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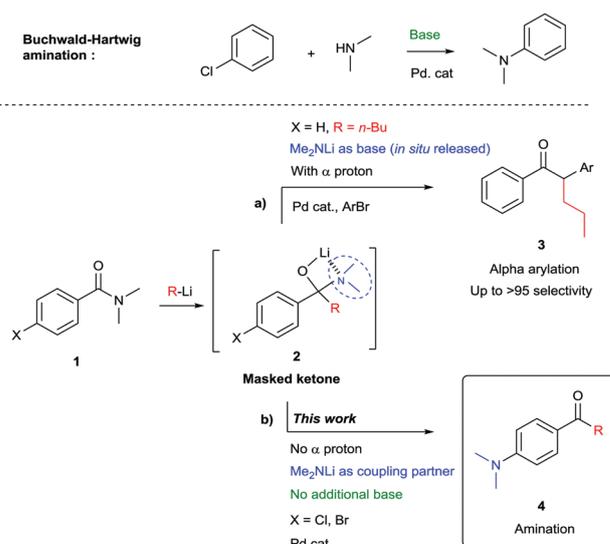
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One-pot, modular approach to functionalized ketones *via* nucleophilic addition/Buchwald–Hartwig amination strategy†

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A general one-pot procedure for the 1,2-addition of organolithium reagents to amides followed by the Buchwald–Hartwig amination with *in situ* released lithium amides is presented. In this work amides are used as masked ketones, revealed by the addition of organolithium reagents which generates a lithium amide, suitable for subsequent Buchwald–Hartwig coupling in the presence of a palladium catalyst. This methodology allows for rapid, efficient and atom economic synthesis of aminoarylketones in good yields.

The palladium catalysed amination of aromatic bromides was discovered in 1983 and has since proven to be one of the most important and versatile transformations in organic synthesis. Pioneered by Migita¹ and co-workers, the groups of Buchwald and Hartwig among others developed the method towards its current status of privileged transformation in organic chemistry,^{2–6} with widespread applications in areas ranging from materials science to medicinal chemistry.^{6,7} Traditionally cross-coupling reactions to form a C–N bond require the use of additional base to achieve a full catalytic cycle. Stoichiometric amounts of *tert*-butanolate salts or cesium carbonate are often used for this purpose, though the use of lithium amide as base has also been reported to be a valuable substitute in Buchwald–Hartwig couplings.⁸ Alternatively, LiHMDS is chosen for its non-nucleophilic properties. Few reports describe aminations where lithium amides are directly playing the role of coupling partners.^{9,10} Our group recently disclosed a one pot procedure for the 1,2-addition of organolithium reagents to (Weinreb) amides, followed by alpha-arylation, which required no additional base^{11,12} (Scheme 1a). Optimizing the alpha-arylation step, the product arising from the competing Buchwald–Hartwig coupling was sometimes observed as a minor side product. We envisioned this amination process to be a very useful transformation. In the present study we take advantage of the nucleophilic



Scheme 1 Lithium hemiaminal as a versatile building block.

properties of organolithium reagents by performing a 1,2-addition to an amide yielding a masked ketone.^{13–16} Collapse of the tetrahedral intermediate generates *in situ* a lithium amide¹⁷ allowing direct Buchwald–Hartwig amination without the need for additional base (Scheme 1b). This approach gives rapid access to a variety of amino substituted benzophenones which are widely used, among others, in cosmetics due to their UV protecting properties. Furthermore they are being employed as photoinitiator and have found use in medicinal chemistry, for instance as kinase inhibitors.¹⁸

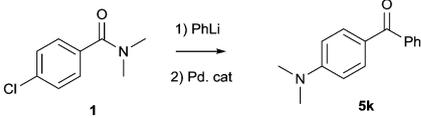
The competition between alpha-deprotonation or transmetallation to palladium could be avoided by the use of organolithium reagents lacking alpha hydrogen atoms. Therefore the lithium amide resulting from the 1,2-addition of an organolithium reagent to amide **1** – after dissociation of the tetrahedral intermediate **2** – is only available for Buchwald–Hartwig amination type reaction. In order to determine the optimal conditions for the reaction a ligand screening was performed and the results

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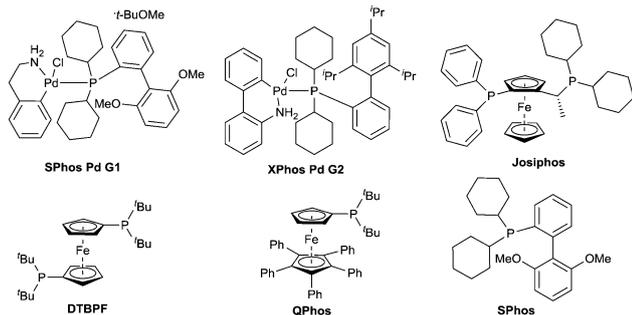
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Table 1 Catalyst optimisation^a


