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Palladium-Catalyzed Amidation and Amination of (Hetero)aryl Chlorides under Homogeneous Conditions Enabled by a Soluble DBU/NaTFA Dual-Base System

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Supporting Information

ABSTRACT: The palladium-catalyzed coupling of aryl and heteroaryl chlorides with primary amides under mild homogeneous reaction conditions is reported. Successful C−N coupling is enabled by the use of a unique "dual-base" system consisting of DBU and NaTFA, which serve as proton acceptor and halide scavenger, respectively, using low catalyst loadings (0.5 mol %) with readily available, air-stable palladium precatalysts. The DBU/NaTFA system also enables the room-temperature coupling of primary aryl amines with aryl chlorides and is tolerant of a variety of base-sensitive functional groups.

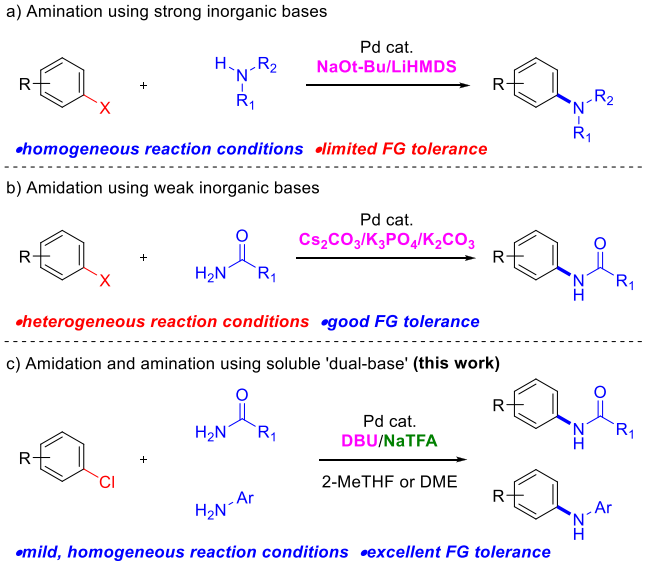
KEYWORDS: *C−N coupling, Pd-catalyzed, homogeneous, DBU, halide scavenger, sodium trifluoroacetate*

INTRODUCTION

The palladium-catalyzed C−N coupling of aryl halides and amines is a highly valuable transformation for the industrial-scale synthesis of complex amines[1] and is particularly important in the preparation of active pharmaceutical ingredients (APIs) and their synthetic intermediates.[2] Simple aryl bromides and chlorides often undergo amination with high efficiency when strong inorganic bases such as NaO*t*-Bu, KO*t*-Bu, and LiHMDS are employed[1c] (Scheme 1a), as exemplified by room-temperature couplings with anilines and secondary alkyl amines[3] and the arylation of primary alkyl amines catalyzed by parts per million levels of Pd.[4] However, these conditions are generally incompatible with many base-sensitive functional groups that are prevalent in pharmaceutically relevant substrates, such as keto, ester, nitrile, and nitro groups,[5] necessitating the use of weak inorganic bases such as Cs_2CO_3,[6] K_3PO_4,[3a,4c,7] or K_2CO_3[3c] for couplings with substrates containing these moieties. Similarly, the arylation of amides, which are among the most challenging substrates for Pd-catalyzed C−N coupling,[1d] inherently generates products that are prone to base-mediated hydrolysis, and the couplings of such nucleophiles also are most frequently performed with Cs_2CO_3,[8] K_3PO_4,[9] or K_2CO_3[10] (Scheme 1b).

The use of weak inorganic bases in Pd-catalyzed C−N coupling is notoriously complicated by their poor solubility in organic solvents.[11] Not only does this dictate that elevated reaction temperatures (typically ≥80 °C) and high catalyst loadings are often required to achieve reasonable reaction rates, but the heterogeneous nature of the reaction mixture also leads to a number of other factors impacting the reaction kinetics that are difficult to predict, including effects of the lot, form, particle size, and particle shape of the base[12,13] as well as effects of water content (both added and adventitious).[13,14] Furthermore, pronounced changes in reaction rate are often observed when moving from small-scale reactions conducted with magnetic stirring, where a grinding effect of the stir bar can lead to an increase in base surface area, to overhead stirring where such grinding effects are absent.[15] While milling of the base can compensate for the lack of beneficial grinding with overhead stirring,[16,17] mixing effects may be observed when

Scheme 1. Bases Employed in the Pd-Catalyzed Amination and Amidation of Aryl Halides



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reactions are performed in vessels with different size or configuration[18] or when different agitation speeds are employed.[16b] The combined impact of these complex factors renders the development and scale-up of transformations employing heterogeneous bases a highly challenging and time-consuming process.[15,16b,18a,19]

