Journal of Organometallic Chemistry 696 (2011) 2108–2115

Contents lists available at ScienceDirect

Journal of Organometallic Chemistry

journal homepage: www.elsevier.com/locate/jorganchem

Synthesis and properties of 5-ferrocenyl-1*H*-pyrazole-3-carbaldehydes

Alexey N. Rodionov [a,*], Alexander A. Simenel [a,b], Alexander A. Korlyukov [a], Vadim V. Kachala [c], Svetlana M. Peregudova [a], Kira Ya. Zherebker [a], Elena Yu. Osipova [a]

[a] A.N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 28 Vavilov St., 119991 GSP-1 Moscow, Russian Federation
[b] Moscow State Mining University, 6 Leninsky Ave., Moscow 119991, Russian Federation
[c] N.D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 47 Leninsky Ave., 119991 Moscow, Russian Federation

ARTICLE INFO

Article history:
Received 24 May 2010
Received in revised form
31 October 2010
Accepted 12 November 2010

Keywords:
Ferrocene
Pyrazoles
Reductive amination
Cyclic voltammetry
X-ray structure determination

ABSTRACT

New ferrocene derivatives – ethyl esters of 1-aryl-5-ferrocenyl-1*H*-pyrazole-3-carboxylic acids were synthesized. The corresponding aldehydes were obtained from acid esters in two steps. The reductive amination reaction of 5-ferrocenyl-1-phenyl-1*H*-pyrazole-3-carbaldehyde was studied. Several of these compounds were investigated by cyclic voltammetry. All of them exhibited a reversible one-electron oxidation–reduction wave owing to the ferrocene–ferricinium redox couple with a positive shift (0.51–0.69 V) compared with that of ferrocene (0.46 V). The X-ray crystal structure of the ethyl ether 1-(3-chloro-2-fluorophenyl)-5-ferrocenyl-1*H*-pyrazole-3-carboxylic acid is also presented.

1. Introduction

Ferrocene-heterocyclic compounds are of great interest both as exhibiting biological activity and as ligands for asymmetric catalysis. Earlier, heterocyclic ferrocene-containing compounds were shown to exhibit a wide range of biological activities such as antianemic, antibacterial, antitumor, and fungicidal ones [1–4]. Besides, ligands having ferrocenylheterocyclic moieties are suitable for the reactions of hydration, allylation, silylation, cyanation and many others [5,6].

The including of pyrazoles as key motifs in biologically active compounds has grown rapidly in the past decade. Both the pharmaceutical and agrochemical industries employ them as the central building blocks for the synthesis of compound libraries. At present, commercial drugs on the base of pyrazole are widely used in the clinical practice, e.g., sildenaphyl (Viagra™), phenybutasole (an antiphlogistic drug), or herbicidal diphenzoquat.

Recently, it was shown that the derivatives of 3-ferrocenyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde (FPCA), i.e. the products of reductive amination by different amines (especially *tret*-butilamine and cyclohexylamine) exhibited antimicrobial activity comparable with amikacin and tetracycline [2] in tests on a wide range of microorganisms, whereas 5-alkyl-2-ferrocenyl-6,7-dihydropyrazolo [1,5-a]pyrazin-4(5*H*)-one derivatives demonstrated antitumor activity [3]. Besides, Vukićević et al. showed that FPCA derivatives of the amino acids (especially those containing heteroaromatic rings such as histidine and tryptophan) appeared to be the most active against myelogenous leukemia K562 cell lines with a better cytotoxic potential than the starting FPCA precursor [4].

Therefore, the purpose of this study was the development of the method for synthesis of isomeric ferrocenylpyrazolecarbaldehydes and investigation of their reactivity in the reaction of direct reductive amination. In the present paper we report the obtainment of *N*-substituted 5-ferrocenyl-1-aryl-1*H*-pyrazole-3-aldehydes and the corresponding ethyl carboxylates, the cyclic voltammetry study of several compounds synthesized and X-ray determination of the molecular structure of ethyl ether 1-(3-chloro-2-fluorophenyl)-5-ferrocenyl-1*H*-pyrazole-3-carboxylic acid.

2. Results and discussion

2.1. Synthesis of ethyl esters of 5-ferrocenyl-1H-azole-3-carboxylic acids

The condensation of 1,3-dicarbonyl compounds and hydrazine or monosubstituted hydrazines is known to be the most suitable method for the synthesis of pyrazole ring. Ethyl ester of ferrocenoylpyruvic acid was used as the starting materials. The Claisen condensation of acetylferrocene (**1**) and diethyl oxalate in the

* Corresponding author.
E-mail address: rodalex@ineos.ac.ru (A.N. Rodionov).

0022-328X/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.jorganchem.2010.11.018

presence of NaOEt was reported to furnish ethyl 2,4-dioxo-4-ferrocenylbutanoate (**2**) (52%) [7]. To choose a base – solvent system providing the best results we have tested several reaction systems (Scheme 1). In general, it turned out that the reactions produced the corresponding product in good yields in almost all tested base systems.

The use of potassium *tert*-butoxide in benzene allows a facile isolation and purification of the intermediate potassium salt of ethyl 2,4-dioxo-4-ferrocenylbutanoate. Addition of an equimolar amount of acetic acid to the suspension of salt in CH_2Cl_2 eliminated the free ester (89% overall yield). The presence of a broad singlet at 15 ppm (OH proton) and a singlet (1H) at 6.54 ppm in the ^{1}H NMR spectrum recorded in $CDCl_3$ solution at room temperature proves that the ester **2** exists entirely in enol form.

Esters of 5-ferrocenyl-1-aryl-1*H*-pyrazole-3-carboxylic acids were synthesized in high to quantitative yields by the condensation between ethyl 2,4-dioxo-4-ferrocenylbutanoate **2** (enol form) and monosubstituted arylhydrazines. Noteworthy, the reaction with catalytic amounts of acetic acid in boiling ethanol affords one isomer only (Scheme 2). The structures of compounds were assigned on the basis of ^{1}H and ^{13}C NMR spectra, ^{1}H/^{13}C heteronuclear correlations, and NOE-experiments. The coupling of ethyl esters of acetyl- or benzoylpyruvic acid with monoarylhydrazine yields pyrazoles with the same arrangement of substituents in the heterocyclic fragment [8–10].

The ^{1}H NMR spectra of compounds shows several sets of signals assigned, respectively, to the protons of substituted and unsubstituted cyclopentadienyl rings (3.90–4.44 ppm), the CH-pyrazole proton (6.54–7.13 ppm), and the protons of the ethyl and aryl substitutes. The assignments of the signals in the ^{13}C NMR spectra of ferrocenyl-compounds were based on the HSQC spectra. In NOE-experiments, the interaction between protons of the aryl substituent and those of the substituted cyclopentadienyl ring revealed that counted in favor the assigned structures of ethyl esters of 1-aryl-5-ferrocenyl-1*H*-pyrazole-3-carboxylic acids. Moreover, for ethyl 1-(2-fluoro-3-chlorophenyl)-5-ferrocenyl-3-pyrazolecarboxylate **3j**, the molecular structure was determined by means of X-ray analysis (Fig. 1). It can be mentioned that pyrazole and one of Cp moieties are almost coplanar (the magnitude of the respective interplanar angle is 4.8°). At the same time, the phenyl group is perpendicular to the plane of the pyrazole moiety. The reason of these structural peculiarities is the presence of Cl and F atoms which increase the steric hindrance in 3-ethylcarboxypyrazole fragment.

The reaction of **2** with hydroxylamine hydrochloride leads to the single product, ethyl ester 5-ferrocenyl-3-isoxazole carboxylic acid **3l** (Scheme 5). At the same time, the condensation of **2** and methyl hydrazine in boiling ethanol with catalytic amounts of acetic acid yielded a mixture of two possible isomers with a ratio 60:40 (based on ^{1}H NMR-data), with ethyl ester 5-ferrocenyl-1-methyl-3-pyrazole carboxylic acid **3k** being the major one (Scheme 3). Crystallization from ethanol-chloroform mixture (50/1) repeated twice allowed us to separate **3k** in analytically pure form. The reaction of **2** and methyl hydrazine in glacial acetic acid leads to the formation of ethyl ester 5-ferrocenyl-1-methyl-3-pyrazole carboxylic acid **3k** in 85% yield; its structure was assigned on the basis of ^{1}H and ^{13}C NMR spectra, and ^{1}H/^{13}C (HSQC and HMBC) heteronuclear correlations.

2.2. Synthesis of aldehydes

The corresponding alcohols were obtained in 90–95% yields by reduction of esters **3a**–**k** with $LiAlH_4$ in a THF-1,4-dioxane mixture.

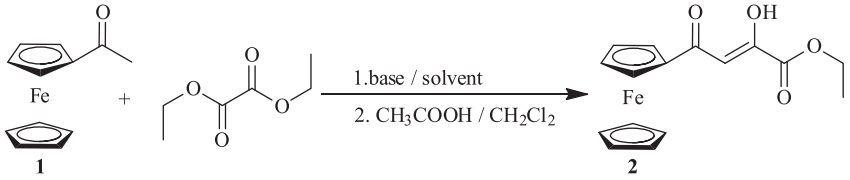
(5-Ferrocenyl-1-phenyl-1*H*-pyrazol-3-yl)methanol **4a** was chosen as a model compound for carrying out the oxidation reaction (Scheme 4). The use of the Corey's reagent (pyridinium chlorochromate) in dichloromethane at room temperature in argon atmosphere allows preparation of the target aldehyde in 12% yield [11]. The Pfitzner–Moffatt oxidation (DMSO-DCC) [12] and oxidation with MnO_2 in CH_2Cl_2 at room temperature [13] lead to the formation of aldehyde in similar yields (85 and 87%, respectively), the former mode requiring an additional purification of the product. The purification was carried out either *via* the bisulphite derivative or by means of column chromatography (SiO_2, eluent – chloroform).

