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COMMUNICATION

# A Catalyst-Free Flow Amination of Functional Organolithium Reagents

Heejin Kim, Yuya Yonekura, Jun-ichi Yoshida*

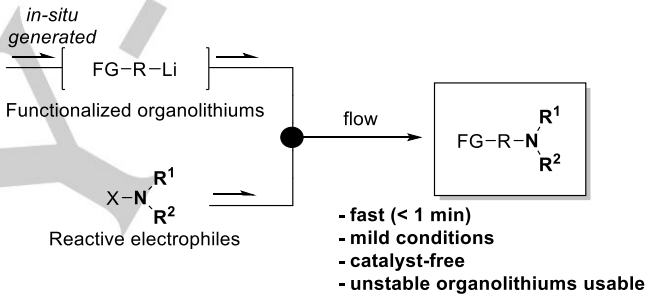
***Abstract:*** We report an electrophilic amination of functional organolithium intermediates with well-designed aminating reagents under mild conditions using flow microreactors. The aminating reagents were explored and optimized to achieve an efficient C–N bond formation without using any catalyst. The electrophilic amination reactions of functionalized aryllithiums were successfully conducted under mild conditions within 1 min using flow microreactors. The aminating reagent was also prepared by the flow method. Based on stopped-flow NMR analysis, the reaction time for the preparation of the aminating reagent was quickly optimized without any necessity of work-up. Integrated one-flow synthesis consisting of generation of an aryllithium, the preparation of an aminating reagent, and their reaction was successfully achieved to give desired amine product within 5 min of total reaction time.

A synthetic methodology for the formation of carbon–nitrogen bond has become an important subject of considerable attentions in organic synthesis.[1] With an advancement of transition-metal-catalyzed coupling reactions, Ullman–Goldberg amination,[2] Buchwald–Hartwig amination,[3] and Chan–Lam coupling reactions[4] have been developed as highly reliable means of carrying out the C–N bond formation as a nucleophilic amination. Recently, C–H amination reactions based on electrochemical[5] and photoredox methods[6] have also been reported.

Electrophilic amination of carbanions (typically, organometallic compounds)[7] serves as an alternative tool, which is based on the umpolung strategy.[8] Many electrophilic aminating reagents have been developed for the electrophilic amination of organometallic compounds such as organo-magnesiums,[9] organozincs,[10] organocoppers,[11] and organoaluminums.[12] These compounds, however, are often prepared by the metal exchange from corresponding organolithiums. Therefore, the direct use of organolithiums would serve as more efficient synthetic way from a viewpoint of atom[13] and step economy.[14] Though the direct amination of organolithiums[15,16] has also been studied from the beginning of organolithium chemistry, it still remains an ongoing challenge. The direct amination of organolithiums has suffered from low yields, formations of by-products, and limited scopes, due to an instability and low selectivity of organolithiums.[7a,7d]

The field of flow chemistry which is often based on microfluidics has rapidly been growing up in last two decades.[17] To keep up with recent demands on safe and environmentally benign chemical methods,[18] continuous flow technology has come into the spotlight with its high potential as well as previously reported numerous merits on chemical synthesis. As well described in the concept of flash chemistry,[19] the controllability of rapid reactions is one of the most unique and powerful advantages of flow chemistry.[20] Using flow microreactors, the reaction time can be precisely adjusted to milliseconds or less, so that reactions can proceed or stop in accordance with synthetic purpose.[21]

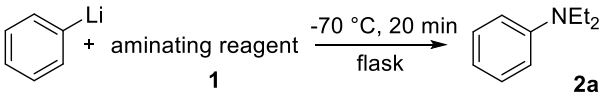
Herein, we report a design, preparation, and synthetic use of aminating reagents for a flow amination of functionalized organolithiums under mild conditions (Scheme 1). Various in-situ generated organolithiums could be reacted with optimized aminating reagents in flow for C–N bond formation without using any catalyst. In particular, the amination of unstable organolithiums was achieved under mild conditions in a short time by using flow microreactors.




