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Halogen Dance on 2-Iodobenzofuran and 2-Iodobenzothiophene and Related Reactions

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Abstract: When 2-iodobenzofuran was treated sequentially with lithium 2,2,6,6-tetramethylpiperidine in tetrahydrofuran at $-50\text{ }^{\circ}\text{C}$ and an aldehyde, the 2-substituted 3-iodobenzofuran resulting from the halogen dance was the only isolated product. However, from 2-iodobenzothiophene, these conditions led to mixtures in which the 2-substituted 3-iodobenzothiophene was always accompanied by the 2-substituted benzothiophene. The use of 2-bromobenzothiophene as a catalyst made it possible to significantly reduce this competitive dehalogenation. To confirm the halogen dance reaction, the products were unambiguously synthesized by using direct halogenations and deprotolithiation-trapping sequences as key steps. Our efforts to access 2,7-disubstituted and 7-substituted derivatives of benzofuran and benzothiophene have also been reported.

Introduction

Benzo[*b*]furan¹ and benzo[*b*]thiophene² are aromatic heterocycles present in many compounds of biological interest such as the estrogen receptor modulator raloxifene,³ the kinase inhibitor liphagal,⁴ and tubulin polymerization inhibitors.⁵ Moreover, they have also found interesting applications in organic materials.⁶ Although these aromatic heterocycles can be easily functionalized by many reactions^{1,7} such as deprotometallation-electrophilic trapping sequences⁸ and C-H functionalizations,⁹ there is surprisingly only one example of a halogen dance, involving 2-bromobenzothiophene.¹⁰

The halogen dance is an elegant reaction, mediated by a base (usually a hindered lithium amide in the modern version), by which a halogenated aromatic substrate is isomerized.¹¹ It consists of a succession of halogen/metal exchanges triggered by deprotometallation and driven by the stability of the arylmetal species formed.¹² Thiophenes were among the first aromatic systems on which the reaction was studied. For example, 2,3-dibromo,¹³ 2,5-dibromo¹³ and other 2-bromothiophenes¹⁴ have been successfully isomerized using lithium diisopropylamide in tetrahydrofuran (THF). Although less efficient, the reaction was also later extended to bromofurans.¹⁵ Concerning 2-iodothiophenes¹⁶ and 2-iodofurans,¹⁷ very few examples have been described. Although the yields are lower, these reports show that halogen dance remains possible in these series from iodinated substrates.

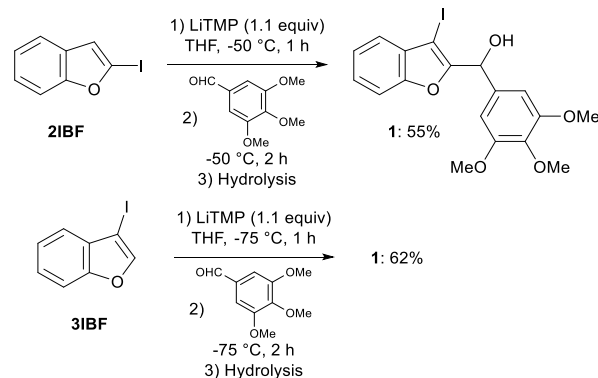
Since 2-benzofuryllithium and 2-benzothiennyllithium¹⁸ are more stabilized than the corresponding 3-lithiated derivatives¹⁹ owing to the presence of the neighbouring heteroatom, we reasoned that the corresponding 2-brominated and 2-iodinated derivatives would be suitable substrates to attempt the halogen

dance reaction in these series. Additionally, due to their potential applications²⁰ and our own interest in the copper-mediated *N*-arylation of anilines with 2- and 3-iodinated derivatives of benzofuran and benzothiophene,²¹ we focused our study on the iodinated derivatives. Here we describe the application of the halogen dance reaction in these series and discuss the difficulties encountered.

Results and Discussion

In the benzofuran series

Based on our experience in the halogen dance of iodoferrrocenes,²² we selected lithium 2,2,6,6-tetramethylpiperidine (LiTMP) as the base. In a first attempt, 2-iodobenzofuran²³ (**2IBF**), prepared from benzofuran (**BF**) by deprotolithiation-iodolysis, was treated with LiTMP (1.1 equiv) in THF at $-50\text{ }^{\circ}\text{C}$ for 1 h before adding excess methanol. Under these conditions, the formation of 3-iodobenzofuran (**3IBF**) was observed (estimated yield: 40%) but its separation from the crude proved impossible. Also, we decided to use an electrophile likely to lead to a more polar product, and therefore chose 3,4,5-trimethoxybenzaldehyde. Thus, by repeating the reaction between **2IBF** and LiTMP in this way, 3-iodo- α -(3,4,5-trimethoxyphenyl)benzofuran-2-methanol (**1**) was obtained in 55% yield while approximately 32% of the starting **2IBF** was recovered (Scheme 1, top).



Scheme 1. Halogen dance reaction from 2-iodobenzofuran (**2IBF**) to the alcohol **1** (top) and formation of **1** from 3-iodobenzofuran (**3IBF**; bottom).

