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Robust Acenaphthoimidazolylidene Palladacycles: Highly Efficient Catalysts for the Amination of *N*-heteroaryl Chlorides

Qinyue Deng,[a] Yang Zhang,[a] Haibo Zhu,[a] and Tao Tu* [a,b]

Abstract: A series of robust *N*-heterocyclic carbene palladacycles have been successfully developed, which exhibited high catalytic activity and selectivity toward the challenging amination of *N*-heteroaryl chlorides. Diverse primary and secondary amines are fully compatible with our new developed catalytic system. Remarkably, no double amination products could be detected when primary amines were utilized in our catalytic transformation. Furthermore, the protocol has been successfully extended to synthesize Rosiglitazone, a clinical drug for diabetes mellitus, highlighting its potential pharmaceutical feasibility.

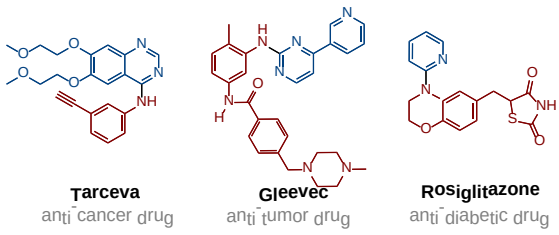

Figure 1. Selected pharmaceuticals containing the *N*-heteroaryl amine motifs.

N-heterocyclic aromatic amines constitute a class of bioactive and functional molecules in pharmaceuticals and material sciences.[1] For instance, Tarceva, Gleevec and Rosiglitazone all contain *N*-heteroaryl amine motifs and exhibit strong anti-tumor, anti-cancer and anti-diabetic activity, respectively (Figure 1).[2] Therefore, tremendous endeavors have been devoted to develop practical and efficient protocols to construct these crucial functional motifs.[3] Among them, palladium-catalyzed amination reactions constitute one of powerful tools for this purpose.[4] However, in contrast with normal aryl halides, the direct amination of *N*-heteroaryl halides is extremely challenging, especially with inactive chloride substrates.[5] The possible strong coordination ability of *N*-atom of the substrates to the Pd center may poison the catalyst leading to the inferior outcomes.[6] In order to tackle this obstacle, a broad number of phosphines and *N*-heterocyclic carbene (NHC) ligands have been designed and synthesized,[7] however, the selective mono-amination of *N*-heteroaryl halides with primary amines is still in high demand. [8]

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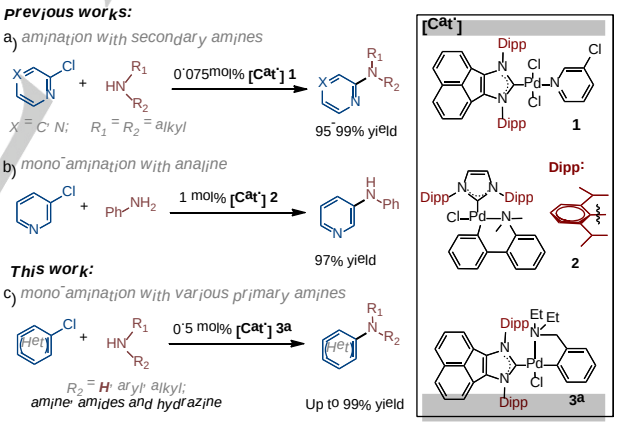
Recently, we have successfully developed a series of robust Pd-NHC complexes derived from acenaphthoimidazolium salts, which exhibit extremely high catalytic activity toward several steric-hindered cross-coupling reactions.[9] Among them, Pd-NHC complex **1** (Scheme 1a), containing 3-chloropyridine as a throw-away ligand, has been demonstrated as a powerful precatalyst in the amination of steric hindered (hetero)aryl chlorides with a variety of amines even at low catalyst loading.[10] In this study, secondary amines are readily coupled with *N*-heteroaryl chlorides. However, primary amines still functioned as poor coupling partners. The possible explanation is the steric environment around the Pd-center is less congested after throw-away ligand leaving during the transformation. After the first amination by primary amine, the newly formed secondary amine is more nucleophilic, and the second amination may take place in the case of less-congested catalyst involved. Therefore, how to design active Pd-NHC complexes which can maintain the congested environment during the transformation may help us to realize the selective mono-amination of *N*-heteroaryl chlorides by primary amines.

