Use of a "Catalytic" Cosolvent, N,N-Dimethyl Octanamide, Allows the Flow Synthesis of Imatinib With No Solvent Switch

Jeffrey C. Yang, Dawen Niu, Bram Karsten, Fabio Lima and Stephen L. Buchwald*[a]

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 that converted phenols into biarylamines via the intermediacy of triflates or toslates. 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 results in clogging of the continuous-flow reactorMoreover, downstream solvent switches are often required due to the limited range of solvents suitable for cross-coupling. The formation of byproducts may also impact downstream reactions, thus complicating multistep synthesis in a continuous flow reactor. As a consequence, multistep continuous flow processes that 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, which may mitigate crystallization and minimize the need for solvent switches 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.

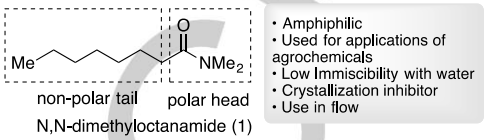

Figure 1. Properties of N,N-dimethyloctanamide

Here we report the identification and use of *N,N*-dimethyloctanamide (DMO, 1, Figure 1) as an amphiphilic organic co-solvent that enabled the synthesis of a wide range of (hetero)arylamines via palladium catalyzed C–N cross-coupling reaction under continuous flow conditions. Furthermore, we demonstrate that this method could be integrated into a two-step sequence for the direct conversion of phenols to amines, as well as a three-step synthesis of imatinib, the active pharmaceutical ingredient of the anti-cancer 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.

We have previously reported a system where 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 due to its similar Hansen solubility parameters to dichloromethane[6b], low solubility in water (4.3 g/L)[6c], reported toxicological profile comparable to common laboratory solvents[6c,d], ready availability as a high production volume chemical,[6c] and previous use 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 XPhos-based[8] precatalyst **7** under 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 due to 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 (~~Table 1,~~ entry 2). Full conversion and excellent yield were obtained when the BrettPhos-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 DMO as a neat solvent (entry 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 toluene or 2-MeTHF in the absence of DMO resulted in incomplete conversion~~ of starting material~~ within the designated reaction times. Upon extended reaction

[a] J. Yang, D. Niu, B. Karsten, F. Lima and Prof. Dr. S. L. Buchwald
Department of Chemistry, Room 18-490
Massachusetts Institute of Technology
Cambridge, MA 02139 (USA)
E-mail: sbuchwal@mit.edu

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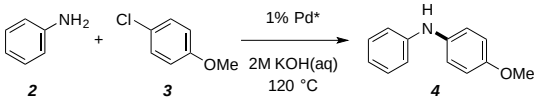
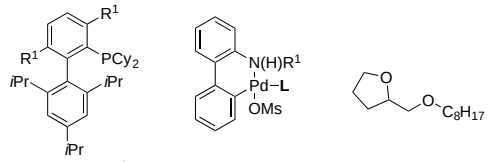
times to achieve full conversion in toluene (entry 7), the reaction vessel clogged due to the poor solubility of the product. Although the use of amphiphilic solvent **9** also gave high conversion of starting material and yield of product **4**, clogging of the reactor occurred after prolonged reaction times. Therefore, the conditions in entry 5 or 6 of this table 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

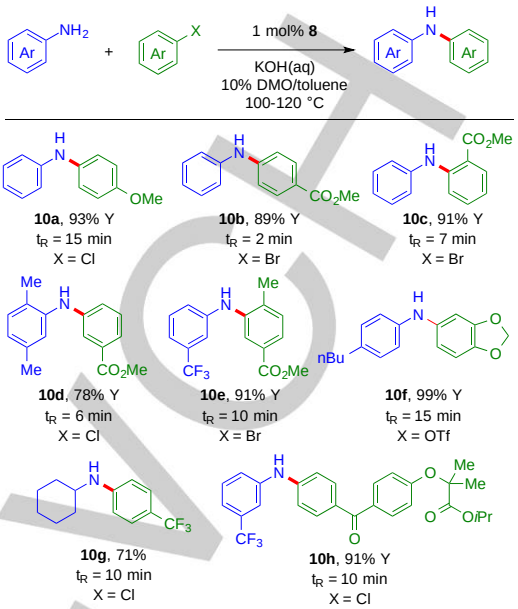
7; **L** = **5**, R = H
8; **L** = **6**, R = Me

9

[a] Conversions and yields were determined by GC analysis of the crude reaction mixture. See supporting information for details. [b] 0.04" PTF tubing was used as the reaction vessel. [c] Prolonged reaction times resulted in full conversion along with clogging of the reaction vessel due to the low solubility of the product.

