A Unified Continuous Flow Assembly-Line Synthesis of Highly Substituted Pyrazoles and Pyrazolines

A Unified Continuous Flow Assembly Line Synthesis of Highly Substituted Pyrazoles and Pyrazolines

Joshua Britton and Timothy F. Jamison*

Abstract: *A rapid and modular continuous flow synthesis of highly functionalized fluorinated pyrazoles and pyrazolines has been developed. Flowing fluorinated amines through sequential reactor coils mediates diazoalkane formation and [3+2] cycloaddition to generate more than 30 azoles in a telescoped fashion. Pyrazole cores are then sequentially modified through additional reactor modules performing N-alkylation and arylation, deprotection, and amidation to install broad molecular diversity in short order. Continuous flow synthesis enables the safe handling of diazoalkanes at elevated temperatures, and the use of aryl alkyne dipolarphiles under catalyst free conditions. This assembly line synthesis provides a flexible approach for the synthesis of agrochemicals and pharmaceuticals, as demonstrated by a four-step, telescoped synthesis of measles therapeutic, AS-136A, in a total residence time of 31.7 min (1.76 g h^{-1}).*

In recent years, continuous flow synthesis has emerged as an enabling technology.[1] At its core, pumps drive fluids through reactor coils where solutions can be heated above their atmospheric boiling points,[2] rapidly cooled,[2a, 3] and effectively irradiated.[4] Additionally, hazardous reactions can be safely processed on scale by ensuring only small quantities of hazardous material exist at any given time.[1d, 5] With these benefits in mind, our laboratory is interested in improving the synthesis of active pharmaceutical ingredients (APIs),[6] commodity chemicals[6e, 7] and new materials[8] through the use of continuous flow technology.

A large fraction of agrochemicals and pharmaceuticals contain highly substituted pyrazole cores with CF_2H or CF_3 moieties at the 3-position (Fig. 1). To create a rapid and divergent synthesis of these molecules, we envisaged the use of an assembly line synthesis.[9] In an assembly line process, organic scaffolds are passed through sequential reactor modules to accrue molecular complexity. In our system, a common pyrazole core would first be synthesized, and then modified through a series of subsequent, downstream, modules to generate agrochemicals and pharmaceuticals. Choosing the order, and type, of modules would govern the substitution pattern and complexity of the final product. Herein, a multi-step continuous flow synthesis of fluorinated pyrazole cores, and their subsequent modification with additional modules is described.

The [3+2] cycloaddition of diazomethane with acetylene yielding pyrazole was first reported in 1898.[10] More recently, 2,2-difluoromethyl diazomethane and 2,2,2-trifluoromethyl diazomethane (**1** and **2**, Fig. 2) have become common synthons in organic synthesis.[11] Highly substituted pyrazoles and pyrazolines can be obtained in a single step through a reaction

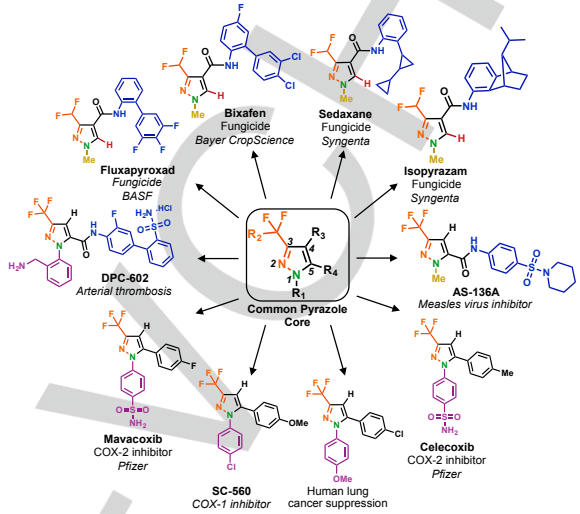

Fig. 1 Pharmaceuticals and agrochemicals containing common 3-fluoromethyl pyrazole cores. Colours indicate structural similarities.

of **1** and **2** with alkynes and alkenes.[11a, 12] In this respect, the use of **1** and **2** would provide a cost effective approach to the construction of common pyrazole cores. However, several advancements were required to realize this goal.

