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New Approaches to Bicylic Vinyl Heterocycles from Propargylic Acetals

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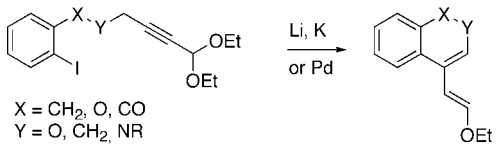

The paper describes further studies on the intramolecular carbolithiation of propargylic acetals with aryllithiums leading to 2-vinylbenzofurans and 3-vinylfuropyridines. Attempts to extend the cascade to [4.4.0] binuclear heterocycles met with limited success. An alternative, two-step entry to such ring systems has been developed using the palladium-induced cyclization/hydride capture methodology. A new route to isoquinilinones from simple benzamides is also disclosed.

Introduction

A large number of polynuclear heterocycles are to be found in nature, and many exhibit interesting and useful biological activity.[1] The Diels−Alder cycloaddition reaction is frequently used to access such skeletons when they include a nonaromatic six-membered ring fused to the heterocyclic core.[2] In that context, the use of vinyl heterocycles as the dienic component has been studied extensively in recent years. Indeed, the work of Pindur's team and others provides ample evidence of the usefulness of the approach when the reactivity of the diene is not compromised to any great extent by the aromatic character of one of the double bonds. Polycyclic structures have been prepared in this way from vinylbenzofurans,[3] vinylindoles,[4] and vinylisoquinolinones[5] through reaction with activated dienophiles such as dimethyl acetylene dicarboxylate,[4b,6] tetracyanoethylene,[3a] arynes,[7] quinones,[6,8] and maleimides.[3a,c,4a] Related intramolecular strategies have also been examined and used in the synthesis of a number of indole alkaloids.[9]

Vinyl-heterocycles have been prepared by a variety of methods, including Wittig-type olefinations,[9a,c,d,10] the *O*-alkylation of enolates,[4d,9b] elimination[4b,6] and crotonization[4c] procedures, and metal-catalyzed coupling reactions.[11] Recently, we reported a new approach to vinyl-

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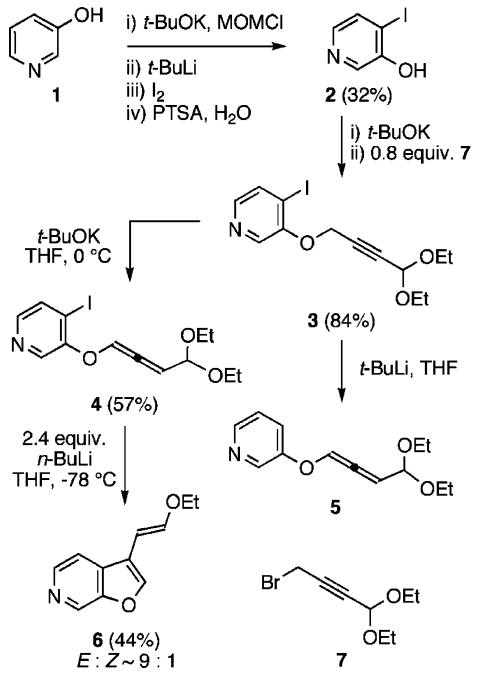
SCHEME 1. Synthesis of Furo[2,3-*c*]pyridine 6



heterocycles featuring a carbanionic cyclization to a propargylic acetal. The method was effective for the synthesis of 3-vinylindoles and benzofurans as well as the more exotic furo[3,2-*b*]pyridine ring system.[12] We now report some extensions to that work leading, in some cases surreptitiously, to 2-vinylbenzofurans, 3-vinylfuro-[2,3-*c*]pyridine, 4-vinylisochromenes, and 4-vinylisoquinolinones.

Results and Discussion

To extend the scope of our carbanionic heterocyclization method to 3-vinylfuro[2,3-*c*]pyridines, we first prepared 4-iodo-3-hydroxypyridine **2** from 3-hydroxypyridine **1**[13] and effected its union with propargylic bromide **7**.[12] On treatment of the resulting iodopyridyl ether **3** with *t*-BuLi,[14] cyclization to **6** was found to be a minor pathway, with deiodinated allene **5** being tentatively identified as the main component of the product mixture. The result suggested that iodine−lithium exchange was followed by deprotonation at the propargylic center and that this had suppressed cyclization. If true, we reasoned that the unwanted side reaction might be overcome by deliberately effecting the alkyne to allene isomerization before triggering cyclization by iodine−lithium exchange. The isomerization of **3** to **4** was duly achieved through the action of *t*-BuOK in THF. Pleasingly, when **4** was treated with *n*-BuLi at −78 °C, the expected 3-vinylfuro-[2,3-*c*]pyridine was formed in modest yield and with satisfying stereoselectivity (*E*:*Z* ~ 9:1). We presume that addition of the intermediate aryllithium occurs at the central carbon of the allenic moiety and that this induces elimination of lithium ethoxide (Scheme 1).[15]

Attempted Extensions of the Procedure to [4.4.0] Bicyclic Heterocycles. We next sought to extend the method by homologation to access various [4.4.0] bicyclic heterocycles, although those have rarely been prepared by carbanionic routes.[16] To that end, we prepared propargyl acetals **9**, **12**, **14**, and **15** and allenic acetals **11** and **16**[17] as described in Scheme 2. Disappointingly, only **12** gave the anticipated vinyl-heterocycle **13** on treatment with BuLi and in modest yield. The reaction displayed good stereoselectivity, giving an *E*:*Z* ratio of 4:1 when BuLi was added to a THF solution of **12** and 10:1 when the order of addition was reversed. In every other case studied a complex and intractable product mixture was returned. Replacing *n*-BuLi by mesityllithium[18] did not improve these results.

At first we presumed that isoquinolinone **13** had been formed by sequential halogen-to-lithium exchange, cyclization to the proximal alkyne, and isomerization of the resulting allene. However, we later found that benzamide **17** also gave isoquinolinone **13** in low yield on treatment with BuLi and 50% yield on treatment with *t*-BuOK in THF. In the latter case, acetal **21** was observed as a minor product in 18% yield. These results led us to reconsider the mechanistic course of the reaction as directed orthometalation of **17** seemed improbable under such conditions. A more plausible explanation is that alkyne to allene isomerization and amide deprotonation first gives **19** and that this intermediate then undergoes the electrocyclization and hydride shift sequence indicated in Scheme 3. Related oxidative cyclizations of aniline-derived benzamides using oxygen and a Pd catalyst[19] or phenyliodine(III) bis(trifluoroacetate) (PIFA)[20] are known but follow different mechanistic pathways. An electrocyclization reaction related to that postulated was the subject of a recent theoretical examination.[21]

Two related systems, the isomeric propargyl acetals, **24** and **31**, also gave unexpected outcomes that are worthy of comment. Thus, all attempts to induce the halogen-to-metal exchange and cyclization sequence with *o*-iodobenzyl propargyl ether **24** failed. However, on treatment with potassium hexamethyldisilazane (KHMDS) in toluene at 0 °C, **24** was transformed into a 10:1 mixture of (*E*)- and (*Z*)-vinylbenzofuran **28** in 49% yield (Scheme 4). The reaction is thought to proceed by deprotonation to **25** and cyclization to dihydrobenzofuran **26**. A second deprotonation then leads to allene **27**, a precursor of 2-vinylbenzofuran **28**.[22]A related ring closure leading to a dihydrobenzofuran provides some support for this mechanism.[23]

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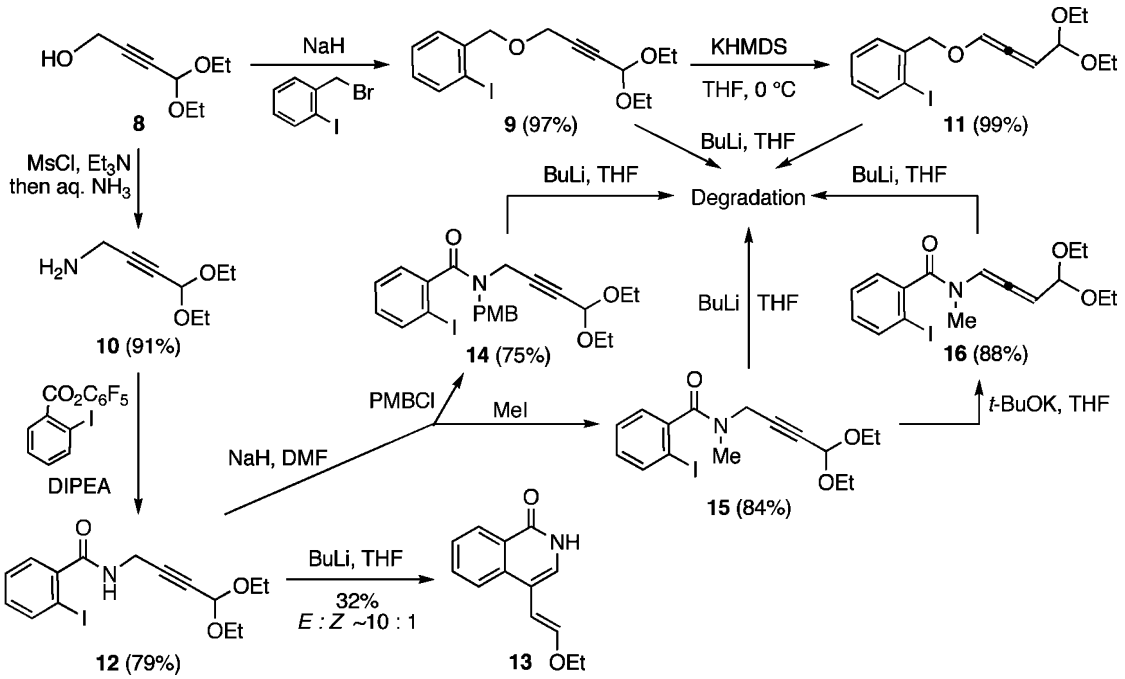
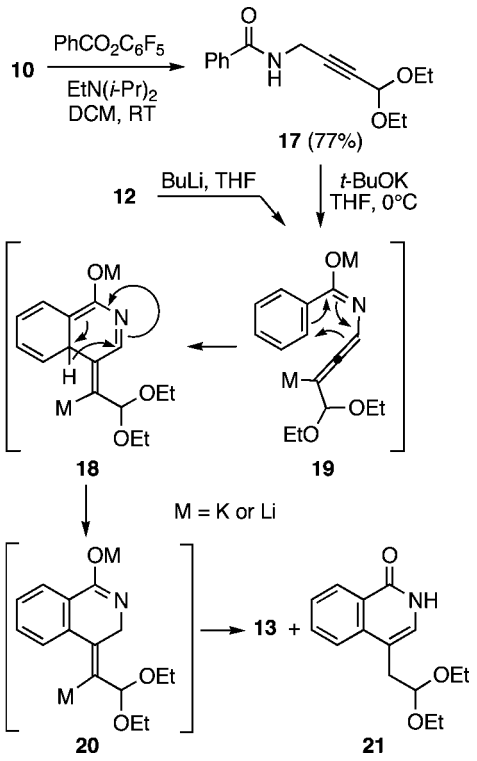
SCHEME 2. Attempted Synthesis of [4.4.0] Bicyclic Heterocycles



