

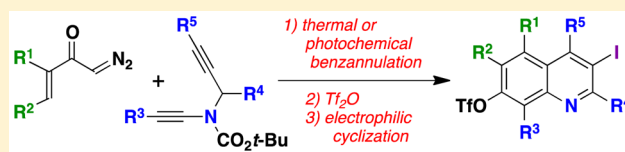
Synthesis of Highly Substituted Quinolines via a Tandem Ynamide Benzannulation/Iodocyclization Strategy

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S Supporting Information

ABSTRACT: A two-stage “tandem strategy” for the regiocontrolled synthesis of very highly substituted quinolines is described. Benzannulation based on the reaction of cyclobutenones or diazo ketones with *N*-propargyl-substituted ynamides proceeds via a cascade of several pericyclic reactions to generate multiply substituted aniline derivatives. In the second stage of the tandem strategy, triflate derivatives of the phenolic benzannulation products undergo Larock cyclization upon exposure to iodine to form products that are further elaborated by methods such as palladium-catalyzed coupling to generate quinolines that can be substituted at every position of the bicyclic system.



INTRODUCTION

The introduction of the Woodward–Hoffmann rules¹ 50 years ago provided chemists for the first time with a unified framework for understanding the disparate processes that have come to be known as pericyclic reactions.² This new theoretical model played a key role in enabling the extensive application of pericyclic reactions in the chemical synthesis of complex molecules. Cascades of pericyclic reactions³ afford a particularly effective strategy for the rapid assembly of complex organic compounds, and the design and invention of new synthetic methods based on pericyclic cascade processes has been a particular goal of research in our laboratory. Cascades involving cycloadditions, electrocyclic reactions, and sigma-tropic rearrangements based on vinyl- and dienylketenes have been one focus of our research in this area,^{4,5} and herein we describe the application of a pericyclic cascade process in a strategy for the regiocontrolled synthesis of very highly substituted quinolines.

The quinoline ring system is found in the structure of numerous natural products, pharmaceutical agents, advanced materials, and commercially significant compounds.⁶ The importance of quinolines as synthetic targets has stimulated the development of numerous useful methods,⁷ most of which involve the cyclization or annulation of aniline derivatives with formation of the nitrogen heterocyclic ring.⁸ While these methods are generally effective for the synthesis of quinolines bearing multiple substituents on the heterocyclic ring, the synthesis of quinolines that bear a high level of substitution on the benzenoid ring remains a formidable challenge.⁹

RESULTS AND DISCUSSION

The challenges associated with the efficient preparation of highly substituted quinolines derive in many cases from the difficulties associated with the regiocontrolled synthesis of the requisite polysubstituted aniline precursors. Convergent benzannulation strategies¹⁰ provide an exceptionally attractive

approach for the regiocontrolled construction of multiply substituted benzenoid aromatic systems. Our laboratory has developed two complementary benzannulation strategies^{5,11,12} based on the reaction of alkynes and vinylketenes,¹³ and recently we have extended this chemistry to include ynamides as benzannulation partners in tandem benzannulation/cyclization strategies leading to several classes of polycyclic carbocyclic and heterocyclic compounds.¹⁴

For the synthesis of highly substituted quinolines, we envisioned the two-stage “tandem” strategy outlined in Scheme 1 which would begin with benzannulation employing *N*-propargyl ynamides of general type 3. In the second stage of the tandem strategy, exposure of the *N*-propargyl aniline benzannulation products (4) to a suitable electrophilic reagent (“X⁺”) such as molecular iodine would afford dihydroquinolines that would be easily oxidized to quinolines. As a bonus, trifluoromethylsulfonation of the phenolic hydroxyl group could provide a useful handle for the further elaboration of the quinoline products at C-7 by employing well-established transition-metal-catalyzed coupling reactions.

Operationally the vinylketene-based benzannulation outlined in Scheme 1 involves a single synthetic step, but mechanistically it proceeds via a “cascade” involving up to four discrete pericyclic transformations. In the original version of the benzannulation, thermolysis or irradiation of a cyclobutenone serves as the triggering step for the cascade, effecting reversible four-electron electrocyclic ring opening to produce the transient vinylketene intermediate 6. This vinylketene is immediately intercepted by the ynamide reaction partner in a regioselective [2 + 2] cycloaddition that affords a new cyclobutenone, 7. Under the conditions of the reaction, this

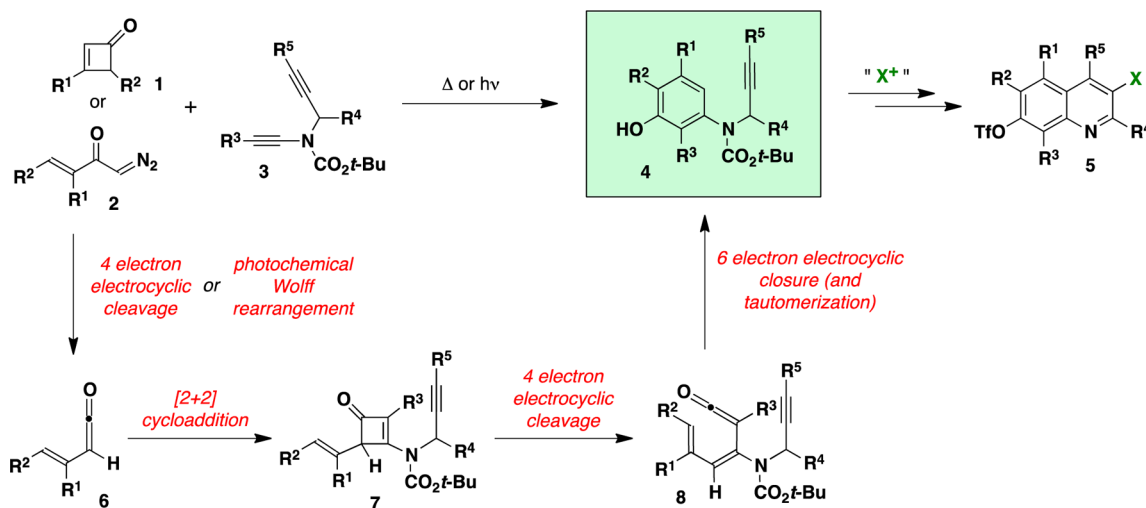
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Scheme 1. Tandem Benzannulation-Electrophilic Cyclization Strategy for the Synthesis of Quinolines

Table 1. Synthesis of Ynamides via Copper-Catalyzed Alkynylation of Carbamates^a

entry	propargyl carbamate		R ³	alkynyl bromide	ynamide	yield (%) ^b	
	R ¹	R ²					
1	Ph	H	9 ^c	Hex	12	14	80
2	CH ₃	H	10 ^d	Hex	12	15	83
3	isopropenyl	CH ₃	11 ^e	(CH ₂) ₂ OTBS	13	16	59–68

^aConditions: carbamate (1.0 equiv), alkynyl bromide (1.2 equiv), CuSO₄·5H₂O (0.2 equiv), 1,10-phenanthroline (0.4 equiv), K₃PO₄ (2.0 equiv), toluene, 80–85 °C, 49–70 h. ^bIsolated yield of products purified by column chromatography. ^cFor the preparation of 9 see ref 23. ^dFor the preparation of 10 see ref 24. ^eFor the preparation of 11, see the Experimental Section.

intermediate undergoes reversible four-electron electrocyclic ring opening to generate the dienylketene 8, which rapidly cyclizes via 6- π electrocyclic ring closure to furnish the desired *N*-propargyl aniline benzannulation product 4 following tautomerization. In an alternate "second-generation" version of the strategy, photochemical Wolff rearrangement of α -diazo ketones of type 2 serves as the triggering step for the benzannulation, generating vinylketene intermediates 6 which then participate in the same cascade of pericyclic reactions involved in the cyclobutenone version.

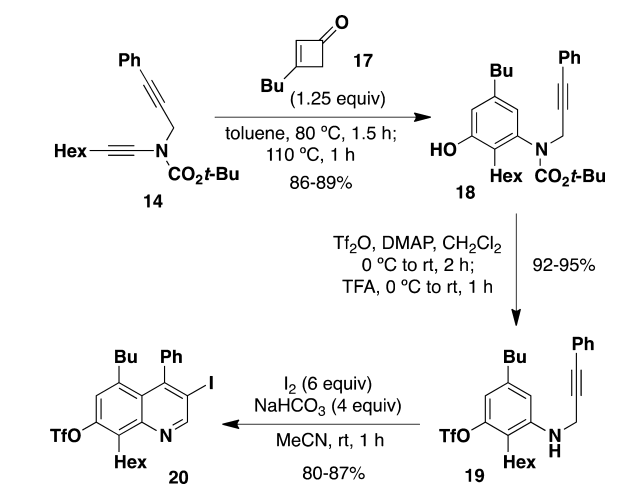
At the outset of our investigation we recognized that in order for the strategy outlined in Scheme 1 to be successful, it would be necessary that the vinylketene [2 + 2] cycloaddition proceed chemoselectively at the more electron-rich ynamide triple bond in 3 in the presence of the propargylic alkyne and any other unsaturated moieties in the reaction substrates. Efficient benzannulation would also require that the *N*-propargyl ynamide be stable under the thermal and photochemical reaction conditions and not be diverted by competing processes such as [3,3]-sigmatropic rearrangement.^{15,16} Finally, success would also depend on the rate of 6- π electrocyclic ring closure of 8 being faster than alternative reactions such as intramolecular [2 + 2] cycloaddition of the ketene with the pendant alkyne.

Synthesis of Benzannulation Reaction Partners. The synthesis of the benzannulation partners employed in our investigation was conveniently accomplished using previously

developed methods. Cyclobutenones are available in 1–2 steps via ketene-alkyne cycloadditions,¹⁷ and the α,β -unsaturated diazo ketones that serve as vinylketene precursors were prepared by employing the detrifluoroacetylative diazo transfer protocol previously developed in our laboratory.¹⁸ For the synthesis of ynamides,¹⁹ we employed the closely related copper-promoted *N*-alkynylation methods pioneered in our laboratory²⁰ and the laboratory of Hsung.²¹ Both methods involve the reaction of amine derivatives with alkynyl bromides, which are themselves readily obtained from terminal alkynes (or silyl alkynes) by reaction with NBS in the presence of catalytic silver nitrate.²² Table 1 summarizes the synthesis of *N*-propargyl ynamides 14, 15, and 16 from propargyl carbamates 9–11. In the case of these *N*-propargyl ynamides, we found that slightly better yields were obtained by employing the Hsung protocol.

Cyclobutenone-Based Quinoline Synthesis. The feasibility of employing *N*-propargyl ynamides in the cyclobutenone version of the benzannulation was examined by using readily available 3-butylcyclobutenone (17)¹⁷ as the vinylketene precursor. As expected from our previous studies with *N*-allyl ynamides,^{14a,b} the optimal conditions for benzannulation with *N*-propargyl ynamide 14 were found to involve a staged heating protocol as outlined in Scheme 2. This procedure minimizes [3,3]-sigmatropic rearrangement of the 1,5-diyne moiety which occurs at temperatures above ca. 125 °C. In our optimized benzannulation protocol, initial thermolysis was performed at

Scheme 2. Feasibility of the Tandem Benzannulation/Iodocyclization Strategy



80 °C until all of the ynamide was consumed. This led to a mixture of the desired benzannulation product and intermediate 4-vinylcyclobutenone (i.e., **7** in Scheme 1). Further heating at 110 °C then converted the remaining vinylcyclobutenone to the desired phenol product. As predicted, ketene [2 + 2] cycloaddition occurred chemoselectively at the electron-rich ynamide π bond, and no products resulting from competitive reaction at the other triple bond were detected.

The next stage of our proposed tandem strategy called for electrophilic cyclization of the *N*-propargyl aniline benzannulation products to generate the nitrogen heterocyclic ring. After considering several alternatives, we decided to focus our attention on the excellent iodocyclization protocol introduced by Larock.^{25,26} Attractive features of this method include its mild reaction conditions and the fact that the products incorporate a carbon–iodine bond at C-3, providing opportunities for further synthetic elaboration of the quinolines by metalation and transition-metal-catalyzed coupling reactions. The corresponding bromocyclization processes were not examined since Larock has reported that such reactions proceed in significantly lower yield as compared to the analogous iodocyclizations.^{25b}

In the event, attempted cyclization of phenolic benzannulation products such as **18** resulted in the formation of significant amounts of diiodide byproducts produced by iodination of the desired 7-hydroxyquinolines at the position ortho to the hydroxyl group. Fortunately, we found that this side reaction could be suppressed by conversion of the phenol to its triflate derivative prior to iodocyclization. This was a particularly attractive solution since the C-7 triflate would provide an additional handle for the synthetic elaboration of the quinoline products.