Generally, [3+2] cycloadditions between alkynes and **1** require several hours to days,[11a, 13] while the use of **2** requires several hours and super stoichiometric amounts of Ag_2O and NaOAc.[12b] Interestingly, **1** and **2** have been synthesized in continuous flow before,[13-14] however, in the case of **1,** all reactants were placed into a syringe prior to entering the continuous flow system, posing a safety concern as the diazoalkane can be formed in the syringe.[13] Furthermore, although **1** was generated in continuous flow, the [3+2] cycloaddition was performed at room temperature in a round bottom flask. Our control reactions indicated that generating **1** in continuous flow is inconsequential if the [3+2] cycloaddition is performed at room temperature (Supplementary Information). To enable the safe and beneficial use of **1** and **2** in our continuous flow system, the reactive components must be separated prior to entry, the [3+2] cycloaddition should be rapid for immediate diazoalkane consumption (removing a safety concern), and if possible, transformations should be catalyst free.

Our investigation began by optimizing the formation of **1** in the first module, and its subsequent consumption in a telescoped [3+2] cycloaddition with ethyl propiolate in the second module (Fig. 2). To our surprise, the formation of **1** required only five min at 60 °C, and the telescoped [3+2] cycloaddition only 10 min at 90 °C to give **3** in an excellent 92% yield (Table S1). The ability to synthesize **1** in the first module, and feed it into the second enhances reaction efficiency; passing all reagents through a single reactor coil yielded only 57%. The lower yield observed is due to less diazoalkane formation at elevated temperatures, further highlighting the benefit of reaction isolation during multi-step reactions.

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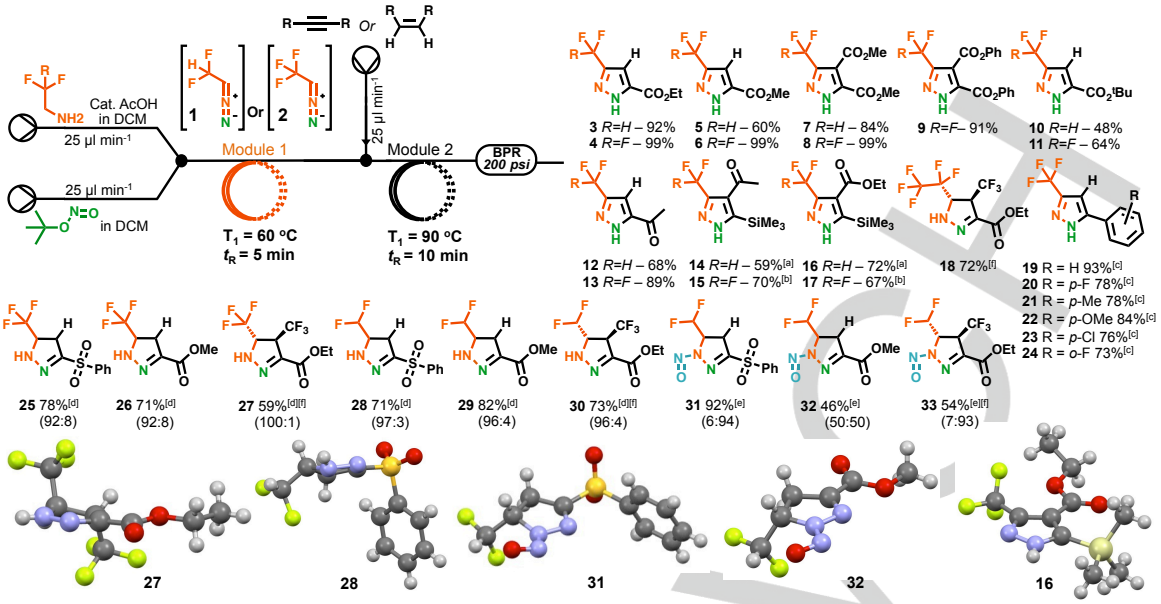


