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ORIGINAL PAPER

Synthesis, characterization, and crystal structures of aryl-substituted ferrocenylpyrimidines by site-selective stepwise couplings of 2,4,6-trichloropyrimidine

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Abstract A new ferrocenylpyrimidine containing chlorine was conveniently prepared via the coupling reaction of chloromercuriferrocene and 2,4,6-trichloropyrimidine, and a monoaryl-substituted ferrocenyl-pyrimidine was also readily obtained from the Suzuki coupling of the former with phenylboronic acid. The following Suzuki coupling of the monoaryl-substituted derivative with arylboronic acids in the presence of $Pd(OAc)_2/P(Cy)_3{\cdot}HBF_4$ gave diaryl-substituted ferrocenylpyrimidines. These compounds were characterized by elemental analysis, IR, MS, ^1H and ^{13}C NMR. Additionally, the structures of the three compounds were determined by single-crystal X-ray analysis.

Keywords Coupling reaction · Pyrimidine · Ferrocene · Crystal structure

Introduction

Pyrimidines are widespread heterocyclic motifs found in many natural products, pharmaceuticals, and agrochemicals [1, 2]. In addition, some pyrimidines are used in supramolecular chemistry, functional materials, and organometallic catalysis [3–5]. The syntheses of these pyrimidine entities have therefore attracted extensive attention [6–8]. Most of the syntheses known to date for the preparation of substituted pyrimidines rely on the condensation of two or more building blocks [9–11]. Compared to these conventional methods, the direct arylation of halopyrimidine is an alternative approach that does not involve the preparation of product-specific intermediates. However, examples of this chemistry are limited [12–15]. Pyrimidine halides are very reactive in metal-catalyzed cross-couplings [16, 17], and 2,4,6-trichloropyrimidine represents an interesting substrate for multiple coupling reactions because it has three halogenated carbon atoms. To our knowledge, there have been no other reports concerning diaryl-substituted ferrocenylpyrimidines.

On the other hand, numerous ferrocene-containing heterocycles have also proven to be of pharmacological and therapeutical interest [18, 19]. In recent years, part of our research effort has focused on the synthesis and application of ferrocene derivatives containing heterocyclic rings. We have developed an efficient method for the synthesis of ferrocenylpyrimidines by the coupling of chloromercuriferrocene with mono- and dihalopyrimidine [20–22]. The application of chloromercuriferrocene as a source of a ferrocenyl group in Pd-catalyzed coupling reactions has some advantages, including extra stability and easy availability by a direct mercuration of ferrocene [23, 24]. Herein, we report our results related to site-selective stepwise couplings of 2,4,6-trichloropyrimidine, and provide convenient access to a variety of diaryl-substituted ferrocenylpyrimidines that are not readily available by other methods.

Results and discussion

Initially, the coupling of chloromercuriferrocene (1.1 equiv) and 2,4,6-trichloropyrimidine was performed in the presence

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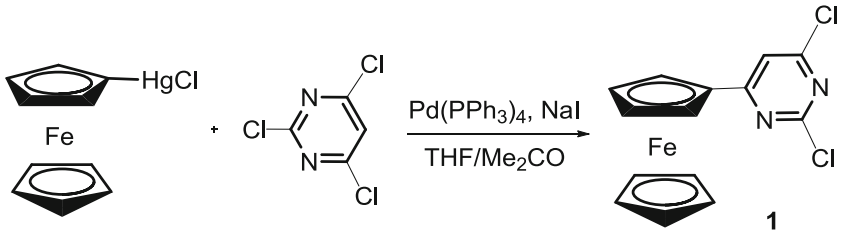
Scheme 1



