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Cu- and Mo-Catalysed Expedient Synthesis of Alkynyl-Substituted Derivatives of 1,2-Dihydropyridines, -quinolines and -isoquinolines

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An efficient synthesis of 1,2-dihydroisoquinolines and -quinolines by employing dimethyl acetylenedicarboxylate activated isoquinolines and quinolines in conjuction with the $CuCl_2/Et_3N$ catalytic system is described herein. Furthermore, the MoO_3-catalysed alkynylation of pyridines and substituted pyridines has also been achieved. Moreover, this process has allowed the rapid synthesis of alkynyl derivatives of dihydroisoquinoline and -quinoline with functional group variations of the alkynyl group by using a low catalyst loading (i.e., 1 mol-%).

Introduction

Aza-aromatic nuclei such as pyridine, quinoline and isoquinoline are frequently found as components of a wide range of natural products, chiral ligands and synthetic building blocks.[1] In general, the 1,2- or 3,4-dihydro and 1,2,3,4-tetrahydro reduced species of these privileged structural units act as pharmacophores. Among them, prominent examples include indenoisoquinoline[2] (topoisomerase I inhibitor), narciclasine[3] (anti-tumour agent) and papaverin[4] (smooth-muscle relaxant). Frequently aza-aromatic nuclei are alkynylated through activation by *N*-acylation using alkyl chloroformates or acyl chloride.[5] Another approach is the generation of a 1,4-dipolar intermediate with electron-deficient acetylene compounds (the Huisgen protocol) and subsequent addition of either the alkynyl moiety without any catalyst[6] or coupling with the corresponding alkynyl moiety, which is activated mostly by copper salts.[7]

Recently, gold(III) chloride was found to catalyse the facile synthesis of 1,2-dihydroquinolines and -isoquinolines by employing dimethyl acetylenedicarboxylate activated quinolines and isoquinolines followed by in situ coupling with various substituted ethynylbenzenes.[8] Despite their interest, all these protocols suffer from a lack of generality. For example, many of these catalytic systems allowed the use of only aromatic alkynes for carbon–carbon bond formation. Moreover, the high cost and air sensitivity of the gold(III) chloride catalyst system limits any further potential application of carbon–carbon bond-forming reactions. Consequently, an easy and rather general process for the synthesis of 1,2-dihydropyridines, -quinolines and -isoquinolines using various alkynyl moieties is highly desirable.

As part of our programme for the rapid synthesis of bioactive molecules, we focused our attention on copper-catalysed multicomponent reactions.[9] Herein we report our results of the synthesis of substituted 1,2-dihydropyridines, -quinolines and -isoquinolines using various terminal alkynyl moieties.

Results and Discussion

Initially we considered performing the one-pot reaction by employing isoquinoline (**1a**) (1 equiv.) and the terminal alkyne methyl propiolate (**2a**; 2.1 equiv.) in the presence of 5 mol-% of CuI in dichloromethane (Scheme 1). After stirring for 1 h at ambient temperature, we isolated the desired product **3a** in 70% yield. The same reaction in the absence of the catalyst did not yield the required compound. In copper-promoted reactions, the efficacy of the reaction depends on the copper source. Therefore, we screened 5 mol-% of copper sources such as CuOTf (5%), CuCl (20%), CuCN (0%), $[Cu(tmeda)Cl]_2$ (0%), $CuCl_2$ (75%), $Cu(acac)_2$ (15%) and $Cu(Piv)_2$ (0%). Only one of the copper catalysts, $CuCl_2$, gave the expected product, and this showed slightly better activity and yield than CuI. Note that the reaction proceeds with as little as 1 mol-% of $CuCl_2$ and furnished the product **3a** in 90% yield. Significantly, the same reaction with 5 mol-% $AuCl_3$ did not give the target compound **3a**.[8] Chlorinated solvents such as CH_2Cl_2, $ClCH_2CH_2Cl$ and $CHCl_3$ were the solvents of choice; reactions performed in

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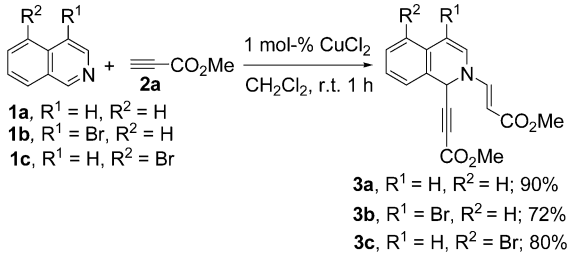
CH_3CN, DMSO, DMF and THF did not yield a trace of the required product. In addition to the ^1H and ^{13}C NMR and MS analytical data, the product **3a** was unambiguously confirmed by single-crystal X-ray analysis (Figure 1).



Scheme 1.

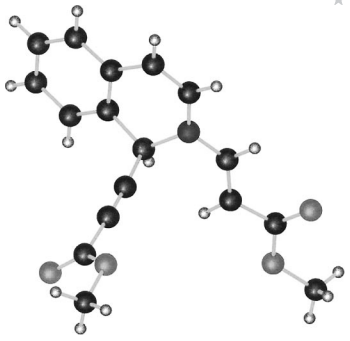


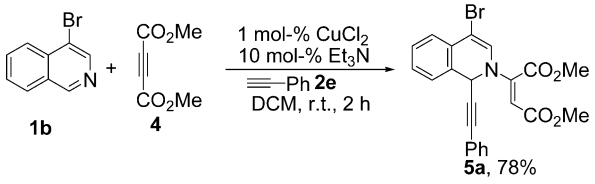
Figure 1. X-ray crystal structure of **3a**.[10]

Under these optimized reaction conditions, 4- and 5-bromoisoquinolines (**1b** and **1c**) were treated with **2a**, and the corresponding products **3b** and **3c** were isolated in 72 and 80% yields, respectively, whereas the reaction carried out using **1b** (1 equiv.), dimethyl acetylenedicarboxylate (DMAD, **4**; 1.2 equiv.) and **2e** (1.2 equiv.) in the presence of 1 mol-% of $CuCl_2$ in DCM on stirring for 2 h at ambient temperature led to the recovery of the starting material. With a catalytic amount of Et_3N (10 mol-%), the same reaction under otherwise identical conditions led to the expected product **5a** in 78% isolated yield (Scheme 2). Inorganic bases K_2CO_3, Cs_2CO_3 and CsOH were not effective for this transformation.

