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ORGANOCOPPER-MEDIATED TWO-COMPONENT S_N2' -SUBSTITUTION CASCADE TOWARDS *N*-FUSED HETEROCYCLES*

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Abstract

Organocuprates efficiently undergo reaction with heterocyclic propargyl mesylates at low temperature to produce *N*-fused heterocycles. The copper reagent plays a "double duty" in this cascade transformation, which proceeds through an S_N2' -substitution followed by a consequent cycloisomerization step.

Keywords

allenes; indolizines; propargyl mesylates; cycloisomerization; synthetic methods

The transition-metal (TM)-catalyzed cycloisomerization approach is a powerful tool for the assembly of various heterocyclic scaffolds [1–3]. We have developed the base-assisted Cu-catalyzed cycloisomerization of conjugated alkynylpyridines **1** into monosubstituted *N*-fused heterocycles **2** [4–7] (Scheme 1, equiv. 1). Later, our group and others reported alternative methods for cycloisomerization of skipped propargyl imines **3** into 1,2- or 1,3-disubstituted *N*-fused heterocycles **4** [8–13] (Scheme 1, eq. 2). Although both approaches are quite general with respect to the heterocyclic cores, they still have certain limits. Thus, the former method is restricted to the synthesis of heterocycles that do not possess substituents at the C-1 and C-2 positions, whereas the latter approach is limited to the oxygen-based substituents at C-1 (OR^2), as propargylic precursors **3** are normally prepared from the corresponding heterocyclic aldehydes. Aiming at the development of alternative approaches toward heterocyclic units with different substitution patterns, as well as at expanding the scope of heterocyclic scaffolds, we have recently developed a complementary protocol for cycloisomerization of propargyl-containing substrates **5** into *N*-fused heterocycles **6** (Scheme 1, eq. 3) [14]. Not only does this method give access to C-1 alkyl- or aryl-substituted heterocycles, unavailable by existing cycloisomerization techniques, but it also holds promise for a quick assembly of libraries of heterocyclic compounds *via* the two-component coupling/cycloisomerization strategy. Herein, we summarize our recent developments in this area and present a more detailed discussion of the scope and mechanism of this promising transformation.

It was suggested that the copper-catalyzed cycloisomerization of alkynylpyridines **1** into the monosubstituted heterocycles **2** proceeds *via* a 1,3-disubstituted allenyl intermediate (Scheme 1, eq. 1) [4–7]. Accordingly, we aimed at the analogous 1,1,3-trisubstituted allenyl

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intermediates *en route* to 1,3-disubstituted *N*-fused heterocyclic cores. Apparently, these reactive allenyl intermediates **8** can be generated in situ *via* the S_N2' -substitution [15–17] of the corresponding propargyl esters **5** with soft nucleophiles (Scheme 2). Scheme 2

We chose to employ the organocopper nucleophiles **7** [18–20], based on the reasoning that, potentially, the copper reagent (or the copper byproduct) can also mediate the subsequent cycloisomerization step of allene **8** into the heterocycle **6**, thus playing a "double duty" in this transformation [21, 22]. A feasibility of the substitution/cycloisomerization cascade was examined employing pyridyl-containing propargyl alcohol derivatives **5** (LG = carboxylate, sulfonate, phosphate) in the presence of various copper reagents [23–25] (Table 1). It was found that the higher-order alkyl cuprate reagents were not efficient in this transformation (entries 1–3). In contrast, the lower-order cyanocuprate [MeCu(CN)Li] reacted with mesylate **5** (LG = OMs) very efficiently, affording the C-1 alkylated indolizine derivative in 90% yield (entry 5). Attempts to substitute mesylate with another leaving group [26, 27] were not successful (entries 6–12). Brief optimization indicated that employment of a phenyl copper reagent was reasonably efficient for the construction of the C-1 phenylsubstituted indolizine (entry 16). Importantly, in all cases, the corresponding allenes **8** were observed at early stages of the reaction, thus suggesting that the cycloisomerizations of propargyl imines proceed *via* allenic intermediates (Scheme 1) [4–13] and **8** (Scheme 2).

Next, the generality of this novel cascade transformation with differently substituted propargyl mesylates **5** was examined (Table 2). Thus, secondary alkyl-substituted mesylates **5a** and **5b** underwent smooth cyclization upon treatment with primary (**7a–c**), secondary (**7d**), and tertiary (**7e**) lower-order cyanocuprates to produce the corresponding indolizines **6** in modest to excellent yields (Table 2, entries 1–9). Noteworthy, primary mesylate **5e** can also be employed in this reaction, giving access to monosubstituted indolizine **6ea**, a heterocycle, which can be further elaborated at C-3 *via* a direct C–H functionalization protocol [28–30]. The secondary aryl-substituted mesylates **5f–k** were also efficient in this cyclization, producing (C-3)-arylated indolizines in good yields. Markedly, methoxy (entry 12), ester (entry 13), chloro (entry 14), cyano (entry 15), and nitro (entry 16) functionalities were perfectly tolerated under these reaction conditions. It was also shown that pyrroloquinoline (entries 18 and 19) and pyrroloisoquinoline (entry 20) cores can efficiently be assembled *via* this protocol. As discussed above, phenyl copper-mediated cyclization of mesylate **5a** produced (C-1)-arylsbstituted indolizine **6af** in 71% yield. Likewise, application of the same reagent to cyclization of **5l** led to formation of arylated pyrroloquinolines **6lf**, although in only 51% yield (Table 2, entry 19).

We also inspected the feasibility of a stepwise approach toward *N*-fused heterocycles **6** (Table 3, Scheme 3). It was found that addition of cuprate reagents to the mesylates **5** at -78°C in 1 h led to formation of the allenes **8** in varying yields (27–89%).

