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# NHC-Catalyzed Aza-Benzoin Condensation of *N,N′*-Dipyridin-2-yl Aminals with Aldehydes

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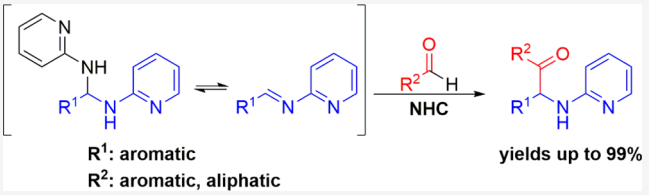
**ABSTRACT:** α-Amino ketones are useful compounds because of their synthetic utility and bioactivities. After observing the ability of *N,N′*-dipyridin-2-yl aminals to form imines in situ, the synthesis of α-amino ketones using *N,N′*-dipyridin-2-yl aminals was proposed. Through the NHC-catalyzed aza-benzoin reaction between aromatic/aliphatic aldehydes and *N,N′*-dipyridin-2-yl aminals, α-amino ketones, including aromatic, heterocyclic, and aliphatic versions, were synthesized with yields up to 99%. A direct route toward *N*-Boc-protected α-amino ketones from *N,N,N′*-tris-Boc aminals was also discovered, yielding the desired *N*-Boc-protected α-amino ketones in yields up to 73%.



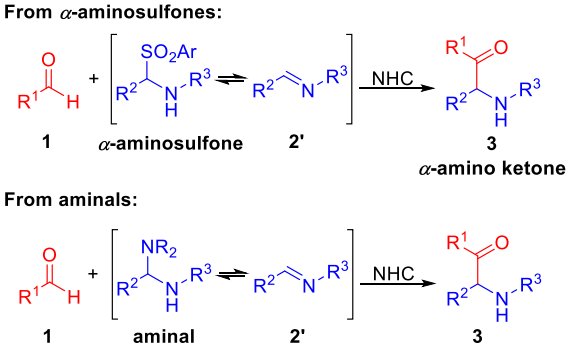



## INTRODUCTION

α-Amino ketones[1] have been fundamental substrates in the syntheses of nitrogen-containing heterocyclic compounds[2−6] such as indoles,[2] indolines,[3] and pyrroles.[4] Furthermore, the α-amino ketone framework is an important motif in biologically active molecules. For instance, it is found in the antidepressant bupropion[7a,b] and the vasoconstrictor adrenalone.[7c] α-Amino ketones can be accessed from various substrates,[1,8−12] including α-amino acids,[8a,b] alkenes,[9] and ketones.[10a−e] Imines provide another synthetic starting point toward α-amino ketones.[13a−f] The NHC-catalyzed aza-benzoin condensation reaction between aldehydes and imines is a convenient synthetic method for α-amino ketones.[14−18] However, since imines may be unstable, it is common to form them in situ (Scheme 1).[16−18]

The in situ formation of imines can be achieved using α-aminosulfones[16] or aminals (Scheme 1).[17,18] Aminals can be easily prepared and are bench-stable. These properties make aminals attractive precursors to imines, which also make them ideal starting materials for the NHC-catalyzed synthesis of α-amino ketones.

**Scheme 1. In Situ Formation of Imines**




To the best of our knowledge, only two previous reports on the NHC-catalyzed synthesis of α-amino ketones from aminal-derived intermediates exist. Both reports used benzotriazole-based aminals (Scheme 2).[17,18] Over the course of previous research, we found *N,N′*-dipyridin-2-yl aminals to be bench-stable in the solid form but to quickly form imines in solution at room temperature. We believed that the ability of these aminals to form imines efficiently and previous reports of the removal of pyridin-2-yl groups[19] make these compounds attractive starting materials. Thus, we attempted the application of *N,N′*-dipyridin-2-yl aminals in the aza-benzoin condensation reaction. Herein, we report the synthesis of α-amino ketones by the use of *N,N′*-dipyridin-2-yl aminals as imine precursors in the NHC-catalyzed aza-benzoin reaction.

## RESULTS AND DISCUSSION

Initial studies were conducted using 4-chlorobenzaldehyde and aminal **2a** in ethanol (Table 1, see Table S1 in the Supporting Information for a full list of screening conditions). The reaction using commercially available thiazolium salt **A** as the catalyst precursor with $Et_3N$ as the base provided the desired α-amino ketone **3a** in 71% yield (entry 1). Mesityl-substituted thiazolium perchlorate salt **B** afforded the desired product in

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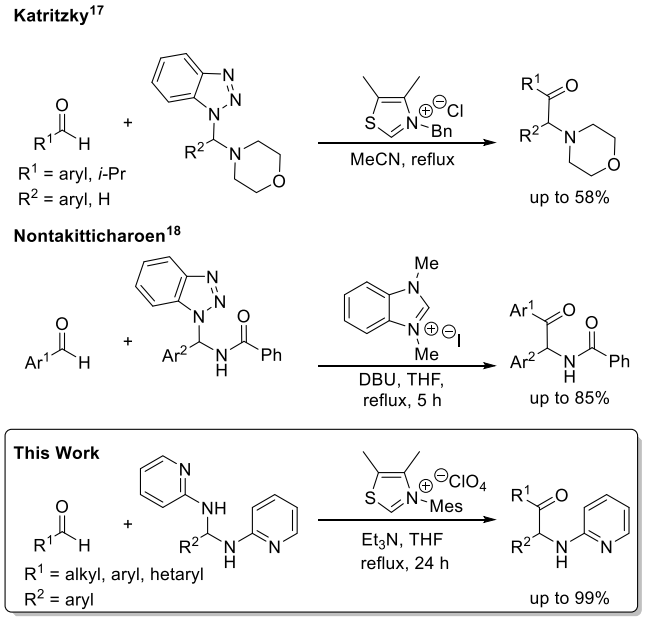
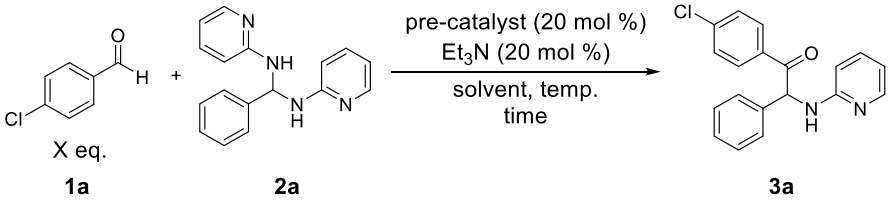
**Scheme 2. Previous Work and This Work**

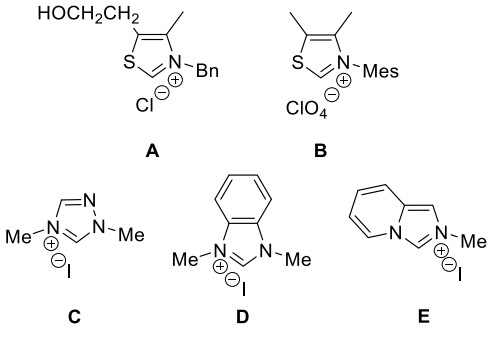



82% yield (entry 2). Despite these promising results, further experiments using ethanol revealed the yields to be inconsistent, and the formation of varying amounts of ethyl 4-chlorobenzoate originating from **1a** and ethanol was observed. As a result, an alternative solvent was desired. A solvent screening revealed tetrahydrofuran (THF) and chloroform as effective solvents for this reaction (entries 3−8). The reaction using catalyst precursor **B** in chloroform at reflux temperature with 1.5 equiv of aldehyde afforded **3a** in 78% yield (entry 7). The reaction in THF at reflux temperature with 1.2 equiv of aldehyde gave **3a** in 77% yield (entry 8). Chloroform was not considered for further reactions due to its potential toxicity. As a result, THF was chosen as the solvent for all further reactions. To test whether catalyst precursor **B** was the optimal salt for this reaction, a catalyst screening was conducted. Thiazolium salt **A** proved to be poorly soluble in THF and yielded the desired product in only 46% yield (entry 9). No product was detected with the use of triazolium salt **C** (entry 10). Benzimidazolium salt **D** and imidazo[1,5-*a*]-pyridinium salt **E** led to the yields lower than salt **B** (58 and 15%, entries 11 and 12, respectively). The reaction conditions were then examined using thiazolium salt **B**. Reduction of the reaction time to 6 h dramatically decreased the yield to only

**Table 1. Catalyst and Condition Screening**[b]




| entry | pre-cat. | *X* equiv | solvent | temp (°C) | time (h) | yield (%) |
|---|---|---|---|---|---|---|
| 1 | **A** | 1.2 | EtOH | 70 | 48 | 71 |
| 2 | **B** | 1.2 | EtOH | 70 | 48 | 82 |
| 3 | **B** | 2 | $CH_2Cl_2$ | reflux | 48 | 68 |
| 4 | **B** | 1.0 | DMSO | 70 | 48 | 34 |
| 5 | **B** | 1.2 | $iPr_2O$ | reflux | 24 | 45 |
| 6 | **B** | 1.0 | MeCN | 70 | 48 | 4 |
| 7 | **B** | 1.5 | $CHCl_3$ | reflux | 24 | 78 |
| 8 | **B** | 1.2 | THF | reflux | 48 | 77 |
| 9 | **A** | 1.2 | THF | reflux | 48 | 46 |
| 10[a] | **C** | 1.2 | THF | reflux | 48 | n.d. |
| 11[a] | **D** | 1.2 | THF | reflux | 48 | 58 |
| 12[a] | **E** | 1.2 | THF | reflux | 48 | 15 |
| 13 | **B** | 1.2 | THF | reflux | 6 | 38 |
| 14 | **B** | 2 | THF | reflux | 48 | 88 |
| 15 | **B** | 1.5 | THF | reflux | 24 | 90 |
| 16 | **B** | 2 | THF | r.t. | 24 | 41 |




[a]DBU (20 mol %) was used as the base. [b]n.d. = not detected.



