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Scalable synthesis of enaminones utilizing Gold's reagents

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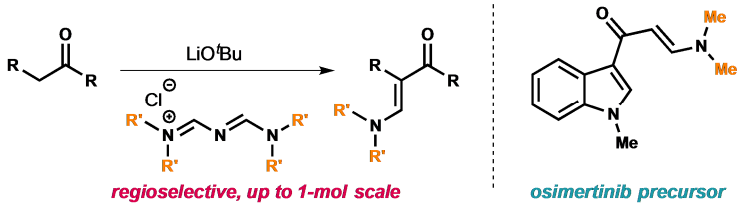

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ABSTRACT

Several Gold's reagents were synthesized from cyanuric chloride and *N,N*-dialkylformamides. These synthetic equivalents of *N,N*-dimethylformamide-dimethyl acetal were used in an optimized and scalable procedure for the regioselective synthesis of a variety of enaminones from ketone starting materials, whose utility was demonstrated by the stereoselective synthesis of Rawal-type dienes.

Keywords:
Enaminones;
Rawal Diene;
Diels-Alder

1. Introduction

The use of dienes with electron-donating groups in the Diels-Alder reaction leads to increased rates of reaction, thus allowing for more mild reaction conditions and broader functional group compatibility.[1] In particular, Danishefsky- and Rawal-type dienes,[2-3] which possess two constructively oriented electron-donating groups, have been widely used in natural product synthesis.[4-5] This is because of their ease of preparation, increased reactivity toward thermal cycloadditions, and the utility of the oxidation states introduced as the heteroatom substituents.[2-3] Both of these types of dienes have been conveniently prepared by enolization and trapping of a β-substituted enone – a methoxy-enone in the case of Danishefsky dienes and an enaminone for Rawal dienes.[2-3]

Enaminones, which are also powerful building blocks for heterocycle formation and Michael addition-elimination reactions,[6-10] are usually accessed through functionalization of a ketone directly with *N,N*-dimethylformamide dimethyl acetal (**2**, DMF-DMA)[11] or Bredereck's reagent (**3**)[12] as shown in Figure 1a. While this approach is simple and direct, it can lead to non-selective enolization and thus constitutional isomeric products wherein the two different ketone α-positions have been functionalized (e.g. **4a** and **4b**). This problem has been circumvented through stepwise enone formation via β-elimination of an acetal formed from trimethylorthoformate, followed by addition-elimination with dimethylamine (Figure 1b).[13] It is noteworthy that this latter approach allows for the synthesis of a wide variety

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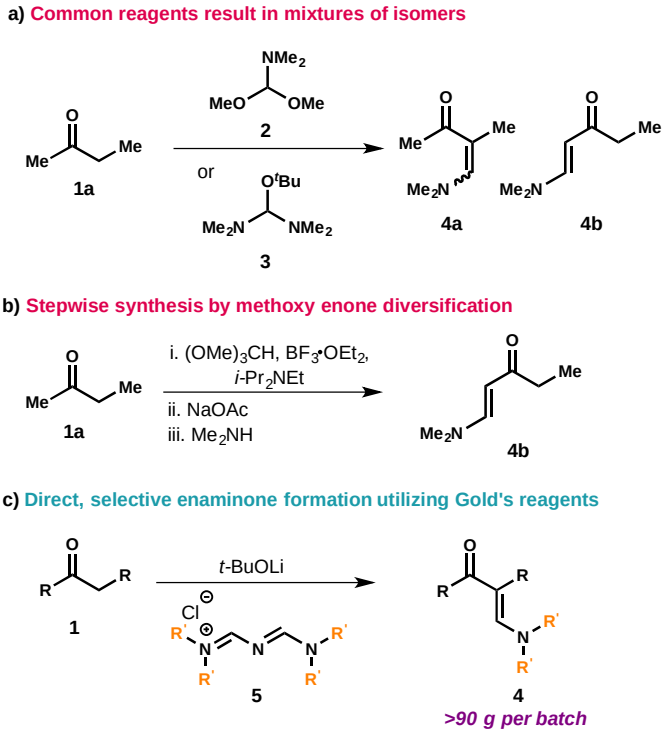
Fig. 1. Enaminone formation from ketones by multiple approaches



of β-amino substituted enones from a single β-methoxy enone precursor.

During the course of a total synthesis of andirolide N,[14] we examined these conventional approaches for enaminone synthesis

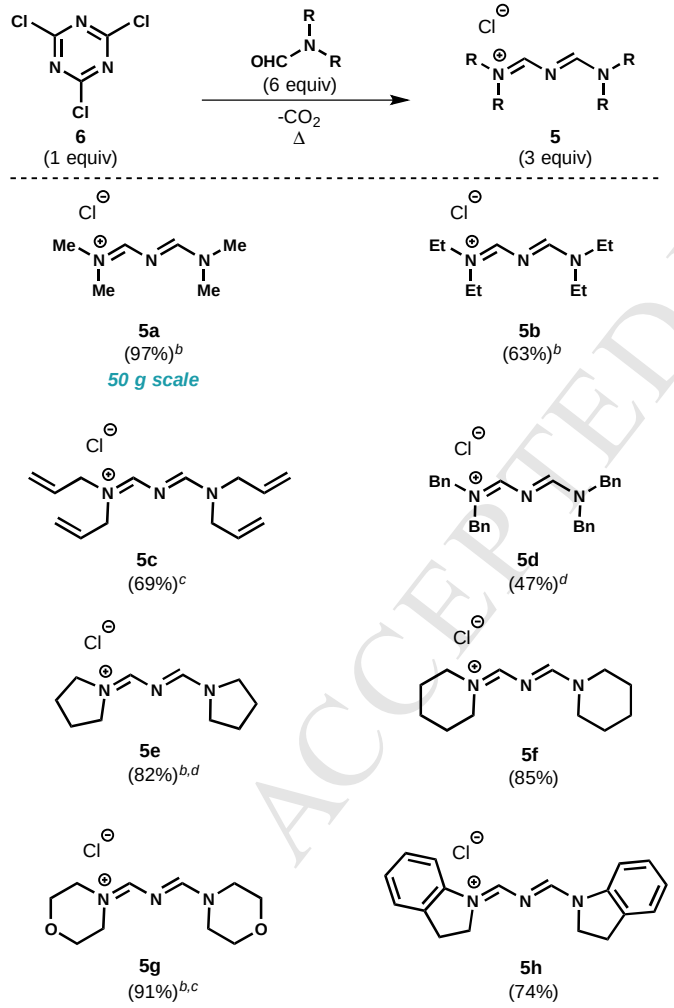
and ultimately found the most scalable approach utilized the aminomethylene electrophile equivalent (**5**), known as Gold's reagent.[15-17] This approach allowed for the direct regio- and diastereoselective functionalization of 2-butanone using Gold's reagent, a bench stable reagent which can be prepared in a single step and purified by recrystallization.[17] The straightforward preparation of this valuable equivalent to DMF-DMA employs inexpensive cyanuric chloride and DMF. In this report we describe the synthesis of a small library of sterically and electronically varied Gold's reagents using readily available formamides, and investigate their utility in enaminone synthesis.

2. Results and discussion

2.1. Synthesis of a library of Gold's reagents

In order to expand the synthetic utility of Gold's reagents, various [3-(dialkylamino)-2-azaprop-2-en-1-ylidene]dialkylammonium chloride salts (**5**) were synthesized, in addition to the one known tetramethyl analog (**5a**).[17] The synthesis of these reagents proceeded smoothly by heating one equivalent of cyanuric chloride (**6**) and six equivalents of *N*,*N*-dialkylformamide, either neat or using 1,4-dioxane as

Scheme 1. Formation of Gold's reagents using formamides [a-d]



[a]Isolated yield [b]1,4-dioxane was used as solvent (4 M) [c]3 equiv of formamide was used [d]4 equiv of formamide was used.

solvent (**5a**, **5b**, **5e**, and **5g**), to produce three equivalents of the corresponding Gold's reagent (**5**, Scheme 1). It should be noted that during the course of this exothermic reaction three equivalents of CO_2 are produced, and thus caution should be exercised when this reaction is performed on large scale.

