# Synthesis and Hydrolysis of Thiol Derivatives of Molybdocene Dichloride Incorporating Electron-Withdrawing Substituents

Jenny B. Waern,[†] Peter Turner,[†] and Margaret M. Harding*[,‡]

*School of Chemistry, The University of Sydney, NSW 2006, Australia, and School of Chemistry, The University of New South Wales, NSW 2052, Australia*

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Hydrolysis studies of derivatives of molybdocene dichloride in which the two chloride ligands were replaced by 3,5-bis(trifluoromethyl)thiophenol, 3,5-bis(trifluoromethyl)benzyl thiol, and 2,2,2-trifluoroethane thiol ligands confirmed that the electron-withdrawing groups affect the lability of the Mo−S bonds and promote slow generation of the putative biologically active species "$Cp_2Mo^{2+}$"; the trifluoroethane thiol derivative underwent 50% hydrolysis in 14 h in 10% $D_2O$/DMSO-$d_6$. The structure of molybdocene bis(S-3,5-bis(trifluoromethyl)benzyl thiol) was confirmed by X-ray crystal structure analysis.

## Introduction

The bioorganometallic chemistry of the antitumor metallocenes, particularly titanocenes,[1,2] has attracted significant attention, given the promising preclinical and phase I clinical trials of titanocene dichloride.[3,4] Given the hydrolytic instability[5,6] and disappointing phase II results of titanocene dichloride,[7,8] we have focused on evaluation of molybdocene dichloride, $Cp_2MoCl_2$ (**1**), and derivatives based on this framework as a potential new class of organometallic antitumor agents.[9−12] In contrast to the extensive testing of titanocene dichloride against animal and human cancers,[1,2] only limited antitumor data have been reported for molybdocene dichloride (**1**) with cytotoxicity studies restricted to Erhlich Ascites tumors[13] and two human cancer cell lines.[9]

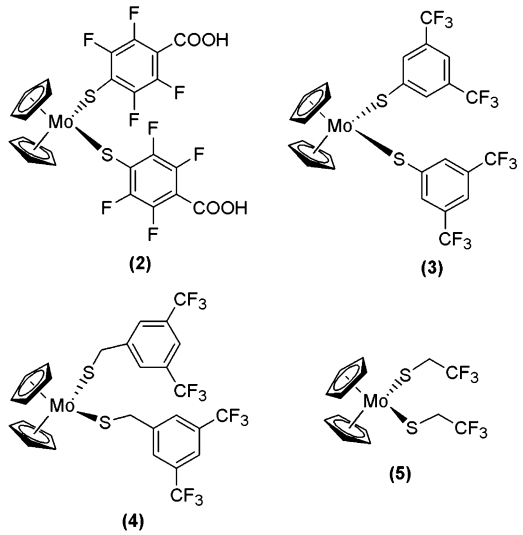


**Figure 1.** Trifluoromethyl derivatives of molybdocene dichloride and the previously studied[9] tetrafluorinated derivative **2**.

The coordination chemistry and proposed mechanism of antitumor action of molybdocene chemistry (**1**) is significantly different from titanocene dichloride.[11] The complex **1** forms strong, nonlabile complexes with thiols,[10,14,15] including glutathione, which almost certainly leads to deactivation and excretion of a large amount of administered complex. We have demonstrated that the in vitro cytotoxicity of molybdocene dichloride (**1**) against V79 cells is dependent on the lability of the Mo−X ligand.[9] An unexpected outcome of this study was the high cellular uptake of molybdocene bis(*S*-4-thiol-2,3,5,6-tetrafluorobenzoic acid) (**2**) (Figure 1), which was attributed to the combination of the lipophilic aromatic rings and good water solubility.[9] This derivative incorporated electron-withdrawing fluorine substituents on the aromatic rings in order to decrease the strength of the Mo−S bond and promote formation of the putative active species "$Cp_2Mo^{2+}$" in vivo.[16] However, while

* To whom correspondence should be addressed. E-mail: harding@chem.usyd.edu.au.

[†] The University of Sydney.

[‡] The University of New South Wales.

