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Brønsted acid catalyzed intramolecular benzylic cyclizations of alkylpyridines†

Ashabha I. Lansakara, Daniel P. Farrell and F. Christopher Pigge*

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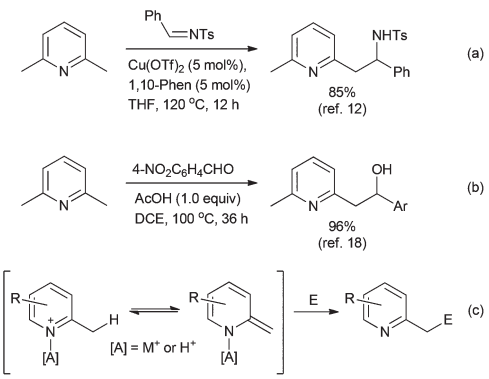
Aldehyde and ketone electrophiles incorporated into the side chains of 2- and 4-alkylpyridines participate in intramolecular aldol-like condensations with pyridine benzylic carbons in the presence of Brønsted acid catalysts. Pyridines featuring β-ketoamide side chains undergo cyclization in the presence of 10 mol% TfOH to afford pyridyl-substituted hydroxy lactams in good yield. These products were found to be resistant to further dehydration under a variety of conditions, however treatment with thionyl chloride elicited an unusual dehydration/oxidation reaction sequence. In contrast, acid-catalyzed cyclization of pyridines tethered to aliphatic aldehydes with amine linkers gives pyridyl-substituted dehydro-piperidine products. Similarly, intramolecular condensation of salicylaldehyde- and salicylketone-substituted pyridines affords pyridyl-substituted benzofurans.

Introduction

Aza-heterocyclic structural motifs are important components of numerous natural products, bio-active pharmaceutical agents, and functional organic materials. Pyridine and related aza-arenes in particular are commonly encountered in many diverse types of organic compounds that display wide-ranging and desirable physical properties.[1–4] Consequently, preparative methods for the synthesis of substituted pyridines,[5,6] along with methods suitable for manipulation of pre-formed pyridine derivatives,[7–11] are valuable tools in the synthetic organic and medicinal chemistry communities.

Recently, several reports have described condensation reactions of 2-methyl(aza-arenes) that proceed in the presence of Brønsted or Lewis acid catalysts. For example, treatment of a 2-alkyl(aza-arene) such as 2,6-lutidine with sulfonyl imines in the presence of a Cu(II) Lewis acid additive affords products of Mannich-type reactions (Scheme 1a).[12] In addition to Cu,[13] other Lewis acidic metals such as Sc,[14,15] Fe,[16] and Yb[17] have proven effective in promoting reaction between 2-methyl(aza-arenes) and activated imines, ketones, aldehydes, and Michael acceptors. Similarly, Brønsted acids have also been employed as catalysts capable of mediating reaction between 2-methyl-(aza-arenes) and activated aldehydes,[18] ketones,[19,20] and Michael acceptors[21] (Scheme 1b).

In each of these transformations the acid additive is envisioned to facilitate interconversion between imine and enamine tautomers of the 2-methyl(aza-arene) substrate. Reaction of the enamine tautomer with added electrophile then leads to the observed products (Scheme 1c). In some instances thermal activation alone has been shown to be effective in promoting similar reactions, presumably by also providing access to reactive enamine-like tautomers.[22–24] The activating effects observed under these reaction conditions, however, generally do not extend to 4-substituted aza-arenes, such as 4-picoline.[12,14,18] Thus, the proximity of the alkyl substituent to an aza-arene nitrogen atom appears to be an important structural feature.[25]

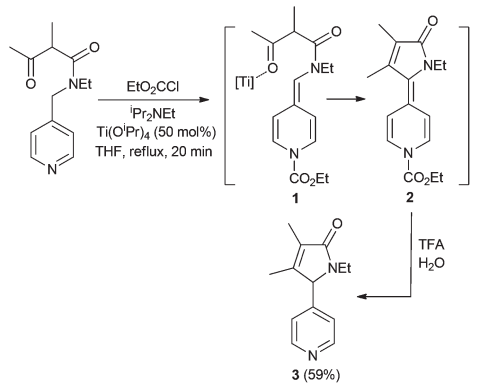


Scheme 1 Acid catalysed condensation reactions of 2-alkyl(aza-arenes).

We recently reported Lewis acid-promoted intramolecular condensation reactions involving 4-alkylpyridines possessing attached carbonyl electrophiles.[26] These reactions were conducted by first acylating the pyridine with ethyl chloroformate in the presence of $^{i}Pr_2NEt$. Under these conditions the

Department of Chemistry, University of Iowa, Iowa City, Iowa 52242, USA. E-mail: chris-pigge@uiowa.edu; Fax: +1-319-335-1270; Tel: +1-319-335-3805

†Electronic supplementary information (ESI) available: Experimental procedures, copies of ^{1}H and ^{13}C NMR spectra. See DOI: 10.1039/c3ob42039f



Scheme 2 4-Alkylpyridine benzylic cyclization *via* anhydrobase intermediates.[26]

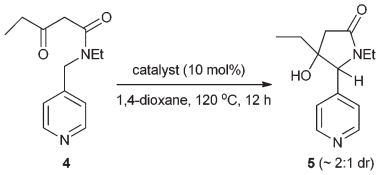
pyridine substrate is converted to the corresponding anhydrobase, which then reacts with the activated carbonyl (Scheme 2). Subsequent processing under aqueous conditions afforded substituted pyridine products that had undergone formal benzylic cyclization.

Given the similarity of acyl anhydrobase intermediates **1** and **2** to enamine tautomers of alkyl pyridines, we became intrigued by the possibility of using an acid catalyst to effect intramolecular alkylpyridine condensation reactions analogous to that depicted in Scheme 2. If successful, then the need for pyridine activation with stoichiometric quantities of an acylating agent would be circumvented, resulting in greatly simplified cyclization procedures. With this goal in mind, we initiated a study examining the efficiency of Brønsted acid catalysed benzylic cyclization of 4- and 2-alkylpyridines.[27]

Results and discussion

The 4-alkylpyridine derivative **4** was selected as a test substrate for initial investigations (Table 1) due to its straightforward preparation from commercially available *N*-ethyl-4-aminomethylpyridine and ethyl-3-oxo-valerate.[26] Dioxane was chosen as the reaction solvent as it features a reasonably high boiling point and has been used as a reaction medium in several related intermolecular alkyl(aza-arene) condensation reactions.[15,17,19,20] As a control experiment, **4** alone in dioxane was heated to 120 °C to determine if thermal activation would result in cyclization.[22] No reaction was observed after 12 h (Table 1, entry 1). Next, **4** was heated (dioxane, 120 °C) in the presence of various Brønsted acid catalysts (10 mol%). Gratifyingly, an aldol-like condensation was observed in each case, and pyridine derivative **5** was isolated as a ~2 : 1 mixture of diastereomers inseparable by flash column chromatography (Table 1, entries 2–6). Reaction in the presence of TfOH afforded the highest isolated yield of **5**. Notably, however, all the Brønsted acids screened in this assay were effective to varying degrees in promoting benzylic cyclization.

Table 1 Acid catalysed cyclization of **4**



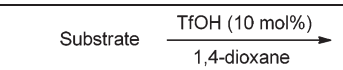
Entry	Catalyst[a]	% Yield **5**[b]
1	None	0[c]
2	TfOH	97
3	TFA	90
4	AcOH	78
5	*p*-TSA	70
6	CSA[d]	72

[a] Reactions performed on 100 mg scale, [**4**] ~ 0.3 M in dioxane. [b] Isolated yield after purification by chromatography, ~2 : 1 dr of products in each case. [c] Recovered starting material (93%). [d] Camphorsulfonic acid.

