ORGANOMETALLICS

ARTICLE

pubs.acs.org/Organometallics

# Synthesis and Structural Characterization of Ferrocenyl-Substituted Aurones, Flavones, and Flavonols

Keshri Nath Tiwari,[†,‡,⊥] Jean-Philippe Monserrat,[†,‡,⊥] Fréderic de Montigny,[†,‡] Gérard Jaouen,[†,‡] Marie-Noelle Rager,[*,§] and Elizabeth Hillard[*,†,‡]

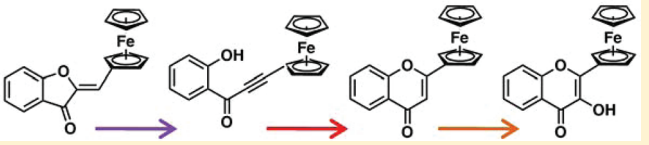
[†]Laboratoire Charles Friedel (LCF), ENSCP Chimie ParisTech, 75005 Paris, France

[‡]CNRS, UMR 7223, 75005 Paris, France

[§]NMR Facility, ENSCP Chimie ParisTech, 11 Rue Pierre et Marie Curie, 75231 Paris Cedex 05, France

Supporting Information

**ABSTRACT:** In the context of our studies on the modification of bioactive molecules with ferrocene, we here report the first examples of ferrocenyl flavonoids, where ferrocene replaces the B ring of the flavonoid skeleton. Ferrocenyl aurones possessing an electron-withdrawing or an electron-donating group in the 5′-position were obtained from 5′-R-2′-hydroxy-3-ferrocenyl chalcones via 1,5 oxidative exocyclization using $Hg(OAc)_2$ or AgOTf. Treatment of the ferrocenyl aurones with LDA resulted in a ring opening to form ferrocenyl ynones, which could then be selectively recyclized to the flavone isomer by treatment with NaOEt. Ferrocenyl flavones were also obtained by isomerization of the aurones with KCN and were hydroxylated in the 3-position to form ferrocenyl flavonols with oxone in a biphasic reaction. In many cases the reactivity of the ferrocenyl compounds was significantly different from that of their organic analogues. This reactivity and regioselectivity can be rationalized by ferrocene's particular ability to destabilize $\alpha$-anions in reaction intermediates. Representative examples of ferrocenyl aurones, ynones, and flavones were characterized by 2D NMR and X-ray crystallography, and the molecules all show a planar arrangement of the organic skeleton with the cyclopentadienyl ring of the ferrocene group. Putative MLCT bands in the visible region are responsible for the variety of highly saturated colors observed.




## INTRODUCTION

Flavonoids, such as flavanones, flavones, aurones, and flavonols and their precursor chalcones (Chart 1), are plant-based dietary polyphenols associated with a wide range of medicinal activities including beneficial effects against cancer,[1] cardiovascular disease,[2] inflammation,[3] and parasitic[4] and viral[5] infections. The salutary effects of flavonoids have often been attributed to their antioxidant properties,[6] although interactions with proteins and cell signaling pathways have also been revealed.[7]

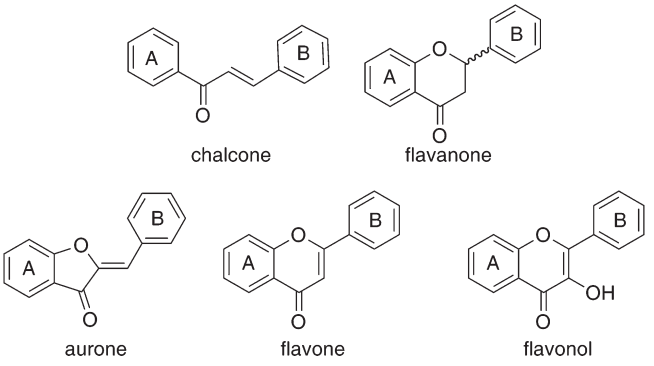
The role of ferrocene in medicinal chemistry has received much attention in the last twenty years,[8] primarily due to the observation that modification of natural products or drugs by the introduction of ferrocene can have dramatic effects on the biological activity of such molecules. In one such class of ferrocenyl compounds, based on the resveratrol skeleton, the nanomolar antiproliferative activities against cancer cells have been attributed to the redox behavior of ferrocene.[9] More recently, a report of the modification of SAHA with ferrocene revealed nanomolar and selective inhibition of histone deacetylases and low micromolar cancer cytotoxicity in vitro.[10] Modification of curcuminoids,[11] indoles,[12] oxyindoles,[13] and aminoquinolines[14] by ferrocene has also been shown to enhance their anticancer activity.

In the context of our studies in ferrocenyl medicinal chemistry,[8b,15] we became interested in how the introduction of an additional redox-active group might affect the biological effects of flavonoids. Several coordination complexes with chalcones[16] and other flavonoids[17] are known; indeed, the ability of flavonoids to coordinate metals is considered to be part of their antioxidant arsenal.[18] Examples of organometallic flavonoids, on the other hand, are rarer. Examples include zerovalent complexes of Fe, Cr, Mo, and W, where the chalcone is coordinated to the metal via the enone,[19] examples of $Fe(CO)_3$ coordinated through the A or B ring,[20] and a broad series of ferrocenyl chalcones.[21] Indeed, ferrocenyl chalcones have been studied since the 1950s,[22] and some of their biological activities have more recently been evaluated.[21,23] However, to our knowledge, ferrocenyl chalcones have never been exploited for the synthesis of higher ferrocenyl flavonoids, for which no examples exist.

We have recently shown that aurones wherein ferrocene replaces the B ring and with halogen substitution on the A ring (Chart 1) can be obtained in high yield by treating the corresponding 2-hydroxychalcones with AgOTf and NaH.[24] We now report further studies on the synthesis and reactivity of such compounds, including the sequential synthesis of ferrocenyl aurones, ynones, flavones, and flavonols. In many cases we find that the presence of ferrocene significantly changes the reactivity

**Received:** July 18, 2011
**Published:** September 29, 2011

**Chart 1. Some of the Principal Classes of Flavonoids**




of such molecules compared to their organic analogues. For example, the ring opening of the aurone to form a ferrocenyl ynone, which can then be "recyclized" to quantitatively yield the corresponding flavone, is a sequence of reactions not observed for organic flavonoids. The reactivity and regioselectivity found in the ferrocene series is likely due to the particular ability of ferrocene to stabilize adjacent cations[25] and to consequently destabilize adjacent anions in reaction intermediates. All of these novel and strongly colored compounds have been obtained in moderate to high yields and have been characterized by X-ray crystallography and/or 2D NMR spectroscopy and UV/visible spectroscopy.

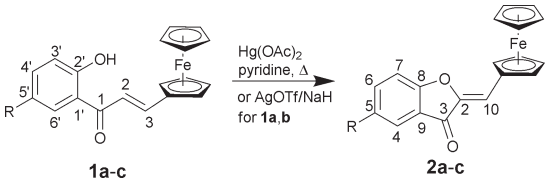
## RESULTS AND DISCUSSION

**Synthesis and Reactivity of Ferrocenyl Flavonoids.** With the future aim of exploring how the addition of ferrocene can influence the biological properties of flavonoids, we set out to synthesize a series of compounds where ferrocene replaces the B ring of the flavonoid skeleton. This strategy was inspired by several examples demonstrating that integration of ferrocene into the skeleton of a bioactive molecule can potentiate the biological effects. As is common in flavonoid synthesis and the rule in flavonoid biosynthesis, we began our synthetic pathway with the chalcone precursor. In this way a variety of substituted compounds can be obtained, using a range of commercially available substituted acetophenones. We selected for this study 2′-hydroxychalcones substituted in the 5′-position by an electron-withdrawing group (bromido), an electron-donating group (methoxy), and the standard unsubstituted compound.

*Ferrocenyl Aurones.* Ferrocene chalcones **1a**−**c** were obtained by a standard Claisen−Schmidt condensation between ferrocene carboxaldehyde and 2-hydroxyacetophenone, 2-hydroxy-5-bromidoacetophenone, or 2-hydroxy-5-methoxyacetophenone with NaOH in refluxing EtOH.[22] Our first target was the flavanone, classically formed by the cyclization of the chalcone by a simple acid- or base-catalyzed 1,4-nucleophilic attack. However, in our hands, treatment of the ferrocenyl chalcones with common flavanone-forming reagents such as AcOH, pyridine, L-proline, or various bases led to only decomposition products.

Oxidative cyclization of 2′-hydroxychalcones is a common methodology for the synthesis of the aurone or flavone scaffold. We therefore investigated the reactivity of the ferrocene chalcone with a variety of metal salts and found that treatment of **1a** and **1b** with AgOTf and NaH in THF resulted in a quantitative conversion (by TLC) to a deep violet compound in about 72% yield after silica gel column chromatography (Scheme 1). On the basis of mass, elemental analyses, and 1D $^1$H NMR spectra, we initially and erroneously attributed the flavone structure to these products.[24] However, subsequent crystallographic and 2D NMR characterization of **2b** showed that this compound was instead the aurone isomer (vide infra).

