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Synthesis of 1-ferrocenyl-2-aryl(heteroaryl)acetylenes and 2-ferrocenylindole derivatives via the Sonogashira–Heck–Cassar reaction

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Abstract—The Sonogashira–Heck–Cassar reaction of ferrocenylacetylene with aryl- and heteroaryl halides was shown to be a facile and convenient route for the synthesis of 1-ferrocenyl-2-aryl- and 1-ferrocenyl-2-heteroarylacetylenes in high yields. Additionally, annulation reactions of some of the 1-ferrocenylacetylene compounds gave 2-ferrocenyl-2-benzo[*b*]furan and 2-ferrocenylindoles in good yields.

1. Introduction

Since its discovery, ferrocene[1] has been widely used in asymmetric catalysis,[2] materials science[2d,3] and recently, in the synthesis of compounds with biological activity.[4] Several compounds bearing the ferrocenyl group have been developed as interesting alternatives for the chemotherapy of drug-resistance in cancer and tropical diseases.[4] For example, a ferrocene–hydroxytamoxifen analogue in which a phenyl ring was replaced by a ferrocenyl group was tested against a human breast cell-line and found to be more cytotoxic than the parent tamoxifen (Fig. 1).[4a,p] Futhermore, a ferrocene–chloroquine analogue, obtained by substituting part of the carbon chain of the antimalarial chloroquine with a ferrocenyl group, showed activity against resistant strains of *Plasmodium falciparum*, *P. berghei* N and *P. yoelii* NS.[4l,m]

Several syntheses of ferrocenylacetylene derivatives by cross-coupling reactions have been reported in the literature.[5–7] However, no reports were found on the annulation reactions of 1-ferrocenyl-2-aryl(heteroaryl)-acetylenes. The annulation reaction is a powerful method for constructing benzofuran,[8–10] benzothiophene[9,10] and indole[8–11] systems which are present in several biologically active compounds.[9] In view of this, we undertook a systematic investigation of the synthesis of 1-ferrocenyl-2-aryl-(heteroaryl)acetylenes, 2-ferrocenylbenzo[*b*]furan and 2-ferrocenylindole derivatives via the Sonogashira–Heck–Cassar reaction,[12] whose results are presented herein.

2. Results and discussion

Our initial efforts to synthesize the 1-ferrocenyl-2-aryl-(heteroaryl)acetylenes focused on the Sonogashira–Heck–Cassar reaction between aryl(heteroaryl)acetylenes and iodoferrocene, in triethylamine (TEA) or diethylamine (DEA) and were frustrated by poor yields. Instead, the reaction of ferrocenylacetylene **1** with iodonitrobenzene **2a** in the presence of catalytic amounts of 2.5 mol% $[PdCl_2(PPh_3)_2]$ and 5 mol% CuI, in TEA gave the coupling product **3a** in good yields (Scheme 1, Fig. 2 and Table 1, entry 1). The reaction of 4-bromopyridine hydrochloride **2b** with alkyne **1** in the presence of $[PdCl_2(PPh_3)_2]$/CuI, in TEA, gave the 1,4-biferrocenyl-1,3-butadiyne **4**[13] (34%) as the result of the oxidative homo-coupling of **1**, but when this reaction was carried out in the presence of DEA in place of TEA, the desired coupling product was obtained as the pyridinium salt. Upon stirring this salt in a biphasic

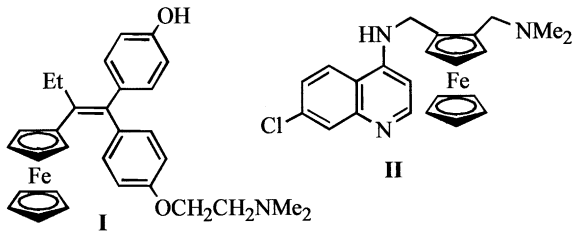

Figure 1. Ferrocenyl hydroxytamoxifen **I** and ferrocenyl chloroquine **II**.

Keywords: ferrocene; alkyne; Sonogashira–Heck–Cassar reaction; annulation; palladium catalyst.
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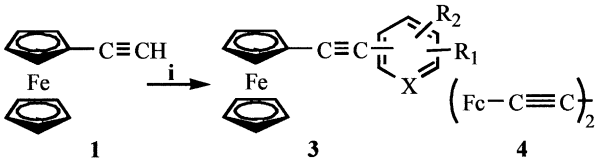


Scheme 1. (i) ArX/2.5 mol% $[PdCl_2(PPh_3)_2]$/5 mol% CuI/Base/*T*(°C)/*t*(h).

system composed of CH_2Cl_2 and a saturated solution of Na_2CO_3, 1-ferrocenyl-2-(4-pyridyl)acetylene **3b** was formed in 22–89% yield (Table 1, entries 2–4).