Trifluoromethylsulfonylation of **18** proceeded smoothly under standard conditions as shown in Scheme 2, and we found that cleavage of the Boc group could be achieved in the same flask simply by adding excess $\text{CF}_3\text{CO}_2\text{H}$ to the reaction mixture and stirring at 0 °C to rt for 1 h. Exposure of **19** to the

Table 2. Synthesis of Quinolines via Tandem Benzannulation/Iodocyclization Strategy^a

entry	diazo ketone	ynamide	benzannulation product ^a	yield (%) ^b	quinoline ^c	yield (%) ^b
1		14		58		82–84 ^d
2		15		55–57		69–73 ^d
3		16				40–44 ^e

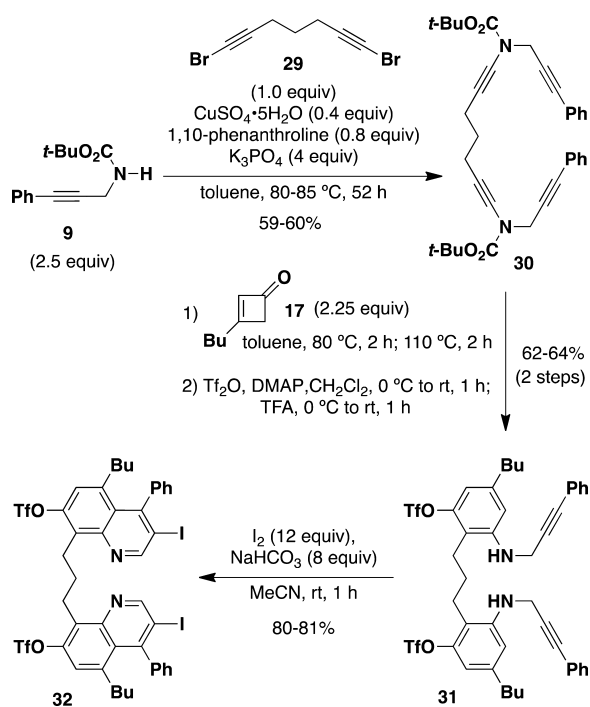
^aConditions: ynamide (1.0 equiv), diazo ketone (2.5 equiv), CH_2Cl_2 , $h\nu$, rt, 30–33 h; then toluene, reflux, 2–2.5 h. ^bIsolated yield of products purified by column chromatography. ^cConditions: (1) DMAP (2.5–3 equiv), Tf_2O (1.1–1.3 equiv), CH_2Cl_2 , 0 °C to rt, 1–2 h; then add TFA (20 equiv), 0 °C to rt, 40–90 min. (2) I_2 (6 equiv), NaHCO_3 (4 equiv), MeCN, rt, 40–60 min. ^dOverall yield for two steps from benzannulation product. ^eOverall yield for three steps from ynamide.

action of iodine in acetonitrile in the presence of NaHCO_3 then led directly to the desired quinoline **20** in excellent overall yield from benzannulation product **18**. As suggested by Larock, excess I_2 presumably effects dehydrogenation of the dihydroquinoline initially generated in the cyclization. It should be noted that we found that the optimal conditions for conversion of **19** to quinoline **20** require the use of twice the amount of iodine and NaHCO_3 employed by Larock in his studies.

Diazo Ketone-Based Quinoline Synthesis. The photo-Wolff rearrangement of α,β -unsaturated α -diazo ketones provides an alternative means of generating the key vinylketene intermediates involved in the pericyclic cascade mechanism of our benzannulation strategy. This “second generation” version of the benzannulation provides expeditious access to certain highly substituted aromatic systems that are not readily available by using the cyclobutenone-based method.^{5b,14c} As shown in Table 2, *N*-propargyl ynamides participate in this variant of the benzannulation furnishing very highly substituted *N*-propargyl anilines such as **23–25** in good yield. In the optimal protocol, irradiation of a solution of ynamide and excess diazo ketone is carried out in dichloromethane to produce a mixture of the desired phenol and varying amounts of the intermediate vinylcyclobutenone (i.e., intermediate **7** in Scheme 1). Brief heating of the crude product at reflux in toluene then serves to complete the transformation of any vinylcyclobutenone present to the desired phenol. Conversion of the benzannulation products to quinolines **26–28** was then accomplished in two steps using the procedure previously developed for *N*-propargyl aniline **18**. As illustrated with these examples, the tandem benzannulation/cyclization strategy has the capability to furnish densely substituted quinolines including compounds with alkenyl substituents and quinolines bearing substituents at every position of the bicyclic system.

Synthesis of a Bis-Quinoline. Scheme 3 describes the application of the tandem benzannulation/cyclization strategy to the synthesis of bis-quinoline **32**. Bromination of 1,6-

Scheme 3. Synthesis of Bis-quinoline **32**



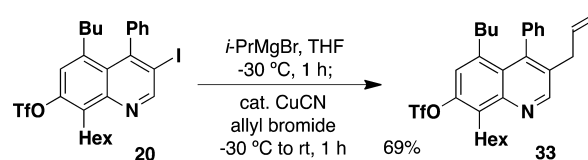
heptadiyne was accomplished in 93% yield by reaction with NBS in the presence of catalytic silver nitrate and *N*-alkynylation using the Hsung protocol furnished the bis-ynamide **30** in 59–60% yield. Benzannulation, trifluoromethylsulfonylation, and double iodocyclization then provided the expected bis-quinoline in good overall yield.

In summary, the examples presented in Table 2 and Schemes 2 and 3 establish that *N*-propargyl ynamides participate in both versions of the benzannulation without complications due to the competing pericyclic processes discussed earlier and without interference due to the presence of other unsaturated moieties in the substrates. These results suggest that benzannulations involving *N*-propargyl ynamides should proceed smoothly with the wide range of other cyclobutenones and vinylketenes that have been demonstrated to function as vinylketene precursors in our benzannulation.^{5,11,14}

Synthetic Elaboration of Quinoline Products. As noted above, the quinolines produced in the tandem benzannulation/iodocyclization strategy all incorporate iodo and trifluoromethylsulfonyloxy substituents at the C-7 and C-3 positions of the bicyclic system. It was evident that the synthetic utility of this methodology would be significantly enhanced if site-selective replacement of these substituents with a wide range of carbon moieties could be achieved.

Knochel has reported procedures for the generation of a variety of magnesiated heterocycles under mild conditions by iodine–magnesium exchange,²⁷ and this chemistry appeared to be ideally suited for the chemoselective elaboration of our quinoline products at the C-3 position. In fact, as illustrated in Scheme 4, exposure of 3-iodoquinoline **20** to *i*-PrMgBr under

Scheme 4. Alkylation of Iodoquinoline **20** via Iodine–Magnesium Exchange

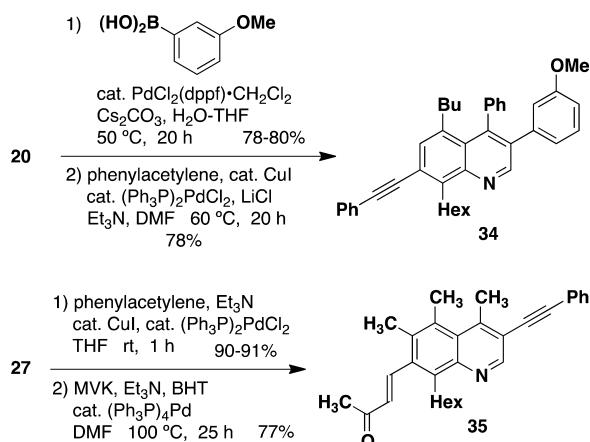


Knochel's conditions generates a Grignard derivative that can be allylated after transmetalation to copper to afford quinoline **33** in good yield.

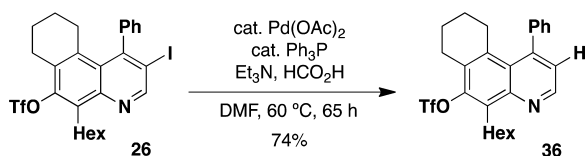
The fact that oxidative addition of palladium generally takes place more rapidly with aryl and heteroaryl iodides as compared to triflates suggested to us that it might be possible to achieve sequential site-selective cross-coupling reactions of our benzannulation/iodocyclization products.^{28,29} The examples shown in Scheme 5 confirmed the feasibility of this approach. Suzuki coupling proceeded selectively at the carbon–iodine bond in **20** as expected, and reaction of the product with phenylacetylene under standard Sonogashira alkylation conditions furnished quinoline **34** in good overall yield. In a similar fashion, site-selective Sonogashira coupling of **27** took place smoothly to provide a quinoline triflate that was then reacted with methyl vinyl ketone under standard Heck reaction conditions to afford the highly functionalized quinoline **35**.

Synthesis of Quinolines Unsubstituted at C-3. We next turned our attention to the preparation of quinolines lacking a substituent at C-3. Two alternative strategies were developed. Deiodination of **26** could be effected by reduction with tributyltin hydride, but better results were obtained as shown in Scheme 6 by using catalytic $\text{Pd}(\text{OAc})_2$ in the presence of Et_3N

Scheme 5. Synthetic Elaboration of Quinolines via Palladium-Catalyzed Coupling

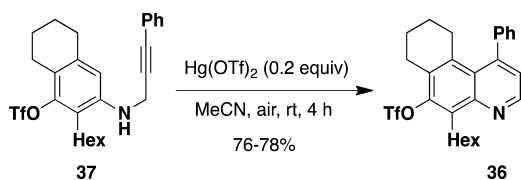


Scheme 6. Deiodination of Quinoline 26



and HCO₂H.^{30,31} It should be noted that a more direct route to the same quinoline (36) is available by employing the Hg(II)-catalyzed cyclization protocol introduced by Larock^{25b} as outlined in Scheme 7.

Scheme 7. Hg(II)-Catalyzed Cyclization



CONCLUSION

An efficient tandem benzannulation/iodocyclization strategy for the synthesis of highly substituted quinolines has been developed. Two alternative vinylketene-based benzannulation reactions involving *N*-propargyl ynamides provide regiocontrolled access to highly substituted *N*-propargyl aniline derivatives, and iodocyclization according to the method of Larock proceeds in good yield to afford polysubstituted quinoline products that can be further elaborated by site-selective carbon–carbon bond forming reactions to generate a diverse array of quinolines that can be substituted at every position of the bicyclic system if desired.

EXPERIMENTAL SECTION

General Procedures. All reactions were performed in flame-dried or oven-dried glassware under a positive pressure of argon. Reaction mixtures were stirred magnetically unless otherwise indicated. Air- and moisture-sensitive liquids and solutions were transferred by syringe or cannula and introduced into reaction vessels through rubber septa. Reaction product solutions and chromatography fractions were concentrated by rotary evaporation at ca. 20 mmHg and then at ca. 0.1 mmHg (vacuum pump) unless otherwise indicated. Thin-layer chromatography was performed on precoated glass-backed silica gel 60

F-254 0.25 mm plates. Column chromatography was performed on silica gel 60 (230–400 mesh) or on basic alumina (80–325 mesh).

Materials. Commercial grade reagents and solvents were used without further purification except as indicated below. Dichloromethane, diethyl ether, and tetrahydrofuran were purified by pressure filtration through activated alumina. Toluene was purified by pressure filtration through activated alumina and Cu(II) oxide. Acetonitrile and triethylamine were distilled under argon from calcium hydride. Triflic anhydride was distilled under argon from P₂O₅. Iodine was ground to a fine powder before use. DMF was stirred over CaH₂ for 24 h and then distilled under argon from MgSO₄ at 20 mmHg. Formic acid was distilled under argon at 40 mmHg. Phenylacetylene, allyl bromide, and isopropenylacetylene were filtered through a plug of activated alumina prior to use. *N*-Bromosuccinimide was recrystallized from boiling water. Triphenylphosphine was recrystallized from boiling hexanes. 4-DMAP was recrystallized from boiling toluene. Copper(I) iodide was extracted with THF for 24 h in a Soxhlet extractor and then dried under vacuum (0.1 mmHg). LiCl was dried under vacuum (0.1 mmHg) at 150 °C for 24 h before use. Molecular sieves (4 Å) were dried under vacuum (0.1 mmHg) at 300 °C for 16 h before use. *i*-Propylmagnesium bromide was prepared from magnesium turnings and 2-bromopropane.³² *n*-Butyllithium and *i*-propylmagnesium bromide were titrated using menthol in THF with 1,10-phenanthroline as an indicator.³³ Deactivated alumina was prepared by first generating Brockman I grade by heating 150 g of alumina at 250 °C under vacuum (0.050 mmHg) for 12–18 h and then cooling under argon. The alumina was then transferred to a 500 mL Erlenmeyer flask with a screw cap, and the requisite amount of water was added to obtain the desired grade (grade II: 3%; grade III: 6%; grade IV: 10%; grade V: 15% w/w water). The alumina was then vigorously shaken for 10–15 min until a free-flowing powder was obtained. The powder was allowed to stand at rt for 24 h with occasional mixing prior to use.

Instrumentation. Melting points were determined with a Fisher-Johns melting point apparatus and are uncorrected. ¹H NMR chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane (with the CHCl₃ peak at 7.27 ppm used as a standard). ¹³C NMR chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane (with the central peak of CHCl₃ at 77.23 ppm used as a standard).

