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# Generation of 3- and 5-Lithiothiophene-2-carboxylates via Metal−Halogen Exchange and Their Addition Reactions to Chalcogenoxanthones

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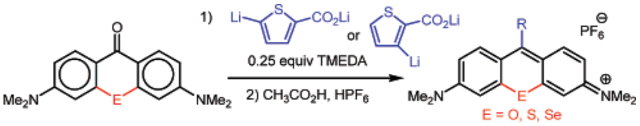
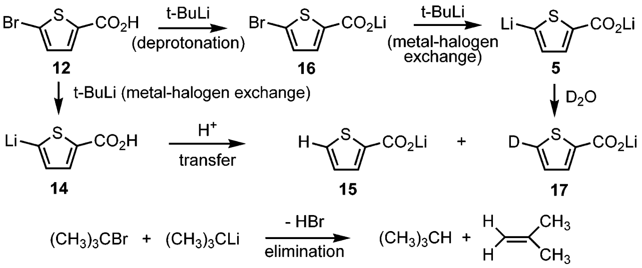


Deprotonation and lithium−bromine exchange in 5- or 3-bromothiophene-2-carboxylic acids with *t*-BuLi form the corresponding dianion, which reacts highly regioselectively in the presence of 0.25 equiv of tetramethyl-1,2-ethylenediamine with 3,6-bis(dimethylamino) chalcogenoxanthones to give S- and Se-containing rhodamines. Quenching studies with $D_2O$ indicate that an extra equivalent of *t*-BuLi is not necessary in these reactions. Deprotonation is faster than metal-halogen exchange with the bromothiophene-2-carboxylic acids using *t*-BuLi.

We have recently described the synthesis of thio and seleno analogues of tetramethylrosamine and initial studies of their photophysical[1] and biological properties.[2−4] Currently, we are developing synthetic routes to heavy-chalcogen analogues of true rhodamines; i.e., derivatives bearing a carboxy substituent in the 9-aryl group. Rhodamines with a thienyl group in the 9-position of the xanthylium core absorb at longer wavelengths than 9-phenyl derivatives and the parent compounds in this series were prepared by the addition of 2-lithiothiophene (**1**, Chart 1) to the **2-S** and **2-Se**[5] to give dyes **3** and **4** in excellent yield.[2c,3] The addition of lithium 5-lithiothiophene-2-carboxylate (**5**) and lithium 3-lithiothiophene-2-carboxylate (**6**) to the xanthones **2** appeared to be a direct route to rhodamine-related structures with a 9-thienyl substituent bearing a carboxylic acid oxidation state without masking/protecting the carboxy substituent. Dianions **5** and **6** are both known in the literature from acid−base chemistry—not from metal−halogen exchange. Thiophene-2-carboxylic acid is deprotonated with lithium diisopropylamide (LDA) in THF at −78 °C to give dianion **5**[6] and with *n*-BuLi in THF at −78 °C to give dianion **6**.[7]

**CHART 1**



In this paper, we describe the preparation of chalcogenorhodamines **7**−**11** (Chart 1) using dianions **5** and **6** generated from 5-bromothiophene-2-carboxylic acid (**12**) and 3-bromothiophene-2-carboxylic acid (**13**), respectively, via metal−halogen exchange with *tert*-butyllithium (*t*-BuLi). These studies include our observations with respect to rates of lithium−bromine exchange relative to rates of deprotonation of the carboxylic acids and the relative rate of elimination of HBr from the 2-bromo-2-methylpropane generated in the metal−halogen exchange.

**Synthesis of 9-(Heteroaryl)chalcogenorhodamines.** Our initial studies with dianions **5** and **6** generated by acid−base chemistry[6,7] suggested that either these dianions were not formed regiospecifically or they were equilibrating under reaction conditions. Metal−halogen exchange in 5-bromothiophene-2-carboxylic acid (**12**) and 3-bromothiophene-2-carboxylic acid (**13**) was examined as a means of generating dianions **5** and **6** regiospecifically. As described below, reactions with *t*-BuLi gave better regioselectivity than reactions with *s*-BuLi.

