Streamlining the Synthesis of Pyridones through Oxidative Amination

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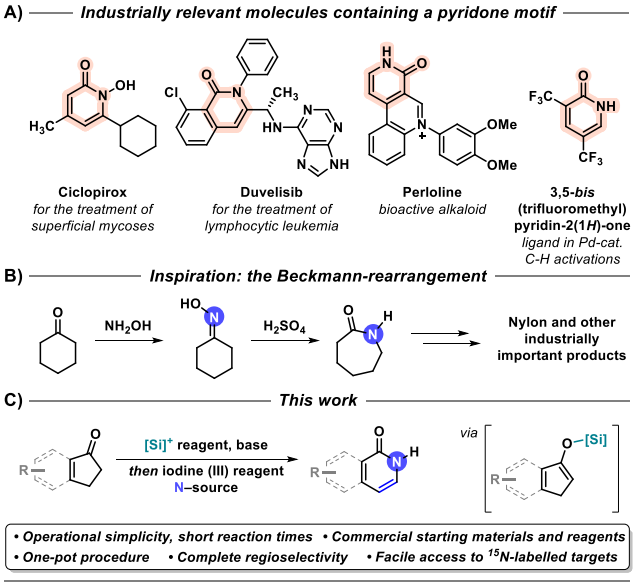
Abstract: Herein we report the development of an oxidative amination process for the streamlined synthesis of pyridones from cyclopentenones. Cyclopentenone building blocks can undergo *in situ* silyl enol ether formation, followed by the introduction of a nitrogen atom into the carbon skeleton with successive aromatisation to yield pyridones. The reaction sequence is operationally simple, rapid, and carried out in one pot. The reaction proceeds under mild conditions, exhibits broad functional group tolerance, complete regioselectivity, and is well scalable. The developed method provides facile access to the synthesis of ^{15}N-labelled targets, industrially relevant pyridone products and their derivatives in a fast and efficient way.

N-Heterocyclic compounds are ubiquitous motifs in organic chemistry, both in industrial and academic research. Their prevalence is well reflected by the fact that more than half of FDA-approved drugs feature an *N*-heterocycle.[1] Pyridones are commonly found among drug molecules (Scheme 1A), with five examples present among the top 200 drug molecules by retail sales as of 2024.[2] Pyridones are also widely used in organometallic chemistry,[3] often employed as ligands in C-H functionalisation reactions.[4,5] Furthermore, pyridones are useful intermediates *en route* to densely functionalised pyridines, which are challenging to access otherwise.[6,7]

The traditional methods for the synthesis of 2-pyridones include classical condensation processes of acyclic building blocks such as the Guareschi synthesis and Knoevenagel-type condensations,[8,9] the reaction of 2*H*-pyran-2-one derivatives with ammonia,[9] the rearrangements of pyridine-*N*-oxides or pyridinium salts,[10,11] and transformations of the corresponding pyridine derivatives,[9] among other methods.[9,12,13] However, these pathways are often lengthy, require pre-functionalised building blocks, employ harsh conditions, or lack generality.

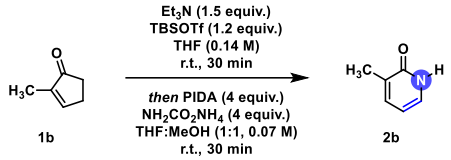
An alternative, more facile access to pyridones would be the direct ring expansion of readily available carbocycles. Cyclopentenones, which are abundant and versatile building blocks in synthetic organic chemistry,[14] could be ideal precursors for the synthesis of a wide range of pyridones through oxidatively introducing a nitrogen atom in the carbon skeleton.[15–27] An analogous process is the Beckmann rearrangement, which has found broad applications in the synthesis of saturated lactams from cyclic ketones through oxime intermediates under acid catalysis, as illustrated by the industrial synthesis of Nylon (Scheme 1B). [28–34]



Scheme 1. Context of this work.

