

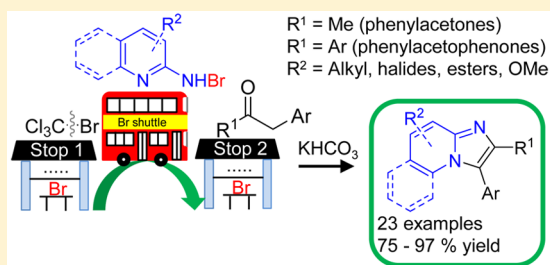
Synthesis of Disubstituted 3-Phenylimidazo[1,2-*a*]pyridines via a 2-Aminopyridine/CBrCl₃ α -Bromination Shuttle

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S Supporting Information

ABSTRACT: A versatile protocol for the synthesis of disubstituted 3-phenylimidazo[1,2-*a*]pyridines by coupling 2-aminopyridine with phenylacetophenones, phenylacetones, or β -tetralone has been developed. Isolated yields of up to 97% were obtained at 80 °C within 5 h. The 2-aminopyridine/CBrCl₃ system acts as an α -bromination shuttle by transferring Br from CBrCl₃ to the α -carbon of the carbonyl moiety. This triggers a series of steps with double C–N/C–N bond formation to the final product. The distinct advantages of this protocol include the use of commercially available inexpensive substrates, simplicity of a metal-free one-pot synthesis, and ease of scale-up to multigram quantities.



INTRODUCTION

The regioselective α -bromination of 1,3-dicarbonyls and related 1,3-diacetylated derivatives, such as phenylacetones and phenylacetophenones, is an important transformation in organic synthesis.¹ These α -brominated products serve as important synthetic intermediates to construct more complex molecules.^{2–6} A large variety of brominating reagents have been utilized for α -bromination, including Br₂,^{7,8} NBS,^{9–15} bromodimethylsulfonium bromide,¹⁶ tetraethylammonium bromide,¹⁷ CuBr₂,¹⁸ NaOBr,¹⁹ and CBrCl₃.^{20,21} The reaction normally requires catalytic or stoichiometric amounts of reagents including Lewis and Brønsted acids, inorganic or organic bases, oxidants, and transition metal complexes.^{7–21} Recently, the *in situ* α -halogenation of acetophenones or 1,3-dicarbonyls and their derivatives has been exploited for the construction of heteroaromatics, with an emphasis on step economy. In these transformations, α -halogenation of the 1,3-dicarbonyl is the first step of a cascade reaction that leads to the heteroaromatic structures. *In situ* α -iodination and bromination has been utilized in constructing various heteroaromatic backbones including oxazoles,^{22–24} thiazoles^{25–27} and benzothiazoles,^{28,29} quinoxalines,³⁰ pyrido[1,2-*a*] benzimidazoles,³¹ and imidazo[1,2-*a*]pyridines.^{32–36} Most of these methods use highly energetic species such as NBS and NIS as the halogenating reagent and/or require overstoichiometric amounts of peroxide oxidants such as TBHP or corrosive Brønsted acids such as *p*-toluenesulfonic acid (PTSA). Therefore, these reactions face challenging safety concerns for scale-ups.

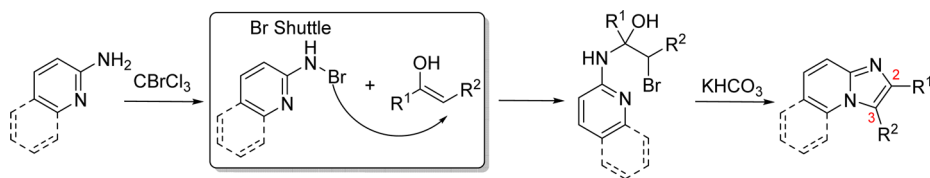
In a recent communication, we employed an *in situ* α -bromination strategy to synthesize imidazo[1,2-*a*]pyridines in high yields from 2-aminopyridines and 1,3-dicarbonyls.³⁷ Bromotrichloromethane, CBrCl₃, was used as the brominating reagent. The low toxicity and exothermicity of CBrCl₃ and its low boiling point which allows for easy removal via rotary

evaporation are distinct advantages. The reaction follows a unique α -Br shuttle mechanism where 2-aminopyridine not only is the substrate but also transfers the Br from CBrCl₃ to the α -carbon of the 1,3-dicarbonyl. This then initiates a cascade reaction that forms the imidazo[1,2-*a*]pyridine structure. The study draws inspiration on the synthesis of oxazoles via *in situ* α -iodination by Zhu's group.²² In contrast to the direct α -halogenation hypothesis, they proposed that the iodine atom is transferred to the α -carbon with the help of TBHP reagent. The concept of the *N*-brominated 2-aminopyridine as a shuttle was drawn from the work of Antonchick's group on pyrido[1,2-*a*]benzimidazole, where in the mechanism an *N*-iodinated form of 2-aminopyridine was introduced.³⁸

Particular advantages of our methodology are that it is a one-pot synthesis, does not require any oxidants or prefunctionalization of the substrates, and employs commercially available and inexpensive substrates and reagents. The transition-metal-free nature makes it suitable for applications in the pharmaceutical industry, for example, to synthesize libraries of physiologically active compounds. Hence, we investigated the feasibility of extending it to other 1,3-diacetylated derivatives, including phenylacetones, phenylacetophenones, and β -tetralones (Scheme 1). This would give ready access to a large diversity of disubstituted 3-phenylimidazo[1,2-*a*]pyridines, which are less reported in the literature. The reported reactions couple 2-aminopyridines with α -bromo phenylacetaldehyde,³⁹ α -bromoacetophenones,^{40–44} alkynyl-iodonium salts, and (bromoethynyl)benzene.^{45,46} Shortcomings of these reactions include the need to prefunctionalize the substrate with a halide which requires additional steps, high reaction temperatures, and low to moderate yields of up to 80% only. Hence, an efficient

Received: July 18, 2016

Published: September 8, 2016

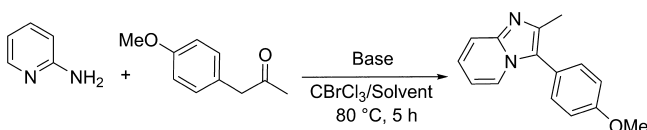
Scheme 1. Coupling Reaction with 2-Aminopyridine as an α -Bromination Shuttle

Previous work: R¹ = Alkyl, Ar; R² = ester, ketone, amide
This work: R¹ = Me, Ar; R² = Ar

one-pot synthesis of 3-phenylimidazo[1,2-*a*]pyridines with *in situ* halogenation is highly desirable. In this work, substitutions at the C-2 and C-3 position of the imidazo[1,2-*a*]pyridines backbone are explored. This structural motif is prevalent in psychoactive drugs known as nonbenzodiazepines, which includes Zolpidem, Zolimidine, TP-003, and Miroprofen.⁴⁷

