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PAPER

Ruthenium-catalyzed intramolecular cyclization of diazo-β-ketoanilides for the synthesis of 3-alkylideneoxindoles†

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With [Ru(*p*-cymene)Cl_2]$_2$ as catalyst, diazo-β-ketoanilides would undergo intramolecular carbenoid arene C–H bond functionalization to afford 3-alkylideneoxindoles in up to 92% yields. The reaction occurs under mild conditions and exhibits excellent chemoselectivity. The lack of primary KIE ($k_H/k_D \sim 1$) suggests that the reaction should not proceed by rate-limiting C–H bond cleavage; a mechanism involving cyclopropanation of the arene is proposed.

Introduction

3-Alkylideneoxindoles are important motifs of bioactive natural products[1] and some pharmaceutical compounds such as Tenidap,[2a] which is used to treat rheumatoid arthritis, and BIBF0775[2c], which can be potentially used for the treatment of fibrotic diseases and cancer (Fig. 1).[2] Several strategies have been pursued for the effective synthesis of the skeleton. For instance, direct acylation of oxindoles with acyl chlorides and derivatives offers a simple route to 3-alkylideneoxindoles.[3] Another approach involves the carbonylative cyclization of 2 alkynylanilines;[4] Pd-, Rh- and Fe-catalyzed cyclizations of 2-alkynylaryl isocyanates have proven value in the construction of the oxindole core.[5] Lu and Ma also achieved the Cu-catalyzed intramolecular arylations of β-ketoamides and 3-alkylideneoxindoles, which were obtained in good yields.[6] Despite these apparent successes, these transformations are limited in substrate scope because of the need of specially functionalized starting materials. In this regard, efforts have been directed to the direct intramolecular arylations of *N*-arylpropiolamides *via* C–H bond functionalization.[7] Yet, these reactions often operate at rather high temperatures (>100 °C) for effective substrate conversion.

Transition metal-catalyzed carbenoid functionalizations constitute a powerful method for C–C bond formation.[8] Extensive investigations have been focused on the use of dirhodium(II, II) carboxylates as catalysts for carbenoid transformations.[9] The research groups of Doyle and Durst demonstrated that $Rh_2(OAc)_4$ could effect catalytic intramolecular cyclization of diazo-β-ketoamides in refluxing benzene to afford 3-alkylideneoxindoles in up to 95% yield.[10] More recently, AgOTf was also found to catalyze the analogous cyclization of diazo-β-ketoamides in dioxane at 100 °C.[11] As a continuing effort to develop transition metal catalysis for C–H bond functionalization under mild conditions,[12] we reported earlier that [Ru(*p*-cymene)Cl_2]$_2$ is a highly effective catalyst for carbenoid cyclization of α-diazoacetamides to give *cis*-β-lactams in >99% stereoselectivity.[12e] Unlike the analogous Rh catalysis, [Ru(*p*-cymene)Cl_2]$_2$ can effect C2-selective catalytic carbenoid C–H bond functionalization of NH-free indoles.[12a] Here, we describe the [Ru(*p*-cymene)Cl_2]$_2$-catalyzed intramolecular cyclization of diazo-β-ketoanilides to afford 3-alkylideneoxindoles in up to 92% yield at 40 °C.

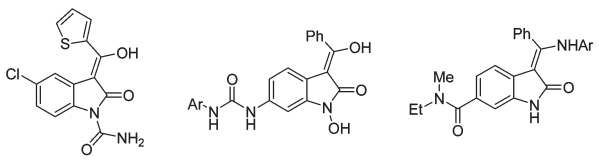

Fig. 1 Medicinally active 3-alkylideneoxindoles.

Results and discussion

When diazo-β-ketoanilide **1a** was treated with [Ru(*p*-cymene)Cl_2]$_2$ (2.5 mol%) in toluene at room temperature overnight, 3-alkylideneoxindole **2a** was obtained in 86% yield (entry 1, Table 1). When the analogous reaction was performed at 40 °C, complete substrate consumption was achieved in 2.5 h with **2a** being obtained in 95% yield (entry 2, Table 1). In this work, formation of **2a** (75% yield) was observed when heating **1a** at 100 °C in metal-free toluene for 24 h (entry 3, Table 1). However, it is noteworthy that no product formation was observed at 40 °C without the Ru catalyst (entry 4, Table 1).

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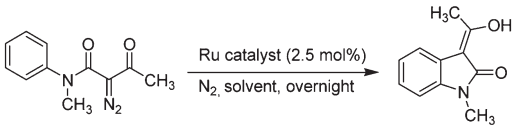
Table 1 Reaction optimization[a]



Entry	Catalyst	Solvent	Temp. (°C)	Yield[b] (%)
1	[Ru(*p*-cymene)Cl_2]$_2$	Toluene	r.t.	86
2[c]	—	Toluene	40	95
3	Catalyst-free	Toluene	100	75
4	Catalyst-free	Toluene	40	0
5	[Ru(*p*-cymene)Cl_2]$_2$	DCM	r.t.	72
6	—	THF	r.t.	68
7	—	MeCN	r.t.	55
8	—	MeOH	r.t.	37
9[d]	$CpRu(PPh_3)_2Cl$	Toluene	40	19
10[d,e]	Ru(pybox-*ip*)$Cl_2(C_2H_4)$	Toluene	40	18
11[d]	[Ru(*p*-cymene)$(OAc)_2$]	Toluene	40	4

[a] Reaction conditions: **1a** (0.2 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (2.5 mol%), solvent (1 mL). [b] Determined by ^{1}H NMR. [c] Reaction time: 2.5 h. [d] Catalyst loading: 5 mol%. [e] pybox = bis(oxazolinyl)pyridine.

Other solvents such as dichloromethane, THF, acetonitrile and methanol failed to give better results (entries 5–8, Table 1). According to the literature, [$CpRu(PPh_3)_2Cl$][13] and [Ru(pybox-*ip*)Cl_2][14] are known to catalyze some carbenoid transformations (*e.g.* cyclopropanations). However, in this work, we found that these Ru complexes are poor catalysts for the cyclization of **1a** (entries 9–10, Table 1). Notably, [Ru(*p*-cymene)$(OAc)_2$] is practically ineffective for the cyclization reaction (entry 11, Table 1).

