

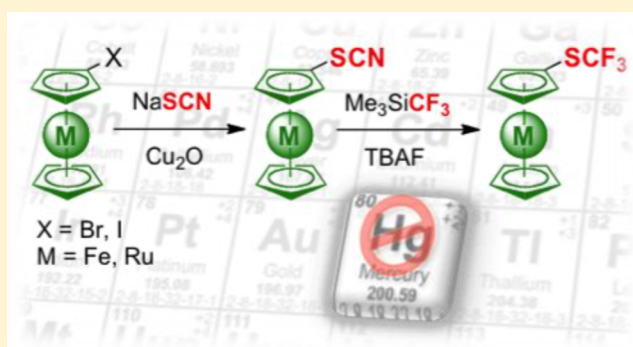
# Novel, Mercury-Free Synthetic Pathway for Trifluoromethylthio-Substituted Metallocenes

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## Supporting Information

**ABSTRACT:** A novel synthetic pathway for trifluoromethylthioferrocene (**3**), which does not involve the use of toxic mercury(II)-based reagents, is described. The novel approach involves first the treatment of the commercially available bromoferrocene (**1a**) with NaSCN in the presence of copper(+I) to yield thiocyanatoferrocene (**1**), and then the reaction of **1** with the Rupper-Prakash reagent and tetrabutylammonium fluoride (TBAF) to give **3** in an overall yield of 60%. This approach could be extended for the preparation of thiocyanato-(**4**) and trifluoromethylthio-ruthenocene (**7**), which are herein both reported for the first time. Interestingly, diferrocenyl disulfide (**2a**) and diruthenocenyl disulfide (**5**) could be isolated as side-products during the synthesis of **3** and **7**, respectively. All new compounds were unambiguously characterized by <sup>1</sup>H, <sup>13</sup>C, and <sup>19</sup>F NMR spectroscopy, mass spectrometry, cyclic voltammetry, elemental analysis, as well by X-ray crystallography for **1**, **4**, **4b**, **5**, **6**, and **7**. **1**–**7** were further tested for their toxic activity on cervical cancer (HeLa) and noncancerous (MRC-5) cell lines. All organometallic compounds were found either to be nontoxic or to have a moderate toxicity toward the cell lines used in this study.



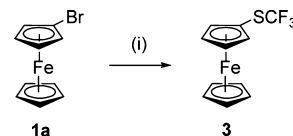
## INTRODUCTION

Fluorinated compounds are playing a pivotal role in modern drug design. Several blockbuster drugs such as the anticancer drug 5-fluorouracil or the antidepressant drug Fluoxetine (Prozac) bear one or several fluorine atom(s).<sup>1–3</sup> In fact, 20–25% of the drugs in the pharmaceutical pipeline contain at least one fluorine atom.<sup>3</sup> This number is even more impressive if we take into account that organofluorine compounds are not present in natural products.<sup>3</sup>

In recent years, the trifluoromethylthio group (-SCF<sub>3</sub>) has become an important pharmacophore in many agrochemical and pharmaceutical compounds notably due to its extremely high lipophilicity. The antiparasitic drug Toltrazuril and the insecticide Fipronil are two successful examples of this class of compounds.<sup>4–7</sup> Lipophilicity is often crucial for drug uptake and intracellular accumulation and can therefore determine the bioactivity of a drug molecule.<sup>3</sup> An impressive number of procedures and reagents have been recently reported to introduce an S-CF<sub>3</sub> group into various molecules.<sup>4,7–9</sup> However, the currently available publications in this field are mainly focused on purely organic compounds. The number of reports describing the preparation of S-CF<sub>3</sub>-containing and more generally of fluorine-containing organometallic complexes is indeed relatively scarce.<sup>10–17</sup> This is rather surprising since, in recent years, organometallic compounds, and especially ferrocenyl derivatives,<sup>18,19</sup> were shown to hold great promise

as antimalarial,<sup>20</sup> antibacterial,<sup>21</sup> or anticancer<sup>22</sup> agents.<sup>23–26</sup> Of special synthetic interest is a recent article by Metzler-Nolte et al. describing the synthesis of trifluoromethylthioferrocene (**3**, Scheme 1).<sup>12</sup> In this work, the authors successfully prepared **3**

**Scheme 1. Synthetic Procedure for 3 Described by Metzler-Nolte et al.**<sup>12a</sup>



<sup>a</sup>Conditions: (i) Hg(SCF<sub>3</sub>)<sub>2</sub>/Cu, hexane, reflux, overnight, 82%.

