Synthesis C.-Y. Liu et al. Special Topic

Selective C(8)–H Activation of Imidazopyridines Mediated by Cooperative Nickel–Aluminum Catalysis

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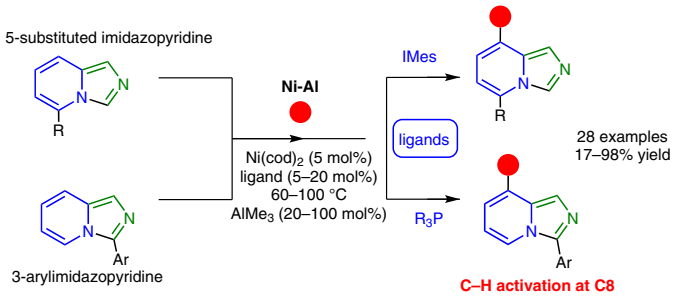
This work is dedicated to the victims of the recent Tainan earthquake.



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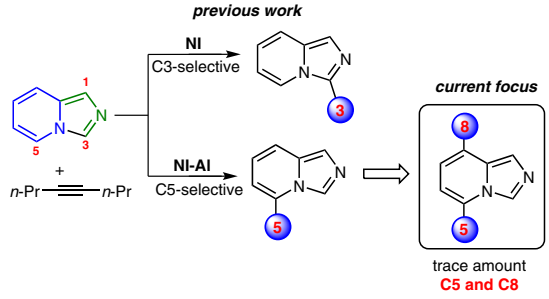
Abstract A catalytic paradigm is described featuring a synergistic interaction between nickel, aluminum and different ligands to impart a rather remote C–H alkenylation of imidazo[1,5-*a*]pyridines at the C-8 position without the necessity of installing a directing group. The scope of the direct C–H activation reactions of various 5-aryl- and 3-arylimidazopyridines is established using different sterically hindered alkynes.

Key words C–H activation, nickel, aluminum, imidazopyridines, cooperative catalysis



Scheme 1 C–H derivatizations of imidazo[1,5-*a*]pyridine

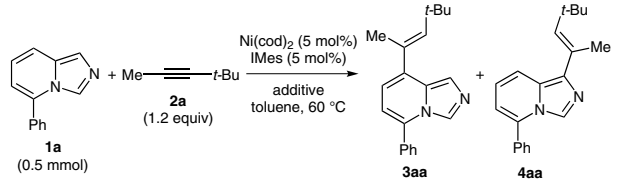
Over the past decade, transition-metal-promoted C–H bond activation has emerged as a powerful and pervasive catalytic synthetic strategy, avoiding additional steps associated with prefunctionalized coupling partners.[1] Nevertheless, research concerning C–H activation of imidazo[1,5-*a*]pyridines remains surprisingly under-represented, in spite of the importance of these compounds as electronic and photo-responsive materials,[2] carbene-like ancillary ligands[3] and bioactive agents.[4] So far, the majority of C–H functionalizations of imidazo[1,5-*a*]pyridines have been established exclusively at the more acidic regions, namely the C-3 and C-1 positions.[5]

Previously, our group,[6] as well as those of Nakao and Hiyama[7] and Chatani[8] have embraced the cooperative catalysis paradigm based on nickel and aluminum to promote and control one particular unique C–H derivatization in pyridines or azoles with high precision. More recently, we developed a general approach featuring a controlled regiodivergent C–H alkenylation of imidazo[1,5-*a*]pyridine at the C-5 and C-3 positions (Scheme 1).[9] Such highly regioselective C–H reactions at these positions are enabled by the cooperative interaction between Ni and Al. During the course of this work, we also obtained, unexpectedly, a trace amount of a side product in which C–H functionalization with the alkyne had occurred at the rather remote C-8 position simultaneously with the C-5 position. So far, no single example of the direct C-8 functionalization of imidazo[1,5-*a*]pyridine has been reported. Thus, a new strategy for selective C(8)–H bond activation of imidazopyridine would be an obvious choice to pursue for synthetic curiosity as well as to increase the synthetic utility of nickel catalysis.

To test our initial hypothesis for remote C–H activation at the C-8 position (Table 1), we selected the alkenylation of 5-phenylimidazo[1,5-*a*]pyridine (**1a**) with 4,4-dimethyl-2-pentyne (**2a**) in the presence of $Ni(cod)_2$ (5 mol%) in toluene

at 60 °C as a model system. Two regioisomeric products, **3aa** (C8-H) and **4aa** (C1-H) were obtained under these reaction conditions in yields of 32% and 6%, respectively, with low selectivity. The addition of $AlMe_3$ (10 mol%) not only had a beneficial effect upon the yield of the reaction (68%), but also essentially promoted exclusive selectivity for C–H functionalization at the C-8 position. Finally, the yield of the reaction could be further optimized to 95% by increasing the amount of $AlMe_3$ to 20 mol%. It is also noteworthy that the reaction between **1a** and the unsymmetrical alkyne was highly selective, giving the corresponding *E*-configured stereoisomeric adduct bearing the smaller methyl substituent on the same side as the imidazopyridine.

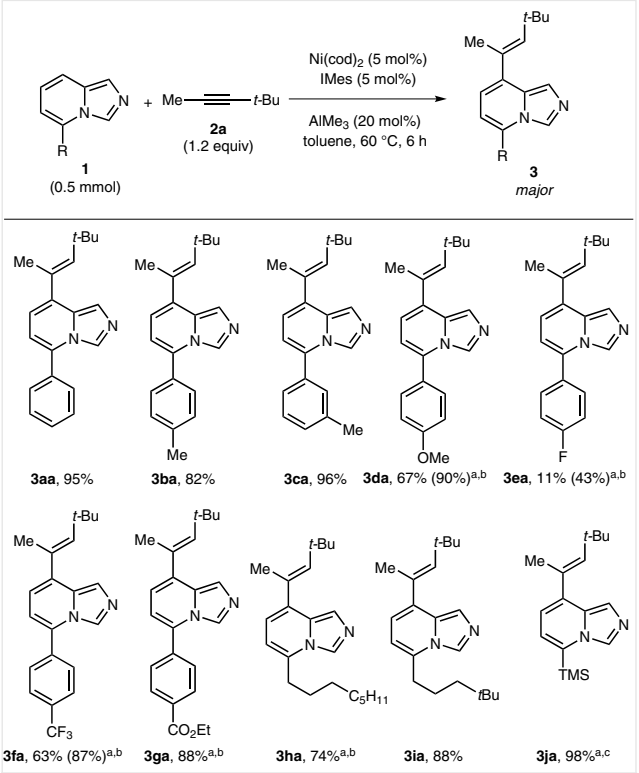
Table 1 Optimization of the Process



Entry	Additive (mol%)	Time (h)	Yield of **3aa** (%)[a]	Yield of **4aa** (%)[a]	*E*/*Z* (**3aa**)[b]
1[c]	–	17	32	6	99:1
2	$AlMe_3$ (10)	6	68	–	99:1
3	$AlMe_3$ (20)	6	95	–	99:1

