Stereodiversified modular synthesis of non-planar five-membered cyclic *N*-hydroxylamidines: reactivity study and application to the synthesis of cyclic amidines.

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Abstract. A modular, stereodiversified and scalable synthesis of 5-membered cyclic *N*-hydroxylamidines endowed with three contiguous stereogenic centres is reported. The synthesis utilizes 2-cyano-3-aryl-4-nitroalkynoates as key building blocks, which are provided by a novel 3-component Knoevenagel-Michael addition manifold carried out as an aqueous emulsion (on water). The key building blocks are obtained as separable mixtures of two series of diastereomers: 2,3,4-*syn,syn* and 2,3,4-*syn,anti*. Both series were separately transformed into the corresponding 5-membered 3,4,5-trisubstituted *N*-hydroxylamidines by a tandem hydrogenation cyclization reaction (stereodiversification phase). These *N*-hydroxylamidines are functionalized at C₃-methinic position of the ring (alpha to

the amidine function) by a robust and unprecedented *N*-amidinoxyl radical-mediated auto-oxidation process (hydroxylation), or by a diastereoselective enamine-based C-C bond forming manifold (creation of an all-carbon quaternary centre). The outcome of the latter is biased by the relative disposition of substituents in the ring, affording C₃-quaternized 5-membered cyclic *N*-hydroxylamidines or 2,9-diazabicyclo[4.3.0]non-1-en motives. Finally, the Ti(III)-reduction of these quaternized *N*-hydroxylamidines generates the corresponding amidines in excellent yields.

Keywords: multicomponent • on water • amidines • amidinoxyl radical • auto-oxidation.

Introduction

Amidines constitute a family of nitrogen-containing compounds with an important array of pharmacological properties.^[1] Non-planar cyclic members have emerged as privileged scaffolds with special application in the design of therapeutics for Alzheimer's disease. Among them, amidines **1**^[2a-c] or **2**^[2d] (Scheme 1a) constitute valid examples of pharmacophore archetypes for inhibition of the enzyme B-Secretase 1 (BACE1),^[2] an important therapeutic target in the treatment of Alzheimer's disease.^[3] In spite of their pharmacological interest, the number of practical methodologies to construct these structures with three-dimensionality (3D), stereogenicity and functional diversity at the ring is scarce.^[4] To the best of our knowledge, only one

example of modular synthesis of *N*-sulfonyl amidines related to **2** has been reported to date.^[4h] Because the importance of the double binding mode of amidines (they are L-arginine mimetics),^[5] it would be desirable to have these pharmacophores in their free form, mainly for their use in medicinal chemistry research programs. With this idea in mind, we have designed a modular and stereodiversified synthetic approach to these structures based on the multicomponent synthesis of γ -nitronitriles **6**^[6] (building blocks featuring 3 contiguous stereogenic centres) and their reductive cyclization to *N*-hydroxylamidines **7**, non-planar scaffolds endowed with two different reactivity profiles: a radical reactivity based on the generation of an *N*-amidinoxyl radical and an ionic reactivity based on the enamine tautomer of the *N*-hydroxylamidine function. (Scheme 1b, inset). These scaffolds were used as

convenient platforms to explore direct functionalization protocols aimed to increase their 3D character (installation of a quaternary centre) and chemical complexity (functional group density), two important properties demanded in current drug discovery programs.^[7] The ambiphilic reactivity encoded in these structures allowed us to develop two robust and practical protocols for the selective functionalization of the methinic C₃-position of the ring. The first one exploited the radical reactivity mode to install a hydroxyl group at that position via an auto-oxidation process (C₃-hydroxylation). The second one, the ionic reactivity mode, allowed us to address the stereoselective installation of an all-carbon quaternary centre at the ring (C₃-alkylation). We report herein the successful development of this strategy and its application to the synthesis of fully substituted non-planar five-membered cyclic amidines endowed with a quaternary centre at the ring.

1a) Non-planar cyclic amidine BACE 1 inhibitors

1b) Modular synthetic planning

Scheme 1. Amidine pharmacophores and synthetic strategy. [H] = Hydrogenation; [F] = Functionalization; [Re] = Reduction.

Results and Discussion

The multicomponent manifold. The key γ -nitronitriles **6** were synthesized via the 3-component Knoevenagel-Michael addition reaction (3C-KMAR)⁸ outlined in Scheme 1b. The multicomponent reaction was designed to be carried out as aqueous emulsions (the so-called “on water” conditions)^[9a] to ensure sustainability^[9b] and instrumental simplicity.^[9c] At the onset of this study, only one example of 3C-KMAR in organic medium had been reported.^[8a] It used a

chiral solid catalyst to generate γ -nitro esters in good yields and enantioselectivity, but with limited diversity. With this precedent and guided by our own experience in the development of H-bond catalysed 3CRs involving nitronates in aqueous emulsions,^[10] we initiated an intensive experimental work to implement a robust and efficient protocol for the 3CR manifold, using the reaction of ethyl 2-cyanoacetate (**3a**), benzaldehyde (**4a**) and nitroethane (**5a**) as a working model (see SI, Schemes S1-S2 for reaction design, and Table S1 for optimization). The optimized reaction conditions called for the combined use of Schreiner’s thiourea **12**^[11] (10 mol%; H-bond directed catalysis) and *N,N*-dimethylcyclohexylamine (**13**) (10 mol%; nitronate ion formation) as catalysts to deliver the mixture of γ -nitronitriles **6a-syn,syn**,^[12] **6a-syn,anti** and **6a-anti,syn** in excellent yield (95%) and modest diastereoselectivity (dr: 1:07:0.8 respectively) (Scheme 2). Fortunately, the diastereomer **6a-anti,syn**^[13] (30%) could be isolated from the crude isomeric mixture by simple flash chromatography, whereas the unresolved mixture of diastereomers **6a-syn,syn**/**6a-syn,anti** could be quantitatively transformed into a single diastereomer **6a-syn,syn** (65%) by diastereoconvergent crystallization^[14] of the mixture (see Schemes 2 and S3). In terms of sustainability, the reaction could be carried out on a 20 mmol scale using a reduced charge of thiourea (5 mol%) without a decrease in the reaction yield (95%), but with a slight loss in diastereoselectivity (dr: 1:0.4:1).

