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Pd/PTABS: Catalyst for Room Temperature Amination of Heteroarenes

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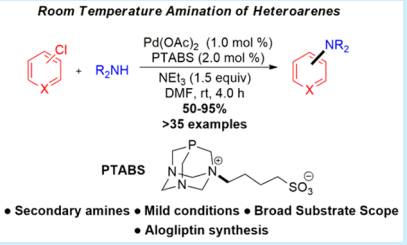
Supporting Information

ABSTRACT: A mild and highly efficient catalytic amination procedure for chloroheteroarenes at ambient temperature using the Pd/PTABS catalytic system is reported. The protocol is selective for the amination of chloroheteroarenes using secondary amines such as piperidine, pyrrolidine, and several others. The exceptional mildness of the developed protocol is beneficial for the synthesis of a crucial Buparlisib intermediate as well as the formal synthesis of Alogliptin in competitive yields.



Heteroaromatic compounds with substituted amine functionalities have found wide applicability as molecules of biological and pharmaceutical relevance.[1] Their regular occurrence as structural motifs in commercially available drugs (Figure 1), such as Buparlisib (**1**, anticancer),[2] ZSTK474 (**2**),[3] Uptravi (**3**, hypertension),[4] and BuSpar (**4**, antidepressants),[5] further substantiates their case for developing respective efficient synthetic methodologies.

Palladium-catalyzed Buchwald−Hartwig amination of halo-(hetero)arenes[6] is a successful synthetic strategy for the installation of amine functionalities via efficient activation of C−X bonds (X = I, Br, and Cl). Notably, the introduction of the commercially available Buchwald ligand series has brought about an accelerated development in this area of research owing to Buchwald and his research group.[7] Several other catalyst systems have been reported in recent years allowing the catalytic amination of bromo- or iodo(hetero)arenes to be carried out efficiently, even at ambient temperature.[8] Given the abundant commercial availability and inexpensive nature of the heteroaryl chlorides, however, the development of efficient catalytic amination protocols addressing such substrates is desired.

The amination of chloro arenes has been described by several research groups such as Beller (diadamantylphosphine ligand system),[9] Buchwald (series of active phosphine ligand systems),[10] Plenio,[11] Reetz (phosphoramidite ligand),[12] Organ (Pd-PEPPSI complexes),[13] and many others in combination with common palladium precursors. Most of these protocols provided the amination products in competitive yields, but at relatively high temperatures of 80−130 °C, with use of strong bases and high catalyst concentration, rendering them synthetically less attractive. Only a few protocols are known from the research groups of Buchwald,[14] Hartwig,[15] Stradiotto,[16] and Nolan,[17] which have allowed only chloroarenes to be aminated at ambient temperature. Given the deficiency in finding efficient coupling protocols for chloroheteroarenes, we report a highly efficient

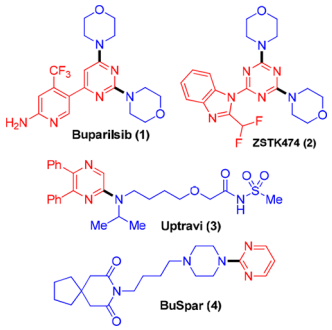


Figure 1. Aminated heteroarene bearing commercial drugs.

synthetic protocol for the palladium-catalyzed amination of chloroheteroarenes with secondary amines using the $Pd(OAc)_2$/PTABS system at ambient temperature. At the outset of this study, the screening of catalytic systems was performed involving different activating phosphine ligands in combination with $Pd(OAc)_2$ (Table 1). Uncatalyzed amination protocols are not uncommon. A recent study by Moody and co-workers[18] into the transition-metal-free amination of heteroaryl chlorides prompted us to test the involvement of the SNAr reaction under the conditions envisaged for obtaining the coupling at ambient temperature. In the presence of 2.0 equiv of pyrrolidine (acting as both, starting material and base), without added metal precursor, in DMF as solvent, and at ambient temperature (23 °C), the reaction failed to furnish the target product.

