer 74900–05 single-syringe infusion pump (**P2**; Cole-Parmer, Vernon Hills, IL, USA) employing a custom-made stainless steel Luer lock to tubing connector (Figure S2(b)).

PTFE tubing (1/16" outer diameter and 0.8 mm inner diameter) and flangeless PEEK fittings with PEEK ferrules were used to connect the units (purchased from commercial vendors). Internal volume of connecting tubing was taken into account for the calculation of residence times.

The first reaction step was conducted by mixing the streams from **P1** and **P2** in a two-feed, 250 μL volume glass chip microreactor (**R1**; Syrris Ltd., Royston, UK) thermostated by Asia Chip Climate Controller (Syrris Ltd., Royston, UK). The second step was carried out utilizing a PTFE T-adaptor (Omnifit 1.5 mm inner diameter, Diba Industries Ltd., Cambridge, UK) as mixing unit (**M1**) for combining the streams exiting from **R1** and **P3**, followed by a custom-made 1 mL volume PTFE coil (1/16" outer diameter and 0.8 mm inner diameter) reactor (**R2**).

Product stream exiting from **R2** was directly introduced to the Harrick TFC-S13–3 flow cell (**FC**; 100 μm optical path and ZnSe windows) inside the Bruker ALPHA FT-IR spectrometer.

Procedure for Optimization of the Flow Synthesis of Urea 7a. The continuous syringe pump **P1** was used to transfer the stock solutions of *tert*-butyl cyclohexylcarbamate (**4a**; 0.03 M concentration) in dichloromethane premixed with 2-ClPy (concentration varied 0.015–0.09 M; 0.5–3 equiv) at fixed 0.5 mL/min flow rate. Commercially available 1 M solution of Tf₂O in dichloromethane was introduced using infusion syringe pump **P2** at varied (7.5–22.5 μL/min; 0.5–1.5 equiv) flow rates.

The dichloromethane solution of piperidine (**6a**, 0.27 M concentration) was introduced through continuous syringe pump **P3** at varied (0.028–0.5 mL/min; 0.5–9 equiv) flow rates. Optionally, one-quarter or one-half of piperidine was substituted with TEA in the stock solution.

The temperature of microreactor **R1** was varied between 0 and 35 °C, while **M1** and **R2** were kept at room temperature. The product stream was analyzed by FT-IR after reaching a steady state (collecting at least 4 mL reaction mixture to the waste). Conversion of the first step is based on the ratio of integrated absorbance of ν(CO_{carbamate}) = 1706 cm^{−1} and ν(CO_{urea}) = 1640 cm^{−1} bands, and the ratio of integrated absorbance of ν(NCO) = 1706 cm^{−1} and ν(CO_{urea}) = 2263 cm^{−1} bands in the second step (Figures S4–S5).

General Procedure for the Flow Synthesis of Ureas 7a–

i. The continuous syringe pump **P1** transferred the solution of carbamate substrates (**4a–b**; 0.03 M concentration) in dichloro-

methane premixed with 2-ClPy (0.06 M concentration; 2 equiv) at 0.5 mL/min flow rate. Commercially available 1 M solution of Tf₂O in dichloromethane was introduced using infusion syringe pump **P2** at 16.5 μL/min flow rate (1.1 equiv).

The dichloromethane solution of the secondary amines (**6a–c** and **6e**, 0.27 M concentration) was introduced through continuous syringe pump **P3** at 0.194–0.5 mL/min flow rate (3.5–9 equiv; optimized for each particular reaction). Dimethylamine hydrochloride (**6d** · HCl, 0.09 M concentration) was dissolved together with TEA (0.27 M) in dichloromethane and pumped with **P3** at 0.25 mL/min flow rate (1.5 equiv **6d** · HCl + 4.5 equiv TEA; optimized). Optimal parameters are shown in Table S2.

Microreactors **R1**, **R2**, and mixing unit **M1** were kept at room temperature. The product stream was constantly monitored by the FT-IR spectrometer. After reaching steady state, product stream exiting the flow cell (**FC**) was collected for 20 min (molar amount of substrate is equal to the batch procedure). The crude mixture was concentrated under reduced pressure and subjected to flash chromatography using cyclohexane and 20% → 80% ethyl acetate eluent.