In order to ensure that the compound formed was not 2-iodo- α -(3,4,5-trimethoxyphenyl)benzofuran-3-methanol, we devised a complementary approach to **1** based on the deprotolithiation of 3-iodobenzofuran (**3IBF**). For this, we decided to prepare 3-bromobenzofuran (**3BBF**) in order to reach **3IBF** by a bromine/lithium exchange-iodolysis sequence. A first attempt at C3 bromination of **BF**, as previously claimed,²⁴ resulted in the concomitant formation of inseparable 2-bromobenzofuran (**2BBF**). However, we managed to achieve **3BBF** by using the procedure reported by Hecht and co-workers which involves the addition of bromine on the double bond followed by elimination.²⁵ Then, bromine/lithium exchange on **3BBF** was performed by using *n*-butyllithium (1.2 equiv) in diethyl ether at -75 °C for 1 h.²⁶ After trapping with iodine, **3IBF** was isolated in a moderate 36% yield. To functionalize the latter, we employed LiTMP in THF at -75 °C for 1 h before aldehyde interception. The alcohol formed, isolated in 62% yield (Scheme 1, bottom), was found to be identical to **1**, showing unambiguously that the halogen dance did indeed occur by treating **2IBF** with LiTMP.

In a published study, benzofuran (**BF**) was converted to α,α' -(4-tolyl)benzofuran-2,7-dimethanol in 40% yield by successive treatments with 2.2 equivalents of the *n*-butyllithium-TMEDA (TMEDA = *N,N,N',N'*-tetramethylethylenediamine) chelate in hexane at reflux for 1.5 h and 4-tolualdehyde.²⁷ In order to prepare 2-substituted 7-iodobenzofurans, we also thought of functionalizing *in situ* the lithium salt of α -(3,4,5-trimethoxyphenyl)benzofuran-2-methanol (**2**). We initially treated **BF** with *n*-butyllithium (1.1 equiv) in THF at -20 °C for 1 h before adding 3,4,5-trimethoxybenzaldehyde to obtain the alcohol **2**, isolated in 79% yield (Scheme 2, top). With the alcohol **2** as reference compound, we directly involved its lithium salt in a second deprotometallation-trapping sequence. For this, we first tested the base prepared from ZnCl₂-TMEDA (1 equiv) and LiTMP (3 equiv),²⁸ and assumed to be a 1:1 mixture of LiTMP and Zn(TMP)₂.^{23a,28-29} However, when used in THF at -15 °C for 1 h, the only compound formed after iodolysis was the known 2-(3,4,5-trimethoxybenzoyl)benzofuran³⁰ (**3**; Figure 1, left), isolated in 27% yield. Since *sec*-butyllithium-TMEDA has already been used to deprotometallate 2,3-diphenylbenzofuran in THF (-78 °C for 1 h),³¹ we also tested this combination (3 equiv) on the lithium salt in THF; however, even after 6 h of base-substrate contact at 0 °C before iodolysis, the alcohol **2** was again mostly recovered. Without TMEDA, treatment with *sec*-butyllithium (1.1 equiv) in THF at -15 °C for 0.5 h followed by addition of iodine not only resulted in the recovery of **2** (\sim 60%) but also provided an unidentified product. Finally, the use of the *sec*-butyllithium-TMEDA chelate (2 equiv) in hexane or diethyl ether at room temperature overnight led, after iodolysis, to the recovery of **2** (respectively 47% or 33%) as well as the formation of **3** (respective yields of 24% or 12% yield), the rest being degradation.

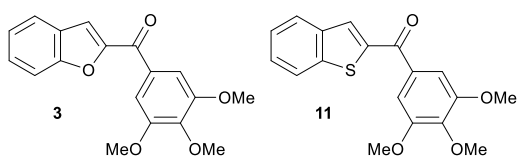
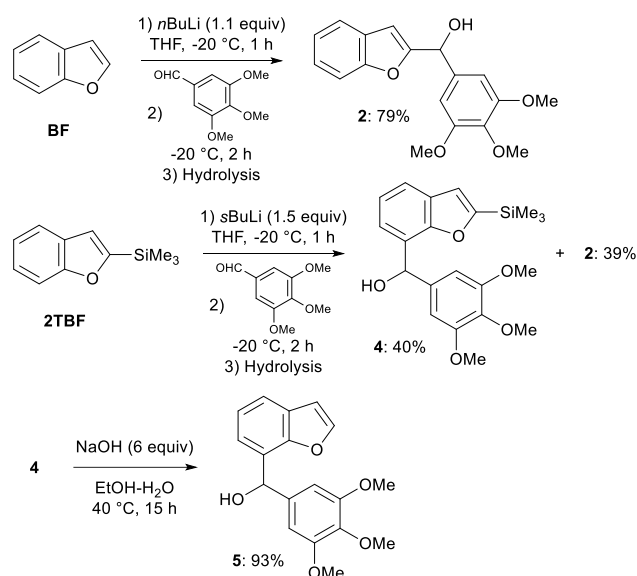


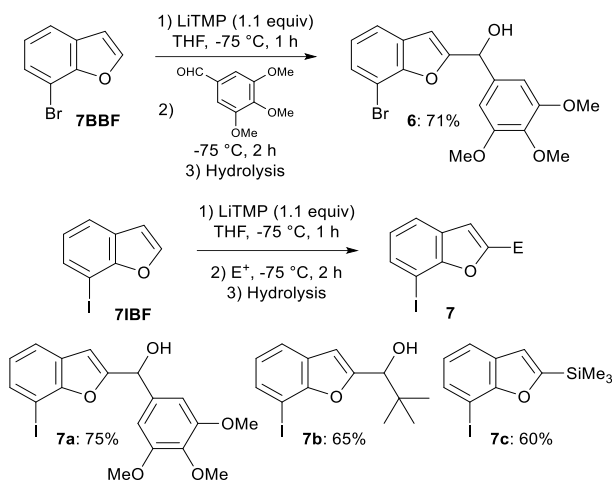
Figure 1. The ketones **3** and **11** obtained.

