Magnesium Bisamide-Mediated Halogen Dance of Bromothiophenes

Yamane, Yoshiki
Sunahara, Kazuhiro
Okano, Kentaro
Mori, Atsunori

(Citation)
Organic Letters,20(6):1688-1691

(Issue Date)
2018-03-16

(Resource Type)
journal article

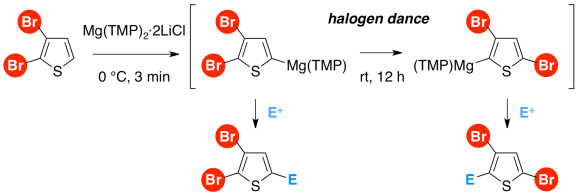
(Version)
Accepted Manuscript

Magnesium Bisamide-Mediated Halogen Dance of Bromothiophenes

Yoshiki Yamane, Kazuhiro Sunahara, Kentaro Okano,* and Atsunori Mori

Department of Chemical Science and Engineering, Kobe University, 1-1 Rokkodai, Nada, Kobe 657-8501, Japan

Supporting Information Placeholder

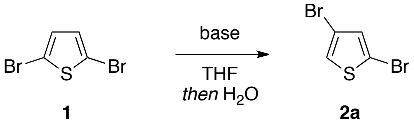


ABSTRACT: A magnesium bisamide-mediated halogen dance of bromothiophenes is described. The thienylmagnesium species generated in situ is more stable than the corresponding thienyllithium species, which was applied to trap the transient anion species with several electrophiles, such as allyl iodide, phenyl isocyanate, and tributylstannyl chloride. The utility of the magnesium bisamide-mediated halogen dance is useful in the concise synthesis of a medicinally advantageous compound via a one-pot, ester-directed halogen dance/Negishi cross coupling.

In 1951, the treatment of 2-bromothiophene with sodium acetylide in liquid ammonia was reported to lead to the formation of a mixture of di-, tri-, and tetrabromothiophene.[1] The base-induced halogen migration has been referred to as halogen scrambling, halogen isomerization, or halogen dance.[2] The reaction mechanism by which this occurs was elucidated to be sequential deprotonation and halogen–metal exchange, which gives a thienyl anion species bearing a halogen atom.[3] From the viewpoint of synthetic chemistry, the halogen dance reaction allows the formation of two chemical bonds in one pot, which in turn, reduces the number of reaction pots needed for this particular transformation when compared with conventional stepwise introduction of functional groups. In addition, the halogen dance reaction enables facile access to aromatic/heteroaromatic halides, whose substitution pattern is often difficult to achieve via general synthetic methods, such as electrophilic aromatic substitution. Despite this attractive synthetic potential, the scope of this substrate has not been investigated in detail probably because of difficulties in controlling the reactivity of the transient thienyllithium species. Recently, our research group published the first one-pot halogen dance/Negishi coupling for rapid access to multiple arylated thiophenes and furans in a regiocontrolled manner.[4] During the course of the investigation, transmetalation of the transient organolithium species to organozinc species proved essential for smooth transformation. We also noticed that either alkyl lithium or lithium amides were employed as bases in halogen dance reactions. Herein, we report the magnesium amide-mediated halogen dance of bromothiophenes, and several examples that cannot be performed with lithium amides. The mild reaction conditions also allow for ester-directed 1,3-migration of a bromo group. The applicability of this method is demonstrated by the concise synthesis of a key intermediate for an inhibitor of HCV NS5B polymerase through a one-pot ester-directed halogen dance/Negishi cross coupling.

First, related amide bases were investigated using 2,5-dibromothiophene (**1**) as a substrate (Table 1). According to previous reports,[2] the halogen dance of **1** was performed with LiTMP[5] at –78 °C. The reaction was quenched with water to give 2,4-dibromothiophene (**2a**) in 68% ^{1}H-NMR yield (entry 1). The starting material **1** was not consumed with Knochel–Hauser base[6] (TMPMgCl·LiCl, TMP = 2,2,6,6-tetramethyl piperidide), even after the experiment was performed at room temperature for 24 h (entry 2). $Mg(TMP)_2·2LiCl$[7] proved to be effective for the completion of the reaction (entry 3). Structurally similar $Mg(N\textit{i}\text{-}Pr_2)_2·2LiCl$[7c,8] led to the formation of **2a** in a lower yield (entry 4). In the magnesium amide-mediated halogen dance, we identified 2-bromothiophene (<10%) as an intermediate among several byproducts, which has not been reported in lithium amide-promoted reactions.