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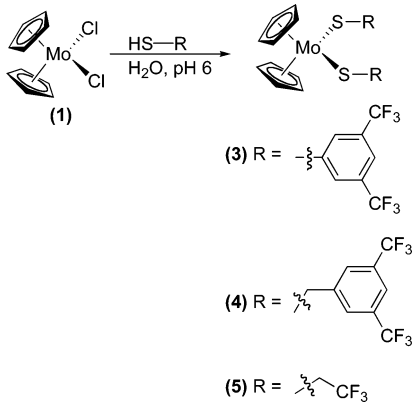
**Scheme 1**




hydrolysis of the thiol ligands in **2** occurred in aqueous solutions, the rate of formation of "$Cp_2Mo_2^+$" was too slow to be relevant on a biological time scale. Hence while significantly higher amounts of complex **2** entered the cell compared with **1** at the same concentration, **2** was not cytotoxic, as the thiol ligands remained metal bound.[9]

In this paper, the design, synthesis, and hydrolytic stability of thiol derivatives **3**, **4**, and **5** (Figure 1) are reported. These derivatives were studied in order to evaluate the effect of the trifluoromethyl groups on the stability of the Mo−S bond and thus provide fundamental data needed to guide the design of potential prodrugs of $Cp_2MoCl_2$ that hydrolyze on an hour time scale to release the active "$Cp_2Mo^{2+}$" species[16] in the cell. Given the excellent cellular uptake of the aromatic derivative **2**,[9] lipophilic ligands were incorporated into the design of complexes **3** and **4** in an effort to maximize both cellular uptake and subsequent release of "$Cp_2Mo^{2+}$" in the cell and thus test the hypothesis that increased delivery of the active species would translate to improved cytotoxicity. For comparison, derivative **5** lacked a lipophilic ligand but was designed to measure the effect of a single trifluoromethyl group on the hydrolytic stability of the Mo−S bonds. Given that the derivatives were designed to hydrolyze in water, making purification difficult, derivatives **3**, **4**, and **5** were designed to be soluble in water-miscible solvents in order to facilitate isolation of analytically pure material for biological testing.

**Table 1. Crystallographic Data and Details of Refinement for Molybdocene Bis(*S*-3,5-bis(trifluoromethyl)benzyl thiol) (4)**

| | |
|---|---|
| formula of the refinement model | $C_{28}H_{20}F_{12}MoS_2$ |
| model molecular weight | 744.50 |
| cryst syst | monoclinic |
| space group | *C*2/*c* (#15) |
| *a* | 14.787(2) Å |
| *b* | 6.9222(9) Å |
| *c* | 27.656(4) Å |
| $\beta$ | 96.901(7)° |
| *V* | 2810.4(7) Å$^3$ |
| $D_c$ | 1.760 g cm$^{-3}$ |
| *Z* | 4 |
| cryst size | 0.120 × 0.030 × 0.015 mm |
| cryst color | orange |
| cryst habit | needle |
| temperature | 103(2) K |
| $\lambda$(synchrotron) | 0.48595 Å |
| $\mu$(synchrotron) | 1.792 mm$^{-1}$ |
| $2\theta_{max}$ | 45.02° |
| *hkl* range | −22 22, −10 10, −41 43 |
| *N* | 38 587 |
| $N_{ind}$ | 5266 ($R_{merge}$ 0.0735) |
| $N_{obs}$ | 4698 ($I > 2\sigma(I)$) |
| $N_{var}$ | 195 |
| residuals[a] $R_1(F)$, $wR_2(F^2)$ | 0.0481, 0.1230 |
| GoF(all) | 1.305 |
| residual extrema | −1.317, 1.645 e Å$^{-3}$ |

[a] $R_1 = \sum||F_o| - |F_c||/\sum|F_o|$ for $F_o > 2\sigma(F_o)$; $wR_2 = (\sum w(F_o^2 - F_c^2)^2/\sum(wF_c^2)^2)^{1/2}$ all reflections. $w = 1/[\sigma^2(F_o^2) + (0.05P)^2 + 5.0P]$, where $P = (F_o^2 + 2F_c^2)/3$.

