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Regioselective synthesis of functionalized ferrocenylphenols based on cyclocondensation reactions of free and masked 1,3-dicarbonyl dianions

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ABSTRACT

Highly functionalized ferrocenyl-substituted phenols were prepared by cyclization of masked or free dianions with 1,3-dielectrophilic 1-η5-ferrocenyl-3,3-bis(methylthio)prop-2-en-1-ones. While the cyclizations of 1,3-bis(silyloxy)-1,3-butadienes (masked dianions) proceed by initial 1,2-addition, the reactions of free 1,3-dicarbonyl dianions proceed by initial 1,4-addition. Therefore, both regioisomeric ferrocenylphenols are available from one and the same electrophile dependent on the type of nucleophile and reaction conditions employed. The reactions reported represent the first examples of the application of formal [3 + 3] cyclizations to the synthesis of organometallic compounds.

1. Introduction

Aryl-substituted ferrocenes (arylferrocenes) are of considerable relevance in the field of medicinal chemistry, material sciences and catalysis. Ferrocenyl-substituted cyclopropanes have been reported to show anti-inflammatory activity [1]. 3-Aryl-1-ferrocenyl-2-(1*H*-1,2,4-triazol-1-yl)-2-propen-1-one derivatives possess antifungicidal activity against *C. ara* and plant growth-regulatory activity [2]. Glycosylated ferrocenylphenols show antianemic activity [3]. Hydroxy-substituted arylferrocenes have been used as mediators in biosensors [4]. The antiproliferative effect of ferrocifen drug candidates on malignant pleural mesothelioma cell lines has been studied (Chart 1) [5]. The optical properties of chiral arylferrocenes have been studied [6]. Ferrocenylsalicylates represent promising candidates for the development of optical recording materials [7]. *para*-Substituted arylferrocenes have been used to generate shaped carbon nanomaterials (SCNMs), such as carbon nanotubes (CNTs), amorphous carbon, carbon fibres (CFs) and carbon spheres (CSs) [8]. Ferrocenylphenols have been successfully used as Walphos-type ligands in the Ru-, Rh- and Ir-catalyzed asymmetric hydrogenation of alkenes, ketones, and imines [9]. Chiral ferrocene-based quinone ligands have been employed for highly selective Negishi cross-coupling reactions [10].

The synthesis of ferrocenyl-substituted *p*- and *o*-benzoquinones has been previously reported [11]. Aryl-substituted ferrocenes have been prepared by application of the Suzuki–Miyaura reaction [12]. *p*-Ferrocenylbenzoic acid, *m*-, *o*-, and *p*-ferrocenylphenol, and *m*- and *p*-ferrocenylnitrobenzene have been prepared by phase-transfer-catalyzed ferrocene arylation using aromatic diazonium salts. These compounds have been used as intermediates for the synthesis of ferrocene-containing non-linear-optical materials and of thermotropic liquid crystals [13]. The synthesis and condensation reactions of formyl- and acetyl-substituted phenylferrocenes have been reported [14]. Methoxy- and hydroxy-substituted arylferrocenes are also known [15]. Aryl-substituted ferrocenes have been prepared using a palladium β-diketonate complex as the catalyst [16]. Most of the previous syntheses of arylferrocenes rely on coupling reactions of functionalized ferrocenes. The application of these methods to the synthesis of functionalized or highly substituted arylferrocenes is difficult, because of problems related to the low regioselectivity and low conversion (for sterically encumbered substrates). In recent years, we have studied the synthesis of functionalized arenes by formal [3 + 3] cyclocondensation reactions of 1,3-bis(silyloxy)-1,3-butadienes which can be regarded as masked 1,3-dicarbonyl dianions [17]. In this context, we have also reported the synthesis of 6-(methylthio)salicylates by cyclization of 1,3-bis(silyloxy)-1,3-butadienes with 3,3-bis(methylthio)prop-2-en-1-ones [18].

Herein, we report what are, to the best of our knowledge, the first application of formal [3 + 3] cyclocondensation reactions to the regioselective synthesis of organometallic compounds by using

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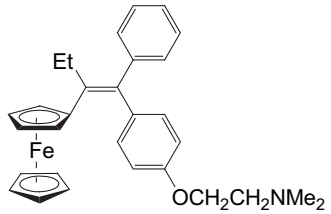
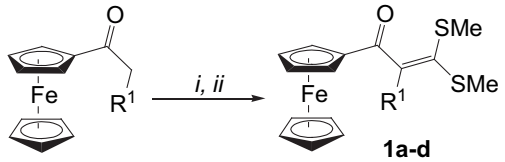


Chart 1. Structure of *Z*-ferrocifen.



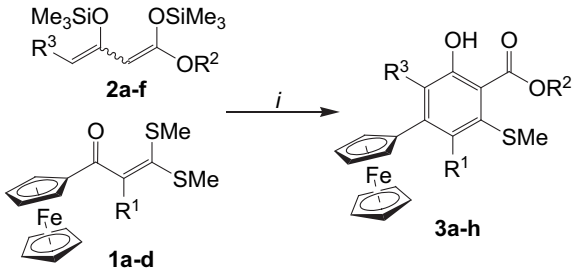
Scheme 1. Synthesis of **1a**–**d**. *Conditions*: i: KOtBu, CS_2, THF, 15 min, 0–20 °C; ii: MeI or Me_2SO_4, 1.5–10 h, 0–20 °C.

1-η^5-ferrocenyl-3,3-bis(methylthio)prop-2-en-1-ones as the 1,3-electrophile. The products, highly functionalized and substituted arylferrocenes, are not readily available by other methods. In addition, we have found that the regioselectivity of cyclization can be controlled by the type of nucleophile employed. While the reactions of 1,3-bis(silyloxy)-1,3-butadienes (masked dianions) with 1-η^5-ferrocenyl-3,3-bis(methylthio)prop-2-en-1-ones proceed by initial 1,2-addition, the reactions of free 1,3-dicarbonyl dianions proceed by initial 1,4-addition. Therefore, both regioisomeric products are available from one and the same electrophile dependent on the type of nucleophile and reaction conditions employed. This type of change of the regioselectivity in formal [3 + 3] cyclocondensations has, to the best of our knowledge, not been reported to date.