Other aldehydes, i.e. 1-aryl-5-ferrocenyl-1*H*-pyrazole-3-aldehydes, 5-ferrocenyl-1-methyl-1*H*-pyrazole-3-aldehyde and 5-ferrocenylisoxazole-3-aldehyde were obtained similarly. The overall yields of the products from reduction and oxidation reactions were 82–94% (Scheme 5).

2.3. Reductive amination of *5a*

The reactions of aldehydes or ketones with ammonia, primary or secondary amines in the presence of reducing agents to give primary, secondary, or tertiary amines, respectively, known as reductive aminations (of the carbonyl compounds) or reductive alkylations (of the amines) are among the most useful and important tools in the synthesis of different kinds of amines. The reductive amination reaction described as a direct reaction without prior formation of the intermediate imine or iminium salt when a carbonyl compound and an amine are mixed with the proper reducing agent. The stepwise or indirect reaction involves the formation of the intermediate imine followed by reduction in a separate step.

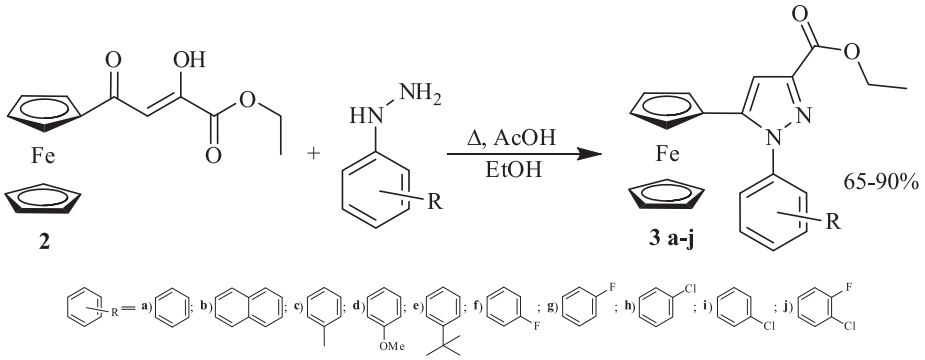
The obtainment of amino derivatives of 3-ferrocenyl-1-phenyl-4-formylpyrazole that exhibited antimicrobial activity was reported in a recently published paper [2]. These amino derivatives were



Entry	Base	Solvent	Time	Yield[a]
1[b]	NaH	THF	3 h	62
2[b]	*t*-BuOK	Benzene	2 h	89
3[b]	*t*-BuOK	THF	1 h	74

[a] Isolated yields. [b] Reaction conditions: acetylferrocene (10 mmol), base (10 mmol), diethyl oxalate (10 mmol), solvent (25 mL), Ar atmosphere, reflux

Scheme 1. Formation of ethyl 2,4-dioxo-4-ferrocenylbutanoate **2**.



Scheme 2. Synthesis of esters of 5-ferrocenyl-1-aryl-1*H*-pyrazole-3-carboxylic acids.

prepared in overall yields of 80% by a two-step protocol. We have prepared isomeric aminomethyl derivatives in the yields up to 92% *via* a one-step procedure.

The primary and non-hindered secondary amines were used successfully in these reactions (Scheme 6). However, the sterically hindered diisopropylamine proved to yield another product, the corresponding alcohol **4a**.

2.4. Electrochemistry

It is well known that ferrocene is easily oxidized to the ferricinium cation by one-electron oxidants [14]. The redox-potentials for the ferrocene–ferricinium couple range from 0.3 to 0.5 V. The redox-potentials for ferrocene derivatives change within wider limits. The potential depends on the electron-donating or electron withdrawing abilities of the substituents. Thus, the redox properties can be rather strongly affected by altering the substituent nature.

The anodic electrochemistry of some compounds was investigated by cyclic voltammetry in MeCN solution with [*n*-Bu_4N][PF_6] as a supporting electrolyte. The results are summarized in Table 1 and a representative cyclic voltammetric scan (CV) for **3l** is shown in Fig. 2.

All the compounds exhibit reversible one-electron waves. The electrode potentials for all investigated compounds showed a positive shift compared to that of ferrocene (0.46 V) indicative of the electron withdrawing effect of the heterocyclic substituent, the electron withdrawing effect of the isoxazole substituent being greater than that of the pyrazole one. This is most likely connected with the more electron-accepting effect of the isoxazole ring. The introduction of electron-donating (CH_3O^-, **3d**) or electron-withdrawing groups (Cl^-, F^- **3j**) to the phenyl ring of pyrazole derivatives exerts no effect on the value of oxidation potentials. The electrode potentials for all investigated species are comparable to those previously reported for analogous compounds [4]. We can suggest that this is a common property of all ferrocenyl-azole compounds of such type.

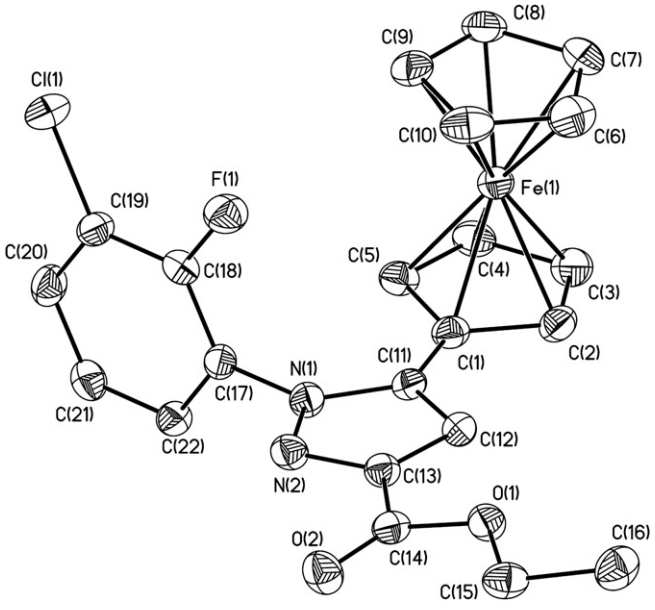


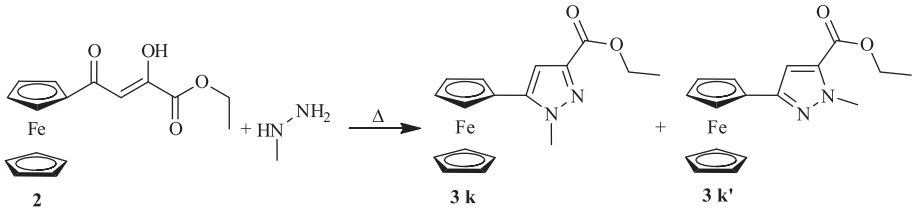
Fig. 1. The molecular structure of **3j** presented in thermal ellipsoids at 50% probability. Principal bonds (Å and °): O(1)–C(14) 1.339(3), O(1)–C(15) 1.452(3), O(2)–C(14) 1.200 (3), N(1)–N(2) 1.356(3), N(1)–C(11) 1.377(3), N(1)–C(17) 1.432(3), N(2)–C(13) 1.329 (3), Cl(1)–C(19) 1.728(3), F(1)–C(18) 1.341(3).

3. Experimental

Melting points were determined with a Boethius microstage and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker DRX-300 and Bruker DRX-500 spectrometers at 300.13 (500.13) MHz and 75.5 (125.76) MHz for protons and ^{13}C, respectively, at 30 °C in $CDCl_3$ and DMSO. Chemical shifts are given in ppm relative to solvent residual protons. The full assignments of all reported NMR signals were made by the use of 1D and 2D NMR experiments such as HSQC, HMBC, COSY, and NOESY correlation techniques. IR spectra were recorded on a Carl Zeiss UR-20 spectrometer using a KBr disk. EI mass spectra were taken on a FINNIGAN POLARIS Q spectrometer at 70 eV and the temperature of the ion chamber 250°C. The solvents were purified by standards techniques. All reagents employed were purchased from Acros Organics and used without purification.

3.1. Synthesis of ferrocenoylpyruvic acid ethyl ester (*2*)

To the suspension of 24.64 g (0.22 mol) of *t*-BuOK in benzene (300 ml) was added acetylferrocene 45.6 g (0.2 mol). Diethyl oxalate 27 ml (0.22 mol) was then added dropwise. The reaction mixture was refluxed for 2 h and cooled to rt. The potassium salt was filtered off, washed with ether, and suspended in CH_2Cl_2. The CH_2Cl_2 suspension was treated with glacial acetic acid up to pH = 5 and washed with water, saturated $NaHCO_3$ and brine. The organics were dried over Na_2SO_4, solvent was removed *in vacuo*. Deep purple crystals, yield 89%, m.p. 77 °C (m.p. 68–70 °C [6]). ^1H NMR (500 MHz, $CDCl_3$): 1.38 (t, J = 7 Hz, 3H, CH_3); 4.19 (s, 5H, Fc); 4.34 (q, J = 7 Hz, 2H, CH_2); 4.62 (s, 2H, Fc); 4.85 (s, 2H, Fc); 6.54 (s, 1H, CH); 14.95 (br.s, 1H, OH). ^{13}C NMR (126 MHz, $CDCl_3$): 14.0, 62.2, 69.3,



Reaction medium	Ratio of compounds (%)	
	3k	**3k′**
EtOH - 1 drop AcOH	60	40
AcOH	85	15

Scheme 3. Condensation of **2** with methyl hydrazine.