This result rules out a SNAr-type amination taking place under these conditions. Addition of $Pd(OAc)_2$ promotes the formation of the desired product but in poor yields (up to 20% only). Next, the role of activating ligands in the catalytic amination reaction

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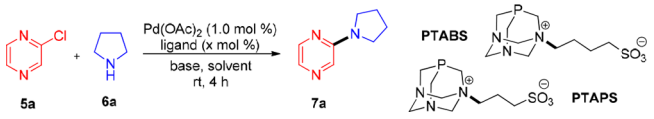
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. Screening for Room Temperature Amination of Chloroheteroarenes[a]



entry	6a (equiv.)	ligands	ligand (mol%)	base (equiv.)	solvent	yield[a] (%)
1.[b]	2.0	--	--	--	DMF	0
2.[c]	2.0	--	--	--	DMF	20
3.	2.0	PPh_3	1.0	--	DMF	30
4.	2.0	SPhos	1.0	--	DMF	63
5.	2.0	XPhos	1.0	--	DMF	70
6.	2.0	XPhos	2.0	--	DMF	73
7.	2.0	tBu_3P	1.0	--	DMF	54
8.	2.0	$tBu_3P.HBF_4$	1.0	--	DMF	62
9.	2.0	$(Ad)_2BuP$	2.0	--	DMF	69
10.	2.0	PEPPSI (1.0 mol %)	-	--	DMF	75
11.	2.0	PTABS	1.0	--	DMF	60
12.	2.0	PTAPS	1.0	--	DMF	55
13.	**2.0**	**PTABS**	**2.0**	**--**	**DMF**	**79**
14.[d]	2.0	PTABS	2.0	--	DMF	0
15.[e]	2.0	PTABS	1.0	--	DMF	58
16.[f]	2.0	PTABS	0.2	--	DMF	50
17.	1.2	PTABS	2.0	K_2CO_3 (1.0)	DMF	72
18.	1.2	PTABS	2.0	tBuOK (1.0)	DMF	74
19.	1.2	PTABS	2.0	NEt_3(1.0)	DMF	83
20.	1.2	PTABS	2.0	NEt_3(1.5)	DMF	88
21.	1.2	PTABS	2.0	NEt_3(1.5)	ACN	72
22.	1.2	PTABS	2.0	NEt_3(1.5)	H_2O	69
23.	1.2	PTABS	2.0	NEt_3(1.5)	H_2O:ACN	75

