

ChemComm

Accepted Manuscript



This article can be cited before page numbers have been issued, to do this please use: J. de Jong, D. Heijnen, H. Helbert and B. L. Feringa, *Chem. Commun.*, 2019, DOI: 10.1039/C8CC08444K.



This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this Accepted Manuscript with the edited and formatted Advance Article as soon as it is available.

You can find more information about Accepted Manuscripts in the [author guidelines](#).

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard [Terms & Conditions](#) and the ethical guidelines, outlined in our [author and reviewer resource centre](#), still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.

COMMUNICATION

One-Pot, Modular Approach to Functionalized Ketones via Nucleophilic Addition/Buchwald-Hartwig Amination Strategy†

Jorn de Jong^{‡a}, Dorus Heijnen^{‡a}, Hugo Helbert^{‡a}, Ben L. Feringa^{*a}

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

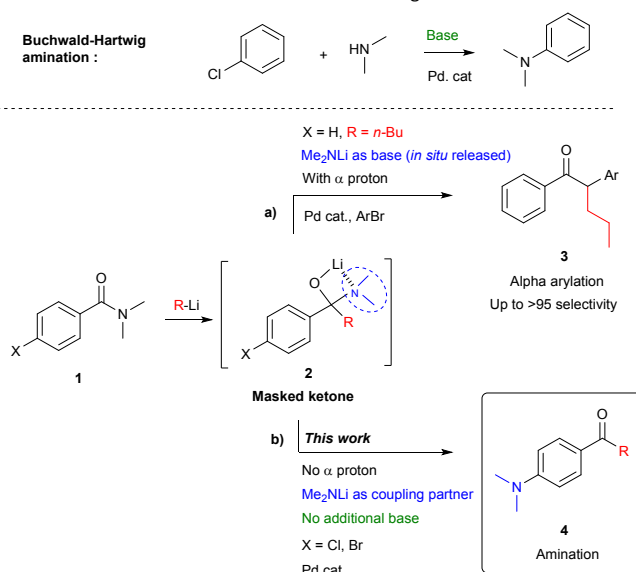
www.rsc.org/

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 transformation 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 couplings⁸. 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 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 inhibitors¹⁸.

Scheme 1 Lithium hemiaminal as a versatile building block



The competition between *alpha*-deprotonation or transmetalation 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 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.

^a Stratingh Institute for Chemistry, University of Groningen, Nijenborgh 4, 9747 AG, Groningen, The Netherlands

[‡] J. de Jong, D. Heijnen and H. Helbert contributed equally to this work

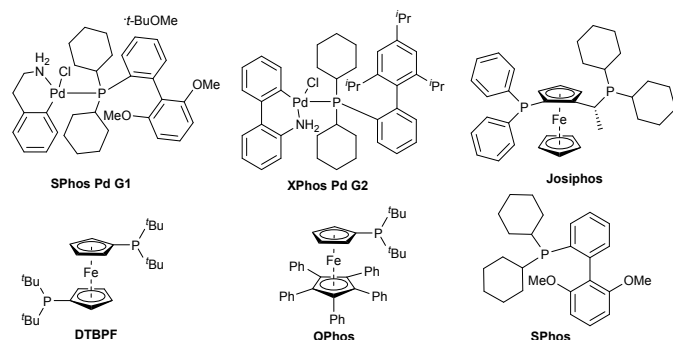
[†] Electronic Supplementary Information (ESI) available: General, experimental procedures and characterisation of compounds. See DOI: 10.1039/x0xx00000x

