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From 2- to 3-Substituted Ferrocene Carboxamides or How to Apply Halogen ‘dance’ to the Ferrocene Series

Mehdi Tazi, † William Erb, *, † Yury S. Halauko, *, ‡ Oleg A. Ivashkevich, † Vadim E. Matulis, ‡ Thierry Roisnel, † Vincent Dorcet † and Florence Mongin †

1 Equipe Chimie Organique et Interfaces, Institut des Sciences Chimiques de Rennes, UMR 6226 CNRS-Université de Rennes 1, Bâtiment 10A, Case 1003, Campus Scientifique de Beaulieu, 35042 Rennes Cedex, France
2 UNESCO Chair of Belarusian State University, 14 Leningradskaya Str., Minsk 220030, Belarus
3 Research Institute for Physico-Chemical Problems of Belarusian State University, 14 Leningradskaya Str., Minsk 220030, Belarus
4 Centre de Diffractions X, Institut des Sciences Chimiques de Rennes, UMR 6226 CNRS-Université de Rennes 1, Bâtiment 10B, Campus de Beaulieu, 35042 Rennes Cedex, France

Supporting Information Placeholder

ABSTRACT: Two methods were compared to convert ferrocene into N,N-diisopropylferrocencarboxamide, N,N-diethylferrocencarboxamide, N,N-dimethylferrocencarboxamide and (4-morpholinocarbonyl)ferrocene, namely deprotonatalation followed by trapping using dialkylcarbamoyl chlorides and amide formation from the intermediate carboxylic acid. The four ferrocencarboxamides were functionalized at C₂; in the case of the less hindered and more sensitive amides, recourse to a mixed lithium-zinc 2,2,6,6-tetramethylpiperidino-based base allowed to achieve the reactions. Halogen migration using lithium amides was next optimized. Whereas it appeared impossible to isolate the less hindered 3-iodoferrocencarboxamides, 3-iodo-N,N-diisopropylferrocencarboxamide proved stable and was converted to new 1,3-disubstituted ferrocenes by Suzuki coupling or amide reduction. DFT calculations were used to rationalize the results obtained.

INTRODUCTION

Polysubstituted ferrocenes are much appreciated scaffolds for various applications including catalysis, fuel additives, material sciences and medicinal chemistry.¹

Methods to access 1,2-disubstituted ferrocenes have been largely developed from monosubstituted ferrocenes.² Among the methods used, deprotonative lithiations directed at neighboring sites by coordinating or acidifying groups are of crucial importance. Ferrocencarboxylic acid derivatives such as hindered N,N-dialkylcarboxamides³ and oxazolines⁴ have been often employed to this purpose, with stereoselective reactions being possible by using chiral ligands or chiral directing groups, respectively.

In sharp contrast, if 1,3-disubstituted ferrocenes appear as promising for different applications,³ their synthesis is far less developed. Obtaining such structures by building the ferrocene core⁶ is possible but subjected to tedious preparation of the required substrates. Thus, access by functionalization of ferrocene is an attractive approach. From monosubstituted ferrocenes, direct electrophilic substitutions are hardly regioselective.⁷ Stoichiometric and catalytic CH-functionalizations can take place at positions remote from substituents, but these reactions are limited to specific groups⁸ or bases,⁹ and can hardly be made stereoselective. Alternative ways to access 1,3-disubstituted ferrocenes consist in using retractable directing groups. Chlorine,¹⁰ bromine¹¹ and sulfoxide¹² have been successfully used to this purpose, and enantiopure derivatives could be obtained.¹²,¹³

Base-catalyzed aromatic halogen ‘dance’ is an elegant way to convert 2-halogeno substituted benzenes (I>Br) into the corresponding 3-substituted derivatives.¹³ Relatively well-developed in the benzene series, the reaction has been subjected to very few studies from ferrocenes. In 2010, we reported the competitive formation of 1-bromo-3-iodoferrocene in the course of the deprotonatalation-iodolysis of bromoferrocene using the base in situ prepared from ZnCl₂·TMEDA (TMEDA = N,N,N′,N’-tetramethylenediamine) and LiTMP (TMP = 2,2,6,6-tetramethylpiperidino) in a 1:3 ratio,¹⁴ and supposed to be a 1:1 mixture of LiTMP and Zn(TMP)₂.¹⁵ More recently, Wang, Weisensteiner and co-workers showed that the reactions performed on ferrocenyl 1,2-dihalides (1-chloro-2-ido-, 1-bromo-2-ido-, 1,2-dibromo- and 1,2-diiodoferrocene) using LiTMP more look like a ‘scrambling’ than a ‘dance’, with complex mixtures obtained.¹⁶ We thought a way to reduce this complexity was to involve in such reactions 1,2-disubstituted ferrocenes bearing only one halogen and a fixed N,N-dialkylcarboxamide directing group. We thus chose 2-iodoferrocencarboxamides to attempt base-catalyzed halogen migration. Herein, we describe our efforts to efficiently synthesize the required substrates and to convert them into the corresponding 3-iodoferrocencarboxamides. The molecular structure of the above mentioned ferrocenes was studied by ¹H and ¹³C NMR spectroscopy, and DFT calculations were used to rationalize the results.
RESULTS AND DISCUSSION

