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Journal Name

COMMUNICATION

Palladium-Catalyzed α-Arylation of Indolin-3-ones

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A method for the catalytic α-arylation of indolin-3-ones was developed. The catalytic system comprising $Pd(dba)_2$ and PAd_3 was found to be optimal for the transformation. The protocol features broad functional group compatibility in that a range of arylated indoxyl derivatives bearing a fully substituted carbon center was synthesized with high efficiency. A preliminary bioassay study revealed that selected indole-substituted indolin-3-ones exhibit favorable cytotoxic activities against HCT-116 cancer cell line.

Indolin-3-ones (indoxyls) are a key structural motif in naturally occurring alkaloids, bioactive compounds, dyeing agents and fluorescent probes.[1] In particular, 2-aryl-2-alkyl indolin-3-ones constitute a class of small organic molecules with great potential for biomedicinal applications (Figure 1).[2] To broadly search for new leads from this chemotype, reliable and efficient synthetic methods for accessing indolin-3-ones possessing a C2-fully substituted benzylic carbon are eminently desirable. A conventional route to such frameworks involves oxidative dearomatizations of 2-aryl-substituted indoles,[3] but the utilities of these methods are compromised by the limited availability of the starting arylindoles. Alternatively, elegant de novo syntheses of the indolinone scaffold with a concomitant installation of an aryl group at the C2 position have been delineated, typically requiring the use of sophisticatedly tailored precursors.[4] To gain entry to a wider array of 2-arylated indoxyls, we deemed that the direct α-arylation[5] of indolin-3-ones is a synthetically appealing option for rapid assembly of the compound libraries. The significance of 2-aryl-indolin-3-ones combined with our interests in the development of α-arylation reactions[6] motivated us to explore the direct coupling of the title compounds and haloarenes. In sharp contrast to extensively studied arylation of 2-oxindoles,[7] related chemistry with indoxyls remains rare. At the outset of this study, published methods for the α-arylation of indolin-3-ones only encompass non-catalytic approaches using aryllead triacetates[8] and diaryliodonium salts,[9] respectively, as the aryl donors. Until recently, Zhao, Xu, Yang and their co-workers developed an elegant Pd-catalyzed α-arylation of C2-unsubstituted indolin-3-ones for the construction of aza-tertiary benzylic centers, but the substrate scope on heteroaryl electrophiles is rather limited.[10] Mindful of all the above issues, developing an aza-quaternary center-forming arylation, which is still of great challenge in synthesis,[11] and establishing a broad (hetero)aryl bromide scope were critical considerations in this study. In the event, a general, high-yielding protocol for the palladium-catalyzed α-arylation of indolin-3-ones was developed, and we describe our results below.

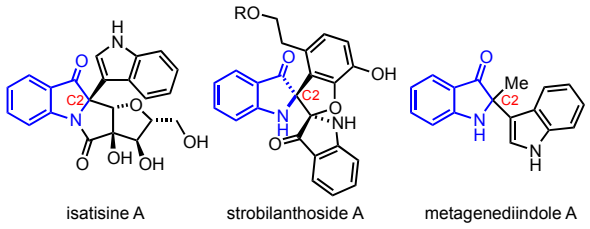

Figure 1 Examples of Bioactive Indolin-3-one Natural Products Containing a C2 Benzylic aza-Quaternary Center.

Our exploration commenced with evaluating the α-arylation of a model substrate **1a** with bromobenzene under palladium catalysis (Table 1). An initial screen for ligands in the presence of $Pd(OAc)_2$ indicated that *in situ* generated tri-*tert*-butylphosphine[12] is capable to marginally promote the arylation (entries 1-7). Significant decomposition to intractable materials was occurring in the case with KO*t*-Bu (entry 8), and the progress of the reaction with K_3PO_4 was sluggish (entry 9). Moving on to the more electron-releasing ligand, tris(1-adamantyl)phosphine (PAd_3)[13] was ultimately identified as the enabling choice (entry 10). On the other hand, switching the

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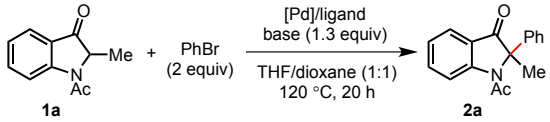
palladium source from $Pd(OAc)_2$ to $Pd(dba)_2$ posed a favorable effect on yields (entry 11). Attempted variations on solvents, reaction temperature, and a use of lower catalyst loadings led to inferior outcomes (entries 12-16).

