CHEMISTRY
A European Journal

A Journal of
ChemPubSoc Europe

Accepted Article

Title: From p-Xylene to Ibuprofen in Flow: 3-Step Synthesis via Unified Sequence of Chemoselective C–H Metalations

Authors: Hyune-Jea Lee, Heejin Kim, and Dong-Pyo Kim

To be cited as: *Chem. Eur. J.* 10.1002/chem.201903267

Link to VoR: http://dx.doi.org/10.1002/chem.201903267

Supported by
ACES

WILEY-VCH

10.1002/chem.201903267

WILEY-VCH

COMMUNICATION

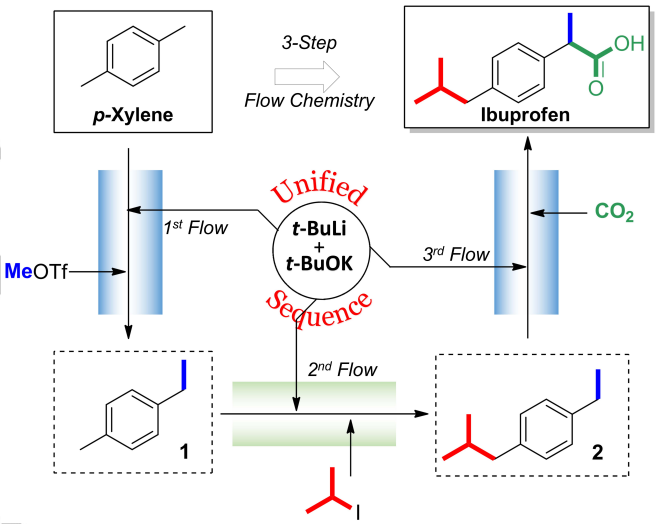
From *p*-Xylene to Ibuprofen in Flow: 3-Step Synthesis via Unified Sequence of Chemoselective C–H Metalations

Hyune-Jea Lee,[a] Heejin Kim,*[b] and Dong-Pyo Kim*[a]

Abstract: Ibuprofen was prepared from an inactive and inexpensive *p*-xylene by 3-step flow functionalizations through chemoselective metalations of benzyl positions in sequence using an in-situ generated LICKOR-type superbase. The flow approach in the microreactor facilitated to comprehensively explore over 100 conditions in the first-step reaction by varying concentrations, temperatures, solvents, and equivalents of reagents, enabling to find the optimal condition with 95% yield by significantly suppressing the formation of byproducts, followed by the second C–H metalation step in 95% yield. Moreover, gram-scale synthesis of ibuprofen in the final step was achieved by biphasic flow reaction of solution-phase intermediate with CO_2, isolating 2.3 g for 10 min of operation time.

Flow chemistry based on microfluidics has been recognized as the promising technology in modern synthetic chemistry.[1] The application area of flow chemistry has been well expanded to wide range of research field including synthesis of pharmaceutical and agrochemical compounds. Recently, flow synthesis of active pharmaceutical ingredients (APIs) has also been caught great attentions in pharmaceutical industries as well as academic laboratories from the viewpoint of better safety and sustainability than the conventional synthesis in a batch reactor.[2] Among various advantages of the flow synthesis, the rapid and precise control over reaction conditions is one of the most distinct and unique features. The small dimension and high surface-to-volume ratio of reactors are very efficient for the heat management.[3] Also, the reaction time and stoichiometry of reagents can be accurately adjusted by meticulously changing the flow rate of each solutions. In particular, flash chemistry often requires the control of reaction time in extremely short scale down to milliseconds order or less.[4] Therefore, the flow microreactors would be ideal platforms to handle highly unstable intermediates that are rapidly generated and decomposed.[5]

Ibuprofen is an analgesic, antipyretic and nonsteroidal anti-inflammatory drug (NSAID) used to relive the pain and fever, which is listed by World Health Organization (WHO) as an essential medicine. In the medication statistics of United States, there was more than 21 million prescriptions in 2016.[6] Since the general synthetic process was developed by Boot Pure Drug Company in early 1960s, many research groups have reported various synthetic methodologies not only using conventional batch reactors,[7] but using flow devices.[8] In all cases of flow synthesis reported by three research groups, isobutylbenzene was used in common as a starting material for Friedel-Crafts acylation at high temperature. We envisage alternative flow synthesis of ibuprofen from a low-cost substrate at favorable conditions, inspired by previous studies on sequential generations of benzylic anions for the synthesis in a flask.[9] Especially, we could improve the previous method[9b] on the basis of the flow synthetic manner. It would be highly desirable for value-added API production from commodity chemicals.