RESULTS AND DISCUSSION

The reaction between 2-aminopyridine **1a** and 4-methoxyphenylacetone **2a** was tested at 80 °C using various solvents containing 10% v/v of CBrCl₃ (Table 1). After 5 h, the yield of

Table 1. Reaction Optimization^a

1a	2a	3a	
entry	solvent	base	yield 3a (%) ^{b,c}
1	MeCN	KHCO ₃	78 (72)
2	DMAc	KHCO ₃	70 (57)
3	DMF	KHCO ₃	69 (58)
4	NO ₂ Me	KHCO ₃	55 (44)
5	DMSO	KHCO ₃	0
6	toluene	KHCO ₃	0
7	MeCN	–	45 (29)
8	MeCN	KOtBu	0
9	MeCN	K ₂ CO ₃	49 (33)
10	MeCN	NaHCO ₃	65 (60)
11	MeCN	CsHCO ₃	84 (79)
12 ^d	MeCN	KHCO ₃	67 (54)
13 ^e	MeCN	KHCO ₃	93 (91)
14 ^f	MeCN	KHCO ₃	94 (91)
15 ^{e,g}	MeCN	KHCO ₃	80 (77)
16 ^h	MeCN	KHCO ₃	33

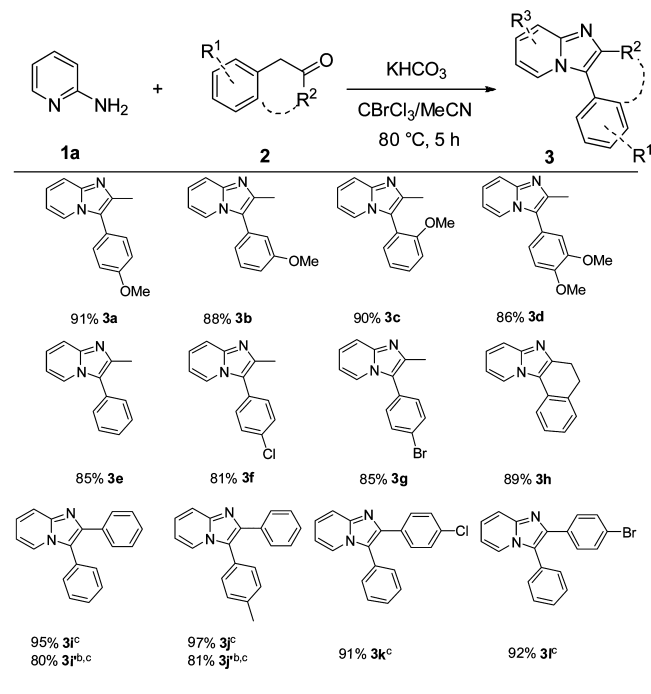
^aReaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), and base (1.0 mmol) in 2 mL of 1:9 (v/v) CBrCl₃/solvent mixture (2.0 equiv wrt **1a**) at 80 °C for 5 h. ^bYield from GC with respect to **2a**. ^cIsolated yields in parentheses. ^d1.25 equiv of **1a** was used ^e1.1 equiv of **2a** was used. ^f1.25 equiv of **2a** used. ^gRatio of CBrCl₃/MeCN changed to 1:18 (v/v). ^hReaction at 50 °C.

3a was 78% in MeCN while slightly lower yields were obtained in DMAc, DMF, and NO₂Me (Table 1, entries 1–4). No conversion was observed with DMSO which could be due to its radical quenching ability (Table 1, entry 5).⁴⁸ Toluene, a nonpolar solvent, was not suitable for the reaction (Table 1, entry 6). Without a base such as KHCO₃, the yield of **3a** dropped significantly (Table 1, entry 7). Hence, several bases were screened for the reaction (Table 1, entries 8–11). No **3a** was formed with KOtBu which may be due to the fact that its

conjugate acid, *tert*-butanol, is a radical scavenger and could quench any radicals formed in the reaction.⁴⁹ Both NaHCO₃ and K₂CO₃ gave lower yields than KHCO₃, whereas with CsHCO₃, the yield of **3a** was slightly higher, 84%. However, as CsHCO₃ is more expensive than KHCO₃, we used KHCO₃ for subsequent reactions.

To further optimize the yield of **3a**, the amounts of **1a**, **2a**, and CBrCl₃ were varied. Increasing 4-methoxyphenylacetone **2a** to 1.25 equiv decreased the yield of **3a** to 67% (Table 1, entry 12). On the other hand, 93–94% of **3a** was obtained when **1a** was increased to overstoichiometric 1.1 and 1.25 equiv (Table 1, entries 13 and 14). Decreasing CBrCl₃ from 2 to 1 equiv and reducing the reaction temperature to 50 °C caused significant drops in yield (Table 1, entries 15 and 16). Hence, the highest **3a** yield was obtained using 1 mmol of 4-methoxyphenylacetone **2a** together with 1.1 equiv of 2-aminopyridine **1a** and 1 equiv of KHCO₃ in a solvent system of CBrCl₃/MeCN (1:9 v/v) at 80 °C for 5 h.

Using the optimized conditions, various phenylacetones were tested as substrates (Table 2). Methoxyphenylacetones with OMe substituents at the *para*, *meta*, or *ortho* position and even

