Ex-Situ Generation and Synthetic Utilization of Bare Trifluoromethyl Anion in Flow via Rapid Biphasic Mixing

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The trifluoromethyl (CF_3) group has been recognized as an important functional group in medicinal chemistry, because it can improve the therapeutic efficacy and metabolic stability of bioactive molecules. Additionally, it has been discovered that it can play a significant role in enhancing the binding affinity to intracellular proteins, which is crucial for the pharmacological efficacy of organic compounds. Therefore, the development of pharmaceuticals containing the trifluoromethyl functional group has been a booming research field, and according to the World Drug Index (WDI), fluorine-containing new drugs are leading the trend. Professor Dong-Pyo Kim at the Pohang University of Science and Technology (Republic of Korea) and co-workers have been working on novel approaches to CF_3-containing molecules, which are exclusively man-made, resulting in this paper in *Nature Communications*. Professor Kim said: "Among the extensive synthetic strategies for introducing the CF_3 group, various synthetic methodologies for nucleophilic trifluoromethylation have been developed, but there is no better way than to directly use fluoroform (CF_3H) as the simplest precursor of the CF_3 group in the viewpoint of atom- and step-economy (Figure 1a). However, the synthetic utility of gaseous CF_3H still remains limited because of its difficult handling and low reactivity." Above all, as remarked by Professor Kim, the reaction intermediate of the nucleophilic trifluoromethylation, the CF_3 anion (CF_3^-), rapidly decomposes into difluorocarbene ($:CF_2$) and fluoride anion. "To avoid these issues, many researchers have adopted the *in-situ* quenching method (Figure 1b), where the reaction substrate (or partner)

