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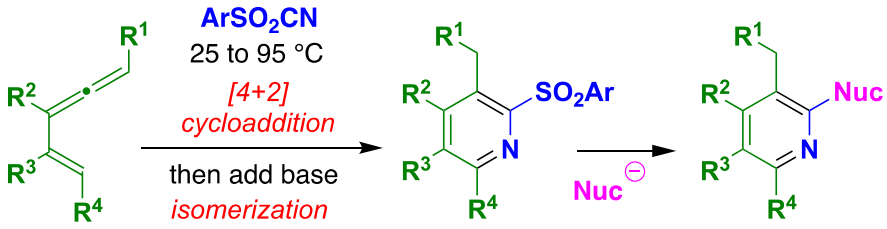
Synthesis of Highly Substituted Pyridines via [4 + 2] Cycloadditions of Vinylallenes and Sulfonyl Cyanides

Samuel G. Bartko, Phillip J. Hamzik, Leandro Espindola, Christian Gomez, and Rick L. Danheiser*

Department of Chemistry
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139

E-mail: danheisr@mit.edu



ABSTRACT: A convergent strategy for the synthesis of multisubstituted pyridines is described. Vinylallenes combine with commercially available arylsulfonyl cyanides in Diels-Alder cycloadditions to generate isopyridine cycloadducts that are converted to pyridines upon further heating or addition of base. The 2-sulfonylpyridine products undergo nucleophilic aromatic substitution reactions with oxygen and carbon nucleophiles to provide access to a variety of highly substituted pyridines.

INTRODUCTION

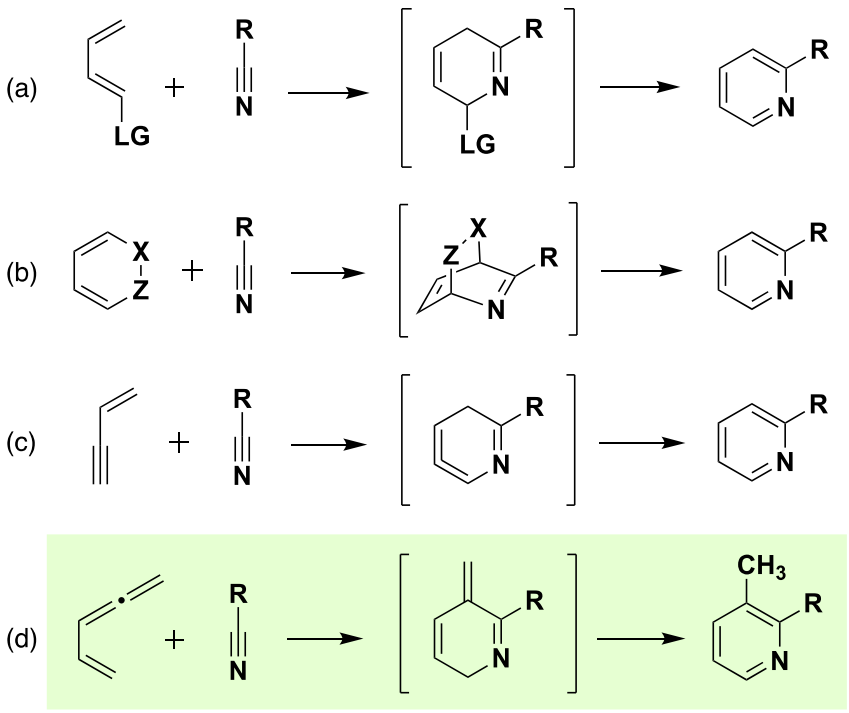
The design and invention of new strategies for the synthesis of highly substituted pyridines continues to command significant attention due to the incorporation of this heterocycle in the structures of a number of natural products, functional materials, and pharmaceutical compounds.[1] In this area an important challenge is the development of efficient methods with the ability to deliver unsymmetrical, multisubstituted pyridines from readily available precursors.[2] Transition-metal-catalyzed [2 + 2 + 2] cycloadditions involving nitriles and imine derivatives[3] and convergent annulation strategies[4] have been

the focus of significant attention and provide some satisfactory solutions to this problem. A particularly powerful approach to the synthesis of highly substituted pyridines employs hetero Diels-Alder reactions involving azadienes and azadienophiles.[5] These [4 + 2] cycloadditions frequently proceed with excellent regiochemistry and take place under metal-free conditions simply upon heating.

One limitation of the aza Diels-Alder strategy is that it initially generates di- and tetrahydropyridines, therefore requiring one or more additional steps to furnish the aromatic pyridine oxidation state. Aromatization in some cases can be achieved by dehydrogenation, but this process often requires harsh reaction conditions. An alternative approach employs suitably functionalized azadienes designed to furnish the desired pyridine via cycloreversion or fragmentation following the cycloaddition reaction.[6] Although a number of ingenious methods have been reported, the development of Diels-Alder strategies that provide pyridines directly from readily available precursors without the need for post-cycloaddition aromatization steps continues to be an active area of investigation.

Research in our laboratory has focused on the application of various classes of azadienophiles to the synthesis of highly substituted pyridines.[7] We have regarded Diels-Alder reactions of cyano compounds to be particularly attractive since the resulting cycloadducts require the introduction of only one additional degree of unsaturation to achieve the pyridine oxidation state. As outlined in Scheme 1, this transformation can be accomplished via elimination (pathway a, LG = leaving group), cycloreversion (pathway b), and by double-bond isomerization (pathways c[8] and d). Our studies have focused on the latter two pathways, particularly reactions of vinylallenes (pathway d) in which the isoaromatic cycloadducts are expected to undergo isomerization to pyridines spontaneously or under very mild conditions.

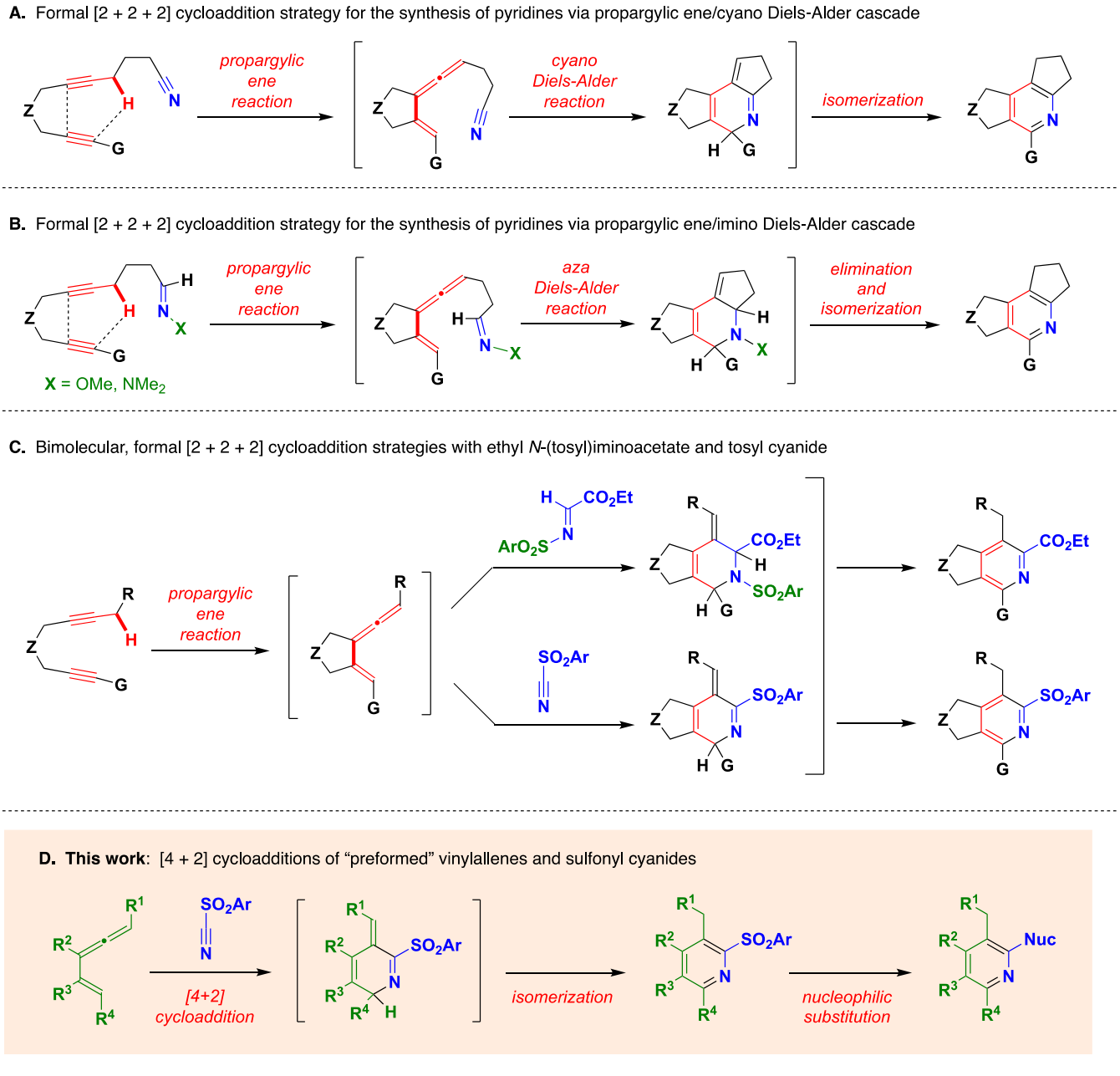
Scheme 1. Strategies for the Synthesis of Pyridines via Cyano Diels-Alder Reactions



Recent reports from our laboratory and that of Palenzuela[9] have demonstrated the ability of vinylallenes to serve as 4-π cycloaddition partners in Diels-Alder strategies for the synthesis of pyridines. In 2010, we described a formal [2 + 2 + 2] cycloaddition strategy for the synthesis of polycyclic pyridines involving a two-stage pericyclic cascade mechanism (Scheme 2A).[10] The cascade begins with an intramolecular propargylic ene reaction that produces a vinylallene that is locked in an s-cis conformation. This vinylallene is an unusually reactive Diels-Alder reaction partner[11,12] and engages in [4 + 2] cycloadditions with normally unreactive azadienophiles including unactivated cyano groups (Scheme 2A) and heterosubstituted imine derivatives such as dimethylhydrazones and oximino ethers (Scheme 2B).[13] The products generated in these cycloadditions isomerize to pyridines upon further heating or, in some cases, upon addition of base. Initial attempts to extend these fully intramolecular processes to the more challenging synthesis of pyridines via "bimolecular" [2 + 2 + 2] strategies were not successful. Unactivated nitriles did not prove reactive enough to efficiently trap vinylallenes in intermolecular cycloadditions, but we did discover that ethyl *N*-(tosyl)iminoacetate and commercially available tosyl

cyanide do react and form intermediates that undergo elimination and isomerization to furnish pyridines (Scheme 2C).[14] The products obtained from reactions of TsCN proved particularly useful since they react with carbon and heteroatom nucleophiles via addition/elimination pathways to provide products with a variety of new substituents at C2 (vide infra).

Scheme 2. Strategies for the Synthesis of Pyridines via [4 + 2] Cycloadditions of Vinylallenes

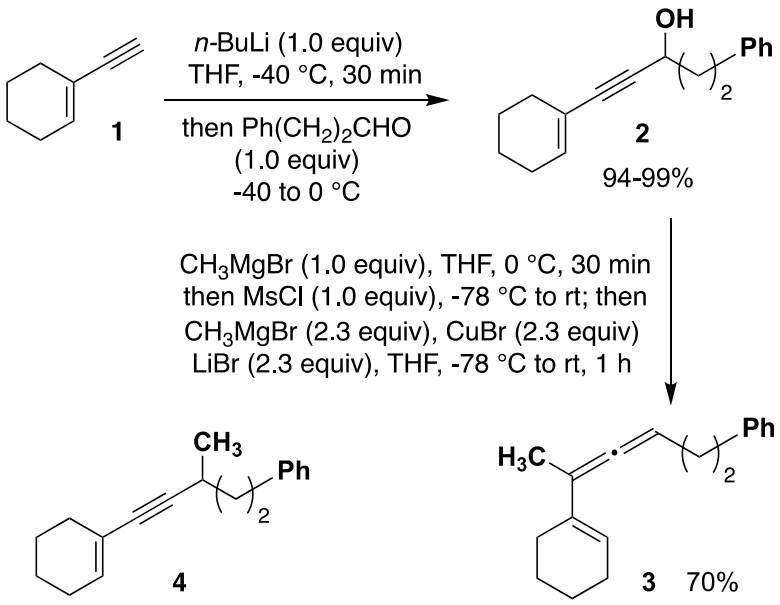


One limitation associated with these previous methods is the constraint that the vinylallene be generated via an intramolecular propargylic ene reaction, thus leading to tricyclic products in the case of unimolecular reactions (Schemes 2A and 2B), and bicyclic systems in the case of the bimolecular variant (Scheme 2C). The effectiveness of the hetero Diels-Alder reactions of tosyl cyanide with vinylallenes generated by propargylic ene reactions led us to wonder whether this cycloaddition might proceed efficiently with a wider range of vinylallenes prepared and isolated via alternative routes. Many functionalized and multisubstituted vinylallenes are readily available by well-established methods,[15] suggesting that vinylallene-tosyl cyanide cycloadditions, when applied in conjunction with sulfonylpyridine substitution chemistry, might provide expeditious routes to a variety of highly substituted pyridines (Scheme 2D).

RESULTS AND DISCUSSION

Preparation of Vinylallenes via Organocopper Chemistry. The initial goal in our investigation was to explore the effect of vinylallene substituents on the efficiency and regiochemistry of cycloadditions with tosyl cyanide. The requisite vinylallenes for this study were prepared by S_N2'-type substitution reactions of propargylic alcohol derivatives with organocopper compounds, one of the most general and reliable methods for the synthesis of substituted allenes.[15,16] In this fashion a series of vinylallenes was obtained in good yield in 2-3 steps via readily available propargylic ethers, benzoates, and sulfonates.[17] Scheme 3 describes a representative synthesis using this approach. In this case reaction of the methyl organocopper reagent with the mesylate derivative[18] of **2** proceeded regioselectively to furnish the desired vinylallene **3** in good yield, although reaction of the corresponding benzoate under the same conditions afforded a mixture of allene **3** (35%) and the direct substitution product **4** (25%).

Scheme 3. Synthesis of Vinylallene 3 via an Organocopper Substitution Reaction



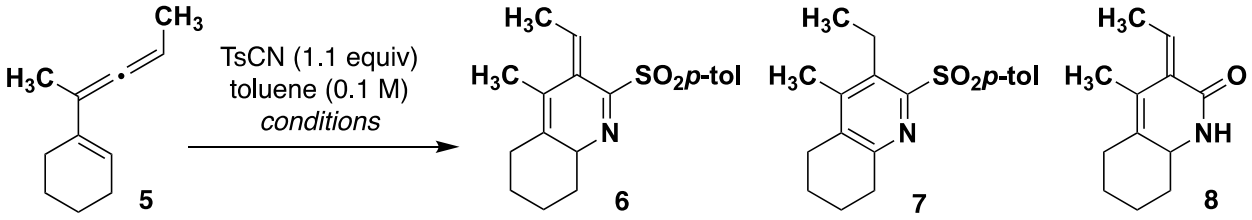
Optimization of Conditions for the Vinylallene-Tosyl Cyanide Cycloaddition. The application of tosyl cyanide as an azadienophile was pioneered by van Leusen in the 1970s[19] and the utility of this commercially available reagent in hetero Diels-Alder reactions has since been demonstrated in a number of laboratories.[14,20] Unfortunately, the reactions of tosyl cyanide with acyclic dienes were found by van Leusen to be complicated by the generation of significant amounts of lactam byproducts. These side products result from hydrolysis of the intermediate dihydropyridines,[19b] a process that is autocatalytic in water, which is generated by disproportionation of the sulfinic acid formed in the hydrolysis.[21]

Vinylallene **5** was chosen as the substrate for the optimization of conditions for the proposed Diels-Alder/isomerization strategy (Table 1). Reaction of **5** with 1.1 equiv of tosyl cyanide in carefully dried toluene at either room temperature or at reflux resulted in the formation of a complex mixture of

products in which the major component was the lactam **8**. Reaction in the presence of various bases to scavenge any sulfinic acid that formed failed to effectively suppress hydrolysis and less hindered bases were observed to react with tosyl cyanide. For example, both DBU and potassium *t*-butoxide were observed to react with tosyl cyanide even at room temperature, and an attempt to use $(i\text{-Pr})_2\text{EtN}$ as base (entry 5) led to a complex mixture due to reaction of the base with the dienophile.

We next turned our attention to performing the reaction in the presence of 4 Å molecular sieves as a water scavenger. Heating the vinylallene at 50 °C overnight in the presence of sieves led to the formation of cycloadduct **6** accompanied by only trace amounts of the lactam byproduct. We next found that isomerization of the isopyridine cycloadduct to pyridine **7** could be conveniently achieved in the same flask by cooling the reaction mixture to room temperature and adding either DBU or potassium *t*-butoxide. By using freshly purified vinylallene, the desired pyridine could be isolated in 68% yield after chromatographic purification. The regiochemical assignment for **7** was confirmed by differential nOe experiments.

