



LJMU Research Online

Roesner, S and Buchwald, SL

Continuous-Flow Synthesis of Biaryls by Negishi Cross-Coupling of Fluoro- and Trifluoromethyl-Substituted (Hetero)arenes

<http://researchonline.ljmu.ac.uk/id/eprint/23120/>

Article

Citation (please note it is advisable to refer to the publisher's version if you intend to cite from this work)

Roesner, S and Buchwald, SL (2016) Continuous-Flow Synthesis of Biaryls by Negishi Cross-Coupling of Fluoro- and Trifluoromethyl-Substituted (Hetero)arenes. *Angewandte Chemie - International Edition*, 55 (35). pp. 10463-10467. ISSN 1433-7851

LJMU has developed **LJMU Research Online** for users to access the research output of the University more effectively. Copyright © and Moral Rights for the papers on this site are retained by the individual authors and/or other copyright owners. Users may download and/or print one copy of any article(s) in LJMU Research Online to facilitate their private study or for non-commercial research. You may not engage in further distribution of the material or use it for any profit-making activities or any commercial gain.

The version presented here may differ from the published version or from the version of the record. Please see the repository URL above for details on accessing the published version and note that access may require a subscription.

For more information please contact researchonline@ljmu.ac.uk

<http://researchonline.ljmu.ac.uk/>

Continuous Flow Synthesis of Biaryls by Negishi Cross-Coupling of Fluoro- and Trifluoromethyl-Substituted (Hetero)arenes

Stefan Roesner and Stephen L. Buchwald*

Abstract: A continuous flow method for the regioselective arylation of fluoroarenes and fluoropyridines has been developed. The telescoped protocol reported here consists of a three-step metalation, zincation, and Negishi cross-coupling sequence, providing efficient access to a variety of functionalized 2-fluorobiaryl products. Precise temperature control of the metalation step, made possible by continuous flow technology, allowed for the efficient preparation of the arylated products in high yield and short residence times. Additionally, several examples of the regioselective arylation of benzotrifluoride derivatives are also provided.

Fluorinated aromatic compounds are important synthetic targets by virtue of their presence in a variety of pharmaceutical and agrochemical agents. Compared to non-fluorinated analogues, aryl fluorides often exhibit superior biological activity as a consequence of their enhanced metabolic stability and membrane permeability.^[1] As a subset of aryl fluorides, the 2-fluorobiaryls are particularly important in light of their presence in several classes of biologically active compounds, including drugs with anti-inflammatory, immunosuppressant and antibiotic properties (Figure 1).^[2] Thus, the efficient preparation of this class of compounds from readily available starting materials is of considerable interest.

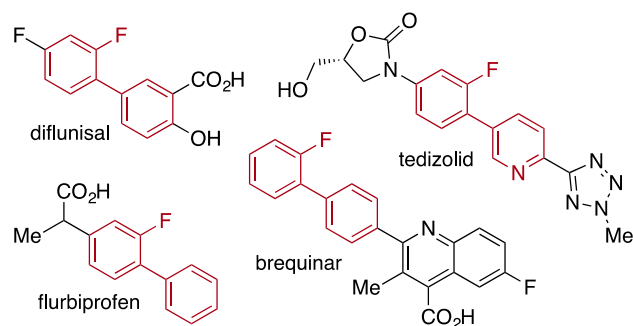
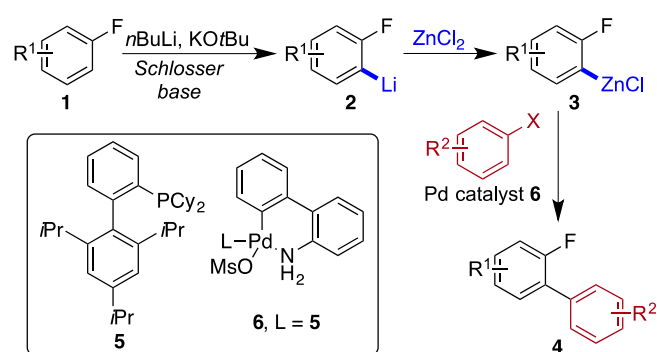


Figure 1. Examples of 2-fluorobiaryl-containing biologically active compounds.