The reactions of haloderivatives containing one or more substituents, amongst which an electron withdrawing group, proceeded similarly to the reaction of the iodo derivative **2a** to give the respective coupling products in high yields (Table 1, entries 5–10). Thus, the iodo derivative **2d** reacted with **1** in the presence of catalytic amounts of $[PdCl_2(PPh_3)_2]$/CuI, at room temperature, in TEA, to give the coupling product **3d** (67%), besides unreacted **1** (17%) (entry 6). Furthermore, when carried out at 90°C, the reaction was completed after 4 h and gave product **3d** in 96% yield after purification by column chromatography (entry 7). The *N*-acetylated iodo derivatives **2e** and **f** were slightly more reactive than the iodo derivative **2d** and their respective coupling products were also obtained in high yields (entries 8–10). In contrast, the presence of a methyl group in place of a chlorine atom (compounds **2f** and **g**, respectively) led to a decrease in the reactivity of the iodo derivative and the coupling product was obtained in 69–78% yield (entries 11 and 12).

The use of 5-iodoisatin,[14,15a] 5-iodo-*N*-methylisatin[16a] and 7-iodo-5-methylisatin[15a] in reactions with **1**, in the presence of catalytic amounts of $[PdCl_2(PPh_3)_2]$/CuI, in TEA, at room temperature, did not give the coupling product, but the alkyne **1** and halides were recovered in 83–91%. However, when the reactions were carried out in TEA or DEA under reflux, formation of the oxidative homo-coupling product **4** (23–52%) was observed and no halide was isolated upon workup. According to the literature, the Suzuki[17a,c] and Stille[17d] reactions of haloisatins with arylboronic acid and aryl stannane derivatives using palladium complexes or $Pd(OAc)_2$ as catalysts lead to the desired products albeit in modest yields. Nevertheless, Rault et al.[17b] recently reported en efficient cross-coupling reaction of 7-iodoisatin under Suzuki conditions. However the *N*-benzyl-7-halo-5-methylisatins do not yield cyclization products under Heck conditions.[17e] Lathourakis and Litinas have shown that

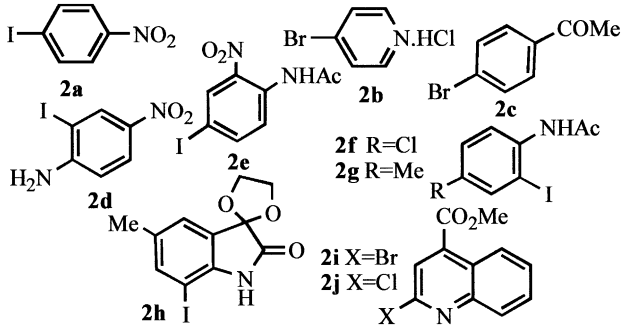


Figure 2. Aryl and heteroaryl halides employed in the coupling reactions.

Table 1. Conditions for the coupling reactions of **1** with **2a–j**

Entry	ArX	Base	*T* (°C)	*t* (h)	Product (%)[a]
1	**2a**	TEA	RT	4	**3a** (74–92)
2	**2b**	DEA	RT	11	**3b** (22)
3	**2b**	DEA	Reflux	13	**3b** (51)
4	**2b**	DEA	90–100[b]	11	**3b** (77–89)
5	**2c**	TEA	RT	18	**3c** (67–88)
6	**2d**	TEA	RT	24	**3d** (67)
7	**2d**	TEA	90	4	**3d** (96)
8	**2e**	TEA	RT	4	**3e** (91)
9	**2f**	TEA	RT	6	**3f** (94)
10	**2f**	TEA	Reflux	3	**3f** (92)
11	**2g**	TEA	RT	22	**3g** (69–78)
12	**2g**	TEA	Reflux	6	**3g** (73)
13	**2h**	TEA	RT	4	**3h** (94)
14	**2i**	TEA	RT	2	**3i** (80)
15	**2j**	TEA	RT	20	**3i** (82)
16	**2j**	TEA	75–80	7	**3i** (38)

[a] Yields after purification using column chromatography on silica gel.
[b] Sealed tube.

