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Regioselective Synthesis of α-Functional Stilbenes via Precise Control of Rapid *cis*–*trans* Isomerization in Flow

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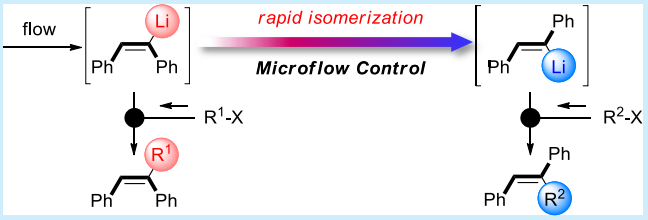
ABSTRACT: The rapid *cis*–*trans* isomerization of α-anionic stilbene was regioselectively controlled by using flow microreactors, and its reaction with various electrophiles was conducted. The reaction time was precisely controlled within milliseconds to seconds at −50 °C to selectively give the *cis*- or *trans*-isomer in high yields. This synthetic method in flow was well-applied to synthesize precursors of commercial drug compound, (*E*)- and (*Z*)-tamoxifen with high regioselectivity and productivity.



Stilbene is a well-known subunit occurring naturally in polyphenols of various plants.[1] Advances in spectroscopic techniques facilitate the analysis of not only the intricate structures of stilbenes but also the elucidation of their biological efficacy. Stilbene derivatives have been at the forefront of pharmaceutical research and development, because of their potential therapeutic or preventive applications, exemplified by tamoxifen,[2] resveratrol,[3] and combretastatin A-4.[4] Furthermore, they have been often used in material applications as dye precursors, optical brighteners, phosphors, and scintillators.[5]

The widespread applications of stilbene derivatives in various research fields led the development of synthetic method for regioselective functionalization of the stilbenes;[6] however, the reactions are restricted, because of their rapid isomerization. The geometry of the *trans*-stilbene is slightly lower in energy than *cis*-stilbene by ∼4.6 kcal/mol, with an isomerization barrier of 48.3 kcal/mol,[7] because the steric interactions force the aromatic rings out-of-plane and prevent conjugation.[8] Therefore, the formation of *trans*-isomer is preferred in nature and the *cis*-isomer is sensitive to isomerization, even to mild conditions, such as minor light irradiation[9] and exposure to heat.[10] The preference for the *trans*-isomer also strongly dominates the product conformation. The α-functionalization of stilbene through vinylic metal species is difficult, because of the its rapid *trans*formation from *cis* to *trans* (Scheme 1a), as reported.[11] A directing group for high regioselectivity is required in order to control the olefin geometry as part of a general synthetic methodology.

The carbolithiation of diphenylethylene and selective α-lithiation of stilbene, one of the simplest and direct functionalization methods[12] is challenging, because the formation of the *trans*-isomer cannot be prevented, even under extremely low temperature conditions, because of the rapid isomerization. The regioselective synthesis of α-function-

Scheme 1. Synthetic Methodology for the Functionalization of α-Anionic Stilbenes

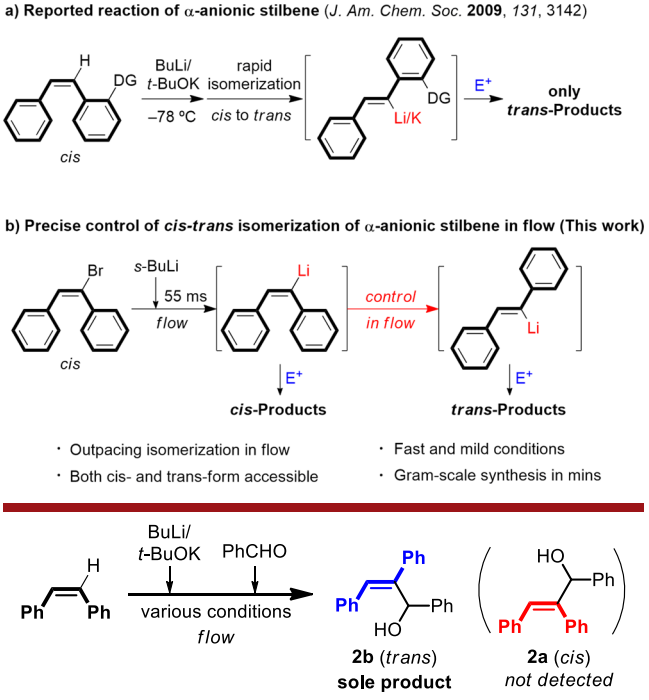


Figure 1. Vinyl C–H metalation of *cis*-stilbene to result in the formation of the *trans*-isomer in the flow.

