Synthesis Y. Chikayuki et al. Paper

Transition-Metal-Free Synthesis of Pyridine Derivatives by Thermal Cyclization of *N*-Propargyl Enamines

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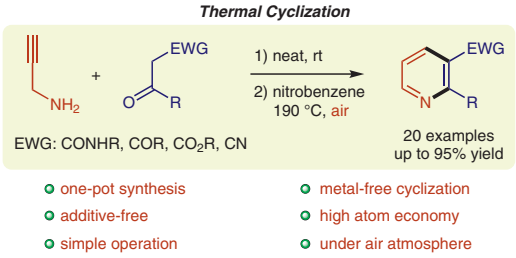

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Abstract A transition-metal-free synthesis of pyridine derivatives by 6-*endo*-*dig* cyclization of *N*-propargyl enamines was developed. This method is environmentally friendly and is a high atom economy reaction that is easily accessed to provide pyridine derivatives in moderate to good yield by heating *N*-propargyl enamines in solvent without additives. The total synthesis of onychine was achieved in 51% yield in only two steps by using this method.

Key words enaminone, onychine, high atom economy, green chemistry, one-pot synthesis, additive-free

Pyridine, a nitrogen-containing heterocycle, is frequently found in natural products and bioactive compounds, but it is also an important part of the skeleton found in molecules used in a broad range of fields including pharmaceuticals, agrichemicals, and functional materials.[1] Moreover, pyridines are also employed as key intermediates to prepare biologically active compounds, such as purinergic $P2Y_{12}$ receptor antagonists,[2] histone deacetylase inhibitors,[3] and phosphodiesterase 10A PET tracers (Figure 1).[4] Toward these practical applications, a great deal of effort has been devoted by many researchers to the development of various pyridine derivatives.

Enaminones are readily obtained by condensation of amines, and β-ketoamides, β-diketones, and β-ketoesters have been used as important synthons for ambident nucleophiles.[5] In the past few decades, synthesis of pyridine derivatives by cyclization using transition metals has been reported.[6] In 2008, Cacchi et al. reported the selective transformation from *N*-propargyl β-enaminone into pyridines by using CuBr as a catalyst.[7a] Additionally, Kelgokmen et al. achieved the synthesis of polysubstituted pyridine derivatives by a cyclization reaction with $ZnCl_2$ (Scheme 1).[7b] In

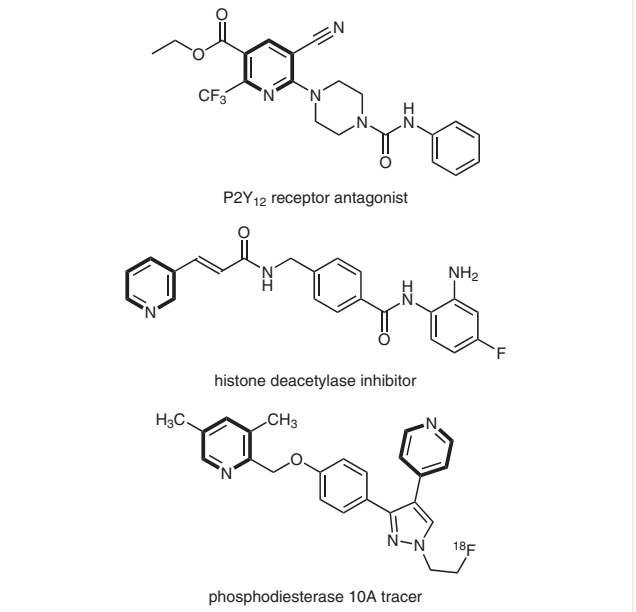

Figure 1 Chemical structures of biologically active compounds containing pyridine

general, although transition-metal-catalyzed reactions are an efficient strategy to synthesize heterocycles, they have serious drawbacks such as the use of an expensive, environmentally unfriendly and poisonous reagent and potential contamination of the final drug product.[8] From the viewpoint of the development of sustainable chemistry and the pharmaceutical industry, metal-free conditions are strongly desired to achieve target chemical conversion.[9] Several syntheses of pyridine derivatives by transition-metal-free reactions have been reported, but the use of NaOH[10] or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[11] is required, and some of the reactions have to be carried out under an inert

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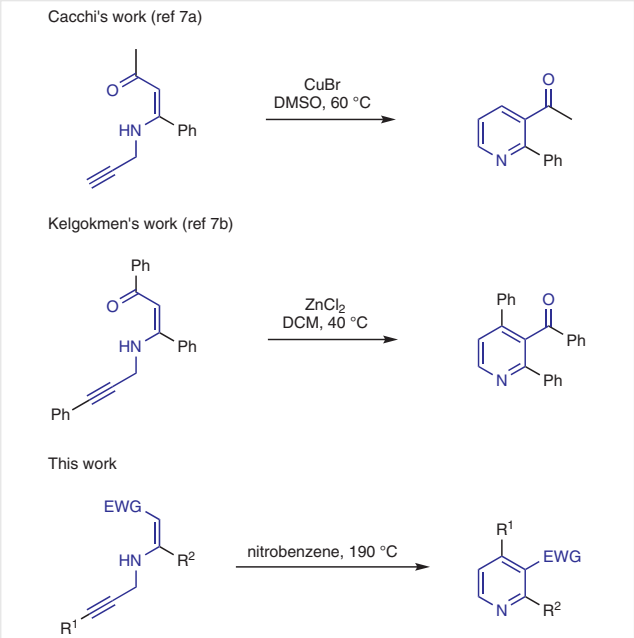
gas. To solve these problems, we have developed a strategy for synthesizing pyridine derivatives by using only solvent and substrate without other additives.

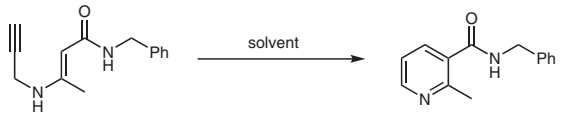


Scheme 1 Conversion of *N*-propargylenamines into pyridine derivatives

In preliminary studies, *N*-benzyl-3-(propargylamino)-but-2-enamide (**1a**), easily prepared by the condensation of *N*-benzyl-3-oxobutanamide and propargylamine, was chosen as the model substrate for the optimization of the reaction conditions; the results are summarized in Table 1. Initially, after heating of **1a** with ethylene glycol as a solvent at 140 °C, only a trace of pyridine derivative was obtained without pyrrole (entry 1). When an aprotic polar solvent such as DMF, DMAc or DMSO was used, a cyclized product was formed in trace, trace and 16% yield, respectively (entries 2–4). It was found that cyclized product **2a** was obtained, albeit in low yield, by using an aromatic solvent such as *o*-dichlorobenzene, anisole, or nitrobenzene (entries 5–7). Based on these results, an aromatic compound was found to be suitable as the solvent in this reaction, and nitrobenzene was used to further improve the yield. As shown in entry 7, since the progress of the reaction was slow at 140 °C, the temperature was increased to 190 °C, the reaction time was shortened and the yield improved (entry 8). In the ^{1}H NMR spectra of the crude product in this reaction, nothing was observed other than cyclized pyridine. We anticipate that thermal decomposition of the substrate or intermediates occurred.

