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Modular Continuous Flow Synthesis of Imatinib and Analogues

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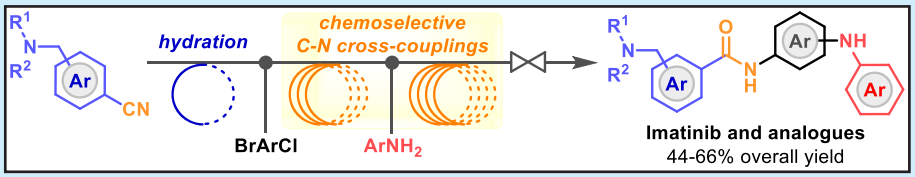
Supporting Information



ABSTRACT: A modular continuous flow synthesis of imatinib and analogues is reported. Structurally diverse imatinib analogues are rapidly generated using three readily available building blocks via a flow hydration/chemoselective C−N coupling sequence. The newly developed continuous flow hydration and amidation modules each exhibit a broad scope with good to excellent yields. Overall, the method described does not require solvent switches, in-line purifications, or packed-bed apparatuses due to the judicious manipulation of flow setups and solvent mixtures.

The Bcr-Abl tyrosine kinase inhibitor imatinib is the active pharmaceutical ingredient (API) of Gleevec.[1] It is currently listed on the World Health Organization's List of Essential Medicines as a treatment for chronic myelogenous leukemia (CML) and gastrointestinal stromal tumor (GIST).[2] The batch production process of this API is labor-intensive and time-consuming and involves multistep reaction sequences and purifications.[3] Recently, continuous flow technology has emerged as an efficient tool in API synthesis owing to its power in telescoping multiple synthetic steps into a streamlined system and circumventing laborious purification processes of intermediates.[4] The many characteristic benefits of flow chemistry[5] have prompted our laboratory to develop continuous flow platforms for greater access to various APIs.[6]

A large body of work has summarized imatinib-resistant mutations in the Bcr-Abl kinase domain.[7] One of the major constraints associated with current imatinib syntheses, either in batch or flow, is the limited availability and variation in substitution patterns of functionalized substrates which render a narrow derivatization scope for high throughput discovery of new tyrosine kinase inhibitors.[3,8] While following literature precedents, we also identified a multitude of challenges for the continuous production of imatinib. In 2010, the Ley group utilized a strategic disconnection that enabled the synthesis of imatinib in flow with minimal intervention (Figure 1a).[9] However, solvent-switching apparatuses and scavenger columns were required for in-line workup and purification due to solvent and reagent incompatibilities between individual reaction steps.[8,9] The use of solid-supported reagents and purification cartridges can offset the continuity of a flow system because of the eventual replacement of consumable materials. The formation of inorganic solids and thus clogging of microreactors has also been a long-standing problem in the deployment of transition-metal-mediated C−N bond forming steps. Although these concerns have been addressed by means of acoustic irradiation[10] or packed-bed mixing under biphasic conditions,[11] prolonged continuous operation of Pd-catalyzed reactions in packed-bed reactors may result in the aggregation of palladium black precipitate within the packing materials or filtering frits, wherein undesirable side reactions or clogging problems might arise.