The next step, cycloisomerization of allenes **8** under the standard conditions [4], was even less efficient, producing trace to low yields of indolizines **6** (Scheme 3). Evidently, due to low stability of the pyridyl allenes **8** and low yields of their cyclization under the catalytic cyclization conditions [4], the two-step process appeared to be much less efficient compared to the cascade substitution/cycloisomerization process (Table 2). Moreover, treatment of the freshly prepared allene **8d** with one equivalent of organocopper reagent **7d** did not result in the formation of the desired indolizine **6ad** at all, thus suggesting that the copper by-product, but not the cuprate reagent, is responsible for the cycloisomerization step under one-pot cycloisomerization conditions.

We envision the following mechanism for the substitution/cycloisomerization cascade of propargyl mesylates **5** with copper reagents into the *N*-fused heterocycles **6** (Scheme 4).

Initially, S_N2' -substitution of the mesylate group in compound **5** leads to allene **8**, which, upon intramolecular nucleophilic attack of a pyridyl nitrogen at the Cu-activated distal double bond of allene, produces cyclic intermediates **10**. The latter can transform into product **6** either *via* the deprotonation-protonation sequence (Path A) or through the 1,2-hydride shift in the carbene intermediate **10** (Path B). To verify which mechanism operates, we performed a deuterium-labeling experiment. To this end the isotopically pure alkyne **5b-d** was synthesized [14] and subjected to the standard cycloisomerization conditions.

Indeed, if the reaction proceeds *via* Path A, then the cyclization of alkyne **5b-d** should produce indolizine **6ba**, a product with significant or total deuterium loss [4]. In comparison, the end game *via* Path B would give **6ba-d** with absolute preservation of the deuterium label [31, 32]. It was found that the reaction produced indolizine **6ba** with total deuterium loss, hence strongly supporting Path A.

Alternatively (Path C), the S_N2' -substitution of mesylate may lead to the intermediate **11**, which upon 5-*exo-trig* cyclization would form the zwitterion **12**. Deprotonation-protonation of the latter would produce heteroaryl copper intermediate **13**. Subsequent reductive elimination (RE) of **13** would form the product **6ba**. The feasibility of this path was supported by the observed (GC/MS analysis) formation of monosubstituted indolizine **14** upon aqueous quench of the reaction mixture at early stages of the reaction.

In summary, we have developed a novel organocopper-mediated two-component coupling/cycloisomerization cascade transformation. This mild and efficient method allows for easy synthesis of C-1 alkyl- and aryl-substituted *N*-fused heterocycles, such as indolizines, pyrroloquinolines, and pyrroloisoquinolines, from easily available starting materials. It deserves mentioning that these important heterocyclic scaffolds [33–35] with alkyl or aryl substituents at C-1 are not available *via* the existing cycloisomerization methods.

EXPERIMENTAL

NMR spectra were recorded on a Bruker Avance DRX-500 and Bruker Avance DRX-400 instruments. HRMS analysis was performed on a Micromass 70-VSE high-resolution mass spectrometer. GC/MS analysis was performed on a Hewlett-Packard Model 6890 GC interfaced to a Hewlett Packard Model 5973 mass selective detector (15 m $\times$ 0.25 mm capillary column, HP-5MS). Column chromatography was carried out employing Silicycle Silica-P Flash silica gel (40–63 μ m). Precoated silica gel plates F-254 were used for thinlayer analytical chromatography. All manipulations with air-sensitive materials were conducted under argon atmosphere using a combination of glovebox and standard Schlenk techniques.

1-Alkylindolizines **6** (General Method)

Mesylate **5** was prepared from the respective propargylic alcohol [14] (1.0 mmol), which was placed into a flame-dried round-bottomed flask which was then filled with 6 ml of dry THF and cooled to -50°C under Ar. After that, 121 mg (167 μ l, 1.2 mmol) Et_3N was added neat *via* a syringe, followed by 137 mg (93 μ l, 1.2 mmol) of neat MsCl . The solution was stirred for 30 min at -50°C , controlling the formation of mesylate **5** by TLC. Meantime, 116 mg (1.3 mmol) CuCN was placed into another flame-dried roundbottomed flask, which was then filled with *ca* 2.5 ml of dry THF and cooled to -50°C under Ar. An appropriate organolithium reagent (1.3 mmol) was added dropwise, and the yellowish suspension was stirred for 30 min at -50°C until no CuCN was visible at the bottom of the flask. After complete conversion of alcohol to mesylate **5**, the flask with cyanocuprate **7** was cooled to -78°C and the mesylate was transferred to a flask with cyanocuprate *via* a cannula with cotton at the end, avoiding transfer of precipitated triethylammonium chloride. The mixture

was stirred for 2 h at -78°C , and then it was allowed to warm to room temperature, controlling the formation of indolizine **6** by GC/MS and TLC. After 5 h at room temperature, the reaction was complete, and it was quenched with 15 ml NH_4Cl (aq) sat. NH_3 (aq) sat., 10:1 and extracted with diethyl ether (3×15 ml). The organic extracts were then dried over MgSO_4 , followed by filtration and evaporation. Purification by column chromatography (silica gel, EtOAc–hexane, 1:20) provided product **6**.