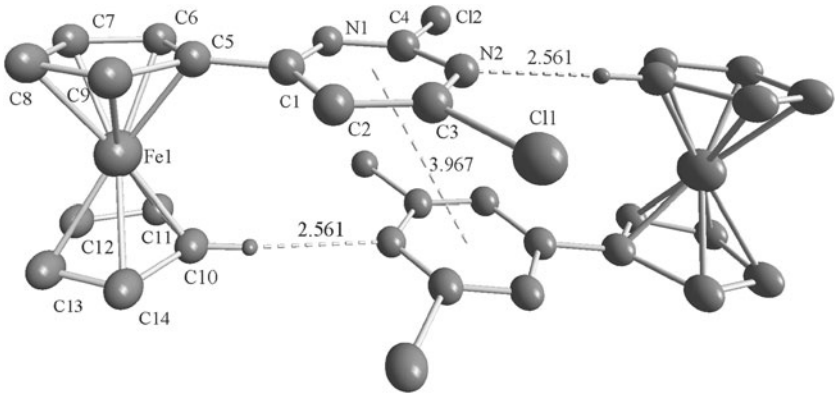


Fig. 1 The dimeric structure of **1** showing the C–H···N hydrogen bonds and π-π stacking interactions. Non-hydrogen-bonding H atoms are omitted for clarity

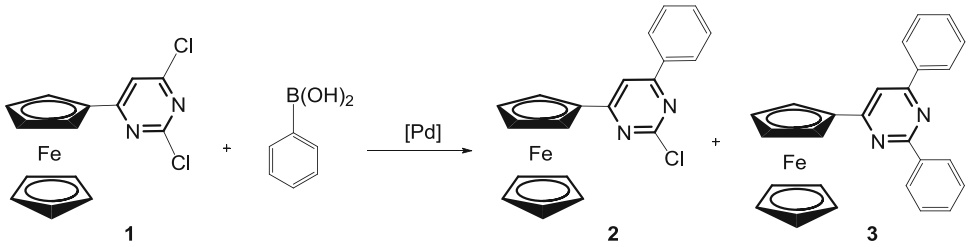
of 3 mol% of $Pd(PPh_3)_4$ (Scheme 1). As expected, the above coupling product is monoferrocenylpyrimidine. Increasing chloromercuriferrocene loading to 2.2 equiv, the reaction did not afford the diferrocenylpyrimidine. The halogen atom at the 2-position of pyrimidine is known to be less reactive for the oxidative addition of palladium than positions 4 and 6 [25, 26]. In comparison with the corresponding signal of 2,4,6-trichloropyrimidine [27], the pyrimidine proton of the product (appearing at $\delta = 7.20$ ppm) is obviously shifted upfield. Moreover, the ^{13}C NMR spectrum of **1** exhibited four signals for the pyrimidine ring, indicating that the product **1** was 4-ferrocenylpyrimidine. The structure of the product has been confirmed by single-crystal X-ray diffraction. Figure 1 shows that compound **1** exists as a dimer in the crystal due to intermolecular C–H···N hydrogen bonds and π-π stacking interactions [28, 29].

It is known that the palladium-catalyzed Suzuki reaction is a versatile technique for the formation of asymmetrical biaryls [30, 31]. In the following experiments, the Suzuki coupling of **1** with phenylboronic acid was investigated (Table 1). The use of $Pd(PPh_3)_4$ in the presence of Cs_2CO_3 in dioxane at 110 °C for 12 h afforded the coupled product **2** in 87 % yield (entry 1). However, the double-coupled product **3** was not isolated. Other reaction conditions such as K_3PO_4 in dioxane and K_2CO_3 in toluene also afforded good yields (entries 2 and 3 yielded 84 and 80 %, respectively). Increasing phenylboronic acid loading to 2.5 equiv did not give product **3** for the present catalytic systems (entry 4). In order to obtain trisubstituted pyrimidine, we employed $Pd(OAc)_2/P(Cy)_3{\cdot}HBF_4$ (3/6 mol%) as a catalyst [32], and the reaction gave a mixture of products with the trisubstituted pyrimidine **3** as a side product (entry 5). To our delight, under the same conditions, the coupling of **1** with 2.5 instead of 1.2 equiv of phenylboronic acid afforded **3** in a good yield (entry 6, 82 %). This protocol provides an efficient access to a variety of symmetric diaryl-ferrocenylpyrimidines.