2. Results and discussion

Our starting point was the synthesis of ferrocenyl-substituted alkanones by Friedel-Crafts-acylation of alkanoylferrocenes. While acetylferrocene is commercially available, propanoylferrocene, butanoylferrocene and 2-chloroacetylferrocene were prepared according to known procedures [19]. The base-mediated reaction of these compounds with carbon disulfide and methyl iodide or dimethyl sulfate afforded the 1-η^5-ferrocenyl-3,3-bis(methylthio)prop-2-en-1-ones **1a**–**d** (Scheme 1) [20]. The known 1,3-bis(silyloxy)-1,3-butadienes **2a**–**f** have been prepared according to the literature [21].

The $TiCl_4$-mediated reaction of **1a**–**d** with 1,3-bis(silyloxy)-1,3-butadienes **2a**–**f** afforded the 4-η^5-ferrocenyl-2-hydroxy-6-(methylthio)benzoates **3a**–**h** in moderate to good yields (Scheme 2, Table 1). Due to thermal instability of the 1-η^5-ferrocenyl-3,3-bis(methylthio)prop-2-en-1-ones **1a**–**d**, the best yields were obtained when freshly prepared starting materials were used, when the solution was slowly warmed from −78 to 20 °C, when the reaction was carried out in a highly concentrated solution (4 mL/mmol), and when an excess (2.0 equiv.) of **2** was employed. Beside decomposition of the starting material, we observed incomplete degrees of conversion of the cyclocondensation reactions In fact, unreacted 1-η^5-ferrocenyl-3,3-bis(methylthio)prop-2-en-1-one could be recovered. The reaction of **1b**–**d**, carrying an alkyl- or chloro-substituent at the 2-position of the prop-2-en-1-one, with 1,3-bis(silyloxy)-1,3-butadienes **2b**–**f** was not successful, presumably due to steric reasons.



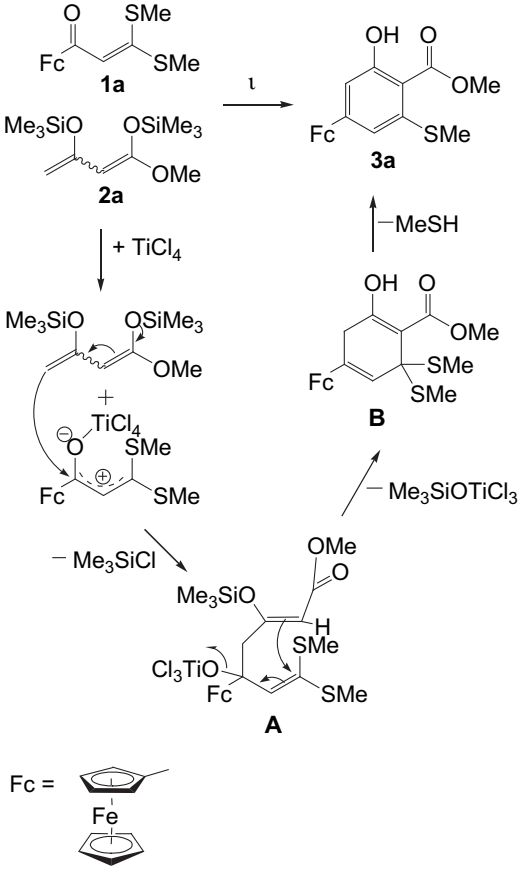
Scheme 2. Synthesis of **3a**–**h**. *Conditions*: i: 1) $TiCl_4$, CH_2Cl_2, −78 to 20 °C, 16 h; 2) 10% HCl.

Table 1
Synthesis of 4-ferrocenyl-2-hydroxy-6-(methylthio)benzoates **3a**–**h**.

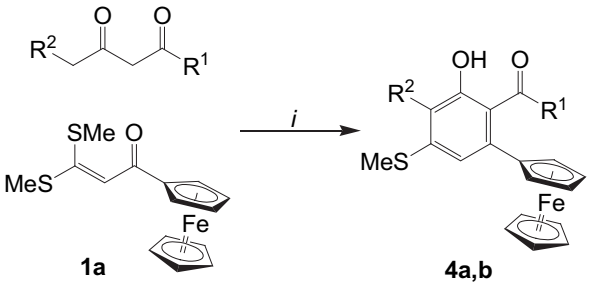
1	2	3	R^1	R^2	R^3	% (**3**)[a]
a	**a**	**a**	H	Me	H	40
a	**b**	**b**	H	Me	Et	44
a	**c**	**c**	H	Me	OMe	31
a	**d**	**d**	H	*i*Pr	H	35
a	**e**	**e**	H	Me	$(CH_2)_3Cl$	55
b	**f**	**f**	Me	Et	H	60
c	**a**	**g**	Et	Me	H	52
d	**a**	**h**	Cl	Me	H	50

[a] Yields of isolated products.

The formation of **3a** can be explained first by reaction of **1a** with $TiCl_4$ to give an allylic cation. The attack of the terminal carbon atom of **2a** onto the activated dithioketene ketal afforded, after elimination of Me_3SiCl, the open-chain intermediate **A**. Subsequent cyclization under formal exclusion of $Me_3SiOTiCl_3$ gave intermediate **B**. The elimination of MeSH (before or during the aqueous work-up) and aromatization resulted in the formation of **3a** (Scheme 3). The product, containing the methylthio-group located *ortho* to the ester group, was formed with excellent regioselectivity.



Scheme 3. Possible mechanism for the formation of **3a**.



Scheme 4. Synthesis of **4a**,**b**. Conditions: i: 1) LDA, 0 °C, 1 h; 2) **1a**, 20 °C, 14 h; 3) HCl (10%).

