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Article

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An Aminocatalyzed Michael Addition/Iron-mediated Decarboxylative Cyclization Sequence for the Preparation of 2,3,4,6-Tetrasubstituted Pyridines: Scope and Mechanistic Insights

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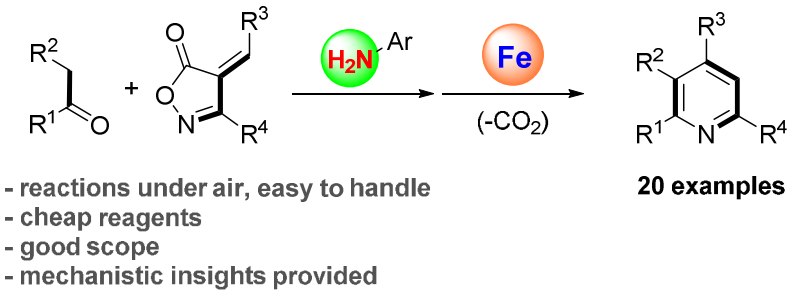


Abstract. A novel, scalable strategy for the preparation of 2,3,4,6-tetrasubstituted pyridines is described. This protocol has two steps: an aminocatalyzed addition of ketones to alkylidene isoxazol-5-ones, followed by an iron-mediated decarboxylative cyclization event. Mechanistic insights for both steps are provided based on HRMS-ESI(+) studies.

Keywords: Pyridines; Isoxazolones; Organocatalysis; Iron; Mass-spectrometry

Introduction

The pyridine heterocycle is an aromatic motif found in numerous alkaloids,[1] pharmaceuticals,[2] agrochemicals,[3] chiral ligands,[4] and materials,[5] often present in R&D programs. Therefore, perhaps not surprisingly, synthetic approaches leading to this heteroaromatic nucleus are abundant. These approaches generally rely on condensation reactions of amines with carbonyl compounds,[6]

cycloisomerizations[7] and cycloadditions,[8] among others,[9] via the employment of a variety of substrates and promoters.

Despite the tremendous advances in the field, the regioselective preparation of these molecules is still challenging. In this context, numerous solutions have been described employing O-acetyl oximes as precursors, in the presence of a variety of partners, so that often a N-O bond cleavage event can be mediated by catalytic amounts of Cu,[10] Pd,[11] Fe,[12] Ru,[13] or iodine,[14] thus triggering the cyclization step toward the corresponding pyridines. Other powerful protocols involving α,β-unsaturated ketoximes and olefins, or alkynes, have also been described employing Rh-[15] and Cu-catalysts.[16]

Although structurally similar to O-acetyl oximes, isoxazol-5-ones have been much less frequently employed in similar transformations. This is somehow surprising, because the presence of an active methylene in the cyclic structure of the isoxazol-5-one ring allows prior α-functionalizations, such as alkylation protocols and condensation reactions (when $R^2 = H$) with aldehydes and ketones, thus allowing the direct access to the corresponding Michael acceptors,[17] that are not as easily available to O-acetyl oximes (Figure 1).

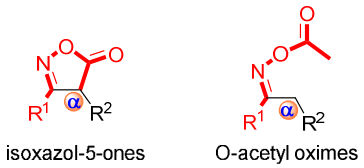
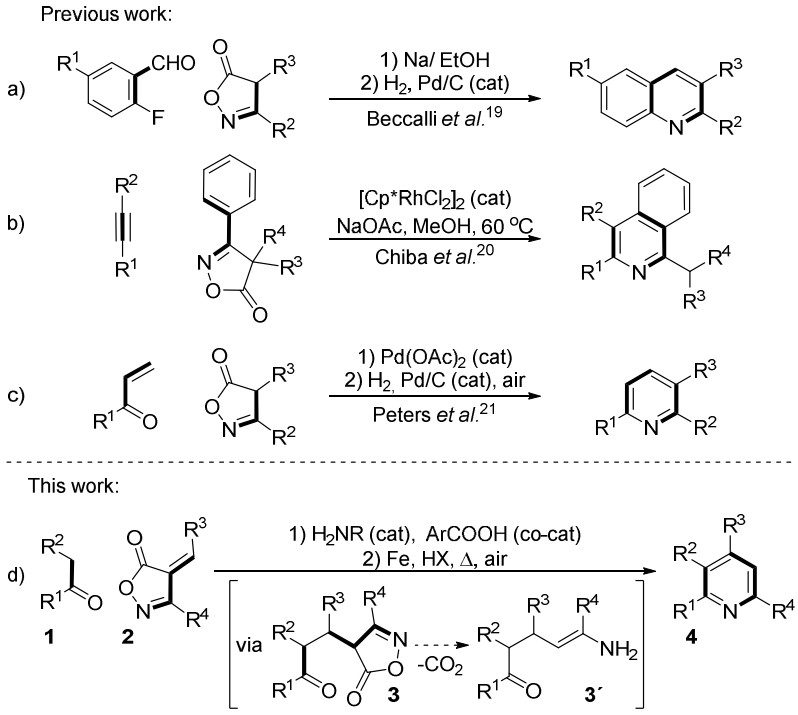


Figure 1. Identification of structural similarity between isoxazol-5-ones and O-acetyl oximes.

Based on the structural similarity, and following our interest in the chemistry of isoxazol-5-ones,[18] we recognized the value of developing a synthetic route toward pyridines, starting from an appropriate isoxazol-5-one precursor. In this context, previous works from the groups of Beccalli[19] and Chiba[20] described the preparation of quinolines and isoquinolines, via formal [3+3] and [2+4] approaches, respectively (Scheme 1a and 1b), while Peters[21] reported the preparation of pyridines via a formal [3+3] strategy (Scheme 1c). In this work, a synthetic route based on a two-step sequence is described. The first step takes advantage of an aminocatalyzed conjugate addition of ketones **1** to alkylidene isoxazol-5-ones **2**, thus leading to intermediates **3**, which are then decarboxylated

and cyclized in the presence of Fe, under air, to produce the corresponding 2,3,4,6-tetrasubstituted pyridines **4** (Scheme 1d).

Scheme 1. Presentation of previous syntheses of the pyridine core starting from different isoxazol-5-one precursors and the strategy developed in this work, which allows the preparation of 2,3,4,6-tetrasubstituted pyridines 4.



Results and Discussion

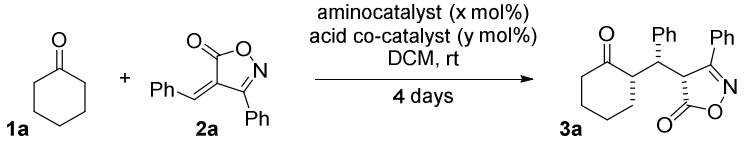
The synthetic route showcased in Scheme 1d has been designed based on the previous observation that Fe can decarboxylate isoxazol-5-ones to afford the corresponding ketones.[18a] In that context, it was imagined that an iminium ion intermediate would be involved. If this hypothesis was true, its enamine tautomer would be equally accessible in acidic media. Therefore, by placing an appropriately positioned carbonyl group from the enamine nitrogen atom (considering an intermediate such as **3´**, see Scheme 1), one would produce an intramolecular cyclization event, which could then further undergo an oxidation step promoted by the presence of air,[22] thus generating the corresponding pyridine **4**. After preliminary experiments, the envisioned synthetic plan was demonstrated feasible and further extensive optimization followed.

Considering the optimization for the conjugate addition, the model reaction involved the use of cyclohexanone **1a** and alkylidene isoxazol-5-one **2a**, thus leading to adduct **3a**. Remarkably, this reaction proceeds with perfect control of diastereoselectivity. For all aminocatalysts employed, and for all isoxazol-5-one intermediates **3** obtained, they are all produced as a single, all-*syn* diastereoisomer. In the context of this work, this is not relevant, because all stereogenic centers are later destroyed, when pyridines **4** are produced. Nevertheless, this observation is certainly useful for the development of other chemistry.[23]

Among the achiral aminocatalysts employed (Table 1, entries 1-7) in the presence of benzoic acid (60 mol%), in DCM, at room temperature, *o*-anisidine (40 mol%) provided the best yield, 67% (Table 1, entry 7), when compared to the other amines (Table 1, entries 1-6). Next, different amounts of *o*-anisidine were evaluated (Table 1, entries 8-12), but all performed less efficiently than the previous amount of 40 mol% (Table 1, entry 7).

Then, by varying the nature of the acid employed (Table 1, entries 13-22), 4-fluorobenzoic acid was identified as the best choice, thus providing this time a 70% yield (Table 1, entry 22). Finally, a systematic investigation on the amount of 4-fluorobenzoic acid needed (Table 1, entries 24-28) demonstrated that 40 mol% is the optimal choice (Table 1, entry 25). Remarkably, the absence of any acid co-catalyst also affords a productive reaction, thus delivering a 67% yield (Table 1, entry 23). A plausible explanation for this observation derives from the high acidity of the α-proton of the carbonyl group at the isoxazol-5-one ring of **3a** (pKa ~ 4-6):[24] this proton presumably acts as a promoter of the reaction, thus enabling tautomerization events needed for the whole process to proceed.

Table 1. Selected entries for the optimization of the aminocatalyzed conjugate addition of ketone 1a to alkylidene isoxazol-5-one 2a.



entry	amine (x mol%)	acid (y mol%)	y (%)[a]
1	$BnNH_2$ (40)	$PhCO_2H$ (60)	44
2	Cyclopropylamine (40)	$PhCO_2H$ (60)	50
3	4-$(OH)C_6H_4NH_2$ (40)	$PhCO_2H$ (60)	63

4	$PhNH_2$ (40)	$PhCO_2H$ (60)	62
5	$CyNH_2$ (40)	$PhCO_2H$ (60)	55
6	4-(MeO)$C_6H_4NH_2$ (40)	$PhCO_2H$ (60)	53
7	2-(OMe)$C_6H_4NH_2$ (40)	$PhCO_2H$ (60)	67
8	-	$PhCO_2H$ (60)	0
9	2-(OMe)$C_6H_4NH_2$ (10)	$PhCO_2H$ (60)	59
10	2-(OMe)$C_6H_4NH_2$ (20)	$PhCO_2H$ (60)	60
11	2-(OMe)$C_6H_4NH_2$ (60)	$PhCO_2H$ (60)	66
12	2-(OMe)$C_6H_4NH_2$ (100)	$PhCO_2H$ (60)	55
13	2-(OMe)$C_6H_4NH_2$ (40)	AcOH (60)	<5
14	2-(OMe)$C_6H_4NH_2$ (40)	4-(NO_2)$C_6H_4CO_2H$ (60)	62
15	2-(OMe)$C_6H_4NH_2$ (40)	2-(NO_2)$C_6H_4CO_2H$ (60)	39
16	2-(OMe)$C_6H_4NH_2$ (40)	2,4-(NO_2)$_2C_6H_3CO_2H$ (60)	48
17	2-(OMe)$C_6H_4NH_2$ (40)	4-(CF_3)$C_6H_4CO_2H$ (60)	65
18	2-(OMe)$C_6H_4NH_2$ (40)	3-(CF_3)$C_6H_4CO_2H$ (60)	54
19	2-(OMe)$C_6H_4NH_2$ (40)	3,5-(CF_3)$_2C_6H_3CO_2H$ (60)	44
20	2-(OMe)$C_6H_4NH_2$ (40)	$C_6F_5CO_2H$ (60)	34
21	2-(OMe)$C_6H_4NH_2$ (40)	2,6-(F)$_2C_6H_3CO_2H$ (60)	49
22	2-(OMe)$C_6H_4NH_2$ (40)	4-(F)$C_6H_4CO_2H$ (60)	70
23	2-(OMe)$C_6H_4NH_2$ (40)	-	67
24	2-(OMe)$C_6H_4NH_2$ (40)	4-(F)$C_6H_4CO_2H$ (20)	64
25	**2-(OMe)$C_6H_4NH_2$ (40)**	**4-(F)$C_6H_4CO_2H$ (40)**	**74**
26	2-(OMe)$C_6H_4NH_2$ (40)	4-(F)$C_6H_4CO_2H$ (100)	67
27	2-(OMe)$C_6H_4NH_2$ (40)	4-(F)$C_6H_4CO_2H$ (200)	65
28	2-(OMe)$C_6H_4NH_2$ (40)	4-(F)$C_6H_4CO_2H$ (300)	66

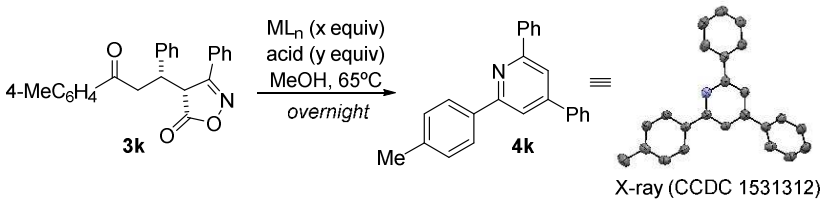
[a]Yields are estimated based on ^{1}H NMR of crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard.

Next, the decarboxylative cyclization event converting **3** to the desired pyridines **4** was optimized. In this context, the acyclic isoxazol-5-one **3k** was chosen as a model substrate.

Only benzoic acid does not promote the reaction (Table 2, entry 1). A number of iron salts are also ineffective for this transformation (Table 2, entries 2-4). Good yields were only obtained when Fe was employed as a single electron reducing agent. The use of Fe (10 equiv.) in the presence of $PhCO_2H$ (10 equiv.) produced a 70% yield (Table 2, entry 5), while decreasing the amount of benzoic acid to 1 equiv. significantly decreased the efficiency of the reaction, this time producing a 46% yield (Table 2, entry 6). Then, we turned our attention to the optimization of the acid. Among the different acid sources investigated, the use of NH_4Cl, and AcOH seems to be not strong enough to promote this reaction (Table 2, entries 7 and 8, respectively), while the presence of water in the HCl solution presumably hydrolyzes the intermediates formed, thus affording also low yields for this transformation (Table 2, entry 9). The use of stronger acids (*i.e.* compared to NH_4Cl and AcOH) produces higher yields (Table 2, entries 10-15), with 3,5-dimethoxybenzoic acid producing the best result, 76% (Table 2, entry 11).