Table 1. Optimization of Conditions for the Cycloaddition of Vinylallene 5



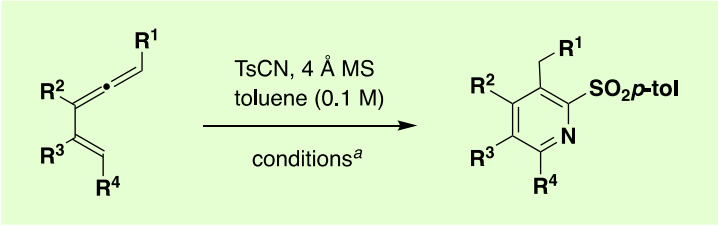
entry	conditions	% **6**	**% 7**	**% 8**
1	reflux, 1 h		complex mixture	
2	rt, 72 h		complex mixture	
3	$CaCO_3$,[a] reflux, 1 h		complex mixture	
4	$CaCO_3$,[a] 50 °C, 15 h	--	trace	51

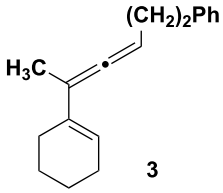
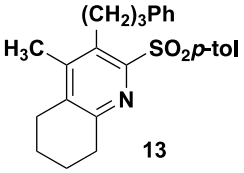
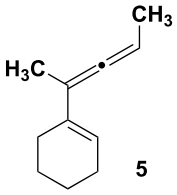
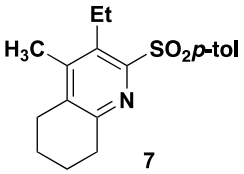
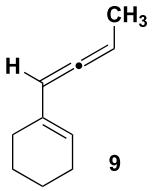
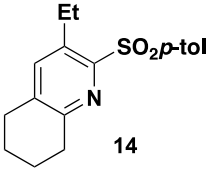
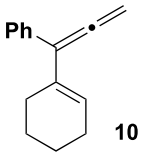
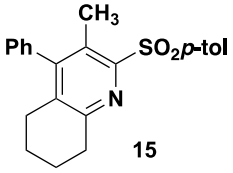
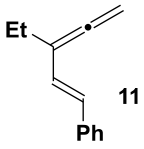
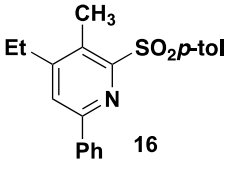
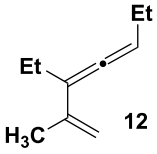
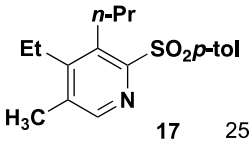
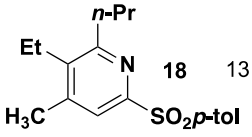
5	(i-Pr)$_2$EtN,[b] 50 °C, 15 h		complex mixture	
6	2,6-di-*tert*-butylpyridine[b] 50 °C, 15 h		mixture of **7** and **8**	
7	4 Å MS,[c] 50 °C, 15 h	56[d]	--	trace
8	4 Å MS,[c] reflux, 5 h		complex mixture	
9	4 Å MS,[c] 2,6-di-*tert*-butylpyridine[b] 50 °C, 20 h	38	15	--
10	4 Å MS,[c] 50 °C, 15 h then DBU[a], rt, 1 h	--	55, 68[e]	--
11	4 Å MS,[c] 50 °C, 15 h then KO*t*-Bu[a], rt, 1 h	--	55	--

[a] 1.0-1.1 equiv of base was used. [b]2 equiv of base was used. [c]1:1 wt/wt sieves/vinylallene was employed. [d]Yield estimated by H NMR analysis; product was obtained in ca. 80% purity. [e]Yield using freshly purified vinylallene.

Scope of the Cycloaddition. With optimized conditions for the cycloaddition and in situ isomerization in hand, we next turned our attention to investigating the scope of this strategy for the synthesis of highly substituted pyridines. Table 2 summarizes our results for reactions using vinylallenes generated by organocopper substitution reactions.

Table 2. Cycloadditions of Vinylallenes and Tosyl Cyanide



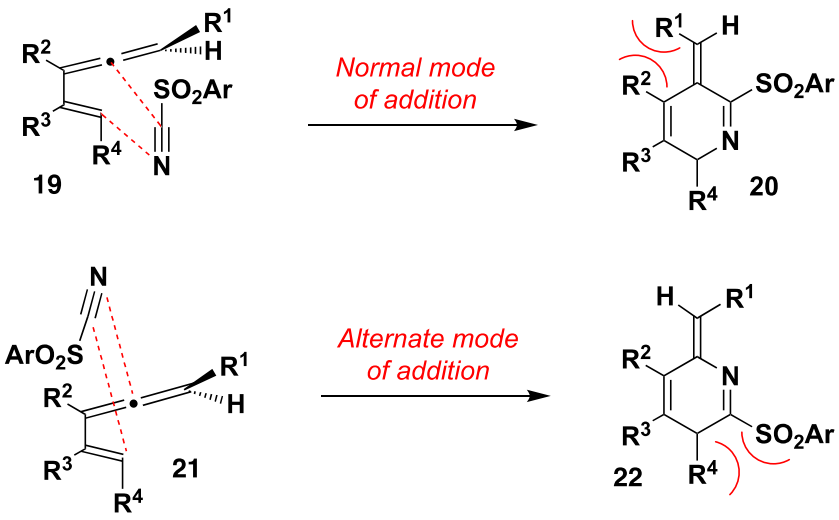
entry	vinylallene	conditions[a]	product	yield (%)[b]
1	 **3**	60 °C, 12 h or 90 °C, 3 h then DBU rt, 1 h	 **13**	68
2	 **5**	50 °C, 12 h then DBU rt, 1 h	 **7**	68
3	 **9**	80 °C, 8 h then DBU rt, 1 h	 **14**	45
4	 **10**	95 °C, 8 h[c] then DBU rt, 1 h	 **15**	42
5	 **11**	50 °C, 24 h	 **16**	73
6	 **12**	80 °C, 8 h then DBU rt, 15 h	 **17**	25
			 **18**	13

[a] Reaction of vinylallene with 1.1 equiv of TsCN in the presence of 4 Å MS (1:1 by weight) in toluene at the indicated bath temperature. For entries 1-4 and 6, the reaction mixture was cooled to rt and treated with 1.1 equiv of DBU at rt for 1-15 h. [b] Isolated yield of products purified by column chromatography. [c]In this case the vinylallene was slowly added (5 h) to the solution of TsCN and sieves.

While the optimal conditions for cycloaddition of tetrasubstituted vinylallenes **3** and **5** were found to involve heating overnight at 50-60 °C, the less substituted allene **9** required heating at 80 °C for 8 h to achieve complete reaction (entry 3). The success of this cycloaddition is noteworthy as Palenzuela reported that vinylallene **9** fails to undergo Diels-Alder reaction with *N*-benzylimines in the presence of Lewis acids.[22] Application of the cycloaddition/isomerization strategy to vinylallenes lacking substituents at the allene terminus provides access to pyridines bearing methyl substituents (entries 4 and 5), and in the case of the phenyl-substituted substrate **11,** base treatment was not necessary as the initial cycloadduct isomerized to pyridine **16** under the conditions of the cycloaddition.

Only a single regioisomeric pyridine was detected in the cycloadditions described in entries 1 to 5. These results are consistent with previous observations on the regiochemical course of vinylallene Diels-Alder reactions[11,12] in which the favored transition state involves bond formation between the sp carbon of the vinylallene and the more electron deficient atom of the dienophile π bond.[23] Scheme 4 depicts this "normal" regiochemical mode of cycloaddition with TsCN, which is favored electronically and also avoids a destabilizing steric interaction between R^4 and the arylsulfonyl group that develops in the transition state leading to the alternate regioisomer **22**. Note also that the favored transition state involves approach of the dienophile from the face of the vinylallene opposite to the larger group (R^1) on the terminus of the allene,[24] thus avoiding an unfavorable non-bonding interaction between R^1 and the arylsulfonyl group.

Scheme 4. Alternatives for the Regiochemical Course of the Cycloaddition

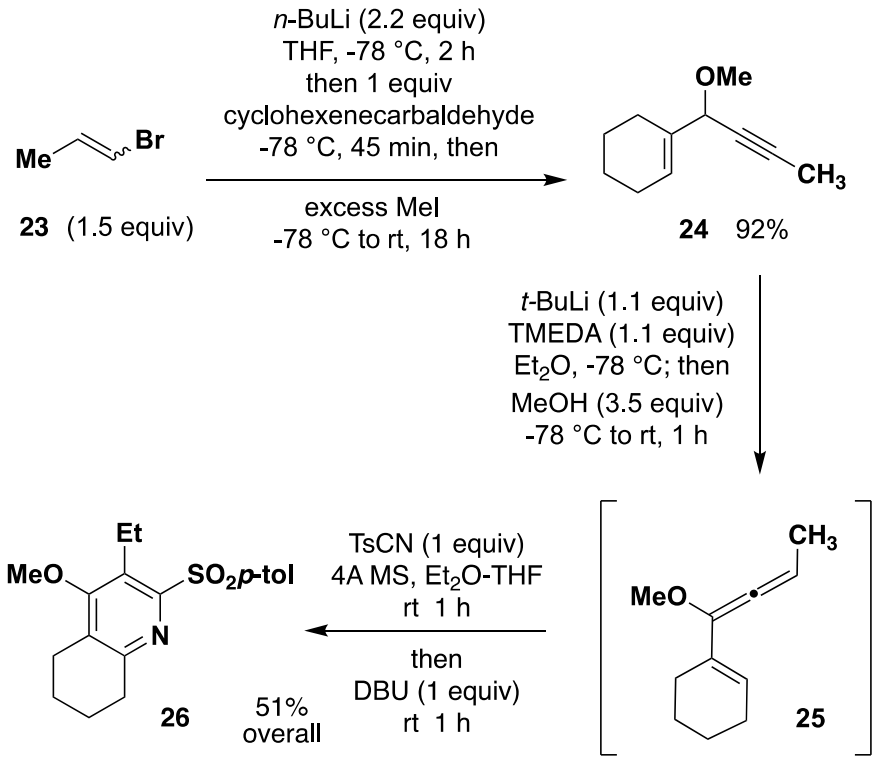


In contrast to the reactions in entries 1-5, reaction of vinylallene **12** lacking a substituent at the vinyl terminus (R^4) gave a 66:34 mixture of the expected product **17** and the regioisomeric pyridine **18** (entry 6). We believe that the normal mode of addition is less favorable in this case due to the absence of an electron-donating alkyl group (R^4), and the unfavorable steric interaction that develops between the two ethyl groups in the transition state leading to **20**. Consistent with this is the observation that related substrates with bulky groups at the terminal position of the allene (e.g., cyclohexyl in place of ethyl at the terminal position of **21**) react very sluggishly and afford complex mixtures of products that include the desired pyridines in only 5-10% yield. Note, however, that this limitation can be overcome by using more reactive vinylallenes bearing electron-donating methoxy substituents (vide infra).

Synthesis and Cycloadditions of Vinylallenyl Ethers. We next turned our attention to cycloadditions involving vinylallenes substituted with an electron-donating alkoxy group at the internal vinylallene carbon. It was our expectation that vinylallenes of this type would be particularly reactive as diene partners and that their cycloadditions would proceed with high regioselectivity. Allenyl ethers are valuable synthetic building blocks and are easily prepared by base-promoted isomerization of propargylic

ethers.[25] Scheme 5 outlines the preparation of allenyl ether **25**. Addition of propynyllithium (generated by Suffert's procedure[26]) to cyclohexenecarbaldehyde furnished the propargylic ether **24** after trapping in situ with methyl iodide. Isomerization to the alkoxyallene **25** then proceeded smoothly using the protocol described by Frontier.[27] All attempts to isolate and purify this allenyl ether were complicated by decomposition that occurred upon concentration, and we consequently found it best to employ the ether solution of **25** obtained from the aqueous workup directly and immediately in the cycloaddition. In this fashion, the desired pyridine **26** was obtained in 51% overall yield from the propargylic ether by reaction with tosyl cyanide and then DBU under the indicated conditions.

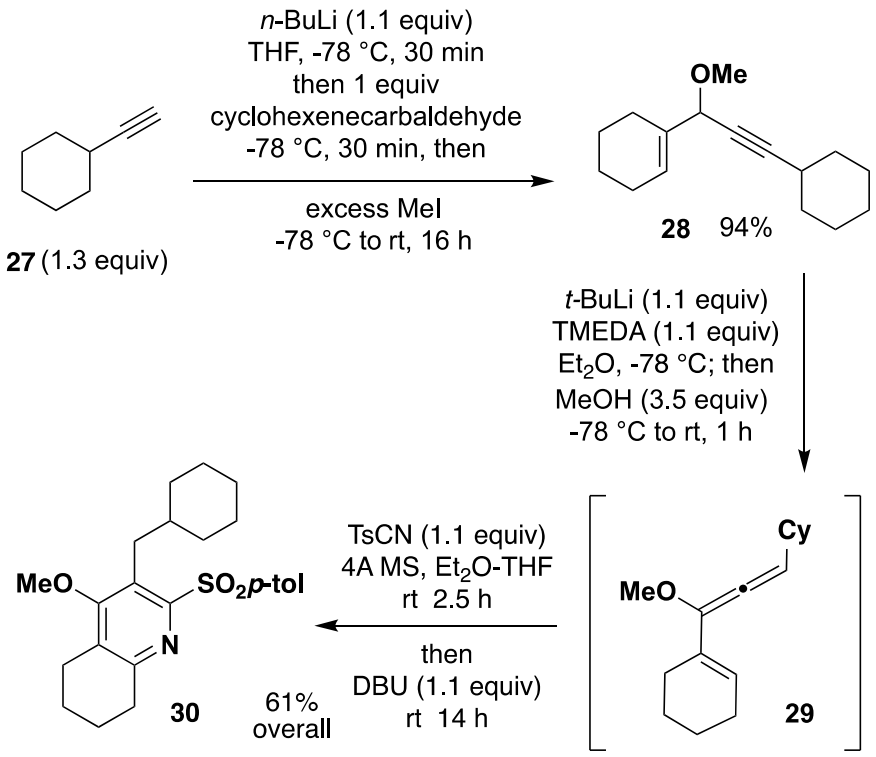
Scheme 5. Synthesis and Cycloaddition of Vinylallenyl Ether 25



The facility of the Diels-Alder reaction of this methoxy-substituted vinylallene is noteworthy as the cycloaddition in this case took place rapidly at room temperature. We next examined the reaction of vinylallenyl ether **29** bearing a more sterically demanding cyclohexyl substituent (Scheme 6) and were

pleased to find that this substrate underwent cycloaddition/isomerization with equal facility to afford the 4-methoxy-substituted pyridine **30** in good overall yield.

Scheme 6. Synthesis and Cycloaddition of Vinylallenyl Ether 29

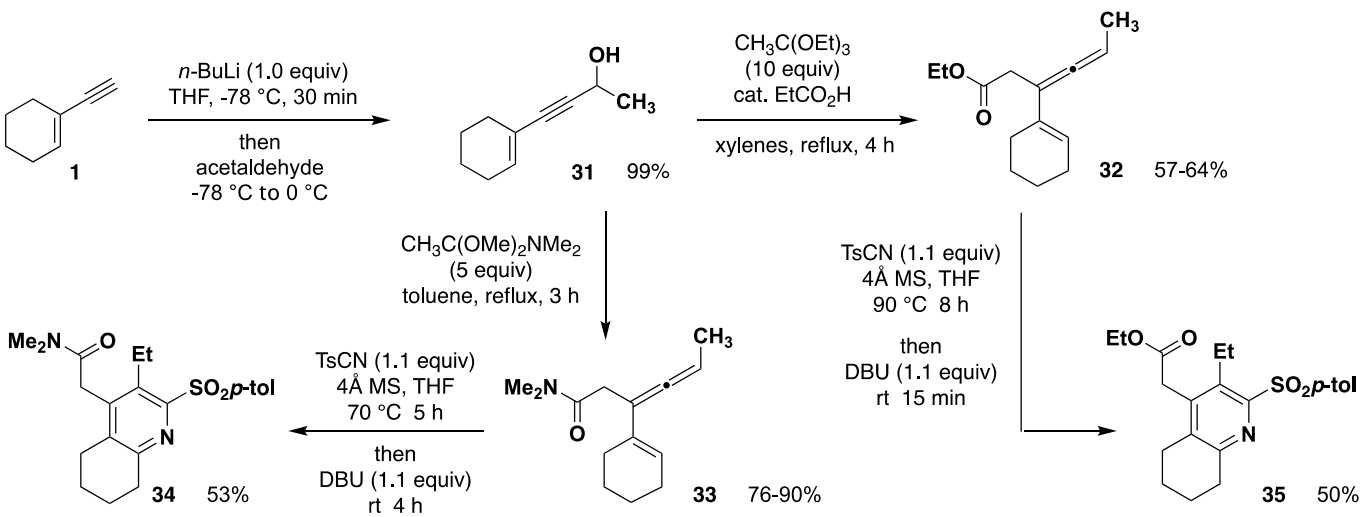


Synthesis and Cycloadditions of Vinylallenes Prepared by Sigmatropic Rearrangements.

Sigmatropic rearrangement involving propargylic alcohol derivatives[28] provides another attractive route to substituted allenes, and we next investigated the application of this chemistry in the synthesis of pyridines substituted at the C4 position with functionalized side chains. As outlined in Scheme 7, the Johnson orthoester and Eschenmoser rearrangements[29] of enynyl alcohol **31** furnished convenient access to vinylallenes **32** and **33**, respectively, and reaction of each with tosyl cyanide produced the expected isopyridines which isomerized to the desired pyridines upon exposure to DBU. The reaction of **32** with

tosyl cyanide was very slow at 60 °C and was best carried out at 90 °C. Similarly, the Diels-Alder reaction of the vinylallenyl amide **33** required 24 h when effected at 50 °C and gave the desired pyridine in only 31% yield after treatment with DBU. Attempts to carry out both sigmatropic rearrangement and Diels-Alder reaction as a "one-flask" operation were not successful due to the interference of side reactions involving reaction of tosyl cyanide at elevated temperature with the alcohols liberated in the rearrangement step.

