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Studies on Pd/imidazolium salt protocols for aminations of aryl bromides and iodides using lithium hexamethyldisilazide (LHMDS)

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Abstract

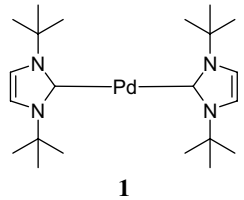
The reactions of a range of secondary amines with aryl bromides and iodides have been performed using an in situ protocol involving palladium and imidazolium salts. Many of these reactions proceed at room temperature, providing a mild protocol for aminations of aryl iodides and bromides. Key to the success of this procedure is the use of lithium hexamethyldisilazide (LHMDS) as base.

Keywords: *N*-heterocyclic carbenes; Aminations; Coupling reactions; Palladium; Lithium hexamethyldisilazide; Imidazolium salts

1. Introduction

Palladium-catalysed couplings now provide important tools for organic synthesis, and are used in a wide range of synthetically important transformations [1]. In recent years, extensive research has been carried out in the search for new ligands for use with palladium, with advances leading to improvements in the versatility of a number of palladium-mediated reactions [2]. The *N*-heterocyclic carbene (NHC) system is now seriously regarded as a prospective replacement ligand for phosphines [3,4]. The NHC motif is finding recognition in palladium chemistry, as Pd–carbene complexes have shown excellent catalytic activity in Heck, Suzuki–Miyaura and amination reactions [3,5]. Additionally, Hartwig et al. [6], Nolan et al. [7] and Furstner et al. [8] have designed techniques in which imidazolium salts are useful additives in palladium-catalysed transformations via either cationic or neutral Pd–NHC complexes.

Our groups have carried out extensive research in using NHC complexes as catalysts for organic synthesis. The Cloke group was the first to prepare the 14 electron, two-coordinate Pd–NHC complex **1** using metal vapour synthesis (MVS) [9]. Complex **1** was shown to exhibit very good catalytic behaviour and was found to mediate Sonogashira couplings more efficiently than $Pd(PPh_3)_4$, with better recovery levels of starting material [10].



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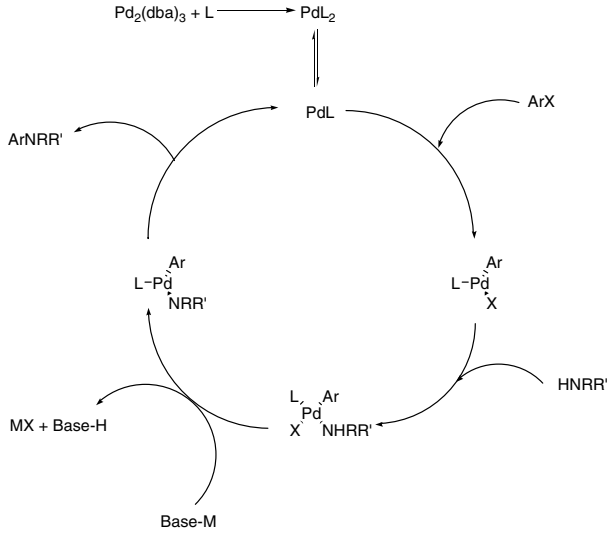
The group has also extensively studied Pd–NHC complexes for the reactions of aryl chlorides. It was reasoned that the strong Pd–NHC bond and the powerful donating capabilities of the NHC ligand would render these catalysts highly active and that the oxidative addition of aryl chlorides might be more facile using these ligand types. This led to the identification of a new protocol for aminations using neutral two-coordinate Pd–NHC complexes [11].

A model for the mechanism of amination reactions using imidazolium salts and two-coordinate palladium–NHC complexes has been proposed (Scheme 1). We have used this model as a basis for further experimental work [12].



