Arylation of Pyridines via Suzuki–Miyaura Cross-Coupling and Pyridine-Directed C–H Activation Using a Continuous-Flow Approach

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Dedicated to Professor Manfred Schlosser who is missing in the Swiss alps he loved so much

Abstract: Suzuki–Miyaura cross-coupling reactions between heteroaryl bromides and arylboronic acids were performed employing a continuous-flow approach using a simple flow reactor designed in-house. $Pd(PPh_3)_4$ was used as catalyst, and arylboronic acids containing both electron-withdrawing and electron-donating groups were applied. The coupling process required 23 minutes of residence time to be completed and generally good yields were obtained. Subsequent arylation of 2-phenyl pyridine was carried out via a C–H activation strategy using substituted bromobenzene compounds and a ruthenium(II) catalyst. To the best of our knowledge in this work we present for the first time the possibility of performing intermolecular C–H activation in a continuous-flow system.

Key words: heterocycles, cross coupling, flow chemistry, C–H activation, catalysis

The formation of arylated heterocycles is a process of great importance due to their presence in molecules with interesting biological activities or interesting properties in material science.[1] To synthesize such compounds, the Suzuki–Miyaura cross-coupling reaction is a very successful method and is considered as a general and versatile protocol for the formation of C–C bonds.[2] Beneficial features are the stability of the boronic acids towards moisture and air as well as the comparatively low toxicity of byproducts. Many examples of Suzuki–Miyaura reactions have been reported in the literature using standard batch conditions. Recently, significant scientific interest has been raised to further develop this strategy in a process-friendly fashion.[3]

Maria Christakakou (left) received her degree in chemistry from Aristotle University of Thessaloniki and then she continued her studies with a Master of Science in Chemical Research under the supervision of Professor Laurence Harwood. After the completion of her master thesis she joined Professor's Marko Mihovilovic group as a research assistant and subsequently continued with a PhD thesis under his supervision. Her research project aims at the development of synthetic small molecules (SSMs) which have the ability to convert an easily accessible cell type, for example, a muscle cell, into nerve cells or neurons. The aforementioned compounds shall be synthesized via continuous-flow chemistry to allow rapid library generation.

Michael Schön (middle left) was born in Vienna (Austria) in 1984. He finished his diploma studies in 'Synthesis of pharmaceutically relevant, disubstituted 5-membered heterocycles' at the University of Applied Sciences for Biotechnology (FH Campus Vienna) in 2007. In 2008, he started at Vienna University of Technology, synthesizing colchicine derivatives. From January 2009 on, he is working on his PhD thesis in the group of Prof. Marko D. Mihovilovic conducting research in the field of furan derivatives from renewable carbohydrate sources. During his work, implementation of flow chemistry methods and custom reactor design play a major role.

Michael Schnürch (middle right) was born in Klagenfurt, Austria in 1978. He started to study chemistry in Vienna in 1996 and carried out his diploma and PhD thesis in the group of Professor Peter Stanetty. In 2005 he received his PhD from Vienna University of Technology (VUT). During his PhD studies, he was on a four-month sabbatical in Canada where he worked in the group of Professor Victor Snieckus at Queens University (Kingston, Ontario). He was then postdoc with Professor Dalibor Sames at the Columbia University in New York City (as Erwin Schrödinger fellow) and conducted research in the field of decarboxylative arylation reactions of sp^3 centers. After his return, he became full university assistant at VUT. He was granted a noteworthy research grant by the Austrian Science Foundation (FWF) which allows him to carry out independent research in the field of asymmetric C–H activation. Additionally, he is about to defend his habilitation to become assistent professor. His research interests are located in the field of synthesis of heterocyclic compounds for the manipulation of cell differentiation, asymmetric C–H activation, green chemistry, and flow chemistry.