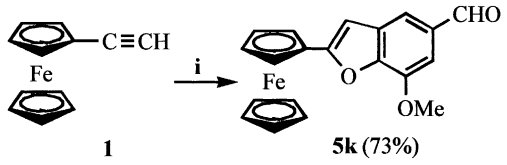
phosphines react with isatins at the keto carbonyl group and this may explain the observed reactivity.[17f]

When the isatin derivative containing the protected ketone carbonyl, ketal **2h**,[16b,c] was reacted with **1** in the presence of $[PdCl_2(PPh_3)_2]$/CuI, in TEA at room temperature, the coupling product **3h** was obtained in excellent yield (entry 13). Similarly, the coupling reactions of **1** with the 2-haloquinolines **2i**,**j**[18], in TEA, gave **3i** in high yields (Table 1, entries 14 and 15) when the reaction was carried out at room temperature. However, when the reaction of **1** with **2j** was carried out at 75–80°C, in an attempt to reduce the reaction time, product **3i** was obtained in lower yield (38%), along with other unidentified products (entry 16).

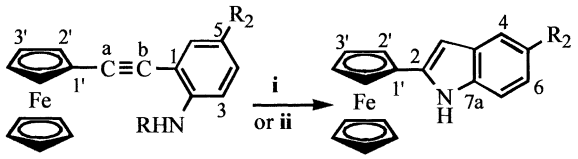
The coupling reactions between ferrocenylacetylene **1** and the aromatic systems shown in Fig. 2 and whose conditions are summarized in Table 1 were therefore extremely successful and it is expected that they can be extended to other aromatic systems bearing electron withdrawing and/or electron donating substituents.

Although the reactions of ferrocenylacetylene **1** with 2-iodo-4-nitroaniline **2d** or *N*-acetyl-2-iodoanilines **2f** and **g** in the presence of $[PdCl_2(PPh_3)_2]$/CuI, in TEA, under heating, only led to the formation of the respective coupling products (**3d**, **f** and **g**), when 5-iodovanilin[15a] **2k** was reacted with **1**, under the same conditions, the coupling-annulation product **5k**[19a] was obtained in good yield (Scheme 2).

This result led us to investigate the conditions for the formation of the annulation products from **3d** and **f**. No reaction was observed when compound **3d** was left stirring in a biphasic system constituted by aqueous 3 mol L^{-1} HCl/



Scheme 2. (i) 5-Iodovanilin **2k**/2.5 mol% $[PdCl_2(PPh_3)_2]$/5 mol% CuI/TEA/reflux/7–8 h.



3d R=H, R_2=NO_2 **5d (52-58%)**
3f R=Ac, R_2=Cl **5f (81%)**
3g R=Ac, R_2=Me **5g (64%)**

Scheme 3. (i) (R=H) 3–6 mol L^{-1} HCl/CH_2Cl_2/20 mol% Bu_4NBr/10 mol% $PdCl_2$/r.t./24 h; (ii) (R=Ac) $Bu_4NF{\cdot}xH_2O$ exc/THF/reflux/6 h.

CH_2Cl_2 (1:1). However, when **3d** was stirred in the presence 20 mol% Bu_4NBr for 19 h and then 10 mol% $PdCl_2$[10j] was added to the reaction mixture, which was stirred for a further 24 h at room temperature, formation of the annulation product 2-ferrocenyl-5-nitroindole **5d** was observed. This compound was isolated in 58% yield, along with unreacted **1** (23%) (Scheme 3). Increasing the acid concentration and reaction time did not affect the outcome of this reaction, which produced **5d** in up to 52–58% yields.

Compound **3f** did not react under the same reaction conditions investigated for the transformation of compound **3d** and the substrate was recovered from the reaction (67%). The inertness of **3f** is possibly due to the lower nucleophilicity of its nitrogen atom, compared with the free NH_2 group in **3d**. However, stirring this compound with excess $Bu_4NF{\cdot}xH_2O$,[19b,c] for 26 h, in THF at room temperature, gave indole **5f** (33%) and unreacted **3f** (49%). When the reactions of compounds **3f** and **g** with $Bu_4NF{\cdot}xH_2O$ were performed under reflux, indoles **5f** and **g** were obtained in 81 and 64%, respectively (Scheme 3).

