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Synthesis of Heterocycles by $HNTf_2$-Catalyzed C–H Functionalization of Vinyldiazo Compounds with 3-Phenyl-3-hydroxyisoindolinone

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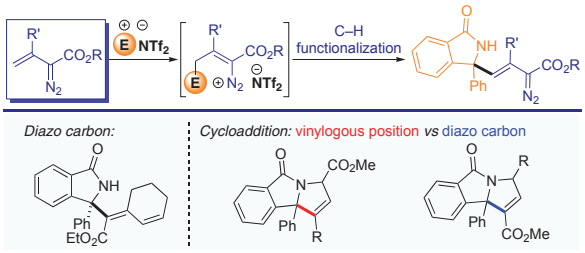

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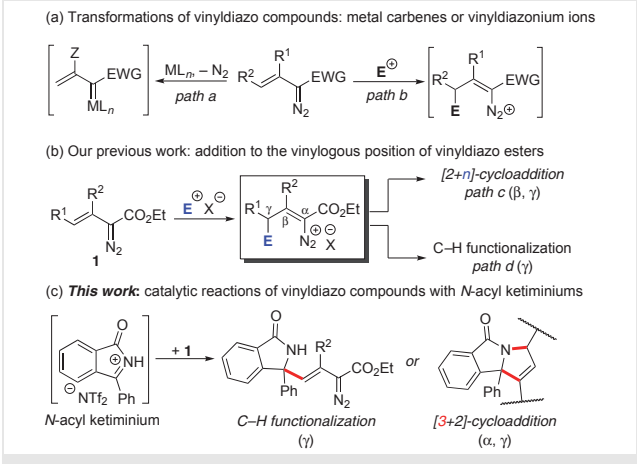
Abstract A Brønsted acid catalyzed C–H functionalization of vinyldiazoacetates with 3-hydroxyisoindolinone is developed. This methodology provides a general access to *E*-substituted isoindolinone vinyldiazo compounds in good yields and excellent diastereoselectivities with broad substrate generality under mild conditions, and with 4-substituted 2-diazo-3-butenoates produces fused bicyclic pyrrolidines. The reaction generally involves addition of the *N*-acyl ketiminium electrophile, formed from the 3-hydroxyisoindolinone, to the vinylogous position of the vinyldiazo compound resulting in vinyldiazonium ion intermediates that undergo deprotonation to new vinyldiazo compounds or ring closure to fused bicyclic pyrrolidines.

Key words Brønsted acid catalysis, vinyldiazo compound, electrophilic addition, C–H functionalization, heterocycles

Vinyldiazo compounds are easily accessible, versatile and useful reagents for the construction of complex molecular frameworks through a variety of metal carbene transformations (Scheme 1a, path a), including C–H insertion,[1] C–C bond formation,[2] and cycloaddition.[3] Meanwhile, their dipolar nature makes them susceptible to addition by different electrophilic reagents at the vinylogous position rather than the diazo carbon, affording diazonium ion intermediates that undergo substitution or migration reactions (Scheme 1a, path b).[4] Recently, we reported the $HNTf_2$-catalyzed electrophilic addition of quinone oxonium ions from quinone ketals[5] and quinone imine ketals,[6] and isobenzopyrylium ions from 1*H*-isochromene acetals[7] to the vinylogous carbon of vinyldiazo compounds **1** to form vinyldiazonium ion intermediates that result in the synthesis of substituted α-diazo esters and polycyclic compounds (Scheme 1b, path c). Using the stable Eschenmoser salt as the electrophile, an alternative C–H functionalization occurs at the γ-position of vinyl diazo compounds to form γ-substituted vinyldiazo esters (Scheme 1b, path d).[5] Inspired by these advances, we envisioned that a C–H functionalization process of vinyldiazoacetates with in situ generated *N*-acyl ketiminium electrophiles, which is well-known in nucleophilic substitution reactions,[8] might be facilitated by $HNTf_2$ catalysis to synthesize structurally complex diazo compounds with a quaternary carbon center. Herein, we report that highly selective C–H functionalization of vinyldiazo acetates with 3-phenyl-3-hydroxyisoindolinone provides a general methodology for the synthesis of γ-isoindolin-1-one-substituted vinyldiazo esters. In addition, in the case of 4-substituted 2-diazo-3-butenoates, a catalytic stepwise [3+2]-cycloaddition reaction occurred with the *N*-acyl ketiminium electrophile for the construction of fused bicyclic pyrrolidines (Scheme 1c).



