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Catalyst-Free and Regioconvergent Substitution Reactions of Bromothiophenes with a BH_3-Substituted Phosphide Anion

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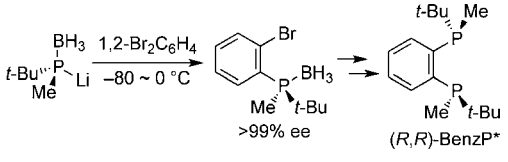
Supporting Information

ABSTRACT: A range of bromothiophenes reacted with lithium boranato(*tert*-butyl)methylphosphide in the absence of transition-metal catalysts under mild conditions to provide the same 2,5-disubstituted and 2-monosubstituted products regardless of the substitution patterns of the starting bromothiophenes.

Phosphine-substituted thiophenes play important roles in transition-metal catalysis and materials science.[1,2] They are generally synthesized by the transition-metal-catalyzed phosphination of halothiophenes with phosphide anions[1d,3] or by the reactions of lithiated thiophenes with dialkyl- or diarylhalophosphines.[1b,e,h,2a,c,4] Although the direct nucleophilic aromatic substitution (S_NAr) reaction of halothiophenes with phosphide anions is a convenient method, the reaction proceeds only when thiophenes bearing electron-withdrawing substituents, such as a carbonyl group, are used as the substrate.[1c,5] Herein we report the first example of the regioconvergent substitution reactions of nonactivated bromothiophenes with a phosphide anion under catalyst-free conditions.

In 2012, Jugé and co-workers reported that 1,2-dihalobenzenes reacted with the lithium derivatives of secondary phosphine boranes to give *o*-halophenylphosphine boranes in good yields.[6] They revealed that the use of optically active secondary phosphine boranes provided products with excellent enantiomeric excesses of up to 99%. We adopted Jugé's methodology in the preparation of a P-stereogenic diphosphine ligand, 1,2-bis(*tert*-butylmethylphosphino)benzene (BenzP*), using 1,2-dibromobenzene and enantiopure *tert*-butylmethylphosphine borane as the starting materials (Scheme 1).[7] The reaction of 1,2-dihalobenzene with the phosphide anion is quite interesting, because it does not proceed via the S_NAr (addition−elimination) mechanism but involves benzyne as the key intermediate.[6a] On the other hand, 3,4- and 2,3-didehydrothiophenes (thiophynes) are known as reactive intermediates, although their generation requires a thiophene molecule bearing a trimethylsilyl group and a powerful leaving group (phenyliodonium triflate) at the 3,4-position[8] or harsh reaction conditions.[9] Judging from the previously reported results, it seems to be quite difficult or almost impossible to generate thiophynes from dihalothiophenes. Nevertheless, we were interested in whether the reactions of dihalothiophenes with phosphide anions would take place or not.

Scheme 1. Preparation of BenzP*



An initial experiment was conducted, which involved the reaction of 3,4-dibromothiophene with lithium (±)-boranato(*tert*-butyl)methylphosphide ((±)-**1**) under the conditions employed for the preparation of the precursor of BenzP*.[7] The reaction of 3,4-dibromothiophene with (±)-**1** in a 1.5:1 molar ratio proceeded rapidly even at −80 °C to form a complex reaction mixture from which we isolated major product **2** in 15% yield (Table 1, entry 1). The structure of **2** was assigned on the basis of NMR and HRMS data and unequivocally determined by single-crystal X-ray analysis. Although the isolated yield of the product was low, we were surprised to find that the two bromine atoms remained unchanged and the hydrogen atom at 2-position was replaced by the boranato(*tert*-butyl)methylphosphino group. The reaction employing a 3:1 molar ratio was also carried out but gave an even lower yield (7%) (entry 2).

Then, the reaction of 2,3-dibromothiophene with (±)-**1** was conducted under the same conditions to provide two products **3** and **4** whose structures were determined on the basis of spectroscopic data (entry 3). The structure of major product **3** was confirmed by single-crystal X-ray analysis. To our surprise, the P-CH_3 group was subjected to bromination to provide compound **3**. Remarkably, the yield of **3** was significantly improved to 63% by increasing the molar ratio of 2,3-dibromothiophene to (±)-**1** to 3:1 or 5:1 (entries 4 and 5).