In an attempt to produce the coupling–annulation products **5f** and **g** from a one-pot reaction, the reaction of **1** with the iodoanilines **2f** and **g** were reinvestigated under a variety of conditions. When compounds **1** and **2f** or **g** were heated in the presence of $[PdCl_2(PPh_3)_2]$/CuI in TEA for 3–6 h, and then an excess of TBAF (in THF) was added and the reaction was heated for a further 8 h, the indoles **5f** and **g** were obtained in 79 and 60%, respectively.

3. Conclusion

In summary, both coupling and coupling–annulation reactions were successfully employed to prepare a number of novel ferrocene derivatives, among which quinoline, benzo[*b*]furan and indole derivatives.

4. Experimental

4.1. General

All compounds were satisfactorily characterized by analytical and spectroscopic data.

All solvents were distilled over standard drying agents under argon directly before use. Ferrocenylacetylene **1** was prepared according to Polin and Schottenberger[20a] and $[PdCl_2(PPh_3)_2]$ was prepared according to R. F. Heck.[20b] All other starting materials were prepared according to cited references or obtained from commercial suppliers and were used without further purification.

Melting points were determined on a Mel-Temp II capillary apparatus and are reported as uncorrected values. Column chromatography was performed on silica gel 60 (70–230 mesh, ASTM, Merck). ^1H and ^{13}C NMR spectra were recorded using Bruker (300 MHz) or Varian (500 or 300 MHz) spectrometers. Mass spectra were obtained by electron impact (70 eV) on a VG Autospec spectrometer. Infra-red spectra were recorded using a BOMEM FT-IR as KBr discs.

4.2. General procedure for the coupling reactions

To a mixture of the aryl or heteroaryl halide (1.00 mmol) and ferrocenylacetylene **1** (231 mg; 1.10 mmol) in TEA (5 mL) were added $[PdCl_2(PPh_3)_2]$ (17 mg, 0.025 mmol) and CuI (9 mg, 0.05 mmol). The reaction mixture was then heated under reflux or stirred at room temperature under argon for the time shown in Table 1. After removal of the solvents, the residue was purified by column chromatography and recrystallized using CH_2Cl_2/hexane (1:4).

4.2.1. 1-Ferrocenyl-2-(4-nitrophenyl)acetylene (3a). Red crystals, 74–92%, mp: 204–206°C (Lit.[20c]: 204°C); IR (ν_{max}, cm^{-1}): 2150 (C≡C); MS (rel. int.) *m/z* 331(M^+, 100), 285(48), 229(16), 163(36), 121(31), 56(34); ^1H NMR (300 MHz, $CDCl_3$): δ 4.27(s, 5H, Cp), 4.32(t, J=1.8 Hz, 2H, H-3′ and H-4′), 4.55(t, J=1.8 Hz, 2H, H-2′ and H-5′), 7.60(d, J=8.8 Hz, 2H, H-2 and H-6), 8.19(d, J=8.8 Hz, 2H, H-3 and H-5); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 63.6(C-1′), 69.6(C-2′ and C-5′), 70.1(Cp), 71.8(C-3′ and C-4′), 84.4(C*a*), 95.2(C*b*), 123.5(C-3 and C-5), 130.9(C-1), 131.7(C-2 and C-6), 146.2(C-4); HRMS for $C_{18}H_{13}NO_2Fe$: 331.0296 (calcd), 331.0296 (found).

4.2.2. 1-Ferrocenyl-2-(4-pyridinyl)acetylene (3b). Orange crystals, 22–89%, mp: 159–161°C (dec.); IR (ν_{max}, cm^{-1}): 2210 (C≡C). MS (rel. int.) *m/z* 287(M^+, 100), 166(6), 139(6), 121(20), 56(13); ^1H NMR (500 MHz, $CDCl_3$) δ 4.25(s, 5H, Cp), 4.29(t, J=1.8 Hz, 2H, H-3′ and H-4′), 4.53(t, J=1.8 Hz, 2H, H-2′ and H-5′), 7.31(d, J=4.9 Hz, 2H, H-2 and H-6), 8.55(d, J=4.9 Hz, 2H, H-3 and H-5); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 63.5(C-1′), 69.4(C-2′ and C-5′), 70.1(Cp), 71.7(C-3′ and C-4′), 83.4(C*a*), 94.2(C*b*), 125.3(C-2 and C-6), 132.1(C-1), 146.6(C-3 and C-5); HRMS for $C_{17}H_{13}NFe$: 287.0398 (calcd), 287.0397 (found).

