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Iron-catalyzed intramolecular C(sp³)-H lactonization of hydroxamate derivatives promoted by a 1,5-HAT.

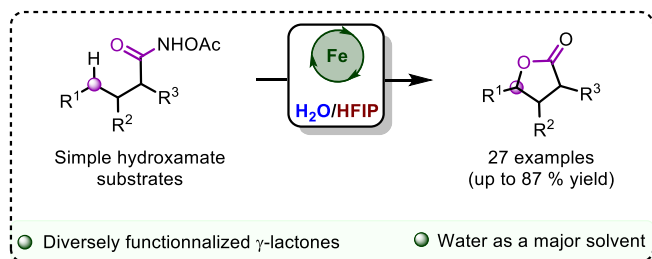
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ABSTRACT. An iron-catalyzed lactonization reaction via an intramolecular C(sp³)-H functionalization is described. The process employs easily accessible hydroxamate derivatives from which the non-common insertion of the oxygen occurred through a 1,5-Hydrogen Atom Transfer. A mixture of water and HFIP as solvent appeared to be the key parameter of this transformation to reach a high selectivity and efficiency.



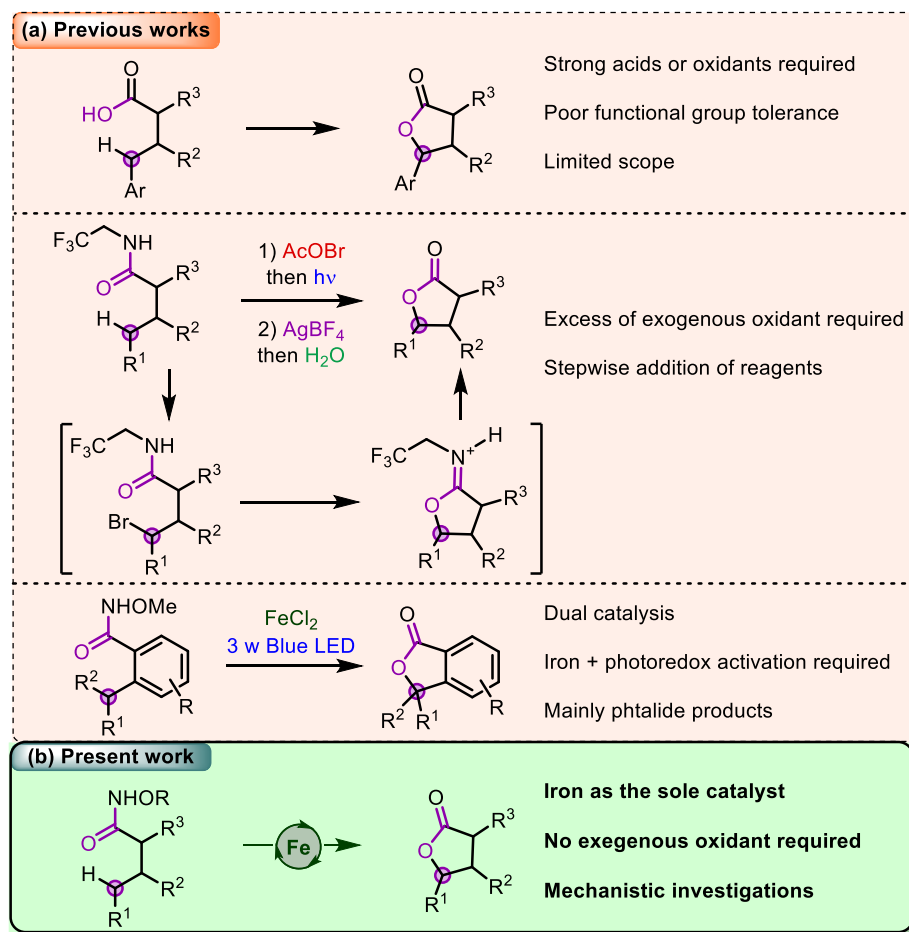
The γ -butyrolactone synthon, as a 5-membered oxygenated heterocycle, is of significant importance in chemistry. This scaffold is remarkably present in a wide variety of natural products and a privileged structure found in many pharmaceutical compounds displaying a broad range of biological activities.¹ The most obvious method to prepare γ -butyrolactones remains the intramolecular esterification of an acyclic 4-hydroxy-carbonyl synthon. However, this strategy requires a pre-functionalized substrate usually obtained via an homoaldolisation reaction which is not as trivial as the classical aldolisation.² The direct intramolecular C(sp³)-H lactonization of butanoic acids is, in contrast, the most straightforward way to get access to the γ -butyrolactone synthon. The benzylic position of aryl substituted butyric acids being easily prompt to oxidation, the early reports described the formation of lactones from the corresponding carboxylic acids using strong oxidants. Potassium peroxodisulfate and hypervalent iodine were typically employed with or without metal catalysis or photochemical activation. In addition, electrochemical methods have also been reported.³ The mechanism commonly accepted for this process starts with the formation of a benzylic radical species via C(sp³)-H abstraction, followed by its oxidation and a ring closing reaction as the final step. In a similar vein, White's group developed an iron-based directed aliphatic C-H hydroxylation

process which provided the lactones in moderate yields.⁴ The use of carboxylic acids seems quite practical in an atom-economy point of view, however most of the work reported so far employs strong acids or oxidants which are additionally present in stoichiometric quantities in the most favorable cases. This entails, on the one hand, a poor functional groups tolerance and a scope restricted to aryl-functionalized lactones, and on the other hand, processes that are less sustainable (Scheme 1a). Alternatively, the 1,5-Hydrogen Atom Transfer (1,5-HAT) initiated by nitrogen-centered radicals followed by the functionalization of the carbo-radical moiety represents a convenient approach for the regioselective formation of diversely functionalized 5-membered heterocycles. Historically the 1,5-HAT process was first observed in the XIXth century in the Hofmann-Löffler-Freytag reaction from which a pyrrolidine was generated by thermal or photochemical degradation of *N*-haloamines.⁵ Since these pioneering reports many efforts have been done to develop practical conditions for the generation of *N*-centered radicals from different sources of nitrogenated substrates.⁶ Nonetheless, selective direct lactonization reactions through a 1,5-HAT involving *N*-centered radicals such as amidyl species are poorly described.⁷ An appealing example was reported by Tiefenbacher using an electron-deficient amide as a directing group.⁸ Acetyl hypobromite and white light-emitting diodes (LEDs) were used to first generate a *N*-bromo species which then can initiate the radical reaction to lead to the corresponding γ -brominated compound. In a second step the addition of silver(I) tetrafluoroborate provided an iminium lactone intermediate which was then hydrolyzed to the corresponding lactone by a final addition of water to the reaction mixture (Scheme 1a). Despite the wide scope of products described, the process employs an excess of