Using the above-described conditions, we explored the generality applicability (Table 2). A wide variety of aryl bromides and chlorides, bearing electron-donating or -withdrawing substituents, were efficiently coupled with aniline partners (**10a-b**, and **g-h**). Ortho-substitution in either aryl halide or arylamine reaction partner was accommodated (**10c-e**). In addition, aryl triflates (**10f**) were also excellent substrates under these conditions, with minimal hydrolysis observed. Besides aryl amines, primary alkyl amines could also successfully converted to product (**10g**). As a consequence of the precise control of 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.

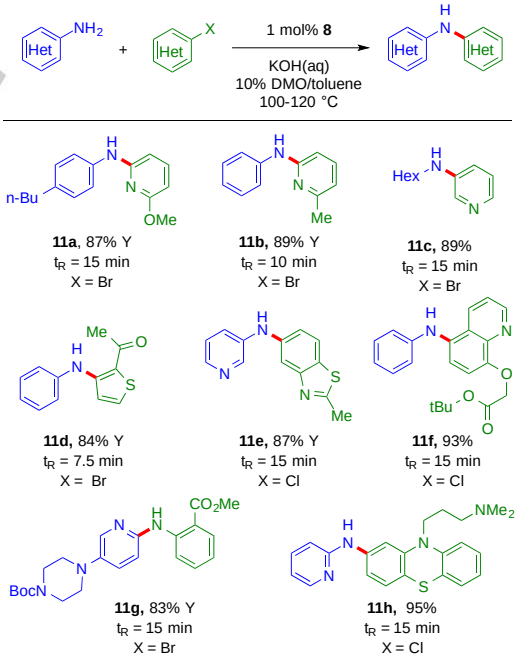
Table 2. Substrate scope of C–N cross-coupling reaction between arylamines and aryl (pseudo)halides.[a]



[a] Isolated yields are reported (average of 2 runs, approximately 1 - 4 mmol collected). See 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.

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



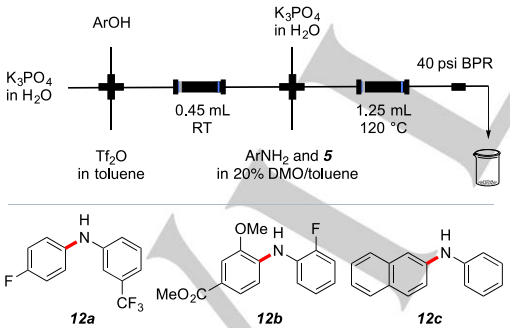
[a] Isolated yields are reported (average of 2 runs, approximately 1 - 4 mmol collected). See supporting information for details.

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, could be coupled with 2-aminopyridine under these conditions to give **11h** in excellent yield. Substrates containing base-sensitive functional groups like 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 to biarylamines via aryl triflate intermediates (Scheme 1). Aryl triflates are recognized as highly reactive coupling partners in C–N cross-coupling reactions. However, the lack of commercially available triflates and their instability necessitate their preparation prior to their use ~~in later reactions~~, which significantly hampers their application. We reasoned that the two-step conversion of phenols to arylamines without isolating the triflate intermediate would be of considerable interest. We have previously reported a similar sequence in flow, the complete removal of methylene chloride from the first step via microfluidic distillation and solvent exchange to dimethylformamide was required for a subsequent Heck coupling.[2f] After experimentation, we found that this could be accomplished in a flow system as shown in Scheme 1. While the triflation of a phenol often is carried out at low temperature and with the slow addition of triflic anhydride in a batch reactor,[11] 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, Pd 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, no in line purification or solvent switch were required in this process. In addition, we found that a phenol tosylation/C–N cross-coupling sequence could also be similarly accomplished (**12c**).[12]