Furthermore, reactions using Fe (1 equiv.) or Fe (5 equiv.), both in the presence of 3,5-dimethoxybenzoic acid (10 equiv.) produced 50% and 60% yields, respectively (Table 2, entries 16 and 17). On the other hand, the use of Fe (20 equiv.), in the presence of 3,5-dimethoxybenzoic acid (10 equiv.), does not improve the reaction performance. In this case, a 76% yield is also obtained (Table 2, entry 18).

Table 2. Optimization of the Iron-promoted decarboxylative cyclization of isoxazol-5-ones 3 toward 2,3,4,6-tetrasubstituted pyridines 4.

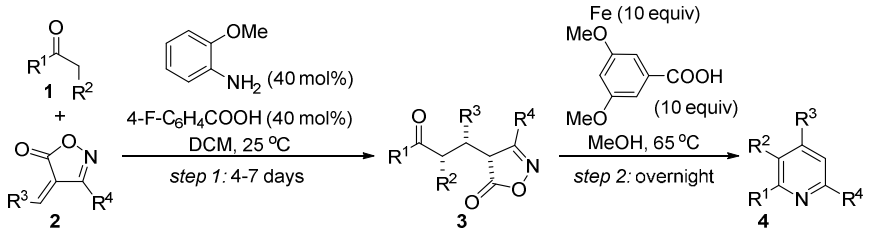


entry	Fe source (x equiv)	acid (y equiv)	yield (%)
1	-	$PhCO_2H$ (10)	<5
2	$FeCl_3$ (1)	$PhCO_2H$ (10)	<5
3	$Fe(acac)_3$ (1)	$PhCO_2H$ (10)	<5
4	$FeSO_4.7H_2O$ (10)	$PhCO_2H$ (10)	<5
5	Fe (10)	$PhCO_2H$ (10)	70
6	Fe (10)	$PhCO_2H$ (1)	46
7	Fe (10)	NH_4Cl (10)	25
8	Fe (10)	AcOH (10)	34
9	Fe (10)	HCl (10)	37
10	Fe (10)	TFA (10)	67
11	**Fe (10)**	**3,5-$(OMe)_2C_6H_3CO_2H$ (10)**	**76**
12	Fe (10)	4-$(NH_2)C_6H_4CO_2H$	57
13	Fe (10)	2,4,6-$(OMe)_3C_6H_2CO_2H$ (10)	58
14	Fe (10)	2,6-$(F)_2C_6H_3CO_2H$ (10)	36
15	Fe (10)	$(CF_3SO_2)_2NH$ (10)	72
16	Fe (1)	3,5-$(OMe)_2C_6H_3CO_2H$ (10)	55
17	Fe (5)	3,5-$(OMe)_2C_6H_3CO_2H$ (10)	65
18	Fe (20)	3,5-$(OMe)_2C_6H_3CO_2H$ (10)	76

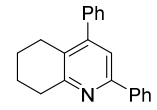
[a]Yields are estimated based on ^1H NMR of crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard.

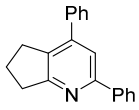
With the optimized conditions in hand, the scope of this two-step sequence was evaluated considering different ketones **1** and alkylidene isoxazol-5-ones **2** (Scheme 2). Concerning the Michael addition, cyclic and linear ketones produced good general reactivity, although cyclic ketones typically afforded better results.

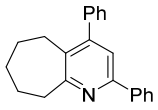
Scheme 2. Pyridines prepared in this work.

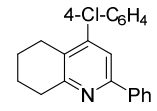


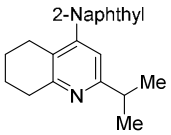
Pyridine **4** (yield step 1/ yield step 2)[a]

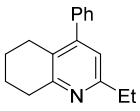

4a (74/60)

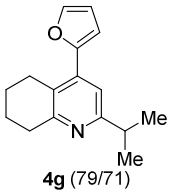

4b (38/48)

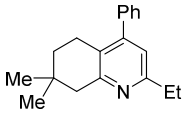

4c (40/67)

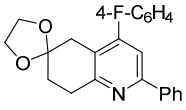

4d (69/63)

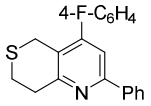

4e (80/67)

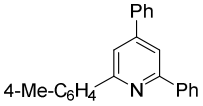

4f (78/63)

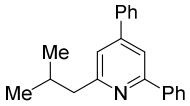

4g (79/71)

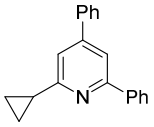

4h (49/50)

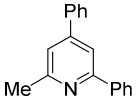

4i (76/75)

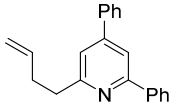

4j (41/50)

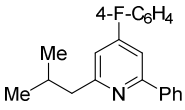

4k (40/76)

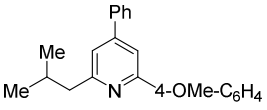

4l (53/70)

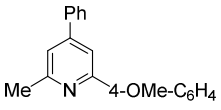

4m (50/60)

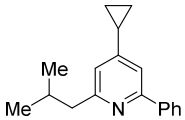

4n (44/64)

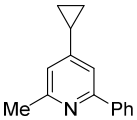

4o (30/61)

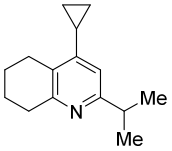

4p (74/62)


4q (64/57)


4r (50/55)


4s (56/52)


4t (63/57)

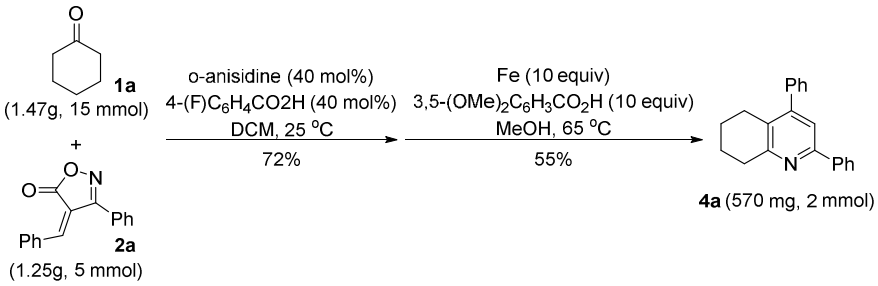

4u (<10/-)

Nevertheless, cyclopentanone (Scheme 2, molecule **4b**) and cycloheptanone (Scheme 2, molecule **4c**) afforded somehow lower yields than 6-membered cyclic ketones (Scheme 2, molecule **4a**, **4d-4j**). Acyclic ketones typically produced the corresponding Michael adducts in slightly lower yields, under more forcing reaction conditions: a larger excess of ketone (5 equiv) was employed and the reactions were stirred for a longer period (7 days) (Scheme 2, molecules **4k-4t**).

In relation to the alkylidene isoxazol-5-ones **2**, either one or two aromatic substitutuents (in R^3 and/or R^4) allowed good results for this 1,4-addition step. No significant conversion was obtained when two aliphatic substituents were present (Scheme 2, molecule **4u**). At this point, it is possible to speculate that π-π stacking interactions might play an important role for the first aminocatalyzed addition step.[25] Concerning the preparation of pyridines **4** from adducts **3**, all of them were produced somehow in similar yields, 48-76% (Scheme 2, molecules **4a-4t**).

Furthermore, this two-step protocol was also evaluated in gram-scale employing cyclohexanone **1a** and alkylidene isoxazol-5-one **2a**, thus affording the corresponding pyridine **4a** in similar yield as previously established (Scheme 3).

Scheme 3. Synthesis of 4a in a preparative scale.



Finally, the reaction mechanisms involved in both steps were investigated. In this context, a high resolution mass-spectrometer (HRMS) operating by positive electronspray ionization was employed.[26] The use of such an equipment is attractive in this case, because the low concentrations of the reactive species involved in both steps, as well as the presence of paramagnetic species derived from a SET reduction mechanism (in the case of the decarboxylative cyclization

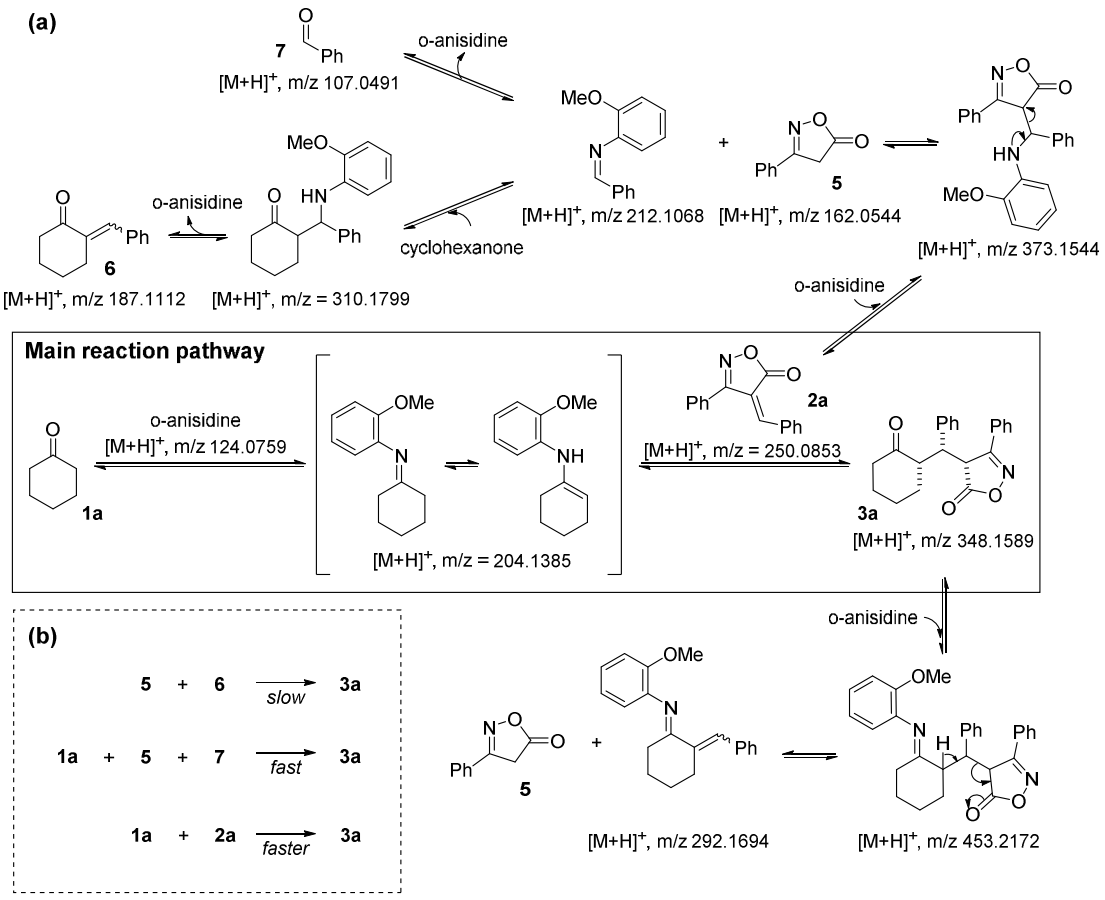
event, promoted by Fe) makes NMR studies challenging. For the examination of these reactions by HRMS-ESI(+), aliquots were collected from the reaction mixture at different periods (see SI for details).

In the study of the aminocatalyzed conjugate addition employing cyclohexanone **1a** and alkylidene isoxazol-5-one **2a**, ions of *m/z* 107.0491, 124.0759, 162.0544, 187.1112, 204.1385, 212.1068, 250.0853, 292.1694, 310.1799, 348.1589, 373.1544, 453.2172 were found and identified. The observation of these ions support a classical aminocatalyzed conjugate addition mechanism of an enamine intermediate, derived from the condensation between cyclohexanone **1a** and *o*-anisidine, on the Michael acceptor **2a**, but also reveals the presence of unanticipated intermediates, which presumably indicates the involvement of a more complex equilibrium (Scheme 4a).

In order to obtain more information about the formation of these intermediates, a series of control experiments were performed. For instance, when isolated pure compound **3a** is stirred at room temperature under the reaction conditions, ^{1}H NMR of the crude reaction mixture indicates that no appreciable amount of isoxazol-5-one **5**, enone **6** or benzaldehyde are formed, while the monitoring of this same reaction by HRMS reveals the presence of both components. Therefore, these compounds must be formed in the reaction mixture only in very small amounts (Scheme 4).

When studying the reaction of isoxazol-5-one **5** (3 equiv) with enone **6** (1 equiv) under the same reaction conditions, the addition product **3a** is obtained as a single diastereoisomer in 35% yield. Furthermore, when cyclohexanone **1a**, benzaldehyde **7** and isoxazol-5-one **5**, in a 3:1:1 ratio, respectively, are submitted to the established aminocatalytic conditions, **3a** is produced again as a single diasteroisomer, this time in 52% yield. In this case, the monitoring of the reaction by ^{1}H NMR reveals the formation of **2a**, thus strongly suggesting that isoxazol-5-one **5** undergoes Knoevenagel condensation with benzaldehyde **7** to generate alkylidene isoxazol-5-one **2a** as an intermediate, that is subsequently attacked by the enamine of cyclohexanone **1a**.

Scheme 4. a) Proposed equilibrium involved in the formation of 3a, based on HRMS-ESI(+) experiments. b) Qualitative assessment of relative reaction rates, based on control experiments.