This notion is exemplified through the development of several approaches to the synthesis of 2-fluorobiaryls. Beller demonstrated a strategy for the synthesis of 2-aryl- and 2-heteroaryl fluoroarenes employing an intermolecular domino Grignard-coupling-fluorination sequence.^[3] More recently

Yoshida reported the insertion of arynes into the F–Sn bond of tributyltin fluoride to afford diverse 2-fluoroarylstannanes, which could be further functionalized by Stille coupling.^[4] We envisioned a complementary approach where the synthesis of 2-fluorobiaryls starting from an aryl fluoride **1** would be achieved in a continuous flow process (Scheme 1). In particular, we reasoned that lithiation of **1** under continuous flow conditions could be used to efficiently and regioselectively generate aryllithium species **2**. Subsequent transmetalation of **2** with zinc chloride, followed by palladium-catalyzed Negishi cross-coupling^[5] of arylzinc **3** with an aryl electrophile would provide the desired 2-fluorobiaryl product (**4**). Although the regioselective metalation of **1** using the *n*BuLi/KOtBu superbases to form aryllithium **2** has previously been reported,^[6,7] we hypothesized that continuous flow chemistry would be the ideal platform for the rapid generation and safe handling of these thermally unstable intermediates. Moreover, we expected that in conjunction with efficient mixing under continuous flow conditions, the use of rapidly activating palladium precatalysts would allow for reduced reaction times for the cross-coupling step.^[8] We anticipated that XPhos-based precatalyst **6**, which has previously been shown to provide excellent results for C(*sp*²)–C(*sp*²) Negishi cross-coupling reactions under batch conditions, would prove suitable in the current system.^[9]



Scheme 1. Synthesis of 2-fluorobiaryls (**4**) by a lithiation/zincation/Negishi cross-coupling sequence; XPhos ligand **5** and third generation precatalyst **6**.

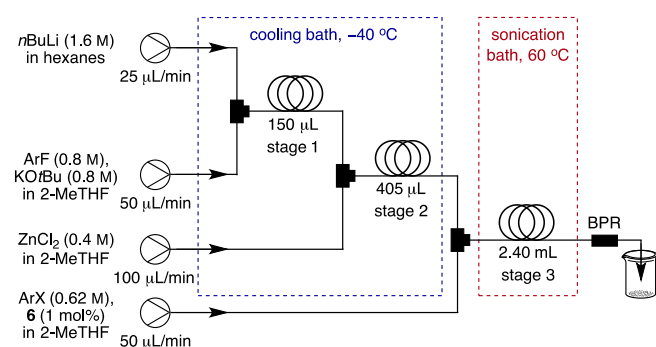
Flow conditions offer a safe alternative to batch reactions whenever dangerous/unstable intermediates or reagents are involved.^[10,11] Due to the improved heat transfer of continuous flow reactors, the temperature of exothermic organometallic reactions can be accurately controlled, thus providing scalable and reproducible processes. The field of organolithium species in continuous flow syntheses was pioneered by Yoshida.^[12,13] Several examples demonstrated the successful transfer of organolithium reactions from batch to continuous flow conditions, resulting in improvements of yield and functional group

[*] Dr. S. Roesner, Prof. Dr. S. L. Buchwald
Department of Chemistry
Massachusetts Institute of Technology
77 Massachusetts Avenue, Cambridge, MA 02139 (USA)
E-mail: sbuchwald@mit.edu

Supporting information for this article is given via a link at the end of the document.

compatibility.^[13,14] In addition, modular cryo-flow reactors have been developed.^[15] Knochel recently reported the formation of (hetero)aryl zincates in flow followed by Negishi cross-coupling under batch conditions.^[16] Besides this semi-batch approach, the Negishi cross-coupling for the formation of C(sp²)-C(sp³) bonds under flow conditions has also been described.^[17] Yet, the formation of biaryl compounds employing Negishi coupling using continuous conditions exclusively is still unknown. Herein we describe the regioselective lithiation of fluoro- and trifluoromethyl-substituted arenes and pyridines, followed by zincation and Negishi cross-coupling in a telescoped continuous flow process.

We initiated our study by optimizing the reaction of fluorobenzene with bromobenzene to provide biaryl **4a**. A three-stage reactor was assembled – stage 1: directed lithiation, stage 2: zincation, stage 3: cross-coupling (Scheme 2).^[18] We found that intermediate **2** was stable up to -30 °C. Above this temperature benzyne formation via LiF elimination took place, as indicated by a strong discoloration of the reaction mixture. In order to avoid undesired side-reactions through benzyne-formation, lithiation and zincation were conducted at -40 °C. Another challenge encountered during method development was an undesired pulsation of flow caused by gas generation in stage 3. This problem was mitigated by utilizing a back-pressure regulator (BPR). The last challenge of optimization was avoiding clogging in stage 3 due to precipitation of inorganic salts. Thus, the cross-coupling portion of the flow reactor necessitated the use of a heated ultrasonic bath to keep particles in suspension.^[19,20] The total residence time in the flow reactor was 15 min. Biaryl products were obtained after aqueous workup and chromatographic purification.