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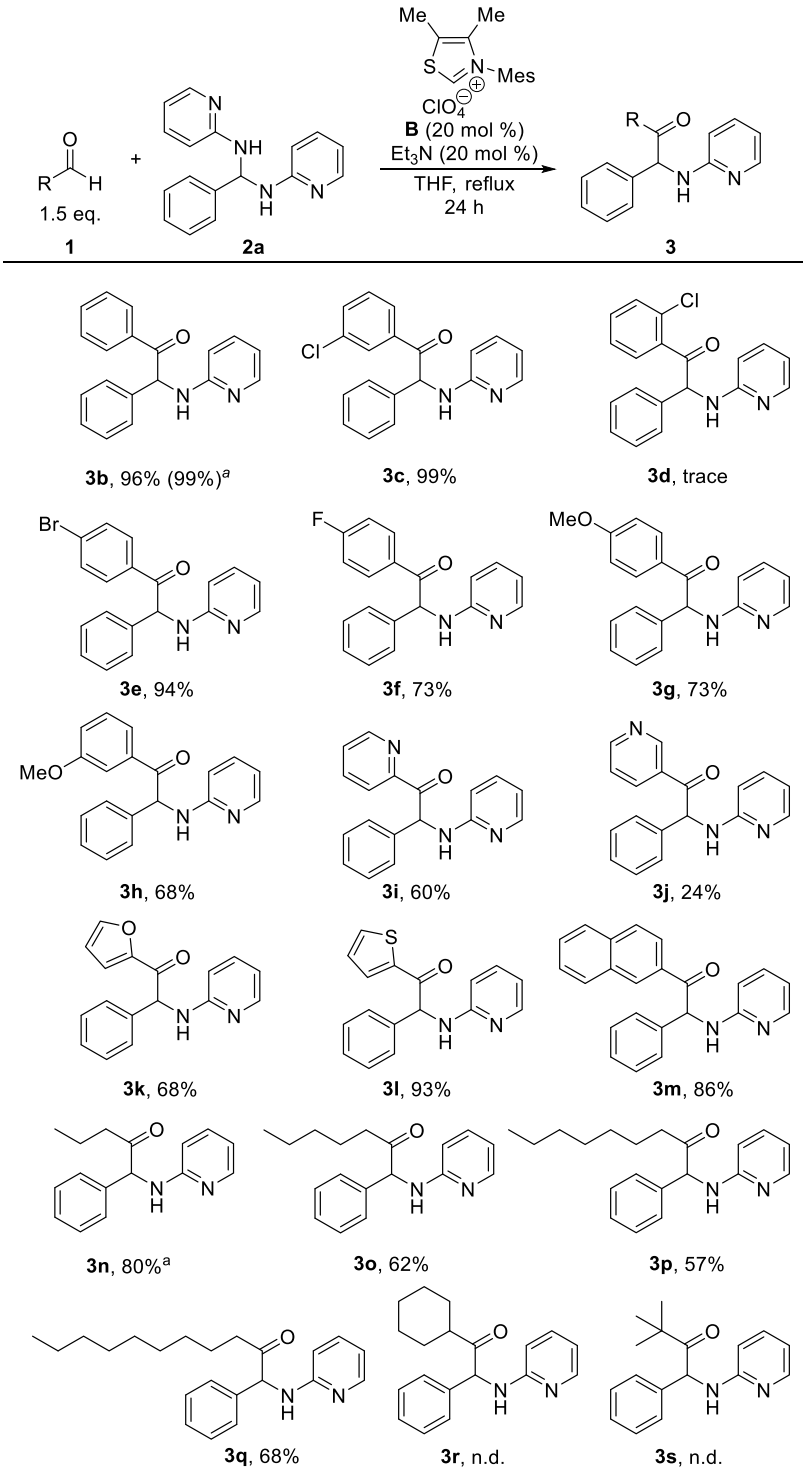
**Scheme 3. Aldehyde Substrate Screening**[a]




[a]2 equiv of aldehyde. [b]n.d. = not detected.

38% (entry 13). Further adjustments to the aldehyde loading revealed that a larger excess of aldehyde could significantly improve the yield. Compound **3a** was obtained in 88% yield after 48 h at reflux temperature using 2 equiv of aldehyde in comparison to 77% when 1.2 equiv was used (entries 14 and 8, respectively). Further adjustments of the aldehyde loading revealed 1.5 equiv to be appropriate as **3a** was afforded in 90% yield with a reaction time of only 24 h (entry 15). Reducing the reaction temperature to room temperature negatively impacted the yield with the reaction affording the desired compound in only 41% yield, even with an increased aldehyde loading of 2 equiv (entry 16). The results of these screening reactions revealed the conditions shown in entry 15 to be optimal.

With the optimal conditions investigated, the substrate screening began with aromatic aldehydes. The reaction with both benzaldehyde and 3-chlorobenzaldehyde proceeded smoothly, yielding the desired products **3b** and **3c** in



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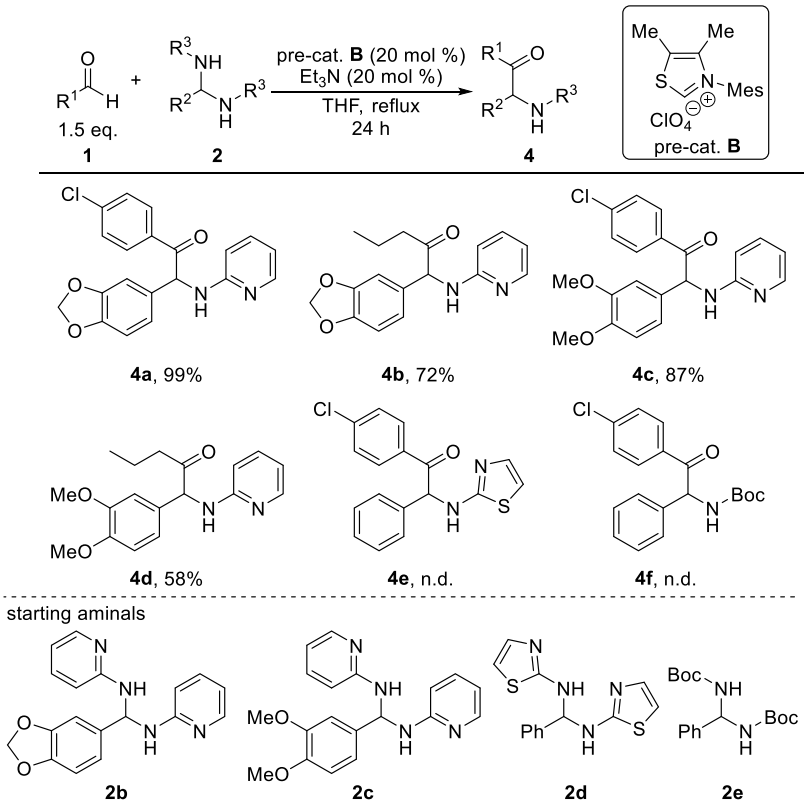
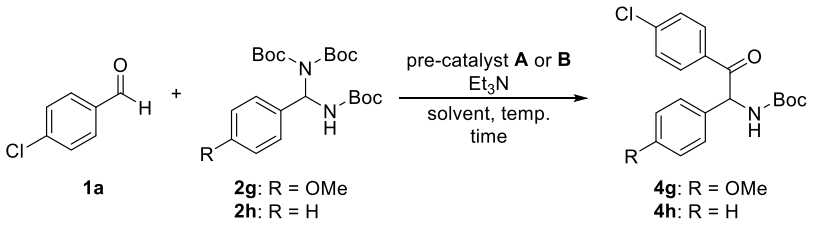
**Scheme 4. Substrate Scope Expansion**[a]




[a]n.d. = not detected.

**Table 2. Reactions with *N,N,N′*-Tris-Boc Aminals**[g,h]




| entry | aminal | pre-cat. | solvent | temp (°C) | time (h) | yield (%) |
|---|---|---|---|---|---|---|
| 1[a,b] | 2g | **A** | EtOH | 70 | 48 | 73 |
| 2[c,d] | 2g | **A** | EtOH | 70 | 48 | n.d. |
| 3[c,d] | 2g | **B** | EtOH | 70 | 48 | n.d. |
| 4[c,e] | 2h | **A** | EtOH | 70 | 48 | 10 |
| 5[c,e] | 2h | **B** | EtOH | 70 | 48 | 5 |
| 6[f] | 2h | **A** | THF | reflux | 24 | n.d. |
| 7[f] | 2h | **B** | THF | reflux | 24 | n.d. |

[a]Pre-catalyst (40 mol %), $Et_3N$ (40 mol %), and **1a** (3.3 equiv). [b]0.12 mmol scale. [c]3 Å molecular sieves were added. [d]0.22 mmol scale. [e]1 mmol scale. [f]0.24 mmol scale. [g]n.d. = not detected. [h]Standard reaction conditions: **1a** (1.5 equiv), **2g** or **2h** (1 equiv), pre-catalyst (20 mol %), and $Et_3N$ (20 mol %).

quantitative yields (Scheme 3). 2-Chlorobenzaldehyde proved to be a poor substrate for this reaction, with only a trace amount of **3d** being obtained. 4-Bromobenzaldehyde and 4-fluorobenzaldehyde afforded the corresponding products **3e** and **3f** in 94 and 73% yields, respectively. 4-Methoxybenzaldehyde provided $\alpha$-amino ketone **3g** in 73% yield. 3-Methoxybenzaldehyde was also a good substrate for this reaction, affording **3h** in 68% yield. Heterocyclic aldehydes proved to be suitable substrates for this reaction. The use of 2-pyridinecarboxaldehyde and 3-pyridinecarboxaldehyde yielded products **3i** and **3j** with yields of 60 and 24%, respectively. Furfural and 2-thiophenecarboxaldehyde afforded the corresponding products **3k** and **3l** in 68 and 93% yields, respectively. 2-Napthaldehyde also proved to be a suitable substrate in this reaction, providing **3m** in 86% yield. Linear aliphatic aldehydes afforded the desired products **3n**−**3q** in moderate to good yields (57−80%). More sterically demanding aliphatic aldehydes such as cyclohexanecarboxaldehyde and pivalaldehyde did not yield the desired products **3r** and **3s**, respectively.