Initial metal−halogen exchange reactions followed conditions used for generating dianions from aromatic bromo carboxylic acids.[9,10] Bromo acid **12** was treated with 3.1 equiv of *t*-BuLi at −78 °C in THF in the presence or absence of 1 equiv (relative to *t*-BuLi) of *N*,*N*,*N′*,*N′*-tetramethylethylenediamine (TMEDA) to generate dianion **5**, which was then added to thioxanthone **2-S** or selenoxanthone **2-Se** at −78 °C. After 3 h, the desired rhodamines **8** and **9** were isolated in low yields (<10%) and little chalcogenoxanthone was recovered.

Dianion **5**, generated from **12** and 2.1 equiv of *t*-BuLi at −78 °C in THF, showed little reactivity toward either **2-S** or **2-Se** after 3 h at either 0 °C or −78 °C in the absence of TMEDA.

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The addition of TMEDA to the reaction mixtures gave higher yields of the desired chalcogenorhodamine dyes. However, *the optimal conditions found for the generation of dianion* ***5*** *for addition to chalcogenoxanthones* ***2*** *were the addition of 2.1 equiv of t-BuLi to 5-bromothiophene-2-carboxylic acid (**12**) and 0.25 equiv of TMEDA (relative to **12**) in anhydrous THF at −78 °C to generate the dianion* ***5***. A 4-fold excess of **5** was then added to a solution of **2-O**, **2-S**, or **2-Se** in THF at ambient temperature. The reaction was stopped via the addition of AcOH and then $HPF_6$. The acids **7**−**9** (as the hexafluorophosphate salts, Chart 1) were formed as a single regioisomer in the reaction mixture and were isolated in 85, 84, and 79% yields, respectively, following recrystallization.

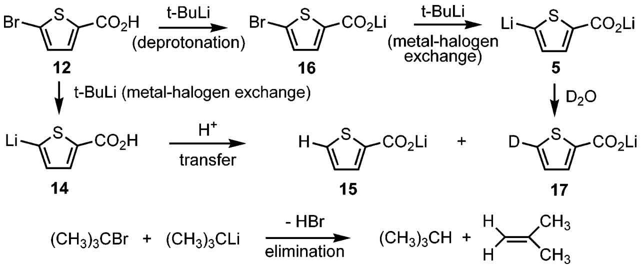
Lithium−bromine exchange was also used to generate 3-lithiothiophene-2-carboxylate (**6**) from bromo carboxylic acid **13**. Again, the optimal conditions for generation and reaction of the dianion **6** with **2-S** or **2-Se** were identical to those above for dianion **5**: 2.1 equiv of *t*-BuLi and 0.25 equiv of TMEDA relative to **13** in anhydrous THF at −78 °C. The $^1$H NMR spectra of the crude reaction mixtures of rhodamine derivatives **10** and **11** showed a 32:1 mixture of the 9-(3-thienyl-2-carboxylic acid) derivative **10** and the 2-thienyl-5-carboxylic acid derivative **8** and a 40:1 mixture of the 9-(3-thienyl-2-carboxylic acid) derivative **11** and the 2-thienyl-5-carboxylic acid derivative **9**. Both **10** and **11** were isolated as single regioisomers in 68 and 58% yields, respectively, following recrystallization.

The 3.6-Hz coupling constant observed between the thiophene protons at the 3- and 4-positions of **7**−**9** and the 5.2-Hz coupling constant observed between the thiophene protons at the 4- and 5-positions of **10** and **11** are consistent with the 2,5- and 2,3-disubstituted thiophene groups, respectively.[10] *The high regioselectivity observed in these reactions suggests that dianions* ***5*** *and* ***6*** *maintain their regiochemical integrity during the addition to chalcogenoxanthones* ***2***.

