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

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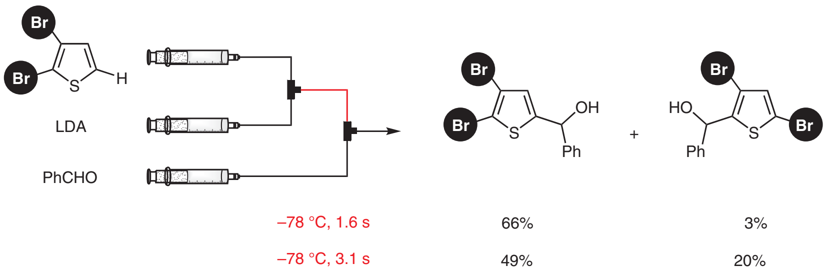

In memory of Jun-ichi Yoshida

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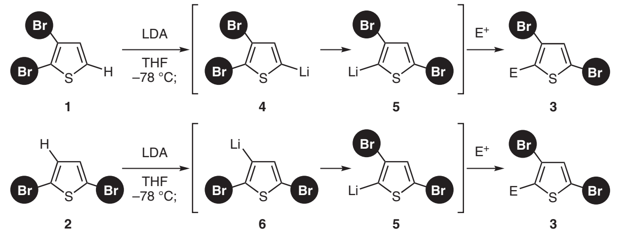
Abstract Selective trapping of (4,5-dibromo-2-thienyl)lithium, known to undergo halogen dance, was achieved in a flow microreactor. This transient thienyllithium, generated by mixing 2,3-dibromothiophene and lithium diisopropylamide at –78 °C for 1.6 seconds, reacted with benzaldehyde. The reaction system is also applicable to other carbonyl compounds to afford the corresponding adducts in good yields. Moreover, the established conditions permit the conversion of 2,5-dibromothiophene into a mixture of the two constitutional isomers. The contrasting results are discussed on the basis of the reaction pathway.

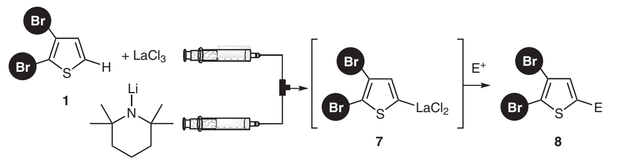
Key words halogen dance, microreactors, dibromothiophenes, substituent effects, deprotonation, lithiation

Functionalized thiophenes are structural constituents of many agrochemicals, pharmaceuticals, and functional materials.[1] A number of substituted thiophenes have been synthesized by reactions of thienylmetal species with electrophiles,[2,3] as well as by electrophilic aromatic substitutions,[4] cross-coupling reactions,[5] or cyclizations of acyclic carbonyl compounds.[6] Several thienyllithium species bearing one or more bromo and iodo groups undergo swapping of lithium and the halogen atoms, a process referred to as 'halogen dance'.[4b,7] Both 2,3-dibromothiophene (**1**) and 2,5-dibromothiophene (**2**) undergo sequential deprotolithiation, halogen dance, and reaction with an electrophile to provide the same 2,4-dibromothiophene derivative **3** (Scheme 1).[8,9] Deprotonation of **1** selectively proceeds at the more acidic α-position to give thienyllithium **4**, which undergoes halogen dance to give the thermodynamically more stable thienyllithium **5**.[8] Similarly, thienyllithium **6**, which is generated from 2,5-dibromothiophene (**2**), is also converted into the more stable thienyllithium **5**.[8c,9]

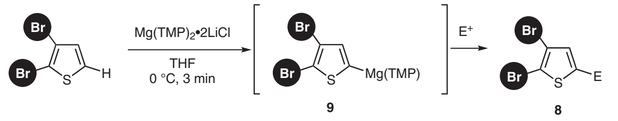


Scheme 1 Halogen dance of dibrominated thienyllithium species generated by deprotonation of 2,3-dibromothiophene and 2,5-dibromothiophene

