

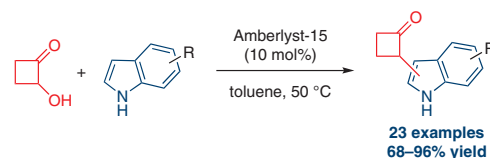
A Catalytic One-Pot Synthesis of Indolyl Cyclobutanones

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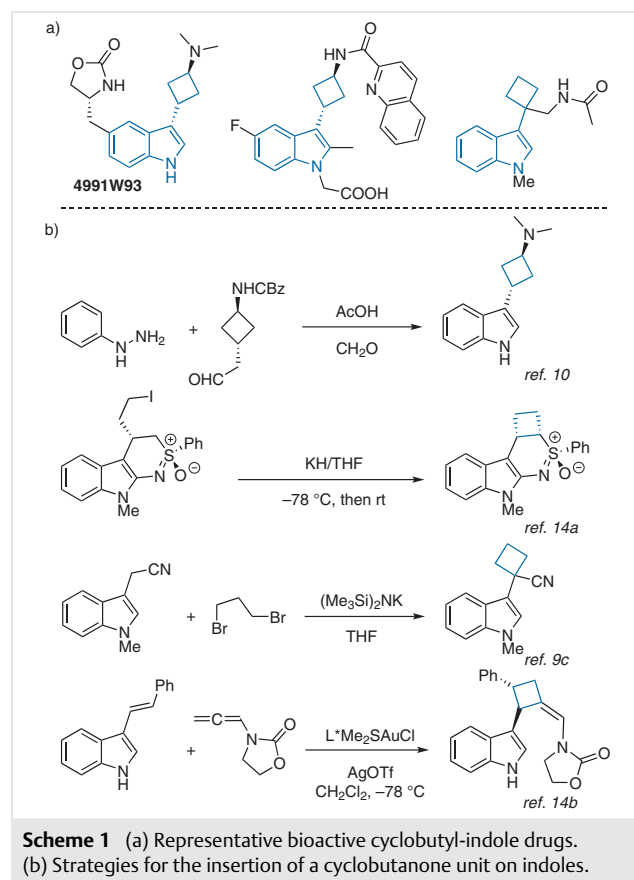
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Abstract A general strategy for the synthesis of indolyl cyclobutanones via a tandem Brønsted acid catalyzed 2-hydroxycyclobutanone activation–indole nucleophilic addition has been exploited. The procedure leads to a wide range of 2- and 3-functionalized indole derivatives in good to high yields with broad substrate scope.

Key words indoles, cyclobutanones, Brønsted acids, tandem reactions, catalysis

Due to the extremely high number of natural bioactive compounds containing an indole unit,¹ a wide number of chemoselective syntheses and functionalizations of this heterocycle have been exploited.² In particular, many investigations were focused on the identification of new and specific therapeutic agents for the treatment of several human diseases such as glaucoma,³ hypertension,⁴ depression,⁵ Alzheimer's disease,⁶ cardiovascular diseases,⁷ and viral infections.⁸ A number of strained cyclobutyl- and cyclopropylindole derivatives have aroused significant interest, not only for their pharmacological properties but, above all, for their usefulness in drug–receptor affinity studies. Indeed, the affinity of lead compounds can be studied by performing radioligand binding assays using constrained molecular architectures that, by reducing the rotations around certain bonds, clarify the way in which these molecules interact with biological targets.⁹ Examples include compound 4991W93, a 5HT1B/1D receptor and partial agonist with potential for the treatment and prophylaxis of migraine,¹⁰ the inhibition of leukotriene production,¹¹ CRTH2 antagonists¹² and estrogen receptor modulators¹³ (Scheme 1, a).

Despite their biological activity, direct insertion of a cyclobutane unit on the indole skeleton is limited to a few multistep approaches, generally requiring the preparation of prefunctionalized substrates (Scheme 1, b).^{9c,10,14}



In this context, a versatile one-pot catalytic and chemoselective procedure would represent a significant advance for drug design and synthesis. We recently reported the preparation of indole cyclopropylcarbaldehydes **3** through a tandem acid-catalyzed addition/ring-contraction reaction of 2-hydroxycyclobutanone (**1**) and indole (**2a**) (Scheme 2, a).¹⁵ Continuing our studies in this research field,¹⁶ we dis-

covered that functionalized aldehyde **3a** furnished the corresponding indolylcyclobutanone derivative **4a** on treatment with PTSA at 50 °C (Scheme 2, b).