Scheme 2. Synthesis of γ -nitronitriles **6a**.

Once the 3CR was optimized, we studied its scope with respect to the aldehyde and the nitroalkane (Table 1). In general, the 3CR was tolerant with both the electronic nature of the aromatic aldehyde (**6a-d**, **6h-i**) and the size of the primary nitroalkane (**6j-k**). Except for **6h** and **6i**, all the other γ -nitronitriles were efficiently resolved into their corresponding *syn,syn* (major) and *anti,syn* (minor) diastereomers. The complete *syn,syn*-selectivity observed for γ -nitronitrile **6k** (74%) was remarkable when compared with **6j** (dr:~2:1): a simple two methylene elongation in the alkyl chain of the nitroalkane was enough to funnel the reaction toward the formation of the diastereomer **6k-anti,syn** (74%). Unfortunately, 1-naphthaldehyde (**4e**) and biphenyl aldehyde **4f** were not good substrates for the reaction. Finally, the use of bromonitromethane (**5d**) afforded the

cyclopropane **14**^[15] (74%, unique isomer. It was ratified by tandem reduction and acetylation of the corresponding alcohol. See SI for additional details). This last example, although beyond of the aim of this work, highlights the complexity generation power of this 3CR. Although irrelevant for this work, it should be noted that when the 3C-KMAR was performed in organic solvents, lower yields and inverted stereoselectivity (the *anti,syn*-diastereomer is the major diastereomer) were observed. (see SI for a mechanistic proposal for the 3C-KMAR manifold).

Table 1. Scope of the multicomponent manifold.^[a]

^[a]Yields refer to isolated products. ^[b]The *syn,syn/syn,anti* mixture could not be resolved by diastereoisomeric crystallization. ^[c] H₂O-NaAcO (2M, pH 7)

Stereodiversified synthesis of *N*-hydroxylamidines.

With the two series of γ -nitronitriles **6** in hand, we studied their transformations into *N*-hydroxylamidines **7**. We explored several reducing systems using γ -nitronitrile **6a-syn,syn** as model (see SI, Table S3 for the search of conditions), to find that only the medium-pressure hydrogenation (5 bar) over Pd/C (10 mol%) in ethanol was able to provide **7a-cis,cis**^[16] in a reproducible and efficient manner (69%) (Table 2). Under these conditions, the diastereomer **6a-anti,syn** was also cleanly transformed into *N*-hydroxylamidine **7a-cis,trans** (78%). From this point, the synthetic route was

carried out transforming each series of γ -nitronitriles **6** separately (branching, stereo-differentiating phase). The transformation proved to be general for both series of γ -nitronitriles (Table 2), with the only exception of **6k**, which could not be transformed into **7k**.^[17] In general, γ -nitronitriles **6-anti,syn** were better substrates for this transformation than **6-syn,syn**. Interestingly, the mixture of **6i-syn,syn** and **6i-syn,anti** (dr: 1.7:1) was collectively transformed into a unique **7i-cis,cis** diastereomer in 68% yield, making unnecessary a previous resolution (although the standardized protocol entailed the previous crystallographic resolution of both diastereomers, this was not necessary as the reductive cyclization was in all cases diastereoselective, affording a unique diastereomer).

Table 2. Synthesis of *N*-hydroxylamidines **7**.

Radical reactivity profile: the auto-oxidation manifold. During the course of these studies, we discovered that *N*-hydroxylamidines **7** experienced auto-oxidation processes when they were kept in solution in contact with air, generating the corresponding C₃-hydroxyl derivatives (Table 3).^[18] The reaction of organic molecules with ³O₂ usually requires the use of metal catalysis,^[19] or in some instances, the mediation of nitroxyl radicals.^[20] The observed auto-oxidation in the absence of metals, allowed us to assume the mediation of a unprecedented *N*-amidinoxyl radical such as **7-NR**^[21a] in these processes (Scheme 3a). Interestingly, the auto-oxidation was totally inhibited by *O*-methylation of the *N*-hydroxylamidine, but it was still operative under strict anaerobic conditions (oxygen atom transfer), confirming the mediation of a nitroxyl radical (Scheme 3b). The novelty of these *N*-

hydroxylamides as nitroxyl radical precursors, the greenness associated to the use of O₂ (g) as oxidant and the potential interest of the generated C₃-hydroxylated derivatives prompted us to search for a practical and robust protocol for this reaction. Fortunately, it could be established and involved the irradiation with blue LED light^[21b] of a solution of *N*-hydroxylamide in acetonitrile for 24 h and under an O₂ atmosphere (balloon) (See SI, Table S4 for optimization).^[22] Under these conditions, both series of *N*-hydroxylamides **7** were efficiently auto-oxidized to their corresponding 3-hydroxyl derivatives with a clear predominance of the α -isomer (O₂ approaches by the opposite face of the phenyl group).^[23] (Table 3). The observed face selectivity takes value when the size of the ring, the radical nature of the process and the small size of the reactant are considered. The reaction proved to be general for the two series of *N*-hydroxylamides **7**,

Table 3. Scope of the auto-oxidation reaction.

