N-Metallocenyl Ynamides: Preparation, Oxidative Functionalization and Synthesis of an *ansa*[3]-Ferrocenylamide

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Abstract: The discovery of new organometallic frameworks is of high interest for the field of bioorganometallic chemistry. In this work, to the best of our knowledge, we report the first synthesis of various *N*-metallocenyl ynamides and some of their reactivity. In particular, the use of hypervalent iodine(III) reagents triggered an unprecedented oxidative cyclization leading to *ansa*[3]-ferrocenyl compounds while the same reaction conditions with the ruthenocene analogues led to an acyclic acetoxy-adduct. The mechanism of the cyclization has been studied by means of DFT calculations, showing that it proceeds through a Concerted Iodination Deprotonation (CID) step. This study not only expands further the chemistry of ynamides but also opens up new avenues in bioorganometallic chemistry by providing an exclusive access to an original ferrocephane moiety to be employed in this research field.

Introduction

In the last 10 years, ynamides, have emerged as very attracting reagents and building blocks for organic synthesis.[1,2] Thanks to their highly polarized triple bond, ynamides have become partners of choice for a myriad of reactions, including cyclizations[3] or asymmetric transformations,[4] through a variety of activation modes.[5–9] In parallel, efficient and robust methods for the synthesis of a broader range of ynamides have been developed.[1,2,10] Taking into consideration the recent surge of interest for redox strategies in synthetic chemistry,[11–13] we sought to design original ynamide derivatives that could be redox-activated under mild conditions, to trigger unprecedented reaction pathways. Because of its highly interesting structural and electrochemical properties,[14] ferrocene (Fc) is a privileged moiety for such an endeavor. To the best of our knowledge, only two ferrocene-containing ynamides have been reported in the literature: acridinone derivative **1** by Robinson *et al.* [15] and *N*-tosylynamide **2** by Anderson *et al.*[16] (Figure 1). In both cases, the metallocene is connected to the triple bond and no chemical reactivity was explored, although the group of Robinson did perform some spectroelectrochemistry studies on **1**. At our end, we decided to tackle the synthesis of ynamides, where the ferrocene moiety would be borne by the nitrogen (**3** and **4**) and to explore their reactivity, under oxidative conditions.

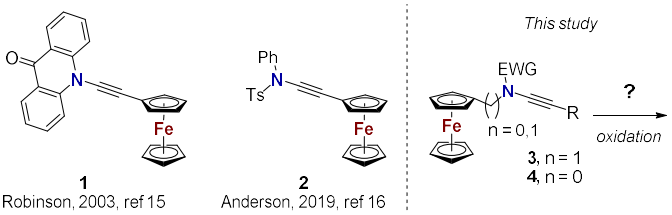


Figure 1. Previously reported ferrocenyl ynamides and objective of the study.

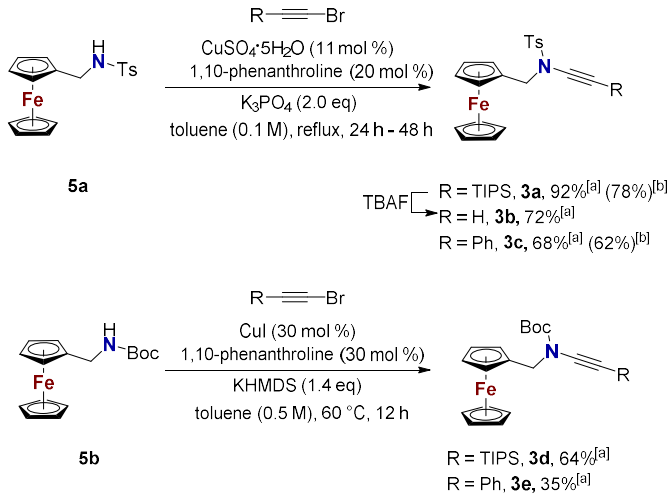
As ferrocenyl derivatives have a low potential of oxidation of about 0.4 V (vs SCE), a mild oxidation could be sufficient to trigger reactivities, with the Fc acting as an internal redox relay.[17–19]

Synthesis of the ynamides

Most methods to access ynamides start from the preparation of the corresponding amide, tosylamide or carbamate upon which the triple bond is then grafted. Both *N*-methylferrocenylamine and aminoferrocene can be obtained through described procedures, from ferrocenecarboxaldehyde[20] and bromoferrocene,[21] respectively (see the Supporting Information for details). While their tosylation went smoothly,[22] appending the triple bond turned out to be far from trivial.

