JOC The Journal of Organic Chemistry

Article

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J. Org. Chem., **Just Accepted Manuscript** • Publication Date (Web): 20 Sep 2017

Just Accepted

ACS Publications

The Journal of Organic Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

Synthesis of Spiro[pyrazolin-3,3'-oxindoles] and 3-Arylcarbonylmethyl Substituted Ylideneoxindoles by 1,3-Dipolar Cycloadditions of 3-Ylideneoxindoles and in situ-generated α-Diazoketones

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Key Laboratory of Pesticide & Chemical Biology, Ministry of Education, College of Chemistry, Central China Normal University, 152 Luoyu Road, Wuhan, Hubei 430079, China.

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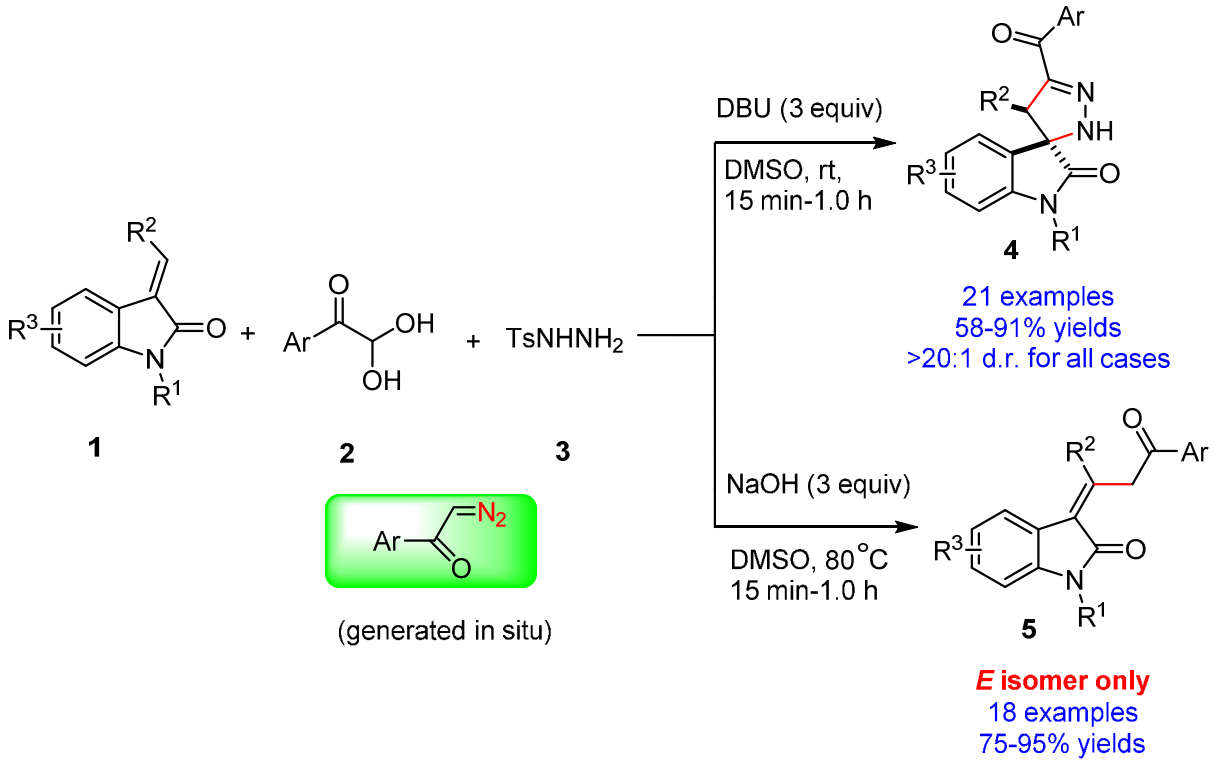


Abstract

An efficient 1,3-dipolar cycloaddition of 3-ylideneoxindoles with in situ-generated α-diazoketones to potentially biological active spiro[pyrazolin-3,3'-oxindoles] **4** with excellent regioselectivity and diastereoselectivity and synthetically useful building block 3-arylcarbonylmethyl substituted

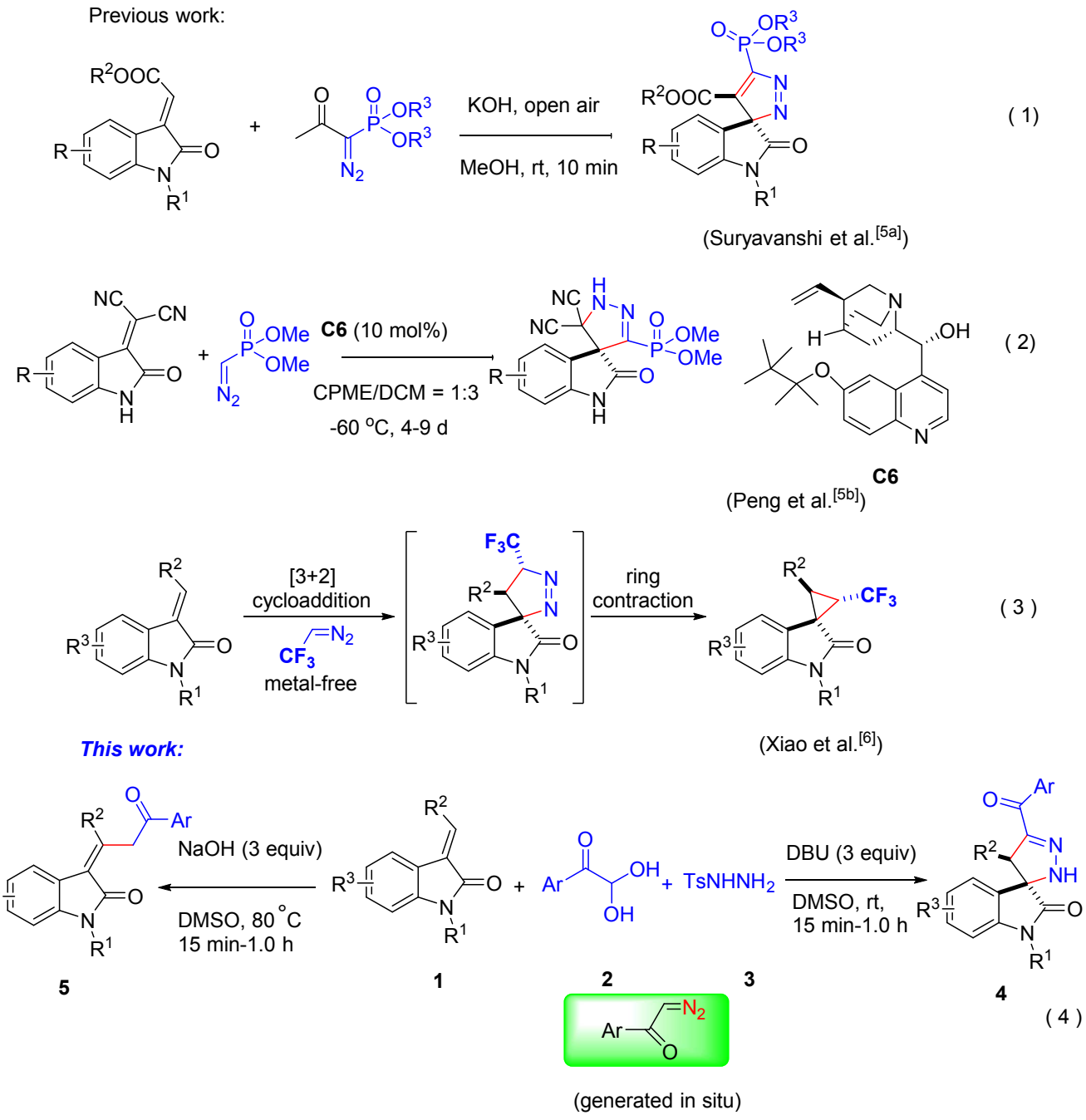
ylideneoxindoles **5** in different conditions has been developed. This method has advantages of mild conditions, simple work-up, wide substrate scopes as well as without using any transition metal catalyst.

Introduction

The spirocyclic oxindoles as an ubiquitous skeleton are widely found in both natural alkaloids and synthetic therapeutic agents.[1, 2] Owing to the importance in modern organic synthetic and medicinal chemistry, numerous efficient synthetic strategies to construct these diverse spirocyclic oxindole derivatives have been developed over the past decades.[3] Spiro[pyrazolin-3,3'-oxindoles] are not only a kind of heterocyclic compounds with biologically activities,[4] but also important intermediates for the transformation to spiro[cyclopropyl-3,3'-oxindoles] and other compounds. 1,3-Dipolar cycloaddition of 3-ylidene-oxindoles and α-diazocarbonyl compounds is a straightforward approach for the construction of spiro[pyrazolin-3,3'-oxindoles] (**Scheme 1**).[5, 6] However, α-diazocarbonyl compounds are not stable, hazardous and potentially explosive, which limited the application of α-diazocarbonyl compounds in laboratory and industry. Recently, a method of in situ-generated α-diazocarbonyl compounds using arylglyoxal monohydrate and tosylhydrazine as the substrates were developed and their application in the [3+2] cycloaddition additions were documented.[7]

On the other hand, the highly functionalized 1,4-enedione derivatives have attracted extensive research interest from synthetic and medical chemists, which are building blocks for the synthesis of various heterocylic compounds such as furans, pyrroles, thiophenes, pyrazines, hydantoins, isoxazoles, and indolizines.[8] As part of our ongoing research program on developing new cascade reactions to construct carbo- and heterocyclic systems,[6, 9] we have recently developed 1,3-dipolar cycloaddition of 3-ylideneoxindoles with in situ-generated α-diazoketones under metal-free conditions. The reaction provides a convenient approach to potentially biological active spiro[pyrazolin-3,3'-oxindoles] **4** with excellent regioselectivity and diastereoselectivity, synthetically useful building block and highly functionalized 3-arylcarbonylmethyl substituted ylideneoxindoles **5** in high yields in different conditions (**Scheme 1**, Eq. 4).

Scheme 1 The [3+2] cycloadditions of 3-ylideneoxindoles and α-diazo compounds for the synthesis of spiro[pyrazolin-3,3'-oxindoles]

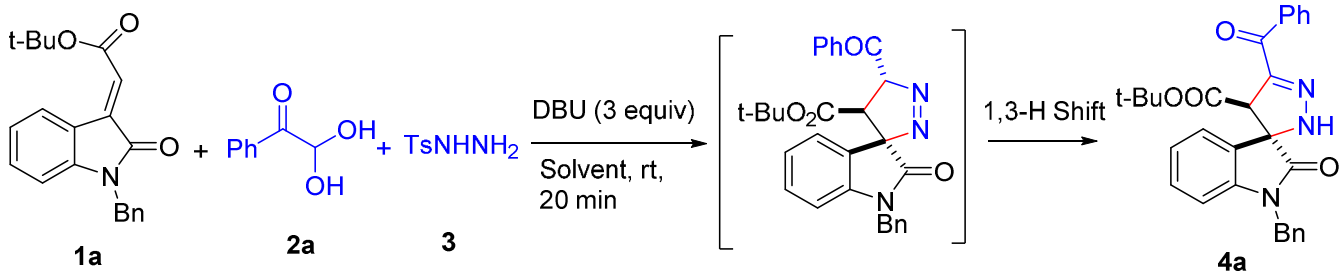


Results and Discussion

Initially, tert-butyl (*E*)-2-(1-benzyl-2-oxoindolin-3-ylidene)acetate **1a** was chosen as the model substrate to react with α-diazoacetophenone, which was generated in situ from phenylglyoxal

monohydrate **2a** and $TsNHNH_2$ **3** in DMSO at room temperature. To our delight, the initial [3+2] cycloaddition occurred smoothly to give the corresponding cycloadduct **4a** in 80% isolated yield with excellent regioselectivity and diastereoselectivity (**Table 1**, entry 1). This result encouraged us to investigate other reaction parameters to further improve the reaction efficiency. Subsequently, a variety of bases were evaluated, it was found that the bases have remarkable effect on the reaction efficiency, Cs_2CO_3, K_2CO_3, KOH, and DBU can trigger the reaction and gave the desired product **4a** in good yields (**Table 1**, entries 1-4), and DBU gave the best result (**Table 1**, entry 4); However, DMAP, Et_3N are not effective base in this [3+2] cycloaddition (Table 1, entries 5-6). Then, a brief screen of reaction medium showed that DMSO was still the best solvent of choice (**Table 1**, entry 4), and the protic solvent EtOH, medium polar solvent DCM, THF and CH_3CN proved detrimental for the reaction (**Table 1**, entries 7-10).