N-Cyclohexylpiperidine-1-carboxamide (7a). This was accomplished utilizing *tert*-butyl cyclohexylcarbamate (**4a**) and piperidine (**6a**): white crystalline solid, 61 mg, 97% yield. Physical and spectral data (see Supporting Information) were consistent with the literature.^{11,91}

N-Cyclohexylpyrrolidine-1-carboxamide (7b). This was accomplished utilizing **4a** and pyrrolidine (**6b**): white crystalline solid, 52 mg, 88% yield. Spectral data (see Supporting Information) were consistent with the literature.⁹²

N-Cyclohexylmorpholine-4-carboxamide (7c). This was accomplished utilizing **4a** and morpholine (**6c**): white crystalline solid, 51 mg, 79% yield. Physical and spectral data (see Supporting Information) were consistent with the literature.⁹³

3-Cyclohexyl-1,1-dimethylurea (7d). This was accomplished utilizing **4a** and dimethylamine hydrochloride (**6d** · HCl): white crystalline solid, 42 mg, 83% yield. Physical and spectral data (see Supporting Information) were consistent with the literature.⁹⁴

3-Cyclohexyl-1,1-diisopropylurea (7e). This was accomplished utilizing **4a** and diisopropylamine (**6e**): white crystalline solid, 50 mg, 74% yield. Physical and spectral data (see Supporting Information) were consistent with the literature.⁹¹

Ethyl 2-(trans-4-(Piperidine-1-carboxamido)cyclohexyl)-acetate (7f). This was accomplished utilizing ethyl 2-(trans-4-((*tert*-butoxycarbonyl)amino)cyclohexyl)acetate (**4b**) and piperidine (**6a**): white crystalline solid, 57 mg, 64% yield; mp. 104.4–105.9 °C. IR (9 mg/mL): ν_{max} 3460 (νNH), 2938 (νCH₂), 2855 (νCH₂), 1727 (νC=O ester), 1639 (νC=O urea), 1510 (δNH) cm^{−1}; ¹H NMR: δ 6.02 (d, *J* = 7.8 Hz, 1H, NH), 4.04 (q, *J* = 7.1 Hz, 2H, OCH₂CH₃), 3.38–3.33 (m, 1H, C4–H), 3.24–3.20 (m, 4H, C2′-H₂), 2.16 (d, *J* = 7.1 Hz, 2H, C1–CH₂), 1.77–1.71 (m, 2H, C3–H_e), 1.70–1.64 (m, 2H, C2–H_e), 1.61–1.53 (m, 1H, C1–H), 1.48–1.52 (m, 2H, C4′-H₂), 1.41–1.36 (m, 4H, C3′-H₂), 1.25–1.13 (m, 2H, C3–H_a), 1.17 (t, *J* = 7.1 Hz, 3H, OCH₂CH₃), 1.07–0.91 (m, 2H, C2–H_a) ppm; ¹³C NMR: δ 172.1 (ester CO), 156.7 (urea CO), 59.6 (OCH₂CH₃), 48.9 (C4), 44.2 (C2′), 40.8 (C1–CH₂), 33.9 (C1), 32.6 (C3), 31.3 (C2), 25.3 (C3′), 24.2 (C4′), 14.1 (OCH₂CH₃) ppm; EI-HRMS: calcd for C₁₆H₂₈O₃N₂ [M]⁺: 296.20944; found: 296.21007; δ = 2.1 ppm.

Ethyl 2-(trans-4-(Pyrrolidine-1-carboxamido)cyclohexyl)-acetate (7g). This was accomplished utilizing **4b** and pyrrolidine (**6b**): white crystalline solid, 66 mg, 78% yield; mp. 149.6–150.4

$^{\circ}\text{C}$. IR (8.3 mg/mL): ν_{max} 3446 (νNH), 2932 (νCH_2), 2856 (νCH_2), 1727 ($\nu\text{C}=\text{O}$ ester), 1642 ($\nu\text{C}=\text{O}$ urea), 1515 (δNH) cm^{-1} ; ^1H NMR: δ 5.64 (d, $J = 8.1$ Hz, 1H, NH), 4.04 (q, $J = 7.2$ Hz, 2H, OCH_2CH_3), 3.39–3.29 (m, 1H, C4–H), 3.20–3.14 (m, 4H, C2'–H₂), 2.17 (d, $J = 7.0$ Hz, 2H, C1–CH₂), 1.79–1.71 (m, 6H, C3'–H₂, C3–H_e), 1.69–1.64 (m, 2H, C2–H_e), 1.63–1.54 (m, 1H, C1–H), 1.25–1.15 (m, 2H, C3–H_a), 1.17 (t, $J = 7.2$ Hz, 3H, OCH_2CH_3), 1.05–0.94 (m, 2H, C2–H_a) ppm; ^{13}C NMR: δ 172.1 (ester CO), 155.8 (urea CO), 59.6 (OCH_2CH_3), 48.6 (C4), 45.2 (C2'), 40.8 (C1–CH₂), 33.9 (C1), 32.7 (C3), 31.4 (C2), 25.0 (C3'), 14.1 (OCH_2CH_3) ppm; ESI-HRMS: calcd for $\text{C}_{15}\text{H}_{27}\text{O}_3\text{N}_2$ [$\text{M} + \text{H}$] $^+$: 283.20162; found: 283.20208; $\delta = 1.6$ ppm.

