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Regiodirecting effects in difunctionalised tricarbonyl[(1,2,3,4,5-η)-cyclohexadienyl]iron(1+) salts: building blocks for alkaloids

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Dedicated to Professor Philip J. Parsons, Senior Research Investigator, Chemistry Department, Imperial College London, SW7 2AZ, UK to mark his 60th birthday

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ABSTRACT

Electrophilic tricarbonyl[(1,2,3,4,5-η)-cyclohexadienyl]iron(1+) salts that incorporate methoxy and 2-ethanoyl ester substituents have been prepared, and the regiochemistry of their reactions with nucleophiles in arylation reactions has been examined using the model nucleophile diphenylzinc. The 1-carbomethoxymethyl-2-methoxy salt **1** reacts selectively by the ω addition pathway, but the 2-carbomethoxymethyl-3-methoxy salt **9** gave a 6:1 mixture of ω and α addition products. The 1-carbomethoxymethyl-2-methoxy regioisomer **1** was prepared in >95% purity without recourse to chromatography and shows the correct regiocontrol for use as a starting material in organoiron-mediated routes to alkaloids such as lycorine and parkacine.

Our work to establish the use of stereodominant organoiron control groups[1] as a general method of asymmetric synthesis has, over the last decade, focused on a series of alkaloids[2] which are structurally diverse and yet, through related biogenesis, contain the same substructure components. For example, lycorine[3] and hippeastrine[4] differ from lycoramine[5,6] and maritidine[6,7] in the relative positions of the arene and a two-carbon side-chain (Fig. 1). Conventional synthesis design would analyse the activation effects of substituents in each of these structures to choose disconnections based on natural or umpolung polarities,[8] or radical methods. Strategies for stereocontrol are typically based on the properties of the substitution pattern in intermediates, or external chiral auxiliaries. When transition metal control groups are used, substituents on the 'working ligand'[9] remain important, but in a different way. The chirality is present in the planar chirality of metal complex, and the substituents are crucial for regiocontrol, but stereocontrol is entirely derived from the metal.[10] Understanding the regiodirecting effects of substituents in new combinations on the working ligand is a prerequisite for the reliable planning of new synthetic routes to incorporate efficiently the working ligand into the target structure.

We describe here a series of studies that explore the properties of electrophilic tricarbonyl[(1,2,3,4,5-η)-cyclohexadienyl]-iron(1+) salts that incorporate methoxy and 2-ethanoyl ester substituents in different relative positions on the cyclohexadienyl ligand. For example, the isomers **1** and **2** (Fig. 2) are expected to be suitable for synthetic routes to lycorine[3] and parkacine,[11] based on the ω-directing property of the OMe group at C-2. The regioisomer **1** is known from our earlier work[12] that studied the ipso directing effect of a 1-methoxy substituent in the η^5 series, but was obtained by an inconvenient route that required separation of regioisomers of the intermediate neutral η^4 diene complexes.

To launch a major synthetic route to our chosen target molecules, we wanted access to the difunctionalised cyclohexadienyliron complexes that could be performed without chromatography. Starting from 2-methoxybenzyl cyanide (**3**), we used a Pinner reaction (Scheme 1) to prepare 1-methoxy-2-(2,2,2-trimethoxyethyl)benzene[13] on a 20 g scale. Birch reduction followed by complexation of 1,4-diene with pentacarbonyliron at reflux in di-*n*-butyl ether gave the expected mixture of two 1,3 diene complexes **4** and **5** (box: Scheme 1) in a 2:1 ratio. Hydride abstraction followed by hydrolysis was performed on the mixture of regioisomers to produce **1**[14,15] (>95% purity[16]) which was separated from the

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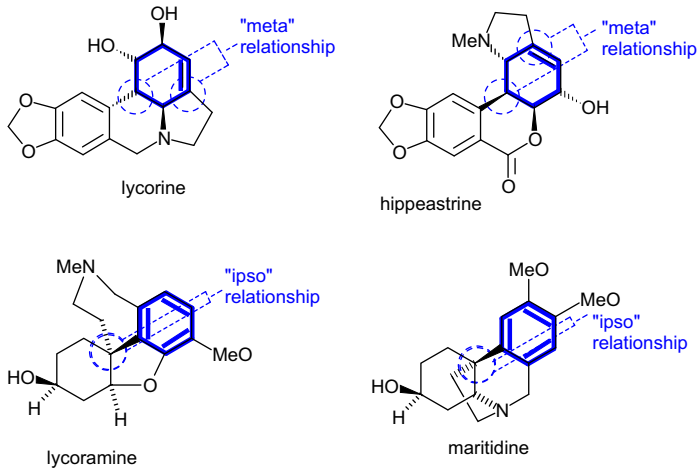


Figure 1. Structural features of target alkaloids for iterative organoiron-mediated synthetic routes (the ring to be introduced as the 'working ligand' is highlighted in bold).

