COMMUNICATION

Ferrocene-Decorated Phenol Derivatives by Trapping of *ortho*-Quinone Methide Intermediates with Ferrocene

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Dedication ((optional))

Abstract: We report the $InCl_3$-catalyzed reaction of ferrocene with *ortho*-hydroxybenzyl alcohols which represents a convenient route for the synthesis of ferrocenyl phenols. This carbon-carbon bond forming process is believed to proceed through an *ortho*-quinone methide intermediate that can be intercepted by ferrocene through a Friedel-Crafts like process. Preliminary cytotoxic screening carried out on several cancer cell lines revealed that some of the compounds exhibit moderate cytotoxicity.

Introduction

Since its discovery in 1951,[1] no other organometallic compound has drawn as much attention from the chemical community as ferrocene.[2] In particular, recent decades have witnessed impressive achievements in the field of ferrocene functionalization. In this regard, although transition metal-catalyzed C-H bond functionalization has very recently evolved into a powerful strategy,[3] classical methodologies such as Friedel-Crafts-type electrophilic substitution reactions[4] or a sequence of initial metallation followed by reaction with an electrophilic reagent[5] have proved extremely useful. Very likely, a major driving force for most of these developments has been the countless applications displayed by functionalized ferrocenes in diverse fields. Indeed, functionalized ferrocenes are key components in ligands widely used in catalysis,[6] polymers and materials,[7] molecular-based devices,[8] etc. Ferrocene derivatives are also of steadily increasing importance in medicinal organometallic chemistry.[9] Indeed, a number of ferrocene derivatives have been reported to display relevant activity (Figure 1). For example, ferroquine, a ferrocene-based analogue of chloroquine, was found to display promising antimalarial properties.[10] Several contributions have also demonstrated the potential of some ferrocene derivatives in cancer therapeutics.[11] In fact, several ferrocenyl phenols are reported to be highly active against several cancer cell lines. In particular, ferrocifens developed by Jouen and co-workers, have been extensively studied, showing promising results for breast cancer.[12] On the basis of electrochemical and chemical oxidation studies, a new mode of action involving ferrocenyl quinone methides has been proposed for these ferrocenyl phenols.[13] Although less studied, unconjugated ferrocenyl diphenols have also found to display significant antitumoral properties. [14,15]

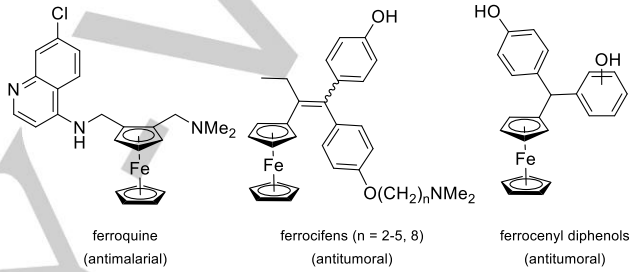

Figure 1. Ferrocene-based organometallic drugs.

On the other hand, *ortho*-quinone methides (*o*-QMs) are highly reactive intermediates that have found a wealth of synthetic applications.[16] Generated *in situ* from different precursors, they exhibit a rich chemistry that resembles that of unsaturated carbonyl compounds. In fact, they are reactive 4π partners in [4+n] cycloaddition reactions[17] and excellent Michael acceptors towards carbo- and heteronucleophiles.[18] In some cases, these transformations have been conducted in an asymmetric manner.[19]

Given our ongoing interest in functionalization of ferrocene derivatives based on the generation and subsequent trapping of highly electrophilic species,[20] we posited that *o*-QMs could be intercepted by ferrocene through a Friedel-Crafts-type reaction, thus delivering ferrocene derivatives featuring a phenolic moiety. Since, as stated before, phenol groups endow several ferrocene derivatives with therapeutic properties, our proposal was not only synthetically appealing, but also potentially relevant in the field of medicinal organometallic chemistry. Consequently, herein we report the Lewis acid-catalyzed reaction of *o*-hydroxybenzyl alcohols with ferrocene as a convenient route to ferrocene-decorated phenol derivatives. Control experiments support the participation of *o*-QMs, which may be subsequently involved in a Friedel-Crafts-type reaction. A preliminary study demonstrates that some of the prepared ferrocene derivatives are cytotoxic against various cancer cell lines.

