Flow Chemistry

International Edition: DOI: 10.1002/anie.201605584
German Edition: DOI: 10.1002/ange.201605584

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

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Abstract: *A continuous-flow method for the regioselective arylation of fluoroarenes and fluoropyridines has been developed. The telescoped procedure 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 yields 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 their 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, 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.

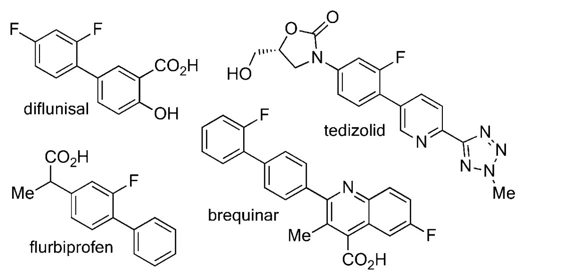
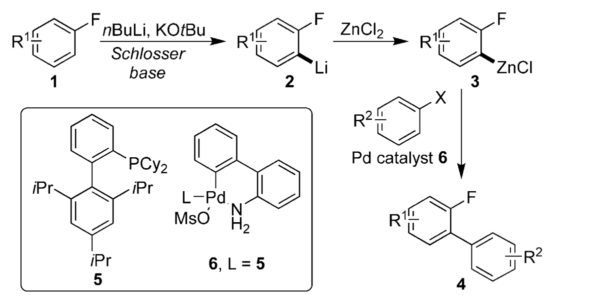


Figure 1. Examples of 2-fluorobiaryl-containing biologically active compounds.

This notion is exemplified through the development of several approaches to the synthesis of 2-fluorobiaryls. Beller and co-workers 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 and co-workers reported the insertion of arynes into the F−Sn bond of tributyltin fluoride to afford diverse 2-fluoroaryl stannanes, which could be further functionalized by using Stille couplings.[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



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

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/KO*t*Bu superbase 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]

Flow conditions offer a safe alternative to batch reactions whenever dangerous or unstable intermediates or reagents are involved.[10,11] Owing to the improved heat transfer in continuous-flow reactors, the temperature of exothermic organometallic reactions can be accurately controlled, thus providing scalable and reproducible processes. The utilization

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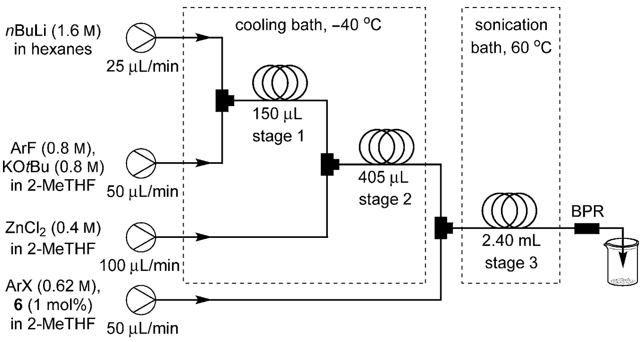
Supporting information for this article can be found under: http://dx.doi.org/10.1002/anie.201605584.

of organolithium species in continuous-flow synthesis was pioneered by Yoshida and co-workers.[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 compatibility.[13,14] Furthermore, modular cryo-flow reactors have been developed.[15] Knochel and co-workers recently reported the formation of (hetero)aryl zincates in flow followed by Negishi cross-coupling under batch conditions.[16] Aside from this semi-batch approach, a Negishi cross-coupling for the formation of C(sp^2)$-$C(sp^3) bonds under flow conditions has also been described.[17] Yet, the formation of biaryl compounds through Negishi couplings using continuous-flow 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]

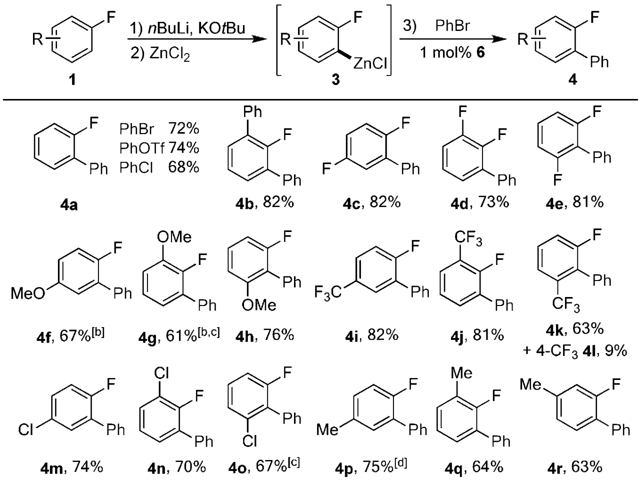


Scheme 2. Experimental setup for the synthesis of 2-fluorobiaryls by directed lithiation, zincation, and Negishi cross-coupling.

