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Rhodium catalyzed synthesis of isoindolinones *via* C-H activation of *N*-benzoylsulfonamides

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Abstract

An efficient approach to a wide range of isoindolinones, including 3-monosubstituted and 3,3-disubstituted isoindolinones, from the annulation of *N*-benzoylsulfonamides with olefins and diazoacetate has been developed. The transformation is broadly compatible with both terminal and internal olefins. Moreover, diazoacetate is for the first time incorporated into an amide-directed C-H functionalization reaction. Specifically, the rhodium complex [{$RhCl_2Cp^*$}$_2$] enables the *in situ* dimerization of diazoacetate in addition to its role in catalyzing C-H functionalization/cross-coupling.

Keywords

N-benzoylsulfonamide; C-H activation; diazoacetate; isoindolinone; rhodium catalysis

1. Introduction

Transition-metal catalyzed direct transformations of C-H bonds has becomes a promising strategy for the construction of complex structures due to its undeniable synthetic efficiency and atom economy.[1] Isoindolinone represents a significant subunit of nitrogen-containing heterocycles well represented amongst natural products and biologically active compounds (Figure 1).[2] Apart from a variety of documented conventional methods,[3] isoindolinone can be readily prepared by the means of C-H activation. Our group,[4] the Lloyd-Jones/Booker-Milburn groups,[5] and the Wang group[6] recently revealed palladium-catalyzed sequences of C-H olefination/annulation to generate 3-monosubstituted isoindolinones; the Li group,[7] the Glorius group[8] and the Ackermann group[9] also disclosed a similar process but accomplished by rhodium or ruthenium catalysis. Regarding the broadly structural diversity of isoindolinones, it is clear that it will continue to remain an area of active investigations.

Amongst many efficient catalytic systems for C-H activation, the utility of the rhodium complex [{$RhCl_2Cp^*$}$_2$] has been cogently demonstrated in numerous concise syntheses of oxygen- and nitrogen-containing heterocycles.[10,11] We recently developed an efficient rhodium-catalyzed approach to a wide range of 3,3-disubstituted isoindolinones from the

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Supplementary Material
NMR spectra. Supplementary data related to this article can be found online at

annulation of *N*-benzoylsulfonamides with internal olefins by means of C-H olefination.[12] Two intriguing facts were referred in the preliminary study: the internal olefins were the first time systematically investigated in the C-H olefination and a new *N*-substituted quaternary centre was constructed during the reaction.

Based on that, herein we wish to report a full article about rhodium-catalyzed C-H activation of *N*-benzoylsulfonamides, that *N*-benzoylsulfonamides are annulated with a variety of olefins including terminal and internal olefins to generate both 3-monosubstituted and 3,3-disubstituted isoindolinones (Scheme 1). Moreover, the one-pot synthesis of 3,3-disubstituted isoindolinones *via* the coupling with diazoacetate is also described. It is noteworthy that, besides the known effect of facilitating C-H bond cleavage, a novel function of the rhodium complex [{$RhCl_2Cp^*$}$_2$], i.e., *in situ* dimerization of methyl diazoacetate, is demonstrated in the transformation.

2. Results and discussion

2.1 Annulation with olefins

For the initial survey of reaction conditions and optimization, *tert*-butyl acrylate was selected as model substrate. Subsequent screening experiments established some reaction parameters: (a) toluene affords a better yield than other common solvents; (b) the reaction at 130 °C ensures the full conversions within 24 h.

With the optimized conditions in hand, we applied the method to a variety of substituted *N*-benzoylsulfonamides (Table 1). The tandem process readily provided 3-monosubstituted isoindolinones regardless of the electronic properties of the substituents. The electron-rich methyl (**1b**) and methoxy groups (**1c**) as well as electron-deficient fluoro (**1d**) and trifluoromethyl groups (**1e**) all furnished their respective products in high chemical yields (entries 2–5). Even the *ortho*-substituted substrate **1f** could afford the corresponding adduct **3f** in good yield with prolonged reaction time (entry 6).

We next investigated the range of suitable alkenes (Table 2). When subjected to the standard reaction conditions, the terminal olefins (conjugated ketone **2b** and amide **2c**) smoothly evolved the corresponding products (entries 1–2). Subsequently, we extended the methodology into the annulation with internal olefins that would result in the formation of 3,3-disubstituted isoindolinones. The olefin configuration was observed to be unimportant to the reaction, since either fumarate **2d** or maleate **2e** led to the similar results (entries 3–4). *E*-1,2-Diketone conjugated olefin **2f** was also a suitable substrate and gave rise to the corresponding adduct **3j** in useful yield (entry 5). The transformation displayed excellent electronic discrimination with respect to the unsymmetric olefin **2g** so that the regioisomeric product **3k** was exclusively generated (entry 6). Cyclic olefins were also compatible with the reaction conditions (entry 7). Coupling with maleimide **2h** offered a facile access to the spiroisoindolinone **3l**.

2.2 Annulation with diazoacetate

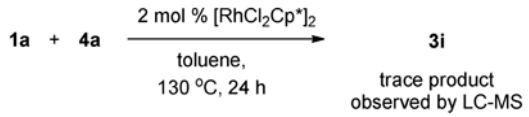
As part of our contribution to the construction of isoindolinones from *N*-benzoylsulfonamides,[4,12,13] we envisioned that if the rhodacycle **a** formed at the stage of C-H activation encounters diazoacetate **4a**, the rhodium-carbene species **b** might be *in situ* generated followed by carbene insertion, affording 3-carboxy isoindolinone adduct **5**, a new type of isoindolinone which could not be produced *via* benzamide-directed C-H olefination (Scheme 2).

Under the previous reaction conditions, the proposed product **5** was not detected. But, an unexpected adduct **3i** was alternatively isolated in good yield. This finding intrigued us since

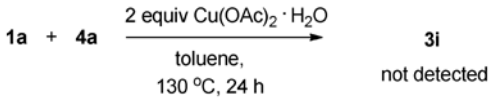
it involved the first incorporation of diazoacetate into the annulation reaction of an amide and offered another efficient approach for the synthesis of 3,3-disubstituted isoindolinones.

Encouraged by the above results, we commenced to determine the substrate scope (Table 3). The satisfactory results were obtained with a wide range of *N*-benzoylsulfonamides in spite of their electronic or steric properties. The electron-donating 4-methyl and 4-methoxy groups furnished their respective adducts in high yields (entries 3–4). Weak or even strong electron-deficient substitution, such as 4-fluoro and 4-trifluoromethyl groups, consistently resulted in good outcomes (entries 5–6). The chemoselective transformation in the presence of aryl bromide is noteworthy, as the bromide could incur subsequently competitive cross coupling reactions (entry 7). Moreover, *meta*-substituted substrates delivered not only good chemical yields but excellent regioselectivities, so that *para*-positional products were predominantly obtained (entries 8–9). Even the *ortho*-fluoro group was tolerated and the reaction readily proceeded without compromising the chemical yield (entry 10). However, significantly increasing the steric hindrance on either substrate hampered the reaction. For example, conversions were sluggish when ethyl diazoacetate **2a** was replaced with *tert*-butyl diazoacetate **2b** (entry 2), or possessed a crowded spatial environment around the reaction site (entry 11).