These results contrast with the functionalization of 2-(trimethylsilyl)benzofuran (**2TBF**) at C7 under similar conditions. Indeed, in 2007, Crich and Grant converted **2TBF** into the 7-iodinated derivative in 41% yield by treating it successively with *sec*-butyllithium in THF at room temperature for 1 h and iodine.³² However, when we repeated this reaction by using 3,4,5-trimethoxybenzaldehyde as an electrophile, we observed the formation of two alcohols, the expected one **4** and α -(3,4,5-trimethoxyphenyl)benzofuran-2-methanol (**2**). By decreasing the deprotonation temperature to -20 °C, **4** was obtained in 40% yield while we also isolated 39% of the alcohol **2** (Scheme 2, middle; the rest is **2TBF**). We also attempted to deprotonate **2TBF** by using a base prepared from ZnCl₂-TMEDA (1 equiv) and LiTMP (3 equiv) in THF at -15 °C for 1 h before iodolysis, but only recovered the starting material. Eventually, the trimethylsilyl group was easily removed by reacting **4** with sodium hydroxide in an ethanol-water mixture at 40 °C³³ to provide the alcohol **5** (Scheme 2, bottom).



Scheme 2. Efforts to functionalize benzofuran (**BF**) at its 7-position.

Since we could hardly introduce a C7 substituent from 2-substituted benzofurans, we reversed the step order and considered the likely easier C2 deprotometallation from 7-substituted benzofurans. For this, we prepared 7-bromobenzofuran (**7BBF**) and 7-iodobenzofuran (**7IBF**) in two steps from the corresponding 2-halophenols, as described previously.³⁴ Their functionalization was successfully achieved by applying the protocol used above to prepare **1** from **3IBF** (Scheme 1, bottom). Thus, the brominated alcohol **6**, the iodinated alcohols **7a** and **7b**, and the iodinated silane **7c** were isolated with good yields (Scheme 3).



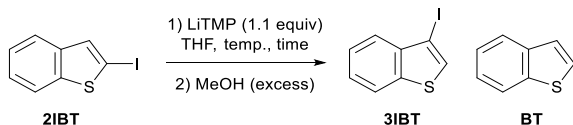
Scheme 3. Formation of **6** and **7a-c** from 7-bromobenzofuran (**7BBF**) and 7-iodobenzofuran (**7IBF**), respectively.

In the benzothiophene series

Compared with benzofuran (**BF**), benzothiophene (**BT**) benefits from a slightly lower pK_a value at its 2-position (32.4 vs. 33.2),¹⁸ which will favour its conversion to 2-benzothiophenyllithium. However, either alkylolithiums or lithium amides can be used to deprotonate both of them.³⁵

In order to study the behaviour of 2-iodobenzothiophene (**2IBT**) towards LiTMP, it was prepared from **BT** as previously reported.²³ As shown in Table 1, whatever the temperature used between -75 °C and -25 °C for the reaction with the lithium amide (1.1 equiv) in THF, we always obtained mixtures of 3-iodobenzothiophene³⁶ (**3IBT**), **2IBT** and **BT** after subsequent addition of methanol. At -75 °C, the quantity of **BT** being greater than that obtained at -50 °C or -25 °C after 1 h of contact, we did not repeat the reaction with longer reaction times. At -50 °C or -25 °C, the quantity of **BT** increases significantly only after 5-6 h of contact while **2IBT** reaches a minimum value; however, there is no significant change in the amount of **3IBT** produced as a function of the reaction time. If, after long reaction times at -50 °C or -25 °C, the reaction mixture is quenched with a solution of iodine in THF, 2,3-diiodobenzothiophene (**DIBT**) is observed in the crude instead of **3IBT**;³⁷ this indicates that **3IBT** is still lithiated at C2 and therefore intercepted with iodine. **2IBT** and **BT** being also present in these two crudes, it indicates that **BT** is only partially lithiated at C2 before trapping.

Table 1. Halogen dance reaction from 2-iodobenzothiophene (**2IBT**) followed by methanol quenching.

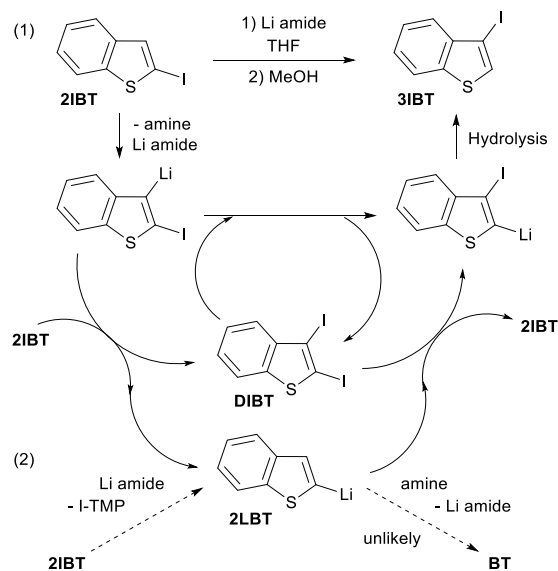


Entry	Conditions	2IBT (%) ^[a]	3IBT (%) ^[a]	BT (%) ^[a]
1	-75 °C, 1 h	26	22	53
2	-50 °C, 1 h	30	47	23
3	-50 °C, 4 h	25	56	18

4 ^[b]	-50 °C, 6 h	10	48	42
5	-25 °C, 1 h	31	45	24
6	-25 °C, 2 h	31	47	22
7	-25 °C, 4 h	25	54	21
8 ^[b]	-25 °C, 5 h	21	44	34

[a] Yields estimated from the NMR spectra of the crude. [b] Iodolysis after 7 h at -50 °C or 6 h at -25 °C showed the disappearance of **3IBT** and formation of **DIBT**.