Table 1. $CuCl_2/Et_3N$-catalysed alkynylation of isoquinoline (**1a**) and DMAD (**4**) with various terminal alkynes.[a]

Entry	Terminal alkyne	Product[b] (yield [%])[c]	Entry	Terminal alkyne	Product[b] (yield [%])[c]
1	**2a**	**5b** (76)	5	**2e**	**5f** (80)
2	**2b**	**5c** (80)	6	**2f**	**5g** (78)
3	**2c**	**5d** (76)	7	**2g**	**5h** (80)
4	**2d**	**5e** (82)	8	**2h**	**5i** (80)

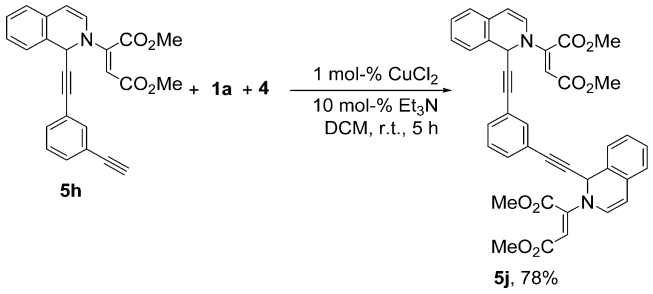
[a] All reactions were carried out with a terminal alkyne (1.2 mmol), isoquinoline (**1a**; 1 mmol), **4** (1.2 mmol), $CuCl_2$ (1 mol-%) and Et_3N (10 mol-%) in CH_2Cl_2 (5 mL) at ambient temperature with stirring for 2 h. [b] All products were fully characterized. [c] Unoptimized isolated yields.



Scheme 2.

The optimized reaction conditions were then applied to isoquinoline (**1a**) activated by **4** with varying terminal alkynes, and our results are shown in Table 1. Various terminal acetylenes, irrespective of their steric and electronic nature, underwent coupling with isoquinolines activated by dimethyl acetylenedicarboxylate. This was in contrast to previous reports that only the reactions of substituted phenylacetylenes with modular variations of isoquinoline were successful.[8] For example, under typical conditions, 1-heptyne (**2d**) and 2-methoxy-1-naphthylethyne (**2h**) reacted with equal efficacy with activated isoquinoline and furnished the products **5e** and **5i** (Entries 4 and 8, Table 1) in fairly good yields.

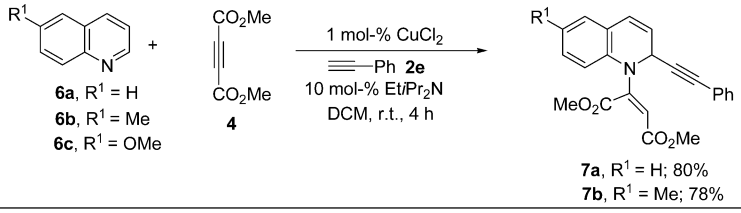
Methyl propiolate (**2a**) and propargyl bromide (**2c**) were also coupled with activated isoquinoline, producing the corresponding 1,2-dihydroisoquinolines **5b** and **5d** (Entries 1 and 3, Table 1) in slightly lower yields. Interestingly, 1,3-diethynylbenzene (**2g**; 1.1 equiv.) also underwent coupling with activated isoquinoline, and the anticipated monocoupling product **5h** was isolated in 80% yield (Entry 7, Table 1). Even when using 2.2 equiv. of **1a** and **4**, only the product **5h** was isolated, and no trace of compound **5j** was observed. In another experiment, the reaction of **5h** with **1a** and **4** in the presence of 1 mol-% $CuCl_2$ and 10 mol-% Et_3N with stirring at room temperature resulted in compound **5j** in 78% yield (Scheme 3).

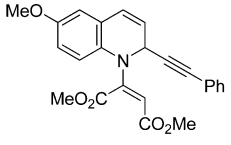
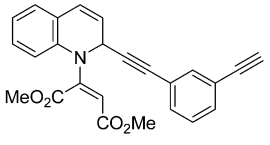
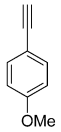
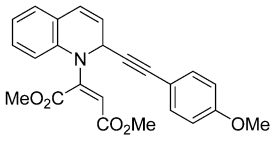
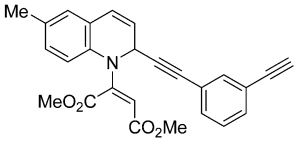
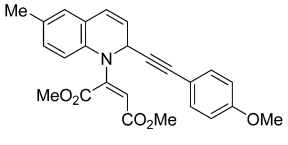
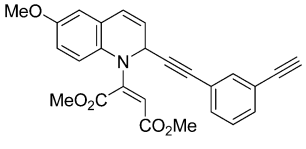


Scheme 3.

Under a similar protocol, the reaction of quinoline (**6a**), activated by dimethyl acetylenedicarboxylate (**4**), with **2e** resulted in the desired substituted alkyne product **7a**, but in poor yield (10%) after prolonged stirring at room temperature. This problem was circumvented by employing a catalytic amount of Hünig's base in place of Et_3N. The reaction

Table 2. $CuCl_2$/EtN(*i*Pr)$_2$-catalysed alkynylation of DMAD (**4**) activated quinolines **6a**–**c**.[a]

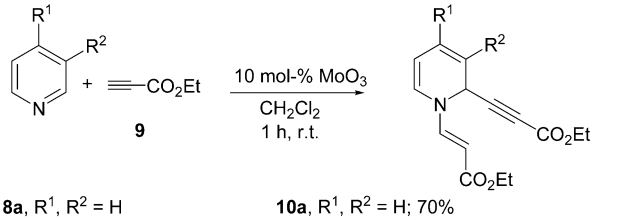


Entry	Terminal alkyne	Product[b] (yield [%])[c]	Entry	Terminal alkyne	Product[b] (yield [%])[c]
1	2e	 **7c** (75)	4	2g	 **7f** (81)
2	 2i	 **7d** (75)	5	2g	 **7g** (81)
3	2i	 **7e** (73)	6	2g	 **7h** (84)

[a] All reactions were carried out with a terminal alkyne (1.2 mmol), quinoline (1 mmol), **4** (1.2 mmol), $CuCl_2$ (1 mol-%) and Et*i*Pr$_2$N (10 mol-%) in CH_2Cl_2 (5 mL) at ambient temperature with stirring for 4 h. [b] All products were fully characterized. [c] Unoptimized isolated yields.

carried out using 10 mol-% of Hünig's base, **6a** (1 equiv.), dimethyl acetylenedicarboxylate (**4**; 1.2 equiv.) and **2e** (1.2 equiv.) in the presence of 1 mol-% of $CuCl_2$ in DCM with stirring for 4 h at ambient temperature led to the desired substituted alkyne product **7a** in 80% yield. Gratifyingly, under the standard protocol, dimethyl acetylenedicarboxylate (**4**) activated various substituted quinolines **6a**–**c**, which were coupled with substituted phenylacetylenes. The resulting corresponding adducts **7b**–**h** were obtained in fairly good yields (Table 2). Under typical conditions, our efforts to couple aliphatic alkynes such as 1-octyne (**2d**) and methyl propiolate (**2a**) with dimethyl acetylenedicarboxylate activated **6a** were not successful.