Compared methods to access N,N-dialkyl ferrocenecarboxamides, N,N-dialkyl ferrocenecarboxamides are important substrates for subsequent elaboration. Therefore, we planned the synthesis of four ferrocenecarboxamides, namely the N,N-diisopropyl, N,N-diethyl, N,N-dimethyl and morpholino. Direct reaction of ferrocene with dialkylcarbamoyl chlorides was reported to give the corresponding carboxamides in moderate yields.\(^{17}\) In our hands, reacting ferrocene with diethylcarbamoyl chloride in the presence of AlCl\(_3\) (1.1 equiv) at dichloromethane reflux provided N,N-dithiophenecarboxamide in 33% yield (5% yield by using 2 equiv of AlCl\(_3\); no product and 66% recovered ferrocene by employing 1.1 equiv of SnCl\(_2\)). This disappointing yield led us to consider alternative syntheses.

We considered and evaluated two routes toward these substrates: ferrocene deprotometalation followed by trapping using dialkylcarbamoyl chlorides (Route A)\(^{18}\) and amide formation from ferrocenecarboxylic acid\(^{19}\) (Route B).\(^{20}\) As shown in Table 1, the two routes work in similar yields although Route A provides the ferrocenecarboxamides 1-4 in only one step from cheap ferrocene. All the products obtained were fully characterized, and their main spectroscopic and X-ray diffraction data are furnished in Supporting Information.

Deprotometalation to afford N,N-dialkyl 2-iodoferrocenecarboxamides (Table 2). N,N-diisopropyl- and N,N-diethylferrocenecarboxamide (1 and 2) can be deprotolithiated by butyllithium in Et\(_2\)O at -80 °C.\(^{3a,b}\) From 1, using the chelate BuLi·TMEDA followed by iodolysis led to the expected iodide \(^{5}\) in 88% yield. Alternatively, employing at room temperature the base in situ prepared from ZnCl\(_2\)·TMEDA (0.5 equiv) and LiTMP (1.5 equiv)\(^{14}\) (supposed to be a 1:1 mixture of LiTMP and Zn(TM)p\(_2\)) furnished 5 in 84% yield. From 2, we preferred the latter method, and isolated the 2-iodo derivative 6 in 88% yield.

When compared to 1 and 2, N,N-dimethylferrocenecarboxamide (3) and morpholinoferrocenecarboxamide (4) are more sensitive to nucleophilic attacks. Consequently, ketones are concomitantly formed upon their treatment by organolithiums, and lower yields of 2-substituted derivatives are noticed after subsequent quenching. Recourse to LiTMP with in situ trapping (e.g. C(isi)Me\(_2\)) makes functionalization of such substrates possible.\(^{22}\) Although iodine cannot be used as in situ trap, the zinc species formed next to the directing group by deprotolitiation→trans-metal trapping\(^{23}\) using the combination of LiTMP (0.5 equiv) and Zn(TM)p\(_2\) (0.5 equiv) can be converted to the corresponding iodides 7 and 8 which were isolated in 78 and 84% yield, respectively. The main spectroscopic and X-ray diffraction data are given in Supporting Information and/or Figure 1.

Halogen ‘dance’ to afford N,N-dialkyl 3-iodoferrocenecarboxamides. Deprotonation-triggered heavy halogen migration\(^{13}\) appeared to be a suitable approach for the conversion of 1-substituted 2-iodoferrocenes into their 1-substituted 3-iodo isomers.\(^{14,18}\) A N,N-dialkylcarboxamide being capable of coordinating lithium when located at a neighboring position on a ring, it can contribute to the stabilization of a lithio compound and thus direct halogen migration. To the best of our knowledge, such a group has only been used to direct halogen migration in the case of 3-iodo-N,N-diisopropyl-2-pyridinecarboxamide (Chart 1, left).\(^{21}\) According to the generally accepted mechanism,\(^{13}\) the reaction promoted by a lithium amide (LiDA = lithium diisopropylamide) proceeds through deprotonation at the 4 position and repetitive halogen/metal exchanges.

Table 1. Formation of the N,N-dialkyl ferrocenecarboxamides 1-4 using Route A and Route B.

| Entry | Product | Route | Yield (%)\(^{a}\) |
|-------|---------|-------|----------------|
| 1     | 1       | A     | 71             |
| 2     | 1       | B     | 94 (80)        |
| 3     | 2       | A     | 86.5           |
| 4     | 2       | B     | 95 (81)        |
| 5     | 3       | A     | 77             |
| 6     | 3       | B     | 82 (70)        |
| 7     | 4       | A     | 76             |
| 8     | 4       | B     | 83 (71)        |

\(^{a}\) The yields (after purification by column chromatography over silica gel) for Route A and B were calculated from ferrocene and ferrocenecarboxylic acid, respectively. The yields in parentheses are calculated from ferrocene.

Table 2. Formation of the N,N-dialkyl 2-iodoferrocenecarboxamides 5-8.

| Entry | Product | Base | Yield (%)\(^{b}\) |
|-------|---------|------|----------------|
| 1     | 5       | Li   | 88             |
| 2     | 5       | Li-Zn| 84             |
| 3     | 6       | Li-Zn| 88             |
| 4     | 7       | Li-Zn| 78             |
| 5     | 8       | Li-Zn| 84             |

\(^{b}\) Yields after purification by column chromatography over silica gel.

