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A General and Practical Palladium-Catalyzed Direct α-Arylation of Amides with Aryl Halides

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Abstract: An efficient system for the direct catalytic intermolecular α-arylation of acetamide derivatives with aryl bromides and chlorides is presented. The palladium catalyst is supported by Kwong's indole-based phosphine ligand and provides monoarylated amides in up to 95% yield. Excellent chemoselectivities (>10:1) in the mono- and diarylation with aryl bromides were achieved by careful selection of bases, solvents, and stoichiometry. Under the coupling conditions, the weakly acidic α-protons of amides (pK_a up to 35) were reversibly depotonated by lithium *tert*-butoxide (LiO-*t*-Bu), sodium *tert*-butoxide (NaO-*t*-Bu) or sodium bis(trimethylsilyl)amide [$NaN(SiMe_3)_2$].

Keywords: amides; aryl halides; C–C bond formation; chemoselectivity; cross-coupling; palladium

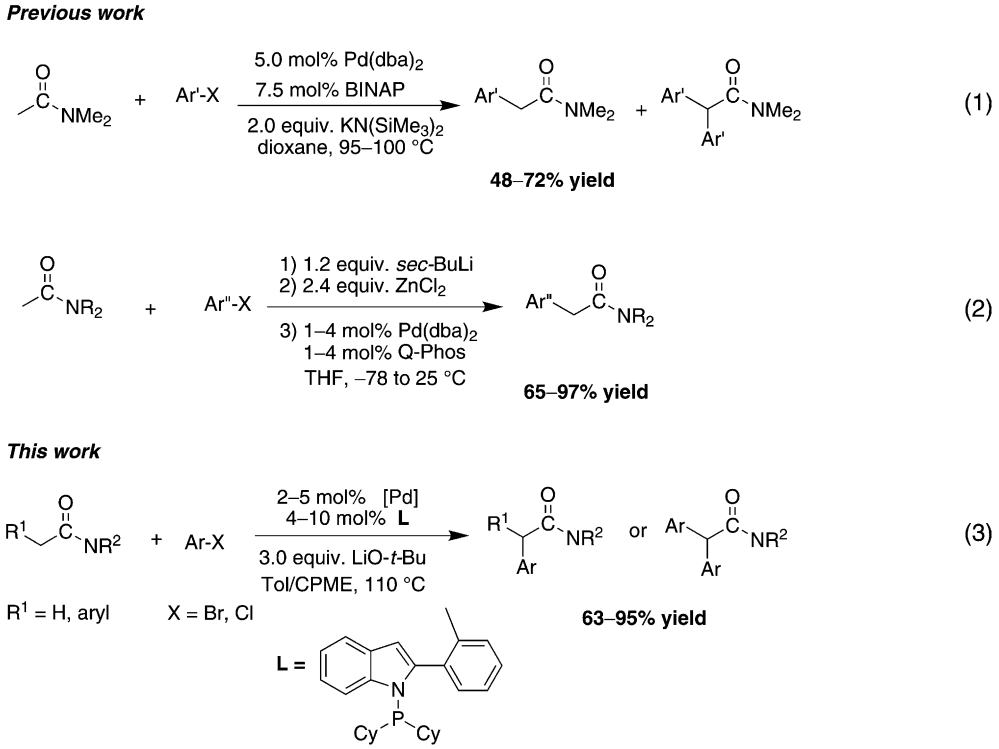
Introduction

Amides are synthetically versatile intermediates for the synthesis of biologically active molecules[1,2] and pharmaceuticals.[3] An efficient strategy to access a diverse array of amides is *via* the direct arylation of unfunctionalized amides.[4,5] Although remarkable progress has been made in the palladium catalyzed α-arylation of ketones, esters,[6,7,8] and oxindoles,[9] only limited examples of catalytic intermolecular α-arylation of amides have been reported.[5a–c] This is most likely due to the high pK_a values of amide α-C–H bonds[10] and the potential formation of over-arylation by-products.[5a]

In pioneering investigations on the α-arylation of amides, Hartwig and co-workers demonstrated that aryl bromides reacted with *N,N*-dialkylacetamide derivatives in the presence of $KN(SiMe_3)_2$, catalytic $Pd(dba)_2$ and BINAP at 95–100 °C [Scheme 1, Eq. (1)].[5c] The α-arylation products were obtained in 48–72% yield. The moderate yields were partially due to formation of diarylated byproducts. In light of the challenging nature of this reaction, the scope of aryl bromides and acetamide derivatives reported was limited.

In 2006, Hartwig and co-workers introduced a two-step approach to the palladium-catalyzed arylation of zinc amide enolates,[5b] which exhibited higher yields and broader substrate scope [Scheme 1, Eq. (2)].[5a] To circumvent the challenges of direct arylation, the zinc amide enolates[11] were generated by deprotonation of the amides with *sec*-BuLi in the presence of $ZnCl_2$ at −78 °C.[12,13,14] The resulting zinc enolates smoothly underwent palladium-catalyzed arylation at 25–70 °C. Despite these advances, more general, practical and atom-economical approaches for the α-arylation of amides remain desirable.

Following our interest in the catalytic functionalization of weakly acidic sp^3-hybridized C–H bonds[15] (pK_a values 28–35 in DMSO), we developed approachs for deprotonative cross-coupling processes (DCCP), wherein *in situ* deprotonation of a substrate is performed in the presence of a palladium catalyst that promotes the arylation. Examples of substrates amenable to this approach include diarylmethanes,[16] chromium-activated benzylic amines,[15] sulfoxides[17] and sulfones.[18a] Based on our success with these substrates, we explored the palladium-catalyzed DCCP amides (pK_a >35) with aryl halides. Herein we report the selective mono- and bisarylation of *N,N*-dialkylacetamide derivatives employing Kwong's indole-based palladium catalyst in the presence of alkoxide and amide bases [Scheme 1, Eq. (3)]. A portion of this work has been communicated.[18b]



Scheme 1. Intermolecular α-arylation of amides.

Results and Discussion

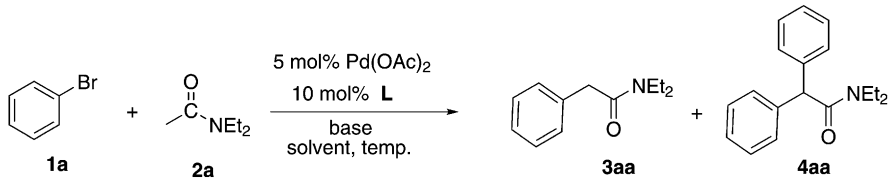
Given the high pK_a values of amides and our successful direct arylation of sulfoxides[17] (pK_a 32–35) and sulfones[18] (pK_a 28–32) with palladium and Kwong's indole-based ligand **L** [Scheme 1, Eq. (3)],[19] we initiated our study with the same catalyst. The challenge was perceived to control the extent of arylation, because the monoarylation product is more acidic than the starting acetamide. Therefore, a second arylation could be problematic.[20]

Optimization of Base and Solvent Combinations for the α-Arylation of Amides

Using 5 mol% $Pd(OAc)_2$ and 10 mol% Kwong's ligand **L**[19] [Scheme 1, Eq. (3)] at 110 °C in the presence of bromobenzene (**1a**, 2 equiv.) and *N,N*-diethylacetamide (**2a**, 1 equiv.) as coupling partners, we first set out to identify bases and solvents. The results of these experiments are summarized in Table 1. Six bases [LiO-*t*-Bu, NaO-*t*-Bu, KO-*t*-Bu, $LiN(SiMe_3)_2$, $NaN(SiMe_3)_2$, and $KN(SiMe_3)_2$] were examined in toluene and led to the monoarylated product **3aa** in up to 60% yield. LiO-*t*-Bu was the most effective base under these conditions, affording **3aa** in 60% yield and the diarylated product **4aa** in 9% yield (entry 1). In contrast, NaO-*t*-Bu and KO-*t*-Bu led to mixtures of monoarylated **3aa** and diarylated **4aa** in approximately a 1:1 ratio (entries 2 and 3). Of the silylamide bases screened, $NaN(SiMe_3)_2$ generated the diarylation product **4aa** in quantitative assay yield (entry 5) and $LiN(SiMe_3)_2$ afforded the diarylation product in 82% yield (entry 4). The stronger base $KN(SiMe_3)_2$ resulted in lower yields, most likely due to decomposition of starting materials (entry 6). It is interesting that the bases have such a strong impact on the ratios of the mono- and diarylated products, especially considering that the alkoxide bases are stronger than the silylamide bases in solvents like DMSO. With the optimal base in hand, three common solvents were next examined. Cyclopentyl methyl ether (CPME), dioxane and THF all afforded mixtures of mono- and bisarylated products. With LiO-*t*-Bu as the base, less than 3:1 selectivity was observed (entries 7–9). Lowering the temperature to 80 °C in toluene resulted in only trace formation of **3aa** (entry 10).

