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# Tandem Amination/Cycloisomerization of Aryl Propargylic Alcohols with 2-Aminopyridines as an Expedient Route to Imidazo[1,2-*a*]pyridines

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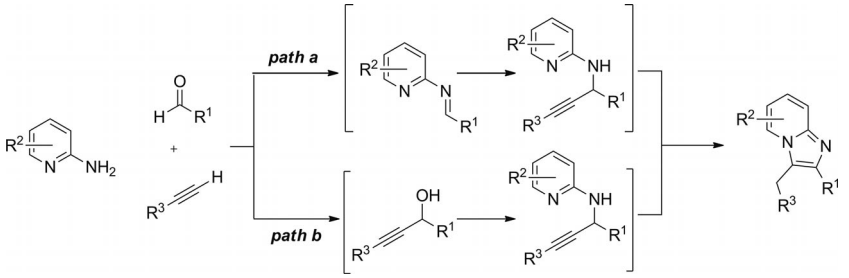
A new tandem route leading to imidazo[1,2-*a*]pyridines has been explored through the direct amination of aryl propargylic alcohols with 2-aminopyridines and their subsequent intramolecular cycloisomerization. A $ZnCl_2$/CuCl system has been developed to promote this transformation, which resulted in various imidazo[1,2-*a*]pyridines in moderate to good yields.

## Introduction

The design and exploration of new tandem reactions with two or more components has emerged as one of the current topics in organic synthesis due to their contribution to the diversity and complexity of the compound library, synthetic efficiency of target molecules, and usually the atom economics of the reaction as well.[1] The commonly devised strategy for tandem reactions depends on two or more separate functional groups in the participants, of which one functionality is initiated in the first process and then the others are sequentially evoked to proceed to the next process. Propargyl alcohols, a class of readily-available bifunctional components, which contain both hydroxy and alkynyl groups, are of great potential in tandem reactions. Recently, direct propargylic substitution reactions of propargylic alcohols with C- or heteroatom-centered nucleophiles[2–5] have been accomplished with propargylic cations or metal–allenylidene complexes. Intramolecular cycloisomerization of alkynes catalyzed by transition metals is well established.[6] In principle, a combination of direct propargylic substitution and subsequent cycloisomerization could open a new window of tandem reactions for the synthesis of various heterocyclic structures.[7]

Imidazo[1,2-*a*]pyridine is recognized as a "drug prejudice" scaffold because of its broad occurrence in a number of drug candidates and clinical drugs, which include Zolpidem, Alpidem, Olprinone, and Minodronic acid,[8] and several synthetic approaches for the scaffold are available.[9] However, these approaches can suffer from inappropriate substitution patterns, precursors that are difficult to obtain, poor atom economics, and sluggish reactions (up to 10 d).[10] Recently, both we and Gevorgyan et al. have independently explored a new approach to imidazo[1,2-*a*]pyridines by a three-component tandem reaction of 2-aminopyridines, aldehydes, and alkynes.[11] This one-pot reaction is believed to undergo three cascade processes according to




Scheme 1. Routes to imidazo[1,2-*a*]pyridines.

*path a*, namely imination/addition/cycloisomerization (Scheme 1); however, *path b*, namely addition/amination/cycloisomerization, has not been absolutely excluded. To the best of our knowledge, the reaction sequence according to *path b* has not been explored to date, despite the fact that it could afford an alternative method for the synthesis of

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imidazo[1,2-*a*]pyridines and have the same attractiveness in terms of atom-economics as *path a*. This prompted us to envisage a new tandem reaction route to imidazo[1,2-*a*]pyridines through the amination and cycloisomerization of propargylic alcohols with 2-aminopyridines.

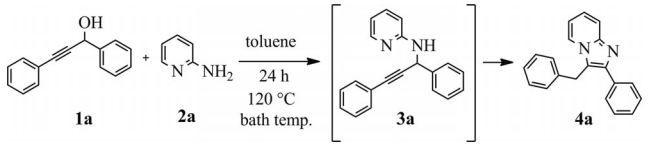
In the envisaged reaction, the first challenge is the direct amination of propargylic alcohols with basic 2-aminopyridines because basic amines as N-nucleophiles are seldom able to directly aminate propargylic alcohols.[4c–4d,4g–4j] However, many neutral and acidic N-nucleophiles, such as amides or sulfonamides, have been reported for propargylation.[4] The challenge stems from the transformation mechanism regarding the formation of the propargylic cation: amines as nucleophiles are not only basic but also coordinative and could neutralize acidic catalysts or coordinate transition-metal catalysts commonly used in the transformation, which would interrupt the formation of the propargylic cation. The second challenge is the risk of competing allenyl cations.[4a–4b,7e–1] In addition, Friedel–Crafts reactions[2] or Meyer–Schuster rearrangement[12] usually occur in the propargylation process. Herein, we present our efforts to overcome these problems and develop a tandem amination/cycloisomerization reaction of aryl propargylic alcohols with 2-aminopyridines.

## Results and Discussion

Initially, we conducted the reaction of **1a**, which was easily prepared from phenylacetylene and benzaldehyde, with **2a** (Table 1) under the standard conditions [$Cu(OTf)_2$/CuCl or $TsOH/CuSO_4$] adopted for the three-component tandem reaction of 2-aminopyridines, aldehydes, and alkynes[11] and found that no reaction took place. This result demonstrated that the previous three-component tandem reaction might proceed by *path a* rather than *path b*. We then reacted **1a** with **2a** in hot toluene in the presence of a variety of other acids and transition metal salts, and observed that some of these additives promoted the reaction, although in quantitative instead of catalytic amounts (Table 1).

In the presence of Brønsted acids, **1a** was almost totally consumed by *p*TsOH ($pK_a$ = –2.80)[13] and $CF_3CO_2H$ ($pK_a$ = –0.25) and converted to the major product **4a** in isolable yields (Table 1, Entry 1–2). In particular, *p*TsOH gave the best result of **4a** in 39% yield accompanied by intermediate **3a**. However, other Brønsted acids, such as $CF_3SO_3H$ ($pK_a$ = –14), $H_3PO_4$ ($pK_a$ = 2.12), AcOH ($pK_a$ = 4.76), and $B(OH)_3$ ($pK_a$ = 9.23), did not lead to the desired product even when the reaction time was prolonged. In search of a clue to improve the *p*TsOH-mediated reaction, our attempts to isolate and purify the other side products (besides **3a**) from the reaction mixture were unsuccessful due to their low amounts or instabilities. The attempt to improve selectivity by reducing the reaction temperature to 100 °C also failed, and **1a** was recovered almost quantitatively. To reduce the possible side products from the Friedel–Crafts reaction of the propargylic cation[3] with toluene, other solvents, such as EtOH, $CH_3CN$, dioxane, dimethyl sulfoxide, and *N*,*N*-dimethylformamide (DMF), were tested but even worse results were obtained. In addition, higher or lower amounts of *p*TsOH dramatically suppressed the reaction (Table 1, Entries 3–4).

Table 1. Screening of acids and transition metal salts for the model reaction of **1a** and **2a** under different conditions.[a,b]




| Entry | Catalyst (equiv.) | Yield of **4a** (**3a**) [%][c] |
|---|---|---|
| 1 | *p*TsOH·$H_2O$ (1.0) | 39 (16) |
| 2 | $CF_3COOH$ (1.0) | 35 (0) |
| 3 | *p*TsOH·$H_2O$ (0.5) | 5 (0) |
| 4 | *p*TsOH·$H_2O$ (1.5) | trace (0) |
| 5 | $FeCl_3$ (1.0) | 27 (0) |
| 6 | $FeBr_2$ (1.0) | 52 (0) |
| 7 | $BiCl_3$ (1.0) | 15 (trace) |
| 8 | $AlMe_2Cl$ (1.0) | 29 (13) |
| 9 | $ZnCl_2$ (1.0) | 57 (0) |
| 10 | $ZnBr_2$ (1.0) | 54 (0) |
| 11 | $ZnI_2$ (1.0) | 37 (0) |
| 12 | $BF_3$·OEt (1.0) | 51 (0) |
| 13 | $NH_4BF_4$ (1.0) | 13 (0) |
| 14 | AgOTf (1.0) | 20 (trace) |
| 15 | $CuBr_2$ (1.0) | 44 (0) |
| 16 | $CuCl_2$ (1.0) | 42 (trace) |
| 17 | CuCl (1.0) | 56 (0) |
| 18 | CuBr (1.0) | 25 (0) |

[a] Other Lewis acids, such as $FeCl_2$, $Ti(OiPr)_4$, $TiCl_4$, $MoCl_5$, $CdCl_2$, $AlCl_3$, $Zn(OAc)_2$, $Cu(OTf)_2$, CuI, $CrCl_3$, $H_3Mo_{12}O_{40}P$·$xH_2O$, and trimethylsilyl trifluoromethanesulfonate, did not promote the desired reaction of **1a** and **2a** under these conditions, which usually resulted in either no reaction or undesired reactions. Notably, catalytic amounts of $InCl_3$, $AuCl_3$ or $Yb(OTf)_3$ did not enable the transformation either (not shown). [b] Reaction conditions: **1a** (0.5 mmol), **2a** (1.05 equiv.), catalyst, toluene (2 mL), heating to reflux under Ar for 24 h. [c] Isolated yields.

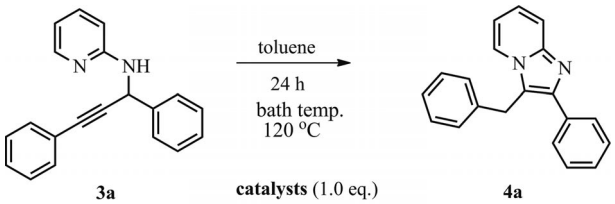
In the presence of Lewis acids, we observed that a number of Fe, Bi, Al, Zn, B, Ag, and Cu salts promoted the desired reaction (Table 1, Entries 5–18) but long reaction times were required to convert **1a** or **3a** into **4a**. The most promising results were provided by $FeBr_2$, $ZnCl_2$, $BF_3$·$OEt_2$, and CuCl (Table 1, Entries 6, 9, 12, 17).

