Synthetic Methods

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A Concise Flow Synthesis of Efavirenz**

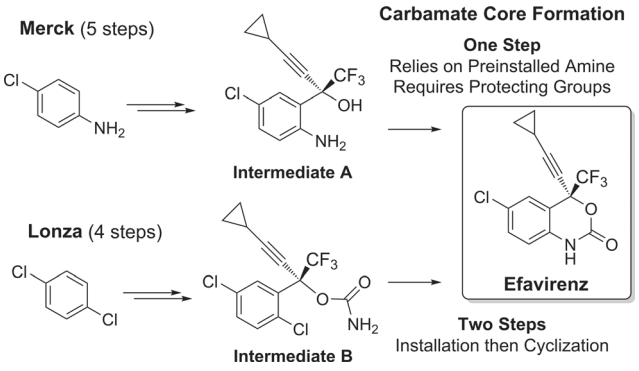
*Camille A. Correia, Kerry Gilmore, D. Tyler McQuade, and Peter H. Seeberger**

Abstract: *Efavirenz is an essential medicine for the treatment of HIV, which is still inaccessible to millions of people worldwide. A novel, semi-continuous process provides rac-Efavirenz with an overall yield of 45 %. This streamlined proof-of-principle synthesis relies on the efficient copper-catalyzed formation of an aryl isocyanate and a subsequent intramolecular cyclization to install the carbamate core of Efavirenz in one step. The three-step method represents the shortest synthesis of this life-saving drug to date.*

For the developing world, the affordability of critical medicines still remains the greatest obstacle to therapy.[1] While competition from generic manufacturers has led to a decrease in prices, virtually all active pharmaceutical ingredients (APIs) are still produced by multiple distinct chemical transformations in batch reactors. Over the past decade, continuous processes have emerged as an effective means to conduct chemical syntheses, as they offer increased control over the reaction conditions. Improved product quality and safety are accompanied by a reduced environmental impact compared to traditional batch syntheses.[2,3] Accordingly, production costs can be significantly lowered through flow-enabled, improved manufacturing.[4] Efforts to streamline API syntheses have led to several linear[5,6] and divergent[7] continuous processes to meet the rising global demand for medicines.

An efficient synthesis of Efavirenz, a drug that is still inaccessible to millions of people worldwide, holds great potential both scientifically and socially.[8] This potent non-nucleoside reverse transcriptase inhibitor (NNRTI) is one of the preferred agents used in combination therapy for first-line treatment of the human immunodeficiency virus (HIV).[9] We sought to develop a concise, atom-economic, and continuous synthetic route that avoids the toxic or expensive reagents previously utilized. Herein, we describe a proof-of-principle flow synthesis that provides Efavirenz in a novel three-step process.

Two major routes to Efavirenz have been disclosed thus far (Scheme 1): a five-step production method from *para*-chloroaniline developed by Merck[10] and Lonza's[11] recently patented four-step synthesis from 1,4-dichlorobenzene. Inspired by Lonza's route, which avoids the wasteful amine protection and deprotection steps, we became interested in designing a more efficient synthesis through the direct installation/cyclization of the carbamate core. For this key step, Merck utilizes the pre-installed amine group of the aniline core in intermediate **A**, which is then reacted with phosgene or a phosgene equivalent. Alternatively, Lonza obtained the bicyclic core by a copper-catalyzed Ullman-type cyclization of intermediate carbamate **B**, the key functional group having been installed by a preceding reaction of the propargylic alcohol with chlorosulfonyl isocyanate. Both procedures have drawbacks associated with the toxicity as well as with the quenching or removal of unreacted reagents. We envisioned that the installation and cyclization of the carbamate core could be achieved in one step using more cost-effective, less toxic reagents.



Scheme 1. The two major synthetic routes to Efavirenz.

