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Titanium-Catalyzed, One-Pot Synthesis of 2-Amino-3-cyanopyridines

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Abstract: Earth-abundant and inexpensive titanium can catalyze alkyne iminoamination, which generates tautomers of 1,3-diimines. Upon treatment with base (DBU) and malononitrile, the multicomponent coupling product is converted to 2-amino-3-cyanopyridines in a one-pot procedure in good to modest yields. There is substantial control of regioselectivity for the substituents on the pyridine ring and on the 2-amino group. Several studies were done that provide significant evidence for a Dimroth rearrangement mechanism for 2-aminopyridine formation, including isolation of a 2-imino-1,2-dihydropyridine intermediate that undergoes rearrangement under the reaction conditions.

Keywords: heterocycles; multicomponent reactions; pyridines; titanium

Introduction

The pyridine[1] core is one of the most important heterocyclic ring structures found in pharmaceuticals and natural products. Among pyridine structures, 2-amino-3-cyanopyridine derivatives have been found to be an important subclass. Substituted 2-amino-3-cyanopyridine derivatives exhibit biological activities and are, for example, kinase inhibitors,[2] antimicrobial agents,[3] antitumour agents,[4] anti-inflammatory agents,[5] cannabinoid receptor agonists[6] and anticonvulsants.[7] In addition, they are also being studied for their optical properties.[8]

In recent studies we have applied earth-abundant, non-toxic titanium to the synthesis of important heterocyclic classes.[9] The procedures involve a titanium-catalyzed multicomponent coupling reaction between a primary amine, isonitrile, and an alkyne to generate tautomers of 1,3-diimines; the alkyne undergoes iminoamination, addition of imine and amine across the triple bond (Figure 1).[10]

Here, we report that 2-amino-3-cyanopyridines (**1**) are available in a one-pot procedure from the coupling of alkynes, primary amines, isonitriles, and malononitrile in good to modest yields.[11] The overall transformation is shown in Scheme 1. Of particular mechanistic interest is the fact that the primary amine is on the same carbon as R^2 from the alkyne in the iminoamination intermediate (brackets), but the amine is on one of the carbons derived from the malononitrile in the 2-aminopyridine product, a detail that needed to be accounted for in the proposed mechanism (*vide infra*).

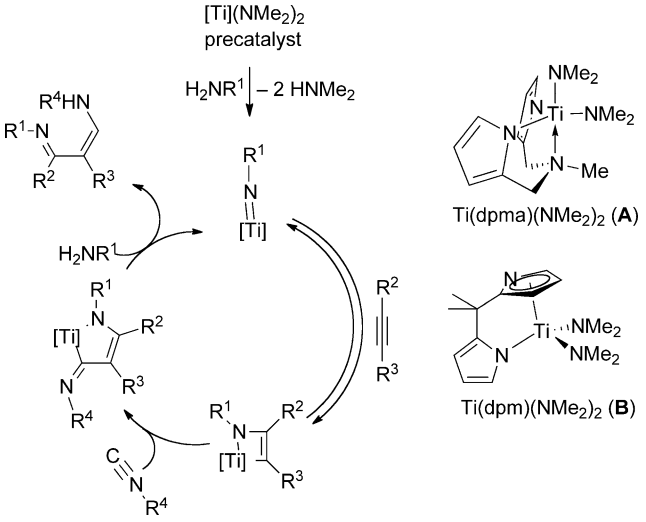
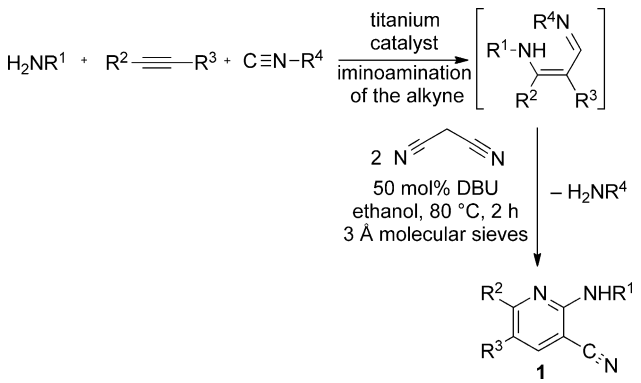
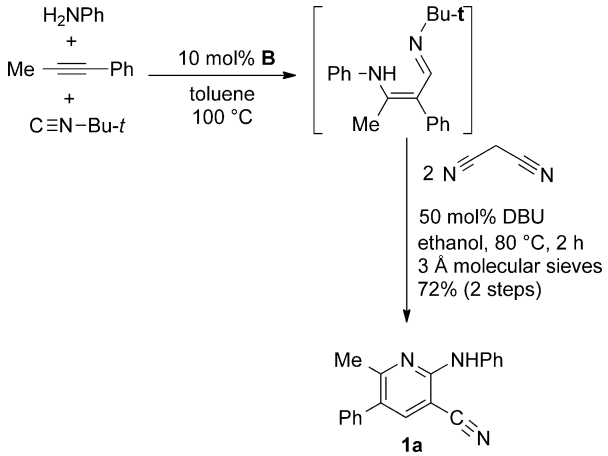


Figure 1. Proposed catalytic cycle for iminoamination of an alkyne and structures of the precatalysts Ti(dpma)$(NMe_2)_2$ (**A**) and Ti(dpm)$(NMe_2)_2$ (**B**).



Scheme 1. One-pot synthesis of 2-amino-3-cyanopyridines (**1**) using a titanium-catalyzed multicomponent coupling.



Scheme 2. One-pot synthesis **1a**.

Results and Discussion

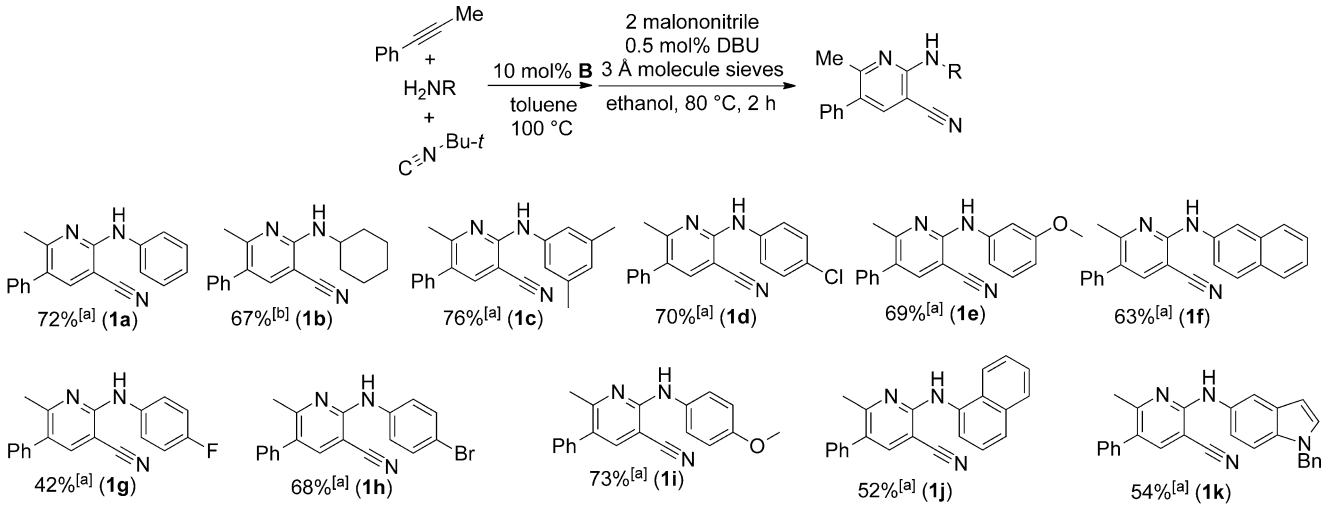
The two titanium catalysts employed in this work are shown in Figure 1. The pyrrole-based ancillary ligands are available in a single step from commercially available compounds.[12] Placement of the ligands on titanium occurs in high yield with commercially available $Ti(NMe_2)_4$.[13]

Catalyst **A** is less active but is also less prone to side reactions with more reactive terminal alkynes. Catalyst **B** is more active and is often used for less reactive internal alkynes. In the end, each catalyst can exhibit somewhat different regioselectivities, and these two catalysts were screened during optimization. For most reactions explored here, the dipyrrolylmethane-based **B** was optimal.

Our initial screens utilized multicomponent coupling between aniline, 1-phenylpropyne, *tert*-butyl isonitrile and malononitrile. The 2-amino-3-cyanopyridine (**1a**) was obtained in 72% yield using catalytic DBU in dry ethanol (Scheme 2).