Inspired by the Beckmann rearrangement and the experience of our group in electrophilic amination,[35–38] we hypothesised that instead of N-O reagents, the highly electrophilic species formed upon mixing an iodine(III) reagent and a nitrogen source could serve as an efficient reactant in achieving a direct cyclopentenone to pyridone conversion.[23–25,39–44] Such bis-electrophilic species would not only serve as a nitrogen source, but also provide a synthon in which the nitrogen atom has the correct oxidation state to directly enable the desired oxidative process. We further reasoned that forming silyl enol ethers from the cyclopentenones *in situ* would be highly beneficial, firstly for leveraging their high nucleophilicity, and secondly for enabling full control over the regioselectivity of the subsequent nitrogen atom insertion step (Scheme 1C). Herein, the successful development, optimisation, and applications of this reaction are presented.

Table 1. Selected optimisation data for the transformation of cyclopentenones to pyridones.[a]

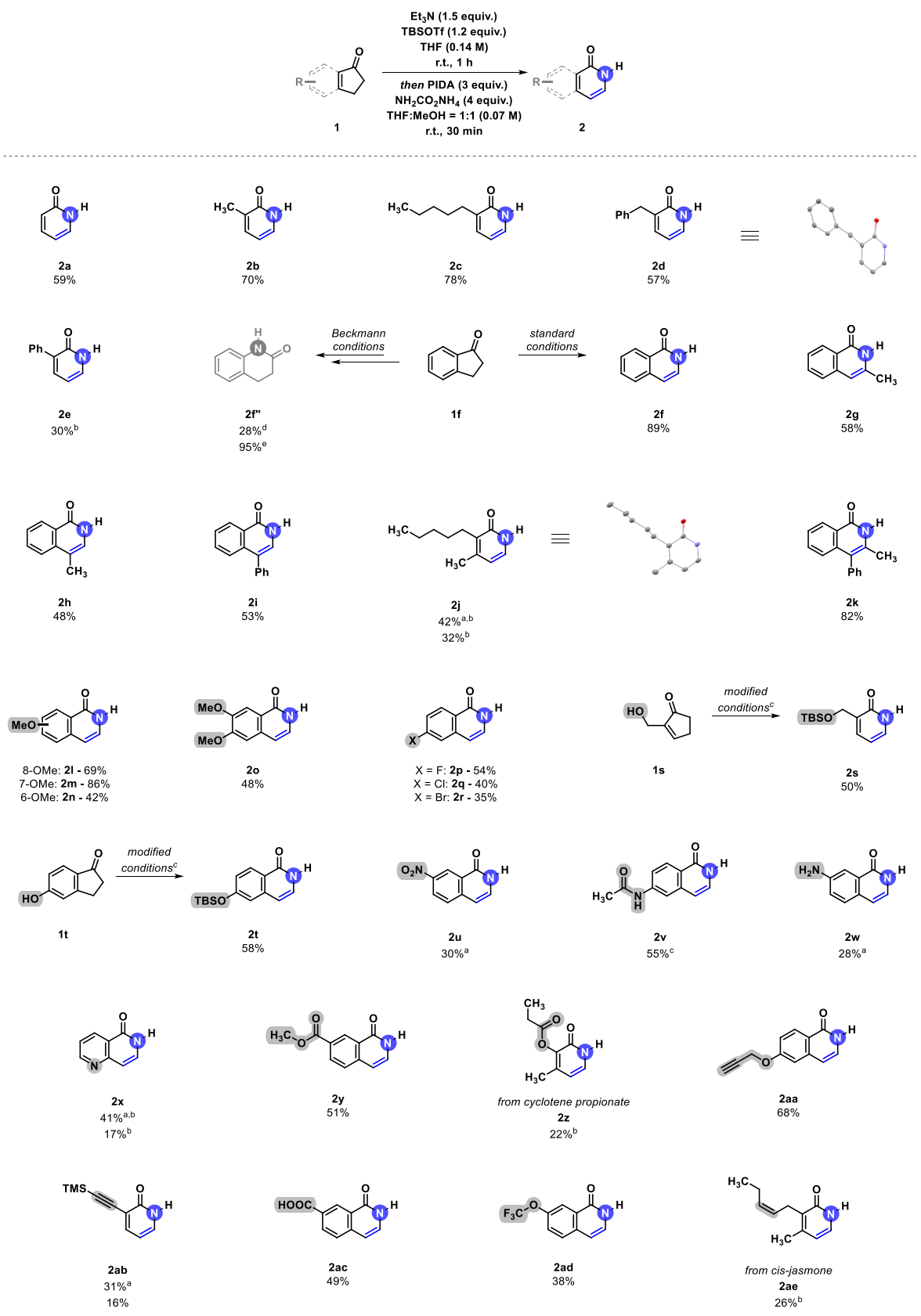


Entry	Deviations from above	Yield[b] of **2b** [%]
1	None	66
2	6 equiv. PIDA instead of 4 equiv.	67
3	**3 equiv. PIDA instead of 4 equiv.**	**67**
4	2 equiv. PIDA instead of 4 equiv.	14
5	6 equiv. $NH_2CO_2NH_4$ instead of 4 equiv., 3 equiv. PIDA instead of 4 equiv.	63
6	TIPSOTf instead of TBSOTf	31
7	TMSOTf instead of TBSOTf	57
8	PIFA instead of PIDA	36
9	NH_4Cl (4 equiv.) + K_2CO_3 (4 equiv.) instead of $NH_2CO_2NH_4$	65
10	THF:MeOH = 4:1 instead of 1:1	60
11	Pentane instead of THF	55

[a] Reaction conditions: 1st step: 2-methylcyclopentenone (0.30 mmol), Et_3N (0.45 mmol), TBSOTf (0.36 mmol), THF (0.14 M), r.t., 30 min.; 2nd step: ammonium carbamate (1.20 mmol), PIDA (1.20 mmol), THF:MeOH (1:1, 0.07 M), r.t., 30 min. [b] Determined by ^{1}H-NMR using mesitylene as internal standard.