Beside different electronic and geometrical features (e.g. angles), the position next to the carboxamide is locked by the pyridine nitrogen in the reported examples whereas it can be
attacked by a base in the case of the ferrocenecarboxamides 5-8 (Chart 1). Although silyl protection is possible, we did not consider this strategy as studies showed that hindered ferrocene carboxamides bearing such silanes at C2 can hardly be deprotonated at C5, but rather on the unsubstituted Cp ring. Carboxamide orientation seems to impact the metalation efficiency, the reaction being favored when the C=O group is in the plane of the substituted Cp ring.

Chart 1. Substrate on which a carboxamide has been used to direct halogen migration (left) and planned substrates to attempt ferrocene halogen ‘dance’ (right).

![Chart 1](image)

Different aspects of the molecular structure of ferrocenes and their derived properties were studied by quantum chemical calculations.26 It is established that ferrocenes can exist as eclipsed and staggered conformations with a low internal rotation barrier.27 In our case (see Supporting Information), the investigated ferrocenes are predominantly in an eclipsed form with hydrogens slightly bent inward. We considered the carboxamide conformation space next.

Due to the presence of the heavy halogen at C2 in 5, as in the case of silyl-protected carboxamide, the favored conformation seems to have the carboxamide C=O out of the Cp plane (even nearly perpendicular, see Figure 1), and thus not suitable to induce metalation at C5. We thus tried to assess, for 1 and 5, the energy difference between the most stable conformation and the conformation with coplanar C=O and Cp ring. Because we could not get this information by using dynamic NMR studies (see Supporting Information), we calculated their energy profiles upon rotation around their C1-C=O bond (Figure 2). It was found earlier28 that for ferrocene carboxamides the bulkier the substituent is, the greater the value of angle between the Cp and amide planes is.

Whereas the computed conformations of lowest energy are very close to the structures obtained by X-ray diffraction, a local maximum (+24 kJ/mol) is noticed for the conformation of 1 with the C=O group in the plane of the Cp (even nearly perpendicular, see Figure 1), and two maxima (local at +30 and global at +50 kJ/mol) were recorded for the two ‘in-plane’ conformers of 5 (Figure 2, bottom; respectively 0° in the case of the C=O group on the iodine side (syn) and 180° for the C=O group on the opposite side (anti)).28 This large value led us to suppose that the C=O group can hardly stabilize a 2-iodo-5-lithioferrocenecarboxamide by lithium coordination, and we were confident that halogen migration will take place without protective group.

We decided to optimize the reaction on 2-iodo-N,N-diisopropylferrocenecarboxamide (5) and to next apply the best conditions to the other N,N-dialkyl-2-idoferrocenecarboxamides 6, 7 and 8. On the basis of the mechanism proposed in Scheme 1, we considered LiTMP as a better lithium amide than LiDA.29 Indeed, 2,2,6,6-tetramethylpiperidine (HTMP; pKa = 37.3)30 is less prone to protonate 2-lithio-N,N-diisopropylferrocenecarboxamide than diisopropylamine (pKa = 35.7).30

![Figure 1](image)

Figure 1. ORTEP diagrams (30% probability level) of the ferrocenecarboxamides 5 (C9-C10-C11-O12 torsion angle: 94.36°), 7 (C9-C10-C11-O12: 121.02°), 8 (C9-C10-C11-O12: -70.86°) and 9 (C9-C10-C11-O12: 27.01°).

![Figure 2](image)

Figure 2. Energy profiles (kJ/mol) of 1 (top) and 5 (bottom) upon torsion angle (°) C2-C1-C=O change.

Thus, we treated the 2-idoferrocenecarboxamide 5 by LiTMP (1.1 equiv) in THF (THF = tetrahydrofuran) for 2 h at different reaction temperatures (from -30 to -80 °C) before subsequent hydrolysis. In all these experiments, we observed (gas chromatography (GC) mass spectrometry) the formation of 3-iodo-N,N-diisopropylferrocenecarboxamide (9) as well as the deiodinated compound 1 in addition to the recovered start-
ing material 5. Whereas -30 °C favored deiodination (1 formed in ≈40% estimated yield), starting material 5 was importantly recovered at -80 °C (≈55% estimated yield). Regarding the expected isomerized iodide 9, its formation was favored at -50 °C. Other mono- and diiodides were formed, but in general as minority products.

Consequently, we kept -50 °C, and checked different reaction times (5 min, 15 min, 30 min, 6 h, 14 h and 20 h; see Supporting Information). The results show that the 2-lithioferrocenecarboxamide is rapidly formed (giving 1 by hydrolysis), but the conversion to the 3-iodo-2-lithio derivative (affording 9 by hydrolysis) takes more time. Once the starting 5 exhausted (~14 h), there is no benefit to use longer reaction times.

Scheme 1. Proposed mechanism for halogen ‘dance’ on 2-iodoferrocenecarboxamides.