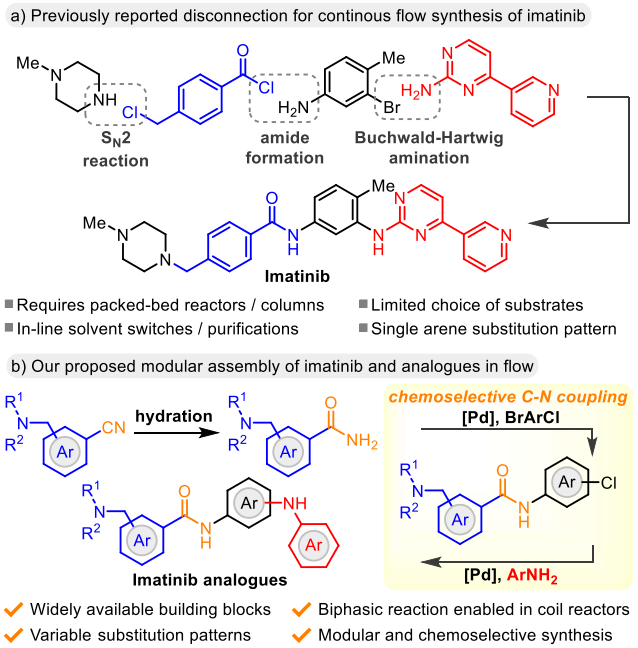


Figure 1. Continuous flow synthesis of imatinib and analogues.

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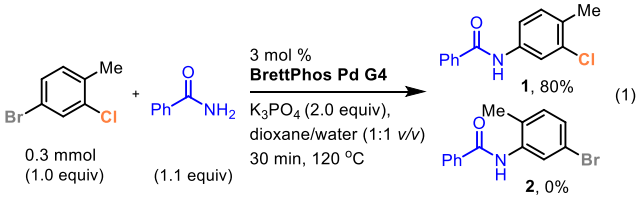
Herein we devised a new modular assembly of imatinib and structural analogues in a single uninterrupted reaction stream (Figure 1b). A Pd-catalyzed chemoselective amidation/amination process directly employing anilines and amides avoids cumbersome reaction steps to reveal $-NH_2$ from nitro or protecting groups.[3a] From a standpoint of versatility and practicality, aryl halides and nitriles are generally cost-effective and more accessible than their corresponding anilines or acid chlorides[12] and are often more stable toward light, heat, and moisture.[13] Furthermore, a catalytic flow hydration of nitriles was developed to give amides with minimal byproduct formation, posing less uncertainty in downstream processes.

Our investigations commenced with the proposed chemoselective amidation using a model reaction between benzamide and 2,4-dihalotoluene under batch conditions. The optimization process has been detailed in the Supporting Information (Tables S1 and S2). Although low chemoselectivity and product yields were observed when dichloro- or dibromotoluene was used, favorable results were obtained using 4-bromo-2-chlorotoluene. Buchwald's precatalyst **BrettPhos Pd G4** proved to be the best catalyst while its improved solubility in organic solvents was deemed beneficial for utilization in a flow process.[14] A biphasic mixture of K_3PO_4(aq)/1,4-dioxane was optimal for the reaction as the base and solvent, and also ensured the solubility of the inorganic salts in flow. Complete chemoselectivity with an 80% yield of **1** was obtained under the optimized batch reaction conditions (eq 1).



(1)

Next, we set out to translate the batch process to flow. It was found that when three separate streams of catalyst, substrates, and base were mixed in a cross mixer with a small inner diameter (0.02" id), a near-homogeneous mixture resulted as shown in Figure 2a. We reasoned that minimized aqueous microdroplets were produced from the vigorous mixing between dioxane and the alkaline solution which is different from a typical segmented flow afforded from a 2-MeTHF/water mixture (Figure 2b).[11b] Although packed-bed mixing was previously shown to be critical for biphasic C–N couplings in flow,[11] we postulated that generation of aqueous microdroplets