To address the inherent limitations associated with the use of insoluble inorganic bases, several groups have reported conditions for C−N coupling using soluble inorganic or organic bases. Organ and co-workers have elegantly employed the hindered phenoxide salts potassium chromanoxide[20] and NaBHT[21] for the palladium-catalyzed arylation of primary amines. Unfortunately, these bases are currently not commercially available and must be freshly prepared prior to use for optimal performance.[21a] Scientists at Merck reported the use of the organic superbase P_2Et phosphazene for room-temperature palladium-catalyzed C−N coupling of aryl halides in nano- and microscale experiments.[22] While suitable for application in drug discovery, the high cost (ca. $40,000/mol) and limited commercial availability of this base are prohibitive for use on a manufacturing scale. Thus, there remains a need for the identification of conditions under which the coupling of pharmaceutically relevant (hetero)aryl halides and nitrogen nucleophiles can be effected with a mild, soluble base that is inexpensive and readily available in bulk quantities. Here we report the development of a cost-effective, homogeneous dual-base system that addresses the complications associated with insoluble inorganic bases and demonstrate its applicability to the coupling of aryl chlorides with primary amide and aryl amine coupling partners. The DBU/NaTFA dual-base system (ca. $40/mol) disclosed herein (Scheme 1c) satisfies the aforementioned criteria for a readily scalable process and can be employed in the coupling of (hetero)aryl chlorides with a variety of nitrogen nucleophiles.

Motivated by a challenging late-stage amidation of a complex heteroaryl chloride in an API synthesis that employed K_2CO_3,[23] we sought to identify a soluble base that would obviate the scale- and particle-size-dependent reaction kinetics inherent to heterogeneous bases. The moderately strong organic base DBU was an ideal candidate since it is both inexpensive and readily available on a bulk scale.[24] However, prior theoretical studies on Pd/P(*t*-Bu)$_3$-catalyzed amination reactions with DBU identified a prohibitively high energy barrier for amine deprotonation due to the energetic penalty of charge separation in dissociating bromide from the oxidative addition complex in nonpolar solvents.[25] While a cationic complex was calculated to be energetically accessible in polar solvents, it was found to form a stable complex with DBU that hinders the subsequent transmetalation. In addition, concurrent experimental studies conducted with Pd/BINAP using DBU, as well several other strong organic bases,[26] all gave <5% conversion, in stark contrast to the >99% conversion using NaO*t*-Bu.[25] Thus, soluble organic bases are unlikely to be effective for Pd-catalyzed C−N coupling of aryl chlorides using simple phosphine ligands.[27]

Until recently, the sole example of a DBU-mediated, Pd-catalyzed C−N coupling was a single report on the coupling of aryl nonaflates with aniline, imine, and amide nucleophiles at elevated temperatures (115−175 °C) under microwave-assisted conditions.[28,29] In 2018, while our studies were in progress, Buchwald and co-workers disclosed that a bulky dialkyl triarylmonophosphine-containing Pd(0) complex was capable of promoting the amination and amidation of a range of aryl triflates and bromides using DBU.[30] However, a single coupling of an aryl chloride was demonstrated, and the Pd(0) complex employed for the majority of the reported examples currently has limited commercial availability. Thus, despite this important advance, generally effective conditions for Pd-catalyzed C−N coupling of aryl chlorides under mild homogeneous conditions using widely available ligands remained unknown.

We considered that an additional factor limiting the utility of organic bases in Pd-catalyzed C−N coupling could arise from a buildup of soluble halide species in the reaction mixture that may inhibit coordination of the amine nucleophile to the arylpalladium intermediate and slow the transmetalation step, which has been shown to be rate-limiting for the arylation of primary and secondary amides.[31] The addition of soluble chloride[31a,32] and iodide[31c,32b] salts has been reported to give a marked decrease in both the rates and yields of couplings of aryl triflates and bromides. On the basis of these observations, we hypothesized that the use of a salt additive containing a weakly coordinating counteranion[33] might render a suitable organic base effective for Pd-catalyzed C−N coupling of aryl chlorides by sequestering the liberated chloride as an "M"Cl salt. A related halide-scavenging approach was employed recently by Morken and co-workers, who reported the use of NaOTf[34] and KOTf[35] as scavengers for chloride and bromide, respectively, in Pd-catalyzed conjunctive cross-couplings.[36,37] Becica and Dobereiner reported the use of both main-group and lanthanide triflate salts as additives in the Pd/Xantphos-catalyzed C−N coupling of aryl bromides and amides using Cs_2CO_3 as the base,[38] which lends further support for the halide-scavenging hypothesis but notably does not address the inherent challenges associated with heterogeneous reaction conditions.

RESULTS AND DISCUSSION

Investigation of Amine Bases and Chloride Scavengers. Our efforts toward the development of a scalable, homogeneous reaction system for C−N coupling focused on the use of aryl chlorides, which generally are more readily available and significantly less expensive than the corresponding aryl bromides and are thus more desirable for large-scale syntheses.[39] We first investigated couplings with primary amide nucleophiles. The tB-BrettPhos ligand developed by Buchwald and co-workers is a highly effective ligand for this challenging transformation and has been shown to promote such couplings with 1.0 mol % Pd and K_3PO_4 as the base in *t*-BuOH at 110 °C.[9b,31a] For our initial studies, we elected to use the complex [(tB-BrettPhos)Pd(Allyl)]OTf [**Pd-1**] recently developed by Johnson Matthey as a convenient single-component catalyst precursor.[40] As expected, the use of DBU alone gave very low conversion of **1a**[41] (Table 1, entry 1). In accord with our hypothesis, NaOTf and KOTf both proved to be effective additives that led to full conversion of **1a** in conjunction with DBU as the base (entries 2 and 3).[34,36] We were pleased to find that sodium trifluoroacetate (NaTFA), which is approximately 7.5 times less expensive than NaOTf on a kilogram scale, gave virtually identical reaction performance compared to NaOTf (entry 4). Incomplete conversion was observed in the presence of the more nucleophilic 2-ethylhexanoate anion of NaEHA (entry 5), while the use of NaOPh (entry 6) gave full conversion of **1a** but also led to detectable amounts of a C−O coupling byproduct. Other strong organic bases such as MTBD (entry 7) also proved