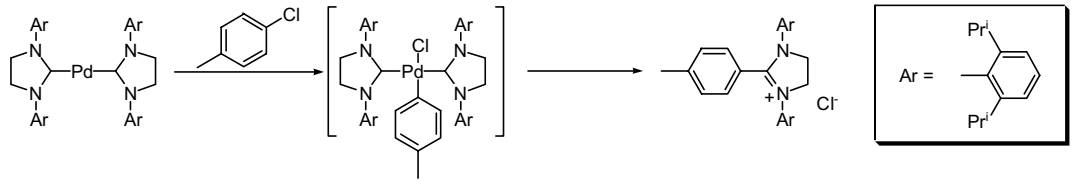
Scheme 1.

In studies of the oxidative addition of aryl chlorides to Pd–NHC complexes, one of the major obstacles has been the susceptibility of these systems to undergo reductive elimination, analogous to that observed by Cavell et al. [13] (Scheme 2).

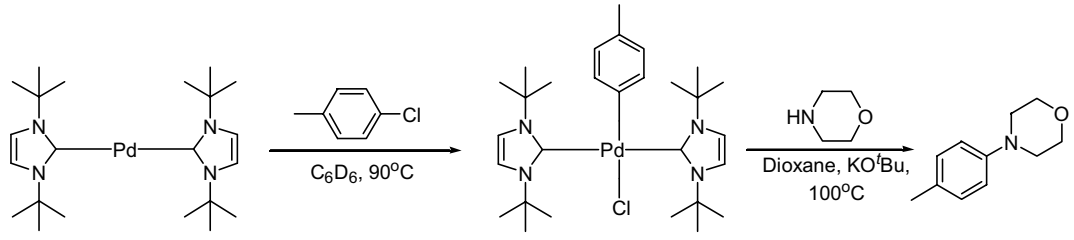
Nevertheless, with the appropriate choice of complex it has been possible to observe and isolate the product of oxidative addition **2**. The amination of the oxidative addition products has also been performed (Scheme 3) [14]. In addition to this, further investigations have shown that ligand dissociation is necessary for oxidative addition and that excess ligand can also cause retardation of the rate of oxidative addition. Reversible carbene dissociation has been found to be possible in some Pd–NHC complexes, which has allowed the calculation of a Pd–NHC bond dissociation energy [12].

All of these fundamental studies have enabled us to build up a reasonable working model of how these reactions proceed and we have attempted to incorporate the information gleaned from these studies into the development of practical new protocols for organic synthesis. This has led to a new in situ method for the amination of aryl chlorides, which employs a microwave-mediated protocol [15]. We have also developed a new intramolecular Heck protocol for aryl chloride substrates, which benefits from the use of tetra-*n*-alkylammonium salts [16]. A new protocol for the high yielding Suzuki–Miyaura cross-couplings of aryl chlorides with aryl boronic acids using a palladium/imidazolium salt catalytic system has been reported by us. This latter system also shows promise in mediating sp^3–sp^3 Suzuki–Miyaura couplings of alkyl halides [17].

One key area which our group has not previously explored is the development of generic room tempera-



Scheme 2.



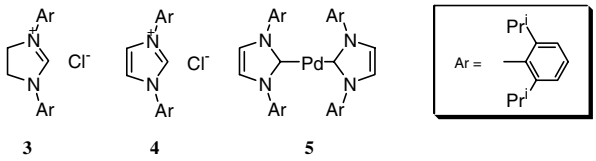
2

Scheme 3.

ture protocols for amination of aryl halides. Whilst a number of groups have highlighted the use of palladium–NHC systems for amination of aryl chlorides [6], we have initiated investigations on the development of a practical protocol based on palladium/imidazolium salts for amination of aryl halides. We have specifically focused on bromides and iodides in the first phases of this study. This is, in part because of the lack of general studies on these apparently simpler classes of substrate. We believe that the development of an imidazolium salt based protocol for bromides and iodides will be a valuable addition to the arsenal of methods currently available. In this work we describe our initial studies on this class of transformation and report on a new and practical protocol. The key finding has been the use of lithium hexamethyldisilazide (LHMDS) as a base to aid reproducibility in these reactions. This base has been used for palladium/phosphine-catalysed reactions by Urgaonkar and Verkade [18], Louie and Hartwig [19] and Buchwald et al. [20]. LHMDS has also been employed as an ammonia equivalent in the palladium/phosphine-catalysed reaction with aryl halides to form primary anilines [21,22]. However, to our knowledge, LHMDS has not been used as the base for the Pd–NHC mediated amination of aryl halides.