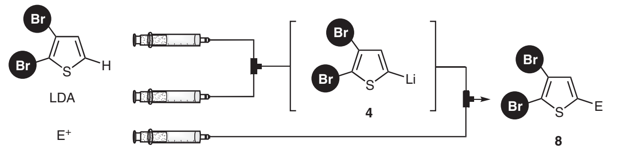
(A) Deprotonation by LiTMP and in situ transmetalation with $LaCl_3$ in a flow reactor (Ref. 10)



(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)

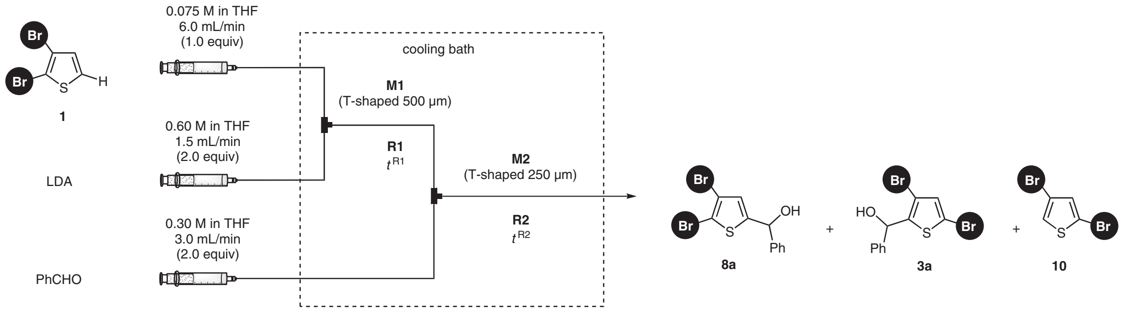


Scheme 2 Trapping of the thienylmetal species generated by deprotonation of 2,3-dibromothiophene

Although thienyllithium **5** has been employed for the synthesis of various thiophenes, only one model reaction involving trapping of thienyllithium **4** has been reported, despite its usefulness in the synthesis of constitutional isomers (Scheme 2A). In this example, in situ transmetalation of the transient thienyllithium **4** into the organolanthanum derivative **7** in a flow reactor gave **8**.[10] Our group recently reported the generation of the thienylmagnesium derivative **9** (TMP = 2,2,6,6-tetramethylpiperidinyl) by deprotonation of 2,3-dibromothiophene (**1**) with $Mg(TMP)_2\cdot 2LiCl$.[11] Although the thienylmagnesium **9** underwent halogen dance at room temperature,[12] this reaction was sufficiently sluggish at 0 °C to permit trapping of the transient **9** by several electrophiles (Scheme 2B). The recent development of flash chemistry in a flow microreactor[13] prompted us to investigate the direct trapping of thienyllithium **4** with an electrophile (Scheme 2C). Here, we describe the selective trapping of thienyllithium **4** generated from 2,3-dibromothiophene (**1**) and commercially available LDA.

First, we explored the optimal reaction conditions to trap the transient thienyllithium **4** with benzaldehyde as an electrophile (Table 1). The microflow system consisted of a T-shaped micromixer (M1: 500 μm), a second T-shaped micromixer (M2: 250 μm), and two microtube reactors (R1 and R2). Thienyllithium **4** was generated from 2,3-dibromothiophene (**1**) and LDA at various reaction temperatures of the cooling bath and with various residence times (t^{R1}) in R1. It was subsequently trapped with benzaldehyde in R2 to afford the desired adduct **8a**, together with its constitutional isomer **3a** (formed by halogen dance of **4**) and 2,4-dibromothiophene (**10**; formed by halogen dance and protonation). The flow rate of the 0.075 M solution of 2,3-dibromothiophene (**1**) in THF was adjusted to 6.0 mL/min. The 0.60 M solution of LDA in THF was prepared just before use, and its flow rate was set to 1.5 mL/min. The flow rate of the 0.30 M solution of benzaldehyde in THF was set to 3.0 mL/min. Both the reaction temperature and the residence time (t^{R1}) in R1 were found to be important for trapping the short-lived thienyllithium species. We first investigated the effects of the reaction temperature on the product distribu-