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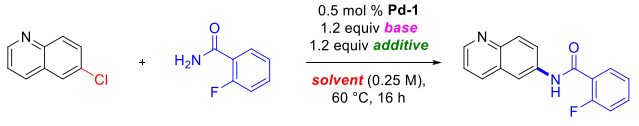
Table 1. Survey of Amine Bases and Soluble Chloride Scavengers[a]



1a 2a 3a

entry	base	additive	solvent	conv. (%)	yield (%)[b]
1	DBU	–	DME	11	11
2	DBU	NaOTf	DME	>99	94
3	DBU	KOTf	DME	>99	94
4	DBU	NaTFA	DME	>99	95
5	DBU	NaEHA	DME	57	46
6	DBU	NaOPh	DME	>99	93
7	MTBD	NaTFA	DME	>99	95
8	DIPEA	NaTFA	DME	<5	ND
9	DBU	NaTFA	2-MeTHF	>99	90
10	DBU	NaTFA	*t*-AmOH	>99	92
11	DBU	NaTFA	EtOAc	>99	92
12	DBU	NaTFA	DMF	96	86

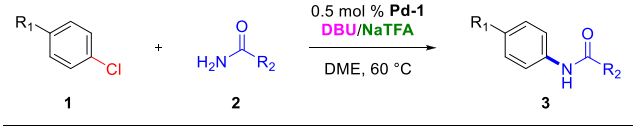
[a]Reaction conditions: 0.25 mmol of ArCl, 1.2 equiv of amide, 0.5 mol % [(tB-BrettPhos)Pd(Allyl)]OTf [**Pd-1**], 1.2 equiv of base, 1.2 equiv of additive, solvent (0.25 M), 60 °C, 16 h. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene. [b]Solution yields determined by ^{19}F NMR spectroscopy.

effective, whereas weaker bases such as DIPEA gave minimal conversion (entry 8; also see Table S2). Because of the lower cost of DBU and NaTFA compared with other bases and chloride scavengers, we focused on the DBU/NaTFA "dual-base" system for further studies. Guided by solubility screening data that indicated high solubility of NaTFA in a range of organic solvents[42] (Table S3), we subsequently discovered that the DBU/NaTFA-mediated coupling conditions are comparably effective in a variety of common solvents, including 2-MeTHF, *t*-AmOH, and EtOAc[16b] (entries 9–11; also see Table S4). Remarkably, the C–N coupling also proceeds in dipolar aprotic solvents such as DMF (entry 12), albeit with slightly diminished conversion and yield.

Couplings of Base-Sensitive Aryl Chlorides with Primary Amides. With a suitable chloride scavenger identified, we first sought to determine whether the DBU/NaTFA conditions could be utilized with aryl chlorides containing functional groups that are generally incompatible with strong inorganic bases. As shown in Table 2, the DBU/NaTFA dual-base system is tolerant of a wide range of base-sensitive moieties, with aryl chloride substrates containing ester (**3b**), nitrile (**3c**), nitro (**3d**), ketone (**3e** and **3f**), and aldehyde (**3g**) functional groups undergoing amidation in 64–86% isolated yield. While it is known that electron-deficient aryl chlorides (e.g., **1b–g**) are generally more reactive substrates in Pd-catalyzed cross-couplings compared with electron-neutral and electron-rich aryl chlorides, we were pleased to find that chlorobenzene also underwent amidation under the DBU/NaTFA dual-base conditions with comparable efficiency (**3h**, 72% yield). This latter finding thus prompted further study of less activated (hetero)aryl chloride substrates.

Couplings of (Hetero)aryl Chlorides with Primary Amides. Having established an encouraging functional group tolerance for the DBU/NaTFA conditions, we sought to more broadly investigate the scope of the (hetero)aryl chloride amidation reaction. As shown in Table 3, a variety of amide

Table 2. Amidation of Base-Sensitive Aryl Chlorides under DBU/NaTFA Dual-Base Conditions[a,b]



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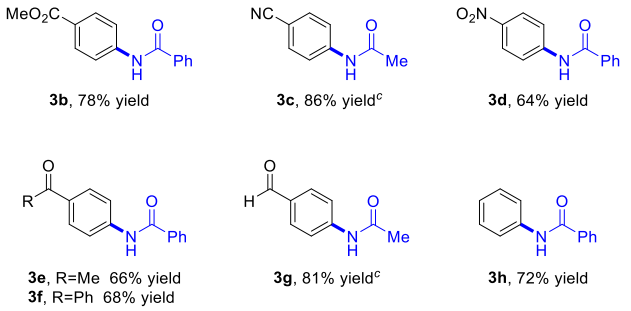