Marko D. Mihovilovic (right) was born in Steyr, Upper Austria, Austria in 1970. He is married to Dr. Barbara Krumpak-Mihovilovic (14.7.2001) and has two children, Gregor and Martin. After the A-levels in Linz, he started to study Technical Chemistry/Organic Chemistry in 1988 at the Vienna University of Technology (VUT), Vienna, Austria. His diploma thesis was entitled 'Synthesis of Thieno[2,3-*d*]thiadiazole Derivatives' and was supervised by Professor Peter Stanetty. He started his PhD thesis in 1994 ('Synthesis of Azasteroid Partial Structures as Potential Inhibitors of the Ergosterol Biosynthesis') again in the group of Professor Peter Stanetty and finished this work in June 1996. From 1994 to 1998 he was research assistant at the Institute of Organic Chemistry (IOC). He was then on two postdoctoral stays as Erwin Schrödinger Fellow of the FWF (Project no. J1471-CHEM 'Designer Yeasts – New Bioreagents in Enantioselective Synthesis') with Professor Margaret M. Kayser, University of New Brunswick, Saint John, N.B., Canada and Professor Jon D. Stewart, University of Florida, Gainesville, Florida, USA. From 1999 to 2003 he was again university assistant at the Institute of Applied Synthetic Chemistry (IAS, former IOC), VUT. In November 2003 he received his habilitation (venia docendi) in the field of bioorganic chemistry and was promoted to 'University Dozent' (assistant professor) at the IAS, VUT. Since March 2004 he is associate university professor at the IAS, VUT. In May 2008 he declined the appointment to full professor in bioorganic chemistry at Johannes Kepler University Linz, Austria. From 2009 up to now he coordinates the graduate school program *AB-Tec* (Applied Bioscience Technology) at Vienna University of Technology. Since January 2013 he is the head of institute at the Institute of Applied Synthetic Chemistry (Vienna University of Technology, Vienna, Austria).

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In this regard, continuous-flow chemistry has gained increasing recognition in the synthetic community due to several advantages such as rapid optimization of reaction conditions, easy scale up, high reaction rates, efficient heat transfer, and potential automation.[4] The latter point is of particular interest to the pharmaceutical industry since it enables accelerated synthesis of diverse compound libraries leading to more time-efficient structure–activity relationship studies. Furthermore, performing reactions in flow provides an inherently safer process which has many additional advantages such as increased surface-to-volume ratios, excellent mass and heat transfer capabilities, facile scale-up, and eventually even higher product yields.[5] Several examples for cross-coupling reactions in continuous flow have been reported to date.[6]

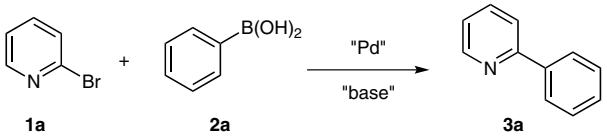
Within this work, our efforts were focused on synthesizing several arylated pyridines and further decorating these products via C–H activation chemistry taking advantage of an in-house developed continuous-flow reactor system. Recently, C–C bond formation via C–H activation has stirred much attention since these transformations allow direct use of a C–H bond for the C–C coupling step.[7] To the best of our knowledge this is the first example of a intermolecular direct arylation reaction under continuous-flow conditions since only one intramolecular example was disclosed, so far.[8]

We began our investigation optimizing the reaction conditions for the Suzuki–Miyaura coupling of 2-bromopyridine (**1**) and phenylboronic acid (**2a**). Since the reactions should be carried out in continuous flow ultimately, it had to be assured that the reaction solution is homogeneous at all times at room temperature. This is a prerequisite since before and after the heated reaction zone the tubing is at room temperature. Hence, we conducted several batch experiments with microwave irradiation initially, using different catalysts, bases, solvents, and temperatures in order to identify conditions enabling a transfer of the procedure to continuous flow without clogging the system. Selected screening results are summarized in Table 1 (for a complete list see Supporting Information). In all cases biphenyl and bipyridine were observed as side products (see Supporting Information). It has to be mentioned that in the initial series of batch experiments encapsulated palladium catalysts were used since such heterogeneous catalysts could be packed in a cartridge eventually. However, when such a method was used in flow significant palladium leaching occurred and this approach was abandoned.

We screened two different catalysts, $Pd(PPh_3)_4$ and $Pd(OAc)_2$, three different bases, K_3PO_4, Cs_2CO_3, and K_2CO_3 with 180 seconds hold time. $Pd(OAc)_2$ performed significantly worse than $Pd(PPh_3)_4$. The different bases showed only negligible differences in conversion. Overall, we observed the best relation between conversion, homogeneity, and reaction time using the conditions shown in Table 1, entry 6.

Transferring these conditions to a flow process required a second round of optimization in order to adjust the protocol to the respective flow system. Initially, it was tried to use an immobilized palladium catalyst in a prepacked cartridge but due to significant leaching of the catalyst and concomitant lower conversion over time this approach was abandoned early on.

