

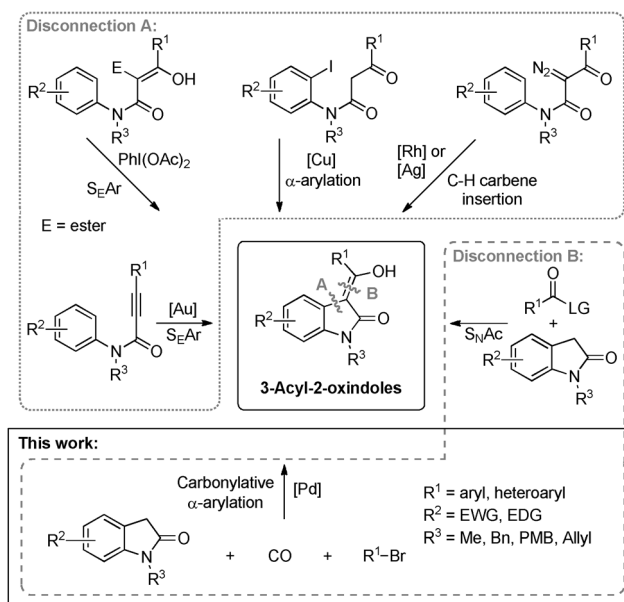
# Palladium-Catalyzed Carbonylative $\alpha$ -Arylation of 2-Oxindoles with (Hetero)aryl Bromides: Efficient and Complementary Approach to 3-Acyl-2-oxindoles\*\*

Zhong Lian, Stig D. Friis, and Troels Skrydstrup\*

**Abstract:** An efficient Pd-catalyzed carbonylative  $\alpha$ -arylation of 2-oxindoles with aryl and heteroaryl bromides for the one-step synthesis of 3-acyl-2-oxindoles has been developed. This reaction proceeds efficiently under mild conditions and is complementary to the more common oxindole forming reactions. The transformation only requires a mild base and provides good to excellent yields even with heteroaromatic substrates. Employing a near stoichiometric amount of  $^{13}\text{CO}$ , the methodology was easily extended to  $^{13}\text{C}$  acyl labeling. The general applicability of the reaction conditions was demonstrated in the synthesis of a structure related to the pharmaceutically active 3-acyl-2-oxindoles, tenidap.

Indoles and oxindoles are highly privileged structures, found in countless natural products and drug candidates.<sup>[1]</sup> Accordingly, the derivatization of these structural motifs is of continuing interest to both the medicinal industry and the academic society.<sup>[2]</sup> The formation of 3-acyl-2-oxindoles is no exception as these compounds are featured in a number of natural products and biologically active molecules, e.g., GSK3 kinase inhibitors,<sup>[3]</sup> influenza endonuclease inhibitors,<sup>[4]</sup> and Tendipap,<sup>[5]</sup> a potent inhibitor of cyclooxygenase.

Despite their versatile significance, only a limited number of synthetic routes to 3-acyl-2-oxindoles have been reported in the literature. The reactions can be grouped into two approaches on the basis of the bond formed (Scheme 1). In the oxindole forming approach (Scheme 1, disconnection A, dotted box), a number of transition-metal-catalyzed transformations have been described. These include the gold-catalyzed  $\text{S}_{\text{E}}\text{Ar}$  cyclization of *N*-arylnamides with subsequent oxidation of the gold carbene,<sup>[6]</sup> a copper-catalyzed  $\alpha$ -arylation of 2-iodoanilines carrying a 1,3-dicarbonyl on the aniline,<sup>[7]</sup> and a rhodium- or silver-catalyzed C–H carbene insertion starting from  $\alpha$ -diazoketoamides.<sup>[8]</sup> Recently, another  $\text{S}_{\text{E}}\text{Ar}$ -type transformation mediated by hypervalent



**Scheme 1.** Synthetic routes to 3-acyl-2-oxindoles. PMB: *p*-methoxybenzyl.

iodine was published.<sup>[9]</sup> Common to all these transformations is the use of relatively complex starting materials, which all originate from substituted anilines.

