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Trapping of Transient Thienyllithiums Generated by Deprotonation of 2,3- and 2,5-Dibromothiophenes in a Flow Microreactor

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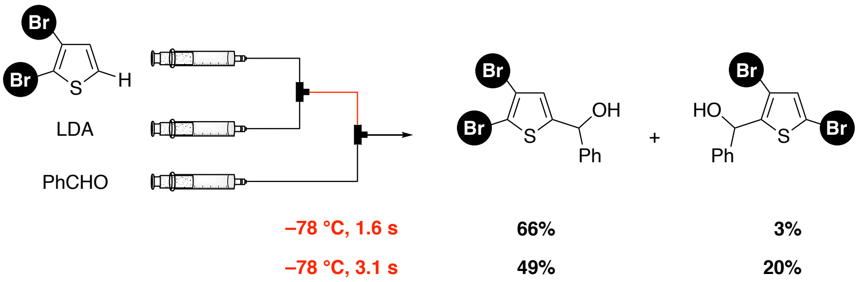
In memory of Jun-ichi Yoshida



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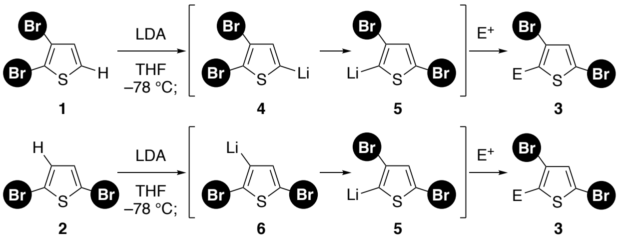
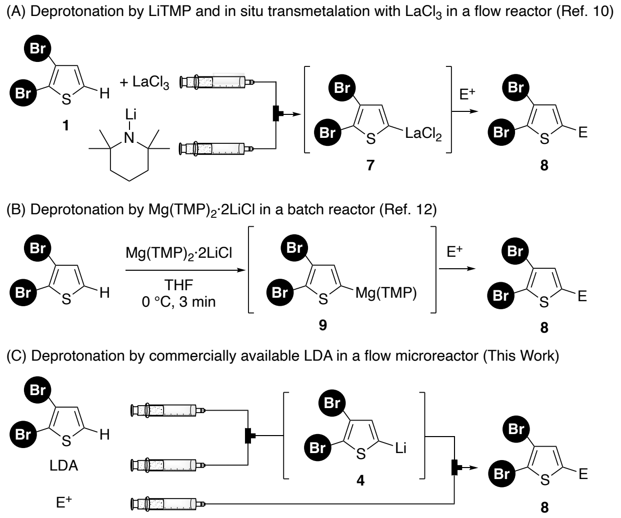
Abstract Selective trapping of 2,3-dibromo-5-lithiothiophene, which is known to undergo halogen dance, was achieved in a flow microreactor. This transient thienyllithium is generated by mixing 2,3-dibromothiophene and lithium diisopropylamide (LDA) at –78 °C for 1.6 s, which reacted with benzaldehyde. The reaction system is applicable to other carbonyl compounds to afford the corresponding adducts in good yields. In addition, the established conditions are able to convert 2,5-dibromothiophene to provide a mixture of the two constitutional isomers. The contrasting results are discussed based on the reaction pathway.

Key words halogen dance, microreactors, heterocycles, substituent effects, deprotonation, lithiation, halogen–lithium exchange, rearrangement