Table 1 Screening Conditions for Palladium-Catalyzed Suzuki–Miyaura Cross-Coupling Reactions between 2-Bromopyridine (**1**) and Phenyl Boronic Acid (**2a**)



1a **2a** **3a**

Entry[a]	Base	[Pd][b]	Conv. (%)[c]
1	K_3PO_4	$Pd(OAc)_2$	45
2	K_3PO_4	$Pd(PPh_3)_4$	82
3	Cs_2CO_3	$Pd(OAc)_2$	52
4	Cs_2CO_3	$Pd(PPh_3)_4$	90
5	K_2CO_3	$Pd(OAc)_2$	35
6	K_2CO_3	$Pd(PPh_3)_4$	92

Alternatively we used a flow system designed in our laboratory consisting of one (or potentially more) syringe pump(s) and an aluminum reactor. The reactor is wrapped around with a coil which can be of different materials such as steel or perfluoroalkoxy (PFA). The reactor is placed on top of a hot plate (see Supporting Information) in order to adjust to the required temperature. The syringe pump is connected with the reactor through the coil. This system allows performing reactions with ease in flow when it is not required to pressurize a reaction mixture. Early on $Pd(PPh_3)_4$ was identified as best performing catalyst and hence it was chosen for further optimization of the reac-

Table 2 Optimization in Flow[a]

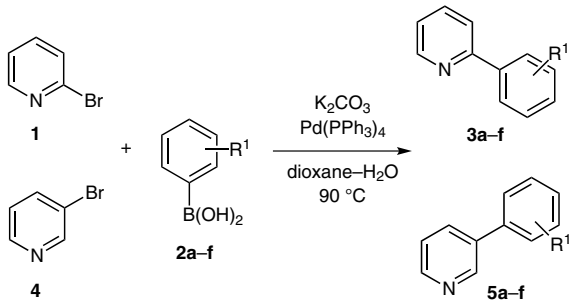
Entry	Catalyst load (mol%)	Flow rate (mL/min)	Residence time (min)	Conv. (%)[b]
1	0.35	0.5	8	30
2	0.35	0.5	23	40
3	1.05	0.5	23	59
4	1.4	0.5	23	63
5	1.7	0.5	23	80
6	2.1	0.5	23	82

[a] Reaction conditions: **1** (1equiv), **2a** (1.2 equiv), K_2CO_3, $Pd(PPh_3)_4$, dioxane–H_2O (1:1), 90 °C, 0.05 M; steel coil.
[b] As determined by GC using dodecane as internal standard.

tion conditions in flow (Table 2) under homogeneous conditions.

Starting with low catalyst loading (0.35 mol%) and a residence time of eight minutes gave only 30% conversion (Table 2, entry 1). Extending the reaction time to 23 minutes gave only a minor improvement to 40% (Table 2, entry 2). However, increasing the catalyst loading to an amount of 2.1% ultimately gave a satisfying conversion of 82% (Table 2, entry 6). These conditions are a good compromise between catalyst loading and flow rate and, hence, subsequent substrate-scope investigations were performed using this protocol. It has to be mentioned that the process in flow takes significantly longer than the batch experiment. This can be attributed to a difference in temperature eventually: temperature measurement in microwave is usually very accurate. In the flow process we measure the temperature of our aluminum block but cannot measure the temperature inside the coil. Hence there could be a significant difference. Additionally, a higher temperature at the metal center in microwave cannot be excluded due to the better microwave absorbing capacity of the metal compared to the solvent.

Then, 2-bromopyridine and 3-bromopyridine were coupled with various boronic acids bearing electron-donating or electron-withdrawing groups (Scheme 1). We were also interested to investigate if the material of the coil had any influence on reaction performance. Therefore we conducted experiments either using a steel coil or a PFA coil and in some cases both for comparison. The advantage of the PFA coil is the easier handling and the lower price (approx. 40% less) and easier to wash and unclog when it is necessary.



Scheme 1 Suzuki reaction with 2-bromopyridine and 3-bromopyridine with arylboronic acids in dioxane–H_2O (1:1). *Reagents and conditions*: (a) **1** (1equiv), **2a** (1.2 equiv), K_2CO_3, $Pd(PPh_3)_4$, dioxane–H_2O (1:1), 90 °C, 0.05 M. (b) As determined by GC using dodecane as internal standard.

Table 3, entries 1–4 show the coupling reaction of **1** with phenylboronic acid (1.2 or 3.0 equiv) in both coil materials. It can be seen that when 1.2 equiv of boronic acid were used the results are comparable for both coil materials (Table 3, entries 1 and 3). However, when 3.0 equiv boronic acid were used the PFA coil performed significantly better.