Under the optimized reaction conditions, LiTMP proved superior to LiDA, often employed as halogen ‘dance’ mediator. With LiDA, extending the reaction time favored the deiodinated product 1 to the detriment of the expected 3-iodoferrocenecarboxamide 9 (see Supporting Information). These results, that could be due to the higher propensity of disopropylamine to protonate the 2-lithioferrocenecarboxamide when compared with LiTMP, led us to abandon LiDA.

These optimized conditions (1.1 equiv of LiTMP, THF, -50 °C, 14 h) in hand, we studied the behavior of the less hindered 2-iodoferrocenecarboxamides 6-8 in the reaction. For more sensitive 2-iodo-N,N-diethylferrocenecarboxamide (7), the estimated yield of the 3-iodo product 11 was improved at a lower temperature. From N,N-diethyl-2-iodoferrocenecarboxamide (6) and 1-iodo-2-(4-morpholino-carbonyl)ferrocene (8), conducting the reaction at a larger scale (4.0 mmol instead of 1.0) provided the respective 3-iodo derivatives 10 and 12 more efficiently (see Supporting Information).

One main issue of the approach is to isolate the isomerized products 9-12. Unlike the N,N-diisopropylferrocenecarboxamide 9, separable from the deiodinated compound 1 and the other iodides by column chromatography over silica gel (36% yield at a 1.0 mmol scale; 53% yield at a 4.0 mmol scale), the less hindered N,N-dialkyl ferrocenecarboxamides 10-12 proved much less stable. The N,N-diethylcarboxamide 10 could be purified by column chromatography over silica gel (32% yield at a 1.0 mmol scale), but in a non-reproducible way. Even worse, the N,N-dimethylcarboxamide 11 and the morpholino-based carboxamide 12 were never isolated. As a consequence, crystals suitable for X-ray diffraction were only obtained for the 3-iodo derivative 9 (Figure 1).

To understand why deiodination competes, we treated the ferrocenecarboxamide 1 by LiTMP (1.1 equiv) in THF at -50 °C for 6 h. After subsequent iodolysis, we isolated the 2-iodo derivative 5 in a low 7% yield. Similarly, iodolysis of the halogen ‘dance’ reaction mixture after 6 h at -50 °C produces much more 1 (~60% yield) than 2-lithioferrocenecarboxamide (~10%). That the latter easily reacts with H-TMP could explain why 1 first and easily accumulates in the reaction mixture before disappearing. In order to reduce such a protonation, we tried to use 2 equiv of LiTMP. Unfortunately, the formation of 9 is not favored under these conditions. By decreasing the amount of lithium amide to 0.5 equiv, the halogen ‘dance’ is considerably prevented with 5 remaining present in ~30% yield and deiodination similarly taking place (see Supporting Information).

Last but not least, as N,N-diisopropyl-2-lithioferrocenecarboxamide, 3-iodo-N,N-diisopropyl-2-lithioferrocenecarboxamide is prone to in situ protonation by H-TMP. Indeed, trapping by electrophiles (PhCHO, PhSSPh, CIPPh2) the halogen ‘dance’ reaction mixture led to complex mixtures while using DCl-D2O only allowed 2-deutero-3-iodo-N,N-diisopropylferrocenecarboxamide to be isolated as a 1:1 mixture (~30% yield) with 9.

In most cases, the deiodination is accompanied by formation of unwanted unstable mono- and diiodides. Because we could not isolate any of the side products, we tried to get information from the NMR spectra of fractions containing them. First, we completely assigned the 1H and 13C NMR signals of 1, 5 and 9, and deduced the NMR increments of both the CONiPr2 and iodo substituents (see Supporting Information).

In several experiments (notably by using an excess of base to attempt the reaction), we observed the formation (~10% yield estimated by GC mass spectrometry) of an isomer of 5 and 9. This compound was identified as being 1'-iodo-N,N-diisopropylferrocenecarboxamide by NMR and GC comparison with the product resulting from silyl deprotection of 1'-iodo-N,N-diisopropyl-2-(trimethylsilyl)ferrocenecarboxamide.

Concerning the diiodides, we could get information from the 13C NMR spectra of fractions containing them. In particular, the chemical shift of the C' carbon (connected to C=O) largely depends on the presence of iodine atoms at C2 and C'. Indeed, at 81.3 ppm in the absence of neighboring iodine (compound 1), this signal moves to 92.6 ppm in the presence of iodine at C2 (compound 5), but is not modified significantly with iodine at C3 (82.8 ppm, compound 9). Thus, with a C' at 97.2 ppm, we are inclined to think that the diiodide most often formed in our halogen ‘dance’-hydrolysis sequences is the 2,5-diiodocarboxamide. After halogen ‘dance’-iodolysis, a new diiodide is formed (longer retention time on GC mass spectrometry); we supposed it is the 2,3-diiodocarboxamide shown in Scheme 1, formed by iodolysis of the 3-iodo-2-lithioferrocenecarboxamide. Nevertheless, this second diiodide is rarely observed in our halogen ‘dance’-hydrolysis reactions;
instead, in addition to the 2,5-diiodocarboxamide, a third diiodide is often noticed. We have no clue to identify it, but the 2,4-diiodo derivative could be a possible candidate. This NMR study at least seems to show that deprotonetalation of 5 lacks of regioselectivity (next to iodine vs. carboxamide).