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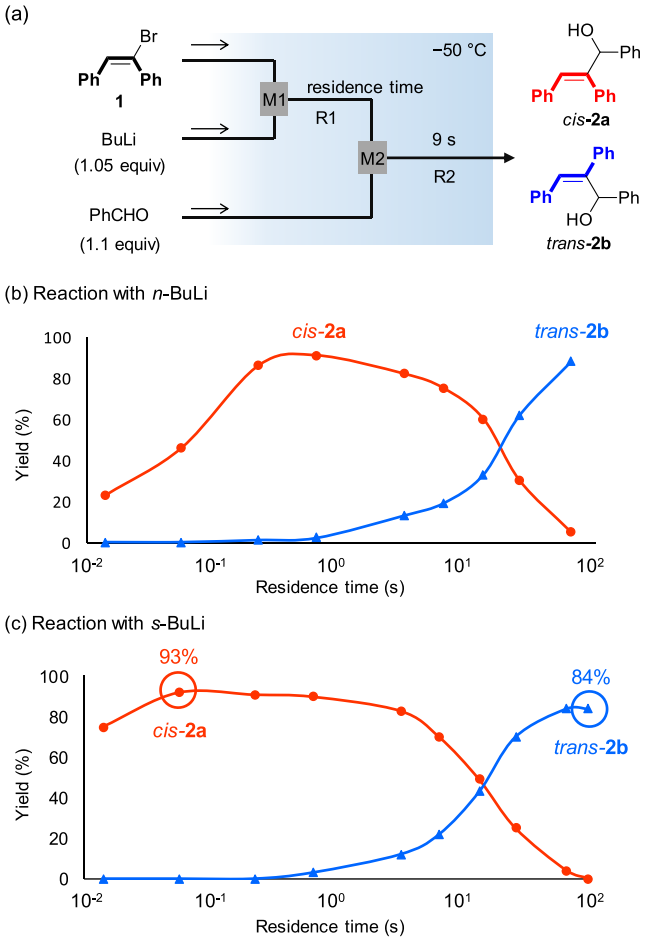

Figure 2. Generation of α-lithiated stilbene and the control of isomerization by changing the residence time in R1 in a flow microreactor: (a) the Br−Li exchange reaction of *cis*-α-bromo stilbene (**1**) and subsequent reaction with benzaldehyde in flow, (b) the reaction using *n*-BuLi as a lithiating reagent, and (c) the reaction using *s*-BuLi as a lithiating reagent.

alized *cis*- and *trans*-stilbene derivatives is an ongoing challenging issue using transition-metal catalysts.[13]

Flow chemistry based on microfluidics has been developed and widely applied in the field of organic chemistry, pharmaceutical chemistry, and materials science in the last two decades.[14] The flow reactor has emerged as a fascinating alternative to conventional flask, especially as a safe and environmentally friendly synthetic tool.[15] Continuous flow chemistry is increasingly recognized as a cutting-edge synthetic technique that can be combined with artificial intelligence and autonomous reaction system.[16] Flow microreactors contributed advance in organic synthesis due to fast mixing, effective control of reaction conditions, and time.[17] Based on the precise control of short reaction time (milliseconds or less) in the flow reactor, our research group has reported several studies involving rapid reaction control including rearrangement and decomposition of intermediates,[18] and this concept is referred to as "flash chemistry".[19]

