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Practical and economic lithiations of functionalized arenes and heteroarenes using Cy_2NLi in the presence of Mg, Zn or La halides in a continuous flow†‡

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The economic amide base lithium dicyclohexylamide (Cy_2NLi) allows fast and convenient (40 s, 0 °C) *in situ* trapping flow metalations of a broad range of functionalized arenes, heteroarenes and acrylate derivatives in the presence of various metal salts ($ZnCl_2 \cdot 2LiCl$, $MgCl_2$, $LaCl_3 \cdot 2LiCl$). The resulting Zn-, Mg- or La-organometallic intermediates are trapped with various electrophiles in high yields. These flow metalations are easily scaled-up without further optimization.

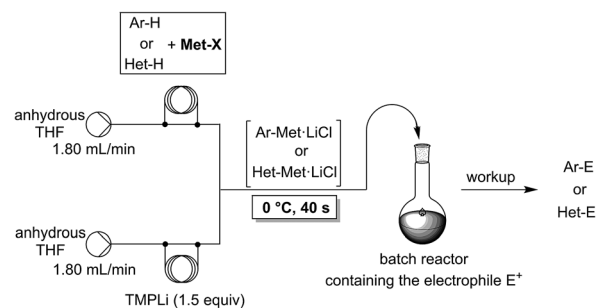
Introduction

The lithiation of arenes and heteroarenes is a common method for the functionalization of unsaturated molecules.¹ Pioneering work of Snieckus² and others³ have demonstrated the utility of aromatic lithiations for the preparation of pharmaceutical and agrochemical targets. Nevertheless, the use of powerful lithium bases has some drawbacks such as low metalation temperatures and a moderate functional group tolerance. Also, it requires a careful choice of the lithium base used for the metalation step.

Recently, we have shown that an *in situ* trapping metalation sequence using TMPLi (TMP = 2,2,6,6-tetramethylpiperidyl) allows the performance of selective lithiations of various arenes and heteroarenes at 0 °C within 40 s if conducted in a continuous flow system (Scheme 1).^{4,5} Under conventional batch conditions, these *in situ* trapping metalations require cryogenic temperatures (−78 °C) in order to avoid unwanted side reactions or decomposition of the organometallic intermediate. Furthermore, the scale-up of these batch metalations proved to be difficult, requiring much optimization. Despite the convenient reaction conditions in flow mode, the use of stoichiometric amounts of TMPLi makes this lithiation still expensive (TMPLi = ca. 630 \$ mol^{−1}).⁶ The steric hindrance of the TMP-moiety was required in order to avoid side-reactions. Due to the fast mixing of the reaction components and the prevention of hot spot formation,⁷ such highly sterically hindered bases may no longer be mandatory when using the flow

methodology.⁸ Preliminary experiments attempting to perform metalations of various aromatics using cheaper readily available lithium or other metallic amides R_2NMe (R = iPr (isopropyl), Cy (cyclohexyl), TMS (trimethylsilyl); Met = Li, MgHal, ZnHal) were disappointing either due to insufficient reactivity or unwanted side-reactions. The *in situ* trapping methodology developed in our laboratory, in which we mix the aromatic substrate with a metallic salt and add TMPLi proves to be compatible with the replacement of TMPLi with much cheaper bases, since this Barbier-type lithiation minimizes the contact time of the lithium base with the aromatic substrate. The replacement of TMPLi by Cy_2NLi is of special importance since the price of the corresponding amine Cy_2NH (ca. 6.40 \$ mol^{−1}) is only ca. 1% of TMPLi.^{6,9}

Herein we wish to report the use of the economic amide base lithium dicyclohexylamide (Cy_2NLi) instead of TMPLi for *in situ* trapping metalations under continuous flow conditions. Cy_2NLi has – to the best of our knowledge – not yet been used for extensive lithiations of functionalized arenes and heteroarenes.¹⁰



Scheme 1 Continuous flow set-up for *in situ* trapping metalations using TMPLi in the presence of metal salts (Met-X = $ZnCl_2 \cdot 2LiCl$, $MgCl_2$, $CuCN \cdot 2LiCl$, $LaCl_3 \cdot 2LiCl$) and subsequent batch quenching with electrophiles (E^+).