Table 1 Evaluation of Conditions.[a]



entry	[Pd] (mol %)	ligand (mol %)	base	yield (%)[b]
1	$Pd(OAc)_2$ (6)	BINAP (8)	Cs_2CO_3	0
2	$Pd(OAc)_2$ (6)	DPPF (8)	Cs_2CO_3	0
3	$Pd(OAc)_2$ (6)	Xantphos (8)	Cs_2CO_3	0
4	$Pd(OAc)_2$ (6)	PhDavePhos (8)	Cs_2CO_3	0
5	PEPPSI-IPr (6)	-	Cs_2CO_3	0
6	$Pd(OAc)_2$ (6)	P(*t*-Bu)$_3$·HBF_4 (8)	Cs_2CO_3	19
7[c]	$Pd(OAc)_2$ (6)	P(*t*-Bu)$_3$·HBF_4 (8)	Cs_2CO_3[d]	7
8	$Pd(OAc)_2$ (6)	P(*t*-Bu)$_3$·HBF_4 (8)	KO*t*-Bu	0
9	$Pd(OAc)_2$ (6)	P(*t*-Bu)$_3$·HBF_4 (8)	K_3PO_4[d]	13
10	$Pd(OAc)_2$ (6)	PAd_3 (8)	Cs_2CO_3	60
11	$Pd(dba)_2$ (6)	PAd_3 (8)	Cs_2CO_3	67
12[e]	$Pd(dba)_2$ (6)	PAd_3 (8)	Cs_2CO_3	43
13[f]	$Pd(dba)_2$ (6)	PAd_3 (8)	Cs_2CO_3	24
14[g]	$Pd(dba)_2$ (6)	PAd_3 (8)	Cs_2CO_3	4
15[h]	$Pd(dba)_2$ (6)	PAd_3 (8)	Cs_2CO_3	0
16[i]	$Pd(dba)_2$ (3)	PAd_3 (4)	Cs_2CO_3	25

[a]Reactions were conducted with 0.2 mmol of **1a**. For detailed procedures, see the Supporting Information. [b]Yield of isolated product based on **1a**. [c]With THF/toluene (1:1) as the co-solvent. [d]1.1 equiv of base. [e]With THF as the sole solvent. [f]With dioxane as the sole solvent. [g]With dioxane as the sole solvent. The reaction was conducted at 80 °C. [h]The reaction was conducted at room temperature. [i]The reaction progress is relatively slow; compound **1a** was not fully consumed in 20 h.

With the optimized conditions in hand, we then explored the generality of this catalytic arylation (Table 2). A range of electron-neutral and electron-rich aryl bromides coupled with **1a** to give the corresponding products **2b**-**f** in good to excellent yields. The 1 mmol-scale synthesis of **2b** is of high efficiency, thus promising the scalability of this reaction (See the Supporting Information). Bromoarenes bearing electron-withdrawing fluoro, ester, and nitro groups are well compatible with the reaction (see **2g**-**i**). Heteroarylated products possessing a 5-indolyl, a 3-thienyl group or a 3-furyl were also prepared in good yields (see **2j**-**l**). Indolin-3-ones **1b**-**d** having different α-alkyl substituents were uneventfully converted to the target molecules **2m**-**q**. In the example of **1d** containing two enolizable carbonyls, relatively acidic C2-H of the indolinone nucleus was chemoselectively arylated. To further probe the scope of this reaction, the parent compound

Table 2 Scope of the C2-Arylation of Indolin-3-ones.

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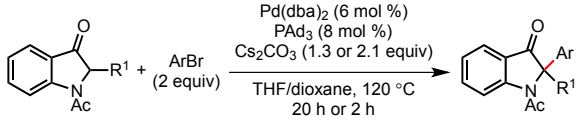
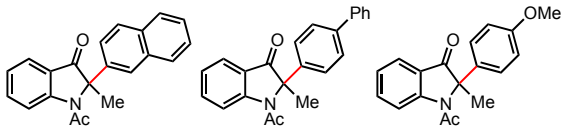


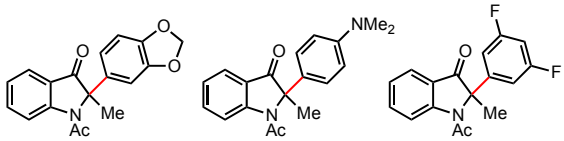
(0.2 mmol of **1**) R^1 = Bn; **1c**
R^1 = Me; **1a** R^1 = CH_2CO_2Et; **1d**
R^1 = crotyl; **1b** R^1 = H; **1e**