## Results and Discussion

Molybdocenes **3**, **4**, and **5** were prepared by reaction of the relevant thiol with an aqueous solution of $Cp_2MoCl_2$ (**1**) (Scheme 1), which resulted in the precipitation of the crude product. Crystals of **4** suitable for X-ray diffraction analysis were obtained by slow crystallization from aqueous acetonitrile. The crystals were thin and weakly diffracting, and a structure was ultimately obtained from a data collection at the ChemMatCARS beamline of the Advanced Photon Source. The ORTEP[17] depiction of the structure is shown in Figure 2, and key crystallographic details are summarized in Table 1. The Mo−S distance of 2.4643(7) Å is comparable to those reported in the literature, which range from 2.455 Å for Mo−*S*-Cys[15] complexes to 2.516 Å for Mo−*S*-thiouracil complexes.[18]

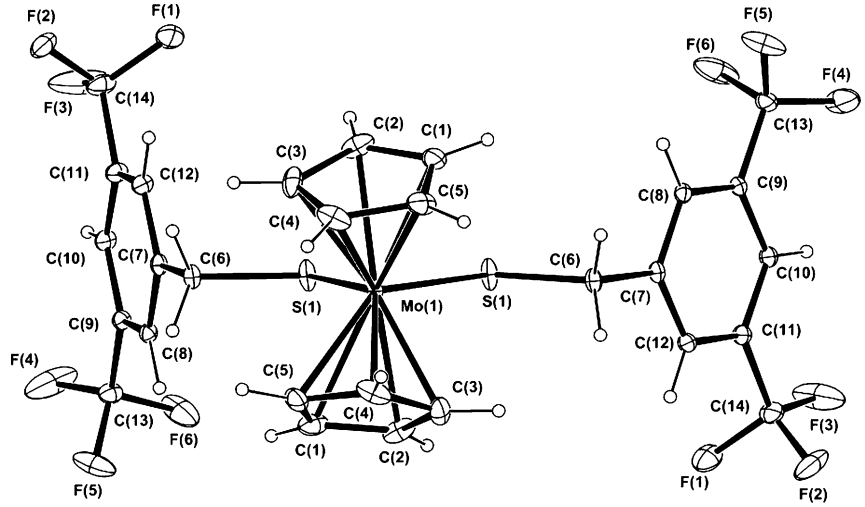



**Figure 2.** ORTEP depiction of molybdocene bis(*S*-3,5-bis(trifluoromethyl)benzyl thiol) (**4**), with 20% atomic ellipsoids. Selected bond lengths (Å), angles (deg), and torsional angles (deg): Mo(1)−S(1) 2.4643(7), S(1)−C(6) 1.830(2), C(6)−C(7) 1.5043(3), Mo(1)−C(1) 2.376(3), Mo(1)−C(2) 2.326(3), Mo(1)−C(3) 2.292(3), Mo(1)−C(4) 2.294(3), Mo(1)−C(5) 2.341(3), S(1)−Mo(1)−S(1) 73.03(3), Mo(1)−S(1)−C(6) 111.47(8), S(1)−C(6)−C(7) 106.16(16), S(1)−Mo(1)−S(1)−C(6)−178.32(11), Mo(1)−S(1)−C(6)−C(7) 178.52(14).

**Scheme 2**

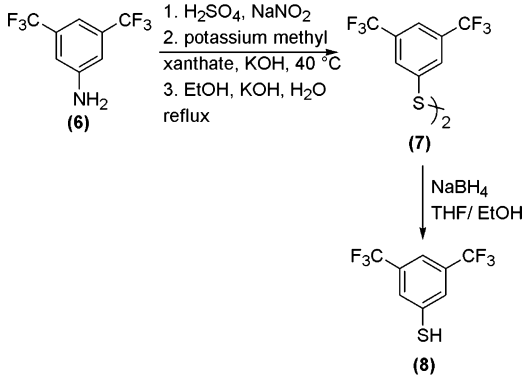



**Table 2. Summary of Percent Hydrolysis of Thiol Ligands in Derivatives 2−5 in Solvents Indicated after 12 and 24 h**

| | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| 12 h | | | | |
| 10% $D_2O$/DMSO-$d_6$ | <10 | 0 | nd[a] | 50 |
| 10% $D_2O$/$CD_3CN$ | nd[a] | 0 | 20 | <5 |
| 24 h | | | | |
| 10% $D_2O$/DMSO-$d_6$ | <10 | 0 | nd[a] | 75 |
| 10% $D_2O$/$CD_3CN$ | nd[a] | 5−10 | 30 | 5−10 |

[a] Not determined.

Thiophenol **8**, required for the preparation of **3**, was prepared as shown in Scheme 2. The diazonium salt of aniline **6** was converted to the corresponding xanthate salt, followed by hydrolysis to the disulfide **7** and reduction to the thiol **8** with sodium borohydride. As the thiol **8** was particularly prone to reoxidation to the disulfide **7**, thiol **8** was not fully characterized but used immediately in the next reaction. 3,5-Bis(trifluoromethyl)benzyl thiol, required for the preparation of **4**, was prepared in two steps from the corresponding benzyl bromide.