The reaction conditions outlined in Table 1, entry 2 represent a greatly simplified experimental protocol for achieving intramolecular alkylpyridine functionalization as compared to our original procedure (see Scheme 2).[26] To explore the generality of acid catalyzed cyclization, several other 4- and 2-alkylpyridines structurally related to **4** were also subjected to the reaction conditions illustrated in Table 1, and the results are shown in Table 2. The alkylpyridine substrates for this study were each prepared by condensation of the corresponding *N*-alkyl aminomethyl- or aminoethylpyridine with the appropriate β-ketoester to install the indicated β-amidocarbonyl side chains.[26] Cyclization reactions involved heating a solution of the substrate (~0.3 M) and 10 mol% TfOH in dioxane to 120 °C for 12 h. Crude reaction mixtures were then directly purified by silica gel flash column chromatography to afford the isolated products as mixtures of diastereomers. Diastereomer ratios were estimated on the basis of ^{1}H NMR spectra. In particular, signals for the benzylic hydrogens of the individual diastereomers were sufficiently separated in most cases so as to allow determination of stereoisomer ratios.

As shown in Table 2, entries 1–4, TfOH acid catalysis was effective in converting **6a–9a** to the corresponding pyridine-substituted γ-lactams in good to excellent yield, and in all cases cyclized products **6b–9b** were isolated as mixtures of diastereomers inseparable by flash column chromatography. In the case of **7b** and **8b** (entries 2 and 3), two diastereomers were evident in the NMR spectra, which we attribute to formation of *cis*-ring fusions in the 5,5- and 6,5-bicyclic moieties. Compounds **6b** and **9b** (Table 2, entries 1 and 4) however, were obtained as mixtures of all possible diastereomers. Due to overlapping signals for many of the hydrogens, the relative stereochemistry for individual diastereomers could not be assigned. In similar fashion, this procedure was effective for inducing cyclization of aminoethylpyridine derivatives as revealed in Table 2, entries 5 and 6. The pyridyl-substituted

Table 2 TfOH catalyzed benzylic cyclization of alkylpyridines[a]



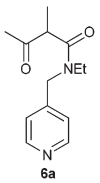
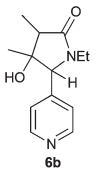
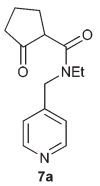
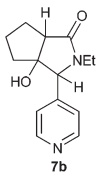
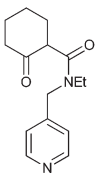
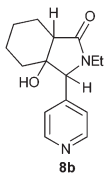
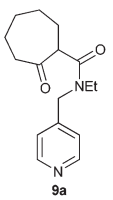
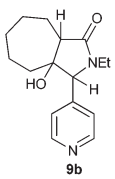
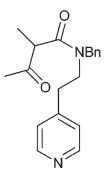
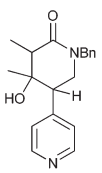
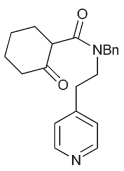
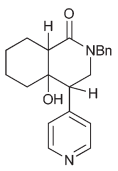
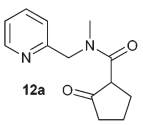
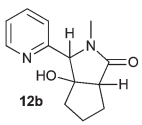
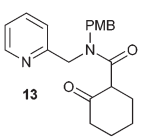
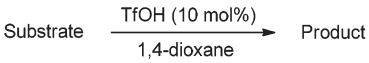
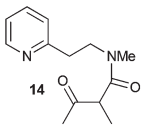
Entry	Substrate	Product	% Yield[b]
1	 **6a**	 **6b**	97% (3.4 : 2.6 : 2.3 : 1)
2	 **7a**	 **7b**	60% (3.9 : 1)
3	 **8a**	 **8b**	98% (9.0 : 1)
4	 **9a**	 **9b**	89% (3.0 : 1.6 : 1.3 : 1)
5	 **10a**	 **10b**	97%[c]
6	 **11a**	 **11b**	70% (7.5 : 1)
7	 **12a**	 **12b**	59%[d] (1.5 : 1.2 : 1 : 1)
8	 **13**	n.p.[e]	—[f]

Table 2 *(Contd.)*



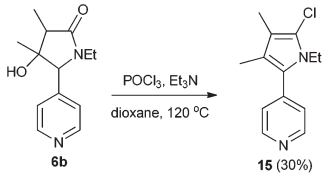
Entry	Substrate	Product	% Yield[b]
9	 **14**	n.p.[e]	—[g]

[a] Reactions performed on 100 mg scale, [substrate] ~ 0.3 M in dioxane. [b] Isolated yield, diastereomeric ratio of products indicated in parentheses. [c] Diastereomeric ratio could not be determined due to overlapping signals in the ^{1}H NMR spectrum. [d] Based on 20% recovered **12a**. [e] No cyclized product was obtained. [f] 60% recovered starting material. [g] 68% recovered starting material.

δ-lactams **10b** and **11b** also were isolated as mixtures of diastereomers in good yield. Table 2, entry 7, illustrates the successful conversion of 2-alkylpyridine substrate **12a** to the corresponding cyclized product **12b** in reasonable yield. This transformation represents an expansion of substrate scope compared to our original cyclization procedure (Scheme 2), under which 2-substituted pyridines are unreactive.[26] Unfortunately, two other 2-alkylpyridine substrates examined in this study failed to undergo benzylic cyclization, and only unreacted starting material was recovered (Table 2, entries 8 and 9). At present, factors responsible for the differing reactivity of 2-substituted pyridines remain obscure.

The results in Table 2 demonstrate the utility of Brønsted acid catalysis in promoting intramolecular aldol-type reactions of alkylpyridines. It is additionally noteworthy that 4-alkylpyridines are good substrates for this reaction, in contrast to related Lewis and Brønsted acid catalyzed intermolecular condensation reactions of methyl-substituted aza-arenes.[15,17,19,20] We were somewhat surprised, however, to isolate tertiary alcohol products exclusively as we anticipated the initial aldol-like products would undergo facile elimination of H_2O under the acidic reaction conditions.[28] Dehydration of initial cyclization products would produce the added benefit of greatly simplified product mixtures by removing the possibility of diastereoisomers. Consequently, we briefly explored reaction conditions designed to effect dehydration of selected cyclized products.

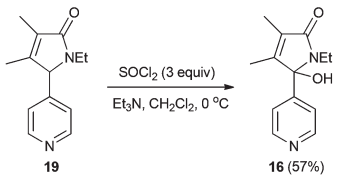
Lactam **6b** was selected as the initial substrate for these studies. Unexpectedly, however, we found **6b** to be remarkably resistant to dehydration under a variety of reaction conditions. For example, in separate experiments **6b** was exposed to $BF_3{\cdot}OEt_2$, MsCl–Et_3N, Ac_2O–Et_3N, P_2O_5, H_2SO_4, H_3PO_4, HCl, KO^{t}Bu, or NaH, and in each case none of the anticipated unsaturated lactam was observed (in some cases unreacted **6b** was recovered while in others substrate decomposition occurred). A reaction was observed upon treatment of **6b** with $POCl_3$–Et_3N, but transformation of the amide group occurred concomitantly with elimination of the tertiary alcohol to afford chloropyrrole **15** (eqn (1)).