The isomeric homopropargylic ether **31** was readily prepared in two steps from alkyne **29**. Deprotonation with BuLi followed by addition of ethylene oxide gave alcohol **30** in 94% yield when 10% HMPA was included as a cosolvent.[24] A Mitsunobu condensation between **30** and 2-iodophenol then gave aryl ether **31**.[25] To our surprise, treatment of **31** with an excess of *n*-BuLi gave cumulene **35** as a 1:1 mixture of *E*- and *Z*-isomers in 89% yield (Scheme 4)![26] Its formation is presumed to begin with a halogen−metal exchange to aryllithium **32**. An intramolecular deprotonation of the propargylic carbon next facilitates elimination of lithium phenoxide. Residual butyllithium then adds to the newly created olefin **34**, triggering loss of lithium ethoxide and the formation of cumulene **35** (Scheme 5).

SCHEME 3. Proposed Mechanism for the Formation of Vinylisoquinolinone 13



Synthesis of [4.4.0] Bicyclic Heterocycles from Propargyl Acetals by Palladium-Catalyzed Cyclizations. The shortcomings of the carbolithiation methodology with respect to the synthesis of vinylchromenes, isochromenes, and isoquinolinones prompted us to examine an alternative approach based on palladium-mediated cyclizations. We reasoned that a palladium-catalyzed cyclization and hydride capture sequence ought to generate the desired bicyclic skeletons efficiently.[5b,27] The resulting exocyclic α,β-unsaturated acetals could then, in a separate step, undergo δ-elimination to the vinyl-heterocycle.

To that end, a solution of homopropargyl ether **31**, palladium acetate, triphenylphosphine, formic acid, tetraethylammonium bromide, and piperidine was warmed to 60 °C in acetonitrile. The expected chromane **37** was produced in reasonable yield (51%), though it could not be separated from a byproduct, alkyne **36**, by chromatography on silica gel (Scheme 6). The same product ratio was given when tetraethylammonium bromide was replaced with either thallium(I) or thallium(II) salts.[28,18b] The mixture was treated with various acids, Lewis acids, and Lewis bases in an attempt to promote δ-elimination

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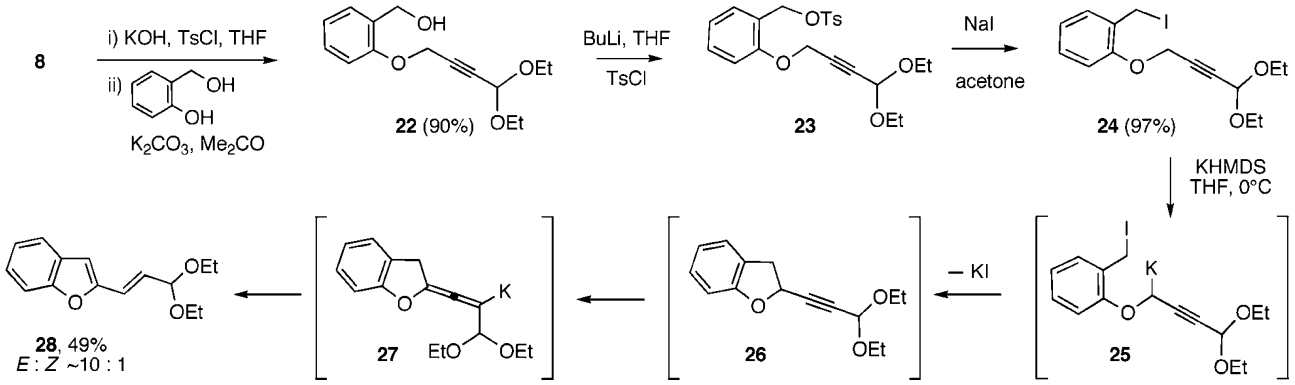
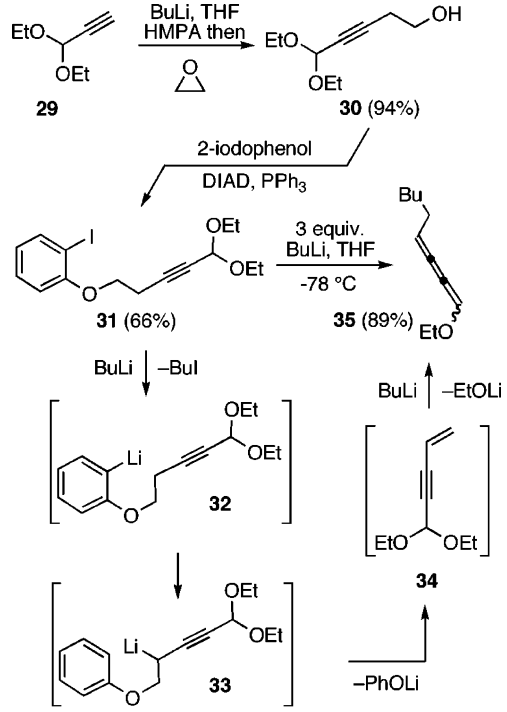
SCHEME 4. Synthesis of 2-Vinylbenzofuran 11



to the corresponding vinyl chromene but without success. The destructive removal of alkyne **36** from the product mixture was observed on reaction with *t*-BuLi, giving access to **37** in pure form.

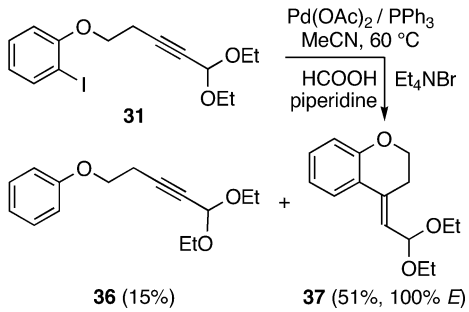
SCHEME 5. Synthesis and Reactivity of Homopropargyl Ether 30



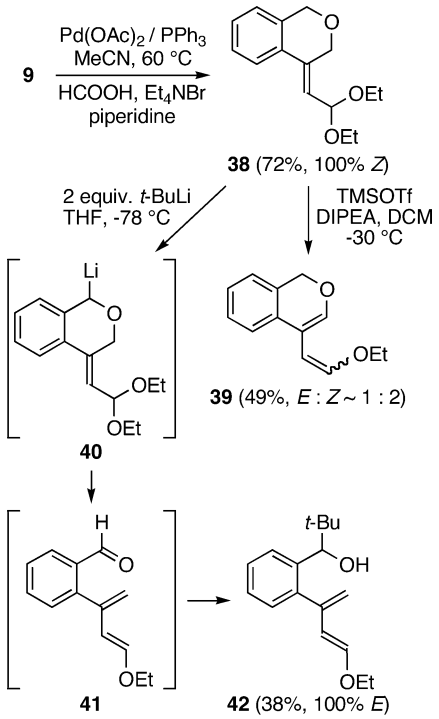
The palladium-catalyzed cyclization was next applied to propargylic acetal **9**. Using conditions similar to those described above, methyleneisochromene **38** was furnished as a single stereoisomer in good yield (Scheme 7). Treatment of a THF solution of **38** with *tert*-butyllithium at −78 °C failed to induce the anticipated δ-elimination to vinylisochromene **39**, giving instead dienol **42**. Pleasingly, elimination could be induced with TMSOTf, leading to an inseparable 1:2 mixture of (*E*)- and (*Z*)-**39**.

The formation of diene **42** is presumed to occur via deprotonation of the benzylic carbon in **38**. Conjugate elimination of lithium ethoxide next gives aldehyde **41**, which in turn is captured by a second equivalent of *tert*-butyllithium (Scheme 7). The intermediate aldehyde was not observed when a single equivalent of the organolithium reagent was employed—TLC monitoring showing only the presence of starting material **38** and alcohol **42**. This suggests that the elimination and addition steps outpace deprotonation at the benzylic carbon.

