Supporting Information

Copper-Catalyzed Stereoselective Alkylhydrazination of Alkynes

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I. General Considerations

**Reagents.** Unless otherwise indicated, all reactions were carried out in Schlenk tube under an argon atmosphere with dry solvents. Anhydrous MeCN was purchased from Alfa Aesar and used as received. Ether/THF was dried and purified by distillation from sodium/benzophenone. MeOH and CH$_2$Cl$_2$ were distilled from CaH$_2$. CuBr was purchased from Aladdin. Other copper catalysts were purchased from Alfa Aesar, Strem, Aladdin or JK Chemical and used as received. All other reagents were purchased from commercial sources and used as received.

**Analytical Methods.** All new compounds were characterized by $^1$H NMR, $^{13}$C NMR, and HRMS. NMR spectra were recorded on a Bruker AV-400 or 500 MHz instrument in CDCl$_3$. All $^1$H NMR spectra are reported in ppm downfield from tetramethylsilane (0 ppm). All $^{13}$C NMR spectra are reported in ppm relative to residual CHCl$_3$ (77.0 ppm). Coupling constants are reported in Hz with multiplicities denoted as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Reactions were monitored by thin-layer chromatography (TLC) carried out on commercial silica gel plates (GF254) using UV light as a visualizing agent. Flash chromatography was performed on silica gel 60 (200-300 mesh). High resolution mass spectra (HRMS) was obtained on an ESI-LC-MS/MS or APCI-LC-MS/MS spectrometer.
II. Optimization of Reaction Conditions

Screening of **equiv. of alkyne**

3.0 equiv. of alkyne was selected.

Screening of **loading of copper catalyst**

20 mol% CuBr was selected.
Screening of reductant

<table>
<thead>
<tr>
<th>reductant</th>
<th>NMR yield(%)</th>
</tr>
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<tr>
<td>Na₂SO₃</td>
<td>19</td>
</tr>
<tr>
<td>Na₂S₂O₃·5H₂O</td>
<td>38</td>
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<tr>
<td>NaHSO₃</td>
<td>20</td>
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<tr>
<td>Na₂S₂O₅</td>
<td>17</td>
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<tr>
<td>1,4-cyclohexadiene</td>
<td>28</td>
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<tr>
<td>Et₃SiH</td>
<td>22</td>
</tr>
</tbody>
</table>
III. Synthesis and characterization of alkynes

These alkynes were prepared according to the reported literatures. The $^1$H NMR spectral data matched those of previous reported.

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\begin{array}{c}
\text{Ethynylisoquinoline (1r): the title compound was prepared according to the previous reported protocols using 6-bromoisoquinoline as starting material;}^{[2]} \text{ a white solid, m.p. 115-117 °C; } ^1\text{H NMR (400 MHz, CDCl}_3\text{)} \delta 9.24 (s, 1H), 8.55 (d, } J = 6.0 \text{ Hz, 1H}, 7.98 (s, 1H), 7.92 (d, } J = 8.4 \text{ Hz, 1H}, 7.64 (dd, } J = 8.4, 1.6 \text{ Hz, 1H), 7.60 (d, } J = 6.0 \text{ Hz, 1H), 3.27 (s, 1H); } ^1\text{C NMR (100 MHz, CDCl}_3\text{)} \delta 152.3, 143.8, 135.2, 130.6, 130.0, 127.8, 127.6, 124.1, 120.0, 83.0, 79.7; \text{ HRMS (ESI) calcd for C}_{11}\text{H}_8\text{N}^+ [M+H]^+ 154.0651, found 154.0651.}
\end{array}
\]
IV. General procedure for the alkylhydrazination of alkynes

**General Procedure:** In an oven-dried resealable screw-cap test tube, CuBr (5.7 mg, 0.04 mmol, 20 mol%), alkyne (1) (0.6 mmol, 3.0 equiv.), dimethyl 2,2'-azobis(2-methylpropionate) or its analogues (2) (0.2 mmol, 1.0 equiv.) and azocarboxylic esters (3) (0.2 mmol, 1.0 equiv.) were mixed in anhydrous MeCN (2.5 mL) under argon atmosphere. The reaction mixture was stirred at 80 °C oil bath for 8 h. The mixture was cooled down to room temperature, filtered over Celite and the solvent was removed by rotary evaporation. The crude product was purified by flash chromatography (silica gel) or preparative TLC to afford the related alkenylhydrazines.

V. Characterization data for the products and side products

Diisopropyl 1-[(E)-4-methoxy-1-(4-methoxyphenyl)-3,3-dimethyl-4-oxobut-1-en-1-yl]-1,2-hydrazinedicarboxylate (4a): The representative procedure was followed using 4-ethynylanisole (1a) (79.2 mg, 0.6 mmol), dimethyl 2,2'-azobis(2-methylpropionate) (2a) (46.1 mg, 0.2 mmol) and diisopropyl azodicarboxylate (3a) (40.4 mg, 0.2 mmol). The crude product was purified by flash chromatography (silica gel, 4:1 petroleum ether:EtOAc) to afford 4a (67.2 mg, 77% yield) as yellow sticky. Due to the presence of amide rotamers, the product gives two sets of NMR signals. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.16 (d, $J$ = 8.5 Hz, 2H), 6.83 (d, $J$ = 8.5 Hz, 2H), 6.56-6.12 (m, 1H, -NH), 5.93 (br s, 1H), 4.94 (sept, $J$ = 6.0 Hz, 2H), 3.80 (s, 3H), 3.29 (br s, 3H), 1.27 (s, 6H), 1.23 (d, $J$ = 6.0 Hz, 6H), 1.21 (d, $J$ = 6.0 Hz, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 176.2, 159.5, 155.6, 154.7, 137.5, 133.5, 130.9, 127.6, 113.2, 70.4, 69.7, 55.2, 51.6, 42.8, 27.3, 21.90, 21.88; C$_{22}$H$_{18}$N$_2$O$_7$ [M+H]$^+$ 437.2282, found 437.2284.
Diisopropyl 1-[(E)-1-(4-fluorophenyl)-4-methoxy-3,3-dimethyl-4-oxobut-1-en-1-yl]-1,2-hydrazinedicarboxylate (4b): The representative procedure was followed using 4-fluorophenylacetylene (1b) (72.1 mg, 0.6 mmol), dimethyl 2,2'-azobis(2-methylpropionate) (2a) (46.1 mg, 0.2 mmol) and diisopropyl azodicarboxylate (3a) (40.4 mg, 0.2 mmol). The crude product was purified by flash chromatography (silica gel, 5:1 petroleum ether:EtOAc) to afford 4b (55.5 mg, 66% yield) as slightly yellow sticky. Due to the presence of amide rotamers, the product gives two sets of NMR signals. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.31-7.21 (m, 2H), 7.01 (dd, $J = 9.0$, 8.5 Hz, 2H), 6.64-6.22 (m, 1H, -NH), 5.96 (s, 1H), 4.99-4.86 (m, 2H), 3.32 (br s, 3H), 1.27 (s, 6H), 1.24 (d, $J = 6.0$ Hz, 6H), 1.23-1.16 (m, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 175.9, 162.6 (d, $J = 246.5$ Hz), 155.6, 154.5, 137.1, 133.7, 131.5 (d, $J = 8.3$ Hz), 114.8 (d, $J = 21.5$ Hz), 70.6, 69.9, 51.6, 42.8, 27.3, 21.9; HRMS (ESI) calcd for C$_{22}$H$_{30}$FN$_2$O$_6$ [M+H]$^+$ 425.2082, found 425.2086.

Diisopropyl 1-[(E)-1-(4-chlorophenyl)-4-methoxy-3,3-dimethyl-4-oxobut-1-en-1-yl]-1,2-hydrazinedicarboxylate (4c): The representative procedure was followed using 4-chlorophenylacetylene (1c) (81.9 mg, 0.6 mmol), dimethyl 2,2'-azobis(2-methylpropionate) (2a) (46.1 mg, 0.2 mmol) and diisopropyl azodicarboxylate (3a) (40.4 mg, 0.2 mmol). The crude product was purified by flash chromatography (silica gel, 5:1 petroleum ether:EtOAc) to afford 4c (48.7 mg, 56% yield) as colorless solid, m.p. 105-109 °C. Due to the presence of amide rotamers, the product gives two sets of NMR signals. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.29 (d, $J = 8.0$ Hz, 2H), 7.21 (d, $J = 8.0$ Hz, 2H), 6.64-6.25 (m, 1H, -NH), 5.96 (s, 1H), 5.00-4.82
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(1H, m, 2H), 3.30 (br s, 3H), 1.26 (s, 6H), 1.23 (d, J = 6.5 Hz, 6H), 1.19 (d, J = 6.0 Hz, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 175.9, 155.6, 154.4, 137.0, 134.3, 133.9, 131.0, 128.0, 70.7, 70.0, 51.7, 42.8, 27.3, 21.9; HRMS (ESI) calcd for C$_{23}$H$_{30}$ClN$_2$O$_6$ [M+H]$^+$ 441.1787, found 441.1781.