Scheme 1. Flow approach for the three-step synthesis of ibuprofen from *p*-xylene through sequential and chemoselective C–H functionalizations.

We herein report an efficient three-step flow synthesis of ibuprofen from *p*-xylene using sequential and chemoselective C–H metalations in a precisely controlled manner (Scheme 1). Three metalation steps of the benzyl position as an unified sequence were carried out by in-situ generated LICKOR-type superbase[10] under the optimal flow conditions which were comprehensively explored over 100 conditions to suppress competitive side reactions. As a starting material, we used a simple and inactive starting compound, *p*-xylene, to achieve an atom-economic flow process. Moreover, in the final step, synthesis of ibuprofen in the high productivity was attained by efficient flow reaction of biphasic segments between highly reactive intermediate in the solution and CO_2 gas,[11] which was fully utilized the merit of microreactor with high surface-to-volume ratio.

In order to establish the suitable synthetic route for a flow process, we firstly looked over the selective benzylic C–H metalation of *p*-xylene using a superbase, in-situ generated from butyllithium (BuLi) and potassium *tert*-butoxide (*t*-BuOK).

[a] H. –J. Lee, Prof. Dr. D. –P. Kim
Centre for Intelligent Microprocess of Pharmaceutical Synthesis
Department of Chemical Engineering
POSTECH (Pohang University of Science and Technology),
Pohang, 790-784 (South Korea)
E-mail: dpkim@postech.ac.kr
[b] Prof. Dr. H. Kim
Department of Chemistry, College of Science, Korea University
Seoul, 02841 (South Korea)
E-mail: heejinkim@korea.ac.kr

Supporting information for this article is given via a link at the end of the document.((Please delete this text if not appropriate))

10.1002/chem.201903267

COMMUNICATION

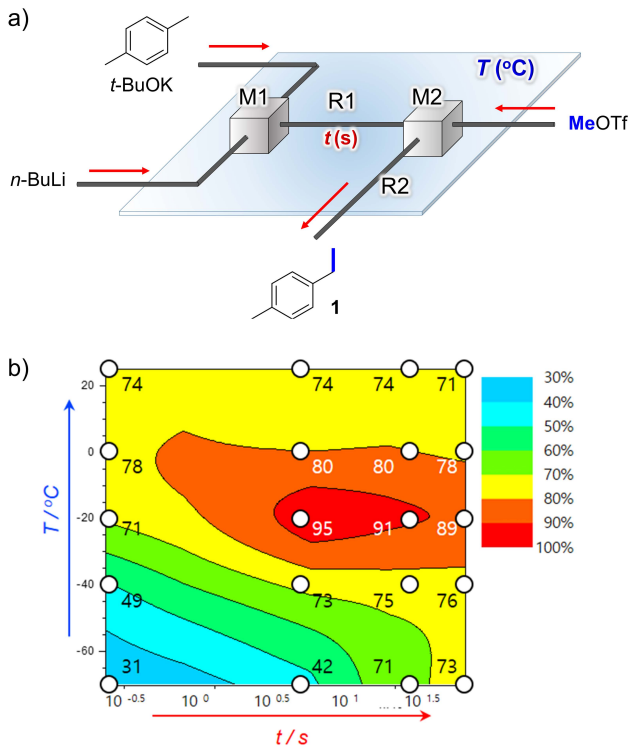


Figure 1. Benzyl-metalation of *p*-xylene and reaction with MeOTf in flow. a) the reaction scheme in a flow reactor (micromixers: M1 and M2, tube reactors: R1 and R2). b) Correlation map of the effects of temperature (*T*) and residence time (*t*) on the yield [%] of *p*-ethyl toluene **1** (A solution of *p*-xylene (0.3 M with 1.2 equiv of *t*-BuOK in 2-MeTHF and a solution of *t*-BuLi (1.2 M in penatne:hexane 2:1 v/v) were used for reaction).

