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ARTICLE

Synthesis of multiply substituted 1,6-dihydropyridines through Cu(I)-catalyzed 6-*endo* cyclization†

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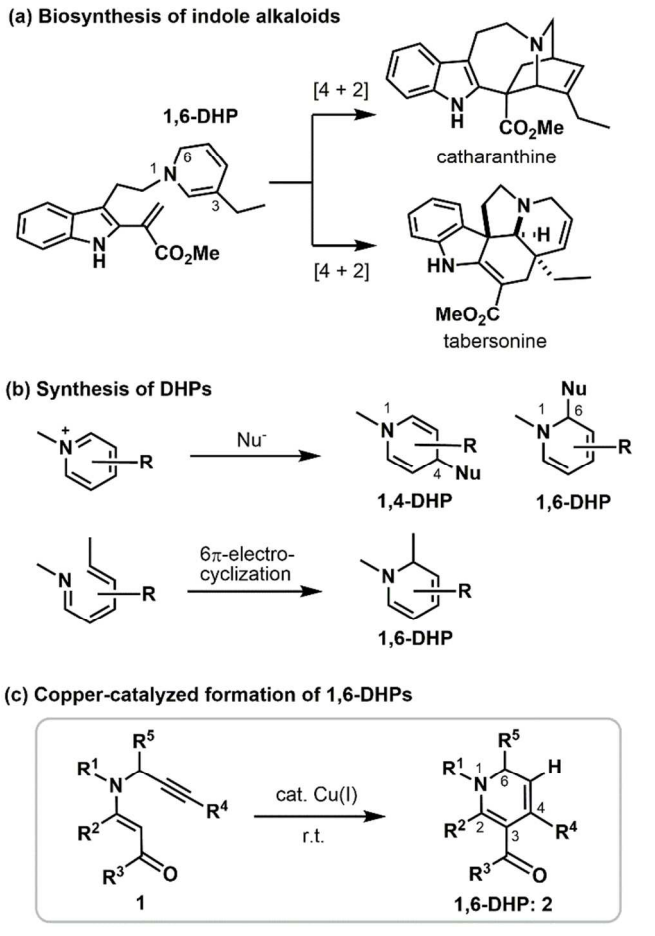
Copper-catalyzed 6-*endo* cyclization of *N*-propargylic β-enaminocarbonyls was developed for the synthesis of oxidation-labile 1,6-dihydropyridines. This synthetic method allows flexible and regio-defined assembly of various substituents at the N1, C2, C3, C4, and C6 positions of 1,6-dihydropyridines under mild conditions.

Introduction

Dihydropyridines (DHPs) exhibit intriguing biological functions, examples of which include the redox coenzymes NAD(P)H and calcium channel blockers for the treatment of cardiovascular disease.[1] From a synthetic point of view, DHPs have significant potential as a versatile platform for the construction of densely functionalized piperidines and pyridines, the most ubiquitous frameworks of natural products and medicinal drugs.[2] In the biosynthesis of terpene indole alkaloids, 1,6-DHP could be exploited as a pluripotent intermediate for divergent synthesis of natural products (Scheme 1a).[3] Synthetic methodologies for 1,6-DHPs (or 1,2-DHPs), however, remain far more limited[4,5] than those for the widely studied 1,4-DHP, readily prepared via Hantzsch synthesis.[1,6] Synthesis of 1,6-DHPs mainly relies on nucleophilic addition onto pyridinium salts, which often results in the formation of inseparable regio-isomeric mixtures of adducts at the C2, C4, or C6 position (Scheme 1b). In recent years, different approaches to the generation of oxidation-labile 1,6-DHPs (or 1,2-DHP) via 6π-electrocyclization of 1-azatrienes have emerged.[7] For example, Ellman and co-workers reported Rh(I)-catalyzed C-H activation–alkyne coupling followed by electrocyclization.[8,9]

To develop an alternative method of access to sensitive 1,6-DHPs with flexible and regio-controlled installation of substituents on the N1, C2, C3, C4, and C6 positions, we conceived Cu(I)-catalyzed 6-*endo* cyclization of propargylic enaminocarbonyls (**1** → **2**) (Scheme 1c). In a recent investigation, we found that *N*-alkylated 1,6-DHPs, with installation of an electron-withdrawing carbonyl group at C3, showed stability to handling in the laboratory as a solution and also allowed biomimetic synthesis of skeletally diverse alkaloids.[10] Herein, we report the development of a potentially general synthetic protocol for regio-defined synthesis of multiply substituted 1,6- DHPs through Cu(I)-catalyzed cyclization under mild conditions.

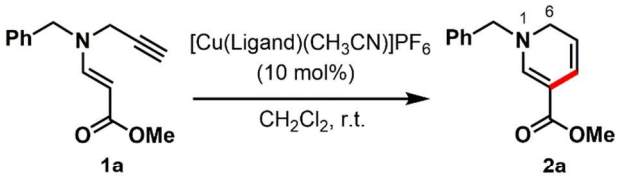


Scheme 1.

Results and discussion

Exploration of the proposed 6-*endo* cyclization began with exposure of substrate **1a**, bearing alkyne and enamine groups, to copper complexes. Whilst a variety of transition metals, such as gold,[11] platinum,[12] rhodium,[13] and silver,[14] have been reported to promote chemo-selective activation of alkyne groups, we focused on copper salts due to their broad tolerance to polar functional groups, as well as abundance. Cacchi and Fabrizi reported CuBr-catalyzed cyclization of *N*-propargylic β-enaminones bearing a tri-substituted *Z*-double bond, which requires heating (60–80 °C) in DMSO and entails oxidation of transiently generated DHPs to form pyridines.[15] Despite the differences between the substrates, a more reactive activator which was more tolerant of functional groups should be required to obtain sensitive 1,6-DHPs (**2**) by suppressing oxidation and undesired side-reactions. We thus employed a cationic cuprous catalyst and screened a series of phosphine ligands (Table 1). While a copper complex composed of monodentate phosphine necessitated gentle heating (45 °C) to produce 1,6-DHP **2a** in moderate yield (entry 1), the use of bidentate phosphine ligands with wide bite angles allowed the formation of **2a** at room temperature with substantial improvement of the product yield (entries 2–4). Dichloromethane and 1,2-dichloroethane were found to be the optimal solvents. As shown in entry 4, treatment of **1a** with 10 mol% [Cu(Xantphos)(CH_3CN)]PF_6[16] in dichloromethane at room temperature afforded the desired 1,6-DHP **2a** in 98% yield (calculated yield based on ^{1}H-NMR) as a labile compound that was not amenable to chromatographic isolation. Reducing the amount of catalyst to 5 mol% (entry 5)

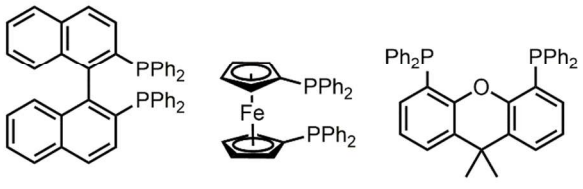
Table 1. Optimization of Cu-catalyzed formation of 1,6-DHP (**2a**)