As expected, due to the lack of ionizable or hydrogen-bonding functionality, none of the derivatives **3**, **4**, or **5** were water soluble. Hence hydrolysis experiments were carried out in aqueous DMSO or aqueous acetonitrile, to determine the effect of the electron-withdrawing substituents on the lability of the Mo−S bond. Hydrolysis experiments were carried out by addition of 10% $D_2O$ to a solution of the complex at 37 °C, and the reactions were monitored by $^1H$ and $^{19}F$ NMR spectroscopy. Under these conditions, the Cp ligands remain metal bound, as evidenced by the appearance of the characteristic Cp signal in the $^1H$ NMR spectrum.[19] The hydrolysis of the thiol ligands in complex **2**, which has been studied previously in water (pH 7),[9] was also determined in aqueous DMSO to allow direct comparison of the results with those obtained with **3**−**5**. In both aqueous DMSO and aqueous acetonitrile, there was some precipitation of unidentified hydrolysis species.

Table 2 summarizes the rates of hydrolysis of the derivatives in different solvents. The rate of hydrolysis of the thiophenol ligands in **2** in aqueous DMSO was similar to previously reported data in $D_2O$ (50 mM NaCl), where <5% hydrolysis was observed after 48 h.[9] In contrast, significant solvent effects on the rate of hydrolysis were observed with the other derivatives. Thus, while there was no evidence for hydrolysis of the thiophenol ligands in **3** in aqueous DMSO after 24 h, new signals in both the $^1H$ and $^{19}F$ NMR spectra were observed in aqueous acetonitrile, consistent with 5−10% hydrolysis of the thiol ligands after 24 h.

The hydrolysis of the benzyl thiol derivative **4** could be studied only in aqueous acetonitrile since addition of 10% water to a DMSO solution of the complex resulted in complete and immediate precipitation of the complex. In aqueous acetonitrile, there was some free thiol ligand (labeled L) present in the acetonitrile solution before the addition of water (Figure 3a). The signals arising from the hydrolyzed ligand (labeled L, plus aromatic resonaces at $\delta$ 7.9 ppm) increased over time after the addition of 10% $D_2O$, and after 5 h, approximately 20% hydrolysis of the thiol ligand had occurred (Figure 3b), while after 3 days, approximately 50% hydrolysis of the thiol ligands had occurred (Figure 3c).

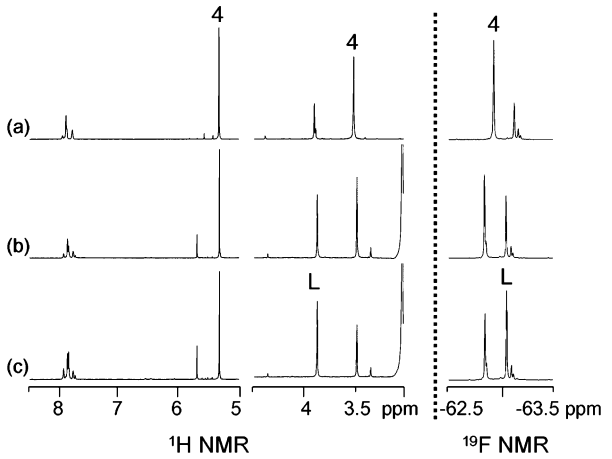



**Figure 3.** $^1H$ (300 MHz) and $^{19}F$ (282 MHz) NMR spectra (310 K; acetonitrile-$d_3$) of **4**: (a) prior to $D_2O$ addition, (b) after addition of $D_2O$, 5 h, (c) 3 days. The resonances arising from the hydrolyzed ligand are indicated by L.

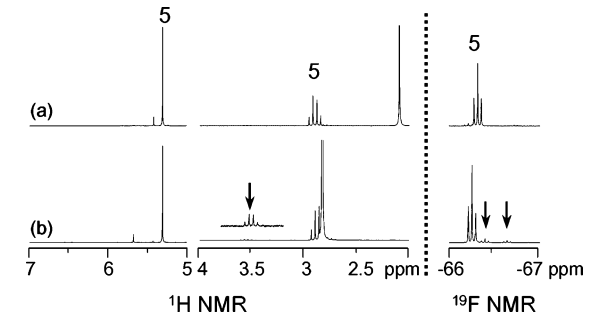



**Figure 4.** $^1H$ (300 MHz) and $^{19}F$ (282 MHz) NMR spectra (310 K; acetonitrile-$d_3$) of **5**: (a) prior to $D_2O$ addition, (b) after addition of $D_2O$, 22 h. Arrows indicate resonances arising from the hydrolysis product trifluoroethanol.

