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FULL PAPER

# Enantioselective Synthesis of Planar Chiral Ferrocifens that Show Chiral Discrimination in Antiproliferative Activity on Breast Cancer Cells

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**Abstract:** The design and first enantioselective synthesis of a series of chiral ferrocifens and ferrociphenols was realised via enantioselective palladium-catalysed intramolecular direct C-H bond activation followed by McMurry coupling. Biological evaluation revealed moderate anticancer activities on breast cancer cells and evidence of chiral discrimination between enantiomers. Treatment of these novel ferrocifens with $Ag_2O$ revealed that these systems are unable to form a neutral quinone methide, yet still demonstrate marked antiproliferative properties versus both the hormone-dependent MCF-7 and hormone-independent MDA-MB-231 cell lines. This bioactivity arises from two mechanisms: Fenton-type chemistry and the anti-estrogenic activity associated with the tamoxifen-like structure.

## Introduction

Despite its world-wide status as the most widely prescribed medication to combat breast cancer, tamoxifen **1a** (Figure 1) is only efficacious against hormone-dependent cancer cell lines that over-express estrogen receptors (ER+), which make up 70% of all breast cancers.[1] The remaining 30%, however, are impervious to treatment with selective estrogen receptor modulators (SERMs) such as tamoxifen and often require the use of harsh non-targeted therapies. Ferrociphenols, **2**, and ferrocifens, **3**, (Figure 1), are ferrocene-containing analogues of tamoxifen which have been extensively investigated in the last 25 years due to their dramatic antiproliferative activity not only against ER+ cell lines, but also hormone-independent (ER-) cancers.[2]

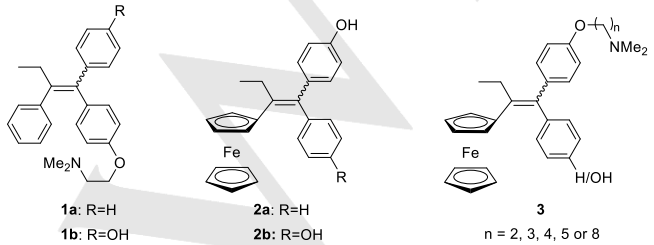
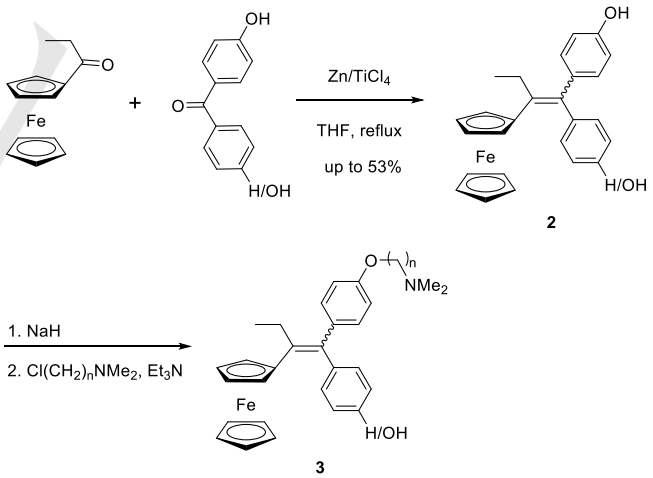



**Figure 1.** Structures of tamoxifen, **1a**, hydroxytamoxifen (OH-Tam) 1b, ferrociphenols, **2**, and ferrocifens, (Fc-Tam and Fc-OH-Tam) **3**.

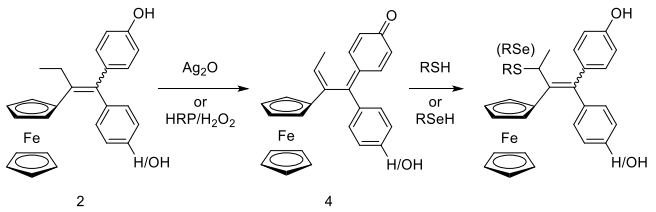
In the realm of bioorganometallic chemistry,[3-8] the ferrocifen system continues to attract significant attention.[9-16] These molecules possess a ferrocenyl-ene-*p*-phenol motif,[17,18] and a basic dimethylaminoalkoxy chain, as in 3. They are readily prepared by McMurry coupling of a ferrocenyl ketone and an appropriate benzophenone, typically in low to moderate yield (10-53%) followed by incorporation of the basic chain (Scheme 1).[19,20] Subsequently, it was found that in many cases the precursor ferrociphenols, 2, which lack the basic side chain, also exhibit marked antiproliferative properties.[21]




**Scheme 1.** Preparation of ferrociphenols, **2**, and ferrocifens, **3**.

Ferrociphenols operate not only as the result of reversible redox of the ferrocenyl moiety ($Fe^{2+} \leftrightarrow Fe^{3+}$) which leads to the generation of reactive oxygen species (ROS), in particular hydroxyl radicals, but also by the formation of quinone methides (QMs) as primary metabolites.[2,22-24] These QMs are highly electrophilic and react with overexpressed nucleophilic peptides or proteins in the cell, such as those bearing thiols or selenols (Scheme 2), and can lead to cell death by interference with oxidative stress or inactivation of enzymes.[25] Treatment of

ferrociphenols or ferrocifens, either chemically with $Ag_2O$, or enzymatically by incubation with horseradish peroxidase (HRP) or rat liver microsomes and NADPH, provides a convenient laboratory route to the corresponding QMs.[22-24]




2 4

**Scheme 2**. Reaction of a ferrocenyl quinone methide with a thiol (e.g. glutathione) or a selenol (e.g. thioredoxin reductase).

A wide range of ferrocifens and ferrociphenols (> 300) has been prepared and their bioactivity evaluated. In the early phase of these studies, the molecules all possessed an ethyl substituent, as in hydroxytamoxifen – the current first line adjuvant therapy for hormone-dependent breast cancers – on which they were originally modelled.[1] Subsequent work revealed that incorporation of hydroxyalkyl[22-24] (or, even better, imidoalkyl[26,27]) substituents dramatically lowered $IC_{50}$ values into the low nanomolar range, and also greatly extended their spectrum of activity to include lung, prostate, renal, colon, ovarian and CNS tumours, as well as leukemia and melanomas.[24] However, in all cases, except for those in which the ferrocenyl moiety possessed a polymethylene chain, as in **5**, [28] and also the ansa systems, **6**,[29-32] the ferrocenyl unit remained constant. We here report the first such molecules in which the ferrocene moiety is now derived from ferroceno[2,3]indene, as in **7**. The novelty here is that the precursor ketone can be conveniently prepared in either enantiomerically pure form prior to its use in the McMurry coupling procedure. Hence, a number of optically active ferrocifens and ferrociphenols have been synthesised for the first time and their bioactivity evaluated.

