Article
DOI: 10.1002/bkcs.11228 *H. J. Park and J.-G. Jun* **BULLETIN** OF THE KOREAN CHEMICAL SOCIETY

# An Efficient Copper-catalyzed Nucleophilic Addition to *N*-Acyliminium Ions Derived from *N*-Benzyloxycarbonylamino Sulfones: A Novel Approach to C-3 Functionalization of 2-Phenylimidazo[1,2-*a*]pyridine

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*Received April 24, 2017, Accepted July 17, 2017*

A general and efficient method for C-3 functionalization of 2-phenylimidazo[1,2-*a*]pyridine has been developed. The reaction employs $Cu(OTf)_2$ as a catalyst at 10 mol% loading, proceeds in dimethyl sulfoxide solvent, and utilizes bench-stable solid *N*-benzyloxycarbonylamino sulfones derived from aromatic and aliphatic aldehydes as *N*-acyliminium ion precursors. The imidazo[1,2-*a*]pyridine products are obtained in moderate to good yields.

**Keywords:** Imidazo[1,2-*a*]pyridines, *N*-Benzyloxycarbonylamino sulfones, *N*-Acyliminium ions, C—C bond formation, Copper(II) triflate

## Introduction

Imidazopyridine has been recognized as an indispensable pharmacophore due to its ubiquitous presence in numerous bioactive natural products and pharmaceuticals.[1] In particular, imidazo[1,2-*a*]pyridine, a fused bicyclic 5-6-heterocycle with one ring junction nitrogen atom and one extra nitrogen atom in the five-membered ring, is widely encountered in a number of commercial drugs such as alpidem, zolpidem, saripidem, and necopidem (Figure 1). It also embedded in a plethora of compounds involved in the drug development pipeline.[2] Functionalized imidazo[1,2-*a*]pyridines have been investigated as antibacterial,[3] anticancer,[4] antiviral,[5] antifungal,[6] antiulcer,[7] anti-inflammatory,[8] antihypertensive,[9] and β-amyloid detection agents.[10] In addition, few derivatives exhibited enzyme inhibition[11] and antituberculosis activity.[12] As a result, in the past decades, much attention has been devoted toward its synthesis and functionalization by distinct methods.[13] However, some of the methods have been plagued by multiple limitations. Hence, a more general and novel approach for the functionalization of imidazo[1,2-*a*] pyridines is in great demand.

Synthesis of nitrogen-containing compounds *via* easily accessible imine intermediates is one of the most important and convenient routes. As we compared with its counterpart, C═O double bond, C═N double bond is a less reactive group. In general, imines are unstable and *in situ* formation of imines followed by nucleophile addition in one-pot is more convenient approach. However, in this process, several Lewis acids would be deactivated or decomposed due to the presence of amine and that of water formation in the reaction. We can modify the electrophilic aptitude of the C═N bond through a proper choice of the nitrogen-linked group. Electron-withdrawing substituents at the nitrogen atom are able to exert a marked enhancement of the reactivity of the imino derivative. In this context, *N*-acyliminium ions are widely used as electrophiles for the intermolecular addition of carbon-centered nucleophiles for the synthesis of substituted amines that has found widespread use in the rapid assembly of alkaloids and active pharmaceutical ingredients.[14] *N*-Benzyloxycarbonylamino sulfones (**1**), generally referred to as α-amido sulfones, can be conveniently prepared from aldehydes and are generally bench-stable solids, which can be stored for prolonged times.[15] It is known that they can be converted into the corresponding protected imines (*N*-acyliminium ions) on treatment with an appropriate Lewis acid (Scheme 1).[16] These imino derivatives contain a positively charged nitrogen atom and are thus highly suitable for nucleophilic addition. The resulting *N*-acyliminium ions have been widely used in combination with hard metallic reagents, other nonstabilized carbanions, metal-stabilized enolates, and other nucleophiles to prepare a large array of amino derivatives.[15]