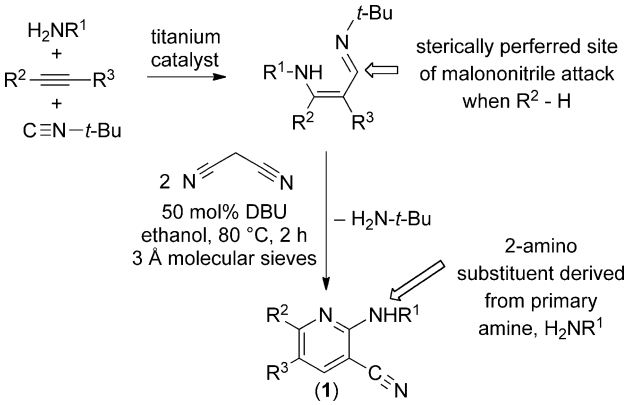
First, we examined a single alkyne, 1-phenylpropyne, with a variety of amines and *tert*-butyl isonitrile; these reactions gave a host of 2-amino-3-cyano-5-phenyl-6-methylpyridines with different groups on the 2-amino nitrogen. The results with 1-phenylpropyne are found in Figure 2. The multicomponent coupling reaction is regioselective, and the phenyl group derived from 1-phenylpropyne is found in the 5-position of all the pyridine products.[14]

The reaction was amenable to the use of a variety of aromatic and heterocyclic amines as well as some alkylamines. A few similar alkylamines such as 1-aminohexane, benzylamine, and benzhydrylamine provid-



[a] Isolated yields after 2 steps.
[b] 10 mol% **A** was used in coupling.

Figure 2. Examples of substituted 2-amino-3-cyanopyridine syntheses using 1-phenylpropyne and a variety of primary aryl and alkylamines.



Scheme 3. Primary amine selectively becomes the 2-amino substituent in **1** when internal alkynes are employed.

ed the 3-component coupling product; however, the cyclization with malononitrile to generate the pyridine was not successful with the conditions developed. Yields ranged from 76–42% with the average being 64% for 11 examples in Figure 2 with this one-pot procedure.

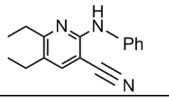
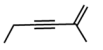
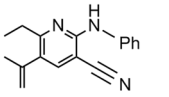
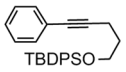
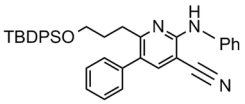
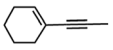
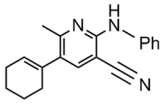
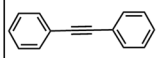
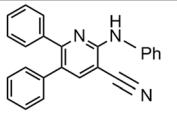
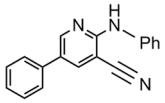
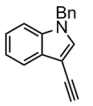
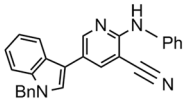
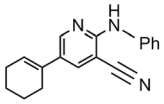
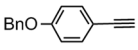
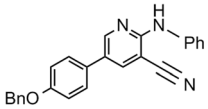
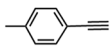
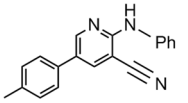
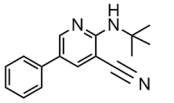
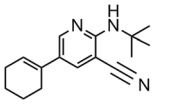
The primary amine in the reaction is selectively found as the group in the 2-position of the product (Scheme 3) when using internal alkynes. This is likely due to initial malononitrile attack on the more sterically available formimine carbon rather than the ketimine carbon of the multicomponent coupling intermediate and is true for all the compounds derived from internal alkynes examined.

In a second series of reactions, the amine was held constant as either aniline or cyclohexylamine and the alkyne was varied. For these studies, we explored a mix of terminal and internal alkynes with aromatic and alkyl substituents. The results are shown in Table 1. In general, if one of the alkyne substituents binds to the alkyne with an sp^2-carbon, that aromatic or vinyl group is in the 5-position of the isolated pyridine product.[14]

Several possible reaction mechanisms for the formation of **1** can be envisioned. Among these is the possibility of a Dimroth rearrangement[15] being involved in the formation of the 2-aminopyridines. The proposed mechanism is shown in Scheme 4 starting from the 3-component coupling product. A key intermediate in the Dimroth rearrangement, which involves isomerization where exo- and endocyclic nitrogen atoms are exchanged, (Scheme 4) for this system is 2-imino-1,2-dihydropyridine **2**. Rearrangement of **2** would lead to the observed product and would be thermodynamically driven by aromatization of the pyridine ring.

We postulated that intermediate **2** might be available from the same multicomponent coupling product by use of a less nucleophilic base, e.g., NEt_3, which would be sufficient to reach this intermediate but per-

Table 1. Other examples of substituted 2-amino-3-cyanopyridine syntheses.[a]

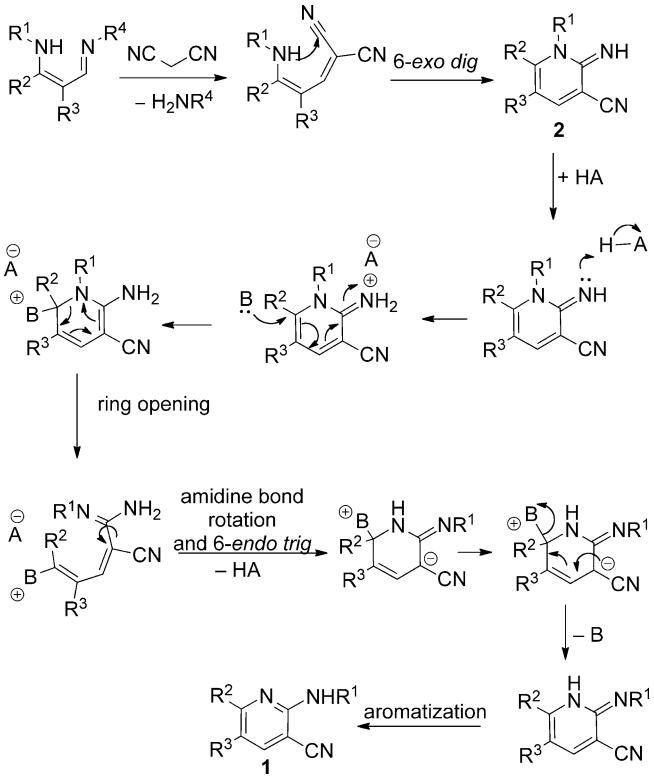
	Alkyne	Product	Yield[b]
1l			64
1m			60
1n			68
1o			55
1p			43[c]
1q			62
1r			49
1s			56
1t			66
1u			58
1v			58[d]
1w			53[d]

[a] *Conditions:* 1.2–1.5 mmol *tert*-butyl isonitrile, 1 mmol aniline, 1 mmol alkyne, 10 mol% **B**, 2 mL toluene, 100 °C, 48 h. Then, 2 mmol malononitrile, 0.5 mmol DBU, 200 mg of 3 Å sieves, 2 mL absolute ethanol, 2 h, 80 °C.

[b] Isolated yield.

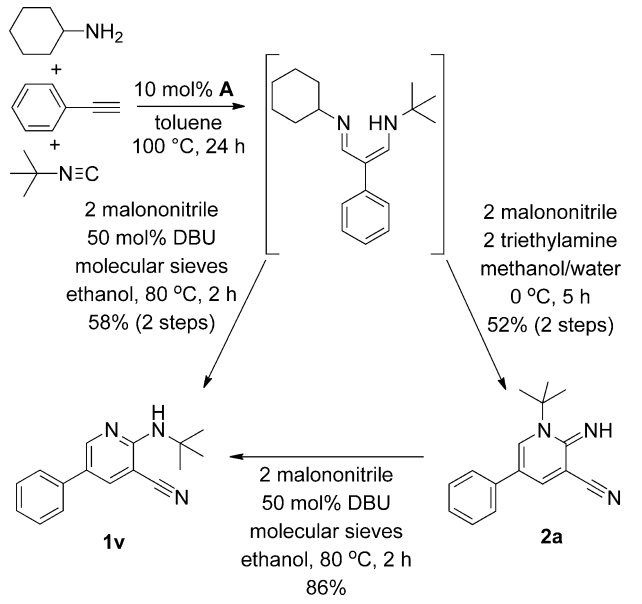
[c] 20 mol% **B** was used.

[d] 1 mmol cyclohexylamine used in place of aniline and 10 mol% **A** used in place of **B**.



Scheme 4. Proposed mechanism for 2-aminopyridine formation. B = base, HA = acid.

haps not strong enough for the ring opening step that DBU can accomplish.[16] Once isolated, submitting the 2-iminopyridine intermediate **2** to the DBU cyclization conditions should give the 2-aminopyridine product **1** *via* exo-/endocyclic nitrogen exchange.



Scheme 5. Synthesis of **2a** and **1v** from the same multicomponent coupling product and conversion of **2a** to **1v**.