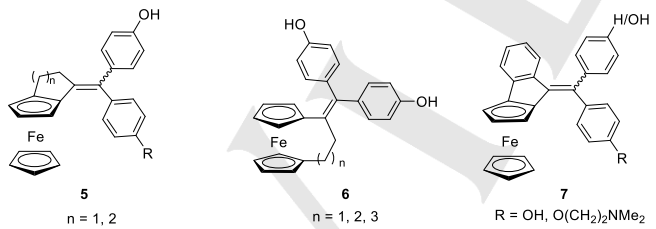



**Figure 2.** Ferrociphenols and ferrocifens in which the ferrocenyl moiety has been modified, including one target enantiopure chiral ferrocifen, **7**, (only one enantiomeric series shown).

We note several earlier studies in which the influence of planar chirality on bioactivity was investigated. In 1985, it was reported that the diastereomers of **8**, whereby the $Cr(CO)_3$ moiety was positioned on the α- or ß-face of the steroid, could be separated and unambiguously distinguished by NMR spectroscopy (Figure 3).[33] Subsequently, it was shown that the relative binding affinity (RBA) values of these α- and ß-isomers for the estradiol receptor site were strikingly different (28% v. 2%, respectively), and provided the first example of such facial discrimination.[3]

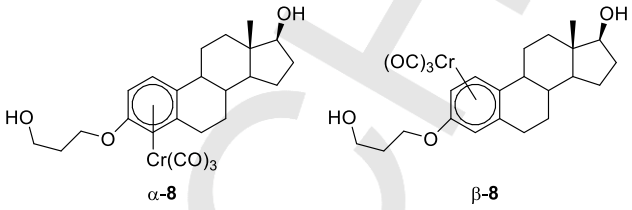



**Figure 3**. Planar chiral estradiol analogues which demonstrate facial discrimination of the estradiol receptor.

Continuing in the steroid field, the diastereomers of *o*-formylcyclopentadienyl metal complexes of 17α-ethynyl-estradiol, ($R_p$)-**9** and ($S_p$)-**9**, (Figure 4) were prepared in pure form and their bioactivity evaluated. In the ferrocenyl and manganese complexes, the affinity of the $R_p$-diastereomers for the estradiol α receptor is almost twice that of their $S_p$-counterparts, clearly exhibiting receptor discrimination between organometallic systems possessing planar chirality. However, these complexes show a proliferative effect on MCF-7 breast cancer cells, indicating estrogenic behaviour.[34]

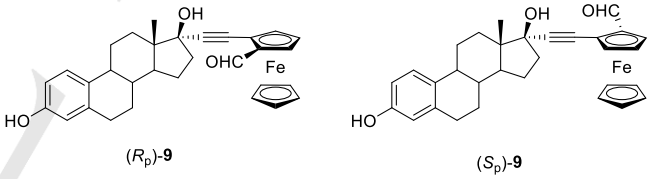



**Figure 4.** Planar chiral ferrocenyl estradiol derivative diastereomers which demonstrate distinct RBA for the ER.

In the area of currently prescribed metallodrugs, the enantiomers of ferroquine, the organometallic antimalaria drug derived by incorporation of a ferrocenyl unit into the chloroquine structure, have been independently tested to probe whether planar chirality has a beneficial effect. However, their bioactivity did not differ substantially, indeed the racemic version now widely used clinically is more effective.[35] Finally, we note that the ferrocenyl-containing platensimycin derivatives were each synthesised in enantiomerically pure form and tested against a range of methicilline- or vancomycin- resistant bacterial strains; unfortunately, they showed no bioactivity up to 200 µg/mL[36]

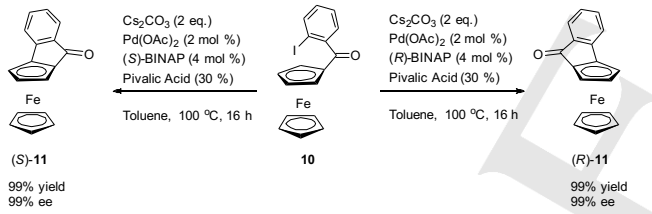
With these results in mind, it seemed highly likely that each enantiomeric pair of planar chiral ferrocifens will effect different $IC_{50}$ values, given that the two cases described above in which the sense of planar chirality influences relative binding affinities were those involving the estradiol scaffold. To this end, we sought to prepare a series of ferrocifen analogues in which the planar chirality is controlled to afford enantiomeric pairs of ferrocifens

and ferrociphenols and compare their biological effect on hormone-dependent and -independent breast cancer cell lines.

## Results and Discussion

### *Synthetic aspects*

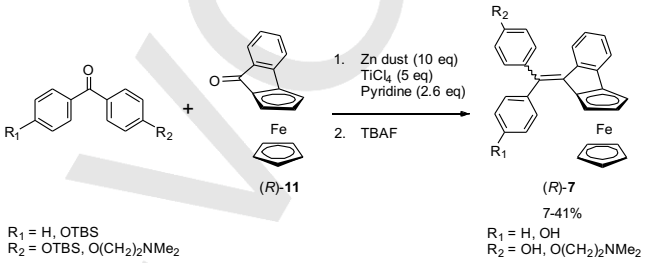
Chiral ferrocifens of this novel type were prepared via McMurry coupling of the corresponding benzophenone and enantiopure planar chiral ferrocenyl ketone. The design of these novel analogues is based on the previous bioactivity profiles of related compounds **5** and **6** (Figure 2). While acyclic ferrocifens of the type **3** exhibit considerable efficacy against cancers for which tamoxifen proved ineffective, ansa-ferrocifens **6** demonstrate up to seven-fold reductions in $IC_{50}$ values versus their acyclic analogues.[29] Shortly after this observation, other ferrocifens, such as **5**, derived from ferrocene fused to monocyclic ketones were also studied; such molecules are planar chiral.[28] However, they were prepared only in a racemic fashion, whereas it is, of course, of particular interest to be able to prepare and test separately each enantiomer of a novel biologically active compound. Chiral ferrocifens of type **7** were selected as ideal targets since methodology to access the related ferrocenyl ketone enantioselectively has previously been employed in our laboratory,[37] based on methodology developed by Gu and You,[38,39] thus enabling an efficient route to the first reported enantiopure chiral ferrocifens.