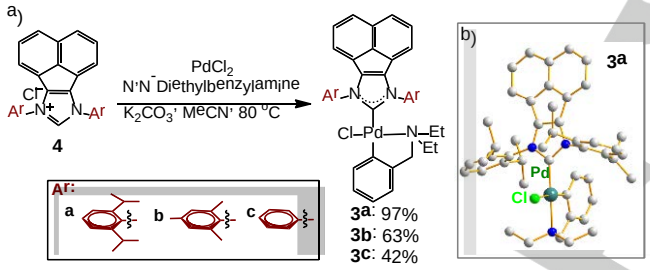


Scheme 1. NHC-Pd catalyzed aminations of *N*-heteroaryl chlorides.

Palladacycles are considered as robust and privilege catalysts in various cross-coupling reactions, generally, the steric environment around Pd-center is hardly alternative during the transformation.[11] Nolan and co-workers reported the first NHC-based palladacycle **2**, which functioned as an efficient catalyst in the amination of aryl chlorides.[8] Although no other primary amine was investigated, aniline was found as a suitable substrate and the corresponding mono-amination product was selectively obtained in 92% yield by using 1 mol% of **2** at 70 °C. Following our recent research interests in developing new NHC-based organometallics and their catalytic application,[12] we would like to incorporate acenaphthoimidazolylidinene and palladacycles to fabricate robust and steric defined NHC-Pd complexes and further investigate their catalytic activity and

selectivity in the amination of *N*-heteroaryl chlorides by various primary and secondary amines as well as less-studied amides under low catalyst loadings.

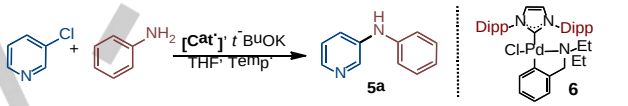
By simply stirring equivalent amount of $PdCl_2$, *N*-Benzyl-diethylamine, acenaphthoimidazolium chlorides **4a-c**,[13] in CH_3CN with K_2CO_3 as a base at 80 °C for 24 hours, acenaphthoimidazolylidene palladacycles **3a-c** were readily obtained in good to moderate yields (Scheme 2a). To our delight, yellow crystals of palladacycle **3a**, which are suitable for single crystal diffraction analysis, was obtained by slow diffusion of petroleum ether into a dichloromethane solution of complex **3a**. As shown in Scheme 2b, the space around the Pd-center of palladacycle **3a** is relatively congested, leading to a distorted square-planar geometry, in which the NHC and the diethylamino ligands are *trans* to each other (the bond angle C_{NHC}-Pd-N_{NMe2} = 174.23º). The position between the NHC-ring and the camber palladacycle ring is close to perpendicular (dihedral angle N_{Im}-C_{NHC}-Pd-C_{Ph} = 81.154). The Pd-C bond lengths all fall into the single bond ranges. Pd-C_{NHC} and Pd-C_{Ph} are 1.973 and 2.007 Å respectively, although, which are shorter than the corresponding bonds observed in the **IPr** [1,3-bis(2,6-diisopropylphenyl)-imidazol-2-yliden] analogous **4a**.[14] These important bond distances also indicate there are strong interactions between Pd-center and the NHC ligand as well as aniline carbon, which may be hardly dissociated or broken during the Pd-catalyzed cross-coupling transformations.