SCHEME 6. Synthesis of Chromene 37

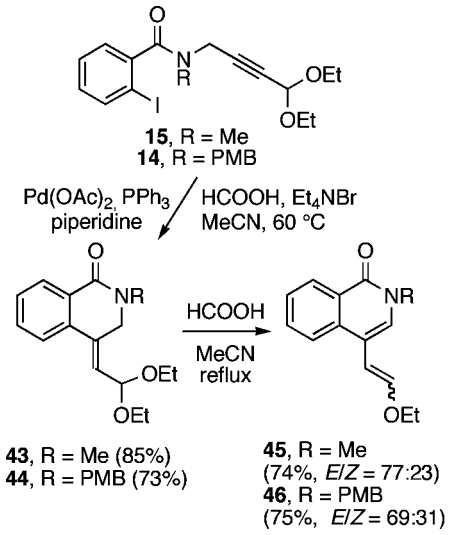


SCHEME 7. Synthesis of Vinylisochromene 39



The palladium-catalyzed cyclization−hydride capture process also proceeded smoothly with tertiary amides **14** and **15**, giving methyleneisoquinolinones **44** and **43**, respectively, in good yields and as their *Z*-isomers

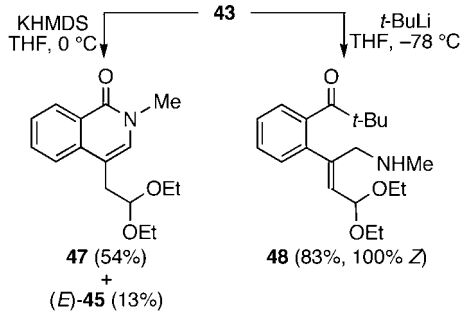
SCHEME 8. Synthesis of Vinylisoquinolinones 45 and 46



exclusively (Scheme 8).[5b] When cyclization of **15** was carried out at 80 °C, we noted the formation of **45** as a minor byproduct. That observation provided us with a useful means of transforming the methyleneisoquinolinones into the corresponding vinylisoquinolinones. Indeed, simply warming an acetonitrile solution of either **43** or **44** at reflux in the presence of formic acid brought about their smooth conversion to **45** and **46**, respectively. That these dienes may serve as synthons for alkaloids of the amarylidaceae family is noteworthy.[29]

For completeness, two further experiments deserve mention. Through the action of 1.2 equiv of *t*-BuLi, **43** was transformed into *tert*-butyl ketone **48**, while treatment of **43** with 2.2 equiv of KHMDS induced double-bond migration to give isoquinolinone **47** as the major product (Scheme 9).

SCHEME 9. Reactions of 43 with Strong Bases



Conclusions

Vinyl-heterocycles are useful in Diels–Alder cycloaddition reactions with classical dienophiles. Our study, reported here and in a previous publication,[12] has shown that the intramolecular carbolithiation of propargylic acetals with aryllithiums provides a useful entry to a broad range of vinyl-[4.3.0] binuclear heterocycles but is of little value in the synthesis of homologous [4.4.0] systems. The latter are readily prepared by means of a two-step procedure involving a palladium-induced cyclization and hydride capture sequence, followed by an acid- or Lewis-acid-promoted δ-elimination. New routes to cumulenes, vinylbenzofurans, and vinylisoquinolinones, initiated by the deprotonation of propargyl acetals, have been uncovered.

Experimental Section

4-Iodopyridin-3-ol (2). To a solution of 3-hydroxypyridine (2.85 g, 30 mmol) in a DMF/THF mixture (8:3, 21 mL) at −15 °C under a nitrogen atmosphere was added potassium *tert*-butoxide (3.71 g, 33 mmol, 1.1 equiv). After 20 min methoxymethyl chloride (MOMCl, 2.5 mL, 31.5 mmol, 1.05 equiv) was added, and after a further 1 h brine (20 mL) and water (20 mL) were added successively. The mixture was extracted with ethyl acetate (3 × 30 mL), and the combined organic phases were washed with brine (2 × 40 mL), dried with magnesium sulfate, and concentrated in vacuo. The residue was distilled under vacuum to provide 3-methoxymethoxy-pyridine (2.76 g, 19.8 mmol, 66%), giving spectral and physical data consistent with those described in the literature.[13] To a solution of 3-methoxymethoxypyridine (1.39 g, 10 mmol) in anhydrous Et_2O (50 mL) at −78 °C under a nitrogen atmosphere was added a solution of *tert*-butyllithium (1.35 M in pentane, 8.2 mL, 11 mmol, 1.1 equiv). After 20 min iodine (3.04 g, 12 mmol, 1.2 equiv) in Et_2O (30 mL) was added, and the reaction mixture was kept at −78 °C for 1 h. Water (40 mL) was added and the phases separated. The aqueous phase was extracted with Et_2O (2 × 25 mL), and the combined organic phases were washed with brine (40 mL), dried with magnesium sulfate, and concentrated in vacuo. The residue was purified by column chromatography (50% ethyl acetate in heptane) to give 4-iodo-3-methoxymethoxypyridine (2.05 g, 7.73 mmol, 77%), giving spectral and physical data consistent with those described in the literature.[13] 4-Iodo-3-methoxymethoxypyridine (1.55 g, 5.84 mmol) and PTSA (100 mg) were partitioned between water (10 mL) and Et_2O (5 mL). The resulting mixture was heated at reflux for 16 h; then the ether was evaporated and a further aliquot of water (10 mL) was added. After a further 8 h at reflux, the mixture was cooled to RT and the precipitated beige solid, 4-iodo-pyridin-3-ol **2** (807 mg, 3.65 mmol, 62%), was collected by filtration. Spectral and physical data were consistent with those described in the literature.[30] Mp 148 °C (lit. 140 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.75 (bs, 1H), 8.08 (s, 1H), 7.73 (d, J = 4.9 Hz, 1H), 7.68 (d, J = 4.9 Hz, 1H); MS (CI$^+$) *m/z* (%) 250 (8) [M + Et]$^+$, 222 (100) [M + H]$^+$.

3-(4,4-Diethoxybut-2-ynyloxy)-4-iodopyridine (3). Potassium *tert*-butoxide (0.45 g, 3.94 mmol, 1.2 equiv) was added to a solution of 4-iodo-pyridin-3-ol **2** (872 mg, 3.94 mmol, 1.2 equiv) in a mixture of DMF and THF (8/3, 12 mL) at −15 °C under a nitrogen atmosphere. After 15 min, a solution of bromide **3** (738 mg, 3.29 mmol) in the same mixture of solvents (4 mL) was added and the reaction was allowed to warm to RT. After a further 90 min, water (20 mL) and brine (20 mL) were successively added. The aqueous phase was separated and extracted with ethyl acetate (3 × 25 mL). The combined organic phases were washed with water (2 × 20 mL) and brine (2 × 20 mL), dried with magnesium sulfate, and concentrated in vacuo to provide acetal **3** (1.00 g, 2.77 mmol, 84%) as a beige solid. Mp 66–67 °C; ν_{max}/cm^{-1} 2971, 1139; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.88 (d, J = 4.9 Hz, 1H), 7.71 (d, J = 4.9 Hz, 1H), 5.25 (s, 1H), 4.88 (s, 2H), 3.66 (dq, J = 9.4 7.2 Hz, 2H), 3.52 (dq, J = 9.4, 7.2 Hz, 2H), 1.17 (t, J = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.9, 144.3, 135.5, 134.8, 98.3, 91.5, 84.5, 79.0, 61.5, 58.0, 15.4; MS (CI$^+$, CH_4) *m/z* (%) 390

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(30) Lindström, S.; Ripa, L.; Hallberg, A. *Org. Lett.* **2000**, *2*, 2291–2293.

(28) $[M + Et]^+$, 362 (19) $[M + H]^+$, 222 (19), 141 (100); HRMS (CI, NH_3) *m/z* 362.0248, $C_{13}H_{17}NO_3I$ (M + H) requires 362.0253. Anal. Calcd for $C_{13}H_{16}NO_3I$: C, 43.23; H, 4.47; N, 3.88. Found: C, 43.21; H, 4.48; N, 3.82.

3-(4,4-Diethoxybuta-1,2-dienyloxy)-4-iodopyridine (4). Potassium *tert*-butoxide (180 mg, 1.60 mmol, 1.6 equiv) was added to a solution of alkyne **3** (361 mg, 1.0 mmol) in anhydrous THF (10 mL) at 0 °C under a nitrogen atmosphere. After 20 min, water (10 mL) and brine (25 mL) were successively added. The aqueous phase was separated and extracted with Et_2O (2 × 25 mL). The combined organic phases were washed with brine (2 × 20 mL), dried with magnesium sulfate, and concentrated in vacuo. The residue was purified by column chromatography (60% ethyl acetate in heptane) to provide allene **4** (206 mg, 0.57 mmol, 57%) as a brown oil. ν_{max}/cm^{-1} 2973, 1972, 1055; ^1H NMR (300 MHz, $CDCl_3$) δ 8.33 (s, 1H), 7.92 (d, J = 5.1 Hz, 1H), 7.70 (d, J = 5.1 Hz, 1H), 6.99 (d, J = 5.1 Hz, 1H), 5.79 (t, J = 5.1 Hz, 1H), 4.90 (d, J = 5.1 Hz, 1H), 3.60−3.31 (m, 4H), 1.14 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.7, 153.6, 145.7, 140.6, 134.5, 121.3, 107.1, 99.7, 99.5, 61.8, 61.5, 15.5.

3-(Ethoxyvinyl)furo[2,3-*c*]pyridine (6). To a solution of allene **4** (213 mg, 0.59 mmol) in anhydrous THF (6 mL) at −78 °C under a nitrogen atmosphere was added a solution of *n*-butyllithium (2.45 M in hexane, 0.58 mL, 1.41 mmol, 2.4 equiv). After 20 min, water (5 mL) was added and the reaction was warmed to RT. The aqueous phase was separated and extracted with Et_2O (2 × 5 mL). The combined organic phases were washed with brine (5 mL), dried with magnesium sulfate, and concentrated in vacuo. The residue was purified by column chromatography (60% ethyl acetate in heptane) to provide an inseparable 9:1 mixture of (*E*)- and (*Z*)-furopyridines **6** (49.5 mg, 0.26 mmol, 44%) as a brown oil. ν_{max}/cm^{-1} 2978, 1655, 1606, 1162, 1093. *E*-Isomer: ^1H NMR (300 MHz, $CDCl_3$) δ 8.83 (s, 1H), 8.42 (d, J = 5.3 Hz, 1H), 7.60 (s, 1H), 7.56 (d, J = 5.3 Hz, 1H), 7.04 (d, J = 13.2 Hz, 1H), 5.78 (d, J = 13.2 Hz, 1H), 3.93 (q, J = 7.2 Hz, 2H), 1.32 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.0, 149.3, 143.2, 142.7, 134.5, 133.0, 117.1, 115.7, 94.3, 66.0, 15.1; MS (EI^+) *m/z* (%) 189 (19) $M^{\bullet+}$, 161 (10), 132 (29), 103 (100). *Z*-Isomer: ^1H NMR (300 MHz, $CDCl_3$) δ 5.33 (d, J = 9.0 Hz, 1H), 6.41 (d, J = 9.0 Hz, 1H), 8.10 (s, 1H). Other signals are superimposed with those of *E*-isomer.