7 **A** or **B** **3 -OH-7**

A(aerobic): LED (blue), O_2 (g), MeCN, RT., 16 h.

B (stoichiometric): MCPBA (1.1 equiv), CH_2Cl_2 , 0 °C to RT, 2h.

3 -OH-7a-cis,cis ^[a]
(A: 82%; α/β : 7:1)
(B: 98%; α/β : $\geq 20:1$)

3 -OH-7a-cis,cis

3 -OH-7a-cis,trans
(A: 87%; α/β : 6:1)
(B: 87%; α/β : 3:1)

3 -OH-7c-cis,cis
(A: 76%; α/β : 7:1)
(B: 99%; α/β : $\geq 20:1$)

3 -OH-7c-cis,trans
(A: 99%; α/β : 4:1)
(B: 98%; α/β : 2.5:1)

3 -OH-7d-cis,cis
(A: 85%; α/β : 10:1)
(B: 93%; α/β : $\geq 20:1$)

3 -OH-7d-cis,trans
(A: 82%; α/β : 3:1)
(B: 82%; α/β : 1.5:1)

3 -OH-7g-cis,cis
(A: 79%; α/β : 1.5:1)
(B: 93%; α/β : 1.6:1)

3 -OH-7g-cis,trans
(A: 92%; α/β : 1.4:1)
(B: 93%; α/β : 4:1)

3 -OH-7i-cis,cis
(A: 79%; α/β : 13:1)
(B: 89%; α/β : $\geq 20:1$)

3 -OH-7i-cis,trans
(A: 88%; α/β : 4:1)
(B: 81%; α/β : 2:1)

affording the corresponding tertiary alcohols with good average yields (85%) and diastereoselectivity as high as 13:1. Interestingly, the stereochemical outcome of the reaction was comparable to that of the oxidation with meta-chloroperbenzoic acid (ionic), although the latter showed better diastereoselectivity towards the α -epimer (Table 3, method B).

Mechanism of auto-oxidation. With regard to the mechanism of this auto-oxidation reaction, we postulate the radical process outlined in Scheme 3a, which is initiated by the *N*-amidinoxyl radical **7-NR**^[21] and propagated by the C-radical **7-CR**. Density Functional Theory calculations support this mechanism (see Figures S2-S3 for computational details). Irradiation with blue LED light facilitates the formation of **7-NR** and in turn, the initiation of the radical process (in the absence of irradiation, this step is less efficient and the reaction needs 48 h to be completed). The process goes forward through the formation of a stable (persistent, tertiary) and electrophilic (conjugated) C-centred radical **7-CR** via an endergonic hydrogen atom transfer (HAT) ($\Delta G \sim 2$ kcal/mol; $\Delta G^\ddagger \sim 28$ kcal/mol) (step ii). In spite of the endergonicity of this HAT step, the subsequent highly exergonic reaction with ³O₂ to finally form **3 α -OH-7** drives the transformation forward (see Figure S3). Thus, once **7-CR** forms, it reacts with the ³O₂ to generate the peroxy radical **7-PR** (step iii). Although the rate for the reaction of oxygen with alkyl radicals is usually fast and diffusion controlled,^[24] some stabilized radicals can coexist in equilibrium with the peroxy radical generated in the reaction.^[25] This is the case of **7-CR** which is stable (tertiary, conjugated) and electrophilic (conjugated), and reacts with **7-PR** to generate the peroxide **7-SP** (step iv). The possible dimerization of the own peroxy radical **7-PR** to generate the corresponding tetraperoxide is an inherently slow reaction in the case of tertiary radicals (i.e., 10³-10⁴ M⁻¹s⁻¹), and much slower in this case, considering the low value of the peroxide radical concentration.

Once the symmetrical peroxide **7-SP** forms, it decomposes to generate two units of radical **7-AR** (step v), which progresses towards the final oxidation product by a highly favoured HAT with *N*-hydroxylamide **7**, to generate **3 α -OH-7** and a new unit of **7-CR** to reinitiate the cycle (step vi). It must be noted that this HAT is highly favoured because it forms a strong OH bond (BDE = 105 kcal/mol) at the expense of a much weaker tertiary C-H bond (for a simple tertiary alkyl radical, BDE = 90-92 kcal/mol). Theoretical calculations supported the exergonic nature of this HAT (ΔG : ~ -40 kcal/mol for both series) and assigned the highest reaction barrier to the step v, the homolytic cleavage of dimer **7-SP** ($\Delta G^\ddagger_{cis,cis}$: 29.7 kcal/mol; $\Delta G^\ddagger_{cis,trans}$: 25.4 kcal/mol). When the reaction was performed in the presence of TEMPO, the yield dropped considerably. This result seems to confirm the presence of a radical mechanism. Unfortunately, we were unable to isolate

coupling products with TEMPO and the intermediate radicals. In fact, the ^1H NMR of the reaction crudes were complex and we were unable to get practical information from them.

Scheme 3. Radical mechanism for the auto-oxidation.