(1)

Several substrates (in addition to **6b**) were examined for their reactivity toward thionyl chloride ($SOCl_2$) as a putative dehydration agent (Scheme 3). While loss of the 3° alcohol did occur in the presence of $SOCl_2$, oxidation of the lactam ring was also observed. Thus, **6b** and **8b** were converted to **16** and **17**, respectively, in moderate to good yield. The δ lactam **10b** also suffered dehydrative oxidation in the presence of $SOCl_2$ to afford **18**, albeit in modest yield. While oxidation was not the anticipated outcome, the use of $SOCl_2$ as an oxidizing agent is not unprecedented.[29] Moreover, a somewhat related $SOCl_2$-mediated oxidation has been studied in some detail by Cushman and co-workers.[30]

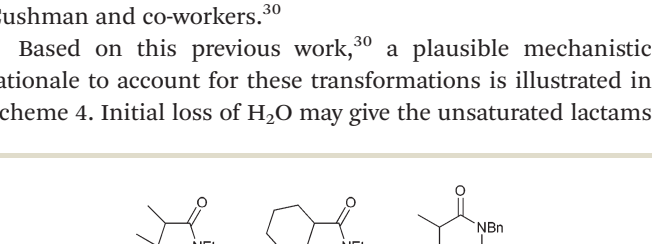
Based on this previous work,[30] a plausible mechanistic rationale to account for these transformations is illustrated in Scheme 4. Initial loss of H_2O may give the unsaturated lactams **19** and **20**.[31] Subsequently, the presence of excess $SOCl_2$ may result in further reaction at the lactam carbonyl and/or the pyridine ring to give species such as **21a,b** and **22a,b**. Addition of H_2O then leads to **16** while loss of H^+ leads to **18**. As a test of this mechanistic formulation, the known lactam **19**[26] was treated with $SOCl_2$–Et_3N. Oxidized lactam **16** was obtained in 57% isolated yield (eqn (2)).



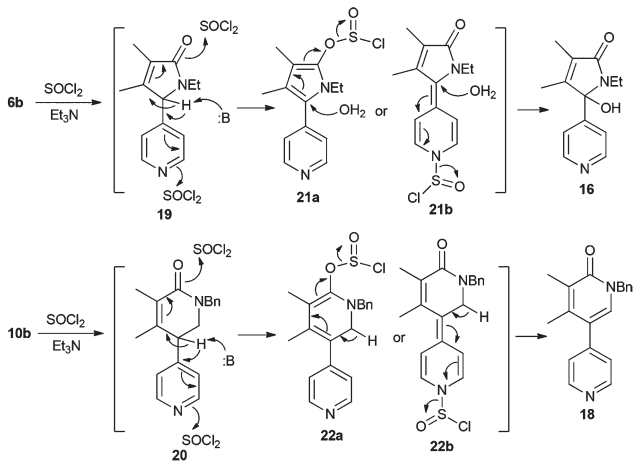
(2)

Two additional types of cyclization substrates distinct from the β-amido carbonyl starting materials discussed thus far were also examined. An approach to pyridyl-substituted piperidines was explored through preparation of (aminoethyl)pyridine derivatives featuring pendant aldehyde electrophiles as depicted in Scheme 5. 4-(Aminoethyl)pyridine was converted to the corresponding benzoyl or tosyl amide. Allylation of the amide nitrogen followed by hydroboration/oxidation provided primary alcohols **23** and **24** in good yield. Swern oxidation of the benzoyl amide derivative afforded aldehyde **25**. Exposure of **25** to acid catalyzed cyclization reaction conditions, however, failed to generate the expected cyclized product, and only substrate decomposition was observed. Cyclization of **25** to **27** could be achieved in good yield *via* discrete anhydrobase intermediates using our previously reported procedure.[26] In contrast, the tosyl amide derivative **26** proved stable to acid catalysis, and **28** was obtained in reasonable isolated yield (52%). Thus, in this reaction elimination of the secondary alcohol intermediate readily occurs to deliver the conjugated olefin. Tosyl amide **26** could also be cyclized in slightly higher yield upon activation with EtO_2CCl and $^iPr_2NEt$ in the presence of $Ti(O^iPr)_4$.[26]

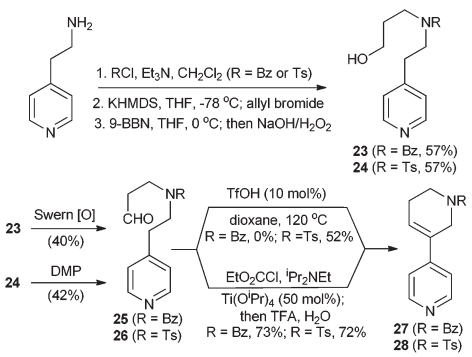
Reactions of cyclization substrates based on derivatives of salicylaldehyde were also examined. We envisioned that alkylation of salicylaldehyde with appropriate aza-arenes would afford precursors to heterocycle-substituted benzofurans



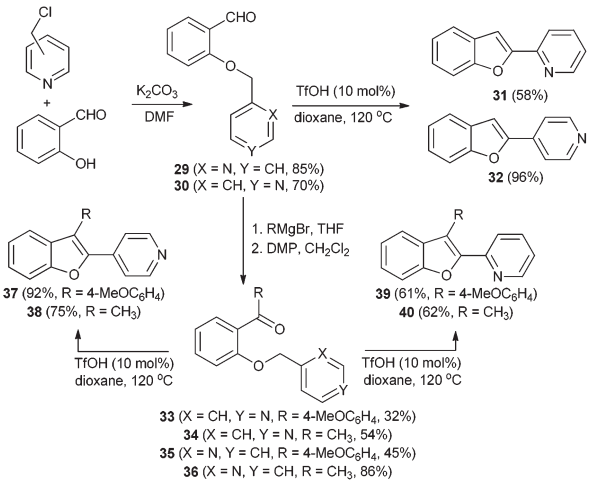
Scheme 3 Lactam elimination/oxidation with $SOCl_2$.



Scheme 4 Mechanistic rationale for $SOCl_2$-mediated oxidation.



Scheme 5 Acid catalyzed pyridine benzylic cyclization with aldehyde electrophiles.

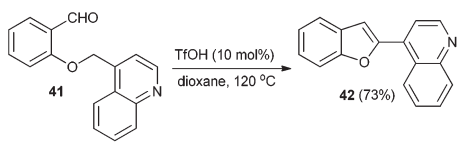


Scheme 6 Synthesis of pyridyl-substituted benzofurans.

which could be assembled through subsequent intramolecular benzylic cyclization. Benzofurans in general possess a wealth of desirable activities in both biological and materials settings,[32] and incorporation of an aza-arene substituent (*e.g.*, pyridine) provides a handle for further molecular and supramolecular (*e.g.*, H-bonding, metal ion binding) elaboration.

To begin, alkylation of salicylaldehyde with 4- and 2-picolyl chloride yielded precursors to functionalized benzofurans in straightforward fashion (Scheme 6).[33] As anticipated, exposure of **29** and **30** to acid catalyzed benzylic cyclization reaction conditions returned the corresponding benzofuran products (**31**, **32**) in good to excellent yield. Notably, the 2-substituted pyridine proved to be a suitable substrate for this transformation. In each case, elimination of H_2O was observed during the course of cyclization, undoubtedly facilitated by formation of the aromatic benzofuran ring system. This approach also proved amenable to construction of 2,3-disubstituted benzofurans. Addition of Grignard reagents to **29** and **30** followed by oxidation with the Dess–Martin periodinane gave ketones **33–36**. Acid catalyzed cyclization proceeded smoothly with each of these substrates, and benzofurans **37–40** were isolated in good yield.