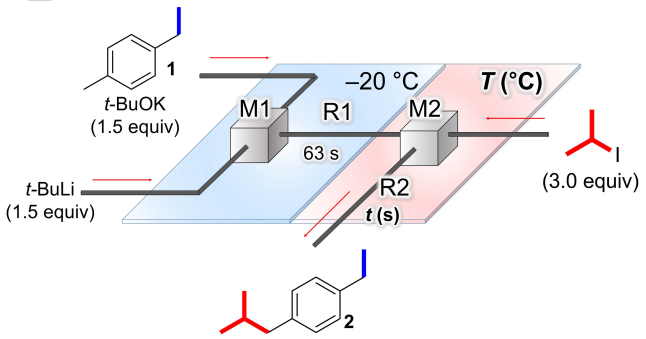
In addition, it was found that the one-pot synthetic method as reported[9b] showed lack of reproducibility even when we followed the protocol (Table S1, See the Supporting Information for details). We explored different types of lithium reagents (*n*-BuLi or *t*-BuLi) for the selective and rapid generation of benzyl-metalated xylene. The metalation time was kept to 10 min at –78 ºC in a flask. The use of *n*-BuLi led to form methylated product **1** in 68% yield (entry 1, Table S1), whereas the use of *t*-BuLi was inefficient with decreased conversion probably due to the competitive side reaction with THF solvent (entry 2, Table S1).[12] Notably, it demands to establish the well-controlled synthetic protocol for suppressing the unwanted side reactions by thorough study on various reaction parameters.

We next examined a continuous-flow generation of benzyl-metalated xylene and its methylation in a capillary microreactor consisting of two micromixers M1 and M2 (inner diameter ø of M1: 250 µm, ø of M2: 500 µm) and two tube reactors R1 and R2 (ø: 1 mm) as illustrated in Figure 1-a. We explored 111 reactions by varying the concentration of each reagent, types of the solvent, and equivalents of the base (See the Supporting Information for details). From the obtained experimental results (Table S3), we could conclude that; 1) the use of *n*-BuLi lowered the conversion (Figure S1-a); 2) the use of THF accelerated the reaction but caused more side reaction between superbase and THF, compared to those in 2-MeTHF (Figure S1-a and b);[13] 3) the reaction at low temperature was inevitable to inhibit the side reactions; 4) the moderate concentration of reagents was crucial for efficient reaction, because the viscosity may affect to the mixing efficiency (Figure S1-c).[14] In addition, it is noteworthy that the flow methodology facilitates to conduct the labor-consuming parameter study, whereas conventional batch reactor takes much longer to complete the experiments.

We then conducted the flow reactions under the optimized concentration of solutions and the equivalent of reagents. A mixture of *p*-xylene with *t*-BuOK (1.2 equiv) was mixed with *t*-BuLi (1.2 equiv) in M1 and reacted in R1. The resulting solution was sequentially mixed with methyl triflate in M2 and reacted in R2. The reaction was carried out under various residence times in R1 (*t*; from 0.25 s to 24.8 s) and temperature (*T*; from –70 °C to 25 °C). The residence time in R1 was precisely controlled by changing the length of tube reactor. At high temperatures such as 25 °C, the yields were moderate probably because of unselective side reactions. At low temperature less than –40 °C, the low yields were probably due to the low reactivity and reduced mixing efficiency. The best result was obtained when the residence time in R1 was 3.14 s at –20 °C (Figure 1-b) to give the desired product in 95% yield. In this reaction condition, the formation of dimethylated byproduct (1,4-diethylbenzene) was suppressed to 1% (entry 101, Table S3).

In a similar vein, the second reaction step in flow was optimized using isopropyl iodide as an electrophile (Table 1). Because isopropyl iodide is relatively less reactive than MeOTf, benzyl-metalation was carried out under relatively long residence time (63 s) in R1 at –20 °C.

Table 1. Metalation of *p*-ethyl toluene and the subsequent reaction with isopropyl iodide using a flow reactor.

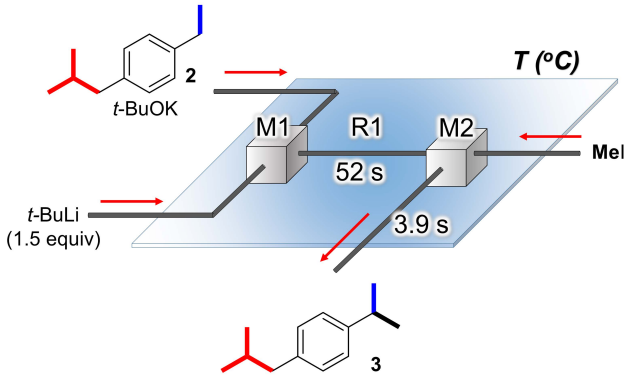


Entry	*t* [s]	*T* [ºC]	Conv. of **1** [%][a]	Yield of **2** [%][a]
1	4.5	50	78	77
2	4.5	25	81	79
3	4.5	–20	85	82
4	17.9	50	89	88
5	17.9	25	90	89
6	**17.9**	**–20**	**98**	**95 (93)[b]**

[a] Determined by GCMS using 1,3,5-trimethoxybenzene as an internal standard. [b] Yield of isolated product.