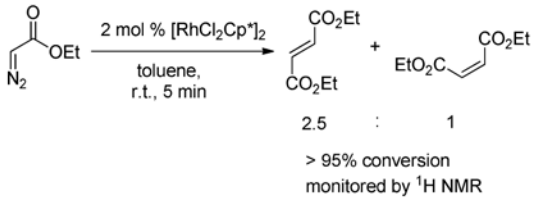
Some control experiments were carried out to elucidate the reaction pathways. The evidence in eqs 1 and 2 suggested that the rhodium complex rather than copper acetate is essential to the transformation. The experiment that exposure of diazoacetate to the complex $[\{RhCl_2Cp^*\}_2]$ rapidly generated the dimerization product (a 2.5:1 mixture of fumarate and maleate) is noteworthy (eq 3), as the decomposition of diazo compounds is prompted generally by Rh(II),[14] rarely by Rh(III) species.[15,16] Based on these observations, we speculate that at the beginning of the overall transformations, the diazoacetate is quickly converted into the corresponding internal olefin, which is the reactive species in the subsequent C-H olefination and annulation (Table 2, entries 3–4).



(1)



(2)



(3)

The KIE value (k_H/k_D = 1) might suggest that the C-H cleavage is fast, thus not involved as the rate-limiting step (Scheme 3). The postulated mechanism is depicted in Figure 2. Two roles of the rhodium complex [{$RhCl_2Cp^*$}$_2$] were involved in the transformation. At first, the diazoacetate **4a** is rapidly converted into the corresponding fumarate/maleate under the rhodium catalysis. Rapid C-H functionalization of **1** generates five-membered rhodacycle (**I**), which subsequently undergoes the insertion of fumarate/maleate and β-H elimination to generate Rh-H complex (**III**). Then, the following reductive elimination and Michael addition are proposed to give rise to the annulated isoindolinone product **3**. Meanwhile, the rhodium catalyst is regenerated by copper oxidation.

3. Conclusion

We have described the rhodium catalyzed synthesis of isoindolinones from the annulation of *N*-benzoylsulfonamides with a variety of olefins. The transformation is broadly compatible with both terminally and internally electron-deficient olefins, efficiently producing 3-monosubstituted and 3,3-disubstituted isoindolinones.

Moreover, diazoacetate is for the first time incorporated into an amide-directed C-H functionalization reaction. The tandem process that dimerization of diazoacetate followed by subsequent C-H olefination offers another interesting approach to 3,3-disubstituted isoindolinones. In addition to facilitating C-H bond cleavage, the rhodium complex [{$RhCl_2Cp^*$}$_2$] unexpectedly dimerized diazoacetate *in situ* to a mixture of fumarate/maleate that then participated in the annulation.

4. Experimental section

General Methods

All reactions were maintained under an argon atmosphere unless otherwise stated. Anhydrous solvents (THF, DME) were freshly distilled from sodium benzophenone ketyl or from CaH_2 (CH_2Cl_2, toluene) under argon. Commercially available reagents were used without further purification. Flash chromatography (FC) was performed using E. Merck silica gel 60 (240–400 mesh). Thin layer chromatography (TLC) was performed using pre-coated plates purchased from E. Merck (silica gel 60 PF254, 0.25 mm). NMR spectra were recorded in $CDCl_3$, unless otherwise stated, on spectrometers at operating frequencies of 400/500 MHz (1H) or 100/125 MHz (13C) as indicated in the individual spectrum.

Typical Procedure for Annulation of *N*-Benzoylsulfonamide with Olefins

N-Benzoylsulfonamide **1a** (27.5 mg, 0.1 mmol), [$RhCl_2Cp^*$]$_2$ (1.2 mg, 0.002 mmol) and $Cu(OAc)_2 \cdot H_2O$ (40.0 mg, 0.20 mmol) were loaded in a dry vial which was subjected to evacuation/flushing with dry argon three times. Anhydrous toluene (1.0 mL) solution of *tert*-butyl acrylate **2a** (17.4 uL, 0.12 mmol) was syringed into the mixture which was then stirred at 130 °C for 24 h or until the starting material had been consumed as determined by TLC. Upon cooling to room temperature, all volatiles were evaporated and the residue was purified by preparative TLC (ethyl acetate/hexane 1:2) to give isoindolinone **3a** in 88% yield.

Typical Procedure for Annulation of *N*-Benzoylsulfonamide with Ethyl Diazoacetate

N-Benzoylsulfonamide **1a** (27.5 mg, 0.1 mmol), [$RhCl_2Cp^*$]$_2$ (1.2 mg, 0.002 mmol) and $Cu(OAc)_2 \cdot H_2O$ (40.0 mg, 0.20 mmol) were loaded in a dry vial which was subjected to evacuation/flushing with dry argon three times. An anhydrous toluene (1.0 mL) solution of ethyl diazoacetate **4a** (30 uL, 0.30 mmol) was syringed into the mixture which was then stirred at 130 °C for 24 h or until the starting material had been consumed as determined by

TLC. Upon cooling to room temperature, all volatiles were evaporated and the residue was purified by preparative TLC (ethyl acetate/hexane = 1:2) to give isoindolinone **3i** in 80% yield.

4.1 3-*tert*-Butoxycarbonylmethyl-2-tosylisoindolin-1-one (3a)—^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24 (s, 9H), 2.42 (s, 3H), 3.01 (dd, *J* = 7.5, 16.5 Hz, 1H), 3.41 (dd, *J* = 3.5, 16.5 Hz, 1H), 5.55 (dd, *J* = 3.0, 7.5 Hz, 1H), 7.33 (d, *J* = 8.5 Hz, 2H), 7.47 (dd, *J* = 7.5, 8.0 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.63 (dd, *J* = 7.5, 8.0 Hz, 1H), 7.79 (d, *J* = 7.5 Hz, 1H), 8.05 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.9, 28.0, 40.2, 58.8, 82.0, 123.2, 125.1, 128.7, 129.3, 129.8, 129.9, 134.4, 136.0, 145.4, 145.6, 166.8, 169.0. FT-IR (CH_2Cl_2) 2360, 1727, 1597, 1366, 1292, 1170, 1090, 668 cm^{-1}. HRMS calcd for $C_{21}H_{24}NO_5S$ [M +H]$^+$ 402.1370, found 402.1358.

4.2 3-*tert*-Butoxycarbonylmethyl-5-methyl-2-tosylisoindolin-1-one (3b)—^{1}H NMR (500 MHz, $CDCl_3$) δ 1.27 (s, 9H), 2.41 (s, 3H), 2.44 (s, 3H), 2.96 (dd, *J* = 7.5, 16.0 Hz, 1H), 3.40 (dd, *J* = 3.5, 16.5 Hz, 1H), 5.50 (dd, *J* = 3.5, 7.5 Hz, 1H), 7.27 (d, *J* = 7.5 Hz, 1H), 7.29 (s, 1H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.66 (d, *J* = 8.0 Hz, 1H), 8.04 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.9, 22.4, 28.0, 40.5, 58.6, 81.9, 123.6, 124.9, 127.1, 128.6, 129.8, 130.4, 136.1, 145.3, 145.7, 146.0, 166.7, 169.1. FT-IR (CH_2Cl_2) 2979, 1731, 1618, 1366, 1337, 1284, 1171, 1091, 815, 691, 659 cm^{-1}. HRMS calcd for $C_{22}H_{26}NO_5S$ [M +H]$^+$ 416.1526, found 416.1511.

