Organic LETTERS

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

Palladium-Catalyzed Site-Selective Amidation of Dichloroazines

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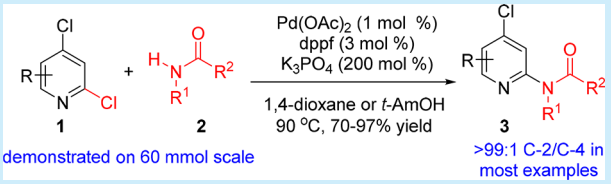
Supporting Information

ABSTRACT: A highly site-selective amidation reaction of substituted 2,4-dichloroazines is reported. Palladium acetate/1,1′-bis(diphenylphosphino)ferrocene (dppf) was identified as the optimal catalyst system, producing >99:1 C-2/C-4 selectivity for most examples. The generality of this transformation was demonstrated through a survey of a diverse amide/substituted 2,4-dichloroazine scope, leading to the preparation of the desired C-2 amidated products in good to excellent yields.



Highly functionalized heterocycles are valuable pharmacophores in drug discovery.[1] Chemoselective or regioselective formation of a C−N bond[2] on polyhalogenated heterocyclic scaffolds[3] has been an intriguing challenge for synthetic chemists, and the development of selective processes could allow for the construction of such diverse targets through sequential transformations. The need for predictability and reproducibility is especially important in a pharmaceutical setting where stringent requirements on the acceptable levels of the minor isomer in the active pharmaceutical ingredient (API) are enforced by tight specifications.[4]

Pioneering work by Houk and co-workers through a computational approach indicated that bond-dissociation energies (BDEs) could be one determining factor in achieving selective couplings on polyhalogenated heterocycles under palladium catalysis.[5] Although reports exist detailing selective transition-metal-catalyzed C−N aminations on 2,4-dichloropyridine derivatives,[6] examples where the C−N bond is forged via an amidation reaction are scarce.[7] Morgentin and co-workers reported a Pd-catalyzed site-selective coupling of a series of *N*-acetylanilines with the C-6 position of 4,6-dichloronicotinonitrile in moderate yields (27−85%) using Xantphos as a ligand.[8] In this study, the acetyl group served as a protecting group to minimize the bis-arylation side product commonly observed in Pd-catalyzed amination reactions involving primary amines and was subsequently removed to yield a net amination. Examples also exist for Pd-catalyzed C-2 selective ureidations of 2,4-dichloropyridines using Xantphos as the ligand, although the reported substrate scope was limited to only a few examples.[9]

In the course of chemical development efforts on an internal program in our laboratories, we were tasked with developing a highly site-selective amidation protocol with substituted 2,4-dichloropyridines. Due to the lack of literature guidance with regard to this challenge, we hoped to develop a general solution to this problem and relied on high-throughput experimentation[10] to rapidly determine a starting point for further optimization.

Initial screening of a series of palladium catalysts to evaluate the regioselectivity of the amidation was conducted for the coupling of 2,4-dichloropyridine (**1a**) and 2-pyrrolidinone (**2a**) using 5 mol % of palladium catalyst, potassium carbonate as base, and toluene as the solvent (Figure 1). Among all of the

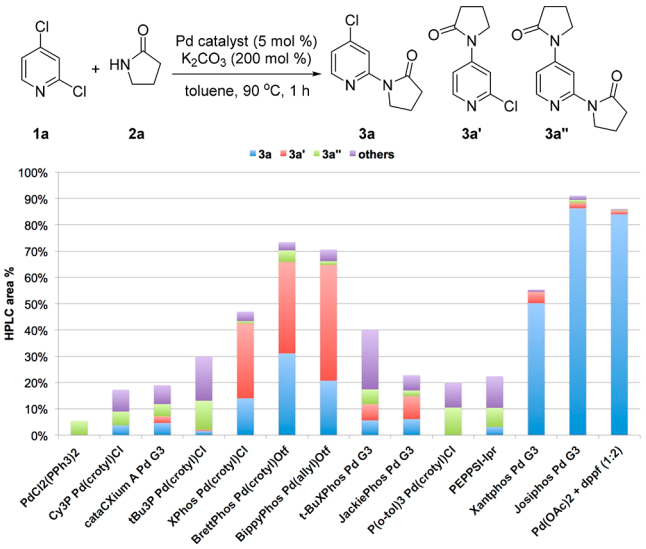


Figure 1. Ligand screening for regioselective amidation of **1a** with **2a**.