**Scheme 1. Synthesis of Ferrocenyl Aurones 2a−c via Oxidative Cyclization of 2-Hydroxychalcones 1a−c**[a]




[a] R = H (**a**); R = Br (**b**); R = OMe (**c**).

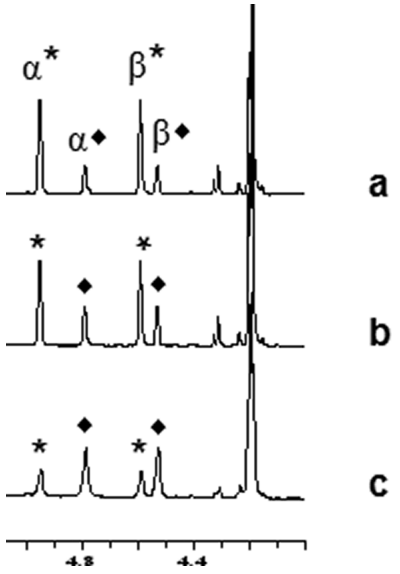


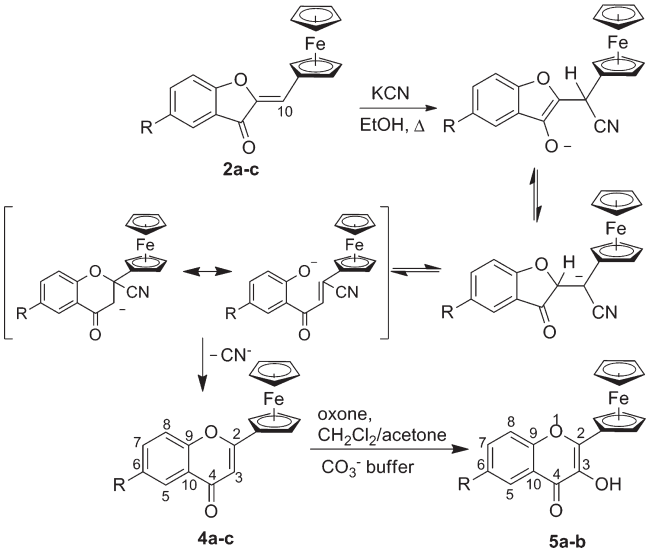

**Figure 1.** $^1$H NMR spectrum of the ferrocene region in pyridine-$d_5$ and $Hg(OAc)_2$. Diamonds = **1b** and stars = **2b**; (a) after 18 h; (b) after 12 h; (c) after 1 h.

While the AgOTf system gave aurones **2a** and **2b** after only 10 min at rt, the conversion of the methoxy compound **1c** to **2c** using this method was sluggish and accompanied by the formation of insoluble side products. Subsequently we found that treatment of **1a**−**c** with mercury(II) acetate in pyridine at 80 °C for 3−5 h cleanly yielded **2a**−**c** in about 73% yield after purification on silica gel.

An interesting aspect of these reactions is their regioselectivity. Oxidative cyclizations of 2′-hydroxychalcones are rarely selective, and the mixture of products (aurones, flavones, isoflavones, flavanones) obtained is highly dependent on the reagents used.[26,27] Flavones have been the major product of oxidative cyclization of chalcones using DDQ (often mixed with aurones),[27a] palladium lithium chloride (often mixed with flavanones),[27b] and thallium(III) nitrate trihydride.[27c] Conversely, aurones are the sole product found using $Hg(OAc)_2$ and pyridine in the organic series.[26a]


dx.doi.org/10.1021/om200644e |*Organometallics* 2011, 30, 5424–5432

**Scheme 2. Synthesis of Ferrocenyl Flavones 4a−c via Isomerization of Aurones 2a−c and Hydroxylation of 4a,b to Flavonols 5a,b[a]**




[a] R = H (**a**); R = Br (**b**); R = OMe (**c**).

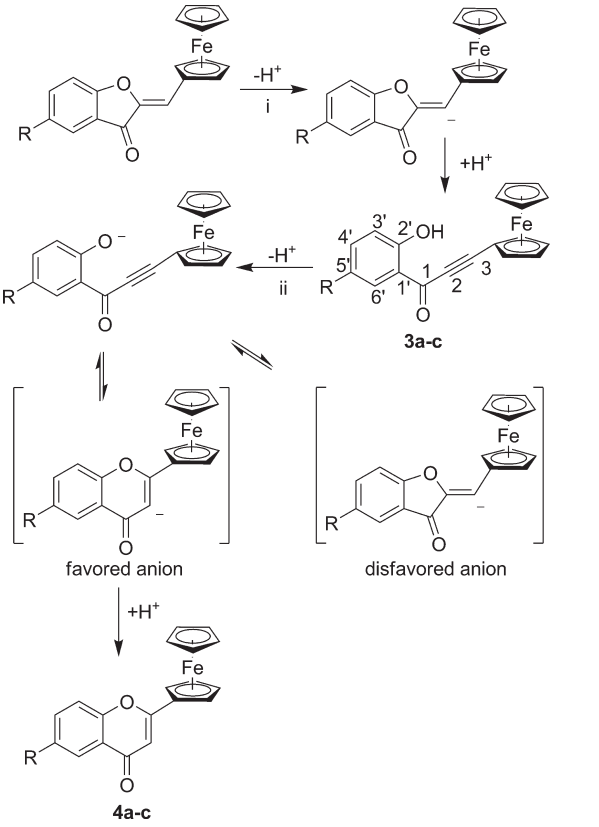
Previous work suggests that $[HgOAc]^+$ forms complexes with the phenolate and double bond, leading eventually to a four-centered pericyclic addition of ArO and HgOAc over the double bond;[26b,c] it is not immediately obvious if AgOTf plays the same role as $Hg(OAc)_2$. The reaction with AgOTf being very rapid, we attempted to follow the reaction of **1b** with $Hg(OAc)_2$ by $^1H$ NMR in pyridine-$d_5$ at rt over 18 h. As shown in Figure 1, at $t = 1$ h, a 2/1 proportion of chalcone to aurone signals was observed. Over time, those signals corresponding to the chalcone diminished and those corresponding to the aurone increased. No signals of any intermediate or other product were observed.

In another effort to understand the role of $Hg(OAc)_2$, we attempted to prevent cyclization by using a protected chalcone. Methylation of the phenol group of **1b** was effected with MeI/NaH in THF at room temperature after 6 h. The new compound, (*E*)-1-(5′-bromido-2′-methoxyphenyl)-3-ferrocenylprop-2-en-1-one, was dissolved in pyridine-$d_5$, and an excess of $Hg(OAc)_2$ was added and monitored by $^1H$ NMR over 13 h. No change in the spectrum was observed, suggesting Hg does not simply add over the double bond of the enone. Finally, the interaction of **1b** and $Hg(OAc)_2$ was examined in the absence of base. Likewise, no reaction was observed via $^1H$ NMR in MeOD over 12 h. Other experiments monitored by TLC also demonstrated the necessity of an external base, the replacement of pyridine with a stronger base considerably enhancing the reaction rate.

These results support a mechanism of cyclization involving initial coordination of HgOAc to the oxygen atom of the phenolate. This could very well be followed by the addition of ArO-HgOAc over the double bond to form a metalated intermediate, as previously proposed for the organic series.[26b,c] The partial negative charge on the carbon would be destabilized by the adjacent ferrocene group, promoting rapid $\beta$-elimination. This interpretation explains why the mercurated intermediate was observed in the organic series but not in the ferrocene series.

The reaction with AgOTf could, a priori, proceed similarly. This type of reaction should be strongly dependent on the nature

**Scheme 3. Selective Synthesis of Ferrocenyl Flavones 4a−c via Cyclization of Ynones 3a−c[a]**




[a] Conditions: (i) LDA in THF, −78 °C; (ii) NaOEt in EtOH.

of the phenolate−metal−olefin complex, in that a silver atom with a weakly coordinating anion would be expected to strongly complex to the chalcone and hinder cyclization. Accordingly, in our hands, silver salts with $PF_6$, $BF_4$, and $ClO_4$ did not yield any aurone product, according to TLC analysis. Trifluoroacetate would be expected to make a stronger ion pair with silver, thus activating the O−Ag−olefin complex, and an aurone product was indeed obtained with this reagent.