1a **2a**

entry	ligand	Cu catalyst	yield[a]
1	PPh_3[b]	10 mol%	42%
2	BINAP	10 mol%	72%
3	dppf	10 mol%	95%
4	Xantphos	10 mol%	**98%**
5	Xantphos	5 mol%	**98%**
6	Xantphos	3 mol%	54%

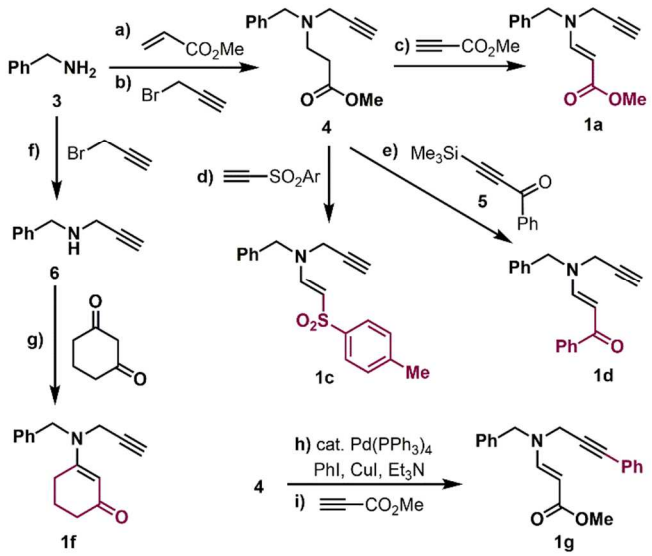
[a] Calculated yield based on ^{1}H-NMR analysis with an internal standard.
[b] [Cu(CH_3CN)$_4$]PF_6 (10 mol%), PPh_3 (22 mol%), 45 °C.



BINAP dppf Xantphos

was turned to be acceptable for the almost quantitative conversion. The attempt with 3 mol% of catalyst (entry 6) resulted in a longer reaction time (24 h), giving a lower yield (54%). The reaction employing a catalyst generated *in situ* by mixing CuCl and Xantphos resulted in almost no conversion, which supported the importance of cationic cuprous species.

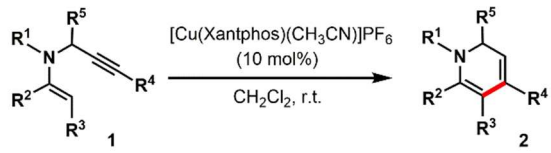
Having optimized the conditions, we next synthesized cyclization precursors with various substitution patterns (R^1–R^5) as shown in Scheme 2. Conjugate addition of benzyl amine **3** to methyl acrylate followed by *N*-propargylation gave tertiary amine **4** as a common intermediate. Treatment of **4** with methyl propiolate in the presence of 2,2,2-trifluoroethanol effected Hoffman elimination to afford the eneyne **1a** in 90% yield. This protocol could be efficiently applicable for installation of aryl sulfone and phenyl ketone group at R^3 of the precursors (**1c** and **1d**). *N*-propargylation of **3** followed by condensation of the resulting secondary amine **6** with 1,3-cyclohexanedione produced **1f** bearing substituents R^2 and R^3 in a moderate yield. Manipulation of terminal alkyne of **4** allowed installation of R^4 and subsequent treatment with methyl propiolate produced **1g** in good yields.

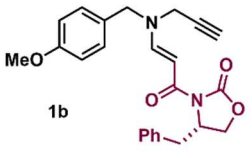
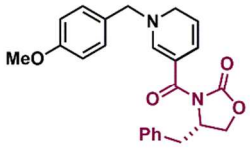
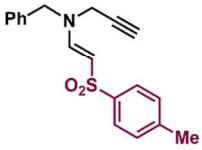
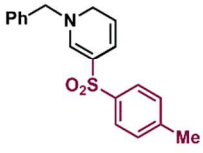
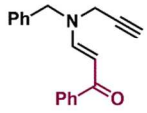
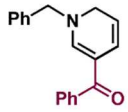
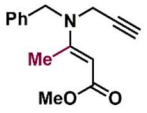
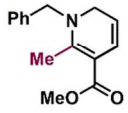
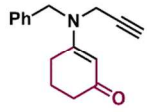
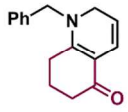
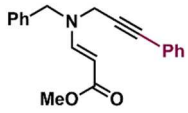
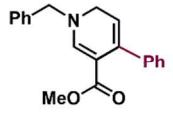
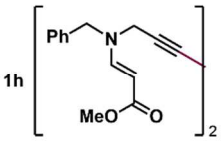
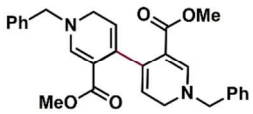
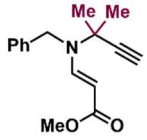
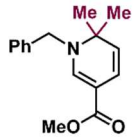
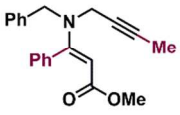
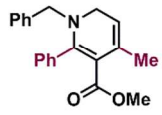


Scheme 2. Reagents and conditions: (a) CH_2=$CHCO_2Me$, MeOH, 65 °C, 83%, (b) propargyl bromide, K_2CO_3, Et_3N, CH_3CN, 85 °C, **4** (75%), (c) methyl propiolate, CF_3CH_2OH, $ClCH_2CH_2Cl$, **1a** (90%), (d) ethynyl *p*-tolylsulfone, CF_3CH_2OH, $ClCH_2CH_2Cl$, **1c** (80%), (e) **5**, CF_3CH_2OH, $ClCH_2CH_2Cl$, **1d** (92%), (f) propargyl bromide, toluene, **6** (89%), (g) 1,3-cyclohexanedione, *p*-TsOH, benzene, reflux, **1f** (46%), (h) $Pd(PPh_3)_4$ (2 mol%), PhI, CuI, Et_3N, CH_3CN, 60 °C, (i) methyl propiolate, CF_3CH_2OH, $ClCH_2CH_2Cl$, **1g** (99% for 2 steps).

The scope of 6-*endo* cyclization was then investigated with the series of precursors, generating multiply substituted 1,6-DHPs (Table 2). Range of electron-withdrawing groups at R^3 were well tolerated, producing 1,6-DHPs containing acyl oxazolidinone (**2b**), aryl sulfone (**2c**) at the C3 position in good to excellent yields. Although cyclization of a substrate **1d** bearing a ketone conjugated to an enamine moiety required heating (65 °C) for