Considering that bromide or iodide catalysts could contaminate the product due to the generation of bromine or iodine during the reaction, which could additionally affect the overall cascade process, we focused our attention on four catalysts (*p*TsOH, $BF_3$·$OEt_2$, $ZnCl_2$, CuCl) and searched for a breakthrough among them. Thus, we investigated the behavior of the four catalysts with **1a**, **2a**, and **3a** under the same conditions.

When **1a** was treated with the catalysts, it was converted completely into low polarity products in the presence of *p*TsOH, $BF_3$·$OEt_2$ or $ZnCl_2$, which indicates the formation of the propargylic cation. However, **1a** was stable in the presence of CuCl and could be recovered quantitatively. The results of the reactions of **2a** with the four catalysts

demonstrated that 2-aminopyridine was not decomposed. Compound **3a** was partially consumed in the presence of *p*TsOH, which afforded many side products accompanied with a trace amount of **4a** (Scheme 2), whereas it was consumed in the presence of $ZnCl_2$ or $BF_3{\cdot}OEt_2$ to give **4a** in 50 and 37% yield, respectively, together with some unidentified side products. Interestingly, CuCl converted **3a** into **4a** in 79% yield with less side products and the same result was achieved with only 0.1 equiv. loading of the catalyst over 3 h.




| catalysts (1.0 eq.) | 4a |
|---|---|
| TsOH | undesired reaction |
| $ZnCl_2$ | 50% |
| $BF_3{\cdot}OEt_2$ | 37% |
| CuCl | 79% |
| CuCl (0.1eq.) | 78% |

Scheme 2. Cycloisomerization of the propargylic amines with the four catalysts.

Based on these results, we applied the $ZnCl_2$/CuCl system to the tandem amination/cycloisomerization, in which $ZnCl_2$ was an efficient promoter for the formation of the propargylic cation to give **3a**, and CuCl was an accelerator for the cycloisomerization of **3a** to **4a**. The reaction was optimized as shown in Table 2, and the optimum conditions were **1a**/**2a**/$ZnCl_2$/CuCl (1.0:1.5:1.5:0.1, molar equiv.) in hot toluene for 24 h, which resulted in **4a** in 78% yield (Table 2, Entry 6).

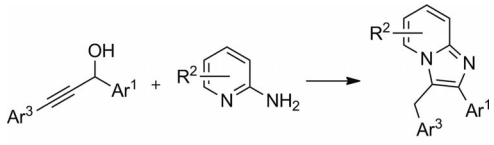
Table 2. Optimization of the conditions for the model reaction.[a]

| Entry | Equiv. of **1a** | Equiv. of **2a** | Catalyst (equiv.) | Additive (equiv.) | Yield[b] [%] |
|---|---|---|---|---|---|
| 1 | 1.0 | 0.83 | $ZnCl_2$ (1.0) | – | 45[c] |
| 2 | 1.0 | 0.67 | $ZnCl_2$ (1.0) | – | 42[c] |
| 3 | 1.0 | 1.0 | $ZnCl_2$ (1.0) | – | 57 |
| 4 | 1.0 | 1.5 | $ZnCl_2$ (1.0) | – | 30 |
| 5 | 1.0 | 1.5 | $ZnCl_2$ (1.5) | – | 61 |
| 6 | 1.0 | 1.5 | $ZnCl_2$ (1.5) | CuCl (1.0) | 79 |
| 7 | 1.0 | 1.0 | – | CuCl (1.0) | 56 |
| 8 | 1.0 | 1.5 | $ZnCl_2$ (1.5) | CuCl (0.1) | 78 |
| 9 | 1.0 | 1.5 | – | CuCl (0.1) | trace |
| 10 | 1.0 | 1.5 | $ZnCl_2$ (1.0) | CuCl (0.1) | 65 |
| 11 | 1.0 | 1.5 | $ZnCl_2$ (0.5) | CuCl (0.1) | 44 |

[a] Reaction conditions: **1a** (0.5 mmol), **2a**, catalyst/additive, 120 °C, toluene (2 mL), under Ar, 24 h. [b] Isolated yield of **4a**. [c] Yield based on **2a**.

With the optimized conditions in hand, we examined the scope and limitations of the tandem reaction (Table 3). For the aryl-substituted propargylic alcohols, the reaction was able to tolerate various substituents on the aromatic ring attached to the triple bond and resulted in good yields (Table 3, **4a**–**f**, **4l**–**m**). However, ester groups were not compatible with the reaction to some extent because of the ammonolysis of the ester with 2-aminopyridine (Table 3, **4g**). The use of an acid-sensitive cyano group led to a lower yield (Table 3, **4h**). The substrate bearing a nitro group did not afford the desired product **4i**, possibly due to the difficulty in forming the corresponding propargylic cation.[4c] The thienyl-substituted substrate was also tolerant to the reaction, whereas the furanyl-substituted substrate gave a lower yield due to the instability of the corresponding alcohol (Table 3, **4j**–**k**). The same substituent on the other aromatic ring ($Ar^1$) of the propargylic alcohols led to slightly lower yields than when the substituted aryl group was attached to the triple bond (Table 3, **4n**–**q**). The possible side products **4b**–**d** were not observed via the allenynic cation[4a,4b,7e–7i] in the preparation of **4n**–**p**. Similarly, different substituents on the pyridine ring of **2a** gave the desired product in moderate to good yields (Table 3, **4r**–**v**) except with the amino group, possibly because of the competitive amination of the propargylic alcohol (Table 3, **4w**).

Table 3. Synthesis of polysubstituted imidazo[1,2-*a*]pyridines by tandem amination/cycloisomerization of aryl propargylic alcohols.[a]



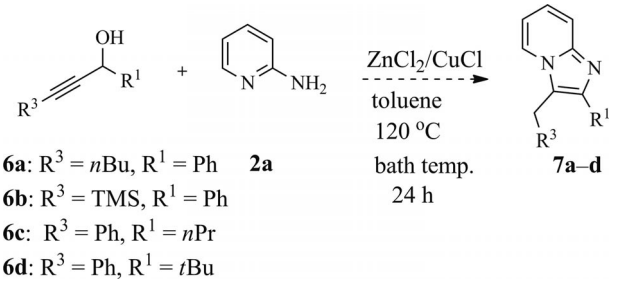

**1** **2** **4a**–**w**

| Product | $Ar^1$ | $Ar^3$ | $R^2$ | Yield [%][b] |
|---|---|---|---|---|
| **4a** | Ph | Ph | H | 78 |
| **4b** | 4-Me-$C_6H_4$ | Ph | H | 72 |
| **4c** | 4-MeO-$C_6H_4$ | Ph | H | 64 |
| **4d** | 4-F-$C_6H_4$ | Ph | H | 67 |
| **4e** | 4-Cl-$C_6H_4$ | Ph | H | 72 |
| **4f** | 4-Br-$C_6H_4$ | Ph | H | 66 |
| **4g** | 4-$MeO_2C$-$C_6H_4$ | Ph | H | 40 |
| **4h** | 4-NC-$C_6H_4$ | Ph | H | 17 |
| **4i** | 4-$NO_2$-$C_6H_4$ | Ph | H | n.d.[c] |
| **4j** | 2-thienyl | Ph | H | 59 |
| **4k** | 2-furanyl | Ph | H | 20 |
| **4l** | 3-Cl-$C_6H_4$ | Ph | H | 74 |
| **4m** | 2-Cl-$C_6H_4$ | Ph | H | 51 |
| **4n** | Ph | 4-Me-$C_6H_4$ | H | 58 |
| **4o** | Ph | 4-MeO-$C_6H_4$ | H | 38 |
| **4p** | Ph | 4-F-$C_6H_4$ | H | 61 |
| **4q** | Ph | 3-Cl-$C_6H_4$ | H | 81 |
| **4r** | Ph | Ph | 5-Me | 68 |
| **4s** | Ph | Ph | 5-Cl | 57 |
| **4t** | Ph | Ph | 5-Br | 53 |
| **4u** | Ph | Ph | 3-MeO | 50 |
| **4v** | Ph | Ph | 3-F | 70 |
| **4w** | Ph | Ph | 3-$NH_2$ | n.d.[c] |

[a] Reaction conditions: **1** (0.5 mmol), **2** (1.5 equiv.), $ZnCl_2$/CuCl (1.5/0.1 equiv.), toluene (2 mL), 120 °C, under Ar, 24 h. [b] Yield of isolated product. [c] Not determined.