**Effect of TMEDA on Product Yields.** In the reactions described above, the number of equivalents of TMEDA impacted the yields obtained from the addition of dianions **5** and **6** to the chalcogenoxanthones **2**. While products were observed with 1 equiv of TMEDA relative to the starting bromo carboxylic acid **12** or **13** or 1 equiv of TMEDA relative to t-BuLi, significantly higher yields were obtained using substoichiometric TMEDA (0.25 equiv relative to bromo carboxylic acid). While this is an empirical observation on our part, the use of substoichiometric amounts of TMEDA has been documented to accelerate directed metalation reactions in various aromatic systems,[11] which provides precedent for our observations.

**Product Distributions Based on Relative Rates of Metal−Halogen Exchange/Deprotonation.** The use of metal-halogen exchange to generate dianions **5** and **6** brings several different reactions into competition. These reactions are summarized in Scheme 1 for the conversion of 5-bromothiophene-2-carboxylic acid (**12**) to dianion **5**. If metal−halogen exchange in **12** were fast relative to deprotonation, then 5-lithiothiophene-2-carboxylic acid (**14**) would be the first-formed product and intermolecular proton transfer would generate lithium thiophene-2-carboxylate (**15**). However, if deprotonation of the carboxylic acid were fast relative to metal−halogen exchange, then the lithium carboxylate **16** would be the first-formed product and metal−halogen exchange in **16** would then give dianion **5**. One probe of the participation of each of these pathways is to quench the dianion **5** with $D_2O$ to give 2-deuterothiophene **17**. The percentage of deuterium incorporation would distinguish the extent of formation of **5** relative to **15**. This type of analysis has been elegantly used to evaluate comparative rates of metal−halogen exchange relative to intra- and/or intermolecular proton (deuteron) transfer.[12]

**SCHEME 1**



**SCHEME 2**

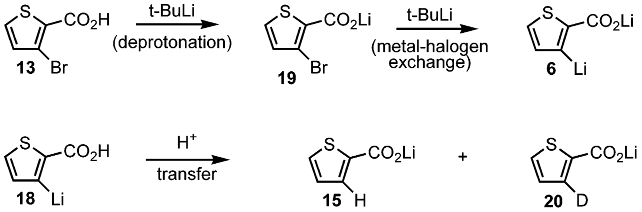
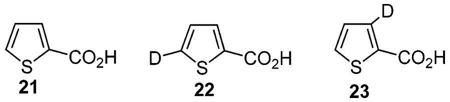


**CHART 2**



A third competitive reaction in Scheme 1 is the elimination of HBr from the 2-bromo-2-methylpropane produced in the metal−halogen exchange with *t*-BuLi. If this reaction is comparable in rate or faster relative to metal−halogen exchange or deprotonation, then the elimination reaction will be competitive with these reactions, and, as described below, unreacted **12** should be isolated with *t*-BuLi as limiting reagent.

Similar reactions can be drawn for the reaction of bromo carboxylic acid **13** (Scheme 2). One major difference in the reaction pathways of **12** and **13** is that the 5-lithiothiophene-2-carboxylic acid (**14**)—if formed—is unlikely to give intramolecular proton-transfer relative to 3-lithiothiophene-2-carboxylic acid (**18**) to give thiophene-2-carboxylate **15**. From **18**, the formation of **15** would most likely be due to intramolecular proton transfer. Deprotonation of **13** would generate lithium carboxylate **19** and metal-halogen exchange in **19** would then give dianion **6**. Quenching the dianion **6** with $D_2O$ would give 3-deuterothiophene-2-carboxylate **20**.