We found that synthesis of a 2-iminopyridine product **2a** was possible using the conditions shown in Scheme 5. Then, **2a** was converted to the 2-aminopyridine **1v** in the presence of DBU and malononitrile in ethanol in 86% yield.

Both DBU and malononitrile were required for conversion of **2a** to **1v**; leaving either reagent out of the solution resulted in no reaction. Apparently, malononitrile has a dual role in 2-aminopyridine synthesis; it acts as both reagent and as catalytic acid for the rearrangement. Consistent with this, replacing malononitrile with phenol as the acid also resulted in Dimroth rearrangement of **2a** in the presence of DBU. Consequently, we propose that protonation of **2** is required prior to base-promoted ring opening (Scheme 4).

Conclusions

Titanium-catalyzed multicomponent coupling provides an expedient route to the pyridine core structure with good control of regioselectivity. This new 4-component, one-pot route provides 2-amino-3-cyanopyridines in good to modest yields.

The reaction involves the initial 3-component coupling (3CC) of an amine, isonitrile and alkyne in the presence of a titanium catalyst. The product is not isolated. Instead, it is treated with malononitrile, ethanol, molecular sieves and catalytic DBU to give the 2-amino-3-cyanopyridine products from the one-pot procedure.

In all cases where an internal alkyne was used (Scheme 1, R^2 and $R^3 \neq H$), the amine substituent found in the 2-position of the product is derived from the primary amine used in the multicomponent coupling reaction (Figure 2, Table 1 **1l–1p**). If $R^2 = H$ and the primary amine is an aniline derivative, then the 2-amino group bears the aromatic group of the aniline (Table 1 **1q–1u**). If $R^2 = H$ and both the primary amine and isonitrile bear alkyl groups, the larger of the two alkyl groups preferentially is found on the 2-amino group (Table 1, **1v–1u**).

If the alkyne has an sp^2-hybridized substituent (vinyl, aromatic, or heteroaromatic), there is usually a strong preference for this group to be placed as R^3 in Scheme 1.[14]

A Dimroth mechanism was proposed for the transformation (Scheme 4). Dimroth rearrangements involve exchange of endo- and exocyclic nitrogen atoms, often with aromatization of a heterocycle driving the reaction. In this case, it was found that addition of malononitrile and triethylamine in methanol/water provides the 2-imino-1,2-dihydropyridine (**2**), at least in the case where the 3-component coupling compound is derived from cyclohexylamine, phenylacetylene, and *tert*-butyl isonitrile (Scheme 5). Com-

pound **2** is likely derived from simple replacement of NR^4 (Scheme 1) in the multicomponent coupling product by the central carbon of malononitrile, catalyzed by triethylamine. After this first step in the proposed mechanism (Scheme 4), the compound can undergo 6-*endo dig* cyclization to give **2**, and if the base is NEt_3 this is where the reaction stops.

If the reaction with malononitrile and the 3CC product is run in the presence of the more nucleophilic DBU, the reaction proceeds to the 2-amino-3-cyanopyridine (**1**). Consistent with a Dimroth rearrangement, subjecting **2** to the reaction conditions, malononitrile and DBU, also provides **1** in good yield. In the conversion of **2** to **1** (Scheme 5), both the malononitrile and DBU were required for the rearrangement to take place, otherwise **2** was simply recovered. The base, DBU, is required for the Dimroth ring opening, but what is the purpose of the malononitrile in the rearrangement? Naturally, malononitrile is acidic, and we postulated that an acid was also required. Replacement of malononitrile with phenol, a compound with a comparable pK_a in water,[17] leads to Dimroth rearrangement of **2** to **1** in the presence of DBU. Consequently, we propose that malononitrile has a duel role in the synthesis of **1**, reagent and catalytic acid. It may be that the optimized reaction conditions involve 2 equiv. of malononitrile because of these two roles, and that reoptimization of the reaction could be done with 1 equivalent of malononitrile and an external acid if desired.

Experimental Section

General Considerations:

All manipulations of air-sensitive compounds were carried out in an MBraun drybox under a purified nitrogen atmosphere. Toluene was purified by first sparging with dry nitrogen to remove oxygen and then running through activated alumina to remove water. ^1H and ^{13}C NMR spectra were recorded on VXR-500 spectrometers. Melting points are uncorrected and measured on a Mel-Temp II apparatus (Laboratory Devices Inc, USA) with a mercury thermometer in an open capillary tube. $Ti(NMe_2)_2(dpma)$ (**A**) and $Ti(NMe_2)_2(dpm)$ (**B**) were made following the literature procedures.[13] Alkynes were purchased either from Sigma–Aldrich or Oakwood chemicals and were distilled from CaO under dry nitrogen. Amines were purchased from Sigma–Aldrich, dried over KOH, and distilled under dry nitrogen. *tert*-Butyl isonitrile was prepared from H_2NBu-*t*, $CHCl_3$, and aqueous base according to the literature procedure and purified by distillation under dry nitrogen.[18] Malononitrile, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and silica gel were purchased from Sigma–Aldrich and used as received. Molecular sieves as 3 Å, 1/16" pellets were purchased from Spectrum chemicals and were activated by heating under dynamic vacuum. Absolute ethanol was purchased from KOPTEC and used as received. Hexanes and ethyl acetate were purchased from Mallinckrodt Chemicals and used as received. Extinction coefficients for all compounds were acquired in CH_2Cl_2 solutions using a Varian Cary 50 UV-Visible spectrophotometer.

6-Methyl-5-phenyl-2-(phenylamino)nicotinonitrile (1a)[19]

In a N_2 filled glove box, a 40-mL pressure tube, equipped with a magnetic stirbar, containing catalyst **B** (30.8 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with aniline (95 mg, 1 mmol), 1-phenylpropyne (116 mg, 1 mmol), and *tert*-butyl isonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 48 h at 100 °C in a silicone oil bath. The pressure tube was cooled to room temperature. Then, the tube was charged with malononitrile (132 mg, 2 mmol), DBU (76 mg, 0.5 mmol), molecular sieves (200 mg), and absolute ethanol (2 mL). The mixture was heated for 2 h at 80 °C in a silicone oil bath. After completion of the reaction, the crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford the desired compound as a yellow solid; yield: 205 mg (72%); mp 119–121 °C. ^1H NMR ($CDCl_3$, 500 MHz): $\delta = 2.53$ (3H, s, CH_3), 7.14–7.17 (2H, br, CH-Ar, NH-aniline), 7.32–7.34 (2H, d, 8 Hz, CH-Ar), 7.40–7.45 (3H, m, CH-Ar), 7.47–7.51 (2H, m, CH-Ar), 7.66 (1H, s, 4-CH-pyridine), 7.76–7.78 (2H, d, 8.5 Hz, CH-Ar); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): $\delta = 23.9$, 90.3, 116.5, 119.9, 123.2, 127.5, 127.9, 128.4, 128.7, 128.9, 138.0, 138.9, 141.9, 153.9, 159.9; MS (EI): $m/z = 285$; electronic absorption (CH_2Cl_2): λ (ε, $M^{-1}cm^{-1}$) = 294 (24,800), 342 nm (1,100); elemental analysis: found: C 80.10, H 5.25, N 14.65; calcd.; C 79.98, H 5.30, N 14.73.

2-(Cyclohexylamino)-6-methyl-5-phenylnicotinonitrile (1b)

In a N_2 filled glove box, a 40-mL pressure tube, equipped with a magnetic stirbar, containing catalyst **B** (30.8 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with cyclohexylamine (99 mg, 1 mmol), 1-phenylpropyne (116 mg, 1 mmol), and *tert*-butyl isonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 48 h at 100 °C in a silicone oil bath. The pressure tube was cooled to room temperature. Then, the tube was charged with malononitrile (132 mg, 2 mmol), DBU (76 mg, 1 mmol), molecular sieves (200 mg), and absolute ethanol (2 mL). The mixture was heated for 2 h at 80 °C in a silicone oil bath. After completion of the reaction, the crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford the desired compound as a brown solid; yield: 195 mg (67%); mp 144–147 °C. ^1H NMR ($CDCl_3$, 500 MHz): $\delta = 1.25$–1.32 (4H, m, CH_2), 1.43–1.48 (2H, m, CH_2) 1.79–1.83 (2H, m, CH_2), 2.07–2.12 (2H, m, CH_2), 2.42 (3H, s, CH_3), 4.12–4.13 (1H, m, CH), 4.96–4.98 (1H, d, 8 Hz, NH-cyclohexyl), 7.26–7.27 (2H, d, 7 Hz, CH-Ar), 7.36–7.39 (1H, m, 7 Hz, CH-Ar), 7.44–7.41 (2H, t, 7 Hz, CH-Ar), 7.50 (1H, s, 4-CH-pyridine); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): $\delta =$ 24.1, 24.9, 25.7, 33.2, 49.7, 88.3, 117.2, 125.6, 127.2, 128.4, 129.1, 138.8, 141.8, 156.4, 160.3; MS (EI): $m/z = 291$; electronic absorption (CH_2Cl_2): λ (ε, $M^{-1}cm^{-1}$) = 272 (14,400),

347 nm (4,400); elemental analysis: found: C 78.29, H 7.20, N 14.51; calcd.: C 78.32, H 7.26, N 14.42.

