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Flash functional group-tolerant biaryl-synthesis based on integration of lithiation, zincation and negishi coupling in flow

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We achieved an integration of a lithiation of aryl bromides, a zincation of thus-generated aryllithiums, and a Negishi coupling of the arylzinc with an aryl halide in one flow. Taking advantages of flow microreactors, biaryls bearing a wide range of functional groups, especially biaryls bearing multiple electrophilic-functionalities were synthesized.

KEYWORDS

flow microreactor, negishi coupling, reaction integration, functional group-tolerance, biaryl synthesis

Introduction

As awarded the Nobel Prize in Chemistry in 2010, palladium-catalyzed cross-couplings, particularly coupling of aryl metals with aryl halides, are ubiquitous in our society. A wide range of molecules have been obtained through cross-coupling in the pharmaceutical, agrochemical, and material-chemistry fields (Nicolaou et al., 2005; Corbet and Mignani, 2006; Magano and Dunetz, 2011, respectively). Current social development has accelerated the demand for novel and high-performance organic molecules. Thus, a rapid process that allows chemists in R&D to prepare libraries of candidate molecules quickly and manufacturers to promptly supply their customers with sufficient products for cross-coupling reactions is urgently required.

We focused on the coupling process referred to as the Murahashi coupling (Murahashi et al., 1979; Giannerini et al., 2013) using aryl lithium as the aryl metal. Because of the low electronegativity of lithium (Pauling scale: 0.98, *c.f.* 1.3 for Mg and 2.0 for B), Murahashi coupling was assumed to be a rapid synthetic method. We demonstrated continuous-flow Murahashi-coupling (Nagaki et al., 2010; Nagaki et al., 2012b) that enables the syntheses of biaryls and biheteroaryls in high yields within 90 s under mild conditions (temperature for coupling: 50 °C). However, because of the high reactivity of aryl lithium, the functional groups were limited and no electrophilic functionalities were utilized for both aryl lithium and its coupling partner (aryl halide). This resulted in lower product diversity and overshadowed the utility of this process.

To achieve rapid and functional group-tolerant cross-coupling, we applied the strategy of flash chemistry (Yoshida, 2008; Colella et al., 2020; Nagaki et al., 2021; Takumi, et al., 2022) and reaction integration (Figure 1) using flow reactors. The use of

