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

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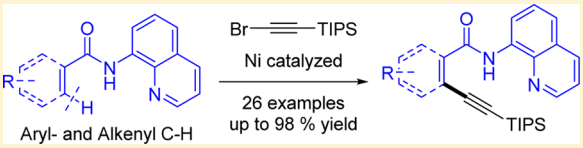
Supporting Information

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 was found 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 an aryl moiety through a Sila−Sonogashira coupling reaction. This Ni-catalyzed alkynylation procedure provides an alternative approach to construct a C(sp^2)−C(sp) bond.

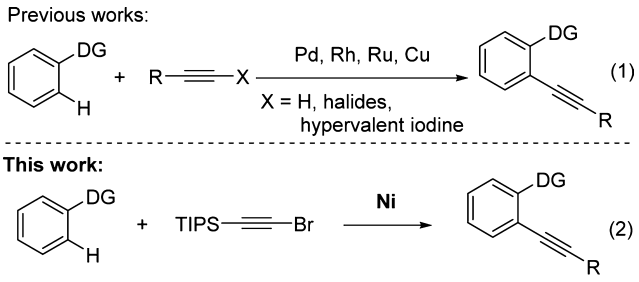


INTRODUCTION

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]

Alkyne motifs are ubiquity in pharmaceuticals, materials, and other functional compounds.[4] It is known that the Sonogashira coupling reaction is the classical choice to synthesize aryl alkynes,[5] but 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] and 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 the 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 worth noting 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.

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



In recent years, nickel has emerged as a promising catalyst for C−H functionalization; pioneering works developed by Chatani, Ge, Ackermann, You, Shi, Zeng, and Zhang have greatly broadened the reaction type.[10,11] However, unfortunately, most of these methods have limitations such as high reaction temperature (>140 °C) and limited substrate scope. Thus, it is highly desirable to develop a new synthetic strategy procedure based on nonprecious 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 a 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).

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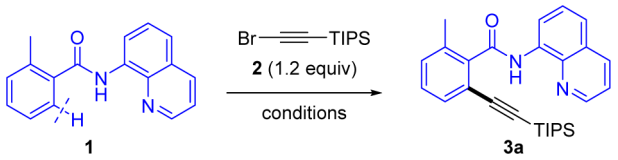
RESULTS AND DISSCUSION

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 the 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 gave even 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 °C (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 a nearly quantitative product yield (entry 11). As expected, no product was detected in the absence of $NiCl_2$ or BDMAE (entries 12 and 13), indicating the 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)$_2$) was 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 and 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 (entries 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 a similar flexible skeleton (TMEDA) showed better performance than the corresponding tridentate-nitrogen ligand (PMTDA), possibly due to the suitable coordination ability to nickel catalysis (entry 21). However, the bidentate nitrogen ligand with a rigid skeleton gave poor reactivity (entries 22 and 23). When all nitrogen ligands were replaced by corresponding structurally similar pure oxygen ligands, the yields were obviously reduced (entries 24 and 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 24 h under an argon atmosphere. [b]Yield was calculated based on **1**. [c]Conditions: 40 mol % ligand, 5.0 equiv of Na_2CO_3. [d]At 100 °C. OTf = trifluoromethanesulfonate, 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 (Scheme 2). To our delight, the 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 monoselectivity 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 chances for further modification of the products (**3f, 3g, 3h**). Surprisingly, the nitro group which was scarcely tolerated in the nickel-catalyzed reactions was also compatible with the present transformation (**3i**).[15] The acetyl group, which was sensitive to strong base, also retained a good yield (**3j**). Ortho-fluoride-substituted benzamide gave a moderate yield of the expected (**3k**). In addition, alkynylation of the corresponding 2-naphthamide smoothly occurred at the less hindered position, affording **3l** in 88% yield. When the para-substituted substrates were used, a small amount of dialkynylation products was 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**).