Electron-donating substituents on the boronic acids gave generally better yields. This is also true for sterically hindered *o*-tolylboronic acid (**2c**) where 91% yield were obtained in the PFA coil (Table 3, entry 9). *p*-Methoxyphenylboronic acid (**2d**) gave a good yield already in the steel coil (Table 3, entries 10 and 11). 3-Nitrophenylboronic acid (**2e**) gave a low yield of 12% in the steel coil using 1.2 equivalents of **2e** (Table 3, entry 12). Increasing this to 3.0 equivalents improved the yield to 51% (Table 3, entry 13). A comparable yield was obtained in the PFA coil with 1.2 equivalents of **2e** already (Table 3, entry 14). 3-Cyanophenylboronic acid (**2f**) gave an acceptable yield only in the PFA coil and 3.0 equivalents of **2f** (Table 3, entry 19).

Using **4** as substrate in combination with **2a** gave the best results using 3.0 equivalents of **2a** and the PFA coil (80%, Table 3, entry 23). Hence, all subsequent coupling reactions on **4** were carried out under these conditions. Best tolerated were methyl substituents no matter whether in 2- or 4-position of the boronic acid (Table 3, entries 24 and 25). 4-Methoxy-, 3-nitro-, and 3-cyanophenylboronic acids gave similar yields just below 60% (Table 3, entries 26–28).

Comparing results using the steel and the PFA coil material it was found that PFA performed significantly better. The overall better performance of the PFA coil could be due to the fact that the metal coil might undergo metal–metal interactions with the metal center of our palladium catalyst resulting in decreased catalyst activity. However, for a detailed explanation more experiments would be necessary (e.g., analyzing the inner surface of the steel coil) which was beyond the scope of this work.

Besides Suzuki–Miyaura coupling, we were also interested in direct arylation reactions under continuous flow. Due to the ubiquity of C–H bonds, their use as a 'functional group' has been explored in recent years by an increasing number of research groups.[9] One common substrate for direct functionalization reactions is 2-phenylpyridine where the pyridine nitrogen directs the catalyst in *ortho* position of the adjacent phenyl ring.[10] Since we could efficiently synthesize this compound with our flow process, we decided to investigate its further application in C–H activation chemistry, also via a continuous-flow approach. To the best of our knowledge there is no literature precedence for direct intermolecular arylation in continuous-flow systems. Recently, one example of intramolecular direct arylation of aryl bromides was reported.[8] Syringe pumps were used as the preferred flow system, and ultrasound irradiation was employed for avoiding clogging of the microreactors due to a precipitate formed during the experiment, a technique applied previously by Buchwald and Jensen.[11]

Table 3 Suzuki Reaction with 2-Bromopyridine and 3-Bromopyridine with Arylboronic Acids in Dioxane–H_2O (1:1) and 2.1 mol% Catalyst Loading