an exogenous oxidant and requires a stepwise addition of the reagents to access the lactones, which makes the process poorly sustainable. In the context of green chemistry, hydroxamic acid derivatives are interesting reagents for such a transformation. They are able to generate amidyl radicals through metal catalysis or photocatalytic activation without addition of any external oxidant.⁹ Chang's group described the use of *N*-benzoylamide and dioxazolone substrates as appropriate reagents to initiate a 1,5-HAT through iridium, rhodium, or iron catalysis.¹⁰ The conditions developed are highly suitable for the selective synthesis of γ -lactams via an intramolecular C(sp³)-H amidation reaction. In a similar approach, Meggers' group reported the formation of imidazolidinone and carbonate products via iron and ruthenium catalysis through acyl nitrenoid species generated from hydroxyl amine derivatives.¹¹ On the other hand, the use of hydroxamates as substrates for the formation of the corresponding lactones via C(sp³)-H oxygenation reactions is still scarcely reported. In relation with our research projects dedicated to iron-catalyzed functionalization of alkenes using hydroxylamine derivatives as nitrene precursors,¹² we thus investigated for new C(sp³)-H functionalization reactions using easily accessible iron salts and ligands. Our objective was to deviate the reactivity of *N*-acetoxy amides, commonly observed for the formation of lactams, in order to obtain the corresponding γ -butyrolactones selectively. The use of iron as a catalyst in combination with hydroxamates as nitrene precursors for C(sp³)-H oxygenation reactions has never been reported, except from Zhang's group who published during the development of our study a similar process using *N*-methoxy benzamide as substrates. However, their method required a double activation with the combination of iron and photoredox catalysis

and the report is mainly focused on the formation of phthalides products. (Scheme 1a).¹³ We report herein, our results for an original intramolecular iron-catalyzed C(sp³)-H lactonization reaction promoted by a 1,5-HAT process, without photoredox assistance. The reaction conditions developed are particularly sustainable: a catalytic amount of iron complex, the absence of external oxidants thanks to the use of hydroxylamines as nitrene source, and a reaction running in water in the presence of an HFIP co-solvent restricted to 10 %. The process allows the synthesis of a large array of γ -lactones. A plausible mechanism is provided, supported by an extensive mechanistic study (Scheme 1b).

Scheme 1. Context of the work

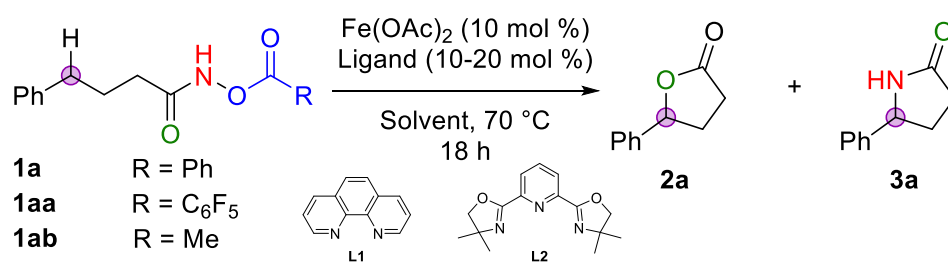


In our previous work on the functionalization of alkenes using iron catalysis and hydroxylamine derivatives as nitrene precursors, we highlighted the impact of the hydroxamate moieties on the efficiency of the transformation.¹² Based on this experience, three different carboxylate groups were selected as representative examples due to the difference in their electronic properties. The hydroxamates derived from 4-phenylbutyric acid **1a**, **1aa** and **1ab** bearing respectively benzoate, pentafluorobenzoate and acetate moieties were thus used as model substrates for the optimization of the reaction conditions. In combination with iron(II) acetate as a catalyst and phenanthroline as a ligand in acetonitrile at 70 °C, hydroxamates **1a** and **1aa** produced lactone **2a** in respectively 58 % and 51 % yields. The lactam

3a was also formed and isolated as a minor product in respectively 26 % and 18 % yields (Table 1, entries 1 and 2). In contrast, starting with **1ab** did not afford any product, and decomposition of the starting material was observed under these conditions (Table 1, entry 3). Aiming to improve the yield in favor of the lactone, a classical evaluation of the various reaction parameters was carried out. The use of PyBox ligand **L2** in association with iron(II) acetate interestingly led to a more selective catalyst than phenanthroline **L1**. Lactam **3a** was not detected, and lactone **2a** was formed in a 52 % yield using substrate **1a**, and a 54 % yield was obtained starting with substrate **1aa** (Table 1, entries 4 and 5). Moreover, the hydroxamate **1ab** appeared to be reactive in the presence of **L2** as lactone **2a** was isolated in 24 % yield (Table 1, entry 6). Inspired by the work of Tiefenbacher, we anticipated that the addition of water as a co-solvent could facilitate the formation of the lactone through an in situ hydrolysis of the potential imine-lactone key intermediate. Gratifyingly, when the reaction was run in a 1:1 mixture of water and acetonitrile, the targeted lactone was obtained with a higher yield using compound **1a** (60 %, Table 1, entry 7). Hydroxamate **1aa** and **1ab** were found to be better substrates in this solvent mixture as product **2a** was isolated in 76 % and 77 % yield respectively (Table 1, entries 8 and 9). Hexafluoroisopropanol (HFIP) is known to be a unique solvent to promote a variety of reactions due to its high polarity and strong hydrogen-bond donor ability.¹⁴ We reported recently that HFIP accelerated the nitrene transfer in iron-catalyzed aziridination reaction and moreover that it mediated the opening of those aziridines.^{12d} When HFIP was used instead of ACN as a 1:1 mixture with water, the three substrates **1a**, **1aa** and **1ab** led to excellent yields of **2a** 81 %, 87 % and 88 % respectively (Table 1, entries 10-12). The

slight yield difference appeared difficult to rationalize in terms of pKa or steric hindrance of the leaving group (benzoate, pentafluorobenzoate, and acetate for **1a**, **1aa** and **1ab** respectively). The acetate substrate **1ab** was thus selected on the basis of atom and cost economy and the influence of the proportion of HFIP in water was next evaluated. The percentage of HFIP in water appeared to have a negligible impact on the reactivity outcome as comparable yields were obtained with ratios ranging from a 1:1 to a 1:4 H₂O/HFIP mixture (88 % vs 90 % yield respectively, Table 1, entries 12 and 13). It was even possible to reduce the amount of HFIP in water to 10 % as well as reducing the iron/ligand ratio to 1:1 (10 mol %) without any significant impact, making the process much more in line with the green chemistry principles (90 % and 87 %, Table 1, entries 14 and 15). Even though HFIP is required to maintain a high reactivity, the reaction can also be conducted in pure water as a satisfying 60 % yield of the product was obtained (Table 1, entry 16). Classical control experiments were then conducted. No reaction occurred in the absence of catalyst (Table 1, entry 17) and the same outcome was observed when using a copper(I) or a copper(II) catalyst, confirming the role of iron in the transformation (Table 1, entries 18 and 19).