70.5, 73.4, 77.4, 100.0, 162.6, 163.6, 197.7. EIMS, *m/z* (RI%): 328 (M^+, 62); 254 ($[M-C_2H_4-CO_2]^+$, 100); 228 ($[FcC(O)CH_3]^+$, 8); 213 ($[FcCO]^+$, 17); 185 ($[Fc]^+$, 17).

3.2. General procedure 1. Synthesis of ethyl ferrocenylpyrazole-carboxylate (**3a**–**k**)

To a solution of ethyl ester of ferrocenoylpyruvic acid (**2**) (1.64 g, 5 mmol) in 20 ml of ethanol was under argon added the corresponding monosubstituted hydrazines hydrochlorides or hydroxylamine hydrochloride (5.1 mmol). The resulting mixture was then heated while refluxing for 4 h. Upon completion of the reaction, the mixture was cooled to 0 °C, the precipitate was isolated by filtration, washed with cold ethanol (10 ml), recrystallized from ethanol and dried by Na_2SO_4.

3.2.1. Ethyl 5-ferrocenyl-1-phenyl-1H-pyrazole-3-carboxylate (**3a**)

Orange crystals, yield 95%, m.p. 151–152 °C. ^{1}H NMR (500 MHz, $CDCl_3$): 1.43 (t, J = 7.1 Hz, 3H, CH_3); 4.06 (s, 5H, Fc); 4.13 (s, 2H, Fc); 4.19 (s, 2H, Fc); 4.45 (q, J = 7.1 Hz, 2H, CH_2); 7.03 (s, 1H, Pz); 7.39–7.43 (m, 5H, Ph). ^{13}C NMR (126 MHz, $CDCl_3$): 14.4, 61.1, 68.6, 68.9, 69.8, 73.6, 108.4, 126.6, 128.8, 139.8, 143.8, 144.1, 162.3. EI/MS, *m/z* (RI%): 400 (M^+, 100); 372 ($[M-C_2H_4]^+$, 20); 328 ($[M-C_2H_4-CO_2]^+$, 20); 263 ($[M-C_2H_4-CO_2-Cp]^+$, 23).

3.2.2. Ethyl 5-ferrocenyl-1-(naphthalen-1-yl)-1H-pyrazole-3-carboxylate (**3b**)

Orange crystals, yield 89%, m.p. 200–201 °C. ^{1}H NMR (300 MHz, $CDCl_3$): 1.42 (t, J = 6.5 Hz, 3H, CH_3); 3.90 (br.s, 2H, Fc); 3.96 (s, 5H, Fc); 4.05 (s, 2H, Fc); 4.44 (q, J = 6.5 Hz, 2H, CH_2); 7.13 (s, 1H, Pz); 7.29 (d, J = 7.5 Hz, 1H, Ar); 7.49–7.56 (m, 4H, Ar); 7.95 (d, J = 7 Hz, 1H, Ar); 8.04 (m, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): 14.5, 61.1, 67.6, 69.0, 69.9, 72.6, 106.7, 122.9, 125.0, 125.9, 126.9, 127.5, 128.1, 130.3, 130.8, 134.0, 136.6, 144.6, 145.9, 162.7. *Anal.* Calcd. for $C_{26}H_{22}FeN_2O_2$: C, 69.35; H, 4.92; N, 6.22; Fe, 12.40. Found: C, 69.26; H, 4.91; N, 6.08; Fe, 12.5. EI/MS, *m/z* (RI%): 450 (M^+, 100); 422 ($[M-C_2H_4]^+$, 14); 378 ($[M-C_2H_4-CO_2]^+$, 10); 313 ($[M-C_2H_4-CO_2-Cp]^+$, 17).

3.2.3. Ethyl 5-ferrocenyl-1-p-tolyl-1H-pyrazole-3-carboxylate (**3c**)

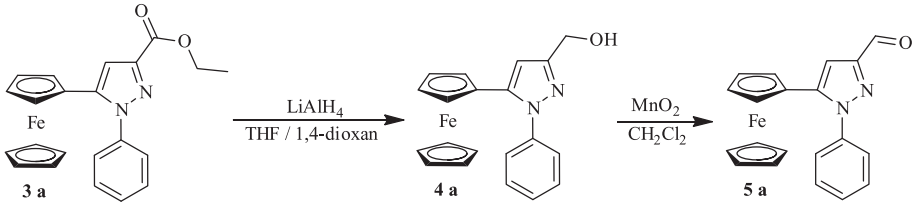
Orange crystals, yield: 91%, m.p. 135–136 °C. ^{1}H NMR (500 MHz, $CDCl_3$): 1.44 (t, J = 7 Hz, 3H, CH_3); 2.42 (s, 3H, CH_3); 4.07 (s, 5H, Fc); 4.14 (s, 2H, Fc); 4.20 (s, 2H, Fc); 4.46 (q, J = 7 Hz, 2H, CH_2); 7.02 (s, 1H, Pz); 7.24–7.26 (m, 4H, Ar). ^{13}C NMR (126 MHz, $CDCl_3$): 14.4, 21.2, 61.0, 68.4, 68.9, 69.8, 73.5, 108.1, 126.4, 129.4, 137.4, 138.9, 143.7, 143.9, 126.2. *Anal.* Calcd. for $C_{23}H_{22}FeN_2O_2$: C, 66.68; H, 5.35; N, 6.76; Fe, 13.48. Found: C, 66.71; H, 5.38; N, 6.69; Fe, 13.2. EI/MS, *m/z* (RI%): 414 (M^+, 100); 386 ($[M-C_2H_4]^+$, 17); 342 ($[M-C_2H_4-CO_2]^+$, 19); 277 ($[M-C_2H_4-CO_2-Cp]^+$, 23).

3.2.4. Ethyl 5-ferrocenyl-1-(4-methoxyphenyl)-1H-pyrazole-3-carboxylate (**3d**)

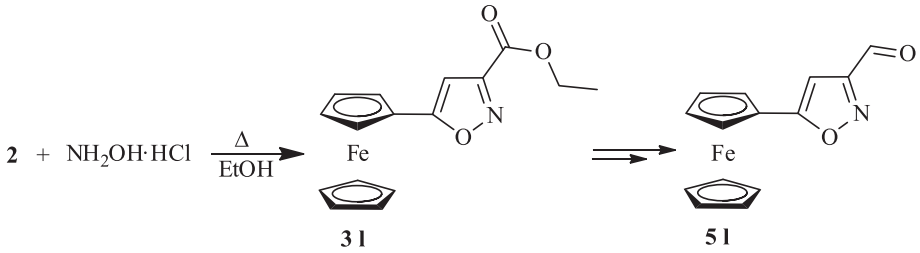
Deep orange crystals, yield: 86%, m.p. 170–171 °C. ^{1}H NMR (500 MHz, $CDCl_3$): 1.40 (t, J = 7 Hz, 3H, CH_3); 3.86 (s, 3H, CH_3); 4.06 (s, 5H, Fc); 4.13 (s, 2H, Fc); 4.20 (s, 2H, Fc); 4.41 (q, J = 7 Hz, 2H, CH_2); 6.93 (d, J = 8.3 Hz, 2H, Ar); 7.00 (s, 1H, Pz); 7.29 (d, J = 8.3 Hz, 2H, Ar). ^{13}C NMR (126 MHz, $CDCl_3$): 14.4, 55.5, 61.0, 68.4, 68.8, 69.8, 73.5, 107.8, 114.0, 128.0, 132.9, 143.8, 144.0, 159.9, 162.6. *Anal.* Calcd. for $C_{23}H_{22}FeN_2O_3$: C, 64.20; H, 5.15; N, 6.51; Fe, 12.98. Found: C, 64.41; H, 5.14; N, 6.54; Fe, 12.8. EI/MS, *m/z* (RI%): 430 (M^+, 100); 402 ($[M-C_2H_4]^+$, 13); 358 ($[M-C_2H_4-CO_2]^+$, 13); 293 ($[M-C_2H_4-CO_2-Cp]^+$, 11).

3.2.5. Ethyl 1-(4-tert-butylphenyl)-5-ferrocenyl-1H-pyrazole-3-carboxylate (**3e**)

Yellow crystals, yield: 92%, m.p. 124–125 °C. ^{1}H NMR (300 MHz, $CDCl_3$): 1.36 (s, 9H, CH_3); 1.40 (t, J = 7 Hz, 3H, CH_3); 4.08 (s, 5H, Fc); 4.18 (s, 2H, Fc); 4.22 (s, 2H, Fc); 4.41 (q, J = 7 Hz, 2H, CH_2); 7.00 (s, 1H, Pz); 7.29 (d, J = 8.1 Hz, 2H, Ar); 7.42 (d, J = 8.1 Hz, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): 14.4, 31.24, 34.71, 60.9, 68.5, 68.9, 69.9, 73.7, 108.1, 125.7, 126.0, 137.3, 143.7, 143.9, 152.2, 162.6. *Anal.* Calcd. for $C_{26}H_{28}FeN_2O_2$: C, 68.43; H, 6.18; N, 6.14; Fe, 12.24. Found: C, 68.18; H, 6.10; N, 5.98; Fe, 11.6. EI/MS, *m/z* (RI%): 456 (M^+, 100); 428 ($[M-C_2H_4]^+$, 19); 384 ($[M-C_2H_4-CO_2]^+$, 6); 263 ($[M-C_2H_4-CO_2-Cp]^+$, 8).



Scheme 4. Synthesis of aldehydes **5a**.



Scheme 5. Synthesis of ferrocenylisoxazoles **3l**–**5l**.