10.1002/chem.201903267

Table 2. Metalation of 1-ethyl-4-isobutylbenzene and the subsequent reaction with methyl iodide using a flow reactor.



Entry	Concentration of **2** [M]	Equiv of *t*-BuLi/*t*-BuOK	*T* [°C]	Yield [%][a]
1	0.2	1.5	–20	13
2	0.2	1.5	–40	20
3	0.2	3.0	–20	24
4	0.2	3.0	–40	31
5	0.4	3.0	–20	57
6	0.4	3.0	–40	59
7	0.5	3.0	–20	65
8	**0.5**	**3.0**	**–40**	**67**

[a] Determined by GCMS using 1,3,5-trimethoxybenzene as an internal standard.

We optimized the reaction by changing the residence time and temperature in second micromixer and tube reactor (M2 and R2). Although the yield of 1-ethyl-4-isobutylbenzene **2** was moderate in 4.5 s of reaction time at 50 °C (entry 1, Table 1), it was improved with decreasing the temperature to –20 °C (entries 2 and 3, Table 1) due to the better stability of the generated intermediate under low temperature.[15] At increased residence time in R2 and decreased temperature, the yields were gradually increased (entries 4–6, Table 1). Finally, the reaction for 17.9 s of residence time in R2 at –20 °C rendered the desired product in high isolated yield (93%) without any detectable byproduct (entry 6, Table 1).

For the optimization of final step to produce the ibuprofen, the reaction condition for the direct metalation of compound **2** was optimized using methyl iodide (Table 2). Through the trapping with methyl iodide, the yield of generated metalized intermediate can be indirectly confirmed, as often reported in many literatures.[16] It is much more difficult to metalize the benzyl position of compound **2** compared to that of *p*-xylene or compound **1**, because of the steric hindrance as well as electronic nature of benzylic position. The residence time for the metalation using 1.5 equivalents of *t*-BuLi/*t*-BuOK was fixed to 52 s.

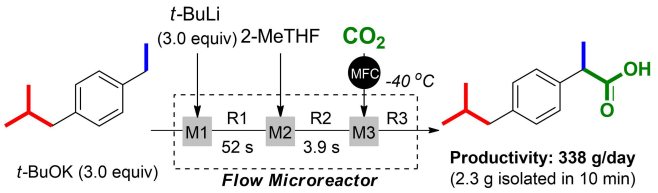


Figure 2. Gram-scale synthesis of ibuprofen through the biphasic reaction of compound **2** with carbon dioxide in flow.

At –40 °C and –20 °C, the yields of product **3** were 20% and 13%, respectively (entry 1 and 2, Table 2), due to the low conversion. When the equivalent of the base was increased from 1.5 equiv to 3.0 equiv, only slight increase of the yield was observed (entries 3 and 4, Table 2). However, the use of higher concentration of reagents significantly increased the yield of product to 67% (entries 5–8, Table 2). These results imply that the lower concentration of reagents enhanced side reaction of superbase with solvent, resulting in low yields.

Along with the optimal conditions (0.5 M of **2** with 52 s residence time in R1) to generate anionic intermediate of **2** at –40 °C, synthesis of ibuprofen was conducted by biphasic reaction with CO_2 (Figure 2). The flow microreactor was constructed from three micromixers (ø of M1: 250 μm, ø of M2 and M3: 500 μm) and three tube reactors (ø: 1 mm, length *L* of R1: 10 m, *L* of R2 and R3: 1 m). For the efficient biphasic reaction, the resulting solution after the metalation was slightly diluted using identical solvent (2-MeTHF) in 3.9 s of residence time in R2, because high concentration of intermediate limits the dissolution of CO_2 gas as well as the practical issue of possible clogging in flow. Three equivalents of CO_2 gas introduced through a mass flow controller formed the biphasic segment flow to produce the ibuprofen. For a gram-scale synthesis, the flow reaction was continuously operated for 10 min to produce 2.3 g of ibuprofen (57% isolated yield by recrystallization).

In conclusion, we have developed a 3-step flow-assisted synthesis of ibuprofen from *p*-xylene via in-situ generation of LICKOR-type superbase by optimizing the reaction parameters. The chemoselective C–H metalation of benzyl proton was sequentially optimized in very high yields 95% at both 1st and 2nd step by minimizing the competitive side reactions. Eventually, the gram-scale productivity of ibuprofen (2.3 g in 10 min) was successfully achieved by biphasic reaction between metalized intermediate solution and CO_2 in the microreactor. We believe that the chemoselective metalation by superbase in a flow manner could be further utilized to synthesize various bioactive molecules including drugs and APIs.