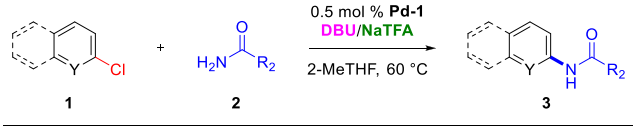
3b, 78% yield **3c**, 86% yield[c] **3d**, 64% yield

3e, R=Me 66% yield
3f, R=Ph 68% yield

3g, 81% yield[c] **3h**, 72% yield

[a]Isolated yields. [b]Reaction conditions: 1.0 mmol of ArCl, 1.2 equiv of amide, 0.5 mol % [(tB-BrettPhos)Pd(Allyl)]OTf [**Pd-1**], 1.5 equiv of DBU, 1.2 equiv of NaTFA, DME (0.50 M), 60 °C. [c]0.5 mmol of ArCl, 1.5 equiv of amide, 0.7–0.9 mol % **Pd-1**, MeCN, 65 °C.

Table 3. Amidation of (Hetero)aryl Chlorides under DBU/NaTFA Dual-Base Conditions[a,b]



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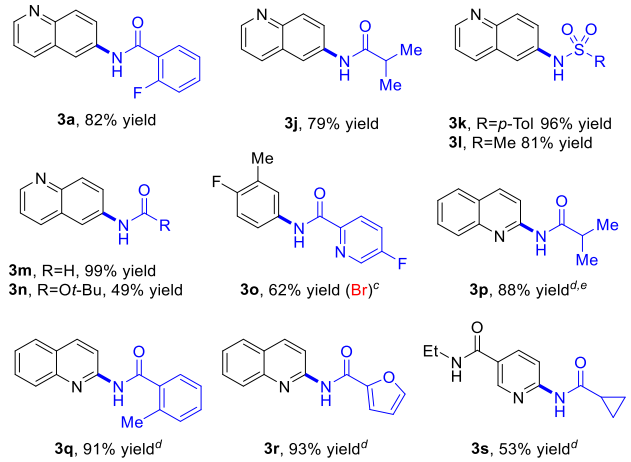

3a, 82% yield **3j**, 79% yield **3k**, R=*p*-Tol 96% yield
3l, R=Me 81% yield

3m, R=H, 99% yield
3n, R=O*t*-Bu, 49% yield

3o, 62% yield (Br)[c] **3p**, 88% yield[d,e]

3q, 91% yield[d] **3r**, 93% yield[d] **3s**, 53% yield[d]

[a]Isolated yields. [b]Reaction conditions: 2.0 mmol of ArCl, 1.2 equiv of amide, 0.5 mol % [(tB-BrettPhos)Pd(Allyl)]OTf [**Pd-1**], 1.2 equiv of DBU, 1.2 equiv of NaTFA, 2-MeTHF (0.50 M), 60 °C. [c]2.0 mmol of ArBr. [d]0.25 mol % $[(Allyl)PdCl]_2$, 0.55 mol % SL-J009-1 [**Pd-2**]. [e]1.0 mmol of ArCl.

nucleophiles were successfully coupled with 5-chloroquinoline using the DBU/NaTFA dual-base system, including aryl and alkyl amides (**3a** and **3j**) and sulfonamides (**3k** and **3l**) as well as the ammonia surrogates formamide (**3m**) and *tert*-butyl carbamate (**3n**). While not studied extensively, aryl bromides also proved to be viable coupling partners, with 5-bromo-2-fluorotoluene undergoing coupling with 5-fluoropicolinamide[43] to give **3o**. While 2-chloropyridine derivatives were found to react sluggishly with **Pd-1** as the catalyst, these substrates were readily coupled using a catalyst generated in situ from $[(Allyl)PdCl]_2$ and SL-J009-1 (CyPF-^{t}Bu).[1b,4b] With

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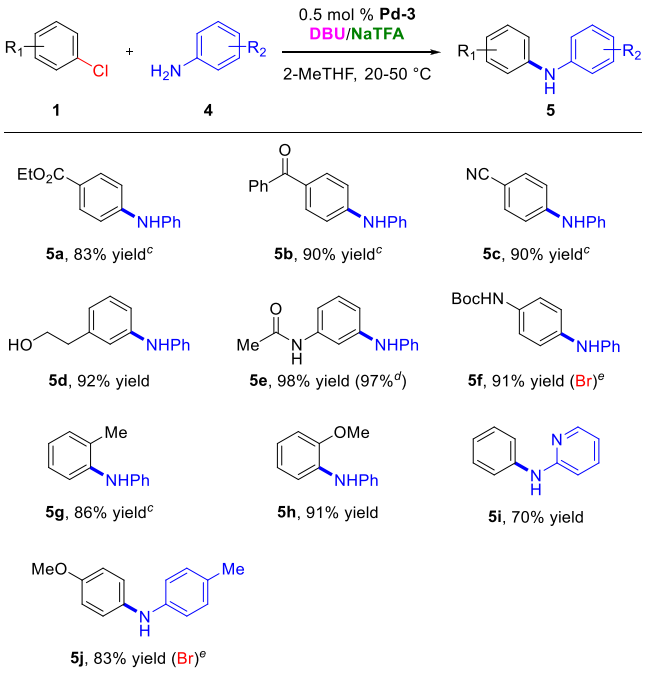
this catalyst system, denoted as [**Pd-2**], amidation was successfully achieved with both 2-chloroquinoline (**3p**–**r**) and a secondary-amide-containing 2-chloropyridine substrate (**3s**).

