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Synthesis of Ester-Substituted Indolizines from 2-Propargyloxypyridines and 1,3-Dicarbonyls

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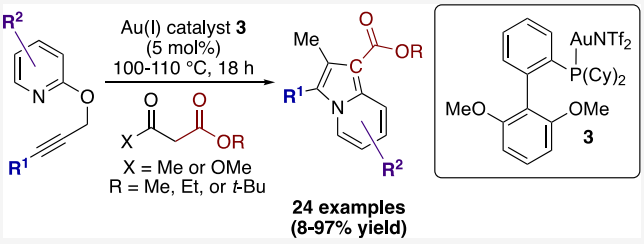
ABSTRACT: Two new complementary Au(I)-catalyzed methods for the preparation of ester-substituted indolizines from easily accessible 2-propargyloxypyridines and either acetoacetates or dimethyl malonate are reported. These reactions tolerate a wide range of functionality, allowing for diversification at three distinct positions of the product (R, R^1, R^2). For electron-poor substrates, the highest yields are observed upon reaction with acetoacetates, while neutral and electron-rich substrates give higher yields upon treatment with dimethyl malonate.



■ INTRODUCTION

Highly substituted indolizines, especially those bearing a carbonyl-containing substituent at C1 (indolizine numbering), have been shown to be versatile heterocyclic cores for medicinal applications across a broad array of therapeutic indications (Figure 1).[1] Given their significance, a variety of methods have been devised for their preparation.[2] Beyond the classical strategies of Scholtz[3] and Tschichibabin,[4] methods for synthesizing the indolizine core largely fall into one of four categories: 1,3-dipolar cycloaddition to pyridinium ions,[5] cyclocondensations,[6] transition metal catalyzed cycloisomerization reactions,[7] or radical cyclization/cross coupling cascades.[8] Our group recently added an efficient Au(I)-catalyzed method to this array, allowing for the preparation of indolizines **2**, bearing an aryl ketone at C1, from readily available 2-propargyloxypyridines **1** (Scheme 1).[9] This method benefits from the use of simple and easily prepared 2-propargyloxypyridines **1**, which have been shown to be an extremely versatile feedstock for heterocycle synthesis.[10] Further, this method provides an easy way to access synthetically diverse trisubstituted indolizines **2**.

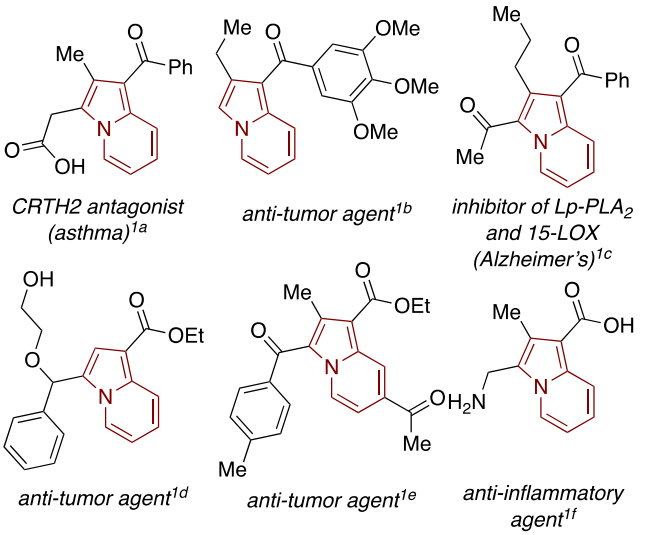
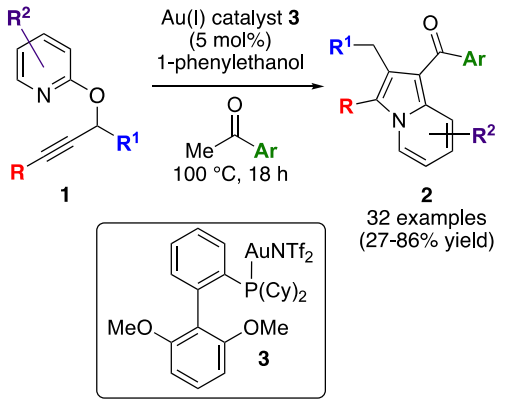


Figure 1. Pharmaceutical targets containing indolizine cores.

Scheme 1. Synthesis of Aryl Ketone Substituted Indolizines (Adapted from ref 9. Copyright 2019 American Chemical Society)



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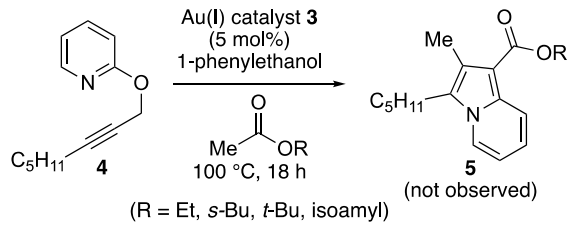
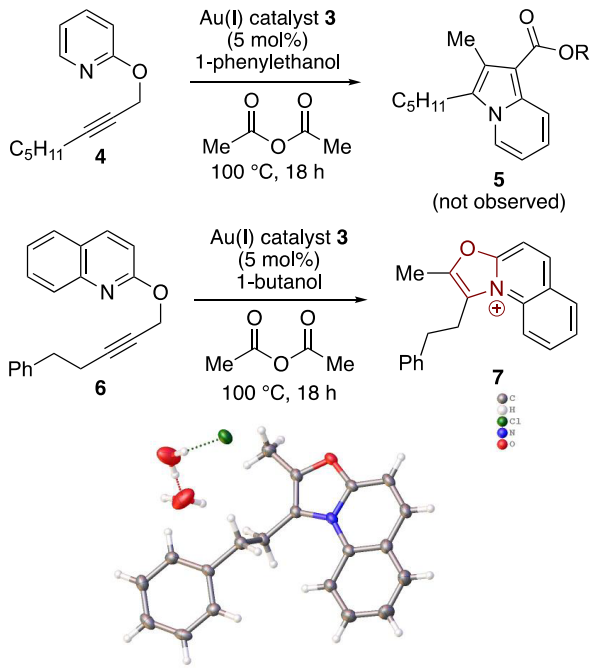
RESULTS AND DISCUSSION

Given the prevalence of pharmaceutical targets bearing an indolizine with an ester functionality at C1, extension of our Au(I)-catalyzed method was pursued. Efforts began by simply replacing the aryl ketones with various acetates, under otherwise similar reaction conditions; however, no reaction was detected (Scheme 2). In the hopes of providing a more reactive acetate unit, 2-propargyloxypyridine **4** was next treated with acetic anhydride and catalyst **3**. In this case, indolizine **5** was not observed, but an extremely polar unknown was isolated in low yields (Scheme 3). In the hopes of determining the structure of this compound, phenethyl-substituted quinoline substrate **6** was utilized in the reaction, leading to the isolation of compound **7** as a crystalline solid. X-ray quality crystals were achieved upon slow evaporation of a solution of product **7** from a 1:1 mixture of diethyl ether and CH_2Cl_2. Analysis of these crystals revealed that compound **7** and its previously prepared analogues were in fact pyridinium salts. It is proposed that salts of this type occur upon intramolecular addition of the pyridonium oxygen of intermediate **9** onto the pendant allene (Scheme 4). This alternate mode of reactivity hinges on the lack of an available external nucleophile, due to the increased pK_a of the α-protons of acetic anhydride, and presumably acetates, relative to aryl ketones.

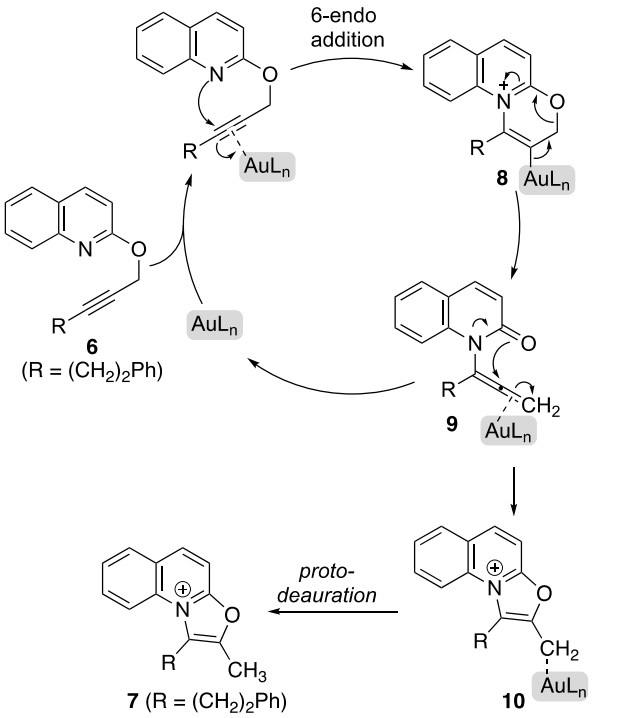
Scheme 2. Failure To React with Acetates



Scheme 3. Reaction with Acetic Anhydride



Scheme 4. Proposed Mechanism for the Formation of Pyridinium Salt 7



As a more acidic α-proton appeared to be required, we considered the possibility of utilizing acetoacetates, although either the activated methyl or methylene carbons could serve as the nucleophile. Since enolates formed from α-methyl groups had been incorporated into indolizines previously, we anticipated that a successful reaction might yield elongated adduct **11** (Scheme 5). However, when pyridine **4** was subjected to ethyl acetoacetate in the presence of catalyst **3**, the desired ester-substituted indolizine **5a** was observed directly in 88% yield, suggesting that the reaction proceeds via the methylene carbon. Further optimization revealed that the reaction occurs in comparable yields and higher purity in the absence of any alcohol additive and was somewhat more consistent at 110 °C (see Supporting Information). In addition, it was shown that both ethyl and *tert*-butyl acetoacetate worked efficiently in the reaction.