This transformation also has been extended to include incorporation of a quinoline moiety as a benzofuran substituent, as shown in eqn (3). Similar to pyridine analogues, exposure of **41** to TfOH (10 mol%) in dioxane at 120 °C produced benzofuran **42** in 73% isolated yield. The successful cyclization of **41** indicates that this acid catalyzed procedure may be applicable to transformations of aza-arenes other than pyridine.



(3)

Conclusions

An experimentally simple Brønsted acid catalyzed procedure effective for inducing intramolecular aldol-like condensations of alkylpyridine derivatives has been developed. Positioning of carbonyl electrophiles in the side chain of 4-alkylpyridines in particular affords viable cyclization precursors across a range of substrate types. Appropriately functionalized 2-alkylpyridines also gave the reaction, especially those featuring salicylaldehyde-derived side chains. Other 2-alkylpyridines, however, were resistant to acid catalyzed benzylic cyclization for reasons that remain under investigation. An unusual $SOCl_2$-mediated oxidation of pyridyl-substituted lactams has also been uncovered. The construction of intriguing heterocyclic ring systems of relevance to medicinal, natural product, and materials chemistry has been demonstrated. Continuing research seeks to expand upon these results by harnessing the reactivity of putative enamine-like anhydrobase intermediates available to pyridine and related aza-arenes in additional and novel bond-forming processes.[34]

Experimental

General procedure for intramolecular acid catalyzed benzylic cyclization

The preparation of pyridine derivative **5** is representative. Reaction mixtures were prepared open to air. Pyridine **4** (100 mg, 0.40 mmol, 1 equiv.) was placed in a scintillation vial equipped with a Teflon-lined screw cap and dissolved in 1,4-dioxane (1 mL). Trifluoromethanesulfonic acid (TfOH) (4 μL, 0.04 mmol, 0.1 equiv.) was added and the reaction was heated to 120 °C. The reaction was maintained at this temperature for 12 h, then allowed to cool to room temperature. The solvent was removed under vacuum and the crude product was purified by silica gel flash column chromatography using 70–100% EtOAc in hexanes as eluent. *N*,4-Diethyl-4-hydroxy-5-(pyridin-4-yl)pyrrolidin-2-one **5** (~2 : 1 mixture of diastereomers, 96 mg, 96%) was isolated as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55 (d, J = 5.4 Hz, 0.7H), 8.46 (d, J = 5.7 Hz, 1.3H), 7.18 (d, J = 5.9 Hz, 1.3H), 7.09 (d, J = 4.9 Hz, 0.7H), 4.55 (s, 0.35H), 4.47 (s, 0.65H), 3.93–3.67 (m, 1H), 3.48 (s, 1H), 2.81–2.60 (m, 1H), 2.60–2.39 (m, 2H), 1.77 (q, J = 7.4 Hz, 1H), 1.39–1.29 (m, 1H), 1.09–1.02 (m, 3H), 0.99 (t, J = 7.2 Hz, 2H), 0.93–0.88 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 173.4, 150.2, 149.4, 146.7, 145.0, 124.0, 77.3, 75.5, 73.8, 70.0, 43.3, 36.3, 35.8, 33.1, 30.6, 12.4, 12.1, 8.2, 8.1. IR (film) 3350, 2972, 2936, 2874, 1672 cm^{-1}. HRMS (ESI) $C_{13}H_{19}N_2O_2$ $[M + H]^+$, calculated 235.1447; found 235.1434.

Cyclized products **6b–12b** (Table 2) were prepared from 100 mg of the corresponding pyridine substrates using the procedure given above.

***N*-Ethyl-4-hydroxy-3,4-dimethyl-5-(pyridin-4-yl)pyrrolidin-2-one (6b).** Mixture of diastereomers, 97 mg, 97%, yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 (d, J = 4.9 Hz, 0.7H), 8.50–8.41 (m, 1.3H), 7.22 (d, J = 5.3 Hz, 0.5H), 7.16 (d, J = 5.1 Hz, 0.9H),

7.11 (d, J = 3.8 Hz, 0.5H), 7.06 (d, J = 4.2 Hz, 0.1H), 4.61 (s, 0.1H), 4.50 (s, 0.3H), 4.43 (s, 0.2H), 4.34 (m, 0.4H), 3.96–3.68 (m, 1H), 3.41 (s, 1H), 2.86–2.59 (m, 1H), 2.59–2.49 (m, 0.4H), 2.49–2.33 (m, 0.6H), 1.38 (d, J = 7.2 Hz, 2H), 1.29–1.21 (m, 1H), 1.21–1.12 (m, 2.5H), 1.07–0.96 (m, 3H), 0.93 (t, J = 7.1 Hz, 0.5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.8, 176.7, 175.8, 175.5, 150.2, 149.8, 149.4, 149.3, 146.8, 145.8, 145.4, 143.9, 124.5, 123.6, 123.1, 77.1, 76.9, 76.1, 74.9, 72.1, 71.4, 69.8, 69.6, 60.5, 49.9, 48.1, 46.6, 45.3, 36.4, 36.0, 35.6, 24.2, 23.4, 23.3, 20.7, 14.3, 12.5, 12.3, 11.9, 11.3, 9.6, 7.8, 7.2. IR (film) 3368, 2976, 2939, 2870, 1683, 1657 cm^{-1}. HRMS (ESI) $C_{13}H_{19}N_2O_2$ $[M + H]^+$, calculated 235.1447; found 235.1466.

***N*-Ethyl-3a-hydroxy-3-(pyridin-4-yl)hexahydrocyclopenta[*c*]-pyrrol-1(2*H*)-one (7b).** Mixture of diastereomers, 60 mg, 60%, yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55–8.43 (m, 0.4H), 8.38 (d, J = 5.9 Hz, 1.6H), 7.12 (d, J = 6.0 Hz, 2H), 4.52 (s, 0.3H), 4.49 (s, 0.7H), 3.81 (dq, J = 14.6, 7.4 Hz, 1H), 3.27 (dd, J = 14.0, 6.8 Hz, 0.4H), 2.85 (dd, J = 9.6, 4.3 Hz, 0.2H), 2.76 (dd, J = 9.0, 2.8 Hz, 0.8H), 2.65 (dq, J = 14.1, 7.1 Hz, 0.6H), 2.21–1.80 (m, 5H), 1.80–1.58 (m, 1H), 1.11–0.90 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.0, 149.8, 149.5, 146.8, 123.3, 83.8, 69.1, 52.9, 42.3, 36.3, 27.6, 24.8, 12.2. IR (film) 3367, 2958, 2872, 1667, 1601 cm^{-1}. HRMS (ESI) $C_{14}H_{19}N_2O_2$ $[M + H]^+$, calculated 247.1447; found 247.1436.

***N*-Ethyl-3a-hydroxy-3-(pyridin-4-yl)octahydro-1*H*-isoindol-1-one (8b).** Mixture of diastereomers, 98 mg, 98%, yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (d, J = 5.9 Hz, 0.2H), 8.28 (d, J = 6.0 Hz, 1.8H), 7.19 (d, J = 6.0 Hz, 0.2H), 7.08 (d, J = 6.0 Hz, 1.8H), 4.52 (s, 0.1H), 4.20 (s, 0.9H), 3.98–3.79 (m, J = 14.6, 7.3 Hz, 1H), 3.70 (s, 1H), 2.77 (dq, J = 14.1, 7.0 Hz, 1H), 2.56 (d, J = 5.8 Hz, 0.1H), 2.49–2.36 (m, 0.9H), 2.01–1.83 (m, J = 15.9, 5.3 Hz, 2H), 1.80–1.48 (m, 4H), 1.43–1.29 (m, 2H), 1.06 (t, J = 7.2 Hz, 2.7H), 0.96 (t, J = 7.1 Hz, 0.3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4, 149.2, 145.6, 123.3, 74.7, 68.8, 46.1, 36.11, 36.08, 22.7, 21.46, 21.42, 12.3. IR (film) 3404, 2939, 2859, 1676, 1665, 1603 cm^{-1}. HRMS (ESI) $C_{15}H_{21}N_2O_2$ $[M + H]^+$, calculated 261.1603; found 261.1594.