2. Results and discussion

We evaluated a variety of aryl bromides and iodides in aminations catalysed by palladium/imidazolium salts. Dimeric tris(dibenzylideneacetone)dipalladium(0), $Pd_2(dba)_3$, was used as the Pd(0) source in this reaction, as the monomeric bis(dibenzylideneacetone)palladium(0) was found to be ineffective. The saturated ligand, 1,3-bis(2,6-diisopropylphenyl)-imidazolinium chloride (SIPr · Cl) **3** was used for the reactions with aryl bromides, as previous research has shown it to be the most suitable for this reaction [6]. However, preliminary results indicated that the unsaturated 1,3-bis(2,6-diisopropylphenyl)-imidazolium chloride (IPr · Cl) **4** was slightly better for reactions of aryl iodides. The imidazolium chloride ligands were prepared using literature procedures [23]. Despite previous findings of this group and others, a 1:1 Pd/ligand ratio did not appear to be the optimum ratio in this reaction. Instead, for reasons that are not yet understood, a 1:2 Pd/ligand ratio was preferred, with modest improvements in conversion. The use of the pre-formed two-coordinate Pd–NHC complex of bis(1,3-bis(2,6-diisopropylphenyl)imidazolin-2-ylidene) palladium(0) ($Pd(IPr)_2$) **5** was also investigated for the amination of aryl iodides, but was found to be slightly less effective than the corresponding in situ palladium/imidazolium chloride protocol, consistent with results we have observed elsewhere [15].



3 **4** **5**

Additionally, we focused on the nature of the base employed, as a variety have been used previously in palladium-catalysed aminations and the nature of the base can have a profound impact on reactivity. Initial experiments using potassium *tert*-butoxide usually required elevated temperatures, but a brief assessment of a variety of bases indicated that LHMDS was preferred [18], with other inorganic bases (cesium carbonate, sodium tetraborate and potassium phosphate) and organic bases (2,6-lutidine and DBU) being less effective. Commercially available LHMDS was used as a 1 M solution in THF, as this gave faster reactions than the alternative 1 M solution in toluene.

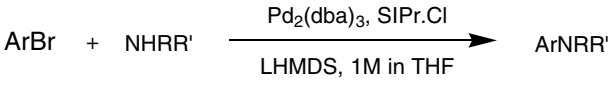
The use of this base saw improved yields and shortened reaction times. In the case of aryl iodides, reactions that only worked at 100 °C with KO^{t}Bu, now worked at room temperature. Trials with other hexamethyldisilazides (i.e. NaHMDS and KHMDS) showed that they could also be used as the base for the amination, but that LHMDS gave the best results. The results of the optimised amination protocols for bromides and iodides are presented in Tables 1 and 2.

As expected, our best results were obtained in reactions with cyclic secondary amines, most notably piperidine and morpholine. Good yields were obtained for *N*-methylaniline and secondary amines containing aromatic rings (e.g. *N*-methylbenzylamine) or short alkyl chains (e.g diethylamine). Acyclic secondary amines (e.g. di-*n*-butylamine) did work at room temperature, but were somewhat disappointing by comparison to their cyclic counterparts. Slower reactions could however be accelerated with higher loadings of palladium and imidazolium ligand.

Elevated temperatures were required for the reactions of primary amines with aryl bromides. Whilst these reactions were usually complete within 24 h, they were generally low-yielding. For example, in the case of *n*-hexylamine (Scheme 4), a bisarylated species was the major product observed. Here, an excess of amine (3.6 eq.) was used to hinder this reaction, which was favoured due to the secondary aniline product being more reactive than the primary alkyl amine. This also required an increase in the quantity of catalyst used (2 mol% $Pd_2(dba)_3$ and 8% SIPr · Cl).