Under anaerobic conditions, the C-radical **7-CR** accumulates in the reaction medium and reacts with the nitroxyl radical to give the **7,7-NOC** intermediate (Scheme 3b). The homocoupling reaction of radical **7-CR** to give the symmetrical dimer **7,7-CC** should be very slow (two stable and tertiary radicals) and should not compete with the heterocoupling reaction. Once the dimer **7,7-NOC** forms, it decomposes to deliver the final product **3α-OH-7**. The pathway of this decomposition is unknown. The reactions were not clean, and unfortunately, we were not able to detect or isolate other species in these reactions besides the own **3α-OH-7**. Overall, the anaerobic process constitutes a net oxygen transfer process, which utilizes two molecules of *N*-hydroxylamine **7** to transfer one atom of oxygen. The process is not atom economical, and consumes 2 moles of **7** for each mol of **3α-OH-7** generated.

Ionic radical profile: the C-C bond-forming manifold. We next explored the extension of this radical platform to C-C bond forming processes with the aim to generate a quaternary centre at the C₃-position of the ring. We hoped that under strict anaerobic conditions, the electrophilic C-radical **7-CR** could be trapped with nucleophilic radical acceptors to deliver the corresponding C₃-alkylated

products. With this idea in mind, we reacted **7a-cis,cis** with methyl vinyl ether and styrene under blue LED light irradiation and strict anaerobic conditions (see Table S6). Unfortunately, the radical proved to be unreactive even in the presence of a large excess of alkene. Unexpectedly, we observed a net reaction with electrophilic acceptors (e.g., methyl vinyl ketone (MVK) or ethyl acrylate) to give the corresponding C₃-alkylated products **8** (Table 4). Because these results were not consistent with the electronic mismatching between radical and acceptor, the observed reactivity was rationalized assuming an ionic process mediated by the enamine tautomer of the *N*-hydroxylamine (**7a-en**, Table 4). Thus, we explored the synthetic scope of this C-C bond forming manifold, eliminating the LED irradiation but maintaining strict anaerobic conditions (Table 4). The reaction proved to be general for *N*-hydroxylamines **7-cis,cis**, providing the 3α-alkylated products **8** with good average yield (~80%) and excellent diastereoselectivity (dr: ≥ 20:1). Overall, the reaction constitutes an efficient manoeuvre for the selective generation of an all-carbon quaternary centre in the ring, incorporating an alkyl chain endowed with different chemical handles (e.g., ester, nitrile, ketone or sulfone) for further manipulation. Interestingly, trifluoroethyl acrylate afforded the bicyclic lactam **20** (98%; dr: ≥ 20:1), extending the reaction outcome to bicyclic motives based on the 2,9-diazabicyclo[4.3.0]non-1-en core.^[26]

Table 4. Scope of the C-C bond-forming manifold.

^[a] Alkene (12 equiv.), 24 h. ^[b] Alkene (12 equiv.), 48 h. ^[c] 4h.

Surprisingly, *N*-hydroxylamine **7a-cis,trans** proved to be less reactive and only reacted with MVK and

acrolein to generate the corresponding diazabicycles **9a** and **9b**, (Scheme 4). The diminished reactivity of this *N*-hydroxylamine required a large excess of MVK (12 equiv.) and 16 h in acetonitrile to afford synthetically useful amounts of **9a** (51%, dr: 2:1) and **3 α -OH-7a-*cis,cis*** (20-25%) (anaerobic oxidation).^[27] The use of ethanol as solvent, which favours the enamine form of **7** (see SI for details), did not improve the efficiency of the reaction with MVK but it was an excellent solvent for the reaction with acrolein, which required a lower amount of acceptor (2 equiv.) and a shorter reaction time (4 h) to generate **9b** (80%, unique diastereomer), incorporating a molecule of ethanol into the final structure and a new stereogenic centre (Scheme 4).^[28] The observed different outcomes can be explained assuming that **9a** forms by cyclization of **21**, whereas **9b** comes from the cyclization of diethyl-acetal **22**. In this latter case, it is illustrative to observe how the relative configuration of the ring substituents determines the feasibility of the cyclization, being allowed for the *cis,trans* series but constrained for the *cis,cis* (compare **8a** and **21**). The high reactivity of the trifluoroethyl ester function overcomes this constraint (compare **9b** and **20**).

Scheme 4. The reaction of *N*-hydroxylamine **7a-*cis,trans*** with π -acceptors.

Generation of non-planar 5-membered amidines. Finally, we explored the transformation of these fully substituted *N*-hydroxylamines into the corresponding amidines. In this exploration, we used the *N*-hydroxylamines **3 α -OH-7a-*cis,cis*** and **8b-*cis,cis*** as representative examples of 3-hydroxylated and 3-alkylated *N*-hydroxylamines, respectively. After exploring different reaction conditions, we arrived to TiCl_3 , which proved to be an excellent reducing agent providing the corresponding amidines **10** and **11** in excellent yields (Scheme 5)

Conclusion

In summary, we have developed a modular and stereodiversified methodology to construct non-planar cyclic *N*-hydroxylamines **7**. The protocol uses an aqueous 3CR to construct two diastereomeric series of 2-cyano-3-aryl-4-nitro-alkynoate platforms

Scheme 5. Transformation of *N*-hydroxylamines into amidines.