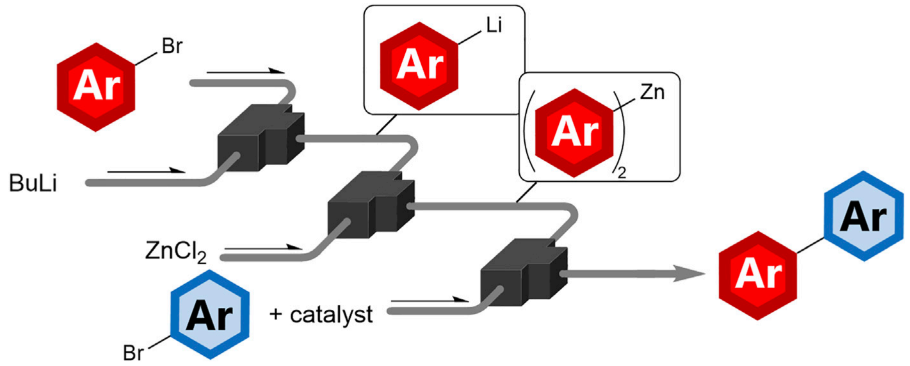
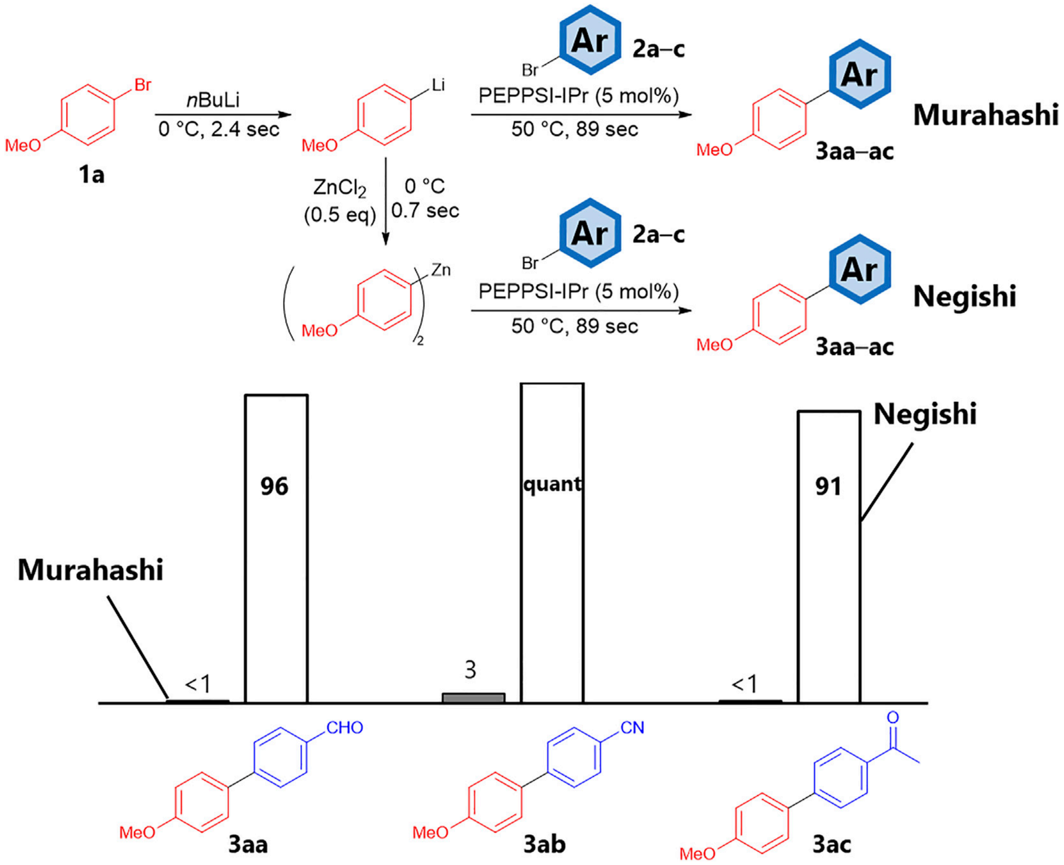


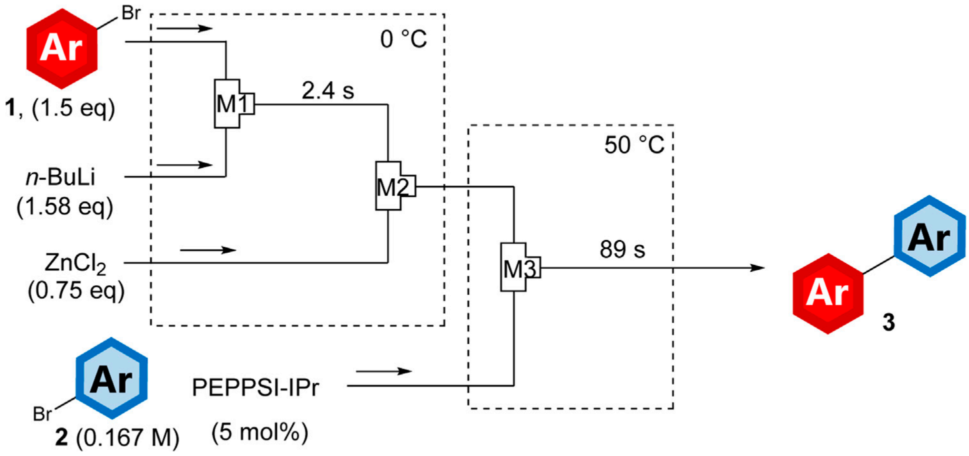
FIGURE 1
Schematic for integration of lithiation, zincation and negishi coupling in one flow.

flow reactors, especially micro-meter-sized flow reactors, has several benefits, such as an efficient heat transfer, a rapid mixing, a precise control of the reaction time and a direct use of transient unstable species, in the organic synthesis field (Heinz et al., 2021; Mazzarella et al., 2021; Ashikari, et al., 2022; Miyamura and Kobayashi, 2022; Nogami et al., 2022). Taking



SCHEME 1
Reaction yields of Murahashi (left) and Negishi (right) coupling using aryl halides bearing electrophilic functionalities (**2a**–**2c**) in flow microreactor. Bars are the reaction yields determined by GC.