2-[(3,5-Dimethylphenyl)amino]-6-methyl-5-phenyl-nicotinonitrile (1c)

In a N_2 filled glove box, a 40-mL pressure tube, equipped with a magnetic stirbar, containing catalyst **B** (30.8 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with 3,5-dimethylaniline (121 mg, 1 mmol), 1-phenylpropyne (116 mg, 1 mmol), and *tert*-butyl isonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 48 h at 100 °C in a silicone oil bath. The pressure tube was cooled to room temperature. Then, the tube was charged with malononitrile (132 mg, 2 mmol), DBU (76 mg, 0.5 mmol), molecular sieves (200 mg), and absolute ethanol (2 mL). The mixture was heated for 2 h at 80 °C in a silicone oil bath. After completion of the reaction, the crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford the desired compound as a brown solid; yield: 237 mg (76%); mp 98–100 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 2.40$ (6H, s, CH_3), 2.54 (3H, s, CH_3), 6.82 (1H, br, NH-3,5-dimethylaniline), 7.01 (1H, s, CH-Ar), 7.32–7.34 (2H, d, 8.5 Hz, CH-Ar), 7.39 (2H, s, CH-Ar), 7.43–7.44 (1H, m, CH-Ar), 7.47–7.51 (2H, m, CH-Ar), 7.65 (1H, s, 4-CH-pyridine); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): $\delta = 21.3$, 23.9, 90.2, 116.5, 117.8, 125.1, 127.4, 127.7, 128.4, 128.9, 138.1, 138.4, 138.7, 141.9, 154.1, 160.0; MS (EI): $m/z =$ 313; electronic absorption (CH_2Cl_2): λ (ε, $M^{-1}cm^{-1}$) = 297 (20,600), 342 nm (4,900); elemental analysis: found: C 80.53, H 6.19, N, 13.28; calcd.: C 80.48, H 6.11, N 13.41.

2-[(4-Chlorophenyl)amino]-6-methyl-5-phenyl-nicotinonitrile (1d)

In a N_2 filled glove box, a 40-mL pressure tube, equipped with a magnetic stirbar, containing catalyst **B** (30.8 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with 4-chloroaniline (127 mg, 1 mmol), 1-phenylpropyne (116 mg, 1 mmol), and *tert*-butyl isonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 48 h at 100 °C in a silicone oil bath. The pressure tube was cooled to room temperature. Then, the tube was charged with malononitrile (132 mg, 2 mmol), DBU (76 mg, 0.5 mmol), molecular sieves (200 mg), and absolute ethanol (2 mL). The mixture was heated for 2 h at 80 °C in a silicone oil bath. After completion of the reaction, the crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford the desired compound as a brown solid; yield: 223 mg (70%); mp 167–169 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 2.51$ (3H, s, CH_3), 7.08 (1H, br, NH-4-chloroaniline), 7.30–7.32 (2H, d, 8.5 Hz, CH-Ar), 7.34–7.36 (2H, d, 9 Hz, CH-Ar), 7.42–7.44 (1H, m, CH-Ar), 7.46–7.49 (2H, m, CH-Ar), 7.67 (1H, s, 4-CH-pyridine), 7.69–7.70 (2H, d, 9 Hz, CH-Ar); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): $\delta = 24.0$, 90.5, 103.6, 107.7, 121.2, 127.6, 128.1, 128.2, 128.4, 128.5, 128.8, 128.9, 142.1, 153.7, 160.1; MS (EI): $m/z = 319$; electronic absorption (CH_2Cl_2): λ (ε, $M^{-1}cm^{-1}$) = 298 (24,400), 347 nm (4,900); elemental analysis: found: C 71.25, H 4.37, N 13.21; calcd.: C 71.36, H 4.41, N 13.14.

2-[(3-methoxyphenyl)amino]-6-methyl-5-phenyl-nicotinonitrile (1e)

In a N_2 filled glove box, a 40-mL pressure tube, equipped with a magnetic stirbar, containing catalyst **B** (30.8 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with 3-methoxyaniline (123 mg, 1 mmol), 1-phenylpropyne (116 mg, 1 mmol), and *tert*-butyl isonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 48 h at 100 °C in a silicone oil bath. The pressure tube was cooled to room temperature. Then, the tube was charged with malononitrile (132 mg, 2 mmol), DBU (76 mg, 0.5 mmol), molecular sieves (200 mg), and absolute ethanol (2 mL). The mixture was heated for 2 h at 80 °C in a silicone oil bath. After completion of the reaction, the crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford the desired compound as a brown solid; yield: 217 mg (69%); mp 129–130 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 2.53$ (3H, s, CH_3), 3.88 (3H, s, OCH_3), 6.69–6.71 (2H, dd, 1 Hz, 6 Hz, CH-Ar), 7.09 (1H, br, NH-3-methoxyaniline), 7.20–7.28 (1H, m, CH-Ar), 7.29–7.33 (3H, m, CH-Ar), 7.42–7.44 (2H, d, 7.5 Hz, CH-Ar), 7.46–7.50 (2H, m, CH-Ar). 7.59–7.60 (1H, m, CH-Ar). 7.66 (1H, s, 4-CH-pyridine); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): $\delta = 21.3$, 23.9, 90.2, 116.5, 117.8, 125.1, 127.4, 127.7, 128.4, 128.9, 138.1, 138.4, 138.7, 141.9, 154.1, 160.0; MS (EI): $m/z =$ 315; electronic absorption (CH_2Cl_2): λ (ε, $M^{-1}cm^{-1}$) = 299 (22,900), 340 nm (4,700); elemental analysis: found: C 76.02, H 5.37, N 13.39; calcd.: C 76.17, H 5.43, N 13.32.

6-Methyl-2-(naphthalen-2-ylamino)-5-phenyl-nicotinonitrile (1f)

In a N_2 filled glove box, a 40-mL pressure tube, equipped with a magnetic stirbar, containing catalyst **B** (30.8 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with naphthalen-2-amine (143 mg, 1 mmol), 1-phenylpropyne (116 mg, 1 mmol), and *tert*-butyl isonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 48 h at 100 °C in a silicone oil bath. The pressure tube was cooled to room temperature. Then, the tube was charged with malononitrile (132 mg, 2 mmol), DBU (76 mg, 0.5 mmol), molecular sieves (200 mg), and absolute ethanol (2 mL). The mixture was heated for 2 h at 80 °C in a silicone oil bath. After completion of the reaction, the crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford the desired compound as a yellow solid; yield: 211 mg (63%); mp 144–146 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 2.56$ (3H, s, CH_3), 7.21 (1H, br, NH-naphthalen-1-amine), 7.32–7.34 (2H, m, CH-Ar), 7.42–7.43 (2H, m, CH-Ar), 7.44–7.51 (3H, m, CH-Ar), 7.69 (1H, s, 4-CH-pyridine), 7.70–7.73 (1H, d, 8.5 Hz, CH-Ar), 7.83–7.87 (3H, m, CH-Ar). 8.37–8.38 (1H, d, 2 Hz, CH-Ar); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): $\delta = 24.1$, 90.6, 120.8, 124.5, 126.4, 127.4, 127.5, 127.6, 128.1, 128.3, 128.5, 128.6, 129.0, 130.2, 131.4, 134.0, 136.5, 138.0, 142.0, 154.0, 160.2; MS (EI): $m/z = 335$; electronic absorption (CH_2Cl_2): λ (ε, $M^{-1}cm^{-1}$) = 278 (32,900), 311 nm (31,900); elemental analysis: found: C 82.41, H 5.16, N 12.43; calcd.: C 82.36, H 5.11, N 12.53.

