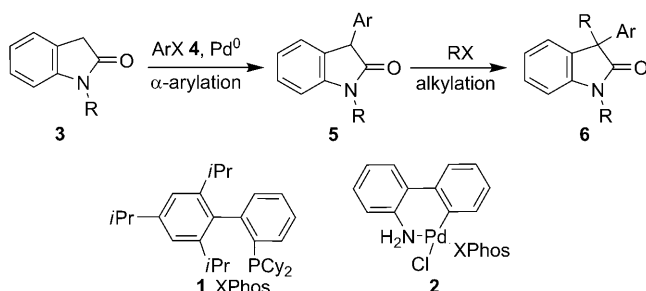


Continuous-Flow Synthesis of 3,3-Disubstituted Oxindoles by a Palladium-Catalyzed α -Arylation/Alkylation Sequence**

Pengfei Li and Stephen L. Buchwald*

Continuous-flow reactors and their application in chemical synthesis have been recognized as an effective alternative strategy to the conventional batch-based regime.^[1] In general, continuous-flow multistep processes involve less manual intervention, therefore, eliminating the handling of intermediates and offering good reproducibility. Microfluidics allow more efficient mass- and heat-transfer, which enables precise control over the reaction parameters. In addition, the use of microreactors provides easy scale-up, either by increasing the dimensions of the device or by simply operating multiple microreactors in parallel (numbering up). However, many reactions are currently not suited for continuous-flow microreactors because of the formation of solids during the reaction that lead to irreversible clogging, inefficient multiphase mixing, slow reaction rates, and/or instability of the preformed reagents or catalyst solutions. As part of our ongoing work on palladium-catalyzed cross-coupling reactions in continuous-flow systems,^[2] we herein disclose a continuous-flow α -arylation/alkylation sequence, in which we are able to overcome the problems stated above (Scheme 1).



Scheme 1. α -arylation of *N*-alkyl-2-oxindoles.

The palladium-catalyzed α -arylation reaction, during which a new C–C bond between the α -position of a carbonyl and an aryl or vinyl group is formed, is an important reaction

for the synthesis of natural products and active pharmaceutical ingredients (APIs).^[3] Compounds containing a 3,3-disubstituted 2-oxindole substructure comprise a large family of naturally occurring alkaloids, many of which display significant biological activity.^[4] As such, developing convenient methods for their preparation is of considerable interest. A subclass of these, (spiro)pyrrolidine-3,3-oxindoles, is regarded as a privileged structural unit in drug design.^[5] Some structurally related bioactive alkaloids, for example, pyrroloindolines,^[6] are also readily derived from 3,3-disubstituted oxindoles. Consequently, as a starting point for our work on α -arylation methodology under flow conditions, we selected 2-oxindoles **3** as the first substrate class for our investigations.

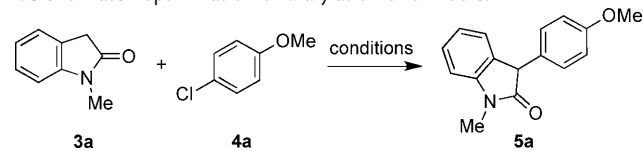
Palladium-catalyzed α -arylation of 2-oxindoles was first disclosed by Hartwig and Lee, and additional methods have been reported by our group and by Willis and Durbin.^[7] Our experience (as well as Willis' work) indicated that XPhos (**1** in Scheme 1) was an excellent supporting ligand. However, all of the previous conditions reported for this process required the use of high catalyst loadings and/or long reaction times. In addition, these conditions inevitably proceeded as heterogeneous mixtures, due to either the use of sparingly soluble inorganic bases or the salts that were produced and precipitated from the reaction solution. Notably, no examples with heteroaryl halides as coupling partners have been reported. Based on this background information, we felt that modifications of the reaction conditions would be necessary to develop an efficient system for this transformation in flow.