Kumar and co-workers reported one-pot three-component synthesis of 1-amidomethyl-imidazo[1,2-*a*]pyridines by condensation of 2-arylimidazo[1,2-*a*]pyridines, aryl/heterocyclic aldehydes, and acetamide using $Yb(OTf)_3$ (ytterbium(III) trifluoromethanesulfonate) as a catalyst.[17] Earlier to this study, Chaubet *et al.* also reported similar type aza-Friedel-Crafts reaction on imidazo[1,2-*a*]pyridine using $TiCl_4$ or thiamine–HCl as catalyst.[18] We were attracted to this important product synthesis but needed a more convenient strategy with greater substrate scope and better reproducibility to reliably deliver a variety of substrates for an ongoing project. In continuation of our research efforts towards the synthesis of bioactive heterocycles using novel approaches,[19] herein, a general and efficient method for C-3 functionalization of 2-phenylimidazo[1,2-*a*]pyridine (**2**)

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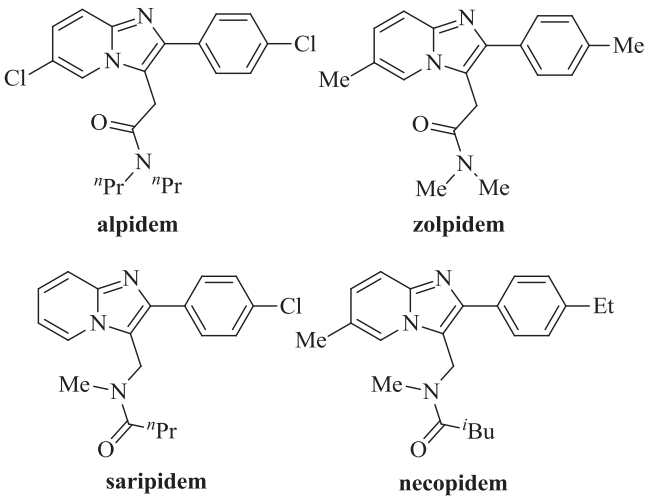



**Figure 1.** Structures of alpidem, zolpidem, saripidem, and necopidem.

by copper-catalyzed nucleophilic addition to *N*-acyliminium ions derived from **1** is described.

## Experimental

All chemicals were obtained from local sources and used as received unless noted otherwise. All solvents were distilled from proper dehydrating agents under nitrogen atmosphere prior to use. For chromatography, commercially available solvents were used without further purification. $^1$H-NMR spectra were recorded on a Varian Mercury-300 MHz FT-NMR (Varian. Inc., Palo Alto, CA, USA) and 75 MHz for $^{13}$C, with the chemical shift (δ) reported in parts per million (ppm) downfield relative to tetramethylsilane (TMS) and the coupling constants (*J*) quoted in Hz. $CDCl_3$ was employed as a solvent and an internal standard. High resolution mass spectra electrospray ionization (HRMS-ESI) was obtained on an Agilent 6220 TOF LC/MS spectrometer (Agilent Technologies, Santa Clara, CA, USA) spectrometer. Melting points were recorded on a MEL-TEMP II (Triad Scientific, Manasquan, NJ, USA) apparatus and were uncorrected. All reactions were monitored by thin-layer chromatography (TLC), followed by exposure of the mixtures to UV light and/or staining with *p*-anisaldehyde and phosphomolybdic acid (PMA) stain to visualize the reaction spots. Column chromatography was performed using silica gel (60–120 mesh, Merck, Darmstadt, Germany).

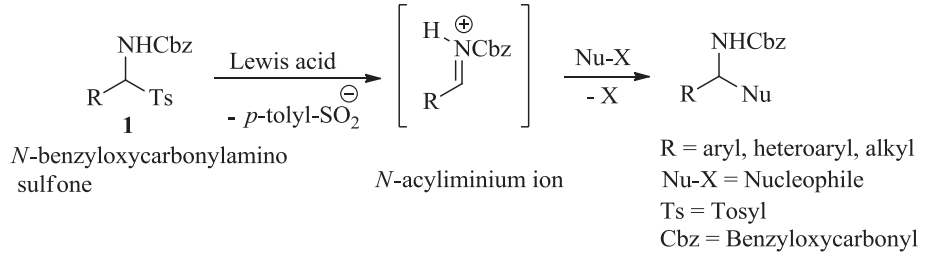
**General Experimental Procedure for the Preparation of 1.** Aldehyde (2.75 mmol) was added to a solution of benzyl carbamate (2.5 mmol) and sodium *p*-toluenesulfinate (2.5 mmol) in water (2.5 mL). The pH was adjusted to approximately 2 with 88% formic acid (*ca*. 0.5 mL) and the mixture was heated at 70°C for 1 h. After cooling, the white solid was filtered and washed sequentially with water and petroleum ether to give α-amido sulfone **1**.