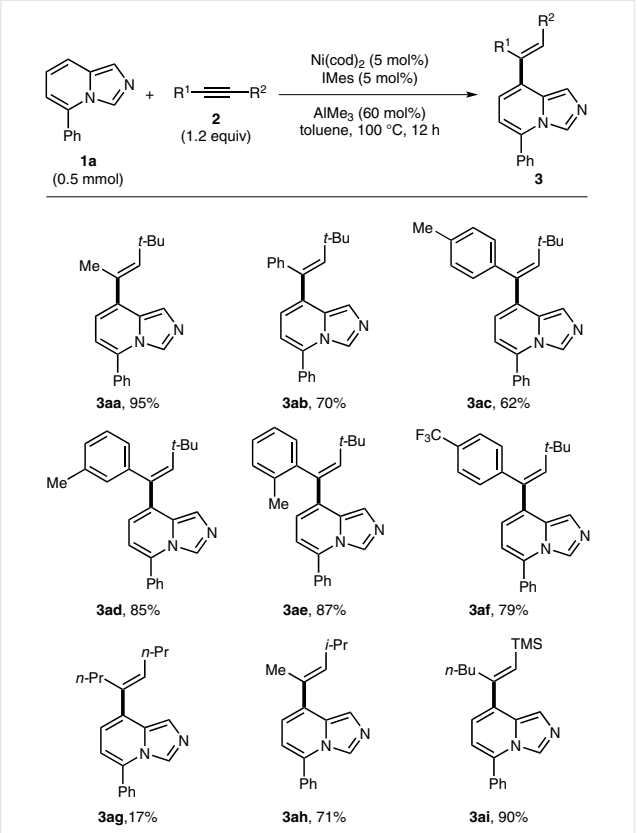
[a] Yield of isolated product.
[b] Determined by ^1H NMR spectroscopy.
[c] Reaction temperature was 100 °C.

With optimized reaction conditions in hand, we next examined the scope of the process with various 5-substituted imidazo[1,5-*a*]pyridines **1** (Scheme 2). Electron-donating functional groups such as methyl at different positions (**1b**,**c**) afforded C8-alkenylation products in superior yields (~90%), with the exception that a methoxy group (**1d**) gave an average yield of 67%. Nevertheless, the yield of this reaction could be increased to 90% by elevating the temperature of the reaction to 100 °C in the presence of $AlMe_3$ (60 mol%). 5-Arylimidazopyridines possessing electron-withdrawing groups such as CF_3 (**1f**) and CO_2Et (**1g**) were also feasible substrates producing high yields of the corresponding alkenylated products **3fa** and **3ga**. However, fluoro derivative **1e** was a less impressive substrate in terms of the isolated yield of the alkenylated product **3ea**. Notably, this procedure could also be extended to long-chain and sterically hindered 5-alkylimidazopyridines **1h**–**j** leading to good conversions.



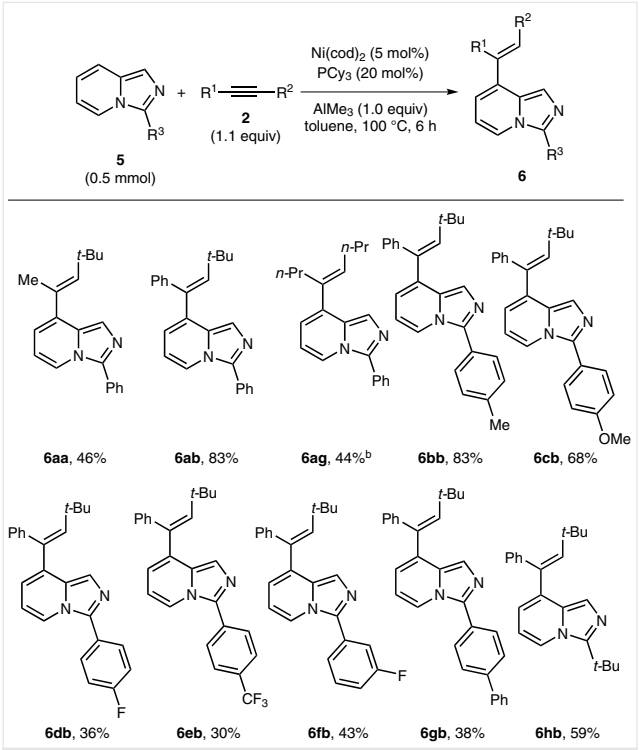
Scheme 2 C8-Alkenylation of various imidazopyridines **1** with **2a**. *Reagents and conditions*: **1** (0.5 mmol), **2a** (0.6 mmol), $Ni(cod)_2$ (5 mol%), IMes (5 mol%), toluene (2 mL), $AlMe_3$ (20 mol%), 60 °C; *E*/*Z* ratio = 99:1. [a] $AlMe_3$ (0.6 equiv). [b] 100 °C, 12 h. [c] 24 h.

To further illustrate the catalytic utility of this protocol, we expanded the scope to different alkynes (Scheme 3). A good yield (70%) with high C-8 selectivity was observed with phenyl(*tert*-butyl)-alkyne **2b**, albeit a higher temperature of 100 °C was required along with an increased Lewis acid loading (60 mol%) compared to several of the previous cases in Scheme 2. An electron-donating methyl substituent at different positions of phenyl alkynes **2c**–**e** afforded C-8 alkenylated products **3ac**–**ae** selectively, and in good to moderate yields. Alternatively, a similar type of alkyne derivative bearing an electron-withdrawing CF_3 group (**2f**) was also suitable for this reaction. The yield and regioselectivity were both good, demonstrating the non-sensitivity of the reaction toward electronic perturbation of the phenyl group. Unfortunately, symmetrical oct-4-yne (**2g**) experienced rather sluggish reactivity (17%), but still maintained a favorable regioselectivity for C-8. We attributed the poor yield to a lack of steric hindrance in the alkyne, with the other competing alkyne cyclotrimerization process prevailing. Again, increasing the steric demand of the alkyne had a beneficial effect on the yield of the reaction, as witnessed in the cases of **2h** and **2i** containing larger isopropyl and trimethylsilyl groups, respectively. Finally, it should be mentioned that styrene and other olefinic substrates were not compatible with this reaction protocol.



Scheme 3 C8-Alkenylation of **1a** with different alkynes. *Reagents and conditions*: **1a** (0.5 mmol), **2** (0.6 mmol), $Ni(cod)_2$ (5 mol%), IMes (5 mol%), toluene (2 mL), $AlMe_3$ (60 mol%), 100 °C; *E*/*Z* ratio = 99:1.