X-Ray structure of 4c (CCDC 1948643)

Diisopropyl 1-[(E)-1-(4-bromophenyl)-4-methoxy-3,3-dimethyl-4-oxobut-1-en-1-yl]-1,2-hydrazinedicarboxylate (4d): The representative procedure was followed using 4-bromophenylacetylene (1d) (108.6 mg, 0.6 mmol), dimethyl 2,2’-azobis(2-methylpropionate) (2a) (46.1 mg, 0.2 mmol) and diisopropyl azodicarboxylate (3a) (40.4 mg, 0.2 mmol). The crude product was purified by flash chromatography (silica gel, 5:1 petroleum ether:EtOAc) to afford 4d (53.7 mg, 55% yield) as slightly yellow sticky. Due to the presence of amide rotamers, the product gives two sets of NMR signals. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.44 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 8.0 Hz, 2H), 6.60-6.17 (m, 1H, -NH), 5.96 (s, 1H), 5.00-4.84 (m, 2H), 3.30 (br s, 3H), 1.26 (s, 6H), 1.23 (d, J = 6.5 Hz, 6H), 1.19 (d, J = 5.5 Hz, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 175.8, 155.6, 154.4, 137.0, 134.4, 133.8, 131.3, 130.9, 122.5, 70.7, 69.9, 51.7, 42.8, 27.3, 21.8; HRMS (ESI) calcd for C$_{23}$H$_{30}$BrN$_2$O$_6$ [M+H]$^+$ 485.1282, found 485.1285.
Diisopropyl 1-[(E)-4-methoxy-3,3-dimethyl-4-oxo-1-phenylbut-1-en-1-yl]-1,2-hydrazinedicarboxylate (4e): The representative procedure was followed using phenylacetylene (1e) (61.2 mg, 0.6 mmol), dimethyl 2,2’-azobis(2-methylpropionate) (2a) (46.1 mg, 0.2 mmol) and diisopropyl azodicarboxylate (3a) (40.4 mg, 0.2 mmol). The crude product was purified by preparative TLC (silica gel, 3:1 petroleum ether:EtOAc) to afford 4e (18.4 mg, 23% yield) as colorless sticky, because the polarity of 4e is very close to that of the byproduct SP-1. Due to the presence of amide rotamers, the product gives two sets of NMR signals. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.34-7.28 (m, 3H), 7.26-7.20 (m, 2H), 6.59-6.17 (m, 1H, -NH), 6.06-5.82 (br s, 1H), 5.02-4.83 (m, 2H), 3.23 (br s, 3H), 1.27 (s, 6H), 1.23 (d, $J = 6.0$ Hz, 6H), 1.19 (d, $J = 6.0$ Hz, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 176.0, 155.6, 154.7, 137.6, 135.4, 133.8, 129.5, 128.4, 127.8, 70.5, 69.8, 51.5, 42.8, 27.4, 21.9; HRMS (ESI) calcd for C$_{21}$H$_{31}$N$_2$O$_6$ [M+H]$^+$ 407.2177, found 407.2182.

Diisopropyl 1-[(E)-1-(4-ethylphenyl)-4-methoxy-3,3-dimethyl-4-oxobut-1-en-1-yl]-1,2-hydrazinedicarboxylate (4f): The representative procedure was followed using 4-ethylphenylacetylene (1f) (78.1 mg, 0.6 mmol), dimethyl 2,2’-azobis(2-methylpropionate) (2a) (46.1 mg, 0.2 mmol) and diisopropyl azodicarboxylate (3a) (40.4 mg, 0.2 mmol). The crude product was purified by preparative TLC (silica gel, 2.5:1 petroleum ether:EtOAc) to afford 4f (54.5 mg, 63% yield) as slightly yellow sticky. Due to the presence of amide rotamers, the product gives two sets of NMR signals. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.13 (br s, 4H), 6.60-
6.18 (m, 1H, -NH), 5.96 (br s, 1H), 4.94 (sept, J = 6.4 Hz, 2H), 3.22 (br s, 3H), 2.63 (q, J = 7.6 Hz, 2H), 1.28 (s, 6H), 1.25-1.15 (m, 15H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 176.1, 155.6, 154.7, 144.4, 137.6, 133.7, 132.6, 129.4, 127.3, 70.3, 69.7, 51.5, 42.7, 28.6, 27.3, 21.9, 15.5; HRMS (ESI) calcd for C$_{23}$H$_{35}$N$_2$O$_6$ [M+H]$^+$ 435.2490, found 435.2496.

Diisopropyl 1-{[(E)-1-[4-(cyanomethyl)phenyl]-4-methoxy-3,3-dimethyl-4-oxobut-1-en-1-yl]-1,2-hydrazinedi carboxylate} (4g): The representative procedure was followed using 4-ethynylbenzeneacetonitrile (1g) (84.7 mg, 0.6 mmol), dimethyl 2,2'-azobis(2-methyl-propionate) (2a) (46.1 mg, 0.2 mmol) and diisopropyl azodicarboxylate (3a) (40.4 mg, 0.2 mmol). The crude product was purified by flash chromatography (silica gel, 200:1 dichloromethane:methanol) to afford 4g (52.4 mg, 59% yield) as yellow sticky. Due to the presence of amide rotamers, the product gives two sets of NMR signals. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.30 (br s, 4H), 6.67-6.23 (m, 1H, -NH), 5.99 (s, 1H), 5.00-4.88 (m, 2H), 3.76 (s, 2H), 3.30 (br s, 3H), 1.28 (s, 6H), 1.25 (d, J = 6.5 Hz, 6H), 1.21 (d, J = 5.5 Hz, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 175.9, 155.6, 154.5, 137.2, 135.5, 134.0, 130.5, 127.4, 117.5, 69.9, 51.6, 42.8, 27.3, 23.4, 21.9; HRMS (ESI) calcd for C$_{23}$H$_{32}$N$_3$O$_6$ [M+H]$^+$ 446.2286, found 446.2281.

Diisopropyl 1-{[(E)-4-methoxy-3,3-dimethyl-4-oxo-1-[4-(trifluoromethyl)phenyl]but-1-en-1-yl]-1,2-hydrazinedicarboxylate} (4h): The representative procedure was followed using 4-
ethynyl-α,α,α-trifluorotoluene (1h) (102.1 mg, 0.6 mmol), dimethyl 2,2'-azobis(2-methylpropionate) (2a) (46.1 mg, 0.2 mmol) and diisopropyl azodicarboxylate (3a) (40.4 mg, 0.2 mmol). The crude product was purified by flash chromatography (silica gel, 500:1 dichloromethane:methanol) to afford 4h (37.3 mg, 39% yield) as yellow sticky. Due to the presence of amide rotamers, the product gives two sets of NMR signals. 1H NMR (500 MHz, CDCl₃) δ 7.58 (d, J = 8.0 Hz, 2H), 7.47-7.37 (m, 2H), 6.68-6.25 (m, 1H, -NH), 6.01 (br s, 1H), 5.01-4.82 (m, 2H), 3.23 (br s, 3H), 1.28 (s, 6H), 1.27-1.10 (m, 12H); 13C NMR (125 MHz, CDCl₃) δ 175.7, 155.6, 154.3, 139.3, 136.8, 134.1, 130.3 (q, J = 32.1 Hz), 130.0, 124.7 (q, J = 3.8 Hz), 123.9 (q, J = 270.5 Hz), 70.8, 70.1, 51.6, 42.8, 27.4, 21.84, 21.81; HRMS (ESI) calcd for C₂₂H₃₀F₃N₂O₆ [M+H]+ 475.2050, found 475.2044.