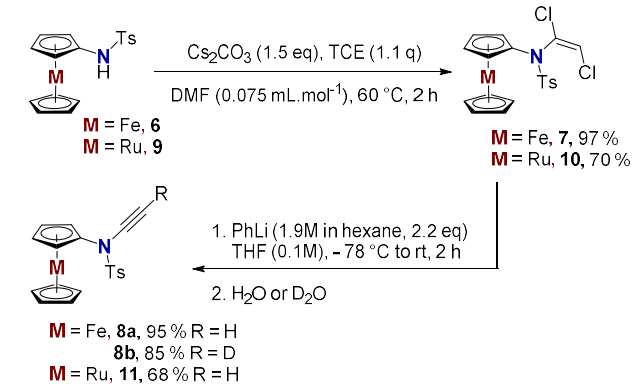
Starting from *N*-methylferrocenyl,*N*-tosylamide **5a**, electrophilic alkynylation[23] using iodonium salts[24] proved unsuccessful (see Supporting Information for details). We then focused on the Ullmann-type copper-catalyzed coupling developed by Hsung and coworkers.[25] Tosylamide **5a** was thus reacted with a bromoalkyne, in the presence of a catalytic amount of copper (II) sulfate pentahydrate, with potassium phosphate as the base,[26] in toluene at reflux. 4-Methyl-*N*-methylferrocenyl-((triisopropylsilyl)ethynyl)benzene-sulfonamide **3a** was

successfully obtained in 59% yield. The yield was improved to 92% (Scheme 1) when the solvent was carefully degassed to prevent the formation of oxidation side-products. Performing the reaction on gram-scale, a 78% yield of **3a** was obtained after 48 h of reaction. From **3a**, desilylation using tetrabutylammonium fluoride gave **3b** with 72% yield. The Ullmann coupling was also performed with bromophenylacetylene and **3c** was isolated with 68% yield when the reaction was run on a small scale and 62 % on gram-scale. To achieve the synthesis of *N*-Boc ynamides, the best coupling conditions were the ones developed by the group of Danheiser using CuI and KHMDS.[27] Ynamides **3d** and **3e** have been obtained in this fashion in 64% and 35%, respectively.



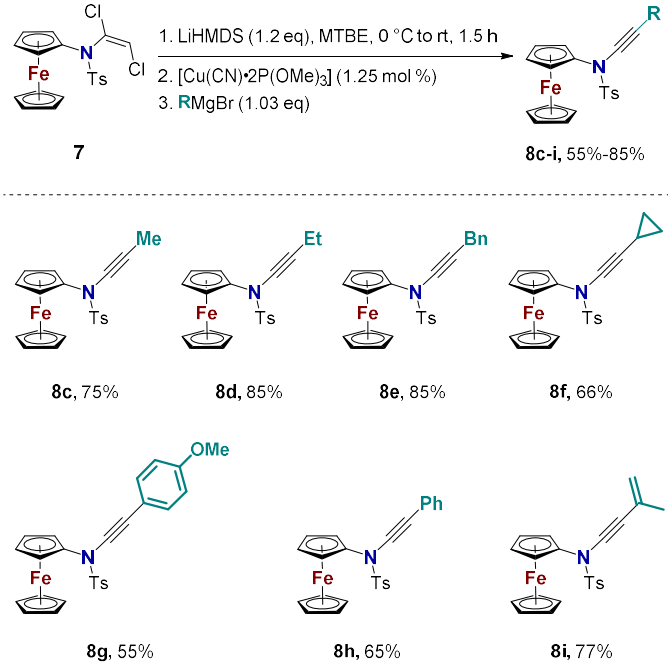
Scheme 1. Synthesis of *N*-methylferrocenyl-ynamides **3**. [a] Isolated yields. [b] Reaction ran with 1 g of **5a**.