Experimental Section

Synthesis of *p*-ethyl toluene (**1**): A microfluidic system consisting of two T-shaped micromixers (M1 and M2), two tube reactors (R1 and R2) and three tube pre-temperature-retaining units (for P1 and P3, 1 mm of inner diameter (ø) and 50 cm of length (*L*); for P2, 1 mm of inner diameter and 1 m of length) were used. A solution of *p*-xylene and potassium *tert*-butoxide (0.3 M in 2-MeTHF) and a solution of *t*-BuLi (1.44 M in hexane or pentane/hexane) were individually introduced to M1 (ø: 250 μm) by syringe

pumps. The resulting solution was passed through R1 (ø: 1 mm, *L*: 50 cm) and was mixed with a solution of methyl trifluoromethanesulfonate (MeOTf; 3.0 equiv in ether) in M2 (ø: 500 µm). The resulting solution was passed through R2 (ø: 1 mm, *L*: 1 m). The flow rate for solution of *p*-xylene, *t*-BuLi and MeOTf was kept at 6.0: 1.5: 3.0 mL/min, respectively. After a steady state was reached, the product solution was collected for 30 s while being quenched with saturated aqueous NH_4Cl solution (5 mL). Then, the crude product was extracted with ether (3 x 20mL) and was washed with brine (15 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane) to give desired product **1** in 94% yield.

Synthesis of 1-ethyl-4-isobutylbenzene (**2**): A microfluidic system consisting of two T-shaped micromixers (M1 and M2), two tube reactors (R1 and R2) and three tube pre-temperature-retaining units (for P1 and P3, ø: 1 mm, *L:* 50 cm; for P2, ø: 1 mm, *L:* 1 m) were used. A solution of *p*-ethyl toluene (**1**) and potassium *tert*-butoxide (0.20 M and 0.24 M in 2-Me THF, respectively) and a solution of *t*-BuLi (1.2 M in pentane:hexane=2:1 v/v) were individually introduced to M1 (ø: 250 µm) by syringe pumps. The resulting solution was passed through R1 (ø: 1 mm, *L*: 10 m) and was mixed with a solution of 2-iodopropane (0.6 M in 2-MeTHF) in M2 (ø: 500 µm). The resulting solution was passed through R2 (ø: 1 mm, *L*: 1 m and ø: 1 mm, *L*: 4 m). The flow rate for *p*-ethyl toluene (**1**), *t*-BuLi and 2-iodopropane was kept at 6.0:1.5:3.0 mL/min, respectively. After a steady state was reached, the product solution was collected for 30 s while being quenched with saturated aqueous NH_4Cl solution (5 mL). Then, the crude product was extracted with ether (3 x 20mL) and was washed with brine (15 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane) to give desired product **2** in 93% yield.

Synthesis of ibuprofen: A microfluidic system consisting of two T-shaped micromixers (M1 and M2), two tube reactors (R1 and R2) and three tube pre-temperature-retaining units (for P1 and P3, ø: 1 mm, *L:* 50 cm; for P2, ø: 1 mm and *L:* 1 m) were used. A solution of 1-ethyl-4-isobutylbenzene (**2**) and potassium *tert*-butoxide (0.5 M and 1.5 M in 2-MeTHF) and a solution of *t*-BuLi (1.2 M in pentane:hexane=2:1 v/v) were individually introduced to M1 (ø: 250 µm) by syringe pumps. The resulting solution was passed through R1 (ø: 1 mm, *L*: 10 m) and was mixed with 2-MeTHF in M2 (ø: 500 µm). The resulting solution was passed through R2 (ø: 1 mm, *L*: 1 m). The resulting solution of which concentration was decreased was mixed in M3 with CO_2 (ø: 500 µm) and passed through R3 (ø: 1 mm, *L*: 1 m). The flow rate for 1-ethyl-4-isobutylbenzene (**2**), *t*-BuLi and 2-MeTHF was kept at 4.0:5.0:3.0 mL/min, respectively. The flow rate of CO_2 was controlled by mass flow controller (MFC) and kept at 144.4 mL/min (3.0 equiv). After a steady state was reached, the product solution was collected for 30 s while being quenched with H_2O (5 mL). Then aqueous phase was washed with ether (3 x 20 mL). After acidification with 1 M hydrochloric acid to pH 2, and then extracted with ether (3 x 20 mL). The organic layer was washed with a 1% aqueous solution of $NaHCO_3$ (2 x 10 mL) and dried. After the concentration, the crude product was recrystallized from hexane to give ibuprofen in 57% isolated yield.