**Scheme 1.** Concept of this work: electrophilic amination of functionalized organolithiums using flow microreactors

We began our investigation by carrying out the reaction of phenyllithium with a common electrophilic aminating reagent, *O*-benzoyl-*N*,*N*-diethylhydroxylamine (**1a**)[7] in a flask (Table 1, entry 1). At −78 °C, PhLi was reacted with **1a** for 20 min. The desired *N*,*N*-diethylaniline (**2a**) was not obtained at all, but major products were benzophenone (68%) and triphenylmethanol (20%), due to unwanted nucleophilic attacks to a carbonyl moiety of the aminating reagent. Thus, our interests in the amination of organolithiums was piqued by the direct nucleophilic attack of the potential leaving group on the nitrogen atom. We prepared various candidate reagents bearing sterically hindered leaving groups (entries 2–6).

**Table 1.** Electrophilic amination of PhLi with various amine reagents in a flask.




| Entry | Aminating reagent | Yield [%][a] |
|---|---|---|

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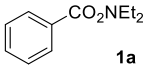
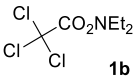
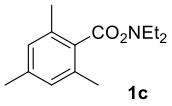
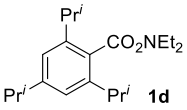
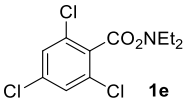
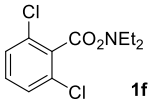
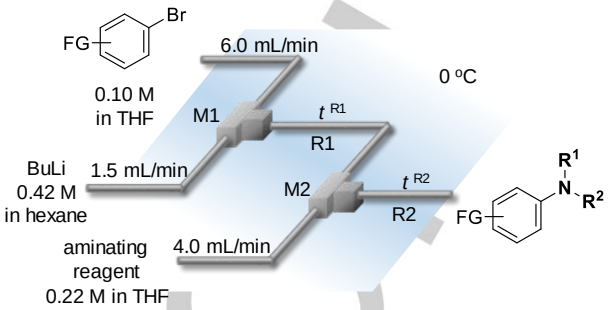
| | | |
|---|---|---|
| 1 |  **1a** | n.d.[b] |
| 2 |  **1b** | n.d.[b] |
| 3 |  **1c** | 33 |
| 4 |  **1d** | 54 |
| 5 |  **1e** | 6 |
| 6 |  **1f** | 81 |

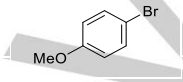
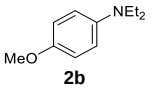
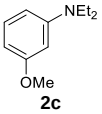
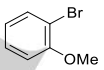
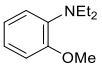
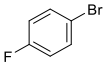
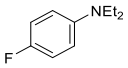
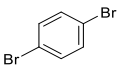
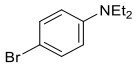
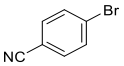
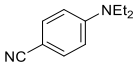
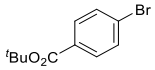
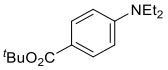
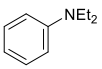
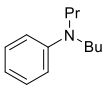
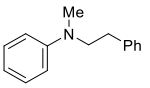
[a] Determined by GC spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [b] Not detected.

Although the reaction with aminating reagent **1b** bearing a trichloromethyl moiety (Table 1, entry 2) did not give any aniline product, the reaction with **1c** bearing a mesityl moiety gave the aminated product in 33% yield (entry 3). Then, other aminating reagents **1d**–**1f** bearing sterically more demanding groups such as isopropyl or chloro groups on the benzene ring were examined (entries 4–6). The best result was obtained with aminating reagent **1f** bearing 2,6-dichlorobenzoyl group (entry 6), which gave the desired product in 81% yield. The steric effect of two chloro groups to prohibit an undesired nucleophilic attack on the carbonyl carbon as well as the electron-withdrawing effect to enhance the electrophilicity of the nitrogen seems to be responsible.