The key element of our succinct synthetic route to Efavirenz is the one-step copper-catalyzed installation/cyclization of the carbamate ring (Scheme 2). This method builds on two previous reports for the formation of acyclic *N*-aryl carbamates by copper-catalyzed cross-couplings of potassium cyanate with aryl boronic acids[12] or aryl bromides and iodides.[13] In both cases, the *N*-aryl carbamate is formed by intermolecular nucleophilic trapping of an in situ generated isocyanate by an alcoholic solvent. Encouraged by this precedence, we hypothesized that Efavirenz may be directly accessible via intermediate **C**. However, unlike previous methods that rely on superstoichiometric amounts of an

[*] Dr. C. A. Correia, Dr. K. Gilmore, Prof. Dr. P. H. Seeberger
Department of Biomolecular Systems
Max Planck Institute of Colloids and Interfaces
Am Mühlenberg 1, 14476 Potsdam (Germany)
E-mail: peter.seeberger@mpikg.mpg.de
Prof. Dr. P. H. Seeberger
Institute for Chemistry and Biochemistry
Freie Universität Berlin
Arnimallee 22, 14195 Berlin (Germany)
Prof. Dr. D. T. McQuade
Department of Chemistry and Biochemistry
Florida State University
Tallahassee, FL 32306 (USA)

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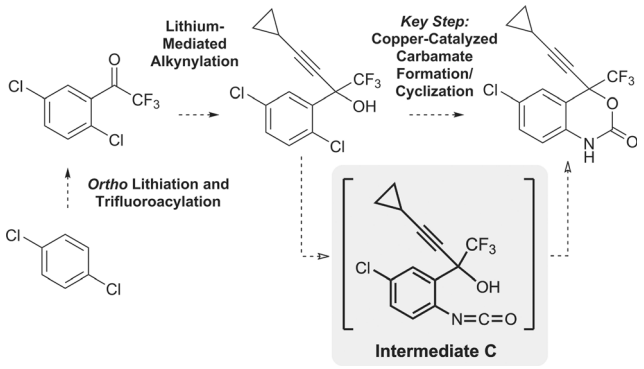


Scheme 2. Our synthetic route to Efavirenz featuring a one-step carbamate formation/cyclization sequence.

alcohol and facile aryl coupling partners, our procedure requires the activation of an aryl chloride followed by an efficient intramolecular cyclization.

Lithium-mediated reactions have unequivocally proven to be superior in flow processes compared with the corresponding batch conditions.[14,15] The most efficient method to establish the key propargylic alcohol **2** was thus expected to feature two *n*-butyllithium-mediated steps (Scheme 2). In tackling the initial *ortho* lithiation of 1,4-dichlorobenzene and subsequent trifluoroacylation, certain factors needed to be considered. Owing to the highly reactive nature and ease of decomposition of the intermediate formed in loop 1 (2,5-dichlorophenyllithium), careful control of the temperature in all three reactor loops had to be exercised. Decomposition and clogging were observed when the reactor loops were warmed too quickly before the quench. A partitioned cold bath with a submerged passage prevents exposure of the reaction mixture to ambient conditions and allows for variable temperatures between the two sets of reactor loops (Scheme 3).

With such a telescoped process in mind, we could not employ trifluoroacetic esters, as the alcohol that is obtained after quenching the reaction is not compatible with the second *n*-butyllithium-mediated step (see above). Instead, trifluoroacetylmorpholine,[16] which is easily prepared from inexpensive starting materials, was utilized as the resulting morpholine by-product could be removed in-line with an acidic scavenger. Anhydrous silica was found to be effective in quenching the lithium-mediated reaction as well as in trapping the morpholine by-product. Furthermore, silica was also mild enough to prevent side reactions of the electrophilic trifluoromethyl-substituted ketone **3**.[17]

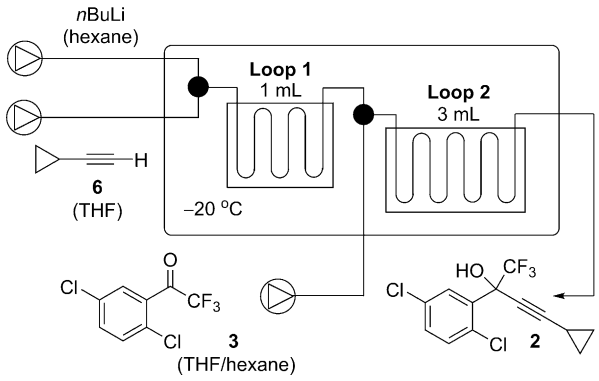
The yield of the trifluoroacylation reaction proved to be highly time- and temperature-dependent (Table 1). The best yield at −45 °C (87 %) was obtained at a residence time of 4 minutes in loop 1 and 13.3 minutes in loop 2 (entry 3).