***N*-Ethyl-3a-hydroxy-3-(pyridin-4-yl)octahydrocyclohepta[*c*]-pyrrol-1(2*H*)-one (9b).** Mixture of diastereomers, 89 mg, 89%, yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57 (d, J = 4.9 Hz, 0.8H), 8.54–8.41 (m, J = 5.9 Hz, 1.2H), 7.26–7.13 (m, J = 5.5 Hz, 1.5H), 7.14–6.94 (m, 0.5H), 4.61 (s, 0.1H), 4.46 (s, 0.2H), 4.44 (s, 0.5H), 4.40 (s, 0.2H), 4.02–3.59 (m, 1H), 3.39–2.85 (m, 1H), 2.85–2.38 (m, 2H), 2.26–1.93 (m, 2H), 1.93–1.12 (m, 8H), 1.12–1.00 (m, 1H), 1.00–0.76 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.2, 176.9, 176.3, 175.4, 174.4, 150.2, 150.2, 149.5, 149.3, 147.5, 146.8, 144.4, 143.8, 143.5, 124.5, 124.3, 124.2, 79.6, 79.4, 78.5, 77.9, 73.9, 73.0, 70.3, 70.0, 58.3, 56.4, 50.5, 47.7, 42.7, 39.5, 38.4, 37.9, 37.8, 36.4, 36.2, 35.7, 31.2, 31.1, 30.9, 30.0, 29.9, 28.0, 26.2, 26.1, 25.5, 25.4, 24.7, 22.7, 20.8, 12.6, 12.2, 12.0. IR (film) 3364, 2932, 2849, 1683, 1661 cm^{-1}. HRMS (ESI) $C_{16}H_{23}N_2O_2$ $[M + H]^+$, calculated 275.1760; found 275.1755.

***N*-Benzyl-4-hydroxy-3,4-dimethyl-5-(pyridin-4-yl)piperidin-2-one (10b).** Mixture of diastereomers, 97 mg, 97%, yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54–8.31 (m, 2H), 7.48–7.19 (m, 6H), 7.19–6.92 (m, 1H), 4.95–4.26 (m, 2H), 3.99–2.77 (m, 4H), 2.76–2.67 (m, 0.1H), 2.67–2.54 (m, 0.2H), 2.54–2.38 (m, 0.7H), 1.50–1.29 (m, 3H), 1.26 (s, 0.3H), 1.18 (s, 0.2H), 1.10–0.81 (m, 2.5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 171.2, 149.6, 149.5, 149.4, 149.2, 148.2, 147.9, 137.0, 136.9, 136.8, 129.2, 128.8, 128.77, 128.74, 128.4, 128.2, 127.9, 127.8, 127.4, 126.3, 125.0, 124.9, 124.5, 124.4, 72.3, 71.7, 51.7, 50.4, 50.2, 50.08, 50.02, 49.2, 48.4, 47.6, 47.2, 47.1, 44.6, 25.7, 25.2, 16.3, 10.1. IR (film) 3419, 2983, 2928, 1697, 1625, 1617 cm^{-1}. HRMS (ESI) $C_{19}H_{23}N_2O_2$ $[M + H]^+$, calculated 311.1760; found 311.1764.

***N*-Benzyl-4a-hydroxy-4-(pyridin-4-yl)octahydroisoquinolin-1(2*H*)-one (11b).** Mixture of diastereomers, 70 mg, 70%, yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.46 (d, J = 5.9 Hz, 1.8H), 8.39 (dd, J = 4.6, 1.4 Hz, 0.2H), 7.41–7.19 (m, 6.8H), 7.00 (d, J = 6.1 Hz, 0.2H), 4.86 (d, J = 14.9 Hz, 1H), 4.49 (d, J = 14.4 Hz, 0.1H), 4.37 (d, J = 14.9 Hz, 0.9H), 3.83–3.68 (m, 1H), 3.23 (dd, J = 11.8, 6.0 Hz, 1H), 2.98 (dd, J = 12.2, 6.0 Hz, 1H), 2.71 (s, 1H), 2.37 (dd, J = 13.9, 2.3 Hz, 1H), 2.29 (dd, J = 12.5, 3.8 Hz, 1H), 1.93–1.78 (m, 1H), 1.66–1.47 (m, 2H), 1.47–1.34 (m, 1H), 1.34–1.06 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 149.8, 147.2, 137.2, 128.79, 128.72, 128.0, 127.5, 124.7, 124.0, 71.0, 50.2, 50.2, 50.0, 48.9, 35.9, 25.3, 22.4, 20.6. IR (film) 3386, 2928, 2852, 1630, 1625 cm^{-1}. HRMS (ESI) $C_{21}H_{25}N_2O_2$ $[M + H]^+$, calculated 337.1916; found 337.1907.

3a-Hydroxy-2-methyl-3-(pyridin-2-yl)hexahydrocyclopenta[*c*]-pyrrol-1(2*H*)-one (12b). Mixture of diastereomers, 47 mg, 59% (based on 20% recovery of unreacted **12a**), yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64–8.57 (m, 0.8H), 8.57–8.50 (m, 0.2H), 8.30 (s, 0.2H), 8.19 (s, 0.2H), 7.80–7.63 (m, 1H), 7.31–7.14 (m, 2H), 4.85 (s, 0.3H), 4.66 (s, 0.4H), 4.53 (s, 0.5H), 4.50 (s, 0.3H), 3.43–3.06 (m, 0.4H), 2.99 (s, 0.6H), 2.97–2.90 (m, 0.6H), 2.85 (s, 0.7H), 2.83 (s, 0.8H), 2.72 (s, 0.9H), 2.60–2.25 (m, 0.5H), 2.24–2.07 (m, 1H), 2.07–1.80 (m, 1.5H), 1.80–1.60 (m, 0.7H), 1.60–1.44 (m, 0.3H), 1.44–1.29 (m, 0.5H), 1.29–1.08 (m, 0.6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.0, 176.4, 163.3, 162.8, 157.2, 157.0, 156.3, 156.1, 150.1, 150.0, 149.7, 149.4, 137.4, 137.2, 137.1, 136.9, 123.4, 123.2, 123.0, 123.0, 122.7, 122.4, 121.5, 86.0, 84.1, 74.8, 73.3, 55.3, 55.0, 53.8, 49.9, 42.4, 38.2, 34.9, 30.1, 29.5, 29.0, 28.2, 28.1, 25.3, 25.0. IR (film) 3404, 2965, 2885, 1665, 1643 cm^{-1}. HRMS (ESI) $C_{13}H_{17}N_2O_2$ $[M + H]^+$, calculated 233.1290; found 233.1286.