At this stage, we also wanted to further examine the viability of this catalytic reaction with various 3-phenylimidazo[1,5-*a*]pyridines **5**, which might perhaps be valuable for the future study of photosensitive compounds (Scheme 4). Using $Ni(cod)_2$ (5 mol%), PCy_3 (20 mol%) and $AlMe_3$ (1 equiv) as the additive, we found that alkyne **2b** (**6ab**, 83%) was more reactive than the less bulky alkynes **2a** (**6aa**, 46%) and **2g** (**6ag**, 44%). These results again stressed the need for bulky alkynes in order to avoid the possible competing alkyne cyclotrimerization reaction. Interestingly, we also found that the 1,3-dimesitylimidazolium (IMes) ligand was not the suitable for the reaction of 3-phenylimidazopyridine **5a**, affording an isolated yield of 8%.[10] We speculated that the electronic difference between the topologies of 3-phenyl- and 5-phenylimidazopyridine derivatives might dictate the reactivity based on the nature of the ligand as a strong σ-donor or π-acceptor. In this regard, a π-acceptor ligand such as phosphine is a more effective scaffold than IMes to mediate the C–H activation of 3-phenylimidazopyridine.[10] Next, we systematically investigated the influence of different 3-arylimidazopyridine derivatives. Substrates with methyl (**5b**) and methoxy (**5c**) functional groups were converted in good 83% and 68% yields into the final products **6bb** and **6cb**, respectively. In contrast, substrates possessing electron-withdrawing components **5d**–**g** furnished rather lower yields (~45%) in this reaction, but still maintained high selectivity toward C(8)–H activation. Finally, hydroheteroarylation of alkyne **2b** could also be performed with 3-*tert*-butylimidazopyridine (**5h**) to afford a good yield of product **6hb**.



Scheme 4 C8-Alkenylation with 3-imidazopyridines **5**. *Reagents and conditions*: **5** (0.5 mmol), **2** (5.5 mmol), $Ni(cod)_2$ (5 mol%), PCy_3 (20 mol%), toluene (2 mL), $AlMe_3$ (1.0 equiv), 100 °C; *E*/*Z* ratio = 99:1.
[a] 130 °C, alkyne **2g** (1.5 equiv).

In summary, without resorting to installing a directing group on the imidazopyridine, we have established a new method for the C–H bond functionalization of imidazo[1,5-*a*]pyridines. The catalytic paradigm features a synergistic interaction between Ni, Al and different ligands to impart rather remote C–H activation via alkenylation at the C-8 position of the substrate, which is considered to be unprecedented. Ongoing work seeks to gain a detailed mechanistic understanding of the behavior of the C–H activation occurring at the C-8 position.

Dry solvents were obtained by purification methods according to the literature.[11] IMes,[12] IPr,[12a,13] and imidazo[1,5-*a*]pyridines[14] were prepared according to literature procedures. Unless otherwise noted, all other reagents were purchased from Acros, Alfa Aesar, Merck, Sigma-Aldrich and Strem and were used without purification. All air-sensitive manipulations were performed under an atmosphere of nitrogen

using Schlenk techniques or in a glovebox. ^{1}H and ^{13}C NMR spectra were recorded using Bruker 300 MHz or 400 MHz spectrometers. The residual proton of the deuterated solvent ($CDCl_3$, ^{1}H NMR: 7.24 ppm) or the carbon of the solvent ($CDCl_3$, ^{13}C NMR: 77.0 ppm) were used as references. Data are reported in the following order: chemical shift (δ); multiplicity [s (singlet), d (doublet), t (triplet), q (quartet), sext (sextet), m (multiplet)]; coupling constant, *J* (Hz); integration. High-resolution mass spectra were obtained with a JEOL, JMS-700 spectrometer.

C8-Alkenylation of 5-Substituted Imidazo[1,5-*a*]pyridines; General Procedure A

In a glovebox, a vial (20 mL) was charged with $Ni(cod)_2$ (7 mg, 5 mol%), IMes (7.7 mg, 5 mol%) and **1** (0.5 mmol) in dry toluene (2 mL). The mixture was stirred for 5 min, followed by the addition of $AlMe_3$ (0.1 mL, 1.0 M in toluene, 20 mol%). After stirring for 5 min, alkyne **2** (1.2 equiv) was added. The vial was screw-capped and taken outside the glovebox. Following 6 h of stirring at 60 °C, the reaction mixture was added to CH_2Cl_2, stirred under air for 10 min, filtered through a pad of Celite and then concentrated in vacuo. The residue was purified by flash chromatography on silica gel (EtOAc–hexane, 1:1) to afford the product.

(*E*)-8-(4,4-Dimethylpent-2-en-2-yl)-5-phenylimidazo[1,5-*a*]pyridine (3aa)

The reaction was performed according to general procedure A.

Yield: 138 mg (95%); yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.16 (s, 1 H), 7.64–7.45 (m, 6 H), 6.62 (d, $^3J_{HH}$ = 6.8 Hz, 1 H), 6.47 (d, $^3J_{HH}$ = 6.8 Hz, 1 H), 5.98–5.95 (m, 1 H), 2.19 (d, $^3J_{HH}$ = 1.1 Hz, 3 H), 1.25 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.2, 136.2, 133.8, 132.9, 130.7, 130.6, 129.3, 128.9, 128.0, 126.8, 121.0, 116.4, 113.0, 32.8, 30.6, 17.4.

HRMS (APCI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{23}N_2$: 291.1861; found: 291.1862.

(*E*)-8-(4,4-Dimethylpent-2-en-2-yl)-5-(*p*-tolyl)imidazo[1,5-*a*]pyridine (3ba)

The reaction was performed according to general procedure A, but reduced to 0.1 mmol scale.

Yield: 25 mg (82%); yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.17 (s, 1 H), 7.49 (d, $^3J_{HH}$ = 7.9 Hz, 3 H), 7.31 (d, $^3J_{HH}$ = 8.0 Hz, 2 H), 6.61 (d, $^3J_{HH}$ = 7.0 Hz, 1 H), 6.44 (d, $^3J_{HH}$ = 6.9 Hz, 1 H), 5.97–5.94 (m, 1 H), 2.43 (s, 3 H), 2.19 (d, $^3J_{HH}$ = 1.1 Hz, 3 H), 1.24 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.4, 139.6, 136.2, 133.2, 131.2, 130.9, 130.8, 129.8, 128.1, 127.0, 121.1, 116.6, 113.0, 33.0, 30.8, 21.3, 17.6.

HRMS (APCI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{25}N_2$: 305.2018; found: 305.2012.

(*E*)-8-(4,4-Dimethylpent-2-en-2-yl)-5-(*m*-tolyl)imidazo[1,5-*a*]pyridine (3ca)

The reaction was performed according to general procedure A.

Yield: 146 mg (96%); yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.17 (s, 1 H), 7.50 (s, 1 H), 7.45–7.37 (m, 3 H), 7.32–7.25 (m, 1 H), 6.61 (d, $^3J_{HH}$ = 6.9 Hz, 1 H), 6.45 (d, $^3J_{HH}$ = 6.9 Hz, 1 H), 5.98–5.94 (m, 1 H), 2.42 (s, 3 H), 2.19 (d, $^3J_{HH}$ = 1.5 Hz, 3 H), 1.25 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.2, 138.7, 136.0, 133.8, 133.1, 130.6, 130.0, 128.8, 128.6, 126.9, 125.0, 121.0, 116.4, 112.9, 32.8, 30.6, 21.2, 17.4.

HRMS (APCI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{25}N_2$: 305.2018; found: 305.2010.