4.3 3-*tert*-Butoxycarbonylmethyl-5-methoxy-2-tosylisoindolin-1-one (3c)—^{1}H NMR (500 MHz, $CDCl_3$) δ 1.33 (s, 9H), 2.41 (s, 3H), 2.89 (dd, *J* = 8.0, 16.5 Hz, 1H), 3.46 (dd, *J* = 2.0, 16.5 Hz, 1H), 3.84 (s, 3H), 5.63 (dd, *J* = 2.0, 7.5 Hz, 1H), 6.96 (s, 1H), 6.97 (d, *J* = 9.0 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.68 (d, *J* = 9.0 Hz, 1H), 8.03 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.9, 28.1, 40.7, 56.0, 58.4, 82.0, 107.3, 116.8, 121.9, 126.8, 128.6, 129.8, 136.2, 145.3, 148.4, 165.0, 166.4, 169.4. FT-IR (CH_2Cl_2) 2978, 1728, 1608, 1493, 1366, 1260, 1170, 1090, 693, 659 cm^{-1}. HRMS calcd for $C_{22}H_{26}NO_6S$ [M+H]$^+$ 432.1475, found 432.1472.

4.4 3-*tert*-Butoxycarbonylmethyl-5-fluoro-2-tosylisoindolin-1-one (3d)—^{1}H NMR (500 MHz, $CDCl_3$) δ 1.31 (s, 9H), 2.42 (s, 3H), 2.93 (dd, *J* = 8.0, 16.5 Hz, 1H), 3.44 (dd, *J* = 3.5, 16.5 Hz, 1H), 5.52 (dd, *J* = 3.0, 8.0 Hz, 1H), 7.15–7.19 (m, 1H), 7.21–7.23 (m, 1H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.76–7.80 (m, 1H), 8.04 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.9, 28.1, 40.2, 58.4, 82.3, 110.9 (d, $J_{C\text{-}F}$ = 29.2 Hz), 117.5 (d, $J_{C\text{-}F}$ = 24.2 Hz), 125.7 (d, $J_{C\text{-}F}$ = 11.5 Hz), 127.5 (q, $J_{C\text{-}F}$ = 5.0 Hz), 128.6, 129.9, 135.8, 145.6, 148.3 (d, $J_{C\text{-}F}$ = 10.6 Hz), 165.6 (d, $J_{C\text{-}F}$ = 267 Hz), 167.7, 168.9. FT-IR (CH_2Cl_2) 2981, 2360, 2342, 1733, 1624, 1603, 1485, 1358, 1245, 1173, 1105, 860, 813, 690, 668 cm^{-1}. HRMS calcd for $C_{21}H_{23}FNO_5S$ [M+H]$^+$ 420.1275, found 420.1275.

4.5 3-*tert*-Butoxycarbonylmethyl-5-trifluoromethyl-2-tosylisoindolin-1-one (3e) —^{1}H NMR (500 MHz, $CDCl_3$) δ 1.30 (s, 9H), 2.43 (s, 3H), 2.92 (dd, *J* = 8.0, 16.5 Hz, 1H), 3.51 (dd, *J* = 3.5, 16.5 Hz, 1H), 5.62 (dd, *J* = 3.5, 8.0 Hz, 1H), 7.35 (d, *J* = 8.5 Hz, 2H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.82 (s, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 8.05 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.9, 28.0, 40.1, 58.8, 82.4, 120.9, 122.1, 125.8, 126.5, 128.7, 130.0, 132.9, 135.9, 136.0 (q, $J_{C\text{-}F}$ = 32.3 Hz), 145.8, 146.0, 165.3, 168.8. FT-IR (CH_2Cl_2) 2980, 1729, 1598, 1440, 1367, 1312, 1171, 1131, 1092, 1061, 841, 696, 672 cm^{-1}. HRMS calcd for $C_{22}H_{23}F_3NO_5S$ [M$^+$+H] 470.1244, found 470.1230.

4.6 3-*tert*-Butoxycarbonylmethyl-7-fluoro-2-tosylisoindolin-1-one (3f)—^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25 (s, 9H), 2.43 (s, 3H), 3.05 (dd, *J* = 7.0, 16.5 Hz, 1H), 3.36 (dd, *J* =

3.5, 16.5 Hz, 1H), 5.55 (dd, *J* = 3.0, 7.0 Hz, 1H), 7.10 (dd, *J* = 8.5, 8.5 Hz, 1H), 7.27 (d, *J* = 7.5 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.58–7.63 (m, 1H), 8.05 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.9, 28.0, 40.1, 58.3, 82.1, 116.4, 116.5, 117.5, 117.6, 119.08, 119.12, 128.8, 129.9, 135.7, 136.4, 136.5, 145.6, 147.9, 158.6, 160.7, 163.4, 168.7; FT-IR (CH_2Cl_2) 2979, 2360, 2341, 1731, 1626, 1599, 1482, 1366, 1313, 1292, 1252, 1207, 1172, 1102, 1036, 979, 684, 668 cm^{-1}. HRMS calcd for $C_{21}H_{23}FNO_5S$ $[M+H]^+$ 420.1275, found 420.1259.

4.7 3-Ethylcarbonylmethyl-2-tosylisoindolin-1-one (3g)—^{1}H NMR (500 MHz, $CDCl_3$) δ 1.12 (t, *J* = 7.0 Hz, 3H), 2.41 (s, 3H), 2.41–2.46 (m, 1H), 2.56–2.62 (m, 1H), 2.90 (dd, *J* = 9.0, 18.0 Hz, 1H), 3.81 (dd, *J* = 3.0, 18.0 Hz, 1H), 5.69 (dd, *J* = 3.0, 9.0 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.42–7.46 (m, 2H), 7.59 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.76 (d, *J* = 7.5 Hz, 1H), 7.99 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 7.83, 21.9, 36.8, 48.0, 58.2, 123.7, 125.2, 128.5, 129.1, 129.3, 130.0, 134.6, 135.7, 145.6, 146.6, 166.7, 208.5. FT-IR (CH_2Cl_2) 2938, 1729, 1597, 1358, 1290, 1169, 1092, 694, 664 cm^{-1}. HRMS calcd For $C_{19}H_{20}NO_4S$ $[M+H]^+$ 358.1108, found 358.1093.

