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Asymmetric intermolecular cyclopropanation of alkenes and N–H insertion of aminoesters by diazoacetylferrocene catalyzed by ruthenium and iron porphyrins

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Dedicated to Paul Le Maux for his large contribution in porphyrin chemistry.

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ABSTRACT

The asymmetric addition of diazoacetylferrocene to styrene derivatives to give optically active cyclopropyl acetylferrocenes (ee up to 96%) was carried out using chiral ruthenium porphyrins as homogeneous catalysts. Intermolecular N–H functionalization of anilines and amino esters by means of carbenoid-induced N–H insertion was also observed using tetraphenylporphyrin iron chloride as catalyst.

1. Introduction

Since ferrocene discovery in 1951 [1], the chemistry of this organometallic molecule has been intensively investigated with many applications in synthesis, materials [2] and medecine [3]. Remarkably, diazoacetylferrocene, first prepared by Regitz in 1968 [4] and later by Toma [5] has been used more recently for the preparation of ferrocenylketene [6,7]. Many other reactions such as C–H insertion [8], palladium-mediated polymerization [9] and unsaturated ester synthesis [10] have been also reported with various diazoferrocene derivatives.

Recent growth in the area of transition metal porphyrin chemistry has, in part, been driven by the increased interest associated with metal-catalyzed carbene transfer reactions using diazo derivatives [11]. Both asymmetric cyclopropanation [12] and N–H insertion reactions [13,14] using such catalyts and diazo compounds are now well developed. However, the use of organometallic diazo derivatives is a new challenge in this field of research because of the presence of a metal complex in the reagent. In the course of our work on synthetic application of chiral metalloporphyrins [15], we also found that rarely used diazo derivatives such as diazomethylphosphonate [16], trifluorodiazoethane [17] and diazoacetonitrile [12] can be quite also efficient for in asymmetric cyclopropanation. Surprisingly, if many of these diazo derivatives have been proven to be efficient for asymmetric cyclopropanation of styrenes, they have not been extended to diazoacetylferrocene. Consequently, we examined herein the uses of ruthenium complexes of optically active porphyrins (Fig. 1) as catalysts for intermolecular asymmetric cyclopropanation of styrene derivatives with diazoacetylferrocene. N–H insertion of amino esters by diazoacetylferrocene catalyzed by iron porphyrins was also explored as possible application for bioconjugation of proteins.

2. Experimental section

2.1. General

All reactions were performed under argon. Solvents were distilled from an appropriate drying agent prior to use: CH_2Cl_2 from CaH_2. Commercially available reagents were used without further purification unless otherwise stated. All reactions were monitored by TLC with Merck precoated aluminum foil sheets (Silica gel 60 with fluorescent indicator UV254). Compounds were visualized with UV light at 254 nm. Column chromatographies were carried out using silica gel from Merck (0.063–0.200 mm). ^1H NMR and ^{13}C NMR in $CDCl_3$ were recorded using Bruker (Advance 400dpx spectrometer) at 400 MHz and 125 MHz, respectively. High

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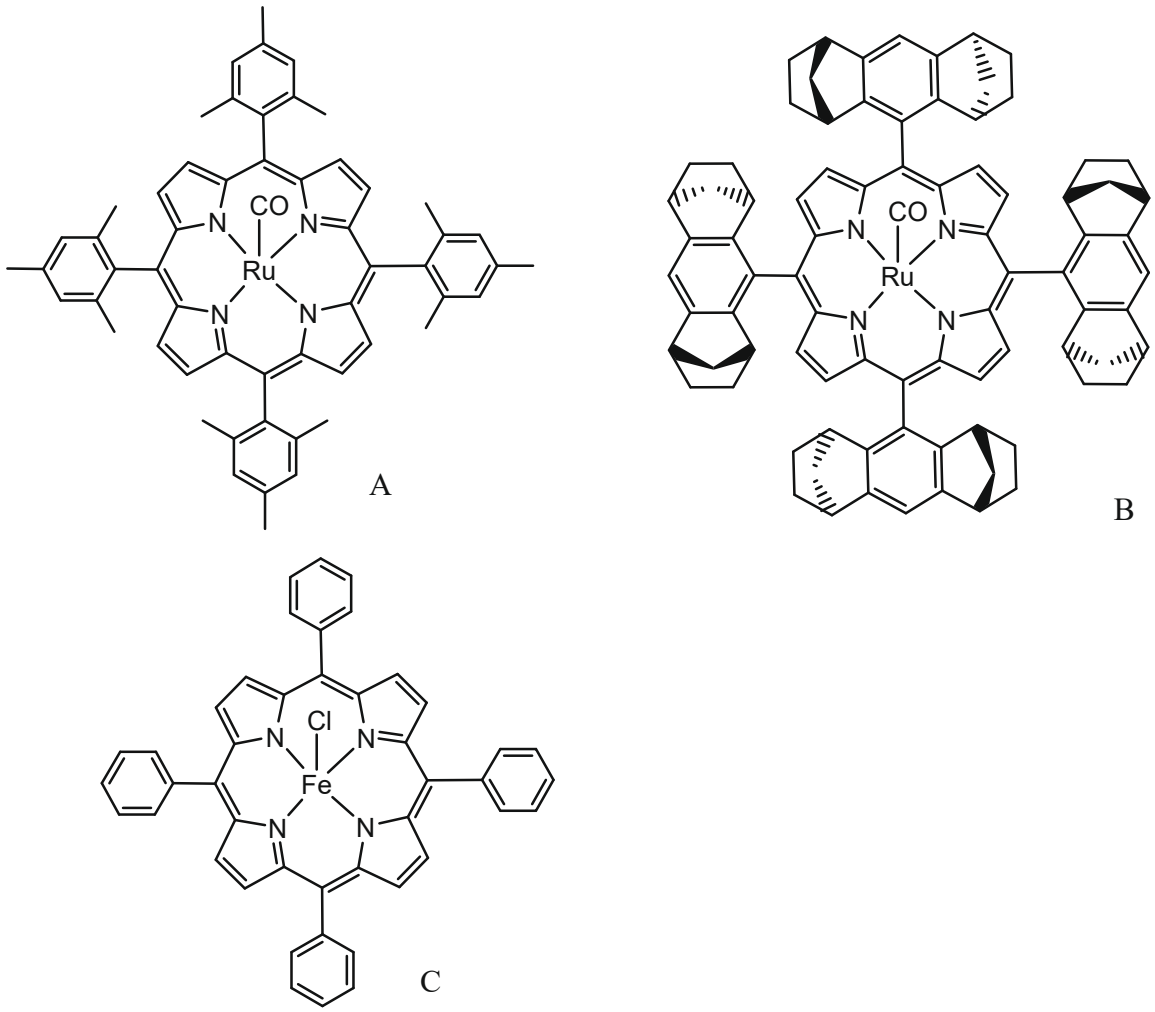


