N-Metallocenyl Ynamides: Preparation, Reactivity and Synthesis of *ansa*[3]-Ferrocenylamides

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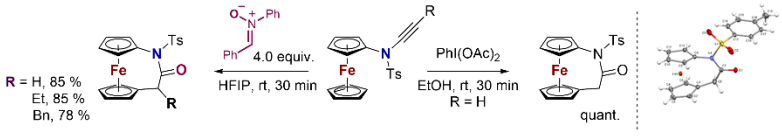


ABSTRACT: The first synthesis of various *N*-metallocenyl ynamides has been developed and two strategies for the oxidative cyclization of *N*-ferrocenyl ynamide into ansa[3]-ferrocenylamide are also reported. The mechanism for the iodine(III)-triggered transformation has been studied by means of DFT calculations, showing that it proceeds through a Concerted Iodination Deprotonation step.

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. 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] 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 aminoferro-

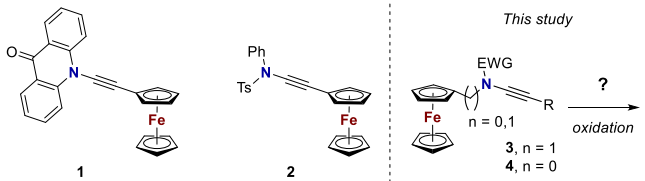
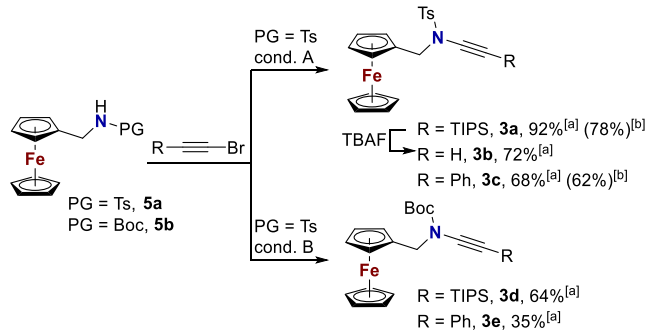


Figure 1. Previously reported ferrocenyl ynamides and objective of the study.

-cene 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 SI 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. *N*-methylferrocenyl,*N*-tosylynamide **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.

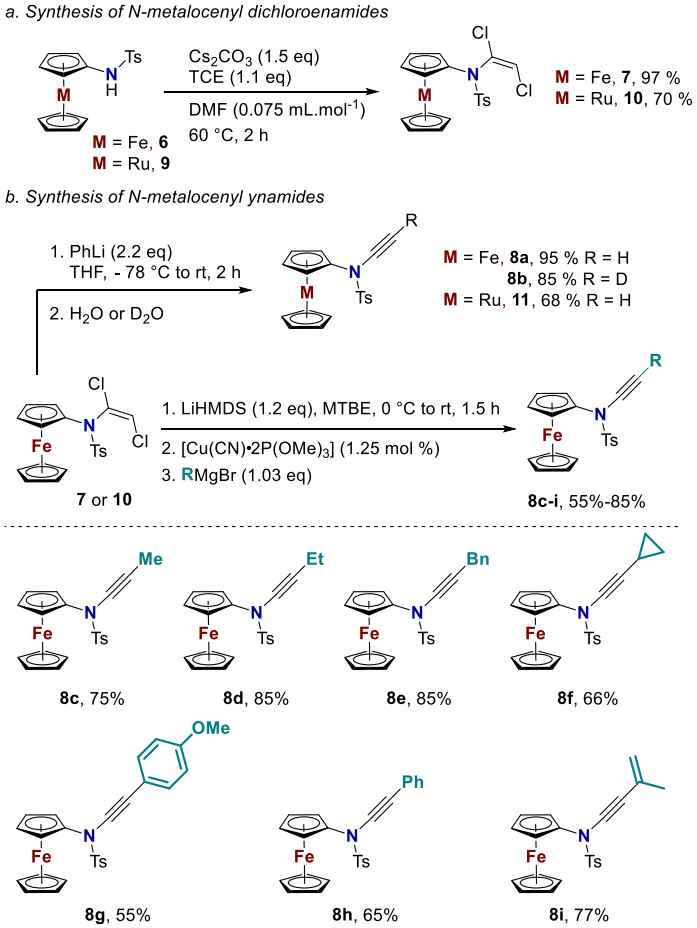


Conditions A: $CuSO_4$ $5H_2O$ (11 mol %), 1,10-phenanthroline (20 mol %), K_3PO_4 (2.0 eq), toluene (0.1 M), reflux, 24 h - 48 h; **Conditions B**: CuI (30 mol %), 1,10-phenanthroline (30 mol %), KHMDS (1.4 eq), toluene (0.5 M), 60 °C, 12 h; [a] Isolated yields. [b] Reaction was performed with 1 g of **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 2a). 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 (Scheme 2b). Among group 8 metallocenes, ruthenocene is close to 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 2b, bottom). In this fashion, alkyl (**8c-e**), cyclopropyl (**8f**), aryl (**8g,h**) and vinyl (**8i**) groups could be incorporated with good to excellent yields.