Unfortunately the Cu-catalyzed cross coupling with bromo-alkynes could not be successfully applied for *N*-ferrocenyl,*N*-tosylamide **6**. To overcome this issue, we used the strategy developed by Anderson, which relies on a dichloroenamide as the key intermediate.[16,28] Thus, 1,2-dichloroenamide intermediate **7** was obtained in 97% yield through the reaction of amide **6** with dichloroacetylene generated *in situ* by deprotonation of trichloroethylene (TCE, Scheme 2). The synthesis of ynamide **8** was then achieved through a lithium base-mediated deprotonation followed by Cl-Li exchange using an excess of PhLi. The resulting lithiated ynamide was quenched with water or D_2O to provide **8a** or **8b**, respectively, with excellent yields. Among group 8 metallocenes, ruthenocene is close to



Scheme 2. Synthesis of *N*-ferrocenyl ynamides **8a** and **8b** and of *N*-ruthenocenyl ynamide **11**.

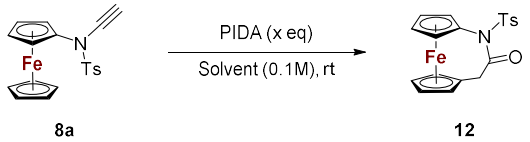
ferrocene in terms of structure [29] and chemical reactivity,[30] yet it possesses very different biological properties.[31] To expand the scope of our study, we thus envisioned the synthesis of *N*-ruthenocenyl-ynamides. After redesigning and optimizing the synthesis of aminoruthenocene,[32] the same sequence was applied to **9** to obtain first dichloroenamine **10** and then *N*-ruthenocenyl ynamide **11** with very good yields. The range of *N*-ferrocenylynamides **8** attainable using Anderson's method could be broadened since the intermediate lithiated ynamide can be transmetallated with copper to undergo cross-coupling with Grignard reagents (Scheme 3). In this fashion, alkyl (**8c-e**), cyclopropyl (**8f**), aryl (**8g**,**h**) and vinyl (**8i**) groups could be incorporated with good to excellent yields.



Scheme 3. Synthesis of alkyl- and aryl-substituted *N*-ferrocenyl ynamides **8c-i.**

With this original and diverse library of *N*-metallocenyl ynamides in hand, we went on to probe their behavior under oxidative reaction conditions, using hypervalent iodine(III) reagents.[24] The reaction between **8a** and 2 equivalents of (diacetoxyiodo)benzene (PIDA) in acetonitrile led to the isolation of *ansa*-ferrocene derivative **12** with 25% yield (Table 2, entry 1). The unique structure of **12** encouraged us to optimize its synthesis. Increasing the number equivalents of PIDA was not effective (entry 2) but changing the solvent to dichloromethane was (75%, entry 3). The best results were obtained with alcoholic solvents (quant., entries 4 & 5). In ethanol, it was even possible to decrease the amount of PIDA to 1.1 equivalents and the reaction time to 30 minutes, to isolate **12** quantitatively (entry 6). The use of (bis(trifluoroacetoxy)iodo)-benzene (PIFA) was less efficient (entry 7).

Table 2. Formation of *ansa*-ferrocene **12**[a].



8a **12**

ntry	Eq. PIDA	Solvent	Time	Yield **18**[b]
1	2.0	CH_3CN	12 h	25%
2	**3.0**	CH_3CN	12 h	18%
3	3.0	**CH_2Cl_2**	6 h	75%
4	3.0	**EtOH**	6 h	Quant.
5	3.0	**MeOH**	6 h	Quant.
6	**1.1**	**EtOH**	**30 min**	**Quant.**
7	**1.1**[c]	EtOH	30 min	75%

[a] Reactions were carried out using **10** (30 mg, 0.79 mmol),1.0 mL of acetonitrile in a dry sealed tube. Reaction was bubbled through N_2 for ten minutes before addition of PIDA and additive [b] Isolated yield. [c] PIFA was used instead of PIDA.