However, while the use of $Hg(OAc)_2$ to obtain aurones is well known in the organic series,[26a−d] reactions of organic 2′-hydroxychalcones with AgOTf yielded only intractable mixtures, strongly implicating the ferrocene group in the mechanism of cyclization. We originally hypothesized that a one-electron oxidation of the ferrocene group by AgOTf could be the first step in the reaction. However, reaction with the chalcone **1a** and **1b** with AgOTf in THF or pyridine gave only a brown, diamagnetic product that could not be eluted on a TLC plate, ruling out the likelihood of this mechanism. We next investigated if an inductive effect by the ferrocene group modified the electronic structure of the $\alpha,\beta$-unsaturated ketone in order to promote a nucleophilic attack in the 3-position. On the basis of $^1H$ and $^{13}C$ NMR of **1b** (Supporting Information), while the double bond is less polarized in the ferrocene chalcone than in the analogous organic chalcone, the differences are too small to alone drive 5-exocyclization. Therefore, if the silver reagents act similarly to $Hg(OAc)_2$, the ferrocene group may then be involved in the elimination step. As a one-electron oxidant, a radical reaction or homolytic elimination of Ag cannot be ruled out, and this will be the subject of a future study.

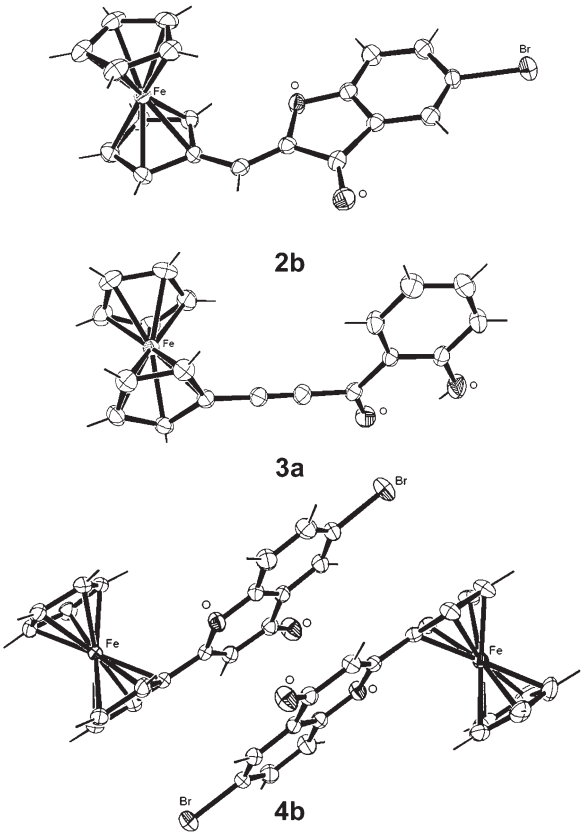



**Figure 2.** Asymmetric units for *Z*-**2b**, **3a**, and **4b** grown from a $CH_2Cl_2$/pentane solution. Thermal ellipsoids are shown at the 50% probability level.

*Ferrocenyl Flavones.* The standard method of forming flavones is via 1,6-oxidative cyclization of chalcones. However, treatment of ferrocenyl chalcones **1a**−**c** with reagents known to effect this transformation, such as $I_2$, DDQ, $SeO_2$, and $Br_2$, produced only intractable mixtures with no trace of flavone visible in TLC. $^1$H NMR spectra of these mixtures furthermore suggest the loss of the ferrocene group.

Direct isomerization of aurones to flavones is known to occur in basic media and in the presence of KCN.[28] Isomerization of **2** to **4** was not observed during the formation of **2** in the presence of NaH or pyridine. However, treatment of isolated **2a** with KO$^t$Bu in EtOH slowly yielded the flavone **4a** along with decomposition products. The use of KCN gave better results: treatment of aurones **2a**−**c** with KCN in refluxing EtOH allowed an effective isomerization to flavones **4a**−**c**, complete after 2 h with isolated yields of 75−80% (Scheme 2). The mechanism of isomerization is very likely enhanced by the presence of ferrocene. The attack of the cyanide on $C_{10}$ (the 4-position of the enone) would be expected to generate an unstable negative charge on this position adjacent to the ferrocene, after proton migration. This unstable anion would be expected to rearrange following either a 1,2-migration of the phenolic oxygen to generate the more stable enolate or a ring opening to the phenolate. An attack of the phenolate on $C_{10}$ and ejection of the cyanide would yield the flavone structure.

Ferrocenyl flavones were also synthesized via another route involving an ynone intermediate, which has been isolated. Treatment of ferrocenyl aurones **2a**−**c** with lithium diisopropylamide (LDA) in THF yielded, after workup, deep red solids, which were identified as 1-(2′-hydroxyphenyl)-3-ferrocenylprop-2-yn-1-one derivatives (Scheme 3). Presumably, deprotonation of the vinyl proton creates an anion, which is destabilized by the adjacent ferrocene, resulting in a rapid rearrangement and ring opening, yielding the ynones **3a**−**c** as the sole products in about 70% purified yield. Interestingly, it has been previously observed that organic aurones do not react readily with LDA, although in some cases, a minor amount of ynone product has been detected.[29] This clearly demonstrates the destabilizing influence of ferrocene on the adjacent anion, which promotes rapid ynone formation.

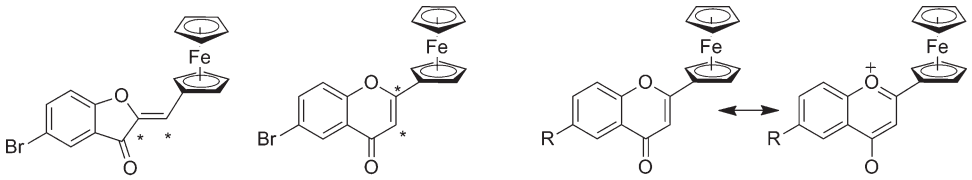
**Table 1. Crystal Data for a Representative Aurone, Ynone, and Flavone**

| | *Z*-**2b** | **3a** | **4b** |
|---|---|---|---|
| | $C_{19}H_{13}BrFeO_2$ | $C_{19}H_{14}FeO_2$ | $C_{19}H_{13}BrFeO_2$ |
| *M* | 409.06 | 330.17 | 409.06 |
| cryst syst | monoclinic | monoclinic | monoclinic |
| space group | $P2_1/a$ | $P2_1/c$ | $P2_1/c$ |
| *a* (Å) | 7.5434(7) | 9.8786(6) | 7.3599(2) |
| *b* (Å) | 14.7364(17) | 13.7386(7) | 15.1457(5) |
| *c* (Å) | 13.8726(8) | 10.6891(6) | 27.5266(8) |
| $\beta$ (deg) | 99.146(8) | 95.745(5) | 90.2090(10) |
| *V* (Å$^3$) | 1522.5(2) | 1443.42(14) | 3068.39(16) |
| *Z* | 4 | 4 | 8 |
| *T* (K) | 200 | 200 | 200 |
| no. reflns | 21 523 | 13 536 | 36 796 |
| no. indep reflns | 3471 | 4177 | 9784 |
| $R_{int}$ | 0.059 | 0.000 | 0.037 |
| $2\theta$ (deg) | 52.8 | 54.6 | 61.1 |
| $R_1$ (all data) | 0.0644 | 0.0526 | 0.0624 |
| $wR_2$ (all data) | 0.0622 | 0.0610 | 0.0655 |
| $R_1$ (with cutoff) | 0.0365 | 0.0322 | 0.0388 |
| $wR_2$ (with cutoff) | 0.0506 | 0.0502 | 0.0556 |

With the ferrocenyl ynones **3a**−**c** in hand, we investigated their base-catalyzed cyclization. Treatment of **3a**−**c** with NaOEt in EtOH at room temperature gave a single orange product that was identified as having the flavone structure with 65−70% purified yield (Scheme 3). Conversely, such reactions of organic ynones usually give a mixture of flavones and aurones,[30] often with the aurone isomer predominating.[31] The presence of ferrocene, however, exclusively favors attack on $C_3$ (the 4-position of the enone). In line with our previous argumentation, the production of ferrocenyl aurones should not be favored, because it requires an unstable $\alpha$-ferrocenyl anion as an intermediate. Conversely, an attack on $C_3$ places the anion on $C_2$, further from the ferrocene group, thus yielding an equilibrium favoring evolution to the flavone. We have previously seen that treatment of ferrocenyl aurones with LDA rapidly generates the ynone, suggesting that the lifetime of the aurone anion is very short.