In principle, 3-acyloxindole may exist in another tautomeric form, namely 3-acetyl-2-hydroxyindole. According to the literature, the 3-acetyl-2-hydroxyindole is characterized by a downfield ^{13}C NMR signal at $\delta_c \sim 200$ ppm, assigned to the carbonyl group of the acetyl moiety.[10a,11] In this work, it seems that keto form on C2 is more preferable for **2a**. The 3-alkylideneoxindole skeleton of **2a** was confirmed by a characteristic ^{13}C NMR signal at $\delta_c \sim 173$ ppm, which is assigned to the amido carbon atom.

The substrate scope of the Ru-catalyzed cyclization of diazo-β-ketoanilides is shown in Table 2. With the *N*-benzyl diazoanilide **1b** as substrate, oxindole **2b** was exclusively obtained in 70% yield (entry 2), and no β-lactam formation due to carbenoid C–H bond insertion to the benzyl group was observed. For substrate **1c** bearing a *meta*-methyl substituent at the aryl ring, the Ru-catalyzed cyclization occurred selectively at the less hindered C–H bond leading to **2c** formation in 86% yield. We found that cyclizations of the substrates bearing electron-releasing groups such as Me and OMe at the anilide moiety were more facile under the standard reaction conditions (*i.e.*, [Ru(*p*-cymene)Cl_2]$_2$ (2.5 mol%), toluene at 40 °C) (entries 3–5, Table 2). However, cyclizations of the electron-poor derivatives were apparently slower. For example, complete transformation of **1f** to **2f** was achieved at slightly higher temperature (50 °C) overnight (entry 6, Table 2). Nevertheless, the analogous reactions of **1g** and **1h** afforded the product oxindoles in 42 and 25% yields under similar conditions (entries 7–8, Table 2). In contrast to the result of **1d** containing a *para*-OMe group at the anilide ring, the analogous *ortho*-OMe derivative would afford **2i** in 17% yield (entry 9, Table 2). Similar findings were also obtained in the related [Ru(*p*-cymene)Cl_2]$_2$ catalyzed intermolecular carbenoid C–H bond insertion to indoles.[15] We hypothesize that the *ortho*-OMe group may have coordinated to the putative Ru–carbene intermediate and it hindered the product formation.

Noting that some pharmaceutically active 3-alkylideneoxindoles (Fig. 1) contain an aromatic substituent, we were interested in testing our protocol for the cyclization of diazoanilides bearing a benzoyl substituent. When diazoanilide **1j** was treated with [Ru(*p*-cymene)Cl_2]$_2$ (2.5 mol%) in toluene at 40 °C overnight, 3-arylideneoxindole **2j** was obtained in 81% yield (entry 10, Table 2). Likewise, other heteroaryl-substituted diazoanilides (**1k** and **1l**) were also converted to their product oxindoles in 83–86% yields (entries 11–12, Table 2). As noted earlier, substrates with electron-withdrawing groups at the anilide ring are less reactive for the cyclization reaction. Yet, comparing the reactivity of **1m** and **1n**, the presence of a chloro group at the aryl-keto substituent seems to be well tolerated and **2n** was formed in 79% yield (entry 14, Table 2).

To probe the nature of the cyclization of the diazoanilides, we performed a primary H/D kinetic isotope effect (KIE) study by competitive cyclization involving equimolar amounts of **1a** and **1a**-d_5 as substrates. Subjecting **1a** and **1a**-d_5 to the Ru-catalyzed conditions (*i.e.*, [Ru(*p*-cymene)Cl_2]$_2$ (2.5 mol%), toluene at 40 °C) for 5 min, substrate consumptions were determined by ^{1}H NMR analysis of the reaction mixture (see Experimental section for details). By repeating the KIE experiment for three times, the average KIE (k_H/k_D) of the Ru-catalyzed cyclization of diazoanilides was found to be ~1.1. This result indicates that the reaction should not involve rate-limiting C–H bond cleavage. A similar finding was also obtained for the Ru-catalyzed intermolecular carbenoid C–H bond functionalization of NH-free indoles.[13]

Based on the KIE study, we proposed that this cyclization reaction may be initiated by a reactive ruthenium–carbene intermediate **A** (Scheme 1).[15,16] Then, intramolecular aromatic cyclopropanation would occur to form a strained cyclopropane **B**,[17] whose subsequent ring-opening would afford the corresponding 3-alkylideneoxindole **2** (Scheme 1). By inspection of the transition state model, it is conceivable that the C3 substituents of the anilide ring would hinder the C(2)-H functionalization.

Conclusion

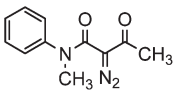
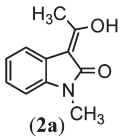
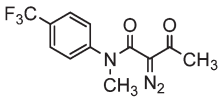
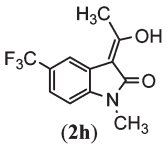
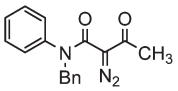
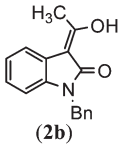
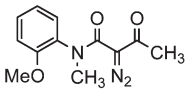
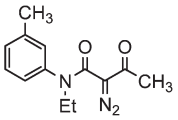
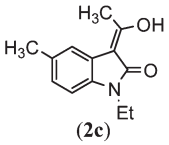
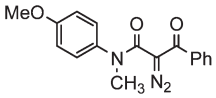
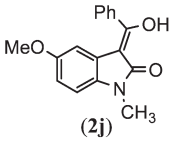
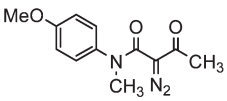
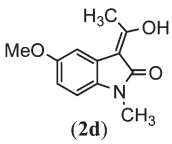
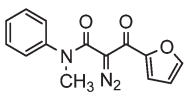
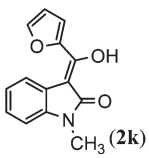
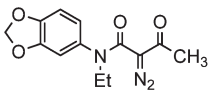
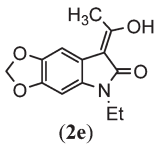
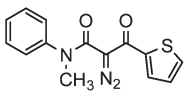
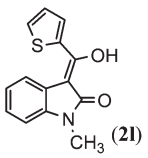
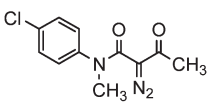
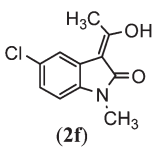
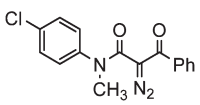
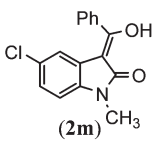
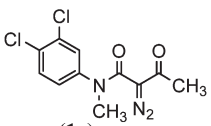
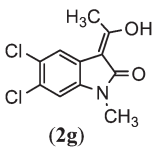
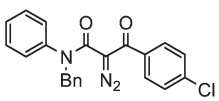
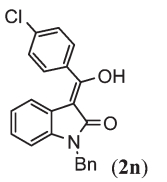
In conclusion, we have developed an effective synthesis of 3-alkylideneoxindoles *via* intramolecular carbenoid cyclization of diazo-β-ketoanilides using [Ru(*p*-cymene)Cl_2]$_2$ as catalyst under mild conditions. Considering the availability of [Ru(*p*-cymene)Cl_2]$_2$ and the ease of handling of the diazo compounds, this catalytic carbenoid reaction would complement the current strategies for 3-alkylideneoxindoles synthesis.

