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Palladium-Catalyzed Synthesis of Aryl Amides through Silanoate-Mediated Hydrolysis of Nitriles

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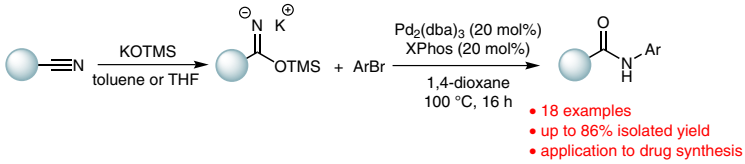
Dedicated to Professor Steven V. Ley on the occasion of his 70th birthday



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Abstract A procedure for the formation of aryl amides through the palladium-catalyzed coupling of nitriles and aryl bromides, via the formation of intermediary silanoate derived imidate species is reported. Optimization was undertaken and examples of the process are described that furnish the products in up to 86% isolated yield.

Key words amidation, palladium, catalysis, nitriles, hydrolysis

The amide functional group is pervasive within nature and medicinal chemistry, where it is commonly encountered in peptide bonds in proteins and small-molecule drugs, respectively.[1,2] Within medicinal chemistry, the formation of amide bonds is one of the most frequently performed operations, and reactions that can be conducted under mild conditions and that enable the efficient synthesis of amides are of great importance.[3] Accordingly, a wide variety of methods and reagents have been reported; however, many of these approaches have considerable drawbacks that limit their effective use, particularly with regard to atom economy and sustainability.[4–6] In recent years, methods have been developed that allow amide condensations to be performed catalytically[7–12] as an alternative to the more traditional stoichiometric approaches.

In relation to this important objective, and continuing a program focused on catalytic methods of amide bond formation,[13] we were interested in developing a catalytic approach that can be used to form aryl amides from nitrile starting materials. The aryl amide motif is an abundant pharmacophoric feature in many drug molecules, and some representative examples are shown in Figure 1. Thus, catalytic methods that can be used to prepare such substrates and that would enable access to this highly important class of compound would clearly be worthwhile.

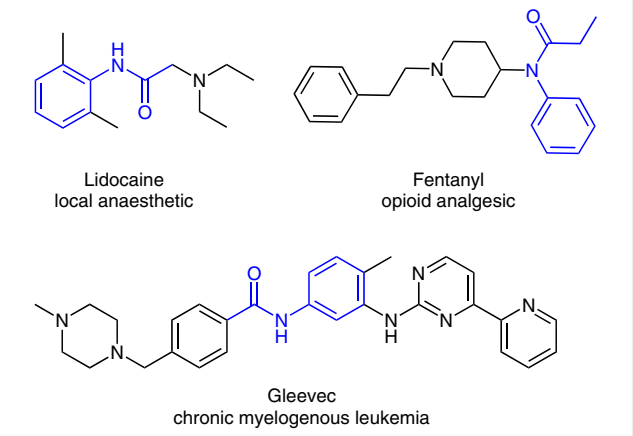
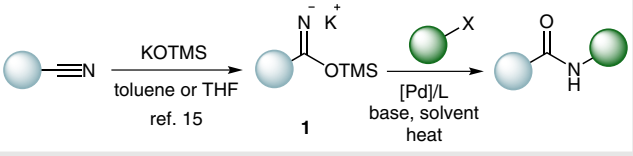


Figure 1 Examples of pharmaceutical products containing an aryl amide motif

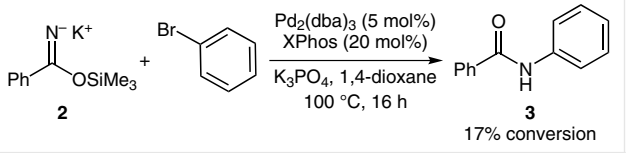
A review of the literature indicated that nitrile derivatives could be competently converted into the corresponding primary amide product via intermediate salt **1** (Scheme 1) through reaction with potassium trimethylsilanolate.[14] By analogy with the Pd-catalyzed synthesis of aniline derivatives with LiHMDS,[15] we reasoned that reagents of this type could participate in a Buchwald–Hartwig coupling reaction with aryl bromides to furnish aryl amide derivatives upon hydrolytic workup (Scheme 1).