Scheme 1 Catalytic transformations of vinyldiazo compounds

Effective construction of γ-substituted vinyldiazoacetate **3a** was realized via the $HNTf_2$-catalyzed C–H functionalization of ethyl 2-diazo-3-phenylbut-3-enoate (**1a**) with

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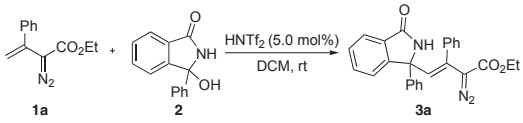
3-phenyl-3-hydroxyisoindolinone (**2**) in dichloromethane (DCM) at room temperature (Table 1, entry 1). Surprisingly, only 5 mol% of the very strong acid triflimide[9] was required for complete reaction to occur within 5 hours. A series of control experiments verified the necessity of each reaction component. Other Brønsted acid catalysts were tested, but the outcome was either a low yield or no C–H functionalization product **3a** (Table 1, entries 2–4). Furthermore, attempts to optimize the yield of **3a** by varying the solvent and increasing the amount of catalyst were unsuccessful (Table 1, entries 5 and 6). In addition, the yield of **3a** was significantly reduced when the reaction was performed at 0 °C because some vinyldiazo compound **1a** remained unreacted over the same reaction time (Table 1, entry 7).

Table 1 Optimization of the C–H Functionalization Reaction Conditions[a]

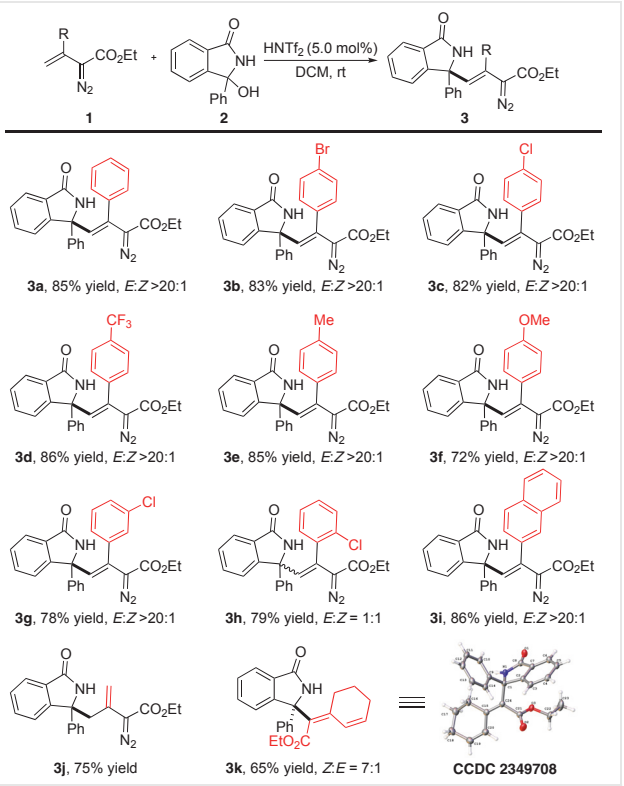


1a 2 3a

Entry	Variation from the standard conditions	Yield (%)[b]
1	none	85
2	TfOH instead of $HNTf_2$	32
3	CF_3CO_2H instead of $HNTf_2$	NR
4[c]	chiral phosphoric acid (10 mol%) instead of $HNTf_2$	<10
5	$CHCl_3$ instead of DCM	84
6	$HNTf_2$ (10 mol%)	81
7	0 °C instead of rt	75

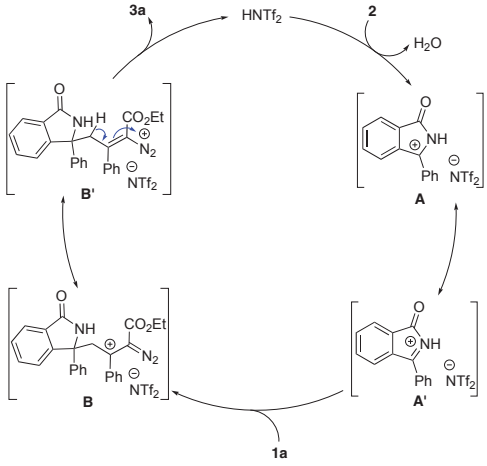
[a] Unless otherwise noted, reactions were carried out on a 0.1 mmol scale. To vinyldiazo compound **1a** (21.6 mg, 0.1 mmol), 3-phenyl-3-hydroxyisoindolinone (**2**) (35.6 mg, 0.2 mmol, 2.0 equiv.), and 4 Å MS (50 mg) in anhydrous DCM (1.0 mL) was added a solution of $HNTf_2$ (5.0 mol%) in anhydrous DCM (1.0 mL) via a syringe pump over 1 h at room temperature (rt).
[b] Isolated yields of **3a**. NR = no reaction.
[c] Chiral phosphoric acid = (11b*R*)-2,6-bis(triphenylsilyl)-4-hydroxy-4-oxide-dinaphtho[2,1-*d*:1′,2′-*f*][1,3,2]dioxaphosphepin.