It would appear from the data that the reactions of aryl iodides are more facile and higher-yielding than the reactions of aryl bromides. For example, iodobenzene reacted with adamantylamine at room temperature in a yield of 70%; conversely, bromobenzene failed to react

Table 1
Amination of aryl bromides[a]



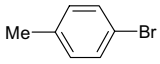
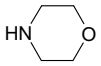
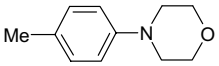
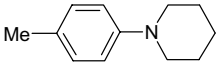
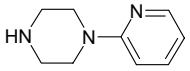
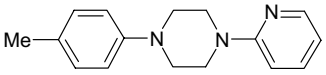
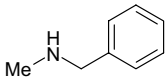
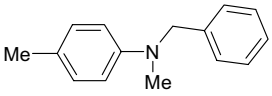
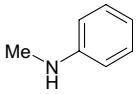
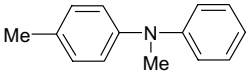
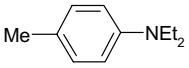
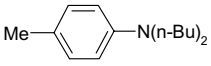
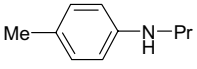
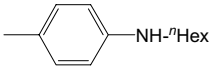
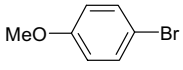
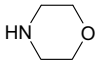
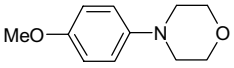
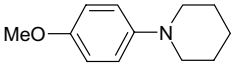
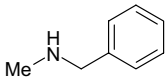
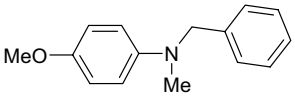
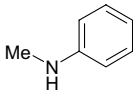
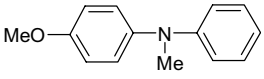
Entry	Ar–Br	NHRR′	ArNRR′	Yield (%)[b]	Reaction time (h)
1				89	7
2				98	10
3				66	24
4				73	24
5				98[c]	48
6		$HNEt_2$		74	20
7		$HN(n\text{-}Bu)_2$		17[d]	5 days
8		H_2N^nPr		27[e]	24
9		H_2N^nHex		61[c,f]	24
10				78	24
11				88	24
12				75	48
13				83[c]	72

Table 1 (*continued*)

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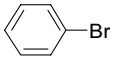
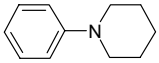
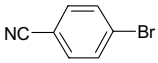
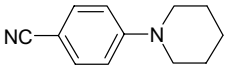
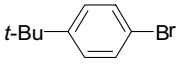
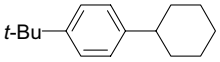
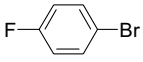
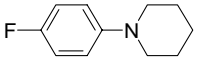
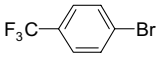
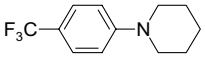
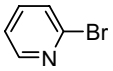
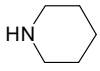
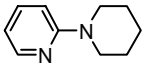
15				89	20
16				36	5 days
17				18	96
18				54	72
19				75	72
20				73	48

[a] *Reaction conditions*: 1.0 mmol of aryl bromide, 1.2 mmol of amine, 1.5 mmol of LHMDS as 1 M solution in THF, 1.0 mol% $Pd_2(dba)_3$, 4.0 mol% SIPr · HCl, 22 °C. Reactions times were not optimised.

[b] Isolated yields.

[c] 2.0 mol% $Pd_2(dba)_3$, 8.0 mol% SIPr · HCl.

[d] 3.0 mol% $Pd_2(dba)_3$, 12 mol% SIPr · HCl.

[e] Major product was from bisarylation (54% yield). Reaction performed at 80 °C.

[f] 3.6 eq. amine used and minor bisarylation product also formed (15%).

with this amine at the same temperature. Also, the coupling of 4-iodoanisole and morpholine afforded a 96% yield of the desired aniline, whereas the same reaction with 4-bromoanisole only afforded 78% of the same product.