Hydrolysis of molybdocene bis(*S*-2,2,2-trifluoroethane thiol) (**5**) was studied in both aqueous DMSO and aqueous acetonitrile at 310 K, by monitoring the appearance of the methylene group by $^1H$ and $^{19}F$ NMR spectroscopy and the Cp resonance by $^1H$ NMR spectroscopy. While in aqueous acetonitrile only 5−10% of the thiol had hydrolyzed after 24 h (Figure 4), in aqueous DMSO approximately 50% hydrolysis occurred within 14 h. Quantitative measurement of the amount of hydrolysis was difficult, as the overlap of the ligand methylene resonance and the residual water peak did not permit accurate signal integration of this signal relative to the Cp resonances.

The limited aqueous solubility of the derivatives makes direct comparison of the hydrolysis results in Table 2 difficult. The rate of hydrolysis of the thiol ligands is clearly highly dependent on the solvent mixture, as illustrated by the different results for **3** and **5** in 10% $D_2O$/DMSO-$d_6$ or 10% $D_2O$/acetonitrile-$d_3$. Presumably, this is related to the different properties of DMSO

versus acetonitrile stabilizing the transition states and hydrolysis products differently.

Surprisingly, the rate of hydrolysis of **4** was faster than the hydrolysis of **3**. On consideration of the inductive effects of two *meta*-oriented trifluoromethyl groups, the thiophenol ligands were predicted to reduce the Mo−S bond strength in **3** relative to the thiobenzylic ligands in **4**. The difference between the predicted results and the observed result may be related to differences in solubility of the complexes.

## Conclusions

The hydrolysis of the trifluoroethane thiol ligands in **5** clearly demonstrates that the incorporation of a trifluoromethyl group one carbon away from the Mo−S bond results in increased lability of the Mo−S bonds in molybdocene derivatives $Cp_2Mo(SR)_2$. In aqueous DMSO, the rate of hydrolysis (approximately 50% in 14 h) is on a time scale that is potentially useful in the design of prodrugs of $Cp_2MoCl_2$. However as this complex lacks the lipophilic aromatic groups of **2**, which exhibited high cellular uptake relative to other neutral and polar thiol derivatives of molybdocene dichloride previously studied,[9] the derivative **5** is predicted to show reduced cellular uptake relative to derivative **2**. The results show that incorporation of electron-withdrawing groups on the aromatic rings of thiol ligands is insufficient to achieve hydrolysis within hours and strongly suggests that if a lipophilic analogue of **5** can be prepared that retains the trifluoroethane thiol fragment, high cell uptake followed by slow hydrolysis can be achieved in cells.

## Experimental Section

**General Procedures.** Molybdocene dichloride was obtained from the Aldrich Chemical Company and was used as provided. NMR spectra were recorded using a Bruker WM AMX 400 (400 MHz, $^1$H; 100 MHz, $^{13}$C) or a Bruker Avance 300 (300 MHz, $^1$H; 282 MHz, $^{19}$F) spectrometer at 300 K, unless otherwise indicated, in the solvent stated, and referenced to 3-(trimethylsilyl)propionic acid-$d_4$, sodium salt at $\delta$ 0 ppm ($^1$H), to external $CDCl_3$ at $\delta$ 77 ppm ($^{13}$C), or to external hexafluorobenzene at $\delta$ −163 ppm ($^{19}$F). Electrospray ionization mass spectra were recorded on a Finnigan LCQ ion trap mass spectrometer. High-resolution electrospray ionization mass spectra were recorded on a Bruker ApexII Fourier transform ion cyclotron resonance mass spectrometer, with a 7.0 T magnet fitted with an off-axis analytical electrospray source. Melting points were recorded on a Reichert melting point stage and are uncorrected. Molybdocene bis(*S*-4-thiol-2,3,5,6-tetrafluorobenzoic acid) (**2**) was synthesized as described previously.[9]