With the designed aminating reagent in hand, we examined reactions with various functionalized aryllithiums using a flow microreactor system consisting of two micromixers (M1 and M2; 250 μm of inner diameter) and two microtube reactors (R1 and R2; Table 2). Aryllithiums having various functional groups were effectively generated in reactor R1 under optimized conditions which were previously reported.[22] The resulting functionalized aryllithiums were reacted with the aminating reagent to give desired aniline derivatives.

**Table 2.** Continuous flow amination of various functionalized aryllithiums using flow microreactors.




| Entry | Substrate | $t^{R1}$ [s] | $t^{R2}$ [s] | Product | Yield [%][a] |
|---|---|---|---|---|---|
| 1[b] |  | 3.1 | 9.0 |  **2b** | 93 |
| 2 |  | 3.1 | 8.2 |  **2c** | 87 |
| 3 |  | 3.1 | 8.2 |  **2d** | 81 |
| 4 |  | 0.01 | 8.2 |  **2e** | 93 |
| 5 |  | 0.01 | 8.2 |  **2f** | 83 |
| 6 |  | 0.01 | 8.2 |  **2g** | 50 |
| 7 |  | 0.01 | 18 |  **2h** | 85 |
| 8 | PhLi | -[c] | 8.2 |  **2a** | 91 |
| 9 | PhLi | -[c] | 8.2 |  **2i** | 62[d] |
| 10 | PhLi | -[c] | 8.2 |  **2j** | 85[d] |

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| | | | | | |
|---|---|---|---|---|---|
| 11 | BuLi | –[c] | 8.2 | Bu–NEt$_2$ **2k** | 89 |

[a] Determined by GC spectroscopy using an internal standard. [b] 1.1 equiv of the aminating reagent was used. [c] PhLi or BuLi was directly used. [d] Yield of isolated product.

Note that all flow reactions were carried out at 0 °C, which is much milder than that for typical organolithium reactions using flasks.[20a,22] Aryllithium compounds bearing a methoxy group at para, meta, and ortho positions were aminated to give the corresponding products in high yields (Table 2, entries 1–3). Aryllithiums bearing electron-withdrawing groups could be also effectively generated and aminated at 0 °C (entries 4–7). Other aminating reagents bearing dibuthylamino or methyl 2-phenylethyl amino group were effective to give corresponding products (entries 9 and 10). Direct use of PhLi and BuLi also gave desired products in high yields (entries 9–11).

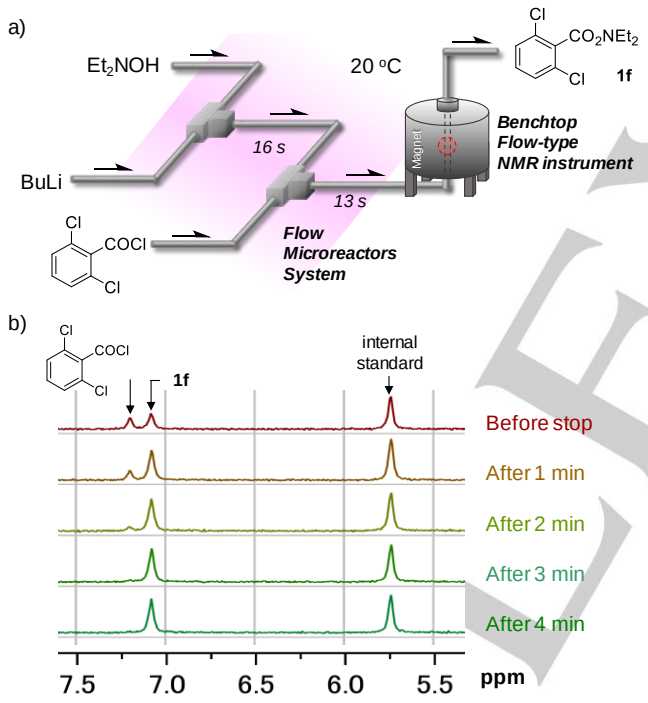


**Figure 1.** Integrated flow system for sequential reactions. a) A flow system including microreactors and a benchtop flow-type NMR instrument. b) Results from $^1$H NMR spectroscopy which were detected after 1 min, 2 min, 3 min, and 4 min as well as before stop.