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






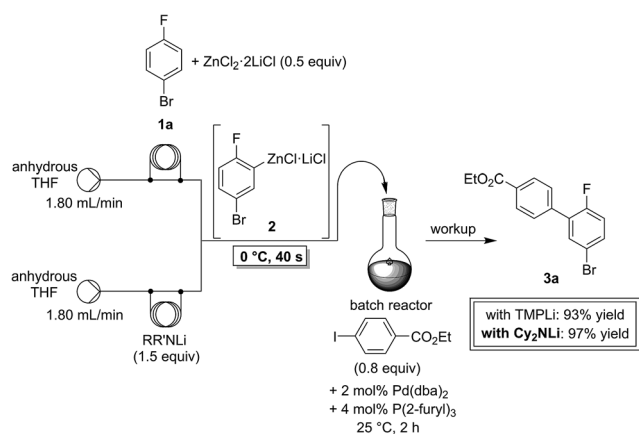
Results and discussion

In a first experiment, we have metalated 1-bromo-4-fluorobenzene (**1a**) under flow conditions (Scheme 2). Thus, **1a** (1.0 equiv.) was mixed with $\text{ZnCl}_2 \cdot 2\text{LiCl}$ (0.5 equiv.) and submitted to flow metalation¹¹ (0 °C, 40 s) using respectively TMPLi and Cy_2NLi . The corresponding arylzinc intermediate (**2**) was quenched *via* a Pd-catalyzed Negishi cross-coupling¹² in a batch reactor containing ethyl 4-iodobenzoate (0.8 equiv.) and a standard Pd-catalytic system (2 mol% $\text{Pd}(\text{dba})_2$; dba = dibenzylideneacetone and 4 mol% $\text{P}(2\text{-furyl})_3$)¹³ providing the expected biphenyl (**3a**) in 93% (using TMPLi) and 97% (using Cy_2NLi) yield. Like for reactions with TMPLi, *in situ* trapping metalations with Cy_2NLi can be simply scaled up without further optimization just by running the reaction for a longer time. Therefore, the reaction of **2** with 3-iodoanisole (0.8 equiv.) affords after a Negishi cross-coupling the expected product **3b** in 97% yield on a 1.7 mmol scale and in 95% yield on a 11 mmol scale (Table 1, entry 1). Using Cy_2NLi for the *ortho*-lithiation of 1,3-dihaloarenes (**1b**, **c**) abstracts under our standard reaction conditions (0 °C, 40 s) the most acidic hydrogen at position 2. *In situ* transmetalations with $\text{ZnCl}_2 \cdot 2\text{LiCl}$ or MgCl_2 (0.5 equiv., respectively) generate the corresponding aryl-zinc and -magnesium species, which are quenched in subsequent batch reactions with aryl iodides (0.8 equiv.), *S*-phenyl benzenethiosulfonate (0.8 equiv.) and ethyl cyanofornate (0.8 equiv.) leading to the trisubstituted arenes (**3c–f**) in 67–98% yield (entries 2–5). The *in situ* metalations with Cy_2NLi are not limited to haloarenes, and sensitive functionalities such as esters and nitriles are tolerated as well. Thus, diethyl 4-bromoisophthalate (**1d**) is smoothly flow-zincated in position 6 and a Negishi cross-coupling with ethyl 4-iodobenzoate (0.8 equiv.) produces the expected triester (**3g**) in 72% yield (entry 6). Similarly, substituted nitriles such as **1e** and **1f** are *in situ* metalated in the presence of $\text{ZnCl}_2 \cdot 2\text{LiCl}$ (0.5 equiv.) within 40 s at 0 °C, and subsequent quenching reactions with aryl iodides (0.8 equiv.) having either electron-donating or

electron-withdrawing substituents lead to the cyano-substituted biphenyls (**3h–j**) in 70–97% yield (entries 7–9).