***N*-(*tert*-Butoxycarbonyl)-*N*-(3-phenylprop-2-yn-1-yl)-oct-1-yn-1-ylamine (14).** A 100 mL recovery flask equipped with a rubber septum and argon inlet needle was charged with carbamate **9**²³ (3.29 g, 14 mmol, 1.0 equiv), K₃PO₄ (6.05 g, 28 mmol, 2.0 equiv), CuSO₄·5H₂O (0.356 g, 1.4 mmol, 0.10 equiv), 1,10-phenanthroline (0.514 g, 2.9 mmol, 0.20 equiv), and 10 mL of toluene. A solution of 1-bromooctyne **12**^{20a} (3.0 g, 16 mmol, 1.1 equiv) in 5 mL of toluene was added via cannula over 2 min (3 mL of toluene rinse). The septum was replaced with a coldfinger condenser fitted with an argon inlet adapter, and the heterogeneous reaction mixture was stirred at 85 °C for 25 h. The resulting mixture was allowed to cool to rt, and CuSO₄·5H₂O (0.356 g, 1.4 mmol, 0.10 equiv) and 1,10-phenanthroline (0.514 g, 2.9 mmol, 0.20 equiv) were added. The reaction mixture was stirred at 88 °C for 24 h, allowed to cool to rt, and diluted with 10 mL of EtOAc. The resulting mixture was filtered through a ca. 4 g plug of Celite with the aid of five 15 mL portions of EtOAc, and the filtrate was concentrated to yield 6.69 g of red-brown oil. Purification by column chromatography on 150 g of silica gel (elution with 1% EtOAc-hexanes) afforded 3.88 g (80%) of ynamide **14** as a yellow oil: IR (neat) 2931, 2858, 2264, 1721, 1290, 1161 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.43–7.45 (m, 2H), 7.28–7.31 (m, 3H), 4.41 (s, 2H), 2.33 (t, *J* = 6.8 Hz, 2H), 1.49–1.55 (m, 2H), 1.52 (s, 9H), 1.36–1.47 (m, 2H), 1.25–1.28 (m, 4H), 0.87 (t, *J* = 6.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 154.0, 131.9, 128.5, 128.3, 122.8, 84.6, 83.6, 82.6, 73.7, 70.4, 40.0, 31.5, 29.1, 28.6, 28.2, 22.7, 18.7, 14.2; HRMS-ESI (*m/z*) [M + Na]⁺ calculated for C₂₂H₂₉NNaO₂⁺: 362.2091, found: 362.2098.

***N*-(*tert*-Butoxycarbonyl)-*N*-(but-2-yn-1-yl)-oct-1-yn-1-amine (15).** A 25 mL pear-shaped flask equipped with a rubber septum and argon inlet needle was charged with carbamate **10**²⁴ (0.177 g, 1.0 mmol, 1.0 equiv), K₃PO₄ (0.444 g, 0.21 mmol, 2.0 equiv), CuSO₄·

5H₂O (0.026 g, 0.11 mmol, 0.10 equiv), 1,10-phenanthroline (0.036 g, 0.21 mmol, 0.20 equiv), and 0.5 mL of toluene. A solution of 1-bromooctyne **12**^{20a} (0.217 g, 1.2 mmol, 1.1 equiv) in 0.5 mL of toluene was added via cannula over 1 min (0.5 mL of toluene rinse). The septum was replaced with a coldfinger condenser fitted with an argon inlet adapter, and the heterogeneous mixture was stirred at 85–90 °C for 24 h. The resulting mixture was allowed to cool to rt, and CuSO₄·5H₂O (0.026 g, 0.11 mmol, 0.10 equiv) and 1,10-phenanthroline (0.036 g, 0.21 mmol, 0.20 equiv) were added. The reaction mixture was stirred at 85–90 °C for 26 h, allowed to cool to rt, and diluted with 3 mL of EtOAc. The mixture was filtered through a ca. 2 g plug of Celite with the aid of five 5 mL portions of EtOAc, and the filtrate was concentrated to yield 0.376 g of red-brown oil. Purification by column chromatography on 19 g of silica gel (elution with 3% EtOAc-hexanes) afforded 0.239 g (83%) of ynamide **15** as a pale yellow oil: IR (neat) 2932, 2859, 2265, 1721, 1292, 1163 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 4.05–4.19 (m, 2H), 2.31 (t, *J* = 7.0 Hz, 2H), 1.83 (t, *J* = 2.2 Hz, 3H) 1.48–1.55 (m, 2H), 1.49 (s, 9H), 1.36–1.45 (m, 2H), 1.24–1.34 (m, 4H), 0.89 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 154.4, 82.8, 81.0, 74.2, 73.8, 70.5, 40.1, 31.9, 29.4, 28.9, 28.5, 23.1, 19.0, 14.6, 4.1; HRMS-DART-ESI (*m/z*) [*M* + NH₄]⁺ calculated for C₁₇H₃₁N₂O₂⁺: 295.2380, found: 295.2389.

***N*-(*tert*-Butoxycarbonyl)-1-tosyleth-1-ylamine (38).**^{34,35} A 50 mL pear-shaped flask equipped with a rubber septum and argon inlet needle was charged with *tert*-butyl carbamate (0.703 g, 6.0 mmol, 1.0 equiv), sodium *p*-toluenesulfonate dihydrate (1.29 g, 6.0 mmol, 1.0 equiv), acetaldehyde (0.37 mL, 6.6 mmol, 1.1 equiv), formic acid (1.6 mL, 42.4 mmol, 7.0 equiv), 0.7 mL methanol, and 6 mL H₂O. The septum was replaced with a coldfinger condenser fitted with an argon inlet, and the heterogeneous reaction mixture was stirred at 70 °C for 1 h. The condenser was replaced with a cap and the reaction was cooled at 4 °C for 5 h. The resulting crystals were collected by filtration, washed with 30 mL of cold water, and then transferred to a 25 mL recovery flask and dried overnight at 0.1 mmHg to provide 1.36 g (76%) of carbamate **38** as a white solid: mp 108–109 °C (lit.³⁴ 104–106 °C); IR (neat) 3441, 2981, 2933, 1728, 1494, 1322, 1168, 1146 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.79 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 5.10 (d, *J* = 11.0 Hz, 1H), 4.83–4.88 (d, minor rotamer), 4.91–4.99 (qd, *J* = 7.0, 11.0 Hz, 1H), 4.75–4.84 (m, minor rotamer), 2.44 (s, minor rotamer), 2.41 (s, 3H), 2.61 (d, *J* = 7.0 Hz, 3H) 1.22 (s, 9H), 1.13 (s, minor rotamer); ¹³C NMR (125 MHz, CDCl₃) δ 153.6, 145.1, 133.7, 129.9, 129.6, 80.9, 66.9, 28.1, 21.8, 13.2; HRMS-DART-ESI (*m/z*) [*M* + NH₄]⁺ calculated for C₁₄H₂₅N₂O₄S⁺: 317.1530, found: 317.1522.

***N*-(*tert*-Butoxycarbonyl)-5-methylhex-5-en-3-yn-2-ylamine (11).**³⁶ A 50 mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, two rubber septa, and a thermocouple probe was charged with isopropenylacetylene (0.23 mL, 0.16 g, 2.4 mmol, 2.0 equiv) and 10 mL of THF. The reaction mixture was cooled to –20 °C, and *n*-BuLi solution (2.6 M in hexanes, 0.95 mL, 2.5 mmol, 2.1 equiv) was added dropwise over 5 min. The bright yellow reaction mixture was stirred at –20 °C for 20 min and then cooled to –78 °C. A solution of carbamate **38** (0.361 g, 1.2 mmol, 1.0 equiv) in 2.5 mL of THF was added via cannula over 7 min (0.5 mL THF rinse). The reaction mixture was stirred at –78 °C for 1 h, and then 4 mL of satd aq NH₄Cl was added dropwise over 2 min. The resulting mixture was allowed to warm to rt and then diluted with 7 mL of H₂O and extracted with four 12 mL portions of CH₂Cl₂. The combined organic phases were washed with 40 mL of brine, dried over MgSO₄, filtered, and concentrated to afford 0.247 g of a pale yellow solid. Column chromatography on 13 g of silica gel (elution with 2% EtOAc-hexanes) afforded 0.228 g (90%) of carbamate **11** as a white solid: mp 71–72 °C; IR (neat) 3456, 2980, 2932, 1719, 1453, 1368, 1244, 1173 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.22–5.26 (m, 1H), 5.17–5.21 (m, 1H), 4.72–4.85 (m, 1H), 4.54–4.64 (m, 1H), 1.84–1.88 (m, 3H), 1.46 (s, 9H), 1.40 (d, *J* = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 154.8, 126.6, 122.1, 89.0, 83.6, 79.9, 39.1, 28.6, 23.7, 23.1; HRMS-DART-ESI (*m/z*) [*M* + H]⁺ calculated for C₁₂H₂₀NO₂⁺: 210.1489, found: 210.1486.

***N*-(*tert*-Butoxycarbonyl)-*N*-(4-((*tert*-Butyldimethylsilyloxy)-but-1-yn-1-yl)-5-methylhex-5-en-3-yn-2-ylamine (16).** A 25 mL pear-shaped flask equipped with a rubber septum and argon inlet needle was charged with bromo alkyne **13**³⁷ (0.319 g, 1.2 mmol, 1.2 equiv), carbamate **11** (0.209 g, 1.0 mmol, 1.0 equiv), K₃PO₄ (0.425 g, 2.0 mmol, 2.0 equiv), CuSO₄·5H₂O (0.025 g, 0.1 mmol, 0.10 equiv), 1,10-phenanthroline (0.036 g, 0.2 mmol, 0.20 equiv), and 1.4 mL of toluene. The septum was replaced with a coldfinger condenser fitted with an argon inlet adapter, and the heterogeneous reaction mixture was stirred at 85 °C for 24 h. The resulting mixture was allowed to cool to rt, and CuSO₄·5H₂O (0.025 g, 0.1 mmol, 0.10 equiv) and 1,10-phenanthroline (0.036 g, 0.2 mmol, 0.20 equiv) were added. The reaction mixture was stirred at 85 °C for 46 h, allowed to cool to rt, and diluted with 5 mL of EtOAc. The mixture was filtered through a ca. 2 g plug of Celite with the aid of five 5 mL portions of EtOAc, and the filtrate was concentrated to yield 0.568 g of brown oil. Purification by column chromatography on 60 g of silica gel (elution with 2% EtOAc-hexanes) afforded 0.234 g (60%) of ynamide **16** as a yellow oil: IR (neat) 2955, 2931, 2857, 2262, 1720, 1305, 1166, 1106 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.26–5.29 (m, 1H), 5.20–5.22 (m, 1H), 5.03 (m, 1H), 3.74 (t, *J* = 7.5 Hz, 2H), 2.55 (t, *J* = 7.5 Hz, 2H), 1.87 (s, 3H), 1.49 (s, 9H), 1.46 (d, *J* = 7.0 Hz, 3H), 0.89 (s, 9H), 0.65 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 153.7, 126.5, 122.2, 86.7, 85.1, 82.7, 72.0, 68.9, 62.6, 42.3, 28.2, 26.1, 23.6, 23.2, 20.4, 18.5, –5.1; HRMS-ESI (*m/z*) [*M* + Na]⁺ calculated for C₂₂H₃₇NNaO₃Si⁺: 414.2435, found: 414.2447.

5-Butyl-2-hexyl-3-(*N*-*tert*-butoxycarbonyl(3-phenylprop-2-yn-1-yl)amino)-phenol (18). A 25 mL pear-shaped flask equipped with a rubber septum and argon inlet needle was charged with ynamide **14** (0.309 g, 0.92 mmol, 1.0 equiv), cyclobutenone **17**¹⁷ (0.141 g, 1.1 mmol, 1.25 equiv), and 2.3 mL of toluene. The septum was replaced with a coldfinger condenser fitted with argon inlet adapter, and the reaction mixture was heated at 80 °C for 1.5 h and then at reflux for 1 h. Concentration of the reaction mixture afforded 0.570 g of amber oil. Column chromatography on 60 g of silica gel (gradient elution with 5–10% EtOAc-hexanes) provided 0.378 g (89%) of carbamate **18** as an off-white solid: mp 90–91 °C; IR (neat) 3365 (broad), 2956, 2929, 2858, 1673, 1435, 1394, 1367, 1163 cm⁻¹; ¹H NMR (400 MHz, CDCl₃, 60:40 mixture of rotamers) for the major rotamer: δ 7.28–7.42 (m, 5H), 6.76 (s, 1H), 6.61 (s, 1H), 5.71 (bs, 1H), 4.80 (d, *J* = 17.5 Hz, 1H), 4.27 (d, *J* = 17.5 Hz, 1H), 2.34–2.62 (m, 4H), 1.49–1.63 (m, 4H), 1.39 (s, 9H), 1.20–1.48 (m, 8H), 0.80–0.94 (m, 6H); additional resonances appeared for the minor rotamer at: δ 6.67 (s, 1H), 6.49 (s, 1H), 6.20 (bs, 1H), 4.62 (d, *J* = 17.5 Hz, 1H), 4.23 (d, *J* = 17.5 Hz, 1H), 1.61 (s, 9H); ¹³C NMR (100 MHz, CDCl₃, mixture of two rotamers) for the major rotamer: δ 155.5, 155.2, 141.0, 140.6, 131.6, 128.3, 128.1, 124.7, 123.2, 120.5, 115.8, 85.2, 83.6, 80.6, 40.6, 35.2, 33.1, 31.9, 30.1, 29.2, 28.3, 26.1, 22.8, 22.2, 14.2, 14.0; additional resonances appeared for the minor rotamer at: δ 155.6, 155.3, 141.5, 140.8, 131.8, 128.4, 128.2, 125.3, 120.0, 115.1, 85.7, 84.1, 81.2, 41.8, 33.4, 32.0, 30.2, 29.6, 28.5, 22.6. anal. calcd for C₃₀H₄₁NO₃: C, 77.71; H, 8.91; N, 3.02. Found: C, 77.54; H, 8.93; N, 3.02.