Table 1. Exploration of bases in the halogen dance[a]



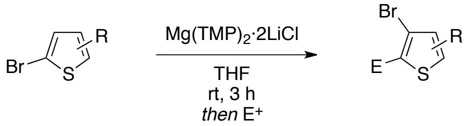
1 **2a**

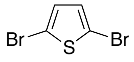
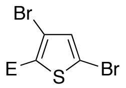
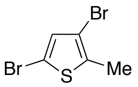
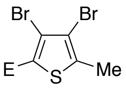
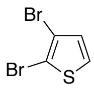
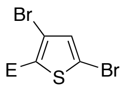
entry	base	temp	time	**1**[b] (%)	**2a**[b] (%)
1	LiTMP	–78 °C	5 min	–[c]	68
2	TMPMgCl·LiCl	rt	24 h	15	40
3	$Mg(TMP)_2·2LiCl$	rt	3 h	–[c]	63
4	$Mg(N\textit{i}\text{-}Pr_2)_2·2LiCl$	rt	3 h	–[c]	36

[a] Reaction conditions: 2,5-dibromothiophene (**1**) (0.50 mmol), base (0.60 mmol, 1.2 equiv), THF, then H_2O. [b] The yield was determined by ^{1}H-NMR of the crude material using 1,1,2,2-tetrachloroethane as an internal standard. [c] Not observed.

Having found that $Mg(TMP)_2 \cdot 2LiCl$ facilitated the halogen dance of 2,5-dibromothiophene (**1**), we subsequently investigated the scope of dibromothiophenes and electrophiles in the said reactions (Table 2). First, upon treatment of 2,5-dibromothiophene (**1**) with $Mg(TMP)_2 \cdot 2LiCl$ at room temperature for 3 h, the generated anion species were trapped using several electrophiles. The reaction was quenched with water to give 2,4-dibromothiophene (**2a**) in 63% yield. Treatment with benzaldehyde provided the desired alcohol **2b** in 51% yield. Trapping the resultant anion species with ethyl chloroformate gave compound **2c** in 42% yield. An allyl group was also introduced using allyl iodide to provide the corresponding product **2d** in 50% yield. Halogen dance of dibromothiophene **3** smoothly occurred to give 3,4-dibromothiophenes **4a** and **4b** in moderate yields. Next, we examined 2,3-dibromothiophene (**5**), which gave the same substitution pattern as the above example using 2,5-dibromothiophene (**1**). Compared with 2,5-dibromothiophene (**1**), prolonged reaction time (12 h) was necessary for the halogen dance of 2,3-dibromothiophene (**5**) to provide the corresponding products **2a** and **2d**.

Table 2. Scope and limitations of the halogen dance[a]

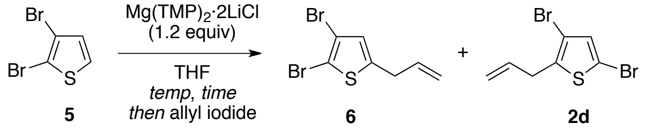


substrate	product	E^+	E	yield[b] (%)
 **1**	 **2**	H_3O^+	H	**2a** 63[c]
		PhCHO	CH(OH)Ph	**2b** 51
		$ClCO_2Et$	CO_2Et	**2c** 42[d]
		allyl–I	allyl	**2d** 50[d]
 **3**	 **4**	H_3O^+	H	**4a** 37
		allyl–I	allyl	**4b** 50
 **5**	 **2**	H_3O^+	H	**2a** 73[c,e]
		allyl–I	allyl	**2d** 39[e,f]

[a]Reaction conditions: dibromothiophene (0.50 mmol), base (0.60 mmol, 1.2 equiv), THF, rt, 3 h, then E^+ (1.0 mmol, 2.0 equiv). [b]Isolated yield. [c]The yield was determined by ^{1}H-NMR of the crude material using 1,1,2,2-tetrachloroethane as an internal standard. [d]Electrophile: 2.4 equiv. [e]Reaction time: 12 h (for the halogen dance). [f]The yield was determined by ^{1}H-NMR of the crude material using 1,2-diiodoethane as an internal standard.

