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Full Paper

Generation and Reactions of Pyridyllithiums via Br/Li Exchange Reactions Using Continuous Flow Microreactor Systems

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A continuous flow microreactor method for generating and carrying out reactions on pyridyllithiums has been developed based on Br/Li exchange reactions of bromopyridines and dibromopyridines. The reactions can be carried out without using cryogenic conditions by virtue of short residence times and efficient heat transfer, while very low temperatures such as −78 or −110°C are required for conventional batch macro methods. Moreover, sequential introduction of two different electrophiles has been successfully achieved using dibromopyridines in an integrated flow microreactor system composed of four micromixers and four microtube reactors.

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Introduction

Substituted pyridines have attracted significant research interest not only because there are many biologically active pyridine-containing natural products and pharmaceuticals but also because many pyridine-containing compounds are used in materials chemistry and supramolecular chemistry.[1] The use of pyridyl metals offers an attractive and promising route to these compounds.[2] Br/Li exchange reactions of bromopyridines serve as a powerful method for generating pyridyl metals.[3,4] However, these reactions often require very low temperatures such as −78 or −110°C, because the reactions at higher temperatures lead to side reactions such as deprotonation, addition to the pyridine ring, and lithium migration.[5] Thus, the requirement for energy-consuming and high-cost cryogenic conditions causes severe limitations for the industrial use of Br/Li exchange reactions. Therefore, the development of a method that does not require cryogenic conditions has been highly desired from a viewpoint of industrial production of substituted pyridines.

Flow microreactors[6–8] are attractive for synthetic applications because heat and mass transfer in these devices is considerably more efficient than in larger batch flasks because of short diffusion paths and a high surface-to-volume ratio. By virtue of these characteristic features fast and highly exothermic reactions can be favourably performed in flow microreactors.[9] It is also noteworthy that residence times in flow microreactors can be precisely tuned to achieve maximum yields and selectivities.[10,11] In fact, recently, we have reported that generation of highly unstable organolithiums such as aryllithiums bearing electrophilic subsitutents,[12] oxyranyllithiums,[13] aziridinyllithiums,[14] perfluoroalkyllithiums,[15] and chiral organolithiums[16] followed by subsequent reactions with electrophiles could be conducted in flow microreactors. These findings prompted us to study the generation of pyridyllithiums and their reactions with electrophiles using flow microreactors.[17] In a preliminary communication, we reported that bromopyridyllithiums are easily generated from dibromopyridines using flow microreactors at much higher temperatures than those required for conventional methods using batch macro reactors.[18] We also reported that the space integration[19] of two sequences consisting of Br/Li exchange followed by a reaction with an electrophile serves as an effective method for synthesising disubstituted pyridines from dibromopyridines. We wish to report herein the full details of this study.

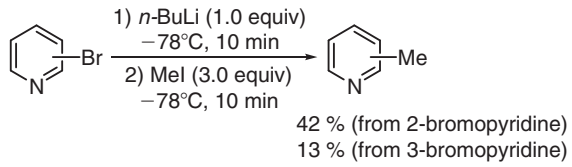
Results and Discussion

Generation and Reactions of Pyridyllithiums via Br/Li Exchange of Bromopyridines

First, we examined Br/Li exchange reactions of bromopyridines to generate the corresponding pyridyllithiums. It is well known that Br/Li exchange reactions of bromopyridines should be performed at very low temperatures such as −78 or −100°C, if we use a conventional batch macro reactor. To confirm this, we reexamined the Br/Li exchange reaction of 2-bromopyridine and 3-bromopyridine in a conventional batch macro reactor (Scheme 1). Thus, a solution of *n*-BuLi (0.40 M in hexane) was added dropwise (1 min) to a solution of each bromopyridine (0.10 M in THF) in a 25 mL round-bottomed flask at −78°C. The resulting solution was stirred for 10 min at the same temperature, and a solution of iodomethane (0.60 M in THF) was added. After being stirred for 10 min the solution was analysed by gas

chromatography, which indicated that the yields of the desired products, i.e. the respective methylpyridine was very low, presumably because of decomposition of the pyridyllithium species. Pyridine was also detected as a byproduct by gas chromatography-mass spectrometry (GCMS) (see Supplementary Material for details).