Diisopropyl 1-[(E)-1-(3-methoxyphenyl)-4-methoxy-3,3-dimethyl-4-oxobut-1-en-1-yl]-1,2-hydradzinedicarboxylate (4i): The representative procedure was followed using 3-ethynylanisole (1i) (79.2 mg, 0.6 mmol), dimethyl 2,2'-azobis(2-methylpropionate) (2a) (46.1 mg, 0.2 mmol) and diisopropyl azodicarboxylate (3a) (40.4 mg, 0.2 mmol). The crude product was purified by flash chromatography (silica gel, 4:1 petroleum ether:EtOAc) to afford 4i (72.5 mg, 83% yield) as yellow sticky. Due to the presence of amide rotamers, the product gives two sets of NMR signals. 1H NMR (500 MHz, CDCl₃) δ 7.22 (dd, J = 8.0, 8.0 Hz, 1H), 6.87-6.74 (m, 3H), 6.78 (br s, 1H), 6.58-6.17 (m, 1H, -NH), 5.98 (br s, 1H), 5.01-4.88 (m, 2H), 3.80 (s, 3H), 3.27 (br s, 3H), 1.29 (s, 6H), 1.24 (d, J = 6.5 Hz, 6H), 1.21 (d, J = 6.5 Hz, 6H); 13C NMR (125 MHz, CDCl₃) δ 176.0, 159.0, 155.6, 154.7, 137.4, 136.7, 133.9, 128.9, 121.8, 114.9, 114.1, 70.5, 69.8, 55.2, 51.5, 42.8, 27.3, 21.9; HRMS (ESI) calcd for C₂₂H₃₃N₂O₇ [M+H]+ 437.2282, found 437.2275.
Diisopropyl 1-[(E)-4-methoxy-1-(2-methoxyphenyl)-3,3-dimethyl-4-oxobut-1-en-1-yl]-1,2-hydrazinedicarboxylate (4j): The representative procedure was followed using 2-ethynylanisole (1j) (79.2 mg, 0.6 mmol), dimethyl 2,2’-azobis(2-methylpropionate) (2a) (46.1 mg, 0.2 mmol) and diisopropyl azodicarboxylate (3a) (40.4 mg, 0.2 mmol). The crude product was purified by flash chromatography (silica gel, 5:1 petroleum ether:EtOAc) to afford 4j (50.0 mg, 58% yield) as yellow sticky. Due to the presence of amide rotamers, the product gives two sets of NMR signals. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.27 (ddd, $J = 8.0, 8.0, 2.0$ Hz, 1H), 7.16 (d, $J = 8.0$ Hz, 1H), 6.90 (ddd, $J = 8.0, 8.0, 2.0$ Hz, 1H), 6.84 (dd, $J = 8.0, 2.0$ Hz, 1H), 6.78-6.31 (m, 1H, -NH), 6.14-5.94 (m, 1H), 4.97 (sept, $J = 6.0$ Hz, 1H), 4.92-4.77 (m, 1H), 3.82 (s, 3H), 3.36-3.13 (m, 3H), 1.32-1.10 (m, 18H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 175.9, 157.0, 155.7, 154.6, 136.3, 134.0, 133.0, 129.9, 124.0, 119.8, 110.1, 70.1, 69.5, 55.5, 51.4, 42.9, 27.2, 21.9, 21.7; HRMS (ESI) calcd for C$_{22}$H$_{33}$N$_2$O$_7$ [M+H]$^+$ 437.2282, found 437.2290.

Diisopropyl 1-[(E)-1-(3-methylphenyl)-4-methoxy-3,3-dimethyl-4-oxobut-1-en-1-yl]-1,2-hydrazinedicarboxylate (4k): The representative procedure was followed using 3-ethynyltoluene (1k) (69.7 mg, 0.6 mmol), dimethyl 2,2’-azobis(2-methylpropionate) (2a) (46.1 mg, 0.2 mmol) and diisopropyl azodicarboxylate (3a) (40.4 mg, 0.2 mmol). The crude product was purified by preparative TLC (silica gel, 2.5:1 petroleum ether:EtOAc) to afford 4k (52.1 mg, 62% yield) as slightly yellow liquid. Due to the presence of amide rotamers, the product gives two sets of NMR signals. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.19 (dd, $J = 7.6, 7.6$ Hz, 1H), 7.10 (d, $J = 7.6$ Hz, 1H), 7.024 (d, $J = 7.6$ Hz, 1H), 7.015 (s, 1H), 6.58-6.17 (m, 1H, -NH),
6.04-5.78 (m, 1H), 4.95 (sept, \( J = 6.4 \) Hz, 2H), 3.23 (br s, 3H), 2.33 (s, 3H), 1.27 (s, 6H), 1.24 (d, \( J = 6.4 \) Hz, 6H), 1.21 (d, \( J = 6.4 \) Hz, 6H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 176.0, 155.6, 154.7, 137.7, 137.3, 135.2, 133.8, 130.1, 129.0, 127.7, 126.5, 70.4, 69.7, 51.4, 42.8, 27.3, 21.9, 21.3; HRMS (ESI) calcd for C\(_{26}\)H\(_{36}\)N\(_2\)O\(_7\) [M+Na\(^+\)] 487.2439, found 487.2445.

Diisopropyl 1-[(\(E\))-4-methoxy-1-(6-methynaphthalen-2-yl)-3,3-dimethyl-4-oxobut-1-en-1-yl]-1,2-hydrazinedicarboxylate (4l): The representative procedure was followed using 2-ethynyl-6-methoxynaphthalene (II) (109.3 mg, 0.6 mmol), dimethyl 2,2'-azobis(2-methylpropionate) (2a) (46.1 mg, 0.2 mmol) and diisopropyl azodicarboxylate (3a) (40.4 mg, 0.2 mmol). The crude product was purified by flash chromatography (sila gel, 4:1 petroleum ether:EtOAc) to afford 4l (54.6 mg, 56% yield) as yellow sticky. Due to the presence of amide rotamers, the product gives two sets of NMR signals. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 7.70 (d, \( J = 8.5 \) Hz, 1H), 7.67 (d, \( J = 8.5 \) Hz, 1H), 7.60 (s, 1H), 7.32 (d, \( J = 8.5 \) Hz, 1H), 7.14 (dd, \( J = 8.5, 2.5 \) Hz, 1H), 7.10 (d, \( J = 2.5 \) Hz, 1H), 6.62-6.23 (m, 1H, -NH), 6.11-5.89 (m, 1H), 5.00-4.88 (m, 2H), 3.92 (s, 3H), 3.25-2.99 (m, 3H), 1.30 (s, 6H), 1.25-1.14 (m, 12H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 176.0, 158.0, 155.6, 154.8, 137.7, 134.2, 133.9, 130.4, 129.6, 128.9, 128.0, 127.3, 126.3, 119.1, 105.6, 70.5, 69.7, 55.2, 51.5, 42.9, 27.4, 21.88, 21.85; HRMS (ESI) calcd for C\(_{26}\)H\(_{38}\)N\(_2\)O\(_7\) [M+H\(^+\)] 487.2439, found 487.2445.

Diisopropyl 1-[(\(E\))-1-(benzo[d][1,3]dioxol-5-yl)-4-methoxy-3,3-dimethyl-4-oxobut-1-en-1-
yl]-1,2-hydrazone dicarboxylate (4m): The representative procedure was followed using 5-ethynylbenzo[1,3]dioxole (1m) (87.7 mg, 0.6 mmol), dimethyl 2,2′-azois(2-methylpropionate) (2a) (46.1 mg, 0.2 mmol) and diisopropyl azodicarboxylate (3a) (40.4 mg, 0.2 mmol). The crude product was purified by flash chromatography (silica gel, 5:1 petroleum ether:EtOAc) to afford 4m (68.8 mg, 77% yield) as yellow sticky. Due to the presence of amide rotamers, the product gives two sets of NMR signals. \(^1\)H NMR (500 MHz, CDCl\(_3\)) δ 6.77-6.66 (m, 3H), 6.55-6.21 (m, 1H, -NH), 5.99-5.80 (m, 1H), 4.99-4.88 (m, 2H), 3.39 (br s, 3H), 1.27 (s, 6H), 1.25-1.19 (m, 12H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) δ 176.1, 155.5, 154.6, 147.5, 147.1, 137.3, 133.8, 129.0, 123.7, 109.8, 107.6, 101.1, 70.5, 69.8, 51.7, 42.7, 27.2, 21.92, 21.87; HRMS (ESI) calcd for C\(_{22}\)H\(_{31}\)N\(_2\)O\(_8\) [M+H]\(^+\) 451.2075, found 451.2082.