The detailed structures of **2** and **3** were confirmed by single-crystal X-ray diffraction analysis. Like **1**, **2** also exists as a dimer in the crystal due to π-π stacking interactions between the pyrimidine rings and benzene rings (Fig. 2). The molecular structure of **3** was shown in Fig. 3. The pyrimidine rings and substituted cyclopentadienyl rings are approximately coplanar (dihedral angles of 2.4° and 1.3°) in the two independent molecules. However, one of benzene rings and the pyrimidine rings are not coplanar, with dihedral angles of 25.3° and 31.0°. It is worth noting that the intermolecular C–H···π and π-π stacking interactions are present in the crystal of **3**, resulting in a 2D supramolecular architecture (Fig. 4).

Finally, this newly developed coupling protocol was also successfully applied to the synthesis of asymmetric diaryl-substituted ferrocenylpyrimidines via the Suzuki coupling of **2**. Other arylboronic acids could be coupled efficiently under the same reaction conditions (Cs_2CO_3, $Pd(OAc)_2/P(Cy)_3{\cdot}HBF_4$) (Table 2). Electron-donating

Table 1 Suzuki coupling reaction of **1** with phenylboronic acid



Entry	Conditions	Equiv. $PhB(OH)_2$	Yields/%[a]	
			2	**3**
1[b]	Cs_2CO_3, dioxane	1.2	87	Trace
2[b]	K_3PO_4, dioxane	1.2	84	Trace
3[b]	K_2CO_3, toluene	1.2	80	Trace
4[b]	Cs_2CO_3 (3.0 equiv), dioxane	2.5	89	Trace
5[c]	$Pd(OAc)_2/P(Cy)_3{\cdot}HBF_4$ (3/6 mol%)	1.2	61	15
6[d]	$Pd(OAc)_2/P(Cy)_3{\cdot}HBF_4$ (3/6 mol%)	2.5	trace	82

Reaction conditions: **1** (1.0 mmol), base (1.5 equiv), 5 cm^3 solvent, 110 °C, 12 h

[a] Isolated yields

[b] $Pd(PPh_3)_4$ (3 mol%)

[c] Cs_2CO_3 (1.5 equiv), 5 cm^3 dioxane

[d] Cs_2CO_3 (3.0 equiv)

