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Oxidative ring-opening of ferrocenylcyclopropylamines to *N*-ferrocenylmethyl β-hydroxyamides†

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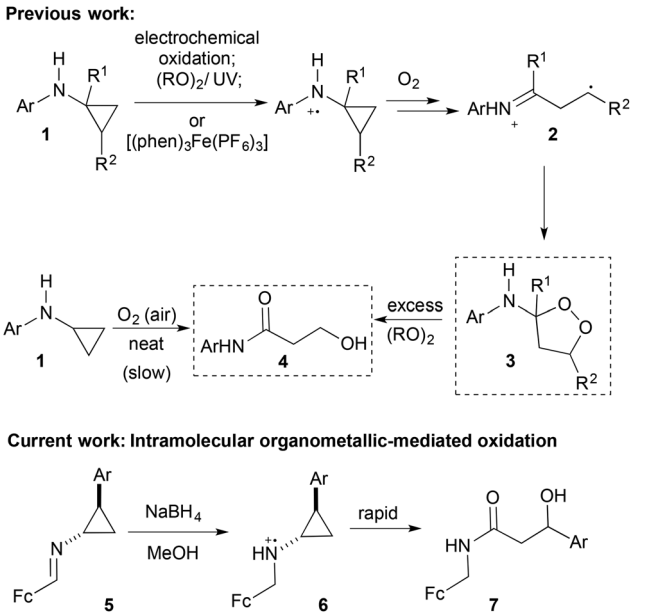
The *in situ* reduction of ferrocenyl cyclopropylimines to the corresponding amines triggers a facile oxidative ring-opening to yield the formal four-electron oxidation products: *N*-ferrocenylmethyl β-hydroxyamides. This process is believed to proceed *via* generation of a ferrocinium ion in the presence of air, leading to facile formation of a distonic radical cation that is ultimately trapped by oxygen.

Introduction

Cyclopropylamines **1** are found in a broad variety of biologically active compounds, such as the antibiotics Ciprofloxacin, Moxifloxacin, Trovafloxacin and the antidepressant 2-phenylcyclopropylamine (2-PCPA).[1,2] Therefore, much attention has been paid to understanding the reactivity of these important structures.[3,4] Cyclopropylamines **1** can undergo characteristic, irreversible ring-opening reactions *via* a single-electron transfer mechanism to yield a distonic radical cation **2** (Scheme 1). This process is particularly important in biological systems; for example, 2-PCPA inhibits monoamine oxidase by flavin adenine dinucleotide (FAD) oxidation of the cyclopropylamine nitrogen and subsequent ring-opening to a distonic radical cation similar to **2**.[5] The ability of cyclopropylamines to undergo this ring-opening process has also seen them used as tools for studying biological amine-oxidation.[6,7] Given this widespread importance, several groups have studied the ring-opening of cyclopropylamines initiated by single electron oxidation and subsequent reaction with oxygen (Scheme 1). Endoperoxides **3** derived from aminocyclopropanes **1** have been prepared by aerobic electrochemical oxidation[8] as well as autocatalytic radical ring-opening under aerobic conditions using an oxidising agent [$(phen)_3Fe(PF_6)_3$] or hydrogen-abstracting agents ($(RO)_2$/UV) (Scheme 1).[9] In the latter case, excess peroxide can convert the endoperoxide into a simple β-hydroxyamide **4**. Epoxy-ketones can also be formed by $CuCl_2$-catalysed oxygenation of 1-pyrrolidino[*n*,1,0]-bicycloalkanes.[10] It has also been shown that *N*-cyclopropylanilines can undergo slow air oxidation under ambient conditions to yield simple β-hydroxyamides **4**.[11] However, to date we are unaware of any studies into the reactivity of organometallic derivatives of cyclopropylamines.



Scheme 1 Previous work on ring-opening of cyclopropylamines **1** initiated by oxidation of amine nitrogen and subsequent reaction with oxygen. Current study on the internal oxidation of ferrocenyl-aminocyclopropanes. Fc = ferrocene.