In preliminary experiments, the effect of the reaction parameters was investigated for the nitrogen atom insertion step using isolated silyl enol ether starting material **1a'** for the formation of unsubstituted 2-pyridone **2a** (Tables S1-S9, see Supporting Information). The reaction was found to proceed only in the presence of protic solvents, among which methanol proved to be the most efficient for the formation of the desired product. However, binary solvent mixtures, such as methanol:tetrahydrofuran (THF) or methanol:pentane in a 1:1 ratio were also suitable for the reaction. This is especially opportune, as the silylation of cyclopentenones typically proceeds in THF or pentane. We thus envisaged that the silyl enol ether formation step and the nitrogen atom insertion step could be carried out in one pot, directly converting cyclopentenones into pyridones, thereby significantly increasing the synthetic utility of the transformation. Therefore, the reaction conditions were next optimised for the one-pot reaction using 2-methylcyclopentenone (**1b**) as the model substrate (Table 1). Different silyl groups were tested, with *tert*-butyl-dimethylsilyl (TBS) significantly outperforming both more and less bulky silylating agents, such as triisopropylsilyl (TIPS) and trimethylsilyl (TMS) groups, respectively. For the subsequent nitrogen atom insertion step (diacetoxyiodo)benzene (PIDA) and *bis*(tert-butoxylcarbonyloxy)iodobenzene were demonstrated to be the most efficient oxidants, with other iodine(III) reagents providing significantly lower yields of the desired product **2b**. The two most effective nitrogen sources were ammonium carbamate, and the combination of ammonium chloride and potassium carbonate. It was observed that 3 equivalents of PIDA and 4 equivalents of ammonium carbamate are needed to achieve high yields, however, further increasing their equivalencies did not lead to significant improvements. The reaction exhibited low dependence on temperature and concentration, and fast reaction kinetics, leading to full conversion of the model substrate within 30 minutes. As a compromise between efficiency and operational simplicity (Tables S10-S11, see Supporting Information), the optimal conditions were determined to be 3 equivalents of PIDA and 4 equivalents of ammonium carbamate in a 1:1 mixture of THF and methanol, carrying out both steps at room temperature (Table 1, entry 3).