Table 1. Optimization of reaction conditions[a]



entry	base	solvent	yield of **4a**[%][b]	dr of **4a**[c]	entry	base	solvent	yield of **4a**[%][b]	dr of **4a**[c]
1	Cs_2CO_3	DMSO	80	>20:1	6	Et_3N	DMSO	15	n.d.
2	K_2CO_3	DMSO	77	>20:1	7	DBU	EtOH	40	n.d.
3	KOH	DMSO	72	>20:1	8	DBU	CH_3CN	70	>20:1
4	**DBU**	**DMSO**	**83**	**>20:1**	9	DBU	THF	62	>20:1
5	DMAP	DMSO	45	n.d.[d]	10	DBU	DCM	46	n.d.

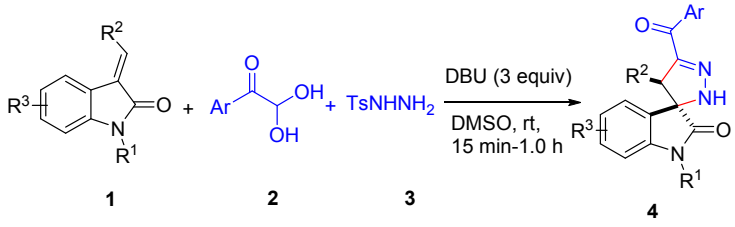
[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), $TsNHNH_2$ (0.5 mmol), base (1.5 mmol, 3 equiv.),

solvent (2.5 mL). [b] Isolated yields based on **1a**. [c] Determined by ^{1}H NMR analysis. [d] Not determined.

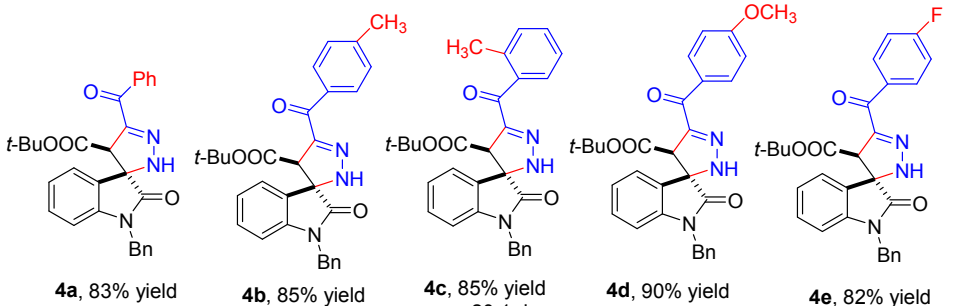
Under the optimized reaction condition, we then investigated the substrate scope of this [3+2] cycloaddition reaction. As shown in **Scheme 2**, a variety of arylglyoxal monohydrates **2** were found to be suitable for the reaction. Both electron-donating (e.g. Me and MeO) and electron-withdrawing groups (e.g. F, Cl, Br and NO_2) were well tolerated under the reaction conditions, and the corresponding spiro[pyrazolin-3,3'-oxindoles] **4a-i** were obtained in a range of 69-90% yields with > 20:1 dr values (**Scheme 2**, **4a**-**4i**). Notably, the above-mentioned halo-substituted products allowed for further transformations through transition metal-catalyzed cross-coupling reactions. Moreover, naphthyl and furyl-substituted substrates were also compatible here (**Scheme 2**, **4j**-**4k**: 87% and 75% yields).

As shown in **Scheme 2**, a wide range of 3-ylideneoxindoles were also found to be suitable for the reaction. Both electron-donating (e.g. Me) and electron-withdrawing groups (e.g. Cl and Br) were compatible well and the desired products **4l-o** were obtained in a range of 82-90% yields with > 20:1 dr values. Then, the effect of *N*-protecting groups and variation of ester moiety of 3-ylideneoxindoles were also examined. Importantly, variation of ester moieties (e.g. Me, Et, and ^{t}Bu) had less effect on both reaction efficiency and stereo-selectivity (**Scheme 2**, **4a**, **4p**-**4q**). Moreover, the 3-ylideneoxindoles with N-protecting groups, such as methyl, or without protection groups could participate in this reaction very well to provide the corresponding products **4r** and **4s** in 91% and 83% yields, respectively. It is noteworthy that the reaction can also be successfully extended to benzoyl-substituted 3-ylideneoxindoles. For example, benzoyl-substituted component was compatible well and the desired products **4t** and **4u** were obtained in moderate yields (**Scheme 2**, **4a**, **4t**-**4u**). All of these products have been fully characterized by IR, ^{1}H NMR, ^{13}C NMR, and HRMS analysis. The structure and stereochemistry of the product **4t** was also unambiguously confirmed by single-crystal X-ray analysis (see supporting information).

Scheme 2. Scope of the [3+2] cycloaddition/1,3-H shift sequence reaction[a]



1 2 3 4



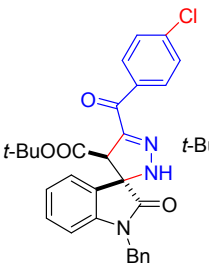
4a, 83% yield
> 20:1 d.r.

4b, 85% yield
> 20:1 d.r.

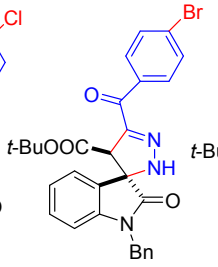
4c, 85% yield
> 20:1 d.r.

4d, 90% yield
> 20:1 d.r.

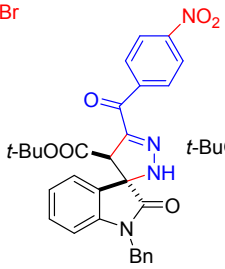
4e, 82% yield
> 20:1 d.r.



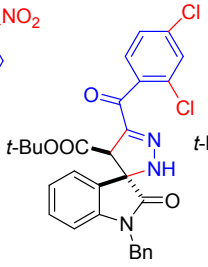
4f, 81% yield
> 20:1 d.r.



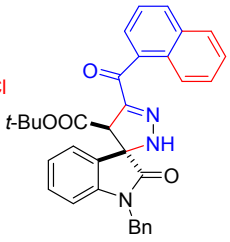
4g, 81% yield
> 20:1 d.r.



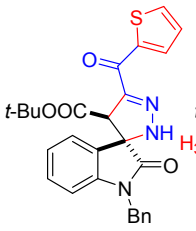
4h, 72% yield
> 20:1 d.r.



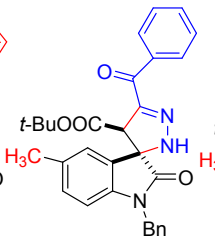
4i, 69% yield
> 20:1 d.r.



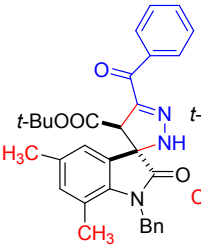
4j, 87% yield
> 20:1 d.r.



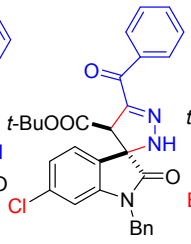
4k, 75% yield
> 20:1 d.r.



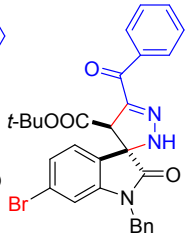
4l, 90% yield
> 20:1 d.r.



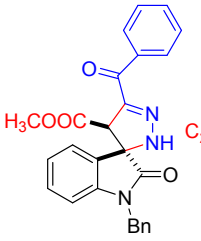
4m, 88% yield
> 20:1 d.r.



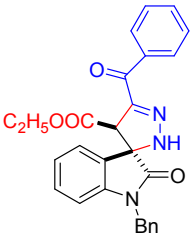
4n, 85% yield
> 20:1 d.r.



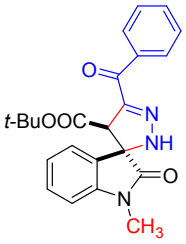
4o, 82% yield
> 20:1 d.r.



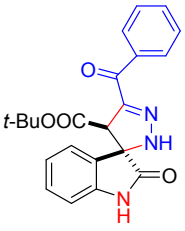
4p, 88% yield
> 20:1 d.r.



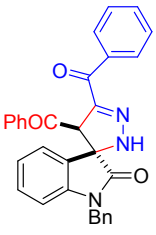
4q, 87% yield
> 20:1 d.r.



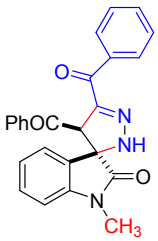
4r, 91% yield
> 20:1 d.r.



4s, 83% yield
> 20:1 d.r.



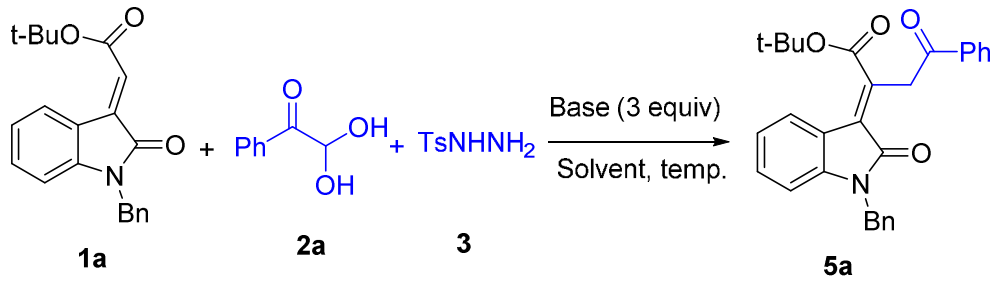
4t, 62% yield
> 20:1 d.r.



4u, 58% yield
> 20:1 d.r.

Interestingly, when tert-butyl (*E*)-2-(1-benzyl-2-oxoindolin-3-ylidene)acetate **1a** reacted with α-diazoacetophenone, which was generated in situ from phenylglyoxal monohydrate **2a** and $TsNHNH_2$ **3** in the presence of Cs_2CO_3 in DMSO at 80 °C, an unprecedented decomposition product 3-benzoylmethyl substituted 3-ylideneoxindole **5a** was obtained in 70% isolated yield (**Table 2**, entry 1). This result encouraged us to explore reaction parameters to further improve the reaction efficiency. As shown in Table 2, a variety of bases such as Cs_2CO_3, NaOH, Na_2CO_3 and DBU were also evaluated (**Table 2**, entries 1-4), and NaOH gave the highest yield (**Table 2**, entry 4); Subsequently, a brief screen of reaction medium showed that DMSO was still the best solvent of choice (**Table 2**, entries 2, 5-9). Finally, the reaction temperature was also explored (**Table 2**, entries 2, 10-12), the results indicated that 80 °C is the most suitable temperature, and elevating or decreasing the reaction temperature cannot improve the reaction efficiency (**Table 2**, entries 10-12).

Table 2. Optimization of reaction conditions for synthesis of 5a[a]



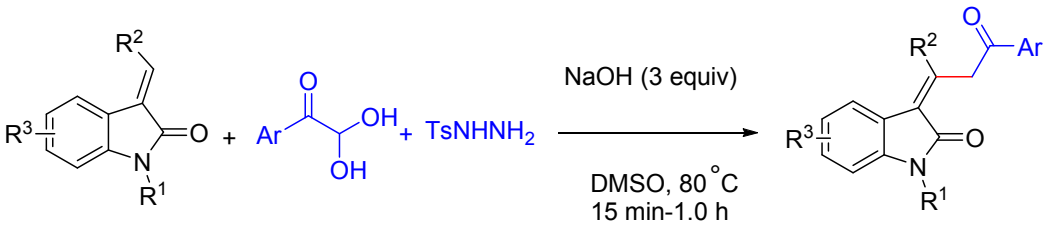
1a **2a** **3** **5a**

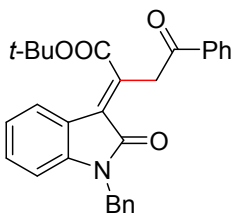
entry	base	solvent	temp [° C]	*t* (min)	yield of **4a**[%][b]	entry	base	solvent	temp [° C]	*t* (min)	yield of **4a**[%][b]
1	Cs_2CO_3	DMSO	80	20	70	7	NaOH	CH_3CN	80	60	42
2	**NaOH**	**DMSO**	**80**	**20**	**85**	8	NaOH	Dioxane	80	120	38
3	Na_2CO_3	DMSO	80	120	58	9	NaOH	Toluene	80	120	25
4	DBU	DMSO	80	120	62	10	NaOH	DMSO	60	60	35
5	NaOH	DMF	80	20	78	11	NaOH	DMSO	100	20	81
6	NaOH	EtOH	80	20	36	12	NaOH	DMSO	110	20	78

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), $TsNHNH_2$ (0.5 mmol), base (1.5 mmol, 3 equiv.), solvent (2.5 mL). [b] Isolated yields based on **1a**.