The results obtained here are different from those observed from **2IBF** for which no competitive deiodination is observed. The formation of dehalogenated products during halogen dance reactions has already been reported,³⁸ and we have previously proposed a pathway to rationalize it in the ferrocene series, by protonation of the less stable ferrocenyllithium intermediate with the formed 2,2,6,6-tetramethylpiperidine (H-TMP).^{22a} The halogen dance mechanism³⁹ applied to **2IBT** is illustrated in Scheme 4.1. Here, the formation of **BT** by protonation of 2-lithiobenzothiophene (**2LBT**) is unlikely given the respective pK_a values of benzothiophene at C2¹⁸ (32.4) and H-TMP (37.3).⁴⁰ These observations led us to believe that a competitive iodine/lithium exchange by LiTMP could be responsible for the loss of iodine observed in these experiments (Scheme 4.2). A similar explanation was advanced by de Bie, van der Plas and co-workers to explain the competitive dehalogenation observed upon treatment of 2-bromobenzothiophenes with potassium amide in liquid ammonia (e.g. 3-methylbenzothiophene formed from 2-bromo-3-methylbenzothiophene in 70% yield after 1 h reaction at -33 °C).^{10a}



Scheme 4. Mechanism proposed^{22a} to rationalize the halogen dance reaction (1; full line arrows) and the competitive loss of iodine (2; dotted arrows).

To our knowledge, the reactivities of **2IBF** and **2IBT** in halogen/metal exchange reactions have never been compared. However, Mayr and co-workers performed competition experiments between bromofurans and bromothiophenes by









using $i\text{PrMgCl}\cdot\text{LiCl}$ in THF at 0 °C.⁴¹ The study shows that if 3-bromofuran (**3BF**) and 3-bromothiophene (**3BT**) share similar reactivities, 2-bromofuran (**2BF**; with a k_{rel} value 90 times greater than those of **3BF** and **3BT**) and especially 2-bromothiophene (**2BT**; with a 2500 times greater k_{rel} value) are significantly more reactive. Iodoarenes are known to be more reactive than the corresponding bromoarenes, and benzo-fused five-membered heterocycles are known to be more reactive than the parent five-membered heterocycles (e.g., 3-bromobenzothiophene (**3BBT**) is 9 times more reactive than **3BT**).⁴¹ Therefore, the order of reactivity should be preserved, with easier halogen/metal exchange on **2IBT** than on **2IBF**, in agreement with the observed results. Moreover, the fact that 2-iodothiophene and **DIBT** have recently been identified as good iodine transfer reagents⁴² also points in the same direction. Such a transfer of iodine from 2-benzothiophenyl to TMP could take place by a halogenophilic reaction,⁴³ either by an $\text{S}_{\text{N}}2@I$ type reaction (as described to explain the dehalogenation of arenes),⁴⁴ or by formation of an iodine ate-complex intermediate (as proposed for the classical iodine/lithium exchange).⁴⁵

When de Bie, van der Plas and co-workers studied the halogen dance reaction on 2-bromobenzothiophenes using potassium amide in liquid ammonia, they hypothesized that a bromamine was formed during the competitive debromination.^{10a} Accordingly, the species formed by reacting H-TMP with *N*-iodosuccinimide, and which should be I-TMP based on related species similarly prepared from 9-azabicyclo[3.3.1]nonane,⁴⁶ was here found to partially iodinate 2-lithiobenzothiophene (**2LBT**), affording **2IBT** and **BT** in 65% and 10% estimated yields, respectively. In a further experiment, we treated a mixture of **BT** and iodine (1 equiv) with LiTMP (1.1 equiv) in THF at -75 °C for 1 h before addition of methanol to obtain a 37:63 mixture of **2IBT** and **BT**. We also noticed that the species formed between LiTMP and iodine (1 equiv each) is able to partially iodinate **2LBT**, albeit in a lower conversion; indeed, if methanol is added after 1 h contact at -75 °C in THF, a 37:63 mixture of **2IBT** and **BT** is obtained. Finally, we observed that the equilibration in THF at -75 °C between 2-lithio-1,3-dimethoxybenzene and **2IBT** on the one hand, and 2-iodo-1,3-dimethoxybenzene and **2LBT** on the other hand, was faster in the presence of 0.1 equivalent of H-TMP. All these data tend to indicate that LiTMP could play an additional role in the succession of halogen/metal exchanges during the halogen dance reaction.