In an attempt to extend this protocol to the synthesis of substituted 1,2-dihydropyridine adducts, we performed the one-pot reaction with pyridine (**8a**; 1 equiv.) and the terminal alkyne ethyl propiolate (**9**; 2.1 equiv.) in the presence of 1 mol-% of $CuCl_2$ in DCM. Stirring at ambient temperature for 1 h showed the complete disappearance of the starting material. Workup followed by column chromatography resulted in a trace amount of the desired substituted alkyne product **10a**. After considerable experimentation,[11] in the presence of 10 mol-% of MoO_3, pyridine (**8a**; 1 equiv.) and the terminal alkyne ethyl propiolate (**9**; 3 equiv.) in DCM with stirring for 1 h at ambient temperature yielded the desired product **10a** in 70% isolated yield (Scheme 4).



8a, R^1, R^2 = H	**10a**, R^1, R^2 = H; 70%
8b, R^1 = H, R^2 = CH_3	**10b**, R^1 = H, R^2 = CH_3; 0%[12]
8c, R^1 = CH_3, R^2 = CH_2CH_3	**10c**, R^1 = CH_3, R^2 = CH_2CH_3; (3:1) 82%
8d, R^1, R^2 = CH_3	**10d**, R^1, R^2 = CH_3; (5:1) 65%
8e, R^1 = CH_2CH_3, R^2 = H	**10e**, R^1 = CH_2CH_3, R^2 = H; 80%
8f, R^1 = Ph, R^2 = H	**10f**, R^1 = Ph, R^2 = H; 0%
8g, R^1 = H, R^2 = CO_2Me	**10g**, R^1 = H, R^2 = CO_2Me; 0%

Scheme 4.

In the light of a recent study of the regioselective addition of metallo-alkynyl reagents to pyridinium salts,[12] we explored the addition of alkynyl reagents to substituted pyridines. Accordingly, 3-picoline (**8b**) and **9** were subjected to the standard protocol. Analysis of the reaction mixture by TLC indicated a multitude of products.[13] The reaction of 3-ethyl-4-methylpyridine (**8c**) with **9** proceeded to yield the expected 2- and 6-substituted adducts of **10c** in a 3:1 ratio (82%). Similarly, the reaction of **8d** with **9** resulted in **10d** in a moderate yield (65%) in a 5:1 isomeric ratio,[14] which indicates the synthetic viability of the reaction. 4-Ethylpyridine (**8e**) also reacted with the same efficiency, furnishing the product **10e** in 80% yield. However, 4-phenylpyridine (**8f**) and 3-methylnicotine (**8g**) under these conditions gave no traces of the coupled products (Scheme 4).[15]

Conclusions

We have developed an efficient strategy for the synthesis of alkynyl derivatives of 1,2-dihydroisoquinolines, -quinolines and -pyridines. This methodology is significant in that the reactions are catalysed by low-cost raw materials such as $CuCl_2$ and MoO_3.[16] Moreover, the process allows the rapid synthesis of alkynyl derivatives of dihydroisoquinoline and -quinoline with functional-group variations on the alkynyl by using a low level of catalyst loading (i.e., 1 mol-%). Further work is in progress for the synthesis of various heteroatom-containing alkynyl 1,2-dihydro nitrogen heterocyclic derivatives.

Experimental Section

General: Melting points are uncorrected. ^{1}H NMR spectra were recorded at 200, 300 or 400 MHz and ^{13}C NMR spectra at 50, 75 or 100 MHz in $CDCl_3$. FTIR spectra were measured for samples prepared as KBr pellets or as films between KBr plates. MS data were compiled by using electrospray ionization (ESI). Column chromatography was carried out with silica gel (grade 60–120 and 100–200 mesh). CH_2Cl_2 was distilled from P_2O_5. All other chemicals used were commercially available. All reactions were conducted under nitrogen (IOLAR Grade I). Organic extracts were dried with anhydrous Na_2SO_4.

Typical Procedure for the Synthesis of Alkynyl-Substituted Derivatives of Quinolines and Isoquinolines: Dimethyl acetylenedicarboxylate (**4**; 1.2 mmol) was added to a stirred solution of $CuCl_2$ (0.01 mmol), quinoline/isoquinoline (1 mmol), acetylene (1.2 mmol) and triethylamine (0.1 mmol) in dichloromethane (5 mL). The resulting reaction mixture was stirred at room temp. for 1 h. The reaction mixture was passed through a Celite pad and washed with dichloromethane (2 × 3 mL). The combined filtrate solutions were concentrated under reduced pressure. The crude residue when subjected to silica gel column chromatography (100–200 mesh) using hexane/ethyl acetate (9:1) as eluent afforded the pure product.

Methyl (*E*)-3-[1-(3-Methoxy-3-oxoprop-1-ynyl)isoquinolin-2(1*H*)-yl-]acrylate (3a): Isoquinoline (1 mmol), methyl propiolate (2.1 mmol) and $CuCl_2$ (0.01 mmol) were subjected to the typical procedure described above. Yield: 268 mg (90%), pale-yellow solid, m.p. 140–142 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45 (d, $^3J_{H,H}$ = 13.59 Hz, 1 H), 7.28–7.18 (m, 3 H), 7.04 (d, $^3J_{H,H}$ = 6.79 Hz, 1 H), 6.35 (d, $^3J_{H,H}$ = 7.55 Hz, 1 H, 3-H), 5.8 (d, $^3J_{H,H}$ = 7.55 Hz,1 H, 4-H),5.72 (s, 1 H, 1-H), 5.19 (d, $^3J_{H,H}$ = 13.59 Hz, 1 H), 3.71 (s, 3 H, CO_2Me), 3.70 (s, 3 H, CO_2Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.2, 146.1, 129.2, 128.6, 127.5, 126.4,125.3, 106.5, 92.8, 82.5, 52.7, 51.4, 48.95 ppm. IR (KBr): $\tilde{\nu}$ = 3393, 2951, 2228, 1707, 1616, 1166, 772 cm^{-1}. MS (ESI): *m*/*z* = 298 [M + 1]$^+$. HRMS: calcd. for $C_{17}H_{15}NO_4Na$ 320.0898; found 320.088.

Methyl (*E*)-3-[4-Bromo-1-(3-methoxy-3-oxoprop-1-ynyl)isoquinolin-2(1*H*)-yl]acrylate (3b): Yield: 270 mg (72%), pale-red solid, m.p.121–123 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.50–7.16 (m, 5 H), 6.74 (s, 1 H, 3-H), 5.70 (s, 1 H, 1-H), 5.27 (d, $^3J_{H,H}$ = 13.22 Hz, 1 H), 3.71 (s, 6 H, CO_2Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.9, 144.9, 129.7, 129.1, 128.9, 127.6, 126.3, 125.5, 125.5, 93.9, 52.9, 51.4, 49.4 ppm. IR (KBr): $\tilde{\nu}$ = 3415, 2920, 2225, 1712, 1617, 1250, 1167, 1050, 763, 530 cm^{-1}. MS (ESI): *m*/*z* = 376 [M + 1]$^+$.