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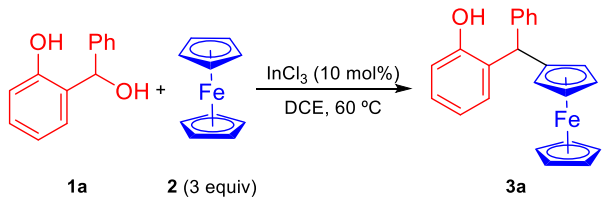
Results and Discussion

Using *o*-hydroxybenzyl alcohol **1a** as a model substrate, we first examined its reaction with ferrocene (**2**) in the presence of different promoters for the generation of the required *ortho*-quinone methide intermediate (Table 1). To our delight, we found that heating a solution of **1a** (1 equiv) and **2** (3 equiv) in the presence of 10 mol% of $InCl_3$ in 1,2-dichloroethane (DCE) at 60 ºC afforded the targeted functionalized ferrocene derivative **3a** in 64% isolated yield (Table 1, entry 1).

Table 1. Optimization of reaction conditions[a)]



1a **2** (3 equiv) **3a**

Entry	Conditions	yield (%)[b)]
1	standard conditions	64
2	No $InCl_3$	-
3	InI_3 instead of $InCl_3$	-
4	$In(OTf)_3$ instead of $InCl_3$	33
5	$AgSbF_6$ instead of $InCl_3$	-
6	$ZnCl_2$ instead of $InCl_3$	-
7	$Sc(OTf)_3$ instead of $InCl_3$	-
8	$[Cu(CH_3CN)_4][BF_4]$ instead of $InCl_3$	-
9	50 mol% of TFA at rt	-
10	10 mol % of TfOH at rt	-
11	50 mol % of TfOH at rt	20
12	100 mol% of TfOH at rt	-
13	5 mol% instead of 10 mol%	5
14	20 mol% instead of 10 mol%	38
15	rt instead of 60 ºC	-
16	Tol, MeOH or THF instead of DCE	-
17	1.5 equiv instead of 3 equiv	36

[a)] These exploratory experiments were performed on a 0.1 mmol scale. [b)] Isolated yield after chromatographic purification (silica gel; hexanes/ethyl acetate 5:1).

A control experiment demonstrated that no reaction occurred in the absence of catalyst (entry 2). On the other hand, under otherwise similar conditions, InI_3 and $In(OTf)_3$ displayed a lower activity (entries 3 and 4). Other Lewis or Brønsted acids proved ineffective in promoting the formation of the desired functionalized ferrocene derivative (entries 4-12). Various reaction conditions were tested using $InCl_3$ as promoter (entries 13-17). Thus, conducting the reaction with a catalyst loading of 5 mol% resulted in a decreased yield of the desired product **3a**, as did the use of 20 mol% (entries 13 and 14). On the other hand, $InCl_3$ (10 mol%) was completely ineffective at room temperature and the starting materials were recovered unchanged (entry 15). Various solvents were also tested (entry 16). Toluene, methanol or THF were completely ineffective in the present reaction. Finally, it was found that the use of 3 equivalents of ferrocene was required in order to obtain a moderate yield of the coupling product. In fact, the use of only 1.5 equivalents of ferrocene led to a significant decrease in yield (compare entries 1 and 17, 64 *vs* 36%). The structure of ferrocene **3a** was ascertained by NMR spectroscopy and X-ray analysis (Figure 2).[21] The crystallographic study not only confirmed the initially proposed structure but also revealed some interesting structural features.[22]