To further study the halogen dance reaction in the benzothiophene series, we selected aldehydes as electrophiles in order to generate more polar compounds, easier to purify by column chromatography (Table 2). As expected, the use of 3,4,5-trimethoxybenzaldehyde and pivaldehyde allowed the isolation of the alcohols **8a** and **8b**, but with moderate yields of 34% and 32% (entries 2 and 4). Since **3IBT** has never been observed in the crudes of the attempted reactions, 3-iodo-2-lithiobenzothiophene survives until the trapping step, which shows its high stability and its ability to displace the migration process of halogen towards its end. Moreover, while the alcohols **9a** and **9b** are always produced competitively in these reactions, **DIBT** is never isolated, which shows that its high reactivity. All of this converges to a competitive pathway to halogen migration, as discussed above, to explain the accumulation of 2-lithiobenzothiophene (**2LBT**) in the reaction mixture. Since **2LBT** is less stable than 3-iodo-2-lithiobenzothiophene and LiTMP is consumed during the

reaction, **2LBT** can be gradually protonated by the H-TMP formed, leading to **BT**. Finally, the effect of concentration was studied by also performing the reaction at 0.1 M (entry 7) and 0.05 M (entry 8). The comparison with the reference reaction at 0.4 M (entry 6) showed the deleterious effect of dilution on the course of the reaction, resulting in lower conversion of **2IBT**.

Table 2. Halogen dance reaction from 2-iodobenzothiophene (**2IBT**) followed by trapping with aldehydes.

Entry	R	Conditions	8 (%) ^[a]	9 (%) ^[a]	2IBT (%) ^[a]	BT (%) ^[a]
1 ^[a]		-50 °C, 2 h	8a , 27 ^[b]	9a , 28 ^[b]	37 ^[b]	8 ^[b]
2 ^[a]		-50 °C, 4 h	8a , 34 ^[c]	9a , 24 ^[c]	25 ^[c]	17 ^[c]
3 ^[a]		-90 °C, 0.5 h	8a , 10 ^[b]	9a , 25 ^[b]	60 ^[b]	5 ^[b]
4 ^[a]		-50 °C, 2 h	8b , 32 ^[c]	9b , 32 ^[c]	35 ^[c]	1 ^[c]
5 ^[a]		-50 °C, 4 h	8b , 25 ^[b]	9b , 24 ^[b]	31 ^[b]	12 ^[b]
6 ^[a]		-50 °C, 1 h	8b , 17 ^[c]	9b , 36 ^[c]	30 ^[c]	0
7 ^[a]		-50 °C, 1 h	8b , 20 ^[c]	9b , 41 ^[c]	34 ^[c]	0
8 ^[a]		-50 °C, 1 h	8b , 12 ^[c]	9b , 21 ^[c]	55 ^[c]	4 ^[c]

[a] Before the reaction starts, the concentration of **2IBT** in THF is 0.4 M, except in the case of entry 7 (0.1 M) and entry 8 (0.05 M). [b] Yield estimated from the NMR spectra of the crude. [c] Yield after purification.

To validate the structure of the alcohols **8** and rule out the possible 2-iodobenzothiophene-3-methanol isomers, we also synthesized **8a** by deprotolithiation-trapping of 3-iodobenzothiophene (**3IBT**). For this, **3BBT** was first prepared in 93% yield by bromination of **BT** according to a described protocol.⁴⁷ **3IBT** was then obtained in 60% yield by bromine/lithium exchange followed by iodolysis using the protocol used above to prepare **3IBF**.²⁶ Finally, the functionalization of **3IBT** was carried out as for **3IBF**, by using LiTMP in THF at -75 °C for 1 h before trapping with aldehyde. The alcohol isolated here in 70% yield was found to be identical to **8a**. In addition, the structure of **8a** was later confirmed by X-ray diffraction (Figure 2, top).

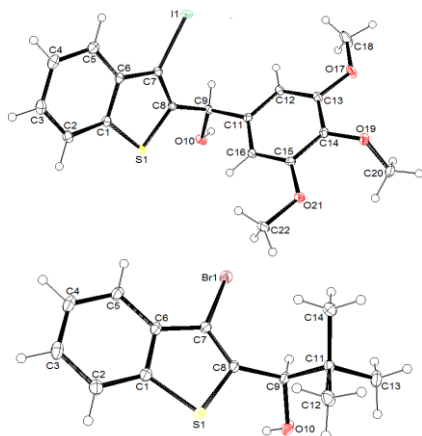
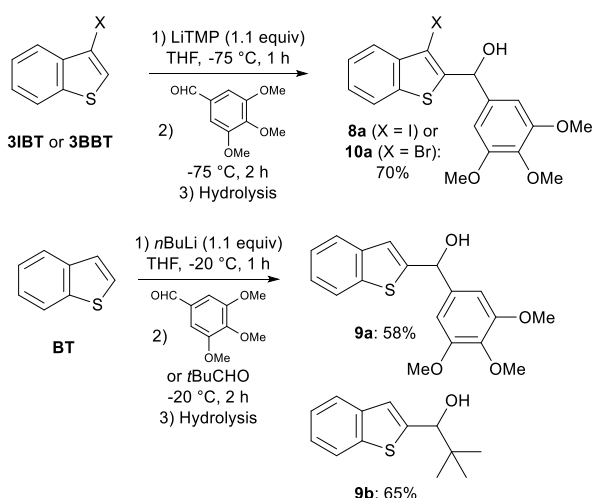


Figure 2. ORTEP diagrams (30% probability) of **8a** (top; intermolecular H-bonds are present between the oxygen of the central methoxy group and the alcohol function; 2.776 Å) and **10b** (bottom).

We have also extended the reported lithium diisopropylamide-mediated C2 deprotonation of **3BBT**⁴⁸ to the use of LiTMP, with the formation of the alcohol **10a** (Scheme 5, top). Regarding the alcohols **9a** and **9b**, they were also unambiguously prepared from benzothiophene (BT), by deprotonation followed by interception with the desired aldehydes (Scheme 5, bottom).