Herein, we report a remarkable control of isomerization of α-lithiated stilbene using the flow reaction system. To the best of our knowledge, this is the first report of α-functionalization of both *cis*- and *trans*-stilbene with high regioselectivity (Scheme 1b). We also established the successful introduction of various electrophiles into highly controlled *cis*- and *trans*-

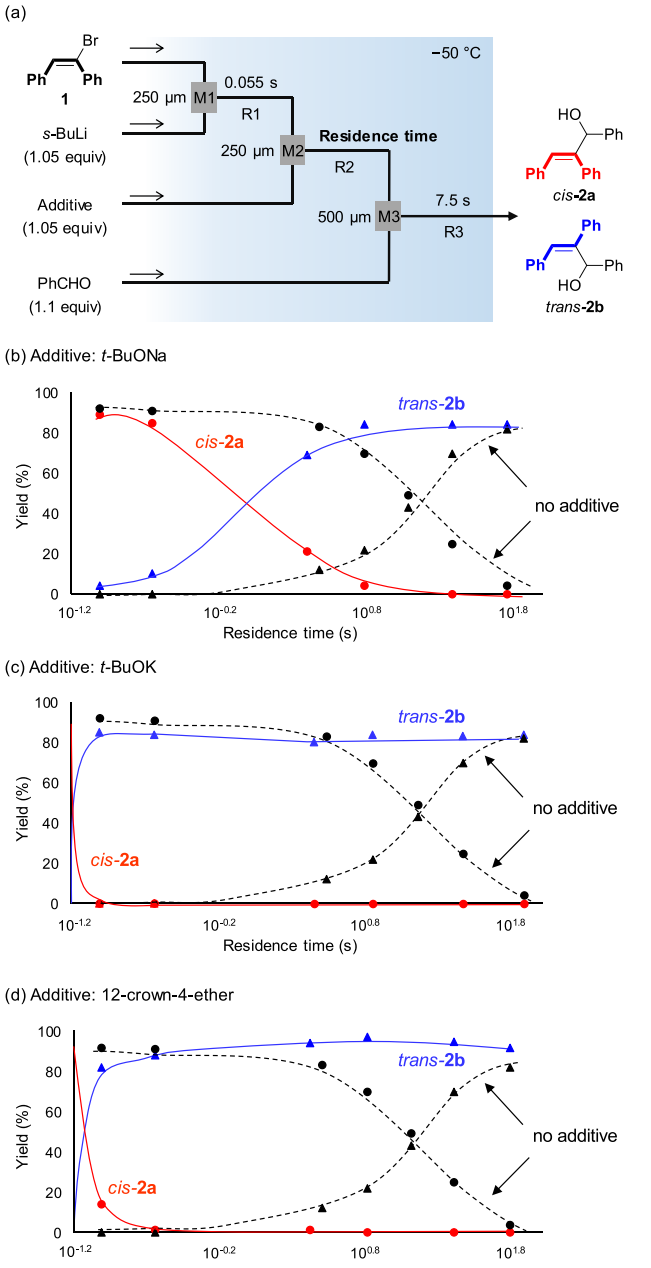

Figure 3. Investigation of the relationship between cationic species and the isomerization rate: (a) the flow scheme for the reaction with the cationic species, (b) the reaction with *t*-BuONa as an additive (the reaction without an additive was represented by black dashed lines), (c) the reaction using *t*-BuOK as an additive, and (d) the reaction using 12-crown-4-ether as an additive.

lithiated stilbene including *cis*-stilbenyl borate, which could be used in various synthetic reactions such as Pd-catalyzed cross-coupling. The flash synthesis method is illustrated by the synthesis of the precursors of the well-known pharmaceutical compounds (*E*)- and (*Z*)-tamoxifen.