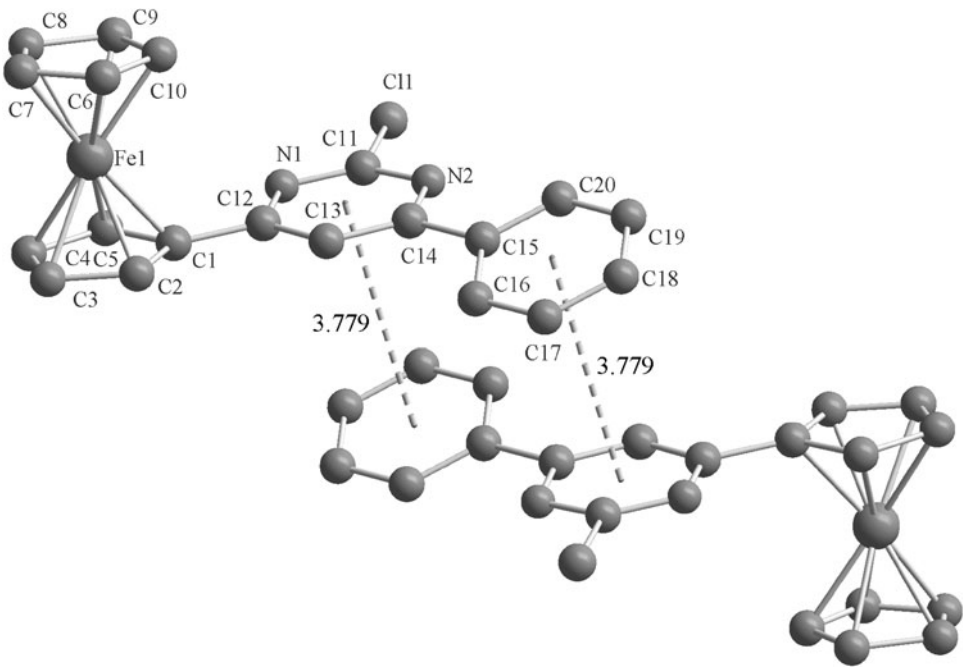


Fig. 2 The dimeric structure of **2** showing the π-π stacking interactions. H atoms are omitted for clarity

substrates 4-methylphenylboronic acid and 3-methoxyphenylboronic acid reacted with **2** to give the corresponding products **4** and **5**. Their yields (95 and 93 %) are slightly higher than the yield (83 %) of the electron-withdrawing substrate, 4-acetylphenylboronic acid (entries 1-3).

In summary, we have reported a convenient synthesis of diaryl-substituted ferrocenylpyrimidines by site-selective stepwise couplings of 2,4,6-trichloropyrimidine. The products reported herein are not readily available by other methods.