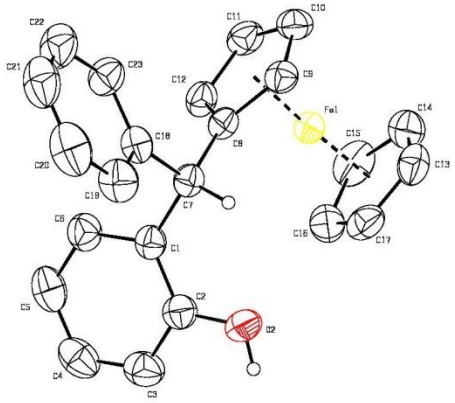
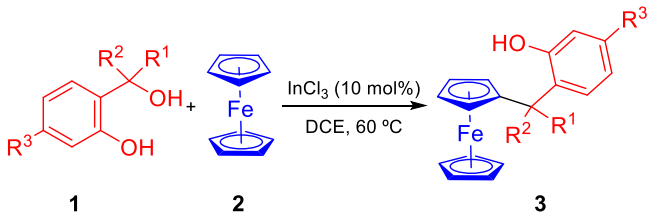


Figure 2. X-ray structure of ferrocene derivative **3a**. Thermal ellipsoids are drawn at the 30% probability level. Hydrogen atoms are excluded, except those bonded to C7 (H7) and O2 (H2O).

Having demonstrated the validity of our hypothesis and with suitable conditions in hand for the reaction of **1a** and ferrocene, our attention turned to assess the scope of this coupling process (Table 2). First, we found that *o*-hydroxybenzyl alcohols **1b**-**d** (R^1 = tolyl, $R^2 = R^3 = H$) with electron-neutral aryl groups installed in the benzylic position are suitable substrates for this transformation. Interestingly, all three isomeric substrates performed comparably, furnishing the desired ferrocene-containing unsymmetrical triarylmethane derivatives **3b**-**d** in moderate isolated yields (60-68%). In contrast, the reaction was less efficient with a strongly electron-donating substituent on the aromatic ring (**1e**; R^1 = *p*-$MeOC_6H_4$, $R^2 = R^3 = H$) providing the corresponding ferrocenyl phenol derivative **3e** in a significantly lower yield. Substrates having alkyl groups in the benzylic position were also investigated. Both primary and secondary alkyl groups were well tolerated as demonstrated by the synthesis of ferrocene derivatives **3f**-**i** in moderate isolated yields (41-64%). However, a substrate bearing a tertiary group (**1j**; R^1 = ^{t}Bu, $R^2 = R^3 = H$)

reacted more sluggishly, affording ferrocene derivative **3j** in a modest yield of 28%. A substrate featuring an unsaturated group (**1k**; R^1 = allyl, R^2 = R^3 = H) posed no problems affording the expected coupling product in acceptable yield. On the other hand, substitution in the benzylic position is not mandatory as judged by the formation of ferrocene derivative **3l** in 48% isolated yield when the parent substrate (**1l**; R^1 = R^2 = R^3 = H) was subjected to the standard conditions. Additionally, a disubstituted substrate (**1m**; R^1 = R^2 = Me, R^3 = H) was found to undergo the coupling to give ferrocene derivative **3m** in synthetically useful yield. Finally, the reaction could be extended to substrates with additional substitution at the aryl backbone (substrate **1m**; R^1 = R^2 = H, R^3 = MeO). Thereby, the expected functionalized ferrocene **3n** was obtained in 41% yield.

Table 2. $InCl_3$-catalyzed synthesis of ferrocene derivatives **3**.[a)]

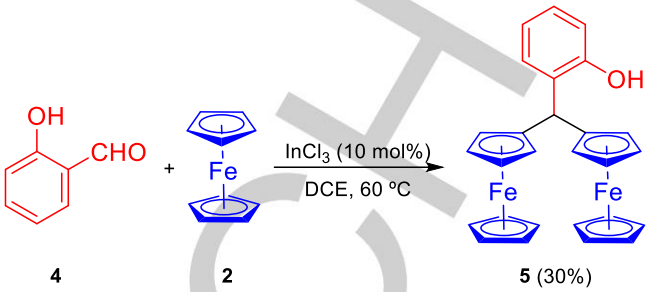


1 **2** **3**

entry	R^1	R^2	R^3	**3**	yield (%)[b)]
1	Ph	H	H	**3a**	64
2	*o*-MeC_6H_4	H	H	**3b**	64
3	*m*-MeC_6H_4	H	H	**3c**	68
4	*p*-MeC_6H_4	H	H	**3d**	60
5	*p*-$MeOC_6H_4$	H	H	**3e**	28
6	Me	H	H	**3f**	41
7	Et	H	H	**3g**	64
8	^{n}Bu	H	H	**3h**	56
9	^{i}Pr	H	H	**3i**	48
10	^{t}Bu	H	H	**3j**	28
11	allyl	H	H	**3k**	52
12	H	H	H	**3l**	48
13	Me	Me	H	**3m**	56
14	H	H	OMe	**3n**	41