Selective trapping of two thienyl anion species from 2,3-dibromothiophene (**5**) was achieved by using the magnesium amide (Table 3). The halogen dance of **5** provided a mixture of allylated dibromothiophenes **6**[9] and **2d** in 28% and 39% yields, respectively (entry 1). A prolonged reaction time (12 h) resulted in the formation of **2d** as a major product (entry 2). On the other hand, treatment of **6** with $Mg(TMP)_2 \cdot 2LiCl$ at 0 °C for 3 min followed by allyl iodide provided **6** as a major isomer (entry 3). Addition of a mixture of allyl iodide and **5** to $Mg(TMP)_2 \cdot 2LiCl$ led to exclusive formation of **6** in 59% isolated yield (entry 4). These findings indicate that the magnesium amide-mediated halogen dance could be used to provide each regioisomer simply by controlling reaction conditions.

Table 3. Selective trapping of two thienyl anion species from 2,3-dibromothiophene[a]

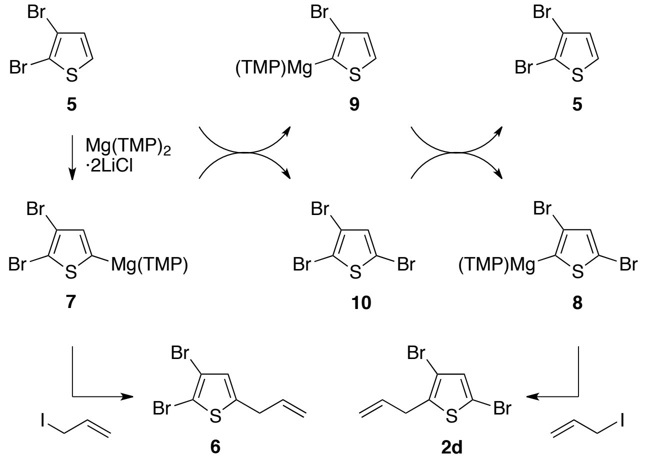


entry	temp	time	6[b] (%)	2d[b] (%)
1	rt	3 h	28	39
2	rt	12 h	3	39
3	0 °C	3 min	71	10
4	0 °C	–[c]	59[d]	–[e]

[a]Reaction conditions: bromothiophene **5** (0.50 mmol), base (0.60 mmol, 1.2 equiv), THF, then allyl iodide (1.0 mmol, 2.0 equiv). [b]NMR yield using 1,2-diiodoethane as an internal standard. [c]A mixture of 2,3-dibromothiophene **5** and allyl iodide was added to the magnesium amide at 0 °C. [d]Isolated yield. [e]Not observed in ^{1}H-NMR of the crude material.

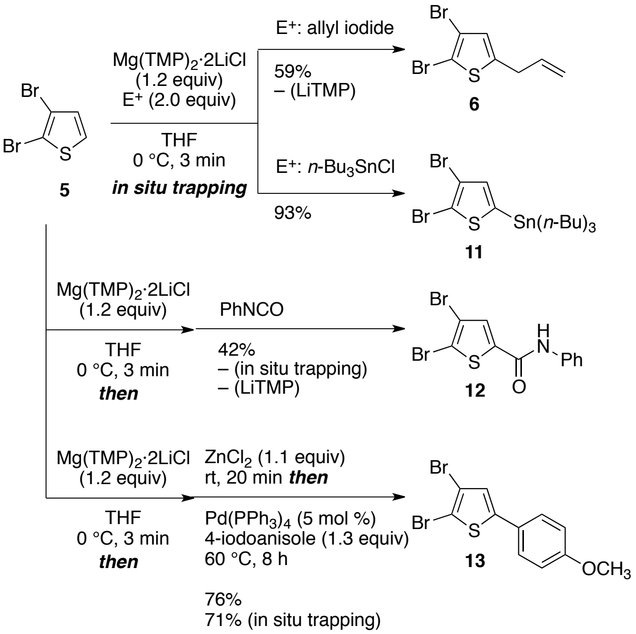
In the case of 2,3-dibromothiophene (**5**), the initial deprotonation was expected to be faster than the subsequent halogen–magnesium exchange (Scheme 1). Thus, the thienylmagnesium species **7** should be a transient carbanion, which when allylated, provides thiophene **6**. Prolonged reaction times or elevated reaction temperatures allowed the formation of the thermodynamically favored thienylmagnesium species **8** through halogen–magnesium exchange of transient thienylmagnesium **9** and tribromothiophene **10**, thus giving allylated thiophene **2d**.

