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Citation for published version (APA):
Gemoets, H. P. L., Laudadio, G., Verstraete, K., Hessel, V., & Noël, T. (2017). A modular flow design for the meta-selective C-H arylation of anilines. Angewandte Chemie - International Edition, 56(25), 7161-7165. https://doi.org/10.1002/anie.201703369

DOI:
10.1002/anie.201703369

Document status and date:
Published: 12/06/2017

Document Version:
Publisher’s PDF, also known as Version of Record (includes final page, issue and volume numbers)

Please check the document version of this publication:

• A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
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A Modular Flow Design for the meta-Selective C–H Arylation of Anilines

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Abstract: Described herein is an effective and practical modular flow design for the meta-selective C–H arylation of anilines. The design consists of four continuous-flow modules (i.e., diaryliodonium salt synthesis, meta-selective C–H arylation, inline copper extraction, and aniline deprotection) which can be operated either individually or consecutively to provide direct access to meta-arylated anilines. With a total residence time of 1 hour, the desired product could be obtained in high yield and excellent purity without the need for column chromatography, and the residual copper content meets the standards for parenterally administered pharmaceutical substances.

Site-selective C–H bond functionalization strategies are of paramount importance in modern organic synthesis.[1] However, because of the ubiquitous presence of C–H bonds in organic molecules, the regioselective assembly of substituted arenes remains a major challenge. Traditionally, the ortho and, to some extent, the para substitution of arenes have been thoroughly explored with the use of Friedel–Crafts chemistry. More recently, much work has been carried out on the transition metal catalyzed ortho-functionalization of arenes, and it proceeds by a cyclometalation strategy.[2] In contrast, the development of meta-selective transformations has required much more scientific investigation. Besides traditional approaches which rely on tuning steric and electronic properties of aromatic substrates, novel robust catalytic strategies have emerged.[3] For example, the incorporation of directing-group templates[4] or the use of transient ligand mediators[5] (e.g., Pd/norbornene) have been exploited to carefully navigate transition metals to the meta-position.

Among the reported meta-selective C–H functionalization strategies, the meta-arylation of electron-rich arenes is of high interest to access novel biaryl motifs, which represent a common moiety within medicines, agrochemicals, and functional materials.[6] In particular, Gaunt and co-workers first reported the meta-selective C–H arylation of protected anilines.[7] This transformation was believed to proceed via a highly electrophilic Cu(II)/aryl intermediate, obtained from CuI, and in presence of diaryliodonium salts as both oxidant and arylation agent.[8] However, despite being shelf-stable, nontoxic, and synthetically useful, diaryliodonium salts have limited availability and are expensive.[9] The main cause is associated with its cumbersome preparation. Hereeto, stoichiometric amounts of hazardous reagents (e.g., mCBPA and TIOH) are necessary to oxidize iodine to its hypervalent state (i.e., I(IV)) and the greatly exothermic nature of the reaction makes hot-spot formation highly probable, thus resulting in reduced selectivities and safety issues on a large scale.

A central theme of our research is to develop continuous-flow methods, thus delivering a set of new tools to facilitate challenging synthetic transformations and provide additional advantages over batch in terms of, for example, safety,[10] scalability,[11] time-reduction,[12] or selectivity.[13] Given the importance of meta-arylated anilines and its limited scalability potential in batch, we felt that a continuous-flow strategy to access such compounds would represent an important advance. To prepare these compounds, we identified four key steps in its synthesis, including the synthesis of the diaryliodonium salt, the meta-selective C–H arylation, and the removal of both the copper catalyst and the directing group (Scheme 1). While all these modules have great potential on its own, combining them would allow straightforward access to the meta-arylated anilines within a reasonable time scale and effort.