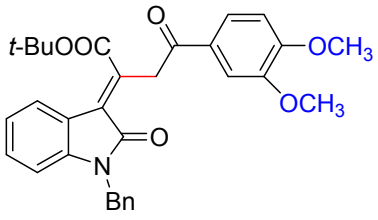
With the optimized reaction condition in hand, we then investigated the substrate scope of this [3+2] cycloaddition/decomposition cascade reactions. As shown in **Scheme 3**, a variety of 3-ylideneoxindoles substrates **1** and arylglyoxal monohydrates **2** were found to be compatible for the reactions and gave the desired products **5a**-**5r** in 75%-95% yields. All of these products **5** have been fully characterized by IR, ^{1}H NMR, ^{13}C NMR, and HRMS analysis. The structure and stereochemistry of the product **5p** was also unambiguously confirmed by single-crystal X-ray analysis (see supporting information).

Scheme 3. Scope of the [3+2] cycloaddition/decomposition sequence reaction[a]

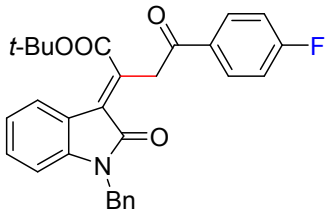




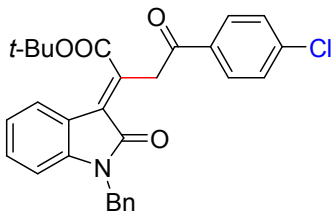
5a, 85% yield



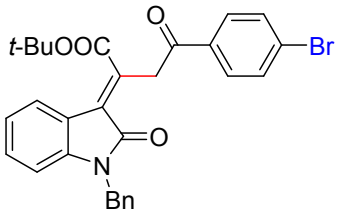
5b, 75% yield



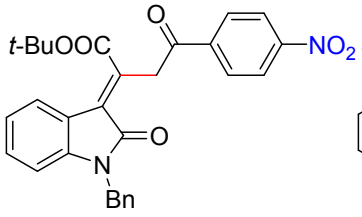
5c, 92% yield



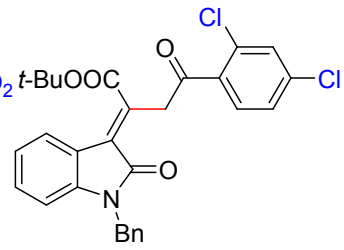
5d, 89% yield



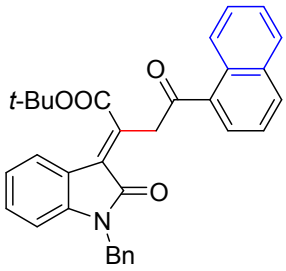
5e, 93% yield



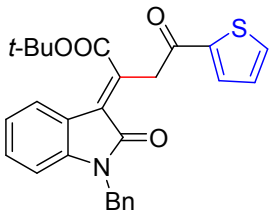
5f, 90% yield



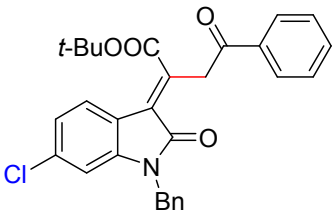
5g, 89% yield



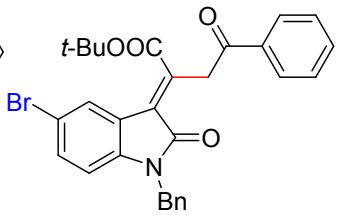
5h, 91% yield



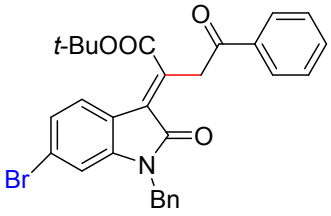
5i, 86% yield



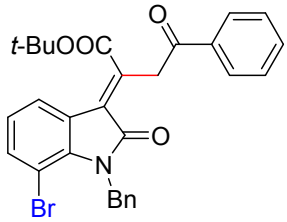
5j, 83% yield



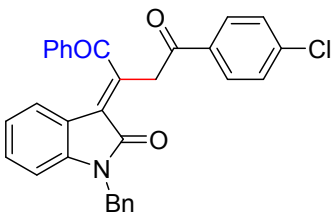
5k, 85% yield



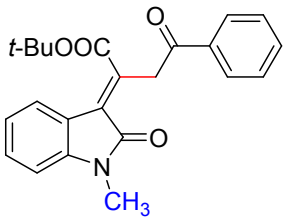
5l, 79% yield



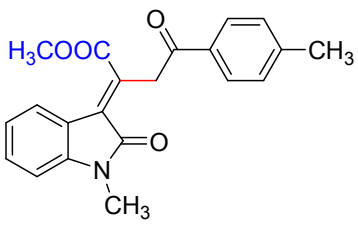
5m, 82% yield



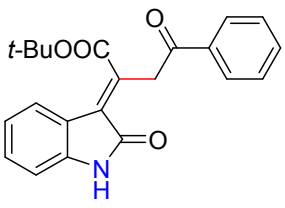
5n, 95% yield



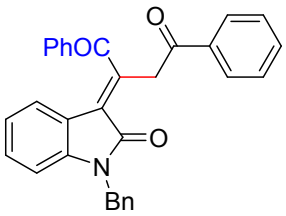
5o, 86% yield



5p, 89% yield



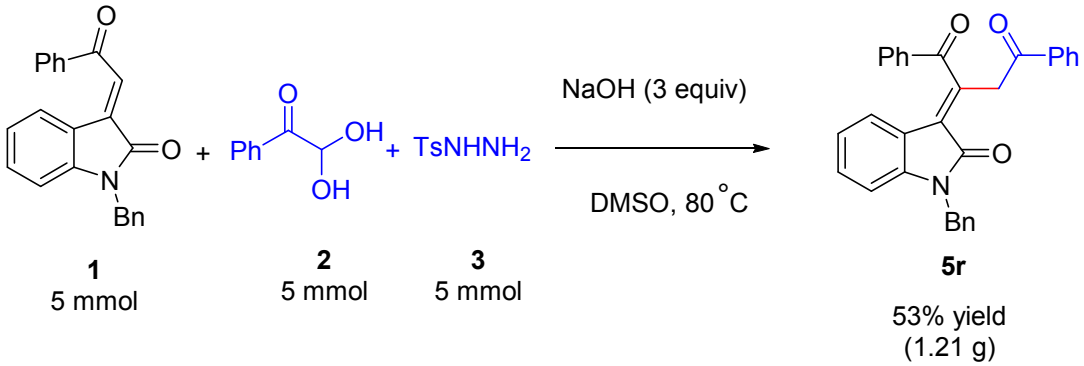
5q,78% yield



5r,79% yield

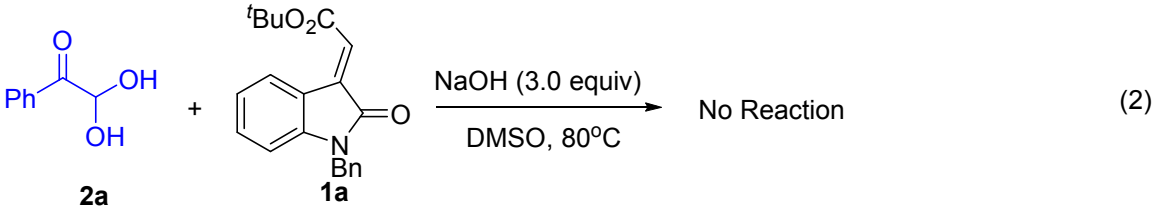
Scheme 4. A gram-scale reaction of the [3+2] cycloaddition/decomposition reaction and some of control experiments

A gram scale reaction

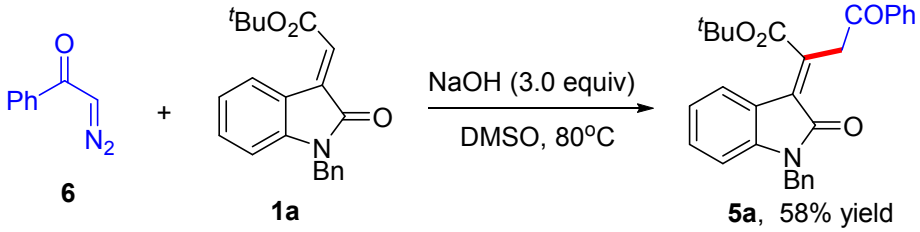


(1)

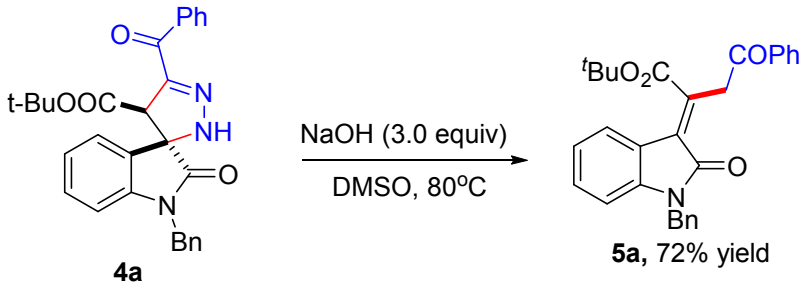
Some control experiments



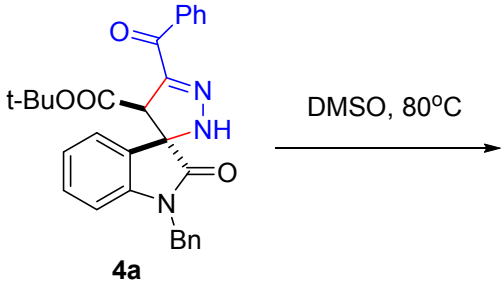
(2)



(3)



(4)



(5)

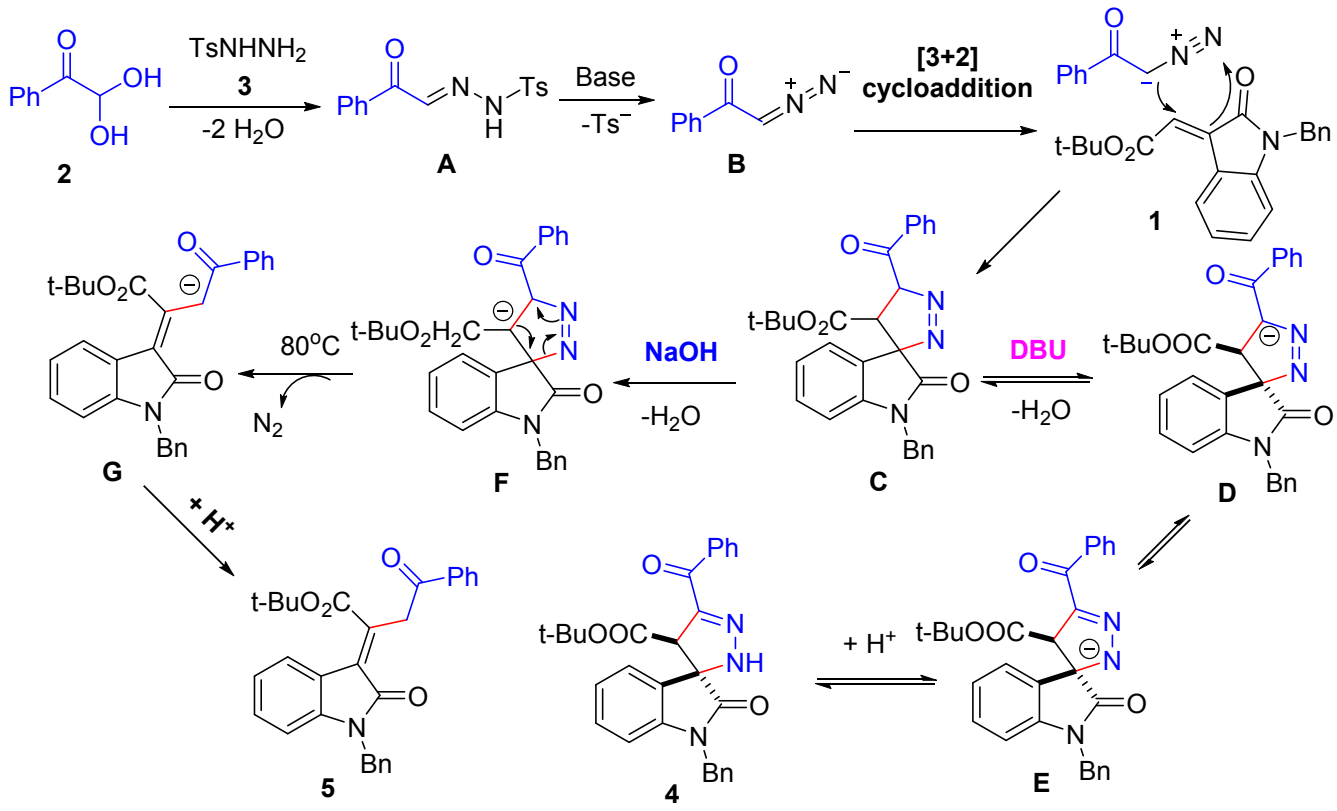
Moreover, a gram-scale reaction of the [3+2] cycloaddition/decomposition reaction was performed, the desired product **5r** was obtained in 53% yield (1.21 g) (**Scheme 4**, eq. 1). In addition, some of

control reactions were carried out in order to gain more insights into the mechanism. Firstly, no reaction occurred according to the reaction condition of the model reaction in the absence of $TsNHNH_2$ (**Scheme 4**, eq 2). Subsequently, when α-diazoacetophenone **6** reacted with tert-butyl (*E*)-2-(1-benzyl-2-oxoindolin-3-ylidene)acetate **1a** in the presence of NaOH in DMSO at 80°C, the desired product **5a** was obtained in 58% yield (**Scheme 4**, eq 3). Moreover, **4a** was transformed to **5a** in 72% yield in the presence of NaOH in DMSO at 80°C (**Scheme 4**, eq 4). However, in the absence of NaOH, the reaction did not occur (**Scheme 4**, eq 5).