Table 1. Optimization of the reaction conditions ^a



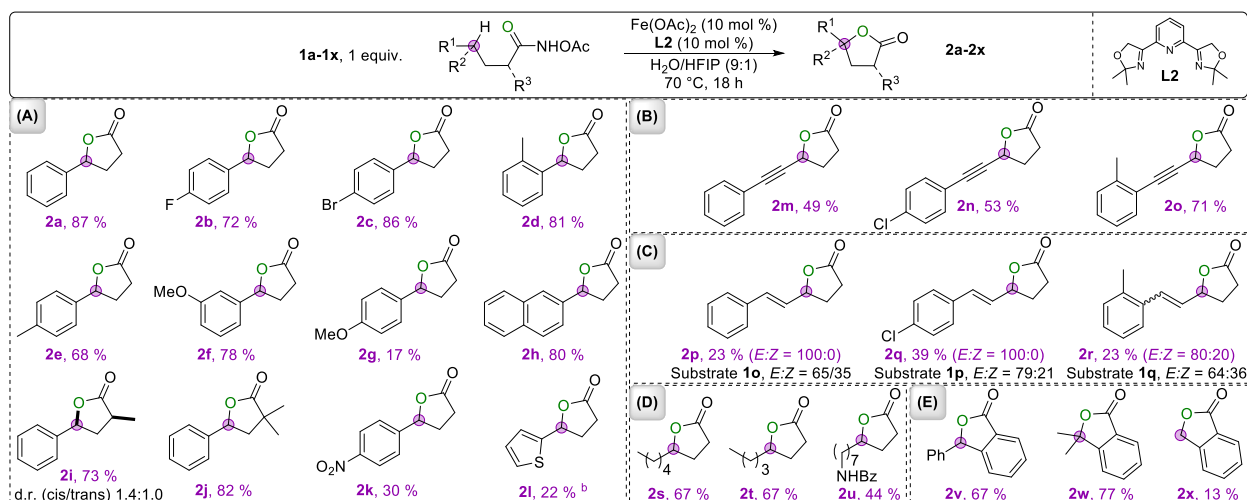
Entry ^a	R	Ligand	Solvent	Yield (%) 2a / 3a ^b
1	Ph	L1	ACN	58 / 26
2	C ₆ F ₅	L1	ACN	51 / 18
3	Me	L1	ACN	–
4	Ph	L2	ACN	52 / –
5	C ₆ F ₅	L2	ACN	54 / –
6	Me	L2	ACN	24 / –
7	Ph	L2	H ₂ O/ACN (1:1)	60 / –
8	C ₆ F ₅	L2	H ₂ O/ACN (1:1)	76 / –
9	Me	L2	H ₂ O/ACN (1:1)	77 / –
10	Ph	L2	H ₂ O/HFIP (1:1)	81 / –
11	C ₆ F ₅	L2	H ₂ O/HFIP (1:1)	87 / –
12	Me	L2	H ₂ O/HFIP (1:1)	88 / –
13	Me	L2	H ₂ O/HFIP (1:4)	90 / –
14	Me	L2	H ₂ O/HFIP (9:1)	90 / –
15 ^c	Me	L2	H ₂ O/HFIP (9:1)	87 / –
16	Me	L2	H ₂ O	60 / –
17 ^d	Me	–	H ₂ O/HFIP (9:1)	–
18 ^e	Me	L2	H ₂ O/HFIP (9:1)	–
19 ^f	Me	L2	H ₂ O/HFIP (9:1)	–

(a) Reaction conditions: in a sealed tube, substrate **1** (0.2 mmol, 1 eq), Fe(OAc)₂ (0.02 mmol, 10 mol %) and ligand (0.04 mmol, 20 mol %) were mixed with solvent (C = 0.1 M) before stirring at 70 °C for 18 h. (b) isolated yields. (c) **L2** 10 mol % (0.02 mmol) was used. (d) no metal and no ligand used. (e) Cu(OTf)₂ was used as a catalyst. (f) CuI was used as a catalyst.

The scope and the limitations of this reaction were then investigated (Scheme 2). Various hydroxamate derivatives were synthesized from abundant carboxylic acid feedstock via an easy two-step synthesis.¹⁵ The exemplification for the insertion onto C(sp³)-H benzylic positions of diversely functionalized aryl substrates was first conducted with the optimized conditions (Table 1, entry 15). Substrates bearing electron-withdrawing fluoro and bromo groups in para-position of the phenyl moieties smoothly cyclized to give products **2b** and **2c** in 72 % and 86 % yield respectively (Scheme 2A). The reaction was also tolerant to phenyl moieties substituted by a methyl group at the ortho- and para- positions (**2d**, 81 % and **2e**, 68 % respectively). The high yield obtained for product **2d** showed that steric hindrance did not interfere in the reactivity of the transformation. Phenyl groups bearing strongly donating methoxy substituents were also studied. The lactone **2g** bearing the *p*-methoxy phenyl moiety gave a low 17 % yield, whereas the lactone **2f** bearing the *m*-methoxy phenyl moiety successfully cyclized with a 78 % yield. Lactone **2h** with the extended π -system from the naphthyl moiety was also obtained with an excellent yield of 80 %. The α -functionalized phenyl hydroxamate compounds appeared to be valuable substrates for this reaction as 3-methyl lactone **2i** and 3,3-dimethyl lactone **2j** were isolated in 73 % and 82 % yield respectively with **2i** giving both cis and trans products with little discrimination (dr = 1.4:1). Finally, the 4-nitro-phenyl and the 2-thienyl substrates were found to be tolerated but less efficient, the corresponding lactones **2k** and **2l** being isolated in 30 % and 22 % yield respectively. Insertions onto propargylic and allylic C(sp³)-H positions were then investigated using substrates bearing phenyl, 4-chloro-phenyl and 2-methyl-phenyl functional groups. Alkynyl lactones **2m**, **2n** and

2o were obtained in moderate to good yields (Scheme 2B, 49 %, 53 % and 71 % respectively). In contrast, the functionalization of alkenyl derivatives was poorly efficient, as the corresponding lactones **2p**, **2q** and **2r** were obtained with yields ranging from 23 to 39 % (Scheme 2C). Worthy of note both products **2p** and **2q** were isolated as a single (*E*) isomer although arising from *E:Z* isomers mixture of substrates **1p** and **1q** (65:35 and 79:21 respectively). Product **2r** was obtained as a 80:20 *E:Z* isomers mixture from a 64:36 *E:Z* mixture of **1r** (Scheme 2C). We next evaluated the use of this method for the insertion onto more challenging aliphatic C(sp³)-H bonds (Scheme 2D). The γ -lactones **2s** and **2t** bearing a pentyl and a butyl chain were successfully isolated in a good 67 % yield. Product **2u** with a longer aliphatic chain terminated by a benzoyl amine was successfully obtained in a 44 % yield. In parallel, phthalide derivatives were also investigated (Scheme 2E). Lactones **2v** and **2w** bearing a phenyl or a dimethyl group were isolated with 67 % and 77 % yield respectively. By comparison, the simple phthalide **2x** was obtained with a poor 13 % yield.

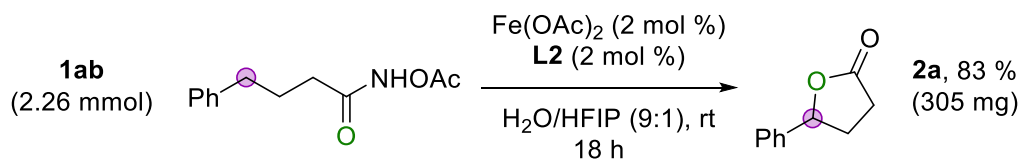
Scheme 2. Scope and limitations ^a



(a) Reaction conditions: in a sealed tube, **1** (0.2 mmol, 1 eq), Fe(OAc)₂ (0.02 mmol, 10 mol %) and ligand **L2** (0.02 mmol, 10 mol %) were mixed with H₂O/HFIP (9:1, C = 0.1 M) before stirring at 70 °C for 18 h. Depending on the substrate, the reaction time can be shorter and vary from 4 h to 18 h. For the homogeneity of the conditions, the reactions were all run for 18 h. (b) A 1:9 ratio of H₂O/HFIP was used. All yields referred to isolated yields.

The efficiency of this reaction was next evaluated through an up-scale experiment. To make this process even more sustainable, catalyst loading was decreased to 2 mol % and the reaction was carried out at room temperature using 2.26 mmol of substrate **1ab**. A complete conversion was observed after 18 h with the exclusive formation of the lactone which was isolated with an excellent 83 % yield (Scheme 3).