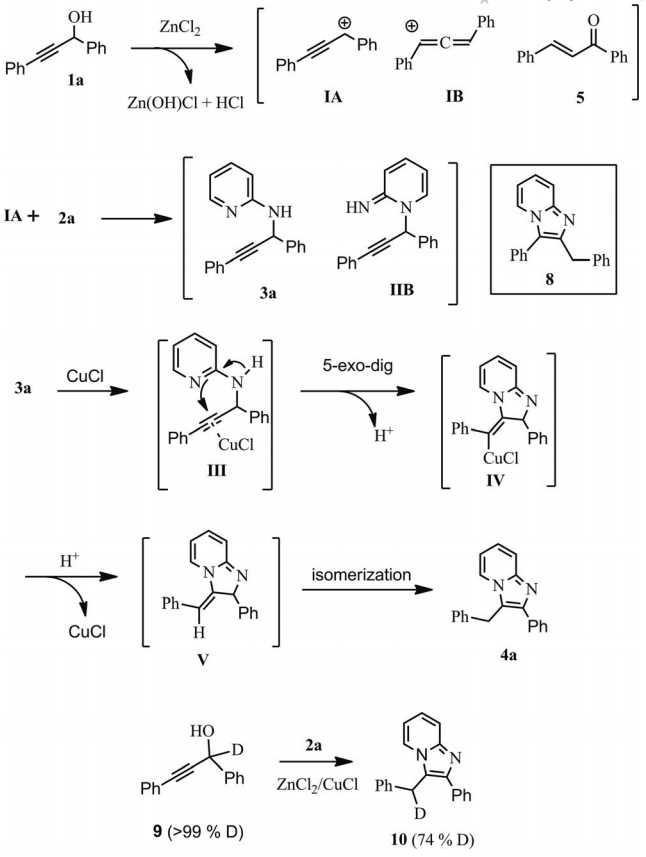
Subsequently, the tandem reaction was performed with 2-aminopyridine and other propargylic alcohols, such as **6a**–**d** with $R^1$ and $R^3$ being alkyl or $SiMe_3$, respectively (Scheme 3). Unexpectedly, **6a** and **6b** were consumed and led to many complicated products under the above conditions, and neither the corresponding propargylic amine nor the desired product **7** was isolated, which suggests that the resultant propargylic cation did not undergo the nucleophilic substitution with 2-aminopyridine. A plausible explanation is that the propargylic cations derived from **6a** and **6b** were less stable than those from aryl-substituted propargylic alcohols and did not have long enough lifetimes to trap the *N*-centered nucleophile. In contrast to **6a** and **6b**, **6c** and **6d** might not produce the corresponding propargylic cation under the standard conditions, which was demonstrated by their almost quantitative recovery from the reaction mixture. The reason could be that the formation of the propargylic cation was more sensitive to the electron-stabilizing effect of $R^1$ than that of $R^3$, in other words, when $R^1$ is alkyl (**6c** and **6d**) instead of aryl (**6a** and **6b**) the formation of the corresponding cation is more difficult due to the lack of conjugation from $R^1$.




**6a**: $R^3$ = *n*Bu, $R^1$ = Ph **2a** **7a–d**
**6b**: $R^3$ = TMS, $R^1$ = Ph
**6c**: $R^3$ = Ph, $R^1$ = *n*Pr
**6d**: $R^3$ = Ph, $R^1$ = *t*Bu

Scheme 3. Other propargylic alcohols used in the tandem reaction conditions.

A plausible mechanism was proposed for the tandem reaction (Scheme 4). The propargylic alcohol **1a** was first converted into **IA** in the presence of $ZnCl_2$. The possible allenyl **IB** was excluded on the basis that no regioisomers were observed when the $Ar^1$ and $Ar^3$ groups were exchanged (**4b**–**d** vs. **4n**–**4p**). The possible Meyer–Schuster rearrangement was also ruled out because the reaction of **5** with **2a** did not provide **4a** under the reaction conditions. Although 2-aminopyridine has two potential nucleophilic N atoms,[16] the propargylic cation **IA** should be attacked by the $NH_2$ group to give propargylic amine **3a** instead of **IIB**. This was strongly supported by the fact that neither **IIB** nor its cycloisomerized product **8**[17] were detected. Subsequently, **3a** underwent intramolecular cyclization in the common 5-*exo*-*dig* manner[6d–6k] catalyzed by CuCl to give intermediate **IV** together with the release of a proton. After protonation and isomerization, **IV** was converted into **4a** and CuCl was recovered. Interestingly, the deuterium-labeling experiment (from **9** to **10**) showed 74% deuterium substitution at the benzylic position, which indicates a possible partial [1,3] H-shift during the CuCl-promoted cycloisomerization process (from **V** to **4a**).




Scheme 4. Proposed processes and mechanism for the tandem reaction.

## Conclusions

A tandem amination/cycloisomerization of aryl-substituted propargylic alcohols with 2-aminopyridine has been explored in the presence of $ZnCl_2$/CuCl, which provides a concise method for the preparation of polysubstituted imidazo[1,2-*a*]pyridines. Various substituents on the aryl ring tolerate the reaction conditions and give the corresponding products in moderate to good yields.

## Experimental Section

**General Remarks:** Solvents were distilled from appropriate drying agents before use. All the reagents were purchased from Acros, Alfa Aesar, and National Chemical Reagent Group Co. Ltd., P. R. China and used as received. The progress of the reactions was monitored by TLC (silica-coated glass plates and visualized under UV light or in iodine). $^1H$ NMR spectra were recorded in $CDCl_3$ with a 400 MHz spectrometer. Chemical shifts ($\delta$) are reported in ppm using $SiMe_4$ ($\delta$ = 0.0 ppm) as an internal standard. Multiplicities of NMR signals are designated as s (singlet), d (doublet), t (triplet), q (quartet), br (broad), m (multiplet, for unresolved lines). $^{13}C$ NMR spectra were recorded with a 100 MHz spectrometer. HRMS were recorded with a Finnigan-Mat-95 mass spectrometer equipped with an ESI source. Flash column chromatography was performed with silica gel (300–400 mesh).

**General Procedure for the Synthesis of Aryl Propargylic Alcohols 1a–q and 9 (except 1i):** A hexane solution of *n*BuLi (1.32 mL,

3.3 mmol, 2.5 M) was added to a THF (dry, 6 mL) solution of phenylacetylene (0.36 mL, 3.3 mmol) at –78 °C under Ar. The mixture was stirred for 1 h at –78 °C before benzaldehyde (0.305 mL, 3.0 mmol) was added. The reaction mixture was warmed to room temperature and stirred for 1 h, and quenched with a saturated aqueous $NH_4Cl$ solution. The aqueous solution was extracted with EtOAc (2 × 15 mL), and the combined organic layers were washed with brine (20 mL). After the organic layer was dried with $NaSO_4$, the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography with petroleum ether and EtOAc (PE/EA) to give propargylic alcohola **1a**–**h**, **1j**–**q**. All the aryl propargylic alcohols are known products and the $^1H$ NMR spectroscopic data were consistent with the literature.[14]

**1,3-Diphenylprop-2-yn-1-ol (1a):** Yield 97%; $R_f$ = 0.42 (PE/EA = 9:1); light yellow oil. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.62 (d, $J$ = 6.8 Hz, 2 H), 7.46–7.49 (m, 2 H), 7.30–7.43 (m, 6 H), 5.69 (d, $J$ = 6.4 Hz, 1 H), 2.39 (d, $J$ = 4.8 Hz, 1 H) ppm. ESI-MS: $m/z$ = 191.1 $[M – OH]^+$.

**3-Phenyl-1-(*p*-tolyl)prop-2-yn-1-ol (1b):** Yield 97%; $R_f$ = 0.27 (PE/EA = 9:1); light yellow oil. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.46–7.52 (m, 4 H), 7.29–7.33 (m, 3 H), 7.21 (d, $J$ = 8.0 Hz, 2 H), 5.66 (d, $J$ = 6.4 Hz, 1 H), 2.37 (s, 3 H), 2.26 (d, $J$ = 6.0 Hz, 1 H) ppm. ESI-MS: $m/z$ = 205.1 $[M – OH]^+$.

**1-(4-Methoxyphenyl)-3-phenylprop-2-yn-1-ol (1c):** Yield 98%; $R_f$ = 0.41 (PE/EA = 4:1); white solid. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.54 (d, $J$ = 8.4 Hz, 2 H), 7.46–7.48 (m, 2 H), 7.28–7.32 (m, 3 H), 6.92 (d, $J$ = 8.8 Hz, 2 H), 5.64 (d, $J$ = 6.0 Hz, 1 H), 3.81 (s, 3 H), 3.35 (d, $J$ = 6.4 Hz, 1 H) ppm. ESI-MS: $m/z$ = 221.2 $[M – OH]^+$.

**1-(4-Fluorophenyl)-3-phenylprop-2-yn-1-ol (1d):** Yield 98%; $R_f$ = 0.31 (PE/EA = 9:1); colorless oil. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.57–7.61 (m, 2 H), 7.46–7.47 (m, 2 H), 7.29–7.36 (m, 3 H), 7.08 (t, $J$ = 8.8 Hz, 2 H), 5.67 (d, $J$ = 5.6 Hz, 1 H), 2.41 (d, $J$ = 5.6 Hz, 1 H) ppm. ESI-MS: $m/z$ = 209.1 $[M – OH]^+$.

**1-(4-Chlorophenyl)-3-phenylprop-2-yn-1-ol (1e):** Yield 97%; $R_f$ = 0.25 (PE/EA = 9:1); light yellow oil. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.55 (d, $J$ = 8.4 Hz, 2 H), 7.46 (d, $J$ = 7.6 Hz, 2 H), 7.32–7.38 (m, 5 H), 5.67 (s, 1 H), 2.39 (s, 1 H) ppm. ESI-MS: $m/z$ = 225.1 $[M – OH]^+$.

**1-(4-Bromophenyl)-3-phenylprop-2-yn-1-ol (1f):** Yield 96%; $R_f$ = 0.24 (PE/EA = 9:1); light yellow solid. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.45–7.54 (m, 6 H), 7.30–7.35 (m, 3 H), 5.65 (d, $J$ = 5.6 Hz, 1 H), 2.35 (d, $J$ = 6.0 Hz, 1 H) ppm. ESI-MS: $m/z$ = 269.0 $[M – OH]^+$.

**Methyl 4-(1-Hydroxy-3-phenylprop-2-ynyl)benzoate (1 g):** Yield 79%; $R_f$ = 0.39 (PE/EA = 4:1); light yellow solid. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 8.06 (d, $J$ = 8.4 Hz, 2 H), 7.68 (d, $J$ = 8.8 Hz, 2 H), 7.45–7.47 (m, 2 H), 7.29–7.34 (m, 3 H), 5.74 (s, 1 H), 3.92 (s, 3 H), 2.92 (br., 1 H) ppm. ESI-MS: $m/z$ = 249.1 $[M – OH]^+$.