With the optimal reaction conditions in hand, we proceeded to explore the scope of the transformation (Scheme 2). Unsubstituted pyridone **2a** and its 3-alkylated derivatives **2b-2d** were isolated in good yields, alongside 3-arylated **2e**. The benzo-fused system of isoquinolinone **2f** was also obtained in excellent yield. As an interesting result of the reaction design, in the case of 1-indanone derived starting materials, the reaction resulted in the regioselective formation of isoquinolinones, which is the opposite of the nitrogen insertion regioselectivity observed in traditional Beckmann rearrangements (**2f"**),[29,31] which further increases the synthetic appeal of our reaction for this class of substrates. First, different substitution patterns were examined, with the successful formation of 3-substituted (**2g**) and 4-substituted (**2h** and **2i**) isoquinolinones, as well as 3,4-disubstituted pyridone (**2j**). Remarkably, tetrasubstituted pyridone **2k** was also obtained in high yield. Different methoxy-substitution patterns on the benzene ring of 1-indanone substrates were well tolerated (**2l**-**2o**). Since a variety of substituted 1-indanone derivatives are commercially available, the functional group tolerance of the transformation was examined using this class of starting materials. Substrates bearing halogens, including fluoro-, chloro-, and bromo- derivatives (**2p**-**2r**) were obtained in moderate yields. The reaction is compatible with free hydroxy groups, which are silylated in the first step, as showcased by entry **2s** and **2t**. Among others, nitro (**2u**), amide (**2v**), primary amine (**2w**), pyridine (**2x**), ester (**2y**), alkyne (**2aa** and **2ab**), carboxylic acid (**2ac**), and trifluoromethoxy (**2ad**) functionalities were found to be tolerated in the reaction. Moreover, cyclotene propionate-derived **2z** and *cis*-jasmone derived **2ae** could also be accessed.