We found that intermediate **2** was stable up to -30 °C. Above this temperature, benzyne formation through LiF elimination took place, as indicated by a strong discoloration of the reaction mixture. 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 the clogging in stage 3, which is due to the 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. The biaryl products were obtained after aqueous workup and chromatographic purification.

Using the reaction setup described above (Scheme 2), the substrate scope was explored with a variety of fluoro-substituted arenes (Table 1). Aside from bromo-substituted arenes, aryl triflates and chlorides were also suitable cross-coupling partners. Subjecting **4a** to these reaction conditions

Table 1: Substrate scope of the C−C cross-coupling reaction between aryl fluorides and bromobenzene.[a]



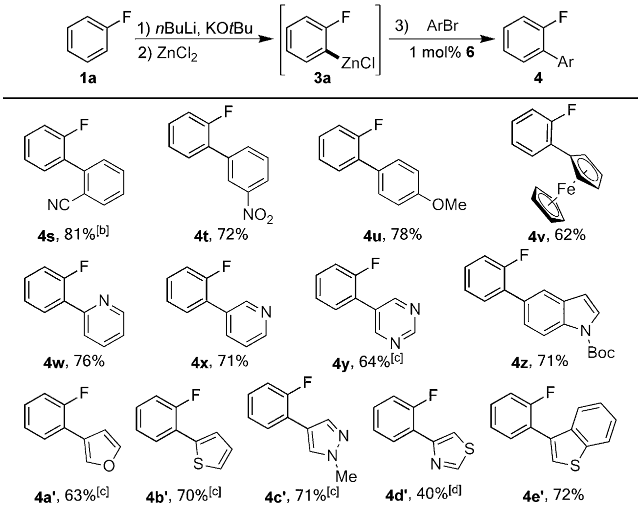
[a] 1.0 mmol scale; yields of isolated products are given (average of two runs). See the Supporting Information for details. [b] Yield of isolated product after conversion into the corresponding phenol. [c] Lithiation at -60 °C for 240 s. [d] Yield of isolated product on 5.0 mmol scale.

resulted in further arylation to provide triaryl compound **4b**. Difluoro-substituted arenes[7c] gave the desired biaryls in high yields (**4c**–**4e**). 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**–**4h** as single regioisomers. The same applied to the use of trifluoromethyl-substituted fluoroarenes (**4i**–**4k**).[7c] However, in the case of 3-fluorobenzotrifluoride, a small amount of the regioisomer **4l** was isolated, which is likely due to the steric hindrance at the *ortho* position next to the bulky CF_3 group. Chloro-substituted fluoroarenes[7f] were also suitable substrates, giving the desired biaryl products in good yield (**4m**–**4o**) without formation of either homocoupled or dechlorinated side products. Furthermore, fluoro-substituted toluene[7d] derivatives were well tolerated (**4p**–**4r**). In the case of 3-fluorotoluene, the methyl group directs the lithiation to the *para* position (**4r**), presumably for steric reasons.

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**–**4u**). Bromoferrocene could be employed under our reaction conditions to give **4v**. A variety of brominated heterocycles, including pyridine (**4w**, **4x**), 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 the product (Table 1, **4p**; Table 2, **4s**). These examples highlight the ease of scale-up in continuous-flow chemistry.

Next, we turned our attention to the arylation of fluoro-substituted pyridines. The regioselective *ortho* lithiation of

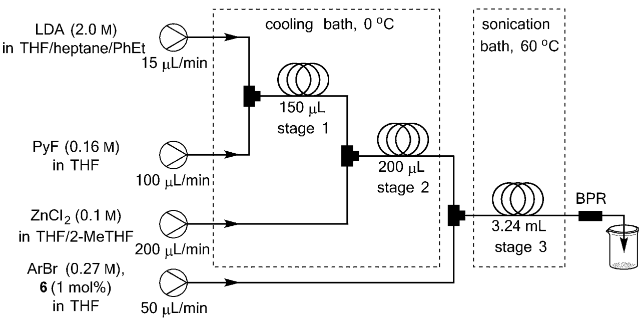
Table 2: Substrate scope of the C–C cross-coupling reaction between fluorobenzene and (hetero)aryl bromides.[a]



