Cross-Coupling

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Use of a "Catalytic" Cosolvent, *N,N*-Dimethyl Octanamide, Allows the Flow Synthesis of Imatinib with no Solvent Switch

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Abstract: *A general, efficient method for C–N cross-coupling has been developed using N,N-dimethyloctanamide as a catalytic cosolvent for biphasic continuous-flow applications. The described method was used to generate a variety of biarylamines and was integrated into a two-step sequence which converted phenols into biarylamines via either triflates or tosylates. Additionally, the method was applied to a three-step synthesis of imatinib, the API of Gleevec, in good yield without the need of solvent switches.*

The use of continuous-flow technology in synthesis has received an increasing amount of attention over the past decade in both academia and industry.[1] Compared to traditional batch methods, continuous-flow offers many benefits, including safer manipulation of reactions at high pressure and temperature, the ability to scale chemical reactions in a more straightforward manner, and the in situ generation and consumption of intermediates, thus combining multiple synthetic steps into a single process.[1,2]

The importance of aromatic amines and their derivatives is demonstrated by their prevalence in pharmaceutical agents and organic materials. Palladium-catalyzed C–N cross-coupling[3] has become a widely applied method for the preparation of these compounds. As a continuation of our interest in developing practical methods for C–N bond construction, we initiated a program for the development of general methods to perform palladium-catalyzed amination in continuous-flow reactors.[4] Previous studies by us and other research groups have revealed several difficulties with transitioning C–N cross-coupling to continuous-flow conditions.[5] The formation and precipitation of crystalline products and inorganic salts during cross-coupling reactions often result in clogging of the continuous-flow reactor. Moreover, downstream solvent switches are often required because of the limited range of solvents suitable for cross-coupling. The formation of byproducts may also impact downstream reactions, thus complicating multistep sequences in a continuous-flow reactor. As a consequence, multistep continuous-flow processes which utilize a C–N cross-coupling step remain rare.

A large body of work has demonstrated the advantages of amphiphilic organic solvents and additives in batch chemistry.[16] Amphiphilic solvents facilitate contact between organic- and water-soluble components of a reaction while maintaining a high local concentration of the organic reactants, thereby accelerating mass-transfer and overall reaction rates. In addition to these benefits, amphiphilic solvents are capable of solubilizing a wide range of compounds, and may mitigate crystallization and minimize the need for switching solvents in a multistage continuous-flow process. As a result, we believed that the use of organic amphiphiles in biphasic solvent systems might permit a broader range of C–N cross-coupling reactions to be performed under continuous-flow conditions.

Herein we report the identification and use of *N,N*-dimethyloctanamide (DMO, **1**; Figure 1) as an amphiphilic organic cosolvent which enabled the synthesis of a wide range of (hetero)arylamines by a palladium-catalyzed C–N cross-coupling reaction under continuous-flow conditions. Furthermore, we demonstrate that this method can be integrated into a two-step sequence for the direct conversion of phenols into amines, as well as a three-step synthesis of imatinib, the active pharmaceutical ingredient of the anticancer agent Gleevec, under continuous-flow conditions. Notably, these multistep reaction syntheses were performed without in-line purification of any intermediates or solvent exchanges between steps.

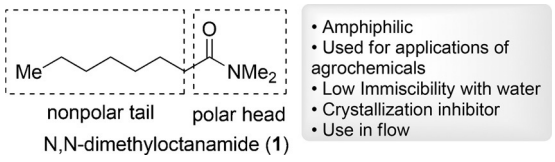

Figure 1. Properties of *N,N*-dimethyloctanamide.