In taking on this challenge, we anticipated that diaryliodonium salt synthesis as the first module could highly benefit from continuous-flow processing to alleviate the current safety limitations (i.e., highly exothermic nature and hazardous reagents handling).[14] The one-pot synthesis
developed by the group of Olofsson was identified as the most convenient strategy to produce a diverse set of diaryliodonium salts.\textsuperscript{\textcolor{red}{146}} A 0.1 mL PFA reactor coil (750 μm I.D.) was constructed and reagents were introduced by three separate feed streams (i.e., reagent feed, oxidant feed, and acid feed; see Figure S4 in the Supporting Information). To prevent microreactor clogging and to ensure excellent heat dissipation, the reactor assembly was submerged in an ultrasonic bath kept at room temperature. After initial optimization (see Table S1), it was found that the target di-p-tolylidium triflate (4a) could be obtained, after only a two-seconds residence time, in excellent yield (89%) after crystallization (Table 1). Notably, our flow protocol was highly reproducible.

| Table 1: Scope for the synthesis of (un)symmetrical diaryliodonium salts in flow.\textsuperscript{\textcolor{red}{147}} |
| --- |
|  | 1 | 2 | 3 (Mes) or 4 (R) |
|  | R-Mes | PFA tubing | OTf |
| 1 | 750 μm I.D. | 0.1 mL |  |
| 2 | RT, sonication, \( t = 2 \) s |  |
| 3 |  |

| 3a, 85% | 3b, 87% | 3c, 20%[b] |
| --- | --- | --- |
| 3d, 80% | 3e, 67%[c] | 3f, 64%[c] |
| 3g, 51%[g] | 3h, 32%[c] |  |
| 3i, 85% | 3j, 46%[c] | 3k, 86% |
| 3l, 50%[c] |  |

[a] Reaction conditions: Syringe 1: 5.0 mmol of aryl iodide (1) and 5.5 mmol of arene (2) in 25 mL DCE at 0.75 mL min\(^{-1}\); syringe 2: 5.5 mmol of m-CBPA in 25 mL of DCE at 0.75 mL min\(^{-1}\); syringe 3: 10.0 mmol TFOH in 50 mL DCE at 1.5 mL min\(^{-1}\). Added to the reactor by syringe pump. [b] Mesityl iodide was used. [c] 3 mL reactor volume with \( t = 60 \) s, 6.5 mmol m-CBPA, and 15 mmol TFOH. Note: The 3 series refers to unsymmetrical diaryliodonium salts with mesitylene as arene, and the 4 series to symmetrical diaryliodonium salts. \( m = \) chloroperbenzoic acid, \( T = \) trifluoromethanesulfonfyl.

and the yields were typically higher than those obtained with conventional batch labware (52–67%).\textsuperscript{\textcolor{red}{148,150}} The procedure can be readily scaled and, as an example, we obtained 2.04 grams of 4a (5 mmol scale, 89%). Next, a small library of symmetrical and unsymmetrical diaryliodonium salts was established in flow (Table 1). A wide variety of unsymmetrical diaryliodonium triflates bearing diverse substituents and mesitylene as the counterligand were successfully synthesized on a gram scale (3a–l). In particular, the compounds 3d (80%) and 3i (85%) were obtained in significantly higher yields than previously reported.\textsuperscript{\textcolor{red}{17,144}} Moreover, the unsymmetrical diaryliodonium triflates bearing electron-rich substituents (3c and 3l) were synthesized for the first time by this one-step procedure. We believe that this module provides a useful tool to enable the large-scale preparation of valuable and costly diaryliodonium salts in a safe and time-efficient fashion.