Using *N*-methyl-2-oxindole (**3a**, Table 1) as the substrate, we initially compared a variety of conditions in a batch process. Selected results are shown in Table 1. At 60 °C, and with 1.0 mol % [Pd(dba)₂] (dba = dibenzylideneacetone) and 1.5 mol % XPhos (**1**), very low conversion was observed with either KHMDS (Table 1, entry 1) or LiHMDS (Table 1, entry 2) as the base (3 min reaction time). In the case of KHMDS, some insoluble material was generated during the reaction. To solubilize both the organic and inorganic materials, a biphasic system (Table 1, entry 3) was also investigated, unfortunately with little success.^[2b] At this point, we hypothesized that a 3 min reaction time might be inadequate for complete formation of the catalytically active Pd⁰–phosphine complex. Led by our recent successes in the development and application of single-component precatalysts for C–C and C–N cross couplings,^[8] we tested palladacycle **2** as a precatalyst in the α -arylation reaction, since it has been shown to be rapidly converted to the monoligated Pd⁰–XPhos complex by deprotonation and reductive elimination. This precatalyst was prepared from commercially available chemicals by an operationally simple one-pot process in high

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Table 1: Batch optimization of α -arylation of oxindole.^[a]


Entry	Pd Source	Base	Solvent	Yield [%] ^[b]
1	[Pd(dba) ₂]	KHMDS	THF/Tol	< 5
2	[Pd(dba) ₂]	LiHMDS	THF/Tol	12
3	[Pd(dba) ₂]	2.0 M KOH	THF/H ₂ O	< 5
4	2	LiHMDS	THF/Tol	5
5	2	2.0 M KOH	THF/H ₂ O	42
6	2 ^[c]	2.0 M KOH	THF/H ₂ O	30
7	2	2.0 M KOH	Tol/H ₂ O	< 5
8	2 ^[d]	2.0 M KOH	Tol/H ₂ O	43
9	2	2.0 M KOH	THF/H ₂ O	88
10	2 ^[d]	2.0 M KOH	Tol/H ₂ O	91

[a] Reaction conditions: A mixture of **3a** (0.5 mmol), **4a** (0.55 mmol), dodecane (50 μ L), catalyst (Pd 1 mol%, XPhos 1–1.5 mol%), and base in the indicated solvent (0.5 mL THF or Tol when 1.0 mL of aq. 2.0 M KOH was used as the base, and 0.25 mL THF when 1.1 mL of 0.5 M KHMDS in Tol or 0.55 mL of 1.0 M LiHMDS in Tol as the base) was stirred at 60°C for 3 min. [b] determined by GC with dodecane as internal standard. [c] with 0.5 mol% XPhos added. [d] 5.0 mol% of tetrabutylammonium bromide (TBAB) was added as phase-transfer catalyst (PTC). [e] The reactions were run at 100°C for 3 min.

yield.^[8b] Using **2** as the palladium source, a variety of different reaction conditions were compared. While the use of **2** did not offer any improvement when LiHMDS was used as the base (Table 1, entry 4), we observed promising results with a biphasic, THF/aqueous KOH system (Table 1, entry 5). Interestingly, the addition of 0.5 mol% XPhos provided no improvement (Table 1, entry 6). We next examined a toluene/aqueous KOH biphasic system, for which the addition of a phase-transfer catalyst (PTC) was required to observe significant conversion to product (Table 1, entry 7 and 8). Among several tested PTCs, tetrabutylammonium bromide (TBAB) was found to be superior in terms of conversion and commercial cost. When the reactions were run at elevated temperature (100°C) for 3 min, both THF/aqueous KOH and toluene/aqueous KOH systems gave full conversion and similar yields (Table 1, entry 9 and 10). To our knowledge, these results are the first example of significantly increased reaction rates for α -arylation in a biphasic system.^[9,10] Thus, by using palladacycle **2** as the precatalyst, and water as a cosolvent to dissolve all inorganic salts, two efficient systems were identified for further study under continuous-flow conditions.