Couplings of Aryl Chlorides with Primary Aryl Amines. With a promising substrate scope demonstrated for the amidation of (hetero)aryl chlorides using two complementary catalyst systems, we next sought to extend our studies to other nitrogen nucleophiles. We discovered that the DBU/NaTFA dual-base system also enables the coupling of aryl chlorides and primary aryl amines under mild conditions using Buchwald's tB-XPhos-Pd-G3 palladacycle [**Pd-3**].[44] The scope of the couplings of primary aryl amines is shown in Table 4. In

Table 4. Amination of Aryl Chlorides and Bromides under DBU/NaTFA Dual-Base Conditions[a,b]



[a]Isolated yields. [b]Reaction conditions: 2.0 mmol of ArCl, 1.2 equiv of amine, 0.5 mol % tB-XPhos-Pd-G3 [**Pd-3**], 1.2 equiv of DBU, 1.2 equiv of NaTFA, 2-MeTHF (0.50 M), 20–50 °C. [c]1.0 mmol of ArCl, 1.5 equiv of DBU, DME (0.50 M), 20 °C. [d]0.5 mol % [(tB-XPhos)Pd(Allyl)]OTf [**Pd-4**]. [e]2.0 mmol of ArBr.

line with the previous results with amide nucleophiles, aryl chlorides bearing base-sensitive functional groups such as ester (**5a**), ketone (**5b**), and nitrile (**5c**) proved to be excellent coupling partners, readily undergoing amination with aniline catalyzed by 0.5 mol % **Pd-3** at room temperature in good yields. Protic functionalities were also compatible with the DBU/NaTFA conditions, including hydroxyl (**5d**), amide (**5e**), and carbamate (**5f**), with the latter coupling employing the aryl bromide electrophile. Though not tested extensively for these couplings, the Johnson Matthey precatalyst [(tB-XPhos)Pd(Allyl)]OTf [**Pd-4**][40a] gave virtually identical performance in the reaction to form **5e** (97% yield with 0.5 mol % **Pd-4** vs 98% yield with 0.5 mol % **Pd-3**). Ortho substitution on the aryl chloride was also well-tolerated (**5g** and **5h**), with the amination of 2-chlorotoluene proceeding at room temperature. A heteroaryl amine nucleophile also underwent coupling (**5i**), as did an electron-rich aryl bromide (**5j**).

Robustness Study of Primary Aryl Amine Couplings. To facilitate a detailed comparison of the functional group tolerance of the DBU/NaTFA dual-base system to that of classic aryl amine coupling conditions employing strong inorganic bases, we conducted a Glorius robustness study[45] for the coupling of 2-chlorotoluene with aniline at room temperature. Twenty-three different additives were spiked into the reaction mixture (each at 1.0 equiv) to probe the scope and limitations of the C–N coupling. On the basis of the initial data set, several additives were also tested at 50 °C. A summary of the key results can be seen in Figure 1.[46] Similar results were observed for the DBU/NaTFA and NaO*t*-Bu conditions with several additives, such as an alkyl chloride, dialkyl ketone, and protected pyrrole. In general, however, the NaO*t*-Bu conditions provided higher levels of conversion at room temperature compared with the dual-base system. For example, the addition of 4*H*-chromen-4-one, butyl thiophene, and oct-4-yne inhibited the DBU/NaTFA dual-base system, whereas complete conversion was observed with NaO*t*-Bu, even though the amount of additive remained between 53 and 95%.

On the other hand, the strength of the dual-base system is evident from a comparison of the results for base-sensitive additives. Although the conversion at room temperature is generally high for both systems with additives such as nitrobenzene, methyl benzoate, benzonitrile, acetophenone, and *p*-tolualdehyde, the amount of additive remaining varies greatly. In all cases, >95% of the additive remains for the DBU/NaTFA dual-base system, whereas appreciable consumption is observed in the case of NaO*t*-Bu. While simple substrates may perform well in C–N coupling at room temperature, the increased molecular complexity typical of many pharmaceutically relevant substrates could require an increase in reaction temperature to observe high levels of conversion. Therefore, we also tested the reactions with these base-sensitive additives at 50 °C, and the results are more interesting compared with those at room temperature. The mild nature of the dual-base system is again confirmed, with high levels of conversion still observed and >85% additive remaining in all cases. However, the same set of reactions utilizing NaO*t*-Bu perform worse at higher temperature, with lower amounts of product formed in all cases. While the amount of additive remaining for methyl benzoate and benzonitrile with NaO*t*-Bu is greater at 50 °C compared with room temperature, several new impurities are observed at the end of the reaction.