*3.2.6. Ethyl 5-ferrocenyl-1-(3-fluorophenyl)-1H-pyrazole-3-carboxylate (**3f**)*

Deep orange crystals, yield: 85%, m.p. 143–144 °C. ^{1}H NMR (500 MHz, $CDCl_3$): 1.43 (t, J = 7 Hz, 3H, CH_3); 4.10 (s, 5H, Fc); 4.19 (s, 2H, Fc); 4.24 (s, 2H, Fc); 4.44 (q, J = 7 Hz, 2H, CH_2); 7.03 (s, 1H, Pz); 7.12–7.18 (m, 3H, Ar); 7.38 (m, 1H, Ar). ^{13}C NMR (126 MHz, $CDCl_3$): 14.4, 61.1, 68.8, 69.0, 69.9, 73.4, 109.0, 113.9 (d, J = 24.4 Hz), 115.7 (d, J = 21.0 Hz), 122.1, 130.0 (d, J = 8.8 Hz), 141.0 (d, J = 10.1 Hz), 143.8, 144.4, 161.3 (d, J = 249.1 Hz), 162.4. *Anal.* Calcd. for $C_{22}H_{19}FFeN_2O_2$: C, 63.18; H, 4.58; N, 6.70; Fe, 13.35. Found: C, 63.28; H, 4.51; N, 6.69; Fe, 13.35. EI/MS, *m*/*z* (RI%): 418 (M^+, 100); 390 ($[M-C_2H_4]^+$, 24); 346 ($[M-C_2H_4-CO_2]^+$, 27); 281 ($[M-C_2H_4-CO_2-Cp]^+$, 27).

*3.2.7. Ethyl 5-ferrocenyl-1-(4-fluorophenyl)-1H-pyrazole-3-carboxylate (**3g**)*

Yellow crystals, yield: 91%, m.p. 145 °C. ^{1}H NMR (500 MHz, $CDCl_3$): 1.39 (t, J = 7.1 Hz, 3H, CH_3); 4.06 (s, 5H, Fc); 4.10 (s, 2H, Fc); 4.20 (s, 2H, Fc); 4.41 (q, J = 7.1 Hz, 2H, CH_2); 7.00 (s, 1H, Pz); 7.08 (t, J = 8.4 Hz, 2H, Ar); 7.32–7.35 (m, 2H, Ar). ^{13}C NMR (126 MHz, $CDCl_3$): 14.3, 61.0, 68.5, 68.9, 69.8, 73.2, 108.4, 115.6 (d, J = 22.7 Hz), 128.2, 128.3, 135.7, 143.8 (d, J = 27.7 Hz), 161.3 (d, J = 249.5 Hz), 162.4. *Anal.* Calcd. for $C_{22}H_{19}FFeN_2O_2$: C, 63.18; H, 4.58; N, 6.70; Fe, 13.35. Found: C, 63.21; H, 4.67; N, 6.58; Fe, 13.3. EI/MS, *m*/*z* (RI%): 418 (M^+, 100); 390 ($[M-C_2H_4]^+$, 26); 346 ($[M-C_2H_4-CO_2]^+$, 28); 281 ($[M-C_2H_4-CO_2-Cp]^+$, 24).

*3.2.8. Ethyl 1-(2-chlorophenyl)-5-ferrocenyl-1H-pyrazole-3-carboxylate (**3h**)*

Yellow powder, yield: 84%, m.p. 146 °C. ^{1}H NMR (500 MHz, $CDCl_3$): 1.44 (t, J = 7 Hz, 3H, CH_3); 4.11 (s, 5H, Fc); 4.14 (br.s, 2H, Fc); 4.22 (s, 2H, Fc); 4.45 (q, J = 7 Hz, 2H, CH_2); 7.02 (s, 1H, Pz); 7.42–7.51 (m, 3H, Ar); 7.57 (d, J = 7.5 Hz, 1H, Ar). ^{13}C NMR (126 MHz, $CDCl_3$): 14.4, 61.1, 67.7, 69.4, 70.2, 72.8, 106.9, 127.5, 130.0, 130.3, 131.1, 133.1, 137.9, 144.8, 145.4, 162.5. *Anal.* Calcd. for $C_{22}H_{19}ClFeN_2O_2$: C, 60.79; H, 4.41; N, 6.44; Fe, 12.85. Found: C, 60.64; H, 4.44; N, 6.29; Fe, 12.9. EI/MS, *m*/*z* (RI%): 434 (M^+, 100); 406 ($[M-C_2H_4]^+$, 12); 362 ($[M-C_2H_4-CO_2]^+$, 5); 297 ($[M-C_2H_4-CO_2-Cp]^+$, 17).

*3.2.9. Ethyl 1-(3-chlorophenyl)-5-ferrocenyl-1H-pyrazole-3-carboxylate (**3i**)*

Orange crystals, yield: 86%, m.p. 121–122 °C. ^{1}H NMR (500 MHz, $CDCl_3$): 1.44 (t, J = 7 Hz, 3H, CH_3); 4.12 (s, 5H, Fc); 4.18 (s, 2H, Fc); 4.25 (s, 2H, Fc); 4.45 (q, J = 7 Hz, 2H, CH_2); 7.04 (s, 1H, Pz); 7.23 (d, J = 7 Hz, 1H, Ar); 7.32–7.35 (m, 1H, Ar); 7.40 (d, J = 7.5 Hz, 1H, Ar); 7.50 (c, 1H, Ar). ^{13}C NMR (126 MHz, $CDCl_3$): 14.4, 61.2, 68.8, 69.1, 69.9, 73.4, 109.0, 124.6, 126.7, 129.0, 129.7, 134.5, 140.7, 143.9, 144.5, 162.4. *Anal.* Calcd. for $C_{22}H_{19}ClFeN_2O_2$: C, 60.79; H, 4.41; N, 6.44; Fe, 12.85. Found: C, 60.58; H, 4.39; N, 6.24; Fe, 12.6. EI/MS, *m*/*z* (RI %): 434 (M^+, 100); 406 ($[M-C_2H_4]^+$, 25); 362 ($[M-C_2H_4-CO_2]^+$, 24); 297 ($[M-C_2H_4-CO_2-Cp]^+$, 22).

*3.2.10. Ethyl 1-(3-chloro-2-fluorophenyl)-5-ferrocenyl-1H-pyrazole-3-carboxylate (**3j**)*

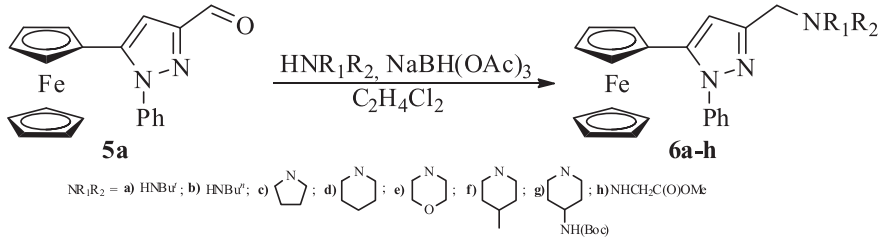
Yellow powder, yield: 84%, m.p. 177–178 °C. ^{1}H NMR (300 MHz, $CDCl_3$): 1.41 (t, J = 7 Hz, 3H, CH_3); 4.08 (s, 5H, Fc); 4.13 (s, 2H, Fc); 4.24 (s, 2H, Fc); 4.42 (q, J = 7 Hz, 2H, CH_2); 7.02 (s, 1H, Pz); 7.22 (m, 1H, Ar); 7.37 (m, 1H, Ar); 7.55 (m, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): 14.4, 61.2, 67.5, 69.3, 69.9, 72.3, 107.4, 122.2 (J = 16.3 Hz), 124.4 (J = 5.3 Hz), 128.1, 129.2 (J = 12.3 Hz), 132.0, 145.3, 145.7, 152.2 (J = 254.1 Hz), 162.2. *Anal.* Calcd. for $C_{22}H_{19}ClFFeN_2O_2$: C, 58.37; H, 4.01; N, 6.19; Fe, 12.34. Found: C, 58.41; H, 4.04; N, 6.25; Fe, 12.3. EI/MS, *m*/*z* (RI%): 452 (M^+, 100); 424 ($[M-C_2H_4]^+$, 21); 380 ($[M-C_2H_4-CO_2]^+$, 24); 315 ($[M-C_2H_4-CO_2-Cp]^+$, 27).

*3.2.11. Ethyl 5-ferrocenyl-1-methyl-1H-pyrazole-3-carboxylate (**3k**)*

Yellow crystals, yield: 75%, m.p. 139–140 °C. ^{1}H NMR (300 MHz, $CDCl_3$): 1.39 (t, J = 7 Hz, 3H, CH_3); 4.02 (s, 3H, CH_3); 4.16 (s, 5H, Fc); 4.36 (s, 2H, Fc); 4.38 (q, J = 7 Hz, 2H, CH_2); 4.51 (s, 2H, Fc); 6.83 (s, 1H, Pz). ^{13}C NMR (75 MHz, $CDCl_3$): 14.3, 38.5, 60.8, 68.3, 69.2, 69.6, 73.8, 108.2, 142.3, 142.8, 162.4. *Anal.* Calcd. for $C_{17}H_{18}FeN_2O_2 \cdot 0.5H_2O$: C, 58.81; H, 5.52; N, 8.07; Fe, 16.08. Found: C, 59.06; H, 5.55; N, 7.92; Fe, 16.9. EI/MS, *m*/*z* (RI%): 338 (M^+, 100); 310 ($[M-C_2H_4]^+$, 28); 265 ($[M-C_2H_4-CO_2]^+$, 27); 201 ($[M-C_2H_4-CO_2-Cp]^+$, 22).