Scheme 2. Synthesis of Pd-NHC complex 3a-c and its X-ray structure**.**

To evaluate the catalytic efficiency of the newly developed palladacycles **3a-c**, the challenging amination of 3-chloropyridine with aniline was selected as a model reaction (Table 1). In light of possible aryl palladium alkoxide species involving in the elimination step,[15] initially, *t*-BuOK was selected as a suitable base to optimize a variety of solvents at 30 ºC. When 0.5 mol% of complex **3a**, 2.25 equiv. of *t*-BuOK and THF were applied, only a trace amount of desired mono-amination product **5a** was isolated (entry 1, Table 1). The yield could be further increased to 79%, when the reaction temperature was elevated to 70 ºC (entry 2, Table 1). Delightedly, no double-amination product was detected. Further increasing the temperature to 80 ºC resulted in a lower yield (71%, entry 3, Table 1). In the presence of 1 mol% palladacycle **3a**, only slightly improvement of yield was observed (74%, entry 4, Table 1). However, decreasing the catalyst loading strongly affects the outcomes. Only a 10% yield of product **5a** could be produced at 0.25 mol% catalyst loading (entry 5, Table1). To our delight, a 98% yield of product **5a** was successfully achieved when less amount of *t*-BuOK was applied under the identical reaction conditions (1.5 equiv., entry 6, Table 1). Further decreasing the amount of *t*-BuOK also leads to lower outcomes (entry 7, Table 1). Other selected inorganic and organic bases all resulted in unsatisfactory results (see the Supporting Information), indicating the choice of base is crucial for this transformation. When less bulky palladacycles **3b** and **3c** were applied, slightly lower yields were attained (entry 8 and entry 9, Table 1). When the NHC-Pd complex **1** was used in this reaction, a moderate yield of **5a** was produced along with double amination by product (64%, entry 8, Table 1). Although Nolan and co-workers have demonstrated that palladacycle **2** are active for the amination of 3-chloropyridine with aniline, no product was formed under our optimized reaction conditions (entry 10, Table 1). Similar outcome was found with catalyst generated *in situ* from $Pd(OAc)_2$ and Sphos. (entry 13, Table 1). When palladacycle **6**,[14d] a **IPr** analogue of palladacycle **3a**, was utilized, only 58 % yield was observed, which further confirmed that ylidenes derived from acenaphthoimidazolium salts show better catalytic activity than their imidazolium analogues due to its stronger σ-donor and weaker π-acceptor properties.

Table 1. Palladacycle-catalyzed amination of 3-chloropyridine by aniline.[a]



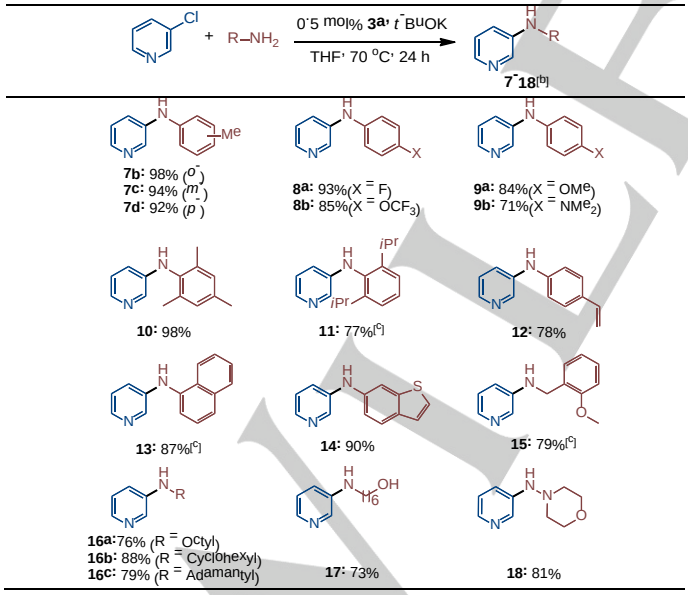
Entry	**[Cat.]** / (mol%)	*t*-BuOK (equiv.)	T (ºC)	Yield (%)[b]
1	**3a** / 0.5	2.25	30	Trace
2	**3a** / 0.5	2.25	70	79
3	**3a** / 0.5	2.25	80	71
4	**3a** / 1	2.25	70	74
5	**3a** / 0.25	2.25	70	10
6	**3a** / 0.5	1.5	70	98
7	**3a** / 0.5	1.0	70	90
8	**3b** / 0.5	1.5	70	95
9	**3c** / 0.5	1.5	70	92
10	**1** / 0.5	1.5	70	64
11	**2** / 0.5	1.5	70	Trace
12	**6** / 0.5	1.5	70	58
13	$Pd(OAc)_2$+Sphos / 0.5	1.5	70	Trace

[a] Conditions: 3-chloropyridine (1.0 mmol, 1.0 equiv.), aniline (1.2 equiv.) were stirred in 2 mL THF under N_2 at 70 °C for 24 h. [b] Isolated yield.