1,3-Dimethylindolizine (6aa)

^1H NMR spectrum (500 MHz, C_6D_6), δ , ppm (J , Hz): 7.21 (1H, d, $J = 9.0$); 7.09 (1H, d, $J = 7.1$); 6.37–6.43 (2H, m); 6.17 (1H, t, $J = 6.7$); 2.35 (3H, s); 2.00 (3H, s). ^{13}C NMR spectrum (126 MHz, C_6D_6), δ , ppm: 130.2; 121.9; 118.7; 118.1; 114.8; 113.8; 109.9; 107.7; 11.5; 11.1. Found, m/z (EI): 145.0893 $[\text{M}]^+$. $\text{C}_{10}\text{H}_{11}\text{N}$. Calculated, m/z : 145.0891.

1-Butyl-3-methylindolizine (6ab)

^1H NMR spectrum (500 MHz, CDCl_3), δ , ppm (J , Hz): 7.59 (1H, d, $J = 7.1$); 7.33 (1H, d, $J = 9.0$); 6.51–6.57 (1H, m); 6.43–6.49 (2H, m); 2.74 (2H, t, $J = 7.6$); 2.44 (3H, s); 1.64 (2H, quin, $J = 7.6$); 1.36–1.43 (2H, m); 0.95 (3H, t, $J = 7.3$). ^{13}C NMR spectrum (126 MHz, CDCl_3), δ , ppm: 128.9; 121.4; 118.4; 117.4; 113.4; 112.9; 112.8; 109.5; 33.8; 25.2; 22.6; 14.0; 11.5. Found, m/z (EI): 187.1359 $[\text{M}]^+$. $\text{C}_{13}\text{H}_{17}\text{N}$. Calculated, m/z : 187.1361.

1-Hexyl-3-methylindolizine (6ac)

^1H NMR spectrum (500 MHz, C_6D_6), δ , ppm (J , Hz): 7.31 (1H, d, $J = 9.0$); 7.09 (1H, d, $J = 7.2$); 6.46 (1H, s); 6.42 (1H, dd, $J = 8.9$, $J = 6.5$); 6.18 (1H, t, $J = 6.3$); 2.82 (2H, t, $J = 7.5$); 2.02 (3H, s); 1.65–1.78 (2H, m); 1.40 (2H, s); 1.22–1.33 (4H, m); 0.88 (3H, t, $J = 7.0$). ^{13}C NMR spectrum (126 MHz, C_6D_6), δ , ppm: 129.9; 121.9; 118.7; 118.1; 113.9; 113.8; 113.6; 109.9; 32.6; 32.4; 30.0; 26.4; 23.5; 14.7; 11.6. Found, m/z (EI): 215.1672 $[\text{M}]^+$. $\text{C}_{15}\text{H}_{21}\text{N}$. Calculated, m/z : 215.1674.

1-sec-Butyl-3-methylindolizine (6ad)

^1H NMR spectrum (500 MHz, C_6D_6), δ , ppm (J , Hz): 7.30 (1H, d, $J = 9.1$); 7.08 (1H, d, $J = 7.1$); 6.38–6.43 (2H, m); 6.18 (1H, t, $J = 6.7$); 2.96 (1H, d, $J = 7.2$); 2.01 (3H, s); 1.65–1.76 (2H, m); 1.37 (3H, d, $J = 7.0$); 0.92 (3H, t, $J = 7.3$). ^{13}C NMR spectrum (126 MHz, C_6D_6), δ , ppm: 129.5; 121.9; 118.9 (2C); 118.1; 113.9; 111.3; 110.0; 33.2; 32.5; 23.3; 13.1; 11.7. Found, m/z (EI): 187.1359 $[\text{M}]^+$. $\text{C}_{13}\text{H}_{17}\text{N}$. Calculated, m/z : 187.1361.

1-tert-Butyl-3-methylindolizine (6ae)

^1H NMR spectrum (500 MHz, CDCl_3), δ , ppm: 7.53–7.70 (2H, m); 6.44–6.65 (3H, m); 2.47 (3H, s); 1.50 (9H, s). ^{13}C NMR spectrum (126 MHz, CDCl_3), δ , ppm: 127.5; 122.3; 121.7; 119.6; 117.5; 113.3; 111.2; 109.3; 31.8; 31.6; 11.5. Found, m/z (EI): 187.1360 $[\text{M}]^+$. $\text{C}_{13}\text{H}_{17}\text{N}$. Calculated, m/z : 187.1361.

1-Methyl-3-pentylindolizine (6ba)

^1H NMR spectrum (500 MHz, C_6D_6), δ , ppm (J , Hz): 7.27 (1H, d, $J = 7.2$); 7.23 (1H, d, $J = 8.9$); 6.46 (1H, s); 6.41 (1H, dd, $J = 8.7$, $J = 6.5$); 6.17–6.22 (1H, m); 2.47 (2H, t, $J = 7.6$); 2.37 (3H, s); 1.52–1.60 (2H, m); 1.19–1.26 (4H, m); 0.85 (3H, t, $J = 6.97$). ^{13}C NMR spectrum (126 MHz, C_6D_6), δ , ppm: 123.7; 121.9; 118.3; 113.9 (2C); 109.8; 107.7; 101.6; 32.4; 27.7; 26.4; 23.2; 14.6; 11.1. Found, m/z (EI): 201.1519 $[\text{M}]^+$. $\text{C}_{14}\text{H}_{19}\text{N}$. Calculated, m/z : 201.1517.