Based on our control experimental results and the related literatures,[6,7] a possible mechanism is proposed (**Scheme 5**). Firstly, phenylglyoxal monohydrate **2a** reacts with $TsNHNH_2$ to generate the corresponding hydrazone intermediate **A**, which can subsequently translate to α-diazoacetophenone **B** in the presence of a base. The [3+2] cycloaddition of α-diazoacetophenone **B** with tert-butyl (*E*)-2-(1-benzyl-2-oxoindolin-3-ylidene)acetate **1a** yields intermediate **C,** product **4** is obtained through the proton transfer between intermediate **D** and **E** in the presence of DBU. Moreover, intermediate **G** is formed by the deprotonation of **C** in the presence of NaOH, followed by the release of a nitrogen gas in a higher temperature (80°C); then, the protonation of **G** can yield product **5**.

In summary, we have developed 1,3-dipolar cycloaddition of 3-ylideneoxindoles with in situ-generated α-diazoketones under transition metal-free conditions. This method provided a straightforward approach to highly substituted and functionalized potential biologically spiro[pyrazolin-3,3'-oxindoles] **4** in high yields with excellent regioselectivity and diastereoselectivity. Moreover, an unprecedented sequential [3+2] cycloaddition/decomposition reaction promoted in the presence of NaOH at 80°C was also disclosed, which provides an access to synthetically useful building block 3-arylcarbonylmethyl substituted ylideneoxindoles **5**.

Scheme 5 A possible mechanism



Experimental Section

Unless otherwise noted, materials were purchased from commercial suppliers and used without further purification. All the solvents were treated according to general methods. Flash column chromatography was performed using 200-300 mesh silica gel, and reactions were monitored by thin layer chromatography (TLC). Melting points were determined with a WRS-1B digital melting point apparatus, and the thermometer was uncorrected. 1H NMR spectra were recorded on 400 or 600 MHz spectrometers in $CDCl_3$ or DMSO-d6. Chemical shifts (δ) are reported in ppm relative to the singlet (0 ppm) for tetramethylsilane (TMS). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublets, m = multiplet), coupling constants (Hz) and integration. 13C NMR spectra were recorded on 100 or 150 MHz with complete proton decoupling spectrophotometers (CDCl3: 77.0 ppm). HRMS was recorded on Agilent technologies 6224 TOF LC/MS instrument or Bruker ultrafleXtreme MALDI-TOF/TOF mass spectrometer. X-ray diffraction analysis was carried out with a Bruker APEX-II CCD X-ray diffraction instrument.

General procedure for the synthesis of 3-ylideneoxindoles. [9b] To a stirred solution of tert-butyl 2-(triphenylphosphoranylidene) acetate (11 mmol, 1.1 eq.) in anhydrous THF (30 mL), the N-benzylindoline-2, 3-dione (10 mmol, 1.0 equiv.) was added at 0 °C. The mixture was stirred at the same temperature until the reaction was completed monitored by TLC analysis. The crude product was purified by flash chromatography on silica gel (petroleum ether/ ethyl acetate 5:1). Compound **1a** was obtained as a red solid (2.78 g, 83% yield).

The other 3-ylideneoxindoles were prepared according to the above procedure.

General procedure for the sequential [3+2] Cycloaddition/1,3-H shift reaction for the preparation of products 4. The 3-ylideneoxindole **1** (0.50 mmol), arylglyoxal monohydrate **2** (0.50 mmol) and $TsNHNH_2$ **3** (93 mg, 0.50 mmol) were stirred in 2.0 mL of DMSO at room temperature in a 10 mL schlenk tube for 5 min. Then, the solution of DBU (228 mg, 1.50 mmol) (3 equiv.) in 0.5 mL of DMSO was added dropwise slowly and the reaction mixture was stirred at room temperature for 20-60 min. Upon the completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature and diluted with water (5 mL) and extracted with EtOAc (3 times). The organic layers were combined and washed with brine, dried over anhydrous Na_2SO_4. After the solvent was removed under reduced pressure, the crude product was purified by flash column chromatography on silica gel (petroleum ether/EtOAc =5:1) to afford the desired product **4**.

tert-butyl 5'-benzoyl-1-benzyl-2-oxo-2',4'-dihydrospiro [indoline-3,3'-pyrazole]-4'-carboxylate (**4a**): colorless solid; yield 200 mg (83%); mp 157.8-159.2 ºC; dr > 20:1; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) = 8.18 (d, J = 7.8 Hz, 2H), 7.56 (t, J = 7.2 Hz, 1H), 7.46 (t, J = 7.2 Hz, 2H), 7.22-7.34 (m, 7H), 7.02 (t, J = 7.2 Hz, 1H), 6.75 (d, J = 7.2 Hz, 1H), 6.66 (s, 1H), 5.11 (d, J = 15.6 Hz, 1H), 4.80 (s, 1H), 4.73 (d, J = 15.6 Hz, 1H), 1.02 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) =186.2, 175.6, 165.1, 146.1, 142.4, 136.3, 134.8, 132.4, 130.4, 129.7, 128.6, 128.3, 127.8, 127.6, 127.0, 125.7, 123.0, 109.3, 82.1, 71.9, 60.6, 44.21, 27.41; HRMS (ESI) *m/z* $[M-H]^-$ calcd for $C_{29}H_{26}N_3O_4$ 480.1929, found 480.1942; IR(KBr, cm^{-1}) υ 3500, 3351, 3030, 2968, 1729, 1642, 1613, 1551, 1368.

tert-butyl 1-benzyl-5'-(4-methylbenzoyl)-2-oxo-2',4'-dihydrospiro [indoline-3,3'-pyrazole] -4'-carboxylate (**4b**): colorless solid; yield 210 mg (85%); mp 83.8-84.9 ºC; dr > 20:1; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) = 8.11 (d, J = 7.8 Hz, 2H), 7.27-7.34 (m, 9H), 7.02 (t, J = 7.2 Hz, 1H), 6.75 (d, J = 7.8 Hz, 1H), 6.53 (s, 1H), 5.10 (d, J = 15.6 Hz, 1H), 4.81 (s, 1H), 4.75 (d, J = 15.6 Hz, 1H), 2.42 (s, 3H), 1.03 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 185.9, 175.6, 165.1, 146.8, 143.2, 142.4, 134.8, 133.7, 130.4, 129.9, 128.7, 128.6, 127.7, 127.1, 125.9, 125.8, 123.0, 109.3, 82.1, 71.8, 60.9, 44.4, 27.5, 21.8; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{30}H_{30}N_3O_4$ 496.2231, found 496.2226; IR (KBr, cm^{-1}) υ 3451, 3335, 3063, 2978, 1730, 1609, 1646, 1178, 1154.

tert-butyl 1-benzyl-5'-(2-methylbenzoyl)-2-oxo-2',4'-dihydrospiro[indoline-3,3'-pyrazole] -4'-carboxylate (**4c**): colorless solid; yield 218 mg (88%); mp 192.8-193.3 ºC; dr > 20:1; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.64 (d, J = 6.8 Hz, 1H), 7.27-7.34 (m, 6H), 7.22-7.25 (m, 4H), 7.02 (t, J = 7.2 Hz, 1H), 6.74 (d, J = 8.0 Hz, 1H), 6.56 (s, 1H), 5.11 (d, J = 16.0 Hz, 1H), 4.76 (s, 1H), 4.71 (d, J = 15.6 Hz, 1H), 2.47 (s, 3H), 1.05 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) = 190.7, 175.7, 165.3, 147.5, 142.6, 137.5, 137.1, 134.9, 130.9, 130.8, 130.7, 129.3, 128.9, 127.9, 127.3, 126.0, 125.8, 125.0, 123.3, 109.5, 82.4, 72.7, 59.9, 44.3, 27.4, 20.1; HRMS (ESI) *m/z* $[M-H]^-$ calcd for $C_{30}H_{28}N_3O_4$ 494.2085, found 494.2097; IR (KBr, cm^{-1}) υ 3442, 2930, 1723, 1646, 1613, 1487.

tert-butyl 1-benzyl-5'-(4-methoxybenzoyl)-2-oxo-2',4'-dihydrospiro[indoline-3,3'-pyrazole]-4'-carboxylate (**4d**): yellow oil; yield 230 mg (90%); dr > 20:1; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) = 8.23 (s, 2H), 7.18-7.30 (m, 7H), 6.90-6.96 (m, 4H), 6.69 (s, 1H), 5.07 (d, J = 14.4 Hz, 1H), 4.74 (s, 1H), 4.64 (d, J = 15.6 Hz, 1H), 3.82 (s, 3H), 0.99 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) = 184.7, 175.8, 165.34, 163.1, 146.6, 142.4, 134.9, 132.2, 130.4, 129.1, 128.7, 127.6, 127.1, 125.9, 125.7, 123.0, 113.2, 109.2, 81.9, 71.6, 60.7, 55.23, 44.0, 27.2; HRMS (ESI) *m/z* $[M+H]^+$calcd for $C_{30}H_{30}N_3O_5$ 512.2180, found 512.2169; IR (KBr, cm^{-1}) υ 3444, 3063, 2977, 1729, 1600, 1572, 1369, 1160.

tert-butyl 1-benzyl-5'-(4-fluorobenzoyl)-2-oxo-2',4'-dihydrospiro[indoline-3,3'-pyrazole] -4'-carboxylate (**4e**): colorless solid; yield 205 mg (82%); mp 82.7-83.5 °C; dr > 20:1; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) = 8.27 (dd, J = 6.0 Hz, J = 7.8 Hz, 2H), 7.23-7.34 (m, 6H), 7.13 (t, J = 8.4 Hz, 2H), 7.02 (t, J = 7.8 Hz, 2H), 6.76 (d, J = 7.8 Hz, 1H), 6.63 (s, 1H), 5.11 (d, J = 15.6 Hz, 1H), 4.79 (s, 1H), 4.74 (d, J = 15.6 Hz, 1H), 1.03 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) = 184.8, 175.8, 165.4, 147.1, 146.7, 142.7, 134.9, 132.7, 130.7, 128.9, 127.9, 127.3, 126.0, 125.8, 123.3, 115.2 (d, J = 21.5 Hz), 109.5, 82.3, 71.8, 60.7, 44.3, 27.4; HRMS (ESI) *m/z* $[M-H]^-$ calcd for $C_{29}H_{25}N_3O_4F$ 498.1835, found 498.1846; IR (KBr, cm^{-1}) υ 3448, 2979, 1729, 1634, 1487, 1369, 1233.

tert-butyl 1-benzyl-5'-(4-chlorobenzoyl)-2-oxo-2',4'-dihydrospiro[indoline-3,3'-pyrazole] -4'-carboxylate (**4f**): colorless solid; yield 209 mg (81%); mp 158.6-160.2 °C; dr > 20:1; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) = 8.13 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 7.27-7.31 (m, 6H), 7.21 (t, J = 7.8 Hz, 1H), 6.97-6.99 (m, 2H), 6.71 (d, J = 7.8 Hz, 1H), 5.08 (d, J = 15.6 Hz, 1H), 4.71 (s, 1H), 4.65 (d, J = 15.6 Hz, 1H), 1.01 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) = 184.9, 175.7, 165.3, 146.0, 142.6, 138.9, 134.8, 134.7, 131.4, 130.6, 128.8, 128.3, 127.8, 127.1, 125.9, 125.6, 123.2, 109.4, 82.2, 71.8, 60.4, 44.1, 27.3; HRMS (ESI) *m/z* $[M-H]^-$ calcd for $C_{29}H_{25}N_3O_4Cl$ 514.1539, found 514.1553; IR (KBr, cm^{-1}) υ 3448, 2979, 1728, 1632, 1548, 1468, 1369.