Acknowledgements

We gratefully acknoledge the support from the National Research Foundation (NRF) of Korea grant funded by the Korean government (NRF-2017R1A3B1023598).

Keywords: ibuprofen • flow chemistry • superbase • reaction optimization • C-H metalation

[1] For recent reviews and articles, see: a) F. E. Valera, M. Quaranta, A. Moran, J. Blacker, A. Armstrong, J. T. Cabral, D. G. Blackmond, *Angew. Chem. Int. Ed.* **2010**, *49*, 2478; b) K. S. Elvira, X. C. Solvas, R. C. R. Wootton, A. J. deMello, *Nat. Chem.* **2013**, *5,* 905; c) S. G. Newman, K. F. Jensen, *Green. Chem.* **2013**, *15*, 1456; d) D. Ghislieri, K. Gilmore, P. H. Seeberger, *Angew. Chem. Int. Ed.* **2015**, *54*, 678; e) S. V. Ley, D. E. Fitzpatrick, R. M. Myers, C. Battilocchio, R. J. Inham, *Angew. Chem. Int. Ed.* **2015**, *54,* 10122; f) R. Porta, M. Benaglia, A. Puglisi, *Org. Process Res. Dev.* **2016**, *20*, 2; g) S. Kobayashi, *Chem. Asian J.* **2016**, *11*, 425; h) R. Singh, H. -J. Lee, A. K. Singh, D. -P. Kim, *Korean J. Chem. Eng.* **2016**, *33,* 2253; i) M. B. Plutschack, B. Pieber, K. Gilmore, P. H. Seeberger, *Chem. Rev.* **2017**, *117,* 11796; j) C. Dixon, J. Lamanna, A. R. Wheeler, *Adv. Func. Mater.* **2017,** *27*, 1604824; k) S. Budzaki, G. Miljic, M. Tisma, S. Sundaram, V. Hessel, *Applied Energy,* **2017**, *201,* 124; l) F. Fanelli, G. Parisi, L. Degennaro, R. Luisi, *Beilstein J. Org. Chem.* **2017***, 13,* 520; m) K. F. Jensen, *AIChE J*, **2017,** *63,* 858; n) Faith M. Akwi, P. Watts, *Chem. Commun.* **2018**, *54,* 13894.

[2] a) N. Kockmann, D. M. Roberge, *Chem. Eng. Technol.* **2009**, *32*, 1682; b) J. Yoshida, H. Kim, A. Nagaki, *ChemSusChem* **2011**, *4*, 331; c) B. Gutmann, D. Cantillo, C. O. Kappe, *Angew. Chem. Int. Ed.* **2015**, *54*, 6688; d) M. Baumann, I. R. Baxendale, *Beilstein J. Org. Chem.* **2015**, *11,* 1194; e) T. Tsubogo, H. Oyamada, S. Kobayashi, *Nature* **2015**, *520,* 329; f) C. J. Mallia, I. R. Baxendale, *Org. Process. Res. Dev.* **2016**, *20*, 327; g) H. P. L. Gemoets, Y. Su, M. Shang, V. Hessel, R. Luque, T. Noel, *Chem. Soc. Rev.* **2016**, *45*, 83; h) A. Adamo, R. L. Beingessner, M. Behnam, J. Chen, T. F. Jamison, K. F. Jensen, J. -C. M. Monbaliu, A. S. Myerson, E. M. Revalor, D. R. Snead, et al. *Science* **2016**, *352*, 61; i) S. Triemer, K. Gilmore, G. T. Vu, P. H. Seeberger, A. Siedel-Morgenstern, *Angew. Chem. Int. Ed.* **2018**, *57,* 5525; j) R. E. Ziegler, B. K. Desai, J. -A. Jee, B. F. Gupton, T. D. Roper, T. F. Jamison, *Angew. Chem. Int. Ed.* **2018**, *57,* 7181; k) R. Labes, C. Mateos, C. Battilocchio, Y. Chen, P. Dingwall, G. R. Cumming, J. A. Rincón, M. José Nieves-Remacha, S. V. Ley, *Green Chem.* **2019**, *21*, 59.