Initially, the generation of α-anionic stilbene was attempted via vinyl C−H metalation of *cis*-stilbene using Schlosser's base (a mixture of BuLi and potassium *tert*-butoxide)[20] in both a flask and the flow reactor (Figure 1; see the Supporting Information). In the various reaction conditions, only *trans*-isomer **2b** was obtained as a sole product, even using a flow reactor where the time for the metalation was set to

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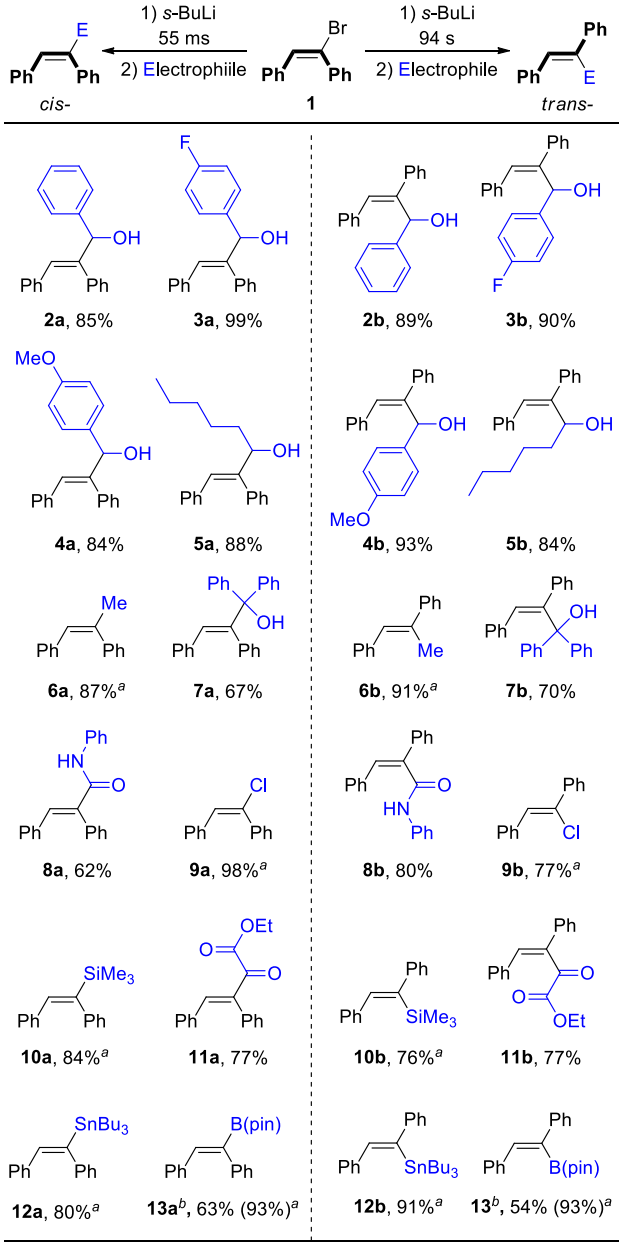

Figure 4. Regioselective functionalization of stilbene with various electrophiles.

milliseconds at −78 °C. All of the attempts to get the *cis*-isomer **2a** failed. The results suggest that the rate of isomerization was much faster than the rate of metalation by the Schlosser's base, which was not possible to control the isomerization. For this reason, we modified the strategy to generate the α-anionic stilbene via the rapid halogen−lithium exchange reaction.

In a preliminary study using *cis*-α-bromo stilbene (**1**), the generation of α-lithiated stilbene, followed by the reaction with benzaldehyde, was conducted in a flask. A mixture of *cis*- and *trans*-products was obtained in the ratio of 2:1 (63% and 34%, respectively), although the lithiation time was kept to 1 min at −78 °C. This result indicates that the regioselective functionalization of stilbene is difficult to achieve in flask, because of the rapid isomerization even at −78 °C (See the Supporting Information).