Reaction Kinetics for Amidation with DBU/NaTFA versus K_2CO_3. As noted previously, the heterogeneous reaction conditions that are inherent to the use of the weak inorganic bases most commonly employed for C–N coupling of amide nucleophiles present numerous challenges for scale-up. Among these complications, highly variable reaction rates that depend on a variety of complex parameters are frequently observed. The homogeneous reaction conditions afforded by the DBU/NaTFA dual-base system obviate many of these challenges, specifically effects of the form, particle size, and shape of the base as well as grinding effects from magnetic stirring. Additionally, the dual-base system also has the potential to overcome the reaction temperature limitations commonly resulting from the low solubility of inorganic bases in organic solvents,[11] which often lead to very low reaction rates at temperatures below 60 °C.

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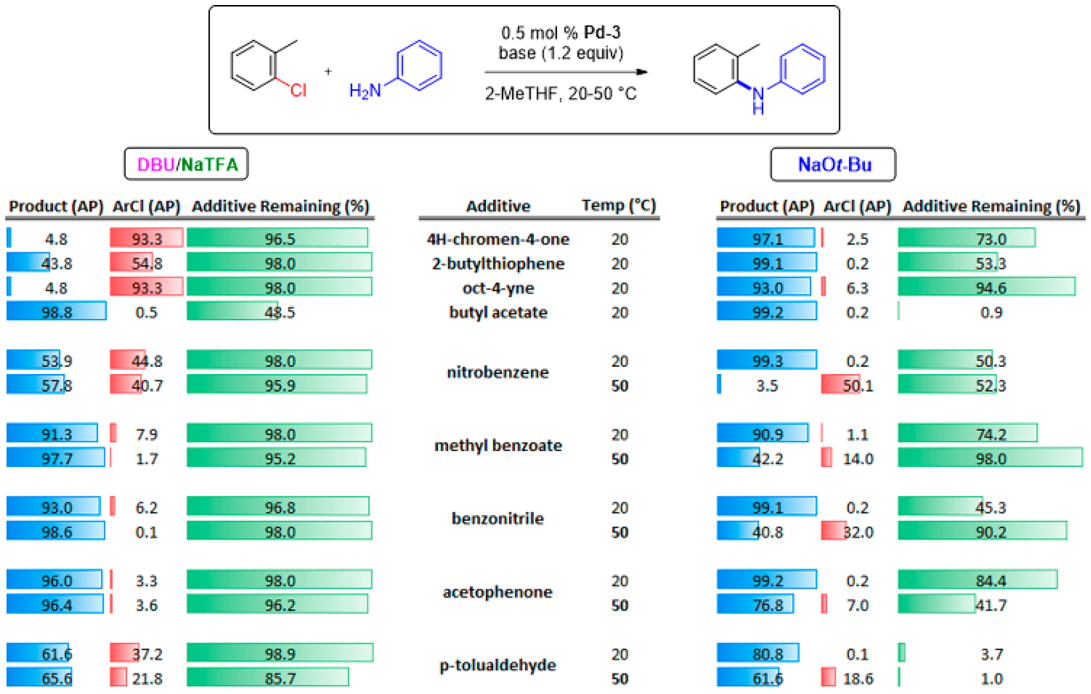

Figure 1. Robustness study for the amination of 2-chlorotoluene with DBU/NaTFA and NaO*t*-Bu. Note: for Additive Remaining values, 98.0 corresponds to >98% and 1.0 corresponds to <1.0%.

To gain preliminary insight into the reaction kinetics with DBU/NaTFA in comparison with commonly used weak inorganic bases, we monitored the amidation of 2-chloroquinoline with isobutyramide using DBU/NaTFA or K_2CO_3 as the base. As shown in Figure 2, the reaction catalyzed by 0.5 mol % **Pd-2** at 45 °C proceeds smoothly with DBU/NaTFA, reaching >99% conversion in approximately 7 h. In contrast, with K_2CO_3 as base the reaction is significantly slower, reaching ~50% conversion after 12 h. The use of commercially available 325 mesh K_2CO_3 provides a slight increase in reaction rate compared with granular K_2CO_3 (see Figures S1 and S2), an effect that can be expected to become more pronounced when moving to overhead stirring, but the reaction is still sluggish compared with the DBU/NaTFA dual-base conditions. Interestingly, the combination of DBU and K_2CO_3 leads to a slightly lower reaction rate compared with K_2CO_3 alone, consistent with the reversible formation of an off-cycle DBU-bound catalyst resting state.[30b] In line with our observations with **Pd-1**, DBU alone gave only trace conversion.

Amidation on a Multigram Scale under DBU/NaTFA Dual-Base Conditions. To test of the scalability of the dual-base system, we conducted the amidation of 2-chloroquinoline with isobutyramide on a 15 g scale using DBU/NaTFA conditions. As shown in Figure 3, the profile for this reaction, conducted with overhead mechanical stirring, matched very closely with the profile that was observed in the vial-scale kinetics runs using magnetic stir bars. Similarly, the 82% yield of **3p** for the 15 g reaction is also in line with the value from the 2.0 mmol scale reaction (88% yield). These data suggest that the DBU/NaTFA dual-base system is not subject to the same scale-dependent reaction variability typically observed with inorganic bases.

