

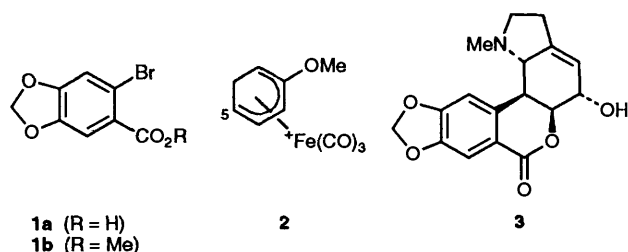
Preparation and Reactivity of Cuprate Derivatives of Lithium 6-Lithiopiperonylate with Tricarbonyl(2-methoxycyclohexadienyl)iron(1+) Hexafluorophosphate(1-)

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Arylcuprate species derived from 6-bromopiperonylic acid have been prepared, and evaluated as nucleophiles in reactions with tricarbonyl(2-methoxycyclohexadienyl)iron(1+) hexafluorophosphate(1-). Use of CuCN in place of CuI for the preparation of the arylcuprate species, gave improved yields of the products obtained from C-C bond formation. Furthermore, by preparing the arylcuprate species at low temperature, competing orthometallation processes were avoided.

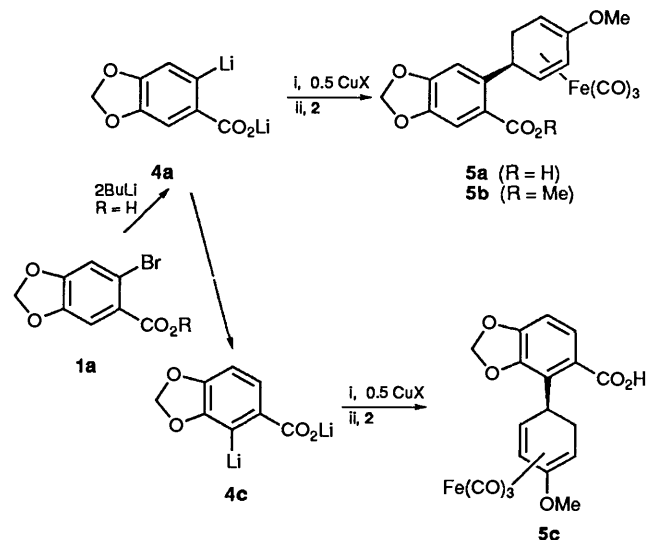
A wide variety of reagents have been used in nucleophilic additions to cationic (cyclohexadienyl)iron complexes, and this reaction has proved to be of great value in synthesis.¹ Surprisingly, there are only relatively few examples in which a metallated arene is used as the nucleophilic reagent in a reaction of this type, despite the value of this approach in providing a direct regio- and stereo-specific route to molecules containing two unsaturated six-membered rings. This is a strategy in which we have ongoing interest, as part of work exploring the utility of organoiron complexes in stereoselective natural product synthesis. Although Ph₂Zn, Ph₂Cd and PhLi have all been shown to arylate tricarbonyl(cyclohexadienyl)iron(1+) complexes satisfactorily,² we have found arylcuprates to be the reagents of choice in typical cases where there are nitrogen substituents present on the metallated arene.³ In order to obtain further information regarding the utility of this reaction, we have studied the reactions of cuprate derivatives of 6-bromopiperonylic acid **1a** with the readily available⁴ compound tricarbonyl(2-methoxycyclohexadienyl)iron(1+) **2**. A C-C bond-forming reaction of this type can provide a key step in an organoiron approach^{5,6} to hippastrine⁷ **3**. Part of this work has been the subject of a preliminary communication.⁵



Results and Discussion

Tricarbonyl(2-methoxycyclohexadienyl)iron(1+) **2** was chosen as a substrate for reactions with cuprate derivatives of lithium 6-lithiopiperonylate because of the ready availability of the dienyl complex and its known property of directing nucleophiles to the 5-position to give a single regioisomer.⁴ In general, the arylcuprate species were prepared by addition of a stoichiometric amount (see Table 1) of butyllithium to the aryl bromide **1** at low temperature in THF, followed by addition of 0.5 equiv. of the appropriate Cu^I salt. The reagent was stirred for 30 min at -78 °C before addition of the substrate **2**. The reaction mixture was then allowed to warm to 0 °C before work-up and column chromatography. The products were typically obtained as pale yellow solids.