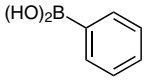
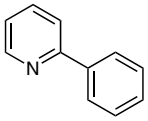
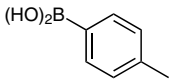
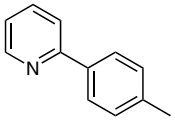
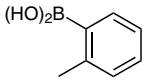
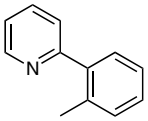
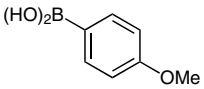
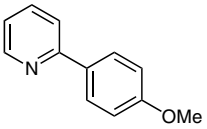
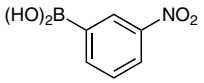
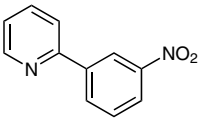
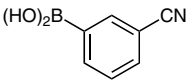
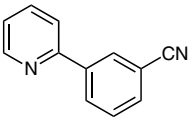
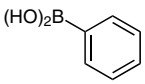
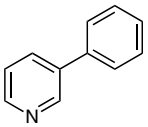
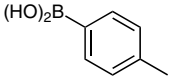
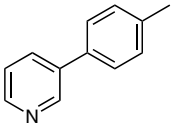
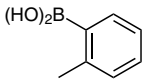
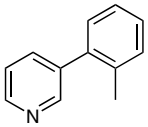
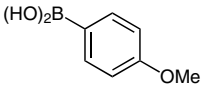
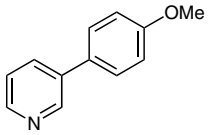
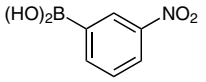
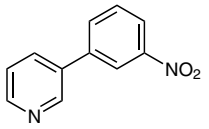
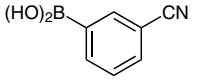
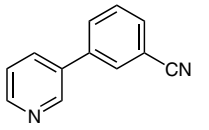
Entry	Substrate	Boronic acid	Boronic acid (equiv)	Coil type	Product	Yield (%)
1	**1**	 **2a**	1.2	steel	 **3a**	64
2	**1**		3.0	steel		76
3	**1**		1.2	PFA		68
4	**1**		3.0	PFA		93
5	**1**	 **2b**	1.2	steel	 **3b**	60
6	**1**		3.0	steel		61
7	**1**	 **2c**	1.2	steel	 **3c**	62
8	**1**		3.0	steel		64
9	**1**		1.2	PFA		91
10	**1**	 **2d**	1.2	steel	 **3d**	85
11	**1**		3.0	steel		89
12	**1**	 **2e**	1.2	steel	 **3e**	12
13	**1**		3.0	steel		51
14	**1**		1.2	PFA		44
15	**1**		3.0	PFA		45
16	**1**	 **2f**	1.2	steel	 **3f**	4
17	**1**		3.0	steel		6
18	**1**		1.2	PFA		24
19	**1**		3.0	PFA		45
20	**4**	 **2a**	1.2	steel	 **5a**	18
21	**4**		3.0	steel		53
22	**4**		1.2	PFA		64
23	**4**		3.0	PFA		80
24	**4**	 **2b**	3.0	PFA	 **5b**	87
25	**4**	 **2c**	3.0	PFA	 **5c**	75

Table 3 Suzuki Reaction with 2-Bromopyridine and 3-Bromopyridine with Arylboronic Acids in Dioxane–H_2O (1:1) and 2.1 mol% Catalyst Loading (continued)

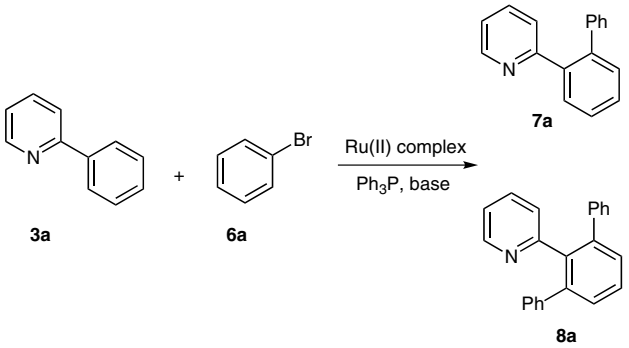
Entry	Substrate	Boronic acid	Boronic acid (equiv)	Coil type	Product	Yield (%)
26	**4**	 **2d**	3.0	PFA	 **5d**	58
27	**4**	 **2e**	3.0	PFA	 **5e**	58
28	**4**	 **2f**	3.0	PFA	 **5f**	56

Prerequisites for direct arylation in flow are of course the same as for cross-coupling, most importantly homogeneity of the reaction solution at all times. Initially, we wanted to use a palladium catalyst as well since then it would be possible to combine both reaction steps in a single operation potentially. When testing literature-known palladium-catalyzed protocols[12] it turned out that they did not result in homogeneous solutions and, additionally, reaction times of 24 hours were required in batch; far too long for a useful continuous-flow process. Therefore, we abandoned palladium-catalyzed methods and decided to switch to ruthenium catalysts which have been used in many C–H activation protocols effectively.[13]

Again we started screening for homogeneous reaction conditions. A promising method was reported by Oi et al.[14,15] where NMP was used as solvent, benzeneruthenium(II) chloride dimer as catalyst, and K_2CO_3 as a base at 120 °C for 20 hours. Even though the base is insoluble in this case, NMP allows increasing the reaction temperature and shorten the reaction time below one hour simultaneously. The initial screening was conducted with **3a** as substrate, bromobenzene **6a** as aryl source, and different bases under microwave irradiation (Scheme 2). Additionally, different temperatures and ruthenium(II) catalysts were tested (see Supporting Information for details).

We found that both catalysts investigated, benzeneruthenium(II) chloride dimer and dichloro(*p*-cymene)ruthenium(II) gave almost identical results in terms of conversion. Since the latter is significantly cheaper we continued further optimization using this catalyst.