Ferrocene (Fc) can undergo reversible oxidation and this has rendered it important in bioorganometallic drugs, such as

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ferroquine[12] and ferrocifens.[13] In ferrocifens it is likely that the active quinone methide form of the drug is only formed following oxidation of the ferrocene to the ferrocinium ion. As such, we postulated that cyclopropylamine-ferrocene conjugates could harness the redox ability of ferrocene to initiate oxidative ring-opening processes in the presence of air.

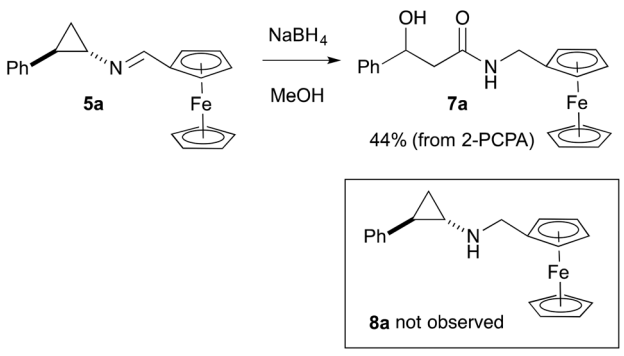
Given the importance of both the ferrocene moiety and cyclopropylamines in biological systems, understanding of these ring-opening processes could provide important information for the utilisation of organometallic derivatives of cyclopropylamines in biological applications. Herein, we describe the $NaBH_4$ initiated oxidative ring-opening of ferrocenyl cyclopropylimines **5** to *N*-ferrocenylmethyl β-hydroxyamides **7** (Scheme 1). This is the first process where ferrocene initiates an oxidative cyclopropane ring-opening, allowing synthesis of a series of novel organometallic β-hydroxyamides.

Results and discussion

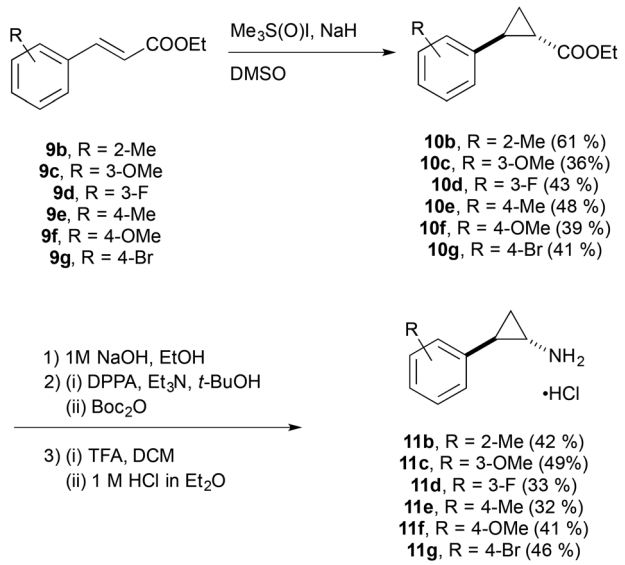
Work commenced with commercially available 2-PCPA, which was transformed to imine **5a** by condensation with ferrocenecarboxyaldehyde. Upon reduction of this imine with stoichiometric sodium borohydride none of the amine **8a** was observed – instead the ring-opened and oxidised *N*-ferrocenylmethyl β-hydroxyamide product **7a** was observed to form rapidly (Scheme 2). The same product was formed when Bu_3SnH on silica gel was used as the reducing agent.

It is of note that unlike the previously reported electrochemical and autocatalytic ring-opening reactions no dioxolane products were observed under these present conditions.