Encouraged by the results, which demonstrated the feasibility of a straightforward synthesis of pyridine by cyclization of **1a**, we decided to study the conditions further using nitrobenzene as solvent. However, when optimizing the conditions using **1a**, there was concern that the low cyclization yield would make it difficult to judge the differences in reactivity. Therefore, we decided to proceed with using **1c**, which was estimated to be more stable (Table 2). When the reaction was carried out at 170 °C, the reaction was not completed; when the temperature was raised to 190 °C, the starting material disappeared and **2c** was obtained in 42% yield (entry 1). The reaction was then carried out at 190 °C, and the yield of **2c** was improved further (entry 2). From this result, it was established that 190 °C was the most efficient temperature for the cyclization condition. When the experiment was carried out in the presence

Table 1 Screening of the Reaction Conditions[a]

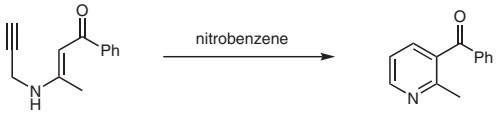


1a **2a**

Entry	Solvent	Temp. (°C)	Time (h)	Yield (%)
1	ethylene glycol	140	16	trace
2	DMF	140	6	trace
3	DMAc	140	23	trace
4	DMSO	140	18	16
5	*o*-dichlorobenzene	140	22	20
6	anisole	140	44	14
7	nitrobenzene	140	45	21
8	nitrobenzene	190	1.5	41

[a] Reactions were carried out by heating **1a** (0.4 mmol) in solvent (40 mL) under air.

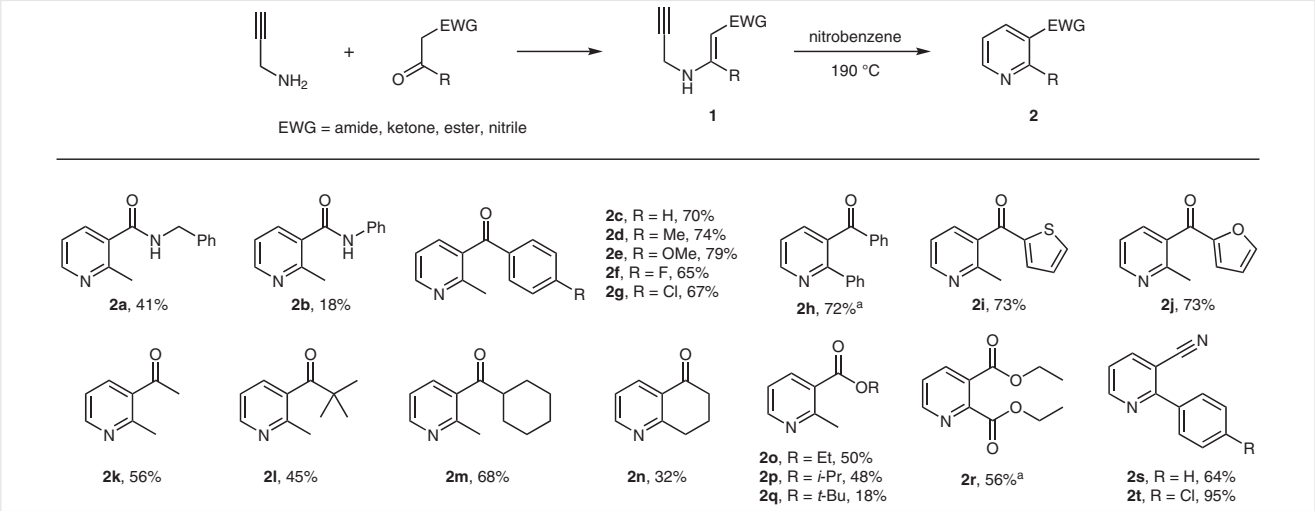
Table 2 Screening of the Reaction Temperature and Nitrobenzene Concentration[a]



1c **2c**

Entry	Conc. (M)	Temp. (°C)	Time (h)	Yield (%)
1	0.01	170–190	18	42
2	0.01	190	15	70
3	0.02	190	20	47
4	0.04	190	19	53
5	0.08	190	14	46
6	0.2	190	15	50
7[b]	0.2	190	8	51

[a] Reactions were carried out by heating **1c** (0.4 mmol) in nitrobenzene under air.
[b] Reaction was performed under microwave irradiation.

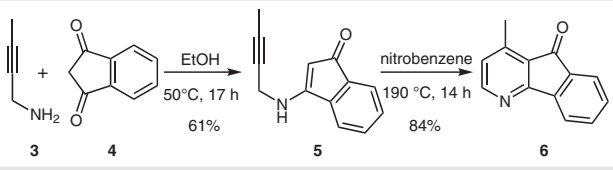


Scheme 2 Synthesis of pyridine derivatives. *Reagents and conditions*: Reactions were carried out with crude **1** in nitrobenzene by heating at 190 °C under air. Isolated yield for two steps are given. [a] Enamines were synthesized from propargylamine and the corresponding ynones.

of a reduced amount of solvent, **2c** was obtained with the highest yield when 40 mL of nitrobenzene was used (entries 2–7).

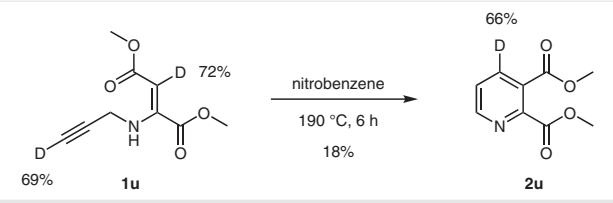
Based on the optimal conditions (Table 2, entry 2), the generality of this reaction and the scope of its application for intramolecular cyclization was investigated; the results are summarized in Scheme 2. First, the enamines were prepared from propargylamine and β-keto carbonyl compounds or ynones. Then, nitrobenzene was added to the obtained crude enamines and the mixture was heated at 190 °C open to the atmosphere. Amides **2a** and **2b** were obtained low yields; however, pyridine derivatives were obtained in good yields from aryl and heterocyclic ketones **2c–j**. Among the alkyl ketones, **2k**, **2l** and **2m** were obtained with moderate to good yields; however, cyclization of cyclic ketone **1n** resulted in low yield. In the cyclization of the esters **1o–q**, moderate yields were obtained along with a small amount of carboxylic acid. Additionally, it seems that the *tert*-butyl ester **1q** decomposed at high temperature, resulting in a remarkably low yield. When *N*-propargyl cyanoenamines **1s** and **1t** were used as the starting material, the corresponding 3-cyanopyridine derivatives were obtained with excellent yield.