We next carried out an optimization of the reaction time for preparing the aminating reagent in flow systems using a benchtop flow-type NMR instrument (Magritek Spinsolve benchtop NMR spectrometer, 43 MHz, Figure 1a).[23] The NMR instrument is equipped with a compact permanent magnet. A solution of diethylhydroxylamine was sequentially mixed with a solution of BuLi and 2,6-dichlorobenzoyl chloride in flow, and resulting solution was passed through the NMR equipment. Then, the solution was stopped and the progress of the reaction in the NMR chamber was monitored by $^1$H NMR spectroscopy (Figure 1b). A broad signal at 7.25 ppm was assigned to three protons of the benzene ring of 2,6-dichlorobenzoyl chloride. A broad signal at 7.10 ppm was assigned to three benzene-ring protons of **1f**. Because these two signals and a signal due to 1,3,5-trimethoxybenzene as an internal standard were well separated from the signals of the solvents, inexpensive non-deuterated solvents can be used. This micromixer-based time-resolved $^1$H NMR monitoring[24] based on the stopped-flow method clearly indicated that the reaction was complete in 4 minutes at 20 °C. Thus, the optimization was easily achieved without any work-up and purification.

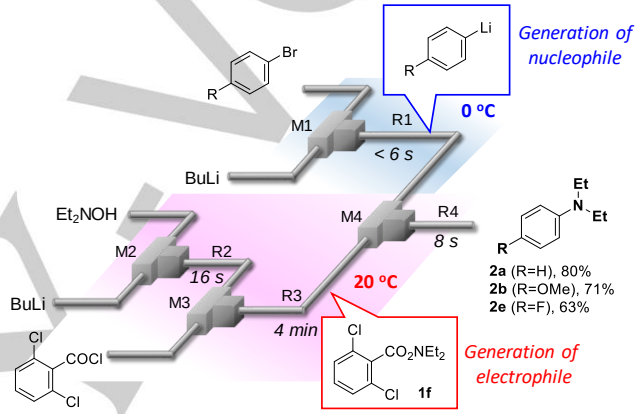


**Figure 2.** Three-step-integrated electrophilic aminations including generation of an aryllithium intermediate, preparation of an aminating reagent, and electrophilic amination.

The optimized conditions for the preparation of the aminating reagent were applied to one-flow three-reaction-integrated synthesis (Figure 2).[25] An aryllithium reagent bearing a functional group and the aminating reagent **1f** were separately generated in flow. Then, they were reacted to give the desired products in good yields. The total reaction time for the integrated amination was less than 5 min.

In conclusion, we have achieved the flow amination of functional organolithiums under mild conditions without any catalyst and additives. Various organolithiums were in-situ generated in flow microreactors, and reacted with the well-designed aminating reagents. Also, the preparation condition of the aminating reagent was easily optimized by micromixing-based time-resolved stopped-flow analysis using a benchtop flow-type NMR instrument. Finally, an integrated one-flow synthesis consisting of the generation of aryllithiums, the preparation of the aminating reagent, and their combination reaction was achieved to give aniline derivatives within 5 minutes of total reaction time.

## Acknowledgements

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**Keywords:** electrophilic amination • organolithium • flow chemistry • microreactor • benchtop NMR

[1] For reviews, see: a) S. H. Cho, J. Y. Kim, J. Kwak, S. Chang, *Chem. Soc. Rev.* **2011**, *40*, 5068–5083; b) Y. Yamamoto, *Heterocycles* **2012**, *85*, 799–819; c) J. Bariwal, E. Van der Eycken, *Chem. Soc. Rev.* **2013**, *42*, 9283–9303.

