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Nickel-Catalyzed Alkynylation of C(sp^2)-H Bond Directed by an 8-Aminoquinoline Moiety

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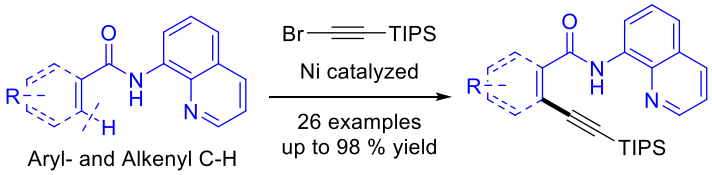
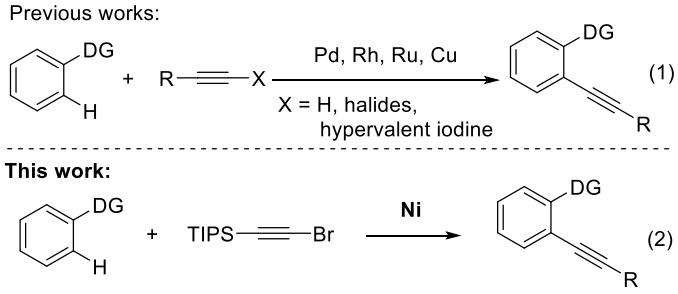


ABSTRACT: An efficient nickel catalyst system for the direct ortho C-H alkynylation of the amides has been successfully developed with the directing assistance of 8-aminoquinoline. It has been investigated that the flexible bis(2-dimethylaminoethyl) ether (BDMAE) ligand was critical to achieve the optimized reactivity. This protocol showed good tolerance toward not only a wide range of (hetero)aryl amides but also the rarely studied α, β-unsaturated alkenyl amide. The directing amide group could be easily transformed to aldehyde or ester in high yields. Meanwhile, the removable TIPS substituent on the resultant aryl/alkenyl alkynes could be further converted to aryl moiety through Sila-Sonogashira coupling reaction. This Ni-catalyzed alkynylation procedure provides an alternative approach to construct C(sp^2)-C(sp) bond.

INTRODUCTION

Transition-metal catalyzed direct C-H functionalization is perhaps the ideal method to construct organic molecules.[1] In the past decade, significant advances to promote C-H functionalization have been achieved with second- and third-row transition metals,[2] and recently the earth-abundant first-row transition metals have been intensively studied to emulate the reactivity of a noble transition metal catalyst and broaden the C-H functionalization reactions at a lower cost.[3]



Scheme 1. Transition-Metal Catalyzed C-H Alkynylation.

Alkyne motifs are ubiquity in pharmaceuticals, materials and other functional compounds.[4] As is known that Sonogashira coupling reaction is the classical choice to synthesize aryl alkynes,[5] but the direct C-H alkynylation has been developed as a more attractive route to construct C(sp^2)-C(sp) bonds, which was mainly realized by Pd,[6] Rh,[7] Ru.[8] (Scheme 1, eq 1) Recently, Shi and Yu respectively reported their elegant Cu-mediated ortho C-H alkynylation of the directed arenes and heteroarenes, demonstrating the significant potential of first-row metal in C-H alkynylation,[9] unfortunately, these transformations required either stoichiometric copper catalyst[9a] or metallic oxidants[9b]. In addition, it is worthy to note that the direct alkynylation of another kind of C(sp^2)-H bond, alkenyl C-H, has not yet been investigated. In comparison with the booming advances of the first-row transition metal

catalyzed C-H functionalization, their successful application in the alkynylation of inert C(sp^2)-H bonds still remains at an early stage.

In recent years, nickel has emerged as a promising catalyst for C-H functionalization, pioneer works developed by Chatani, Ge, Ackermann, You, Shi, Zeng and Zhang greatly broadened the reaction type.[10, 11] However, unfortunately, most of these methods have limitations such as high reaction temperature (> 140 ^{o}C) and limited substrate scope. Thus, it is highly desirable to develop a new synthetic strategy procedure based on non-precious metal catalyst to facilely introduce alkyne motifs onto different carbon skeletons considering their great importance in diverse transformations.[12] Herein, we report a nickel-catalyzed C−H alkynylation reaction between two kinds of inactivated C(sp^2)-H and triisopropylsilyl (TIPS)-substituted bromoalkyne (Scheme 1, eq 2). The present alkynylation has remarkably broad substrate scope, which is enabled by a bidentate directing group along with the assistance of the bis(2-dimethylaminoethyl) ether (BDMAE) as a ligand to enhance the catalytic activity. To the best of our knowledge, this is the first report on Ni-catalyzed C(sp^2)-C(sp) bond formation via 8-quinolinyl-chelation assistance. [13, 14] Besides the C-H bonds of arylamides and heteroarylamides, the alkynylation of alkenylamides also proceeded smoothly (26 examples, up to 98% yield).

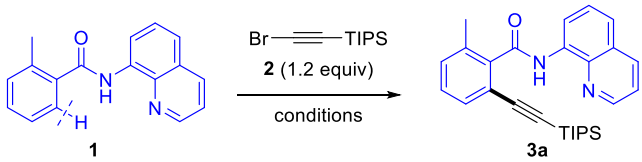
RESULTS AND DISSCUSION

We began our investigation by exploring the reaction between 2-methyl-N-(quinolin-8-yl)benzamide (**1**) and TIPS-protected bromoalkyne (**2**) (Table 1). When we screened the previous reported protocols of Ni-catalyzed C-H functionalization, fortunately, Ackermann's method gave the desired product with 25% yield (entries 1-4).[10d]

BDMAE was investigated to be a critical ligand in promoting present Ni-catalyzed C-H alkynylation,[10d] base screening showed that Na_2CO_3 produced the optimal yield (entries 4-8), and appropriate combination of Na_2CO_3 and BDMAE even gave better performance (entry 9). At higher reaction temperature, the decomposition of the raw material into 8-aminoquinoline was detected, and the side reaction could be successfully depressed by lowering the reaction temperature to 100 ^oC (entry 10). Notably, this is the lowest reaction temperature in Ni-catalyzed C-H functionalizations directed by 8-quinolinyl.[10, 13] Gratifyingly, the simple salt $NiCl_2$ could be used to perfectly replace [(DME)$NiCl_2$], giving nearly quantitative product yield (entry 11). As expected, no product was detected in the absence of $NiCl_2$ or BDMAE (entries 12-13), indicating indispensability of both $NiCl_2$ and ligand for the reaction. Replacement of BDMAE by classical phase transfer catalyst, tetrabutylammonium iodide (TBAI), only gave 30% yield of the desired product, demonstrating that the role of BDMAE was more than a phase transfer reagent. To disclose the role of anion, a series of nickel salts ($NiBr_2$, NiI_2, $Ni(OTf)_2$, $Ni(acac)_2$ and $Ni(COD)_2$) were evaluated under the optimal reaction condition (entries 15-19). $NiBr_2$ and $NiCl_2$ showed nearly identical activity (entry 15). Surprisingly, iodine ion hampered the reaction (entry 16), OTf^- and $acac^-$ also greatly reduced the yield (entries 17-18). Not only Ni(II) complexes but also Ni(0) complex showed high catalytic activity in such alkynylation (entry 19). To learn more coordination information in the active metal species, other bidentate and tridentate ligands were tested (entry 20-25). When PMTDA, like changing the oxygen atom on BDMAE into nitrogen, was used as the N-N-N tridentate ligand, the yield was significantly reduced to 65% (entry 20). Moreover, the bidentate nitrogen ligand with similar flexible skeleton (TMEDA) showed better performance

than the corresponding tridentate-nitrogen ligand (PMTDA), possibly due to the suitable coordination ability to the nickel catalysis (entry 21). However, the bidentate nitrogen ligand with rigid skeleton gave poor reactivity (entries 22-23). When all the nitrogen ligands were replaced by corresponding structurally similar pure oxygen ligands, the yields were obviously reduced (entries 24-25). All these results indicated that the coordination atom and environment are equally important to achieve the optimized catalytic reactivity.