Methyl (*E*)-3-[5-Bromo-1-(3-methoxy-3-oxoprop-1-ynyl)isoquinolin-2(1*H*)-yl]acrylate (3c): Yield: 300 mg (80%), pale-red solid, m.p.122–124 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.50–7.41 (m, 2 H), 7.11–7.04 (m, 2 H), 6.44 (d, $^3J_{H,H}$ = 8.08 Hz, 1 H, 3-H), 6.16 (d, $^3J_{H,H}$ = 7.34 Hz, 1 H, 4-H), 5.71 (s, 1 H, 1-H), 5.27 (d, $^3J_{H,H}$ = 13.95 Hz, 1 H), 3.71 (s, 6 H, CO_2Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.0, 153.1, 145.6, 133.4, 130.4, 129.6, 128.3, 127.0, 125.8, 120.7, 105.1, 93.9, 81.9, 52.9, 51.3, 48.9 ppm. IR (KBr): $\tilde{\nu}$ = 3416, 2925, 2852, 1713, 1615, 1552, 1309, 1052, 801, 763 cm^{-1}. MS (ESI): *m*/*z* = 376 [M + 1]$^+$. HRMS: calcd. for $C_{17}H_{14}NO_4NaBr$ 398.0003; found 398.0009.

Dimethyl 2-[4-Bromo-1-(phenylethynyl)isoquinolin-2(1*H*)-yl]maleate (5a): Yield: 352 mg (78%), red solid, m.p.122–124 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.51 (d, $^3J_{H,H}$ = 7.5 Hz, 1 H), 7.37–7.28 (m, 3 H), 7.24–7.18 (m, 5 H), 6.63 (s, 1 H, 3-H), 5.73 (s, 1 H), 5.43 (s, 1 H, 1-H), 3.97 (s, 3 H, CO_2Me), 3.70 (s, 3 H, CO_2Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.7, 148.1, 131.8, 129.0, 128.9, 128.9, 128.5, 128.2, 125.9, 125.7, 125.3, 121.6, 104.1,93.5, 86.5, 84.0, 53.5, 51.5, 51.7 ppm. IR (KBr): $\tilde{\nu}$ = 3422, 2951, 1741, 1704, 1593, 1383, 1179, 1154, 751 cm^{-1}. MS (ESI): *m*/*z* = 452 [M + 1]$^+$.

Dimethyl 2-[1-(3-Methoxy-3-oxoprop-1-ynyl)isoquinolin-2(1*H*)-yl]-maleate (5b): Yield: 270 mg (76%), white solid, m.p. 138–142 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29–7.071 (m, 4 H), 6.27 (d, $^3J_{H,H}$ = 8.30 Hz, 1 H, 3-H), 5.93 (d, $^3J_{H,H}$ = 7.55 Hz, 1 H, 4-H), 5.64 (s, 1 H), 5.28 (s, 1 H, 1-H), 3.95 (s, 3 H, CO_2Me), 3.72 (s, 3 H, CO_2Me), 3.70 (s, 3 H, CO_2Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.7, 129.3, 127.9, 126.3, 125.4, 124.8, 109.2, 93.2, 81.8, 53.3, 52.8, 51.4, 49.5 ppm. IR (KBr): $\tilde{\nu}$ = 3408, 2924, 2852, 2233, 1714, 1600, 1167, 1105, 769 cm^{-1}. MS (ESI): *m*/*z* = 356 [M + 1]$^+$. HRMS: calcd. for $C_{19}H_{17}NO_6NaBr$ 378.0953; found 378.0960.

Dimethyl 2-{1-[(Trimethylsilyl)ethynyl]isoquinolin-2(1*H*)-yl}maleate (5c): Yield: 296 mg (80%), white solid, m.p. 116–118 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.2–7.10 (m, 3 H), 7.05–7.01 (m, 1 H), 6.22 (d, $^3J_{H,H}$ = 7.56 Hz, 1 H, 3-H), 5.86 (d, $^3J_{H,H}$ = 7.56 Hz, 1 H, 4-H), 5.5 (s, 1 H), 5.33 (s, 1 H, 1-H), 3.93 (s, 3 H, CO_2Me), 3.69 (s, 3 H, CO_2Me), 0.11 (s, 9 H, $SiMe_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.1, 165.0, 148.9, 128.8, 127.5, 126.2, 124.9, 108.8, 100.0, 92.3, 91.6, 53.2, 51.8, 50.5, 0.2 ppm. IR (KBr): $\tilde{\nu}$ = 3441, 3023, 2956, 1733, 1698, 1589, 1564, 1387, 1205, 1169, 995, 845, 751 cm^{-1}. MS (ESI): *m*/*z* = 370 [M + 1]$^+$. HRMS: calcd. for $C_{20}H_{24}NO_4Si$ 370.1474; found 370.1477.

Dimethyl 2-[1-(3-Bromoprop-1-ynyl)isoquinolin-2(1*H*)-yl]maleate (5d): Yield: 296 mg (76%), pale-yellow solid, m.p. 117–119 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.24–7.03 (m, 4 H), 6.24 (d, $^3J_{H,H}$ = 8.08 Hz, 1 H, 3-H), 5.68 (d, $^3J_{H,H}$ = 8.08 Hz, 1 H, 4-H), 5.58 (s, 1 H), 5.30 (s, 1 H, 1-H), 3.94 (s, 3 H, CO_2Me), 3.82 (s, 2 H, CH_2Br), 3.70 (s, 3 H, CO_2Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.9, 148.8, 128.8, 127.7, 126.1, 125.2, 124.8, 108.9, 92.6, 82.0, 53.3, 51.3, 49.9, 13.7 ppm. IR (KBr): $\tilde{\nu}$ = 2925, 2854, 1792, 1741, 1637, 1440, 1363, 1262, 1215, 1051, 1007, 758 cm^{-1}. MS (ESI): *m*/*z* = 391 [M + 1]$^+$.

Dimethyl 2-[1-(Hept-1-ynyl)isoquinolin-2(1*H*)-yl]maleate (5e): Yield: 301 mg (82%), white solid, m.p. 119–121 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.24–7.00 (m, 4 H), 6.22 (d, $^3J_{H,H}$ = 8.08 Hz, 1 H, 3-H), 5.84 (d, $^3J_{H,H}$ = 8.08 Hz, 1 H, 4-H), 5.48 (s, 1 H), 5.34 (s, 1 H, 1-H), 3.93 (s, 3 H, CO_2Me), 3.69 (s, 3 H, CO_2Me), 2.15–2.07 (m, 2 H), 1.44 (t, $J_{H,H}$ = 6.61 Hz, 2 H), 1.31–1.25 (m, 4 H), 0.86 (t, $J_{H,H}$ = 7.34 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.2, 149.1, 129.1, 128.7, 128.3, 127.4, 126.0, 125.4, 108.6, 92.1, 53.2, 51.3, 50.1, 30.9, 27.9, 22.0, 18.6, 13.8 ppm. IR (KBr): $\tilde{\nu}$ = 3446, 2939, 1731, 1707, 1595, 1570, 1384, 1250, 1161, 771, 704 cm^{-1}. MS (ESI): *m*/*z* = 368 [M + 1]$^+$. HRMS: calcd. for $C_{22}H_{25}NO_4Na$ 390.1681; found 390.1672.