Table 2. Scope of Reaction (1,3-Diactivated Compounds)^a

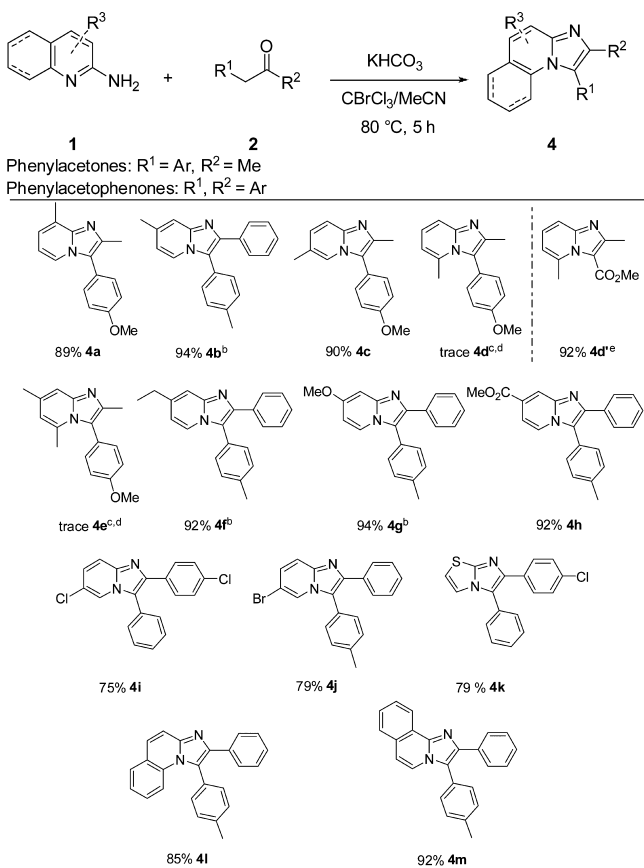
^aReaction conditions: **1a** (1.1 equiv), **2** (1.0 mmol), and KHCO₃ (1.0 equiv) in 2 mL of 1:9 (v/v) CBrCl₃/MeCN mixture (2.0 equiv wrt **2**) at 80 °C for 5 h. Percentage isolated yields. ^b1 equiv of phenylacetophenone derivative used. ^cReaction time of 4 h.

disubstituted derivatives were well tolerated (Table 2, 3a–3d). Good yields were achieved with phenylacetone and its *p*-Cl and *p*-Br derivatives (Table 2, 3e–3g). Interestingly, the cyclic phenylacetone derivative, β -tetralone, also reacted smoothly with 2-aminopyridine to form the multiply fused ring product 3h with an 89% isolated yield.

Phenylacetophenones were more reactive substrates than phenylacetones, and a shorter reaction time of 4 h was sufficient for adequate yields. Excellent yields of 95% 3i and 97% 3j were obtained with phenylacetophenone and 4-methylbenzyl phenyl ketone, respectively. However, as observed with 3a, using a lower stoichiometric ratio of 1 equiv of phenylacetophenone decreased the yields of 3i and 3j significantly. The reaction also proceeded well with substituents at the other phenyl ring. Hence, 4'-chloro-2-phenylacetophenones and 4'-bromo-2-phenylacetophenones formed 3k and 3l with yields of 91% and 93%, respectively.

Next, we investigated the scope of 2-aminopyridines and their heteroaromatic analogues for the reaction with derivatives of phenylacetone and phenylacetophenone (Table 3). 2-Aminopyridines with a methyl or an ethyl substituent at the C-3, C-4, and C-5 position reacted smoothly with both phenylacetone and phenylacetophenone derivatives to give

Table 3. Scope of Reaction (2-Aminopyridine Derivatives)^a



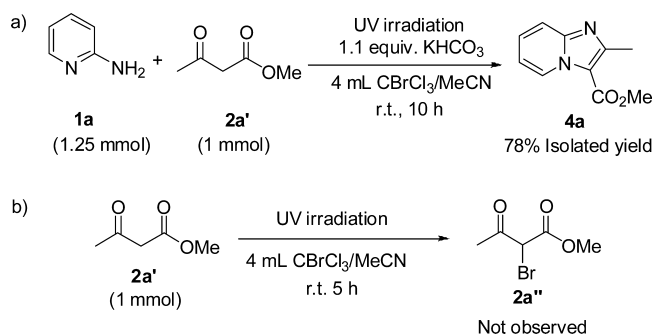
^aReaction conditions: 1 (1.1 equiv with 2), 2 (1.0 mmol), and K₂CO₃ (1.0 equiv with 2) in 2 mL of 1:9 (v/v) CBrCl₃/MeCN mixture (2.0 equiv wrt 2) at 80 °C for 5 h. Percentage isolated yields. ^bAfter 4 h. ^cAdditional experiments with CsHCO₃ and with 4-methylbenzyl phenyl ketone also gave trace amounts of products. ^d10 h reaction time. ^eIsolated yield of 4d' from previous work³⁷ for comparison with 4d.

excellent yields (Table 3, 4a–4c and 4f). Interestingly, 2-amino-6-methylpyridine was unreactive with phenylacetone and phenylacetophenone derivatives. Even after extending the reaction time to 10 h, only traces of the product was formed (Table 3, 4d). This did not improve when the stronger base CsHCO₃ was used. This surprising trend was also observed with 2-amino-4,6-dimethylpyridine which likewise has a methyl group at the C-6 position (Table 3, 4e). This is in sharp contrast to our previous observation that 2-amino-6-methylpyridine was an excellent substrate to methyl acetoacetate (Table 3, 4d').³⁷ The results show that the reaction with phenylacetone or phenylacetophenone derivatives is sensitive to the presence of a substituent at the carbon adjacent to the N atom of the pyridine ring, in contrast to methyl acetoacetate. The sluggish reaction rate for C-6 methyl-substituted aminopyridines in the synthesis of 3-phenylimidazo[1,2-*a*]pyridine derivatives has been reported in literature and was attributed to steric hindrance.^{50–52}

Both electron- and electron-withdrawing substituents, including OMe, Cl, Br, and CO₂Me, on the 2-aminopyridine substrate were well tolerated when coupled to various derivatives of phenylacetophenones, with good to excellent yields of 75–95% (Table 3, 4g–4j). Heteroaromatic derivatives, including 2-aminothiazole, 2-aminoquinoline and 1-aminoisoquinolines, also reacted smoothly with these derivatives to give their respective desired products with isolated yields of up to 92% (Table 3, 4k–4m).

The formation of imidazo[1,2-*a*]pyridines from 2-aminopyridine and 1,3-dicarbonyl was shown to occur via a radical pathway rather than an ionic one.³⁷ The reaction was severely inhibited by the addition of the radical scavenger 2,2,6,6-tetramethyl piperidinoxyl (TEMPO). Hence, we anticipate that the reaction should be able to proceed under UV irradiation. As CBrCl₃ absorbs in the UV range with maxima at ~240 and 280 nm,^{53–57} homolytic fission to CBr₂· and Br· is possible. A reaction mixture of 2-aminopyridine and methyl acetoacetate in CBrCl₃/MeCN was irradiated with UV light (30 W, UVC) at room temperature. Gratifyingly, when the reaction mixture was worked up after 10 h, 4a was obtained in 78% isolated yield (Scheme 2a). The possibility to use UV light instead of heat for

Scheme 2. Reactions under UV Irradiation



the reaction is useful for substrates that are thermally labile. We also investigated if direct α -bromination of methyl acetoacetate 2a' can occur under UV irradiation (Scheme 2b). However, this can be discounted, as no monobrominated products were observed after 5 h.