Table 1. Optimization of the Reaction Conditions[a]



1 3a

entry	Catalyst (10 mol %)	Ligand (20 mol %)	Base (2 equiv)	yield[b] (%)
1	$Ni(OTf)_2$	PPh_3	Na_2CO_3	Trace
2	$Ni(OTf)_2$	MesCOOH	Na_2CO_3	Trace
3	$Ni(acac)_2$	dppbz	Cs_2CO_3	Trace
4	$(DME)NiCl_2$	BDMAE	LiO*t*Bu	25
5	$(DME)NiCl_2$	BDMAE	Cs_2CO_3	52
6	$(DME)NiCl_2$	BDMAE	K_3PO_4	67
7	$(DME)NiCl_2$	BDMAE	K_2CO_3	70
8	$(DME)NiCl_2$	BDMAE	Na_2CO_3	75
9[c]	$(DME)NiCl_2$	BDMAE	Na_2CO_3	89
10[c, d]	$(DME)NiCl_2$	BDMAE	Na_2CO_3	95
11[c, d]	**$NiCl_2$**	**BDMAE**	**Na_2CO_3**	**98**
12[c, d]	$NiCl_2$	-	Na_2CO_3	Trace
13[c, d]	-	BDMAE	Na_2CO_3	Trace
14[c, d]	$NiCl_2$	TBAI	Na_2CO_3	30
15[c, d]	$NiBr_2$	BDMAE	Na_2CO_3	94
16[c, d]	NiI_2	BDMAE	Na_2CO_3	65
17[c, d]	$Ni(OTf)_2$	BDMAE	Na_2CO_3	50
18[c, d]	$Ni(acac)_2$	BDMAE	Na_2CO_3	30
19[c, d]	$Ni(COD)_2$	BDMAE	Na_2CO_3	83

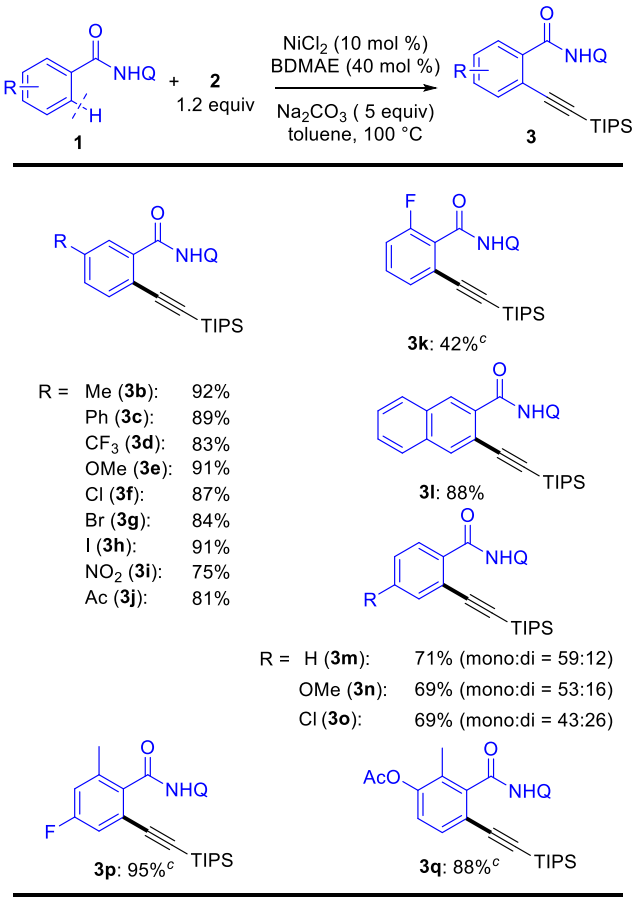
20 [c, d]	$NiCl_2$	PMDTA	Na_2CO_3	65
21 [c, d]	$NiCl_2$	TMEDA	Na_2CO_3	77
22 [c, d]	$NiCl_2$	2,2-dipyridyl	Na_2CO_3	8
23 [c, d]	$NiCl_2$	dtbpy	Na_2CO_3	12
24 [c, d]	$NiCl_2$	DME	Na_2CO_3	14
25 [c, d]	$NiCl_2$	Diglyme	Na_2CO_3	26

[a]Unless otherwise stated, all reactions were carried out with **1** (0.2 mmol), **2** (1.2 equiv), 10 mol% catalyst, 20 mol% ligand, base (2 equiv.) and toluene (2 mL) at 160 °C for 24h under an argon atmosphere. [b]Yield was calculated based on **1**. [c]40 mol% ligand, 5.0 equiv Na_2CO_3. [d]At 100 °C. OTf = trifluoromethane sulfonate, acac = acetylacetonate, DME = 1,2-dimethoxyethane, dppbz = 1,2-bis(diphenylphosphino)benzene, Q = 8-quinolinyl, BDMAE = bis(2-dimethylaminoethyl)ether, TBAI = tetrabutylammonium iodide, TMEDA = N,N,N',N'-Tetramethylethylenediamine, dtbpy = 4,4'-di-tert-butyl bipyridine, PMDTA = Pentamethyldiethylenetriamine.

With the optimal conditions in hand, we then explored the substrate scope of the protocol with various decorated benzamides (Table 2). To our delight, present Ni-catalyzed alkynylation reaction is compatible with various benzamides containing an electron-rich or electron-deficient substituent at the *meta*-position, affording the expected alkynes (**3b**-**3j**) in excellent yields (75-92%) and with good mono-selectivity at the less hindered C-H bond.[10] Among them, many synthetically valuable groups such as halide (Cl, Br, I) could be reserved under mild reactions, which gave the chances for further modification of the products (**3f, 3g, 3h**). Surprisingly, nitro group which was scarcely tolerated in the nickel-catalyzed reactions was also compatible with present transformation (**3i**).[15] Acetyl group which was sensitive to strong base also retained with good yield (**3j**). *Ortho*-fluoride substituted benzamide gave a moderate yield of the expected (**3k**). Additionally, alkynylation of the corresponding 2-naphthamide smoothly solely occurred at the less hinder position, affording (**3l**) in a 88% yield. When the *para*-substituted substrates were used, small amount of dialkynylation products were found irrespective of the electronic nature of the substituent (**3m, 3n, 3o**).

Disubstituted benzamides also gave the desired alkynylation products in excellent yields (**3p, 3q**).

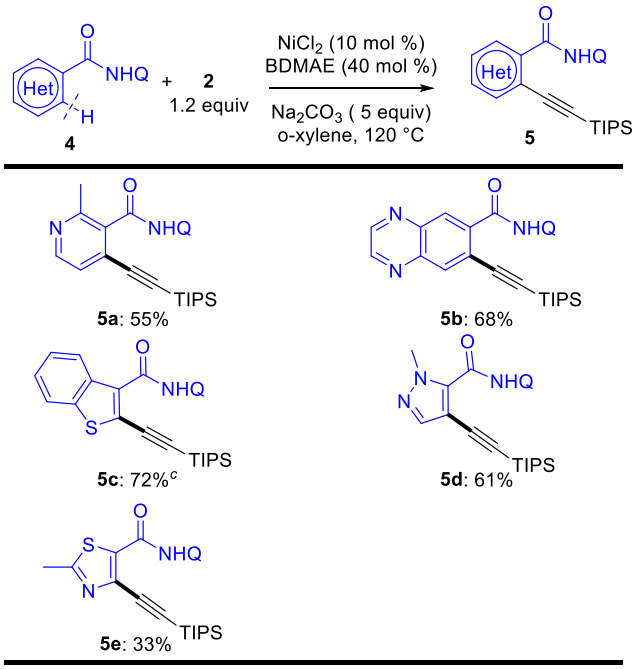
Scheme 2. Scope of Aromatic Amides[a, b]



[a]Condition A: **1** (0.20 mmol), **2** (1.2 equiv), $NiCl_2$ (10 mol%), BDMAE (40 mol%), Na_2CO_3 (5 equiv), toluene (2 mL), 100 °C, 24 h. [b]Yield was calculated based on **1**. [c]36h.

Encouraged by these results, we turned our interest to heterocyclic substrates which were common motifs in medicinal chemistry (Table 3).[16] To our delight, alkynylation of heteroaromatic amides with pyridine, quinoxaline, benzothiophene, pyrazole and thiazole moiety all gave the corresponding products with synthetically useful yields (**5a-5e**, 33-72%). Interestingly, strongly coordinating heteroatoms like sulfur and nitrogen have no interference to the reaction. Because of the good compatibility of heterocyclic substrates, this method has potential application in the pharmaceutical chemistry.

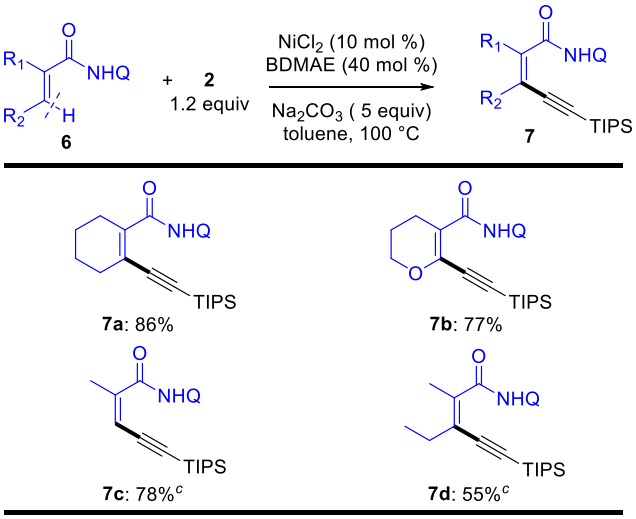
Scheme 3. Scope of Heteroaromatic Amides[a, b]



[a]Condition B: **4** (0.2 mmol), **2** (1.2 equiv), $NiCl_2$ (10 mol%), BDMAE (40 mol%), Na_2CO_3 (5.0 equiv), *o*-xylene (2 mL), 120 °C, 36 h. [b]Yield was calculated based on **4**. [c]toluene (2 mL), 100 °C, 24 h.