Table 2. Substrate scope for Cu-catalyzed formation of 1,6-DHPs

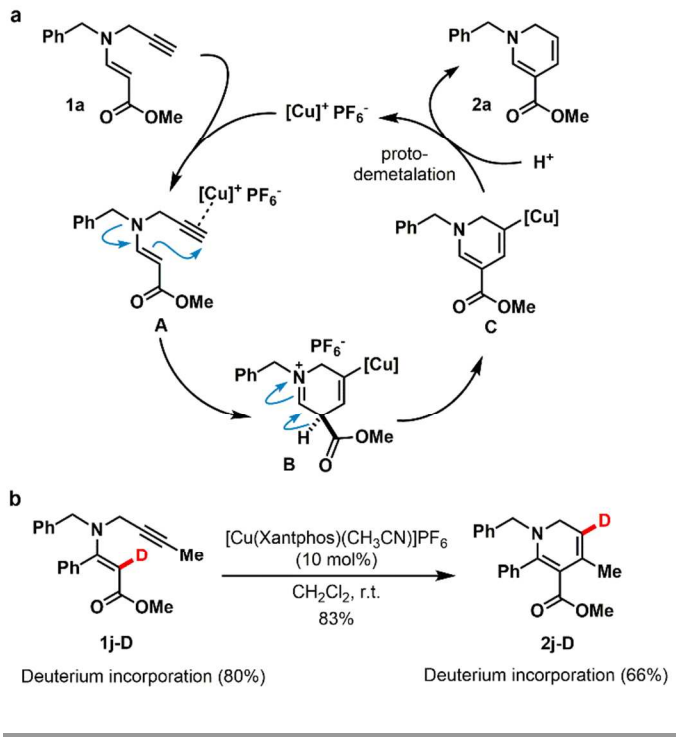


N-propargylenamine	1,6-DHP	yield[a]
 **1b**		**2b**, 84%
 **1c**		**2c**, 99%
 **1d**		**2d**, 93%[b]
 **1e**		**2e**, 80%
 **1f**		**2f**, 94%[b]
 **1g**		**2g**, 82%
 **1h**		**2h**, 75%
 **1i**		**2i**, 99%[b] (86%)[c]
 **1j**		**2j**, 89%

[a] Calculated yield based on ^{1}H-NMR analysis with an internal standard
[b] 65 °C in 1,2-dichloroethane, [c] Yield of isolated product

completion, 1,6-DHP **2d** was formed in 93% yield. The installation of methyl substituents for R^2 was well tolerated, furnishing **2e** at room temperature in good yield (80%). A substrate composed of a cyclic enaminocarbonyl group was also applicable to cyclization at 65 °C to give **2f** in 94% yield. Furthermore, both an internal phenyl alkyne and a diyne were good substrates for cyclization, leading to **2g** and **2h** in greater than 75% yield. Incorporation of geminal dimethyl substituents as R^5 retarded cyclization, resulting in a requirement for heating to 65 °C in 1,2-dichloroethane. Nonetheless, the desired **2i**, bearing a quaternary center, was formed in almost quantitative yield. As expected, **2i** without hydrogen at the C6 position was sufficiently stable for chromatographic purification through silica gel, and thereby it was isolated in 86% yield. Furthermore, cyclization of a substrate **1j** bearing substituents at the C2 and C4 positions also underwent to produce **2j** in good yield. As described above, its tolerance of different substituents at R^1–R^5 underscored the generality and potential of Cu(I)-catalyzed cyclization for the construction of multiply substituted 1,6-DHPs.

On the basis of these results, we postulated a plausible mechanism, which is shown in Scheme 3a. The reaction is thought to be initiated by coordination and activation of the alkyne group with copper(I) to form the electrophilic π-complex **A**. Subsequent nucleophilic attack of the pendant enamine effects 6-*endo* cyclization. The resulting ionic intermediate **B** undergoes a deprotonation and protodemetalation sequence (**B** to **C**) to produce 1,6-DHP (**2a**) with regeneration of the catalyst. To substantiate this hypothesis, we then conducted cyclization of a



Scheme 3. (a) Proposed mechanism; (b) conversion with a deuterium-labeled substrate.

deuterium-labeled substrate, **1j-D** (Scheme 3b). Actually, translocation of deuterium from the β-position of enamine to the C5-position of 1,6-DHP occurred. Whilst the substantial decrease (approximately 20-30%) of deuteration at the C5 position was reproducibility observed,[17] this result is consistent with the proposed mechanism on the whole.

Conclusion

In summary, we have developed a copper(I)-catalyzed cyclization to form multiply substituted 1,6-dihydropyridines under mild conditions. Substrates composed of alkyne and enamine were cyclized in a 6-*endo* manner with chemoselective activation of terminal and internal alkynes to furnish 1,6-DHP, with a broad tolerance of substitution at the N1, C2, C3, C4, and C6 positions. We are currently exploring further synthetic manipulation for regio- and stereo-controlled synthesis of densely functionalized tetrahydropyridines and piperidines, exploiting the versatile reactivity of 1,6-DHPs conjugated with a carbonyl group at the C3 position.

Experimental

General Methods

All reactions were performed under a nitrogen atmosphere unless otherwise specified. Microwave reactions were performed using a Biotage Initiator. NMR spectra were recorded on JEOL JNM-ECP 300 (^{1}H/300 MHz, ^{13}C/75 MHz) spectrometer, JEOL JNM-ECX 400 (^{1}H/400 MHz, ^{13}C/100 MHz) spectrometer, JEOL JNM-ECX 600 (^{1}H/600 MHz, ^{13}C/150 MHz) spectrometer and Bruker VSP 500 (^{1}H/500 MHz, ^{13}C/125 MHz) spectrometer. Chemical Shifts are reported in δ (ppm) using chloroform, acetonitrile as an internal standard of δ 7.26, 1.94, and 77.16, 118.26 for ^{1}H and ^{13}C-NMR, respectively. Data for ^{1}H-NMR are reported as follows: chemical shift (number of hydrogens, multiplicity, coupling constant). Multiplicity is abbreviated as follows: s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), m (multiplet), br (broad). ESI-Mass spectra were recorded on JEOL AccuTOF LC-Plus JMS-T100. The medium pressure liquid chromatography (MPLC) purifications were performed on a YAMAZEN YFLC-AI-580. Where necessary, solvents were distilled from appropriate drying agents prior to use. Reactions were monitored by thin layer chromatography using Merck Millipore TLC Silica gel F_{254} plates (0.25 mm) which were visualized using UV light, *p*-anisaldehyde stain and PMS stain. Flash column chromatography was performed using Kanto Silica Gel 60N.

Materials

Commercial solvents and reagents were used as received with the following exceptions. The cationic Cu(I) complex, $[Cu(BINAP)(MeCN)]PF_6$, $[Cu(dppf)(MeCN)]PF_6$, were

prepared with modified protocol reported by Lee and co-workers[18] and purified by precipitation from CH_2Cl_2/Et_2O=1/1 solution. [Cu(Xantphos)(MeCN)]PF_6,[16] and (*S*)-4-benzyl-3-propioloyloxazolidin-2-one[19] were prepared by applying reported protocols.