Fig. 1. Tetramesitylporphyrin ruthenium carbon monoxide (TMP)Ru(CO) (A), Chiral Halterman ruthenium porphyrin (B) and tetraphenylporphyrin iron chloride (FeTPPCl) (C).

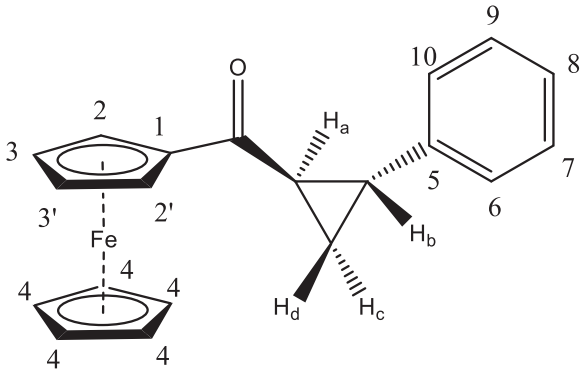
resolution mass spectra were recorded on a Thermo-Fisher Q-Exactive (Q-Tof 2) spectrometer in ESI positive mode at the CRMPO at Rennes. Enantiomeric excesses were determined by chiral HPLC (Chiralpak IE, 70/30 heptane/ethanol).

2.2. Diazoacetylferrocene preparation

A solution of 200 µl (2.5 eq) of oxalyl chloride was added dropwise (30 min) to 87 mmol of ferrocene carboxylic acid suspended in CCl_4 under argon. The mixture was stirred for 12 h. The solvent was then evaporated under vacuum to give quantitatively the known ferrocenylacetyl chloride [6]. The solid was dissolved in 5 ml of CH_3CN in presence of 1 eq of triethylamine. To this solution, 4 eq of $TMSCHN_2$ in hexane (2 N solution in hexane) was added dropwise at 0 °C and stirred for 2 h at 0 °C and then 12 h at room temperature. After evaporation of the solvent under vacuum, the residue was chromatographied on silica gel plates (CH_2Cl_2 as eluent) to give 94.3 mg diazoacetylferrocene (43% yield).

2.3. Cyclopropanation reaction

A solution of diazoacetylferrocene (20.4 mg, 0.08 mmole) in 0.5 ml was added dropwise (45 min) to a 1 ml dichloromethane solution of complex B (0.5 mg) and styrene (42 mg, 0.4 mmol) at room temperature. The reaction was stirred for 12 h. The solvent was then removed under vacuum and the residue was chromatographied on preparative silica plates (dichloromethane) to give ferrocenyl 2-phenylcyclopropyl Ketone (13.6 mg, 0.04 mmol) (53% yield).



Ferrocenyl 2-Phenylcyclopropyl Ketone: ^1H NMR (400 MHz, $CDCl_3$): δ 7.45–7.15 (m, 5H, H6-7-8-9-10); 4.87 (m, 2H, H2-2′);

4.53 (m, 2H, H3-3′), 4.21 (s, 5H, Cp-H4); 2.73–2.70 (m, 1H, H_a); 2.52–2.45 (m, 1H, H_b); 1.92–1.85 (m, 1H, H_c or H_d);1.55–1.45 (m, 1H, H_c or H_d). ^{13}C NMR (400 MHz, CD_2Cl_2): δ 202.14 (CO); 140.98 (C5); 128.60 (2C, C6-10);126.46 (C, C8); 126.17 (2C, C7-9), 79.85 (C, C1); 72.56 (C, C3 or C3′); 72.51 (C, C3 or C3′); 69.93 (5C, C4); 69.67 (C, C2 or C2′); 69.46 (C, C2 or C2′); 30.63 (CH_b); 29.05 (CH_a); 18.53 (CH_2). HR-MS (m/z): calcd for $C_{20}H_{18}O$ Na ^{56}Fe (M +Na)$^+$: 353.05992. Found 353.0600.