tert-butyl 1-benzyl-5'-(4-bromobenzoyl)-2-oxo-2',4'-dihydrospiro[indoline-3,3'-pyrazole]-4'-carboxylate (**4g**): colorless solid; yield 224 mg (80%); mp 158.2-159.8 °C; dr > 20:1; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) = 8.03 (d, J = 7.8 Hz, 2H), 7.53 (d, J = 7.2 Hz, 2H), 7.18-7.29 (m, 8H), 6.96 (t, J = 7.2 Hz , 1H), 6.69 (d, J = 7.8 Hz, 1H), 5.07 (d, J = 15.6 Hz, 1H), 4.68 (s, 1H), 4.61 (d, J = 15.0 Hz, 1H), 1.00 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) = 185.0, 175.7, 165.2, 142.4, 135.1, 134.8, 134.2, 131.4, 131.1, 130.5, 128.7, 127.7, 127.5, 127.0, 125.8, 125.5, 123.1, 109.3, 82.1, 71.8, 60.2, 44.0,

27.2. HRMS (ESI) *m/z* [M-H]$^-$ calcd for $C_{29}H_{25}N_3O_4Br$ 558.1034, found 558.1042; IR (KBr, cm^{-1}) υ 3450, 3272, 3068, 2977, 1744, 1705, 1631, 1585, 1476, 1328.

tert-butyl 1-benzyl-5'-(4-nitrobenzoyl)-2-oxo-2',4'-dihydrospiro[indoline-3,3'-pyrazole] -4'-carboxylate (**4h**): colorless solid; yield 189 mg (72%); mp 123.9-125.1 °C; dr > 20:1; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 8.31 (d, J = 9.2 Hz, 2H), 8.25 (d, J = 8.8 Hz, 2H), 7.24-7.32 (m, 6H), 7.01 (t, J = 7.6 Hz, 1H), 6.84 (s, 1H), 6.75 (d, J = 7.6 Hz, 1H), 5.10 (d, J = 15.6 Hz, 1H), 4.74 (s, 1H), 4.70 (d, J = 14.8 Hz, 2H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 184.2, 175.2, 164.9, 149.6, 145.6, 142.6, 141.3, 134.6, 130,8, 130.7, 128.8, 127.8, 127.0, 126.0, 125.2, 123.2, 123.0, 109.4, 82.6, 72.1, 60.1, 44.4, 27.6. HRMS (ESI) *m/z* [M-H]$^-$ calcd for $C_{29}H_{25}N_4O_6$ 525.1780, found 525.1784; IR (KBr, cm^{-1}) υ 3451, 2979, 1737, 1703, 1632, 1487, 1347.

tert-butyl 1-benzyl-5'-(2,4-dichlorobenzoyl)-2-oxo-2',4'-dihydrospiro[indoline-3,3'-pyrazole] -4'-carboxylate (**4i**): colorless solid; yield 189 mg (69%); mp 133.6-134.5 °C; dr > 20:1; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.45 (d, J = 8.0 Hz, 1H), 7.36 (s, 1H), 7.17-7.27 (m, 8H), 6.96-6.98 (m, 2H), 6.69 (d, J = 7.6 Hz, 1H), 5.05 (d, J = 15.2 Hz, 1H), 4.64 (d, J = 15.2 Hz, 1H), 4.62 (s, 1H), 1.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 185.9, 175.0, 164.5, 145.2, 142.2, 136.4, 135.6, 134.5, 132.4, 130.8, 130.6, 129.7, 128.6, 127.6, 126.9, 126.4, 125.8, 125.0, 123.0, 109.4, 82.4, 73.1, 59.1, 44.2, 27.4; HRMS (ESI) *m/z* [M-H]$^-$ calcd for $C_{29}H_{24}N_3O_4Cl_2$ 548.1149, found 548.1163; IR (KBr, cm^{-1}) υ 3349, 3061, 2980, 1725, 1654, 1612, 1257.

tert-butyl 5'-(1-naphthoyl)-1-benzyl-2-oxo-2',4'-dihydrospiro[indoline-3,3'-pyrazole]-4'-carboxylate (**4j**): colorless solid; yield 231 mg (87%); mp 184.4-185.7 °C; dr > 20:1; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) = 8.35 (d, J = 8.4 Hz, 1H), 7.95 (t, J = 6.0 Hz, 2H), 7.86 (d, J = 7.8 Hz, 1H), 7.56 (t, J = 7.2 Hz, 1H), 7.50-7.52 (m, 2H), 7.21-7.32 (m, 7H), 7.00 (t, J = 7.8 Hz, 1H), 6.70 (d, J = 7.8 Hz, 1H), 6.61 (s, 1H), 5.10 (d, J = 15.6 Hz, 1H), 4.85 (s, 1H), 4.65 (d, J = 15.6 Hz, 1H), 1.06 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) = 190.0, 175.6, 165.4, 147.6, 142.5, 134.9, 134.8, 133.5, 131.6, 130.7, 130.6, 128.8, 128.6, 128.2, 127.8, 127.3, 127.2, 126.2, 126.0, 125.6, 125.5, 124.2, 123.2, 109.4, 82.36, 72.70, 60.0, 44.2, 27.4; HRMS (ESI) *m/z* [M-H]$^-$ calcd for $C_{33}H_{28}N_3O_4$ 530.2085, found 530.2099; IR (KBr, cm^{-1}) υ 3455, 3031, 1729, 1641, 1510, 1485, 1176.

tert-butyl 1-benzyl-2-oxo-5'-(thiophene-2-carbonyl)-2',4'-dihydrospiro [indoline-3, 3'-pyrazole]-4'-carboxylate (**4k**): colorless solid; yield 183 mg (75%); mp 103.3-104.8 °C; dr > 20:1; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) = 8.27 (d, J = 3.0 Hz, 1H), 7.82 (s, 1H), 7.63 (d, J = 5.4 Hz, 1H), 7.46-7.48 (m, 1H), 7.24-7.33 (m, 5H), 7.21 (t, J = 7.8 Hz, 1H), 7.13 (t, J = 4.8 Hz, 1H), 6.72-6.74 (m, 2H), 5.10 (d, J = 15.6 Hz, 1H), 4.73 (s, 1H), 4.71 (d, J = 15.6 Hz, 1H), 1.03 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) = 177.6, 175.8, 165.2, 146.1, 142.6, 141.0, 134.9, 134.7, 134.1, 130.6, 128.8, 127.8, 127.7, 127.2, 126.1, 125.7, 123.2, 109.3, 88.2, 71.9, 60.3, 44.2, 27.4; HRMS (ESI) *m/z* [M-H]$^-$ calcd for $C_{27}H_{24}N_3O_4S$ 486.1493, found 486.1507; IR (KBr, cm^{-1}) υ 3454, 3023, 1639, 1512, 1420, 1384.

tert-butyl 5'-benzoyl-1-benzyl-5-methyl-2-oxo-2',4'-dihydrospiro[indoline-3,3'-pyrazole] -4'-carboxylate (**4l**): colorless solid; yield 223 mg (90%); mp 168.2-170.0 °C; dr > 20:1; ^{1}H NMR (600 MHz, $CDCl_3$) δ

(ppm) = 8.20 (d, J = 7.2 Hz, 2H), 7.56 (t, J = 6.9 Hz, 1H), 7.46 (t, J = 7.2 Hz, 2H), 7.27-7.33 (m, 6H), 7.14 (s, 1H), 7.03 (d, J = 7.2 Hz, 1H), 6.62 (d, J = 7.8 Hz, 1H), 5.08 (d, J = 15.6 Hz, 1H), 4.78 (s, 1H), 4.71 (d, J = 15.6 Hz, 1H), 2.24 (s, 3H), 1.05 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) = 186.6, 175.7, 165.4, 146.7, 140.2, 136.5, 135.0, 132.9, 132.6, 130.8, 129.9, 128.8, 128.1, 127.8, 127.2, 126.6, 125.8, 109.2, 82.1, 71.9, 60.5, 44.2, 27.3, 20.8; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{30}H_{30}N_3O_4$ 496.2231, found 496.2226; IR (KBr, cm^{-1}) υ 3447, 2981, 1730, 1712, 1647, 1232.

tert-butyl 5'-benzoyl-1-benzyl-5,7-dimethyl-2-oxo-2',4'-dihydrospiro[indoline-3,3'-pyrazole]-4'-carboxylate (**4m**): colorless solid; yield 224 mg (88%); mp 174.8-176.4 °C; dr > 20:1; 1H NMR (600 MHz, $CDCl_3$) δ (ppm) = 8.20 (d, J = 7.8 Hz, 2H), 7.56 (t, J = 7.2 Hz, 1H), 7.47 (t, J = 7.2 Hz, 2H), 7.33 (t, J = 7.2 Hz, 2H), 7.27 (t, J = 7.2 Hz, 2H), 7.20 (d, J = 7.2 Hz, 2H), 7.03 (s, 1H), 6.82 (s, 1H), 5.33 (d, J = 16.8 Hz, 1H), 4.99 (d, J = 16.8 Hz, 1H), 4.78 (s, 1H), 2.22 (s, 3H), 2.20 (s, 3H), 1.14 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) = 186.6, 176.9, 165.5, 146.6, 138.2, 136.8, 136.6, 134.9, 132.9, 132.6, 129.9, 128.9, 128.1, 127.3, 126.6, 125.5, 124.5, 120.0, 82.2, 71.3, 60.8, 45.4, 27.5, 20.5, 18.5; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{31}H_{32}N_3O_4$ 510.2387, found 510.2393; IR (KBr, cm^{-1}) υ 3440, 3057, 2932, 1728, 1708, 1632, 1575, 1236.

tert-butyl 5'-benzoyl-1-benzyl-6-chloro-2-oxo-2',4'-dihydrospiro[indoline-3,3'-pyrazole] -4'-carboxylate (**4n**): colorless solid; yield 219 mg (85%); mp 135.8-136.4 °C; dr > 20:1; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 8.13 (d, J = 8.0 Hz, 2H), 7.52 (t, J = 6.8 Hz, 1H), 7.41 (t, J = 7.2 Hz, 2H), 7.20-7.31 (m, 6H), 6.95 (d, J = 8.0 Hz, 1H), 6.68-6.72 (m, 2H), 5.05 (d, J = 15.6 Hz, 1H), 4.71 (s, 1H), 4.61 (d, J = 15.6 Hz, 1H), 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 186.0, 175.5, 165.0, 146.4, 143.7, 136.3, 136.2, 134.3, 132.5, 129.8, 128.8, 127.9, 127.1, 127.0, 126.8, 124.0, 122.9, 109.9, 82.5, 71.4, 60.8, 44.4, 27.6; HRMS (ESI) *m/z* $[M-H]^-$ calcd for $C_{29}H_{25}N_3O_4Cl$ 514.1539, found 514.1551; IR (KBr, cm^{-1}) υ 3330, 3033, 2931, 1717, 1651, 1608, 1488, 1214.

tert-butyl 5'-benzoyl-1-benzyl-6-bromo-2-oxo-2',4'-dihydrospiro[indoline-3,3'-pyrazole] -4'-carboxylate (**4o**): colorless solid; yield 229 mg (82%); mp 103.6-105.1 °C; dr > 20:1; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 8.13 (d, J = 7.2 Hz, 2H), 7.52 (t, J = 7.4 Hz, 1H), 7.41 (t, J = 7.6 Hz, 2H), 7.25-7.29 (m, 4H), 7.11-7.15 (m, 3H), 6.84 (s, 1H), 6.79 (s, 1H), 5.04 (d, J = 15.4 Hz, 1H), 4.70 (s, 1H), 4.59 (d, J = 15.4 Hz, 1H), 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 186.0, 175.4, 165.0, 146.4, 143.8, 136.2, 134.3, 132.5, 129.8, 128.9, 127.9, 127.1, 127.0, 125.9, 124.6, 124.2, 122.7, 112.6, 82.5, 71.4, 60.8, 44.4, 27.6; HRMS (ESI) *m/z* $[M-H]^-$ calcd for $C_{29}H_{25}N_3O_4Br$ 558.1034, found 558.1040; IR (KBr, cm^{-1}) υ 3442, 2980, 1722, 1604, 1546, 1256.

Methyl 5'-benzoyl-1-benzyl-2-oxo-2',4'-dihydrospiro[indoline-3,3'-pyrazole] -4'-carboxylate (**4p**): colorless solid; yield 193 mg (88%); mp 83.5-84.7 °C; dr > 20:1; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 8.21 (d, J = 7.6 Hz, 2H), 7.55 (t, J = 7.3 Hz, 1H), 7.45 (t, J = 7.6 Hz, 2H), 7.20-7.32 (m, 7H), 7.00 (t, J = 7.4 Hz, 1H), 6.71 (d, J = 7.6 Hz, 1H), 6.64 (s, 1H), 5.11 (d, J = 15.6 Hz, 1H), 4.86 (s, 1H), 4.73 (d, J = 15.6 Hz, 1H), 3.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 185.7, 175.1, 166.5, 145.0, 142.0, 136.0, 134.6, 132.5, 130.4, 129.7, 128.5, 127.8, 127.5, 126.7, 125.1, 124.7, 122.9, 109.4, 71.8, 59.5,

51.9, 44.0; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{22}N_3O_4$ 440.1605, found 440.1607; IR (KBr, cm^{-1}) υ 3346, 3062, 2951, 1727, 1613, 1576, 1254.