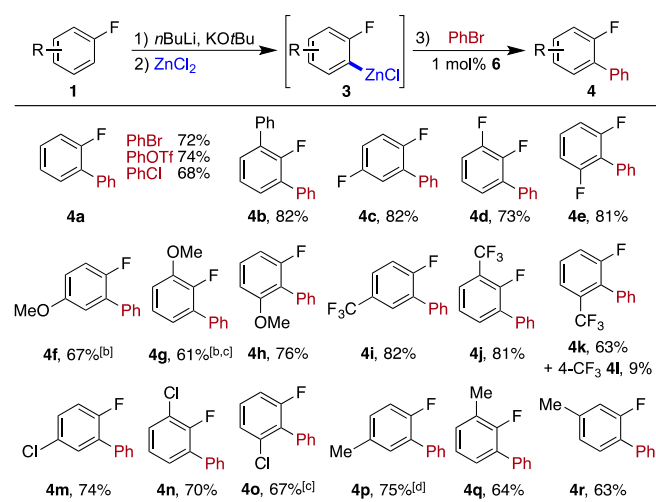


Scheme 2. Experimental setup for the synthesis of 2-fluorobiaryls via directed lithiation, zincation, and Negishi cross-coupling.

Using the reaction setup described above (Scheme 2), the substrate scope of a variety of fluoro-substituted arenes was explored (Table 1). In addition to bromo-substituted arenes, aryl triflates and chlorides were also suitable cross-coupling partners. Subjecting **4a** to these reaction conditions resulted in further arylation to provide triaryl **4b**. Difluoro-substituted arenes^[7c] gave the desired biaryls in high yields (**4c–e**). In the case of fluoro-substituted anisoles,^[7e] the fluoro substituent proved to be the stronger directing group as demonstrated by the formation of **4f–h** as single regioisomers. The same applied to the use of

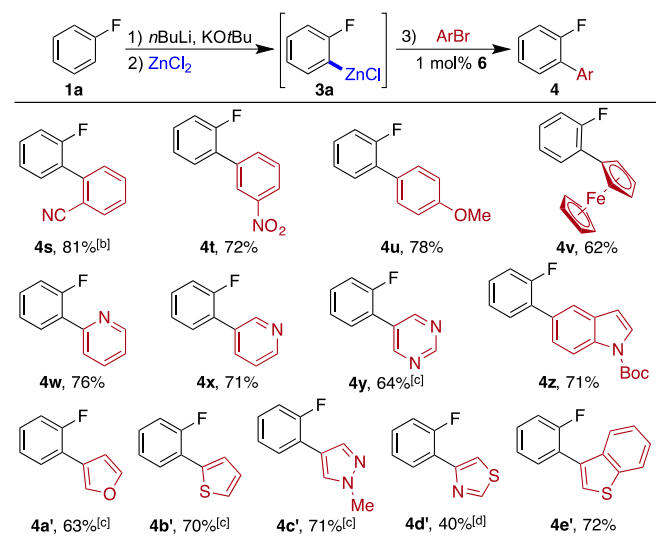
trifluoromethyl-substituted fluoroarenes (**4i–k**).^[7c] However, in the case of 3-fluorobenzotrifluoride a small amount of the regioisomer **4l** was isolated, likely due to the steric hindrance of the *ortho*-position next to the bulky CF₃-group. Chloro-substituted fluoroarenes^[7f] were also suitable substrates, giving the desired biaryl products in good yield (**4m–o**) without formation of either homo-coupled or dechlorinated side products. In addition, fluoro-substituted toluenes^[7d] were well tolerated (**4p–r**). In the case of 3-fluorotoluene, the methyl group directs the lithiation to the *para*-position (**4r**), presumably for steric reasons.

Table 1. Substrate scope of C–C cross-coupling reaction between aryl fluorides and bromobenzene.^[a]



[a] 1.0 mmol scale, yields are of isolated products (average of two runs). See Supporting Information for details. [b] Isolated yield after conversion to the corresponding phenol. [c] Lithiation at -60 °C for 240 s. [d] Yield of isolated product on 5.0 mmol scale.