[3] a) T. Fukuyama, T. Kawamoto, M. Kobayashi, I. Ryu, *Beilstein J. Org. Chem.* **2013**, *9*, 1791; b) B. Pieber, D. Dallinger, C. O. Kappe, *Angew. Chem. Int. Ed.* **2013**, *52*, 1088; c) S. Newton, C. F. Carter, C. M. Pearson, L. de C Alves, H. Lange, P. Thansandote, S. V. Ley, *Angew. Chem. Int. Ed.* **2014**, *53,* 4915; d) M. R. Becker, P. Knochel, *Angew. Chem. Int. Ed.* **2015**, *54*, 12501; e) S. Vukelić, D. B. Ushakov, K. Gilmore, B. Koksch, P. H. Seeberger, *Eur. J. Org. Chem.* **2015**, *2015*, 3036; f) X. Yao, Y. Zhang, L. Du, H. Liu, S. Jiang, *Korean J. Chem. Eng.* **2016**, *33,* 2622; g) H. -H. Jeong, D. Issadore, D. Lee, *Korean J. Chem. Eng.* **2016**, *33,* 1757; h) A. -C. Bédard, A. Adamo, K. C. Aroh, M. G. Russel, A. A. Bedermann, J. Torosian, B. Yue, K. F. Jensen, T. F. Jamison, *Science,* **2018**, *361,* 1220; i) D. E. Fitzpatrick, T. Maujean, A. C. Evans, S. V. Ley, *Angew. Chem. Int. Ed.* **2018**, *57*, 15128.

[4] a) J. Yoshida, A. Nagaki, T. Yamada, *Chem. Eur. J.* **2008**, *14*, 7450; b) J. Yoshida, *Flash Chemistry: Fast Organic Synthesis in Microsystems,* Wiley-Blackwell, Oxford, **2008**; c) J. Yoshida, Y. Takahashi, A. Nagaki, *Chem. Commun.* **2013**, *49*, 9896.

[5] a) A. Nagaki, H. Kim, J. Yoshida, *Angew. Chem. Int. Ed.* **2008**, *47*, 7833; b) A. Nagaki, H. Kim, J. Yoshida, *Angew. Chem. Int. Ed.* **2009**, *48*, 8063; c) A. Nagaki, H. Kim, H. Usutani, C. Matsuo, J. Yoshida, *Org. Biomol. Chem.* **2010**, *8*, 1212; d) Y. Tomida, A. Nagaki, J. Yoshida, *J. Am. Chem. Soc.* **2011**, *133,* 3744; e) H. Kim, A. Nagaki, J. Yoshida, *Nat. Commun.* **2011**, *2*, 264; f) W. Ren, H. Kim, H. -J. Lee, J. Wang, H. Wang, D. -P. Kim, *Lab Chip* **2014**, *14,* 4263; g) H. Kim, H. -J. Lee, D. -P. Kim, *Angew. Chem. Int. Ed.* **2015**, *54*, 1877; h) H. Kim, H. -J. Lee, D. -P. Kim, *Angew. Chem. Int. Ed.* **2016**, *55*, 1422; i) S. T. R. Müller, T. Hokamp, S. Ehrmann, P. Hellier, T. Wirth, *Chem. Eur. J.* **2016**, *22,* 11940; j) H. Kim, K. Inoue, J. Yoshida, *Angew. Chem. Int. Ed.* **2017**, *56,* 7863.

[6] The Top 300 Drugs of 2016 in the United States for details see website: https://clincalc.com/DrugStats/Top300Drugs.aspx

[7] For selected patent references towards ibuprofen, see: a) D. A. Ryan, U.S. Patent US 4,929,773, May 29, **1990**; b) D. D. Lindley, T. A. Curtis, T. R. Ryan, E. M. de la Garza, C. B. Hilton, T. M. Kenesson, U.S. Patent

US 5,068, 448, Nov 26, **1991**; c) V. Elango, M. A. Murphy, B. L. Smith, K. G. Davenport, G. Mott, E. G. Zey, G. L. Moss, U.S. Patent US 4,981,995, Jan 1, **1991**.

[8] a) A. R. Bogdan, S. L. Poe, D. C. Kubis, S. J. Broadwater, D. T. McQuade, *Angew. Chem. Int. Ed.* **2009**, *48*, 8547; b) D. R. Snead, T. F. Jamison, *Angew. Chem. Int. Ed.* **2015**, *54,* 983; c) M. Baumann, I. R. Baxendale, *React. Chem. Eng.* **2016**, *1,* 147.

[9] a) S. Takagishi, M. Schlosser, *Synlett* **1990**, 119; b) F. Faigl, M. Schlosser, *Tetrahedron Lett.* **1991**, *32,* 3369; c) M. Schlosser, H. Geneste, *Chem. Eur. J.* **1998**, *4,* 1969.