To get more information on these diiodides, we attempted the use of the base in situ prepared from ZnCl₂·TMEDA (0.5 equiv) and LiTMP (1.5 equiv)⁴⁰ to prepare diiodides from the iodocarboxamide 5. Under the conditions used in Table 2, the preponderant formation of 2,5-diiodinated ferrocencarboxamides was suspected on the basis of the ¹³C NMR data of the mixture obtained (peaks at 97.2 and 98.1 ppm for the main polyiodides formed). This evidences a favored kinetic deprotonetalation of 5 next to the carboxamide function.

All these observations led us to consider the results in the light of the pKₐ values of key ferrocene derivatives. In 1973, Denisovich and Gubin described ferrocene as being more acidic than benzene, with a pKₐ value of 39±3 in MSAD scale (polarography).³¹ To our knowledge, this represents the only ferrocene pKₐ determination. Thus, we calculated the CH acidity (pKₐ values) in THF solution of Fe-H, Fe-I, 1, 5 and 9 within the DFT framework by using the approach elaborated earlier¹² (Chart 2). Whereas iodine exerts its known short- and long-range acidifying effects, the carboxamide function as such acidifies more moderately. When coordinated to lithium (calculations performed by using LiF), the carboxamide becomes a stronger directing group, as demonstrated in Chart 3.

Upon carboxamide coordination to lithium, the 1’ position of Ferrocene 5 is greatly acidified and amenable to deprotonation; this might explain why 1’-iodo-N,N-diisopropylferrocencarboxamide is observed in experiments. Besides, when compared to the site next to iodine, the position adjacent to the carboxamide is somewhat more activated; this could explain why deprotonation competitively takes place at C⁵, as demonstrated by 2,5-diiodocarboxamide formation.

Once coordinated to the metal, the C² position of the 3-iodoferrocencarboxamide 9 is highly activated; this allows to explain why the equilibria between the different lithioferro- cenes are shifted toward the expected 3-iodo-2-lithioferrocencarboxamide.

The reason why reaction times exceeding 14 h are not suitable to reach high yields could be due to LiTMP destruction,⁴¹ favoring 2-lithioferrocencarboxamide reproto- nation. Competitive iodine/lithium exchange by LiTMP⁴² could also be advanced to rationalize the iodine loss observed all along the reaction.

In order to obtain new kinds of ferrocenes, we made derivatives from the 3-iodoferrocencarboxamide 9 (Scheme 2). Using 4-methoxyphenyl- and 4-(trifluoromethyl)phenylboronic acid in the presence of cesium fluoride,³⁶ and catalytic amounts of Pd(dba)₂ (dba = dibenzylideneacetone) and triphenylphosphine, at the reflux temperature of toluene, respectively afforded the Suzuki coupling products 13 and 14 in moderate yields. The N,N-diisopropylaminomethylferrocene 15 was in turn prepared by reduction of the carboxamide function using BH₃·THF, as documented previously.³³⁻³⁴

![Chart 2. Selected calculated pKₐ values in THF solution for Fe-H, Fe-I, 1, 5 and 9 (top and middle: most stable conformation; bottom: Cp and C=O coplanar – 9² and 9⁵ with the C=O group respectively pointing toward C² and C⁵).](chart2.png)

![Chart 3. Selected calculated pKₐ values in THF solution for 5-LiF (most stable conformation of 5) and 9-LiF (Cp and C=O coplanar).](chart3.png)

We have thus shown that it is possible to access 1,3-disubstituted ferrocenes, which are promising substrates for different applications,³ with recourse to halogen ‘dance’.

**CONCLUSION**

We studied the halogen ‘dance’ reaction from different N,N-dialkyl 2-iodoferrocencarboxamides. In spite of the low stability of the less hindered 3-iodoferrocencarboxamides, we could optimize the reaction giving 3-iodo-N,N-diisopropylferrocencarboxamide (9) and identify possible reasons at the origin of the side products formation.

One limit encountered in this halogen ‘dance’ is the formation of undesirable diiodides, notably due to the relatively high acidity found at C⁵, on 2-iodo-N,N-diisopropylferrocencarboxamide (5). By using deuterium to protect this position toward deprotonation,⁴⁰ one could favor the formation of the expected 3-iodo-2-lithioferrocencarboxamide.

Competitive deiodination and lithioferrocene reproto- nation proved to be main issues of the reaction. We will devote efforts in order to identify ferrocene substituents capable of making the generated ferrocenyllithiums more stable toward H-TMP.
Scheme 2. Conversion of 9 by Suzuki coupling and carboxamide reduction.

EXPERIMENTAL SECTION

General Details. All the reactions were performed under an argon atmosphere using standard Schlenk techniques. THF was distilled over sodium/benzophenone. Column chromatography separations were achieved on silica gel (40-63 μm). Melting points were measured on a Kofler apparatus. IR spectra were taken on a Perkin-Elmer Spectrum 100 spectrometer. 1H and 13C Nuclear Magnetic Resonance (NMR) spectra were recorded either (i) on a Bruker Avance III spectrometer at 500 MHz and 126 MHz, respectively. 1H chemical shifts (δ) are given in ppm relative to the solvent residual hydrogen atoms were refined with anisotropic atomic displacement parameters. H atoms were finally included in their calculated positions. The molecular diagrams were generated by ORTEP-3 (version 2.02).