As shown in Table 1 (entry 1), lithiation at -78 °C over 1.5 h, with CuI as the Cu^I source, gave a mixture of two isomers **5a**, **5c** (see Scheme 1) in a combined yield of 20%. The ratio of



Scheme 1

the two isomers was determined by ¹H NMR spectroscopy. A likely mechanism for the formation of the two isomers (see Scheme 1) involves reaction of the Ar-Li bond in **4a** with a C-H bond in a second molecule of **4a** in a typical orthometallation process.⁸ The ability of PhLi to act in this fashion is well established.⁹

In order to suppress the isomerisation of **4a** to **4c**, the lithiation of **1a** was carried out at -100 °C over 2 h, conditions that have previously been employed by Parham *et al.*¹⁰ for the formation of **4a**. In this procedure, CuI was added to the reaction mixture whilst the temperature was still -100 °C; the temperature of the reaction mixture was then allowed to rise to -78 °C. Stirring was continued at this temperature for 30 min before the salt **2** was added. Product formation occurred as the mixture was allowed to warm to 0 °C. In this case (Table 1, entry 2) the product was found to consist of primarily the desired isomer **5a**, formed in a slightly improved yield of 26%. For comparison, the dilithiated species was allowed to warm to 0 °C, and then cooled again to -78 °C before addition of CuI. This then led to the formation of **5c** as the major product (entry 3). This reaction demonstrates that the isomerisation of **4a** to **4c** does not go to completion at 0 °C, and that a small amount of **4a** had survived. This was a surprising result as the dianion **4a**

Table 1

Entry	Aryl halide	BuLi (equiv.)	Lithiation conditions	$n\text{CuX}$	Yield (%)	Ratio 5a : 5c
1	1a	2	-78°C , 1.5 h	0.5 CuI	20	2:3
2	1a	2	-100°C , 2 h	0.5 CuI	26	10:1
3	1a	2	-78°C – 0°C	0.5 CuI	17	1:7
4	1a	2	-100°C , 2 h	—	Trace	—
5	1a	2	-78°C – 0°C	—	Trace	—
6	1a	2	-100°C , 2 h	1.0 CuI	3	6:1
7	1a	2	-100°C , 2 h	0.5 CuCN	43	18:1
8	1a	2	-100°C , 2 h	1.0 CuCN	40	8:1
9	1a	2	25°C , 3 h	0.5 CuCN	47	<1:50
10	1b	1	-100°C , 2 h	0.5 CuCN	54	<i>a</i>

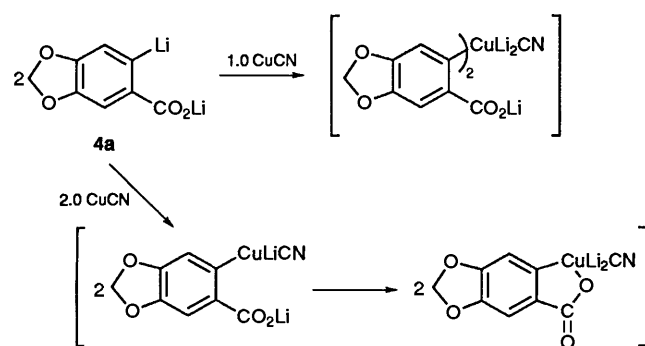
^a No isomers of **5b** were observed.

was not expected to be stable at this temperature since there is the possibility that it could combine with itself, as has been observed for lithium 2-lithiobenzoate even at -20°C .¹¹ In our example, a small amount of **4a** survived both isomerisation to **4c** and coupling side-reactions.