Entry	Catalyst	Solvent (temp.)	Conversion ^b
1	SPhos Pd G1	Toluene (80 °C)	42
2	XPhos Pd G2	Toluene (80 °C)	83
3	Pd ₂ (dba) ₃ /Josiphos	Toluene (80 °C)	29
4	Pd ₂ (dba) ₃ /DTBPF	Toluene (80 °C)	0
5	Pd ₂ (dba) ₃ /QPhos	Toluene (80 °C)	49
6	Pd ₂ (dba) ₃ /SPhos	Toluene (80 °C)	69
7	XPhos Pd G2	THF (reflux)	95
8	SPhos Pd G1	THF (reflux)	94
9	Pd₂(dba)₃/SPhos	THF (reflux)	95
10	PEPPSI-iPr	THF (reflux)	87
11	Pd ₂ (dba) ₃ /SPhos	2-MeTHF (60 °C)	62
12	Pd ₂ (dba) ₃ /SPhos	1,4-Dioxane (60 °C)	93
13	Pd ₂ (dba) ₃ /SPhos	MTBE (reflux)	84
14	Pd ₂ (dba) ₃ /SPhos	Hexane (60 °C)	0
15	Pd ₂ (dba) ₃ /SPhos	Et ₂ O (reflux)	< 5
16	Pd ₂ (dba) ₃ /SPhos	CPME	95



^a Reactions were carried on a 0.2 mmol scale, organolithium reagent was added dropwise and the mixture was stirred 15 min at 0 °C followed by the addition of Pd catalyst (5% loading) and stirred for additional 1 h at the indicated temperature. ^b Conversion determined by GC-MS. CPME = cyclopentyl methyl ether.

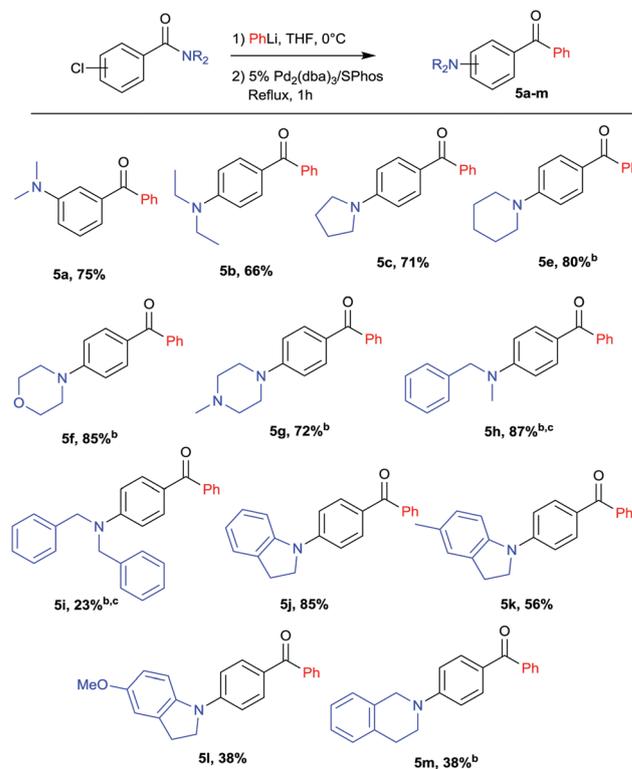
are shown in Table 1. XPhos palladacycle G2 (entry 2) proved to be the most efficient catalyst in toluene at 80 °C. Other well established catalysts for Buchwald–Hartwig amination based on mono and bidentate phosphine ligands^{19,20} (entries 3–6) or the use of palladacycle G1 (entry 1) were found to be less or not active in our case.

Conversion towards the desired product was increased with the catalyst XPhos Pd G2 in THF at reflux (entry 7). Using Pd-PEPPSI^{21,22} (entry 10) in this solvent didn't improve the conversion, but Pd₂(dba)₃/SPhos (entry 9) and SPhos palladacycle G1 (entry 8) gave comparable conversion. Pd₂(dba)₃/SPhos was preferred to palladacycles (G1, G2) as it is a cheaper catalyst. The influence of solvents was also tested, identifying THF at reflux (entry 9) as the solvent of choice for this reaction. Etheral solvents show good conversion (entries 11–13) whilst the reaction doesn't proceed in hexane (entry 14). Low conversion was observed when the reaction was performed in Et₂O at reflux (entry 15) indicating that elevated temperature was required for the coupling step. 1,4-Dioxane (entry 12) also proved to be efficient and can be considered as an alternative

if higher temperatures are required. Finally 2-MeTHF and cyclopentyl methyl ether (CPME)²³ were tested. These solvents are reported as environmental friendly alternatives to THF. Whereas 2-MeTHF gave lower conversion (entry 11), CPME proved to be a valuable substitute (entry 16).