[2] a) F. Ullmann, *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 2382–2384; b) I. Goldberg, *Ber. Dtsch. Chem. Ges.* **1906**, *39*, 1691–1692.

[3] a) J. F. Hartwig, *Angew. Chem. Int. Ed.* **1998**, *37*, 2046–2067; b) J. P. Wolfe, S. Wagaw, J. –F. Marcoux, S. L. Buchwald, *Acc. Chem. Res.* **1998**, *31*, 805–818; c) B. Schlummer, U. Scholz, *Adv. Synth. Catal.* **2004**, *346*, 1599–1626.

[4] a) D. Chan, K. Monaco, R. Wang, M. Winter, *Tetrahedron Lett.* **1998**, *39*, 2933–2936; b) P. Lam, C. Clark, S. Saubern, J. Adams, M. Winters, D. Chan, A. Combs, *Tetrahedron Lett.* **1998**, *39*, 2941–2944.

[5] a) T. Morofuji, A. Shimizu, J. Yoshida, *J. Am. Chem. Soc.* **2013**, *135*, 5000–5003; b) T. Morofuji, A. Shimizu, J. Yoshida, *J. Am. Chem. Soc.* **2015**, *137*, 9816–9819.

[6] a) N. A. Romero, K. A. Margrey, N. E. Tay, D. A. Nicewicz, *Science* **2015**, *349*, 1326–1330; b) Y. –W. Zheng, B. Chen, P. Ye, K. Feng, W. Wang, Q. –Y. Meng, L. –Z. Wu, C.-H. Tung, *J. Am. Chem. Soc.* **2016**, *138*, 10080–10083; c) L. Niu, H. Yi, S. Wang, T. Liu, J. Liu, A. Lei, *Nat. Commun.* **2017**, *8*:*14226*, 1–7.

[7] For reviews, see: a) E. Erdik, M. Ay, *Chem. Rev*. **1989**, *89*, 1947–1980; b) P. Dembech, G. Seconi, A. Ricci, *Chem. Eur. J*. **2000**, *6*, 1281–1286; c) T. Daskapan, *Arkivoc* **2011**, 230–262; d) X. Dong, Q. Liu, Y. Dong, H. Liu, *Chem. Eur. J.* **2017**, *23*, 2481–2511.

[8] a) D. Seebach, *Angew. Chem. Int. Ed.* **1979**, *18*, 239–258; b) B. T. Grobel, D. Seebach, *Synthesis* **1977**, 6, 357–402.

[9] a) I. Sapountzis, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 897–900; b) M. Kitamura, T. Suga, S. Chiba, K. Narasaka, *Org. Lett.* **2004**, *6*, 4619–4621; c) M. J. Campbell, J. S. Johnson, *Org. Lett.* **2007**, *9*, 1521–1524; d) T. Hatakeyama, Y. Yoshimoto, S. K. Ghorai, M. Nakamura, *Org. Lett.* **2010**, *12*, 1516–1519.

[10] a) R. Velarde-Ortiz, A. Guijarro, R. D. Rieke, *Tetrahedron Lett.* **1998**, *39*, 9157–9160; b) A. M. Berman, J. S. Johnson, *J. Am. Chem. Soc.* **2004**, *126*, 5680–5681; c) T. J. Barker, E. R. Jarvo, *J. Am. Chem. Soc.* **2009**, *131*, 15598–15599; d) S. L. McDonald, C. E. Hendrick, Q. Wang, *Angew. Chem. Int. Ed.* **2014**, *53*, 4667–4670.

[11] a) A. Casarini, P. Dembech, D. Lazzari, E. Marini, G. Reginato, A. Ricci, G. Seconi, *J. Org. Chem.* **1993**, *58*, 5620–5623; b) M. Kienle, C. Dunst, P. Knochel, *Org. Lett.* **2009**, *11*, 5158–5161.