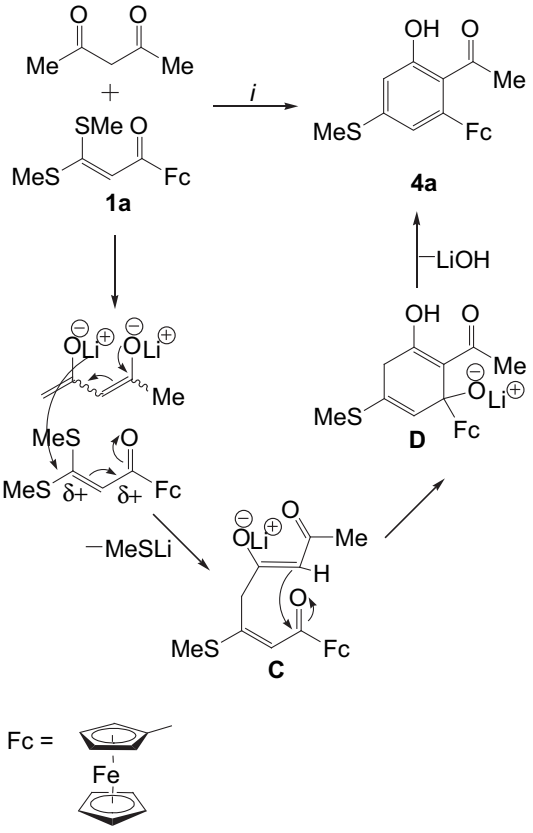
Table 2
Synthesis of 3-ferrocenyl-5-(methylthio)phenols **4a**,**b**

4	R^1	R^2	% (**4**)[a]
a	Me	H	36
b	Et	Me	65

[a] Yields of isolated products.

The formation of the other regioisomer, containing the methylthio-group located *para* to the ester group, was not observed.

The reaction of **1a** with 1,3-dicarbonyl dianions, generated by twofold deprotonation of 2,4-pentandione and 3,5-heptandione with 2 equivalents of LDA, resulted in the formation of 3-η^5-ferrocenyl-5-(methylthio)phenols **4a**,**b** (Scheme 4, Table 2). Noteworthy, these compounds are regioisomers of **3a**–**h** and are formed also with excellent regioselectivity. Since the dicarbonyl dianions are much more nucleophilic than 1,3-bis(trimethylsilyloxy)-1,3-butadienes, the reaction could be carried out without using a Lewis acid. In contrast to the $TiCl_4$-mediated syntheses of salicylates **3**, the best yields were obtained when the reaction was carried out in a more dilute solution (17 mL/mmol). The formation of **4a**,**b** can be explained by attack of the terminal carbon atom of the dianion onto the carbon atom attached to the two methylthio groups to give the open-chain intermediate **C**. The subsequent cyclization gave intermediate **D** and elimination of LiOH (before or during aqueous work-up) and aromatization resulted in formation of the final product **4a** (Scheme 5). The employment of 1,3-dicarbonyl compounds derived from β-ketoesters failed (low conversion).



Scheme 5. Possible mechanism for the formation of **4a**.

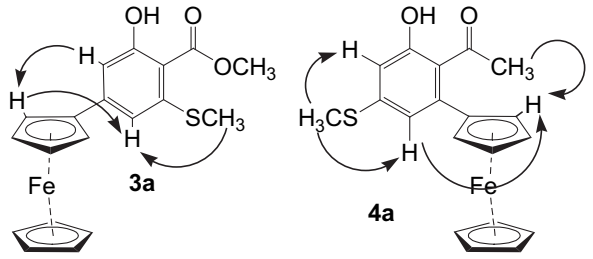


Chart 2. NOESY experiments.

The structures of all products were confirmed by spectroscopic methods. The hydroxyl protons (^{1}H NMR) of **3a**–**e** and **4a**,**b** show low field resonances (δ = 10.96–11.86 ppm) which indicate that the protons are involved in an intramolecular hydrogen bond O–H···O. In case of **3a**,**d**, a ^{1}H,^{1}H-long-range-coupling is observed between protons H-3 and H-5 (^4J = 1.5 Hz). For **3f**–**h**, chemical shifts between 8.98 ppm and 9.14 ppm were observed for the hydroxyl protons (^{1}H NMR). Obviously, the presence of a substituent at the 3-position of the benzoate-moiety causes a high field shift of the signal of the hydroxyl proton with regard to the corresponding unsubstituted benzoates. The signals of the methylthio-group of **3a**–**g**,**i**,**j** appear at chemical shifts between 14.0 ppm and 16.6 ppm (^{13}C NMR), whereas for **3h** a low field shift to 19.7 ppm was observed, due to the electron withdrawing effect of the chloro-substituent located *ortho* to the methylthio carbon atom. For **3a** and **4a**, ^{1}H,^{1}H-NOESY NMR experiments were carried out to prove the structure and the regiochemistry of the cyclization (Chart 2). For **3a**, cross-signals were observed for the protons of the methylthio-

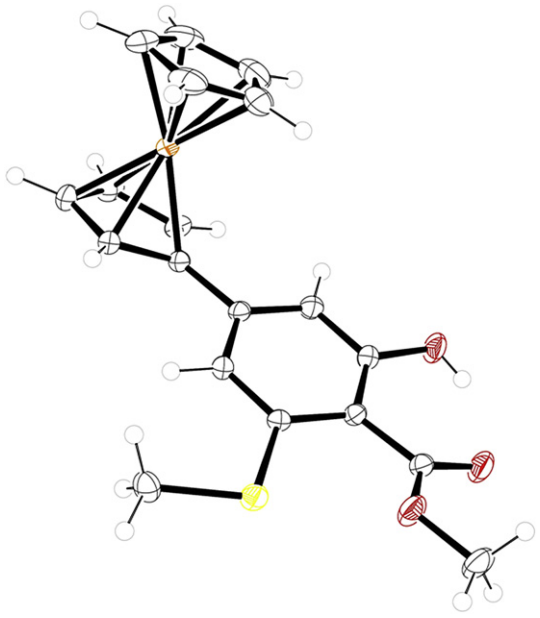


Fig. 1. Ortep plot of **3a**.