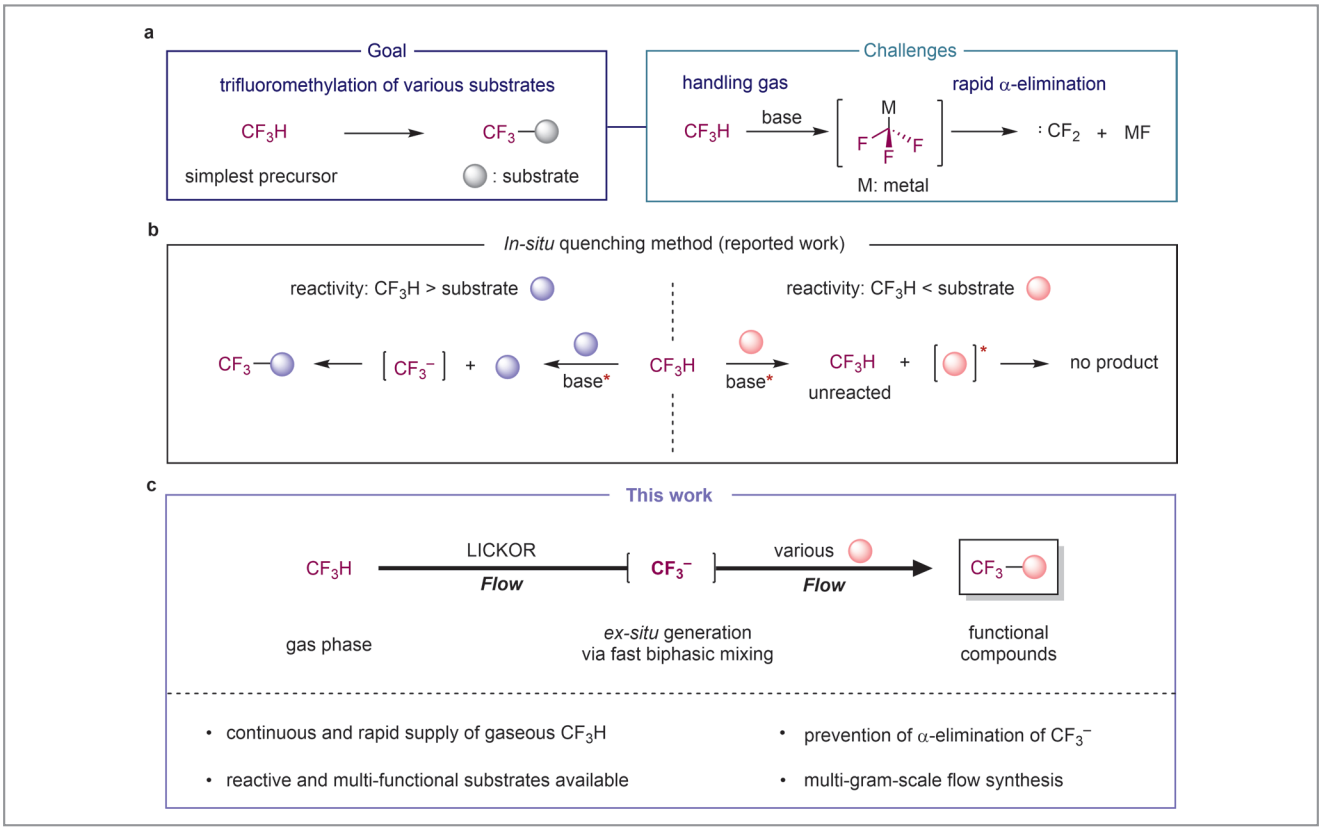

Figure 1 Methods for nucleophilic trifluoromethylation using CF_3H

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coexists with CF_3^-," explained Professor Kim. He continued: "Nevertheless, this *in-situ* quenching requires additional reagents for the stabilization of CF_3^- and has fatal problems of narrowing down the reaction scope and selectivity when this reaction substrate is hardly compatible with the reaction conditions for generating the desired intermediate. To overcome the critical limitations of the *in-situ* quenching method and preserve the original strong reactivity of the unstable CF_3^-, the latter should be formed in the absence of any reaction partner or stabilizing reagent, prior to its subsequent reaction (i.e., *ex-situ* quenching method) (Figure 1)."

Professor Kim emphasized that despite the fact that the ex-situ quenching method is a powerful approach for synthesizing and utilizing CF_3^-, it has not been applicable to the generation of CF_3^- from CF_3H. This is because it is challenging to achieve both a fast biphasic mixing of gaseous CF_3H with liquid deprotonating reagent within the short lifetime of CF_3^- and a precise time-control for the external trapping reaction with generated CF_3^-, even using flow-type reactors that are well-known to afford rapid mixing efficacy unachievable in flask. "In this study, we designed and fabricated a specialized gas-liquid flow device (GLD) to address the long-standing problem in gas-liquid chemical processes," said Professor Kim. He continued: "Based on the fact that efficient biphasic mixing for rapid dissolution can be achieved by a large contact area between gas and liquid with a smaller size gas bubble, we conceptually designed flow channel structured dissolvers composed of highly permeable nano-porous membrane sandwiched between upper and lower channels with staggered baffle structure (Figure 2). The baffle structured channels induced chaotic advection involving rapid distortion of the fluid interface when the gas-liquid mixture flows over the upper and the lower channels, while the nano-porous membrane in the middle acted as a static mixer and bubble breaker by preventing coalescence of gas segments which must severely reduce the contact area. By developing this novel gas-liquid mixing reactor concept, we were able to efficiently generate the CF_3^- intermediate solely and subsequently introduce the reactant compound to perform the fluorination reaction."

With this method, the researchers found that the reaction with various electrophilic substrates was successfully achieved in 51–94% yield, which is quite remarkable. Professor Kim remarked: "In particular, the powerful advantage of the *ex-situ* method was demonstrated by the chemoselective nucleophilic addition with substrates bearing two electron-withdrawing groups (Scheme 1). Additionally, the multi-gram