Fig. 2 Module 1 and 2 for the synthesis of highly substituted pyrazole and pyrazoline cores. Unless otherwise indicated, the system used the following three solutions: a solution of $CF_2RCH_2NH_2$ (2.0 equiv) and AcOH (0.4 equiv) dissolved in DCM, a second solution of ^tBuONO (2.4 equiv) in DCM, and a third solution of the alkyne or alkene (0.79 M, 1.0 equiv) in DCM. *[a]* $CF_3CH_2NH_2$ (4.0 equiv), ^tBuONO (4.0 equiv), ACOH (0.15 equiv) and alkyne (0.79 M, 1.0 equiv). *[b]* $CF_2HCH_2NH_2$ (0.5 equiv), ^tBuONO (0.8 equiv), AcOH (0.1 equiv) and alkyne (0. 79 M, 1.0 equiv). *[c]* $CF_3CH_2NH_2$ (2.38 M, 4.0 equiv) and ^tBuONO (2.86 M, 4.8 equiv) and ACOH (0.48 M, 0.8 equiv) and the alkyne (0.60 M, 1.0 equiv) with a 28 min residence time in module 2 at 132 °C with a back pressure of 325 psi. *[d]*. $CF_2RCH_2NH_2$ (2.0 equiv), ^tBuONO (2.0 equiv), AcOH (0.4 equiv) and alkyne (0.79 M, 1.0 equiv). *[e]* $CF_2RCH_2NH_2$ (2.0 equiv), ^tBuONO (4.0 equiv), AcOH (0.5 equiv) and alkyne (0.79 M, 1.0 equiv). *[f]* Relative stereochemistry. The number indicated in the parentheses under compounds **25**-**33** indicates product selectivity for pyrazoline *vs* n-nitroso pyrazoline respectively. For additional details on the reactor set-up see the supporting information.

The optimized system was then used to generate **2** for subsequent cycloaddition with ethyl propiolate to afford **4** in 99% yield, demonstrating this reactor set up can generate high yields of 3-trifluoromethyl pyrazoles.

With optimized conditions in hand, a range of alkynes were reacted with both **1** and **2** to yield **5-17** in moderate to excellent yields (48-99%). Importantly, the system accommodated sterically demanding alkynes **7-9** and **14-18**, and larger fluoroamines to generate **18**. As **3-6** house an ester moiety at the 5-position, it would be possible to access DPC-602 and AS-136A (Fig. 1). Other targets, however, required a synthetic handle at the 4-position. Conceivably, additional modification to **3-6** would achieve this, but forcing the electronically disfavored isomer with a malleable functional group at the 4-position would be more efficient.

Using TMS-protected alkynes drives formation of the electronically disfavored isomers **14-17** due to steric interactions between the TMS and CF_2R (R=F or H) moieties.[11a, 15] Prior to this work, three days reactivity and five equivalents of **1** yielded **14** in only 41%.[11a] Here, reducing the concentration of AcOH to 15% to avoid TMS deprotection before cycloaddition while increasing both the concentration of difluoroethylamine and ^tBuONO yielded **14-17** in good yield (59-72%) for a *15 min* residence time**.** Controlling the regiochemical outcome of the [3+2] cycloaddition generates the pyrazole core for Bixafen, Fluxapyroxad, Sedaxane and Isopyrazam (Fig. 1). Importantly, novel pyrazoles **16** and **17** have the correct oxidation state for directly achieving the target compounds.

Next, cycloaddition of **2** with terminal aryl alkynes was explored. Previous reports require stoichiometric Ag_2O and NaOAc for 5 h, or two weeks in a sealed tube devoid of light.[16] Attempting a catalyst free transformation in our continuous flow setup initially yielded no product. However, increasing the temperature and residence time (28 min) of module 2 yielded **19-24** as single regioisomers in good to excellent yields (53-93%). This continuous flow approach has several important advancements. First, requirements for super stoichiometric Ag_2O and NaOAc have been removed. Second, the reaction time has been reduced to ~30 min. Third, the transformation is now scalable, and finally, **19** was obtained in improved yields.

This high temperature transformation again draws on a benefit of continuous flow synthesis. Operating a back pressure of 325 psi allows DCM (bp 40 °C) and **2** (bp ~13 °C)[11b] to be super heated without vaporization; such conditions are not amenable to round bottom flasks. Furthermore, heating diazoalkanes at high temperatures in a round bottom flask would be highly dangerous. Interestingly, the use of **1** under these conditions yielded <30% of the desired difluoro analogue. The higher temperatures required for a catalyst free approach most likely degrades **1** as gas evolution in the reactor was observed. The use of **2** under these conditions opens up the possibility for synthesizing Celecoxib, Mavacoxib, SC-560 and the human lung cancer suppression candidate (Fig. 1) in a rapid, catalyst free, and scalable environment.