1-((4,4-Diethoxybut-2-ynyloxy)methyl)-2-iodobenzene (9). To a suspension of sodium hydride (60% in mineral oil, 0.81 g, 20 mmol, 2 equiv) in anhydrous THF (15 mL) under a nitrogen atmosphere was added a solution of alcohol **8** (1.58 g, 10 mmol) in anhydrous THF (15 mL) at RT. The mixture was stirred at this temperature for 20 min, and a solution of 2-iodobenzyl bromide (3.12 g, 10 mmol, 1 equiv) in THF (15 mL) was added. The mixture was refluxed for 90 min before carrying out the hydrolysis at RT with water (20 mL). The aqueous phase was extracted with Et_2O (2 × 20 mL). The combined organic phases were dried with magnesium sulfate and concentrated in vacuo to give benzylic ether **9** (3.65 g, 9.75 mmol, 97%) as a yellow oil, which was used without further purification. ν_{max}/cm^{-1} 2925, 1137; ^1H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, J = 7.5 Hz, 1H), 7.41 (dd, J = 1.5, 7.5 Hz, 1H), 7.32 (t, J = 7.5 Hz, 1H), 6.97 (dt, J = 1.5, 7.5 Hz, 1H), 5.32 (t, J = 1.1 Hz, 1H), 4.56 (s, 2H), 4.31 (d, J = 1.1 Hz, 2H), 3.75 (dq, J = 9.4, 7.2 Hz, 2H), 3.58 (dq, J = 9.4, 7.2 Hz, 2H), 1.23 (t, J = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.1, 139.6, 129.8, 129.4, 128.3, 98.3, 91.7, 82.5, 81.5, 75.6, 61.4, 58.3, 15.5; MS (EI^+) *m/z* (%) 374 (10) $M^{\bullet+}$, 217 (100). Anal. Calcd for $C_{15}H_{19}IO_3$: C, 48.14; H, 5.12. Found: C, 47.97; H, 4.98.

4,4-Diethoxy-2-yn-1-amine (10). To a solution of alcohol **8** (5.53 g, 35 mmol) and triethylamine (15.0 mL, 105 mmol, 3 equiv) in anhydrous Et_2O (140 mL) at 0 °C under a nitrogen atmosphere was added dropwise methanesulfonyl chloride (3.25 mL, 42 mmol, 1.2 equiv). After 1 h, saturated $NaHCO_3$ (70 mL) was added. The aqueous phase was separated and extracted with Et_2O (2 × 40 mL). The combined organic phases were dried with magnesium sulfate and concentrated in vacuo. Aqueous ammonia (28%, 200 mL) was added to the residue, and this mixture was stirred at RT for 150 min. After extraction with ethyl acetate (200 then 100 mL), the combined organic phases were washed with brine (50 mL), dried with magnesium sulfate, and concentrated in vacuo to provide amine **10** (5.04 g, 32.0 mmol, 91%) as a yellow oil, which was used without further purification. Known compound.[31] ν_{max}/cm^{-1} 3371, 2973, 1129; ^1H NMR (300 MHz, $CDCl_3$) δ 5.24 (s, 1H), 3.70 (dq, J = 9.4, 7.2 Hz, 2H), 3.54 (dq, J = 9.4, 7.2 Hz, 2H), 3.44 (s, 2H), 1.50 (bs, 2H), 1.20 (t, J = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 91.7, 86.6, 78.1, 61.1, 31.8, 15.4.

1-(4,4-Diethoxybuta-1,2-dienyloxy)methyl)-2-iodobenzene (11). To a solution of alkyne **9** (604 mg, 1.61 mmol) in anhydrous THF (10 mL) at 0 °C under a nitrogen atmosphere was added a solution of KHMDS (0.5 M in THF, 6.44 mL, 3.22 mmol, 2 equiv). After 20 min, water (5 mL) was added. The aqueous phase was separated and extracted with Et_2O (2 × 5 mL). The combined organic phases were dried with magnesium sulfate and concentrated in vacuo to provide allene **11** (598 mg, 1.60 mmol, 99%) as a yellow oil, which was used without further purification. ^1H NMR (200 MHz, $CDCl_3$) δ 7.79 (d, J = 8.0 Hz, 1H), 7.41−7.28 (m, 2H), 7.01−6.93 (m, 2H), 5.88 (t, J = 5.7 Hz, 1H), 4.82 (dd, J = 5.7, 1.0, 1H), 4.59 (s, 2H), 3.52−3.37 (m, 4H), 1.19 (t, J = 7.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.4, 137.9, 137.8, 128.0, 127.3, 126.8, 121.6, 105.0, 99.3, 96.0, 73.2, 60.1, 13.9.

***N*-(4,4-Diethoxy-but-2-ynyl)-2-iodobenzamide (12).** A solution of DCC (3.73 g, 18.1 mmol, 1 equiv) in anhydrous THF (30 mL) was added to a mixture of 2-iodobenzoic acid (2.84 g, 18.1 mmol, 1 equiv) and pentafluorophenol (3.70 g, 19.91 mmol, 1.1 equiv) in THF (40 mL) at RT under a nitrogen atmosphere. After 1 h, the mixture was filtered and concentrated in vacuo. Dicyclohexylurea was then removed by precipitation from EtOAc. The filtrate was concentrated in vacuo, and the residue was dissolved in anhydrous CH_2Cl_2 (40 mL) and placed under an atmosphere of nitrogen. Amine **10** (2.84 g, 18.1 mmol) and diisoproylethylamine (7 mL, 40 mmol, 2.2 equiv) were successively added to the solution dropwise over 10 min. After 16 h, water (25 mL) was added. The aqueous phase was separated and extracted with CH_2Cl_2 (15 mL). The combined organic phases were washed with saturated $NaHCO_3$ (15 mL), dried with magnesium sulfate, and concentrated in vacuo. Purification by column chromatography (45% ethyl acetate in heptane) gave benzamide **12** (5.50 g, 14.2 mmol, 79%) as a yellow solid. Mp 76−78 °C; ν_{max}/cm^{-1} 3243, 2969, 1642, 1141; ^1H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, J = 7.9 Hz, 1H), 7.38−7.35 (m, 2H), 7.11−7.06 (m, 1H), 5.64 (bs, 1H), 5.26 (t, J = 1.5 Hz, 1H), 4.30 (dd, J = 1.5, 5.3 Hz, 2H), 3.72 (dq, J = 9.4, 7.2 Hz, 2H), 3.56 (dq, J = 9.4, 7.2 Hz, 2H), 1.21 (t, J = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 141.6, 140.3, 131.8, 128.7, 128.6, 92.7, 91.6, 80.9, 79.8, 61.4, 30.3, 15.4; MS (CI^+, NH_3) *m/z* (%) 405 (37) $[M + NH_4]^+$, 342 (100). Anal. Calcd for $C_{15}H_{18}INO_3$: C, 46.53; H, 4.69; N, 3.62. Found: C, 46.58; H, 4.62; N, 3.61.

4-(2-Ethoxyvinyl)isoquinolin-1(2*H*)-one (13). *From Iodobenzamide (**12**), Normal Addition.* To a solution of iodobenzamide **12** (387 mg, 1.0 mmol) in anhydrous THF (10 mL) at −78 °C under a nitrogen atmosphere was added a solution of *n*-butyllithium (2.1 M in hexane, 2.2 mL, 4.4 mmol, 4.4 equiv) dropwise over 5 min. After 30 min, water (5 mL) was added and the mixture was allowed to warm to RT. The aqueous phase was separated and extracted with Et_2O (2 × 5 mL). The combined organic phases were dried with magnesium sulfate and concentrated in vacuo. Purification by column chromatography (30% ethyl acetate in heptane) gave an inseparable 4:1 mixture of (*E*)- and (*Z*)-isoquinolinones **13** (60 mg, 0.28 mmol, 28%) as a brown oil.

*From Iodobenzamide (**12**), Reversed Addition.* To a solution of *n*-butyllithium (2.1 M in hexane, 5.4 mL, 11.3 mmol, 4.4

(31) Haidoune, M.; Giffard, M.; Mornet, R.; Gorgues, A. *Tetrahedron Lett.* **1989**, *30*, 3967−3968.

equiv) at −78 °C under a nitrogen atmosphere were added successively anhydrous THF (4 mL) and a solution of iodobenzamide **12** (1.00 g, 2.58 mmol) in anhydrous THF (20 mL). After 30 min, water (15 mL) was added and the solution was allowed to warm to RT. The aqueous phase was separated and extracted with Et_2O (2 × 10 mL). The combined organic phases were dried with magnesium sulfate and concentrated in vacuo. Purification by column chromatography (30% ethyl acetate in heptane) gave an inseparable 9:1 mixture of (*E*)- and (*Z*)-isoquinolinones **13** (180 mg, 0.84 mmol, 32%) as a brown oil.