literature precedents for Pd-catalyzed amidation of aryl halides,[11] a catalyst system consisting of a bidentate ligand such as Xantphos, Josiphos, and dppf proved to afford the best selectivity of the desired C-2 coupled product **3a**.[12] Dppf[13] was chosen over Josiphos as the optimal ligand for further optimizations because of its more affordable cost. Following this lead, potassium phosphate tribasic was identified as an optimal

Received: May 10, 2018

DOI: 10.1021/acs.orglett.8b01483
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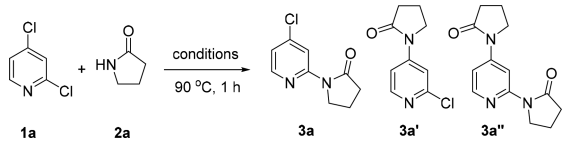
base, affording higher conversion using only 1 mol % of $Pd(OAc)_2$ (Table 1, entries 2 and 3). Subsequent examination

Table 1. Condition Optimizations for the Pd-Catalyzed Coupling Reaction of 1a and 2a[a]



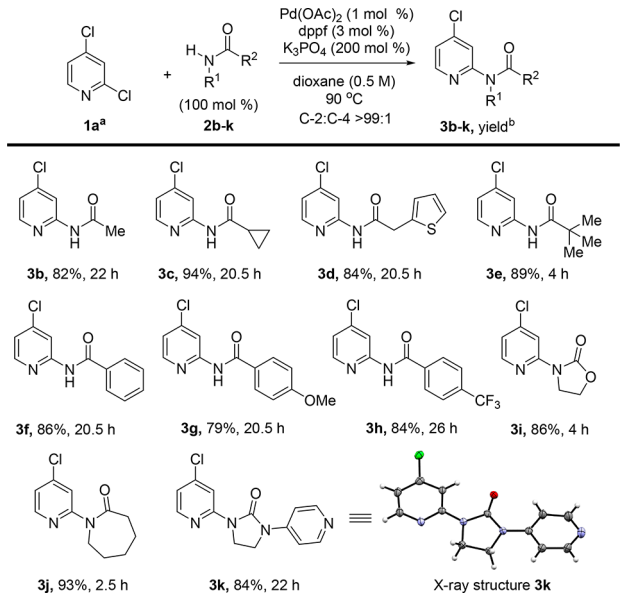
entry	$Pd(OAc)_2$/dppf (mol %)	base	solvent	conv/ 3a[b]	3a/3a′[b,c]
1	5/10	K_2CO_3	toluene	86/84	98.5:1.5
2	1/2	K_3PO_4	toluene	98/97	98.6:1.4
3	1/2	K_3PO_4	dioxane	94/93	>99:1
4	1/0	K_3PO_4	dioxane	0/0	N/A
5	1/1	K_3PO_4	dioxane	56/54	>99:1
6	1/3	K_3PO_4	dioxane	100/99	>99:1
7	0.5/1.5	K_3PO_4	dioxane	82/81	98.8:1.2
8	1/3	K_3PO_4	*t*-AmOH	97/95	98.8:1.2

[a]Reaction conditions: **1a** (3 mmol), **2a** (100 mol %), $Pd(OAc)_2$ (0.5−5 mol %), ligand (1.5−10 mol %), base (200 mol %), solvent (0.5 M). [b]Determined by HPLC analysis of crude reaction mixture. [c]<1% **3a′′** observed in all cases.

of the Pd precatalyst to ligand ratio revealed that the optimal rate could be achieved using 1:3 $Pd(OAc)_2$/dppf (entries 3−6). An attempt to lower the palladium loading to 0.5 mol % based on the optimal 1:3 Pd/ligand ratio gave an incomplete 82% conversion after 1 h at 90 °C (entry 7). Though 1,4-dioxane was found to be the best solvent for this transformation, providing the highest C-2/C-4 product ratio and fast reaction rate, we identified *tert*-amyl alcohol (*t*-AmOH) as a greener alternative, giving only a slightly slower reaction rate compared to the reaction in 1,4-dioxane (entries 8 vs 6).[14] The utility of the *t*-AmOH conditions was demonstrated on 60 mmol scale (100 mol % of **2a** utilized) to produce a crude reaction profile of 99.0 area % of **3a**, 0.6 area % of **3a′**, and 0.4 area % of **3a′′** by HPLC analysis and a 96% isolated yield after purification by column chromatography.

