ChemComm

Cite this: *Chem. Commun.*, 2011, **47**, 12358–12360

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COMMUNICATION

A highly efficient precatalyst for amination of aryl chlorides: synthesis, structure and application of a robust acenaphthoimidazolylidene palladium complex†

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Received 6th September 2011, Accepted 10th October 2011
DOI: 10.1039/c1cc15503b

A robust palladium NHC complex was synthesized and exhibits exceptional activity and selectivity as a precatalyst in the amination of aryl chlorides and tolerates a wide range of substrates at low catalyst loadings.

Due to various potential applications of aryl amines in chemistry, materials science and industries,[1] it is a very active and intriguing research field to develop an efficient practical protocol to synthesize them. In comparison with other traditional methodologies,[2] the palladium catalyzed amination of aryl halides represents a powerful tool for its high level of selectivity, mild reaction conditions and excellent tolerance to functional groups.[3] In terms of cost, robustness and availability, aryl chlorides represent highly desirable electrophiles as alternatives for aryl bromides, iodides and triflates,[4] although their reactivity is relatively low. Therefore, the amination of chloroarenes is still considered as a challenge, especially, at a low catalyst loading.

Until now, a variety of bulky tertiary phosphines were designed and synthesized for this purpose, and some of them like Buchwald's biaryl phosphines revealed high activity in the amination.[5] In contrast to air sensitive phosphines, *N*-heterocyclic carbenes (NHCs) represent environmentally friendly robust ligands and have exhibited much promise in palladium catalyzed amination.[6,7] Recently, Organ and coworkers reported pyridine stabilized NHC palladium complexes **1** (Fig. 1), which demonstrated high activity towards amination,[6] in some cases, the precatalysts even tolerated sterically encumbered substrates. However, their application as a practical protocol is still hampered by the facts that (1) a high catalyst loading (usually 2–10 mol%) is required to achieve a satisfied conversion, (2) the arylation of weak nucleophilic anilines and heterocyclic substrates still represents a challenging task, and (3) a mild catalytic system that tolerates secondary amines and primary amines at the same time is still unknown.[8]

Recently, we have developed a series of pyridine-bridged pincer NHC metal complexes and have demonstrated their potential applications in catalysis and soft matter aspects.[9,10] And we found that the less intensively studied ylidenes derived from benzimidazolium or other π-extended arylimidazolium salts behave differently. As stronger σ-donors and weaker π-acceptors they increase the electron density of the metal center improving the catalytic activity.[10,11] Following this concept, we now report the synthesis of a robust palladium NHC complex **2** and explore its catalytic potential towards amination at low catalyst loadings.

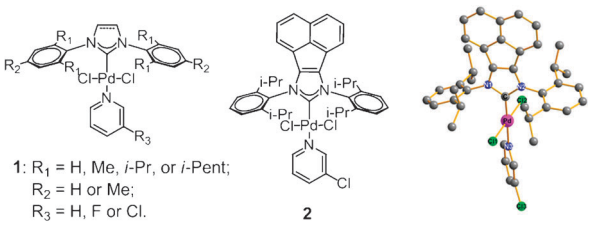

Fig. 1 Pyridine-stabilized palladium NHC complexes.

Palladium complex **2** was readily accessible in a good yield from the corresponding acenaphthoimidazolium salt by heating with $PdCl_2$ and K_2CO_3 in neat 3-chloropyridine. Yellow needle-shaped crystals were obtained by slow diffusion of petroleum ether into a dichloromethane solution of complex **2**, which were suitable for single crystal diffraction analysis. The molecular structure of complex **2** is depicted in Fig. 1. As anticipated the space around the Pd center is quite congested in contrast to its imidazol-2-ylidene analogues. The two phenyl rings are almost perpendicular to the plane of the acenaphtho-ring; the distance of Pd–C is 1.960(6) Å, which is shorter than that in **1**[12] due to the stronger σ-donor property of the acenaphtho-ring.

Initially, various reaction conditions were investigated in the amination of chlorobenzene with morpholine (Table 1). In the presence of DME, *t*-BuOK and complex **2**, the yield of product **3** was merely unchanged when the catalyst loading was reduced from 1 mol% to 0.5 mol%, even when the temperature was lowered from 80 °C to 25 °C (94–96%, entries 1–4, Table 1). Upon further decrease of the catalyst loading to 0.05 mol% after 24 hours at 80 °C, a 73% yield was still obtained (entry 5, Table 1). By extending the reaction time to 48 hours or slightly increasing the catalyst loading to 0.075 mol%, 83% and 91% yields of **3** were observed, respectively (entries 6 and 7, Table 1). Other inorganic and organic bases such as

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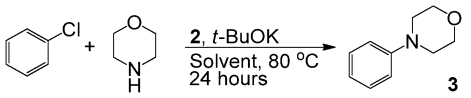
† Electronic supplementary information (ESI) available: Synthesis of complex **2** and other experimental details. CCDC 847153. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1cc15503b

Table 1 Condition screening and optimization[a]



Entry	**2** (mol%)	Solvent	Temp./°C	Yield[b] (%)
1	1	DME	80	96
2	0.5	DME	80	96
3	0.5	DME	50	95
4	0.5	DME	25	94
5	0.05	DME	80	73
6	0.05	DME	80	83[c]
7	0.075	DME	80	91
8	0.075	Toluene	80	93
9	0.075	THF	80	92
10	0.075	Dioxane	80	98
11	0.075	Dioxane	50	30
12	/	Dioxane	80	29[d]

[a] 2 mmol scale for 24 h. [b] Isolated yield. [c] After 48 h. [d] After 72 h.