*From Benzamide (**17**).* To a solution of benzamide **17** (131 mg, 0.5 mmol) in anhydrous THF (5 mL) at 0 °C under a nitrogen atmosphere was added potassium *tert*-butoxide (150 mg, 1.25 mmol, 2.5 equiv). After 30 min, water (10 mL) was added. The aqueous phase was separated and extracted with Et_2O (2 × 5 mL). The combined organic phases were dried with magnesium sulfate and concentrated in vacuo to provide an inseparable mixture (77 mg) of (*E*)- and (*Z*)-isoquinolines **13** (0.25 mmol, 50%, *E*/*Z* = 3:1) and 4-(2,2-diethoxyethyl)isoquinolin-1(2*H*)-one **25** (0.087 mmol, 18%). Isoquinolinone **13**: ν_{max}/cm^{-1} 2924, 1654, 1179, 909, 735. *E*-Isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01−7.96 and 7.44−7.37 (m, 4H), 7.11 (d, J = 12.8 Hz, 1H), 6.82 (s, 1H), 5.68 (d, J = 12.8 Hz, 1H), 3.90 (q, J = 7.2 Hz, 2H), 1.36 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.8, 149.7, 149.4 (2 carbons), 130.2, 129.0, 128.0, 126.4, 126.3, 122.6, 93.1, 66.3, 15.1. *Z*-Isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01−7.96 and 7.44−7.37 (m, 4H), 7.27 (s, 1H), 6.21 (d, J = 6.6 Hz, 1H), 5.42 (d, J = 6.6 Hz, 1H), 4.06 (q, J = 7.2 Hz, 2H), 1.31 (t, J = 7.2 Hz, 3H); MS (EI$^+$) *m/z* (%) 215 (100) M$^{\bullet+}$, 186 (44), 158 (44), 83 (76). 4-(2,2-Diethoxyethyl)-isoquinolin-1(2*H*)-one **21**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.95 and 7.30 (m, 4H), 6.93 (s, 1H), 4.77 (t, J = 5.8 Hz, 1H), 3.70−3.40 (m, 4H), 3.02 (d, J = 5.8 Hz, 2H), 1.16 (t, J = 7.0 Hz, 6H).

***N*-(4,4-Diethoxy-but-2-ynyl)-2-iodo-*N*-(4-methoxybenzyl)benzamide (14).** To a suspension of sodium hydride (60% in mineral oil, 240 mg, 6.0 mmol, 1 equiv) in anhydrous DMF (10 mL) at RT under a nitrogen atmosphere was added a solution of amide **12** (2.32 g, 6.0 mmol) in DMF (30 mL). After 10 min, the solution was cooled to 0 °C and *p*-methoxybenzyl chloride (1.0 mL, 7.2 mmol, 1.2 equiv) added. After a further 1 h at RT, water (40 mL) was added. The aqueous phase was separated and extracted with ethyl acetate (3 × 30 mL). The combined organic phases were washed with brine (30 mL), dried with magnesium sulfate, and concentrated in vacuo. Purification by column chromatography (50% ethyl acetate in heptane) gave amide **14** (2.29 g, 4.51 mmol, 75%) as viscous yellow oil comprised of two rotamers. ν_{max}/cm^{-1} 2971, 1646, 1138; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83−6.80 (m, 8H), 5.27 and 4.35 (two m, 1H + 2H), 4.70 (d, J = 16.9 Hz, 1H), 3.95 (d, J = 16.9 Hz, 1H), 3.79−3.50 (m, 7H), 1.22 (t, J = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 170.6, 159.8, 159.7, 141.8, 139.7, 131.0, 130.9, 130.8, 129.5, 129.0, 128.7, 128.2, 127.8, 127.7, 127.4, 114.5, 114.3, 93.2, 92.7, 91.7, 91.5, 80.9, 80.0, 79.9, 79.7, 61.3, 55.7, 51.2, 46.8, 37.7, 33.2, 15.5; MS (EI$^+$) *m/z* (%) 461 (7) [M − EtOH]$^{\bullet+}$, 231 (52), 121 (100).

***N*-(4,4-Diethoxybut-2-ynyl)-2-iodo-*N*-methylbenzamide (15).** To a suspension of sodium hydride (60% in mineral oil, 113 mg, 2.58 mmol, 1 equiv) in anhydrous DMF (5 mL) at RT under a nitrogen atmosphere was added a solution of benzamide **12** (1.00 g, 2.58 mmol) in DMF (10 mL). After 10 min, the solution was cooled to 0 °C and methyl iodide (0.3 mL, 4.84 mmol, 1.9 equiv) added. After a further 16 h at RT, water (15 mL) was added. The aqueous phase was separated and extracted with ethyl acetate (3 × 10 mL). The combined organic phases were dried with magnesium sulfate and concentrated in vacuo. Purification by column chromatography (30% ethyl acetate in heptane) gave amide **15** (0.87 g, 2.17 mmol, 84%) as viscous yellow oil comprised of two rotamers in a 3:2 ratio. ν_{max}/cm^{-1} 2969, 2243, 1640, 1141. Major rotamer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, J = 8.3 Hz, 1H), 7.40−7.02 (m, 3H), 5.27 (t, J = 1.5 Hz, 1H), 4.46 (bs, 2H), 3.78−3.48 (m, 4H), 2.87 (s, 3H), 1.21 (t, J = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 142.2, 139.6, 130.7, 128.8, 127.4, 92.5, 91.6, 80.2, 79.9, 61.3, 36.7, 36.0, 15.5. Minor rotamer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, J = 8.3 Hz, 1H), 7.40−7.02 (m, 3H), 5.23 (t, J = 1.5 Hz, 1H), 3.92 (bs, 2H), 3.78−3.48 (m, 4H), 3.16 (s, 3H), 1.20 (t, J = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 142.0, 139.6, 130.9, 128.8, 127.6, 92.8, 91.5, 81.1, 79.4, 61.3, 41.2, 32.6, 15.5; MS (EI$^+$) *m/z* (%) 401 (0.5), 400 (2) [M − H]$^{\bullet+}$, 372 (18), 231 (100); HRMS (CI, NH_3) *m/z*, 356.0145, $C_{14}H_{15}INO_2$ (M + H$^+$ − EtOH) requires 356.1847. Anal. Calcd for $C_{16}H_{20}INO_3$: C, 47.88; H, 4.99; N, 3.49. Found: C, 47.74; H, 4.93; N, 3.42.

***N*-(4,4-Diethoxybuta-1,2-dienyl)-2-iodo-*N*-methyl-benzamide (16).** To a solution of benzamide **15** (452 mg, 1.126 mmol) in anhydrous THF (10 mL) at 0 °C under a nitrogen atmosphere was added potassium *tert*-butoxide (193 mg, 1.69 mmol, 1.5 equiv). After 10 min, water (10 mL) was added. The aqueous phase was separated and extracted with Et_2O (2 × 10 mL). The combined organic phases were washed with brine (10 mL), dried with magnesium sulfate, and concentrated in vacuo to provide allene **16** (397 mg, 0.99 mmol, 88%) as a yellow oil comprised of two rotamers in a ratio of 55:45. ν_{max}/cm^{-1} 2973, 1656, 1072; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84−7.76 (m, 1H), 6.48 (1H, d, J = 6.5 Hz, 1H), 7.38 (t, J = 7.6 Hz, 1H), 7.24 (m, 1H), 7.09 (dt, J = 1.5, 7.6 Hz, 1H), 5.92−5.82 (m, 1H), 5.00−4.92 (m, 1H), 3.72−3.46 (m, 4H), 3.15 and 2.83 (two s, 3H), 1.25−1.14 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.2, 195.6, 169.2, 142.0, 141.5, 139.8, 139.6, 131.1, 130.9, 128.8, 128.2, 127.7, 104.7, 103.2, 103.0, 102.7, 101.7, 100.7, 93.2, 92.6, 62.0, 35.1, 31.2, 15.7, 15.6; MS (CI$^+$, CH_4) *m/z* (%) 402 (60) [M + H]$^+$, 356 (52), 229 (95), 103 (100).

***N*-(4,4-Diethoxy-but-2-ynyl)benzamide (17).** A solution of DCC (1.48 g, 7.2 mmol, 1.6 equiv) in anhydrous THF (12 mL) was added to a mixture of benzoic acid (0.73 g, 6 mmol, 1.3 equiv) and pentafluorophenol (1.21 g, 6.6 mmol, 1.4 equiv) in THF (13 mL) at RT under a nitrogen atmosphere. After 1 h, the mixture was filtered and the filtrate concentrated in vacuo. Dicyclohexylurea was then removed by precipitation from EtOAc (10 mL). The filtrate was concentrated in vacuo, dissolved in anhydrous CH_2Cl_2 (40 mL), and placed under an atmosphere of nitrogen. Amine **10** (0.70 g, 4.5 mmol) and diisoproylethylamine (1.8 mL, 10.3 mmol, 2.3 equiv) were successively added to the solution. After 16 h, water (15 mL) was added. The aqueous phase was separated and extracted with CH_2Cl_2 (2 × 15 mL). The combined organic phases were washed with 4 M NaOH (2 × 15 mL), dried with magnesium sulfate, and concentrated in vacuo to provide benzamide **17** (0.90 g, 3.44 mmol, 77%) as a white solid. Mp 122−124 °C; ν_{max}/cm^{-1} 3219, 2971, 1639, 1054; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (dd, J = 1.4, 7.7 Hz, 2H), 7.50−7.37 (m, 3H), 6.27 (bs, 1H), 5.27 (t, J = 1.5 Hz, 1H), 4.31 (dd, J = 1.5, 5.1 Hz, 2H), 3.72 (dq, J = 9.4, 7.2 Hz, 2H), 3.56 (dq, J = 9.4, 7.2 Hz, 2H), 1.22 (t, J = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4, 134.1, 132.1, 129.0, 127.4, 91.6, 81.4, 79.5, 61.4, 30.2, 15.4; MS (EI$^+$) *m/z* (%) 215 (95) [M − EtOH]$^{\bullet+}$, 149 (69), 105 (100).