We next addressed the development of module 2, which involves the continuous-flow meta-selective C–H arylation of anilines. It is generally accepted that the reported meta-selective C–H arylation reaction operates by a homogeneous mechanism, thus making the use of heterogeneous catalysts superfluous. Nevertheless, the use of heterogeneous precursor materials, which can serve as cheap and convenient reservoirs for the release of homogeneous catalytically active species, can be of highly added value.\textsuperscript{\textcolor{red}{17}} We hypothesized that the catalytically active species could be readily formed from Cu\textsuperscript{0} in the presence of highly electrophilic diaryliodonium salts.\textsuperscript{\textcolor{red}{18}} Preliminary batch investigations revealed that inexpensive copper powder enabled the meta-arylation of N-(o-tolyl)pi- valamide (5a) with di-p-tolylidium triflate (4a; see Table S2). Moreover, these experiments revealed that copper powder was more active than the benchmark Cu(OTf)\(_2\) catalyst source reported by Gaunt, thus reducing the batch reaction time from 24 to 2 hours (see Figure S1). In addition, reactions with surface-treated copper turnings revealed that both Cu\textsuperscript{0} and Cu\textsuperscript{1} can be used as catalyst source (see Figure S1 b).\textsuperscript{\textcolor{red}{19}} Translating this concept to continuous manufacturing, we speculated that the meta-selective C–H arylation could highly benefit from the use of copper tube flow reactors (CTFRs),\textsuperscript{\textcolor{red}{20}} which would allow for a significant breakthrough in operational simplicity for C–H activation chemistry.\textsuperscript{\textcolor{red}{21}} To test this hypothesis, a 20 mL CTFR (1.65 mm I.D.) was constructed from cheap and commercially available copper tubing (see Figure S5). After initial optimization of the reaction parameters, full conversion was obtained within only 20 minutes residence time, thus yielding 88% of 6a (see Table 2 and Tables S3 and S4). Next, various pivanilides with 4a as the coupling partner were subjected to our flow protocol (Table 2). Pivanilides bearing either ortho-alkyl, ortho-aryly, or ortho-methoxy substituents were well tolerated and yielded the monoarylated compounds 6b, 6c, and 6d respectively, in excellent yields (86–91%). In the absence of ortho substituents, both meta positions became highly accessible, thus resulting in a high-yielding mixture of both mono- and diarylated products 6e/6e (80% yield, mono/di 1:2.3). Also, the heterocyclic substrate indoline was readily converted into 6f in our flow reactor, thus yielding the pure compound in 80% yield upon isolation. Generally, meta-substituted substrates are perceived as more challenging substrates but could nevertheless be acquired in flow within 20 minutes (6g,h). More complex ortho,para-disubstituted pivanilides were also compatible (6i–l), thus obtaining 6i and a 6j/6j mixture in high yields (85–86%). Modest yields (30–42%) were obtained for 6k and 6l because of incomplete conversion.

Next, a diverse set of diaryliodonium salts, all prepared on a gram scale in flow by module 1, were evaluated as coupling
partners with N-(o-tolyl)pivalamide (5a) as a benchmark substrate (Table 2). The transfer of various aryl groups was effective for a broad range of symmetrical and unsymmetrical diaryliodonium triflates (6m–w) bearing either electron-neutral, electron-donating, or electron-withdrawing substituents, thus yielding the desired meta-arlated products in fair to excellent yields (21–90%). Note that for unsymmetrical diaryliodonium salts, the sterically hindered mesitylene could be successfully used as a “dummy ligand” allowing selective transfer of the functionalized aryl groups. Interestingly, a gram-scale reaction was readily carried out and resulted in the formation of 6a in near quantitative yield (1.384 g, 98%), thus highlighting the excellent scale-up potential of our continuous-flow protocol. It should be noted that the complete scope (6a–w) was performed with only a single copper capillary without any apparent loss of reactivity. Moreover, the accelerated reaction conditions (20 min vs. 24–48 h) and improved yields highlight the potential of these CTFRs, as readily available flow reactors, to enable copper-catalyzed C–H activation chemistry for gram-scale drug manufacturing.

Operating the meta-arlation reaction in a continuous-flow manner, evidently raised the question of whether significant copper leaching was taking place. Leaching can become apparent at longer operation times, since copper will be progressively chromatographed through the reactor tubing as a result of subsequent leaching/redeposition cycles. To investigate the leaching behavior, ICP-OES analysis was conducted on reaction samples (see Section 2.3 in the Supporting Information). As can be seen from Table 3, the crude reaction sample from module 2 contained about 4720 ppm of Cu, and is in the same range as previously reported transformations in CFTRs. To remove the leached copper from the target compound, we considered a continuous-flow inline extraction module (module 3). The extraction module consisted of a 5 mL PFA extraction coil. Organic phase was checked for Cu content by ICP-OES analysis.

| Entry | Purification | Cu content [ppm] |
|-------|--------------|------------------|
| Crude mixture from module 2 | n.a. | 4720 |
| Extracted org. phase | 1 extraction | 14.3 |
| Extracted org. phase | 3 extractions | 6.3 |

[a] Crude mixture from module 2 and NH$_3$ (32 wt%) aqueous solution was pumped by syringe pump and mixed together in a T-mixer. A Zaiput membrane separator was connected at the end of the 5 mL PFA extraction coil. Organic phase was checked for Cu content by ICP-OES analysis.