[12] a) S. Zhou, Z. Yang, X. Chen, Y. Li, L. Zhang, H. Fang, W. Wang, X. Zhu, S. Wang, *J. Org. Chem.* **2015**, *80*, 6323–6328; b) H. Yoon, Y. Kim, Y. Lee, *Org. Biomol. Chem.* **2017**, *15*, 790–795.

[13] a) B. M. Trost, *Science* **1991**, *254*, 1471–1477; b) B. M. Trost, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 259–281.

[14] P. A. Wender, V. A. Verma, T. J. Paxton, T. H. Pillow, *Acc. Chem. Res.* **2008**, *41*, 40–49.

[15] a) G. Boche, N. Mayer, M. Bernheim, K. Wagner, *Angew. Chem. Int. Ed.* **1978**, *17*, 687–688; b) G. Boche, M. Bernheim, M. Niessner, *Angew. Chem. Int. Ed.* **1983**, *12*, 53–54.

[16] M. H. Nguyen, A. B. Smith III, *Org. Lett.* **2013**, *15*, 4872–4875.

[17] For recent reviews, see: a) Kirschning, L. Kupracz, J. Hartwig, *Chem. Lett.* **2012**, *41*, 562; b) K. S. Elvira, X. C. Solvas, R. C. R. Wootton, A. J. deMello, *Nat. Chem*. **2013**, *5*, 905; c) J. C. Pastor, D. L. Browne, S. V. Ley, *Chem. Soc. Rev.* **2013**, *42*, 8849; d) T. Fukuyama, T. Totoki, I. Ryu, *Green Chem.* **2014**, *16*, 2042; e) C. J. Mallia, I. R. Baxendale, *Org. Process Res. Dev*. **2016**, *20*, 327; f) D. Cambie, C. Bottecchia, N. J. W. Straathof, V. Hessel, T. Noel, *Chem. Rev.* **2016**, *116*, 10276; g) S. Kobayashi, *Chem. Asian J.* **2016**, *11*, 425; h) M. B. Plutschack, B. Pieber, K. Gilmore, P. H. Seeberger, *Chem. Rev.* **2017**, *117*, 11796.

[18] For reviews, see: a) J. Yoshida, H. Kim, A. Nagaki, *ChemSusChem* **2011**, *4*, 331–340; b) C. Wiles, P. Watts, *Green Chem.* **2012**, *14*, 38–54; c) S. G. Newman, K. F. Jensen, *Green Chem.* **2013**, *15*, 1456–1472; d) B. Gutmann, D. Cantillo, C. O. Kappe, *Angew. Chem. Int. Ed.* **2015**, *54*, 6688–6728; e) M. Movsisyan, E. I. P. Delbeke, J. K. E. T. Berton, C. Battilocchio, S. V. Ley, C. V. Stevens, *Chem. Soc. Rev.* **2016**, *45*, 4892–4928; f) F. Fanelli, G. Parisi, L. Degennaro, R. Luisi, *Beilstein J. Org. Chem.* **2017**, *13*, 520–542; g) J. A. M. Lummiss, P. D. Morse, R. L. Beingessner, T. F. Jamison, *Chem. Rec.* **2017**, *17*, 1–15.

[19] a) J. Yoshida, *Chem. Commun.* **2005**, 4509; b) J. Yoshida, A. Nagaki, T. Yamada, *Chem. Eur. J.* **2008**, *14*, 7450; c) J. Yoshida, *Chem. Rec.* **2010**, *10*, 332; d) J. Yoshida, Y. Takahashi, A. Nagaki, *Chem. Commun.* **2013**, *49*, 9896.