**Scheme 3.** Enantioselective syntheses of (*S*)-**11** and (*R*)-**11**.

The aryl halide substrate **10** required for the enantioselective cyclisation was prepared via a one-pot/two-step reaction involving the *in situ* preparation of the iodobenzoic acid derived acid chloride followed by a Friedel-Crafts acylation. This afforded compound **10** in quantitative yield on a 15 g scale (35 mmol), without the need for column chromatography. The palladium-catalysed C-H activation functionalisation/cyclisation procedure, shown in Scheme 3, allowed for the preparation of both enantiomers of the planar chiral ketone, **11**, in quantitative yield with >99% ee by simply selecting the required hand of BINAP. This synthesis is based on work from the groups of You and Gu for the preparation of the enantioenriched ketones (*R*)-**11** and (*S*)-**11**; You noted that these conditions result in a reduction of ee when the scale was increased to 1 g.[38,39] Minor modifications to their methodology enabled the scale up of the reaction to 6 g (19 mmol) while simultaneously increasing the ee from 97% (as reported by You) to 99%; in line with the procedure previously described by us,[37] there is, no need for the use of column chromatography.

With both *R*- and *S*-forms of the required ferrocenyl ketone in hand, we next prepared the necessary benzophenone coupling partners for the McMurry coupling. Unlike most previous reports of the synthesis of ferrocenyl-polyphenols by this method,[2,28,29] in our hands unprotected phenolic groups were found to hinder the reaction. Indeed, up to 11 different products, most of them unwanted, can be generated from the McMurry coupling of two unique ketones; moreover, the desired ferrociphenol-type compounds were not isolable. However, TBS protection of the hydroxy groups not only significantly increased the yields of the McMurry hetero-coupling products from trace amounts to up to 41%, but also enabled purification of the target molecules (Scheme 4).




**Scheme 4.** Route from enantiopure ketone **11** to ferrocifen **7**. In this case, only the synthesis of the (*R*)-enantiomer is depicted.

In an attempt at rational design of our initial library of enantiopure ferrociphenols and ferrocifens, we selected a number of target molecules, shown in Figure 5, based on key functionalities identified as being significant in previous research.[2,40] Ferrocifen **7a** was chosen because the dimethylaminoethoxy group has previously been shown to confer a greater ER binding affinity on ferrocifen derivatives compared to those lacking it.[41] Both enantiomers of **7a** were prepared to determine whether one elicited a greater response. The 4'-hydroxyferrocifen derivative, **7b**, was also selected, since the phenol precursors to QMs exhibit superior anti-estrogenic activity to that of the non-hydroxylated parent compounds.[6,9,10] The monophenol **7c**, was chosen to afford insight into the significance of removing the dimethylaminoethoxy basic chain. The bisphenol **7d** was targeted as it exists solely as enantiomers, in contrast to **7a**-**7c** which exist as *E*/*Z*-mixtures.

Despite the target compounds appearing to be formed in modest to low yields, it is noteworthy that as a result of the large number of by-products from the McMurry coupling, and the resulting inherently challenging purification process, the yields reported here are similar to those reported for other analogues prepared in this fashion. Indeed, the typical yields of such reactions are below 30%.[28,29]

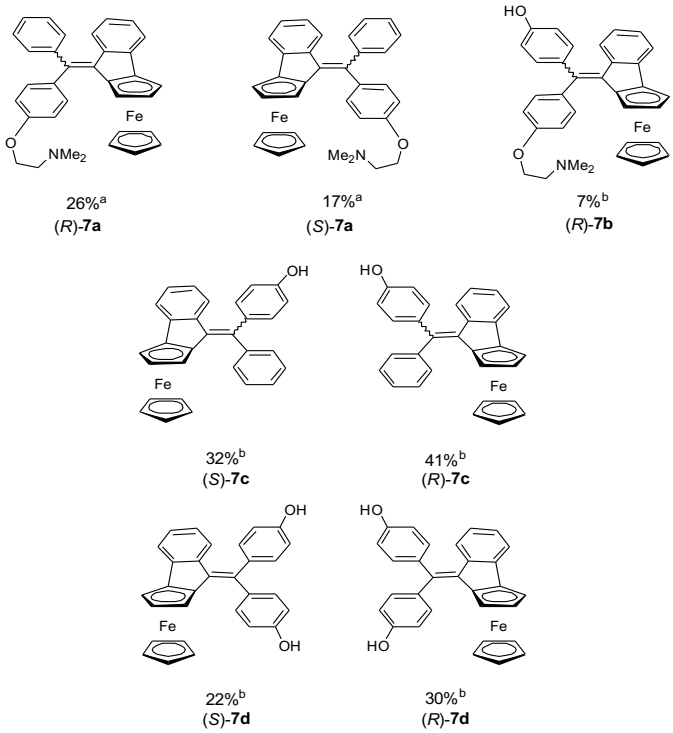
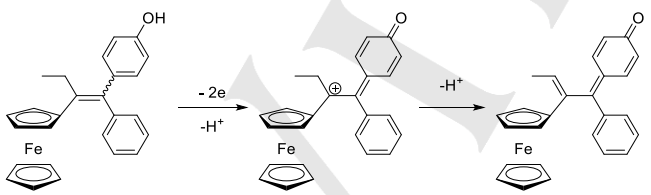


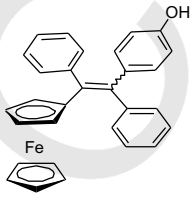

**Figure 5**. Isolated yields of novel ferrocifens. (a) Yield after McMurry coupling. (b) Yield after McMurry coupling and deprotection. Note: (*S*)-**7b** was accessed in ca. 5% yield and proved difficult to purify in sufficient quantities for biological evaluation.

Upon synthesizing these compounds, it was immediately apparent from their $^{1}$H and $^{13}$C NMR spectra that compounds **7a**, **7b** and **7c** were each produced as a 1:1 mixture of geometric (*E*/*Z*) isomers that were inseparable by column chromatography. Nevertheless, our current understanding of the mechanism of action of 4-hydroxyferrocifens suggests that only the isomer in which the 4-hydroxyphenyl group is *trans* to the ferrocene moiety will affect any significant QM-mediated bioactivity.[17,18,42] In addition, it is recognized that interconversion of the *E*/*Z* occurs *in vivo* so there is no benefit to attempt to separate these geometric isomers.[1] However, the 4,4'-dihydroxy derivative **7d**, obviously does not possess this type of isomerism and precludes the *E*/*Z* ratio from having an impact on the activity of the compound.