Ferrocenyl 2-*p*-Methylphenylcyclopropyl Ketone : ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25–6.98 (m, 4H, H4-7-9-10); 4.86 (m, 2H, H2-2′); 4.53 (m, 2H, H3-3′), 4.21 (s, 5H, Cp-H4); 2.75–2.60 (m, 1H, H_a); 2.52–2.43 (m, 1H, H_b); 2.36 (s, 3H, Me); 1.90–1.82 (m, 1H, H_c or H_d); 1.52–1.43 (m, 1H, H_c or H_d). ^{13}C NMR (400 MHz, CD_2Cl_2): δ 202.26 (CO); 137.89 (C5); 136.07 (C8); 129.27 (C6-10); 126.11 (C7-9); 79.88 (C1); 72.51 (C3 or C3′); 72.45 (C3 or C3′); 69.92 (C4); 69.65 (C2 or C2′); 69.45 (C2 or C2′); 30.53 (CH_b); 28.89 (CH_a); 21.04 (CH_3); 18.41 (CH_2). HR-MS (m/z): calcd for $C_{21}H_{20}O$ Na ^{56}Fe (M + Na)$^+$: 367.07557. Found 367.0759.

Ferrocenyl 2-*p*-Methoxyphenylcyclopropyl Ketone: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15 (d, 2H, H6-10, J = 8.13 Hz); 6.89 (d, 2H, H7-9, J = 8.13 Hz); 4.87 (m, 2H, H2-2′); 4.54 (m, 2H, H3-3′); 4.22 (s, 5H, Cp-H4); 2.74–2.60 (m, 1H, H_a); 2.52–2.35 (m, 1H, H_b); 1.92–1.77 (m, 1H, H_c or H_d);1.53–1.36 (m, 1H, H_c or H_d). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.18 (CO); 150.33 (C8); 132.92 (C5); 127.30 (C6-10); 114.05 (C7-9); 79.80 (C1); 72.37 (C3 or C3′); 72.32 (C3 or C3′); 69.81 (C4); 69.56 (C2 or C2′); 69.32 (C2 or C2′); 55.33 (OCH_3); 30.38 (CH_b); 28.59 (CH_a); 18.25 (CH_2). HR-MS (m/z): calcd for $C_{21}H_{20}O_2$ Na ^{56}Fe (M+Na)$^+$: 383.07049. Found 383.0704.

Ferrocenyl 2-*p*-Chlorophenylcyclopropyl Ketone: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36–7.05 (m, 4H, H6-7-9-10); 4.92–4.78 (m, 2H, H2-2′); 4.54 (m, 2H, H3-3′); 4.21 (s, 5H, Cp-H4); 2.73–2.62 (m, 1H, H_a); 2.51–2.40 (m, 1H, H_b); 1.94–1.83 (m, 1H, H_c or H_d);1.53–1.40 m, 1H, H_c or H_d). ^{13}C NMR (400 MHz, CD_2Cl_2): δ 201.74 (CO); 139.53 (C5); 132.13 (C8); 128.72 (C7-9); 127.46 (C6-10); 79.56 (C1); 72.54 (C3 or C3′); 72.51 (C3 or C3′); 69.84 (C4); 69.58 (C2 or C2′); 69.34 (C2 or C2′); 30.55 (CH_b); 28.23 (CH_a); 18.49 (CH_2). HR-MS (m/z): calcd for $C_{20}H_{17}O^{35}ClNa$ ^{56}Fe (M+Na)$^+$: 387.02095. Found 387.0206.

Ferrocenyl 2-*p*-Trifluoromethylphenylcyclopropyl Ketone: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, 2H, H6-10, J = 7.88 Hz); 7.30 (d, 2H, H7-9, J = 7.88 Hz); 4.87 (m, 2H, H2-2′); 4.57 (m, 2H, H3-3′), 4.22 (s, 5H, Cp-H4); 2.80–2.70 (m, 1H, H_a); 2.57–2.46 (m, 1H, H_b); 1.98–1.88 (m, 1H, H_c or H_d); 1.56–1.47 (m, 1H, H_c or H_d).

^{13}C NMR (100 MHz, $CDCl_3$): δ 201.43 (CO); 145.24 (C5); 128.71 (CF_3, q, J_1 = 32.42 Hz); 126.32 (C6-10); 125.55 (C7-9); 122.85 (C8); 79.44 (C1); 72.61 (C3 or C3′); 72.59 (C3 or C3′); 69.86 (C3 or C3′); 69.56 (C2 or C2′); 69.39 (C2 or C2′); 30.70 (CH_b); 28.28 (CH_a); 18.71 (CH_2). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ −62.38 (CF_3). HR-MS (m/z): calcd for $C_{21}H_{17}OF_3$ Na ^{56}Fe (M+Na)$^+$: 421.04731. Found 421.0472.