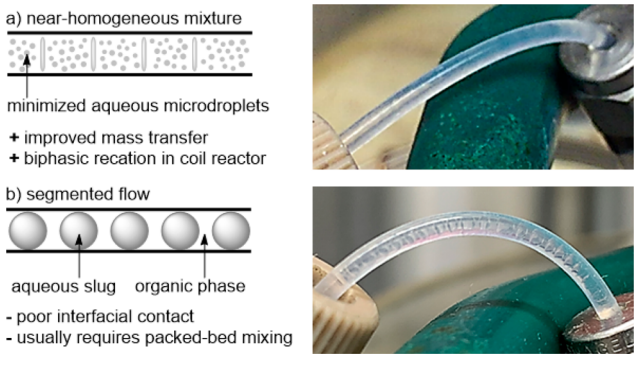
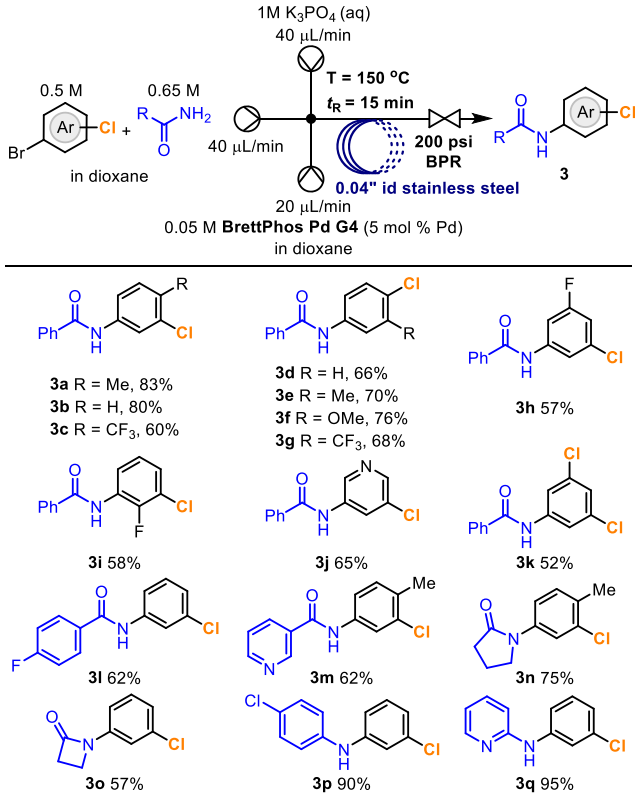


Figure 2. An illustrated comparison of (a) segmented and (b) near-homogeneous flow.

may significantly increase the interfacial contact. In practice, compound **3a** (Scheme 1) was obtained in 69% yield within a

Scheme 1. Substrate Scope of Chemoselective Amidation in Continuous Flow[a]



[a]Isolated yields are reported. See Supporting Information for details.

residence time (t_R) of 15 min at 120 °C in a stainless-steel coil reactor (0.04" inner diameter). Utilization of a 200 psi back pressure regulator (BPR) allowed for the superheating of water and dioxane at 150 °C without solvent vaporization and increased the isolated yield of **3a** to 83%. Notably, replacing the coil reactor with a sand packed-bed reactor resulted in clogging due to aggregation of palladium black on the frit of the reactor output.

Next, we explored the generality of our chemoselective amidation module (Scheme 1). Both electron-rich and -deficient aryl dihalides (**3a**–**3g**) were amidated to give the desired products in good yields and complete chemoselectivity. Importantly, sterically unhindered bromoaryl chlorides (**3b**, **3d**, **3h**–**3l**) reacted smoothly and afforded chloroaryl amides in moderate to good yields. Heteroatoms incorporated in the aryl dihalides (**3j**) or amides (**3m**) were tolerated. The scope of our flow reaction could be further expanded to lactams (**3n**–**3o**) and anilines (**3p**–**3q**). For polar amides with a low solubility in dioxane (**3m**, **3o**), 2–15% (v/v) of methanol was employed as a cosolvent.

Having established the C–N coupling key to our synthetic sequence, we next developed a continuous flow hydration of nitriles for the preparation of amides. In 2014, Ley and co-workers developed a continuous flow hydration by passing the nitriles through a manganese dioxide packed-bed reactor.[15]

However, the nitrile precursor to **4a** and thus imatinib (Scheme 2) was found to be not compatible with MnO_2 and the flow reaction only gave a trace amount of formylbenzoni-