**General Experimental Procedure for the Preparation of 3 using 1 and 2.** To a stirred solution of *N*-benzyloxycarbonylamino sulfone (**1**) (0.24 mmol) and 2-phenylimidazo[1,2-*a*]pyridine (**2**) (0.04 g, 0.20 mmol) in anhydrous dimethyl sulfoxide (DMSO) (2 mL) was added $Cu(OTf)_2$ (0.01 g, 0.02 mmol) at room temperature. The reaction mixture was stirred at 100°C for 24 h under nitrogen atmosphere. After completion of the reaction, cooled to room temperature, water (10 mL) was added and extracted with EtOAc (2 × 20 mL). The combined organic layer was washed with $H_2O$ (2 × 15 mL), brine (15 mL), dried over anhydrous $Na_2SO_4$ and concentrated *in vacuo*. The crude was purified by column chromatography (EtOAc/hexane = 1/3:1/2) to afford the pure product (**3**).

***Benzyl (Phenyl(2-phenylimidazo[1,2-a]pyridin-3-yl)methyl) carbamate (3a).*** Yield: 66%; $R_f$ = 0.27 (EtOAc/hexane = 1/1); white solid; mp 187–189°C; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.70–7.64 (4H, m), 7.40–7.27 (11H, m), 7.22–7.15 (3H, m), 6.76 (1H, d, *J* = 7.8 Hz), 6.65 (1H, t, *J* = 6.9 Hz), 5.70 (1H, d, *J* = 7.8 Hz), 5.09 (2H, s); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 155.8, 145.4, 145.2, 137.9, 136.1, 134.2, 129.2, 129.0, 128.7, 128.6, 128.4, 128.2, 128.1, 126.4, 124.8, 124.0, 118.5, 118.2, 112.6, 67.5, 50.5; HRMS-ESI *m/z* $[M + H]^+$ calcd for $C_{28}H_{24}N_3O_2$: 434.1869, found 434.1861.

***Benzyl ((2-Phenylimidazo[1,2-a]pyridin-3-yl)(p-tolyl)methyl) carbamate (3b).*** Yield: 33%; $R_f$ = 0.25 (EtOAc/hexane = 1/1); off-white solid; mp 180–182°C; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.71–7.60 (4H, m), 7.38–7.29 (8H, m), 7.14–7.09 (5H, m), 6.71 (1H, d, *J* = 8.4 Hz), 6.56 (1H, t, *J* = 6.9 Hz), 5.96 (1H, br s), 5.06 (2H, s), 2.32 (3H, s); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 155.8, 145.2, 145.1 137.8, 136.1, 134.8, 134.2, 129.9, 128.9, 128.6, 128.5, 128.3, 128.1, 126.2, 124.7, 124.2, 118.6, 117.9, 112.4, 67.4, 50.5, 21.3; HRMS-ESI *m/z* $[M + Na]^+$ calcd for $C_{29}H_{25}N_3O_2Na$: 470.1844, found 470.1855.

***Benzyl ((4-Methoxyphenyl)(2-phenylimidazo[1,2-a]pyridin-3-yl)methyl)carbamate (3c).*** Yield: 35%; $R_f$ = 0.31 (EtOAc/




**Scheme 1.** *N*-Benzyloxycarbonylamino sulfones (**1**) as precursors to *N*-acyliminium ions in nucleophilic addition.

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hexane = 1/1); off-white solid; mp 190–192°C; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.67 (2H, d, *J* = 9.0 Hz), 7.64 (2H, d, *J* = 9.0 Hz), 7.39–7.30 (8H, m), 7.17 (1H, td, *J* = 8.7, 1.5 Hz), 7.10 (2H, d, *J* = 8.7 Hz), 6.82 (2H, d, *J* = 8.7 Hz), 6.67 (1H, d, *J* = 8.4 Hz), 6.63 (1H, t, *J* = 8.4 Hz), 5.75 (1H, d, *J* = 7.8 Hz), 5.05 (2H, s), 3.77 (3H, s); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 159.5, 155.8, 145.4, 145.2, 136.3, 134.6, 130.2, 129.1, 128.6, 128.3, 128.2, 127.7, 124.5, 124.1, 118.9, 118.2, 114.8, 112.5, 67.5, 55.6, 50.5; HRMS-ESI *m/z* $[M + Na]^+$ calcd for $C_{29}H_{25}N_3O_3Na$: 486.1794, found 486.1799.