COMMUNICATION

ChemComm

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

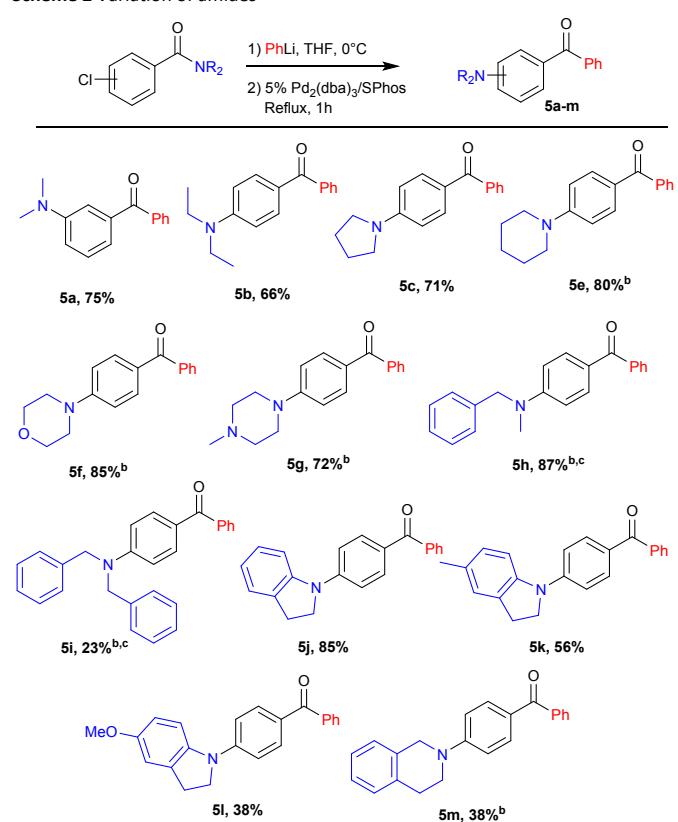


^aReaction were carried on a 0.2 mmol scale, organolithium reagent was added dropwise and the mixture was stirred 15 min at 0°C followed by the addition of Pd catalyst (5% loading) and stirred for additional 1 h at the indicated temperature.

^bConversion determined by GC-MS. CPME = Cyclopentyl methyl ether.

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).

Scheme 2 Variation of amides^a

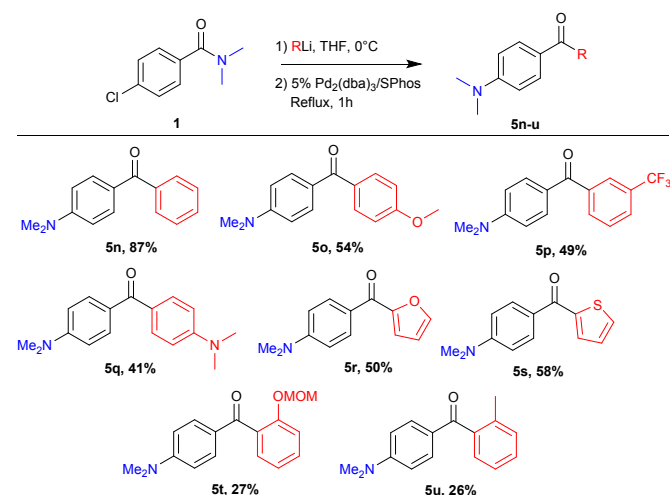
^aYields refer to isolated yields after column chromatography, for an overview of unsuccessful attempts see ESI. ^bPhLi added dropwise and reaction mixture stirred for 1 h before addition of the catalyst. ^cAfter addition of the catalyst the reaction mixture was heated at reflux overnight.

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 place²⁴.

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 reported²⁷⁻²⁹ but they usually require large excess of ammonia,

high pressure or 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.

Scheme 3 Variation of lithium reagents^a



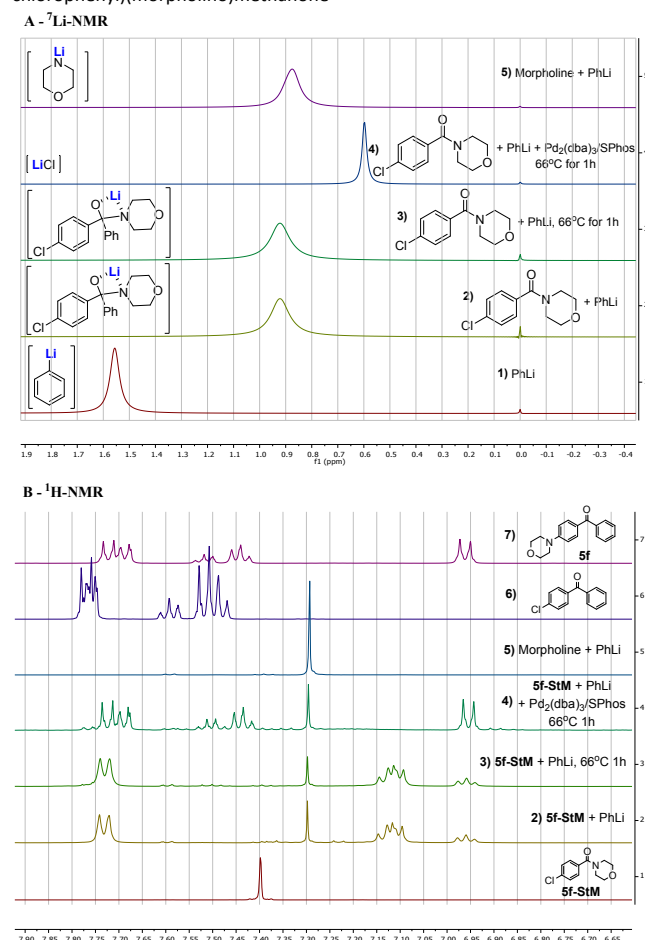
^aYields refer to isolated yields after column chromatography.