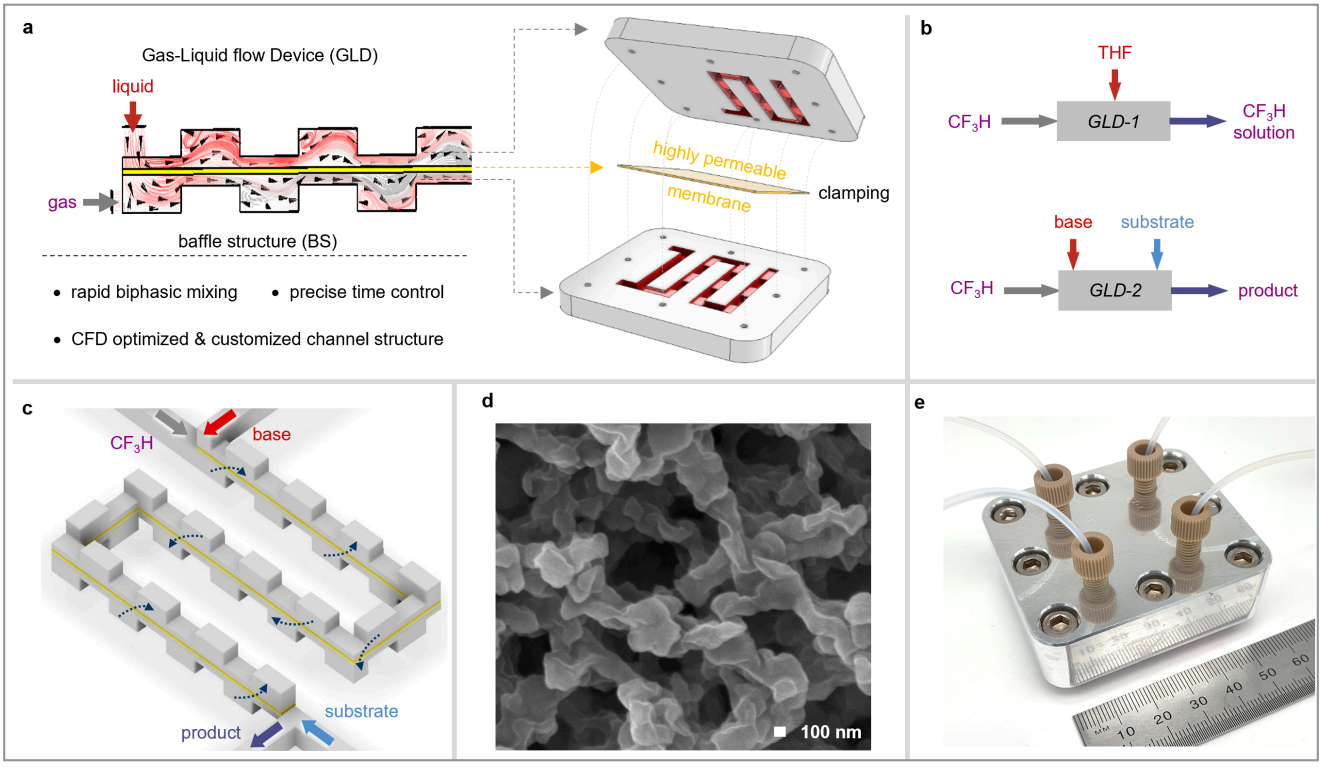
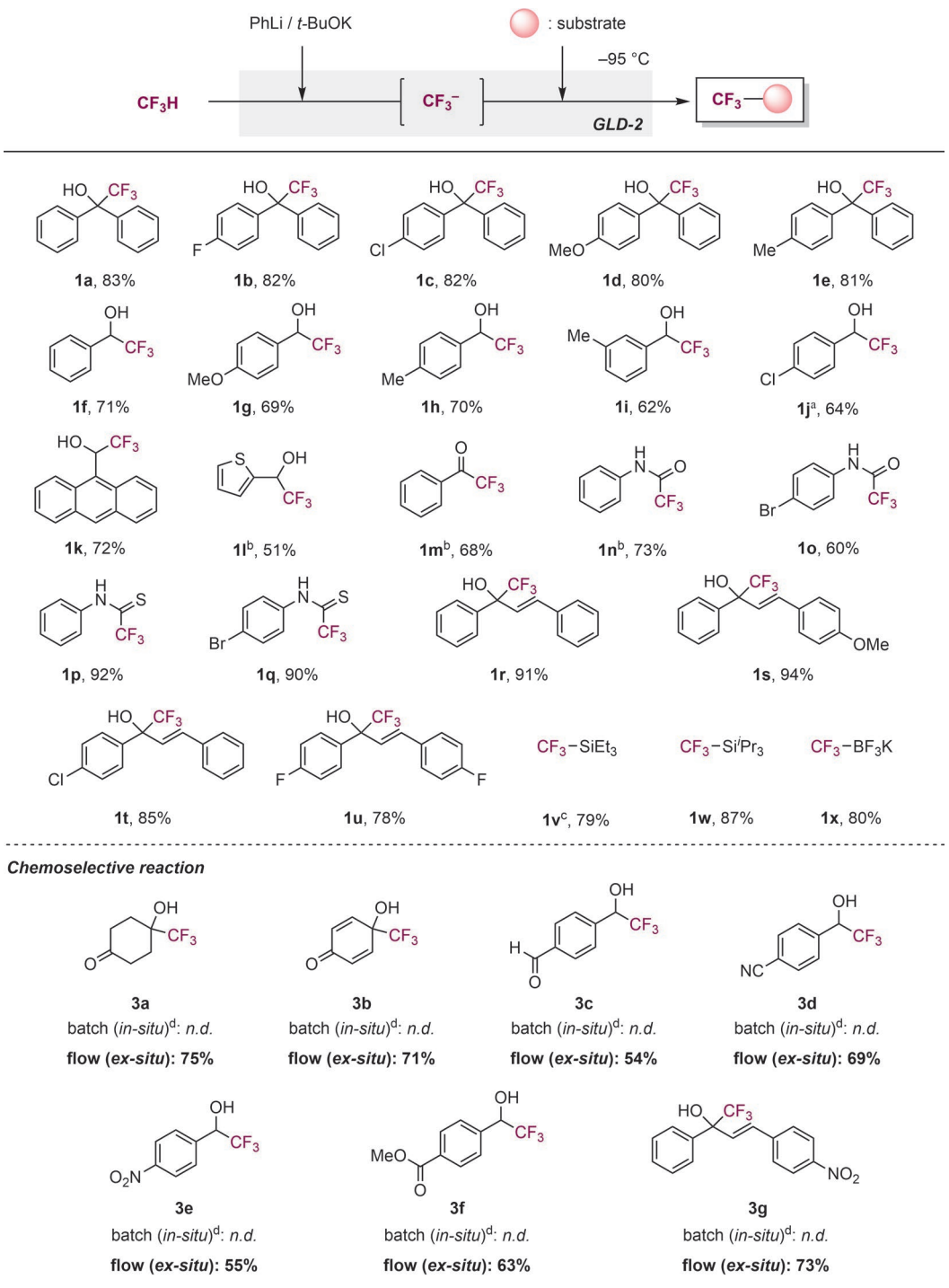