Following a $D_2O$ quench, an acidic workup would generate thiophene-2-carboxylic acid (**21**) from **15**, 5-deuterothiophene-2-carboxylic acid (**22**) from **17**, and 3-deuterothiophene-2-carboxylic acid (**23**) from **20** (Chart 2). The ratio of **21** to **22**/**23** provides a direct comparison of the rate of metal-halogen

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exchange and deprotonation of the carboxylic acid with *t*-BuLi. The ratio of unreacted starting bromo acid **12** or **13** to **21**−**23** indicates the rate of HBr elimination from 2-bromo-2-methylpropane relative to metal-halogen exchange and deprotonation.

**Relative Rate of HBr Elimination from 2-Bromo-2-methylpropane.** Bromo compounds **12** and **13** were treated with 2.1 equiv of *t*-BuLi as limiting reagent at −78 °C with 0.25−2.0 equiv of TMEDA relative to the bromocarboxylic acid. The resulting anions were quenched via the addition of the anion solutions to stirred mixtures of THF/$D_2O$ at −78 °C, 0 °C, and ambient temperature. The anions were also quenched via the addition of $D_2O$ directly to the anion solutions at −78 °C. Once quenched with $D_2O$, the reaction mixtures were diluted with saturated $NaHCO_3$ and extracted with ether. The aqueous phase was acidified with HCl and reextracted with ether to isolate the carboxylic acids in >90% yields.

*Reactions of bromothiophene-2-carboxylic acids **12** and **13** with 2.1 equiv of t-BuLi returned no trace of unreacted **12** or **13** by $^1$H NMR.* These results indicate that elimination of HBr from the 2-bromo-2-methylpropane with *t*-BuLi (or any other “base” generated during reaction) is slow relative to metal−halogen exchange and deprotonation of the carboxylic acid; i.e., both of these reactions are complete and consume the *t*-BuLi. Furthermore, the reaction of dianion **5** or **6** with 2-bromo-2-methylpropane must also be relatively slow.

**Quenching Dianion 5 with $D_2O$.** The $D_2O$ quench of the products from the reaction of bromothiophene carboxylic acid **12** with 2.1 equiv of *t*-BuLi and 0.25 equiv of TMEDA (relative to **12**) showed (100 ± 2)% incorporation of one deuterium by $^1$H NMR to give an (82 ± 2)/(18 ± 2) ratio of **22** to **23** (Chart 2). In the synthetic studies, dianion **5** only gave the 9-(2-thienyl-5-carboxy)rhodamine derivatives **7**−**9**. No products were detected in the crude reaction mixture from dianion **6**, which suggests that **5** is stable under the conditions of reaction. Consequently, it is logical that **23** must be formed during the $D_2O$ quench of **5**. While **22** arises directly from the $D_2O$ quench of dianion **5**, **23** most likely arises from proton transfer to dianion **5** to give carboxylate **15**. The subsequent reaction of either **15** or **21** with residual t-BuLi or with dianion **5** could generate dianion **6**, which would produce **23** via the $D_2O$ quench. Isotope ratios from mass spectrometry data are consistent with the incorporation of a single deuterium in the thiophene-2-carboxylic acids while the thiophene protons in the $^1$H NMR spectra of the product mixtures all show doublet multiplicity, which is again consistent with monodeuterated species.

The real question is whether dianion **6** is formed during the initial reaction of **12** with *t*-BuLi or whether carboxylic acid **23** is formed during the $D_2O$ quench. In similar reactions, metal−halogen exchange, protonation, and deprotonation have been more rapid than mixing of reagents.[13] The inverse addition of $D_2O$ to the **12**/*t*-BuLi mixture at −78 °C gave (77 ± 3)% incorporation of deuterium and a (68 ± 2)/(32 ± 2) ratio of **22** to **23**. The increase in the “rearranged” product again supports the idea that dianion **6** is generated during the $D_2O$ quench.