Based on these observations, the proposed mechanism is as follows (Figure 1). Upon UV irradiation or thermal activation, chain initiation occurs with cleavage of the C–Br bond in

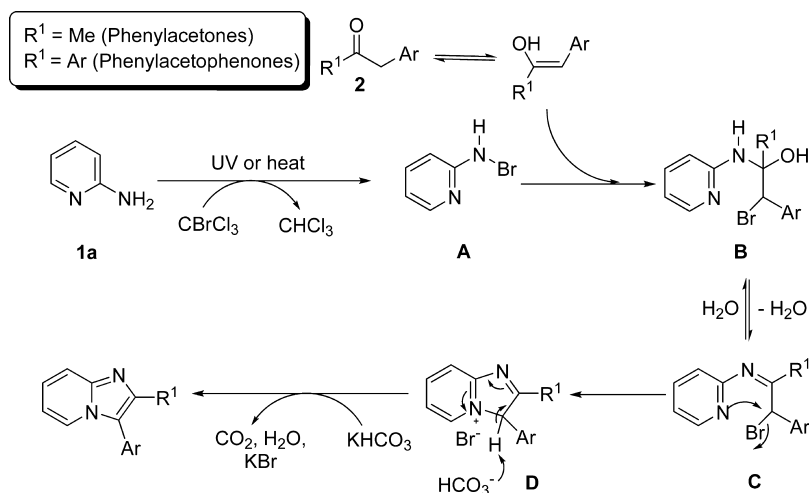


Figure 1. Proposed mechanism.

CBrCl_3 , forming $\text{CCl}_3\cdot$ and $\text{Br}\cdot$ (see Supporting Information).⁵⁸ The $\text{CCl}_3\cdot$ removes a H \cdot from the NH_2 moiety of 2-aminopyridine to form $\text{C}_6\text{H}_5\text{NH}\cdot$ and CHCl_3 . The $\text{C}_6\text{H}_5\text{NH}\cdot$ abstracts a Br \cdot from another CBrCl_3 molecule to form the intermediate A. Intermediate A then couples to the enol form of the dielectrophile 2 via an addition reaction to form the bromo-hemiaminal intermediate B. A similar intermediate has been postulated in the one-pot synthesis of 3-arylimidazo[1,2-*a*]pyridines employing NIS as the α -iodination source.³² The 2-aminopyridine 1a thus functions as an α -bromination shuttle, transferring Br from CBrCl_3 to the enol tautomer of 2. Dehydration of B leads to the α -bromo imine intermediate C which undergoes intramolecular cyclization to form the ionic salt D. This step involves an $\text{S}_{\text{N}}2$ -type nucleophilic attack at the α -carbon. The trace amounts of products obtained with the coupling of 2-amino 6-methylpyridine with phenylacetones or phenylacetophenones can be explained by the close proximity of the phenyl H to the CH_3 moiety of 2-amino 6-methylpyridine which prevents the pyridine N atom from attacking the α -carbon (Figure 2). In contrast, this steric effect

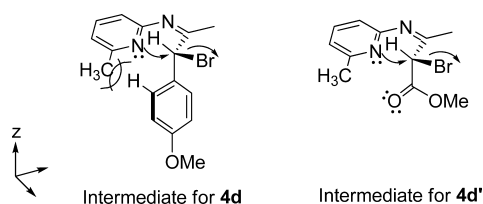


Figure 2. Steric interactions during intramolecular cyclization of C.

is absent when the phenyl group is replaced by an ester moiety; hence, high product yields are obtained with methyl acetoacetate. Deprotonation by HCO_3^- affords the desired product.

Support for the mechanism comes from *in situ* ^1H NMR studies (Figure 3). As proposed, CHCl_3 should be formed in the initial bromination of 1a to intermediate A. A mixture of 0.5 mmol each of 2-aminopyridine and methyl acetoacetate together with 3 equiv of CBrCl_3 were added into 0.65 mL of CD_3CN in an NMR tube and a spectrum recorded at room temperature (Run 1). A very small chloroform peak at 7.62 ppm could be observed which is due to trace amounts of CHCl_3 in the CBrCl_3 solvent. The chemical shift of the CHCl_3

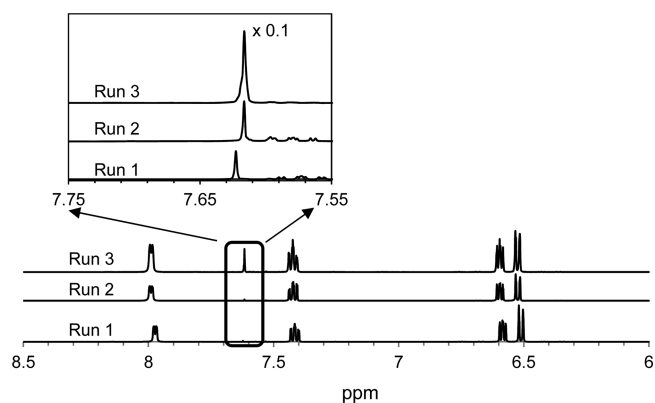
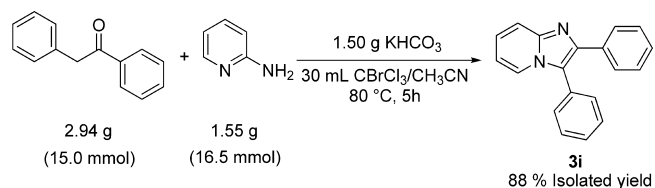


Figure 3. *In situ* ^1H kinetic study using 0.5 mmol of 1a, 0.5 mmol of 2a', 3 equiv of CBrCl_3 in 0.65 mL of CD_3CN . Run 1 at room temperature, Run 2 at 50 °C, and Run 3 at 50 °C spiked with CHCl_3 . Inset: chloroform peak.

peak in CD_3CN agrees with reported literature.⁵⁹ The temperature was raised to 50 °C, and the spectrum was measured again (Run 2). The chloroform peak became more pronounced indicating the formation of additional CHCl_3 . The chemical shift of ~ 0.006 ppm is due to the higher temperature. To confirm that this peak was indeed that of CHCl_3 , the reaction mixture was spiked with chloroform (Run 3). The area of the peak at 7.61 ppm increased significantly, showing unambiguously that CHCl_3 was indeed formed as postulated.

To demonstrate the practicality and versatility of this methodology, a scaled-up synthesis of 3i was conducted (Scheme 3). Using 15 mmol of phenylaceto-phenone and 16.5 mmol of 2-aminopyridine, 2,3-diphenylimidazo[1,2-*a*]pyridine, 3i, was obtained as a light yellow solid with an isolated

Scheme 3. Scaled-up Synthesis of 3-Phenylimidazo[1,2-*a*]pyridine 3i



yield of 88% (3.55 g) after workup, purification via column chromatography, and recrystallization from ethanol.