To further probe the synthetic potential of this method, we attempted to apply it to the synthesis of a natural product. Onychine, an azafluorenone alkaloid, was isolated from a plant of the *Annonaceae* family,[12] and has attracted attention for its potent antifungal and cytotoxic activities.[13] Several methods for the synthesis of onychine have been developed using a limited number of steps.[14] Our method, as shown in Scheme 3, is one of the most simple and efficient. First, enamine **5** was obtained in a yield of 61% by dehydration condensation of commercially available but-2-yn-1-amine (**3**) and 1,3-indanedione (**4**). Then, by applying the above conditions to this enamine, onychine **6** was produced in a high yield. Thus, this method does not require complex operations, and should be useful to easily access various natural products using a limited number of steps.



Scheme 3 Total synthesis of onychine

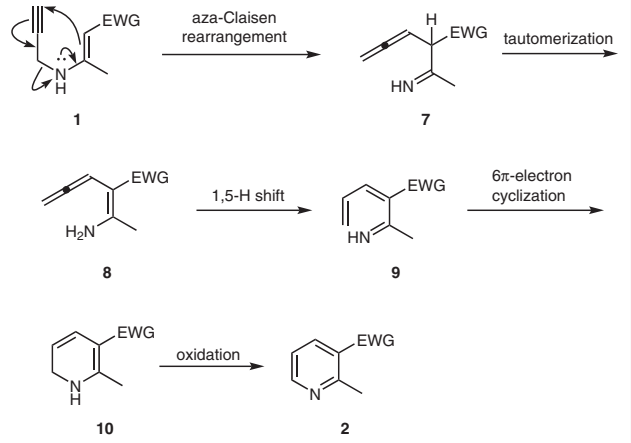
To investigate the reaction mechanism of this transformation, a control experiment was carried out using the same method; the results are shown in Scheme 4. When the substrate **1u**, in which the terminal alkyne was 69% deuterated, was reacted under the same conditions as **1r**, pyridine derivative **2u** labeled with 66% deuterium at the C4-position was obtained. This demonstrated that the alkyne terminus of **1u** corresponds to the C4-position of the pyridine **2u**.



Scheme 4 Cyclization with deuterated enaminone **1u**

On the basis of a previous study[15] and the above result, we propose that the reaction mechanism involves the steps shown in Scheme 5. First, an aza-Claisen rearrangement followed by tautomerization of *N*-propargyl enamine

provides the allenic enamine **8**. This rearranges by a 1,5-sigmatropic hydrogen shift to the intermediate **9**, which undergoes 6π electron cyclization to the dihydropyridine **10**. Finally, oxidation occurs and pyridine derivative **2** is obtained.



Scheme 5 Plausible reaction mechanism

In summary, a transition-metal-free synthesis of pyridine derivatives by intramolecular cyclization of *N*-propargyl enamines was developed. This is applicable to substrates with various substituents, and in the case of substrates with aromatic rings, pyridine derivatives were obtained in good yield. This method is efficacious for the synthesis of natural products and pharmaceuticals because it is environmentally friendly and proceeds with high atom economy.

^{1}H and ^{13}C NMR spectra were measured with a Bruker BioSpin AVANCE III-400 spectrometer at 400 and 100 MHz, respectively. All NMR spectra were measured in $CDCl_3$. Chemical shifts are reported downfield from TMS (0 ppm) for ^{1}H NMR. For ^{13}C NMR, chemical shifts are reported relative to $CDCl_3$ (77.2 ppm). Mass spectra were recorded with a JEOL JMS-T100LP mass spectrometer by electrospray ionization (ESI). Infrared spectra were measured with a Perkin–Elmer Spectrum Two. Microwave-assisted reactions were performed in a Biotage Initiator 1 EXP using a sealed reaction vessel. Purification was achieved by column chromatography using 63–210 mm silica gel 60N (Kanto Chemical Co. Inc.). All melting points were measured with a Yanagimoto Micro melting point apparatus without collection. Unless otherwise noted, all materials were purchased from commercial sources, and commercially available reagents were used without further purification.

Cyclization of *N*-Propargyl Enamine; General Procedure

Propargylamine and β-ketocarbonyl compound were stirred at r.t. without solvent. After evaporating, crude *N*-propargyl enamine **1** was stirred in nitrobenzene (40 mL) at 190 °C. The progress of reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled and passed through a short silica gel column to remove nitrobenzene (chloroform to EtOAc). The residue was purified again by silica gel chromatography to afford the corresponding pyridine **2**.

N-Benzyl-2-methylnicotinamide (2a)

N-Benzyl-3-oxobutanamide (76.1 mg, 0.40 mmol) was added to propargylamine (0.13 mL, 2.0 mmol) at r.t. and the mixture was stirred for 23 h. The reaction mixture was evaporated to afford **1a**, which was taken forward without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.98 (s, 3 H), 2.25 (t, *J* = 2.5 Hz, 1 H), 3.94 (dd, *J* = 2.5, 6.4 Hz, 2 H), 4.41–4.48 (m, 3 H), 5.18 (br, 1 H), 7.28–7.35 (m, 5 H).

Compound **1a** was reacted as described in the general procedure (1.5 h) and the product was purified by silica gel chromatography ($CHCl_3$/MeOH = 20:1) to afford **2a**.

Yield: 36.8 mg (0.16 mmol, 41%); black oil.

IR (film): 1634, 3270 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.66 (s, 3 H), 4.61 (s, 1 H), 4.63 (s, 1 H), 6.24 (br, 1 H), 7.13 (dd, *J* = 4.9, 7.7 Hz, 1 H), 7.31–7.37 (m, 5 H), 7.66 (dd, *J* = 1.7, 7.7 Hz, 1 H), 8.51 (dd, *J* = 1.7, 4.9 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.9, 44.0, 120.7, 127.7, 127.9, 128.9, 131.7, 134.7, 137.9, 150.0, 156.1, 168.5.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{15}N_2O$: 227.1184; found: 227.1151.