Scheme 5. Initial Reaction with Acetoacetates

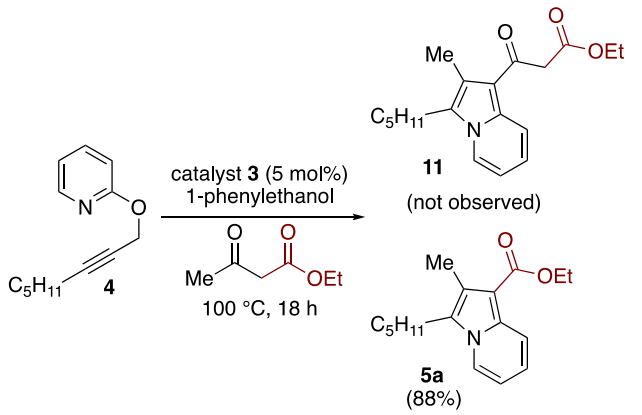


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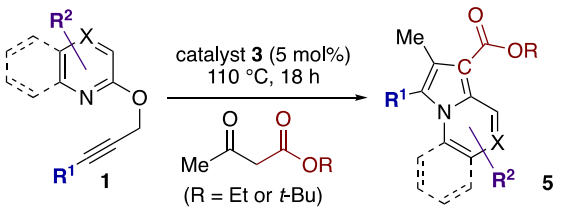
Table 1. Formation of Ester-Substituted Indolizines 5 with Acetoacetates



entry	R	R^1	R^2	X		yield (%)[a]
1	Et	C_5H_{11}	H	CH	**5a**	90
2	Et	$(CH_2)_2Ph$	H	CH	**5b**	73
3	Et	Cy	H	CH	**5c**	67
4	Et	C_5H_{11}	5-Me	CH	**5d**	81
5	Et	C_5H_{11}	5-CF_3	CH	**5e**	86
6	Et	C_5H_{11}		CH	**5f**	83
7	Et	C_5H_{11}	H	N	**5g**	48
8	*t*-Bu	C_5H_{11}	H	CH	**5h**	87[b]
9	*t*-Bu	$(CH_2)_2Ph$	H	CH	**5i**	79
10	*t*-Bu	$(CH_2)_3Ph$	H	CH	**5j**	75
11	*t*-Bu	Cy	H	CH	**5k**	76
12	*t*-Bu	C_5H_{11}	5-Me	CH	**5l**	84
13	*t*-Bu	C_5H_{11}	5-CF_3	CH	**5m**	89
14	*t*-Bu	C_5H_{11}		CH	**5n**	73
15	*t*-Bu	C_5H_{11}	H	N	**5o**	51

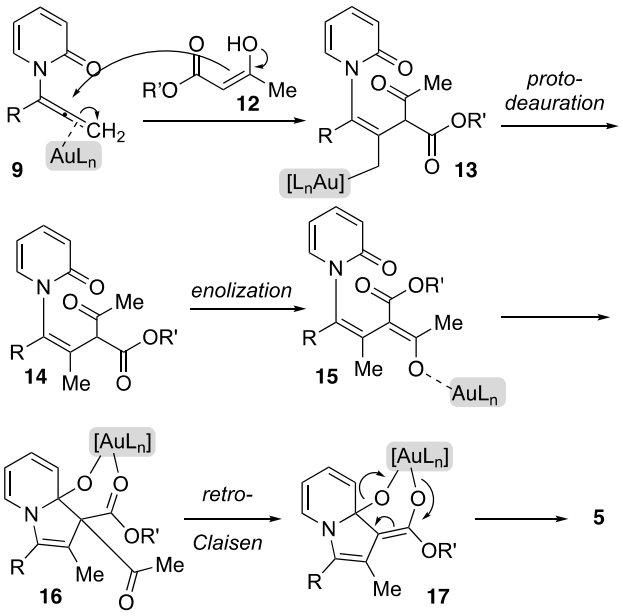
[a]Isolated yields. Mean values from multiple experiments (±2%). [b]1.1 mmol scale.

Using these optimized conditions, an array of 2-propargyloxypyridines **1** were evaluated in the reaction (Table 1). A variety of propargyl substituents (R^1) were well tolerated (entries 2−3 and 9−11), as were substituents at C5 of the pyridine ring (entries 4−5 and 12−13). Replacement of the pyridine ring with either a quinoline or pyrazine moiety was also viable; however, pyrazine substrates resulted in somewhat reduced yields (entries 7 and 15).

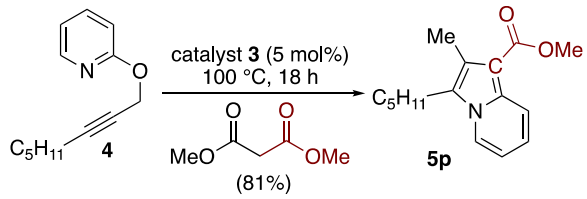
It is proposed that this reaction proceeds via addition of enolate **12** to allene intermediate **9**, followed by protodeauration and enolization (Scheme 6). Cyclization of extended enolate **15** then provides indolizine core **16**, which can undergo a retro-Claisen type reaction to yield intermediate **17**. While such a process is likely to be promoted by an external nucleophile, the nature of that nucleophile is unclear, as the reaction proceeds in comparable yields in the presence and absence of an added alcohol. Aromatization of intermediate **17** then yields indolizine **5**.

Given that an activated methylene carbon can serve as the initial nucleophile in these reactions, dimethyl malonate, another 1,3-dicarbonyl compound, was explored and found to produce indolizine methyl ester **5p** in 81% yield under similar reaction conditions (Scheme 7). Optimization of the reaction conditions showed that, in this case, adding an alcohol, particularly ethanol, to the reaction increased the yield,

Scheme 6. Proposed Mechanism for Acetoacetate Addition



Scheme 7. Initial Reaction with Dimethyl Malonate



while changing the reaction temperature was deleterious (see Supporting Information).

Utilizing the optimized reaction conditions, a range of 2-propargyloxypyridine analogues **1** were evaluated (Table 2). In general, reactions with dimethyl malonate resulted in somewhat higher yields, compared to acetoacetates, for electron-rich propargyl groups and pyridine substituents (Table 2, entries 1−7 versus Table 1, entries 1−4 and 8−12). However, substrates bearing electron-withdrawing groups or modified heterocycles provided higher yields with acetoacetates (Table 2, entries 8−10 versus Table 1, entries 5−7 and 13−15). For reactions with both acetoacetates and dimethyl malonate, substituents at C6 of the pyridine ring introduced significant steric constraints, leading to low yields or no reaction (Table 2, entry 7; no reaction with acetoacetates [not shown]).

The differences in yield between the reaction of acetoacetates and malonates with 2-propargyloxypyridines **1** is likely attributable to the penultimate mechanistic step of each process. As shown in Scheme 6, it is speculated that formation of indolizines from acetoacetates proceeds via a retro-Claisen reaction, prior to aromatization. By comparison, upon reaction with dimethyl malonate, we suspect that a nucleophilic decarboxylation of intermediate **21** produces the observed methyl ester substituted indolizines **5** (Scheme 8).