Functionalized thiophenes are structural constituents of agrochemicals, pharmaceuticals, and functional materials.[1] Reactions of thienylmetal species with an electrophile have been widely used to synthesize substituted thiophenes,[2,3] in addition to electrophilic aromatic substitution,[4] cross-coupling reaction,[5] and cyclization of acyclic carbonyl compounds.[6] Several thienyllithium species bearing one or more bromo and iodo groups undergo swapping of lithium and the halogen atom, which is referred to as the 'halogen dance'.[4b,7] Both 2,3-dibromothiophene (**1**) and 2,5-dibromothiophene (**2**) undergo deprotolithiation followed by halogen dance to provide the same 2,4-dibromothiophene **3**, after treatment with an electrophile (Scheme 1).[8,9] Deprotonation of **1** selectively proceeds at the more acidic α position to give thienyllithium **4**, which leads to the formation of thermodynamically more stable thienyllithium **5**.[8] Thienyllithium **6**, which is generated from 2,5-dibromothiophene (**2**), is also converted to thienyllithium **5**.[8c,9] Although thienyllithium **5** has been employed for the synthesis of various thiophenes, only one model reaction for trapping thienyllithium **4** has been reported, in spite of the usefulness of **4** for synthesizing constitutional isomers (Scheme 2A). In this example, in situ transmetalation to organolanthanum **7** in a flow reactor gives **8**.[10] Recently, our group has reported generation of thienylmagnesium **9** by deprotonation of dibromothiophene **1** with Mg(TMP)$_2$·2LiCl,[11] which underwent halogen dance at room temperature.[12] This reaction is sufficiently sluggish at 0 °C to trap the transient thienylmagnesium **9** with several electrophiles (Scheme 2B). The recently developed flash chemistry using a flow microreactor[13] prompted us to investigate the direct trapping of thienyllithium **4** with an electrophile (Scheme 2C). Herein, we describe selective trapping of thienyllithium **4** that is generated from 2,3-dibromothiophene (**1**) and commercially available LDA.



Scheme 1 Halogen dance of dibrominated thienyllithium species generated by deprotonation of 2,3-dibromothiophene and 2,5-dibromothiophene


(A) Deprotonation by LiTMP and in situ transmetalation with LaCl$_3$ in a flow reactor (Ref. 10)

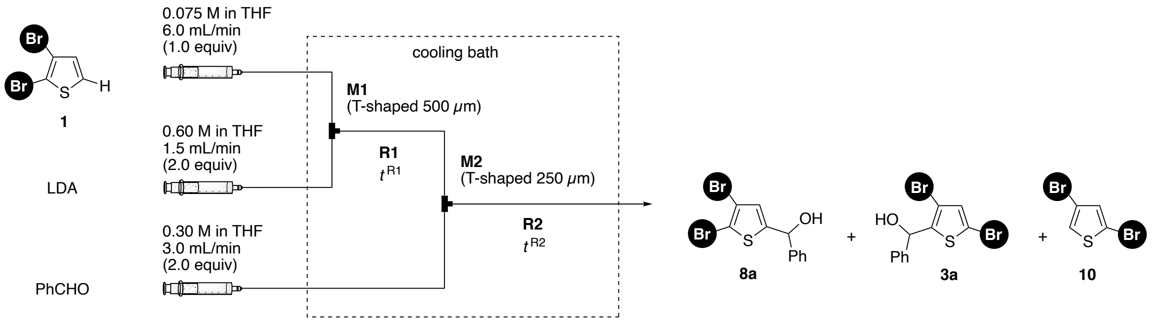
(B) Deprotonation by Mg(TMP)$_2$·2LiCl in a batch reactor (Ref. 12)

(C) Deprotonation by commercially available LDA in a flow microreactor (This Work)

Scheme 2 Trapping of the thienylmetal species generated by deprotonation of 2,3-dibromothiophene