(i.e., **6-*syn, syn*** and **6-*anti, syn***) which were separately transformed into the corresponding cyclic *N*-hydroxylamines **7**. The dual reactivity encoded into these structures allowed their diastereoselective ring functionalization at the C₃-position (quaternary centre). This was achieved by a robust auto-oxidation protocol mediated by an unprecedented *N*-amidinoxyl radical (radical reactivity; C₃-oxidation; tertiary alcohol), or by a practical enamine-based C-C bond forming reaction (ionic reactivity; C₃-alkylation; all-carbon quaternary centre). The outcome of this latter reaction was strongly dependent of the relative stereochemistry of the ring substituents, affording quaternized 5-membered cyclic *N*-hydroxylamines **8** (series *cis,cis*) or diazabicycles **9** (series *cis,trans*). Finally, it was demonstrated that the Ti(III) reduction of these fully substituted 5-membered *N*-hydroxylamines generates the corresponding amidines in excellent yields. The full scope of this methodology and its application to the synthesis of other important pharmacophores (e.g., 1,2,4-oxadiazoles)^[29] from these scaffolds is in progress in our lab.

Experimental Section

¹H NMR and ¹³C NMR spectra were recorded either at 400 and 100 MHz or at 500 and 125 MHz (Bruker Ac 200 and AMX2-500), respectively. FT-IR spectra were measured in chloroform solutions using a Perkin Elmer FT-IR Spectrum BX spectrophotometer. Mass spectra (low resolution) (EI/CI) were obtained with a Hewlett-Packard 5995 gas chromatograph/mass spectrometer. High-resolution mass spectra were recorded with a Micromass Autospec mass spectrometer. Microanalyses were performed with a Fisons Instruments EA 1108 carbon, hydrogen, and nitrogen analyzer. Analytical thin-layer chromatography plates used were E. Merck Brinkman UV-active silica gel (Kieselgel 60 F254) on aluminium. Flash column chromatography was carried out with E. Merck silica gel (particle size: <0.020 mm or 0.063-0.200 mm) using appropriate mixtures of ethyl acetate and hexanes, hexanes and dichloromethane or dichloromethane and methanol as eluents. Size exclusion chromatography was carried out using Sephadex LH-20 (Pharmacia Fine Chemical). All reactions were performed in oven-dried glassware. All materials were obtained from commercial suppliers and used as received.

General procedure for the synthesis of γ -nitronitriles **6.** In a 25 mL round-bottomed flask equipped with a stirring bar was placed distilled water (15 mL). While stirring at 200 r.p.m. at room temperature, aldehyde **4** (1.4 mmol), ethyl-2-cyanoacetate (**3**) (1.4 mmol), nitroalkane **5** (2.8 mmol), thiourea **12** (10 mol%) and *N,N*-dimethylcyclohexylamine (**13**) (10 mol%) were sequentially added, in this order, to generate a biphasic system. The stirring was increased to 1200 r.p.m. and the

biphasic system broke into a multitude of small hydrophobic drops. The reaction mixture was left under these conditions for 16 h more and then was extracted with CH₂Cl₂ (2x10 mL) and the combined organic extracts were dried over sodium sulphate, filtered and the filtrate concentrate to give the crude γ -nitronitriles **6** as a mixture of diastereomers (yellow oil). Flash chromatography of the crude residue (gradient eluent from 95/5 to 85/15 v/v of n-hexanes/ethyl acetate) delivered the reaction products in two bands: a less polar band corresponding to the **6-anti,syn** diastereomer and a more polar band formed by the mixture of **6-syn,syn/syn,anti** isomers. Diastereoconvergent crystallization of the more polar band delivered the **6-syn,syn** isomer pure.

(±) **Ethyl (2S,3S,4R)-2-cyano-4-nitro-3-phenylpentanoate (6a-syn,syn)**. Following the general procedure: 251 mg, 65%; crystalline solid, m.p. 74 - 75 °C (EtOAc/Hexanes); ¹H NMR (400 MHz, C₆D₆): δ 7.20-7.18 (m, 2H), 6.95-6.88 (m, 3H), 4.90 (dq, J = 9.7, 6.7 Hz, 1H), 3.64-3.56 (m, 3H), 3.26 (d, J = 6.2 Hz, 1H), 0.92 (d, J = 6.6 Hz, 3H), 0.59 ppm (t, J = 7.1 Hz, 3H); ¹³C NMR (100 MHz, C₆D₆): δ 164.6, 134.6, 129.8, 129.7 (2C), 129.3 (2C), 115.1, 85.4, 63.4, 49.5, 40.6, 17.8, 14.1 ppm; IR (CHCl₃): ν 3030, 2988, 2251, 1747, 1560, 1261 cm⁻¹; HRMS (ESI⁺): m/z calcd for C₁₄H₁₆N₂O₄Na [M+Na]: 299.1008; found: 299.1009; elemental analysis calcd (%) for C₁₄H₁₆N₂O₄: C 60.86, H 5.84, N 10.14; found: C 60.86, H 5.75, N 9.