We have previously reported a system wherein biphasic conditions were utilized for C–N cross-coupling. However, even though phase-transfer catalyst additives were able to greatly increase the efficiency of the reaction, the generality of such a system was still severely impaired by the solubility of reagents and products in toluene, particularly heteroaromatic compounds. We envisioned that DMO would be a practical solution for continuous-flow chemistry because it has similar Hansen solubility parameters to those of dichloromethane,[6b] low solubility in water (4.3 $g\,L^{-1}$),[6c] a reported toxicological profile comparable to common laboratory solvents,[6c,d] is readily availabile as a high production volume chemical,[6c] and was previously used as a crystallization inhibitor and for crop protection formulations.[6,7] We therefore evaluated its use in the cross-coupling of aniline (**2**) and 4-chloroanisole (**3**) in the presence of the XPhos-based[8] precatalyst **7** under

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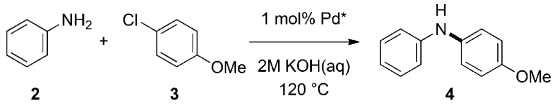
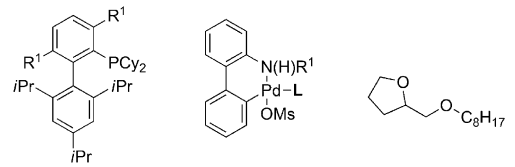
biphasic conditions with aqueous KOH as the base. When the reaction was performed in a perfluoroalkoxyalkane (PFA) tube reactor with neat DMO as the solvent, low conversion was observed, presumably because of inefficient mixing of the two phases (Table 1, entry 1). The use of a stainless steel packed-bed reactor apparatus,[4a] a device previously described for achieving efficient mixing in a biphasic flow system, improved the yield significantly (entry 2). Full conversion and excellent yield were obtained when the Brett-Phos-based[9] precatalyst **8** was used instead of **7** (entry 3). Further optimization revealed that toluene/DMO mixtures containing as little as 10% DMO gave similar results to those obtained using DMO as a neat solvent (entries 4 and 5). In addition, we found that 2-methyltetrahydrofuran (2-MeTHF), a solvent derived from renewable sources and suitable for large-scale production,[10] also gave comparable results when 10% DMO was utilized as an additive (entry 6). Control experiments showed that the use of either toluene or 2-MeTHF in the absence of DMO resulted in incomplete conversion within the designated reaction times. Upon extended reaction times to achieve full conversion in toluene (entry 7), the reaction vessel clogged because of the poor solubility of the product. Although the use of the amphiphilic solvent **9** also gave high conversion of the starting material and yield of the product **4**, clogging of the reactor occurred after prolonged reaction times. Therefore, the reaction conditions outlines in either entry 5 or 6 of Table 1 were selected for most of the following studies.

Table 1: Optimization of the palladium-catalyzed C–N cross-coupling reaction under continuous-flow conditions.[a]



2 **3** **4**

Entry	Solvent	Pd*	Y [%] (C [%])	t_R [min]
1[b]	**1**	**7**	7 (11)	15
2	**1**	**7**	68 (74)	15
3	**1**	**8**	97 (>95)	15
4	toluene/**1** = 1:1	**8**	98 (>95)	7.5
5	toluene/**1** = 9:1	**8**	95 (>95)	7.5
6	2-MeTHF/**1** = 9:1	**8**	93 (>95)	7.5
7	toluene	**8**	70 (71)[c]	7.5
8	2-MeTHF	**8**	80 (84)	7.5
9	**9**	**8**	93 (94)[c]	7.5

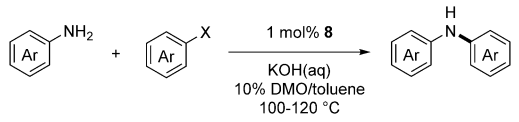


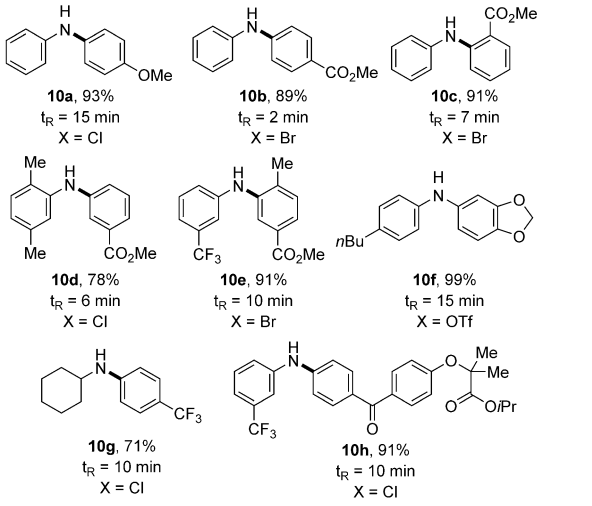
5, XPhos, R^1 = H
6, BrettPhos, R^1 = OMe
7; **L** = **5**, R = H
8; **L** = **6**, R = Me
9