Experimental section

General methods

All the reactions were performed under a nitrogen atmosphere. All the solvents were freshly distilled and dried according to the

Table 2 Ru-catalyzed intramolecular cyclization of diazo-β-ketoanilides[a]

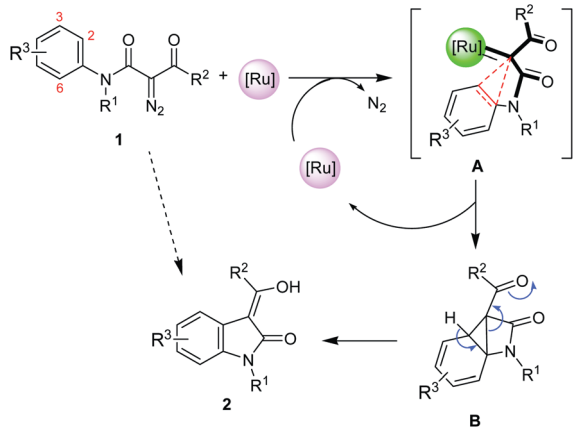
Entry	Substrate	Product	Yield[b] (%)	Entry	Substrate	Product	Yield[b] (%)
1	 (**1a**)	 (**2a**)	92	8[c]	 (**1h**)	 (**2h**)	25
2	 (**1b**)	 (**2b**)	70	9[c,e,f]	 (**1i**)	 (**2i**)	17
3	 (**1c**)	 (**2c**)	86	10[f]	 (**1j**)	 (**2j**)	81
4	 (**1d**)	 (**2d**)	82	11[f]	 (**1k**)	 (**2k**)	83
5	 (**1e**)	 (**2e**)	80	12[f]	 (**1l**)	 (**2l**)	86
6[c,d]	 (**1f**)	 (**2f**)	70	13[f]	 (**1m**)	 (**2m**)	45
7[c,d]	 (**1g**)	 (**2g**)	42	14[f]	 (**1n**)	 (**2n**)	79

[a] Reaction conditions: **1** (0.2 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol%), toluene (1 mL), 40 °C. Consumption of **1** was monitored by TLC. [b] Isolated yields. [c] Catalyst loading: 5 mol%. [d] Reaction at 50 °C. [e] Reaction at 70 °C. [f] Reaction: overnight.

standard methods[1] prior to use. Substituted *N*-methylanilines were obtained commercially and used without purification. Thin layer chromatography was performed on silica gel plates. Flash column chromatography was performed on silica gel (Merck, 230–400 mesh). ^{1}H and ^{13}C NMR spectra were recorded to a Bruker DPX-400 MHz spectrometer. The chemical shift (δ) values are given in ppm and are referenced to residual solvent peaks, carbon multiplicities were determined by DEPT-135 and DEPT-90 experiments. Coupling constants (J) were reported in hertz (Hz). Multiplicity abbreviations are: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dt = doublet of triplets, td = triplet of doublets, and br = broad. Mass spectra and high resolution mass spectra (HRMS) were obtained on a VG MICROMASS Fison VG platform, a Finnigan Model Mat 95 ST instrument, or a Bruker APEX 47e FT-ICR mass spectrometer. Infrared spectra were obtained by a Bruker Vector 22 FT-IR spectrometer.

General procedures for the preparation of diazo-β-ketoanilides 1a–1i

A mixture of aniline (10 mmol) and 2,2,6-trimethyl-4*H*-dioxin-4-one (11 mmol, 1.1 equiv) in xylene (5 mL) was heated under reflux at 120 °C for 10–15 min and 150 °C for further 1 h. Upon complete consumption of the starting materials, the solvent was removed by vacuum. The residue was purified by flash column chromatography to afford the acetoacetates. To the corresponding acetoanilide (5 mmol), triethylamine (10 mmol, 2 equiv) and tosyl azide (5.5 mmol, 1.1 equiv) in CH_3CN (10 mL) were added. The solution was stirred at room temperature overnight.



Scheme 1 Proposed mechanism.

The solvent was removed and the residue was dissolved in diethyl ether (25 mL) and washed successively with brine solution (3 × 25 mL) and then H_2O (3 × 25 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography to afford the α-diazo anilides.

***N*-Methyl-*N*-phenyl-2-diazo-3-oxobutanamide (1a).** Eluant: 50% *n*-hexane/50% ethyl acetate. The product was obtained as a yellow oily liquid (85% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.42 (t, J = 7.6 Hz, 2H, ArH), 7.34 (t, J = 7.4 Hz, 1H, ArH), 7.20 (d, J = 7.2 Hz, 2H, ArH), 3.38 (s, 3H, NCH_3), 2.50 (s, 3H, $COCH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 191.8 (C═O), 161.0 (C═O), 143.1 (C), 130.3 (C–H), 128.0 (C–H), 126.2 (C–H), 38.4 (CH_3), 28.4 (CH_3). IR (KBr, cm^{-1}): 2112, 1645, 1594. HRMS (ESI): calcd for $C_{11}H_{11}N_3O_2Na^+$: 240.0749, found: 240.0742.