In order to assess the importance of the presence or the stoichiometry of the Cu^{I} salt, the above reactions were carried out using different quantities of copper salts. As can be seen from Table 1, in the absence of CuI, only trace amounts of the desired adduct were observed by TLC analysis of the crude product. Furthermore, under identical conditions used for entry 2, but with the addition of 1.0 equiv. of CuI, only a very poor yield of product was obtained. These reactions demonstrate the importance of the addition of 0.5 equiv. of CuI to form a diarylcuprate species of stoichiometry Ar_2CuLi .

At this point, it was decided to change the Cu^{I} salt in an attempt to improve yields. It was found that the use of 0.5 equiv. CuCN under conditions optimised for the formation of **5a** (entry 2) gave a better yield and selectivity (43%, 18:1). When the same reaction was repeated using 1.0 equiv. of CuCN (instead of 0.5), a marginally worse result was obtained (entry 8). Both of these reactions afforded **5a** in an almost isomerically pure form. Pure **5a** was obtained by crystallisation of the product from dichloromethane–light petroleum.

Clearly, in these reactions, the presence of CN^- as a counterion is important to ensure that reasonable yields are obtained. However, the number of equivalents of CuCN added did not prove to be critical. Possibly, the two stoichiometries allowed formation of two different higher order cuprate species¹² of stoichiometry $\text{R}_2\text{CuLi}_2\text{CN}$ or RXCuLi_2CN (Scheme 2) which had similar reactivity. The ability of CuCN



Scheme 2

to give higher yields in reactions of cuprate species with electrophiles has been previously observed.¹³

We have also prepared the second isomer, **5c**, under optimised conditions. This was achieved by stirring the dilithiated species **4** for 3 h at 25°C before addition of 0.5 equiv.

of CuCN at -78°C . After completion of the reaction and work-up in the normal fashion, the desired compound was obtained in an isomerically pure form in 47% yield. Under these conditions, the dilithiated species **4a** could not survive.

To probe further the scope of this nucleophilic addition, it was decided to examine the reactivity of a cuprate derivative of the methyl ester **1b**. This was of both synthetic and mechanistic interest, as the metallated ester derivative is expected to be of much lower stability than the deprotonated carboxylate analogue.¹⁴ Consequently, **1b** was metallated for 30 min at -100°C , before addition of 0.5 equiv. of CuCN, with reaction and work-up as before. This gave the desired ester adduct in 54% yield after column chromatography. The slightly higher yield in this case is thought to be a result of the easier column chromatography of the more soluble ester derivative.

This work has demonstrated that the primary product in these nucleophilic additions has resulted from C–C bond formation. A number of other minor products were formed, as observed by TLC analysis of all the fractions obtained from column chromatography of the crude products. These minor products were not further investigated, however, there are a number of possible pathways from which they could arise. These pathways include rearrangement or coupling of the anionic nucleophiles, nucleophilic addition of the anionic oxygen centre, incomplete regio- or stereo-selectivity in the reaction, or electron-transfer pathways. Electron-transfer pathways are known to be a common problem in nucleophile additions to cationic transition metal complexes.¹⁵ For the carboxylic acid complexes, the yields were hampered by the need for column chromatography of the poorly soluble complexes. However, since the reaction can form part of a simple two-step route to highly functionalised tricyclic structures, we consider the yields to be acceptable to allow the reaction to be developed in target-orientated applications. This work also provides a good example of the stabilisation of reactive organolithium species by the formation of an organocuprate, such that upon warming the cuprate, reaction with an organoiron electrophile can occur.¹⁶

Our studies in this area have been extended to include reactions of cuprate derivatives of **1a** with tricarbonyl(6-methoxycyclohexadienyl)iron(1+).⁵ Further work, including additions of other functionalised nucleophiles to give products suitable for alkaloid synthesis, is now being undertaken.