The decreased deuteration when $D_2O$ is added to the dianion suggests an endogenous proton source in the reaction such as the 2-bromo-2-methylpropane generated during metal-halogen exchange. Local heating upon addition of $D_2O$ or the generation of relatively unsolvated $DO^-$ might accelerate the elimination of HBr by either **5** or $DO^-$ (to generate HOD, which could then act as a proton source). To investigate this possibility, **12** was treated with 2.1 equiv of *s*-BuLi as limiting reagent at −78 °C with 0.25 of TMEDA relative to **12**. The dianion **5** was quenched via the addition of $D_2O$ directly to the anion solution at −78 °C to give (99 ± 2)% incorporation of deuterium and a (53 ± 2)/(47 ± 2) ratio of **22** to **23**. The reduced reactivity of 2-bromobutane (produced in the metal−halogen exchange with *s*-BuLi) relative to 2-bromo-2-methylpropane toward elimination of HBr is consistent with the observed results.

**Quenching Dianion 6 with $D_2O$.** The addition of the products from the reaction of 3-bromothiophene-2-carboxylic acid (**13**) with 2.1 equiv of *t*-BuLi to THF/$D_2O$ at 0 °C showed (99 ± 3)% incorporation of one deuterium by $^1$H NMR to give a (48 ± 2)/(52 ± 2) ratio of **22** to **23**. The addition of $D_2O$ to the anion had no impact on the **22**/**23** ratio, suggesting equilibrium is rapidly attained upon exposure to $D_2O$. The addition of the **13**/*t*-BuLi mixture immediately after mixing of reagents at −78 °C to chalcogenoxanthones **2** at ambient temperature gave products from the addition of dianion **6** with >30:1 regioselectivity suggesting that **6** is relatively stable to the conditions of reaction. These results also suggest that 5-deuterothiophene-2-carboxylic acid **21** is primarily formed from reactions of **6** during the $D_2O$ quench.

The addition of $D_2O$ directly to the **13**/*t*-BuLi reaction mixture gave (78 ± 3)% incorporation of deuterium, which again suggests an endogenous proton source. 2-Bromo-2-methylpropane was identified as the likely proton source by treating **13** with 2.1 equiv of *sec*-BuLi as limiting reagent at −78 °C with 0.25 of TMEDA relative to **13**. The dianion **6** was quenched via the addition of $D_2O$ directly to the anion solution at −78 °C to give (100 ± 2)% incorporation of deuterium and a (29 ± 2)/(71 ± 2) ratio of **22** to **23**.

**Effect of Temperature and TMEDA on Product Ratios from the Addition of Dianions 5 and 6 to THF/$D_2O$ Mixtures.** In the $D_2O$ quenching experiments described above, the temperature of the THF/$D_2O$ quench and the number of equivalents of TMEDA had minimal impact on product ratios. For dianion **5**, which was most sensitive to conditions, the **22**:**23** ratio varied over the range (76−82)/(24−18) as a function of temperature (0 °C, −78 °C, ambient) and over the range (74−82)/(26−18) for 0−2.0 equiv of TMEDA relative to bromo carboxylic acid (**12**).

**Kinetic Accessibility and Steric Interactions.** Dianions **5** and **6** maintained their regiochemistry during addition to chalcogenoxanthones **2**. When one compares the nearly 1:1 ratio of **22** to **23** formed from the quenching of dianion **6** with $D_2O$ and the 4:1 ratio of **22** to **23** from the quenching of dianion **5**, one is drawn to the conclusion that the 5-position is kinetically more accessible to deprotonation than the 3-position in thiophene-2-carboxylic acid (**21**) under the quenching conditions. The observation that dianion **6** is formed by treating thiophene-2-carboxylic acid (**21**) with 2 equiv of the relatively unhindered *n*-BuLi while dianion **5** is formed with 2 equiv of the hindered base LDA[7] is consistent with this argument.