Ethyl 5'-benzoyl-1-benzyl-2-oxo-2',4'-dihydrospiro[indoline-3,3'-pyrazole]-4'-carboxylate (**4q**): colorless solid; yield 197 mg (87%); mp 121.8-122.5 °C; dr > 20:1; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) = 8.20 (d, J = 7.2 Hz, 2H), 7.55 (t, J = 6.9 Hz, 1H), 7.44 (t, J = 7.8 Hz, 3H), 7.18-7.32 (m, 6H), 6.98 (t, J = 7.4 Hz, 1H), 6.90 (s, 1H), 6.69 (d, J = 7.8 Hz, 1H), 5.15 (d, J = 16.2 Hz, 1H), 4.83 (s, 1H), 4.64 (d, J = 16.2 Hz, 1H), 3.77 (q, J = 7.2 Hz, 2H), 0.64 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 185.9, 175.2, 166.0, 145.5, 142.2, 136.1, 134.6, 132.4, 130.4, 129.8, 128.5,127.8, 127.6, 126.9, 125.4, 125.0, 123.0, 109.4, 71.7, 61.2, 59.7, 44.1, 13.4; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{24}N_3O_4$ 454.1761, found 454.1765; IR (KBr, cm^{-1}) υ 3450, 2981, 1723, 1633, 1613, 1236.

tert-butyl 5'-benzoyl-1-methyl-2-oxo-2',4'-dihydrospiro[indoline-3,3'-pyrazole] -4'-carboxylate (**4r**): colorless solid; yield 184 mg (91%); mp 141.2-143.0 °C; dr > 20:1; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 8.13 (d, J = 7.6 Hz, 2H), 7.54 (t, J = 7.2 Hz, 1H), 7.43 (t, J = 7.6 Hz, 2H), 7.29-7.32 (m, 2H), 7.03 (t, J = 7.6 Hz, 1H), 6.83 (d, J = 8.0 Hz, 1H), 5.24 (s, 1H), 4.69 (s, 1H), 3.23 (s, 3H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 186.3, 175.1, 164.9, 146.6, 143.3, 136.3, 132.5, 130.6, 129.7, 127.9, 125.8, 125.4, 123.1, 108.35, 82.12, 72.0, 60.6, 27.5, 26.9; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{24}N_3O_4$ 406.1761, found 406.1769; IR (KBr, cm^{-1}) υ 3449, 3068, 2977, 1713, 1609, 1575, 1261.

tert-butyl 5'-benzoyl-2-oxo-2',4'-dihydrospiro[indoline-3,3'-pyrazole]-4'-carboxylate (**4s**): colorless solid; yield 162 mg (83%); mp 151.7-153.2 °C; dr > 20:1; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 9.23 (s, 1H), 8.11 (d, J = 7.6 Hz, 2H), 7.54 (t, J = 7.6 Hz, 1H), 7.42 (t, J = 7.2 Hz, 2H), 7.23 (d, J = 6.8 Hz, 1H), 7.18 (t, J = 7.6 Hz, 1H), 6.95 (t, J = 7.6 Hz, 1H), 6.81 (d, J = 7.6 Hz, 1H), 4.64 (s, 1H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 186.3, 177.9, 165.1, 146.1, 140.6, 136.2, 132.5, 130.6, 129.8, 128.0,126.0, 125.7, 123.0, 110.6, 82.5, 72.5, 60.3, 27.5; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{22}N_3O_4$ 392.1605, found 392.1612; IR (KBr, cm^{-1}) υ 3323, 2935, 1734, 1700, 1635, 1263.

(1-benzyl-2-oxo-2',4'-dihydrospiro[indoline-3,3'-pyrazole]-4',5'-diyl)bis(phenylmethanone) (**4t**): colorless solid; yield 150 mg (62%); mp 184.5-186.0 °C; dr > 20:1; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) = 8.25 (d, J = 7.8 Hz, 2H), 7.53-7.56 (m, 3H), 7.46 (t, J = 7.8 Hz, 2H), 7.40 (t, J = 7.2 Hz, 1H), 7.27-7.29 (m, 4H), 7.18-7.21 (m, 3H), 7.14 (t, J = 7.8 Hz, 2H), 7.03 (t, J = 7.8 Hz, 1H), 6.88 (t, J = 7.2 Hz, 1H), 6.52 (d, J = 7.8 Hz, 1H), 5.79 (s, 1H), 4.97 (d, J = 15.6 Hz, 1H), 4.65 (d, J = 15.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) = 193.2, 185.3, 175.7, 148.4, 142.1, 136.4, 136.2, 134.9, 133.9, 133.4, 132.7, 130.4, 130.1, 128.9, 128.4, 128.1, 127.9, 127.4, 126.6, 124.9, 123.5, 109.3, 72.1, 60.4, 44.3; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{31}H_{23}N_3O_3Na$ 508.1632, found 508.1629; IR (KBr, cm^{-1}) υ 3450, 3302, 3060, 2930, 1696, 1680, 1577, 1152.

(1-methyl-2-oxo-2',4'-dihydrospiro[indoline-3,3'-pyrazole]-4',5'-diyl)bis(phenylmethanone) (**4u**): colorless oil; yield 119 mg (58%); dr > 20:1; ^{1}H NMR (600 MHz, DMSO-d6) δ (ppm) = 9.69 (s, 1H), 8.13 (d, J = 8.4 Hz, 2H), 7.65 (t, J = 7.8 Hz, 1H), 7.54-7.57 (m, 5H), 7.36 (t, J = 8.4 Hz, 2H), 7.17 (t, J = 7.8 Hz, 1H), 6.97 (d, J = 7.2 Hz, 1H), 6.90 (t, J = 7.8 Hz, 1H), 6.84 (d, J = 7.8 Hz, 1H), 5.55 (s, 1H),

3.14 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d6) δ (ppm) = 193.6, 185.4, 174.9, 144.8, 143.3, 136.6, 135.9, 133.8, 132.6, 130.3, 129.6, 128.7, 128.3, 127.8, 125.8, 124.5, 122.8, 108.9, 71.6, 58.9, 26.5; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{25}H_{19}N_3O_3Na$ 432.1319, found 432.1320; IR (KBr, cm^{-1}) υ 3450, 3025, 1637, 1446, 1207.

General procedure for the synthesis of products 5. 3-ylideneoxindole **1** (0.50 mmol), arylglyoxal monohydrate **2** (0.50 mmol), $TsNHNH_2$ **3** (93 mg, 0.50 mmol) and NaOH (60 mg, 1.5 mmol) in 2.5 mL of DMSO were added to a 10 mL schlenk tube and stirred at 80 ^oC for 20-60 min. Upon the completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature and diluted with water (5 mL) and extracted with EtOAc (3 times). The organic layers were combined and washed with brine, dried over anhydrous Na_2SO_4. After the solvent was removed under reduced pressure, the crude product was purified by flash column chromatography on silica gel (petroleum ether/EtOAc =5:1) to afford the desired product **5**.

(E)-tert-butyl 2-(1-benzyl-2-oxoindolin-3-ylidene)-4-oxo-4-phenylbutanoate (**5a**): yellow solid; yield 193 mg (85%); mp 89.1-90.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 8.04 (d, J = 8.0 Hz, 2H), 7.80 (d, J = 8.0 Hz, 1H), 7.52 (t, J = 7.6 Hz, 1H), 7.43 (t, J = 7.6 Hz, 2H), 7.19-7.25 (m, 5H), 7.14 (t, J = 7.2 Hz, 1H), 6.93 (t, J = 7.6 Hz, 1H), 6.65 (d, J = 7.6 Hz, 1H), 5.12 (s, 2H), 4.88 (s, 2H), 1.54 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 195.5, 167.6, 166.2, 142.2, 138.0, 136.6, 135.4, 133.0, 130.1, 128.5, 128.4, 128.1, 127.5, 127.3, 126.9, 124.5, 122.0, 120.3, 108.8, 83.3, 43.5, 39.3, 28.1; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{29}H_{28}NO_4$ 454.2013, found 454.2012; IR (KBr, cm^{-1}) υ 3029, 2970, 1703, 1609, 1468, 1235.

(E)-tert-butyl 2-(1-benzyl-2-oxoindolin-3-ylidene)-4-(3,4-dimethoxyphenyl)-4-oxobutanoate (**5b**): red solid; yield 192 mg (75%); mp 81.6-82.5 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) = 7.78 (d, J = 7.8 Hz, 2H), 7.61 (s, 1H), 7.27-7.31 (m, 4H), 7.19 (t, J = 7.8 Hz, 2H), 6.98 (t, J = 7.6 Hz, 1H), 6.91 (d, J = 8.4 Hz, 1H), 6.70 (d, J = 7.8 Hz, 1H), 5.11 (s, 2H), 4.94 (s, 2H), 3.95 (s, 3H), 3.92 (s, 3H), 1.57 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) = 194.5, 167.9, 166.6, 153.3, 148.8, 142.5, 142.3, 138.8, 135.6, 130.2, 129.9, 128.7, 127.5, 127.0, 124.5, 123.1, 122.2, 120.5, 110.3, 110.0, 108.9, 83.4, 60.4, 56.0, 43.4, 39.4, 28.0; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{31}H_{32}NO_6$ 514.2224, found 514.2233; IR (KBr, cm^{-1}) υ 2964, 1727, 1697, 1672, 1610, 1263.

(E)-tert-butyl 2-(1-benzyl-2-oxoindolin-3-ylidene)-4-(4-fluorophenyl)-4-oxobutanoate (**5c**): orange solid; yield 217 mg (92%); mp 117.6-119.3 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) = 8.10 (dd, J = 6.3 Hz, J = 7.8 Hz, 2H), 7.81 (d, J = 8.4 Hz, 1H), 7.30 (d, J = 7.2 Hz, 2H), 7.27 (d, J = 7.8 Hz, 2H), 7.19 (t, J = 7.8 Hz, 2H), 7.14 (t, J = 7.8 Hz, 2H), 6.98 (t, J = 7.8 Hz, 1H), 6.70 (d, J = 7.8 Hz, 1H), 5.09 (s, 2H), 4.93 (s, 2H), 1.56 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 194.1, 167.6, 166.2, 142.2, 137.7, 135.3, 133.0, 132.5, 132.4, 130.8, 130.7, 130.2, 128.6, 127.4, 126.9, 124.5, 122.1, 120.3, 115.6 (d, J = 21.4 Hz), 108.8, 83.4, 43.4, 39.8, 28.1; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{29}H_{27}NO_4F$ 472.1919, found 472.1911; IR (KBr, cm^{-1}) υ 3066, 2976, 1705, 1689, 1597, 1329.

(E)-tert-butyl 2-(1-benzyl-2-oxoindolin-3-ylidene)-4-(4-chlorophenyl)-4-Oxobutanoate (**5d**): orange solid; yield 217 mg (89%); mp 137.4-138.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.98 (d, J = 8.4

Hz, 2H), 7.78 (d, J = 7.6 Hz, 1H), 7.41 (d, J = 8.0 Hz, 2H), 7.22-7.27 (m, 5H), 7.15 (d, J = 7.6 Hz, 1H), 6.95 (t, J = 7.6 Hz, 1H), 6.66 (d, J = 8.0 Hz, 1H), 5.07 (s, 2H), 4.89 (s, 2H), 1.55 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 194.5, 167.6, 166.2, 142.3, 139.4, 137.5, 135.3, 134.9, 130.3, 129.6, 128.8, 128.6, 127.6, 127.5, 126.9, 124.6, 122.1, 120.3, 108.9, 83.5, 43.5, 39.9, 28.1; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{29}H_{27}NO_4Cl$ 488.1623, found 488.1609; IR (KBr, cm^{-1}) υ 2980, 1703, 1690, 1589, 1159.

(E)-tert-butyl 2-(1-benzyl-2-oxoindolin-3-ylidene)-4-(4-bromophenyl)-4-Oxobutanoate (**5e**): yellow solid; yield 247 mg (93%); mp 123.5-125.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.90 (d, J = 8.4 Hz, 2H), 7.77 (d, J = 7.6 Hz, 1H), 7.58 (d, J = 8.4 Hz, 2H), 7.22-7.25 (m, 5H), 7.15 (t, J = 7.2 Hz, 1H), 6.94 (t, J = 7.6 Hz, 1H), 6.66 (d, J = 7.6 Hz, 1H), 5.05 (s, 2H), 4.89 (s, 2H), 1.55 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 194.6, 184.9, 167.6, 166.2, 142.3, 137.5, 135.3, 132.0, 131.7, 130.3, 129.7, 128.6, 128.2, 127.4, 126.9, 124.6, 122.1, 120.3, 108.8, 83.5, 43.5, 39.9, 28.1; HRMS (ESI) *m/z* $[M-H]^-$ calcd for $C_{29}H_{25}NO_4Br$ 530.0972, found 530.0980; IR (KBr, cm^{-1}) υ 2979, 1702, 1642, 1585, 1235.