*3.2.12. Ethyl 5-ferrocenylisoxazole-3-carboxylate (**3l**)*

Deep orange crystals, yield: 86%, m.p. 92–93 °C. ^{1}H NMR (500 MHz, $CDCl_3$): 1.43 (t, J = 7.2 Hz, 3H, CH_3); 4.14 (s, 5H, Fc); 4.44 (s, 2H, Fc); 4.46 (q, J = 7.2 Hz, 2H, CH_2); 4.77 (s, 2H, Fc); 6.54 (s, 1H, Az). ^{13}C NMR (126 MHz, $CDCl_3$): 14.1, 62.1, 67.2, 69.9, 70.0, 70.4, 98.4, 156.7, 160.2, 173.8. *Anal.* Calcd. for $C_{17}H_{18}FeN_2O_2 \cdot H_2O$: C, 56.00; H, 4.99; N, 4.08. Found: C, 55.69; H, 4.99; N, 4.09. EI/MS, *m*/*z* (RI%): 325 (M^+, 100); 297 ($[M-C_2H_4]^+$, 10); 253 ($[M-C_2H_4-CO_2]^+$, 44); 188 ($[M-C_2H_4-CO_2-Cp]^+$, 22).



Scheme 6. Reductive amination of **5a**.

Table 1
Electrochemical data of some compounds.

№	Oxidation $E_{1/2}$, *V*	$\Delta E_{1/2}$, *V*	Reduction E_p, *V*
3a	0.69	0.23	
3d	0.54	0.08	
3j	0.57	0.11	
3l	0.64	0.18	−1.97
4a	0.51	0.05	
4l	0.59	0.13	
5a	0.54	0.08	−2.05
FcH	0.46		

3.3. General procedure 2. Synthesis of alcohols **4a**–**l**

Ethyl 5-ferrocenyl-3-carboxylates **3a**–**l** (5 mmol) dissolved in anhydrous THF (50 ml) were slowly added to a stirred solution of lithium aluminum hydride (0.2 g, 5 mmol) in the 1,4-dioxane (50 ml). The mixture was refluxed for 1 h, stirred overnight at room temperature, cooled with an ice bath and treated by brine (0.5 ml). The resulting mixture was filtered, the inorganic precipitate was washed three times with diethyl ether, the solution was dried (sodium sulfate), and the solvent evaporated under reduced pressure to give the fine products.

3.3.1. (5-Ferrocenyl-1-phenyl-1H-pyrazol-3-yl)methanol (**4a**)

Yellow powder, yield: 95%, m.p. 105–106. ^{1}H NMR (500 MHz, $CDCl_3$): 2.67 (br.s, 1H, OH); 4.07 (s, 5H, Fc); 4.14 (s, 2H, Fc); 4.18 (s, 2H, Fc); 4.75 (s, 2H, CH_2); 6.53 (s, 1H, Pz); 7.33–7.42 (m, 5H, Ar). ^{13}C NMR (126 MHz, $CDCl_3$): 52.7, 67.8, 68.5, 69.2, 78.3, 118.4, 125.7, 125.7, 127.6, 129.3, 140.1, 150.7, 155.2. *Anal.* Calcd. for $C_{20}H_{18}FeN_2O\cdot 1/3H_2O$: C, 65.95; H, 5.17; N, 7.69. Found: C, 65.94; H, 5.04; N, 7.26. EI/MS, *m*/*z* (RI%): 358 (M^+, 100); 356 ([M−2H]$^+$, 16); 293 ([M−Cp]$^+$, 7).

3.3.2. (5-Ferrocenyl-1-(naphthalen-1-yl)-1H-pyrazol-3-yl) methanol (**4b**)

Orange oil, yield: 89%. ^{1}H NMR (500 MHz, $CDCl_3$): 1.92 (br.s, 1H, OH); 4.16 (s, 5H, Fc); 4.39 (s, 2H, Fc); 4.90 (s, 2H,); 4.93 (s, 2H, Fc); 7.48–7.57 (m, 2H, Ar); 7.87–7.96 (m, 4H, Ar); 8.04 (s, 1H, Ar); 8.13 (s, 1H, Ar). ^{13}C NMR (126 MHz, $CDCl_3$): 56.2, 67.4, 68.9, 69.4, 77.6, 115.6, 118.2, 120.7, 125.7, 126.9, 127.3, 127.8, 127.9, 129.4, 131.7, 133.7, 137.4, 150.3. EI/MS, *m*/*z* (RI%): 408 (M^+, 100); 406 ([M−2H]$^+$, 14); 343 ([M−Cp]$^+$, 9).

3.3.3. (5-Ferrocenyl-1-(p-tolyl)-1H-pyrazol-3-yl)methanol (**4c**)

Orange oil, yield: 93%. ^{1}H NMR (500 MHz, $CDCl_3$): 2.39 (s, 3H, CH_3); 3.39 (br.s, 1H, OH); 4.05 (s, 5H, Fc); 4.13 (s, 2H, Fc); 4.16 (s, 2H, Fc); 4.71 (s, 2H, CH_2); 6.50 (s, 1H, Pz); 7.18 (d, J = 8.5 Hz, 2H, Ar); 7.30 (d, J = 8.4 Hz, 2H, Ar). ^{13}C NMR (126 MHz, $CDCl_3$): 21.1, 58.7, 68.5, 69.7, 74.6, 104.7, 126.0, 129.3, 137.7, 138.1, 142.8, 152.6. EI/MS, *m*/*z* (RI%): 372 (M^+, 100); 370 ([M−2H]$^+$, 27); 352 ([M−CH_2O]$^+$, 5); 307 ([M−Cp]$^+$, 8).

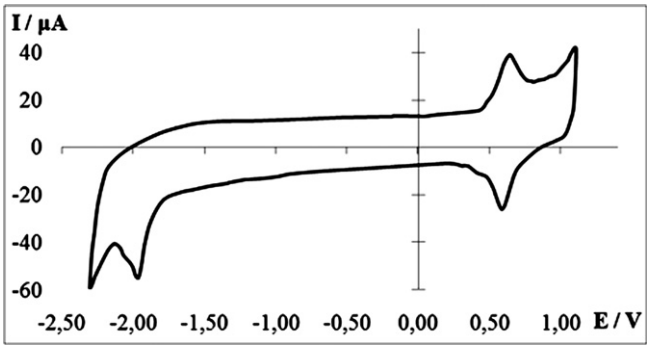


Fig. 2. Cyclic voltammogram for ferrocenylisoxazole **3l** in MeCN.

3.3.4. (5-Ferrocenyl-1-(4-methoxyphenyl)-1H-pyrazol-3-yl) methanol (**4d**)

Orange powder, yield: 96%, m.p. 150–151. ^{1}H NMR (500 MHz, $CDCl_3$): 3.44 (br.s, 1H, OH); 3.83 (s, 3H, CH_3); 4.05 (s, 5H, Fc); 4.12 (s, 2H, Fc); 4.17 (s, 2H, Fc); 4.71 (s, 2H, CH_2); 6.49 (s, 1H, Pz); 6.91 (d, J = 8.8 Hz, 2H, Ar); 7.25 (d, J = 8.8 Hz, 2H, Ar). ^{13}C NMR (126 MHz, $CDCl_3$): 55.4, 58.6, 68.3, 68.5, 69.6, 74.4, 104.2, 113.8, 127.6, 133.2, 142.9, 152.4, 159.3. EI/MS, *m*/*z* (RI%): 386 (M^+, 100); 384 ([M−2H]$^+$, 12); 356 ([M−CH_2O]$^+$, 4); 321 ([M−Cp]$^+$, 12).

3.3.5. (1-(4-tert-Butylphenyl)-5-ferrocenyl-1H-pyrazol-3-yl) methanol (**4e**)

Dark orange oil, yield: 85%. ^{1}H NMR (500 MHz, $CDCl_3$): 1.37 (s, 9H, CH_3); 2.04 (br.s, 1H, OH); 4.08 (s, 5H, Fc); 4.17 (s, 2H, Fc); 4.20 (s, 2H, Fc); 4.75 (s, 2H, CH_2); 6.52 (s, 1H, Pz); 7.26 (d, J = 8.3 Hz, 2H, Ar); 7.42 (d, J = 8.3 Hz, 2H, Ar). ^{13}C NMR (126 MHz, $CDCl_3$): 31.3, 34.7, 58.8, 68.5, 68.6, 69.7, 74.6, 104.7, 125.6, 125.7, 137.5, 142.8, 151.4, 152.5. EI/MS, *m*/*z* (RI%): 414 (M^+, 100); 412 ([M−2H]$^+$, 10); 349 ([M−Cp]$^+$, 14).

3.3.6. (5-Ferrocenyl-1-(3-fluorphenyl)-1H-pyrazol-3-yl)methanol (**4f**)

Dark orange oil, yield: 90%. ^{1}H NMR (300 MHz, $CDCl_3$): 2.83 (br.s, 1H, OH); 4.10 (s, 5H, Fc); 4.18 (s, 2H, Fc); 4.22 (s, 2H, Fc); 4.74 (s, 2H, CH_2); 6.55 (s, 1H, Pz); 7.03–7.11 (m, 3H, Ar); 7.29–7.39 (m, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): 58.8, 68.7, 68.9, 69.8, 74.6, 105.8, 113.1 (d, J = 14.5 Hz), 114.6 (d, J = 12.5 Hz), 122.4, 129.7 (d, J = 5.3 Hz), 141.3 (d, J = 5.7 Hz), 142.8, 153.1, 161.3 (d, J = 147.7 Hz). EI/MS, *m*/*z* (RI%): 376 (M^+, 100); 311 ([M−Cp]$^+$, 8).