4.8 3-Dimethylaminocarbonylmethyl-2-tosylisoindolin-1-one (3h)—^{1}H NMR (500 MHz, $CDCl_3$) δ 2.40 (s, 3H), 2.69 (dd, *J* = 10.0, 16.5 Hz, 1H), 2.99 (s, 3H), 3.04 (s, 3H), 3.78 (dd, *J* = 2.5, 16.5 Hz, 1H), 5.77 (dd, *J* = 2.5, 10.0 Hz, 1H), 7.32 (d, *J* = 8.5 Hz, 2H), 7.43 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.58 (dd, *J* = 7.5, 8.0 Hz, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 7.5 Hz, 1H), 8.00 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.9, 35.7, 37.4, 39.9, 59.8, 124.7, 125.0, 128.5, 129.0, 129.2, 129.9, 134.6, 135.7, 145.5, 146.9, 166.9, 169.5; FT-IR (CH_2Cl_2) 2360, 1732, 1645, 1402, 1358, 1290, 1169, 1090, 695, 663 cm^{-1}. HRMS calcd for $C_{19}H_{21}N_2O_4S$ $[M+H]^+$ 373.1217, found 373.1217.

4.9 3-Ethoxycarbonyl-3-ethoxycarbonylmethyl-2-tosylisoindolin-1-one (3i)—^{1}H NMR (500 MHz, $CDCl_3$) δ 0.79 (t, *J* = 7.0 Hz, 3H), 1.25 (t, *J* = 7.0 Hz, 3H), 2.42 (s, 3H), 3.52–3.64 (m, 2H), 3.70 (d, *J* = 17.5 Hz, 1H), 3.94 (d, *J* = 17.5 Hz, 1H), 4.16–4.24 (m, 1H), 4.28–4.36 (m, 1H), 7.33 (d, *J* = 8.5 Hz, 2H), 7.44 (d, *J* = 7.5 Hz, 1H), 7.51 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.63 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.82 (d, *J* = 7.5 Hz, 1H), 8.10 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 14.0, 21.9, 38.5, 60.8, 63.4, 70.5, 121.3, 125.1, 129.2, 129.4, 129.9, 130.1, 134.4, 136.1, 143.7, 145.4, 166.6, 167.9, 168.6. FT-IR (CH_2Cl_2) 2982, 1738, 1468, 1366, 1248, 1169, 1123, 1089, 1028, 693, 664 cm^{-1}. HRMS calcd for $C_{22}H_{24}NO_7S$ $[M+H]^+$ 446.1268, found 446.1252.

4.10 3-Ethylcarbonyl-3-ethylcarbonylmethyl-2-tosylisoindolin-1-one (3j)—^{1}H NMR (400 MHz) δ 0.57 (t, *J* = 7.2 Hz, 3H), 0.95 (t, *J* = 7.2 Hz, 3H), 2.06–2.16 (m, 3H), 2.41 (s, 3H), 2.80–2.92 (m, 1H), 3.70 (d, *J* = 19.2 Hz, 1H), 3.78 (d, *J* = 19.2 Hz, 1H), 7.14 (d, *J* = 7.6 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.51 (dd, *J* = 7.2, 7.6 Hz, 1H), 7.58 (dd, *J* = 7.2, 7.6 Hz, 1H), 7.93 (d, *J* = 7.6 Hz, 1H), 8.02 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz) δ 6.9, 8.5, 21.9, 28.6, 36.3, 42.5, 75.4, 121.1, 125.6, 128.3, 129.8, 130.0, 130.6, 134.6, 135.8, 143.1, 145.7, 167.0, 205.3, 205.6. FT-IR (CH_2Cl_2) 1745, 1716, 1357, 1169, 1123, 1087, 1057, 822, 702, 658 cm^{-1}. HRMS calcd for $C_{22}H_{24}NO_5S$ $[M+H]^+$ 414.1370, found 414.1368.

4.11 3-Ethoxycarbonyl-3-cyanomethyl-2-tosylisoindolin-1-one (3k)—^{1}H NMR (400 MHz) δ 1.25 (t, *J* = 7.2 Hz, 3H), 2.43 (s, 3H), 3.78 (d, *J* = 17.6 Hz, 1H), 3.90 (d, *J* = 17.6 Hz, 1H), 4.16–4.24 (m, 1H), 4.32–4.40 (m, 1H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.52 (d, *J* = 7.6 Hz, 1H), 7.60 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.73 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.87 (d, *J* = 7.6 Hz, 1H), 8.09 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz) δ 14.0, 22.0, 26.2, 64.1, 69.5, 114.7, 121.5, 126.0, 129.1, 129.2, 129.8, 131.3, 135.2, 135.3, 141.9, 146.2, 165.5, 167.3.

FT-IR (CH_2Cl_2) 2987, 1743, 1598, 1468, 1365, 1294, 1267, 1169, 1128, 1088, 815, 748, 698, 666 cm^{-1}. HRMS calcd for $C_{20}H_{19}N_2O_5S$ $[M+H]^+$ 399.1009, found 399.1009.

4.12 3,3-spiro[3′-*N*-Methyl-2′,4′-dicarbonylpyrrolidine]-2-tosylisoindolin-1-one (3l)—^1H NMR (400 MHz) δ 2.44 (s, 3H), 3.21 (d, *J* = 14.4 Hz, 1H), 3.27 (s, 3H), 3.89 (d, *J* = 14.4 Hz, 1H), 7.27 (d, *J* = 7.6 Hz, 1H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.55 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.68 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.81 (d, *J* = 7.6 Hz, 1H), 8.05 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz) δ 22.0, 26.3, 41.6, 69.3, 120.5, 125.8, 128.6, 129.6, 129.7, 130.7, 134.8, 135.4, 144.6, 146.3, 165.4, 172.9, 173.4. FT-IR (CH_2Cl_2) 1791, 1738, 1715, 1597, 1436, 1382, 1359, 1286, 1263, 1168, 1123, 1091, 1059, 702, 665 cm^{-1}. HRMS calcd for $C_{19}H_{17}N_2O_5S$ $[M+H]^+$ 385.0853, found 385.0827.

4.13 3-Ethoxycarbonyl-3-ethoxycarbonylmethyl-5-methyl-2-tosylisoindolin-1-one (3n)—^1H NMR (400 MHz, $CDCl_3$) δ 0.77 (t, *J* = 7.2 Hz, 3H), 1.24 (t, *J* = 7.2 Hz, 3H), 2.40 (s, 3H), 2.43 (s, 3H), 3.52–3.62 (m, 2H), 3.66 (d, *J* = 17.6 Hz, 1H), 3.90 (d, *J* = 17.6 Hz, 1H), 4.12–4.22 (m, 1H), 4.28–4.36 (m, 1H), 7.20 (s, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.68 (d, *J* = 8.0 Hz, 1H), 8.08 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 14.0, 21.9, 22.4, 38.5, 60.7, 63.4, 70.2, 121.6, 125.0, 127.4, 129.2, 129.4, 131.2, 136.2, 144.0, 145.3, 145.7, 166.6, 168.0, 168.8. FT-IR (CH_2Cl_2) 2983, 1737, 1613, 1598, 1364, 1284, 1250, 1169, 1133, 1088, 1027, 853, 808, 704, 666 cm^{-1}. HRMS calcd for $C_{23}H_{26}NO_7S$ $[M+H]^+$ 460.1424, found 460.1413.