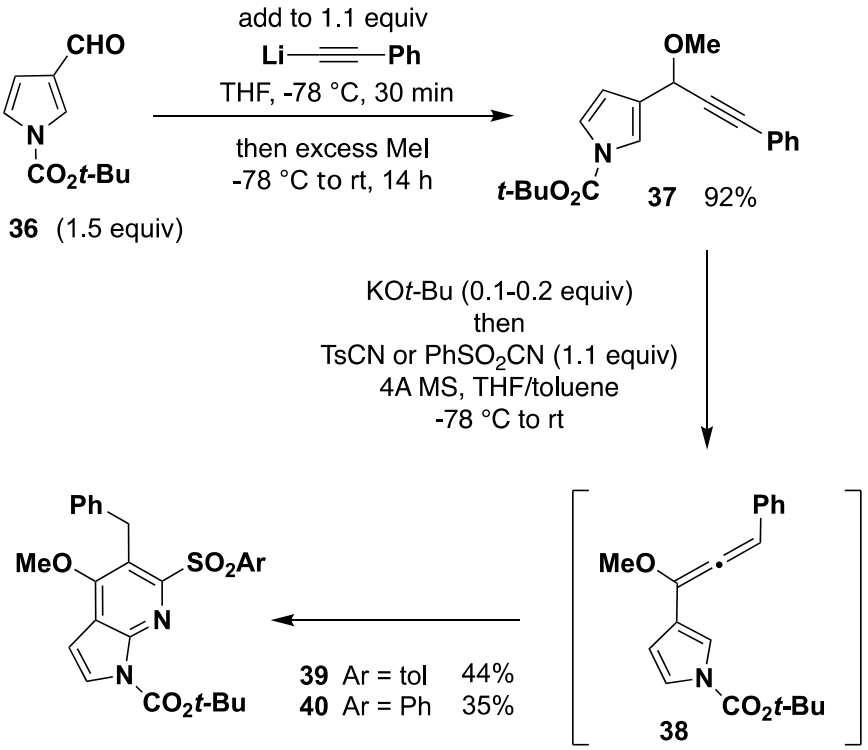
Scheme 7. Synthesis and Cycloaddition of Vinylallenes 32 and 33



Synthesis of 7-Azaindoles. Azaindoles comprise a class of pharmacologically important heterocyclic compounds that have been the subject of considerable recent interest from synthetic and medicinal chemists.[30] Schemes 8 and 9 outline the application of 2- and 3-(allenyl)pyrrole cycloadditions for the synthesis of 7-azaindoles. Although Diels-Alder reactions of 2- and 3-vinylpyrroles are well known,[31] to our knowledge no cycloadditions involving allenypyrroles[32] have been reported previously. Addition of the known[33] protected 3-formylpyrrole **36** to lithium phenylacetylide afforded the propargylic methyl ether **37** in excellent yield after in situ trapping with methyl iodide. In this case isomerization to

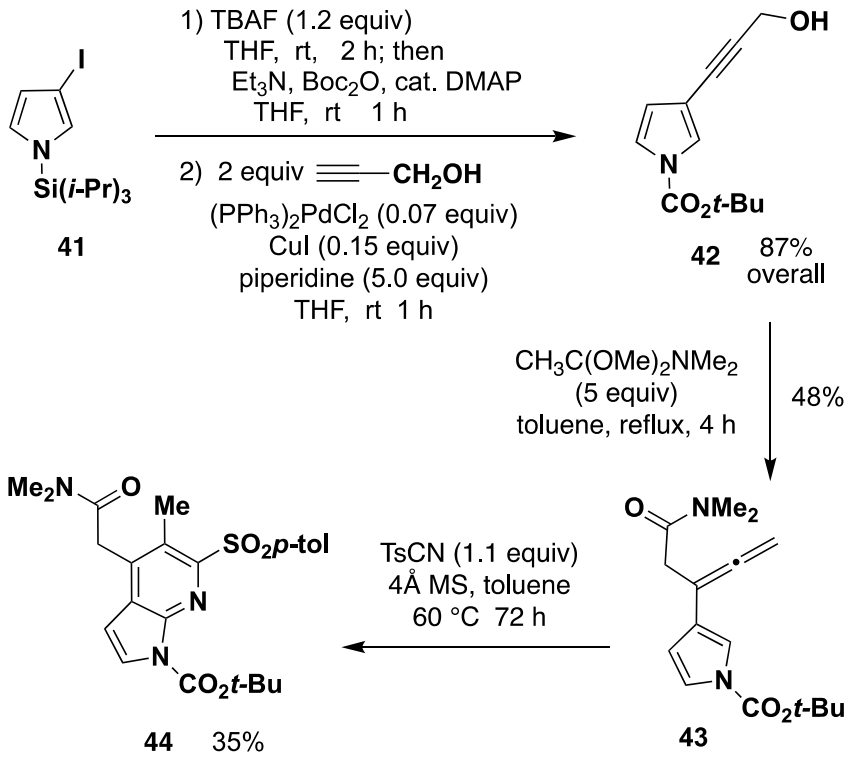
the allenyl ether was best achieved at -78 °C with catalytic potassium *t*-butoxide since metalation of the pyrrole ring was observed in reactions with *t*-butyllithium using our prior protocol. Slow addition of tosyl cyanide or benzenesulfonyl cyanide to the solution of allenyl ether and sieves at -78 °C and warming to room temperature then provided the desired 7-azaindole.

Scheme 8. Synthesis and Cycloaddition of Allenylpyrrole 38



As shown in Scheme 9, Diels-Alder reaction of tosyl cyanide with allenylpyrrole **43,** which was prepared via Eschenmoser rearrangement was also successful, and in this case isomerization of the initial cycloadduct to the aromatic azaindole did not require the addition of base.

Scheme 9. Synthesis and Cycloaddition of Allenylpyrrole 43



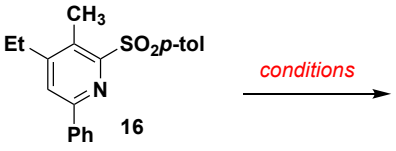
Ipso Substitution Reactions. The 2-sulfonyl groups attached at C2 of the new pyridine ring are useful handles for further synthetic elaboration. Nucleophilic substitution reactions of both 2- and 4-halopyridines as well as analogous sulfonyl pyridine derivatives are well documented.,[34] Barlin and Furukawa[35] carried out key early work in this area, and these reactions have since been utilized for the synthesis of a wide range of pyridines.[36]

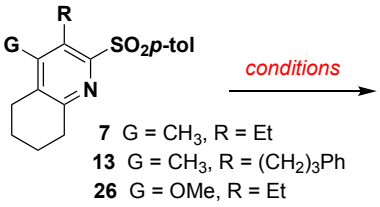
Table 3 describes the scope of the nucleophilic aromatic substitution reactions of several of our pyridine cycloadducts. Monocyclic pyridine **16** reacts with various alkyl and aryl Grignard reagents to produce the corresponding substituted pyridines in generally good yield. In these cases, an excess of the Grignard reagent is required for full conversion; with fewer equivalents a significant amount of unreacted starting material is recovered. Cyanide is also a competent nucleophile for this reaction, although elevated temperature is necessary for efficient reaction. Potassium ethoxide (generated in situ from KO*t*-Bu and EtOH) reacts with **16** in THF at room temperature to afford ethoxypyridine **49** in excellent yield.

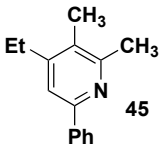
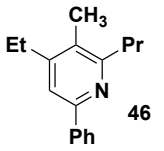
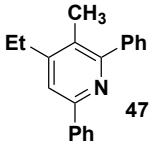
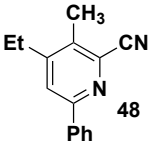
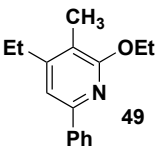
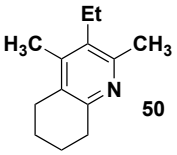
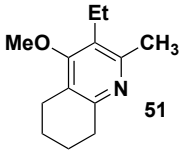
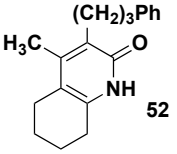
Unfortunately, to date we have not developed conditions for the efficient substitution reactions of these sulfonylpyridines with nitrogen nucleophiles.

Bicyclic sulfonylpyridine cycloadducts are also suitable substrates for *ipso*-substitution reactions. For example, pyridine **7** reacts with an excess of CH_3MgBr to give the expected product **50**, and pyridine **26** incorporating a methoxy substituent also undergoes the substitution reaction in good yield. Finally, 2-pyridone **52** was obtained by reaction of pyridine **13** with potassium hydroxide generated according to the procedure developed by Gassman and co-workers.[37]

Table 3. *Ipso*-Substitution Reactions of 2-Sulfonylpyridines





entry	conditions	product	yield (%)[a]
1	CH_3MgBr (3.0 equiv) THF, reflux, 15 h	 **45**	90
2	PrMgBr (3.0 equiv) THF, reflux, 13 h	 **46**	77-82
3	PhMgCl (6 equiv) THF, reflux, 16 h	 **47**	87
4	NaCN (5 equiv) 18-crown-6 (5 equiv) DMF, reflux, 48 h	 **48**	86
5	KO*t*-Bu (2.4 equiv) EtOH (2.4 equiv) THF, rt, 40 min	 **49**	91
6	**7** CH_3MgBr (6 equiv) THF, 70 °C, 1.5 h	 **50**	53
7	**7** CH_3MgBr (12 equiv) THF, rt, 24 h		54
8	**26** CH_3MgCl (12 equiv) THF, rt, 16 h	 **51**	78
9	**13** KO*t*-Bu (6 equiv) H_2O (2.0 equiv) THF, reflux, 16 h	 **52**	75

[a] Isolated yield of products purified by column chromatography.

CONCLUSION

We have developed a convergent method for the synthesis of highly substituted pyridines based on the Diels-Alder reaction of vinylallenes with arylsulfonyl cyanides. An initial Diels-Alder addition leads to isopyridine cycloadducts, which isomerize to the aromatic pyridines upon further heating or after exposure to base. In the case of most alkyl- and aryl-substituted vinylallenes, optimal conditions for the cycloaddition involve heating at 50-60 °C. For those cases in which reaction was found to be sluggish at that temperature, heating at 80-95 °C brings about Diels-Alder reaction at a reasonable rate. In contrast, cycloadditions of vinylallenes bearing electron-donating methoxy substituents undergo reaction at or below room temperature.

The resulting 2-sulfonylpyridines undergo nucleophilic aromatic substitution reactions with various nucleophiles. Further studies are underway in our laboratory aimed at the application of this chemistry in the total synthesis of pyridine containing natural products.

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. Triethylamine was distilled under argon from calcium hydride. DMF was stirred over CaH_2 for 24 h and then distilled under argon from $MgSO_4$ at 20 mmHg. Phenylpropanal was distilled under reduced pressure (98 °C at 12 mmHg), cyclohexenecarbaldehyde distilled under reduced pressure (86 °C at 60 mmHg), and acetaldehyde was distilled at atmospheric pressure. MsCl was distilled under reduced pressure from P_2O_5 (60 °C at 20 mmHg). Phenylacetylene and methyl iodide were filtered through a plug of activated alumina prior to use. 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). LiBr was dried under vacuum (0.02 mmHg) at 200 ºC (bath temperature) for 18 h before use. Molecular sieves (4 Å) were dried under vacuum (0.1 mmHg) at 300 °C for 16 h before use. *n*-Butyllithium was titrated using menthol in THF with 1,10-phenanthroline as an indicator. $CH_3C(OMe)_2NMe_2$ was distilled from CaH_2 at atmospheric pressure.

Instrumentation. Melting points were determined with a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were obtained using a Perkin Elmer 2000 FT-IR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were measured with Inova 500, Inova 300, Bruker 600, and Bruker 400 spectrometers. ^{1}H Chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane (with the $CHCl_3$ resonance at 7.27 ppm, the C_6H_6 resonance at 7.15 ppm, or the CD_2Cl_2 resonance at 5.33 ppm used as a standard). ^{13}C NMR chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane (with the central peak of $CHCl_3$ at 77.23 ppm used as a standard). High resolution mass spectra (HRMS) were measured on a Bruker Daltronics APEXII 3 tesla Fourier transform mass spectrometer or an Ion Sense AccuTOF 4G LC-Plus Q-TOF DART mass spectrometer.

1-(Cyclohex-1-en-1-yl)-5-phenylpent-1-yn-3-ol (2). A 100-mL, two-necked, round-bottomed flask equipped with two rubber septa and an argon inlet needle was charged with cyclohexenylacetylene (0.584 g, 5.50 mmol, 1.2 equiv) and 40 mL of THF. The solution was cooled to -40 °C, and 1.81 mL of *n*-butyllithium solution (2.33 M in hexane, 4.58 mmol, 1.0 equiv) was added dropwise via syringe over 5 min. The resulting solution was stirred at -40 °C for 30 min. A solution of 3-phenylpropionaldehyde (0.615 g, 4.58 mmol, 1.0 equiv) in 3 mL of THF was then added via cannula over 5 min, the cooling bath was replaced with an ice bath, and the solution was stirred at 0 °C for 30 min. The reaction mixture was treated with 13 mL of satd aq NH_4Cl solution and 10 mL of water, and the aqueous phase was separated and extracted with three 30-mL portions of EtOAc. The combined organic extracts were washed with 70 mL of satd aq NaCl solution, dried over $MgSO_4$, filtered, and concentrated to furnish 1.31 g of a yellow oil. Column chromatography on 30 g of silica gel (elution with 0-5% EtOAc-hexanes) afforded 1.073 g (97%) of **2** as a pale green oil: IR (NaCl) 3348, 2859, 2937, 2217, 1493, 1449, 1436, 1336, 1206, 1049, 1008, 919, 842, 800, 749 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.18-7.33 (m, 5 H), 6.11-6.16 (m, 1 H), 4.47-4.53 (t, J = 6.5 Hz, 1 H), 2.78-2.86 (t, J = 7.5 Hz, 2 H), 1.98-2.17 (m, 6 H), 1.84-1.94 (br s, 1 H), 1.56-1.69 (m, 4 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 141.6, 135.6, 128.7, 128.6, 126.1, 120.3, 87.34, 87.29, 62.4, 39.7, 31.7, 29.4, 25.8, 22.5, 21.6; HRMS (DART-FTICR) *m/z:* $[M + NH_4]^+$ calcd for $C_{17}H_{24}NO$ 258.1852; found 258.1857.

5-(Cyclohex-1-en-1-yl)hexa-3,4-dien-1-yl)benzene (3). A 25-mL, pear-shaped flask equipped with a rubber septum and an argon inlet needle was charged with propargylic alcohol **2** and 0.5 mL of THF. The solution was cooled at -10 °C and 0.13 mL of methylmagnesium bromide solution (2.8 M in ether, 0.35 mmol, 1.0 equiv) was added dropwise via syringe over 4 min. The resulting solution was stirred for 30 min at -10 °C and then cooled at -78 °C. Methanesulfonyl chloride (27 μL, 0.039 g, 0.35 mmol, 1.0 equiv) was added dropwise via microliter syringe over 1 min. The reaction mixture was stirred for 30 min at -78 °C and then allowed to warm to rt and stirred for 1 h.

A 25-mL, two-necked, pear-shaped flask equipped with two rubber septa and an argon inlet needle was charged with LiBr (0.068 g, 0.790 mmol, 2.3 equiv), CuBr (0.119 g, 0.790 mmol, 2.3 equiv), and 3 mL of THF. The solution was cooled at 0 °C while 0.32 mL of methylmagnesium bromide solution (2.8 M in ether, 0.79 mmol, 2.3 equiv) was added dropwise via syringe over 2 min. The resulting mixture was stirred at 0 °C for 30 min and then cooled to -78 °C.

The solution of mesylate prepared previously was added to the cuprate reaction mixture dropwise via cannula over 5 min (0.25 mL THF wash) and the reaction mixture was then allowed to warm to rt and stirred for 1 h. The reaction mixture was treated with 2 mL of satd aq NH_4Cl solution and 3 mL of water. The resulting mixture was filtered through Celite under reduced pressure with the aid of hexanes, and the aqueous phase of the filtrate was extracted with three 30-mL portions of hexanes. The combined organic extracts were washed with 30 mL of satd aq NaCl solution, dried over $MgSO_4$, filtered, and concentrated to furnish 0.096 g of a yellow oil. Column chromatography on 7 g of silica gel (elution with pentane) afforded 0.058 g (70%) of **3** as a colorless oil: IR (NaCl) 2940, 2902, 2856, 2834, 2361, 1943, 1490, 1452, 1364, 1335, 1272, 1237, 1135, 1077, 1029, 915, 841, and 756 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.16-7.35 (m, 5 H), 5.65-5.71 (m, 1 H), 5.26-5.36 (m, 1 H), 2.76 (t, J = 7.5 Hz, 2 H), 2.32-2.42 (m, 2 H), 2.12-2.22 (m, 2 H), 1.85-2.12 (m, 2 H), 1.81 (d, J = 2.4 Hz, 3 H), 1.55-1.70 (m, 4 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 204.4, 142.1, 134.0, 128.8, 128.4, 126.0, 122.4, 103.2, 91.6, 35.7, 31.3, 27.2, 26.2, 23.2, 22.6, 16.7; HRMS (DART-FTICR) *m/z* $[M + H]^+$ calcd for $C_{18}H_{23}$ 239.1794; found 239.1795.

3-Ethyl-4-methyl-2-tosyl-5,6,7,8 tetrahydroquinoline (7). A 10-cm, threaded Pyrex tube (25 mm O.D.; 17 mm I.D.) equipped with a rubber septum fitted with an argon inlet needle was charged with 4 Å molecular sieves (0.150 g), tosyl cyanide (0.201 g, 1.11 mmol, 1.1 equiv), vinylallene **5**[22] (0.150 g, 1.01 mmol, 1.0 equiv), and 10 mL of toluene. The tube was sealed with a threaded Teflon cap and the reaction mixture was heated at 50 °C for 12 h and then allowed to cool to rt. DBU (0.17 mL, 0.17 g, 1.1 mmol, 1.1 equiv) was added dropwise via syringe over 0.5 min, and the reaction mixture was stirred at rt for 1 h. The resulting yellow suspension was washed with 20 mL of water and the aqueous phase was

extracted with three 20-mL portions of EtOAc. The combined organic layers were washed with 10 mL of water, washed with 10 mL saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.309 g of a yellow solid. Column chromatography on 30 g of silica gel (elution with 0-30% EtOAc-hexanes) afforded 0.226 g (68%) of **7** as a white solid: mp 149–152 °C; IR (NaCl) 2985, 2936, 2870, 1597, 1543, 1453, 1428, 1315, 1288, 1137, 1090, 1066, 810, 737, 678, 664 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, J = 8.0 Hz, 2 H), 7.24 (d, J = 8.0 Hz, 2 H), 3.17 (q, J = 7.5 Hz, 2 H), 2.63 (t, J = 6.5 Hz, 2 H), 2.59 (t, J = 6.0 Hz, 2 H), 2.37 (s, 3 H), 2.17 (s, 3 H), 1.67–1.76 (m, 4 H), 1.21 (t, J = 7.5 Hz, 3 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 153.8 (2C), 147.3, 143.5, 137.9, 134.8, 134.1, 129.2, 128.9, 32.7, 26.9, 22.7, 22.3, 21.4, 20.9, 14.4, 14.1; HRMS (DART-FTICR) *m/z* $[M + H]^+$ calcd for $C_{19}H_{24}NO_2S$ 330.1522; found 330.1502. Confirmation of cycloaddition regiochemistry is based on differential nOe experiments (500 MHz, $CDCl_3$): 1.6% from 3.17 ppm to 7.82 ppm, 6.8% from 3.17 ppm to 2.17 ppm, 5.7% from 3.17 ppm to 1.21 ppm.

(1-(Cyclohex-1-en-1-yl)propa-1,2-dien-1-yl)benzene (10). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and an argon inlet adapter was charged with CuBr (0.039 g, 0.26 mmol, 0.2 equiv), propargyl ether **S1**[38] (0.200 g, 1.33 mmol, 1.0 equiv), and 8 mL of Et_2O. The resulting solution was cooled at -30 °C, and 1.15 mL of phenylmagnesium bromide solution (3.0 M in Et_2O, 3.32 mmol, 2.5 equiv) was added dropwise via syringe. The resulting solution was allowed to warm to rt and stirred for 15 h. The reaction mixture was treated with 3 mL of satd aq NH_4Cl solution and the resulting mixture was diluted with 3 mL of water. The resulting mixture was washed with three 20-mL portions of Et_2O, and the combined organic layers were washed with 15 mL of water and 15 mL of satd aq NaCl solution, dried over $MgSO_4$, filtered, and concentrated to furnish 0.3 g of a pale-yellow oil. Column chromatography on 20 g of silica gel (elution with hexanes) furnished 0.189 g (72%) of **10** as a pale-yellow oil: IR (thin film) 3031, 2928, 1929, 1598, 1490, 1446, 849, 762, and 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26-7.28 (m, 4 H), 7.21 (m, 1 H), 5.54 (m, 1 H), 5.02 (s, 2 H), 2.17 (m, 2 H), 2.06

(m, 2 H), 1.68 (m, 2 H), 1.58 (m, 2 H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 209.2, 136.8, 132.6, 129.2, 129.0, 127.4, 127.1, 127.0, 111.2, 27.7, 26.1, 23.2, 22.5; HRMS (DART-FTICR) *m/z* $[M + H]^+$ calcd for $C_{15}H_{17}$ 197.1325; found 197.1337.