3.3.7. (5-Ferrocenyl-1-(4-fluorphenyl)-1H-pyrazol-3-yl)methanol (**4g**)

Dark orange oil, yield: 95%. ^{1}H NMR (300 MHz, $CDCl_3$): 2.56 (br.s, 1H, OH); 4.09 (s, 5H, Fc); 4.18 (s, 2H, Fc); 4.20 (s, 2H, Fc); 4.70 (s, 2H, CH_2); 6.54 (s, 1H, Pz); 7.08–7.12 (m, 2H, Ar); 7.32–7.39 (m, 2H, Ar). EI/MS, *m*/*z* (RI%): 376 (M^+, 100); 311 ([M−Cp]$^+$, 10).

3.3.8. (1-(2-Chlorophenyl)-5-ferrocenyl-1H-pyrazol-3-yl)methanol (**4h**)

Orange oil, yield: 94%. ^{1}H NMR (500 MHz, $CDCl_3$): 3.32 (br.s, 1H, OH); 4.02 (s, 5H, Fc); 4.03 (s, 2H, Fc); 4.11 (s, 2H, Fc); 4.64 (s, 2H, CH_2); 6.52 (s, 1H, Pz); 7.29–7.41 (m, 3H, Ar); 7.49 (d, J = 7.5 Hz, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): 58.5, 67.4, 68.8, 69.8, 73.4, 103.3, 127.5, 130.1, 130.2, 130.7, 133.0, 138.1, 144.5, 153.6. EI/MS, *m*/*z* (RI%): 392 (M^+, 100); 390 ([M−2H]$^+$, 20); 327 ([M−Cp]$^+$, 8).

3.3.9. (1-(3-Chlorophenyl)-5-ferrocenyl-1H-pyrazol-3-yl)methanol (**4i**)

Orange oil, yield: 90%. ^{1}H NMR (500 MHz, $CDCl_3$): 3.20 (br.s, 1H, OH); 4.10 (s, 5H, Fc); 4.16 (s, 2H, Fc); 4.22 (s, 2H, Fc); 4.73 (s, 2H, CH_2); 6.50 (s, 1H, Pz); 7.16 (d, J = 7.5 Hz, Ar); 7.26–7.30 (m, 1H, Ar); 7.32 (d, J = 8.5 Hz, Ar); 7.42 (s, 1H, Ar). ^{13}C NMR (126 MHz, $CDCl_3$): 58.6, 68.6, 68.8, 69.8, 74.5, 105.8, 124.0, 126.0, 127.9, 129.6, 134.3, 141.0, 142.9, 153.3. EI/MS, *m*/*z* (RI%): 392 (M^+, 100); 390 ([M−2H]$^+$, 22); 327 ([M−Cp]$^+$, 5).

3.3.10. (1-Methyl-5-ferrocenyl-1H-pyrazol-3-yl)methanol (**4k**)

Orange powder, yield: 96%, m.p. 106–107. ^{1}H NMR (300 MHz, $CDCl_3$): 2.54 (br.s, 1H, OH); 3.92 (s, 3H, CH_3); 4.16 (s, 5H, Fc); 4.33 (t, 2H, J = 1.8 Hz, Fc); 4.47 (t, 2H, J = 1.8 Hz, Fc); 4.67 (s, 2H, CH_2); 6.30 (s, 1H, Pz). ^{13}C NMR (75 MHz, $CDCl_3$): 26.8, 58.3, 68.2, 68.8, 69.4, 74.4, 104.2, 142.0, 151.0, 159.3. EI/MS, *m*/*z* (RI%): 296 (M^+, 100); 384 ([M−2H]$^+$, 13); 231 ([M−Cp]$^+$, 4).

*3.3.11. (5-Ferrocenylisoxazol-3-yl)methanol (**4l**)*

Dark orange powder, yield: 90%, m.p. 103–104 °C. ^{1}H NMR (500 MHz, $CDCl_3$): 2.28 (br.s, 1H, OH); 4.15 (s, 5H, Fc); 4.42 (s, 2H, Fc); 4.74 (s, 2H, CH_2); 4.79 (s, 2H, Fc); 6.22 (s, 1H, CH). ^{13}C NMR (126 MHz, $CDCl_3$): 57.1, 67.0, 68.5, 69.8, 70.8, 96.7, 163.7, 172.1. *Anal.* Calcd. for $C_{14}H_{13}FeNO_2$: C, 59.40; H, 4.63; N, 4.95; Fe, 19.73. Found: C, 59.22; H, 4.61; N, 4.65; Fe, 19.7.

*3.4. General procedure 3. Synthesis of aldehydes **5a**–**l***

To a vigorously stirred suspension of manganese (IV) oxide (0.87 g, 10 mmol) in dry methylene chloride (10 ml) was dropwise added a solution of the appropriate alcohols **4a**–**l** (2 mmol) in methylene chloride (10 ml). The resulting slurry was stirred at room temperature for 3 h. Addition of diethyl ether (20 ml) followed by filtration through a Celite pad and concentration *in vacuo* afforded azole aldehydes **5a**–**l**.

*3.4.1. 5-Ferrocenyl-1-phenyl-1H-pyrazole-3-carbaldehyde (**5a**)*

Orange powder, yield: 86%, m.p. 142 °C. IR: 1700 cm^{-1} (CO). ^{1}H NMR (300 MHz, $CDCl_3$): 4.09 (s, 5H, Fc); 4.16 (s, 2H, Fc); 4.23 (s, 2H, Fc); 7.03 (s, 1H, Pz); 7.37–7.41 (m, 2H, Ar); 7.47–7.49 (m, 3H, Ar); 10.04 (s, 1H, CHO). ^{13}C NMR (126 MHz, $CDCl_3$): 68.9, 69.1, 70.0, 73.5, 105.2, 126.0, 129.0, 139.6, 144.6, 151.5, 187.0. *Anal.* Calcd. for $C_{20}H_{16}FeN_2O$: C, 67.44; H, 4.53; N, 7.86; Fe, 15.68. Found: C, 67.52; H, 4.60; N, 7.76; Fe, 15.17. EI/MS, *m*/*z* (RI%): 356 (M^+, 100); 391 ([M–Cp]$^+$, 9).

*3.4.2. 5-Ferrocenyl-1-(naphthalen-1-yl)-1H-pyrazole-3-carbaldehyde (**5b**)*

Deep orange powder, yield: 87%, m.p. 187–189 °C. IR: 1713 cm^{-1} (CO). ^{1}H NMR (300 MHz, $CDCl_3$): 3.84 (br.s, 2H, Fc); 3.96 (s, 5H, Fc); 4.08 (s, 2H, Fc); 7.11 (s, 1H, Pz); 7.37–7.41 (m, 2H, Ar); 7.47–7.49 (m, 3H, Ar); 10.04 (s, 1H, CHO). ^{13}C NMR (76 MHz, $CDCl_3$): 67.7, 69.2, 69.8, 72.1, 103.1, 122.5, 125.0, 125.6, 127.1, 127.8, 128.3, 130.4, 130.5, 134.1, 136.2, 146.8, 151.9, 187.1. *Anal.* Calcd. for $C_{24}H_{18}FeN_2O$: C, 70.95; H, 4.47; N, 6.90; Fe, 13.75. Found: C, 70.59; H, 4.41; N, 6.71; Fe, 14.0. EI/MS, *m*/*z* (RI%): 406 (M^+, 100); 341 ([M–Cp]$^+$, 24).

*3.4.3. 5-Ferrocenyl-1-(p-tolyl)-1H-pyrazole-3-carbaldehyde (**5c**)*

Orange powder, yield: 90%, m.p. 140–141 °C. IR: 1710 cm^{-1} (CO). ^{1}H NMR (300 MHz, $CDCl_3$): 2.44 (s, 3H, CH_3); 4.08 (s, 5H, Fc); 4.16 (t, J = 1.7 Hz, 2H, Fc); 4.22 (t, J = 1.7 Hz, 2H, Fc); 7.01 (s, 1H, Pz); 7.27 (m, 4H, Ar); 10.03 (s, 1H, CHO). ^{13}C NMR (76 MHz, $CDCl_3$): 21.2, 68.7, 69.0, 69.9, 73.3, 104.9, 125.8, 129.6, 137.1, 139.2, 144.6, 151.3, 187.1. *Anal.* Calcd. for $C_{21}H_{18}FeN_2O$: C, 68.13; H, 4.90; N, 7.57; Fe, 15.2. Found: C, 68.19; H, 4.91; N, 7.44; Fe, 15.08. EI/MS, *m*/*z* (RI%): 370 (M^+, 100); 305 ([M–Cp]$^+$, 12).

*3.4.4. 5-Ferrocenyl-1-(4-methoxyphenyl)-1H-pyrazole-3-carbaldehyde (**5d**)*

Orange powder, yield: 87%, m.p. 174 °C. IR: 1703 cm^{-1} (CO). ^{1}H NMR (300 MHz, $CDCl_3$): 3.87 (s, 3H, CH_3); 4.07 (s, 5H, Fc); 4.15 (s, 2H, Fc); 4.22 (s, 2H, Fc); 6.96 (d, J = 8.6 Hz, 2H, Ar); 6.99 (s, 1H, Pz); 7.30 (d, J = 8.6 Hz, 2H, Ar); 10.02 (s, 1H, CHO). ^{13}C NMR (76 MHz, $CDCl_3$): 55.5, 68.6, 69.0, 69.8, 73.2, 104.6, 114.1, 127.4, 132.6, 144.7, 151.2, 159.9, 187.1. EI/MS, *m*/*z* (RI%): 386 (M^+, 100); 321 ([M–Cp]$^+$, 11).