■ CONCLUSION

Two new complementary methods for the synthesis of ester-containing trisubstituted indolizines **5** from 2-propargyloxypyridines **1** have been discovered, allowing for the synthesis of indolizines bearing a methyl, ethyl, or *tert*-butyl ester at C1,

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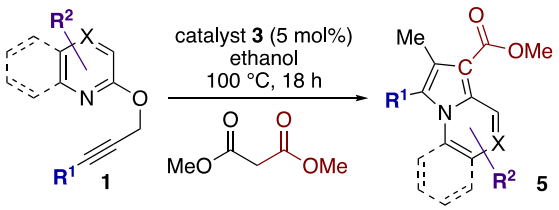
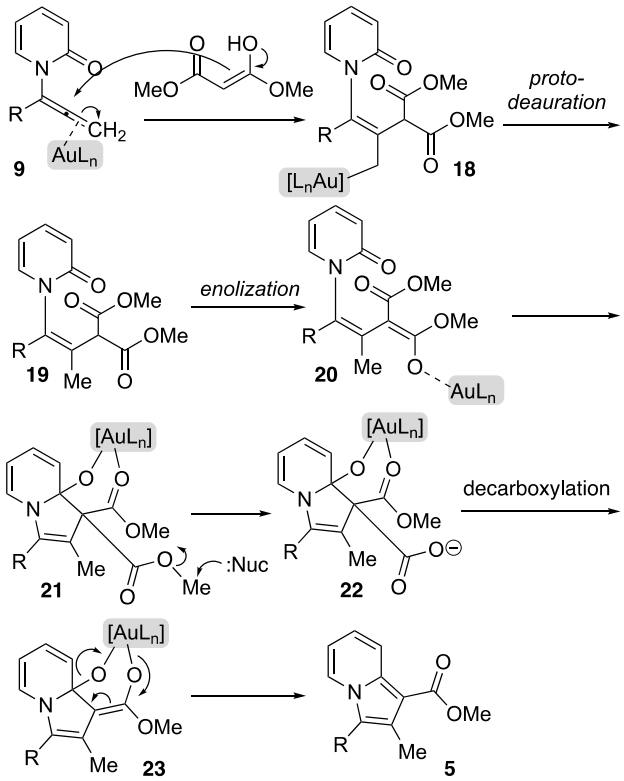
Table 2. Formation of Ester-Substituted Indolizines 5 in the Presence of Dimethyl Malonate



entry	R^1	R^2	X		yield (%)[a]
1	C_5H_{11}	H	CH	**5p**	91
2	$(CH_2)_2Ph$	H	CH	**5q**	89
3	$(CH_2)_3Ph$	H	CH	**5r**	83
4	Cy	H	CH	**5s**	75
5	C_5H_{11}	3-Me	CH	**5t**	39
6	C_5H_{11}	5-Me	CH	**5u**	97[b]
7	C_5H_{11}	6-Me	CH	**5v**	8
8	C_5H_{11}	5-CF_3	CH	**5w**	63
9	C_5H_{11}		CH	**5x**	28
10	C_5H_{11}	H	N	**5y**	–[c]

[a]Isolated yields. Mean values from multiple experiments (±2%). [b]2.3 mmol scale. [c]Product was formed but could not be separated from other reaction byproducts.

Scheme 8. Proposed Mechanism for Reaction with Dimethyl Malonate



depending on the reaction partner. The wide scope of this reaction, the simplicity of the starting materials, and the importance of ester-substituted indolizines as medicinal targets make these transformations important new synthetic tools.

■ EXPERIMENTAL SECTION

General Experimental Details. All reagents, including catalyst **3**, were purchased from commercial venders. Solvents, including 1-phenylethanol, all acetates, acetic anhydride, ethyl acetoacetate, *tert*-butyl acetoacetate, and dimethyl malonate, were distilled and sparged with argon prior to use. All other reagents, including catalyst **3**, were used as received. ^{1}H and ^{13}C{^{1}H} NMR spectra were obtained on a 400 or 500 MHz NMR spectrometer, as indicated. Chemical shifts are reported in ppm relative to $CDCl_3$. Multiplicity is indicated as follows: s (singlet); d (doublet); t (triplet); q (quartet); m (multiplet); dd (doublet of doublets); ddd (doublet of doublet of doublets); dt (doublet of triplets); tt (triplet of triplets); app (apparent). HRMS were collected on an ESI-TOF mass spectrometer.

General Experimental Procedure for the Synthesis of 2-Propargyloxypyridines. 2-(2-Octynyloxy)pyridine (4). To 2-chloropyridine (0.88 mL, 8.0 mmol) in 1,4-dioxane (24 mL) was added 2-octyn-1-ol (2.29 mL, 16.0 mmol). Potassium *tert*-butoxide (1.35 g, 12.0 mmol) was added, and the flask was rinsed with 1,4-dioxane (12 mL). The reaction was equipped with an air condenser and heated to 98 °C in an oil bath, open to air, for 18 h. After the mixture cooled to room temperature, ethyl acetate (30 mL) and H_2O (30 mL) were added. The layers were separated, and the aqueous layer was extracted with ethyl acetate (30 mL × 2). The combined organic layers were washed with 1:1 brine/H_2O (30 mL) and brine (30 mL) and dried ($MgSO_4$). After filtration, the reaction mixture was concentrated *in vacuo*. Purification by column chromatography (SiO_2, 19:1 hexanes/ethyl acetate) provided 1.55 g (95% yield) of **4** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (dd, J = 2.0, 4.8 Hz, 1H), 7.56 (ddd, J = 2.0, 6.8, 8.4 Hz, 1H), 6.88 (ddd, J = 0.8, 4.8, 7.2 Hz, 1H), 6.79 (d, J = 7.6 Hz, 1H), 4.95 (t, J = 2.0 Hz, 2H), 2.23 (tt, J = 2.0, 7.2 Hz, 2H), 1.52 (quintet, J = 7.2 Hz, 2H), 1.24−1.38 (m, 4H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CHCl_3$): δ 162.9, 147.0, 138.8, 117.3, 111.5, 87.4, 75.5, 54.4, 31.2, 28.4, 19.1, 14.2; IR (neat): 2932, 2237, 1749, 1594, 1570, 1472, 1432, 1272 cm^{-1}; HRMS (ESI) [M + Na]$^+$ Calcd for $C_{13}H_{17}NONa$ 226.1208; found 226.1201.

2-(5-Phenyl-2-pentynoxy)quinoline (6). Following the general procedure outlined above for the synthesis of compound **4**, potassium *tert*-butoxide (773 mg, 6.9 mmol) was added to 2-chloroquinoline (751 mg, 4.6 mmol) and 5-phenyl-2-pentyn-1-ol[11] (1.1 g, 6.9 mmol) in 1,4-dioxane (21 mL). After 20 h, the reaction was worked up and purified by column chromatography (SiO_2, 97:3 hexanes/ethyl acetate) to afford 1.15 g (87%) of **6** as a yellow solid. Mp: 52−54 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.00 (d, J = 8.5 Hz, 1H), 7.85 (app d, J = 8.5 Hz, 1H), 7.72 (dd, J = 1.3, 7.4 Hz, 1H), 7.63 (ddd, J = 1.7, 7.2, 8.5 Hz, 1H), 7.39 (ddd, J = 1.6, 7.3, 8.4 Hz, 1H), 7.16−7.28 (m, 5H), 6.96 (d, J = 9.0 Hz, 1H), 5.13 (t, J = 2.2 Hz, 2H), 2.86 (t, J = 8.0 Hz, 2H), 2.56 (tt, J = 2.5, 8.0 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CHCl_3$): δ 160.9, 146.3, 140.6, 138.9, 129.5, 128.4, 128.3, 127.43, 127.36, 126.3, 125.3, 124.2, 112.9, 86.4, 76.1, 54.2, 34.9, 21.1; IR (neat): 3055, 3025, 2946, 2926, 2859, 2237, 1617, 1605, 1363, 1256, 1238, 1111, 1025 cm^{-1}; HRMS (ESI) [M + H]$^+$ Calcd for $C_{20}H_{18}NO$ 288.1383; found 288.1386.