Encouraged by these results, we turned our interest to heterocyclic substrates which were common motifs in medicinal chemistry (Scheme 3).[16] To our delight, alkynylation of heteroaromatic amides with pyridine, quinoxaline, benzothiophene, pyrazole, and thiazole moieties all gave the corresponding products with synthetically useful yields (**5a**−**5e**, 33−72%). Interestingly, strongly coordinating heteroatoms like sulfur and

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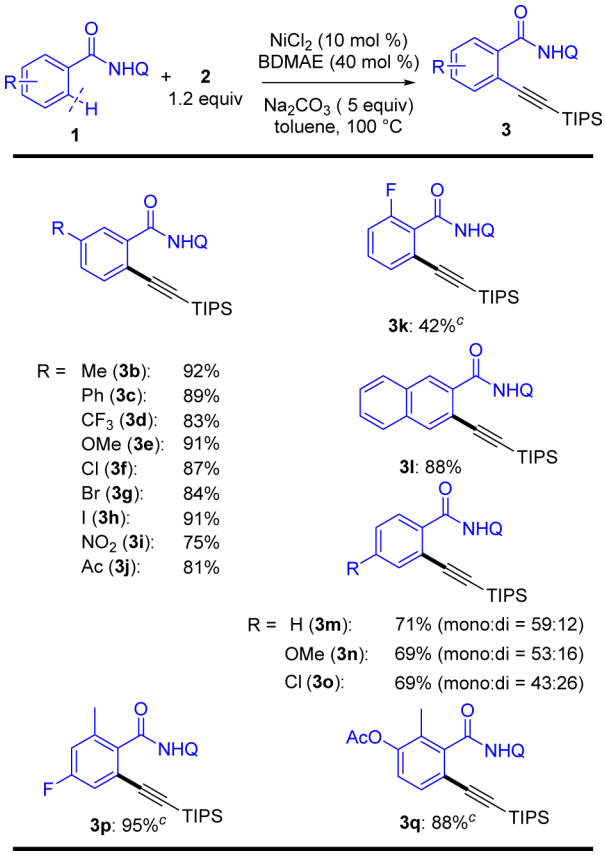
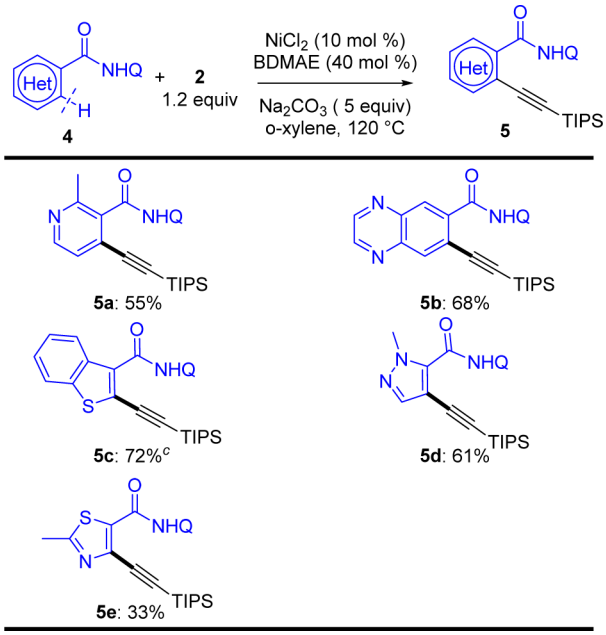
Scheme 2. Scope of Aromatic Amides[a,b]



[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]Thirty six hours.