Amination under DBU/NaTFA Dual-Base Conditions with Complex Substrates. Our initial findings also indicate that the DBU/NaTFA dual-base conditions can be applied to the amination of complex substrates representative of the

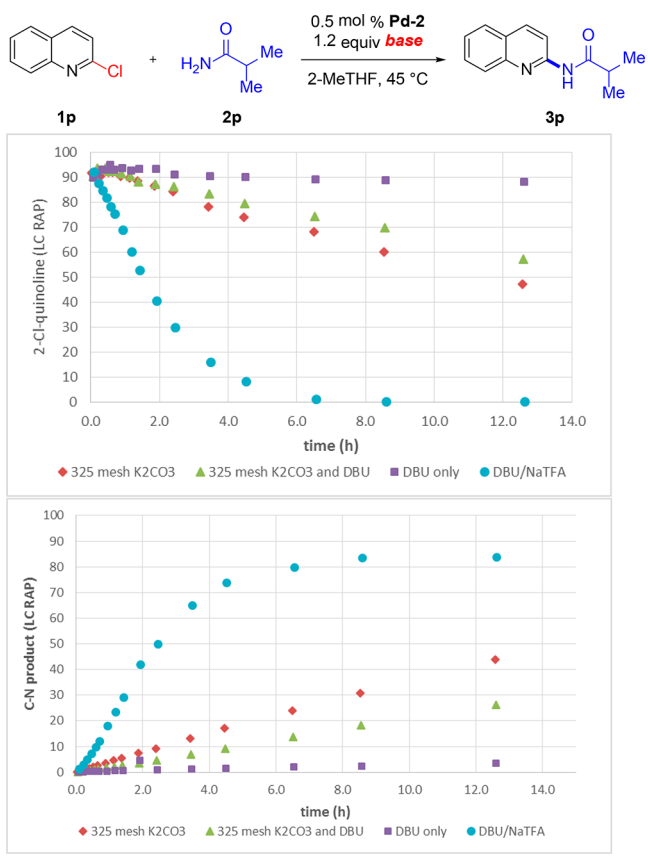

Figure 2. Reaction profiles for the amidation of 2-chloroquinoline with DBU/NaTFA and K_2CO_3 using 0.25 mol % $[(Allyl)PdCl]_2$ and 0.55 mol % SL-J009-1 [**Pd-2**] at 45 °C: (top) disappearance of 2-chloroquinoline; (bottom) formation of C−N-coupled product **3p**.

intermediates typically found in the synthesis of APIs. As shown in Scheme 2, the challenging C−N coupling of

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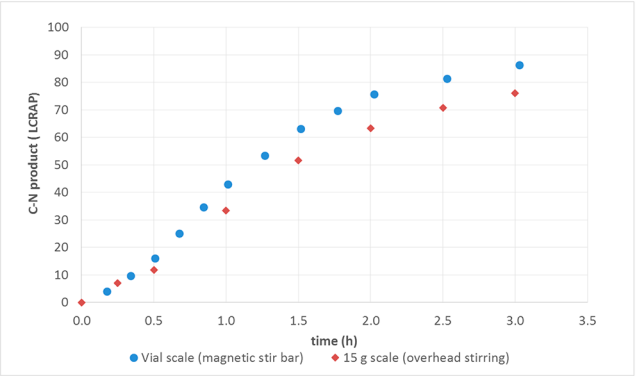
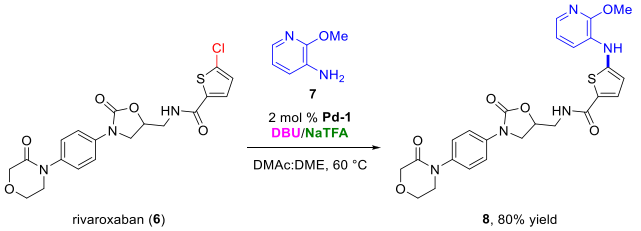


Figure 3. Reaction profiles for the amidation of 2-chloroquinoline with DBU/NaTFA using 0.25 mol % $[(Allyl)PdCl]_2$ and 0.55 mol % SL-J009-1 [**Pd-2**] at 50 °C on the vial scale (with a magnetic stir bar) and on a 15 g scale (with overhead mechanical stirring).

Scheme 2. Amination of Rivaroxaban under DBU/NaTFA Dual-Base Conditions



rivaroxaban (**6**) with heteroaryl amine **7**[47] was readily achieved under dual-base conditions catalyzed by 2 mol % **Pd-1**, delivering **8** in 80% isolated yield.[48] The use of DMAc as a cosolvent was essential for the success of this coupling because of the low solubility of **6** in the solvents typically used for C−N coupling. This cosolvent strategy may prove beneficial for effecting related C−N couplings of substrates with challenging solubility properties using dual-base conditions.