With the optimized reaction conditions in hand, the feasibility of various amines was then investigated. In consideration it is challenging to selectively produce mono-amination products in the reported systems. A series of aryl and alkyl primary amines were therefore selected for investigation at first. Pleasantly, all selected primary amines readily converted to desired mono-amination products in good to excellent yields (Table 2). Similar

excellent yields were obtained with *o-, m-, p*-methyl anilines (**7b-d**, 98-92%), indicating the relative position of the substituents on the phenyl ring barely trammeled coupling process. The electronic property on the anilines only showed slightly impact, electron-rich and electron-deficient substrates (**8a-b and 9a-b**) all gave out very good yields. Sterically hindered substrates, including 2,4,6-trimethylaniline, also successfully mono-aminated and provided product **10** in a quantitative yield. When more bulky 2,6-diisopropylaniline was applied, a moderate yield (56%) for **11** was still achieved. Delightedly, the yield could be further increased into 77% with 1 mol% catalyst loading. In the case of 4-vinylaniline, a satisfactory yield for desired amination product **12** was obtained (78%), no corresponding Heck reaction product was detected, highlighting the good selectivity of the protocol.[16] Under the identical reaction conditions, the mono-amination of 3-chloropyridine with bulky 1-naphthylamine was also proceeded smoothly and produced a corresponding product **13** in a good yield (87%). Heteroaryl amines are also suitable substrates and delivery the corresponding bi-heterocyclic products in good yields. Pleasingly, an excellent yield of product **14** was obtained even with strong coordination S containing primary bulky amine (90%). When benzyl amines were applied, 1 mol % catalyst loading was required to achieve good yield for product **15** under the optimized reaction conditions. In addition, less-active aliphatic primary amines are also fully compatible; moderate to good yields could be achieved (**16a-c** and **17**, 73-88%) whenever acyclic, cyclic, bulky and free OH-group containing aliphatic primary amines were applied. To our delight, besides normal primary amines, the protocol is also effective in the amination of 3-chloropyridine by *N*-amino morpholine, and the corresponding hydrazine **18** was obtained in an 81% yield.

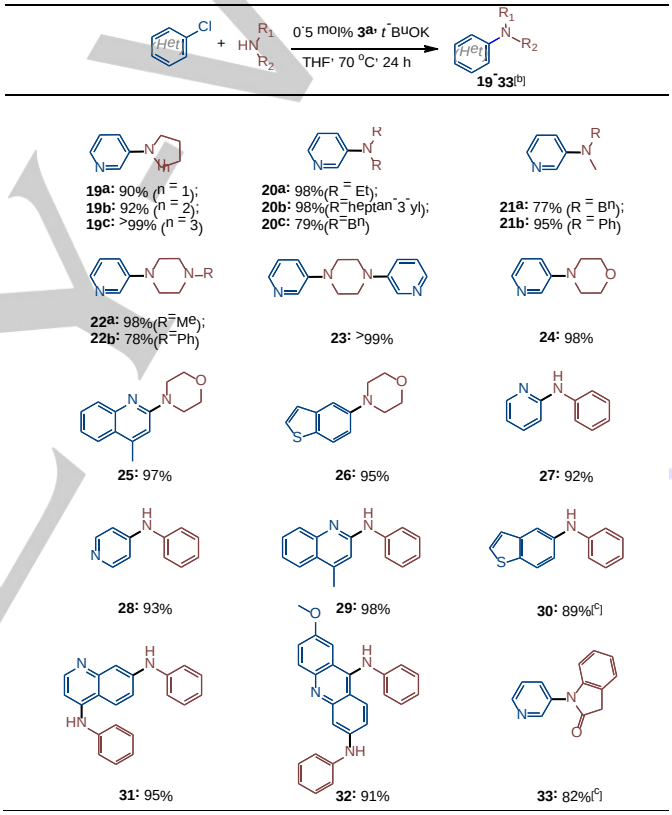
Table 2. Palladacycle-catalyzed amination of 3-chloropyridine by various primary amines and hydrazine.[a]



[a] Conditions: 3-chloropyridine (1.0 mmol, 1.0 equiv.), *t*-BuOK (1.5 equiv.), **3a** (0.5 mol%) and aniline (1.2 equiv.) were stirred in 2 mL THF under N_2 at 70 °C for 24 h. [b] Isolated yield. [c] 1 mol% catalyst loading.