In comparison, reported protocols for the synthesis of **3i** require Cu(I) or Pd(II) catalysts for the coupling of bromo- or iodobenzene with 2-phenylimidazo[1,2-*a*]pyridine.^{60–62} Another protocol uses Pd(II)-catalyzed Suzuki coupling of phenylboronic acid and bromo- or 3-iodo-2-phenylimidazo[1,2-*a*]pyridine.^{63–65} The phenylimidazo[1,2-*a*]pyridines substrates in these protocols are not commercially available and need to be presynthesized. In comparison, the present protocol using commercially available inexpensive reagents without requiring any transition metals is straightforward and offers a much greener alternative with comparable yields to previous methodologies found in the literature. The ease of scale up together with the wide scope of substrates is useful for applications in industry. However, one limitation is that it cannot be extended to the use of 2-aminopyridines with a substituent at the C-6 position due to steric hindrance.

CONCLUSION

In conclusion, we have demonstrated a novel and efficient protocol employing a unique α -bromination system of 2-aminopyridine/CBrCl₃ to synthesize disubstituted 3-phenylimidazo[1,2-*a*]pyridines by C–N/C–N bond formation. 2-Aminopyridines and phenylacetones, phenylacetophenones, or β -tetralones are coupled in this one-pot synthesis to give good to excellent yields at a relatively low temperature of 80 °C. Being radical-based, the reaction can also proceed under UV radiation at room temperature. The 2-aminopyridine acts as both the substrate and an α -bromination shuttle, transferring a Br atom to the α -carbon of its coupling partner for *in situ* bromination. The synthesis was successfully scaled up to gram quantity with an 88% yield of **3i** as an example. Hence, this protocol offers a practical and economical alternative to the syntheses disclosed in earlier literature.

EXPERIMENTAL SECTION

General Information. Thin layer chromatography (TLC) was performed using TLC silica gel 60 F₂₅₄ glass plates. Silica gel 60 (230–400 mesh) was used for column chromatography. The ¹H NMR and ¹³C NMR of samples in CDCl₃, DMSO-*d*₆, or CD₃CN were measured using a 300 or 500 MHz spectrometer with tetramethylsilane (TMS) as an internal standard. For ¹H NMR spectra, chemical shifts were reported in ppm (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), and coupling constant (Hz). Detection and analysis of compounds by gas chromatography and gas chromatography mass spectrometry were performed. Mass spectra measurements were recorded on TOFQ under electrospray ionization (ESI) mode. Melting points were recorded with samples in capillary tubes using an automated melting point system. The following chemicals were purchased and used as received: CBrCl₃, KHCO₃, CsHCO₃, MeCN, and derivatives of phenylacetones, phenylacetophenones, and 2-aminopyridine.

Representative Procedure for Formation of 3-Phenylimidazo[1,2-*a*]pyridines. A 10 mL round-bottomed flask was charged with 2-aminopyridine **1a** (104 mg, 1.1 mmol), 4-methoxyphenylacetone **2a** (107.9 μ L, 1 mmol), and KHCO₃ (100 mg, 1.0 mmol) in 2 mL of CBrCl₃/MeCN solvent mixture (1/9 v/v). The reaction mixture was stirred at 80 °C for 5 h. Thereafter, the reaction was diluted with H₂O and extracted with EtOAc (15 mL \times 5). The combined organic layers were washed with brine and dried with anhydrous Na₂SO₄. After filtration, the solvent was removed by rotary evaporation, and the residue was cleaned up by column chromatography using ethyl acetate and hexane (v/v = 4/1) as eluent to afford **3a** in 91% yield.

Scaled-up Synthesis for Compound 3i. A 100 mL round-bottomed flask was charged with 2-aminopyridine **1a** (1.55 g, 16.5 mmol), 2-phenylacetophenone (2.94, 15.0 mmol), and KHCO₃ (1.50 g, 15.0 mmol) in 300 mL of CBrCl₃/MeCN solvent mixture (1/9 v/v). The reaction mixture was stirred at 80 °C for 5 h. Thereafter, the reaction was diluted with H₂O and extracted with EtOAc (200 mL \times 5). The combined organic layers were washed with brine and dried with anhydrous Na₂SO₄. After filtration, the solvent was removed by rotary evaporation, and the residue was cleaned up by column chromatography using hexane and ethyl acetate (v/v = 4/1) as eluent. Further recrystallization with ethanol afforded **3i** in 88% yield.

3-(4-Methoxyphenyl)-2-methylimidazo[1,2-*a*]pyridine (3a). Obtained as a brown amorphous solid; yield: 216 mg (91%). ¹H NMR (300 MHz, CDCl₃) δ 8.00 (d, *J* = 6.9 Hz, 1H), 7.53 (d, *J* = 9.0 Hz, 1H), 7.35 (d, *J* = 8.7 Hz, 2H), 7.10 (t, *J* = 8.0 Hz, 1H), 7.05 (d, *J* = 8.7 Hz, 2H), 6.68 (t, *J* = 6.8 Hz, 1H), 3.87 (s, 3H), 2.43 (s, 3H); ¹³C NMR (300 MHz, CDCl₃) δ 159.4, 144.2, 140.5, 130.9, 123.8, 123.0, 121.5, 121.1, 116.8, 114.6, 111.7, 55.3, 13.7. HRMS (ESI) calcd for C₁₅H₁₅N₂O [M + H]⁺: 239.1179; found 239.1181.

3-(3-Methoxyphenyl)-2-methylimidazo[1,2-*a*]pyridine (3b). Obtained as a brown amorphous solid; yield: 210 mg (88%). ¹H NMR (300 MHz, CDCl₃) δ 8.07 (d, *J* = 6.9 Hz, 1H), 7.51 (d, *J* = 9.0 Hz, 1H), 7.39 (t, *J* = 7.8 Hz, 1H), 7.09 (t, *J* = 7.8 Hz, 1H), 7.00 (d, *J* = 7.5 Hz, 1H), 6.96–6.89 (m, 2H), 6.65 (t, *J* = 6.8 Hz, 1H), 3.81 (s, 3H), 2.45 (s, 3H); ¹³C NMR (300 MHz, CDCl₃) δ 160.0, 144.3, 140.8, 130.6, 130.1, 123.9, 123.0, 121.5, 121.1, 116.8, 115.0, 113.2, 111.7, 55.2, 13.8. HRMS (ESI) calcd for C₁₅H₁₅N₂O [M + H]⁺: 239.1179; found 239.1182.