*Ferrocenyl Flavonols.* Organic flavonols can directly be prepared from chalcones, via the Algar−Flynn−Oyamada reaction, involving an oxidative cyclization and treatment with hydrogen peroxide in basic media.[32] Once again, however, this reaction led only to decomposition of the ferrocenyl chalcone. Another method to form flavonols involves flavone hydroxylation with DMDO[33] or with LDA followed by $H_2O_2$.[30] Nonetheless, in the ferrocenyl flavone series, these methods failed to give any of the desired product. However, dissolution of **4a**,**b** in a 2/1 dichloromethane/

Table 2. Selected $^1$H and $^{13}$C NMR and IR Spectroscopic Data for Aurones 2a−c and Flavones 4a−c[a]




| | $\delta$ ($H_{vinyl}$)/ppm | $\delta$ ($CH_{vinyl}$)/ppm | $\delta$ ($C_{q\ vinyl}$)/ppm | $\nu_{max}$ (C=O)/cm$^{-1}$ | $\nu_{max}$ (C=C)/cm$^{-1}$ |
|---|---|---|---|---|---|
| **2a** | 6.90 | 116.6 | 146.1 | 1698 | 1642 |
| **2b** | 6.91 | 117.6 | 146.5 | 1701 | 1639 |
| **2c** | 6.88 | 116.4 | 146.6 | 1689 | 1632 |
| **4a** | 6.48 | 105.9 | 168.3 | 1631 | 1605 |
| **4b** | 6.47 | 105.8 | 168.8 | 1643 | 1612 |
| **4c** | 6.47 | 105.1 | 167.9 | 1627 | ca. 1612 (sh) |
| $\Delta\delta$ or $\nu$ | +0.43 ± 0.02 | +11 ± 1 | −22 ± 1 | +62 ± 9 | +28 ± 9 |

[a] Locations of the vinyl proton and vinyl carbon atoms under discussion are marked with an asterisk.

acetone solution in carbonate buffer as a biphasic medium and addition of oxone solution in water provided the flavonols as orange solids in 78−80% yields (Scheme 2).[34]

**Structural Characterization.** The aurones, flavones, and ynones reported here are all structural isomers and thus cannot be differentiated by mass spectrometry or elemental analysis alone. The ynones **3a**−**c** could be identified by IR and $^1$H NMR spectroscopy, but the structural similarity between aurones and flavones made the structural attribution nontrivial. Indeed, some mischaracterizations and subsequent corrections can be found in the literature.[35]

Crystals of **2b**, **3a**, and **4b** suitable for X-ray diffraction were obtained from slow evaporation of dichloromethane/pentane solutions. Ortep diagrams are shown in Figure 2, and crystallographic data are given in Table 1. Consistent with $^1$H NMR data, **2b** exists as the *Z* isomer in the X-ray structure, with a quasi-planar arrangement of the benzofuranone moiety with the $C_5H_4$ ring of the ferrocene, the angle created by the planes being 8.5°. The bond distances are normal, and there is no significant distortion of the ferrocene, with an angle created by the iron atom and the cyclopentadienyl centroids of 177°. Likewise, for **3a**, the phenol ring is almost coplanar with the $C_5H_4$ ring of the ferrocene (8.6°), and no distortion of the ferrocene ($Cp_{centroid}$−Fe−$Cp_{centroid}$ = 179°) was observed. For **4b**, two molecules make up the asymmetric unit. Here it appears that repulsions between the Cp $\alpha$ proton and that of $C_3$ (according to Scheme 2) are minimized by the ferrocene twisting out of the benzopyrone plane by an average angle of 18.3°.

The bulk solids of representative aurones, flavones, and flavonols were furthermore structurally characterized by 2D HMQC and HMBC (Supporting Information). For **2b**, the HMBC experiment showed vinylic proton ($H_{10}$) correlations with the ketone carbon ($C_3$) and $C_\alpha$ of $C_5H_4$, indicating an aurone structure. For **4b**, we observed correlations involving the vinylic $H_3$ with $C_5H_4$−$C_{ipso}$ and aromatic $C_{10}$ and weaker correlations with the aromatic $C_5$, consistent with a flavone structure. The flavonols were differentiated from isoflavanols by the chemical shifts of the C=C group; $C_2$ was observed at around 150 ppm and $C_3$ at around 135 ppm. In the case of the isoflavonol, $C_2$ would be expected to appear around 180 ppm, due to the influence of the OH group, while $C_3$ should appear around 100 ppm.[36]

Table 3. UV/Vis Spectroscopic Data

| | $\lambda_{max}$ (nm) | $\varepsilon$ | | $\lambda_{max}$ (nm) | $\varepsilon$ |
|---|---|---|---|---|---|
| **1a** | 526 | 1740 | **3a** | 497 | 1730 |
| | 342 | 6720 | | 317 | 8840 |
| **1b** | 535 | 2570 | **3b** | 477 | 3180 |
| | 344sh | 9690 | | 368 | 5340 |
| **1c** | 526 | 1790 | **3c** | 497 | 2027 |
| | 351 | 7690 | | 399 | 5170 |
| **2a** | 545 | 2140 | **4a** | 466 | 622 |
| | 386 | 7600 | | 362sh | 1330 |
| **2b** | 559 | 2710 | **4b** | 475 | 935 |
| | 392 | 10040 | | 369 | 1800 |
| **2c** | 545 | 2020 | **4c** | 463 | 979 |
| | 400 | 4720 | | 364sh | 3360 |
| **5a** | 483 | 2150 | **5b** | 494 | 3190 |
| | 348 | 12410 | | 352 | 14190 |

The 2D NMR experiments furthermore allowed the full attribution of the $^1$H and $^{13}$C spectra of all molecules. The chemical shifts of the vinyl proton, vinyl carbon, and quaternary carbon adjacent to the oxo group clearly differentiate **2a**−**c** from **4a**−**c** (Table 2). In the aurone, the vinyl proton and carbon are in the 4-position of the ketone and thus are deshielded compared to the flavone structure, where these atoms are in the 3-position of the ketone. Similarly, the quaternary carbon is in the shielded 3-position in the aurone and the deshielded 4-position in the flavone. While substitution on the phenyl ring of the benzofurone or benzopyrone groups only slightly influences the chemical shifts of characteristic peaks, a given structural isomer can be easily identified by the large difference in chemical shifts.

Likewise, characteristic absorption frequencies in the IR allow the differentiation between the two isomers (Table 2). Contributions of mesomeric canonical structures in the flavone result in C=O and C=C bond orders of less than 2. Therefore, in the flavone geometry, the C=O and C=C stretching frequencies are expected at lower energy than those found in the aurones, which is exactly what is observed.

**UV−Visible Spectroscopy.** One of the most attractive features of these molecules is their strong colors. The prefix "flavo"

comes from the Latin "flavus" (yellow), and indeed, with the exception of the anthocyanidins, most organic flavonoids are yellow to orange in color, due to $\pi \rightarrow \pi^*$ transitions. The addition of ferrocene gives rise to a gamut of colors: in solution ferrocenyl chalcones are red-violet, ferrocenyl aurones are indigo-violet, ferrocenyl ynones are red, and ferrocenyl flavones and flavonols are red-orange. The relatively large extinction coefficients and previous studies on donor−acceptor complexes of ferrocene[37] suggest that the transition in the visible region has the nature of a MLCT transition, that is, from a molecular orbital based primarily on ferrocene to one involving the $\pi^*$ orbitals of the ligand (Table 3). It is likely that the substituted Cp ring contributes significantly to the frontier orbitals, in that the molar absorptivity of this transition is lower in the flavone series, consistent with the X-ray structure that shows the ferrocene being twisted out of the plane created by the ligand. In general, electron-withdrawing groups decrease the energy of $\lambda_{max}$ relative to the unsubstituted molecule. This is likely due to a stabilization of the $\pi^*$ molecular orbital by electron-withdrawing groups, consistent with previous theoretical calculations for organic chalcones.[38] The higher energy bands are similar in energy to those found in organic chalcones and can be attributed to $\pi \rightarrow \pi^*$ transitions on the ligand.

## EXPERIMENTAL SECTION

**General Remarks.** All reactions were carried out under argon. THF was distilled over sodium/benzophenone, and all other chemical reagents and solvents were used without further purification. Silica gel chromatography was performed with Merck 60 (40−63 $\mu$m) silica. $^1$H and $^{13}$C NMR spectra were recorded with a 300 or 400 MHz Bruker Avance spectrometer, and $\delta$ are given in ppm and referenced to the residual solvent peaks ($^1$H, $\delta$ 7.26 and $^{13}$C{$^1$H}, $\delta$ 77.1 for $CDCl_3$ and $^1$H, $\delta$ 2.05 and $^{13}$C{$^1$H}, $\delta$ 29.7 for acetone-$d_6$). Mass spectra were measured on a Thermoscientific ITQ1100 spectrometer using the direct exposure probe method by the mass spectrometry service at the École Nationale Supérieure de Chimie de Paris. High-resolution mass spectra were obtained by ESI/ESCI-TOF using a Waters LCT Premier XE or a Thermo Fischer LTQ-Orbitrap XL. Melting points were determined using an Electrothermal 9100 apparatus. IR data were collected on a JASCO FT/IR-4100 using a KBr pellet.

**Synthesis and Characterization of Ferrocenyl Chalcones 1a−c.** The synthesis and characterization of compounds **1a−c** have been previously described.[24,39]

**Synthesis and Characterization of Ferrocenyl Aurones 2a−c.** Ferrocene chalcone **1** (200 mg) was dissolved in pyridine. After stirring for 5 min at room temperature, $Hg(OAc)_2$ (2.5 equiv) was added, and the mixture was stirred at reflux until the starting chalcone was consumed (2−3 h). The reaction mixture was poured into $H_2O$ and 12 M HCl, extracted with $CH_2Cl_2$, and washed with water. The organic phase was dried over $MgSO_4$, filtered, and evaporated. The product was purified using a silica gel column, with petroleum ether/dichloromethane, 1/1, as an eluent. Compounds **2a** and **2b** were previously synthesized using AgOTf;[24] here the yields of these compounds synthesized by the above method are reported with their fully attributed $^1$H and $^{13}$C NMR spectra.