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

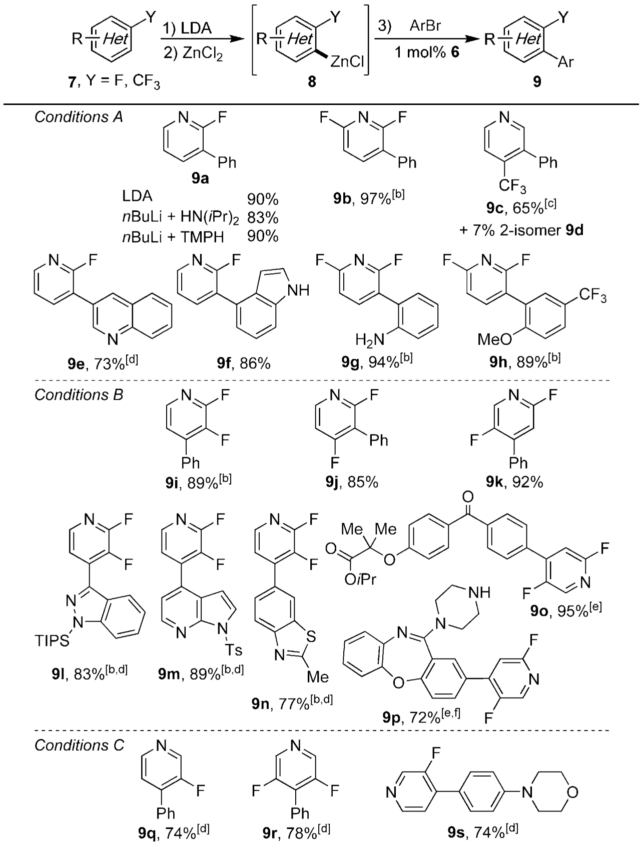
halopyridines with lithium diisopropylamide (LDA) and other amide bases is well established.[22] As pyridines are considerably more acidic than arenes, we were able to lithiate them under milder reaction conditions using LDA. However, we encountered significant salt formation after addition of zinc chloride. 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 the results previously obtained under 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.

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**–**9c**). Instead of a commercial LDA solution, the amide base could also be generated in situ from *n*BuLi solution and diisopropylamine.[18] Furthermore, 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**, **9h**) performed well in the cross-coupling reaction under these conditions.



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

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



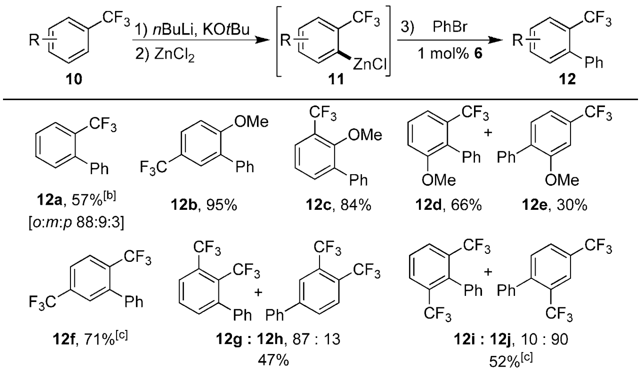
[a] 0.5 mmol scale; yields of isolated products are given (average of two runs). See the Supporting Information for details. [b] Lithiation at −10 °C. [c] Lithiation at −20 °C. [d] Catalyst loading: 2 mol%. [e] ArCl as the cross-coupling partner. [f] Catalyst loading: 4 mol%.

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^{-1} to avoid clogging (conditions B).[18] Coupling with bromobenzene provided regioisomerically pure products in excellent yield in all three cases (**9i**–**9k**). 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 method, 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.

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 equiv 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 $\mu L\,min^{-1}$ (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**–**9s**) were cross-coupled with **8** in synthetically useful yields.

In addition to the 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*BuLi/KO*t*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

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



[a] 1.0 mmol scale; yields of isolated products are given (average of two runs). See the Supporting Information for details. [b] Catalyst loading: 2 mol%. [c] Lithiation at −60 °C.

ortho-selective, and small amounts of the *meta*- and *para*-coupled products were also generated. Nevertheless, the 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 mixtures of regioisomers (**12g**–**12j**).

In summary, we have developed a highly regioselective arylation of fluoro- and trifluoromethyl-substituted arenes and pyridines under continuous-flow conditions. A directed lithiation, a zincation, and a Negishi cross-coupling were telescoped into a single process. This sequence constitutes 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 Novartis International AG for funding and are grateful to Dr. Benjamin Martin, Dr. Berthold Schenkel, and Dr. Gerhard Penn for helpful discussions. We thank Dr. Yi-Ming Wang, Dr. Mycah Uehling, and Dr. Christine Nguyen for assistance with the preparation of this manuscript.

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

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 10463–10467
Angew. Chem. **2016**, *128*, 10619–10623

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Received: June 8, 2016
Revised: June 17, 2016
Published online: July 26, 2016