***Benzyl ((4-Bromophenyl)(2-phenylimidazo[1,2-a]pyridin-3-yl)methyl)carbamate (3d).*** Yield: 53%; $R_f$ = 0.27 (EtOAc/hexane = 1/1); off-white solid; mp 191–193°C; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.66–7.62 (4H, m), 7.41–7.32 (10H, m), 7.18 (1H, td, *J* = 7.8, 0.9 Hz), 7.05 (2H, d, *J* = 7.8 Hz), 6.66 (1H, d, *J* = 7.8 Hz), 6.64 (1H, t, *J* = 7.5 Hz ), 5.84 (1H, br s), 5.10 (2H, s); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 155.9, 145.8, 145.4, 137.5, 136.3, 134.4, 132.3, 129.1, 128.7, 128.5, 128.4, 128.3, 128.2, 124.8, 123.9, 122.2, 118.4, 118.3, 112.8, 67.7, 50.5; HRMS-ESI *m/z* $[M + H]^+$ calcd for $C_{28}H_{23}BrN_3O_2$: 512.0974, found 512.0961.

***4-((((Benzyloxy)carbonyl)amino)(2-phenylimidazo[1,2-a]pyridin-3-yl)methyl)phenyl acetate (3e).*** Yield: 51%; $R_f$ = 0.49 (EtOAc/hexane = 1/1); white solid; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.66 (2H, d, *J* = 6.6 Hz), 7.62 (1H, d, *J* = 6.9 Hz), 7.55 (1H, d, *J* = 8.7 Hz), 7.37–7.28 (8H, m), 7.15 (2H, d, *J* = 8.4 Hz), 7.10 (1H, td, *J* = 6.9, 1.2 Hz), 6.98 (2H, d, *J* = 8.4 Hz), 6.72 (1H, d, *J* = 7.8 Hz ), 6.47 (1H, t, *J* = 6.0 Hz), 5.85 (1H, br s), 5.06 (2H, s), 2.25 (3H, s); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 168.9, 155.9, 150.5, 145.4, 145.2, 136.2, 135.6, 134.2, 129.0, 128.6, 128.5, 128.2, 128.1, 128.0, 127.4, 124.6, 124.1, 122.1, 118.4, 117.9, 112.5, 67.4, 50.3, 21.2; HRMS-ESI *m/z* $[M + Na]^+$ calcd for $C_{30}H_{25}N_3O_4Na$: 514.1743, found 514.1752.

***Benzyl ((4-Cyanophenyl)(2-phenylimidazo[1,2-a]pyridin-3-yl)methyl)carbamate (3f).*** Yield: 31%; $R_f$ = 0.17 (EtOAc/hexane = 1/1); off-white solid; mp 193–195°C; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.64 (2H, d, *J* = 9.9 Hz), 7.57–7.50 (4H, m), 7.35–7.28 (10H, m), 7.20 (1H, td, *J* = 8.1, 0.9 Hz), 6.75 (1H, d, *J* = 7.8 Hz), 6.69 (1H, t, *J* = 6.9 Hz), 5.89 (1H, br d, *J* = 8.1 Hz ), 5.15 (2H, s); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 156.0, 146.0, 145.4, 143.7, 136.0, 133.9, 132.8, 129.0, 128.8, 128.7, 128.6, 128.5, 128.4, 127.2, 125.2, 123.6, 118.4, 118.3, 117.6, 113.1, 112.1, 68.0, 50.5; HRMS-ESI *m/z* $[M + H]^+$ calcd for $C_{29}H_{23}N_4O_2$: 459.1821, found 459.1807.