**4-(1-Hydroxy-3-phenylprop-2-ynyl)benzonitrile (1h):** Yield 94%; $R_f$ = 0.31 (PE/EA = 4:1); white solid. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.72 (m, 4 H), 7.45–7.47 (m, 2 H), 7.32–7.38 (m, 3 H), 5.75 (d, $J$ = 4.4 Hz, 1 H), 2.54 (d, $J$ = 5.6 Hz, 1 H) ppm. ESI-MS: $m/z$ = 216.1 $[M – OH]^+$.

**1-(4-Nitrophenyl)-3-phenylprop-2-yn-1-ol (1i):** According to a reported method,[15] a toluene solution of $Me_2Zn$ (3.75 mL, 4.5 mmol,1.2 M) was added to a toluene (dry, 2 mL) solution of phenylacetylene (0.53 mL, 4.8 mmol) at room temperature under Ar. After the mixture was stirred for 1 h, a toluene (dry, 5 mL) solution of 4-nitrobenzaldehyde (0.453 g, 3.0 mmol) was added dropwise. The reaction mixture was stirred for 24 h, and quenched with water (20 mL). The aqueous solution was extracted with EtOAc (3 × 20 mL), and the combined organic layers were washed with brine (30 mL). After the organic layer was dried with $NaSO_4$, the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (PE/EA = 9:1) to give **1i** (0.201 g, 26%) as a light yellow solid (59% of 4-nitrobenzaldehyde was also recovered). $R_f$ = 0.37 (PE/EA = 4:1). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 8.27 (d, $J$ = 8.8 Hz, 2 H), 7.80 (d, $J$ = 8.8 Hz, 2 H), 7.47 (dd, $J1$ = 7.6, $J2$ = 0.8 Hz, 2 H), 7.32–7.39 (m, 3 H), 5.80 (d, $J$ = 5.2 Hz, 1 H), 2.55 (d, $J$ = 6.0 Hz, 1 H) ppm. ESI-MS: $m/z$ = 236.1 $[M – OH]^+$.

**3-Phenyl-1-(thiophen-2-yl)prop-2-yn-1-ol (1j):** Yield 96%; $R_f$ = 0.34 (PE/EA = 9:1); light yellow oil. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.48–7.50 (m, 2 H), 7.31–7.37 (m, 4 H), 7.25–7.26 (m, 1 H), 6.99–7.02 (m, 1 H), 5.89 (d, $J$ = 7.6 Hz, 1 H), 2.55 (d, $J$ = 6.8 Hz, 1 H) ppm. ESI-MS: $m/z$ = 197.1 $[M – OH]^+$.

**1-(Furan-2-yl)-3-phenylprop-2-yn-1-ol (1k):** Yield 95%; $R_f$ = 0.25 (PE/EA = 9:1); light yellow oil. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.45–7.50 (m, 3 H), 7.30–7.37 (m, 3 H), 6.53 (d, $J$ = 3.6 Hz, 1 H), 6.38–6.39 (m, 1 H), 5.69 (d, $J$ = 3.2 Hz, 1 H), 2.45 (d, $J$ = 4.4 Hz, 1 H) ppm. ESI-MS: $m/z$ = 181.0 $[M – OH]^+$.

**1-(3-Chlorophenyl)-3-phenylprop-2-yn-1-ol (1l):** Yield 98%; $R_f$ = 0.42 (PE/EA = 9:1); light yellow oil. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.61 (s, 1 H), 7.45–7.50 (m, 3 H), 7.30–7.37 (m, 5 H), 5.66 (d, $J$ = 4.8 Hz, 1 H), 2.52 (d, $J$ = 5.6 Hz, 1 H) ppm. ESI-MS: $m/z$ = 224.9 $[M – OH]^+$.

**1-(2-Chlorophenyl)-3-phenylprop-2-yn-1-ol (1m):** Yield 95%; $R_f$ = 0.36 (PE/EA = 9:1); light yellow oil. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.83–7.85 (m, 1 H), 7.46–7.49 (m, 2 H), 7.40–7.42 (m, 1 H), 7.27–7.36 (m, 5 H), 6.05 (d, $J$ = 5.6 Hz, 1 H), 2.58 (d, $J$ = 5.6 Hz, 1 H) ppm. ESI-MS: $m/z$ = 224.9 $[M – OH]^+$.

**1-Phenyl-3-(*p*-tolyl)prop-2-yn-1-ol (1n):** Yield 95%; $R_f$ = 0.30 (PE/EA = 9:1); white solid. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.62 (d, $J$ = 6.8 Hz, 2 H), 7.33–7.43 (m, 5 H), 7.12 (d, $J$ = 7.6 Hz, 2 H), 5.68 (d, $J$ = 6.4 Hz, 1 H), 2.35 (s, 3 H), 2.32 (d, $J$ = 6.4 Hz, 1 H) ppm. ESI-MS: $m/z$ = 205.1 $[M – OH]^+$.

**3-(4-Methoxyphenyl)-1-phenylprop-2-yn-1-ol (1o):** Yield 96%; $R_f$ = 0.49 (PE/EA = 3:1); light yellow oil. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.61–7.63 (m, 2 H), 7.32–7.42 (m, 5 H), 6.82–6.86 (m, 2 H), 5.68 (d, $J$ = 5.6 Hz, 1 H), 3.80 (s, 3 H), 2.34 (d, $J$ = 6.4 Hz, 1 H) ppm. ESI-MS: $m/z$ = 221.1 $[M – OH]^+$.

**3-(4-Fluorophenyl)-1-phenylprop-2-yn-1-ol (1p):** Yield 97%; $R_f$ = 0.60 (PE/EA = 3:1); colorless oil. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.61 (d, $J$ = 7.6 Hz, 2 H), 7.34–7.47 (m, 5 H), 7.01 (t, $J$ = 9.2 Hz, 2 H), 5.68 (d, $J$ = 6.0 Hz, 1 H), 2.34 (d, $J$ = 5.6 Hz, 1 H) ppm. ESI-MS: $m/z$ = 209.1 $[M – OH]^+$.

**3-(3-Chlorophenyl)-1-phenylprop-2-yn-1-ol (1q):** Yield 98%; $R_f$ = 0.34 (PE/EA = 9:1); light yellow oil. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.59–7.61 (m, 2 H), 7.29–7.46 (m, 6 H), 7.22–7.25 (m, 1 H), 5.68 (d, $J$ = 5.2 Hz, 1 H), 2.42 (d, $J$ = 5.6 Hz, 1 H) ppm. ESI-MS: $m/z$ = 224.9 $[M – OH]^+$.

***N*-(1,3-Diphenylprop-2-ynyl)pyridin-2-amine (3a):** To a THF solution (dry, 15 mL) of phenylacetylene (0.55 mL, 5.0 mmol) was added a hexane solution of BuLi (3.13 mL, 5.0 mmol, 1.6 M) at –78 °C under Ar. After the mixture was stirred for 1 h, $BF_3{\cdot}Et_2O$ (0.63 mL, 5.0 mmol) and a THF solution (dry, 5 mL) of (*E*)-*N*-benzylidenepyridin-2-amine (0.456 g, 2.5 mmol) were added. The reaction mixture was warmed to room temperature, stirred overnight, and quenched with saturated aqueous $NH_4Cl$ solution

(10 mL). The aqueous solution was extracted with EtOAc (3× 20 mL), and the combined organic layers were washed with brine (20 mL). After the organic layer was dried with $NaSO_4$, the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (PE/EA = 20:1) to give **3a** (0.517 g) as light yellow solid; yield 73%; m.p. 112–113 °C, $R_f$ = 0.31 (PE/EA = 9:1). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 8.15 (d, $J$ = 4.0 Hz, 1 H), 7.66 (d, $J$ = 7.6 Hz, 2 H), 7.36–7.46 (m, 5 H), 7.24–7.33 (m, 4 H), 6.64 (dd, $J$ = 6.8, 2.0 Hz, 1 H), 6.51 (d, $J$ = 8.0 Hz, 1 H), 6.09 (d, $J$ = 8.4 Hz, 1 H), 5.04 (d, $J$ = 7.6 Hz, 1 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 157.1, 148.1, 139.7, 137.4, 131.7, 128.6, 128.2, 128.2, 127.9, 127.1, 122.7, 113.9, 108.0, 88.4, 84.3, 47.8 ppm. ESI-MS: $m/z$ = 285.1 [M + H]$^+$. HRMS (ESI): calcd. for $C_{20}H_{17}N_2$ [M + H]$^+$ 285.1392; found 285.1392.

**General Procedure for the Synthesis of Imidazo[1,2-*a*]pyridines 4a–v:** To a 25 mL flask were sequentially added anhydrous $ZnCl_2$ (dried before the reaction, 136 mg, 0.75 mmol, 1.5 equiv.), CuCl (5 mg, 0.05 mmol, 0.1 equiv.), a toluene (dry, 2 mL) solution of aryl propargylic alcohol **1** (0.5 mmol), and 2-aminopyridine 2 (0.75 mmol) under Ar. The reaction mixture was stirred at 120 °C for 24 h, cooled to room temperature, and the reaction mixture was quenched with $NH_3{\cdot}H_2O$ (1.5 mL), diluted with water (5 mL), and extracted with $CH_2Cl_2$ (2× 10 mL). The combined organic layers were washed with brine (10 mL), dried with $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (PE/EA/$Et_3N$ = 16:2:1) to afford the desired product.