1-Butyl-3-pentylindolizine (6bb)

¹H NMR spectrum (500 MHz, C₆D₆), δ, ppm (*J*, Hz): 7.26–7.33 (2H, m); 6.52 (1H, s); 6.42 (1H, dd, *J* = 9.2, *J* = 6.6); 6.20 (1H, t, *J* = 6.8); 2.82 (2H, t, *J* = 7.5); 2.48 (2H, t, *J* = 7.7); 1.67–1.75 (2H, m); 1.53–1.62 (2H, m); 1.36–1.46 (2H, m); 1.19–1.28 (4H, m); 0.93 (3H, t, *J* = 7.4); 0.83–0.89 (3H, m). ¹³C NMR spectrum (126 MHz, C₆D₆), δ, ppm: 130.0; 123.8; 122.0; 118.4; 114.0; 113.6; 112.8; 109.9; 34.6; 32.4; 27.7 (2C); 26.5; 26.2; 23.3; 23.2; 14.6. Found, *m/z* (EI): 243.19805 [M]⁺. C₁₇H₂₅N. Calculated, *m/z*: 243.19870.

1,3,6-Trimethylindolizine (6ca)

¹H NMR spectrum (500 MHz, CDCl₃), δ, ppm (*J*, Hz): 7.41 (1H, s); 7.27 (1H, d, *J* = 9.1); 6.46 (1H, d, *J* = 8.9); 6.40 (1H, s); 2.45 (3H, s); 2.39 (3H, s); 2.29 (1H, s). ¹³C NMR spectrum (126 MHz, CDCl₃), δ, ppm: 128.3; 118.8; 118.6; 117.9; 116.8 (2C); 113.3; 106.7; 18.6; 11.4; 10.4. Found, *m/z* (EI): 159.1046 [M]⁺. C₁₁H₁₃N. Calculated, *m/z*: 159.1048.

1-Butyl-3-methyl-6-(trifluoromethyl)indolizine (6db)

¹H NMR spectrum (500 MHz, C₆D₆), δ, ppm (*J*, Hz): 7.33 (1H, s); 7.15 (1H, s); 6.89 (1H, d, *J* = 9.4); 6.51 (1H, d, *J* = 9.5); 2.69 (2H, t, *J* = 7.5); 1.68 (3H, s); 1.56–1.65 (2H, m); 1.28–1.38 (2H, m); 0.91 (3H, t, *J* = 7.3). ¹³C NMR spectrum (126 MHz, C₆D₆), δ, ppm: 141.2; 126.0; 120.5; 120.4; 119.3; 117.4; 117.3; 114.1; 112.4; 110.2; 32.8; 23.5; 22.5; 13.9; 8.0. Found, *m/z* (EI): 254.11581 [M–H]⁺. C₁₄H₁₅F₃N. Calculated, *m/z*: 254.11566.

1-Methylindolizine (6ea)

¹H NMR spectrum (500 MHz, C₆D₆), δ, ppm (*J*, Hz): 7.25–7.27 (1H, m); 7.22 (1H, d, *J* = 9.2); 6.96 (1H, d, *J* = 2.6); 6.71 (1H, d, *J* = 2.4); 6.43 (1H, ddd, *J* = 9.0, *J* = 6.4, *J* = 1.0); 6.10–6.08 (1H, m); 2.40 (3H, s). ¹³C NMR spectrum (126 MHz, C₆D₆), δ, ppm: 130.7; 125.5; 118.1; 115.4; 115.3; 111.8; 109.9; 108.5; 11.1. Found, *m/z* (EI): 131.08588 [M]⁺. C₉H₉N. Calculated, *m/z*: 131.07350.

1-Methyl-3-phenylindolizine (6fa)

¹H NMR spectrum (500 MHz, CDCl₃), δ, ppm (*J*, Hz): 8.03 (1H, d, *J* = 7.1); 7.33 (1H, d, *J* = 8.9); 7.07–7.19 (4H, m); 6.89–6.98 (2H, m); 6.50–6.67 (1H, m); 6.34 (1H, t, *J* = 6.7); 2.09 (3H, s). ¹³C NMR spectrum (126 MHz, CDCl₃), δ, ppm: 132.0; 123.0; 129.07; 128.3; 126.2; 121.8; 121.5; 117.5; 115.0; 109.6; 109.5; 109.3; 9.3. Found, *m/z* (EI): 207.1044 [M]⁺. C₁₅H₁₃N. Calculated, *m/z*: 207.1048.

1-Butyl-3-(4-methoxyphenyl)indolizine (6gb)

¹H NMR spectrum (500 MHz, C₆D₆), δ, ppm (*J*, Hz): 7.96 (1H, d, *J* = 7.2); 7.26–7.35 (3H, m); 6.76–6.85 (3H, m); 6.41 (1H, dd, *J* = 8.6, *J* = 6.8); 6.10 (1H, t, *J* = 7.3); 3.33 (3H, s); 2.81 (2H, t, *J* = 7.5); 1.65–1.78 (2H, m); 1.35–1.47 (2H, m); 0.94 (3H, t, *J* = 7.4). ¹³C NMR spectrum (126 MHz, C₆D₆), δ, ppm: 159.6; 131.1; 130.2 (2C); 126.1; 125.0; 122.6; 118.5; 115.4; 115.1; 114.7; 110.6; 55.2; 34.4; 26.1; 23.3; 14.6. Found, *m/z* (EI): 279.16160 [M]⁺. C₁₉H₂₁NO. Calculated, *m/z*: 279.16232.

Methyl 4-(1-methylindolizin-3-yl)benzoate (6ha)

¹H NMR spectrum (500 MHz, CDCl₃), δ, ppm (*J*, Hz): 8.14–8.20 (2H, m); 8.08 (1H, dd, *J* = 7.2, *J* = 0.9); 7.52–7.60 (2H, m); 7.31–7.36 (1H, m); 6.69 (1H, ddd, *J* = 8.9, *J* = 6.5, *J* = 0.9); 6.38–6.47 (2H, m); 3.97 (3H, s); 2.35 (3H, s). ¹³C NMR spectrum (126 MHz, CDCl₃), δ, ppm: 166.8; 136.5; 133.1; 130.1; 129.1 (2C); 128.3; 124.2; 122.0; 118.6; 117.7; 110.2; 101.4; 52.1; 12.5. Found, *m/z* (EI): 265.1104 [M]⁺. C₁₇H₁₅NO₂. Calculated, *m/z*: 265.1103.