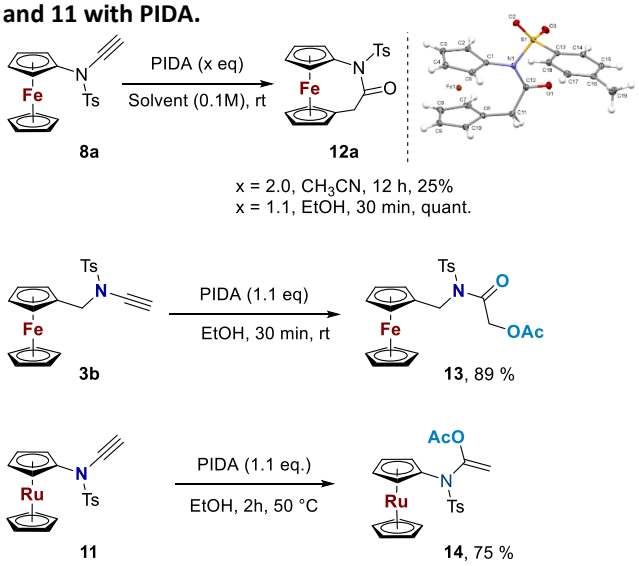
With this original and diverse library of *N*-metallocenyl ynamides in hand, we first went on to probe their behavior under oxidative reaction conditions, using hypervalent iodine(III) reagents.[24] The reaction between **8a** and 2 equivalents of (diacetoxyiodo)benzene (PIDA) in acetonitrile led to the isolation of *ansa*-ferrocene derivative **12a** with 25% yield (Scheme 3). The unique structure of **12**, quite different from previously reported nitrogen-containing ferrocenophanes,[32–34] encouraged us to optimize its synthesis (see SI for details).

Scheme 2. Synthesis of *N*-metalocenyl dichloroenamides 7 and 10 and of *N*-ferrocenyl ynamides 8a-i and *N*-ruthenocenyl ynamide 11.



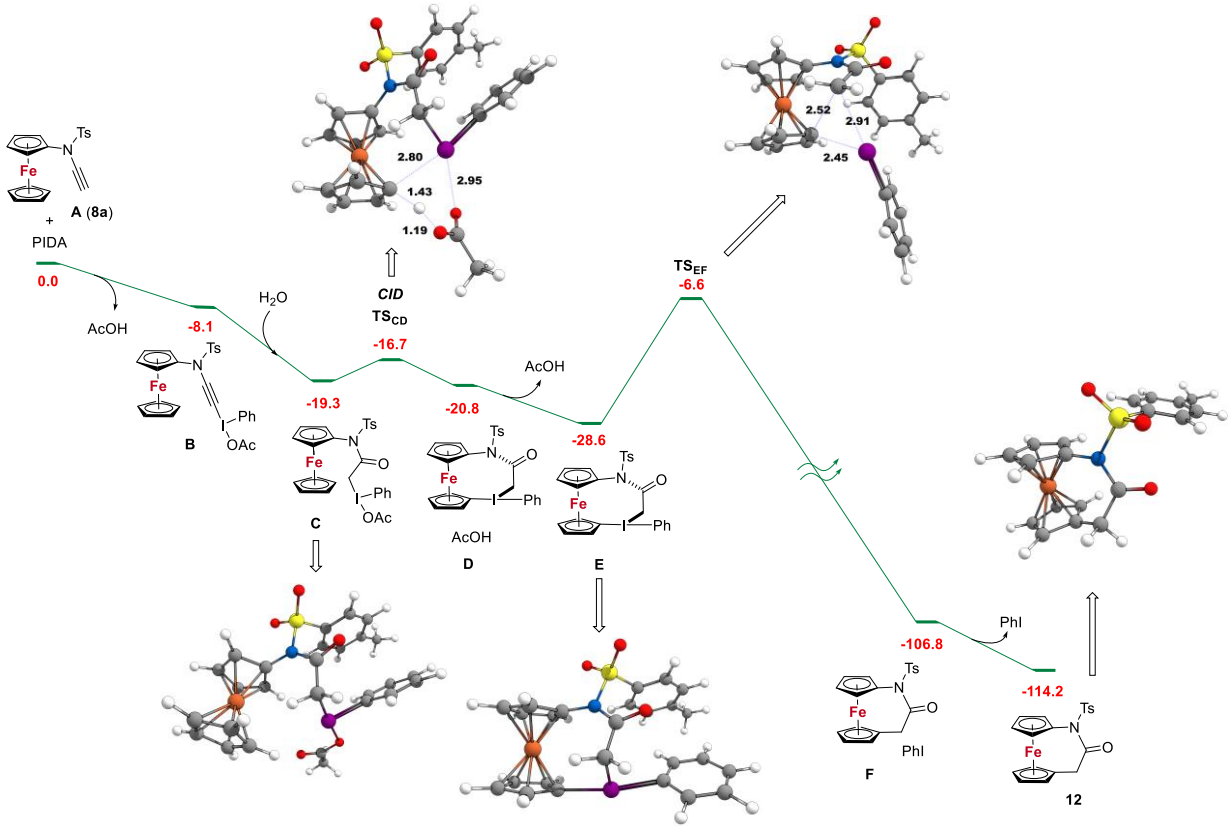
The best results were obtained ethanol by decrease the amount of PIDA to 1.1 equivalents and the reaction time to 30 minutes, which allowed to isolate **12a** quantitatively.Ferrocenophane **12a** could be crystallized and subjected to X-ray analysis, which confirmed the proposed structure. The analysis 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 Cp-Cp distance measured for the Fc-ynamides **3a**, **8c** and **8e**, which could also be crystallized and subjected to X-ray analysis, see SI). Despite numerous attempts, when submitted to these optimized conditions, none of the ynamides **8c-i** 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 3). This transformation is analogous to the one originally described by Hou with alkynes,[35,36] and can readily be applied to *N*-phenyl- and *N*-benzyl-*N*-tosylynamides to give the corresponding α-acyloxy-amides quantitatively (see SI). 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, the structure of which was confirmed by X-ray analysis.