(2-(4,4-Diethoxybut-2-ynyloxy)phenyl)methanol (22). Freshly ground potassium hydroxide (9.0 g, 160 mmol, 8 equiv) was added to a solution of alcohol **8** (3.04 g, 19.2 mmol) and tosyl chloride (4.03 g, 21.1 mmol, 1.1 equiv) in THF (90 mL) at −30 °C. After 40 min, water (45 mL) was added and the reaction mixture was warmed to RT. The aqueous phase was separated and extracted with Et_2O (2 × 20 mL). The combined organic phases were washed with brine (50 mL), dried with magnesium sulfate, and concentrated in vacuo to provide 4,4-diethoxybut-2-ynyl 4-methylbenzenesulfonate (6.00 g, 19.2 mmol, 100%), which was used without further purification. A solution of 2-(hydroxymethyl)phenol (2.71 g, 19.2 mmol, 1 equiv) and potassium carbonate (3.45 g, 25 mmol, 1.3 equiv) in freshly distilled acetone (25 mL) was stirred for 15 min at RT before being added to a solution of 4,4-diethoxybut-2-ynyl 4-methylbenzenesulfonate (6.00 g, 19.2 mmol) in acetone (25 mL). The mixture was refluxed for 20 h, concentrated in vacuo,

and partitioned between water (50 mL) and chloroform (30 mL). The aqueous phase was separated and extracted with chloroform (2 × 30 mL). The combined organic phases were washed with 4 M sodium hydroxide (30 mL), dried with magnesium sulfate, and concentrated in vacuo, and the residue was purified by column chromatography (30% ethyl acetate in heptane) to provide alcohol **22** (4.57 g, 17.3 mmol, 90%) as a colorless oil. ν_{max}/cm^{-1} 3448, 2975, 1118; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26−7.17 (m, 2H), 6.95−6.89 (m, 2H), 5.20 (t, J = 1.5 Hz, 1H), 4.73 (d, J = 1.5 Hz, 2H), 4.62 (s, 2H), 3.61 (dq, J = 9.4, 7.2 Hz, 2H), 3.48 61 (dq, J = 9.4, 7.2 Hz, 2H), 2.27 (bs, 1H), 1.13 (t, J = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.7, 130.3, 129.3, 129.1, 122.1, 112.4, 91.5, 83.3, 80.4, 61.9, 61.4, 56.5, 15.4; MS (EI$^+$) *m/z* (%) 264 (4) M$^{\bullet+}$, 219 (5), 96 (100). Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.17; H, 7.69.

1-(4,4-Diethoxybut-2-ynyloxy)-2-(iodomethyl)benzene (24). To a solution of alcohol **22** (4.62 g, 17.47 mmol) in anhydrous THF (30 mL) at −78 °C under a nitrogen atmosphere was added a solution of *n*-butyllithium (2.4 M in hexane, 8.0 mL, 19.2 mmol, 1.1 equiv). After 20 min, a solution of *p*-toluenesulfonyl chloride (3.33 g, 17.47 mmol, 1 equiv) in THF (20 mL) was added, and the mixture was allowed to warmed to −10 °C. After 30 min, water (20 mL) was added. The aqueous phase was separated and extracted with Et_2O (2 × 15 mL). The combined organic phases were dried with magnesium sulfate and concentrated in vacuo without heating. The residue was dissolved in acetone (150 mL), cooled to 0 °C, and sodium iodide (17.0 g, 110 mmol, 6.5 equiv) added. After 1 h at RT, water (50 mL) was added. The resulting solution was concentrated in vacuo to ca. 50 mL and then extracted with ethyl acetate (3 × 50 mL). The combined organic phases were washed with brine (50 mL), dried with magnesium sulfate, and concentrated in vacuo to give alkyne **24** (6.36 g, 17.0 mmol, 97%) as a yellow solid, which was used without further purification. Mp 56−58 °C; ν_{max}/cm^{-1} 2974, 1137; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31−7.20 (m, 2H), 6.94−6.87 (m, 2H), 5.27 (t, J = 1.1 Hz, 1H), 4.83 (d, J = 1.1 Hz, 2H), 4.46 (s, 2H), 3.68 (dq, J = 9.4, 7.2 Hz, 2H), 3.54 (dq, J = 9.4, 7.2 Hz, 2H), 1.19 (t, J = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.4, 128.4, 130.7, 129.7, 121.9, 112.9, 91.5, 83.0, 80.4, 61.3, 56.3, 15.3, 1.0; MS (EI$^+$) *m/z* (%) 329 (1) [M − OEt]$^{\bullet+}$, 247 (15) [M − I]$^{\bullet+}$, 202 (42); 68 (100). Anal. Calcd for $C_{15}H_{19}IO_3$: C, 48.14; H, 5.12. Found: C, 48.09; H, 5.29.

2-(3,3-Diethoxyprop-1-enyl)benzofuran (28). To a solution of alkyne **24** (414 mg, 1.1 mmol) in anhydrous toluene (11 mL) at 0 °C under a nitrogen atmosphere was added a solution of KHMDS (0.5 M in toluene, 5.5 mL, 2.75 mmol, 2.5 equiv). After 30 min, water (10 mL) was added. The aqueous phase was separated and extracted with Et_2O (2 × 10 mL). The combined organic phases were washed with brine (10 mL), dried with magnesium sulfate, and concentrated in vacuo. The residue was then purified by column chromatography (5% ethyl acetate in heptane) to give an inseparable 9:1 mixture of (*E*)- and (*Z*)-benzofuran **28** (120 mg, 0.49 mmol, 49%) as a yellow oil. ν_{max}/cm^{-1} 2970, 1680, 1121, 1051. *E*-Isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, J = 7.9 Hz, 1H), 7.42 (d, J = 7.9 Hz, 1H), 7.28−7.14 (m, 2H), 6.67 (d, J = 16.3 Hz, 1H), 6.61 (s, 1H), 6.40 (dd, J = 4.5, 16.3 Hz, 1H), 5.12 (d, J = 4.5 Hz, 1H), 3.71 (dq, J = 9.4, 7.2 Hz, 2H), 3.56 (dq, J = 9.4, 7.2 Hz, 2H), 1.25 (t, J = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.3, 154.2, 129.2, 129.1, 125.2, 123.5, 121.6, 121.4, 111.4, 106.1, 100.7, 61.4, 15.7. *Z*-Isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55−7.14 (m, 4H), 6.79 (s, 1H), 6.45 (m, 1H), 5.79 (m, 2H), 3.71 (dq, J = 9.4, 7.2 Hz, 2H), 3.56 (dq, J = 9.4, 7.2 Hz, 2H), 1.25 (t, J = 7.2 Hz, 6H); MS (CI$^+$, CH_4) *m/z* (%) 247 (28) [M + H]$^+$, 217 (5), 201 (100); HRMS (CI, NH_3) *m/z* 246.1234, $C_{15}H_{18}O_3$ requires 246.1256.

5,5-Diethoxypent-3-yn-1-ol (30). To a solution of propiolaldehyde diethyl acetal **29** (5.28 g, 40 mmol) in anhydrous THF (55 mL) containing HMPA (5 mL), at −30 °C under a nitrogen atmosphere was added a solution of *n*-butyllithium (2.2 M in hexane (18.5 mL, 40.7 mmol, 1 equiv). After 30 min, a large excess of ethylene oxide was condensed into the reaction mixture by means of a dry ice condenser. The mixture was stirred at RT until the starting material had been consumed (TLC monitoring), whereupon water (50 mL) was added. The aqueous phase was separated and extracted successively with Et_2O (30 mL) and ethyl acetate (2 × 30 mL). The combined organic phases were washed with a solution of 50% saturated solution of ammonium chloride (4 × 50 mL), dried with magnesium sulfate, and concentrated in vacuo to give alcohol **30** (6.47 g, 37.5 mmol, 94%) as a yellow oil, which was used without further purification. ν_{max}/cm^{-1} 3466, 2977, 1120; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.20 (t, J = 1.5 Hz, 1H), 3.73−3.63 (m, 4H), 3.52 (dq, J = 9.4, 7.2 Hz, 2H), 2.46 (dt, J = 1.5 ,6.4 Hz, 2H), 1.18 (t, J = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 91.7, 83.4, 77.7, 61.1, 61.0, 23.3, 15.4); MS (EI$^+$) *m/z* (%) 171 (3) [M − H]$^{\bullet+}$, 127 (100) [M − OEt]$^{\bullet+}$; HRMS (CI, NH_3) *m/z* 190.1419, $C_9H_{20}O_3N$ (M + NH_4^+) requires 190.1443.

1-(5,5-Diethoxypent-3-ynyloxy)-2-iodobenzene (31). Diisopropyl azodicarboxylate (7.25 mL, 35 mmol, 1 equiv) was added dropwise to a mixture of 2-iodophenol (7.85 g, 35 mmol, 1 equiv), alcohol **30** (6.02 g, 35 mmol), and triphenylphosphine (9.18 g, 35 mmol, 1 equiv) in anhydrous Et_2O (180 mL) at 0 °C under a nitrogen atmosphere. After 4 h, the mixture was allowed to warm to RT and then stirred at that temperature for 16 h. The mixture was filtered, concentrated in vacuo to ca. 50 mL, and then washed with 0.4 M sodium hydroxide (3 × 50 mL). The organic phase was separated, dried with magnesium sulfate, and concentrated in vacuo. Triphenylphosphine oxide was then removed by precipitation and filtration, first from Et_2O and then from pentane. Purification by column chromatography (10% ethyl acetate in heptane) provided alkyne **31** (8.61 g, 23.0 mmol, 66%) as a yellow oil. ν_{max}/cm^{-1} 2975, 1121; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (dd, J = 7.9, 1.5 Hz, 1H), 7.25 (m, 1H), 6.77 (dd, J = 8.1, 1.5 Hz, 1H), 6.69 (dt, J = 1.5, 7.9 Hz, 1H), 5.25 (t, J = 1.5 Hz, 1H), 4.11 (t, J = 7.2 Hz, 2H), 3.73 (dq, J = 9.4, 7.2 Hz, 2H), 3.55 (dq, J = 9.4, 7.2 Hz, 2H), 2.78 (dt, J = 1.5, 7.2 Hz, 2H), 1.21 (t, J = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.4, 140.0, 129.8, 123.4, 112.9, 91.7, 87.1, 82.2, 77.9, 67.4, 61.2, 20.0, 15.5; MS (EI+) *m/z* (%) 374 (2) M$^{\bullet+}$, 220 (100). Anal. Calcd for $C_{15}H_{19}IO_3$: C, 48.14; H, 5.12. Found: C, 48.12; H, 5.46.