[10] a) M. Schlosser, *J. Organomet. Chem.* **1967**, *8,* 9; b) L. Lochmann, J. Trekoval, *J. Organomet. Chem.* **1987**, *326***,** 1; c) M. Schlosser, *Pure & Appl. Chem.* **1988**, *60*, 1627; d) M. Schlosser, J. H. Choi, S. Takagishi, *Tetrahderon* **1990**, *46*, 5633; e) L. Lochmann, H. Jakubův, L. Brandsma, *Collect. Czech. Chem. Commun.* **1993**, *58,* 1445; f) M. Schlosser, F. Faigl, L. Franzini, H. Geneste, G. Katsoulos, G. -F. Zhong, *Pure & Appl. Chem.* **1994**, *66,* 1439; g) M. Schlosser, *Mod. Synth. Methods,* **1992**, *6*, 227; h) M. Schlosser, H. Geneste, *Chem. Eur. J.* **1998**, *4,* 1969; i) H. Kim, Z. Yin, H. Sakurai, J. Yoshida, *React. Chem. Eng.* **2018**, *3*, 635.

[11] a) A. Nagaki, Y. Takahashi, J. Yoshida, *Chem. Eur. J.* **2014**, *20,* 7931; b) J. Wu, X. Yang, Z. He, X. Mao, T. A. Hatton, T. F. Jamison, *Angew. Chem. Int. Ed.* **2014**, *153*, 8416.

[12] J. Clayden, S. A. Yasin, *New J. Chem.* **2002**, *26,* 191.

[13] S. Rosner, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2016**, *55,* 10463.

[14] a) D. M. Hobbs, F. J. Muzzio, *Chem. Eng. J.* **1997**, *67*, 153; b) M. Regner, K. Östergren, C. Tragärdh, *Ind. Eng. Chem. Res.* **2008**, *47,* 3030; c) S. Wang, X. Huang, and C. Yang, *Lab Chip* **2011**, *11,* 2081; d) H. Meng, F. Wang, Y. Yu, M. Song, J. Wu, *Ind. Eng. Chem. Res.* **2014**, *53,* 4084.

[15] a) A. Nagaki, D. Ichinari, J. Yoshida, *J. Am. Chem. Soc.* **2014**, *136*, 12245; b) H. Kim, K. -I. Min, K. Inoue, D. J. Im, D. -P. Kim and J. Yoshida, *Science* **2016**, *352*, 691; c) H. Kim, Y. Yonekura, J. Yoshida, *Angew. Chem. Int. Ed.* **2018**, *57,* 4063.

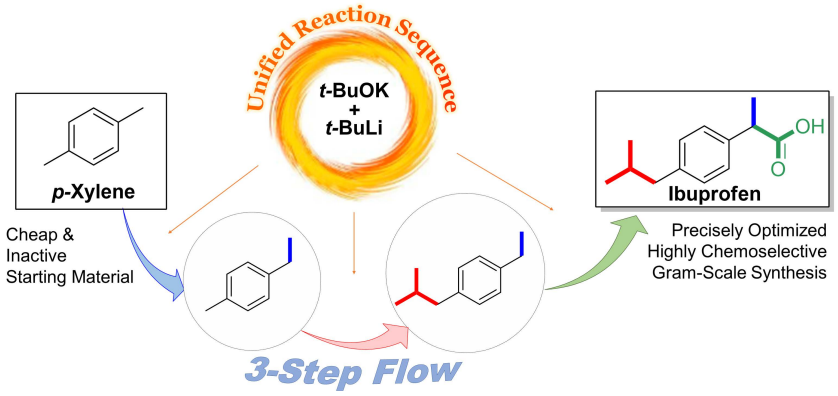
[16] a) A. Nagaki, E. Takizawa, J. Yoshida, *Chem. Eur. J.* **2010**, *16,* 14149; b) T. Asai, A. Takata, A. Nagaki, J. Yoshida, *ChemSusChem,* **2012**, *5,* 339; c) H. -J. Lee, H. Kim, D. -P. Kim, *Chem. Commun.* **2018,** *54*, 547.

10.1002/chem.201903267

WILEY-VCH

Entry for the Table of Contents

COMMUNICATION



H.-J. Lee, H. Kim, D.-P. Kim**

Page No. – Page No.
From *p*-Xylene to Ibuprofen in Flow: 3-Step Synthesis via Unified Sequence of Chemoselective C–H Metalations