2-Methyl-1-(2-phenylethyl)oxazolo[3,2-*a*]quinolinium (7). To 2-(5-phenyl-2-pentynoxy)quinoline (**6**, 128 mg, 0.45 mmol) in a G10 microwave vial in an inert atmosphere glovebox were added bis(trifluoromethanesulfonyl)imide (2-dicyclohexylphosphino-2′,6′-dimethoxy-1,1′-biphenyl)gold(I) (catalyst **3**, 21 mg, 0.024 mmol), 1-butanol (0.2 mL), and acetic anhydride (1.79 mL, 0.25 M). After the vial was closed and removed from the glovebox, it was heated at 100 °C in an oil bath for 18 h. After cooling to room temperature, the reaction was filtered through a cotton plug, rinsing with ethyl acetate. The volatiles were removed *in vacuo* followed by Kugelrohr distillation. Saturated aqueous $NaHCO_3$ (15 mL) and CH_2Cl_2 (15 mL) were added, and the layers were separated, followed by extraction of the aqueous layer with CH_2Cl_2 (3 × 15 mL). The

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organic layer was then washed with 1:1 brine/water. Glacial acetic acid (5 mL) and CH_2Cl_2 (15 mL) were added to the aqueous phase, and the layers were separated. The aqueous layer was then extracted with CH_2Cl_2 (3 × 15 mL). The final four CH_2Cl_2 layers were then combined and washed with 1:1 brine/water, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford 28 mg (22% yield, ~70% pure) of **7** as a pale tan solid. X-ray quality crystals were achieved upon slow evaporation of a solution of **7** in 1:1 diethyl ether/CH_2Cl_2. Mp: 203−205 °C. ^{1}H NMR (500 MHz, *acetone-d6*): δ 9.18 (d, *J* = 9.2 Hz, 1H), 8.99 (d, *J* = 8.5 Hz, 1H), 8.61 (dd, *J* = 1.3, 8.6 Hz, 1H), 8.37 (d, *J* = 9.2 Hz, 1H), 8.31 (ddd, *J* = 1.4, 7.0, 8.7 Hz, 1H), 8.06 (app t, *J* = 7.3 Hz, 1H), 7.19−7.30 (m, 3H), 7.10−7.18 (m, 2H), 3.93 (t, *J* = 7.4 Hz, 2H), 3.29 (t, *J* = 5.8 Hz, 2H), 2.35 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, *acetone-d6*): δ 154.1, 150.2, 143.0, 139.9, 139.4, 134.0, 131.4, 129.0, 128.9, 128.6, 126.7, 126.5, 117.9, 109.1, 33.4, 26.5, 9.4; IR (neat): 3327 (broad), 3088, 3047, 2931, 2882, 1669, 1607, 1541, 1449 cm^{-1}; HRMS (ESI) [M]$^+$ Calcd for $C_{20}H_{18}NO$ 288.1383; found 288.1382.

General Experimental Procedure for the Formation of Ester-Substituted Indolizines with Acetoacetates. Ethyl 2-methyl-3-pentylindolizine-1-carboxylate (5a). To 2-(2-octynoxy)pyridine (**4**, 101 mg, 0.5 mmol) in a G10 microwave vial in an inert atmosphere glovebox were added bis(trifluoromethanesulfonyl)imide (2-dicyclohexylphosphino-2′,6′-dimethoxy-1,1′-biphenyl)gold(I) (catalyst **3**, 22 mg, 0.025 mmol) and ethyl acetoacetate (1.0 mL, 0.5 M). After the vial was closed and removed from the glovebox, it was heated at 110 °C in an oil bath for 18 h. After cooling to room temperature, the reaction was filtered through a cotton plug, rinsing with ethyl acetate. The volatiles were removed *in vacuo* followed by removal of the remainder of the ethyl acetoacetate by either Kugelrohr distillation or placement on a high vacuum manifold. The residual was purified by column chromatography (SiO_2, 92:8 hexanes/ethyl acetate) to afford 123 mg (90% yield) of **5a** as a pale yellow oil. ^{1}H NMR (500 MHz, *CDCl*$_3$): δ 8.18 (dt, *J* = 1.3, 9.0 Hz, 1H), 7.83 (dt, *J* = 1.2, 7.0 Hz, 1H), 6.97 (ddd, *J* = 1.1, 6.8, 9.1 Hz, 1H), 6.70 (td, *J* = 1.4, 6.8 Hz, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 2.85 (t, *J* = 7.6 Hz, 2H), 2.47 (s, 3H), 1.52−1.59 (m, 2H), 1.42 (t, *J* = 6.8 Hz, 3H), 1.30−1.37 (m, 4H), 0.89 (app t, *J* = 6.8 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, *CDCl*$_3$): δ 165.9, 135.6, 124.6, 123.5, 122.2, 120.7, 119.8, 111.8, 101.9, 59.0, 31.5, 27.1, 23.3, 22.5, 14.7, 14.0, 11.6; IR (neat): 2962, 2926, 2857, 1677, 1505, 1233, 1211, 1098 cm^{-1}; HRMS (ESI) [M + H]$^+$ Calcd for $C_{17}H_{24}NO_2$ 274.1802; found 274.1806.

Ethyl 2-Methyl-3-(2-phenylethyl)indolizine-1-carboxylate (5b). Following the general procedure outlined above for the synthesis of compound **5a**, catalyst **3** (23 mg, 0.026 mmol) and ethyl acetoacetate (1.0 mL, 0.5 M) were added to 2-(5-phenyl-2-pentynoxy)pyridine[10a] (121 mg, 0.51 mmol). After 18 h, the reaction was worked up and purified by column chromatography (SiO_2, 19:1 hexanes/ethyl acetate) to afford 116 mg (73% yield) of **5b** as a pale yellow oil. ^{1}H NMR (500 MHz, *CDCl*$_3$): δ 8.20 (dt, *J* = 1.5, 8.9 Hz, 1H), 7.56 (dt, *J* = 1.0, 6.9 Hz, 1H), 7.23−7.27 (m, 2H), 7.19−7.22 (m, 1H), 7.06−7.09 (m, 2H), 6.98 (ddd, *J* = 1.3, 6.6, 9.1 Hz, 1H), 6.66 (td, *J* = 1.2, 4.8 Hz, 1H), 4.37 (q, *J* = 7.3 Hz, 2H), 3.15 (t, *J* = 7.3 Hz, 2H), 2.85 (t, *J* = 7.8 Hz, 2H), 2.32 (s, 3H), 1.42 (t, *J* = 6.9 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, *CDCl*$_3$): δ 165.9, 140.8, 135.7, 128.5, 128.4, 126.3, 125.2, 122.2, 122.0, 120.9, 119.8, 111.9, 101.9, 59.1, 33.9, 25.8, 14.7, 11.3; IR (neat): 3069, 2985, 2926, 2859, 1674, 1505, 1235, 1213, 1104, 1055 cm^{-1}; HRMS (ESI) [M + H]$^+$ Calcd for $C_{20}H_{22}NO_2$ 308.1645; found 308.1645.

Ethyl 2-Methyl-3-cyclohexylindolizine-1-carboxylate (5c). Following the general procedure outlined above for the synthesis of compound **5a**, catalyst **3** (23 mg, 0.026 mmol) and ethyl acetoacetate (1.0 mL, 0.5 M) were added to 2-(3-cyclohexyl-2-propynoxy)-pyridine[10a] (107 mg, 0.5 mmol). After 18 h, the reaction was worked up and purified by column chromatography (SiO_2, 19:1 hexanes/ethyl acetate) to afford 95 mg (67% yield) of **5c** as a yellow oil. ^{1}H NMR (500 MHz, *CDCl*$_3$): δ 8.20 (dt, *J* = 1.5, 8.8 Hz, 1H), 8.03 (d, *J* = 6.9 Hz, 1H), 6.94 (ddd, *J* = 1.0, 6.7, 9.3 Hz, 1H), 6.65 (td, *J* = 1.7, 7.1 Hz, 1H), 4.37 (q, *J* = 7.3 Hz, 2H), 3.03 (tt, *J* = 3.1, 12.0 Hz, 1H), 2.57 (s, 3H), 1.88−1.97 (m, 4H), 1.75−1.84 (m, 4H), 1.42 (t, *J* = 7.1 Hz, 3H), 1.28−1.48 (m, 2H); ^{13}C{^{1}H} NMR (125 MHz, *CDCl*$_3$): δ 165.9, 135.6, 127.2, 124.1, 123.1, 120.4, 119.9, 111.5, 102.3, 59.1, 35.9, 30.0, 27.2, 26.1, 14.7, 14.0, 12.1; IR (neat): 2979, 2925, 2852, 1679, 1543, 1210, 1097, 1057 cm^{-1}; HRMS (ESI) [M + H]$^+$ Calcd for $C_{18}H_{24}NO_2$ 286.1802; found 286.1809.

Ethyl 2,6-Dimethyl-3-pentylindolizine-1-carboxylate (5d). Following the general procedure outlined above for the synthesis of compound **5a**, catalyst **3** (23 mg, 0.026 mmol) and ethyl acetoacetate (1.0 mL, 0.5 M) were added to 5-methyl-2-(2-octynoxy)pyridine[10a] (101 mg, 0.47 mmol). After 18 h, the reaction was worked up and purified by column chromatography (SiO_2, 19:1 hexanes/ethyl acetate) to afford 108 mg (81% yield) of **5d** as a yellow oil. ^{1}H NMR (500 MHz, *CDCl*$_3$): δ 8.08 (dd, *J* = 0.9, 9.2 Hz, 1H), 7.58 (app sextet, *J* = 1.7 Hz, 1H), 6.83 (dd, *J* = 1.7, 9.2 Hz, 1H), 4.36 (q, *J* = 7.0 Hz, 2H), 2.80 (t, *J* = 7.8 Hz, 2H), 2.45 (s, 3H), 2.29 (s, 3H), 1.54 (quintet, *J* = 7.8 Hz, 2H), 1.41 (t, *J* = 7.0 Hz, 3H), 1.30−1.36 (m, 4H), 0.89 (app t, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, *CDCl*$_3$): δ 165.9, 134.4, 124.2, 123.8, 123.0, 121.2, 120.1, 119.2, 101.4, 58.9, 31.5, 27.1, 23.3, 22.5, 18.5, 14.7, 14.0, 11.6; IR (neat): 2959, 2954, 2858, 1679, 1509, 1238, 1089 cm^{-1}; HRMS (ESI) [M + H]$^+$ Calcd for $C_{18}H_{26}NO_2$ 288.1958; found 288.1963.