Encouraged by the results obtained by diverse primary amines, we would like to test the protocol scope of diverse *N*-heteroaryl chlorides and amines. Although the sterically space around Pd-center in palldacycle **3a** is rather congested, it is surprise to find out that a variety of cyclic and acyclic secondary amines are also well tolerated (Table 3). The ring size of cyclic secondary amines only exhibited slightly influence; excellent to quantitative yields were found with pyrrolidine, piperidine and azepane (**19a-c**, 90%, 92%, >99%, respectively). To our delight, symmetrical (**20a-c)** and unsymmetrical secondary amines (**21a-b)** are all suitable candidates for the couplings, and good to excellent yields were obtained (77%-98%). When *N*-methylpiperazine, *N*-phenylpiperazine and morpholine were selected, up to 98% yields were produced (**22a, b** and **24)**. The protocol was successfully extended to double amination of 3-chloropyridine. When diamines piperazine was applied, the desired di-*N*-heteroaryl product **23** was isolated in a quantitative yield even at 0.5 mol% catalyst loading.

Table 3. The Amination of heteroaryl chlorides and various amines.[a]



[a] Conditions: 3-chloropyridine (1.0 mmol, 1.0 equiv.), *t*-BuOK (1.5 equiv.), **3a** (0.5 mol%) and aniline (1.2 equiv.) were stirred in 2 mL THF under N_2 at 70 °C for 24 h. [b] Isolated yield. [c] 1 mol% catalyst loading.

In light of *N*-heteroaryl amines playing crucial role in the pharmaceuticals, a variety of *N*-heteroaryl amines containing different heterocyclic structures were constructed. As shown in Table 3, 2-chloro-4-methylquinoline was used to reacted with morpholine delivering the corresponding *N*-heteroaryl amines **25** in excellent yields. Beside *N*-heterocyclics, selected heteroaromatic chlorides, 5-chlorobenzo*[b]*thiophene containing S atoms also resulted in good outcomes **26.** Subsequently, we sought to investigate the feasibility of other heteroaryl chlorides with aniline. The results indicate that the relative position of *N*-atom hardly affected the coupling efficiency; 2- and 4-chloro

pyridines smoothly produced the corresponding mono-amination products in excellent yields (95% and 98% for product **27** and **28** respectively). To our delight, 2-chloro-4-methylquinoline and 5-chlorobenzo*[b]*thiophene are suitable reactive partners with aniline under the optimized reaction conditions (**29** and **30**). The protocol efficiency could be further supported by double mono-amination of *N*-heteroaryl dichlorides, and excellent yields were provided for the corresponding products **31** and **32**. It has to be pointed out that molecules with antileukemic activity are including msacrine (m-AMSA) and Asulacrine (CI-921) [17] all have the similar structure motif of **32** (Figure 2). Generally, amides are poor coupling partners in the Pd-catalyzed amination reactions because of their low nucleophility.[18] However, when indolone, a kind of amide, is aplllied, a good yield of bi-heterocycle **33** was obtained in the presence of 1 mol% palladacyle **3a**.

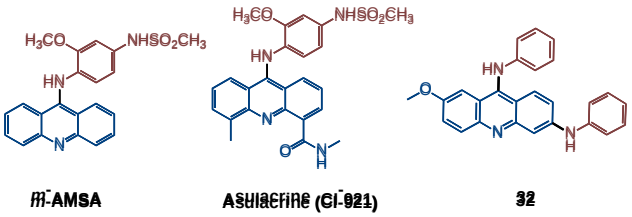
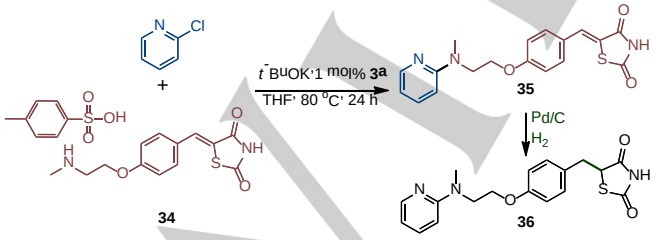


Figure 2. Msacrine and Asulacrine and their analogue **32**.