To improve the yield and selectivity for the monoarylated product **3aa**, various Pd to phosphine ratios and Pd sources were investigated (Table 2). Interestingly, decreasing the catalyst loading from 5 mol% to 2.5 mol% resulted in an increase in the yield of **3aa** from 60% to 74% with only 8% of diarylated **4aa** (Table 2, entries 1–2).[21] Further decreasing the catalyst loading to 2.0 or 1.25 mol% led to lower yields of monoarylated product (entries 2 *vs.* 3–4). In addition, we found that $Pd(dba)_2$ generally gave lower yields than $Pd(OAc)_2$ (Table 2, entries 5 and 6 *vs.* entries 1 and 2).

Table 1. Optimization of bases and solvents for the α-arylation of *N,N*-diethylacetamide (**2a**) with bromobenzene (**1a**).[a]

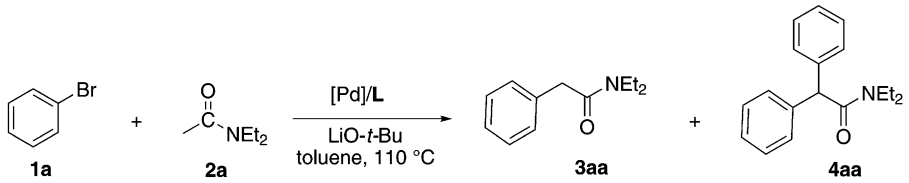


1a 2a 3aa 4aa

Entry	Base	Solvent	Temperature [°C]	Yield of **3aa**[b] [%]	Yield of **4aa**[b] [%]
1	LiO-*t*-Bu	toluene	110	60	9
2	NaO-*t*-Bu	toluene	110	36	38
3	KO-*t*-Bu	toluene	110	46	28
4	$LiN(SiMe_3)_2$	toluene	110	6	82
5	$NaN(SiMe_3)_2$	toluene	110	0	>95
6	$KN(SiMe_3)_2$	toluene	110	4	50
7	LiO-*t*-Bu	CPME	110	35	20
8	LiO-*t*-Bu	dioxane	110	34	14
9	LiO-*t*-Bu	THF	80	15	6
10	LiO*t*Bu	toluene	80	trace	trace

[a] Reactions performed using 2.0 equiv. of **1a**, 1.0 equiv. of **2a** and 3.0 equiv. of base on a 0.2-mmol scale.
[b] NMR yield.

Table 2. Optimization of the catalysts and Pd:**L** ratios in the α-arylation with bromobenzene (**1a**) and *N,N*-diethylacetamide (**2a**).[a]



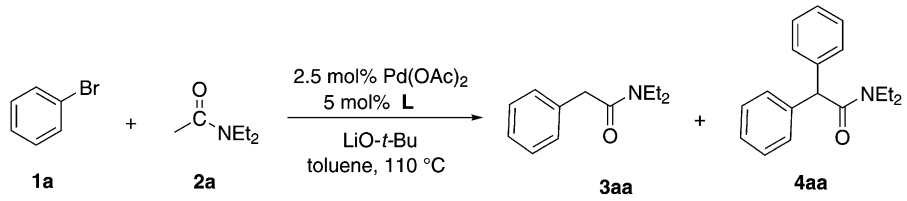
1a 2a 3aa 4aa

Entry	[Pd]/**L** [mol%]	[Pd]	Yield of **3aa**[b] [%]	Yield of **4aa**[b] [%]
1	5/10	$Pd(OAc)_2$	60	9
2	2.5/5	$Pd(OAc)_2$	74	8
3	2/4	$Pd(OAc)_2$	65	6
4	1.25/2.5	$Pd(OAc)_2$	38	4
5	5/10	$Pd(dba)_2$	65	12
6	2.5/5	$Pd(dba)_2$	33	5

[a] Reactions performed using 2.0 equiv. of **1a**, 1.0 equiv. of **2a** and 3.0 equiv. of LiO-*t*-Bu on a 0.2-mmol scale.
[b] NMR yield.

After $Pd(OAc)_2$ was identified as the palladium source with Kwong's ligand **L**, we examined the impact of the ratios of bromobenzene (**1a**) to amide **2a** (Table 3). In general, increasing the equivalence of amide **2a** resulted in higher yields of **3aa**. The best result was observed when the reaction was conducted with a 2:1 ratio of **2a**:**1a** (92% yield, Table 3, entry 1), where only trace amounts of **4aa** formed (~2%). When the equivalents of amide **2a** were lowered to 1.8, the yield decreased to 79% (entry 2). Use of 1.5 equiv. **2a** provided the monoarylated product **3aa** in 82% yield while further decreasing **2a** to 1.2 equiv. resulted in 85% yield of the monoarylation product and 6% bisarylation (entries 3 and 4). Further experimentation indicated that moderate yields (60–71%) of **3aa** as well as 11–24% of bisarylation by-product **4aa** were obtained when 1.2–1.8 equiv. of aryl bromide **1a** were employed (entries 5–7). Increasing or decreasing the reaction concentrations did not result in improved yields (entries 9 and 10). Thus, our best conditions for the synthesis of monoarylated amide **3aa** entailed 2 equiv. of amide, 1 equiv. of aryl bromide, and 3 equiv. LiO-*t*-Bu in the presence of 2.5 mol% $Pd(OAc)_2$ and 5.0 mol% **L** in toluene at 110 °C for 12 h.

Table 3. Optimization of the ratio of **2a**:**1a** in the α-arylation of amides.[a]



1a 2a 3aa 4aa

Entry	Ratio of **2a:1a**	NMR yield of **3aa** [%]	NMR yield of **4aa** [%]
1	2/1	92	2
2	1.8/1	79	4
3	1.5/1	82	10
4	1.2/1	85	6
5	1/1.2	62	13
6	1/1.5	71	11
7	1/1.8	60	24
8	1/2	74	8
9[b]	2/1	79	1
10[c]	2/1	83	2

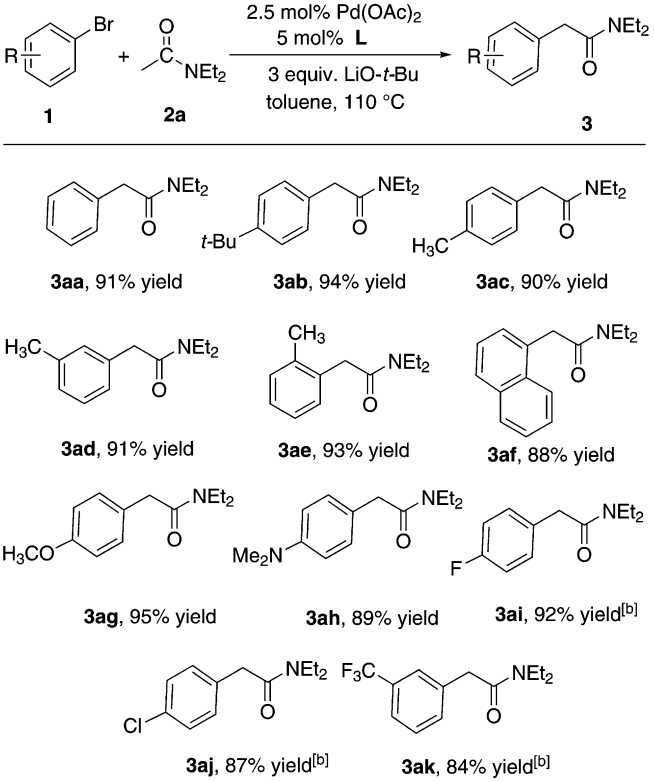
[a] Reactions performed using **1a**, **2a** and 3.0 equiv. of LiO-*t*-Bu on a 0.2-mmol scale.
[b] Concentration was 0.1 mol/L.
[c] Concentration was 0.3 mol/L.