***N*-Benzyl-*N*-phenyl-2-diazo-3-oxobutanamide (1b).** Eluant: 50% *n*-hexane/50% ethyl acetate. The product was obtained as a yellow solid (82% yield), mp 66–67 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.36–7.22 (m, 8H, ArH), 7.06 (d, J = 8,2 Hz, 2H, ArH), 4.97 (s, 2H, CH_2Ph), 2.53 (s, 3H, $COCH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 191.8 (C═O), 160.9 (C═O), 141.5 (C), 136.8 (C), 130.1 (C–H), 128.6 (C–H), 128.5 (C–H), 128.2 (C–H), 127.7 (C–H), 127.3 (C–H), 54.1 (CH_2), 28.6 (CH_3). IR (KBr, cm^{-1}): 2109, 1643, 1593. HRMS (ESI): calcd for $C_{17}H_{15}N_3O_2Na^+$: 316.1062, found: 316.1057.

***N*-Ethyl-*N*-(3-methylphenyl)-2-diazo-3-oxobutanamide (1c).** Eluant: 50% *n*-hexane/50% ethyl acetate. The product was obtained as a pale yellow solid (97% yield), mp 67–68 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.29 (t, J = 8 Hz, 1H, ArH), 7.15 (d, J = 7.8 Hz, 1H, ArH), 6.96 (m, 2H, ArH), 3.81 (q, J = 7.1 Hz, 2H, NEt), 2.50 (s, 3H, CH_3), 2.36 (s, 3H, $COCH_3$), 1.17 (t, J = 7.2Hz, 3H, NEt). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 192.1 (C═O), 160.4 (C═O), 141.2 (C), 140.4 (C), 129.9 (C–H), 128.9 (C–H), 127.7 (C–H), 124.3 (C–H), 45.6 (CH_2), 28.5 (CH_3), 21.3 (CH_3), 13.0 (CH_3). IR (KBr, cm^{-1}): 2109, 1644, 1603. HRMS (ESI): calcd for $C_{13}H_{15}N_3O_2Na^+$: 268.1062, found: 268.1051.

***N*-Methyl-*N*-(4-methoxyphenyl)-2-diazo-3-oxobutanamide (1d).** Eluant: 50% *n*-hexane/50% ethyl acetate. The product was obtained as a yellow solid (98% yield), mp 48–50 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.10 (d, J = 8.8 Hz, 2H, ArH), 6.90 (d, J = 8.8 Hz, 2H, ArH), 3.80 (s, 3H, OMe), 3.31 (s, 3H, NCH_3), 2.48 (s, 3H, $COCH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 192.0 (C═O), 161.1 (C═O), 159.2 (C), 135.6 (C), 127.8 (C–H), 115.4 (C–H), 55.6 (CH_3), 39.5 (CH_3), 28.5 (CH_3). IR (KBr, cm^{-1}): 2110, 1644, 1510. HRMS (ESI): calcd for $C_{12}H_{13}N_3O_3Na^+$: 270.0855, found: 270.0842.

***N*-Ethyl-*N*-[3,4-(methylenedioxy)phenyl]-2-diazo-3-oxobutanamide (1e).** Eluant: 50% *n*-hexane/50% ethyl acetate. The product was obtained as a green solid (86% yield), mp 78–81 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 6.80 (d, J = 8.8 Hz, 1H, ArH), 6.63 (m, 2H, ArH), 6.03 (s, 2H, OCH_2O), 3.75 (q, J = 7.1 Hz, 2H, NEt), 2.50 (s, 3H, $COCH_3$), 1.16 (t, J = 7.2 Hz, 3H, NEt). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 192.1 (C═O), 160.5 (C═O), 148.9 (C), 147.7 (C), 134.8 (C), 121.4 (C–H), 108.9 (C–H), 108.3 (C–H), 102.1 (CH_2), 45.7 (CH_2), 28.6 (CH_3), 12.9 (CH_3). IR (KBr, cm^{-1}): 2109, 1642, 1485. HRMS (ESI): calcd for $C_{13}H_{13}N_3O_4Na^+$: 298.0804, found: 298.0812.

***N*-(4-Chlorophenyl)-*N*-methyl-2-diazo-3-oxobutanamide (1f).** Eluant: 50% *n*-hexane/50% ethyl acetate. The product was obtained as a pale yellow solid (88% yield), mp 75–76 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.40 (d, J = 6.8 Hz, 2H, ArH), 7.14 (d, J = 6.6 Hz, 2H, ArH), 3.35 (s, 3H, NCH_3), 2.46 (s, 3H, $COCH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 191.2 (C═O), 161.0 (C═O), 141.6 (C), 133.8 (C), 130.4 (C–H), 127.4 (C–H), 38.5 (CH_3), 28.3 (CH_3). IR (KBr, cm^{-1}): 2111, 1647, 1490. HRMS (ESI): calcd for $C_{11}H_{10}N_3O_2NaCl^+$: 274.0359, found: 274.0346.

***N*-(3,4-Dichlorophenyl)-*N*-methyl-2-diazo-3-oxobutanamide (1g).** Eluant: 50% *n*-hexane/50% ethyl acetate. The product was obtained as a yellow solid (80% yield), mp 96–98 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.49 (d, J = 8.8 Hz, 1H, ArH), 7.32 (s, 1H, ArH), 7.07 (d, J = 8.8 Hz, 1H, ArH), 3.34 (s, 3H, NCH_3), 2.45 (s, 3H, $COCH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 190.7 (C═O), 160.9 (C═O), 142.5 (C), 134.0 (C), 132.0 (C), 131.7 (C–H), 127.8 (C–H), 125.3 (C–H), 38.6 (CH_3), 28.3 (CH_3). IR (KBr, cm^{-1}): 2111, 1648, 1473. HRMS (ESI): calcd for $C_{11}H_9N_3O_2Cl_2Na^+$: 307.9970, found: 307.9957.