2-Methyl-*N*-phenylnicotinamide (2b)[16]

3-Oxo-*N*-phenylbutanamide (67.6 mg, 0.38 mmol) was added to propargylamine (0.13 mL, 2.0 mmol) at r.t. and the mixture was stirred for 7 h. The reaction mixture was evaporated to afford **1b**, which was taken forward without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.03 (s, 3 H), 2.27 (t, *J* = 2.5 Hz, 1 H), 3.98 (dd, *J* = 2.5, 6.4 Hz, 2 H), 4.54 (s, 1 H), 6.63 (br, 1 H), 7.03 (t, *J* = 7.5 Hz, 1 H), 7.23 (t, *J* = 7.5 Hz, 2 H), 7.44 (d, *J* = 7.5 Hz, 2 H), 9.32 (br, 1 H).

Compound **1b** was reacted as described in the general procedure (1.5 h) and the product was purified by silica gel chromatography ($CHCl_3$/MeOH = 10:1) to afford **2b**.

Yield: 14.2 mg (0.067 mmol, 18%); black oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.67 (s, 3 H), 7.15–7.20 (m, 2 H), 7.38 (t, *J* = 7.8 Hz, 2 H), 7.62 (d, *J* = 7.9 Hz, 2 H), 7.74 (d, *J* = 7.4 Hz, 1 H), 7.97 (br, 1 H), 8.53 (dd, *J* = 1.5, 4.9 Hz, 1 H).

3-Benzoyl-2-methylpyridine (2c)[17]

1-Phenyl-1,3-butanedione (64.4 mg, 0.40 mmol) was added to propargylamine (0.21 mL, 3.3 mmol) at r.t. and the mixture was stirred for 13 h. The reaction mixture was evaporated to afford **1c**, which was taken forward without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.17 (s, 3 H), 2.32 (t, *J* = 2.5 Hz, 1 H), 4.09 (dd, *J* = 2.5, 6.1 Hz, 2 H), 5.76 (s, 1 H), 7.37–7.46 (m, 3 H), 7.84–7.89 (m, 2 H), 11.38 (br, 1 H).

Compound **1c** was reacted as described in the general procedure (8 h) and the product was purified by silica gel chromatography (*n*-hexane/EtOAc = 1:1) to afford **2c**.

Yield: 54.8 mg (0.28 mmol, 70%); black oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.55 (s, 3 H), 7.24 (dd, *J* = 4.7, 7.4 Hz, 1 H), 7.50 (t, *J* = 7.7 Hz, 2 H), 7.60–7.66 (m, 2 H), 7.77–7.82 (m, 2 H), 8.65 (dd, *J* = 1.8, 4.9 Hz, 1 H).

(2-Methylpyridin-3-yl)(*p*-tolyl)methanone (2d)

1-(*p*-Tolyl)butane-1,3-dione (69.1 mg, 0.39 mmol) was added to propargylamine (0.13 mL, 2.0 mmol) at r.t. and stirred for 21 h. The reaction mixture was evaporated to afford **1d**, which was taken forward.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.16 (s, 3 H), 2.31 (t, *J* = 2.5 Hz, 1 H), 2.38 (s, 3 H), 4.08 (dd, *J* = 2.5, 6.1 Hz, 2 H), 5.75 (s, 1 H), 7.20 (d, *J* = 8.0 Hz, 2 H), 7.77 (d, *J* = 8.2 Hz, 2 H), 11.34 (br, 1 H).

Compound **1d** was reacted as described in the general procedure (17 h) and the product was purified by silica gel chromatography (*n*-hexane/EtOAc = 2:1) to afford **2d**.

Yield: 61.2 mg (0.29 mmol, 74%); black oil.

IR (film): 1605, 1661 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.44 (s, 3 H), 2.53 (s, 3 H), 7.23 (dd, *J* = 5.0, 7.5 Hz, 1 H), 7.28 (d, *J* = 7.9 Hz, 2 H), 7.62 (dd, *J* = 1.8, 7.7 Hz, 1 H), 7.69 (d, *J* = 8.2 Hz, 2 H), 8.63 (dd, *J* = 1.8, 4.9 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.9, 23.4, 120.5, 129.6, 130.3, 134.4, 134.5, 136.0, 145.0, 150.4, 156.4, 196.8.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{14}NO$: 212.1075; found: 212.1069.

(4-Methoxyphenyl)(2-methylpyridin-3-yl)methanone (2e)

1-(4-Methoxyphenyl)butane-1,3-dione (79.6 mg, 0.41 mmol) was added to propargylamine (0.18 mL, 2.8 mmol) at r.t. and the mixture was stirred for 7 h. The reaction mixture was evaporated to afford **1e**, which was taken forward without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.16 (s, 3 H), 2.31 (t, *J* = 2.5 Hz, 1 H), 3.84 (s, 3 H), 4.07 (dd, *J* = 2.5, 6.1 Hz, 2 H), 5.73 (s, 1 H), 6.91 (d, *J* = 8.9 Hz, 2 H), 7.85 (d, *J* = 8.9 Hz, 2 H), 11.29 (br, 1 H).

Compound **1e** was reacted as described in the general procedure (14 h) and the product was purified by silica gel chromatography (*n*-hexane/EtOAc = 2:1) to afford **2e**.

Yield: 74.0 mg (0.32 mmol, 79%); black oil.

IR (film): 1598, 1658 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.52 (s, 3 H), 3.89 (s, 3 H), 6.95 (d, *J* = 9.0 Hz, 2 H), 7.22 (dd, *J* = 5.0, 7.4 Hz, 1 H), 7.60 (dd, *J* = 1.7, 7.6 Hz, 1 H), 7.77 (d, *J* = 9.0 Hz, 2 H), 8.63 (dd, *J* = 1.8, 4.9 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.3, 55.7, 114.1, 120.5, 129.9, 132.6, 134.6, 135.7, 150.3, 156.2, 164.3, 195.7.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{14}NO_2$: 228.1025; found: 228.1026.

(4-Fluorophenyl)(2-methylpyridin-3-yl)methanone (2f)

1-(4-Fluorophenyl)butane-1,3-dione (72.6 mg, 0.40 mmol) was added to propargylamine (0.21 mL, 3.2 mmol) at r.t. and the mixture was stirred for 4 h. The reaction mixture was evaporated to afford **1f**, which was taken forward without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.17 (s, 3 H), 2.32 (t, *J* = 2.5 Hz, 1 H), 4.09 (dd, *J* = 2.5, 6.1 Hz, 2 H), 5.71 (s, 1 H), 7.07 (t, *J* = 8.8 Hz, 2 H), 7.87 (dd, *J* = 5.5, 8.9 Hz, 2 H), 11.34 (br, 1 H).