(*E*)-8-(4,4-Dimethylpent-2-en-2-yl)-5-(4-methoxyphenyl)imidazo[1,5-*a*]pyridine (3da)

The reaction was performed according to general procedure A, with the exception that 0.6 equiv of $AlMe_3$ were used at 100 °C for 12 h.

Yield: 144 mg (90%); yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.16 (s, 1 H), 7.56–7.47 (m, 3 H), 7.01 (d, $^3J_{HH}$ = 8.7 Hz, 2 H), 6.60 (d, $^3J_{HH}$ = 6.9 Hz, 1 H), 6.41 (d, $^3J_{HH}$ = 6.9 Hz, 1 H), 5.97–5.93 (m, 1 H), 3.86 (s, 3 H), 2.18 (d, $^3J_{HH}$ = 0.9 Hz, 3 H), 1.23 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.4, 141.4, 136.0, 133.0, 130.9, 130.8, 129.6, 127.0, 126.4, 121.1, 116.6, 114.5, 112.9, 55.4, 33.0, 30.8, 17.6.

HRMS (APCI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{25}N_2O$: 321.1967; found: 321.1960.

(*E*)-8-(4,4-Dimethylpent-2-en-2-yl)-5-(4-fluorophenyl)imidazo[1,5-*a*]pyridine (3ea)

The reaction was performed according to general procedure A, with the exception that 0.6 equiv of $AlMe_3$ were used at 100 °C for 12 h.

Yield: 66 mg (43%); yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.09 (s, 1 H), 7.62–7.54 (m, 2 H), 7.51 (s, 1 H), 7.25–7.16 (m, 2 H), 6.61 (d, $^3J_{HH}$ = 6.8 Hz, 1 H), 6.43 (d, $^3J_{HH}$ = 6.8 Hz, 1 H), 5.97–5.94 (m, 1 H), 2.18 (d, $^3J_{HH}$ = 1.1 Hz, 3 H), 1.24 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.2 (d, $^1J_{CF}$ = 248.3 Hz), 141.6, 136.7, 132.0, 131.0, 130.7, 130.3 (d, $^3J_{CF}$ = 8.2 Hz), 126.8, 121.4, 116.4 (d, $^2J_{CF}$ = 21.5 Hz), 113.4, 33.1, 30.8, 17.6.

HRMS (APCI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{22}N_2F$: 309.1767; found: 309.1766.

(*E*)-8-(4,4-Dimethylpent-2-en-2-yl)-5-[4-(trifluoromethyl)phenyl]imidazo[1,5-*a*]pyridine (3fa)

The reaction was performed according to general procedure A, with the exception that 0.6 equiv of $AlMe_3$ were used at 100 °C for 12 h.

Yield: 156 mg (87%); yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.12 (s, 1 H), 7.80–7.69 (m, 4 H), 7.53 (s, 1 H), 6.62 (d, $^3J_{HH}$ = 6.8 Hz, 1 H), 6.47 (d, $^3J_{HH}$ = 6.9 Hz, 1 H), 5.97–5.94 (m, 1 H), 2.18 (d, $^3J_{HH}$ = 1.1 Hz, 3 H), 1.23 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.8, 137.5 (d, $^3J_{CF}$ = 13.8 Hz), 131.4 (q, $^2J_{CF}$ = 33.0 Hz), 131.4, 130.9, 130.5, 128.6, 126.6, 126.2 (d, $^4J_{CF}$ = 3.3 Hz), 123.7 (q, $^1J_{CF}$ = 270.8 Hz), 121.7, 116.3, 114.1, 33.0, 30.7, 17.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{22}N_2F_3$: 359.1735; found: 359.1743.

Ethyl (*E*)-4-{8-(4,4-Dimethylpent-2-en-2-yl)imidazo[1,5-*a*]pyridin-5-yl}benzoate (3ga)

The reaction was performed according to general procedure A, with the exception that 0.6 equiv of $AlMe_3$ were used at 100 °C for 12 h.

Yield: 159 mg (88%); yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.21–8.14 (m, 3 H), 7.68 (d, $^3J_{HH}$ = 8.3 Hz, 2 H), 7.52 (s, 1 H), 6.61 (d, $^3J_{HH}$ = 6.9 Hz, 1 H), 6.50 (d, $^3J_{HH}$ = 6.9 Hz, 1 H), 5.95 (s, 1 H), 4.40 (q, $^3J_{HH}$ = 7.1 Hz, 2 H), 2.18 (s, 3 H), 1.40 (t, $^3J_{HH}$ = 7.2 Hz, 3 H), 1.23 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.7, 141.8, 138.2, 137.2, 132.0, 131.4, 130.9, 130.6, 130.4, 128.1, 126.8, 121.6, 116.4, 114.0, 61.2, 33.0, 30.8, 17.6, 14.3.

HRMS (APCI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{27}N_2O_2$: 363.2073; found: 363.2071.

(*E*)-8-(4,4-Dimethylpent-2-en-2-yl)-5-octylimidazo[1,5-*a*]pyridine (3ha)

The reaction was performed according to general procedure A, with the exception that 0.6 equiv of $AlMe_3$ were used at 100 °C for 12 h.

Yield: 121 mg (74%); yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.04 (s, 1 H), 7.47 (s, 1 H), 6.49 (d, $^3J_{HH}$ = 6.9 Hz, 1 H), 6.30 (d, $^3J_{HH}$ = 6.9 Hz, 1 H), 5.88–5.85 (m, 1 H), 2.78 (t, $^3J_{HH}$ = 7.6 Hz, 2 H), 2.12 (d, $^3J_{HH}$ = 1.2 Hz, 3 H), 1.82–1.67 (m, 2 H), 1.50–1.10 (m, 19 H), 0.90–0.79 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.1, 135.0, 132.9, 130.8, 130.5, 125.4, 121.0, 116.2, 110.3, 32.8, 31.7, 31.3, 30.7, 29.3, 29.2, 29.1, 25.6, 22.5, 17.6, 14.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{35}N_2$: 327.2800; found: 327.2792.

(*E*)-8-(4,4-Dimethylpent-2-en-2-yl)-5-(4,4-dimethylpentyl)imidazo[1,5-*a*]pyridine (3ia)

The reaction was performed according to general procedure A.

Yield: 138 mg (88%); yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.02 (s, 1 H), 7.46 (s, 1 H), 6.48 (d, $^3J_{HH}$ = 6.8 Hz, 1 H), 6.30 (d, $^3J_{HH}$ = 6.8 Hz, 1 H), 5.87–5.83 (m, 1 H), 2.73 (t, $^3J_{HH}$ = 7.6 Hz, 2 H), 2.10 (d, $^3J_{HH}$ = 0.9 Hz, 3 H), 1.78–1.63 (m, 2 H), 1.35–1.10 (m, 11 H), 0.83 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.0, 135.0, 132.9, 130.7, 130.4, 125.3, 120.9, 116.1, 110.2, 43.8, 32.8, 32.0, 30.7, 30.2, 29.1, 20.8, 17.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{33}N_2$: 313.2644; found: 313.2644.