5-Butyl-2-hexyl-3-(3-phenylprop-2-ynylamino)phenyl trifluoromethanesulfonate (19). A 25 mL pear-shaped flask equipped with a rubber septum and argon inlet needle was charged with phenol **18** (0.487 g, 1.1 mmol, 1.0 equiv), 4-DMAP (0.206 g, 1.7 mmol, 1.6 equiv), and 5 mL of CH₂Cl₂. The yellow solution was cooled to 0 °C, and triflic anhydride (0.25 mL, 1.5 mmol, 1.4 equiv) was added dropwise by syringe over ca. 3 min. The reaction mixture was allowed to warm to rt and stirred for 2 h. The resulting yellow slurry of white solid was cooled to 0 °C, and trifluoroacetic acid (1.2 mL, 16 mmol, 15 equiv) was added dropwise over 5 min. The resulting golden orange solution was allowed to warm to rt, stirred for 1 h, and then diluted with 25 mL of dichloromethane and washed with 25 mL of satd aq K₂CO₃ solution. The aqueous layer was extracted with three 10 mL portions of CH₂Cl₂, and the combined organic layers were washed with 50 mL of brine, dried over MgSO₄, filtered, and concentrated to afford 0.777 g of a dark red oil. Column chromatography on 19 g of silica gel (elution with 1% EtOAc-hexanes) afforded 0.480 g (92%) of

triflate **19** as a pale yellow oil: IR (neat) 3449 (broad), 2958, 2931, 2860, 1416, 1213, 1141 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.47–7.54 (m, 2H), 7.31–7.40 (m, 3H), 6.72 (s, 1H), 6.66 (s, 1H), 4.22–4.30 (m, 2H), 4.19 (bs, 1H), 2.61–2.74 (m, 4H), 1.59–1.75 (m, 4H), 1.34–1.55 (m, 8H), 0.93–1.06 (m, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 148.5, 146.4, 143.3, 131.9, 128.5, 128.4, 122.9, 118.8 (q, J = 318 Hz), 117.5, 111.2, 110.5, 85.9, 83.8, 35.8, 34.8, 33.5, 31.7, 29.6, 28.1, 24.8, 22.8, 22.5, 14.1, 14.0; HRMS-ESI (m/z) [$M + H$] $^+$ calculated for $\text{C}_{26}\text{H}_{33}\text{F}_3\text{NO}_3\text{S}^{+}$: 496.2128; found 496.2111.

5-Butyl-8-hexyl-3-iodo-4-phenylquinolin-7-yl trifluoromethanesulfonate (20). A 25 mL pear-shaped flask equipped with a rubber septum and argon inlet needle was charged with triflate **19** (0.480 g, 0.97 mmol, 1.0 equiv), NaHCO_3 (0.326 g, 3.9 mmol, 4.0 equiv), iodine (1.48 g, 5.8 mmol, 6.0 equiv), and 10 mL of CH_3CN . The reaction mixture was stirred at rt for 40 min, diluted with 30 mL of Et_2O , and then washed with 12 mL of satd aq $\text{Na}_2\text{S}_2\text{O}_3$ solution. The aqueous layer was extracted with three 10 mL portions of Et_2O , and the combined organic layers were washed with 25 mL of brine, dried over MgSO_4 , filtered, and concentrated to afford 0.634 g of a yellow oil. Column chromatography on 91 g of silica gel (elution with 1% EtOAc-5% benzene-94% hexanes) yielded 0.522 g (87%) of quinoline **20** as a yellow oil: IR (neat) 2929, 1421, 1214, 1141 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 9.32 (s, 1H), 7.45–7.60 (m, 3H), 7.15–7.30 (m, 3H), 3.24–3.40 (m, 2 H), 2.02–2.19 (m, 2H), 1.66–1.76 (m, 2H), 1.43–1.53 (m, 2H), 1.30–1.41 (m, 4H), 1.17–1.26 (m, 2H), 0.92 (t, J = 7.2 Hz, 3H) 0.83–0.93 (m, 2H), 0.72 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 156.2, 151.8, 148.3, 147.0, 144.7, 141.2, 132.8, 128.9, 128.9, 128.7, 127.5, 122.6, 118.8 (d, J = 318 Hz), 102.0, 35.8, 34.3, 31.8, 30.4, 29.8, 26.2, 22.8, 22.6, 14.3, 13.9; HRMS-ESI (m/z) [$M + H$] $^+$ calculated for $\text{C}_{26}\text{H}_{30}\text{F}_3\text{INO}_3\text{S}^{+}$: 620.0938; found 620.0917.

2-Hexyl-3-(*N*-tert-butoxycarbonyl-(3-phenylprop-2-yn-1-yl)-amino)-5,6,7,8-tetrahydronaphthalen-1-ol (23). A 20 cm quartz tube (7 mm I.D., 10 mm O.D.) equipped with a rubber septum and argon inlet needle was charged with diazo ketone **21**¹⁸ (0.276 g, 1.8 mmol, 2.5 equiv), ynamide **14** (0.250 g, 0.74 mmol, 1.0 equiv), and 2.9 mL of CH_2Cl_2 . The yellow solution was degassed for 10 min with a stream of argon. The quartz tube was placed ca. 20 cm from a 450 W Hanovia lamp (quartz immersion well, cooled by recirculating tap water) and irradiated under argon at 25 °C for 33 h. The reaction mixture was transferred to a 25 mL pear-shaped flask with the aid of two 4 mL portions of CH_2Cl_2 and concentrated to afford 0.507 g of an orange oil. This material was dissolved in 3.7 mL of toluene, the flask was equipped with a stir bar and coldfinger condenser, and the reaction mixture was heated at reflux for 2.5 h. The resulting mixture was concentrated to afford 0.515 g of a dark orange oil. Column chromatography on 52 g of silica gel (elution with 5% EtOAc-hexanes) provided 0.241 g of a yellow-orange foam. This material was dissolved in ca. 10 mL of hot hexanes and then cooled at –20 °C for 12 h. The resulting crystals were collected by filtration, washed with 20 mL of cold hexane, then transferred to a 25 mL pear-shaped flask, and dried overnight at 0.1 mmHg to provide 0.158 g (58%) of carbamate **23** as an off-white solid: mp 124–126 °C; IR (neat) 3428 (broad), 2929, 2858, 1685, 1490, 1436, 1394, 1367, 1307, 1246, 1162 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3 , 50:50 mixture of rotamers) for the major rotamer: δ 7.36–7.47 (m, 2H), 7.23–7.36 (m, 3H), 6.75 (s, 1H), 5.13 (s, 1H), 4.75 (d, J = 18 Hz, 1H), 4.32 (d, J = 18 Hz, 1H), 2.65–2.80 (m, 2H), 2.45–2.65 (m, 4H), 1.68–1.92 (m, 4H), 1.60 (s, 9H), 1.35–1.58 (m, 4H), 1.22–1.35 (bs, 4H), 0.87 (m, 3H); additional resonances appeared for the minor rotamer at: δ 6.66 (s, 1H), 4.94 (s, 1H), 4.59 (d, J = 18 Hz, 1H), 4.26 (d, J = 18 Hz, 1H), 1.41 (s, 9 H); ^{13}C NMR (125 MHz, CDCl_3 , mixture of two rotamers) for the major rotamer: δ 155.2, 152.5, 138.8, 136.3, 131.8, 128.4, 128.2, 124.2, 123.3, 123.0, 121.2, 86.1, 83.9, 80.8, 41.9, 40.8, 32.0, 30.2, 29.5, 29.4, 28.6, 26.3, 23.2, 22.9, 22.8, 14.3; additional resonances appeared for the minor rotamer at: δ 154.8, 152.2, 138.2, 135.8, 131.7, 128.3, 123.7, 122.1, 121.0, 85.7, 83.4, 80.4, 31.9, 28.5, 23.1; anal. calcd for $\text{C}_{30}\text{H}_{39}\text{NO}_3$; C, 78.05; H, 8.52; N, 3.03. Found: C, 77.81; H, 8.71; N, 3.03.

2-Hexyl-3-(3-phenylprop-2-ynylamino)-5,6,7,8-tetrahydronaphthalen-1-yl trifluoromethanesulfonate (37). A 25 mL pear-

shaped flask equipped with a rubber septum and argon inlet needle was charged with phenol **23** (0.140 g, 0.30 mmol, 1.0 equiv), 4-DMAP (0.093 g, 0.76 mmol, 2.5 equiv), and 1.7 mL of CH_2Cl_2 . The yellow solution was cooled to 0 °C, and triflic anhydride (0.07 mL, 0.39 mmol, 1.3 equiv) was added dropwise by syringe over ca. 2 min. The reaction mixture was allowed to warm to rt and stirred for 1 h. The resulting yellow slurry of white solid was cooled to 0 °C, and trifluoroacetic acid (0.45 mL, 6.1 mmol, 20 equiv) was added dropwise over 6 min. The resulting golden orange solution was allowed to warm to rt and stirred for 1 h. The reaction mixture was then diluted with 15 mL of CH_2Cl_2 and washed with 15 mL of satd aq K_2CO_3 solution. The aqueous layer was extracted with two 10 mL portions of dichloromethane, and the combined organic layers were washed with 30 mL of brine, dried over MgSO_4 , filtered, and concentrated to afford 0.236 g of an orange semisolid. Column chromatography on 5 g of silica gel (elution with 3% EtOAc-hexanes) afforded 0.137 g (91%) of triflate **37** as a yellow oil: IR (neat) 3442, 2932, 2860, 1402, 1243, 1212, 1140, 919 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.39–7.44 (m, 2H), 7.29–7.34 (m, 3H), 6.55 (s, 1H), 4.18 (d, J = 6.0 Hz, 2H), 3.92 (t, J = 6.0 Hz, 1H), 2.78 (m, 2H), 2.72 (m, 2H), 2.60 (m, 2H), 1.74–1.80 (m, 4H), 1.49–1.57 (m, 2H), 1.35–1.42 (m, 2H), 1.28–1.35 (m, 4H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 146.8, 143.9, 137.9, 131.9, 128.6, 128.5, 122.9, 120.3, 119.1, 118.9 (q, J = 318 Hz), 112.1, 86.2, 83.7, 35.1, 31.7, 29.9, 29.6, 28.4, 25.4, 24.0, 22.4, 22.8, 22.7, 14.3; HRMS-ESI (m/z) [$M + H$] $^+$ calculated for $\text{C}_{26}\text{H}_{31}\text{F}_3\text{NO}_3\text{S}^{+}$: 494.1971; found 494.1980.

5-Hexyl-2-iodo-1-phenyl-7,8,9,10-tetrahydrobenzo[*f*]-quinolin-6-yl trifluoromethanesulfonate (26). A 25 mL pear-shaped flask equipped with a rubber septum and argon inlet needle was charged with triflate **37** (0.065 g, 0.13 mmol, 1.0 equiv), NaHCO_3 (0.044 g, 0.52 mmol, 4.0 equiv), iodine (0.199 g, 0.78 mmol, 6.0 equiv), and 1.3 mL of CH_3CN . The reaction mixture was stirred at rt for 45 min, diluted with 15 mL of Et_2O , and then washed with 15 mL of satd aq $\text{Na}_2\text{S}_2\text{O}_3$ solution. The aqueous layer was extracted with three 10 mL portions of Et_2O , and the combined organic layers were washed with 15 mL of brine, dried over MgSO_4 , filtered, and concentrated to afford 0.082 g of a yellow oil. Column chromatography on 20 g of silica gel (elution with 1% EtOAc-5% benzene-94% hexanes) provided 0.075 g (92%) of quinoline **26** as a pale yellow oil: IR (neat) 2932, 2861 1404, 1218, 1137 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 9.26 (s, 1H), 7.43–7.54 (m, 3H), 7.14–7.22 (m, 2H), 3.31–3.40 (m, 2H), 2.92 (t, J = 6.4 Hz, 2H), 2.14 (t, J = 6.2 Hz, 2H), 1.61–1.78 (m, 4H), 1.40–1.53 (m, 4H), 1.28–1.40 (m, 4H), 0.92 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 155.4, 151.2, 147.0, 146.4, 145.9, 135.2, 133.4, 131.3, 129.4, 128.6, 128.5, 118.8 (q, J = 318 Hz), 102.4, 31.9, 31.6, 30.6, 29.9, 26.7, 25.8, 23.0, 22.8, 21.4, 14.3 (one carbon overlapped in the region 144–152); HRMS-ESI (m/z) [$M + H$] $^+$ calculated for $\text{C}_{26}\text{H}_{28}\text{O}_3\text{F}_3\text{INS}^{+}$: 618.0781; found 618.0795.