Ethyl 6-Trifluoromethyl-2-methyl-3-pentylindolizine-1-carboxylate (5e). Following the general procedure outlined above for the synthesis of compound **5a**, catalyst **3** (22 mg, 0.025 mmol) and ethyl acetoacetate (1.0 mL, 0.5 M) were added to 5-trifluoromethyl-2-(2-octynoxy)pyridine[10c] (133 mg, 0.49 mmol). After 18 h, the reaction was worked up and purified by column chromatography (SiO_2, 97:3 hexanes/ethyl acetate) to afford 144 mg (86% yield) of **5e** as a bright orange solid. Mp: 67−69 °C; ^{1}H NMR (500 MHz, *CDCl*$_3$): δ 8.25 (d, *J* = 9.4 Hz, 1H), 8.12 (app d, *J* = 1.6 Hz, 1H), 7.06 (dd, *J* = 1.6, 9.4 Hz, 1H), 4.38 (q, *J* = 7.2 Hz, 2H), 2.87 (t, *J* = 7.5 Hz, 2H), 2.48 (s, 3H), 1.56 (quintet, *J* = 7.7 Hz, 2H), 1.42 (t, *J* = 7.7 Hz, 3H), 1.29−1.38 (m, 4H), 0.89 (app t, *J* = 6.8 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, *CDCl*$_3$): δ 165.3, 135.0, 126.4, 125.0, 123.8 (q, *J* = 269 Hz), 120.8 (q, *J* = 5.0 Hz), 120.3, 115.9, 115.8 (q, *J* = 34 Hz), 104.1, 59.5, 31.4, 27.1, 23.2, 22.4, 14.6, 13.9, 11.6; IR (neat): 2993, 2929, 2862, 1672, 1320, 1235, 1158, 1054 cm^{-1}; HRMS (ESI) [M + H]$^+$ Calcd for $C_{18}H_{23}F_3NO_2$ 342.1675; found 342.1673.

Ethyl 2-Methyl-3-pentylpyrrlo[1,2-*a*]quinoline-1-carboxylate (5f). Following the general procedure outlined above for the synthesis of compound **5a**, catalyst **3** (22 mg, 0.025 mmol) and ethyl acetoacetate (1.0 mL, 0.5 M) were added to 2-(2-octynoxy)-quinoline[10c] (125 mg, 0.49 mmol). After 18 h, the reaction was worked up and purified by column chromatography (SiO_2, 19:1 hexanes/ethyl acetate) to afford 131 mg (83% yield) of **5f** as a bright orange oil. ^{1}H NMR (500 MHz, *CDCl*$_3$): δ 8.26 (d, *J* = 9.3 Hz, 1H), 8.25 (d, *J* = 8.6 Hz, 1H), 7.71 (dd, *J* = 1.4, 7.8 Hz, 1H), 7.52 (ddd, *J* = 1.4, 6.9, 8.7 Hz, 1H), 7.38 (app ddd, *J* = 0.9, 6.8, 7.7 Hz, 1H), 7.24 (d, *J* = 9.6 Hz, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 3.24 (dd, *J* = 8.1, 8.1 Hz, 2H), 2.49 (s, 3H), 1.75 (quintet, *J* = 7.8 Hz, 2H), 1.44 (t, *J* = 7.1 Hz, 3H), 1.34−1.50 (m, 4H), 0.93 (t, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, *CDCl*$_3$): δ 165.9, 134.8, 134.5, 129.0, 128.9, 127.5, 125.6, 123.9, 123.7, 122.4, 118.8, 116.7, 105.5, 59.4, 31.5, 28.6, 27.3, 22.4, 14.6, 14.1, 11.6; IR (neat): 2954, 2925, 2870, 1685, 1433, 1331, 1254, 1081 cm^{-1}; HRMS (ESI) [M + H]$^+$ Calcd for $C_{21}H_{26}NO_2$ 324.1958; found 324.1960.

Ethyl 2-Methyl-3-pentylpyrazine-1-carboxylate (5g). Following the general procedure outlined above for the synthesis of compound **5a**, catalyst **3** (23 mg, 0.026 mmol) and ethyl acetoacetate (1.0 mL, 0.5 M) were added to 2-(2-octynoxy)pyrazine[10c] (103 mg, 0.5 mmol). After 18 h, the reaction was worked up and purified by column chromatography (SiO_2, 3:1 hexanes/ethyl acetate) to afford 66 mg (48% yield) of **5g** as a yellow oil. ^{1}H NMR (500 MHz, *CDCl*$_3$): δ 9.41 (d, *J* = 1.3 Hz, 1H), 7.70 (d, *J* = 4.8 Hz, 1H), 7.67 (dd, *J* = 1.2, 5.1 Hz, 1H), 4.39 (q, *J* = 7.2 Hz, 2H), 2.83 (t, *J* = 7.9 Hz, 2H), 2.49 (s, 3H), 1.55 (quintet, *J* = 7.2 Hz, 2H), 1.42 (t, *J* = 7.2 Hz, 3H), 1.25−1.35 (m, 4H), 0.86 (t, *J* = 7.3 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, *CDCl*$_3$): δ 164.7, 145.3, 132.9, 129.0, 127.1, 126.0, 114.8, 106.0, 59.8, 31.4, 26.9, 23.1, 22.4, 14.5, 13.9, 11.2; IR (neat): 2955, 2927,

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2858, 1693, 1505, 1222, 1134, 1056 cm^{-1}; HRMS (ESI) $[M + H]^+$ Calcd for $C_{16}H_{34}N_2O_2$ 275.1754; found 275.1758.

***tert*-Butyl 2-Methyl-3-pentylindolizine-1-carboxylate (5h).** Following the general procedure outlined above for the synthesis of compound **5a** in a G20 vial, catalyst **3** (102 mg, 0.12 mmol) and *tert*-butyl acetoacetate (4.6 mL, 0.5 M) were added to 2-(2-octynoxy)-pyridine (**4**, 469 mg, 2.3 mmol). After 20 h, the reaction was worked up and purified by column chromatography (SiO_2, 19:1 hexanes/ethyl acetate) to afford 603 mg (87% yield) of **5h** as a thick yellow oil. ^1H NMR (500 MHz, $CDCl_3$): δ 8.16 (dt, J = 1.3, 9.1 Hz, 1H), 7.80 (dt, J = 1.1, 7.0 Hz, 1H), 6.94 (ddd, J = 1.1, 6.6, 9.1 Hz, 1H), 6.67 (td, J = 1.4, 6.8 Hz, 1H), 2.83 (t, J = 7.6 Hz, 2H), 2.46 (s, 3H), 1.64 (s, 9H), 1.50−1.58 (m, 2H), 1.30−1.37 (m, 4H), 0.89 (t, J = 6.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 165.4, 135.3, 124.4, 123.3, 122.1, 120.4, 119.7, 111.6, 103.3, 79.2, 31.5, 28.8, 27.1, 23.3, 22.5, 14.0, 11.7; IR (neat): 3014, 2956, 2927, 2858, 1679, 1506, 1393, 1366, 1243, 1159, 1099 cm^{-1}; HRMS (ESI) $[M + H]^+$ Calcd for $C_{19}H_{28}NO_2$ 302.2115; found 302.2109.