4-(5-Chloro-*N*-ethyl-3,4-dimethyl-1*H*-pyrrol-2-yl)pyridine (15). Pyridine substrate **6b** (100 mg, 0.4 mmol, 1 equiv.) was dissolved in 1,4-dioxane (1 mL). $POCl_3$ (0.12 mL, 1.3 mmol, 3 equiv.) was added dropwise. The reaction was maintained for 10 min, then Et_3N (0.24 mL, 1.7 mmol, 4 equiv.) was added and the reaction was heated to 120 °C for 12 h. After cooling to room temperature the solvent was removed under vacuum. The residue was combined with saturated aqueous Na_2CO_3 solution and extracted with EtOAc (3 × 10 mL). The combined organic layer was concentrated under vacuum and purified *via* flash column chromatography (SiO_2, 70–100% EtOAc–hexanes) to afford **15** (30 mg, 30%) as a brown oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.64 (d, J = 4.5 Hz, 2H), 7.19 (dd, J = 4.5, 1.6 Hz, 2H), 3.90 (q, J = 7.1 Hz, 2H), 2.01 (s, 3H), 1.99 (s, 3H), 1.15 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.0, 140.6, 126.9,

124.6, 118.3, 116.2, 115.4, 39.9, 16.2, 10.4, 9.35. IR (film) 1654, 1636, 1632 cm^{-1}. HRMS (ESI) $C_{13}H_{16}N_2Cl$ $[M + H]^+$, calculated 235.1002; found 235.1017.

General procedure for $SOCl_2$-mediated oxidation of hydroxy lactams

The preparation of **16** is representative. Compound **6b** (100 mg, 0.4 mmol, 1 equiv.) was dissolved in CH_2Cl_2 (5 mL) and the resulting solution cooled to 0 °C. Thionyl chloride (100 μL, 1.3 mmol, 3 equiv.) was added dropwise. After stirring at 0 °C for 10 min, Et_3N (0.30 mL, 2.2 mmol, 5 equiv.) was added dropwise over 5 min. The reaction was maintained at 0 °C for 12 h, and then quenched by addition of saturated aqueous Na_2CO_3 solution. After warming to room temperature the layers were separated and the aqueous was re-extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified *via* flash column chromatography (SiO_2, 70–100% EtOAc–hexanes as eluent) to give *N*-ethyl-5-hydroxy-3,4-dimethyl-5-(pyridin-4-yl)-1*H*-pyrrol-2(5*H*)-one **16** (45 mg, 45%) as a brown oil. ^1H NMR (500 MHz, $CDCl_3$) δ 8.53 (d, J = 4.3 Hz, 2H), 7.35 (d, J = 4.3 Hz, 2H), 5.52–4.86 (m, 1H), 3.42 (dq, J = 14.4, 7.2 Hz, 1H), 3.02 (dq, J = 14.3, 7.2 Hz, 1H), 1.82 (s, 3H), 1.66 (s, 3H), 1.00 (t, J = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 151.9, 149.6, 148.5, 128.9, 121.6, 91.6, 34.5, 14.7, 9.9, 8.6. IR (film) 3436, 1659, 1638, 1630 cm^{-1}. HRMS (ESI) $C_{13}H_{17}N_2O_2$ $[M + H]^+$, calculated 233.1290; found 233.1313.

Compound **16** (0.15 g, 57%) was also obtained when the known lactam[26] **19** (0.24 g, 1.1 mmol) was subjected to the conditions described above (see eqn (2)).

***N*-Ethyl-3-hydroxy-3-(pyridin-4-yl)-2,3,4,5,6,7-hexahydro-1*H*-isoindol-1-one (17).** Using the procedure given for the preparation of **16**, **8b** (100 mg, 0.4 mmol) was converted to **17** (65 mg, 70%, yellow oil). ^1H NMR (300 MHz, $CDCl_3$) δ 8.50 (d, J = 6.0 Hz, 2H), 7.36 (d, J = 6.0 Hz, 2H), 5.97 (s, 1H), 3.44 (dd, J = 14.2, 7.2 Hz, 1H), 3.02 (dd, J = 14.2, 7.2 Hz, 1H), 2.37–2.06 (m, 4H), 1.72–1.43 (m, 4H), 1.03 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 156.0, 149.6, 148.6, 132.0, 121.5, 91.2, 34.2, 22.0, 21.8, 20.62, 20.1, 14.8. IR (film) 3383, 2983, 2925, 2848, 1667 cm^{-1}. HRMS (ESI) $C_{15}H_{19}N_2O_2$ $[M + H]^+$, calculated 259.1447; found 259.1455.

***N*-Benzyl-[3,4′-bipyridin]-6(1*H*)-one (18).** Using the procedure for the preparation of **16**, compound **18** (27 mg, 30%) was isolated as a yellow oil from 100 mg of **10b**. ^1H NMR (300 MHz, $CDCl_3$) δ 8.61 (dd, J = 4.5, 1.6 Hz, 2H), 7.38–7.28 (m, 5H), 7.14 (dd, J = 4.4, 1.6 Hz, 2H), 7.08 (s, 1H), 5.18 (s, 2H), 2.22 (s, 3H), 2.08 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.0, 150.0, 145.8, 143.7, 136.5, 132.9, 129.0, 128.3, 128.2, 127.7, 124.6, 120.5, 52.6, 17.9, 13.6. IR (film) 1654, 1639, 1625 cm^{-1}. HRMS (ESI) $C_{19}H_{19}N_2O$ $[M + H]^+$, calculated 291.1497; found 291.1512.

***N*-(3-Hydroxypropyl)-*N*-(2-(pyridine-4-yl)ethyl)benzamide (23) and *N*-(3-hydroxypropyl)-*N*-(2-(pyridine-4-yl)ethyl)toluenesulfonamide (24).** 4-(2-Aminoethyl)pyridine (2.9 mL, 24 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (100 mL) and Et_3N (5.1 mL, 36 mmol, 1.5 equiv.) was added. The reaction was cooled to 0 °C and benzoyl chloride (3.1 mL, 27 mmol, 1.1 equiv.) dissolved in CH_2Cl_2 (50 mL) was added dropwise *via* addition funnel. Once the addition was complete, the reaction was maintained at 0 °C for an additional 20 min, then quenched with H_2O (100 mL). The layers were separated and the aqueous was re-extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated to afford the crude benzamide derivative (4.4 g, 80%, ^1H NMR (300 MHz, $CDCl_3$) δ 8.37 (dd, J = 4.4, 1.6 Hz, 2H), 7.76 (dd, J = 7.1, 1.5 Hz, 2H), 7.54–7.27 (m, 3H), 7.08 (dd, J = 4.5, 1.5 Hz, 2H), 3.67 (dd, J = 13.0, 6.9 Hz, 2H), 2.90 (t, J = 7.0 Hz, 2H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 149.6, 148.5, 134.4, 131.5, 128.5, 127.0, 124.3, 40.4, 35.0). Without further purification/characterization, the benzamide (4.4 g, 19.5 mmol, 1 equiv.) was dissolved in THF (100 mL) and cooled to −78 °C. A solution of KHMDS (0.5 M in THF, 98 mL, 49 mmol, 2.5 equiv.) was added dropwise. After stirring at −78 °C for 1 h, allyl bromide (5.1 mL, 59 mmol, 3 equiv.) was added and the reaction was maintained an additional 1 h at −78 °C, and then allowed to warm to room temperature and stirred overnight. The reaction was quenched with H_2O and extracted with EtOAc (3 × 100 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified *via* flash column chromatography (SiO_2, 50–100% EtOAC–hexanes as eluent) to afford the desired *N*-allyl amide as a brown oil (4.0 g, 77%, mixture of rotamers, ^1H NMR (300 MHz, $CDCl_3$) δ 8.70–8.32 (m, 2H), 7.56–7.03 (m, 6.6H), 7.00–6.54 (m, 0.5H), 6.06–5.51 (m, 1H), 5.40–5.01 (m, 2H), 4.37–3.96 (m, 0.6H), 3.94–3.31 (m, 3.5H), 3.16–2.61 (m, 2H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 149.9, 148.2, 136.2, 133.2, 129.7, 128.5, 126.4, 124.3, 117.8, 52.5, 45.9, 32.9). Without further characterization, the allyl amide (4.0 g, 15 mmol, 1 equiv.) was dissolved in THF (100 mL) and cooled to 0 °C. 9-BBN (30 mL, 45 mmol, 3 equiv.) was added *via* syringe and the reaction was stirred at 0 °C overnight. After this time, a solution prepared from 10 mL 1 M aq. NaOH and 10 mL 30% aq. H_2O_2 was added and the reaction was allowed to warm to room temperature. The reaction was then quenched with additional H_2O and extracted with EtOAc (3 × 100 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification *via* flash column chromatography (SiO_2, 50–100% EtOAc–hexanes as eluent) gave **23** as a yellow oil (3.9 g, 92%). ^1H NMR (300 MHz, $CDCl_3$, mixture of rotamers) δ 8.56–8.36 (m, 2H), 7.47–7.07 (m, 6H), 6.91–6.72 (m, 1H), 3.84–3.57 (m, 3H), 3.56–3.34 (m, 2H), 3.25 (m, 1H), 3.13–2.89 (m, 1H), 2.89–2.66 (m, 2H), 1.97–1.79 (m, 1H), 1.79–1.55 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 149.9, 146.7, 136.0, 129.7, 128.7, 126.2, 124.1, 58.6, 49.8, 41.4, 34.6, 30.5. IR (film) 3266, 3063, 2928, 2867, 1607 cm^{-1}. HRMS (ESI) $C_{17}H_{21}N_2O_2$ $[M + H]^+$, calculated 285.1603; found 285.1598.