TABLE 1 Integrated lithiation-zincation-coupling process of substituted aryl zinc precursors 1 with substituted coupling partner 2 in flowmicro reactor.[a]



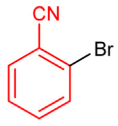
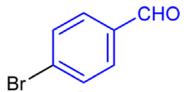
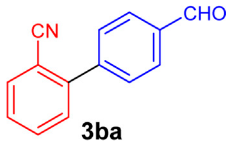
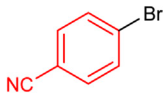
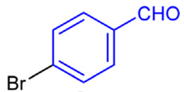
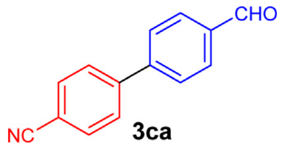
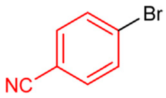
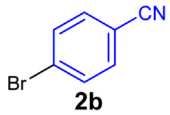
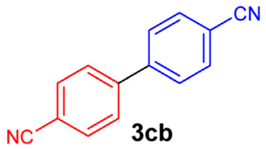
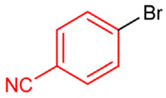
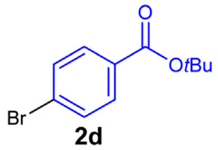
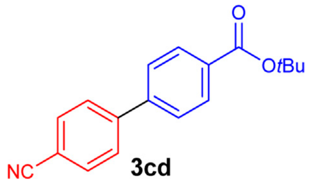
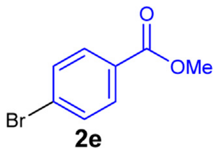
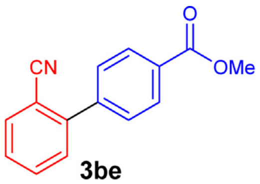
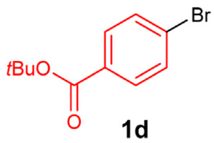
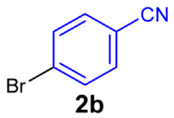
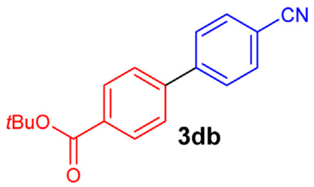
Entry	Aryl zinc precursor 1	Coupling partner 2	Product	Yield (%)
1	 **1b**	 **2a**	 **3ba**	98
2	 **1c**	 **2a**	 **3ca**	98[b]
3	 **1c**	 **2b**	 **3cb**	90[b]
4	 **1c**	 **2d**	 **3cd**	73[b]
5	 **1b**	 **2e**	 **3be**	80[b]
6	 **1d**	 **2b**	 **3db**	57[b,c]

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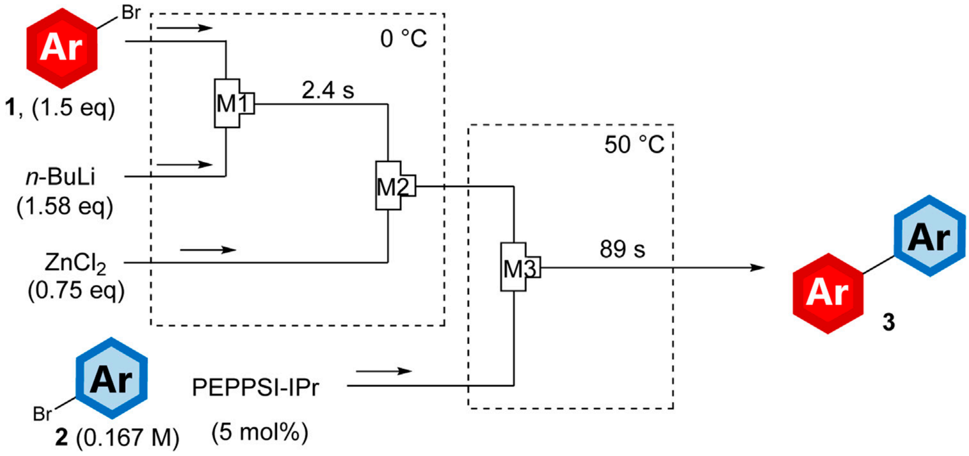
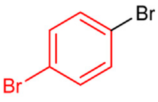
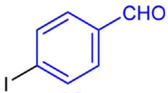
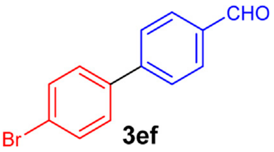
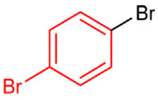
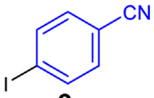
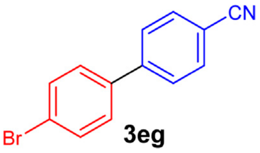
TABLE 1 (*Continued*) Integrated lithiation-zincation-coupling process of substituted aryl zinc precursors 1 with substituted coupling partner 2 in flowmicro reactor.[a]