Next, we examined the reactions using a flow microreactor system consisting of two T-shaped micromixers (**M1** and **M2**) and two microtube reactors (**R1** and **R2**) (Fig. 1). A solution of each bromopyridine (0.10 M in THF) (flow rate: 6.00 mL min^{-1}) and a solution of *n*-BuLi (0.40 M in hexane) (flow rate: 1.50 mL min^{-1}) was introduced to **M1** (internal diameter $\phi = 250$ μm) by syringe pumps. The mixture was passed through **R1** and was introduced to **M2** ($\phi = 500$ μm), where a solution of iodomethane (0.60 M in THF) (flow rate: 3.00 mL min^{-1}) was introduced. The resulting mixture was passed through **R2** ($\phi = 1000$ μm, $L = 200$ cm). The residence time in **R1** (t^{R1}) was adjusted by changing the length and the diameter of **R1** with a fixed flow rate. After a steady-state was reached, an aliquot of the product solution was taken for 30 s. The yields of methylpyridines were determined by GC.



Scheme 1. Br/Li exchange of bromopyridines using *n*-BuLi followed by the reaction with iodomethane using a batch macro reactor.

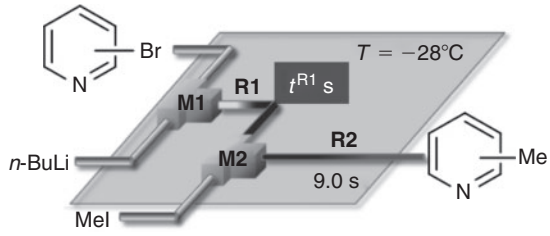


Fig. 1. A flow microreactor system for Br/Li exchange of bromopyridines using *n*-BuLi followed by the reaction with iodomethane. T-shaped micromixers: **M1** ($\phi = 250$ μm) and **M2** ($\phi = 500$ μm), microtube reactors: **R1** and **R2** ($\phi = 1000$ μm, $L = 200$ cm). Flow rate of solution of bromopyridine (0.10 M in THF): 6.00 mL min^{-1}; flow rate of a solution of *n*-BuLi (0.40 M in hexane): 1.50 mL min^{-1}, flow rate of a solution of iodomethane (0.60 M in THF): 3.00 mL min^{-1}.

Notably, methylpyridines were obtained in high yields even at −28°C with short residence times as shown in Fig. 2. The yield of 3-methylpyridine decreased with an increase in t^{R1}, although the yield of 2-methylpyridine did not change appreciably. Presumably 3-pyridyllithium is less stable than 2-pyridyllithium and decomposition took place to some extent with longer residence times. The reactions at higher temperatures such as 0°C led to lower yields ($t^{R1} = 0.055$ s: 57 % for 2-methylpyridine; 10 % for 3-methylpyridine), presumably because the decomposition took place faster (see Supplementary Material for details).

Under the optimised conditions ($t^{R1} = 0.055$ s, $T = -28$°C), the reactions with various electrophiles such as iodomethane, chlorotrimethylsilane, and benzaldehyde were examined. As shown in Table 1, the reactions took place successfully and the corresponding products were obtained in good yields. Moreover, the reaction of other bromopyridine derivatives such as 2-bromo-3-methylpyridine, 2-bromo-5-methylpyridine, and 2-bromo-6-methylpyridine could be achieved, giving the corresponding products in good yields. In the cases of bromomethylpyridines, longer residence times such as $t^{R1} = 0.78$ s gave better yields. Presumably, the electron-donating methyl group decelerated the Br/Li exchange reaction, and a longer residence time was required for complete exchange.

Generation and Reactions of Bromopyridyllithiums via Br/Li Exchange of Dibromopyridines

We have been interested in the sequential introduction of two electrophiles by space integration of two sequences consisting of Br/Li exchange followed by reactions with electrophiles, starting from dibromopyridines. This type of transformation serves as one of the most straightforward methods for synthesising disubstituted pyridines (Scheme 2).