Scheme 1 Conversion of nitrile derivatives into the corresponding primary amide product via intermediate salt **1**

The proposed reaction would then formally represent an Umpolung approach to amide bond formation, and would compliment, for example, copper-mediated arylation of primary and secondary amide derivatives.[16] Here, we wish to report our efforts at enabling this useful transformation and provide details of its scope and limitations, as well as showcasing its utility in the preparation of bioactive compounds.

Our survey commenced by selecting a range of bases, ligands and solvents to screen conditions in a model reaction, building on established precedent for the coupling of aryl bromides.[17,18] Conditions in the absence of base were also assessed to examine whether the negative charge residing on the nitrogen of the intermediate was sufficient to allow the reaction to proceed, based on precedence established with LiHMDS.[15] The palladium(0) catalyst $Pd_2(dba)_3$ (initial loading 5 mol%) was selected for use in all screening reactions to avoid the necessary reduction of Pd(II) catalysts. From this study, it was determined that the palladium-catalyzed conversion of benzonitrile adduct **2** into anilide **3** could be achieved as shown in Scheme 2, providing proof of principle that imidate species such as **2** were capable of undergoing Buchwald–Hartwig arylation.



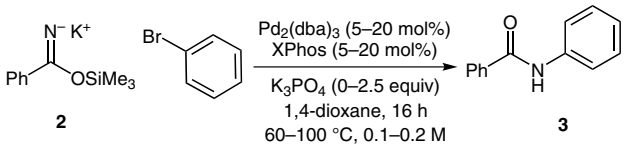
Scheme 2 Palladium-catalyzed conversion of benzonitrile adduct **2** into anilide **3**; conversion determined by HPLC analysis (see the Supporting Information for further details)

Having established the feasibility of achieving this transformation, albeit in relatively low conversion, we next sought to optimize the process in order to render this approach to forming amide bonds an attractive alternative to existing stoichiometric methods. We had previously used the statistical technique of Design of Experiments (DoE)[19,20] as an expedient means of optimizing amide bond forming processes; therefore, this approach was applied in the current study. Accordingly, a half-fractional, two-level factorial design was utilized, examining the following variables (Table 1): equivalents of base (0–2.5 equiv), catalyst loading (0–20 mol%), ligand loading (0–20 mol%), concentration (0.1–0.2 M), and temperature (60–100 °C). Two center point reactions were also performed to allow estimation of error and variability associated with the process (entries 1 and 2).

Initial inspection of the data generated in Table 1 indicated that the optimum conditions for the formation of **3** by using a Buchwald–Hartwig approach was through the use of XPhos and $Pd_2(dba)_3$, both at a loading of 20 mol%, without the requirement for exogenous base, and at a concentration of 0.1 M, affording **3** in 59% conversion (entry 9). Closer examination of the data through the use of a response surface[20] (Figure 2) implied that the most important factors affecting the conversion were both catalyst and ligand loading. The other parameters studied in the experimental design were not found to influence the conversion over the ranges studied. Pleasingly, the isolated yield using the optimum conditions was determined to be 77% (Table 2, entry 1). We believe that the discrepancy between the solution conversion calculated and isolated yield obtained can be attributed to the somewhat limited solubility of the product in the reaction milieu.

With optimal conditions for the palladium-mediated arylation of imidate derivative **2** in hand, the next phase of our study focused on establishing the scope and limitations of this nascent process (Table 2).[21] The requisite imidate derivatives were, in each case, prepared according to the pro-