3-(*N*-tert-butoxycarbonyl(but-2-yn-1-yl)amino)-2-hexyl-5,6-dimethylphenol (24). A 20 cm quartz tube (7 mm I.D., 10 mm O.D.) equipped with a rubber septum and argon inlet needle was charged with diazo ketone **22**¹⁸ (0.450 g, 3.6 mmol, 2.5 equiv), ynamide **15** (0.398 g, 1.4 mmol, 1.0 equiv), and 6 mL of CH_2Cl_2 . The yellow solution was degassed for 10 min with a stream of argon. The quartz tube was placed ca. 20 cm from a 450 W Hanovia lamp (quartz immersion well, cooled by recirculating tap water) and irradiated under argon at 25 °C for 30 h. The reaction mixture was transferred to a 25 mL pear-shaped flask with the aid of two 4 mL portions of CH_2Cl_2 and concentrated to afford 0.81 g of an orange oil. This material was dissolved in 7 mL of toluene, the flask was equipped with a stir bar and coldfinger condenser, and the reaction mixture was heated at reflux for 2.5 h. The resulting mixture was concentrated to afford 0.832 g of a dark orange oil. Column chromatography on 85 g of silica gel (elution with 3% EtOAc-hexanes) provided 0.420 g of a yellow solid. This material was dissolved with 10 mL of pentane and then cooled at –20 °C for 12 h. The resulting crystals were collected by filtration, washed with 10 mL of cold pentane, then transferred to a 25 mL pear-shaped flask, and dried overnight at 0.1 mmHg to provide 0.290 g (55%) of carbamate **24** as an off-white solid: mp 89–91 °C; IR (neat) 3419 (broad), 2928, 2859, 1681, 1574, 1395, 1367, 1321, 1251,

1166 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3 , 60:40 mixture of rotamers) for the major rotamer: δ 6.62 (s, 1H), 4.81 (s, 1H), 4.39 (d, J = 17 Hz, 1H), 4.04 (d, J = 17 Hz, 1H), 2.40–2.57 (m, 2H), 2.24 (s, 3H), 2.14 (s, 3H), 1.78 (s, 3H), 1.54 (s, 9H), 1.32–1.65 (m, 4H), 1.24–1.32 (m, 4H), 0.89 (t, J = 7.0 Hz, 3H); additional resonances appeared for the minor rotamer at: δ 6.72 (s, 1H), 5.06 (s, 1H), 4.29 (d, J = 17 Hz, 1H), 3.97 (d, J = 17 Hz, 1H), 2.21 (s, 3H), 2.08 (s, 3H), 1.81 (s, 3H), 1.35 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3 , mixture of two rotamers) for the major rotamer: δ 155.2, 152.3, 138.3, 135.0, 124.1, 122.1, 121.4, 80.2, 79.6, 75.1, 40.5, 32.0, 30.2, 29.3, 28.5, 26.4, 22.9, 20.2, 14.3, 12.0, 3.9; additional resonances appeared for the minor rotamer at: δ 154.8, 152.6, 138.4, 135.5, 124.6, 80.6, 79.1, 75.6, 41.3, 31.9, 3.7 HRMS-DART-ESI (m/z) [$M - H$] $^-$ calculated for $\text{C}_{23}\text{H}_{34}\text{NO}_3$ $^-$, 372.2544; found: 372.2548. anal. calcd for $\text{C}_{23}\text{H}_{33}\text{NO}_3$: C, 73.96; H, 9.44; N, 3.75. Found: C, 74.18; H, 9.50; N, 3.70.

3-(But-2-yn-1-ylamino)-2-hexyl-5,6-dimethylphenyl trifluoromethanesulfonate (39). A 25 mL pear-shaped flask equipped with a rubber septum and argon inlet needle was charged with phenol **24** (0.153 g, 0.41 mmol, 1.0 equiv), 4-DMAP (0.125 g, 1.0 mmol, 2.5 equiv), and 2.4 mL of CH_2Cl_2 . The yellow solution was cooled to 0 $^\circ\text{C}$, and triflic anhydride (0.09 mL, 0.53 mmol, 1.3 equiv) was added dropwise by syringe over ca. 3 min. The reaction mixture was allowed to warm to rt and stirred for 1 h. The resulting yellow slurry of white solid was cooled to 0 $^\circ\text{C}$, and trifluoroacetic acid (0.61 mL, 8.2 mmol, 20 equiv) was added dropwise over 5 min. The resulting golden orange solution was allowed to warm to rt and stirred for 40 min. The reaction mixture was then diluted with 10 mL of dichloromethane and washed with two 10 mL portions of satd aq K_2CO_3 solution. The aqueous layer was extracted with two 10 mL portions of CH_2Cl_2 , and the combined organic layers were washed with 30 mL of brine, dried over MgSO_4 , filtered, and concentrated to afford 0.303 g of a golden semisolid. Column chromatography on 5 g of silica gel (elution with 3% EtOAc-hexanes) afforded 0.149 g (90%) of triflate **39** as a yellow oil: IR (neat) 3444, 2928, 2860, 1402, 1246, 1218, 1140, 909 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 6.57 (s, 1H), 3.90–3.94 (m, 2H), 3.83 (bs, 1H), 2.58–2.63 (m, 2H), 2.29 (s, 3H), 2.20 (s, 3H), 1.84 (t, J = 2.0 Hz, 3H), 1.49–1.57 (m, 2H), 1.36–1.44 (m, 2H), 1.31–1.38 (m, 4H), 0.92 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 146.9, 144.1, 137.2, 118.9 (q, J = 318 Hz), 118.8, 118.5, 113.0, 79.5, 76.0, 34.5, 31.7, 29.6, 28.2, 25.4, 22.8, 20.7, 14.2, 13.3, 3.6; HRMS-ESI (m/z) [$M + H$] $^+$ calculated for $\text{C}_{19}\text{H}_{27}\text{F}_3\text{NO}_3\text{S}^+$, 406.1658; found: 406.1658.

8-Hexyl-3-iodo-4,5,6-trimethylquinolin-7-yl trifluoromethanesulfonate (27). A 25 mL pear-shaped flask equipped with a rubber septum and argon inlet needle was charged with triflate **39** (0.100 g, 0.25 mmol, 1.0 equiv), NaHCO_3 (0.084 g, 0.99 mmol, 4.0 equiv), iodine (0.376 g, 1.5 mmol, 6.0 equiv), and 2.5 mL of CH_3CN . The reaction mixture was stirred at rt for 30 min, diluted with 30 mL of Et_2O , and then washed with two 15 mL portions of satd aq $\text{Na}_2\text{S}_2\text{O}_3$ solution. The aqueous layer was extracted with two 15 mL portions of Et_2O , and the combined organic layers were washed with 40 mL of brine, dried over MgSO_4 , filtered, and concentrated to afford 0.167 g of a yellow oil. Column chromatography on 42 g of silica gel (elution with 10% benzene-hexanes) furnished 0.103 g (79%) of quinoline **27** as a off-white waxy solid: mp 36–38 $^\circ\text{C}$; IR (neat) 2958, 2929, 2858, 1406, 1217, 1138 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 9.07 (s, 1H), 3.27–3.32 (m, 2H), 2.88 (s, 3H), 2.63 (s, 3H), 2.47 (s, 3H), 1.59–1.68 (m, 2H), 1.38–1.46 (m, 2H), 1.27–1.36 (m, 4H), 0.89 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 155.7, 147.0, 146.1, 145.8, 133.3, 132.9, 131.2, 130.3, 118.9 (q, J = 318 Hz), 102.6, 31.9, 31.5, 30.5, 29.8, 26.6, 22.8, 21.8, 15.3, 14.3; anal. calcd for $\text{C}_{19}\text{H}_{23}\text{F}_3\text{INO}_3\text{S}$: C, 43.11; H, 4.38; N, 2.65. Found: C, 43.32; H, 4.33; N, 2.68.

2-(2-Hydroxyethyl)-5,6-dimethyl-3-((5-methylhex-5-en-3-yn-2-yl)amino)phenyl trifluoromethanesulfonate (40). A 20 cm quartz tube (7 mm I.D., 10 mm O.D.) equipped with a rubber septum and argon inlet needle was charged with diazo ketone **28** 18 (0.177 g, 1.43 mmol, 2.5 equiv), ynamide **16** (0.224 g, 0.572 mmol, 1.0 equiv), and 2.4 mL of CH_2Cl_2 . The yellow solution was degassed for 10 min with a stream of argon. The quartz tube was placed ca. 20 cm from a 450 W Hanovia lamp (quartz immersion well, cooled by recirculating

tap water) and irradiated under argon at 25 $^\circ\text{C}$ for 38 h. The reaction mixture was transferred to a 25 mL pear-shaped flask with the aid of two 4 mL portions of CH_2Cl_2 and concentrated to afford 0.392 g of an orange oil. This material was dissolved in 3.0 mL of toluene, the flask was equipped with a stir bar and coldfinger condenser, and the reaction mixture was heated at reflux for 2 h. The resulting mixture was concentrated to afford 0.362 g of an orange oil. Filtration through a 4 g plug of silica gel (elution with 80 mL of 2% EtOAc-hexanes) afforded 0.220 g of crude phenol **25** as a yellow oil. This material was transferred to a 25 mL pear-shaped flask equipped with a rubber septum and argon inlet needle. 4-DMAP (0.165 g, 1.35 mmol, 3.0 equiv) and 4.5 mL of CH_2Cl_2 were added, and the yellow solution was cooled to 0 $^\circ\text{C}$, while triflic anhydride (0.09 mL, 0.15 g, 0.54 mmol, 1.2 equiv) was added dropwise by syringe over ca. 5 min. The reaction mixture was allowed to warm to rt and stirred for 1.5 h. The resulting red slurry of white solid was cooled to 0 $^\circ\text{C}$, and trifluoroacetic acid (1.04 mL, 1.54 g, 13.5 mmol, 30 equiv) was added dropwise over 15 min. The resulting brown solution was allowed to warm to rt and stirred for 2 h. The reaction mixture was then diluted with 30 mL of dichloromethane and washed with three 20 mL portions of satd aq K_2CO_3 solution. The combined aqueous layers were extracted with two 10 mL portions of CH_2Cl_2 , and the combined organic layers were washed with 50 mL of brine, dried over MgSO_4 , filtered, and concentrated to afford 0.363 g of an orange-brown oil. Column chromatography on 40 g of silica gel (elution with CH_2Cl_2) afforded 0.125 g (54%) of triflate **40** as a yellow oil: IR (neat) 3583, 3332, 2977, 2928, 2885, 1403, 1246, 1214, 1139, 913 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 6.75 (s, 1H), 5.22–5.24 (m, 1H), 5.18–5.20 (m, 1H), 4.82 (bs, 1H), 4.24 (q, J = 6.5 Hz, 1H), 3.86–3.95 (m, 2H), 2.88–2.97 (m, 2H), 2.29 (s, 3H), 2.18 (s, 3H), 1.93 (bs, 1H), 1.83–1.87 (m, 3H), 1.56 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 147.1, 145.2, 138.1, 126.7, 122.6, 122.0, 118.8 (q, J = 318 Hz), 116.8, 115.0, 89.9, 83.8, 63.3, 41.9, 28.7, 23.7, 22.6, 20.9, 13.4; HRMS-ESI (m/z) [$M + H$] $^+$ calculated for $\text{C}_{18}\text{H}_{23}\text{F}_3\text{NO}_4\text{S}^+$, 406.1294; found, 406.1294.

8-(2-Hydroxyethyl)-3-iodo-2,5,6-trimethyl-4-(prop-1-en-2-yl)quinolin-7-yl trifluoromethanesulfonate (28). A 25 mL pear-shaped flask equipped with a rubber septum and argon inlet needle was charged with triflate **40** (0.107 g, 0.26 mmol, 1.0 equiv), NaHCO_3 (0.089 g, 1.1 mmol, 4.0 equiv), iodine (0.402 g, 1.6 mmol, 6.0 equiv), and 2.6 mL of CH_3CN . The reaction mixture was stirred at rt for 1 h, diluted with 25 mL of Et_2O , and then washed with three 10 mL portions of satd aq $\text{Na}_2\text{S}_2\text{O}_3$ solution. The combined aqueous layers were extracted with two 10 mL portions of Et_2O , and the combined organic layers were washed with 50 mL of brine, dried over MgSO_4 , filtered, and concentrated to afford 0.140 g of a yellow oil. Column chromatography on 21 g of silica gel (elution with 2% Et_2O - CH_2Cl_2) furnished 0.110 g (79%) of quinoline **28** as a yellow oil: IR (neat) 3357, 2957, 2920, 2870, 1406, 1214, 1140 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.50–5.53 (m, 1H), 4.98–5.01 (m, 1H), 4.90 (bs, 1H), 3.96–4.04 (m, 2H), 3.54–3.59 (m, 2H), 3.00 (s, 3H), 2.68 (s, 3H), 2.46 (s, 3H), 2.22–2.24 (m, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 159.8, 155.2, 149.2, 146.7, 146.1, 134.2, 130.2, 129.9, 125.9, 120.0, 118.8 (q, J = 318 Hz), 103.3, 63.4, 32.0, 30.1, 24.7, 20.3, 15.8; HRMS-ESI (m/z) [$M + H$] $^+$ calculated for $\text{C}_{18}\text{H}_{20}\text{F}_3\text{INO}_4\text{S}^+$, 530.0104; found, 530.0078.