**3,5-Bis(trifluoromethyl)phenyl Disulfide (7).** 3,5-Bis(trifluoromethyl)aniline (1 g, 4.4 mmol) was dissolved in water (10 mL), and concentrated sulfuric acid (1 mL) was added with stirring. The solution was cooled to <5 °C, and a solution of sodium nitrite (0.45 g, 6.5 mmol) in water (5 mL) was added dropwise. The resulting solution was added to a solution of potassium methyl xanthate (0.95 g, 6.5 mmol) and potassium hydroxide (1 g) in water (5 mL) at 40 °C. The reaction mixture was then stirred at 60 °C for 1 h. The product was extracted into diethyl ether, the solvent removed, and the residual oil dissolved in ethanol (95%, 50 mL). A solution of potassium hydroxide (1 g) in water (5 mL) was added, and the reaction mixture was heated at reflux for 14 h. The reaction mixture was acidified with concentrated HCl, the product was extracted into diethyl ether and dried over sodium sulfate, and the solvent was removed to give the crude product. Purification by flash chromatography (hexanes) and recrystallization from methanol afforded pure **7** (270 mg, 25%) as white crystals, mp 62−64 °C (lit.[20] 74−75 °C). IR ($CHCl_3$) $\nu_{max}$ 845, 887, 1107, 1146, 1184, 1220, 1263, 1279, 1348 cm$^{-1}$. $^1$H NMR (300 MHz; $CDCl_3$): $\delta$ 7.78 (1 H, s, H4), 7.93 (2 H, s, H2, H6) ppm. $^{13}$C NMR (100 MHz; $CDCl_3$): $\delta$ 121.8 (m, C4), 122.7 (q, $^1J_{CF}$ = 273 Hz, $CF_3$), 127.5 (m, C2, C6), 132.9 (q, $^2J_{CF}$ = 34 Hz, C3, C5), 139.0 (s, C1) ppm. $^{19}$F NMR (282 MHz; $CDCl_3$): $\delta$ −63.4 (s) ppm. ESI-MS (negative ion): *m*/*z* 245 ([M − [Ph(CF$_3$)$_3$S]]$^-$, 100%), 490 ([M]$^-$, 20%). ESI-HRMS (negative ion): $C_{16}H_5S_2F_{12}^-$ ([M − H]$^-$) requires 488.9650, found 488.9640.

**3,5-Bis(trifluoromethyl)thiophenol (8).** 3,5-Bis(trifluoromethyl)phenyl disulfide (277 mg, 0.57 mmol) was dissolved in tetrahydrofuran (10 mL) and ethanol (10 mL), and the mixture cooled to 0 °C. Sodium borohydride (75 mg, 2 mmol) was added slowly, and the reaction was warmed to room temperature and stirred for 4 h. The solvent was removed, water (10 mL) was added, and the solution was acidified to pH 4 with dilute HCl. The resultant white precipitate was extracted into diethyl ether and dried over sodium sulfate, and the solvent was removed to give **8** as a malodorous liquid (141 mg, 51%), which was used immediately without purification in the following step. IR ($CHCl_3$): $\nu_{max}$ 843, 883, 999, 1107, 1136, 1182, 1279, 1356, 1456, 1604, 1618, 1789, 2584 (S−H), 2856, 2926, 2958 cm$^{-1}$. $^1$H NMR (300 MHz; $CDCl_3$): $\delta$ 3.76 (1 H, s, −SH), 7.65 (1 H, s, H4), 7.69 (2 H, s, H2, H6) ppm. $^{13}$C NMR (100 MHz; $CDCl_3$): $\delta$ 119.4 (m, C4), 122.9 (q, $^1J_{CF}$ = 273 Hz, $CF_3$), 128.7 (m, C2, C6), 132.4 (q, $^2J_{CF}$ = 33.5 Hz, C3, C5), 134.9 (s, C1) ppm. $^{19}$F NMR (282 MHz; $CDCl_3$): $\delta$ −63.8 (s) ppm. ESI-MS (negative ion): *m*/*z* 245 ([M]$^-$, 50%), 490 ([2M]]$^-$, 100%). ESI-HRMS (negative ion): $C_8H_3S_2F_6^-$ ([M − H]$^-$) requires 244.9867, found 244.9862.