Recently, our group has reported that a packed-bed microreactor was successful in promoting biphasic C–N cross-coupling in flow because of its dramatically enhanced mixing capacity in comparison to that observed with open tubing.^[2b] In the current α -arylation case, we observed that a packed-bed microreactor was also required for effective mixing. Thus, we applied our biphasic conditions in continuous-flow using a set-up including a stainless steel packed-bed reactor (see the Supporting Information). All liquid streams were introduced by syringe pumps. Substrate **3a**, halide **4a**, and internal standard (dodecane) were dissolved in THF or toluene,

denoted as solution A. Precatalyst **2** was dissolved in THF or toluene, indicated as solution B. Due to the rapid activation of precatalyst **2** in the presence of a base, we added 0.2 mol% of acetic acid to prevent any base-induced decomposition. Solution C contained aqueous KOH (with TBAB added when toluene was used as the solvent). The three streams passed through three check valves and were mixed in a cross. The resulting biphasic mixture was further flowed through a heated stainless steel packed-bed for the indicated time. After the reactor, a back-pressure regulator (BPR) was placed to prevent any boiling of solvent. After passing the BPR, the reaction mixture was quenched with degassed saturated aqueous NH₄Cl and ethyl acetate, and collected in a sampler. After variations of reaction time, temperature, amount of KOH, and concentration, the optimal conditions for the reaction between **3a** and **4a** were found as shown in Table 2.

Table 2: Optimized flow conditions for α -arylation of **3a**.^[a]

Solvent	t [s]	Flow rate [μ L min ⁻¹]			Yield [%] ^[b]
		A	B	C	
THF	120	64	16	160	> 95
Tol	80	89	22	224	> 95

[a] Reaction conditions: The volume of the packed bed was 448 μ L; Solution A: **3a** (1.25 M), **4a** (1.28 M), dodecane (0.35 M) in THF or Tol; Solution B: **2** (0.05 M) and AcOH (0.01 M) in THF or Tol; Solution C: KOH (2.0 M) (and 0.025 M of TBAB for Tol reaction) in water. [b] Determined by GC with dodecane as the internal standard.

As this reaction proceeded best at 100°C, a toluene/H₂O mixture was more suitable due to the lower pressure and slightly higher reaction rates observed in flow than that for THF/H₂O. Accordingly, in the remainder of this study, a toluene/H₂O system was employed.

Next we wanted to integrate these arylation conditions into an α -arylation/alkylation sequence for a modular and continuous synthesis of 3,3-disubstituted oxindoles (Scheme 1, **3** to **6**). Multistep continuous-flow reactions are challenging due to increased complexity as compared to a single-step flow reaction; flow rate (i.e., reaction time) synergy, solvent compatibility, and the effect of byproducts and impurities must be considered and optimized. Only a few multistep continuous flow syntheses have been described.^[11,1g] Nonetheless, we felt that 3-alkyl-3-aryl-2-oxindoles could be produced in a continuous-flow fashion by taking advantage of the biphasic system and eliminating any intermediate workup and purification. To examine the feasibility of this transformation, we first tested the benzylation of isolated **5a** under biphasic conditions (Table 3, **5a** to **6a**). In batch, using TBAB in a toluene/1.5 M KOH mixture, this benzylation was complete in less than 5 min at 100°C. Preliminary study under flow conditions of this alkylation step indicated that mixing efficiency was critical, as use of an open tubing reactor led to generally lower and variable yields depending on the flow rate employed. When a packed-bed reactor was employed we found that the reaction was complete in 40 s.