Ferrocenyl 2-*m*-Trifluoromethylphenylcyclopropyl Ketone: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64–7.34 (m, 4H, H8-9-10); 4.89–4.86 (m, 2H, H2-2′); 4.57 (m, 2H, H3-3′), 4.23 (s, 5H, Cp-H4); 2.83–2.71 (m, 1H, H_a); 2.55–2.45 (m, 1H, H_b); 1.97–1.86 (m, 1H, H_c or H_d); 1.57–1.47 (m, 1H, H_c or H_d). ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.51 (CO); 142.04 (C5); 131.04 (CF_3, q, J_1 = 32.42 Hz); 129.92 (C9); 129.04 (C10); 125.44 (C7); 123.28 (C6); 122.63 (C8); 79.47 (C1); 72.58 (2C, C3 and C3′); 69.85 (C4); 69.55 (C2 or C2′); 69.41 (C2 or C2′); 29.71 (CH_b); 28.19 (CH_a); 18.46 (CH_2). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ −62.64 (CF_3). HR-MS (m/z) : calcd for $C_{21}H_{17}OF_3$ Na ^{56}Fe (M+Na)$^+$: 421.04731. Found 421.0471.

2.4. Dimer formation

TMPRuCO (0.5 mg) and diazoacetylferrocene (109 mg, 43.5 mmol) were stirred in a solution of CH_2Cl_2 at room temperature under argon for until complete consumption of diazo was evident by TLC (12 h). The solvent was then removed and the residue was purified by column chromatography on silica gel (dichloromethane) to give the dimer (53 mg, 55% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.77 (br, 2H, HC=); 4.78 (br, 4H, H2-2′); 4.61 (br, 2H, H3-3′), 4.29 (br, 10H, Cp-H4). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.37 (CO); 134.12 (CH=); 78.89 (C-CO); 72.87 (C3 and C3′); 70.13 (C4); 69.45 (C2 and C2′). HR-MS (m/z): calcd for $C_{24}H_{20}O_2$ Na $^{56}Fe_2$ (M+Na)$^+$: 475.00543. Found: 475.0052.

2.5. General procedure for N–H insertion in organic solvent

In a typical experiment, the α-amino ester (0.18 mmol) and FeTPPCl (1.3 mg, 1.8 μmol) were placed in a Schlenk tube under argon and dissolved in 2 ml of distilled CH_2Cl_2. NEt_3 (0.27 mmol) was added to the solution. Diazoacetylferrocene (0.18 mmol) was then added at room temperature. After 2 min of stirring, the insertion product was purified by column chromatography on silica gel (CH_2Cl_2/Methanol: 95/5).

N-acetylferrocene aniline: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27–7.23 (m, 2H, H_{oPh}); 6.80–6.68 (m, 3H, H_{m+pPh}); 4.93 (m, 2H, H2-2′); 4.87 (bs, 1H, NH); 4.64 (m, 2H, H3-3′); 4.36 (br, 2H, CH_2); 4.27 (s, 5H, Cp-H4). ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.21 (CO); 147.56 (CNH); 129.23 (C_{oPh}); 117.40 (C_{pPh}); 112.89 (C_{mPh}); 76.62 (C1); 72.59 (C3 and C3′); 70.07 (C4); 68.85 (C2 and C2′); 50.63 (CH_2). HR-MS (m/z): calcd for $C_{18}H_{17}NO$ Na ^{56}Fe (M +Na)$^+$:342.05517. Found: 342.0555.

N-Acetylferrocene D-phenylalanine methyl ester: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42–7.20 (m, 5H, H_{PhAla}); 4.77 (bs, 2H, H2-2′); 4.54 (bs, 2H, H3-3′); 4.22 (s, 5H, Cp-H4), 3.89–3.73 (2H, CH_2-CO); 3.71 (s, 3H, OCH_3); 3.67 (t, 1H, CH-NH, J = 6.97 Hz); 3.14–2.97 (2H, CH_2Ph). ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.04 (CO); 174.26 (OCO); 137.67 (Cq, C_{Ph}); 129.23 (C_{mPh});128.31 (C_{oPh});126.55 (C_{pPh}); 76.80 (C1); 73.20 (C3 and C3′); 69.98 (C4); 68.79 (C2 and C2′); 62.41 (CH_{Ala}); 54.03 (CH_2CO); 51.62 (OCH_3); 39.44 ($CHCH_2$). HR-MS (m/z) : calcd for $C_{22}H_{23}NO_3$ Na ^{56}Fe (M+Na)$^+$: 428.09195. Found: 428.0922.