3-(2-Methoxyphenyl)-2-methylimidazo[1,2-*a*]pyridine (3c). Obtained as a brown amorphous solid; yield: 215 mg (90%). ¹H NMR (300 MHz, CDCl₃) δ 7.62 (d, *J* = 6.6 Hz, 1H), 7.53 (d, *J* = 9.0 Hz, 1H), 7.41 (t, *J* = 7.8 Hz, 1H), 7.30 (t, *J* = 7.2 Hz, 1H), 7.12–6.99 (m, 3H), 6.63 (t, *J* = 6.8 Hz, 1H), 3.72 (s, 3H), 2.40 (s, 3H); ¹³C NMR (300 MHz, CDCl₃) δ 157.4, 144.5, 141.2, 132.3, 130.0, 124.5, 123.5, 120.8, 118.6, 117.8, 116.4, 111.1, 110.9, 55.2, 13.8. HRMS (ESI) calcd for C₁₅H₁₅N₂O [M + H]⁺: 239.1179; found 239.1181.

3-(3,4-dimethoxyphenyl)-2-methylimidazo[1,2-*a*]pyridine (3d). Obtained as a brown amorphous solid; yield: 231 mg (86%). ¹H NMR (300 MHz, CDCl₃) δ 8.03 (d, *J* = 6.9 Hz, 1H), 7.53 (d, *J* = 9.0 Hz, 1H), 7.13 (t, *J* = 7.8 Hz, 2H), 7.00 (s, 2H), 7.00 (s, 2H), 6.92 (s, 1H), 6.70 (t, *J* = 6.8 Hz, 1H), 3.94 (s, 3H), 3.89 (s, 3H), 2.45 (s, 3H); ¹³C NMR (300 MHz, CDCl₃) δ 149.4, 149.0, 144.0, 140.3, 124.0, 123.0, 122.4, 121.6, 121.3, 116.7, 112.6, 111.9, 111.7, 56.0, 55.9, 13.7. HRMS (ESI) calcd for C₁₆H₁₇N₂O₂ [M + H]⁺: 269.1285; found 269.1286.

2-Methyl-3-phenylimidazo[1,2-*a*]pyridine (3e).⁶⁶ Obtained as a brown oil; yield: 177 mg (85%). ¹H NMR (300 MHz, CDCl₃) δ 8.07 (d, *J* = 6.9 Hz, 1H), 7.57–7.47 (m, 3H), 7.46–7.36 (m, 3H), 7.12 (t, *J* = 7.8 Hz, 1H), 6.68 (t, *J* = 6.9 Hz, 1H), 2.46 (s, 3H); ¹³C NMR (300 MHz, CDCl₃) δ 144.3, 140.8, 129.4, 129.3, 129.1, 128.0, 124.0, 122.9, 121.4, 116.8, 111.8, 13.8. HRMS (ESI) calcd for C₁₄H₁₃N₂ [M + H]⁺: 209.1073; found 209.1075.

3-(4-Chlorophenyl)-2-methylimidazo[1,2-*a*]pyridine (3f).⁶⁶ Obtained as a brown amorphous solid; yield: 196 mg (81%). ¹H NMR (300 MHz, CDCl₃) δ 8.03 (d, *J* = 6.9 Hz, 1H), 7.58 (d, *J* = 9.0 Hz, 1H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.17 (t, *J* = 7.2 Hz, 1H), 6.74 (t, *J* = 6.9 Hz, 1H), 2.46 (s, 3H); ¹³C NMR (300 MHz, CDCl₃) δ 144.5, 141.1, 134.1, 130.7, 129.5, 127.8, 124.5, 122.8, 120.3, 117.0, 112.2, 13.8. HRMS (ESI) calcd for C₁₄H₁₂ClN₂ [M + H]⁺: 243.0684; found 243.0682.

3-(4-Bromophenyl)-2-methylimidazo[1,2-*a*]pyridine (3g). Obtained as a brown solid; yield: 245 mg (85%). ¹H NMR (300 MHz, CDCl₃) δ 7.99 (d, *J* = 6.9 Hz, 1H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 9.3 Hz, 1H), 7.27 (d, *J* = 8.4 Hz, 2H), 7.10 (t, *J* = 7.8 Hz, 1H), 6.68 (t, *J* = 6.8 Hz, 1H), 2.41 (s, 3H); ¹³C NMR (300 MHz, CDCl₃) δ 144.5, 141.1, 132.3, 130.8, 128.2, 124.2, 122.7, 122.0, 120.1, 116.9, 112.0, 13.7. HRMS (ESI) calcd for C₁₄H₁₂ClN₂ [M + H]⁺: 243.0684; found 243.0682.

2,3-Dihydronaphthylimidazo[1,2-*a*]pyridine (3h). Obtained as a yellowish-brown amorphous solid; yield: 196 mg (89%). ¹H NMR

(300 MHz, CDCl₃) δ 8.55 (d, J = 6.9 Hz, 1H), 7.62 (d, J = 9.0 Hz, 2H), 7.29 (t, J = 7.5 Hz, 2H), 7.15 (q, J = 6.6 Hz, 2H), 6.87 (t, J = 6.9 Hz, 1H), 3.05 (s, 4H); ¹³C NMR (300 MHz, CDCl₃) δ 146.6, 145.9, 135.3, 128.8, 128.1, 126.7, 124.0, 123.5, 119.5, 118.6, 117.6, 112.7, 30.1, 23.9. HRMS (ESI) calcd for C₁₅H₁₃N₂ [M + H]⁺: 221.1073; found 221.1072.

2,3-Diphenylimidazo[1,2-a]pyridine (3i):⁵⁰ Obtained as a light yellow solid; yield: 257 mg (95%). ¹H NMR (300 MHz, CDCl₃) δ 7.83 (d, J = 6.3 Hz, 1H), 7.71–7.57 (m, 3H), 7.43–7.29 (m, 5H), 7.25–7.13 (m, 3H), 7.06 (t, J = 7.8 Hz, 1H), 6.57 (t, J = 6.5 Hz, 1H); ¹³C NMR (300 MHz, CDCl₃) δ 144.4, 142.0, 133.9, 130.2, 129.4, 129.1, 128.5, 127.9, 127.7, 127.1, 124.2, 122.8, 120.6, 117.0, 111.8. HRMS (ESI) calcd for C₁₉H₁₅N₂ [M + H]⁺: 271.1230; found 271.1229.