Compound **1f** was reacted as described in the general procedure (24 h) and the product was purified by silica gel chromatography (*n*-hexane/EtOAc = 2:1) to afford **2f**.

Yield: 55.8 mg (0.26 mmol, 65%); black oil.

IR (film): 1598, 1665 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.54 (s, 3 H), 7.16 (t, *J* = 8.8 Hz, 2 H), 7.24 (dd, *J* = 4.9, 7.7 Hz, 1 H), 7.62 (dd, *J* = 1.7, 7.7 Hz, 1 H), 7.82 (dd, *J* = 5.4, 8.9 Hz, 2 H), 8.64 (dd, *J* = 1.8, 4.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.3, 116.0 (d, *J* = 22.0 Hz), 120.4, 132.7 (d, *J* = 9.5 Hz), 133.3 (d, *J* = 2.9 Hz), 133.7, 135.9, 150.6, 156.4, 166.1 (d, *J* = 256.5 Hz), 195.4.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{11}FNO$: 216.0825; found: 216.0820.

(4-Chlorophenyl)(2-methylpyridin-3-yl)methanone (2g)

1-(4-Chlorophenyl)butane-1,3-dione (78.7 mg, 0.40 mmol) was added to propargylamine (0.20 mL, 3.0 mmol) at r.t. and the mixture was stirred for 20 h. The reaction mixture was evaporated to afford **1g**, which was taken forward without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.17 (s, 3 H), 2.33 (t, *J* = 2.5 Hz, 1 H), 4.09 (dd, *J* = 2.5, 6.2 Hz, 2 H), 5.71 (s, 1 H), 7.37 (d, *J* = 8.6 Hz, 2 H), 7.80 (d, *J* = 8.6 Hz, 2 H), 11.38 (br, 1 H).

Compound **1g** was reacted as described in the general procedure (18 h) and the product was purified by silica gel chromatography (*n*-hexane/EtOAc = 2:1) to afford **2g**.

Yield: 62.0 mg (0.27 mmol, 67%); black oil.

IR (film): 1586, 1670 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.54 (s, 3 H), 7.24 (dd, *J* = 4.9, 7.7 Hz, 1 H), 7.47 (d, *J* = 8.9 Hz, 2 H), 7.62 (dd, *J* = 1.7, 7.7 Hz, 1 H), 7.73 (d, *J* = 8.9 Hz, 2 H), 8.66 (dd, *J* = 1.8, 4.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.5, 120.6, 129.2, 131.5, 133.6, 135.4, 136.1, 140.5, 150.8, 156.7, 195.9.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{11}ClNO$: 232.0529; found: 232.0530.

Phenyl(2-phenylpyridin-3-yl)methanone (2h)

1,3-Diphenylprop-2-yn-1-one (82.5 mg, 0.40 mmol) was added to propargylamine (0.13 mL, 2.0 mmol) at r.t. and the mixture was stirred for 15 h. The reaction mixture was evaporated to afford **1h**, which was taken forward without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.31 (t, *J* = 2.5 Hz, 1 H), 3.95 (dd, *J* = 2.5, 6.3 Hz, 2 H), 5.85 (s, 1 H), 7.39–7.49 (m, 8 H), 7.90 (dd, *J* = 1.5, 8.1 Hz, 2 H), 11.33 (br, 1 H).

Compound **1h** was reacted as described in the general procedure (8 h) and the product was purified by silica gel chromatography (*n*-hexane/EtOAc = 3:1) to afford **2h**.

Yield: 75.1 mg (0.29 mmol 72%); black oil.

IR (film): 1426, 1666 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21–7.26 (m, 3 H), 7.30 (t, *J* = 7.8 Hz, 2 H), 7.39–7.47 (m, 2 H), 7.49–7.53 (m, 2 H), 7.63–7.77 (m, 2 H), 7.86 (dd, *J* = 1.8, 7.7 Hz, 1 H), 8.86 (dd, *J* = 1.8, 4.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 121.6, 128.3, 128.4, 128.8, 129.1, 129.8, 133.4, 134.4, 136.5, 137.1, 139.2, 150.8, 157.4, 197.2.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{14}NO$: 260.1075; found: 260.1049.

(2-Methylpyridin-3-yl)(thiophen-2-yl)methanone (2i)

1-(Thiophen-2-yl)butane-1,3-dione (67.2 mg, 0.40 mmol) was added to propargylamine (0.18 mL, 2.8 mmol) at r.t. and the mixture was stirred for 20 h. The reaction mixture was evaporated to afford **1i**, which was taken forward without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.15 (s, 3 H), 2.31 (t, *J* = 2.5 Hz, 1 H), 4.06 (dd, *J* = 2.5, 6.1 Hz, 2 H), 5.64 (s, 1 H), 7.06 (dd, *J* = 3.7, 5.0 Hz, 1 H), 7.45 (dd, *J* = 1.1, 5.0 Hz, 1 H), 7.55 (dd, *J* = 1.1, 3.7 Hz, 1 H), 11.02 (br, 1 H).

Compound **1i** was reacted as described in the general procedure (8 h) and the product was purified by silica gel chromatography (*n*-hexane/EtOAc = 2:1) to afford **2i**.

Yield: 59.0 mg (0.29 mmol, 73%); black oil.

IR (film): 1410, 1641 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.61 (s, 3 H), 7.15 (dd, *J* = 3.8, 4.8 Hz, 1 H), 7.24 (dd, *J* = 4.9, 7.6 Hz, 1 H), 7.40 (dd, *J* = 1.0, 3.8 Hz, 1 H), 7.74 (dd, *J* = 1.7, 7.7 Hz, 1 H), 7.79 (dd, *J* = 1.1, 4.9 Hz, 1 H), 8.64 (dd, *J* = 1.7, 4.9 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.0, 120.2, 128.3, 133.7, 135.4, 135.6, 135.7, 144.1, 150.5, 156.3, 188.7.

HRMS (ESI+): *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{10}NOS$: 204.0483; found: 204.0453.