This observation inspired us to develop a two-step, one-pot synthesis of cyclobutanone indoles **4** following the general procedure shown in Scheme 2, c. To explore the feasibility of this process, a series of experiments was performed to identify the best reaction conditions. A summary of the results is reported in Table 1 (see also Table S1 in the

Biographical Sketches



Angelo Frongia was born in Cagliari (Italy) in 1973. He graduated and received his Ph.D. in organic chemistry from the University of Cagliari under the supervision of Prof. P. P. Piras. In 2001, he joined Dr. Jacques Salaün at the Laboratoire des Carbocycles (CNRS) Paris (France) as a postdoctoral fellow. During his studies (2002–

2008), he completed an internship in the group of Prof. P. P. Piras at the University of Cagliari, and following collaborative postdoctoral research (2009) in the group of Prof. D. J. Aitken at the 'Institut de Chimie Moléculaire et des Matériaux d'Orsay', University Paris Sud (France), he started his independent career at the 'Dipartimen-

to di Scienze Chimiche e Geologiche' (University of Cagliari) in 2010. He is currently Associate Professor of Organic Chemistry at the Faculty of Sciences. His research interests focus on the synthesis and reactivity of strained carbocycles and asymmetric organocatalytic reactions.



Stefania Porcu obtained her Master's degree from the University of Cagliari (Italy) under the supervision of Prof. Francesco Secci. Since 2017, she has

been a Ph.D. student under the supervision of Prof. Francesco Secci and Prof. Pier Carlo Ricci (Italy). Her research interests include acid-catalyzed synthesis

and functionalization of N-heterocycles, their photo-physical characterization and their use as photocatalysts.



Carla Aira Rodriguez obtained her Bachelor's degree in chemistry from the University of Vigo (Spain) in 2020. To com-

plete her M.Sc. degree, she moved to Cagliari and since October 2019 she has worked on the development of novel eco-

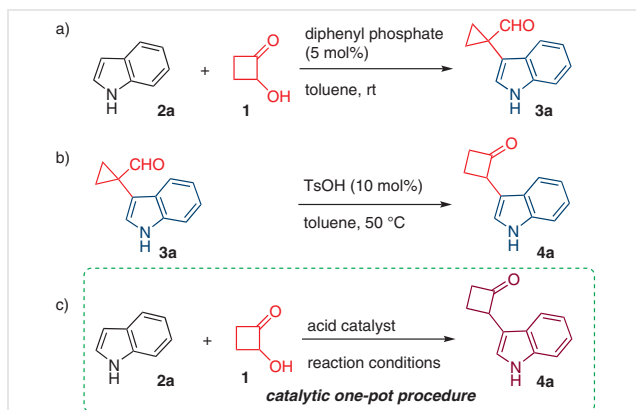
friendly one-pot functionalizations of indole derivatives under the supervision of Prof. Francesco Secci (Italy).



Francesco Secci was born in Cagliari (Italy) in 1977. He received his Ph.D. in 2006 from the University of Cagliari and Université Paris-Sud (Orsay, France) under the supervision of Prof. P. P. Piras and Dr. J. Ollivier. After a postdoctoral stay (2007–2010) at the University

of York (UK) with Prof. P. O'Brien, he moved back to Cagliari to start his own research with a grant from the Fund for Investment in Basic Research (FIRB) (Italy). Since 2013, he has served as a lecturer at the same university, and in 2019 he was promoted to Associate Profes-

sor. His research interests are focused on the development of new synthetic methodologies involving strained carbocyclic and heterocyclic compounds, the study of novel catalytic transformations and their synthetic applications.



Scheme 2 (a) Acid-catalyzed synthesis of indole cyclopropylcarbaldehyde **3a**. (b) The C3–C4 ring expansion of aldehyde **3a** to give cyclobutanone **4a**. (c) A catalytic one-pot synthesis of indolyl cyclobutanone derivative **4a**.