The alternative approach to 3-acyl-2-oxindoles is through a C–C bond forming reaction directly with the oxindole (Scheme 1, disconnection B, dashed box). So far, this approach has found limited application and only a narrow range of compounds have been synthesized in low to moderate yields.<sup>[10]</sup> This may be attributed to the relatively harsh reactions conditions employed, because acid halides or a strong base are required. Furthermore, the need for a stoichiometric amount of coupling reagent makes this approach less appealing.

Despite considerable efforts to develop three-component carbonylative coupling reactions of (hetero)aryl (pseudo)halides, carbon monoxide, and nucleophiles,<sup>[11,12]</sup> the first carbonylative  $\alpha$ -arylation was only reported recently.<sup>[13,14]</sup> However, these transformations generally require a strong base or an adjacent electron withdrawing group to ensure efficient enolization to furnish synthetically useful yields.<sup>[15]</sup> Furthermore, the utilization of more complex, enolizable compounds, which upon carbonylative  $\alpha$ -arylation generate products that are directly applicable in medicinal chemistry, has not yet been demonstrated.

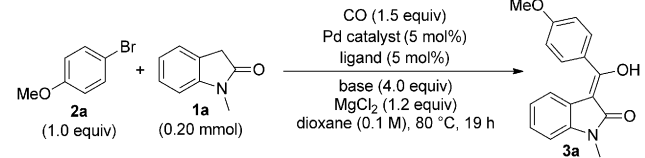
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With the apparent need for a practical and general method to prepare 3-acyl-2-oxindoles in mind, we set out to identify conditions for the carbonylative  $\alpha$ -arylation of 2-oxindoles with aryl bromides. The optimization of this transformation was initiated with *N*-methyl-2-oxindole (**1a**) and 4-bromoanisole (**2a**), using a XantPhos-based catalytic system, which has frequently been used in carbonylation chemistry (Table 1).<sup>[11a,c,16]</sup> The combination of  $\text{MgCl}_2$  and

**Table 1:** Optimization of the carbonylative  $\alpha$ -arylation of 2-oxindoles.<sup>[a]</sup>



| Entry             | Pd catalyst                               | Ligand                                    | Base                    | Yield <sup>[b]</sup> [%] |
|-------------------|-------------------------------------------|-------------------------------------------|-------------------------|--------------------------|
| 1                 | $\text{Pd}(\text{dba})_2$                 | XantPhos                                  | $\text{Et}_3\text{N}$   | 20                       |
| 2                 | $[\text{Pd}(\text{cinnamyl})\text{Cl}]_2$ | XantPhos                                  | $\text{Et}_3\text{N}$   | 57                       |
| 3                 | $\text{PdCl}_2$                           | XantPhos                                  | $\text{Et}_3\text{N}$   | 54                       |
| 4                 | $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$    | XantPhos                                  | $\text{Et}_3\text{N}$   | 23                       |
| 5                 | $\text{Pd}(\text{cod})\text{Cl}_2$        | XantPhos                                  | $\text{Et}_3\text{N}$   | 44                       |
| 6                 | $\text{Pd}(\text{OAc})_2$                 | XantPhos                                  | $\text{Et}_3\text{N}$   | 64                       |
| 7                 | $\text{Pd}(\text{OAc})_2$                 | DPEPhos                                   | $\text{Et}_3\text{N}$   | 20                       |
| 8 <sup>[c]</sup>  | $\text{Pd}(\text{OAc})_2$                 | $\text{PPh}_3$                            | $\text{Et}_3\text{N}$   | 0                        |
| 9 <sup>[c]</sup>  | $\text{Pd}(\text{OAc})_2$                 | $(\text{tBu})_3\text{P}\cdot\text{HBF}_4$ | $\text{Et}_3\text{N}$   | 0                        |
| 10 <sup>[c]</sup> | $\text{Pd}(\text{OAc})_2$                 | CataCXium A                               | $\text{Et}_3\text{N}$   | 0                        |
| 11 <sup>[c]</sup> | $\text{Pd}(\text{OAc})_2$                 | XPhos                                     | $\text{Et}_3\text{N}$   | 0                        |
| 12                | $\text{Pd}(\text{OAc})_2$                 | XantPhos                                  | $\text{Cy}_2\text{NMe}$ | 34                       |
| 13                | $\text{Pd}(\text{OAc})_2$                 | XantPhos                                  | DIPEA                   | 25                       |
| 14                | $\text{Pd}(\text{OAc})_2$                 | XantPhos                                  | DBU                     | 33                       |
| 15 <sup>[d]</sup> | $\text{Pd}(\text{OAc})_2$                 | XantPhos                                  | $\text{Et}_3\text{N}$   | 0                        |
| 16 <sup>[e]</sup> | $\text{Pd}(\text{OAc})_2$                 | XantPhos                                  | $\text{Et}_3\text{N}$   | 84                       |