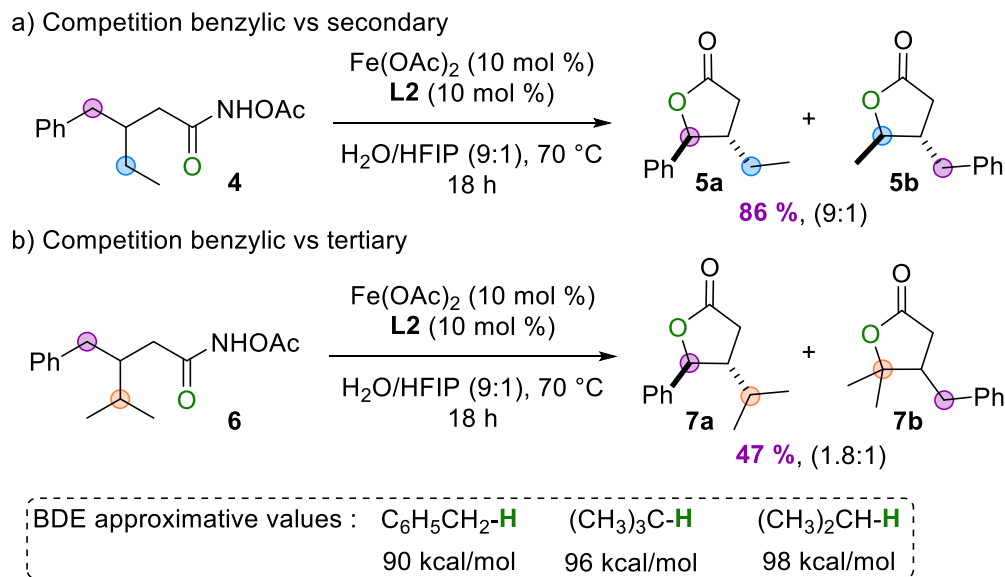
Scheme 3. Upscale experiment



Discrimination toward the functionalization of multiple C(sp³)-H bonds is known to be governed by a complex interaction of kinetic, thermodynamic, and conformational factors. Bond dissociation energies (BDE) of C-H bonds are of significant importance to understand the selectivity between multiple bonds, nonetheless, rationalizing and predicting the insertion remains a difficult task. As a result, we conducted several competitive experiments to determine the selectivity of our catalytic system between non-equivalent C(sp³)-H bonds. The insertion onto a benzylic position in the presence of a competitive secondary C-H bond at the same distance provided a mixture of the γ -butyrolactones **5a** and **5b** isolated with an excellent 86 % yield and a 9:1 ratio in favor of compound **5a** (Scheme 4a). As expected on the basis of

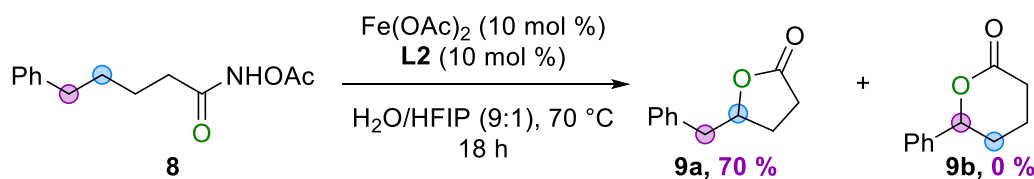
BDE (see Scheme 4),¹⁶ the discrimination between a benzylic and a tertiary position was less significant. The substrate **6** provided the products **7a** and **7b** with a moderate 47 % yield and a 1.8:1 ratio in favor of the γ -butyrolactone **7a** (Scheme 4b).

Scheme 4. Competitive site selectivity experiments



The regioselectivity was next investigated between γ -cyclization or δ -cyclization. The hydroxamate derivative **8** subjected to our standard conditions furnished exclusively the γ -butyrolactone **9a** isolated with a good 70 % yield (Scheme 5). The absence of δ -lactone **9b** suggested that the 6-membered quasi-chair-like transition-state of the 1,5-HAT is a prevalent factor over BDE for the C-H insertion in our conditions.

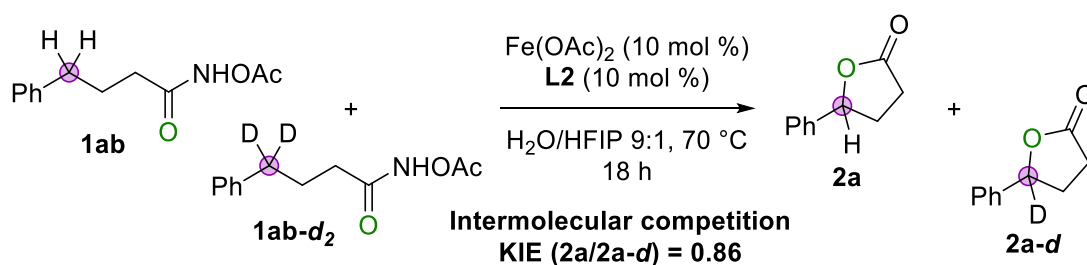
Scheme 5. Competitive 1,5- vs 1,6-HAT experiment



In order to get data about the mechanism and the rate-determining step of the lactonization, a kinetic isotope effect (KIE) experiment was performed. A primary KIE takes place when the considered labeled bond is broken in the rate-determining step. The difference of vibration frequency between a C-H bond and a C-D bond induces isotopically substituted molecules to react at different rates. The value of a primary KIE is thus greater than 1 (normal KIE) and usually quite high (>4). A secondary KIE occurs from rate differences that are caused by a labeled bond, located at the α or β position of the reactive bond, which is not involved in the rate-determining step. The value is slightly higher than 1 in the case of a normal KIE, but values lower than 1 can also be observed in the case of an inverse KIE. The latter, which suggests that the reaction proceeds faster with the D-labeled molecule than the H-labeled molecule, typically arises from changes in hybridization state from sp^2 to sp^3 .¹⁷ The intermolecular competition reaction between the compound **1ab** and its deuterated labeled analogue **1ab-d₂** was run in the same flask using our standard conditions. Following the procedure reported by Du Bois, a quantitative ¹³C NMR experiment was conducted on the mixture of purified products.¹⁸ Measurement of ratio **2a** and **2a-d** gave a KIE value of 0.86. The quantitative ¹H NMR experiment carried out on the same mixture confirmed the KIE of 0.86 (Scheme 6).¹⁵ From our substrates, a primary or a secondary KIE can be observed as two deuterium atoms are present in **1ab-d₂**, one involved on the cleavage of the bond and the other one not affected by the transformation. Based on the discussion about the classification of the KIE (vide supra), our value excludes a primary KIE and thus the C-H abstraction as the rate determining step.¹⁹ The observed value is consistent with a secondary inverse kinetic isotope

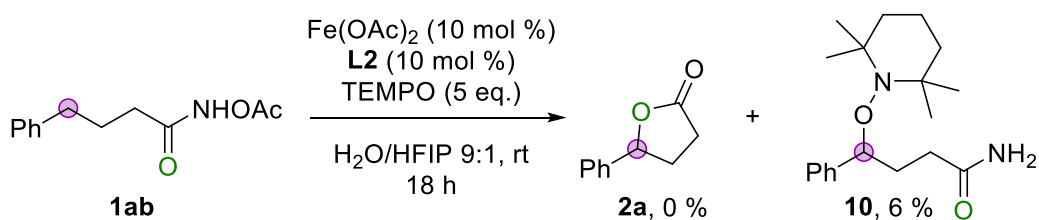
effect and suggests that the transition state involves a sp^2 to sp^3 rehybridization during the formation of the lactone, which is compatible with both a benzylic carboradical or a benzylic carbocation leading then to a sp^3 carbon.^{17, 20}