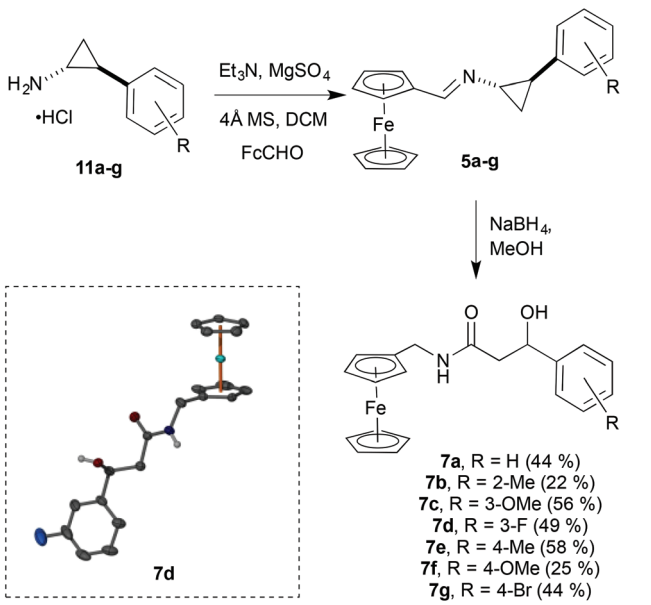
Following this intriguing result, a series of 2-PCPA analogues were prepared (Scheme 3). The procedure originated with cinnamic esters **9b–g**, which were subjected to Corey–Chaykovsky cyclopropanation to yield cyclopropanes **10b–g**. After basic hydrolysis, the carboxylic acids were converted to 2-PCPA analogues **11b–g** by a Curtius rearrangement and deprotection. These 2-PCPA analogues **11b–g** were then subjected to condensation with ferrocenecarboxaldehyde to yield imines **5b–g** (Scheme 4). In all cases, treatment of these cyclopropylamines with sodium borohydride, gave the ring-opened *N*-ferrocenylmethyl β-hydroxyamides **7b–g** (22–58% yield over two steps from the amine salt). A range of differently substituted aromatic groups, including *ortho*, *meta* and *para* substituents could be tolerated. The structure of **7d** was confirmed unambiguously by X-ray crystallography (Scheme 4).



Scheme 2 Oxidative ring-opening of **5a** initiated by treatment with $NaBH_4$.



Scheme 3 Syntheses of 2-PCPA derivatives.

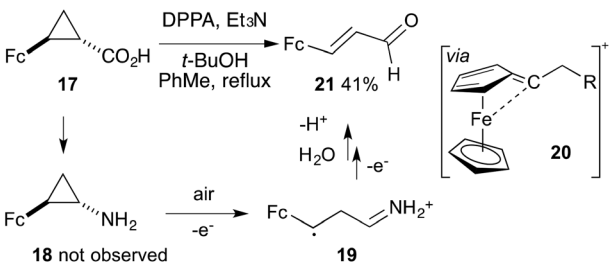


Scheme 4 Reductive amination of ferrocenecarboxaldehyde and 2-PCPA analogues **11a–g** to yield *N*-ferrocenylmethyl β-hydroxyamides **7a–g**. Molecular structure of **7d**. Thermal ellipsoids are shown at the 50% probability level. All methine, methylene and aromatic-ring hydrogen atoms are omitted for clarity. Intra-/intermolecular H-bonding is also not shown for clarity. The asymmetric unit contains another similar molecule of **7d**, featuring a 120° rotation of the C(methylene)–C(methine) bond to allow intramolecular H-bonding to the carbonyl carbon (C═O···H–O).

Mechanistically, it is proposed that the ferrocene moiety plays a key role in the reaction, especially as the corresponding benzyl-derivatives have been reported to be air stable.[14] Air-generated ferrocinium ions have been recently utilised as the terminal oxidant in asymmetric dehydrogenative Heck reactions.[15] Therefore, it is proposed the ferrocinium ion **12**, generated *in situ* by air that acts as an internal oxidant to generate aminium radical **6** from cyclopropylamines **8**, which are the initial $NaBH_4$ reduction products (Fig. 1). Cyclopropane ring-opening of **6** then occurs exclusively by cleavage of the C1–C2 bond as this pathway gives the more stable benzylic carbon-centred radical. This is consistent with Wimalasena *et al.* who suggest the carbon-centered radical is a discrete intermediate in radical ring-opening of cyclopropylamines and therefore, ring-opening and molecular oxygen insertion are not concerted.[9] The resulting distonic radical cation **13** is able to be trapped with dioxygen to give adduct **14** which can undergo 5-*exo-trig* cyclisation to radical cation **15**. The catalytic cycle is propagated by abstraction of an electron from **8** by radical cation **15**, which yields dioxolane **16** as an intermediate.