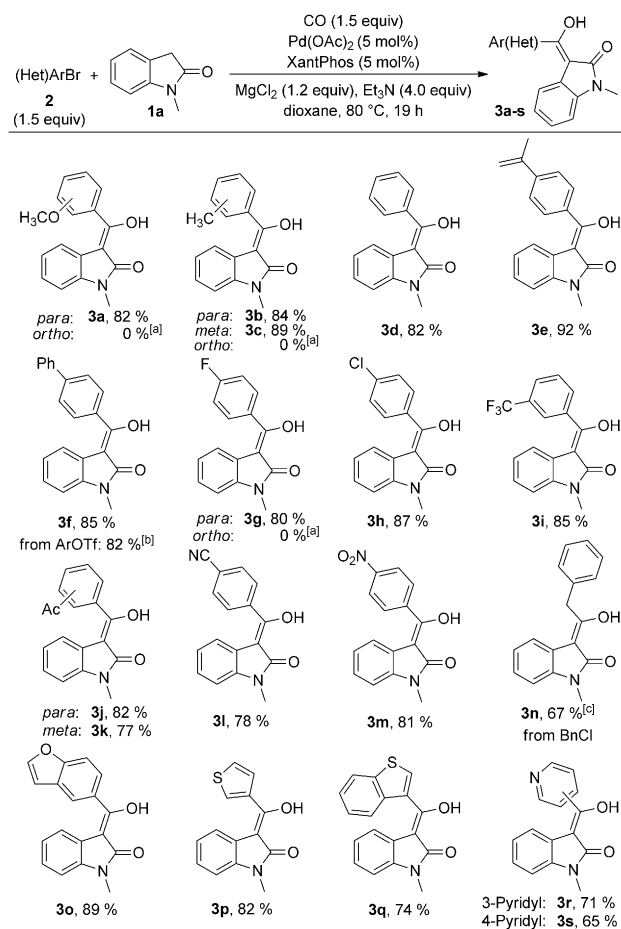
[a] CO generated from COgen. [b]  $^1\text{H}$  NMR yield with internal standard. [c] Ligand (10 mol %). [d]  $\text{MgCl}_2$  was omitted. [e] **2a** (0.30 mmol). cod: cyclooctadiene; dba: dibenzylideneacetone; XantPhos: 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene; DPEPhos: bis[(2-diphenylphosphino)phenyl] ether; CataCXium A: di(1-adamantyl)-*n*-butylphosphine; XPhos: 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl; DIPEA: *N,N*-diisopropylethylamine; DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene.

triethylamine as base is known to improve the ratio of C-acylation versus O-acylation of the formed enol and thereby furnish the desired compound in higher yield.<sup>[15b,c]</sup> When the reaction was performed in dioxane at 80 °C in the presence of 1.5 equivalents of carbon monoxide, which is generated ex situ from 9-methylfluorene-9-carbonyl chloride (COgen), the desired product **3a** was produced in 20% NMR yield (entry 1).<sup>[11f,17]</sup> The use of  $\text{Pd}(\text{dba})_2$  proved detrimental, because the yields were significantly increased when other Pd sources were tested (entries 2–6). Only  $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$  did not perform notably better, suggesting that excess phosphine ligand retards the reaction (entry 4). Employing the inexpensive and easy to handle palladium(II) acetate proved to be optimal for this reaction (entry 6).