Entry	Aryl zinc precursor 1	Coupling partner 2	Product	Yield (%)
7	 **1e**	 **2f**	 **3ef**	99[d]
8	 **1e**	 **2g**	 **3eg**	99[d]

[a] Yields were determined by GC.

[b] Residence time for the coupling reaction is 172 s.

[c] *Sec*-BuLi was used. Temperature of the first bath (lithiation and zincation) is −30°C.

[d] Temperature of the second bath (coupling) is 20°C, and residence time for coupling is 131 s. A 5 mol% of $Pd(PPh_3)_4$ and 0.75 eq of $ZnCl_2$ were used.

the advantage of the flow microreactors, highly-selective chemical reactions have been achieved (Ashikari et al., 2019; Sugisawa et al., 2020; Ashikari et al., 2021). Based on this idea, we envisaged that aryl lithiums bearing electrophilic functionalities are generated by functional-group-tolerant halogen–lithium exchange reactions and, before they decompose, are converted to aryl zincs. Reaction integration (Nagaki, 2021) allows the generated aryl zincs to be subsequently engaged in Negishi coupling in one flow. The modest electronegativity of zinc (1.7) causes adequate reactivity, resulting in functional group tolerance. Herein, we report the flow microsynthesis of functionalized biaryls by integrating lithiation, zincation, and coupling reactions mediated by functionalized aryl zinc. We applied this strategy to metal-selective cross-coupling reactions and demonstrated the synthesis of biaryls bearing metal substituents. Moreover, by utilizing flash chemistry thoroughly, we demonstrated room-temperature coupling of aryl halides.

Materials and methods

Materials

Chemicals were purchased from Kanto Chemical, FUJIFILM Wako Pure Chemical, Tokyo Chemical Industry, and Sigma–Aldrich, and were used without further purification unless otherwise stated.

Flow synthesis

T-shaped stainless steel (SUS304) micromixers with inner diameters of 500 and 250 µm were manufactured by Sanko Seiki. Stainless steel (SUS316) flow reactors with inner diameters of 1000 and 2,170 µm were purchased from GL Sciences. PTFE tubes with inner diameters of 1000 and 1588 µm were purchased from ISIS. Syringe pumps (Harvard Model PHD 2000 or PHD