Tosylamide **24** was prepared in similar fashion starting from 4-(2-aminoethyl)pyridine and tosyl chloride (90%, ^1H NMR (300 MHz, $CDCl_3$) δ 8.41 (dd, J = 4.4, 1.6 Hz, 2H), 7.70 (d, J = 8.3 Hz, 2H), 7.37–7.21 (m, 2H), 7.03 (dd, J = 4.5, 1.5 Hz,

2H), 5.32 (t, J = 6.2 Hz, 1H), 3.23 (q, J = 6.8 Hz, 2H), 2.78 (t, J = 6.9 Hz, 2H), 2.43 (s, 3H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.0, 147.3, 143.7, 137.0, 129.9, 127.2, 124.3, 43.4, 35.6, 21.7). Allylation was performed as described above (70%, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (d, J = 5.8 Hz, 2H), 7.68 (d, J = 8.2 Hz, 2H), 7.30 (d, J = 8.1 Hz, 2H), 7.08 (d, J = 5.6 Hz, 2H), 5.60 (ddt, J = 16.4, 9.8, 6.5 Hz, 1H), 5.26–5.11 (m, 2H), 3.78 (d, J = 6.4 Hz, 2H), 3.46–3.20 (m, 2H), 2.98–2.75 (m, 2H), 2.43 (s, 3H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.1, 147.6, 143.7, 136.7, 133.1, 129.9, 127.3, 124.3, 119.4, 51.4, 47.9, 35.0, 21.7). Hydroboration/oxidation of the allyl tosylamide afforded **24** (90%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, J = 5.7 Hz, 2H), 7.70–7.63 (m, 2H), 7.31 (dd, J = 8.5, 0.6 Hz, 2H), 7.11 (d, J = 5.9 Hz, 2H), 3.68 (t, J = 5.7 Hz, 2H), 3.39–3.31 (m, 2H), 3.27 (t, J = 6.7 Hz, 2H), 2.89 (dd, J = 8.8, 6.9 Hz, 2H), 2.43 (s, 4H), 1.77–1.61 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0, 147.6, 143.8, 136.2, 130.0, 127.2, 124.3, 58.9, 49.7, 45.8, 35.3, 31.4, 21.7. IR (film) 3291, 2925, 2870 cm^{-1}. HRMS (ESI) $C_{17}H_{23}N_2O_3S$ $[M + H]^+$, calculated 335.1429; found 335.1422.

***N*-(3-Oxopropyl)-*N*-(2-(pyridine-4-yl)ethyl)benzamide (25).** Dichloromethane (40 mL) was cooled to −78 °C. Oxalyl chloride (0.6 mL, 7.0 mmol, 2 equiv.) and DMSO (1 mL, 14 mmol, 4 equiv.) were added dropwise while maintaining the temperature below −70 °C. After 10 min, a solution of **23** (1.0 g, 3.5 mmol, 1 equiv.) in CH_2Cl_2 (10 mL) was added dropwise. Once the addition was complete the reaction was stirred an additional 15 min followed by addition of Et_3N (2 mL, 14 mmol, 4 equiv.). The reaction was allowed to warm to 0 °C and stirred for 10 min. The solvent was then evaporated and the residue was purified by flash column chromatography (SiO_2, 50–100% EtOAc–hexanes as eluent) to give **25** (0.4 g, 40%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$ mixture of rotamers) δ 9.93–9.47 (m, 1H), 8.65–8.19 (m, 2H), 7.48–6.96 (m, 6H), 6.96–6.53 (m, 1H), 4.02–3.22 (m, 4H), 3.15–2.43 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.5, 172.0, 170.5, 149.8, 149.4, 146.7, 135.9, 129.6, 128.5, 126.8, 126.2, 124.1, 123.5, 50.6, 42.6, 39.4, 34.6. IR (film) 2921, 2856, 1726, 1636 cm^{-1}. HRMS (ESI) $C_{17}H_{19}N_2O_2$ $[M + H]^+$, calculated 283.1447; found 283.1452.

***N*-(3-Oxopropyl)-*N*-(2-(pyridine-4-yl)ethyl)toluenesulfonamide (26).** To a solution of **24** (1.0 g, 3.0 mmol, 1 equiv.) in CH_2Cl_2 (50 mL) was added the Dess–Martin periodinane (1.9 g, 4.5 mmol, 1.5 equiv.) at room temperature. After 30 min the reaction was quenched with 1 M aqueous NaOH solution (20 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL) and the combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography (SiO_2, 50–100% EtOAc–hexanes as eluent) gave **26** (0.42 g, 42%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.72 (s, 1H), 8.49 (d, J = 5.8 Hz, 2H), 7.68–7.63 (m, 2H), 7.31 (d, J = 8.0 Hz, 2H), 7.12 (dd, J = 4.5, 1.5 Hz, 2H), 3.44 (t, J = 6.8 Hz, 2H), 3.39–3.31 (m, 2H), 2.89–2.83 (m, 2H), 2.75 (td, J = 6.8, 0.6 Hz, 2H), 2.42 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.1, 149.8, 147.2, 143.8, 135.7, 129.9, 127.1, 124.2, 49.7, 43.7, 42.0, 34.7, 21.5. IR (film) 3291, 2925, 2870 cm^{-1}. HRMS (ESI) $C_{17}H_{21}N_2O_3S$ $[M + H]^+$, calculated 333.1265; found 333.1284.

***N*-Benzoyl-1,2,5,6-tetrahydro-3,4′-bipyridine (27).** Cyclization of **25** (100 mg) was achieved by application of previously reported reaction conditions[26] to yield **27** (68 mg, 73%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotamers) δ 8.71–8.41 (m, 2H), 7.54–6.90 (m, 7H), 6.55–6.43 (m, 1H), 4.72–4.44 (m, 1.4H), 4.44–4.18 (m, 0.6H), 4.02–3.73 (m, 0.6H), 3.73–3.27 (m, 1.4H), 2.62–2.25 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.2, 150.3, 145.8, 136.0, 132.8, 130.1, 128.8, 127.0, 125.7, 119.6, 44.1, 43.2, 26.5. IR (film) 3060, 3027, 2921, 2893, 2852, 1626 cm^{-1}. HRMS (ESI) $C_{17}H_{17}N_2O$ $[M + H]^+$, calculated 265.1341; found 265.1334.