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 bromo-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 R_2NLi 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 (Figure 1). As expected, when 1 eq. of PhLi (spectrum A-1) was added to (4-chlorophenyl)(morpholino)methanone **5f-StM**, 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).

Figure 1: 7Li (A) and 1H (B) -NMR analysis of the reaction with (4-chlorophenyl)(morpholino)methanone
DOI: 10.1039/C8CC08444K



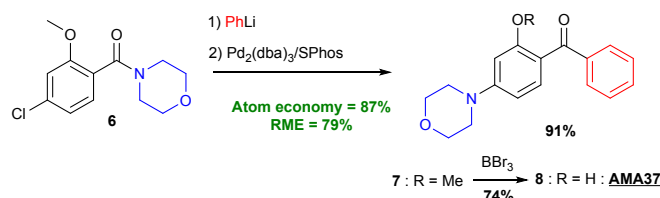
Conditions : 0.1 mmol in 0.7mL of THF- d_8 at 25°C with LiCl in D_2O as internal standard. Hypothesized structure of lithium species between brackets.

This hypothesis is also supported by 1H -NMR (full spectrum available in the supporting information) were no lithium morpholin-4-ide (B-5) nor 4-chlorobenzophenone (B-6) can be detected. The *in-situ* formed intermediate (B-2) was then heated at reflux for 1h 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 $Pd_2(dba)_3/SPhos$ was added to the intermediate and the solution was heated at reflux for 1h, 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 inhibitors³². 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 supporting information). The environmental friendly character of this transformation should also be highlighted as it exhibits a high reaction mass efficiency³³ (RME) of 79% and produces only a light waste product LiCl with low toxicity.

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



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.

Conflicts of interest

There are no conflicts to declare.

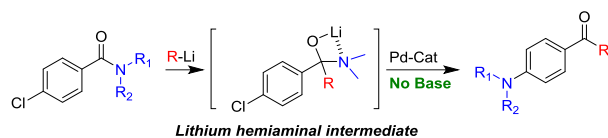
Acknowledgements

This work was supported financially by the European Research Council (Advanced Investigator Grant, No. 227897 to B.L.F.); The Netherlands Organization for Scientific Research (NWO–CW); funding from the Ministry of Education, Culture, and Science (Gravitation program 024.001.035); The Royal Netherlands Academy of Arts and Sciences (KNAW); and NRSC-Catalysis are gratefully acknowledged.

Notes and references

- 1 M. Kosugi, M. Kameyama and T. Migita, *Chem. Lett.*, 1983, **12**, 927–928.
- 2 A. S. Guram, R. A. Rennels and S. L. Buchwald, *Angew. Chem. Int. Ed.*, 1995, **34**, 1348–1350.
- 3 J. Louie and J. F. Hartwig, *Tetrahedron Lett.*, 1995, **36**, 3609–3612.
- 4 B. P. Fors and S. L. Buchwald, *J. Am. Chem. Soc.*, 2010, **132**, 15914–15917.
- 5 D. S. Surry and S. L. Buchwald, *Angew. Chem. Int. Ed.*, 2008, **47**, 6338–6361.
- 6 P. Ruiz-Castillo and S. L. Buchwald, *Chem. Rev.*, 2016, **116**, 12564–12649.