in good yield starting from bromoferrocene (**1a**) by nucleophilic substitution of the bromo group with SCF<sub>3</sub><sup>-</sup> using Hg(SCF<sub>3</sub>)<sub>2</sub> and copper bronze (Scheme 1).<sup>12</sup> Unfortunately, this procedure depends on a mercury(+II) based reagent, which is highly toxic and of limited commercial availability.<sup>27</sup> Taking into consideration the potential of fluorine-containing organometallic compounds, our group decided to explore an alternative approach, using less toxic

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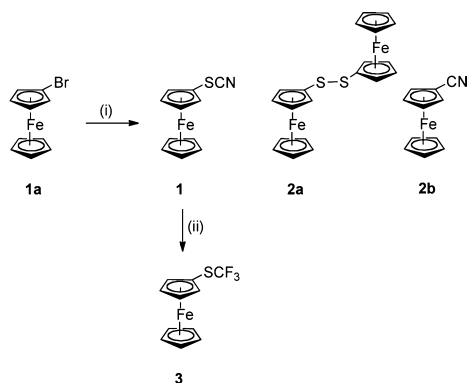
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reagents and mild conditions, to prepare not only **3** but also its heavier congener, trifluoromethylthioruthenocene (**7**). In this article, we describe the successful preparation of **3** and **7**. In addition, the toxic profile of all compounds synthesized in this work (**1–7**) on the cervical cancer (HeLa) and on the noncancerous (MRC-5) cell lines is reported. Furthermore, the electrochemical behavior of **1**, **1a**, **2a**, and **3** is also described to evaluate the influence of the different electron-withdrawing substituent on the reduction potentials of the ferrocenyl moieties present in **1–3**.

## RESULTS AND DISCUSSION

**Syntheses and Characterization.** The synthetic pathway used in our study to prepare **3** is outlined in Scheme 2. In a first

Scheme 2. Synthetic Pathway for **3**<sup>b</sup>



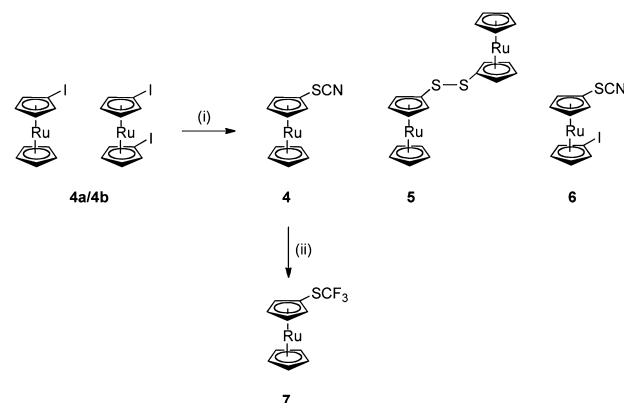
<sup>b</sup>Conditions: (i) NaSCN, Cu<sub>2</sub>O, dry MeCN, 64 h, reflux; 67%. (ii) Me<sub>3</sub>SiCF<sub>3</sub>, TBAF (THF soln. 1 M), dry THF, 10 min, –10 °C, 90%.

attempt, we aimed to synthesize **3** in a single reaction step by applying a modified procedure reported by Chen et al.,<sup>28</sup> namely, by treatment of **1a** with S<sub>8</sub>, copper(I) iodide and methyl fluorosulfonyldifluoroacetate in *N*-methylpyrrolidinone (NMP) at 100 °C overnight. These conditions only led to the formation of trace amounts of **3**. However, when the commercially available bromoferrocene (**1a**) was refluxed in the presence of sodium thiocyanate and catalytic amounts of Cu<sub>2</sub>O, thiocyanatoferrocene (**1**) could be obtained as an orange solid in 67% yield.<sup>29,30</sup> In addition to the unreacted bromoferrocene, which could be recovered, the major side-product of this reaction is diferrocenyl disulfide (**2a**) which is literature known. Cyanoferrocene (**2b**) could also be found in trace amounts as a minor side-product.<sup>31</sup> The desired compound **3** was obtained by treating **1** with an excess of the commercially available Ruppert-Prakash reagent (Me<sub>3</sub>SiCF<sub>3</sub>) and a catalytic amount of a tetrabutylammonium fluoride solution in THF using slightly different conditions to those reported by Langlois et al.<sup>32–34</sup> **3** was obtained as a yellow oil in excellent yield (90%) and the spectroscopic data matched those previously described by Metzler-Nolte et al.<sup>12</sup>