Table 1 Reaction Optimization



Entry	Base (equiv)	Cat. (mol%)	Ligand (mol%)	Concn (M)	Temp (°C)	Conv. (%)[a]
1	1.25	12.5	12.5	0.15	80	28
2	1.25	12.5	12.5	0.15	80	25
3	0	5	20	0.20	100	14
4	2.5	20	5	0.20	60	2
5	0	20	5	0.10	60	3
6	0	20	5	0.20	100	16
7	0	5	20	0.10	60	0
8	2.5	20	20	0.20	100	51
9	0	20	20	0.10	100	59
10	2.5	5	5	0.10	60	0
11	2.5	20	5	0.10	100	11
12	2.5	5	5	0.20	100	1
13	2.5	20	20	0.10	60	24
14	0	20	20	0.20	60	20
15	2.5	5	20	0.10	100	7
16	0	5	5	0.20	60	0
17	2.5	5	20	0.20	60	1
18	0	5	20	0.10	100	1

[a] Conversion determined by HPLC analysis using an internal standard. See the Supporting Information.

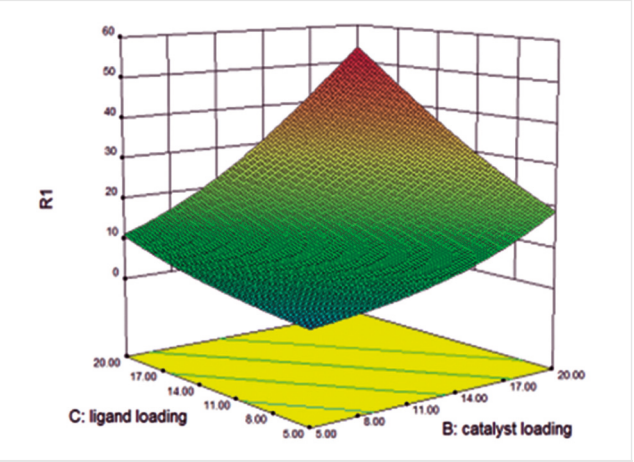


Figure 2 Response surface for the half-fractional design

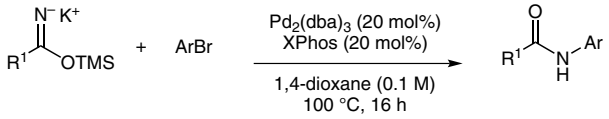
cedure previously intimated by Merchant,[14] and were used directly without purification in the Buchwald–Hartwig step.

Focusing on a benzonitrile derived imidate as the nucleophilic coupling partner, a range of aryl bromides were examined (Table 2, entries 1–9). As discussed previously, bromobenzene provided the anilide product in excellent yield (entry 1). Using either a more electron-withdrawing (entries 2 and 3) or electron-donating substituent (entry 4) resulted in higher or lower yields of the amide product, respectively. The relatively low yields observed with an electron-donating substituent is consistent with the reduced propensity towards oxidative addition, and may indicate a potential limitation associated with the methodology. Nevertheless, the current approach retains the advantage of being catalytic in nature and offers efficient access to electron-deficient aryl amides, which frequently require more forcing conditions (e.g., use of acid chlorides) for their preparation. This observation is borne out in the synthesis of the highly electron-deficient anilide **7**, which would again require more aggressive reagents such as acid chlorides to enable its preparation from the corresponding aniline.

Subjecting 4-bromobenzyl alcohol to our conditions furnished the corresponding anilide (**8**) containing an aldehyde moiety. The palladium(0)-mediated oxidation of the primary benzylic alcohols is a known process,[22] which accounts for the fact that the aldehyde product was isolated in this instance.

Turning our attention to heterocyclic aryl bromide derivatives, pyridyl systems proved to be competent substrates, furnishing the associated benzamide systems in good to excellent yields (Table 2, entries 7 and 8). In contrast, however, π-excessive heterocycles were not compatible with this newly developed reaction manifold (entry 9).