Alkenes were also explored for the synthesis of pyrazolines. From a versatility and cost standpoint, alkenes typically have greater commercial availability, and are often more affordable. Furthermore, oxidation of certain pyrazolines can afford pyrazoles in a single step.[13, 17] Pyrazolines **25-30** were obtained in good to excellent yields (59-82%) over a *15 min* residence time, improving upon previous conditions requiring 14 h.[13]

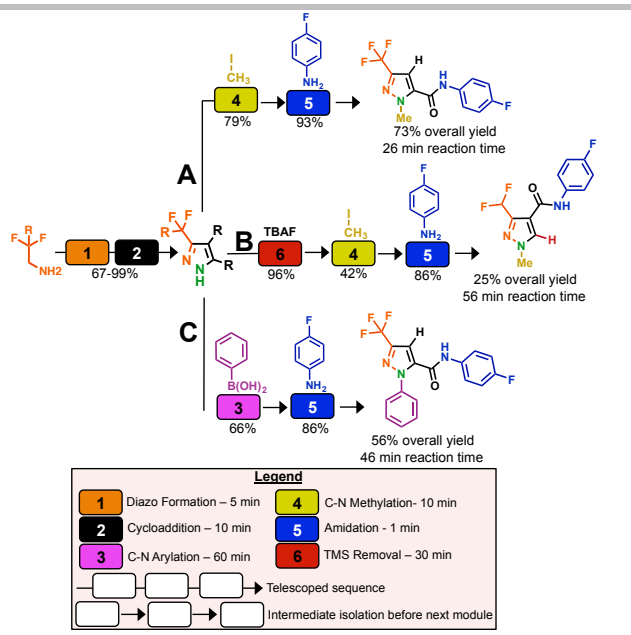
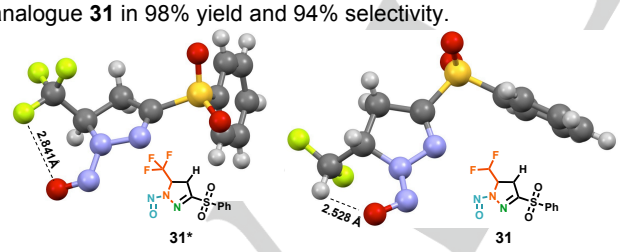


Fig. 3 Individual continuous flow modules for the generation of agrochemical and pharmaceutical like targets. *Module 3*; pyrazole (0.12 M in DCM, 2.0 equiv), $Cu(OAc)_2$ (1.5 equiv in DCM) and pyridine (1.0 equiv in DCM) at 90°C. *Module 4*; pyrazole (0.26 M in DMF, 1.0 equiv), 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU, 4.0 equiv in DMF), iodomethane (MeI, 4.0 equiv in DMF) at 120 °C. *Module 5*; Pyrazole (0.30 M in DMF, 1.0 equiv), 4-fluoroaniline (1.3 equiv in DMF) and lithium bis(trimethylsilyl)amide (3.3 equiv in THF) at 40 °C. *Module 6*; Pyrazole (0.25 M, 1.0 equiv), TBAF (1.75 equiv) and AcOH (1.75 equiv) at 70 °C. For additional details on reactor set-up, see the supporting information

A novel n-nitrosopyrazoline byproduct was also observed through a second condensation with ^{t}BuONO. Interestingly, pyrazolines **25-30**, or their n-nitroso counterparts **31-33** could be selectively synthesized by simply changing the concentration of ^{t}BuONO and AcOH entering the system. For example, pyrazoline **28** was achieved in 75% yield and 97% selectivity through standard conditions ($CF_2HCH_2NH_2$ (2 equiv), ^{t}BuONO (2 equiv), AcOH (0.4 equiv)). Then, increasing the concentration of ^{t}BuONO (4 equiv) and AcOH (0.5 equiv) generated the n-nitroso analogue **31** in 98% yield and 94% selectivity.



Scheme 1. Crystal structures for the tri- and di-fluoro n-nitroso pyrazolines. Highlighted are bond distances from the oxygen of the n-nitroso group to the CF_3 or CF_2H moiety.