Scheme 6. KIE experiment



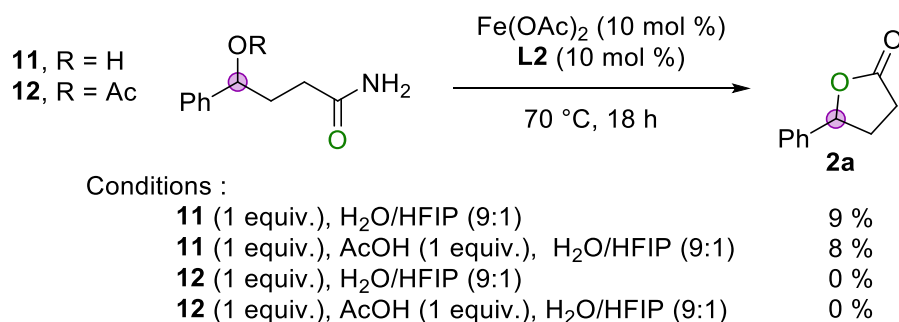
To collect more information about the nature of the nitrene species involved in this transformation, the aminoxyl reagent TEMPO was next added to trap any potential radical species. A complete inhibition of the reaction was observed using 5 equivalents of TEMPO at room temperature, as lactone **2a** was not detected. Interestingly, the amide compound **10** was isolated in a 6 % yield. This product corresponds to the insertion of a molecule of TEMPO at the benzylic position and would suggest the presence of a benzylic radical arising from a triplet nitrene (Scheme 7).

Scheme 7. Radical trap experiment



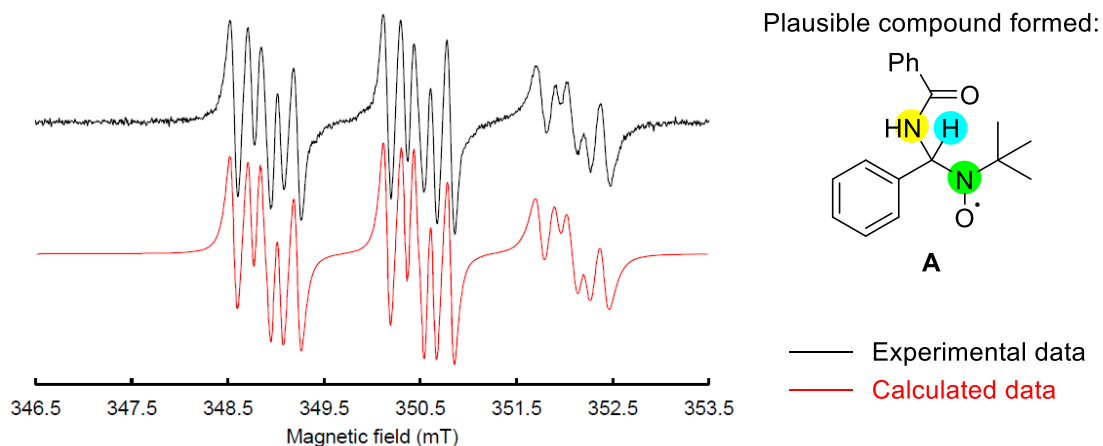
From this result we hypothesized that the benzylic carboradical species, or the corresponding carbocation obtained after its oxidation, could be trapped by the oxygen atom of the carbonyl group to give an imine-lactone intermediate furnishing the target product. Alternatively, the intermediate carbocation could react with water or even with the released carboxylate to give the hydroxyl amide **11** or the acetyl amide **12**, which would, in the reaction conditions, cyclize to generate the lactone **2a**. To evaluate these hypotheses, compounds **11** and **12** were synthesized and submitted to our reaction conditions (Scheme 8).¹⁵ The substrate **11** in the presence of the iron catalyst and the solvent mixture produced the lactone **2a** with a poor 9 % yield. The addition of 1 equivalent of acetic acid to the previous reaction did not change the reaction course affording the lactone in 8 % yield. Similarly, the procedures were then applied to substrate **12** which appeared to be non-reactive since no conversion was observed in both conditions (i.e. with or without acetic acid). Thereby, these results invalidated the alternative cyclization routes. Worthy of note, compound **11** was neither observed during the optimization process nor the evaluation of the scope and limitations of the reaction.

Scheme 8. Ring closing experiments



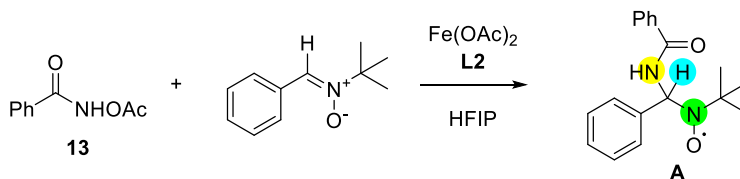
To get more insight about the mechanism, different spectroscopic experiments were carried out. In relation with the work of Chang,²¹ a low-temperature X-band EPR experiment was conducted using substrate **1ab** in the presence of Fe(OAc)₂ and **L2** in HFIP. Unfortunately, no signal was detected. The same procedure was also carried out using the model hydroxamate **13**, but again no signal could be observed. Experiments involving *N-tert-butyl- α -phenylnitrone* (PBN) as a spin trapping agent were then conducted. Interestingly, the mixture of Fe(OAc)₂, **L2** and model substrate **13** with PBN in HFIP under argon led to the generation of a well-resolved EPR signal (Figure 1). The Spin-Hamiltonian parameters elucidated from the simulated spectrum ($a_N = 1.593$ mT, $a_H = 0.300$ mT, $a_N = 0.180$ mT; $g = 2.005$) are consistent with the trapping of a nitrogen-centered radical by PBN, as evidenced by the second hyperfine coupling to nitrogen. The spin of the unpaired electron of the nitroxide spin adduct couples to nearby non-zero nuclear spins (i.e. nitrogen nucleus, $I = 1$, and proton, $I = 1/2$), which leads to the splitting of the EPR line (number of lines = $\sum_i (2I_i + 1)$). Thus, the EPR signal could be attributed to the radical compound **A** (Figure 1).

Figure 1. EPR spectra obtained at 21°C in HFIP under argon with a mixture of Fe(OAc)₂ (10 mM), **L2** (10 mM), model substrate **13** (100 mM) and PBN (500 mM).