Table 1 Continuous flow trapping-metalation of arenes **1** followed by reaction with electrophiles leading to products of type **3**

Entry	Substrate	Electrophile	Product ^a
1	1a		3b : 97% ^{b,d} (95%) ^e
2	1b		3c : 98% ^{b,d}
3	1b	Ph-SO ₂ -SPh	3d : 75% ^c
4	1c		3e : 94% ^{b,d}
5	1c	NC-CO ₂ Et	3f : 67% ^c
6	1d		3g : 72% ^{b,d}
7	1e		3h : 70% ^{b,d}
8	1f	R = <i>m</i> -OMe	3i : 97% ^{b,d}
9	1f	R = <i>p</i> -CN	3j : 73% ^{b,d}



Scheme 2 Continuous flow *in situ* trapping zincation of 1-bromo-4-fluorobenzene (**1a**) using TMPLi and Cy_2NLi and subsequent Pd-catalyzed Negishi cross-coupling with ethyl 4-iodobenzoate in a batch reactor.

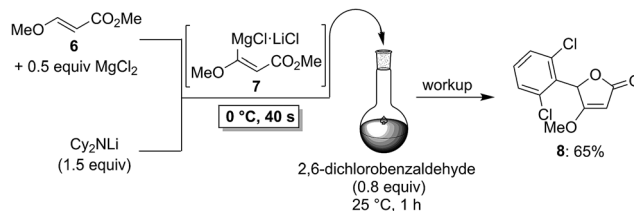
^a Yield of isolated product. ^b $\text{ZnCl}_2 \cdot 2\text{LiCl}$ (0.5 equiv.) was used. ^c MgCl_2 (0.5 equiv.) was used. ^d Obtained using 2% $[\text{Pd}(\text{dba})_2]$ and 4% $\text{P}(2\text{-furyl})_3$. ^e Yield obtained on a 11 mmol scale.



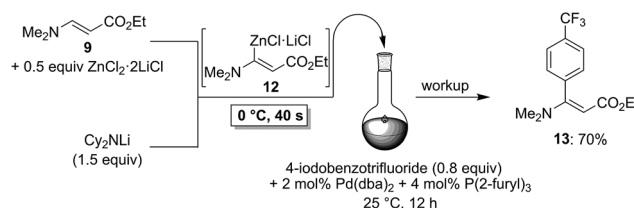
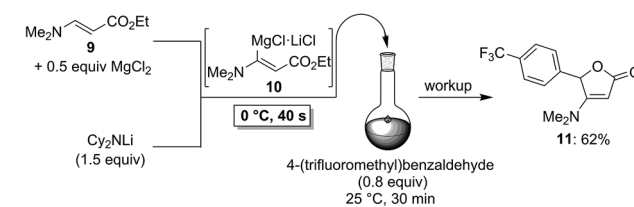
Table 2 Continuous flow trapping-metalation of heterocycles **4** followed by reaction with electrophiles leading to products of type **5**

Entry	Substrate	Electrophile	Product ^a
1			 5a : 94% ^{b,e}
2		Me-SO ₂ -SMe	 5b : 75% ^c
3			 5c : 67% ^{b,e}
4			 5d : 88% ^{b,f}
5			 5e : 77% ^{b,e}
6			 5f : 62% ^d
7			 5g : 76% ^{b,f}
8		R = <i>p</i> -CF ₃	 5h : 91% ^{b,e}
9		R = <i>m</i> -NO ₂	 5i : 89% ^{b,e}

^a Yield of isolated product. ^b ZnCl₂·2LiCl (0.5 equiv.) was used. ^c MgCl₂ (0.5 equiv.) was used. ^d LaCl₃·2LiCl (0.5 equiv.) was used. ^e Obtained using 2% [Pd(dba)₂] and 4% P(2-furyl)₃. ^f Obtained by a Cu-catalyzed allylation.



Scheme 3 *In situ* trapping magnesiation of (*E*)-methyl 3-methoxyacrylate (**6**) using Cy₂NLI in a flow reactor.



Scheme 4 *In situ* trapping magnesiation and zincation of (*E*)-ethyl 3-(dimethylamino)acrylate (**9**) using Cy₂NLI in a flow reactor.