Subjecting **2** to optimized conditions for n-nitrosopyrazoline formation yielded <20% in all cases. Single crystal X-ray analysis of **31*** and **31** revealed that the van der Waals radii of the fluorine atom (147 pm) overlapped with the oxygen atom (152 pm) of the n-nitroso group, suggesting interaction in the solid state. For the CF_2H moiety however, a strong hydrogen bond is present that could drive the higher yields (46-92%) experimentally observed.

With an assembly line synthesis in mind, modules 1 and 2 were scaled up (2.25 mL and 7.75 mL coils respectively) and combined with Syrris® pumping modules (total flow rate of 750 μL min^{-1}) to produce **4** at 2.16 g h^{-1} (87% yield). Next, additional modules to facilitate a range of transformations were explored. We envisaged that N-arylation of **21-24** would yield Celecoxib, Mavacoxib, SC-560 and the human lung cancer suppression candidate. Both DPC-602 and AS-136A could be accessed through N-methylation or arylation of **4** or **6,** and subsequent amidation. Finally, Bixafen, Fluxapyroxad, Sedaxane and Isopyrazam could be achieved through TMS cleavage of **17**, followed by N-methylation, and then amidation (Fig. 3C). As a proof of concept, individual modules were used to create highly substituted pyrazoles on route to pharmaceuticals and agrochemicals (Fig. 3).

Module 3 mediates Chan-Lam-Evans C-N arylation (Fig. 3C). Although notable examples of azole Chan-Lam-Evans couplings exist, these were performed with less demanding azoles.[18] Initially, 22% of the desired product was achieved with Ph-$B(OH)_2$ after 16 h at 40 °C in a round bottom flask. Removing Et_3N and translating to continuous-flow with a reactor temperature of 90 °C provided a satisfactory 66% yield. Once again, the use of DCM at 90 °C is well suited for continuous flow; this temperature would be difficult to achieve in a round bottom flask. Module 4 mediates N-methylation (Fig. 3A and B). Here, the sensitivity of the CF_2H group became apparent. While **4** can be readily methylated with MeI and tetramethylpiperidine (1 min, microwave, 120 °C, DMF, 99% yield), immediate decomposition of the CF_2H analogues was observed. Further optimization revealed that DBU and MeI at 120 °C for 10 mins in continuous flow provides suitable conditions to methylate both the di, and tri-fluorinated pyrazoles in good yield. Module 5 performs direct amidation of pyrazole esters; combining solutions of 1M LiHMDS with the pyrazole and amide at 40 °C for 1 min gave the corresponding amides in excellent yields (86-96%, Fig. 3A-C). Finally, module 6 performs TMS removal (Fig. 3B). Although KOH at elevated temperatures proved effective for **17** (2 equi. KOH in EtOH, 150 °C, 30 min, microwave), immediate decomposition was observed for **16**. Pleasingly, TBAF (buffered with AcOH) at 70 °C with a 30 min residence time afforded the desired product in 96% yield.

Through a combination of modules 1-6, it is theoretically possible to synthesize a large number of APIs and agrochemicals. To demonstrate this opportunity, measles therapeutic AS-136A was synthesized. Using modules 1 and 2 in a telescoped fashion, and then modules 4 and 5 individually yielded AS-136A (75% yield, 99% purity) for a 26 min total reaction time (Fig. S1). Next, all of the required modules (1, 2, 4 and 5) were telescoped into a single multi-step continuous flow system to produce AS-136A (34% isolated yield, 72% purity) at a rate of 1.73 g h^{-1} (Fig. 4). Additionally, module 4 not only drives rapid methylation (120 °C, 10-16 min), but controlled gas formation was observed; presumably excess diazoalkane is destroyed releasing N_2. Furthermore, this telescoped synthesis uses LiHMDS directly from the supplier's bottle removing the need to handle this toxic and flammable substance.