Thus, we examined the Br/Li exchange of dibromopyridines to generate bromopyridyllithiums, because this is the first step of the desired transformation. At first, we focussed on the Br/Li exchange reaction of 2,3-dibromopyridine. It is known that this reaction in a conventional batch macro reactor gives a complex mixture even at −78°C, presumably because of extremely fast decomposition of 2-bromo-3-pyridyllithium.[20] To confirm this, we examined the reaction using a conventional batch macro reactor (Scheme 3). A solution of *n*-BuLi (0.40 M in hexane) was added dropwise (1 min) to a solution of 2,3-dibromopyridine (0.10 M in THF) in a 25 mL round-bottom flask at temperatures

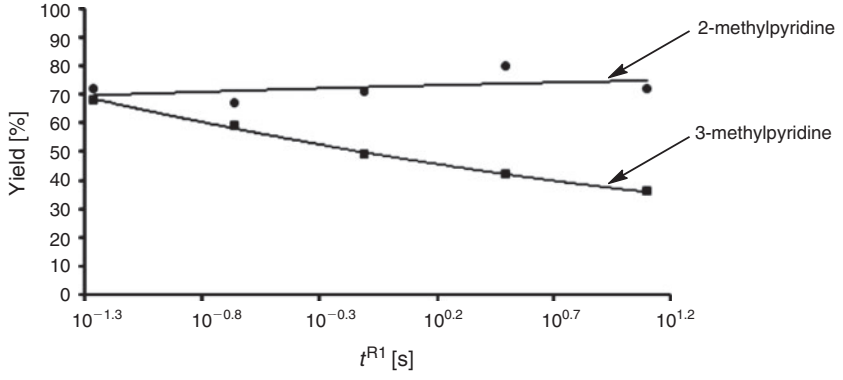
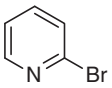
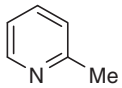
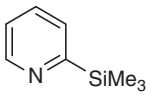
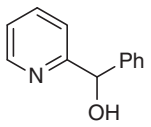
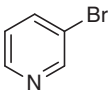
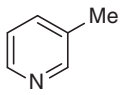
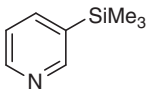
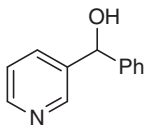
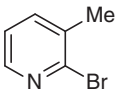
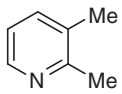
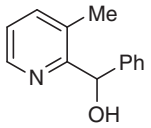
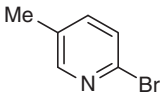
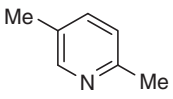
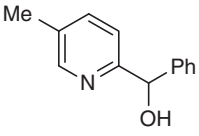
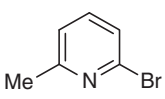
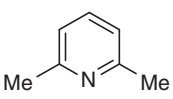
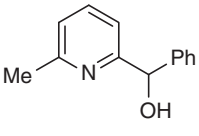
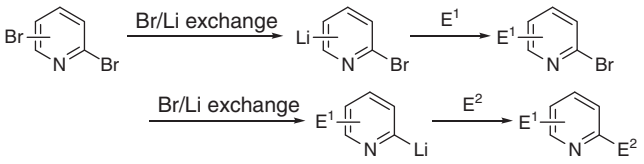


Fig. 2. Plots of the yield of methylpyridine against the residence time (t^{R1}) in the Br/Li exchange of bromopyridines using *n*-BuLi followed by the reaction with iodomethane in the flow microreactor at −28°C.

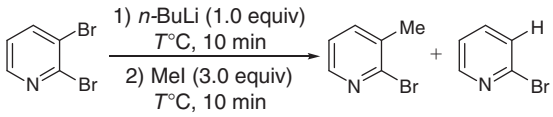
Table 1. Br/Li exchange of bromopyridines followed by the reactions with an electrophile using flow microreactor systems[A]

Bromopyridine	Reaction condition		Electrophile	Product	Yield [%]
	T [°C]	t^{R1} [s]			
	−28	0.055	MeI		84
	−28	0.055	Me_3SiCl		78
	−28	0.055	PhCHO		70[B]
	−28	0.055	MeI		68
	−28	0.055	Me_3SiCl		78
	−28	0.055	PhCHO		70[B]
	−28	0.055	MeI		43
	−28	0.78			76
	−28	0.78	PhCHO		74[B]
	−28	0.055	MeI		47
	−28	0.78			90
	−28	0.78	PhCHO		76[B]
	−28	0.055	MeI		53
	−28	0.78			92
	−28	0.78	PhCHO		67[B]

[A]Solutions of the bromopyridine (0.10 M in THF), *n*-BuLi (0.40 M in hexane), and an electrophile (0.24 M in THF) were reacted in the flow microreactor system. The yields were determined by GC analysis using an internal standard (pentadecane).
[B]Isolated yield.