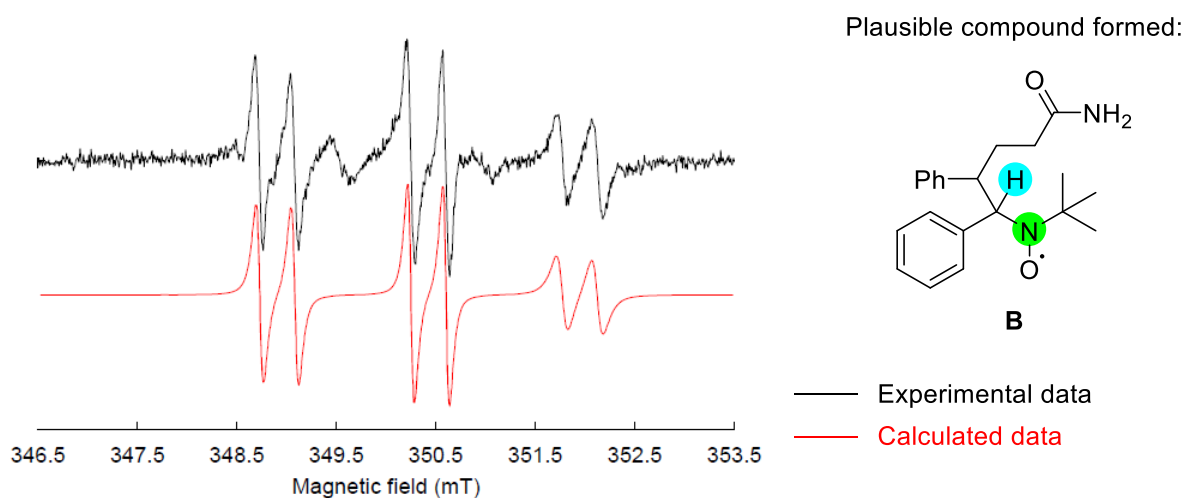
The formation of this radical can be rationalized by the reaction between PBN and the amidyl radical arising from the iron nitrene intermediate generated by the reaction of **13** with the iron complex (Scheme 9).

Scheme 9. Plausible formation of **A**



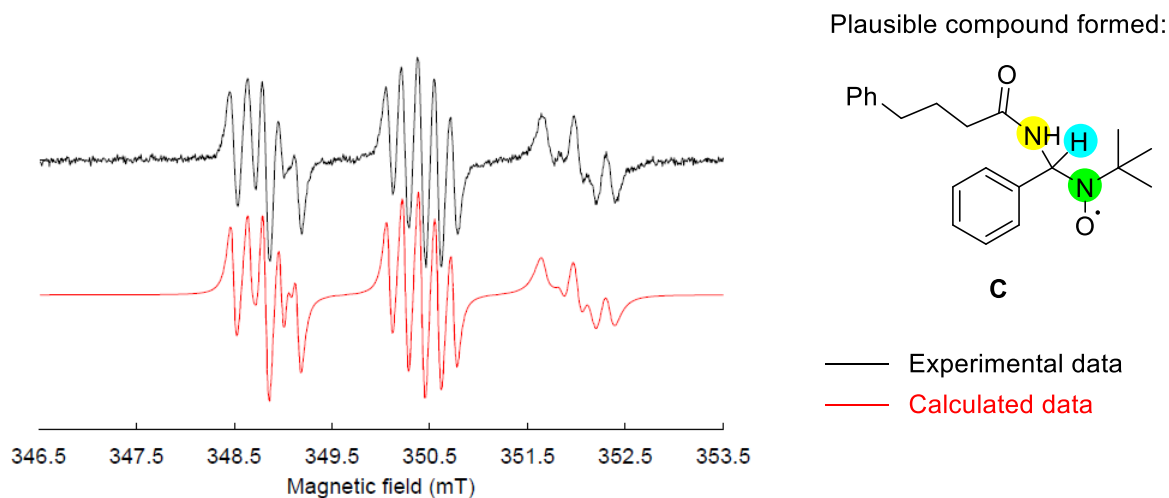
By analogy, the reaction between substrate **1ab**, Fe(OAc)_2 , **L2** and PBN in HFIP was studied by X-band EPR. The generation of two successive well-resolved EPR signals was obtained. First, a six-line EPR spectrum characteristic of a PBN adduct ($a_N = 1.521$ mT, $a_H = 0.353$ mT; $g = 2.005$) was observed (Figure 2). Considering the lack of reference data for hyperfine coupling constants in HFIP, it could not be concluded at this stage if this adduct resulted from the trapping of a putative benzylic carbon-centered radical, or from the nucleophilic attack of an oxygen nucleophile (acetate anion).

Figure 2. EPR spectra obtained at 21°C in HFIP under argon with a mixture of Fe(OAc)₂ (10 mM), L2 (10 mM), substrate **1ab** (100 mM) and PBN (500 mM) immediately after analysis start.



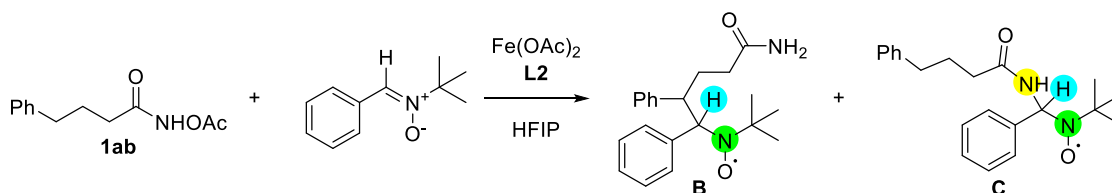
Overtime, this first signal decayed and a new signal similar to the one obtained from compound **13** appeared (see Figure 1 vs Figure 3). Thus, the resulting signal is attributed to the trapping of a nitrogen-centered radical considering the contribution of an additional hyperfine coupling constant to nitrogen ($a_N = 1.592$ mT, $a_H = 0.317$ mT, $a_N = 0.169$ mT; $g = 2.005$) and could be attributed to radical **C** (Figure 3). In spin trapping experiments, the intensities of the spectra do not directly reflect the concentration of trapped radicals because the steady-state concentration of spin adduct is dependent on both the spin trapping rate and the rate of decomposition of the adduct. The nitrogen-centered radical could be formed from the start but have a slower trapping rate than the first observed species, therefore the adduct could take more time to accumulate above the detection limit.

Figure 3. EPR spectra obtained at 21°C in HFIP under argon with a mixture of Fe(OAc)₂ (10 mM), L2 (10 mM), substrate **1ab** (100 mM) and PBN (500 mM) 35 min after analysis start. (16 % of the initial species is present in the spectrum).



Compounds **B** and **C** could prove the presence of a benzylic carboradical and an amidyl radical, which would be formed during the reaction between **1ab** and the iron complex (Scheme 10).

Scheme 10. Plausible formation of **B** and **C**



However, similar EPR signals could be obtained by addition of nucleophiles on PBN, followed by oxidation of the resulting residues (Forrester-Hepburn mechanism).²² In order to

rule out the nucleophilic addition of the different reagents involved in the mixture with PBN, control experiments were conducted. Hydroxamate **13**, as well as sodium acetate and benzamide which could be formed by decomposition of **13**, were individually mixed with PBN in HFIP during few minutes. Then, potassium ferricyanide was added to act as an oxidant. Interestingly, no signal was observed in all three cases invalidating the nucleophilic addition onto PBN followed by oxidation. Thus, the obtained EPR signals could be attributed to the trapping of amidyl and benzylic radical species.