We next determined the preferred ligand for this reaction. The more flexible DPEPhos did provide conversion to the desired product (entry 7), albeit in a low yield, whereas the use of monodentate ligands proved detrimental for the

catalyst stability and no product was observed (entries 8–11).<sup>[18]</sup> Employing more sterically encumbered bases (entries 12 and 13) or using the stronger base DBU (entry 14) only reduced the yield. Triethylamine, in combination with  $\text{MgCl}_2$ , was therefore the selected base system, because the omission of  $\text{MgCl}_2$  halted the reaction (entry 15). Finally, a slight increase of the amount of aryl bromide raised the yield of **3a** to 84% (entry 16).

Having identified the optimal reaction conditions for this carbonylative  $\alpha$ -arylation of 2-oxindoles with aryl bromides and a near stoichiometric amount of carbon monoxide, we set out to probe the scope of the (hetero)aryl bromides employed (Scheme 2). The product **3a**, resulting from the coupling of



**Scheme 2.** Carbonylative  $\alpha$ -arylation of *N*-methyl-2-oxindole with various (hetero)aryl bromides, **1a** (0.50 mmol, 0.25 M). CO was generated from COgen. [a] Also examined at 100 °C. [b] **2** was exchanged for 4-biphenyl triflate (0.75 mmol). [c] **2** was exchanged for BnCl (0.75 mmol).

the electron-rich 4-bromoanisole, was isolated in 82% yield. With a methyl group in either the *para*- or the *meta*-position (**3b** and **3c**) also provided the isolated products in good yields, whereas the increased steric bulk associated with an *ortho*-substituent was detrimental to the reaction (*ortho* analogues of **3a**, **3b**, and **3g**). Besides the coupling of the simple bromobenzene, which afforded the product **3d** in good yield, the presence of a terminal olefin was also tolerated, with no

observation of Heck-type side reactions. This was exemplified by the isolation of compound **3e** in 92 % yield. The coupling of 4-bromobiphenyl gave product **3f** in a satisfactory yield of 85 %. Remarkably, using identical reaction conditions, the corresponding triflate was coupled with a similar yield, thereby expanding the scope of this transformation.

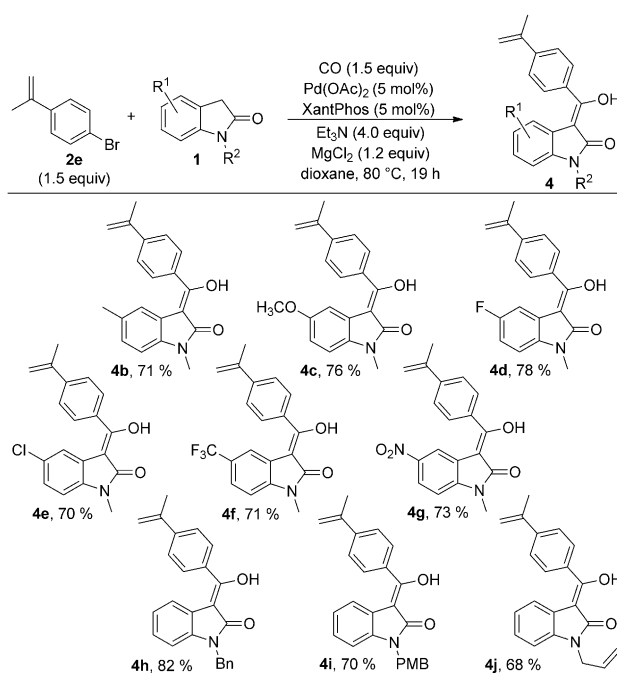
The tolerance of the reaction for other halides on the aryl bromide ring was demonstrated by the synthesis of compounds **3g** and **3h**. Derivative **3h** allows for post coupling modification, e.g., by Suzuki or Buchwald–Hartwig coupling of the aryl chloride.<sup>[19]</sup> The coupling of electron-poor aryl bromides also worked well, as exemplified by the preparation of the trifluoromethyl-substituted compound **3i**, which was isolated in 85 % yield. Despite their electrophilic nature, both 3-acyl-2-oxindole products **3j** and **3k**, generated from *para*- and *meta*-bromoacetophenone, were isolated in good yields and no aldol-type side reactions were detected. This was also the case for the preparation of the benzonitrile containing **3l**, which could be isolated in 78 % yield. The presence of a nitro group is potentially problematic in carbonylation chemistry as it may be reduced by carbon monoxide under Pd catalysis.<sup>[20]</sup> However, in this transformation, no such side reaction was observed and **3m** was isolated in 81 % yield.