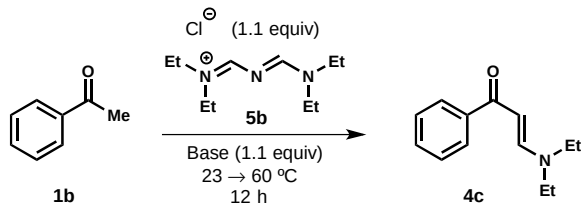
Careful control of the temperature was critical for minimizing byproduct formation during the exothermic release of CO_2. Concomitant with the release of CO_2 was a distinct change in color of the reaction mixture to a dark red or brown, occurring at a different temperature for each substrate. As a precaution, a modified protocol involving a double-walled reflux condenser and an oil-bubbler outlet was employed (see Supplementary Materials) for the scalable synthesis of the parent methyl-substituted Gold's reagent (**5a**). While this procedure was successful on a 50-gram scale to provide 120 g of **5a** in 97% yield, further optimization is likely necessary for larger scale preparations due to the exotherm and gas release.

Using this protocol, a number of Gold's reagents could be prepared, as depicted in Scheme 1. Ethyl substitution on the formamide yielded the corresponding ethyl Gold's reagent (**5b**) in 63% yield. Activated alkyl substituents, such as allyl (**5c**) and benzyl (**5d**), were also tolerated in the synthesis of the corresponding Gold's reagents in 69% and 47% yield, respectively. The synthesis of several reagents derived from cyclic formamides proceeded well: pyrrolidine (**5e**), piperidine (**5f**), morpholine (**5g**), and indoline (**5h**) Gold's reagents were synthesized in 74-91% yield. In order to observe complete conversion for some of the more challenging substrates (**5c**, **5d**, **5e**, and **5g**), fewer equivalents of the formamide were used relative to cyanuric chloride. Purification of the Gold's reagents could be readily performed by simple trituration with combinations of ethereal and hydrocarbon solvents.

2.2. Development of optimized conditions for the transformation of ketones to enaminones

With a library of novel Gold's reagents in hand, we turned to optimization of the conditions for enaminone formation (Table 1). Previous conditions described by Gupton and co-workers[16a] employed using the newly synthesized Gold's reagents were ineffective, thus alternative reaction conditions were examined. Optimization efforts focused on variation of the base employed along with modification of solvent and temperature (Table 1).

Table 1. Optimization of enaminone formation[a]



Entry	Base	Solvent	% Yield[a]
1	MeONa	MeOH	<5
2	*i*-PrONa	*i*-PrOH	29
3	*t*-BuONa	*t*-BuOH	0
4	*t*-BuONa	THF	24
5	*t*-BuOK	THF	<5
6	*t*-BuOLi	THF	96

[a] Yield determined by ^{1}H-NMR analysis after aqueous work-up using 1,3,5-trimethoxybenzene as an internal standard.

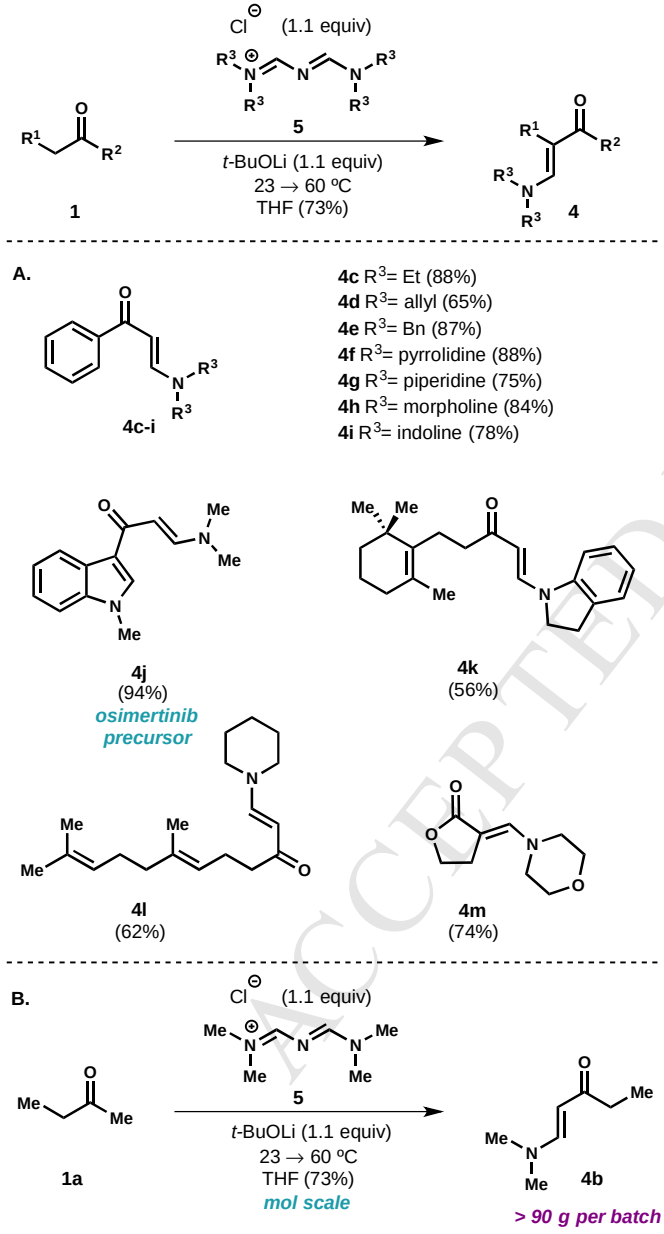
When the previously described conditions using NaOMe in MeOH[16a] or NaO-*i*-Pr in *i*-PrOH[15] were employed for the transformation of **1b** to **4c**, modest yields up to 29% were observed (Entries 1 and 2). Alteration of the alkoxide base to NaO-*t*-Bu in *t*-BuOH did not result in product formation (Entry 3). Use of THF as solvent resulted in an improved yield (Entry

4), and it was found that the optimal counterion of the *tert*-butoxide base was lithium (Entry 6), which resulted in formation of the product 4c in 96% yield. Metal amide bases (LiHMDS, NaHMDS, KHMDS, LDA, and LiTMP) were also investigated but led to only modest yields of enaminone **4c.**

2.3. Substrate scope of the formation of enaminones with Gold's reagents

After the reaction conditions for enaminone formation had been optimized with acetophenone, the generality of these conditions was probed by testing the library of Gold's reagents (Scheme 2A). By using acetophenone to directly compare the efficiency of enaminone formation with various Gold's reagents, it was found that the corresponding enaminones were prepared (**4c**-**4i**) with similar efficiencies.

Scheme 2. Substrate scope of enaminone formation[a]



[a] isolated yield

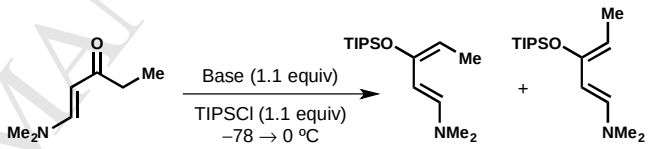
The reaction conditions utilizing dimethyl Gold's reagent (**5a**) could be employed to synthesize an intermediate (**4j**) en route to an FDA approved treatment for non-small cell lung carcinoma, osimertinib,[18b] in 94% yield, which has previously been reported to proceed in 84% yield using commercially available DMF-DMA.[17] Derivatization of commercially available terpene compounds, dihydro-β-ionone and geranylacetone, with Gold's reagent (**5h** and **5f** respectively) led to regioselective formation of the heterocyclic enaminones **4k** and **4l** at the less hindered primary position in 56% and 62% yield. Functionalization of γ-butyrolactone with **5g** resulted in the synthesis of the morpholine-derived enaminone (**4m**) in 74% yield.