(Furan-2-yl)(2-methylpyridin-3-yl)methanone (2j)

1-(Furan-2-yl)butane-1,3-dione (60.0 mg, 0.40 mmol) was added to propargylamine (0.13 mL, 2.0 mmol) at r.t. and the mixture was stirred for 33 h. The reaction mixture was evaporated to afford **1j**, which was was taken forward without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.15 (s, 3 H), 2.31 (t, *J* = 2.5 Hz, 1 H), 4.07 (dd, *J* = 2.5, 6.1 Hz, 2 H), 5.70 (s, 1 H), 6.47 (dd, *J* = 1.7, 3.5 Hz, 1 H), 7.00 (dd, *J* = 0.6, 3.5 Hz, 1 H), 7.47 (dd, *J* = 0.7, 1.7 Hz, 1 H), 11.06 (br, 1 H).

Compound **1j** was reacted as described in the general procedure (9 h) and the product was purified by silica gel chromatography (*n*-hexane/EtOAc = 2:1) to afford **2j**.

Yield: 53.7 mg (0.29 mmol, 73%); black oil.

IR (film): 1649 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.62 (s, 3 H), 6.60 (dd, *J* = 1.7, 3.6 Hz, 1 H), 7.07 (dd, *J* = 0.7, 3.6 Hz, 1 H), 7.24 (dd, *J* = 4.9, 7.7 Hz, 1 H), 7.72 (dd, *J* = 0.7, 1.6 Hz, 1 H), 7.79 (dd, *J* = 1.8, 7.7 Hz, 1 H), 8.64 (dd, *J* = 1.8, 4.9 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.1, 112.7, 120.3, 121.4, 132.9, 136.0, 148.1, 150.8, 152.3, 157.0, 183.5.

HRMS (ESI+): *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{10}NO_2$: 188.0712; found: 188.0685.

3-Acetyl-2-methylpyridine (2k)[17]

Acetylacetone (39.6 mg, 0.40 mmol) was added to propargylamine (0.030 mL, 0.48 mmol) at r.t. and the mixture was stirred for 1 h. The reaction mixture was evaporated to afford **1k**, which was taken forward without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.02 (s, 3 H), 2.02 (s, 3 H), 2.28 (t, *J* = 2.5 Hz, 1 H), 3.99 (dd, *J* = 2.5, 6.2 Hz, 2 H), 5.06 (s, 1 H), 10.77 (br, 1 H).

Compound **1k** was reacted as described in the general procedure (4 h) and the product was purified by silica gel chromatography (*n*-hexane/EtOAc = 2:1) to afford **2k**.

Yield: 30.0 mg (0.22 mmol, 56%); black oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.60 (s, 3 H), 2.76 (s, 3 H), 7.24 (dd, *J* = 4.7, 7.8 Hz, 1 H), 7.97 (dd, *J* = 1.7, 7.8 Hz, 1 H), 8.60 (dd, *J* = 1.7, 4.8 Hz, 1 H).

2,2-Dimethyl-1-(2-methylpyridin-3-yl)propan-1-one (2l)

5,5-Dimethylhexane-2,4-dione (57.0 mg, 0.40 mmol) was added to propargylamine (0.13 mL, 2.0 mmol) at r.t. and the mixture was stirred for 16 h. The reaction mixture was evaporated to afford **1l**, which was was taken forward without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.14 (s, 9 H), 2.05 (s, 3 H), 2.28 (t, *J* = 2.5 Hz, 1 H), 3.99 (dd, *J* = 2.5, 6.1 Hz, 2 H), 5.23 (s, 1 H), 10.96 (br, 1 H).

Compound **1l** was reacted as described in the general procedure (11 h) and the product was purified by silica gel chromatography (*n*-hexane/EtOAc = 2:1) to afford **2l**.

Yield: 32.0 mg (0.18 mmol, 45%); black oil.

IR (film): 1647, 1688 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26 (s, 9 H), 2.46 (s, 3 H), 7.12 (dd, *J* = 4.7, 7.8 Hz, 1 H), 7.45 (dd, *J* = 1.8, 7.7 Hz, 1 H), 8.53 (dd, *J* = 1.7, 4.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.3, 27.1, 45.5, 119.9, 132.6, 135.9, 149.3, 154.2, 212.8.

HRMS (ESI+): *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{10}NO$: 178.1232; found: 178.1216.

Cyclohexyl(2-methylpyridin-3-yl)methanone (2m)

1-Cyclohexylbutane-1,3-dione (67.9 mg, 0.40 mmol) was added to propargylamine (0.13 mL, 2.0 mmol) at r.t. and the mixture was stirred for 12 h. The reaction mixture was evaporated to afford **1m**, which was taken forward without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.22–1.41 (m, 6 H), 1.76–1.81 (m, 4 H), 2.03 (s, 3 H), 2.15 (tt, *J* = 2.9, 14.6 Hz, 1 H), 2.28 (t, *J* = 2.5 Hz, 1 H), 3.99 (dd, *J* = 2.5, 6.1 Hz, 2 H), 5.06 (s, 1 H), 10.87 (br, 1 H).

Compound **1m** was reacted as described in the general procedure (10 h) and the product was purified by silica gel chromatography (*n*-hexane/EtOAc = 2:1) to afford **2m**.

Yield: 55.4 mg (0.27 mmol, 68%); black oil.

IR (film): 1434, 1516, 1688, 2855, 2931 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.19–1.51 (m, 5 H), 1.66–1.75 (m, 1 H), 1.78–1.90 (m, 4 H), 2.63 (s, 3 H), 3.00 (tt, *J* = 3.2, 14.5 H, 1 H), 7.20 (dd, *J* = 4.7, 7.8 Hz, 1 H), 7.76 (dd, *J* = 1.7, 7.8 Hz, 1 H), 8.57 (dd, *J* = 1.7, 4.9 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.9, 25.7, 25.9, 28.7, 49.0, 120.6, 134.0, 134.9, 150.5, 157.2, 207.5.

HRMS (ESI+): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{18}NO$: 204.1388; found: 204.1358.

7,8-Dihydroquinolin-5(6*H*)-one (2n)[16]

Cyclohexane-1,3-dione (45.0 mg, 0.40 mmol) was added to propargylamine (0.13 mL, 2.0 mmol) at r.t. and the mixture was stirred for 14 h. The reaction mixture was evaporated to afford **1n**, which was taken forward without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.95–2.03 (m, 2 H), 2.30–2.41 (m, 5 H), 3.87 (dd, *J* = 2.5, 5.2 Hz, 2 H), 5.17 (s, 1 H), 5.19 (br, 1 H).

Compound **1n** was reacted as described in the general procedure (12 h) and the product was purified by silica gel chromatography (*n*-hexane/EtOAc = 2:1) to afford **2n**.