**3-Benzyl-2-phenylimidazo[1,2-*a*]pyridine (4a):** Yield 78%; m.p. 159–160 °C, $R_f$ = 0.44 (PE/EA = 4:1); white solid. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.86 (d, $J$ = 7.2 Hz, 2 H), 7.72–7.75 (m, 2 H), 7.47–7.50 (m, 2 H), 7.27–7.42 (m, 4 H), 7.18–7.23 (m, 3 H), 6.71–6.74 (m, 1 H), 4.53 (s, 2 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 144.8, 144.1, 136.8, 134.5, 129.0,128.6, 128.2, 127.7, 127.7, 126.9, 124.1, 123.4, 117.6, 117.5, 112.1, 29.8 ppm. ESI-MS: $m/z$ = 285.1 [M + H]$^+$. HRMS (ESI): calcd. for $C_{20}H_{17}N_2$ [M + H]$^+$ 285.1392; found 285.1390.

**3-Benzyl-2-(*p*-tolyl)imidazo[1,2-*a*]pyridine (4b):** Yield 72%; m.p. 161–162 °C, $R_f$ = 0.58 (PE/EA/$Et_3N$ = 1:1:0.04); light yellow solid. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.66–7.71 (m, 4 H), 7.23–7.32 (m, 5 H), 7.13–7.18 (m, 3 H), 6.66–6.69 (m, 1 H), 4.48 (s, 2 H), 2.38 (s, 3 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 144.8, 144.2, 137.5, 136.9, 131.6, 129.3, 129.0, 128.0, 127.7,126.9, 124.0,123.3,117.4,117.4, 112.1, 29.9, 21.3 ppm. ESI-MS: $m/z$ = 299.2 [M + H]$^+$. HRMS (ESI): calcd. for $C_{21}H_{19}N_2$ [M + H]$^+$ 299.1548; found 299.1544.

**3-Benzyl-2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine (4c):** Yield 64%; m.p. 152–153 °C, $R_f$ = 0.41 (PE/EA = 2:1); white solid. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.72 (d, $J$ = 9.2 Hz, 2 H), 7.65–7.68 (m, 2 H), 7.22–7.32 (m, 3 H), 7.13–7.18 (m, 3 H), 6.97 (d, $J$ = 9.2 Hz, 2 H), 6.67–6.70 (m, 1 H), 4.47 (s, 2 H), 3.83 (s, 3 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 159.5, 144.9, 144.2, 137.1, 129.5, 129.2, 127.9, 127.3, 127.0, 124.1, 123.4, 117.5, 117.1, 114.3, 112.2, 55.5, 30.1 ppm. ESI-MS: $m/z$ = 315.1 [M + H]$^+$. HRMS (ESI): calcd. for $C_{21}H_{19}N_2O$ [M + H]$^+$ 315.1497; found 315.1492.

**3-Benzyl-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridine (4d):** Yield 67%; m.p. 71–73 °C, $R_f$ = 0.33 (PE/EA = 3:1); white solid. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.66–7.77 (m, 4 H), 7.24–7.34 (m, 3 H), 7.17–7.22 (m, 1 H), 7.09–7.15 (m, 4 H), 6.71–6.74 (m, 1 H), 4.47 (s, 2 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 162.6 (d, $^1J_{CF}$ = 244.6 Hz), 144.8, 143.2, 136.6, 130.6, 129.8, 129.8, 129.1, 127.6, 127.0, 124.3, 123.4, 117.5, 115.6 (d, $^2J_{CF}$ = 21.4 Hz), 112.3, 29.8 ppm. ESI-MS: $m/z$ = 303.1 [M + H]$^+$. HRMS (ESI): calcd. for $C_{20}H_{16}FN_2$ [M + H]$^+$ 303.1298; found 303.1296.

**3-Benzyl-2-(4-chlorophenyl)imidazo[1,2-*a*]pyridine (4e):** Yield 72%; m.p. 124–125 °C, $R_f$ = 0.56 (PE/EA/$Et_3N$ = 1:1:0.04); white solid. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.65–7.74 (m, 4 H), 7.39 (d, $J$ = 8.8, 2.0 Hz, 2 H), 7.22–7.33 (m, 3 H), 7.15–7.20 (m, 1 H), 7.11 (d, $J$ = 6.8 Hz, 2 H), 6.69–6.72 (m, 1 H), 4.46 (s, 2 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 144.9, 143.0, 136.5, 133.6, 133.0, 129.4, 129.1, 128.8, 127.6, 127.0, 124.4, 123.4, 117.8, 117.6, 112.3, 29.8 ppm. ESI-MS: $m/z$ = 319.1 [M + H]$^+$. HRMS (ESI): calcd. for $C_{20}H_{16}ClN_2$ [M + H]$^+$ 319.1002; found 345.1001.

**3-Benzyl-2-(4-bromophenyl)imidazo[1,2-*a*]pyridine (4f):**[11] Yield 66%; m.p. 169–171 °C, $R_f$ = 0.26 (PE/EA = 2:1); white solid. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.65–7.71 (m, 4 H), 7.55 (d, $J$ = 8.0 Hz, 2 H), 7.24–7.33 (m, 3 H), 7.17–7.21 (m, 1 H), 7.12 (d, $J$ = 7.6 Hz, 2 H), 6.71–6.74 (m, 1 H), 4.47 (s, 2 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 144.9, 143.0, 136.4, 133.5, 131.7, 129.6, 129.1, 127.6, 127.0, 124.4, 123.4, 121.9, 117.8, 117.6, 112.3, 29.8 ppm. ESI-MS: $m/z$ = 363.1 [M + H]$^+$.

**Methyl 4-(3-Benzylimidazo[1,2-*a*]pyridin-2-yl)benzoate (4 g):** Yield 40%; m.p. 176–178 °C, $R_f$ = 0.45 (PE/EA = 1:1); white solid. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 8.10 (d, $J$ = 8.4 Hz, 2 H), 7.88 (d, $J$ = 8.4 Hz, 2 H), 7.68–7.74 (m, 2 H), 7.24–7.33 (m, 3 H), 7.19–7.23 (m, 1 H), 7.14 (d, $J$ = 7.2 Hz, 2 H), 6.72–6.76 (m, 1 H), 4.51 (s, 2 H), 3.92 (s, 3 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 166.9, 145.0, 142.9, 139.1, 136.3, 129.9, 129.1, 129.1, 127.9, 127.6, 127.0, 124.6, 123.4, 118.6, 117.7, 112.5, 52.1, 29.9 ppm. ESI-MS: $m/z$ = 343.1 [M + H]$^+$. HRMS (ESI): calcd. for $C_{21}H_{19}N_2O$ [M + H]$^+$ 343.1447; found 343.1422.

**4-(3-Benzylimidazo[1,2-*a*]pyridin-2-yl)benzonitrile (4h):**[11] Yield 17%; m.p. 164–166 °C, $R_f$ = 0.44 (PE/EA = 1:1); light yellow solid. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.90 (d, $J$ = 8.0 Hz, 2 H), 7.68–7.75 (m, 4 H), 7.22–7.35 (m, 4 H), 7.12 (d, $J$ = 6.8 Hz, 2 H), 6.75–6.79 (m, 1 H), 4.50 (s, 2 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 145.1, 141.9, 139.1, 135.9, 132.4, 129.2, 128.4, 127.5, 127.1, 124.9, 123.4, 119.0, 118.9, 117.7, 112.7, 110.9, 29.8 ppm. ESI-MS: $m/z$ = 310.1 [M + H]$^+$.

**3-Benzyl-2-(thiophen-2-yl)imidazo[1,2-*a*]pyridine (4j):** Yield 59%; m.p. 152–153 °C, $R_f$ = 0.32 (PE/EA = 3:1); light yellow solid. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.72 (d, $J$ = 6.8 Hz, 1 H), 7.65 (d, $J$ = 8.8 Hz, 1 H), 7.40 (d, $J$ = 4.0 Hz, 1 H), 7.34 (d, $J$ = 5.2 Hz, 1 H), 7.21–7.30 (m, 3 H), 7.14–7.18 (m, 3 H), 7.07–7.10 (m, 1 H), 6.68–6.72 (m, 1 H), 4.54 (s, 2 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 144.7, 138.6, 137.5, 136.3, 128.9, 127.7, 127.7, 126.9, 125.5, 124.4, 124.4, 123.1, 117.3, 117.3, 112.3, 29.8 ppm. ESI-MS: $m/z$ = 291.1 [M + H]$^+$. HRMS (ESI): calcd. for $C_{18}H_{15}N_2S$ [M + H]$^+$ 291.0956; found 291.0943.

**3-Benzyl-2-(furan-2-yl)imidazo[1,2-*a*]pyridine (4k):**[11] Yield 20%; m.p. 121–123 °C, $R_f$ = 0.37 (PE/EA = 2:1); white solid. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.73 (d, $J$ = 6.4 Hz, 1 H), 7.61 (d, $J$ = 9.2 Hz, 1 H), 7.50 (d, $J$ = 1.2 Hz, 1 H), 7.25–7.28 (m, 2 H), 7.12–7.22 (m, 4 H), 6.91 (dd, $J$ = 3.6, 0.8 Hz, 1 H), 6.66–6.70 (m, 1 H), 6.52–6.53 (m, 1 H), 4.62 (s, 2 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 150.1, 145.0, 142.1, 136.8, 135.2, 128.8, 127.9, 126.7, 124.5, 123.2, 118.0, 117.3, 112.2, 111.4, 107.6, 29.6 ppm. ESI-MS: $m/z$ = 275.2 [M + H]$^+$.