Upon identification of a C-2-selective catalytic system (Table 1, entry 6), we surveyed the reaction generality with respect to amide. For analogue preparation, the amide was limited to 100 mol % to prevent unwanted conversion of the desired product to the bis-amidated impurity. Even without an excess of either coupling partner, all reactions with 2,4-dichloropyridine (**1a**) reached >60% conversion in 1 h and >98% conversion after overnight heating (Scheme 1).[15] The amide scope was found to be broad, with primary aliphatic amides of varying steric bulk yielding product in good to excellent yields (**3b−e**). Secondary cyclic amides such as ε-caprolactam (**3j**) and other nucleophiles such as oxazolidinones (**3i**) and cyclic ureas (**3k**) also performed well in the coupling. For the examples mentioned above, a simple workup consisting of filtration to remove the inorganics, concentration of the filtrate, and purification of the crude residue by column chromatography was utilized. When the products derived from aromatic amides (**3f**/**3h**) were subjected to a similar isolation protocol, lower yields (45−55%) were encountered in multiple attempts. This discrepancy was surprising, as the reaction profiles showed that product was formed in >95 area % as indicated by HPLC. It was subsequently discovered that the higher

Scheme 1. Scope of Amides in Pd-Catalyzed Coupling Reactions with 2,4-Dichloropyridine (1a)



[a]Reactions performed on 3 mmol scale. [b]Isolated yields.

acidity of the aromatic amide N−H led to partial formation of the product potassium salt, leading to 40−50% of the material being removed during filtration. Incorporation of an aqueous workup for these two examples restored the yields to levels in line with the other substrates. It should be noted that although we did not prepare the C-4 markers for each example in Scheme 1, in all cases no impurities were observed over 1 area % by HPLC in the crude reaction mixture by LC−MS analysis, indicating a >99:1 selectivity for the C-2 position. The positional selectivity was confirmed by single-crystal X-ray crystallographic analysis of **3b** and **3k**.[16]

We next examined how additional substituents on the 2,4-dichloropyridine scaffold impacted coupling efficiency with 2-pyrrolidinone (**2a**, Scheme 2). Both electron-donating and electron-withdrawing substituents were tolerated at the 3-position (**4b−g**), although substrates bearing electron-donating groups required extended reaction times (−Me, **4f**) or increased catalyst loading (−OMe, **4g**). No reaction was observed when preparation of **4o** bearing a free amino group was attempted, which can be attributed to either chelation of the catalyst or the increased electron density inhibiting oxidative addition. The yield for **4d** was the lowest reported, resulting from the generation of significant double-addition product. Additional substitution patterns (**4h**/**4i**) as well as other heterocycle derivatives such as pyridazines (**4j**), quinolines (**4k**), and 7-azaindoles (**4l**) all resulted in good to excellent yields of products.[15] The reaction to produce free phenol containing **4m** did proceed cleanly, although under the standard conditions the conversion did not proceed past 70%. The discrepancy between observed conversion and isolated yield is the result of loss during purification. Attempts to synthesize **4n** led to complicated reactions profiles. The site-selectivity was again confirmed by obtaining single-crystal X-ray structures for compounds **4d**, **4h**, and **4i**.[17]

One discrepancy observed with these more advanced pyridine substrates was that higher levels (1−4 area % by HPLC analysis) of a minor impurity were observed in some of the crude reaction mixtures in Scheme 2 (vs Scheme 1). HPLC−MS