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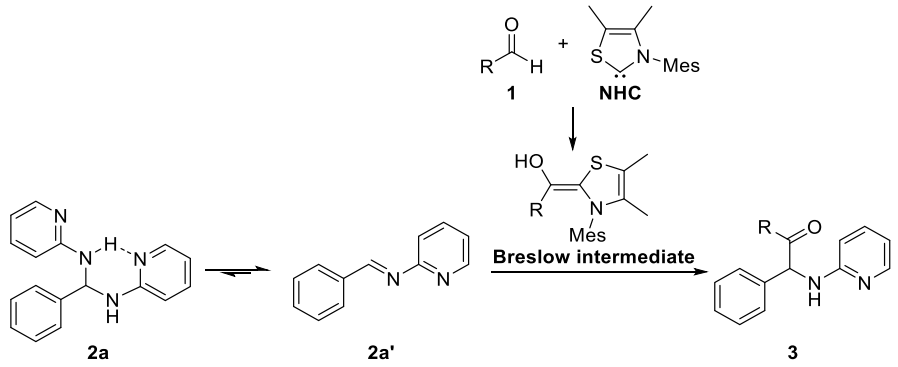


**Figure 1.** Key mechanistic step—conversion of aminal **2a** into imine **2a′**.

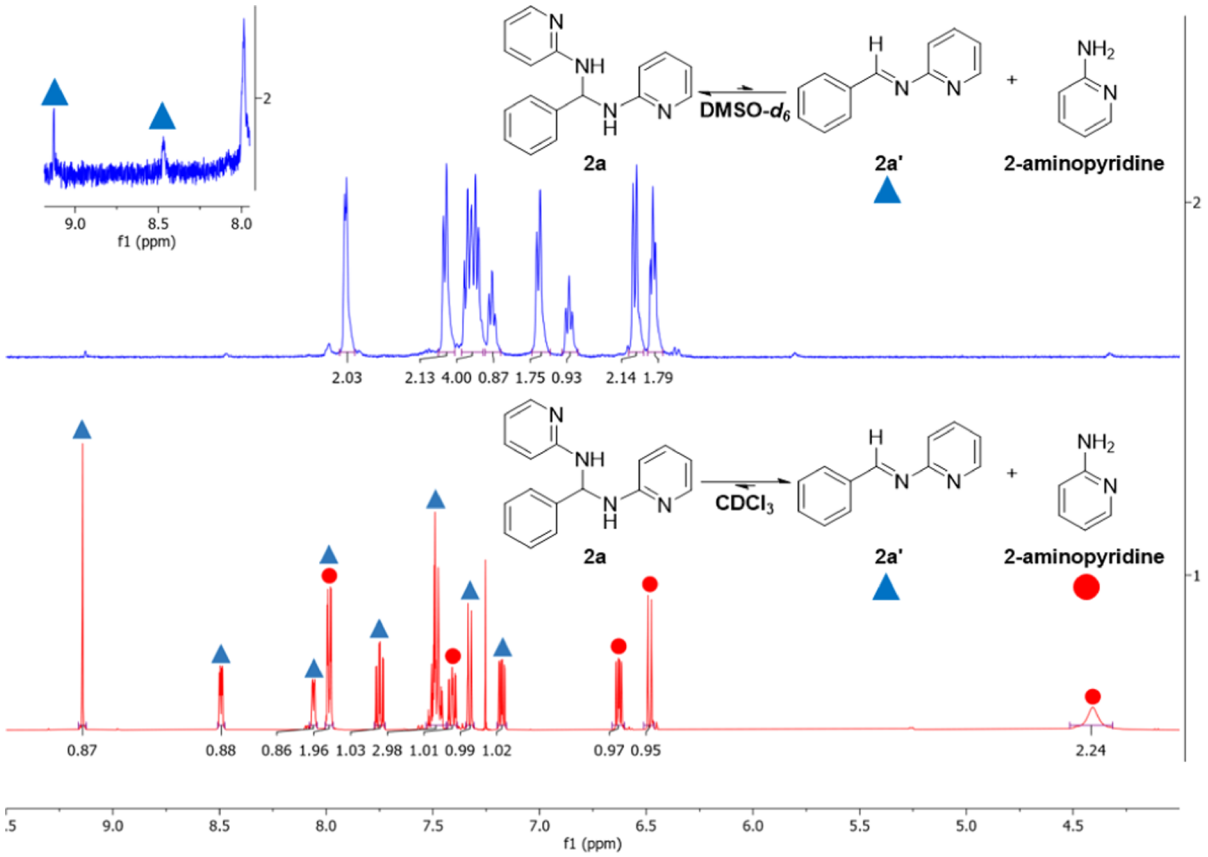


**Figure 2.** Compound **2a** in DMSO-$d_6$ and $CDCl_3$. Comparison of aminal **2a** dissolved in DMSO-$d_6$ (top) and $CDCl_3$ (bottom) is shown. When aminal **2a** is dissolved in DMSO-$d_6$, the equilibrium is shifted heavily toward aminal **2a**, allowing for the observation of aminal **2a**. When aminal **2a** is dissolved in $CDCl_3$, the equilibrium is shifted heavily toward imine **2a′** and 2-aminopyridine, allowing for the clear observation of both imine **2a′** (blue triangles) and 2-aminopyridine (red circles).

Expansion of the substrate scope began with derivatives of piperonal and 3,4-dimethoxybenzaldehyde (Scheme 4). Benzodioxole aminal **2b** gave product **4a** in quantitative yield when reacted with 4-chlorobenzaldehyde. Compound **4b** was obtained in 72% yield by the reaction of **2b** with butyraldehyde. The reaction between the dimethoxyphenyl-substituted aminal **2c** and 4-chlorobenzaldehyde afforded **4c** in 87% yield. The use of **2c** with butyraldehyde provided the corresponding product **4d** in 58% yield. To compare the reactivity of *N,N′*-dipyridin-2-yl aminals with other *N,N′*-substituted aminals, *N,N′*-bis(2-thiazolyl) and *N,N′*-bis-Boc-substituted aminals were tested. *N,N′*-Bis(2-thiazolyl) aminal **2d** provided no desired product **4e**. *N,N′*-Bis-Boc aminal **2e** failed to afford the desired amino ketone **4f**. *N,N′*-bis-Boc aminals have previously been shown to be unreactive under basic conditions by Kano and co-workers.[20] The conversion[20] of the corresponding *N,N′*-bis-Boc aminal **2f** into *N,N,N′*-tris-Boc aminal **2g** allowed for the synthesis of amino ketone **4g** in 73% yield (Table 2, entry 1). However, further experiments revealed the reaction in ethanol to be poorly reproducible (entries 2 and 3), similar to what was found with *N,N′*-dipyridin-2-yl aminals. The formation of significant amounts of ethyl 4-chlorobenzoate was observed in these reactions. Strict exclusion of oxygen is likely necessary for reproducible high yields when ethanol is used as the solvent. Reactions using phenyl-substituted *N,N,N′*-tris-Boc aminal **2h** gave the desired


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product **4h** in 10% yield when pre-catalyst **A** was used and 5% yield when pre-catalyst **B** was used (entries 4 and 5, respectively). When *N,N,N′*-tris-Boc aminal **2h** was used with the optimized conditions previously found, the desired α-amino ketone **4h** was not observed (entries 6 and 7).

The reaction most likely proceeds through an aza-benzoin condensation mechanism. The prerequisite step for this transformation using aminals is the conversion of the aminal into the imine. With *N,N′*-dipyridin-2-yl aminals, hydrogen bonding between the amine hydrogen atom and the pyridine's nitrogen atom likely promotes the leaving group ability of the aminopyridine moiety (Figure 1). The increased leaving group ability of the aminopyridine moiety allows for the conversion of the starting aminal into the imine. Reaction between the intermediate imine and the Breslow intermediate leads to the formation of the desired α-amino ketone.[16]

Conversion of aminal **2a** into imine **2a′** and 2-aminopyridine at room temperature can be observed by $^1$H NMR. When aminal **2a** was dissolved in DMSO-$d_6$, only a trace amount of imine **2a′** can be observed (Figure 2, top). However, when aminal **2a** was dissolved in $CDCl_3$, imine **2a′** and 2-aminopyridine were clearly observed. A characteristic imine singlet from imine **2a′** was observed at 9.14 ppm, and the amine protons from 2-aminopyridine were observed as a broad singlet at 4.40 ppm when **2a** was dissolved in $CDCl_3$ (Figure 2, bottom). These data help confirm both the synthesis of aminal **2a** and the proposed mechanistic step of the in situ formation of the desired, reactive imine **2a′** from aminal **2a**.

## CONCLUSIONS

In conclusion, α-amino ketones have been synthesized from *N,N′*-dipyridin-2-yl aminals via the NHC-catalyzed aza-benzoin condensation reaction. The aminals provide stable, easily synthesized, and easily handled imine precursors. The reaction using mesityl-substituted thiazolium salt **B** showed good tolerance to both aromatic and aliphatic aldehydes. Yields were typically good to excellent when aromatic aldehydes were used. Yields were moderate when linear aliphatic aldehydes were used. The reaction was applied to a variety of different *N,N′*-dipyridin-2-yl aminals, obtaining up to quantitative yields of the corresponding *N*-pyridin-2-yl α-amino ketones. Previous reports show that *N*-pyridin-2-yl groups can be removed with high yields using multiple methods.[19] Additionally, we have uncovered evidence that *N*-Boc-protected α-amino ketones can be directly synthesized from *N,N,N′*-tris-Boc aminals using the aza-benzoin condensation reaction. Further investigation of the reaction conditions necessary to realize an effective, reproducible transformation of *N,N,N′*-tris-Boc aminals to α-amino ketones is currently underway in our laboratory.