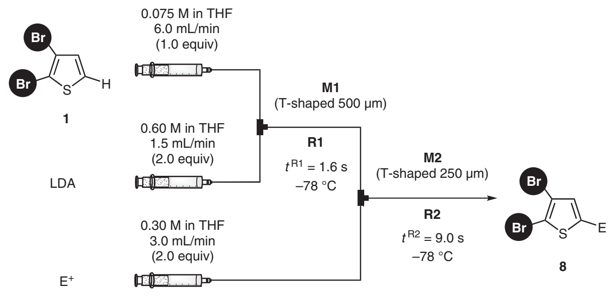
Table 1 Optimization of the Reaction Conditions for the Deprotonation and Functionalization of 2,3-Dibromothiophene (**1**) in a Flow Microreactor

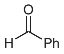
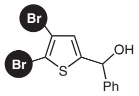
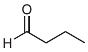
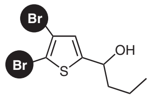
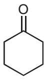
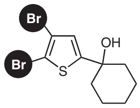
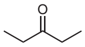
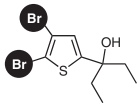
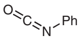
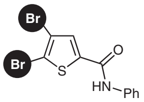
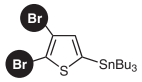


Entry	Temp (°C)	t^{R1} (s)	t^{R2} (s)	Yield[a] (%)			
				1[b]	**8a**	**3a**	**10**
1	–78	0.38	2.2	45	44	<1	1
2	–42	0.38	2.2	40	50	2	1
3	0	0.38	2.2	11	48	25	4
4	–78	0.38	9.0	44	41	1	1
5	–42	0.38	9.0	38	44	6	2
6	0	0.38	9.0	10	38	31	8
7	–78	1.6	9.0	25[c]	66[c]	3[c]	3[c]
8	–42	1.6	9.0	9	43	37	5
9	0	1.6	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] Determined from the ^1H NMR spectrum of the crude product, with 1,2-diiodoethane as an internal standard.
[b] Recovered reactant.
[c] Average of two runs.

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	Bu_3SnCl	 **8f**	89 (78)[b]

[a] Isolated yield.
[b] Yield from the corresponding batch reaction, performed by adding a solution of 2,3-dibromothiophene (**1**) and the appropriate electrophile to a stirred solution of LDA in THF at –78 °C.

tion. When the residence time (t^{R1}) in R1 was set to 0.38 seconds, the desired adduct **8a** was obtained in 44% yield with 45% recovery of the starting 2,3-dibromothiophene (**1**). Compounds **3a** and **10** were observed in trace amounts in the ^{1}H NMR spectrum of the crude product (Table 1, entry 1). Raising the reaction temperature led to consumption of the starting 2,3-dibromothiophene (**1**); however, the yield of the desired alcohol **8a** slightly improved. When the reaction was performed at 0 °C, a substantial amount of compound **3a** was observed (entries 2 and 3). We then performed the reaction with a longer residence time in R2 (t^{R2} = 9.0 s) and we found that the product distribution remained almost unchanged (entries 4–6). These results indicated that the reaction was complete within about 2.2 s. The slight increases in the yields of compounds **3a** and **10** also indicated that halogen dance proceeded in R2 to some extent. We then examined the effect of a prolonged residence time in R1 (t^{R1} = 1.6 s) at various reaction temperatures. At –78 °C, the desired product **8a** was obtained in a significantly improved yield of 66%, together with 3% of its constitutional isomer **3a** and 3% of 2,4-dibromothiophene (**10**) (entry 7). The ratios of compounds **8a** and **3a** were about 1:1 and 2:1 at –42 °C and 0 °C, respectively (entries 8 and 9). A further increase in the residence time in R1 (t^{R1} = 3.1 s) resulted in the formation of the undesired alcohol **3a** in 20% NMR yield, even at –78 °C, with 16% recovery of 2,3-dibromothiophene (**1**); this reduced the yield of the desired adduct **8a** to 49% (entry 10). The ratios of compounds **8a** and **3a** were about 2:3 and 3:2 at –42 °C and 0 °C, respectively (entries 11 and 12).