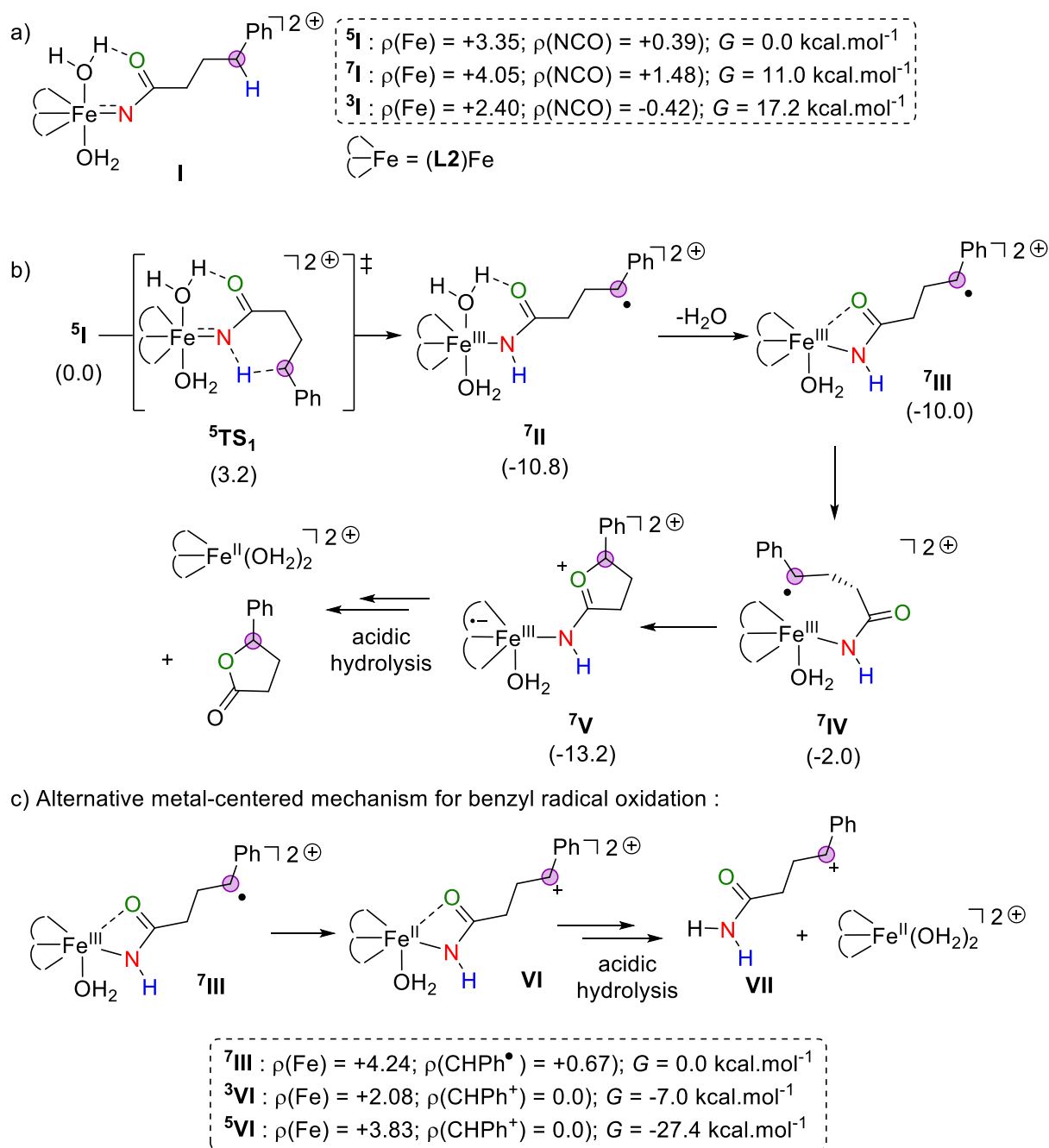
The mixture between compound **13** and the stable complex **L2**-Fe(II)Cl₂ was also studied by IR spectroscopy. The spectra did not show any clear evidence of the formation of an iron nitrene species, however a strong decrease of the intensity of the carbonyl pics of substrate **13** was observed suggesting a cleavage of the N-O bond when the hydroxamate is mixed with the catalyst complex.¹⁵

The feasibility of the 1,5-HAT step followed by oxidation of the benzylic radical has been investigated by DFT calculations. This computational work was carried out using the Gaussian16 v. B.01 code,²³ and OPBE functional was chosen, since it proved to efficiently reproduce both electronic and thermic properties of iron complexes, regardless of their oxidation and spin states.^{24a-c} Implicit PCM solvation model^{24d-e} was associated with explicit solvation of the iron by H₂O molecules.¹⁵ Complex *trans*-[(**L2**)Fe=NC(O)(CH₂)₃Ph(OH₂)₂]²⁺ (**I**, Scheme 11a) has been chosen as a model for nitrenoid species, taking into account solvation of the dicationic iron center by two water molecules. The geometry of **I** has been optimized for several spin multiplicities ($S = 1$, ³**I**; $S = 2$, ⁵**I**, and $S = 3$, ⁷**I**), which all featured an intramolecular hydrogen bond between the oxygen atom of the amide and one of the iron-ligated H₂O molecules. A spin quintet ($S = 2$) has

been found as a ground state, featuring a formally intermediate-spin ferric Fe(III) ion ($S = 3/2$; computed Mulliken spin density $\rho(\text{Fe}) = +3.35$) ferromagnetically coupled with an unpaired electron delocalized onto the $\pi(\text{NCO})$ system (computed spin densities : +0.21 (N), +0.18 (O)). A computed distance $d(\text{Fe-N}) = 1.72 \text{ \AA}$ has been obtained, which is similar to that of diketonate-stabilized ferric iminyl radicals evaluated *in silico* ($d(\text{Fe-N}) \sim 1.74\text{-}1.86 \text{ \AA}$).²⁵ Conversely, the triplet state **3I** can be described as a ferric Fe(III) ion ($S = 3/2$; computed spin density : +2.40) involved in an antiferromagnetic coupling with one unpaired electron borne by the $\pi(\text{NCO})$ system (computed spin densities : -0.36 (N), -0.06 (O)). This state has been located 17.2 kcal.mol⁻¹ above the ground **5I** state. The septuplet state, **7I**, featuring a high-spin Fe(III) ion ferromagnetically coupled with an unpaired electron in the $\pi(\text{NCO})$ system (computed spin densities : +4.05 (Fe); +1.13 (N); +0.35 (O)) was located in-between, at 11.0 kcal.mol⁻¹ above **5I**. Starting from **5I**, a transition state for the 1,5-HAT involving a low 3.2 kcal.mol⁻¹ barrier has been located on the same spin quintet surface (**5TS₁**, Scheme 11b). In this process, the Fe-N bond increases ($d(\text{Fe-N}) = 1.86 \text{ \AA}$), in line with the evolution of an iron nitrenoid species (**I**) towards an iron amido complex (**II**). High-spin complex **7II** was found to be stabilized by ca. 10.8 kcal.mol⁻¹ with respect to the starting material, and featured a high spin ferric core with one unpaired electron located on the benzylic position as a result of the 1,5-HAT step (computed spin densities : +4.14 (Fe); +0.33 (O from Fe-ligated H₂O molecules); +0.73 (CHPh)). In line with the genuine σ -ligation of the amido moiety to the Fe(III) ion in **7II**, an increase of the Fe-N distance is observed ($d(\text{Fe-N}) = 2.04 \text{ \AA}$). Overall, this demonstrates the feasibility of this 1,5-HAT step, requiring a modest barrier (*vide supra*). The oxidation of the C-centered benzylic radical by the ferric ion has then been investigated. In order to make possible the approach of the radical in the iron coordination sphere, decoordination of a water molecule from **7II** has been computed, since the latter complex is a saturated octahedral