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

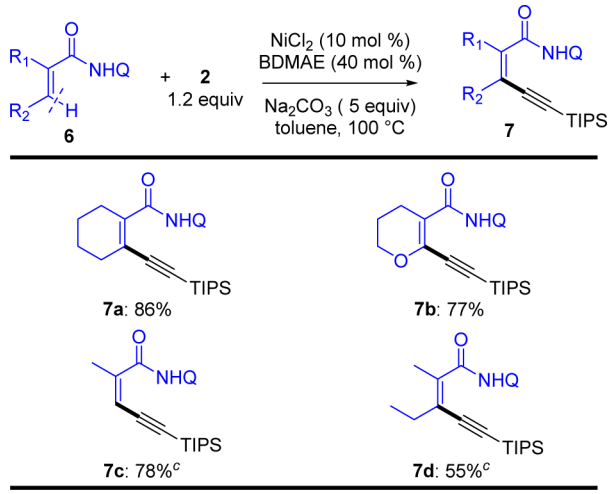


[a]Condition B: **4** (0.2 mmol), 2 (1.2 equiv), $NiCl_2$ (10 mol %), BDMAE (40 mol %), Na_2CO_3 (5.0 equiv), *o*-xylene (2 mL), 120 °C, 36 h. [b]Yield was calculated based on **4**. [c]Toluene (2 mL), 100 °C, 24 h.

nitrogen have no interference in the reaction. Because of the good compatibility of heterocyclic substrates, this method has potential application in pharmaceutical chemistry.

Compared with the above-mentioned arylamide, 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 Scheme 4, the present

Scheme 4. Scope of Alkenylamides[a,b]

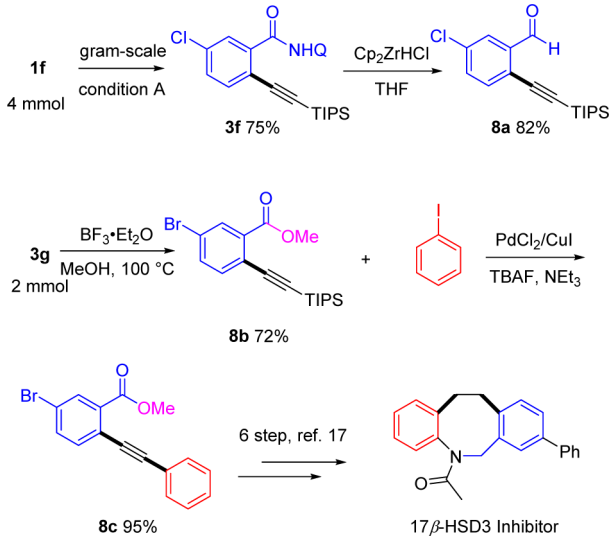


[a]Condition C: **6** (0.2 mmol), **2** (1.2 equiv), $NiCl_2$ (10 mol %), BDMAE (40 mol %), Na_2CO_3 (5.0 equiv), toluene (2 mL), 100 °C, 24 h. [b]Yield was calculated based on **6**. [c]Thirty six hours.

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**). However, the substituent at the α carbon was essential for the reactivity of the substrate. Otherwise, no alkynylation reaction occurred.

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

Scheme 5. Gram-Scale Reaction and Further Conversion



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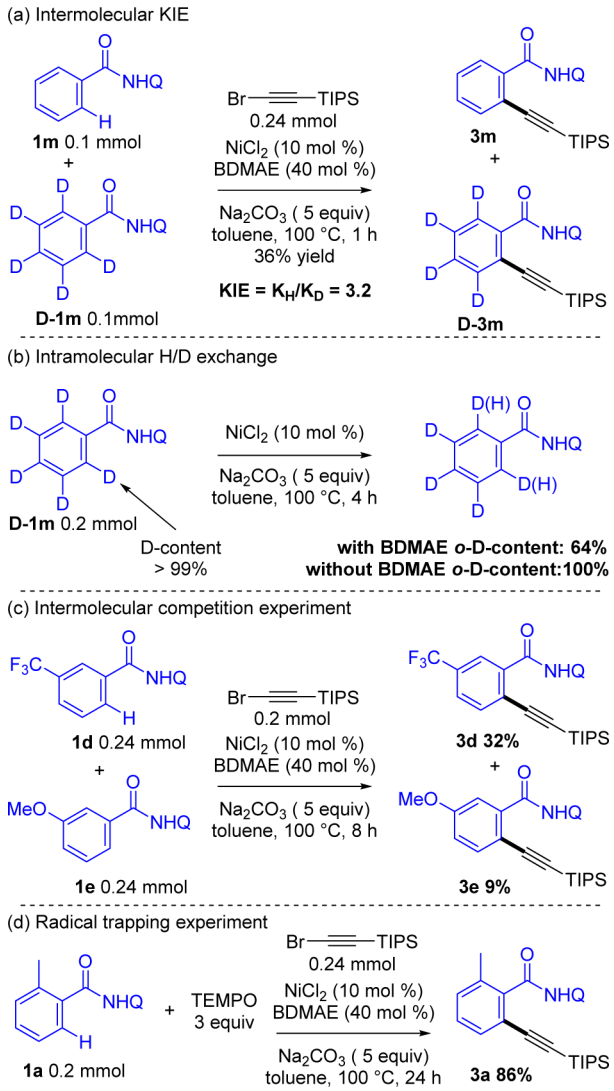
condition. Next, conversion of the directing amide group was also illustrated by treating **3f** with Schwartz's reagent, providing the corresponding aldehyde **8a** in 82% yield. On the other hand, the amide moiety of **3g** could also transfer to ester **8b** by reaction with $BF_3{\cdot}Et_2O$ and MeOH in 72% yield. Subsequently, the TIPS could be easily converted to a 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 17β-hydroxysteroid dehydrogenase type-3 (17β-HSD3) inhibitor, which was considered to be a clinical candidate for treatment of prostate cancer.[17]