The use of *s*-BuLi in the synthetic reactions generated dianion **6** unambiguously from 3-bromothiophene-2-carboxylic acid (**13**), but gave mixtures of **5** and **6** when bromo carboxylic acid **12** was treated with 2.1 equiv of *s*-BuLi. The addition of the **12**/*s*-BuLi reaction mixture (conditions identical to the **12**/*t*-BuLi reaction) to **2-S** gave a 3:1 mixture of **11**/**8**. Deprotonation

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[13] Parham, W. E.; Jones, L. D.; Sayed, Y. *J. Org. Chem.* **1975**, *40*, 2394.

at C-3 may be competitive with metal−halogen exchange when *s*-BuLi is used.

In summary, the addition of dianions **5** and **6** (Chart 1), generated by lithium−bromine exchange with *t*-BuLi, to chalcogenoxanthones **2** provides a general route to rhodamine derivatives bearing a 9-(2-thienyl-5-carboxy) or 9-(3-thienyl-2-carboxy) substituent. Addition of 0.25 equiv of TMEDA during generation of the dianions **5** and **6** from bromothiophene-2-carboxylic acids **12** and **13** at −78 °C gives species that (1) have sufficient reactivity to add to chalcogenoxanthones **2** at ambient temperature and (2) maintain their regiochemistry upon addition to solutions of the chalcogenoxanthones **2**. The substoichiometric levels of TMEDA required for reaction suggest that 2:2 complexes of TMEDA and organolithium reagents are not optimal in these reactions.[14]

Quenching studies with $D_2O$ indicate that elimination of HBr from 2-bromo-2-methylpropane generated from metal−halogen exchange with *t*-BuLi is slow relative to metal−halogen exchange and deprotonation using bromo carboxylic acids **14**, **19**, and **20**. Bromothiophene-2-carboxylic acids **12** and **13** are completely converted to dianions **5** and **6**, respectively, with 2.1 equiv of *t*-BuLi. *An additional equiv of t-BuLi is not required in these reactions to scavenge HBr from 2-bromo-2-methylpropane.* The high regioselectivity observed in the reactions of dianions **5** and **6** is consistent with rapid deprotonation of the carboxylic acid substituents of **12** and **13** followed by metal−halogen exchange.

## Experimental Section

**General Procedure for Generation of Chalcogenorhodamines 7−11.** *t*-BuLi (1.7 M in hexanes, 3.3 mL, 5.6 mmol) was added dropwise to a stirred solution of 5-bromothiophene-2-carboxylic acid (**12**) or 3-bromothiophene-2-carboxylic acid (**13**, 2.7 mmol) and TMEDA (81 mg, 0.70 mmol) in 25 mL of anhydrous THF at −78 °C. The resulting solution was immediately transferred via cannula to the chalcogenoxanthones **2** (0.67 mmol) dissolved in 7 mL of anhydrous THF at ambient temperature. The resulting mixture was heated at reflux for 12 min. Acetic acid (0.33 g, 5.6 mmol) was added, and the reaction mixture was poured into a 10% by wt. solution of aqueous $HPF_6$. The precipitate was collected after 1.0 h of stirring and washed with water and ether. The final dyes were obtained following recrystallization from $CH_3CN/Et_2O$.

For **7**: 85%; mp 280−282 °C; $^1H$ NMR (400 MHz, $CD_3CN$) $\delta$ 7.95 (d, 1 H, $J = 3.6$ Hz), 7.58 (d, 2 H, $J = 9.6$ Hz), 7.38 (d, 1 H, $J = 3.6$ Hz), 7.04 (dd, 2 H, $J = 1.6$, 9.6 Hz), 6.82 (d, 2 H, $J = 1.6$ Hz), 3.26 (s, 12 H); $^{13}C$ NMR (75.5 MHz, DMSO-$d_6$) $\delta$ 162.4, 156.9, 156.8, 147.9, 139.4, 136.3, 133.1, 132.8, 130.9, 115.0, 113.1, 96.4, 40.6; $\lambda_{max}$ ($H_2O$) 571 nm ($\epsilon$ 57 000 $M^{-1}$ $cm^{-1}$); HRMS (ESI) *m/z* 393.1270 (calcd for $C_{22}H_{21}N_2O_3S$ 393.1273). Anal. Calcd for $C_{22}H_{21}N_2O_3S{\cdot}PF_6$: C, 49.07; H, 3.93; N, 5.20. Found: C, 48.77; H, 4.36; N, 5.22.