N-Acetylferrocene L-tyrosine ethyl ester : ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.14 (d, 2H, H_{mPh}, J = 7.68 Hz); 6.78 (d, 2H, H_{oPh}, J = 7.68 Hz); 4.79 (br, 2H, H2-2′); 4.57 (br, 2H, H3-3′), 4.22 (s, 5H, Cp-H4); 4.18 (q, 2H, CH_2O, J = 7.12 Hz); 3.90–3.78 (2H, CH_2CO); 3.65 (t, 1H,CHCO, J = 6.66 Hz); 3.13–2.84 (2H, CH_2CH); 1.27 (t, 3H, CH_2CH_3, J = 7.12 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 201.37 (CO); 173.75 (OCO); 171.18 (COH); 130.39 (C_{mPh}); 128.52 (C, C_{Ph}); 115.41 (C_{oPh}); 76.63 (C, C1); 72.56 (C3 and C3′); 70.03 (C4); 68.87 (C2 and C2′); 62.39 (CH_{Tyr}); 60.89 (OCH_2); 53.95 (CH_2-CO);38.42 (CH_{2Tyr}); 14.04 (CH_3). HR-MS (m/z) : calcd for $C_{23}H_{25}NO_4$ Na ^{56}Fe (M+Na) : 458.10252. Found : 458.1020.

N-Acetylferrocene L-valine *tert*-butyl ester : ^{1}H NMR (400 MHz, $CDCl_3$) : δ 4.81 (br, 2H, H2-2′); 4.55 (br, 2H, H3-3′); 4.25 (s, 5H, Cp-H4); 3.80 (2H, CH_2CO); 2.99 (d, 1H, CHNH, J = 5.84 Hz); 2.10–1.90 (m, 1H, CH_{iPr}); 1.52 (s, 9H, CH_{3tBu}); 1.03 (d, 6H, CH_{3iP}r, J = 6.82 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 201.05 (CO); 173.76 (OCO); 80.79 C_{tBu});77.25 (C1) 72.21 (C3 and C3′); 69.91 (C4); 68.78 (C2 and C2′); 67.46 (CHNH); 54.98 (CH_2CO); 31.59 (CH_{iPr}); 27.92 (CH_{3tBu}); 18.36 (CH_{3iPr}). HR-MS (m/z) : calcd for $C_{21}H_{29}NO_3$ Na ^{56}Fe (M +Na) : 422.1389. Found : 422.1387.

2.6. X-ray structure determination

Single crystals of the complexes of diazoacetylferrocene and ferrocenyl 2-phenylcyclopropyl ketone were grown by slow diffusion of hexane onto dichloromethane solutions. Data collection was carried out at 250 K for diazoacetylferrocene and 296 K for ferrocenyl 2-phenylcyclopropyl ketone on a D8 Venture diffractometer equipped with a (CMOS) Photon 100 detector, using Mo-K_α radiation (λ = 0.71073 Å), multilayer monochromator. The structure was solved by dual-space algorithm using the SHELXT program [18] and then refined with full-matrix least-squares methods based on F2 (SHELXL program) [19]. All non hydrogen atoms were refined with anisotropic atomic displacement parameters. For diazoacetylferrocene, a final refinement on F^2 with 4499 unique intensities and 290 parameters converged at $\omega R(F^2)$ = 0.0987 (R_F = 0.0401) for 4240 observed reflections with ($I > 2\sigma$) and for ferrocenyl 2-phenylcyclopropyl ketone, a final refinement on F^2 with 2797 unique intensities and 200 parameters converged at $\omega R(F^2)$ = 0.1094 (R_F = 0.0523) for 2288 observed reflections with ($I > 2\ \sigma$).

Diazoacetylferrocene complex ($C_{12}H_{10}FeN_2O$); M = 254.07. Crystal structure has been described in monoclinic symmetry and *P* 2_1 (I.T.#4) acentric space group. Cell parameters have been refined as follows: a = 9.4037(9), b = 507292(6), c = 19.623(2) Å, β = 90.141(4)°, V = 1057.18(18) Å^3. Number of formula unit Z is equal to 4 and calculated density d and absorption coefficient μ values are 1.596 g.cm^{-3} and 1.402 mm^{-1} respectively.

Ferrocenyl 2-phenylcyclopropyl ketone complex ($C_{20}H_{18}FeO$); M = 330.19. Crystal structure has been described in monoclinic symmetry and *P* 2_1 (I.T.#4) acentric space group. Cell parameters have been refined as follows: a = 5.9391(5), b = 12.2635(16), c = 10.7050(13) Å, β = 91.532(3)°, V = 779.41(15) Å^3. Number of formula unit Z is equal to 2 and calculated density d and absorption coefficient μ values are 1.407 g.cm^{-3} and 0.966 mm^{-1} respectively.

Final atomic positional coordinates, with estimated standard deviations, and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre.

3. Results

3.1. Synthesis of diazoacetylferrocene and X-ray structure determination

For the synthesis of diazoacetylferrocene, it was first decided to use trimethylsilyldiazomethane ($TMSCHN_2$) as a substitute of diazomethane because the latter is not only highly toxic but also explosive. $TMSCHN_2$ has been previously used in the preparation of a variety of diazoketones from the corresponding acyl chloride by treatment with $TMSCHN_2$ [20–23]. Herein, we successfully adapted this recent method with ferrocene acyl chloride that was prepared from acid. Conversion of this acid to its acyl chloride with thionyl chloride gave a quasi-quantitative yield. The ferrocene acyl chloride was then allowed to react with 2 equivalents of $TMSCHN_2$ in the presence of an excess of triethylamine dissolved in THF at low temperature (0 °C) (Scheme 1). The expected diazoacetylferrocene was obtained with 43% yield after 2 days together with a 10% yield of ferrocenecarboxylic anhydride [24]. To better characterize the diazo group, an X-ray structure determination was undertaken. The diazoacetylferrocene was the first ferrocenic diazo compound to have its structure investigated by X-ray diffraction analysis (Fig. 2). The interatomic C–N (1.312(10) Å) and N–N (1.113(9) Å) distances for the diazo compound are however quite similar to the bond length distances for other diazoketones [25,26].