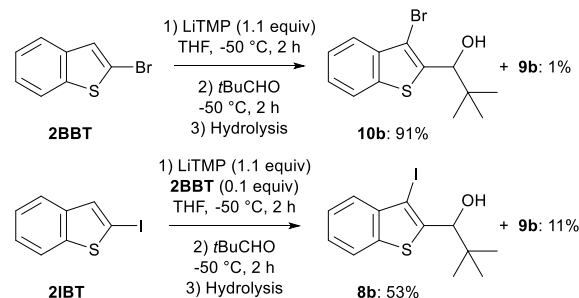


Scheme 5. Formation of **8a**, **9a** and **9b** by alternative ways and synthesis of **10a**.

Then, we verified that such a loss of halogen in the presence of LiTMP could also occur with other substrates close to **2IBT**. By treating 2-iodobenzothiazole²³ with LiTMP (1.1 equiv) in THF at $-50\text{ }^{\circ}\text{C}$ for 2 h before adding methanol, a similar conversion of 46% to benzothiazole was observed. In the case of 2,3-dibromobenzothiophene,⁴⁹ dehalogenation took place from $-75\text{ }^{\circ}\text{C}$, as shown by the addition of methanol after 2 h, giving **3BBT**⁴⁷ with a conversion of 63%. Finally, from 2-iodobenzothiazole,⁵⁰ an attempt at migration of iodine (1.1 equiv LiTMP, THF, $-95\text{ }^{\circ}\text{C}$, 10 min before addition of methanol) led to a complex mixture, this time probably due to degradation.⁵¹ In

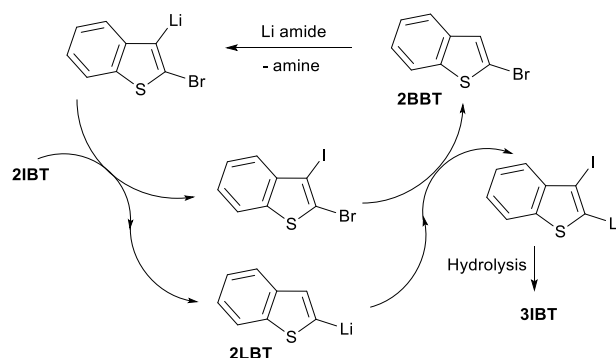
contrast, when 2-bromobenzothiophene (**2BBT**)⁵² was similarly involved in the reaction with LiTMP (THF, $-50\text{ }^{\circ}\text{C}$, 2 h), the alcohol **10b** was surprisingly isolated in 91% yield after interception by pivaldehyde; indeed, only traces of the product **9b** resulting from a bromine/lithium exchange followed by a trapping were observed (Scheme 6, top; Figure 2, bottom).

This could be explained by the poorer capacity of LiTMP to carry out a bromine/lithium exchange compared to an iodine/lithium, but also to the greater facility of **2BBT** to be deprotonated at C3 compared to **2IBT**. It reminded us of a study reported by Stambuli and co-workers in 2011 in which they catalysed the halogen dance reaction of 2-(*n*-butylthio)-5-iodoisoxazole by the corresponding bromide, capitalizing on the larger ability of bromine relative to iodine to direct deprotonation to the neighbouring site, and on the higher ability of iodine relative to bromine to be exchanged against lithium.⁵³ Thus, in a similar way, the reaction from **2IBT** was carried out in the presence of a catalytic amount of **2BBT** (0.1 equiv). Under these conditions, the competitive iodine/lithium exchange was reduced (11% yield in **9b**) while the expected 3-iodinated alcohol **8b** was isolated with a better 53% yield (the rest being mainly **2IBT** and **BT**; Scheme 6, bottom). It is interesting to note that most of the catalyst (**2BBT**) was recovered at the end of the reaction.



Scheme 6. Halogen dance reaction from 2-bromobenzothiophene (**2BBT**; top) and attempt to catalyse the halogen dance from 2-iodobenzothiophene (**2IBT**; bottom).

The role that catalytic **2BBT** could play in our case is illustrated in Scheme 7.



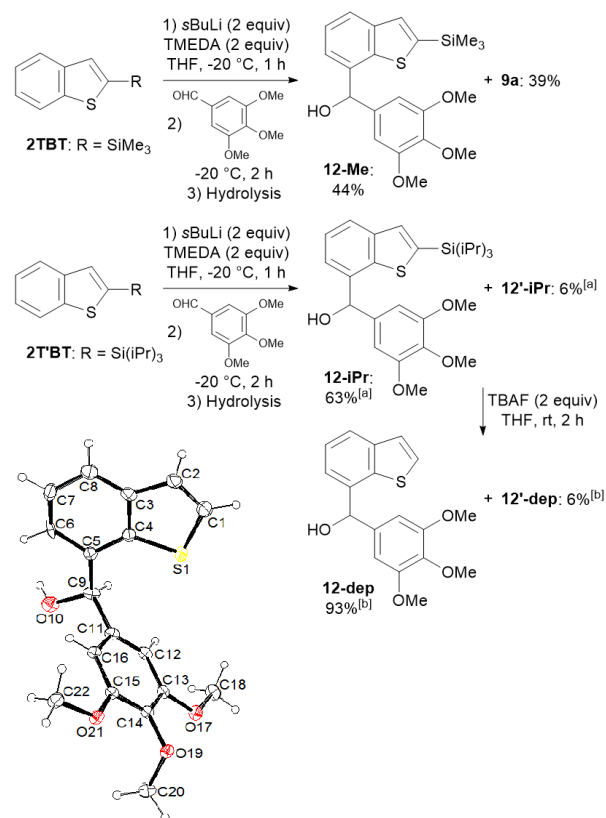
Scheme 7. Mechanism proposed (adapted from the study of Stambuli)⁵³ to rationalize the catalytic effect of **2BBT** on the halogen dance reaction from **2IBT** to **3IBT**.