***tert*-Butyl 2-Methyl-3-(2-phenylethyl)indolizine-1-carboxylate (5i).** Following the general procedure outlined above for the synthesis of compound **5a**, catalyst **3** (22 mg, 0.025 mmol) and *tert*-butyl acetoacetate (1.0 mL, 0.5 M) were added to 2-(5-phenyl-2-pentynoxy)pyridine[10a] (116 mg, 0.49 mmol). After 18 h, the reaction was worked up and purified by column chromatography (SiO_2, 19:1 hexanes/ethyl acetate) to afford 130 mg (79% yield) of **5i** as a brown oil. ^1H NMR (500 MHz, $CDCl_3$): δ 8.19 (dt, J = 1.2, 9.0 Hz, 1H), 7.74 (dt, J = 1.1, 7.0 Hz, 1H), 7.24−7.29 (m, 2H), 7.19−7.24 (m, 1H), 7.11 (d, J = 7.7 Hz, 2H), 6.96 (ddd, J = 1.1, 6.6, 9.2 Hz, 1H), 6.64 (td, J = 1.4, 6.8 Hz, 1H), 3.14 (t, J = 7.5 Hz, 2H), 2.84 (t, J = 7.8 Hz, 2H), 2.34 (s, 3H), 1.65 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 165.4, 140.9, 135.4, 128.5, 128.4, 126.3, 125.0, 122.1, 121.9, 120.6, 119.7, 111.7, 103.4, 79.3, 34.0, 28.8, 28.8, 11.4; IR (neat): 3021, 2972, 2925, 1676, 1506, 1394, 1106 cm^{-1}; HRMS (ESI) $[M + H]^+$ Calcd for $C_{22}H_{26}NO_2$ 336.1958; found 336.1952.

***tert*-Butyl 2-Methyl-3-(3-phenylpropyl)indolizine-1-carboxylate (5j).** Following the general procedure outlined above for the synthesis of compound **5a**, catalyst **3** (22 mg, 0.025 mmol) and *tert*-butyl acetoacetate (1.0 mL, 0.5 M) were added to 2-(6-phenyl-2-hexynoxy)pyridine[9] (123 mg, 0.49 mmol). After 18 h, the reaction was worked up and purified by column chromatography (SiO_2, 19:1 hexanes/ethyl acetate) to afford 128 mg (75% yield) of **5j** as a brown oil. ^1H NMR (500 MHz, $CDCl_3$): δ 8.18 (d, J = 11.0 Hz, 1H), 7.67 (dt, J = 1.1, 7.0 Hz, 1H), 7.31 (t, J = 7.6 Hz, 2H), 7.17−7.24 (m, 3H), 6.95 (dd, J = 6.6, 9.0 Hz, 1H), 6.64 (td, J = 1.4, 6.8 Hz, 1H), 2.88 (t, J = 7.5 Hz, 2H), 2.69 (t, J = 7.6 Hz, 2H), 2.46 (s, 3H), 1.90 (quintet, J = 7.8 Hz, 2H), 1.66 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 165.4, 141.6, 135.4, 128.42, 128.38, 126.0, 124.6, 122.7, 122.1, 120.5, 119.7, 111.7, 103.4, 79.3, 35.4, 28.9, 28.8, 22.9, 11.7; IR (neat): 3021, 2958, 2926, 1683, 1507, 1395, 1243, 1105 cm^{-1}; HRMS (ESI) $[M + H]^+$ Calcd for $C_{23}H_{28}NO_2$ 350.2115; found 350.2106.

***tert*-Butyl 2-Methyl-3-cyclohexylindolizine-1-carboxylate (5k).** Following the general procedure outlined above for the synthesis of compound **5a**, catalyst **3** (22 mg, 0.025 mmol) and *tert*-butyl acetoacetate (1.0 mL, 0.5 M) were added to 2-(3-cyclohexyl-2-propynoxy)pyridine[10a] (105 mg, 0.49 mmol). After 18 h, the reaction was worked up and purified by column chromatography (SiO_2, 19:1 hexanes/ethyl acetate) to afford 116 mg (76% yield) of **5k** as a gray solid. Mp: 92−95 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 8.17 (dt, J = 1.2, 9.1 Hz, 1H), 8.02 (d, J = 6.8 Hz, 1H), 6.91 (ddd, J = 1.1, 6.6, 9.0 Hz, 1H), 6.63 (td, J = 1.5, 7.1 Hz, 1H), 3.03 (tt, J = 3.4, 12.4 Hz, 1H), 2.56 (s, 3H), 1.88−1.98 (m, 4H), 1.75−1.84 (m, 4H), 1.63 (s, 9H), 1.30−1.47 (m, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 165.4, 135.3, 127.0, 123.9, 123.0, 120.1, 119.9, 111.3, 103.7, 79.3, 35.9, 30.0, 28.8, 27.2, 26.1, 12.1; IR (neat): 3011, 2976, 2926, 2853, 1677, 1542, 1507, 1162, 1112, 1099 cm^{-1}; HRMS (ESI) $[M + H]^+$ Calcd for $C_{20}H_{28}NO_2$ 314.2115; found 314.2117.

***tert*-Butyl 2,6-Dimethyl-3-pentylindolizine-1-carboxylate (5l).** Following the general procedure outlined above for the synthesis of compound **5a**, catalyst **3** (24 mg, 0.027 mmol) and *tert*-butyl acetoacetate (1.0 mL, 0.5 M) were added to 5-methyl-2-(2-octynoxy)pyridine[10a] (108 mg, 0.50 mmol). After 18 h, the reaction was worked up and purified by column chromatography (SiO_2, 19:1 hexanes/ethyl acetate) to afford 133 mg (84% yield) of **5l** as a pale yellow oil. ^1H NMR (500 MHz, $CDCl_3$): δ 8.06 (dd, J = 0.9, 9.1 Hz, 1H), 7.58 (d, J = 1.4 Hz, 1H), 6.81 (dd, J = 1.6, 9.2 Hz, 1H), 2.81 (t, J = 7.5 Hz, 2H), 2.43 (s, 3H), 2.30 (d, J = 1.1 Hz, 3H), 1.62 (s, 9H), 1.51−1.59 (m, 2H), 1.31−1.36 (m, 4H), 0.89 (t, J = 6.9 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 165.4, 124.1, 123.5, 122.9, 121.0, 120.0, 119.1, 102.8, 79.1, 31.5, 28.8, 27.1, 23.3, 22.5, 18.5, 14.0, 11.7; IR (neat): 3014, 2955, 2928, 2871, 1714, 1649, 1367, 1155, 1097 cm^{-1}; HRMS (ESI) $[M + H]^+$ Calcd for $C_{20}H_{30}NO_2$ 316.2271; found 316.2272.

***tert*-Butyl 6-Trifluoromethyl-2-methyl-3-pentylindolizine-1-carboxylate (5m).** Following the general procedure outlined above for the synthesis of compound **5a**, catalyst **3** (22 mg, 0.025 mmol) and *tert*-butyl acetoacetate (1.0 mL, 0.5 M) were added to 5-trifluoromethyl-2-(2-octynoxy)pyridine[10c] (133 mg, 0.49 mmol). After 18 h, the reaction was worked up and purified by column chromatography (SiO_2, 19:1 hexanes/ethyl acetate) to afford 161 mg (89% yield) of **5m** as an orange oil. ^1H NMR (500 MHz, $CDCl_3$): δ 8.25 (dt, J = 0.9, 9.4 Hz, 1H), 8.11 (q, J = 1.3 Hz, 1H), 7.05 (dd, J = 1.7, 9.4 Hz, 1H), 2.87 (t, J = 7.5 Hz, 2H), 2.47 (s, 3H), 1.63 (s, 9H), 1.52−1.60 (m, 2H), 1.30−1.38 (m, 4H), 0.90 (t, J = 6.8 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 164.7, 134.7, 126.3, 124.8, 124.0 (q, J = 269 Hz), 120.7 (q, J = 6.3 Hz), 120.3, 115.7 (q, J = 34 Hz), 115.5 (q, J = 2.5 Hz), 105.5, 80.1, 31.4, 28.6, 27.1, 23.2, 22.4, 13.9, 11.7; IR (neat): 3011, 2958, 2929, 2860, 1685, 1406, 1355, 1224, 1121, 1054 cm^{-1}; HRMS (ESI) $[M + H]^+$ Calcd for $C_{20}H_{27}F_3NO_2$ 370.1988; found 370.1978.

***tert*-Butyl 2-Methyl-3-pentylpyrrlo[1,2-*a*]quinoline-1-carboxylate (5n).** Following the general procedure outlined above for the synthesis of compound **5a**, catalyst **3** (22 mg, 0.025 mmol) and *tert*-butyl acetoacetate (1.0 mL, 0.5 M) were added to 2-(2-octynoxy)quinoline[10c] (124 mg, 0.49 mmol). After 18 h, the reaction was worked up and purified by column chromatography (SiO_2, 19:1 hexanes/ethyl acetate) to afford 126 mg (73% yield) of **5n** as an orange solid. Mp: 68−70 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 8.25 (d, J = 9.8 Hz, 1H), 8.24 (d, J = 8.8 Hz, 1H), 7.70 (dd, J = 1.9, 7.9 Hz, 1H), 7.15 (ddd, J = 1.3, 7.3, 8.4 Hz, 1H), 7.37 (ddd, J = 0.7, 6.7, 7.8 Hz, 1H), 7.21 (d, J = 9.1 Hz, 1H), 3.24 (dd, J = 6.9, 6.9 Hz, 2H), 2.48 (s, 3H), 1.75 (quintet, J = 7.8 Hz, 2H), 1.65 (s, 9H), 1.35−1.50 (m, 4H), 0.93 (t, J = 6.8 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 165.3, 134.5, 128.83, 128.78, 127.4, 125.6, 123.7, 123.6, 122.0, 118.9, 116.7 (2C), 106.9, 79.8, 31.5, 28.7, 28.6, 27.3, 22.4, 14.1, 11.7; IR (neat): 3073, 3059, 3011, 2980, 2948, 2866, 1674, 1551, 1427, 1406, 1176, 1161, 1083 cm^{-1}; HRMS (ESI) $[M + H]^+$ Calcd for $C_{23}H_{30}NO_2$ 352.2271; found 352.2269.