(*E*)-8-(4,4-Dimethylpent-2-en-2-yl)-5-(trimethylsilyl)imidazo[1,5-*a*]pyridine (3ja)

The reaction was performed according to general procedure A, with the exception that 0.6 equiv of $AlMe_3$ were used for 24 h.

Yield: 140 mg (98%); black oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.17 (s, 1 H), 7.46 (s, 1 H), 6.66 (d, $^3J_{HH}$ = 6.6 Hz, 1 H), 6.48 (d, $^3J_{HH}$ = 6.8 Hz, 1 H), 5.92–5.89 (m, 1 H), 2.15 (d, $^3J_{HH}$ = 1.1 Hz, 3 H), 1.22 (s, 9 H), 0.41 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.3, 138.2, 133.5, 130.7, 129.5, 128.7, 121.4, 120.2, 115.1, 32.8, 30.6, 17.3, –2.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{27}N_2Si$: 287.1944; found: 287.1947.

(*E*)-8-(3,3-Dimethyl-1-phenylbut-1-en-1-yl)-5-phenylimidazo[1,5-*a*]pyridine (3ab)

The reaction was performed according to general procedure A, with the exception that 0.6 equiv of $AlMe_3$ were used at 100 °C for 12 h.

Yield: 123 mg (70%); yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.17 (s, 1 H), 7.59 (s, 1 H), 7.58–7.42 (m, 5 H), 7.34–7.25 (m, 5 H), 6.45–6.34 (m, 3 H), 1.03 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.8, 140.0, 135.4, 134.2, 133.9, 133.2, 130.9, 130.0, 129.5, 129.1, 128.1, 127.7, 127.1, 127.0, 121.6, 119.1, 113.0, 34.3, 31.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{25}N_2$: 353.2018; found: 353.2010.

(*E*)-8-[3,3-Dimethyl-1-(*p*-tolyl)but-1-en-1-yl]-5-phenylimidazo[1,5-*a*]pyridine (3ac)

The reaction was performed according to general procedure A, with the exception that 0.6 equiv of $AlMe_3$ were used at 100 °C for 12 h.

Yield: 114 mg (62%); yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.22 (s, 1 H), 7.64–7.62 (m, 3 H), 7.57–7.51 (m, 3 H), 7.25–7.18 (m, 4 H), 6.47–6.42 (m, 3 H), 2.42 (s, 3 H), 1.10 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.6, 139.8, 137.2, 135.5, 134.3, 133.9, 133.1, 131.0, 130.6, 129.4, 129.0, 128.1, 127.8, 127.5, 127.1, 126.9, 121.5, 119.0, 113.0, 34.2, 31.1, 21.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{27}N_2$: 367.2169; found: 367.2166.

(*E*)-8-[3,3-Dimethyl-1-(*m*-tolyl)but-1-en-1-yl]-5-phenylimidazo[1,5-*a*]pyridine (3ad)

The reaction was performed according to general procedure A, with the exception that 0.6 equiv of $AlMe_3$ were used at 100 °C for 12 h.

Yield: 156 mg (85%); yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21 (s, 1 H), 7.64–7.59 (m, 3 H), 7.54–7.48 (m, 3 H), 7.28–7.23 (m, 1 H), 7.15–7.13 (m, 3 H), 6.45–6.40 (m, 3 H), 2.38 (s, 3 H), 1.08 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.6, 139.8, 137.2, 135.5, 134.3, 133.9, 133.1, 131.0, 130.6, 129.4, 129.0, 128.1, 127.8, 127.5, 127.1, 126.9, 121.5, 119.0, 113.0, 34.2, 31.1, 21.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{27}N_2$: 367.2169; found: 367.2166.

(*E*)-8-[3,3-Dimethyl-1-(*o*-tolyl)but-1-en-1-yl]-5-phenylimidazo[1,5-*a*]pyridine (3ae)

The reaction was performed according to general procedure A, with the exception that 0.6 equiv of $AlMe_3$ were used at 100 °C for 12 h.

Yield: 159 mg (87%); yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.23 (s, 1 H), 7.80 (s, 1 H), 7.61–7.59 (m, 2 H), 7.53–7.50 (m, 3 H), 7.32–7.20 (m, 4 H), 6.99 (s, 1 H), 6.36 (d, $^3J_{HH}$ = 7.2 Hz, 1 H), 6.30 (d, $^3J_{HH}$ = 6.8 Hz, 1 H), 2.16 (s, 3 H), 1.04 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.8, 139.3, 136.6, 134.3, 133.9, 133.2, 133.0, 131.0, 130.9, 130.0, 129.5, 129.1, 128.1, 127.5, 127.1, 124.8, 121.6, 118.7, 113.1, 34.4, 30.5, 19.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{27}N_2$: 367.2169; found: 367.2166.

(*E*)-8-{3,3-Dimethyl-1-[4-(trifluoromethyl)phenyl]but-1-en-1-yl}-5-phenylimidazo[1,5-*a*]pyridine (3af)

The reaction was performed according to general procedure A, with the exception that 0.6 equiv of $AlMe_3$ were used at 100 °C for 12 h.

Yield: 166 mg (79%); yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.20 (s, 1 H), 7.63–7.42 (m, 10 H), 6.47 (s, 1 H), 6.42 (d, $^3J_{HH}$ = 7.5 Hz, 1 H), 6.33 (d, $^3J_{HH}$ = 6.9 Hz, 1 H), 1.04 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 143.94, 143.89, 134.1, 133.6, 133.7, 133.5, 130.8, 130.4, 129.6, 129.4, 129.2, 128.2, 127.2, 124.8 (d, $^3J_{CF}$ = 3.8 Hz), 124.1 (q, $^1J_{CF}$ = 270.4 Hz), 121.5, 119.4, 112.9, 34.4, 32.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{24}F_3N_2$: 421.1886; found: 421.1884.

(*E*)-8-(Oct-4-en-4-yl)-5-phenylimidazo[1,5-*a*]pyridine (3ag)

The reaction was performed according to general procedure A, with the exception that 0.6 equiv of $AlMe_3$ were used at 100 °C for 12 h.

Yield: 26 mg (17%); yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.17 (s, 1 H), 7.67–7.43 (m, 6 H), 6.63 (d, $^3J_{HH}$ = 6.8 Hz, 1 H), 6.46 (d, $^3J_{HH}$ = 6.9 Hz, 1 H), 5.91 (t, $^3J_{HH}$ = 7.3 Hz, 1 H), 2.52 (t, $^3J_{HH}$ = 7.1 Hz, 2 H), 2.32–2.16 (m, 2 H), 1.60–1.30 (m, 4 H), 0.98 (t, $^3J_{HH}$ = 7.4 Hz, 3 H), 0.88 (t, $^3J_{HH}$ = 7.3 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 136.8, 134.1, 133.9, 133.1, 131.6, 131.4, 129.5, 129.1, 128.2, 126.9, 121.2, 116.9, 113.2, 32.1, 30.3, 22.9, 21.8, 13.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{25}N_2$: 305.2018; found: 305.2018.

(*E*)-8-(4-Methylpent-2-en-2-yl)-5-phenylimidazo[1,5-*a*]pyridine (3ah)

The reaction was performed according to general procedure A, with the exception that 0.6 equiv of $AlMe_3$ were used at 100 °C for 12 h.