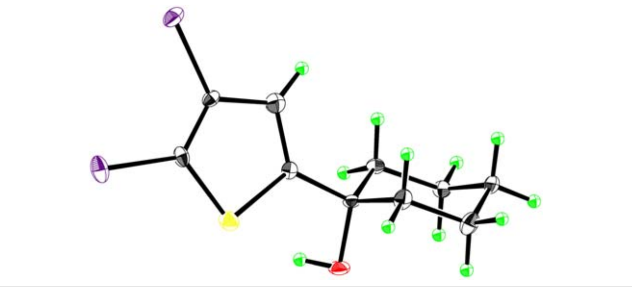
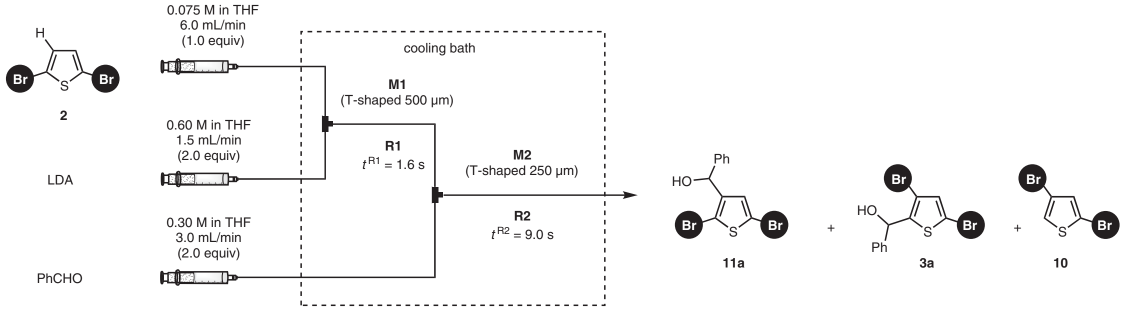


Figure 1 ORTEP drawing of the molecular structure of **8c** with thermal ellipsoids at 30% probability levels

Having established appropriate reaction conditions to trap the transient thienyllithium **4**, we then investigated the incorporation of other electrophiles (Table 2).[14] The reaction with benzaldehyde provided the desired alcohol **8a**[15] in 55% isolated yield (Table 2, entry 1). The use of aliphatic butanal gave the corresponding alcohol **8b**[15] in 84% isolated yield (entry 2). Treatment of the generated thienyllithium **4** with cyclohexanone gave the tertiary alcohol **8c**[16,17] in 78% yield as colorless prisms (entry 3). The structure of this product was confirmed by X-ray crystallographic analysis (Figure 1). The reaction with acyclic pentan-3-one gave adduct **8d**[10,18] in a slightly reduced yield (entry 4). Phenyl isocyanate reacted with the thienyllithium **4** to provide amide **8e**[12] in 32% yield (entry 5), whereas the reaction of **4** with tributylstannyl chloride gave the organotin derivative **8f**[12] in 89% yield (entry 6). We also performed the same reaction as a batch process. A solution of 2,3-dibromothiophene (**1**) and the appropriate electrophile in THF was added to a solution of LDA in THF at –78 °C, and the mixture was stirred at –78 °C for 5 min. The reaction mixture was then treated with saturated aqueous NH_4Cl. After the standard workup and purification, we isolated the corresponding