4.2.3. 1-Ferrocenyl-2-(4-acetylphenyl)acetylene (3c). Orange crystals, 67–88%, mp: 149–151°C (Lit.[20c]: 148°C); IR (ν_{max}, cm^{-1}): 2207 (C≡C), 1677(CO); MS (rel. int.) *m/z* 328(M^+, 100), 285(10), 156(7), 121(7), 56(4); ^1H NMR (300 MHz, $CDCl_3$) δ 2.60(s, 3H, CH_3), 4.26(s, 5H, Cp), 4.28(t, J=1.8 Hz, 2H, H-3′ and H-4′), 4.53(t, J=1.8 Hz, 2H, H-2′ and H-5′), 7.55(d, J=8.4 Hz, 2H, H-2 and H-6), 7.91(d, J=8.4 Hz, 2H, H-3 and H-5); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 26.6(CH_3), 64.2(C-1′), 69.2(C-2′ and C-5′), 70.0(Cp), 71.6(C-3′ and C-4′), 85.2(C*a*); 92.5(C*b*), 128.2(C-2 and C-6), 129.0(C-1),

131.3(C-3 and C-5), 135.6(C-4), 197.3(CO); HRMS for $C_{20}H_{16}OFe$: 328.0440 (calcd), 328.0440 (found).

4.2.4. 1-Ferrocenyl-2-(2-amino-5-nitrophenyl)acetylene (3d). Orange crystals, 67–96%, mp: 155–157°C (dec.); IR (ν_{max}, cm^{-1}): 3480(NH_2), 3361(NH_2), 2203(C≡C); MS (rel. int.) *m/z* 346(M^+, 100), 300(3), 244(2), 121(2), 56(3); ^1H NMR (300 MHz, $CDCl_3$) δ 4.26(s, 5H Cp), 4.30(t, *J*=1.8 Hz, 2H, H-3′ and H-4′), 4.53(t, *J*=1.8 Hz, 2H, H-2′ and H-5′), 4.95(bs, 2H, NH_2), 6.68(d, *J*=9.0 Hz, 1H, H-3), 8.02(dd, *J*=2.7 and 9.0 Hz, 1H, H-4), 8.26(d, *J*=2.7 Hz, 1H, H-6); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 63.8(C-1′), 69.3(C-2′ and C-5′), 70.1(Cp), 71.6(C-3′ and C-4′), 79.7(C*a*), 95.8(C*b*), 108.1(C-1), 112.7(C-3), 125.4(C-6), 128.3(C-4), 138.2(C-2), 152.7(C-5); HRMS for $C_{18}H_{14}N_2O_2Fe$: 346.0405 (calcd), 346.0405 (found).

4.2.5. 1-Ferrocenyl-2-[4-(*N*-acetylamino)-3-nitrophenyl]-acetylene (3e). Red crystals, 91%, mp: 174–176°C; IR (ν_{max}, cm^{-1}): 3348(NH), 2211(C≡C), 1702(CO); MS (rel. int.) *m/z* 388(M^+, 100), 340(3), 264(51), 193(28), 117(55), 84(59); ^1H NMR (300 MHz, $CDCl_3$) δ 2.31(s, 3H, CH_3), 4.26(s, 5H, Cp), 4.28(t, *J*=1.8 Hz, 2H, H-3′ and H-4′), 4.52(t, *J*=1.8 Hz, 2H, H-2′ and H-5′), 7.70(dd, *J*=2.8 and 8.8 Hz, 1H, H-6), 8.30(d, *J*=2.8 Hz, 1H, H-2), 8.75(d, *J*=8.8 Hz, 1H, H-5), 10.35(bs, 1H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 25.8(CH_3), 64.1(C-1′), 69.2(C-2′ and C-5′), 70.0(Cp), 71.5(C-3′ and C-4′), 83.1(C*a*), 90.6(C*b*), 114.9(C-1), 119.4(C-4), 121.9(C-2), 128.0(C-5), 133.1(C-3), 138.0(C-6), 168.8(CO); HRMS for $C_{20}H_{16}N_2O_3Fe$: 388.0532 (calcd), 388.0534 (found).