2-[(4-Fluorophenyl)amino]-6-methyl-5-phenyl-nicotinonitrile (1g)

In a N_2 filled glove box, a 40-mL pressure tube, equipped with a magnetic stirbar, containing catalyst **B** (30.8 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with 4-fluoroaniline (111 mg, 1 mmol), 1-phenylpropyne (116 mg, 1 mmol), and *tert*-butyl isonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 48 h at 100 °C in a silicone oil bath. The pressure tube was cooled to room temperature. Then, the tube was charged with malononitrile (132 mg, 2 mmol), DBU (76 mg, 0.5 mmol), molecular sieves (200 mg), and absolute ethanol (2 mL). The mixture was heated for 2 h at 80 °C in a silicone oil bath. After completion of the reaction, the crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford the desired compound as a light brown solid; yield: 127 mg (42%); mp 126–128 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 2.50$ (3H, s, CH_3), 7.08–7.11 (1H, t, 9 Hz, CH-Ar), 7.16 (1H, br, NH-4-fluoroaniline), 7.31–7.33 (2H, d, 5.5 Hz, CH-Ar), 7.43–7.44 (1H, m, CH-Ar), 7.47–7.50 (2H, m, CH-Ar), 7.65 (1H, s, 4-CH-pyridine), 7.68–7.71 (2H, m, CH-Ar); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): $\delta = 23.9$, 90.0, 103.5, 107.6, 115.2, 116.5, 121.9, 127.5, 128.4, 134.9, 137.9, 142.0, 154.0, 157.8, 159.7; ^{19}F NMR ($CDCl_3$, 500 MHz): $\delta = -119.1$ (m); MS (EI): $m/z = 303$; electronic absorption (CH_2Cl_2); λ (ε, $M^{-1}cm^{-1}$) = 291 (23,200), 342 nm (4,700); elemental analysis: found: C 75.31, H 4.69, N 13.79; calcd.: C 75.23, H 4.65, N 13.85.

2-[(4-Bromophenyl)amino]-6-methyl-5-phenyl-nicotinonitrile (1h)

In a N_2 filled glove box, a 40-mL pressure tube, equipped with a magnetic stirbar, containing catalyst **B** (30.8 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with 4-bromoaniline (170 mg, 1 mmol), 1-phenylpropyne (116 mg, 1 mmol), and *tert*-butyl isonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 48 h at 100 °C in a silicone oil bath. The pressure tube was cooled to room temperature. Then, the tube was charged with malononitrile (132 mg, 2 mmol), DBU (76 mg, 0.5 mmol), molecular sieves (200 mg), and absolute ethanol (2 mL). The mixture was heated for 2 h at 80 °C in a silicone oil bath. After completion of the reaction, the crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford the desired compound as a brown solid; yield: 247 mg (68%); 164–166 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 2.51$ (3H, s, CH_3), 7.08 (1H, br, NH-4-bromoaniline), 7.30–7.32 (2H, d, 8 Hz, CH-Ar), 7.42–7.43 (1H, m, CH-Ar), 7.46–7.50 (4H, m, CH-Ar), 7.64–7.67 (3H, m, CH-Ar, 4-CH-pyridine); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): $\delta = 21.3$, 90.2, 116.5, 117.8, 125.1, 127.4, 127.7, 128.4, 128.9, 138.1, 138.4, 138.7, 141.9, 154.1, 160.0; MS (EI): $m/z = 363$; electronic absorption (CH_2Cl_2): λ (ε, $M^{-1}cm^{-1}$) = 299 (41,600), 342 nm (7,400); elemental analysis: found: C 62.57, H 3.82, N 11.59; calcd.: C 62.65, H 3.87, N 11.54.

2-[(4-Methoxyphenyl)amino]-6-methyl-5-phenyl-nicotinonitrile (1i)

In a N_2 filled glove box, a 40-mL pressure tube, equipped with a magnetic stirbar, containing catalyst **B** (30.8 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with 4-methoxyaniline (123 mg, 1 mmol), 1-phenylpropyne (116 mg, 1 mmol), and *tert*-butyl isonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 48 h at 100 °C in a silicone oil bath. The pressure tube was cooled to room temperature. Then, the tube was charged with malononitrile (132 mg, 2 mmol), DBU (76 mg, 0.5 mmol), molecular sieves (200 mg), and absolute ethanol (2 mL). The mixture was heated for 2 h at 80 °C in a silicone oil bath. After completion of the reaction, the crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford the desired compound as a yellow solid; yield: 230 mg (73%); mp 108–110 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 2.48$ (3H, s, CH_3), 3.86 (3H, s, OCH_3), 6.95–6.97 (2H, d, 8.5 Hz, CH-Ar), 6.99 (1H, br, NH-4-methoxyaniline), 7.30–3.32 (2H, d, 8.5 Hz, CH-Ar), 7.41–7.42 (1H, m, CH-Ar), 7.46–7.49 (2H, m, CH-Ar), 7.60–7.63 (3H, m, CH-Ar, 4-CH-pyridine); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): $\delta = 23.9$, 55.3, 89.6, 103.5, 114.0, 116.7, 122.4, 127.4, 128.4, 128.9, 131.9, 138.1, 142.0, 154.4, 155.9, 160.1; MS (EI): $m/z = 315$; electronic absorption (CH_2Cl_2): λ (ε, $M^{-1}cm^{-1}$) = 296 (19,100), 345 nm (3,900); elemental analysis: found: C 76.26, H 5.51, N 13.22; calcd.: C 76.17, H 5.43, N 13.32.

6-Methyl-2-(naphthalen-1-ylamino)-5-phenyl-nicotinonitrile (1j)

In a N_2 filled glove box, a 40-mL pressure tube, equipped with a magnetic stirbar, containing catalyst **B** (30.8 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with naphthalen-1-amine (143 mg, 1 mmol), 1-phenylpropyne (116 mg, 1 mmol), and *tert*-butyl isonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 48 h at 100 °C in a silicone oil bath. The pressure tube was cooled to room temperature. Then, the tube was charged with malononitrile (132 mg, 2 mmol), DBU (76 mg, 0.5 mmol), molecular sieves (200 mg), and absolute ethanol (2 mL). The mixture was heated for 2 h at 80 °C in a silicone oil bath. After completion of the reaction, the crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford the desired compound as a brown solid; yield: 174 mg (52%); mp 152–156 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 2.45$ (3H, s, CH_3), 7.32 (1H, br, NH-naphthalen-2-amine), 7.33–7.34 (1H, m, CH-Ar), 7.41–7.50 (4H, m, CH-Ar), 7.56–7.62 (3H, m, CH-Ar), 7.71 (1H, s, 4-CH-pyridine), 7.77–7.79 (1H, d, 8.5 Hz, CH-Ar), 7.94–7.96 (1H, d, 8 Hz, CH-Ar), 8.09–8.11 (1H, d, 8 Hz, CH-Ar), 8.18–8.19 (1H, d, 7.5 Hz, CH-Ar); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): $\delta = 24.0$, 90.2, 116.6, 120.0, 120.9, 125.1, 125.5, 125.9, 126.2, 127.5, 127.7, 128.1, 128.5, 128.6, 128.9, 133.7, 134,2, 138.1, 142.1, 155.1, 160.3; MS (EI): $m/z = 335$; electronic absorption (CH_2Cl_2): λ (ε, $M^{-1}cm^{-1}$) = 272 (11,100), 328 nm (12,500); elemental analysis: found: C 82.14, H 5.21, N 12.65; calcd.: C 82.36, H 5.11, N 12.53.

2-[(1-Benzyl-1*H*-indol-5-yl)amino]-6-methyl-5-phenylnicotinonitrile (1k)[19]

In a N_2 filled glove box, a 40-mL pressure tube, equipped with a magnetic stirbar, containing catalyst **B** (30.8 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with 1-benzyl-1*H*-indol-5-amine (222 mg, 1 mmol), 1-phenylpropyne (116 mg, 1 mmol), and *tert*-butyl isonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 48 h at 100 °C in a silicone oil bath. The pressure tube was cooled to room temperature. Then, the tube was charged with malononitrile (132 mg, 2 mmol), DBU (76 mg, 0.5 mmol), molecular sieves (200 mg), and absolute ethanol (2 mL). The mixture was heated for 2 h at 80 °C in a silicone oil bath. After completion of the reaction, the crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford the desired compound as a yellow solid; yield: 223 mg (54%); mp 143–146 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 2.47$ (3H, s, CH_3), 5.36 (2H, s, CH_2), 6.57–6.58 (1H, d, $J = 4$ Hz, 2-pyrrole-C*H*), 7.03 (1H, br, NH-1-benzyl-1H-indol-5-amine), 7.11–7.18 (3H, m, CH-Ar), 7.27–7.41 (9H, m, CH-Ar), 7.44–7.46 (2H, t, 1.5 Hz, CH-Ar), 7.63 (1H, s, 4-CH-pyridine), 8.00 (1H, s, CH-Ar); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): $\delta = 24.1$, 50.2, 89.5, 101.7, 109.8, 113.6, 116.9, 117.3, 126.7, 127.3, 127.4, 127.6, 128.5, 128.7, 128.9, 129.0, 129.0, 131.2, 133.7, 137.4, 138.4, 142.1, 155.6, 160.2; MS (EI): $m/z = 414$; electronic absorption (CH_2Cl_2): λ (ε, $M^{-1}cm^{-1}$) = 283 (21,000), 353 nm (3,800); elemental analysis: found: C 81.33, H 5.27, N 13.40; calcd.: C 81.13, H 5.35, N 13.52.