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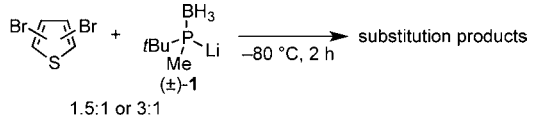
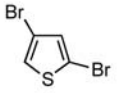
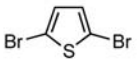
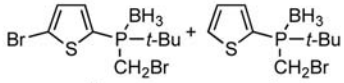
Table 1. Reactions of Dibromothiophenes with Lithium (±1)-Boranato(*tert*-butyl)methylphosphide ((±)-1)



entry[a]	dibromothiophene	products, yields[b]		
				
		2	**2** (X-ray)	
1		molar ratio = 1.5:1	15%	
2		molar ratio = 3:1	7%	
				
		3	**3** (X-ray)	**4**
3		molar ratio = 1.5:1	36%	2%
4		molar ratio = 3:1	63%	4%
5		molar ratio = 5:1	63%	9%
6[c]		molar ratio = 3:1	62%	4%
		**3** + **4**		
7		molar ratio = 1.5:1	8%	11%
8		molar ratio = 3:1	34%	10%
				
		5		**6**
9		molar ratio = 1.5:1	10%	8%
10		molar ratio = 3:1	21%	6%

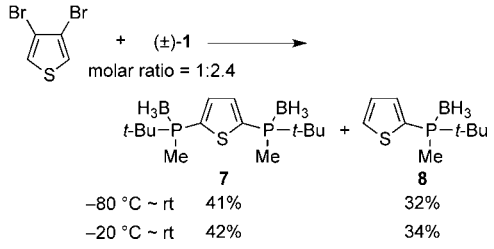
[a]All reactions were carried out at −80 °C for 2 h unless otherwise noted. [b]Isolated yields based on (±)-**1**. [c]The reaction time was 0.1 h.

Another notable finding was that compound **3** was produced within a very short reaction time (0.1 h) in almost the same yield (62%) (entry 6).

Two other regioisomeric dibromothiophenes were allowed to react with (±)-**1** under the same conditions, and the results are included in Table 1. It should be noted that the reaction of 2,4-dibromothiophene provided compounds **3** and **4**, which were the same as those obtained in the reaction of 2,3-dibromothiophene (entries 7 and 8). We could not clarify the detailed mechanism for the formation of these products; nevertheless, we supposed that the substitutions took place not at the 2-position but at the 5-position in a *tele*-substitution manner, although the 5-position was subject to steric hindrance by the adjacent bromine atom. Entries 9 and 10 show the results of the reaction of 2,5-dibromothiophene. Both products **5** and **6** were found to have a bromomethyl group at the phosphorus atom, and the yield of **5** was increased in comparison with that of **6** when a high molar ratio (3:1) was employed.

Motivated by the above-mentioned results, we examined the reaction of 3,4-dibromothiophene with (±)-**1** in a 1:2.4 molar ratio with the expectation that the two bromine atoms would be replaced by the phosphine moieties. In this case, the substitution reaction did not occur at −80 °C but was initiated at around −20 °C (TLC monitoring) and was completed at room temperature, delivering two major products, *cine*-disubstitution product **7** (41%) and monosubstitution product **8** (32%).[10] The reaction that initiated at −20 °C to room temperature afforded almost the same yields of **7** and **8** (Scheme 2). Whereas their structures could be assigned by

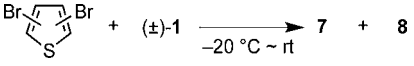
Scheme 2. Reaction of 3,4-Dibromothiophene with (±)-1 in a 1:2.4 Molar Ratio



NMR and HRMS analyses, we confirmed them by comparing their NMR spectra with those of authentic samples prepared by the reactions of bromo(*tert*-butyl)methylphosphine borane with 2,5-dilithiothiophene or 2-lithiothiophene.[11−13]

Three other regioisomeric dibromothiophenes were reacted with (±)-**1** under the same conditions. Table 2 shows the

Table 2. Reactions of Dibromothiophenes with (±)-1



		products, yield (%)[a]	
entry	dibromothiophene	**7**	**8**
1	$3,4\text{-}Br_2C_4H_2S$	42	34
2	$2,3\text{-}Br_2C_4H_2S$	46	34
3	$2,4\text{-}Br_2C_4H_2S$	43	30
4	$2,5\text{-}Br_2C_4H_2S$	13	24
5	$Br_2C_4H_2S$[b]	38	29