***tert*-Butyl 2-Methyl-3-pentylpyrazine-1-carboxylate (5o).** Following the general procedure outlined above for the synthesis of compound **5a**, catalyst **3** (22 mg, 0.025 mmol) and *tert*-butyl acetoacetate (1.0 mL, 0.5 M) were added to 2-(2-octynoxy)-pyrazine[10c] (106 mg, 0.52 mmol). After 18 h, the reaction was worked up and purified by column chromatography (SiO_2, 4:1 hexanes/ethyl acetate) to afford 80 mg (51% yield) of **5o** as a yellow oil. ^1H NMR (500 MHz, $CDCl_3$): δ 9.41 (s, 1H), 7.66−7.71 (m, 2H), 2.85 (t, J = 7.9 Hz, 2H), 2.49 (s, 3H), 1.65 (s, 9H), 1.48−1.60 (m, 2H), 1.28−1.36 (m, 4H), 0.88 (t, J = 7.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 164.1, 145.3, 128.9, 128.8, 127.0, 125.8, 114.7, 107.5, 80.5, 31.5, 28.6, 27.0, 23.1, 22.5, 14.0, 11.3; IR (neat): 3014, 2956, 2927, 2858, 1687, 1503, 1365, 1234, 1130 cm^{-1}; HRMS (ESI) $[M + H]^+$ Calcd for $C_{18}H_{27}N_2O_2$ 303.2067; found 303.2061.

General Experimental Procedure for the Formation of Ester-Substituted Indolizines with Dimethyl Malonate. Methyl 2-Methyl-3-pentylindolizine-1-carboxylate (5p). To 2-(2-octynoxy)pyridine (**4**, 100 mg, 0.49 mmol) in a G10 microwave vial in an inert atmosphere glovebox were added bis(trifluoromethanesulfonyl)imide (2-dicyclohexylphosphino-2′,6′-dimethoxy-1,1′-biphenyl)gold(I) (catalyst **3**, 22 mg, 0.025 mmol), ethanol (0.6 mL), and dimethyl malonate (2.0 mL, 0.25 M). After the vial was closed and removed from the glovebox, the vial was heated at 100 °C

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in an oil bath for 18 h. After cooling to room temperature, the reaction was filtered through a cotton plug, rinsing with ethyl acetate. The volatiles were removed *in vacuo* followed by removal of the remainder of the dimethyl malonate by either Kugelrohr distillation or placement on a high vacuum manifold. The residual was purified by column chromatography (SiO_2, 19:1 hexanes/ethyl acetate) to afford 116 mg (91% yield) of **5p** as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.17 (dt, J = 1.2, 9.0 Hz, 1H), 7.83 (dt, J = 1.2, 7.0 Hz, 1H), 6.98 (ddd, J = 1.1, 6.7, 9.0 Hz, 1H), 6.71 (td, J = 1.3, 6.7 Hz, 1H), 3.89 (s, 3H), 2.85 (t, J = 7.6 Hz, 2H), 2.47 (s, 3H), 1.51−1.60 (m, 2H), 1.31−1.37 (m, 4H), 0.89 (app t, J = 7.3 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 166.3, 135.6, 124.5, 123.6, 122.3, 120.8, 119.7, 111.9, 101.7, 50.4, 31.5, 27.1, 23.4, 22.5, 14.0, 11.6; IR (neat): 2956, 2925, 2856, 1682, 1505, 1442, 1391, 1236, 1213, 1099 cm^{-1}; HRMS (ESI) [M + H]$^+$ Calcd for $C_{16}H_{22}NO_2$ 260.1645; found 260.1651.

Methyl 2-Methyl-3-(2-phenylethyl)indolizine-1-carboxylate (5q). Following the general procedure outlined above for the synthesis of compound **5p**, catalyst **3** (22 mg, 0.025 mmol), ethanol (0.6 mL), and dimethyl malonate (2.0 mL, 0.25 M) were added to 2-(5-phenyl-2-pentynoxy)pyridine[10a] (121 mg, 0.51 mmol). After 18 h, the reaction was worked up and purified by column chromatography (SiO_2, 19:1 hexanes/ethyl acetate) to afford 133 mg (89% yield) of **5q** as a pale yellow syrup. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.18 (dt, J = 1.3, 9.1 Hz, 1H), 7.76 (dt, J = 0.9, 6.9 Hz, 1H), 7.22−7.26 (m, 2H), 7.14−7.21 (m, 1H), 7.05−7.08 (m, 2H), 6.99 (ddd, J = 1.3, 6.4, 8.8 Hz, 1H), 6.67 (td, J = 1.3, 6.5 Hz, 1H), 3.89 (s, 3H), 3.15 (t, J = 8.7 Hz, 2H), 2.85 (t, J = 6.7 Hz, 2H), 2.30 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 166.2, 140.8, 135.7, 128.5, 128.4, 126.3, 125.2, 122.3, 122.0, 121.0, 119.7, 112.0, 101.7, 50.5, 33.9, 25.8, 11.2; IR (neat): 3066, 3025, 2946, 2857, 1678, 1504, 1391, 1236 cm^{-1}; HRMS (ESI) [M + H]$^+$ Calcd for $C_{19}H_{20}NO_2$ 294.1489; found m/z 294.1484.

Methyl 2-Methyl-3-(3-phenylpropyl)indolizine-1-carboxylate (5r). Following the general procedure outlined above for the synthesis of compound **5p**, catalyst **3** (22 mg, 0.025 mmol), ethanol (0.6 mL), and dimethyl malonate (2.0 mL, 0.25 M) were added to 2-(6-phenyl-2-hexynoxy)pyridine[9] (123 mg, 0.49 mmol). After 18 h, the reaction was worked up and purified by column chromatography (SiO_2, 19:1 hexanes/ethyl acetate) to afford 125 mg (83% yield) of **5r** as a brown syrup. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.17 (dt, J = 1.2, 9.1 Hz, 1H), 7.68 (dt, J = 1.1, 7.0 Hz, 1H), 7.27−7.31 (m, 2H), 7.16−7.22 (m, 3H), 6.98 (ddd, J = 1.2, 6.7, 9.0 Hz, 1H), 6.67 (td, J = 1.4, 6.8 Hz, 1H), 3.89 (s, 3H), 2.89 (t, J = 7.2 Hz, 2H), 2.69 (t, J = 7.5, 2H), 2.45 (s, 3H), 1.90 (quintet, J = 7.6 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 166.2, 141.5, 135.7, 128.41, 128.35, 126.0, 124.7, 123.0, 122.2, 120.9, 119.7, 111.9, 101.8, 50.5, 35.4, 28.8, 22.9, 11.6; IR (neat): 3024, 2943, 2856, 1680, 1505, 1391, 1213, 1105 cm^{-1}; HRMS (ESI) [M + H]$^+$ Calcd for $C_{20}H_{22}NO_2$ 308.1645; found 308.1649.

Methyl 2-Methyl-3-cyclohexylindolizine-1-carboxylate (5s). Following the general procedure outlined above for the synthesis of compound **5p**, catalyst **3** (22 mg, 0.025 mmol), ethanol (0.6 mL), and dimethyl malonate (2.0 mL, 0.25 M) were added to 2-(3-cyclohexyl-2-propynoxy)pyridine[10a] (113 mg, 0.53 mmol). After 18 h, the reaction was worked up and purified by column chromatography (SiO_2, 19:1 hexanes/ethyl acetate) to afford 108 mg (75% yield) of **5s** as a white solid. Mp: 71−73 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.18 (dt, J = 1.3, 9.2 Hz, 1H), 8.04 (d, J = 6.8 Hz, 1H), 6.95 (ddd, J = 1.2, 6.7, 9.7 Hz, 1H), 6.67 (td, J = 1.5, 6.7 Hz, 1H), 3.89 (s, 3H), 3.03 (app t, J = 12.3 Hz, 1H), 2.56 (s, 3H), 1.88−1.97 (m, 4H), 1.76−1.85 (m, 4H), 1.29−1.48 (m, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 166.3, 135.6, 124.5, 127.3, 124.0, 123.1, 120.5, 119.9, 111.6, 102.1, 50.4, 35.9, 30.0, 27.2, 26.1, 12.0; IR (neat): 3014, 2952, 2850, 1673, 1503, 1446 1252, 1117, 1098 cm^{-1}; HRMS (ESI) [M + H]$^+$ Calcd for $C_{17}H_{22}NO_2$ 272.1645; found 272.1646.