## EXPERIMENTAL SECTION

**General Information.** Reagents and solvents were purchased from commercial sources. Solid aldehydes were used without further purification. Liquid aldehydes were purified by distillation before use. All other reagents were used without further purification. All solvents were of the dehydrated or super dehydrated form. All reactions were performed under argon and stirring unless otherwise noted. Column chromatography was performed using spherical silica gel (63−219 μm) (Kanto Chemicals). Medium-pressure liquid chromatography was performed using a Yamazen EPC LC W-Prep 2XY system equipped with a Yamazen Ultra Pack B silica column or a Yamazen Hi-Flash silica column. Recycling size-exclusion chromatography was conducted using a Japan Analytical Industry (JAI) recycling preparative high-performance liquid chromatography (HPLC) LC-918 system equipped with JAIGEL-1HR and JAIGEL-2HR columns using chloroform as the solvent. Merck thin-layer chromatography (TLC) plates (silica gel 60G F254 0.25 mm) were used. TLC plates were visualized by fluorescence under a UV lamp (254 or 365 nm). $^1$H NMR was recorded on a JEOL JNM-ECX (500 MHz) or a Bruker Ascend 400 (400 MHz) spectrometer. Chemical shifts were recorded in parts per million (ppm, δ), relative to tetramethylsilane (δ 0.00). $^1$H NMR splitting patterns are reported as singlet (s), doublet (d), triplet (t), dd (doublet of doublets), dt (doublet of triplets), m (multiplet), etc. $^{13}$C NMR spectra were recorded on a JEOL JNM-ECX (125 MHz) spectrometer or a Bruker Ascend 400 (100 MHz) spectrometer. Mass spectra were recorded using a TOF (ESI) analyzer or a magnetic sector (FAB) analyzer. Melting points were measured using an ATM-02, AS ONE melting point apparatus and were uncorrected.

**General Procedure for the Synthesis of *N,N′*-Dipyridin-2-yl Aminals (General Procedure A).** 2-Aminopyridine was added to a dried flask containing activated 4 Å molecular sieves and a magnetic stirring bar. The flask was then purged with argon. Aldehyde (1 equiv) and dehydrated toluene (20 mL for the 10 mmol scale; 10 mL for the 6 mmol scale) were added, and the reaction mixture was stirred under argon for 24 h at 70 °C in an EYELA ChemiStation Personal Synthesizer PPS-CTRL1 machine. The mixture was then filtered and washed with hot toluene. The filtrate was concentrated under reduced pressure, yielding either an off-white powder or a yellow oil. The powder was washed with cool ether and dried in vacuo. The oil was allowed to crystallize overnight. The crystals were then filtered, washed with cool ether, and dried in vacuo. Oils which did not crystallize overnight where purified by silica gel medium-pressure liquid chromatography (5% ethyl acetate in *n*-hexane).

*1-Phenyl-N,N′-di-2-pyridinylmethanediamine (**2a**).*[21,22] The compound was prepared from benzaldehyde (1.02 mL, 10 mmol) and 2-aminopyridine (1.88 g, 20 mmol) following general procedure A. White solid; 2.48 g, 90% yield; $^1$H NMR (500 MHz, DMSO-$d_6$): δ 7.93−7.88 (m, 2H), 7.44 (d, *J* = 7.7 Hz, 2H), 7.37−7.19 (m, 5H), 7.00 (d, *J* = 7.8 Hz, 2H), 6.86 (t, *J* = 7.7 Hz, 1H), 6.55 (d, *J* = 8.8 Hz, 2H), 6.47 (t, *J* = 6.5 Hz, 2H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): δ 158.2, 148.0, 143.1, 137.2, 128.6, 127.7, 127.3, 112.8, 109.1, 61.6.

*1-(1,3-Benzodioxol-5-yl)-N,N′-di-2-pyridinylmethane-diamine (**2b**).*[22] The compound was prepared from 1,3-benzodioxole-5-carbaldehyde (900 mg, 6 mmol) and 2-aminopyridine (1.13 g, 12 mmol) following general procedure A. Off-white solid; 1.42 g, 74% yield; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 8.00−7.93 (m, 2H), 7.43−7.34 (m, 2H), 7.04 (d, *J* = 1.7 Hz, 1H), 7.01−6.94 (m, 3H), 6.87 (d, *J* = 8.0 Hz, 1H), 6.78 (t, *J* = 7.6 Hz, 1H), 6.61−6.55 (m, 2H), 6.55−6.49 (m, 2H), 5.99 (s, 2H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 158.0, 148.0, 147.6, 146.8, 137.2, 137.1, 120.4, 112.8, 108.9, 108.3, 107.6, 101.3, 61.5.

*1-(3,4-Dimethoxyphenyl)-N,N′-di-2-pyridinylmethane-diamine (**2c**).*[22] The compound was prepared from 3,4-dimethoxybenzaldehyde (895 μL, 6 mmol) and 2-aminopyridine (1.13 g, 12 mmol) following general procedure A. Off-white solid; 1.80 g, 89% yield; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 8.00−7.93 (m, 2H), 7.43−7.34 (m, 2H), 7.13 (s, 1H), 7.05−6.98 (m, 1H), 6.98−6.87 (m, 3H), 6.79 (t, *J* = 7.6 Hz, 1H), 6.59 (d, *J* = 8.3 Hz, 2H), 6.55−6.48 (m, 2H), 3.74 (d, *J* = 4.2 Hz, 6H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 158.2, 149.1, 148.6, 148.0, 137.2, 135.4, 119.2, 112.8, 112.0, 111.2, 108.8, 61.7, 56.1, 56.0.

*1-Phenyl-N,N′-bis(2-thiazolyl)methanediamine (**2d**).*[23] 2-Aminothiazole (1.00 g, 10 mmol, 2 equiv) was added to a flask containing 3 Å molecular sieves. The flask was then purged with argon. Distilled benzaldehyde (510 μL, 5 mmol, 1 equiv) and dehydrated toluene (5 mL) were subsequently added by syringe. The mixture was stirred for 16 h at 70 °C. The reaction mixture was then filtered (washed with hot toluene), and the solvent was removed under reduced pressure. The title product was obtained as a yellow solid and was recrystallized from *n*-hexane/ethyl acetate (350 mg, 25% yield). $^1$H NMR (400 MHz, DMSO-$d_6$): δ 8.36 (d, *J* = 7.3 Hz, 2H), 7.54−7.48 (m, 2H), 7.42−7.30 (m, 3H), 7.03 (d, *J* = 3.6 Hz, 2H), 6.67 (d, *J* = 3.6 Hz,


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2H), 6.49 (t, $J$ = 7.2 Hz, 1H). HRMS (ESI) $m/z$: $[M + Na]^+$ calcd for $C_{13}H_{12}N_4S_2Na$, 311.0401; found, 311.0399.

*Di-tert-butyl (Phenylmethylene)dicarbamate (**2e**).*[24,25] *tert*-Butyl carbamate (1.3 g, 11 mmol) was added to a flask which was then purged with argon. Benzaldehyde (670 μL, 6.6 mmol) was added by syringe, followed by acetic anhydride (1.5 mL). Trifluoroacetic acid (41 μL, 0.55 mmol) was then added. The mixture was stirred at room temperature for 18 h. The aminal precipitated from the solution as a white solid. The solid was filtered off and washed with *n*-hexane (880 mg, 49% yield). $^1$H NMR (500 MHz, $CDCl_3$): δ 7.44−7.27 (m, 5H), 6.10 (t, $J$ = 7.9 Hz, 1H), 5.43 (br s, 2H), 1.44 (s, 18H).

*Di-tert-butyl (4-Methoxyphenylmethylene)dicarbamate (**2f**).*[24] *tert*-Butyl carbamate (640 mg, 5.5 mmol) was added to a flask which was then purged with argon. *p*-Anisaldehyde (400 μL, 3.3 mmol) was added by syringe, followed by acetic anhydride (750 μL). Trifluoroacetic acid (21 μL, 0.27 mmol) was then added. The mixture was stirred at room temperature for 24 h. The aminal precipitated from the solution as a white solid. The solid was filtered off and washed with *n*-hexane (454 mg, 47%). $^1$H NMR (400 MHz, $CDCl_3$): δ 7.35−7.28 (m, 2H), 6.92−6.84 (m, 2H), 6.05 (t, $J$ = 7.8 Hz, 1H), 5.36 (br s, 2H), 3.80 (s, 3H), 1.44 (s, 18H).

*N,N,N′-Tris(tert-butoxycarbonyl)-1,1-diamino-1-(4-methoxyphenyl)methane (**2g**).* The procedure is based on the work of Kano and co-workers.[20] Aminal **2f** (454 mg, 1 mmol) was added to a dried flask containing 4-(dimethylamino)pyridine (16 mg, 0.13 mmol). The flask was then purged with argon. Dry THF (6 mL) was added, and the flask was then cooled to 0 °C. Freshly distilled di-*tert*-butyl dicarbonate (450 μL, 2.2 mmol) was then added. The reaction mixture was stirred at 0 °C for 48 h. Aqueous $NH_4Cl$ solution (10 mL) was added, and the mixture was extracted with $CH_2Cl_2$ twice. The organic layers were combined, washed with brine, and dried with $Na_2SO_4$. The mixture was filtered, and the solvent was removed under reduced pressure. The resulting oil was purified by silica gel medium-pressure liquid chromatography (9:1 *n*-hexane/ethyl acetate). The title compound was obtained as a colorless oil. 303 mg; 52% yield; $R_f$ ca. 0.38 (9:1 *n*-hexane/ethyl acetate). $^1$H NMR (500 MHz, $CDCl_3$): δ 7.23 (d, $J$ = 8.4 Hz, 2H), 7.04 (d, $J$ = 10.6 Hz, 1H), 6.84 (d, $J$ = 8.8 Hz, 2H), 5.97 (d, $J$ = 10.7 Hz, 1H), 3.76 (s, 3H), 1.46 (s, 9H), 1.39 (s, 18H). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 159.1, 154.8, 152.2, 131.4, 126.6, 113.8, 83.2, 80.1, 64.9, 55.4, 28.4, 28.0. HRMS (ESI) $m/z$: $[M + Na]^+$ calcd for $C_{23}H_{36}N_2O_7Na$, 475.2421; found, 475.2415.