General procedure 1 (Route A). The protocol was adapted from a previously reported procedure. To a stirred mixture of ferrocene (0.93 g, 5.0 mmol) and BuOK (56 mg, 0.5 mmol) in THF (45 mL) at -80 °C, was added dropwise BuLi (~1.9 M in pentane, 10 mmol). After 1.5 h at this temperature, the mixture was allowed to warm to -40 °C before quenching by an aqueous saturated solution of Na2S2O3 (75 mL), extraction with EtO (20 mL), drying over MgSO4, removal of the solvents and purification by chromatography on silica gel (the eluent is given in the product description) led to the expected compound (see Supporting Information for experimental data on the compound 1).

2-ido-N,N-diisopropylferrocenecarboxamide (5, racemic mixture). To Et2O (15 mL) containing TMEDA (1.6 g, 21.1 mL, 13 mmol) was added dropwise at -80 °C, under stirring, BuLi (~1.6 M in hexanes, 13 mmol). After 15 min at this temperature, a solution of N,N-diisopropylferrocenecarboxamide (I, 3.6 g, 11.5 mmol) in EtO (20 mL) was added, and the mixture was stirred for 1 h before addition of a solution of I2 (5.8 g, 23 mmol) in EtO2 (15 mL) and THF (8 mL). After 30 min stirring, the cooling bath was removed and the mixture was allowed to reach room temperature. Addition of an aqueous saturated solution of Na2S2O3 (75 mL), extraction with Et2O (3 x 20 mL), drying over MgSO4, removal of the solvents and purification by chromatography on silica gel (eluent: heptane-AcOEt 95:5; Rf = 0.65) gave 5 in 88% yield as an orange powder: mp 138 °C; IR (ATR): 686, 811, 1002, 1024, 1036, 1368, 1455, 1620, 2970, 3094 cm⁻¹; 1H NMR (300 MHz, CDCl3, 291 K) δ 0.99 (br s, 3H, CH3), 1.11 (br s, 3H, CH3), 1.51 (br s, 6H, 2CH2), 3.41 (br s, 1H, CH=Me), 3.62 (br s, 1H, CH=Me), 4.17 (s, 1H, Cp-H), 4.28 (s, 1H, Cp-H), 4.34 (s, 5H, Cp-H), 4.42 (s, 1H, Cp-H); 13C NMR (500 MHz, CDCl3, 298 K) δ 0.94 (d, 3J = 6.7 Hz, CH3), 1.05 (d, 3J = 6.8 Hz, CH3), 1.47 (t, 6J = 6.2 Hz, CH3), 3.36 (t, 1J = 7.1 Hz, CH2Me), 3.57 (t, 1J = 7.1 Hz, CH2Me), 4.13 (t, 1J = 2.4 Hz, H4), 4.24 (dd, 1J = 2.6 and 1.3 Hz, H5), 4.30 (s, 5H, Cp-H), 4.38 (dd, 1J = 2.4 and 1.3 Hz, H3); 13C NMR (500 MHz, CD2D2SO, 298 K) δ 0.95 (br s, 3H, CH3), 1.04 (br s, 3H, CH3), 1.41 (br s, 6H, 2CH2), 3.44 (br s, 1H, CH=Me), 3.50 (br s, 1H, CH=Me), 3.72 (t, 1H, J = 2.4 Hz), 4.28 (s, 1H, Cp-H), 4.41 (dd, 1J = 2.5 and 1.3 Hz), 4.50 (dd, 1J = 2.4 and 1.3 Hz); 13C NMR (500 MHz, CD2D2SO, 383 K) δ 1.21 (d, 6J = 6.7 Hz, CH3), 1.26 (d, 6J = 6.5 Hz, CH3), 3.56 (sept, 2J = 2.4 and 2.5 Hz, 2CH2Me), 4.27 (t, 1J = 2.5 Hz, 2J = 6.7 Hz, 5CH), 4.29 (s, 5H, Cp-H), 4.39 (br s, 1H, Cp-H), 4.48 (br s, 1H, Cp-H); 13C NMR (75 MHz, CDCl3, 291 K) δ 21.0 (4CH2), 40.6 (C-I), 46.0 (CH2Me), 50.9 (CH2Me), 66.9 (CH), 67.7 (CH), 72.9 (SCH), 73.7 (CH), 92.8 (C=O), 166.4 (C=O); 13C NMR (126 MHz, CDCl3, 298 K) δ 20.7 (CH2), 20.8 (CH2), 21.0 (CH2), 21.0 (CH3), 40.5 (C-I), 45.9 (CH2Me), 50.8 (CH2Me), 66.8 (CH3), 67.7 (CH, C4), 72.7 (SCH), 73.6 (CH, C3), 92.6 (C=O), 166.3 (C=O). These data are similar to those reported previously. The obtained crystal structure was found to be similar to that described (CCDC 170421; NEMLAS).