Diisopropyl 1-[(E)-4-methoxy-3,3-dimethyl-4-oxo-1-(pyridin-2-yl)but-1-en-1-yl]-1,2-hydrazone dicarboxylate (4n): The representative procedure was followed using 2-ethynylpyridine (1n) (61.9 mg, 0.6 mmol), dimethyl 2,2′-azois(2-methylpropionate) (2a) (46.1 mg, 0.2 mmol) and diisopropyl azodicarboxylate (3a) (40.4 mg, 0.2 mmol). The crude product was purified by flash chromatography (silica gel, 50:1 dichloromethane:methanol) to afford 4n (34.1 mg, 42% yield) as brown sticky. Due to the presence of amide rotamers, the product gives two sets of NMR signals. \(^1\)H NMR (500 MHz, CDCl\(_3\)) δ 8.52 (br s, 1H), 7.65 (dd, J = 8.0, 8.0 Hz, 1H), 7.44 (br s, 1H), 7.19-7.13 (m, 1H), 7.04-6.63 (m, 1H, -NH), 6.12 (s, 1H), 5.08-4.93 (m, 1H), 4.93-4.80 (m, 1H), 3.28 (s, 3H), 1.38 (s, 6H), 1.27 (d, J = 5.5 Hz, 6H), 1.20-1.02 (m, 6H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) δ 176.2, 155.8, 155.0, 154.3, 148.5, 137.7, 136.6, 136.0, 122.8, 122.5, 70.5, 69.9, 51.4, 43.0, 27.4, 22.0, 21.8; HRMS (ESI) calcd for C\(_{20}\)H\(_{30}\)N\(_2\)O\(_6\) [M+H]\(^+\) 408.2129, found 408.2136.
**Diisopropyl 1-[(E)-4-methoxy-3,3-dimethyl-4-oxo-1-(pyridin-3-yl)but-1-en-1-yl]-1,2-hydrazinedicarboxylate (4o):** The representative procedure was followed using 3-ethylpyridine (1o) (61.9 mg, 0.6 mmol), dimethyl 2,2'-azobis(2-methylpropionate) (2a) (46.1 mg, 0.2 mmol) and diisopropyl azodicarboxylate (3a) (40.4 mg, 0.2 mmol). The crude product was purified by flash chromatography (silica gel, 50:1 dichloromethane:methanol) to afford 4o (58.4 mg, 72% yield) as yellow sticky. Due to the presence of amide rotamers, the product gives two sets of NMR signals. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.72-8.36 (m, 2H), 7.66 (s, 1H), 7.33-7.21 (m, 1H), 7.03-6.62 (m, 1H, -NH), 6.08 (br s, 1H), 4.99-4.84 (m, 2H), 3.30 (br s, 3H), 1.27 (s, 6H), 1.25-1.13 (m, 12H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 175.6, 155.6, 154.2, 150.4, 149.2, 137.3, 135.2, 131.5, 122.7, 70.8, 70.0, 51.8, 42.8, 27.4, 21.8; HRMS (ESI) calcd for C$_{20}$H$_{30}$N$_3$O$_6$ [M+H]$^+$ 408.2129, found 408.2130.

**Diisopropyl 1-[(E)-4-methoxy-3,3-dimethyl-4-oxo-1-(thiophen-2-yl)but-1-en-1-yl]-1,2-hydrazinedicarboxylate (4p):** The representative procedure was followed using 2-ethylthiophene (1p) (64.9 mg, 0.6 mmol), dimethyl 2,2'-azobis(2-methylpropionate) (2a) (46.1 mg, 0.2 mmol) and diisopropyl azodicarboxylate (3a) (40.4 mg, 0.2 mmol). The crude product was purified by flash chromatography (silica gel, 500:1 dichloromethane:methanol) to afford 4p (50.5 mg, 62% yield) as slightly brown sticky. Due to the presence of amide rotamers, the product gives two sets of NMR signals. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.33-7.29 (m, 1H), 6.98-6.91 (m, 2H), 6.63-6.26 (m, 1H, -NH), 6.24-5.97 (m, 1H), 4.96 (sept, $J = 6.5$ Hz, 1H), 4.95
(sept, $J = 6.5$ Hz, 1H), 3.37 (br s, 3H), 1.34 (s, 6H), 1.25 (d, $J = 6.5$ Hz, 6H), 1.24 (d, $J = 6.5$ Hz, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 175.9, 155.6, 154.6, 137.8, 136.6, 131.2, 129.3, 126.7, 126.6, 70.7, 69.9, 51.7, 42.9, 27.1, 21.9; HRMS (ESI) calcd for C$_{19}$H$_{29}$N$_2$O$_6$S [M+H]$^+$ 413.1741, found 413.1743.

![Diisopropyl 1-[(E)-4-methoxy-3,3-dimethyl-4-oxo-1-(quinolin-3-yl)but-1-en-1-yl]-1,2-hyrazinedicarboxylate (4q):](image)

Diisopropyl 1-[(E)-4-methoxy-3,3-dimethyl-4-oxo-1-(quinolin-3-yl)but-1-en-1-yl]-1,2-hyrazinedicarboxylate (4q): The representative procedure was followed using 3-ethynylquinoline (1q) (91.9 mg, 0.6 mmol), dimethyl 2,2'-azobis(2-methylpropionate) (2a) (46.1 mg, 0.2 mmol) and diisopropyl azodicarboxylate (3a) (40.4 mg, 0.2 mmol). The crude product was purified by flash chromatography (silica gel, 2:1 petroleum ether:EtOAc) to afford 4q (66.1 mg, 73% yield) as yellow sticky. Due to the presence of amide rotamers, the product gives two sets of NMR signals. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.77 (d, $J = 2.0$ Hz, 1H), 8.13-7.93 (m, 2H), 7.78 (dd, $J = 8.0, 2.0$ Hz, 1H), 7.70 (ddd, $J = 8.0, 8.0, 2.0$ Hz, 1H), 7.54 (ddd, $J = 8.0, 8.0, 2.0$ Hz, 1H), 7.25-6.83 (m, 1H, -NH), 6.31-6.02 (m, 1H), 5.06-4.83 (m, 2H), 3.12 (br s, 3H), 1.30 (s, 6H), 1.27-1.09 (m, 12H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 175.6, 155.7, 154.4, 151.0, 147.1, 136.9, 135.8, 135.1, 129.9, 129.0, 128.6, 128.0, 127.0, 126.9, 70.8, 69.9, 51.7, 42.9, 27.4, 21.9, 21.8; HRMS (ESI) calcd for C$_{24}$H$_{32}$N$_3$O$_6$ [M+H]$^+$ 458.2286, found 458.2288.

![Diisopropyl 1-[(E)-1-(isoquinolin-6-yl)-4-methoxy-3,3-dimethyl-4-oxobut-1-en-1-yl]-1,2-hyrazinedicarboxylate (4r):](image)

Diisopropyl 1-[(E)-1-(isoquinolin-6-yl)-4-methoxy-3,3-dimethyl-4-oxobut-1-en-1-yl]-1,2-hyrazinedicarboxylate (4r): The representative procedure was followed using 6-
ethynylisoquinoline (1r) (91.9 mg, 0.6 mmol), dimethyl 2,2’-azobis(2-methylpropionate) (2a) (46.1 mg, 0.2 mmol) and diisopropyl azodicarboxylate (3a) (40.4 mg, 0.2 mmol). The crude product was purified by flash chromatography (silica gel, 1:1 petroleum ether:EtOAc) to afford 4r (60.2 mg, 66% yield) as yellow sticky. Due to the presence of amide rotamers, the product gives two sets of NMR signals. 1H NMR (400 MHz, CDCl$_3$) δ 9.17 (s, 1H), 8.50 (d, $J = 5.6$ Hz, 1H), 7.89 (d, $J = 8.4$ Hz, 1H), 7.69 (s, 1H), 7.61 (d, $J = 5.6$ Hz, 1H), 7.56 (d, $J = 8.4$ Hz, 1H), 7.01-6.76 (m, 1H, -NH), 6.09 (s, 1H), 5.01-4.83 (m, 2H), 3.09 (br s, 3H), 1.30 (s, 6H), 1.26-1.09 (m, 12H); 13C NMR (100 MHz, CDCl$_3$) δ 175.7, 155.7, 154.5, 152.0, 143.4, 137.6, 137.2, 135.0, 134.5, 128.5, 127.9, 127.6, 127.1, 120.6, 70.7, 69.9, 51.5, 42.9, 27.4, 21.9; HRMS (ESI) calcd for C$_{24}$H$_{32}$N$_3$O$_6$ [M+H]$^+$ 458.2286, found 458.2284.