1-Ethoxynona-1,2,3-triene (35). A solution of *n*-butyllithium (2.1 M in hexane, 0.80 mL, 1.70 mmol, 3.4 equiv) was added to a solution of alkyne **31** (187 mg, 0.50 mmol) in anhydrous THF (5 mL) at −78 °C under a nitrogen atmosphere. After 20 min, water (5 mL) was added. The aqueous phase was separated and extracted with Et_2O (2 × 5 mL). The combined organic phases were dried with magnesium sulfate and concentrated in vacuo to provide a mixture of isomers *E* and *Z* (*E*/*Z* = 1:1) of trienes **35** (74 mg, 0.445 mmol, 89%) as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.56 (m, 1H), 5.13 (dt, J = 5.6, 7.5 Hz, 0.5H), 5.04 (dt, J = 6.0, 7.1 Hz, 0.5H), 3.94−3.84 (m, 2H), 2.18−2.09 (m, 2H), 1.50−1.23 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 125.9, 125.7, 95.8, 95.7, 65.5, 65.4, 31.8, 31.7, 31.3, 30.9, 29.3, 29.1, 23.0, 22.9, 14.9, 14.4; MS (EI$^+$) *m/z* (%) 166 (17) M$^{\bullet+}$, 109 (23), 81 (100); HRMS (EI) *m/z* 166.1364, $C_{11}H_{18}O$ requires 166.1358.

(*E*)-4-(2,2-Diethoxyethylidene)-3,4-dihydro-2*H*-chromene (37). A mixture of alkyne **31** (748 mg, 2 mmol), palladium acetate (44 mg, 0.2 mmol, 0.1 equiv), triphenylphosphine (106 mg, 0.4 mmol, 0.2 equiv), tetraethylammonium bromide (480 mg, 2.2 mmol, 1.1 equiv), formic acid (0.22 mL, 5.8 mmol, 2.9 equiv), and piperidine (0.81 mL, 8.1 mmol, 4 equiv) in acetonitrile (60 mL) was stirred at 60 °C under a nitrogen atmosphere for 16 h and then cooled to RT, filtered, and concentrated in vacuo. The residue was dissolved in Et_2O (30 mL) and washed with water (20 mL). The organic phase was dried with magnesium sulfate and concentrated in vacuo. Purification by column chromatography (10% ethyl acetate in heptane) gave a yellow oil (0.33 g) comprised of an inseparable 3:1 mixture of chromene **37** (51%) and alkyne **36** (15%). ν_{max}/

cm^{-1} 2974, 1600, 1050. Chromene **37**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.53−6.76 (m, 4H), 6.02 (d, J = 6.2 Hz, 1H), 5.28 (d, J = 6.2 Hz, 1H), 4.15 (t, J = 5.4 Hz, 2H), 3.68−3.42 (m, 4H), 2.71 (t, J = 5.4 Hz, 2H), 1.17 (t, J = 7.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.4, 133.3, 129.9, 124.7, 121.8, 121.2, 119.8, 118.0, 98.6, 66.2, 60.7, 26.7, 15.7; MS (CI$^+$, CH_4) *m/z* (%) 249 (7) [M + H]$^+$, 203 (100). Alkyne **36**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.20−6.76 (m, 5H), 5.21 (s, 1H), 4.04 (t, J = 7.2 Hz, 2H), 3.68−3.42 (m, 4H), 2.71 (t, J = 7.2 Hz, 2H), 1.17 (t, J = 7.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.8, 121.4, 119.9, 114.8, 91.8, 82.5, 78.0, 66.0, 61.1, 20.1, 15.7.

(*Z*)-4-(2,2-Diethoxyethylidene)-3,4-dihydro-1*H*-isochromene (38). A mixture of alkyne **9** (1.87 g, 5 mmol), palladium acetate (110 mg, 0.5 mmol, 0.1 equiv), triphenylphosphine (264 mg, 1 mmol, 0.2 equiv), tetraethylammonium bromide (1.07 g, 5 mmol, 1 equiv), formic acid (0.57 mL, 15 mmol, 3 equiv), and piperidine (2 mL, 20 mmol, 4 equiv) in acetonitrile (150 mL) was stirred at 60 °C under a nitrogen atmosphere for 16 h. The mixture was then cooled to RT, filtered, and concentrated in vacuo. Purification by column chromatography (10% ethyl acetate in heptane) gave isochromene **38** (0.89 g, 3.58 mmol, 72%) as a yellow oil. ν_{max}/cm^{-1} 2974, 1104, 1485; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (dd, J = 3.0 4.5 Hz, 1H), 7.21 (m, 2H), 7.01 (dd, J = 3.6, 5.3 Hz, 1H), 6.11 (dt, J = 5.4, 2.0 Hz, 1H), 5.28 (d, J = 5.4 Hz, 1H), 4.71 (s, 2H), 4.60 (d, J = 2.0 Hz, 2H), 3.65 (dq, J = 9.4, 7.2 Hz, 2H), 3.52 (dq, J = 9.4, 7.2 Hz, 2H), 1.20 (t, J = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.4, 134.5, 131.2, 128.4, 127.5, 125.1, 123.7, 120.8, 98.3, 68.9, 66.7, 60.9, 15.7; MS (EI$^+$) *m/z* (%) 202 (100) [M − EtOH]$^{\bullet+}$, 115 (55); HRMS (CI, NH_3) *m/z* 266.1745, $C_{15}H_{24}NO_3$ (M + NH_4^+) requires 266.1756.

4-(Ethoxyvinyl)-1*H*-isochromene (39). To a solution of isochromene **38** (1.24 g, 5 mmol) and diisopropylethylamine (2.61 mL, 15 mmol, 3 equiv) in anhydrous dichloromethane (25 mL) at −40 °C under a nitrogen atmosphere was added trimethylsilyl trifluoromethanesulfonate (2.26 mL, 12.5 mmol, 2.5 equiv). After 40 min, 1 M NaOH (0.46 mL) and pentane (35 mL) were successively added. The mixture was maintained at −20 °C for 36 h and then filtered, dried with magnesium sulfate, and concentrated in vacuo. Purification by column chromatography (10% ethyl acetate and 1% triethylamine in heptane) gave an inseparable 1:2 mixture of (*E*)- and (*Z*)-isochromenes **39** (0.50 g, 2.47 mmol, 49%) as a yellow oil. ν_{max}/cm^{-1} 2972, 1655, 1150, 1097. *E*-Isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33−7.00 (m, 4H), 6.62 (d, J = 12.8 Hz, 1H), 6.57 (s, 1H), 5.58 (d, J = 12.8 Hz, 1H), 4.98 (s, 2H), 3.86 (q, J = 6.8 Hz, 2H), 1.27 (t, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.3, 141.7, 132.0, 128.9, 128.5, 127.2, 124.4, 121.4, 114.3, 98.9, 68.8, 65.9, 15.3. *Z*-Isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (s, 1H), 7.33−7.00 (m, 4H), 6.21 (d, J = 7.2 Hz, 1H), 5.06 (d, J = 7.2 Hz, 1H), 4.98 (s, 2H), 3.92 (q, J = 6.8 Hz, 2H), 1.33 (t, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.1, 145.7, 131.5, 129.0, 128.5, 126.7, 124.4, 120.9, 112.6, 97.4, 69.1, 68.5, 15.8; MS (EI$^+$) *m/z* (%) 202 (65) M$^{\bullet+}$, 173 (7), 115 (77), 57 (100).

1-(2-((*E*)-4-Ethoxybuta-1,3-dien-2-yl)phenyl)-2,2-dimethylpropan-1-ol (42). To a solution of isochromene **38** (246 mg, 0.99 mmol) in anhydrous THF (6 mL) at −78 °C under a nitrogen atmosphere was added dropwise a solution of *tert*-butyllithium (1.45 M in pentane, 1.38 mL, 2 mmol, 2 equiv). After 20 min, water (5 mL) was added and the reaction was allowed to warm to RT. The aqueous phase was extracted with Et_2O (2 × 5 mL). The combined organic phases were washed with brine (10 mL), dried with magnesium sulfate, and concentrated in vacuo. Purification by column chromatography (10% ethyl acetate in heptane) gave alcohol **42** (98 mg, 0.38 mmol, 38%) as a colorless oil. ν_{max}/cm^{-1} 3424, 1725, 1108; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (dd, J = 1.5, 7.9 Hz, 1H), 7.30−7.17 (m, 2H), 7.05 (dd, J = 1.5, 7.1 Hz, 1H), 5.95 (d, J = 12.4 Hz, 1H), 5.81 (d, J = 12.4 Hz, 1H), 5.15 (d, J = 2.2 Hz, 1H), 4.71 (d, J = 2.2 Hz, 1H), 4.65 (s, 1H), 3.70 (q, J = 7.2 Hz, 2H), 1.88 (bs, 1H), 1.19 (t, J = 7.2 Hz, 3H), 0.89 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.2, 145.9, 140.7, 140.3, 130.1, 123.9, 127.5, 127.3, 114.8, 110.4, 77.9, 66.1, 36.7, 27.0, 15.1; MS (EI+) *m/z* (%) 245 (11) [M − CH_3]$^{\bullet+}$, 173 (51), 129 (76), 57 (100).

(*Z*)-4-(2,2-Diethoxyethylidene)-3,4-dihydro-2-methylisoquinolin-1(2*H*)-one (43). A mixture a alkyne **15** (0.75 g, 1.87 mmol), palladium acetate (44 mg, 0.2 mmol, 0.1 equiv), triphenylphosphine (108 mg, 0.41 mmol, 0.2 equiv), tetraethylammonium bromide (427 mg, 2 mmol, 1 equiv), formic acid (0.21 mL, 5.5 mmol, 3 equiv), and piperidine (0.76 mL, 7.6 mmol, 4 equiv) in acetonitrile (60 mL) was stirred at 60 °C under a nitrogen atmosphere for 16 h then cooled to RT, filtered, and concentrated in vacuo. Purification by column chromatography (30% ethyl acetate in heptane) gave isoquinolinone **43** (0.44 g, 1.60 mmol, 85%) as a brown oil. ν_{max}/cm^{-1} 2973, 1640, 1599, 1117; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (d, J = 7.9 Hz, 1H), 7.54 (d, J = 7.5 Hz, 1H), 7.41 (m, 2H), 6.11 (dt, J = 5.3, 1.9 Hz, 1H), 5.32 (d, J = 5.3 Hz, 1H), 4.32 (d, J = 1.9 Hz, 2H), 3.65 (dq, J = 9.4, 7.2 Hz, 2H), 3.54 (dq, J = 9.4, 7.2 Hz, 2H), 3.14 (s, 3H), 1.21 (t, J = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.4, 135.7, 132.4, 128.1, 132.2, 129.2, 128.6, 125.4, 123.1, 98.1, 60.7, 49.8, 35.2, 15.6; MS (EI$^+$) *m/z* (%) 230 (36) [M − OEt]$^{\bullet+}$, 229 (100), 200 (65); HRMS (CI, NH_3) *m/z* 276.1581, $C_{16}H_{22}NO_3$ (MH^+) requires 276.1600.