Scheme 2. Substrate scope of the reaction. Yields are isolated yields, unless stated otherwise. [a] Determined by ^{1}H-NMR using mesitylene as internal standard. [b] Pentane used as solvent in the first step instead of THF, and pentane:methanol = 1:1 mixture as solvent in the second step. [c] 2.5 equiv. of Et_3N and 2.2 equiv. TBSOTf used in the first step. [d] Traditional Beckmann-conditions. 1) NH_2OH 2) PPA[45] [e] Modified Beckmann-conditions. NH_2OH, thiamine hydrochloride.[46] For details, see Supporting Information.

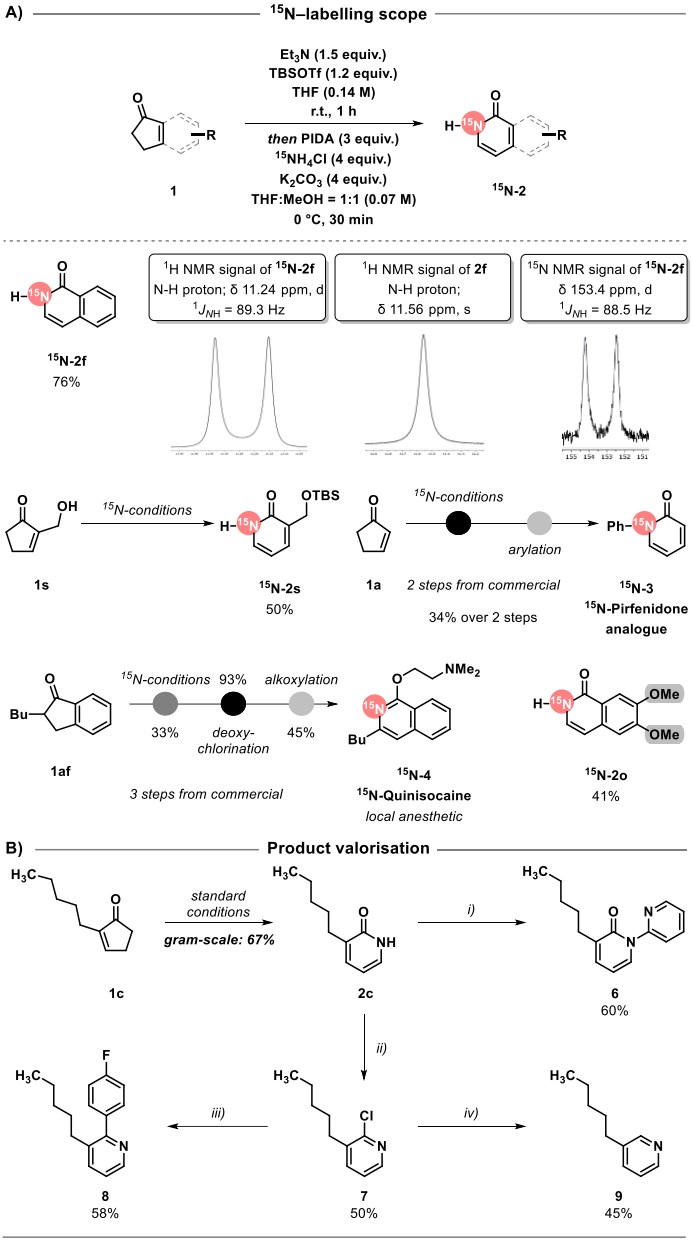
The developed strategy also offers an attractive opportunity to rapidly and cost-effectively synthesise ^{15}N-labelled pyridone products (Scheme 3A). Due to the favourable magnetic properties of the ^{15}N-nucleus (I = ½), ^{15}N-NMR is a widely used tool in biological and medical contexts, and has significant importance in investigating reaction mechanisms and structure-reactivity relationships.[19,47–51] However, its low natural abundance of 0.4% often necessitates the use of isotope-enriched probes for sufficient detection in NMR experiments.[48] The use of $^{15}NH_4Cl$ as an inexpensive isotopic source was possible in our methodology in the presence of an equivalent amount of K_2CO_3. Using slightly modified conditions allowed the formation of pyridones **^{15}N-2f**, **^{15}N-2o** and **^{15}N-2s** in yields comparable to those obtained with the use of ammonium carbamate as the nitrogen source. ^{15}N-insertion into cyclopentenone **1a**, followed by arylation has provided a short synthesis of a ^{15}N-Pirfenidone analogue (**^{15}N-3**). Furthermore, we synthesised the ^{15}N-labelled variant of the anesthetic drug Quinisocaine (**^{15}N-4**) in three steps from commercially available starting materials. Moreover, palladium-catalysed C–H activation reactions often employ pyridone ligands, such as **2f**.[3,5] We believe that the facile access to ^{15}N-labelled ligands of this class that our methodology provides could offer a convenient way for mechanistic elucidations of such reactions.[52,53]