General procedure 3. To a stirred, cooled (0 °C) solution of H-TMP (0.85 mL, 5.0 mmol) in THF (4 mL) were successively added BuLi (~1.6 M in hexanes, 4.5 mmol) and, 5 min later, ZnCl2·TMEDA (0.38 g, 1.5 mmol). The mixture was stirred for 10 min at 0 °C before introduction of the required ferrocene (3.0 mmol) at 10-15 °C. After 2 h at room temperature, a solution of I2 (0.75 g, 3.0 mmol) in THF (4 mL) was added. The mixture was stirred overnight before addition of an aqueous saturated solution of Na2S2O3 (10 mL) and extraction with AcOEt (3 x 20 mL). The combined organic layers were dried over MgSO4 and concentrated under reduced pressure. The crude product was purified by chromatography over silica gel (the eluent is given in the product description; see Supporting Information for experimental data on the compound 6).

2-ido-N,N,dimethylferrocenecarboxamide (7, racemic mixture). The general procedure 3 using N,N-dimethylferrocenecarboxamide (3, 0.77 g) gave 7 (eluent: heptane-AcOEt 70:30; Rf = 0.28) in 78% yield as an orange powder: mp 58 °C; IR (ATR): 689, 816, 872, 961, 999, 1008, 1106, 1117, 1224, 1262, 1306, 1379, 1418, 1453, 1496, 1631, 2926 cm⁻¹; 1H NMR (500 MHz, CDCl3, 298 K) δ 2.71 (br s, 3H, CH3), 2.92 (br s, 3H, CH3), 4.13 (t, 1J = 2.5 Hz, Cp-
H), 4.21 (s, 5H, Cp), 4.26 (dd, 1H, J = 2.6 and 1.3 Hz, Cp-H), 4.37 (dd, 1H, J = 2.4 and 1.3 Hz, Cp-H). 13C NMR (126 MHz, CDCl3, 298 K) δ 35.3 (CH3), 38.8 (CH3), 40.3 (C-I), 68.3 (CH2), 68.4 (CH2), 72.7 (5CH, Cp), 74.4 (CH), 87.7 (C-C≡O), 167.8 (C≡O). Anal. Calcld. for C24H24FeN2O: C, 78.4; H, 4.02; N, 4.05. Found: C, 78.2; H, 4.04; N, 3.99. Crystal data for 6. C24H24FeN2O, M = 439.14, T = 293(2) K, β = 101.480(4) °, V = 17382.2 Å3, Z = 4, d = 1.678 g cm−3, μ = 2.642 mm−1. A final refinement on F2 with 3955 unique intensities and 194 parameters converged at χ2(F2) = 0.3012 (RF) = 0.1108 for 3229 observed reflections with I > 2σ(I). CCDC 1565042.

6-N,Diethyl-3-idoferrocenecarboxamide (10, racemic mixture). The general procedure 4 using 2-ido-N,N-diethylferrocenecarboxamide (6, 0.41 g, 1.0 mmol) gave 10 (Rc = 0.10) in 32% yield as an orange powder: mp 86-87 °C; IR (ATR): 688, 823, 1001, 1290, 1449, 1474, 1604, 2967 cm−1; 1H NMR (500 MHz, CDCl3, 298 K) δ 1.16 (t, 6H, J = 6.9 Hz, 2CH3), 2.32 (br s, 4H, 2CH2), 2.41 (s, 5H, Cp), 4.51 (dd, 1H, J = 2.5 and 1.3 Hz, H4), 4.60 (dd, 1H, J = 2.6 and 1.4 Hz, H5), 4.77 (t, 1H, J = 1.4 Hz, H2); 13C NMR (126 MHz, CDCl3, 298 K) δ 12.9 (CH3), 14.8 (CH3), 39.6 (C-I), 40.9 (CH2), 42.7 (CH), 71.2 (CH, C5), 72.9 (5CH, Cp), 75.5 (CH, C4), 75.9 (CH, C2), 80.3 (C-C≡O), 168.1 (C≡O).

General procedure 5 (Suzuki coupling). The protocol was adapted from a previously reported procedure.36 A solution of CsF (0.30 g, 2.0 mmol), 3-ido-N,N-diisopropylferrocenecarboxamide (9, 0.44 g, 1.0 mmol) and boronic acid (4.0 mol in toluene (10 mL) was degassed with Ar before addition of Pd(dba)2 (28 mg, 50 μmol) and PPh3 (52 mg, 0.20 mmol). The resulting mixture was heated for 14 h under reflux before cooling and dilution with Et2O (60 mL), washing with H2O, and extraction with CH2Cl2 (3 x 20 mL). After drying over anhydrous Na2SO4, the solvent was evaporated under reduced pressure, and the coupled product was isolated by purification by flash chromatography on silica gel.