Table 3 Attempts to Trap Thienyllithium **6** Generated from 2,5-Dibromothiophene (**2**) in a Flow Microreactor

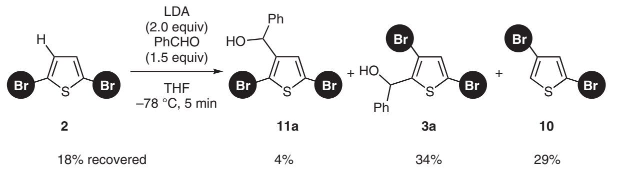


Entry	Temp (°C)	t^{R1} (s)	t^{R2} (s)	Yield[a] (%)			
				2[b]	**11a**	**3a**	**10**
1	–78	1.6	9.0	85	<1	1	<1
2	–42	1.6	9.0	76	1	8	3
3	0	1.6	9.0	21	8	49	16

[a] Determined from the ^{1}H NMR spectrum of the crude product, with 1,2-diiodoethane as an internal standard.
[b] Recovered reactant.

products in lower yields than those from the continuous reactor, showing that our developed method is superior to the batch process.[19] In particular, the batch reaction with phenyl isocyanate gave the a urea product formed by nucleophilic addition of LDA to phenyl isocyanate, and the amide **8e** was isolated in only 7% yield. The lower yields of the products can be attributed to the reactivity of the electrophiles toward LDA.

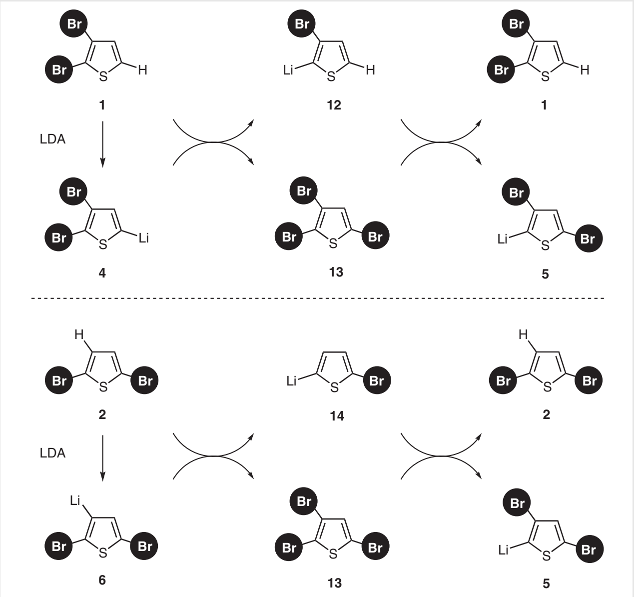
We then focused our attention on trapping by benzaldehyde of the thienyllithium **6** generated by deprotonation of 2,5-dibromothiophene (**2**) (Table 3). The corresponding product **11a** is a constitutional isomer of compound **3a**, and is a promising intermediate for the synthesis of substituted thiophenes. However, thienyllithium **6** had not previously been trapped by an electrophile in a batch reactor.[8c,9b] When we attempted to intercept thienyllithium **6** under our established reaction conditions, we found that almost no reaction occurred with the residence time in R1 (t^{R1} = 1.6 s) at –78 °C (Table 3, entry 1). Traces of compounds **3a**, **10**, and **11a** were observed in the ^{1}H NMR spectrum of the crude product. Raising 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 and 76% of the starting 2,5-dibromothiophene (**2**) was recovered (entry 2). Most of the starting dibromothiophene **2** was consumed at 0 °C to provide an approximately 1:6 mixture of compounds **11a** and **3a** (entry 3).