[a]Isolated yields based on dibromothiophene. [b]Mixture of four regioisomers in a 1:1:1:1 molar ratio.

results together with that of the above-mentioned reaction of 3,4-dibromothiophene. In all cases, the substitutions occurred at the positions adjacent to the sulfur atom. Notably, *cine*- and *tele*-substitution products **7** and **8** were obtained in good combined yields (entries 1−3).[14] In contrast, the reaction of 2,5-dibromothiophene afforded relatively lower yields of the products, suggesting that the reaction did not proceed via direct metal−halogen exchange (entry 4). The reaction of a mixture of the four regioisomers afforded the corresponding products **7** and **8** in reasonable yields (entry 5).

Based on the results described above, we examined the reactions of other bromothiophenes with (±)-**1** to clarify the scope of these regioconvergent substitutions. The results are summarized in Table 3. Interestingly, the reactions of monobromothiophenes proceeded under the specified conditions to produce not only monosubstituted product **8** but also disubstituted **7** (entries 1 and 2). Tribromo- and tetrabromothiophenes underwent the reactions to afford the same substitution products in moderate yields (entries 3−5).[15]

In order to understand the mechanistic aspect of these substitution reactions including the stereochemistry at the stereogenic phosphorus atom, we used enantiopure lithium (*S*)-boranato(*tert*-butyl)methylphosphide ((*S*)-**1**) for the reactions with 2,3- and 3,4-dibromothiophenes. Scheme 3 shows the result of the former reaction. The formation of product **3** with

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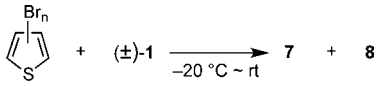
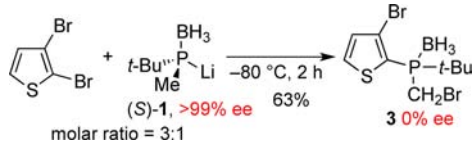
Table 3. Reactions of Bromothiophenes with (±)-1



entry[a]	Br$_n$	bromothiophene:(±)-1	products, yield (%)[b] 7	8
1	2-Br	1:1.2	6	15
2	3-Br	1:1.2	11	18
3	2,3,4-Br$_3$	1:3.6	45	19
4	2,3,5-Br$_3$	1:3.6	35	18
5	2,3,4,5-Br$_4$	1:4.8	32	17

[a]The reaction conditions were not optimized. [b]Isolated yields based on bromothiophenes.

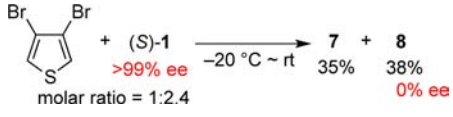
Scheme 3



0% ee indicates that complete racemization took place even at −80 °C. This result is in stark contrast to the reaction of 1,2-dibromobenzene with (*S*)-**1**, delivering a product with almost complete retention of configuration (Scheme 1),[7] and suggests that the reaction would proceed through a different pathway, probably not involving an aryne species (2,3-didehydrothiophene) as a key intermediate. In addition, the reaction may involve a reactive phosphorus species that is stereochemically unstable and undergoes rapid racemization under the conditions. Another major difference in comparison with the reaction of 1,2-dibromobenzene is that the reaction accompanies the bromination of the P-CH$_3$ group. Although the bromination mechanism has not yet been well clarified, it is apparent that another 2,3-dibromothiophene molecule participates in the reaction as a bromination reactant.

The latter reaction, which was carried out at −20 °C to room temperature at a 1:2.4 molar ratio, provided completely racemized product **8** (Scheme 4). We suppose that relatively

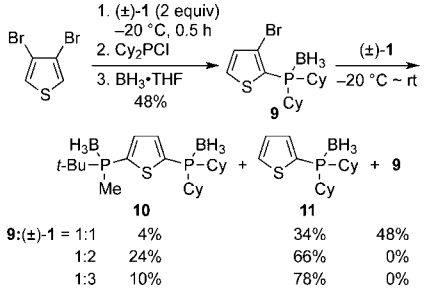
Scheme 4



stable 2,5-dilithiothiophene and 2-thienyllithium would be generated and they would undergo a nucleophilic displacement reaction with concomitantly formed bromo(*tert*-butyl)methylphosphine borane or bis(*tert*-butylmethylphosphine) diborane. This pathway may be supported by the fact that 2-thienyllithium reacted with (*R*)-bromo(*tert*-butyl)methylphosphine borane in diethyl ether at −80 °C to room temperature to afford compound **8** with 8% ee in 83% yield.[16−18]