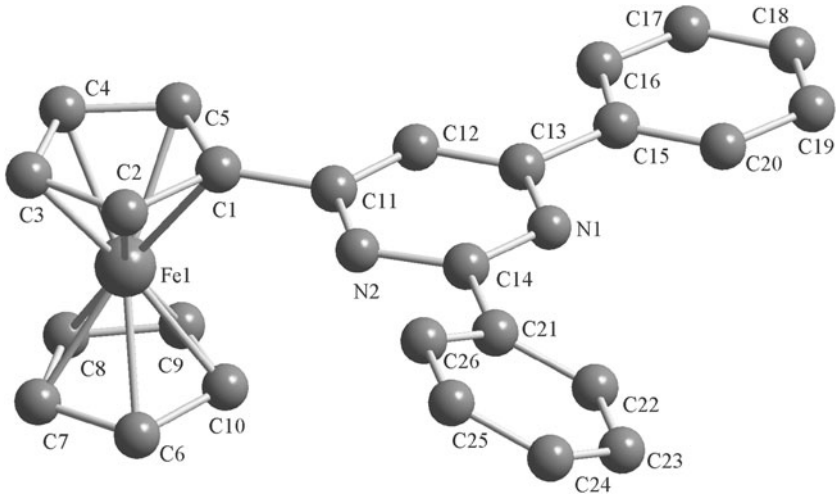


Fig. 3 Molecular structure of **3** H atoms are omitted for clarity

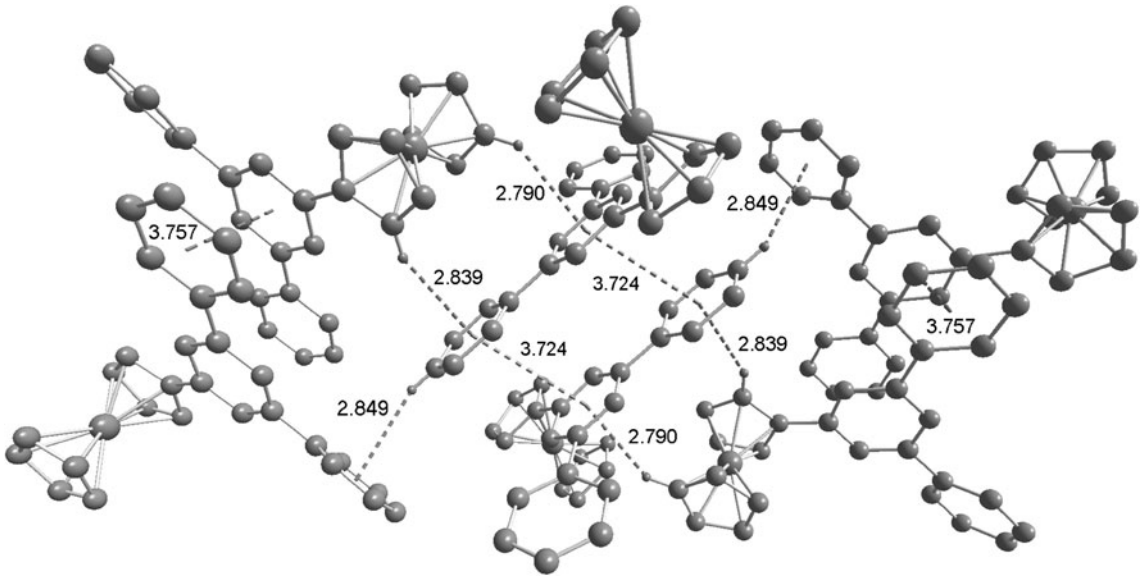


Fig. 4 Two-dimensional network structure of **3** formed by C–H···π and π-π stacking interactions. Non-hydrogen bonding H atoms are omitted for clarity

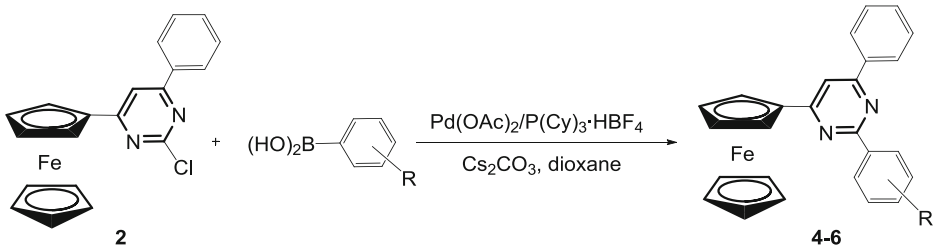
Experimental

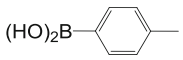
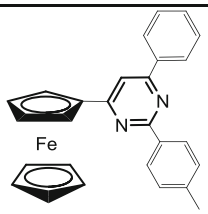
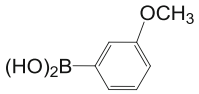
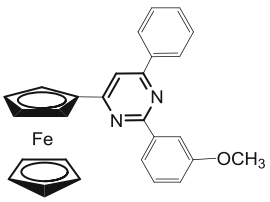
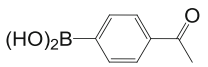
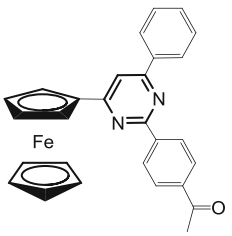
All reactions were carried out under a dry nitrogen atmosphere using standard Schlenk techniques. All other chemicals were commercially available expect for chloromercuriferrocene [33]. IR spectra were collected on a Bruker VECTOR22 spectrophotometer using KBr pellets. NMR spectra were recorded on a Bruker DPX-400 spectrometer in $CDCl_3$ with TMS as an internal standard. The MS spectra were obtained on an LC-MSD-Trap-XCT instrument at 70 eV. Elemental analyses were determined with a Thermo Flash EA 1112 elemental analyzer.

(2,6-Dichloropyrimidin-4-yl)ferrocene
(**1**, $C_{14}H_{10}Cl_2FeN_2$)

In a flask equipped with a reflux condenser and gas inlet, 2,4,6-trichloropyrimidine (1 mmol), chloromercuriferrocene (1.1 mmol), NaI (2 mmol), $Pd(PPh_3)_4$ (0.03 mmol), 18 cm^3 THF, and 12 cm^3 Me_2CO were placed under N_2 atmosphere. The reaction mixture was then placed in an oil bath and heated at 70 °C for 6 h. After removal of the solvent, the residue was purified by column chromatography on silica gel using CH_2Cl_2 as an eluent to give the red solid **1**. Yield: 203 mg (61 %); IR (KBr): $\overline{\nu}$ = 3,097, 1,549, 1,515, 1,479, 1,389, 1,257, 1,183, 1,147, 1,105, 864, 818, 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.20 (s, 1H,

