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Hydroxylamine *O*-benzyl ether as an ammonia equivalent in the catalytic amination of aryl halides

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Abstract—The palladium catalysed amination of aryl bromides with hydroxylamine *O*-benzyl ether leads to the formation of diaryl or triarylamines depending on the size of the aryl bromide, the number of equivalents used or the conditions employed.
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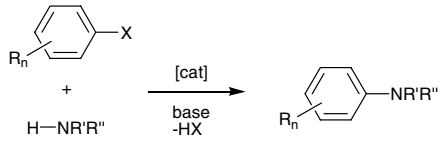
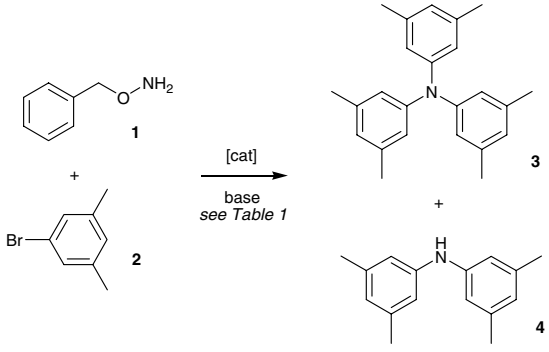
The Buchwald–Hartwig amination reaction (Scheme 1) has developed into a powerful synthetic method for the formation of carbon–nitrogen bonds.[1] While the reaction works very efficiently for aryl- and alkylamine precursors, the use of ammonia as the starting amine has only recently been reported.[2]



Scheme 1. The Buchwald–Hartwig amination of aryl halides.

More typically various 'ammonia equivalents' are employed instead as convenient solid or liquid precursors. Ammonia equivalents that have enjoyed success in this regard include allylamines,[3] benzophenone imine,[4] *N*-trialkylsilylimines,[5] lithium amides,[2,6] lithium silylamides[6,7] and $Zn\{N(SiMe_3)\}_2$.[8] While these ammonia substitutes provide easy access to primary amines, the reactions typically stop at that point. We were interested in developing an ammonia equivalent that could be used to produce primary, secondary or tertiary amines depending on the conditions and the number of equivalents of aryl halide added. Since hydroxylamine derivatives can be used as electrophilic amination reagents,[9] we wondered whether commercially available hydroxylamine *O*-benzyl ether (**1**) could be exploited as an ammonia equivalent in Buchwald–Hartwig aminations. This indeed turns out to be the case and the preliminary findings from this investigation are presented below.

In the first instance we examined the reactions of **1** with 4 equiv of 3,5-dimethylbromobenzene, **2** (Eq. 1) using the catalysts, bases and conditions summarised in Table 1. As can be seen the catalyst formed in situ from palladium acetate and tri-*tert*-butylphosphine gives good conversion to triarylamine **3** with no contamination from diarylamine **4** in toluene using sodium *tert*-butoxide as base (entry 1).



(1)

When the milder bases potassium phosphate and potassium carbonate are used then no triarylamine is observed, instead small amounts of diarylamine **4** are obtained (entries 2 and 3).

No amination is seen when triethylamine is used as the base. Changing the solvent is deleterious to the performance (entries 5 and 6) as is changing the palladium precursor (entries 7–9). Neither triarylphosphines

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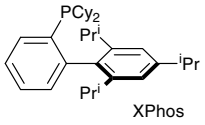
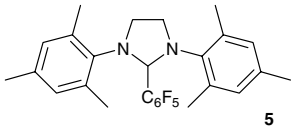
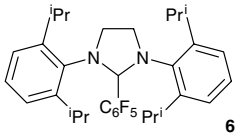
Table 1. Optimisation of the amination of **2** with **1**[a]

Entry	Pd source	Ligand	Equivs. of **2**	Solvent	Base	Conversion to **3**	**4**[b] (%)
1	$Pd(OAc)_2$	$[HP^tBu_3][BF_4]$	4	Toluene	NaO^tBu	86	0
2					K_3PO_4	0	28
3					K_2CO_3	0	9
4					NEt_3	0	0
5				1,4-Dioxane	NaO^tBu	37	0
6				DMF	NaO^tBu	0	0
7	$PdCl_2(NCMe)_2$			Toluene	NaO^tBu	39	0
8	$Pd(dba)_2$					51	16
9	$Pd(TFA)_2$					21	0
10	$Pd(OAc)_2$	PPh_3				0	0
11		P(*o*-tolyl)$_3$				0	0
12		$P(OC_6H_3\text{-}2,4\text{-}^tBu_2)_3$				0	0
13		PCy_3				12	0
14		 XPhos				17	0
15		 **5**				0	0
16		 **6**				3	22
17		$[HP^tBu_3][BF_4]$	3			55	0
18			2			13	28
19			1			0	30

[a] Conditions: **1** (0.5 mmol), **2** (0.5–2.0 mmol), Pd precursor (4 mol %), ligand (5 mol %), base (2.5 mmol), solvent (5 ml), reflux (except DMF, 115 °C), 18 h.