1,7-Dibromohepta-1,6-diyne (29). A 100 mL, two-necked, round-bottomed flask equipped with an argon inlet adapter and glass stopper was charged with 1,6-heptadiyne (0.62 mL, 5.4 mmol, 1.0 equiv), NBS (2.13 g, 11.9 mmol, 2.2 equiv), AgNO_3 (0.100 g, 0.54 mmol, 0.1 equiv), and 18 mL of acetone. The resulting mixture was stirred in the dark at rt for 1 h and then diluted with 25 mL of pentane and 37 mL of water. The organic layer was washed with three 10 mL portions of satd aq $\text{Na}_2\text{S}_2\text{O}_3$ solution and 25 mL of brine, dried over MgSO_4 , filtered, and concentrated to yield 1.30 g of a pale yellow oil. Filtration through a 6 g plug of silica gel (elution with pentane) afforded 1.25 g (93%) of alkynyl bromide **29** as a pale yellow oil: IR (thin film) 2956, 2938, 2908, 2218, 1452, 1430, 1345, 1327, 1309, 1291 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 2.34 (t, J = 7.0 Hz, 4H), 1.73 (quint, J = 7.0 Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 79.3,

38.9, 27.2, 19.0; HRMS-ESI (m/z) [$M + H$]⁺ calculated for $C_7H_7Br_2^+$, 250.8892; found, 250.8901.

Di-*N*-(*tert*-butoxycarbonyl)-hepta-1,6-diyne-1,7-diylbis(3-phenylprop-2-ynylamine) (30). A 25 mL pear-shaped flask equipped with a rubber septum and argon inlet needle was charged with carbamate **9**³⁴ (0.238 g, 1.0 mmol, 2.5 equiv), K_3PO_4 (0.350 g, 1.6 mmol, 4.0 equiv), $CuSO_4 \cdot 5H_2O$ (0.041 g, 0.16 mmol, 0.40 equiv), 1,10-phenanthroline (0.059 g, 0.33 mmol, 0.80 equiv), 1,7-dibromohepta-1,6-diyne **29** (0.103 g, 0.41 mmol, 1 equiv), and 1.6 mL of toluene. The septum was replaced with a coldfinger condenser fitted with an argon inlet adapter, and the reaction mixture was stirred at 80–85 °C for 52 h and then allowed to cool to rt. The resulting mixture was diluted with 5 mL of EtOAc and filtered through a ca. 2 g plug of Celite with the aid of five 5 mL portions of EtOAc. Concentration of the filtrate yielded 0.317 g of a brown oil. Purification by column chromatography on 64 g of Brockman II alumina (elution with benzene) afforded 1.73 g of a yellow oil which was further purified by column chromatography on 18 g of silica gel (elution with 5% EtOAc-hexanes) to afford 0.137 g (60%) of ynamide **30** as a yellow oil: IR (neat) 2979, 2933, 2265, 1720, 1490, 1389, 1291, 1160 cm^{-1} ; ¹H NMR (500 MHz, $CDCl_3$) δ 7.43–7.46 (m, 4H), 7.28–7.31 (m, 6H), 4.40 (s, 4H), 2.49 (t, $J = 7.0$ Hz, 4H), 1.77 (quint, $J = 7.0$ Hz, 2H), 1.51 (s, 18H); ¹³C NMR (125 MHz, $CDCl_3$) δ 154.0, 132.0, 128.5, 128.4, 122.8, 84.7, 83.5, 82.7, 74.3, 69.5, 40.0, 28.6, 28.2, 17.8; HRMS-ESI (m/z) [$M + Na$]⁺ calculated for $C_{35}H_{38}N_2NaO_4^+$ 573.2724; found, 573.2737.

2,2'-(1,3-Propanediyl)bis-5,5'-butyl-3,3'-(3-phenylprop-2-ynylamino)phenyl trifluoromethanesulfonate (31). A 25 mL pear-shaped flask equipped with a rubber septum and argon inlet needle was charged with ynamide **30** (0.140 g, 0.25 mmol, 1.0 equiv), cyclobutenone **17**¹⁷ (0.073 g, 0.58 mmol, 2.3 equiv), and 1.2 mL of toluene. The septum was replaced with a coldfinger condenser fitted with argon inlet adapter, and the reaction mixture was heated at 80 °C for 2.5 h and then at reflux for 2.5 h. Concentration of the reaction mixture provided 0.243 g of crude phenol **41** as an orange solid. 4-DMAP (0.155 g, 1.3 mmol, 5 equiv) and 1.7 mL dichloromethane were added, and the resulting orange solution was cooled at 0 °C, while triflic anhydride (0.10 mL, 0.58 mmol, 2.3 equiv) was added dropwise by syringe over ca. 5 min. The reaction mixture was allowed to warm to rt and stirred for 1 h. The resulting red slurry of white solid was cooled to 0 °C, and trifluoroacetic acid (0.75 mL, 10 mmol, 40 equiv) was added dropwise over 10 min. The resulting red-brown solution was allowed to warm to rt and stirred for 1 h. The reaction mixture was then diluted with 20 mL of CH_2Cl_2 and washed with three 15 mL of satd aq K_2CO_3 solution, 20 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.386 g of a red-brown solid. Column chromatography on 39 g of silica gel (gradient elution 30–50% CH_2Cl_2 -hexanes) furnished 0.136 g (62%) of triflate **31** as a white solid: mp 98–101 °C; IR (neat) 3446 (broad), 2959, 2933, 2862, 1406, 1222, 1141 cm^{-1} ; ¹H NMR (500 MHz, $CDCl_3$) δ 7.36–7.40 (m, 4H), 7.25–7.32 (m, 6H), 6.65 (s, 2H), 6.49 (s, 2H), 4.21–4.27 (m, 2H), 4.15–4.20 (m, 4H), 2.62–2.76 (m, 4H), 2.57 (t, $J = 7.5$ Hz, 4H), 1.77–1.86 (m, 4H), 1.59 (quint, $J = 7.5$ Hz, 4H), 1.35 (app hex, $J = 7.5$ Hz, 4H), 0.90 (t, $J = 7.5$ Hz, 6H); ¹³C NMR (125 MHz, $CDCl_3$) δ 148.3, 146.5, 143.8, 131.9, 128.4, 128.4, 123.0, 118.7 (q, $J = 318$ Hz), 116.5, 111.4, 110.4, 85.9, 83.6, 35.9, 34.6, 33.5, 26.4, 24.9, 22.5, 14.1; anal. calcd for $C_{43}H_{44}F_6N_2O_6S_2$: C, 59.85; H, 5.14; N, 3.25. Found: C, 60.08; H, 5.29; N, 3.29.

8,8'-(1,3-Propanediyl)bis-5,5'-butyl-3,3'-iodo-4,4'-phenylquinolin-7,7'-yl trifluoromethanesulfonate (32). A 25 mL pear-shaped flask equipped with a rubber septum and argon inlet needle was charged with triflate **31** (0.102 g, 0.12 mmol, 1.0 equiv), $NaHCO_3$ (0.079 g, 0.95 mmol, 8.0 equiv), iodine (0.360 g, 1.4 mmol, 12.0 equiv), and 2.4 mL of CH_3CN . The reaction mixture was stirred at rt for 1 h, diluted with 30 mL of Et_2O , and then washed with two 15 mL portions of satd aq $Na_2S_2O_3$ solution. The aqueous layer was extracted with two 15 mL portions of Et_2O , and the combined organic layers were washed with 60 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.137 g of a yellow oil. Column chromatography on 14 g of silica gel (elution with 2% EtOAc-hexanes) yielded

0.106 g (81%) of quinoline **32** as an off-white solid: mp 190–192 °C; IR (neat) 2959, 2931, 2873, 1420, 1217, 1141 cm^{-1} ; ¹H NMR (500 MHz, $CDCl_3$) δ 9.27 (s, 2H), 7.49–7.54 (m, 6H), 7.20–7.24 (m, 6H), 3.45–3.54 (m, 4H), 2.20 (quint, $J = 7.5$ Hz, 2H), 2.04–2.14 (m, 4H), 1.22 (app quint, $J = 7.5$ Hz, 4H), 0.89 (app hex, $J = 7.5$ Hz, 4H), 0.72 (t, $J = 7.5$ Hz, 6H); ¹³C NMR (125 MHz, $CDCl_3$) δ 156.1, 151.7, 148.3, 147.1, 144.7, 141.4, 132.0, 128.9, 128.8, 128.7, 127.5, 122.6, 118.8 (d, $J = 318$ Hz), 102.0, 35.9, 34.3, 30.5, 26.0, 22.6, 13.9; anal. calcd for $C_{43}H_{38}F_6I_2N_2O_6S_2$: C, 46.50; H, 3.45; N, 2.52. Found: C, 46.48; H, 3.46; N, 2.42.

5-Butyl-8-hexyl-3-(2-propenyl)-4-phenylquinolin-7-yl trifluoromethanesulfonate (33). A 10 mL two-necked pear-shaped flask equipped with a rubber septum, argon inlet adapter, and thermocouple probe was charged with quinoline **20** (0.102 g, 0.16 mmol, 1.0 equiv) and 0.5 mL of THF. The reaction mixture was cooled at –30 °C, while *i*-PrMgBr solution (0.47 M in THF, 0.37 mL, 0.17 mmol, 1.1 equiv) was added dropwise over 5 min, and the resulting gold-colored solution was stirred for 1 h at –30 °C. CuCN (2 mg, 0.016 mmol, 0.10 equiv) and then allyl bromide (0.018 mL, 0.025 g, 0.21 mmol, 1.2 equiv) were added, and the resulting yellow solution was stirred at –30 °C for 1 h, then allowed to warm to 0 °C, and treated with 1 mL of brine. The resulting mixture was diluted with 4 mL of brine, and the aqueous layer was separated and extracted with two 5 mL portions of EtOAc. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated to afford 0.086 g of an orange oil. Purification by column chromatography on 22 g of silica gel (elution with 1% EtOAc-hexanes) afforded 0.069 g of an orange oil which was further purified by column chromatography on 22 g of silica gel (elution with 10% benzene-hexanes) to afford 0.061 g (69%) of quinoline **33** as a yellow oil: IR (neat) 2958, 2931, 2859, 1582, 1421, 1215, 1142, 830 cm^{-1} ; ¹H NMR (500 MHz, $CDCl_3$) δ 8.88 (s, 1H), 7.43–7.49 (m, 3H), 7.23–7.27 (m, 2H), 7.18 (s, 1H), 5.78–5.87 (m, 1H), 5.03 (dq, $J = 1.5, 10.0$ Hz, 1H), 4.87 (dq, $J = 1.5, 17.0$ Hz, 1H), 3.31–3.36 (m, 2H), 3.21 (dt, $J = 1.5, 6.0$ Hz, 2H), 2.09–2.15 (m, 2H), 1.71–1.79 (m, 2H), 1.47–1.54 (m, 2H), 1.30–1.41 (m, 4H), 1.18–1.27 (m, 2H), 0.85–0.95 (m, 5H), 0.72 (t, $J = 7.3$ Hz, 3H); ¹³C NMR (125 MHz, $CDCl_3$) δ 151.7, 147.7, 146.6, 146.4, 141.3, 139.7, 136.6, 132.3, 131.8, 129.1, 128.4, 128.2, 125.7, 122.0, 116.8 (2C, q, $J = 318$ Hz), 35.5, 35.3, 34.3, 31.9, 30.4, 29.9, 26.2, 22.9, 22.6, 14.3, 13.9; HRMS-ESI (m/z) [$M + H$]⁺ calculated for $C_{29}H_{35}F_3NO_3S^+$ 534.2284; found 534.2269.