**(*Z*)-2-(Ferrocenylidene)benzofuran-3-one, 2a.** Violet solid, 150 mg, 75%, $R_f$ = 0.36 (silica gel, hexanes/EtOAc, 3/1). $^1$H NMR (400 MHz; $CDCl_3$): $\delta$ 4.19 (s, 5H, $C_5H_5$), 4.56 (t, 2H, $^3J$ = 2.0 Hz, $H_\beta$), 4.88 (t, 2H, $^3J$ = 2.0 Hz, $H_\alpha$), 6.90 (s, 1H, $H_{10}$), 7.18−7.22 (m, 1H, $H_5$), 7.30 (d, 1H, $^3J$ = 7.8 Hz, $H_7$), 7.62−7.66 (m, 1H, $H_6$), 7.81 (d, 1H, $^3J$ = 7.8 Hz, $H_4$). $^{13}$C NMR (100 MHz; $CDCl_3$): $\delta$ 70.0 ($C_5H_5$), 71.6 ($C_5H_4-C_\alpha$), 71.9 ($C_5H_4-C_\beta$), 75.1 ($C_5H_4-C_{ipso}$), 113.0 ($C_7$), 116.6 ($C_{10}$), 122.7 ($C_9$), 123.1 ($C_5$), 124.6 ($C_4$), 136.2 ($C_6$), 146.1 ($C_2$), 165.5 ($C_8$), 183.0 ($C_3$).

**(*Z*)-5-Bromido-2-(ferrocenylidene)benzofuran-3-one, 2b.** Violet solid, 142 mg, 71%, $R_f$ = 0.33 (silica gel, hexanes/EtOAc, 3/1). $^1$H NMR (400 MHz; acetone-$d_6$): $\delta$ 4.24 (s, 5H, $C_5H_5$), 4.64 (t, 2H, $^3J$ = 1.7 Hz, $H_\beta$), 4.97 (t, 2H, $^3J$ = 1.7 Hz, $H_\alpha$), 6.91 (s, 1H, $H_{10}$), 7.48 (d, 1H, $^3J$ = 8.6 Hz, $H_7$), 7.86 (d, 1H, $^4J$ = 2.0 Hz, $H_4$), 7.89 (dd, 1H, $^3J$ = 8.6 Hz, $^4J$ = 2.0 Hz, $H_6$). $^{13}$C NMR (100 MHz; acetone-$d_6$): $\delta$ 70.6 ($C_5H_5$), 72.4 ($C_5H_4-C_\alpha$), 72.7 ($C_5H_4-C_\beta$), 75.6 ($C_5H_4-C_{ipso}$), 116.1 ($C_7$), 116.2 ($C_{5,}$), 117.6 ($C_{10}$), 125.1 ($C_9$), 127.0 ($C_4$), 139.4 ($C_6$), 146.5 ($C_2$), 164.7 ($C_8$), 181.0 ($C_3$).

**(*Z*)-5-Methoxy-2-(ferrocenylidene)benzofuran-3-one, 2c.** Violet solid, 160 mg, 80%, mp 142 °C, $R_f$ = 0.31 (silica gel, hexanes/EtOAc, 3/1). IR $\nu_{max}$/cm$^{-1}$ 1689 (C═O), 1632 (C═C). $^1$H NMR (300 MHz; $CDCl_3$): $\delta$ 3.83 (s, 3H, OMe), 4.17 (s, 5H, $C_5H_5$), 4.54 (t, 2H, $^3J$ = 1.8 Hz, $H_\beta$), 4.85 (t, 2H, $^3J$ = 1.8 Hz, $H_\alpha$), 6.88 (s, 1H, $H_{10}$), 7.21−7.25 (m, 3H, $H_4$, $H_6$, $H_7$). $^{13}$C NMR (75 MHz; $CDCl_3$): $\delta$ 55.8 (OMe), 69.8 ($C_5H_5$), 71.3 ($C_5H_4-C_\alpha$), 71.6 ($C_5H_4-C_\beta$), 75.0 ($C_5H_4-C_{ipso}$), 104.8 ($C_4$), 113.6 ($C_7$), 116.4 ($C_{10}$) 122.5 ($C_9$), 125.4 ($C_6$), 146.6 ($C_2$), 155.7 ($C_5$), 160.3 ($C_8$), 182.9 ($C_3$). MS (CI $NH_3$): $m/z$ 361.0 ($MH^+$). HRMS (ESI): calcd for $C_{20}H_{16}FeO_3Na^+$ 383.03466, found 383.03411.

**Synthesis and Characterization of Ferrocenyl Ynones 3a−c.** Ferrocene aurone **2** (100 mg) was dissolved in THF and cooled in an acetone/liquid nitrogen bath. Lithium diisopropylamide (1.1 equiv, 2 M in THF) was added, and the solution color changed from deep violet to pale red. The solution was allowed to return to rt, poured into $H_2O$ and 12 M HCl, extracted with EtOAc, and washed with water. The organic phase was dried over $MgSO_4$, filtered, and evaporated. The product was purified using a silica gel column, using petroleum ether/dichloromethane, 1/1, as an eluent.

**1-(2′-Hydroxyphenyl)-3-ferrocenylprop-2-yn-1-one, 3a.** Red solid, 78 mg, 78%, mp 130 °C, $R_f$ = 0.39 (silica gel, hexanes/EtOAc, 3/1). IR: $\nu_{max}$/cm$^{-1}$ 2175 (C≡C), 1612 (C═O). $^1$H NMR (400 MHz; $CDCl_3$): $\delta$ 4.30 (s, 5H, $C_5H_5$), 4.47 (t, 2H, $^3J$ = 1.7 Hz, $C_5H_4$), 4.71 (t, 2H, $^3J$ = 1.7 Hz, $C_5H_4$), 6.96−7.02 (m, 2H, $H_{3'}$, $H_{5'}$), 7.52 (td, 1H, $^3J$ = 8.2 Hz, $^4J$ = 1.3 Hz, $H_{4'}$), 8.05 (dd, 1H, $^3J$ = 8.2 Hz, $^4J$ = 1.3 Hz, $H_{6'}$). $^{13}$C NMR (100 MHz; $CDCl_3$): $\delta$ 59.8 ($C_5H_4-C_{ipso}$), 70.7 ($C_5H_5$), 71.3 ($C_5H_4$), 73.4 ($C_5H_4$), 84.5 ($C_2$), 100.2 ($C_3$), 118.2 ($C_{3'}$), 119.4 ($C_{5'}$), 121.0 ($C_{1'}$), 132.9 ($C_{6'}$), 136.7 ($C_{4'}$), 162.8 ($C_{2'}$), 181.9 ($C_1$),. MS (CI $NH_3$): $m/z$ 330 ($MH^+$). HRMS (ESI): calcd for $C_{19}H_{14}FeO_2^+$ 330.03432, found 330.03377.

**1-(5′-Bromido-2′-hydroxyphenyl)-3-ferrocenylprop-2-yn-1-one, 3b.** Red solid, 65 mg, 65%, mp 132 °C, $R_f$ = 0.36 (silica gel, hexanes/EtOAc, 3/1). IR: $\nu_{max}$/cm$^{-1}$ 2179 (C≡C), 1619 (C═O). $^1$H NMR (400 MHz; $CDCl_3$): $\delta$ 4.32 (s, 5H, $C_5H_5$), 4.50 (t, 2H, $^3J$ = 1.8 Hz, $C_5H_4$), 4.74 (t, 2H, $^3J$ = 1.8 Hz, $C_5H_4$), 6.90 (d, 1H, $^3J$ = 8.9 Hz, $H_{3'}$), 7.58 (dd, 1H, $^3J$ = 8.9 Hz, $^4J$ = 2.5 Hz, $H_{4'}$), 8.13 (d, 1H, $^4J$ = 2.5 Hz, $H_{6'}$). $^{13}$C NMR (100 MHz; $CDCl_3$): $\delta$ 59.3, ($C_5H_4-C_{ipso}$), 70.7 ($C_5H_5$), 71.5 ($C_5H_4$), 73.5 ($C_5H_4$), 84.2 ($C_2$), 101.8 ($C_3$), 110.8 ($C_{5'}$), 120.3 ($C_{3'}$), 122.2 ($C_{1'}$), 134.9 ($C_{6'}$), 139.3 ($C_{4'}$), 161.7 ($C_{2'}$), 180.6 ($C_1$). MS (CI $NH_3$): $m/z$ 409.04 ($MH^+$). HRMS (ESI): calcd for $C_{19}H_{13}BrFeO_2^+$ 407.9448 and 409.9428, found 407.9482 and 409.9530.