Encouraged by the promising results obtained for **3** and the importance of small functionalized metallocenes,<sup>35</sup> we decided to investigate the possibility of preparing ruthenocenyl analogues of **1** and **3**. Of note, ruthenocene derivatives were shown, over the past years, to have interesting biological properties and to be an interesting surrogate for ferrocenyl derivatives to understand the mechanism of action of these ferrocenyl compounds.<sup>36–40</sup> The synthetic sequence to obtain the desired ruthenocene analogue trifluoromethylthiorutheno-

cene (**7**) is outlined in Scheme 3. A mixture of mono- and diiodoruthenocene (**4a/4b**) was prepared according to a

Scheme 3. Synthetic Pathway for **7**<sup>c</sup>

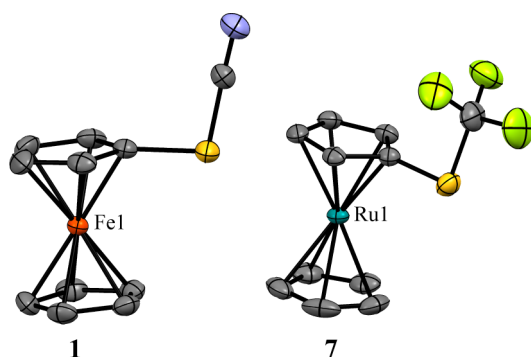


<sup>c</sup>Conditions: (i) NaSCN, Cu<sub>2</sub>O, dry MeCN, 64 h, reflux, 89%. (ii) Me<sub>3</sub>SiCF<sub>3</sub>, TBAF (THF soln. 1 M), dry THF, 10 min, –10 °C, 77%.

literature procedure and then refluxed in a similar fashion to **1a** with an excess of NaSCN and a catalytic amount of Cu<sub>2</sub>O.<sup>41</sup> Thiocyanatoruthenocene (**4**) was isolated as a colorless solid as the major product in 89% yield in addition to 1,1'-thiocyanatiodoruthenocene (**6**) and diruthenocenyldisulfide (**5**) in 20% and 4% yields, respectively. The formation of **4**, **5**, and **6** was confirmed by EI-MS with peaks at *m/z* = 288, 263, and 415 corresponding to [M<sup>+</sup>], [M-C<sub>10</sub>H<sub>9</sub>SRu]<sup>+</sup>, and [M<sup>+</sup>], respectively. Interestingly, the formation of a bis-substituted ruthenocenyl analogue, namely, dithiocyanatoruthenocene, was never observed during our trials to obtain **4**. In the last reaction step, **4** was reacted with an excess of the Ruppert-Prakash reagent and a catalytic amount of TBAF in THF at –10 °C to afford **7** in excellent yield (77%). The presence of **7** was ascertained by <sup>1</sup>H NMR spectroscopy with the characteristic peak pattern at 4.85–4.84, 4.72–4.71, and 4.62 ppm, corresponding to the protons of the ruthenocenyl unit. Furthermore, only one single peak could be observed in <sup>19</sup>F NMR spectroscopy at –46.3 ppm which can be attributed to the SCF<sub>3</sub> group.

**X-ray Crystallography.** Single crystals of **1**, **4**, **4b**, **5**, **6**, and **7** suitable for X-ray crystallography analysis could be grown by slow evaporation of the corresponding solutions of **1**, **4**, **4b**, **5**, **6**, and **7** in chloroform. The ORTEP representations of **1** and **7** are shown in Figure 1 and those of **4**, **4b**, **5**, and **6** in Figures S14 – S17 (see SI). All additional crystallographic information is presented in the SI. **1** crystallized in the orthorhombic space group *Pnma* and measurements indicate classical bond angles and distances for such types of bonds.<sup>42–44</sup> **4** is essentially isostructural to **1** with the same space group *Pnma* and a slightly bigger cell. In both cases, the complexes display C<sub>s</sub> symmetry that is shared with the mirror plane of the space group. **5** is not crystallizing in the same space group (*P2<sub>1</sub>*) as the already published X-ray structure of **2a**.<sup>45</sup>

**Electrochemical Studies.** Voltammetric studies on compounds **1**, **1a**, **2a**, and **3** at 1 mM concentrations in CH<sub>3</sub>CN were carried out in order to investigate the influence of different substituted cyclopentadienyl rings on the oxidation/reduction of the ferrocene redox couple. For this purpose, a stationary glassy carbon (GC) working electrode was used to perform the cyclic voltammetry with a scan rate of 100 mV·s<sup>–1</sup>



**Figure 1.** Molecular structures of **1** and **7** with atoms shown as thermal ellipsoids (drawn at 50% probability; hydrogen atoms were omitted for clarity).

in  $\text{CH}_3\text{CN}$  with tetrabutylammonium hexafluorophosphate ( $\text{Bu}_4\text{NPF}_6$ , 0.1 M) as the supporting electrolyte. A Pt electrode was used as the counter electrode and Ag/AgCl as the reference electrode. As an internal reference, decamethylferrocene (DMFc, 0.25 mM) was used instead of the usual ferrocene in order to avoid overlaps of the studied compounds with the ferrocene oxidation process. The cyclic voltammogram of **1a**, **1**, **2a**, and **3** are presented in the SI and the results are summarized in Table 1.

