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Palladium-Catalyzed Synthesis of *N*-Aryl-2-benzylindolines via Tandem Arylation of 2-Allylaniline: Control of Selectivity through in Situ Catalyst Modification

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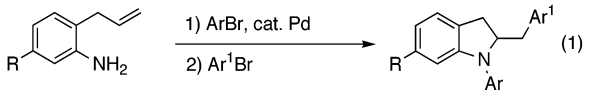
Single-pot catalysis of two different transformations holds great promise for the rapid buildup of molecular complexity.[1] Strategies that can potentially be applied to combinatorial or diversity-oriented approaches to libraries of compounds bearing common pharmacophores (e.g., indolines or other nitrogen heterocycles)[2] from readily available starting materials may prove to be highly valuable in areas of drug discovery and chemical biology.[3] However, the development of processes that involve distinctly different sequential metal-catalyzed reactions is complicated by the fact that many transformations require very specific catalysts or ligands in order to achieve optimal yields and selectivity.[1]

In this Communication, we describe a Pd-catalyzed sequential N-arylation[4]/cyclization/C-arylation reaction between 2-allylaniline and two different aryl halides.[5] The selective installation of two different aryl groups in these reactions is accomplished by in situ modification of the palladium catalyst through ligand exchange. This one-pot sequence of transformations leads to the formation of two C−N bonds and one C−C bond and provides a straightforward method for the three-component synthesis of a diverse variety of indoline derivatives (eq 1).[6,7]

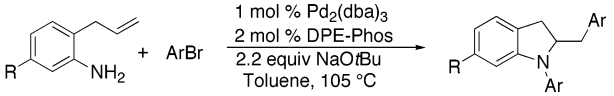


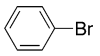
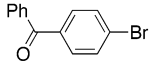
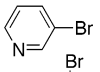
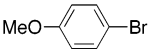
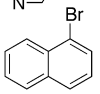
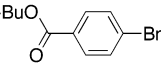
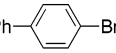
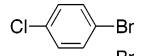
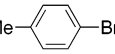
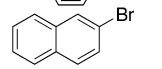
To determine the feasibility of the N-arylation/carboamination process, we first examined the reaction of 2-allylaniline with 2 equiv of bromobenzene. We were pleased to find that use of a catalyst comprised of $Pd_2(dba)_3$ and dpe-phos[8] in the presence of NaO*t*Bu (2.2 equiv) provided the desired *N*-phenyl-2-benzylindoline in 92% isolated yield (Table 1, entry 1). A variety of electron-neutral and -deficient aryl bromides are effectively transformed under these conditions, several functional groups are tolerated (entries 6−9), and the heterocyclic substrate 3-bromopyridine also afforded the indoline product in good yield (entry 2). Reactions of the electron-rich substrate 2-allyl-5-methoxyaniline proceeded smoothly (entries 8−10), but transformation of the electron-rich 4-bromoanisole required use of the Xantphos ligand[8] to prevent Heck arylation of the substrate (entry 7).[9]

Having demonstrated the viability of the one-pot diarylation process, we set out to achieve the selective addition of two different aryl bromides. However, when 2-allylaniline was treated with a single equivalent of 2-bromonaphthalene in the presence of a $Pd_2(dba)_3$/dpe-phos catalyst at 105 °C, the formation of a 4:1 mixture of N-arylated 2-allylaniline **2** and the *N*-aryl-2-benzylindoline product **3** was observed (eq 2).[10]

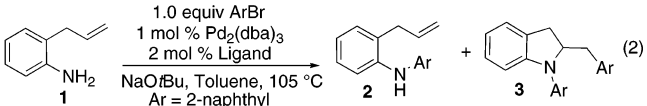
We felt the selective formation of **2** could be achieved by employing a bulky, electron-rich phosphine ligand,[4] and we were pleased to find that use of a catalyst comprised of $Pd_2(dba)_3$ and *t*-Bu_2P(*o*-biphenyl) (**4**)[11] afforded exclusively the N-arylated product

Table 1. *N*-Aryl-2-benzylindoline Synthesis[a]



Entry	R	ArBr	Yield	Entry	R	ArBr	Yield
1	H		92	6	H		93
2	H		87	7	H		44[b,c]
3	H		84	8	OMe		78
4	H		88	9	OMe		75
5	H		73	10	OMe		70

[a] Conditions: 1.0 equiv of 2-allylaniline, 2.05 equiv of ArBr, 2.2 equiv of NaO*t*Bu, 1 mol % $Pd_2(dba)_3$, 2 mol % dpe-phos, toluene (0.25 M), 105 °C. [b] Xantphos used in place of dpe-phos. [c] *N*-(4-Methoxyphenyl)-2-methylindole was also isolated from the reaction mixture in 24% yield.