2-Phenyl-3-p-tolylimidazo[1,2-a]pyridine (3j):⁶¹ Obtained as a light yellow solid; yield: 275 mg (97%). ¹H NMR (300 MHz, CDCl₃) δ 7.87 (d, J = 6.9 Hz, 1H), 7.70 (d, J = 6.9 Hz, 2H), 7.64 (d, J = 9.0 Hz, 1H), 7.30–7.18 (m, 7H), 7.10 (t, J = 7.8 Hz, 1H), 6.61 (t, J = 6.9 Hz, 1H), 2.40 (s, 3H); ¹³C NMR (300 MHz, CDCl₃) δ 144.4, 141.9, 138.5, 134.1, 130.3, 130.0, 128.0, 127.8, 127.1, 126.5, 124.2, 123.0, 120.9, 117.2, 111.9, 21.2. HRMS (ESI) calcd for C₂₀H₁₇N₂ [M + H]⁺: 285.1386; found 285.1384.

2-(4-Chlorophenyl)-3-phenylimidazo[1,2-a]pyridine (3k):⁶⁶ Obtained as a light yellow solid; yield: 276 mg (91%). ¹H NMR (300 MHz, CDCl₃) δ 7.65 (d, J = 6.6 Hz, 1H), 7.47–7.39 (m, 3H), 7.30–7.11 (m, 5H), 7.01 (d, J = 8.1 Hz, 2H), 6.90 (t, J = 7.7 Hz, 1H), 6.40 (t, J = 6.5 Hz, 1H); ¹³C NMR (300 MHz, CDCl₃) δ 144.1, 140.5, 132.6, 132.3, 129.9, 129.0, 128.8, 128.6, 128.4, 127.8, 124.2, 122.5, 120.5, 116.7, 111.7. HRMS (ESI) calcd for C₁₉H₁₄ClN₂ [M + H]⁺: 305.0840; found 305.0843.

2-(4-Bromophenyl)-3-phenylimidazo[1,2-a]pyridine (3l):⁶⁷ Obtained as a yellow solid; yield: 321 mg (92%). ¹H NMR (300 MHz, CDCl₃) δ 7.91 (d, J = 6.9 Hz, 1H), 7.65 (d, J = 9.0 Hz, 1H), 7.55–7.46 (m, 5H), 7.43–7.35 (m, 4H), 7.18 (t, J = 7.4 Hz, 1H), 6.71 (t, J = 6.8 Hz, 1H); ¹³C NMR (300 MHz, CDCl₃) δ 144.1, 141.0, 133.1, 131.3, 130.5, 129.6, 129.5, 129.4, 129.0, 128.7, 124.9, 123.2, 121.5, 117.4, 112.4. HRMS (ESI) calcd for C₁₉H₁₄BrN₂ [M + H]⁺: 349.0335; found 349.0338.

3-(4-Methoxyphenyl)-2,8-dimethylimidazo[1,2-a]pyridine (4a). Obtained as a brown amorphous solid; yield: 226 mg (89%). ¹H NMR (300 MHz, CDCl₃) δ 7.81 (d, J = 6.6 Hz, 1H), 7.28 (d, J = 8.4 Hz, 2H), 6.98 (d, J = 8.4 Hz, 2H), 6.85 (d, J = 6.6 Hz, 1H), 6.53 (t, J = 8.4 Hz, 1H), 3.79 (s, 3H), 2.56 (s, 3H), 2.41 (s, 3H); ¹³C NMR (300 MHz, CDCl₃) δ 159.2, 144.3, 139.4, 130.7, 129.4, 126.2, 122.7, 121.5, 120.7, 114.4, 111.6, 55.1, 16.9, 13.5. HRMS (ESI) calcd for C₁₆H₁₇N₂O [M + H]⁺: 253.1335; found 253.1337.

7-Methyl-2-phenyl-3-p-tolylimidazo[1,2-a]pyridine (4b). Obtained as a light yellow solid; yield: 281 mg (94%); mp 150–152 °C. ¹H NMR (300 MHz, CDCl₃) δ 7.74 (d, J = 6.9 Hz, 1H), 7.68 (d, J = 6.9 Hz, 2H), 7.39 (s, 1H), 7.27–7.15 (m, 7H), 6.44 (d, J = 6.9 Hz, 1H), 2.38 (s, 3H), 2.32 (s, 3H); ¹³C NMR (300 MHz, CDCl₃) δ 144.9, 141.5, 138.3, 135.2, 134.2, 130.2, 129.9, 127.9, 127.7, 126.9, 126.7, 122.2, 120.3, 115.5, 114.5, 21.1, 21.0. HRMS (ESI) calcd for C₂₁H₁₉N₂ [M + H]⁺: 299.1543; found 299.1545.

3-(4-Methoxyphenyl)-2,6-dimethylimidazo[1,2-a]pyridine (4c). Obtained as a brown amorphous solid; yield: 227 mg (90%). ¹H NMR (300 MHz, CDCl₃) δ 7.89 (d, J = 6.9 Hz, 1H), 7.37–7.27 (m, 3H), 7.04 (d, J = 9.0 Hz, 2H), 6.52 (d, J = 6.9 Hz, 1H), 3.87 (s, 3H), 2.41 (s, 3H), 2.37 (s, 3H); ¹³C NMR (300 MHz, CDCl₃) δ 159.3, 144.4, 139.6, 135.1, 130.8, 122.3, 121.6, 120.6, 115.1, 114.6, 114.5, 55.3, 21.2, 13.6. HRMS (ESI) calcd for C₁₆H₁₇N₂O [M + H]⁺: 253.1335; found 253.1333.

7-Ethyl-2-phenyl-3-p-tolylimidazo[1,2-a]pyridine (4f). Obtained as a light yellow solid; yield: 288 mg (92%). ¹H NMR (300 MHz, CDCl₃) δ 7.78 (d, J = 6.9 Hz, 1H), 7.69 (d, J = 6.9 Hz, 2H), 7.44 (s, 1H), 7.28–7.17 (m, 7H), 6.51 (d, J = 7.2 Hz, 1H), 2.64 (q, J = 7.5 Hz, 2H), 2.39 (s, 3H), 1.24 (t, J = 7.5 Hz, 3H); ¹³C NMR (300 MHz, CDCl₃) δ 145.2, 141.8, 141.5, 138.5, 134.4, 130.5, 130.1, 128.1, 127.9, 127.1, 126.9, 122.6, 120.5, 114.3, 113.7, 28.3, 21.4, 14.4. HRMS (ESI) calcd for C₂₂H₂₁N₂ [M + H]⁺: 313.1699; found 313.1703.