Scope of the Amide Arylation with Aryl Bromides

With optimized conditions in hand, the scope of aryl bromides was investigated with amide **2a** (Table 4). Aryl bromides with alkyl substituents (**1a–f**) were good substrates, providing the desired products in 88–94% yields. It is noteworthy that sterically demanding 2-bromotoluene (**1e**) and 1-bromonaphthalene (**1f**) generated the corresponding products in 93 and 88% yield, respectively. Aryl bromides with electron-donating groups, such as 4-methoxy (**1g**) and 4-*N,N*-dimethylamino (**1h**) underwent coupling reactions smoothly giving **3ag** and **3ah** in 95% and 89% yield, respectively. Aryl bromides with electron-withdrawing substituents, such as 4-bromofluorobenzene (**1i**), 4-bromochlorobenzene (**1j**) and 3-trifluoromethylbromobenzene (**1k**), however, required slightly higher $Pd(OAc)_2$ (4 mol%) and ligand loadings (8 mol%) to achieve satisfactory yields (84–92%). Under the optimal conditions, the ratio of monoarylation to diarylation products in the crude reaction mixtures were greater than 15:1, as determined by ^1H NMR.

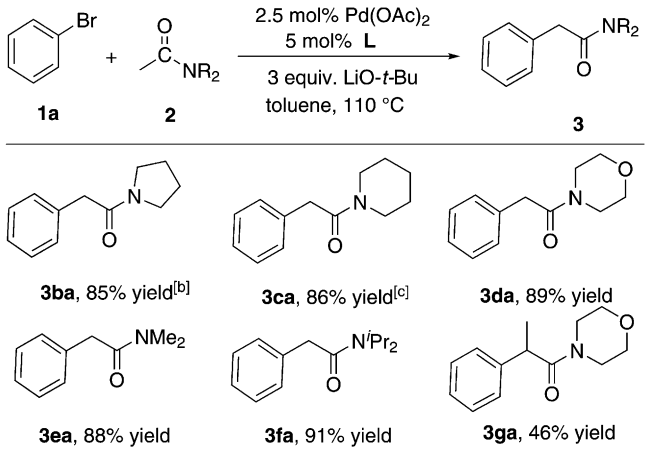
We next examined the reactivity of substrates with different substituents on the acetamide nitrogen (Table 5).[22,23] The arylation of pyrrolidine-substituted amide (**2b**) proceeded in 85% yield at lower temperature (90 °C) with bromobenzene (**1a**). The piperidine- (**2c**) and morpholine- (**2d**) substituted amides coupled with bromobenzene to give the products **3ca** and **3da** in 86 and 89% yield, respectively. In the case of the piperidine-substituted amide (**2c**), the loading of LiO-*t*-Bu was decreased to 2 equiv. to avoid over-arylation. Both *N,N*-dimethyl- (**2e**) and *N,N*-diisopropylacet-

Table 4. Substrate scope of aryl bromides in the α-arylation with **2a**.[a]



[a] Reactions performed using 1.0 equiv. of **1** and 2.0 equiv. of **2a** on a 0.2-mmol scale.
[b] 4 mol% $Pd(OAc)_2$ and 8 mol% **L** used.

Table 5. Substrate scope of amides in the α-arylation with **1a**.[a]



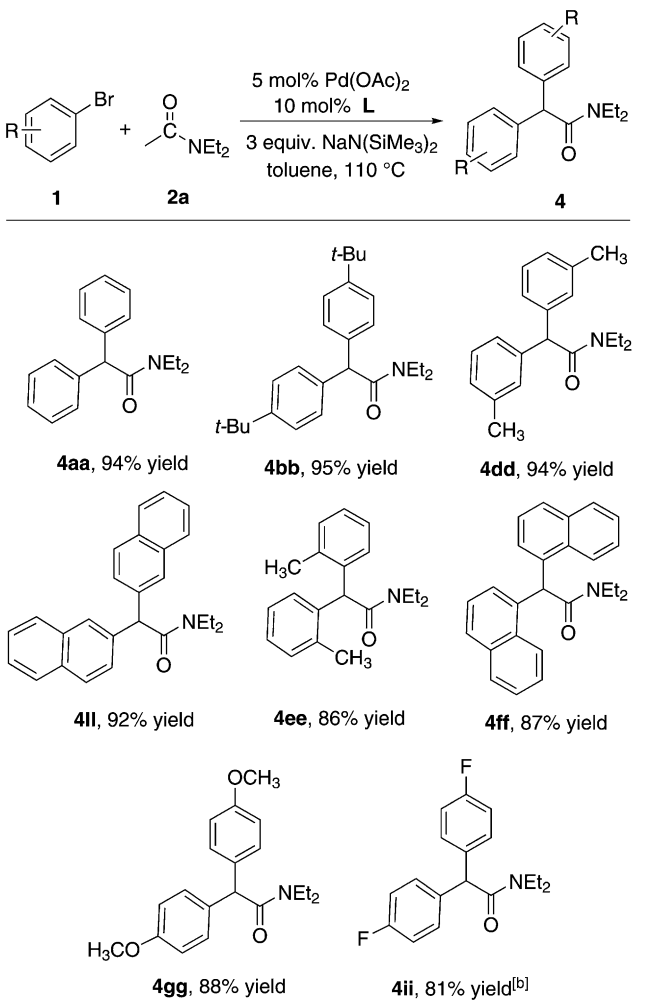
[a] Reactions performed using 1.0 equiv. of **1a**, 2.0 equiv. of **2** on a 0.2-mmol scale.
[b] 90 °C.
[c] 2.0 equiv. LiO-*t*-Bu employed.

amides (**2f**) reacted with bromobenzene (**1a**) to form the monoarylated products **3ea** and **3fa** in 88 and 91% yield, respectively. Extending the amide carbon chain to proprionamide proved to be challenging, resulting in 46% yield of **3ga**, despite significant efforts to optimize this substrate. There are several factors that could account for the lower yield, including the higher pK_a of the α-C–H. A β-hydride elimination pathway is also possible, although no such products were isolated. Overall, the results in Table 4 and Table 5 support the generality of the acetamide substrates.