Benzylic chlorides were demonstrated to be equally good substrates for this reaction and by using the same reaction conditions as for the aryl bromides, compound **3n** was isolated in a 67 % yield. Heteroaromatic groups were also tolerated and 5-bromobenzofuran could be coupled in 89 % yield. The reactions with heteroaromatic bromides such as 3-bromothiophene and 3-bromobenzothiophene under the optimized conditions gave good yields of the desired products **3p** and **3q**. The formation of 3-acyl-2-oxindoles starting from the rather electron-deficient 3- and 4-bromopyridine also resulted in the smooth formation of **3r** and **3s**.

Next, we turned our attention to the scope of the 2-oxindoles (Scheme 3). The presence of a methyl substituent in the 5-position, as in **4b**, slightly hampered the reaction and led to a moderately reduced yield of 71 %, compared to **3e**, whereas the 5-methoxy-2-oxindole yielded 76 % of **4c**. Both the 5-fluoro- and the 5-chloro-*N*-methyl-2-oxindole were coupled to provide the desired products **4d** and **4e** in satisfactory yields. The therapeutically important trifluoromethoxy group or a nitro group in the 5-position of the oxindole were tolerated well, which was illustrated by the isolation of compounds **4f** and **4g**.

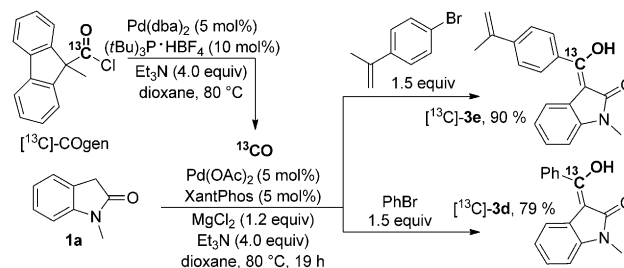
We also tested different N-protecting groups for the oxindole motif. The reaction with a simple benzyl protecting group worked nicely and 3-acyl-2-oxindole **4h** was isolated in 82 % yield. The *p*-methoxybenzyl (PMB) protected oxindole gave a slightly lower, but synthetically still useful yield of 70 %, whereas the *N*-allyl protected 2-oxindole was coupled to give **4j** in 68 % yield. Efforts toward the coupling of the unprotected 2-oxindole proved unfruitful even at higher temperature (results not shown).

The isotopic labeling of organic compounds is an important area of research, constituting for example the <sup>14</sup>C labeling of potential drug molecules for metabolic studies.<sup>[21]</sup> Working with radioactive carbon-14, however, requires specialized laboratories. The capability of this transformation for the



**Scheme 3.** Carbonylative  $\alpha$ -arylation of various substituted 2-oxindoles, **1** (0.50 mmol, 0.25 M). CO was generated from COgen.