Like benzofuran, benzothiophene (**BT**) has already been doubly functionalized at its 2- and 7-positions by successive treatments with *n*-butyllithium-TMEDA (2.2 equiv) under hexane reflux for 1.5 h and 4-tolualdehyde (47% yield).²⁷ Thus, we also considered the *in situ* functionalization of the lithium salt of **9a**. However, as evidenced by subsequent iodolysis, the reaction failed with *sec*-butyllithium (1.1 equiv) in THF at $-15\text{ }^{\circ}\text{C}$ for 0.5 h ($\sim 20\%$ conversion to an alcohol not identified), with *sec*-butyllithium-TMEDA (3 equiv) in THF at $0\text{ }^{\circ}\text{C}$ for 6 h (recovery of **9a** and degradation), or alternatively with *sec*-butyllithium-TMEDA (1 equiv) in diethyl ether at room temperature overnight (recovery of **9a** in 38% yield and formation of the ketone **11** in 36% yield; Figure 1, right). As the reaction of the isolated alcohols **9a** and **9b** with iodine (1 equiv) in THF at room temperature for 2 h did not lead to the corresponding ketones **3** and **11**, they are likely to be formed from the alkoxides, by oxidation in the presence of iodine.⁵⁴

These results are also surprising because 2-(triisopropylsilyl)benzothiophene⁵⁵ and 2-(triethylsilyl)benzothiophene⁵⁶ have already been functionalized at C7 by using *n*-butyllithium-TMEDA (1.5 equiv) in diethyl ether at room temperature for 20 h. To see to which extent trimethylsilyl is tolerated in a similar functionalization, 2-(trimethylsilyl)benzothiophene⁵⁷ (**2TBT**) was reacted with *sec*-butyllithium (1.5 equiv) in THF at $-20\text{ }^{\circ}\text{C}$ for 1 h before interception with 3,4,5-trimethoxybenzaldehyde. Under these conditions, in addition to **2TBT** recovered (20%), two alcohols were formed, the 7-substituted derivative **12-Me** (35% yield) and **9a** (32% yield). Indeed, the structure of the latter was confirmed by comparison of its NMR spectra with those of the alcohol prepared from **BT** (Scheme 5, bottom). With *sec*-butyllithium-TMEDA (2 equiv) in THF at $-20\text{ }^{\circ}\text{C}$ for 1 h, **12-Me** was isolated in 44% yield, but the side reaction was not excluded (Scheme 8, top; the rest is **2TBT**). Finally, our attempts to deprotonate **2TBT** by using a base prepared from ZnCl_2 -TMEDA (0.5 or 1 equiv) and LiTMP (1.5 or 3 equiv) in THF at $-15\text{ }^{\circ}\text{C}$ for 1 h before iodolysis failed to yield the corresponding iodide.

It should be noted that our attempt to convert **12-Me** to its 2-brominated derivative by ipso-desilylation led to a mixture whose expected product could not be isolated due to partial oxidation of the alcohol under these conditions (1 equiv Br_2 , CH_2Cl_2 , rt, 20 h).⁵⁸

We also verified the greater efficiency of triisopropylsilyl compared to trimethylsilyl as a protecting group. For this purpose, 2-(triisopropylsilyl)benzothiophene⁵⁵ (**2T'BT**) was similarly treated with *sec*-butyllithium-TMEDA (2 equiv) in THF at $-20\text{ }^{\circ}\text{C}$ for 1 h before interception with the aldehyde. Under these conditions, while the formation of **9a** was ruled out, the expected product **12-iPr** was isolated as a 91:9 mixture with an inseparable isomer **12'-iPr**. This mixture was therefore treated with tetrabutylammonium fluoride (TBAF; 2 equiv) in order to separate the two desilylated alcohols. However, while the 7-substituted derivative **12-dep** could be partially separated (73% yield), the rest was found to be a 76:24 mixture with the deprotected isomer **12'-dep** (26% yield) (Scheme 8, bottom).



Scheme 8. Efforts to functionalize benzothiophene (**BT**) at its 7-position and ORTEP diagram (30% probability) of **12-dep** (H-bonds are present between the oxygen of the central methoxy group and the alcohol function; 2.822 Å). [a] Estimated yields, these compounds being inseparable. [b] Estimated yields, these compounds being only partially separated (see text).

Conclusion

The results obtained in the present study show a contrasting behaviour between 2-iodobenzofuran and 2-iodobenzothiophene in the halogen dance reaction. While only isomerization was noticed after treatment with LiTMP for the former, a competitive dehalogenation reaction was always observed for the latter; however, the use of a catalytic amount of 2-bromobenzothiophene has been shown to improve selectivity in favour of the halogen dance. Furthermore, experimental evidence suggests a role of LiTMP in this dehalogenation process.

We have also highlighted the difficulty of sequentially functionalizing the 2- and 7-positions of benzofuran and benzothiophene, particularly in the case where the first deprotonation-trapping sequence leads to an alcohol. From 2-trimethylsilylbenzofuran and -benzothiophene, competitive silyl cleavage was observed upon treatment with lithiated bases while the use of a less sensitive triisopropylsilyl group protected more efficiently the 2-position and redirected the reaction to the 7-position.