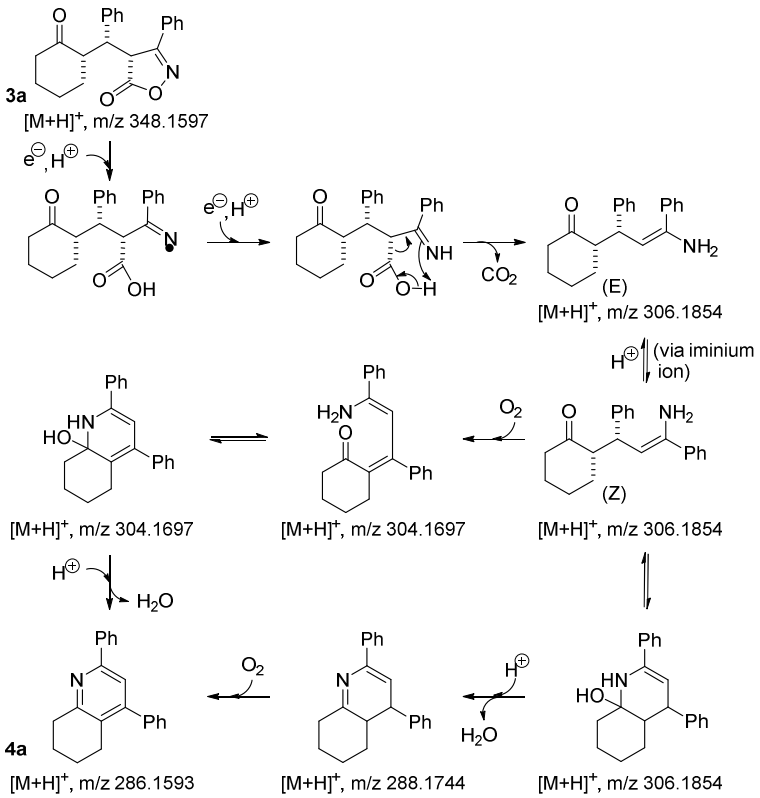


Next, the conversions derived of all three possible combinations of reagents that have been previously identified, all in equimolar amounts to each other, were measured. As a consequence, a qualitative assessment of relative reaction rates could be established (Scheme 4b). In more details, after 4 days, the reaction of isoxazol-5-one **5** and enone **6** affords **3a** in 22% yield (+ 60% **6**), while the reaction between the individual components cyclohexanone **1a**, isoxazol-5-one **5** and benzaldehyde **7** affords **3a** in 46% yield (+ 9% **2a** and 0% **7**). Finally, the reaction between cyclohexanone **1a** and alkylidene isoxazol-5-one **2a** is the fastest, this time affording **3a** in 60% yield (+ 5% **2a**). This data strongly suggests that the aminocatalyzed Michael addition of ketones **1** to alkylidene isoxazol-5-ones **2** is in equilibrium and explains the excellent

diastereoselectivities for compounds **3** as a result of thermodynamic control (see SI for more details).

In the study of the decarboxylative cyclization event promoted by Fe, ions of m/z 286.1593, 288.1744, 304.1697, 306.1854, 326.1519, 348.1597, 370.1418 were found and identified. The presence of these ions suggests that there is a bifurcation in the reaction pathway. Accordingly, the adduct **3a** is reduced by Fe, in the presence of 3,5-dimethoxybenzoic acid, thus promoting a decarboxylation event, that leads to an enamine intermediate. In one pathway, this enamine intermediate can undergo an oxidation step, followed by a cyclization event. In the second pathway, this same enamine intermediate can first undergo a cyclization step, then being followed by an oxidation event. In both cases, the final outcome is the preparation of the pyridine **4a** (Scheme 5).[27] At this point, it is not possible to determine which pathway has a greater contribution for the formation of the observed pyridines (see SI for more details).

Scheme 5. Proposed reaction mechanism for the decarboxylative cyclization of isoxazol-5-one 3a toward pyridine 4a, based on HRMS-ESI(+) experiments.



Conclusions

In summary, this work describes a two-step sequence for the preparation of densely substituted pyridines **4** starting from ketones **1** and alkylidene isoxazol-5-ones **2**. This process has been demonstrated to be scalable and both steps have been studied by HRMS-ESI(+). In the first step, the results demonstrate that a more complex equilibrium is involved in the synthesis of adducts **3**, which is ultimately responsible for a thermodynamic control, that explains the high diastereoselectivities observed for this step. In the second step, two reaction pathways seem to be occurring simultaneously (but not necessarily to the same extent) in the synthesis of pyridines **4**. In one pathway, the cyclization event occurs first, then being followed by the oxidation step, while in the second pathway, oxidation occurs first, then being followed by the cyclization event.

Experimental Section

Materials and Methods

All reactions were carried out under air, in oven dried glassware with magnetic stirring, unless otherwise noted. All reagents employed in this work were purchased from Sigma-Aldrich and used without further purification. All solvents employed in the reactions were distilled from appropriate drying agents prior to use. Organic solutions were concentrated under reduced pressure on a IKA rotary evaporator RV-10 Control. Reactions were monitored by thin-layer chromatography (TLC) on Silica gel 60 F_{254} aluminium plates (Merck). Chromatograms were visualized by fluorescence quenching with UV light at 254 nm or by staining using *para*-anisaldehyde solution. Flash column chromatography was performed using Merck silica gel 60 (particle size 35-70μm). ^{1}H and ^{13}C NMR spectra were recorded on either Bruker DPX-250, AV-400, AV-500 or AV-600 MHz spectrometers. Chemical shifts (δ) are given in parts per million, referenced to the residual peak of $CDCl_3$, δ = 7.26 (^{1}H NMR) and δ = 77.0 (^{13}C NMR) as internal references. The following abbreviations were used to designate chemical shift multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, quint. = quintuplet, sext. = sextuplet, sept. = septuplet, m = multiplet, br s = broad singlet. High-resolution mass spectra were recorded on Thermo Scientific LTQ FT Ultra and Q Exactive Orbitrap spectrometers working with an electronspray ionization (ESI).

Alkylidene isoxazolones **2a-i** have been prepared in two steps, according to the literature, using the appropriate β-ketoester and aldehyde.[18,23]

***(Z)*-4-benzylidene-3-phenylisoxazol-5(4H)-one (2a):** Prepared in two steps.[23] For the first step, the crude material obtained is washed with DCM/ hexanes to afford the intermediate 3-phenylisoxazol-5(4H)-one as a light pink solid (3.49 g, 92%). In the second step, the title product crashes out of the solution and is isolated by filtration, while washing with ^{i}PrOH, to afford a yellow solid (1.94 g, 78%). ^{1}H (250 MHz, $CDCl_3$) δ: 8.31-8.32 (m, 2H), 7.62-7.49 (m, 9H).^{13}C (150 MHz, $CDCl_3$) δ: 168.0, 164.0, 152.7, 134.1, 134.0, 132.4, 131.0, 129.3, 129.0, 128.7, 127.4, 118.9. HRMS (ESI+): Calcd. for $[C_{16}H_{11}NO_2+H]^+$: 250.0863, found: 250.0861.

***(Z)*-4-(4-chlorobenzylidene)-3-phenylisoxazol-5(4H)-one (2b):** Prepared in two steps.[23] For the first step, 3-phenylisoxazol-5(4H)-one is synthesized as previously described for molecule **2a**. In the second step, the title product crashes out of the solution and is isolated by filtration, while washing with ^{i}PrOH, to afford a yellow solid (1.5 g, 70%). ^{1}H (400 MHz, $CDCl_3$) δ: 8.30-8.28 (m, 2H), 7.63-7.53 (m, 6H), 7.50-7.47 (m, 2H). ^{13}C (100 MHz, $CDCl_3$) δ: 168.0, 163.9, 150.9, 140.7, 135.2, 131.2, 130.8, 129.4, 129.4, 128.8, 127.2, 119.3. HRMS (ESI+): Calcd. for $[C_{16}H_{10}NO_2Cl+H]^+$: 284.0473, found: 284.0483.

***(Z)*-3-isopropyl-4-(naphthalen-2-ylmethylene) isoxazol-5(4H)-one (2c):** Prepared in two steps.[23] For the first step, the crude material obtained is purified by flash column chromatography (SiO_2, gradient: Hex - 9:1 Hex:AcOEt - 8:2 Hex:AcOEt - 7:3 Hex:AcOEt) to afford the intermediate 3-isopropylisoxazol-5(4H)-one as a yellow oil (2.5 g, 98%). In the second step, the title product crashes out of the solution and is isolated by filtration, while washing with ^{i}PrOH, to afford a bright yellow solid (762 mg, 56%). ^{1}H (400 MHz, $CDCl_3$) δ: 8.82 (s, 1H), 8.45 (dd, J = 8.7Hz, J = 1.7Hz, 1H), 8.97 (d, J = 8.1Hz, 1H), 7.91 (d, J = 8.7Hz, 1H), 7.86 (d, J = 8.1Hz, 1H), 7.65-7.54 (m, 3H), 3.07 (sept, J = 6.9Hz, 1H), 1.42 (d, J = 6.9Hz, 6H). ^{13}C (100 MHz, $CDCl_3$) δ: 168.5, 168.0, 149.2, 136.5, 135.6, 132.7, 130.0, 129.8, 129.4, 128.6, 128.4, 127.8, 127.0, 118.1, 26.5, 20.2. HRMS (ESI+): Calcd. for $[C_{17}H_{15}NO_2+H]^+$: 266.1176, found: 266.1173.

4-benzylidene-3-ethylisoxazol-5(4H)-one (2d) [10:1 Z:E]: Prepared in two steps.[18] For the first step, the crude material obtained is purified by flash column chromatography (SiO_2, gradient: Hex - 9:1 Hex: Et_2O - 7:3 Hex:Et_2O - 1:1 Hex: Et_2O - 7:3 Et_2O:Hex - Et_2O) to afford the intermediate 3-ethylisoxazol-5(4H)-one as a yellow oil (2.25 g, 99%). In the second step, the title product crashes out of the solution and is isolated by filtration, while washing with ^{i}PrOH, to afford a pale yellow solid (10:1 Z: E, 2.1 g, 54%). ^{1}H (500 MHz, $CDCl_3$) (only major isomer Z described) δ: 8.34 (d, J = 7.5Hz, 2H), 7.60-7.57 (m, 1H), 7.54-7.50 (m, 2H), 7.45 (s, 1H), 2.69 (q, J = 7.5Hz, 2H), 1.37 (t, J = 7.5Hz, 3H). ^{13}C (125 MHz, $CDCl_3$) (only major isomer Z described) δ: 168.1, 164.8, 149.3, 133.9, 133.7, 132.3, 129.0, 119.1, 19.7, 10.4. HRMS (ESI+): Calcd. for $[C_{12}H_{11}NO_2+Na]^+$: 224.0682, found: 224.0678.

***(Z)*-4-(furan-2-ylmethylene)-3-isopropylisoxazol-5(4H)-one (2e):** Prepared in two steps.[18] For the first step, 3-isopropylisoxazol-5(4H)-one is synthesized as previously described for molecule **2c**. In the second step, the title product is purified by flash column chromatography (SiO_2, gradient: Hex- 9:1 Hex:AcOEt - 8:2 Hex:AcOEt - 6:4 Hex:AcOEt)), to afford a yellow solid (1.38 g, 78%). ^{1}H (600 MHz, $CDCl_3$) δ: 8.58 (d, J = 4.0Hz, 1H), 7.78 (d, J = 1.2Hz, 1H), 7.40 (s, 1H), 6.75 (dd, J = 4.0Hz, J =1.2Hz, 1H), 2.98 (sept, J = 6.9Hz, 1H), 1.37 (d, J = 6.9Hz, 6H). ^{13}C (150 MHz, $CDCl_3$) δ: 168.8, 167.5, 150.1, 149.2, 131.4, 125.8, 115.2, 113.0, 26.6, 20.2. HRMS (ESI+): Calcd. for $[C_{11}H_{11}NO_3+H]^+$: 206.0812, found: 206.0810.

***(Z)*-4-(4-fluorobenzylidene)-3-phenylisoxazol-5(4H)-one (2f):** Prepared in two steps.[18] For the first step, 3-phenylisoxazol-5(4H)-one is synthesized as previously described for molecule **2a**. In the second step, the title product crashes out of the solution and is isolated by filtration, while washing with ^{i}PrOH, to afford a yellow solid (857 mg, 64%). m.p. 173-175 ^{o}C. ^{1}H (400 MHz, $CDCl_3$) δ: 8.45 – 8.42 (m, 2H), 7.63 – 7.58 (m, 6H), 7.22 (t, J = 8,6Hz, 2H). ^{13}C (100 MHz, $CDCl_3$) δ: 168.2, 166.1 (d, J = 258.2Hz), 164.0, 151.1, 136.9 (d, J = 9.4Hz), 131.1, 129.3, 128.9 (d, J = 3.1Hz), 128.7, 127.3, 118.3, 116.4 (d, J = 21.8Hz). HRMS (ESI+): Calcd. for $[C_{16}H_{10}NO_2F+H]^+$: 268.0768, found: 268.0766.

***(Z)*-4-benzylidene-3-(4-methoxyphenyl)isoxazol-5(4H)-one (2g):** Prepared in two steps.[23] For the first step, the reaction mixture is concentrated to afford the intermediate 3-(4-methoxyphenyl)isoxazol-5(4H)-one a reddish solid (1.97 g, 99%). In the second step, the title product crashes out of the solution and is isolated by filtration, while washing with ^{i}PrOH, to afford a pale yellow solid (1.17 g, 80%). ^{1}H (400 MHz, $CDCl_3$) δ: 8.33 (d, *J* = 8.1Hz, 2H), 7.64-7.51 (m, 6H), 7.09 (d, *J* = 8.1Hz, 2H), 3.91(s, 3H). ^{13}C (100 MHz, $CDCl_3$) δ**:** 168.2, 163.6, 161.8, 152.7, 134.1, 134.0, 132.4, 130.2, 128.0, 119.5, 119.0, 114.8, 55.5. HRMS (ESI+): Calcd. for $[C_{17}H_{13}NO_3+H]^+$: 280.0968, found: 280.0967.

4-(cyclopropylmethylene)-3-phenylisoxazol-5(4H)-one (2h) [9:1 *Z*:*E*]: Prepared in two steps.[23] For the first step, 3-phenylisoxazol-5(4H)-one is synthesized as previously described for molecule **2a**. In the second step, the title product is purified by flash column chromatography (SiO_2, gradient: Hex- 95:5 Hex:AcOEt - 9:1 Hex:AcOEt - 8:2 Hex:AcOEt) to afford the title compound as a pink solid (9:1 Z:E, 400 mg, 63%). ^{1}H (400 MHz, $CDCl_3$) δ: 7.54-7.48 (m, 5H), 6.62 (d, *J* = 12.0Hz, 0.1H), 6.49 (d, *J* = 11.6Hz, 0.9H), 3.37-3.27 (m, 0.9H), 1.85-1.78 (m, 0.1H), 1.47-1.45 (m, 1.8H), 1.27-1.23 (m, 0.2H), 1.02-0.98 (m, 2H). ^{13}C (100 MHz, $CDCl_3$) (only major isomer Z described) δ: 170.0, 166.0, 161.1, 130.9, 129.2, 128.1, 127.4, 118.7, 14.7, 13.6. HRMS (ESI+): Calcd. for $[C_{13}H_{11}NO_2+H]^+$: 214.0863, found: 214.0860.