***N*-Methyl-*N*-(4-trifluoromethylphenyl)-2-diazo-3-oxobutanamide (1h).** Eluant: 50% *n*-hexane/50% ethyl acetate. The product was obtained as a yellow solid (83% yield), mp 84–85 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.68 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 3.39 (s, 3H, NCH_3), 2.45 (s, 3H, $COCH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 190.7 (C═O), 161.1 (C═O), 146.4 (C), 129.5 (q, CF_3), 127.4 (C), 126.1 (C–H), 124.9 (C–H), 122.2 (C–H), 38.2 (CH_3), 28.2 (CH_3). ^{19}F NMR (376 MHz, $CDCl_3$): δ_F −69.7 (CF_3). IR (KBr, cm^{-1}): 2114, 1650, 1612. HRMS (ESI): calcd for $C_{12}H_{10}N_3O_2F_3Na^+$: 308.0623, found: 308.0610.

***N*-Methyl-*N*-(2-methoxyphenyl)-2-diazo-3-oxobutanamide (1i).** Eluant: 50% n-hexane/50% ethyl acetate. The product was obtained as a yellow solid (69% yield), mp 68–70 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.33 (dt, J = 8 Hz, 1H, ArH), 7.13 (dd, J = 7.6 Hz, 1H, ArH), 6.98 (m, 2H, ArH), 3.83 (s, 3H, OMe), 3.24 (s, 3H, NCH_3), 2.46 (s, 3H, $COCH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 192.2 (C═O), 162.1 (C═O), 154.5 (C), 131.2 (C), 130.0 (C–H), 128.6 (C–H), 121.7 (C–H), 112.3 (C–H), 55.6

(CH_3), 37.2 (CH_3), 28.0 (CH_3). IR (KBr, cm^{-1}): 2108, 1650, 1500. HRMS (ESI): calcd for $C_{12}H_{13}N_3O_3Na^+$: 270.0855, found: 270.0854.

General procedures for the preparation of diazo-β-ketoanilides 1j–1n

To a mixture of meldrum's acid (10 mmol) and DMAP (20 mmol, 2 equiv) in CH_2Cl_2 (20 mL) at 0 °C, benzoyl chloride (12 mmol, 1.2 equiv) was added dropwise over 10 min. The mixture was then allowed to warm to room temperature and stirred for further 1 h. The reaction was diluted with CH_2Cl_2 (20 mL) and washed with 10% HCl solution (20 mL), brine solution (30 mL) and then H_2O (30 mL) successively. The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was dissolved in dioxane (15 mL) and aniline (10 mmol) was then added. The mixture was heated under reflux for 1 h. Upon complete consumption of the starting materials, the solvent was removed by vacuum. The residue was purified by flash column chromatography to afford the corresponding benzoylacetanilides. The procedures of subsequent diazo transfer reaction were similar with that of the preparation of **1a–1i**.

***N*-(4-Methoxyphenyl)-*N*-methyl-2-diazo-3-oxo-3-phenylpropanamide (1j).** Eluant: 50% *n*-hexane/50% ethyl acetate. The product was obtained as a yellow solid (91% yield), mp 83–84 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.48 (t, J = 7.2 Hz, 1H, ArH), 7.42–7.34 (m, 4H, ArH), 6.85 (d, J = 8.8 Hz, 2H, ArH), 6.74 (d, J = 8.8 Hz, 2H, ArH), 3.78 (s, 3H, OMe), 3.30 (s, 3H, NCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 186.8 (C═O), 162.0 (C═O), 158.7 (C), 137.7 (C), 136.3 (C), 132.6 (C–H), 128.5 (C–H), 128.0 (C–H), 127.4 (C–H), 115.0 (C–H), 55.8 (CH_3), 38.8 (CH_3). IR (KBr, cm^{-1}): 2109, 1626, 1510. HRMS (ESI): calcd for $C_{17}H_{15}N_3O_3Na^+$: 332.1011, found: 332.1012.

3-(Furan-2-yl)-*N*-methyl-2-diazo-3-oxo-*N*-phenylpropanamide (1k). Eluant: 50% *n*-hexane/50% ethyl acetate. The product was obtained as a yellow solid (91% yield), mp 85–86 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.51 (s, 1H, ArH), 7.32 (t, J = 7.6 Hz, 2H, ArH), 7.24–7.21 (m, 1H, ArH), 7.17 (d, J = 7.2 Hz, 2H, ArH), 7.06 (d, J = 3.6 Hz, 1H, ArH), 6.49 (d of d, 1H, ArH), 3.43 (s, 3H, NCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 172.5 (C═O), 161.3 (C═O), 151.3 (C), 145.6 (C), 143.6 (C–H), 129.9 (C–H), 127.6 (C–H), 126.1 (C–H), 117.5 (C–H), 112.8 (C–H), 30.7 (CH_3). IR (KBr, cm^{-1}): 2114, 1639, 1594. HRMS (ESI): calcd for $C_{14}H_{11}N_3O_3Na^+$: 292.0698, found: 292.0685.

***N*-Methyl-2-diazo-3-oxo-*N*-phenyl-3-(thiophen-2-yl)propanamide (1l).** Eluant: 50% *n*-hexane/50% ethyl acetate. The product was obtained as a yellow solid (91% yield), mp 117–119 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.59–7.57 (m, 2H, ArH), 7.30 (t, J = 7.6 Hz, 2H, ArH), 7.22 (t, J = 7.6 Hz, 1H, ArH), 7.08–7.06 (m, 3H, ArH), 3.41 (s, 3H, NCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 177.6 (C═O), 161.6 (C═O), 143.4 (C), 142.0 (C), 133.4 (C–H), 131.9 (C–H), 130.1 (C–H), 127.9 (C–H), 127.5 (C–H), 126.0 (C–H), 38.7 (CH_3). IR (KBr, cm^{-1}): 2117, 1643, 1593. HRMS (ESI): calcd for $C_{14}H_{11}N_3O_2NaS^+$: 308.0470, found: 308.0467.

***N*-(4-Chlorophenyl)-*N*-methyl-2-diazo-3-oxo-3-phenylpropanamide (1m).** Eluant: 50% *n*-hexane/50% ethyl acetate. The product was obtained as a yellow solid (91% yield), mp 124–126 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.50–7.48 (m, 1H, ArH), 7.38–7.33 (m, 4H, ArH), 7.15 (d, J = 8.4 Hz, 2H, ArH), 6.81 (d, J = 8.4 Hz, 2H, ArH), 3.31 (s, 3H, NCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 186.0 (C═O), 162.0 (C═O), 142.1 (C), 137.4 (C), 132.80 (C–H), 132.78 (C), 129.8 (C–H), 128.7 (C–H), 127.9 (C–H), 127.1 (C–H), 38.6 (CH_3). IR (KBr, cm^{-1}): 2113, 1627, 1491. HRMS (ESI): calcd for $C_{16}H_{12}N_3O_2NaCl^+$: 336.0516, found: 336.0502.