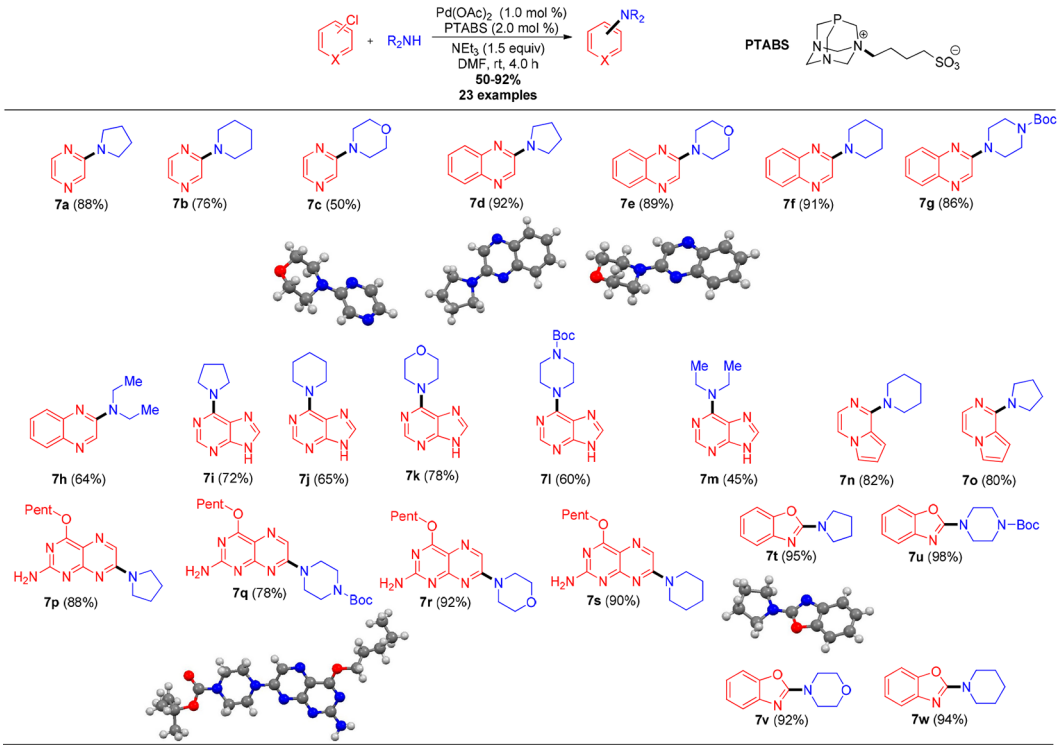
[a]Reaction conditions: 1.0 mmol of **5a**, 1.0 mol % of $Pd(OAC)_2$, 3 mL of solvent, H_2O/ACN (1:1), stirring at room temperature for 4 h. Isolated yields. [b]Without added $Pd(OAc)_2$ and ligand. [c]Without added ligand. [d]Without added $Pd(OAc)_2$. [e]0.5 mol % of $Pd(OAc)_2$. [f]0.1 mol % of $Pd(OAc)_2$.

was assessed. The addition of triphenylphosphine brought about only a slight improvement in the catalytic activity, while strongly activating SPhos or XPhos ligands provided good yields of the amination product. Addition of electron-rich and sterically demanding $^tBu_3P$, $^tBu_3P{\cdot}HBF_4$, and $(Ad)_2BuP$ (the Beller ligand) was found to provide satisfactory yields, while the commercially available PEPPSI-Ipr catalyst provided the highest yield of the cross-coupled product (75%). Finally, the PTABS and PTAPS ligand systems were employed, which were recently reported by our group as efficient water-soluble ligands for the palladium-catalyzed coupling of halo nucleosides, and the conditions were optimized.[19] Best results were obtained when PTABS (2.0 mol %) was employed as ligand in combination with $Pd(OAc)_2$ (1.0 mol %) in DMF as solvent and pyrrolidine as reactant and base (entry 13, 79%). It was also found that the removal of $Pd(OAc)_2$ resulted in the complete absence of catalytic activity (entry 14). It was also observed that reduction in concentration of the catalyst had a deteriorating impact on the catalytic activity. The choice of not incorporating an exogenous base was intriguing, but the potential dependence of the catalytic protocol on the pK_a of the added amine might be detrimental in further stages of the investigation.

We decided to incorporate an exogenous base, and triethylamine was found to provide the coupled product in very good yield (entry 20, 88%). This allowed us to reduce the amount of the secondary amine to 1.2 equiv in the presence of 1.5 equiv of Et_3N for reaching optimum catalytic efficiency. DMF was found to be the solvent of choice with other solvents including water providing lower yields. With an efficient optimized catalytic protocol in hand, we envisaged being able to couple a wide variety of heteroaryl chlorides with secondary amines at ambient temperature. 2-Chloropyrazine was initially coupled with three different cyclic secondary amines, namely, pyrrolidine, piperidine, and morpholine (Scheme 1, **7a**–**7c**). Although, a slightly lower yield of the coupled product was obtained for morpholine, overall the yields were very good. Similarly in the case of 2-chloroquinoxaline, all three heterocyclic bases gave excellent yields of the aminated product, which was also the case with *N*-Boc protected piperazine (**7d**–**7g**). Notably, an acyclic amine such as diethylamine also could be coupled in good yields (**7h**).