N,N-Diisopropyl-3-(4-methoxyphenyl)ferrocenecarboxamide (13, racemic mixture). The general procedure 5 using 4-methoxyphenylboronic acid (0.61 g) gave 13 (eluent: hexane-AcOEt 80:20; Rf = 0.43) in 46% yield as an orange powder (slow crystallization): mp 134-136 °C; IR (ATR): 791, 807, 831, 1024, 1036, 1158, 1178, 1246, 1272, 1321, 1342, 1372, 1437, 1452, 1457, 1525, 1609, 2929, 2965, 3001 cm−1; 1H NMR (500 MHz, CDCl3, 298 K) δ 1.15-1.36 (br s, 6H, 2CH3), 1.40-1.58 (br s, 6H, 2CH3), 1.80-1.92 (br s, 6H, CH2Me), 1.78 (s, 3H, OCH3), 4.10 (s, 5H, Cp), 4.56 (br s, 1H, CHMe4), 6.46 (dd, 1H, J = 2.5 and 1.4 Hz, Cp-H5), 4.67 (dd, 1H, J = 2.4 and 1.5 Hz, Cp-H4), 5.01 (t, 1H, J = 1.4 Hz, Cp-H2), 6.85-6.89 (m, 2H, H3), 7.41-7.43 (m, 2H, H2), 7.00-7.03 (m, 3H, H1), 7.13-7.26 (m, 3H, H1), 7.30-7.37 (m, 3H, H1), 7.43-7.48 (m, 3H, H1). A final refinement on F2 with 4632 unique intensities and 225 parameters converged at χ2(F2) = 0.0998 (RF = 0.0440) for 4212 observed reflections with I > 2σ(I). CCDC 1565043.

N,N-Diisopropyl-3-(4-trifluoromethylphenyl)ferrocenecarboxamide (14, racemic mixture). The general procedure 5 using 4-(trifluoromethyl)phenylboronic acid (0.76 g) gave 14 (eluent: heptane-AcOEt 85:15; Rf = 0.23) in 26% yield as an orange oil: IR (ATR): 690, 729, 807, 822, 842, 908, 1040, 1068, 1106, 1121, 1162, 1285, 1321, 1371, 1446, 1468, 1615, 2241, 2933, 2969 cm−1; 1H NMR (500 MHz, CDCl3, 298 K) δ 1.15-1.35 (br s, 6H, 2CH3), 1.40-1.60 (br s, 6H, 2CH3), 3.47 (br s, 1H, CHMe4), 4.12 (br s, 5H, Cp), 4.62 (br s, 1H, CHMe4), 4.72 (dd, 1H, J = 2.6 and 1.4 Hz, Cp-H5), 4.77 (dd, 1H, J = 2.6 and 1.5 Hz, Cp-H4), 5.12 (t, 1H, J = 1.8 Hz, Cp-H2), 7.54 (d, 2H, J = 8.6 Hz, H3'), 7.57 (d, 2H, J = 8.5 Hz, H3); 13C NMR (126 MHz, CDCl3, 298 K) δ 21.3 (4CH3), 46.5 (CHMe4), 49.9 (CHMe4), 71.7 (CH, C5), 71.5 (5CH, Cp), 72.6 (CH, C4), 82.8 (C-C≡O), 167.8 (C≡O). Anal. Calcld. for C24H22FeC6F3O: C, 56.0; H, 4.3; N, 4.1. Found: C, 55.6; H, 4.3; N, 4.1. Crystal data for 14. C24H22FeC6F3O. M = 439.10, T = 293(2) K, β = 101.480(4) °, V = 17382.2 Å3, Z = 4, d = 1.678 g cm−3, μ = 2.642 mm−1. A final refinement on F2 with 3955 unique intensities and 194 parameters converged at χ2(F2) = 0.3012 (RF) = 0.1108 for 3229 observed reflections with I > 2σ(I). CCDC 1565042.




extraction with EtO (3 x 20 mL), drying over MgSO₄, concentration under reduced pressure, and purification by chromatography over silica gel (eluent: heptane-AcOEt 60:40 v/v:10). The compound 15 was isolated in 68% yield: yellow oil; IR (ATR): 748, 818, 871, 933, 1001, 1031, 1106, 1137, 1160, 1202, 1463, 1673, 2926, 2961, 3096 cm⁻¹; 1H NMR (500 MHz, CDCl₃, 298 K) δ 0.98-1.01 (m, 12H, 4CH₃), 3.03 (sept, 2H, J = 6.6 Hz, 2CH₂Me), 3.34 (d, 1H, J = 14.4 Hz, CH₂N), 3.40 (d, 1H, J = 14.5 Hz, CH₂N), 4.13 (s, 5H, Cp), 4.20 (s, 1H, H5), 4.31 (s, 1H, H4), 4.46 (s, 1H, H2); 13C NMR (126 MHz, CDCl₃, 298 K) δ 20.9 (4CH₃), 39.8 (C-I), 43.8 (CH₂N), 47.6 (2CH₂Me), 70.1 (CH, C5), 71.7 (5CH, Cp), 73.7 (CH, C4), 75.9 (CH, C2), 89.9 (C=CH₂). Anal. Calcd for C₂₄H₂₃NO (3 x 20 mL), drying over MgSO₄; C (88.02-88.17). (f) Scottwell, S. O.; Crowley, J. D. Chem. Commun. 2016, 52, 2451-2464. (g) Astruc, D. Eur. J. Inorg. Chem. 2017, 6-29.

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2) Hydrolysis

(53% yield)