Scheme 1. Plausible reaction pathway of halogen dance



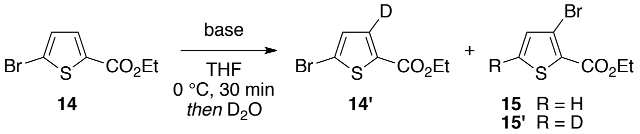
Notably, only one example of the termination of the halogen dance of 2,3-dibromothiophene (**5**) has been reported using flow metalation with LiTMP in the presence of $LaCl_3 \cdot 2LiCl$.[10] We then investigated the trapping of the transient thienyl anion species with a batch system using $Mg(TMP)_2 \cdot 2LiCl$ because the intermolecular halogen–magnesium exchange is much slower than halogen–lithium exchange (Scheme 2). Instead of $Mg(TMP)_2 \cdot 2LiCl$, a mixture of 2,3-dibromothiophene (**5**) and allyl iodide was treated with LiTMP to give 2,4-dibromothiophene (**2a**) as a major product with none of the corresponding allylated thiophene **6**. In addition, n-Bu_3SnCl smoothly reacted to give the corresponding product **11** in 93% yield. Similarly, phenylisocyanate was successfully trapped to provide amide **12** in 42% yield after generation of the initial thienyl anion species **7**, whereas in situ trapping caused the reaction of magnesium amide and phenylisocyanate to give the corresponding urea, resulting in recovery of the starting 2,3-dibromothiophene (**5**). The transient thienyl magnesium species **7** could be transmetalated to organozinc species without halogen dance, which underwent Negishi coupling to provide arylated thiophene **13**[11] in 76% yield. In situ trapping of the thienyl magnesium species **9** with $ZnCl_2 \cdot TMEDA$ resulted in the reduction of the yield of **13**.

Scheme 2. Trapping of the transient thienyl magnesium species



During the course of the investigation of the scope of the reaction, we found that bromothiophene **14**, which bears an ester group, underwent halogen dance through an unusual 1,3-migration of the bromo group (Table 4). After treatment of **14** with LiTMP at −78 °C for 5 min, the reaction was quenched with D_2O to provide **15’** and **15** in 52% and 5% yields, respectively (entry 1). Switching the base to $TMPMgCl \cdot LiCl$ led to the formation of **15’** and **15** in 30% and 15% yields with 12% recovery of the starting material **14** (entry 2). In this case, none of deuterated **14’** was observed, which indicates that, once generated, the initial anion species immediately undergoes subsequent halogen–magnesium exchange. The combined NMR yield of **15** and **15’** improved up to 69% when the reaction was conducted using $Mg(TMP)_2 \cdot 2LiCl$ (entry 3).[12]

Table 4. Ester-directed 1,3-halogen dance[a]