Diethyl 1-[(E)-4-methoxy-1-(4-methoxyphenyl)-3,3-dimethyl-4-oxobut-1-en-1-yl]-1,2-hydrazinedicarboxylate (4s): The representative procedure was followed using 4-ethynylanisole (1a) (79.2 mg, 0.6 mmol), dimethyl 2,2’-azobis(2-methylpropionate) (2a) (46.1 mg, 0.2 mmol) and diethyl azodicarboxylate (3b) (34.8 mg, 0.2 mmol). The crude product was purified by preparative TLC (silica gel, 2.5:1 petroleum ether:EtOAc, twice) to afford 4s (53.0 mg, 65% yield) as slightly yellow sticky. Due to the presence of amide rotamers, the product gives two sets of NMR signals. 1H NMR (400 MHz, CDCl$_3$) δ 7.17 (d, $J = 8.0$ Hz, 2H), 6.83 (d, $J = 8.0$ Hz, 2H), 6.72-6.32 (m, 1H, -NH), 5.96 (br s, 1H), 4.20-4.13 (m, 4H), 3.80 (s, 3H), 3.29 (br s, 3H), 1.27 (s, 3H), 1.26-1.19 (m, 6H); 13C NMR (100 MHz, CDCl$_3$) δ 176.1, 159.5, 155.9, 155.2, 137.4, 133.8, 130.8, 127.4, 113.2, 62.6, 61.9, 55.1, 51.6, 42.8, 27.3, 14.33, 14.28; HRMS (ESI) calcd for C$_{20}$H$_{29}$N$_2$O$_7$ [M+H]$^+$ 409.1969, found 409.1962.
Di(tert-butyl) 1-[(E)-4-methoxy-1-(4-methoxyphenyl)-3,3-dimethyl-4-oxobut-1-yl]-1,2-hydrazinedicarboxylate (4t): The representative procedure was followed using 4-ethynylanisole (1a) (79.2 mg, 0.6 mmol), dimethyl 2,2’-azobis(2-methylpropionate) (2a) (46.1 mg, 0.2 mmol) and di-tert-butyl azodicarboxylate (3c) (46.1 mg, 0.2 mmol). The crude product was purified by flash chromatography (silica gel, 6:1 petroleum ether:EtOAc) to afford 4t (48.4 mg, 52% yield) as yellow sticky. Due to the presence of amide rotamers, the product gives two sets of NMR signals. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.15 (d, $J$ = 8.0 Hz, 2H), 6.83 (d, $J$ = 8.0 Hz, 2H), 6.44-5.95 (m, 1H, -NH), 5.89 (br s, 1H), 3.80 (s, 3H), 3.29 (br s, 3H), 1.44 (br s, 18H), 1.27 (s, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 176.3, 159.5, 155.0, 153.9, 138.0, 133.0, 130.8, 128.1, 113.1, 81.6, 81.1, 55.2, 51.6, 42.7, 28.2, 28.1, 27.4; HRMS (ESI) calcd for C$_{24}$H$_{37}$N$_2$O$_7$ [M+H]$^+$ 465.2595, found 465.2603.

Dibenzyl 1-[(E)-4-methoxy-1-(4-methoxyphenyl)-3,3-dimethyl-4-oxobut-1-yl]-1,2-hydrazinedicarboxylate (4u): The representative procedure was followed using 4-ethynylanisole (1a) (79.2 mg, 0.6 mmol), dimethyl 2,2’-azobis(2-methylpropionate) (2a) (46.1 mg, 0.2 mmol) and dibenzyl azodicarboxylate (3d) (59.3 mg, 0.2 mmol). The crude product was purified by preparative TLC (silica gel, 2:1 petroleum ether:EtOAc) to afford 4u (50.7 mg, 48% yield) as yellow sticky. Due to the presence of amide rotamers, the product gives two sets of NMR signals. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.37-7.25 (m, 10H), 7.17-7.00 (m, 2H), 6.76 (d, $J$ = 8.0 Hz, 2H), 6.72-6.34 (m, 1H, -NH), 6.09-5.72 (m, 1H), 5.16 (s, 2H), 5.12 (s, 2H), 3.77 (s, 3H).
3H), 3.23 (s, 3H), 1.22 (br s, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 176.0, 159.6, 155.6, 155.0, 137.2, 135.65, 135.60, 134.3, 130.8, 128.5, 128.4, 128.2, 128.1, 128.0, 127.8, 127.0, 113.3, 68.3, 67.6, 55.1, 51.6, 42.7, 27.2; HRMS (ESI) calcd for C$_{30}$H$_{33}$N$_2$O$_7$ [M+H]$^+$ 533.2282, found 533.2288.

Di((2-methoxyethoxy)methyl) 1-[(E)-4-methoxy-1-(4-methoxyphenyl)-3,3-dimethyl-4-oxobut-1-en-1-yl]-1,2-hydrazinedicarboxylate (4v): The representative procedure was followed using 4-ethynylanisole (1a) (79.2 mg, 0.6 mmol), dimethyl 2,2'-azobis(2-methylpropionate) (2a) (46.1 mg, 0.2 mmol) and di-2-methoxyethyl azodicarboxylate (3e) (46.8 mg, 0.2 mmol). The crude product was purified by flash chromatography (silica gel, 150:1 dichloromethane:methanol) to afford 4v (59.5 mg, 64% yield) as yellow sticky. Due to the presence of amide rotamers, the product gives two sets of NMR signals. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.18 (d, $J = 8.5$ Hz, 2H), 6.83 (d, $J = 8.5$ Hz, 2H), 6.81-6.40 (m, 1H, -NH), 5.99 (s, 1H), 4.32-4.21 (m, 4H), 3.80 (s, 3H), 3.60-3.52 (m, 4H), 3.36 (s, 3H), 3.35 (s, 3H), 3.29 (s, 3H), 1.27 (s, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 176.1, 159.6, 155.4, 155.1, 137.1, 134.3, 130.9, 127.2, 113.2, 70.45, 70.36, 65.6, 64.9, 58.9, 58.8, 55.2, 51.6, 42.8, 27.2; HRMS (ESI) calcd for C$_{22}$H$_{33}$N$_2$O$_9$ [M+H]$^+$ 469.2181, found 469.2186.

Diisopropyl 1-[(E)-3-cyano-1-(4-methoxyphenyl)-3-methylbut-1-en-1-yl]-1,2-hydrazinedicarboxylate (4w): The representative procedure was followed using 4-ethynylanisole (1a)
(79.2 mg, 0.6 mmol), 2,2'-azobis(2-methylpropionitrile) (2b) (32.8 mg, 0.2 mmol) and diisopropyl azodicarboxylate (3a) (40.4 mg, 0.2 mmol). The crude product was purified by flash chromatography (silica gel, 4:1 petroleum ether:EtOAc) to afford 4w (61.7 mg, 76% yield) as yellow sticky. Due to the presence of amide rotamers, the product gives two sets of NMR signals. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.31 (d, $J$ = 8.0 Hz, 2H), 6.90 (d, $J$ = 8.0 Hz, 2H), 6.54-6.19 (m, 1H, -NH), 5.84-5.58 (m, 1H), 5.01-4.88 (m, 2H), 3.82 (s, 3H), 1.44 (s, 6H), 1.30-1.17 (m, 12H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 160.3, 155.6, 154.4, 140.2, 131.2, 128.2, 126.3, 123.1, 113.6, 70.8, 70.1, 55.2, 31.1, 29.1, 21.91, 21.88; HRMS (ESI) calcd for C$_{21}$H$_{30}$N$_3$O$_5$ [M+H]$^+$ 404.2180, found 404.2184.

Diisopropyl 1-[(E)-3-cyano-1-(4-methoxyphenyl)-3-methylpent-1-en-1-yl]-1,2-hydrazinedicarboxylate (4x): The representative procedure was followed using 4-ethynylanisole (1a) (79.2 mg, 0.6 mmol), 2,2'-azodi(2-methylbutyronitrile) (2c) (38.5 mg, 0.2 mmol) and diisopropyl azodicarboxylate (3a) (40.4 mg, 0.2 mmol). The crude product was purified by flash chromatography (silica gel, 4:1 petroleum ether:EtOAc) to afford 4x (60.0 mg, 72% yield) as yellow sticky. Due to the presence of amide rotamers, the product gives two sets of NMR signals. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.29 (d, $J$ = 8.0 Hz, 2H), 6.89 (d, $J$ = 8.0 Hz, 2H), 6.60-6.20 (m, 1H, -NH), 5.79-5.46 (m, 1H), 5.00-4.89 (m, 2H), 3.82 (s, 3H), 1.78-1.64 (m, 2H), 1.42 (s, 3H), 1.28-1.18 (m, 12H), 1.07 (t, $J$ = 7.5 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 160.2, 155.5, 154.4, 140.2, 131.2, 128.2, 126.3, 121.9, 113.4, 70.8, 69.9, 55.1, 36.6, 35.2, 26.8, 21.88, 21.85, 9.4; HRMS (ESI) calcd for C$_{22}$H$_{32}$N$_3$O$_5$ [M+H]$^+$ 418.2336, found 418.2334.
Diisopropyl 1-[(E)-3-cyano-1-(4-methoxyphenyl)-3,5-dimethylhex-1-en-1-yl]-1,2-hydrazinedicarboxylate (4y): The representative procedure was followed using 4-ethynylanisole (1a) (79.2 mg, 0.6 mmol), 2,2’-azobis(2,4-dimethyl)valeronitrile (2d) (49.7 mg, 0.2 mmol) and diisopropyl azodicarboxylate (3a) (40.4 mg, 0.2 mmol). The crude product was purified by flash chromatography (silica gel, 5:1 petroleum ether:EtOAc) to afford 4y (42.0 mg, 47% yield) as slightly yellow sticky. Due to the presence of amide rotamers, the product gives two sets of NMR signals. ¹H NMR (500 MHz, CDCl₃) δ 7.29 (d, J = 8.0 Hz, 2H), 6.90 (d, J = 8.0 Hz, 2H), 6.58-6.09 (m, 1H, -NH), 5.85-5.52 (m, 1H), 5.00-4.89 (m, 2H), 3.82 (s, 3H), 1.97-1.87 (m, 1H), 1.67-1.55 (m, 2H), 1.46 (s, 3H), 1.29-1.17 (m, 12H), 1.00 (d, J = 6.0 Hz, 3H), 0.98 (d, J = 6.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 160.3, 155.6, 154.4, 139.4, 131.2, 129.2, 126.3, 122.3, 113.4, 70.1, 55.2, 50.6, 35.2, 28.7, 25.7, 23.9, 23.4, 21.92, 21.89, 21.87; HRMS (ESI) calcd for C₂₄H₃₆N₃O₅ [M+H]⁺ 446.2649, found 446.2643.