Synthesis of *N*-propargylenamines

Methyl 3-(benzyl(prop-2-yn-1-yl)amino)propanoate, a common intermediate for the synthesis of *N*-propargylenamines. A solution of benzyl amine (**3**) (1.83 ml, 16.8 mmol) and methyl acrylate (1.66 ml, 18.5 mmol) in MeOH (5.0 ml) was stirred at 65 °C for 10 min under microwave irradiation. After concentration of the mixture *in vacuo*, the residue was purified by silica-gel chromatography to afford methyl 3-(benzylamino)propanoate (2.68 g, 13.9 mmol, 83%). A solution of methyl 3-(benzylamino)propanoate (6.43 g, 33.3 mmol), propargyl bromide (3.16 ml, 36.6 mmol), K_2CO_3 (9.20 g, 66.6 mmol), and Et_3N (4.64 ml, 33.3 mmol) in acetonitrile (133 ml) was stirred at 70 °C for 16 h. The resulting mixture was then added with propargyl bromide (1.44 ml, 16.7 mmol). After being stirred at 85 °C for 6 h, the mixture was concentrated *in vacuo* and then added with EtOAc and H_2O. Organic phase was washed with water, brine and the dried over Na_2SO_4. After concentration, the residue was purified by silica-gel chromatography to afford methyl 3-(benzyl(prop-2-yn-1-yl)amino)propanoate (**4**) (5.78 g, 25.0 mmol, 75%) as a common intermediate for the synthesis of *N*-propargylenamines; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.37-7.20 (5H, m), 3.68 (3H, s), 3.65 (2H, s), 3.32 (2H, d, *J* = 2.2 Hz), 2.91 (2H, t, *J* = 6.9 Hz), 2.53 (2H, t, *J* = 6.9 Hz), 2.24 (1H, t, *J* = 2.2 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 172.92, 138.55, 129.14, 128.43, 127.35, 78.32, 73.47, 57.79, 51.74, 49.15, 41.44, 33.27; HRMS (ESI, *m/z*): $[M+H]^+$ calcd. for $C_{14}H_{18}NO_2$ 232.1332; found 232.1330.

(*E*)-Methyl 3-(benzyl(prop-2-yn-1-yl)amino)acrylate (1a). A solution of 3-(benzyl(prop-2-yn-1-yl)amino)propanoate (**4**) (1.08 g, 4.67 mmol) and methyl propiolate (0.91 ml, 10.2 mmol) in 1,2-dichloroethane/2,2,2-trifluoroethanol = 1/1 (24 ml) was stirred at r.t. for 14 h. The mixture was added saturated aqueous solution of $NaHCO_3$ and extracted with EtOAc. The combined organic extracts were washed with brine and dried over Na_2SO_4. The residue was concentrated *in vacuo* and purified by silica-gel chromatography to afford **1a** (962 mg, 4.20 mmol, 90%). **1a**: TLC R_f = 0.35 (Hex:AcOEt = 4:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.60 (1H, d, *J* = 13.1 Hz), 7.38-7.27 (3H, m), 7.24 (2H, d, *J* = 6.9 Hz), 4.83 (1H, d, *J* = 13.1 Hz), 4.41 (2H, s), 3.81 (2H, d, *J* = 2.2 Hz), 3.68 (3H, s), 2.30 (1H, t, *J* = 2.2 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$): 169.83, 151.42, 135.70, 128.98, 128.16, 127.81, 87.43, 73.67, 50.87; HR-MS (ESI, *m/z*): $[M+H]^+$ calcd. For $C_{14}H_{16}NO_2$ 230.1176; found 230.1216.

(*E*)-4-Benzyl-3-(3-((4-methoxybenzyl)(prop-2-yn-1-yl)amino)acryloyl)oxazolidin-2-one (1b). A solution of *N*-(4-methoxybenzyl)prop-2-yn-1-amine[20] (858 mg, 4.90 mmol) and (*S*)-4-benzyl-3-propioloyloxazolidin-2-one (1.12 g, 4.90 mmol) in CH_2Cl_2 (16 ml) was stirred at r.t. for 1.5 h. The residue was concentrated *in vacuo* and purified by silica-gel chromatography to afford **1b** (1.91 g, 4.72 mmol, 96%). **1b:** ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.89 (1H, d, *J* = 12.6 Hz), 7.33 (2H, t, *J* = 7.3 Hz), 7.29-7.18 (5H, m), 6.89 (2H, m), 6.40 (1H, br-d, *J* = 12.6 Hz), 4.75 (1H, m), 4.45 (2H, s), 4.14 (1H, dd, *J* = 16.4, 8.8 Hz), 4.11 (1H, dd, *J* = 8.8, 3.2 Hz), 3.89 (2H, br-s), 3.81 (3H, s), 3.37 (1H, dd, *J* = 13.2, 3.2 Hz), 2.78 (1H, dd, *J* = 13.2, 9.8 Hz), 2.35 (1H, br-s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 166.61, 159.74, 154.17, 153.13, 136.20, 129.68, 129.62, 128.98, 127.22, 114.43, 87.62, 65.86, 55.58, 55.45, 38.61; HRMS (ESI, *m/z*): $[M+Na]^+$ calcd. for $C_{24}H_{24}N_2O_4Na$, 427.1628; found, 427.1641.

(*E*)-*N*-Benzyl-*N*-(2-tosylvinyl)prop-2-yn-1-amine (1c). A solution of 3-(benzyl(prop-2-yn-1-yl)amino)propanoate (**4**) (62.4 mg, 0.270 mmol) and ethynyl *p*-tolylsulfone (58.6 mg, 0.330 mmol) in 1.2-dichloroethane/2,2,2-trifluoroethanol = 1/1 (540 µl) was stirred at r.t. for 12 h. The mixture was treated with saturated aqueous solution of $NaHCO_3$ at 0 °C and extracted with EtOAc. The combined organic extracts were washed with saturated aqueous solution of $NaHCO_3$, brine and dried over Na_2SO_4. The residue was concentrated and purified by silica-gel chromatography to afford **1c** (70.1 mg, 0.215 mmol, 80%). **1c**: TLC R_f = 0.61 (Hex:AcOEt = 1:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (2H, d, *J* = 8.2 Hz), 7.50 (1H, d, *J* = 12.9 Hz), 7.37-7.29 (3H, m), 7.27 (2H, d, *J* = 8.20 Hz), 7.23-7.19 (2H, m), 5.20 (1H, d, *J* = 12.9 Hz), 4.39 (2H, s), 3.77 (2H, s), 2.41 (2H, s), 2.30 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$): 149.19, 142.64, 141.68, 135.00, 129.61, 129.07, 128.37, 127.84, 126.51, 96.64, 76.72, 74.32, 21.61; HRMS (ESI, *m/z*): $[M+Na]^+$ calcd. for $C_{19}H_{19}NO_2SNa$ 348.1028, found 348.1044.

(*E*)-3-(benzyl(prop-2-yn-1-yl)amino)-1-phenylprop-2-en-1-one (1d). A mixture of 3-(benzyl(prop-2-yn-1-yl)amino)propanoate (**4**) (1.77 g, 7.65 mmol) and 1-phenyl-3-(trimethylsilyl)prop-2-yn-1-one **5** (2.32 g, 11.5 mmol) in 1,2-dichloroethane/2,2,2-trifluoroethanol=1/1 (26 ml) was stirred at 45 °C for 10 h 40 min. After concentrated *in vacuo*, the residue was purified by silica-gel chromatography to afford **1d** (1.93 g, 7.01 mmol, 92%). **1d**: ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.95 (1H, d, *J* = 12.6 Hz), 7.89 (2H, d, *J* = 7.3 Hz), 7.49-7.45 (1H, m), 7.44-7.34 (4H, m), 7.35-7.31 (1H, m), 7.30-7.26 (2H, m), 6.02 (1H, d, *J* = 12.6 Hz), 4.54 (2H, s), 3.93 (2H, br-s), 2.36 (1H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 189.28, 152.59, 140.13, 135.24, 131.34, 129.01, 128.27, 127.83, 127.71, 94.55, 76.99, 74.08; HRMS (ESI, *m/z*): $[M+H]^+$ calcd. for $C_{19}H_{18}NO$, 276.1383; found, 276.1385.