4.14 3-Ethoxycarbonyl-3-ethoxycarbonylmethyl-5-methoxy-2-tosylisoindolin-1-one (3o)—^1H NMR (400 MHz, $CDCl_3$) δ 0.80 (t, *J* = 7.2 Hz, 3H), 1.26 (t, *J* = 7.2 Hz, 3H), 2.42 (s, 3H), 3.54–3.64 (m, 2H), 3.66 (d, *J* = 17.6 Hz, 1H), 3.86 (s, 3H), 3.92 (d, *J* = 17.6 Hz, 1H), 4.14–4.24 (m, 1H), 4.30–4.38 (m, 1H), 6.86 (d, *J* = 2.0 Hz, 1H), 6.99 (dd, *J* = 2.0, 8.8 Hz, 1H), 7.31 (d, *J* = 8.4 Hz, 2H), 7.73 (d, *J* = 8.4 Hz, 1H), 8.09 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 14.0, 21.9, 38.7, 56.1, 60.8, 63.5, 70.0, 105.8, 116.9, 122.2, 126.8, 129.1, 129.4, 136.3, 145.2, 146.1, 164.9, 166.2, 167.9, 168.7. FT-IR (CH_2Cl_2) 2982, 1738, 1604, 1495, 1362, 1343, 1291, 1254, 1168, 1126, 1085, 1026, 855, 659 cm^{-1}. HRMS calcd for $C_{23}H_{26}NO_8S$ $[M+H]^+$ 476.1374, found 476.1376.

4.15 3-Ethoxycarbonyl-3-ethoxycarbonylmethyl-5-fluoro-2-tosylisoindolin-1-one (3p)—^1H NMR (400 MHz, $CDCl_3$) δ 0.86 (t, *J* = 7.2 Hz, 3H), 1.27 (t, *J* = 7.2 Hz, 3H), 2.42 (s, 3H), 3.63 (q, *J* = 7.2 Hz, 2H), 3.65 (d, *J* = 17.6 Hz, 1H), 3.94 (d, *J* = 17.6 Hz, 1H), 4.18–4.26 (m, 1H), 4.30–4.39 (m, 1H), 7.12 (dd, *J* = 2.0, 7.6 Hz, 1H), 7.20 (ddd, *J* = 2.0, 8.4, 8.8 Hz, 1H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.82 (dd, *J* = 4.8, 8.4 Hz, 1H), 8.08 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 14.0, 21.9, 38.4, 60.9, 63.7, 70.1, 109.0 (d, $J_{C\text{-}F}$ = 25.0 Hz), 118.1 (d, $J_{C\text{-}F}$ = 23.4 Hz), 126.1 (d, $J_{C\text{-}F}$ = 2.2 Hz), 127.5 (d, $J_{C\text{-}F}$ = 9.9 Hz), 129.2, 129.4, 135.9, 145.5, 146.3 (d, $J_{C\text{-}F}$ = 10.0 Hz), 165.2, 166.8 (d, $J_{C\text{-}F}$ = 267 Hz), 167.7, 167.8. FT-IR (CH_2Cl_2) 2983, 1736, 1606, 1488, 1365, 1287, 1250, 1170, 1124, 1084, 1027, 853, 814, 655 2 cm^{-1}. HRMS calcd for $C_{22}H_{23}FNO_7S$ $[M+H]^+$ 464.1174, found 464.1158.

4.16 3-Ethoxycarbonyl-3-ethoxycarbonylmethyl-5-trifluoromethyl-2-tosylisoindolin-1-one (3q)—^1H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, *J* = 7.2 Hz, 3H), 1.27 (t, *J* = 7.2 Hz, 3H), 2.43 (s, 3H), 3.63 (q, *J* = 7.2 Hz, 2H), 3.72 (d, *J* = 17.6 Hz, 1H), 3.98 (d, *J* = 17.6 Hz, 1H), 4.18–4.27 (m, 1H), 4.33–4.42 (m, 1H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.69 (s, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 8.10 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 14.0, 21.9, 38.2, 61.0, 63.9, 70.6, 118.6 (q, $J_{C\text{-}F}$ = 3.8 Hz), 123.3 (q, $J_{C\text{-}F}$ = 272 Hz), 125.8, 127.3 (q, $J_{C\text{-}F}$ = 3.5 Hz), 129.2, 129.5, 133.3, 135.6, 136.0 (q, $J_{C\text{-}F}$ = 32.9 Hz), 144.2, 145.8, 165.3, 167.7, 167.9. FT-IR (CH_2Cl_2) 2986, 1739, 1369,

1329, 1259, 1171, 1133, 1099, 1028, 846, 696, 659 cm^{-1}. HRMS calcd for $C_{23}H_{23}F_3NO_7S$ $[M+H]^+$ 514.1142, found 514.1158.

4.17 3-Ethoxycarbonyl-3-ethoxycarbonylmethyl-5-bromo-2-tosylisoindolin-1-one (3r)—^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, *J* = 7.2 Hz, 3H), 1.28 (t, *J* = 7.2 Hz, 3H), 2.42 (s, 3H), 3.63 (q, *J* = 7.2 Hz, 2H), 3.65 (d, *J* = 17.6 Hz, 1H), 3.93 (d, *J* = 17.6 Hz, 1H), 4.16–4.26 (m, 1H), 4.32–4.42 (m, 1H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.59 (s, 1H), 7.66 (dd, *J* = 8.0, 16.8 Hz, 2H), 8.08 (d, *J* = 8.4 Hz, 2H); ^{13} C NMR (100 MHz, $CDCl_3$) δ 13.8, 14.0, 21.9, 38.3, 61.0, 63.8, 70.0, 124.7, 126.4, 129.0, 129.1, 129.2, 129.5, 133.6, 135.8, 145.3, 145.6, 165.7, 167.7, 168.1. FT-IR (CH_2Cl_2) 2983, 1737, 1605, 1593, 1367, 1278, 1247, 1170, 1131, 1090, 1028, 839, 664 cm^{-1}. HRMS calcd for $C_{22}H_{23}BrNO_7S$ $[M+H]^+$ 524.0373, found 524.0378.

4.18 3-Ethoxycarbonyl-3-ethoxycarbonylmethyl-2-tosyl-5,6-benzo isoindolin-1-one (3s)—^{1}H NMR (400 MHz, $CDCl_3$) δ 0.74 (t, *J* = 7.2 Hz, 3H), 1.24 (t, *J* = 7.2 Hz, 3H), 2.41 (s, 3H), 3.51 (q, *J* = 7.2, 2H), 3.82 (d, *J* = 18.0 Hz, 1H), 4.01 (d, *J* = 18.0 Hz, 1H), 4.14–4.20 (m, 1H), 4.30–4.38 (m, 1H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.57 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.62 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.84 (s, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.99 (d, *J* = 8.0 Hz, 1H), 8.12 (d, *J* = 8.4 Hz, 2H), 8.36 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 14.0, 21.9, 39.1, 60.8, 63.5, 70.2, 120.5, 126.3, 127.4, 127.6, 128.7, 129.1, 129.2, 129.5, 130.1, 133.6, 136.1, 136.2, 138.3, 145.4, 166.6, 168.1, 169.1. FT-IR (CH_2Cl_2) 2983, 1736, 1365, 1252, 1180, 1163, 1130, 1086, 1027, 764, 664 cm^{-1}. HRMS calcd for $C_{26}H_{26}NO_7S$ $[M+H]^+$ 496.1424, found 496.1421.