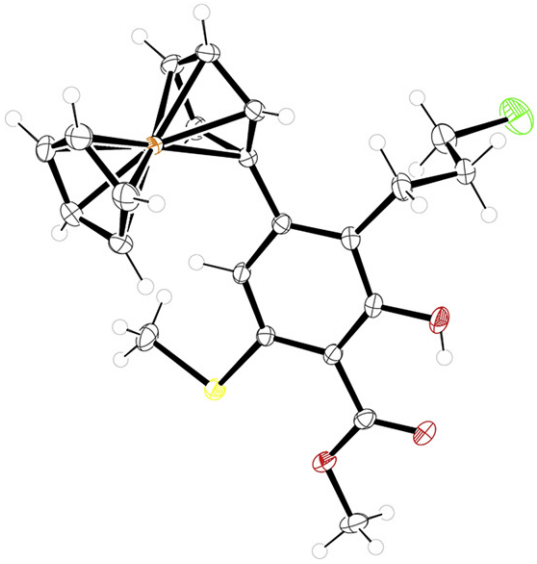


Fig. 2. Ortep plot of **3e**.

group with the *ortho*-proton located at the 5-position of the benzoate moiety; correlations were observed between the protons located at C-3 and C-5-position with the adjacent protons of the linked cyclopentadienyl moiety. For **4a**, NOE-correlations were observed for both protons located *ortho* to the methylthio-group. Furthermore, the protons of the acetyl-group and the proton located at the 4-position of the phenol system correlate with the protons of the cyclopentadienyl moiety.

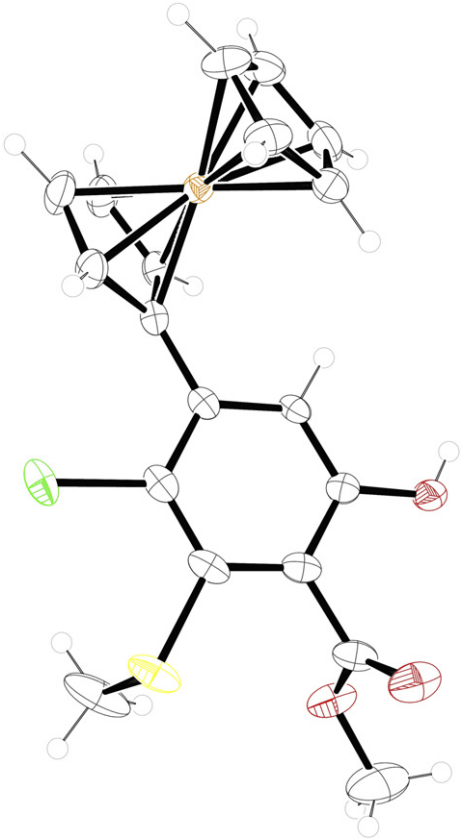


Fig. 3. Ortep plot of **3h**.

The structures of **3a**,**e**,**h** were unambiguously confirmed by X-ray crystal structure analyses (Figs. 1–3).

3. Conclusions

In conclusion, we have reported a regioselective approach to highly functionalized ferrocenyl-substituted phenols by cyclization of masked or free dianions with 1,3-dielectrophilic 1-η^5-ferrocenyl-3,3-bis(methylthio)prop-2-en-1-ones **1**. While the reactions of 1,3-bis(silyloxy)-1,3-butadienes (masked dianions) with **1** proceed by initial 1,2-addition, the reactions of free 1,3-dicarbonyl dianions with **1** proceed by initial 1,4-addition. Therefore, both regioisomeric products are available from one and the same electrophile dependent on the type of nucleophile and reaction conditions employed.

4. Experimental Section

*4.1. General procedure for synthesis of 1-η^5-ferrocenyl-3,3-bis(methylthio)prop-2-en-1-ones **1a-d***

To a stirred, ice-cooled solution of KO*t*Bu (18 mmol) in 8 mL of THF was added a solution of the ferrocenyl alkyl ketone (5 mmol) in 8 mL of THF. After stirring for 15 min, carbon disulfide (6 mmol) was added and the solution was vigorously stirred at 0 °C for 90 min. To this solution dimethyl sulfate (6 mmol) or methyl iodide (10 mmol) was slowly added and the solution was stirred at 0 °C for further 90 min. Subsequently, water (50 mL) was added and the mixture was extracted with dichloromethane (3 × 50 mL). The organic layers were dried (Na_2SO_4), filtered, and the solvent of the filtrate was removed in vacuo. The residue was purified by chromatography (silica gel).

*4.2. 1-η^5-Ferrocenyl-2-methyl-3,3-bis(methylthio)prop-2-en-1-one (**1b**)*

Starting with 1-η^5-ferrocenylpropan-1-one (4.07 mmol, 980 mg), KOtBu (8.14 mmol, 913 mg), CS_2 (4.07 mmol, 0.25 mL), MeI (8.14 mmol, 0.51 mL) in 13 mL of THF, **1b** was isolated (803 mg, 57%) by chromatography (silica gel, heptanes/EtOAc = 40/1 → 5/1) as a red oil. ^{1}H NMR (300 mHz, $CDCl_3$): δ = 2.10 (s, 3H, CH_3), 2.33 (s, 3H, SCH_3), 2.35 (s, 3H, SCH_3), 4.22 (s, 5H, CH), 4.53 (m, 2H, CH), 4.73 (m, 2H, CH). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 16.0 (SCH_3), 17.0 (SCH_3), 20.6 (CH_3), 69.4 (CH), 69.8 (CH), 72.0 (CH), 78.7 (*C*CO), 132.7 (*C*CH_3), 144.2 (*C*$(SCH_3)_2$), 201.9 (CO).