5,6-Diethyl-2-(phenylamino)nicotinonitrile (1l)

In a N_2 filled glove box, a 40-mL pressure tube, equipped with a magnetic stirbar, containing catalyst **B** (30.8 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with aniline (93 mg, 1 mmol), hex-3-yne (82 mg, 1 mmol), and *tert*-butyl isonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 48 h at 100 °C in a silicone oil bath. The pressure tube was cooled to room temperature. Then, the tube was charged with malononitrile (132 mg, 2 mmol), DBU (76 mg, 0.5 mmol), molecular sieves (200 mg), and absolute ethanol (2 mL). The mixture was heated for 2 h at 80 °C in a silicone oil bath. After completion of the reaction, the crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford the desired compound as a brown solid; yield: 160 mg (64%); mp 100–102 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 1.21$–1.25 (3H, t, $J = 8$ Hz, CH_3), 1.34–1.37 (3H, t, $J = 8$ Hz, CH_3), 2.57–2.62 (2H, t, $J = 8$ Hz, CH_2), 2.79–2.84 (2H, t, $J = 8$ Hz, CH_2), 6.96 (1H, br, NH-aniline), 7.09–7.11 (1H, t, 2.5 Hz, CH-Ar), 7.36–7.39 (2H, m, CH-Ar), 7.54 (1H, s, 4-CH-pyridine), 7.72–7.74 (2H, d, 8.5 Hz, CH-Ar); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): $\delta = 12.4$, 14.2, 23.9, 28.0, 90.0, 117.0, 119.5, 122.6, 127.2, 128.6, 139.4, 140.4, 153.6, 164.8; MS (EI): $m/z = 251$; electronic absorption (CH_2Cl_2): λ (ε, $M^{-1}cm^{-1}$) = 286 (14,500), 342 nm (3,600); elemental analysis: found: C 76.32, H 6.92, N 16.76; calcd.: C 76.46, H 6.82, N 16.72.

6-Ethyl-2-(phenylamino)-5-(prop-1-en-2-yl)nicotinonitrile (1m)

In a N_2 filled glove box, a 40-mL pressure tube, equipped with a magnetic stirbar, containing catalyst **B** (30.8 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with aniline (93 mg, 1 mmol), 2-methylhex-1-en-3-yne (94 mg, 1 mmol), and *tert*-butyl isonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 48 h at 100 °C in a silicone oil bath. The pressure tube was cooled to room temperature. Then, the tube was charged with malononitrile (132 mg, 2 mmol), DBU (76 mg, 0.5 mmol), molecular sieves (200 mg), and absolute ethanol (2 mL). The mixture was heated for 2 h at 80 °C in a silicone oil bath. After completion of the reaction, the crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford the desired compound as a brown solid; yield: 157 mg (60%); mp 72–74 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 1.26$–1.30 (3H, t, 7.5 Hz CH_3), 2.00 (3H, m, CH_3), 2.75–1.79 (2H, q, 7.5 Hz, CH_2), 4.88–4.89 (1H, m, CH), 5.22–5.23 (1H, m, CH), 6.94 (1H, br, NH-aniline), 7.05–7.07 (1H, t, 7.5 Hz, CH-Ar), 7.32–7.35 (2H, m, CH-Ar), 7.48 (1H, s, 4-CH-pyridine), 7.66–7.68 (2H, d, 10 Hz, CH-Ar); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): $\delta = 13.1$, 24.4, 28.9, 89.8, 116.7, 116.9, 119.8, 123.1, 128.8, 129.3, 139.1, 140.7, 142.1, 154.1, 164.0; MS (EI): m/z 263; electronic absorption (CH_2Cl_2): λ (ε, $M^{-1}cm^{-1}$) = 290 (20,700), 344 nm (4,400); elemental analysis: found: C 77.47, H 6.58, N 15.95; calcd.: C 77.54, H 6.51, N 15.96.

6-{3-[(*tert*-Butyldiphenylsilyl)oxy]propyl}-5-phenyl-2-(phenylamino)nicotinonitrile (1n)

In a N_2 filled glove box, a 40-mL pressure tube, equipped with a magnetic stirbar, containing catalyst **B** (30.8 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with aniline (93 mg, 1 mmol), *tert*-butyldiphenyl[(5-phenylpent-4-yn-1-yl)oxy]silane (398 mg, 1 mmol), and *tert*-butyl isonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 48 h at 100 °C in a silicone oil bath. The pressure tube was cooled to room temperature. Then, the tube was charged with malononitrile (132 mg, 2 mmol), DBU (76 mg, 0.5 mmol), molecular sieves (200 mg), and absolute ethanol (2 mL). The mixture was heated for 2 h at 80 °C in a silicone oil bath. After completion of the reaction, the crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford the desired compound as a yellow solid; yield: 345 mg (61%); mp 90–92 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 1.15$ (9H, s, Si-CCH_3), 2.16–2.19 (2H, m, $CH_2CH_2CH_2$OTBDMS), 3.01–3.04 (2H, t, $J = 7.5$ Hz, $CH_2CH_2CH_2$OTBDMS), 3.81–3.84 (2H, t, $J = 6$ Hz, $CH_2CH_2CH_2$OTBDMS), 7.19–7.22 (1H, t, 7.5 Hz, CH-Ar), 7.29 (1H, br, NH-aniline), 7.38–7.39 (2H, m, CH-Ar), 7.45–7.55 (12H, m, CH-Ar), 7.72 (1H, s, 4-CH-pyridine), 7.75–7.76 (4H, m, CH-Ar), 7.84–7.86 (2H, d, 8.5 Hz, CH-Ar); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): $\delta = 19.0$, 26.7, 31.2, 32.3, 63.3, 90.0, 116.5, 120.0, 123.0, 127.4, 127.5, 127.9, 128.4, 128.6, 129.0, 129.3, 133.7, 135.3, 135.4, 137.9, 138.9, 142.1, 154.1, 163.1; ^{29}Si NMR ($CDCl_3$, 500 MHz): $\delta = -4.39$; electronic absorption (CH_2Cl_2): λ (ε, $M^{-1}cm^{-1}$) = 294 (15,000),

344 nm (3,300); elemental analysis: found: C 78.22, H 6.64, N 7.32; calcd.: C 78.27, H 6.57, N 7.40.

5-(Cyclohex-1-en-1-yl)-6-methyl-2-(phenylamino)-nicotinonitrile (1o)

In a N_2 filled glove box, a 40-mL pressure tube, equipped with a magnetic stirbar, containing catalyst **B** (30.8 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with aniline (93 mg, 1 mmol), 1-(prop-1-yn-1-yl)cyclohex-1-ene (120 mg, 1 mmol), and *tert*-butyl isonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 48 h at 100 °C in a silicone oil bath. The pressure tube was cooled to room temperature. Then, the tube was charged with malononitrile (132 mg, 2 mmol), DBU (76 mg, 0.5 mmol), molecular sieves (200 mg), and absolute ethanol (2 mL). The mixture was heated for 2 h at 80 °C in a silicone oil bath. After completion of the reaction, the crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford the desired compound as a brown solid; yield: 159 mg (55%); mp 127–129 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.70–1.73 (2H, m, CH_2), 1.78–1.81 (2H, m, CH_2), 2.19–2.21 (4H, m, CH_2), 2.51 (3H, s, CH_3), 5.65–5.66 (1H, d, 1.5 Hz, CH), 7.02 (1H, br, NH-aniline), 7.10–7.11 (1H, t, 8 Hz, CH-Ar), 7.36–7.39 (2H, m, CH-Ar), 7.49 (1H, s, 4-CH-pyridine), 7.71–7.72 (2H, d, 8.5 Hz, CH-Ar); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ = 21.7, 22.7, 23.3, 25.2, 29.7, 89.8, 116.6, 119.7, 122.8, 128.1, 128.6, 130.4, 135.2, 139.1, 140.8, 153.5, 159.8; MS (EI): *m/z* = 289; electronic absorption (CH_2Cl_2): λ (ε, $M^{-1}cm^{-1}$) = 290 (19,000), 344 nm (3,900); elemental analysis: found: C 78.94, H 6.56, N 14.50; calcd.: C 78.86, H 6.62, N 14.52.