**3,5-Bis(trifluoromethyl)benzyl Thiol.** Crude 3,5-bis(trifluoromethyl)benzyl disulfide from the previous step was dissolved in ethanol, and dithiothreitol was added. The reaction mixture was heated at reflux for 14 h, and the product was extracted into diethyl ether. The organic phase was washed with saturated sodium chloride and water and dried over sodium sulfate, and the solvent was removed to give the crude 3,5-bis(trifluoromethyl)benzyl thiol as a yellow oil. $^1$H NMR (300 MHz; $CDCl_3$): $\delta$ 1.88 (1 H, t, $J$ = 8 Hz, SH), 3.85 (2 H, d, $J$ = 8 Hz, $CH_2$), 7.77 (1 H, s, H4), 7.81 (2 H, s, H2, H6) ppm. $^{13}$C NMR (100 MHz; $CDCl_3$): $\delta$ 28.8 ($CH_2$), 121.1 (p, $^3J_{CF}$ = 3.7 Hz, C4), 123.2 (q, $^1J_{CF}$ = 272 Hz, $CF_3$), 128.3 (m), 132.4 (q, $^2J_{CF}$ = 33.5 Hz, C3, C5), 143.6 (s, C1) ppm. $^{19}$F NMR (282 MHz; $CDCl_3$): $\delta$ −63.39 (s) ppm. ESI-HRMS (negative ion): *m*/*z* 227 ([M − SH]$^-$, 100%), 259 ([M − H]$^-$, 25%). As rapid oxidation of the thiol to the corresponding disulfide occurred if further purification was attempted, the thiol was directly treated with molybdocene dichloride in the next step.

**Molybdocene Bis(*S*-3,5-bis(trifluoromethyl)thiophenol) (3).** Molybdocene dichloride (**1**) (8.9 mg, 30 mmol) was sonicated in water (2 mL) until dissolution was complete (2−3 h) to form a deep maroon solution. The pH was adjusted to 6 with dilute sodium hydroxide. A solution of 3,5-bis(trifluoromethyl)thiophenol (**8**) (22 mg, 90 mmol) in water (1 mL, pH 8) was added, resulting in the immediate precipitation of a pink-brown solid, and the reaction mixture was stirred at room temperature for 14 h. The reaction mixture was acidified to pH 2 with dilute hydrochloric acid, the product was extracted into diethyl ether and dried over sodium sulfate, and the solvent was removed to give the crude product as a green-brown residue. Purification by flash chromatography (30%

(16) The exact species formed in solution is highly dependent on the solution pH, concentration, and ionic strength, and hence the notation "$Cp_2Mo^{2+}$" is used to indicate that a number of different labile pseudohalide ligands may be present to give species $Cp_2Mo(OH)_2$, $[Cp2Mo(OH)(OH_2)]^+$, $Cp_2Mo(OH)(Cl)$, etc.

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ethyl acetate in hexanes) afforded **3** as a red solid. $^1$H NMR (300 MHz; $CDCl_3$): $\delta$ 5.35 (10 H, s, CpH), 7.46 (2 H, s, H4), 7.65 (4 H, s, H2, H6) ppm. $^{19}$F NMR (282 MHz; $CDCl_3$): $\delta$ −63.26 (s) ppm. ESI-HRMS (negative ion): *m*/*z* 245 ($[Ph(CF_3)_2S]^-$, 100%), 718 ($[M]^-$, 35%), ($[M + 2Na]^-$, 55%).

**Molybdocene Bis(*S*-3,5-bis(trifluoromethyl)benzyl thiol) (4).** Molybdocene dichloride (**1**) (33.4 mg, 120 mmol) was sonicated in water (6 mL) until dissolution was complete (2−3 h) to form a deep maroon solution. The pH was adjusted to 6 with dilute sodium hydroxide. A solution of 3,5-bis(trifluoromethyl)benzyl thiol (**15**) (61.4 mg, 240 mmol) in water (1 mL, pH 8) was added, resulting in the immediate precipitation of a green-brown precipitate. The reaction mixture was stirred for 2 days, after which the suspension was pink-brown in color. The product was extracted into diethyl ether and dried over sodium sulfate, and the solvent was removed to give the crude product as a brown residue. Recrystallization from aqueous acetonitrile afforded **4** as brown needlelike crystals. $^1$H NMR (300 MHz; acetonitrile-$d_3$; 310 K): $\delta$ 3.89 (4 H, s, $CH_2$), 5.34 (10 H, s, CpH), 7.78 (2 H, s, H4), 7.89 (4 H, s, H2, H6) ppm. $^{19}$F NMR (282 MHz; $CDCl_3$): $\delta$ −62.93 (s) ppm. ESI-HRMS (positive ion): *m*/*z* 700 (100%), 769 ($[M + Na]^+$, 35%), 785 ($[M + K]^+$, 75%). ESI-HRMS (negative ion): $C_{28}H_{19}S_2F_{12}Mo^-$ ($[M - H]^-$) requires 744.9797, found 744.9789. Crystals suitable for X-ray diffraction were obtained by slow diffusion of water into a solution of **4** in acetonitrile.