DOI: 10.1021/acs.orglett.8b01483
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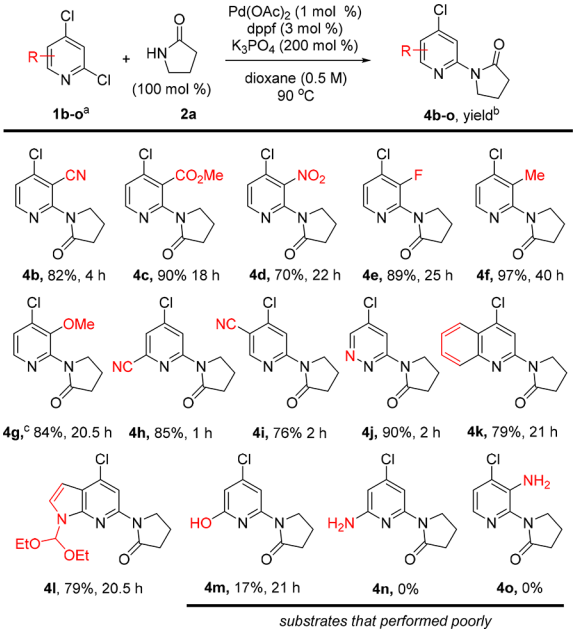
Scheme 2. Scope of Dichloroazines in Pd-Catalyzed Coupling Reactions with 2-Pyrrolidinone (2a)

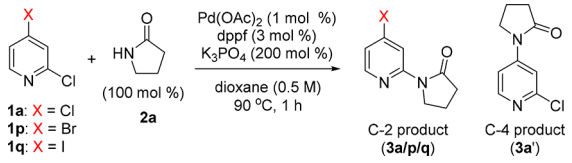


[a]Reactions performed on 3 mmol scale unless otherwise indicated in the Supporting Information. [b]Isolated yields. [c]5 mol % of $Pd(OAc)_2$ and 15 mol % of dppf used.

analysis indicated that this new impurity had the same mass as the desired product, leading to the conclusion that it was likely the C-4 regioisomer. Closer examination indicated that the levels of the C-4 products were the highest in pyridine derivatives containing an electron-withdrawing substituent. This led us to question whether this was the result of reduced catalyst selectivity, or instead due to background S_NAr reactivity that favored the C-4 position. Performing the appropriate control reactions [$Pd(OAc)_2$ and dppf ligand omitted] led to significant amounts of both the C-2/C-4 products for **4b**, **4c**, **4d**, **4h**, and **4i** (7−41% conversions compared to 73−100% conversions in Pd-catalyzed reactions after 1 h).[18] Fortunately, even for these electron-deficient substrates, the Pd-catalyzed C-2 amidation process was found to outcompete the nonselective background S_NAr reaction favoring the C-4 amidation and provide excellent selectivity (>96:4 C-2/C-4).

There are two most probable scenarios to account for the observed selectivity: (1) The product ratio is determined by a rate-limiting oxidative addition step to form the corresponding LPd(Het-Ar)(X) species which would undergo fast amide−halide exchange and reductive elimination steps subsequently to provide the C−N coupled products resembling the ratio of the corresponding oxidative addition adducts. (2) The product ratio is largely dependent on the rate of amide−halide exchange step with the corresponding C-2 and C-4 oxidative addition adducts being in a fast equilibrium under the Curtin−Hammett principle.[19] In the latter scenario, we envisioned that the reaction would still favor the C-2 product even with a faster oxidative addition to the C-4 position induced by a weaker C−X bond. The coupling of 2-chloro-4-iodopyridine (**1q**) with 2-pyrrolidinone (**2a**) under the standard reaction conditions afforded complete C-4-coupled product shown in Table 2, albeit with a slower reaction rate after 1 h (50% vs complete conversion using 2,4-dichloropyridine **1a**); while in the case of 2-chloro-4-bromopyridine (**1p**), C-4 coupled product was still

Table 2. Preliminary Mechanistic Study To Probe the Selectivity-Determining Step



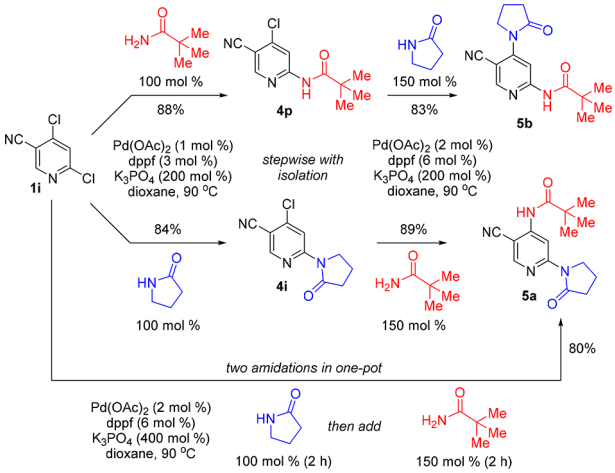
substrate	conv[a] (%)	C-2 product[a] (A %)	C-4 product[a] (A %)	C-2/C-4
1a	100	99.4	0.4	99.6/0.4
1p	86.3	6.4	79.9	7.4/92.6
1q	50	nd	50	0/100