3.2. Cyclopropanation reaction

meso-Tetramesitylporphyrin carbonyl ruthenium (TMP)Ru(CO) (Fig. 1, compound A) catalyzed decomposition of diazoacetylferrocene in the presence of styrene in dichloromethane resulted in the formation of the corresponding cyclopropane in 61% yield (Table 1) with a *trans* stereoselectivity (Scheme 2) and a moderate amount of olefin resulting to the dimerization of the carbene (30%)

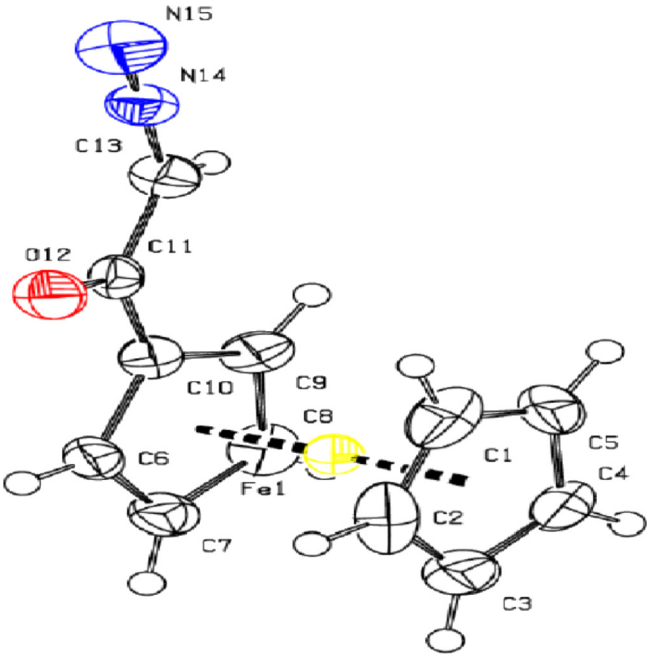
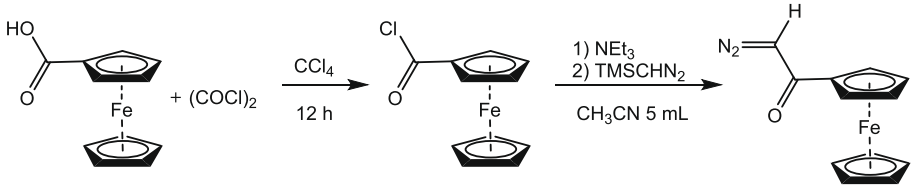


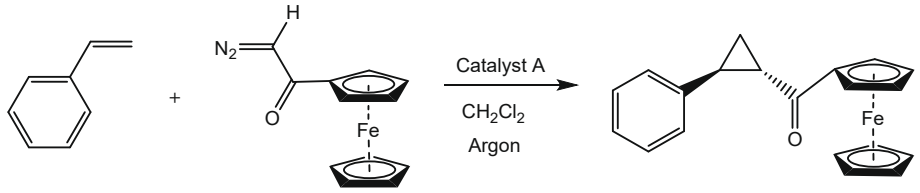
Fig. 2. ORTEP structure of diazoacetylferrocene.

Table 1
Cyclopropanation of styrene derivatives with diazoacetylferrocene catalyzed by TMPRuCO (catalyst A).

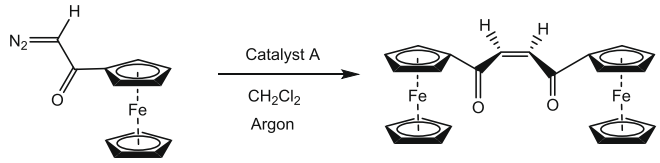
Entry	Alkene	Yield (%)	Dimer (%)
1	C_6H_5	61	30
2	4-$CH_3C_6H_4$	48	32
3	4-$CH_3OC_6H_4$	41	33
4	4-$CF_3C_6H_4$	29	31
5	4-ClC_6H_4	35	32
6	3-$CF_3C_6H_4$	39	41



Scheme 1. Synthesis of diazoacetylferrocene.



Scheme 2. Cyclopropanation catalyzed by ruthenium porphyrin.



Scheme 3. Dimerization of diazoacetylferrocene catalyzed by ruthenium porphyrin.