With the optimal reaction conditions established, the substrate scope with respect to the vinyldiazoacetates was investigated (Scheme 2). Vinyldiazoacetates with various electron-withdrawing or electron-donating substituents on the aryl ring at the *para*- or *meta*-position and naphthyl all reacted with 3-phenyl-3-hydroxyisoindolinone smoothly to form the *E*-substituted vinyldiazo products (**3a–g** and **3i**) in high yields and stereoselectivities (>72% yield, *E*:*Z* >20:1). However, the *ortho*-chlorophenyl-substituted vinyldiazo compound gave the desired product **3h** in 79% yield but with a 1:1 *E*:*Z* ratio. Notably, for the β-methyl-substituted vinyldiazo compound **1j**, the addition/elimination product **3j** was isolated in 75% yield. Also significant, the nucleophilic substitution reaction occurred at the diazo carbon with 1-cyclohexenyldiazoacetate **1k** to form product **3k** in 65% yield, the structure of which was confirmed by single-crystal X-ray diffraction analysis.



Scheme 2 Catalytic C–H functionalization of vinyldiazoacetates with 3-phenyl-3-hydroxyisoindolinone. *Reaction conditions*: vinyldiazo compound **1** (0.1 mmol), 3-phenyl-3-hydroxyisoindolinone (**2**) (0.2 mmol, 2.0 equiv.), and 4 Å MS (50 mg) in anhydrous DCM (1.0 mL) were treated with a solution of $HNTf_2$ (0.9 mg, 5 mol%) in anhydrous DCM (1.0 mL) using a syringe pump over 1 h at room temperature. Isolated yields are given.

Based on the experimental data and previous reports,[5,8,10] a probable mechanism for electrophile-induced transformations of these vinyldiazo compounds is proposed in Scheme 3. Initially, the dehydration of 3-phenyl-3-hydroxyisoindolinone (**2**) in the presence of $HNTf_2$ affords the corresponding *N*-acyl ketiminium ion **A**/**A′**. Subsequently, selective addition of this species onto the vinylogous position of vinyldiazo compound **1a** gives the vinyldiazonium ion intermediate **B**/**B′**, followed by deprotonation to deliver the formal C–H functionalization product **3a**.

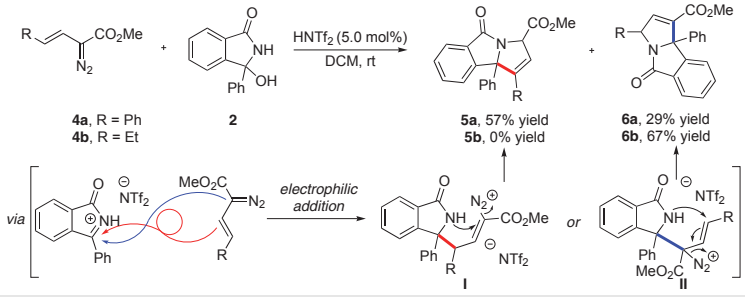


Scheme 3 Proposed reaction mechanism for the electrophilic C–H functionalization of vinyldiazoacetates with 3-phenyl-3-hydroxyisoindolinone

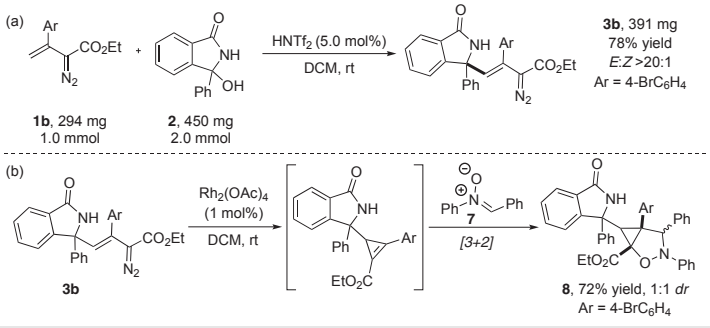
To our surprise, the reaction of styryldiazoacetate **4a** with **2** catalyzed by triflimide at room temperature gave cyclization products **5a** and **6a**, via presumed intermediates **I** and **II**, in 57% and 29% yields, respectively (see Figure S1 in the Supporting Information). However, only product **6b** from electrophilic addition to the diazo carbon of 4-substituted 2-diazo-3-butenoate **4b** was obtained in 67% yield without evidence of the product **6a** from the corresponding addition to the vinylogous position (Scheme 4). These reactions contrast with those of dirhodium(II)-catalyzed [3+2]-cycloaddition transformations with indole.[11]

To demonstrate the scalability and the practicality of the current method, a 1.0 mmol scale reaction was carried out from which 391 mg of **3b** were isolated (0.78 mmol, 78% yield, *E*:*Z* >20:1) (Scheme 5a). A further transformation of product **3b** was performed. $Rh_2(OAc)_4$-catalyzed [3+2]-cycloaddition occurred with nitrone **7** via the cyclopropene intermediate formed from **3b** by catalytic dinitrogen extrusion.[12] Isoxazolidine **8** was formed under these mild conditions in 72% yield with 1:1 *dr* (Scheme 5b).