(E)-tert-butyl 2-(1-benzyl-2-oxoindolin-3-ylidene)-4-(4-nitrophenyl)-4-Oxobutanoate (**5f**): yellow solid; yield 224 mg (90%); mp 106.3-108.0 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) = 8.30 (d, J = 8.4 Hz, 2H), 8.22 (d, J = 8.4 Hz, 2H), 7.82 (d, J = 7.8 Hz, 1H), 7.29-7.32 (m, 3H), 7.22-7.26 (m, 2H), 7.20 (t, J = 7.8 Hz, 1H), 6.99 (t, J = 7.8 Hz, 1H), 6.71 (d, J = 7.8 Hz, 1H), 5.10 (s, 2H), 4.91 (s, 2H), 1.57 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 194.3, 167.5, 166.1, 150.0, 142.3, 141.0, 136.3, 135.2, 130.5, 129.1, 128.6, 127.5, 126.9, 126.8, 124.7, 123.7, 122.2, 120.1, 108.6, 83.7, 43.5, 40.5, 28.1; HRMS (ESI) *m/z* $[M-H]^-$ calcd for $C_{29}H_{25}N_2O_6$ 497.1718, found 497.1737; IR (KBr, cm^{-1}) υ 3111, 2978, 1700, 1647, 1608, 1208.

(E)-tert-butyl 2-(1-benzyl-2-oxoindolin-3-ylidene)-4-(2,4-dichlorophenyl)-4-oxobutanoate (**5g**): orange solid; yield 232 mg (89%); mp 100.8-101.6 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) = 7.84 (d, J = 7.8 Hz, 1H), 7.72 (d, J = 8.4 Hz, 1H), 7.46 (s, 1H), 7.32-7.34 (m, 3H), 7.23-7.25 (m, 3H), 7.20 (t, J = 7.8 Hz, 1H), 6.98 (t, J = 7.8 Hz, 1H), 6.68 (d, J = 7.8 Hz, 1H), 4.97 (s, 2H), 4.92 (s, 2H), 1.61 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 196.4, 167.5, 166.3, 142.5, 137.1, 136.9, 136.1, 135.3, 131.8, 130.4, 130.3, 130.2, 128.6, 128.4, 127.4, 127.2, 126.9, 124.8, 122.2, 120.2, 108.9, 83.5, 44.1, 43.5, 28.2; HRMS (ESI) *m/z* $[M-H]^-$ calcd for $C_{29}H_{24}NO_4Cl_2$ 520.1088, found 520.1098; IR (KBr, cm^{-1}) υ 2980, 1720, 1693, 1640, 1219.

(E)-tert-butyl 2-(1-benzyl-2-oxoindolin-3-ylidene)-4-(naphthalen-1-yl)-4-oxobutanoate (**5h**): yellow solid; yield 229 mg (91%); mp 116.3-117.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 8.62 (d, J = 8.0 Hz, 1H), 8.11 (d, J = 7.2 Hz, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.80-7.84 (m, 3H), 7.54 -7.45 (m, 6H), 7.18 (t, J = 7.6 Hz, 1H), 7.13 (d, J = 7.6 Hz, 1H), 6.94 (t, J = 7.6 Hz, 1H), 6.64 (d, J = 8.0 Hz, 1H), 5.17 (s, 2H), 4.88 (s, 2H), 1.58 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 199.0, 167.6, 166.5, 142.3, 137.6, 135.4, 135.3, 133.2, 132.5, 130.2, 129.9, 128.5, 128.1, 128.0, 127.7, 127.6, 127.3, 126.9, 126.2, 125.6, 124.6, 124.2, 122.0, 120.3, 108.8, 83.3, 42.4, 28.2, 27.6; HRMS (ESI) *m/z* $[M-H]^-$ calcd for $C_{33}H_{28}NO_4$ 502.2024, found 502.2026; IR (KBr, cm^{-1}) υ 3021, 1727, 1637, 1368.

(E)-tert-butyl 2-(1-benzyl-2-oxoindolin-3-ylidene)-4-oxo-4-(thiophen-2-yl)butanoate (**5i**): red solid; yield 197 mg (86%); mp 73.6-75.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 8.16 (s, 1H), 7.96 (d, J = 7.6 Hz, 1H), 7.79 (d, J = 7.6 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.16-7.25 (m, 5H), 6.94 (t, J = 7.6 Hz, 1H), 6.65 (d, J = 8.0 Hz, 1H), 5.06 (s, 2H), 4.88 (s, 2H), 1.55 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 194.2, 167.5, 166.2, 142.3, 138.2, 137.1, 135.8, 135.3, 131.0, 130.3, 130.0, 128.5, 127.4, 126.9, 126.6, 124.6, 122.8, 122.1, 120.2, 108.8, 83.4, 43.4, 40.0, 28.1; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{27}H_{25}NO_4NaS$ 482.1397, found 482.1393; IR (KBr, cm^{-1}) υ 3063, 2977, 1698, 1608, 1469, 1157.

(E)-tert-butyl 2-(1-benzyl-6-chloro-2-oxoindolin-3-ylidene)-4-oxo-4-Phenylbutanoate (**5j**): orange solid; yield 202 mg (83%); mp 146.9-148.2 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) = 8.06 (d, J = 7.8 Hz, 2H), 7.80 (d, J = 8.4 Hz, 1H), 7.58 (t, J = 7.2 Hz, 1H), 7.48 (t, J = 7.2 Hz, 2H), 7.32 (t, J = 7.2 Hz, 2H), 7.24-7.28 (m, 3H), 6.95 (d, J = 7.8 Hz, 1H), 6.68 (s, 1H), 5.12 (s, 2H), 4.89 (s, 2H), 1.54 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) = 195.8, 167.9, 166.3, 143.6, 138.8, 136.7, 136.0, 135.0, 133.3, 128.9, 128.6, 128.2, 127.8, 127.2, 127.0, 126.0, 122.1, 119.0, 109.3, 83.5, 43.5, 39.9, 28.0; HRMS (ESI) *m/z* $[M-H]^-$ calcd for $C_{29}H_{25}NO_4Cl$ 486.1478, found 486.1483; IR (KBr, cm^{-1}) υ 3018, 1640, 1447, 1373, 1130.

(E)-tert-butyl 2-(1-benzyl-5-bromo-2-oxoindolin-3-ylidene)-4-oxo-4-Phenylbutanoate (**5k**): yellow solid; yield 226 mg (85%); mp 122.4-123.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 8.02 (d, J = 7.6 Hz, 2H), 7.94 (s, 1H), 7.52 (t, J = 6.8 Hz, 1H), 7.43 (t, J = 7.6 Hz, 2H), 7.20-7.25 (m, 6H), 6.52 (d, J = 8.4 Hz, 1H), 5.12 (s, 2H), 4.85 (s, 2H), 1.58 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 195.2, 167.0, 166.0, 144.0, 139.7, 136.4, 134.9, 133.0, 132.5, 128.6, 128.4, 128.0, 127.5, 127.2, 126.8, 126.3, 122.0, 114.7, 110.1, 83.9, 43.5, 40.0, 28.0; HRMS (ESI) *m/z* $[M-H]^-$ calcd for $C_{29}H_{25}NO_4Br$ 530.0972, found 530.0983; IR (KBr, cm^{-1}) υ 3031, 2928, 1725, 1700, 1672, 1261.

(E)-tert-butyl 2-(1-benzyl-6-bromo-2-oxoindolin-3-ylidene)-4-oxo-4-Phenylbutanoate (**5l**): orange solid; yield 210 mg (79%); mp 129.3-131.2 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) = 8.06 (d, J = 7.2 Hz, 2H), 7.73 (d, J = 8.4 Hz, 1H), 7.57 (t, J = 7.2 Hz, 1H), 7.47 (t, J = 7.8 Hz, 2H), 7.31-7.35 (m, 3H), 7.25-7.28 (m, 2H), 7.11 (d, J = 8.4 Hz, 1H), 6.84 (s, 1H), 5.11 (s, 2H), 4.88 (s, 2H), 1.53 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) = 195.7, 167.7, 166.3, 143.6, 139.0, 136.7, 135.0, 133.2, 128.8, 128.6, 128.2, 127.7, 127.2, 127.0, 126.1, 125.2, 124.2, 119.4, 112.1, 83.5, 43.5, 39.9, 27.9; HRMS (ESI) *m/z* $[M-H]^-$ calcd for $C_{29}H_{25}NO_4Br$ 530.0972, found 530.0980; IR (KBr, cm^{-1}) υ 2974, 1699, 1674, 1600, 1207.

(E)-tert-butyl 2-(1-benzyl-7-bromo-2-oxoindolin-3-ylidene)-4-oxo-4-Phenylbutanoate (**5m**): orange solid; yield 218 mg (82%); mp 95.3-96.7 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) = 8.03 (d, J = 7.8 Hz, 2H), 7.77 (d, J = 7.8 Hz, 1H), 7.55 (t, J = 7.8 Hz, 1H), 7.45 (t, J = 7.8 Hz, 2H), 7.36 (d, J = 8.4 Hz, 1H), 7.27-7.29 (m, 3H), 7.17 (d, J = 7.8 Hz, 2H), 6.85 (t, J = 7.8 Hz, 1H), 5.44 (s, 2H), 5.09 (s, 2H), 1.55 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) = 195.3, 186.5, 166.4, 139.6, 139.5, 137.1, 136.5, 136.0, 133.2, 128.8, 128.5, 128.4, 128.2, 126.9, 126.1, 125.8, 123.6, 123.2, 102.3, 83.7, 44.3, 40.3, 27.8; HRMS (ESI) *m/z* $[M-H]^-$ calcd for $C_{29}H_{25}NO_4Br$ 530.0972, found 530.0976; IR (KBr, cm^{-1}) υ 3031, 2928, 1701, 1597, 1496, 1247.

(E)-2-(1-benzyl-2-oxoindolin-3-ylidene)-4-(4-chlorophenyl)-1-phenylbutane-1,4-dione (**5n**): orange solid; yield 233 mg (95%); mp 201.3-202.6 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ (ppm) = 8.99 (s, 1H), 8.06 (s, 1H), 7.81 (d, J = 8.4 Hz, 2H), 7.64 (d, J = 6.8 Hz, 2H), 7.52 (d, J = 8.4 Hz, 2H), 7.21-7.36 (m, 9H), 6.94 (t, J = 7.4 Hz, 1H), 6.80 (d, J = 7.6 Hz, 1H), 6.60 (t, J = 7.4 Hz, 1H), 5.04 (d, J = 15.6 Hz, 1H), 4.91 (d, J = 15.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d6) δ (ppm) = 179.4, 166.7, 165.5, 155.7, 140.4, 137.6, 136.7, 135.9, 128.9, 128.3, 128.1, 127.3, 127.0, 125.0, 123.9, 123.7, 120.6, 114.1, 113.7, 113.2, 111.4, 108.1, 101.2, 42.4, 40.1; HRMS (ESI) *m/z* [M+H] $^{+}$ calcd for $C_{31}H_{23}NO_3Cl$ 492.1361, found 492.1363; IR (KBr, cm^{-1}) υ 3182, 1656, 1607, 1566, 1175.

(E)-tert-butyl 2-(1-methyl-2-oxoindolin-3-ylidene)-4-oxo-4-phenylbutanoate (**5o**): yellow solid; yield 162 mg (86%); mp 68.5-70.1 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) = 8.06 (d, J = 7.8 Hz, 2H), 7.81 (d, J = 7.8 Hz, 1H), 7.56 (t, J = 7.2 Hz, 1H), 7.47 (t, J = 7.8 Hz, 2H), 7.29 (t, J = 7.5 Hz, 1H), 7.00 (t, J = 7.8 Hz, 1H), 6.78 (d, J = 7.8 Hz, 1H), 5.08 (s, 2H), 3.19 (s, 3H), 1.54 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) = 195.9, 167.8, 166.5, 143.3, 137.7, 136.7, 133.1, 130.3, 130.0, 128.5, 128.2, 124.6, 122.1, 120.3, 107.9, 83.2, 39.7, 27.9, 25.9; HRMS (ESI) *m/z* [M-H]$^{-}$ calcd for $C_{23}H_{22}NO_4$ 376.1554, found 376.1554; IR (KBr, cm^{-1}) υ 2926, 1703, 1609, 1471, 1215.