4.2.6. 1-Ferrocenyl-2-[2-(*N*-acetylamino)-5-chloro phenyl]-acetylene (3f). Yellow crystals, 92–94%, mp: 139–141°C; IR (ν_{max}, cm^{-1}): 3317(NH), 2212(C≡C), 1673(CO); MS (rel. int.) *m/z* 379(M+2, 32), 377(M^+, 100), 312(52), 269(10), 242(8), 177(13), 152(10), 121(13), 56(14); ^1H NMR (300 MHz, $CDCl_3$) δ 2.18(s, 3H, CH_3), 4.26(s, 5H, Cp), 4.32(t, *J*=1.8 Hz, 2H, H-3′ and H-4′), 4.53(t, *J*=1.8 Hz, 2H, H-2′ and H-5′), 7.27(dd, *J*=2.6 and 8.8 Hz, 1H, H-4), 7.42(d, *J*=2.6 Hz, 1H, H-6), 8.26(d, *J*=8.8 Hz, 1H, H-3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 24.9(CH_3), 63.3(C-1′), 69.5(C-2′ and C-5′), 70.1(Cp), 71.7(C-3′ and C-4′), 79.4(C*a*), 97.2(C*b*), 105.1(C-1), 120.2(C-3), 128.1(C-2), 129.0(C-4), 130.8(C-6), 137.6(C-5), 168.0 (CO); HRMS for $C_{20}H_{16}NOClFe$: 377.0271 (calcd), 377.0273 (found).

4.2.7. 1-Ferrocenyl-2-[2-(*N*-acetylamino)-5-methyl phenyl]-acetylene (3g). Yellow crystals, 69–78%, mp: 120–122°C; IR (ν_{max}, cm^{-1}): 3386(NH), 2209(C≡C), 1697(CO); MS (rel. int.) *m/z* 315(M^+, 100), 249(6), 220(6), 205(9), 121(2); ^1H NMR (300 MHz, $CDCl_3$) δ 2.24(s, 3H, CH_3), 2.31(s, 3H, CH_3), 4.26(s, 5H, Cp), 4.30(t, *J*=1.8 Hz, 2H, H-3′ and H-4′), 4.52(t, *J*=1.8 Hz, 2H, H-2′ and H-5′), 7.12(dd, *J*=1.5 and 8.4 Hz, 1H, H-4), 7.27(d, *J*=1.5 Hz, 1H, H-6), 7.88(bs, 1H, NH), 8.25(d, *J*=8.4 Hz, 1H, H-3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.7(CH_3), 25.0(CH_3), 64.2(C-1′), 69.2(C-2′ and C-5′), 70.1(Cp), 71.5(C-3′ and C-4′), 80.8(C*a*), 95.3(C*b*), 112.3(C-1), 119.1(C-3), 129.8(C-2), 131.5(C-6), 132.8(C-4), 136.3(C-5), 167.7 (CO); HRMS for $C_{21}H_{19}NOFe$: 315.0711 (calcd), 315.0711 (found).

4.2.8. 1-Ferrocenyl-2-[7-(3,3-ethylenedioxy-5-methyl-2-oxindolyl)]acetylene (3h). Orange crystals, 94%, mp: 253–256°C; IR (ν_{max}, cm^{-1}): 3208(NH), 2207 (C≡C), 1742(CO); MS (rel. int.) *m/z* 413(M^+, 100), 385(30), 341(22), 313(13), 246(6), 190(6), 121(16), 56(6); ^1H NMR (500 MHz, $CDCl_3$): δ 2.31(s, 3H, CH_3), 4.24(s, 5H, Cp), 4.28(t, *J*=1.8 Hz, 2H, H-3′ and H-4′), 4.28–4.36(m, 2H, CH_2), 4.48(t, *J*=1.8 Hz, 2H, H-2′ and H-5′); 4.53–4.60(m, 2H, OCH_2CH_2O), 7.13(s, 1H, H-4), 7.22(s, 1H, H-6), 7.39(bs, 1H, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 20.8(CH_3), 64.1(C-1′), 65.8(CH_2), 69.2(C-2′ and C-5′), 70.1(Cp), 71.7(C-3′ and C-5′), 79.4(C*a*), 94.1(C*b*), 102.6(C-3), 105.1(C-7), 124.0(C-3a); 125.3(C-4), 132.9 (C-5), 133.6(C-6), 140.6(C-7a), 174.1(C-2); HRMS for $C_{23}H_{19}NO_3Fe$: 413.0746 (calcd), 413.0744 (found).