*3.4.5. 1-(4-tert-Butylphenyl)-5-ferrocenyl-1H-pyrazole-3-carbaldehyde (**5e**)*

Orange powder, yield: 92%, m.p. 169–170 °C. IR: 1700 cm^{-1} (CO). ^{1}H NMR (300 MHz, $CDCl_3$): 1.38 (s, 9H, CH_3); 4.09 (s, 5H, Fc); 4.19 (t, J = 1.9 Hz, 2H, Fc); 4.24 (t, J = 1.9 Hz, 2H, Fc); 7.01 (s, 1H, Pz); 7.29–7.34 (m, 2H, Ar); 7.46–7.50 (d, J = 8.6 Hz, 2H, Ar); 10.03 (s, 1H, CHO). ^{13}C NMR (76 MHz, $CDCl_3$): 31.3, 34.8, 68.8, 69.0, 69.9, 73.3, 104.9, 125.5, 126.0, 137.0, 144.6, 151.3, 152.4, 187.2. EI/MS, *m*/*z* (RI%): 412 (M^+, 100); 347 ([M–Cp]$^+$, 8).

*3.4.6. 5-Ferrocenyl-1-(3-fluorphenyl)-1H-pyrazole-3-carbaldehyde (**5f**)*

Orange powder, yield: 84%, m.p. 118–120 °C. IR: 1705 cm^{-1} (CO). ^{1}H NMR (500 MHz, $CDCl_3$): 4.12 (s, 5H, Fc); 4.20 (s, 2H, Fc); 4.27 (s, 2H, Fc); 7.03 (s, 1H, Pz); 7.16–7.17 (m, 3H, Ar); 7.40–7.41 (m, 1H, Ar); 10.04 (s, 1H, CHO). ^{13}C NMR (126 MHz, $CDCl_3$): 69.0, 69.2, 69.9, 73.3, 105.9, 113.4 (d, J = 25.5 Hz), 115.8 (d, J = 21 Hz), 130.2 (d, J = 9 Hz), 140.7 (d, J = 10.5 Hz), 144.6, 151.7, 161.5 (d, J = 247.5 Hz), 186.8. EI/MS, *m*/*z* (RI%): 374 (M^+, 100); 309 ([M–Cp]$^+$, 5).

*3.4.7. 5-Ferrocenyl-1-(4-fluorphenyl)-1H-pyrazole-3-carbaldehyde (**5g**)*

Orange powder, yield: 82%, m.p. 124–125 °C. IR: 1704 cm^{-1} (CO). ^{1}H NMR (500 MHz, $CDCl_3$): 4.09 (s, 5H, Fc); 4.15 (s, 2H, Fc); 4.25 (s, 2H, Fc); 7.01 (s, 1H, Pz); 7.13 (t, J = 8.5 Hz, 2H, Ar); 7.35–7.40 (m, 2H, Ar); 10.02 (s, 1H, CHO). ^{13}C NMR (126 MHz, $CDCl_3$): 68.8, 69.0, 69.8, 73.2, 105.3, 115.9 (d, J = 23.9 Hz), 127.8 (d, J = 8.8 Hz), 135.7, 144.7, 151.5, 161.5 (d, J = 250.7 Hz), 186.8. *Anal.* Calcd. for $C_{20}H_{15}FFeN_2O$: C, 64.20; H, 4.04; N, 7.49; Fe, 14.92. Found: C, 64.14; H, 4.05; N, 7.61; Fe, 15.0. EI/MS, *m*/*z* (RI%): 374 (M^+, 100); 309 ([M–Cp]$^+$, 6).

*3.4.8. 5-Ferrocenyl-1-methyl-1H-pyrazole-3-carbaldehyde (**5k**)*

Orange powder, yield: 94%, m.p. 98 °C. IR: 1694 cm^{-1} (CO). ^{1}H NMR (300 MHz, $CDCl_3$): 4.03 (s, 3H, CH_3); 4.22 (s, 5H, Fc); 4.43 (s, 2H, Fc); 4.56 (s, 2H, Fc); 6.79 (s, 1H, Pz); 9.93 (s, 1H, CHO). EI/MS, *m*/*z* (RI%): 294 (M^+, 100).

*3.4.9. 5-Ferrocenylisoxazole-3-carbaldehyde (**5l**)*

Orange powder, yield: 87%, m.p. 140–141 °C. IR: 1691 cm^{-1} (CO). ^{1}H NMR (500 MHz, $CDCl_3$): 4.15 (s, 5H, Fc); 4.67 (s, 2H, Fc); 4.79 (s, 2H, Fc); 6.51 (s, 1H, Az); 10.16 (s, 1H, CHO). ^{13}C NMR (150 MHz, $CDCl_3$): 67.3, 69.6, 70.0, 70.5, 94.7, 162.5, 174.3, 185.0. *Anal.* Calcd. for $C_{14}H_{11}FeNO_2$: C, 59.82; H, 3.94; N, 4.98. Found: C, 59.74; H, 3.91; N, 4.95. EI/MS, *m*/*z* (RI%): 281 (M^+, 100); 253 ([M–CO]$^+$, 54); 309 ([M–CO–Cp]$^+$, 42).

3.5. General procedure for reductive amination

Ferrocenylformylpyrazole **5a** (1 mmol 0.356 g) and the corresponding amine (1.2 mmol) were mixed in 1,2-dichloroethane (35 ml) for 1 h at rt and treated with sodium triacetoxyborohydride (0.3 g, 1.4 mmol). The mixture was refluxed for 1 h. The reaction mixture was quenched by adding aqueous saturated $NaHCO_3$, and the product was extracted with dichloromethane (2 × 30 ml). The organic layers were combined, washed with small amounts of brine, and dried over Na_2SO_4. The solvent was evaporated and the residue purified by means of column chromatography (SiO_2, eluent $CHCl_3$–MeOH 9/1).

*3.5.1. 3-(t-Butylaminomethyl)-5-ferrocenyl-1- phenyl-1H-pyrazole (**6a**)*

Orange powder, yield: 72%, m.p. 200–202 °C. ^{1}H NMR (500 MHz, $CDCl_3$): 1.43 (s, 9H, CH_3); 4.06 (s, 5H, Fc); 4.10 (s, 2H, Fc); 4.12 (s, 2H, Fc); 4.14 (s, 2H, CH_2); 7.01 (s, 1H, Pz); 7.30–7.42 (m, 5H, Ar). ^{13}C NMR (126 MHz, $CDCl_3$): 12.8, 26.8, 39.6, 68.4, 68.6, 69.6, 74.0, 107.2, 126.0, 128.1, 128.6, 139.8, 143.2, 146.1. *Anal.* Calcd. for $C_{24}H_{27}FeN_3O$: C, 69.74; H, 6.58; N, 10.17. Found: C, 69.89; H, 6.51; N, 10.08. EI/MS, *m*/*z* (RI%): 413 (M^+, 28); 341 ([M–((CH$_3$)$_3$NH$_2$)]$^+$, 100).

*3.5.2. 3-(n-Butylaminomethyl)-5-ferrocenyl-1-phenyl-1H-pyrazole (**6b**)*

Orange oil, yield: 81%. ^{1}H NMR (500 MHz, $CDCl_3$): 0.87 (t, 3H, CH_3); 1.23–1.28 (m, 2H, CH_2); 1.30–1.35 (m, 2H, CH_2); 1.48–1.53 (m, 2H, CH_2); 3.28 (s, 2H, CH_2); 4.08 (s, 5H, Fc); 4.17 (s, 2H, Fc); 4.25 (s, 2H, Fc); 6.66 (s, 1H, Pz); 7.32–7.35 (m, 2H, Ar); 7.46–7.50 (m, 3H,

Ar). ^{13}C NMR (126 MHz, $CDCl_3$): 13.7, 19.8, 30.6, 47.0, 48.8, 68.1, 68.5, 69.5, 74.3, 106.8, 126.0, 128.1, 128.8, 140.0, 143.5, 146.2. EI/MS, *m*/*z* (RI%): 413 (M^+, 30); 342 ([M–(C_3H_7CH=NH)]$^+$, 100).

3.5.3. 5-Ferrocenyl-1-phenyl-3-(pyrrolidin-1-ylmethyl)-1H-pyrazole (**6c**)

Orange oil, yield: 87%. ^{1}H NMR (500 MHz, $CDCl_3$): 1.90 (m, 4H, CH_2); 2.96 (m, 4H, CH_2); 3.95 (s, 2H, CH_2); 4.04 (s, 5H, Fc); 4.10 (s, 2H, Fc); 4.14 (s, 2H, Fc); 6.70 (s, 1H, Pz); 7.28–7.35 (m, 5H, Ar). ^{13}C NMR (126 MHz, $CDCl_3$): 23.3, 51.9, 53.0, 68.4, 68.5, 69.7, 74.3, 107.2, 125.8, 127.9, 128.6, 139.9, 142.8, 147.0. EI/MS, *m*/*z* (RI%): 413 (M^+, 35); 341 ([M–C_4H_9N]$^+$, 100).

3.5.4. 5-Ferrocenyl-1-phenyl-3-(piperidine-1-ylmethyl)-1H-pyrazole (**6d**)

Orange powder, yield: 89%, m.p. 178 °C. ^{1}H NMR (500 MHz, $CDCl_3$): 1.49 (m, 2H, CH_2); 1.71–1.76 (m, 4H); 2.68 (m, 4H); 3.78 (s, 2H, CH_2); 4.04 (s, 5H, Fc); 4.14 (s, 2H, Fc); 4.15 (s, 2H, Fc); 6.67 (s, 1H, Pz); 7.31–7.39 (m, 5H, Ar). ^{13}C NMR (126 MHz, $CDCl_3$): 23.5, 24.8, 53.8, 55.7, 68.4, 68.6, 69.6, 74.5, 107.3, 125.9, 127.8, 128.6, 140.0, 142.6, 147.5. *Anal*. Calcd. for $C_{25}H_{27}FeN_3O$: C, 70.59; H, 6.40; N, 9.88. Found: C, 70.29; H, 6.31; N, 9.86. EI/MS, *m*/*z* (RI%): 424 ([M–H]$^+$, 100); 342 ([M–C_5H_9N]$^+$, 46).