In summary, we have developed a Brønsted acid catalyzed C–H functionalization of vinyldiazoacetates that provides a general access for the synthesis of γ-isoindolin-1-one-substituted vinyldiazo compounds in good yields, excellent diastereocontrol, and with broad substrate generality under mild reaction conditions. The reaction is initiated by electrophilic addition of the in situ generated *N*-acyl ketiminium species to the vinylogous position of the vinyldiazo compound to afford a vinyldiazonium ion intermediate, followed by deprotonation. Notably, polycyclic compounds are obtained by formal [3+2]-cycloaddition of γ-substituted vinyldiazoacetates with 3-phenyl-3-hydroxyisoindolinone.



Scheme 4 Catalytic C–H functionalization of styryldiazoacetate **4a** and 4-substituted 2-diazo-3-butenoate **4b**



Scheme 5 Scaled synthesis of vinyldiazoacetate **3b** and a subsequent cycloaddition reaction

Unless otherwise noted, all reactions were performed in oven-dried (120 °C) glassware under a N_2 atmosphere. Solvents were dried using a JC Meyer solvent purification system. Analytical thin-layer chromatography was performed using glass plates pre-coated with 200–300 mesh silica gel impregnated with a fluorescent indicator (254 nm). Column chromatography was performed on CombiFlash® Rf200 and Rf+ purification systems using normal phase silica gel columns (300–400 mesh). High-resolution mass spectrometry (HRMS) was performed on a Bruker MicroTOF-ESI mass spectrometer with an ESI resource using CsI or an LTQ ESI positive ion calibration solution as the standard. Accurate masses are reported for the molecular ions $[M + H]^+$ or $[M + Na]^+$. Melting points were obtained uncorrected from an Electro Thermo Mel-Temp DLX 104 device. ^{1}H NMR spectra were recorded on a Bruker spectrometer (500 MHz and 300 MHz). Chemical shifts are reported in ppm downfield from tetramethylsilane (TMS) with the solvent resonance as the internal standard ($CDCl_3$, δ = 7.26). Spectra are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, comp = composite of magnetically non-equivalent protons), coupling constant(s) (Hz), and integration. ^{13}C NMR spectra were collected on Bruker instruments (125 MHz and 75 MHz) with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$, δ = 77.16). Enantioselectivities were determined by HPLC analysis at 25 °C using an Agilent 1260 Infinity HPLC system equipped with a G1311B quaternary pump, a G1315D diode array detector, a G1329B auto-sampler, a G1316A thermostatted column compartment and a G1170A valve drive. For instrument control and data processing, Agilent OpenLAB CDS ChemStation Edition for LC & LC/MS Systems (Rev. C.01.07 [26]) software was used. Chiralpak OD-H or (*R*,*R*-Whelk-O1) columns were employed.

C–H Functionalization of Vinyldiazo Compounds; General Procedure

To a 10 mL oven-dried vial containing a magnetic stir bar, vinyldiazo compound **1** (0.1 mmol), 3-phenyl-3-hydroxyisoindolinone (**2**) (0.2 mmol, 2.0 equiv.), and 4 Å MS (50 mg) in anhydrous DCM (1.0 mL) was added a solution of $HNTf_2$ (0.9 mg, 5 mol%) in anhydrous DCM (1.0 mL) via a syringe pump over 1 h at room temperature. When the reaction was complete (monitored by TLC), the crude reaction mixture was purified by flash column chromatography on silica gel without additional treatment (hexanes/EtOAc = 10:1) to give the C–H functionalization product **3**.

Ethyl (*E*)-2-Diazo-4-(3-oxo-1-phenylisoindolin-1-yl)-3-phenylbut-3-enoate (3a)

Yellow oil; yield: 36.0 mg (85%); *E*:*Z* >20:1.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 7.5 Hz, 1 H), 7.47 (t, *J* = 7.5 Hz, 1 H), 7.41–7.33 (comp, 4 H), 7.30–7.23 (comp, 7 H), 6.92 (d, *J* = 7.5 Hz, 1 H), 5.66 (s, 1 H), 4.28 (q, *J* = 7.1 Hz, 2 H), 1.28 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.3, 165.1, 152.3, 144.1, 135.1, 132.8, 129.4, 129.2, 129.03, 128.95, 128.7, 128.4, 128.2, 127.9, 126.5, 125.9, 124.0, 122.9, 67.2, 61.2, 14.6.