Ethyl 2-(trans-4-(Morpholine-4-carboxamido)cyclohexyl)-acetate (7h). This was accomplished utilizing **4b** and morpholine (**6c**): white crystalline solid, 78 mg, 87% yield; mp. 134.9–137.0 $^{\circ}\text{C}$. IR (7.7 mg/mL): ν_{max} 3458 (νNH), 2929 (νCH_2), 2856 (νCH_2), 1727 ($\nu\text{C}=\text{O}$ ester), 1648 ($\nu\text{C}=\text{O}$ urea), 1511 (δNH), 1355 (γCH_3), 1119 ($\nu\text{C}-\text{O}$) cm^{-1} ; ^1H NMR: δ 6.17 (d, $J = 7.7$ Hz, 1H, NH), 4.04 (q, $J = 7.1$ Hz, 2H, OCH_2CH_3), 3.56–3.48 (m, 4H, C3'–H₂), 3.41–3.33 (m, 1H, C4–H), 3.26–3.17 (m, 4H, C2'–H₂), 2.17 (d, $J = 7.0$ Hz, 2H, C1–CH₂), 1.80–1.72 (m, 2H, C3–H_e), 1.71–1.63 (m, 2H, C2–H_e), 1.63–1.52 (m, 1H, C1–H), 1.25–1.15 (m, 2H, C3–H_a), 1.17 (t, $J = 7.1$ Hz, 3H, OCH_2CH_3), 1.00 (qd, $J = 12.7, 3.2$ Hz, 2H, C2–H_a) ppm; ^{13}C NMR: δ 172.1 (ester CO), 157.0 (urea CO), 65.9 (C3'), 59.6 (OCH_2CH_3), 49.0 (C4), 43.8 (C2'), 40.8 (C1–CH₂), 33.9 (C1), 32.5 (C3), 31.3 (C2), 14.1 (OCH_2CH_3) ppm; ESI-HRMS: calcd for $\text{C}_{15}\text{H}_{27}\text{O}_4\text{N}_2$ [$\text{M} + \text{H}$] $^+$: 299.19653; found: 299.19696; $\delta = 1.4$ ppm.

Ethyl 2-(trans-4-(3,3-Dimethylureido)cyclohexyl)acetate (7i). This was accomplished utilizing **4b** and dimethylamine hydrochloride (**6d** · HCl): white crystalline solid, 66 mg, 86% yield. Spectral data (see [Supporting Information](#)) were consistent with the literature.⁹⁵

Procedure for the Flow Synthesis of Cariprazine (3) Using TEA. The continuous syringe pump **P1** transferred the solution of *tert*-butyl (trans-4-(2-(4-(2,3-dichlorophenyl)piperazin-1-yl)ethyl)cyclohexyl)carbamate (**8**; 0.03 M concentration) in dichloromethane premixed with 2-CIPy (0.09 M concentration; 3 equiv) at 0.5 mL/min flow rate. Commercially available 1 M solution of TiF_2O in dichloromethane was introduced using infusion syringe pump **P2** at 27 $\mu\text{L}/\text{min}$ flow rate (1.7 equiv).

Dimethylamine hydrochloride (**6d** · HCl, 0.09 M concentration) was dissolved together with TEA (0.27 M) in dichloromethane and pumped with **P3** at 0.333 mL/min flow rate (2 equiv **6d** · HCl + 6 equiv TEA).

Micoreactors **R1**, **R2**, and mixing unit **M1** were kept at room temperature. The product stream was constantly monitored by the FT-IR spectrometer. After reaching steady state, product stream exiting the flow cell (**FC**) was collected for 20 min (molar amount of substrate is equal to the batch procedure). The crude mixture was concentrated under reduced pressure and subjected to flash chromatography using 5% methanol + 0.5% aqueous ammonia in dichloromethane eluent.

The product was obtained as white crystalline solid, 96 mg, 76% yield, which was identical to the authentic sample of cariprazine.

Procedure for the Flow Synthesis of Cariprazine (3) Using Potassium Phosphate. Dimethylamine hydrochloride (**6d** · HCl, 0.27 M concentration) was dissolved in the dichloromethane suspension of K_3PO_4 . After complete dis-

solution of the hydrochloride salt and settling of the remaining solids, the clear liquid was pumped with **P3** at 0.273 mL/min flow rate (5 equiv) through an inlet filter.

Other parts and settings of the system were unchanged. The product was obtained as white crystalline solid, 105 mg, 83% yield, which was identical (see [Supporting Information](#)) to the authentic sample of cariprazine.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/acs.oprd.7b00019](https://doi.org/10.1021/acs.oprd.7b00019).

Pictorial description of the flow system, optimization data, schematics of the modified flow systems and characterization data of known compounds ([PDF](#))

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

This paper is dedicated to the memory of Prof. Csaba Szántay, an inspirational organic chemist for generations.

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