Methyl (*E*)-3-(benzyl(prop-2-yn-1-yl)amino)but-2-enoate (1e). To a solution of benzyl amine (**3**) (4.26 ml, 39.0 mmol) in toluene (6.34 ml) was added propargyl bromide (0.560 ml, 6.50 mmol) and stirred at r.t. for 14 h. After concentrated *in vacuo*, the residue was purified by silica-gel chromatography to afford *N*-benzylprop-2-yn-1-amine (**6**) (839 mg, 5.78 mmol, 89%). To a solution of *N*-benzylprop-2-yn-1-amine (475 mg, 3.27 mmol) and methyl acetoacetate (0.705 ml, 6.54 mmol) in benzene (8.8 ml) was added *p*-toluenesulfonic acid monohydrate (37.3 mg, 0.196 mmol) and stirred at 95 °C for 12 h using a Dean - Stark apparatus. After cooled to room temperature, the mixture was washed with aqueous 1M solution of NaOH, water and brine, dried over Na_2SO_4. After filtration, the residue was concentrated *in vacuo* and purified by silica-gel chromatography to

afford **1e** (318 mg, 1.31 mmol, 40%). **1e**: TLC R_f = 0.60 (Hex:AcOEt = 1:1); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.34 (2H, t, *J* = 7.3 H), 7.28 (1H, t, *J* = 7.3 Hz), 7.18 (2H, d, *J* = 7.3 Hz), 4.92 (1H, s), 4.53 (2H, s), 3.93 (2H, d, *J* = 2.2 Hz), 3.63 (3H, s), 2.56 (3H, s), 2.28(1H, t, *J* = 2.2 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$): 169.41, 160.38, 136.70, 128.93, 127.67, 126.82, 87.46, 78.24, 73.04, 53.05, 50.38, 39.35, 15.60; HR-MS (ESI, *m/z*): $[M+H]^+$ calcd. for $C_{15}H_{18}NO_2$ 244.1332, found 244.1357.

3-(benzyl(prop-2-yn-1-yl)amino)cyclohex-2-en-1-one (1f). To a solution of *N*-benzylprop-2-yn-1-amine (145 mg, 1.00 mmol) in benzene (10 ml) was added 1,3-cyclohexanedione (178 mg, 1.60 mmol) and *p*-toluenesulfonic acid monohydrate (11.4 mg, 0.06 mmol) and heated under reflux for 12 h using a Dean - Stark apparatus. After cooled to room temperature, the mixture was washed with aqueous 1M solution of NaOH and brine, dried over Na_2SO_4. The residue was concentrated *in vacuo* and purified by silica-gel chromatography to afford **1f** (109 mg, 0.455 mmol, 46%). **1f**: TLC R_f = 0.20 (Hex:AcOEt = 1:5); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.38-7.33 (2H, m), 7.32-7.27 (1H, m), 7.18 (2H, d, *J* = 7.9 Hz), 5.41 (1H, s), 4.56 (2H, s), 3.97 (2H, d, *J* = 2.2 Hz), 2.55 (2H, t, *J* = 6.3 Hz), 2.39-2.30 (2H, m), 2.31 (1H, s), 2.05-1.99 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): 197.62, 164.56, 136.15, 129.10, 127.95, 126.77, 101.21, 77.78, 73.60, 53.31, 39.53, 35.88, 27.10, 22.37; HRMS (ESI, *m/z*): calcd. for $C_{16}H_{18}NO$ $[M+H]^+$ 240.1383, found 240.1388.

Methyl (*E*)-3-(benzyl(3-phenylprop-2-yn-1-yl)amino)acrylate (1g). A mixture of 3-(benzyl(prop-2-yn-1-yl)amino)propanoate (**4**) (762 mg, 3.29 mmol), $Pd(PPh_3)_4$ (87.7 mg, 0.076mmol), CuI (43.4 mg, 0.228 mmol), Et_3N (0.530 ml, 3.80 mmol) and PhI (0.282 ml, 2.53 mmol) in MeCN (16.5 ml) was heated at 60 °C for 3 h. After concentrated *in vacuo*, the residue was purified by silica-gel chromatography to afford methyl 3-(benzyl(3-phenylprop-2-yn-1-yl)amino)propanoate (867 mg). To a solution of 3-(benzyl(3-phenylprop-2-yn-1-yl)amino)propanoate (867 mg) in 1,2-dichloroethane/2,2,2-trifluoroethanol = 1/1 (14.7 ml) was added methyl propiolate (0.277 ml, 3.10 mmol) and stirred at r.t. for 12 h. The mixture was quenched with saturated aqueous solution of $NaHCO_3$ and extracted with EtOAc. The combined organic extracts were washed with brine and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by silica-gel chromatography to afford **1g** (775 mg, 2.54 mmol, quant. for 2 steps). **1g**: TLC R_f = 0.35 (Hex:AcOEt = 4:1); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.68 (1H, d, *J* = 13.2 Hz), 7.43-7.26 (10H, m), 4.88 (1H, d, *J* = 13.2 Hz), 4.47 (2H, s), 4.05 (2H, br-s), 3.69 (3H, s); ^{13}C-NMR (75 MHz, $CDCl_3$): 169.85, 151.49, 135.85, 131.79, 128.85, 128.62, 128.36, 127.97, 127.69, 122.33, 86.99, 85.45, 82.72, 55.68, 50.73, 40.81; HRMS (ESI, *m/z*): calcd. for $C_{20}H_{20}NO_2$ $[M+H]^+$ 306.1489, found 306.1489.

Dimethyl 3,3'-(hexa-2,4-diyne-1,6-diylbis(benzylazanediyl))(2*E*,2'*E*)-diacrylate (1h). To a solution of 3-(benzyl(prop-2-yn-1-yl)amino)propanoate (**4**) (565 mg, 2.44 mmol) in acetone (2.0 ml) was added a solution of preliminary mixed CuCl (21.4 mg, 0.216 mmol) and *N,N,N',N'*-tetramethylethylenediamine (11 µl, 0.072 mmol) in acetone (2.0 ml) and stirred at r.t. for 12 h under O_2 atmosphere. After concentrated *in vacuo*, the residue was purified by silica-gel column chromatography to afford the corresponding dimer bearing a conjugated diyne linkage (553 mg, 1.20 mmol, 98%). To a solution of the dimer (530 mg, 1.15 mmol) in 1,2-dichloroethane/2,2,2-trifluoroethanol=1/1 (9.0 ml) was added methyl propiolate (383 µl, 4.60 mmol) and stirred at r.t. for 19 h. After concentrated *in vacuo*, the residue was purified by silica-gel chromatography to afford **1h** (423 mg, 0.927 mmol, 81%). **1h**: ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.56 (2H, d, *J* = 12.9 Hz), 7.38-7.28 (6H, m), 7.22 (4H, d, *J* = 6.9 Hz), 4.83 (2H, d, *J* = 12.9 Hz), 4.39 (4H, s), 3.85 (4H, s), 3.68 (6H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 169.66, 151.28, 135.45, 129.04, 128.29, 127.87, 87.94, 72.81, 69.18, 56.25, 50.90, 40.08; HRMS (ESI, *m/z*): $[M+H]^+$ calcd. for $C_{28}H_{29}N_2O_4$, 457.2122; found, 457.2117.