The reaction proved to scale well, and the gram-scale synthesis of **2c** allowed us to explore different product valorisation pathways (Scheme 3B). Pyridone derivatives can be quickly accessed, including the *N*-arylated product **6** and deoxychlorination product **7**. Through **7**, both 2-arylated product **8** and pyridine-derivative **9** could be rapidly synthesised.

We carried out a number of control experiments to better understand the mechanism of the transformation (Scheme 4A). Cyclopentenone starting material **1b** subjected to the nitrogen insertion reaction conditions without the silylation step did not yield the corresponding pyridone product **2b**, and mainly unreacted starting material was observed by NMR analysis, ruling out an aza-Bayer Villiger[54] type reactivity (I).

A different type of reactivity was observed when 3,3-dimethylindan-1-one **1ba** was subjected to the reaction conditions, which produced 25% of hemiaminal product **2ba** alongside remaining starting material (II), indicating that no β-hydrogens are required for the nitrogen atom insertion, which proceeds even without the strong driving force of subsequent aromatisation. Furthermore, 2-indanone **1ca** produced hydroxyisoquinoline product **2ca** upon being subjected to the reaction conditions (III).

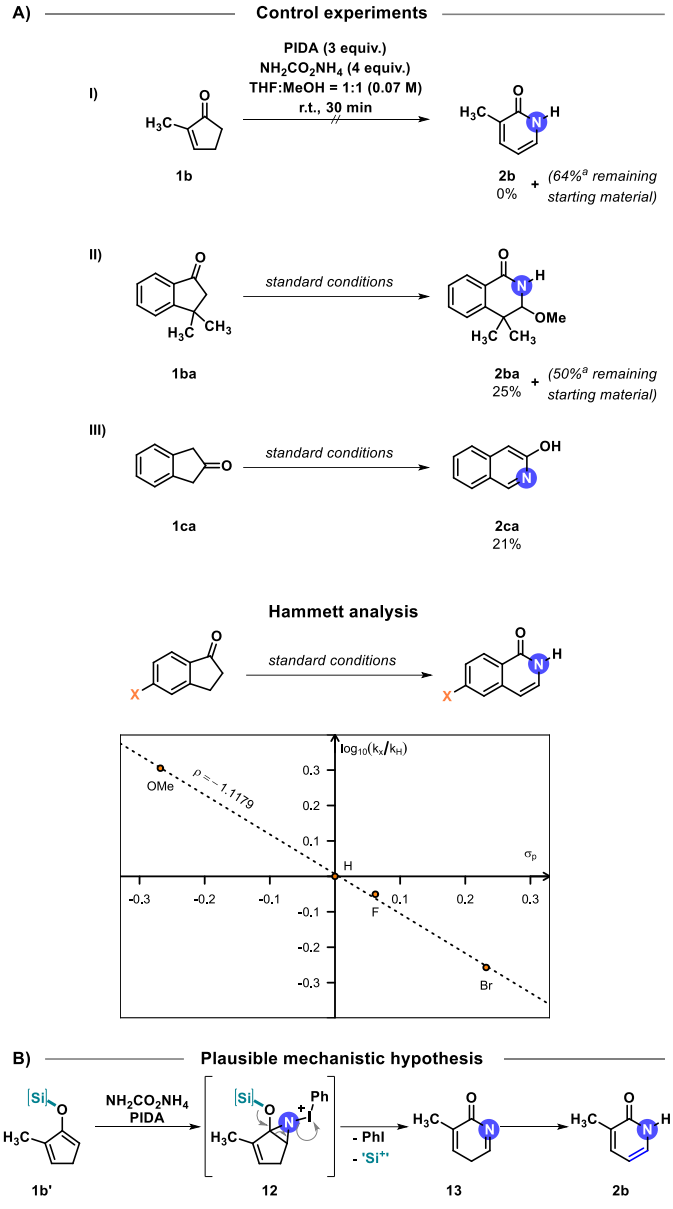
We also carried out a Hammett-analysis to understand the reaction profile better, which revealed the build-up of positive charge in the rate determining step, which is consistent with the oxidative nature of the process.



Scheme 3. Applications of the developed methodology for ^{15}N-labelling, and product derivatisation. Conditions for the derivatisation of pyridone **2c**: (i) 2-iodopyridine (2 equiv.), CuI (10 mol%), K_2CO_3 (1.2 equiv.), DMF, 150 °C, 24 h (ii) $POCl_3$ (neat), 100 °C, 16 h (iii) (4-fluorophenyl)boronic acid (1.2 equiv.), $Pd(OAc)_2$, (2.5 mol%), PPh_3 (10 mol%), K_2CO_3 (2.7 equiv.), DME/H_2O, 90 °C, 18 h (iv) Pd/C, $HCOONH_4$ (2 equiv.), MeOH, 55 °C, 16 h

Based on these preliminary results, a mechanism consistent with all observations could first involve the reaction of the electron-rich silyl enol ethers (**1b'**) to form aziridinium intermediates (**12**), facilitated by the hypervalent iodine reagent and the nitrogen source. These aziridinium intermediates can then undergo ring opening upon the release of iodobenzene and the cleavage of the silyl group which acts as an electrofuge. This results in the formation of

intermediate **13** which subsequently tautomerises to the pyridone product **2b** (Scheme 4B).



Scheme 4. Control experiments and working hypothesis for the plausible mechanism of the reaction. [a] Determined by ^{1}H-NMR using mesitylene as internal standard. For details, see Supporting Information.

In conclusion, we have developed an oxidative ring expansion protocol capable of directly transforming cyclopentenone derivatives into pyridones, through a strategy of silyl enol ether formation, followed by the introduction of a nitrogen atom mediated by a hypervalent iodine reagent, and subsequent aromatisation. The reaction is operationally simple, rapid, exhibits good functional group tolerance and complete regioselectivity. The scalability of the transformation was demonstrated, as well as pathways for further diversification of the pyridone products. This strategy has allowed us to install ^{15}N-labels in various synthetic targets, including the drug molecules Quinisocaine and a Pirfenidone analogue, and in pyridones commonly used as non-innocent ligands in transition metal catalysis. Control experiments have provided insight into the mechanism of the reaction, and showcased other reactivity pathways, such as the formation of hemiaminals and 3-hydroxyisoquinolines. We believe that the transformation will find interest in further academic research as well as in industrial settings, both for its synthetic utility of streamlining pyridone synthesis and for the wide range of applications it provides.

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