Table 2 Suzuki coupling reactions of **2** with arylboronic acids



Entry	Arylboronic acid	Product	Yield /%[a]
1		**4** 	95
2		**5** 	93
3		**6** 	83

Reaction conditions: **2** (1.0 mmol), arylboronic acid (1.2 mmol), $Pd(OAc)_2$ (3 mol%), $P(Cy)_3{\cdot}HBF_4$ (6 mol%), Cs_2CO_3 (1.5 mmol), 5 cm^3 dioxane, 110 °C, 12 h

[a] Isolated yields

PyH), 4.99 (s, 2H, C_5H_4), 4.61 (s, 2H, C_5H_4), 4.13 (s, 5H, C_5H_5) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 173.6$, 161.5, 160.8, 114.4, 78.3, 72.6, 70.6, 68.8 ppm; MS (EI): $m/z = 333.0$ ($[M + H]^+$).

(2-Chloro-6-phenylpyrimidin-4-yl)ferrocene
(**2**, $C_{20}H_{15}ClFeN_2$)
In a Schlenk tube, a mixture of **1** (1.0 mmol), $PhB(OH)_2$ (1.2 mmol), $Pd(PPh_3)_4$(0.03 mmol), and Cs_2CO_3 (1.5 mmol) in 5 cm^3 dioxane was evacuated and charged with nitrogen. The reaction mixture was then placed in an oil bath and heated at 110 °C for 12 h. After being cooled, the mixture was extracted with ethyl acetate and evaporated, the residue was purified by column chromatography on silica gel using CH_2Cl_2 as an eluent to give the red solid **2.** Yield: 325 mg (87 %); IR (KBr): $\bar{\nu} = 3{,}080$, 1,569, 1,507, 1,496, 1,409, 1,355, 1,243, 1,189, 1,032, 853, 821, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.12$ (brs, 2H, ArH), 7.58 (s, 1H, PyH), 7.48 (brs, 3H, ArH), 5.06 (s, 2H, C_5H_4), 4.57 (s, 2H, C_5H_4), 4.12 (s, 5H, C_5H_5) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 172.4$, 166.1, 136.0, 131.5, 129.2, 127.4, 110.5, 79.2, 72.0, 70.4, 68.6 ppm; MS (EI): $m/z = 375.0$ ($[M + H]^+$).

*General procedure for the synthesis of **3–6***

In a Schlenk tube, a mixture of **2** (1.0 mmol), arylboronic acid (1.5 mmol), $Pd(OAc)_2$(0.03 mmol), $P(Cy)_3{\cdot}HBF_4$ (0.06 mmol), and Cs_2CO_3 (2.0 mmol) in 5 cm^3 dioxane was evacuated and charged with nitrogen. The reaction mixture was then placed in an oil bath and heated at 110 °C for 12 h. After being cooled, the mixture was extracted with ethyl acetate and evaporated; the residue was purified by column chromatography on silica gel using CH_2Cl_2 as an eluent to give the red solid **3–6**.

(2,6-Diphenylpyrimidin-4-yl)ferrocene (**3**, $C_{26}H_{20}FeN_2$)
Yield: 383 mg (92 %); IR (KBr): $\bar{\nu}$ = 3,091, 1,587, 1,564, 1,524, 1,497, 1,372, 1,244, 1,105, 1,074, 863, 821, 752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.70 (d, 2H, J = 8.2 Hz, ArH), 8.27 (d, 2H, J = 7.8 Hz, ArH), 7.61 (s, 1H, PyH), 7.55 (m, 6H, ArH), 5.16 (s, 2H, C_5H_4), 4.53 (s, 2H, C_5H_4), 4.09 (s, 5H, C_5H_5) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.7, 164.1, 163.4, 138.5, 137.8, 130.7, 130.6, 129.0, 128.5, 127.3, 110.0, 81.4, 71.1, 70.1, 68.3 ppm; MS (EI): m/z = 417.1 ($[M + H]^+$).