To probe the mechanism of the reaction, some deuterium-labeling experiments were carried out as shown in Scheme 6. A

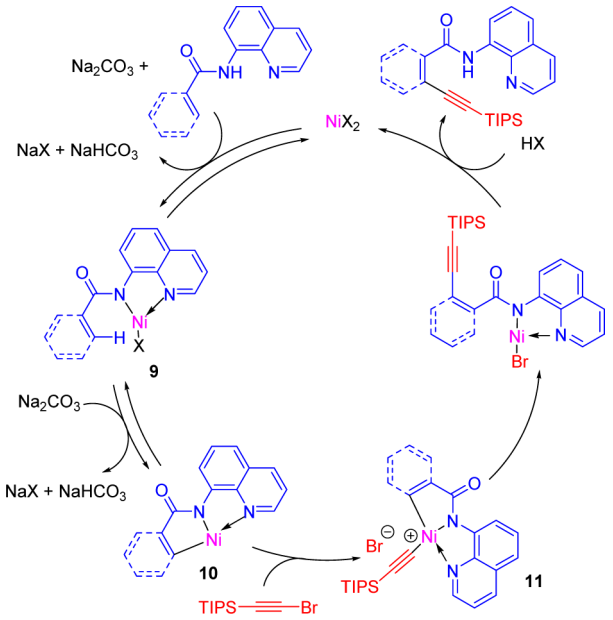
Scheme 6. Mechanistic Experiments



significant intermolecular kinetic isotope effect (KIE = 3.2) was observed (Scheme 6a),[18] indicating 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 the N–H bond of the amide and its ortho C–H bonds with chelation assistance was observed in the absence of TIPS-substituted bromoalkyne (Scheme 6b). These two control experiments suggest that rapid and reversible cleavage of C–H bonds is involved in the process. In addition, a competition experiment with a different electronic substituent shows that the reaction favors the electron-withdrawing group (Scheme 6c). The electronic effect of substituents and high KIE value both indicate that cleavage of the ortho C–H bond may experience a concerted metalation–deprotonation (CMD) mechanism.[10c,f,19] Furthermore, no obvious yield change was observed, although 3.0 equiv of TEMPO was added (Scheme 6c), indicating the single-electron transfer (SET) in this reaction could be ruled out. On the basis of our investigations and the reported results, it is believed that the BDMAE ligand may have 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,[15,20] which could be seen from the obvious catalytic difference of the 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 exchange occurred without BDMAE (Scheme 6b).

On the basis of the above investigations and previous reports,[13] we propose a plausible mechanism as shown in Scheme 7. Initially coordination of amide to nickel catalyst was

Scheme 7. Proposed Reaction Mechanism



followed by ligand exchange to form complex **9**, which could go through cyclometalation to give intermediate **10**; 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.