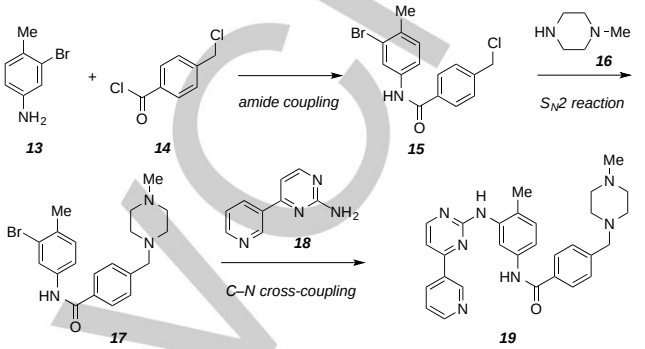
Scheme 1. Two step flow conversion of phenols to biarylamines via aryl triflates or tosylates.[a]



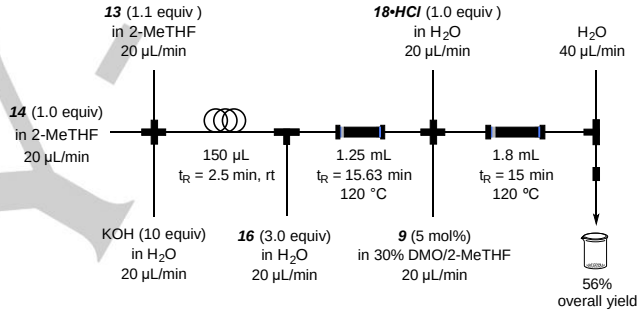
a] Isolated yields are reported (average of 2 runs, approximately 1 - 4 mmol collected). See supporting information for details.

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[2g,h] described the flow synthesis of imatinib, as depicted in Scheme 2. Based on this synthetic sequence, Ley 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.

Scheme 2. Three step flow synthesis of imatinib.



Scheme 3. Flow synthesis for imatinib.



We have also reported on the synthesis of imatinib using batch protocols.[15] 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-chloromethyl-benzoyl chloride (**14**) to form 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 the product **15** could be 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 of the crude reaction mixture. The last step in the synthesis of imatinib is the C–N cross-coupling of **15** with 2-aminopyrimidine **18** using precatalyst **8** (5 mol %). The outlet of the previous reactor was again used directly. Due to 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 to 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 in order 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 via acid/base extraction followed by 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 co-solvent in a biphasic system. The use of the biphasic system serves as a convenient solution to address the precipitation of inorganic byproduct generated during C–N cross-coupling reactions. A wide range of biarylamines, including those derived from commercial drugs, have 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 that converts phenols into biarylamines, via the intermediacy of triflates or tosylates. We have also showcased this technology in the three-step synthesis of the anti-cancer agent imatinib. Compared with previous synthetic routes, our synthesis does not require in-line manipulation of reaction intermediates or solvent exchange between steps, uses lower catalyst loading, and produces the target product in higher overall yield. We expect this strategy of using DMO as a co-solvent in biphasic system to be applicable to other multistep flow sequences, especially those involving cross-coupling reactions.

Acknowledgements

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Keywords: amination • cross-coupling • flow chemistry • synthetic methods