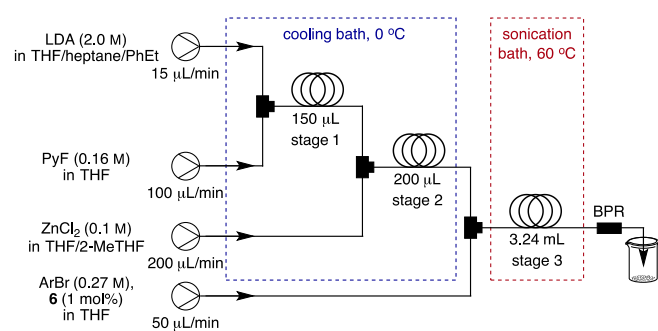
Table 2. Substrate scope of C–C cross-coupling reaction between fluorobenzene and (hetero)aryl bromides.^[a]



[a] 1.0 mmol scale, yields are of isolated products (average of two runs). See Supporting Information for details. [b] Yield of isolated product on 5.0 mmol scale. [c] 2 mol% catalyst loading. [d] 5 mol% catalyst loading.

Given the importance of heterocyclic compounds in medicinal chemistry,^[21] we next examined the Negishi coupling of **3a** with heteroaryl bromides and other functionalized bromoarenes (Table 2). Aryl bromides with electron-withdrawing and electron-donating substituents were efficiently coupled (**4s–u**). Bromoferrocene could be employed under our reaction conditions to give **4v**. A variety of brominated heterocycles, including pyridine (**4w,x**), pyrimidine (**4y**), indole (**4z**), furan (**4a'**), thiophene (**4b'**), pyrazole (**4c'**), thiazole (**4d'**), and benzothiophene (**4e'**), were efficiently coupled to provide the desired biaryls. To demonstrate the utility of our system, we were able to run experiments for more than 2.5 h without any interruption to collect a total of 5 mmol of product (Table 1, **4p** and Table 2, **4s**). These examples highlight the ease of scale-up in continuous flow chemistry.

Next, we turned our attention to arylation of fluoro-substituted pyridines. The regioselective *ortho*-lithiation of halopyridines with lithium diisopropylamide (LDA) and other amide bases is well established.^[22] Since pyridines are considerably more acidic than arenes, we were able to lithiate them under milder reaction conditions using LDA. However, we encountered significant salt formation after addition of zinc chloride. In order to avoid clogging of the flow reactor, it was necessary to change the solvent to THF, reduce the concentration of the reagents, and increase the flow rates. Additionally, we found that *ortho*-lithiated 2-fluoropyridine was less prone to eliminate LiF. Hence, the lithiation with LDA could be performed at 0 °C under continuous flow conditions within seconds, which is in strong contrast to previously reported batch conditions (−78 °C for several hours).^[22] The optimized flow process for 2-fluoropyridine is depicted in Scheme 3. The total residence time for this process was less than 11 min.



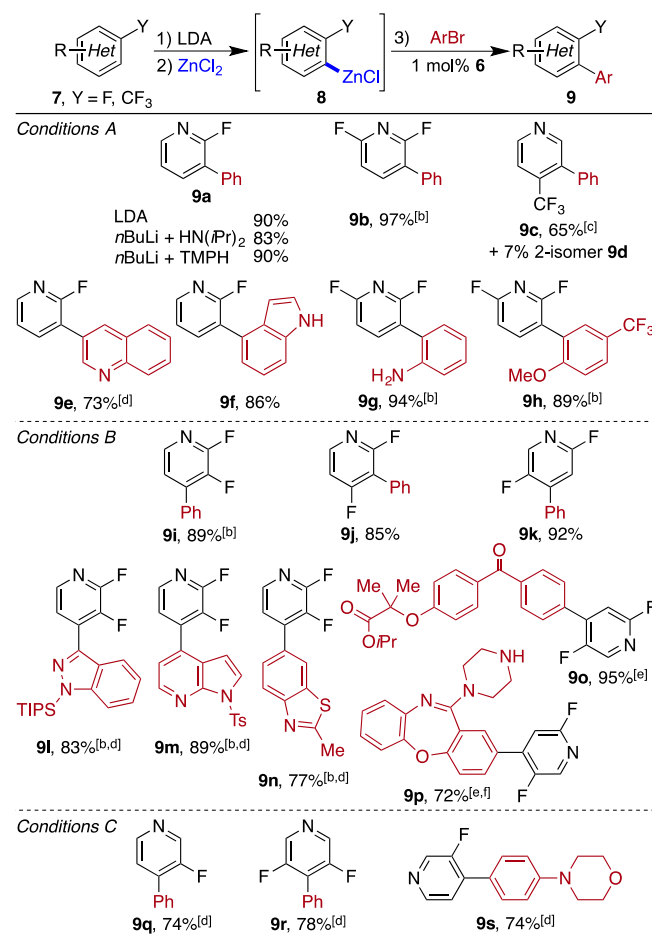
Scheme 3. Experimental setup for the coupling of fluoro-substituted pyridines (conditions A).