*4.3. 2-Ethyl-1-η^5-ferrocenyl-3,3-bis(methylthio)prop-2-en-1-one (**1c**)*

Starting with 1-η^5-ferrocenylbutan-1-one (25.00 mmol, 6.403 g), KOtBu (90 mmol, 10.100 g), CS_2 (30 mmol, 3.50 mL), dimethyl sulfate (30 mmol, 3.70 mL) in 90 mL of THF, **1b** was isolated (4.434 mg, 50%) by chromatography (silica gel, heptanes/EtOAc = 40/1 → 7/1) as a red oil. ^{1}H NMR (250 mHz, $CDCl_3$): δ = 1.24 (t, ^{3}J = 7.6 Hz, 3H, CH_3), 2.09 (s, 3H, SCH_3), 2.31 (s, 3H, SCH_3), 2.74 (q, ^{3}J = 7.5 Hz, 2H, CH_2), 4.22 (s, 5H, CH_{Cp}), 4.51 (s, 2H, CH_{Cp}), 4.71 (s, 2H, CH_{Cp}). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.5 (CH_3), 16.3 (SCH_3), 17.1 (SCH_3), 27.9 (CH_2), 69.7 (2xCH_{Cp}), 69.9 (5xCH_{Cp}), 71.7 (2xCH_{Cp}), 80.1 ($C_{q,Cp}$), 133.4 (CCH_2CH_3), 150.7 (*C*$(SCH_3)_2$), 202.1 (CO). IR (ATR, cm^{-1}): ν = 3094 (w), 2964 (w), 2919 (w), 2872 (w), 1639 (s). MS (EI, 70 eV): *m*/*z* (%) = 360 (M^+, 100), 213 (18), 185 (9), 129 (13), 121 (13). HRMS (EI, 70 eV): calcd. for $C_{17}H_{20}OFeS_2$: 360.02995; found 360.029641.

*4.4. 2-Chloro-1-η^5-ferrocenyl-3,3-bis(methylthio)prop-2-en-1-one (**1d**)*

Starting with chloroacetylferrocene (1.74 mmol, 458 mg), KOtBu (3.44 mmol, 386 mg), CS_2 (1.74 mmol, 0.11 mL), MeI (3.44 mmol,

0.22 mL) in 26 mL of THF, **1d** was isolated (250 mg, 40%) by chromatography (silica gel, heptanes/EtOAc = 50/1 → 5/1) as a red oil; ^{1}H NMR (300 mHz, $CDCl_3$): = 2.18 (s, 3H, SCH_3), 2.45 (s, 3H, SCH_3), 4.29 (s, 5H, CH), 4.60 (s, 2H, CH), 4.79 (s, 2H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.0 (SCH_3), 18.6 (SCH_3), 70.1 (CH), 70.8 (CH), 73.0 (CH), 77.5 (*C*CO), 128.1, 136.1 (C_q), 194.2 (CO).

4.5. General procedure for the [3 + 3]-Cyclocondensation

To a mixture of 1-η^5-ferrocenyl-3,3-bis(methylthio)prop-2-en-1-one **1** (1.0 mmol) and 1,3-bis(trimethylsilyloxy)-1,3-butadiene **2** (2.0 mmol) in dry CH_2Cl_2 (4 mL/mmol) was added $TiCl_4$ (1.1 mmol) at −78 °C. The reaction mixture was stirred for 14–16 h while warming to room temperature. After addition of 10% HCl (10 mL per 1 mmol of **1**) and extraction with CH_2Cl_2 (3 × 50 mL), the combined organic extracts were dried over Na_2SO_4, filtered and the solvent was evaporated in vacuo. The residue was purified by column chromatography to give products **3a**–**h**.

4.6. Methyl 4-η^5-ferrocenyl-2-hydroxy-6-(methylthio)benzoate (*3a*)

Starting with **1a** (1.0 mmol, 332 mg), **2a** (2.0 mmol, 521 mg) and $TiCl_4$ (1.0 mmol, 0.11 mL) in 2 mL of CH_2Cl_2, **3a** was isolated (152 mg, 40%) by chromatography (silica gel, heptanes/EtOAc = 100/1 → 15/1) as a red solid; mp 166–167 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.50 (s, 3H, SCH_3), 4.01 (s, 3H, OCH_3), 4.07 (s, 5H, CH_{Cp}), 4.39 (m, 2H, CH_{Cp}), 4.67 (m, 2H, CH_{Cp}), 6.77 (d, 1H, ^4J = 1.5 Hz, H-5), 6.87 (d, 1H, ^4J = 1.5 Hz, H-3), 11.47 (s, 1H, OH). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 15.6 (SCH_3), 51.9 (OCH_3), 67.2 (2xCH_{Cp}), 70.0 (7xCH_{Cp}), 83.0 ($C_{q,Cp}$), 107.8 (*C*C[O]OCH_3), 110.7 (C-3), 113.3 (C-5), 143.4 (*C*SCH_3), 146.8 (C_q), 163.4 (COH), 170.9 (*C*O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3089(m), 2945(w), 2919(m), 2843(w), 1665(s), 1598(s), 1544(s), 1504(w). MS (EI, 70 eV): *m/z* = 382 ($M^{\pm}$, 67), 351 (24), 350 (100), 285 (20), 189 (9). Anal. calc. for $C_{19}H_{18}FeO_3S$ (382.254): C, 59.70; H, 4.75; found: C, 59.52; H, 4.985.