Yield: 18.9 mg (0.13 mmol, 32%); black oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.18–2.25 (m, 2 H), 2.68–2.74 (m, 2 H), 3.14–3.20 (m, 2 H), 7.30 (dd, *J* = 4.8, 7.8 Hz, 1 H), 8.28 (dd, *J* = 1.8, 7.8 Hz, 1 H), 8.68 (dd, *J* = 1.8, 4.8 Hz, 1 H).

Ethyl 2-Methylnicotinate (2o)[18]

Ethyl 3-oxobutanoate (54.1 mg, 0.40 mmol) was added to propargylamine (0.13 mL, 2.0 mmol) at r.t. and the mixture was stirred for 16 h. The reaction mixture was evaporated to afford the *cis*/*trans* isomers (**1o**/**1o′** = 5:2), and was taken forward without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ (**1o**) = 1.23 (t, *J* = 7.1 Hz, 3 H), 2.01 (s, 3 H), 2.29 (t, *J* = 2.5 Hz, 1 H), 3.97 (dd, *J* = 2.5, 6.3 Hz, 2 H), 4.09 (q, *J* = 7.1 Hz, 2 H), 4.56 (s, 1 H), 8.63 (br, 1 H); δ (**1o′**) = 1.26 (t, *J* = 7.1 Hz, 3 H), 2.31 (s, 3 H), 2.32 (t, *J* = 2.5 Hz, 1 H), 3.81 (dd, *J* = 2.5, 5.2 Hz, 2 H), 4.10 (q, *J* = 7.1 Hz, 2 H), 4.43 (br, 1 H), 4.65 (s, 1 H).

The mixture of **1o** and **1o′** was reacted as described in the general procedure (7 h) and the product was purified by silica gel chromatography (*n*-hexane/EtOAc = 2:1) to afford **2o**.

Yield: 32.9 mg (0.20 mmol, 50%); black oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.41 (t, *J* = 7.2 Hz, 3 H), 2.85 (s, 3 H), 4.39 (q, *J* = 7.1 Hz, 2 H), 7.22 (dd, *J* = 4.8, 7.9 Hz, 1 H), 8.19 (dd, *J* = 1.8, 7.8 Hz, 1 H), 8.60 (dd, *J* = 1.8, 4.8 Hz, 1 H).

Isopropyl 2-Methylnicotinate (2p)

Isopropyl 3-oxobutanoate (57.6 mg, 0.40 mmol) was added to propargylamine (0.13 mL, 2.0 mmol) at r.t. and the mixture was stirred for 23 h. The reaction mixture was evaporated to afford *cis*/*trans* isomers (**1p**/**1p′** = 10:3), which was taken forward without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ (**1p**) = 1.23 (d, *J* = 6.2 Hz, 6 H), 2.00 (d, *J* = 0.4 Hz, 3 H), 2.28 (t, *J* = 2.5 Hz, 1 H), 3.96 (dd, *J* = 2.5, 6.3 Hz, 2 H), 4.54 (s, 1 H), 4.99 (sept, *J* = 6.3 Hz, 1 H), 8.64 (br, 1 H); δ (**1p′**) = 1.23 (d, *J* = 6.2 Hz, 6 H), 2.31 (s, 3 H), 2.31 (t, *J* = 2.5 Hz, 1 H), 3.81 (dd, *J* = 2.5, 5.0 Hz, 2 H), 4.20 (br, 1 H), 4.61 (s, 1 H), 5.01 (sept, *J* = 6.3 Hz, 1 H).

The mixture of **1p** and **1p′** was reacted as described in the general procedure (9 h) and the product was purified by silica gel chromatography (*n*-hexane/EtOAc = 2:1) to afford **2p**.

Yield: 34.3 mg (0.19 mmol, 48%); black oil.

IR (film): 1591, 1722, 2981 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.38 (d, *J* = 6.2 Hz, 6 H), 2.84 (s, 3 H), 5.26 (sept, *J* = 6.2 Hz, 1 H), 7.20 (dd, *J* = 4.8, 7.8 Hz, 1 H), 8.16 (dd, *J* = 1.8, 7.8 Hz, 1 H), 8.60 (dd, *J* = 1.8, 4.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.0, 24.7, 69.2, 121.2, 126.4, 138.7, 151.4, 159.6, 166.2.

HRMS (ESI+): *m*/*z* $[M + H]^+$ calcd for $C_{10}H_{14}NO_2$: 180.1025; found: 180.1018.

***tert*-Butyl 2-Methylnicotinate (2q)**

tert-Butyl 3-oxobutanoate (63.3 mg, 0.40 mmol) was added to propargylamine (0.13 mL, 2.0 mmol) at r.t. and the mixture was stirred for 19 h. The reaction mixture was evaporated to afford *cis*/*trans* isomers (**1q**/**1q′** = 10:3), which was taken forward without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ (**1q**) = 1.46 (s, 9 H), 1.98 (d, *J* = 0.5 Hz, 3 H), 2.27 (t, *J* = 2.5 Hz, 1 H), 3.95 (dd, *J* = 2.5, 6.3 Hz, 2 H), 4.50 (q, *J* = 0.5 Hz, 1 H), 8.59 (br, 1 H); δ (**1q′**) = 1.47 (s, 9 H), 2.28 (s, 3 H), 2.30 (t, *J* = 2.5 Hz, 1 H), 3.79 (dd, *J* = 2.5, 5.0 Hz, 2 H), 4.05 (br, 1 H), 4.57 (s, 1 H).

The mixture of **1q** and **1q′** was reacted as described in the general procedure (3 h) and the product was purified by silica gel chromatography (*n*-hexane/EtOAc = 2:1) to afford **2q**.

Yield: 13.6 mg (0.070 mmol, 18%); black oil.

IR (film): 1438, 1570, 1720, 2978 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.61 (s, 9 H), 2.81 (s, 3 H), 7.20 (dd, *J* = 4.8, 7.8 Hz, 1 H), 8.11 (dd, *J* = 1.8, 7.8 Hz, 1 H), 8.58 (dd, *J* = 1.8, 4.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.0, 28.3, 82.1, 121.0, 127.5, 138.3, 151.4, 159.3, 166.2.

HRMS (ESI+): *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{16}NO_2$: 194.1181; found: 194.1141.