Dioxolane **16** is not observed for the current reaction, as it is likely isomerisation with concomitant O–O bond cleavage to yield *N*-ferrocenylmethyl β-hydroxyamides **7** is a facile process under basic conditions. This isomerisation step to the hydroxyamide could occur *via* several pathways. While it has been reported that 1,2-dioxolanes can undergo conversion to β-ketoalcohols in the presence of silica gel,[16] in our case this is unlikely as signals corresponding to the hydroxyamide were observed in the ^1H NMR of the crude reaction material prior to contact with silica gel. Therefore, it is more likely that the isomerisation occurs *via* base-mediated[17] or radical abstraction[9] of H. Of these two possibilities the base-mediated mechanism would appear more likely as no clear mechanism for generation of $RO^{\bullet}$ is apparent and our conditions are intrinsically basic due to the presence of $NaBH_4$.

The analogue **18** of 2-PCPA, where the phenyl ring is replaced with ferrocene, also displays a strong propensity to undergo these ferrocene-mediated ring-opening processes (Scheme 5). When carboxylic acid **17** was subjected to a Curtius rearrangement, enal **21** was observed instead of cyclopropylamine **18**. The analogous cinnamaldehyde product has been reported to be obtained from the oxidation of 2-PCPA by horseradish peroxidase.[18] Similarly to the 2-PCPA analogues **8**, it is thought that amine **18** is intrinsically unstable in the presence of air and likely undergoes a similar oxidation/ring-opening sequence. Interestingly, the distonic radical cation **19** does not appear to be trapped by molecular oxygen, prefering to undergo a second oxidation, then elimination and hydrolysis to the enal. The preference for oxidation to an α-ferrocenylcarbenium ion **20**, rather than trapping with molecular oxygen, may be related to the well-established stabilisation of



Scheme 5 Attempted Curtius rearrangement of **17** to yield enal **21**.

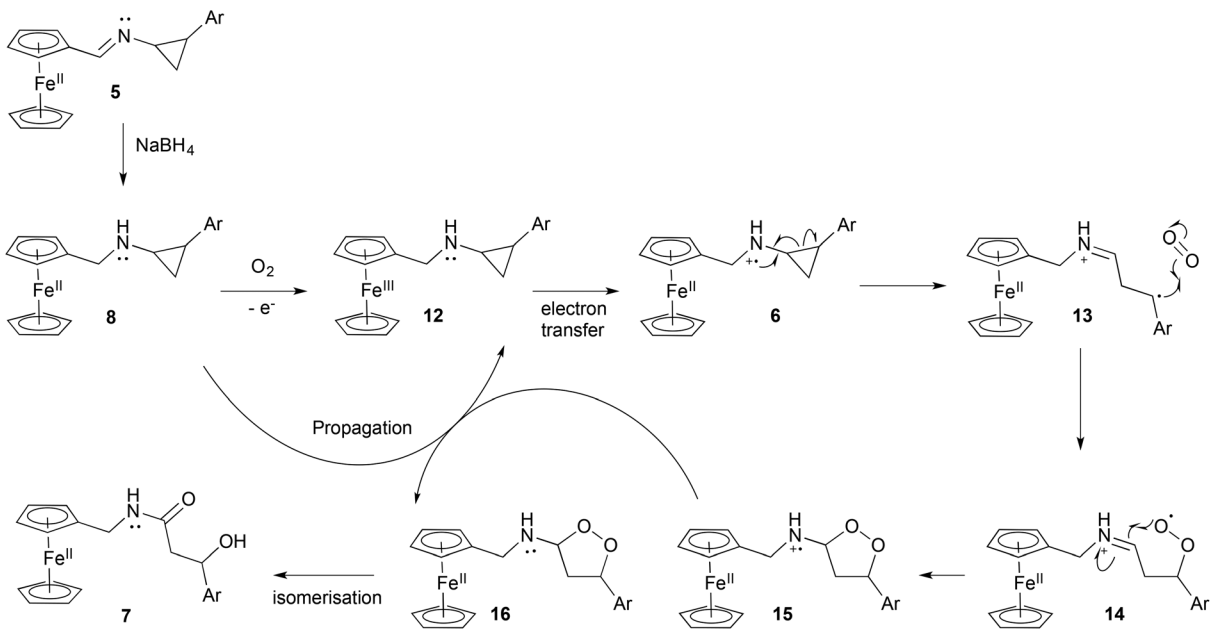


Fig. 1 Proposed mechanism of $NaBH_4$-initiated ring-opening-oxidation of cyclopropylimines **5**.