Dimethyl 2-[(1-Phenylethynyl)isoquinolin-2(1*H*)-yl]maleate (5f): Yield: 299 mg (80%), pale-yellow solid, m.p. 142–144 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.32 (m, 2 H), 7.24–7.21 (m, 6 H), 7.07–7.05 (m, 1 H), 6.28 (d, $^3J_{H,H}$ = 7.55 Hz, 1 H, 3-H), 5.91 (d, $^3J_{H,H}$ = 7.55 Hz, 1 H, 4-H), 5.74 (s, 1 H), 5.42 (s, 1 H, 1-H), 3.95 (s, 3 H, CO_2Me), 3.70 (s, 3 H, CO_2Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.6, 164.5, 148.6, 131.3, 128.4, 128.1, 127.9, 127.6, 127.1, 125.75, 124.7, 124.4, 108.5, 91.9, 85.5, 84.1, 52.8, 50.9, 49.9 ppm. IR (KBr): $\tilde{\nu}$ = 3446, 2947, 1731, 1706, 1599, 1384, 1166, 771, 544 cm^{-1}. MS (ESI): *m*/*z* = 374 [M + 1]$^+$. HRMS: calcd. for $C_{23}H_{20}NO_4$ 374.1392; found 374. 1396.

Dimethyl 2-{1-[3-(Benzyloxy)prop-1-ynyl]isoquinolin-2(1*H*)-yl}maleate (5g): Yield: 326 mg (78%), pale-yellow solid, m.p. 110–112 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.27–7.13 (m, 8 H), 7.07–7.04 (m, 1 H), 6.25 (d, $^3J_{H,H}$ = 7.55 Hz, 1 H, 3-H), 5.88 (d, $^3J_{H,H}$ = 7.55 Hz, 1 H, 4-H), 5.57 (s, 1 H), 5.36 (s, 1 H, 1-H), 4.45 (s, 2 H, CH_2Ph), 4.04 (s, 2 H), 3.94 (s, 3 H, CO_2Me), 3.68 (s, 3 H, CO_2Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.9, 164.8, 148.9, 137.0, 128.8, 128.7, 128.22 127.7, 126.1, 125.1, 124.8, 108.7, 92.4, 82.2, 71.3, 57.0, 53.2, 51.3, 49.8 ppm. IR (KBr): $\tilde{\nu}$ = 3441, 2942, 1730, 1595, 1571, 1386, 1209, 1165, 773, 407 cm^{-1}. MS (ESI): *m*/*z* = 418 [M + 1]$^+$. HRMS: calcd. for $C_{25}H_{24}NO_5$ 418.1654; found 418.1652.

Dimethyl 2-{1-[(3-Ethynylphenyl)ethynyl]isoquinolin-2(1*H*)-yl}-maleate (5h): Yield: 318 mg (80%), pale-yellow solid, m.p. 165–167 °C. ^{1}H NMR (75 MHz, $CDCl_3$): δ = 7.47 (s, 1 H), 7.37–7.31 (m, 2 H), 7.25–7.17 (m, 4 H), 7.08–7.06 (m, 1 H), 6.28 (d, $^3J_{H,H}$ = 7.74 Hz, 1 H, 3-H), 5.91 (d, $^3J_{H,H}$ = 7.74 Hz, 1 H, 4-H), 5.72 (s, 1 H), 5.39 (s, 1 H, 1-H), 3.95 (s, 3 H, CO_2Me), 3.71 (s, 3 H, CO_2Me), 2.97 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.1, 164.9, 149.1, 135.3, 132.1, 128.8, 128.2, 127.6, 126.1, 125.1, 122.2, 108.9, 92.4, 85.2, 84.9, 82.4, 53.3, 51.4, 50.3 ppm. IR (KBr): $\tilde{\nu}$ = 3289, 2923, 2853, 1742, 1704, 1592, 1568, 1439, 1205, 1164, 1040, 900, 767 cm^{-1}. MS (ESI): *m*/*z* = 420 [M + Na]$^+$. HRMS: calcd. for $C_{25}H_{19}NO_4Na$ 420.1211; found 420.1214.

Dimethyl 2-{1-[(2-Methoxynaphthalen-1-yl)ethynyl]isoquinolin-2(1*H*)-yl}maleate (5i): Yield: 363 mg (80%), red solid, m.p. 128–130 °C. ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 7.86 (d, $^3J_{H,H}$ = 8.43 Hz, 1 H), 7.77 (d, $^3J_{H,H}$ = 9.20 Hz, 1 H), 7.72–7.63 (m, 1 H), 7.41–7.11 (m, 7 H), 6.34 (d, $^3J_{H,H}$ = 7.66 Hz, 1 H, 3-H), 6.02 (d, $^3J_{H,H}$ = 4.60 Hz, 1 H, 4-H), 5.97 (s, 1 H), 5.62 (s, 1 H, 1-H), 3.94 (s, 6 H, CO_2Me, OMe), 3.70 (s, 3 H, CO_2Me) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 167.2, 165.1, 159.4, 149.1, 130.5, 128.8, 128.5, 128.2, 127.6, 126.2, 126.1, 124.9, 124.0, 112.8, 108.8, 94.2, 92.6, 56.7, 53.7, 51.5 ppm. IR (KBr): $\tilde{\nu}$ = 3422, 2945, 2254, 1734, 1711, 1599, 1382, 1271, 1167, 1027, 1002, 823, 769 cm^{-1}. MS (ESI): *m*/*z* = 454 [M + 1]$^+$. HRMS: calcd. for $C_{28}H_{23}NO_5Na$ 476.1473; found 476.1484.

Tetramethyl (*E*)-2,2′-[1,1′-(1,3-Phenylenediethynyl)diisoquinolin-2(1*H*)-yl]dimaleate (5j): Yield: 522 mg (78%), white solid, m.p. 140–142 °C. ^{1}H NMR (75 MHz, $CDCl_3$): δ = 7.5–7.05 (m, 12 H), 6.27 (t, $^3J_{H,H}$ = 7.17 Hz, 2 H), 5.91 (t, $^3J_{H,H}$ = 6.79 Hz, 2 H), 5.71 (d, $^3J_{H,H}$ = 9.06 Hz, 2 H), 5.38 (d, $J_{H,H}$ = 8.30 Hz, 2 H, 1 H), 3.95 (s, 3 H, CO_2Me), 3.94 (s, 3 H, CO_2Me), 3.71 (s, 3 H, CO_2Me), 3.69 (s, 3 H, COOMe) ppm. IR (KBr): $\tilde{\nu}$ = 3020, 2952, 2853, 1741, 1705, 1568, 1439, 1252, 1209, 1166, 755 cm^{-1}. MS (ESI): *m*/*z* = 691 [M + Na]$^+$.