**3-Benzyl-2-(3-chlorophenyl)imidazo[1,2-*a*]pyridine (4l):** Yield 74%; m.p. 110–111 °C, $R_f$ = 0.25 (PE/EA = 3:1); white solid. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.85 (s, 1 H), 7.66–7.73 (m, 2 H), 7.61–7.64 (m, 1 H), 7.23–7.37 (m, 5 H), 7.17–7.22 (m, 1 H), 7.13 (d, $J$ = 7.2 Hz, 2 H), 6.71–6.74 (m, 1 H), 4.49 (s, 2 H) ppm. $^{13}$C NMR

(100 MHz, $CDCl_3$): $\delta$ = 144.8, 142.6, 136.4, 136.3, 134.6, 129.8, 129.0, 128.2, 127.7, 127.6, 127.0, 126.0, 124.4, 123.4, 118.1, 117.6, 112.4, 29.8 ppm. ESI-MS: *m/z* = 319.1 $[M + H]^+$. HRMS (ESI): calcd. for $C_{20}H_{16}ClN_2$ $[M + H]^+$ 319.1002; found 319.1003.

**3-Benzyl-2-(2-chlorophenyl)imidazo[1,2-*a*]pyridine (4m):** Yield 51%; m.p. 126–127 °C, $R_f$ = 0.38 (PE/EA = 2:1); white solid. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.65–7.68 (m, 2 H), 7.53–7.56 (m, 1 H), 7.47–7.50 (m, 1 H), 7.30–7.33 (m, 2 H), 7.14–7.26 (m, 4 H), 7.06 (d, *J* = 7.2 Hz, 2 H), 6.68 (t, *J* = 6.8 Hz, 1 H), 4.28 (s, 2 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 144.6, 142.2, 136.5, 134.0, 133.6, 132.5, 129.7, 129.4, 128.7, 127.8, 126.6, 126.6, 124.0, 123.7, 119.6, 117.7, 112.1, 29.9 ppm. ESI-MS: *m/z* = 319.1 $[M + H]^+$. HRMS (ESI): calcd. for $C_{20}H_{16}ClN_2$ $[M + H]^+$ 319.1002; found 319.1004.

**3-(4-Methylbenzyl)-2-phenylimidazo[1,2-*a*]pyridine (4n):** Yield 58%; m.p. 93–94 °C, $R_f$ = 0.35 (PE/EA = 2:1); white solid. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.79–7.82 (m, 2 H), 7.67–7.72 (m, 2 H), 7.41–7.46 (m, 2 H), 7.33–7.38 (m, 1 H), 7.15–7.20 (m, 1 H), 7.12 (d, *J* = 8.0 Hz, 2 H), 7.04 (d, *J* = 8.4 Hz, 2 H), 6.68–6.72 (m, 1 H), 4.46 (s, 2 H), 2.33 (s, 3 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 144.8, 144.0, 136.5, 134.5, 133.6, 129.7, 128.6, 128.1, 127.6, 127.5, 124.0, 123.4, 117.8, 117.5, 112.1, 29.4, 21.0 ppm. ESI-MS: *m/z* = 299.2 $[M + H]^+$. HRMS (ESI): calcd. for $C_{21}H_{19}N_2$ $[M + H]^+$ 299.1548; found 299.1544.

**3-(4-Methoxybenzyl)-2-phenylimidazo[1,2-*a*]pyridine (4o):** Yield 38%; m.p. 98–100 °C, $R_f$ = 0.25 (PE/EA = 2:1); light yellow solid. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.79–7.81 (m, 2 H), 7.67–7.72 (m, 2 H), 7.42–7.46 (m, 2 H), 7.33–7.37 (m, 1 H), 7.15–7.20 (m, 1 H), 7.06 (d, *J* = 8.6 Hz, 2 H), 6.84 (d, *J* = 8.6 Hz, 2 H), 6.69–6.72 (m, 1 H), 4.44 (s, 2 H), 3.78 (s, 3 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 158.5, 144.8, 143.9, 134.5, 128.6, 128.6, 128.5, 128.1, 127.6, 124.0, 123.4, 118.0, 117.5, 114.4, 112.1, 55.2, 29.0 ppm. ESI-MS: *m/z* = 315.2 $[M + H]^+$. HRMS (ESI): calcd. for $C_{21}H_{19}N_2O$ $[M + H]^+$ 315.1497; found 315.1498.

**3-(4-Fluorobenzyl)-2-phenylimidazo[1,2-*a*]pyridine (4p):** Yield 61%; m.p. 98–99 °C, $R_f$ = 0.30 (PE/EA = 2:1); white solid. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.76–7.79 (m, 2 H), 7.66–7.71 (m, 2 H), 7.42–7.46 (m, 2 H), 7.34–7.38 (m, 1 H), 7.17–7.22 (m, 1 H), 7.08–7.12 (m, 2 H), 6.97–7.02 (m, 2 H), 6.70–6.75 (m, 1 H), 4.46 (s, 2 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 161.8 (d, $^1J_{CF}$ = 243.8 Hz), 144.9, 144.1, 134.3, 132.3, 132.3, 129.1 (d, $^3J_{CF}$ = 8.8 Hz), 128.6, 128.1, 127.8, 124.2, 123.2, 117.6, 117.4, 115.8 (d,$^2J_{CF}$ = 20.6 Hz), 112.2, 29.1 ppm. ESI-MS: *m/z* = 303.2 $[M + H]^+$. HRMS (ESI): calcd. for $C_{20}H_{16}FN_2$ $[M + H]^+$ 303.1298; found 303.1296.

**3-(3-Chlorobenzyl)-2-phenylimidazo[1,2-*a*]pyridine (4q):** Yield 81%; $R_f$ = 0.29 (PE/EA = 3:1); colorless oil. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.73–7.76 (m, 3 H), 7.67 (d, *J* = 6.8 Hz, 1 H), 7.43–7.47 (m, 2 H), 7.35–7.39 (m, 1 H), 7.20–7.25 (m, 3 H), 7.16 (s, 1 H), 6.98–7.00 (m, 1 H), 6.74–6.77 (m, 1 H), 4.46 (s, 2 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 145.0, 144.3, 138.9, 135.0, 134.1, 130.4, 128.7, 128.2, 128.0, 127.9, 127.3, 125.8, 124.6, 123.2, 117.6, 116.8, 112.6, 29.6 ppm. ESI-MS: *m/z* = 319.0 $[M + H]^+$. HRMS (ESI): calcd. for $C_{20}H_{16}ClN_2$ $[M + H]^+$ 319.1002; found 319.1007.

**3-Benzyl-6-methyl-2-phenylimidazo[1,2-*a*]pyridine (4r):** Yield 68%; m.p. 208–209 °C, $R_f$ = 0.24 (PE/EA = 3:1); white solid. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.76–7.80 (m, 2 H), 7.60 (d, *J* = 8.8 Hz, 1 H), 7.49 (s, 1 H), 7.40–7.44 (m, 2 H), 7.24–7.36 (m, 4 H), 7.16 (d, *J* = 7.2 Hz, 2 H), 7.04 (dd, *J* = 9.2, 1.6 Hz, 1 H), 4.47 (s, 2 H), 2.24 (s, 3 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 143.9, 143.9, 137.0, 134.6, 129.0, 128.6, 128.0, 127.7, 127.5, 127.3, 126.8, 121.8, 120.9, 117.3, 116.9, 29.8, 18.4 ppm. ESI-MS: *m/z* = 299.2 $[M + H]^+$. HRMS (ESI): calcd. for $C_{21}H_{19}N_2$ $[M + H]^+$ 299.1548; found 299.1547.

**3-Benzyl-6-chloro-2-phenylimidazo[1,2-*a*]pyridine (4s):** Yield 57%; m.p. 195–196 °C, $R_f$ = 0.58 (PE/EA = 2:1); light yellow solid. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.73–7.78 (m, 3 H), 7.62 (d, *J* = 9.6 Hz, 1 H), 7.41–7.45 (m, 2 H), 7.28–7.38 (m, 4 H), 7.13–7.16 (m, 3 H), 4.47 (s, 2 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 145.2, 143.2, 136.1, 134.0, 129.1, 128.7, 128.1, 128.0, 127.6, 127.1, 125.5, 121.1, 120.4, 118.3, 117.9, 29.8 ppm. ESI-MS: *m/z* = 319.1 $[M + H]^+$. HRMS (ESI): calcd. for $C_{20}H_{16}ClN_2$ $[M + H]^+$ 319.1002; found 319.0994.

**3-Benzyl-6-bromo-2-phenylimidazo[1,2-*a*]pyridine (4t):** Yield 53%; m.p. 212–214 °C, $R_f$ = 0.58 (PE/EA = 2:1); light yellow solid. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.83 (d, *J* = 0.8 Hz, 1 H), 7.76 (d, *J* = 8.0 Hz, 2 H), 7.58 (d, *J* = 9.6 Hz, 1 H), 7.41–7.45 (m, 2 H), 7.23–7.38 (m, 5 H), 7.13 (d, *J* = 7.6 Hz, 2 H), 4.47 (s, 2 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 145.0, 143.2, 136.1, 133.9, 129.1, 128.7, 128.1, 128.0, 127.6, 127.5, 127.1, 123.3, 118.2, 106.9, 29.7 ppm. ESI-MS: *m/z* = 363.1 $[M + H]^+$. HRMS (ESI): calcd. for $C_{20}H_{16}BrN_2$ $[M + H]^+$ 363.0497; found 363.0508.

**3-Benzyl-8-methoxy-2-phenylimidazo[1,2-*a*]pyridine (4u):** Yield 50%; m.p. 178–180 °C, $R_f$ = 0.26 (PE/EA = 1:1); white solid. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.82 (d, *J* = 7.2 Hz, 2 H), 7.38–7.42 (m, 2 H), 7.22–7.35 (m, 5 H), 7.13 (d, *J* = 7.2 Hz, 2 H), 6.59–6.62 (m, 1 H), 6.46 (d, *J* = 7.6 Hz, 1 H), 4.47 (s, 2 H), 4.03 (s, 3 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 149.0, 143.3, 139.2, 136.9, 134.4, 128.9, 128.3, 128.2, 127.6, 127.5, 126.7, 118.6, 116.3, 112.0, 100.3, 55.7, 30.0 ppm. ESI-MS: *m/z* = 315.2 $[M + H]^+$. HRMS (ESI): calcd. for $C_{21}H_{19}N_2O$ $[M + H]^+$ 315.1497; found 315.1502.