Scheme 3 Reactivity of *N*-metallocenyl ynamides 8a, 3b and 11 with PIDA.



The formation of **13** and **14** can be rationalized by extrapolating from the mechanistic proposal initially made by Hou for the formation of α-acyloxy ketones from alkyne.[35] Yet the formation of **12a** appeared to stem from a very specific mechanism.

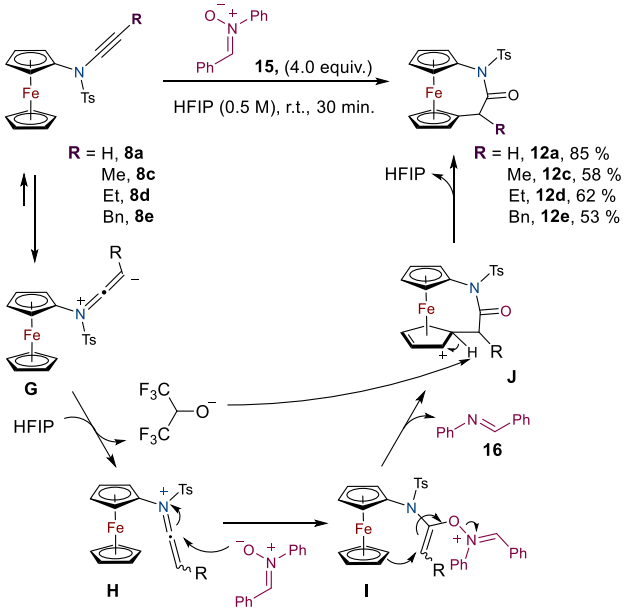
Scheme 4. Computed Gibbs Energy Profile from 8a to 12 (PBE0D3-def2-TZVPP//M06-def2-SVP (SMD); ΔG_{298}, kcal/mol; CID = Concerted Iodination Deprotonation; selected geometries with distances in Å).



To gain further insight into the peculiar cyclization leading to ferrocenophane **12a**, some deuterium labeling experiments were performed (see SI) that did not allowed us to conclude on the nature of the mechanism at this stage. We thus used a computational approach inspired by a recently implemented method describing hypercoordinated iodine species.[37] 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 SI 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 Gibbs 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 4, -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 **C**, located at -19.3 kcal/mol on the Gibbs energy surface. With the ferrocene moiety in close vicinity, a concerted iodination-deprotonation (CID) then takes place through $\mathbf{TS_{CD}}$ (-16.7 kcal/mol). This step requires only 2.6 kcal/mol of Gibbs energy of activation. The resulting ferrocene/AcOH adduct **D** (-20.8 kcal/mol) then gives **E** after elimination of the acetic acid residue (-28.6 kcal/mol). The reductive elimination faces a 22.0 kcal/mol barrier to reach $\mathbf{TS_{FG}}$ (-6.6 kcal/mol). This step leads to adduct **F** (-106.8 kcal/mol) and then **12** after elimination of PhI (-114.2 kcal/mol). 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.