**1-(5′-Methoxy-2′-hydroxyphenyl)-3-ferrocenylprop-2-yn-1-one, 3c.** Red solid, 73 mg, 73%, mp 120 °C, $R_f$ = 0.33 (silica gel, hexanes/EtOAc, 3/1). IR: $\nu_{max}$/cm$^{-1}$ 2179 (C≡C), 1731 (C═O), $^1$H NMR (400 MHz; acetone-$d_6$): $\delta$ 3.91 (s, 3H, OMe), 4.37 (s, 5H, $C_5H_5$), 4.59 (t, 2H, $^3J$ = 1.9 Hz, $C_5H_4$), 4.84 (t, 2H, $^3J$ = 1.9 Hz, $C_5H_4$), 6.94 (d, 1H, $^3J$ = 9.1 Hz, $H_{3'}$), 7.26 (dd, 1H, $^3J$ = 9.1 Hz, $^4J$ = 3.1 Hz, $H_{4'}$), 7.58 (d, 1H, $^4J$ = 3.1 Hz, $H_{6'}$). $^{13}$C NMR (100 MHz; acetone-$d_6$): $\delta$ 56.0 (OMe), 60.1 ($C_5H_4-C_{ipso}$), 71.3 ($C_5H_5$), 72.2 ($C_5H_4$), 74.0 ($C_5H_4$), 84.6 ($C_2$), 100.9 ($C_3$), 114.8 ($C_{6'}$), 119.7 ($C_{3'}$), 121.0 ($C_{1'}$), 125.9 ($C_{4'}$), 153.1 ($C_{5'}$), 157.8 ($C_{2'}$), 181.8 ($C_1$). MS (CI $NH_3$): $m/z$ 361.11 ($MH^+$). HRMS (ESI): calcd for $C_{20}H_{16}FeO_3^+$ 360.04489, found 360.04422.

**Synthesis and Characterization of Ferrocenyl Flavones 4a−c.** *From Ynone.* Ferrocene ynone **3** (40 mg) was dissolved in EtOH. NaOEt (excess) was added, and the solution was stirred at rt for 24 h, with a color change from red to orange. The reaction mixture was poured into $H_2O$ and 12 M HCl, extracted with $CH_2Cl_2$, and washed with water. The organic phase was dried over $MgSO_4$, filtered, and evaporated. The crude product was purified using a silica gel column, using petroleum ether/dichloromethane, 1/1, as an eluent and was isolated as an orange solid. Yields after purification: 68% (**4a**), 65% (**4b**), and 63% (**4c**).

*From Aurone.* Alternatively, ferrocenyl aurone (30 mg) and potassium cyanide (1.5 equiv) were dissolved in ethanol (25 mL) and stirred at reflux for 2 h; the solution color changed from deep violet to deep red. The solution was then allowed to return to rt before being poured into an aqueous solution of 1 M NaOH (100 mL). The mixture was extracted with EtOAc (3 × 50 mL) and washed with water. The organic phase was dried over $MgSO_4$, filtered, and evaporated, and the crude product was purified using a silica gel column, using petroleum ether/ethyl acetate, 60/40, as an eluent and was isolated as an orange solid. Yields after purification: 88% (**4a**), 75% (**4b**), and 78% (**4c**).

**2-Ferrocenylchromen-4-one, 4a.** Mp 110 °C, $R_f$ = 0.24 (silica gel, hexanes/EtOAc, 3/1). IR: $\nu_{max}/cm^{-1}$ 1631 (C═O), 1605 (C═C). $^1H$ NMR (400 MHz; $CDCl_3$): $\delta$ 4.18 (s, 5H, $C_5H_5$), 4.54 (t, 2H, $^3J$ = 1.8 Hz, $C_5H_4$), 4.88 (t, 2H, $^3J$ = 1.8 Hz, $C_5H_4$), 6.48 (s, 1H, $H_3$), 7.39 (td, 1H, $^3J$ = 7.9 Hz, $^4J$ = 1.1 Hz, $H_6$), 7.51 (dd, 1H, $^3J$ = 7.2 Hz, $^4J$ = 1.1 Hz, $H_8$), 7.63−7.69 (m, 1H, $H_7$), 8.21 (dd, 1H, $^3J$ = 7.9 Hz, $^4J$ = 1.6 Hz, $H_5$). $^{13}C$ NMR (100 MHz; $CDCl_3$): $\delta$ 67.6 ($C_5H_4$), 70.3 ($C_5H_5$), 71.5 ($C_5H_4$), 75.1 ($C_5H_4$−$C_{ipso}$), 105.9 ($C_3$), 117.8 ($C_8$), 124.3 ($C_{10}$), 125.1($C_6$), 125.8 ($C_5$), 133.4 ($C_7$), 156.3 ($C_9$), 168.3 ($C_2$), 177.6 ($C_4$). MS (CI $NH_3$): $m/z$ 330.1 ($MH^+$). HRMS (ESI): calcd for $C_{19}H_{14}FeO_2Na^+$ 353.02409, found 353.02354.

**6-Bromido-2-ferrocenylchromen-4-one, 4b.** Mp 177 °C, $R_f$ = 0.22 (silica gel, hexanes/EtOAc, 3/1). IR: $\nu_{max}/cm^{-1}$ 1643 (C═O), 1612 (C═C). $^1H$ NMR (400 MHz; $CDCl_3$): $\delta$ 4.18 (s, 5H, $C_5H_5$), 4.56 (t, 2H, $^3J$ = 1.9 Hz, $C_5H_4$), 4.87 (t, 2H, $^3J$ = 1.9 Hz, $C_5H_4$), 6.47 (s, 1H, $H_3$), 7.40 (d, 1H, $^3J$ = 8.8 Hz, $H_8$), 7.75 (dd, 1H, $^3J$ = 8.8 Hz, $^4J$ = 2.4 Hz, $H_7$), 8.34 (d, 1H, $^4J$ = 2.4 Hz, $H_5$). $^{13}C$ NMR (100 MHz; $CDCl_3$): $\delta$ 67.6 ($C_5H_4$), 70.4 ($C_5H_5$), 71.8 ($C_5H_4$), 74.6 ($C_5H_4$−$C_{ipso}$), 105.8 ($C_3$), 118.5 ($C_6$), 119.8 ($C_8$), 125.7 ($C_{10}$), 128.5 ($C_5$), 136.3 ($C_7$), 155.1 ($C_9$), 168.8 ($C_2$), 176.0 ($C_4$). MS (CI $NH_3$): $m/z$ 408.9−410.9 ($MH^+$). HRMS (ESI): calcd for $C_{19}H_{13}BrFeO_2^+$ 430.93460 and 432.93256, found 430.93406 and 432.93201.

**6-Methoxy-2-ferrocenylchromen-4-one, 4c.** Mp 140 °C, $R_f$ = 0.20 (silica gel, hexanes/EtOAc, 3/1). IR: $\nu_{max}/cm^{-1}$ 1627 (C═O), ca. 1612(sh) (C═C). $^1H$ NMR (300 MHz; $CDCl_3$): $\delta$ 3.91 (s, 3H, OMe), 4.17 (s, 5H, $C_5H_5$), 4.52 (t, 2H, $^3J$ = 1.7 Hz, $C_5H_4$), 4.87 (t, 2H, $^3J$ = 1.7 Hz, $C_5H_4$), 6.47 (s, 1H, $H_3$), 7.26 (dd, 1H, $^3J$ = 9.1 Hz, $^4J$ = 3.0 Hz, $H_7$), 7.44 (d, 1H, $^3J$ = 9.1 Hz, $H_8$), 7.59 (d, 1H, $^4J$ = 3.0 Hz, $H_5$). $^{13}C$ NMR (75 MHz; $CDCl_3$): $\delta$ 55.9 (OMe), 67.4 ($C_5H_4$), 70.2 ($C_5H_5$), 71.3 ($C_5H_4$), 75.0 ($C_5H_4$−$C_{ipso}$), 104.9 ($C_5$), 105.1 ($C_3$), 119.1 ($C_8$), 123.1 ($C_7$), 124.7 ($C_{10}$), 151.0 ($C_9$), 156.8 ($C_6$), 167.9 ($C_2$), 177.3 ($C_4$). MS (CI $NH_3$): $m/z$ 361.0 ($MH^+$). HRMS (ESI): calcd for $C_{20}H_{16}FeO_3^+$ 383.03466, found 383.03411.

**Synthesis and Characterization of Ferrocenyl Flavanols 5a,b.** Carbonate buffer (15 mL) was added to a solution of ferrocenyl flavone **4** (40 mg) in $CH_2Cl_2$/acetone (2:1, 10 mL) and stirred vigorously at rt. A 5 mL aqueous solution of oxone (0.6 g) was added in four portions every 10 min, and the pH of the solution was checked to ensure that it remained alkaline (pH 9). The consumption of starting material was followed by TLC. After the reaction was complete, the two phases were separated and the aqueous phase was extracted with $CH_2Cl_2$ (3 × 50 mL). The combined organic layer was washed with sodium thiosulfate solution, dried with $MgSO_4$, filtered, and evaporated. The crude product was purified using a silica gel column with petroleum ether/ethyl acetate (80:20) as eluent.