[b] Conversion to amines **3** and/or **4**, based on the amount of **1**, determined by ^1H NMR spectroscopy (1,3,5-trimethoxybenzene internal standard).

nor a bulky triarylphosphite ligand prove effective (entries 10–12). Increasing the electron-donor ability of the phosphine leads to the emergence of some activity with both PCy_3 and XPhos[10] giving small amounts of triarylamine **3** (entries 13 and 14). Similarly some activity is seen when a highly electron-donating carbene ligand is employed (entry16).[11,12]

Lowering the ratio of the aryl bromide to **1** leads to a switch in selectivity from the triarylamine to the diarylamine with only **3** observed at three or more equivalents of **1**, a mixture of **3** and **4** produced with 2 equiv and **4** obtained as the sole product at 1 equiv (entries 1 and 17–19, respectively).

Having established that optimum activity is observed with P^tBu_3 in toluene using sodium *tert*-butoxide as base, these conditions were then exploited in the synthesis of a range of amines and the results from this study are summarised in Table 2.[13] The phosphonium salt $[HP^tBu_3][BF_4]$ was used throughout as it is an air-stable solid, unlike the free phosphine, which is highly air-sensitive.[14]

As can be seen from Table 2, entries 1–5, electronically non-activated and deactivated bromides give reasonable to good conversions to the desired triarylamines. By contrast little or no activity is seen with analogous aryl chlorides or an aryl triflate, respectively. With *para*-substituted arene substrates only the triarylamine products are formed under these conditions.

Similarly triarylamines are the sole products from the mono- and di-*meta*-substituted aryl bromides shown in entries 6–9, even when the substituents are *tert*-butyl groups.[15] This tolerance to *meta*- and *para*-substitution allows for the facile synthesis of tris(4-diphenylamino)phenylamine, TDATA, (entry 10) and its *meta*-substituted isomer (entry 11), both of which are used extensively in photonics applications, in particular as hole transport materials in OLED devices.[16]

By contrast, *ortho*-substituted substrates can give di- and/or triarylamines, depending on the nature of the substitution (entries 12–17). Thus the introduction of *ortho*-methyl, methoxy or phenyl groups shows a very strong preference for diarylation, with little or no

Table 2. Amination of aryl halides with **1**[a]

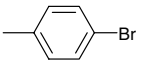
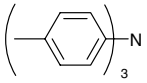
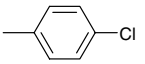
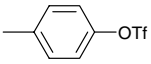
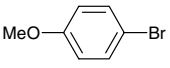
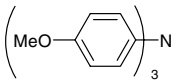
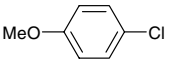
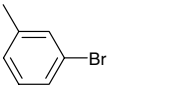
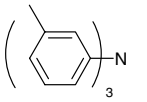
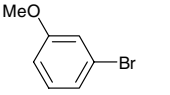
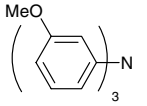
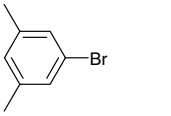
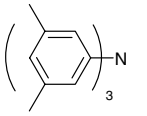
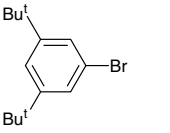
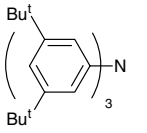
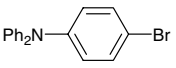
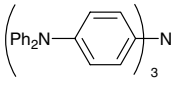
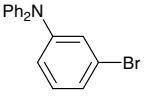
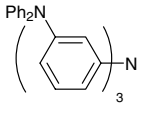
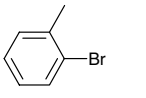
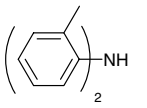
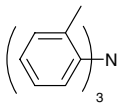
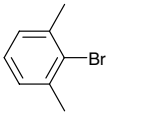
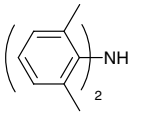
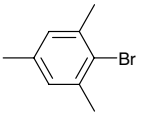
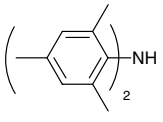
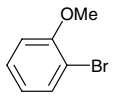
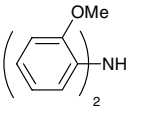
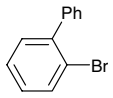
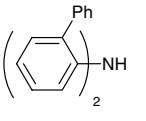
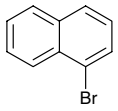
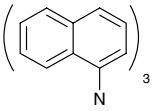
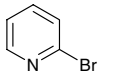
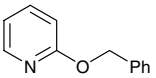
Entry	ArX	Product(s) (relative ratio) [conv. %][b] {yield}[c]
1		 [79]{69}
2		[13]
3		[0]
4		 [56]{45}
5		[9]
6		 [67]{56}
7		 [42]{31}
8		 [86]{77}
9		 [79]{53}
10		 [76]
11		 [66]
12		  (97:3) [80]{69}[d]
13		 {75}{71}
14		 [69]{60}