Supporting Information). We first examined the reaction between 2-hydroxycyclobutanone (**1**) and indole (**2a**) in the presence of TsOH (10 mol%) under neat conditions and isolated the desired product **4a** in only 18% yield after 24 hours (entry 1). The reaction carried out in toluene at 40 °C gave the product **4a** in an improved 48% yield (entry 2), and this increased to 58% when the reaction was performed at 50 °C (entry 3). Increasing the temperature to 60 °C did not lead to any further improvement in the yield of **4a** (entry 4). Furthermore, no significant benefits were obtained from the use of 3 Å molecular sieves or other anhydrous reaction conditions. Finally, a catalyst screen using recyclable NR-50

(Nafion resin 50), AR-15 (Amberlyst resin 15) and AR-35 (Amberlyst resin 35) (entries 5, 6 and 7) showed that the optimum yield of **4a** (96%) was obtained when using AR-15 (10 mol% loading) at 50 °C in toluene.

With optimized reaction conditions in hand, we next studied the scope of this one-pot, two-step procedure using substituted indoles **2a–v** (Scheme 3). Good functional group tolerance was observed for indoles **2**, allowing access to a variety of cyclobutanone adducts **4**. Indoles **2a–d** furnished the corresponding adducts **4a–d** in good to high yields (73–96%). Satisfactory results were achieved by reacting 2-hydroxycyclobutanone (**1**) with *N*-substituted indoles **2e–i**, affording the cyclobutanones **4e–i** in 89–94% yields.¹⁷ The 2- and 3-alkyl/aryl indoles **2j–q** gave good conversions and yields of the corresponding indolyl ketones **4j–p**, with **4q** being recovered as a 50:50 mixture of diastereoisomers (90% yield), probably due to epimerization at C2 of the cyclobutanone moiety during the chromatographic purification step. On the other hand, reactions of **1** with indoles **2r–v**, bearing electron-withdrawing groups at the C4 or C5 positions, did not occur as desired. In these cases, cyclopropyl carbaldehydes **3r–v** were isolated as unique reaction products in yields of 74–90%.

Further experiments carried out with *N*-benzylpyrrole afforded the corresponding cyclopropanes **3w/3w'** (as an 80:20 mixture of regioisomers) in 68% overall yield. The reaction of **1** with 3,5-dimethoxyphenol yielded the cyclobutanone **4x** in 86% yield.

The results obtained during this study allowed us to put forward a plausible mechanism for the acid-catalyzed one-pot addition of a cyclobutanone to the indole skeleton

Table 1 Initial Screening Studies^a

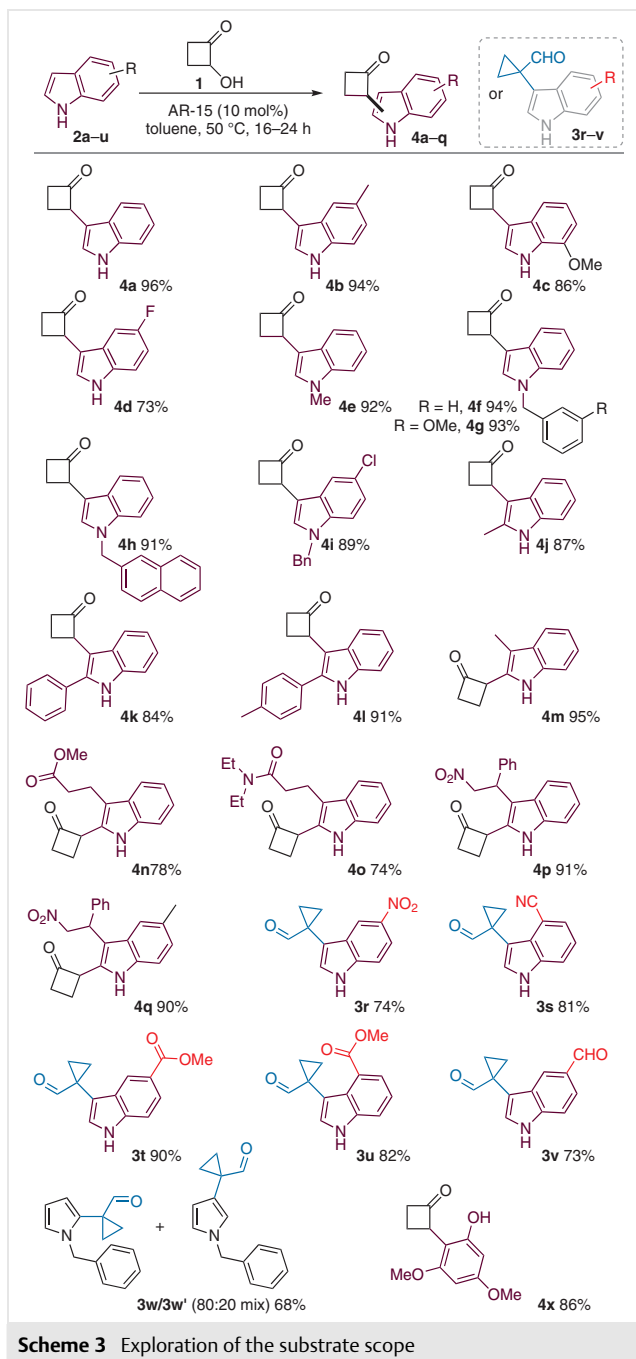
Entry	Catalyst (mol%)	Solvent	Temp (°C)	Ratio of 3a/4a ^b	Conv. (%) ^c	Yield (%) ^d
1	TsOH (10)	neat	40	2:1	21	18
2	TsOH (10)	toluene	40	1:1	50	48
3	TsOH (10)	toluene	50	1:3	63	58
4	TsOH (10)	toluene	60	1:16	60	54
5	NR-50 (10)	toluene	50	1:22	96	94
6	AR-15 (10)	toluene	50	1:28	97	96
7	AR-35 (10)	toluene	50	1:28	93	90