In order to demonstrate the scalability of the newly developed reaction conditions, we applied them in the synthesis of enaminone **4b**, which was required for the total synthesis of andirolide N. Reaction of 2-butanone (**1a**) and **5a** on 1-mole scale provided enaminone **4b** in 73% yield after vacuum distillation (Scheme 2B), which is a notable improvement over the previously reported yield of 48%.[14] The modified procedure additionally replaced the alcoholic solvent used in reaction workup with diethyl ether to allow for a facile extractive isolation and recovery of product.

2.4. Diastereoselective Rawal diene synthesis

As a demonstration of the utility of enaminones, the substrate **4b** was converted to the diastereomeric Rawal-type dienes **7a** and **7b** as shown in Table 2. While not previously examined in detail,[19-20] we hypothesized that the identities of the amide base and additives used would be crucial for controlling enoxysilane geometry.[21] Indeed, **7a** and **7b** could be formed diastereoselectively through simply modifying these parameters.

Table 2. Diastereoselective Rawal diene synthesis[a-e]



Entry	Base	Additives	% Yield[a]	E/Z Ratio
1	LiTMP	LiCl, DMPU	59%[b]	>20:1
2	LiTMP	DMPU[c]	46%	20:1
3	LiTMP	DMPU	74%	10:1
4	LiTMP	none	30%	2:1
5	LiHMDS	DMPU	63%[b]	1:10
6	LiHMDS	none	23%	2:1
7	NaHMDS	none	71%	1:1
8	KHMDS	none	92%	2:1

[a]Yield determined by ^{1}H-NMR analysis after aqueous work-up using 1,2,4,5-tetramethylbenzene as an internal standard. [b]Isolated yield after vacuum distillation. [c]**4b** was pre-mixed with TIPSCl (2 equiv) before addition of base.

Formation of the *E*-diene (**7a**) could be performed selectively (>20:1 *E*:*Z*) by deprotonation with lithium 2,2,6,6-tetramethylpiperidine (LiTMP) in the presence of LiCl (0.3 equiv)[21a] and DMPU (1 equiv), with TIPSCl as the silylating agent (Entry 1). Slightly diminished yield was observed using inverse order of addition, wherein TIPSCl was pre-mixed with DMPU (1 equiv) and **4b** prior to the introduction of LiTMP (Entry 2).[22] LiCl was an essential additive for maintaining high levels of diastereoselectivity – a 10:1 ratio was observed in its absence (Entry 3), and exclusion of DMPU led to even further diminished diastereoselectivity (2:1) (Entry 4). Reversal of the diastereoselectivity to form the *Z*-diene (**7b**) in a 1:10 *E*:Z ratio was observed when LiHMDS with DMPU was employed (Entry 5). Comparison of HMDS amides in the absence of DMPU displayed similarly modest diastereoselectivities (Entries 6-8).[20a] Although modest diastereoselectivity was observed with KHMDS, these reaction conditions provided the highest yield

(Entry 8). Other lithium amides (LDA or $LiNCy_2$) were less successful.

The origin of diastereoselection is worthy of comment. While minimization of 1,3-diaxial interactions in chair-like transition states or reactions that proceed via more open transition states are generally used to rationalize diastereoselective enolate formation,[23] these results suggest other factors may be operable.[20c]

3. Conclusion

This report details the synthesis of a library of Gold's reagents, which were shown to be generally effective for ketone and ester one-carbon homologation to form enaminones. An enaminone recently employed in the synthesis of andirolide N[14] was prepared on mole scale and conditions were described to selectively form *E*- and *Z*-Rawal-type dienes. We hope that the development of these scalable processes will enable broader application of Gold's reagents to challenges in multistep synthesis.

4. Experimental

4.1 General Experimental

General Experimental Procedures: All reactions were carried out under an inert nitrogen atmosphere with dry solvents under anhydrous conditions unless otherwise stated. All reactions were capped with a rubber septum or Teflon-coated silicon microwave cap unless otherwise stated. Stainless steel cannula or syringes were used to transfer solvent, and air- and moisture- sensitive liquid reagents. Reactions were monitored by thin-layer chromatography (TLC) and carried out on 0.25 mm Merck silica gel plates (60F-254) using UV light as the visualizing agent and potassium permanganate, an acidic solution of *p*-anisaldehyde, and Seebach as developing agents. Flash column chromatography employed SiliaFlash® P60 (40-60 μm, 230-400 mesh) silica gel purchased from SiliCycle Inc.

Materials: All reaction solvents were purified using a Seca solvent purification system by Glass Contour, with the exception of methanol, *iso*-propyl alcohol, and *tert*-butyl alcohol. Methanol was purified by distillation over magnesium, and anhydrous *iso*-propyl alcohol, *tert*-butyl alcohol, and 1,4-dioxane were purchased from Sigma Aldrich and used as received. *N*,*N*-dicyclohexylamine, 2,2,6,6-tetramethylpiperidine, and DMPU were distilled over CaH_2. *n*-butyllithium (in hexanes) was purchased from Sigma-Aldrich. The molarity of *n*-butyllithium solutions were determined by titration with *N*-benzylbenzamide. All other reagents were used as received without further purification, unless otherwise stated.

Instrumentation: All new compounds were characterized by means of ^{1}H-NMR, ^{13}C-NMR, FT-IR (thin film from CH_2Cl_2), and HR-MS. Copies of the ^{1}H- and ^{13}C-NMR spectra can be found in the supplementary materials. NMR spectra were recorded using a Varian 400 MHz NMR spectrometer, Varian 500 MHz NMR spectrometer, or a Varian 600 MHz NMR spectrometer. All ^{1}H-NMR data are reported in δ units, parts per million (ppm), and were calibrated relative to the signals for residual chloroform (7.26 ppm) in deuterochloroform ($CDCl_3$). All ^{13}C-NMR data are reported in ppm relative to $CDCl_3$ (77.16 ppm) and were obtained with ^{1}H decoupling unless otherwise stated. The following abbreviations or combinations thereof were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet, and a = apparent. All IR spectra were taken on an FT-IR/Raman Thermo Nicolet 6700. High resolution mass spectra (HR-MS) were recorded on a Bruker microTOF mass spectrometer using ESI-TOF (electrospray ionization-time of flight).

4.2 Experimental procedures

*4.2.1. Methyl Gold's reagent (**5a**):*

[CAUTION!]: This reaction produces a large amount of CO_2 gas and thus appropriate reaction setup should be used (see Supplementary Materials for pictures of reaction setup).

To a flame-dried 500-mL round-bottomed flask equipped with a magnetic stir bar was added cyanuric chloride (50.0 g, 271 mmol, 1.0 equiv). The solid was diluted with 1,4-dioxane (67 mL, 4 M). To the stirred heterogeneous mixture was added *N*,*N*-dimethylformamide (126 mL, 1.6 mol, 6 equiv) dropwise over 20 minutes at room temperature, which resulted in a pale yellow heterogeneous mixture.