[a] Conversions and yields were determined by GC analysis of the crude reaction mixture. See the Supporting Information for details. [b] 0.04″ PFA tubing was used as the reaction vessel. [c] Prolonged reaction times gave full conversion and clogging of the reaction vessel because of low product solubility. Ms = methanesulfonyl.

Using the above-described reaction conditions, we explored the generality and applicability of the protocol (Table 2). A wide variety of aryl bromides and chlorides, bearing either electron-donating or electron-withdrawing substituents, were efficiently coupled with aniline partners (**10a**,**b**, and **10g**,**h**). *Ortho* substitution in either the aryl halide or arylamine was accommodated (**10c–e**). In addition, aryl triflates (**10f**) were excellent substrates under these reaction conditions, with minimal hydrolysis observed. Besides aryl amines, primary alkyl amines could also be successfully converted into product (**10g**). As a consequence of the precise control of the reaction times under continuous flow conditions, even readily hydrolyzed methyl esters, provided high yield of desired product (**10b–e**, and **10h**). To demonstrate the potential applicability of this method, fenofibrate, a medicine used to reduce cholesterol levels, was subjected to the reaction conditions and coupled with 3-trifluoromethylaniline to give **10h** in excellent yield.

Table 2: Substrate scope of C–N cross-coupling reaction between arylamines and aryl (pseudo)halides.[a]

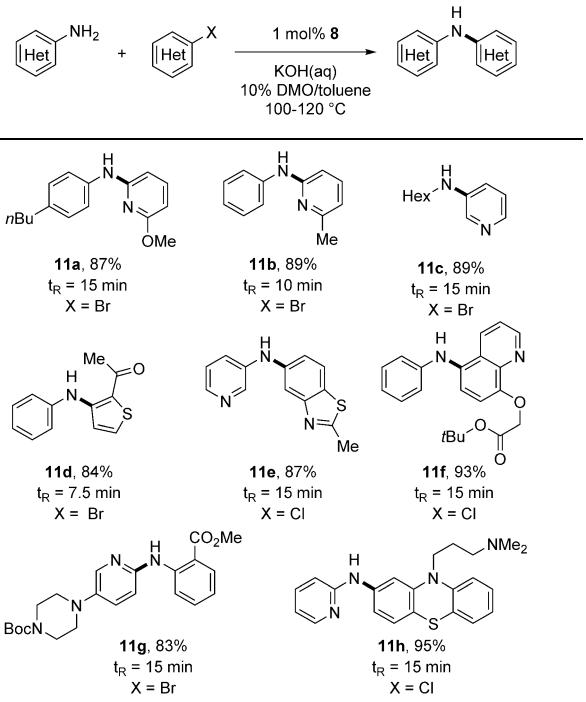




[a] Yields of isolated products are reported (average of 2 runs, approximately 1–4 mmol collected). See the Supporting Information for details.

Next, we turned our attention to expanding the scope of this method to include heteroaromatic compounds. The results are summarized in Table 3. A variety of heterocycles, including pyridines (**11a–c**), thiophene (**11d**), benzothiazole (**11e**), quinoline (**11f**), piperazine (**11g**), and phenothiazine (**11h**), were efficiently coupled with aromatic, heteroaromatic, or aliphatic amine partners. Notably, chlorpromazine, an anti-psychotic drug, was coupled with 2-aminopyridine under our reaction conditions to give **11h** in excellent yield. Substrates containing base-sensitive functional groups, such