^a Reaction conditions: **1** (50 mg, 0.58 mmol), **2a** (1.0 equiv), acid catalyst [Nafion resin 50 (NR-50), Amberlyst resin 15 (AR-15) or Amberlyst resin 35 (AR-35): 10 mol%], solvent (1.5 mL), 8–24 h, 40–50 °C.

^b The **3a:4a** ratio was determined by ¹H NMR analysis.

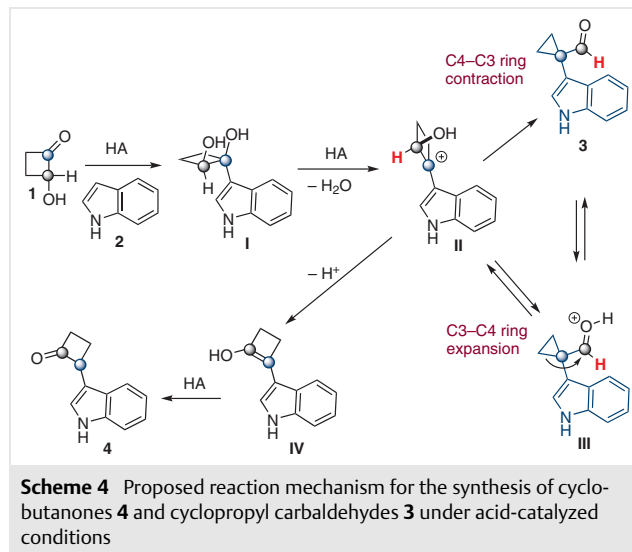
^c The conversion into **4a** was determined by ¹H NMR analysis.

^d Yield of isolated product **4a** after flash chromatography.



(Scheme 4). In our hypothesis, the protonation of cyclobutanone **1** promotes indole nucleophilic attack leading to the formation of the adduct **I**.^{15,16a,b} At room temperature, this intermediate undergoes a rapid C4–C3 ring contraction via carbocationic species **II**, mainly affording the cyclopropyl carbaldehydes **3**.¹⁶ At higher temperatures (50 °C), the establishment of an equilibrium between the three-membered-ring species **3** and the cyclobutane carbocationic intermediate **II** leads to the formation of derivatives **4**.^{18,19}

However, this process is favored by the presence of electron-donating groups on the heterocyclic system. On the other hand, reactions carried out with indoles bearing electron-withdrawing groups (e.g., **2r–v**) destabilize the carbocationic species **II** and promote the C4–C3 ring contraction as a preferential stabilization process.^{19,20}



In summary, a new one-pot catalytic functionalization of indoles has been established under mild conditions. This method provides a straightforward access to diverse indolyl cyclobutanone compounds in good to excellent yields, underlining a broad substrate scope and some limitations related to the presence of electron-withdrawing groups. This two-step, one-pot process has been studied by using a recyclable polystyrene-based ion exchange resin. Further studies aimed toward adapting this reaction to a continuous-flow process are currently underway in our laboratories.