4.7. Methyl 3-ethyl-4-η^5-ferrocenyl-2-hydroxy-6-(methylthio) benzoate (*3b*)

Starting with **1a** (1.0 mmol, 332 mg), **2b** (2.0 mmol, 577 mg) and $TiCl_4$ (1.0 mmol, 0.11 mL) in 2 mL of CH_2Cl_2, **3b** was isolated (178 mg, 44%) by chromatography (silica gel, heptanes/EtOAc = 100/1 → 25/1) as a red solid; mp 135–136 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.14 (t, 3H, ^3J = 7.4 Hz, CH_2CH_3), 2.76 (q, 2H, ^3J = 7.4 Hz, CH_2CH_3), 4.01 (s, 3H, OCH_3), 4.16 (s, 5H, CH_{Cp}), 4.35 (m, 2H, CH_{Cp}), 4.52 (m, 2H, CH_{Cp}), 7.12 (s, 1H, Ar), 11.80 (s, 1H, OH). ^{13}C NMR (63 MHz, $CDCl_3$) δ = 14.2 (CH_2CH_3), 16.4 (SCH_3), 20.0 (CH_2CH_3), 51.9 (OCH_3), 68.6 (2xCH_{Cp}), 69.6 (5xCH_{Cp}), 70.2 (2xCH_{Cp}), 86.6 ($C_{q,Cp}$), 107.5 (C-1), 117.9 (CH_{Ar}), 127.0, 138.6, 144.0 (C_q), 162.0 (COH), 171.4 (CO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3097(w), 3083(w), 2969(m), 2949(w), 2927(m), 2869(w), 1729 (m), 1644(s), 1594(s), 1546(s). MS (EI, 70 eV): *m/z* = 410 ($M^{\pm}$, 88), 379 (22), 378 (100), 197 (14), 121 (6). Anal. calcd. for $C_{21}H_{22}FeO_3S$ (410.31): C, 61.47; H, 5.40; found: C, 61.276; H, 5.754.

4.8. Methyl 4-η^5-ferrocenyl-2-hydroxy-6-methylthio-3-methoxybenzoate (*3c*)

Starting with **1a** (1.0 mmol, 332 mg), **2c** (2.0 mmol, 581 mg) and $TiCl_4$ (1.0 mmol, 0.11 mL) in 2 mL of CH_2Cl_2, **3c** was isolated (125 mg, 31%) by chromatography (silica gel, heptanes/EtOAc = 100/1 → 7/1) as a red solid; mp 181–182 °C; ^{1}H NMR(250 MHz, $CDCl_3$) δ = 2.51 (s, 3H, SCH_3), 3.78 (s, 3H, OCH_3), 4.01 (s, 3H, OCH_3), 4.08 (s, 5H, CH_{Cp}), 4.41 (s, 2H, CH_{Cp}), 4.88 (s, 2H, CH_{Cp}), 6.86 (s, 1H, Ar), 11.62 (s, 1H, OH). ^{13}C NMR (63 MHz, $CDCl_3$) δ = 16.6 (SCH_3), 52.1 (OCH_3), 59.9 (OCH_3), 69.5 (2xCH_{Cp}), 69.7 (5xCH_{Cp}), 69.9 (2xCH_{Cp}), 79.9 ($C_{q,Cp}$), 108.6 (*C*C[O]OCH_3), 114.8 (CH_{Ar}), 136.4, 138.4, 142.6 (C_q), 157.5 (COH), 171.0 (CO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3089(m), 2950(w), 2921(m), 2848(w), 2825(w), 1732(s), 1651(s), 1594(s), 1557(s). MS (EI, 70 eV): *m/z* = 412 ($M^{\pm}$, 75), 381 (19), 380 (100), 337 (7), 322 (14). HRMS (EI; 70 eV) calcd. for $C_{20}H_{20}O_4FeS$ ($M^{\pm}$): 412.041459, found: *m/z* = 412.04262.

4.9. Isopropyl 4-η^5-ferrocenyl-2-hydroxy-6-(methylthio)benzoate (*3d*)

Starting with **1a** (0.5 mmol, 116 mg), **2d** (1.0 mmol, 289 mg) and $TiCl_4$ (0.55 mmol, 0.06 mL) in 2 mL CH_2Cl_2, **3d** was isolated (72 mg, 35%) by chromatography (silica gel, heptanes/EtOAc = 17/1) as a red solid; mp 79–80 °C ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.47 (s, 3H, CH[*CH*$_3$]$_2$), 1.49 (s, 3H, CH[*CH*$_3$]$_2$), 2.48 (s, 3H, SCH_3), 4.06 (s, 5H, CH_{Cp}), 4.38 (m, 2H, CH_{Cp}), 4.67 (m, 2H, CH_{Cp}), 5.36 (m, 1H, *CH*[CH_3]$_2$), 6.76 (d, 1H, ^{4}J = 1.5 Hz, H-5), 6.85 (d, 1H, ^{4}J = 1.5 Hz, H-3), 11.64 (s, 1H, OH). ^{13}C NMR (63 MHz, $CDCl_3$) δ = 16.6 (SCH_3), 22.0 (CH[*CH*$_3$]$_2$), 67.1 (2xCH_{Cp}), 69.8 (*CH*[CH_3]$_2$), 69.9 (5xCH_{Cp}), 70.6 (2xCH_{Cp}), 83.0 ($C_{q,Cp}$), 108.3 (C_q), 110.6 (C-3), 113.1 (C-5), 143.6, 146.3 (C_q), 163.4 (COH), 170.0 (CO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3083 (w), 2983 (m), 2918 (m), 1729 (w), 1639 (s), 1598 (s), 1556 (s), 1514 (w). MS (ESI, 70 eV): *m/z* = 410.0636 ($[M + H]^{\pm}$). Anal. calcd. for $C_{21}H_{22}O_3FeS$ (410.31): C, 61.47; H, 5.40; S, 7.81. found: C, 61.364; H, 5.546; S, 8.022.