5-Butyl-8-hexyl-3-(3-methoxyphenyl)-4-phenylquinolin-7-yl trifluoromethanesulfonate (42). A 10 cm threaded Pyrex tube (12 mm I.D., 18 mm O.D.) equipped with a rubber septum and argon inlet needle was charged with 3-methoxyphenyl boronic acid (0.065 g, 0.43 mmol, 1.2 equiv), $PdCl_2(dppf) \cdot CH_2Cl_2$ (0.059 g, 0.07 mmol, 0.2 equiv), quinoline **20** (0.223 g, 0.36 mmol, 1.0 equiv), 2.8 mL of THF, and 0.7 mL of Cs_2CO_3 solution (1.0 M in water, 0.23 g Cs_2CO_3 , 0.7 mmol, 2.0 equiv). The resulting mixture was degassed for 10 min with a stream of argon, the septum was replaced with a threaded Teflon cap, and the reaction mixture was heated at 45–50 °C for 20.5 h. The reaction mixture was then diluted with 30 mL of EtOAc, washed with two 15 mL portions of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.282 g of a brown oil. Column chromatography on 30 g of silica gel (elution with 1% EtOAc-hexanes) yielded 0.169 g (78%)³⁸ of quinoline **42** as a white solid: mp 69–71 °C; IR (neat) 2957, 2930, 2860, 1581, 1419, 1218, 1142 cm^{-1} ; ¹H NMR (500 MHz, $CDCl_3$) δ 8.95 (s, 1H), 7.23–7.32 (m, 4H), 7.15–7.10 (m, 3H), 6.74 (dd, $J = 2.5, 8.3$ Hz, 1H), 6.65 (dt, $J = 1, 8.3$ Hz, 1H), 6.49–6.51 (m, 1H), 3.62 (s, 3H), 3.34–3.39 (m, 2H), 2.13–2.18 (m, 2H), 1.73–1.82 (m, 2H), 1.52 (app quint, $J = 7.5$ Hz, 2H), 1.31–1.42 (m, 4H), 1.14–1.22 (m, 2H), 0.91 (t, $J = 7.0$ Hz, 3H), 0.83 (app hex, $J = 7.5$ Hz, 2H), 0.67 (t, $J = 7.5$ Hz, 3H); ¹³C NMR (125 MHz, $CDCl_3$) δ 159.0, 150.9, 148.3, 147.0, 145.7, 141.9, 139.5, 139.3, 135.2, 132.3, 130.2, 129.0, 127.9, 127.9, 125.4, 122.8, 122.4, 118.8 (d, $J = 318$ Hz), 115.6, 113.2, 55.3, 35.7, 34.3, 31.9, 30.4, 29.9, 26.2, 22.9, 22.6, 14.3, 13.9; HRMS-ESI (m/z) [$M + H$]⁺ calculated for $C_{33}H_{37}F_3NO_4S^+$ 600.2390; found 600.2369.

5-Butyl-8-hexyl-3-(3-methoxyphenyl)-4-phenyl-7-(phenylethynyl)quinoline (34). A 25 mL pear-shaped flask

equipped with a rubber septum and argon inlet needle was charged with quinoline **42** (0.131 g, 0.22 mmol, 1.0 equiv), LiCl (0.03 g, 0.66 mmol, 3.0 equiv), (Ph₃P)₂PdCl₂ (0.015 g, 0.02 mmol, 0.1 equiv), CuI (0.004 g, 0.02 mmol, 0.1 equiv), 1.4 mL of DMF, and 2.2 mL of Et₃N. The reaction mixture was stirred for 5 min, phenylacetylene (0.04 mL, 0.04 g, 0.36 mmol, 1.6 equiv) was added, and the solution was degassed for 10 min with a stream of argon. The septum was replaced with a coldfinger condenser fitted with an argon inlet adapter, and the reaction mixture was stirred at 60 °C for 20 h. The resulting brown solution was allowed to cool to rt, diluted with 20 mL of H₂O, and extracted with three 20 mL portions of EtOAc. The combined organic phases were washed with two 20 mL portions of H₂O and two 30 mL portions of brine, dried over MgSO₄, filtered, and concentrated to afford 0.142 g of a brown oil. Column chromatography on 20 g of silica gel (elution with 1% EtOAc-5% benzene-94% hexanes) yielded 0.093 g (78%) of quinoline **34** as a white solid: mp 78–80 °C; IR (neat) 2955, 2856, 2828, 1599, 1465, 1218, 1142 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.93 (s, 1H), 7.62 (dd, *J* = 1.5, 8.0 Hz, 2H), 7.47 (s, 1H) 7.35–7.44 (m, 4H), 7.23–7.31 (m, 2H), 7.10–7.17 (m, 3H), 6.75 (dd, *J* = 2.5, 8.5 Hz, 1H), 6.68 (d, *J* = 7.5 Hz), 6.51–6.53 (m, 1H), 3.62 (s, 3H), 3.57–3.64 (m, 2H), 2.18–2.11 (m, 2H), 1.87 (app quint, *J* = 7.5 Hz, 2H), 1.60 (app quint, *J* = 7.5 Hz, 2H), 1.32–1.47 (m, 4H), 1.15–1.23 (m, 2H), 0.90 (t, *J* = 7.5 Hz, 3H) 0.83 (app hex, *J* = 7.5 Hz, 2H), 0.68 (t, *J* = 7.5 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 158.9, 150.0, 147.6, 145.3, 143.4, 140.1, 139.9, 138.9, 134.5, 132.1, 131.8, 130.3, 128.9, 128.6, 128.5, 127.8, 127.6, 125.7, 123.7, 122.8, 122.6, 115.6, 113.1, 94.5, 89.2, 55.3, 35.6, 34.7, 32.2, 31.1, 30.7, 30.2, 23.0, 22.7, 14.4, 14.0; HRMS-ESI (*m/z*) [*M* + *H*]⁺ calculated for C₄₀H₄₂NO⁺ 552.3261; found 552.3242.

8-Hexyl-4,5,6-trimethyl-3-(phenylethynyl)quinolin-7-yl trifluoromethanesulfonate (43). A 25 mL pear-shaped flask equipped with a rubber septum and argon inlet needle was charged with quinoline **27** (0.110 g, 0.21 mmol, 1.0 equiv), (Ph₃P)₂PdCl₂ (0.007 g, 0.01 mmol, 5 mol %), CuI (0.002 g, 0.01 mmol, 5 mol %), Et₃N (0.09 mL, 0.07 g, 0.62 mmol, 3.0 equiv), phenylacetylene (0.03 mL, 0.03 g, 0.27 mmol, 1.3 equiv), and 1.1 mL of THF, and the reaction mixture was stirred at rt for 1 h. The resulting brown solution was diluted with 20 mL of Et₂O, filtered through a ca. 2 g plug of Celite with the aid of five 5 mL portions of Et₂O, and concentrated to yield 0.134 g of a brown oil and solid. Column chromatography on 14 g of silica gel (elution with 2% EtOAc-hexanes) furnished 0.094 g (90%) of quinoline **43** as a yellow solid: mp 85–88 °C; IR (neat) 2959, 2930, 2859, 1405, 1217, 1138 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.90 (s, 1H), 7.59–7.63 (m, 2H), 7.38–7.44 (m, 3H), 3.37–3.31 (m, 2H), 3.04 (s, 3H), 2.73 (s, 3H), 2.48 (s, 3H), 1.62–1.71 (m, 2H), 1.41–1.48 (m, 2H), 1.29–1.36 (m, 4H), 0.90 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 150.8, 146.6, 146.5, 145.6, 133.7, 133.3, 131.8, 129.8, 129.0, 128.9, 128.7, 123.0, 119.9, 118.9 (q, *J* = 318 Hz), 97.3, 86.7, 31.9, 30.5, 29.8, 26.7, 23.4, 22.8, 21.3, 15.4, 14.3; HRMS-DART-ESI (*m/z*) [*M* – *H*][–] calculated for C₂₇H₂₇F₃NO₃S[–], 502.1669; found, 502.1686.

(E)-4-(8-Hexyl-4,5,6-trimethyl-3-(phenylethynyl)quinolin-7-yl)but-3-en-2-one (35). A 14 cm threaded Pyrex tube (1 cm I.D., 1.6 cm O.D.) equipped with a rubber septum and argon inlet needle was charged with triflate **43** (0.070 g, 0.14 mmol, 1 equiv), MVK (0.06 mL, 0.05 g, 0.70 mmol, 5 equiv), Et₃N (0.06 mL, 0.04 g, 0.42 mmol, 3 equiv), and 1.4 mL of DMF. The gold-colored reaction mixture was degassed for 10 min with a stream of argon, and then a crystal of BHT and (Ph₃P)₄Pd (0.008 g, 0.07 mmol, 5 mol %) were added. The septum was replaced with a threaded Teflon cap, and the tube was heated at 100 °C for 25 h. The resulting gold-orange reaction mixture was cooled to rt, diluted with 20 mL of EtOAc, washed with three 10 mL portions of H₂O and 30 mL of brine, dried over MgSO₄, filtered, and concentrated to afford 0.068 g of a yellow oil. Column chromatography on 7 g of silica gel (elution with CH₂Cl₂) furnished 0.046 g (77%) of quinoline **35** as an off white solid: mp 133–135 °C; IR (neat) 3050, 2957, 2929, 2848, 1674, 1363 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.86 (s, 1H), 7.87 (d, *J* = 16.5 Hz, 1H), 7.57–7.63 (m, 2H), 7.36–7.42 (m, 3H), 6.30 (d, *J* = 16.5 Hz, 1H), 3.25–3.19 (m, 2H), 3.01 (s, 3H), 2.68 (s, 3H), 2.46 (s, 3H), 2.37 (s, 3H), 1.57–

1.62 (m, 2H), 1.38–1.44 (m, 2H), 1.28–1.35 (m, 4H), 0.90 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 198.2, 150.0, 146.3, 144.9, 143.8, 138.0, 136.2, 134.1, 133.7, 131.8, 131.1, 128.8, 128.8, 128.7, 123.3, 119.0, 96.7, 87.2, 31.9, 31.2, 29.9, 29.2, 27.8, 23.4, 22.9, 21.3, 19.0, 14.3; HRMS-ESI (*m/z*) [*M* + *H*]⁺ calculated for C₃₀H₃₄NO⁺ 424.2635; found, 424.2636.

5-Hexyl-1-phenyl-7,8,9,10-tetrahydrobenzo[*f*]quinolin-6-yl trifluoromethanesulfonate (36). A 12 cm Pyrex tube (7 mm I.D., 12 mm O.D.) equipped with a rubber septum and argon inlet needle was charged with Pd(OAc)₂ (0.003 g, 0.013 mmol, 5 mol %), Ph₃P (0.007 g, 0.026 mmol, 10 mol %), quinoline **26** (0.158 g, 0.26 mmol, 1.0 equiv), Et₃N (65 μL, 47 mg, 0.46 mmol, 1.8 equiv), and 1.0 mL of DMF. The resulting mixture was degassed for 10 min with a stream of argon, then formic acid (13 μL, 16 mg, 0.31 mmol, 1.2 equiv) was added, and the reaction mixture was heated at 60–65 °C for 42 h. The reaction tube was then cooled to room temperature, Pd(OAc)₂ (0.003 g, 0.013 mmol, 5 mol %), Ph₃P (0.007 g, 0.026 mmol, 10 mol %), and formic acid (4 μL, 5 mg, 0.14 mmol, 0.5 equiv) were added, and the resulting mixture was heated at 60–65 °C for 23 h. The reaction mixture was then cooled to room temperature, diluted with 10 mL of brine, and washed with two 10 mL portions of Et₂O. The combined organic phases were washed with two 10 mL portions of H₂O and 20 mL of brine, dried over MgSO₄, filtered, and concentrated to afford 0.143 g of a brown oil. Column chromatography on 29 g of silica gel (elution with 30% benzene-hexanes) yielded 0.093 g (74%) of quinoline **36** as a pale yellow oil: IR (neat) 2932, 2860 1405, 1215, 1139, 909, 735 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.88 (d, *J* = 4.0 Hz, 1H), 7.41–7.49 (m, 3H), 7.29–7.35 (m, 2H), 7.25 (d, *J* = 4.0 Hz, 1H), 3.40–3.46 (m, 2H), 2.96 (t, *J* = 6.8 Hz, 2H), 2.28 (t, *J* = 6.3 Hz, 2H), 1.70–1.78 (m, 4H), 1.42–1.55 (m, 4H), 1.32–1.41 (m, 4H), 0.92 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 148.6, 148.0, 147.3, 147.0, 143.2, 135.4, 133.1, 130.2, 128.7, 128.4, 128.0, 126.6, 125.0, 119.0 (q, *J* = 318 Hz), 32.0, 31.9, 30.6, 29.9, 26.8, 25.4, 22.9, 22.8, 21.8, 14.3; HRMS-ESI (*m/z*) [*M* + *H*]⁺ calculated for C₂₆H₂₉F₃NO₃S⁺ 492.1815; found, 492.1811.

5-Hexyl-1-phenyl-7,8,9,10-tetrahydrobenzo[*f*]quinolin-6-yl trifluoromethanesulfonate (36). A 25 mL pear-shaped flask equipped with a rubber septum and argon inlet needle was charged with triflate **37** (0.126 g, 0.26 mmol, 1.0 equiv), Hg(OTf)₂ (0.025 g, 0.05 mmol, 0.2 equiv), and 2.6 mL of CH₃CN. The reaction mixture was stirred under air at rt for 4 h, then diluted with 20 mL of Et₂O, and washed with two 10 mL portions of satd aq NaI solution. The combined aqueous phases were extracted with three 10 mL portions of Et₂O, and the combined organic layers were washed with 40 mL of brine, dried over MgSO₄, filtered, and concentrated to afford 0.148 g of a yellow oil. Column chromatography on 30 g of silica gel (elution with 30% benzene-hexanes) furnished 0.098 g (78%) of quinoline **36** as a pale yellow oil.

■ ASSOCIATED CONTENT

● Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01648.