α-carbocations by ferrocene. Such systems show fulvene character and direct iron–α-carbon bonding.[19]

Conclusion

In conclusion, we have unveiled a novel ring-opening process of cyclopropylamine facilitated by the redox ability of ferrocene in air. This process yields novel *N*-ferrocenylmethyl β-hydroxyamides and provides information about the reactivity of organometallic cyclopropylamine derivatives. The increased reactivity of the ferrocenyl derivatives of 2-PCPA towards oxidation with molecular oxygen and ring-opening suggests the possibility of modulating aminocyclopropane reactivity with less-readily oxidised metallocene fragments. It may also be possible to employ ferrocene as a catalytic additive to enhance the oxidative ring-opening of aminocyclopropanes. It is worth noting that distonic radical cations can participate in useful reactions like [3 + 2] cycloadditions with olefins.[20] As such, the current method of generating such species under environmentally friendly conditions could lead to reaction with species other than molecular oxygen to obtain more complex organometallic compounds.

It is also the first report of a very facile conversion to the hydroxyamide skeleton by internal redox. As β-hydroxyamide products feature in bioactive compounds, such as Cruentaren A (antifungal)[21] and Octreotide (growth hormone inhibitor),[22] organometallic derivatives of this moiety are of potential interest to medicinal chemists.[23]

Experimental

General information

Unless stated specifically, all chemicals were purchased from commercial suppliers and used without purification. All reactions were conducted in oven-dried glassware under nitrogen atmosphere. Reaction solvents were dried by passing through a column of activated alumina and then stored over 4 Å molecular sieves. Progress of reactions was tracked by TLC and was performed on aluminium backed silica gel sheets (Grace Davison, UV254). TLC plates were visualised under UV lamp at 254 nm and/or by treatment with one of the following TLC stains: Phosphomolybdic acid (PMA) stain: PMA (10 g), absolute EtOH (100 mL); Potassium permanganate stain: $KMnO_4$ (1.5 g), 10% NaOH (1.25 mL), water (200 mL); Vanillin stain: Vanillin (15 g), concentrated H_2SO_4 (2.5 mL), EtOH (250 mL). Preparative TLC was carried out on glass backed TLC plates with silica matrix. Column chromatography was performed using silica gel (40–75 μm) as the solid phase. For NMR spectroscopy analytes were dissolved in deuterated chloroform or stated otherwise. NMR spectra for each compound were collected from one of the following instrument: Mercury 2000 spectrometer operates at 500 and 125 MHz for ^{1}H and ^{13}C NMR respectively, or Varian spectrometer operates at 300 and 75 MHz for ^{1}H and ^{13}C NMR respectively. NMR data are expressed in parts per million (ppm) and referenced to the solvent (7.26 ppm for ^{1}H NMR and 77.16 ppm for ^{13}C NMR). The following abbreviations are used to assign the multiplicity of the ^{1}H NMR signal: s = singlet; bs = broad singlet; d = doublet; t = triplet; q = quartet; quin = quintet; dd = doublet of doublets; m = multiplet. For mass spectroscopy analytes were dissolved in HPLC grade methanol. Spectra of low-resolution mass spectrometry were obtained from a Shimadzu LC-2010 mass spectrometer (ESI) or a Shimadzu QP5050 mass spectrometer (EI). High-resolution mass spectra were collected from a Waters Xevo G1 QTOF mass spectrophotometer (ESI or ASAP) or Thermo Scientific LTQ Orbitrap XL (ESI). Infrared spectra were obtained from a Shimadzu IRAffinity-1 Fourier transform infrared spectrophotometer with ATR attachment. Melting point measurements were taken on a Buchi M-560. The 2-PCPA derivatives (**11a–g**) were prepared according to literature procedures; their syntheses and characterisation are provided in the ESI.†