4.19 3-Ethoxycarbonyl-3-ethoxycarbonylmethyl-6-methoxy-2-tosylisoindolin-1-one (3t)—^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81 (t, *J* = 7.2 Hz, 3H), 1.23 (t, *J* = 7.2 Hz, 3H), 2.40 (s, 3H), 3.55–3.65 (m, 2H), 3.64 (d, *J* = 17.2 Hz, 1H), 3.80 (s, 3H), 3.87 (d, *J* = 17.2 Hz, 1H), 4.14–4.22 (m, 1H), 4.26–4.34 (m, 1H), 7.14 (dd, *J* = 2.4, 8.4 Hz, 1H), 7.24 (d, *J* = 2.4 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 8.08 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 14.0, 21.9, 38.3, 56.0, 60.7, 63.4, 70.2, 107.6, 122.4, 122.7, 129.2, 129.4, 131.3, 135.8, 136.0, 145.3, 161.3, 166.6, 168.0, 168.7. FT-IR (CH_2Cl_2) 2983, 1736, 1494, 1365, 1289, 1251, 1169, 1129, 1091, 1028, 664 cm^{-1}. HRMS calcd for $C_{23}H_{26}NO_8S$ $[M+H]^+$ 476.1374, found 476.1382.

4.20 3-Ethoxycarbonyl-3-ethoxycarbonylmethyl-7-fluoro-2-tosylisoindolin-1-one (3u)—^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (t, *J* = 7.2 Hz, 3H), 1.26 (t, *J* = 7.2 Hz, 3H), 2.43 (s, 3H), 3.56–3.68 (m, 2H), 3.67 (d, *J* = 17.6 Hz, 1H), 3.94 (d, *J* = 17.6 Hz, 1H), 4.16–4.26 (m, 1H), 4.30–4.38 (m, 1H), 7.14 (dd, *J* = 8.4, 8.4 Hz, 1H), 7.22 (d, *J* = 7.6 Hz, 1H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.61 (ddd, *J* = 4.8, 7.6, 8.0 Hz, 1H), 8.09 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 14.0, 21.9, 38.6, 60.9, 63.7, 70.1, 117.2 (d, $J_{C\text{-}F}$ = 4.2 Hz), 117.4 (d, $J_{C\text{-}F}$ = 18.8 Hz), 129.3, 129.5, 135.7, 136.4 (d, $J_{C\text{-}F}$ = 7.9 Hz), 145.6, 145.9 (d, $J_{C\text{-}F}$ = 2.3 Hz), 159.4 (d, $J_{C\text{-}F}$ = 274 Hz), 163.3 (d, $J_{C\text{-}F}$ = 2.6 Hz), 167.8, 168.2. FT-IR (CH_2Cl_2) 2984, 1740, 1622, 1483, 1367, 1256, 1236, 1196, 1171, 1122, 1090, 1073, 1035, 814, 691, 664 cm^{-1}. HRMS calcd for $C_{22}H_{23}FNO_7S$ $[M+H]^+$ 464.1174, found 464.1186.

4.21 3-Ethoxycarbonyl-3-ethoxycarbonylmethyl-4,6-dimethoxy-2-tosylisoindolin-1-one (3v)—^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84 (t, *J* = 7.2 Hz, 3H), 1.24 (t, *J* = 7.2 Hz, 3H), 2.42 (s, 3H), 3.57–3.65 (m, 2H), 3.79 (d, *J* = 17.2 Hz, 1H), 3.81 (s, 3H), 3.83 (s, 3H), 3.90 (d, *J* = 17.2 Hz, 1H), 4.16–4.24 (m, 1H), 4.26–4.34 (m, 1H), 6.61 (d, *J* = 2.0 Hz, 1H), 6.87 (d, *J* = 2.0 Hz, 1H), 7.31 (d, *J* = 8.4 Hz, 2H), 8.07 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 14.1, 21.9, 36.0, 56.0, 56.1, 60.5, 62.9, 69.3, 98.7, 105.1, 124.3, 129.1, 129.4, 132.5, 136.1, 145.3, 155.1, 162.9, 166.7, 167.8, 168.6. FT-

IR (CH_2Cl_2) 2982, 1741, 1625, 1598, 1503, 1459, 1356, 1323, 1244, 1169, 1151, 1090, 1068, 1031, 827, 664 cm^{-1}. HRMS calcd for $C_{24}H_{28}NO_9S$ $[M+H]^+$ 506.1479, found 506.1458.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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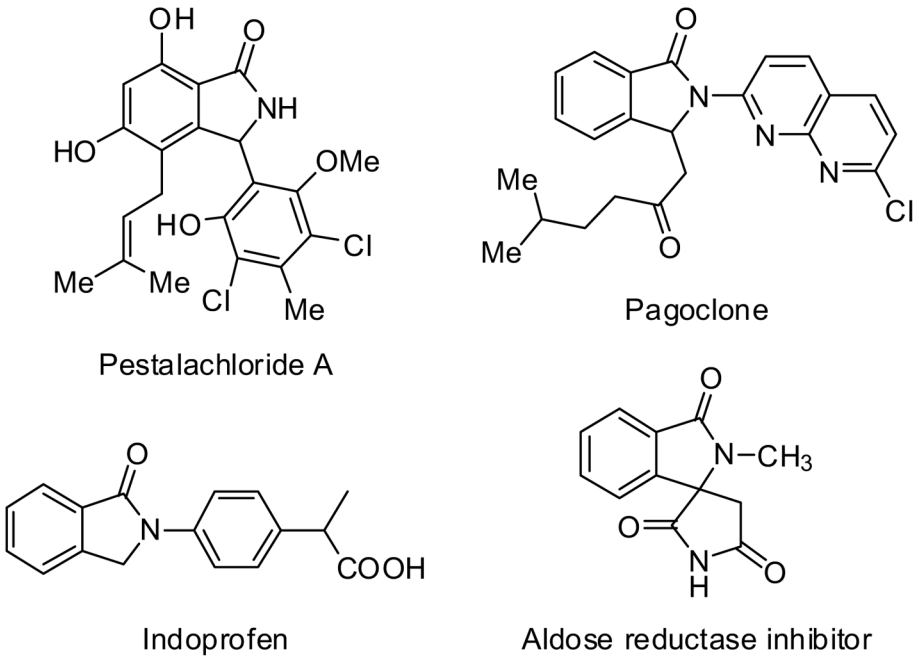