(E)-methyl 2-(1-methyl-2-oxoindolin-3-ylidene)-4-oxo-4-(p-tolyl)butanoate (**5p**): orange solid; yield 155 mg (89%); mp 128.7-129.6 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) = 7.96 (d, J = 8.4 Hz, 1H), 7.67 (d, J = 7.8 Hz, 1H), 7.27-7.32 (m, 4H), 7.02 (t, J = 7.2 Hz, 1H), 6.80 (d, J = 7.8 Hz, 1H), 5.10 (s, 2H), 3.93 (s, 3H), 3.20 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d6) δ (ppm) = 194.2, 167.4, 166.0, 143.6, 143.0, 135.5, 133.5, 130.6, 129.1, 128.2, 127.9, 123.5, 121.9, 119.0, 108.7, 52.6, 25.8, 21.2, 21.0; HRMS (ESI) *m/z* [M+H] $^{+}$ calcd for $C_{21}H_{20}NO_4$ 350.1387, found 350.1384; IR (KBr, cm^{-1}) υ 2949, 1723, 1698, 1677, 1206.

(E)-tert-butyl 4-oxo-2-(2-oxoindolin-3-ylidene)-4-phenylbutanoate (**5q**): yellow solid; yield 142 mg (78%); mp 182.7-184.4 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) = 9.10 (d, J = 15.6 Hz, 1H), 8.06 (d, J = 7.2 Hz, 2H), 7.76 (d, J = 7.8 Hz, 1H), 7.58 (t, J = 7.2 Hz, 1H), 7.48 (t, J = 6.9 Hz, 2H), 7.16 (t, J = 7.2 Hz, 1H), 6.94 (t, J = 7.5 Hz, 1H), 6.69 (d, J = 7.8 Hz, 1H), 5.02 (s, 2H), 1.54 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) = 196.0, 170.0, 166.5, 140.8, 138.1, 136.8, 133.2, 130.4, 128.6, 128.4, 128.3, 124.9, 122.0, 120.9, 109.9, 83.3, 39.8, 28.0; HRMS (ESI) *m/z* [M-H] $^{-}$ calcd for $C_{22}H_{20}NO_4$ 362.1398, found 362.1403; IR (KBr, cm^{-1}) υ 3446, 2928, 1699, 1680, 1615, 1226.

(E)-2-(1-benzyl-2-oxoindolin-3-ylidene)-1,4-diphenylbutane-1,4-dione (**5r**): red solid; yield 181 mg (79%); mp 155.6-157.3 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ (ppm) = 8.96 (s, 1H), 8.03 (s, 1H), 7.80 (d, J = 6.8 Hz, 2H), 7.63 (d, J = 7.6 Hz, 2H), 7.46-7.48 (m, 3H), 7.21-7.35 (m, 9H), 6.94 (t, J = 7.6 Hz, 1H), 6.80 (d, J = 8.0 Hz, 1H), 6.60 (t, J = 7.6 Hz, 1H), 5.04 (d, J = 15.6 Hz, 1H), 4.91 (d, J = 15.6 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d6) δ (ppm) = 167.4, 167.1, 156.5, 140.6, 137.9, 137.1, 131.7, 129.2, 128.7, 128.6, 128.5, 127.4, 127.3, 127.0, 126.7, 125.3, 124.1, 120.9, 120.8, 113.4, 111.5, 108.3, 100.9, 54.9, 42.4; HRMS (ESI) *m/z* [M+H] $^{+}$ calcd for $C_{31}H_{24}NO_3$ 458.1751, found 458.1756; IR (KBr, cm^{-1}) υ 1644, 1604, 1578, 1208.

A gram-scale reaction of the [3+2] cycloaddition/decomposition reaction

To a 250 mL round-bottomed flask equipped with a magnetic stir bar was added (E)-1-benzyl-3-(2-oxo-2-phenylethylidene)indolin-2-one (5.0 mmol, 1.09 g), phenylglyoxal monohydrate (5.0 mmol, 760.65 mg), $TsNHNH_2$ (5.0 mmol, 931.15 mg), NaOH (15.0 mmol, 600.0 mg) and 60 mL of DMSO. The solution was then stirred at 80° C for 1.5 h. Then, 0.1 M hydrochloric acid (10 mL) was added and the product extracted into EtOAc (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel [200-300 silica gel, petroleum ether: ethyl acetate 5:1(V/V)] to afford pure product (1.21g) as a red solid in 53% yield.

Control experiments

The procedure of the control experiment 1 is according to the one of synthesis of **5** except for in the absence of $TsNHNH_2$.

The procedure for the control experiment 2. tert-butyl (*E*)-2-(1-benzyl-2-oxoindolin-3-ylidene)acetate **1a** (167.5 mg, 0.50 mmol), α-diazoacetophenone **6** (73 mg, 0.50 mmol) and NaOH (60 mg, 1.5 mmol) in 2.5 mL of DMSO were added to a 10 mL schlenk tube and stirred at 80 °C for 1 h. Upon the completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature and diluted with water (5 mL) and extracted with EtOAc (3 times). The organic layers were combined and washed with brine, dried over anhydrous Na_2SO_4. After the solvent was removed under reduced pressure, the crude product was purified by flash column chromatography on silica gel (petroleum ether/EtOAc =5:1) to afford the desired product **5a** in 58% yield.

The procedure for the control experiment 3. compound **4a** (240.6 mg, 0.50 mmol) and NaOH (60 mg, 1.5 mmol) in 2.5 mL of DMSO were added to a 10 mL schlenk tube and stirred at 80 °C for 1 h. Upon the completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature and diluted with water (5 mL) and extracted with EtOAc (3 times). The organic layers were combined and washed with brine, dried over anhydrous Na_2SO_4. After the solvent was removed under reduced pressure, the crude product was purified by flash column chromatography on silica gel (petroleum ether/EtOAc =5:1) to afford the desired product **5a** in 72% yield.

The procedure for the control experiment **4** is according to the control experiment 3, except for in the absence of NaOH.

Acknowledgment: We are grateful to the National Natural Science Foundation of China (No. 21342004 and 51573066), and the Syngenta Ph.D. (postgraduate) program for support of this research.

Supporting Information Available Full experimental details, spectroscopic data of **4** and **5**, CIF file for **4t** and **5p**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For selected reviews, see: (a) Ye, N.; Chen, H.; Wold, E. A.; Shi, P.-Y.; Zhou, J. ACS Infect. Dis. **2016**, *2*, 382. (b) Pavlovska, T. L.; Redkin, R. G.; Lipson, V. V.; Atamanuk, D. V. *Mol. Diversity* **2016**, *20*, 299. (c) Yu, B.; Zheng, Y.-C.; Shi, X.-J.; Qi, P.-P.; Liu, H.-M. *Anti-Cancer Agents Med. Chem.* **2016**, *16*, 1315. (d) Yu, B.; Yu, D.-Q.; Liu, H.-M. *Eur. J. Med. Chem*. **2015**, *97*, 673.

(2) For selected papers, see: (a) Sampson, P. B.; Liu, Y.; Forrest, B.; Cumming, G.; Li, S. -W.; Pauls, H. W. *J. Med. Chem*. **2015**, *58* (1), 147. (b) Greshock, T. J.; Grubbs, A. W.; Jiao, P.; Wicklow, D. T.; Gloer, J. B.; Williams, R. M. *Angew. Chem., Int. Ed*. **2008**, *47*, 3573. (c) Bagley, J. R.; Thomas, S. A.; Rudo, F. G.; Spencer, H. K.; Doorley, B. M.; Ossipov, M. H.; Jerussi, T. P.; Benvenga, M. J.; Spaulding, T. *J. Med. Chem.* **1991**, *34*, 827. (d) Robertson, D. W.; Krushinski, J. H.; Pollock, G. D.; Wilson, H.; Kauffman, R. F.; Hayes, J. S. *J. Med. Chem.* **1987**, *30*, 824.

(3) (a) Cheng, D.; Ishihara, Y.; Tan, B.; Barbas, C. F., III. *ACS Catal*. **2014**, *4*, 743. (b) Narayan, R.; Potowski, M.; Jia, Z. J.; Antonchick, A. P.; Waldmann, H. *Acc. Chem. Res*. **2014**, *47*, 1296. (c) Hong, L.; Wang, R. *Adv. Synth. Catal*. **2013**, *355*, 1023. (d) Zhou, F.; Liu, Y.; Zhou, J. *Adv. Synth. Catal.* **2010**, *352*, 1381. (e) Gicquel, M.; Gomez, C.; Retailleau, P.; Voituriez, A.; Marinetti, A. *Org. Lett*. **2013**, *15*, 4002. (f) Tan, B.; Candeias, N. R.; Barbas, C. F., III. *J. Am. Chem. Soc*. **2011**, *133*, 4672. (g) Deng, H.; Wei, Y.; Shi, M. *Org. Lett*. **2011**, *13*, 3348. (h) Yin, C.-K.; Lin L.-L.; Zhang D.; Feng J.-H.; Liu X.-H.; Feng X.-M; *J. Org. Chem.,* **2015**, *80*, 9691.

(4) (a) Elguero, J. Pyrazoles in Comprehensive Heterocyclic Chemistry; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, UK, **1996**; Vol. 5, p 1. (b) Yet, L. Pyrazoles in Comprehensive Heterocyclic Chemistry III; Pergamon: Oxford, UK, **2008**; Vol. 4, p 1. (c) Liu, X.-H.; Ruan, B.-F.; Li, J.; Chen, F.-H.; Song, B.-A.; Zhu, H.-L.; Bhadury, P. S.; Zhao, J. *Mini. Rev. Med. Chem.* **2011**, *11*, 771. (d) Kumar, S.; Bawa, S.; Drabu, S.; Kumar, R.; Gupta, H. *Recent Pat. Anti-infect Drug Discovery* **2009**, *4*, 154. (e) Turan-Zitouni, G.; Chevallet, P.; Kilic, F. S.; Erol, K. *Eur. J. Med. Chem.* **2000**, *35*, 635. (f) McDonald, E.; Jones, K.; Brough, P. A.; Drysdale, M. J.; Workman, P. *Curr. Top. Med. Chem*. **2006**, *6*, 1193.

(5) (a) Shelke, A. M.; Suryavanshi, G. *Org. Biomol. Chem.* **2015**, *13*, 8669. (b) Du, T.; Du, F.; Ning, Y.; Peng, Y. *Org. Lett.* **2015**, *17*, 1308.

(6) Li, T.-R.; Duan, S.-W.; Ding, W.; Liu, Y.-Y.; Chen, J.-R.; Lu, L.-Q.; Xiao, W.-J. *J. Org. Chem.* **2014**, *79*, 2296.

(7) (a) Shu, W.-M.; Ma, J.-R.; Zheng, K.-L.; Sun, H.-Y.; Wang, M.; Yang, Y.; Wu, A.-X. Tetrahedron **2014**, *70*, 9321. (b) Shu, W.-M.; Zheng, K.-L.; Ma, J.-R.; Sun, H.-Y.; Wang, M.; Wu, A.-X. *Org. Lett.* **2015**, *17*, 1914.

(8) (a) Gao, M.; Yang, Y.; Wu, Y.-D.; Deng, C.; Shu, W.-M.; Zhang, D.-X.; Cao, L.-P.; She, N.-F.; Wu, A.-X. *Org. Lett*. **2010**, *12*, 4026. (b) Yang, Y.; Ni, F.; Shu, W.-M.; Yu, S.-B.; Gao, M.; Wu, A.-X. *J. Org. Chem*. **2013**, *78*, 5418. (c) Yang, Y.; Gao, M.; Wu, L.-M.; Deng, C.; Zhang, D.-X.; Gao, Y.; Zhu, Y.-P.; Wu, A.-X. *Tetrahedron* **2011**, *67*, 5142. (d) Yang, Y.; Ni, F.; Shu, W.-M.; Wu, A.-X. *Tetrahedron* **2014**, *70*, 6733.

(9) For a recent account, see: (a) Lu, L.-Q.; Chen, J.-R.; Xiao, W.-J. *Acc. Chem. Res.* **2012**, *45*, 1278. For selected recent examples, see: (b) Duan, S.-W.; Li, Y.; Liu, Y.-Y.; Zou, Y.-Q.; Shi, D.-Q.; Xiao, W.-J. *Chem. Commun.* **2012**, *48*, 5160. (c) Yang, Q.-Q.; Xiao, C.; Lu, L.-Q.; An, J.; Tan, F.; Li, B.-J.; Xiao, W.-J. *Angew. Chem. Int. Ed.* **2012**, *51*, 9137. (d) Cheng, H.-G.; Lu, L.-Q.; Wang, T.; Yang, Q.-Q.; Liu, X.-P.; Li, Y.; Deng, Q.-H.; Chen, J.-R.; Xiao, W.-J. *Angew. Chem. Int. Ed.* **2013**, *52*, 3250. (e) Zheng, H.-F.; Yu, Z.-H.; Yuan, W.; Tang, Z.-L.; Clough, J.; Gu, Y.-C.; Shi, D.-Q. *Chem. Eur. J.* **2014**, *20*, 1711.