***N*-Benzyl-3-(4-chlorophenyl)-2-diazo-3-oxo-*N*-phenylpropanamide (1n).** Eluant: 50% *n*-hexane/50% ethyl acetate. The product was obtained as a yellow solid (91% yield), mp 108–109 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.33–7.20 (m, 12H, ArH), 6.87 (d, J = 7.6 Hz, 2H, ArH), 4.94 (s, 2H, CH_2Ph). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 185.7 (C═O), 161.6 (C═O), 141.9 (C), 138.9 (C), 136.9 (C), 135.9 (C), 129.9 (C–H), 129.5 (C–H), 129.1 (C–H), 128.9 (C–H), 128.8 (C–H), 128.1 (C–H), 127.8 (C–H), 127.2 (C–H), 54.5 (CH_2). IR (KBr, cm^{-1}): 2112, 1624, 1490. HRMS (ESI): calcd for $C_{22}H_{16}N_3O_2NaCl^+$: 412.0829, found: 412.0818.

Typical procedures for the Ru-catalyzed intramolecular cyclization of diazo-β-ketoanilides 1

A sealed vial equipped with a magnetic stirrer was charged with $[Ru(p\text{-cymene})Cl_2]_2$ (3.1 mg, 2.5 mol%) and diazo-β-ketoanilide **1** (0.2 mmol). The vial was evacuated and refilled with nitrogen three times. Dry toluene (1 mL) was added *via* a syringe and the mixture was stirred and heated at 40 °C. Upon complete consumption of the diazo-β-ketoanilides, based on TLC monitoring, the reaction was allowed to cool to room temperature and was then concentrated. The residue was purified by flash chromatography to give the desired 3-alkylideneoxindoles.

3-(1-Hydroxyethylidene)-1-methylindolin-2-one (2a). Eluant: 80% *n*-hexane/20% ethyl acetate. The product was obtained as a purple solid (92% yield), mp 90–92 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 13.60 (br, s, 0.8H, OH), 7.35 (d, J = 7.6 Hz, 1H, ArH), 7.22 (t, J = 7.6 Hz, 1H, ArH), 7.10 (t, J = 7.4 Hz, 1H, ArH), 6.93 (d, J = 7.6 Hz, 1H, ArH), 3.33 (s, 3H, NCH_3), 2.44 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 172.9 (C═O), 171.1 (C═C), 138.9 (C), 125.2 (C–H), 122.2 (C), 122.1 (C–H), 119.7 (C–H), 108.4 (C–H), 101.8 (C), 25.6 (CH_3), 20.3 (CH_3). IR (KBr, cm^{-1}): 3434, 3065, 2924, 1654, 1607. HRMS (ESI): calcd for $C_{11}H_{10}NO_2H^+$: 190.0868, found: 190.0864.

1-Benzyl-3-(1-hydroxyethylidene)indolin-2-one (2b). Eluant: 70% *n*-hexane/30% ethyl acetate. The product was obtained as a purple solid (70% yield), mp 117–119 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 13.67 (br, s, 0.7H, OH), 7.39 (d, J = 7.2 Hz, 1H, ArH), 7.34–7.24 (m, 5H, ArH), 7.15–7.09 (m, 2H, ArH), 6.86 (d, J = 7.6 Hz, 1H, ArH), 5.06 (s, 2H, CH_2Ph), 2.49 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 173.3 (C═O), 171.2 (C═C), 138.1 (C), 136.1 (C), 128.8 (C–H), 127.6 (C–H), 127.2 (C–H), 125.2 (C–H), 122.4 (C), 122.2 (C–H), 119.8 (C–H), 109.4 (C–H), 101.7 (C), 43.3 (CH_2), 20.4 (CH_3). IR (KBr,

cm^{-1}): 3435, 3060, 2920, 1657, 1607, 1465. HRMS (ESI): calcd for $C_{17}H_{14}NO_2H^+$: 266.1181, found: 266.1188.

1-Ethyl-3-(1-hydroxyethylidene)-6-methylindolin-2-one (2c). Eluant: 80% *n*-hexane/20% ethyl acetate. The product was obtained as a purple solid (86% yield), mp 51–52 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 13.50 (br, s, 0.7H, OH), 7.23 (d, J = 7.6 Hz, 1H, ArH), 6.90 (d, J = 7.6 Hz, 1H, ArH), 6.80 (s, 1H, ArH), 3.88 (q, J = 7.2 Hz, 2H, NEt), 2.41 (s, 6H, $2CH_3$), 1.31 (t, J = 7.2 Hz, 3H, NEt). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 171.8 (C═O), 170.9 (C═C), 138.2 (C), 135.2 (C), 122.6 (C–H), 119.8 (C), 119.6 (C–H), 109.3 (CH), 101.8 (C), 34.2 (CH_2), 21.8 (CH_3), 20.2 (CH_3), 13.3 (CH_3). IR (KBr, cm^{-1}): 3440, 2971, 2928, 1660, 1615. HRMS (ESI): calcd for $C_{13}H_{14}NO_2H^+$: 218.1181, found: 218.1175.

3-(1-Hydroxyethylidene)-5-methoxy-1-methylindolin-2-one (2d). Eluant: 70% *n*-hexane/30% ethyl acetate. The product was obtained as a purple solid (82% yield), mp 78–81 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 13.67 (br, s, 0.7H, OH), 6.92 (s, 1H, ArH), 6.81 (d, J = 8.4 Hz, 1H, ArH), 6.75 (dd, J = 8.4 Hz, 1H, ArH), 3.82 (s, 3H, OMe), 3.29 (s, 3H, NCH_3), 2.40 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 173.1 (C═O), 170.9 (C═C), 155.7 (C), 133.1 (C), 123.3 (C), 109.7 (C–H), 108.4 (C–H), 107.2 (C–H), 102.0 (C), 55.9 (CH_3), 25.7 (CH_3), 20.2 (CH_3). IR (KBr, cm^{-1}): 3433, 3052, 2926, 2846, 1658, 1593, 1490, 1284. HRMS (ESI): calcd for $C_{12}H_{13}NO_3H^+$: 220.0974, found: 220.0976.