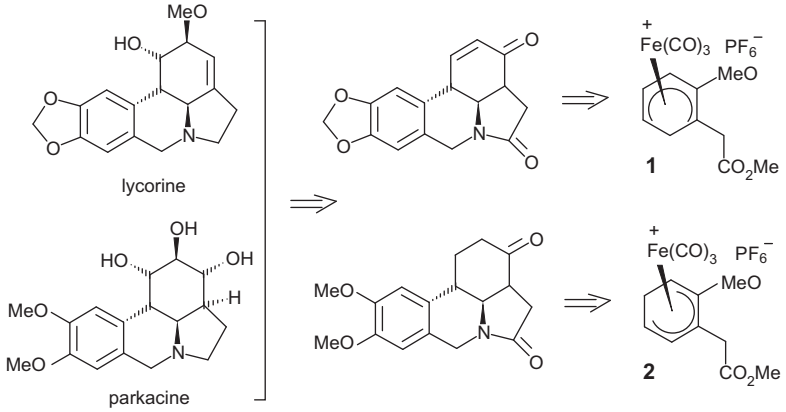
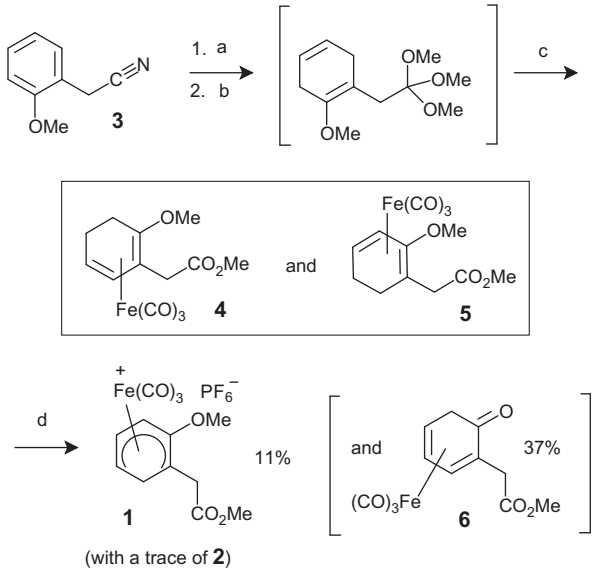


Figure 2. Proposed retrosyntheses for lycorine and parkacine.

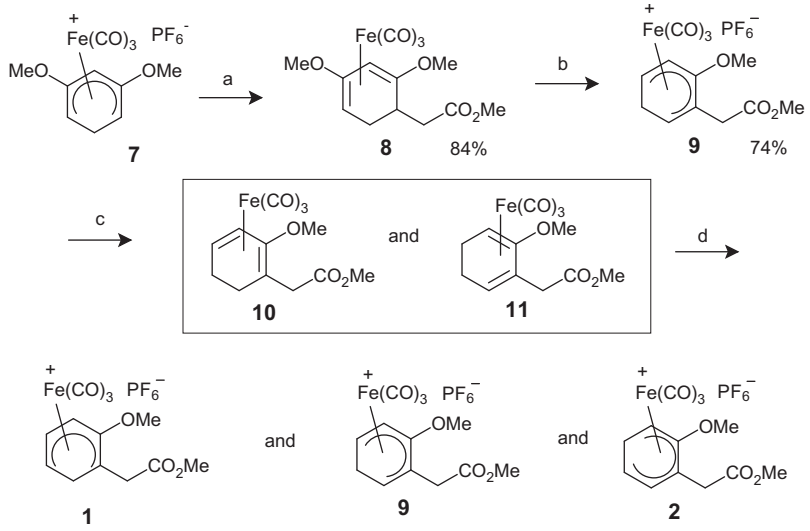


Scheme 1. Reagents and conditions: (a) AcCl, MeOH, 4 °C, collect the imino ether by filtration, then dry MeOH, hexane, 6 d; (b) Li, IPA, THF, liq. NH_3; (c) $Fe(CO)_5$, *n*-Bu_2O, reflux, 16 h; 11% for three steps from **3** (allowing for recovered diene[20]); (d) Ph_3CBF_4, K_2CO_3, CH_2Cl_2, reflux, 1 h, NH_4PF_6, 48%.