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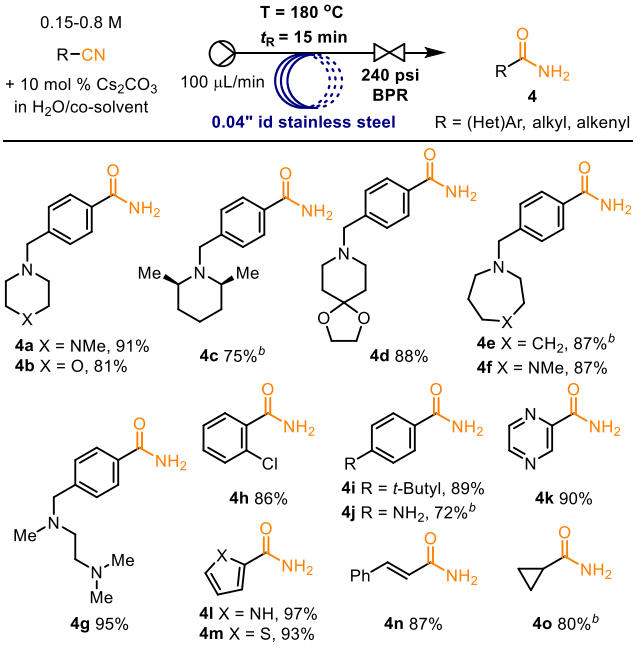
Scheme 2. Substrate Scope for Continuous Flow Hydration of Nitriles[a]

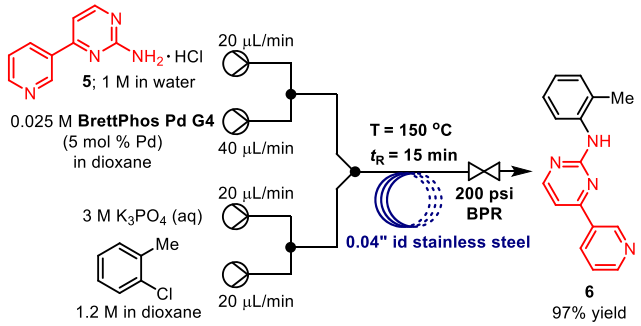


[a]Isolated yields are reported. See Supporting Information for details. [b]20 mol % of Cs_2CO_3 was used.

trile as a result of oxidative cleavage. Recently, the hydration of nitriles was found to proceed in the presence of a stoichiometric amount of K_2CO_3 using conventional heating in 3 h.[16] We anticipated that heating the reaction mixture above its atmospheric boiling point under continuous flow conditions would allow for a significantly increased reaction rate.[5b,c] Indeed, stoichiometric quantities of K_2CO_3 promoted the hydration in a stainless steel coil reactor at 150 °C and yielded 75% of **4a** after a t_R of 5 min (Table S3). Reaction optimization led to complete conversion employing 10 mol % Cs_2CO_3 and a 240 psi BPR within 15 min at 180 °C. In practice, a solution of the nitrile in 1,4-dioxane/DI water (0.8 M, 2:3 v/v) was passed through a coil reactor to give **4a** in 91% isolated yield (Scheme 2). Importantly, this catalytic hydration process generates minimal wastes and shares the same solvent mixture with the C–N coupling reactions to eliminate the need for either in-line solvent switches or purification between individual steps. Other nitrile precursors applicable to imatinib analogues similarly underwent hydrolysis smoothly to afford the corresponding amides in 75–95% isolated yield (**4a**–**4g**). Chloro- (**4h**), amino- (**4j**), and heterocycles (**4k**, **4l**, **4m**) were well tolerated under the continuous flow conditions. Alkenyl (**4n**) and aliphatic (**4o**) nitriles were also applicable substrates. Organic cosolvents such as *i*-PrOH and *t*-BuOH could be used without affecting the reaction in cases where the starting materials possessed low solubility in water and 1,4-dioxane.