**Table 1.** Cyclic Voltammetric Data for **1a**, **1**, **2a**, and **3** in the Presence of an Internal Reference (DMFc) at a GC Electrode in  $\text{CH}_3\text{CN}/\text{Bu}_4\text{NPF}_6$  (0.1 M) with a Scan Rate of  $100 \text{ mV}\cdot\text{s}^{-1}$ <sup>a</sup>

compound	$\Delta E_f^0$ vs DMFc <sup>0/+</sup> [mV]	$\Delta E_p$ [mV]
<b>1a</b>	+674	80
<b>1</b>	+802	89
<b>2a</b>	+615	90
	+779	79
<b>3</b>	+804	89

<sup>a</sup>Oxidation peak potential =  $E_p^{\text{ox}}$ ; reduction peak potential =  $E_p^{\text{red}}$ ; formal redox potential  $E_f^0 = (E_p^{\text{ox}} + E_p^{\text{red}})/2$ .

All oxidation potentials are assigned to the reversible oxidation/reduction of the ferrocene redox couple and are in the expected range. **1a**, **1**, and **3** show one reversible single oxidation wave, while **2a** has two reversible oxidation waves, one at +615 mV and the other at a slightly higher potential of +784 mV. The stronger electron withdrawing effect of the SCN- and  $\text{SCF}_3$ -group vs the Br-functionality is clearly visible in the higher oxidation potential of **1** and **3** (+802 mV and +804 mV) compared to **1a** (+674 mV).

**Cytotoxicity Studies.** With the metallocene derivatives **1**–**7** in hand, we then investigated their toxicity toward the cervical cancer (HeLa) and noncancerous (MRC-5) cell lines. Cisplatin was used as reference compound. As can be seen in Table 2, the seven organometallic compounds showed either moderate cytotoxicity in the range of 29.0–61.2  $\mu\text{M}$  or no toxicity at all toward HeLa cells.

## CONCLUSION

In summary, we present herein an efficient synthetic pathway for thiocyanato- and trifluoromethylthio-ferrocene and ruthenocene. Importantly, the synthetic route employed toward the trifluoromethylthio-metallocenes does not rely on a highly toxic

**Table 2.** Cytotoxicity Activity ( $\text{IC}_{50}$ ) of **1**–**7** against HeLa and MRC-5 Cells

compound	$\text{IC}_{50}$ values ( $\mu\text{M}$ )	
	HeLa	MRC-5
<b>1a</b>	>100	>100
<b>1</b>	$38.5 \pm 3.3$	$48.5 \pm 1.0$
<b>2a</b>	>100	>100
<b>3</b>	>100	>100
<b>4</b>	$61.2 \pm 3.3$	$47.2 \pm 7.5$
<b>5</b>	$38.7 \pm 7.4$	$57.4 \pm 10.9$
<b>6</b>	$29.0 \pm 1.9$	$25.2 \pm 4.1$
<b>7</b>	>100	>100
Cisplatin	$9.6 \pm 1.2$	$17.6 \pm 4.3$

and limited commercially available mercury(+II) salt. In addition, the crystallographic data of six organometallic compounds are reported. We could also demonstrate that all organometallic complexes prepared in this work had either modest or no toxic activity on a cervical cancer (HeLa) and noncancerous (MRC-5) cell line. We are confident that the synthetic conditions reported in this article will enable the preparation of higher substituted metallocenes with interesting biological properties.