Compared with above mentioned arylamide, the alkynylation of α, β-unsaturated amides is far more challenging due to the higher flexibility of alkenylamides, and so far has been rarely investigated. Interestingly, as shown in Table 4, present Ni/BDMAE catalyst system showed good tolerance toward, both cyclic- and open-chain α, β-unsaturated alkenylamides, giving corresponding alkenyl alkynes in good yield (**7a-7d**). But the substituent at α-carbon was essential for the reactivity of the substrate. Otherwise, no alkynylation reaction occured.

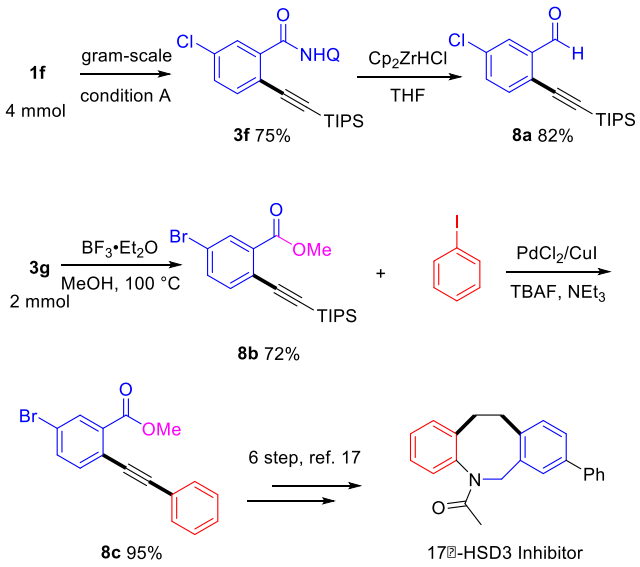
Scheme 4. Scope of Alkenylamides[a, b]



[a]Condition C: **6** (0.2 mmol), **2** (1.2 equiv), $NiCl_2$ (10 mol%), BDMAE (40 mol%), Na_2CO_3 (5.0 equiv), toluene (2 mL), 100 °C, 24 h. [b]Yield was calculated based on **6**. [c]36h.

To further probe the practical utility of this nickel-catalyzed C-H alkynylation, a gram-scale reaction was conducted. As depicted in Scheme 5, 1.130 g (4.0 mmol) scale of **1f** could be converted to **3f** in 75% yield under the optimized reaction condition. Next, conversion of the directing amide group was also illustrated by treating **3f** with Schwartz's reagent, providing the corresponding aldehyde **8a** in 82% yield. On the other hand, the amide moiety of **3g** could also transfer to ester **8b** by reaction with $BF_3 \cdot Et_2O$ and MeOH in 72% yield. Subsequently, the TIPS could be easily converted to phenyl group to yield **8c** in 95% yield through the Sila-Sonogashira coupling reaction, which means other aryl substituents could be similarly introduced. Notably, **8c** is the key intermediate in the synthesis of 17 β-hydroxysteroid dehydrogenase type-3 (17 β-HSD3) inhibitor which was considered to be clinical candidate for the treatment of prostate cancer.[17]

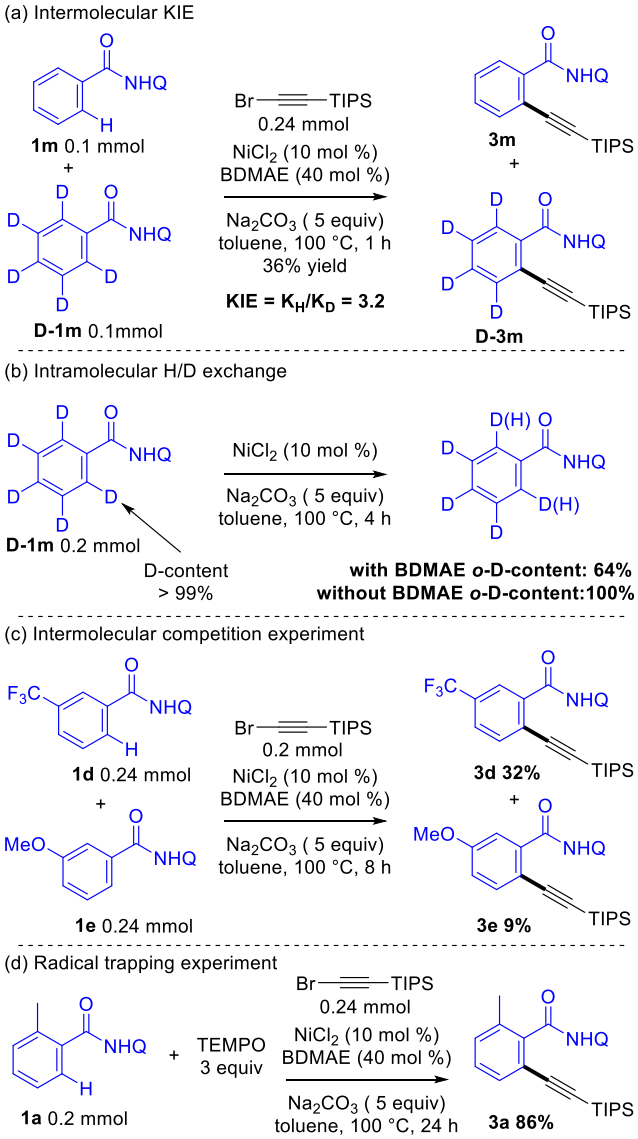
Scheme 5. Gram-Scale Reaction and Further Conversion



To probe the mechanism of the reaction, some deuterium-labeling experiments were carried out as shown in Scheme 6. A significant intermolecular kinetic isotope effect (KIE = 3.2) was observed (Scheme 6a),[18] indicating the cleavage of the *ortho*-C-H bond of the substrate may be the rate-determining step in the catalytic cycle. Moreover, intramolecular H/D exchange between N-H bond of the amide and its *ortho*-C-H bonds with the chelation assistance was observed in the absence of TIPS-substituted bromoalkyne (Scheme 6b). These two control experiments suggest that rapid and reversible cleavages of C-H bonds are involved in the process. Additionally, the competition experiment with different electronic substituent shows that the reaction favors with electron-withdrawing group (Scheme 6c). The electronic effect of substituents and high KIE value both indicate that the cleavage of *ortho*-C-H bond may be experienced a concerted-metalation-deprotonation (CMD) mechanism.[10c, f, 19] Furthermore, no obvious yield changing was observed although 3.0 equiv TEMPO was added (Scheme 6c), indicating the single-electron transfer (SET) in this reaction could be ruled out. Based on our investigations and the reported results, it is believed that BDMAE ligand may take multiple roles in this protocol, first, it could stabilize the active organometallic species with a suitable geometry to prevent it

against decomposition and enhance the catalytic activity,[15, 21] which could be seen from the obvious catalytic difference of catalytic system with (98%, entry 11 of Table 1) and without BDMAE (trace, entry 12 of Table 1). In addition, BDMAE could help the C-H cleavage step because no H/D exchanged was occurred without BDMAE (Scheme 6b).

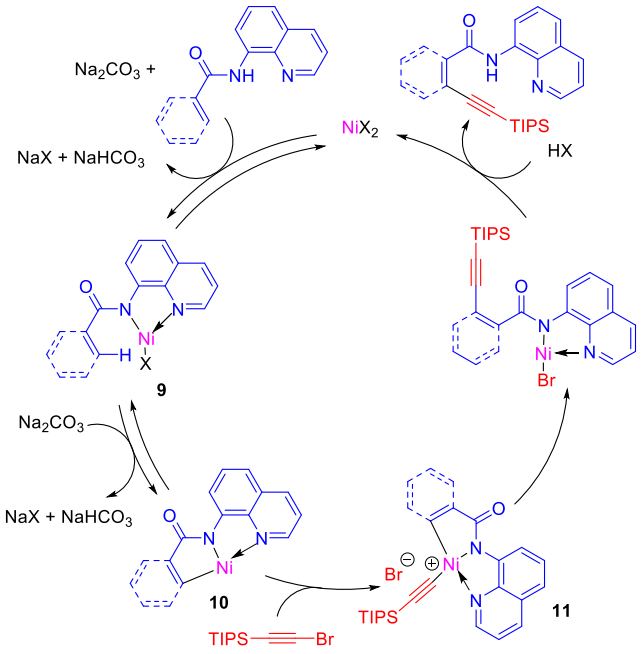
Scheme 6. Mechanistic Experiments



Based on the above investigations and previous reports,[13] we propose a plausible mechanism shown in Scheme 7. Initially, the coordination of amide to nickel catalyst followed by ligand exchange to form complex **9,** which could go through cyclometalation to give intermediate **10**, the

oxidative addition of the bromoalkyne afforded the high valent Ni(IV) complex **11**, which underwent reductive elimination and protonation to yield the alkynylation product with regeneration of the Ni(II) catalyst.