[a]Determined by HPLC analysis of crude reaction mixture.

observed as the major one with a 7:93 C-2/C-4 product ratio. These results are consistent with the first scenario, suggesting oxidative addition is likely to be the selectivity determining step that is in accord with the BDE proposal outlined by Houk and co-workers (86.3 kcal/mol for C_2−Cl bond vs 89.5 kcal/mol for C_4−Cl bond using B3LYP in the case of 2,4-dichloropyridine).[5]

The ability to further functionalize the C-2-amidated products at the C-4-position could extend the utility of this method. Based on the lack of observed bis-amidated product with $Pd(OAc)_2$/dppf catalyst system (Schemes 1 and 2), we increased both the amide stoichiometry (150 mmol %) and catalyst loading (2 mol % $Pd(OAc)_2$/6 mol % dppf) for the initial attempts at installing the second amide. Gratifyingly, the second amidation was rapid, reaching >99% conversion in 2 h for two examples (**5a**/**5b**, Scheme 3). This strategy for the

Scheme 3. Synthesis of Differentially Substituted Bis-amidated Pyridines



preparation of positional isomers **5a**/**5b** offered the advantage that development and optimization of a second catalyst system was not necessary to access diversely functionalized pyridine derivatives in high overall yield. Based on these findings, we hypothesized that it should be possible to arrive at the same double adduct by a sequential addition of two different amides to a single reaction flask. Proof of concept was obtained by preparation of **5a** via this strategy. The ease at which diversely functionalized bis-amidated pyridines can be prepared via this methodology should allow medicinal chemists to quickly generate analogs. Although this process is initially selective for

DOI: 10.1021/acs.orglett.8b01483
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C-2 amidation, tailoring the order of which the amide reactants are added allows for indirect selectivity at the 4-position (compare **5a**/**b**). It should be noted that development of a highly C-4 selective Pd-catalyzed process on 2,4-dichloropyridine remains an unsolved problem.[20]

In summary, we have identified a catalyst system that amidates dichloroazines such as substituted 2,4-dichloropyridines with a high level of C-2 selectivity. The substrate scope with respect to both amide and dichloroazine is broad, allowing for the preparation of a diverse series of functionalized heterocycles in good to excellent yields (70−97%). The utility of this method was further expanded through development of sequential amidation protocols to form differentially substituted bisamidated pyridines. The high level of site-selectivity imparted by this catalyst system is intriguing from a mechanistic perspective, and additional studies will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01483.

General experimental procedures, characterization details, and ^{1}H, ^{13}C, and ^{19}F NMR (PDF)
Single-crystal X-ray reports (PDF)

Accession Codes

CCDC 1842393−1842398 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Professor Stephen Buchwald (Massachusetts Institute of Technology) for helpful discussions, Dr. Antonio DiPasquale for single-crystal X-ray analysis, and Dr. Kenji Kurita for collecting HRMS data (Genentech, Inc.).

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(15) In most cases, the reactions were heated overnight to ensure full consumption of **1**. See the Supporting Information for relative rates of reaction comparison based on amide/substituted dichloroazine.

(16) See the Supporting Information for more details. NOESY analysis of compounds **3i**, **3j**, and **3k** could not conclusively distinguish between C-2 vs C-4 amidation.

(17) See the Supporting Information for more details. NOESY analysis of compounds **4h**, **4j**, and **4m** could not conclusively distinguish between C-2 vs C-4 amidation.

DOI: 10.1021/acs.orglett.8b01483
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(18) See the Supporting Information for more details. Running the control reactions in a polar aprotic solvent such as DMSO to mimic standard S_NAr conditions led to higher ratios of the C-4 product. Similar competing background reactivity was observed during the selective Pd-catalyzed amination of 2,4-dichloropyrimidines; see ref 3b.
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DOI: 10.1021/acs.orglett.8b01483
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