Figure 2 Design and fabrication of gas-liquid flow device (GLD) including highly permeable membrane and staggered baffle channel



Scheme 1 The reaction of bare CF_3^- with various electrophilic substrates in GLD-2. Isolated yields are given. [a] The resulting CF_3^- solution was allowed to react with an electrophile at –50 °C. [b] The resulting CF_3^- solution was allowed to react with an electrophile at –78 °C. [c] TESCl (2 equiv) was used. [d] The yield was determined by ^{1}H NMR spectroscopy using an internal standard.

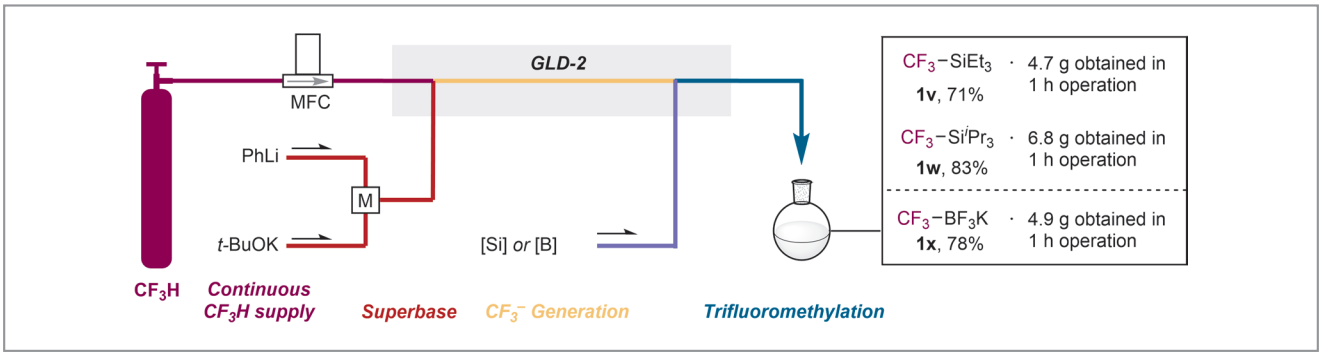


Figure 3 The multi-gram-scale synthesis using an integrated flow system involving GLD-2