[1] a) D. Webb, T. F. Jamison, *Chem. Sci.* **2010**, *1*, 675; b) T. Noël, S. L. Buchwald, *Chem. Soc. Rev.* **2011**, *40*, 5010; c) R. L. Hartman, J. P. McMullen, K. F. Jensen, *Angew. Chem. Int. Ed.* **2011**, *50*, 7502; d) C. Wiles, P. Watts, *Chem. Commun.* **2011**, *47*, 6512; e) J. Wegner, S. Ceylan, A. Kirschning, *Adv. Synth. Catal.* **2012**, *354*, 17; f) J. C. Pastre, D. L. Browne, S. V. Ley, *Chem. Soc. Rev.* **2013**, *42*, 8849; g) D. T. McQuade, P. H. Seeberger, *J. Org. Chem.* **2013**, *78*, 6384; ~~h) J. Bariwal, E. Van der Eycken, Chem. Soc. Rev. 2013, 42, 9283~~; h) J.-I. Yoshida, Y. Takahashi, A. Nagaki, *Chem. Commun.* **2013**, *49*, 9896; i) S. G. Newman, K. F. Jensen, *Green Chem.* **2013**, *15*, 1456; j) R. J. Ingham, C. Battilocchio, D. E. Fitzpatrick, E. Sliwinski, J. M. Hawkins, S. V. Ley, *Angew. Chem. Int. Ed.* **2015**, *54*, 144; k) B. Gutmann, D. Cantillo, C. O. Kappe, *Angew. Chem. Int. Ed.* **2015**, *54*, 6688.

[2] For selected examples, see: a) D. Cantillo, M. Damm, D. Dallinger, M. Bauser, M. Berger, C. O. Kappe, *Org. Process Res. Dev.* **2014**, *18*, 1360; b) P. Filipponi, C. Ostacolo, E. Novellino, R. Pellicciari, A. Gioiello, *Org. Process Res. Dev.* **2014**, *18*, 1345; c) L. Dalla-Vechia, B. Reichart, T. Glasnov, L. S. M. Miranda, C. O. Kappe, R. O. M. A. de Souza, *Org. Biomol. Chem.* **2013**, *11*, 6806; d) M. Chen, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2013**, *52*, 4247; e) T. Noël, S. Kuhn, A. J. Musacchio, K. F. Jensen, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2011**, *50*, 5943; f) R. L. Hartman, J. R. Naber, S. L. Buchwald, K. F. Jensen, *Angew. Chem. Int. Ed.* **2010**, *49*, 899; g) M. D. Hopkin, I. R. Baxendale, S. V. Ley, *Chem. Commun.* **2010**, *46*, 2450; h) M. D. Hopkin, I. R. Baxendale, S. V. Ley, *Org. Biomol. Chem.* **2013**, *11*, 1822.

[3] a) J. F. Hartwig, *Acc. Chem. Res.* **2008**, *41*, 1534; b) D. S. Surry, S. L. Buchwald, *Chem. Sci.* **2011**, *2*, 27; c) N. Marion, O. Navarro, J. Mei, E. D. Stevens, N. M. Scott, S. P. Nolan, *J. Am. Chem. Soc.* **2006**, *128*, 4101; d) M. G. Organ, M. Abdel-Hadi, S. Avola, I. Dubovyk, N. Hadei, E. A. B. Kantchev, C. J. O' Brien, M. Sayah, C. Valente, *Chem. Eur. J.* **2008**, *14*, 2443; e) S. M. Raders, J. N. Moore, J. K. Parks, A. D. Miller, T. M. Leißing, S. P. Kelley, R. D. Rogers, K. H. Shaughnessy, *J. Org. Chem.* **2013**, *78*, 4649. For other methods of making Csp2-N bonds, see: f) D. M. T. Chan, K. L. Monaco, R.-P. Wang, M. P. Winters, *Tetrahedron Lett.* **1998**, *39*, 2933; g) P. Y. S. Lam, C. G. Clark, S. Saubern, J. Adams, M. P. Winters, D. M. T. Chan, A. Combs, *Tetrahedron Lett.* **1998**, *39*, 2941; h) P. Y. S. Lam, C. G. Clark, S. Saubern, J. Adams, K. M. Averill, D. M. T. Chan, A. Combs, *Synlett* **2000**, 674.

[4] a) J. R. Naber, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2010**, *49*, 9469; b) T. Noël, J. R. Naber, R. L. Hartman, J. P. McMullen, K. F. Jensen, S. L. Buchwald, *Chem. Sci.* **2011**, *2*, 287.