## EXPERIMENTAL SECTION

**Materials.** All chemicals were of reagent grade quality or better, obtained from commercial suppliers and used without further purification. Solvents were used as received or distilled using standard procedures.<sup>46</sup> All preparations were carried out using standard Schlenk techniques and all reactions/compounds were protected from light as much as possible using aluminum foil. *Thin layer chromatography* (TLC) was performed using silica gel 60 F-254 (Merck) plates with detection of spots being achieved by exposure to UV light. *Column chromatography* was performed using Silica gel 60 (0.040–0.063 mm mesh, Merck). Eluent mixtures are expressed as volume to volume (v/v) ratios. Ruthenocene was synthesized according to a literature procedure.<sup>47</sup>

**Instrumentation and Methods.** <sup>1</sup>H, <sup>13</sup>C, and <sup>19</sup>F NMR spectra were recorded in deuterated solvents on Bruker AV2–401, AV2–400, AV-500, AV-501, and DRX-500 spectrometers, at room temperature. The chemical shifts,  $\delta$ , are reported in ppm (parts per million). The signals from the residual protons of deuterated solvent have been used as an internal reference.<sup>48,49</sup> The abbreviations for the peak multiplicities are as follows: s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), m (multiplet), and br (broad). *ESI mass spectrometry* was performed using a Bruker Esquire 6000 spectrometer. In the assignment of the mass spectra, the most intense peak is listed. *Cyclic voltammetric measurements* were performed at room temperature in acetonitrile solutions containing 0.1 M tetrabutyl ammonium hexafluorophosphate as the supporting electrolyte with a scan rate of  $100 \text{ mV}\cdot\text{s}^{-1}$  using a Methrom 757 VA Computrace electrochemical workstation. Solutions used in electrochemical measurements were deoxygenated by purging with nitrogen for at least 10 min before commencing the experiments. A conventional three electrode cell was employed which comprised a glassy carbon working electrode, a large surface area Pt counter electrode, and an Ag/AgCl reference electrode. *EI-MS:* Mass spectrometry was performed on a Thermo DFS (ThermoFisher Scientific, Bremen, Germany) double-focusing magnetic sector mass spectrometer (geometry BE). Mass spectra were measured in electron impact (EI) mode at 70 eV, with solid probe inlet, source temperature of 200 °C, acceleration voltage of 5 kV, and resolution of 2500. The instrument was scanned between  $m/z$  30 and 900 at scan rate of 2 s/decade in the magnetic scan mode. Perfluorokerosene (PFK, Fluorochem, Derbyshire, UK) served for calibration. *HR-EI-MS:* High-resolution mass spectrometry was performed on a Thermo DFS (ThermoFisher

Scientific, Bremen, Germany) double-focusing magnetic sector mass spectrometer (geometry BE). Mass spectra were measured in electron impact (EI) mode at 45 eV, with solid probe inlet, a source temperature of 200 °C, an acceleration voltage of 5 kV, and a resolution of 10000. The instrument was scanned between, e.g.,  $m/z$  300 and 350 at scan rate of 100–200 s/decade in the electric scan mode. Perfluorokerosene (PFK, Fluorochem, Derbyshire, UK) served for calibration. Infrared spectra were recorded on Perkin-Elmer FTIR spectrometer fitted with an ATR platform.

**Synthesis. Thiocyanatoferrrocene (1) and Diferrocenyl Disulfide (2a).** **1** was synthesized by refluxing bromoferrrocene (**1a**, 500 mg, 1.90 mmol) in dry acetonitrile (65 mL), together with sodium thiocyanate (1.15 g, 14.22 mmol) in the presence of a catalytic amount of  $\text{Cu}_2\text{O}$  (0.07 g, 0.47 mmol) for 64 h. The reaction mixture was then allowed to reach room temperature, filtered and the solvent was removed *in vacuo*. The beige to orange crude solid was purified by column chromatography on silica using hexane:ethyl acetate (25:1) as eluent to give **1** ( $R_f = 0.35$ ) as an orange solid and **2a** ( $R_f = 0.46$ ) as bright orange crystals, respectively. Yields: **1**: 0.30 g (67%, 1.25 mmol); **2a**: 0.06 g (7.5%, 0.14 mmol). Spectroscopic data for **1** and **2a** matched those previously reported by Knox et al.<sup>30</sup> and Herberhold et al.,<sup>50</sup> respectively. To confirm the purity of **1** and **2a** for biological experiments, microanalysis and HR EI-MS were performed. Elemental Analysis for **1**: calcd. for  $\text{C}_{11}\text{H}_9\text{FeNS}$  = C, 54.35; H, 3.73; N, 5.76. Found = C, 54.39; H, 3.58; N, 5.10. HR EI-MS of **1**: calcd. for  $\text{C}_{11}\text{H}_9\text{FeNS}$  ( $\text{M}^+$ )  $m/z$  (%) = 242.97996. Found  $m/z$  (%) = 242.97994. Elemental Analysis for **2a**: calcd. for  $\text{C}_{20}\text{H}_{18}\text{Fe}_2\text{S}_2$ : C, 55.30; H, 4.18. Found: C, 55.51; H, 4.12. HR EI-MS for **2a**: calcd. for  $\text{C}_{20}\text{H}_{18}\text{Fe}_2\text{S}_2$  ( $\text{M}^+$ )  $m/z$  (%) = 433.95432. Found  $m/z$  (%) = 433.95484.