Diisopropyl 1-[(E)-2-(1-cyanocyclohexyl)-1-(4-methoxyphenyl)vinyl]-1,2-hydrazinedicarboxylate (4z): The representative procedure was followed using 4-ethynylanisole (1a) (79.2 mg, 0.6 mmol), 1,1’-azobis(cyclohexanecarbonitrile) (2e) (48.9 mg, 0.2 mmol) and diisopropyl azodicarboxylate (3a) (40.4 mg, 0.2 mmol). The crude product was purified by flash chromatography (silica gel, 4:1 petroleum ether:EtOAc) to afford 4z (37.5 mg, 43% yield) as yellow sticky. Due to the presence of amide rotamers, the product gives two sets of NMR signals. ¹H NMR (500 MHz, CDCl₃) δ 7.33 (d, J = 8.0 Hz, 2H), 6.89 (d, J = 8.0 Hz, 2H), 6.51-6.13
(m, 1H, -NH), 5.82-5.53 (m, 1H), 4.94 (sept, J = 6.0 Hz, 2H), 3.82 (s, 3H), 1.93-1.85 (m, 2H), 1.65-1.46 (m, 7H), 1.28-1.18 (m, 13H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 160.2, 155.5, 154.5, 140.6, 131.0, 128.1, 126.8, 121.9, 113.6, 70.8, 70.0, 55.2, 36.8, 36.7, 24.8, 22.1, 21.9; HRMS (ESI) calcd for \(\text{C}_{24}\text{H}_{34}\text{N}_3\text{O}_5\) [M+H]+ 444.2493, found 444.2498.

Diisopropyl 1-(1-methoxy-2-methyl-1-oxopropan-2-yl)-1,2-hydrazone dicarboxylate (SP-1): the title product was purified by flash column chromatography (silica gel, 5:1 petroleum ether:EtOAc) to afford SP-1 as slight yellow liquid. Due to the presence of amide rotamers, the product gives two sets of NMR signals. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 6.52-6.20 (m, 1H, -NH), 5.07-4.84 (m, 2H), 3.72 (s, 3H), 1.68 (br s, 3H), 1.40 (s, 3H), 1.29 (d, \(J = 6.4\) Hz, 3H), 1.27 (d, \(J = 6.4\) Hz, 3H), 1.24 (d, \(J = 6.4\) Hz, 3H), 1.21 (d, \(J = 6.4\) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 174.8, 156.6, 154.9, 70.4, 69.8, 64.1, 52.4, 24.9, 23.7, 21.9, 21.8; HRMS (ESI) calcd for \(\text{C}_{13}\text{H}_{24}\text{N}_2\text{O}_6\text{Na}\) [M+Na]+ 327.1527, found 327.1530.

1,4-bis(4-methoxyphenyl)buta-1,3-diyne (SP-2) the title product was purified by flash column chromatography (silica gel, 40:1 petroleum ether:EtOAc) to afford SP-2 as slight yellow solid. \(^1\)H, \(^{13}\)C NMR spectral data matched those of previously reported.\(^{[4]}\) \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.46 (d, \(J = 8.8\) Hz, 4H), 6.85 (d, \(J = 8.8\) Hz, 4H), 3.82 (s, 6H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 160.2, 134.0, 114.1, 113.9, 81.2, 72.9, 55.3. HRMS (ESI) calcd for \(\text{C}_{18}\text{H}_{15}\text{O}_2\) [M+H]+ 263.1067, found 263.1065.
Substrates that didn’t work:

\[
\begin{align*}
&\text{\[\text{structure 1}\]} \\
&\text{\[\text{structure 2}\]} \\
&\text{\[\text{structure 3}\]} \\
&\text{\[\text{structure 4}\] TMS}
\end{align*}
\]
VI. Synthetic applications

**Erlotinib derivative (4aa):** Following the general procedure of alkylhydrazination of alkynes, Erlotinib (236.1 mg, 0.6 mmol), dimethyl 2,2'-azobis(2-methylpropionate) (2a) (46.1 mg, 0.2 mmol) and diisopropyl azodicarboxylate (3a) (40.4 mg, 0.2 mmol) were used. The crude product was purified by flash chromatography (silica gel, 30:1 dichloromethane:methanol) to afford 4aa (86.1 mg, 61% yield) as white gem. *Due to the presence of amide rotamers, the product gives two sets of NMR signals.*

\[
\begin{align*}
\text{H NMR (400 MHz, CDCl}_3\text{)} & \delta 8.50 (s, 1H), 8.12 (s, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.61 (s, 1H), 7.52-7.41 (m, 1H, \text{-NHCO}), 7.37 (s, 1H), 7.27 (dd, J = 8.0, 8.0 Hz, 1H), 7.16 (s, 1H), 6.98 (d, J = 8.0 Hz, 1H), 6.10-5.86 (m, 1H), 5.03-4.81 (m, 2H), 4.31-4.10 (m, 4H), 3.89-3.67 (m, 4H), 3.41 (s, 3H), 3.40 (s, 3H), 3.29 (br s, 3H), 1.30 (s, 6H), 1.28-1.11 (m, 12H); \\
\text{13C NMR (100 MHz, CDCl}_3\text{)} & \delta 176.2, 156.3, 155.7, 154.9, 154.1, 153.3, 148.5, 147.2, 138.7, 137.4, 135.9, 133.9, 128.1, 125.0, 122.5, 121.7, 109.2, 108.5, 102.8, 70.7, 70.5, 70.3, 69.6, 68.8, 68.1, 59.0, 51.6, 42.9, 27.1, 21.8; \\
\text{HRMS (ESI) calcd for C}_{35}H_{47}N_{5}O_{10}Na [M+Na]^+ & \text{720.3215, found 720.3234.}
\end{align*}
\]

**Methyl 4-(4-methoxyphenyl)-2,2-dimethyl-4-oxobutyrate (5).** 4a (87.3 mg, 0.2 mmol) dissolved in MeOH (1.0 mL) was added 40% aqueous solution of HBr (2.0 mL). The mixture was stirred at room temperature for 10 min. The reaction was quenched by addition of saturated aqueous NaHCO₃ (20 mL) at 0 °C. After quenching the reaction, the mixture was allowed to warm to room temperature and was extracted with EtOAc (10 mL×3). The organic layer was
dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated. The crude material was purified by flash chromatography (silica gel, 6:1 petroleum ether:EtOAc) to afford the desired compound 5 (49.1 mg, 98% yield) as colorless liquid. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.92 (d, $J = 8.5$ Hz, 2H), 6.92 (d, $J = 8.5$ Hz, 2H), 3.86 (s, 3H), 3.68 (s, 3H), 3.25 (s, 2H), 1.31 (s, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 196.1, 177.9, 163.4, 130.1, 130.0, 113.6, 55.4, 51.8, 48.2, 40.0, 25.7; HRMS (ESI) calcd for C$_{14}$H$_{19}$O$_4$ [M+H]$^+$ 251.1278, found 251.1280.