*N,N,N′-Tris(tert-butoxycarbonyl)-1,1-diamino-1-phenylmethane (**2h**).* The synthesis of this compound has been reported by Kano and co-workers.[20] Aminal **2e** (2.04 g, 6.3 mmol) was added to a dried flask containing 4-(dimethylamino)pyridine (230 mg, 1.88 mmol). The flask was then purged with argon. Dry THF (20 mL) was added, and the flask was then cooled to 0 °C. Freshly distilled di-*tert*-butyl dicarbonate (2.18 mL, 9.47 mmol) was then added. The reaction mixture was stirred at 0 °C for 48 h. Aqueous $NH_4Cl$ solution (30 mL) was added, and the mixture was extracted with $CH_2Cl_2$ twice. The organic layers were combined, washed with brine, and dried with $Na_2SO_4$. The mixture was filtered, and the solvent was removed under reduced pressure. The resulting oil was purified by silica gel medium-pressure liquid chromatography (9:1 *n*-hexane/ethyl acetate). The title compound was obtained as a colorless oil which crystallized overnight in a freezer into a white solid (1.45 g, 54% yield). $^1$H NMR (500 MHz, $CDCl_3$): δ 7.30 (d, $J$ = 4.6 Hz, 4H), 7.26−7.18 (m, 1H), 7.11 (d, $J$ = 10.6 Hz, 1H), 5.96 (d, $J$ = 10.6 Hz, 1H), 1.46 (s, 9H), 1.36 (s, 18H).

**General Procedure for the Synthesis of α-Amino Ketones (General Procedure B).** 3-Mesityl-4,5-dimethylthiazol-3-ium perchlorate (thiazolium salt **B**; 33 mg, 0.1 mmol) was added to a dried two-necked flask. The flask was then purged with argon. Triethylamine (14 μL, 0.1 mmol) and super dehydrated THF (3 mL) were then added. The mixture was stirred under argon for 5 min at room temperature. Aminal **2a** (138 mg, 0.5 mmol) and aldehyde (0.75 or 1 mmol) were then added. The flask was flushed with argon, and the reaction mixture was stirred under an argon atmosphere at reflux for 24 h in an EYELA ChemiStation Personal Synthesizer PPS-CTRL1 machine. The solvent was removed under reduced pressure, and the resulting mixture was purified by silica gel medium-pressure liquid chromatography (9:1 *n*-hexane/ethyl acetate). Further purification was conducted, as necessary, by a second run of silica gel medium-pressure liquid chromatography (9:1 *n*-hexane/ethyl acetate), followed by, for oils, recycling size-exclusion HPLC (JAIGEL-1HR and JAIGEL-2HR columns, with chloroform as the solvent) or, for solids, recrystallization.

*1-(4-Chlorophenyl)-2-(2-pyridinylamino)-2-phenylethanone (**3a**).* The title compound was prepared following general procedure B with 4-chlorobenzaldehyde (105 mg, 0.75 mmol). Purified by silica gel medium-pressure liquid chromatography (9:1 *n*-hexane/ethyl acetate). Recrystallized from EtOH. White solid; 145.8 mg, 90% yield; $R_f$ ca. 0.15 (9:1 *n*-hexane/ethyl acetate); mp: 122−123 °C; $^1$H NMR (500 MHz, $CDCl_3$): δ 8.05−8.02 (m, 1H), 8.00−7.94 (m, 2H), 7.47−7.43 (m, 2H), 7.41−7.34 (m, 3H), 7.33−7.28 (m, 2H), 7.26−7.22 (m, 2H), 6.63 (d, $J$ = 7.3 Hz, 1H), 6.58−6.54 (m, 1H), 6.49 (d, $J$ = 8.4 Hz, 1H), 5.68 (d, $J$ = 7.3 Hz, 1H). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 196.8, 156.9, 147.9, 139.9, 137.7, 137.3, 133.7, 130.5, 129.3, 129.1, 128.5, 128.4, 113.8, 109.2, 60.4. HRMS (FAB) $m/z$: $[M + H]^+$ calcd for $C_{19}H_{16}ClN_2O$, 323.0946; found, 323.0962.

*1,2-Diphenyl-2-(2-pyridinylamino)ethanone (**3b**).* 3-Mesityl-4,5-dimethylthiazol-3-ium perchlorate (332 mg, 1.0 mmol) was added to a dried two-necked flask. The flask was then purged with argon. Triethylamine (140 μL, 1.0 mmol) and super dehydrated THF (5 mL) were then added. The mixture was stirred under argon for 5 min at room temperature. Aminal **2a** (1.45 g, 5 mmol) and benzaldehyde (770 μL, 1.5 equiv, 7.5 mmol) were then added. The flask was flushed with argon, and the reaction mixture was stirred under an argon atmosphere at reflux for 24 h in an EYELA ChemiStation Personal Synthesizer PPS-CTRL1 machine. The solvent was removed under reduced pressure, and the resulting mixture was purified by silica gel medium pressure liquid chromatography (9:1 *n*-hexane/ethyl acetate) to afford the title compound as a yellow-white solid. The solid was recrystallized from ethanol, yielding a white solid (1.45 g, 95% yield). The reaction at the 0.5 mmol scale with 1.5 equiv of benzaldehyde (76 μL) afforded the title compound in 96% yield (138 mg). The reaction at the 0.5 mmol scale with 2 equiv of benzaldehyde (102 μL) afforded the title compound in 99% yield (143 mg). $R_f$ ca. 0.19 (9:1 *n*-hexane/ethyl acetate); mp: 108−109 °C; $^1$H NMR (500 MHz, $CDCl_3$): δ 8.07−8.01 (m, 3H), 7.54−7.45 (m, 3H), 7.44−7.38 (m, 2H), 7.38−7.33 (m, 1H), 7.32−7.26 (m, 2H), 7.24−7.19 (m, 1H), 6.68 (d, $J$ = 7.3 Hz, 1H), 6.58−6.52 (m, 1H), 6.49 (d, $J$ = 8.1 Hz, 1H), 5.80 (d, $J$ = 7.4 Hz, 1H). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 197.8, 157.0, 148.0, 138.1, 137.2, 135.3, 133.5, 129.1, 128.7, 128.5, 128.2, 113.6, 109.1, 60.3. HRMS (ESI) $m/z$: $[M + H]^+$ calcd for $C_{19}H_{17}N_2O$, 289.1336; found, 289.1341.

*1-(3-Chlorophenyl)-2-(2-pyridinylamino)-2-phenylethan-one (**3c**).* The title compound was prepared following general procedure B with 3-chlorobenzaldehyde (105 mg, 0.75 mmol). Purified by silica gel medium-pressure liquid chromatography (9:1 *n*-hexane/ethyl acetate). Yellow oil; 160 mg, 99% yield; $R_f$ ca. 0.12 (9:1 *n*-hexane/ethyl acetate); $^1$H NMR (500 MHz, $CDCl_3$): δ 8.06−8.02 (m, 1H), 8.02−7.98 (m, 1H), 7.93−7.88 (m, 1H), 7.50−7.43 (m, 3H), 7.40−7.28 (m, 4H), 7.28−7.20 (m, 1H), 6.63 (d, $J$ = 7.1 Hz, 1H), 6.57 (dd, $J$ = 7.3, 5.1 Hz, 1H), 6.50 (d, $J$ = 8.4 Hz, 1H), 5.69 (d, $J$ = 7.1 Hz, 1H). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 196.9, 156.9, 147.8, 137.4, 137.3, 137.0, 135.0, 133.3, 130.0, 129.3, 129.1, 128.5, 128.5, 127.2, 113.8, 109.2, 60.6. HRMS (FAB) $m/z$: $[M + H]^+$ calcd for $C_{19}H_{16}ClN_2O$, 323.0946; found, 323.0936.

*1-(4-Bromophenyl)-2-(2-pyridinylamino)-2-phenyl-ethanone (**3e**).* The title compound was prepared following general procedure B with 4-bromobenzaldehyde (139 mg, 0.75 mmol). Purified by silica gel medium-pressure liquid chromatography (9:1 *n*-hexane/ethyl acetate). Recrystallized from EtOH. White solid; 173 mg, 94% yield; $R_f$ ca. 0.17 (9:1 *n*-hexane/ethyl acetate); mp: 136−137 °C; $^1$H NMR (500 MHz, $CDCl_3$): δ 8.06−8.01 (m, 1H), 7.92−7.86 (m, 2H), 7.57−7.51 (m, 2H), 7.48−7.42 (m, 2H), 7.39−7.33 (m, 1H), 7.33−7.27 (m, 2H), 7.27−7.21 (m, 1H), 6.62 (d, $J$ = 7.2 Hz, 1H), 6.59−6.53 (m, 1H), 6.49 (d, $J$ = 8.3 Hz, 1H), 5.67 (d, $J$ = 7.3 Hz, 1H). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 197.0, 156.9, 147.9, 137.7, 137.3, 134.1,


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132.0, 130.6, 129.3, 128.7, 128.5, 128.4, 113.8, 109.2, 60.4. HRMS (ESI) $m/z$: $[M + H]^+$ calcd for $C_{19}H_{16}BrN_2O$, 367.0441; found, 367.0444.

*1-(4-Fluorophenyl)-2-(2-pyridinylamino)-2-phenylethan-one* (**3f**). The title compound was prepared following general procedure B with 4-fluorobenzaldehyde (80.5 μL, 0.75 mmol). Purified by silica gel medium-pressure liquid chromatography (9:1 *n*-hexane/ethyl acetate). Recrystallized twice from *n*-hexane/ethyl acetate. White solid; 111 mg, 73% yield; $R_f$ ca. 0.18 (9:1 *n*-hexane/ethyl acetate); mp: 105−106 °C; $^1$H NMR (500 MHz, $CDCl_3$): δ 8.11−8.02 (m, 3H), 7.50−7.43 (m, 2H), 7.39−7.33 (m, 1H), 7.33−7.27 (m, 2H), 7.27−7.20 (m, 1H), 7.11−7.03 (m, 2H), 6.67 (d, $J$ = 7.4 Hz, 1H), 6.58−6.53 (m, 1H), 6.49 (d, $J$ = 8.2 Hz, 1H), 5.76 (d, $J$ = 7.3 Hz, 1H). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 196.4, 165.9 (d, $J$ = 257.2 Hz), 157.0, 147.9, 138.0, 137.2, 131.78 (d, $J$ = 9.6 Hz), 131.76 (d, $J$ = 3.6 Hz), 129.2, 128.5, 128.3, 115.9 (d, $J$ = 22.2 Hz), 113.7, 109.2, 60.3. HRMS (ESI) $m/z$: $[M + H]^+$ calcd for $C_{19}H_{16}FN_2O$, 307.1241; found, 307.1234.