3-(1-Hydroxyethylidene)-5,6-(methylenedioxy)-1-methylindolin-2-one (2e). Eluant: 70% *n*-hexane/30% ethyl acetate. The product was obtained as a green solid (80% yield), mp 129–130 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 13.62 (br, s, 1H, OH), 6.89 (s, 1H, ArH), 6.56 (s, 1H, ArH), 5.94 (s, 2H, OCH_2O), 3.83 (q, J = 7.1 Hz, 2H, NEt), 2.38 (s, 3H, CH_3), 1.28 (t, J = 7.2 Hz, 3H, NEt). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 171.4 (C═O), 170.6 (C═C), 145.5 (C), 143.0 (C), 132.4 (C), 114.9 (C), 102.2 (C), 101.4 (C–H), 101.0 (C–H), 92.1 (CH_2), 34.4 (CH_2), 20.1 (CH_3), 13.2 (CH_3). IR (KBr, cm^{-1}): 3389, 2905, 1660, 1614, 1476. HRMS (ESI): calcd for $C_{13}H_{11}NO_4H^+$: 246.0766, found: 246.0764.

5-Chloro-3-(1-hydroxyethylidene)-1-methylindolin-2-one (2f). Eluant: 30% *n*-hexane/70% dichloromethane. The product was obtained as a purple solid (70% yield), mp 124–125 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 13.60 (br, s, 0.8H, OH), 7.27 (s, 1H, ArH), 7.16 (d, J = 6.4 Hz, 1H, ArH), 6.82 (d, J = 7.2Hz, 1H, ArH), 3.31 (s, 3H, NCH_3), 2.42 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 174.3 (C═O), 170.9 (C═C), 137.2 (C), 127.6 (C), 124.8 (C–H), 123.6 (C), 119.7 (C–H), 109.1 (C–H), 101.2 (C), 25.8 (CH_3), 20.4 (CH_3). IR (KBr, cm^{-1}): 3425, 2916, 1657, 1607. HRMS (ESI): calcd for $C_{11}H_{10}NO_2ClH^+$: 224.0478, found: 224.0474.

5,6-Dichloro-3-(1-hydroxyethylidene)-1-methylindolin-2-one (2g). Eluant: 30% *n*-hexane/70% dichloromethane. The product was obtained as a purple solid (42% yield), mp 153–155 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 13.63 (br, s, 0.9H, OH), 7.37 (s, 1H, ArH), 7.00 (s, 1H, ArH), 3.32 (s, 3H, NCH_3), 2.44 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 174.5 (C═O), 171.0 (C═C), 138.1 (C), 128.7 (C), 125.6 (C), 122.2 (C), 120.9 (C–H), 110.1 (C–H), 100.7 (C), 25.9 (CH_3), 20.5 (CH_3). IR (KBr, cm^{-1}): 3410, 2912, 1659, 1612, 1264. HRMS (ESI): calcd for $C_{11}H_9NO_2Cl_2H^+$: 258.0089, found: 258.0099.

5-(Trifluoromethyl)-3-(1-hydroxyethylidene)-1-methylindolin-2-one (2h). Eluant: 30% *n*-hexane/70% dichloromethane. The product was obtained as a purple solid (25% yield), mp 104–106 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 13.62 (br, s, 1H, OH), 7.57 (s, 1H, ArH), 7.50 (d, J = 8 Hz, 1H, ArH), 7.02 (d, J = 8 Hz, 1H, ArH), 3.39 (s, 3H, NCH_3), 2.51 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 174.8 (C═O), 171.3 (C═C), 141.1 (C), 126.0 (C), 124.4 (q, CF_3), 123.3 (C), 122.5 (C–H), 116.4 (C–H), 108.1 (C–H), 101.1 (C), 25.9 (CH_3), 20.5 (CH_3). ^{19}F NMR (376 MHz, $CDCl_3$): δ_F -61.2 (CF_3). IR (KBr, cm^{-1}): 3421, 2944, 1663, 1616, 1326, 1277, 1110. HRMS (ESI): calcd for $C_{12}H_{10}NO_2F_3H^+$: 258.0742, found: 258.0746.

3-(1-Hydroxyethylidene)-7-methoxy-1-methylindolin-2-one (2i). Eluant: 70% *n*-hexane/30% ethyl acetate. The product was obtained as a purple solid (17% yield), mp 88–90 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 14.05 (br, s, 0.8H, OH), 7.02–7.00 (m, 2H, ArH), 6.79–6.76 (m, 1H, ArH), 3.88 (s, 3H, OMe), 3.62 (s, 3H, NCH_3), 2.44 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 173.7 (C═O), 170.9 (C═C), 146.0 (C), 126.8 (C), 123.9 (C), 122.5 (C–H), 112.9 (C–H), 108.8 (C–H), 101.9 (C), 55.9 (CH_3), 29.0 (CH_3), 20.4 (CH_3). IR (KBr, cm^{-1}): 3433, 2912, 1652, 1588, 1249. HRMS (ESI): calcd for $C_{12}H_{13}NO_3H^+$: 220.0974, found: 220.0969.

3-(Hydroxy(phenyl)methylene)-5-methoxy-1-methylindolin-2-one (2j). Eluant: 20% *n*-hexane/80% dichloromethane. The product was obtained as a yellow solid (81% yield), mp 120–122 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 14.10 (br, s, 0.7H, OH), 7.77 (d, J = 7.6 Hz, 1H), 7.57–7.52 (m, 3H, ArH), 6.82 (d, J = 8.4 Hz, 1H, ArH), 6.78–6.73 (m, 2H, ArH), 3.65 (s, 3H, OMe), 3.37 (s, 3H, NCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 172.2 (C═O), 171.6 (C═C), 155.7 (C), 134.4 (C), 133.7 (C), 131.8 (C–H), 129.0 (C–H), 128.7 (C–H), 123.0 (C), 111.4 (C–H), 108.9 (C–H), 106.9 (C–H), 102.1 (C), 56.0 (CH_3), 26.3 (CH_3). IR (neat, cm^{-1}): 3471, 2982, 1732.3. IR (KBr, cm^{-1}): 3433, 2924, 1644, 1589, 1473. HRMS (ESI): calcd for $C_{17}H_{15}NO_3H^+$: 282.1130, found: 282.1134.