**Scheme 5.** Stepwise mechanism of quinone methide formation.

Conversion of a ferrociphenol or ferrocifen into a QM requires the removal of two hydrogens, a process now known to proceed in a stepwise manner by sequential loss of electrons and protons (Scheme 5).[43,44] We note in particular the requirement that the system possesses an available abstractable proton in the final step, a criterion *not* satisfied in these ferroceno[2,3]indene derivatives. Indeed, the oxidation of 7d, lacking a labile proton β to the ferrocenyl group, with silver oxide in acetone afforded only unreacted starting compounds. Its oxidation under comparatively mild (i.e., biologically relevant) oxidation conditions has also been performed in the presence of HRP and $H_2O_2$, yet still only the unreacted 7d was observed. This result parallels the case of the ferrociphenol 12, in which the ethyl group was replaced by a phenyl (Figure 6), thereby lacking an abstractable proton.[45]




**12**

**Figure 6.** Ferrociphenol **12**, in which the ethyl group was replaced by a phenyl.

## *Biological studies*

Table 1 lists the $IC_{50}$ values for all new compounds against the MCF-7 (ER+) and MDA-MB-231 (ER-) cell lines. Considering first the ferrocifens (*R*)-**7a** and (*S*)-**7a** that are derived from the ferrocenoindenones (*R*)-**11** and (*S*)-**11**, respectively, their McMurry coupled products are formed as 50/50 *E*/*Z* mixtures, as revealed by the intensities of the $^{1}$H NMR spectral resonances of the $C_5H_5$ rings. Thus, the *E*-(*R*)-**7a** and *E*-(*S*)-**7a** isomers are enantiomeric, as are their *Z*-(*R*)-**7a** and *Z*-(*S*)-**7a** counterparts.

**Table 1**. The $IC_{50}$ values of chiral ferrocifen compounds on MCF-7 (ER+) and MDA-MB-231 (ER-) breast cancer cells

| Compound | $IC_{50}$ (μM) | |
|---|---|---|
| | MCF-7 | MDA-MB-231 |
| **2b** | 0.9 | 0.6 |
| **3,** n=3 | 0.8 | 0.5 |
| **5,** n=1, R=OH | -- | 2.7 ± 0.1 |
| **10** | -- | 9.0 ± 1.0 |
| (*R*)-**7a** | 6.7 ± 0.7 | 8.8 ± 0.4 |
| (*S*)-**7a** | 5.2 ± 0.1 | 5.9 ± 1.1 |
| (*R*)-**7b** | 2.7 ± 0.7 | 11.5 ± 0.5 |
| (*R*)-**7c** | 16.0 ± 0.3 | 16.1 ± 2.4 |
| (*S*)-**7c** | 12.8 ± 1.7 | 14.1 ± 1.0 |
| (*R*)-**7d** | 6.3 ± 0.1 | 4.2 ± 0.5 |
| (*S*)-**7d** | 5.5 ± 2.0 | 7.1 ± 0.5 |

Since these molecules all possess the dimethylaminoethoxy basic side-chain, they would be expected to show antiproliferative behaviour against an ER+ cell line, such as MCF-7, and they do. Of these, the ferrocifens of the *S*-series exhibit slightly better activity. As both ($S_p$)- and ($R_p$)-**7a** are present in 50/50 *E/Z* mixtures, any differences in $IC_{50}$ necessarily arise from the influence of planar chirality. Interestingly, these molecules bearing a dimethylaminoethoxy basic side-chain exhibit enhanced activity against the ER+ cells, but are noticeably worse in the ER- case, especially in the case of *E/Z*-(*R*)-**7b**. Its $IC_{50}$ value decreases 5-fold on ER+ cells compared with that on ER- cells. We have proposed this potent cytotoxicity on ER+ cells results from the anti-estrogenic effect previously observed for hydroxytamoxifen, **2b**, and the hydroxyferrocifen **3** [20]. Indeed, the effect of the new complexes on the growth of MCF-7 hormone-dependent cells was then studied and *E/Z*-(*R*)-**7b** was observed to show similar anti-estrogenic behaviour to that of Fc-OH-Tam (Figure 7).

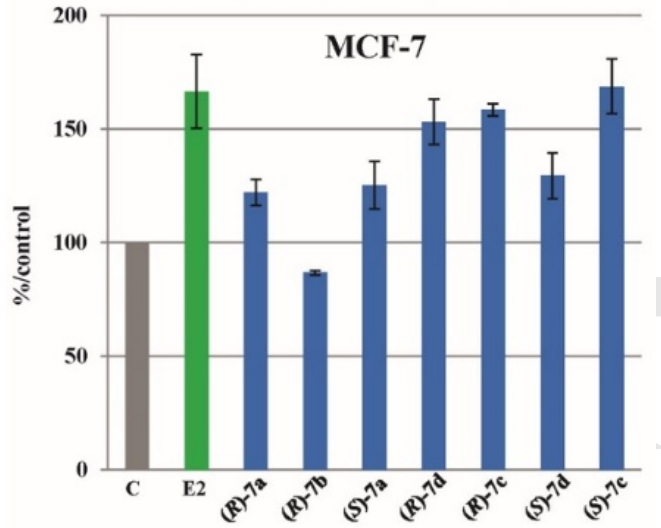



**Figure 7**. Antiproliferative and proliferative effects of chiral ferrocifen compounds (1 µM) on MCF-7 cells after 5 days culture. E2 = estradiol, C = control.