(Z)-4-(cyclopropylmethylene)-3-isopropylisoxazol-5(4H)-one (2i): Prepared in two steps.[23] For the first step, 3-isopropylisoxazol-5(4H)-one is synthesized as previously described for molecule **2c**. In the second step, the title product is purified by flash column chromatography (SiO_2, gradient: Hex- 95:5 Hex:AcOEt - 9:1 Hex:AcOEt - 8:2 Hex:AcOEt) to afford the title compound as a white solid (463 mg, 86%). ^{1}H (500 MHz, $CDCl_3$) δ: 6.31 (d, *J* = 11.4Hz, 1H), 3.24-3.22 (m, 1H), 2.85-2.81 (m, 1H), 1.42-1.40 (m, 2H), 1.28 (d, *J* = 6.9Hz, 6H), 0.97-0.96 (m, 2H). ^{13}C (125 MHz, $CDCl_3$) δ: 170.1, 165.8, 162.5, 118.8, 26.6, 20.1, 14.0, 13.0. HRMS (ESI+): Calcd. for $[C_{10}H_{13}NO_2+H]^+$: 180.1019, found: 180.1017.

General reaction conditions for racemic aminocatalyzed addition of ketones to alkylidene isoxazol-5-ones (Step 1): ketone (0.6 mmol for cyclic and 1 mmol for acyclic ones), alkylidene isoxazol-5-one (0.2 mmol), o-anisidine (0.08 mmol), 4-fluorobenzoic acid (0.08 mmol) and DCM (1 mL) are added under air, at room temperature to a round-bottom flask and stirred at room temperature for 4-7 days, being followed by TLC analysis. Upon completion, the reaction mixture is diluted in DCM, washed once with an aqueous saturated solution of $NaHCO_3$, dried ($MgSO_4$), concentrated under reduced pressure and purified by flash column chromatography.

4-((2-oxocyclohexyl)(phenyl)methyl)-3-phenylisoxazol-5(4H)-one[23] **(3a):** *Reaction time: 96h***.** Purification by flash column chromatography (SiO_2, gradient: Hex - 9:1 Hex:AcOEt - 8:2 Hex:AcOEt - 7:3 Hex:AcOEt - 1:1 Hex:AcOEt) affords the title compound as a yellow solid (51 mg, 74%). ^{1}H (500 MHz, $CDCl_3$) δ: 7.76-7.74 (m, 2H), 7.55- 7.48 (m, 3H), 7.22-7.13 (m, 3H), 6.73 (br s, 2H), 4.81 (d, *J* = 4.6Hz, 1H), 3.79 (td, *J* = 11.8Hz, *J* = 4.6Hz, 1H), 3.53 (dd, *J* = 11.1Hz, *J* = 4.6Hz, 1H), 2.70-2.62 (m, 1H), 2.55- 2.51 (m, 1H), 2.21-2.18 (m, 1H), 1.76-1.61 (m, 4H), 1.08-0.98 (m, 1H). ^{13}C (100 MHz, $CDCl_3$) δ: 214.5, 178.0, 166.6, 135.7, 131.7, 129.2, 128.8, 128.2, 128.1, 127.7, 127.3, 48.7, 47.5, 45.2, 43.2, 34.0, 29.3, 25.5. HRMS (ESI+): Calcd. for $[C_{22}H_{21}NO_3+H]^+$: 348.1594, found: 348.1600.

4-((2-oxocyclopentyl)(phenyl)methyl)-3-phenylisoxazol-5(4H)-one[23] **(3b):** *Reaction time: 96h*. Purification by flash column chromatography (SiO_2, gradient: Hex - 9:1 Hex:AcOEt - 8:2 Hex:AcOEt - 1:1 Hex:AcOEt) affords the title compound as an orange solid (25 mg, 38%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.65-7.63 (m, 2H), 7.56-7.54 (m, 3H), 7.22-7.14 (m, 3H), 6.77 (d, *J* = 7.0Hz, 2H), 5.52 (d, *J* = 4.0Hz, 1H), 3.70-3.62 (m, 1H), 3.27 (dd, *J* = 11.3Hz, *J* = 4.0Hz, 1H), 2.60-2.52 (m, 1H), 2.33-2.23 (m, 1H), 1.96-1.85 (m, 3H), 1.22-1.11 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.7, 166.4, 136.3, 131.6, 129.3, 129.3, 129.1, 128.6, 128.2, 128.1, 127.7, 127.3, 47.2, 46.1, 38.5, 29.9, 19.5. HRMS (ESI+): Calcd. for $[C_{21}H_{19}NO_3+H]^+$: 334.1438, found: 334.1434.

4-((2-oxocycloheptyl)(phenyl)methyl)-3-phenylisoxazol-5(4H)-one[23] **(3c):** *Reaction time: 96h*. Purification by flash column chromatography (SiO_2, gradient: Hex - 9:1 Hex:AcOEt - 8:2 Hex:AcOEt - 1:1 Hex:AcOEt) affords the title compound as an orange

solid (29 mg, 40%). ^{1}H (600 MHz, $CDCl_3$) δ: 7.65-7.64 (m, 2H), 7.56-7.53 (m, 1H), 7.52-7.49 (m, 2H), 7.22-7.19 (m, 1H), 7.17-7.14 (m, 2H), 6.75 (br s, 2H), 4.37 (d, *J* = 5.0Hz, 1H), 4.01 (td, *J* = 11.3Hz, *J* = 2.6Hz, 1H), 3.60 (dd, *J* = 11.3Hz, *J* = 5.0Hz, 1H), 2.93 (ddt, *J* = 16.8Hz, *J* = 4.3Hz, *J* = 1.3Hz, 1H), 2.56 (quint., *J* = 8.6Hz, 1H), 2.00-1.92 (m, 2H), 1.71-1.66 (m, 2H), 1.45 (dq, *J* = 14.2Hz, *J* = 2.6Hz, 1H), 1.39-1.32 (m, 1H), 1.24-1.18 (m, 1H), 1.04-0.98 (m, 1H). ^{13}C (150 MHz, $CDCl_3$) δ: 216.4, 177.7, 166.4, 136.0, 131.7, 130.2, 129.2, 128.8, 128.2, 127.6, 127.2, 49.5, 47.2, 45.9, 44.3, 30.3, 29.3, 27.9, 22.7. HRMS (ESI+): Calcd. for $[C_{23}H_{23}NO_3+H]^+$: 362.1751 Found: 362.1756.

4-((4-chlorophenyl)(2-oxocyclohexyl)methyl)-3-phenylisoxazol-5(4H)-one[23] (3d): *Reaction time: 96h*. Purification by flash column chromatography (SiO_2, gradient: Hex - 9:1 Hex:AcOEt - 8:2 Hex:AcOEt - 7:3 Hex:AcOEt - 1:1 Hex:AcOEt) affords the title compound as an yellow solid (53 mg, 69%). ^{1}H (400 MHz, $CDCl_3$) δ: 7.77-7.75 (m, 2H), 7.56-7.50 (m, 3H), 7.13 (d, *J* = 8.4Hz, 2H), 6.67 (br s, 2H), 4.80 (d, *J* = 4.7Hz, 1H), 3.75 (td, *J* = 12.0Hz, *J* = 4.7Hz, 1H), 3.52 (dd, *J* = 11.1Hz, *J* = 4.5Hz, 1H), 2.64 (td, *J* = 12.6Hz *J* = 6.4Hz, 1H), 2.55-2.50 (m, 1H), 2.22-2.17 (m, 1H), 1.76-1.64 (m, 3H), 1.29-1.20 (m, 1H), 1.05-0.97 (m, 1H). ^{13}C (100 MHz, $CDCl_3$) δ: 214.1, 177.8, 166.3, 134.2, 134.0, 131.8, 129.5, 129.3, 129.0, 127.4, 127.3, 48.5, 47.3, 44.6, 43.2, 33.9, 29.2, 25.4. HRMS (ESI+): Calcd. for $[C_{22}H_{20}NO_3Cl+H]^+$: 382.1204, found: 382.1199.

3-isopropyl-4-(naphthalen-2-yl(2-oxocyclohexyl)methyl)isoxazol-5(4H)-one[23] (3e): *Reaction time: 96h*. Purification by flash column chromatography (SiO_2, gradient: Hex - 9:1 Hex:AcOEt - 8:2 Hex:AcOEt - 7:3 Hex:AcOEt - 1:1 Hex:AcOEt) affords the title compound as an orange solid (58 mg, 80%). ^{1}H (500 MHz, $CDCl_3$) δ: 7.85-7.79 (m, 3H), 7.58 (s, 1H), 7.54-7.49 (m, 2H), 7.26 (dd, *J* = 8.5Hz, *J* = 1.5Hz, 1H), 4.48 (d, *J* = 5.2Hz, 1H), 3.84 (dt, *J* = 12.5Hz, *J* = 4.9Hz, 1H), 3.60 (dd, *J* = 10.9Hz, *J* = 5.2Hz,1H), 2.75 (sept., *J* = 6.9Hz, 1H), 2.69-2.63 (m, 1H), 2.52 (d, *J* = 12.5Hz, 1H), 2.23-2.18 (m, 1H), 1.74-1.66 (m, 5H), 1.41 (d, *J* = 6.9Hz, 3H), 1.02 (d, *J* = 6.9Hz, 3H). ^{13}C (125 MHz, $CDCl_3$) δ: 213.9, 178.8, 173.3, 134.4, 133.3, 132.9, 129.3, 127.8, 127.7, 127.3, 126.6, 126.3, 125.1, 49.2, 47.5, 44.2, 43.1, 34.2, 29.3, 28.6, 25.5, 20.8, 16.8. HRMS (ESI+): Calcd. for $[C_{23}H_{25}NO_3+H]^+$: 364.1907 Found: 364.1909.

3-ethyl-4-((2-oxocyclohexyl)(phenyl)methyl) isoxazol-5(4H)-one (3f): *Reaction time: 96h*. Purification by flash column chromatography (SiO_2, gradient: Hex - 9:1 Hex:AcOEt - 8:2 Hex:AcOEt - 7:3 Hex:AcOEt - 1:1 Hex:AcOEt) affords the title compound as an yellow oil (47 mg, 78%). ^{1}H (500 MHz, $CDCl_3$) δ: 7.29-7.26 (m, 3H), 7.10-7.08 (m, 2H), 4.36 (d, *J* = 5.2Hz, 1H), 3.66 (td, *J* = 12.5Hz, *J* = 5.0Hz, 1H), 3.36 (dd, *J* = 10.9Hz , *J* = 5.0Hz, 1H), 2.64-2.56 (m, 1H), 2.48-2.45 (m, 1H), 2.38 (dq, *J* = 7.5Hz, *J* = 3.6Hz, 2H), 2.18-2.14 (m, 1H), 1.79-1.70 (m, 1H), 1.69-1.59 (m, 4H), 1.18 (t, *J* = 7.5Hz, 3H). ^{13}C (125 MHz, $CDCl_3$) δ: 213.9, 178.4, 170.3, 136.8, 129.2, 128.2, 127.8, 49.2, 47.9, 43.8, 43.0, 34.1, 29.3, 25.5, 21.7, 9.6. HRMS (ESI+): Calcd. for $[C_{18}H_{21}NO_3+H]^+$: 300.1594, found: 300.1596.

4-(furan-2-yl(2-oxocyclohexyl)methyl)-3-isopropylisoxazol-5(4H)-one (3g): *Reaction time: 96h*. Purification by flash column chromatography (SiO_2, gradient: Hex - 9:1 Hex:AcOEt - 8:2 Hex:AcOEt -7:3 Hex:AcOEt - 1:1 Hex:AcOEt) affords the title compound as an orange oil (48 mg, 79%). ^{1}H (600 MHz, $CDCl_3$) δ: 7.30 (d, *J* = 1.8Hz, 1H), 6.25 (dd, *J* = 3.1Hz, *J* = 1.8Hz, 1H), 6.08 (d, *J* = 3.1Hz, 1H), 4.14 (d, *J* = 5.0Hz, 1H), 3.71 (dt, *J* = 10.7, *J* = 5.0Hz, 1H), 3.58 (dd, *J* = 10.7Hz, *J* = 4.8Hz, 1H), 2.66 (sept, *J* = 7.0Hz, 1H), 2.54 (td, *J* = 12.9Hz, *J* = 6.1Hz, 1H), 2.46-2.42 (m, 1H), 2.18-2.14 (m, 1H), 1.83-1.79 (m, 1H), 1.74-1.60 (m, 4H), 1.32 (d, *J* = 7.0Hz, 3H), 1.14 (d, *J* = 7.0Hz, 3H). ^{13}C (150 MHz, $CDCl_3$) δ: 213.2, 177.8, 172.8, 150.5, 142.6, 110.2, 108.2, 48.1, 46.1, 42.8, 37.7, 33.5, 29.0, 28.3, 25.3, 20.4, 17.0. HRMS (ESI+): Calcd. for $[C_{17}H_{21}NO_4+H]^+$: 304.1543, found: 304.1537.