First, we explored the optimal reaction conditions for trapping the transient thienyllithium **4** with benzaldehyde as an electrophile (Table 1). The microflow system consisted of a T-shaped micromixer (M1: 500 μm) and a T-shaped micromixer (M2: 250 μm) and two microtube reactors (R1 and R2). Thienyllithium **4** was generated from 2,3-dibromothiophene (**1**) and LDA by varying the reaction temperature of the cooling bath for the residence time (t^{R1}) in R1, followed by trapping with benzaldehyde in R2 to afford the desired adduct **8a**, its constitutional isomer **3a**, and 2,4-dibromothiophene (**10**) that was derived by halogen dance and protonation of **1**. The flow rate of the solution of 2,3-dibromothiophene (**1**) (0.075 M) in THF was adjusted to 6.0 mL/min. The solution of LDA (0.60 M) in THF was prepared just before use, and the flow rate was set to 1.5 mL/min. The flow rate of the solution of benzaldehyde (0.30 M) in THF was set to 3.0 mL/min. Both reaction temperature and the residence time (t^{R1}) in R1 were important for trapping the short-lived thienyllithium species. We first investigated the effects of the reaction temperatures on the product distribution. When the residence time (t^{R1}) in R1 was set to 0.38 s, the desired adduct **8a** was obtained in 44% yield with 45% recovery of the starting dibromothiophene **1**. Compounds **3a** and **10**, which were produced through halogen dance of 2,3-dibromo-5-lithiothiophene (**4**), were observed in trace amounts based on the ^{1}H NMR spectrum of the crude product (entry 1). Elevating the reaction temperatures led to consumption of the starting dibromothiophene **1**; however, the yields of the desired alcohol **8a** were slightly improved. When the reaction was performed at 0 °C, a substantial amount of compound **3a** was observed (entries 2 and 3). We then executed the reaction with a longer residence time (t^{R2} = 9.0 s) in R2 and found that the product distributions remained almost unchanged (entries 4–6). These results indicate that the reaction roughly finished within 2.2 s. The slight increases of the yields of compounds **3a** and **10** also indicate that halogen dance proceeds in R2 to some extent. We then prolonged the residence time (t^{R1} = 1.6 s) in R1 at various reaction temperatures. The yield of the desired product **8a** was significantly improved to 66% yield with 3% of its constitutional isomer **3a** and 3% of 2,4-dibromothiophene (**10**) (entry 7). The ratio of compounds **8a** and **3a** was ca. 1:1 to 2:1 at –42 °C and 0 °C (entries 8 and 9). A further prolonged residence time (t^{R1} = 3.1 s) in R1 resulted in the formation of the undesired alcohol **3a** in 20% NMR yield even at –78 °C with 16% recovery of dibromothiophene **1**, which reduced the yield of the desired adduct **8a** to 49% (entry 10). The ratio of compounds **8a** and **3a** ranged from ca. 2:3 to 3:2 at –42 °C and 0 °C (entries 11 and 12).

Table 1 Optimization of reaction conditions of deprotonation and functionalization of 2,3-dibromothiophene in a flow microreactor

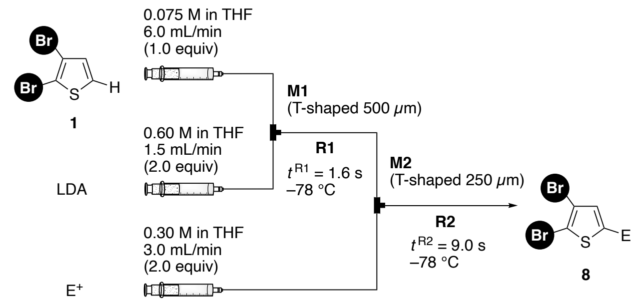


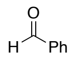
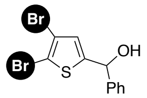
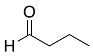
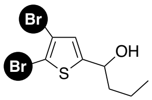
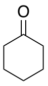
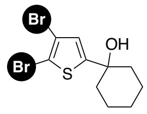
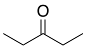
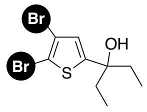
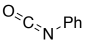
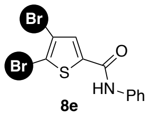
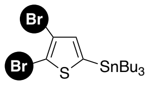
Entry	Temp (°C)	t^{R1} (s)	t^{R2} (s)	1 (%)[a]	8a (%)[a]	3a (%)[a]	10 (%)[a]
1	–78	0.38	2.2	45	44	<1	1
2	–42	0.38	2.2	40	50	2	1
3	0	0.38	2.2	11	48	25	4
4	–78	0.38	9.0	44	41	1	1
5	–42	0.38	9.0	38	44	6	2
6	0	0.38	9.0	10	38	31	8
7	–78	1.6	9.0	25[b]	66[b]	3[b]	3[b]
8	–42	1.6	9.0	9	43	37	5
9	0	1.6	9.0	11	53	22	3
10	–78	3.1	9.0	16	49	20	5
11	–42	3.1	9.0	10	28	43	8
12	0	3.1	9.0	11	43	29	6

[a] The yield was determined from the ^{1}H NMR spectrum of the crude product using 1,2-diiodoethane as an internal standard. [b] Average of two runs.