A genuine comparison of the behaviour of pure enantiomers is revealed by the ferrocidiphenols (*R*)-**7d** and (*S*)-**7d**. Here, the (*R*)-enantiomer is somewhat better than its (*S*)-counterpart against the ER- cell line, but the situation is less clear in the ER+ case because of the larger error limits for the favoured (*S*)-enantiomer, despite repeated assays. Finally, the $IC_{50}$ values for the ferrociphenols (*R*)-**7c** and (*S*)-**7c** (both as 50/50 *E/Z* mixtures) are markedly higher than were found for the ferrocifens **7a** and **7b**, and the ferrocidiphenols **7d**. Significantly, monophenol **7c**, which exists as a 50:50 mixture of *E* and *Z* isomers, exhibits $IC_{50}$ values at least twice that of diphenol **7d**. This result parallels the observed 2-fold difference in cytotoxicity between the ferrociphenol, **2a**, and its corresponding diphenol, **2b**; in the latter case an *E*-phenol substituent is always available for QM formation.[2] After five days culture on MCF-7 cells, ferrociphenols **7c** and **7d** show estrogenic behaviour similar to that of the natural hormone estradiol. Meanwhile, as shown above, the oxidation of ferroceno[2,3]indene derivatives cannot produce the corresponding QM, hence the observed anti-proliferative effect can be attributed only to a cytotoxic effect potentially induced by the ferrocenyl unit, as in the case of compound **10**.[45]

When incubated with breast cancer cells, ferrocifens initiate a sequence of Fenton-type reactions[46] thus generating ROS. [2] in particular hydroxyl radicals, which are highly genotoxic. The cell can respond in a number of ways, such as by abstraction of a hydrogen from a cysteine thiol moiety in thioredoxin, thus forming water and a disulfide by intramolecular coupling of thiol radicals. Regeneration of the dithiol unit requires the presence of thioredoxin reductase but, if the ferrocifen forms a QM, the selenocysteine therein readily undergoes Michael addition, thus mitigating the cell's ability to counteract the ROS. In sum, in the absence of a QM, the cytotoxicity of ferroceno[2,3]indene derivatives should result from the combined effects of the ROS generation of the ferrocenyl unit and the estrogenic/anti-estrogenic properties of the tamoxifen-type motif.

Finally, for comparison, in Table 2 we note the perhaps surprisingly low $IC_{50}$ values of the ferrocidiphenol, **7d**, and the ferrocifen, **7b**, (even though they cannot form QMs), and the bicyclo complex, **5**. In all three cases, the (*E*)-ferrocenyl-ene-*p*-phenol framework is readily accessible, but we emphasise that **5** was prepared only in the racemic form and so, unlike in the present study, no experimental investigation of chiral discrimination was possible. We note, however, that in an exhaustive molecular modelling/energy minimisation study, whereby each enantiomer of the polycyclic ferrocidiphenol **5** was allowed to dock with ERα and ERß, binding of the (*S*)-**5** enantiomer was clearly superior to that of its (*R*)-**5** counterpart.[28]

**Table 2.** A comparison of ferrocidiphenol (*R*)-**7d**, ferrocifen (*R*)-**7b** and racemic ferrocidiphenol **5**.

| | | (*R*)-**7d** | (*R*)-**7b** | *rac*-**5** |
|---|---|---|---|---|
| $IC_{50}$ (µM) | MCF-7 | 6.3 ± 0.1 | 2.7 ± 0.7 | -- |
| | MDA-MB-231 | 4.2 ± 0.5 | 11.5 ± 0.5 | 2.7 ± 0.1 |

## Conclusion

The key step in the preparation of these enantiopure ferrocifens and ferrociphenols is the efficient preparation of the chiral ferrocenyl ketone **11** in >99% ee and quantitative yield using a palladium-catalysed intramolecular direct C-H bond activation/cyclisation. It is apparent from previous reports that chiral ferrocifens such as **5** have not been prepared even in an enantioenriched form due to the relative inaccessibility of a single enantiomer of the ferrocenyl ketones because of the extensive time-consuming preparations and purifications.[28] Indeed, it is the robust and rapid synthesis of our enantiopure ketones that enables the facile synthesis of the first enantiopure ferrocifens for biological evaluation.

The bioactivity of ferrociphenols and ferrocifens derived from enantiomerically pure (*S*)- and (*R*)-ferroceno[2,3]indanones against breast cancer cell lines is somewhat reduced from that of their ferrocenyl counterparts, but there is chiral discrimination.

The $IC_{50}$ values reveal that, in general, the molecules possessing the (*S*)-configuration perform better against the ER+ cell line, MCF-7, but the result is less clear in the ER- case. It is noticeable, however, that, even though complete transformation to a neutral QM is not possible because of the lack of an abstractable proton, these systems are bioactive.

## Experimental Section

**General Information:** Unless otherwise noted, all commercial reagents were used as received without further purification. Planar chiral ketones (*S*)-9 and (*R*)-9 were prepared by a modified procedure based on those originally reported by the groups of You and Gu.[37,38] Substituted benzophenones 4-(dimethylaminoethoxy)benzophenone,[47] 4,4'-(di-tert-butyldimethylsilyloxy)benzophenone[48] and (4-((*tert*-butyldimethylsilyl)oxy)phenyl)(phenyl)methanone[49] were prepared by known literature procedures. Standard Schlenk line techniques were employed for moisture sensitive reactions. Column chromatography was performed on Davisil LC60A 40-63 micron silica gel. Thin-layer chromatography (TLC) was performed on aluminium-backed sheets purchased from Merck pre-coated with silica gel 60 $F_{254}$. $^1$H NMR spectra were recorded on Varian-Inova spectrometers (300, 400, 500 and 600 MHz) using tetramethylsilane as an internal standard. $^{13}$C NMR spectra were recorded on 400 MHz, 500 and 600 MHz Varian-Inova spectrometers (101, 126 and 151 MHz) using tetramethylsilane as an internal standard and were proton decoupled. HRMS were measured on a Micromass/Waters LCT mass spectrometer. Supercritical fluid chromatography (SFC) was performed on a Waters Acquity UPC$^2$® instrument with Chiralpak® IA3, IB3, IC3 and ID3 columns. Optical rotation measurements were recorded using a Schmidt-Haensch Unipol L2000 polarimeter at 589 nm and are quoted in units of deg $dm^{-1}$ $cm^3$ $g^{-1}$ (concentration c is given in g/100 mL).