4.2.9. 1-Ferrocenyl-2-[(4-carboxylate methyl quinolinyl)]-acetylene (3i). Red crystals, 38–82%, mp: 164–166°C; IR (ν_{max}, cm^{-1}): 2205(C≡C), 1728(CO); MS (rel. int.) *m/z* 3395(M^+, 100), 279(3), 235(5), 214(5), 121(9), 101(8), 75(5), 56(9); ^1H NMR (300 MHz, $CDCl_3$): δ 3.93(s, 3H, CH_3), 4.22(s, 5H, Cp), 4.27(t, *J*=1.8 Hz, 2H, H-3′ and H-4′), 4.58(t, *J*=1.8 Hz, 2H, H-2′ and H-5′), 7.57(t, *J*=8.0 Hz, 1H, H-6), 7.70(t, *J*=8.0 Hz, 1H, H-7), 7.99(s, 1H, H-3), 8.10(d, *J*=8.0 Hz, 1H, H-8), 8.65(d, *J*=8.0 Hz, 1H, H-8). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 52.8(CH_3), 63.2(C-1′), 69.6(C-2′ and C-5′), 70.2(Cp), 72.2(C-3′ and C-4′), 85.9(C*a*), 91.9(C*b*), 123.5(C-4a), 125.3(C-3), 125.6(C-6), 128.1(C-5), 129.5(C-7), 130.1(C-8), 134.7 (C-4), 143.5(C-2), 149.1(C-8a), 166.0(CO_2); HRMS for $C_{23}H_{17}NO_2Fe$: 395.0619 (calcd), 395.0620 (found).

4.2.10. 1,4-Biferrocenyl-1,3-butadiyne (4). Red crystals, 23–52%, mp: 195–196°C (Lit.[20d]: 194–195°C); IR(ν_{max}, cm^{-1}): 2202 (C≡C); ^1H NMR (300 MHz, $CDCl_3$) δ 4.19–4.38(m, 7H, Cp, H-2 and H-5), 4.45–4.60(m, 2H, H-3 and H-4); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 63.6(C-1), 69.2(C-2 and C-5), 70.1(Cp), 70.9(C*a*), 72.1(C-3 and C-4), 79.1(C*b*).

4.2.11. 2-Ferrocenyl-5-formyl-7-methoxy-benzo[*b*]furan (5k). Red crystals, 73%, mp: 132–134°C; IR (ν_{max}, cm^{-1}): 1692 (CHO); MS (rel. int.) *m/z* 360(M^+, 100), 345(6), 260(3), 179(5), 121(7), 56(3); ^1H NMR (500 MHz, $CDCl_3$) δ 4.09 (s, 3H, CH_3), 4.14(s, 5H, Cp), 4.39(t, *J*=1.5 Hz, 2H, 3-H′ and 4-H′), 4.82(t, *J*=1.5 Hz, 2H, H-2′ and H-5′), 6.70(s, 1H, 3-H), 7.33(s, 1H, H-6), 7.63(s, 1H, H-4), 9.99(s, 1H, CHO). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 56.1(CH_3), 66.5(C-2′ and C-5′), 69.6(C-3′ and C-4′), 69.8(Cp), 73.8(C-1′), 100.1(C-3), 104.0(C-6), 118.4(C-4), 131.2(3a), 133.3(C-5), 145.7(C-7), 147.3(C-7a), 159.3 (C-2), 191.9(CHO); HRMS for $C_{20}H_{16}O_3Fe$: 360.0445 (calcd), 360.0443 (found).

4.3. Annulation of 3d catalyzed by $PdCl_2$

To a mixture of the 2-ethynylaniline **3d** (346 mg, 1.00 mmol), Bu_4NBr (64 mg, 0.20 mmol) and $PdCl_2$ (18 mg, 0.10 mmol) in CH_2Cl_2 (5 mL) was added aqueous 3 mol L^{-1} HCl (5 mL). The reaction mixture was stirred at room temperature for 24 h, diluted with water and extracted with CH_2Cl_2 (4×15 mL). The organic phase was washed with saturated $NaHCO_3$ solution (1×15 mL), water

(1×15 mL), dried over Na_2SO_4 and the solvent, evaporated. The residue was purified by column chromatography and the product was recrystallized using CH_2Cl_2/hexane (1:2).