Diethyl Pyridine-2,3-dicarboxylate (2r)[19]

Diethyl but-2-ynedioate (67.5 mg, 0.40 mmol) in EtOH (2 mL) was added to propargylamine (0.026 mL, 0.40 mmol) at 0 °C. Subsequently, the mixture was stirred at r.t. for 14 h. The reaction mixture was evaporated to afford *cis*/*trans* isomers (**1r**/**1r′** = 10:7), which was taken forward without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ (**1r**) = 1.28 (t, *J* = 7.1 Hz, 3 H), 1.35 (t, *J* = 7.1 Hz, 3 H), 2.27 (t, *J* = 2.5 Hz, 1 H), 4.16 (q, *J* = 7.1 Hz, 2 H), 4.20 (dd, *J* = 2.5, 6.1 Hz, 2 H), 4.30 (q, *J* = 7.1 Hz, 2 H), 5.35 (s, 1 H), 8.11 (br, 1 H); δ (**1r′**) = 1.26 (t, *J* = 7.1 Hz, 3 H), 1.36 (t, *J* = 7.1 Hz, 3 H), 2.34 (t, *J* = 2.5 Hz, 1 H), 3.82 (dd, *J* = 2.5, 5.2 Hz, 2 H), 4.13 (q, *J* = 7.1 Hz, 2 H), 4.34 (q, *J* = 7.1 Hz, 2 H), 4.50 (br, 1 H), 4.83 (s, 1 H).

The mixture of **1r** and **1r′** was reacted as described in the general procedure (5 h) and the product was purified by silica gel chromatography (*n*-hexane/EtOAc = 3:1) to afford **2r**.

Yield: 49.2 mg (0.22 mmol, 56%); black oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.39 (t, *J* = 7.1 Hz, 3 H), 1.43 (t, *J* = 7.2 Hz, 3 H), 4.40 (q, *J* = 7.2 Hz, 2 H), 4.47 (q, *J* = 7.2 Hz, 2 H), 7.49 (dd, *J* = 4.8, 8.0 Hz, 1 H), 8.20 (dd, *J* = 1.7, 8.0 Hz, 1 H), 8.77 (dd, *J* = 1.7, 4.8 Hz, 1 H).

2-Phenylnicotinonitrile (2s)[20]

3-Oxo-3-phenylpropanenitrile (58.1 mg, 0.40 mmol) in EtOH (0.8 mL) was added to propargylamine (51 μL, 0.80 mmol) and AcOH (47 μL, 0.80 mmol) at r.t. This mixture was heated to 50 °C and stirred for 12 h. The reaction mixture was evaporated to afford **1s**, which was taken forward without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.36 (t, *J* = 2.5 Hz, 1 H), 3.93 (dd, *J* = 2.5, 5.3 Hz, 2 H), 4.20 (s, 1 H), 4.56 (br, 1 H), 7.41–7.51 (m, 3 H), 7.55–7.60 (m, 2 H).

Compound **1s** was reacted as described in the general procedure (used 20 mL of nitrobenzene, 5 h) and the product was purified by silica gel chromatography (*n*-hexane/EtOAc = 3:1) to afford **2s**.

Yield: 45.9 mg (0.26 mmol, 64%); yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 (dd, *J* = 4.8, 7.9 Hz, 1 H), 7.48–7.57 (m, 3 H), 7.90–7.95 (m, 2 H), 8.07 (dd, *J* = 1.7, 7.9 Hz, 1 H), 8.87 (dd, *J* = 1.7, 4.8 Hz, 1 H).

2-(4-Chlorophenyl)nicotinonitrile (2t)[21]

3-(4-Chlorophenyl)-3-oxopropanenitrile (71.8 mg, 0.40 mmol) in EtOH (4 mL) was added to propargylamine (0.13 mL, 2.0 mmol) and AcOH (0.11 mL, 2.0 mmol) at r.t. This mixture was heated to 50 °C and stirred for 20 h. The reaction mixture was evaporated to afford **1t**, which was taken forward without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.37 (t, *J* = 2.5 Hz, 1 H), 3.93 (dd, *J* = 2.5, 5.3 Hz, 2 H), 4.22 (s, 1 H), 4.51 (br, 1 H), 7.43 (d, *J* = 8.6 Hz, 2 H), 7.52 (d, *J* = 8.6 Hz, 2 H).

Compound **1t** was reacted as described in the general procedure (20 mL of nitrobenzene, 3 h) and the compound was purified by silica gel chromatography (*n*-hexane/EtOAc = 3:2) to afford **2t**.

Yield: 79.5 mg (0.38 mmol, 95%); white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 (dd, *J* = 4.8, 7.9 Hz, 1 H), 7.51 (dd, *J* = 2.0, 6.7 Hz, 5 H), 7.89 (dd, *J* = 2.0, 6.7 Hz, 1 H), 8.08 (dd, *J* = 1.8, 7.9 Hz, 1 H), 8.88 (dd, *J* = 1.8, 7.9 Hz, 1 H).

3-(But-2-yn-1-ylamino)-1*H*-inden-1-one (5)

But-2-yn-1-ylamine (106 mg, 1.0 mmol) in EtOH (2 mL) was added to 10 M NaOH aq (0.1 mL, 0.1 mmol) and stirred at 50 °C for 30 min. After filtering the precipitate, 1,3-indanedione (731 mg, 5.0 mmol) was added to the filtrate, and the mixture was stirred at 50 °C for 17 h. The reaction mixture was evaporated and purified by silica gel chromatography (*n*-hexane/EtOAc = 1:1) to afford **5**.

Yield: 120 mg (0.61 mmol, 61%); yellow solid. This compound was unstable that it was used immediately for the next reaction.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.86 (t, *J* = 2.4 Hz, 3 H), 4.08 (dq, *J* = 2.5, 7.6 Hz, 2 H), 4.96 (s, 1 H), 5.36 (br, 1 H), 7.07–7.12 (m, 1 H), 7.31–7.38 (m, 2 H), 7.44–7.49 (m, 1 H).

Onychine (6)[14]

Compound **5** (39.4 mg, 0.2 mmol) was reacted as described in the general procedure (20 mL of nitrobenzene, 14 h) and the product was purified by silica gel chromatography (*n*-hexane/EtOAc = 1:1) to afford **6**.

Yield: 32.6 mg (0.17 mmol, 84%); yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.64 (d, *J* = 0.4 Hz, 3 H), 6.98 (dd, *J* = 0.5, 5.3 Hz, 1 H), 7.43 (dt, *J* = 1.0, 7.5 Hz, 1 H), 7.59 (dt, *J* = 1.0, 7.5 Hz, 1 H), 7.70 (d, *J* = 7.4 Hz, 1 H), 7.84 (d, *J* = 7.4 Hz, 1 H), 8.42 (d, *J* = 5.3 Hz, 1 H).

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1691575.

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