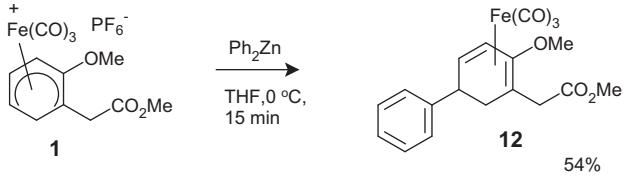
major 1-methoxy regioisomer by the standard hydrolysis method.[17] In this way, the required salt can be precipitated and the neutral dienone (presumably **6**[18]) is separated by extraction into ether. The reaction sequences described here were performed on the racemic series.[19]

The well-established regiocontrolled demethoxylation approach[21] offers a more iterative alternative, starting from the 2,4-dimethoxycyclohexadienyl complex **7**[22] (Scheme 2), reaction with 1-trimethylsilyloxy-1-methoxyethene[23] gave **8**[15] which was demethoxylated using trifluoroacetic acid at 0 °C. The product **9**[15,24] was precipitated as a single regioisomer with ammonium hexafluorophosphate. Reduction of **9** ($NaBH_4$ in MeCN) gave a 1:1 mixture of the regioisomeric diene complexes **10** and **11**[15] (box: Scheme 2). Hydride abstraction gave the alternative regioisomer **2**[25] of the target salts (Fig. 2) as a mixture with **1** and **9**.

Both salts **1** and **2** have 2-methoxy substituents, so unlike the 1-methoxy series used in our syntheses of *O*-methyl joubertiamine, mesembrine, lycoramine, and maritidine, which employed aryllithium reagents as nucleophiles, organozinc reagents were expected[26] to be more suitable in this study. The simple diphenylzinc nucleophile was chosen as a benchmark to investigate the regiocontrol effects in the series of dienyl cations **1**, **2**, and **9**. Reaction of **1** with diphenylzinc gave the expected ω addition product **12**[27] (mp 62–66 °C; found *m*/*z* found 399.0530 $[M+H]^+$; $C_{19}H_{19}FeO_6$ requires 399.0531). The strong ω directing effect of the OMe group, and the weaker (steric) ω directing effect of



Scheme 2. Reagents and conditions: (a) $H_2C{=}C(OMe)(OSiMe_3)$, MeCN, exothermic reaction followed by 80 °C, 15 min; (b) TFA, 0 °C, 6 h, NH_4PF_6; (c) $NaBH_4$, MeCN, rt, 83% (1:1 mixture); (d) Ph_3CBF_4, CH_2Cl_2, NH_4PF_6, 57% (7:1:2 mixture).



Scheme 3. Regiocontrol studies using diphenylzinc in THF at 0 °C.

CH_2CO_2Me are mutually supporting in this example. A trace (<4%) of a second regioisomer was observed in the ^1H NMR spectrum of the product. To identify it, NMR spectra were recorded for products obtained by diphenylzinc addition to salt **9** and to the mixture of salts **1**, **2**, and **9** shown in Scheme 2. From **9**, a 6:1 mixture of regioisomers[28,29] was obtained, with the major product resulting, as expected, from addition of the phenyl ring by the ω addition pathway. The corresponding reaction with the mixture of **1**, **2**, and **9**, gave **12** as the major product (Scheme 3). The minor product[30] (7:2 ratio) from this reaction corresponded to the trace impurity from the reaction of **1**. This product is formed by the addition of the phenyl group ω to the 2-methoxy directing group in **2**.

The differences in regioselectivity reported here are consistent with the strong ω directing influence of 2-methoxy groups on η^5 working ligands, and confirm that salt **1** is suitable as a starting point for synthetic applications provided that deprotonation of the methylene group next to the ester in the C-1 substituent can be adequately controlled, since the directing effects of both substituents are mutually reinforcing. In the case of **9**, the methoxy group is centrally placed and so is not a regiodirecting group, and only the weak directing influence of the C-2 CH_2CO_2Me group is present. In the case of **2**, the CH_2CO_2Me group is centrally placed and only the strong ω directing effect of the C-2 methoxy group influences the regiocontrol of the reaction.