4.10. Methyl 4-ferrocenyl-2-hydroxy-6-(methylthio)-3-(3′-chloropropyl)benzoate (*3e*)

Starting with **1a** (1.0 mmol, 332 mg), **2e** (2.0 mmol, 642 mg) and $TiCl_4$ (1.0 mmol, 0.11 mL) in 2 mL CH_2Cl_2, **3e** was isolated (252 mg, 55%) by chromatography (silica gel, heptanes/EtOAc = 50/1) as a red solid; mp 132–133 °C ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.93–2.03 (m, 2H, CH_2), 2.54 (s, 3H, SCH_3), 2.88–2.93 (m, 2H, CH_2), 3.53–3.55 (m, 2H, CH_2), 4.01 (s, 3H, OCH_3), 4.17 (s, 5H, CH_{Cp}), 4.36–4.37 (m, 2H, CH_{Cp}), 4.50–4.51 (m, 2H, CH_{Cp}), 7.13 (s, 1H, Ar), 11.86 (s, 1H, OH). ^{13}C NMR (63 MHz, $CDCl_3$) δ = 16.3 (SCH_3), 24.5, 32.3 (CH_2), 45.4 (CH_2Cl), 52.0 (OCH_3), 68.7 (2xCH_{Cp}), 69.7 (5xCH_{Cp}), 70.2 (2xCH_{Cp}), 86.5 ($C_{q,Cp}$), 107.6 (C_q), 118.0 (CH_{Ar}), 123.8, 139.3, 144.5 (C_q), 162.0 (COH), 171.3 (CO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3079 (w), 2997 (w), 2951 (m), 2912 (m), 2873 (w), 1731 (m), 1645 (s), 1592 (s), 1542 (s), 1505 (w). MS (ESI, 70 eV): *m/z* = 458.04 ($[M + H]^{\pm}$). Anal. calcd. for $C_{22}H_{23}O_3FeSCl$ (458.78): C, 57.60; H, 5.05; S, 6.99; found: C, 57.629; H, 4.878; S, 7.326.

4.11. Ethyl 4-η^5-ferrocenyl-2-hydroxy-5-methyl-6-(methylthio) benzoate (*3f*)

Starting with **1b** (0.9 mmol, 310 mg), **2h** (1.8 mmol, 494 mg) and $TiCl_4$ (0.9 mmol, 0.1 mL) in 2 mL of CH_2Cl_2, **3f** was isolated (219 mg, 60%) by chromatography (silica gel, heptanes/EtOAc = 100/1 → 7/1) as a deep red solid; mp 148–150 °C; ^{1}H NMR (300 mHz, $CDCl_3$): δ = 1.45 (t, ^3J = 7.0 Hz, 3H, CH_2CH_3), 2.34 (s, 3H, SCH_3), 2.55 (s, 3H, CH_3), 4,23 (s, 5H, CH_{Cp}), 4.40 (s, 2H, CH_{Cp}), 4.46 (q, ^3J = 7.0 Hz, 2H, CH_2CH_3), 4.55 (s, 2H, CH_{Cp}), 7.21 (s, 1H, Ar), 8.98 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 18.8, 19.8 (CH_3), 61.9 (OCH_2CH_3), 68.4 (2xCH_{Cp}), 69.9 (5xCH_{Cp}), 70.7 (2xCH_{Cp}), 87.2 ($C_{q,Cp}$), 117.9 (CC[O]OCH_2), 119.3 (CH_{Ar}), 132.7, 136.8, 144.6 (C_q), 155.8 (COH), 170.0 (CO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3331 (m), 3082 (w), 2988 (w), 2918 (w), 1694 (s), 1590 (m), 1446 (m), 1298 (m), 1235 (s), 1206 (m), 1189 (m), 1120 (m), 1102 (m), 1016 (m). MS (CI, isobutane): *m/z* (%) = 410 ($M^{\pm}$, 100). Anal. calcd. for $C_{21}H_{22}O_3FeS$ (410.06): C, 61.47; H, 5.40; S, 7.81; found: C, 61.245; H, 5.563; S, 7.912.

4.12. Methyl 5-ethyl-4-η^5-ferrocenyl-2-hydroxy-6-(methylthio) benzoate (**3g**)

Starting with **1c** (1.0 mmol, 360 mg), **2a** (2 mmol, 520 mg) and $TiCl_4$ (1 mmol, 0.11 mL) in 3 mL of CH_2Cl_2, **3g** was isolated (213 mg, 52%) by chromatography (silica gel, heptanes/EtOAc = 100/1 → 15/1) as a brown solid; mp 147–149 °C; ^{1}H NMR (300 mHz, $CDCl_3$): δ = 1.05 (t, ^{3}J = 7.3 Hz, 3H, CH_2CH_3), 2.34 (s, 3H, SCH_3), 3.00 (q, ^{3}J = 7.3 Hz, 2H, CH_2CH_3), 4.01 (s, 3H, OCH_3), 4.18 (s, 5H, CH_{Cp}), 4.33 (s, 2H, CH_{Cp}), 4.47 (s, 2H, CH_{Cp}), 7.44 (s, 1H, Ar), 9.14 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.1 (SCH_3), 21.0 (CH_2CH_3), 24.3 (CH_2CH_3), 52.5 (OCH_3), 68.3 (2xCH_{Cp}), 69.7 (5xCH_{Cp}), 70.5 (2xCH_{Cp}), 87.3 (C_q), 117.1 (*C*C[O]OCH_3), 120.1 (CH_{Ar}), 136.7, 139.1, 144.2 (C_q), 156.4 (COH), 170.4 (CO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3239 (br, m), 2959 (w), 2924 (w), 2866 (w), 1694 (s), 1589 (s), 1402 (m), 1302 (m), 1264 (s), 1227 (s), 1123 (m), 1107 (m), 948 (m), 814 (s), 664 (m). GC–MS (EI, 70 eV): *m/z* (%): 410 ($M^{\pm}$, 60), 379 (22), 378 (100), 360 (28), 213 (17). Anal. calcd. for $C_{21}H_{22}O_3FeS$ (410.06): C, 61.47; H, 5.40; S, 7.81; found: C, 61.459; H, 5.576; S, 7.57.