Methyl (*E*)-3-(benzyl(2-methylbut-3-yn-2-yl)amino)acrylate (1i). To a solution of amine *N*-benzyl-2-methylbut-3-yn-2-amine[21] (182 mg, 1.25 mmol) in 1,2-dichloroethane/2,2,2-trifluoroethanol=1/1 (6 ml) was added methyl propiolate (209 µl, 2.51 mmol) and stirred at 45 °C for 19 h. After concentrated *in vacuo*, the residue was purified by silica-gel chromatography to afford **1i** (263 mg, 0.970 mmol, 78%). **1i**: ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.06 (1H, d, *J* = 12.9 Hz), 7.30 (2H, t, *J* = 7.6 Hz), 7.23 (1H, t, *J* = 7.6 Hz), 7.20 (2H, d, *J* = 7.6 Hz), 4.54 (1H, d, *J* = 12.9 Hz), 4.52 (2H, s), 3.61 (3H, s), 2.47 (1H, s), 1.64 (6H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 169.97, 147.59, 137.01, 128.7, 127.1, 126.24, 88.45, 85.86, 72.94, 56.95, 50.69, 50.42, 29.57; HRMS (ESI, *m/z*): $[M+H]^+$ calcd. for $C_{16}H_{20}NO_2$, 258.1489; found, 258.1482.

Methyl (*E*)-3-(benzyl(but-2-yn-1-yl)amino)-3-phenylacrylate (1j). To a solution of *N*-benzylbut-2-yn-1-amine (195 mg, 1.23 mmol) in methanol (1.2 ml) was added methyl 3-phenylpropiolate (0.19 ml, 1.29 mmol) at room temperature and then stirred at 70 °C for 16 h. After concentrated *in vacuo*, the residue was purified by silica-gel chromatography to afford **1j** (176 mg, 0.551 mmol, 45%). **1j**: TLC R_f = 0.38 (Hex:AcOEt = 2:1); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.43-7.40 (3H, m), 7.33-7.31 (4H, m), 7.29-7.25 (1H, m), 7.23 (1H, br-d, *J* = 7.4 Hz), 5.13 (1H, s), 4.33 (2H, br-s), 3.74 (2H, br-s), 3.48 (3H, s), 1.84 (3H, t, *J* = 2.2 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$): 167.97, 162.56, 136.75, 136.08, 128.73 128.58, 128.48, 128.23, 127.40, 89.75, 80.78, 73.36, 52.63, 50.20, 39.34, 3.52.

General procedure for Cu(I)-catalyzed Cyclization of *N*-propargylenamine

A solution of *N*-propargylenamine (0.200 mmol) and $[Cu(Xantphos)(MeCN)]PF_6$ (0.020 mmol) in CH_2Cl_2 (2.0 ml) was stirred at r.t. for several hours. The reaction mixture was then treated with 1,10-phenanthroline (0.020 mmol) to deactivate the copper catalyst. After concentration *in vacuo*, 4-nitrobenzonitrile (0.200 mmol) was added as internal standard for ^{1}H-NMR. Yield of desired product was calculated based on the value of integral for a signal of 4-nitrobenzonitrile and that of desired product.

Methyl 1-benzyl-4-phenyl-1,6-dihydropyridine-3-carboxylate (2a). A solution of *N*-propargylenamine **1a** (251 mg, 1.09 mmol) and [Cu(Xantphos)(MeCN)]PF_6 (90.6 mg, 0.109 mmol) in CH_2Cl_2 (11 ml) was stirred at r.t. for 40 min. The reaction mixture was then treated with 1,10-phenanthroline (25.2 mg, 0.140 mmol) to deactivate the copper catalyst. After concentrated *in vacuo*, 4-nitrobenzonitrile (162 mg, 1.09 mmol) was added. Due to instability of **2a** to silica-gel chromatography, the yield of **2a** (98%) was calculated based on ^{1}H-NMR. **2a**: TLC R_f = 0.45 (Hex:Acetone = 4:1); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.43-7.28 (6H, m), 6.30 (1H, m), 4.96 (1H, dt, *J* = 10.1, 3.1 Hz), 4.20 (2H, s), 4.01 (2H, dd, *J* = 3.1, 1.9 Hz), 3.68 (3H, s); ^{13}C-NMR (75 MHz, $CDCl_3$): 167.00, 147.94, 134.95, 128.92, 128.20, 127.89, 122.20, 109.85, 96.04, 60.08, 50.63, 47.98; HR-MS (ESI): calcd. for $C_{20}H_{19}NO_2Na$ $[M+Na]^+$ 328.1298, found 328.1311. calcd. for the corresponding pyridinium salt $C_{14}H_{14}NO_2[M]^+$ 228.1019, found 228.1019.

4-Benzyl-3-(1-(4-methoxybenzyl)-1,6-dihydropyridine-3-carbonyl)oxazolidin-2-one (2b). A solution of *N*-propargylenamine **1b** (63.7 mg, 0.170 mmol) and [Cu(Xantphos)(MeCN)]PF_6 (14.1 mg, 0.0170 mmol) in CH_2Cl_2 (1.7 ml) was stirred at r.t. for 180 min. The reaction mixture was then treated with 1,10-phenanthroline (3.1 mg, 0.017 mmol) to deactivate the copper catalyst. After concentration *in vacuo*, 4-nitrobenzonitrile (26.8 mg, 0.181 mmol) was added. Due to instability of **2b** to silica-gel chromatography, the yield of **2b** (84%) was calculated based on ^{1}H-NMR. **2b**: TLC R_f = 0.38 (Hex:AcOEt = 1:1); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.45 (1H, s), 7.32-7.17 (7H, m), 6.92 (2H, d, *J* = 8.5 Hz), 6.33 (1H, d, *J* = 10.4 Hz), 5.05 (1H, dt, *J* = 10.1, 3.2 Hz), 4.90 (1H, ddd, *J* = 17.0, 8.5, 3.5 Hz), 4.30-4.24 (2H, m), 4.18 (1H, d, *J* = 14.5 Hz), 4.12-4.06 (3H, m), 3.18 (3H, s), 3.26 (1H, dd, *J* = 13.6, 3.5 Hz), 2.83 (1H, dd, *J* = 13.6, 8.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): 164.98, 159.78, 155.33, 152.49, 135.63, 129.59, 129.55, 128.73, 127.09, 125.84, 122.31, 114.42, 109.88, 98.58, 66.57, 60.38, 55.54, 55.37, 48.36, 37.89; HR-MS (ESI): calcd. for $C_{24}H_{24}N_2O_4Na$ $[M+Na]^+$ 427.1628, found 427.1565.