The last module in our synthetic sequence constituted the C–N bond formation of 2-aminopyrimine **5** and a sterically hindered aryl chloride (Scheme 3). Notably, the low solubility of **5** in organic solvents proved challenging. Hence, **5** was dissolved in water as its conjugate acid for injection into the system to form a homogeneous solution after mixing with the Pd catalyst in a T-mixer. This homogeneous solution was then combined with the flow slugs afforded from the streams of K_3PO_4 and 2-chlorotoluene to give a near-homogeneous

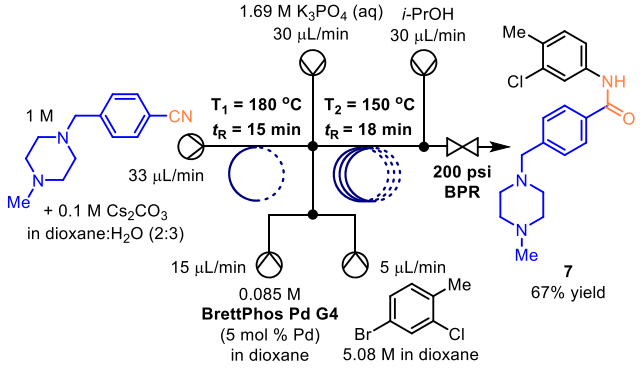
Scheme 3. Biphasic Continuous Flow C–N Cross-Coupling Using a Coil Reactor



mixture. The Y-mixer offered milder laminar mixing, preventing the precipitation and thus aggregation of **5** upon forming the free base with K_3PO_4. The C–N coupling furnished a 97% isolated yield of **6** with a t_R of 15 min in a stainless-steel coil reactor. Prior to this work, this biphasic coupling reaction was only successful in a packed-bed reactor.[11]

We next sought to telescope the three optimized modules to establish a three-step streamlined flow synthesis of imatinib. The outlet of the hydration module was directly used without any purification or workup steps (Scheme 4). The aryl halide

Scheme 4. Telescoped Synthesis of Intermediate 7



and Pd precatalyst were first mixed and subsequently combined with separate streams of K_3PO_4 and the newly generated amide intermediate in a cross-mixer (0.02" id) to form a mixture as shown in Figure 2a. Here, 0.306 M was found to be an optimal concentration for the Pd-catalyzed flow amidation with a stoichiometry of the amide and aryl halide of 1.3:1. Decreasing the global concentration of the system by half led to significant losses in overall product yield while increasing the concentration ultimately led to clogging in the cross-mixer due to crystallization of polar amide intermediates. A stream of *i*-PrOH was introduced after the reactors to prevent precipitation of polar compounds and clogging of the BPR. Within 33 min, intermediate **7** was delivered in 67% isolated yield over two reaction steps.

Finally, the remaining C–N cross-coupling of **7** and 2-aminopyrimidine **5** was integrated into the hydration/amidation sequence (Scheme 5). However, the poor solubility of **5** in the reaction mixture again presented a significant challenge. Neutralization of **5**·HCl with a basic aqueous solution caused crystal aggregation in the mixing unit. Thus, K_3PO_4, Pd precatalyst, and the reaction mixture from the first