- 7 C. Torborg and M. Beller, *Adv. Synth. Catal.*, 2009, **351**, 3027–3043. DOI: 10.1039/C8CC08444K
- 8 S. Meiries, A. Chartoire, A. M. Z. Slawin and S. P. Nolan, *Organometallics*, 2012, **31**, 3402–3409.
- 9 H. Xu and C. Wolf, *Chem. Commun.*, 2009, **21**, 3035–3037.
- 10 X. Huang and S. L. Buchwald, *Org. Lett.*, 2001, **3**, 3417–3419.
- 11 A. T. Wolters, V. Hornillos, D. Heijnen, M. Giannerini and B. L. Feringa, *ACS Catal.*, 2016, **6**, 2622–2625.
- 12 S. Nahm and S. M. Weinreb, *Tetrahedron*, 1981, **22**, 3815–3818.
- 13 R. K. Dieter, *Tetrahedron*, 1999, **55**, 4177–4236.
- 14 M. Adler, S. Adler and G. Boche, *J. Phys. Org. Chem.*, 2005, **18**, 193–209.
- 15 C. Liu, M. Achtenhagen and M. Szostak, *Org. Lett.*, 2016, **18**, 2375–2378.
- 16 D. A. Evans, G. Borg and K. A. Scheidt, *Angew. Chem. Int. Ed.*, 2002, **41**, 3188–3191.
- 17 A. Salomone, F. M. Perna, F. C. Sassone, A. Falcicchio, J. Bezenšek, J. Svete, B. Stanovnik, S. Florio and V. Capriati, *J. Org. Chem.*, 2013, **78**, 11059–11065.
- 18 M. Andrs, J. Korabecny, D. Jun, Z. Hodny, J. Bartek and K. Kuca, *J. Med. Chem.*, 2015, **58**, 41–71.
- 19 N. Kataoka, Q. Shelby, J. P. Stambuli and J. F. Hartwig, *J. Org. Chem.*, 2002, **67**, 5553–5566.
- 20 Q. Shen, T. Ogata and J. F. Hartwig, *J. Am. Chem. Soc.*, 2008, **130**, 6586–6596.
- 21 M. G. Organ, M. Abdel-Hadi, S. Avola, I. Dubovyk, N. Hadei, E. A. B. Kantchev, C. J. O'Brien, M. Sayah and C. Valente, *Chem. Eur. J.*, 2008, **14**, 2443–2452.
- 22 Y. Zhang, V. César and G. Lavigne, *European J. Org. Chem.*, 2015, **2015**, 2042–2050.
- 23 U. Azzena, M. Carraro, L. Pisano, S. Monticelli, R. Bartolotta and V. Pace, *ChemSusChem*, 2019, **12**, 40–70.
- 24 R. Luisi and V. Capriati, *Lithium Compounds in Organic Synthesis. From Fundamentals to Applications. Edited by Renzo Luisi and Vito Capriati.*, Wiley-VCH, Weinheim., 2014, vol. 53.
- 25 M. Al-Ghorbani, A. Bushra Begum, Z. Zabiulla, S. V. Mamatha and S. A. Khanum, *Res. J. Pharm. Technol.*, 2015, **8**, 611–628.
- 26 N. Chadha and O. Silakari, *Eur. J. Med. Chem.*, 2017, **134**, 159–184.
- 27 G. D. Vo and J. F. Hartwig, *J. Am. Chem. Soc.*, 2009, **131**, 11049–11061.
- 28 Y. Aubin, C. Fischmeister, C. M. Thomas and J.-L. Renaud, *Chem. Soc. Rev.*, 2010, **39**, 4130.
- 29 J. Schranck and A. Tlili, *ACS Catal.*, 2018, **8**, 405–418.
- 30 M. Adler, M. Marsch, N. S. Nudelman and G. Boche, *Angew. Chem. Int. Ed.*, 1999, **38**, 1261–1263.
- 31 D. L. Comins, *Synlett*, 1992, 615–625.
- 32 Z. A. Knight, G. G. Chiang, P. J. Alaimo, D. M. Kenski, C. B. Ho, K. Coan, R. T. Abraham and K. M. Shokat, *Bioorg. Med. Chem.*, 2004, **12**, 4749–4759.
- 33 R. A. Sheldon, I. W. C. E. Arends and U. Hanefeld, *Green Chemistry and Catalysis*, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, 2007.



View Article Online
DOI: 10.1039/C8CC08444K

A one-pot procedure for 1,2-addition of organolithium reagents to amides followed by Buchwald-Hartwig amination with *in-situ* released lithium amides is presented.