In conclusion, the ω addition pathway for transfer of an aryl group from diphenylzinc to the cyclohexadienyliron complex **1** has been confirmed, preparing the way for more detailed investigations with functionalised diarylzinc reagents bearing dimethoxy, methylenedioxy, benzyl ether, and amine substituents (see Fig. 2) for synthetic routes to targets such as lycorine and parkacine. The difunctionalised tricarbonyl[(1,2,3,4,5-η)-cyclohexadienyl]iron(1+) salts **1** and **9** have been prepared in >95% purity by reaction sequences that avoid the need for chromatography and so are suitable for scale-up.[16] The salt **9** lacked complete regioselectivity when used in combination with diphenylzinc.

Acknowledgments

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References and notes

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13. 1-Methoxy-2-(2,2,2-trimethoxyethyl)benzene is commercially available in gram quantities from specialist suppliers.
14. Salt **1** ^{1}H NMR δ_H (400 MHz, CD_3CN) 6.95 (1H, d, J = 6 Hz, H-3), 5.84 (1H, apparent t, J = 6 Hz, H-4), 4.33 (1H, apparent t, J = 6 Hz, H-5), 4.04 (3H, s, CO_2Me), 3.66 (3H, s, OMe), 3.09 (1H, d, J = 17 Hz, CH_2CO_2), 3.02 (1H, dd, J = 15, 6 Hz, H-6β), 2.91 (1H, d, J = 17 Hz, CH_2CO_2), 2.32 (1H, d, J = 15 Hz, H-6α); δ_C 199.6 (FeCO), 169.7 (CO_2–), 148.4 (C-2), 98.1 (C-4), 72.7 (C-3), 66.9 (C-5), 58.4 (OMe), 56.2 (C-1), 52.9 (OMe), 37.3 (CO_2–), 33.1 (C-6) ppm.
15. Microanalytical data: Salt **1**: Found: C, 33.3; H, 2.7. $C_{13}H_{13}F_6FeO_6P$ requires C, 33.5; H, 2.8. Regioisomeric diene complexes **4** and **5**: Found: C, 48.9; H, 4.4. $C_{13}H_{14}FeO_6$ requires C, 48.5; H, 4.4. Salt **8**: Found: C, 47.7; H, 4.6. $C_{14}H_{16}FeO_7$ requires C, 47.8; H, 4.6. Salt **9**: Found: C, 33.4; H, 2.6. $C_{13}H_{13}F_6FeO_6P$ requires C, 33.5; H, 2.8. Regioisomeric diene complexes **10** and **11**: Found: C, 48.1; H, 4.3. $C_{13}H_{14}FeO_6$ requires C, 48.5; H, 4.4.
16. The salt **1** was purified by simple precipitation from acetonitrile by addition of diethyl ether, and appeared pure by NMR, However, a trace amount (ca. 4%) of the regioisomeric phenyl derivative **13** was identified in the NMR spectrum of the products from reaction with diphenylzinc. When **1** is prepared on a large scale, repeated precipitation improves the purity. It is anticipated that the route described here will be more suitable than the original procedure (Ref. 12) for access on a large scale.
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20. The reaction mixture was filtered through a pad of celite to remove pyrophoric iron particles, and then concentrated on a rotary evaporator fitted with a dry ice cooled condenser (caution: pentacarbonyliron in distillate) and then Kugelrohr distilled. In practice, the recovered diene can be recycled by returning it to the blackened reaction vessel (in our experience this is more effective than using a clean flask, and also more convenient), adding additional pentacarbonyliron and heating at reflux for 8–10 h. For a description of this recycling procedure, see: Curtis, H.; Johnson, B. F. G.; Stephenson, G. R. *J. Chem. Soc., Dalton Trans.* **1985**, *1*, 1723–1725.
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24. Salt **9**: ^{1}H NMR δ_H (400 MHz, CD_3CN) 6.05 (1H, d, J = 8 Hz, H-4), 4.14 (3H, s, OMe), 4.00 (1H, m, H-1), 3.88 (1H, m, H-5), 3.86 (1H, d, J = 16 Hz, CH_2CO_2), 3.73 (3H, s, CO_2Me), 3.03 (1H, d, J = 16 Hz, CH_2CO_2), 2.93 (dt, J = 15, 6 Hz, H-6β), 1.83 (dt, J = 15, 1.8 Hz, H-6α) ppm.
25. Salt **2**: ^{1}H NMR δ_H (400 MHz, CD_3CN) 6.00 (1H, d, J = 7 Hz, H-4), 3.80 (3H, s, CO_2Me), 3.64 (3H, s, OMe), other signals obscured by signals of **1**; ^{13}C NMR δ_C 199.6 (FeCO), 171.7 (CO_2–), 154.3 (C-2), 101.6 (C-4), 91.2 (C-3), 62.0 (C-5), 58.4 (OMe), 53.2 (OMe) 41.5 (C-1), 33.5 (CH_2CO_2), 27.3 (C-6) ppm.
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27. Phenylation product **12** from the ω addition pathway to **1**: ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 7.20 (5H, m, Ar-H), 5.05 (1H, d, J = 6.5 Hz, H-3), 3.77 (3H, OMe), 3.72 (3H, OMe), 3.23 (1H, dt, J = 11, 6.5 Hz, H-5), 3.04 (2H, s, CH_2CO_2), 2.71 (1H, dd, J = 6.5, 3.5, H-4), 2.45 (1H, dd, J = 14.5, 11 Hz, H-6β), 1.94 (1H, dd,