Scheme 7. Proposed Reaction Mechanism



CONCLUSIONS

In conclusion, we have developed a Ni-catalyzed direct C-H alkynylation via bidentate-chelation strategy using BDMAE as an additional ligand, which significantly promoted the C-H bond cleavage. The protocol was characterized by good compatibility with biologically important heterocyclic amides and more challenging α, β-unsaturated alkenyl amides. Mechanistic studies reveal that the C-H cleavage may be the rate-determining step and single-electron transfer route is less possible. This method provided a new approach to synthesize aryl- and alkenyl-alkynes, and may also inspire useful ideas for the development of Ni-catalyzed C-H functionalization.

EXPERIMENT SECTION

General Information

Solvents and chemicals were used as received. ^{1}H NMR, ^{13}C NMR spectra were recorded on a 400 MHz spectrometer at the ambient temperature, using TMS as an internal standard (chemical shifts in δ). Data are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet, dt = doublet of triplet, etc.), coupling constant (Hz), and integration. Gas chromatographic (GC) analyses were performed on a GC equipped with a flame-ionization detector. High resolution mass spectra were obtained on a HRMS-TOF spectrometer. Analytical thin layer chromatography (TLC) was performed on pre-coated silica gel plates. After elution, plate was visualized under UV illumination at 254 nm for UV active materials. Organic solutions were concentrated under reduced pressure on a rotary evaporator. Column chromatography was performed on silica gel (200−300 mesh) by standard techniques eluting with solvents as indicated. Melting points were obtained on IA9000 SERIES Digital Melting Point Apparatus.

Preparation of 8-Aminoquinoline-bearing carboxamides.

8-Aminoquinoline-bearing carboxamides were prepared according to the conditions reported in literatures. The acid chlorides were prepared from the corresponding acid by reaction with oxalic dichloride. Purification of the crude product by silica gel column chromatography gave the final product.

General Procedure for Examples Described in Table 2, 3, 4

In a glove box, $NiCl_2$ (10 %, 2.6 mg), Na_2CO_3 (5.0 equiv., 106 mg) and 0.2 mmol corresponding amide (if solid) were added to a 15 mL Schlenk tube equipped with a stir bar. The vessel was evacuated and filled with nitrogen (three cycles). 0.2 mmol amide (if liqid), 2.0 mL solvent, 15 μL BDMAE and 0.24 mmol TIPS-substituted bromoalkyne was added in turn under

nitrogen atmosphere. The reaction mixture was stirred for particular time and temperature. Then the reaction was diluted with EtOAc and filtered through silica gel with copious washings. Purification of the crude product by flash chromatography on silica gel using the indicated solvent system afforded the desired product.

*6-methyl-N-(quinolin-8-yl)-2-((triisopropylsilyl)ethynyl)benzamide (**3a**)*: According to the general procedure, the reaction mixture was stirred at 100 ^{o}C for 24 h. The product was isolated by flash chromatography (PE : EA = 5 : 1, R_f = 0.2) as a colorless oil. Yield: 86.7 mg, 98%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.13 (brs, 1H), 9.02 (dd, *J* = 7.4, 1.5 Hz, 1H), 8.74 (dd, *J* = 4.3, 1.6 Hz, 1H), 8.18 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.64 – 7.51 (m, 2H), 7.47 – 7.38 (m, 2H), 7.32 – 7.19 (m, 2H), 2.46 (s, 3H), 0.85 – 0.67 (m, 21H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 167.3, 147.9, 140.1, 138.2, 136.5, 135.6, 134.6, 130.5, 130.4, 128.9, 127.9, 127.4, 121.8, 121.5, 120.9, 117.2, 103.9, 94.9, 19.5, 18.3, 11.0; HRMS (ESI-TOF) m/z Calcd for $C_{28}H_{35}N_2OSi^+$ $[M+H]^+$ 443.2513, found 443.2510.

*5-methyl-N-(quinolin-8-yl)-2-((triisopropylsilyl)ethynyl)benzamide (**3b**)*: According to the general procedure, the reaction mixture was stirred at 100 ^{o}C for 24 h. The product was isolated by flash chromatography (PE : EA = 10 : 1, R_f = 0.3) as a colorless oil. Yield: 81.4 mg, 92%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.50 (brs, 1H), 8.92 (dd, *J* = 7.5, 1.1 Hz, 1H), 8.76 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.63 – 7.49 (m, 4H), 7.43 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.28 – 7.21 (m, 1H), 2.42 (s, 3H), 0.90 – 0.73 (m, 21H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 166.8, 148.3, 139.2, 139.2, 139.0, 136.4, 134.8, 134.0, 131.1, 129.4, 128.1, 127.5, 122.0, 121.6, 117.9, 117.3, 104.2, 96.2, 21.6, 18.5, 11.2; HRMS (ESI-TOF) m/z Calcd for $C_{28}H_{35}N_2OSi^+$ $[M+H]^+$ 443.2513, found 443.2511.

*N-(quinolin-8-yl)-4-((triisopropylsilyl)ethynyl)-[1,1'-biphenyl]-3-carboxamide (**3c**)*: According to the general procedure, the reaction mixture was stirred at 100 ^{o}C for 24 h. The product was isolated by

flash chromatography (PE : EA = 10 : 1, R_f = 0.35) as a colorless oil. Yield: 89.8 mg, 89%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.57 (brs, 1H), 8.95 (d, *J* = 7.4 Hz, 1H), 8.77 (dd, *J* = 4.2, 1.4 Hz, 1H), 8.17 (dd, *J* = 8.3, 1.4 Hz, 1H), 8.05 (d, *J* = 0.9 Hz, 1H), 7.72 – 7.53 (m, 6H), 7.50 – 7.34 (m, 4H), 0.97 – 0.72 (m, 21H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 166.5, 148.2, 141.5, 139.7, 139.5, 138.8, 136.4, 134.6, 134.4, 129.0, 128.6, 128.0, 128.0, 127.4, 127.3, 127.1, 122.0, 121.5, 119.5, 117.3, 103.8, 97.8, 18.4, 11.1; HRMS (ESI-TOF) m/z Calcd for $C_{33}H_{37}N_2OSi^+$ $[M+H]^+$ 505.2670, found 505.2673.

N-(quinolin-8-yl)-5-(trifluoromethyl)-2-((triisopropylsilyl)ethynyl)benzamide ***(3d)***: According to the general procedure, the reaction mixture was stirred at 100 °C for 24 h. The product was isolated by flash chromatography (PE : EA = 10 : 1, R_f = 0.35) as a white solid. Mp = 116 °C; Yield: 82.4 mg, 83%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.55 (brs, 1H), 8.91 (dd, *J* = 7.1, 1.6 Hz, 1H), 8.77 (dd, *J* = 4.2, 1.5 Hz, 1H), 8.19 (dd, *J* = 8.3, 1.5 Hz, 1H), 8.07 (s, 1H), 7.71 (dd, *J* = 20.5, 8.2 Hz, 2H), 7.65 – 7.54 (m, 2H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 0.89 – 0.79 (m, 21H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 165.0, 148.3, 139.8, 138.7, 136.4, 134.3, 134.3, 130.6 (q, *J* = 33.2 Hz), 127.9, 127.4, 126.7 (q, *J* = 3.5 Hz), 125.9 (q, *J* = 3.7 Hz), 124.3, 123.5 (q, *J* = 272.2 Hz), 122.3, 121.6, 117.4, 102.5, 100.6, 18.3, 11.0; HRMS (ESI-TOF) m/z Calcd for $C_{28}H_{32}F_3N_2OSi^+$ $[M+H]^+$ 497.2231, found 497.2233.

5-methoxy-N-(quinolin-8-yl)-2-((triisopropylsilyl)ethynyl)benzamide ***(3e)***: According to the general procedure, the reaction mixture was stirred at 100 °C for 24 h. The product was isolated by flash chromatography (PE : EA = 10 : 1, R_f = 0.15) as a yellow solid. Mp = 62-63 °C; Yield: 83.4 mg, 91%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.54 (brs, 1H), 8.93 – 8.88 (m, 1H), 8.75 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.13 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.60 – 7.49 (m, 3H), 7.40 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.32 (d, *J* = 2.7 Hz, 1H), 6.95 (dd, *J* = 8.6, 2.8 Hz, 1H), 3.84 (s, 3H), 0.88 – 0.70 (m, 21H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 166.1, 159.7, 148.2, 140.6, 138.9, 136.1, 135.4, 134.6, 127.9, 127.2, 121.9, 121.4, 117.1, 117.0, 113.1,

112.9, 103.9, 95.1, 55.5, 18.3, 11.1; HRMS (ESI-TOF) m/z Calcd for $C_{28}H_{35}N_2O_2Si^+$ $[M+H]^+$ 459.2462, found 459.2461.