Furthermore we observed no difference under inert conditions (as used by Oi et al.) or under air. Therefore all screening reactions as well as compound syntheses have been carried out under air.



Scheme 2 Ruthenium-catalyzed *ortho* arylation of 2-phenyl pyridine with bromobenzene

The biggest issue was the bad solubility of the base. We tested several bases. Some of them were the following: K_2CO_3, Cs_2CO_3, NaOH, KOAc, KO*t*-Bu, and NaO*t*-Bu. With Cs_2CO_3 we received promising GC yields of **7a** and **8a** (MW, 1.5 equiv of bromobenzene, 2 equiv of the base, 120 °C, 30 min, 74% GC yield), but the reaction mixture was not homogeneous and when adding various amounts of water to dissolve the base a significant drop of the GC yield was observed. In other solvents such as DMF, anisole, or mixtures of NMP–EtOAc, the base was not soluble at all (see Supporting Information).

When KO*t*-Bu and NaO*t*-Bu were used, we observed better solubility but again a significant drop of the GC yield to only 2–3%. Using NaOH or KOAc gave inhomogeneous solutions as well.

Changing to an organic base such as DABCO or Hünig's base solved the solubility issue but led again to a significant drop in yield (1–3% GC yield). Attempts to improve solubility by changing the concentration did not help either.

The breakthrough came by switching to DBU where we obtained a homogeneous solution which we used for further optimization in flow. We performed several screenings regarding equivalents of bromobenzene, DBU, catalyst loading, and a synopsis of the most important results is provided in Table 4 (for a more comprehensive table see Supporting Information). In all cases we found that mixtures of **7a** and **8a** were formed. However, for the optimization we looked at overall conversion and yield.

Table 4 Optimization in Flow[a]

Entry	Aryl source (equiv)	DBU (equiv)	Cat. load (mol%)	GC yield of **7a** + **8a** (%)[b]
1	1.5	1	2.5	29
2	1.5	2	2.5	35
3	1.5	4	2.5	55
4	3	4	2.5	58
5	3	4	5	89

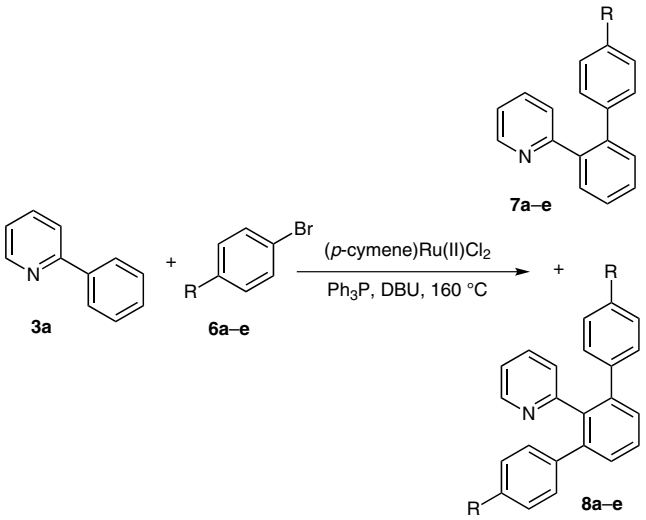
[a] Reaction conditions: DBU, dichloro(*p*-cymene)ruthenium(II)chloride dimer, 10 mol% Ph_3P, NMP, 0.25 M, 30 min residence time, 160 °C.
[b] As determined by GC using dodecane as internal standard.

One equivalent of DBU gave 29% GC yield of **7a** and **8a** (Table 4, entry 1). Increasing the amount up to four equivalents gave an improvement to 55% (Table 4, entry 3). Increasing the catalyst loading to 5% and the equivalents of bromobenzene to three finally gave a good GC yield of 89% of **7a** and **8a** (Table 4, entry 5). Next we tried to transfer these conditions to a continuous-flow process.

Applying the optimized conditions (Table 3, entry 5), we were able to isolate **7a** in 26% and **8a** in 69% yield, respectively (ratio 1:2.65). This result differs from Oi's findings where a total yield of 82% of the same two products was obtained but in favor of the monoarylated one (6.7:1). However, in his case only one equivalents of bromobenzene was used. Using 2.2[14] or 3.0[15] equivalents, **8a** was formed exclusively. Of course a different base was applied which can be responsible for the observed differences.