Dimethyl 2-[2-(Phenylethynyl)quinolin-1(2*H*)-yl]maleate (7a): Yield: 299 mg (80%), dark-yellow semi-solid. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.4–7.21 (m, 6 H), 7.14–6.99 (m, 3 H), 6.51 (d, $^3J_{H,H}$ = 9.46 Hz, 1 H, 4-H), 6.01 (dd, $^3J_{H,H}$ = 9.46, $^3J_{H,H}$ = 5.82 Hz, 1 H, 3-H), 5.78 (s, 1 H), 5.20 (d, $^3J_{H,H}$ = 5.82 Hz, 1 H, 2-H), 3.73 (s, 3 H, CO_2Me), 3.70 (s, 3 H, CO_2Me) ppm. ^{13}C NMR (75 MHz,

$CDCl_3$): δ = 166.7, 150.4, 136.0, 131.7, 128.3, 127.0, 125.6, 125.2, 124.1, 120.1, 100.4, 52.4, 51.9, 29.8 ppm. IR (KBr): $\tilde{\nu}$ = 3446, 2944, 1737, 1698, 1566, 1493, 1222, 1154, 1034, 979, 758 cm^{-1}. MS (ESI): *m*/*z* = 374 $[M + 1]^+$. HRMS: calcd. for $C_{23}H_{19}NO_4Na$ 396.1211; found 396.1204.

Dimethyl 2-[6-Methyl-2-(phenylethynyl)quinolin-1(2*H*)-yl]maleate (7b): Yield: 302 mg (78%), pale-yellow solid, m.p. 134–136 °C. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.33–7.30 (m, 2 H), 7.24–7.21 (m, 3 H), 6.92 (d, $^3J_{H,H}$ = 6.04 Hz, 3 H), 6.51 (d, $^3J_{H,H}$ = 9.06 Hz, 1 H, 4-H), 5.99 (dd, $^3J_{H,H}$ = 9.06, $^3J_{H,H}$ = 6.04 Hz, 1 H, 3-H), 5.71 (s, 1 H), 5.18 (d, $^3J_{H,H}$ = 6.04 Hz, 1 H, 2-H), 3.75 (s, 3 H, CO_2Me), 3.70 (s, 3 H, CO_2Me), 2.30 (s, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.8, 165.1, 150.5, 134.1, 133.5, 131.7, 128.7, 127.9, 125.3, 123.9, 120.1, 99.2, 85.7, 83.8, 52.8, 51.2, 20.7 ppm. IR (KBr): $\tilde{\nu}$ = 3438, 2924, 2853, 2151, 1741, 1698, 1567, 1495, 1223, 1156, 1034, 816, 752 cm^{-1}. MS (ESI): *m*/*z* = 410 $[M + Na]^+$. HRMS: calcd. for $C_{24}H_{21}NO_4Na$ 410.1368; found 410.1368.

Dimethyl 2-[6-Methoxy-2-(phenylethynyl)quinolin-1(2*H*)-yl]maleate (7c): Yield: 303 mg (75%), pale-yellow semi-solid. ^1H NMR (75 MHz, $CDCl_3$): δ = 7.32–7.30 (m, 2 H), 7.25–7.21 (m, 3 H), 6.99 (d, $^3J_{H,H}$ = 8.67 Hz, 1 H), 6.69–6.65 (m, 2 H), 6.52 (d, $^3J_{H,H}$ = 9.46 Hz, 1 H, 4-H), 6.04 (dd, $^3J_{H,H}$ = 9.46, $^3J_{H,H}$ = 6.30 Hz, 1 H, 3-H), 5.64 (s, 1 H), 5.18 (d, $^3J_{H,H}$ = 6.30 Hz, 1 H, 2-H), 3.77 (s, 3 H, CO_2Me), 3.76 (s, 3 H, OMe), 3.69 (s, 3 H, CO_2Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.1, 150.8, 131.7, 128.5, 128.1, 125.2, 124.9, 121.6, 113.3, 112.5, 98.1, 85.7, 83.6, 52.9, 51.3, 51.1 ppm. IR (KBr): $\tilde{\nu}$ = 3444, 2924, 2853, 1741, 1705, 1587, 1495, 1220, 1158, 1034, 756 cm^{-1}. MS (ESI): *m*/*z* = 426 $[M + Na]^+$. HRMS: calcd. for $C_{24}H_{21}NO_5Na$ 426.1317; found 426.1314.

Dimethyl 2-{2-[(4-Methoxyphenyl)ethynyl]quinolin-1(2*H*)-yl}-maleate (7d): Yield: 303 mg (75%), pale-yellow solid, m.p. 175–177 °C. ^1H NMR (75 MHz, $CDCl_3$): δ = 7.25–7.22 (m, 3 H), 7.16–7.09 (m, 1 H), 7.04–7.00 (m, 2 H), 6.72 (d, $^3J_{H,H}$ = 9.06 Hz, 2 H), 6.55 (d, $^3J_{H,H}$ = 9.06 Hz, 1 H, 4-H), 6.01 (dd, $^3J_{H,H}$ = 9.06, $^3J_{H,H}$ = 6.04 Hz, 1 H, 3-H), 5.78 (s, 1 H), 5.18 (d, $^3J_{H,H}$ = 6.04 Hz, 1 H, 2-H), 3.76 (s, 3 H, CO_2Me), 3.74 (s, 3 H, OMe-Ph), 3.71 (s, 3 H, CO_2Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.7, 165.1, 159.8, 150.4, 136.1, 133.2, 128.2, 127.1, 125.6, 124.9, 124.2, 120.1, 113.7, 100.3, 85.9, 82.4, 52.2, 52.9, 51.4 ppm. IR (KBr): $\tilde{\nu}$ = 3445, 2924, 2851, 1748, 1711, 1605, 1368, 1291, 1242, 1168, 1032, 837, 753 cm^{-1}. MS (ESI): *m*/*z* = 426 $[M + Na]^+$. HRMS: calcd. for $C_{24}H_{21}NO_5Na$ 426.1317; found 426.1314.

Dimethyl 2-{2-[(4-Methoxyphenyl)ethynyl]-6-methylquinolin-1(2*H*)-yl}maleate (7e): Yield: 304 mg (73%), pale-yellow solid, m.p. 135–138 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.23 (m, 2 H), 6.92 (d, $^3J_{H,H}$ = 6.59 Hz, 3 H), 6.73 (d, $^3J_{H,H}$ = 8.79 Hz, 2 H), 6.92 (d, $^3J_{H,H}$ = 6.59 Hz, 3 H), 6.50 (d, $^3J_{H,H}$ = 9.52 Hz, 1 H, 4-H), 5.90 (dd, $^3J_{H,H}$ = 9.52, ^3J = 5.86 Hz, 1 H, 3-H), 5.72 (s, 1 H), 5.17 (d, $^3J_{H,H}$ = 5.86 Hz, 1 H, 2-H), 3.76 (s, 3 H, CO_2Me), 3.75 (s, 3 H, OMe-Ph), 3.70 (s, 3 H, CO_2Me), 2.29 (s, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.8, 159.7, 150.64, 133.2, 128.8, 127.8, 125, 124.2, 120, 133.7, 99.1, 55.2, 52.8, 51.3, 29.6, 20.7 ppm. IR (KBr): $\tilde{\nu}$ = 3389, 2948, 2218, 1740, 1702, 1569, 1504, 1439, 1287, 1252, 1157, 1034, 823 cm^{-1}. MS (ESI): *m*/*z* = 418 $[M + H]^+$.