(*E*)-(3-Ethylpenta-1,3,4-trien-1-yl)benzene (11). A 50-mL two-necked round-bottomed flask equipped with two rubber septa and an argon inlet needle was charged with **S2**[39] (0.400 g, 2.32 mmol, 1.0 equiv), 20 mL of THF, and CuBr (0.066 g, 0.464 mmol, 0.2 equiv). The mixture was cooled at 0 °C and ethylmagnesium bromide (3.0 M in Et_2O, 1.54 mL, 4.64 mmol, 2.0 equiv) was added dropwise via syringe over 1 min. The resulting green solution was warmed to rt and stirred for 45 min and then 5 mL of satd aq NH_4Cl solution was added followed by 5 mL of water. The aqueous phase was separated and extracted with three 20-mL portions of Et_2O, and the combined organic layers were washed with 50 mL of satd aq NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give 0.399 g of a yellow solid. Column chromatography on 50 g of silica gel (elution with hexanes) afforded 0.317 g (80%) of **11** as a colorless solid: mp 38-41 °C; IR (film) 3031, 2965, 2933, 2913, 2872, 1928, 1448, 963, 861, and 690 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.5 Hz, 2 H), 7.37 (t, *J* = 7.5 Hz, 2 H), 7.27 (t, *J* = 7.5 Hz, 1 H), 6.79 (d, *J* = 16.5 Hz, 1 H), 6.55 (d, *J* = 16.5 Hz, 1 H), 5.06-5.07 (m, 2 H), 2.31-2.37 (m, 2 H), 1.22 (t, *J* = 7.5 Hz, 3 H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 212.0, 137.8, 128.8, 127.3, 127.1, 127.0, 126.3, 106.6, 77.0, 21.3, 12.3; HRMS (DART-FTICR) *m/z* $[M + H]^+$ calcd for $C_{13}H_{15}$ 171.1168; found 171.1171.

6-Methylhept-6-en-4-yn-3-yl benzoate (S4). A 50-mL, two-necked round-bottomed flask equipped with a stir bar, rubber septum, and an argon inlet adapter was charged with propargylic alcohol **S3**[40] (0.314 g, 2.53 mmol, 1.0 equiv), 25 mL of CH_2Cl_2, and DMAP (0.031 g, 0.253 mmol, 0.1 equiv). Triethylamine (0.49 mL, 0.36 g, 3.5 mmol, 1.4 equiv) and benzoyl chloride (0.41 mL, 0.50 g, 3.5 mmol, 1.4 mmol) were added via syringe in that order and the resulting solution was stirred at rt for 5 h. The reaction mixture was extracted with two 20-mL portions of 1 N aq HCl, 20 mL of satd aq $NaHCO_3$

solution, and 20 mL of satd aq NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give ca. 1 g of a colorless oil. Column chromatography on 25 g silica gel (elution with 0-50% CH_2Cl_2-hexanes) afforded 0.570 g (99%) of **S4** as a colorless oil: IR (NaCl) 3064, 2974, 2939, 2880, 2227, 1725, 1602, 1452, 1375, 1267, 1177, 1106, 1069, 1026, 928, 901, and 710 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.08-8.12 (m, 2 H), 7.56-7.59 (m, 1 H), 7.44-7.48 (m, 2 H), 5.72 (t, *J* = 6.5 Hz, 1 H), 5.33-5.35 (m, 1 H), 5.25-5.27 (m, 1 H), 1.96 (app quint, *J* = 8.0 Hz, 2 H), 1.89-1.90 (m, 3 H), 1.11 (t, *J* = 7.5 Hz, 3 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 165.7, 133.3, 130.3, 130.0, 128.5, 126.3, 122.9, 86.8, 85.6, 66.2, 28.5, 23.5, 9.7; HRMS (DART) *m/z* $[M + NH_4]^+$ calcd for $C_{15}H_{20}NO_2$ 246.1489; found 246.1488.

3-Ethyl-2-methylhepta-1,3,4-triene (12). A 50-mL round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with LiBr (0.684 g, 7.88 mmol, 6.0 equiv) and then flame-dried under vacuum (100 mTorr) for 5 min. The flask was cooled to rt under argon and 10 mL of THF was added followed by CuBr (1.13 g, 7.88 mmol, 6.0 equiv). The solution was cooled at -60 °C as EtMgBr (3.0 M in Et_2O, 2.62 mL, 7.88 mmol, 6.0 equiv) was added dropwise via syringe over 2 min and the resulting brown solution was stirred at -60 °C for 10 minutes. A solution of propargylic benzoate **S4** (0.300 g, 1.31 mmol, 1.0 equiv) in 2 mL of THF was added dropwise via cannula over 1 min (2 mL THF rinse). The resulting mixture was allowed to warm to rt and stirred for 1 h. Satd aq NH_4Cl solution (10 mL) was added followed by 10 mL of pentane. The resulting mixture was filtered through a pad of Celite with the aid of ca. 50 mL of pentane. The aqueous phase was separated and extracted with three 10-mL portions of pentane and the combined organic layers were washed with 20 mL of satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated (0 °C, 40 Torr) to give ca. 0.2 g of a colorless oil. Column chromatography on 25 g of silica gel (elution with pentane) afforded 0.135 g (76%) of **12** as a colorless oil: IR (NaCl) 3094, 2965, 2933, 2873, 2361, 2342, 1943, 1619, 1457, 1375, 1290, and 878 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.45-5.48 (m, 1 H), 4.94-4.95 (m, 1 H), 4.87-4.88 (m, 1 H), 2.18-2.24 (m, 2 H), 2.05-2.11 (m, 2 H), 1.86 (s, 3 H), 1.07 (t, *J* = 7.5 Hz, 3 H), 1.04 (t, *J* = 7.0 Hz, 3 H); $^{13}C\{^1H\}$ NMR

(125 MHz, $CDCl_3$) δ 204.5, 141.1, 110.1, 109.6, 96.0, 22.5, 22.3, 22.2, 13.6, 12.7; HRMS (DART-FTICR) *m/z* $[M + H]^+$ calcd for $C_{10}H_{17}$ 137.1325; found 137.1332.

4-Methyl-3-(3-phenylpropyl)-2-tosyl-5,6,7,8-tetrahydroquinoline (13). A 10-mL, pear-shaped flask equipped with a rubber septum and an argon inlet needle was charged with 4 Å molecular sieves (0.045 g), tosyl cyanide (0.033 g, 0.19 mmol, 1.1 equiv), vinylallene **3** (0.040 g, 0.17 mmol, 1.0 equiv), and 1.7 mL of toluene. The rubber septum was replaced with a reflux condenser fitted with a rubber septum and argon inlet needle, and the reaction mixture was heated at 90 °C for 3 h. The resulting mixture was allowed to cool to rt, 28 μL of DBU (0.028 g, 0.19 mmol, 1.1 equiv) was added dropwise via syringe over 1 min, and the reaction mixture was stirred for 1 h at rt. The resulting yellow suspension was washed with 5 mL of water and the aqueous phase was extracted with three 10-mL portions of EtOAc. The combined organic extracts were washed with 20 mL of satd aq NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.085 g of a yellow oil. Preparative thin layer chromatography (elution with 10% EtOAc-hexanes) afforded 0.048 g (68%) of **13** as a pale gum: IR (NaCl) 3026, 2934, 1598, 1430, 1298, 1140, 1087, 912, 813, 733, 665 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.4 Hz, 2 H), 7.15-7.35 (m, 7 H), 3.05-3.13 (m, 2 H), 2.69-2.82 (m, 4 H), 2.59 (m, 2 H), 2.42 (s, 3 H), 2.06 (s, 3 H), 1.68-1.9 (m, 6 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) 154.2, 153.5, 147.6, 143.9, 142.1, 137.8, 135.2, 132.8, 129.3, 129.1, 128.7, 128.5, 126.0, 36.4, 33.0, 31.9, 27.8, 27.2, 22.8, 22.4, 21.8, 14.4; HRMS (DART) *m/z* $[M + H]^+$calcd. for $C_{26}H_{30}NO_2S$; 420.1992, found 420.1971.

3-Ethyl-2-tosyl-5,6,7,8-tetrahydroquinoline (14). A 10-cm, threaded Pyrex tube (25 mm O.D.; 17 mm I.D.) equipped with a rubber septum fitted with an argon inlet needle was charged with 4 Å molecular sieves (0.100 g), tosyl cyanide (0.137 g, 0.754 mmol, 1.1 equiv), vinylallene **9**[22] (0.092 g, 0.685 mmol, 1.0 equiv), and 7 mL of toluene. The tube was sealed with a threaded Teflon cap and the reaction mixture was heated at 80 °C for 8 h and then allowed to cool to rt. DBU (0.11 mL, 0.114 g, 0.754 mmol, 1.1 equiv) was added dropwise via syringe over 0.5 min, and the reaction mixture was stirred at rt for 1 h. The resulting yellow suspension was washed with 20 mL of water and the aqueous phase was extracted

with three 20-mL portions of EtOAc. The combined organic layers were washed with two 10-mL portions of water then 20 mL saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.189 g of an orange oil. Column chromatography on 25 g of silica gel (elution with 0-30% EtOAc-hexanes) afforded 0.085 g (39%) of **14** as a colorless oil: IR (NaCl) 3029, 2936, 2876, 1597, 1440, 1300, 1145, 1090, 925, 814, 711, 674, and 587 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, J = 8.5 Hz, 2 H), 7.28 (s, 1 H), 7.27 (d, J = 8.5 Hz, 2 H), 3.05 (q, J = 7.5 Hz, 2 H), 2.71-2.76 (m, 4 H), 2.39 (s, 3 H), 1.70-1.81 (m, 4 H), 1.23 (t, J = 7.5 Hz, 3 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 155.1, 152.9, 144.0, 140.2, 137.6, 136.6, 136.3, 129.4, 129.0, 32.0, 28.7, 24.4, 22.9, 22.4, 21.8, 15.7; HRMS (DART-FTICR) *m/z* $[M + H]^+$ calcd for $C_{18}H_{22}NO_2S$ 316.1366; found 316.1345.

3-Methyl-4-phenyl-2-tosyl-5,6,7,8 tetrahydroquinoline (15). A 10-cm, threaded Pyrex tube (25 mm O.D.; 17 mm I.D.) equipped with a rubber septum fitted with an argon inlet needle was charged with 4 Å molecular sieves (0.170 g), tosyl cyanide (0.120 g, 0.66 mmol, 1.1 equiv), and 3 mL of toluene. The resulting suspension was heated at 95 °C, and a solution of vinylallene **10** (0.119 g, 0.60 mmol, 1.0 equiv) in 3 mL of toluene was added dropwise via syringe pump over 5 h. The reaction mixture was stirred for an additional 3 h at 95 °C, and was then allowed to cool to rt and 0.1 mL of DBU (0.100 g, 0.66 mmol, 1.1 equiv) was added dropwise via syringe and the resulting suspension was stirred at rt for 1 h. The resulting yellow suspension was washed with 20 mL of water and the aqueous phase was extracted with three 20-mL portions of EtOAc. The combined organic layers were washed with 20 mL of water and 20 mL satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.220 g of a pale-yellow oil. Column chromatography on 40 g of silica gel (elution with 0-15% EtOAc-hexanes) afforded 0.093 g (42%) of **15** as a colorless oil: IR (thin film) 2946, 2862, 1291, 1142, and 568 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 8.2 Hz, 2 H), 7.47 (m, 2 H), 7.40 (m, 1 H) 7.34 (d, J = 8.5 Hz, 2 H), 7.03 (d, J = 8.2 Hz, 2 H) 2.82 (t, J = 6.4 Hz, 2 H), 2.46 (s, 3 H), 2.32 (s, 3 H) 2.30 (t, J = 6.3 Hz, 2 H) 1.77 (m, 2 H), 1.65 (m, 2 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 154.8, 154.0, 153.1, 144.1, 137.6, 137.2, 134.6, 129.4,

129.3, 129.2, 128.2, 128.1, 128.0, 53.6, 32.8, 28.3, 22.7, 21.9, 15.7; HRMS (DART-FTICR) *m/z* $[M + H]^+$ calcd for $C_{23}H_{24}NO_2S$ 378.1528; found 378.1528.

4-Ethyl-3-methyl-6-phenyl-2-tosylpyridine (16). A 16-cm, threaded Pyrex tube (38 mm O.D., 17 mm I.D., 100 mL capacity) equipped with a rubber septum fitted with an argon inlet needle was charged with 4 Å molecular sieves (0.780 g), tosyl cyanide (0.889 g, 4.93 mmol, 1.1 equiv), vinylallene **11** (0.763 g, 4.480 mmol, 1.0 equiv), and 45 mL of toluene. The tube was sealed with a threaded Teflon cap, and the reaction mixture was heated at 50 °C for 24 h and then allowed to cool to rt. Concentration gave 2.60 g of a yellow solid. Column chromatography on 140 g of silica gel (elution with CH_2Cl_2) afforded 1.136 g (72%) of **16** as a white solid: mp 180-183 °C; IR (film) 3059, 2980, 2927, 2890, 1590, 1433, 1286, 1152, 1085, 775, and 668 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.5 Hz, 2 H), 7.65 (s, 1 H), 7.59-7.61 (m, 2 H), 7.41 (d, *J* = 8.0 Hz, 2 H), 7.30-7.34 (m, 3 H), 2.79 (s, 3 H), 2.78 (q, *J* = 7.5 Hz, 2 H), 2.51 (s, 3 H), 1.30 (t, *J* = 7.5 Hz, 3 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 157.2, 155.9, 152.6, 144.3, 137.3, 136.2, 129.8, 129.4, 129.2, 128.9, 128.7, 126.4, 121.7, 26.4, 21.8, 13.7, 13.2; HRMS (DART-FTICR) *m/z* $[M + H]^+$ calcd for $C_{21}H_{22}NO_2S$ 352.1366; found 352.1354.

3-Ethyl-4-methyl-2-propyl-6-tosylpyridine (17) and 4-Ethyl-5-methyl-3-propyl-2-tosylpyridine (18). A 10-cm, threaded Pyrex tube (25 mm O.D.; 17 mm I.D.) equipped with a rubber septum fitted with an argon inlet needle was charged with 4 Å molecular sieves (0.140 g), tosyl cyanide (0.198 g, 1.09 mmol, 1.1 equiv), vinylallene **12** (0.135 g, 1.0 mmol, 1.0 equiv), and 10 mL of toluene. The tube was sealed with a threaded Teflon cap and the reaction mixture was heated at 80 °C for 8 h and then allowed to cool to rt. DBU (0.16 mL, 1.09 mmol, 1.1 equiv) was added dropwise via syringe over 0.5 min, and the reaction mixture was stirred at rt for 15 h. The resulting yellow suspension was washed with 20 mL of satd aq NH_4Cl and the aqueous phase was extracted with three 10-mL portions of EtOAc. The combined organic layers were washed with 10 mL of satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford ca. 0.4 g of a yellow oil. Column chromatography on 25 g of silica gel (elution with 50-100% CH_2Cl_2-hexanes, then 0-5% EtOAc-CH_2Cl_2) and combining fraction 0.102 g of impure **17**

and 0.078 g of impure **18**, each as a yellow oil. The impure **17** was further purified via column chromatography on 15 g of silica gel (elution with 0-30% Et_2O-pentane) to give 0.078 g (25%) of **17** as a colorless oil: IR (neat) 2969, 2872, 1597, 1577, 1455, 1314, 1148, 1086, 909, 729, and 672 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, J = 8.0 Hz, 2 H), 7.76 (s, 1 H), 7.30 (d, J = 8.0 Hz, 2 H), 2.75 (t, J = 7.5 Hz, 2 H), 2.66 (q, J = 7.5 Hz, 2 H), 2.40 (s, 3H), 2.38 (s, 3 H), 1.65-1.72 (m, 2 H), 1.10 (t, J = 7.5 Hz, 3 H), 0.88 (t, J = 7.5 Hz, 3 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 161.2, 155.1, 147.1, 144.3, 140.0, 136.8, 129.6, 129.1, 122.3, 36.5, 22.0, 21.8, 21.8, 19.6, 14.1, 13.4; HRMS (DART-FTICR) *m/z* $[M + H]^+$ calcd for $C_{18}H_{24}NO_2S$ 318.1522; found 318.1506.

The impure **18** was further purified via column chromatography on 15 g of silica gel (elution with 0-30% Et_2O-pentane) to give 0.042 g (13%) of **18** as a colorless oil: IR (neat) 2967, 2872, 1596, 1456, 1299, 1287, 1140, 1070, 908, 728, and 685 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.10 (s, 1 H), 7.87 (d, J = 8.0 Hz, 2 H), 7.33 (d, J = 8.0 Hz, 2 H), 3.07-3.10 (m, 2 H), 2.71 (q, J = 7.5 Hz, 2 H), 2.44 (s, 3 H), 2.30 (s, 3 H), 1.61-1.68 (m, 2 H), 1.14 (t, J = 7.5 Hz, 3 H), 1.10 (t, J = 7.5 Hz, 3 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 155.4, 153.2, 147.4, 146.5, 144.1, 137.4, 135.6, 129.5, 129.1, 29.7, 25.2, 22.0, 21.8, 16.8, 14.9, 13.5; HRMS (DART-FTICR) *m/z* $[M + H]^+$ calcd for $C_{18}H_{24}NO_2S$ 318.1522; found 318.1512. Confirmation of cycloaddition regiochemistry is based on differential nOe experiments (500 MHz, $CDCl_3$): 1.3% from 3.07-3.10 ppm to 7.87 ppm, 3.5% from 3.07-3.10 ppm to 2.71 ppm, 3.1% from 3.07-3.10 ppm to 1.61-1.68 ppm, 4.6% from 3.07-3.10 to 1.14 and 1.10.