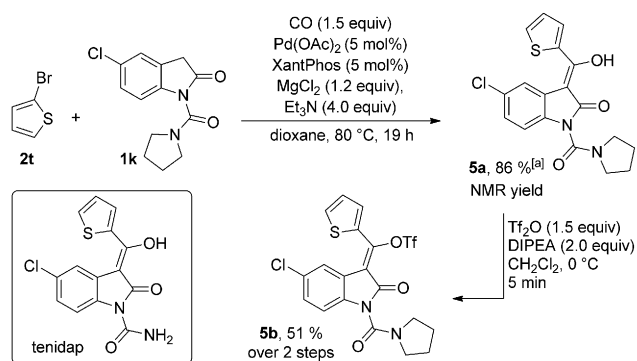
labeling of the acyl carbon in 3-acyl-2-oxindoles was therefore demonstrated using <sup>13</sup>CO generated from [<sup>13</sup>C]-COgen.<sup>[22]</sup> In this way, products [<sup>13</sup>C]-**3e** and [<sup>13</sup>C]-**3d** were isolated in yields comparable to those obtained for their unlabeled counterparts (Scheme 4).



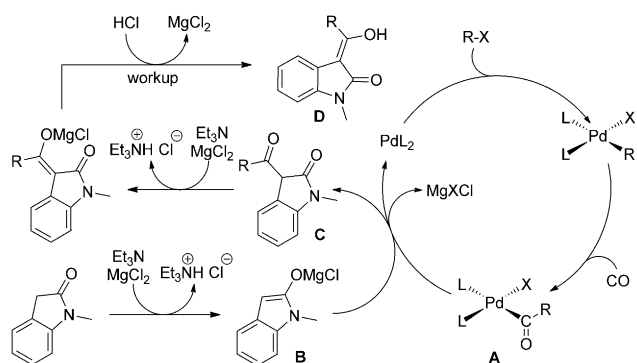
**Scheme 4.** Carbonylative  $\alpha$ -arylation to access [<sup>13</sup>C]-acyl 3-acyl-2-oxindoles using near stoichiometric amount of <sup>13</sup>CO (generated from [<sup>13</sup>C]-COgen).

The synthetic potential of this reaction was demonstrated by applying the methodology to the synthesis of a biologically interesting molecule (Scheme 5). An analogue of tenidap, a potent cyclooxygenase inhibitor,<sup>[5]</sup> was easily synthesized through the carbonylative  $\alpha$ -arylation of oxindole **1k** with 2-bromothiophene, affording product **5a** in 86 % NMR yield. Subsequent triflation of the enol allowed for purification by flash column chromatography and the isolation of compound **5b** in 51 % yield over two steps.

Finally, a proposed mechanistic scenario for this Pd-catalyzed transformation is illustrated in Figure 1. An oxidative addition of Pd<sup>0</sup> into the (hetero)aryl (pseudo)halide



**Scheme 5.** Application of the methodology for the synthesis of a tenidap analogue. The product was isolated as the corresponding triflate to allow purification. [a]  $^1\text{H}$  NMR yield with 1,3,5-trimethoxybenzene as internal standard.



**Figure 1.** Proposed mechanism for the carbonylative  $\alpha$ -arylation of 2-oxindoles.

bond, followed by coordination and migratory insertion of carbon monoxide provides the Pd acyl complex **A**.

Meanwhile, the oxindole coordinates to  $\text{MgCl}_2$  and is subsequently deprotonated by triethylamine, giving enolate **B**.<sup>[23]</sup> It is speculative whether this reacts directly with complex **A** through a nucleophilic acyl-type substitution, or undergoes a ligand exchange with the (pseudo)halide **X** followed by reductive elimination. Either way, the Pd catalyst is reformed along with the  $\beta$ -ketoamide **C**, which is immediately deprotonated by the combination of  $\text{MgCl}_2$  and triethylamine. Upon acidic work-up, the enolate is reprotonated to afford the desired 3-acyl-2-oxindole **D**.

In summary, a protocol for the direct transformation of a variety of aryl and heteroaryl bromides to 3-acyl-2-oxindoles through a Pd-catalyzed carbonylative  $\alpha$ -arylation of N-substituted 2-oxindoles has been described. The methodology is versatile, high yielding, and complementary to the majority of transformations providing access to this important structural motif. The potential for the transformation to be used in the radiolabeling of 3-acyl-2-oxindoles was demonstrated, along with the applicability to the synthesis of biologically relevant compounds.

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