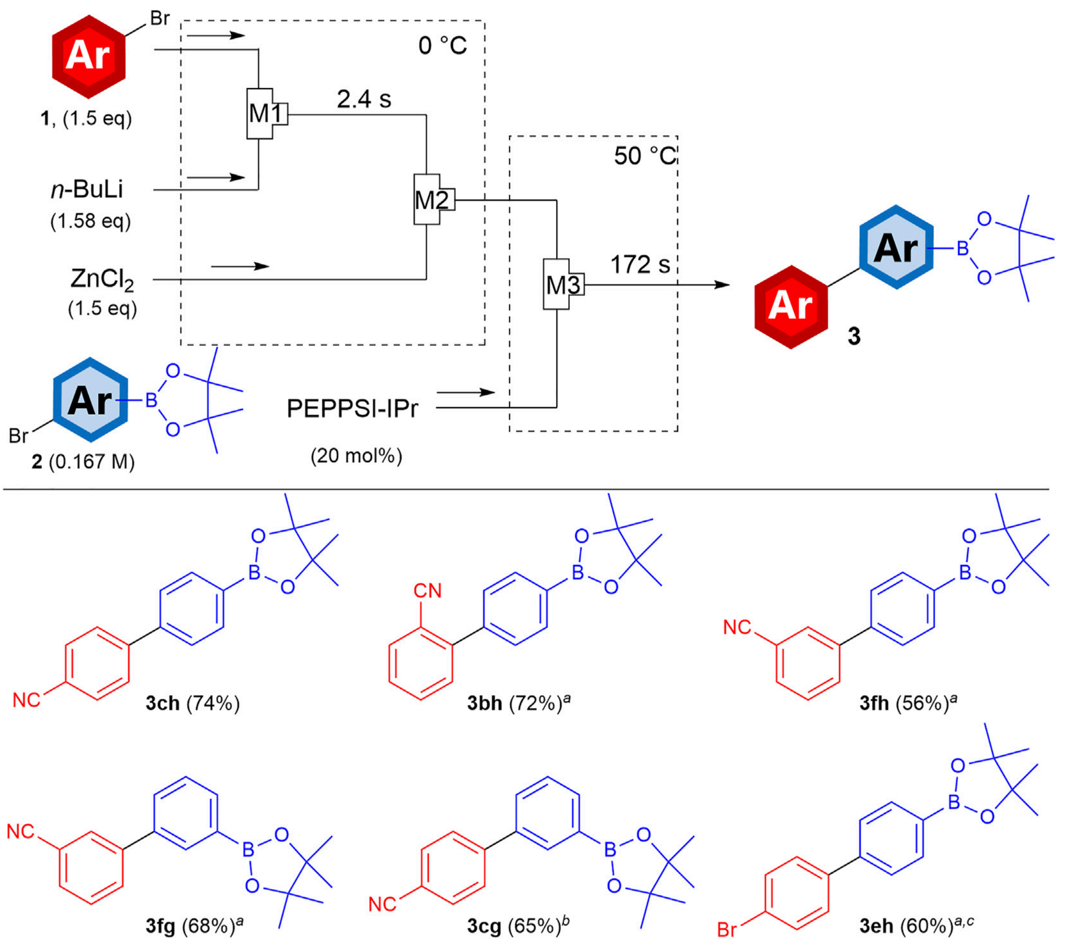


FIGURE 2
Schematic for metal-selective cross-coupling in flow microreactor. Yields were determined by GC. [a]Additional stirring in batch for 30 min [b]Additional stirring in batch for 12 h at 50°C, [c] Aryl iodide was used as the coupling partner, and Pd(PPh$_3$)$_4$ was used as the catalyst. 0.75 eq of ZnCl$_2$ was used. For the coupling, the temperature was 20°C and the residence time was 131 s.

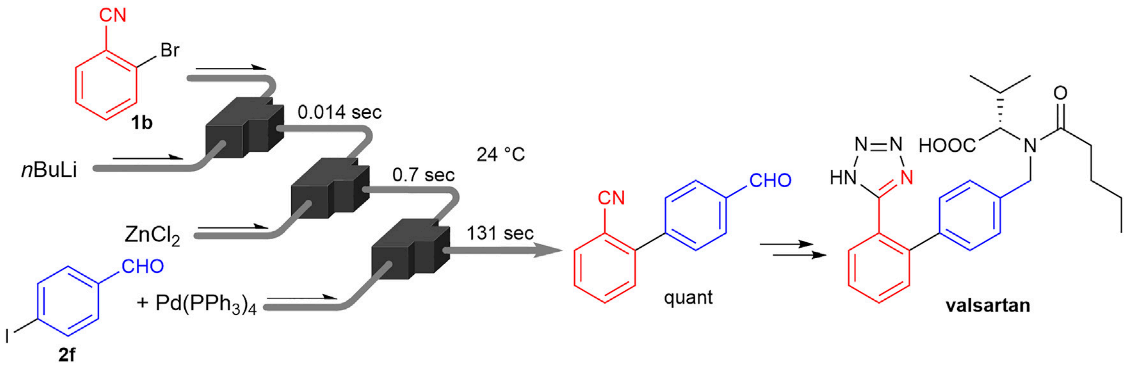


FIGURE 3
Full-room-temperature process of integrated lithiation-metalation-coupling for synthesizing the key intermediate of valsartan.