(E)-4-[1,2-bis(isopropoxycarbonyl)hydrazinyl]-4-(4-methoxyphenyl)-2,2-dimethylbut-3-enoic acid (6): To the solution of 4a (87.3 mg, 0.2 mmol) in THF (2.0 mL) was added aqueous lithium hydroxide (1 M, 0.5 mL). The mixture was stirred at room temperature for 20 minutes and then stirred at 70 °C for 9 hours. After cooled to room temperature, the mixture was acidified to pH 1 with 10% HCl. Ethyl acetate (10 mL) was added to dilute the solution. The organic layer was separated and the aqueous layer was extracted with EtOAc (10 mL × 3). The organic layer was dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated. The crude material was purified by flash chromatography (silica gel, gradient from 50:1 to 10:1 dichloromethane:methanol) to afford the corresponding compound as colorless sticky (81.1 mg, 96% yield). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.25-7.13 (m, 2H), 6.82-6.60 (m, 3H), 6.02-5.83 (m, 1H), 5.00-4.83 (m, 2H), 3.77 (s, 3H), 1.34-1.11 (m, 18H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 181.3, 159.7, 155.5, 154.8, 138.1, 132.6, 131.2, 127.4, 113.1, 70.5, 69.8, 55.1, 42.7, 26.8, 21.91, 21.88; HRMS (ESI) calcd for C$_{21}$H$_{31}$N$_2$O$_7$ [M+H]$^+$ 423.2126, found 423.2123.
To a solution of the 4 (0.2 mmol, 1 equiv.) in dry THF (1.0 mL) was added DIBAL-H (1.0 mL, 1.0 M in hexanes, 5.0 equiv.) over 5 min at -78 °C. The reaction mixture was stirred at -78 °C for 1 h, then slowly warmed to room temperature overnight and quenched with saturated NH₄Cl (5 mL). The precipitate was filtered off and washed with EtOAc (10 mL). The filtrate was dried over Na₂SO₄, filtered, and concentrated. The crude material was purified by flash chromatography (silica gel, 100:1 dichloromethane:methanol) to afford the corresponding primary alcohol 7.

**Diisopropyl 1-[(E)-4-hydroxy-1-(4-methoxyphenyl)-3,3-dimethylbut-1-en-1-yl]-1,2-hydrazinedicarboxylate (7a):** colorless sticky (32.1 mg, 41% yield); ¹H NMR (400 MHz, CDCl₃) δ 7.20 (d, J = 8.0 Hz, 2H), 6.84 (d, J = 8.0 Hz, 2H), 6.44-6.08 (m, 1H, -NH), 5.90-5.65 (m, 1H), 5.00 (sept, J = 6.4 Hz, 1H), 4.91 (sept, J = 6.4 Hz, 1H), 3.81 (s, 3H), 3.26 (s, 2H), 1.27 (d, J = 6.4 Hz, 6H), 1.21 (d, J = 6.4 Hz, 6H), 0.89 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 159.7, 155.4, 155.2, 137.4, 136.9, 131.4, 127.9, 113.2, 72.7, 70.8, 69.7, 55.2, 38.7, 25.2, 22.1, 22.0, 21.9; HRMS (ESI) calcd for C₂₁H₂₂N₂O₆Na [M+Na]⁺ 431.2153, found 431.2153.
Diisopropyl 1-[(E)-4-hydroxy-1-(chlorophenylphenyl)-3,3-dimethylbut-1-en-1-yl]-1,2-hydrazinedicarboxylate (7b): colorless sticky (72.3 mg, 88% yield); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.32-7.22 (m, 4H), 6.64-6.37 (m, 1H), 5.96-5.71 (m, 1H), 5.04-4.81 (m, 2H), 3.27 (s, 2H), 1.25 (d, $J$ = 6.4 Hz, 6H), 1.23-1.14 (m, 6H), 0.87 (s, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 155.4, 155.0, 137.3, 136.6, 134.4, 134.3, 131.6, 127.9, 72.6, 70.9, 69.8, 38.6, 25.0, 21.9, 21.8; HRMS (ESI) calcd for C$_{20}$H$_{29}$ClN$_2$O$_5$Na $[M+Na]^+$ 435.1657, found 435.1658.

\[
\begin{align*}
\text{MeO-} & \quad \text{N} \quad \text{N} \quad \text{COOPr} \\
\text{PrOOC-} & \quad \text{rt} \quad \text{BnBr} \\
\text{COOMe} & \quad \text{MeCN} \\
\text{MeO-} & \quad \text{N} \quad \text{N} \quad \text{COOPr} \\
\text{Bn} & \quad \text{8}
\end{align*}
\]

Diisopropyl (E)-1-benzyl-2-[4-methoxy-1-(4-methoxyphenyl)-3,3-dimethyl-4-oxobut-1-en-1-yl]-1,2-hydrazinedicarboxylate (8): To a solution of 4a (87.3 mg, 0.2 mmol, 1.0 equiv.) in MeCN (2.0 mL) were added cesium carbonate (162.9 mg, 0.5 mmol, 2.5 equiv.) and benzyl bromide (68.4 mg, 0.4 mmol, 2.0 equiv.). The reaction mixture was stirred for 12 h at room temperature. The reaction was diluted with water (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic phases were washed with brine (3 × 10 mL), dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography (silica gel, 4:1 petroleum ether:EtOAc) to afford 8 (103.0 mg, 98% yield) as colorless sticky. *Tetrasubstituted hydrazines were reported and explained by the existence of up to four conformations, which have complicated $^1$H and $^{13}$C spectra.*$^{[5]}$ $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.39-7.22 (m, 5H), 7.11-6.89 (m, 2H), 6.79-6.63 (m, 2H), 5.67-5.44 (m, 1H), 4.92-4.41 (m, 4H), 3.83-3.72 (m, 3H), 3.39-3.19 (m, 3H), 1.36-0.88 (m, 18H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 176.1, 159.44, 159.39, 155.9, 154.1, 153.9, 137.0, 136.7, 136.2, 133.9, 131.3, 129.4, 128.8, 128.11, 128.07, 127.4, 127.3, 127.1, 112.9, 112.6, 70.2, 69.98, 69.93, 55.12, 55.09, 53.3, 51.6, 51.5, 42.7, 42.1, 27.5, 27.0, 22.0, 21.8, 21.5; HRMS (ESI) calcd for C$_{29}$H$_{38}$N$_2$O$_7$Na [M+Na]$^+$ 549.2571, found 549.2576.
Diisopropyl 1-[(E)-4-methoxy-1-(4-methoxyphenyl)-3,3-dimethyl-4-oxobut-1-en-1-yl]-2-[(E)-oct-1-en-1-yl]-1,2-hydrazinedicarboxylate (9): To an oven-dried resealable screw-cap test tube, CuI (2.9 mg, 0.015 mmol, 10 mol%), 1,10-phenanthroline (5.4 mg, 0.03 mmol, 20 mol%), 4a (68.7 mg, 0.16 mmol, 1.05 equiv.) and Cs₂CO₃ (48.9 mg, 0.15 mmol) were added. The tube was evacuated and backfilled with argon. The (E)-1-iodo-1-octene (35.7 mg, 0.15 mmol, 1.0 equiv.) and anhydrous DMF (0.8 mL) were added via syringe. The tube was sealed and stirred at 80 °C for 48 h. The reaction mixture was cooled to room temperature, diluted with water (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic phases were washed with brine (3 × 10 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography (silica gel, 6:1 petroleum ether:EtOAc) to afford 9 (47.0 mg, 57% yield) as slightly yellow sticky. Tetrasubstituted hydrazines were reported and explained by the existence of up to four conformations, which have complicated ¹H and ¹³C spectra.[⁵] ¹H NMR (400 MHz, CDCl₃) δ 7.25-7.08 (m, 2H), 6.87-6.74 (m, 2H), 6.70-6.44 (m, 1H), 6.06-5.50 (m, 1H), 5.03-4.79 (m, 3H), 3.85-3.72 (m, 3H), 3.42-3.32 (m, 3H), 2.08-1.88 (m, 2H), 1.36-1.07 (m, 26H), 0.95-0.81 (m, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 176.4, 176.2, 159.52, 159.48, 153.1, 152.8, 151.7, 136.9, 136.1, 131.7, 131.5, 126.3, 125.0, 124.6, 112.8, 112.6, 111.1, 110.6, 70.7, 70.4, 70.1, 55.1, 51.65, 51.6, 42.7, 31.7, 30.2, 30.1, 29.5, 29.4, 28.7, 28.6, 27.5, 27.40, 27.37, 22.6, 21.98, 21.89, 21.81, 21.77, 21.67, 14.1; HRMS (ESI) calcd for C₃₀H₄₆N₂O₇Na [M+Na]⁺ 569.3197, found 569.3198.
Diisopropyl 1-[(Z)-1-(4-chlorophenyl)-4-methoxy-3,3-dimethyl-4-oxobut-1-en-1-yl]-1,2-hydratizedicarboxylate (4c-Z): To an oven-dried resealable screw-cap test tube, 4c-E (88.2 mg, 0.2 mmol, 1 equiv.), dry toluene (2.0 mL), trifluoroacetic acid (68.4 mg, 0.6 mmol, 3.0 equiv.) was added. The reaction mixutre was stirred at 60 °C for 24 h. The reaction mixture was cooled to room temperature, then quenched with saturated NaHCO₃ (3 mL) and washed with EtOAc (3 × 10 mL). The combined organic phases were washed with brine (3 × 10 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography (silica gel, 8:1 petroleum ether:EtOAc) to afford 4c-Z as colorless sticky (43.8 mg, 50% yield); Due to the presence of amide rotamers, the product gives two sets of NMR signals. ¹H NMR (400 MHz, CDCl₃) δ 7.82-7.40 (m, 2H), 7.32-7.21 (m, 2H), 7.02-6.55 (m, 1H, -NH, deuterium exchange), 5.71-5.51 (m, 1H), 5.01-4.76 (m, 2H), 3.79-3.62 (m, 3H), 1.43 (s, 6H), 1.35-0.92 (m, 12H); ¹³C NMR (100 MHz, CDCl₃) δ 178.0, 177.7, 155.3, 154.9, 154.0, 153.7, 138.4, 136.7, 135.7, 134.1, 133.9, 132.6, 128.9, 128.1, 128.0, 71.0, 70.8, 69.8, 69.6, 52.8, 52.6, 43.5, 26.5, 26.4, 21.9, 21.6; HRMS (ESI) calcd for C₂₁H₂₅ClN₂O₆Na [M+Na]⁺ 463.1606, found 463.1610.