2, isolated yield

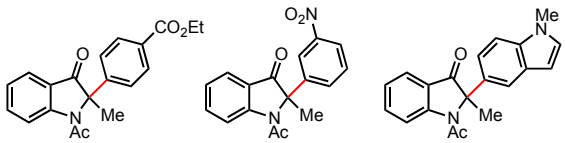
Formation of benzylic aza-quaternary center: 1.3 equiv of Cs_2CO_3, 20 h



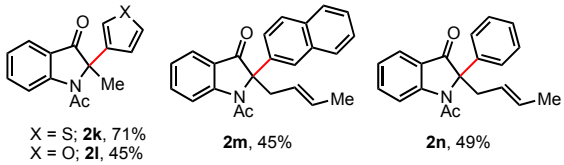
2b, 94% **2c**, 91% **2d**, 99%



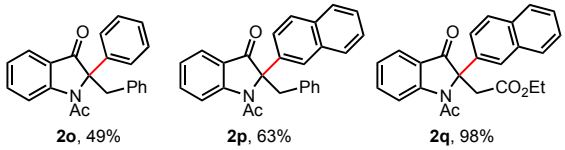
2e, 44% **2f**, 99% **2g**, 46%



2h, 86% **2i**, 63% **2j**, 69%

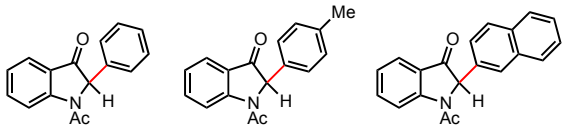


X = S; **2k**, 71%
X = O; **2l**, 45%
2m, 45% **2n**, 49%

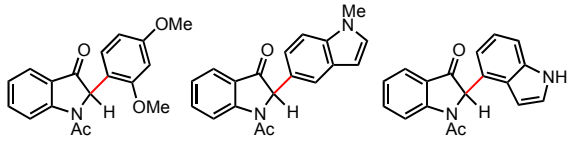


2o, 49% **2p**, 63% **2q**, 98%

Formation of benzylic aza-tertiary center: 2.1 equiv of Cs_2CO_3, 2 h



2r, 83% **2s**, 76% **2t**, 98%

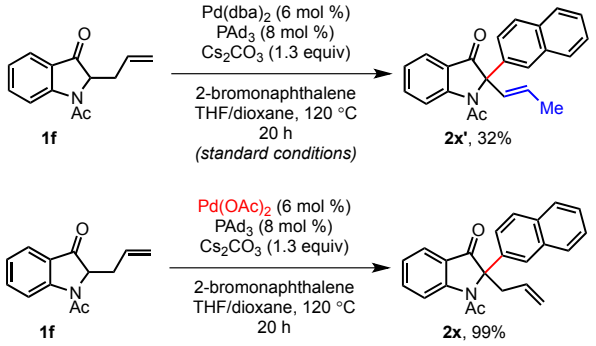


2u, 95% **2v**, 97% **2w**, 55%

1e was tested under the developed catalytic system. Since **1e** possesses two enolizable protons at C2, 2.1 equivalent of Cs_2CO_3 was applied to ensure a sufficient amount of base is in action for the first enolate formation. The arylation of **1e** also tolerated structurally diverse aryl donors (see **2r**-**w**) and is generally faster than the one with **1a**. It is noteworthy that **1e** reacted smoothly with 1-bromo-2,4-dimethoxybenzene without hampering by the *ortho*-methoxy group. An

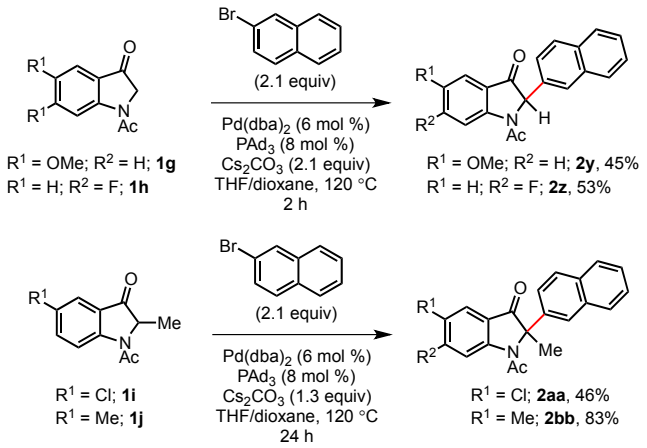
unprotected bromoindole is a viable coupling partner, showcasing the gentle nature of these conditions (see **2w**).