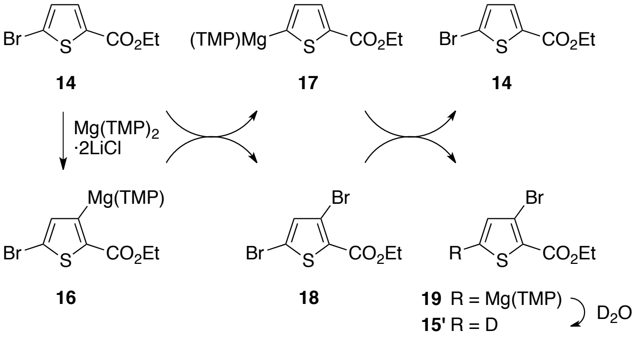


entry	base	**14**[b] (%)	**14’**[b] (%)	**15**[b] (%)	**15’**[b] (%)
1[c]	LiTMP	6	2	5 (66[e])	52
2	$TMPMgCl \cdot LiCl$	12	–[d]	15	30
3	$Mg(TMP)_2 \cdot 2LiCl$	<1	<1	14 (68[e,f])	55

[a]Reaction conditions: bromothiophene **14** (0.50 mmol), base (0.60 mmol, 1.2 equiv), THF, 0 °C, 30 min, then D_2O. [b]NMR yield using 1,1,2,2-tetrachloroethane as an internal standard. [c]Halogen dance was performed at −78 °C for 5 min. [d]Not observed. [e]The reaction was quenched with H_2O. [f]Isolated yield.

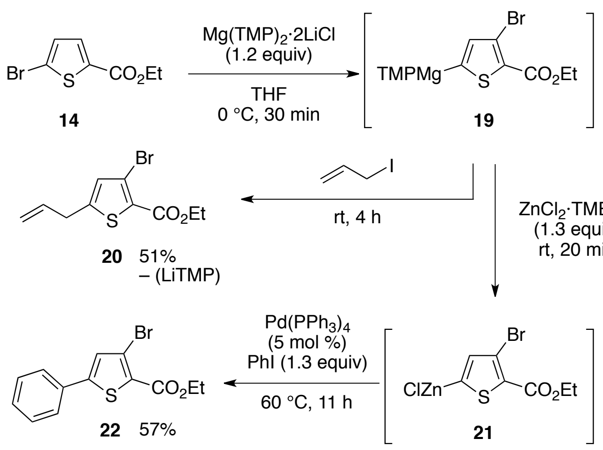
The regiochemistry of the novel 1,3-halogen dance can be rationalized by invoking the directing effect of the ester group in the first deprotonation step (Scheme 3). The proton adjacent to the ester group is thought to be preferably abstracted to generate anion species **16**, which is also supported by Eaton and Knochel’s reports that utilized magnesium amides for deprotonation/functionalization reactions.[13] The resultant thienylmagnesium species **16** then reacts with the starting bromothiophene **14** to generate thienylmagnesium species **17** and dibromothiophene **18**, which in turn, undergo halogen–magnesium exchange to regenerate bromothiophene **14** with production of the thermodynamically stable thienylmagnesium species **19**. This is trapped using an electrophile to give **15’**.

Scheme 3. Plausible reaction pathway for an ester-directed 1,3-halogen dance



The resultant thienylmagnesium species **19** proved effective for the synthesis of functionalized thiophenes (Scheme 4). The established conditions were suitable for introducing an allyl group to give the corresponding product **20** in 51% yield, whereas LiTMP facilitated the halogen dance, but gave a complex mixture of unidentified products. Halogen dance of bromothiophene **14** was successfully applied for the concise synthesis of a key intermediate for an inhibitor of HCV NS5B polymerase,[14a] ultimately leading to the prevention of Hepatitis C virus infection[14b]/flavivirus infection[14c] (Scheme 4). The resultant thienylmagnesium species **19** was transmetalated using the $ZnCl_2 \cdot TMEDA$ complex[15] to generate thienylzinc species **21**, and subsequent Negishi coupling[16] provided the arylated compound **22** in 57% yield in one pot.

Scheme 4. Synthesis of functionalized thiophenes



In summary, we have demonstrated a magnesium bisamide-promoted halogen dance of bromothiophenes. The reaction rate was much slower than that of a lithium amide-mediated halogen dance. The magnesium bisamide-induced deprotonation of 2,3-dibromothiophene incorporated the trapping of the transient thienyl anion species by several electrophiles to provide dibrominated thiophene derivatives with different substitution pattern. An ester group was tolerated during the halogen dance reaction and facilitated the novel 1,3-migration of the bromo group. The method can be applied for the synthesis of the medicinally important compound.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.xxxxxxx. Experimental procedure, compound characterization data, and copies of ^{1}H and ^{13}C-NMR spectra for all new compounds (PDF).