5-chloro-N-(quinolin-8-yl)-2-((triisopropylsilyl)ethynyl)benzamide ***(3f)***: According to the general procedure, the reaction mixture was stirred at 100 °C for 24 h. The product was isolated by flash chromatography (PE : EA = 10 : 1, R_f = 0.3) as a white solid, Mp = 67-68 °C; Yield: 80.4 mg, 87%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.50 (brs, 1H), 8.89 (dd, *J* = 7.1, 1.7 Hz, 1H), 8.77 (dd, *J* = 4.2, 1.5 Hz, 1H), 8.17 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.78 (d, *J* = 2.2 Hz, 1H), 7.64 – 7.50 (m, 3H), 7.47 – 7.37 (m, 2H), 0.94 – 0.66 (m, 21H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$) δ 164.9, 148.3, 140.6, 138.8, 136.3, 135.1, 134.8, 134.4, 130.3, 128.9, 127.9, 127.3, 122.2, 121.6, 119.2, 117.3, 102.8, 98.4, 18.3, 11.0; HRMS (ESI-TOF) m/z Calcd for $C_{27}H_{32}ClN_2OSi^+$ $[M+H]^+$ 463.1967, found 463.1971.

5-bromo-N-(quinolin-8-yl)-2-((triisopropylsilyl)ethynyl)benzamide ***(3g)***: According to the general procedure, the reaction mixture was stirred at 100 °C for 24 h. The product was isolated by flash chromatography (PE : EA = 10 : 1, R_f = 0.3) as a white solid, Mp = 81-82 °C; Yield: 85.0 mg, 84%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.50 (brs, 1H), 8.89 (d, *J* = 7.1 Hz, 1H), 8.77 (dd, *J* = 4.2, 1.4 Hz, 1H), 8.17 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.78 (d, *J* = 2.1 Hz, 1H), 7.62 – 7.52 (m, 3H), 7.42 (ddd, *J* = 10.5, 8.3, 3.2 Hz, 2H), 0.92 – 0.72 (m, 21H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$) δ 165.0, 148.3, 140.6, 138.8, 136.3, 135.1, 134.8, 134.4, 130.3, 128.9, 127.9, 127.4, 122.2, 121.6, 119.2, 117.3, 102.8, 98.4, 18.3, 11.0; HRMS (ESI-TOF) m/z Calcd for $C_{27}H_{32}BrN_2OSi^+$ $[M+H]^+$ 507.1462, found 507.1462.

5-iodo-N-(quinolin-8-yl)-2-((triisopropylsilyl)ethynyl)benzamide ***(3h)***: According to the general procedure, the reaction mixture was stirred at 100 °C for 24 h. The product was isolated by flash chromatography (PE : EA = 10 : 1, R_f = 0.3) as a pink solid, Mp = 86-87 °C; Yield: 100.9 mg, 91%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.49 (brs, 1H), 8.91 (dd, *J* = 7.2, 1.8 Hz, 1H), 8.79 (dd, *J* = 4.2, 1.7 Hz,

1H), 8.19 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.15 (d, *J* = 1.8 Hz, 1H), 7.79 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.64 – 7.55 (td, *J* = 8.7, 4.5 Hz, 2H), 7.46 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.35 (d, *J* = 8.2 Hz, 1H), 0.92 – 0.74 (m, 21H); $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$) δ 164.7, 148.3, 140.6, 139.0, 138.7, 137.5, 136.3, 135.0, 134.4, 127.9, 127.4, 122.1, 121.6, 120.2, 117.3, 103.0, 98.9, 94.3, 18.3, 11.0; HRMS (ESI-TOF) m/z Calcd for $C_{27}H_{32}IN_2OSi^+$ $[M+H]^+$ 555.1323, found 555.1319.

5-nitro-N-(quinolin-8-yl)-2-((triisopropylsilyl)ethynyl)benzamide ***(3i)***: According to the general procedure, the reaction mixture was stirred at 100 °C for 24 h. The product was isolated by flash chromatography (PE : EA = 20 : 1, R_f = 0.45) as a white solid, Mp = 98-99 °C; Yield: 71.0 mg, 75%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.52 (brs, 1H), 8.89 (dd, *J* = 6.4, 2.6 Hz, 1H), 8.76 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.64 (d, *J* = 2.4 Hz, 1H), 8.26 (dd, *J* = 8.5, 2.4 Hz, 1H), 8.18 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.75 (d, *J* = 8.5 Hz, 1H), 7.62 – 7.55 (m, 2H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 0.94 – 0.71 (m, 21H); $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$) δ 163.9, 148.4, 147.0, 140.4, 138.7, 136.3, 134.8, 134.1, 127.9, 127.3, 127.0, 124.5, 124.0, 122.4, 121.6, 117.3, 104.0, 102.0, 18.2, 11.0; HRMS (ESI-TOF) m/z Calcd for $C_{27}H_{32}N_3O_3Si^+$ $[M+H]^+$ 474.2207, found 474.2210.

5-acetyl-N-(quinolin-8-yl)-2-((triisopropylsilyl)ethynyl)benzamide ***(3j)***: According to the general procedure, the reaction mixture was stirred at 100 °C for 24 h. The product was isolated by flash chromatography (PE : EA = 10 : 1, R_f = 0.2) as a yellow solid, Mp = 70-71 °C; Yield: 76.2 mg, 81%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.52 (brs, 1H), 8.89 (dd, *J* = 7.2, 1.7 Hz, 1H), 8.74 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.33 (d, *J* = 1.8 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.99 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.66 (d, *J* = 8.1 Hz, 1H), 7.60 – 7.52 (m, 2H), 7.42 (dd, *J* = 8.3, 4.2 Hz, 1H), 2.62 (s, 3H), 0.88 – 0.72 (m, 21H); $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$) δ 196.6, 165.5, 148.3, 139.5, 138.8, 136.5, 136.2, 134.4, 134.1, 129.1, 128.9, 127.9, 127.3, 125.0, 122.1, 121.5, 117.2, 103.1, 101.3, 26.7, 18.3, 11.0; HRMS (ESI-TOF) m/z

Calcd for $C_{29}H_{35}N_2O_2Si^+$ $[M+H]^+$ 471.2462, found 471.2466.

2-fluoro-N-(quinolin-8-yl)-6-((triisopropylsilyl)ethynyl)benzamide ***(3k)***: According to the general procedure, the reaction mixture was stirred at 100 °C for 24 h. The product was isolated by flash chromatography (PE : EA = 10 : 1, R_f = 0.35) as a white solid, Mp = 105-106 °C; Yield: 37.5 mg, 42%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.20 (brs, 1H), 8.97 (dd, *J* = 7.1, 1.8 Hz, 1H), 8.75 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.17 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.61 – 7.54 (m, 2H), 7.43 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.38 (dd, *J* = 5.8, 4.3 Hz, 2H), 7.18 – 7.13 (m, 1H), 0.88 – 0.72 (m, 21H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 162.1, 159.2 (d, *J* = 250.3 Hz), 148.1, 138.4, 136.2, 134.4, 130.7 (d, *J* = 9.0 Hz), 128.9 (d, *J* = 3.3 Hz), 128.3 (d, *J* = 18.6 Hz), 127.8, 127.3, 123.2 (d, *J* = 4.8 Hz), 122.0, 121.5, 117.0, 116.3 (d, *J* = 21.8 Hz), 102.3 (d, *J* = 3.8 Hz), 97.1, 18.3, 11.0; HRMS (ESI-TOF) m/z Calcd for $C_{27}H_{32}FN_2OSi^+$ $[M+H]^+$ 447.2262, found 447.2265.

N-(quinolin-8-yl)-3-((triisopropylsilyl)ethynyl)-2-naphthamide ***(3l)***: According to the general procedure, the reaction mixture was stirred at 100 °C for 24 h. The product was isolated by flash chromatography (PE : EA = 10 : 1, R_f = 0.2) as a pale yellow solid, Mp = 107-108 °C; Yield: 84.2 mg, 88%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.54 (brs, 1H), 8.98 (d, *J* = 7.6 Hz, 1H), 8.75 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.30 (s, 1H), 8.16 (dd, *J* = 8.8, 2.1 Hz, 2H), 7.93 – 7.81 (m, 2H), 7.64 – 7.51 (m, 4H), 7.42 (dd, *J* = 8.2, 4.2 Hz, 1H), 0.95 – 0.74 (m, 21H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 166.4, 148.2, 138.8, 136.2, 136.0, 134.8, 134.2, 133.4, 132.2, 128.8, 128.6, 127.9, 127.9, 127.5, 127.4, 127.3, 121.8, 121.4, 117.7, 117.1, 104.3, 96.3, 18.4, 11.2; HRMS (ESI-TOF) m/z Calcd for $C_{31}H_{35}N_2OSi^+$ $[M+H]^+$ 479.2513, found 479.2510.