The reaction vessel was fitted with a flame-dried 45-cm double walled reflux condenser with a mineral oil bubbler outlet connected to the top of the condenser. The reaction apparatus was transferred to a room temperature oil bath that was then warmed to 90 ºC. When the oil bath temperature had reached 85 ºC (*ca.* 30 minutes), the reaction mixture turned dark red, and exothermic release of CO_2 commenced. After stirring at 90 ºC for two additional hours, the reaction mixture was removed from the oil bath and cooled to room temperature. Once at room temperature, a dark brown solid formed. The crude brown solid was purified by trituration with pentane (3 x 200 mL). The resulting solid was dried under vacuum to provide the title compound as a light brown solid (127 g, 97%). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 9.79 (s, 2H), 3.40 (s, 6H), 3.21 (s, 6H) **^{13}C NMR** (151 MHz, $CDCl_3$): δ 168.4, 42.7, 36.2 **IR** (cm^{-1}): 3389, 2933, 1604, 1417, 1341, 1124, 1065, 829, 531 **ESI-HRMS** (m/z): $[M-Cl]^+$ calc'd for $C_6H_{14}N_3^+$: 128.1182; found: 128.1183

*4.2.2. Ethyl Gold's reagent (**5b**):*

To a flame-dried 25-mL round-bottomed flask equipped with a magnetic stir bar was added cyanuric chloride (1.0 g, 5.4 mmol, 1.0 equiv) and the stirred solid was diluted with 1,4-dioxane (1.4 mL, 4 M). To the stirred heterogeneous mixture was added *N*,*N*-diethylformamide (3.6 mL, 32.5 mmol, 6 equiv) dropwise over 5 minutes at room temperature. The reaction vessel was fitted with an oven-dried reflux condenser and transferred to a room temperature oil bath that was then warmed to 85 ºC. When the oil bath temperature had reached 85 ºC the reaction mixture turned dark red, and exothermic release of CO_2 commenced. After stirring at 85 ºC for two hours, the reaction was removed from the oil bath and cooled to room temperature. Once at room temperature, a dark brown solid formed. The crude brown solid was purified by trituration with pentane (5 x 4 mL). The resulting solid was concentrated under reduced pressure by rotary evaporation to reveal the title compound as a light brown solid (2.24 g, 63%). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 9.67 (s, 2H), 3.67 (q, *J* = 7.2 Hz, 4H), 3.62 (q, *J* = 7.2 Hz, 4H), 1.35 (t, *J* = 7.2 Hz, 6H), 1.23 (t, *J* = 7.2, Hz, 6H) **^{13}C NMR** (151 MHz, $CDCl_3$): δ 167.5, 48.3, 41.8, 14.3, 12.4 **IR** (cm^{-1}): 3408, 2977, 1706, 1586, 1446, 1341, 1273, 1234, 1138, 994, 764 **ESI-HRMS** (m/z): $[M-Cl]^+$ calc'd for $C_{10}H_{22}N_3^+$: 184.1808; found: 184.1807

*4.2.3. Allyl Gold's reagent (**5c**):*

To a flame-dried 25-mL round-bottomed flask equipped with a magnetic stir bar was added cyanuric chloride (1.0 g, 5.4 mmol, 1.0 equiv). To the stirred solid was added *N*,*N*-diallylformamide[24] (2.03 g, 16.3 mmol, 3.0 equiv) dropwise over 5 minutes at room temperature. The reaction vessel was fitted with an oven-dried reflux condenser and transferred to a room temperature oil bath that was then warmed to 100 ºC. When the oil bath temperature

had reached 80 ºC the reaction mixture gradually turned dark brown, and exothermic release of CO_2 commenced. After stirring at 100 ºC for one hour, the reaction was removed from the oil bath and cooled to room temperature. Once at room temperature, a black oil formed, which was washed with Et_2O (5 x 5 mL), and the ethereal layer was discarded. The oil was concentrated under reduced pressure by rotary evaporation to reveal the title compound as a black oil (1.51 g, 69%). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 9.86 (s, 2H), 5.86–5.80 (m, 2H), 5.73–5.67 (m, 2H), 5.40–5.38 (m, 3H), 5.33 (at, *J* = 9.6 Hz, 3H), 5.25 (ad, *J* = 17.4 Hz, 2H), 4.23 (dd, *J* = 25.8, 6.6 Hz, 8H) **^{13}C NMR** (151 MHz, $CDCl_3$): δ 168.7, 130.5, 129.3, 122.1, 120.8, 55.5, 48.8 **IR** (cm^{-1}): 3390, 2932, 2077, 1709, 1572, 1441, 1418, 1332, 1235, 1170, 929, 844 **ESI-HRMS** (m/z): $[M-Cl]^+$ calc'd for $C_{14}H_{22}N_3^+$: 232.1808; found: 232.1828

*4.2.4. Benzyl Gold's reagent (**5d**):*

To a flame-dried 25-mL round-bottomed flask equipped with a magnetic stir bar was added cyanuric chloride (752 mg, 3.33 mmol, 1.0 equiv). To the stirred solid was added *N*,*N*-dibenzylformamide (1.0 g, 32.5 mmol, 4.0 equiv) in one portion at room temperature. The reaction vessel was fitted with an oven-dried reflux condenser and transferred to a room temperature oil bath that was then warmed to 120 ºC. Once the oil bath temperature had reached 75 ºC, the solids gradually melted to form a red-orange solution, and exothermic release of CO_2 commenced. After stirring at 120 ºC for one hour, the reaction was removed from the oil bath and cooled down to room temperature. Once at room temperature, a yellow-orange solid formed.

To the reaction vessel containing the crude yellow solid was added THF (2 mL) and the mixture was heated to reflux until complete dissolution of solid was observed. Once the solid dissolved, hexanes (6 mL) was added and a yellow solid precipitated after cooling to room temperature. The liquid was decanted and the resulting solid was triturated with hexanes/THF (2:1, 2 x 6 mL). Residual solvent was removed by concentration under reduced pressure to yield the title compound as a yellow solid (1.47 g, 47%). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 10.63 (s, 2H), 7.44–7.33 (m, 16H), 7.14–7.13 (m, 4H), 4.74 (s, 4H), 4.71 (s, 4H) **^{13}C NMR** (151 MHz, $CDCl_3$): δ 169.7, 133.2, 132.9, 129.4, 129.3, 129.3, 129.1, 128.8, 128.4, 56.5, 48.9 **IR** (cm^{-1}): 1589, 1568, 1496, 1453, 1344, 1215, 755, 701 **ESI-HRMS** (m/z): $[M-Cl]^+$ calc'd for $C_{30}H_{30}N_3^+$: 432.2458; found: 432.2434

*4.2.5. Pyrrolidine Gold's reagent (**5e**):*

To a flame-dried 25-mL round-bottomed flask equipped with a magnetic stir bar was added cyanuric chloride (1.0 g, 5.4 mmol, 1.0 equiv) and diluted with 1,4-dioxane (1.4 mL, 4 M). To the stirred heterogeneous mixture was added 1-formylpyrrolidine (2.1 mL, 22 mmol, 4.0 equiv) dropwise over 5 minutes at room temperature. The reaction vessel was fitted with an oven-dried reflux condenser and transferred to a room temperature oil bath that was then warmed to 85 ºC. Once the oil bath temperature had reached 50 ºC, a white precipitate formed in the yellow reaction mixture. When the oil bath temperature reached 85 ºC the reaction mixture turned dark red, and exothermic release of CO_2 commenced. After stirring at 85 ºC for two hours, the reaction was removed from the oil bath and cooled to room temperature. Once at room temperature, a red-brown oil formed. The crude brown solid was purified by trituration with pentane (3 x 5 mL). The pentane layer was discarded and the oil was concentrated under reduced pressure by rotary evaporation to reveal the title compound as a red-brown solid (1.9 g, 82%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.64 (s, 2H), 3.90 (t, *J* = 6.4 Hz, 4H), 3.64 (t, *J* = 6.4 Hz, 4H), 2.05–2.02 (m, 8H) **^{13}C NMR** (151 MHz, $CDCl_3$): δ 164.6, 51.2, 47.6, 25.0, 24.2 **IR** (cm^{-1}): 3392, 2975, 1706, 1581, 1450, 1306, 1110, 855 **ESI-HRMS** (m/z): $[M-Cl]^+$ calc'd for $C_{10}H_{18}N_3^+$: 180.1495; found: 180.1495

*4.2.6. Piperidine Gold's reagent (**5f**):*

To a flame-dried 25-mL round-bottomed flask equipped with a magnetic stir bar was added cyanuric chloride (270 mg, 1.47 mmol, 1.0 equiv). To the stirred solid was added 1-formylpiperdine (1.0 g, 8.8 mmol, 6.0 equiv) dropwise over 5 minutes at room temperature. The reaction vessel was fitted with an oven-dried reflux condenser and transferred to a room temperature oil bath that was then warmed to 100 ºC. Once the oil bath temperature had reached 90 ºC, the reaction mixture gradually turned a dark brown color and exothermic release of CO_2 commenced. After stirring at 100 ºC for two hours, the reaction was removed from the oil bath and cooled to room temperature. Once at room temperature, a red-orange solid formed.