1-(1-Methoxybut-2-yn-1-yl)cyclohex-1-ene (24). A 100-mL, three-necked, round-bottomed flask equipped with two rubber septa and a 20-mL graduated addition funnel fitted with a rubber septum and an argon inlet needle was charged with vinyl bromide **23** (1.38 g, 11.40 mmol, 1.5 equiv) and 7.6 mL of THF. The solution was cooled with a dry ice/acetone bath, and 6.93 mL of *n*-BuLi (2.41 M in hexanes, 6.93 mL, 16.72 mmol, 2.2 equiv) was added dropwise via the addition funnel over 30 min (2-mL THF rinse). The pale yellow solution was stirred at -78 °C for 2 h, and then a solution of cyclohexene carboxaldehyde (0.837 g, 7.60 mmol, 1.0 equiv) in 2 mL of THF was added dropwise via cannula over 10

min (1.8-mL THF rinse). The resulting solution was stirred for 45 min at -78 °C and then a solution of methyl iodide (7.55 g, 53.2 mmol, 7.0 equiv) in 5 mL of THF was added via cannula over 3 min (2-mL THF rinse). The resulting pale-yellow solution was allowed to warm to rt and stirred for 18 h. Saturated aq NH_4Cl solution (2 mL) and 6 mL of water were then added, and the aqueous phase was separated and extracted with three 30-mL portions of ether. The combined organic layers were washed with 50 mL of saturated aq NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 1.406 g of a yellow oil. Column chromatography on 45 g of silica gel (elution with 3% ether/hexanes) afforded 1.14 g (92%) of **24** as a yellow oil: IR (NaCl) 2910, 2234, 1715, 1438, 1083 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.86 (m, 1 H), 4.28 (m, 1 H), 3.29 (s, 3 H), 1.92-2.24 (m, 4 H), 1.88 (d, J=2.1 Hz, 3 H) 1.54-1.73 (m, 4 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 135.5, 126.3, 82.8, 76.6, 75.9, 55.4, 25.1, 24.1, 22.6, 22.4, 3.7; HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{11}H_{17}O$ 165.1274; found 165.1298.

3-Ethyl-4-methoxy-2-tosyl-5,6,7,8-tetrahydroquinoline (26). A 25-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with 0.31 mL of *t*-BuLi (1.53 M in pentane, 0.47 mmol, 1.1 equiv) followed by 0.07 mL of TMEDA (0.054 g, 0.47 mmol, 1.1 equiv). The resulting yellow mixture was cooled at -78 °C while a pre-cooled solution of propargyl ether **24** (0.070 g, 0.43 mmol, 1.0 equiv) in 5 mL of ether was added dropwise over 5 minutes via cannula (1 mL ether rinse). The resulting pale red reaction mixture was stirred for 15 min at -78 °C. MeOH (0.06 mL, 0.047 g, 1.48 mmol 3.5 equiv) was then added dropwise via syringe over 30 sec. After 5 min, the resulting yellow solution was allowed to warm to rt and stirred for 35 min. Saturated aq NH_4Cl solution (1 mL), and then 2.5 mL of saturated aq $CuSO_4$ were added and the resulting mixture was stirred for 2 min. The aqueous layer was separated, and the organic layer was washed with 10 mL of saturated aq NaCl solution, dried over $MgSO_4$, and then filtered into a 50-mL round bottomed flask containing a stir bar and 0.12 g of powdered 4Å MS. The flask was equipped with a rubber septum and flushed with argon for 30 sec. A solution of TsCN (0.078 g, 0.43 mmol, 1.0 equiv) in 4 mL of THF was added (1 mL THF rinse) and the

resulting suspension was stirred at rt for 1 h. DBU (0.07 mL, 0.071 g, 0.43 mmol, 1.0 equiv) was added dropwise via syringe, and the resulting suspension was stirred for 1 h at rt. Water (10 mL) was added, and the aqueous layer was separated and extracted with three 20-mL portions of EtOAc. The combined organic layers were washed with 30 mL of saturated aq NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.154 g of an orange oil. Column chromatography on 25 g of silica gel (elution with 0-10% EtOAc/hex) afforded 0.075 g (51%) of **26** as a sticky beige solid: IR (NaCl) 2938, 1452, 1324, and 1144 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J=8.1 Hz, 2 H), 7.29 (d, J=7.8 Hz, 2 H), 3.78 (s, 3 H), 3.08 (q, J=7.2 Hz, 2 H), 2.72 (m, 4 H), 2.41 (s, 3 H), 1.75 (m, 4 H), 1.21 (t, J=7.5 Hz, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.3, 157.0, 154.6, 144.0, 137.4, 130.5, 130.0, 129.3, 129.2, 60.7, 33.3, 23.8, 22.6, 22.0, 21.8, 18.7, 15.6; HRMS (ESI-FTICR) *m/z* $[M + H]^+$ calcd for $C_{19}H_{24}NO_3S$; 346.1471, found 346.1468.

1-(3-Cyclohexyl-1-methoxyprop-2-yn-1-yl)cyclohex-1-ene (28*).* A 100-mL, two-necked, round-bottomed flask equipped with two rubber septa and an argon inlet needle was charged with cyclohexylacetylene (1.350 g, 12.48 mmol, 1.3 equiv) and 35 mL of THF. The solution was cooled at -78 °C, and 4.40 mL of *n*-butyllithium solution (2.40 M in hexanes, 10.56 mmol, 1.1 equiv) was added dropwise via syringe over 2 min. The resulting pale-yellow solution was stirred at -78 °C for 30 min, and then a solution of cyclohexene carboxaldehyde (1.057 g, 9.60 mmol, 1.0 equiv) in 5 mL of THF was added dropwise via cannula over 5 min. The resulting solution was stirred for 30 min at -78 °C, and 6.5 mL of methyl iodide (14.8 g, 134 mmol, 14 equiv) was added dropwise via syringe over 5 min. The resulting pale-yellow solution was stirred for 1 h at -78 °C, allowed to warm to rt, and stirred for 14 h. The reaction mixture was treated with 20 mL of 0.2 M aq NaH_2PO_4 solution, and the THF was removed via rotary evaporation. The aqueous layer of the residue was separated and extracted with three 30-mL portions of pentane, and the combined organic extracts were washed with 50 mL of satd aq NaCl solution, dried over Na_2SO_4, filtered, and concentrated to afford 2.476 g of a yellow oil. Column chromatography

on 65 g of silica gel (elution with 0-1% ether/pentane) afforded 2.097 g (94%) of **28** as a yellow oil: IR (thin film) 2930, 2856, 2218, 1712, 1449, and 1246 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.96 (m, 1 H), 4.47 (s, 1 H), 3.30 (s, 3 H), 2.34-2.41 (m, 2 H), 2.19 (m, 1 H), 1.93 (m, 2 H), 1.68 (m, 2 H), 1.58 (m, 4 H), 1.45 (m, 4 H), 1.27 (m, 1 H), 1.12 (m, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, C_6D_6) δ 136.4, 125.5, 91.5, 78.4, 76.0, 55.0, 33.1, 29.5, 26.2, 25.4, 25.0, 24.9, 23.1, 22.8; HRMS (ESI-FTICR) *m/z* $[M + H]^+$ calcd for $C_{16}H_{25}O$ 233.1900; found 233.1917.

3-(Cyclohexylmethyl)-4-methoxy-2-tosyl-5,6,7,8-tetrahydroquinoline (30). A 100-mL, two-necked, pear-shaped flask equipped with a rubber septum and a jacketed 50-mL addition funnel was charged with 3.55 mL of *t*-BuLi solution (1.60 M in pentane, 5.68 mmol, 1.1 equiv) and 0.85 mL of TMEDA (0.660 g, 5.68 mmol, 1.1 equiv). The resulting yellow mixture was cooled at -78 °C, and a pre-cooled (-78 °C) solution of propargyl ether **28** (1.201 g, 5.164 mmol, 1.0 equiv) in 25 mL of ether was added dropwise over 5 min via addition funnel (2 mL ether rinse). The resulting milky yellow mixture was stirred for 15 min at -78 °C, 0.70 mL of MeOH (0.546 g, 17.0 mmol 3.5 equiv) was added dropwise via syringe over 30 sec, and the resulting yellow mixture was stirred for 5 min at -78 °C. The reaction mixture was allowed to warm to rt and stirred for 1 h, and then 10 mL of satd aq NH_4Cl solution was added, followed by 20 mL of satd aq $CuSO_4$ solution. The resulting mixture was stirred vigorously for 3 min, and the aqueous layer was separated and extracted with two 30-mL portions of ether. The combined organic extracts were washed with 30 mL of satd aq NaCl solution, dried over $MgSO_4$, and then filtered with the aid of 15 mL of ether into a 250-mL round-bottomed flask containing a stir bar and 1.3 g of powdered 4Å MS. The flask was equipped with a rubber septum and an argon inlet needle, and the suspension was degassed with argon for 5 min. A solution of TsCN (1.029 g, 5.68 mmol, 1.1 equiv) in 5 mL of THF was added rapidly via cannula (1 mL THF rinse). The resulting suspension was stirred at rt for 2.5 h, 0.88 mL of DBU (0.865 g, 5.86 mmol, 1.1 equiv) was added dropwise via syringe, and the resulting suspension was stirred for 14 h at rt. The reaction mixture was treated with 25 mL of water, and

the aqueous layer was separated and extracted with three 40-mL portions of EtOAc. The combined organic extracts were washed with 50 mL of satd aq NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 1.97 g of an orange semisolid. Trituration with three 1-mL portions of MeOH furnished 1.097 g of a colorless solid. The mother liquor was concentrated and further triturated with three 0.5-mL portions of MeOH to furnish 0.122 g of a colorless solid. The mother liquor was concentrated onto 3.5 g of silica gel to yield a free-flowing powder, and the powder was placed at the top of a 40 g column of silica gel. Elution with 0-10% EtOAc-hexanes afforded 0.115 g of a yellow semisolid, which was triturated with three 0.25-mL portions of MeOH to furnish 0.090 g of a colorless solid, for a combined total yield of 1.309 g (61%) of **30** as a colorless solid: mp 105-107 °C; IR (thin film) 2922, 2849, 1737, 1142, and 1091 cm^{-1}; ^1H NMR (500 MHz, CD_2Cl_2) δ 7.85 (d, J = 8.5 Hz, 2 H), 7.33 (d, J = 8.0 Hz, 2 H), 3.73 (s, 3 H), 3.00 (d, J = 7.0 Hz, 2 H), 2.72 (m, 4 H), 2.43 (s, 3 H), 1.59-1.81 (m, 10 H), 1.06-1.18 (m, 5 H); $^{13}C\{^1H\}$ NMR (125 MHz, CD_2Cl_2) δ 166.1, 157.5, 155.3, 144.6, 138.5, 130.2, 129.6, 129.5, 128.5, 60.7, 40.5, 33.7, 32.6, 32.2, 27.1, 27.0, 24.2, 23.0, 22.5, 21.9; HRMS (ESI-FTICR) *m/z* $[M + H]^+$ calcd for $C_{24}H_{32}SO_3N$ 414.2097; found 414.2108.

Ethyl 3-(cyclohex-1-en-1-yl)hexa-3,4-dienoate (32). A 100-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with propargylic alcohol **31**[22] (0.233 g, 1.55 mmol, 1.0 equiv), 31 mL of xylenes, 2.8 mL of triethyl orthoacetate (2.5 g, 15.5 mmol, 10 equiv), and 12 μL of propionic acid (0.011 g, 0.16 mmol, 0.1 equiv). The rubber septum was replaced with a reflux condenser fitted with a rubber septum and an argon inlet needle and the reaction mixture was heated at reflux for 4 h. The resulting mixture was allowed to cool to rt and concentrated to afford 0.406 g of a yellow oil. Column chromatography on 20 g of silica gel (elution with 0-1.5% EtOAc-hexanes) afforded 0.217 g (64%) of **32** as a colorless oil: IR (NaCl) 2981, 2935, 2918, 2859, 2836, 1948, 1741, 1448, 1367, 1320, 1305, 1261, 1234, 1152, and 1036 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.57-5.63 (m, 1 H), 5.29-5.41 (m, 1 H), 4.13 (q, J = 7.2 Hz, 2 H), 3.17 (d, J = 2.1 Hz, 2 H), 2.03-2.15 (m, 4 H), 1.50-1.72 (m, 4 H), 1.68 (d, J = 6.9 Hz, 3 H), 1.25 (t, J = 7.2 Hz, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 205.5, 172.1,

132.7, 122.5, 101.4, 89.0, 60.7, 36.9, 27.2, 26.1, 23.0, 22.5, 14.6, 14.4; HRMS (DART-FTICR) *m/z* [M + H]$^+$ calcd for $C_{14}H_{21}O_2$ 221.1536; found 221.1530.

3-(Cyclohex-1-en-1-yl)-N,N-dimethylhexa-3,4-dienamide (33). A 50-mL, round-bottomed flask equipped with a rubber septum and an argon inlet needle was charged with propargylic alcohol **31**[22] (0.194 g, 1.29 mmol, 1.0 equiv) and 26 mL of toluene. Dimethylacetamide dimethyl acetal (0.94 mL, 0.860 g, 6.45 mmol, 5.0 equiv) was added via syringe over 0.5 min, the rubber septum was replaced with a reflux condenser fitted with a rubber septum and argon inlet needle, and the solution was heated at reflux for 3 h. The reaction mixture was allowed to cool to rt and concentrated to furnish 0.287 g of a yellow oil. Column chromatography on 20 g of silica gel (elution with 0-1% MeOH-CH_2Cl_2) afforded 0.254 g (90%) of **33** as a pale yellow oil: IR (NaCl) 2924, 2858, 1944, 1650, 1498, 1437, 1397, 1264, 1136 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.62-5.68 (m, 1 H), 5.29-5.43 (m, 1 H), 3.14-3.28 (m, 2 H) 2.99 (s, 3 H), 2.93 (s, 3 H), 2.01-2.16 (m, 4 H), 1.52-1.68 (m, 4 H), 1.65 (d, *J* = 7.2 Hz, 3 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) 204.2, 171.4, 132.8, 122.7, 102.1, 89.6, 38.1, 36.4, 35.6, 27.3, 26.1, 23.0, 22.5, 14.5; HRMS (DART-FTICR) *m/z* [M + H]$^+$ calcd for $C_{14}H_{22}NO$: 220.1696; found 220.1685.

2-(3-Ethyl-2-tosyl-5,6,7,8-tetrahydroquinolin-4-yl)-N,N-dimethylacetamide (34). A 10-cm, threaded Pyrex tube (25 mm O.D.; 17 mm I.D.) equipped with a rubber septum fitted with an argon inlet needle was charged with 4 Å molecular sieves (0.230 g), tosyl cyanide (0.213 g, 1.17 mmol, 1.1 equiv), vinylallene **33** (0.234 g, 1.07 mmol, 1.0 equiv), and 10.7 mL of toluene. The tube was sealed with a threaded Teflon cap and the reaction mixture was heated at 70 °C for 5 h and then allowed to cool to rt. DBU (0.18 mL, 0.179 g, 1.17 mmol, 1.1 equiv) was added dropwise via syringe over 1 min, and the resulting mixture was stirred at rt for 4 h, and then treated with 20 mL of water. The aqueous phase was extracted with three 20-mL portions of EtOAc, the combined organic layers were washed with 30 mL of satd aq NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.461 g of a yellow solid. The solid was dissolved in 75 mL of boiling ether, and 0.01 g of activated charcoal was added. After 5 min, the hot solution was filtered into a 100-mL pear-shaped flask, the flask was sealed with a glass

stopper, and the solution was allowed to cool gradually to 0 °C and left to stand at that temperature overnight. The mother liquor was carefully decanted with a cannula filter, and the crystals were washed with three 10-mL portions of cold (0 °C) ether. Residual solvent was removed in vacuo to afford 0.194 g of **34** as colorless crystals. A second crop of crystals (0.030 g) was obtained from the mother liquor in a similar fashion, for a combined total yield of 0.224 g (53%), of **34** as colorless crystals: mp 172-174 °C; IR (NaCl) 3055, 2939, 2866, 1651, 1395, 1299, 1143, 1090, 735, 702, and 674 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.0 Hz, 2 H), 7.28 (d, *J* = 8.0 Hz, 2 H), 3.69 (s, 2 H), 3.18 (s, 3 H), 3.06 (q, *J* = 7.5 Hz, 2 H), 2.98 (s, 3 H), 2.73 (m, 2 H), 2.58 (m, 2 H), 2.42 (s, 3 H), 1.71-1.78 (m, 4 H), 1.23 (t, *J* = 7.5 Hz, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.5, 154.7, 153.6, 145.4, 143.9, 137.6, 136.0, 134.8, 129.24, 129.20, 37.7, 36.0, 32.9, 32.5, 26.6, 22.6, 22.3, 21.8, 21.4, 15.3; HRMS (DART-FTICR) *m/z* $[M + H]^+$ calcd for $C_{22}H_{29}N_2O_3S$ 401.1893; found 401.1888.

Ethyl 2-(3-ethyl-2-tosyl-5,6,7,8-tetrahydroquinolin-4-yl)acetate (35). A 10-cm, threaded Pyrex tube (25 mm O.D.; 17 mm I.D.) equipped with a rubber septum fitted with an argon inlet needle was charged with 4 Å molecular sieves (0.230 g), tosyl cyanide (0.194 g, 1.07 mmol, 1.1 equiv), vinylallene **32** (0.215 g, 0.98 mmol, 1.0 equiv), and 9.8 mL of toluene. The tube was sealed with a threaded Teflon cap and the reaction mixture was heated at 90 °C for 8 h and then allowed to cool to rt. DBU (0.16 mL, 0.163 g, 1.07 mmol, 1.1 equiv) was added dropwise via syringe over 1 min, and the reaction mixture was stirred at rt for 15 min. The resulting yellow suspension was washed with 20 mL of water, and the aqueous phase was extracted with three 20-mL portions of EtOAc. The combined organic layers were washed with 30 mL of satd aq NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.473 g of a dark orange oil. The crude product was concentrated onto 2.2 g of silica gel, and the resulting free-flowing powder was placed at the top of a column of 30 g of silica gel and eluted with 0-10% EtOAc-hexanes to furnish 0.176 g of **35** as an off-white solid and 0.091 g of mixed fractions. Preparative thin layer chromatography (elution with 10% EtOAc-hexanes) of the mixed fractions furnished 0.015 g of **35** for a combined total yield of 0.191 g (50%): IR (NaCl) 2980, 2942, 2919, 1737,

1597, 1559, 1540, 1389, 1286, 1173, 1140, 1088, 1027, 813, 669, 593 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.1 Hz, 2 H), 7.31 (d, *J* = 8.1 Hz, 2 H), 4.16 (q, *J* = 7.2 Hz, 2 H), 3.72 (s, 2 H), 3.18 (q, *J* = 7.4 Hz, 2 H), 2.60-2.75 (m, 4 H), 2.44 (s, 3 H), 1.78 (m, 4 H), 1.18-1.29 (m, 6 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) 169.8, 154.9, 154.1, 144.0, 143.6, 137.3, 135.9, 134.9, 129.4, 129.2, 61.6, 33.9, 32.9, 26.8, 22.6, 22.3, 21.8, 21.2, 15.2, 14.3; HRMS (DART-FTICR) *m/z* $[M + H]^+$ calcd for $C_{22}H_{28}NO_4S$ 402.1734; found 402.1721.