3-(4-Chlorophenyl)-1-methylindolizine (6ia)

¹H NMR spectrum (500 MHz, CDCl₃), δ, ppm (*J*, Hz): 8.20 (1H, d, *J* = 8.4); 7.29–7.57 (6H, m); 6.75 (1H, s); 6.68 (1H, s); 6.48 (1H, t, *J* = 7.4); 2.45 (3H, s). ¹³C NMR spectrum (126 MHz, CDCl₃), δ, ppm: 132.3; 131.4; 131.0; 129.0; 128.8; 122.8; 121.8; 117.8; 115.6; 115.4; 110.5; 109.1; 10.39. Found, *m/z* (EI): 241.0657 [M]⁺. C₁₅H₁₂ClN. Calculated, *m/z*: 241.0658.

4-(1-Methylindolizin-3-yl)benzonitrile (6ja)

¹H NMR spectrum (500 MHz, CDCl₃), δ, ppm (*J*, Hz): 8.06 (1H, d, *J* = 7.2); 7.77 (2H, d, *J* = 8.3); 7.58 (2H, d, *J* = 8.3); 7.35 (1H, d, *J* = 8.9); 6.72 (1H, ddd, *J* = 8.9, *J* = 6.5, *J* = 1.0); 6.46 (1H, ddd, *J* = 7.1, *J* = 6.5, *J* = 1.3); 6.42 (1H, s); 2.34 (3H, s). ¹³C NMR spectrum (126 MHz, CDCl₃), δ, ppm: 136.6; 133.5; 132.6; 129.5; 124.7; 121.8; 120.5; 119.0; 118.7; 118.2; 110.6; 109.9; 101.8; 12.6. Found, *m/z* (EI): 232.1000 [M]⁺. C₁₆H₁₂N₂. Calculated, *m/z*: 232.1001.

1-Methyl-3-(4-nitrophenyl)indolizine (6ka)

¹H NMR spectrum (500 MHz, CDCl₃), δ, ppm (*J*, Hz): 8.36 (2H, d, *J* = 8.7); 8.12 (1H, d, *J* = 7.1); 7.64 (2H, d, *J* = 8.8); 7.36 (1H, d, *J* = 9.0); 6.75 (1H, dd, *J* = 8.6, *J* = 6.7); 6.49 (1H, t, *J* = 6.4); 6.44 (1H, s); 2.37 (3H, s). ¹³C NMR spectrum (126 MHz, CDCl₃), δ, ppm: 145.7; 138.6; 133.9; 129.2; 125.3; 124.3; 121.9; 120.4; 118.8; 118.5; 110.8; 102.2; 12.7. Found, *m/z* (EI): 252.0901 [M]⁺. C₁₅H₁₂N₂O₂. Calculated, *m/z*: 252.0899.

1,3,5-Trimethylpyrrolo[1,2-*a*]quinoline (6la)

¹H NMR spectrum (500 MHz, CDCl₃), δ, ppm (*J*, Hz): 8.29 (1H, d, *J* = 8.4); 7.73 (1H, dd, *J* = 7.9, *J* = 1.3); 7.42–7.47 (1H, m); 7.33 (1H, t, *J* = 7.2); 7.09 (1H, s); 6.34 (1H, s); 2.92 (3H, s); 2.47 (3H, s); 2.33 (3H, s). ¹³C NMR spectrum (126 MHz, CDCl₃), δ, ppm: 136.1; 128.6; 126.2; 125.9; 124.7; 124.4; 122.6; 121.5; 116.9; 115.7; 115.5; 109.0; 19.2; 18.4; 10.4. Found, *m/z* (EI): 209.1206 [M]⁺. C₁₅H₁₅N. Calculated, *m/z*: 209.1204.

1,3-Dimethylpyrrolo[2,1-*a*]isoquinoline (6ma)

¹H NMR spectrum (500 MHz, CDCl₃), δ, ppm (*J*, Hz): 8.15 (1H, d, *J* = 8.2); 7.56–7.52 (2H, m); 7.47 (1H, ddd, *J* = 8.2, *J* = 7.1, *J* = 1.2); 7.30 (1H, ddd, *J* = 7.7, *J* = 7.2, *J* = 1.1); 6.70 (1H, d, *J* = 7.4); 6.34 (1H, s); 2.66 (3H, s); 2.47 (3H, s). ¹³C NMR spectrum (126 MHz, CDCl₃), δ, ppm: 128.2; 127.0; 126.6; 124.0; 122.3; 122.1; 121.5; 121.1; 120.5; 113.9; 111.7; 110.1; 14.9; 11.4. Found, *m/z* (EI): 195.1050 [M]⁺. C₁₄H₁₃N. Calculated, *m/z*: M 195.1048.