1-Benzyl-5-tosyl-1,2-dihydropyridine (2c). A solution of *N*-propargylenamine **1c** (50.2 mg, 0.154 mmol) and [Cu(Xantphos)(MeCN)]PF_6 (13.0 mg, 0.0157 mmol) in CH_2Cl_2 (1.6 ml) was stirred at r.t. for 4 h. The reaction mixture was treated with 1,10-phenanthroline (3.8 mg, 0.0211 mmol) to deactivate the copper catalyst. After concentration *in vacuo*, 4-nitrobenzonitrile (22.8 mg, 0.154 mmol) was added. The yield of **2c** (99%) was calculated based on ^{1}H-NMR. **2c**: TLC R_f = 0.48 (Hex:Acetone = 2:1); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.67 (2H, m), 7.32-7.18 (8H, m), 5.90 (1H, m), 4.90 (1H, dt, *J* = 10.2, 3.2 Hz), 4.13 (2H, s), 3.89 (2H, dd, *J* = 3.2, 1.9 Hz), 2.34 (3H, s); ^{13}C-NMR (75 MHz, $CDCl_3$): 145.57, 142.48, 140.76, 134.35, 129.57, 128.93, 128.30, 127.92, 126.39, 119.35, 111.59, 104.29, 59.91, 47.77, 21.44; HR-MS (ESI): calcd. for the corresponding pyridinium salt $C_{19}H_{18}NO_2SNa$ $[M]^+$ 324.1053, found 324.1091.

(1-Benzyl-1,6-dihydropyridin-3-yl)(phenyl)methanone (2d). A solution of *N*-propargylenamine **1d** (100 mg, 0.364 mmol) and [Cu(Xantphos)(MeCN)]PF_6 (30.2 mg, 0.0365 mmol) in 1,2-dichloroethane (3.6 ml) was stirred at 65 °C for 3 h. The reaction mixture was then treated with 1,10-phenanthroline (11.2 mg, 0.0621 mmol) to deactivate the copper catalyst. After concentration *in vacuo*, 4-nitrobenzonitrile (53.9 mg, 0.364 mmol) was added. The yield of **2d** (93%) was calculated based on ^{1}H-NMR. **2d**: TLC R_f = 0.33 (Hex:AcOEt = 2:1); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.52-7.50 (2H, m), 7.40-7.33 (6H, m), 7.23-7.17 (3H, m), 6.63 (1H, m), 5.14 (1H, dt, *J* = 10.2, 3.3 Hz), 4.19 (2H, s), 4.11 (2H, dd, *J* = 3.3, 1.9 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$): 190.18, 152.71, 140.40, 134.41, 129.88, 129.12, 128.49, 128.34, 128.12, 127.90, 122.25, 111.70, 107.35, 60.46, 48.79; HRMS (ESI): calcd. for $C_{19}H_{17}NONa$ $[M+Na]^+$ 298.1202, found 298.1201.

Methyl 1-benzyl-2-methyl-1,6-dihydropyridine-3-carboxylate (2e). A solution of *N*-propargylenamine **1e** (48.0 mg, 0.197 mmol) and [Cu(Xantphos)(MeCN)]PF_6 (16.7 mg, 0.0202 mmol) in CH_2Cl_2 (2.0 ml) was stirred at r.t. for 2 h. The reaction mixture was then treated with 1,10-phenanthroline (4.7 mg, 0.0261 mmol) to deactivate the copper catalyst. After concentration *in vacuo*, 4-nitrobenzonitrile (29.2 mg, 0.197 mmol) was added. Yield of **2e** (80%) was calculated based on ^{1}H-NMR due to instability of **2e** to silica-gel chromatography. **2e**: TLC R_f = 0.38 (Hex:Acetone = 5:1); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.40-7.37 (2H, m), 7.32-7.24 (3H, m), 6.54 (1H, m), 5.00 (1H, dt, *J* = 9.8, 3.7 Hz), 4.50 (2H, s), 4.01 (2H, m), 3.70 (3H, s), 2.52 (3H, s) ; ^{13}C-NMR (75 MHz, $CDCl_3$): 167.85, 157.65, 136.19, 128.96, 127.59, 126.46, 125.45, 107.19, 97.54, 54.44, 50.63, 50.57, 16.16; HR-MS (ESI): calcd. for $C_{15}H_{17}NO_2Na$ $[M+Na]^+$ 266.1151, found 266.1120.

1-Benzyl-2,6,7,8-tetrahydroquinolin-5(1H)-one (2f). A solution of *N*-propargylenamine **1f** (138 mg, 0.578 mmol) and [Cu(Xantphos)(MeCN)]PF_6 (48.5 mg, 0.0586 mmol) in 1,2-dichloroethane (6.0 ml) was stirred at 65 °C for 2 h. The reaction mixture was treated with 1,10-phenanthroline (13.8 mg, 0.0767 mmol) to deactivate the copper catalyst. After concentration *in vacuo*, 4-nitrobenzonitrile (85.6 mg, 0.578 mmol) was added. The yield of **2f** (94%) was calculated based on ^{1}H-NMR. **2f**: TLC R_f = 0.36 (Hex:Acetone = 1:2); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.37-7,21 (5H, m), 6.60 (1H, m), 5.08 (1H, dt, *J* = 10.1, 3.3 Hz), 4.41 (2H, s), 4.13 (2H, dd, *J* = 3.3, 1.7 Hz), 2.47 (2H, t, *J* = 6.3 Hz), 2.28 (2H, t, *J* = 6.3 Hz), 1.90 (2H, quin, *J* = 6.3 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$): 191.24, 161.45, 135.25, 129.08, 127.81, 126.33, 121.06, 110.71, 106.32, 53.97, 51.41, 35.42, 26.28, 21.23; HR-MS (ESI): calcd. for $C_{16}H_{18}NO$ $[M+H]^+$ 240.1383, found 240.1382.

Methyl 1-benzyl-4-phenyl-1,6-dihydropyridine-3-carboxylate (2g). A solution of *N*-propargylenamine **1g** (70.4 mg, 0.231 mmol) and [Cu(Xantphos)(MeCN)]PF_6 (20.0 mg, 0.0241 mmol) in CH_2Cl_2 (2.3 ml) was stirred at r.t. for 110 min. The reaction mixture was then treated with 1,10-phenanthroline (4.14 mg, 0.0230 mmol) to deactivate the copper catalyst. After concentration *in vacuo*, 4-nitrobenzonitrile (28.7 mg, 0.194 mmol) was added. Yield of **2g** (82%) was calculated based on ^{1}H-NMR. **2g**: TLC R_f = 0.45 (Hex:AcOEt = 4:1); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.70 (1H, s), 7.42-7.37 (2H, m), 7.37-7.30 (3H, m), 7.30-7.21 (3H, m), 7.20-7.16 (2H, m), 4.91 (1H, t, *J* = 4.1 Hz), 4.32 (2H, s), 4.04 (2H, d, *J* = 4.1

Hz), 3.51 (3H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): 166.67, 150.11, 141.49, 137.28, 135.06, 129.02, 128.30, 128.00, 127.45, 127.29, 126.67, 110.60, 98.13, 59.88, 50.41, 48.07; HR-MS (ESI): HR-MS (ESI): calcd. for $C_{20}H_{19}NO_2Na$ $[M+Na]^+$ 328.1308, found 328.1311.