4-((4,4-dimethyl-2-oxocyclohexyl)(phenyl) methyl)-3-ethylisoxazol-5(4H)-one (3h): *Reaction time: 96h*. Purification by flash column chromatography (SiO_2, gradient: Hex - 9:1 Hex:AcOEt - 8:2 Hex:AcOEt - 7:3 Hex:AcOEt - 1:1 Hex:AcOEt) affords the title compound as an yellow oil (48 mg, 49%). ^{1}H (400 MHz, $CDCl_3$) δ: 7.29-7.27 (m, 3H), 7.11-7.08 (m, 2H), 4.35 (d, *J* = 5.2Hz, 1H), 3.64-3.56 (m, 1H), 3.36 (dd, *J* = 11.0Hz, *J* = 5.2Hz, 1H), 2.55 (d, *J* = 12Hz, 1H), 2.37 (qd, *J* = 7.6Hz, *J* = 2.9Hz, 2H), 2.16 (dd, *J* = 12.0Hz, *J* = 2.4Hz, 1H), 1.68-1.61 (m, 2H), 1.49-1.42 (m, 2H) 1.19 (t, *J* = 7.5Hz, 3H), 1.09 (s, 3H), 0.86 (s, 3H). ^{13}C (100 MHz, $CDCl_3$) δ: 213.1, 178.4, 170.3, 136.9, 129.2,

128.2, 127.8, 55.7, 48.3, 47.9, 43.7, 38.4, 38.3, 31.9, 29.5, 24.8, 21.7, 9.7. HRMS (ESI+): Calcd. for $[C_{20}H_{25}NO_3+H]^+$: 328.1907, found: 328.1905.

4-((4-fluorophenyl)(8-oxo-1,4-dioxaspiro[4.5]decan-7-yl)methyl)-3-phenylisoxazol-5(4H)-one (3i): *Reaction time: 96h*. Purification by flash column chromatography (SiO_2, gradient: Hex - 9:1 Hex:AcOEt - 8:2 Hex:AcOEt - 7:3 Hex:AcOEt - 1:1 Hex:AcOEt) affords the title compound as a white solid (64 mg, 76%). m.p. 95-97 ^oC. ^1H (500 MHz, $CDCl_3$) δ: 7.75-7.74 (m, 2H), 7.56-7.50 (m, 3H), 6.85 (t, *J* = 8.4Hz, 2H), 6.70 (s, 2H), 4.82 (d, *J* = 4.5Hz, 1H), 4.16 (ddd, *J* = 16.8Hz, *J* = 11.6Hz, *J* = 5.4Hz, 1H), 4.04-3.99 (m, 1H), 3.93-3.88 (m, 2H), 3.82.3.78 (m, 1H), 3.50 (dd, *J* = 11.3Hz, *J* = 4.5Hz, 1H), 2.98 (td, *J* = 13.8Hz, *J* = 6.6Hz, 1H), 2.48 (ddd, *J* = 13.3Hz, *J* = 5.1Hz, *J* = 2.7Hz, 1H), 2.16-2.11 (m, 1H), 1.98 (td, *J* = 13.8Hz, *J* = 5.1Hz, 1H), 1.65 (ddd, *J* = 13.3Hz, *J* = 5.1Hz, *J* = 3.8Hz, 1H), 1.35 (t, *J* = 13.6Hz, 1H). ^{13}C (125 MHz, $CDCl_3$) δ: 212.8, 177.5, 166.3, 162.4 (d, *J* = 246.2Hz), 131.8, 131.0, (d, *J* = 3.4Hz), 129.8, 129.4, 127.5, 127.3, 115.9 (d, *J* = 21.3Hz), 106.9, 64.8, 64.6, 47.5, 44.3, 44.1, 40.2, 39.0, 35.6. HRMS (ESI+): Calcd. for $[C_{24}H_{22}FNO_5+H]^+$: 424.1555, found: 424.1550.

4-((4-fluorophenyl)(4-oxotetrahydro-2H-thiopyran-3-yl)methyl)-3 phenyl isoxazol-5(4H)-one (3j): *Reaction time: 96h*. Purification by flash column chromatography (SiO_2, gradient: Hex - 9:1 Hex:AcOEt - 8:2 Hex:AcOEt - 7:3 Hex:AcOEt - 1:1 Hex:AcOEt) affords the title compound as an orange oil (31 mg, 41%). ^1H (500 MHz, $CDCl_3$) δ: 7.70 (d, *J* = 7.1Hz, 2H), 7.58-7.51 (m, 3H), 6.88 (t, *J* = 8.3Hz, 2H), 6.73 (br s, 2H), 4.66 (d, *J* = 4.7Hz, 1H), 4.14 (td, *J* = 11.4Hz, *J* = 4.4Hz, 1H), 3.58 (dd, *J* = 11.4Hz, *J* = 4.7Hz, 1H), 3.05 (s, 2H), 2.90-2.88 (m, 2H), 2.51 (dd, *J* = 13.5Hz, *J* = 2.8Hz, 1H), 2.36 (t, *J* = 13.5Hz, 1H). ^{13}C (125 MHz, $CDCl_3$) δ: 211.7, 177.5, 166.1, 162.5 (d, *J* = 246.8Hz), 131.9, 131.4, (d, *J* = 3.1Hz), 129.8, 129.4, 127.4, 127.2, 116.2 (d, *J* = 21.1Hz), 51.9, 47.1, 45.8, 43.9, 36.1, 32.6. HRMS (ESI+): Calcd. for $[C_{21}H_{18}NO_3SF+H]^+$: 384.1064, found: 384.1057.

4-(3-oxo-1-phenyl-3-(p-tolyl)propyl)-3-phenylisoxazol-5(4H)-one[23] **(3k):** *Reaction time: 168h*. Purification by flash column chromatography (SiO_2, gradient: Hex - 9:1 Hex:AcOEt - 8:2 Hex:AcOEt -7:3 Hex:AcOEt - 1:1 Hex:AcOEt) affords the title compound as an brownish solid (31 mg, 40%). ^1H (500 MHz, $CDCl_3$) δ: 8.02 (d, *J* =

8.0Hz, 2H), 7.96-7.94 (m, 2H), 7.62-7.61 (m, 3H), 7.34 (d, *J* = 8.0Hz, 2H), 7.25-7.22 (m, 3H), 6.94 (d, *J* = 8.0Hz, 2H), 4.62 (dd, *J* = 18.7Hz, *J* = 11.6Hz, 1H), 4.52-5.51 (m, 1H), 4.18 (dt, *J* = 11.6Hz, *J* = 3.1Hz, 1H), 3.30 (dd, *J* = 18.7Hz, *J* = 3.1Hz, 1H), 2.47 (s, 3H). ^{13}C (125 MHz, $CDCl_3$) δ: 198.5, 177.4, 166.1, 144.6, 137.3, 134.0, 131.8, 129.4, 129.3, 128.7, 128.2, 128.1, 127.8, 127.5, 127.3, 47.9, 39.9, 38.2, 21.6. HRMS (ESI+): Calcd. for $[C_{25}H_{21}NO_3+H]^+$: 384.1594, found: 384.1606.

4-(5-methyl-3-oxo-1-phenylhexyl)-3-phenylisoxazol-5(4H)-one[23] (3l): *Reaction time: 168h*. Purification by flash column chromatography (SiO_2, gradient: Hex - 9:1 Hex:AcOEt - 8:2 Hex:AcOEt - 1:1 Hex:AcOEt) affords the title compound as an orange solid (37 mg, 53%). ^{1}H (600 MHz, $CDCl_3$) δ: 7.82-7.80 (m, 2H), 7.57-7.54 (m, 3H), 7.21-7.20 (m, 1H), 7.18-7.15 (m, 2H), 6.79 (d, *J* = 7.2Hz, 2H), 4.36 (d, *J* = 4.2Hz, 1H), 4.03-3.97 (m, 1H), 3.94-3.90 (m, 1H), 2.76 (dd, *J* = 18.4Hz, *J* = 2.4Hz, 1H), 2.49 (dd, *J* = 15.8Hz, *J* = 6.9Hz, 1H), 2.40 (dd, *J* = 15.8Hz, *J* = 7.2Hz, 1H), 2.25 (hept, *J* = 6.8Hz, 1H), 0.99 (d, *J* = 6.8Hz, 3H), 0.97 (d, *J* = 6.8Hz, 3H). ^{13}C (150 MHz, $CDCl_3$) δ: 210.1, 177.3, 166.1, 137.1, 131.8, 129.4, 128.7, 128.2, 127.7, 127.5, 127.3, 52.2, 47.7, 42.9, 39.6, 24.8, 22.6, 22.5. HRMS (ESI+): Calcd. for $[C_{22}H_{23}NO_3+H]^+$: 350.1751, found: 350.1758.

4-(3-cyclopropyl-3-oxo-1-phenylpropyl)-3-phenylisoxazol-5(4H)-one (3m): *Reaction time: 168h*. Reaction performed using aniline (0.08 mmol, 40 mol %) as aminocatalyst and benzoic acid (0.12 mmol, 60 mol %) as acid co-catalyst. Purification by flash column chromatography (SiO_2, gradient: Hex - 9:1 Hex:AcOEt - 8:2 Hex:AcOEt - 7:3 Hex:AcOEt - 1:1 Hex:AcOEt) affords the title compound as an orange solid (33 mg, 50%). m.p. 126-128 ^{o}C. ^{1}H (600 MHz, $CDCl_3$) δ: 7.82 (d, *J* = 8.1Hz, 2H), 7.56-7.53 (m, 3H), 7.22-7.16 (m, 3H), 6.82 (d, *J* = 7.Hz, 2H), 4.37 (d, *J* = 4.1Hz, 1H), 4.18 (dd, *J* = 18.8Hz, *J* = 11.5Hz, 1H), 3.93 (dt, *J* = 11.5Hz, *J* = 3.2 Hz, 1H), 2.96 (dd, *J* = 18.8Hz, *J* = 2.8Hz, 1H), 2.11-2.07 (m, 1H), 1.19-1.13 (m, 2H), 1.05-0.96 (m, 2H). ^{13}C (150 MHz, $CDCl_3$) δ: 209.9, 177.4, 166.1, 137.1, 131.8, 129.3, 128.7, 128.2, 127.7, 127.5, 127.3, 47.8, 42.8, 39.7, 21.2, 11.4, 11.3. HRMS (ESI+): Calcd. for $[C_{21}H_{19}NO_3+H]^+$: 334.1438, found: 334.1447.

4-(3-oxo-1-phenylbutyl)-3-phenylisoxazol-5(4H)-one[23] **(3n):** *Reaction time: 168h*. Purification by flash column chromatography (SiO_2, gradient: Hex - 9:1 Hex:AcOEt - 8:2 Hex:AcOEt - 7:3 Hex:AcOEt - 1:1 Hex:AcOEt). affords the title compound as brown oil (27 mg, 44%). ^{1}H (500 MHz, $CDCl_3$) δ: 7.81-7.79 (m, 2H), 7.57-7.52 (m, 3H), 7.23-7.15 (m, 3H), 6.80-6.78 (m, 2H), 4.39 (d, *J* = 4.3Hz, 1H), 4.01 (dd, *J* = 18.8Hz, *J* = 11.3Hz, 1H), 3.91-3.89 (m, 1H), 2.82 (dd, *J* = 18.8Hz, *J* = 2.8Hz, 1H), 2.31 (s, 3H). ^{13}C (125 MHz, $CDCl_3$) δ: 207.8, 177.4, 166.1, 136.1, 136.9, 131.8, 129.3, 128.7, 128.2, 127.6, 127.3, 47.7, 43.2, 39.6, 30.4. HRMS (ESI+): Calcd. for $[C_{19}H_{17}NO_3+H]^+$: 308.1281, found: 308.1279.

4-(3-oxo-1-phenylhept-6-en-1-yl)-3-phenylisoxazol-5(4H)-one[23] **(3o):** *Reaction time: 168h*. Purification by flash column chromatography (SiO_2, gradient: Hex - 9:1 Hex:AcOEt - 8:2 Hex:AcOEt - 7:3 Hex:AcOEt - 1:1 Hex:AcOEt) affords the title compound as an orange solid (21 mg, 30%). ^{1}H (500 MHz, $CDCl_3$) δ: 7.81-7.89 (m, 2H), 7.57-7.53 (m, 3H), 7.21-7.15 (m, 3H), 6.80-6.79 (m, 2H), 5.89-5.81 (m, 1H), 5.08 (dq, *J* = 17.2Hz, *J* = 1.5Hz, 1H), 5.02 (dq, *J* = 10.2Hz, *J* = 1.5Hz, 1H), 4.36 (d, *J* = 4.3Hz, 1H), 4.02 (dd, *J* = 18.5Hz, *J* = 11.4Hz, 1H), 3.95-3.91 (m, 1H), 2.79 (dd. *J* = 18.5Hz, *J* = 2.7Hz, 1H), 2.76-2.71 (m, 1H), 2.67-2.60 (m, 1H), 2.46-2.41 (m, 2H). ^{13}C (125 MHz, $CDCl_3$) δ: 209.4, 177.3, 166.0, 137.0, 136.6, 131.8, 129.4, 128.7, 128.2, 127.6, 127.5, 127.3, 115.6, 47.7, 42.5, 42.1, 39.6, 27.6. HRMS (ESI+): Calcd. for $[C_{22}H_{21}NO_3+H]^+$: 348.1594, found: 348.1590.

4-(1-(4-fluorophenyl)-5-methyl-3-oxohexyl)-3-phenylisoxazol-5(4H)-one (3p): *Reaction time: 168h*. Purification by flash column chromatography (SiO_2, gradient: Hex - 9:1 Hex:AcOEt - 8:2 Hex:AcOEt - 7:3 Hex:AcOEt - 1:1 Hex:AcOEt) affords the title compound as an orange oil (54 mg, 74%). ^{1}H (400 MHz, $CDCl_3$) δ: 7.83-7.80 (m, 2H), 7.58-7.52 (m, 3H), 6.85 (t, *J* = 8.6Hz, 2H), 6.78-6.75 (m, 2H), 4.34 (d, *J* = 3.9Hz, 1H), 3.99-3.89 (m, 2H), 2.73 (d, *J* = 15.8Hz, 1H), 2.48 (dd, *J* = 15.8Hz, *J* = 7.0Hz, 1H), 2.40 (dd, *J* = 15.8Hz, *J* = 7.0Hz, 1H), 2.24 (sept, *J* = 6.7Hz, 1H), 0.98 (d, *J* = 6.7Hz, 3H), 0.96 (d, *J* = 6.7Hz, 3H). ^{13}C (100 MHz, $CDCl_3$) δ: 209.8, 177.2, 165.9, 162.3 (d, *J* = 242.8Hz), 132.8 (d, *J* = 3.3Hz), 131.9, 129.4, 129.3 (d, *J* = 8.1Hz), 127.3, 127.2, 115.6 (d, *J* = 21.3Hz), 52.1, 47.7, 42.9, 38.8, 24.8, 22.6, 22.5. HRMS (ESI+): Calcd. for $[C_{22}H_{22}NO_3F+H]^+$: 368.1656, found: 368.1652.