1-Phenylindolizines (6af,lf) (General Method)

The corresponding propargylic alcohol (1.0 mmol) was placed into a flame-dried round-bottomed flask, which was then filled with 6 ml of dry THF and cooled to –50°C under Ar. After that, Et₃N (121 mg, 167 μl, 1.2 mmol) was added neat *via* a syringe, followed by neat MsCl (137 mg, 93 μl, 1.2 mmol). The solution was stirred for 30 min at –50°C, controlling the formation of mesylate **5** by TLC. Meantime, CuBr·SMe₂ (267 mg, 1.3 mmol) was placed into another flame-dried round-bottomed flask, which was then filled with *ca* 4 ml of dry THF and cooled to –50°C under Ar. A 433 μl volume of phenyl magnesium bromide in diethyl ether (3.06 M, 1.3 mmol) was added and the yellowish suspension stirred for 30 min at –20°C. After complete conversion of the alcohol to mesylate, the flask with phenylcopper was cooled to –78°C, and mesylate was transferred to the flask with phenylcopper *via* a cannula with cotton at the end, avoiding transfer of precipitated triethylammonium chloride. The mixture was stirred for 2 h at –78°C, and then it was allowed to warm to room temperature, controlling the formation of indolizine by GC/MS and TLC. After 3 h at room

temperature, the reaction was complete and it was quenched with 15 ml NH_4Cl (aq) sat.– NH_3 (aq) sat., 10:1 and extracted with diethyl ether (3×15 ml). The organic extracts were then dried over MgSO_4 , followed by filtration and evaporation. Purification by column chromatography (silica gel, EtOAc–hexane, 1:20) provided product **6**.

3-Methyl-1-phenylindolizine (6af)

^1H NMR spectrum (500 MHz, CDCl_3), δ , ppm (J , Hz): 7.76 (1H, d, J = 9.1); 7.71 (1H, d, J = 7.1); 7.62 (1H, d, J = 7.2); 7.44 (1H, t, J = 7.8); 7.19–7.35 (1H, m); 6.81 (1H, s); 6.68–6.78 (2H, m); 6.52–6.66 (2H, m); 2.52 (3H, s). ^{13}C NMR spectrum (126 MHz, CDCl_3) δ , ppm: 136.7; 128.7; 127.4; 125.0; 122.0; 120.1; 118.2; 116.5; 113.5; 112.5; 110.5; 109.6; 11.5. Found, m/z (EI): 207.1050 $[\text{M}]^+$. $\text{C}_{15}\text{H}_{13}\text{N}$. Calculated, m/z : 207.1048.

1,5-Dimethyl-3-phenylpyrrolo[1,2-*a*]quinoline (6lf)

^1H NMR spectrum (500 MHz, CDCl_3), δ , ppm (J , Hz): 8.36 (1H, d, J = 8.5); 7.77 (1H, dd, J = 7.9, J = 1.2); 7.59 (2H, d, J = 7.1); 7.43–7.50 (4H, m); 7.38 (1H, t, J = 7.2); 7.26–7.29 (1H, m); 6.66 (1H, s); 3.00 (3H, s); 2.48 (3H, s). ^{13}C NMR spectrum (126 MHz, CDCl_3) δ , ppm: 136.4; 136.0; 130.4; 128.6; 128.1; 126.6; 126.1; 125.8; 125.5; 124.8; 124.4; 123.1; 117.5; 116.1; 115.8; 114.2; 19.3; 18.7. Found, m/z (EI): 271.1362 $[\text{M}]^+$. $\text{C}_{20}\text{H}_{17}\text{N}$. Calculated, m/z : 271.1361.

Allenenes **8** (General Method)

The corresponding propargylic alcohol (1.0 mmol) was placed into a flame-dried round-bottomed flask, which was then filled with 6 ml of dry THF and cooled to -50°C under Ar. After that, Et_3N (121 mg, 167 μl , 1.2 mmol) was added neat *via* a syringe, followed by neat MsCl (137 mg, 93 μl , 1.2 mmol). The solution was stirred for 30 min at -50°C , controlling the formation of mesylate **5** by TLC. Meantime, CuCN (116 mg, 1.3 mmol) was placed into another flame-dried round-bottomed flask, which was then filled with *ca* 2.5 ml of dry THF and cooled to -50°C under Ar. A corresponding organolithium reagent (1.3 mmol) was added dropwise and the yellowish suspension stirred for 30 min at -50°C until no CuCN was visible at the bottom of the flask. After complete conversion of alcohol to mesylate, the flask with cyanocuprate **7a** was cooled to -78°C and mesylate was transferred to the flask with cyanocuprate *via* a cannula with cotton at the end, avoiding transfer of precipitated triethylammonium chloride. The mixture was stirred for 1 h at -78°C , and then it was quenched with 15 ml NH_4Cl (aq) sat.– NH_3 (aq) sat., 10:1, and extracted with diethyl ether (3×15 ml). The organic extracts were then dried over MgSO_4 , followed by filtration and evaporation. Column chromatography (silica gel, EtOAc–hexane, 1:10) provided the respective product **8**.

2-(Buta-2,3-dien-2-yl)pyridine (8a)

^1H NMR spectrum (500 MHz, CDCl_3), δ , ppm (J , Hz): 8.56 (1H, dd, J = 4.6, J = 1.3); 7.57 (1H, dd, J = 7.3, J = 1.8); 7.50 (1H, d, J = 7.9); 7.06 (1H, dd, J = 6.3, J = 5.8); 5.06–5.13 (2H, m); 2.11–2.17 (3H, m). ^{13}C NMR spectrum (126 MHz, CDCl_3) δ , ppm: 210.7; 156.0; 149.1; 135.8; 121.4; 121.0; 101.9; 77.7; 15.8.