Fig. 1.
Representative structures containing isoindolinone

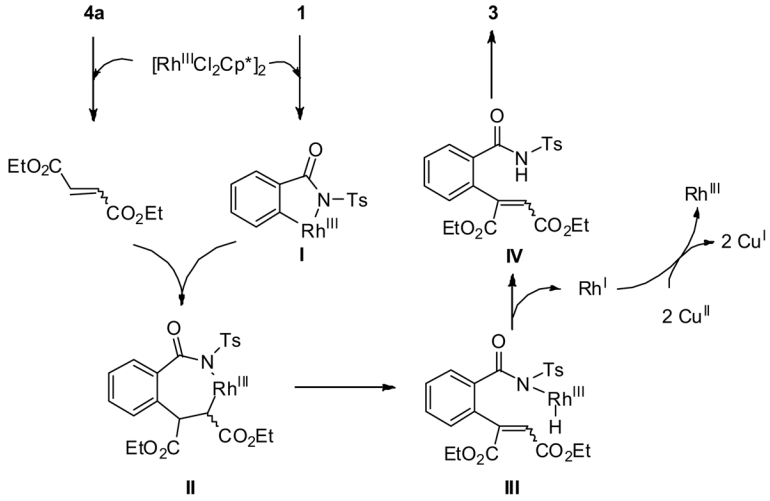
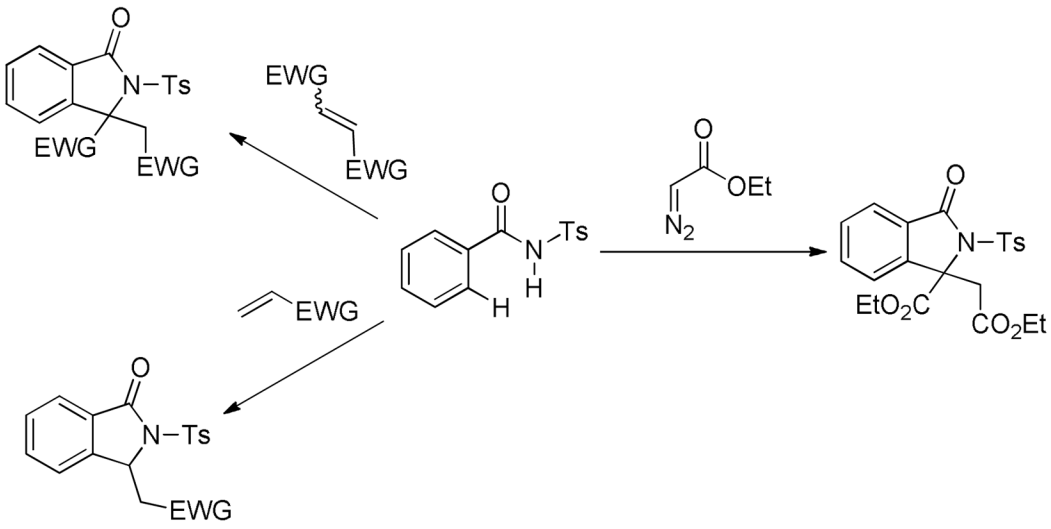
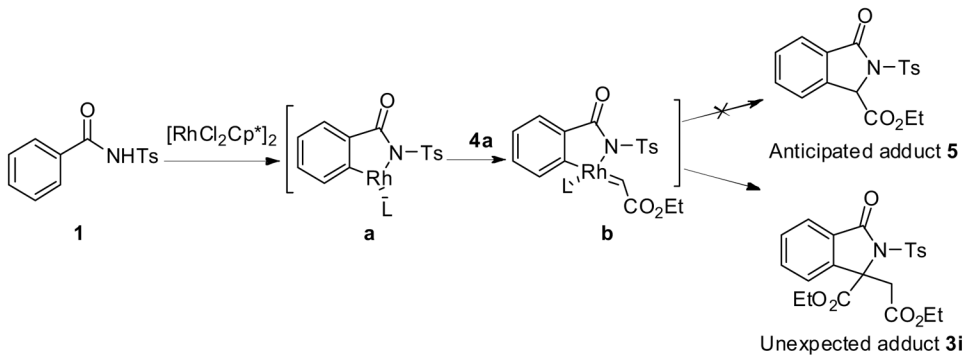


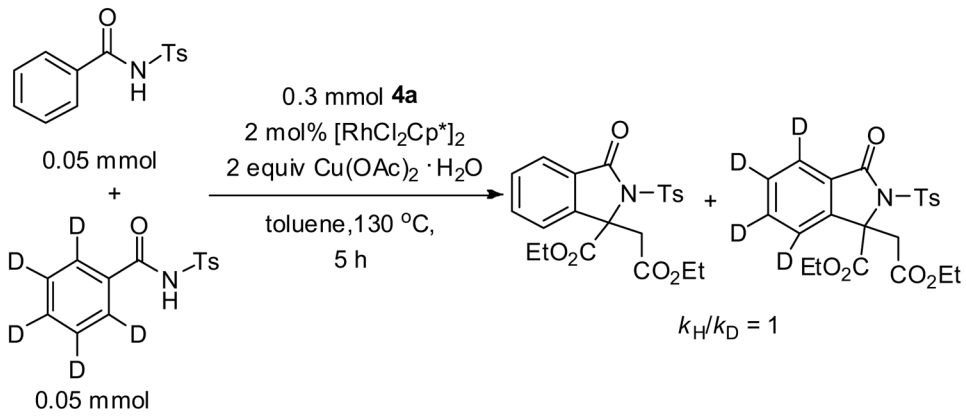
Fig. 2.
Plausible mechanism



Scheme 1.
Rhodium-catalyzed synthesis of isoindolinones



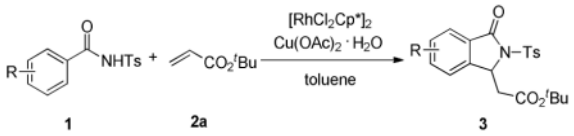
Scheme 2.
Proposed reaction pathway



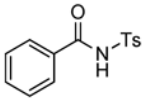
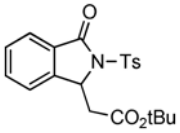
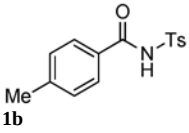
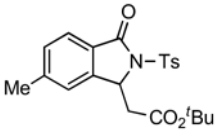
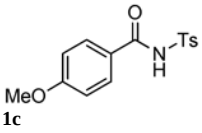
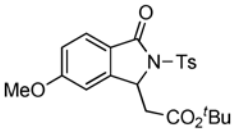
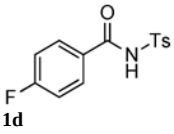
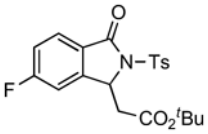
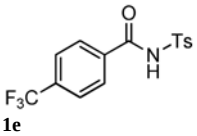
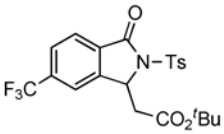
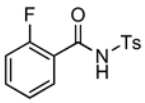
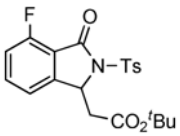
Scheme 3.
KIE experiment

Table 1

Substrate scope of reaction with *tert*-butyl acrylate.[a]



1 2a 3

Entry	Amide	Product	Yield (%)[b]
1	 **1a**	 **3a**	88
2	 **1b**	 **3b**	90
3	 **1c**	 **3c**	87
4	 **1d**	 **3d**	85
5	 **1e**	 **3e**	80
6[c]	 **1f**	 **3f**	84

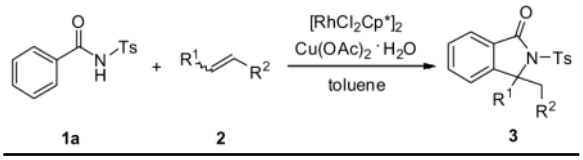
[a] Reaction conditions: **1** (0.10 mmol), **2a** (0.12 mmol), $[RhCl_2Cp^*]_2$ (0.002 mmol) and $Cu(OAc)_2 \cdot H_2O$ (0.20 mmol) in toluene, 130 °C for 24 h.