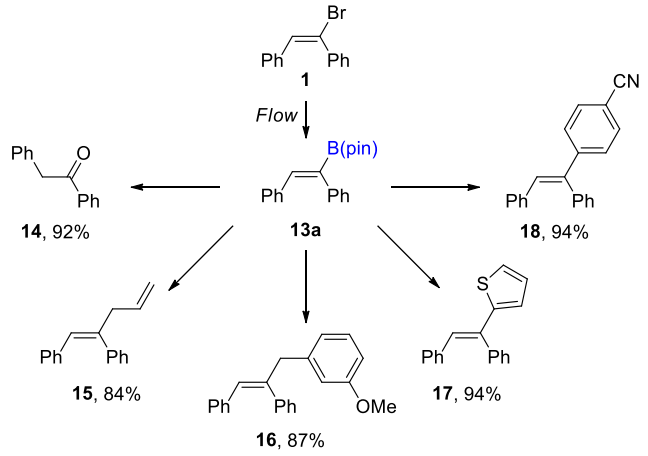

Figure 5. Various reactions of flow-synthesized *cis*-stilbenyl borate **13a**.

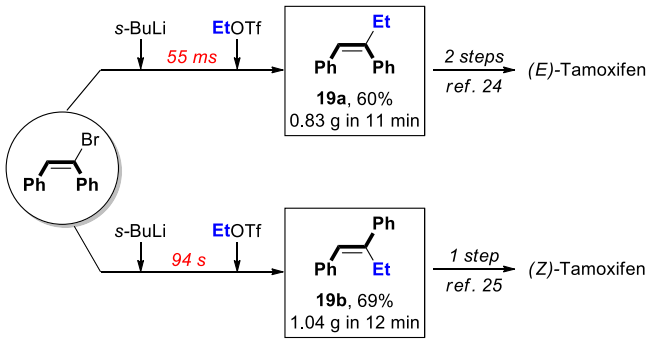

Figure 6. Flow-assisted synthesis of (*E*)- and (*Z*)-tamoxifen precursor with high regioselectivity.

We next performed the flow reaction expecting better controllability. The reaction was conducted in the flow reactors consisting of two micromixers (M1 and M2; 250 μm of inner diameter) and two tube reactors (R1 and R2), as shown in Figure 2a. A solution of *cis*-α-bromo stilbene (**1**) and BuLi was mixed and lithiated in M1 and R1, and the resulting solution was reacted with benzaldehyde in M2 and R2. Because many previous reports indicate that the Br−Li exchange at −78 °C in flow reactors results in low conversions,[21] the temperature of flow reaction was maintained at slightly higher than −50 °C and the residence time in R1 was controlled from 14 ms to 94 s by changing the diameter and length of the tube reactor. First, we used *n*-BuLi as a lithiating reagent (Figure 2b). The yield of **2a** was increased by changing the residence time from 14 ms to 3.1 s, because of the incomplete Br−Li exchange at residence times that are too short under low temperature. However, the yield of **2a** dwindled by further increasing the residence time (from 3.1 s to 63 s), because of the rapid *cis*−*trans* isomerization. When the residence time was 0.63 s, we obtained compound **2a** in 91% yield, but the isomerized *trans*-compound **2b** was also detected (2%). We could confirm that the isomerization began before the complete Br−Li exchange reaction to result in the formation of a mixture of compound **2a** and **2b**. Therefore, we changed the lithiating reagent to *s*-BuLi for faster Br−Li exchange and resulted in the highest yield of compound **2a** without the formation of isomer **2b** at 55 ms of residence time (93% in Figure 2c). At a residence time of 94 s, compound **2b** was obtained as a sole product, with a yield of 84%. The yield of **2a** was decreased by

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increasing the temperature (from −78 °C to 20 °C) at a fixed residence time (3.1 s; see the Supporting Information).

Next, we investigated the effect of cationic species on the isomerization rate. The *cis*-α-lithiated stilbene generated in R1 was mixed with alkali-metal species, and then trapped with benzaldehyde in the flow microreactors (Figure 3a). Interestingly, the kinetics of isomerization was dramatically changed by the cation. Using sodium *tert*-butoxide (*t*-BuONa) as an additive, the rate of isomerization seemed to be slightly increased (Figure 3b). When the potassium *tert*-butoxide (*t*-BuOK) was added, *trans*-isomer **2b** was only detected at all of the residence times in R2 (Figure 3c). The reaction rate of isomerization was increased in the following order of the cation: $Li^+ < Na^+ < K^+$, presumably because of a degree of ionized α-anionic stilbene. The addition of *t*-BuONa and *t*-BuOK can induce the replacement of Li^+ with Na^+ or K^+, which leads to more ionized anions. We also conducted the reaction using 12-crown-4-ether as the additive to generate the more ionized anion by capturing the Li^+ and the rate of isomerization was dramatically accelerated, as shown in Figure 3d. This result indicates that the more ionized anion stilbene facilitates faster *cis*−*trans* isomerization. Based on the results, we realized that our initial attempt to generate *cis*-α-lithiated stilbene using Schlosser's base most likely failed even in the flow, because of the effect of potassium accelerating the rate of isomerization.