[5] a) J. G. Kralj, H. R. Sahoo, K. F. Jensen, *Lab Chip.* **2007**, *7*, 256; b) A. Aota, M. Nonaka, A. Hibara, T. Kitamori, *Angew. Chem. Int. Ed.* **2007**, *46*, 878; c) A.-L. Dessimoz, L. Cavin, A. Renken, L. Kiwi-Minsker, *Chem. Eng. Sci.* **2008**, *63*, 4035; d) T. Maruyama, H. Matsushita, J.-I Uchida, F. Kubota, N. Kamiya, M. Goto, *Anal. Chem.* **2004**, *76*, 4495; ~~e) R. L. Hartman, H. R. Sahoo, B. C. Yen, K. F. Jensen, *Lab Chip* **2009**, *9*, 1843;~~ e) B. J. Deadman, C. Battilocchio, E. Sliwinski, S. V. Ley, *Green Chem.* **2013**, *15*, 2050.

[6] a) T. Vidal, V. Bramati, K. Murthy, B. Abribat, *J. ASTM Int.* **2011**, *8*, 103716; b) A. Benazzouz, L. Moity, C. Pierlot, M. Sergent, V. Molinier, J.-M. Aubry, *Ind. Eng. Chem. Res.* **2013**, 52, 16585. c) Detailed physical and chemical information on DMO can be found under European Chemicals Agency http://www.echa.europa.eu/ and the U.S. Environmental Protection Agency, High Production Volume Information System (HPVIS) http://www.epa.gov/hpvis/index.html d) For side-by-side comparison of reported toxicities, see supporting information.

[7] a) L.A. Trujillo-Cayado, A. Natera, M.C. García , J. Muñoz, M.C. Alfaro, *Grasas Y Aceites,* **2015**, *66, e087*; b) H. B. Lopez, P. J. Porpiglia. Dispersible herbicidal compositions and methods of use. **2014**, US20140031232 A1. b) DMO is listed as an "Intert ingredient used pre-harvest; exempt from the requirement of a tolerance" by the Code of Federal Regulations. "Tolerances and Exemptions for Pesticide Chemical Residues in Food" 40CFR1.180(2015)

[8] X. Huang, K. W. Anderson, D. Zim, L. Jiang, A. Klapars, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 6653.

[9] B. P. Fors, D. A. Watson, M. R. Biscoe, S. L. Buchwald, *J. Am. Chem. Soc.* **2008**, *130*, 13552.

[10] D. Prat, O. Pardigon, H.-W. Flemming, S. Letestu, V. Ducandas, P. Isnard, E. Guntrum, T. Senac, S. Ruisseau, P. Cruciani, P. Hosek, *Org. Process Res. Dev.* **2013**, *17*, 1517.

[11] A. Mori, T. Mizusaki, T. Ikawa, T. Maegawa, Y. Monguchi, H. Sajiki, *Chem. Eur. J.* **2007**, *13*, 1432.

[12] Similarly, benzenesulfonation/C–N cross-coupling could also be done using this scheme (results not shown).

[13] a) R. Capdeville, E. Buchdunger, J. Zimmermann, A. Matter, *Nat. Rev. Drug Discovery* **2002**, *1*, 493; b) M. Deininger, E. Buchdunger, B. J. Druker, *Blood* **2005**, *105*, 2640.

[14] T. D. White, K. D. Berglund, J. M. Groh, M. D. Johnson, R. D. Miller, M. H. Yates, *Org. Process Res. Dev.* **2012**, *16*, 939.

[15] D. Maiti, B. P. Fors, J. L. Henderson, Y. Nakamura, S. L. Buchwald, *Chem. Sci,* **2011**, *2*, 57.a) H. Matsubara, S. Yasuda, H. Sugiyama, I. Ryu, Y. Fujii, K. Kita, Tetrahedron, 2002, 58, 4071; b) B. H. Lipshutz, D. W. Chung. B. Rich, Org. Lett, 2008, 10, 3793

[16] The output of imatinib in our current system is 2.5 mg/min. For comparison, see references 2g, h.

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