Table 2 Substrate Scope



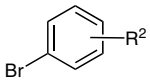
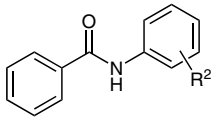
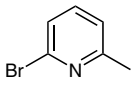
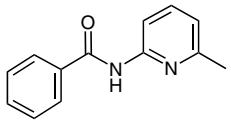
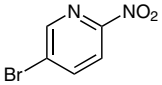
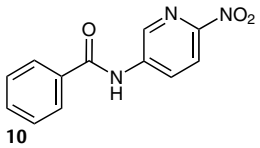
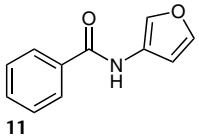
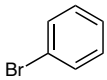
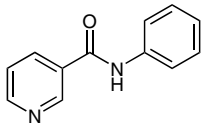
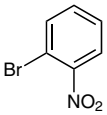
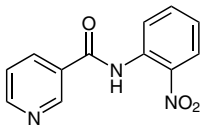
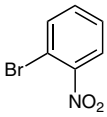
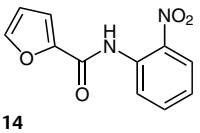
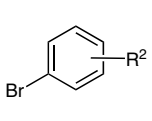
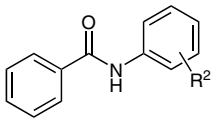
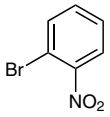
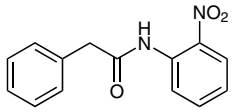
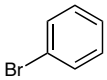
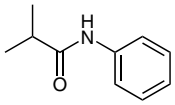
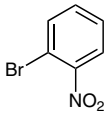
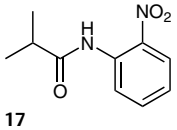
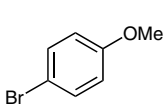
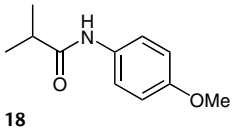
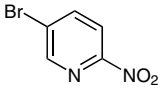
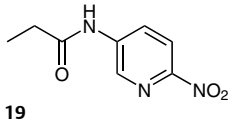
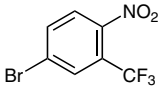
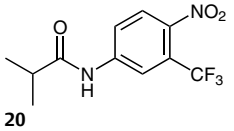
Entry	R^1	ArBr	Product	Yield (%)
				
1	Ph	R^2 = H	**3** R^2 = H	77
2	Ph	R^2 = 2-NO_2	**4** R^2 = 2-NO_2	86
3	Ph	R^2 = 4-NO_2	**5** R^2 = 4-NO_2	72
4	Ph	R^2 = 4-OMe	**6** R^2 = 4-OMe	36
5	Ph	R^2 = 4-NO_2-3-CF_3	**7** R^2 = 4-NO_2-3-CF_3	72
6	Ph	R^2 = 4-CH_2OH	**8** R^2 = 4-CHO	56
7	Ph		 **9**	57
8	Ph		 **10**	81
9	Ph		 **11**	0
10	3-pyridyl		 **12**	37
11	3-pyridyl		 **13**	75
12	2-furoyl		 **14**	46

Table 2 (continued)

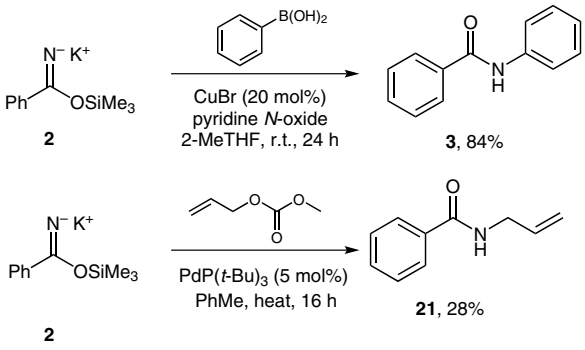
Entry	R^1	ArBr	Product	Yield (%)
				
13	$PhCH_2$		 **15**	60
14	*i*-Pr		 **16**	77
15	*i*-Pr		 **17**	66
16	*i*-Pr		 **18**	43
17	Et		 **19**	67
18	*i*-Pr		 **20**	86

We next examined alternative nitrile-based starting materials to further delineate this aspect of the process. Heterocyclic-derived silanoate adducts such as pyridyl and furoyl based systems were effective (Table 2, entries 10–12) as well as a range of alkyl-derived species (entries 13–18).