Under the optimized residence times (55 ms for *cis*-stilbene derivatives and 94 s for *trans*-stilbene derivatives), we conducted the regioselective reactions with various electrophiles (Figure 4). We obtained the desired *cis*- (**2a**−**5a**) and *trans*- products (**2b**−**5b**) in high yields of 84−99% through the reactions with benzaldehydes bearing electron-withdrawing or electron-donating groups and an aliphatic aldehyde.

Various electrophiles including methyl triflate, benzophenone, phenyl isocyanate, hexachloroethane, trimethylsilyl triflate, diethyl malonate, tributyltin chloride, and trimethoxyborane were effectively trapped the intermediate organometallic to yield the corresponding *cis*- (**3a**−**13a**) and *trans*-stilbene derivatives (**3b**−**13b**) with high yield and regioselectivity.

To demonstrate the synthetic utility of the *cis*-stilbenyl borate compound, we conducted further reactions using compound **13a** (Figure 5). The oxidation reaction was achieved with hydrogen peroxide and sodium hydroxide, resulting in 1,2-diphenylethone (**14**) in 92% isolated yield. The Pd-catalyzed cross-coupling reaction gave the corresponding products (**15**−**18**) in high yields (87%−94%), using coupling partners such as allyl, benzyl, aryl, and heteroaryl bromide.

We next conducted the synthesis of precursors of *cis*- and *trans*-tamoxifen (Figure 6). The remedial effect of tamoxifen is different by the *E*/*Z* geometry, which requires the regioselective synthesis during production of the drug compound. Whereas *cis*- or (*E*)-tamoxifen is a full estrogen agonist,[22] *trans*- or (*Z*)-tamoxifen is a therapeutic agent used for the management of estrogen-dependent breast cancer.[23] The *cis*- or *trans*-α-lithiated stilbenes were generated under the optimized conditions, followed by the reaction with ethyl triflate (EtOTf) in the flow reactors resulting in ethylated compound **19a** or **19b** in the isolated yield of 60% and 69%, respectively. In case of using ethyl iodide as the electrophile, compound **19a** was not obtained as the sole product, because of low reactivity.

A high-yielding, high-throughput synthesis of **19a** (0.83 g) and **19b** (1.04 g) was achieved in 11 and 12 min of operation time, respectively. The *cis*-isomer **19a** can be converted to (*E*)-tamoxifen via epoxidation (see the Supporting Information) and epoxide olefination,[24] and the *trans*-isomer can be directly transformed to (*Z*)-tamoxifen via Heck-type cross-coupling reaction.[25] These results suggest that the flow-assisted approach is useful for the regioselective synthesis of pharmaceutical ingredients with high productivity.

In conclusion, we have achieved the flow-assisted precise *cis*-*trans* isomerization of α-anionic stilbene. We generated the α-lithiated stilbene via rapid Br−Li exchange. Under the optimized conditions, two isomers can be regioselectively trapped with various electrophiles to obtain the desired products in high yields. The *cis*-stilbenyl-borate that was obtained using this method could be used for the synthesis of various *cis*-stilbene derivatives. Moreover, the synthesis of both precursors of *cis*- and *trans*-tamoxifen with enhanced productivity in flow demonstrates the power of flow chemistry in the field of organic synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00538.

Experimental procedures, supplementary figures and compound characterization data (PDF)

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The authors declare no competing financial interest.

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■ DEDICATION

Dedicated in memory of Prof. Jun-ichi Yoshida.

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