The initial success with simple heteroaryl chlorides gave incentive to test the amination protocol for more challenging and

Scheme 1. Scope for Amination of Chloro(heteroarenes)



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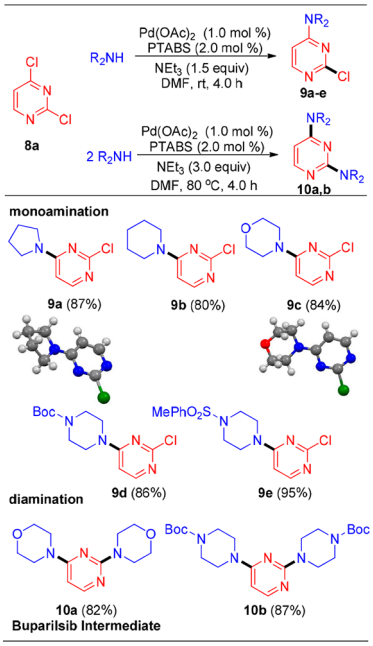
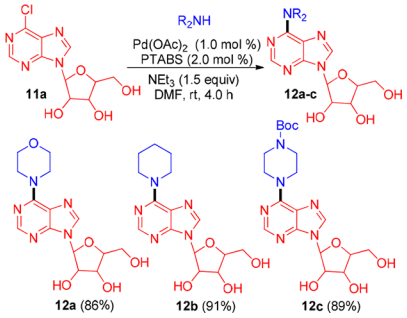
synthetically useful substrates. 6-Chloropurine, for example, is an important starting material for obtaining functionalized purine nucleosides with a variety of synthetic and biological applications.[20] Catalytic amination of 6-chloropurine was performed with the different amines with good yields obtained except for diethylamine (showing slightly reduced activity as more hydro-dehalogenation was observed; entries **7i**−**7m**). Bioactive pyrrolo[1,2-*a*]pyrazines[21] are important structural motifs exhibiting a wide variety of antifungal, antitumor, and antioxidant properties. The introduction of an amine functionality on these moieties would further enhance their bioactivity. With this in mind, different secondary amines were successfully coupled to 1-chloropyrrolo[1,2-*a*]pyrazine in very good yields (**7n**, **7o**).

Further functionalizing pteridines with secondary amines was presumed to be beneficial regarding the enhancement of fluorescent properties as well as biological activity. To achieve this goal, 6-chloropteridine was submitted to the optimized amination conditions as outlined above with different secondary amines. We observed good to excellent yields of the coupled products, further confirming the potential and broad applicability of the developed amination protocol. The crystalline nature of some of the coupled products (**7c**−**e**,**q**,**t**) allowed their molecular structures to be confirmed by single crystal X-ray analysis (see the SI). Achieving efficient regioselectivity constitutes one of the challenges for further synthetic utilization in catalytic coupling reactions. Polyhalogenated heteroarene functionalization in a selective manner has been accomplished most effectively using palladium-catalyzed cross-coupling reactions.[22] We then investigated the selective monoamination of 2,4-dichloropyrimidine with four different secondary amines, namely, pyrrolidine, piperidine, morpholine, and piperazine derivatives (Scheme 2). In each investigated case, monoamination was observed to take place selectively at the 4-position, thus leaving the 2-chloro position to be subjected to further synthetic modification (single crystal X-ray was obtained for **9a** and **9c**).

Scheme 2. Monoselective Amination



Scheme 3. Synthesis of 6-Amine (Secondary Amine)-Functionalized Purine



It is important to note that this selectivity was achieved by performing the catalytic amination at ambient temperature while increasing the reaction temperature to 80 °C allowed for efficient diamination (in the presence of 2.0 equiv of added amine). Such a protocol also provides the possibility of synthesizing the Buparlisib[2] drug intermediate **10a** (Buparlisib is a pan-class 1 phosphoinositide 3-kinase inhibitor) in very good yields.