**Trifluoromethylthioferrrocene (3).** **1** (0.05 g, 0.21 mmol) was dissolved in dry THF (50 mL), then degassed for 30 min and cooled to  $-10$  °C. An excess of trifluoromethyltrimethylsilane (0.47 mL, 3.15 mmol) was then added to this yellow reaction solution. The temperature of the reaction mixture was maintained at  $-10$  °C, while a catalytic amount of tetrabutylammoniumfluoride solution (1 M in THF, 0.09 mL, 0.09 mmol) was added dropwise to the solution containing trifluoromethyltrimethylsilane and **1** over a period of 10 min. The reaction solution was further stirred for 5 min and then directly filtered through a silica plug. The product was further eluted from the plug by dichloromethane. Based on the observed volatility of **3** at low pressure and elevated temperature, the solution was dried by a gentle stream of  $\text{N}_2$  gas to obtain the orange oily product **3**. Yield: 0.054 g (90%, 0.19 mmol). Spectroscopic data matched those previously reported by Metzler-Nolte et al.<sup>12</sup> To confirm the purity of **3** for the biological experiments, microanalysis and HR EI-MS were performed. Elemental Analysis for **3**: calcd. for  $\text{C}_{11}\text{H}_9\text{F}_3\text{SFe}$ : C, 46.18; H, 3.17. Found: C, 46.36; H, 3.34. HR EI-MS of **3**: calcd. for  $\text{C}_{11}\text{H}_9\text{F}_3\text{FeS}$  ( $\text{M}^+$ )  $m/z$  (%) = 285.97210. Found  $m/z$  (%) = 285.97213.

**Monoiodoruthenocene (4a) and Diiodoruthenocene (4b).** The synthesis was carried out according to a modified literature procedure.<sup>41</sup> Ruthenocene (0.565 g, 2.44 mmol) and  $\text{KO}^t\text{Bu}$  (0.034 g, 0.303 mmol) were first dissolved in dry THF (40 mL) and the solution was cooled to  $-78$  °C. To this solution was added a 1.9 M solution of  $t\text{-BuLi}$  in pentane (2.6 mL, 4.94 mmol) over a period of 30 min while maintaining the temperature at  $-78$  °C. After stirring for 30 min at  $-78$  °C, a solution of  $\text{I}_2$  (1.55 g, 6.11 mmol) in dry THF (20 mL) was added slowly to the reaction mixture at the same temperature. The reaction mixture was left to reach room temperature, further stirred for 24 h, and then concentrated under reduced pressure. The crude product was purified by column chromatography on silica, using hexane as eluent, to give **4a** ( $R_f = 0.44$ ) and **4b** ( $R_f = 0.45$ ) as light yellow solids. Yield: **4a**: 0.432 g (49%, 1.21 mmol); **4b**: 0.188 g (16%, 0.39 mmol). The characterization data for **4a** and **4b** matched those previously reported.<sup>41</sup>

**Thiocyanatoruthenocene (4), Diruthenocenylyl Disulfide (5), and 1,1'-Thiocyanatiodoruthenocene (6).** **4** was synthesized according to the procedure described for **1**. A mixture of monoruthenocene (**4a**, 0.17 g, 0.47 mmol) and diiodoruthenocene (**4b**, 0.06 g, 0.12 mmol)

was refluxed in dry acetonitrile (40 mL) with an excess of sodium thiocyanate (0.39 g, 4.83 mmol) and a catalytic amount of  $\text{Cu}_2\text{O}$  (0.01 g, 0.07 mmol) for 64 h. The reaction was then allowed to reach room temperature, filtered, and evaporated *in vacuo*. The crude colorless solid was purified by column chromatography on silica using hexane:ethyl acetate (30:1) as eluent. **4** ( $R_f = 0.24$ , hexane:ethylacetate (25:1)) was obtained as colorless solid. Yield: 0.12 g (89%, 0.42 mmol). **5** ( $R_f = 0.36$ , hexane:ethylacetate (25:1)) and **6** ( $R_f = 0.15$ , hexane:ethylacetate (25:1)) could also be isolated as colorless solids. Yield **5**: 0.01 g (4%, 0.019 mmol). Yield **6**: 0.01 g (20%, 0.024 mmol).