To further demonstrate the applicability of our newly developed protocol, a concise synthesis of Rosiglitazone **36** was then carried out (Scheme 3), which is readily accessed by direct amination of 2-chloropyridine with secondary amine **34**. The traditional approaches to access Rosiglitazone **36** even involving high temperature, microwave assistance, high catalyst loading or other harsh reaction conditions only resulted in unsatisfactory outcomes.[19] It has to be pointed out, the amine **34** containing double bond usually is unstable under harsh reaction conditions. To our delight, in the presence of 1.0 mol% palladacycle **3a**, the amination processes very smoothly and affords intermediate **35** in a 71% yield at 80 ºC. After Pd/C catalyzed hydrogenation, Rosiglitazone (**36**) was obtained in a quantitative yield. This concise synthesis clearly indicated that our newly developed protocol has a great potential in pharmacy.



Scheme 3. Syntheses of Rosiglitazone **36**.

Conclusions

In summary, a series of acenaphthoimidazolylidene palladacycles have been developed, which exhibited high catalytic activity and selectivity toward the challenging amination of *N*-heteroaryl chlorides. Among them, palladacycle **3a** revealed high catalytic activity and chemo-selectivity toward amination of diverse *N*-heteroaryl chlorides even at 0.5 mol% catalyst loadings. Diverse primary and secondary amines were fully compatible; especially, no double amination products were observed when primary aryl- and alkyl- amines were applied. Besides good selectivity for mono-amination product and functional group tolerance even with sensitive free –OH and olefins, the protocol was successfully extended to the direct amination of *N*-heteroaryl chlorides by amide and hydrazine. Furthermore, the palladacycle **3a** was applied in the synthesis of Rosiglitazone, a clinical drug for diabetes mellitus, further highlighting the protocol efficiency. This new catalytic system represents the first general, practical and selective protocol to access various structural intriguing and functionalized *N*-heteroaryl amines under mild reaction conditions.

Experimental Section

General procedure for Pd-catalyzed amination with complex 3a: To a 50 mL Schlenk tube containing base (1.5 mmol), catalyst **3a** (0.5 mol%, 4.0 mg) and heteroaryl chlorides (1.0 mmol) purged with N_2 (3 times), THF (3 mL) was injected *via* a syringe. The amine (1.2 mmol) was added subsequently. (Note: if amine was a solid, it was introduced before adding THF). The result mixture was then heated at 70 ^{o}C for 24 h. After cooling to room temperature, a small amount of silica gel was added and the solvent was removed *in vacuo*. The mixture was loaded directly on a silica gel column and purified by flash chromatography to provide the desired product.

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Keywords: Amination • *N*-heterocyclic carbene complex • palladacycle • *N*-heteroaryl chlorides • *N*-heteroaryl amines

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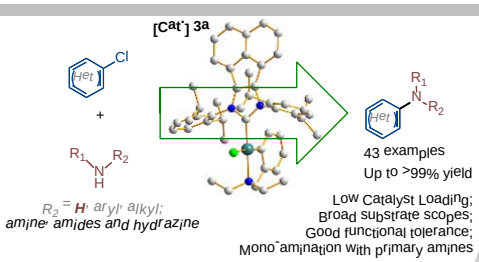
Novel *N*-heterocyclic carbene palladacycles exhibited high catalytic activity and chemo-selectivity toward the amination of *N*-heteroaryl chlorides. Remarkably no double amination products could be isolated when primary amines were utilized, although secondary amines are also suitable coupling partners.



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Robust Acenaphthoimidazolylidene Palladacycles: Highly Efficient Catalysts for the Amination of *N*-heteroaryl Chlorides