Dimethyl 2-{2-[(3-Ethynylphenyl)ethynyl]quinolin-1(2*H*)-yl}maleate (7f): Yield: 322 mg (81%), pale-yellow solid, m.p. 134-136 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.45 (s, 1 H), 7.37–7.00 (m, 7 H), 6.56 (d, $^3J_{H,H}$ = 9.06 Hz, 1 H, 4-H), 5.99 (dd, $^3J_{H,H}$ = 9.06, $^3J_{H,H}$ = 6.04 Hz, 1 H, 3-H), 5.75 (s, 1 H), 5.19 (d, $^3J_{H,H}$ = 6.04 Hz, 1 H, 2-H), 3.75 (s, 3 H, CO_2Me), 3.17 (s, 3 H, CO_2Me), 2.97 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.6, 164.9, 135.9, 135.2, 132.1, 131.9, 128.4, 128.2, 127.2, 125.3, 124.3, 123.6, 122.2, 120.1, 100.4, 52.9, 51.4, 51.2 ppm. IR (KBr): $\tilde{\nu}$ = 3445, 3287, 2995, 1737, 1698, 1591, 1564, 1221, 1157, 784 cm^{-1}. MS (ESI): *m*/*z* = 420 $[M + Na]^+$. HRMS: calcd. for $C_{25}H_{19}NO_4Na$ 420.1211; found 420.1192.

Dimethyl 2-{2-[(3-Ethynylphenyl)ethynyl]-6-methylquinolin-1(2*H*)-yl}maleate (7g): Yield: 333 mg (81%), white solid, m.p. 138–140 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.45 (s, 1 H), 7.37–7.19 (m, 3 H), 6.92 (d, $^3J_{H,H}$ = 6.04 Hz, 3 H), 6.52 (d, $^3J_{H,H}$ = 9.63 Hz, 1 H, 4-H), 5.98 (dd, $^3J_{H,H}$ = 9.44, $^3J_{H,H}$ = 5.85 Hz, 1 H, 3-H), 5.68 (s, 1 H), 5.17 (d, $^3J_{H,H}$ = 5.85 Hz, 1 H, 2 H), 3.75 (s, 3 H, CO_2Me), 3.70 (s, 3 H, CO_2Me), 2.97 (s, 1 H), 2.30 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.7, 165.1, 150.5, 135.2, 134.1, 133.4, 132.1, 128.9, 128.2, 127.8, 125.9, 123.7, 122.3, 120.1, 99.3, 84.6, 82.4, 77.8, 52.9, 51.3, 51.1, 20.7 ppm. IR (KBr): $\tilde{\nu}$ = 3287, 2949, 1738, 1699, 1568, 1497, 1385, 1222, 1153, 1030, 818, 792 cm^{-1}. MS (ESI): *m*/*z* = 434 $[M + Na]^+$. HRMS: calcd. for $C_{26}H_{21}NO_4Na$ 434.1368; found 434.1368.

Dimethyl 2-{2-[(3-Ethynylphenyl)ethynyl]-6-methylquinolin-1(2*H*)-yl}maleate (7h): Yield: 359 mg (84%), pale-yellow semi-solid. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.45 (s, 1 H), 7.3–7.17 (m, 3 H), 6.99 (d, $^3J_{H,H}$ = 8.30 Hz, 1 H), 6.71–6.65 (m, 2 H), 6.53 (d, $^3J_{H,H}$ = 9.82 Hz, 1 H, 4-H), 6.02 (dd, $^3J_{H,H}$ = 9.06, $^3J_{H,H}$ = 6.04 Hz, 1 H, 3-H), 5.61 (s, 1 H), 5.17 (d, $^3J_{H,H}$ = 6.04 Hz, 1 H, 2-H), 3.78 (s, 3 H, CO_2Me), 3.76 (s, 3 H, OMe), 3.70 (s, 3 H, CO_2Me), 2.97 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.1, 150.7, 35.2, 32.1, 132.0, 128.2, 125.4, 124.6, 122.3, 121.6, 113.3, 11.2, 105.0, 98.2, 84.4, 82.4, 55.4, 52.9, 51.3, 50.9, 29.6 ppm. IR (KBr): $\tilde{\nu}$ = 3449, 3290, 2924, 1734, 1705, 1591, 1569, 1384, 1206, 1165, 1111, 768 cm^{-1}. MS (ESI): *m*/*z* = 450 $[M + Na]^+$. HRMS: calcd. for $C_{26}H_{21}NO_5Na$ 450.1317; found 450.1310.

Typical Procedure for the Synthesis of Substituted 1,2-Dihydropyridines: Pyridine (1 mmol) was added to a stirred solution of MoO_3 (0.1 mmol) and ethyl propiolate (3 mmol) in dichloromethane (5 mL). The resulting reaction mixture was stirred at room temp. for 1 h. Then the reaction contents were passed through a Celite pad and washed with dichloromethane (2 × 3 mL). The combined contents were concentrated under reduced pressure. The crude residue was subjected to silica gel column chromatography (100–200 mesh) by using ethyl acetate/hexane (1:9) as eluent to give the product.

Methyl (*E*)-3-[2-(3-Methoxy-3-oxoprop-1-ynyl)pyridin-1(2*H*)-yl]acrylate (10a): Yield: 193 mg (70%), pale-yellow liquid. ^1H NMR (75 MHz, $CDCl_3$): δ = 7.48 (d, $^3J_{H,H}$ = 13.59 Hz, 1 H), 6.25 (d, $^3J_{H,H}$ = 7.36 Hz, 1 H, 6-H), 6.01 (m, 1 H, 5-H), 5.46 (m, 1 H, 4-H), 5.29 (d, $^3J_{H,H}$ = 5.47 Hz, 1 H, 2-H), 5.19 (m, 1 H, 3-H), 5.06 (d, $^3J_{H,H}$ = 13.59 Hz, 1 H), 4.23–4.13 (m, 4 H, CO_2Et), 1.33–1.25 (m, 6 H, CO_2Et) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.8, 152.9, 146.5, 130.4, 123.7, 114.6, 102.9, 93.1, 81.3, 62.9, 59.0, 46.3, 29.1, 14.6, 13.0 ppm. IR (KBr): $\tilde{\nu}$ = 2982, 2929, 1728, 1615, 1371, 1243, 1177, 1030, 753 cm^{-1}. MS (ESI): *m*/*z* = 276 $[M + 1]^+$. HRMS: calcd. for $C_{15}H_{18}NO_4$ 276.1235; found 276.1244.