(Scheme 3). To extend the scope of this cyclopropanation, the reaction of a number of styrene derivatives with diazoacetylferrocene in the presence of TMPRu(CO) at 25 °C in dichloromethane was studied. The results are summarized in Table 1. In these experiments, cyclopropanes are the major products, usually obtained with carbene dimers as by-products. Electron-rich styrenes (4-methoxy or 4-methyl styrene) are cyclopropanated more efficiently than styrenes bearing electron-withdrawing groups (4-Cl or 4-CF_3). In the two later cases, a significant amount of olefins, resulting from dimerization of the carbenes, was also detected (30–41%). With styrene bearing the trifluoromethyl group in meta position, dimerization of the carbene is the main reaction.

3.3. Asymmetric cyclopropanation

The asymmetric version was also tested using Halterman porphyrin [27] as chiral ligand (Fig. 1, compound B). To evaluate the reactivity of the diazoacetylferrocene, its ruthenium-catalyzed decomposition was examined in the presence of styrene in dichloromethane at room temperature by using the chiral complex as catalyst (Table 2). The cyclopropane was formed with 53% yield, complete *trans* selectivity and 74% enantioselectivity for the *trans* isomer (Table 2, entry 1). The presence of the *cis* isomer was not detected after chromatography purification on silica gel. A small amount (8%) of the dimer was also observed. We also investigated the cyclopropanation of *para*-substituted styrenes (Table 2). As shown in the Table 2, *para*-substitution (4-Y-styrene, 4 = MeO, Br, CF_3 and H) has a significant effect upon the enantioselectivity of styrene cyclopropanation (74–96%).The best enantioselectivity was obtained with *para*-methoxystyrene (ee = 96%). As previously observed with other diazo derivatives [28], dimerization is less prominent than cyclopropanation reaction with a bulky porphyrin such as Halterman porphyrin.

To assure the absolute configuration, an X-ray structure determination of cyclopropyl ketone obtained from the styrene adduct was undertaken. Although at the end of the cyclopropanation, the ee was of only 74%, simple recrystallization of the product in hexane/CH_2Cl_2 easily raises the optical purity to nearly 100%. The X-ray structure of monocrystals obtained from the styrene derivatives confirms the 1*S*,2*S* configuration for the *trans* isomer (see Fig. 3).

3.4. Dimerization

In ruthenium-porphyrin catalyzed cyclopropanation, the corresponding carbene complexes which take octahedral coordination in the presence of axial ligand (solvent) are considered as the active intermediates. As an example, we reported the first X-ray structure of a ruthenium porphyrin carbene complex with a methanol as an axial ligand *trans* to the Ru-carbon bond [29]. Since ketocarbenes are found to be easily inserted in metal-nitrogen bond of iron porphyrin [30,31], preparation of the ruthenium ketocarbene complex was undertaken. Thus, reaction of the carbonyl ruthenium complex with excess of diazoacetylferrocene in dichloromethane results in the displacement of the CO ligand and generation of a carbene complex. The carbene complex was not stable

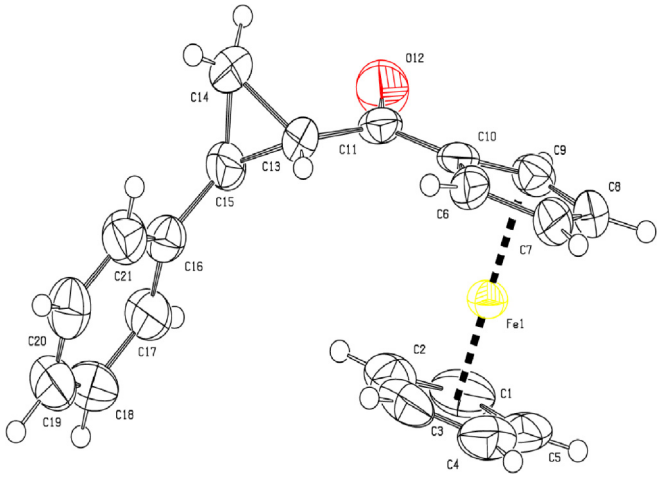


Fig. 3. ORTEP structure of ferrocenyl 2-phenylcyclopropyl ketone.

Table 2
Cyclopropanation with diazoacetylferrocene catalyzed by RuHalt(CO) (catalyst B).

Entry	Alkene	Yield (%)	% ee	Dimer (%)	$[\alpha]_D^{23}$[a]
1	C_6H_5	53	74	8	133
2	4-$CH_3C_6H_4$	69	79	12	152
3	4-$CH_3OC_6H_4$	72	96	10	154
4	4-$CF_3C_6H_4$	53	86	12	111
5	4-ClC_6H_4	78	83	11	135
6	3-$CF_3C_6H_4$	30	76	35	82

[a] (c 1.0, CH_2Cl_2).

enough to be purified by chromatography on silica gel but can be characterized by HMBC NMR at low temperature (210 K). Analysis of the NMR spectrum shows a low-field cross-peak between the carbene carbon at 213 ppm and the carbene proton at 14.28 ppm. The ^{1}H chemical shift is in the range of those previously reported for such Ru = CHR porphyrin complexes [11].