Ferrocephane **12** could be crystallized and subjected to X-ray analysis (Figure 2), which confirmed the proposed structure. The analysis showed a slightly tilted metallocene with a 13.0° dihedral angle between the two Cp rings, the C1-C6 distance being 2.970 Å and the C3-C8 distance 3.507 Å (compared to a 3.290-3.298 Å

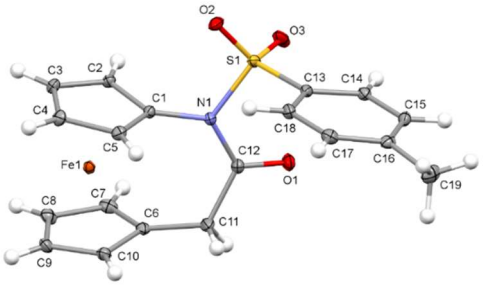
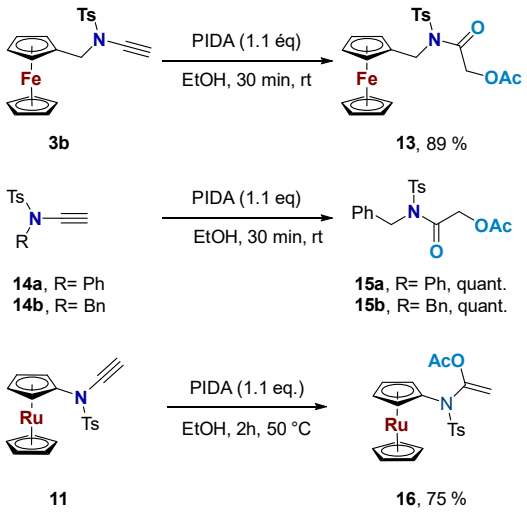


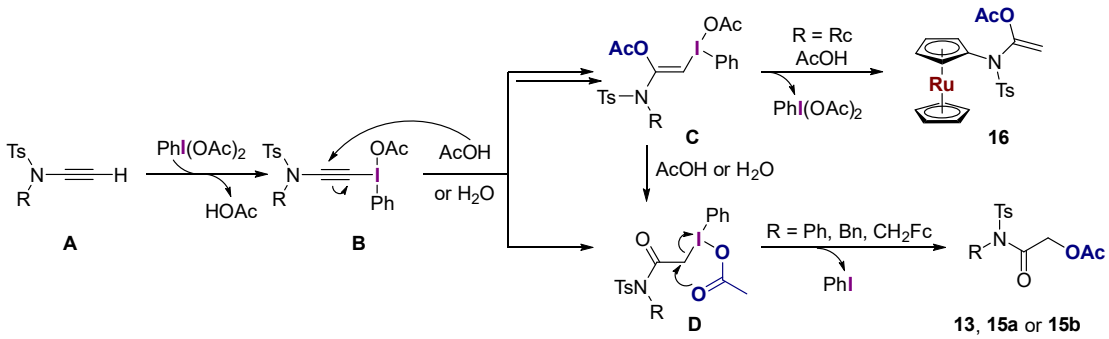
Figure 2. X-ray analysis of ferrocephane **12**.