Methyl (*E*)-3-[3-Ethyl-2-(3-methoxy-3-oxoprop-1-ynyl)-4-methylpyridin-1(2*H*)-yl]acrylate (10c): Yield: 260 mg (82%), liquid. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.36 (d, $^3J_{H,H}$ = 13.59 Hz, 1 H), 6.12 (d, $^3J_{H,H}$ = 7.36 Hz, 1 H, 6-H), 5.10 (d, $^3J_{H,H}$ = 7.36 Hz, 1 H, 5-H), 5.05 (d, $^3J_{H,H}$ = 13.59 Hz, 1 H), 4.98 (s, 1 H, 2-H), 4.22–4.10 (m, 4 H, CO_2Et), 2.33–2.26 (m, 1 H, CH_2), 2.20–2.15 (m, 1 H, CH_2), 1.77 (s, 3 H, CH_3), 1.33–1.26 (m, 6 H, CO_2Et), 1.12–1.07 (m, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.6, 146.1, 126.3, 125, 122.2, 110.9, 108.6, 92.1, 91.3, 82.2, 61.7, 59.9, 59.3, 59.2, 23.2, 22.1, 20.5, 17.9, 16.3, 13, 11.9 ppm. IR (KBr): $\tilde{\nu}$ = 2977, 2935, 1725, 1614, 1371, 1244, 1175, 1033, 755 cm^{-1}. MS (ESI): *m*/*z* = 318 $[M + 1]^+$. HRMS: calcd. for $C_{18}H_{24}NO_4$ 318.1705; found 318.1706.

Methyl (*E*)-3-[2-(3-Methoxy-3-oxoprop-1-ynyl)-3,4-dimethylpyridin-1(2*H*)-yl]acrylate (10d): Yield: 197 mg (65%), liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (d, $^3J_{H,H}$ = 13.18 Hz, 1 H), 6.05 (d, $^3J_{H,H}$ = 7.32 Hz, 1 H, 6-H), 4.99 (d, $^3J_{H,H}$ = 7.32 Hz, 1 H, 5-H), 4.95 (d, $^3J_{H,H}$ = 13.18 Hz, 1 H), 4.83 (s, 1 H, 2-H), 4.13–4.00 (m, 4 H, CO_2Et), 1.76 (s, 3 H, Me), 1.67 (s, 3 H, Me), 1.24–1.17 (m, 6 H, CO_2Et) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.6, 152.6, 145.8, 126.1, 124.9, 116.3, 108, 92, 81.5, 61.7, 59.3, 50.9, 29.2, 16.7, 16.1, 14, 13.8 ppm. IR (KBr): $\tilde{\nu}$ = 2925, 2855, 2225, 1711, 1626, 1594, 1246, 1173, 1120, 1041, 754 cm^{-1}. MS (ESI): *m*/*z* = 304 [M + 1]$^+$. HRMS: calcd. for $C_{17}H_{22}NO_4$ 304.1548; found 304.1564.

Ethyl (*E*)-3-[2-(3-Ethoxy-3-oxoprop-1-ynyl)-4-ethylpyridin-1(2*H*)-yl]acrylate (10e): Yield: 243 mg (80%), liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 (d, $^3J_{H,H}$ = 13.40 Hz, 1 H), 6.12 (d, $^3J_{H,H}$ = 7.88 Hz, 1 H, 6-H), 5.23 (d, $^3J_{H,H}$ = 5.52 Hz, 1 H, 5-H), 5.16 (d, $^3J_{H,H}$ = 5.52 Hz, 1 H, 2-H), 5.09 (dd, $^3J_{H,H}$ = 7.88, $^3J_{H,H}$ = 6.30 Hz, 1 H, 3-H), 5.06 (d, $^3J_{H,H}$ = 14.19 Hz, 1 H), 4.23–4.14 (m, 4 H, CO_2Et), 2.09 (q, $J_{H,H}$ = 7.09 Hz, 2 H, CH_2), 1.32–1.27 (m, 6 H, CO_2Et), 1.05 (t, $J_{H,H}$ = 7.09 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.9, 146.2, 137.6, 129.5, 108.1, 105.3, 92.9, 82.3, 62.1, 59.75, 46.6, 27.4, 14.1, 12.0 ppm. IR (KBr): $\tilde{\nu}$ = 3402, 2978, 2935, 1711, 1625, 1445, 1371, 1246, 1154, 1041, 965, 754 cm^{-1}. MS (ESI): *m*/*z* = 326 [M + Na]$^+$. HRMS: calcd. for $C_{17}H_{21}NO_4Na$ 326.1368; found 326.1365.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra for all compounds and postulated catalytic cycle.

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[10] Colorless block crystals, 0.19 × 0.15 × 0.08 mm, were grown from hexane/EtOAc and belonged to the monoclinic space group $P2_1/n$ with cell parameters a = 9.5483(14), b = 5.0583(8), c = 31.868(5) Å, β = 90.420(6)°, V = 1539.1(4) Å^3, $\rho_{calcd.}$ = 1.283 g/cm^3, μ(Mo-K_α) = 0.092 mm^{-1}. Data were collected with a Bruker SMART APEX CCD diffractometer, Mo-K_α (λ = 0.71073 Å). 13870 reflections were measured of which 2698 were independent. The structure was solved by direct methods (SHELXS97); full-matrix least-squares refinement based on $|F^2|$ was performed (SHELXL97) (G. M. Sheldrick, *SHELXS 97* and *SHELXL 97*, Programs for crystal structure solution and refinement, University of Göttingen, Germany, **1997**). All hydrogen atoms were geometrically fixed and allowed to ride on the parent atoms. The refinement converged to an *R*1 value of 4.54% and an *wR*2 value of 11.74%; max./min. residual electron density 0.176/–0.17 e Å^{-3}. CCDC-725118 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[11] For this transformation, 10 mol-% of neutral and basic Al_2O_3 were also individually evaluated as catalysts. However, their catalytic activity was found to be inferior to that of MoO_3.

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[13] Our efforts to isolate the major spot by silica gel column chromatography were not successful.

[14] The yields of **10c** and **10d** refer to a mixture of two regioisomers. The regioisomeric ratio for **10c** was determined on the basis of integration of the corresponding the 2-proton signal versus the 6-proton signal of the minor regioisomer (not shown). The regioisomeric ratio for compound **10d** was similarly estimated.

[15] In the case of **8f**, the disappearance of the starting material was observed by TLC, but decomposition occurred in the course of isolation by silica column chromatography. With **8g** as the substrate, the starting material was completely recovered.

[16] The reaction mechanism remains to be explored, but the postulated catalytic cycle is shown in the Supporting Information. The observed product can be rationalized on the basis of the transition state between the 1,4-dipolar intermediate with electron-deficient acetylene compounds (the Huisgen protocol) and the subsequent coupling product with the corresponding alkynyl moiety which in turn was activated by either copper salts or molybdenum oxide.

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