N-(quinolin-8-yl)-2-((triisopropylsilyl)ethynyl)benzamide ***(3m-mono)***: According to the general procedure, the reaction mixture was stirred at 100 °C for 24 h. The product was isolated by flash chromatography (PE : EA = 20 : 1, R_f = 0.35) as a colorless oil. Yield: 50.5 mg, 58%. ^{1}H NMR (400

MHz, $CDCl_3$) δ 10.49 (brs, 1H), 8.93 (d, *J* = 7.4 Hz, 1H), 8.75 (dd, *J* = 4.1, 1.5 Hz, 1H), 8.14 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.83 – 7.75 (m, 1H), 7.63 – 7.50 (m, 3H), 7.45 – 7.39 (m, 3H), 0.81 (dt, *J* = 7.1, 4.0 Hz, 21H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$) δ 166.4, 148.2, 139.2, 138.9, 136.2, 134.7, 133.9, 130.1, 128.6, 128.6, 127.9, 127.3, 121.8, 121.4, 120.7, 117.1, 103.9, 97.1, 18.3, 11.1; HRMS (ESI-TOF) m/z Calcd for $C_{27}H_{33}N_2OSi^+$ $[M+H]^+$ 429.2357, found 429.2353.

N-(quinolin-8-yl)-2,6-bis((triisopropylsilyl)ethynyl)benzamide ***(3m-di)***: According to the general procedure, the reaction mixture was stirred at 100 °C for 24 h. The product was isolated by flash chromatography (PE : EA = 50 : 1, R_f = 0.5) as a white oil. Yield: 14.7 mg, 13%. ^1H NMR (400 MHz, $CDCl_3$) δ 10.07 (brs, 1H), 9.00 (dd, *J* = 7.4, 1.4 Hz, 1H), 8.74 (dd, *J* = 4.1, 1.5 Hz, 1H), 8.17 (d, *J* = 8.2 Hz, 1H), 7.60 – 7.50 (m, 4H), 7.43 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.36 – 7.32 (m, 1H), 0.88 (s, 42H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$) δ 165.5, 147.9, 143.5, 138.4, 136.1, 134.8, 132.3, 128.7, 127.7, 127.2, 121.4, 121.4, 121.3, 117.1, 103.0, 95.8, 18.3, 11.1; HRMS (ESI-TOF) m/z Calcd for $C_{38}H_{53}N_2OSi_2^+$ $[M+H]^+$ 609.3691, found 609.3688.

4-methoxy-N-(quinolin-8-yl)-2-((triisopropylsilyl)ethynyl)benzamide ***(3n-mono)***: According to the general procedure, the reaction mixture was stirred at 100 °C for 24 h. The product was isolated by flash chromatography (PE : EA = 20 : 1, R_f = 0.25) as a white solid, Mp = 63 °C; Yield: 46.6 mg, 51%. ^1H NMR (400 MHz, $CDCl_3$) δ 10.51 (brs, 1H), 8.88 (d, *J* = 7.2 Hz, 1H), 8.75 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.13 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.78 (d, *J* = 8.8 Hz, 1H), 7.54 (dt, *J* = 8.2, 7.6 Hz, 2H), 7.40 (dd, *J* = 8.2, 4.1 Hz, 1H), 7.09 (d, *J* = 2.6 Hz, 1H), 6.96 (dd, *J* = 8.7, 2.6 Hz, 1H), 3.86 (s, 3H), 0.91 – 0.71 (m, 21H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$) δ 166.0, 160.7, 148.2, 139.0, 136.1, 134.8, 131.7, 130.8, 127.9, 127.3, 122.1, 121.6, 121.4, 118.5, 117.1, 114.9, 103.9, 97.2, 55.5, 18.3, 11.1; HRMS (ESI-TOF) m/z Calcd for $C_{28}H_{35}N_2O_2Si^+$ $[M+H]^+$ 459.2462, found 459.2465.

*4-methoxy-N-(quinolin-8-yl)-2,6-bis((triisopropylsilyl)ethynyl)benzamide (**3n-di**)*: According to the general procedure, the reaction mixture was stirred at 100 °C for 24 h. The product was isolated by flash chromatography (PE : EA = 40 : 1, R_f = 0.5) as a white solid, Mp = 108-109 °C; Yield: 23.3 mg, 18%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.05 (brs, 1H), 8.99 (dd, *J* = 7.4, 1.5 Hz, 1H), 8.74 (dd, *J* = 4.1, 1.8 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.58 – 7.50 (m, 2H), 7.42 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.04 (s, 2H), 3.87 (s, 3H), 0.88 (s, 42H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 165.5, 159.2, 147.9, 138.5, 136.9, 136.0, 135.0, 127.7, 127.2, 122.6, 121.3, 121.2, 118.0, 116.9, 103.1, 95.6, 55.6, 18.3, 11.1; HRMS (ESI-TOF) m/z Calcd for $C_{39}H_{55}N_2O_2Si_2^+$ $[M+H]^+$ 639.3797, found 639.3801.

*4-chloro-N-(quinolin-8-yl)-2-((triisopropylsilyl)ethynyl)benzamide (**3o-mono**)*: According to the general procedure, the reaction mixture was stirred at 100 °C for 24 h. The product was isolated by flash chromatography (PE : EA = 20 : 1, R_f = 0.3) as a white solid. Mp = 79-80 °C; Yield: 39.6 mg, 43%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.48 (brs, 1H), 8.87 (dd, *J* = 7.3, 1.6 Hz, 1H), 8.74 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.14 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.72 (d, *J* = 8.4 Hz, 1H), 7.62 – 7.50 (m, 3H), 7.44 – 7.37 (m, 2H), 0.92 – 0.65 (m, 21H). ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 165.3, 148.3, 138.8, 137.5, 136.2, 136.1, 134.4, 133.4, 130.1, 129.0, 127.9, 127.3, 122.3, 122.0, 121.5, 117.2, 102.5, 99.0, 18.3, 11.0; HRMS (ESI-TOF) m/z Calcd for $C_{27}H_{32}ClN_2OSi^+$ $[M+H]^+$ 463.1967, found 463.1962.

*4-chloro-N-(quinolin-8-yl)-2,6-bis((triisopropylsilyl)ethynyl)benzamide (**3o-di**)*: According to the general procedure, the reaction mixture was stirred at 100 °C for 24 h. The product was isolated by flash chromatography (PE : EA = 30 : 1, R_f = 0.5) as a white solid. Mp = 97-98 °C; Yield: 33.7 mg, 26%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.07 (brs, 1H), 8.96 (dd, *J* = 7.0, 2.0 Hz, 1H), 8.75 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.17 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.61 – 7.48 (m, 4H), 7.44 (dd, *J* = 8.3, 4.2 Hz, 1H), 0.87 (s, 42H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 164.7, 148.0, 141.8, 138.4, 136.1, 134.7, 134.5, 132.0, 127.7,

127.2, 123.0, 121.6, 121.4, 117.0, 101.7, 97.6, 18.3, 11.0; HRMS (ESI-TOF) m/z Calcd for $C_{38}H_{52}ClN_2OSi_2^+$ $[M+H]^+$ 643.3301, found 643.3299.

*4-fluoro-2-methyl-N-(quinolin-8-yl)-6-((triisopropylsilyl)ethynyl)benzamide (**3p**)*: According to the general procedure, the reaction mixture was stirred at 100 ^oC for 36 h. The product was isolated by flash chromatography (PE : EA = 20 : 1, R_f = 0.25) as a colorless oil. Yield: 95.05mg, 95%. ^1H NMR (400 MHz, $CDCl_3$) δ 10.09 (brs, 1H), 8.97 (dd, *J* = 7.2, 1.6 Hz, 1H), 8.73 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.14 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.59 – 7.51 (m, 2H), 7.41 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.06 (dd, *J* = 8.9, 2.5 Hz, 1H), 6.93 – 6.87 (m, 1H), 2.44 (s, 3H), 0.86 – 0.62 (m, 21H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$) δ 166.4, 162.0 (d, *J* = 248.8 Hz), 148.1, 138.7 (d, *J* = 8.9 Hz), 138.5, 136.6 (d, *J* = 3.1 Hz), 136.2, 134.6, 127.9, 127.2, 122.8 (d, *J* = 10.3 Hz), 121.9, 121.5, 117.6 (d, *J* = 21.4 Hz), 116.8, 116.8 (d, *J* = 22.9 Hz), 102.7 (d, *J* = 3.2 Hz), 96.4, 19.6, 18.2, 11.0; HRMS (ESI-TOF) m/z Calcd for $C_{28}H_{34}FN_2OSi^+$ $[M+H]^+$ 461.2419, found 461.2422.

*2-methyl-3-(quinolin-8-ylcarbamoyl)-4-((triisopropylsilyl)ethynyl)phenyl acetate (**3q**)*: According to the general procedure, the reaction mixture was stirred at 100 ^oC for 36 h. The product was isolated by flash chromatography (PE : EA = 10 : 1, R_f = 0.15) as a white solid. Mp = 141-142 ^oC; Yield: 81.0 mg, 88%. ^1H NMR (400 MHz, $CDCl_3$) δ 10.13 (brs, 1H), 8.98 (dd, *J* = 7.1, 1.9 Hz, 1H), 8.75 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.62 – 7.51 (m, 2H), 7.48 – 7.39 (m, 2H), 7.08 (d, *J* = 8.4 Hz, 1H), 2.34 (s, 3H), 2.28 (s, 3H), 0.97 – 0.54 (m, 21H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$) δ 168.9, 166.1, 149.4, 148.2, 142.0, 138.5, 136.1, 134.6, 131.4, 128.3, 127.8, 127.2, 123.0, 121.9, 121.5, 118.9, 116.9, 103.2, 95.2, 20.8, 18.2, 13.2, 11.0; HRMS (ESI-TOF) m/z Calcd for $C_{30}H_{37}N_2O_3Si^+$ $[M+H]^+$ 501.2568, found 501.2571.