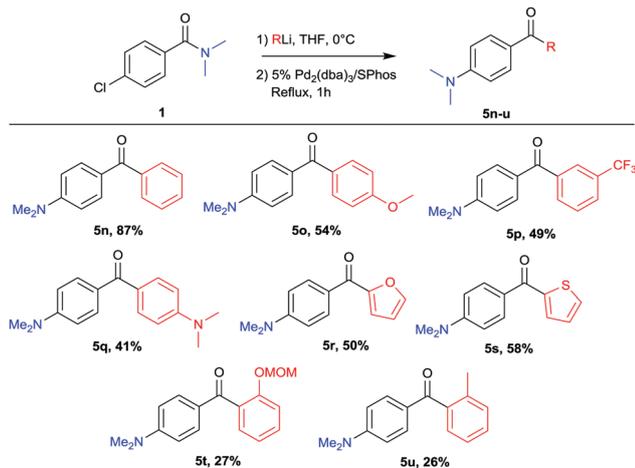
4-Bromo-*N,N*-dimethylbenzamide was also a suitable substrate for this reaction but aryl chlorides were preferred as they generate less waste, are generally cheaper and more widely available. Moreover by using aryl chlorides instead of aryl bromides we drastically decrease the risk of having undesired lithium–halogen exchange taking place.²⁴

With the optimal conditions in hand (Table 1, entry 9), a range of amides was tested leading to a variety of aminobenzophenones represented in Scheme 2. The scope includes both *meta* (**5a**) and *para* chlorobenzamides (**5b–5j**). Cyclic (**5c–5g**) as well as acyclic (**5a**, **5b**) amines were coupled in excellent yields. Interestingly, morpholine (**5f**), methylpiperazine (**5g**), indolines (**5j–5l**) and tetrahydroisoquinoline (**5m**) moieties were also successfully coupled in good yields providing a motif widely used in medicinal chemistry.^{25,26} Notably methylbenzylamine and dibenzylamine were also efficient coupling partners affording protected amines (**5h**, **5i**) that can be further converted, after debenzylation, into free amines or mono-methylated amines. Methodologies to directly synthesize free anilines have been reported^{27–29} but they usually require large excess of ammonia, high pressure or



Scheme 2 Variation of amides.^a ^a Yields refer to isolated yields after column chromatography, for an overview of unsuccessful attempts see ESI.† ^b PhLi added dropwise and reaction mixture stirred for 1 h before addition of the catalyst. ^c After addition of the catalyst the reaction mixture was heated at reflux overnight.





Scheme 3 Variation of lithium reagents.^{a, d} Yields refer to isolated yields after column chromatography.

long reaction time with the problem of selectivity for the primary amine *versus* secondary and tertiary amines. The methodology presented here can be considered as an attractive alternative to target primary and secondary arylamines.

The scope of aryl lithium nucleophiles was investigated and the results are given in Scheme 3. Not only phenyllithium could be coupled (5n) but a diversity of aryllithium reagents, easily prepared *via* Li-halogen exchange or deprotonation, were found to be suitable reagents in this reaction. Aryllithium bearing ether, amine or electron withdrawing functionalities were successfully coupled (5o–5q). Heterocyclic lithium reagents such as 2-thienyllithium or 2-furyllithium were suitable coupling partners and provided the desired products 5r and 5s. Though lower yields were obtained when using more sterically hindered coupling partners the desired products were successfully isolated (5t, 5u).

Small amounts of tertiary alcohol, arising from premature collapse of the tetrahedral intermediate were observed for most entries. It is the decreased reactivity in the second step however, that caused the lower yields for some of the substrates, providing (after hydrolysis) the chloro-ketone intermediate as a final product.

Previous reports already described the equilibrium between the intermediate 2 and products resulting from the 1,2-elimination of R₂NLi being in favour of the tetrahedral intermediate 2.^{30,31} ⁷Li and ¹H-NMR analysis was performed to investigate the formation and stability of intermediate 2 under our reaction conditions (Fig. 1). As expected, when 1 eq. of PhLi (spectrum A-1) was added to (4-chlorophenyl)(morpholino)methanone 5f-SiM, a single signal at 0.92 ppm was observed (spectrum A-2). This intermediate has a different chemical shifts compared to signals of lithium morpholin-4-ide at 0.87 ppm (spectrum A-5), indicating that the equilibrium is completely shifted towards the intermediate 2 (Scheme 1).