(±) **Ethyl (2S,3S,4S)-2-cyano-4-nitro-3-phenylpentanoate (6a-anti,syn)**. Following the general procedure: 116 mg, 30%; crystalline solid, m.p. 107 - 108 °C (EtOAc/Hexanes); ¹H NMR (400 MHz, C₆D₆): δ 7.04-7.01 (m, 2H), 6.92-6.91 (m, 3H), 4.85 (dq, J = 11.3, 6.6 Hz, 1H), 3.66 (dd, J = 11.2, 4.8 Hz, 1H), 3.50 (q, J = 7.1 Hz, 2H), 3.30 (brd, J = 4.7 Hz, 1H), 0.72 (d, J = 6.6 Hz, 3H), 0.55 ppm (t, J = 7.1 Hz, 3H); ¹³C NMR (100 MHz, C₆D₆): δ 164.3, 134.2, 129.7 (4C), 129.6, 115.1, 85.1, 63.1, 49.6, 41.8, 18.7, 14.0 ppm; IR (CHCl₃): ν 3029, 2987, 2251, 1748, 1557, 1259 cm⁻¹; HRMS (ESI⁺): m/z calcd for C₁₄H₁₆N₂O₄Na [M+Na]: 299.1008; found: 299.1002; elemental analysis calcd (%) for C₁₄H₁₆N₂O₄: C 60.86, H 5.84, N 10.14; found: C 60.80, H 5.87, N 9.89.

Scaling of the multicomponent reaction. In a 250 mL round-bottomed flask equipped with a stirring bar was placed distilled water (130 mL). While stirring at 200 r.p.m. and room temperature, benzaldehyde (**4a**) (2.04 mL, 20 mmol), ethyl-2-cyanoacetate (**3**) (2.50 mL, 20 mmol), nitroethane (**5a**) (2.80 mL, 40 mmol), thiourea **12** (500 mg, 1 mol, 5 mol%) and *N,N*-dimethylcyclohexylamine (**13**) (0.3 mL, 2 mmol, 10 mol%) were sequentially added, in this order, to generate a biphasic system. The stirring was increased to 1200 r.p.m. to transform the biphasic system into an aqueous emulsion. The reaction mixture was left under these conditions for 16 h more and then was extracted with CH₂Cl₂ (2x150 mL) and the combined organic extracts were dried over sodium sulfate, filtered and the filtrate concentrate to give the crude γ -nitronitrile **6a** (5.5 g, $\geq$ 95% yield) as a diastereomeric mixture (dr: 1:0.4:1). Flash chromatography of the crude residue (gradient eluent from 95/5 to 85/15 v/v of n-hexanes/ethyl acetate) delivered the reaction products in two bands: less polar band: **6a-anti,syn** diastereomer (2.3 g, 41%); more polar band: mixture of **6a-syn,syn/syn,anti** isomers (3.2 g, 58%; dr: 1:0.4). Quantitative diastereoconvergent crystallization of the more polar band delivered the **6a-syn,syn** isomer pure (3.2 g, 58%).

General procedure for the synthesis of *N*-hydroxylamides **7.** To a solution of γ -nitronitrile **6** (1 equiv.) in ethanol (15 mL) was added Pd/C (10%) (0.4 mg/mg substrate) and the heterogeneous mixture was stirred at room temperature under a hydrogen atmosphere (5 bar) for 16 h. The reaction mixture was filtered on a plug of celite under an atmosphere of N₂. The celite was exhaustively washed with ethanol and the combined filtrates were concentrated at reduced pressure in the rotary evaporator, keeping the bath temperature below 30 °C

(otherwise, the product decomposes). Flash chromatography on silica gel (0.063-0.200 mm) eluting with methylene chloride / methanol (gradient eluent from 95:5 to 90:10 v/v) under a positive nitrogen atmosphere delivered pure *N*-hydroxylamides **7**.

(±) **Ethyl (3R,4R,5S)-4-phenyl-1-hydroxyl-2-imino-5-methylpyrrolidine-3-carboxylate (7a-cis,cis)**. Following the general procedure: 142.1 mg; 69%; foam; ¹H NMR (400 MHz, CDCl₃): δ 7.36-7.29 (m, 3H), 7.14 (brd, J = 6.9 Hz, 2H), 5.75 (brs, 2H), 4.33-4.26 (m, 1H), 4.20 (q, J = 7.1 Hz, 2H), 4.08 (app. triplet, J = 7.8 Hz, 1H), 4.03 (brd, J = 6.0 Hz, 1H), 1.23 (t, J = 7.1 Hz, 3H), 1.00 ppm (d, J = 6.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 168.5, 142.6, 136.9, 129.1 (2C), 128.6, (2C), 128.1, 66.1, 62.8, 49.6, 44.2, 14.8, 14.4 ppm; IR (CHCl₃): ν 3494, 3371, 3033, 2966, 1732, 1685, 1262, 1189, 1094 cm⁻¹; HRMS (ESI⁺): m/z calcd for C₁₄H₁₈N₂O₃Na [M+Na]: 285.1215; found: 285.1220.

(±) **Ethyl (3R,4R,5R)-4-phenyl-1-hydroxyl-2-imino-5-methylpyrrolidine-3-carboxylate (7a-cis,trans)**. Following the general procedure: 148.2 mg; 78%; foam; ¹H NMR (400 MHz, CDCl₃): δ 7.36-7.29 (m, 3H), 7.26-7.24 (m, 2H), 5.75 (brs, 2H), 4.21 (brq, J = 6.9 Hz, 2H), 3.99-3.96 (m, 1H), 3.81 (brd, J = 7.8 Hz, 1H), 3.40 (appt, J = 7.4 Hz, 1H), 1.47 (brd, J = 5.9 Hz, 3H), 1.25 ppm (brt, J = 7.0 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 168.6, 143.0, 139.6, 129.3 (2C), 128.0 (3C), 69.2, 62.6, 52.2, 48.7, 17.8, 14.3 ppm; IR (CHCl₃): ν 3494, 3371, 3033, 2986, 2938, 1732, 1685, 1273, 1184, 1096 cm⁻¹; HRMS (ESI⁺): m/z calcd for C₁₄H₁₈N₂O₃Na [M+Na]: 285.1215; found: 285.1213.