AUTHOR INFORMATION

Corresponding Author

*E-mail: okano@harbor.kobe-u.ac.jp

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

This work was financially supported by JSPS KAKENHI Grant Numbers JP16K05774 in Scientific Research (C), JP16H01153 in the Middle Molecular Strategy, Creation of Innovation Centers for Advanced Interdisciplinary Research Areas (Innovative Bioproduction Kobe), and Kawanishi Memorial ShinMaywa Education Foundation. This work was performed under the Cooperative Research Program of "Network Joint Research Center for Materials and Devices." We thank Dr. Takashi Niwa (The "Compass to Healthy Life" Research Complex program, RIKEN) for mass spectrometric analyses.

REFERENCES

(1) (a) Vaitiekunas, A.; Nord, F. F. *Nature* **1951**, *168*, 875. (b) Vaitiekunas, A.; Nord, F. F. *J. Am. Chem. Soc.* **1953**, *75*, 1764.

(2) (a) Gronowitz, S. *Recent advances in the chemistry of thiophenes*; Academic Press: Cambridge, England, 1963; Vol. 1. (b) Fröhlich, J. Substituted Heterocyclic Compounds by Selective Control of Halogen-Dance Reactions. In *Prog. Heterocycl. Chem.*; Padwa, A., Ed.; Pergamon Press: Oxford, 1994; Vol. 6, pp 1–35. (c) Iddon, B. *Heterocycles* **1995**, *41*, 533. (d) Gronowitz, S.; Holm, B. *Acta Chem. Scand.* **1969**, *23*, 2207. (e) De Bie, D. A.; Van der Plas, H. C.; Geurtsen, G.; Nijdam, K. *Recl. Trav. Chim. Pays-Bas* **1973**, *92*, 245. (f) Kano, S.; Yuasa, Y.; Yokomatsu, T.; Shibuya, S. *Heterocycles* **1983**, *20*, 2035. (g) Sauter, F.; Fröhlich, H.; Kalt, W. *Synthesis* **1989**, 771. (h) Froehlich, H.; Kalt, W. *J. Org. Chem.* **1990**, *55*, 2993. (i) Fröhlich, J.; Hametner, C.; Kalt, W. *Monatsh. Chem.* **1996**, *127*, 325. (j) Peyron, C.; Navarre, J.-M.; Van Craynest, N.; Benhida, R. *Tetrahedron Lett.* **2005**, *46*, 3315. (k) Getmanenko, Y. A.; Tongwa, P.; Timofeeva, T. V.; Marder, S. R. *Org. Lett.* **2010**, *12*, 2136. (l) Tazi, M.; Erb, W.; Halauko, Y. S.; Ivashkevich, O. A.; Matulis, V. E.; Roisnel, T.; Dorcet, V.; Mongin, F. *Organometallics* **2017**, *36*, 4770. (m) Duan, X.-F.; Zhang, Z.-B. *Heterocycles* **2005**, *65*, 2005. (n) Shono, K.; Sumino, Y.; Tanaka, S.; Tamba, S.; Mori, A. *Org. Chem. Front.* **2014**, *1*, 678. (o) Schnurch, M.; Spina, M.; Khan, A. F.; Mihovilovic, M. D.; Stanetty, P. *Chem. Soc. Rev.* **2007**, *36*, 1046.

(3) (a) Moyer, C. E.; Bunnett, J. F. *J. Am. Chem. Soc.* **1963**, *85*, 1891. (b) Bunnett, J. F. *Acc. Chem. Res.* **1972**, *5*, 139.

(4) (a) Okano, K.; Sunahara, K.; Yamane, Y.; Hayashi, Y.; Mori, A. *Chem. Eur. J.* **2016**, *22*, 16450. (b) Miyagawa, N.; Murase, Y.; Okano, K.; Mori, A. *Synlett* **2017**, *28*, 1106. (c) Hayashi, Y.; Okano, K.; Mori, A. *Org. Lett.* **2018**, *20*, 958.