[a)] Reaction conditions: **1** (0.2 mmol), **2** (0.6 mmol), $InCl_3$ (10 mol%), DCE, 60 °C.
[b)] Isolated yields.

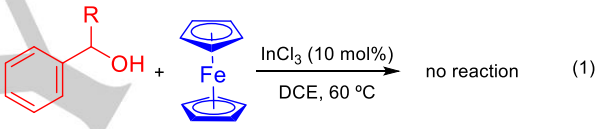
The results obtained with *o*-hydroxybenzyl alcohols prompted us to test whether this coupling protocol might also be suitable for the synthesis of derivatives featuring a diferrocenylmethyl moiety as well. This goal was achieved by using salicylaldehyde (**4**) and an excess (4 equiv) of ferrocene (**2**), which, under the typical reaction conditions (10 mol% of $InCl_3$, DCE, 60 °C), gave 2-(diferrocenylmethyl)phenol derivative **5**, albeit in low yield (Scheme 1).



4 **2** **5** (30%)

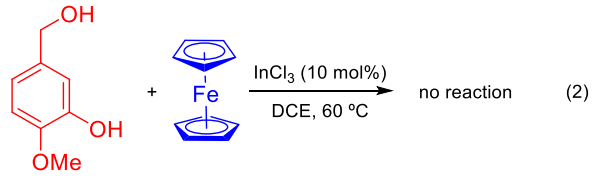
Scheme 1. Synthesis of diferrocenylmethylphenol derivative **5**.

A series of experiments were conducted to gain insight into this coupling reaction. First, under standard reaction conditions, benzylic alcohol (**6a**, R^1 = R^2 = H) was found to be an unproductive reaction partner (Eq 1). A similar outcome was obtained with benzydryl alcohol (**6b**, R^1 = Ph; R^2 = H). These results would rule out a direct Lewis acid-promoted displacement of the hydroxyl group.[23]



6a (R = H)
6b (R = Ph)
2

Next, we evaluated the reactivity toward ferrocene of substrate **7** featuring the phenolic OH group in *meta*-position (Eq 2). Under standard conditions (10 mol% of $InCl_3$, DCE, 60 °C), no reaction occurred, thus demonstrating that a phenolic OH group in the *ortho*-position is critical for a successful outcome.



7 **2**

Taken together, these control experiments would lend support to the participation of *ortho*-quinone methides as key intermediates. Subsequent Lewis acid activation of the quinone methide would provide a highly electrophilic species that would react with ferrocene through a Friedel-Crafts type event.

As stated before, a number of ferrocenyl phenols have been reported to display significant antitumoral properties. For this reason, a preliminary evaluation on the cytotoxic activity of some of the ferrocene derivatives **3** was performed. As shown in Table 3, some compounds display cytotoxic activity on a number of cancer cell lines.[24] First, the activity on A2780 ovarian cancer cell

line was evaluated. Compounds **3a**, **3f** and **3g** showed significant toxicity (IC_{50} of 2.68, 1.66 and 1.86 μM, respectively). We also measured the IC_{50} values on A549 lung cancer cells. Once again, compounds **3a** and **3f** showed moderate toxicity (IC_{50} of 2.77 and 1.36 μM, respectively). In contrast, ferrocene derivative **3g** showed lower toxicity (IC_{50} of 5.96 μM). Interestingly, the OH group seems to play a crucial role on the cytotoxicity since the methoxy derivative **3a**-**Me**[25] showed no significant toxicity on both cancer cell lines (IC_{50} of > 10 μM).