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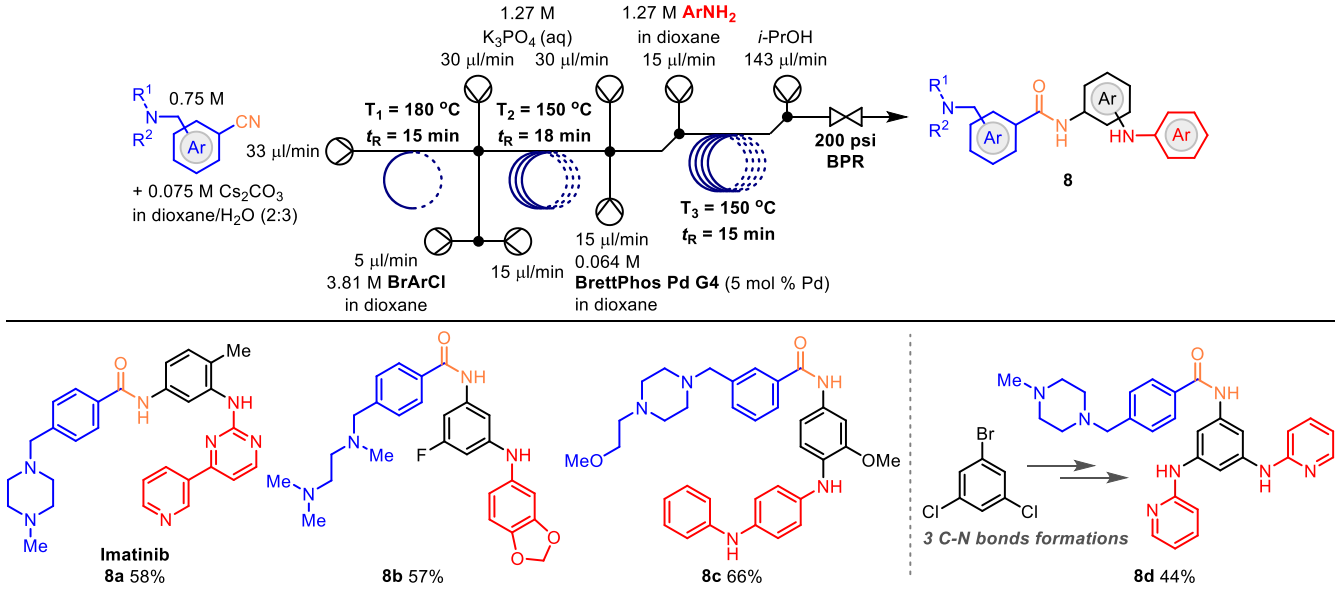
Scheme 5. Continuous Flow Synthesis of Imatinib and Analogues[a]



[a]See the Supporting Information for detailed reaction conditions.

two telescoped steps were first mixed before joining the stream of **5**·HCl to enable faster flow rates and an overall more dilute stream. Additionally, the global concentration of the system was decreased by 25% and **5**·HCl was dissolved in a 1:1 dioxane/DI water mixture to increase the content of organic solvent. Despite these approaches to avoid immediate precipitation, clogging of the Y-mixer before the final reactor still occurred shortly after equilibration of the flow system. The gradual solid aggregation of **5** in the Y-mixer was perceived as a result of seeded crystallization triggered by solvent incompatibilities during system equilibration. To address this, the streams of *i*-PrOH and the hydration module were first pumped into the system for a period of 30 min to equilibrate the telescoped system with *i*-PrOH. The remaining modules were started afterward, as the excess *i*-PrOH could dissolve and carry away the unreacted materials. As described above, the reaction mixtures afforded by the mixing units constituted a semihomogeneity, and the final amination reaction could be performed in a stainless-steel coil reactor. Imatinib (**8a**) was isolated in 58% overall yield with a total t_R of 48 min and a production rate of 0.663 mmol h^{-1}.

To demonstrate the utility of our method, the three individual substrates were varied and two novel imatinib analogues were rapidly generated in 57−66% yield with complete chemoselectivity (**8b**−**8c**) (Scheme 5). Notably, analogue **8d** was prepared by performing two C−N cross-coupling reactions on a *meta*-dichloroarene intermediate in the final step, demonstrating the ability of our system to access commercially unavailable structures *in situ*. We anticipate that the tunability of substitution patterns and structures of both aryl nitriles and halides could provide a higher structural diversity for drug discovery in comparison with the existing methods.[3]

In conclusion, a continuous flow platform for the rapid and modular synthesis of imatinib and analogues has been developed. Our three-step synthetic sequence uses widely available nitriles and aryl halides to assemble imatinib and related analogues via sequential hydration and chemoselective C−N cross-couplings. The newly developed catalytic hydration and amidation modules both exhibited a broad scope with good to excellent yields. To the best of our knowledge, our system delivers the highest production rate of imatinib while packed-bed apparatuses, in-line purifications, and solvent exchanges between individual steps were not required. We have shown that inadequate mass transfer of biphasic C−N cross-coupling reactions under continuous flow conditions can be addressed by meticulous manipulation of the flow setup and solvent mixtures. Taken together, these results would be useful for the future design and implementation of continuous flow sequences employing biphasic reactions using simple components.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02259.

Experimental procedures, characterization data and spectra of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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