species. The corresponding complex, **7III**, has been located 0.8 kcal.mol⁻¹ higher than **7II**, a weak coordination of the oxygen of the amide being observed (Scheme 11b). Starting from **7III**, a less stable conformer **7IV**, bringing the C-centered radical closer to the iron coordination sphere has been located 8.0 kcal.mol⁻¹ above **7III**. Starting from species **7IV**, two possible oxidation paths of the benzylic radical have been investigated. We first examined the possibility of a ligand-centered reduction, given that PyBox-type ligands display formal α -diimine moieties that can act as redox-active ligands, as demonstrated by Diao in the case of Ni complexes of PyRox ligands.²⁶ In our case, it was found that the single-electron reduction of one of the π (NCCN) moieties of the **L2** ligand immediately followed by O-nucleophilic trapping of the subsequently formed benzylic carbocation, leading to compound **7V**, was thermally favored (overall stabilization of 13.2 kcal.mol⁻¹). Given that no solvent reorganization is requested to allow the approach of the radical site towards **L2** π -system in **7IV**, a small barrier is expected. **7V** is formally a high-spin Fe(III) complex associated with a reduced (**L2**)^{•-} ligand, which can restore the starting Fe(II) catalyst at a later stage of the process. A protolysis of the Fe-N bond followed by hydrolysis of the iminium cation further affords the expected lactone (Scheme 11b).

Scheme 11. DFT Investigation on the mechanism of the lactonization.



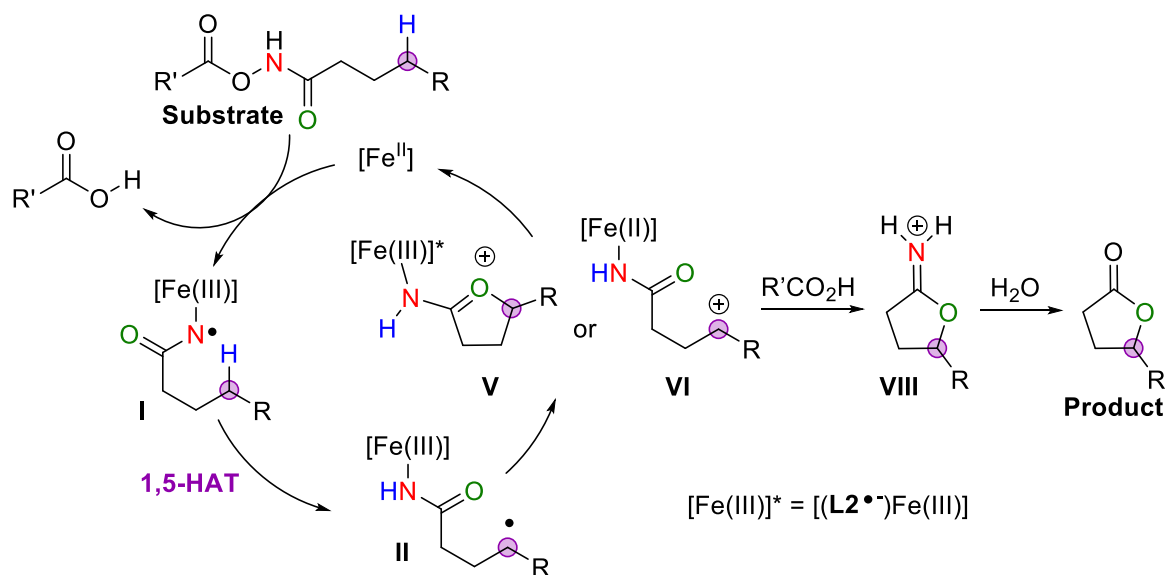
a) ground and excited spin states of nitrenoid complex I (OPBE level), Mulliken spin densities and relative computed free energies; b) computation of 1,5-HAT followed by oxidation of the benzylic radical in a ligand-centered mechanism (OPBE level, computed free energies between parentheses); c) alternative metal-centered oxidation of the benzylic radical (B3LYP level).

Alternatively, a metal-centered reductive path has also been investigated, starting from Fe(III) complex **7III** (Scheme 11c). In this case, a reduction of the Fe(III) ion to the Fe(II) stage can be envisioned, along with formation of a carbocation at the benzylic position (intermediate **VI**). However, no satisfactory modelling of **3VI** and **5VI** at the OPBE level could be obtained, since some extra radical spin density remained on the benzylic position in both cases. This difficulty was circumvented by re-optimizing **7III**, **3VI** and **5VI** at the B3LYP level, which allowed the obtention of genuine Fe(II) complexes associated with a terminal benzylic carbocation, the latter not bearing any unpaired spin density (Scheme 11c). Those results show that this alternative direct metal-centered reduction is also thermally favored. Indeed, both triplet ($S = 1$, **3VI**) and quintet ($S = 2$, **5VI**) Fe(II) complexes can be obtained from the Fe(III) precursor **7III**, respectively stabilized by 7.0 and 27.4 kcal.mol⁻¹. Protolysis of Fe-N bond can then afford carbocation **VII**, which can undergo either *O*-cyclization or *N*-cyclization. The former product, thermodynamically favored by ca. 9.4 kcal.mol⁻¹, affords selectively the expected lactone after hydrolysis of the iminium cation. Taken together, those DFT simulations sustain the feasibility of a 1,5-HAT promoted by an iron nitrenoid species in a low-barrier process. An intermediate benzylic radical is obtained in this step, which can be subsequently oxidized in an intramolecular way following either a ligand-centered or a metal-centered path, both thermodynamically downhill.

According to all the data collected in this study, the following pathway has been postulated. The substrate reacts with the iron complex to give a metal nitrenoid species **I** featuring an iron(III) ion ($S=3/2$) coupled with an unpaired electron on the $\pi(\text{NCO})$. The amidyl radical can then undergo a 1,5-HAT to provide the carboradical intermediate **II** with a low energetic barrier. This species can then be oxidized to lead either to **V** with concomitant SET reduction

of the PyBox ligand or to the corresponding benzylic carbocation **VI** coordinated to an iron(II). The iminium **VIII** is generated via Fe-N bond protolysis from **V** triggered by the released carboxylic acid, thereby regenerating the active catalyst. The protolysis of **VI** releases the catalyst and a benzylic carbocation **VII** that evolves to the iminium **VIII** via a thermodynamically favored *O*-cyclization. Finally, hydrolysis of **VIII** by water provides the expected lactone product (Scheme 12).

Scheme 12. Plausible lactonization mechanism



To conclude, we developed an iron-catalyzed intramolecular C(sp³)-H lactonization of hydroxamate derivatives promoted by a 1,5-HAT. This process was robust enough to allow for the insertion onto benzylic, propargylic, allylic, and aliphatic positions. The mechanism appeared to involve a carbonyl radical intermediate initiated by a C-H abstraction promoted by an iron-nitrenoid species. Competitive insertion reactions demonstrated that our catalytic system

highly favors cyclization at benzylic positions over secondary positions, but shows a lower selectivity over tertiary positions. The exclusive formation of the γ -lactone versus the δ -lactone has proved the complete selectivity of our conditions for a 1,5-HAT compared to a 1,6-HAT without any influence of the BDE.

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ASSOCIATED CONTENT

Supporting Information. The Supporting Information is available free of charge at <https://pubs.acs.org/doi/>

Experimental details for the preparation of the hydroxamate substrates; characterization data for the substrates and the lactones; experimental details for EPR spectroscopy and DFT calculations; copies of ^1H , $^{13}\text{C}\{^1\text{H}\}$ NMR for the unknown compounds.

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This paper is dedicated to our colleague and friend Serge Turcaud on the occasion of his retirement.

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