Another synthetic challenge involves the amination of a ribose nucleoside, 6-chloro-9-β-D-ribofuranosylpurine. In the literature, Koomen,[23a] Schmalz,[23b] and Lakshman[23c,d] reported on the amination of silyl-protected ribose nucleosides in decent yields. The mild nature of the optimized catalytic system, when used for the amination of the ribose nucleoside, provided the coupled product in excellent yields without the requirement for protection of the hydroxyl groups on the sugar moiety (Scheme 3).

Finally, to demonstrate the synthetic potential of the developed protocol toward the synthesis of a commercially important drug, we investigated the possibility of preparing Alogliptin (Scheme 4).[24] Being an orally administered antidiabetic drug, Alogliptin is a uracil based molecule that could be accessed by the protection of amidic N−H followed by a subsequent amination.[24] Accordingly, we first synthesized a structural mimic of Alogliptin involving the methyl protection of both its precursor's N−H groups.

The resultant 6-chloro derivative was subjected to the Pd-catalyzed amination with *N*-Boc protected 3-aminopiperidine to provide the coupled product in very good yield (**13d**). To achieve the actual synthesis of Alogliptin, the N−H protection was carried out using methyl iodide and 2-cyanobenzyl bromide. These two reactions proceeded with essentially quantitative conversions to furnish the protected 6-chlorouracil. The Pd-catalyzed amination with the Pd/PTABS system of the protected 6-chloro uracil with NH-Boc protected 3-aminopiperidine furnished the desired product in very high conversion under milder reaction conditions than those previously reported.[24] An acid-mediated deprotection of the NH-Boc group in the cross-coupled intermediate obtained in the previous step furnished Alogliptin (**14**) in excellent yield. The success of this approach was confirmed by single crystal X-ray analysis of Alogliptin's ammonium derivative with trifluoroacetate counterion.

In conclusion, a novel, mild, and highly efficient Pd-catalyzed amination protocol for chloroheteroarenes using the $Pd(OAc)_2$/PTABS catalytic system, with secondary amines performed at ambient temperature, is reported. The powerful nature of the developed protocol allowed the coupling of a large variety of heteroaryl chlorides, besides providing access to commercially successful drugs, e.g., a Buparilsib intermediate and Alogliptin.

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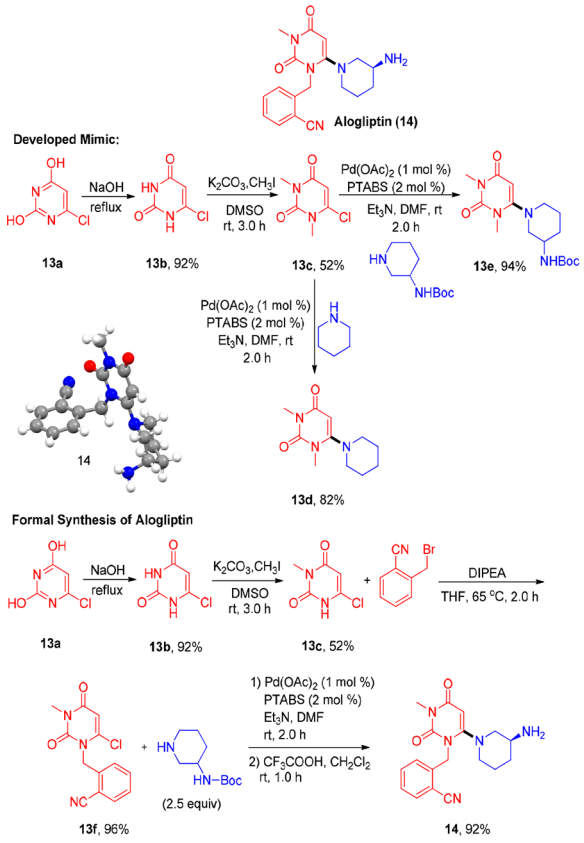
Scheme 4. Actual Synthesis of Alogliptin



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03854.

Syntheses and spectral data (PDF)

Accession Codes

CCDC 1585321−1585328 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.

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