tert-Butyl 3-(1-Methoxy-3-phenylprop-2-yn-1-yl)-1H-pyrrole-1-carboxylate (37). A 50-mL, two-necked, round-bottomed flask equipped with two rubber septa and an argon inlet needle was charged with 0.68 mL of phenylacetylene (0.628 g, 6.147 mmol, 1.2 equiv) and 20 mL of THF. The resulting solution was cooled at -78 ºC and 2.5 mL of butyllithium solution (2.25 M in hexane, 5.63 mmol, 1.1 equiv) was added dropwise via syringe over 3 min. The resulting solution was stirred at -78 ºC for 15 min, and then a solution of aldehyde **36**[33] (1.00 g, 5.12 mmol, 1.0 equiv) in 3 mL of THF was added dropwise via cannula over 5 min (2-mL THF wash). The reaction mixture was stirred at -78 ºC for 15 min, and then 3.1 mL of methyl iodide (7.1 g, 50 mmol, 10 equiv) was added dropwise via syringe and the reaction mixture was allowed to warm to rt. After 14 h, the reaction mixture was treated with 10 mL of half-satd aq NaH_2PO_4 solution and diluted with 100 mL of water and 100 mL of EtOAc. The aqueous layer was separated and extracted with three 50-mL portions of EtOAc, and the combined organic phases were washed with satd aq NaCl solution, dried over $MgSO_4$, filtered, and concentrated to furnish 1.972 g of a dark brown oil. Column chromatography on 75 g of silica gel (elution with 0-5% EtOAc-hexanes) furnished 1.471 g (92%) of **37** as a reddish oil: IR (thin film) 2988, 2934, 2819, 2226, 1740, 1598, 1353, 1290, 1243, 1353, 1290, 1243, 1152, 1066, and 968 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (m, 2 H), 7.41 (m, 1 H), 7.30-7.35 (m, 3 H), 7.25 (dd, ^1J = 3.2 Hz, ^2J = 2.4 Hz, 1 H), 6.39 (dd, ^1J = 3.2 Hz, ^1J = 2.0 Hz, 1 H), 5.30 (s, 1 H), 3.48 (s, 3 H), 1.61 (s, 9 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) 148.9, 132.0, 128.6, 128.4, 125.6, 122.8, 120.9, 118.9, 111.5, 86.7, 86.4, 84.0, 67.3, 55.4, 28.1; HRMS (DART-FTICR) *m/z* $[M + H]^+$ calcd for $C_{19}H_{22}NO_3$ 310.1443; found 310.1466.

tert-Butyl 5-Benzyl-4-methoxy-6-(toluenesulfonyl)-1H-pyrrolo[2,3-b]pyridine-1-carboxylate (39). A 25-mL, two-necked, pear-shaped flask equipped with two rubber septa and an argon inlet needle was charged with pyrrole **37 (**0.231 g, 0.742 mmol, 1.0 equiv), 4 Å MS (0.050 g), and 5 mL of THF. The resulting suspension was cooled at -78 ºC, and then 0.07 mL of KO*t*-Bu solution (1.0 M in THF, 0.07 mmol, 0.1 equiv) was added dropwise via syringe over 1 min. The resulting orange suspension was stirred at -78 ºC for 30 min, and then a solution of tosyl cyanide (0.148 g, 0.816 mmol, 1.1 equiv) in 2 mL of toluene was added dropwise via cannula (0.5-mL tolune wash). The resulting orange mixture was allowed to warm to rt and stirred for 1 h. The resulting mixture was treated with 5 mL of half-satd aq NaH_2PO_4 solution, and then diluted with 100 mL of water and 100 mL of CH_2Cl_2. The aqueous layer was separated and extracted with three 50-mL portions of CH_2Cl_2, and the combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and concentrated to furnish 0.312 g of an orange solid. Recrystallization from MeOH afforded 0.158 g (44%) of **39** as a white solid: mp 185-187 ºC; IR (thin film) 2976, 1756, 1533, 1454, 1318, 1268, 1139, and 573 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J*= 8.0 Hz, 2 H), 7.71 (d, *J*= 4.5 Hz, 1 H), 7.05-7.20 (m, 7H), 6.72 (d, *J*= 4.5 Hz, 1 H), 4.68 (s, 2 H), 4.10 (s, 1 H), 2.37 (s, 3 H), 1.70 (s, 9 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.8, 152.5, 148.2, 147.1, 144.0, 140.3, 137.9, 129.4, 129.1, 128.6, 128.2, 128.1, 125.7, 120.4, 114.3, 102.8, 84.9, 60.0, 30.1, 28.3, 21.8; HRMS (DART) *m/z* $[M + H]^+$ calcd for $C_{27}H_{29}O_5N_2S$ 493.1797; found 493.1793.

tert-Butyl 5-Benzyl-4-methoxy-6-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridine-1-carboxylate (40). A 25-mL, round-bottomed flask equipped with a rubber septum and an argon inlet needle was charged with pyrrole **37** (0.220 g, 0.707 mmol, 1.0 equiv), 4 Å MS (0.100 g), and 5 mL of THF. The resulting suspension was cooled at -78 ºC, and 0.14 mL of KO*t*-Bu solution (1.0 M in THF, 0.14 mmol, 0.2 equiv) was added dropwise via syringe over 1 min. The resulting orange suspension was stirred at -78 ºC for 30 min, and then a solution of benzenesulfonyl cyanide (0.130 g, 0.777 mmol, 1.1 equiv) in 1 mL of THF was added dropwise via cannula (1-mL toluene wash). The resulting orange mixture was allowed to warm to 0 ºC and stirred for 8 h, and then allowed to warm to rt and stirred for 14 h. The resulting

mixture was treated with 2 mL of half-satd aq NaH_2PO_4 solution and then diluted with 50 mL of water and 50 mL of EtOAc. The aqueous layer was separated and extracted with three 25-mL portions of EtOAc, and the combined organic phases were washed with satd aq NaCl solution, dried over $MgSO_4$, filtered, and concentrated to furnish 0.312 g of an orange solid. Trituration of this solid with three 1-mL portions of EtOAc afforded 0.117 g (35%) of **40** as a white solid: mp 167-169 ºC; IR (thin film) 2933, 1741, 1487, 1401, 1154, 970, and 770 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 7.6 Hz, 2 H), 7.72 (d, J = 4 Hz, 1 H), 7.51 (t, J = 7.6 Hz, 1 H), 7.40 (t, J = 7.6 Hz, 2 H), 7.05-7.20 (m, 5 H), 6.72 (d, J = 4 Hz, 1 H), 4.69 (s, 2 H), 4.10 (s, 3 H), 1.69 (s, 9 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.8, 152.2, 148.1, 147.1, 140.9, 140.3, 133.1, 129.0, 128.7, 128.6, 128.24, 128.16, 125.8, 120.5, 114.3, 102.8, 84.9, 60.0, 30.1, 28.3; HRMS (DART-FTICR) *m/z* $[M + H]^+$ calcd for $C_{26}H_{27}O_5N_2S$ 479.1641; found 479.1612.

(1-t-Butoxycarbonyl)-3-(3-hydroxyprop-1-ynyl)pyrrole (42). A 50-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with the silylpyrrole **41**[41] (1.602 g, 4.585 mmol) 10 mL of THF, and 4.6 mL of TBAF solution (1.0 M in THF, 4.6 mmol). The resulting mixture was stirred at rt for 15 min, concentrated, and then diluted with 30 mL of water and 30 mL of hexanes. The organic phase was separated and washed with two 20-mL portions of water, 20-mL of satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated in a 50-mL, round-bottomed flask to which were immediately added 15 mL of THF, triethylamine (0.64 mL, 0.46 g, 4.6 mmol), DMAP (0.056 g, 0.46 mmol), and di-*t*-butyl-dicarbonate (1.200 g, 5.499 mmol). The resulting mixture was stirred at rt for 2 h and then diluted with 30 mL of water and 30 mL of hexanes. The organic phase was separated and washed with two 20-mL portions of water, 20-mL of satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to furnish 2.556 g of a light-brown oil that was added to the top of a column of 50 g of silica gel which had been pre-treated with 5% triethylamine-hexanes. Elution with hexanes furnished 2.084 g of impure 3-iodo-*N*-BOCpyrrole as a light-brown oil that was dissolved in 30 mL of THF in a 50-mL, round-bottomed flask. To this solution were added piperidine (2.3 mL, 2.0 g, 23 mmol), $Pd(Ph_3P)_2Cl_2$ (0.195 g, 0.278 mmol), CuI (0.106 g, 0.557 mmol), and propargyl alcohol (0.54 mL, 0.51 g, 9.1 mmol),

and the resulting mixture was stirred for 2 h at rt and then filtered through 5 g of silica gel in a sintered glass funnel washing with 100 mL of diethyl ether. The filtrate was concentrated under reduced pressure to yield 4.390 g of a dark-red semisolid that was dissolved in 100 mL of CH_2Cl_2 and concentrated onto 10 g of silica gel which was added to the top of a column of 100 g of silica gel. Gradient elution with 0-20% EtOAc-hexanes afforded 0.899 g (87% overall from the silylpyrrole) of **42** as a viscous light red oil: IR (thin film) 3375, 2231, 1747, and 1560 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 7.38 (m, 1 H), 7.15 (m, 1 H), 6.26 (dd, *J* = 3.2, 1.6 Hz, 1 H), 4.46 (d, J = 3.9 Hz, 2 H), 1.80 (m, 1 H), 1.59 (s, 9 H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) 148.1, 123.7, 120.1, 114.7, 107.6, 87.5, 84.6, 79.8, 51.8, and 28.2; HRMS (*m/z*) $[M + Na]^+$ calcd for $C_{12}H_{15}NO_3Na$ 244.0944; found, 244.0950.

tert-Butyl 3-(5-(Dimethylamino)-5-oxopenta-1,2-dien-3-yl)-1H-pyrrole-1-carboxylate (43). A 25-mL pear-shaped flask equipped with a rubber septum and an argon inlet needle was charged with propargylic alcohol **42 (**0.228 g, 1.030 mmol, 1.0 equiv), 0.75 mL of dimethylacetamide dimethyl acetal (0.686 g, 5.15 mmol, 5.0 equiv), and 10 mL of toluene. The rubber septum was replaced with a reflux condenser and the solution was heated at reflux for 4 h. The resulting mixture was allowed to cool to rt, and then diluted with 50 mL of EtOAc, washed with three 25-mL portions of half satd aq $CuSO_4$ solution and 25 mL of satd aq NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give 0.248 g of a red oil. Column chromatography on 12 g of silica gel (elution with 0-10% CH_3CN-CH_2Cl_2) furnished 0.144 g (48%) of **43** as an amber oil: IR (thin film) 3149, 2977, 2933, 2237, 1945, 1737, 1643, 1349, 1155, 969, and 770 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.18 (m, 2 H), 6.24 (app t, J= 2.4 Hz, 1 H), 5.09 (t, J= 3.2 Hz, 2 H), 3.37 (t, J= 3.2 Hz, 2 H), 3.04 (s, 3 H), 2.96 (s, 3 H), 1.59 (s, 9 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 208.4, 170.9, 148.9, 123.4, 121.0, 116.1, 111.1, 95.1, 83.9, 78.8, 38.0, 37.1, 35.7, 28.2; HRMS (DART-FTICR) *m/z* $[M + H]^+$ calcd for $C_{16}H_{23}N_2O_3$ 291.1709; found 291.1730.

tert-Butyl 4-(2-(Dimethylamino)-2-oxoethyl)-5-methyl-6-tosyl-1H-pyrrolo[2,3-b]pyridine-1-carboxylate (44). A 25-mL, pear-shaped flask equipped with a rubber septum and argon inlet needle was charged with allenylpyrrole **43 (**0.079 g, 0.272 mmol, 1.0 equiv), TsCN (0.054 g, 0.299 mmol, 1.1 equiv),

0.030 g of 4 Å MS, and 2.8 mL of toluene. The rubber septum was replaced with a reflux condenser and the mixture was heated at 60 ºC for 72 h. The resulting orange mixture was concentrated to furnish 0.160 g of a dark brown oil. Column chromatography on 12 g of silica gel (elution with 0-20% CH_3CN-CH_2Cl_2) furnished 0.040 g of a light brown oil. Preparative TLC of the mixed fractions (elution with 20% CH_3CN-CH_2Cl_2) furnished an additional 0.004 g of **44** for a total yield of 0.044 g (34%): IR (thin film) 2960, 2929, 1732, 1645, 1369, 1310, 1132, 841, 705, 576 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J= 8.4 Hz, 2 H), 7.77 (d, J= 4.0 Hz, 1 H), 7.28 (d, J= 8.4 Hz, 2 H), 6.48 (d, J= 4.0 Hz, 1 H), 3.93 (s, 2 H), 3.12 (s, 3 H), 2.96 (s, 3 H), 2.65 (s, 3 H), 2.40 (s, 3 H), 1.63 (s, 9 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.4, 151.5, 148.3, 144.1, 143.7, 139.1, 137.9, 130.2, 129.5, 128.9, 126.6, 102.8, 84.7, 37.7, 35.9, 35.0, 28.2, 21.7, 14.4; HRMS (DART) *m/z* $[M + H]^+$ calcd for $C_{24}H_{30}O_5N_3S$ 472.1906; found 472.1896.

4-Ethyl-3-methyl-6-phenyl-2-methylpyridine (45). A 25-mL, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet needle was charged with pyridine **16** (0.150 g, 0.43 mmol, 1.0 equiv) and 7 mL of THF. Methylmagnesium bromide (0.50 mL, 2.54 M in THF, 1.28 mmol, 3.0 equiv) was added dropwise via syringe over 30 sec, and the resulting amber solution was heated at reflux for 15 h. The reaction mixture was allowed to cool to rt and then 4 mL of satd aq NH_4Cl solution and 3 mL water was added. The aqueous layer was separated and extracted with three 10-mL portions of EtOAc, and the combined organic layers were washed with 30 mL of satd aq NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.114 g of a brown oil. Column chromatography on 9 g of silica gel (elution with 0-5% EtOAc/hexanes) afforded 0.081 g (90%) of **45** as a yellow oil: IR (NaCl) 2968, 1592, 1559, 1460, and 1386 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 8.4 Hz, 2 H), 7.46 (t, J = 7.6 Hz, 2 H), 7.39 (m, 2 H), 2.71 (q, J = 7.6 Hz, 2 H), 2.63 (s, 3 H), 2.27 (s, 3 H), 1.27 (t, J = 7.6 Hz, 3 H); $^{13}C\{^1H\}$ (100 MHz, $CDCl_3$) δ 156.9, 154.1, 151.5, 140.1, 128.7, 128.4, 128.1, 118.3, 26.7, 23.7, 14.2, 14.1; HRMS (ESI-FTICR) *m/z* $[M + H]^+$ calcd for $C_{15}H_{18}N$: 212.1434; found 212.1421.

4-Ethyl-3-methyl-6-phenyl-2-propylpyridine (46). A 25-mL, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet needle was charged with pyridine **16** (0.150 g, 0.43 mmol, 1.0 equiv) and 5.5 mL of THF. Propylmagnesium bromide (2.04 mL, 0.62 M in THF, 1.28 mmol, 3.0 equiv) was added dropwise via syringe over 30 sec, and the resulting amber solution was heated at reflux for 12 h. The reaction mixture was allowed to cool to rt and then 2.5 mL of satd aq NH_4Cl solution and 3 mL water were added. The aqueous layer was separated and extracted with three 10-mL portions of EtOAc, and the combined organic layers were washed with 30 mL of satd aq NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.152 g of a brown oil. Column chromatography on 15 g of silica gel (elution with 2% ether/hexanes) afforded 0.082 g (80%) of **46** as a yellow oil: IR (NaCl) 3062, 2964, 2871, 1591, 1557, 1435, 1380 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.03 (m, 2 H), 7.47 (m, 2 H), 7.39 (s, 1 H), 7.38 (m, 1 H), 2.90 (t, J = 7.6 Hz, 2 H) 2.71 (q, J = 7.6 Hz, 2 H), 2.31 (s, 3 H), 1.87 (m, 2 H), 1.29 (t, J = 7.6 Hz, 3 H), 1.09 (t, J = 7.6 Hz, 3 H); $^{13}C\{^1H\}$ (100 MHz, $CDCl_3$) 160.3, 154.0, 151.6, 140.4, 128.7, 128.3, 127.6, 126.9, 117.9, 38.3, 26.8, 22.4, 14.5, 14.1, 13.8; HRMS (ESI-FTICR) *m/z* $[M + H]^+$ calcd for $C_{17}H_{22}N$; 240.1747; found 240.1731.

4-Ethyl-3-methyl-2,6-diphenylpyridine (47). A 10-mL, pear-shaped flask equipped with a rubber septum and argon inlet needle was charged with pyridine **16 (**0.070 g, 0.199 mmol, 1.0 equiv) and 1.4 mL of THF. PhMgCl solution (2.0 M in THF, 0.60 mL, 1.20 mmol, 6.0 equiv) was added, and then the septum was replaced with a reflux condenser equipped with a rubber septum and an argon inlet needle. The reaction mixture was heated at reflux for 16 h, and then allowed to cool to rt and treated with 1 mL of half satd aq NaH_2PO_4 solution. The mixture was diluted with 25 mL of EtOAc and 25 mL of water, and the aqueous layer was separated and extracted with three 20-mL portions of EtOAc. The combined organic phases were washed with satd aq NaCl solution, dried over $MgSO_4$, filtered, and concentrated to furnish 0.071 g of a yellow solid. Column chromatography on 6 g of silica gel (elution with 0-10% EtOAc/hexanes) furnished 0.047 g (87%) of **47** as a yellow oil: IR (thin film) 3057, 2965,

1588, 1547, 1420, 876, and 692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 7.2 Hz, 2 H), 7.63 (d, *J* = 6.8 Hz, 2 H) 7.59 (s, 1 H), 7.38-7.55 (m, 6 H), 2.80 (q, *J* = 7.6 Hz, 2 H), 2.34 (s, 3 H), 1.37 (t, *J* = 7.6 Hz, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.0, 154.4, 152.8, 141.9, 140.0, 129.7, 128.7, 128.6, 128.2, 127.8, 127.7, 127.1, 118.7, 26.8, 15.8, 13.8; HRMS (DART) *m/z* $[M + H]^+$ calcd for $C_{20}H_{20}N$; 274.1596; found 274.1611.

4-Ethyl-3-methyl-6-phenylpicolinonitrile (48). A 25-mL, pear-shaped flask equipped with a rubber septum and an argon inlet needle was charged with pyridine **16** (0.170 g, 0.484 mmol, 1.0 equiv), NaCN (0.118 g, 2.418 mmol, 5.0 equiv), 18-crown 6 (0.640 g, 2.418 mmol, 5.0 equiv) and 5 mL of DMF. The septum was replaced with a reflux condenser fitted with a rubber septum and an argon inlet needle, and the reaction mixture was heated at reflux for 48 h. The resulting mixture was allowed to cool to room temperature and then diluted with 100 mL of water and 100 mL of EtOAc. The organic layer was washed with five 50-mL portions of water and 50 mL of satd aq NaCl solution, dried over $MgSO_4$, filtered, and concentrated to furnish 0.140 g of a light brown solid. The solid was dissolved in 10 mL of CH_2Cl_2 and concentrated onto 0.60 g of silica gel. The resulting free-flowing powder was deposited onto a column of 4 g of silica gel and eluted with 0-10% EtOAc/hexanes to furnish 0.110 g of an off-white solid. This material was triturated with three 1-mL portions of hexanes to furnish 0.080 g of a white solid, and the mother liquor was concentrated and triturated again with three 0.25 mL portions of hexanes to furnish 0.013 g of a white solid, total yield 0.093 g (86%) of **48** as a white solid: IR (thin film) 2973, 2230, 1591, 1456, 915, 875, 780, and 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 6.8 Hz, 2 H), 7.69 (s, 1 H), 7.46 (m, 3 H), 2.72 (q, *J* = 7.6 Hz, 2 H), 2.51 (s, 3 H), 1.30 (t, *J* = 7.6 Hz, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 156.4, 153.5, 137.6, 135.2, 134.0, 129.7, 128.9, 126.9, 122.7, 117.3, 26.2, 15.3, 13.3; HRMS (DART-FTICR) *m/z* $[2M + H]^+$ $C_{30}H_{29}N_4$ calcd for 445.2392; found 445.2380.