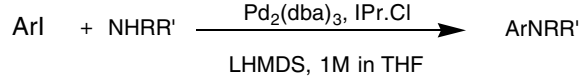
The coupling of 2-bromopyridine and piperidine was successful (73% yield), further illustrating the reported high activity for Pd–NHC catalysts in the amination of halopyridines [6]. However, initial attempts to broaden the scope of the reaction into other N–H containing compounds proved fruitless. Reactions with indole, amides, hydrazines, hydrazones and carbamates were unsuccessful at both room and elevated temperatures. Other trials showed that the reaction time could be significantly decreased to minutes under microwave heating or to less than 5 h under conventional heating. An investigation of aryl chlorides indicated that such substrates would work, but perhaps, as expected, chlorides are still fairly resistant to catalysis at room temperature, at least utilising this protocol (Scheme 5).

3. Experimental

3.1. Typical procedure for amination of aryl bromides

An oven-dried Schlenk tube was charged with aryl bromide (1.0 mmol), amine (1.2 mmol, 1.2 eq.), $Pd_2(dba)_3$ (0.01 mmol, 0.02 eq. Pd), 1,3-bis(2,6-diisopropylphenyl)-imidazolinium chloride (0.04 mmol, 0.04 eq.) and a magnetic stirrer bar. The flask was evacuated and backfilled with argon three times, after which LHMDS (1 M solution in tetrahydrofuran, 1.5 mL, 1.5 eq.) was added. The tap was closed and the tube placed in an oil bath maintained at 22 °C, stirring for generally 7–72 h (reaction times were not optimised). After all starting material had been consumed, as judged by TLC, the mixture was diluted with ether and filtered through a sinter. The solvent was removed under reduced pressure and the crude material purified by flash chromatography on silica gel with an eluent of ethyl acetate/hexane.

Table 2
Amination of aryl iodides[a]



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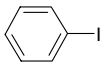
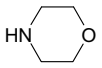
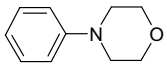
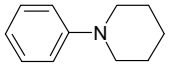
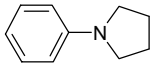
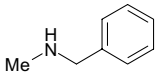
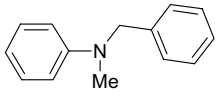
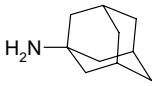
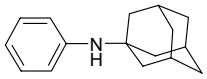
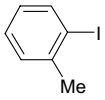
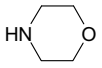
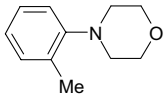
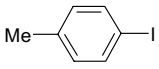
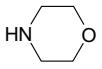
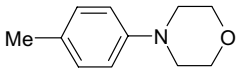
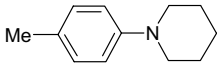
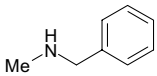
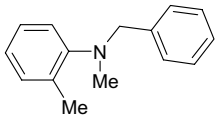
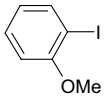
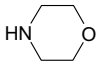
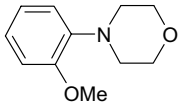
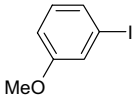
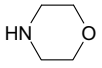
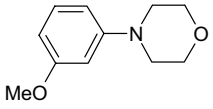
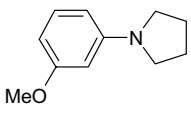
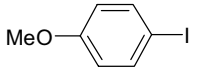
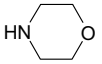
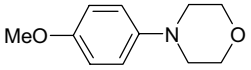
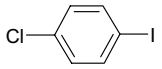
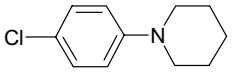
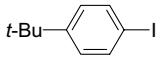
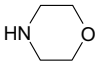
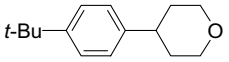
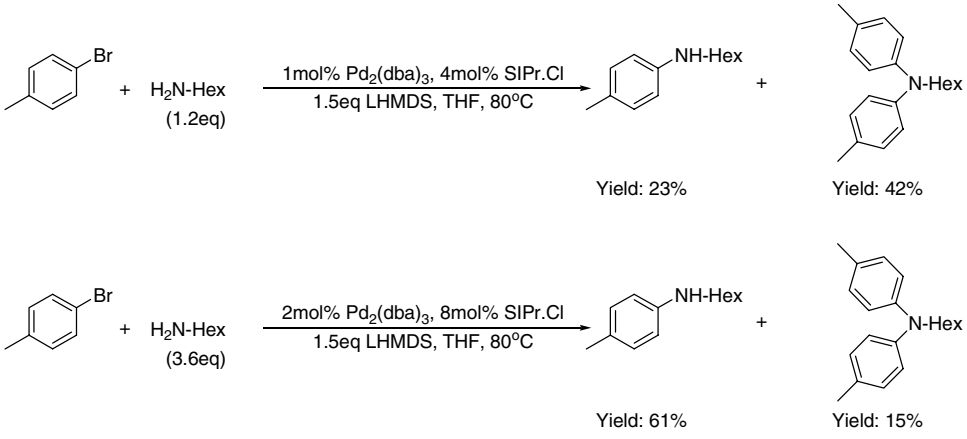
1				92
2				81
3				88
4				89
5				70
6				92
7				90
8				83
9				82
10				78
11				79
12				78