In order to trap thienyl anion species, 3,4-dibromothiophene was allowed to react with (±)-**1** at −20 °C for a short reaction time (0.5 h) and then was subsequently reacted with chlorodicyclohexylphoshine and a borane−THF complex. The formation of compound **9** in 48% yield indicates the generation of a 3-bromo-2-thienyl anion as a reactive intermediate (Scheme 5).[19] It was also found that compound

Scheme 5



9 reacted with (±)-**1** to afford substitution product **10** and reduction product **11**, while the yields largely depend on the molar ratios of **9** and (±)-**1**.

In summary, we have disclosed catalyst-free and regioconvergent substitution reactions of bromothiophenes with lithium boranato(*tert*-butyl)methylphosphide that include *cine*- and *tele*-substitution patterns. These substitution reactions are suggested to involve an initial single-electron transfer process and a subsequent nucleophilic attack of the generated thermodynamically stable 2-lithio- and 2,5-dilithiothiophenes on phosphorus electrophiles.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02094.

Experimental procedures, characterization data for all new compounds (PDF)
Crystallographic data (CIF, CIF)

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Notes

The authors declare no competing financial interest.

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(10) We observed by TLC monitoring that 3,4-dibromothiophene reacted with (±)-**1** at −80 °C to produce bromo(*tert*-butyl)methylphosphine borane and bis(*tert*-butylmethylphosphine) diborane.

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(12) Compound **7** was obtained as a mixture of (±)- and meso-isomers.

(13) For comparison, we prepared 3-[boranato(*tert*-butyl)methylphosphino]thiophene by the reaction of 3-lithiothiophene with bromo(*tert*-butyl)methylphosphine borane (see Supporting Information (SI)). The NMR spectra of the product were apparently different from those of compound **8**, particularly in the aromatic region of their ^{1}H NMR spectra, and we could readily distinguish the two regioisomers. Furthermore, we prepared the corresponding achiral derivatives bearing the boranato(dicyclohexyl)phosphino group at the 2-, 3-, or 2,5-position to compare the ^{1}H NMR patterns at the aromatic regions (see SI).

(14) To the best of our knowledge, these reactions are the first example of C−P bond-forming *cine- and tele*-substitutions on a thiophene ring. For a review dealing with *cine*- and *tele*-substitution reactions, see: Suwinski, J.; Swierczek, K. *Tetrahedron* **2001**, *57*, 1639−1662.

(15) The reactions of chloro- and iodothiophenes with (±)-**1** were also examined. The results are shown in the SI.

(16) The ee of this product was very low (8%), in sharp contrast to the results (97−99% ee) obtained in the reactions of reactive lithium acetylides.[11] We previously observed that the reactions of aryllithiums such as phenyllithium and *o*-methoxyphenyllithium reacted slowly with enantiopure (*R*)-bromo(*tert*-butyl)methylphosphine borane to afford the corresponding substitution products with significantly lower enantiomeric excesses. The low stereospecificity is ascribed to the racemization of bromo(*tert*-butyl)methylphosphine borane under the reaction conditions (higher temperature and longer reaction time).

(17) It has been theoretically predicted that the hydrogen atom at the 2-position of thiophene possesses stronger acidity than that at the 3-position by 5.5 pK_a units. Shen, K.; Fu, Y.; Li, J.-N.; Liu, L.; Guo, Q.-X. *Tetrahedron* **2007**, *63*, 1568−1576.

(18) It has been reported that a less stable carbanion on a thiophene ring bearing halogen atoms is converted into a more stable carbanion, bringing about the so-called halogen dance reaction. Schnürch, M.; Spina, M.; Khan, A. F.; Mihovilovic, M. D.; Stanetty, P. *Chem. Soc. Rev.* **2007**, *36*, 1046−1057 and references cited therein.

(19) The structure of compound **9** was confirmed by comparing its NMR data with those of the authentic sample prepared by the successive reactions of 3-bromothiophene with LDA, chlorodicyclohexylphosphine, and BH_3·THF (see SI).

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