Yield: 98 mg (71%); yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.12 (s, 1 H), 7.63–7.43 (m, 6 H), 6.64 (d, $^3J_{HH}$ = 6.9 Hz, 1 H), 6.45 (d, $^3J_{HH}$ = 6.8 Hz, 1 H), 5.90–5.82 (m, 1 H), 2.85–2.65 (m, 1 H), 2.11–2.07 (m, 3 H), 1.07 (d, $^3J_{HH}$ = 6.7 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.0, 134.5, 134.0, 133.1, 130.7, 129.4, 129.3, 129.1, 128.2, 127.0, 121.3, 116.5, 113.2, 27.7, 22.7, 16.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{21}N_2$: 277.1705; found: 277.1707.

(*E*)-5-Phenyl-8-[1-(trimethylsilyl)hex-1-en-2-yl]imidazo[1,5-*a*]pyridine (3ai)

The reaction was performed according to general procedure A, with the exception that 0.6 equiv of $AlMe_3$ were used at 100 °C for 12 h.

Yield: 157 mg (90%); yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (s, 1 H), 7.64–7.62 (m, 2 H), 7.54–7.47 (m, 4 H), 6.67 (d, $^3J_{HH}$ = 7.2 Hz, 1 H), 6.48 (d, $^3J_{HH}$ = 6.8 Hz, 1 H), 6.00 (s, 1 H), 2.64 (t, $^3J_{HH}$ = 7.2 Hz, 2 H), 1.37–1.30 (m, 4 H), 0.86 (t, $^3J_{HH}$ = 6.8 Hz, 3 H), 0.23 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.1, 134.6, 134.0, 133.6, 131.1, 130.6, 129.6, 129.2, 128.3, 127.0, 121.4, 116.4, 113.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{29}N_2Si$: 349.2095; found: 349.2091.

C8-Alkenylation of 3-Substituted Imidazo[1,5-*a*]pyridines; General Procedure B

In a glovebox, a vial (20 mL) was charged with $Ni(cod)_2$ (7 mg, 5 mol%), PCy_3 (28 mg, 20 mol%) and **5** (0.5 mmol) in dry toluene (2 mL). The mixture was stirred for 5 min, followed by the addition of $AlMe_3$ (0.5 mL, 1.0 M in toluene, 100 mol%). After stirring for 5 min, alkyne **2** (1.1 equiv) was added. The vial was screw-capped and taken outside the glovebox. Following 6 h of stirring at 100 °C, the reaction mixture was added to CH_2Cl_2, stirred under air for 10 min, filtered through a pad of Celite and then concentrated in vacuo. The residue was purified by flash chromatography on silica gel (EtOAc–hexane, 1:9) to afford compounds **6** as the major products.

(*E*)-8-(4,4-Dimethylpent-2-en-2-yl)-3-phenylimidazo[1,5-*a*]pyridine (6aa)

The reaction was performed according to general procedure B.

Yield: 67 mg (46%); yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.15–8.07 (m, 1 H), 7.79–7.73 (m, 2 H), 7.55 (s, 1 H), 7.49 (t, $^3J_{HH}$ = 7.5 Hz, 2 H), 7.40 (t, $^3J_{HH}$ = 7.3 Hz, 1 H), 6.55–6.49 (m, 2 H), 5.93 (d, $^3J_{HH}$ = 1.1 Hz, 1 H), 2.18 (d, $^3J_{HH}$ = 1.0 Hz, 3 H), 1.24 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.5, 138.5, 138.1, 131.3, 130.8, 130.6, 128.9, 128.4, 128.0, 121.1, 119.4, 115.8, 113.2, 33.0, 33.8, 17.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{23}N_2$: 291.1861; found: 291.1862.

(*E*)-8-(3,3-Dimethyl-1-phenylbut-1-en-1-yl)-3-phenylimidazo[1,5-*a*]pyridine (6ab)

The reaction was performed according to general procedure B.

Yield: 146 mg (83%); yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.09 (d, $^3J_{HH}$ = 7.1 Hz, 1 H), 7.77–7.71 (m, 2 H), 7.60 (s, 1 H), 7.53–7.25 (m, 8 H), 6.44 (t, $^3J_{HH}$ = 6.9 Hz, 1 H), 6.38 (s, 1 H), 6.31 (d, $^3J_{HH}$ = 6.6 Hz, 1 H), 1.02 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.1, 140.1, 138.6, 136.0, 135.6, 131.5, 130.6, 130.1, 129.0, 128.6, 128.1, 127.9, 127.3, 121.5, 119.7, 118.5, 113.1, 34.4, 31.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{25}N_2$: 353.2018; found: 353.2012.

(*E*)-8-(Oct-4-en-4-yl)-3-phenylimidazo[1,5-*a*]pyridine (6ag)

The reaction was performed according to general procedure B, with the exception that 1.5 equiv of the alkyne were used at 130 °C.

Yield: 67 mg (44%); yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (d, $^3J_{HH}$ = 6.2 Hz, 1 H), 7.77 (d, $^3J_{HH}$ = 7.6 Hz, 2 H), 7.56 (s, 1 H), 7.49 (t, $^3J_{HH}$ = 7.5 Hz, 2 H), 7.40 (t, $^3J_{HH}$ = 7.3 Hz, 1 H), 6.56–6.47 (m, 2 H), 5.88 (t, $^3J_{HH}$ = 7.3 Hz, 1 H), 2.51 (t, $^3J_{HH}$ = 7.6 Hz, 2 H), 2.23 (q, $^3J_{HH}$ = 7.3 Hz, 2 H), 1.50 (sext, $^3J_{HH}$ = 7.3 Hz, 2 H), 1.37 (sext, $^3J_{HH}$ = 7.4 Hz, 2 H), 0.98 (t, $^3J_{HH}$ = 7.4 Hz, 3 H), 0.88 (t, $^3J_{HH}$ = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.5, 136.9, 135.6, 131.9, 131.6, 130.7, 128.9, 128.5, 128.1, 121.0, 119.5, 116.2, 113.2, 32.2, 30.3, 22.9, 21.8, 14.0, 13.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{25}N_2$: 305.2018; found: 305.2017.

(*E*)-8-(3,3-Dimethyl-1-phenylbut-1-en-1-yl)-3-(*p*-tolyl)imidazo[1,5-*a*]pyridine (6bb)

The reaction was performed according to general procedure B.

Yield: 152 mg (83%); yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.06 (d, $^3J_{HH}$ = 7.1 Hz, 1 H), 7.63 (d, $^3J_{HH}$ = 8.1 Hz, 2 H), 7.57 (s, 1 H), 7.33–7.27 (m, 7 H), 6.42 (t, $^3J_{HH}$ = 7.0 Hz, 1 H), 6.37 (s, 1 H), 6.28 (d, $^3J_{HH}$ = 6.5 Hz, 1 H), 2.40 (s, 3 H), 1.02 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.8, 140.0, 138.5, 138.3, 135.7, 135.4, 131.1, 129.9, 129.4, 127.8, 127.7, 127.5, 127.1, 121.1, 119.5, 118.2, 112.8, 34.2, 31.1, 21.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{27}N_2$: 367.2174; found: 367.2178.