Scheme 2. Space integration of two sequences consisting of Br/Li exchange followed by reactions with electrophiles.



Scheme 3. Br/Li exchange of 2,3-dibromopyridine using *n*-BuLi followed by the reaction with iodomethane in a batch macro reactor.

Table 2. The Br/Li exchange reaction of 2,3-dibromopyridine with *n*-BuLi using a batch macro reactor[A]

Temperature T [°C]	Conversion [%] 2,3-dibromopyridine	Yield [%] 2-bromo-3-methylpyridine	Yield [%] 2-bromopyridine
−78	100	48	24
−48	100	19	26
−28	100	0	34
0	100	0	21

[A]The yields of 2-bromo-3-methylpyridine and 2-bromopyridine, and the conversion of 2,3-dibromopyridine were determined by GC analysis using an internal standard (pentadecane).

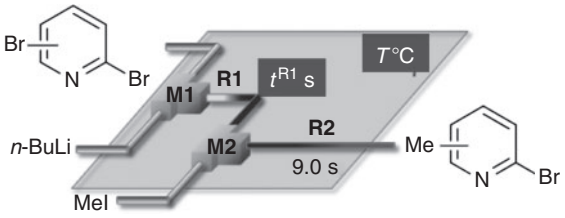


Fig. 3. A flow microreactor system for Br/Li exchange of dibromopyridine using *n*-BuLi followed by the reaction with iodomethane. T-shaped micromixers: **M1** ($\phi = 250\,\mu m$) and **M2** ($\phi = 500\,\mu m$), microtube reactors: **R1** and **R2** ($\phi = 1000\,\mu m$, $L = 200\,cm$). Flow rate of a solution of dibromopyridine (0.10 M in THF): 6.00 mL min^{-1}, flow rate of a solution of *n*-BuLi (0.40 M in hexane): 1.50 mL min^{-1}, flow rate of a solution of iodomethane (0.60 M in THF): 3.00 mL min^{-1}.

such as −78, −48, −28, and 0°C. The resulting solution was stirred for 10 min at the same temperature, and a solution of iodomethane was added. After being stirred for 10 min, the solution was analysed by GC. In addition to the desired product, i.e. 2-bromo-3-methylpyridine, 2-bromopyridine was obtained as a byproduct, indicating that protonation of 2-bromo-3-pyridyllithium took place, although the detailed mechanism is not clear at present.

Reactions at −78°C gave the desired product 2-bromo-3-methylpyridine in 48% yield (Table 2). Increased reaction temperatures caused a decrease in the yield, and 2-bromo-3-methylpyridine was not obtained at all above −28°C.