The electronic nature of the halide had a significant influence on the product distribution (Scheme 3). Electron-rich bromoanisole gave exclusively the monoarylated product **7b** (59%, Table 5, entry 2). Bromotoluene favored the formation of bisarylated **8c** over monoarylated **7c** (1:2, Table 5, entry 3). When an electron-withdrawing substituent was present as in 4-bromo-trifluoromethylbenzene, the bisarylated product was massively favored (1:23.7) with good overall yield (Table 5, entry 4). A nitro group was not tolerated (Table 5, entry 5), however, this we have observed in ruthenium-catalyzed arylations previously and can be attributed to the ability of the nitro group to coordinate to ruthenium leading to catalyst inactivation.[16]

Overall these results show that an increase in electron density favors monoarylation and vice versa.



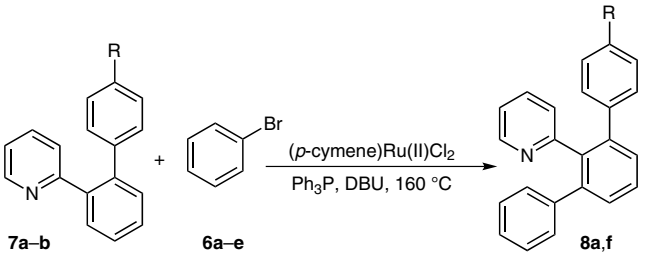
Scheme 3 Arylation of 2-phenylpyridine (**3a**) with substituted bromobenzenes

Table 5 Isolated Yields[a]

Entry	R	**7a**–**e** (%)	**8a**–**e** (%)	Combined yield (%)
1	**6a** H	26	69	95
2	**6b** OMe	59	0	59
3	**6c** Me	17	34	51[b]
4	**6d** CF_3	3	71	74
5	**6e** NO_2	0	0	0

[a] Reaction conditions: aryl source (3 equiv), DBU (4 equiv), 5 mol% catalyst, 10 mol% Ph_3P, NMP, 0.25 M, 30 min residence time, 160 °C.
[b] For this example we isolated an inseparable mixture of the mono- and bisarylated product and the ratio of mono- to bisphenylated product was determined as 1:2 by NMR analysis.

Next, we aimed at the synthesis of bisarylated compounds bearing two different aryl substituents. Monoarylated products **7a** and **7b** were used as starting materials for a second arylation step with bromobenzene (Scheme 4).



8a: R = H 44% (5 mol% cat.)
8f: R = OMe 24% (7.5 mol% cat.)

Scheme 4 Arylation of the monophenylated product with bromobenzene

To our surprise the yield of **8a** (Scheme 4) was significantly lower starting from **7a** (44%) compared to the reaction starting from 2-phenylpyridine (**3a**). The reason for this observation is not clear. A possible explanation is that after the insertion of the Ru(II) into the C–H bond and the first arylation, ruthenium stays coordinated to the pyridine nitrogen (to some extent) leading to a second arylation rapidly. However, when the substrate is the already monosubstituted compound **7a** the phenyl group exhibits steric hindrance, and precoordination of ruthenium to the pyridine nitrogen might be more difficult and hence the reaction might be slower overall. Since at 160 °C catalyst decomposition/inactivation is also an issue, a lower reaction rate will give lower yields. By increasing the catalyst loading to 7.5 mol% we received 59% yield which is in agreement with our explanation. In order to support our hypothesis further, we performed a time course for the arylation of **3a** with bromobenzene. If the catalyst dissociates from pyridine completely after the first arylation step we should see accumulation of **7a** at the beginning and only small amounts of **8a**. When the concentration of **7a** increases and simultaneously that of **3a** decreases, **7a** becomes the preferred substrate and the amount of **8a** will increase. However, if our hypothesis is true, we should see formation of **8a** to a similar extent compared to **7a** already from the beginning and no accumulation of **7a**. Indeed, **8a** is the major product from the very beginning (Table 6, entries 1–5) which supports our line of argument.

We also subjected **7b** to a second arylation step. From the previous result (Table 5, entry 2), it can be expected that arylation of **7b** might be difficult and slow. Indeed, a yield of only 24% was obtained (with 7.5 mol% catalyst) which underlines the importance of electronic effects on the aryl substituents.

Table 6 Time Course

Entry	Time (min)	**7a** (%)[a]	**8a** (%)[a]
1	5	33	45
2	10	30	62
3	20	20	76
4	30	15	82
5	60	9	88

[a] Conversion as determined by GC using dodecane as internal standard.