[6-Phenyl-2-(p-tolyl)pyrimidin-4-yl]ferrocene
(**4**, $C_{27}H_{22}FeN_2$)
Yield: 409 mg (95 %); IR (KBr): $\bar{\nu}$ = 3,050, 1,567, 1,524, 1,488, 1,368, 1,237, 1,216, 1,105, 1,026, 818, 753, 943, 816, 769, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.57 (d, 2H, J = 8.2 Hz, ArH), 8.24 (d, 2H, J = 7.8 Hz, ArH), 7.53–7.57 (m, 4H, ArH + PyH), 7.33 (d, 2H, J = 8.2 Hz, ArH), 5.14 (s, 2H, C_5H_4), 4.51 (s, 2H, C_5H_4), 4.08 (s, 5H, C_5H_5), 2.45 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.5, 164.3, 163.4, 140.7, 138.0, 135.9, 130.6, 129.7, 129.3, 129.0, 128.5, 127.3, 121.7, 109.8, 81.6, 71.0, 70.1, 68.3, 21.6 ppm; MS (EI): m/z = 431.1 ($[M + H]^+$).

[2-(3-Methoxyphenyl)-6-phenylpyrimidin-4-yl]ferrocene
(**5**, $C_{27}H_{22}FeN_2O$)
Yield: 415 mg (93 %); IR (KBr): $\bar{\nu}$ = 2,961, 1,562, 1,522, 1,487, 1,372, 1,352, 1,261, 1,177, 1,104, 1,018, 819, 774, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.24–8.31 (m, 3H, ArH), 7.53–7.60 (m, 4H, ArH + PyH), 7.45 (t, 1H, J = 8.2 Hz, ArH), 7.33 (d, 1H, J = 8.4 Hz, ArH), 7.06 (d, 1H, J = 8.4 Hz, ArH), 5.15 (s, 2H, C_5H_4), 4.52 (s, 2H, C_5H_4), 4.08 (s, 5H, C_5H_5), 3.95 (s, 3H, OCH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.7, 163.4, 160.0, 140.1, 137.8, 130.7, 129.7, 129.0, 127.3, 125.4, 121.8, 121.0, 117.0, 116.4, 113.8, 110.1, 81.4, 71.1, 70.1, 68.3, 55.4 ppm; MS (EI): m/z = 447.1 ($[M + H]^+$).

[2-(4-Acetylphenyl)-6-phenylpyrimidin-4-yl]ferrocene
(**6**, $C_{28}H_{22}FeN_2O$)
Yield: 380 mg (83 %); IR (KBr): $\bar{\nu}$ = 2,922, 1,673, 1,595, 1,499, 1,413, 1,357, 1,259, 1,127, 1,105, 1,015, 961, 907, 821 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.06–8.11 (m, 4H, ArH), 7.92–7.97 (m, 3H, ArH), 7.80 (s, 2H, J = 8.4 Hz, ArH), 7.60 (s, 1H, PyH), 5.09 (s, 2H, C_5H_4), 4.50 (s, 2H, C_5H_4), 4.07 (s, 5H, C_5H_5), 2.65 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.8, 160.4, 148.2, 145.3, 136.8, 136.1, 135.8, 129.8, 129.2, 128.8, 127.5, 126.9, 126.0, 120.2, 83.8, 70.8, 69.9, 68.2 ppm; MS (EI): m/z = 459.1 ($[M + H]^+$).

Crystal structure determination

Crystallographic data for compounds **1–3** were collected on a Bruker SMART APEX-II CCD diffractometer equipped with a graphite monochromator at 296 K using Mo–Ka radiation (λ = 0.071073 Å). The data were corrected for Lorentz polarization factors as well as for absorption. The structures were solved by direct methods and refined by full-matrix least-squares methods on F^2 with the SHELX-97 program [34]. All non-hydrogen atoms were refined anisotropically, while hydrogen atoms were placed in geometrically calculated positions. CCDC reference numbers are 939,184-939,186 for **1–3**, respectively. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

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