Under the standard conditions, the reaction of a 2-allyl indoxyl **1f** gave an unexpected arylated product **2x'** (Scheme 1), implying an apparent olefin isomerization was engaged in the process. We presumed the palladium complexes-mediated isomerization was driven by thermodynamic factors, as it was not observed in the substrates containing a crotyl group (see **2m** and **2n**). Intriguingly, **2x** was obtained in excellent yield when we applied $Pd(OAc)_2$ in lieu of $Pd(dba)_2$ as the catalyst. The rationale for the divergent reaction courses by catalyst control demands further in silico investigations.



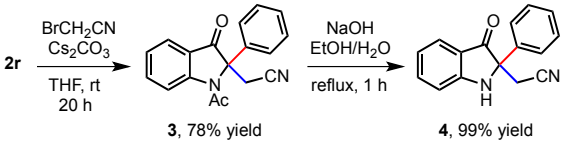
Scheme 1 Pd Catalyst-Controlled Reaction Courses.

The arylation reactions of the indoxyls **1g-j** bearing substituents at the aromatic backbone were also successfully executed (Scheme 2). The isolated yields of these reactions are synthetically useful yet lower as compared with those obtained with the parent compounds (see **1a** and **1e**). These comparisons indicate that the electronic perturbation of the aryl scaffold could subtly cause a reactivity difference.



Scheme 2 The arylation reactions of substituted indolin-3-ones.

We showed a base-promoted cyanomethylation of **2r** resulted in the formation of **3** in good yield (Scheme 3). This sequence represents a complementary, modular approach to set up the fully substituted benzylic carbon center. The acetyl group could be quantitatively removed, thus granting flexibility in further N-functionalization of **4**.



Scheme 3 Synthetic Derivatization of Compound **2r**.

Finally, we examined cytotoxicity of selected compounds against colon (HCT-116) and breast (MCF-7) cancer cells by MTT assay. The preliminary data revealed that **2j** and **2v** exhibit favorable cytotoxic activities against HCT-116 at an IC_{50} = 15.8 and 19.9, respectively. It is worth noting that these two molecules structurally resemble a bioactive indole alkaloid, metagenebiindole A (Figure 1) which demonstrates moderate cytotoxicities against CNE2, Bel7402 and HT1080 cell lines at IC_{50} values = 34.3, 43.6 and 35.8 μg/mL respectively.[2a] Interestingly, we also found both **2j** and **2v** are selectively potent against colon-derived carcinoma but not breast-derived ones, indicating the likely tissue-specific activities. Overall, these results point out a promising direction to explore structure-activity relationship (SAR) based on chemical modifications of the 2-indolyl-indolin-3-one core.

Table 3. In Vitro Activities of the Indole-containing Compounds against Cancer Cell Lines (HCT-116 and MCF-7).[a]

	IC_{50} (μg/mL) against the cell line	
compound	HCT-116	MCF-7
2f	>100	>100
2g	>100	>100
2h	34.9	36.9
2i	95.5	>100
2j	15.8	>100
2q	>100	>100
2v	19.9	63.1
2w	63.0	74.1

[a] IC_{50} (half maximal inhibitory concentration) was determined by MTT assay. HCT-116 = human colorectal carcinoma; MCF-7 = human breast adenocarcinoma.

In summary, we have developed a general protocol for the palladium-catalyzed α-arylation of indolin-3-ones. A wide array of (hetero)arylated indoxyl derivatives were synthesized in good to excellent yields. Selected indole-substited substrates display promising bioactivity profiles against HCT-116. These works encouraged an ongoing SAR investigation, and the results will be reported in due course.

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Conflicts of interest

There are no conflicts of interests to declare.

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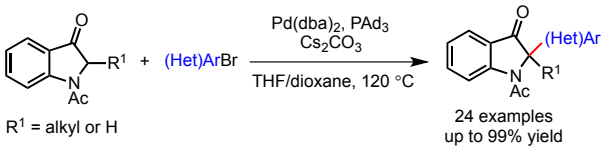

R^1 = alkyl or H

24 examples
up to 99% yield

A general route to C2-(hetero)arylated indolin-3-ones bearing a fully substituted α-center was established.