Dimethyl 1,1'-dibenzyl-1,1',6,6'-tetrahydro-[4,4'-bipyridine]-3,3'-dicarboxylate (2h). A solution of *N*-propargylenamine **1h** (53.1 mg, 0.116 mmol) and [Cu(Xantphos)(MeCN)]PF_6 (19.2 mg, 0.0232 mmol) in CH_2Cl_2 (1.2 ml) was stirred at r.t. for 3 h. The reaction mixture was then treated with 1,10-phenanthroline (4.18 mg, 0.0232 mmol) to deactivate the copper catalyst. After concentration *in vacuo*, 4-nitrobenzonitrile (17.9 mg, 0.121 mmol) was added. The yield of **2h** (75%) was calculated based on ^{1}H-NMR. **2h**: TLC R_f = 0.28 (Hex:AcOEt = 1:1); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.50 (2H, s), 7.39-7.27 (10H, m), 4.78 (2H, t, *J* = 3.5 Hz), 4.28 (2H, br-d, *J* = 14.8 Hz), 4.16 (2H, br-d, *J* = 14.8 Hz), 4.02 (2H, br-d, *J* = 14.2 Hz), 3.95 (2H, br-d, *J* = 14.2 Hz), 3.59 (6H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): 166.48, 147.83, 137.24, 135.39, 128.91, 128.08, 127.97, 108.67, 98.98, 59.96, 50.38, 48.17; HR-MS (ESI): calcd. for $C_{28}H_{28}N_2O_4Na$ $[M+Na]^+$ 479.1898, found 479.1871.

Methyl 1-benzyl-6,6-dimethyl-1,6-dihydropyridine-3-carboxylate (2i). A solution of *N*-propargylenamine **1i** (47.0 mg, 0.183 mmol) and [Cu(Xantphos)(MeCN)]PF_6 (15.7 mg, 0.0190 mmol) in 1,2-dichloroethane (1.8 ml) was stirred at 65 °C for 20 h. The reaction mixture was then treated with 1,10-phenanthroline (5.6 mg, 0.0311 mmol) to deactivate the copper catalyst. After concentration *in vacuo*, 4-nitrobenzonitrile (27.7 mg, 0.187 mmol) was added. The yield of **2i** (99%) was calculated based on ^{1}H-NMR spectra. After concentration of the mixture, the residue was purified by silica-gel chromatography to afford **2i** (40.5 mg, 0.157 mmol, 86%). **2i**: TLC R_f = 0.29 (Hex:AcOEt = 4:1); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.38-7.35 (2H, m), 7.31-7.25 (3H, m), 6.35 (1H, dd, *J* = 9.8, 1.3 Hz), 4.85 (1H, d, *J* = 9.8 Hz), 4.45 (2H, s), 3.68 (3H, s), 1.28 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$): 167.11, 147.60, 138.74, 128.93, 127.69, 126.94, 120.46, 120.13, 97.70, 58.01, 53.35, 50.77, 28.59; HRMS (ESI, *m/z*): calcd. for $C_{16}H_{20}NO_2$ $[M+H]^+$ 258.1489, found 258.1485.

Methyl 1-benzyl-4-methyl-2-phenyl-1,6-dihydropyridine-3-carboxylate (2j). To a solution of *N*-propargylenamine **1j** (70.4 mg, 0.221 mmol) and [Cu(Xantphos)(MeCN)]PF_6 (18.3 mg, 0.022 mmol) in 1,2-dichloroethane (2.2 ml) was stirred at r.t. for 3 h. The reaction mixture was then treated with 1,10-phenanthroline (4.9 mg, 0.0272 mmol) to deactivate the copper catalyst. After concentration *in vacuo*, 4-nitrobenzonitrile (32.7 mg, 0.221 mmol) was added as an internal standard. Yield of **2j** (89%) was calculated based on ^{1}H-NMR. **2j**: TLC R_f = 0.50 (Hex:AcOEt = 2:1); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.36-7.16 (10H, m), 4.81-4.77 (1H, m), 4.11 (2H, s), 3.93-3.91 (2H, m), 3.22 (3H, s), 2.06-2.03 (3H, m); ^{13}C-NMR (75 MHz, $CDCl_3$): 168.82, 156.49, 137.81, 136.83, 133.66, 128.85, 128.69, 128.58, 128.26, 127.38, 127.05, 106.83, 105.17, 55.21, 50.20, 48.85, 21.01.

Cu-catalyzed cyclization of a deuterium labeled *N*-propargylenamine

***N*-Benzyl prop-2-yn-1-amine-d1.** To a solution of benzyl amine (**3**) (2.34 ml, 21.4 mmol) in toluene (4.2 ml) was added 1-bromo-2-butyne (0.380 ml, 4.34 mmol) and stirred at r.t. for 14 h. After concentrated *in vacuo*, the residue was purified by silica-gel chromatography to afford *N*-benzyl but-2-yn-1-amine (636 mg, 3.99 mmol, 92%). This amine (301 mg, 1.89 mmol) was then dissolved in CH_3OD (3.5 ml) and stirred at r.t. for 1 h, and after concentrated *in vacuo*, treated again with CH_3OD (3.0 ml) at r.t. for further 1 h. Removal of the solvent *in vacuo* afforded *N*-benzyl but-2-yn-1-amine-d1 (240 mg, 1.50 mmol, 79%).

Methyl 1-benzyl-4-methyl-2-phenyl-1,6-dihydropyridine-3-carboxylate-5-d1 (2j-D). To a solution of *N*-benzyl but-2-yn-1-amine-d1 (274 mg, 1.71 mmol) in CD_3OD (1.6 ml) was added methyl 3-phenylpropiolate (0.260 ml, 1.76 mmol) and stirred at 70 °C for 10 h. After concentrated *in vacuo*, the residue was purified by silica-gel chromatography to afford **1j-D** (482 mg, 1.51 mmol, 88%). Deuterium incorporation (80%) at C3 proton was determined based on ^{1}H-NMR analysis. A solution of *N*-propargylenamine **1j-D** (70.1 mg, 0.219 mmol) and [Cu(Xantphos)(MeCN)]PF_6 (18.3 mg, 0.0219 mmol) in dichloromethane (2.2 ml) was stirred at r.t. for 3 h. The reaction mixture was then treated with 1,10-phenanthroline (5.0 mg, 0.0277 mmol) to deactivate the copper catalyst. After concentration *in vacuo*, 4-nitrobenzonitrile (32.4 mg, 0.219 mmol) was added as an internal standard. Yield of **2j-D** (83%) as well as percentage of deuteration of C5 proton (66%) were calculated based on ^{1}H-NMR.

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