**3-Benzyl-8-fluoro-2-phenylimidazo[1,2-*a*]pyridine (4v):** Yield 70%; m.p. 159–160 °C, $R_f$ = 0.56 (PE/EA = 3:1); white solid. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.81–7.84 (m, 2 H), 7.53 (d, *J* = 6.8 Hz, 1 H), 7.41–7.46 (m, 2 H), 7.24–7.39 (m, 4 H), 7.14 (d, *J* = 7.2 Hz, 2 H), 6.88 (dd, *J* = 10.0, 7.6 Hz, 1 H), 6.59–6.65 (m, 1 H), 4.50 (s, 2 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 151.6 (d, $^1J_{CF}$ = 251.6 Hz), 144.5, 136.4, 134.0, 129.1, 128.6, 128.3, 128.0, 127.6, 127.0, 119.8, 119.8, 119.4, 111.2, 111.2, 106.9, 106.7, 30.1 ppm. ESI-MS: *m/z* = 303.2 $[M + H]^+$. HRMS (ESI): calcd. for $C_{20}H_{16}FN_2$ $[M + H]^+$ 303.1298; found 303.1300.

**2-Benzyl-3-phenylimidazo[1,2-*a*]pyridine (8):** A $CHCl_3$ (2 mL) solution of $Br_2$ (0.815 g, 5.1 mmol, 0.26 mL) was added dropwise to a $CHCl_3$ (3 mL) solution of 1,3-diphenylpropan-2-one (1.051 g, 5.0 mmol) at room temperature. The reaction mixture was stirred for 3 h and quenched with saturated aqueous $Na_2S_2O_3$ (10 mL). The aqueous solution was extracted with $CH_2Cl_2$ (3 × 10 mL), the combined organic layers were washed with brine (10 mL), dried with $MgSO_4$, and evaporated to give 1-bromo-1,3-diphenylpropan-2-one (1.587 g, crude). The crude bromide (0.174 g), 2-aminopyridine (0.047 g, 0.5 mmol), and $Na_2CO_3$ (0.064 g, 0.6 mmol) were added to dry DMF (5 mL). The reaction mixture was stirred at 100 °C under Ar for 4 h. After cooling to room temperature, the reaction mixture was diluted with EtOAc (20 mL) and washed with water (20 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL), and the combined organic layers were washed with brine (2 × 10 mL), dried with $Na_2SO_4$, and the solvents evaporated to dryness. The residue was purified by silica gel chromatography (PE/EA/$Et_3N$ = 16:2:1) to give **8** (0.046 g, 30% two steps) as yellow solid. M.p. 95–96 °C, $R_f$ = 0.40 (PE/EA = 3:1). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 8.03–8.05 (m, 1 H), 7.59–7.61 (m, 1 H), 7.49–7.53 (m, 2 H), 7.41–7.44 (m, 3 H), 7.21–7.24 (m, 4 H), 7.11–7.18 (m, 2 H), 6.68–6.71 (m, 1 H), 4.14 (s, 2 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 144.7, 143.4, 140.3, 129.8, 129.2, 128.6,

128.4, 128.3, 125.9, 124.1, 123.2, 122.0, 117.4, 111.9, 34.0 ppm. ESI-MS: *m*/*z* = 285.1 $[M + H]^+$. HRMS (ESI): calcd. for $C_{20}H_{17}N_2$ $[M + H]^+$ 285.1392; found 285.1392.

**[1D]-1,3-Diphenylprop-2-yn-1-ol (9):** Yield 64%; $R_f$ = 0.45 (PE/EA = 9:1); light yellow oil. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.59–7.62 (m, 2 H), 7.46–7.49 (m, 2 H), 7.28–7.42 (m, 6 H), 2.47 (s, 1 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 140.6, 131.8, 128.7, 128.6, 128.5, 128.3, 126.8, 122.4, 88.7, 86.6, 64.8 (t, $^1J_{CD}$ = 22.6 Hz) ppm. ESI-MS: *m*/*z* = 192.1 $[M - OH]^+$. HRMS (ESI): calcd. for $C_{15}H_{10}D$ $[M - OH]^+$ 192.0924; found 192.0930.

**Deuterium-Labeling Experiment:** To a 25 mL flask were sequentially added anhydrous $ZnCl_2$ (dried before the reaction, 136 mg, 0.75 mmol), CuCl (5 mg, 0.05 mmol), a toluene (dry, 2 mL) solution of **9** (0.105 g, 0.5 mmol), and 2-aminopyridine (0.07 g, 0.75 mmol) under Ar. The reaction mixture was stirred at 120 °C for 24 h before it was cooled to room temperature and quenched with $NH_3{\cdot}H_2O$ (1.5 mL), diluted with water (5 mL), and extracted with $CH_2Cl_2$ (2× 10 mL). The combined organic layers were washed with brine (10 mL), dried with $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (petroleum ether/EtOAc/$Et_3N$ = 16:2:1) to afford a mixture of **10** and **4a** (37:13, determined by $^1$HNMR; 0.103 g, 72%) as light yellow solid, m.p. 155–158 °C, $R_f$ = 0.44 (PE/EA = 4:1). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.77–7.80 (m, 2 H), 7.67–7.69 (m, 2 H), 7.41–7.45 (m, 2 H), 7.23–7.37 (m, 4 H), 7.13–7.19 (m, 3 H), 6.67–6.71 (m, 1 H), 4.49 (s, 0.52 H of **4a**), 4.47 (s, 0.74 H of **10**) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 144.9, 144.2, 136.8, 136.7, 134.5, 129.0, 128.6, 128.2, 127.7, 126.9, 124.1, 123.4, 117.6, 117.6, 112.2, 29.8, 29.6 (t, $^1J_{CD}$ = 19.6 Hz) ppm. ESI-MS: *m*/*z* = 285.1 (**4a**, 31) $[M + H]^+$, 286.0 (**10**, 100) $[M + D]^+$. HRMS (ESI): calcd. for $C_{20}H_{16}DN_2$ $[M + H]^+$ 286.1455; found 286.1449.

**Supporting Information** (see footnote on the first page of this article): Copies of the $^1H$ and $^{13}C$ NMR spectra.

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[1] For recent reviews, see: a) J. Zhu, H. Bienayme, *Multicomponent Reactions*, Wiley-VCH, Weinheim, Germany, **2005**; b) A. Dömling, *Chem. Rev.* **2006**, *106*, 17–89; c) J. D. Sunderhaus, S. F. Martin, *Chem. Eur. J.* **2009**, *15*, 1300–1308.

[2] For reviews, see: a) Y. Miyake, S. Uemura, Y. Nishibayashi, *ChemCatchem* **2009**, *1*, 342–356; b) N. Ljungdahl, N. Kann, *Angew. Chem.* **2009**, *121*, 652; *Angew. Chem. Int. Ed.* **2009**, *48*, 642–644; for recent examples, see: c) B. M. Trost, A. Breder, *Org. Lett.* **2011**, *13*, 398–401; d) M. Niggemann, M. J. Meel, *Angew. Chem. Int. Ed.* **2010**, *49*, 3684–3687; e) C. C. Silveira, S. R. Mendes, L. Wolf, G. M. Martins, *Tetrahedron Lett.* **2010**, *51*, 4560–4562; f) M. Ikeda, Y. Miyake, Y. Nishibayashi, *Angew. Chem. Int. Ed.* **2010**, *49*, 7289–7293; g) K. Kanao, Y. Tanabe, Y. Miyake, Y. Nishibayashi, *Organometallics* **2010**, *29*, 2381–2384; h) L.-F. Yao, M. Shi, *Chem. Eur. J.* **2009**, *15*, 3875–3881; i) X. Zhang, W. T. Teo, P. W. H. Chan, *Org. Lett.* **2009**, *11*, 4990–4993; j) S. Wang, Y. Zhu, Y. Wang, P. Lu, *Org. Lett.* **2009**, *11*, 2615–2618; k) K. Kanao, Y. Miyake, Y. Nishibayashi, *Organometallics* **2009**, *28*, 2920–2926; l) W. Huang, P. Zheng, Z. Zhang, R. Liu, Z. Chen, X. Zhou, *J. Org. Chem.* **2008**, *73*, 6845–6848; m) M. Yoshimatsu, T. Otani, S. Matsuda, T. Yamamoto, A. Sawa, *Org. Lett.* **2008**, *10*, 4251–4254.

[3] For O-nucleophiles: a) M. Yoshimatsu, H. Watanabe, E. Koketsu, *Org. Lett.* **2010**, *12*, 4192–4194; b) C. Fang, Y. Pang, C. J. Forsyth, *Org. Lett.* **2010**, *12*, 4528–4531; c) P. Srihari, D. C. Bhunia, P. Sreedhar, S. S. Mandal, J. S. S. Reddy, J. S. Yadav, *Tetrahedron Lett.* **2007**, *48*, 8120–8124; d) B. D. Sherry, A. T. Radosevich, F. D. Toste, *J. Am. Chem. Soc.* **2003**, *125*, 6076–6077.