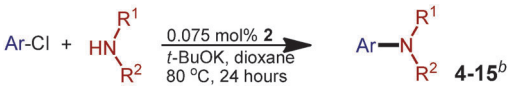
Cs_2CO_3, Et_3N and DBU afforded unsatisfactory results (<58%, see ESI†), which confirmed that the choice of base is critical.[6,13] Dioxane resulted in a better yield than toluene and THF, (98% *vs.* 92 and 93% entries 8–10, Table 1). Upon further decreasing the temperature to 50 °C, a yield comparable to that in the blank test was observed (30 and 29%, entries 11 and 12, Table 1).

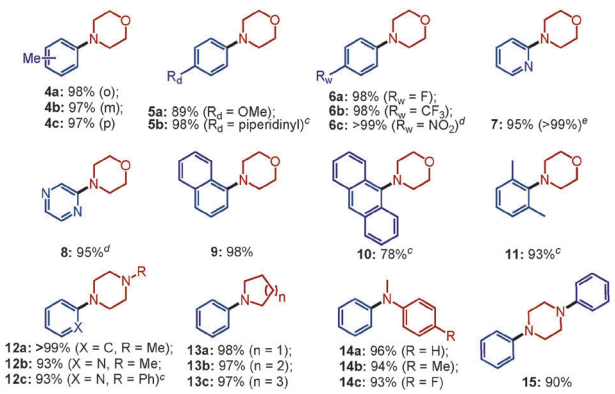
With a defined catalytic system, the scope of reactions with various amines was then explored. As shown in Table 2, the protocol well tolerates diverse electronic and steric substituents on both sides of the reacting partners, as well as heterocyclic substrates. The relative position of substituents in the arenes hardly affected the efficiency of the coupling process; almost identical results were observed with *o*-, *m*-, *p*-chlorotoluene (**4a–c**, 97–98%). The protocol was further extended to other electron-rich substrates; for instance, *p*-chloroanisole afforded an 89% yield of **5a**. Almost a quantitative yield of **5b** was achieved when *p*-piperidylchlorobenzene was tested with a 0.5 mol% catalyst loading. To our delight, electron-deficient, heterocyclic and bulky chloroarenes all afforded excellent yields (**6–9**, 95–98%) indicating an inconspicuous stereo-electronic effect. If the catalyst loading increased to 0.5 mol%, sterically more demanding substrates, such as 9-chloroanthracene and 2-chloro-1,3-dimethylbenzene, were also successfully coupled to provide **10** and **11** in 78% and 93% yields, respectively. The weaker base Cs_2CO_3 promoted reactions when arenes with a specific electronic nature, such as 4-chloronitro-benzene and 2-chloropyrazine, were applied (**6c** and **8**, >99% and 95%) with 0.5 mol% of complex **2**. In addition, under the same conditions **7** could be prepared on a 16 gram (100 mmol) scale in a quantitative yield which demonstrates the protocol scalability.

Encouraged by the aforementioned results, a number of cyclic amines and anilines were also tested. The coupling of *N*-methylpiperazine with chlorobenzene and 2-chloropyridine provided up to quantitative yields (**12a** and **12b**, >99% and 93%, respectively). At 0.5 mol% catalyst loading, *N*-phenylpiperazine was smoothly coupled with 2-chloropyridine to produce **12c** in a 93% yield. The ring size of cyclic amines exhibited an unnoticeable effect; pyrrolidine, piperidine and azepane resulted in similar yields (97–98%, **13a–c**). When *N*-methylanilines were involved, the electronic properties of the substituents in the phenyl ring hardly influenced the results, affording the products **14a–c** in 93–96% yields. The protocol was further extended to diarylation of piperazine in a 90% yield of **15** under the standard conditions indicating the powerful applicability of complex **2**.

Primary amines were regarded as rather poor partners in the previously reported Pd–NHC and most Pd–phosphine catalytic systems. Therefore, various primary amines were also involved to evaluate the catalytic activity of precatalyst **2** (Table 3). To our delight, only monoamination product **16** was obtained (77% yield) in the presence of 0.075 mol% catalyst, which could be further enhanced to 95% by increasing the catalyst loading to 0.5 mol%. The amination of sterically encumbered substrates constitutes a challenging task, especially for primary amines. Therefore, 2,6-dimethylchlorobenzene was selected in the further investigation. Under optimal conditions, the amination by aniline proceeded very

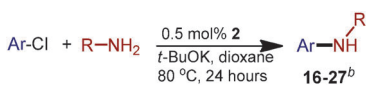
Table 2 Amination of chloroarenes with secondary amines[a]