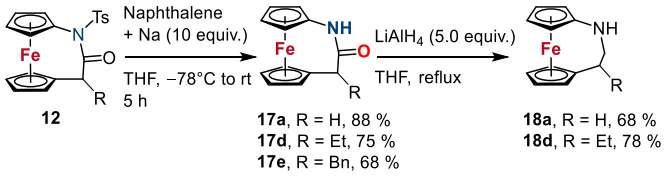
We reasoned that if we wanted to expand the scope ferrocenophanes we could access to, an oxygen donor able to react with the triple bond was needed. We took inspiration from the work of Ohshiro, showing that *N*-phenyl ketenimine could react with diphenylnitrone **15** to yield oxindoles through cyclization.[38] We surmised that a similar activation could be applied to ynamides if the zwitterionic form **G** (Scheme 5) was favored. Using HFIP as the solvent,[39] we found that ferrocephane **12a** could be obtained from **8a** using nitrone **15** as the oxygen donor. After optimization (see SI for details) an 85% yield could be attained, using 4 equivalents of the nitro. We were delighted to see that with these conditions substituted ynamides could be cyclized and ferrocenophanes **12c**, **12d** and **12e** could also be isolated in good yields. We suppose that the high polarity of HFIP favors the zwitterionic **G** form of the ynamide, which can be protonated by the solvent to give keteniminium **H**. From there, by analogy with what has been proposed with ketenimines and ketenes,[38,40–42] *O*-addition of the nitrone would lead to enol intermediate **I**. Cyclization of the ferrocene ring would liberate imine **16** (which was observed in the crude reaction) and intermediate **J**, which would quickly rearomatize to **12** through deprotonation by the alcoholate. Interestingly, for *N*-benzyl or *N*-phenyl ynamides, rather than a cyclization an oxoarylation (with the incorporation of an imine moiety) takes place. This latter reactivity had been previously reported but using a Pt(II) catalyst,[43] whose used can thus be bypassed by using HFIP.

Scheme 5. Formation of ferrocenophanes using nitrones as oxygen donors



It was possible to efficiently cleave the sulfonamide group of **12a**, **12d** and **12e** using sodium-naphthalene to access the unprotected amide **17a,d,e** in 68% to 88% yield (Scheme 6).

Scheme 6. Deprotection of 12 and reduction of amides 17.



Further reduction with $LiAlH_4$ gave the corresponding amine **18a** and **18d** in 68% and 78% yield, respectively, further demonstrating the robustness of this ansa[3]-ferrocene moiety. Both structures could be confirmed by X-ray analysis of **17a** and **18a**.

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 or nitrones as the oxygen donor. In both cases the reactivity drastically differs from the one that can be observed when reacting non-metallocenyl ynamides. Moreover, our approach offers a complementary metal-free strategy for remote C-H-functionalization of ferrocenes. To the best of our knowledge, despite many advances in transition-metal-catalysis for the C–H bond functionalization of ferrocenes,[44–46] there is only one example of such a remote C-H functionalization catalyzed by a transition metal.[47] Further studies are underway to fully explore the exciting chemistry of these original ynamides. Moreover, taking into consideration the potential of ferrocene[31] and more particularly of ferrocenophane[48–50] for medicinal chemistry, incorporation of this cyclic ferrocene moiety onto known drugs will also be sought after.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published

article and its online Supporting InformationSupporting Information

Supplementary information file (PDF) contains: synthetic procedures and characterization of the new compounds, Full optimization studies, cyclic voltammetry, NMR spectra, DFT Calculations details (including coordinates and full discussion) and Crystallographic Data.

CCDC 2191215 (for **6**), CCDC 2191216 (for **8c**), CCDC 2191217 (for **8e**), CCDC 2191218 (for **19**), CCDC 2191219 (for **18a**), CCDC 2191220 (for **11**), CCDC 2191221 (for **12a**), CCDC 2191222 (for **17a**), CCDC 2191223 (for **10**), CCDC 2191224 (for 1**6**), CCDC 2215147 (for **12e**), and CCDC 2215148 (for **12d**) contain the supplementary crystallographic data for these compounds, and can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Author Contributions

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript.

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