5,6-Diphenyl-2-(phenylamino)nicotinonitrile (1p)[19]

In a N_2 filled glove box, a 40-mL pressure tube, equipped with a magnetic stirbar, containing catalyst **B** (62.6 mg, 0.2 mmol) in dry toluene (2 mL) was loaded with aniline (93 mg, 1 mmol), 1,2-diphenylethyne (178 mg, 1 mmol), and *tert*-butyl isonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 48 h at 100 °C in a silicone oil bath. The pressure tube was cooled to room temperature. Then, the tube was charged with malononitrile (132 mg, 2 mmol), DBU (76 mg, 0.5 mmol), molecular sieves (200 mg), and absolute ethanol (2 mL). The mixture was heated for 2 h at 80 °C in a silicone oil bath. After completion of the reaction, the crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford the desired compound as a yellow solid; yield: 149 mg (43%); mp 140–142 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.11–7.15 (4H, m, CH-Ar, NH-aniline), 7.25–7.31 (6H, m, CH-Ar), 7.36–7.39 (2H, t, 8 Hz, CH-Ar), 7.42–7.43 (2H, d, 7.5 Hz, CH-Ar), 7.75–7.76 (2H, d, 8 Hz, CH-Ar), 7.83 (H, s, 4-CH-pyridine); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ = 91.5, 116.5, 120.1, 123.4, 127.1, 127.3, 127.8, 128.5, 128.8, 128.9, 129.3, 130.0, 138.4, 138.8, 138.9, 143.9, 153.9, 159.3; electronic absorption (CH_2Cl_2): λ (ε, $M^{-1}cm^{-1}$) = 299 (37,900), 366 nm (8,800); elemental analysis: found: C 82.82, H 5.00, N 12.18; calcd.: C 82.97, H 4.93, N, 12.10

5-Phenyl-2-(phenylamino)nicotinonitrile (1q)

In a N_2 filled glove box, a 40-mL pressure tube, equipped with a magnetic stirbar, containing catalyst **B** (30.8 mg, 0.1 mmol) in dry toluene (2 mL) was loaded with aniline (93 mg, 1 mmol), ethynylbenzene (102 mg, 1 mmol), and *tert*-butyl isonitrile (137 μL, 1.2 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 24 h at 100 °C in a silicone oil bath. The pressure tube was cooled to room temperature. Then, the tube was charged with malononitrile (132 mg, 2 mmol), DBU (76 mg, 0.5 mmol), molecular sieves (200 mg), and absolute ethanol (2 mL). The mixture was heated for 2 h at 80 °C in a silicone oil bath. After completion of the reaction, the crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford the desired compound as a yellow solid; yield: 168 mg (62%); mp 142–144 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.04 (1H, br, NH-aniline), 7.13–7.14 (1H, t, 1 Hz, CH-Ar), 7.36–7.39 (3H, m, CH-Ar), 7.43–7.49 (5H, m, CH-Ar), 7.60–7.62 (2H, d, 8.5 Hz, CH-Ar), 7.97–7.98 (1H, d, 7 Hz, 4-CH-pyridine), 8.61–8.62 (1H, d, 7 Hz, 1-CH-pyridine); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ = 93.2, 116.3, 120.9, 124.0, 126.2, 127.7, 127.9, 129.0, 129.2, 136.0, 138.4, 139.6, 150.7, 155.0; MS (EI): *m/z* = 271; electronic absorption (CH_2Cl_2): λ (ε, $M^{-1}cm^{-1}$) = 302 (25,500), 350 nm (4,300); elemental analysis: found: C 79.77, H 4.77, N 15.55; calcd.: C 79.68, H 4.83, N 15.49.

5-(1-Benzyl-1*H*-indol-3-yl)-2-(phenylamino)nicotinonitrile (1r)

In a N_2 filled glove box, a 40-mL pressure tube, equipped with a magnetic stirbar, containing catalyst **B** (30.8 mg, 0.1 mmol) in dry toluene (2 mL) was loaded with aniline (93 mg, 1 mmol), 1-benzyl-3-ethynyl-1*H*-indole (231 mg, 1 mmol), and *tert*-butyl isonitrile (137 μL, 1.2 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 24 h at 100 °C in a silicone oil bath. The pressure tube was cooled to room temperature. Then, the tube was charged with malononitrile (132 mg, 2 mmol), DBU (76 mg, 0.5 mmol), molecular sieves (200 mg), and absolute ethanol (2 mL). The mixture was heated for 2 h at 80 °C in a silicone oil bath. After completion of the reaction, the crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford the desired compound as a brown solid; yield: 196 mg (49%); mp 148–151 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 5.32 (2H, s, CH_2), 7.04 (1H, br, NH-aniline), 7.09–7.112 (1H, t, 7 Hz, CH-Ar), 7.15–7.17 (2H, d, 7 Hz, CH-Ar), 7.20–7.38 (9H, m, CH-Ar), 7.60–7.62 (2H, d, 8 Hz, CH-Ar), 7.79–7.80 (1H, d, 7.5 Hz, CH-Ar), 8.01–8.02 (1H, d, 2.5 Hz, 4-CH-pyridine), 8.68–8.69 (1H, d, 2.5 Hz, 6-CH-pyridine); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ = 50.2, 93.3, 110.3, 112.0, 116.5, 119.2, 120.6, 122.7, 122.7, 123.7, 125.5, 125.9, 126.9, 127.9, 128.9, 129.1, 136.7, 136.9, 138.6, 139.7, 150.6, 153.9; electronic absorption (CH_2Cl_2): λ (ε, $M^{-1}cm^{-1}$) = 315 (13,300), 367 nm (1,900); elemental analysis: found: C 80.86, H 5.10, N 14.04; calcd.: C 80.98, H 5.03, N 13.99.

5-(Cyclohex-1-en-1-yl)-2-(phenylamino)nicotinonitrile (1s)

In a N_2 filled glove box, a 40-mL pressure tube, equipped with a magnetic stirbar, containing catalyst **B** (30.8 mg, 0.1 mmol) in dry toluene (2 mL) was loaded with aniline (93 mg, 1 mmol), 1-ethynylcyclohex-1-ene (106 mg, 1 mmol), and *tert*-butyl isonitrile (137 μL, 1.2 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 24 h at 100 °C in a silicone oil bath. The pressure tube was cooled to room temperature. Then, the tube was charged with malononitrile (132 mg, 2 mmol), DBU (76 mg, 0.5 mmol), molecular sieves (200 mg), and absolute ethanol (2 mL). The mixture was heated for 2 h at 80 °C in a silicone oil bath. After completion of the reaction, the crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford the desired compound as a yellow solid; yield: 154 mg (56%); mp 110–112 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 1.61$–1.66 (2H, m, CH_2), 1.74–1.79 (2H, m, CH_2), 2.17–2.20 (2H, m, CH_2), 2.28–2.31 (2H, m, CH_2), 6.04–6.06 (1H, d, 1.5 Hz, CH), 6.97 (1H, br, NH-aniline), 7.08–7.11 (1H, t, 8 Hz, CH-Ar), 7.33–7.36 (2H, m, CH-Ar), 7.55–7.57 (2H, m, CH-Ar), 7.75–7.76 (1H, d, 2 Hz, 4-CH-pyridine), 8.39–8.40 (1H, d, 2 Hz, 6-CH-pyridine); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): $\delta = 21.7$, 22.6, 25.7, 26.8, 92.7, 116.5, 120.6, 123.8, 125.4, 129.0, 129.1, 131.9, 137.8, 138.6, 148.8, 154.4; MS (EI): $m/z = 275$; electronic absorption (CH_2Cl_2): λ (ε, $M^{-1}cm^{-1}$) = 302 (13,700), 359 nm (2,100); elemental analysis: found: C 78.37, H 6.29, N 15.34; calcd.: C 78.52, H 6.22, N 15.26.

5-[4-(Benzyloxy)phenyl]-2-(phenylamino)nicotinonitrile (1t)

In a N_2 filled glove box, a 40-mL pressure tube, equipped with a magnetic stirbar, containing catalyst **B** (30.8 mg, 0.1 mmol) in dry toluene (2 mL) was loaded with aniline (93 mg, 1 mmol), 1-(benzyloxy)-4-ethynylbenzene (208 mg, 1 mmol), and *tert*-butyl isonitrile (137 μL, 1.2 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 24 h at 100 °C in a silicone oil bath. The pressure tube was cooled to room temperature. Then, the tube was charged with malononitrile (132 mg, 2 mmol), DBU (76 mg, 0.5 mmol), molecular sieves (200 mg), and absolute ethanol (2 mL). The mixture was heated for 2 h at 80 °C in a silicone oil bath. After completion of the reaction, the crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford the desired compound as a yellow solid; yield: 248 mg (66%); mp 132–135 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 5.01$ (2H, s, CH_2), 6.99 (1H, br, NH-aniline), 7.04–7.06 (2H, dd, 2.5 Hz and 5.5 Hz CH-Ar), 7.10–7.13 (1H, t, 8 Hz, CH-Ar), 7.32–7.45 (8H, m, CH-Ar), 7.58–7.60 (2H, dd, 2.5 Hz and 5.5 Hz CH-Ar), 7.91–7.92 (1H, d, 2.5 Hz, 4-CH-pyridine), 8.56–8.57 (1H, d, 2.5 Hz, 6-CH-pyridine); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): $\delta = 70.1$, 93.2, 115.6, 116.4, 120.7, 123.9, 127.42, 127.44, 127.5, 128.1, 128.6, 128.7, 129.1, 136.6, 138.5, 139.2, 150.3, 154.6, 158.7; MS (EI): $m/z = 377$; electronic absorption (CH_2Cl_2): λ (ε, $M^{-1}cm^{-1}$) = 306 (11,600), 353 nm (1,600); elemental analysis: found: C 79.47, H 5.13, N 11.08; calcd.: C 79.55, H 5.07, N 11.13.