CONCLUSIONS

We developed a Ni-catalyzed direct C–H alkynylation via a bidentate chelation strategy using BDMAE as an additional ligand, which significantly promoted 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 the single-electron transfer route is less possible. This method

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provided a new approach to synthesize aryl- and alkenylalkynes and may also inspire useful ideas for development of Ni-catalyzed C−H functionalization.

EXPERIMENT SECTION

General Information. Solvents and chemicals were used as received. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer at 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 precoated silica gel plates. After elution, the 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 the literature. 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 Schemes 2, 3, and 4. In a glovebox, $NiCl_2$ (10%, 2.6 mg), Na_2CO_3 (5.0 equiv, 106 mg), and 0.2 mmol of the 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). A 0.2 mmol amount of amide (if liquid), 2.0 mL of solvent, 15 μL of BDMAE, and 0.24 mmol of TIPS-substituted bromoalkyne was added in turn under nitrogen atmosphere. The reaction mixture was stirred for a 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 °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 °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 °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{^{1}H} 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{^{1}H} 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.

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*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{^{1}H} 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%. ^{1}H 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{^{1}H} 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%. ^{1}H 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{^{1}H} 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 °C for 36 h. The product was isolated by flash chromatography (PE:EA = 20:1, R_f = 0.25) as a colorless oil. Yield: 95.05 mg, 95%. ^{1}H 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{^{1}H} 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

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reaction mixture was stirred at 100 °C 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 °C. Yield: 81.0 mg, 88%. ^{1}H 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{^{1}H} 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{^{1}H} 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{^{1}H} 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 (**7b**).* 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 (**7c**).* 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 glovebox, $NiCl_2$ (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). A 40 mL amount of toluene, 300 μL of BDMAE, and 4.8 mmol of TIPS-substituted bromoalkyne were added under a nitrogen atmosphere. The reaction mixture was stirred at 100 °C for 24 h. 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 glovebox, **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 being quenched by saturated ammonium chloride at 0 °C. After being 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)

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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 glovebox, dry methanol (4 mL) was added to the flask. Outside the glovebox, $BF_3{\cdot}Et_2O$ (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 and 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 a 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), and THF (5 mL) were added to a 25 mL Schlenk tube. The reaction mixture was stirred at 50 °C 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 a 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 glovebox, $NiCl_2$ (10%, 2.6 mg), Na_2CO_3 (5.0 equiv, 106 mg), 0.1 mmol of **1m**, and 0.1 mmol of **D-1m** were added to a Schlenk tube equipped with a stir bar. The vessel was evacuated and filled with nitrogen (three cycles). A 2.0 mL amount of toluene, 15 μL of BDMAE, and 0.24 mmol of TIPS-substituted bromoalkyne were added in turn under nitrogen atmosphere. The reaction mixture was stirred 100 °C for 1 h. 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 ^{1}H 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 glovebox, $NiCl_2$ (10%, 2.6 mg), Na_2CO_3 (5.0 equiv, 106 mg), 0.24 mmol of **1d**, and 0.24 mmol of **1e** were added to a Schlenk tube equipped with a stir bar. The vessel was evacuated and filled with nitrogen (three cycles). A 2.0 mL amount of toluene, 15 μL of BDMAE, and 0.20 mmol of TIPS-substituted bromoalkyne were added in turn under a nitrogen atmosphere. The reaction mixture was stirred 100 °C for 4 h. 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**: yield 31.7 mg (32%). **3e**: yield 8.2 mg (9%).

Radical Trapping Experiment. In a glovebox, $NiCl_2$ (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). A 2.0 mL amount of toluene, 15 μL of BDMAE, and 0.24 mmol of TIPS-substituted bromoalkyne were added in turn under a nitrogen atmosphere. The reaction mixture was stirred at 100 °C for 24 h. 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. **3a**: yield 76 mg (86%).

■ ASSOCIATED CONTENT

Supporting Information

Characterization data of all new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00669.

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Notes

The authors declare no competing financial interest.

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