***N*-Tosyl-1,2,5,6-tetrahydro-3,4′-bipyridine (28).** This material was obtained as a yellow oil in 72% isolated yield under previously reported reaction conditions,[26] and in 52% isolated yield using the TfOH-catalyzed procedure given above for the preparation of **5**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55 (dd, J = 4.6, 1.6 Hz, 2H), 7.73 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 7.18 (dd, J = 4.6, 1.7 Hz, 2H), 6.35 (tt, J = 4.0, 1.9 Hz, 1H), 3.93 (dd, J = 4.6, 2.5 Hz, 2H), 3.24 (dt, J = 6.9, 4.0 Hz, 2H), 2.48–2.38 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.3, 145.7, 144.0, 133.4, 131.4, 130.0, 127.8, 126.0, 119.5, 45.6, 42.3, 25.9, 21.7. IR (film) 3026, 2917, 2852 cm^{-1}. HRMS (ESI) $C_{17}H_{19}N_2O_2S$ $[M + H]^+$, calculated 315.1167; found 315.1170.

General procedure for the preparation of 2-pyridylbenzofurans

Benzofuran derivatives shown in Scheme 6 were prepared using the TfOH-catalyzed procedure given for the preparation of **5**. Reactions were performed using 100 mg of alkylated salicylaldehyde substrates.

2-(Benzofuran-2-yl)pyridine (31).[35] Yellow solid, 58%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67 (ddd, J = 4.8, 1.7, 0.9 Hz, 1H), 7.87 (dt, J = 8.0, 1.0 Hz, 1H), 7.78–7.70 (m, 1H), 7.64 (ddd, J = 7.6, 1.4, 0.7 Hz, 1H), 7.60–7.53 (m, 1H), 7.42 (d, J = 0.9 Hz, 1H), 7.37–7.28 (m, 1H), 7.28–7.17 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.5, 155.2, 150.1, 149.4, 136.9, 129.0, 125.4, 123.4, 123.1, 121.9, 120.0, 111.7, 105.0. IR (film) 3056, 3007, 2921, 2844, 1610, 1556 cm^{-1}. HRMS (ESI) $C_{13}H_{10}NO$ $[M + H]^+$, calculated 196.0762; found 196.0754.

4-(Benzofuran-2-yl)pyridine (32). Colorless solid, 96%, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.66 (d, J = 4.3 Hz, 2H), 7.67 (d, J = 5.6 Hz, 2H), 7.64–7.48 (m, 2H), 7.35 (ddd, J = 8.3, 7.3, 1.4 Hz, 1H), 7.30–7.17 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.3, 152.9, 150.3, 137.4, 128.5, 125.7, 123.4, 121.6, 118.7, 111.5, 105.0. IR (film) 3081, 3034, 2928, 2852, 1610, 1541. HRMS (ESI) $C_{13}H_{10}NO$ $[M + H]^+$, calculated 196.0762; found 196.0747.

4-(3-(4-Methoxyphenyl)benzofuran-2-yl)pyridine (37). Yellow solid, 92%, Mp. 105–108 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.53 (d, J = 6.0 Hz, 2H), 7.60–7.51 (m, 3H), 7.48 (dd, J = 7.8, 0.6 Hz, 1H), 7.44–7.34 (m, 3H), 7.25 (t, J = 7.5 Hz, 1H), 7.09–7.00 (m, 2H), 3.89 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.9, 154.4, 149.9, 147.2, 138.4, 130.9, 130.3, 126.2, 123.9, 123.5, 121.6, 120.9, 120.4, 114.9, 111.6, 55.5. IR (film) 3065, 3040, 2960, 2915, 2841, 1603, 1516. HRMS (ESI) $C_{20}H_{16}NO_2$ $[M + H]^+$, calculated 302.1181; found 302.1169.

4-(3-Methylbenzofuran-2-yl)pyridine (38). Yellow solid, 75%, Mp. 40–45 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (d, J = 4.4 Hz,

1H), 7.66–7.57 (m, 1.9H), 7.55–7.46 (m, 1H), 7.46–7.37 (m, 1H), 7.33–7.24 (m, 1H), 7.24–7.13 (m, 1H), 2.46 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.3, 150.2, 147.7, 138.8, 130.8, 126.0, 123.0, 120.3, 120.1, 115.9, 111.5, 9.9. IR (film) 3036, 2929, 2852, 1609, 1540. HRMS (ESI) $C_{14}H_{12}NO$ $[M + H]^+$, calculated 210.0919; found 210.0913.

2-(3-(4-Methoxyphenyl)benzofuran-2-yl)pyridine (39). Colorless solid, 61%, Mp. 50–53 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.69 (ddd, J = 4.8, 1.7, 1.0 Hz, 1H), 7.64 (d, J = 8.2 Hz, 1H), 7.60–7.42 (m, 5H), 7.37 (ddd, J = 8.4, 7.3, 1.3 Hz, 1H), 7.29–7.21 (m, 1H), 7.16 (ddd, J = 7.2, 4.8, 1.4 Hz, 1H), 7.06–6.98 (m, 2H), 3.88 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.53, 154.48, 150.1, 149.9, 149.1, 136.2, 131.2, 130.2, 125.8, 124.6, 123.3, 122.8, 122.5, 120.8, 120.6, 114.6, 111.9, 55.5. IR (film) 3052, 2997, 2925, 2828, 1598, 1581, 1556, 1507. HRMS (ESI) $C_{20}H_{16}NO_2$ $[M + H]^+$, calculated 302.1181; found 302.1163.

4-(3-Methylbenzofuran-2-yl)pyridine (40). Colorless solid, 62%, Mp. 38–41 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67 (ddd, J = 4.8, 1.8, 0.9 Hz, 1H), 7.85 (dt, J = 8.0, 1.0 Hz, 1H), 7.70 (td, J = 7.8, 1.8 Hz, 1H), 7.56 (ddd, J = 7.5, 1.5, 0.7 Hz, 1H), 7.52–7.46 (m, 1H), 7.35–7.27 (m, 1H), 7.27–7.20 (m, 1H), 7.13 (ddd, J = 7.5, 4.8, 1.2 Hz, 1H), 2.70 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.1, 151.5, 149.7, 149.2, 136.6, 131.3, 125.4, 122.8, 122.1, 121.1, 120.2, 116.0, 111.4, 9.8. IR (film) 3048, 2928, 2863, 1603, 1585 cm^{-1}. HRMS (ESI) $C_{14}H_{12}NO$ $[M + H]^+$, calculated 210.0919; found 210.0906.

4-(3-(4-Methoxyphenyl)benzofuran-2-yl)quinoline (42). Brown oil, 73%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.98 (d, J = 4.6 Hz, 1H), 8.56 (d, J = 8.5 Hz, 1H), 8.20 (d, J = 8.5 Hz, 1H), 7.84–7.73 (m, 2H), 7.73–7.57 (m, 3H), 7.47–7.36 (m, 1H), 7.36–7.23 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.4, 152.9, 150.1, 149.2, 135.9, 130.5, 129.8, 128.7, 127.6, 125.8, 125.5, 125.00, 123.6, 121.8, 120.0, 111.7, 108.8. IR (film) 3060, 3027, 2962, 2917, 2856, 1593, 1561. HRMS (ESI) $C_{17}H_{12}NO$ $[M + H]^+$, calculated 246.0919; found 246.0914.

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