***Benzyl ((4-Nitrophenyl)(2-phenylimidazo[1,2-a]pyridin-3-yl)methyl)carbamate (3g).*** Yield: 41%; $R_f$ = 0.17 (EtOAc/hexane = 1/1); pale yellow solid; mp 188–190°C; $^1$H NMR (300 MHz, $CDCl_3$) δ 8.03 (2H, d, *J* = 8.7 Hz), 7.62 (1H, d, *J* = 6.9 Hz), 7.58 (2H, d, *J* = 9.3 Hz), 7.54 (1H, d, *J* = 6.3 Hz), 7.53 (1H, d, *J* = 6.3 Hz), 7.33–7.27 (9H, m), 7.17 (1H, t, *J* = 7.8 Hz), 6.76 (1H, d, *J* = 7.8 Hz), 6.64 (1H, t, *J* = 6.9 Hz), 6.26 (1H, br s), 5.16 (2H, s); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 156.1, 147.8, 145.6, 145.4, 136.1, 129.1, 128.7, 128.6, 128.5, 128.4, 128.3, 127.4, 125.2, 124.1, 123.6, 118.4, 117.7, 113.1, 67.9, 50.5; HRMS-ESI *m/z* $[M + H]^+$ calcd for $C_{28}H_{23}N_4O_4$: 479.1719, found 479.1713.

***Benzyl (Furan-2-yl(2-phenylimidazo[1,2-a]pyridin-3-yl)methyl)carbamate (3h).*** Yield: 52%; $R_f$ = 0.28 (EtOAc/hexane = 1/1); red color solid; mp 160–162°C; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.94 (1H, d, *J* = 6.9 Hz), 7.68 (2H, d, *J* = 6.9 Hz), 7.55 (1H, d, *J* = 9.0 Hz), 7.40–7.25 (9H, m), 7.09 (1H, t, *J* = 6.9 Hz), 6.61 (1H, d, *J* = 6.6 Hz), 6.58 (1H, t, *J* = 6.6 Hz), 6.36 (1H, br s), 6.25 (1H, t, *J* = 3.0 Hz), 6.12 (1H, d, *J* = 2.4 Hz), 5.01 (2H, s); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 155.6, 150.5, 145.1, 145.0, 142.8, 135.9, 134.0, 129.0, 128.6, 128.5, 128.4, 128.2, 128.1, 128.0, 124.7, 124.4, 117.7, 116.8, 112.4, 110.7, 108.0, 67.3, 46.1; HRMS-ESI *m/z* $[M + H]^+$ calcd for $C_{26}H_{22}N_3O_3$: 424.1661, found 424.1666.

***Benzyl ((2-Phenylimidazo[1,2-a]pyridin-3-yl)(thiophen-2-yl)methyl)carbamate (3i).*** Yield: 50%; $R_f$ = 0.29 (EtOAc/hexane = 1/1); pale yellow color solid; mp 164–166°C; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.80 (1H, d, *J* = 6.9 Hz), 7.71 (2H, d, *J* = 6.9 Hz), 7.67 (1H, d, *J* = 9.0 Hz), 7.42–7.27 (9H, m), 7.19 (1H, td, *J* = 7.8, 0.9 Hz), 6.93 (1H, t, *J* = 3.3 Hz), 6.87 (1H, d, *J* = 7.8 Hz), 6.78 (1H, d, *J* = 3.3 Hz), 6.68 (1H, t, *J* = 6.3 Hz), 5.95 (1H, br s), 5.05 (2H, s); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 155.4, 145.3, 145.1, 142.5, 135.9, 134.0, 129.0, 128.7, 128.6, 128.3, 128.2, 127.6, 126.0, 125.4, 124.9, 124.3, 118.2, 118.1, 112.7, 67.6, 47.8; HRMS-ESI *m/z* $[M + H]^+$ calcd for $C_{26}H_{22}N_3O_2S$: 440.1433, found 440.1442.