(*Z*)-2-(4-Methoxybenzyl)-4-(2,2-diethoxyethylidene)-3,4-dihydroisoquinolin-1(2*H*)-one (44). A mixture a alkyne **14** (2.14 g, 4.22 mmol), palladium acetate (97 mg, 0.42 mmol, 0.1 equiv), triphenylphosphine (232 mg, 0.84 mmol, 0.2 equiv), tetraethylammonium bromide (0.89 g, 4.22 mmol, 1 equiv), formic acid (0.48 mL, 12.6 mmol, 3 equiv), and piperidine (1.7 mL, 17 mmol, 4 equiv) in acetonitrile (130 mL) was stirred at 60 °C under a nitrogen atmosphere for 16 h and then cooled to RT, filtered, and concentrated in vacuo. Purification by column chromatography (40% ethyl acetate in heptane) gave isoquinolinone **44** (1.18 g, 3.09 mmol, 73%) as a brown oil. ν_{max}/cm^{-1} 2971, 1647, 1600, 1245; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, J = 7.2 Hz, 1H), 7.53−7.37 (m, 3H), 7.25 (d, J = 9.1 Hz, 2H), 6.83 (d, J = 9.1 Hz, 2H), 6.03 (dt, J = 5.3, 1.5 Hz, 1H), 5.06 (d, J = 5.3 Hz, 1H), 4.72 (s, 2H), 4.21 (d, J = 1.5 Hz, 2H), 3.76 (s, 3H), 3.53 (dq, J = 9.4, 7.2 Hz, 2H), 3.41 (dq, J = 9.4, 7.2 Hz, 2H), 1.14 (t, J = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.2, 159.4, 136.0, 132.5, 129.9, 129.3, 128.3, 125.6, 132.3, 129.1, 128.9, 123.2, 114.3, 98.0, 60.8, 55.4, 49.9, 46.7, 15.6; MS (EI$^+$) *m/z* (%) 381 (3) M$^{\bullet+}$, 231 (4), 121 (100); HRMS (CI, NH_3) *m/z* 382.2020, $C_{23}H_{28}NO_4$ (M + H) requires 382.2019.

4-(2-Ethoxyvinyl)-2-methylisoquinolin-1(2*H*)-one (45). A mixture of acetal **43** (1.93 g, 7.0 mmol) and formic acid (0.81 mL, 21.0 mmol, 5 equiv) in acetonitrile (70 mL) was refluxed for 1 h and then concentrated in vacuo. The residue was dissolved in Et_2O (40 mL) and washed with saturated $NaHCO_3$ (2 × 20 mL). The organic phase was separated, dried with magnesium sulfate, and concentrated in vacuo to provide an inseparable 10:3 mixture of (*E*)- and (*Z*)-isoquinolinones **45** (1.19 g, 5.19 mmol, 74%) as a brown oil. ν_{max}/cm^{-1} 2977, 1644, 1619, 1599, 1185. *E*-Isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 (dd, J = 7.9, 1.0 Hz, 1H), 7.73−7.45 (m, 3H), 6.96 (s, 1H), 6.64 (d, J = 12.4 Hz, 1H), 5.90 (d, J = 12.4 Hz, 1H), 3.92 (q, J = 7.2 Hz, 2H), 3.58 (s, 3H), 1.34 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.2, 148.4, 136.9, 132.9, 128.7, 128.0, 126.9, 125.8, 123.7, 113.5, 99.1, 65.8, 37.0, 15.1. *Z*-Isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46 (d, J = 7.9 Hz, 1H), 7.73−7.45 (m, 3H), 6.78 (s, 1H), 6.31 (d, J = 7.1 Hz, 1H), 5.42 (d, J = 7.1 Hz, 1H), 4.10 (q, J = 7.2 Hz, 2H), 3.61 (s, 3H), 1.23 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.8, 146.1, 136.2, 132.9, 131.9, 128.1, 126.5, 125.9, 122.7, 111.3, 97.1, 69.2, 37.5, 15.7; MS (EI$^+$) *m/z* (%) 229 (100) M$^{\bullet+}$, 200 (66).

2-(4-Methoxybenzyl)-4-(2-ethoxyvinyl)isoquinolin-1(2*H*)-one (46). A mixture of acetal **44** (134 mg, 0.35 mmol) and formic acid (0.40 mL, 1.0 mmol, 2.8 equiv) in acetonitrile (10 mL) was refluxed for 1 h, concentrated in vacuo, and partitioned between Et_2O (10 mL) and saturated $NaHCO_3$ (10 mL). The organic phase was dried with magnesium sulfate and concentrated in vacuo to provide an inseparable 7:3 mixture of (*E*)- and (*Z*)-isoquinolinones **46** (88.5 mg, 0.26 mmol, 75%)

as a brown oil. ν_{max}/cm^{-1} 2976, 1644, 1615, 1175. *E*-Isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (d, J = 8.3 Hz, 1H), 7.73−7.27 (m, 5H), 6.99 (d, J = 0.8 Hz, 1H), 6.83 (d, J = 8.7 Hz, 2H), 6.58 (d, J = 12.4 Hz, 1H), 5.86 (dd, J = 12.4, 0.8 Hz, 1H), 5.15 (s, 2H), 3.89 (q, J = 7.2 Hz, 2H), 3.75 (s, 3H), 1.32 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.7, 149.0, 137.2, 132.8, 130.2, 129.9, 129.1, 129.0, 128.7, 127.3, 125.8, 124.0, 115.4, 114.7, 99.2, 66.1, 55.7, 52.0, 15.2. *Z*-Isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48 (d, J = 8.3 Hz, 1H), 7.86 (s, 1H), 7.73−7.27 (m, 5H), 6.83 (d, J = 8.7 Hz, 2H), 6.29 (d, J = 7.0 Hz, 1H), 5.40 (d, J = 7.0 Hz, 1H), 5.17 (s, 2H), 3.91 (q, J = 7.2 Hz, 2H), 3.75 (s, 3H), 1.25 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.7, 146.8, 136.4, 132.7, 130.0, 129.9, 129.1, 129.0, 127.6, 127.1, 125.8, 123.0, 114.6, 112.9, 97.2, 69.4, 55.7, 52.3, 15.7; MS (EI$^+$) *m/z* (%) 335 (2) M$^{\bullet+}$, 121 (100).

4-(2,2-Diethoxethyl)-2-methylisoquinolin-1(2*H*)-one (47). To a solution of isoquinolinone **43** (275 mg, 1.0 mmol) in anhydrous THF (10 mL) at 0 °C under a nitrogen atmosphere was added a solution of KHMDS (0.5 M in toluene, 4.4 mL, 2.2 mmol, 2.2 equiv). After 20 min, water (10 mL) was added. The aqueous phase was separated and extracted with Et_2O (2 × 10 mL). The combined organic phases were washed with brine (10 mL), dried with magnesium sulfate, and concentrated in vacuo. Purification by column chromatography (50% ethyl acetate in heptane) gave a yellow oil (180 mg) comprised of an inseparable mixture of **45** (0.13 mmol, 13%) and **47** (0.54 mmol, 54%). ν_{max}/cm^{-1} 2975, 1653, 1116; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 (d, J = 7.9 Hz, 1H), 7.68−7.42 (m, 3H), 6.98 (s, 1H), 4.63 (t, J = 5.6 Hz, 1H), 3.65 (dq, J = 9.0, 7.2 Hz, 2H), 3.56 (s, 3H), 3.41 (dq, J = 9.0, 7.2 Hz, 2H), 2.93 (d, J = 5.6 Hz, 2H), 1.12 (t, J = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.5, 137.2, 132.5, 132.1, 128.4, 126.8, 126.3, 123.3, 111.6, 102.7, 62.7, 37.1, 34.7, 15.6; MS (CI$^+$, CH_4) *m/z* (%) 276 (11) [M + H]$^+$, 230 (100).

1-(2-((*Z*)-4,4-Diethoxy-1-(methylamino)but-2-en-2-yl)-phenyl)-2,2-dimethylpropan-1-one (48). To a solution of isoquinolinone **43** (208 mg, 0.755 mmol) in anhydrous THF (10 mL) at −78 °C under a nitrogen atmosphere was added *tert*-butyllithium (1.6 M solution in pentane, 0.57 mL, 0.91 mmol, 1.2 equiv). After 20 min, water (10 mL) and ether (10 mL) were added and the mixture was allowed to warm to RT. The aqueous phase was separated and extracted with Et_2O (2 × 10 mL). The combined organic phases were dried with magnesium sulfate and concentrated in vacuo to give ketone **48** (209 mg, 0.627 mmol, 83%) as a yellow oil. ν_{max}/cm^{-1} 3335, 2973, 1685, 1650, 1050; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.30−7.24 (m, 4H), 5.51 (d, J = 6.2 Hz, 1H), 5.27 (d, J = 6.2 Hz, 1H), 3.72−3.72 (m, 6H), 2.36 (s, 3H), 1.50 (bs, 1H), 1.23−1.16 (m, 15H); MS (EI$^+$) *m/z* (%) 335 (2) [M$^{\bullet+}$], 121 (100); MS (EI$^+$) *m/z* (%) 287 (4) [M − EtOH]$^{\bullet+}$, 241 (32), 230 (42) 184 (100).

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Supporting Information Available: Analytical data (^{1}H and/or ^{13}C NMR spectra) for compounds **6**, **11**, **13**, **15**, **17**−**19**, and **21**−**33**. This material is available free of charge via the Internet at http://pubs.acs.org.

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