Cp-Cp distance measured for the Fc-ynamides **3a**, **8c** and **8e**, which could also be crystallized and subjected to X-ray analysis). Despite numerous attempts, when submitted to these optimized conditions, none of the ynamides **8c-l** bearing a substituent on the triple bond reacted. In all cases, the starting material was recovered as the major compound. Yet, when *N*-methylferrocenyl **3b**, homologous to **8a**, was subjected to PIDA in ethanol, a reaction occurred. Although no cyclization was observed, α-acyloxy amide **13** was readily isolated in 89% yield (Scheme 4). This transformation is analogous to the one originally described by Hou with alkynes.[33,34] As control experiments, we submitted the analogous *N*-phenyl (**14a**) and *N*-benzyl (**14b**) to these conditions and α-acyloxy-amides **15a,b** were obtained quantitatively. This highlights the singularity of the cyclization observed for **8a** as a net deviation from the otherwise apparently favored α-acyloxy-oxidation. Of note, a slightly different outcome was observed for *N*-ruthenocenyl ynamide **11**. To proceed, the reaction required heating to 50 °C and a slightly longer reaction time, eventually yielding amino-vinylacetate **16** with 75% yield, which structure was confirmed by X-ray analysis.



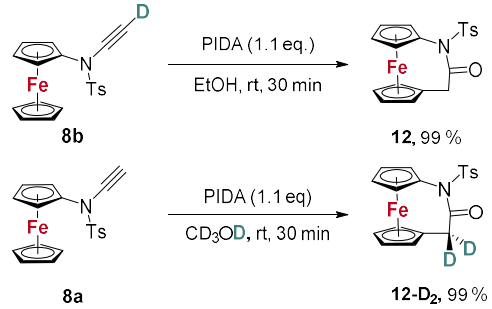
Scheme 4. Formation of α-acyloxy-amides **13** and **15a,b** and of acyloxy-enamides **16**.

In line with the mechanistic proposal initially made by Hou for the formation of α-acyloxy ketones from alkynes,[33] the reaction between an ynamide **A** and PIDA would give akynyl-iodine(III) intermediate **B** (Scheme 5). In Hou's proposal, acyloxylation of this intermediate would give **C** and eventually **D**, although the latter could also be obtained by direct hydration of **B**. In the case of the ruthenocenyl ynamide **11**, protodeiodination of **C** would directly lead to acetoxy-enol **16**.[35] In most cases, that is in the absence of the ferrocenyl moiety (ynamides **14a,b**) or if it lies one methylene away (ynamide **3b**), intermediate **D** is formed and yields α-acyloxy-amides **13**, **15a** or **15b**.



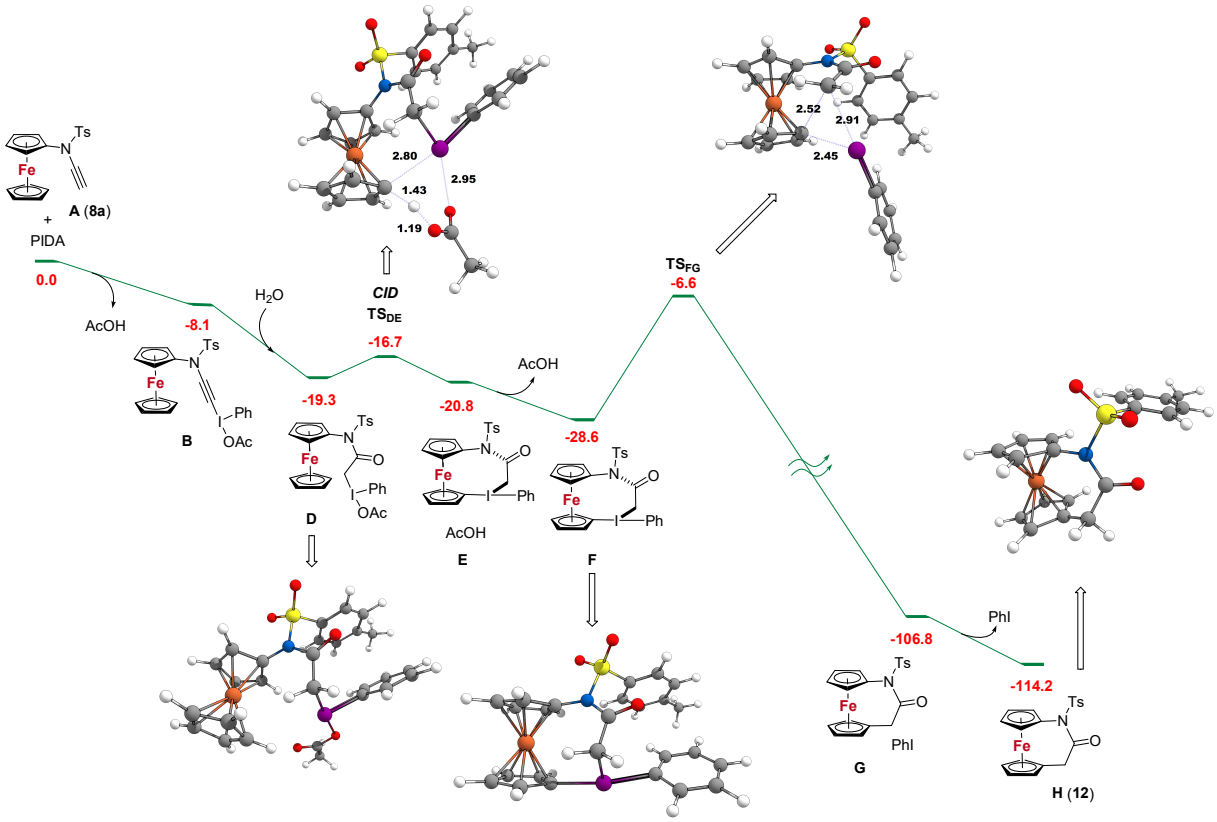
Scheme 5. Mechanism proposal for the formation of **13**, **15a**, **15b** and **16**.