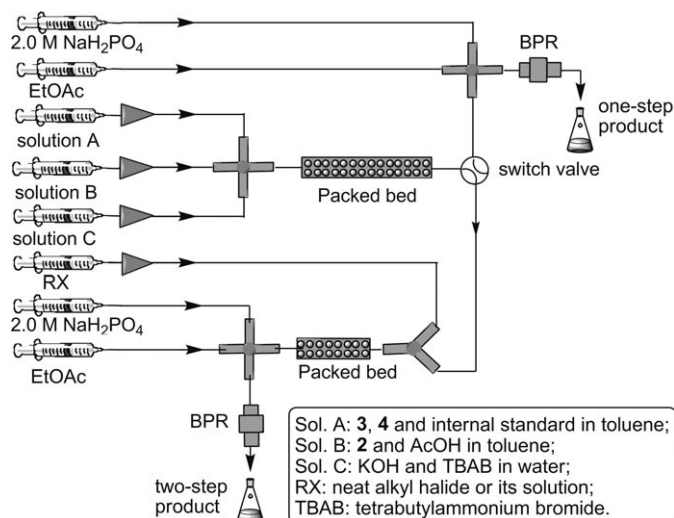
Based on the studies described above, we constructed a flow set-up for the continuous α -arylation/alkylation

Table 3: Continuous synthesis of 3,3-disubstituted oxindoles.^[a]

3-Aryloxindole 5	3,3-Disubstituted oxindole 6 ^[b] (without isolation of 5)
 5a , 94%, X = Cl, (1% 2), 100 °C, 90 s	 6a R = Bn, 93%, X = Br, 100 °C, 43 s; 6a' R = CH ₂ CONHBn, 86%, X = Cl, 100 °C, 3 min
 5b , 87%, X = Br, (1% 2), 100 °C, 120 s	 6b , 86%, X = Br, 100 °C, 58 s
 5c , 86%, X = Cl, (1% 2), 100 °C, 2.5 min	 6c , 84%, X = Br, 100 °C, 1.2 min
 5d , 82%, X = Cl, (2% 2), 110 °C, 10 min	 6d , 74%, X = Br, 100 °C, 5 min
 5e , 94%, X = Br, (1% 2), 100 °C, 60 s	 6e , 94%, X = Br, 100 °C, 120 s
 5f , 88%, X = Cl, (1% 2), 100 °C, 4 min	 6f , 79%, X = OCO ₂ Me, 100 °C, 2 min
 5g , 69%, X = Cl, (4% 2), 120 °C, 23 min	 6g , 62%, RX = BrCH ₂ CH ₂ Br, 80 °C, 23 min

[a] Reaction conditions: Using the set-up in Figure 1, all yields are based on isolated products and calculated based on the collecting time and the flow rates corresponding to 1.0 mmol theoretical products. [b] Yields over two steps. MOM: methoxymethyl.

sequence as shown in Figure 1. The selection of the sizes of the two packed-bed reactors depended on the approximate reaction rates of the two reactions observed in preliminary

**Figure 1.** Flow set-up for the α -arylation/alkylation sequence.

experiments. For example, as α -arylation of **3a** required approximately 80 s and the following benzylation required approximately 40 s, a 180 μ L/90 μ L combination was used for the two-step flow. A switch valve was placed in between the two reactors so that one can collect either the product of the first step or of the two-step process in one experimental setup simply by switching the valve. The three feeds A, B, and C were identical to those described for the arylation process with the exception that biphenyl was used instead of dodecane as the internal standard. Benzyl bromide was added neat as feed RX (Figure 1). With a 180 μ L/90 μ L set-up, a continuous α -arylation/benzylation of **3a** could be achieved in excellent yield (isolated 93%) with a retention time of 90 s/43 s.