**Data for 4: IR (Golden Gate,  $\text{cm}^{-1}$ ).** 3104, 2923, 2154, 1791, 1744, 1709, 1663, 1639, 1409, 1400, 1386, 1346, 1157, 1102, 1019, 1014, 999, 883, 843, 824, 812, 722.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 4.92–4.91 (m, 2H,  $\text{C}_5\text{H}_4$ ), 4.71–4.69 (m, 2H,  $\text{C}_5\text{H}_4$ ), 4.65 (s, 5H,  $\text{C}_5\text{H}_5$ ).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 113.0, 75.9, 73.1, 72.8, 70.9. EI-MS:  $m/z$  (%) = 287.9 ( $[\text{M}^+]$ , 100), 262.9 ( $[\text{M-CN}]^+$ , 26), 198.9 ( $[\text{M-C}_6\text{H}_4\text{N}]^+$ , 13), 166.9 ( $[\text{M-C}_6\text{H}_4\text{SN}]^+$ , 24). HR EI-MS: calcd. for  $\text{C}_{11}\text{H}_9\text{NRuS}$  ( $\text{M}^+$ )  $m/z$  (%) = 288.94937. Found  $m/z$  (%) = 288.94911. Elemental Analysis: calcd. for  $\text{C}_{11}\text{H}_9\text{NRuS}$ : C, 45.82; H, 3.15; N, 4.86. Found: C, 45.65; H, 3.07; N, 4.69.

**Data for 5: IR (Golden Gate,  $\text{cm}^{-1}$ ).** 3104, 2962, 2929, 1799, 1713, 1655, 1407, 1386, 1360, 1260, 1189, 1163, 1100, 1013, 996, 886, 802, 708.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 4.75–4.74 (m, 4H,  $\text{C}_5\text{H}_4$ ), 4.65–4.64 (m, 4H,  $\text{C}_5\text{H}_4$ ), 4.56 (s, 10H,  $\text{C}_5\text{H}_5$ ).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 84.2, 76.3, 72.6, 72.0. EI-MS:  $m/z$  (%) = 263.0 ( $[\text{M-C}_{10}\text{H}_9\text{SRu}]^+$ , 100). HR EI-MS: calcd. for  $\text{C}_{20}\text{H}_{18}\text{Ru}_2\text{S}_2$  ( $\text{M}^+$ )  $m/z$  (%) = 525.89419. Found  $m/z$  (%) = 525.89314. Elemental Analysis: calcd. for  $\text{C}_{20}\text{H}_{18}\text{Ru}_2\text{S}_2$ : C, 42.85; H, 3.96. Found: C, 43.30; H, 4.35.

**Data for 6: IR (Golden Gate,  $\text{cm}^{-1}$ ).** 3103, 2922, 2851, 2147, 1685, 1399, 1375, 1357, 1337, 1260, 1162, 1138, 1051, 1027, 1013, 1006, 915, 887, 866, 835, 820, 809, 727.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 4.94–4.93 (m, 1H,  $\text{C}_5\text{H}_4$ ), 4.92–4.91 (m, 1H,  $\text{C}_5\text{H}_4$ ), 4.73–4.72 (m, 1H,  $\text{C}_5\text{H}_4$ ), 4.57–4.56 (m, 1H,  $\text{C}_5\text{H}_4$ ).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 111.8, 79.8, 78.0, 75.5, 73.8, 72.1, 36.1. EI-MS:  $m/z$  (%) = 414.9 ( $[\text{M}^+]$ , 100), 288.0 ( $[\text{M-I}]^+$ , 78). HR EI-MS: calcd. for  $\text{C}_{11}\text{H}_8\text{NIRuS}$  ( $\text{M}^+$ )  $m/z$  (%) = 414.84602. Found  $m/z$  (%) = 414.84617. Elemental Analysis: calcd. for  $\text{C}_{11}\text{H}_8\text{NIRuS}$ : C, 31.89; H, 1.95; N, 3.38. Found: C, 31.28; H, 1.92; N, 3.13.

**Trifluoromethylthioruthenocene (7).** **7** was synthesized using a similar procedure to the preparation of **3**. **4** (0.05 g, 0.17 mmol) was dissolved in dry THF (50 mL), which was previously degassed for 30 min. The colorless reaction solution was stirred vigorously and cooled to  $-10$  °C. Trifluoromethyltrimethylsilane (0.37 mL, 2.55 mmol) was then added in excess to the reaction solution. A catalytic amount of tetrabutylammonium fluoride solution (1 M in THF, 0.073 mL, 0.073 mmol) was added dropwise over a period of 10 min to the solution containing trifluoromethyltrimethylsilane and **4**. The temperature of the reaction was maintained at  $-10$  °C while adding the tetrabutylammonium fluoride solution. After further stirring for 5 min, the reaction was filtered through a silica plug. The product was further eluted with dichloromethane. Based on the observed volatility of **7** at low pressure and elevated temperature, the crude product was dried by a stream of  $\text{N}_2$  gas and further purified by a column chromatography on silica using hexane as eluent. **7** ( $R_f = 0.56$ ) was obtained as colorless solid. Yield: 0.042 g (77%, 0.13 mmol).