Table 1: Optimization of the flow conditions for the trifluoroacylation.[a]

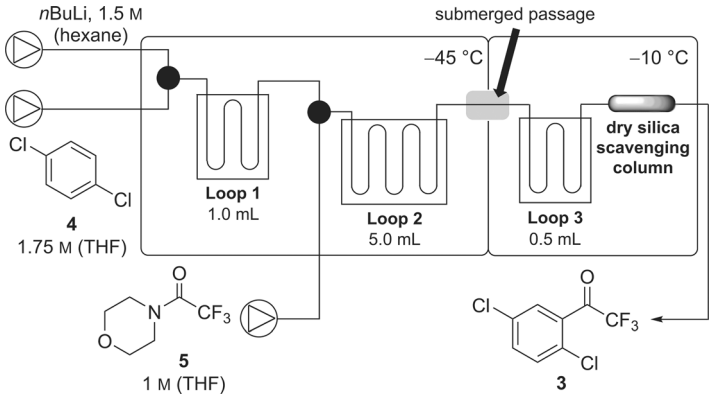
Entry	Residence time [min]		Yield[b] [%]
	Loop 1	Loop 2	
1	2	6.7	67
2	3	10	72
3	**4**	**13.3**	**87**
4	5	16.6	73
5	6	20	63

[a] Conditions: dichlorobenzene (**4**, 1.75 M in THF), *n*BuLi (1.5 M in hexane), electrophile (**5**, 1 M in THF); loops 1 and 2 at −45 °C, loop 3 at −10 °C. [b] Determined by ^{1}H NMR spectroscopy using mesitylene as the internal standard.

The second step of our synthesis is the nucleophilic addition of lithium cyclopropylacetylide to the crude product of the flow synthesis, namely ketone **3** (Scheme 4). The



Scheme 4. Experimental set-up for the lithium-mediated alkynylation of **3**.



Scheme 3. Reactor design for the synthesis of trifluoromethyl ketone **3**.

alkynylation[19] proceeded smoothly and rapidly; 90 % conversion was achieved in less than two minutes at −20 °C (Table 2, entry 1). Increasing the total reaction time to 3 minutes resulted in a slightly better conversion (93 %, entry 2), whereas a further increase in residence time was not beneficial (entry 3). Higher temperatures resulted in significant decomposition (entry 4). Reducing the equivalents of acetylide had no impact on conversion (entry 5). Silica was found to efficiently quench this reaction as well; however, unreacted alkyne and small amounts of other by-products remained in the exiting stream. The coordination or reaction of these compounds with the active copper catalyst in the key transformation would compromise the catalyst. Therefore, the desired quaternary propargylic alcohol **2** was

Table 2: Optimization of the *n*BuLi-mediated alkynylation.[a]

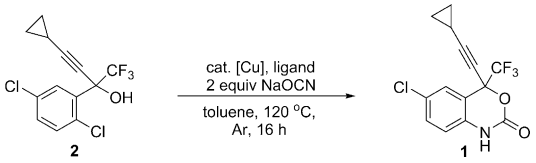
Entry	Rate [mL min^{-1}]	*T* [°C]	Residence time [s] Loop 1	Loop 2	Conversion [%]
1	1.0	−20	30	60	90
2	0.5	−20	60	120	93
3	0.25	−20	120	240	92
4	0.5	−5	60	120	67
5[b]	**0.5**	**−20**	**60**	**120**	**92 (73)**[c]

[a] Conditions: cyclopropylacetylene (0.66 M), *n*BuLi (0.6 M), crude ketone (0.33 M); loop 1: 1 mL, loop 2: 3 mL. [b] Cyclopropylacetylene (0.5 M), *n*BuLi (0.43 M). [c] Yield of isolated product over two steps from **5** (0.5 mmol).

isolated in 73% yield for the multistep continuous process from 1,4-dichlorobenzene (Table 2, entry 5).

With the pure alcohol in hand, we turned to the development and initial optimization of the copper-catalyzed final step a in batch process. Different diamine ligands were tested, and *trans-N,N′*-dimethyl-1,2-cyclohexanediamine (CyDMEDA) emerged as the most effective one (Table 3, entry 3). Increasing the catalyst to ligand ratio and performing the reaction in toluene afforded **1** in 42% yield (entry 4). When a catalytic amount of a phase-transfer catalyst was added to increase the concentration of cyanate ions in solution (entry 5), product formation was not observed. Similar to Buchwald's findings for the analogous intermolecular palladium-catalyzed reaction, the loss of reactivity may result from the formation of an inactive copper isocyanate species.[20] To facilitate adaption to a flow process, copper(I) sources with better solubility were also tested; whereas $(CuOTf)_2$·benzene provided a lower yield, $[Cu(MeCN)_4]BF_4$ performed slightly better (entries 6 and 7). We were surprised