Experimental

All reactions were carried out under a nitrogen atmosphere. Reactions were monitored by IR spectroscopy using a Perkin-Elmer 1720X FT-IR spectrometer. ^1H NMR data were recorded on a Jeol JNM-GX400 FT NMR spectrometer and Jeol PMX-60 NMR spectrometer. Mass spectra were obtained from a Kratos MS25 mass spectrometer. THF was distilled from benzophenone and sodium. Petroleum refers to redistilled

light petroleum (b.p. 40–60 °C). Butyllithium was purchased from the Aldrich Chemical Co. Ltd. The concentration was determined before use by the method of Suffert.¹⁷ Column chromatography was carried out using silica gel 60 (70–230 mesh) which was purchased from Merck. TLC analysis was carried out using silica gel 60 P₂₅₄ precoated aluminium sheets, which were also purchased from Merck. 6-Bromopiperonylic acid was prepared¹⁸ and esterified¹⁹ by literature methods. Tricarbonyl(2-methoxycyclohexadienyl)iron(1+) hexafluorophosphate(1–) **2** was also prepared according to the literature procedure.⁴

Preparation of Tricarbonyl[η^4 -2-methoxy-5-(3',4'-methylene-dioxy-6'-carboxyphenyl)cyclo-1,3-hexadiene]iron(0) **5a.**—Butyllithium (1.49 mol dm⁻³ solution in hexanes; 2.9 cm³, 4.32 mmol) was added dropwise to a solution of 6-bromopiperonylic acid (0.53 g, 2.16 mmol) in THF (9 cm³) at ca. –100 °C (liq. N₂/Et₂O). The mixture was stirred for 2 h and then CuCN (0.097 g, 1.08 mmol) was added. After the mixture had been stirred for a further 10 min, its temperature was allowed to rise to –78 °C, at which point, the substrate tricarbonyl(2-methoxycyclohexadienyl)iron(1+) hexafluorophosphate(1–) **2** (0.375 g, 0.95 mmol) was added. The mixture was warmed to 0 °C before the reaction was quenched by addition of 3% HCl (aq) (20 cm³). The aqueous phase was extracted with Et₂O to give a yellow residue after drying and solvent removal. Column chromatography on silica gel with diethyl ether–petroleum (1:1) as eluent afforded the *title compound* **5a** (0.17 g, 43%) {contaminated by a small amount (ca. 5%) of tricarbonyl[η^4 -2-methoxy-5-(2',3'-methylenedioxy-6'-carboxyphenyl)cyclohexa-1,3-diene]iron(0) **5c**}. Crystallisation from CH₂Cl₂–petroleum afforded pale yellow crystals of **5a**, m.p. 162–166 °C (decomp.) (Found: C, 51.9; H, 3.3. C₁₈H₁₄FeO₈ requires C, 52.2; H, 3.4%); $\nu(\text{CH}_2\text{Cl}_2)/\text{cm}^{-1}$ 2045s, 1971s, 1725w and 1685m; δ_{H} (400 MHz, CDCl₃) 1.57 (1 H, m, 6-H), 2.48 (1 H, m, 6-H), 2.77 (1 H, m, 4-H), 3.45 (1 H, m, 1-H), 3.71 (3 H, s, OMe), 4.28 (1 H, dt, *J* 11.0, 3.8, 5-H), 5.22 (1 H, dd, *J* 5.9, 2.2, 3-H), 6.02 (2 H, s, O–CH₂–O), 6.83 (1 H, s, ArH) and 7.38 (1 H, s, ArH); *m/z* 386 (M⁺ – CO, 2.3%), 358 (M⁺ – 2CO, 20), 330 (M⁺ – 3CO, 14), 328 (M⁺ – 3CO – H₂, 25) 300 (41), 242 (49), 258 (32), 227 (9), 149 (13) and 31 (100).