For **8**: 84%; mp 182−184 °C; $^1H$ NMR (400 MHz, $CD_3CN$) $\delta$ 7.93 (d, 1 H, $J = 3.6$ Hz), 7.55 (d, 2 H, $J = 9.6$ Hz), 7.27 (d, 1 H, $J = 2.8$ Hz), 7.19 (d, 2 H, $J = 2.8$ Hz), 7.03 (dd, 2 H, $J = 2.8$, 9.6 Hz), 3.23 (s, 12 H); $^{13}C$ NMR (125 MHz, $CD_3CN$) $\delta$ 162.7, 154.6, 151.4, 144.7, 142.8, 137.3, 136.4, 134.7, 132.5, 120.3, 116.8, 106.7, 41.1; $\lambda_{max}$ ($H_2O$) 591 nm ($\epsilon$ 54 000 $M^{-1}$ $cm^{-1}$); HRMS (ESI) *m/z* 409.1040 (calcd for $C_{22}H_{21}N_2O_2S_2$ 409.1039). Anal. Calcd for $C_{22}H_{21}N_2O_2S_2{\cdot}PF_6$: C, 47.65; H, 3.82; N, 5.05. Found: C, 47.69; H, 3.95; N, 5.36.

For **9**: 79%; mp 232−234 °C; $^1H$ NMR (400 MHz, $CD_3CN$) $\delta$ 7.91 (d, 1 H, $J = 3.6$ Hz), 7.56 (d, 2 H, $J = 9.6$ Hz), 7.41 (d, 2 H, $J = 2.4$ Hz), 7.29 (d, 1 H, $J = 3.6$ Hz), 6.95 (dd, 2 H, $J = 2.4$, 9.6 Hz), 3.21 (s, 12 H); $^{13}C$ NMR (125 MHz, $CD_3CN$) $\delta$ 162.7, 154.1, 152.7, 145.9, 144.5, 138.3, 137.0, 134.7, 132.3, 120.9, 116.4, 110.1, 41.1; $\lambda_{max}$ ($H_2O$) 603 nm ($\epsilon$ 53 000 $M^{-1}$ $cm^{-1}$); HRMS (ESI) *m/z* 457.0487 (calcd for $C_{22}H_{21}N_2O_2S^{80}Se$ 457.0483). Anal. Calcd for $C_{22}H_{21}N_2O_2SSe{\cdot}PF_6$: C, 43.94; H, 3.52; N, 4.66. Found: C, 44.05; H, 3.72; N, 4.99.

For **10**: 68%; mp 294−295 °C; $^1H$ NMR (400 MHz, $CD_2Cl_2$) $\delta$ 7.61 (d, 1 H, $J = 5.2$ Hz), 7.46 (d, 2 H, $J = 9.2$ Hz), 6.96 (d, 2 H, $J = 2.4$ Hz), 6.92 (d, 1 H, $J = 5.2$ Hz), 6.86 (dd, 2 H, $J = 2.4$, 9.2 Hz), 3.18 (s, 12 H); $^{13}C$ NMR (75 MHz, $CD_3CN$) $\delta$ 162.3, 157.2, 154.7, 144.6, 142.2, 136.1, 134.2, 133.2, 131.8, 119.5, 116.6, 106.6, 41.0; $\lambda_{max}$ ($H_2O$) 574 nm ($\epsilon$ 5.4 × $10^4$ $M^{-1}$ $cm^{-1}$); HRMS (ESI) *m/z* 409.1031 (calcd for $C_{22}H_{21}N_2O_2S_2$ 409.1039). Anal. Calcd for $C_{22}H_{21}N_2O_2S_2{\cdot}PF_6$: C, 47.65; H, 3.82; N, 5.05. Found: C, 47.29; H, 4.16; N, 4.88.