Table 3: Development and optimization of the copper-catalyzed *N*-aryl carbamate formation and cyclization in a batch process.[a]

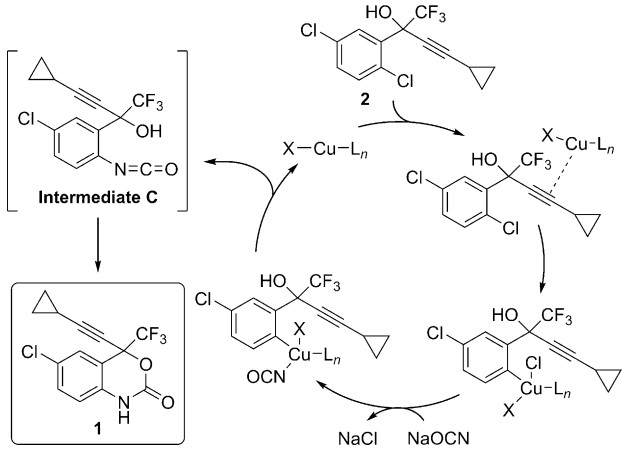


Entry	[Cu] (mol%)	Ligand (Cu/L ratio)	Yield [%][b]
1[c]	CuI (20)	DMEDA (1:2)	trace
2[c]	CuI (20)	phen (1:2)	0
3[c]	CuI (20)	CyDMEDA (1:2)	12
4	CuI (20)	CyDMEDA (1:4)	42
5[d]	CuI (20)	CyDMEDA (1:4)	n.d.
6	$(CuOTf)_2$·benzene (10)	CyDMEDA (1:4)	36
7	$[Cu(MeCN)_4]BF_4$ (20)	CyDMEDA (1:4)	48
8	**$CuSO_4$ (20)**	**CyDMEDA (1:4)**	**62**
9	**$Cu(NO_3)_2$·3 H_2O (20)**	**CyDMEDA (1:4)**	**60**
10[e]	CuI (20)	CyDMEDA (1:4)	9

[a] Conditions unless otherwise noted: alcohol **2** (0.1 mmol), NaOCN (0.2 mmol), copper catalyst, ligand, and toluene (1 mL) in a sealed tube at 120°C for 16 h under argon atmosphere. [b] Yields determined by ^{1}H NMR spectroscopy using mesitylene as the internal standard. [c] Run in dioxane (1 mL). [d] Tetrabutylammonium chloride (10 mol%) was added. [e] Under air. CyDMEDA = *trans-N,N′*-dimethyl-1,2-cyclohexanediamine, DMEDA = *N,N′*-dimethyl-1,2-ethylene diamine, n.d. = not detected, phen = phenanthroline.

that Cu^{II} catalysts were the most effective and robust catalysts for this reaction (entries 8 and 9). It is unlikely that a Cu^{II} species is the active catalyst in this transformation, as a yield of only 9% was achieved when CuI was used in air instead of under argon (entry 10).

A tentative mechanism for this transformation is shown in Scheme 5. It involves the coordination of a Cu^I species to the



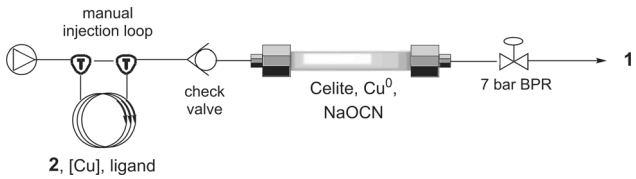
Scheme 5. Proposed mechanism for the one-step copper-catalyzed reaction.

internal alkyne (or hydroxy group) of **2**, bringing the catalyst in close proximity to the reaction center. Oxidative addition of the nearby C−Cl bond to the metal center, transmetalation from sodium cyanate, and subsequent reductive elimination furnish intermediate **C**, and the copper catalyst is regenerated. Upon reductive elimination, intermediary isocyanate **C** is expected to cyclize expediently to yield *rac*-Efavirenz.

The main side product observed in this reaction is the *ortho*-dechlorinated propargylic alcohol, which arises from intra- or intermolecular protonation of the intermediary copper–aryl species.[18] We expected this competing pathway to be suppressed by tighter control of the reaction parameters in a flow process.