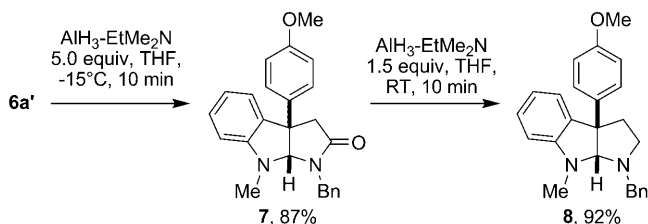
With optimized conditions realized, we explored the scope and limitations of this two-step flow system using various oxindoles, aryl halides, and alkylating reagents. Thus, using the set-up in Figure 1, in a single flow experiment, we could prepare either the α -arylation product **5**, or the α -arylation/alkylation product **6** (in all cases **6** was made without the isolation of **5**). Depending on the solubility of the materials, the concentrations of *N*-alkyl oxindoles in toluene were either 1.0 M or 0.6 M. The results are shown in Table 3. Generally, for the α -arylation reaction, both aryl chlorides and bromides were excellent coupling partners. With only 1 mol % of palladacycle **2** as the precatalyst, several halides could be coupled with *N*-alkyl oxindoles at 100 °C in excellent yields in less than 4 min. Included among these were substrates bearing an ester group (**5b**) and a free hydroxyl group (**5f**). Five-membered heterocycles, including a benzoxazole (**5c**) and a protected indole (**5e**), were also good coupling partners. Notably, MOM-protected oxindole **3b** was successfully coupled in only 60 s (94% isolated yield). Unfortunately, heteroaryl halides, including 3-chloropyridine

and 2-chloro-6-methoxypyridine, were poor substrates and provided lower yields under these conditions (1 % Pd, 100 °C, 10–20 min), making these unsuitable due to the resulting low productivity. However, with flow systems, one can use “non-standard” conditions, for example, temperatures higher than the solvents’ boiling points, without the safety issues faced with batch reactions. Accordingly, a 20 psi back-pressure regulator (BPR) was placed at the end of the reactors and the synthesis of **5d** could be achieved with 2 % Pd at 110 °C in 10 min. Similarly, the reaction of 2-chloro-6-methoxypyridine required 4 % Pd, 120 °C, and 23 min to obtain full conversion, affording **5g** in 69 % isolated yield.

For the continuous α -arylation/alkylation sequence, the alkylating reagents were introduced with an additional syringe pump with the exception of that for synthesis of **6a'**, for which a 1.0 M solution of *N*-benzyl-2-chloroacetamide in 1,4-dioxane was used. These flow syntheses generally produced the 3,3-disubstituted oxindoles in high yields (62–94 %) over the two steps. Allyl methyl carbonate could also be used for a selective C- over O-allylic alkylation in the case of **6f**.

As we hoped to prepare more structurally diverse oxindoles related to naturally occurring alkaloids, we designed an α -arylation/C,N-double alkylation route for the synthesis of spirocyclic oxindoles. Thus, 3-(6-methoxypyridin-2-yl)oxindole **5g** was treated at 80 °C with 1,2-dibromoethane under flow conditions to yield spirocyclic pyridone **6g** in a moderate yield (62 %) over two steps; the second step included two bond-forming and one bond-breaking processes. This strategy represents a very concise approach to this kind of tetracyclic 3,3-spirooxindole core^[4] present in natural products such as strychnofoline.^[12]

The products of this two-step continuous flow synthesis may serve as useful synthetic intermediates towards biologically interesting molecules. To demonstrate this, compound **6a'** was transformed to a pyrroloindoline compound **8** by two high-yielding consecutive reductions (Scheme 2).^[13]



Scheme 2. Synthesis of a pyrroloindoline from **6a'**.

In conclusion, a method for the palladium-catalyzed α -arylation of oxindoles in a continuous-flow manner has been successfully developed. Key to the success included the implementation of a biphasic system with KOH as the base, palladacycle **2** as the rapidly activated precatalyst, and a packed bed as the microreactor that enables efficient mixing. Furthermore, this reaction was integrated into a two-step continuous-flow sequence for rapid, modular, and efficient syntheses of 3,3-disubstituted oxindoles, providing access to pharmaceutically interesting heterocyclic structures.

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