***Benzyl (1-(2-Phenylimidazo[1,2-a]pyridin-3-yl)hexyl)carbamate (3j).*** Yield: 31%; $R_f$ = 0.25 (EtOAc/hexane = 1/1); pale yellow color liquid; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.66 (2H, d, *J* = 6.3 Hz), 7.60 (1H, d, *J* = 8.7 Hz), 7.39–7.27 (9H, m), 7.13 (1H, t, *J* = 7.8 Hz), 6.73, (1H, d, *J* = 7.8 Hz), 5.56 (1H, br s), 5.26 (1H, q, *J* = 7.8 Hz), 5.04 (2H, s), 1.82 (2H, m), 1.18–1.05 (6H, m), 0.73 (3H, t, *J* = 6.9 Hz ); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 156.0, 144.6, 144.2, 136.1, 135.0, 129.4, 128.6, 128.4, 128.2, 128.1, 128.0, 124.3, 120.0, 117.8, 112.4, 67.2, 47.6, 33.3, 31.3, 26.2, 22.5, 14.1; HRMS-ESI *m/z* $[M + Na]^+$ calcd for $C_{27}H_{29}N_3O_2Na$: 450.2157, found 450.2149.

***Benzyl ((4-Hydroxyphenyl)(2-phenylimidazo[1,2-a]pyridin-3-yl)methyl)carbamate (3k).*** To a stirred solution of **3e** (0.12 g, 0.24 mmol) in MeOH (4 mL) was added $K_2CO_3$ (0.07 g, 0.49 mmol) and stirred the mixture at room temperature for 2 h. After completion of the reaction, solvent was removed under reduced pressure. The crude was neutralized with 1 N HCl and extracted with EtOAc (2 × 20 mL). Combined organic layer was washed with water (15 mL), brine (15 mL), dried over anhydrous $Na_2SO_4$ and concentrated *in vacuo* to afford the pure product **3f** (0.08 g, 75%) as white solid. $R_f$ = 0.34 ($CH_2Cl_2$/MeOH = 10/1); mp 213–215°C; $^1$H NMR (300 MHz, DMSO) δ 9.51 (1H,

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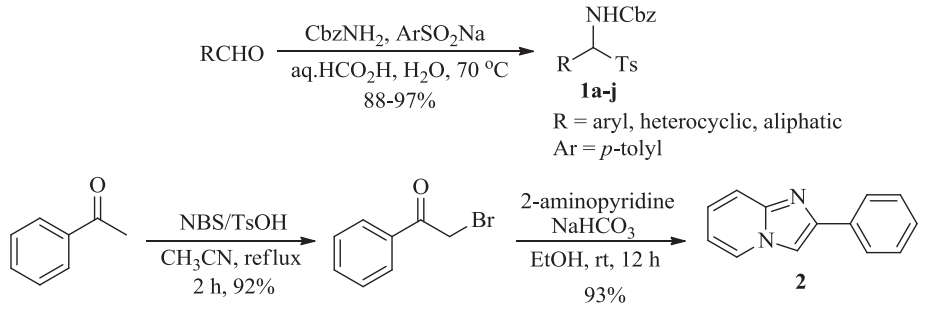



**Scheme 2.** Synthesis of *N*-benzyloxycarbonylamino sulfones (**1**) and 2-phenylimidazo[1,2-*a*]pyridine (**2**).

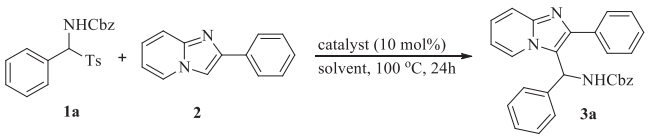
s), 8.74 (1H, d, $J$ = 7.2 Hz), 8.31 (1H, s), 8.14 (1H, d, $J$ = 6.3 Hz), 7.79 (2H, d, $J$ = 6.3 Hz), 7.64 (1H, d, $J$ = 9.0 Hz), 7.46–7.23 (8H, m), 6.87 (2H, d, $J$ = 7.8 Hz), 6.80 (1H, t, $J$ = 6.9 Hz), 6.71 (2H, d, $J$ = 6.3 Hz), 6.59 (1H, d, $J$ = 7.8 Hz), 5.01 (2H, q, $J$ = 8.7 Hz); $^{13}$C NMR (75 MHz, DMSO) δ 156.6, 155.9, 144.2, 143.6, 136.7, 134.2, 128.3, 128.2, 127.7, 127.5, 127.1, 125.9, 124.8, 119.0, 116.9, 115.5, 111.7, 65.8, 49.2; HRMS-ESI *m/z* $[M + H]^+$ calcd for $C_{28}H_{24}N_3O_3$: 450.1818, found 450.1804.