¹H and ¹³C NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

- (1) (a) Woodward, R. B.; Hoffmann, R. *J. Am. Chem. Soc.* **1965**, *87*, 395–397. (b) Hoffmann, R.; Woodward, R. B. *J. Am. Chem. Soc.* **1965**, *87*, 2046–2048. (c) Woodward, R. B.; Hoffmann, R. *J. Am. Chem. Soc.* **1965**, *87*, 2511–2513.
- (2) Woodward, R. B.; Hoffmann, R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 781–853.
- (3) Reviewed in Patalag, L. J.; Werz, D. B. Pericyclic Reactions in Domino Processes. In *Domino Reactions: Concepts for Efficient Organic Synthesis*, Tietze, L. F., Ed.; Wiley-VCH: Weinheim, Germany, 2014; pp 183–217.
- (4) Danheiser, R. L.; Gee, S. K.; Sard, H. J. *Am. Chem. Soc.* **1982**, *104*, 7670–7672.
- (5) (a) Danheiser, R. L.; Gee, S. K. *J. Org. Chem.* **1984**, *49*, 1672–1674. (b) Danheiser, R. L.; Brisbois, R. G.; Kowalczyk, J. J.; Miller, R. F. *J. Am. Chem. Soc.* **1990**, *112*, 3093–3100.
- (6) (a) McAteer, C. H.; Balasubramanian, M.; Murugan, R. Pyridines and their Benzo Derivatives: Applications. In *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K., Eds.; Pergamon Press: Oxford, U.K., 2008; Vol. 7, pp 309–336. (b) Balasubramanian, M.; Keay, J. G. Pyridines and their Benzo Derivatives: Applications. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, U.K., 1996; Vol. 5, pp 245–300. (c) Michael, J. P. *Nat. Prod. Rep.* **2007**, *25*, 166–187. (d) Michale, J. P. *Nat. Prod. Rep.* **2007**, *24*, 223–246.
- (7) For reviews on the synthesis of quinolines, see: (a) Alford, P. E. In *Progress in Heterocyclic Chemistry*; Gribble, G. W., Joule, J. A., Eds.; Elsevier Science: New York, 2011; Vol. 22, pp 349–391. (b) Alford, P. E. In *Progress in Heterocyclic Chemistry*; Gribble, G. W., Joule, J. A., Eds.; Elsevier Science: New York, 2011; Vol. 23, pp 329–369. (c) Madapa, S.; Zehra, T.; Batra, S. *Curr. Org. Chem.* **2008**, *12*, 1116–1183. (d) Larsen, R. D.; Cai, D. In *Science of Synthesis*; Thomas, E. J., Ed.; Thieme: Stuttgart, 2004; Vol. 15, pp 389–550.
- (8) Notable recent examples: (a) Rohlmann, R.; Stopka, T.; Richter, H.; Mancheño, O. G. *J. Org. Chem.* **2013**, *78*, 6050–6064. (b) Wang, Y.; Chen, C.; Peng, J.; Li, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 5323–5327. (c) Reddy, M. S.; Thirupathi, N.; Kumar, Y. K. *RSC Adv.* **2012**, *2*, 3986–3992. (d) Khong, S.; Kwon, O. *J. Org. Chem.* **2012**, *77*, 8257–8267. (e) Huang, H.; Jiang, H.; Chen, K.; Liu, H. *J. Org. Chem.* **2009**, *74*, 5476–5480. (f) Horn, J.; Marsden, S. P.; Nelson, A.; House, D.; Weingarten, G. G. *Org. Lett.* **2008**, *10*, 4117–4120. (g) Movassaghi, M.; Hill, M. D.; Ahmad, O. K. *J. Am. Chem. Soc.* **2007**, *129*, 10096–10097.
- (9) For a discussion of limitations associated with prior methods for quinoline synthesis, see: Tanaka, S.-y.; Yasuda, M.; Baba, A. *J. Org. Chem.* **2006**, *71*, 800–803.
- (10) Reviews: (a) Kotha, S.; Misra, S.; Halder, S. *Tetrahedron* **2008**, *64*, 10775–10790. (b) Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901–2915. (c) Bamfield, P.; Gordon, P. F. *Chem. Soc. Rev.* **1984**, *13*, 441–488.
- (11) For examples of applications of this benzannulation strategy in natural product synthesis, see: (a) Kowalski, C. J.; Lal, G. S. *J. Am. Chem. Soc.* **1988**, *110*, 3693–3695. (b) Smith, A. B., III; Adams, C. M.; Kozmin, S. A.; Paone, D. V. *J. Am. Chem. Soc.* **2001**, *123*, 5925–5937. (c) Dudley, G. B.; Takaki, K. S.; Cha, D. D.; Danheiser, R. L. *Org. Lett.* **2000**, *2*, 3407–3410 and references cited therein.
- (12) A related, complementary strategy has been reported by Liebeskind and Moore, see: (a) Liebeskind, L. S.; Iyer, S.; Jewell, C. F. *J. Org. Chem.* **1986**, *51*, 3065–3067. (b) Perri, S. T.; Foland, L. D.; Decker, O. H. W.; Moore, H. W. *J. Org. Chem.* **1986**, *51*, 3067–3068.
- (13) For reviews of the chemistry of vinylketenes, see: (a) Danheiser, R. L.; Dudley, G. B.; Austin, W. F. Alkenylketenes. In *Science of Synthesis*; Danheiser, R. L., Ed.; Thieme: Stuttgart, 2006; Vol. 23; pp 493–568. (b) Tidwell, T. T. *Ketenes*, 2nd ed.; John Wiley & Sons: Hoboken, NJ, 2006; pp 206–214.
- (14) (a) Mak, X. Y.; Crombie, A. L.; Danheiser, R. L. *J. Org. Chem.* **2011**, *76*, 1852–1873. (b) Lam, T. Y.; Wang, Y.-P.; Danheiser, R. L. *J. Org. Chem.* **2013**, *78*, 9396–9414. (c) Willumstad, T. P.; Haze, O.; Mak, X. Y.; Lam, T. Y.; Wang, Y.-P.; Danheiser, R. L. *J. Org. Chem.* **2013**, *78*, 11450–11469.
- (15) For a review of intramolecular pericyclic reactions of acetylenic compounds, see: Viola, A.; Collins, J. J.; Filipp, N. *Tetrahedron* **1981**, *37*, 3765–3811.
- (16) For examples of [3,3] sigmatropic rearrangements of alkynyl propargyl sulfides, see: (a) Aoyagi, S.; Kikuchi, K.; Shimada, K.; Takikawa, Y. *Synlett* **2007**, 2553–2556. (b) Aoyagi, S.; Hakoishi, M.; Suzuki, M.; Nakanoya, Y.; Shimada, K.; Takikawa, Y. *Tetrahedron Lett.* **2006**, *47*, 7763–7766.
- (17) For the synthesis of cyclobutenone **17** via addition of dichloroketene to hexyne followed by reductive dechlorination with zinc, see: (a) Danheiser, R. L.; Savariar, S. *Tetrahedron Lett.* **1987**, *28*, 3299–3302. (b) Danheiser, R. L.; Savariar, S.; Cha, D. D. *Org. Synth.* **1990**, *68*, 32–38.
- (18) For the preparation of α -diazo ketones **21** and **22** from the corresponding methyl ketones via diazo transfer, see: (a) Danheiser, R. L.; Miller, R. F.; Brisbois, R. G.; Park, S. Z. *J. Org. Chem.* **1990**, *55*, 1959–1964. (b) Danheiser, R. L.; Miller, R. F.; Brisbois, R. G. *Org. Synth.* **1996**, *73*, 134–140.
- (19) For recent reviews on the synthesis and chemistry of ynamides, see: (a) Evano, G.; Jouvin, K.; Coste, A. *Synthesis* **2013**, *45*, 17–26. (b) DeKorver, K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P. *Chem. Rev.* **2010**, *110*, 5064–5106. (c) Evano, G.; Coste, A.; Jouvin, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 2840–2859.
- (20) (a) Dunetz, J. R.; Danheiser, R. L. *Org. Lett.* **2003**, *5*, 4011–4014. (b) Kohnen, A. L.; Dunetz, J. R.; Danheiser, R. L. *Org. Synth.* **2007**, *84*, 88–95.
- (21) (a) Frederick, M. O.; Mulder, J. A.; Tracey, M. R.; Hsung, R. P.; Huang, J.; Kurtz, K. C. M.; Shen, L.; Douglas, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 2368–2369. (b) Zhang, Y.; Hsung, R. P.; Tracey, M. R.; Kurtz, K. C. M.; Vera, E. L. *Org. Lett.* **2004**, *6*, 1151–1154. (c) Zhang, X.; Zhang, Y.; Huang, J.; Hsung, R. P.; Kurtz, K. C. M.; Oppenheimer, J.; Petersen, M. E.; Sagamanova, I. K.; Shen, L.; Tracey, M. R. *J. Org. Chem.* **2006**, *71*, 4170–4177. (d) Sagamanova, I. K.; Kurtz, K. C. M.; Hsung, R. P. *Org. Synth.* **2007**, *84*, 359–367.
- (22) Alkynyl bromides **12** and **13** are known compounds and were prepared from the corresponding terminal alkynes by treatment with NBS and catalytic AgNO₃ according to the general procedure of Hofmeister: Hofmeister, H.; Annen, K.; Laurent, H.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 727–729.
- (23) Prepared in two steps from propargylamine as described in Miller, K. M.; Molinaro, C.; Jamison, T. F. *Tetrahedron: Asymmetry* **2003**, *14*, 3619–3625.
- (24) Prepared in two steps from 2-butyne-1-ol as described in Walters, M. A.; Hoem, A. B. *J. Org. Chem.* **1994**, *59*, 2645–2647.
- (25) (a) Zhang, X.; Campo, M. A.; Yao, T.; Larock, R. C. *Org. Lett.* **2005**, *7*, 763–766. (b) Zhang, X.; Yao, T.; Campo, M. A.; Larock, R. C. *Tetrahedron* **2010**, *66*, 1177–1187. (c) Chen, Y.; Dubrovskiy, A.; Larock, R. C. *Org. Synth.* **2012**, *89*, 294–306.
- (26) For the “bromocyclization” of *N*-tosyl-*N*-propargyl anilines with catalytic Pd(OAc)₂-CuBr₂ leading to dihydroquinolines, see: Gurunathan, S.; Perumal, P. T. *Tetrahedron Lett.* **2011**, *52*, 1783–1787.
- (27) (a) Abarbri, M.; Thibonnet, J.; Bérillon, L.; Dehmel, F.; Rottländer, M.; Knochel, P. *J. Org. Chem.* **2000**, *65*, 4618–4634. (b) Staubitz, A.; Dohle, W.; Knochel, P. *Synthesis* **2003**, 0233–0242. (c) Ila, H.; Baron, O.; Wagner, A. J.; Knochel, P. *Chem. Commun.* **2006**, 583–593.
- (28) For a recent review on cross-coupling reactions of halogenated quinolines, see: Mphahlele, M. J.; Lesenyehlo, L. G. *J. Heterocycl. Chem.* **2013**, *50*, 1–16.
- (29) For a recent example of the chemoselective cross-coupling of a quinoline derivative employing the Suzuki reaction of a bromine substituent in the presence of a triflyloxy group, see: Eleya, N.; Mahal,

A.; Hein, M.; Villinger, A.; Langer, P. *Adv. Synth. Catal.* **2011**, 353, 2761–2774.

(30) (a) For the reduction of carbon–halogen bonds using Pd and triethylammonium formate, see: Cortese, N. A.; Heck, R. F. *J. Org. Chem.* **1977**, 42, 3491–3494. (b) For the application of these conditions to the reduction of a similar 3-iodoquinoline, see: Ozeki, M.; Muroyama, A.; Kajimoto, T.; Watanabe, T.; Wakabayashi, K.; Node, M. *Synlett* **2009**, 2009, 1781–1784.

(31) For an example of the chemoselective reduction of an iodide in the presence of a triflate using cat. Pd(OAc)₂, see: Chu, Q.; Brahmi, M. M.; Solovyev, A.; Ueng, S.-H.; Curran, D. P.; Malacria, M.; Fensterbank, L.; Lacôte, E. *Chem. - Eur. J.* **2009**, 15, 12937–12940.

(32) Jensen, A. E.; Dohle, W.; Sapountzis, I.; Lindsay, D. M.; Vu, V. A.; Knochel, P. *Synthesis* **2002**, 2002, 565–569.

(33) For the titration of *n*-butyllithium see: (a) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, 9, 165–168. (b) Ellison, R. A.; Griffin, R.; Kotsonis, F. N. *J. Organomet. Chem.* **1972**, 36, 209–213. For the titration of *i*-PrMgBr see: (c) Lin, H.-S.; Paquette, L. A. *Synth. Commun.* **1994**, 24, 2503–2506.

(34) Klepacz, A.; Zwierzak, A. *Tetrahedron Lett.* **2002**, 43, 1079–1080.

(35) This procedure is modeled on related procedures of Pearson, W. H.; Lindbeck, A. C.; Kampf, J. W. *J. Am. Chem. Soc.* **1993**, 115, 2622–2636.

(36) This procedure is based on Mecozzi, T.; Petrini, M. *J. Org. Chem.* **1999**, 64, 8970–8972.

(37) Prepared in two steps from 3-butyne-1-ol as described in Li, L.-S.; Wu, Y.-L. *Tetrahedron Lett.* **2002**, 43, 2427–2430.

(38) The product was contaminated with a small amount (ca. 3 mol %) of 3,3'-dimethoxy-1,1'-biphenyl.