Table 2 (*continued*)

Entry	ArX	Product(s) (relative ratio) [conv. %][b] {yield}[c]
15		 [57]
16		 [58]
17		 [79]
18		 [36]

[a] Conditions: **1** (0.5 mmol), aryl halide (2.0 mmol), $Pd(OAc)_2$ (4 mol %), $[HP^tBu_3][BF_4]$ (5 mol %), NaO^tBu (2.5 mmol), toluene (5 ml), reflux, 18 h.

[b] Conversion to amine product, based on **1**, determined by ^1H NMR spectroscopy (1,3,5-trimethoxybenzene internal standard).

[c] Isolated yield.

[d] Conversion to and isolation of diarylamine.

triarylation observed. By contrast the use of 1-naphthyl bromide gives almost exclusively the triarylamine with only trace amounts of the diarylamine seen by ^1H NMR.

When 2-bromopyridine is used as the substrate (entry 18) no aminated product is obtained, instead the pyridine *O*-benzyl ether is produced. This presumably results from decomposition of **1** to benzyl alcohol, under the reaction conditions, which is known to react with 2-halopyridines in the presence of *tert*-butoxide.[17]

The use of hydroxylamine hydrochloride in place of **1** gives no reaction with **2** under the standard conditions. Similarly no product is obtained when hydroxylamine *O*-methyl ether is employed. It seems that the benzyl function is necessary for the reaction to proceed. Our working hypothesis for the mechanism is that **1** couples with 1 equiv of aryl bromide to generate an *O*-benzyl-*N*-aryl hydroxylamine, which subsequently eliminates the aniline and benzaldehyde. This is probably a palladium induced process as *O*-benzyl-*N*-phenyl hydroxylamine is stable to at least 85 °C,[18] whereas the coupling of **1** with **2** at 80 °C shows some (26%) of the diarylamine formed and no evidence of the corresponding *O*-benzyl-*N*-aryl hydroxylamine. GC–MS analysis of a range of crude reaction mixtures proved uninformative in the identification of potential intermediates, but showed variable amounts of benzaldehyde, benzyl alcohol and benzoic acid. Unfortunately varying levels of these compounds are also seen in control experiments leaving out the aryl bromide, the base or the catalyst, while benzaldehyde and benzyl alcohol are also produced when **1** is subjected to the standard work-up procedure.

In summary we have shown that hydroxylamine *O*-benzyl ether is an excellent ammonia equivalent in Buchwald–Hartwig amination reactions. Preliminary results indicate that the extent of the reaction can be controlled by changing the conditions and tuning the ligand sets employed; this is an area that we are currently investigating further.

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13. *Representative procedure*. *Synthesis of* **3** *(Table 2, entry 8)*: $Pd(OAc)_2$ (0.005 g, 0.020 mmol), $[HP^tBu_3][BF_4]$ (0.008 g, 0.025 mmol) and NaO^tBu (0.240 g, 2.5 mmol) were suspended in toluene (5 ml). Hydroxylamine *O*-benzyl ether (**1**) (0.058 ml, 0.5 mmol) and 5-bromo-*m*-xylene (0.272 ml, 2.0 mmol) were added. The reaction was then heated at reflux for 18 h. The reaction was allowed to cool and then quenched by addition of HCl_{aq} (2 M, 3 ml). The aqueous layer was extracted with CH_2Cl_2 (2×20 ml), and the combined organics dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to give a brown solid. The product was then purified by column chromatography (SiO_2) to give **3** as an off-white powder: 0.126 g (77%); R_f 0.9 ($CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.21 (s, 18H, Me), 6.64 (s, 3H, Ar H), 6.67 (s, 6H, Ar H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.40 (s, CH_3), 122.18 (s, CH), 124.33 (s, C), 138.69 (s, CH), 148.19 (s, CN); HRMS (EI) calcd for $C_{24}H_{27}N$ [M^+] 329.2144, found 329.2142. Anal. Calcd for $C_{24}H_{27}N$: C, 87.49; H, 8.26; N, 4.25. Found: C, 87.03; H, 8.64; N, 4.01.
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