**(*o*-Iodobenzoyl)ferrocene (10).** 2-Iodobenzoic acid (8.65 g, 35.0 mmol) was added to a dry, nitrogen-flushed, 250 mL Schlenk tube equipped with a large magnetic stirring bar and nitrogen/vacuum inlet. $CH_2Cl_2$ (50 mL) was added along with 1 drop of DMF to form a white suspension and stirring was commenced. Oxalyl chloride (3.9 mL, 45.5 mmol) was added to this suspension over 2 min at 0 ºC. The reaction was stirred at RT for 1 h until the suspension had turned to a clear solution and the evolution of gas had ceased. The Schlenk tube was then submerged in a water bath at RT and the solvent and remaining oxalyl chloride removed using a high-vacuum and a liquid $N_2$ cooled collection flask. The crude acid chloride was dried under vacuum at RT for a further 1 h before being dissolved in $CH_2Cl_2$ (40 mL) and ferrocene (6.53 g, 35.0 mmol) was then added along with $CH_2Cl_2$ (20 mL). This solution was cooled to 0 ºC before addition of $AlCl_3$ (4.65 g, 35.0 mmol) in 4 equal portions over 5 min and left to stir for a further 10 min while being warmed to RT. The reaction was quenched by pouring the mixture into 100 mL of ice water and the layers were separated before back extracting the aqueous layer with $CH_2Cl_2$ (3 x 30 mL). The organic layers were combined and then washed with a 10% NaOH solution (3 x 30 mL) and dried with $MgSO_4$ before being concentrated *in vacuo*. The crude material was dissolved in $CH_2Cl_2$ (30 mL) and filtered through a pad of Celite 545® with $CH_2Cl_2$ before being concentrated *in vacuo*. This provided the substituted ferrocene (10.0 g, 99%) as a red solid: $^1$H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 7.9 Hz, 1H), 7.56 – 7.47 (m, 1H), 7.43 (t, *J* = 7.4 Hz, 1H), 7.15 (t, *J* = 7.6 Hz, 1H), 4.73 (s, 2H), 4.60 (s, 2H), 4.30 (s, 5H). All other characterization is in agreement with reported literature data.[38,39]

**(*S*)-Ferroceno[2,3-a]inden-1-one (*S*)-11.** (*o*-Iodobenzoyl)ferrocene **10** (1.66 g, 4.0 mmol) was added to a dry, nitrogen-flushed, 50 mL Schlenk flask equipped with a magnetic stirring bar. $Cs_2CO_3$ (2.60 g, 8.0 mmol), $Pd(OAc)_2$ (18.0 mg, 0.08 mmol, 2.0 mol%), (*S*)-BINAP (106 mg, 0.16 mmol, 4.0 mol%) and pivalic acid (134 mg, 0.60 mmol, 30 mol%) were then added sequentially followed by toluene (16 mL, 0.25 M) and stirring was commenced. The Schlenk flask was then immediately placed in an oil bath set to 100 ºC and the conversion monitored by SFC. After 16 h the reaction had reached 100% conversion and was allowed to cool to RT before filtration through a pad of Celite 545® with $CH_2Cl_2$ followed by concentration *in vacuo* to provide the cyclized ferrocene (1.15 g, 99% yield, 99% ee) as a dark purple solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.6 Hz, 1H), 7.27 (m, 1H), 7.12 (m, 2H), 4.97 (d, *J* = 2.4 Hz, 1H), 4.86 (m, 2H), 4.12 (s, 5H); TLC (pentane:$Et_2O$, 5:3), $R_f$: 0.40 (UV, Vis, purple). SFC analysis (CHIRALPAK IB, $scCO_2$/*i*PrOH, 99/1 to 60/40 over 7 min, 3 mL/min) $t_R$ = 3.85 min (*S*) and $t_R$ = 4.08 min (*R*). All other characterization is in agreement with reported literature data. [38,39]

Example procedure for McMurry Coupling of TBS protected benzophenones with ferrocenyl ketone (*S*)-**11:**

**(*S*)-1-[1,1-di(4-hydroxyphenyl)methyliden]ferroceno[2,3-a]indene, (*S*)-7d.** Zn dust (10 μ powder, 588 mg, 9.0 mmol) was added to a dry $N_2$ flushed 50 mL Schlenk flash, suspended in THF (15 mL) before being cooled to 0 ºC. $TiCl_4$ (0.45 mL, 4.5 mmol) was then added dropwise before removing the Schlenk flask from the ice bath and placing it in an oil bath heated to 70 ºC. After 1 h of heating the solution was cooled to 0 ºC and pyridine (0.19 mL, 2.34 mmol) was added and left to stir for 10 min. During this time a 1:3 mixture of ketones (*S*)-**11** (259 mg, 0.9 mmol) and 4,4'-(di-tert-butyldimethylsilyloxy)benzophenone (1195 mg, 2.7 mmol) in THF (15 mL) was prepared and added slowly to the reaction mixture before being heated to 70 ºC and monitored by TLC for the disappearance of (*S*)-**11**. After 2 h the reaction was cooled to RT and quenched by adding 2.0M $K_2CO_3$ (~10 mL), this was diluted with $CH_2Cl_2$ (30 mL) and the organic and aqueous layers were separated. The aqueous layer was back-extracted with $CH_2Cl_2$ (3 x 15 mL), the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude mixture was purified by silica gel chromatography (pentane:$Et_2O$, 99:1) to provide an inseperable mixture of the heterocoupled product and the homocoupled bis(4-((*tert*-butyldimethylsilyl)oxy)phenyl)methanone product. This mixture was deprotected with TBAF (1.0M solution in THF, 5.0 mL, 5.0 mmol) by stirring at RT for 5 min before being diluted with $CH_2Cl_2$ (10 mL) and $H_2O$ (10 mL) and the organic and aqueous layers were separated. The aqueous layer was back-extracted with $CH_2Cl_2$ (10 mL), the combined/ organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. This mixture was then purified by silica gel chromatography ($CH_2Cl_2$:$Et_2O$, 95:5) to provide the heterocoupled product (91 mg, 22% yield) as a red oil/gum: $[\alpha]_{20}^{D}$ = -1923 (c = 0.03, $CHCl_3$); IR (ATR) $\nu_{max}$ 3301, 3028, 2850, 1604 $cm^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 7.4 Hz, 2H), 7.26 – 7.20 (m, 1H), 7.07 (t, J = 7.4 Hz, 1H), 6.88 (d, J = 7.9 Hz, 2H), 6.87 – 6.79 (m, 3H), 6.69 (d, J = 7.9 Hz, 1H), 4.84 (s, 2H), 4.62 (d, J = 2.3 Hz, 1H), 4.21 (t, J = 2.3 Hz, 1H), 3.94 (s, 5H), 3.76 (d, J = 2.3 Hz, 1H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 155.3, 155.1, 142.7, 141.5, 137.6, 136.8, 135.4, 134.3, 131.6, 131.4, 127.4, 125.0, 124.3, 120.0, 115.6, 115.3, 89.9, 89.3, 71.2, 70.8, 64.4, 60.4; HRMS: (ESI-TOF) calculated for $C_{30}H_{22}O_2Fe$ $[M]^+$ 470.0969, found 470.0992; TLC ($CH_2Cl_2$:$Et_2O$, 9:1), $R_f$: 0.55 (UV, Vis, Red).