To the reaction vessel containing the crude red solid was added THF (2 mL), and the mixture was heated to reflux until complete dissolution of solid was observed. Once the solid dissolved, hexanes (6 mL) was added, and a red solid formed. The mixture was allowed to slowly cool to room temperature and the red solid was washed with hexanes/THF (2:1, 2 x 6 mL), and concentrated under reduced pressure to yield the title compound as a red solid (928 mg, 85%). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 9.71 (s, 2H), 3.75 (adt, *J* = 15.6, 5.4 Hz, 8H), 1.78– 1.72 (m, 8H), 1.69–1.66 (m, 4H) **^{13}C NMR** (151 MHz, $CDCl_3$): δ 166.4, 53.1, 45.4, 26.6, 25.5, 23.9 **IR** (cm^{-1}): 3398, 2940, 1588, 1449, 1362, 1335, 1222, 1113, 1024, 1000 **ESI-HRMS** (m/z): $[M-Cl]^+$ calc'd for $C_{12}H_{22}N_3^+$: 208.1808; found: 208.1808

*4.2.7. Morpholine Gold's reagent (**5g**):*

To a flame-dried 25-mL round-bottomed flask equipped with a magnetic stir bar was added cyanuric chloride (1.2 g, 6.5 mmol, 1.0 equiv) and the stirred solid was diluted with 1,4-dioxane (1.6 mL, 4 M). To the stirred heterogeneous mixture was added 4-formylmorpholine (1.9 mL, 19 mmol, 3 equiv) dropwise over 5 minutes at room temperature. The reaction vessel was fitted with an oven-dried reflux condenser and transferred to a room temperature oil bath that was then warmed to 85 ºC. Once the oil bath temperature had reached 85 ºC, the reaction mixture turned a dark red color and exothermic release of CO_2 commenced. After stirring at 85 ºC for one hour, the reaction was removed from the oil bath and cooled to room temperature. Once at room temperature, a brown oil formed. The crude oil was purified by washing with Et_2O/pentane (3:1, 2 x 4 mL). The ethereal layer was discarded and the oil was dried under vacuum overnight (*ca.*100 mtorr) to reveal the title compound as a brown solid (2.18 g, 91%). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 9.87 (s, 2H), 3.90–3.88 (at, *J* = 4.2 Hz, 4H), 3.87–3.84 (m, 8H), 3.76 (at, *J* = 4.8 Hz, 4H) **^{13}C NMR** (151 MHz, $CDCl_3$): δ 167.1, 67.1, 66.1, 51.8, 45.2 **IR** (cm^{-1}): 3386, 2931, 1709, 1585, 1442, 1341, 1261, 1235, 1174, 1110, 1021, 856, 617 **ESI-HRMS** (m/z): $[M-Cl]^+$ calc'd for $C_{10}H_{18}N_3O_2^+$: 212.1394; found: 212.1393

*4.2.8. Indoline Gold's reagent (**5h**):*

To a flame-dried 25-mL round-bottomed flask equipped with a magnetic stir bar was added cyanuric chloride (128 mg, 1.13 mmol, 1.0 equiv). To the stirred solid was added 1-formylindoline (1.0 g, 6.79 mmol, 6.0 equiv)[25] in one portion at room temperature. The reaction vessel was fitted with an oven-dried reflux condenser and transferred to a room temperature oil bath that was then warmed to 115 ºC. Once the oil bath temperature had reached 75 ºC, the solids gradually melted to form an orange mixture, which turned dark red at 95 ºC and

exothermic release of CO_2 commenced. After stirring at 115 ºC for one hour, the reaction was removed from the oil bath and cooled to room temperature. Once at room temperature, an orange solid formed.

To the reaction vessel containing the crude orange solid was added THF (2 mL) and the mixture was heated to reflux until complete dissolution of solid was observed. Once the solid dissolved, hexanes (6 mL) was added, and an orange solid precipitated after cooling to room temperature. The liquid was decanted and the resulting solid was triturated with hexanes/THF (2:1, 2 x 6 mL). Residual solvent was removed by concentration under reduced pressure to yield the title compound as an orange solid (782 mg, 74%). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 11.12 (s, 2H), 8.08 (d, *J* = 10.2 Hz, 2H), 7.38 (t, *J* = 9.0 Hz, 2H), 7.29 (d, *J* = 9.0 Hz, 2H), 7.27–7.24 (m, 2H), 4.34 (t, *J* = 9.0 Hz, 4H), 3.33 (t, *J* = 9.0 Hz, 4H) **^{13}C NMR** (151 MHz, $CDCl_3$): δ 160.8, 139.6, 133.6, 129.3, 128.3, 126.0, 114.5, 48.3, 27.5 **IR** (cm^{-1}): 3368, 2933, 1681, 1602, 1575, 1416, 1342, 1123, 766 **ESI-HRMS** (m/z): $[M\text{-}Cl]^+$ calc'd for $C_{18}H_{18}N_3^+$: 276.1495; found: 276.1495

4.2.9. General procedure for enaminone formation:

An evacuated flame-dried 5-mL microwave vial equipped with magnetic stir bar was brought into a glovebox. Once in the glovebox, the flask was filled with nitrogen atmosphere. Solid LiO-*t*-Bu (17.6 mg, 0.22 mmol, 1.1 equiv) was added and the vial was sealed. The reaction vessel was removed from the glovebox, and the vial was evacuated and backfilled with nitrogen three times.

To the reaction vessel containing stirred solid LiO-*t*-Bu, was added THF (0.4 mL, 0.5 M) at room temperature. To the stirred reaction mixture was added the corresponding ketone (0.2 mmol, 1.0 equiv) dropwise over one minute at room temperature. After stirring at room temperature for 30 minutes, the corresponding Gold's reagent (0.22 mmol, 1.1 equiv) was added in one portion. The reaction vessel was sealed with a Teflon vial microwave cap, and transferred to a pre-warmed oil bath set to 65 ºC. After stirring for the stated time, the reaction was removed from the oil bath, cooled to room temperature, and diluted with sat. aq. NH_4Cl (5 mL). The layers were separated, and the aqueous layer was extracted with chloroform (3 x 5 mL). The combined organics were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure by rotary evaporation to give crude enaminone. Purification by flash column chromatography on silica gel or trituration afforded the title compound.

*4.2.10. Diethyl enaminone of acetophenone (**4c**):*

The title compound was prepared according to the general procedure with acetophenone (23 µL, 0.20 mmol, 1.0 equiv) and ethyl Gold's reagent (**5b**, 47 mg, 0.22 mmol, 1.1 equiv) then heated at 65 ºC for 12 hours. The crude oil was purified by flash column chromatography on silica gel (ethyl acetate/hexanes= 30% to 60%) to yield the title compound (35.3 mg. 88%) as a tan solid. **R_f**: 0.19 (65% ethyl acetate/hexanes) **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.88 (d, *J* = 7.2 Hz, 2H), 7.82 (d, *J* = 12.6 Hz, 1H), 7.46–7.40 (m, 3H), 5.77 (d, *J* = 12.6 Hz, 1H), 3.38–3.27 (m, 4H), 1.24 (t, *J* = 6.0 Hz, 6H) **^{13}C NMR** (151 MHz, $CDCl_3$): δ 188.9, 152.5, 140.9, 130.9, 128.2, 127.6, 91.8, 50.7, 42.9, 15.0, 11.7 **IR** (cm^{-1}): 2975, 2929, 2280, 2188, 2177, 2025, 1992, 1981, 1959, 1640, 1598, 1582, 1547, 1469, 1365, 1282, 1219, 1078, 658 **ESI-HRMS** (m/z): $[M+H]^+$ calc'd for $C_{13}H_{18}NO^+$: 204.1383; found: 204.1384