2-Ethoxy-4-ethyl-3-methyl-6-phenylpyridine (49). A 25-mL, two-necked, pear-shaped flask equipped with two rubber septa and an argon inlet needle was charged with KO*t*-Bu (0.145 g, 1.292 mmol, 2.4 equiv) and 3.8 mL of THF. Ethanol (75 μL, 0.060 g, 1.29 mmol, 2.4 equiv) was added

dropwise via syringe, and the resulting solution was stirred for 10 min at rt. Sulfonylpyridine **16** (0.189 g, 0.54 mmol, 1.0 equiv) was added via an open neck, and the resulting brown mixture was stirred for 40 min at rt. Saturated aq NH_4Cl solution (2 mL) and 3 mL of water were added, the mixture was diluted with 10 mL of water and 10 mL of EtOAc, and the aqueous phase was separated and extracted with three 10-mL portions of EtOAc. The combined organic extracts were washed with 30 mL of satd aq NaCl solution, dried over $MgSO_4$, filtered, and concentrated to furnish 0.132 g of a brown oil. Column chromatography on 2.5 g of silica gel (elution with 0-1% EtOAc-hexanes) afforded 0.118 g (91%) of **49** as a yellow oil: IR (NaCl) 3028, 2972, 2936, 1600, 1570, 1460, 1439, 1402, 1378, 1341, 1270, 1193, 1118, 1046, 774, and 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 7.2 Hz, 2 H), 7.46 (t, J = 7.2 Hz, 2 H), 7.37 (t, J = 7.2 Hz, 1 H), 7.20 (s, 1 H), 4.53 (q, J = 7.1 Hz, 2 H), 2.68 (q, J = 7.6 Hz, 2 H), 2.21 (s, 3 H), 1.47 (t, J = 7.1 Hz, 3 H), 1.26 (t, J = 7.6 Hz, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 162.0, 153.2, 151.1, 139.8, 128.7, 128.4, 126.6, 116.9, 113.3, 61.7, 26.5, 15.1, 14.3, 11.0; HRMS (ESI-FTICR) *m/z* $[M + H]^+$ calcd for $C_{16}H_{120}NO$ 242.1539; found 242.1522.

3-Ethyl-2,4-dimethyl-5,6,7,8-tetrahydroquinoline (50). A 10-cm, threaded Pyrex tube (25 mm O.D.; 17 mm I.D.) equipped with a rubber septum fitted with an argon inlet needle was charged with sulfonylpyridine **7** (0.065 g, 0.20 mmol, 1.0 equiv) and 2 mL of THF. The resulting solution was stirred at rt while 0.40 mL of methylmagnesium bromide solution (3.0 M in ether, 1.18 mmol, 6.0 equiv) was added dropwise via syringe over 1 min. The rubber septum was replaced with a Teflon screw cap and the resulting solution was heated at 70 °C for 1.5 h and then allowed to cool to rt. The reaction mixture was treated with 2 mL of satd aq NH_4Cl solution and 2 mL of water, and the aqueous phase was separated and extracted with three 10-mL portions of EtOAc. The combined organic extracts were washed with 20 mL of satd aq NaCl solution, dried over $MgSO_4$, filtered, and concentrated to furnish 0.050 g of a yellow oil. Preparative thin-layer chromatography (elution with EtOAc) furnished 0.020 g (53%) of **50** as a yellow oil: IR (NaCl) 2965, 2938, 2871, 1568, 1452, 1436, 1414, 1373, 1060; ^1H NMR (400 MHz, $CDCl_3$) δ 2.82-2.88 (m, 2 H), 2.64 (q, J = 7.5 Hz, 2 H), 2.55-2.65 (m, 2 H), 2.50 (s, 3 H), 2.15 (s, 3 H), 1.81 (m, 4

H), 1.01 (t, J = 7.5 Hz, 3 H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 153.1, 152.6, 143.8, 133.1, 128.7, 33.1, 26.7, 23.4, 23.0, 22.6, 22.4, 14.3, 13.7; HRMS (ESI-FTICR) *m/z* $[M + H]^+$ calcd for $C_{13}H_{120}N$ 190.1590; found 190.1581.

3-Ethyl-4-methoxy-2-methyl-5,6,7,8-tetrahydroquinoline (51). A 10-mL, pear-shaped flask equipped with a rubber septum and an argon inlet needle was charged with sulfonylpyridine **26** (0.078 g, 0.226 mmol, 1.0 equiv) and 1 mL of THF. The solution was stirred at rt while 0.9 mL of methylmagnesium chloride solution (3.0 M in THF, 2.7 mmol, 12 equiv) was added dropwise via syringe over 0.5 min. The resulting brown solution was stirred at rt for 18 h, and then treated with 2 mL of half satd aq NaH_2PO_4 solution and diluted with 50 mL of water and 50 mL of EtOAc. The aqueous phase was separated and extracted with three 15-mL portions of EtOAc, and the combined organic extracts were washed with 20 mL of satd aq NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give 0.051 g of a yellow oil. Preparative thin-layer chromatography (elution with 10% EtOAc-hexanes) furnished 0.036 g (78%) of **51** as a yellow oil: IR (thin film) 2933, 2873, 1582, 1561, 1433, 1415, 1331, 1099, and 1074 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (s, 3 H), 2.83 (t, J = 6.3 Hz, 2 H), 2.69 (t, J = 6.6 Hz, 2 H), 2.61 (q, J = 7.5 Hz, 2 H), 2.47 (s, 3 H), 1.70-1.91 (m, 4 H), 1.13 (t, J = 7.5 Hz, 3 H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 163.4, 155.8, 155.2, 127.9, 123.4, 60.5, 32.6, 23.3, 23.2, 22.7, 22.0, 19.5, 14.4; HRMS (DART-FTICR) *m/z* $[M + H]^+$ calcd for $C_{13}H_{20}ON$ 206.1545; found 206.1541.

4-Methyl-3-(3-phenylpropyl)-5,6,7,8-tetrahydroquinolin-2(1H)-one (52). A 25-mL round-bottomed flask equipped with a rubber septum and an argon inlet needle was charged with pyridine **13** (0.390 g, 0.930 mmol, 1.0 equiv), 4 mL of THF, and 33 μL of water (0.033 g, 1.860 mmol, 2.0 equiv). KO*t*-Bu solution (1.0 M in THF, 5.6 mL, 5.6 mmol, 6.0 equiv) was added, the septum was replaced with a reflux condenser fitted with a rubber septum and an argon inlet needle, and the reaction mixture was heated at reflux for 16 h. The resulting dark red mixture was allowed to cool to rt and then treated with 3 mL of half satd aq NaH_2PO_4 solution, diluted with 50 mL of water and 50 mL of EtOAc, and the aqueous layer was separated and extracted with three 25-mL portions of EtOAc. The combined organic extracts

were washed with satd aq NaCl solution, dried over $MgSO_4$, filtered, and concentrated to furnish 0.258 g of an orange solid. Trituration with three 1-mL portions of hexanes and concentration furnished 0.196 g (75%) of **52** as a light orange solid: mp 139-140 ºC; IR (thin film) 2936, 2856, 1630, 1541, 1474, 722, and 692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.06 (br s, 1 H), 7.15-7.32 (m, 5 H), 2.75 (t, J = 7.6 Hz, 2 H), 2.69 (t, J = 7.6 Hz, 2 H), 2.63 (m, 2 H), 2.40 (m, 2 H), 2.05 (s, 3 H), 1.83 (t, J = 7.6 Hz, 2 H), 1.77 (m, 4 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$), 163.9, 148.2, 142.9, 139.2, 128.5, 128.3, 127.1, 125.7, 114.2, 36.2, 30.5, 27.1, 26.4, 24.8, 23.1, 21.8, 15.5; HRMS (DART-TOF) *m/z* $[M + H]^+$ calcd for $C_{19}H_{24}NO$ 282.1858; found 282.1868.

ASSOCIATED CONTENT

Supporting Information

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

Schemes describing the synthesis of cycloaddition substrates and ^1H and ^{13}C NMR spectra (PDF).

AUTHOR INFORMATION

Corresponding Author

*E-mail: danheisr@mit.edu

ORCID

Rick L. Danheiser: 0000-0002-9812-206X

Samuel G. Bartko: 0000-0002-5730-3542

Christian Gomez: 0000-0001-8947-6061

Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Jones, G. In *Comprehensive Heterocyclic Chemistry II*; Katritsky, A. R.; Rees, C. W.; Scriven, E. F. V.; McKillop, A., Eds.; Pergamon: Oxford, 1996; Vol. 5, pp 167–243. (b) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 5th ed.; Wiley-Blackwell: New York, 2010. (c) Kiuru, P.; Yli-Kauhaluoma, J. Pyridine and Its Derivatives. In *Heterocycles in Natural Product Synthesis*; Majumdar, K. C., Chattopadhyay, S. K. Eds.; Wiley-VCH: Weinheim, Germany, 2011, pp 267-297.

(2) For general reviews on the *de novo* synthesis of pyridines, see: (a) Henry, G. D. *De Novo* Synthesis of Substituted Pyridines. *Tetrahedron* **2004**, *60*, 6043–6061. (b) Hill, M. D. Recent Strategies for the Synthesis of Pyridine Derivatives. *Chem. Eur. J.* **2010**, *16*, 12052–12062. (c) Allais, C.; Grassot, J.-M.; Rodriguez, J.; Constantieux, T. Metal-Free Multicomponent Syntheses of Pyridines. *Chem. Rev.* **2014**, *114,* 10829-10868.

(3) Recent reviews: (a) Heller, B.; Hapke, M. The fascinating construction of pyridine ring systems by transition metal-catalysed [2 + 2 + 2] cycloaddition reactions. *Chem. Soc. Rev.* **2007**, *36*, 1085-1094. (b) Shaaban, M. R.; El-Sayed, R.; Elwahy, A. H. M. Construction of fused heterocycles by metal-mediated [2 + 2 + 2] cyclotrimerization of alkynes and/or nitriles. *Tetrahedron* **2011**, *67*, 6095-6130. (c) Broere, D. L. J.; Ruijter, E. Recent Advances in Transition-Metal-Catalyzed [2 + 2 + 2]-Cyclo(co)trimerization Reactions. *Synthesis* **2012,** *44*, 2639-2672. (d) Xu, F. Wang, C.; Wang, D.; Li, X.; Wan, B. Rhodium-Catalyzed [2 + 2 + 2] Cycloaddition of Oximes and Diynes to Give Pyridines. *Chem. Eur. J.* **2013**, *19*, 2252–2255. (e) Amatore, M.; Leboeuf, D.; Malacria, M.; Gandon, V.; Aubert, C. Highly Enantioselective Rhodium-Catalyzed [2 + 2 + 2] Cycloaddition of Diynes to Sulfonimines. *J. Am. Chem. Soc.* **2013**, *135*, 4576–4579. (f) Xu, F.; Wang, C.; Wang, H.; Li, X.; Wan, B. Eco-friendly synthesis of

pyridines via rhodium-catalyzed cyclization of diynes with oximes. *Green Chem.* **2015**, *17*, 799-803.

(4) For notable recent examples, see: (a) Movassaghi, M.; Hill, M. D.; Ahmad, O. K. Direct Synthesis of Pyridine Derivatives. *J. Am. Chem. Soc.* **2007**, *129*, 10096–10097. (b) Liu, S.; Liebeskind, L. S. A Simple, Modular Synthesis of Substituted Pyridines. *J. Am. Chem. Soc.* **2008**, *130*, 6918–6919. (c) Manning, J. R.; Davies, H. M. L. One-Pot Synthesis of Highly Functionalized Pyridines via a Rhodium Carbenoid Induced Ring Expansion of Isoxazoles. *J. Am. Chem. Soc.* **2008**, *130*, 8602–8603. (d) Martin, R. M.; Bergman, R. G.; Ellman, J. A. Synthesis of Pyridines from Ketoximes and Terminal Alkynes via C–H Bond Functionalization. *J. Org. Chem.* **2012**, *77*, 2501–2507 (e) Neeley, J. M.; Rovis, T. Rh(III)-Catalyzed Decarboxylative Coupling of Acrylic Acids with Unsaturated Oxime Esters: Carboxylic Acids Serve as Traceless Activators *J. Am. Chem. Soc.* **2014**, 136, 2735–2738. (f) Wu, J.; Xu, W.; Yu, Z.-X.; Wang, J. Ruthenium-Catalyzed Formal Dehydrative [4 + 2] Cycloaddition of Enamides and Alkynes for the Synthesis of Highly Substituted Pyridines: Reaction Development and Mechanistic Study. *J. Am. Chem. Soc*. **2015**, *137*, 9489-9496.

(5) For reviews on the construction of nitrogen heterocycles via hetero Diels–Alder reactions, see: (a) Boger, D. L.; Weinreb, S. M. *Hetero Diels–Alder Methodology in Organic Synthesis*; Academic Press: San Diego, 1987. (b) Buonora, P.; Olsen, J.-C.; Oh, T. Recent developments in imino Diels-Alder reactions. *Tetrahedron* **2001**, *57*, 6099–6138. (c) Heintzelman, G. R.; Meigh, I. R.; Mahajan, Y. R.; Weinreb, S. M. Diels-Alder Reactions of Imino Dienophiles *Org. React.* **2005**, *65*, 141–599. (d) Rowland, G. B.; Rowland, E. B.; Zhang, Q.; Antilla, J. C. Stereoselective Aza-Diels-Alder reactions. *Curr. Org.Chem.* **2006**, *10*, 981–1005. (e) Blond, G.; Gulea, M.; Mamane, V. Recent Contributions to Hetero Diels-Alder Reactions. *Curr. Org. Chem*. **2016**, *20,* 2161- 2210. (f) Cao, M.-H.; Green, N. J.; Xu, S.-Z. Application of the aza-Diels–Alder reaction in the synthesis of natural products. *Org. Biomol. Chem*. **2017**, *15*, 3105-3129.

(6) For recent examples, see (a) Anderson, E. D.; Boger, D. L. Inverse Electron Demand Diels-Alder Reactions of 1,2,3-Triazines: Pronounced Substituent Effects on Reactivity and Cycloaddition Scope. *J. Am. Chem. Soc.* **2011**, *133*, 12285–12292. (b) Linder, I.; Gerhard, M.; Schefzig, L.; Andrä, M.; Bentz, C.; Reissig, H.-U.; Zimmer, R. A Modular Synthesis of Functionalized Pyridines through Lewis-Acid-Mediated and Microwave-Assisted Cycloadditions between Azapyrylium Intermediates and Alkynes. *Eur. J. Org. Chem.* **2011**, 6070–6077. (c) Anderson, E. D.; Duerfeldt, A. S.; Zhu, K.; Glinkerman, C. M.; Boger, D. L. Cycloadditions of Noncomplementary Substituted 1,2,3-Triazines. *Org. Lett.* **2014**, *16*, 5084–5087. (d) Bachollet, S. P. J. T.; Vivat, J. F.; Cocker, D. C. Adams, H.; Harrity, P. A. Development of a Mild and Versatile Directed Cycloaddition Approach to Pyridines. *Chem. Eur. J.* **2014,** *20,* 12889-

12893. (e) Duret, G.; Quinlan, R.; Martin, R. E.; Bisseret, P.; Neuburger, M.; Gandon, V.; Blanchard, N. Inverse Electron Demand [4 + 2] Cycloadditions of Ynamides: Access to Novel Pyridine Scaffolds. *Org. Lett.* **2016,** *18,* 1610-1613. (f) Duret, G.; Quinlan, R.; Yin, B. Martin, R. E.; Bisseret, P.; Neuburger, M.; Gandon, V.; Blanchard, N. Intramolecular Inverse Electron Demand [4 + 2] Cycloadditions of Ynamides with Pyrimidines: Scope and Density Functional Theory Insights. *J. Org. Chem.* **2017,** *82,* 1726-1742.

(7) For some early contributions from our laboratory, see (a) Renslo, A. R.; Danheiser, R. L. Synthesis of Substituted Pyridines via Regiocontrolled [4 + 2] Cycloadditions of Oximinosulfonates. *J. Org. Chem.* **1998**, *63*, 7840–7850. (b) Danheiser, R. L.; Renslo, A. R.; Amos, D. T.; Wright, G. T. Preparation of Substituted Pyridines via Regiocontrolled [4 + 2] Cycloadditions of Oximinosulfonates: Methyl 5-Methylpyridine-2-carboxylate. *Org. Synth.* **2003***, 80,* 133–143.

(8) For an example of pathway c, see Wang, T.; Naredla, R. R.; Thompson, S. K.; Hoye, T. R.; The Pentadehydro-Diels-Alder Reaction. *Nature* **2016,** *532,* 484-488.

(9) Palenzuela has reported Lewis-acid-promoted cycloadditions of vinylallenes with *N*-benzylimines to give products that can be dehydrogenated to pyridines by heating with Pd on carbon: Regás, D.; Afonso, M. M.; Palenzuela, J. A. Pyridines and pyridine derivatives from vinyl allenes and imines. *Tetrahedron* **2012**, *68*, 9345–9349.

(10) (a) Sakai, T.; Danheiser, R. L. Cyano Diels-Alder and Cyano Ene Reactions. Application in a Formal [2 + 2 + 2] Cycloaddition Strategy for the Synthesis of Pyridines. *J. Am. Chem. Soc.* **2010**, *132*, 13203-13205. (b) Lan, Y.; Danheiser, R. L.; Houk, K. N. Why Nature Eschews the Concerted [2 + 2 + 2] Cycloaddition of a Nonconjugated Cyanodiyne. Computational Study of a Pyridine Synthesis Involving an Ene–Diels–Alder–Bimolecular Hydrogen-Transfer Mechanism. *J. Org. Chem.*, **2012**, *77*, 1533–1538.

(11) For a review of Diels-Alder reactions of vinylallenes, see Murakami, M.; Matsuda, T. Cycloadditions of Allenes. In *Modern Allene Chemistry*; Krause, N.; Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, 2004; Vol. 2, pp 727-815.