Table 2: Scope with respect to anilines$^a$ and diaryliodonium salts$^b$ for the meta-selective C–H arylation in flow.

| Entry | Purification | Cu content [ppm] |
|-------|--------------|------------------|
| Crude mixture from module 2 | n.a. | 4720 |
| Extracted org. phase | 1 extraction | 14.3 |
| Extracted org. phase | 3 extractions | 6.3 |

[a] Reaction conditions: 0.5 mmol aniline (5) and 2.0 equiv [Tol-I-Tol]OTf (4a) in 5.0 mL DCE. [b] Reaction conditions: 0.5 mmol N-(o-tolyl)pivalamid (5a) and 2.0 equiv [Ar-I-Mes]OTf (3) in 5.0 mL DCE. Added to the CTFR by syringe pump. [c] 40 min residence time. [d] 5.03 mmol scale reaction: 1.384 g (98%) of desired product obtained. [e] Symmetrical [Ar-I-Ar]OTf (4) was used. Piv = pivaloyl.
through the module. This step leads to a residual 14.3 ppm of Cu, and is far below the recommended limit for parenterally administered pharmaceutical substances (< 25 ppm according to the European Medicines Agency (EMEA) Guidelines).\[23\]

The final step in our reaction sequence constitutes the removal of the pivalic protecting group. Notably, the cleavage of pivanilides proved to be extremely challenging. Literature procedures utilize reflux conditions and prolonged reaction times ranging from 1–3 days.\[7,24\] Such extended reaction times are not suitable for continuous-flow processing and a thorough screening of potential deprotection strategies was carried out (see Tables S6 and S7). The flow module consisted of a 20 mL PFA capillary (1.65 mm I.D.) equipped with a 140 psi back pressure regulator (BPR) to enable superheated reaction conditions (see Figure S7). Eventually, we found that the deprotection of 6a could be realized within 40 minutes using an HCl/1,4-dioxane (1:1) mixture at 130°C (Table 4), thus yielding the free aniline 7a in excellent yield (94%). A final extraction procedure was used to circumvent chromatography (see Section 4.4). This continuous-flow deprotection protocol appeared to be generally applicable (7a–h) and constitutes a significant improvement compared to the literature procedures.

Finally, with all the individual modules fully explored and optimized, the different modules were combined to enable direct access to meta-arylated anilines. Module 1 provides a unique, safe, and scalable flow method to prepare highly valuable diaryliodonium salts, within a 2 second residence time (15 examples). In module 2, a copper tube flow reactor was used for the first time to enable copper-catalyzed meta-selective C–H arylation of protected anilines within a 20 minute residence time (23 examples). Effective inline copper removal in module 3 led to values suitable for meeting the standards of parenterally administered pharmaceutical substances (i.e., residual Cu content < 25 ppm). Finally, deprotection of the pivanilides was realized in module 4, thus delivering the desired meta-arylated anilines in a straightforward fashion within 40 minutes. Orchestrating all individual modules in an integrated process allowed preparation of meta-arylated anilines within a total time frame of 1 hour in excellent yield and purity, and without the need of chromatography. We believe that the each of the developed modules are of high value and will find widespread use in both academia and industry.

**Acknowledgments**

Financial support is provided by the Dutch Science Foundation (NWO) by an ECHO grant (Grant No. 713.013.001) and a VIDI grant for T.N. (Grant No. 14150). We also acknowledge the support by COST (European Cooperation in Science
Communications

Conflict of interest

The authors declare no conflict of interest.

Keywords: arylation · C–H activation · copper · hypervalent compounds · flow chemistry

How to cite: Angew. Chem. Int. Ed. 2017, 56, 7161–7165
Angew. Chem. 2017, 129, 7267–7271

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