**(*R*)-1-[1,1-di(4-hydroxyphenyl)methyliden]ferroceno[2,3-a]indene, (*R*)-7d.** Using the same procedure as for (*S*)-**7d** above, employing (*R*)-**7d** to provide the heterocoupled product (58 mg, 21% yield) as a red oil/gum. Matching analytical data obtained for the opposite enantiomer (*S*)-7d: $[\alpha]_{20}^{D}$ = +2081 (c = 0.04, $CHCl_3$).

**(*S*)-1-[(1-(4-hydroxyphenyl)-1-phenyl)methyliden]ferroceno[2,3-a]indene, (*S*)-7c.** A 1:3 mixture of (*S*)-**11** (172 mg, 0.6 mmol) and the required benzophenone (562 mg, 1.8 mmol) was used, following the same procedure as for (*S*)-**7d** above to provide the heterocoupled product (86 mg, 32% yield) as a mixture of E/Z isomers as a red solid: Mp 46 °C with decomposition ($CH_2Cl_2$); $[\alpha]_{20}^{D}$ = -2279 (c = 0.086, $CHCl_3$); IR (ATR) $\nu_{max}$ 3508, 3052, 3013, 1605 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.54 – 7.31 (m, 7.5H), 7.16 – 7.02 (m, 1H), 6.95 – 6.53 (m, 4.5H), 5.08 (s, 1H), 4.66 (d, J = 2.3 Hz, 0.5H), 4.63 (d, J = 2.3 Hz, 0.5H), 4.25 (t, J = 2.2 Hz, 0.5H), 4.21 (t, J = 2.3 Hz, 0.5H), 3.98 (s, 2.5H), 3.97 (s, 2.5H), 3.82 (d, J = 2.3 Hz, 0.5H), 3.61 (d, J = 2.3 Hz, 0.5H). $^{13}C$ NMR (126 MHz, $CDCl_3$) δ 158.02, 157.87, 156.66, 156.39, 142.91, 142.68, 141.22, 141.13, 136.76, 135.58, 135.44, 134.17, 133.56, 131.39, 131.27, 131.23, 131.09, 126.99, 124.92, 124.83, 124.16, 124.13, 119.78, 119.72, 115.96, 115.61, 113.78, 89.60, 89.58, 89.39, 89.35, 70.96, 70.91, 70.54, 70.46, 64.41, 64.38, 64.27, 64.23, 60.03, 58.12, 58.10, 45.19, 45.16. HRMS: (ESI-TOF) calculated for $C_{30}H_{22}OFe$ $[M]^+$ 454.1020, found 454.1027; TLC ($CH_2Cl_2$, neat), $R_f$: 0.40 (UV, Vis, Red).

**(*R*)-1-[(1-(4-hydroxyphenyl)-1-phenyl)methyliden]ferroceno[2,3-a]indene, (*R*)-7c.** Using the same procedure as for (*S*)-**7c** above, (*R*)-**7c** to provide the heterocoupled product (113 mg, 41% yield) as a red solid. Matching analytical data obtained for the opposite enantiomer (*S*)-7c: $[\alpha]_{20}^{D}$ = +2133 (c = 0.080, $CHCl_3$).

**(*R*)-1-[(1-(4-dimethylaminoethoxyphenyl)-1-(4-hydroxyphenyl)methyliden]ferroceno[2,3-a]indene, (*R*)-7b** A 2:1 mixture of (*R*)-**11** (290 mg, 1 mmol) and the required benzophenone (210 mg, 0.5 mmol) was used, following the same procedure as for (*S*)-**7d** above to provide the heterocoupled product (24 mg, 7% yield) as a mixture of *E/Z* isomers as a red solid. Mp 102-108 °C; $[\alpha]_{20}^{D}$ = -3084 (c = 0.05, $CH_2Cl_2$); $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.38-7.29 (m, 3H), 7.20 (s, 2H), 7.05 (t, *J* = 7.4 Hz, 1H), 6.93 – 6.78 (m, 3H), 6.77-6.61 (m, 3H), 4.60 (t, *J* = 2.0 Hz, 1H), 4.18 – 4.09 (m, 3H), 3.93 (s, 2.5H), 3.92 (s, 2.5H), 3.80 (d, *J* = 2.4 Hz, 0.5H) 3.77 (d, *J* = 2.4 Hz, 0.5H), 2.91 (q, *J* = 6.0 Hz, 2H), 2.51 (s, 3H) 2.49 (s, 3H); $^{13}C$ NMR (101 MHz, $CDCl_3$) δ 158.02, 157.87, 156.66, 156.39, 142.91, 142.68, 141.22, 141.13, 136.76, 135.58, 135.44, 134.17, 133.56, 131.39, 131.27, 131.23, 131.09, 126.99, 124.92, 124.83, 124.16, 124.13, 119.78, 119.72, 115.96, 115.61, 113.78, 89.60, 89.58, 89.39, 89.35, 70.96, 70.91, 70.54, 70.46, 64.41, 64.38, 64.27, 64.23, 60.03, 58.12, 58.10, 45.19, 45.16. IR (ATR) 3052, 2927, 1604, 1508 $cm^{-1}$. HRMS: (ESI-TOF) calculated for $C_{34}H_{31}FeNO_2$ [M]+ 542.1782, found 542.1758.