Having established the reaction conditions to trap the transient thienyllithium **4**, we then investigate the incorporation of other electrophiles (Table 2).[14] The reaction with benzaldehyde provided the desired alcohol **8a**[15] in 55% isolated yield (entry 1). Aliphatic aldehyde could be applied to the reaction, and the corresponding alcohol **8b**[15] was isolated in 84% yield (entry 2). The generated thienyllithium **4** was treated with cyclohexanone to afford tertiary alcohol **8c**[16,17] in 78% yield as colorless prisms (entry 3). The structure was confirmed by X-ray crystallographic analysis (Figure 1). The use of acyclic ketone resulted in slight reduction of the yield of adduct **8d**[10,18] (entry 4). Phenyl isocyanate reacted with the thienyllithium to provide amide **8e**[12] in 32% yield (entry 5), whereas the reaction with tributylstannyl chloride provided organotin **8f**[12] in 89% yield (entry 6). We also performed the same reaction in a batch reactor; a THF solution of 2,3-dibromothiophene (**1**) and an electrophile was added to the THF solution of LDA at –78 °C. After stirring at –78 °C for 5 min, the reaction mixture

Table 2 Reaction of thienyllithium **4** with several electrophiles



Entry	Electrophile (E⁺)	Product	Yield (%)[a]
1		 **8a**	55 (54[b])
2		 **8b**	84 (61[b])
3		 **8c**	78 (54[b])
4		 **8d**	61 (44[b])
5		 **8e**	32 (7[b])
6	Cl–SnBu₃	 **8f**	89 (78[b])

[a] Isolated yield. [b] The reaction was performed in a batch system. To a stirred LDA in THF was added a solution of 2,3-dibromothiophene and an electrophile at –78 °C.

was treated with saturated aqueous NH_4Cl. After the standard workup and purification, we isolated the corresponding products in lower yields, which indicated that the developed method is superior to the batch conditions.[19] Specifically, the batch reaction with phenyl isocyanate produced the urea that was formed by nucleophilic addition of LDA to phenyl isocyanate, and amide **8e** was isolated in 7% yield. The lower yields of the products can be attributed to the reactivity of the electrophiles toward LDA.

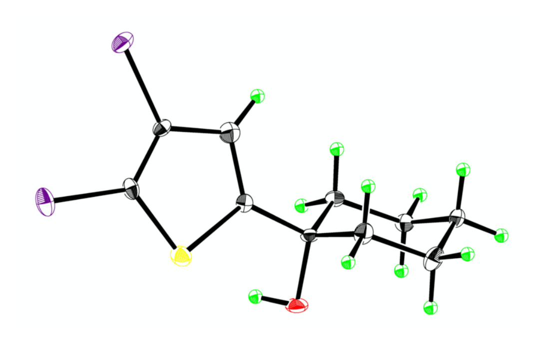
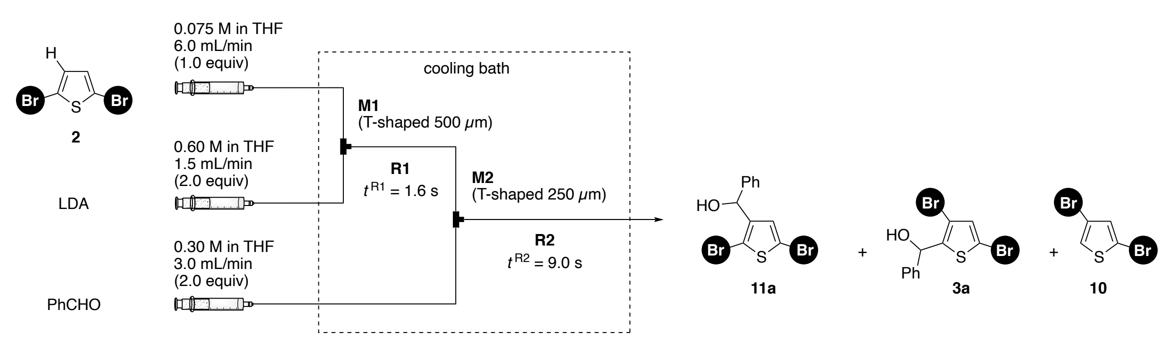


Figure 1 ORTEP drawing of the molecular structure of **8c** with thermal ellipsoids at 30% probability levels.