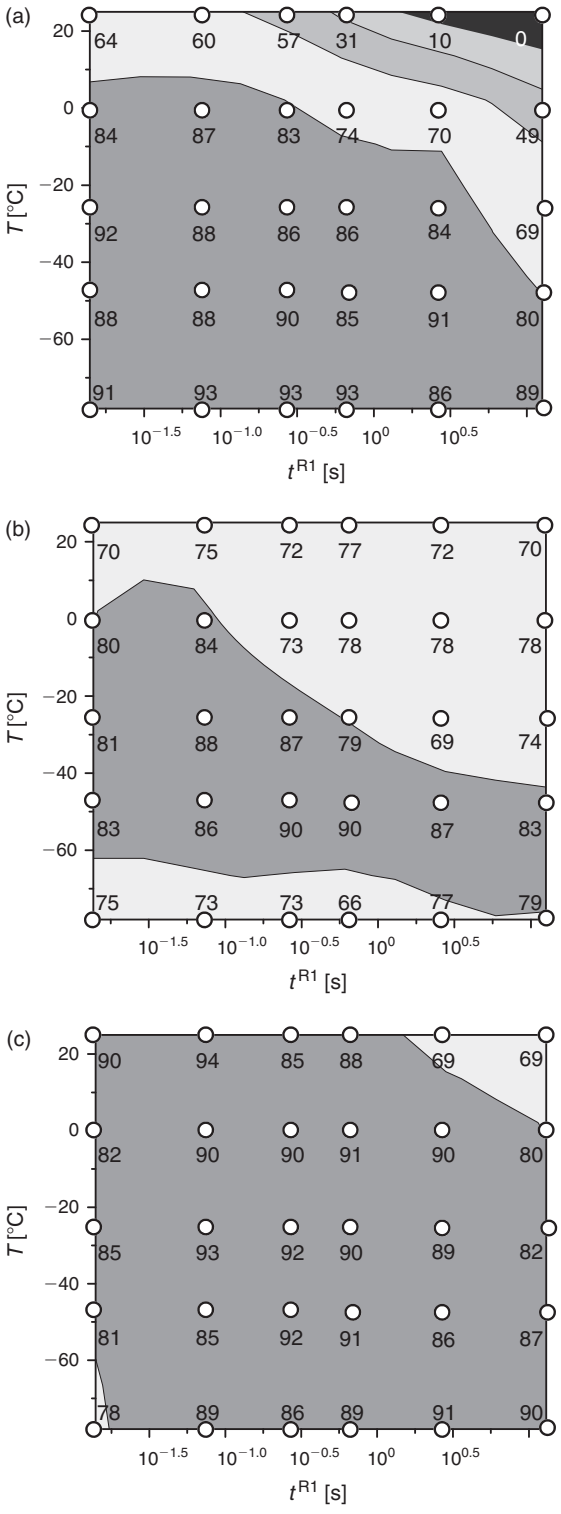
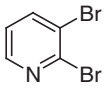
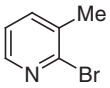
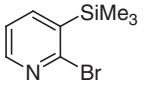
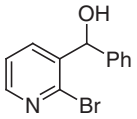
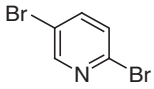
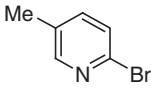
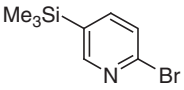
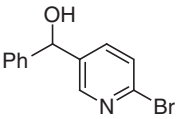
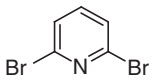
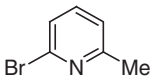
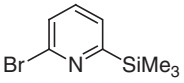
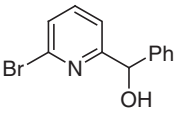


Fig. 4. Effect of the temperature (T) and the residence time (t^{R1}) in Br/Li exchange of (a) 2,3-dibromopyridine, (b) 2,5-dibromopyridine, and (c) 2,6-dibromopyridine, followed by the reaction with iodomethane using the flow microreactor system. Contour maps with scatter overlay of the yields of bromomethylpyridines (%), which are indicated by numbered circles.

Next, the reaction was carried out using a flow microreactor system consisting of two T-shaped micromixers (**M1** and **M2**) and two microtube reactors (**R1** and **R2**) shown in Fig. 3.

The yields of 2-bromo-3-methylpyridine obtained at various residence times (t^{R1} s) and reaction temperatures (T °C) are

Table 3. The Br/Li exchange of dibromopyridines followed by reaction with an electrophile using the flow microreactor systems[A]

Bromopyridine	Reaction condition T [°C]	t^{R1} [s]	Electrophile	Product	Yield [%]
	0	0.055	MeI		87
			Me_3SiCl		80
			PhCHO		78
	0	0.055	MeI		84
			Me_3SiCl		87
			PhCHO		79
	0	0.055	MeI		94
			Me_3SiCl		89
			PhCHO		80

[A]Solution of the dibromopyridine (0.10 M in THF), *n*-BuLi (0.40 M in hexane), and an electrophile (0.24 M in THF) were reacted in the flow microreactor system. The yields were determined by GC analysis using an internal standard (pentadecane).

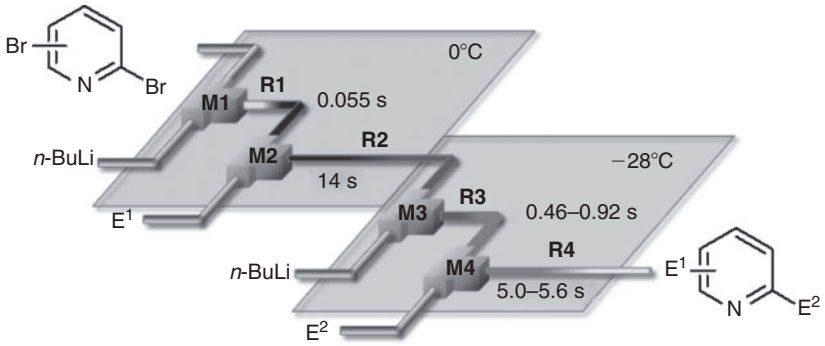
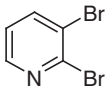
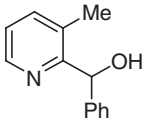
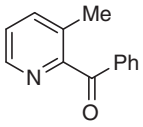
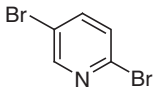
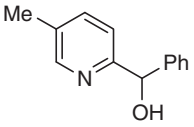
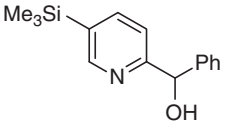
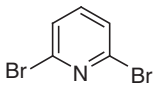
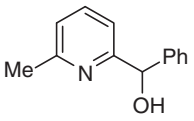
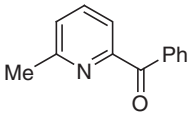
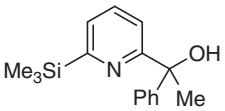