[20] a) A. Nagaki, H. Kim, J. Yoshida, *Angew. Chem. Int. Ed.* **2008**, *47*, 7833–7836; b) A. Nagaki, E. Takizawa, J. Yoshida, *J. Am. Chem. Soc.* **2009**, *131*, 1654–1655; c) A. Nagaki, C. Matsuo, S. Kim, K. Saito, A. Miyazaki, J. Yoshida, *Angew. Chem. Int. Ed*. **2012**, *51*, 3245–3248; d) A. Nagaki, D. Ichinari, J. Yoshida, *J. Am. Chem. Soc.* **2014**, *136*, 12245–12248; e) H. Kim, H. –J. Lee, D. –P. Kim, *Angew. Chem. Int. Ed.* **2015**, *54*, 1877–1880; f) H. Kim, H. –J. Lee, D. –P. Kim, *Angew. Chem. Int. Ed.* **2016**, *55*, 1422–1426; g) A. Nagaki, Y. Takahashi, J. Yoshida, *Angew. Chem. Int. Ed.* **2016**, *55*, 5327–5331.

[21] a) A. Nagaki, H. Kim, J. Yoshida, *Angew. Chem. Int. Ed.* **2009**, *48*, 8063–8065; b) H. Kim, A. Nagaki, J. Yoshida, *Nat. Commun.* **2011**, *2:264*, 1–6; c) H. Kim, K. –I. Min, K. Inoue, D. J. Im, D. –P. Kim, J. Yoshida, *Science* **2016**, 352, 691–694; d) H. Kim, K. Inoue, J. Yoshida, *Angew. Chem. Int. Ed.* **2017**, *56*, 7863–7866.

[22] a) A. Nagaki, Y. Tomida, H. Usutani, H. Kim, N. Takabayashi, T. Nokami, H. Okamoto, J. Yoshida, *Chem. Asian J.* **2007**, *2*, 1513–1523; b) A. Nagaki, H. Kim, C. Matsuo, H. Usutani, J. Yoshida, *Org. Biomol. Chem.* **2010**, *8*, 1212–1217; c) A. Nagaki, H. Kim, Y. Moriwaki, C. Matsuo, J. Yoshida, *Chem. Eur. J.* **2010**, *16*, 11167–11177; d) A. Nagaki, A. Kenmoku, Y. Moriwaki, A. Hayashi, J. Yoshida, *Angew. Chem. Int. Ed.* **2010**, *49*, 7543–7547.

[23] a) M. V. Gomez, A. de la Hoz, *Beilstein J. Org. Chem.* **2017**, *13*, 285–300; b) B. Picard, B. Gouilleux, T. Lebleu, J. Maddaluno, I. Chataigner, M. Penhoat, F. –X. Felpin, P. Giraudeau, J. Legros, *Angew. Chem. Int. Ed.* **2017**, *56*, 7568–7572.

[24] M. Kakuta, D. A. Jayawickrama, A. M. Wolters, A. Manz, J. V. Sweedler, *Anal. Chem.* **2003**, *75*, 956–960.

[25] For an example of integrated flow amination: C. E. Brocklehurst, G. Koch, S. Rothe-Pöllet, L. L. Vecchia, *Synlett* **2017**, *28*, 1636–1640.

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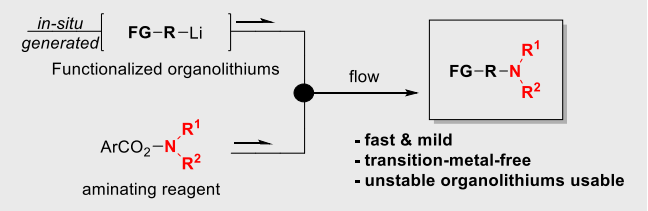


***Go with the Flow:*** We report an electrophilic amination of organolithium intermediates with well-optimized amine reagents under mild conditions using flow microreactors. Flow reaction conditions well applied for fast and mild amination without the use of any additional reagents or catalysts.

*Heejin Kim, Yuya Yonekura, Jun-ichi Yoshida**

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**A Catalyst-Free Flow Amination of Functional Organolithium Reagents**