synthesis was successfully conducted within a 1-hour operation of our gas-liquid flow device to synthesize the three important chemical reagents which are used for nucleophilic trifluoromethylation (71–83%, 4.7–6.8 g/h) (Figure 3). The device enabled the one-flow CF_3H supply, the formation of superbase, CF_3^- generation, and trifluoromethylation. The method allows us not only to reveal accurate information on the lifetime and stability of CF_3^- but also to conduct the chemoselective reaction with various substrates, thus addressing a fundamental obstacle with the *in-situ* quenching method."

"In summary, to the best of our knowledge, this is the first report involving the generation and utilization of CF_3^- from CF_3H via the *ex-situ* quenching method," said Professor Kim, adding: "We expected that the well-established flow device would rationalize the *ex-situ* generation and utilization of CF_3^- from the rapid gas-liquid mixing between the strong base and CF_3H gas, the simplest trifluoromethylation resource. With this device, the *ex-situ* generation and utilization of CF_3^- was conducted within only 0.44 seconds even under highly cryogenic conditions, and various electrophiles were also reacted with CF_3^- anion in a much higher yield, compared to the *in-situ* method. Moreover, we successfully achieved the chemoselective reaction with multi-functionalized electrophiles, which were only successfully conducted by the ex-situ quenching method in the flow reaction." Professor Kim concluded: "We believe that this approach provides an advanced reaction platform for the utilization of various unstable intermediates from the biphasic reaction."

About the authors

Prof. D. P. Kim

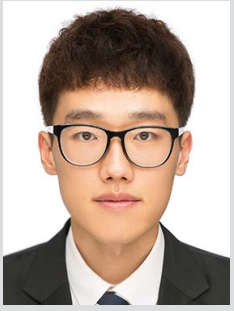
Dong-Pyo Kim graduated with a BSc in chemistry from Sogang University (Seoul) in 1985. Then he moved to the USA where he was awarded his PhD in 1991 from Temple University before becoming a postdoctoral researcher at the University of Illinois from 1991–1993. He then returned to Korea and took up a post as a senior researcher at the Korea Research Institute of Chemistry. In 1995 he moved on to a position as Professor of Applied Chemistry at Chungnam National University (Korea) and was promoted to head of the Center of Applied Microfluidic Chemistry in 2008. In 2012 he was also appointed as Professor of Chemical Engineering at the Pohang University of Science & Technology (Korea). In addition, in 2017 he became Head of the Center for Intelligent Microprocess of Pharmaceutical Synthesis and in 2022 he became the CTO of Flow-medi. He still holds the last three positions.

Prof. HJ Kim

HeeJin Kim was a JSPS Research Fellow in 2010–2011 and spent the first six months of 2011 as a visiting Research Fellow at the Massachusetts Institute of Technology (USA). Following this, he returned to Korea and in lieu of military service spent two years (2011–2013) as a Research Fellow at the Korea Institute of Science and Technology (KIST) and a further two years at the Pohang University of Science and Technology (POSTECH) from 2013–2015. In 2015 he moved to Kyoto University (Japan) as a Research Assistant Professor. Later that same year, he moved back to Korea and took up a post as Assistant Professor at Korea University before being promoted to Associate Professor at the same university in 2020.

Dr. H. J. Lee

Hyune-Jea Lee completed his PhD at the Pohang University of Science and Technology (POSTECH, Korea) in 2019. He then spent six months as a postdoctoral researcher at the same university. In 2019, he moved to Korea University (Korea) for three years as a postdoctoral researcher. Then in 2022 he moved to the Samsung Advanced Institute of Technology (SAIT, Korea) as a researcher.



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