We found that these optimized reaction conditions (conditions A) were suitable for the functionalization of 2-fluoropyridine, 2,6-difluoropyridine and 4-(trifluoromethyl)pyridine (Table 3). These substrates were cleanly coupled with bromobenzene to give the desired biaryl products in good to

excellent yields (**9a–c**). Instead of a commercial LDA solution, the amide base could also be generated in situ from *n*BuLi solution and diisopropylamine.^[18] In addition, the reaction performed well with in situ formed lithium tetramethylpiperidide (LTMP) to provide **9a** in excellent yield. Heterocycles, such as quinoline (**9e**) and an unprotected indole (**9f**), as well as various functionalized arenes (**9g,h**) performed well in the cross-coupling reaction under these conditions.

For 2,3-, 2,4- and 2,5-difluoropyridine it was necessary to increase the flow rate of the zinc chloride solution from 200 to 400 µL/min in order to avoid clogging (conditions B).^[18] Coupling with bromobenzene provided regioisomerically pure products in excellent yield in all three cases (**9i–k**). Pharmaceutically relevant heterocycles such as indazole (**9l**), 7-azaindole (**9m**), and benzothiazole (**9n**) were also coupled with 2,3-difluoropyridine with high efficiency. To further demonstrate the potential applicability of our methodology, fenofibrate, a pharmaceutical used to reduce cholesterol levels, and amoxapine, a tetracyclic antidepressant, were subjected to the reaction conditions. Coupling with 2,5-difluoropyridine gave the desired products **9o** and **9p** as single regioisomers in good to excellent yields.

Table 3. Substrate scope of C–C cross-coupling reaction between fluoropyridines and (hetero)aryl bromides.^[a]

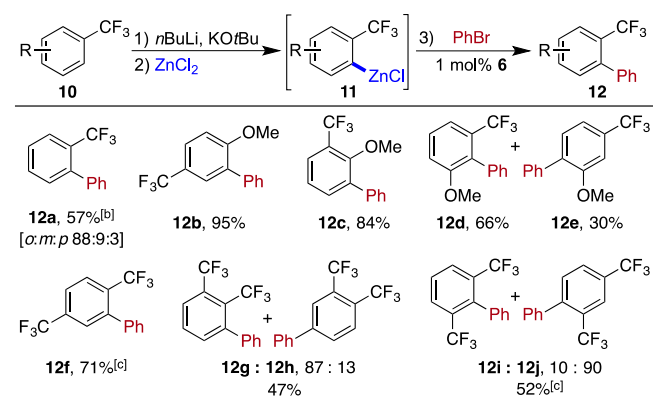


[a] 0.5 mmol scale, yields are of isolated products (average of two runs). See Supporting Information for details. [b] Lithiation at $-10\text{ }^{\circ}\text{C}$. [c] Lithiation at $-20\text{ }^{\circ}\text{C}$. [d] 2 mol% catalyst loading. [e] ArCl as cross-coupling partner. [f] 4 mol% catalyst loading.

Nonetheless, neither conditions A nor B proved to be suitable for the conversion of 3-fluoropyridine or 3,5-difluoropyridine; clogging of the reactor occurred within a few minutes after zincation at stage 2. Through further optimization, we found that the addition of 0.5 equivalents of KO t Bu allowed us to avoid this complication. Additionally, the flow rates of the fluoropyridine and zinc chloride solutions needed to be increased to 400 $\mu\text{L}/\text{min}$ (conditions C).^[18] With these higher flow rates the total residence time was reduced to less than 5 min employing the same reactor setup. Bromobenzene and a morpholine-substituted arene (**9q–s**) were cross-coupled with **8** in synthetically useful yields.