[b] Isolated yield.

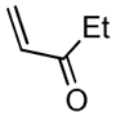
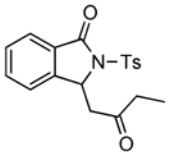
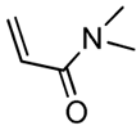
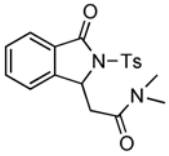
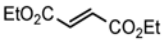
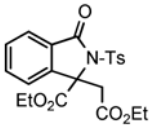
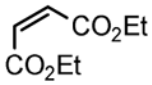
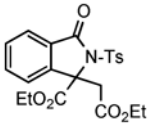
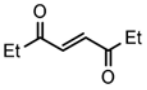
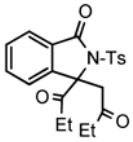
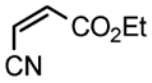
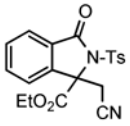
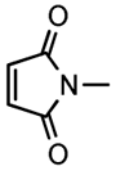
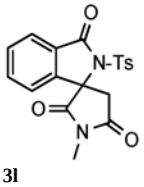
[c] 48 h.

Table 2

Substrate scope of various alkenes.[a]



1a 2 3

Entry	Alkene	Product	Yield (%)[b]
1	 **2b**	 **3g**	78
2	 **2c**	 **3h**	82
3	 **2d**	 **3i**	82
4	 **2e**	 **3i**	80
5	 **2f**	 **3j**	51
6	 **2g**	 **3k**	66
7[c]	 **2h**	 **3l**	73

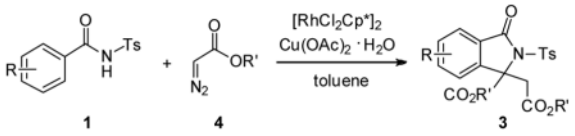
[a] Reaction conditions: **1a** (0.10 mmol), **2** (0.12 mmol), $[RhCl_2Cp^*]_2$ (0.004 mmol) and $Cu(OAc)_2 \cdot H_2O$ (0.20 mmol) in toluene, 130 °C for 24 h.

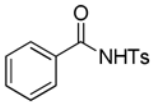
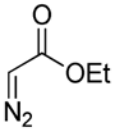
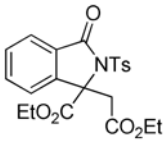
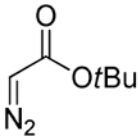
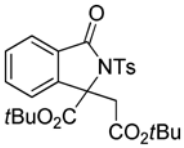
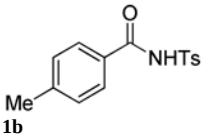
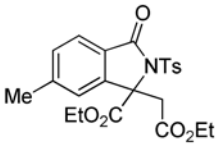
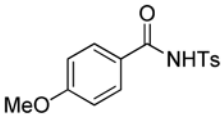
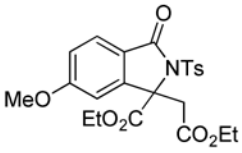
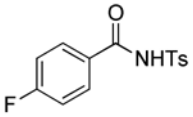
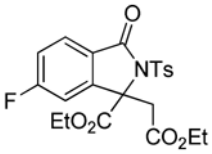
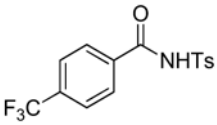
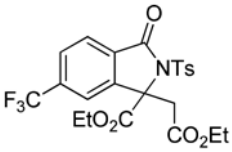
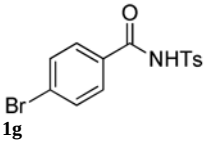
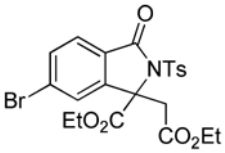
[b] Isolated yield.

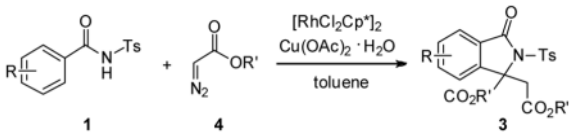
[c] 48 h.

Table 3

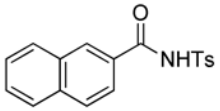
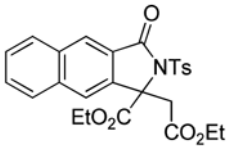
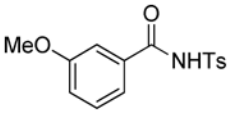
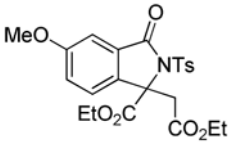
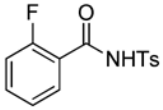
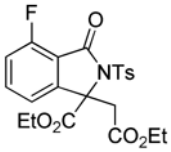
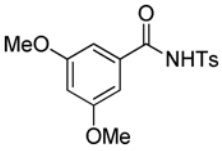
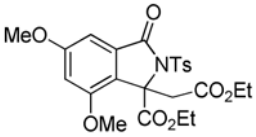
Substrate scope of reaction with diazoacetate.[a]



Entry	Amide	Diazoacetate	Product	Yield (%)[b]
1	 **1a**	 **4a**	 **3i**	80
2	**1a**	 **4b**	 **3m**	< 10
3	 **1b**	**4a**	 **3n**	81
4	 **1c**	**4a**	 **3o**	75
5	 **1d**	**4a**	 **3p**	82
6	 **1e**	**4a**	 **3q**	74
7	 **1g**	**4a**	 **3r**	66



1 4 3

Entry	Amide	Diazoacetate	Product	Yield (%)[b]
8[c,d]	 **1h**	**4a**	 **3s**	76
9[c,e]	 **1i**	**4a**	 **3t**	70
10[c]	 **1f**	**4a**	 **3u**	78
11[c]	 **1j**	**4a**	 **3v**	45

[a] Reaction conditions: **1** (0.10 mmol), **4** (0.30 mmol), $[RhCl_2Cp^*]_2$ (0.002 mmol) and $Cu(OAc)_2 \cdot H_2O$ (0.20 mmol) in toluene, 130 °C for 24 h.

[b] Isolated yield.

[c] 48 h.

[d] Regioisomeric ratio: β/α > 19:1.

[e] Regioisomeric ratio: para/ortho = 15:1.