2-(Phenylamino)-5-(*para*-tolyl)nicotinonitrile (1u)

In a N_2 filled glove box, a 40-mL pressure tube, equipped with a magnetic stirbar, containing catalyst **B** (30.8 mg, 0.1 mmol) in dry toluene (2 mL) was loaded with aniline (93 mg, 1 mmol), 1-ethynyl-4-methylbenzene (116 mg, 1 mmol), and *tert*-butyl isonitrile (137 μL, 1.2 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 24 h at 100 °C in a silicone oil bath. The pressure tube was cooled to room temperature. Then, the tube was charged with malononitrile (132 mg, 2 mmol), DBU (76 mg, 0.5 mmol), molecular sieves (200 mg), and absolute ethanol (2 mL). The mixture was heated for 2 h at 80 °C in a silicone oil bath. After completion of the reaction, the crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford the desired compound as a yellow solid; yield: 165 mg (58%); mp 137–139 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 2.38$ (3H, s, CH_3), 7.01 (1H, br, NH-aniline), 7.10–7.13 (1H, t, 7.5 Hz, CH-Ar), 7.25–7.26 (2H, d, 7.5 Hz, CH-Ar), 7.35–7.38 (3H, m, CH-Ar), 7.59–7.61 (2H, dd, 1 Hz and 3 Hz CH-Ar), 7.95–7.96 (1H, d, 3 Hz, 4-CH-pyridine), 8.59–8.60 (1H, d, 3 Hz, 6-CH-pyridine); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): $\delta = 21.1$, 93.2, 116.4, 120.8, 123.9, 126.0, 127.7, 129.0, 129.9, 133.1, 138.5, 139.4, 150.5, 154.8; MS (EI): $m/z = 285$; electronic absorption (CH_2Cl_2): λ (ε, $M^{-1}cm^{-1}$) = 305 (25,200), 354 nm (2,400); elemental analysis: found: C 79.91, H 5.34, N 14.75; calcd.: C 79.98, H 5.30, N 14.73.

2-(*tert*-Butylamino)-5-phenylnicotinonitrile (1v)[19]

In a N_2 filled glove box, a 40-mL pressure tube, equipped with a magnetic stirbar, containing catalyst **A** (32.4 mg, 0.1 mmol) in dry toluene (2 mL) was loaded with cyclohexylamine (95 mg, 1 mmol), ethynylbenzene (102 mg, 1 mmol), and *tert*-butyl isonitrile (137 μL, 1.2 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 24 h at 100 °C in a silicone oil bath. The pressure tube was cooled to room temperature. Then, the tube was charged with malononitrile (132 mg, 2 mmol), DBU (76 mg, 0.5 mmol), molecular sieves (200 mg), and absolute ethanol (2 mL). The mixture was heated for 2 h at 80 °C in a silicone oil bath. After completion of the reaction, the crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford the desired compound as a yellow oil; yield: 145 mg (58%). ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 1.43$ (9H, s, C-$(CH_3)_3$), 5.43 (1H, br, NH-2-methylpropan-2-amine), 7.25–7.27 (1H, m, CH-Ar), 7.31–7.36 (4H, m, CH-Ar), 7.00–7.01 (1H, d, 2 Hz, 4-CH-pyridine), 8.40–8.41 (1H, d, 2 Hz, 6-CH-pyridine); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): $\delta = 28.9$, 52.5, 91.7, 117.1, 124.6, 125.9, 127.3, 129.0, 136.6, 139.1, 150.4, 157.2; MS (EI): $m/z = 251$; electronic absorption (CH_2Cl_2): λ (ε, $M^{-1}cm^{-1}$): 284 (21,800), 352 nm (4,200); elemental analysis: found: C 76.48, H 6.76, N 16.76; calcd.: C 76.46, H 6.82, N 16.72.

2-(*tert*-Butylamino)-5-(cyclohex-1-en-1-yl)nicotinonitrile (1w)

In a N_2 filled glove box, a 40-mL pressure tube, equipped with a magnetic stirbar, containing catalyst **A** (32.4 mg,

0.1 mmol) in dry toluene (2 mL) was loaded with cyclohexylamine (95 mg, 1 mmol), 1-ethynylcyclohex-1-ene (106 mg, 1 mmol), and *tert*-butyl isonitrile (137 μL, 1.2 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 24 h at 100 °C in a silicone oil bath. The pressure tube was cooled to room temperature. Then, the tube was charged with malononitrile (132 mg, 2 mmol), DBU (76 mg, 0.5 mmol), molecular sieves (200 mg), and absolute ethanol (2 mL). The mixture was heated for 2 h at 80 °C in a silicone oil bath. After completion of the reaction, the crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford the desired compound as a yellow oil; yield: 135 mg (53%). ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta =$ 1.46 (9H, s, $C(CH_3)_3$), 1.60–1.63 (2H, m, CH_2), 1.71–1.74 (2H, m, CH_2), 2.13–2.16 (2H, m, CH_2), 2.24–2.26 (2H, m, CH_2), 4.95 (1H, br, NH-2-methylpropan-2-amine), 5.95 (1H, m, CH), 7.57–7.58 (1H, d, 2.5 Hz, 4-CH-pyridine), 8.28–8.29 (1H, d, 2.5 Hz, 6-CH-pyridine); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): $\delta =$ 21.8, 22.7, 25.6, 26.8, 29.1, 52.4, 91.2, 117.5, 123.9, 126.1, 132.3, 137.2, 148.8, 157.0; MS (EI): $m/z =$ 255; electronic absorption (CH_2Cl_2): λ (ε, $M^{-1}cm^{-1}$) = 280 (20,300), 344 (3,900); elemental analysis: found: C 75.24, H 8.21, N 16.55; calcd.: C 75.26, H 8.29, N 16.46.

1-(*tert*-Butyl)-2-imino-5-phenyl-1,2-dihydropyridine-3-carbonitrile (2a)

In a N_2 filled glove box, a 40-mL pressure tube, equipped with a magnetic stirbar, containing catalyst **A** (32.4 mg, 0.1 mmol) in dry toluene (2 mL) was loaded with cyclohexylamine (95 mg, 1 mmol), ethynylbenzene (102 mg, 1 mmol), and *tert*-butyl isonitrile (137 μL, 1.2 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 24 h at 100 °C in a silicone oil bath. The pressure tube was cooled to room temperature. Then, the tube was charged with malononitrile (132 mg, 2 mmol) and triethylamine (280 μL, 2 mmol) in a methanol (1.5 mL)/water (0.5 mL) solvent mixture. The reaction was stirred for 5 h at 0 °C. After completion, the crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate providing the compound as a yellow brown solid; yield: 130 mg (52%); mp 94–96 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta =$ 1.81 (9H, s, $C(CH_3)_3$), 7.29–7.34 (3H, m, CH-Ar, NH), 7.40–7.44 (2H, m, CH-Ar), 7.47–7.48 (1H, m, CH-Ar), 7.56 (1H, s 4-CH-pyridine), 7.76 (1H, s, 6-CH-pyridine). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): 27.7, 63.9, 105.1, 114.8, 116.8, 124.9, 127.1, 129.1, 136.0, 137.6, 141.7, 155.3; electronic absorption (CH_2Cl_2): λ (ε, $M^{-1}cm^{-1}$) = 272 (12,800), 398 nm (4,600); MS (EI): $m/z =$ 251; elemental analysis: found: C 76.47, H 6.86, N 16.67; calcd.: C 76.46, H 6.82, N 16.72.

Conversion of 2a to 1v

Compound **2a** (60 mg, 0.24 mmol) was dissolved in 1 mL of absolute ethanol in a pressure tube equipped with a magnetic stirbar. Then, the pressure tube was charged with malononitrile (32 mg, 0.48 mmol), DBU (18 mg, 0.24 mmol), and molecular sieves (50 mg) in absolute ethanol (1 mL). The mixture was heated for 2 h at 80 °C in a silicone oil bath. After completion of the reaction, the crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford **1v** isolated as a yellow oil; yield: 51 mg (86%). ^{1}H NMR, ^{13}C{^{1}H} NMR, and MS (EI) were all identical to **1v** prepared using the standard conditions directly from the multicomponent coupling product.

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