Fig. 5. An integrated flow microreactor system for sequential introduction of two electrophiles. T-shaped micromixers: **M1** ($\phi = 250\,\mu m$), **M2** ($\phi = 500\,\mu m$), **M3** ($\phi = 500\,\mu m$), **M4** ($\phi = 500\,\mu m$), and microtube reactors: **R1** ($\phi = 500\,\mu m$, L = 3.5 cm), **R2** ($\phi = 1000\,\mu m$, L = 310 cm), **R3** ($\phi = 1000\,\mu m$, $L = 12.5$ or 25 cm), and **R4** ($\phi = 1000\,\mu m$, $L = 200$ cm). A solution of dibromopyridine (0.10 M in THF): 6.00 mL min^{-1}, flow rate of first *n*-BuLi (0.40 M in hexane): 1.50 mL min^{-1}, flow rate of a solution of E^1 (0.24 M in THF): 3.00 mL min^{-1}, flow rate of second *n*-BuLi (0.40 M in hexane): 2.25 mL min^{-1}, flow rate of a solution of E^2 (0.24 M in THF): 4.00, 5.00 or 6.00 mL min^{-1}.

Table 4. Sequential introduction of two electrophiles using the integrated flow microreactor system[A]

Dibromopyridine	E^1	E^2	Yield [%][E]	Productivity [g h^{-1}]
	MeI[B]	PhCHO[B]	 68[F]	4.85
	MeI[C]	PhCN[C]	 47	3.35
	MeI	PhCHO	 75[G]	5.39
	Me_3SiCl[B]	PhCHO[B]	 51[H]	4.75
	MeI	PhCHO	 67	4.80
	MeI[D]	PhCN[D]	 56	3.95
	Me_3SiCl	PhC(O)Me	 56	5.48

[A]Reactions were carried out under the following conditions unless otherwise stated. Flow rate of a solution of dibromopyridine (0.10 M in THF): 6.00 mL min^{-1}; flow rate of the first solution of *n*-BuLi (0.40 M in hexane): 1.50 mL min^{-1}; flow rate of a solution of E^1 (0.24 M in THF): 3.00 mL min^{-1}; flow rate of the second solution of *n*-BuLi (0.40 M in hexane): 2.25 mL min^{-1}; flow rate of a solution of E^2 (0.24 M in THF): 4.00 mL min^{-1}, **R1**: $\phi = 500\,\mu m$, $L = 3.5$ cm, **R2**: $\phi = 1000\,\mu m$, $L = 310$ cm, **R3**: $\phi = 1000\,\mu m$, $L = 25$ cm, **R4**: $\phi = 1000\,\mu m$, $L = 200$ cm.
[B]**R3**: $\phi = 1000\,\mu m$, $L = 12.5$ cm.
[C]Flow rate of a solution of E^2: 5.00 mL min^{-1}.
[D]Flow rate of a solution of E^2: 6.00 mL min^{-1}.
[E]Isolated yields. Unless otherwise stated, the purity of product was >97 % as judged by GC analysis.
[F]The purity was 88 % (by GC). 3-(α-Hydroxybenzyl)-2-methylpyridine was observed by GCMS as a significant byproduct (9 %, GC).
[G]The purity was 81 % (by GC). 5-(α-Hydroxybenzyl)-2-methylpyridine was observed by GCMS as a significant byproduct (9 %, GC). 2- and 3-Hydroxybenzylpyridines were also observed by GCMS (total 10 %, GC).
[H]The purity was 93 % (by GC). 5-(α-Hydroxybenzyl)-2-trimethylsilylpyridine was observed by GCMS as a significant byproduct (7 %, GC).