*2-methyl-N-(quinolin-8-yl)-4-((triisopropylsilyl)ethynyl)nicotinamide (**5a**)*: According to the general

procedure, the reaction mixture was stirred at 120 °C for 36 h. The product was isolated by flash chromatography (PE : EA = 5 : 1, R_f = 0.15) as a yellow oil. Yield: 48.8 mg, 55%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.11 (brs, 1H), 8.95 (dd, *J* = 6.7, 2.3 Hz, 1H), 8.73 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.51 (d, *J* = 5.2 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.62 – 7.51 (m, 2H), 7.43 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.30 – 7.21 (m, 1H), 2.68 (s, 3H), 0.90 – 0.51 (m, 21H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 165.6, 156.0, 149.3, 148.2, 138.4, 136.2, 134.4, 134.1, 129.0, 127.8, 127.3, 123.7, 122.1, 121.6, 117.0, 101.3, 101.1, 22.7, 18.2, 10.9; HRMS (ESI-TOF) m/z Calcd for $C_{27}H_{34}N_3OSi^+$ $[M+H]^+$ 444.2466, found 444.2466.

N-(quinolin-8-yl)-7-((triisopropylsilyl)ethynyl)quinoxaline-6-carboxamide (***5b***): According to the general procedure, the reaction mixture was stirred at 120 °C for 36 h. The product was isolated by flash chromatography (PE : EA = 5 : 1, R_f = 0.15) as a yellow solid. Mp = 175-176 °C; Yield: 65.3 mg, 68%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.52 (brs, 1H), 8.97 (dd, *J* = 7.3, 1.6 Hz, 1H), 8.90 (dd, *J* = 9.4, 1.8 Hz, 2H), 8.75 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.51 (d, *J* = 4.8 Hz, 1H), 8.39 (d, *J* = 3.0 Hz, 1H), 8.18 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.63 – 7.56 (m, 2H), 7.44 (dd, *J* = 8.3, 4.2 Hz, 1H), 0.97 – 0.79 (m, 21H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 165.0, 148.3, 146.7, 146.1, 143.0, 142.2, 140.3, 138.7, 136.3, 135.2, 134.4, 129.7, 127.9, 127.3, 122.5, 122.2, 121.6, 117.2, 102.8, 99.9, 18.3, 11.1; HRMS (ESI-TOF) m/z Calcd for $C_{29}H_{33}N_4OSi^+$ $[M+H]^+$ 481.2418, found 481.2414.

N-(quinolin-8-yl)-2-((triisopropylsilyl)ethynyl)benzo[b]thiophene-3-carboxamide (***5c***): According to the general procedure, the reaction mixture was stirred at 100 °C for 24 h. The product was isolated by flash chromatography (PE : EA = 10 : 1, R_f = 0.25) as a pink solid. Mp = 84-85 °C; Yield: 69.7 mg, 72%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.66 (brs, 1H), 8.95 (dd, *J* = 7.5, 1.4 Hz, 1H), 8.77 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.36 – 8.31 (dd, *J* = 8.3, 1.6 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.78 – 7.73 (m, 1H), 7.65 – 7.53 (m, 2H), 7.46 – 7.40 (m, 3H), 1.01 – 0.76 (m, 21H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ

161.6, 148.3, 139.0, 138.9, 137.2, 136.2, 135.6, 134.5, 128.0, 127.3, 126.4, 125.5, 124.9, 124.4, 122.0, 121.6, 121.5, 117.4, 105.3, 97.4, 18.3, 11.0; HRMS (ESI-TOF) m/z Calcd for $C_{29}H_{33}N_2OSSi^+$ $[M+H]^+$ 485.2077, found 485.2082.

*1-methyl-N-(quinolin-8-yl)-4-((triisopropylsilyl)ethynyl)-1H-pyrazole-5-carboxamide (**5d**)*: According to the general procedure, the reaction mixture was stirred at 120 °C for 36 h. The product was isolated by flash chromatography (PE : EA = 5 : 1, R_f = 0.3) as a red oil. Yield: 52.7 mg, 61%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.62 (brs, 1H), 8.77 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.70 (t, *J* = 4.5 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.64 (s, 1H), 7.56 (d, *J* = 4.6 Hz, 2H), 7.42 (dd, *J* = 8.3, 4.2 Hz, 1H), 4.15 (s, 3H), 0.99 – 0.75 (m, 21H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$) δ 157.6, 148.7, 141.7, 139.3, 137.7, 136.3, 134.0, 128.0, 127.1, 122.8, 121.7, 118.3, 104.6, 97.6, 96.5, 39.7, 18.5, 11.2; HRMS (ESI-TOF) m/z Calcd for $C_{25}H_{33}N_4OSi^+$ $[M+H]^+$ 433.2418, found 433.2417.

*2-methyl-N-(quinolin-8-yl)-5-((triisopropylsilyl)ethynyl)thiazole-4-carboxamide (**5e**)*: According to the general procedure, the reaction mixture was stirred at 120 °C for 36 h. The product was isolated by flash chromatography (PE : EA = 10 : 1, R_f = 0.3) as a yellow solid. Mp = 82-83 °C; Yield: 29.7 mg, 33%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.77 (brs, 1H), 8.80 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.65 (t, *J* = 4.5 Hz, 1H), 8.17 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.60 – 7.55 (m, 2H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 2.73 (s, 3H), 1.02 – 0.87 (m, 21H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$) δ 168.4, 158.7, 148.5, 139.2, 138.3, 136.3, 135.1, 133.9, 128.0, 127.1, 122.7, 121.5, 118.7, 99.5, 98.9, 19.6, 18.4, 11.1; HRMS (ESI-TOF) m/z Calcd for $C_{25}H_{32}N_3OSSi^+$ $[M+H]^+$ 450.2030, found 450.2028.

*N-(quinolin-8-yl)-2-((triisopropylsilyl)ethynyl)cyclohex-1-ene-1-carboxamide (**7a**)*: According to the general procedure, the reaction mixture was stirred at 100 °C for 24 h. The product was isolated by flash chromatography (PE : EA = 10 : 1, R_f = 0.3) as a white solid. Mp = 81-82 °C; Yield: 74.4 mg,

86%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.31 (s, 1H), 8.84 (dd, *J* = 7.3, 1.4 Hz, 1H), 8.80 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.59 – 7.48 (m, 2H), 7.43 (dd, *J* = 8.2, 4.2 Hz, 1H), 2.53 (brs, 2H), 2.38 (brs, 2H), 1.79 – 1.67 (m, 4H), 0.82 – 0.66 (m, 21H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 168.0, 148.1, 141.4, 138.8, 136.3, 134.6, 128.0, 127.4, 121.7, 121.6, 121.4, 117.2, 105.3, 97.0, 31.2, 26.5, 21.9, 21.6, 18.3, 11.0; HRMS (ESI-TOF) m/z Calcd for $C_{27}H_{37}N_2OSi^+$ $[M+H]^+$ 433.2670, found 433.2673.

*N-(quinolin-8-yl)-6-((triisopropylsilyl)ethynyl)-3,4-dihydro-2H-pyran-5-carboxamide (7**b**)*: According to the general procedure, the reaction mixture was stirred at 100 °C for 24 h. The product was isolated by flash chromatography (PE : EA = 20 : 1, R_f = 0.35) as a white solid. Mp = 60-61 °C; Yield: 66.9 mg, 77%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.30 (brs, 1H), 8.79 – 8.72 (m, 2H), 8.13 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.54 – 7.45 (m, 2H), 7.41 (dd, *J* = 8.2, 4.2 Hz, 1H), 4.13 – 4.08 (m, 2H), 2.55 (t, *J* = 6.5 Hz, 2H), 1.98 – 1.90 (m, 2H), 0.84 – 0.55 (m, 21H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 166.6, 148.1, 139.1, 138.8, 136.2, 134.7, 127.9, 127.3, 121.4, 121.3, 118.1, 117.0, 99.1, 97.6, 66.7, 22.2, 21.1, 18.12, 10.9; HRMS (ESI-TOF) m/z Calcd for $C_{26}H_{35}N_2O_2Si^+$ $[M+H]^+$ 435.2462, found 435.2461.