(*E*)-8-(3,3-Dimethyl-1-phenylbut-1-en-1-yl)-3-(4-methoxyphenyl)imidazo[1,5-*a*]pyridine (6cb)

The reaction was performed according to general procedure B.

Yield: 130 mg (68%); yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.01 (d, $^3J_{HH}$ = 7.1 Hz, 1 H), 7.70–7.63 (m, 2 H), 7.55 (s, 1 H), 7.32–7.26 (m, 5 H), 7.05–6.99 (m, 2 H), 6.41 (t, $^3J_{HH}$ = 6.9 Hz, 1 H), 6.37 (s, 1 H), 6.30–6.24 (m, 1 H), 3.85 (s, 3 H), 1.01 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.7, 142.8, 140.0, 138.3, 135.7, 135.4, 130.9, 130.0, 129.4, 127.7, 127.1, 122.8, 120.9, 119.5, 118.1, 114.2, 112.7, 55.2, 34.2, 31.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{27}N_2O$: 383.2123; found: 383.2122.

(*E*)-8-(3,3-Dimethyl-1-phenylbut-1-en-1-yl)-3-(4-fluorophenyl)imidazo[1,5-*a*]pyridine (6db)

The reaction was performed according to general procedure B.

Yield: 67mg (36%); yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (d, $^3J_{HH}$ = 7.1 Hz, 1 H), 7.74–7.69 (m, 2 H), 7.57 (s, 1 H), 7.35–7.25 (m, 5 H), 7.18 (t, $^3J_{HH}$ = 8.7 Hz, 2 H), 6.44 (t, $^3J_{HH}$ = 6.9 Hz, 1 H), 6.36 (s, 1 H), 6.31 (d, $^3J_{HH}$ = 6.7 Hz, 1 H), 1.02 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.7 (d, $^1J_{CF}$ = 247.4 Hz), 143.1, 140.0, 137.5, 136.0, 135.4, 131.4, 129.9 (d, $^3J_{CF}$ = 8.3 Hz), 127.8, 127.2, 126.7, 121.4, 119.3, 118.4, 116.0 (d, $^2J_{CF}$ = 21.8 Hz), 113.2, 34.3, 31.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{24}N_2F$: 371.1924; found: 371.1916.

(*E*)-8-(3,3-Dimethyl-1-phenylbut-1-en-1-yl)-3-[4-(trifluoromethyl)phenyl]imidazo[1,5-*a*]pyridine (6eb)

The reaction was performed according to general procedure B.

Yield: 63 mg (30%); yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (d, $^3J_{HH}$ = 7.2 Hz, 1 H), 7.90 (d, $^3J_{HH}$ = 8.1 Hz, 2 H), 7.75 (d, $^3J_{HH}$ = 8.3 Hz, 2 H), 7.61 (s, 1 H), 7.36–7.25 (m, 5 H), 6.52 (t, $^3J_{HH}$ = 6.9 Hz, 1 H), 6.38 (d, $^3J_{HH}$ = 6.7 Hz, 1 H), 6.35 (s, 1 H), 1.03 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.4, 139.9, 136.9, 136.2, 135.4, 134.0, 132.1, 130.0, 128.0, 127.9, 127.3, 125.9 (d, $^3J_{CF}$ = 3.3 Hz), 122.1, 119.3, 118.9, 113.8, 34.4, 31.1.

HRMS (APCI): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{24}N_2F_3$: 421.1892; found: 421.1883.

(*E*)-8-(3,3-Dimethyl-1-phenylbut-1-en-1-yl)-3-(3-fluorophenyl)imidazo[1,5-*a*]pyridine (6fb)

The reaction was performed according to general procedure B.

Yield: 80 mg (43%); yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.09 (d, $^3J_{HH}$ = 7.1 Hz, 1 H), 7.58 (s, 1 H), 7.57–7.40 (m, 3 H), 7.35–7.25 (m, 5 H), 7.14–7.05 (m, 1 H), 6.49 (t, $^3J_{HH}$ = 7.0 Hz, 1 H), 7.37–7.32 (m, 2 H), 1.02 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.0 (d, $^1J_{CF}$ = 245.2 Hz), 143.3, 140.0, 137.1, 136.1, 135.4, 132.5 (d, $^3J_{CF}$ = 8.3 Hz), 131.7, 130.5 (d, $^3J_{CF}$ = 8.4 Hz), 130.0, 127.8, 127.3, 123.5, 121.7, 119.4, 118.7, 115.4 (d, $^2J_{CF}$ = 21.0 Hz), 114.9 (d, $^2J_{CF}$ = 22.8 Hz), 113.5, 34.4, 31.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{24}N_2F$: 371.1924; found: 371.1920.

(*E*)-3-([1,1′-Biphenyl]-4-yl)-8-(3,3-dimethyl-1-phenylbut-1-en-1-yl)imidazo[1,5-*a*]pyridine (6gb)

The reaction was performed according to general procedure B.

Yield: 81 mg (38%); yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.16 (d, $^3J_{HH}$ = 7.1 Hz, 1 H), 7.84 (d, $^3J_{HH}$ = 8.3 Hz, 2 H), 7.73 (d, $^3J_{HH}$ = 8.2 Hz, 2 H), 7.68–7.61 (m, 3 H), 7.51–7.26 (m, 8 H), 6.47 (t, $^3J_{HH}$ = 6.9 Hz, 1 H), 6.39 (s, 1 H), 6.33 (d, $^3J_{HH}$ = 6.8 Hz, 1 H), 1.03 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.1, 141.1, 140.3, 140.0, 138.2, 135.9, 135.4, 131.5, 130.0, 129.4, 128.8, 128.3, 128.1, 127.8, 127.5, 127.2, 127.0, 121.6, 119.7, 118.4, 113.1, 34.3, 31.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{31}H_{29}N_2$: 429.2331; found: 429.2325.

(*E*)-3-(*tert*-Butyl)-8-(3,3-dimethyl-1-phenylbut-1-en-1-yl)imidazo[1,5-*a*]pyridine (6hb)

The reaction was performed according to general procedure B.

Yield: 98 mg (59%); yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 (d, $^3J_{HH}$ = 7.4 Hz, 1 H), 7.41 (s, 1 H), 7.32–7.21 (m, 5 H), 6.37 (t, $^3J_{HH}$ = 7.0 Hz, 1 H), 6.31 (s, 1 H), 6.20 (d, $^3J_{HH}$ = 6.8 Hz, 1 H), 1.52 (s, 9 H), 0.98 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.2, 142.8, 140.2, 136.0, 135.5, 131.5, 130.0, 127.7, 127.0, 120.9, 118.8, 116.8, 111.6, 34.3, 33.3, 31.1, 28.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{29}N_2$: 333.2331, found: 333.2338.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561438.