*1-(4-Methoxyphenyl)-2-(2-pyridinylamino)-2-phenyl-ethanone* (**3g**). The title compound was prepared following general procedure B with *p*-anisaldehyde (91 μL, 0.75 mmol). Purified by silica gel medium-pressure liquid chromatography (9:1 *n*-hexane/ethyl acetate). Note: elution of the title compound during column chromatography is slow using a mixture of 9:1 *n*-hexane/ethyl acetate. However, 9:1 *n*-hexane/ethyl acetate provided good separation compared to other ratios. Colorless oil; 116 mg, 73% yield; $R_f$ ca. 0.07 (9:1 *n*-hexane/ethyl acetate); $^1$H NMR (500 MHz, $CDCl_3$): δ 8.07−8.00 (m, 3H), 7.51−7.45 (m, 2H), 7.37−7.32 (m, 1H), 7.31−7.26 (m, 2H), 7.23−7.18 (m, 1H), 6.90−6.86 (m, 2H), 6.63 (d, $J$ = 7.2 Hz, 1H), 6.56−6.52 (m, 1H), 6.48 (d, $J$ = 8.5 Hz, 1H), 5.85 (d, $J$ = 7.4 Hz, 1H), 3.82 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 197.8, 157.0, 148.0, 138.1, 137.2, 135.3, 133.5, 129.1, 128.7, 128.5, 128.2, 113.6, 109.1, 60.3. HRMS (ESI) $m/z$: $[M + H]^+$ calcd for $C_{20}H_{19}N_2O_2$, 319.1441; found, 319.1459.

*1-(3-Methoxyphenyl)-2-(2-pyridinylamino)-2-phenyl-ethanone* (**3h**). The title compound was prepared following general procedure B with *m*-anisaldehyde (91 μL, 0.75 mmol). Purified by silica gel medium-pressure liquid chromatography (9:1 *n*-hexane/ethyl acetate). Recrystallized from *n*-hexane/ethyl acetate. White solid; 108 mg, 68% yield; $R_f$ ca. 0.08 (9:1 *n*-hexane/ethyl acetate); mp: 107−108 °C; $^1$H NMR (500 MHz, $CDCl_3$): δ 8.07−8.02 (m, 1H), 7.64 (d, $J$ = 8.1 Hz, 1H), 7.55−7.50 (m, 1H), 7.49−7.45 (m, 2H), 7.39−7.19 (m, 5H), 7.05 (dd, $J$ = 8.2, 2.6 Hz, 1H), 6.64 (d, $J$ = 7.3 Hz, 1H), 6.58−6.52 (m, 1H), 6.49 (d, $J$ = 8.6 Hz, 1H), 5.79 (d, $J$ = 7.4 Hz, 1H), 3.80 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 197.6, 159.8, 157.0, 148.0, 138.1, 137.2, 136.6, 129.7, 129.1, 128.5, 128.2, 121.7, 120.1, 113.6, 113.2, 109.1, 60.4, 55.5. HRMS (ESI) $m/z$: $[M + H]^+$ calcd for $C_{20}H_{19}N_2O_2$, 319.1441; found, 319.1453.

*1-(2-Pyridinyl)-2-(2-pyridinylamino)-2-phenylethan-one* (**3i**). The title compound was prepared following general procedure B with 2-pyridinecarboxaldehyde (71 μL, 0.75 mmol). Purified by silica gel medium-pressure liquid chromatography (9:1 *n*-hexane/ethyl acetate). Yellow solid; 86.7 mg, 60% yield; $R_f$ ca. 0.11 (4:1 *n*-hexane/ethyl acetate); mp: 122−123 °C; $^1$H NMR (500 MHz, $CDCl_3$): δ 8.71 (d, $J$ = 4.5 Hz, 1H), 8.05 (d, $J$ = 4.9 Hz, 1H), 8.00 (d, $J$ = 7.8 Hz, 1H), 7.80−7.73 (m, 1H), 7.59 (d, $J$ = 7.4 Hz, 2H), 7.45−7.38 (m, 1H), 7.38−7.31 (m, 1H), 7.25 (t, $J$ = 7.6 Hz, 2H), 7.18 (t, $J$ = 7.3 Hz, 1H), 7.11 (d, $J$ = 7.3 Hz, 1H), 6.57−6.51 (m, 1H), 6.47 (d, $J$ = 8.4 Hz, 1H), 5.98 (d, $J$ = 7.4 Hz, 1H). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 197.8, 157.2, 151.8, 149.0, 148.3, 137.6, 137.4, 137.0, 128.7, 127.9, 127.5, 123.4, 113.5, 107.9, 59.3. HRMS (ESI) $m/z$: $[M + H]^+$ calcd for $C_{18}H_{16}N_3O$, 290.1288; found, 290.1290.

*1-(3-Pyridinyl)-2-(2-pyridinylamino)-2-phenylethan-one* (**3j**). The title compound was prepared following general procedure B with 3-pyridinecarboxaldehyde (70 μL; 0.75 mmol). Purified by silica gel medium-pressure liquid chromatography (9:1 *n*-hexane/ethyl acetate). Recrystallized from *n*-hexane/ethyl acetate. White solid, 34.8 mg, 24% yield; $R_f$ ca. 0.03 (4:1 *n*-hexane/ethyl acetate); mp: 160−162 °C; $^1$H NMR (500 MHz, $CDCl_3$): δ 5.62 (d, $J$ = 6.9 Hz, 1H), 6.52 (d, $J$ = 8.0 Hz, 1H), 6.58 (td, $J$ = 6.0, 1.7 Hz, 1H), 6.62 (d, $J$ = 7.4 Hz, 1H), 7.25−7.29 (m, 1H), 7.30−7.41 (m, 4H), 7.46−7.50 (m, 2H), 8.04 (dd, $J$ = 5.2, 1.1 Hz, 1H), 8.27 (dt, $J$ = 7.8, 1.9 Hz, 1H), 8.71 (dd, $J$ = 5.2, 1.7 Hz, 1H), 9.25 (d, $J$ = 1.7 Hz, 1H). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 197.2, 156.8, 153.6, 150.3, 147.8, 137.3, 137.0, 136.3, 131.1, 129.4, 128.6, 123.7, 113.9, 109.2, 61.1. HRMS (ESI) $m/z$: $[M + H]^+$ calcd for $C_{18}H_{16}N_3O$, 290.1288; found, 290.1299.

*1-(2-Furanyl)-2-(2-pyridinylamino)-2-phenylethanone* (**3k**). 3-Mesityl-4,5-dimethylthiazol-3-ium perchlorate (132.7 mg, 0.4 mmol) was added to a dried two-necked flask containing a magnetic stirring bar. The flask was then purged with argon. Triethylamine (60 μL, 0.4 mmol) and super dehydrated THF (5 mL) were then added. The mixture was stirred under argon for 5 min at room temperature. Aminal **2a** (552.7 mg, 2 mmol) and furfural (250 μL, 1.5 equiv, 3 mmol) were then added. The flask was flushed with argon, and the reaction mixture was stirred under an argon atmosphere at reflux for 24 h in an EYELA ChemiStation Personal Synthesizer PPS-CTRL1 machine. The solvent was removed under reduced pressure, and the resulting mixture was purified by silica gel medium-pressure liquid chromatography (9:1 *n*-hexane/ethyl acetate) to afford the title compound as a yellow-white solid. The solid was recrystallized from an *n*-hexane/ethyl acetate mixture, yielding a white solid. 379 mg, 68% yield; $R_f$ ca. 0.23 (4:1 *n*-hexane/ethyl acetate); mp: 106−108 °C; $^1$H NMR (500 MHz, $CDCl_3$): δ 8.06−8.02 (m, 1H), 7.59−7.56 (m, 1H), 7.55−7.50 (m, 2H), 7.38−7.28 (m, 4H), 7.28−7.21 (m, 1H), 6.57−6.53 (m, 1H), 6.52−6.48 (m, 1H), 6.47 (d, $J$ = 8.1 Hz, 1H), 6.39 (d, $J$ = 6.9 Hz, 1H), 5.75 (d, $J$ = 7.4 Hz, 1H). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 186.2, 156.9, 151.2, 148.1, 147.0, 137.8, 137.3, 129.0, 128.4, 128.3, 119.1, 113.7, 112.6, 108.8, 60.6. HRMS (ESI) $m/z$: $[M + H]^+$ calcd for $C_{17}H_{15}N_2O_2$, 279.1128; found, 279.1146.

*1-(2-Thienyl)-2-(2-pyridinylamino)-2-phenylethanone* (**3l**). The title compound was prepared following general procedure B with thiophene-2-carbaldehyde (70 μL; 0.75 mmol). Purified by silica gel medium-pressure liquid chromatography (9:1 *n*-hexane/ethyl acetate). Yellow oil; 137 mg, 93% yield; $R_f$ ca. 0.19 (4:1 *n*-hexane/ethyl acetate); $^1$H NMR (500 MHz, $CDCl_3$): δ 8.07−8.01 (m, 1H), 7.88−7.82 (m, 1H), 7.64−7.57 (m, 1H), 7.55−7.47 (m, 2H), 7.39−7.28 (m, 3H), 7.28−7.23 (m, 1H), 7.11−7.03 (m, 1H), 6.59−6.52 (m, 1H), 6.51−6.42 (m, 2H), 5.70 (d, $J$ = 7.6 Hz, 1H). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 190.4, 156.9, 148.0, 141.8, 138.3, 137.3, 134.4, 133.5, 129.1, 128.4, 128.3, 128.3, 113.8, 109.0, 61.5. HRMS (FAB) $m/z$: $[M + H]^+$ calcd for $C_{17}H_{15}N_2OS$, 295.0900; found, 295.0893.