Development of the Diarylation of Acetamides

To increase the diversity of products accessible by this method,[25] we developed a one-pot strategy to synthesize diarylated amides directly from acetamides. As described in Table 1 (entry 5), diarylated acetamide **4aa** was generated with good yield and excellent selectivity when $NaN(SiMe_3)_2$ was used as the base. A number of diarylated acetamides was readily prepared using a 2:1 ratio of aryl bromide to acetamide with 3 equiv. $NaN(SiMe_3)_2$ (Table 6). Bromobenzene (**1a**), 4-*tert*-butylbromobenzene (**1b**), 3-bromotoluene (**1d**) and 2-bromonaphthalene (**1l**) provided bisarylation products in 92–95% yield. We also investigated the sterically hindered aryl bromides 2-bromotoluene (**1e**) and 1-bromonaphthalene (**1f**), providing the coupling products **4ee** and **4ff** in 86% and 87% yield, respectively. Electron-rich 4-bromoanisole (**1g**) also underwent coupling in good yield (88%). Use of electron-withdrawing 4-bromofluorobenzene (**1i**) proved

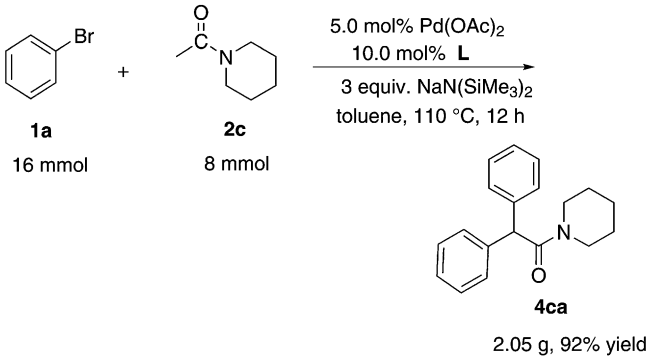
Table 6. Substrate scope of aryl bromides in the diarylation with **2a**.[a]



[a] Reactions performed using 2.0 equiv. of **1**, 1.0 equiv. of **2a** on a 0.2-mmol scale.
[b] 10 mol% $Pd(OAc)_2$ and 20 mol% **L** used.

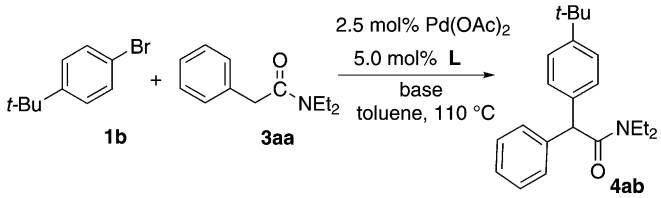
to be more challenging, giving 81% yield of **4ii** at 10 mol% catalyst loading. To illustrate the potential of this protocol for preparative purposes, the reaction of amide **2c** with bromobenzene was carried out on a gram-scale,[26] generating diarylated **4ca** in 92% yield (Scheme 2). Overall, the diarylation of amides outlined above provides easy access to diarylacetamides in high yield.

We were interested in extending the amide α-arylation to *N,N*-diethyl-2-phenylacetamide **3aa** with aryl bromides. Since the pK_a of **3aa**[27] is roughly 8 orders of magnitude lower than that of the corresponding acetamide **2a**,[10] it is much easier to deprotonate the α-proton of **3aa** to generate the amide enolate. Unlike the arylation of acetamide derivatives, the use of LiO-*t*-Bu as the base was not optimal (32% yield, Table 7, entry 1). A short survey of bases revealed



Scheme 2. The α-arylation of amide (**2c**) with **1a** on a gram scale.

Table 7. Optimization of the monoarylation of **3aa** with **1b**.[a]



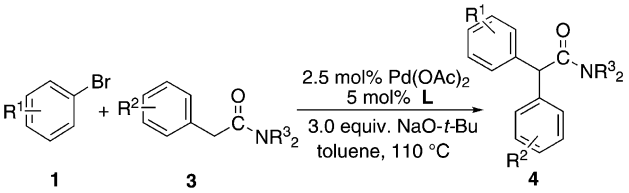
Entry	Base	NMR yield of **4ab** [%]
1	LiO-*t*-Bu	32
2	NaO-*t*-Bu	95[b]
3	KO-*t*-Bu	75
4	$LiN(SiMe_3)_2$	63
5	$NaN(SiMe_3)_2$	55
6	$KN(SiMe_3)_2$	32
7	NaO-*t*-Bu	81[c]

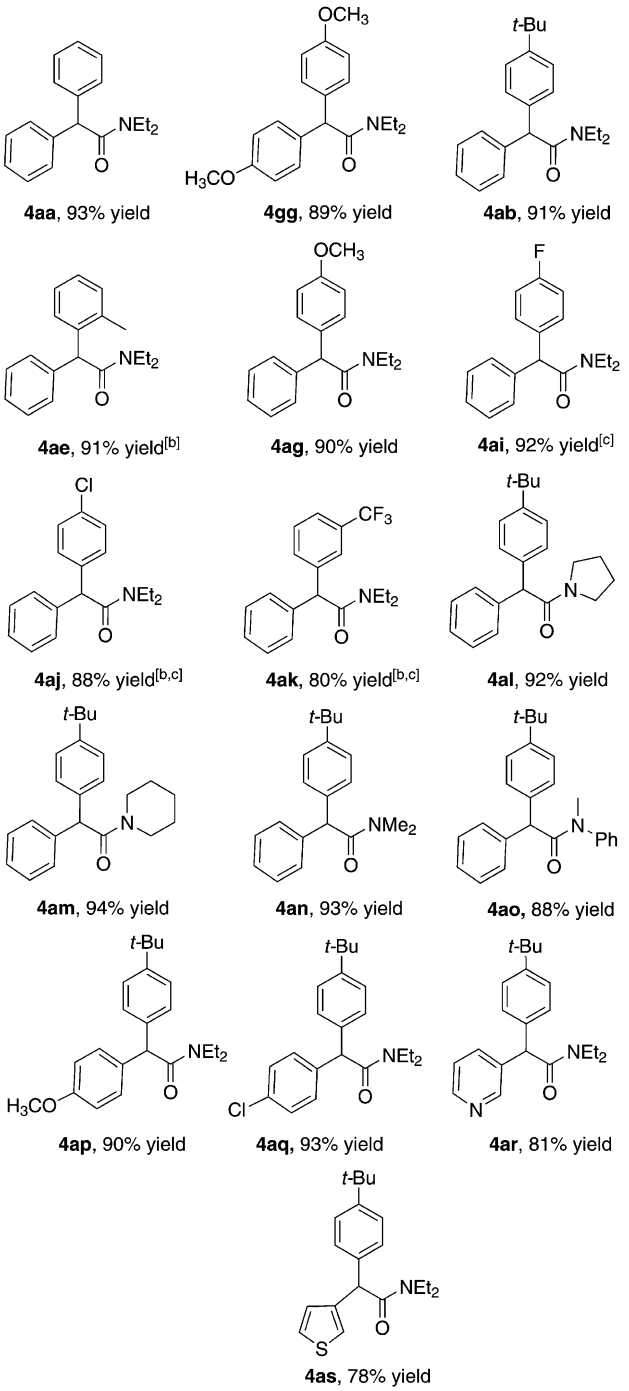
[a] Reactions performed using 1.5 equiv. of **1b**, 1.0 equiv. of **3aa** and 3.0 equiv. of base on a 0.2-mmol scale.
[b] 91% isolated yield.
[c] 1.2 equiv. of **1b** employed.

that NaO-*t*-Bu was the most suitable base under our conditions (Table 7, entry 2 *vs.* 1, 3–6). The reaction furnished the product **4ab** in 95% yield when a 1.5:1 ratio of aryl bromide to amide was employed. However, when the ratio of aryl bromide to **3aa** was lowered to 1.2:1, the yield decreased to 81% (Table 7, entry 7). The yield also dropped to 75% using the more reactive base KO-*t*-Bu (Table 7, entry 4). The data in Table 7 highlight the importance of the cation on this transformation.