Taken together, these results will provide a better understanding of the functionalization of these heteroaromatic compounds by the halogen dance and deprotonation reactions.

Experimental Section

General information, preparation and analyses of the compounds, as well as NMR spectra of the new products are given in Supporting information.

General procedure 1 for the halogen migration-trapping sequences. To a solution of 2,2,6,6-tetramethylpiperidine (H-TMP; 0.20 mL, 1.2 mmol) in THF (2.5 mL) under argon at $-70\text{ }^{\circ}\text{C}$ was added dropwise *n*BuLi (0.69 mL of a 1.6 M solution of in hexane; 1.1 mmol). After 15 min, the iodinated substrate (1.0 mmol) was added at the tested temperature, and the mixture was stirred for the tested time before addition of the electrophile (either pure for the liquids, or in solution in THF for the solids; 1.0 mmol). After 2 h at the same temperature, water (5 mL) was added. Extraction using Et₂O (3 x 10 mL), drying over MgSO₄ and removal of the solvent under reduced pressure led to the crude product which was purified by chromatography on silica gel (eluent given in the product description).

General procedure 2 for the LiTMP-mediated deprotolithiation-trapping sequences. To the aromatic substrate (1.0 mmol) in THF (1 mL) under argon at $-75\text{ }^{\circ}\text{C}$, was cannulated a solution of LiTMP [prepared by adding *n*BuLi (0.69 mL of a 1.6 M solution in hexane, 1.1 mmol) to a solution of 2,2,6,6-tetramethylpiperidine (H-TMP; 0.20 mL, 1.2 mmol) in THF (1 mL) at $-75\text{ }^{\circ}\text{C}$ under argon, and by stirring for 10 min] at the same temperature. After 1 h at $-75\text{ }^{\circ}\text{C}$, the electrophile (either pure for the liquids, or in solution in THF for the solids; 1.0 mmol) was added and the mixture was stirred for 2 h before addition of water (10 mL). The product was extracted with Et₂O (3 x 20 mL). The organic phase was dried over MgSO₄, and the solvent was removed under reduced pressure. The product was purified by chromatography on silica gel (eluent given in the product description).

General procedure 3 for the *n*BuLi-mediated deprotolithiation-trapping sequences. To the aromatic substrate (1.0 mmol) in THF (1 mL) under argon at $-20\text{ }^{\circ}\text{C}$, was added *n*BuLi (0.69 mL of a 1.6 M solution in hexane, 1.1 mmol), and the mixture was stirred for 1 h or 2 h at this temperature (indicated in the product description). The electrophile (either pure for the liquids, or in solution in THF for the solids; 1.0 mmol) was then added and the mixture was stirred for 2 h at $-20\text{ }^{\circ}\text{C}$ before addition of water (10 mL). The product was extracted with Et₂O (3 x 20 mL). The organic phase was dried over MgSO₄ and the solvent was removed under reduced pressure. The product was purified by chromatography on silica gel (eluent given in the product description).

General procedure 4 for the *s*BuLi-TMEDA-mediated deprotolithiation-trapping sequences. To the aromatic substrate (1.0 mmol) and *N,N,N',N'*-tetramethylethylenediamine (TMEDA; 0.30 mL, 2.0 mmol) in THF (1 mL) under argon at $-20\text{ }^{\circ}\text{C}$, was added *s*BuLi (1.6 mL of a 1.3 M solution in cyclohexane, 2.0 mmol), and the mixture was stirred for 1 h at this temperature. The electrophile (either pure for the liquids, or in solution in THF for the solids; 1.8 mmol) was then added and the mixture was stirred for 2 h at $-20\text{ }^{\circ}\text{C}$ before addition of water (10 mL). The product was extracted with Et₂O (3 x 20 mL). The organic phase was dried over MgSO₄ and the solvent was removed under reduced pressure. The product was purified by chromatography on silica gel (eluent given in the product description).

Deposition Numbers 2234750 (for **8a**), 2234751 (for **10b**), 2234752 (for **2T¹BT**) and 2234753 (for **12-dep**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

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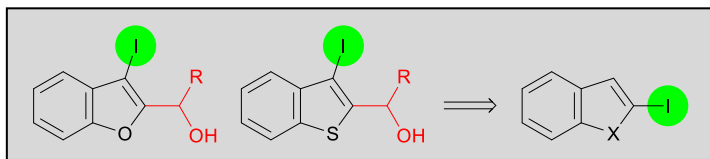
We thank the Université de Rennes 1, the Centre National de la Recherche Scientifique and the Faculté des Sciences Exactes et Appliquées de l'Université Oran1. We acknowledge the Fonds Européen de Développement Régional (FEDER; D8 VENTURE Bruker AXS diffractometer) and Thermofisher (generous gift of 2,2,6,6-tetramethylpiperidine). This research has been partly performed as part of the CNRS PICS project "Bimetallic synergy for the functionalization of heteroaromatics".

Keywords: benzothiophene • benzofuran • iodine • lithium 2,2,6,6-tetramethylpiperidine • base-mediated halogen dance

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Entry for the Table of Contents



New derivatives of benzofuran and benzothiophene were synthesized by halogen dance from the 2-iodinated precursors. In addition, our efforts to deprotometallate 2-substituted (SiR_3 , $\text{CH}(\text{OH})\text{R}$) benzofurans and benzothiophenes at the 7-position are reported.

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