*4.2.11. Diallyl enaminone of acetophenone (**4d**):*

The title compound was prepared according to the general procedure with acetophenone (23 µL, 0.20 mmol, 1.0 equiv) and allyl Gold's reagent (**5c**, 59 mg, 0.22 mmol, 1.1 equiv) then heated at 65 ºC for 12 hours. The crude oil was purified by flash column chromatography on silica gel (ethyl acetate/hexanes= 20% to 45%) to yield the title compound (29.5 mg, 65%) as a yellow oil. **R_f**: 0.14 (30% ethyl acetate/hexanes) **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.88–7.85 (m, 3H), 7.46–7.39 (m, 3H), 5.84 (d, *J* = 12.6 Hz, 1H), 5.83–5.75 (m, 2H), 5.26 (d, *J* = 10.2 Hz, 2H), 5.22 (d, *J* = 16.9 Hz, 2H), 3.92–3.84 (m, 4H) **^{13}C NMR** (151 MHz, $CDCl_3$): δ 189.2, 153.2, 140.6, 133.0, 131.1, 130.6, 128.3, 127.7, 119.2, 118.1, 93.2, 58.6, 50.6 **IR** (cm^{-1}): 2922, 2853, 2214, 1597, 1581, 1546, 1447, 1365, 1274, 1312, 1206, 1051, 1024, 997, 703 **ESI-HRMS** (m/z): $[M+H]^+$ calc'd for $C_{15}H_{18}NO^+$: 228.1383; found: 228.1382

*4.2.12. Dibenzyl enaminone of acetophenone (**4e**):*

The title compound was prepared according to the general procedure with acetophenone (23 µL, 0.20 mmol, 1.0 equiv) and benzyl Gold's reagent (**5d**, 103 mg, 0.22 mmol, 1.1 equiv) then heated at 65 ºC for 12 hours. The crude oil was purified by flash column chromatography on silica gel (Et_2O/DCM= 2% to 10%) to yield the title compound (57.2 mg, 87%) as an orange solid. **R_f**: 0.30 (5% Et_2O/DCM) **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.18 (d, *J* = 12.5 Hz, 1H), 7.85 (d, *J* = 7.5 Hz, 2H), 7.46–7.32 (m, 9H), 7.22 (d, *J* = 7.0 Hz, 3H), 6.02 (d, *J* = 13.0 Hz, 1H), 4.47 (brs, 2H), 4.38 (brs, 2H) **^{13}C NMR** (151 MHz, $CDCl_3$): δ 189.4, 154.3, 140.4, 135.9, 135.3, 131.2, 129.1, 128.8, 128.7, 128.3, 128.0, 127.7, 127.4, 93.3, 59.5, 50.9 **IR** (cm^{-1}): 3028, 2923, 1641, 1597, 1580, 1544, 1452, 1361, 1201, 1076, 1050, 1025, 754, 698 **ESI-HRMS** (m/z): $[M+H]^+$ calc'd for $C_{23}H_{22}NO^+$: 328.1696; found: 328.1703

*4.2.13. Pyrrolidine enaminone of acetophenone (**4f**):*

The title compound was prepared according to the general procedure with acetophenone (23 µL, 0.20 mmol, 1.0 equiv) and pyrrolidine Gold's reagent (**5e**, 47 mg, 0.22 mmol, 1.1 equiv) then heated at 65 ºC for 12 hours. The crude oil was purified by flash column chromatography on silica gel (ethyl acetate/hexanes= 30% to 60%) to yield the title compound (57.2 mg, 88%) as a tan solid. **R_f**: 0.12 (50% ethyl acetate/hexanes) **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.03 (d, *J* = 12.5 Hz, 1H), 7.89 (d, *J* = 7.0, 2H), 7.46–7.39 (m, 3H), 5.68 (d, *J* = 12.5 Hz, 1H), 3.57 (brs, 2H), 3.29 (brs, 2H), 2.04 (brs, 2H), 1.95 (brs, 2H) **^{13}C NMR** (151 MHz, $CDCl_3$): δ 188.4, 150.0, 140.5, 130.8, 128.1, 127.5, 93.1, 52.4, 47.0, 25.2 **IR** (cm^{-1}): 2917, 2849, 1639, 1582, 1548, 1364, 1341, 1272, 1218, 1052, 757 **ESI-HRMS** (m/z): $[M+H]^+$ calc'd for $C_{13}H_{16}NO^+$: 202.1226; found: 202.1222

*4.2.14. Piperidine enaminone of acetophenone (**4g**):*

The title compound was prepared according to the general procedure with acetophenone (23 µL, 0.20 mmol, 1.0 equiv) and piperidine Gold's reagent (**5f**, 54 mg, 0.22 mmol, 1.1 equiv) then heated at 65 ºC for 12 hours. The crude oil was purified by flash column chromatography on silica gel (ethyl acetate/hexanes= 40% to 70%) to yield the title compound (32.4 mg, 75%) as a light yellow solid. **R_f**: 0.15 (50% ethyl acetate/hexanes) **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.88 (d, *J* = 7.0 Hz, 2H), 7.78 (d, *J* = 12.5 Hz, 1H), 7.45–7.38 (m, 3H), 5.81 (d, *J* = 12.5 Hz, 1H), 3.36 (brs, 4H), 1.66 (brs, 6H) **^{13}C NMR** (126 MHz, $CDCl_3$): δ 189.1, 153.2, 140.8, 130.9, 128.2, 127.5, 91.3, 24.2 **IR** (cm^{-1}): 2937, 2854, 1638, 1597, 1581, 1544, 1462, 1448, 1367, 1312, 1275, 1209, 1116, 1053, 1024, 881, 704, 660 **ESI-HRMS** (m/z): $[M+H]^+$ calc'd for $C_{14}H_{18}NO^+$: 216.1383; found: 216.1386

*4.2.15. Morpholine enaminone of acetophenone (**4h**):*

The title compound was prepared according to the general procedure with acetophenone (23 µL, 0.20 mmol, 1.0 equiv) and morpholine Gold's reagent (**5g**, 54 mg, 0.22 mmol, 1.1 equiv) then heated at 65 ºC for 12 hours. The crude oil was purified by flash column chromatography on silica gel (ethyl acetate/hexanes= 60% to 80%) to yield the title compound (36.3 mg, 84%) as a brown oil. **R_f**: 0.13 (70% ethyl acetate/hexanes) **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.88 (d, *J* = 7.5 Hz, 2H), 7.73 (d, *J* = 12.6 Hz, 1H), 7.47–7.40 (m, 3H), 5.88 (d, *J* = 12.6 Hz, 1H), 3.76 (at, *J* = 4.8 Hz, 4H), 3.40 (at, *J* = 4.2 Hz, 4H) **^{13}C NMR** (151 MHz, $CDCl_3$): δ 189.3, 152.9, 140.3, 131.3, 128.3, 127.6, 92.6, 66.3 **IR** (cm^{-1}): 2922, 2853, 1641, 1597, 1582, 1547, 1444, 1372, 1313, 1283, 1207, 1115, 1055, 1022, 927, 885, 760, 705, 662 **ESI-HRMS** (m/z): $[M+H]^+$ calc'd for $C_{13}H_{16}NO_2^+$: 218.1176; found: 218.1179

*4.2.16. Indoline enaminone of acetophenone (**4i**):*

The title compound was prepared according to the general procedure with acetophenone (23 µL, 0.20 mmol, 1.0 equiv) and indoline Gold's reagent (**5h**, 69 mg, 0.22 mmol, 1.1 equiv) then heated at 65 ºC for 12 hours. The crude oil was purified by flash column chromatography on silica gel (ethyl acetate/hexanes= 60% to 80%) to yield the title compound (39.1 mg, 78%) as a yellow solid. **R_f**: 0.19 (20% ethyl acetate/hexanes) **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.41 (d, *J* = 12.4 Hz, 1H), 7.96 (d, *J* = 7.1 Hz, 1H), 7.51–7.43 (m, 3H), 7.20 (d, *J* = 7.7 Hz, 2H), 7.10 (d, *J* = 7.9 Hz, 1H), 6.98 (t, *J* = 7.4 Hz, 1H), 6.04 (d, *J* = 12.6 Hz, 1H), 3.94 (t, *J* = 8.4 Hz, 2H), 3.26 (t, *J* = 8.4 Hz, 2H) **^{13}C NMR** (151 MHz, $CDCl_3$): δ 189.1, 143.9, 141.5, 140.0, 131.5, 131.2, 128.4, 128.1, 127.8, 125.7, 123.2, 109.2, 96.6, 48.3, 27.7 **IR** (cm^{-1}): 2924, 1643, 1579, 1542, 1598, 1496, 1258, 1208, 1052, 883, 747, 703 **ESI-HRMS** (m/z): $[M+H]^+$ calc'd for $C_{17}H_{16}NO^+$: 250.1226; found: 250.1221