ULTRA) equipped with gastight syringes (purchased from SGE) were used to introduce the reaction solutions. Product yields were determined through GC analyses (Shimadzu GC-2014) calibrated using internal standards with commercial samples.

Results and discussion

Initially, we studied the feasibility, rapidity and the flexibility of this concept. Using conditions similar to those described in a previous publication (Nagaki et al., 2010), we attempted the flow Murahashi coupling of 4-anisyl lithium with arylbromides bearing electrophilic functional groups in a flow microreactor (Scheme 1). After the halogen–lithium exchange reaction of 4-bromoanisole (**1a**) with *n*-butyllithium (0°C, 2.4 s), aryl lithium was reacted with aryl bromides (**2a**–**c**) and 5 mol% palladium catalyst (PEPPSI-IPr) at 50 °C for 89 s. As anticipated, the presence of electrophilic groups led to very low yields (less than 3%) if compared to system where such functions are not present (Nagaki et al., 2010). GC-MS analyses indicated that the crude mixture of the reaction using 4-bromobenzaldehyde (**2a**) contained 4-methoxybenzhydrol, which can be generated by a nucleophilic attack of the aryl lithium on the formyl group of **2a**. These results demonstrate that aryl lithiums tend to react with electrophilic functional groups before initiating the Murahashi coupling; therefore, we investigated the integration strategy. After lithiation, aryl lithium was reacted with 0.5 equivalent amount of zinc chloride to be converted to aryl zinc, which was subsequently reacted under similar coupling conditions. The corresponding biaryls (**3aa**–**ac**) were obtained in high yields. Notably, this series of transformations ended within 92 s owing to the fast generation of aryl lithium and the sufficient reactivity of aryl zinc.

Once the feasibility of the flow integration of lithiation, zincation, and coupling was confirmed, the coupling of different aryl zinc and aryl halides bearing electrophilic functional groups was investigated. As summarized in Table 1, aryl halides bearing electrophilic functional groups were introduced into micromixer **M1** (internal diameter: 500 μm) at 0°C, where a solution of *n*-butyllithium was also introduced. After 2.4 s, the resulting solution was introduced into micromixer **M2** (internal diameter: 500 μm) and mixed with a solution of zinc chloride to generate the functionalized aryl zinc. Thereafter, aryl zinc was mixed with another aryl halide bearing electrophilic functionalities and PEPPSI-IPr or $Pd(PPh_3)_4$ in micromixer **M3**. The resulting solution was passed through a tube reactor and heated to 50°C to promote the cross-coupling reaction, and to increase the reaction conversion we utilized longer tube reactor to prolong the reaction time. From the aryl halides bearing a cyano group (**1b** and **1c**, entries 1–5) and an ester moiety (**1d**, entry 6), the corresponding biaryls were obtained in good to high yields. Interestingly, when using aryl iodides (**2f** and **2g**) as coupling partners, bromo-substituted aryl zincs, which were generated from the selective mono-lithiation of dibromobenzene **1e** based on the previously reported conditions (Nagaki et al., 2007; Usutani et al., 2007), selectively reacted at the iodo groups of **2f** and **2g** to generate bromo-substituted biaryls **3ef** and **3eg** (entries 7 and 8), respectively. Notably, because the aryl lithiums were generated by the halogen–lithium exchange reaction, the position of the substituents (*ortho-* and *para*-position) could be controlled by changing the starting materials (for instance, entry 1 vs 2), which deprotonative lithiation such as directed *ortho*-lithiation (Snieckus, 1990) seldom achieved.