The substrate scope of the monoarylation was investigated next. Various aryl bromides were screened under the optimized conditions using NaO-*t*-Bu as the base (Table 8). Similar yields for the synthesis of **4aa** and **4gg** were obtained from either monoarylated precursors **3aa** and **3ag** or acetamide derivative **2a** (Table 8 *vs.* Table 6). We also treated **3aa** with various aryl bromides to generate diarylacetamides with different aryl groups. The alkyl-substituted 4-*tert*-butyl-

Table 8. Substrates scope of aryl bromides and arylacetamides in the α-arylation.[a]





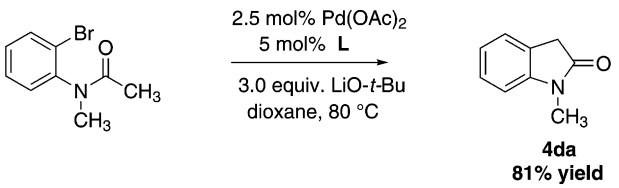
[a] Reactions performed using 1.5 equiv. of **1**, 1.0 equiv. of **3** on a 0.2-mmol scale.
[b] Using 2.0 equiv. $NaN(SiMe_3)_2$.
[c] 5 mol% $Pd(OAc)_2$ and 10 mol% **L** used.

bromobenzene (**1b**) underwent coupling to give **4ab** in 91% yield. Sterically hindered 2-bromotoluene (**1e**) gave only 20% yield of desired product (**4ae**) under conditions using NaO-*t*-Bu. The yield was dramatically increased when $NaN(SiMe_3)_2$ was employed (91% yield). In all cases, the diarylacetamides were obtained in good to excellent yields using aryl bromides with either electron-donating substituents or electron-withdrawing substituents. The arylation of 4-bromoanisole (**1g**) afforded the products **4ag** in 90% yield. In contrast, aryl bromides with electron-withdrawing groups (**1i**, **1j**, **1k**) were found to be less reactive toward **3aa**. When the catalyst loading was increased to 5 mol%, the diarylated acetamides were isolated in 80–92% yield.

Amides derived from cyclic amines are important building blocks in the construction of biologically active compounds.[28,29] Both pyrrolidine- (**3ba**) and piperidine-substituted (**3ca**) acetamide derivatives were suitable substrates, coupling with 4-*tert*-butylbromobenzene (**1b**) to provide the coupling products **4al** and **4am** in 92% and 94% yield, respectively (Table 8).

Amides bearing other nitrogen substituents were also good substrates. Both *N,N*-dimethyl and *N*-methyl-*N*-phenyl precursors coupled with 4-*tert*-butylbromobenzene to provide **4an** and **4ao** in 93 and 88% yield, respectively. Excellent yields were achieved for arylacetamide substrates bearing electron-donating 4-methoxy (**3ag**) or electron-withdrawing 4-chloro (**3aj**) groups on the arylacetamide precursors, with **4ap** being furnished in 90% yield and **4aq** generated in 93% yield. Finally, we examined the reactivity of heterocyclic acetamide derivatives.[30] 3-Pyridyl- and 3-thiophenyl-*N,N*-diethylacetamides **3ar** and **3as** provided the corresponding products **4ar** and **4as** in 81 and 78% yield, respectively. Notably, no triarylated products were observed in any case, despite the use of 1.5 equiv. of aryl bromides.

We were interested in the application of our method to the synthesis of oxindoles (Scheme 3).[9] Oxindoles are known to possess biological activities, and have been employed as substrates in racemic or enantioselective arylation reactions. Oxindoles are less challenging substrates for arylation than the amides outlined above, because of their increased acidity (pK_a 18.5 in DMSO).[31] We were concerned that the oxindole product might undergo a second arylation under the reaction conditions. Upon subjecting the amide to our arylation conditions, however, the cyclized product **4da** was generated in 81% yield at 80 °C (Scheme 3). Thus, this catalytic system is effective for both inter- and intramolecular cross-coupling of amides with aryl bromides and arylation of the oxindole product is not a significant issue.



Scheme 3. Palladium-catalyzed intramolecular α-arylation.

Optimization of the α-Arylation of Amides with Aryl Chlorides

Although α-arylation of amides with aryl bromides has been achieved, before our studies there were no examples of intermolecular arylation of amides with aryl chlorides.[18b] In general, aryl chlorides are less reactive than aryl bromides in cross-coupling reactions.[32] Nevertheless, aryl chlorides are less expensive and more abundant, so their use in the cross-coupling reactions is highly desirable. In the original report by the Hartwig group, BINAP was employed as ligand.[5c] The same group later demonstrated that the mechanism of oxidative addition of aryl chlorides proceeds most readily through a palladium species bearing a single monodentate phosphine.[33] Palladium catalysts ligated with bidentate ligands activate C–Cl bonds of aryl chlorides, but at temperatures around 100 °C.[34]

Initial attempts to directly utilize chlorobenzene to replace bromobenzene with *N,N*-diethylacetamide **2a** under our standard conditions resulted in only 25% yield of **3aa**. Based on our previous experience with the arylation of sulfoxides with aryl chlorides,[17] we hypothesized that catalyst activation might be problematic. We, therefore, employed the palladacyclic precursors (Figure 1), which have been demonstrated to readily form active catalysts.[35] As shown in Table 9, in order to identify the optimal reaction conditions, four common solvents [toluene, CPME, dioxane and dimethoxyethane (DME)] were screened using the μ-Cl Pd dimer[35] (**P1**, Figure 1) with Kwong's indole-based phosphine. CPME was found to be the most suitable solvent under the conditions examined, affording a mixture of the mono- and bisarylated products in a 5:1 ratio. From this mixture

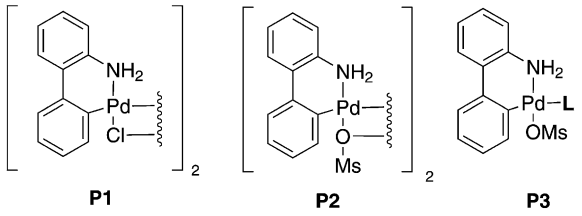
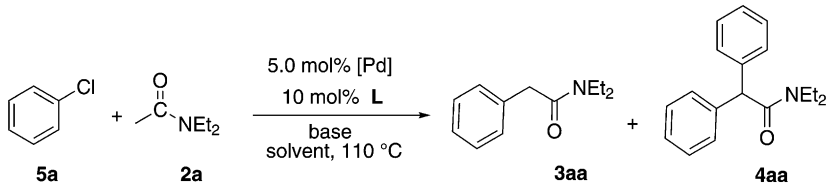


Figure 1. μ-Cl and μ-OMs palladium dimers and the 3rd generation precatalyst bound to Kwong's indole-based phosphine (**L**).

Table 9. Optimization of the α-arylation of *N,N*-diethylacetamide **2a** with chlorobenzene **5a**.[a]



5a 2a 3aa 4aa

Entry	Base	Solvent	Yield of **3aa**[b] [%]	Yield of **4aa**[b] [%]
1[c]	LiO-*t*-Bu	toluene	25	trace
2	LiO-*t*-Bu	toluene	59	14
3	LiO-*t*-Bu	CPME	63[d]	12
4	LiO-*t*-Bu	dioxane	34	14
5	LiO-*t*-Bu	DME	15	3
6	NaO-*t*-Bu	CPME	45	20
7	KO-*t*-Bu	CPME	50	14
8	$LiN(SiMe_3)_2$	CPME	12	trace
9	$NaN(SiMe_3)_2$	CPME	15	trace
10	$KN(SiMe_3)_2$	CPME	6	trace
11[e]	LiO-*t*-Bu	CPME	36	14
12[f]	LiO-*t*-Bu	CPME	29	15

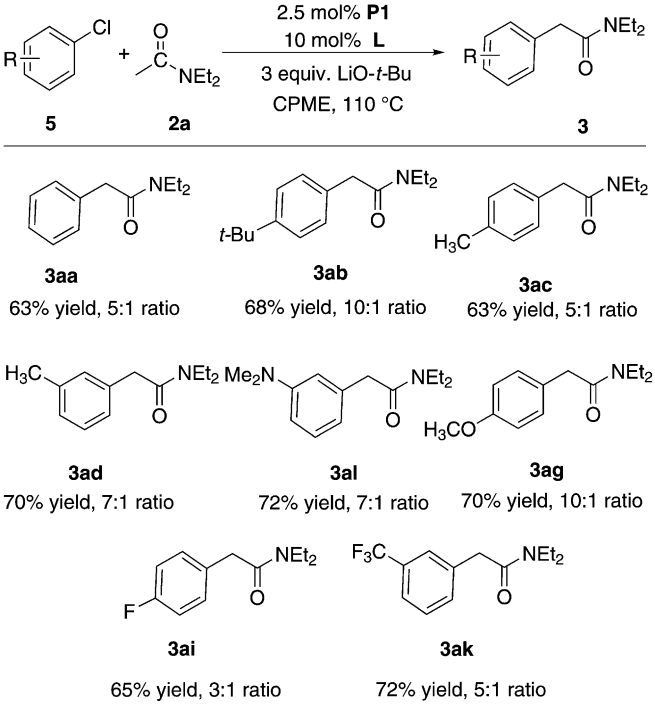
[a] Reactions performed using 1.5 equiv. of **5a**, 1.0 equiv. of **2a** on a 0.2-mmol scale.
[b] NMR yield.
[c] Using 2.0 equiv. $NaN(SiMe_3)_2$.
[d] Isolated yield.
[e] 2.5 mol% **P2** and 10 mol% **L** used.
[f] 5.0 mol% **P3** used.