**(*R*)-1-[(1-(4-dimethylaminoethoxyphenyl)-1-phenyl)methyliden]ferroceno[2,3-a]indene, (*R*)-7a.** Zn dust (10μ powder, 400mg, 6.12 mmol) was added to a dry, $N_2$ flushed 50 mL Schlenk flask equipped with a magnetic stirring bar and suspended in THF (10 mL) before being cooled to 0 ºC. $TiCl_4$ (0.33 mL, 3.0 mmol) was then added dropwise before removing the Schlenk flask from the ice bath and placing i in an oil bath heated to 70 ºC. After 1 h of heating the solution was cooled to 0 ºC and pyridine (0.13 mL, 1.56 mmol) was added and left to stir for 10 min. During this time a 1:2 mixture of ketones (*S*)-**11** (172 mg, 0.6 mmol) and 4-(dimethylaminoethoxy)benzophenone (323 mg, 1.2 mmol) in THF (10 mL) was prepared and added slowly to the reaction mixture before being heated to 70 ºC and monitored by TLC for the disappearance of (*S*)-**11**. After 30 min the reaction was cooled to RT and quenched by adding 2.0 M $K_2CO_3$ (~5 mL), this was diluted with $CH_2Cl_2$ (20 mL) and the organic and aqueous layers were separated. The aqueous layer was back-extracted with $CH_2Cl_2$ (3 x 15 mL), the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude mixture was purified by silica gel chromatography ($CH_2Cl_2$:MeOH, 100:0 to 95:5) to provide the heterocoupled product (81 mg, 26% yield) as a mixture of *E/Z* isomers as a red solid: Mp 50-54 °C ($CH_2Cl_2$); $[\alpha]_{20}^{D}$ = +2420 (c = 0.025, $CHCl_3$); IR (ATR) 3052, 2930, 1603 $cm^{-1}$; $^1H$ NMR (600 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.4 Hz, 1H), 7.45 – 7.30 (m, 7H), 7.07 (qd, *J* = 7.6, 1.1 Hz, 1H), 6.97 (d, *J* = 8.82 Hz, 1H), 6.93 (d, J = 8.31 Hz, 1H), 6.83 (td, *J* = 7.7, 1.3 Hz, 0.5H), 6.78 (td, *J* = 7.7, 1.2 Hz, 0.5H), 6.72 (dt, *J* = 7.8, 0.9 Hz, 0.5H), 6.54 (dt, *J* = 7.9, 0.9 Hz, 0.5H), 4.62 (dd, *J* = 2.3, 0.8 Hz, 0.5H), 4.60 (dd, *J* = 2.3, 0.8 Hz, 0.5H), 4.21 (t, *J* = 2.3 Hz, 0.5H), 4.17 (t, *J* = 2.3 Hz, 0.5H), 4.13 (dt, *J* = 11.1, 5.7 Hz, 2H), 3.95 (s, 2.5H), 3.94 (s, 2.5H), 3.76 (dd, *J* = 2.3, 0.8 Hz, 0.5H), 3.57 (dd, *J* = 2.3, 0.8 Hz, 0.5H), 2.78 (q, *J* = 6.1 Hz, 2H), 2.38 (s, 3H), 2.36 (s, 3H); $^{13}C$ NMR (126 MHz, $CDCl_3$) δ 158.6, 158.4, 144.2, 142.9, 142.6, 141.50, 141.46, 137.93, 137.90, 136.5, 135.1, 134.8, 134.7, 131.1, 130.9, 129.9, 129.7, 128.7, 128.4, 127.7, 127.51, 127.50, 127.4, 125.1, 125.0, 124.42, 124.37, 120.0, 119.9, 119.8, 114.7, 114.4, 89.8, 89.7, 89.0, 88.9, 71.19, 70.84, 70.83, 66.2, 66.1, 64.6, 64.5, 60.41, 60.38, 58.55, 58.52, 46.1. HRMS: (ESI-TOF) calculated for $C_{34}H_{32}NOFe$ $[M+H]^+$ 526.1833, found 526.1844; TLC ($CH_2Cl_2$:MeOH, 9:1), $R_f$: 0.55 (UV, Vis, Red).

**(*S*)-1-[(1-(4-dimethylaminoethoxyphenyl)-1-phenyl)methyliden]ferroceno[2,3-a]indene, (*S*)-7a.** Same procedure as for (*R*)-**7a** above, (*S*)-**7a** to provide the heterocoupled product (24 mg, 7% yield) as a red oil/gum. Matching analytical data obtained for the opposite enantiomer (*R*)-7a: $[\alpha]_{20}^{D}$ = -2389 (c = 0.025, $CHCl_3$).

Characterization data and NMR spectra for all new compounds are available as supplementary data (PDF)

**Biological methods.** Materials. Stock solutions (1 x $10^{-3}$ M) of the ferrocenyl complexes to be tested were prepared in DMSO and were kept at 4°C, serial dilutions in DMSO were prepared just prior to use. A stock solution (1 x $10^{-3}$ M) of estradiol was prepared in ethanol. (Dulbecco's modified eagle medium (DMEM) was purchased from Gibco BRL, fetal calf serum from Dutscher, Brumath, France, glutamine, $E_2$ and protamine sulfate were from Sigma.) MCF-7 and MDA-MB-231 cells were from the Human Tumor Cell Bank.

Culture Conditions. Cells were maintained in monolayer culture in DMEM with phenol red/Glutamax I, supplemented with 9% of decomplemented fetal calf serum and 0.9% kanamycine, at 37°C in a 5% $CO_2$ air humidified incubator. For proliferation assays, cells were plated in 24-well sterile plates at a density of $1.1.10^4$ cells for MDA-MB-231 and of $3.10^4$ cells for MCF-7 in 1 mL of DMEM without phenol red, supplemented with 9% of fetal calf serum desteroided on dextran charcoal, 0.9% Glutamax I and 0.9% kanamycine, and were incubated for 24 h. The following day (D0), 1 mL of the same medium containing the compounds to be tested diluted in DMSO, was added to the plates (final volumes of DMSO: 0.1%). After three days (D3), the incubation medium was removed and 2 mL of fresh medium containing the compounds was added. At different days (D4, D5), the protein content of each well was quantified by methylene blue staining as follows. Cell monolayers were fixed and stained for 1h in methanol with methylene blue (2.5 mg/mL), and then washed thoroughly with water. Two milliliters of HCl (0.1 M) was then added, and the plate was incubated for 1h at 37°C. Then the absorbance of each well was measured at 655 nm with a Biorad spectrophotometer (microplate reader). The results are expressed as the percentage of proteins versus the control. Experiments were performed at least in duplicate.

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**Keywords:** ferrocifen • anti-tumor agents • enantioselective synthesis • chirality • bioorganometallics

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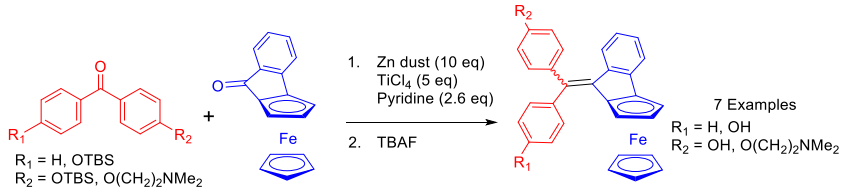


**Enantioselective Synthesis and Biological Evaluation of Novel Planar Chiral Ferrocifens**

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