HRMS (ESI Q-TOF): *m*/*z* $[M + H]^+$ calcd for $C_{26}H_{22}N_3O_3$: 424.1656; found: 424.1658.

Ethyl (*E*)-3-(4-Bromophenyl)-2-diazo-4-(3-oxo-1-phenylisoindolin-1-yl)but-3-enoate (3b)

Yellow oil; yield: 41.6 mg (83%); *E*:*Z* >20:1.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 7.5 Hz, 1 H), 7.47–7.35 (comp, 4 H), 7.35–7.30 (comp, 5 H), 7.29–7.23 (comp, 2 H), 6.76 (d, *J* = 8.1 Hz, 2 H), 5.93 (s, 1 H), 4.27 (q, *J* = 7.1 Hz, 2 H), 1.28 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.5, 164.9, 152.0, 143.9, 133.8, 132.8, 132.2, 130.4, 129.4, 129.1, 128.3, 128.0, 127.8, 127.4, 125.7, 124.0, 123.2, 123.0, 67.1, 61.3, 14.6.

HRMS (ESI Q-TOF): *m*/*z* $[M + H]^+$ calcd for $C_{26}H_{21}BrN_3O_3$: 502.0761; found: 502.0765.

Ethyl (*E*)-3-(4-Chlorophenyl)-2-diazo-4-(3-oxo-1-phenylisoindolin-1-yl)but-3-enoate (3c)

Yellow oil; yield: 37.5 mg (82%); *E*:*Z* >20:1.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 7.5 Hz, 1 H), 7.44 (t, *J* = 7.5 Hz, 1 H), 7.40–7.36 (comp, 2 H), 7.35–7.27 (comp, 5 H), 7.26–7.23 (m, 1 H), 7.19–7.17 (d, *J* = 8.3 Hz, 2 H), 6.83 (d, *J* = 8.3 Hz, 2 H), 5.87 (s, 1 H), 4.28 (q, *J* = 7.1 Hz, 2 H), 1.28 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.5, 164.9, 152.1, 143.9, 135.0, 133.4, 132.8, 130.1, 129.4, 129.3, 129.1, 128.3, 128.0, 127.8, 127.4, 125.7, 124.0, 123.0, 67.1, 61.3, 14.6.

HRMS (ESI Q-TOF): *m*/*z* $[M + H]^+$ calcd for $C_{26}H_{21}ClN_3O_3$: 458.1266; found: 458.1264.

Ethyl (*E*)-2-Diazo-4-(3-oxo-1-phenylisoindolin-1-yl)-3-(4-trifluoromethylphenyl)but-3-enoate (3d)

Yellow oil; yield: 42.2 mg (86%); *E*:*Z* >20:1.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.57 (d, *J* = 7.5 Hz, 1 H), 7.42–7.38 (comp, 5 H), 7.32–7.23 (comp, 6 H), 6.99 (d, *J* = 7.7 Hz, 2 H), 6.13 (s, 1 H), 4.28 (q, *J* = 7.1 Hz, 2 H), 1.28 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.6, 164.8, 151.7, 143.6, 138.5, 132.7, 130.8 (q, *J* = 3.5 Hz), 130.0 (q, *J* = 272.5 Hz), 129.3, 129.1, 128.3, 128.10, 128.08, 127.7, 125.8, 125.7 (q, *J* = 5.0 Hz), 125.6, 124.0, 123.2, 67.0, 61.4, 14.5.

HRMS (ESI Q-TOF): *m*/*z* $[M + H]^+$ calcd for $C_{27}H_{21}F_3N_3O_3$: 492.1530; found: 492.1527.

Ethyl (*E*)-2-Diazo-4-(3-oxo-1-phenylisoindolin-1-yl)-3-(*p*-tolyl)-but-3-enoate (3e)

Yellow oil; yield: 37.2 mg (85%); *E*:*Z* >20:1.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.68 (d, *J* = 7.5 Hz, 1 H), 7.46 (t, *J* = 7.5 Hz, 1 H), 7.39–7.34 (comp, 4 H), 7.30–7.24 (comp, 4 H), 7.05 (d, *J* = 7.5 Hz, 2 H), 6.81 (d, *J* = 7.5 Hz, 2 H), 5.73 (s, 1 H), 4.27 (q, *J* = 7.1 Hz, 2 H), 2.31 (s, 3 H), 1.28 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.5, 165.2, 152.5, 144.3, 139.0, 132.8, 132.1, 129.9, 129.3, 128.9, 128.6, 128.3, 128.2, 127.8, 126.4, 125.9, 123.9, 122.8, 67.3, 61.1, 21.4, 14.6.