Analysis of stereochemistry of 4c-Z and 4c-E

The E-configuration of 4c was confirmed through X-ray analysis. Examples in scheme 3 and scheme 4 also show similar NMR signals to 4c-E. (especially the signal of olefin hydrogen) So the configuration of these compounds were assigned as E-configuration. For Z-isomer, the chemical shifts of OMe (about 0.4 ppm shifts to the low fields), alkyl hydrogen, olefin hydrogen and aryl hydrogen varied. The NOESY experiments of 4c-Z and 4c-E were conducted to further check the configurations of the double bonds. For 4c-Z, NOE effect between olefin hydrogen and aryl hydrogen was observed. Meanwhile, no NOE effect was detected between methyl hydrogen and aryl hydrogen. For 4c-E, the results are contrast to 4c-Z. The following crude spectrum showed the stereoselectivity of the reaction.
NOESY of 4c-Z and 4c-E

4c-Z

4c-E

No NOE between H_a/H_b

No NOE between H_c/H_b
A comparison of $^1\text{H}$ NMR between 4c-Z and 4c-\textit{E}.

Crude $^1\text{H}$ NMR spectrum of standard conditions.
VII. Mechanistic study

7.1 Radical inhibiting experiments

In an oven-dried resealable screw-cap test tube, CuBr (5.7 mg, 0.04 mmol, 20 mol%), alkyne \(1a\) (79.2 mg, 0.6 mmol, 3.0 equiv.), dimethyl 2,2’-azobis(2-methylpropionate) \(2a\) (0.2 mmol, 1.0 equiv.), DIAD \(3a\) (0.2 mmol, 1.0 equiv.) and 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO, 62.5 mg, 0.40 mmol, 2.0 equiv.) were mixed in anhydrous MeCN (2.5 mL) under Ar atmosphere. The reaction mixture was stirred at 80 °C oil bath for 8 h. The residue was detected on High Resolution Mass (MS) analysis. The reaction was totally inhibited, and \(10\) was detected by the HRMS.

HRMS (ESI) [M+H]⁺ 258.2054, found 258.2054.
7.2 Possible intermediates

Preparation of starting material:

Methyl (E)-4-(4-methoxyphenyl)-2,2-dimethylbut-3-enoate (11). The title compound was prepared according to the previous reported protocols\cite{6}, and the $^1$H NMR spectral data matched those of previously reported.

Diisopropyl 1-[1-(4-methoxyphenyl)vinyl]-1,2-hydrazinedicarboxylate (12). The title compound was prepared according to previous reported literature with 4-methoxyacetophenone as starting material.\cite{7} To a solution of 4-methoxyacetophenone (1.50 g, 10.0 mmol) and DIAD (2.42 g, 12.0 mmol) in anhydrous THF (15 mL) was added dropwise PPh$_3$ (3.14 g, 12.0 mmol) in anhydrous THF (15 mL) at 0 °C under argon atmosphere. The solution was stirred at room temperature for 12 h. When the reaction was complete, the solution was concentrated and dissolved in petroleum ether/ EtOAc (3:1) until white solid precipitated, then the mixture was
filtered and the filtrate was concentrated. The crude material was purified by flash column chromatography (silica gel, 6:1 petroleum ether:EtOAc) to afford 12 as slightly yellow sticky.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.43 (d, $J$ = 8.5 Hz, 2H), 6.96-6.67 (m, 3H), 5.28 (s, 1H), 5.25 (s, 1H), 5.06-4.94 (m, 1H), 4.89 (sept, $J$ = 6.0 Hz, 1H), 3.81 (s, 3H), 1.32-1.22 (m, 6H), 1.19-1.05 (m, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 159.7, 155.7, 154.6, 146.6, 129.8, 127.4, 113.6, 108.1, 70.7, 69.9, 55.3, 21.9, 21.7; HRMS (ESI) calcd for C$_{17}$H$_{25}$N$_2$O$_5$ [M+H]$^+$ 337.1758, found 337.1763.

Procedure:

eq b: In an oven-dried resealable screw-cap test tube, CuBr (2.8 mg, 0.02 mmol, 20 mol%), 11 (24.3 mg, 0.1 mmol, 1.0 equiv.) and 3a (20.2 mg, 0.1 mmol, 1.0 equiv.) were mixed in anhydrous MeCN (1.3 mL) under argon atmosphere. The reaction mixture was stirred at 80 °C oil path for 8 h. No desired product was detected.

eq c: In an oven-dried resealable screw-cap test tube, CuBr (5.7 mg, 0.04 mmol, 20 mol%), 12 (67.3 mg, 0.2 mmol, 1.0 equiv.) and 2a (46.1 mg, 0.2 mmol, 1.0 equiv.) were mixed in anhydrous MeCN (2.5 mL) under argon atmosphere. The reaction mixture was stirred at 80 °C oil path for 8 h. After cooled to room temperature, internal standard $p$-nitroacetophenone (33.0 mg, 0.2 mmol) was added for $^1$H NMR experiment, a 16% yield of 4a was detected. Product was also isolated for checking the stereochemistry of new formed C-C double bond.

In an oven-dried resealable screw-cap test tube, CuBr (5.7 mg, 0.04 mmol, 20 mol%), alkyne 1a (79.2 mg, 0.6 mmol, 3.0 equiv.), dimethyl 2,2’-azobis(2-methylpropionate) 2a (46.1 mg, 0.2 mmol, 1.0 equiv.) and 3f (46.5 mg, 0.2 mmol, 1.0 equiv.) were mixed in anhydrous MeCN (2.5 mL) under argon atmosphere. The reaction mixture was stirred at 80 °C oil path for 8 h. A messy TLC profile was observed and 4t was not detected by $^1$H NMR.
In an oven-dried resealable screw-cap test tube, commercially available \(13\) (98.8 mg, 0.6 mmol, 3.0 equiv.), dimethyl 2,2’-azobis(2-methylpropionate) \(2a\) (46.1 mg, 0.2 mmol, 1.0 equiv.) and \(3a\) (40.4 mg, 0.2 mmol, 1.0 equiv.) were mixed in anhydrous MeCN (2.5 mL) under argon atmosphere. The reaction mixture was stirred at 80 °C oil bath for 8 h. \(4e\) was not detected by TLC and \(^1\)H NMR.

**VIII. References**


IX. Copies of NMR spectra
NOESY

Parameter Value
1 Data File Name
D:/chemistry/research/my research/my group/NMR/Jul04-2019-1J-4.33-B1/2.ser
2 Title Jul04-2019-1J-4.33-B1/2
3 Comment
4 Origin Bruker BioSpin GmbH
5 Owner nmrsau
6 Site
7 Spectrometer spect
8 Author
9 Solvent CDCl3
10 Temperature 295.1
11 Pulse Sequence n0esyphpr
12 Experiment NOESY
13 Probe 5 mm PABBO BB/19F-1H/D Z-GRD 2119470/0166
14 Number of Scans 16
15 Receiver Gain 105
16 Relaxation Delay 2.0000
17 Pulse Width 12.7500
18 Pre-saturation Frequency
19 Acquisition Time 0.1862
20 Acquisition Date 2019-07-04T23:54:26
21 Modification Date 2019-07-05T02:36:43
22 Class
23 Spectrometer Frequency