General procedure for the auto-oxidation of *N*-hydroxylamide **7 (Method A).** In a 25 mL round-bottomed flask were placed *N*-hydroxylamide **7** (1.0 equiv.) dissolved in acetonitrile (10 mL) and the solution was stirred under continuous irradiation with blue LED for 24 h at room temperature. The reaction mixture was concentrated at reduced pressure and the oxidation product was purified by flash chromatography on silica gel (0.063-0.200 mm) using methylene chloride / methanol as eluent (gradient eluent from 90:10 to 80:20 v/v).

General procedure for the oxidation of *N*-hydroxylamide **7 with meta-chloroperbenzoic acid (Method B).** To a cooled (ice-water bath, 0 °C) solution of *N*-hydroxylamide **7** (1.0 equiv.) in methylene chloride (10.0 mL/ mmol) was added *m*-chloroperbenzoic acid portion-wise (1.1 equiv.) and the resulting reaction mixture was allowed to stir at this temperature for a few minutes. The ice bath was retired and the reaction mixture was stirred for 2h. The reaction mixture was concentrated at reduced pressure and the oxidation product was purified by flash chromatography on silica gel (0.063-0.200 mm) using methylene chloride / methanol as eluent (gradient eluent from 90:10 to 80:20 v/v).

(±) **Ethyl (3S,4R,5S)-1,3-dihydroxy-2-imino-5-methyl-4-phenylpyrrolidine-3-carboxylate (3 α -OH-7a-cis,cis)**. Following the general procedure: method A: 74.9 mg, 82%, mixture of diastereomers (dr: 7:1; calculated by ¹H NMR analysis of the mixture); amorphous solid; method B: 41.5 mg; 98% (dr: $\geq$ 20:1). ¹H NMR (400 MHz, MeOD): δ 7.34-7.32 (m, 3H), 7.18-7.15 (m, 2H), 4.47 (app. quintet, J = 7.0 Hz, 1H), 4.06-3.90 (m, 2H), 3.78 (d, J = 7.2 Hz, 1H), 1.23 (d, J = 6.9 Hz, 3H), 1.00 ppm (t, J = 7.1 Hz, 3H); ¹³C NMR (100 MHz, MeOD): δ 171.0, 152.8, 136.2, 131.9 (2C), 130.2 (2C), 130.0, 84.2, 65.5, 64.0, 57.6, 14.8, 14.7 ppm; IR (nujol): ν 3420, 3295, 3247, 1733, 1677, 1586, 1254, 1202, 1070 cm⁻¹; HRMS (ESI⁺): m/z calcd for C₁₄H₁₈N₂O₄Na [M+Na]: 301.1164; found: 301.1161; elemental analysis calcd (%) for C₁₄H₁₈N₂O₄: C 60.42, H 6.52, N 10.07; found: C 60.84, H 6.66, N 9.96.

(±) **Ethyl (3S,4R,5R)-1,3-dihydroxy-2-imino-5-methyl-4-phenylpyrrolidine-3-carboxylate (3 α -OH-7a-cis,trans)**.

Following the general procedure: method **A**: 92.4 mg, 87%, mixture of diastereomers (dr: 9:1; calculated by ^1H NMR analysis of the mixture); amorphous solid; method **B**: 102.0 mg; 87%, mixture of diastereomers (dr: 3:1). ^1H NMR (400 MHz, MeOD) major diastereomer: δ 7.40-7.28 (m, 5H), 4.50 (dq, J = 8.9, 6.4 Hz, 1H), 4.03-3.89 (m, 2H), 3.37 (d, J = 9.0 Hz, 1H), 1.49 (d, J = 6.4 Hz, 3H), 1.07 ppm (t, J = 7.1 Hz, 3H); characteristic signals of the minor diastereomer: δ 4.36 (q, J = 7.1 Hz, 2H), 4.32-4.29 (m, 1H), 3.48 (d, J = 7.9 Hz, 1H), 1.42 (d, J = 6.3 Hz, 3H), 1.36 ppm (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, MeOD) major diastereomer: δ 170.7, 152.0, 135.3, 130.6 (2C), 130.2 (2C), 130.1, 83.9, 64.7, 64.4, 60.6, 18.1, 14.9 ppm; characteristic signals of the minor diastereomer: δ 172.3, 151.5, 135.2, 131.9 (2C), 130.3 (2C), 130.0, 81.3, 67.6, 58.4, 58.3, 17.8, 15.2 ppm; IR (nujol): ν 3322, 3265, 3149, 2985, 2938, 1740, 1702, 1603, 1303, 1133 cm^{-1} ; HRMS (ESI $^+$): m/z calcd for $\text{C}_{14}\text{H}_{19}\text{N}_2\text{O}_4$ [M^+]: 297.1345; found: 279.1350.

General procedure for the C-alkylation of *N*-hydroxylamidines **7.** A solution of *N*-hydroxylamidine **7** (1.0 equiv.) in acetonitrile (10.0 mL/mmol) was degassed by immersion of the reaction flask in liquid N_2 . Once the solution was completely frozen, the reaction flask was opened to the vacuum (high vacuum) and pumped 2-3 minutes, keeping the flask immersed in liquid N_2 . The flask was charged with N_2 gas and allowed to warm until the solution was completely melted. The process was repeated three times. Then, the conjugated alkene was added (from 2 to 12 equiv. depending on the alkene). The reaction mixture was allowed to stir at room temperature and darkness until total disappearance of the starting material (from 2 to 48 h depending of the alkene). The reaction mixture was concentrated under reduced pressure and the residue was flash chromatographed on silica gel (0.063-0.200 mm) eluting with methylene chloride – methanol 90:10 v/v .