This hypothesis is also supported by ¹H-NMR (full spectrum available in the ESI⁺) were no lithium morpholin-4-ide (B-5) nor 4-chlorobenzophenone (B-6) can be detected. The *in situ* formed

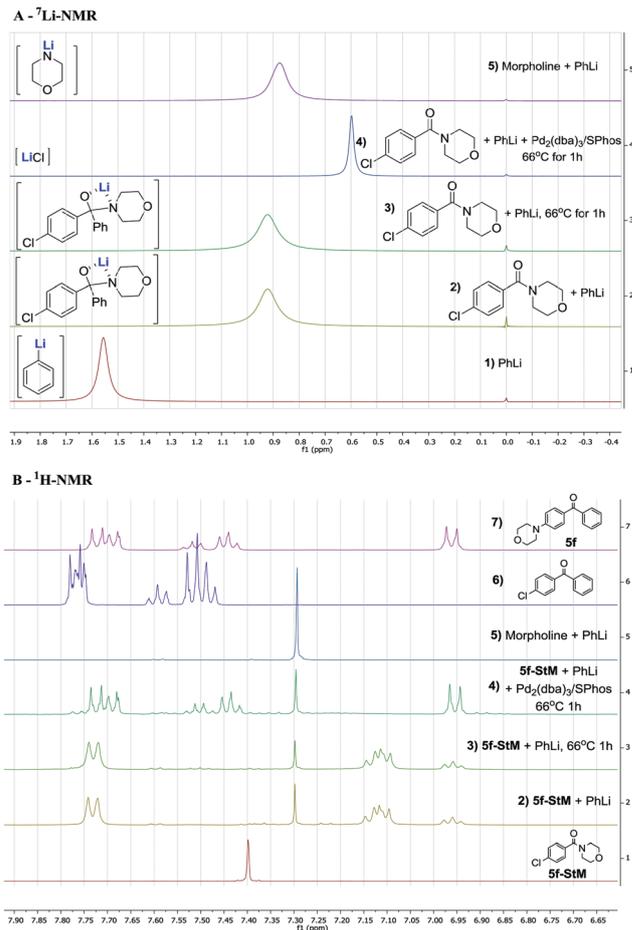
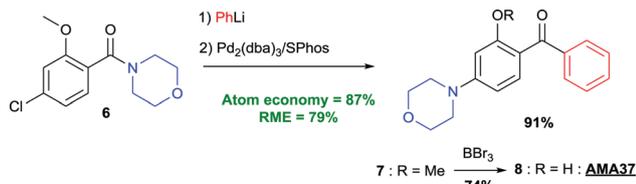


Fig. 1 ⁷Li (A) and ¹H (B)-NMR analysis of the reaction with (4-chlorophenyl)(morpholino)methanone. Conditions: 0.1 mmol in 0.7 mL of THF-d₆ at 25 °C with LiCl in D₂O as internal standard. Hypothesized structure of lithium species between brackets.

intermediate (B-2) was then heated at reflux for 1 h but remain unaffected (B-3) and no product of 1,2-elimination was observed (comparison with B-6), showing the stability of this intermediate under our reaction conditions. When Pd₂(dba)₃/SPhos was added to the intermediate and the solution was heated at reflux for 1 h, the desired product 5f was selectively formed as confirmed by ¹H-NMR (spectrum B-4 and B-7), resulting also in a sharp signal in ⁷Li-NMR at 0.60 ppm, corresponding to the LiCl (spectrum A-4) released. These experiments point toward the existence of a stable tetrahedral lithium hemiaminal intermediate 2 and a slow *in situ* release of lithium amide which is directly consumed in the amination reaction.

Finally, the versatility of this approach was demonstrated with the rapid and efficient synthesis of an isoform-specific phosphoinositide 3-kinase inhibitor.³² The herein described protocol drastically improves the yield compare to the previously reported synthesis and combines the formation of the C–N bond with a 1,2-addition in a one-pot procedure, leading to ketone 7 (a comparison of the two synthetic routes is available in the ESI⁺). The environmental friendly character of this transformation should also be highlighted as it exhibits a high





Scheme 4 Application in the synthesis of a kinase inhibitor (AMA37).

reaction mass efficiency³³ (RME) of 79% and produces only a light waste product LiCl with low toxicity (Scheme 4).

In conclusion, a one-pot procedure toward the synthesis of amine aryl ketones has been developed, enabling Buchwald–Hartwig amination with *in situ* generated lithium amides. Starting from easily accessible amides and organolithium reagents, this strategy allows for fast and efficient modular functionalization with high atom economy generating only LiCl as stoichiometric waste. A diversity of aryllithium nucleophiles and amide coupling partners has been combined following this strategy and the applicability of the methodology was illustrated with the efficient synthesis of a selective kinase inhibitor.

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Conflicts of interest

There are no conflicts to declare.

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