The lower yield observed in the telescoped transformation is due to at least two factors. First, telescoping large sequences means that excess reagents and by-products are carried

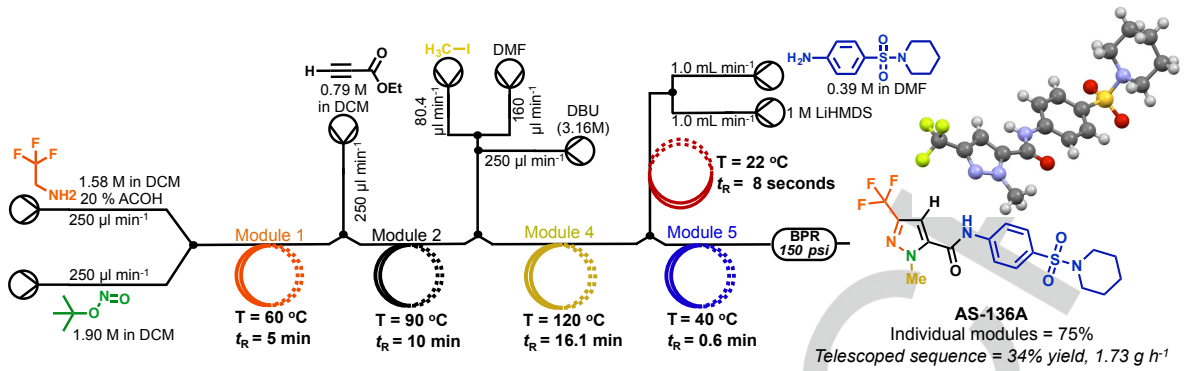


Fig. 4 Continuous flow synthesis of AS-136A. A continuous flow telescoped synthesis with modules 1,2,4 and 5 to yield measles therapeutic AS-136A in a 34% isolated yield at a rate of 1.73 g h^{-1}. Using modules individually yields AS-136A in a 75% yield. See the supporting information for additional details.

through to subsequent steps; decreasing yields through unwanted reactivity. In theory, decreasing the amount of excess reagent in each step could aid the telescoped process. However, when experimentally tested, modules 1, 2 and 3 resulted in significantly decreased yields. For example, a 1:1:1.2 ratio of ethyl propiolate: 2,2-difluoroethylamine: ^{t}BuONO resulted in only 37% yield compared to 70% when using a 1:2:2.4 ratio. Furthermore, using only two equivalents of MeI in module 3 resulted in 39% yield, compared 100% when using eight (Table S2). Second, using Syrris® pumps decreased the efficiency of module 1 and 2 (75-87% compared to 99%) as uneven fluid delivery is observed at the high back pressure (~22-24 bar).

In conclusion, a continuous flow platform for the synthesis of valuable, highly functionalized pyrazoles and pyrazolines has been developed. Generating common pyrazole cores for subsequent modification in a range of modules allows a wide breadth of chemical space to be readily and efficiently accessed. Importantly, modules mediate rapid continuous flow chemistry (1–60 min) by operating solvents above their atmospheric boiling points for improved kinetics. This effect removed the need for stoichiometric Ag_2O and base for terminal aryl alkynes dipolarphiles to participate in [3+2] cycloaddition with **2**. To demonstrate the capabilities of this system, AS-136A was synthesized in 75% yield (99% purity) using three sets of individual modules, or through a telescoped continuous flow multi-step process yielding 1.73 g h^{-1} (34% yield, 72% purity) of isolated product. This approach builds upon previous syntheses of this molecule requiring several additional steps and multiple intermediate isolations.[12b, 19]

Acknowledgements

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Keywords: Multi-Step Continuous Flow Synthesis • Pyrazoles • Assembly Line Synthesis • Active Pharmaceutical Ingredients • Agrochemicals

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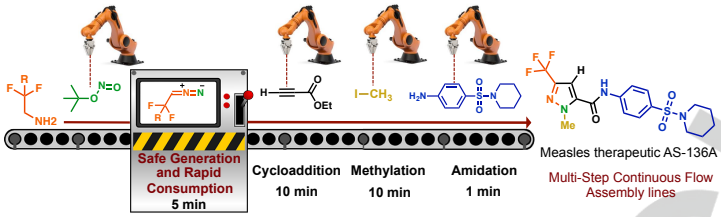
COMMUNICATION

Reaction Modularity Meets Flow: Assembly lines have been used to synthesize highly functionalized pyrazoles and pyrazolines *on route* to agrochemicals and pharmaceuticals through multi-step, continuous flow synthesis.



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