We opted for a packed-bed reactor with Celite as the packing material because of the poor solubility of NaOCN. Initial tests showed low conversion of the starting material (Table 4, entry 1) owing to the slow in situ reduction of Cu^{II} to Cu^I. The addition of Cu^0 powder to the reactor resulted in a faster reduction process and faster oxidative addition of the starting material. However, owing to the slow transmetalation step, the conversion into product did not improve. We noted that a 1:2 ratio of catalyst to ligand performed better in the presence of the Cu^0 additive (entry 3).[18] Lowering the concentration of the copper aryl intermediate by reducing the catalyst loading better matched the slow leaching and transmetalation of NaOCN and led to a higher product ratio. To avoid significant catalyst deactivation at this low loading, the amount of cyanate in the system was also reduced (entry 5), providing us with a moderate yield of 65%. In this solvent system, copper nitrate was found to be insoluble at higher concentrations, restricting productivity. Gratifyingly, the better soluble $Cu(OTf)_2$ performed just as well at higher

Table 4: Optimization of the copper-catalyzed carbamate formation in a flow process.



Entry[a]	[Cu]	[Cu]/L [mol%]	Cu^0 [equiv]	Conc. **2** [M]	Conversion[e] [%] of **2**	into **1**
1	$Cu(NO_3)_2{\cdot}3H_2O$	20/80	0	0.05	43	19
2[b]	$Cu(NO_3)_2{\cdot}3H_2O$	20/80	1	0.05	97	17
3[b]	$Cu(NO_3)_2{\cdot}3H_2O$	20/40	1	0.05	85	32
4[b,c]	$Cu(NO_3)_2{\cdot}3H_2O$	5/10	1	0.1	92	59
5[c]	$Cu(NO_3)_2{\cdot}3H_2O$	5/10	1	0.1	95	65
6[c]	$Cu(OTf)_2$	5/10	1	0.15	99	68
7[c]	$Cu(OTf)_2$	5/10	0.5	0.15	91	63
8[c]	$Cu(OTf)_2$	5/10	0.5	0.2	96	63
9[c,d]	**$Cu(OTf)_2$**	**5/10**	**0.5**	**0.2**	**98**	**71 (62)**[f]

[a] Conditions: alcohol **2**, the copper catalyst, and CyDMEDA were dissolved in PhMe/MeCN (1:1); the resulting mixture was transferred to a 2 mL injection loop under argon atmosphere (all concentrations are based on a 2 mL volume). The reactor was packed using a mixture of anhydrous Celite (750 mg), NaOCN (20 equiv), and the required amount of the copper powder (with respect to **2**). It was then flushed with degassed PhMe and heated to 120 °C under 7 bar pressure. Reactions were performed at 33 $\mu L\,min^{-1}$ for a residence time of 60 minutes. [b] NaOCN (40 equiv). [c] PhMe/MeCN (3:1). [d] 130 °C. [e] Conversions determined by ^{19}F NMR spectroscopy. [f] Yield of isolated product.

concentrations and permitted the use of smaller amounts of the Cu^0 additive (entries 6–8). Pure *rac*-Efavirenz was thus isolated in 62% yield (entry 9). The optimized packed-bed reactor gave us the opportunity to run the process at an increased concentration, with a lower catalyst loading, and for a shorter reaction time (1 h), which represents a significant improvement compared with the batch process (16 h).

In conclusion, we have reported a three-step flow synthesis of *rac*-Efavirenz. The key step of this semi-continuous process is the copper-catalyzed cyclization of an in situ generated aryl isocyanate, which furnishes the cyclic carbamate core of Efavirenz. This one-step flow process, in combination with the efficient and telescoped two-step production of the key propargyl alcohol intermediate **2**, enabled the preparation of *rac*-Efavirenz in an overall yield of 45%, with a total reaction time of less than two hours. To the best of our knowledge, this is the shortest route for this important compound that has been reported to date.

Keywords: API synthesis · carbamates · copper · flow chemistry · homogeneous catalysis

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[18] Please see the Supporting Information for details.
[19] A lithium-mediated enantioselective version was not addressed; however, there is evidence of good selectivity even in the absence of zinc additives; see Ref. [1b] and A. S. Thompson, E. G. Corley, E. J. J. Grabowski, N. Yasuda (Merck & Co.), PCT Int. Appl. WO9637457, **1996**.
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