CONCLUSION

We have reported the development of a scalable, cost-effective (ca. $40/mol) DBU/NaTFA dual-base system that decouples the proton transfer and halide sequestration events in Pd-catalyzed C−N coupling reactions. These dual-base conditions enable the coupling of (hetero)aryl chlorides with primary amide and aryl amine nucleophiles under mild homogeneous conditions using low catalyst loadings (typically 0.5 mol %) of either preformed or in situ-generated Pd complexes ligated by mono- or bisphosphine ligands. A number of electron-deficient and electron-neutral aryl chlorides undergo DBU/NaTFA-mediated amination at room temperature, including those bearing base-sensitive functional groups that render them incompatible with classical C−N coupling conditions employing strong bases such as NaO*t*-Bu and LiHMDS. The DBU/NaTFA dual-base system constitutes the first set of general, practical conditions for homogeneous Pd-catalyzed amidation of aryl chlorides, thereby avoiding the notorious challenges associated with the development and scale-up of couplings involving the insoluble weak inorganic bases Cs_2CO_3, K_3PO_4, and K_2CO_3. Further studies to extend the scope of aryl halides and nucleophiles that can be coupled using dual-base conditions are currently in progress in our laboratories.

EXPERIMENTAL SECTION

General Information. All operations were performed under a nitrogen atmosphere. Starting materials, reagents, and solvents were used as received from the commercial vendors. UPLC analysis was performed using an Agilent Poroshell EC-C18 column (1.9 μm, 2.1 mm × 50 mm) and the following conditions: mobile phase A, 5:95 acetonitrile/water with 0.05% TFA; mobile phase B, 95:5 acetonitrile/water with 0.05% TFA; gradient, 0% B to 100% B over 2.0 min then 100% B for 0.5 min; injection volume, 1 μL; flow rate, 1.0 mL/min; oven temperature, 40 °C; detection by UV at 220 nm.

General Procedures for Amidation and Amination Using DBU/NaTFA Dual-Base Conditions. *Amidation of (Hetero)aryl Chlorides Using [(tB-BrettPhos)Pd(Allyl)]OTf [**Pd-1**].* To an 8 mL screw-cap vial were charged the aryl halide substrate **1** (1−2 mmol), amide nucleophile **2** (1.2 equiv), sodium trifluoroacetate (1.2 equiv), and a magnetic stir bar. Under an atmosphere of N_2, 2-MeTHF (2−4 mL for an aryl halide concentration of 0.50 M) and DBU (1.2 equiv) were added, followed by a solution of [**Pd-1**] in MeCN (100−200 μL for a Pd concentration of 0.050 M). The vial was capped and heated to 60 °C for the specified amount of time.

*Amination of (Hetero)aryl Chlorides and Bromides Using tB-XPhos-Pd-G3 [**Pd-3**].* To an 8 mL screw-cap vial was charged the aryl halide substrate **1** (1−2 mmol), aryl amine nucleophile **4** (1.2 equiv), sodium trifluoroacetate (1.2 equiv), and a magnetic stir bar. Under an atmosphere of N_2, 2-MeTHF (2−4 mL for an aryl halide concentration of 0.50 M) and DBU (1.2 equiv) were added, followed by a solution of [**Pd-3**] in MeCN (100−200 μL for a Pd concentration of 0.050 M). The vial was capped, and the reaction mixture was stirred at 20−50 °C for the specified amount of time.

Coupling of 2-Chloroquinoline (1p) and Isobutyramide (2p) Using DBU/NaTFA and [Pd-2]. *Catalyst Preparation.* The catalyst solution was prepared by combining $[(Allyl)PdCl]_2$ (85.6 mg, 0.25 mol %) and SL-J009-1 (280 mg, 0.55 mol %) in 2-MeTHF (30 mL). The contents of the vial were inerted by subsurface N_2 sparging for 30 min at room temperature.

Reaction. An inert 250 mL glass reactor equipped with an overhead agitator with a half-moon blade was prepared. A portion of the total 2-MeTHF (183 mL, 2 mL/mmol based on **1p**) was charged into the reactor to achieve a minimum stirrable volume, and agitation was started at room temperature. 2-Chloroquinoline (15 g, 91.7 mmol), isobutyramide (9.68 g, 1.2 equiv), and NaTFA (15.3 g, 1.2 equiv) were charged to the reactor through a funnel followed by DBU (16.5 mL, 1.2 equiv). The remainder of the 2-MeTHF was added to the reactor as a rinse of the addition port and reactor wall. The reactor was then sealed, and the solution was inerted via subsurface N_2 sparging until a headspace O_2 level of <700 ppm was achieved. The solution was then heated to the reaction temperature (50 °C) prior to charging with the catalyst solution. At t = 0 min, the catalyst solution was transferred to the main reactor via cannula to keep the contents of the reactor and catalyst solution vial inert. The reactor was kept under a N_2 blanket throughout the reaction age. At specified time intervals, samples were withdrawn from

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the reactor using an Easy Sampler (Mettler Toledo) under inert conditions and quenched in a vial at 350-fold dilution with 50:50 v/v MeCN/water (at 20 °C), which was used as both the quench and diluent. Upon completion of the sampling protocol, samples were transferred to UPLC vials and filtered for UPLC analysis. Quantitative UPLC analysis of the postreaction stream indicated an 82% yield of **3p**.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.9b00196.

Experimental details, characterization data and NMR spectra for C−N coupling products (PDF)

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Notes

The authors declare no competing financial interest.

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