*4.2.17. Osimertinib precursor (**4j**):*

The title compound was prepared according to the general procedure with *N*-Me-3-acetylindole[25] (35 mg, 0.20 mmol, 1.0 equiv) and morpholine Gold's reagent (**5a**, 36 mg, 0.22 mmol, 1.1 equiv) then heated at 65 ºC for 2 hours. The yellow oil was washed with pentane (3 x 2 mL), the pentane layer was discarded, and the oil was dried under vacuum (*ca*.100 mtorr) to reveal the title compound as a yellow-orange foam (43.2 g, 94%). **R_f**: 0.12 Ethyl acetate **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.40–8.37 (m, 1H), 7.76 (d, *J* = 12.5 Hz, 1H), 7.67 (s, 1H), 7.33–7.25 (m, 3H), 5.64 (d, *J* = 12.5 Hz, 1H), 3.81 (s, 3H), 3.00 (brs, 6H) **^{13}C NMR** (151 MHz, $CDCl_3$): δ 184.9, 152.0, 137.5, 133.0, 126.9, 123.2, 122.7, 122.6, 122.2, 121.6, 118.3, 109.5, 94.1, 33.4 **IR** (cm^{-1}): 2919, 1635, 1574, 1549, 1523, 1466, 1369, 1331, 1225, 1081, 1048, 1011, 884, 791, 748, 574 **ESI-HRMS** (m/z): $[M+H]^+$ calc'd for C14H17N_2O^+: 229.1335; found: 229.1336

*4.2.18. Indoline enaminone of dihydro-β-ionone (**4k**):*

The title compound was prepared according to the general procedure with dihydro-β-ionone (42 µL, 0.20 mmol, 1.0 equiv) and indoline Gold's reagent (**5h**, 69 mg, 0.22 mmol, 1.1 equiv) then heated at 65 ºC for 1.5 hours. The crude oil was purified by flash column chromatography on silica gel (ethyl acetate/hexanes= 10% to 30%) to yield the title compound (36.4 mg, 56%) as a yellow solid. **R_f**: 0.22 (20% ethyl acetate/hexanes) **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.12 (d, *J* = 13.0 Hz, 1H), 7.18 (d, *J* = 7.5 Hz, 2H), 7.01 (d, *J* = 8.0 Hz, 1H), 6.94 (t, *J* = 7.4 Hz, 1H), 5.34 (d, *J* = 13.0 Hz, 1H), 3.82 (t, *J* = 8.5 Hz, 2H), 3.23 (t, *J* = 8.5 Hz, 2H), 2.55–2.52 (m, 2H), 2.37–2.33 (m, 2H), 1.92 (t, *J* = 6.5 Hz, 2H), 1.64 (s, 3H), 1.61–1.56 (m, 2H), 1.45–1.42 (m, 2H), 1.02 (s, 6H) **^{13}C NMR** (126 MHz, $CDCl_3$): δ 198.7, 144.1, 139.3, 136.8, 131.0, 128.1, 127.7, 125.7, 122.8, 108.8, 100.5, 48.1, 42.4, 40.0, 35.2, 32.9, 28.7, 27.7, 24.2, 20.0, 19.7 **IR** (cm^{-1}): 2923, 2863, 1665, 1583, 1300, 1262, 1111, 748, 703 **ESI-HRMS** (m/z) $[M+H]^+$ calc'd for $C_{22}H_{30}NO^+$: 324.2322; found: 324.2346

*4.2.19. Piperidine enaminone of geranylacetone (**4l**):*

The title compound was prepared according to the general procedure with geranylacetone (15 µL, 0.20 mmol, 1.0 equiv) and piperidine Gold's reagent (**5f**, 54 mg, 0.22 mmol, 1.1 equiv) then heated at 65 ºC for 2 hours. The crude oil was purified by flash column chromatography on silica gel (ethyl acetate/hexanes= 40% to 60%) to yield the title compound (27.2 mg, 62%) as a yellow solid. **R_f**: 0.29 (60% ethyl acetate/hexanes) **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.48 (d, *J* = 12.8 Hz, 1H), 5.14–5.06 (m, 3H), 3.23 (brs, 4H), 2.34–2.28 (m, 4H), 2.07–2.02 (m, 3H), 1.97–1.94 (m, 1H), 1.67–1.58 (m, 15H) **^{13}C NMR** (126 MHz, $CDCl_3$): δ 198.2, 151.3, 135.6, 131.4, 124.7, 124.5, 123.9, 39.8, 32.1, 26.9, 26.8, 25.8, 25.8, 24.5, 24.4, 24.2, 23.5, 17.8, 16.1. **IR** (cm^{-1}): 2924, 2855, 2348, 2166, 1610, 1563, 1447, 1369, 1239, 1100, 1026, 983, 852, 765 **ESI-HRMS** (m/z): $[M+H]^+$ calc'd for $C_{19}H_{32}NO^+$: 290.2478; found: 290.2501

*4.2.20. Morpholine enaminone of γ-butyrolactone (**4m**):*

The title compound was prepared according to the general procedure with γ-butyrolactone (44 µL, 0.20 mmol, 1.0 equiv) and morpholine Gold's reagent (**5g**, 54 mg, 0.22 mmol, 1.1 equiv) then heated at 65 ºC for 6 hours. The crude oil was purified by flash column chromatography on silica gel (ethyl acetate/hexanes= 40% to 60%) to yield the title compound (36.4 mg, 74%) as a yellow solid. **R_f**: 0.15 (90% ethyl acetate/hexanes) **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.11 (t, *J* = 2.0 Hz, 1H), 4.27 (t, *J* = 7.6 Hz, 2H), 3.72 (t, *J* = 4.4 Hz, 4H), 3.42 (t, *J* = 4.4 Hz, 4H), 3.01 (dd, *J* = 8.0, 2.0 Hz, 2H) **^{13}C NMR** (151 MHz, $CDCl_3$): δ 175.5, 145.2, 88.2, 66.6, 64.6, 49.8, 26.2 **IR** (cm^{-1}): 2922, 2855, 1723, 1622, 1445, 1363, 1270, 1230, 1158, 1114, 1021, 1003, 863, 747 **ESI-HRMS** (m/z): $[M+H]^+$ calc'd for $C_9H_{14}NO_3^+$: 184.0968; found: 184.0980

*4.2.21. Scalable synthesis of dimethyl enaminone of 2-butanone (**4m**):*

To a flame-dried 5-L round-bottomed flask equipped with a magnetic stir bar was added solid LiO-*t*-Bu (88.1 g, 1.1 mol, 1.1 equiv). To the stirred solid, was added THF (2.0 L, 0.5 M) via cannula, and this mixture was allowed to stir at room temperature for 10 minutes to allow for complete dissolution of LiO-*t*-Bu solid. 2-butanone (72.1 g, 1.0 mol, 1.0 equiv) was added dropwise at room temperature to the reaction mixture over 15 minutes, resulting in a light yellow mixture. After stirring at room temperature for 30 minutes, methyl Gold's reagent (**5a**, 182 g, 1.1 mol, 1.1 equiv) was added in 5 portions over 30 minutes. The reaction vessel was fitted with an oven-dried reflux condenser and transferred to a heating mantle that was then warmed to a gentle reflux.