HRMS (ESI Q-TOF): *m*/*z* $[M + H]^+$ calcd for $C_{27}H_{24}N_3O_3$: 438.1812; found: 438.1812.

Ethyl (*E*)-2-Diazo-3-(4-methoxyphenyl)-4-(3-oxo-1-phenylisoindolin-1-yl)but-3-enoate (3f)

Yellow oil; yield: 32.6 mg (72%); *E*:*Z* >20:1.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 7.5 Hz, 1 H), 7.50–7.43 (m, 1 H), 7.40–7.36 (comp, 3 H), 7.34 (d, *J* = 7.5 Hz, 1 H), 7.31–7.28 (comp, 3 H), 7.26–7.22 (m, 1 H), 6.84 (d, *J* = 8.7 Hz, 2 H), 6.75 (d, *J* = 8.7 Hz, 2 H), 5.78 (s, 1 H), 4.30–4.23 (comp, 2 H), 3.78 (s, 3 H), 1.28 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.5, 165.2, 159.9, 152.5, 144.4, 132.8, 130.0, 129.5, 129.3, 128.9, 128.2, 127.8, 127.1, 126.7, 125.8, 123.9, 122.8, 114.6, 67.2, 61.1, 55.4, 14.6.

HRMS (ESI Q-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{27}H_{24}N_3O_4$: 454.1761; found: 454.1763.

Ethyl (*E*)-3-(3-Chlorophenyl)-2-diazo-4-(3-oxo-1-phenylisoindolin-1-yl)but-3-enoate (3g)

Yellow oil; yield: 35.6 mg (78%); *E*:*Z* >20:1.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.63 (d, *J* = 7.4 Hz, 1 H), 7.46 (t, *J* = 7.4 Hz, 1 H), 7.41–7.39 (comp, 2 H), 7.39–7.29 (comp, 5 H), 7.28–7.23 (m, 1 H), 7.21–7.11 (comp, 2 H), 6.84 (d, *J* = 7.1 Hz, 1 H), 6.71 (s, 1 H), 6.07 (s, 1 H), 4.28 (q, *J* = 7.1 Hz, 2 H), 1.28 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.5, 164.9, 151.8, 143.8, 136.5, 134.9, 132.7, 130.2, 129.5, 129.1, 129.0, 128.7, 128.4, 128.0, 127.8, 127.3, 127.0, 125.7, 124.0, 123.0, 67.0, 61.3, 14.6.

HRMS (ESI Q-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{21}ClN_3O_3$: 458.1266; found: 458.1270.

Ethyl 3-(2-Chlorophenyl)-2-diazo-4-(3-oxo-1-phenylisoindolin-1-yl)but-3-enoate (3h)

Yellow oil; yield: 36.1 mg (79%); *E*:*Z* = 1:1.

^{1}H NMR (500 MHz, $CDCl_3$): δ (composite NMR signals of two isomers) = 7.62–7.57 (comp, 2 H), 7.51 (t, *J* = 7.5 Hz, 1 H), 7.45–7.36 (comp, 7 H), 7.34–7.24 (comp, 12 H), 7.24–7.16 (comp, 2 H), 7.09 (t, *J* = 7.5 Hz, 1 H), 6.99–6.97 (comp, 2 H), 6.44 (d, *J* = 7.6 Hz, 1 H), 5.85 (s, 1 H), 5.71 (s, 1 H), 4.31–4.26 (comp, 4 H), 1.31–1.28 (comp, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.5, 168.9, 165.1, 151.8, 150.7, 143.5, 142.8, 133.8, 133.7, 133.4, 132.63, 132.58, 132.5, 130.52, 130.50, 130.3, 130.1, 130.0, 129.9, 129.5, 129.05, 129.03, 128.3, 128.2, 128.1, 128.0, 127.3, 127.2, 127.0, 126.4, 126.0, 125.9, 125.86, 125.84, 123.9, 123.7, 123.3, 123.1, 67.3, 67.2, 61.24, 61.22, 14.6.

HRMS (ESI Q-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{21}ClN_3O_3$: 458.1266; found: 458.1267.

Ethyl (*E*)-2-Diazo-3-(naphthalen-2-yl)-4-(3-oxo-1-phenylisoindolin-1-yl)but-3-enoate (3i)

Yellow oil; yield: 40.7 mg (86%); *E*:*Z* >20:1.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.81–7.76 (comp, 2 H), 7.58 (d, *J* = 7.5 Hz, 1 H), 7.51–7.48 (comp, 2 H), 7.47–7.36 (comp, 6 H), 7.32–7.25 (comp, 5 H), 7.10 (d, *J* = 8.4 Hz, 1 H), 5.76 (s, 1 H), 4.29 (q, *J* = 7.1 Hz, 2 H), 1.29 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.5, 165.1, 152.2, 144.5, 133.0, 132.9, 132.8, 132.4, 129.3, 129.2, 129.0, 128.7, 128.3, 128.23, 128.17, 128.0, 127.8, 127.3, 127.1, 126.9, 125.9, 125.8, 123.9, 122.9, 67.2, 61.2, 14.6.