2-(Hepta-1,2-dien-3-yl)pyridine (8b)

^1H NMR spectrum (500 MHz, C_6D_6), δ , ppm (J , Hz): 8.51 (1H, d, J = 4.8); 7.45 (1H, d, J = 8.1); 7.06 (1H, t, J = 7.7); 6.56 (1H, dd, J = 7.0, J = 5.0); 4.90 (2H, t, J = 3.1); 2.88 (2H, dt, J = 15.3, J = 3.2); 1.69 (2H, ddd, J = 15.3, J = 7.6, J = 7.4); 1.37–1.47 (2H, m); 0.92 (3H, t, J = 7.3). ^{13}C NMR spectrum (126 MHz, C_6D_6) δ , ppm: 210.6; 156.0; 149.0; 135.2; 121.9; 120.7; 109.6; 78.4; 30.6; 28.4; 22.7; 14.0.

2-(Penta-2,3-dien-2-yl)pyridine (8c)

¹H NMR spectrum (400 MHz, CDCl₃), δ, ppm (*J*, Hz): 8.55 (1H, d, *J* = 4.8); 7.54 (1H, dd, *J* = 7.6, *J* = 1.8); 7.45–7.50 (1H, m); 7.03 (1H, td, *J* = 6.3, *J* = 0.8); 5.48 (1H, dd, *J* = 7.0, *J* = 3.1); 2.13 (3H, d, *J* = 2.8); 1.77 (3H, d, *J* = 7.2). ¹³C NMR spectrum (126 MHz, CDCl₃), δ, ppm: 206.8; 156.9; 148.9; 135.6; 121.4; 120.7; 101.8; 88.3; 16.14; 14.0.

2-(5-Methylhepta-2,3-dien-4-yl)pyridine (8d)

¹H NMR spectrum (400 MHz, CDCl₃), δ, ppm (*J*, Hz): 8.52 (1H, d, *J* = 4.5); 7.49–7.56 (1H, m); 7.42–7.47 (1H, m); 6.98–7.03 (1H, m); 5.50–5.59 (1H, m); 3.01–3.11 (1H, m); 1.68–1.95 (4H, m); 1.33–1.47 (1H, m); 1.05–1.12 (3H, m); 0.86–0.94 (3H, m).

2-(2,2-Dimethylhexa-3,4-dien-3-yl)pyridine (8e)

¹H NMR spectrum (400 MHz, CDCl₃), δ, ppm (*J*, Hz): 8.53 (1H, d, *J* = 4.0); 7.52 (1H, td, *J* = 7.7, *J* = 1.8); 7.30 (1H, d, *J* = 7.9); 7.03 (1H, dd, *J* = 6.8, *J* = 5.3); 5.35 (1H, q, *J* = 6.9); 1.73 (3H, d, *J* = 7.0); 1.26 (9H, s). ¹³C NMR spectrum (101 MHz, CDCl₃), δ, ppm: 205.1; 158.0; 148.1; 135.5; 124.1; 120.6; 115.5; 88.0; 30.1; 29.4; 14.3.

Methyl 4-[3-(pyridin-2-yl)buta-1,2-dienyl]benzoate (8f)

¹H NMR spectrum (500 MHz, CDCl₃), δ, ppm (*J*, Hz): 8.60 (1H, dd, *J* = 6.3, *J* = 1.4); 8.03 (1H, d, *J* = 8.3); 7.96 (2H, d, *J* = 8.4); 7.53–7.60 (1H, m); 7.36 (2H, d, *J* = 8.4); 7.10 (1H, dd, *J* = 6.7, *J* = 4.5); 6.56 (1H, q, *J* = 2.7); 3.88 (3H, s); 2.30 (2H, d, *J* = 3.1). ¹³C NMR spectrum (126 MHz, CDCl₃), δ, ppm: 209.8; 166.7; 149.2; 138.8; 136.0; 130.0; 129.9; 126.8; 125.1; 121.8; 121.6; 107.96, 96.76, 51.96, 18.87.

3-Methyl-2-(octa-2,3-dien-4-yl)pyridine (8g)

¹H NMR spectrum (500 MHz, C₆D₆), δ, ppm (*J*, Hz): 8.48 (1H, d, *J* = 3.6); 7.01 (1H, d, *J* = 7.6); 6.61 (1H, dd, *J* = 7.5, *J* = 4.7); 5.06–5.14 (1H, m); 2.86–3.01 (2H, m); 2.24 (3H, s); 1.58–1.67 (2H, m); 1.54 (3H, d, *J* = 7.0); 1.37–1.47 (2H, m); 0.91 (3H, t, *J* = 7.4). ¹³C NMR spectrum (126 MHz, C₆D₆), δ, ppm: 206.5; 156.3; 147.4; 138.4; 132.3; 121.5; 105.9; 87.8; 32.8; 31.2; 23.2; 21.1; 14.7; 14.6. Found, *m/z* (EI): 201.15253 [M]⁺. C₁₄H₁₉N. Calculated, *m/z*: 201.15175.

2-Methoxy-6-(octa-2,3-dien-4-yl)pyridine (8h)

¹H NMR spectrum (500 MHz, C₆D₆), δ, ppm (*J*, Hz): 7.25 (1H, s); 7.14–7.22 (1H, m); 6.54–6.65 (1H, m); 5.35–5.50 (1H, m); 3.90 (3H, s); 2.78–2.95 (2H, m); 1.74–1.85 (2H, m); 1.69 (3H, d, *J* = 7.06); 1.50–1.60 (2H, m); 1.04 (3H, t, *J* = 7.34). ¹³C NMR spectrum (126 MHz, C₆D₆), δ, ppm: 207.3; 164.4; 155.2; 138.8; 115.2; 108.2; 107.8; 89.5; 53.1; 31.4; 29.6; 23.3; 14.7; 14.6. Found, *m/z* (EI): 217.14756 [M]⁺. C₁₄H₁₉NO. Calculated, *m/z*: 217.14666.