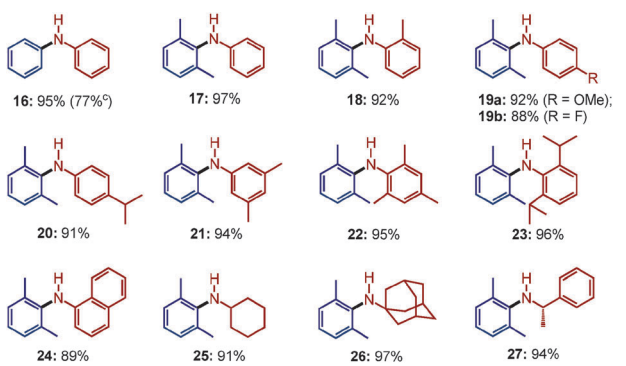




[a] 2 mmol scale for 24 h. [b] Isolated yield. [c] With 0.5 mol% **2**. [d] Cs_2CO_3 with 0.5 mol% **2**. [e] 100 mmol scale with 0.5 mol% **2**.

Table 3 Amination of chloroarenes with primary amines[a]





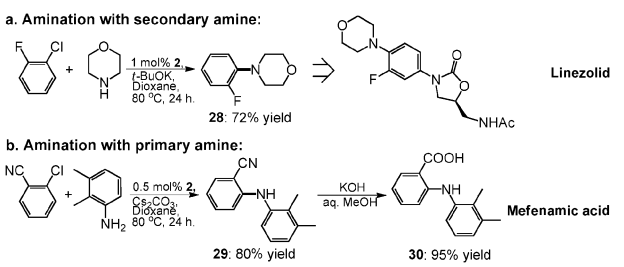
[a] 2 mmol scale with 0.5 mol% **2**. [b] Isolated yield. [c] With 0.075 mol% **2**.

well to afford **17** in a 97% yield. Similar results (88–96%) were also observed with products **18–24**, which further demonstrated that electronic and steric properties of the substituents in the arylamines are fully compatible. Electron-donating groups facilitate the amination and are slightly more efficient than electron-deficient groups (91–92% *vs.* 88% for **19a** and **20** *vs.* **19b**). To our surprise, more hindered substrates, such as 2,4,6-trimethylaniline and 2,6-diisopropyl-aniline, even resulted in better yields (95% and 96% for **22** and **23** respectively) than naphthylamine (89%, **24**). Aliphatic primary amines were also tolerated, again, the bulky amine resulted in a higher yield (97% *vs.* 91%, **26** *vs.* **25**). When a chiral amine was applied, a 94% yield was obtained for the product **27** without influencing the configuration of the chiral center.

In order to clarify the possibility of Pd nanoparticles acting as catalytic species in the amination, catalyst poisoning experiments were involved (see ESI†). At first, a set of mercury tests[14] were performed under standard conditions. With 0.075 mol% precatalyst **2**, one drop of Hg was added to the reaction mixture after 0, 0.5, 1, 3, 6 and 12 hours resulting in 50%, 91%, 91%, 90%, 94%, and 98% yields for product **3**, which suggested that the reaction may follow the NHC–Pd(0) molecular catalytic route. Secondly, an excess of poly(4-vinylpyridine) (PVPy) was also included in the catalyst poisoning experiments.[14] A 97% isolated yield of **3** confirmed that the molecular catalyst derived from complex **2** played the real role in the reaction, which may arise from the strong σ-donating property of acenaphthoimidazol-ylidene which stabilized the Pd–C bond and avoided the formation of Pd nanoparticles.

To further extend the potential application of our protocol in the pharmaceutical targets, the syntheses of key intermediates for the antibiotic drug Linezolid and non-steroidal anti-inflammatory drug Mefenamic acid were performed. The coupling between *o*-chloro-fluorobenzene and morpholine proceeded well with 1 mol% complex **2** and afforded product **28** in 72% (Scheme 1a), which was readily further converted into Linezolid according to the reported procedure.[15a] In the literature, compound **29** was prepared from Mefenamic acid in four steps under harsh reaction conditions.[15b] However, with 0.5 mol% complex **2**, the amination of 2-chlorobenzonitrile with 2,3-dimethylaniline resulted in 80% isolated yield of **29** (Scheme 1b), which can be scaled up to 20 mmol. By hydration of **29**, Mefenamic acid was obtained in 95% yield.

In summary, a robust precatalyst **2** was developed and revealed high activity in the amination of (hetero)-aryl chlorides.



Scheme 1 Synthesis of intermediates of (a) Linezolid and (b) Mefenamic acid.

Beside various secondary amines, a wide range of primary amines were coupled successfully with aryl chlorides in a monoarylation manner at low catalyst loadings demonstrating exceptional reactivity, selectivity and stability of the molecular catalyst derived from complex **2**. The protocol represents a general, practical and scalable approach to access various structurally intriguing and functionalized arylamines.

Financial support from the National Natural Science Foundation of China (No. 20902001), the Shanghai Municipal and Technology Commission (2010MCIMKF04 and Qimingxing Program No. 10A1400500) and the Shanghai Leading Academic Discipline Project (B108) is gratefully acknowledged.

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