In addition to fluoro directed lithiation of arenes and pyridines, we wondered whether a trifluoromethyl-group could also act as a directing group for lithiation with a mixture of $n\text{BuLi}/\text{KO}t\text{Bu}$.^[7g] Employing our optimized reaction conditions for fluoroarenes (Scheme 2) to benzotrifluoride, the *ortho*-coupled biaryl **12a** was obtained in 57% yield (Table 4). However, the metalation was not completely *ortho*-selective and small amounts of the *meta*- and *para*-coupled product were also generated. Nevertheless, methoxy-substituted biaryls **12b** and **12c** were obtained as single regioisomers. In these cases lithiation occurred *ortho* to the methoxy-group. This indicates that the aryl ether is a stronger directing group than the trifluoromethyl group. While symmetric 1,4-bis(trifluoromethyl)benzene gave **12f** in good yield, 1,2- and 1,3- bis(trifluoromethyl)benzene gave a mixture of regioisomers (**12g–j**).

Table 4. Substrate scope of C–C cross-coupling reaction between trifluoromethyl-substituted arenes and bromobenzene.^[a]



[a] 1.0 mmol scale, yields are of isolated products (average of two runs). See Supporting Information for details. [b] 2 mol% catalyst loading. [c] Lithiation at $-60\text{ }^{\circ}\text{C}$.

In summary, we have developed a highly regioselective arylation of fluoro- and trifluoromethyl-substituted arenes and pyridines under continuous flow conditions. In this methodology a directed lithiation, a zincation, and a Negishi cross-coupling are telescoped into a single process. This sequence provides a

convenient and efficient approach to diversely functionalized, pharmaceutically relevant biaryl compounds in short reaction times (5–15 min) from readily available starting materials.

Acknowledgements

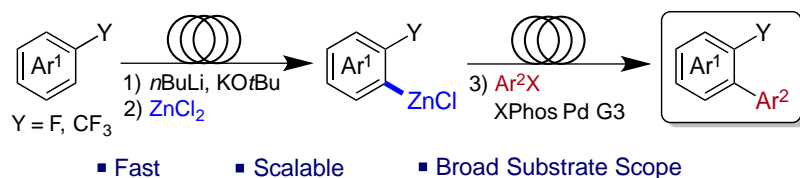
We acknowledge the Novartis International AG for funding and are grateful to Drs. Benjamin Martin, Berthold Schenkel and Gerhard Penn for helpful discussions. We thank Drs. Yi-Ming Wang, Mycah Uehling, and Christine Nguyen for assistance with the preparation of this manuscript.

Keywords: biaryls • cross-coupling • flow chemistry • palladium • synthetic methods