($\pm$) **Ethyl (3R,4S,5S)-1-hydroxy-2-imino-5-methyl-3-(3-oxobutyl)-4-phenylpyrrolidine-3-carboxylate (8a)**. Following the general procedure: methyl vinyl ketone (43 μL , 0.54 mmol), *N*-hydroxylamidine **7a-cis,cis** (70 mg, 0.27 mmol), 2h. **8a** (foam solid): 80.2 mg, 90%, (dr: $\geq 20:1$; calculated by ^1H NMR analysis of the mixture); ^1H NMR (400 MHz, CDCl_3): δ 7.24-7.22 (m, 3H), 6.99-6.97 (m, 2H), 5.86 (brs, 1H), 4.38 (app. quintet, J = 6.7 Hz, 1H), 3.72 (app. dq, J = 7.2, 1.6 Hz, 2H), 3.44 (d, J = 6.5 Hz, 1H), 2.84 (ddd, J = 17.5, 10.2, 5.5 Hz, 1H), 2.48-2.27 (m, 3H), 2.15 (s, 3H), 1.02 (d, J = 6.8 Hz, 3H), 0.69 ppm (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 206.6, 171.2, 147.6, 137.1, 128.8 (4C), 128.2, 63.3, 61.8, 58.2, 53.6, 39.2, 30.9, 30.4, 13.5 (2C) ppm; IR (CHCl_3): ν 3464, 3355, 2967, 2929, 2853, 1721, 1666, 1259, 1093 cm^{-1} ; HRMS (ESI $^+$): m/z calcd for $\text{C}_{18}\text{H}_{24}\text{N}_2\text{O}_4\text{Na}$ [M^+Na]: 355.1634; found: 355.1638; elemental analysis calcd (%) for $\text{C}_{18}\text{H}_{24}\text{N}_2\text{O}_4$: C 65.04, H 7.28, N 8.43; found: C 65.20, H 7.24, N 8.26.

Reductive transformation of *N*-hydroxylamidines into amidines. General procedure.^[30] To a stirred solution of *N*-hydroxylamidine (1.0 equiv.) in methanol-water (1:1 v/v) (15.0 mL/mmol) was added NaOAc (12 equiv.) under a N_2 atmosphere. Then, a 20% solution of TiCl_3 in aqueous 2% HCl (2-4 equiv.) was added drop wise and the reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was concentrated under reduced pressure and the resulting extract was purified by flash chromatography on Shephadex, using a mixture of methylene chloride – methanol (90:10 v/v) as eluent. The progress of the chromatography was monitored by TLC, using ninhydrin as the developing reagent.

($\pm$) **Ethyl (3S,4R,5S)-3-hydroxy-2-imino-5-methyl-4-phenyl-1 λ^2 -pyrrolidine-3-carboxylate (10)**. Following the general procedure: **10** (gummy): 17.2 mg, 91%, ^1H NMR (400 MHz, CDCl_3): δ 7.34-7.32 (m, 3H), 7.16-7.14 (m, 2H), 4.57-4.50 (m, 1H), 4.09-3.94 (m, 2H), 3.82 (d, J = 7.0 Hz, 1H), 1.17 (d, J = 6.8 Hz, 3H), 0.99 ppm (t, J = 7.1

Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 170.4, 170.0, 135.2, 131.9 (2C), 130.4 (2C), 130.3, 85.6, 64.4, 59.9, 59.0, 17.2, 14.7 ppm; IR (CHCl_3): ν 3409, 3033, 2985, 1738, 1704, 1261, 1095 cm^{-1} ; HRMS (ESI $^+$): m/z calcd for $\text{C}_{14}\text{H}_{19}\text{N}_2\text{O}_3$ [M^+]: 263.1396; found: 263.1398.

($\pm$) **Ethyl (3R,4S,5S)-3-(3-ethoxy-3-oxopropyl)-2-imino-5-methyl-4-phenylpyrrolidine-3-carboxylate (11)**. Following the general procedure: **11** (gummy): 40.5 mg, 85%, ^1H NMR (400 MHz, CDCl_3): δ 7.76 (brs, 1H), 7.29-7.28 (m, 3H), 6.97-6.94 (m, 2H), 4.49-4.43 (m, 1H), 4.15 (qd, J = 7.1, 1.9 Hz, 2H), 3.89-3.82 (m, 1H), 3.79-3.71 (m, 1H), 3.47 (d, J = 5.8 Hz, 1H), 2.57-2.35 (m, 4H), 1.27 (t, J = 7.1 Hz, 3H), 0.97 (d, J = 6.7 Hz, 3H), 0.68 ppm (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 171.5, 170.1, 169.6, 135.8, 129.0 (2C), 128.4, 128.3 (2C), 62.4, 61.4, 61.0, 56.0, 55.9, 31.6, 29.9, 16.0, 14.3, 13.3 ppm; IR (CHCl_3): ν 3409, 3019, 2981, 1732, 1684, 1230, 1191 cm^{-1} ; HRMS (ESI $^+$): m/z calcd for $\text{C}_{19}\text{H}_{26}\text{N}_2\text{O}_4$ [M^+]: 347.1971; found: 347.1972.

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