For **11**: 58%; mp 283−284 °C; $^1H$ NMR (400 MHz, $CD_2Cl_2$) $\delta$ 7.61 (d, 1 H, $J = 5.2$ Hz), 7.46 (d, 2 H, $J = 9.2$ Hz), 6.96 (d, 2 H, $J = 2.4$ Hz), 6.92 (d, 1 H, $J = 5.2$ Hz), 6.86 (dd, 2 H, $J = 2.4$, 9.2 Hz), 3.18 (s, 12 H); $^{13}C$ NMR (75 MHz, $CD_3CN$) $\delta$ 162.2, 158.4, 154.2, 145.9, 144.0, 137.9, 134.3, 132.3, 132.0, 120.1, 116.2, 110.0, 41.0; $\lambda_{max}$ ($H_2O$) 584 nm ($\epsilon$ 8.4 × $10^4$ $M^{-1}$ $cm^{-1}$); HRMS (ESI) *m/z* 409.1031 (calcd for $C_{22}H_{21}N_2O_2S^{80}Se$: 457.0483). Anal. Calcd for $C_{22}H_{21}N_2O_2SSe{\cdot}PF_6$: C, 43.94; H, 3.52; N, 4.66. Found: C, 44.14; H, 3.59; N, 4.72.

**Generation of Dianions 5 and 6. A. With *tert*-Butyllithium Followed by Quenching with $D_2O$.** *t*-BuLi (1.7 M in hexanes, 3.3 mL, 5.6 mmol), TMEDA (81 mg, 0.70 mmol to 0.32 g, 0.28 mmol), and bromo carboxylic acid **12** or **13** (0.56 g, 2.7 mmol) were treated as described above at −78 °C. Following addition, the resulting solution was immediately transferred via cannula to a stirred mixture of 7 mL of THF and 1.0 mL (55 mmol) of $D_2O$ cooled to −78 or 0 °C or at ambient temperature. Alternatively, the dianion was quenched at −78 °C via the addition of 200 $\mu$L (11 mmol) of $D_2O$. The $D_2O$-quenched mixtures were stirred with 10 mL of saturated $NaHCO_3$ solution and extracted with ether (2 × 10 mL). The aqueous layer was acidified via the dropwise addition of concentrated HCl, the resulting solution was extracted with ether (2 × 15 mL), and these extracts were dried over $Na_2SO_4$ and concentrated. The yields of recovered of carboxylic acids were >90%. The $^1H$ NMR spectra of the residues were acquired at 500 MHz in $CDCl_3$ using residual $CHCl_3$ as an internal standard and integrals were carefully measured for the following signals in thiophene-2-carboxylic acid: $\delta$ 7.89 (H-*3*), 7.635 (H-*5*), 7.125 (H-*4*) ($^1H$ NMR spectrum in the Supporting Information). Integral values reported are the of average triplicate runs with three independent FIDs for values in each individual run with ± the standard deviation.

**B. With *sec*-Butyllithium Followed by Quenching with $D_2O$.** *s*-BuLi (0.95 M in cyclohexanehexanes, 6.0 mL, 5.7 mmol) was added dropwise to a stirred solution **12** or **13** (0.56 g, 2.7 mmol) and TMEDA (81 mg, 0.70 mmol) in 25 mL of anhydrous THF at −78 °C. The solution of dianion was quenched at −78 °C via the addition of 200 $\mu$L of $D_2O$ (11 mmol). The deuterated thiophene-2-carboxylic acids were isolated as described above.

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**Supporting Information Available:** General experimental and $^1H$ NMR spectra of thiophene-2-carboxylic acid and deuterated acids generated by the quenching of **5** and **6** with $D_2O$. This material is available free of charge via the Internet at http://pubs.acs.org.

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