4.3.1. 2-Ferrocenyl-5-nitroindole (5d). Red crystals, 52–58%, mp: 203–205°C (dec.); IR (ν_{max}, cm^{-1}): 3374 (NH); MS (rel. int.) *m/z* 346(M^+, 58), 323(5), 300(28), 244(9), 179(20), 152(18), 121(100), 56(60); ^1H NMR (300 MHz, DMSO-d_6) δ 4.08(s, 5H, Cp), 4.42(t, J= 1.8 Hz, 2H, H-3′ and H-4′), 4.90(t, J=1.8 Hz, 2H, H-2′ and H-5′), 6.75(d, J=1.4 Hz, 1H, H-3), 7.47(d, J=9.2 Hz, 1H, H-7), 7.94(dd, J=2.2 and 9.2 Hz, 1H, H-6), 8.42(d, J=2.2 Hz, 1H, H-4), 11.88(bs, 1H, NH). ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 66.4(C-2′ and C-5′), 69.3(C-3′ and C-4′), 69.5(Cp), 75.9(C-1′), 99.2(C-3), 110.9(C-7), 115.8(C-4), 116.1(C-6), 128.3(C-3a), 140.0(C-2), 140.8 (C-7a), 142.0(C-5); HRMS for $C_{18}H_{14}N_2O_2Fe$: 346.0428 (calcd), 346.0428 (found).

4.4. Annulation of 3f and g with TBAF

A mixture of 2-ethynylaniline **3f** or **g** (1.00 mmol), TBAF·xH_2O (260 mg) and THF (10 mL) was heated under reflux for 6 h. After removal of the THF, the residue was purified by column chromatography and the product, was recrystallized using CH_2Cl_2/hexane (1:2).

4.4.1. 2-Ferrocenyl-5-chloroindole (5f). Orange crystals, 81%, mp: 210–212°C; IR (ν_{max}, cm^{-1}): 3430 (NH); MS (rel. int.) *m/z* 337(M+2, 32), 335(M^+, 100), 242(3), 214(10), 179(18), 121(13), 99(4), 56(3); ^1H NMR (300 MHz, $CDCl_3$) δ 4.11(s, 5H, Cp), 4.36(t, J=1.8 Hz, 2H, H-3′ and H-4′), 4.63(t, J=1.8 Hz, 2H, H-2′ and H-5′), 6.45(d, J=2.0 Hz, 1H, H-3), 7.09(dd, J=2.0 and 8.4 Hz, 1H, H-6), 7.25(d, J=8.4 Hz, 1H, H-7), 7.49(d, J=2.0 Hz, 1H, H-4), 8.08(bs, 1H, NH). ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 66.1(C-2′ and C-5′), 68.9(C-3′ and C-4′), 69.4(Cp), 76.9(C-1′), 97.0(C-3), 112.1(C-7), 118.1(C-4), 120.2(C-6), 123.6(C-5), 130.1(C-3a), 135.1(C-2), 139.6(C-7a); HRMS for $C_{18}H_{14}NClFe$: 335.0196 (calcd), 335.0194 (found).

4.4.2. 2-Ferrocenyl-5-methylindole (5g). Orange crystals, 64%, mp: 142–143°C (dec.); IR (ν_{max}, cm^{-1}): 3433 (NH); MS (rel. int.) *m/z* 357(M^+, 100), 292(73), 275(26), 233(60), 148(71), 106(30); ^1H NMR (300 MHz, $CDCl_3$) δ 2.46(s, 3H, CH_3), 4.11(s, 5H, Cp), 4.34(t, J=1.4 Hz, 2H, H-3′ and H-4′), 4.63(t, J=1.4 Hz, 2H, H-2′ and H-5′), 6.45(s, 1H, H-3), 6.98(d, J=8.4 Hz, 1H, H-6), 7.24(d, J=8.4 Hz, 1H, H-7), 7.38(s, 1H, H-4), 7.98(bs, 1H, NH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.6(CH_3), 65.8(C-2′ and C-5′), 68.8(C-3′ and C-4′), 76.8(C-1′), 69.5(Cp), 98.3(C-3), 109.9(C-7), 119.4(C-4), 122.8(C-6), 129.0(C-5), 129.5 (C-3a), 134.4(C-2), 137.0(C-7a); HRMS for $C_{19}H_{17}NFe$: 357.0816 (calcd), 357.0817 (found).

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