After stirring at reflux for 12 hours, the reaction apparatus was removed from the heating mantle and allowed to cool to room temperature. Once at room temperature, the reaction was diluted with sat. aq. NH_4Cl (2.5 L) and chloroform (3 L). The layers were separated, and the aqueous layer was extracted with chloroform (3 x 2 L). The combined organics were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure by rotary evaporation to give the crude enaminone as a black oil. The black oil was purified by fractional distillation through a 5 cm vigreux column

to reveal the title compound as a yellow liquid (92.3 g, 73%). **Boiling point**: 82 ºC at 200 mtorr **R_f**: 0.11 (90% ethyl acetate/hexanes) **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.50 (d, *J* = 12.7 Hz, 1H), 5.01 (d, *J* = 12.7 Hz, 1H), 2.90 (brs, 6H), 5.01 (d, *J* = 12.7 Hz, 1H), 2.33 (q, *J* = 7.5 Hz, 2H), 1.09 (t, *J* = 7.5 Hz, 3H) **^{13}C NMR** (151 MHz, $CDCl_3$): δ 199.0, 152.3, 95.3, 44.8, 36.9, 30.4 10.0 **IR** (cm^{-1}): 2931, 2053, 1562, 1433, 1354, 1283, 1221, 1103, 1036, 979, 763 **ESI-HRMS** (m/z): $[M+H]^+$ calc'd for $C_7H_{14}NO^+$: 128.1070; found: 128.1001

*4.2.22. E-Diene (**7a**):*

To a flame-dried 100-mL round-bottomed flask equipped with a magnetic stir bar was added LiCl (100.1 mg, 2.36 mmol, 0.3 equiv). The reaction flask was placed under vacuum and heated with a heat gun for 2 minutes and then back filled with nitrogen (This process was repeated three times). After the flask was cooled to room temperature, the flask was back filled with nitrogen and diluted with THF (26 mL, 0.3M).

2,2,6,6-tetramethylpiperidine (1.6 mL, 9.43 mmol, 1.2 equiv) was added dropwise over 5 minutes at room temperature to the vigorously stirred reaction mixture. The reaction vessel was transferred to a –20 ºC dry-ice acetone bath. After stirring at this temperature for 10 minutes, *n*-BuLi (3.5 mL, 8.7 mmol, 1.1 equiv) was added dropwise over 5 minutes, which resulted in a pale yellow solution. Once 25 minutes had elapsed, the reaction was cooled to –78 ºC in a saturated dry-ice acetone bath, and DMPU (0.95 mL, 7.9 mmol, 1.0 equiv) was added dropwise over 2 minutes, which resulted in a light orange mixture. The reaction mixture was allowed to stir at –78 ºC for 30 minutes.

In a separate flame-dried 25-mL round-bottomed flask was added enaminone **4b** (1.0 g, 7.9 mmol, 1.0 equiv) that was then diluted with THF (5 mL, 1.6 M). This solution was added dropwise over 5 minutes at –78 ºC to the vigorously stirred reaction mixture, which resulted in a red-orange reaction mixture. After stirring at –78 ºC for 30 minutes, a solution of TIPSCl (1.7 mL, 7.7 mmol, 0.98 equiv) in THF (10 mL, 7.7M) was added to the reaction mixture dropwise over 5 minutes, which resulted in a light yellow solution. Following stirring at –78 ºC for 10 minutes, the reaction vessel was transferred to a 0 ºC ice-water bath.

After stirring at 0 ºC for 2 hours, sat. aq. NH_4Cl (10mL) was added and the layers were separated. The aqueous layer was extracted with pentane (3 x 25 mL). The combined organics were washed with sat. aq. $NaHCO_3$ (20 mL), brine (3 x 30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure by rotary evaporation to yield an orange oil as a >20:1 (*E*:*Z*) mixture of diastereomers. The crude mixture was purified by rapid fractional distillation (<5 minutes) with a heat gun to reveal the title compound as a yellow liquid (>20:1 *E*:*Z*, 1.32 g, 59%) **Boiling point**: 80–84 ºC at 200 mtorr **R_f**: 0.8 (5% Et_2O/0.5% Et_3N/pentane) **^{1}H NMR** (600 MHz, $CDCl_3$): δ 6.66 (d, *J* = 15.6 Hz, 1H), 4.89 (d, *J* = 15.6, 1H), 4.36 (q, *J* = 7.0 Hz, 1H), 2.72 (s, 6H), 1.57 (d, *J* = 8.4 Hz, 3H), 1.23–1.17 (m, 3H), 1.11 (s, 9H), 1.10 (s, 9H) **^{13}C NMR** (151 MHz, $CDCl_3$): δ 149.5, 140.6, 95.3, 92.2, 40.8, 18.4, 13.1 **IR** (cm^{-1}): 2939, 2863, 2119, 1653, 1561, 1463, 1421, 1358, 1284, 1224, 1107, 1042, 990, 916, 882, 850 **ESI-HRMS** (m/z): $[M+H]^+$ calc'd for $C_{16}H_{34}NOSi^+$: 284.2404; found: 284.2401

*4.2.23. Z-Diene (**7b**):*

An evacuated flame dried 50-mL round-bottomed flask equipped with magnetic stir bar and Schlenk adaptor was brought into a glovebox. Once in the glovebox, the flask was filled with nitrogen atmosphere. Solid LiHMDS (1.45 g, 8.64 mmol, 1.1 equiv) was added and the flask was sealed. The reaction vessel was removed from the glovebox, and the flask was evacuated and backfilled with nitrogen three times. The Schlenk adaptor was replaced with a rubber septum and placed under a nitrogen atmosphere.

To the stirred solid LiHMDS was added THF (16 mL, 0.5 M) and then placed in a saturated dry-ice acetone bath cooled to –78 ºC. Enaminone **4b** (1.0 g, 7.9 mmol, 1.0 equiv) was added dropwise over 5 minutes to the reaction mixture at –78 ºC, which resulted in an orange mixture. After stirring at –78 ºC for 30 minutes, DMPU (2.9 mL, 24 mmol, 3.0 equiv) was added dropwise over 5 minutes, which resulted in a light orange reaction mixture.

Once 30 minutes had elapsed, TIPSCl (1.9 mL, 8.6 mmol, 1.1 equiv) was added dropwise to the reaction mixture over 5 minutes, which resulted in a yellow reaction mixture. The reaction vessel was transferred to a 0 ºC ice-water bath.

After stirring at 0 ºC for 2 hours, sat. aq. NH_4Cl (10mL) was added and the layers were separated. The aqueous layer was extracted with pentane (3 x 25 mL). The combined organics were washed with sat. aq. $NaHCO_3$ (20 mL), brine (3 x 30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure by rotary evaporation to yield an orange oil as a 1:11 (*E*:*Z*) mixture of diastereomers. The crude mixture was purified by rapid fractional distillation (<5 minutes) with a heat gun to reveal the title compound as a yellow liquid (1:10 *E*:*Z*, 1.4 g, 63%) **Boiling point**: 80–84 ºC at 200 mtorr **R_f**: 0.8 (5% Et_2O/0.5% Et_3N/pentane) **^{1}H NMR** (600 MHz, $CDCl_3$): δ 6.37 (d, *J* = 13.5 Hz, 1H), 4.73 (d, *J* = 13.5 Hz, 1H) 4.43 (q, *J* = 8.4 Hz, 1H), 2.65 (s, 6H), 1.62 (d, *J* = 6.8 Hz, 3H), 1.26–1.20 (m, 3H), 1.13 (s, 9H), 1.12 (s, 9H) **^{13}C NMR** (151 MHz, $CDCl_3$): δ 150.8, 139.5, 98.8, 98.3, 40.8, 18.3, 13.8 **IR** (cm^{-1}): 2943, 2865, 1993, 1648, 1580, 1464, 1350, 1329, 1193, 1039, 937, 882, 937, 801 **ESI-HRMS** (m/z): $[M+H]^+$ calc'd for $C_{16}H_{34}NOSi^+$: 284.2404; found: 284.2403

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