the monoarylated **3aa** was isolated in 63% yield (Table 9, entry 3). Other solvents were less effective and led to the generation of **3aa** in lower yields (15–59%) and in lower ratios of mono- to bisarylated products (Table 9, entry 3 *vs.* 2, 4 and 5). Further survey of the six common bases [LiO-*t*-Bu, NaO-*t*-Bu, KO-*t*-Bu, $LiN(SiMe_3)_2$, $NaN(SiMe_3)_2$, and $KN(SiMe_3)_2$] showed that yields from 6–63% of monoarylated **3aa** with monoarylated **3aa** to bisarylated **4aa** ratios of 2:1 to 5:1 (Table 9, entries 3 and 6–10). The yield and selectivity of **3aa** were not improved using μ-OMs Pd dimer[36] (**P2**) or the 3rd generation indole-based precatalyst[36] (**P3**) with chlorobenzene **5a** and *N,N*-diethylacetamide **2a** (Table 9, entries 11 and 12). Therefore, our best conditions for monoarylation of acetamides with aryl chlorides were 2.5 mol% μ-Cl palladium dimer **P1** and 10 mol% **L** with 3 equiv. LiO-*t*-Bu in CPME at 110 °C for 12 h.

Examination of the Scope of the Amide Arylation with Aryl Chlorides

Using the optimized reaction conditions, we investigated the substrate scope of aryl chlorides in the monoarylation with amide **2a** (Table 10). Chlorobenzene (**5a**) provided a 5:1 ratio of mono-:bisarylated products from which the monoarylated product **3aa** was isolated in 63% yield. Similarly, alkyl-substituted

Table 10. Substrate scope of aryl chlorides in the monoarylation of **2a**.[a]



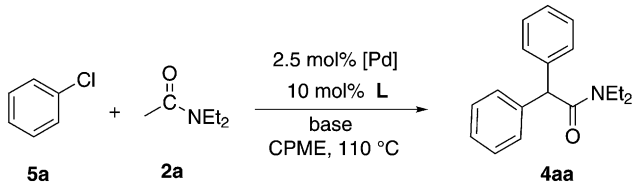
[a] Reactions performed using 1.0 equiv. of **5**, 2.0 equiv. of **2a** on a 0.2-mmol scale.
[b] Ratio is mono-:bisarylated product.

aryl chlorides such as 4-*tert*-butylchlorobenzene (**5b**), 4-chlorotoluene (**5c**), 3-chlorotoluene (**5d**) and 3-chloro-*N,N*-dimethylaniline (**5l**) reacted with **2a** in moderate to good selectivities (5:1–10:1 mono:bisarylated product) and reasonable yields of the monoarylation products (63–72%). Sterically hindered aryl chlorides, such as 2-chlorotoluene and 1-chloronaphthalene, afforded $<10\%$ yield in this reaction, as did all other hindered aryl chlorides. This appears to be a limitation of the palladium catalyst with Kwong's indole-based phosphine. Electron-donating aryl chlorides, such as 4-chloroanisole (**5g**), gave the monocoupled product in 70% yield and 10:1 selectivity. In contrast, lower selectivities (3:1–5:1) and reactivities were observed when electron-withdrawing aryl chlorides, such as 1-chloro-4-fluorobenzene (**5i**) and 1-chloro-3-(trifluoromethyl)benzene (**5k**), were employed. The increased acidity of the monoarylation products could result in the higher percentages of diarylated product. Nonetheless, the yields with these substrates (65–72%) were comparable to others in Table 10.

Development of the Diarylation of Acetamides with Aryl Chlorides

Our starting point for the bisarylation of acetamides with aryl chlorides was entry 6 of Table 9, where the bisarylated **4aa** was formed in 20% yield in the presence of NaO-*t*-Bu and CPME. To increase the yield, palladacyclic precursors (Figure 1) were examined (Table 11). We found that the 3rd generation indole phophine-based precatalyst (**P3**, Figure 1) was the best Pd source in terms of yield (84%) when used with CPME solvent (Table 11, entry 1 *vs.* entries 3 and 5). Two bases (NaO-*t*-Bu and KO-*t*-Bu) were also examined, as summarized in Table 11. Overall, NaO-*t*-Bu was more effective than KO-*t*-Bu with different Pd sources in the bisarylation of **2a** with aryl chlorides (Table 11, entries 1, 3 and 5 *vs.* entries 2, 4 and 6).

Table 11. Optimization of the diarylation of *N,N*-diethylacetamide **2a** with **5a**.[a]



5a **2a** **4aa**

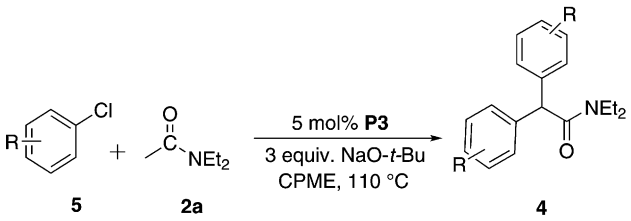
Entry	[Pd]	Base	NMR yield [%]
1[b]	**P3**	NaO-*t*-Bu	84
2[b]	**P3**	KO-*t*-Bu	69
3	**P2**	NaO-*t*-Bu	69
4	**P2**	KO-*t*-Bu	50
5	**P1**	NaO-*t*-Bu	64
6	**P1**	KO-*t*-Bu	56

[a] Reactions performed using 2.0 equiv. of **1a**, 1.0 equiv. of **2a** on a 0.2 mmol scale.
[b] 5 mol% **P3** used.

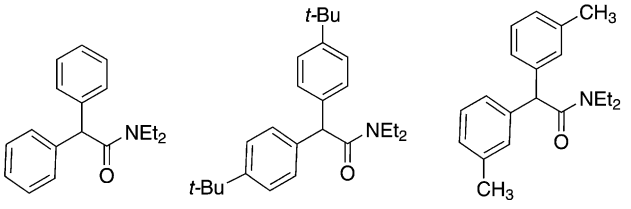
With the optimized conditions (entry 1 in Table 11) in hand, We next investigated the scope of the diarylation of *N,N*-diethylacetamide **2a** with a variety of aryl chlorides in the presence of 5 mol% 3rd generation indole-based precatalyst (**P3**). As shown in Table 12, 70–80% isolated yields were achieved for the diarylation. Chlorobenzene (**5a**), 4-*tert*-butylchlorobenzene (**5b**), and 3-chlorotoluene (**5d**) afforded products **4aa**, **4bb** and **4dd** in 80, 76, and 70% yield, respectively. Electron-donating 4-chloroanisole (**5g**) gave the corresponding bis-coupling product **4gg** in 72% yield. Electron-withdrawing 1-chloro-4-fluorobenzene (**5i**) was also well tolerated in this reaction to provide **4ii** in 72% yield.