Diphenyl phosphate, Amberlyst 15, Amberlyst 35 and indoles **2a,d,i,l,q,r** were purchased from Sigma-Aldrich and used without further purification. Indoles **2b,c,m,s** were purchased from TCI and used without further purification. Unless noted otherwise, all experiments were carried out in a 5 mL vial closed with a screw cap and equipped with a magnetic stir bar. Analytical thin-layer chromatography was performed using 0.25 mm Aldrich silica gel 60-F plates. Flash chromatography was performed using Merck silica gel (70–200 mesh). Yields refer to chromatographically and spectroscopically pure materials. Melting points were determined with a Büchi M-560 apparatus. Infrared spectra were recorded on FT-IR Bruker Equinox-55 or Thermo Fisher Scientific Nicolet IS50 FTIR spectrophotometers and are reported in wavenumbers (cm⁻¹). ¹H and ¹³C NMR spectra were obtained on Bruker DRX 600 (¹H, 600 MHz; ¹³C, 150 MHz) or Varian 500 (¹H, 500 MHz; ¹³C, 126 MHz) spectrometers at 27 °C using CDCl₃ (internal reference = 7.26 ppm) as the solvent. ¹³C NMR were recorded at 126 MHz (internal reference = 77.00 ppm) using CDCl₃ as the solvent. Chemical shifts (δ) are given in ppm. Coupling constants (*J*) are reported in Hz. Low-resolution mass spectrometry was performed

using an Agilent-HP GC-MS (EI, 70 eV). High-resolution mass spectrometry (HRMS) was performed in fast atom bombardment (FAB+) ionization mode (ESI) using Bruker micrOTF-Q II and/or Agilent Q-TOF 6520 instruments.

Cyclobutyl Indoles 4; General Procedure

In a 5 mL glass vial, a mixture of 2-hydroxycyclobutanone (**1a**) (100 mg, 1.1 mmol), indole **2a–v** (1.0 mmol), Amberlyst 15 (10 mol%) and toluene (3.0 mL) was stirred at 50 °C. After completion of the reaction, the crude product was loaded on a silica gel column and purified by flash chromatography using hexanes/diethyl ether (10:1 to 3:1) as the eluent.

2-(1H-Indol-3-yl)cyclobutanone (4a)

Yield: 117 mg (96%); colorless oil.

¹H NMR (500 MHz, CDCl₃): δ = 7.97 (s, 1 H), 7.50 (d, *J* = 7.8 Hz, 1 H), 7.29 (d, *J* = 8.1 Hz, 1 H), 7.17–7.11 (m, 1 H), 7.08 (d, *J* = 1.4 Hz, 1 H), 7.06 (td, *J* = 7.6, 1.0 Hz, 1 H), 4.68 (tdd, *J* = 7.9, 2.5, 1.2 Hz, 1 H), 3.31–3.14 (m, 1 H), 3.07 (dddd, *J* = 17.6, 9.7, 4.9, 2.7 Hz, 1 H), 2.55 (qd, *J* = 10.6, 4.9 Hz, 1 H), 2.14 (ddt, *J* = 11.0, 9.6, 8.1 Hz, 1 H).

¹³C NMR (126 MHz, CDCl₃): δ = 208.8, 136.3, 126.3, 122.4, 121.1, 119.7, 119.0, 112.0, 111.2, 57.0, 45.1, 18.3.

All analytical data were in good accordance with reported data.¹⁶

2-(5-Methyl-1H-indol-3-yl)cyclobutanone (4b)

Yield: 187 mg (94%); colorless oil.

FTIR (film): 2994, 1788, 1612, 1454, 1228, 1129, 1011 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 7.94 (s, 1 H), 7.33 (s, 1 H), 7.25 (d, *J* = 10.0 Hz, 1 H), 7.11 (d, *J* = 1.4 Hz, 1 H), 7.03 (d, *J* = 8.3 Hz, 1 H), 4.80–4.60 (m, 1 H), 3.32–3.23 (m, 1 H), 3.13 (dddd, *J* = 17.6, 9.6, 4.9, 2.7 Hz, 1 H), 2.61 (ddd, *J* = 21.4, 10.6, 4.9 Hz, 1 H), 2.45 (s, 3 H), 2.29–2.13 (m, 1 H).