*1-(2-Naphthyl)-2-(2-pyridinylamino)-2-phenylethan-one* (**3m**). The title compound was prepared following general procedure B with 2-naphthaldehyde (117 mg, 0.75 mmol). Purified by silica gel medium-pressure liquid chromatography (9:1 *n*-hexane/ethyl acetate). Yellow oil; 146 mg, 86% yield; $R_f$ ca. 0.13 (9:1 *n*-hexane/ethyl acetate); $^1$H NMR (500 MHz, $CDCl_3$): δ 8.62 (s, 1H), 8.10−8.03 (m, 2H), 7.94 (d, $J$ = 8.2 Hz, 1H), 7.84 (t, $J$ = 8.9 Hz, 2H), 7.60−7.50 (m, 4H), 7.40−7.35 (m, 1H), 7.28 (t, $J$ = 7.7 Hz, 2H), 7.23−7.17 (m, 1H), 6.85 (d, $J$ = 7.3 Hz, 1H), 6.60−6.55 (m, 1H), 6.53 (d, $J$ = 8.2 Hz, 1H), 5.87 (d, $J$ = 7.4 Hz, 1H). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 197.7, 157.1, 148.0, 138.2, 137.3, 135.8, 132.6, 132.5, 131.1, 129.8, 129.1, 128.8, 128.6, 128.5, 128.2, 127.8, 126.9, 124.6, 113.6, 109.2, 60.3. HRMS (FAB) $m/z$: $[M + H]^+$ calcd for $C_{23}H_{19}N_2O$, 339.1492; found, 339.1510.

*1-Phenyl-1-(2-pyridinylamino)-2-pentanone* (**3n**). 3-Mesityl-4,5-dimethylthiazol-3-ium perchlorate (33 mg, 0.1 mmol) was added to a dried two-necked flask containing a magnetic stirring bar. The flask was then purged with argon. Triethylamine (14 μL, 0.1 mmol) and super dehydrated THF (3 mL) were then added. The mixture was stirred under argon for 5 min at room temperature. Aminal **2a** (138 mg, 0.5 mmol) and butyraldehyde (90 μL, 2 equiv, 1 mmol) were then added. The flask was flushed with argon, and the reaction mixture was stirred under an argon atmosphere at reflux for 24 h in an EYELA ChemiStation Personal Synthesizer PPS-CTRL1 machine. The solvent was removed under reduced pressure, and the resulting mixture was purified by two runs of silica gel medium-pressure liquid chromatography (9:1 *n*-hexane/ethyl acetate) to afford the title compound as a white solid (102 mg, 80% yield). Note: the title compound usually appears as a yellow oil after the initial column.


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Further purification [e.g., a second run of silica gel medium-pressure liquid chromatography (9:1 *n*-hexane/ethyl acetate)] is sometimes needed to yield the white solid form. $R_f$ ca. 0.14 (9:1 *n*-hexane/ethyl acetate); mp: 64−65 °C; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 8.05−8.00 (m, 1H), 7.46−7.40 (m, 2H), 7.39−7.27 (m, 4H), 6.56−6.50 (m, 1H), 6.37 (dt, $J$ = 8.4, 1.0 Hz, 1H), 5.86 (d, $J$ = 5.7 Hz, 1H), 5.50 (d, $J$ = 5.7 Hz, 1H), 2.53−2.34 (m, 2H), 1.64−1.44 (m, 2H), 0.78 (t, $J$ = 7.4 Hz, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 207.0, 157.0, 148.1, 137.8, 137.2, 129.1, 128.4, 128.2, 113.5, 108.4, 65.3, 41.5, 17.3, 13.6. HRMS (ESI) $m/z$: $[M + H]^+$ calcd for $C_{16}H_{19}N_2O$, 255.1492; found, 255.1500.

*1-Phenyl-1-(2-pyridinylamino)-2-heptanone (**3o**).* The title compound was prepared following general procedure B with hexanal (92 μL, 0.75 mmol). Purified by silica gel medium-pressure liquid chromatography (9:1 *n*-hexane/ethyl acetate). Yellow oil; 88.4 mg, 62% yield; $R_f$ ca. 0.26 (4:1 *n*-hexane/ethyl acetate); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.05−7.97 (m, 1H), 7.47−7.38 (m, 2H), 7.36−7.20 (m, 4H), 6.54−6.44 (m, 1H), 6.35 (d, $J$ = 8.4 Hz, 1H), 5.98 (d, $J$ = 5.8 Hz, 1H), 5.52 (d, $J$ = 5.7 Hz, 1H), 2.54−2.32 (m, 2H), 1.62−1.39 (m, 2H), 1.25−1.04 (m, 4H), 0.80 (t, $J$ = 7.1 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 207.0, 157.0, 147.9, 137.8, 137.1, 129.0, 128.2, 128.1, 113.4, 108.4, 65.2, 39.5, 31.1, 23.4, 22.3, 13.9. HRMS (ESI) $m/z$: $[M + H]^+$ calcd for $C_{18}H_{23}N_2O$, 283.1805; found, 283.1798.

*1-Phenyl-1-(2-pyridinylamino)-2-nonanone (**3p**).* The title compound was prepared following general procedure B with octanal (117 μL, 0.75 mmol). Purified by silica gel medium-pressure liquid chromatography (9:1 *n*-hexane/ethyl acetate). Yellow oil; 88.5 mg, 57% yield; $R_f$ ca. 0.14 (9:1 *n*-hexane/ethyl acetate); $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 8.04−7.99 (m, 1H), 7.45−7.40 (m, 2H), 7.35−7.22 (m, 4H), 6.52−6.46 (m, 1H), 6.35 (d, $J$ = 8.2 Hz, 1H), 5.97 (d, $J$ = 5.7 Hz, 1H), 5.52 (d, $J$ = 5.7 Hz, 1H), 2.52−2.36 (m, 2H), 1.60−1.40 (m, 2H), 1.26−1.07 (m, 8H), 0.83 (t, $J$ = 7.1 Hz, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 207.2, 157.1, 148.0, 137.9, 137.2, 129.1, 128.3, 128.2, 113.5, 108.5, 65.3, 39.6, 31.7, 29.0, 23.8, 22.6, 14.2. HRMS (ESI) $m/z$: $[M + H]^+$ calcd for $C_{20}H_{27}N_2O$, 311.2118; found, 311.2136.

*1-Phenyl-1-(2-pyridinylamino)-2-undecanone (**3q**).* The title compound was prepared following general procedure B with decanal (141 μL, 0.75 mmol). Purified by silica gel medium-pressure liquid chromatography (9:1 *n*-hexane/ethyl acetate). Yellow oil; 116 mg, 68% yield; $R_f$ ca. 0.09 (9:1 *n*-hexane/ethyl acetate); $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 8.04−8.00 (m, 1H), 7.45−7.40 (m, 2H), 7.36−7.24 (m, 4H), 6.54−6.48 (m, 1H), 6.36 (dt, $J$ = 8.3, 1.0 Hz, 1H), 6.01 (d, $J$ = 5.8 Hz, 1H), 5.50 (d, $J$ = 4.6 Hz, 1H), 2.53−2.33 (m, 2H), 1.61−1.39 (m, 2H), 1.32−1.08 (m, 12H), 0.86 (t, $J$ = 7.1 Hz, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 207.1, 157.0, 147.9, 137.8, 137.3, 129.1, 128.4, 128.2, 113.5, 108.4, 65.3, 39.6, 31.9, 29.4, 29.32, 29.30, 29.0, 23.8, 22.7, 14.2. HRMS (ESI) $m/z$: $[M + H]^+$ calcd for $C_{22}H_{31}N_2O$, 339.2431; found, 339.2427.

*1-(4-Chlorophenyl)-2-(2-pyridinylamino)-2-(1,3-benzo-dioxol-5-yl)ethanone (**4a**).* 3-Mesityl-4,5-dimethylthiazol-3-ium perchlorate (66.4 mg, 0.2 mmol) was added to a dried two-necked flask containing a magnetic stirring bar. The flask was then purged with argon. Triethylamine (28 μL, 0.2 mmol) and super dehydrated THF (3 mL) were then added. The mixture was stirred under argon for 5 min at room temperature. Aminal **2b** (320.4 mg, 1 mmol) and 4-chlorobenzaldehyde (210.9 mg, 1.5 equiv, 1.5 mmol) were then added. The flask was flushed with argon, and the reaction mixture was stirred under an argon atmosphere at reflux for 24 h in an EYELA ChemiStation Personal Synthesizer PPS-CTRL1 machine. The solvent was removed under reduced pressure, and the resulting mixture was purified by silica gel medium-pressure liquid chromatography (9:1 *n*-hexane/ethyl acetate) to afford the title compound as a white solid (364 mg, 99% yield). $R_f$ ca. 0.07 (9:1 *n*-hexane/ethyl acetate); mp: 118−119 °C; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.08−8.02 (m, 1H), 7.99−7.93 (m, 2H), 7.44−7.33 (m, 3H), 6.96−6.89 (m, 2H), 6.72 (d, $J$ = 7.9 Hz, 1H), 6.62−6.45 (m, 3H), 5.93−5.88 (m, 2H), 5.67 (d, $J$ = 7.2 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 196.5, 156.8, 148.2, 147.8, 147.6, 139.8, 137.1, 133.6, 131.4, 130.4, 129.0, 122.1, 113.7, 109.1, 108.8, 108.6, 101.2, 59.8. HRMS (ESI) $m/z$: $[M + H]^+$ calcd for $C_{20}H_{16}ClN_2O_3$, 367.0844; found, 367.0861.