- [1] a) P. Kirsch, *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*, 2nd ed., Wiley-VCH, Weinheim, **2013**; b) J. Wang, M. Sánchez-Roselló, J. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, *114*, 2432; c) E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly, N. A. Meanwell, *J. Med. Chem.* **2015**, *58*, 8315; d) B. E. Smart, *J. Fluor. Chem.* **2001**, *109*, 3.
- [2] W. B. Im, S. H. Choi, J.-Y. Park, S. H. Choi, J. Finn, S.-H. Yoon, *J. Med. Chem.* **2011**, *46*, 1027.
- [3] P. Anbarasan, H. Neumann, M. Beller, *Chem. Asian J.* **2010**, *5*, 1775.
- [4] H. Yoshida, R. Yoshida, K. Takaki, *Angew. Chem. Int. Ed.* **2013**, *52*, 8629; *Angew. Chem.* **2013**, *125*, 8791.
- [5] a) E. Negishi, *Angew. Chem. Int. Ed.* **2011**, *50*, 6738; *Angew. Chem.* **2011**, *123*, 6870; b) P. Knochel, P. Jones, *Organozinc Reagents, A Practical Approach*, Oxford University Press, New York, **1999**.
- [6] a) M. Schlosser, *J. Organomet. Chem.* **1967**, *8*, 9; b) L. Lochmann, J. Pospišil, D. Lim, *Tetrahedron Lett.* **1966**, *7*, 257.
- [7] For review articles, see: a) M. Schlosser, *Angew. Chem. Int. Ed.* **2005**, *44*, 376; *Angew. Chem.* **2005**, *117*, 380; b) M. Schlosser, *Eur. J. Org. Chem.* **2001**, 3975; For selected publications, see: c) M. Schlosser, G. Katsoulos, S. Takagishi, *Synlett* **1990**, 747; d) M. Schlosser, S. Takagishi, *Synlett* **1991**, 119; e) G. Katsoulos, S. Takagishi, M. Schlosser, *Synlett* **1991**, 731; f) F. Mongin, M. Schlosser, *Tetrahedron Lett.* **1996**, *37*, 6551; g) M. Schlosser, F. Mongin, J. Porwisiak, W. Dmowski, H. H. Bükler, N. M. M. Nibbering, *Chem. Eur. J.* **1998**, *4*, 1281.
- [8] a) J. C. Yang, D. Niu, B. P. Karsten, F. Lima, S. L. Buchwald; *Angew. Chem. Int. Ed.* **2016**, *55*, 2531; *Angew. Chem.* **2016**, *128*, 2577; b) W. Shu, L. Pellegatti, M. A. Oberli, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2011**, *50*, 10665; *Angew. Chem.* **2011**, *123*, 10853; c) T. Noël, S. Kuhn, A. J. Musacchio, K. F. Jensen, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2011**, *50*, 5943; *Angew. Chem.* **2011**, *123*, 6065; d) W. Shu, S. L. Buchwald, *Chem. Sci.* **2011**, *2*, 2321; e) T. Noël, J. R. Naber, L. Hartmann, J. P. McMullen, K. F. Jensen, S. L. Buchwald, *Chem. Sci.* **2011**, *2*, 287; f) J. R. Naber, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2010**, *49*, 9469; *Angew. Chem.* **2010**, *122*, 9659.
- [9] a) Y. Yang, N. J. Oldenhuis, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2013**, *52*, 615; *Angew. Chem.* **2013**, *125*, 643; b) J. R. Colombe, S. Bernhard, C. Stathakis, S. L. Buchwald, P. Knochel, *Org. Lett.* **2013**, *15*, 5754.
- [10] a) T. Wirth, *Microreactors in Organic Synthesis and Catalysis*, 2nd ed., Wiley-VCH, Weinheim, **2013**; b) V. Hessel, A. Renken, J. C. Schouten, J. Yoshida, *Micro Process Engineering: A Comprehensive Handbook*, Wiley-VCH, Weinheim, **2009**.
- [11] For recent reviews, see: a) S. Kobayashi, *Chem. Asian J.* **2016**, *11*, 425; b) S. V. Ley, D. E. Fitzpatrick, R. M. Myers, C. Battilocchio, R. J. Ingham, *Angew. Chem. Int. Ed.* **2015**, *54*, 10122; *Angew. Chem.* **2015**, *127*, 10260; c) B. Gutmann, D. Cantillo, C. O. Kappe, *Angew. Chem. Int. Ed.* **2015**, *54*, 6688; *Angew. Chem.* **2015**, *127*, 6788; d) S. V. Ley, D. E.