3-((Furan-2-yl)(hydroxy)methylene)-1-methylindolin-2-one (2k). Eluant: 20% *n*-hexane/80% dichloromethane. The product was obtained as a yellow solid (83% yield), mp 115–116 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 14.74 (br, s, 0.8H, OH), 8.27 (d, J = 7.6 Hz, 1H, ArH), 7.80 (s, 1H, ArH), 7.31 (d, J = 3.2 Hz, 1H, ArH), 7.26 (t, J = 7.6 Hz, 1H, ArH), 7.12 (t, J = 7.6 Hz, 1H, ArH), 6.96 (d, J = 7.6 Hz, 1H, ArH), 6.70 (d, J = 3.2 Hz, 1H, ArH), 3.39 (s, 3H, NCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 173.1 (C═O), 158.6 (C═C), 149.3 (C), 146.0 (C–H), 139.3 (C), 126.2 (C–H), 122.6 (C–H), 122.5 (C–H), 121.6 (C), 117.2 (C–H), 112.9 (C–H), 108.5 (C–H), 99.9 (C), 26.3 (CH_3). IR (KBr, cm^{-1}): 3421, 3137, 2928, 1625, 1608, 1468. HRMS (ESI): calcd for $C_{14}H_{11}NO_3H^+$: 242.0817, found: 242.0806.

3-(Hydroxy(thiophen-2-yl)methylene)-1-methylindolin-2-one (2l). Eluant: 70% *n*-hexane/30% ethyl acetate. The product was obtained as a yellow solid (86% yield), mp 99–101 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 14.20 (br, s, 0.6H, OH), 7.9 (s, 1H,

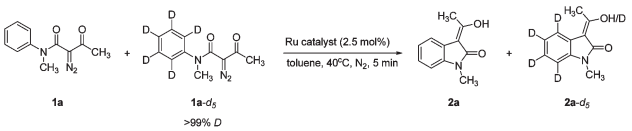
ArH), 7.70–7.65 (m, 2H, ArH), 7.25–7.21 (m, 2H, ArH), 7.01–6.96 (m, 2H, ArH), 3.40 (s, 3H, NCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 172.4 (C═O), 164.5 (C═C), 139.4 (C), 136.8 (C), 131.1 (C–H), 127.8 (C–H), 126.4 (C–H), 122.3 (C), 121.8 (C–H), 120.1 (C–H), 108.9 (C–H), 101.1 (C), 26.3 (CH_3). IR (KBr, cm^{-1}): 3436, 3103, 2928, 1644, 1607, 1467. HRMS (ESI): calcd for $C_{14}H_{11}NO_2SH^+$: 258.0589, found: 258.0587.

5-Chloro-3-(hydroxy(phenyl)methylene)-1-methylindolin-2-one (2m). Eluant: 20% *n*-hexane/80% dichloromethane. The product was obtained as a yellow solid (45% yield), mp 163–165 °C. ^1H NMR (400 MHz, $CDCl_3$): δ_H 14.15 (br, s, 0.8H, OH), 7.75 (d, J = 8.0 Hz, 2H, ArH), 7.61–7.55 (m, 3H, ArH), 7.14 (m, 2H, ArH), 6.85 (d, J = 8.4 Hz, 1H, ArH), 3.39 (s, 3H, NCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 172.7 (C═O), 172.2 (C═C), 137.8 (C), 134.1 (C), 132.2 (C–H), 129.2 (C–H), 128.6 (C–H), 127.8 (C), 125.9 (C–H), 123.4 (C), 120.1 (C–H), 109.5 (C–H), 101.1 (C), 26.4 (CH_3). IR (KBr, cm^{-1}): 3435, 2916, 1635, 1598, 1341. HRMS (ESI): calcd for $C_{16}H_{12}NO_2ClH^+$: 286.0635, found: 286.0634.

1-Benzyl-3-((4-chlorophenyl)(hydroxy)methylene)indolin-2-one (2n). Eluant: 20% *n*-hexane/80% dichloromethane. The product was obtained as a yellow solid (79% yield), mp 123–125 °C. ^1H NMR (400 MHz, $CDCl_3$): δ_H 13.95 (br, s, 1H, OH), 7.77 (d, J = 8.4 Hz, 2H, ArH), 7.53 (d, J = 8.4 Hz, 2H, ArH), 7.35–7.27 (m, 5H, ArH), 7.19 (d, J = 8.0 Hz, 1H, ArH), 7.11 (t, J = 7.6 Hz, 1H, ArH), 6.92–6.87 (m, 2H, ArH), 5.11 (s, 2H, CH_2Ph). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 172.3 (C═O), 170.1 (C═C), 138.7 (C), 137.9 (C), 136.2 (C), 132.9 (C), 130.3 (C–H), 129.4 (C–H), 129.2 (C–H), 128.1 (C–H), 127.7 (C–H), 125.5 (C–H), 122.4 (C–H), 121.8 (C), 120.0 (C–H), 109.9 (C–H), 102.0 (C–H), 43.9 (CH_2). IR (KBr, cm^{-1}): 3436, 3056, 2920, 1645, 1608, 1481. HRMS (ESI): calcd for $C_{22}H_{16}NO_2ClH^+$: 362.0948, found: 362.0933.

Procedure for the KIE experiment

Competition experiments were designed to determine the primary KIE (k_H/k_D) of the Ru-catalyzed intramolecular cyclization of diazo-β-ketoanilides.



To a mixture of **1a** (0.1 mmol), **1a**-d_5 (0.1 mmol) and [Ru(*p*-cymene)Cl_2]$_2$ (2.5 mol%), toluene (1 mL) was added. The reaction mixture was stirred for 5 min at 40 °C under a N_2 atmosphere. The reaction mixture was then concentrated and the substrate conversion was determined by ^1H NMR analysis using CH_2Br_2 as the internal standard. The KIE values were calculated based on the substrate conversions of **1a** and **1a**-d_5. The KIE experiment was repeated three times and the average value ($k_H/k_D \sim 1$) was obtained.

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