Having established a protocol for the diarylation with aryl chlorides, we examined the arylation of arylacetamides to yield diarylated products **4** (Table 13). Since NaO-*t*-Bu was the best base for the diarylation of acetamides, it was used as the base for arylation of arylacetamides. In a short survey of palladacyclic precursors, the 3rd generation indole-based precatalyst (**P3**) provided the desire product **4aa** with 95% yield

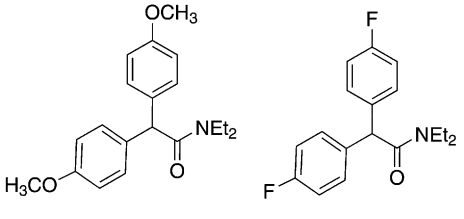
Table 12. Substrate scope of aryl chlorides in the diarylation of **2a**.[a]



5 **2a** **4**



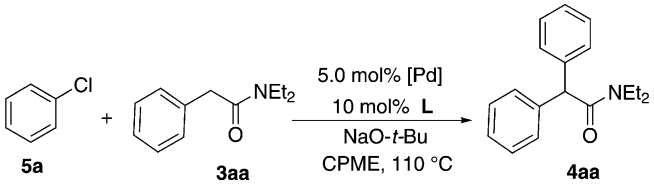
4aa, 80% yield **4bb**, 76% yield **4dd**, 70% yield



4gg, 72% yield **4ii**, 72% yield

[a] Reactions performed using 2.0 equiv. of **5**, 1.0 equiv. of **2a** on a 0.2-mmol scale.

Table 13. Optimization of the conditions of the arylation of **3aa** with **5a**.[a]



5a 3aa 4aa

Entry	[Pd]	Catalyst [mol%]	NMR yield [%]
1[b]	**P3**	5	95
2[c]	**P3**	2.5	91
3	**P2**	2.5	85
4	**P1**	2.5	76

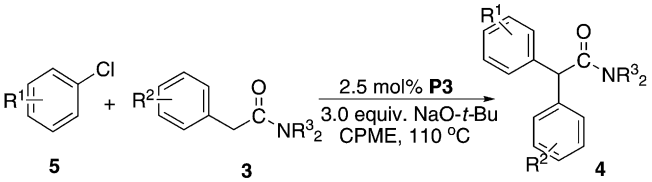
[a] Reactions performed using 1.5 equiv. of **5a**, 1.0 equiv. of **3aa** on a 0.2-mmol scale.
[b] 5 mol% **P3** used.
[c] 2.5 mol% **P3** used.

when 1.5 equiv. chlorobenzene were employed (Table 13, entry 1). Moreover, we were delighted to find that even decreasing the loading of precatalyst from 5.0 mol% to 2.5 mol% still led to a satisfactory yield (91%, entry 2). Other Pd sources, such as μ-Cl Pd dimer (**P1**) and μ-OMs Pd dimer (**P2**), were also examined in the arylation of **3aa** with chlorobenzene, but gave lower yields (Table 13, entries 3 and 4).

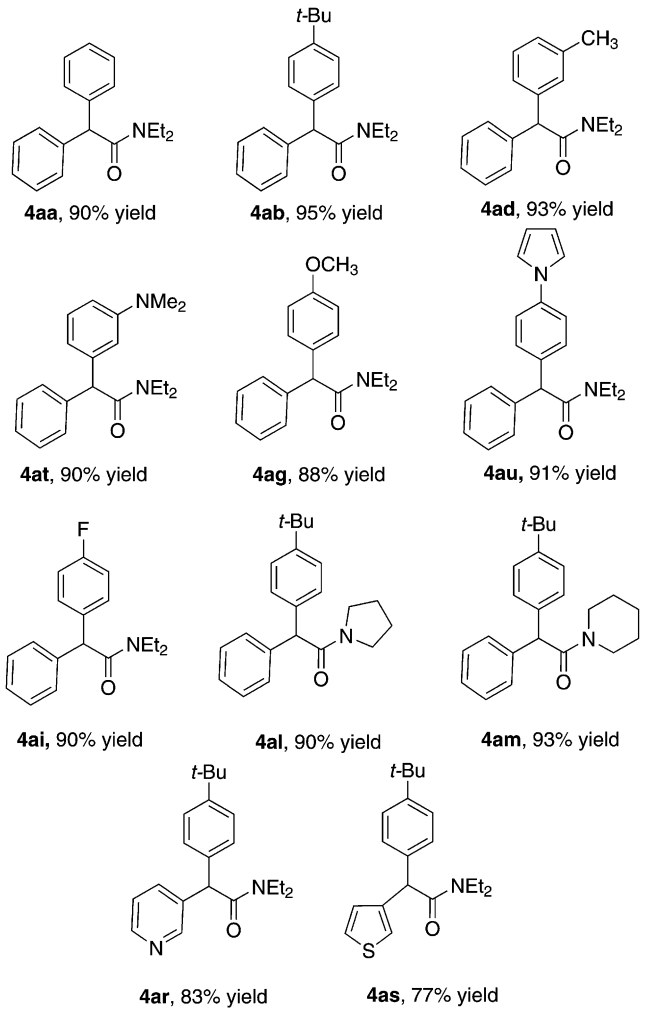
With our optimal conditions (NaO-*t*-Bu and 2.5 mol% of the indole-based precatalyst at 110 °C in CPME) we examined the substrate scope with different aryl chlorides (Table 14). The alkyl-substituted 4-*tert*-butylchlorobenzene (**5b**) and 3-chlorotoluene (**5d**) behaved well in the reactions with **3aa**, providing the desired diarylacetamides **4ab** and **4ad** in 95 and 93% yield, respectively. 3-Chloro-*N,N*-dimethylaniline (**5l**) generated the product **4at** in 90% yield. Electron-donating 4-chloroanisole (**5g**) and 4-pyrrolylchlorobenzene (**5u**) were found to react with **3aa** to give **4ag** and **4au** in 88 and 91% yield, respectively. Similarly, electron-withdrawing 1-chloro-4-fluorobenzene (**5i**) reacted to provide **4ai** in 90% yield.

To further explore the substrate scope and limitations of this process, pyrrolidine- (**3ba**) and piperidine-substituted (**3ca**) acetamide derivatives were found to be effective in providing arylation products **4al** and **4am** in 90 and 93% yield, respectively (Table 14). Substrates that bear heteroaryl groups on the acetamide, such as 3-pyridyl (**3ar**) and 3-thiophenyl (**3as**), underwent the α-arylation in 83 and 77% yield, respectively. It is noteworthy that changing the substituents on the amide nitrogen of the substrates had little impact on the arylation reactivity or yield.

Table 14. Substrate scope of aryl chlorides in the α-arylation of arylacetamides.[a]



5 3 4



[a] Reactions performed using 1.5 equiv. of **5**, 1.0 equiv. of **3** on a 0.2-mmol scale.

Conclusions

The direct α-arylation of amides is challenging, because α-protons of amides have very high pK_a values (up to 35 in DMSO[9]). Prior direct arylation of acetamides with aryl bromides introduced by Hartwig and co-workers resulted in the formation of the arylation products in 48–72% yield. We introduced herein a more general and practical palladium-catalyzed direct α-arylation of acetamides with aryl halides. This chemistry relies on the indole-based phosphine introduced by Kwong and co-workers.[19] A variety of

mono- and bisarylated acetamides was prepared in good to excellent yields. We also report that a palladacyclic precursor formed with the indole-based ligand effectively catalyzes the direct α-arylation of acetamides with aryl chlorides. It is noteworthy that the chemoseletivity between mono- and bisarylated products was effectively controlled by choice of base, solvent, and stoichiometry. We demonstrated that the catalyst exhibited excellent reactivity in the intramolecular arylation to form oxindoles. These studies, reported herein, put us in a position to examine the enantioselective arylation of arylacetamides. Such studies are currently underway in our group.