**Data for 7: IR (Golden Gate,  $\text{cm}^{-1}$ ).** 3087, 2924, 2851, 1671, 1411, 1390, 1167, 1109, 1023, 1013, 995, 892, 866, 839, 824, 809, 750, 723.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 4.85–4.84 (m, 2H,  $\text{C}_5\text{H}_4$ ), 4.72–4.71 (m, 2H,  $\text{C}_5\text{H}_4$ ), 4.62 (s, 5H,  $\text{C}_5\text{H}_5$ ).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 132.5, 130.0, 127.5, 125.1, 77.8, 73.3, 72.3, 69.4.  $^{19}\text{F}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  =  $-46.3$ . EI-MS:  $m/z$  (%) = 332.0 ( $[\text{M}^+]$ , 36), 263.0 ( $[\text{M-CF}_3]^+$ , 100). HR EI-MS: calcd. for  $\text{C}_{11}\text{H}_9\text{F}_3\text{RuS}$  ( $\text{M}^+$ )  $m/z$  (%) = 331.94151. Found  $m/z$  (%) = 331.94178. Elemental Analysis: calcd. for  $\text{C}_{11}\text{H}_9\text{F}_3\text{RuS}$ : C, 39.88; H, 2.74. Found: C, 40.01; H, 2.75.

**Crystallographic Studies.** Crystallographic data were collected at 183(2) K on an Oxford Diffraction Xcalibur system with a Ruby detector using  $\text{Mo K}_\alpha$  radiation ( $\lambda = 0.7107$  Å) that was graphite-monochromated. Suitable crystals were covered with oil (Infiniteum

V8512, formerly known as Paratone N), placed on a nylon loop that is mounted in a CrystalCap Magnetic from Hampton Research and immediately transferred to the diffractometer. The program suite CrysAlis<sup>Pro</sup> was used for data collection, multiscan absorption correction, and data reduction.<sup>51</sup> The structures were solved with direct methods using SIR97<sup>52</sup> and were refined by full-matrix least-squares methods on F<sup>2</sup> with SHELXL-97.<sup>53</sup> The structures were checked for higher symmetry with the help of the program Platon.<sup>54</sup> Crystal **4b** contained 4 molecules in the asymmetric unit and was nonmerohedrally twinned by a 180° rotation around the following vector in reciprocal space (*hkl*): 0 1 0. Both twin domains were integrated and merged into a *hklf5* file. The twin ratio refined to 86.6:13.4. In the crystal structure of **5**, one nonsubstituted cp ring was found to be disordered in a 56:44 ratio.

**Cell Culture.** Human cervical carcinoma cells (HeLa) cells were cultured in DMEM (Gibco) supplemented with 5% fetal calf serum (FCS, Gibco), 100 U/mL penicillin, 100 µg/mL streptomycin at 37 °C and 5% CO<sub>2</sub>. The normal human fetal lung fibroblast MRC-5 cell line was maintained in F-10 medium (Gibco) supplemented with 10% FCS (Gibco), penicillin (100 U/mL), and streptomycin (100 µg/mL).

**Cytotoxicity Studies.** Cytotoxicity studies were performed on two different cell lines, namely, HeLa and MRC-5, by a fluorometric cell viability assay using Resazurin (Promocell GmbH). Briefly, one day before treatment, cells were seeded in triplicate in 96-well plates at a density of 4 × 10<sup>3</sup> cells/well for HeLa and 7 × 10<sup>3</sup> for MRC-5 in 100 µL growth medium. Upon treating cells with increasing concentrations of organometallic compounds for 48 h, the medium was removed, and 100 µL complete medium containing Resazurin (0.2 mg/mL final concentration) was added. After 4 h of incubation at 37 °C, fluorescence of the highly red fluorescent product Resorufin was quantified at 590 nm emission with 540 nm excitation wavelength in a SpectraMax M5 microplate Reader.

## ■ ASSOCIATED CONTENT

### ■ Supporting Information

<sup>1</sup>H, <sup>13</sup>C, and <sup>19</sup>F NMR spectra (Figures S1–9), cyclic voltammograms (Figures S10–13), and crystallographic data (Table S1 and Figures S14–17). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### ■ Notes

The authors declare no competing financial interest.

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