Table 3. IC_{50} [μM] values for selected ferrocenyl compounds on different cell lines.[a)]

	3a	3f	3g	3a-Me
A2780	2.68	1.66	1.86	> 10
A549	2.77	1.36	5.96	> 10

[a)] Measured after 72 h of culture

Conclusions

We have developed an easy and direct synthesis of ferrocene-containing phenol derivatives that makes use of simple and readily available starting materials. In most cases, this C-H bond functionalization takes place in synthetically useful yields and under mild reactions conditions. Control experiments support the participation of *o*-QM intermediates, which would be subsequently intercepted by ferrocene. Although further evaluation is required, a preliminary study demonstrated that some of the ferrocene derivatives prepared display significant cytotoxicity. In our opinion, the easy access to these phenol-containing ferrocene derivatives could pave the way for the development of more active derivatives of this promising class of organometallic compounds.

Experimental Section

Representative Procedure (3a): $InCl_3$ (4.4 mg, 0.02 mmol, 10 mol%) was added to a solution of *o*-hydroxybenzyl alcohol **1a** (40 mg, 0.2 mmol) and ferrocene **2** (111.6 mg, 0.6 mmol) in 1,2-dichloroethane (2 mL). The mixture was stirred at 60 ºC for 2 h (disappearance of **1a** checked by TLC). Removal of solvent and chromatographic purification (silica gel, hexanes/ethyl acetate 5:1) afforded compound **3a** (47.1 mg, 64%) as a yellow solid (m. p. = 109- 110 ºC). Crystals of compound **3a** suitable for X-ray analysis were obtained from diffusion of pentane into dichloromethane at – 20 ºC. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.95-396 (m, 1H), 4.08 (s, 5H), 4.14-4.16 (m, 1H), 4.19-4.21 (m, 1H), 4.22-4.23 (m, 1H), 5.43 (s, 1H), 6.77 (dd, *J* = 1.1, 8.0 Hz, 1H), 6.88 (td, *J* = 1.1, 7.5 Hz, 1H), 7.03 (dd, *J* = 1.7, 7.7 Hz, 1H), 7.12 (td, *J*= 1.7, 8.0 Hz, 1H), 7.24-7.37 (m, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 46.0 (CH), 67.6 (CH), 68.1 (CH), 68.6 (CH), 68.8 (CH), 69.1 (CH), 90.7 (C), 126.6 (CH), 127.7 (CH), 128.3 (CH), 130.0 (CH), 131.6 (C), 143.2 (C), 153.0 (C); HRMS (EI) calculated for $[C_{23}H_{20}FeO]^+$ (M^+): 368.0864, found 368.0856.

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Keywords: Ferrocene • *ortho*-quinone methides • phenol • Friedel-Crafts • cytotoxicity

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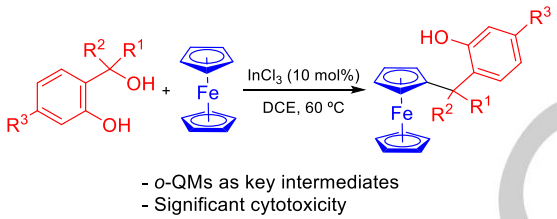
[24] For the sake of comparison, NIH 3T3 cells were used as normal control cell line.

[25] Ferrocene **3a-Me** was prepared in 62% isolated yield by methylation of **3a** with methyl iodide in the presence of sodium hydride.

COMMUNICATION

The $InCl_3$-catalyzed reaction of *ortho*-hydroxybenzyl alcohols with ferrocene provided ferrocenyl phenols. Control experiments support the participation of *ortho*-quinone methides as key intermediates. A preliminary study revealed that some of the functionalized ferrocene derivatives prepared display significant cytotoxicity against various cancer cell lines.



- *o*-QMs as key intermediates
- Significant cytotoxicity

Ferrocene functionalization*

*Silvia González-Pelayo, Enol López, Javier Borge, Noemí de-los-Santos-Álvarez, Luis A. López**

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*one or two words that highlight the emphasis of the paper or the field of the study

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