plotted in Fig. 4. It should be noted that high yields were obtained even at 0°C by choosing an appropriate residence time. The increase in t^{R1} caused a decrease in the yield probably because of the decomposition of 2-bromo-3-pyridyllithium. In addition, we found that the reactions of 2,5-dibromopyridine[21] and 2,6-dibromopyridine[22] also gave the corresponding methylated products in high yields at 0°C by tuning the residence time. Use of the flow microreactor system enabled the reaction without using cryogenic conditions. Moreover, Fig. 4 also shows that the stability of 2-bromo-3-pyridyllithium was lower than that of 2-bromo-5-pyridyllithium and 2-bromo-6-pyridyllithium.

Under these optimised reaction conditions ($T = 0$°C, $t^{R1} = 0.055$ s), the reactions of dibromopyridyllithiums with other electrophiles were examined, and the corresponding 3-substituted 2-bromopyiridines were obtained in high yields (Table 3).

Space Integration of Two Sequences Consisting of Br/Li Exchange Followed by Reactions with Electrophiles Starting from Dibromopyridines

Integration of chemical reactions enhances the power and speed of organic synthesis. Flow microreactors enable integration of reactions in space. Thus, in the next step, we examined the sequential introduction of two electrophiles by space integration of two sequences consisting of Br/Li followed by the reaction with an elctrophile using dibromopyiridines as starting materials. The reactions of dibromopyridines such as 2,3-dibromopyridine, 2,5-dibromopyridine, and 2,6-dibromopyridine were examined using an integrated flow microreactor system composed of four T-shaped micromixers (**M1**, **M2**, **M3**, and **M4**) and four microtube reactors (**R1**, **R2**, **R3**, and **R4**) shown in Fig. 5. A solution of each dibromopyridine (0.10 M in THF) (flow rate: 6.00 mL min^{-1}) and *n*-BuLi (0.40 M in *n*-hexane) (flow rate: 1.5 mL min^{-1}) were introduced to **M1** ($\phi = 250$ μm). The resulting solution was passed through **R1** ($\phi = 500$ μm, $L = 3.5$ cm) and was then mixed with a solution of the first electrophile (E^1) (0.24 M in THF) (flow rate: 3.0 mL min^{-1}) via **M2** ($\phi = 500$ μm). The resulting solution was passed through **R2** ($\phi = 1000$ μm, $L = 310$ cm), and was introduced to **M3** ($\phi = 500$ μm) where the solution was again mixed with *n*-BuLi (0.40 M in hexane) (flow rate: 2.25 mL min^{-1}). The resulting solution was allowed to react via **R3** ($\phi = 1000$ μm, $L = 12.5$ or 25 cm) and was then introduced to **M4** ($\phi = 500$ μm) where the solution was mixed with a solution of a second electrophile (E^2) (0.24 M in THF) (flow rate: 4.0 or 5.0 or 6.0 mL min^{-1}). The resulting solution was passed through **R4** ($\phi = 1000$ μm, $L = 200$ cm). After a steady-state was reached, the product solution was collected for 30 s while being quenched with H_2O. As summarised in Table 4, the desired trasformations were successfully achieved with various combinations of electrophiles without isolating the monobromopyridine intermediates. This integrated flow microreactor synthesis serves as a straightforward and powerful method for synthesising various types of disubstituted pyridines from dibromopyridines in a continuous flow mode. The total residence time ranges from 19.5 to 20.6 s and the desired products were obtained in high yields.

Conclusion

We have developed an efficient method for the synthesis of substituted pyridines by Br/Li exchange followed by reaction with an electrophile using continuous flow microreactor systems. The reactions can be conducted at much higher temperatures, such as 0 and −28°C, than those required for conventional methods using batch macro reactors. Sequential introduction of two electrophiles by space integration of two sequences consisting of Br/Li exchange interspersed by reaction with the electrophiles have also been achieved using the integrated flow microreactor systems. The present method serves as a powerful tool for synthesising a wide range of compounds containing substituted pyridine rings having various biological activities and physical functions. It is hoped that the method can be applied to industrial production because it does not require cryogenic conditions.

Supplementary Material

Experimental procedures and spectroscopic data of compounds are available on the Journal's website.

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