7-Methoxy-2-phenyl-3-p-tolylimidazo[1,2-a]pyridine (4g). Obtained as a yellow solid; yield: 297 mg (94%); mp 149–151 °C. ¹H NMR (300 MHz, CDCl₃) δ 7.67–7.59 (m, 3H), 7.23–7.10 (m, 7H), 6.86 (s, 1H), 6.30 (d, J = 7.5 Hz, 1H), 3.74 (s, 3H), 2.33 (s, 3H); ¹³C NMR (300 MHz, CDCl₃) δ 157.6, 145.7, 141.0, 138.2, 134.1, 130.2, 129.8, 127.8, 127.4, 126.8, 126.5, 123.4, 119.7, 106.7, 94.1, 55.0, 21.0. HRMS (ESI) calcd for C₂₁H₁₉N₂O [M + H]⁺: 315.1492; found 315.1494.

Methyl 2-phenyl-3-p-tolylimidazo[1,2-a]pyridine-7-carboxylate (4h). Obtained as a light yellow solid; yield: 315 mg (92%). ¹H NMR (300 MHz, CDCl₃) δ 8.34 (s, 1H), 7.89 (d, J = 7.2 Hz, 1H), 7.64 (d, J = 6.9 Hz, 2H), 7.29–7.19 (m, 8H), 3.88 (s, 3H), 2.40 (s, 3H); ¹³C NMR (300 MHz, CDCl₃) δ 165.4, 144.6, 143.3, 139.1, 133.5, 130.2, 130.1, 128.1, 127.9, 127.6, 125.8, 125.4, 122.6, 122.5, 119.9, 111.2, 52.2, 21.2. HRMS (ESI) calcd for C₂₂H₁₉N₂O₂ [M + H]⁺: 343.1441; found 343.1444.

6-Chloro-2-(4-chlorophenyl)-3-phenylimidazo[1,2-a]pyridine (4i). Obtained as a light yellow solid; yield: 254 mg (75%); mp 187–189 °C. ¹H NMR (300 MHz, CDCl₃) δ 7.91 (s, 1H), 7.63–7.50 (m, 6H), 7.42 (d, J = 7.8 Hz, 2H), 7.24 (d, J = 8.7 Hz, 2H), 7.17 (d, J = 9.6 Hz, 1H); ¹³C NMR (300 MHz, CDCl₃) δ 143.1, 142.2, 133.6, 132.2, 130.5, 129.8, 129.5, 129.2, 128.9, 128.5, 126.2, 121.7, 121.1, 120.8, 117.9. HRMS (ESI) calcd for C₁₉H₁₃Cl₂N₂ [M + H]⁺: 339.0450; found 339.0451.

6-Bromo-2-phenyl-3-p-tolylimidazo[1,2-a]pyridine (4j). Obtained as a yellow solid; yield: 288 mg (79%); mp 214–216 °C. ¹H NMR (300 MHz, CDCl₃) δ 8.03 (s, 1H), 7.67 (d, J = 7.8 Hz, 2H), 7.55 (d, J = 9.3 Hz, 1H), 7.33–7.19 (m, 8H), 2.45 (s, 3H); ¹³C NMR (300 MHz, CDCl₃) δ 142.9, 142.9, 139.2, 133.7, 130.3, 128.2, 127.8, 127.7, 127.6, 126.0, 123.2, 121.4, 118.0, 106.9, 21.4. HRMS (ESI) calcd for C₂₀H₁₆BrN₂ [M + H]⁺: 363.0491; found 363.0494.

6-(4-Chlorophenyl)-5-phenylimidazo[2,1-b]thiazole (4k). Obtained as a yellow solid; yield: 246 mg (79%). ¹H NMR (300 MHz, CDCl₃) δ 7.53 (d, J = 8.7 Hz, 2H), 7.45–7.37 (m, 5H), 7.32 (d, J = 4.5 Hz, 1H), 7.21 (d, J = 8.7 Hz, 2H), 6.78 (d, J = 4.5 Hz, 1H); ¹³C NMR (300 MHz, CDCl₃) δ 149.0, 142.1, 132.8, 132.8, 130.0, 129.2, 129.0, 128.6, 128.5, 128.3, 122.9, 117.3, 112.7. HRMS (ESI) calcd for C₁₇H₁₂ClN₂S [M + H]⁺: 311.0404; found 311.0407.

2-Phenyl-1-p-tolylimidazo[1,2-a]quinoline (4l). Obtained as a yellow solid; yield: 284 mg (85%); mp 182–184 °C. ¹H NMR (300 MHz, CDCl₃) δ 8.79 (d, J = 8.4 Hz, 1H), 7.58 (d, J = 6.9 Hz, 2H), 7.49–7.41 (m, 3H), 7.38–7.26 (m, 5H), 7.23 (t, J = 7.5 Hz, 1H), 7.16 (d, J = 8.1 Hz, 2H), 6.79 (d, J = 9.6 Hz, 1H), 2.33 (s, 3H); ¹³C NMR (300 MHz, CDCl₃) δ 181.2, 155.5, 140.1, 138.1, 137.6, 137.0, 134.8, 130.9, 129.3, 129.2, 128.5, 128.4, 127.8, 127.3, 127.2, 125.3, 122.3, 118.7, 115.8, 21.0. HRMS (ESI) calcd for C₂₄H₁₉N₂ [M + H]⁺: 335.1543; found 335.1545.

2-Phenyl-3-p-tolylimidazo[2,1-a]isoquinoline (4m). Obtained as a yellow solid; yield: 306 mg (92%); mp 138–140 °C. ¹H NMR (300 MHz, CDCl₃) δ 8.83 (d, J = 7.5 Hz, 1H), 7.79 (d, J = 6.9 Hz, 2H), 7.70 (d, J = 7.5 Hz, 1H), 7.65 (t, J = 7.1 Hz, 2H), 7.54 (t, J = 7.4 Hz, 1H), 7.39–7.25 (m, 7H), 6.93 (d, J = 7.5 Hz, 1H), 2.47 (s, 3H); ¹³C NMR (300 MHz, CDCl₃) δ 142.2, 140.2, 138.7, 134.5, 130.6, 130.1, 129.5, 128.2, 128.0, 127.9, 127.8, 127.0, 126.7, 126.7, 123.8, 123.4, 123.0, 121.0, 112.6, 21.4. HRMS (ESI) calcd for C₂₄H₁₉N₂ [M + H]⁺: 335.1543; found 335.1545.

■ ASSOCIATED CONTENT

📄 Supporting Information

¹H, ¹³C NMR and HSQC spectra and a proposed reaction mechanism for the initial bromination are given in the Supporting Information. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01714.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from the Ministry of Education ARC Tier 1 Grant numbers R-143-000-603-112 and R-143-000-550-112 is gratefully acknowledged. I. I. Roslan thanks NUS for the award of an NUS-PGF Scholarship.

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