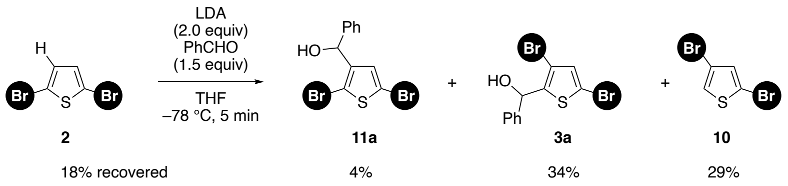
We then focused our attention on trapping thienyllithium **6** that was generated by deprotonation of 2,5-dibromothiophene (**2**) (Table 3). The corresponding product **11a** is a constitutional isomer to compound **3a**, which should be also the promising intermediated for the synthesis of substituted thiophenes. However, this thienyllithium **6** has not been trapped with an electrophile so far in a batch reactor.[8c,9b] We attempted to intercept thienyllithium **6** under the established reaction conditions. We found that almost no reaction was observed when the residence time (t^{R1}) in R1 was set to 1.6 s at –78 °C (Table 3, entry 1). Trace amounts of compounds **3a**, **10**, and **11a** were observed in the ^1H NMR spectrum of the crude product. Elevation of the reaction temperature to –42 °C led to the formation of the undesired alcohol **3a**; however, the yield of the desired product **11** did not improve, with 76% recovery of the starting 2,5-dibromothiophene (**2**) (entry 2). Most of the starting dibromothiophene **2** was consumed at 0 °C to provide a ca. 1:6 mixture of the compounds **11a** and **3a** (entry 3).

Table 3 Attempts to trap thienyllithium **6** generated from 2,5-dibromothiophene in a flow microreactor



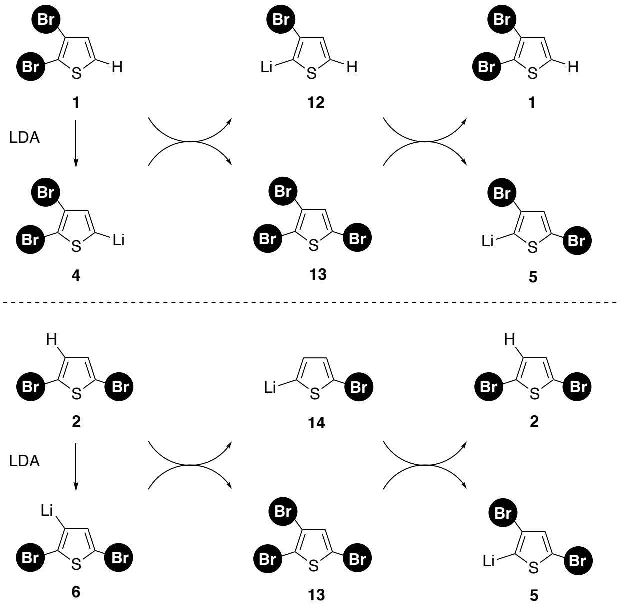
Entry	Temp (°C)	t^{R1} (s)	t^{R2} (s)	**2** (%)[a]	**11a** (%)[a]	**3a** (%)[a]	**10** (%)[a]
1	–78	1.6	9.0	85	<1	1	<1
2	–42	1.6	9.0	76	1	8	3
3	0	1.6	9.0	21	8	49	16

[a] The yield was determined from the ^1H NMR spectrum of the crude product using 1,2-diiodoethane as an internal standard.



Scheme 3 Attempts to trap thienyllithium **6** generated from 2,5-dibromothiophene in a batch reactor

We also performed the same reaction using a batch reactor, where the THF solution of 2,5-dibromothiophene (**2**) (1.0 equiv) and benzaldehyde (1.5 equiv) was added dropwise to the THF solution of LDA (2.0 equiv) at −78 °C (Scheme 3). After stirring for 5 min, the reaction mixture was treated with saturated aqueous NH_4Cl to provide 4% desired adduct **11a**, 34% undesired constitutional isomer **3a**, and 29% 2,4-dibromothiophene (**10**) with 18% recovery of the starting material.