## Results and Discussion

We reasoned that C-3 functionalization of **2** could be achieved by a Lewis-acid catalyzed nucleophilic addition of **2** to the *N*-acyliminium ions generated from **1**. To test this hypothesis, synthesis of **1a–1j** was achieved in high yields (88–95%) following the literature procedure,[15,20] whereas, **2** was obtained in 93% yield by condensation of 2-aminopyridine and phenacyl bromide, which in turn procured from acetophenone (Scheme 2). To check the feasibility of our envisioned nucleophilic addition of **2**, we selected **1a** (R = Ph) as a model substrate. We scanned a variety of catalysts for C-3 functionalization of **2** (Table 1). $Cu(OTf)_2$ (copper(II) trifluoromethanesulfonate) was found to be the best catalyst for the reaction between **1a** and **2** in DMF (dimethylformamide) at 100°C, affording **3a** in 56% yield (Table 1, entry 6). Changing the reaction solvent to DMSO increased the yield from 56 to 66% (Table 1, entry 11). Running the reaction without a catalyst resulted in no product formation and the starting materials were recovered. Other catalysts $Bi(OTf)_3$, $Yb(OTf)_3$, $Zn(OTf)_3$, and $La(OTf)_3$ also produced **3a** in comparable yields (Table 1, entries 13–16). We were pleased that by utilizing $Cu(OTf)_2$, the product **3a** could be obtained in 24 h. Of note, several reactions that we tried were significantly slower and with lower yields when the catalyst loading was less than 10 mol% and yield improvement was not significant when the catalyst loading was more than 10 mol%. In other solvents such as THF, $CH_2Cl_2$, acetonitrile, and acetone lower yields of **3a** were noticed. The synthesis of **3a** was also examined *via* a one-pot three-component reaction (3CR) between benzaldehyde, benzyl carbamate and **2** using 88% aqueous formic acid at 70°C in $H_2O$, like the condition applied for **1a** preparation but **3a** formation was not observed. In addition, **3a** obtained in poor yields when the above 3CR reaction conducted using 10 mol% of $Cu(OTf)_2$ as a catalyst in DMSO at 100°C for 24 h. The scope of this reaction was next investigated with a representative selection of *N*-benzyloxycarbonylamino sulfones (**1**).

As shown in Scheme 3, *N*-benzyloxycarbonylamino sulfones (**1**) derived from various aldehydes (aromatic, heterocyclic, and aliphatic) underwent the present conversion smoothly (Scheme 3). Aromatic aldehydes containing both

**Table 1.** Optimization study for the C-3 functionalization of **2** using **1a**.[a]




| Entry | Catalyst | Solvent | Yield[b] (%) |
|---|---|---|---|
| 1 | No catalyst | DMF | N.R.[c] |
| 2 | $InCl_3$ | DMF | 31 |
| 3 | $AlCl_3$ | DMF | 27 |
| 4 | $FeCl_3$ | DMF | 16 |
| 5 | $BF_3{\cdot}OEt_2$ | DMF | 37 |
| 6 | $Cu(OTf)_2$ | DMF | 56 |
| 7 | $Bi(OTf)_3$ | DMF | 47 |
| 8 | $Yb(OTf)_3$ | DMF | 35 |
| 9 | $Zn(OTf)_3$ | DMF | 42 |
| 10 | $La(OTf)_3$ | DMF | 51 |
| 11 | $Cu(OTf)_2$ | DMSO | 66 |
| 12 | $InCl_3$ | DMSO | 36 |
| 13 | $Bi(OTf)_3$ | DMSO | 63 |
| 14 | $Yb(OTf)_3$ | DMSO | 63 |
| 15 | $Zn(OTf)_3$ | DMSO | 64 |
| 16 | $La(OTf)_3$ | DMSO | 65 |

[a] Reaction conditions: **1a** (0.24 mmol), **2** (0.2 mmol), catalyst (10 mmol%), and solvent (2 mL) at 100°C for 24 h.
[b] Isolated yield.
[c] No reaction.