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

We also performed the same reaction in a batch reactor, by adding a solution of 2,5-dibromothiophene (**2**) (1.0 equiv) and benzaldehyde (1.5 equiv) in THF dropwise to a solution of LDA (2.0 equiv) in THF at –78 °C (Scheme 3). The mixture was stirred for 5 minutes, then treated with saturated aqueous NH_4Cl to provide 4% of the desired adduct **11a**, 34% of the undesired constitutional isomer **3a**, and 29% of 2,4-dibromothiophene (**10**), with an 18% recovery of the starting material.

These different reactivities for deprotonation/functionalization of 2,3-dibromothiophene (**1**) and 2,5-dibromothiophene (**2**) can be explained by the reaction pathways shown in Scheme 4. The bromo group and the lithium atom are believed to exchange in an intermolecular manner to generate thermodynamically favored (3,5-dibromothienyl)lithium (**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 molecule of **1** to provide thienyllithium **12** and 2,3,5-tribromothiophene (**13**). Subsequent halogen–lithium exchange of these two species leads to the formation of the thermodynamically more stable thienyllithium **5**, with regeneration of 2,3-dibromothiophene (**1**). A plausible pathway for the halogen dance of 2,5-dibromothiophene (**2**) can be similarly explained by the thermodynamic stability of the thienyllithium species. The transient thienyllithium **4**, which could



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

be trapped by some electrophiles, is generated faster than the next halogen–lithium exchange to give α-thienyllithium **12**. In contrast, the short-lived thienyllithium **6** is converted into the α-thienyllithium **14** faster than the rate of deprotonation of 2,5-dibromothiophene (**2**). This proposal is consistent with 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 the 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 because α-lithium species are generally more stable than β-lithium species, according to reports on the reactivity of related Grignard reagents.[12,22]

In conclusion, we have developed a method to trap the transient dibrominated thienyllithium species generated by deprotonation of 2,3-dibromothiophene in a flow microreactor. This method permits the direct use of thienyllithium species, without transmetalation, in syntheses of 5-substituted 2,3-dibromothiophene derivatives. Synthetic applications of this method will be reported in due course.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1706479.

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(14) **Trapping of Transient Thienyllithium 4 in a Flow Microreactor; General Procedure** The flow reactor system consisted of two micromixers [Mixer 1 (T-shaped micromixer; φ = 500 µm) and Mixer 2 (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 precooling units [Precooling Unit 1 (φ =1000 µm, *L* = 100 cm), Precooling Unit 2 (φ = 1000 µm, *L* = 50 cm), and Precooling Unit 3 (φ = 1000 µm, *L* = 50 cm)]. A 0.075 M solution of 2,3-dibromothiophene (**1**) in THF (flow rate: 6.00 mL min^{-1}) and a 0.60 M solution of LDA in THF (flow rate: 1.50 mL min^{-1}) were introduced into Mixer 1 by syringe pumps. The resulting mixture passed through Microtube 1 and was mixed with a 0.30 M solution of the appropriate electrophile in THF (flow rate: 3.00 mL min^{-1}) in Mixer 2. The resulting solution then passed through Microtube 2. Once a steady state was reached (60 s), the product solution was collected for 240 s, while being quenched with sat. aq NH_4Cl. The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic extracts were washed with H_2O and brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated under reduced pressure to provide a crude product that was purified by column chromatography (silica gel).

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

(16) **1-(4,5-Dibromo-2-thienyl)cyclohexanol (8c)**
Colorless prisms; yield: 475.6 mg (78%); mp 80–81 °C (hexane); R_f = 0.31 (hexane–CH_2Cl_2, 1:1). IR (ATR): 3348, 2927, 2854, 1445, 1305, 1158, 1131, 1000, 970, 814, 796 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.76 (s, 1 H), 2.03 (s, 1 H), 1.91–1.55 (m, 9 H), 1.36–1.23 (m, 1 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 156.1, 124.8, 113.0, 109.5, 72.7, 39.6, 25.3, 22.2. Anal. 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**. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.

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

(19) For details, see the Supporting Information.

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