The initial trends of reactivity noted above were again observed in this phase of the study; electron-deficient aryl halide coupling partners generally performed better than neutral species, which, in turn, were superior to more electron-rich systems. Notably, the anti-androgen agent Flutamide[23] (**20**), which is used for treatment of prostate cancer, could also be prepared in excellent yield by using the process developed here (Table 2, entry 18).

We also explored a one-pot process for the preparation of **3** that obviates the need to isolate the silanoate adduct **2**. Starting from benzonitrile, hydrolysis to the silanoate adduct in toluene at reflux followed by addition of bromobenzene and $Pd_2(dba)_3$/XPhos (20 mol%) furnished benzamide **3** in 67% isolated yield, which compares favorably to the original hyphenated process.

Lastly, we sought to determine the applicability of silanoate adducts of type **1** in other metal-mediated coupling processes. In recent years, the Chan–Evans–Lam arylation has emerged as a versatile means of preparing aryl amine derivatives from the corresponding aniline and boronic acid coupling partners.[24] Based on this, we explored the reaction of **2** with phenylboronic acid in the presence of a copper catalyst to produce the model benzamide derivative **3** (Scheme 3). Pleasingly, this resulted in an excellent isolated yield of the target benzamide, highlighting the utility of species such as **1** in related catalytic processes.



Scheme 3 Alternative metal-catalyzed cross-couplings

We also explored the applicability of adducts of type **1** in the Tsuji–Trost allylation[25] (Scheme 3). Reaction of **2** with methyl allylcarbonate in the presence of a palladium catalyst enabled the isolation of the target allylic amide **21** in 28% yield (unoptimized).

In summary, we have demonstrated the development of a Pd-catalyzed cross-coupling of nitrile derivatives with aryl bromides through the intermediacy of silanoate adducts, enabling the formation of a range of aryl amide derivatives. The methodology has been applied to the synthesis of pharmaceutically relevant compounds such as Flutamide (**20**) as well as showing utility in other metal-catalyzed reaction manifolds. Optimization and examples of these additional processes will be reported in due course.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560724.

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(21) ***N*-(6-Nitropyridin-3-yl)benzamide (10); Typical Procedure:** To an oven-dried Radley's reaction tube containing potassium {phenyl[(trimethylsilyl)oxy]methylene}amide (**2**; 200 mg, 0.86 mmol, 1 equiv) was added 20 mol% $Pd_2(dba)_3$ (158.2 mg, 0.16 mmol, 0.2 equiv) and 20 mol% XPhos (82.3 mg, 0.16 mmol, 0.2 equiv). The reaction tube was then purged and 1,4-dioxane (8.6 mL) was added. The reaction mixture was then heated at 100 °C for 10 min. 5-Bromo-2-nitropyridine (140 mg, 0.69 mmol, 0.8 equiv) was then added, the reaction tube was purged, and the reaction mixture was then heated at 100 °C for 16 h. The reaction mixture was taken up in EtOAc (30 mL) and washed with brine (3 × 30 mL). The organics were extracted, dried, and concentrated to a residue, which was purified by flash column chromatography [EtOAc–petroleum ether (40–60 °C), 30%] to afford the title compound (135.4 mg, 81%) as an orange–brown solid. IR (neat): 3319, 1683, 1612, 1519, 1495, 1346, 703, 770 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ = 11.02 (s, 1 H), 9.00 (d, *J* = 2.5 Hz, 1 H), 8.62 (dd, *J* = 8.9, 2.5 Hz, 1 H), 8.40 (d, *J* = 8.9 Hz, 1 H), 8.02–8.01 (m, 2 H), 7.66 (t, *J* = 7.4 Hz, 1 H), 7.59 (t, *J* = 7.6 Hz, 2 H); ^{13}C NMR (126 MHz, DMSO-d_6): δ = 166.4, 151.3, 141.3, 139.6, 133.7, 132.5, 129.1, 128.6, 128.0, 119.3; HRMS: *m*/*z* [M + H^+] calcd for $C_{12}H_{10}N_3O_3$: 244.0717; found: 244.0714.
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