(5) Olofson, R. A.; Dougherty, C. M. *J. Am. Chem. Soc.* **1973**, *95*, 582.

(6) (a) Krasovskiy, A.; Krasovskaya, V.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 2958. (b) Piller, F. M.; Appukkuttan, P.; Gavryushin, A.; Helm, M.; Knochel, P. *Angew. Chem. Int. Ed.* **2008**, *47*, 6802. (c) Piller, F. M.; Knochel, P. *Org. Lett.* **2009**, *11*, 445.

(7) (a) Clososki, G. C.; Rohbogner, C. J.; Knochel, P. *Angew. Chem. Int. Ed.* **2007**, *46*, 7681. (b) Rohbogner, C. J.; Wagner, A. J.; Clososki, G. C.; Knochel, P. *Org. Synth.* **2009**, *86*, 374. (c) Eaton, P. E.; Lee, C.-H.; Xiong, Y. *J. Am. Chem. Soc.* **1989**, *111*, 8016. (d) Henderson, K. W.; Kerr, W. J. *Chem. Eur. J.* **2001**, *7*, 3430.

(8) (a) Ashby, E. C.; Lin, J. J.; Goel, A. B. *J. Org. Chem.* **1978**, *43*, 1564. (b) Sanchez, R.; Scott, W. *Tetrahedron Lett.* **1988**, *29*, 139.

(9) (a) Compound **6** was synthesized by treatment of 2-allyl-4-bromothiophene[9b] with TMPMgCl·LiCl at room temperature followed by CBr$_4$. (b) Janssen, C. G. M.; Macco, A. A.; Buck, H. M.; Godefroi, E. F. *Recl. Trav. Chim. Pays-Bas* **1979**, *98*, 448.

(10) Becker, M. R.; Knochel, P. *Angew. Chem., Int. Ed.* **2015**, *54*, 12501.

(11) Kobayashi, K.; Sugie, A.; Takahashi, M.; Masui, K.; Mori, A. *Org. Lett.* **2005**, *7*, 5083.

(12) D$_2$O (99.8% D) was purchased and used as received. Compared to LiTMP, substantial amounts of **15** were generated when TMPMgCl·LiCl or Mg(TMP)$_2$·2LiCl was used as a base. These results indicate that equilibrium between the thermodynamically favored α-magnesiothiophene **19** and **15** exists in the presence of TMPH, generated in the deprotonation step.

(13) Dong, Z.; Clososki, G. C.; Wunderlich, S. H.; Unsinn, A.; Li, J.; Knochel, P. *Chem. Eur. J.* **2009**, *15*, 457. Eaton and Knochel also reported deprotonation of an aromatic proton adjacent to an ester group (references 7a–c)

(14) (a) Yang, H.; Hendricks, R. T.; Arora, N.; Nitzan, D.; Yee, C.; Lucas, M. C.; Yang, Y.; Fung, A.; Rajyaguru, S.; Harris, S. F.; Leveque, V. J. P.; Hang, J. Q.; Le Pogam, S.; Reuter, D.; Tavares, G. A. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 4614. (b). Barnes, D.; Cohen, S. L.; Fu, J.; Shu, L.; Zheng, R. WO2012010663A1, 2012. (c) Green, J.; Wilson, D. M.; Kong, L. C. C.; Das, S. K.; Poisson, C.; Court, J. J.; Tang, Q.; Li, P.; Collier, P. N.; Waal, N.; Lauffer, D. J.; Dorsch, W. WO2012006055A2, 2012.

(15) (a) Isobe, M.; Kondo, S.; Nagasawa, N.; Goto, T. *Chem. Lett.* **1977**, *6*, 679. (b) Snégaroff, K.; Komagawa, S.; Chevallier, F.; Gros, P. C.; Golhen, S.; Roisnel, T.; Uchiyama, M.; Mongin, F. *Chem. Eur. J.* **2010**, *16*, 8191.

(16) (a) Negishi, E.-I.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821. (b) Negishi, E.-I. *Acc. Chem. Res.* **1982**, *15*, 340. (c) Negishi, E.-I., *Angew. Chem. Int. Ed.* **2011**, *50*, 6738.