References

(1) For selected reviews, see: (a) Wang, D. H.; Engle, K. M.; Shi, B. F.; Yu, J.-Q. *Science* **2010**, *327*, 315. (b) Chen, X.; Engle, K. M.; Wang, D. H.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2009**, *48*, 5094. (c) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074. (d) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem. Int. Ed.* **2009**, *48*, 9792. (e) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (f) Chiusoli, G. P.; Catellani, M.; Costa, M.; Motti, E.; Della Ca', N.; Maestri, G. *Coord. Chem. Rev.* **2010**, *254*, 456. (g) McGlacken, G. P.; Bateman, L. M. *Chem. Soc. Rev.* **2009**, *38*, 2447. (h) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**,

107, 174. (i) Godula, K.; Sames, D. *Science* **2006**, *312*, 67. (j) Albrecht, M. *Chem. Rev.* **2010**, *110*, 576. (k) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (l) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200. (m) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem. Int. Ed.* **2012**, *51*, 8960. (n) Kuhl, N.; Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F. *Angew. Chem. Int. Ed.* **2012**, *51*, 10236. (o) Girard, S. A.; Knauber, T.; Li, C.-J. *Angew. Chem. Int. Ed.* **2014**, *53*, 74. (p) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315. (q) Ackermann, L. *Acc. Chem. Res.* **2014**, *47*, 281. (r) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335. (s) Moselage, M.; Li, J.; Ackermann, L. *ACS Catal.* **2016**, *6*, 498. (t) Kim, J. H.; Gensch, T.; Zhao, D.; Stegemann, L.; Strassert, C. A.; Glorius, F. *Angew. Chem. Int. Ed.* **2015**, *54*, 10975.

(2) (a) Yamaguchi, E.; Shibahara, F.; Murai, T. *J. Org. Chem.* **2011**, *76*, 6146. (b) Shibahara, F.; Sugiura, R.; Yamaguchi, E.; Kitagawa, A.; Murai, T. *J. Org. Chem.* **2009**, *74*, 3566. (c) Shibahara, F.; Dohke, Y.; Murai, T. *J. Org. Chem.* **2012**, *77*, 5381. (d) Salassa, L.; Garino, C.; Albertino, A.; Volpi, G.; Nervi, C.; Gobetto, R.; Hardcastle, K. I. *Organometallics* **2008**, *27*, 1427. (e) Volpi, G.; Garino, C.; Salassa, L.; Fiedler, J.; Hardcastle, K. I.; Gobetto, R.; Nervi, C. *Chem. Eur. J.* **2009**, *15*, 6415.

(3) (a) Alcarazo, M.; Roseblade, S. J.; Cowley, A. R.; Fernández, R.; Brown, J. M.; Lassaletta, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 3290. (b) Burstein, C.; Lehmann, C. W.; Glorius, F. *Tetrahedron* **2005**, *61*, 6207. (c) Hahn, F. E. *Angew. Chem. Int. Ed.* **2006**, *45*, 1348. (d) Fürstner, A.; Alcarazo, M.; Krause, H.; Lehmann, C. W. *J. Am. Chem. Soc.* **2007**, *129*, 12676. (e) Hutt, J. T.; Aron, Z. D. *Org. Lett.* **2011**, *13*, 5256.

(4) (a) Davey, D.; Erhardt, P. W.; Lumma, W. C.; Wiggins, J.; Sullivan, M.; Pang, D.; Cantor, E. *J. Med. Chem.* **1987**, *30*, 1337. (b) Ford, N. F.; Browne, L. J.; Campbell, T.; Gemenden, C.; Goldstein, R.; Gude, C.; Wasley, J. W. F. *J. Med. Chem.* **1987**, *30*, 1337. (c) Pettit, G. R.; Collins, J. C.; Knight, J. C.; Herald, D. L.; Nieman, R. A.; Williams, M. D.; Pettit, R. K. *J. Nat. Prod.* **2003**, *66*, 544. (d) Calcul, L.; Longeon, A.; Mourabit, A. A.; Guyot, M.; Bourguet-Kondracki, M. *Tetrahedron* **2003**, *59*, 6539. (e) Rajeshkumar, V.; Lee, T.-H.; Chuang, S.-C. *Org. Lett.* **2013**, *15*, 1468.

(5) (a) Shibahara, F.; Murai, T. *Asian J. Org. Chem.* **2013**, *2*, 624. (b) Liu, B.; Huang, Y.; Lan, J.; Song, F.; You, J. *Chem. Sci.* **2013**, *4*, 2163. (c) Yamaguchi, E.; Shibahara, F.; Murai, T. *Chem. Lett.* **2011**, *40*, 939. (d) Shibahara, F.; Dohke, Y.; Murai, T. *J. Org. Chem.* **2012**, *77*, 5381. (e) Huang, C.; Giokaris, A.; Gevorgyan, V. *Chem. Lett.* **2011**, *40*, 1053.

(6) (a) Tsai, C.-C.; Shih, W.-C.; Fang, C.-H.; Li, C.-Y.; Ong, T.-G.; Yap, G. P. A. *J. Am. Chem. Soc.* **2010**, *132*, 11887. (b) Shih, W.-C.; Chen, W.-C.; Lai, Y.-C.; Yu, M.-S.; Ho, J.-J.; Yap, G. P. A.; Ong, T.-G. *Org. Lett.* **2012**, *14*, 2046. (c) Lee, W.-C.; Wang, C.-H.; Lin, Y.-H.; Shih, W.-C.; Ong, T.-G. *Org. Lett.* **2013**, *15*, 5358.

(7) (a) Nakao, Y.; Idei, H.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2009**, *131*, 15996. (b) Nakao, Y.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2008**, *130*, 2448. (c) Nakao, Y.; Idei, H.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2009**, *131*, 5070. (d) Nakao, Y.; Morita, E.; Idei, H.; Hiyama, T. *J. Am. Chem. Soc.* **2011**, *133*, 3264. (e) Nakao, Y.; Yamada, Y.; Kashihara, N.; Hiyama, T. *J. Am. Chem. Soc.* **2010**, *132*, 13666.

(8) Shiota, H.; Ano, Y.; Aihara, Y.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 14952.

(9) Yu, M.-S.; Lee, W.-C.; Chen, C.-H.; Tsai, F.-Y.; Ong, T.-G. *Org. Lett.* **2014**, *16*, 4826.

(10) See details in Table S3 in the Supporting Information.

(11) *Purification of Laboratory Chemicals*, 6th ed.; Armarego, W. L. F.; Christina, C. L. L., Eds.; Butterworth-Heinemann: Burlington, **2009**.

(12) (a) Ardugngo, A. J.; Krafczyk, R.; Schmutzler, R.; Craig, H. A.; Goerlich, J. R.; Marshall, W. J.; Unverzagt, M. *Tetrahedron* **1999**, *55*, 14523. (b) Hintermann, L. *Beilstein J. Org. Chem.* **2007**, *3*, 22.

(13) Tang, P.; Wang, W.; Ritter, T. *J. Am. Chem. Soc.* **2011**, *133*, 11482.

(14) (a) Hosseini-Sarvari, M.; Sharghi, H. *J. Org. Chem.* **2006**, *71*, 6652. (b) Bower, J. D.; Ramage, G. R. *J. Chem. Soc.* **1955**, 2834.