*1-(1,3-Benzodioxol-5-yl)-1-(2-pyridinylamino)-2-pentanone (**4b**).* 3-Mesityl-4,5-dimethylthiazol-3-ium perchlorate (66.4 mg, 0.2 mmol) was added to a dried two-necked flask containing a magnetic stirring bar. The flask was then purged with argon. Triethylamine (28 μL, 0.2 mmol) and super dehydrated THF (3 mL) were then added. The mixture was stirred under argon for 5 min at room temperature. Aminal **2b** (320.4 mg, 1 mmol) and butyraldehyde (135 μL, 1.5 equiv, 1.5 mmol) were then added. The flask was flushed with argon, and the reaction mixture was stirred under an argon atmosphere at reflux for 24 h in an EYELA ChemiStation Personal Synthesizer PPS-CTRL1 machine. The solvent was removed under reduced pressure, and the resulting mixture was purified by silica gel medium-pressure liquid chromatography (9:1 *n*-hexane/ethyl acetate). Recrystallization from *n*-hexane/ethyl acetate afforded the title compound as a white solid (216 mg, 72% yield). $R_f$ ca. 0.23 (4:1 *n*-hexane/ethyl acetate); mp: 66−67 °C; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.07−8.00 (m, 1H), 7.37−7.29 (m, 1H), 6.93 (dd, $J$ = 8.0, 1.8 Hz, 1H), 6.88 (d, $J$ = 1.8 Hz, 1H), 6.78 (d, $J$ = 7.9 Hz, 1H), 6.58−6.50 (m, 1H), 6.38 (dt, $J$ = 8.4, 1.0 Hz, 1H), 5.94 (q, $J$ = 1.4 Hz, 2H), 5.87 (d, $J$ = 5.7 Hz, 1H), 5.41 (d, $J$ = 5.6 Hz, 1H), 2.53−2.34 (m, 2H), 1.68−1.44 (m, 2H), 0.82 (t, $J$ = 7.4 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 206.8, 156.9, 148.2, 148.0, 147.6, 137.2, 131.5, 121.8, 113.5, 108.6, 108.3, 108.2, 101.3, 64.7, 41.4, 17.3, 13.6. HRMS (FAB) $m/z$: $[M + H]^+$ calcd for $C_{17}H_{19}N_2O_3$, 299.1390; found, 299.1390.

*1-(4-Chlorophenyl)-2-(2-pyridinylamino)-2-(3,4-dimethoxyphenyl)ethanone (**4c**).* 3-Mesityl-4,5-dimethylthiazol-3-ium perchlorate (66 mg, 0.2 mmol) was added to a dried two-necked flask containing a magnetic stirring bar. The flask was then purged with argon. Triethylamine (28 μL, 0.2 mmol) and super dehydrated THF (3 mL) were then added. The mixture was stirred under argon for 5 min at room temperature. Aminal **2c** (336.4 mg, 1 mmol) and 4-chlorobenzaldehyde (210.9 mg, 1.5 equiv, 1.5 mmol) were then added. The flask was flushed with argon, and the reaction mixture was stirred under an argon atmosphere at reflux for 24 h in an EYELA ChemiStation Personal Synthesizer PPS-CTRL1 machine. The solvent was removed under reduced pressure, and the resulting mixture was purified by silica gel medium pressure liquid chromatography (9:1 *n*-hexane/ethyl acetate) to afford the title compound as a white solid (332 mg, 87% yield). $R_f$ ca. 0.12 (4:1 *n*-hexane/ethyl acetate); mp: 150−151 °C; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 8.06−8.01 (m, 1H), 8.00−7.93 (m, 2H), 7.41−7.33 (m, 3H), 7.01−6.94 (m, 2H), 6.78 (d, $J$ = 8.0 Hz, 1H), 6.59−6.53 (m, 2H), 6.50 (dt, $J$ = 8.4, 1.0 Hz, 1H), 5.62 (d, $J$ = 7.2 Hz, 1H), 3.82 (d, $J$ = 12.6 Hz, 6H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 196.9, 157.0, 149.6, 149.1, 147.9, 139.8, 137.3, 133.8, 130.4, 129.9, 129.0, 121.1, 113.8, 111.4, 111.1, 109.2, 60.2, 56.0, 55.9. HRMS (ESI) $m/z$: $[M + Na]^+$ calcd for $C_{21}H_{19}ClN_2O_3Na$, 405.0982; found, 405.0971.

*1-(3,4-Dimethoxyphenyl)-1-(2-pyridinylamino)-2-pentanone (**4d**).* 3-Mesityl-4,5-dimethylthiazol-3-ium perchlorate (66.4 mg, 0.2 mmol) was added to a dried two-necked flask containing a magnetic stirring bar. The flask was then purged with argon. Triethylamine (28 μL, 0.2 mmol) and super dehydrated THF (3 mL) were then added. The mixture was stirred under argon for 5 min at room temperature. Aminal **2c** (336.4 mg, 1 mmol) and butyraldehyde (135 μL, 1.5 equiv, 1.5 mmol) were then added. The flask was flushed with argon, and the reaction mixture was stirred under an argon atmosphere at reflux for 24 h in an EYELA ChemiStation Personal Synthesizer PPS-CTRL1 machine. The solvent was removed under reduced pressure, and the resulting mixture was purified by silica gel medium-pressure liquid chromatography (9:1 *n*-hexane/ethyl acetate) to afford the title compound as a yellow oil (183.5 mg, 58% yield). $R_f$ ca. 0.08 (4:1 *n*-hexane/ethyl acetate); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.07−8.01 (m, 1H), 7.37−7.28 (m, 1H), 7.02 (dd, $J$ = 8.2, 2.1 Hz, 1H), 6.89 (d, $J$ = 2.1 Hz, 1H), 6.85 (d, $J$ = 8.2 Hz, 1H), 6.58−6.50 (m, 1H), 6.38 (dt, $J$ = 8.5, 1.0 Hz, 1H), 5.86 (d, $J$ = 5.7 Hz, 1H), 5.44 (d, $J$ = 5.6 Hz, 1H), 3.86 (d, $J$ = 3.0 Hz, 6H), 2.54−2.33 (m, 2H), 1.68−1.44 (m, 2H), 0.81 (t, $J$ = 7.4 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 207.1, 157.0, 149.5, 149.0, 147.9, 137.2, 130.0, 120.8, 113.4, 111.3, 110.6,


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108.3, 64.8, 55.9, 55.9, 41.3, 17.3, 13.6. HRMS (FAB) $m/z$: $[M + H]^+$ calcd for $C_{18}H_{23}N_2O_3$, 315.1703; found, 315.1705.

*tert-Butyl-(2-(4-chlorophenyl)-1-(4-methoxyphenyl)-2-oxoethyl)-carbamate*[26] ***(4g)***. 3-Benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride (10 mg, 0.037 mmol) was added to a dried two-necked flask containing a magnetic stirring bar. The flask was then purged with argon. Triethylamine (5.2 μL, 0.037 mmol) and dehydrated EtOH (3 mL) were then added. The mixture was stirred under argon for 5 min at room temperature. Tris-Boc aminal **2g** (54.6 mg, 0.12 mmol) and 4-chlorobenzaldehyde (56 mg, 3.3 equiv, 0.4 mmol) were then added. The flask was flushed with argon, and the reaction mixture was stirred under an argon atmosphere at 70 °C for 48 h in an EYELA ChemiStation Personal Synthesizer PPS-CTRL1 machine. The solvent was removed under reduced pressure, and the resulting mixture was purified by silica gel medium pressure liquid chromatography (9:1 *n*-hexane/ethyl acetate) to afford the title compound as a yellow-white solid (32.9 mg, 73% yield). This compound has been previously reported.[26] $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 7.89−7.82 (m, 2H), 7.36−7.29 (m, 2H), 7.27−7.21 (m, 2H), 6.83−6.77 (m, 2H), 6.15 (d, $J$ = 7.5 Hz, 1H), 5.94 (d, $J$ = 7.5 Hz, 1H), 3.71 (s, 3H), 1.41 (s, 9H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 195.2, 159.7, 155.1, 140.0, 133.0, 130.5, 129.5, 129.2, 129.1, 114.7, 80.0, 59.4, 55.3, 28.4.

*tert-Butyl-(2-(4-chlorophenyl)-2-oxo-1-phenylethyl)carbamate*[26] ***(4h)***. 3-Mesityl-4,5-dimethylthiazol-3-ium perchlorate (66.4 mg, 0.2 mmol) or 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride (54.0 mg, 0.2 mmol) and 3 Å molecular sieves were added to a dried two-necked flask containing a magnetic stirring bar. The flask was then purged with argon. $Et_3N$ (28 μL, 0.2 mmol) and dehydrated and degassed (freeze−pump−thaw method, 4 cycles) ethanol were added. The mixture was stirred under argon for 5 min at room temperature. Aminal **2h** (422.5 mg, 1 equiv, 1 mmol) and 4-chlorobenzaldehyde (210.8 mg, 1.5 equiv, 1.5 mmol) were then added. The flask was flushed with argon, and the flask was stirred under an argon atmosphere at 70 °C for 48 h in an EYELA ChemiStation Personal Synthesizer PPS-CTRL1 machine. The solvent was removed under reduced pressure, and the resulting mixture was purified by silica gel medium-pressure liquid chromatography (9:1 *n*-hexane/ethyl acetate) to afford the title compound as a colorless oil which crystallized into a white solid (17.4 mg, 5% yield when-mesityl-4,5-dimethylthiazol-3-ium perchlorate was used as the pre-catalyst; 36 mg, 10% yield when 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride was used as the pre-catalyst). This compound has been previously reported.[26] $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 7.88 (d, $J$ = 8.6 Hz, 2H), 7.38−7.28 (m, 6H), 7.27−7.22 (m, 1H), 6.20 (d, $J$ = 7.6 Hz, 1H), 5.95 (d, $J$ = 7.7 Hz, 1H), 1.42 (s, 9H).

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00973.

Analytical data ($^1$H and $^{13}$C NMR spectra, MS) for all new compounds (PDF)

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All authors have given approval to the final version of the manuscript.

### Notes

The authors declare no competing financial interest.

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