Preparation of Tricarbonyl[η^4 -2-methoxy-5-(2',3'-methylene-dioxy-6'-carboxyphenyl)cyclohexa-1,3-diene]iron(0) **5c.**—6-Bromopiperonylic acid (0.50 g, 2.04 mmol) was dissolved in THF (6 cm³) and cooled to –78 °C. To this solution was added dropwise butyllithium (1.49 mol dm⁻³ solution in hexanes; 2.8 cm³, 4.08 mmol). The mixture was then allowed to warm to 25 °C, and stirring was continued for 3 h at this temperature. The orange solution was then re-cooled to –78 °C before addition of CuCN (0.091 g, 1.02 mmol). The mixture was stirred for a further 30 min at this temperature before addition of tricarbonyl(2-methoxycyclohexadienyl)iron(1+) hexafluorophosphate(1–) **2** (0.375 g, 0.95 mmol). Work-up and column chromatography as above afforded the *title compound* **5c** (0.185 g, 47%), m.p. 144.0–145.6 °C (Found: C, 52.4; H, 3.3. C₁₈H₁₄FeO₈ requires C, 52.2; H, 3.4%); $\nu(\text{CH}_2\text{Cl}_2)/\text{cm}^{-1}$ 2043s, 1967s, 1724w and 1685m; δ_{H} (400 MHz, CDCl₃) 1.94 (1 H, d, *J* 14.6, 6-H), 2.14 (1 H, m, 6-H), 2.76 (1 H, dt, *J* 6.6, 3.7, 4-H), 3.33 (1 H, d, *J* 2.9, 1-H), 3.60 (3 H, s, OMe), 4.10 (1 H, dt, *J* 11.0, 3.7, 5-H) 4.98 (1 H, dd, *J* 6.6, 2.2, 3-H), 5.94 (2 H, m, O–CH₂–O), 6.64 (1 H, d, *J* 8.0, ArH) and 7.52 (1 H, d, *J* 8.0, ArH); *m/z* 358 (M⁺ – 2CO, 2%), 274 (7), 222 (7), 179 (16), 149 (26), 97 (59) and 57 (100%).

Preparation of Tricarbonyl[η^4 -2-methoxy-5-(3',4'-methylene-dioxy-6'-methoxycarbonylphenyl)cyclohexa-1,3-diene]iron(0) **5b.**—Butyllithium (1.55 mol dm⁻³ solution in hexanes; 1.37 cm³,

2.1 mmol) was added to a solution of methyl 6-bromopiperonylate **1b** (0.55 g, 2.1 mmol) in THF at –100 °C and the mixture stirred at this temperature for a further 30 min. CuCN (0.095 g, 1.05 mmol) was then added to the stirred mixture and stirring continued for a further 30 min before addition of the substrate tricarbonyl(2-methoxycyclohexadienyl)iron(1+) hexafluorophosphate(1–) **2** (0.375 g, 0.95 mmol). The mixture was allowed to warm to –20 °C with stirring, before work-up as before. Column chromatography on silica gel with diethyl ether–petroleum (1:7) as eluent, afforded the *title compound* **5b** (0.22 g, 54%) as a pale yellow solid, m.p. 87–88.5 °C (Found: C, 53.6; H, 3.6. C₁₈H₁₄FeO₈ requires C, 53.3; H, 3.8%); $\nu(\text{CH}_2\text{Cl}_2)/\text{cm}^{-1}$ 2042s, 1961s and 1718s; δ_{H} (400 MHz, CDCl₃) 1.50 (1 H, m, 6-H), 2.36 (1 H, m, 6-H), 2.70 (1 H, dd, *J* 6.6, 3.4, 4-H), 3.37 (1 H, m, 1-H), 4.02 (1 H, dt, *J* 11.0, 3.4, 5-H), 5.12 (1 H, dd, *J* 6.4, 2.4, 3-H), 5.91 (2 H, m, OCH₂O), 6.70 (1 H, s, ArH) and 7.14 (1 H, s, ArH); *m/z* 400 (M⁺ – CO, 3.2%), 372 (M⁺ – 2CO, 54.5), 344 (M⁺ – 3CO, 50.0), 342 (M⁺ – 3CO – H₂, 75.2), 284 (100), 227 (28) and 149 (93).

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