This *in situ* trapping methodology with Cy₂NLI in a flow reactor is not limited to functionalized arenes. In fact, it can be readily extended to a broad range of sensitive, electron-deficient heteroarenes (Table 2). Thus, 2-fluoropyridine (**4a**), which is notoriously difficult to metalate,¹⁴ undergoes a smooth zincation or magnesiation in position 3 in the presence of ZnCl₂·2LiCl or MgCl₂ and quenching with ethyl 4-iodobenzoate (0.8 equiv.) or *S*-methyl methanethiosulfonate (0.8 equiv.) produces the disubstituted pyridines (**5a**, **b**) in 75–94% yield (entries 1 and 2). However, using our standard conditions, 2,6-dibromopyridine (**4b**) is *in situ* metalated in position 4 and a subsequent Negishi cross-coupling with ethyl 4-iodobenzoate (0.8 equiv.) affords the desired pyridine (**5c**) in 67% yield (entry 3). Similarly, ethyl 2-chloronicotinate (**4c**) is flow-zincated within 40 s at 0 °C in position 4 affording the trisubstituted pyridine (**5d**) in 88% yield after a Cu-mediated allylation with 3-bromocyclohexene (0.8 equiv.; entry 4). The sensitive 2,3-dichloropyridazine (**4d**) is smoothly flow-metalated (0 °C, 40 s) in the presence of ZnCl₂·2LiCl (0.5 equiv.) and quenching with 3-iodoanisole (0.8 equiv.) leads to the pyridazine (**5e**) in 77% yield (entry 5). The *in situ* trapping metalations with Cy₂NLI can also be used for the functionalization of a broad range of substituted 5-membered ring heterocycles. Thus, the lanthanation of 1-methylpyrazole (**4e**) in the presence of LaCl₃·2LiCl (0.5 equiv.) under standard conditions (0 °C, 40 s) produces the desired alcohol (**5f**) in 62% yield after addition to *p*-chlorobenzaldehyde (0.8 equiv.; entry 6). Ethyl 5-bromo-2-furoate (**4f**) is regioselectively flow metalated in



position 3 and a subsequent Cu-catalyzed reaction with 3-bromocyclohexene (0.8 equiv.) leads to the trisubstituted furan (**5g**) in 76% yield (entry 7). The *in situ* trapping zincation of 2-bromothiophene (**4g**) within 40 s at 0 °C abstracts the most acidic hydrogen at position 5 affording the 2,5-disubstituted thiophenes (**5h, i**) in 89–91% yield after Negishi cross-couplings with 4-iodobenzotrifluoride (0.8 equiv.) and 1-iodo-3-nitrobenzene (0.8 equiv.; entries 8 and 9).

To demonstrate the broad practicability of the *in situ* trapping metalations with Cy_2NLi , we investigated the functionalization of acyclic acrylate derivatives, which are prone to polymerize. However, submitting a mixture of (*E*)-methyl 3-methoxyacrylate (**6**) with MgCl_2 (0.5 equiv.) to the flow metalation with Cy_2NLi (1.5 equiv.) for 40 s at 0 °C leads to the formation of the magnesium intermediate **7** in high conversion (Scheme 3). Subsequent reaction of **7** with 2,6-dichlorobenzaldehyde (0.8 equiv.) produces the lactone **8** in 65% yield. Similarly, (*E*)-ethyl 3-(dimethylamino)acrylate (**9**) is *in situ* metalated (0 °C, 40 s) in the presence of MgCl_2 or $\text{ZnCl}_2 \cdot 2\text{LiCl}$ (Scheme 4). The corresponding magnesium (**10**) and zinc (**12**) organometallic intermediates undergo various quenching reactions, such as an addition to 4-(trifluoromethyl)benzaldehyde (0.8 equiv.) and a Negishi cross-coupling with 4-iodobenzotrifluoride (0.8 equiv.), providing the corresponding lactone (**11**) and the ester **13** in 62–70% yield.

Conclusions

In summary, the economic amide base lithium dicyclohexylamide (Cy_2NLi) undergoes fast and convenient (40 s, 0 °C) *in situ* trapping flow metalations of a broad range of functionalized arenes, heteroarenes and acrylate derivatives in the presence of various metal salts ($\text{ZnCl}_2 \cdot 2\text{LiCl}$, MgCl_2 , $\text{LaCl}_3 \cdot 2\text{LiCl}$). The resulting Zn-, Mg- or La-organometallic intermediates are trapped with numerous electrophiles in high yields. These flow-metalations are easily scaled-up without further optimization simply by running the reaction for a longer time. Further applications and extensions of this method are currently underway.