Typical procedure for the synthesis of *N*-ferrocenylmethyl β-hydroxyamides

Triethylamine (0.93 mmol, 1.9 equiv.) was added to a suspension of 2-PCPA derivative hydrochloride salt (0.48 mmol, 1 equiv.) and magnesium sulphate (1.82 mmol, 3.8 equiv.) in dry dichloromethane (4 mL). This mixture was stirred for 10 minutes before ferrocenecarboxaldehyde (0.58 mmol, 1.2 equiv.) was added. After 3 hours of stirring, another portion of ferrocenecarboxaldehyde (93.4 μmol, 0.2 equiv.) and one spatula of magnesium sulphate were added. The mixture was allowed to stir overnight, after which another portion of ferrocenecarboxaldehyde (67.3 μmol, 0.1 equiv.) and a spatula of magnesium sulphate were added. After 2 hours of stirring, dry toluene (8 mL) was added to precipitate triethylamine hydrochloride and the mixture was filtered. After removal of solvents under reduced pressure, more triethylamine hydrochloride precipitated out, therefore dry toluene (10 mL) was added and the mixture was filtered again. After removal of solvents, sodium borohydride (2.07 mmol, 4.3 equiv.) was added to the solution of crude imine mixture in dry methanol (5 mL) at −10 °C. After stirring for 15 minutes at −10 °C, the reaction was left stirring at room temperature. Another portion of sodium borohydride (0.78 mmol, 1.6 equiv.) was added after 45 min at −10 °C. After stirring for 15 minutes at −10 °C, the reaction solution was left stirring overnight at room temperature. The reaction was quenched with water (5 mL) and methanol was evaporated under reduced pressure. After the aqueous layer was extracted with ethyl acetate (3 × 10 mL), the combined organic extracts were washed with brine (10 mL) and dried over magnesium sulphate. This crude mixture was subjected to column chromatography (typically 40–80% ethyl acetate in hexane), which yielded the *N*-ferrocenylmethyl β-hydroxyamides.

***N*-(Ferrocenylmethyl)-3-hydroxy-3-phenylpropanamide (7a).** Obtained as a yellowish orange solid (77.8 mg, 0.21 mmol) in a 44% overall yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36–7.25 (m, 5H), 6.08 (s, 1H), 5.09 (dd, J = 8.75, 3.5 Hz, 1H), 4.14–4.12 (m, 11H), 2.59–2.50 (m, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$):

δ 171.1, 143.1, 128.5, 127.7, 125.6, 84.4, 70.9, 68.6, 68.2, 68.1, 44.7, 38.8 ppm. IR (Neat): 3300, 1646 cm^{-1}. HRMS (ASAP) Found: M, 363.0914. $C_{20}H_{21}FeNO_2$ requires M, 363.0922. Melting point: 114.7–116.9 °C.

***N*-(Ferrocenylmethyl)-3-hydroxy-3-(*o*-methylphenyl) propanamide (7b).** Obtained as brownish orange solid (46.1 mg, 0.12 mmol) in a 22% overall yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47 (d, J = 7.5 Hz, 1H), 7.21–7.14 (m, 2H), 7.10–7.09 (m, 1H), 6.29 (bs, 1H), 5.27 (d, J = 9 Hz, 1H), 4.14–4.12 (m, 11H), 2.50–2.40 (m, 2H), 2.29 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.3, 141.1, 134.1, 130.5, 127.5, 126.5, 125.3, 84.5, 68.7, 68.3, 68.3, 67.5, 43.4, 38.9, 19.1 ppm. IR (Neat): 3305, 1636 cm^{-1}. HRMS (ESI) Found: M+, 377.10726. $C_{21}H_{23}FeNO_2$ requires M+, 317.10782. Melting point: 103.2–107.3 °C.

***N*-(Ferrocenylmethyl)-3-hydroxy-3-(*m*-methoxyphenyl) propanamide (7c).** Obtained as a brownish orange solid (111.5 mg, 0.28 mmol) in a 56% overall yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26–7.23 (m, 1H), 6.94–6.91 (m, 2H), 6.81 (d, J = 8 Hz, 1H), 6.05 (bs, 1H), 5.08–5.07 (m, 1H), 4.15–4.13 (m, 11H), 3.80 (s, 3H), 2.56–2.54 (m, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.2, 160.0, 145.0, 129.8, 118.0, 113.5, 111.3, 84.6, 71.1, 68.8, 68.4, 68.4, 68.4, 55.5, 44.9, 39.0 ppm. IR (Neat): 3310, 1647 cm^{-1}. HRMS (ESI) Found: (M + Na)+, 416.0918. $C_{21}H_{23}NO_3Fe$ requires (M + Na)+, 416.0925. Melting point: 83.2–86.8 °C.