3.5.5. 5-Ferrocenyl-1-phenyl-3-(morpholine-1-ylmethyl)-1H-pyrazole (**6e**)

Orange powder, yield: 91%, m.p. 116–118 °C. ^{1}H NMR (500 MHz, $CDCl_3$): 2.59 (m, 4H); 3.63 (s, 2H, CH_2); 3.77–3.79 (m, 4H); 4.04 (s, 5H, Fc); 4.13 (s, 2H, Fc); 4.16 (s, 2H, Fc); 6.50 (s, 1H, Pz); 7.33–7.41 (m, 5H, Ar). ^{13}C NMR (126 MHz, $CDCl_3$): 55.4, 56.2, 66.8, 68.3, 68.5, 69.7, 74.7, 106.5, 125.9, 127.7, 128.5, 140.1, 142.3, 149.1. *Anal*. Calcd. for $C_{24}H_{25}FeN_3O$: C, 67.46; H, 5.90; N, 9.83. Found: C, 67.02; H, 5.84; N, 9.43. EI/MS, *m*/*z* (RI%): 427 ([M]$^+$, 44); 342 ([M–C_4H_7NO]$^+$, 100).

3.5.6. 5-Ferrocenyl-1-phenyl-3-(4-methylpiperidine-1-ylmethyl)-1H-pyrazole (**6f**)

Orange powder, yield: 89%, m.p. 109–111 °C. ^{1}H NMR (500 MHz, $CDCl_3$): 0.96 (d, J = 6.3, 3H, CH_3); 1.50 (m, 1H, CH); 1.61–1.75 (m, 4H); 2.48–2.44 (m, 2H); 3.22–3.25 (m, 2H); 3.92 (s, 2H, CH_2); 4.06 (s, 5H, Fc); 4.14 (s, 2H, Fc); 4.17 (s, 2H, Fc); 6.80 (s, 1H, Pz); 7.29–7.40 (m, 5H, Ar). ^{13}C NMR (126 MHz, $CDCl_3$): 21.1, 29.5, 32.1, 52.7, 54.6, 68.5, 68.7, 69.8, 74.1, 107.8, 125.9, 128.0, 128.7, 139.9, 143.1, 145.8. EI/MS, *m*/*z* (RI%): 439 ([M]$^+$, 18); 342 ([M–$C_6H_{11}N$]$^+$, 100).

3.5.7. t-Butyl ((1-(ferrocenyl-1-phenyl-1H-pyrazol-3-yl)methyl) piperidin-4-yl)carbamate (**6g**)

Orange powder, yield: 70%, m.p. 112–114 °C. ^{1}H NMR (500 MHz, $CDCl_3$): 1.40 (s, 9H, CH_3); 1.60–1.62 (m, 2H); 1.95–1.97 (m, 2H); 2.24–2.33 (m, 2H); 3.00–3.2 (m, 2H); 3.69 (s, 2H, CH_2); 4.02 (s, 5H, Fc); 4.11 (s, 2H, Fc); 4.14 (s, 2H, Fc); 4.60 (br.s, 1H, NH); 6.56 (s, 1H, Pz); 7.29–7.34 (m, 5H, Ar). ^{13}C NMR (126 MHz, $CDCl_3$): 28.2, 30.7, 31.6, 51.8, 55.2, 68.4, 68.5, 69.6, 74.5, 106.9, 125.9, 127.8, 128.5, 140.0, 142.5, 147.9, 155.0. EI/MS, *m*/*z* (RI%): 540 ([M]$^+$, 10); 342 ([M–$C_{10}H_{18}N_2O_2$]$^+$, 100).

3.5.8. Methyl 2-(((5-ferrocenyl-1-phenyl-1H-pyrazol-3-yl)methyl) amino)acetate (**6h**)

Orange oil, yield: 88%. ^{1}H NMR (500 MHz, $CDCl_3$): 3.57 (br.s, 2H, CH_2); 3.78 (s, 3H, CH_3); 3.93 (br.s, 2H, CH_2); 4.06 (s, 5H, Fc); 4.13 (s, 2H, Fc); 4.17 (s, 2H, Fc); 6.52 (s, 1H, Pz); 7.32–7.38 (m, 5H, Ar). ^{13}C NMR (126 MHz, $CDCl_3$): 46.4, 49.9, 51.6, 68.4, 68.5, 69.6, 74.7, 105.5, 125.9, 127.7, 128.5, 140.1, 142.4, 150.8, 172.3. *Anal*. Calcd. for $C_{23}H_{23}FeN_3O_2$: C, 64.35; H, 5.40; N, 9.79. Found: C, 64.44; H, 5.43; N, 9.78. EI/MS, *m*/*z* (RI%): 429 ([M]$^+$, 10); 342 ([M–$C_3H_4O_2$]$^+$, 100).

3.6. Electrochemistry

The electrochemical (cyclic voltammetry) measurements were performed on a IPC-Pro potentiostat. The working electrode was a glassy carbon disk (s = 2 mm), the auxiliary electrode was a platinum plate. All the potential values were referred to the Saturated Calomel Electrode (SCE). The experiments were carried out at $c = 2\cdot10^{-3}$ M under argon in deoxygenated acetonitrile solution containing 0.1 M [(n-Bu)$_4$N]PF_6, as a supporting electrolyte. The scan rate was 0.2 Vs^{-1}.

3.7. X-ray analysis of compound **3j**

Crystallographic data for **3j**: crystals of $C_{22}H_{18}ClFFeN_2O_2$ are monoclinic, space group $C2/c$, a = 13.500 (3) Å, b = 16.398 (4) Å, c = 17.622 (4) Å, β = 99.028 (5)°, V = 3852.5 (16) Å^3, Z = 8, M = 452.68, d_{calc} = 1.278 g cm^{-3}, μ(MoKα) = 0.95 mm^{-1}, F(000) = 1856. Intensities of 21982 reflections were measured with a Bruker Smart 1000 diffractometer at 100K [λ(MoKα) = 0.71073 Å], and 5589 independent reflections (R_{int} = 0.0574) were used in the further refinement. The structure was solved by direct method. All non-hydrogen atoms were refined in anisotropic approximation against F^2. Hydrogen atoms were refined in the rigid body approximation with the U_{iso}(H) parameters equal to 1.2 U_{eq}(C) and 1.5 U_{eq}(C) for methyl group, where U_{eq}(C,) respectively are the equivalent thermal parameters of the carbon and nitrogen atoms to which the corresponding H atoms are bonded. The refinement converged to wR_2 = 0.0775 and GOF = 1.020 for all independent reflections [R_1 = 0.0477 was calculated against F for 3356 observed reflections with $I > 2\sigma(I)$].

Acknowledgments

This work was partially supported by the Russian Academy of Sciences (Presidium Programs «Support for Young Scientists» and «Fundamental Sciences – for Medicine»), the Department of Chemistry and Materials Science (Project 10), and the Russian Foundation for Basic Research (RFBR №09-03-00535).

References

[1] A.A. Simenel, E.A. Morozova, L.V. Snegur, S.I. Zykova, V.V. Kachala, L.A. Ostrovskaya, N.V. Bluchterova, M.M. Fomina, Appl. Organometal. Chem. 23 (2009) 219–224.
[2] I. Damljanović, M. Vukićević, N. Radulović, E. Ellmerer, Z. Ratković, M.D. Joksović, R.D. Vukićević, Bioorg. Med. Chem. Lett. 19 (2009) 1093–1096.
[3] Yong-Sheng Xie, Xiao-Hong Pan, Bao-Xiang Zhao, Jin-Ting Liu, Dong-Soo Shin, Jin-Hua Zhang, Liang-Wen Zheng, Jing Zhao, Jun-Ying Miao, J. Organomet. Chem. 693 (2008) 1367–1374.
[4] M.D. Joksović, V. Marković, Z.D. Juranić, T. Stanojković, L.S. Jovanović, I.S. Damljanović, K.M. Szécsényi, N. Todorović, S. Trifunović, R.D. Vukićević, J. Organomet. Chem. 694 (2009) 3935–3942.
[5] T. Hayashi Togni (Ed.), Ferrocenes: Homogenous catalysts, organic synthesis, material science, VCH, Weinheim, 1995.
[6] T.J. Colacot, Chem. Rev. 103 (2003) 3101–3118.
[7] M. Laćan, V. Rapic, Croat. Chem. Acta 42 (1970) 411–416.
[8] N. Pommery, T. Taverne, A. Telliez, L. Goossens, C. Charlier, J. Pommery, J.-F. Goossens, R. Houssin, F. Durant, J.-P. Henichart, J. Med. Chem. 47 (2005) 6195–6206.
[9] A. Schmidt, T. Habeck, M.K. Kindermann, M. Nieger, J. Org. Chem. 68 (2003) 5977–5982.
[10] C. Kashima, S. Shibata, H. Yokoyama, T. Nishio, J. Heterocyclic Chem. 40 (2003) 773–782.
[11] E.J. Corey, W.J. Suggs, Tetrahedron 31 (1975) 2647.
[12] K.E. Pfitzner, J.G. Moffatt, J. Am. Chem. Soc. 85 (1963) 3027.
[13] E. Adler, H.D. Becker, Acta Chem. Scand. 15 (1961) 849; S.R. Hauser, J.K. Lindsay, J. Org. Chem. 22 (1957) 906.
[14] A.J. Deeming, G. Wilkinson, F.G.A. Stone, E.W. Abel (Eds.), Comprehensive Organometallic Chemistry, Pergamon Press, 1982.