3-(4-methoxyphenyl)-4-(5-methyl-3-oxo-1-phenylhexyl)isoxazol-5(4H)-one (3q): *Reaction time: 168h*. Purification by flash column chromatography (SiO_2, gradient: Hex - 9:1 Hex:AcOEt - 8:2 Hex:AcOEt - 7:3 Hex:AcOEt - 1:1 Hex:AcOEt) affords the title compound as an orange solid (49 mg, 64%). m.p. 127-129 ^oC. ^1H (400 MHz, $CDCl_3$) δ: 7.80-7.77 (m, 2H), 7.21-7.14 (m, 3H), 7.07-7.03 (m, 2H), 6.83-6.81 (m, 2H), 4.29 (d, *J* = 4.1Hz, 1H), 4.00 (dd, *J* = 18.4Hz, *J* = 11.4Hz, 1H), 3.93-3.90 (m, 1H), 3.90 (s, 3H), 2.75 (dd, *J* = 18.4Hz, *J* = 2.3Hz, 1H), 2.49 (dd, *J* = 15.7Hz, *J* = 6.9Hz, 1H), 2.41 (dd, *J* = 15.7Hz, *J* = 6.9Hz, 1H), 2.24 (sept, *J* = 6.7Hz, 1H), 0.99 (d, *J* = 6.7Hz, 3H), 0.96 (d, *J* = 6.7Hz, 3H). ^{13}C (100 MHz, $CDCl_3$) δ: 210.1, 177.5, 165.5, 162.3, 137.1, 129.0, 128.7, 128.1, 127.7, 119.9, 114.8, 55.4, 52.2, 47.8, 42.9, 39.7, 24.8, 22.6, 22.5. HRMS (ESI+): Calcd. for $[C_{23}H_{25}NO_4+H]^+$: 380.1856, found: 380.1854.

3-(4-methoxyphenyl)-4-(3-oxo-1-phenylbutyl)isoxazol-5(4H)-one (3r): *Reaction time: 168h*. Purification by flash column chromatography (SiO_2, gradient: Hex - 9:1 Hex:AcOEt - 8:2 Hex:AcOEt - 7:3 Hex:AcOEt - 1:1 Hex:AcOEt) affords the title compound as an orange oil (34 mg, 50%). ^1H (400 MHz, $CDCl_3$) δ: 7.79-7.75 (m, 2H), 7.21-7.15 (m, 3H), 7.06-7.03 (m, 2H), 6.83-6.80 (m, 2H), 4.32 (d, *J* = 4.2Hz, 1H), 4.03 (dd, *J* = 18.8Hz, *J* = 11.4Hz, 1H), 3.90 (s, 3H), 3.89-3.86 (m, 1H), 2.82 (dd, *J* = 18.8Hz, *J* = 2.7Hz, 1H), 2.31 (s, 3H). ^{13}C (100 MHz, $CDCl_3$) δ: 207.9, 177.5, 165.5, 162.3, 137.0, 129.0, 128.7, 128.2, 127.7, 119.9, 114.8, 55.4, 47.8, 43.3, 39.8, 30.4. HRMS (ESI+): Calcd. for $[C_{20}H_{19}NO_4+H]^+$: 338.1387, found: 338.1382.

4-(1-cyclopropyl-5-methyl-3-oxohexyl)-3-phenylisoxazol-5(4H)-one (3s): *Reaction time: 168h*. Purification by flash column chromatography (SiO_2, gradient: Hex - 9:1 Hex:AcOEt - 8:2 Hex:AcOEt - 7:3 Hex:AcOEt - 1:1 Hex:AcOEt) affords the title compound as an yellow solid (35 mg, 56%). m.p. 93-95 ^oC. ^1H (600 MHz, $CDCl_3$) δ: 7.92-7.90 (m, 2H), 7.53-7.51 (m, 3H), 4.16 (d, *J* = 3.2Hz, 1H), 3.55 *(dd, J = 19.1Hz, J* = 11.3Hz, 1H), 2.60 (dd, *J* = 19.1Hz, *J* = 2.8Hz, 1H), 2.43 (dd, *J* = 15.7Hz, *J* = 7.0Hz, 1H), 2.37 (dd, *J* = 15.7Hz, *J* = 7.0Hz, 1H), 2.21 (sept., *J* = 6.8Hz, 1H), 1.89 (tt, *J* = 11.0Hz, *J* = 2.8Hz, 1H), 0.98 (d, *J* = 6.7Hz, 3H), 0.96 (d, *J* = 6.7Hz, 3H), 0.67-0.61 (m, 1H), 0.42-0.34 (m, 2H), -0.18 (sext., *J* = 4.9Hz, 1H), -0.27 (sext., *J* = 4.9Hz, 1H). ^{13}C (150 MHz, $CDCl_3$) δ: 210.9, 177.7, 166.8, 131.7, 129.3, 127.6, 127.1, 52.2, 47.0, 43.7,

39.4, 24.8, 22.6, 22.5, 11.8, 4.8, 2.5. HRMS (ESI+): Calcd. for $[C_{19}H_{23}NO_3+H]^+$: 314.1751, found: 314.1745.

4-(1-cyclopropyl-3-oxobutyl)-3-phenylisoxazol-5(4H)-one (3t): *Reaction time: 168h*. Purification by flash column chromatography (SiO_2, gradient: Hex - 9:1 Hex:AcOEt - 8:2 Hex:AcOEt - 7:3 Hex:AcOEt - 1:1 Hex:AcOEt) affords the title compound as an orange solid (34 mg, 63%). m.p.: decomposition. ^{1}H (500 MHz, $CDCl_3$) δ: 7.92-7.90 (m, 2H), 7.52-7.50 (m, 3H), 4.19 (d, *J* = 3.2Hz, 1H), 3.58 (dd, *J* = 19.3Hz, *J* = 11.3Hz, 1H), 2.68 (dd, *J* = 19.3Hz, *J* = 2.7Hz, 1H), 2.26 (s, 3H), 1.87 (tt, *J* = 11.0Hz, *J* = 2.8Hz, 1H), 0.68-0.61 (m, 1H), 0.43-0.34 (m, 2H), -0.18 (sext., *J* = 4.9Hz, 1H), -0.27 (sext., *J* = 4.9Hz, 1H). ^{13}C (100 MHz, $CDCl_3$) δ: 208.5, 177.8, 166.8, 131.7, 129.3, 127.6, 127.2, 47.0, 44.1, 39.5, 30.3, 11.7, 4.8, 2.5. HRMS (ESI+): Calcd. for $[C_{16}H_{17}NO_3+H]^+$: 272.1281, found: 272.1278.

General reaction conditions for the iron-promoted decarboxylative cyclization of isoxazol-5-ones toward pyridines (Step 2): isoxazol-5-one (0.1 mmol), Fe (1 mmol), 3,5-dimethoxybenzoic acid (1 mmol), and MeOH (1 mL) are added to a round bottom flask, under air, at room temperature. The reaction mixture is capped with a rubber septum and stirred at 65 ^{o}C overnight. Then, the reaction mixture is diluted in AcOEt, washed with an aqueous saturated solution of $NaHCO_3$, dried ($MgSO_4$), concentrated under reduced pressure and purified by flash column chromatography.

2,4-diphenyl-5,6,7,8-tetrahydroquinoline (4a): Purification by flash column chromatography (SiO_2, gradient: Hex - 95:5 Hex:AcOEt - 9:1 Hex:AcOEt - 8:2 Hex:AcOEt) affords the title compound as a white solid (17 mg, 60%). ^{1}H (600 MHz, $CDCl_3$) δ: 7.98-7.97 (m, 2H), 7.47-7.34 (m, 9H), 3.1 (t, *J* = 6.4Hz, 2H), 2.66 (t, *J* = 6.4Hz, 2H), 1.97-1.93 (m, 2H), 1.78-1.74 (m, 2H). ^{13}C (150 MHz, $CDCl_3$) δ: 157.6, 154.3, 150.3, 139.8 (2x), 128.6 (2x), 128.5, 128.4, 128.3, 127.7, 126.9, 119.1, 33.4, 27.3, 23.1, 23.0. HRMS (ESI+): Calcd. for $[C_{21}H_{19}N+H]^+$: 286.1590, found: 286.1591.

2,4-diphenyl-6,7-dihydro-5H-cyclopenta [b]pyridine (4b): Purification by flash column chromatography (SiO_2, gradient: Hex - 98:2 Hex:AcOEt - 95:5 Hex:AcOEt - 9:1 Hex:AcOEt) affords the title compound as an yellow solid (13 mg, 48%). ^{1}H (500

MHz, $CDCl_3$) δ: 7.99 (d, *J* = 7.3Hz, 2H), 7.55-7.53 (m, 3H), 7.50-7.39 (m, 6H), 3.17 (t, *J* = 7.5Hz, 2H), 3.07 (t, J = 7.5Hz, 2H), 2.16 (quint., *J* = 7.5Hz, 2H). ^{13}C (125 MHz, $CDCl_3$) δ: 166.7, 156.5, 145.9, 139.9, 139.0, 133.1, 128.6 (2x), 128.4, 128.2 (2x), 127.0, 118.1, 34.8, 30.6, 23.5. HRMS (ESI+): Calcd. for $[C_{20}H_{17}N+H]^+$: 272.1434, found: 272.1427.

2,4-diphenyl-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine (4c): Purification by flash column chromatography (SiO_2, gradient: Hex - 98:2 Hex:AcOEt - 95:5 Hex:AcOEt - 9:1 Hex:AcOEt) affords the title compound as an yellow solid: 20 mg, 67%. m.p. 87-88 ^oC. ^1H (500 MHz, $CDCl_3$) δ: 8.00 (d, *J* = 7.4Hz, 2H), 7.48-7.32 (m, 9H), 3.24-3.22 (m, 2H), 2.78-2.76 (m, 2H), 1.91-1.89 (m, 2H), 1.84-1.81 (m, 2H), 1.68-1.66 (m, 2H). ^{13}C (125 MHz, $CDCl_3$) δ: 164.1, 153.3, 149.5, 140.4, 139.7, 134.0, 128.8, 128.6, 128.3 (2x), 127.5, 126.8, 119.4, 39.7, 32.4, 29.5, 28.0, 26.7. HRMS (ESI+): Calcd. for $[C_{22}H_{21}N+H]^+$: 300.1747, found: 300.1744.

4-(4-chlorophenyl)-2-phenyl-5,6,7,8-tetrahydroquinoline (4d): Purification by flash column chromatography (SiO_2, gradient: Hex - 98:2 Hex:AcOEt - 95:5 Hex:AcOEt - 9:1 Hex:AcOEt - 8:2 Hex:AcOEt) affords the title compound as an yellow solid (20 mg, 63%). ^1H (400 MHz, $CDCl_3$) δ: 7.98-7.95 (m, 2H), 7.46-7.36 (m, 6H), 7.29-7.27 (m, 2H), 3.09 (t, *J* = 6.4Hz, 2H), 2.63 (t, *J* = 6.4Hz, 2H), 1.97-1.91 (m, 2H), 1.80-1.74 (m, 2H). ^{13}C (100 MHz, $CDCl_3$) δ: 157.9, 154.4, 149.1, 139.6, 138.1, 133.9, 129.9, 128.7, 128.6 (x2), 128.3, 126.9, 118.9, 33.3, 27.3, 23.1, 23.0. HRMS (ESI+): Calcd. for $[C_{21}H_{18}ClN+H]^+$: 320.1201, found:320.1201.

2-isopropyl-4-(naphthalen-2-yl)-5,6,7,8-tetrahydroquinoline (4e): Purification by flash column chromatography (SiO_2, gradient: Hex - 98:2 Hex:AcOEt - 95:5 Hex:AcOEt - 9:1 Hex:AcOEt - 8:2 Hex:AcOEt - 7:3 Hex:AcOEt) affords the title compound as an orange solid (20 mg, 67%). m.p. 68-70 ^oC. ^1H (600 MHz, $CDCl_3$) δ: 7.90-7.86 (m, 3H), 7.75 (d, *J* = 1.0Hz, 1H), 7.54-7.51 (m, 2H), 7.42 (dd, *J* = 8.3Hz, *J* = 1.7Hz, 1H), 6.96 (s, 1H), 3.09 (quint., *J* = 7.0Hz, 1H), 3.02 (t, *J* = 6.4Hz, 2H), 2.63 (t, *J* = 6.4Hz, 2H), 1.94-1.90 (m, 2H), 1.74-1.70 (m, 2H), 1.32 (d, *J* = 7.0Hz, 6H). ^{13}C (100 MHz, $CDCl_3$) δ: 164.1, 156.5, 150.1, 137.5, 133.1, 132.6, 128.0, 127.8, 127.7, 127.4,

127.3, 126.7, 126.4, 126.3, 118.3, 36.1, 33.0, 27.3, 23.1, 23.0, 22.8. HRMS (ESI+): Calcd. for $[C_{22}H_{23}N+H]^+$: 302.1903, found: 302.1903.

2-ethyl-4-phenyl-5,6,7,8-tetrahydroquinoline (4f): Purification by flash column chromatography (SiO_2, gradient: Hex - 95:5 Hex:AcOEt - 9:1 Hex:AcOEt - 8:2 Hex:AcOEt - 7:3 Hex:AcOEt) affords the title compound as an yellow solid (15 mg, 63%). m.p. 56-58 ^oC. ^1H (500 MHz, $CDCl_3$) δ: 7.44-7.36 (m, 3H), 7.30-726 (m, 2H), 6.85 (s, 1H), 2.98 (t, *J* = 6.5Hz, 2H), 2.79 (q, *J* = 7.6Hz, 2H), 2.59 (t, *J* = 6.5Hz, 2H), 1.92-1.87 (m, 2H), 1.73-1.69 (m, 2H), 1.30 (t, *J* = 7.6Hz, 3H). ^{13}C (125 MHz, $CDCl_3$) δ: 160.1, 156.7, 150.0, 139.8, 128.5, 128.2, 127.6, 126.9, 120.1, 33.0, 31.1, 27.1, 23.1, 23.0, 14.3. HRMS (ESI+): Calcd. for $[C_{17}H_{19}N+H]^+$: 238.1590, found: 238.1587.