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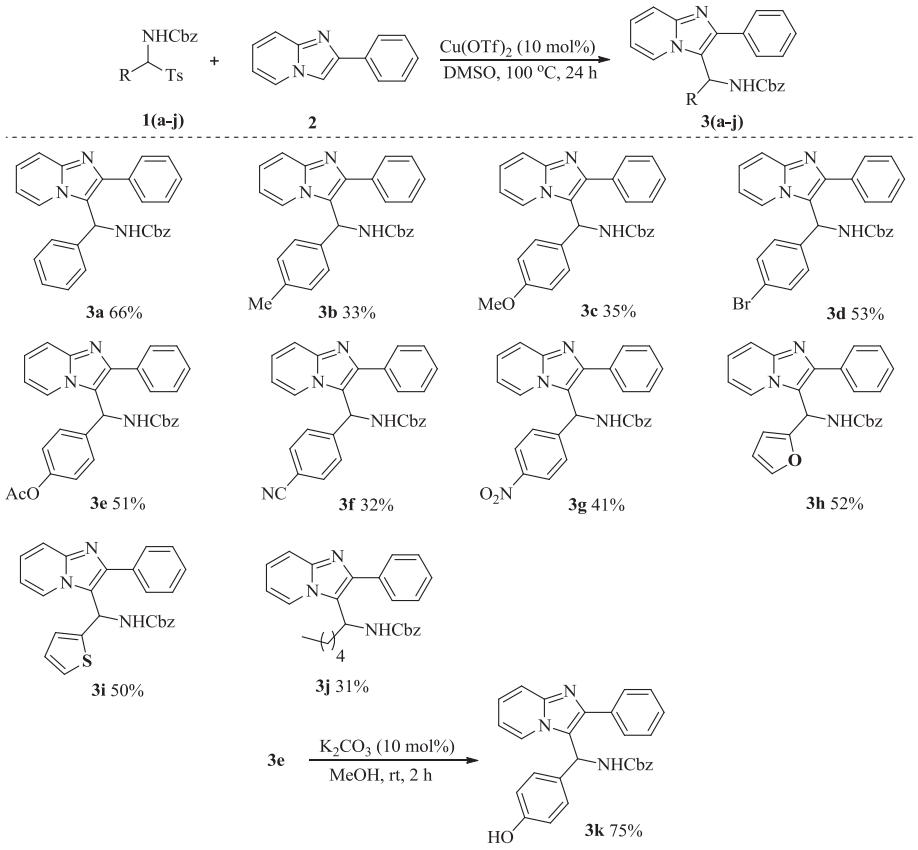


**Scheme 3.** Synthesis of C-3 functionalized imidazo[1,2-*a*]pyridines (**3a–k**) using *N*-benzyloxycarbonylamino sulfones (**1a–j**) and 2-phenylimidazo[1,2-*a*]pyridine (**2**).

electron-donating and electron-withdrawing groups were used to prepare the sulfones. Various functional groups such as methyl, ether, acetoxy, bromo, cyano, and nitro remained intact. The sulfones derived from an acid sensitive aldehyde such as furfuraldehyde also produced the corresponding C-3 functionalized imidazo[1,2-*a*]pyridine, **3h** in moderate yield. Treatment of imidazo[1,2-*a*]pyridine, **3e** with $K_2CO_3$ in MeOH at room temperature afforded the phenolic imidazo[1,2-*a*]pyridine, **3f** in 75% yield. Effortless deprotection of Cbz-(benzyloxycarbonyl) protecting group in the products **3a–3k** under mild conditions is an added advantage of the protocol. The structures of the products were established from their spectroscopic (1H NMR, $^{13}C$ NMR, ESI-MS, and HRMS) data.

## Conclusion

Using the readily accessible bench-stable *N*-benzyloxycarbonylamino sulfones (**1**) as *N*-acyliminium ion precursors, C-3 functionalization of 2-phenylimidazo [1,2-*a*]pyridine (**2**) has been successfully accomplished in moderate to good yields using copper(II) trifluoromethanesulfonate as a catalyst. *N*-Benzyloxycarbonylamino sulfones derived from aromatic, heterocyclic, and aliphatic aldehydes underwent the present conversion. Moreover, this reaction protocol was well tolerated with various functional groups and having Cbz group, which can be easily deprotected. We believe that this method could be found applications in the preparation of functionalized imidazo [1,2-*a*]pyridine library for activity screening.

**Acknowledgments.** This research has been performed as a cooperation project of "Enhancement of Korea Chemical Bank" and also supported by the Korea Research Institute of Chemical Technology (KRICT), South Korea.

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