Methyl 2,8-Dimethyl-3-pentylindolizine-1-carboxylate (5t). Following the general procedure outlined above for the synthesis of compound **5p**, catalyst **3** (22 mg, 0.025 mmol), ethanol (0.6 mL), and dimethyl malonate (2.0 mL, 0.25 M) were added to 3-methyl-2-(2-octynoxy)pyridine[10a] (106 mg, 0.49 mmol). After 18 h, the reaction was worked up and purified by column chromatography (SiO_2, 97:3 hexanes/ethyl acetate) to afford 52 mg (39% yield) of **5t** as a yellow syrup. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69 (dt, J = 0.9, 6.8 Hz, 1H), 6.69 (doublet of quintets, J = 1.1, 6.8 Hz, 1H), 6.59 (t, J = 6.8 Hz, 1H), 3.88 (s, 3H), 2.83 (t, J = 7.6 Hz, 2H), 2.55 (s, 3H), 2.36 (s, 3H), 1.55 (quintet, J = 7.5 Hz, 2H), 1.30−1.36 (m, 4H), 0.89 (t, J = 7.6 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 166.9, 133.3, 128.9, 123.2, 123.0, 121.4, 120.3, 111.3, 104.3, 50.9, 31.5, 27.0, 23.7, 22.5, 21.4, 14.0, 11.4; IR (neat): 2998, 2926, 2856, 1695, 1490, 1375, 1213, 1073 cm^{-1}; HRMS (ESI) [M + H]$^+$ Calcd for $C_{17}H_{24}NO_2$ 274.1802; found 274.1794.

Methyl 2,6-Dimethyl-3-pentylindolizine-1-carboxylate (5u). Following the general procedure outlined above for the synthesis of compound **5p** in a G20 vial, catalyst **3** (47 mg, 0.05 mmol), ethanol (1.3 mL), and dimethyl malonate (4.3 mL, 0.25 M) were added to 5-methyl-2-(2-octynoxy)pyridine[10a] (232 mg, 1.07 mmol). After 20 h, the reaction was worked up and purified by column chromatography (SiO_2, 97:3 hexanes/ethyl acetate) to afford 269 mg (97% yield) of **5u** as a white solid. Mp: 53−54 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07 (d, J = 9.1 Hz, 1H), 7.59−7.60 (m, 1H), 6.85 (dd, J = 1.4, 9.3 Hz, 1H), 3.88 (s, 3H), 2.82 (t, J = 7.3 Hz, 2H), 2.45 (s, 3H), 2.31 (d, J = 1.0 Hz, 3H), 1.51−1.59 (m, 2H), 1.30−1.38 (m, 4H), 0.89 (app t, J = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 166.3, 134.5, 124.2, 124.0, 123.2, 121.3, 120.2, 119.1, 101.3, 50.4, 31.5, 27.1, 23.3, 22.5, 18.5, 14.0, 11.5; IR (neat): 2957, 2927, 2866, 1675, 1509, 1447, 1389, 1094 cm^{-1}; HRMS (ESI) [M + H]$^+$ Calcd for $C_{17}H_{24}NO_2$ 274.1802; found 274.1805.

Methyl 2,5-Dimethyl-3-pentylindolizine-1-carboxylate (5v). Following the general procedure outlined above for the synthesis of compound **5p**, catalyst **3** (22 mg, 0.025 mmol), ethanol (0.6 mL), and dimethyl malonate (2.0 mL, 0.25 M) were added to 6-methyl-2-(2-octynoxy)pyridine[10a] (100 mg, 0.46 mmol). After 18 h, the reaction was worked up and purified by column chromatography (SiO_2, 19:1 hexanes/ethyl acetate) to afford 10 mg (8% yield) of **5v** as a brown paste. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.17 (ddd, J = 0.7, 1.5, 9.0 Hz, 1H), 6.85 (dd, J = 6.7, 9.0 Hz, 1H), 6.41 (td, J = 0.9, 6.7 Hz, 1H), 3.89 (s, 3H), 3.03−3.08 (m, 2H), 2.82 (s, 3H), 2.46 (m, 3H), 1.49−1.56 (m, 2H), 1.31−1.38 (m, 4H), 0.87−0.93 (m, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 166.3, 137.9, 134.7, 126.3, 125.8, 121.0, 117.8, 114.5, 102.0, 50.4, 31.9, 31.3, 26.1, 22.5, 21.9, 14.0, 11.7; IR (neat): 2954, 2926, 2856, 1685, 1515, 1218, 1086 cm^{-1}; HRMS (ESI) [M + H]$^+$ Calcd for $C_{17}H_{24}NO_2$ 274.1802; found 274.1804.

Methyl 6-Trifluoromethyl-2-methyl-3-pentylindolizine-1-carboxylate (5w). Following the general procedure outlined above for the synthesis of compound **5p**, catalyst **3** (22 mg, 0.025 mmol), ethanol (0.6 mL), and dimethyl malonate (2.0 mL, 0.25 M) were added to 5-trifluoromethyl-2-(2-octynoxy)pyridine[10c] (133 mg, 0.49 mmol). After 18 h, the reaction was worked up and purified by column chromatography (SiO_2, 97:3 hexanes/ethyl acetate) to afford 101 mg (63% yield) of **5w** as an orange solid. Mp: 50−52 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.24 (dt, J = 1.1, 9.3 Hz, 1H), 8.12 (sextet, J = 1.5 Hz, 1H), 7.07 (dd, J = 1.5, 9.3 Hz, 1H), 3.91 (s, 3H), 2.86 (t, J = 8.0 Hz, 2H), 2.47 (s, 3H), 1.57 (quintet, J = 6.6 Hz, 2H), 1.29−1.38 (m, 4H), 0.89 (t, J = 8.0 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 165.7, 135.0, 126.4, 125.1, 123.8 (q, J = 269 Hz), 120.8 (q, J = 6.3 Hz), 120.3, 116.0 (q, J = 34 Hz), 115.9 (q, J = 2.5 Hz), 103.8, 50.7, 31.2, 27.0, 23.2, 22.4, 13.9, 11.6; IR (neat): 2998, 2930, 2859, 1699, 1403, 1324, 1239, 1214, 1123, 1059 cm^{-1}; HRMS (ESI) [M + H]$^+$ Calcd for $C_{16}H_{22}NO_2$ 328.1519; found 328.1518.

Methyl 2-Methyl-3-pentylpyrrlo[1,2-*a*]quinoline-1-carboxylate (5x). Following the general procedure outlined above for the synthesis of compound **5p**, catalyst **3** (22 mg, 0.025 mmol), ethanol (0.6 mL), and dimethyl malonate (2.0 mL, 0.25 M) were added to 2-(2-octynoxy)quinoline[10c] (134 mg, 0.53 mmol). After 18 h, the reaction was worked up and purified by column chromatography (SiO_2, 19:1 hexanes/ethyl acetate) to afford 46 mg (28% yield) of **5x** as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.25 (d, J = 8.6 Hz, 1H), 8.24 (d, J = 9.3 Hz, 1H), 7.72 (dd, J = 1.6, 7.9 Hz, 1H), 7.53 (ddd, J = 2.0, 7.2, 9.2 Hz, 1H), 7.38 (ddd, J = 1.1, 7.2, 8.0 Hz, 1H), 7.25 (d, J = 9.5 Hz, 1H), 3.92 (s, 3H), 3.24 (dd, J = 7.6, 7.6 Hz, 2H),

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2.48 (s, 3H), 1.75 (quintet, J = 7.6 Hz, 2H), 1.35−1.50 (m, 4H), 0.93 (t, J = 7.9 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 166.3, 134.9, 134.5, 129.1, 128.9, 127.6, 125.6, 123.9, 123.7, 122.5, 118.8, 116.7, 105.3, 50.7, 31.5, 28.6, 27.3, 22.4, 14.1, 11.6; IR (neat): 3045, 2955, 2925, 2858, 1687, 1441, 1332, 1254, 1214, 1081 cm^{-1}; HRMS (ESI) $[M + H]^+$ Calcd for $C_{20}H_{24}NO_2$ 310.1802; found 310.1802.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.2c01219.

Solid-state packing diagrams for **7**, optimization data, ^1H and ^{13}C NMR spectra for all new compounds. (PDF)

Accession Codes

CCDC 2172536 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

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