Notes and references

- (a) J. Clayden, *Organolithiums: Selectivity for Synthesis*, Elsevier, Oxford, 2002; (b) J. Clayden, F. E. Knowles and I. R. Baldwin, *J. Am. Chem. Soc.*, 2005, **127**, 2412; (c) J. Clayden, J. Dufour, D. M. Grainger and M. Helliwell, *J. Am. Chem. Soc.*, 2007, **129**, 7488; (d) Z. Rappoport, I. Marek, *The Chemistry of Organolithium Compounds*, Wiley-VCH, Chichester, 2004; (e) P. García-Álvarez, R. E. Mulvey and J. A. Parkinson, *Angew. Chem., Int. Ed.*, 2011, **50**, 9668; (f) R. E. Mulvey and S. D. Robertson, *Angew. Chem., Int. Ed.*, 2013, **52**, 11470; (g) D. R. Armstrong, E. Crosbie, E. Hevia, R. E. Mulvey, D. L. Ramsay and S. D. Robertson, *Chem. Sci.*, 2014, **5**, 3031; (h) C. Unkelbach, D. F. O'Shea and C. Strohmman, *Angew. Chem., Int. Ed.*, 2014, **53**, 553; (i) A. Salomone, F. M. Perna, A. Falcicchio, S. O. N. Lill, A. Moliterni, R. Michel, S. Florio, D. Stalke and V. Capriati, *Chem. Sci.*, 2014, **5**, 528; (j) V. Capriati, F. M. Perna and A. Salomone, *Dalton Trans.*, 2014, **43**, 14204; (k) D. R. Armstrong, J. A. Garden, A. R. Kennedy, S. M. Leenhouts, R. E. Mulvey, P. O'Keefe, C. T. O'Hara and A. Steven, *Chem.-Eur. J.*, 2013, **19**, 13492.
- (a) P. Beak and V. Snieckus, *Acc. Chem. Res.*, 1982, **15**, 306; (b) V. Snieckus, *Chem. Rev.*, 1990, **90**, 879; (c) M. C. Whisler, S. MacNeil, V. Snieckus and P. Beak, *Angew. Chem., Int. Ed.*, 2004, **43**, 2206.
- (a) M. Schlosser, *Angew. Chem., Int. Ed.*, 2005, **44**, 376; (b) R. Chinchilla, C. Nájera and M. Yus, *Chem. Rev.*, 2004, **104**, 2667; (c) F. Foubelo and M. Yus, *Chem. Soc. Rev.*, 2008, **37**, 2620; (d) R. E. Mulvey, F. Mongin, M. Uchiyama and Y. Kondo, *Angew. Chem., Int. Ed.*, 2007, **46**, 3802.
- In situ* trapping metalations in batch: A. Frischmuth, M. Fernández, N. M. Barl, F. Achraimer, H. Zipse, G. Berionni, H. Mayr, K. Karaghiosoff and P. Knochel, *Angew. Chem., Int. Ed.*, 2014, **53**, 7928; *In situ* trapping metalations in a continuous flow system: M. R. Becker and P. Knochel, *Angew. Chem., Int. Ed.*, 2015, DOI: 10.1002/anie.201502393.
- For lithiations in flow mode, see: (a) A. Nagaki, Y. Takahashi and J.-i. Yoshida, *Chem.-Eur. J.*, 2014, **20**, 7931; (b) A. Nagaki, D. Ichinari and J.-i. Yoshida, *J. Am. Chem. Soc.*, 2014, **136**, 12245; (c) A. Nagaki, K. Imai, S. Ishiuchi and J.-i. Yoshida, *Angew. Chem., Int. Ed.*, 2015, **54**, 1914; (d) L. Kupracz and A. Kirschning, *Adv. Synth. Catal.*, 2013, **355**, 3375; (e) J. Wu, X. Yang, Z. He, X. Mao, T. A. Hatton and T. F. Jamison, *Angew. Chem., Int. Ed.*, 2014, **53**, 8416; (f) T. Fukuyama, T. Totoki and I. Ryu, *Org. Lett.*, 2014, **16**, 5632; (g) H. Kim, H.-J. Lee and D.-P. Kim, *Angew. Chem., Int. Ed.*, 2015, **54**, 1877.
- The price of the corresponding amine TMPH from Sigma-Aldrich is ca. 630 \$ mol⁻¹ for the largest package.
- J.-i. Yoshida, *Flash Chemistry: Fast Organic Synthesis in Microsystems*, John Wiley & Sons Ltd, West Sussex, 2008.
- For recent advances in flow chemistry, see: (a) T. Noël and S. L. Buchwald, *Chem. Soc. Rev.*, 2011, **40**, 5010; (b) M. Chen and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2013, **52**, 4247; (c) M. Chen, S. Ichikawa and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2015, **54**, 263; (d) Y. Zhang, S. C. Born and K. F. Jensen, *Org. Process Res. Dev.*, 2014, **18**, 1476; (e) T. P. Petersen, M. R. Becker and P. Knochel, *Angew. Chem., Int. Ed.*, 2014, **53**, 7933; (f) R. J. Ingham, C. Battilocchio, D. E. Fitzpatrick, E. Sliwinski, J. M. Hawkins and S. V. Ley, *Angew. Chem., Int. Ed.*, 2015, **54**, 144; (g) D. N. Tran, C. Battilocchio, S.-B. Lou, J. M. Hawkins and S. V. Ley, *Chem. Sci.*, 2015, **6**, 1120; (h) S. V. Ley, D. E. Fitzpatrick, R. J. Ingham and R. M. Myers, *Angew. Chem., Int. Ed.*, 2015, **54**, 3449; (i) J. M. Sauks, D. Mallik, Y. Lawryshyn, T. Bender and M. G. Organ, *Org. Process Res. Dev.*, 2014, **18**, 1310; (j) K. S. Nalivela, M. Tilley, M. A. McGuire and M. G. Organ, *Chem.-Eur. J.*, 2014, **20**, 6603; (k) K. Somerville, M. Tilley, G. Li, D. Mallik and M. G. Organ, *Org. Process Res. Dev.*, 2014, **18**, 1315; (l) K. Gilmore, D. Kopetzki, J. W. Lee, Z. Horváth, D. T. McQuade, A. Seidel-Morgenstern and P. H. Seeberger,