The success of the halogen-selective cross-coupling of this process prompted us to attempt metal-selective cross-coupling to generate metal-substituted biaryls. Based on our previous efforts to synthesize bimettalic arenes, which are arenes bearing multiple metal substituents and their cross-coupling reactions (Ashikari et al., 2020), we designed the flow system shown in Figure 2. In the flow reactors, aryl zincs were generated and subsequently reacted with aryl halides bearing boryl groups catalyzed by PEPPSI-IPr or $Pd(PPh_3)_4$. Using 4-bromobenzonitrile (**1c**) as the precursor of aryl zinc and 4-bromophenylboronic acid pinacol ester as the coupling partner, the corresponding biphenyl bearing the boryl group (**3ch**) was obtained in high yields. This Negishi-selectivity is derived from that the Suzuki coupling basically requires basic conditions and this flow reaction was carried out in the absence of a base. Because the coupling product **3ch** still has a metal substituent (the boryl group), further transformations including Suzuki–Miyaura coupling are achievable. When the position of the cyano group is varied, the corresponding biphenyl with *ortho-* (**3bh**) and *meta*-substitution (**3fh**) can be obtained in high yields, demonstrating the advantage of site-selective lithiation enabled by the halogen–lithium exchange. Notably, from the bromo-substituted aryl zinc and an aryl iodide bearing a boryl group, the corresponding biphenyl bearing the bromo and boryl groups (**3eh**) was obtained in a high yield. This is an excellent example of halogen- (Br vs I) and metal-selective (Zn vs B) cross-couplings.

To prevent side reactions, lithiation and metalation steps for synthesizing aryl metal species were performed at cryogenic temperatures such as −78°C. However, the coupling reaction usually requires high temperatures such as the boiling points of the solvents. Thus, this series of transformations requires both low and high temperatures, leading to a waste of energy. Because the demand for products synthesized through cross-coupling is increasing, the energy loss of this process is also increasing. To save energy, in the context of Sustainable Development Goals, we investigated the integrated lithiation-zincation-coupling process at room temperature as a demonstration for the greener process.

With the flowmicro reactor dipped in a water bath as depicted in Figure 3, the cyano-substituted aryl bromide (**1b**) was mixed with *n*-butyllithium at 24°C, and 0.014 s later, zinc chloride was added to the mixture. After the addition of coupling partner **2f** and palladium catalyst ($Pd(PPh_3)_4$, 5 mol% to the aryl iodide), the resulting mixture was passed through a tube reactor in a water bath (24 °C) until the reaction was quenched (residence time: 131 s). Under this full-room-temperature condition, **2f** was fully consumed and the desired product, which is a key intermediate (Goossen and Melzer, 2007; Nagaki et al., 2016) of valsartan (Diovan, Novartis: US $773 million sales in 2021 (Novartis, 2022)), the angiotensin-II-receptor antagonist, was obtained in a quantitative yield.

Conclusion

In conclusion, we achieved the integration of the halogen–lithium exchange reaction, zincation, and Negishi coupling in a flow microreactor. Using this methodology, a range of biphenyls with multiple electrophilic functionalities were synthesized within several minutes. The use of the zincyl group enables the boryl-group tolerant coupling, which flow Suzuki coupling (Shu et al., 2011; Nagaki et al., 2012a; Takahashi et al., 2020) cannot achieve. Although Knochel (Becker et al., 2015; Becker and Knochel, 2015) and Buchwald (Roesner and Buchwald, 2016) reported numerous examples of flow Negishi coupling, the proposed method has a higher flow rate of the substrate solution (typically 4 ml/min whereas those of the previous reports are 2 ml/min or less) and shorter reaction times, allowing higher productivity. Moreover, since this present method utilizes the halogen–lithium exchange reaction, site-selective lithiation can be achieved, which provides biaryls with varying substitution patterns.

Another aspect of the proposed method is flash chemistry in which intermediates with extremely short lifetimes can be utilized. The integrated lithiation-metalation-coupling process was achieved in a single pass at room temperature by controlling the reaction time of the lithiation step at 14 ms. Because no heating or cooling is required, the cross-coupling of aryl halides saves energy. We assert that this environmentally benign synthetic method will contribute to save energy and satisfy the increasing demand for cross-coupling products by supplying fruitful organic molecules.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions

YA and AN contributed to conception and design of the study. YA and KG operated the investigation. YA wrote the first draft of the manuscript. AN supervised the project. All authors revised the manuscript, approved the manuscript to be published, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher’s note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fceng.2022.964767/full#supplementary-material

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