Overall, we have synthesized a series of Suzuki–Miyaura coupling products employing the efficient and robust technology of a continuous-flow system, using a reactor designed in-house and $Pd(PPh_3)_4$ as cheap catalyst. The low cost required for the production of the reactor and its simple design makes it readily available to synthetic chemists (construction plans are provided in the Supporting Information). Suzuki–Miyaura coupling products of pyridine bromides and arylboronic acids containing both electron-donating and electron-withdrawing groups were obtained in good yields and within 23 minutes residence time.

Furthermore, to the best of our knowledge, in this work we present for the first time the possibility of performing metal-catalyzed C–H activation, using a continuous-flow process in an intermolecular fashion. Both transformations are operationally simple since they do not require inert techniques making them user-friendly and effective at the same time.[17]

Acknowledgment

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(17) **Preparation of 2-Aryl- and 3-Aryl Derivatives 3a–f and 5a–f**

To a round-bottomed flask was added the appropriate amount of 2-bromo- or 3-bromopyridine (**1** or **4**, 1 equiv, 1 mmol), boronic acid **2a**–**f** (1.2 equiv, 1.2 mmol), K_2CO_3 (2 equiv, 276 mg, 2 mmol), $Pd(PPh_3)_4$ (2.1 mol%, 24 mg, 0.021 mmol), and a dioxane–H_2O mixture as solvent (1:1, 20 mL). The mixture was stirred for 5 min at r.t. and was then filtered through filter paper, before being transferred to the syringe pump. The residence time was 23 min, and the temperature of the heating plate was set to 90 °C. The inner diameter of the capillary was 1 mm. The flow rate was 0.695 mL/min, and the volume of the reactor was 16 mL.

Reference NMR Spectra for 2-(4-methoxyphenyl)-pyridine (3d)

^{1}H (200 MHz $CDCl_3$): δ = 3.86 (s, 3 H), 6.95–7.05 (m, 2 H), 7.13–7.23 (m, 1 H), 7.62–7.79 (m, 2 H), 7.90–8.01 (m, 2 H), 8.60–8.71 (m, 1 H). ^{13}C (50 MHz, $CDCl_3$): δ = 55.5 (q), 114.3 (d), 120.0 (d), 121.6 (d), 128.3 (d), 132.1 (s), 136.9 (d), 149.6 (d), 157.2 (s), 160.6 (s).

Preparation of ortho-Arylated 2-Phenylpyridine Derivatives 7a–e, 8a–f

To a round-bottomed flask was added the appropriate amount of 2-arylpyridine derivative **7a** or **7b** (1 equiv, 0.25 mmol), the appropriate bromobenzene derivative **6a**–**e** (3 equiv, 0.75 mmol), DBU (4 equiv, 152 mg, 1 mmol), Ph_3P (10 mol%, 6.5 mg, 0.025 mmol), dichloro(p-cymene)ruthenium(II) dimer [5 mol%, 7.6 mg, 0.0125 mmol; with the exception of the synthesis of **8f**, in which 7.5 mol% of dichloro(p-cymene)ruthenium(II) dimer were used (7.5 mol%, 11.5 mg, 0.01875 mmol) and NMP as solvent (1 mL)]. The mixture was stirred at r.t. until complete dissolution of all reagents. Then this solution was transferred to the syringe pump system. The flow rate was set to 0.533 mL/min which corresponded to a residence time of 30 min, and the temperature of the heating plate was set to 160 °C. After pumping through the reaction mixture, 20 mL pure solvent was pumped through as well. The inner diameter of the capillary was 1 mm. The volume of the reactor was 16 mL.

Reference NMR spectra for 2-[4′-methoxy-(1,1′-biphenyl)-2-yl]pyridine (7b)

^{1}H (200MHz, $CDCl_3$): δ = 3.78 (s, 3 H), 6.72–6.82 (m, 2 H), 6.90 (dt, J = 7.8, 1.0 Hz, 1 H), 7.01–7.15 (m, 3 H), 7.33–7.50 (m, 4 H), 7.61–7.73 (m, 1 H). ^{13}C (50 MHz, $CDCl_3$): δ = 55.3 (q), 113.7 (d), 121.4 (d), 125.6 (d), 127.4 (d), 128.6 (d), 130.6 (d), 130.6 (d), 130.9 (d), 133.8 (s), 135.4 (d), 139.5 (s), 140.3 (s), 149.6 (d), 158.6 (s), 159.6 (s).