**3-Hydroxy-2-ferrocenylchromen-4-one, 5a.** Orange solid, 33 mg, 80%, mp 160 °C, $R_f$ = 0.28 (silica gel, hexanes/EtOAc, 3/1). IR: $\nu_{max}/cm^{-1}$ 3247 (OH), 1731 (C═O), 1608 (C═C). $^1H$ NMR (400 MHz; $CDCl_3$): $\delta$ 4.17 (s, 5H, $C_5H_5$), 4.54 (t, 2H, $^3J$ = 1.8 Hz, $C_5H_4$), 5.19 (t, 2H, $^3J$ = 1.8 Hz, $C_5H_4$), 7.40 (td, 1H, $^3J$ = 8.0 Hz, $^4J$ = 1.1 Hz, $H_6$), 7.54 (d, 1H, $^3J$ = 7.2 Hz, $H_8$), 7.65−7.70 (m, 1H, $H_7$), 8.24 (dd, 1H, $^3J$ = 8.0 Hz, $^4J$ = 1.6 Hz, $H_5$). $^{13}C$ NMR (100 MHz; $CDCl_3$): $\delta$ 68.7 ($C_5H_4$), 70.0 ($C_5H_5$), 71.0 ($C_5H_4$), 74.2 ($C_5H_4$−$C_{ipso}$), 118.1 ($C_8$), 121.3 ($C_{10}$), 124.5 ($C_5$ or $C_6$), 125.4 ($C_5$ or $C_6$), 132.9 ($C_7$), 136.9 ($C_3$), 150.5 ($C_2$), 155.4 ($C_9$), 171.5 ($C_4$). MS (CI $NH_3$): $m/z$ 347.1 ($MH^+$). HRMS (ESI): calcd for $C_{19}H_{14}FeO_3^+$ 346.0292, found 346.0286.

**6-Bromido-3-hydroxy-2-ferrocenylchromen-4-one, 5b.** Orange solid, 31 mg, 76%, mp 178 °C, $R_f$ = 0.25 (silica gel, hexanes/EtOAc, 3/1). IR: $\nu_{max}/cm^{-1}$ 3309 (OH), 1739 (C═O), 1604 (C═C). $^1H$ NMR (400 MHz; $CDCl_3$): $\delta$ 4.16 (s, 5H, $C_5H_5$), 4.55 (t, 2H, $^3J$ = 1.8 Hz, $C_5H_4$), 5.17 (t, 2H, $^3J$ = 1.8 Hz, $C_5H_4$), 7.43 (d, 1H, $^3J$ = 8.8 Hz, $H_8$), 7.74 (dd, 1H, $^3J$ = 8.8 Hz, $^4J$ = 2.3 Hz, $H_7$), 8.36 (d, 1H, $^4J$ = 2.3 Hz, $H_5$). $^{13}C$ NMR (100 MHz; $CDCl_3$): $\delta$ 68.8 ($C_5H_4$), 70.1 ($C_5H_5$), 71.2 ($C_5H_4$), 73.7 ($C_5H_4$−$C_{ipso}$), 117.8 ($C_6$), 120.0 ($C_8$), 122.7 ($C_{10}$), 127.9 ($C_5$), 135.8 ($C_7$), 137.0 ($C_3$), 151.2 ($C_2$), 154.1 ($C_9$), 170.2 ($C_4$). MS (CI $NH_3$): $m/z$ 425.1 ($MH^+$). HRMS (ESI): calcd for $C_{19}H_{13}BrFeO_3^+$ 423.9397 and 425.9377, found 423.9392 and 425.9371.

## CONCLUSIONS

The sequential synthesis of the first ferrocenyl aurones, flavones, and flavonols has been achieved, making use of ferrocenyl chalcones and ferrocenyl ynones as starting materials. Although these are common precursors in flavonoid chemistry, the ferrocenyl species did not always act similarly to organic flavonoids. For example, treatment of ferrocenyl chalcones with known flavanone, flavone, or flavonol-forming reagents typically resulted in the formation of intractable mixtures. From the starting point of the chalcone, we were however able to selectively obtain ferrocenyl *Z*-aurones possessing electron-withdrawing or electron-donating substituents via the known method using $Hg(OAc)_2$ in pyridine. No intermediate could be observed in the reaction with $Hg(OAc)_2$, possibly due to fast $\beta$ elimination due to the destabilizing influence of the adjacent ferrocene group. A new, very rapid method, applicable only to the formation of ferrocenyl aurones, was also discovered. The specificity of AgOTf for the ferrocenyl chalcones is still not well understood and may involve a radical reaction or elimination. Ferrocenyl flavones were obtained directly from isomerization of ferrocenyl aurones, as previously observed in the organic series, and, originally, via a ferrocenyl ynone intermediate. Production of this intermediate is probably assisted by the destabilizing influence of the ferrocene on the anion resulting from deprotonation of the aurone, while 1,6-cyclization is likewise favored by the greater stability of the anion in the 3-position. Thus, in general, contrary to what is observed in organic flavonoid chemistry, these reactions are all very selective, giving only the desired product in high yield. Ferrocenyl flavonols were further obtained via hydroxylation of the 3-position of the $\alpha,\beta$-unsaturated ketone of the flavones in a biphasic reaction with oxone.

Full structural characterization of representative molecules of each class was undertaken by 2D NMR and/or X-ray crystallography experiments. Aurones and flavones can easily be distinguished by the chemical shifts of their vinyl protons, vinyl carbon, and quaternary carbon peaks, as well as by the stretching frequencies of the C═C and C═O groups. The color of the compounds is a result of a transition occurring between 450 and 600 nm, which can be attributed to a charge transfer from the ferrocene to the planar $\pi^*$ system.

The biological properties of these compounds are currently being studied and will be reported in due course.

## ■ ASSOCIATED CONTENT

**Supporting Information.** HMBC NMR spectra for **2b** and **4b**; selected chemical shifts for **1a**−**c** and the organic analogues. CIF files for **2b**, **3a**, and **4b** have also been deposited with the CDCC, Nos. 787468, 823195, and 823196. This material is available free of charge via the Internet at http://pubs.acs.org.

## ■ AUTHOR INFORMATION

### Corresponding Author

*(M.N.R.) Tel: +33 1 44 27 66 96. Fax: +33 1 44 27 66 96. E-mail: marie-noelle.rager@chimie-paristech.fr. (E.A.H.) Tel: +33 1 44 27 66 98. Fax: +33 1 43 26 00 61. E-mail: elizabeth-hillard@chimie-paristech.fr.

### Author Contributions

⊥These authors contributed equally to the work.

## ■ ACKNOWLEDGMENT

We thank P. Herson for crystallographic characterization and Céline Fosse for mass spectrometry experiments. K.N.T. thanks Association pour la Recherche sur le Cancer for the award of a postdoctoral fellowship; J.P.M. thanks the Ministère de l'Enseignement Supérieur et de la Recherche for support of his studies.

## ■ REFERENCES

(1) Link, A.; Balaguer, F.; Goel, A. *Biochem. Pharmacol.* **2010**, *80*, 1771–1792.

(2) Perez-Vizcaino, F.; Duarte, J. *Mol. Aspects Med.* **2010**, *31*, 478–494.

(3) Bisht, K.; Wagner, K.-H.; Bulmer, A. C. *Toxicology* **2009**, *278*, 88–100.

(4) Kaur, K.; Jain, M.; Kaur, T.; Jain, R. *Bioorg. Med. Chem.* **2009**, *17*, 3229–3256.

(5) Naithani, R.; Huma, L. C.; Holland, L. E.; Shukla, D.; McCormick, D. L.; Mehta, R. G.; Moriarty, R. M. *Mini Rev. Med. Chem.* **2008**, *8*, 1106–1133.

(6) Quideau, S.; Deffieux, D.; Douat-Casassus, C.; Pouységu, L. *Angew. Chem., Int. Ed.* **2011**, *50*, 586–621.

(7) (a) Shanmugam, M.; Kannaiyan, R.; Sethi, G. *Nutr. Cancer* **2011**, *63*, 161–173. (b) Spencer, J. *Proc. Nutr. Soc.* **2010**, *69*, 244–260.

(8) (a) van Staveren, D. R.; Metzler-Nolte, N. *Chem. Rev.* **2004**, *104*, 5931–5985.(b) Hillard, E. A.; Vessières, A.; Jaouen, G. In *TopOrgan*; Springer Verlag: Berlin, 2010; Vol. 32, pp 81−117. (c) Metzler-Nolte, N.; Salmain, M. In *Ferrocenes: Ligands, Materials and Biomolecules*; Stepnicka, P., Ed.; Wiley: New York, 2008; pp 499−639. (d) Snegur, L. V.; Babin, V. N.; Simenel, A. A.; Nekrasov, Yu. S.; Ostrovskaya, L. A.; Sergeeva, N. S. *Russ. Chem. Bull. Int. Ed.* **2010**, *59*, 2167–2178.