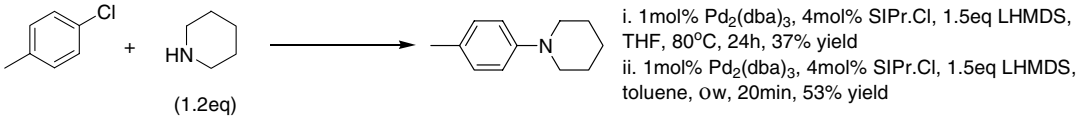
Table 2 (*continued*)

Entry	Ar–I	NHRR′	ArNRR′	Yield (%)[b]
13				96
14				85
15				89

[a] *Reaction conditions*: 1.0 mmol of aryl iodide, 1.2 mmol of amine, 2.5 mmol of LHMDS, 1.0 mol% $Pd_2(dba)_3$, 4.0 mol% IPr · HCl, 25 °C. Reactions were complete in 20 h and times were not optimised.
[b] Isolated yields.



Scheme 4.



Scheme 5.

3.2. Typical procedure for amination of aryl iodides

An oven-dried Schlenk tube was charged with $Pd_2(dba)_3$ (0.01 mmol, 0.02 eq. Pd), 1,3-bis(2,6-diisopropylphenyl)-imidazolium chloride (0.04 mmol, 0.04 eq.) and a magnetic stirrer bar. The flask was evacuated and backfilled with nitrogen three times, after which the aryl iodide (1.0 mmol) and amine (1.2 mmol, 1.2 eq.) were added. Finally, LHMDS (1 M solution in tetrahydrofuran, 2.5 mL, 2.5 eq.) was added to the tube and it was placed in an oil bath, maintained at 25 °C, and stirred for 20 h (reaction times were not optimised). After all starting material had been consumed, as judged by TLC, the mixture was diluted with dichloromethane, absorbed onto silica and purified by flash chromatography on silica gel with an eluent of ether/hexane.

4. Conclusions

Overall, we have shown that in situ Pd–NHC amination of aryl bromides and iodides will proceed at room temperature in good to moderate yields with a range of amines and halides using LHMDS as a base. Further work will focus on the generality of this protocol and its further development in order that it can be applied to more resistant coupling partners. However at present the finding that LHMDS plays a significant role in enhancing this protocol is noteworthy.

Acknowledgements

We gratefully acknowledge financial support of AstraZeneca, GlaxoSmithKline and EPSRC. We are

also very grateful to BBSRC, CEM, Novartis and Key Organics for support of our programme. We acknowledge the EPSRC Mass Spectrometry Service at Swansea for provision of mass spectra.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jorganchem.2005.07.084.

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[2] M.R. Netherton, G.C. Fu, Org. Lett. 3 (2001) 4295–4298.
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D. Bourissou, O. Guerret, P. Gabbai, G. Bertrand, Chem. Rev. 100 (2000) 39;
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