Experimental Section

General Procedures

All reactions were conducted under an inert atmosphere of dry nitrogen. Anhydrous dioxane, CPME, and 2-MeTHF were purchased from Sigma–Aldrich and used without further purification. Dichloromethane and toluene were dried through activated alumina columns under nitrogen. Unless otherwise stated, reagents were commercially available and used as received without further purification. Chemicals were purchased from Sigma–Aldrich, Acros, or Matrix Scientific and solvents were obtained from Fisher Scientific. Flash chromatography was performed with Silica gel (230–400 mesh, Silicycle). NMR spectra were obtained using a Brüker 500 MHz Fourier-transform NMR spectrometer. The infrared spectra were obtained with KBr plates using a Perkin–Elmer Spectrum 1600 Series spectrometer. High resolution mass spectrometry (HR-MS) data were obtained on a Waters LC-TOF mass spectrometer (model LCT-XE Premier) using chemical ionization (CI) or electrospray ionization (ESI) in positive or negative mode, depending on the analyte. Melting points were determined on a Unimelt Thomas-Hoover melting point apparatus and are uncorrected. *N,N*-Diethylacetamide was purchased from Sigma–Aldrich and stored under nitrogen.

Procedures for the Pd-Catalyzed Arylation of Amides

General Procedure A, Monoarylation of Acetamide Derivatives with Aryl Bromides: An oven-dried microwave vial equipped with a stir bar was charged with $Pd(OAc)_2$ (1.1 mg, 0.0050 mmol) and ligand **L** (4.0 mg, 0.010 mmol) under a nitrogen atmosphere, followed by 1.0 mL dry toluene *via* syringe. After the catalyst solution had been stirred for 90 min at 25 °C, LiO-*t*-Bu (48.3 mg, 0.60 mmol, 3 equiv.) was added to the reaction vial and *N,N*-diethylacetamide (46.0 mg, 0.40 mmol, 2.0 equiv.) was added dropwise to this solution. The microwave vial was sealed and bromobenzene (21.2 μL, 0.20 mmol, 1.0 equiv.) was added by syringe under a nitrogen atmosphere. The reaction mixture was stirred at 110 °C for the specified time then allowed to cool to room temperature. The reaction was quenched with H_2O (0.2 mL) and the resulting solution passed through a short pad of silica gel and eluted with ethyl acetate. The combined organics were dried over Na_2SO_4 and concentrated under vacuum. The crude residue was purified by flash column chromatography to yield the purified arylacetamide derivatives **3**. See the Supporting Information for full characterization of all compounds.

General Procedure B, Diarylation of Acetamide Derivatives with Aryl Bromides: An oven-dried microwave vial equipped with a stir bar was charged with $Pd(OAc)_2$ (2.2 mg, 0.01 mmol) and ligand **L** (8.0 mg, 0.02 mmol) under a nitrogen atmosphere, followed by 1.0 mL dry toluene *via* syringe. After the catalyst solution had been stirred for 90 min at 25 °C, $NaN(SiMe_3)_2$ (110.0 mg, 0.60 mmol, 3 equiv.) was added to the reaction vial and *N,N*-diethylacetamide (23.0 mg, 0.20 mmol, 1.0 equiv) was added dropwise to this solution. The microwave vial was sealed and bromobenzene (42.4 μL, 0.40 mmol, 2.0 equiv.) was added by syringe under a nitrogen atmosphere. The reaction mixture was stirred at 110 °C for the specified time then allowed to cool to room temperature. The reaction was quenched with H_2O (0.2 mL) and then was passed through a short pad of silica gel and eluted with ethyl acetate. The combined organics were dried over Na_2SO_4 and concentrated under vacuum. The crude residue was purified by flash column chromatography to yield the diarylacetamide derivatives **4**.

General Procedure C, Arylation of Arylacetamide Derivatives with Aryl Bromides: An oven-dried microwave vial equipped with a stir bar was charged with $Pd(OAc)_2$ (1.1 mg, 0.0050 mmol) and ligand **L** (4.0 mg, 0.010 mmol) under a nitrogen atmosphere, followed by 1.0 mL dry toluene *via* syringe. After the catalyst solution had been stirred for 90 min at 25 °C, NaO-*t*-Bu (57.7 mg, 0.60 mmol, 3 equiv.) was added to the reaction vial and *N,N*-diethyl-2-phenylacetamide (38.2 mg, 0.20 mmol, 1.0 equiv.) was added dropwise to this solution. The microwave vial was sealed and bromobenzene (31.8 μL, 0.30 mmol, 1.5 equiv.) was added by syringe under a nitrogen atmosphere. The reaction mixture was stirred at 110 °C for the specified time then allowed to cool to room temperature. The reaction was quenched with H_2O (0.2 mL) and then was passed through a short pad of silica gel and eluted with ethyl acetate. The combined organics were dried over Na_2SO_4 and concentrated under vacuum. The crude residue was purified by flash column chromatography to yield the diarylated acetamide derivative **4**.

General Procedure D, Monoarylation of Acetamide Derivatives with Aryl Chloride: An oven-dried microwave vial equipped with a stir bar was charged with μ-Cl Pd dimer (3.6 mg, 0.0050 mmol) and ligand **L** (8.1 mg, 0.020 mmol) under a nitrogen atmosphere, followed by 1.0 mL dry CPME *via* syringe. After the catalyst solution had been stirred for 90 min at 25 °C, LiO-*t*-Bu (48.3 mg, 0.60 mmol, 3 equiv.) was added to the reaction vial and *N,N*-diethylacetamide (46.0 mg, 0.40 mmol, 2.0 equiv.) was added dropwise. The microwave vial was sealed and chlorobenzene (20.3 μL, 0.20 mmol, 1.0 equiv.) was added by syringe under a nitrogen atmosphere. The reaction was stirred at 110 °C for the specified time then allowed to cool to room temperature. The reaction mixture was quenched with H_2O (0.2 mL) and passed through a short pad of silica gel and eluted with ethyl acetate. The combined organics were dried over Na_2SO_4 and concentrated under vacuum. The crude residue

was purified by flash column chromatography to yield the monoarylated acetamide derivatives **3**.

General Procedure E: Diarylation of Acetamide Derivatives with Aryl Chlorides: An oven-dried microwave vial equipped with a stir bar was charged with 3rd generation precatalyst (7.7 mg, 0.010 mmol) under a nitrogen atmosphere, followed by 1.0 mL dry CPME *via* syringe. After the catalyst solution had been stirred for 5 min at 25 °C, NaO-*t*-Bu (57.7 mg, 0.60 mmol, 3 equiv.) was added to the reaction vial and *N,N*-diethylacetamide (23.0 mg, 0.20 mmol, 1.0 equiv.) was added dropwise to this solution. The microwave vial was sealed and chlorobenzene (40.6 μL, 0.40 mmol, 2.0 equiv.) was added by syringe under a nitrogen atmosphere. The reaction was stirred at 110 °C for the specified time then allowed to cool to room temperature. The reaction mixture was quenched with H_2O (0.2 mL) and then passed through a short pad of silica gel and eluted with ethyl acetate. The combined organics were dried over Na_2SO_4 and concentrated under vacuum. The crude residue was purified by flash column chromatography to yield diarylacetamide derivatives **4**.

General Procedure F: Arylation of Arylacetamide Derivatives with Aryl Chlorides: An oven-dried microwave vial equipped with a stir bar was charged with the 3rd generation precatalyst (7.7 mg, 0.010 mmol) under a nitrogen atmosphere, followed by 1.0 mL dry CPME *via* syringe. After the catalyst solution had been stirred for 5 min at 25 °C, NaO-*t*-Bu (57.7 mg, 0.60 mmol, 3 equiv.) was added to the reaction vial and *N,N*-diethyl-2-phenylacetamide (38.2 mg, 0.20 mmol, 1.0 equiv.) was added dropwise to this solution. The microwave vial was sealed and chlorobenzene (30.4 μL, 0.30 mmol, 1.5 equiv.) was added by syringe under a nitrogen atmosphere. The reaction was stirred at 110 °C for the specified time then allowed to cool to room temperature. The reaction mixture was quenched with H_2O (0.2 mL) and then was passed through a short pad of silica gel and eluted with ethyl acetate. The combined organics were dried over Na_2SO_4 and concentrated under vacuum. The crude residue was purified by flash column chromatography to yield diarylated acetamide derivatives **4**.

Acknowledgements

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