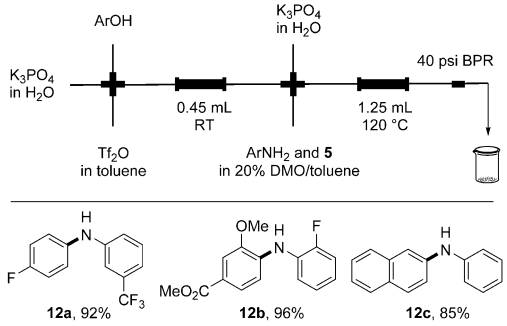
Table 3: Substrate scope of C–N cross-coupling reaction between heteroarylamines and heteroaryl (pseudo)halides.[a]



[a] Yields of isolated products are reported (average of 2 runs, approximately 1–4 mmol collected). See the Supporting Information for details.

as ketones (**11d**) and esters (**11g**), were again well tolerated under these continuous-flow conditions.

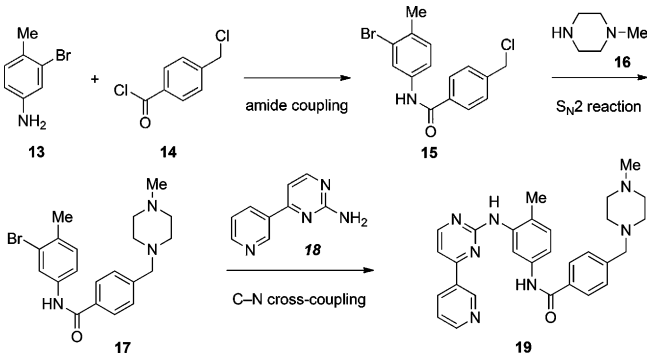
In light of the broad scope demonstrated by our reaction conditions, we next explored the potential of integrating this C–N cross-coupling reaction into multistep sequences in flow. In this context, we were interested in converting phenols into biarylamines via aryl triflate intermediates (Scheme 1). Aryl triflates are recognized as highly reactive coupling partners in C–N cross-coupling reactions.[3f] However, the lack of commercially available triflates and their instability necessitate their preparation prior to their use, significantly hampering their application. We reasoned that the two-step conversion



Scheme 1. Two-step flow conversion of phenols into biarylamines via either aryl triflates or tosylates. Yields of the isolated products are reported (average of 2 runs, approximately 1–4 mmol collected). See the Supporting Information for details. Tf = trifluoromethanesulfonyl.

of phenols into arylamines without isolating the triflate intermediate would be of considerable interest. We have previously reported a similar sequence in flow, and the complete removal of methylene chloride from the first step by microfluidic distillation and solvent exchange to dimethylformamide was required for a subsequent Heck coupling.[2f] After experimentation, we found that the transformation of phenols into secondary amines, without the isolation of the triflate intermediate, could be accomplished in a flow system as shown in Scheme 1. While the triflation of a phenol is often carried out at low temperature and with the slow addition of triflic anhydride in a batch reactor, this transformation could be performed at room temperature in minutes using aqueous K_3PO_4 as the base in a continuous-flow reactor. The reaction mixture from the first step was directly introduced into another packed-bed reactor with an aryl amine substrate, the palladium precatalyst **8**, and additional K_3PO_4 to give the desired biarylamine product in excellent yields over two steps (**12a**,**b**). In contrast to previous reports of the use of in situ generated aryl triflates in continuous flow, neither in-line purification nor solvent switching was required in this process. In addition, we found that a phenol tosylation/C–N cross-coupling sequence could also be similarly accomplished (**12c**).[12]