(9) Hillard, E. A.; Vessières, A.; Thouin, L.; Jaouen, G.; Amatore, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 285–290.

(10) Spencer, J.; Amin, J.; Wang, M.; Packham, G.; Alwi, S. S. S.; Tizzard, G. J.; Coles, S. J.; Paranal, R. M.; Bradner, J. E.; Heightman, T. D. *Med. Chem. Lett.* **2011**, *2*, 358–362.

(11) Arezki, A.; Brulé, E.; Jaouen, G. *Organometallics* **2009**, *28*, 1606–1609.

(12) Quirante, J.; Dubar, F.; González, A.; Lopez, C.; Cascante, M.; Cortés, R.; Forfar, I.; Pradines, B.; Biot, C. *J. Organomet. Chem.* **2011**, *696*, 1011–1017.

(13) Spencer, J.; Mendham, A. P.; Kotha, A. K.; Richardson, S. C. W.; Hillard, E. A.; Jaouen, G.; Male, L.; Hursthouse, M. B. *Dalton Trans.* **2009**, 918–921.

(14) N'Da, D.; Breytenbach, J.; Smith, P.; Lategan, C. *Arzneimittel-forschung* **2010**, *60*, 627–635.

(15) Hillard, E. A.; Jaouen, G. *Organometallics* **2011**, *30*, 20−27.

(16) (a) Sumathi, S.; Tharmaraj, P.; Sheela, C. D.; Ebenezer, R. *J. Coord. Chem.* **2011**, *64*, 1707–1717. (b) Baluja, S.; Movaliya, J.; Bhalodia, R. *J. Instit. Chem. (India)* **2009**, *81*, 102–109. (c) Devi, J. M.; Tharmaraj, P.; Ramakrishnan, S. K.; Ramachandran, K. *Mater. Lett.* **2008**, *62*, 852–856. (d) Li, X.; Sun, H.; Floerke, U.; Klein, H.-F. *Organometallics* **2005**, *24*, 4347–4350. (e) Natarajan, C.; Palaniandavar, M. *J. Indian Chem. Soc.* **1983**, *60*, 1–6. (f) Tambatkar, G. D.; Meshram, Y. K.; Gadpayale, M. R.; Bhutada, P. G.; Kurhade, G. H. *Asian J. Chem.* **2008**, *20*, 5414–5418. (g) Karamunge, K. G.; Vibhute, Y. B. *Pol. J. Chem.* **2008**, *82*, 559–564.

(17) (a) Chen, W.; Sun, S.; Wei, C.; Liang, Y.; Song, J. *J. Mol. Struct.* **2009**, *918*, 194–197. (b) Kostyuk, V. A.; Potapovich, A. I.; Kostyuk, T. V.; Cherian, M. G. *Cell. Mol. Biol.* **2007**, *53*, 62–69. (c) de Souza, R. F. V.; De Giovani, W. F. *Spectrochim. Acta, Part A* **2005**, *61A*, 1985–1990.

(18) Kostyuk, V. A.; Potapovich, A. I.; Vladykovskaya, E. N.; Korkina, L. G.; Afanas'ev, I. B. A. *Arch. Biochem. Biophys.* **2001**, *385*, 129–137.

(19) (a) Zutin, K.; Nogueira, V. M.; Mauro, A. E.; Melnikov, P.; Iluykhin, A. *Polyhedron* **2001**, *20*, 1011–1016. (b) Kuramshin, A. I.; Karpenko, E. A.; Cherkasov, R. A. *Russ. J. Gen. Chem.* **2001**, *71*, 191–195.

(20) (a) Anson, C. E.; Creaser, C. S.; Malkov, A. V.; Mojovic, L.; Stephenson, G. R. *J. Organomet. Chem.* **2003**, *668*, 101–122. (b) Malkov, A. V.; Mojovic, L.; Stephenson, G. R.; Turner, A. T.; Creaser, C. S. *J. Organomet. Chem.* **1999**, *589*, 103–110.

(21) Wu, X.; Tiekink, E. R. T.; Kostetski, I.; Kocherginsky, N.; Tan, A. L. C.; Khoo, S. B.; Wilairat, P.; Go, M.-L. *Eur. J. Pharm. Sci.* **2006**, *27*, 175–187.

(22) Hauser, C. R.; Lindsay, J. K. *J. Org. Chem.* **1957**, *22*, 482–485.

(23) (a) Zsoldos-Mady, V.; Csampai, A.; Szabo, R.; Meszaros-Alapi, E.; Pasztor, J.; Hudecz, F.; Sohar, P. *ChemMedChem* **2006**, *1*, 1119–1125. (b) Wu, X.; Wilairat, P.; Go, M. L. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2299–2302. (c) Ferle-Vidovic, A.; Poljak-Blazi, M.; Rapic, V.; Skare, D. *Cancer Biother. Radiopharm.* **2000**, *15*, 617–624.

(24) Monserrat, J.-P.; Chabot, G. G.; Hamon, L.; Quentin, L.; Scherman, D.; Jaouen, G.; Hillard, E. A. *Chem. Commun.* **2010**, *46*, 5145–5147.

(25) Gleiter, R.; Seeger, R.; Binder, H.; Fluck, E.; Cais, M. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 1028–1030.

(26) (a) Agrawal, N. N.; Soni, P. A. *Indian J. Chem.* **2006**, *45B*, 1301–1303. (b) Grundon, M. F.; Stewart, D.; Watts, W. E. *J. Chem. Soc., Chem. Commun.* **1975**, 772–773. (c) Grundon, M. F.; Stewart, D.; Watts, W. E. *Proc. R. Ir. Acad.* **1989**, *89B*, 185–196. (d) Sekizaki, H. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1407–1409. (e) Lévai, A.; Tõkés, A. *Synth. Commun.* **1982**, *12*, 701–707. (f) Kurosawa, K.; Higuchi, J. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 1132–1136. (g) Kurosawa, K. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 1456–1458.

(27) (a) Rao, Y. K.; Fang, S.-H.; Tzeng, Y.-M. *Bioorg. Med. Chem.* **2005**, *13*, 6850–6855. (b) Kasahara, A.; Izumi, T.; Oshima, M. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 2526–2528. (c) Meyer-Dayan, M.; Bodo, B.; Deschamps-Vallet, C.; Molho, D. *Tetrahedron Lett.* **1978**, *19*, 3359–3360.

(28) Fitzgerald, D. M.; O'Sullivan, J. F.; Philbin, E. M.; Wheeler, T. S. *J. Chem. Soc.* **1955**, 860–862.

(29) Costa, A. M. B. S. R. C. S.; Dean, F. M.; Jones, M. A.; Varma, R. S. *J. Chem. Soc., Perkin Trans. 1* **1985**, 799–808.

(30) Garcia, H.; Iborra, S.; Primo, J.; Miranda, M. A. *J. Org. Chem.* **1986**, *51*, 4432–4436.

(31) Harkat, H.; Blanc, A.; Weibel, J.-M.; Pale, P. *J. Org. Chem.* **2008**, *73*, 1620–1623.

(32) (a) Algar, J.; Flynn, J. P. *Proc. R. Ir. Acad., Sect. B* **1934**, *B42*, 1–8. (b) Oyamada, B. *J. Chem. Soc. Japan* **1934**, *55*, 1256–1261.

(33) Adam, W.; Golsch, D.; Hadjiarapoglou, L. *J. Org. Chem.* **1991**, *56*, 7292–7297.

(34) El Sous, M.; Khoo, M.; Holloway, G.; Owen, D.; Scammells, P.; Rizzacasa, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 7835–7838.

(35) (a) Venkateswarlu, S.; Panchagnula, G. K.; Guraiah, M. B.; Subbaraju, G. V. *Tetrahedron* **2005**, *61*, 3013–3017. (b) Venkateswarlu, S.; Panchagnula, G. K.; Gottumukkala, A. L.; Subbaraju, G. V. *Tetrahedron* **2007**, *63*, 6909–6914.

(36) Breitmaier, E.; Voelter, W., Eds. *Carbon-13 NMR Spectroscopy*; VCH Publishers Inc.: Deerfield Beach, 1987.

(37) Barlow, S.; Marder, S. R. *Chem. Commun.* **2000**, 1555–1562.

(38) Xue, Y.; Mou, J.; Liu, Y.; Gon, X.; Yang, Y.; An, L. *Cent. Eur. J. Chem.* **2010**, *8*, 928–936.

(39) Monserrat, J.-P.; Al-Safi, R. I.; Tiwari, K. N.; Quentin, L.; Chabot, G. G.; Vessières, A.; Jaouen, G.; Neamati, N.; Hillard, E. A. *Bioorg. Med. Chem. Lett.* **2011**, in press, doi: 10.1016/j.bmcl.2011.07.078.