Next, we also report that the tetramesitylporphyrin ruthenium complex (Fig. 1, compound A) catalyzes the stereoselective decomposition of diazoacetylferrocene to form *cis* olefinic products (Scheme 3). This coupling reaction proceeds also through a metallocarbene intermediate to give a *cis* dimer (55% yield). It should be emphasized that synthesis of *cis*-1,2-diferrocenoylethylene was previously attempted from photo-oxidation of 2,5-diferrocenylfuran but without success and it was considered that the *cis*-isomer was isomerized into the *trans*-isomer by thermal condition [32].

3.5. Insertion in N–H bond of amino acid esters by diazoacetylferrocene

We then investigated the reaction of diazoacetylferrocene with aniline and amino esters in organic solvent. In particular, we wanted to check if these reactions can tolerate the presence of ferrocenyl group in the diazo compound. The insertion reactions are shown in Scheme 4 and the results reported in Table 3. In these case, the catalyst used for these reaction was FeTPPCl (Fig. 1C). The reactions are fast (<1h). The yields obtained are quite high (87–88%) with the diazo ketone bearing the ferrocenyl group if we except the results obtained with tyrosine (82%) probably due to solubility difficulty in CH_2Cl_2. Aniline gave also a good yield (87%). As previously observed with ethyl diazoacetate [13], all the insertion products into aminoesters were characterized by ^{1}H NMR, showing also an AB system for CH_2 group in alpha position of the nitrogen (see experimental section).

4. Discussion

Chiral cyclopropyl ketones are a versatile yet underexploited class of functionalized cyclopropanes with only rare isolated examples of enantioselective cyclopropanation involving a diazoketone reagent [33–35]. However, it is now recognized that many functional groups can be tolerated in the transition metal-catalyzed reactions of α-diazo compounds [36]. Consequently, it is possible to design a diazo substrate bearing the necessary functional groups for further use after cyclopropanation. An example is the fullerenes functionalized with ferrocenes via the cyclopropanation reaction which were reported by Tagliatesta [37] and Sokolov [38].

It should also be noted that synthesis of substituted cyclopropyl ferrocenyl ketones have been previously reported by Horspool et al [39] and by Xu et al [40] using a sulfur ylide addition to the corresponding chalcone-containing ferrocenes in solution or under solid state reaction but without enantioselectivity. Cyclopropanation of vinylferrocene is a different way to obtain cyclopropylferrocene. An example of such reaction has been reported by Myamoto and Coll [41] using a ruthenium porphyrin catalyst. More recently, asymmetric synthesis of optically active trifluoromethyl cyclopropane bearing a ferrocenyl group has been described by Iwasa and Coll [42].

Table 3
Insertion in N–H bond of amino acid esters by diazoacetylferrocene catalyzed by FeTPPCl (catalyst C).

Entry	Substrate	Time	Yield (%)
1	Aniline	1 h	87
2	L-Tyrosine ethyl ester	1 h	82
3	D-Phenylalanine methyl ester	1 h	88
4	L-Valine *t*-Butyl ester	1 h	85

Iron porphyrin-catalyzed N–H insertions have been previously studied in organic solvents [14,43,44] and in water [13,14]. This paper suggests that diazo chemistry provides a powerful, attractive alternative to conventional chemistry. As a method for applying metal-catalyzed carbenoid transfer reactions for selective modification of proteins, various amino esters were used as models for NH insertion reactions by diaoacetylferrocene using a porphyrin complex, TSPPFeCl. It also shows a total regioselectivity with tyrosine without O–H insertion. As previously observed with insulin [13], insertion is regioselective onto the NH_2 termini. The introduction of new functional groups on specific sites containing NH groups can modify the stability of the macromolecules, their biological activity and the interactions between them. In the future, the challenge is to optimize all the possible parameters in water and in protic solvents using water-soluble iron porphyrins which tolerate the different functions present on the protein.

5. Conclusion

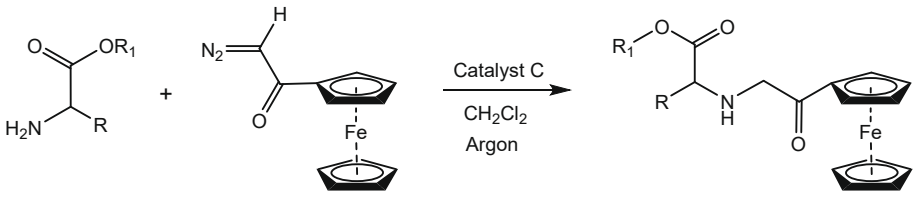
The transition-metal-catalyzed asymmetric cyclopropanation have become important enantioselective C–C bond-forming approaches. By use of ruthenium complexes of chiral porphyrin ligands, the formation of cyclopropyl ferrocenes has been accomplished with high enantioselectivity (ee up to 96%). The N–H insertion of diazoacetylferrocene with aminoesters catalyzed by iron porphyrins has high potential for wide application in bioconjugation of peptides and proteins, as previously reported by us [13] and others [45] with water-soluble ruthenium porphyrins.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

CCDC 2062260 contains the supplementary crystallographic data for diazoacetylferrocene and CCDC 2062261 contains the



Scheme 4. N–H insertion of diazoacetyl ferrocene catalyzed by FeTPPCl (catalyst C).

supplementary crystallographic data for ferrocenyl 2-phenylcyclopropyl ketone. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk.

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