-
- Fitzpatrick, R. J. Ingham, R. M. Myers, *Angew. Chem. Int. Ed.* **2015**, *54*, 3449; *Angew. Chem.* **2015**, *127*, 3514; e) J. C. Pastre, D. L. Browne, S. V. Ley, *Chem. Soc. Rev.* **2013**, *42*, 8849; f) V. Hessel, D. Kralisch, N. Kockmann, T. Noël, Q. Wang, *ChemSusChem* **2013**, *6*, 746; g) J. Wegner, S. Ceylan, A. Kirschning *Adv. Synth. Catal.* **2012**, *354*, 17; h) T. Noël, S. L. Buchwald, *Chem. Soc. Rev.* **2011**, *40*, 5010.
- [12] J. Yoshida, *Flash Chemistry: Fast Organic Synthesis in Microsystems*, Wiley-VCH, Weinheim, **2008**; b) A. Nagaki, J. Yoshida, *Microreactor Technology in Lithium Chemistry*, in *Lithium Compounds in Organic Synthesis: From Fundamentals to Applications*, R. Luisi, V. Capriati, Eds., Wiley-VCH, Weinheim, **2014**.
- [13] For reviews, see: a) J. Yoshida, Y. Takahashi, A. Nagaki, *Chem. Commun.* **2013**, *49*, 9896; b) J. Yoshida, *Chem. Rec.* **2010**, *10*, 332.
- [14] a) A. Nagaki, C. Matsuo, S. Kim, K. Saito, A. Miyazaki, J. Yoshida, *Angew. Chem. Int. Ed.* **2012**, *51*, 3245; *Angew. Chem.* **2012**, *124*, 7705; b) A. Nagaki, A. Kenmoku, Y. Moriwaki, A. Hayashi, J. Yoshida, *Angew. Chem. Int. Ed.* **2010**, *49*, 7543; *Angew. Chem.* **2010**, *122*, 3299; c) A. Nagaki, H. Kim, J. Yoshida, *Angew. Chem. Int. Ed.* **2008**, *47*, 7833; *Angew. Chem.* **2008**, *120*, 7951; d) H. Usutani, Y. Tomida, A. Nagaki, H. Okamoto, T. Nokami, J. Yoshida, *J. Am. Chem. Soc.* **2007**, *129*, 3046. For recent examples, see: e) H. Kim, K.-I. Min, K. Inoue, D. J. Im, D.-P. Kim, J. Yoshida, *Science* **2016**, *352*, 691; f) S. Laue, V. Haverkamp, L. Mleczko, *Org. Process Res. Dev.* **2016**, *20*, 480; g) A. Nagaki, K. Imai, S. Ishiushi, J. Yoshida, *Angew. Chem. Int. Ed.* **2015**, *54*, 1914; *Angew. Chem.* **2015**, *127*, 1934; h) A. Nagaki, D. Ichinari, J. Yoshida, *J. Am. Chem. Soc.* **2014**, *136*, 12245; i) J. A. Newby, D. W. Blaylock, P. M. Witt, J. C. Pastre, M. K. Zacharova, S. V. Ley, D. L. Browne, *Org. Process Res. Dev.* **2014**, *18*, 1211; j) J. A. Newby, D. W. Blaylock, P. M. Witt, R. M. Turner, P. L. Heider, B. H. Harji, D. L. Browne, S. V. Ley, *Org. Process Res. Dev.* **2014**, *18*, 1221.
- [15] D. L. Browne, M. Baumann, B. H. Harji, I. R. Baxendale, S. V. Ley, *Org. Lett.* **2011**, *13*, 3312.
- [16] a) M. R. Becker, P. Knochel, *Angew. Chem. Int. Ed.* **2015**, *54*, 12501; *Angew. Chem.* **2015**, *127*, 12681; b) M. R. Becker, M. A. Ganiek, P. Knochel, *Chem. Sci.* **2015**, *6*, 6649; c) M. R. Becker, P. Knochel, *Org. Lett.* **2016**, *18*, 1462.
- [17] a) B. Egle, J. M. Muñoz, N. Alonso, W. M. De Borggraeve, A. de la Hoz, A. Díaz-Ortiz, J. Alcázar, *J. Flow Chem.* **2014**, *4*, 22; b) N. Alonso, L. Z. Miller, J. M. Muñoz, J. Alcázar, D. T. McQuade, *Adv. Synth. Catal.* **2014**, *356*, 3737; c) G. A. Price, A. R. Bogdan, A. L. Aguirre, T. Iwai, S. W. Djuric, M. G. Organ, *Catal. Sci. Technol.* **2016**, *in press*.
- [18] See Supporting Information for detailed description.
- [19] a) R. L. Hartman, *Org. Process Res. Dev.* **2012**, *16*, 870; b) S. Kuhn, T. Noël, L. Gu, P. L. Heider, K. Jensen, *Lab Chip* **2011**, *11*, 3312; c) J. Sedelmeier, S. V. Ley, I. R. Baxendale, M. Baumann, *Org. Lett.* **2010**, *12*, 3618; d) T. Horie, M. Sumino, T. Tanaka, Y. Matsushita, T. Ichimura, J. Yoshida, *Org. Process Res. Dev.* **2010**, *14*, 405; e) R. L. Hartman, J. R. Naber, N. Zaborenko, S. L. Buchwald, K. F. Jensen, *Org. Process Res. Dev.* **2010**, *14*, 1347.
- [20] Absence of sonication led to clogging under the reported conditions.
- [21] E. Vitaka, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 10257.
- [22] a) C. Bobbio, M. Schlosser, *J. Org. Chem.* **2005**, *70*, 3039; b) M. Schlosser, M. Marull, *Eur. J. Org. Chem.* **2003**, 1569; c) G. W. Gribble, M. G. Saulnier, *Tetrahedron Lett.* **1980**, *21*, 4137.
-

Entry for the Table of Contents



Hey! Ho! Let's flow! A highly regioselective functionalization of fluoro- and trifluoromethyl-substituted arenes and pyridines under continuous flow conditions is described. This methodology telescopes a directed lithiation, a zincation, and a Negishi cross-coupling into a single process to provide diversely functionalized, pharmaceutically relevant biaryls.

S. Roesner, S. L. Buchwald*

Page No. – Page No.

**Continuous Flow Synthesis of Biaryls
by Negishi Cross-Coupling of Fluoro-
and Trifluoromethyl-Substituted
(Hetero)arenes**