4-(furan-2-yl)-2-isopropyl-5,6,7,8-tetrahydroquinoline (4g): Purification by flash column chromatography (SiO_2, gradient: Hex - 95:5 Hex:AcOEt - 9:1 Hex:AcOEt - 8:2 Hex:AcOEt - 7:3 Hex:AcOEt) affords the title compound as an yellow oil (17 mg, 71%). ^1H (500 MHz, $CDCl_3$) δ: 7.55 (d, *J* = 1.3Hz, 1H), 7.35 (s, 1H), 6.69 (d, *J* = 3.4Hz, 1H), 6.53 (dd, *J* = 3.4Hz, *J* = 1.8Hz, 1H), 3.04 (sept., *J* = 7.0Hz, 1H), 2.97 (t, *J* = 6.4Hz, 2H), 2.83 (t, *J* = 6.4Hz, 2H), 1.93-1.88 (m, 2H), 1.85-1.81 (m, 2H), 1.32 (d, *J* = 7.0Hz, 6H). ^{13}C (125 MHz, $CDCl_3$) δ: 164.1, 157.1, 151.5, 142.7, 137.3, 125.1, 114.4, 111.6 (2x), 36.2, 33.5, 27.8, 23.1, 22.8 (x2). HRMS (ESI+): Calcd. for $[C_{16}H_{19}NO+H]^+$: 242.1539, found: 242.1535.

2-ethyl-7,7-dimethyl-4-phenyl-5,6,7,8-tetrahydroquinoline (4h): Purification by flash column chromatography (SiO_2, gradient: Hex - 95:5 Hex:AcOEt - 9:1 Hex:AcOEt - 8:2 Hex:AcOEt) affords the title compound as an yellow oil (13 mg, 50%). ^1H (500 MHz, $CDCl_3$) δ: 7.45-7.41 (m, 2H), 7.39-7.36 (m, 1H), 7.30-7.28 (m, 2H), 6.86 (s, 1H), 2.79 (q, *J* = 7.6Hz, 2H), 2.76 (s, 2H), 2.60 (t, *J* = 6.6Hz, 2H), 1.50 (t, *J* = 6.6Hz, 2H), 1.30 (t, *J* = 7.6Hz, 3H), 1.04 (s, 6H). ^{13}C (125 MHz, $CDCl_3$) δ: 160.4, 156.3, 149.9, 139.9, 128.5, 128.2, 127.6, 125.4, 120.1, 46.9, 35.7, 31.1, 29.7, 28.2, 24.1, 14.2. HRMS (ESI+): Calcd. for $[C_{19}H_{23}N+H]^+$: 266.1903, found: 266.1900.

4-(4-fluorophenyl)-2-phenyl-7,8-dihydro-5H-spiro[quinoline-6,2'-[1,3]dioxolane] (4i): Purification by flash column chromatography (SiO_2, gradient: Hex - 98:2

Hex:AcOEt - 95:5 Hex:AcOEt - 9:1 Hex:AcOEt) affords the title compound as a white solid (27 mg, 75%). m.p. 155-157 °C. ^{1}H (500 MHz, $CDCl_3$) δ: 7.96 (d, *J* = 7.3Hz, 2H), 7.45 (t, *J* = 7.4Hz, 2H), 7.40-7.37 (m, 2H), 7.32-7.29 (m, 2H), 7.15 (t, *J* = 8.6Hz, 2H), 4.02-3.93 (m, 4H), 3.30 (t, *J* = 6.8Hz, 2H), 2.87 (s, 2H), 2.11 (t, *J* = 6.8Hz, 2H). ^{13}C (125 MHz, $CDCl_3$) δ: 162.5 (d, *J* = 246.3Hz), 156.2, 155.1, 149.6, 139.5, 135.0 (d, *J* = 3.4Hz), 130.3, 130.2, 128.7, 126.9, 125.5, 119.3, 115.5 (d, *J* = 21.5Hz), 107.9, 64.6 (x2), 37.1, 31.6, 31.5. HRMS (ESI+): Calcd. for $[C_{23}H_{20}FNO_2+H]^+$: 362.1551, found: 362.1551.

4-(4-fluorophenyl)-2-phenyl-7,8-dihydro-5H-thiopyrano[4,3-b]pyridine (4j): Purification by flash column chromatography (SiO_2, gradient: Hex - 98:2 Hex:AcOEt - 95:5 Hex:AcOEt - 9:1 Hex:AcOEt) affords the title compound as a yellow solid (16 mg, 50%). m.p. 116-117 °C. ^{1}H (400 MHz, $CDCl_3$) δ: 8.00-7.98 (m, 2H), 7.48-7.32 (m, 6H), 7.18 (t, *J* = 8.6Hz, 2H), 3.70 (s, 2H), 3.37 (t, *J* = 6.4Hz, 2H), 3.06 (t, *J* = 6.4Hz, 2H). ^{13}C (100 MHz, $CDCl_3$) δ: 162.7 (d, *J* = 246.6Hz), 157.4, 155.0, 147.7, 139.1, 134.5 (d, *J* = 3.4Hz), 130.5 (d, *J* = 8.1Hz), 128.9, 128.7, 127.2, 126.9, 119.5, 115.7 (d, *J* = 21.5Hz), 34.3, 26.6, 26.4. HRMS (ESI+): Calcd. for $[C_{20}H_{16}NFS+H]^+$: 322.1060, found: 322.1057.

2,4-diphenyl-6-(p-tolyl)pyridine (4k): Purification by flash column chromatography (SiO_2, gradient: Hex - 95:5 Hex:AcOEt - 9:1 Hex:AcOEt - 8:2 Hex:AcOEt) affords the title compound as a yellow solid (24 mg, 76%).^{1}H (400 MHz, $CDCl_3$) δ: 8.23-8.21 (m, 2H), 8.12 (d, *J* = 8.0Hz, 2H), 7.88 (s, 2H), 7.77-7.74 (m, 2H), 7.57-7.44 (m, 6H), 7.33 (d, *J* = 8.0Hz, 2H), 2.45 (s, 3H). ^{13}C (100 MHz, $CDCl_3$) δ: 157.5, 157.4, 150.1, 139.7, 139.2, 139.0, 136.8, 129.4, 129.1, 129.0, 128.9, 128.7, 127.2, 127.1, 127.0, 116.8 (2x), 21.3. HRMS (ESI+): Calcd. for $[C_{24}H_{19}N+H]^+$: 322.1590, found: 322.1588.

2-isobutyl-4,6-diphenylpyridine (4l): Purification by flash column chromatography (SiO_2, gradient: Hex - 98:2 Hex:AcOEt - 95:5 Hex:AcOEt - 9:1 Hex:AcOEt) affords the title compound as an orange oil (20 mg, 70%). ^{1}H (500 MHz, $CDCl_3$) δ: 8.07-8.05 (m, 2H), 7.74 (d, *J* = 1.3Hz, 1H), 7.71-7.69 (m, 2H), 7.52-7.40 (m, 6H), 7.27 (d, *J* = 1.3Hz, 1H), 2.80 (d, *J* = 7.2Hz, 2H), 2.28 (sept., *J* = 6.8Hz, 1H), 1.01 (d, *J* = 6.8Hz, 6H). ^{13}C (125 MHz, $CDCl_3$) δ: 162.0, 157.5, 149.2, 140.0, 139.1, 129.0, 128.8, 127.7 (2x), 127.1

(x2), 120.0, 116.2, 47.8, 29.1, 22.6. HRMS (ESI+): Calcd. for $[C_{21}H_{21}N+H]^+$: 288.1747, found: 288.1743.

2-cyclopropyl-4,6-diphenylpyridine (4m): Purification by flash column chromatography (SiO_2, gradient: Hex - 98:2 Hex:AcOEt - 95:5 Hex:AcOEt - 9:1 Hex:AcOEt) affords the title compound as a yellow oil (16 mg, 60%). ^{1}H (600 MHz, $CDCl_3$) δ: 8.08-8.06 (m, 2H), 7.70-7.68 (m, 3H), 7.51-7.40 (m, 6H), 7.29 (d, *J* = 1.4Hz, 1H), 2.17 (quint., *J* = 4.8Hz, 1H), 1.23-1.20 (m, 2H), 1.05-1.02 (m, 2H). ^{13}C (150 MHz, $CDCl_3$) δ: 163.0, 157.0, 149.1, 139.8, 139.2, 129.0, 128.7 (2x), 128.6, 127.1, 126.9, 117.9, 115.5, 17.4, 9.9. HRMS (ESI+): Calcd. for $[C_{20}H_{17}N+H]^+$: 272.1434, found: 272.1432.

2-methyl-4,6-diphenylpyridine (4n): Purification by flash column chromatography (SiO_2, gradient: Hex - 98:2 Hex:AcOEt - 95:5 Hex:AcOEt - 9:1 Hex:AcOEt) affords the title compound as a yellow solid (16 mg, 64%). ^{1}H (500 MHz, $CDCl_3$) δ: 8.08-8.03 (m, 2H), 7.73 (d, *J* = 1.0Hz, 1H), 7.70-7.68 (m, 2H), 7.52-7.42 (m, 6H), 7.33 (d, *J* = 1.0Hz, 1H), 2.71 (s, 3H). ^{13}C (125 MHz, $CDCl_3$) δ: 158.8, 157.6, 149.6, 139.7, 138.8, 129.0, 128.9, 128.8, 128.7, 127.2, 127.1, 119.8, 116.2, 24.7. HRMS (ESI+): Calcd. for $[C_{18}H_{15}N+H]^+$: 246.1277, found: 246.1276.

2-(but-3-en-1-yl)-4,6-diphenylpyridine (4o): Purification by flash column chromatography (SiO_2, gradient: Hex - 98:2 Hex:AcOEt - 95:5 Hex:AcOEt) affords the title compound as a brown oil (17 mg, 61%). ^{1}H (500 MHz, $CDCl_3$) δ: 8.07-8.06 (m, 2H), 7.75 (d, *J* = 1.5Hz, 1H), 7.70-7.68 (m, 2H), 7.52-7.40 (m, 6H), 7.31 (d, *J* = 1.5Hz, 1H), 6.00-5.93 (m, 1H), 5.12 (dq, *J* = 17.2Hz, *J* = 1.4Hz, 1H), 5.02 (dq, *J* = 10.2Hz, *J* = 1.4Hz, 1H), 3.03 (t, *J* = 7.5Hz, 2H), 2.67-2.62 (m, 2H). ^{13}C (125 MHz, $CDCl_3$) δ: 161.8, 157.5, 149.5, 139.9, 139.0, 138.1, 129.0, 128.8 (2x), 128.7, 127.1 (x2), 119.4, 116.3, 115.0, 37.9, 33.7. HRMS (ESI+): Calcd. for $[C_{21}H_{19}N+H]^+$: 286.1590, found: 286.1586.

4-(4-fluorophenyl)-2-isobutyl-6-phenylpyridine (4p): Purification by flash column chromatography (SiO_2, gradient: Hex - 98:2 Hex:AcOEt - 95:5 Hex:AcOEt - 9:1 Hex:AcOEt) affords the title compound as a yellow oil (19 mg, 62%). ^{1}H (600 MHz, $CDCl_3$) δ: 8.06-8.04 (m, 2H), 7.69 (d, *J* = 1.5Hz, 1H), 7.68-7.65 (m, 2H), 7.50-7.47 (m,

2H), 7.43-7.41 (m, 1H), 7.22 (d, *J* = 1.5Hz, 1H), 7.43-7.17 (m, 2H), 2.79 (d, *J* = 7.2Hz, 2H), 2.28 (sept., *J* = 6.7Hz, 1H), 1.02 (d, *J* = 6.7Hz, 6H). ^{13}C (150 MHz, $CDCl_3$) δ: 163.3 (d, *J* = 247.2Hz), 162.1, 157.6, 148.1, 139.9, 135.1 (d, *J* = 3.3Hz), 128.9 (d, *J* = 8.5Hz), 128.8, 128.7, 127.1, 119.8, 116.1, 115.9 (d, *J* = 4.0 Hz), 47.7, 29.1, 25.5. HRMS (ESI+): Calcd. for $[C_{21}H_{20}NF+H]^+$: 306.1653, found: 306.1649.

2-isobutyl-6-(4-methoxyphenyl)-4-phenylpyridine (4q): Purification by flash column chromatography (SiO_2, gradient: Hex - 98:2 Hex:AcOEt - 95:5 Hex:AcOEt - 9:1 Hex:AcOEt) affords the title compound as an orange oil (18 mg, 57%). ^{1}H (500 MHz, $CDCl_3$) δ: 8.02 (d, *J* = 8.7Hz, 2H), 7.69-7.68 (m, 3H), 7.51-7.42 (m, 3H), 7.22 (s, 1H), 7.01 (d, *J* = 8.7Hz, 2H), 3.87 (s, 3H), 2.78 (d, *J* = 7.2Hz, 2H), 2.28 (sept., *J* = 6.7Hz, 1H), 1.02 (d, *J* = 6.7Hz, 6H). ^{13}C (125 MHz, $CDCl_3$) δ: 161.8, 160.3, 157.1, 149.1, 139.2, 132.7, 129.0, 128.7, 128.4, 127.1, 119.3, 115.4, 114.0, 55.3, 47.8, 29.0, 22.6. HRMS (ESI+): Calcd. for $[C_{22}H_{23}NO+H]^+$: 318.1852, found: 318.1849.