- Chem. Commun.*, 2014, **50**, 12652; (m) D. B. Ushakov, K. Gilmore, D. Kopetzki, D. T. McQuade and P. H. Seeberger, *Angew. Chem., Int. Ed.*, 2014, **53**, 557; (n) D. Ghislieri, K. Gilmore and P. H. Seeberger, *Angew. Chem., Int. Ed.*, 2015, **54**, 678.
- 9 The price of the corresponding amine Cy_2NH from Sigma-Aldrich is ca. 6.40 \$ mol⁻¹ for the largest package.
- 10 For the use of Cy_2N -bases for metalations, see: (a) R. N. McDonald, H. E. Petty, N. L. Wolfe and J. V. Paukstelis, *J. Org. Chem.*, 1974, **39**, 1877; (b) M. Jørgensen, S. Lee, X. Liu, J. P. Wolkowski and J. F. Hartwig, *J. Am. Chem. Soc.*, 2002, **124**, 12557; (c) A. Renaudat, L. Jean-Gérard, R. Jazzar, C. E. Kefalidis, E. Clot and O. Baudoin, *Angew. Chem., Int. Ed.*, 2010, **49**, 7261; (d) T. Truong, J. Alvarado, L. D. Tran and O. Daugulis, *Org. Lett.*, 2010, **12**, 1200.
- 11 Flow reactions were performed with commercially available equipment from Uniqsis Ltd (FlowSyn; <http://www.uniqsis.com>).
- 12 (a) E. Negishi, L. F. Valente and M. Kobayashi, *J. Am. Chem. Soc.*, 1980, **102**, 3298; (b) E. Negishi, *Acc. Chem. Res.*, 1982, **15**, 340.
- 13 V. Farina and B. Krishnan, *J. Am. Chem. Soc.*, 1991, **113**, 9585.
- 14 The metalation of 2-fluoropyridine using LDA (−78 °C, 4 h) and iodolysis afforded 2-fluoro-3-iodopyridine in 85% yield: L. Estel, F. Marsais and G. Quéguiner, *J. Org. Chem.*, 1988, **53**, 2740.