1-Alkylindolizines 6 from Allenes 8 (General Method)

To a 5.0 ml Wheaton microreactor under argon atmosphere CuCl (0.2 mmol), anhydrous Et₃N (0.25 ml) and allene **8** (0.4 mmol) in anhydrous DMA (1.8 ml) were successively added. The mixture was stirred overnight at 130°C with protection from light and then cooled. It was quenched with sat. NH₄Cl (aq) (3 ml) and extracted with ethyl acetate (2×7 ml) and diethyl ether (7 ml). The organic extracts were then dried over MgSO₄, followed by filtration and evaporation. The respective raw product **6** was purified by column chromatography (silica gel, EtOAc–hexane, 1:20).

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Scheme 1.

Scheme 2.

Scheme 3.

6ea $R = \text{H}$, $R^1 = \text{Me}$ (42%), **ad** $R = \text{Me}$, $R^1 = s\text{-Bu}$ (0%), **ha** $R = p\text{-MeO}_2\text{CC}_6\text{H}_4$, $R^1 = \text{Me}$ (27%)

Scheme 4.

TABLE 1

Optimization of Reaction Conditions*

Reaction scheme: **5** $\xrightarrow{[\text{CuR}]}$ **6**

Entry	[CuR]	LG	Solvent	Yield, %
1	<i>s</i> -BuMeCu(CN)Li ₂	OMs	Et ₂ O	11
2	Me ₂ Cu(CN)Li ₂	OMs	Et ₂ O	traces
3	Me ₂ Cu(CN)Li ₂	OMs	THF	0
4	MeCu(CN)Li	OMs	Et ₂ O	8
5	MeCu(CN)Li	OMs	THF	90
6	MeCu(CN)Li	OAc	THF	21
7	MeCu(CN)Li	OTFA	THF	16
8	MeCu(CN)Li	O(C)OEt	THF	0
9	MeCu(CN)Li	OP(O)(OEt) ₂	THF	27
10	MeCu(CN)Li	OTf	THF	5
11	MeCu(CN)Li	OBs	THF	traces
12	MeCu(CN)Li	ONs	THF	traces
13	Ph ₂ Cu(CN)Li ₂	OMs	Et ₂ O	traces
14	Ph ₂ Cu(CN)Li ₂ -BF ₃ ·Et ₂ O	OMs	Et ₂ O-THF	9
15	PhCu(CN)Li	OMs	Et ₂ O	0
16	PhCu ^{*2}	OMs	THF	71

* Reactions were carried out with 1.0 mmol of compound **5** and 1.2 mmol of copper reagent at -78°C for 1 h, then at room temperature for 1 h.

^{*2} Prepared by mixing PhMgBr with CuBr·SMe₂ complex.

TABLE 2

Organocopper-Mediated Synthesis of *N*-Fused Heterocycles **6**

Entry	Starting material 5 *			Reagent 7		Product 6	
	No.	R	R ²	[CuR ¹]	R ¹	No.	Yield, %
1	5a	Me	H	MeCu(CN)Li (7a)	Me	6aa	90
2	5a	Me	H	<i>n</i> -BuCu(CN)Li (7b)	<i>n</i> -Bu	6ab	89
3	5a	Me	H	<i>n</i> -HexCu(CN)Li (7c)	<i>n</i> -Hex	6ac	81
4	5a	Me	H	<i>s</i> -BuCu(CN)Li (7d)	<i>s</i> -Bu	6ad	82
5	5a	Me	H	<i>t</i> -BuCu(CN)Li (7e)	<i>t</i> -Bu	6ae	79
6	5b	<i>n</i> -Pent	H	7a	Me	6ba	70 ^{*2}
7	5b	<i>n</i> -Pent	H	7b	<i>n</i> -Bu	6bb	98
8	5c	Me	5-Me	7a	Me	6ca	80 ^{*3}
9	5d	Me	5-CF ₃	7b	<i>n</i> -Bu	6db	30
10	5e	H	H	7a	Me	6ea	61
11	5f	Ph	H	7a	Me	6fa	75
12	5g	<i>p</i> -MeOC ₆ H ₄	H	7b	<i>n</i> -Bu	6gb	47

Entry	Starting material 5 *		Reagent 7		Product 6		
	No.	R	R ²	[CuR ¹]	R ¹	No.	Yield, %
13	5h	<i>p</i> -MeO ₂ CC ₆ H ₄	H	7a	Me	6ha	62
14	5i	<i>p</i> -ClC ₆ H ₄	H	7a	Me	6ia	74
15	5j	<i>p</i> -NCC ₆ H ₄	H	7a	Me	6ja	63
16	5k	<i>p</i> -O ₂ NC ₆ H ₄	H	7a	Me	6ka	77
17	5a	Me	H	PhCu (7f)	Ph	6af	71
18	5l	Me	—	7a	Me	6la	65
19	5l	Me	—	7f	Ph	6lf	51
20	5m	Me	—	7a	Me	6ma	66

* Mesylate prepared *in situ*.

*² Additionally, 14% of allene was isolated.

*³ Additionally, 4% of allene was isolated.

TABLE 3

Organocopper-Mediated Synthesis of Allenes **8**

Allene	R	R ¹	R ²	R ³	Yield, %		
8a	H	Me	H	H	27		
8b	H	<i>n</i> -Bu	H	H	38		
8c	Me	Me	H	H	48		
8d	Me	<i>s</i> -Bu	H	H	89		
8e	Me	<i>t</i> -Bu	H	H	54		
8f	<i>p</i> -MeO ₂ CC ₆ H ₄	Me	H	H	34		
8g	Me	<i>n</i> -Bu	Me	H	40		
8h	Me	<i>n</i> -Bu	H	MeO	63		