Scheme 4 Plausible reaction pathways for halogen dance of 2,3- and 2,5-dibromothiophenes

These different reactivities for deprotonation/functionalization of 2,3-dibromothiophene (**1**) and 2,5-dibromothiophene (**2**) can be explained in Scheme 4. The swapping of the bromo group and the lithium atom is considered to proceed in an intermolecular manner to generate the thermodynamically favored 3,5-dibromothenyllithium **5**, which is stabilized by the inductive effect of the two bromo groups.[20] Deprotonation of 2,3-dibromothiophene (**1**) gives the transient thienyllithium **4**, which undergoes halogen–lithium exchange with another dibromothiophene **1** to provide thienyllithium **12** and tribromothiophene **13**. Subsequent halogen–lithium exchange of the two species leads to the formation of the thermodynamically most stable thienyllithium **5** with regeneration of dibromothiophene **1**. The plausible pathway for the halogen dance of 2,5-dibromothiophene (**2**) can be similarly explained, by thermodynamic stability of the thienyllithium species. The transient thienyllithium **4**, which could be trapped with some electrophiles, should be generated faster than the next halogen–lithium exchange to give α-thienyllithium **12**. In contrast, the short-lived thienyllithium **6** would be converted to α-thienyllithium **14** faster than the rate of deprotonation of 2,5-dibromothiophene (**2**). This assertion is consistent with the two factors: (1) deprotonation at the α-position is faster than that at the β-position[21] and (2) halogen–lithium exchange of the bromo group at the α-position and lithium atom at the α-position is slower than that of the bromo group at the α-position and lithium atom at the β-position, probably due to the fact that α-lithium species are generally more stable than the β-lithium species, based on the report on the reactivity of the related Grignard reagents.[12,22]

In conclusion, we have developed the method to trap the transient dibrominated thienyllithium that is generated by deprotonation of 2,3-dibromothiophene in a flow microreactor. This method enables to utilize the thienyllithium species without transmetalation and allows the synthesis of 5-substituted 2,3-dibromothiophene derivatives. The synthetic application of this method will be reported in due course.

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Supporting Information

YES

Primary Data

NO

References and Notes

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(14) **General experimental procedure for trapping the transient thienyllithium 4 in a flow microreactor.** Two micromixers, Mixer 1 (a T-shaped micromixer (ϕ = 500 μm)) and Mixer 2 (a T-shaped micromixer (ϕ = 250 μm)), two microtube reactors, Microtube 1 (ϕ = 1000 μm, L = 25 cm) and Microtube 2 (ϕ = 1000 μm, L = 200 cm), and three tube pre-cooling units, Pre-cooling unit 1 (ϕ =1000 μm, L = 100 cm), Pre-cooling unit 2 (ϕ = 1000 μm, L = 50 cm) and Pre-cooling unit 3 (ϕ = 1000 μm, L = 50 cm), consists a flow microreactor system. The solution of 2,3-dibromothiophene (**1**) (0.075 M in THF, flow rate: 6.00 mL min^{-1}) and a solution of LDA (0.60 M in THF, flow rate: 1.50 mL min^{-1}) were introduced to Mixer 1 by the syringe pumps. The resulting solution was passed through Microtube 1 and was mixed with a solution of electrophile (0.30 M in THF, flow rate: 3.00 mL min^{-1}) in Mixer 2. The resulting solution was passed through Microtube 2. After a steady state was reached (60 s), the product solution was collected for 240 s, while being quenched with aqueous saturated NH_4Cl. The layers were separated, and the aqueous

layer was extracted with diethyl ether, and the combined organic extracts were washed with water and brine, dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to provide a crude product, which was purified by silica gel column chromatography to provide the corresponding product.

(15) An NOE enhancement was observed between the aromatic proton on the thiophene ring and the methine proton.

(16) **Physical data of compound 8c.** R_f = 0.31 (hexane/CH_2Cl_2 = 1:1); M.p. 80–81 °C (hexane); IR (ATR, cm^{-1}): 3348, 2927, 2854, 1445, 1305, 1158, 1131, 1000, 970, 814, 796; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.76 (s, 1H), 2.03 (s, 1H), 1.91–1.55 (m, 9H), 1.36–1.23 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 156.1, 124.8, 113.0, 109.5, 72.7, 39.6, 25.3, 22.2; Elemental analysis calcd (%) for $C_{10}H_{12}Br_2OS$: C, 35.32; H, 3.50; found: C, 35.29; H, 3.39.

(17) CCDC 2020290 contains the supplementary crystallographic data for compound **8c**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(18) Chemical shifts of ^{1}H and ^{13}C NMR spectra of the synthesized **8d** were not consistent with those reported by Knochel (Ref. 10).

(19) For the detail, see Supporting Information.

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