***N*-(Ferrocenylmethyl)-3-hydroxy-3-(*m*-fluorophenyl) propanamide (7d).** Obtained as a brown solid (35.2 mg, 0.09 mmol) in a 49% overall yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33–7.26 (m, 1H), 7.13–7.10 (m, 2H), 6.99–6.93 (m, 1H), 5.93 (bs, 1H), 5.11 (t, J = 6.3 Hz, 1H), 4.15–4.14 (m, 11H), 2.53 (d, J = 6 Hz, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.0, 163.0 (d, J = 245 Hz), 145.9 (d, J = 7.5 Hz), 130.1 (d, J = 8.75 Hz), 121.2 (d, J = 3.75 Hz), 114.5 (d, J = 21.25 Hz), 112.7 (d, J = 22.5 Hz), 84.3, 70.3, 68.7, 68.3, 68.3, 68.3, 44.5, 38.9 ppm. IR (Neat): 3238, 1650 cm^{-1}. HRMS (ESI) Found: (M + Na)+, 404.0710. $C_{20}H_{20}NO_2FFe$ requires (M + Na)+, 404.0725. Melting point: 112.3–116.3 °C.

***N*-(Ferrocenylmethyl)-3-hydroxy-3-(*p*-methylphenyl) propanamide (7e).** Obtained as a yellow oil (118.8 mg, 0.32 mmol) in 58% overall yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 (d, J = 7.5 Hz, 2H), 7.15 (d, J = 8 Hz, 2H), 5.99 (bs, 1H), 5.08 (d, J = 8.5 Hz, 1H), 4.15–4.13 (m, 11H), 3.92 (bs, 1H), 2.61–2.50 (m, 2H), 2.34 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.1, 140.1, 137.4, 129.2, 125.5, 84.4, 70.9, 68.6, 68.2, 68.2, 44.8, 38.8, 21.1 ppm. IR (Neat): 3299, 1636 cm^{-1}. HRMS (ESI) Found: (M + Na)+, 400.0979. $C_{21}H_{23}NO_2Fe$ requires (M + Na)+, 400.0976.

***N*-(Ferrocenylmethyl)-3-hydroxy-3-(*p*-methoxyphenyl) propanamide (7f).** Obtained as a yellowish orange solid in 25% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27 (d, J = 8.1 Hz, 2H), 6.86 (d, J = 8.4 Hz, 2H), 6.13 (bs, 1H), 5.04 (d, J = 8.4 Hz, 1H), 4.15–4.14 (m, 11H), 3.79 (s, 3H), 2.61–2.46 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.3, 159.2, 135.4, 127.0, 114.0, 84.5, 70.7, 68.8, 68.7, 68.3, 55.4, 44.9, 38.9 ppm. IR (Neat): 3301, 1636 cm^{-1}. HRMS (ESI) Found: (M + Na)+, 416.0937. $C_{21}H_{23}FeNO_3$ requires (M + Na)+, 416.0925. Melting point: 80.5–83.8 °C.

***N*-(Ferrocenylmethyl)-3-hydroxy-3-(*p*-bromophenyl) propanamide (7g).** Obtained as a yellowish orange solid (82.5 mg, 0.19 mmol) in a 44% overall yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44 (d, J = 8 Hz, 2H), 7.20 (d, J = 8.5 Hz, 2H), 6.13 (bs, 1H), 5.03–5.00 (m, 1H), 4.14–4.09 (m, 11H), 2.48–2.47 (m, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.9, 142.2, 131.7, 127.4, 121.5, 84.2, 70.3, 68.7, 68.4, 68.3, 68.3, 44.5, 38.9 ppm. IR (Neat): 3302, 1636 cm^{-1}. HRMS (ESI) Found: (M + Na)+, 463.9934. $C_{20}H_{20}BrFeNO_2$ requires (M + Na)+, 463.9925. Melting point: 113.6–115.1 °C.

Acknowledgements

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