*(Z)-2-methyl-N-(quinolin-8-yl)-5-(triisopropylsilyl)pent-2-en-4-ynamide (7**c**)*: According to the general procedure, the reaction mixture was stirred at 100 °C for 36 h. The product was isolated by flash chromatography (PE : EA = 20 : 1, R_f = 0.3) as a white solid, Mp = 109-110 °C; Yield: 61.2 mg, 78%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.40 (brs, 1H), 8.84 – 8.74 (m, 2H), 8.13 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.56 – 7.48 (m, 2H), 7.41 (dd, *J* = 8.2, 4.2 Hz, 1H), 5.93 (d, *J* = 1.6 Hz, 1H), 2.14 (d, *J* = 1.6 Hz, 3H), 0.83 – 0.66 (m, 21H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 166.4, 148.2, 145.7, 138.9, 136.1, 134.3, 127.9, 127.3, 121.8, 121.4, 117.2, 111.2, 102.0, 98.7, 20.3, 18.2, 11.0; HRMS (ESI-TOF) m/z Calcd for $C_{24}H_{33}N_2OSi^+$ $[M+H]^+$ 393.2357, found 393.2354.

*(Z)-3-ethyl-2-methyl-N-(quinolin-8-yl)-5-(triisopropylsilyl)pent-2-en-4-ynamide (**7d**)*: According to the general procedure, the reaction mixture was stirred at 100 °C for 36 h. The product was isolated by flash chromatography (PE : EA = 20 : 1, R_f = 0.25) as a pink solid, Mp = 45 °C; Yield: 46.2 mg, 55%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.24 (brs, 1H), 8.84 (dd, *J* = 7.3, 1.6 Hz, 1H), 8.79 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.14 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.56 – 7.48 (m, 2H), 7.42 (dd, *J* = 8.2, 4.2 Hz, 1H), 2.35 (q, *J* = 7.5 Hz, 2H), 2.09 (d, *J* = 0.5 Hz, 3H), 1.22 (t, *J* = 7.5 Hz, 3H), 0.82 – 0.61 (m, 21H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 168.8, 148.1, 138.9, 138.8, 136.1, 134.6, 127.9, 127.3, 125.4, 121.5, 121.3, 116.9, 104.8, 97.3, 26.5, 18.2, 15.7, 12.3, 11.0; HRMS (ESI-TOF) m/z Calcd for $C_{26}H_{37}N_2OSi^+$ $[M+H]^+$ 421.2670, found 421.2674.

Gram Scale Reaction and Further Conversion

In a glove box, $NiCl_2$ (10 %, 52 mg), Na_2CO_3 (5.0 equiv., 2.12 g) and **1f** (4.0 mmol, 1.13 g) were added to a 100 mL Schlenk tube equipped with a stir bar. The vessel was evacuated and filled with nitrogen (three cycles). 40 mL toluene, 300 μL BDMAE and 4.8 mmol TIPS-substituted bromoalkyne was added under nitrogen atmosphere. The reaction mixture was stirred at 100 °C for 24h. Then the reaction was diluted with EtOAc and filtered through silica gel with copious washings. Purification of the crude product by flash chromatography (PE : EA = 10 : 1, R_f = 0.3) on silica gel afforded **3f** with 75% yield.

*5-chloro-2-((triisopropylsilyl)ethynyl)benzaldehyde (**8a**)*: In a glove box, **3f** (1 mmol), Cp_2ZrHCl (2 mmol), and THF (10 mL) were added to a 25 mL Schlenk tube. The reaction mixture was stirred at room temperature for 6 h before carefully quenched by saturated ammonium chloride at 0 °C. After extracted with CH_2Cl_2 (3×25 mL), the combined organic extract was washed with brine, dried over $MgSO_4$ and concentrated in vacuum. Purification of the crude product by flash chromatography (PE :

EA = 50 : 1, R_f = 0.5) on silica gel afforded **8a** as colorless oil with 82% yield (52.5 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.53 (s, 1H), 7.99 – 7.68 (m, 1H), 7.63 – 7.42 (m, 2H), 1.20 – 1.12 (m, 21H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$) δ 190.4, 137.2, 135.2, 135.1, 133.7, 126.9, 125.3, 100.8, 100.5, 18.6, 11.2; HRMS (ESI-TOF) m/z Calcd for $C_{18}H_{26}ClOSi^+$ $[M+H]^+$ 321.1436, found 321.1438.

*methyl 5-bromo-2-((triisopropylsilyl)ethynyl)benzoate (**8b**)*: To a 10 mL Kontes flask equipped with a stir bar was added **3g** (0.3 mmol, 1 equiv.). Inside the glove box, dry methanol (4 mL) was added to the flask. Outside the glove box, $BF_3{\cdot}Et_2O$ (0.25 mL) was added dropwise to the stirred solution. The resulting mixture was stirred at 100 °C for 24 h. After cooling to rt, Et_3N (4 mL) was added dropwise to the reaction mixture with stirring, then concentrated in vacuo. Purification of the crude product by flash chromatography (PE : EA = 100 : 1, R_f = 0.6) on silica gel afforded **8a** as colorless oil with 72% yield (56.8 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 2.1 Hz, 1H), 7.60 (dd, J = 8.3, 2.1 Hz, 1H), 7.49 (d, J = 8.3 Hz, 1H), 3.96 (s, 3H), 1.22 – 1.13 (m, 21H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$) δ 165.7, 136.2, 134.4, 133.9, 133.1, 122.3, 121.9, 104.0, 98.0, 52.5, 18.6, 11.3; HRMS (ESI-TOF) m/z Calcd for $C_{19}H_{28}BrO_2Si^+$ $[M+H]^+$ 395.1036, found 395.1032.

*methyl 5-bromo-2-(phenylethynyl)benzoate (**8c**)*: In a glovebox, **8b (**0.2 mmol**)**, iodobenzene (0.3 mmol), $PdCl_2$ (5%, 1.8 mg), CuI (2.5%, 1 mg), TBAF (0.6 mmol), THF (5 mL) were added to a 25 mL Schlenk tube. The reaction mixture was stirred at 50 ^oC for 6 h. Purification of the crude product by flash chromatography (PE : EA = 100 : 1, R_f = 0.5) on silica gel afforded **8a** as colorless oil with 95% yield (59.7 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J = 2.1 Hz, 1H), 7.69 – 7.48 (m, 4H), 7.45 – 7.31 (m, 3H), 3.99 (s, 3H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$) δ 165.3, 135.2, 134.8, 133.5, 133.2, 131.7, 128.8, 128.4, 123.0, 122.7, 121.8, 95.5, 87.3, 52.5; HRMS (ESI-TOF) m/z Calcd for $C_{16}H_{12}BrO_2^+$ $[M+H]^+$ 315.0015, found 315.0017.

Intermolecular Kinetic Isotope Effect (KIE)

In a glove box, $NiCl_2$ (10 %, 2.6 mg), Na_2CO_3 (5.0 equiv., 106 mg), 0.1 mmol **1m** and 0.1 mmol **D-1m** were added to a Schlenk tube equipped with a stir bar. The vessel was evacuated and filled with nitrogen (three cycles). 2.0 mL toluene, 15 μL BDMAE and 0.24 mmol TIPS-substituted bromoalkyne was added in turn under nitrogen atmosphere. The reaction mixture was stirred 100 °C for 1 hour. Then the reaction was diluted with EtOAc, and filtered through silica gel with copious washings (EtOAc). The residue was concentrated, and purified by column chromatography. The product was analyzed by 1H NMR. The corresponding dialkynylation product was not detected. A KIE value of K_H/K_D = 3.2 was obtained.

Intermolecular competition experiment

In a glove box, $NiCl_2$ (10 %, 2.6 mg), Na_2CO_3 (5.0 equiv., 106 mg), 0.24 mmol **1d** and 0.24 mmol **1e** were added to a Schlenk tube equipped with a stir bar. The vessel was evacuated and filled with nitrogen (three cycles). 2.0 mL toluene, 15 μL BDMAE and 0.20 mmol TIPS-substituted bromoalkyne was added in turn under nitrogen atmosphere. The reaction mixture was stirred 100 °C for 4 hours. Then the reaction was diluted with EtOAc and filtered through silica gel with copious washings (EtOAc). The residue was concentrated, and purified by column chromatography. **3d** was yield 31.7 mg (32%). **3e** was yield 8.2 mg (9%).

Radical trapping experiment

In a glove box, $NiCl_2$ (10 %, 2.6 mg), Na_2CO_3 (5.0 equiv., 106 mg), 0.20 mmol of **1a** , and 0.6 mmol of TEMPO (3.0 equiv. 94 mg) were added to a Schlenk tube equipped with a stir bar. The vessel was evacuated and filled with nitrogen (three cycles). 2.0 mL toluene, 15 μL BDMAE and 0.24 mmol TIPS-substituted bromoalkyne was added in turn under nitrogen atmosphere. The reaction mixture was

stirred 100 °C for 24 hours. Then the reaction was diluted with EtOAc, filtered through silica gel with copious washings (EtOAc). The residue was concentrated, and purified by column chromatography. **3a** was yield 76 mg (86%).

ASSOCIATED CONTENT

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Notes

We declare no competing financial interest.

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Supporting Information.

Characterization data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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