HRMS (ESI Q-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{30}H_{24}N_3O_3$: 474.1812; found: 474.1815.

Ethyl 2-Diazo-3-(3-oxo-1-phenylisoindolin-1-yl)methylbut-3-enoate (3j)

Yellow oil; yield: 27.1 mg (75%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 7.5 Hz, 1 H), 7.53–7.49 (comp, 3 H), 7.44–7.39 (comp, 2 H), 7.36–7.33 (comp, 2 H), 7.28 (d, *J* = 7.2 Hz, 1 H), 7.02 (s, 1 H), 4.73 (s, 1 H), 4.58 (s, 1 H), 4.18 (q, *J* = 7.1 Hz, 2 H), 3.60 (d, *J* = 13.9 Hz, 1 H), 3.45 (d, *J* = 13.9 Hz, 1 H), 1.25 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.3, 165.5, 150.3, 142.0, 132.1, 131.3, 129.0, 128.6, 128.5, 128.0, 125.4, 124.0, 122.8, 114.4, 66.6, 61.1, 41.3, 14.5.

HRMS (ESI Q-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{20}N_3O_3$: 362.1499; found: 362.1500.

Ethyl (*Z*)-2-(Cyclohex-2-en-1-ylidene)-2-(3-oxo-1-phenylisoindolin-1-yl)acetate (3k)

White solid, yield: 24.3 mg (65%); *Z*:*E* = 7:1; mp 101.0–103.0 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.81 (d, *J* = 7.3 Hz, 1 H), 7.53 (d, *J* = 7.8 Hz, 2 H), 7.46–7.39 (comp, 2 H), 7.33–7.28 (comp, 3 H), 7.24 (d, *J* = 7.2 Hz, 1 H), 6.71 (s, 1 H), 6.25 (d, *J* = 10.2 Hz, 1 H), 6.13–5.95 (m, 1 H), 3.87–3.80 (m, 1 H), 3.68–3.62 (m, 1 H), 2.10–2.08 (comp, 2 H), 1.93 (t, *J* = 6.2 Hz, 2 H), 1.56–1.50 (m, 1 H), 1.49–1.45 (m, 1 H), 0.84 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.4, 168.7, 150.4, 143.1, 139.7, 135.1, 132.5, 131.1, 130.1, 129.2, 128.6, 128.0, 126.3, 125.0, 124.2, 124.1, 68.0, 61.0, 27.9, 25.5, 21.7, 13.8.

HRMS (ESI Q-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{24}NO_3$: 374.1751; found: 374.1755.

Methyl 5-Oxo-1,9b-diphenyl-5,9b-dihydro-3*H*-pyrrolo[2,1-*a*]isoindole-3-carboxylate (5a)

Colorless oil; yield: 21.7 mg (57%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.08 (d, *J* = 7.8 Hz, 1 H), 7.71 (d, *J* = 7.5 Hz, 1 H), 7.58 (t, *J* = 7.5 Hz, 1 H), 7.51–7.39 (comp, 3 H), 7.39–7.34 (comp, 3 H), 7.34–7.27 (comp, 3 H), 7.21–7.20 (comp, 2 H), 7.03 (s, 1 H), 5.53 (s, 1 H), 3.86 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.4, 163.6, 147.7, 147.0, 141.8, 136.3, 134.7, 133.9, 132.6, 129.4, 129.0, 128.9, 128.8, 128.7, 128.2, 126.01, 125.99, 124.3, 80.9, 66.0, 52.3.

HRMS (ESI Q-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{25}H_{20}NO_5$: 382.1438; found: 382.1440.

Methyl 5-Oxo-3,9b-diphenyl-5,9b-dihydro-3*H*-pyrrolo[2,1-*a*]isoindole-1-carboxylate (6a)

Colorless oil; yield: 11.1 mg (29%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 7.5 Hz, 1 H), 7.85 (d, *J* = 7.7 Hz, 1 H), 7.58 (t, *J* = 7.5 Hz, 1 H), 7.51 (t, *J* = 7.4 Hz, 1 H), 7.35 (d, *J* = 2.7 Hz, 1 H), 7.26 (s, 1 H), 7.23–7.09 (comp, 6 H), 7.08–7.06 (comp, 3 H), 6.09 (d, *J* = 2.7 Hz, 1 H), 3.84 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.4, 163.7, 150.5, 146.6, 141.4, 137.5, 135.7, 133.2, 132.1, 129.2, 128.5, 128.3, 128.0, 127.6, 127.04, 127.02, 126.7, 124.3, 80.6, 65.7, 52.3.