J = 14.5, 3.5 Hz, H-6α); δ_C 211.0 (FeCO), 171.3 (CO_2–), 146.8 (Ar), 139.3 (C-2), 128.6 (Ar), 126.8 (Ar), 126.2 (Ar), 65.7 (C-1), 63.1 (C-3), 55.9 (C-4), 54.8 (OMe), 51.7 (OMe), 44.7 (C-5), 39.1 (CH_2), 38.6 (CH_2) ppm.

28. Product from ω addition pathway to **9**: ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 7.02 (5H, m, Ar-H), 4.03 (1H, d, J = 17 Hz, CH_2CO_2), 3.83 (3H, s, OMe or CO_2Me), 3.38 (1H, d, J = 3.5, H-4). 3.31 (3H, s, OMe or CO_2Me), 3.28 (1H, dt, J = 11, 3.5 Hz, H-5), 3.08 (1H, d, J = 17 Hz, CH_2CO_2), 2.82 (1H, dd, J = 3.5, 2 Hz, H-1), 2.18 (1H, ddd, J = 14.5, 11, 3.5 Hz, H-6β), 2.38 (1H, ddd, J = 11, 3.5, 2 Hz, H-5), 1.67 (1H, ddd, J = 14.5, 3.5, 2 Hz, H-6α); δ_C 211.1 (FeCO), 171.4 (CO_2–), 147.1 (Ar), 138.3 (C-3), 128.8 (Ar), 126.8 (Ar), 126.3 (Ar), 84.5 (C-2), 55.4 (OMe), 54.5 (C-4 or C-1), 53.9 (C-4 or C-1), 52.1 (OMe), 46.8 (C-5), 36.9 (CH_2), 34.3 (CH_2) ppm.
29. Product from α addition pathway to **9**: ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 7.20 (5H, m, Ar-H), 5.23 (1H, d, J = 6.7 Hz, H-2), 3.77 (3H, s, OMe or CO_2Me), 3.76 (3H, s, OMe or CO_2Me), 3.67 (1H, dd, J = 11, 3.7 Hz, H-5), 2.91 (1H, d, J = 15.3 Hz, CH_2CO_2), 2.71 (1H, ddd, 6.7, 3.7, 2.4 Hz, H-1), 2.37 (1H, d, J = 15.3 Hz, CH_2CO_2), 2.18 (1H, ddd, J = 14.7, 11, 3.7 Hz, H-6β), 1.61 (1H, ddd, J = 14.7, 3.7, 2.4 Hz, H-6α); δ_C 211.1 (FeCO), 171.9 (CO_2–), 174.2 (Ar), 145.0 (C-3), 128.6 (Ar), 127.3 (Ar), 126.4 (Ar), 69.9 (C-4), 64.6 (C-2), 54.9 (OMe), 51.6 (OMe), 48.1 (C-1), 46.5 (C-5), 35.9 (CH_2), 35.7 (CH_2) ppm.
30. Product from ω addition pathway to **2**: ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 7.20 (5H, m, Ar-H), 3.83 (1H, J = 15 Hz, CH_2CO_2), 3.68 (3H, s, OMe), 3.51 (3H, s, OMe), 3.49 (1H, dd, J = 4, 2 Hz, H-1), 3.15 (1H, dt, J = 11, 3.8 Hz, H-5), 2.95 (1H, d J = 15 Hz, CH_2CO_2), 2.90 (1H, d, J = 3.8 Hz, H-4), 2.35 (1H, ddd, J = 14.6, 11, 4 Hz, H-6β), 1.73 (1H, ddd, J = 14.4, 3.8, 2 Hz, H-6α) ppm.