Nevertheless, the outcome when **8a** is submitted to the reaction conditions is very different as, rather than the addition of an acetoxy group, a cyclization takes place.To gain further insight into the peculiar cyclization leading to ferrocephane **12**, some deuterium labeling experiments were performed (Scheme 6). First, deuterated analogue **8b** was subjected to the reaction conditions, yet no deuterium incorporation occured. However, carrying out the transformation of **8a** in a deuterated solvent (MeOD) led to the formation of the doubly deuterated *ansa*-ferrocephane **12-D$_2$**. The former result could indicate that deprotonation of the triple bond occurs during the reaction, which would be in line with the absence of reactivity of substituted ynamides. However, the latter experiment showed that the protons α to the amide are actually exchangeable, thus making it hard to conclude on the nature of the mechanism at this stage.



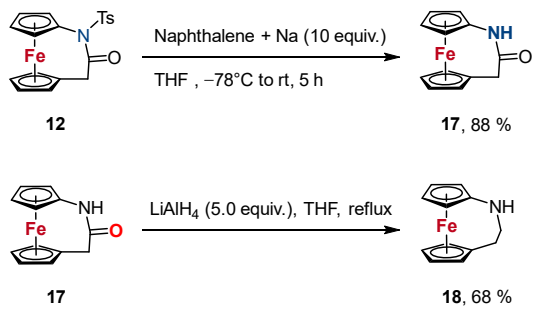
Scheme 6. Deuterium labeling experiments.