(12) For computational studies on Diels-Alder reactions of vinylallenes, see (a) Ferreiro, M. L.; Rodríguez-Otero, J.; Cabaleiro-Lago, E. M. Ab Initio and DFT Study of the Influence of the Allene Group on the Diels–Alder Reaction. *Struct. Chem*. **2004**, *15*, 323-326. (b) Li, Z.-M.; Wang, Q.-R. A Density Functional Theory Study on the Diels-Alder Reactions of Vinylallenes as Dienes. *Intl. J.Quantum Chem*. **2011**, *111*, 3805-3815. (c) Soriano, E.; Fernández, I. Allenes and Computational Chemistry: From Bonding Situations to Reaction Mechanisms. *Chem. Soc. Rev*. **2014**, *43*, 3041-3105.

(13) Hamzik, P. J.; Goutierre, A.-S.; Sakai, T.; Danheiser, R. L. Aza Diels–Alder Reactions of Nitriles, *N*,*N*-Dimethylhydrazones, and Oximino Ethers. Application in Formal [2 + 2 + 2] Cycloadditions for the Synthesis of Pyridines. *J. Org. Chem.* **2017**, *82*, 12975–12991.

(14) Sasaki, M.; Hamzik P. J.; Ikemoto H.; Bartko, S. G.; Danheiser, R. L. Formal Bimolecular [2 + 2 + 2] Cycloaddition Strategy for the Synthesis of Pyridines: Intramolecular Propargylic Ene Reaction/Aza Diels–Alder Reaction Cascades. *Org. Lett.* **2018**, *20*, 6244–6249.

(15) For selected reviews on the synthesis of allenes, see: (a) Egenburg, I. Z. The Methods of Synthesis and Properties of Conjugated Enallenic Hydrocarbons. *Russ. Chem. Rev.* **1978**, *47*, 470-485. (b) Krause, N.; Hoffmann-Röder, A. Synthesis of Allenes with Organometallic Reagents. *Tetrahedron* **2004,** *60*, 11671–11694. (c) Brummond, K. M.; DeForrest, J. E. Synthesizing Allenes Today (1982-2006) *Synthesis* **2007** 795–818. (d) Yu, S.; Ma, S. How easy are the syntheses of allenes? *Chem. Commun.* **2011,** *47*, 5384–5418. For books that include discussions of the synthesis of allenes, see: (e) Brandsma, L. *Synthesis of Acetylenes, Allenes, and Cumulenes: Methods and Techniques*; Elsevier: Oxford, UK, 2004. (f) *Modern Allene Chemistry*; Krause, N., Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, Germany, 2004; Vol. 1.

(16) Pioneering report: Rona, P.; Crabbé, P. A Novel Allene Synthesis. *J. Am. Chem. Soc.* **1968**, 90, 4733-4734.

(17) See the Supporting Information for schemes describing the synthesis of all cycloaddition substrates. Detailed procedures are presented in the Experimental Section.

(18) This procedure was based on: (a) Danheiser, R. L.; Tsai, Y.-M.; Fink, D. M. A General Method for the Synthesis of Allenylsilanes: 1-Methyl-1-(Trimethylsilyl)allene. *Org. Synth.* **1988**, *66*, 1-7. (b) Pioneering studies on the reaction of propargylic sulfonates with organocopper compounds: Vermeer, P.; Meijer, J.; Brandsma, L. A versatile synthesis of allenic hydrocarbons. Evidence for an organocopper(III) intermediate. *Rec. Trav. Chim. Pays-Bas* **1975**, *94*, 112-114.

(19) (a) van Leusen, A. M.; Jagt, J. C. Cycloaddition reactions of sulfonyl cyanides. *Tetrahedron Lett.* **1970**, *12*, 971–973. (b) Jagt, J. C.; van Leusen, A. M. Chemistry of sulfonyl cyanides. Part 4: Diels-alder cycloadditions of sulfonyl cyanides with dienes. *Recl. Trav. Chim. Pays-Bas* **1973**, *92*, 1343–1354. (c) Jagt, J. C.; van Leusen, A. M. Diels-Alder cycloadditions of sulfonyl cyanides with cyclopentadiene. Synthesis of 2-azabicyclo[2.2.1]hepta-2,5-dienes. *J. Org. Chem.* **1974**, *39*, 564–566.

(20) Examples: (a) Pews, R. G.; Nyquist, E. B.; Corson, F. P. The Cycloaddition of Aroyl and Sulfonyl Cyanides with 5,5-Dimethoxy-1,2,3,4-tetrahalocyclopentadienes. *J. Org. Chem.* **1970**, *35*, 4096–4100.

(b) Rüffer, U.; Breitmaier, E. 5-Alkyl-2-(p-tolylsulfonyl)pyridine durch regioselektive Cyano [4 + 2]-Cycloaddition. *Synthesis* **1989**, 623–625. (c) Griffiths, G. J.; Previdoli, F. E. Diels-Alder reaction of methanesulfonyl cyanide with cyclopentadiene. Industrial synthesis of 2-azabicyclo[2.2.1]hept-5-en-3-one. *J. Org. Chem.* **1993**, 58, 6129–6131. (d) Henteman, M. F.; Allen, J. G.; Danishefsky, S. J. Thermal Intermolecular Hetero Diels–Alder Cycloadditions of Aldehydes and Imines via o-Quinone Dimethides. *Angew. Chem. Int. Ed.* **2000**, *39*, 1937–1940. (e) McClure, C. K.; Link, J. S. 2-Azabicyclo[2.2.2]octa-3,5-dione via a Nitrile Diels−Alder Reaction. *J. Org. Chem.* **2003**, *68*, 8256–8257. (f) Hendrickson, J. B.; Wang, J. A Diels-Alder Synthesis of Pyridines. *Org. Prep. Proc. Int.* **2003**, *35*, 623–626. (g) Hussain, I.; Yawer, M. A.; Lalk, M.; Lindequist, U.; Villinger, A.; Fischer, C.; Langer, P. Hetero-Diels–Alder reaction of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with arylsulfonylcyanides. Synthesis and antimicrobial activity of 4-hydroxy-2-(arylsulfonyl)pyridines. *Bioorg. Med. Chem.* **2008**, *16*, 9898-9903. (h) Grafton, M. W.; Farrugia, L. J.; Sutherland, A. Synthesis of Amino-Substituted Indanes and Tetralins via Consecutive Multibond-Forming Tandem Processes. *J. Org. Chem.* **2013**, *78*, 7199–7207.

(21) (a) Allen, P.; Reich, L. The Disproportionation of *p*-Toluenesulfinic Acid in Aqueous Solution. *J. Phys. Chem.* **1960,** *64,* 1928-1933. (b) Kice, J. L.; Bowers, J. W. The Mechanism of the Disproportionation of Sulfinic Acids *J. Am. Chem. Soc.* **1962**, *84,* 605-610.

(22) Regás, D.; Afonso, M. M.; Rodríguez, M. L.; Palenzuela, J. A. Synthesis of Octahydroquinolines through the Lewis Acid Catalyzed Reaction of Vinyl Allenes and Imines. *J. Org. Chem.* **2003**, *68*, 7845–7852.

(23) For examples, see (a) Bertrand, M.; Grimaldi, J.; Waegell, B. Diels–Alder Cycloadditions of Vinyl- and Propenyl-Allene to Methyl Vinyl Ketone. *Chem. Commun.* **1968**, 1141-1142. (b) Bertrand, M.; Grimaldi, J.; Waegell, B. Reaction Mechanism and Structure of the Compounds Formed in the Diels-Alder Reaction between 1,2,4-Trienes and α,β-unsaturated Ketones. *Bull. Soc. Chim. Fr.* **1971,** 962-973. (c) Koop, U.; Handke, G.; Krause, N. Synthesis of Vinylallenes by Conjugate 1,6-, 1,8-, 1,10- and 1,12-Addition Reactions of Organocuprates with Acetylenic Michael Acceptors and Their Use as Dienes in Intermolecular Diels-Alder Reactions. *Liebigs. Ann.* **1996,** 1487-1499. (d) Spino, C.; Thibault, C.; Gingras, S. Stereoselective Construction of Tetrasubstituted Exocyclic Alkenes from the [4 + 2]-Cycloaddition of Vinylallenes. *J. Org. Chem.* **1998,** *63,* 5283-5287. (e) Robinson, J. M.; Sakai, T.; Okano, K.; Kitawaki, T.; Danheiser, R. L. Formal [2 + 2 + 2] Cycloaddition Strategy Based on an Intramolecular Propargylic Ene Reaction/Diels−Alder Cycloaddition Cascade. *J. Am. Chem. Soc.* **2010**, *132*, 11039–11041. (f) Choi, S.; Hwang, H.; Lee, P. H. An Effective Diels-Alder Reaction of Vinyl Allenols with Dienophiles. *Eur. J. Org. Chem.* **2011,** 1351-1356.

(24) Reich, H. J.; Eisenhart, E. K.; Whipple, W. L.; Kelly, M. J.; Stereochemistry of Vinylallene Cycloadditions. *J. Am. Chem. Soc.* **1988,** *110,* 6432-6442.

(25) For reviews on the synthesis and chemistry of allenyl ethers, see (a) Zimmer, R. Alkoxyallenes - Building Blocks in Organic Synthesis.. *Synthesis* **1993**, 165-178. (b) Zimmer, R.; Reissig, H.-U. Donor-Substituted Allenes. In *Modern Allene Chemistry*; Krause, N., Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, Germany, 2004; Vol. 1, pp 425-492. (c) Zimmer, R.; Reissig, H.-U. Alkoxyallenes as building blocks for organic synthesis. *Chem. Soc. Rev.* **2014**, 4*3*, 2888-2903.

(26) (a) Suffert, J.; Toussaint, D. An Easy and Useful Preparation of Propynyllithium from (Z/E)-1-Bromopropene. *J. Org. Chem.* **1995,** *60,* 3550-3553. (b) Toussaint, D.; Suffert, J. Generation of 1-Propynyllithium from (Z/E)-1- Bromo-1-propene: 6-Phenylhex-2-yn-5-en-4-ol. *Org. Synth.* **1999,** *76,* 214-220.

(27) Spencer III, W. T.; Levin, M. D.; Frontier, A. J. Oxidation-Initiated Nazarov Cyclization of Vinyl Alkoxyallenes. *Org. Lett.,* **2011**, *13*, 414–417.

(28) Reviews: (a) Tejedor, D.; Méndez-Abt, G.; Cotos, L.; García-Tellado, F. Propargyl Claisen Rearrangement: Allene Synthesis and Beyond. *Chem. Soc. Rev*. **2013**, *42*, 458-471. (b) Langlois, Y.; Gradl, S. N.; Trauner, D. Claisen-Johnson Orthoester Rearrangement. In *The Claisen Rearrangement,* Hiersemann, M.; Nubbemeyer, U., Eds.; Wiley-VCH: Weinheim, 2007; pp 301-396.

(29) For the reaction of propargylic alcohols with amide acetals, see: Parker, K. A.; Petraitis, J. J.; Kosley, R. W., Jr.; Buchwald, S. L. Reactions of Propargyl Alcohols with Amide Acetals. *J. Org. Chem.* **1982,** *47*, 389-398.

(30) For reviews on the synthesis and reactivity of azaindoles, see (a) Popowycz, F.; Mérour, J. –Y.; Joseph, B. Synthesis and reactivity of 4-, 5- and 6-azaindoles. *Tetrahedron* **2007,** *63,* 8689-8707. (b) Popowycz, F.; Routier, S.; Joseph, B.; Mérour, J. –Y. Synthesis and reactivity of 7-azaindole (1H-pyrrolo[2,3-b]pyridine). *Tetrahedron* **2007,** *63,* 1031-1064. (c) Prokopov, A. A.; Yakhontov, L. N. Methods of synthesis and the production technology of therapeutic substances. Chemistry of the azaindoles (review). *Pharm. Chem. J.* **1994,** *28,* 471-506. (d) Song, J. J.; Reeves, J. T.; Gallou, F.; Tan, Z.; Yee, N. K. Senanayake, C. H. Organometallic methods for the synthesis and functionalization of azaindoles. *Chem. Soc. Rev.* **2007,** *36,* 1120-1132.

(31) (a) Jones, R. A.; Marriott, M. T. P.; Rosenthal, W. P.; Arques, J. S. Pyrrole studies. 22. [4π + 2π] Cycloaddition Reactions with Vinylpyrroles. *J. Org. Chem.* **1980**, *45,* 4515-4519. (b) Muckowski, J. M.; Scheller, M. E. Synthesis of 4-Acylindoles via 2-(2-Phenylsulfinylvinyl)pyrrole. *Tetrahedron Lett.* **1987,** *28,* 3453-3456. (c) Ketcha, D. M.; Xiao, D. "Diels-Alder Reactions of 2 and 3-Vinyl-

1(Phenylsulfonyl)pyrroles. *J. Heterocyclic Chem.* **1995,** *39,* 499-503. (d) Noland, W. E.; Lanzatella, N. P.; Venkatraman, L.; Anderson, N. F.; Gullickson, G. C. Access to Indoles Via Diels-Alder Reactions of 2-Vinylpyrroles with Maleimides. *J. Heterocyclic Chem.* **2009,** *46*, 1154-1176. (e) Noland, W. E.; Lanzatella, N. P. Access to Indoles via Diels-Alder Reactions of 3-Vinylpyrroles. *J. Heterocyclic Chem.* **2009,** *46,* 1285-1295.

(32) We are aware of only one prior report of the preparation of a 2- or 3-(vinylallenyl)pyrrole: McCubbin, J. A.; Nassar, C.; Krokhin, O. V. Waste-Free Catalytic Propargylation/Allenylation of Aryl and Heteroaryl Nucleophiles and Synthesis of Naphthopyrans. *Synthesis* **2011,** 3152-3160.

(33) Beecher, J. E.; Tirrell, D. A. Synthesis of Protected Derivatives of 3-Pyrrolylalanine. *Tetrahedron Lett.* **1998,** *39,* 3927-3930.

(34) Reviewed in (a) Ref. 1b. (b) Blackburn, J. M.; Roizen, J. L. Catalytic Strategies to Convert 2-Halopyridines to 2-Alkylpyridines. *Asian J. Chem*. **2019**, *8*, 920-930.

(35) (a) Barlin, G. B.; Brown, W. V. Kinetics of Reactions in Heterocycles. Part II. Replacement of the Methylsulphonyl Group in Substituted Pyridines, Pyridazines, and Pyrazine by Methoxide Ion. *J. Chem. Soc.* **1967**, 648–652. (b) Barlin, G. B.; Brown, W. V. Useful Reactions of Nucleophiles with Some Methylsulphonyl Derivatives of Nitrogen Heterocycles. *J. Chem. Soc.* **1967**, 2473–2476. (c) Furukawa, N.; Tsuruoka, M.; Fujihara, H. Ipso-substitution Reactions of 2- and 4-Sulfonylpyridines with Nucleophiles. *Heterocycles* **1986**, *24*, 3337–3341. (d) Furukawa, N.; Ogawa, S.; Kawai, T.; Oae, S. Selective ipso-substitution in pyridine ring and its application for the synthesis of macrocycles containing both oxa- and thia-bridges. *Tetrahedron Lett.* **1983**, *24*, 3243–3246. (e) Furukawa, N.; Ogawa, S.; Kawai, T. Ipso-Substitution of a sulphinyl or sulphonyl group attached to pyridine rings and its application for the synthesis of macrocycles. *J. Chem. Soc. Perkin Trans. 1* **1984**, 1839–1845.

(36) Representative examples: (a) Niiyama, K.; Nagase, T.; Fukami, T.; Takezawa, Y.; Takezawa, H.; Hioki, Y. Takeshita, H.; Ishikawa, K. Novel 4-substituted pyridine derivatives: Practical derivatization and biological profiles of reversible H+K+-ATPase inhibitors. *Bioorg. Med. Chem. Lett.* **1997,** *7*, 527-532. (b) Kaupang, Å.; Hildonen, S.; Halvorsen, T. G.; Mortén, M.; Vik, A.; Hansen, T. V. Involvement of covalent interactions in the mode of action of PPARβ/δ antagonists. *RSC Adv.* **2015,** *5*, 76483-76490. (c) Qu, B.; Samankumara, L. P.; Savoie, J.; Fandrick, D. R.; Haddad, N.; Wei, X.; Ma, S.; Lee, H.; Rodriguez, S.; Busacca, C. A.; Yee, N. K.; Song, J. J.; Senanayake, C. H. Synthesis of Pyridyl-dihydrobenzooxaphosphole Ligands and Their Application in Asymmetric Hydrogenation of Unfunctionalized Alkenes. *J. Org. Chem.* **2014**, *79*, 993-1000. (d) Wei, X.; Qu, B.; Zeng, X.; Savoie, J.;

Fandrick, K. R.; Desrosiers, J. N.; Tcyrulnikov, S.; Marsini, M. A.; Buono, F. G.; Li, Z.; Yang, B.-S.; Tang, W.; Haddad, N.; Gutierrez, O.; Wang, J.; Lee, H.; Ma, S.; Campbell, S.; Lorenz, J. C.; Eckhardt, M.; Himmelsbach, F.; Peters, S.; Patel, N. D.; Tan, Z.; Yee, N. K.; Song, J. J.; Roschangar, F.; Kozlowski, M. C.; Senanayake, C. H. Sequential C–H Arylation and Enantioselective Hydrogenation Enables Ideal Asymmetric Entry to the Indenopiperidine Core of an 11β-HSD-1 Inhibitor. *J. Am. Chem. Soc.* **2016,** *138*, 15473-15481.

(37) Gassman, P. G.; Hodgson, P. K. G.; Balchunis, R. J. Base-promoted hydrolysis of amides at ambient temperatures. *J. Am. Chem. Soc.* **1976**, *98*, 1275–1276.

(38) Van den Hoven, B. G.; Alper, H. Regioselective Hydroformylation of Enynes Catalyzed by a Zwitterionic Rhodium Complex and Triphenyl Phosphite. *J. Org. Chem.* **1999**, *64*, 3964-3968.

(39) Feuerstein, M.; Chahen, L.; Doucet, H.; Santelli, M. Efficient Synthesis of Enynes by Tetraphosphine–Palladium-Catalysed Reaction of Vinyl Bromides with Terminal Alkynes. *Tetrahedron* **2006**, *62*, 112–120.

(40) Tao, B.; Ruble, J. C.; Hoic, D. A.; Fu, G. C. Nonenzymatic Kinetic Resolution of Propargylic Alcohols by a Planar−Chiral DMAP Derivative: Crystallographic Characterization of the Acylated Catalyst. *J. Am. Chem. Soc.* **1999***, 121,* 5091–5092.

(41) Álvarez, A.; Guzmán, Á.; Ruiz, A.; Velarde, E. Synthesis of 3-Arylpyrroles and 3-Pyrrolylacetylenes by Palladium-Catalysed Coupling Reactions. *J. Org. Chem.* **1992**, *57*, 1653-1656.