4.13. Methyl 5-chloro-4-η^5-ferrocenyl-2-hydroxy-6-(methylthio) benzoate (**3h**)

Starting with **1d** (0.6 mmol, 216 mg), **2a** (1.2 mmol, 313 mg) and $TiCl_4$ (0.65 mmol, 0.07 mL) in 2 mL of CH_2Cl_2, **3h** was isolated (125 mg, 50%) by chromatography (silica gel, heptanes/EtOAc = 100/1 → 7/1) as a red solid; mp 161–162 °C; ^{1}H NMR (300 mHz, $CDCl_3$): δ = 2.44 (s, 3H, SCH_3), 4.00 (s, 3H, OCH_3), 4.24 (s, 5H, CH_{Cp}), 4.47 (s, 2H, CH_{Cp}), 4.86 (s, 2H, CH_{Cp}), 7.23 (s, 1H, Ar), 9.18 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.66 (SCH_3), 53.67 (OCH_3), 69.8 (2xCH_{Cp}), 70.7 (5xCH_{Cp}), 71.3 (2xCH_{Cp}), 84.4 ($C_{q,Cp}$), 118.0 (*C*C[O]OCH_3), 119.6 (CH_{Ar}), 129.6, 137.2, 144.3 (C_q), 156.5 (COH), 169.7 (CO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3359 (w), 3081 (w), 2925 (w), 1726 (s), 1699 (s), 1588 (s), 1488 (w), 1429 (m), 1368 (s), 1323 (m), 1270 (m), 1228 (s), 1098 (s). MS (ESI, 70 eV): *m/z* = 414.98661 ($[M - H]^-$). Anal. calcd. for $C_{19}H_{17}ClFeO_3S$ (416.699): C, 54.76; H, 4.11; found: C, 54.64; H, 4.18.

4.14. General procedure for the cyclization reactions of 1,3-dicarbonyl dianions

LDA was generated at 0 °C by reaction of *n*BuLi (6.9 mmol) and diisopropylamine (6.9 mmol) in dry THF (2.5 mL/mmol *n*BuLi). To this mixture was added the dicarbonyl compound (3 mmol). After stirring for 1 h at 0 °C, the 1-η^5-ferrocenyl-3,3-bis(methylthio) prop-2-en-1-one **1** (1 mmol) was added. After stirring for 14 h and warming of the mixture to room temperature, the solution was neutralized by addition of hydrochloric acid (10%). The mixture was extracted with CH_2Cl_2 (3 × 50 mL), dried over Na_2SO_4, filtered and the solvent was removed in vacuo. The residue was purified by column chromatography to give products **4a**,**b**.

4.15. 2-Acetyl-3-η^5-ferrocenyl-5-(methylthio)phenol (**4a**)

Starting with **1a** (1.0 mmol, 332 mg), acetylacetone (3.0 mmol, 0.33 mL), *n*BuLi (6.9 mmol, 2.8 mL, 2.5 M in *n*hexane) and diisopropylamine (6.9 mmol, 1 mL) in 17 mL of THF, **4a** was isolated (104 mg, 36%) by chromatography (silica gel, heptanes/EtOAc = 20/1 → 15/1) as a red solid; mp 103–104 °C; ^{1}H NMR (300 mHz, $CDCl_3$): δ = 1.90 (s, 3H, CH_3), 2.55 (s, 3H, SCH_3), 4.14 (s, 5H, CH), 4.35 (s, 2H, CH), 4.46 (s, 2H, CH), 6.66 (s, 1H, H-6), 7.33 (s, 1H, H-4), 11.45 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.6 (SCH_3), 31.4 (CH_3), 69.0 (2xCH_{Cp}), 70.3 (5xCH_{Cp}), 71.0 (2xCH_{Cp}), 89.6 (C_q), 110.8 (C-6), 120.0 (*C*C[O]CH_3), 121.5 (C-4), 141.6, 146.1 (C_q), 160.2 (COH), 206.2 (CO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3091 (w), 2918 (w), 1591 (s), 1574 (w), 1556 (w). MS (CI, isobutane): *m/z* (%) = 367 ($[M + H]^{\pm}$, 100). HMRS (ESI, 70 eV) calcd. for $C_{19}H_{18}FeO_2S$ ($[M + H]^{\pm}$): 366.0372, found: *m/z* = 366.0369.

4.16. 3-η^5-Ferrocenyl-6-methyl-5-methylthio-2-propionylphenol (**4b**)

Starting with *n*BuLi (8.7 mmol, 3.45 mL, 2.5 M/*n*hexan), diisopropylamine (8.7 mmol, 1.21 mL), 3,5-heptandione (3.8 mmol, 0.5 mL) and**1a** (1.3 mmol, 0.420 g), **4b** was isolated (256 mg, 65%) by chromatography (silica gel, heptanes/EtOAc = 15/1) as a red solid; mp 152–154 °C ^{1}H (300 MHz, $CDCl_3$) δ = 0.87 (t, 3H, ^3J = 7.3 Hz, CH_2CH_3), 2.15 (q, 2H, ^3J = 7.3 Hz, CH_2CH_3), 2.22 (s, 3H, SCH_3), 2.60 (s, 3H, CH_3), 4.10 (s, 5H, CH_{Cp}), 4.32 (m, 2H, CH_{Cp}), 4.43 (m, 2H, CH_{Cp}), 7.25 (s, 1H, Ar), 10.96 (s, 1H, OH). ^{13}C (63 MHz, $CDCl_3$) δ = 9.6 (CH_2CH_3), 11.8 (CH_3), 14.9 (SCH_3), 36.6 (CH_2CH_3), 68.6 (2xCH_{Cp}), 69.8 (5xCH_{Cp}), 70.4 (2xCH_{Cp}), 89.7 ($C_{q,Cp}$), 118.5 (CH_{Ar}), 119.7, 120.5, 137.9, 144.0 (C_q), 156.0 (COH), 211.0 (CO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3086 (m), 2974(m), 2935(w), 2918(w), 2877(w), 1614(s), 1580(s), 1537(s), 1504(w); MS (EI, 70 eV): *m/z* = 394 ($M^{\pm}$, 100), 329 (18), 301 (29), 299 (14), 182 (10); HRMS (EI, 70 eV) calcd. for $C_{21}H_{22}FeO_2S$: 394.068341, found: *m/z* = 394.06844.

Appendix. Supplementary material

CCDC 805305–805307 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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