2-(4-methoxyphenyl)-6-methyl-4-phenylpyridine (4r): Purification by flash column chromatography (SiO_2, gradient: Hex - 98:2 Hex:AcOEt - 95:5 Hex:AcOEt - 9:1 Hex:AcOEt) affords the title compound as an orange solid (15 mg, 55%). m.p. 93-95 ^{o}C. ^{1}H (600 MHz, $CDCl_3$) δ**:** 7.99 (d, *J* = 8.8Hz, 2H), 7.68-7.67 (m, 3H), 7.51-7.43 (m, 3H), 7.26 (d, *J* = 1.0Hz, 1H), 7.00 (d, *J* = 8.8Hz, 2H), 3.87 (s, 3H), 2.67 (s, 3H). ^{13}C (150 MHz, $CDCl_3$) δ: 160.3, 158.7, 157.3, 149.4, 139.0, 132.5, 129.0, 128.8, 129.4, 127.1, 119.2, 115.4, 114.1, 55.4, 24.8. HRMS (ESI+): Calcd. for $[C_{19}H_{17}NO+H]^+$: 276.1383, found: 276.1382.

4-cyclopropyl-2-isobutyl-6-phenylpyridine (4s): Purification by flash column chromatography (SiO_2, gradient: Hex - 98:2 Hex:AcOEt - 95:5 Hex:AcOEt - 9:1 Hex:AcOEt) affords the title compound as an orange oil (13 mg, 52 %). ^{1}H (500 MHz, $CDCl_3$) δ: 7.97-7.95 (m, 2H), 7.44 (t, *J* = 7.2Hz, 2H), 7.39-7.36 (m, 1H), 7.18 (d, *J* = 1.2Hz, 1H), 6.72 (d, *J* = 1.2Hz, 1H), 2.67 (d, *J* = 7.2Hz, 2H), 2.20 (sept., *J* = 6.7Hz, 1H), 1.87-1.82 (m, 1H), 1.10-1.06 (m, 2H), 0.97 (d, *J* = 6.7Hz, 6H), 0.86-0.82 (m, 2H). ^{13}C (125 MHz, $CDCl_3$) δ: 161.1, 156.7, 154.2, 140.2, 128.6, 128.5, 127.1, 118.9, 115.1, 47.5, 29.0, 22.5, 15.1, 10.2. HRMS (ESI+): Calcd. for $[C_{18}H_{21}N+H]^+$: 252.1747, found: 252.1745.

4-cyclopropyl-2-methyl-6-phenylpyridine (4t): Purification by flash column chromatography (SiO_2, gradient: Hex - 98:2 Hex:AcOEt - 95:5 Hex:AcOEt - 9:1 Hex:AcOEt) affords the title compound as a yellow oil (12 mg, 57%). ^{1}H (400 MHz, $CDCl_3$) δ: 7.94-7.92 (m, 2H), 7.47-7.36 (m, 3H), 7.18 (d, *J* = 1.0Hz, 1H), 6.76 (d, *J* = 1.0Hz, 1H), 2.57 (s, 3H), 1.92-1.86 (m, 1H), 1.10-1.05 (m, 2H), 0.86-0.81 (m, 2H). ^{13}C (100 MHz, $CDCl_3$) δ: 158.1, 157.0, 154.4, 140.1, 128.6, 128.5, 127.1, 118.6, 115.2, 24.6, 15.1, 10.1. HRMS (ESI+): Calcd. for $[C_{15}H_{15}N+H]^+$: 210.1277, found: 210.1275.

(*E*)-2-benzylidenecyclohexan-1-one (6): Prepared according to the literature.[28] Purification by flash column chromatography (SiO_2, gradient: Hex - 98:2 Hex:AcOEt - 95:5 Hex:AcOEt) affords the title compound as a yellow solid (110 mg, 87%). ^{1}H (400 MHz, $CDCl_3$) δ: 7.49 (t, *J* = 2.1Hz, 1H), 7.41-7.30 (m, 5H), 2.84 (td, *J* = 6.4Hz, *J* = 2.1Hz, 2H), 2.54 (t, *J* = 6.7Hz, 2H), 1.96-1.90 (m, 2H), 1.80-1.74 (m, 2H). ^{13}C (100 MHz, $CDCl_3$) δ: 201.8, 136.7, 135.6 (2x), 130.3 (2x), 128.5, 128.3 (2x), 40.3, 28.9, 23.9, 23.4. HRMS (ESI+): Calcd. for $[C_{13}H_{14}O + H]^+$: 187.1117, found: 187.1115.

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Associated Content

Supporting Information.

^{1}H and ^{13}C NMR spectra and HRMS of all compounds, melting points of new crystalline solids and X-ray crystallographic data of **4k**.

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Notes

The authors declare no competing financial interest.

References

[1] a) Francisco, W.; Pivatto, M.; Danuello, A.; Regasini, L. O.; Baccini, L. R.; Young, M. C. M.; Lopes, N. P.; Lopes, J. L. C.; Bolzani, V. S. *J. Nat. Prod.* **2012**, *75*, 408. b) Groenhagen, U.; Maczka, M.; Dickschat, M. S.; Schulz, S. *Beilstein J. Org. Chem.* **2014**, *10*, 1421. c) Pinder, A. R. *Nat. Prod. Rep.* **1990**, *7*, 447.

[2] a) Roughley, S. D.; Jordan, A. M. *J. Med. Chem.* **2011**, 54, 3451. b) Baumann, M.; Baxendale, I. R. *Beilstein J. Org. Chem.* **2013**, *9*, 2265.

[3] a) Guan, A.-Y.; Liu, C.-L.; Sun, X.-F.; Xie, Y.; Wang, M.-A. *Bioorg. Med. Chem.* **2016**, *24*, 342. b) Jeanmart, S.; Edmunds, A. J. F.; Lamberth, C.; Pouliot, M. *Bioorg. Med. Chem.* **2016**, *24*, 317.

[4] Kwong, H.-L.; Yeung, H.-L.; Yeung, C.-T.; Lee, W.-S.; Lee, C.-S.; Wong, W.-L. *Coord. Chem Rev.* **2007**, *251*, 2188.

[5] a) Fréchet, J. M. J.; de Meftahi, M. V. *Brit. Polym. J.* **1984**, *16*, 193. b) Wang, Y. Z.; Gebler, D. D.; Fu, D. K.; Swager, T. M.; MacDiarmid, A. G.; Epstein, A. J. *Synth. Met.* **1997**, *85*, 1179. c) Susumu, K; Oh, E.; Delehanty, J. B.; Pinaud, F.; Gemmill, K. B.; Walper, S.; Breger, J.; Schroeder, M. J.; Stewart, M. H.; Jain, V.; Whitaker, C. M.; Huston, A. L.; Medintz, I. L. *Chem. Mater.* **2014**, *26*, 5327.

[6] Selected examples: a) Robinson, J. M.; Ahmed, M.; Alaniz, N. J.; Boyles, T. P.; Brasher, C. D.; Floyd, K. A.; Holland, P. L.; Maruffo, L. D.; MacMahan, T. L.; Middleton, S.; O´Hara, K. D.; Pack, M. J.; Reynolds, B. D.; Rodriguez, R. R.; Sawyer, D. E.; Sharp, E.; Simpson, S. L.; Vanlandingham, C. L.; Velasquez, R. S.; Welch, B. M.; Wright, C. D. *J. Heterocyclic Chem.* **1998**, *35*, 65. b) Dediu, O. G.; Yehia, N. A. M.; Oeser, T.; Polborn, K.; Müller, T. J. J. *Eur. J. Org. Chem.* **2005**, *9*, 1834. c) Xi, L.-Y.; Zhang, R.-Y.; Liang, S.; Chen, S.-Y.; Yu, X.-Q. *Org. Lett.* **2014**, *16*, 5269. d) Shen, J.; Cai, D.; Kuai, C.; Liu, Y.; Wei, M.; Cheng, G.; Cui, X. *J. Org. Chem.*, **2015**, *80*, 6584.

[7] Selected examples: a) Andersson, H.; Almqvist, F.; Olsson, R. *Org. Lett.* **2007**, *9*, 1335. b) Movassaghi, M.; Hill, M. D. *J. Am. Chem. Soc.*, **2006**, *128*, 4592. c) Tanaka, K.; Suzuki, N.; Nishida, G. *Eur. J. Org. Chem.*, **2006**, *17*, 3917. d) Medina, S.; Domínguez, G.; Pérez-Castells, J. *Org. Lett.* **2012**, 14, 4982.

[8] Selected examples: a) Palacios, F.; Alonso, C.; Rodríguez, M.; de Marigorta, E. M.; Rubiales, G. *Eur. J. Org. Chem.* **2005**, *9*, 1795. b) Wu, J.; Xu, W.; Yu, Z.-X.; Wang, J. *J. Am. Chem. Soc.* **2015**, *137*, 9489. c) Movassaghi, M.; Hill, M. D.; Ahmad, O. K. *J. Am. Chem. Soc.*, **2007**, *129*, 10096.

[9] For representative examples of other methods, see: a) Allais, C.; Grassot, J. M.; Rodriguez, J.; Constatieux, T. *Chem. Rev.* **2014**, *114*, 10829. b) Nakao, Y. *Synthesis* **2011**, *20*, 3209. c) Wei, H.;

Li, Y.; Xiao, K.; Cheng, B.; Wang, H.; Hu, L.; Zhai, H.; *Org. Lett.*, **2015**, *17*, 5974. d) Gati, W.; Rammah, M. M.; Rammah, M. B.; Couty, F.; Evano, G. *J. Am. Chem. Soc.* **2012**, *134*, 9078. e) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, 130, 3645. f) Manning, J. R.; Davies, H. M. L. *J. Am. Chem. Soc.* **2008**, 130, 8602. g) Chen, M. Z.; Micalizio, G. C. *J. Am. Chem. Soc.* **2012**, 134, 1352.

[10] a) Jiang, H.; Yang, J.; Tang, X.; Li, J.; Wu, W. *J. Org. Chem.* **2015**, *80*, 8763. b) Wei, Y.; Yoshikai, N. *J. Am. Chem. Soc.* **2013**, *135*, 3756. c) Ren, Z.-H.; Zhang, Z.-Y.; Yang, B.-Q.; Wang, Y.-Y.; Guan, Z.-H. *Org. Lett.* **2011**, 13, 5394. d) Fu, Y.; Wang, P.; Guo, X.; Wu, P.; Meng, X.; Chen, B. *J. Org. Chem.* **2016**, 81, 11671.

[11] Zheng, M.; Chen, P.; Wu, W.; Jiang, H. *Chem. Commun.* **2016**, *52*, 84.

[12] Zhao, M.-N.; Ren, Z.-H.; Yu, L.; Wang, Y.-Y.; Guan, Z.-H. *Org. Lett.* **2016**, *18*, 1194.

[13] Zhao, M.-N.; Hui, R.-R.; Ren, Z.-H.; Wang, Y.-Y.; Guan, Z.-H. *Org. Lett.* **2014**, 16, 3082.

[14] Huang, H.; Cai, J.; Tang, L.; Wang, Z.; Li, F.; Deng, G.-J. *J. Org. Chem.* **2016**, *81*, 1499.

[15] a) Neely, J. M.; Rovis, T. *J. Am. Chem. Soc.* **2014**, 136, 2735. b) Neely, J. M.; Rovis, T. *J. Am. Chem. Soc,* **2013**, 135, 66. c) Martin, R. M.; Bergman, R. G.; Ellman, J. A. *J. Org. Chem,* **2012**, 77, 2501. d) Parthasarathy, K.; Jeganmohan, M.; Cheng, C.-H. *Org. Lett.* **2008**, 10, 325. e) Chen, S.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2015**, 17, 2567.

[16] Liu, S.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2008**, *130*, 6918.

[17] Selected references: a) Hellmuth, T.; Frey, W.; Peters, R. *Angew. Chem. Int. Ed.* **2015**, *54*, 2788. b) Zhang, H.; Whang, B.; Cui, L.; Bao, X.; Qu, J.; Song, Y. *Eur. J. Org. Chem.* **2015**, *10*, 2143. c) Jurberg, I. D.; Gagosz, F.; Zard, S. Z. *Org. Lett.* **2010**, *12*, 416. d) Meng, W. T.; Zheng, Y.; Nie, J.; Xiong, H. Y.; Ma, J.-A. *J. Org. Chem.* **2013**, *78*, 559.

[18] a) Capreti, N. M. R.; Jurberg, I. D. *Org. Lett.* **2015**, *17*, 2490. b) Jurberg, I. D.; Davies, H. M. L. *Org. Lett.* **2017**, DOI: 10.1021/acs.orglett.7b02436.

[19] Abbiati, G.; Beccalli, E. M.; Broggini, G.; Zoni, C. *Tetrahedron* **2003**, *59*, 9887.

[20] Too, P. C.; Wang, Y.-F.; Chiba, S. *Org. Lett.* **2010**, *12*, 5688.

[21] Rieckhoff, S.; Hellmuth, T.; Peters, R. *J. Org. Chem.* **2015**, 80, 6822.

[22] Air oxidation of dihydropyridines to the corresponding pyridines is a fairly easy event. See for instance references 16 and 21.

[23] This selectivity has already been remarked and studied by our group in an asymmetric context. See: Jurberg, I. D. *Chem. Eur. J.* **2017**, 23, 9716.

[24] Boulton, A. J.; Katritzky, A. R. *Tetrahedron*, **1961**, *12*, 41.

[25] a) Hunter, C. A.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1990**, *112*, 5525. For a example of precedent, see: b) Kolb, H. C.; Andersson, P. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1994**, *116*, 1278.

[26] Reviews: a) Eberlin, M. N. *Eur. J. Mass Spectrom.* **2007**, *13*, 19. b) Iacobucci, C.; Reale, S.; De Angelis, F. *Angew. Chem. Int. Ed.* **2016**, *55*, 2980.

[27] A 2*H*-azirine intermediate could be also assigned to the ion of m/z 304.1696 in the mechanistic scenario leading to pyridine **4a** (Scheme 5), but its formation seems unlikely under the reducing acidic conditions employed. For examples of the involvement of 2*H*-azirines in the

decarboxylation of isoxazol-5-ones, see: a) Rieckhoff, S.; Titze, M.; Frey, W.; Peters, R. *Org. Lett.* **2017**, 19, 4436. b) Okamoto, K.; Shimbayashi, T.; Yoshida, M.; Nanya, A.; Ohe, K. *Angew. Chem. Int. Ed.* **2016**, 55, 7199.

[28] Warner, M. C.; Nagendiran, A.; Bogár, K.; Bäckvall, J.-E. *Org. Lett.* **2012**, *14*, 5094.