[4] For N-nucleophiles, see: a) Y. Zhu, G. Yin, D. Hong, P. Lu, Y. Wang, *Org. Lett.* **2011**, *13*, 1024–1027; b) G. Yin, Y. Zhu, L. Zhang, P. Lu, Y. Wang, *Org. Lett.* **2011**, *13*, 940–943; c) W. Yan, Q. Wang, Y. Chen, J. L. Petersen, X. Shi, *Org. Lett.* **2010**, *12*, 3308–3311; d) P. Srihari, J. S. S. Reddy, D. C. Bhunia, S. S. Mandal, J. S. Yadav, *Synth. Commun.* **2008**, *38*, 1448–1455; e) Z. Zhan, W. Yang, R. Yang, J. Yu, J. Li, H. Liu, *Chem. Commun.* **2006**, 3352–3354; f) G. V. Karunakar, M. Periasamy, *J. Org. Chem.* **2006**, *71*, 7463–7466; g) Y. Inada, M. Yoshikawa, M. D. Milton, Y. Nishibayashi, S. Uemura, *Eur. J. Org. Chem.* **2006**, 881–890; h) R. V. Ohri, A. T. Radosevich, K. J. Hrovat, C. Musich, D. Huang, T. R. Holman, F. D. Toste, *Org. Lett.* **2005**, *7*, 2501–2504; i) Y. Nishibayashi, M. D. Milton, Y. Inada, M. Yoshikawa, I. Wakiji, M. Hidai, S. Uenura, *Chem. Eur. J.* **2005**, *11*, 1433–1451; j) Y. Nishibayashi, I. Wakiji, M. Hidai, *J. Am. Chem. Soc.* **2000**, *122*, 11019–11020.

[5] For versatile nucleophiles, see: a) M. Zhang, H. Yang, Y. Cheng, Y. Zhu, C. Zhu, *Tetrahedron Lett.* **2010**, *51*, 1176–1179; b) P. N. Chatterjee, S. Roy, *J. Org. Chem.* **2010**, *75*, 4413–4423; c) Z. Zhan, J. Yu, H. Liu, Y. Cui, R. Yang, W. Yang, J. Li, *J. Org. Chem.* **2006**, *71*, 8298–8301; d) R. Sanz, A. Martinez, J. M. Alvarez-Gutierez, F. Rodriguez, *Eur. J. Org. Chem.* **2006**, 1383–1386.

[6] For recent reviews, see: a) A. S. Dudnik, N. Chernyak, V. Gevorgyan, *Aldrichimica Acta* **2010**, *43*, 37–46; b) P. Belmont, E. Parker, *Eur. J. Org. Chem.* **2009**, 6075–6089; c) S. F. Kirsch, *Synthesis* **2008**, 3183–3204; for selected references related to the cycloisomerization of pyridine/ynes: d) Y. Xia, A. S. Dudnik, Y. Li, V. Gevorgyan, *Org. Lett.* **2010**, *12*, 5538–5541; e) D. Chernyak, C. Skontos, V. Gevorgyan, *Org. Lett.* **2010**, *12*, 3242–3245; f) D. Chernyak, S. B. Gadamsetty, V. Gevorgyan, *Org. Lett.* **2008**, *10*, 2307–2310; g) B. Yan, Y. Liu, *Org. Lett.* **2007**, *9*, 4323–4326; h) I. V. Seregin, A. W. Schammel, V. Gevorgyan, *Org. Lett.* **2007**, *9*, 3433–3436; i) Y. Liu, Z. Song, B. Yan, *Org. Lett.* **2007**, *9*, 409–412; j) J. T. Kim, V. Gevorgyan, *Org. Lett.* **2002**, *4*, 4697–4699; k) B. Yan, Y. Zhou, H. Zhang, J. Chen, Y. Liu, *J. Org. Chem.* **2007**, *72*, 7783–7786.

[7] a) R. Sanz, D. Miguel, M. Gohain, P. Garcia-Garcia, M. A. Fernandez-Rodriguez, A. Gonzalez-Perez, O. Nieto-Faza, A. R. de Lera, F. Rodriguez, *Chem. Eur. J.* **2010**, *16*, 9818–9828; b) O. Debleds, E. Gayon, E. Ostaszuk, E. Vrancken, J.-M. Campagne, *Chem. Eur. J.* **2010**, *16*, 12207–12213; c) S. Berger, E. Haak, *Tetrahedron Lett.* **2010**, *51*, 6630–6634; d) E. Gayon, O. Debleds, M. Nicouleau, F. Lamaty, A. van der Lee, E. Vrancken, J.-M. Campagne, *J. Org. Chem.* **2010**, *75*, 6050–6053; e) X. Zhang, W. T. Teo, Sally, P. W. H. Chan, *J. Org. Chem.* **2010**, *75*, 6290–6293; f) M. Egi, K. Azechi, S. Akai, *Org. Lett.* **2009**, *11*, 5002–5005; g) A. Aponick, C.-Y. Li, J. Malinge, E. F. Marques, *Org. Lett.* **2009**, *11*, 4624–4627; h) M. Yoshimatsu, T. Yamamoto, A. Sawa, T. Kato, G. Tanabe, O. Muraoka, *Org. Lett.* **2009**, *11*, 2952–2955; i) X. Zhang, W. T. Teo, P. W. H. Chan, *Org. Lett.* **2009**, *11*, 4990–4993; j) Y. Pan, F. Zheng, H. Lin, Z. Zhan, *J. Org. Chem.* **2009**, *74*, 3148–3151; k) X. Xu, J. Liu, L. Liang, H. Li, Y. Li, *Adv. Synth. Catal.* **2009**, *351*, 2599–2604.

[8] C. Enguehard-Gueiffier, A. Gueiffier, *Mini-Rev. Med. Chem.* **2007**, *7*, 888–899.

[9] a) A. R. Katritzky, Y.-J. Xu, H. Tu, *J. Org. Chem.* **2003**, *68*, 4935–4937, and references cited therein;b) S. Husinec, R. Markovic, M. Petkovic, V. Nasufovic, V. Savic, *Org. Lett.* **2011**, *13*, 2286–2289; c) M. Adib, M. Mahdavi, M. A. Noghani, P. Mirxaei, *Tetrahedron Lett.* **2007**, *48*, 7263–7265; d) M. Adib, M. Mahdavi, A. Abbasi, A. H. Jahromi, H. R. Bijanzadeh, *Tet-*

  

*rahedron Lett.* **2007**, *48*, 3217–3220; e) S. Kumar, D. P. Sahu, *ARKIVOC* **2008**, *15*, 88–98; f) C. Enguehard-Gueiffier, C. Croix, M. Hervet, J.-Y. Kazock, A. Gueiffier, M. Abarbri, *Helv. Chim. Acta* **2007**, *90*, 2349–2367; g) J. S. Yadav, B. V. S. Reddy, Y. G. Rao, M. Srinivas, A. V. Narsaiah, *Tetrahedron Lett.* **2007**, *48*, 7717–7720; h) R. Zhang, Y. Hu, *Synth. Commun.* **2007**, *37*, 377–389; i) A. D. C. Parenty, L. Cronin, *Synthesis* **2008**, *9*, 1479–1489; j) M. Adib, E. Shebani, L.-G. Zhu, P. Mirzaei, *Tetrahedron Lett.* **2008**, *49*, 5108–5110; k) M. Bakherad, A. Keivanloo, M. Hashemi, *Synth. Commun.* **2009**, *39*, 1002–1011; l) J. Koubachi, S. Berteina-Raboin, A. Mouaddib, G. Guillaumet, *Synthesis* **2009**, *2*, 271–276; m) H. Wang, Y. Wang, D. Liang, L. Liu, J. Zhang, Q. Zhu, *Angew. Chem. Int. Ed.* **2011**, *50*, 5678–5681.

[10] P. J. Zimmermann, W. Buhr, C. Brehm, A. M. Palmer, M. P. Feth, J. Senn-Bilfinger, W.-A. Simon, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5374–5378.

[11] a) N. Chernyak, V. Gevorgyan, *Angew. Chem. Int. Ed.* **2010**, *49*, 2743–2746; b) P. Liu, L. Fang, X. Lei, G. Lin, *Tetrahedron Lett.* **2010**, *51*, 4605–4608.

[12] For a recent review, see: a) D. A. Engel, G. B. Dudley, *Org. Biomol. Chem.* **2009**, *7*, 4149–4158; for recent examples: b) M. N. Pennell, M. G. Unthank, P. Turner, T. D. Sheppard, *J. Org. Chem.* **2011**, *76*, 1479–1482; c) D. A. Rooke, E. M. Ferreira, *J. Am. Chem. Soc.* **2010**, *132*, 11926–11928; d) D. Wang, X. Ye, X. Shi, *Org. Lett.* **2010**, *12*, 2088–2091; for the amino-Claisen rearrangement, see: e) A. Saito, T. Konishi, Y. Hanzawa, *Org. Lett.* **2010**, *12*, 372–374; f) P. K. Singh, V. K. Singh, *Org. Lett.* **2010**, *12*, 80–83; g) L. Ye, L. Zhang, *Org. Lett.* **2009**, *11*, 3646–3649; h) B. M. Trost, A. C. Gutierrez, R. C. Livingston, *Org. Lett.* **2009**, *11*, 2539–2542; i) L.-Z. Dai, M. Shi, *Chem. Eur. J.* **2008**, *14*, 7011–7018.

[13] a) F. G. Bordwell, *Acc. Chem. Res.* **1988**, *21*, 456–463, and references cited therein;b) G. Kortum, W. Vogel, K. Andrussow, *Pure Appl. Chem.* **1960**, *1*, 190–536; c) D. D. Perrin, *Pure Appl. Chem.* **1969**, *20*, 133–236.

[14] H. Yamabe, A. Mizuno, H. Kusama, N. Wasawa, *J. Am. Chem. Soc.* **2005**, *127*, 3248–3249.

[15] P. G. Cozzi, J. Rudolph, C. Bolm, P. O. Norrby, C. Tomasini, *J. Org. Chem.* **2005**, *70*, 5733–5736.

[16] J. J. Kaminski, D. G. Perkins, J. D. Frantz, D. M. Solomon, A. J. Elliott, P. J. S. Chiu, J. F. Long, *J. Med. Chem.* **1987**, *30*, 2047–2051.

[17] An authoritative sample of regioisomer **8** was prepared from 1-bromo-1,3-diphenylpropan-2-one and 2-aminopyridine according to ref.[16]

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