To better understand this transformation, we used a computational approach inspired by a recently implemented method describing hypercoordinated iodine species.[36] Our first hypothesis was that the peculiar reactivity observed for **8a** was induced by a specific reaction taking place between the iodine(III) reagent and the ferrocene moiety. In particular, Single-Electron Transfer (SET) events were considered (see Supporting Information for details). However, this pathway eventually led to an *endo* cyclization that required a prohibitively high activation energy of 46.0 kcal/mol to reach the transition state. A diradical cation pathway eventually led to a more stable cyclization transition state but still lying quite high on the free energy surface (30.4 kcal/mol). A more likely pathway starting with the exergonic iodination of **A** by PIDA to give complex **B** and AcOH was computed (Scheme 7, -8.1 kcal/mol). Although the hydroacyloxylation of the alkyne moiety was exergonic (-23.4 kcal/mol), it only converged toward the cyclized product via a high energy TS (43.0 kcal/mol, see SI for details). Thus, instead of considering the hydroacyloxylation of complex **B**, we envisaged its hydration to give complex **D**, located at -19.3 kcal/mol on the free energy surface. Up until this intermediate, this sequence appears consistent with the above mechanistic proposal (see Scheme 5). With the ferrocene moiety in close vicinity, a concerted iodination/deprotonation (CID) then takes place through **TS$_{DE}$** (-16.7 kcal/mol). This step requires only 2.6 kcal/mol of free energy of activation. The resulting ferrocene/AcOH adduct **E** (-20.8 kcal/mol) then gives **F** after elimination of the acetic acid residue (-28.6 kcal/mol). The reductive elimination faces a 22.0 kcal/mol barrier to reach **TS$_{FG}$** (-6.6 kcal/mol). This step leads to adduct **G** (-106.8 kcal/mol) and then **H** (*i.e.* **12**) after elimination of PhI (-114.2 kcal/mol).



Scheme 7. Free Energy Profile from **8a** to **12** (ΔG_{298}, kcal/mol; CID = Concerted Iodination Deprotonation; selected geometries with distances in Å).

The difference in reactivity between **8a** and ruthenocenyl-ynamide **11** is probably due to the larger size of the metallocene. Analysis of the X-ray structure of **11** shows a Cp-Cp distance of 3.613 Å (compared ≈ 3.30 Å for its ferrocenyl counterparts), which precludes the formation of a metallocephane.
It was possible to efficiently cleave the sulfonamide group of **12** using sodium-naphthalene to access the unprotected amide **17** in 88% yield (Scheme 8). Further reduction with $LiAlH_4$ gave the corresponding amine **18** in 68% yield.



Scheme 5. Deuterium labeling experiments.

Both structures could be confirmed by X-ray analysis, further demonstrating the robustness of this *ansa*[3]-ferrocene moiety (Figure 3). The metallocene remains constrained, although the angle between the Cp rings diminishes to 12.1° and 11.4° for ferrocephanes **17** and **18**, respectively.

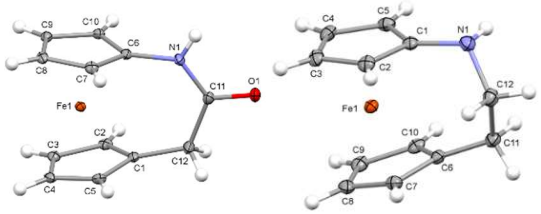


Figure 3. X-ray analysis of ferrocephanes **17** and **18**.

Conclusion

In this work, we have been able to synthesize the first examples of *N*-metallocenyl ynamides and to study their reactivity. The presence of the metallocene moiety clearly modulates the chemical behavior of these ynamides and a straightforward access to *ansa*[3]-ferrocenyl amides and amines was developed using hypervalent iodine(III) reagent. Further studies are underway to fully explore the exciting chemistry of these original ynamides. Moreover, taking into consideration the potential of ferrocene for medicinal chemistry,[31] incorporation of this cyclic ferrocene moiety onto known drugs will also be sought after.

Acknowledgements

C.M., G. G. and K. C. acknowledge the support of the CNRS and Chimie ParisTech, PSL University. C.M. thanks MESRI (Paris-Saclay University) for a Ph.D. fellowship. This work was financially supported by an ERC Consolidator Grant PhotoMedMet to G.G. (GA 681679) and has received support under the program "Investissements d' Avenir" launched by the French Government and implemented by the ANR with the reference ANR-10-IDEX-0001-02 PSL (G.G.). V. G. thanks CNRS, UPS, and Ecole Polytechnique for financial support. This work was granted access to the HPC resources of CINES under the allocation 2020-A0070810977 made by GENCI

Keywords: *Ansa*-Ferrocenes • Bioorganometallic Chemistry • DFT • Hypervalent Iodine • Metallocenes • Ynamides

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