HRMS (ESI Q-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{20}NO_3$: 382.1438; found: 382.1439.

Methyl 3-Ethyl-5-oxo-9b-phenyl-5,9b-dihydro-3*H*-pyrrolo[2,1-*a*]-isoindole-1-carboxylate (6b)

Colorless oil; yield: 22.3 mg (67%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 7.7 Hz, 1 H), 7.80 (d, *J* = 7.5 Hz, 1 H), 7.55–7.52 (m, 1 H), 7.48–7.40 (m, 1 H), 7.33–7.32 (comp, 2 H), 7.29–7.26 (m, 1 H), 7.26–7.21 (comp, 2 H), 7.08 (d, *J* = 1.2 Hz, 1 H), 4.47–4.45 (m, 1 H), 3.83 (s, 3 H), 2.76–2.67 (m, 1 H), 2.20–2.06 (m, 1 H), 1.00 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.4, 163.6, 147.7, 147.6, 141.3, 136.4, 133.8, 132.5, 128.78, 128.76, 128.2, 126.0, 125.9, 124.0, 81.1, 64.0, 52.2, 22.2, 11.1.

HRMS (ESI Q-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{20}NO_3$: 334.1438; found: 334.1440.

Isoxazolidines 8

To a 10-mL oven-dried round-bottom flask containing a magnetic stir bar, nitrone **7** (23.6 mg, 0.12 mmol, 1.2 equiv.), and 4 Å MS (50 mg) in anhydrous DCM (1.0 mL) was added a solution of vinyldiazo compound **3b** (50.1 mg, 0.1 mmol) in anhydrous DCM (1.0 mL) via a syringe pump over 1 h at room temperature. When the reaction was complete (monitored by TLC), the reaction mixture was purified by flash column chromatography on silica gel without additional treatment (hexanes/EtOAc = 10:1) to give pure product **8**.

Ethyl (1*R*,4*R*,5*S*)-5-(4-Bromophenyl)-6-(3-oxo-1-phenylisoindolin-1-yl)-3,4-diphenyl-2-oxa-3-azabicyclo[3.1.0]-hexane-1-carboxylate (8)

Colorless oil; yield: 24.1 mg (36%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 6.8 Hz, 1 H), 7.53–7.52 (comp, 2 H), 7.41–7.37 (comp, 5 H), 7.36–7.25 (comp, 9 H), 7.16 (t, *J* = 7.7 Hz, 2 H), 7.06–6.96 (comp, 2 H), 6.93 (d, *J* = 8.2 Hz, 2 H), 5.22 (s, 1 H), 5.06 (s, 1 H), 4.08–4.02 (m, 1 H), 3.98 (s, 1 H), 3.75–3.68 (m, 1 H), 0.77 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.8, 166.6, 150.9, 148.5, 143.1, 136.6, 133.9, 132.4, 132.0, 129.4, 129.1, 128.8, 128.7, 128.6, 128.4, 128.2, 127.7, 125.4, 124.8, 124.0, 123.3, 122.3, 118.0, 75.4, 74.1, 63.9, 62.0, 47.3, 34.9, 13.5.

HRMS (ESI Q-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{39}H_{32}BrN_2O_4$: 671.1540; found: 671.1542.

Ethyl (1*R*,4*S*,5*S*)-5-(4-Bromophenyl)-6-(3-oxo-1-phenylisoindolin-1-yl)-3,4-diphenyl-2-oxa-3-azabicyclo[3.1.0]hexane-1-carboxylate (8′)

Colorless oil; yield: 24.1 mg (36%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 7.5 Hz, 1 H), 7.76–7.75 (comp, 2 H), 7.60 (t, *J* = 7.5 Hz, 1 H), 7.57–7.53 (comp, 3 H), 7.52–7.40 (comp, 4 H), 7.13 (t, *J* = 7.8 Hz, 2 H), 7.01–6.92 (comp, 2 H), 6.88 (d, *J* = 8.2 Hz, 2 H), 6.83–6.80 (comp, 3 H), 6.77–6.75 (comp, 4 H), 5.59 (s, 1 H), 4.20–4.15 (comp, 2 H), 3.96 (s, 1 H), 1.20 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.2, 168.4, 152.0, 148.2, 142.2, 137.1, 133.0, 132.0, 131.6, 130.7, 129.5, 129.0, 128.8, 128.7, 128.4, 127.7, 127.2, 124.9, 124.2, 124.0, 123.6, 122.8, 117.7, 78.1, 72.1, 63.4, 62.4, 47.1, 37.4, 14.2.

HRMS (ESI Q-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{39}H_{32}BrN_2O_4$: 671.1540; found: 671.1541.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

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