Ligand = dpe-phos: 4:1, 80% conversion
Ligand = (*t*-Bu)$_2$P(*o*-biphenyl) (**4**):93% yield of **2**

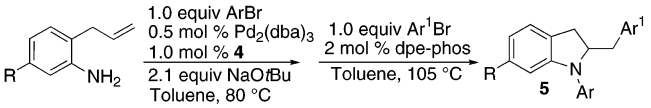
2 (eq 2). However, we were concerned that the properties of this ligand would also favor N-arylation in the second step of the one-pot process,[12] rather than the desired cyclization reaction.[13] As expected, our attempts to use the $Pd_2(dba)_3$/**4** catalyst system for the sequential transformation afforded complex mixtures of products.[14]

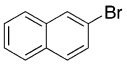
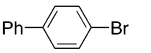
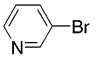
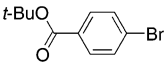
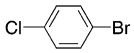
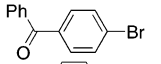
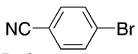
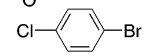
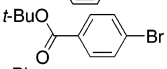
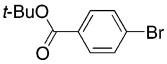
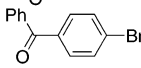
One potential solution to this problem would be simply to isolate the monoarylated material and subject the product to a second transformation. However, this would introduce an additional step into the synthesis and would also require the use of additional palladium. A more desirable solution would be to change the properties of the catalyst in situ after the first N-arylation reaction by using a chelating bis(phosphine) ligand such as dpe-phos to displace **4** from the metal. This ligand exchange should slow the rate of a second N-arylation relative to cyclization,[15] thus facilitating the selective N-arylation/cyclization/C-arylation process.

Accordingly, 2-allylaniline was treated with bromobenzene (1.0 equiv) in the presence of 2.1 equiv of NaO*t*Bu and catalytic $Pd_2(dba)_3$/**4**. Upon complete consumption of the bromobenzene,[16] a solution of a catalytic amount (2 mol %) of dpe-phos was added to the reaction mixture, and after 10 min of stirring at 80 °C, 1 equiv of 2-bromonaphthalene was added. After an additional 45 min of heating at 105 °C, the desired product **5** was cleanly formed; an

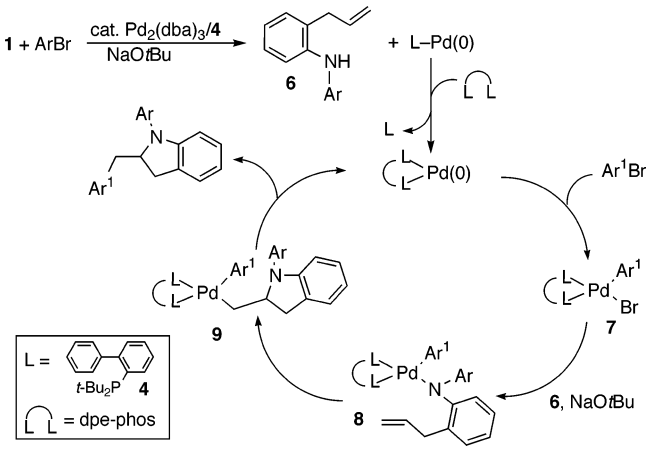
10.1021/ja0460920 CCC: $27.50

Table 2. Sequential Arylation Reactions



Entry	R	ArBr	Ar^{1}Br	Yield
1	H			88%
2	H			84%
3	H			85%
4	H			52%
5	OMe			88%
6	OMe			78%

Scheme 1. Proposed Catalytic Cycle



88% isolated yield was obtained upon workup and purification (Table 2, entry 1). This procedure is effective for several different combinations of aryl halides (Table 2).

Our proposed catalytic cycle for this transformation is shown in Scheme 1. Following the Pd/**4**-catalyzed N-arylation of 2-allylaniline,[4] a key substitution of the dpe-phos ligand for **4** is proposed to occur. This ligand exchange decreases the electron density on the palladium catalyst and facilitates the alkene insertion process. The dpe-phos/Pd(0) species reacts with the aryl bromide substrate to afford Pd(II) complex **7**. This intermediate is likely transformed to palladium amido complex **8** upon reaction with the *N*-aryl-2-allylaniline **6** and NaO*t*Bu.[4] Insertion of the alkene into the Pd−N bond affords **9**,[5,17] which undergoes C−C bond-forming reductive elimination[18] to provide the *N*-aryl-2-benzylindoline.

In conclusion, we have developed a new method for the synthesis of *N*-aryl-2-benzylindoline derivatives via a palladium-catalyzed tandem arylation of 2-allylanilines. This transformation leads to the formation of two C−N bonds and one C−C bond in a one-pot process, and high selectivity is observed for the sequential installation of two different aryl groups. The selectivity is achieved by a key in situ modification of the catalyst such that a bulky, electron-rich, monodentate ligand, which facilitates N-arylation, is exchanged with a chelating ligand that promotes olefin insertion of the intermediate palladium(aryl)amido complex in preference to C−N bond-forming reductive elimination.

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Supporting Information Available: Characterization data for all new compounds in Tables 1−2. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) dpe-phos = bis(2-diphenylphosphinophenyl)ether. Xantphos = 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene.

(9) *N*-(4-Methoxyphenyl)-2-methylindole was also isolated in 24% yield. This side product may arise from β-hydride elimination/isomerization of **9** due to relatively slow reductive elimination of the more electron-rich arylpalladium complex. See: Culkin, D. A.; Hartwig, J. F. *Organometallics* **2004**, *23*, 3398.

(10) Decreasing the reaction temperature to 70 °C failed to increase the selectivity for monoarylation.

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(13) Use of the $Pd_2(dba)_3$/**4** catalyst system in reactions of γ-(*N*-arylamino)-alkenes with aryl halides afforded exclusively N,N-diarylated products. See ref 5a.

(14) A complex mixture of N,N-diarylated- and N-monoarylated olefin isomers was generated along with a small amount of **3**.

(15) Four-coordinate arylpalladium amido complexes undergo C−N bond-forming reductive elimination more slowly than three-coordinate complexes. See: Yamashita, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 5344.

(16) The reaction was monitored by GC analysis, and the N-arylation was found to be complete and essentially quantitative after 30 min at 80 °C.

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