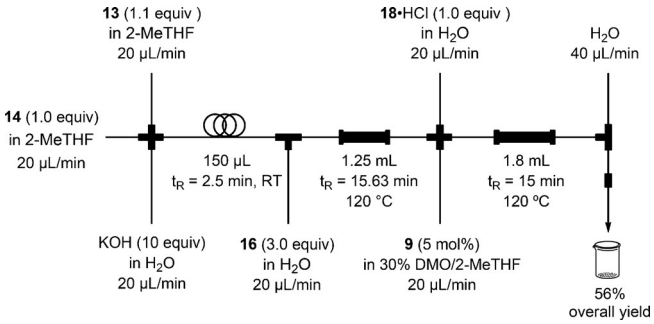
To further demonstrate the utility of this C–N cross-coupling technology, we applied it in a flow-based synthesis of imatinib (**19**; Scheme 3), a tyrosine kinase inhibitor widely used in the treatment of chronic myeloid leukemia.[13] In an elegant demonstration of the power of flow methodology in the preparation of important pharmaceutical substances, Ley and co-workers[2g,h] described the flow synthesis of imatinib, as depicted in Scheme 2. Based on this synthetic sequence, Ley



Scheme 2. Three-step flow synthesis of imatinib.

and co-workers reported a flow synthesis of imatinib featuring the sophisticated use of an in-line solvent switching apparatus, solid supported reagents, and purification cartridges to provide imatinib with minimal manual handling of intermediates. The final product was purified by chromatography to provide pure imatinib in 32% overall yield.

We have also reported the synthesis of imatinib using batch protocols.[15] By using our new C–N cross-coupling technology, a more streamlined continuous-flow process for the synthesis of imatinib is depicted in Scheme 3. The first step, coupling of 3-bromo-4-methylaniline (**13**) with 4-chloro-



Scheme 3. Flow synthesis for imatinib. Boc = *tert*-butoxycarbonyl.

methyl-benzoyl chloride (**14**) to form the amide **15**, was performed in a 2-MeTHF/H_2O biphasic system with KOH as the base (Schotten–Baumann conditions[14]). Complete conversion was achieved within three minutes at room temperature and **15** was isolated in 87% yield. The next reaction step, the nucleophilic substitution of the benzylic chloride **15** with 1-methylpiperazine (**16**), was implemented by directly using the output of the first reactor. An aqueous solution of **16** was injected into the system and the mixture was pumped through a packed-bed reactor at 120 °C. The residence time in the second reactor was 15 minutes and the reaction yield over the first two steps was 84% as determined by ^{1}H NMR analysis of the crude reaction mixture. The last step in the synthesis of imatinib is the C–N cross-coupling of **17** with 2-aminopyrimidine (**18**) using **8** (5 mol %). The outlet of the previous reactor was again used directly. Because of the high selectivity of BrettPhos for the coupling of primary amines,[9] it was not necessary to remove the excess 1-methylpiperazine (**16**) from the reaction mixture. To address the low solubility of **18** in organic solvents, it was converted into its conjugate acid, and injected into the system as an aqueous solution. As was done for C–N couplings described earlier, the reaction was performed in a packed-bed reactor to maximize mixing of the two phases. The residence time in the last reactor was 15 minutes. Imatinib was isolated in 56% overall yield from the crude reaction mixture by acid/base extraction with subsequent trituration in acetonitrile.[16] No solvent exchange or purification of intermediates was necessary throughout the whole synthesis.

In conclusion, we have demonstrated the generality of a flow-based C–N cross-coupling reaction featuring the use of DMO as an organic cosolvent in a biphasic system. The use of the biphasic system serves as a convenient solution to address the precipitation of inorganic byproducts generated during C–N cross-coupling reactions. A wide range of biarylamines, including those derived from commercial drugs, has been made in short reaction times. This C–N cross-coupling methodology employed KOH as the inorganic base and yet was compatible with sensitive functional groups. To further illustrate the utility of this method, we have integrated this method into a two-step flow sequence which converts phenols into biarylamines, via either triflates or tosylates. We have also showcased this technology in the three-step synthesis of the anticancer agent imatinib. Compared with previous synthetic routes, our synthesis does not require either in-line manipulation of reaction intermediates or solvent exchange, uses lower catalyst loading, and produces the target product in higher overall yield. We expect this strategy of using DMO as a cosolvent in biphasic systems to be applicable to other multistep flow sequences, especially those involving cross-coupling reactions.

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[17] The output of imatinib in our current system is 2.5 mg min^{-1}. For comparison, see Refs. [2g,h].

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