**Molybdocene Bis(*S*-2,2,2-trifluoroethane thiol) (5).** Molybdocene dichloride (**1**) (19.6 mg, 66 mmol) was sonicated in water (3 mL) until dissolution was complete (2−3 h) to form a deep maroon solution. The pH was adjusted to 6 with dilute sodium hydroxide. This was added to a solution of 2,2,2-trifluoroethane thiol (76 mg, 660 mmol) in water (5 mL, pH 9.5) at < 5 °C, and the reaction mixture was stirred with gradual warming to room temperature for 14 h. After this time, a precipitate had formed, which was filtered to give **5** as a purple, amorphous solid (15.8 mg, 53%). $^1$H NMR (300 MHz; acetonitrile-$d_3$): $\delta$ 2.91 (4 H, q, $^2J_{HF}$ = 11 Hz, $CH_2$), 5.32 (10 H, s, CpH) ppm. $^{13}$C{$^1$H} NMR (100 MHz; acetonitrile-$d_3$): $\delta$ 38.9 (q, $^2J_{CF}$ = 28 Hz, $CH_2$), 98.2 (s, CpC), 128.3 (q, $^2J_{CF}$ = 275 Hz, $CF_3$) ppm. $^{19}$F NMR (282 MHz; acetonitrile-$d_3$): $\delta$ −66.22 (s, $^2J_{HF}$ = 11.5 Hz) ppm. ESI-MS (positive ion): *m*/*z* 228 ($[Cp_2Mo]^+$, 100%), 259 ($[Cp_2MoS]^+$, 85%), 343 ($[M - SCH_2CF_3]^+$, 20%), 458 ($[M]^+$, 15%). ESI-HRMS (negative ion): $C_{14}H_{14}S_2F_6MoNa^+$ ($[M + Na]^+$) requires 480.9385, found 480.9398.

**X-ray Crystallography.** Data were collected at the ChemMat CARS facility at the Advanced Photon Source of the Argonne National Laboratory, Argonne, IL. Double diamond (111) reflections were used to obtain monochromated 0.48595 Å radiation from the synchrotron source, and harmonics were eliminated with mirrors. A small, orange needlelike crystal was attached with Exxon Paratone N to a short length of fiber supported on a thin piece of copper wire inserted in a copper mounting pin. The crystal was quenched in a cold nitrogen gas stream from an Oxford Diffraction Cryojet. A Bruker three-circle diffractometer platform with a SMART 6000 CCD detector was used for the data collection. Cell constants were obtained from a least-squares refinement against 1015 reflections located between 4° and 45° 2$\theta$. Data were collected at 103(2) K with $\omega/\phi$ scans to 45° 2$\theta$. The data integration and reduction were undertaken with SAINT and XPREP,[21] and subsequent computations were carried out with the WinGX[22] and XTAL[23] graphical user interfaces. Data were normalized to the incident radiation; no absorption correction was applied.

The structure was solved in the space group *C*2/*c* (#15) by direct methods with SIR97[24] and extended and refined with SHELXL-97.[25] The asymmetric unit contains half of the complex, with a 2-fold axis passing through the metal center. The non-hydrogen atoms were modeled with anisotropic displacement parameters, and a riding atom model with group displacement parameters was used for the hydrogen atoms. An ORTEP[17] depiction of the molecule with 20% displacement ellipsoids is provided in Figure 2.

**NMR Hydrolysis Experiments.** The appropriate molybdocene complex **3**, **4**, or **5** (0.010 mmol) was dissolved in DMSO-$d_6$ or acetonitrile-$d_3$ (500 $\mu$L), and water-$d_2$ (50 $\mu$L) was added. The reaction mixture was shaken, then maintained at 37 °C, and $^1$H and $^{19}$F NMR spectra were recorded at 310 K periodically. The percent hydrolysis was estimated by integration of the metal-bound Cp resonances relative to the bound and hydrolyzed thiol ligand resonances.

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**Supporting Information Available:** Crystallographic data for **4** as a CIF file is available free of charge via the Internet at http://pubs.acs.org.

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