¹³C NMR (126 MHz, CDCl₃): δ = 208.8, 136.3, 126.3, 122.4, 121.1, 119.7, 119.0, 112.0, 111.2, 57.0, 45.1, 18.3.

HRMS (ESI): *m/z* [M + Na]⁺ calcd for C₁₃H₁₃NNaO: 222.0895; found: 222.0898.

2-(7-Methoxy-1H-indol-3-yl)cyclobutanone (4c)

Yield: 185 mg (86%); green oil.

FTIR (film): 2998, 1789, 1614, 1460, 1221, 1129, 1009 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 8.12 (s, 1 H), 7.08 (s, 1 H), 7.00 (d, *J* = 7.0 Hz, 1 H), 6.87 (d, *J* = 7.0 Hz, 1 H), 6.59 (dd, *J* = 6.5, 3.5 Hz, 1 H), 4.90 (t, *J* = 6.5 Hz, 1 H), 3.80 (s, 3 H), 2.72–2.67 (m, 1 H), 2.40–2.37 (m, 1 H), 2.08–2.01 (m, 2 H).

¹³C NMR (126 MHz, CDCl₃): δ = 210.9, 154.4, 131.3, 128.3, 124.8, 116.5, 112.6, 112.1, 100.6, 55.9, 40.8, 29.1, 19.0.

HRMS (ESI): *m/z* [M + Na]⁺ calcd for C₁₃H₁₃NNaO₂: 238.0844; found: 238.0851.

2-(5-Fluoro-1H-indol-3-yl)cyclobutanone (4d)

Yield: 148 mg (73%); yellow oil.

FTIR (film): 2986, 1790, 1463, 1227, 1145, 986 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 7.97 (br s, 1 H), 7.22–7.19 (m, 1 H), 7.12 (td, *J* = 9.8, 2.1 Hz, 2 H), 6.88 (td, *J* = 9.1, 2.3 Hz, 1 H), 4.62 (t, *J* = 9.2 Hz, 1 H), 3.30–3.12 (m, 1 H), 3.14–2.93 (m, 1 H), 2.55 (qd, *J* = 10.7, 5.0 Hz, 1 H), 2.17–2.00 (m, 1 H).

¹³C NMR (126 MHz, CDCl₃): δ = 208.7, 129.7, 122.9, 111.9 (d, *J* = 1.8 Hz), 111.8, 110.9 (d, *J* = 1.9 Hz), 110.7, 104.1 (d, *J* = 1.8 Hz), 104.0, 56.8, 45.1, 18.2.

HRMS (ESI): *m/z* [M + Na]⁺ calcd for C₁₂H₁₀FNNaO: 226.0644; found: 226.0651.

2-(1-Methyl-1H-indol-3-yl)cyclobutanone (4e)

Yield: 183 mg (92%); orange oil.

All analytical data were in good accordance with reported data.¹⁵

2-(1-Benzyl-1H-indol-3-yl)cyclobutanone (4f)

Yield: 258 mg (94%); yellow oil.

¹H NMR (500 MHz, CDCl₃): δ = 7.49 (d, *J* = 7.9 Hz, 1 H), 7.22 (dd, *J* = 11.7, 4.2 Hz, 3 H), 7.18 (d, *J* = 8.4 Hz, 2 H), 7.06–7.03 (m, 3 H), 7.00 (s, 1 H), 5.18 (s, 2 H), 4.67 (td, *J* = 8.4, 2.0 Hz, 1 H), 3.29–3.12 (m, 1 H), 3.04 (dddd, *J* = 17.5, 9.6, 4.9, 2.7 Hz, 1 H), 2.53 (qd, *J* = 10.6, 4.9 Hz, 1 H), 2.22–1.95 (m, 1 H).

¹³C NMR (126 MHz, CDCl₃): δ = 202.1, 137.3, 136.7, 128.7, 127.6, 126.8, 125.2, 122.1, 119.7, 119.4, 119.2, 111.0, 109.8, 57.0, 50.0, 45.1, 18.4.

All analytical data were in good accordance with reported data.¹⁶

2-[1-(3-Methoxybenzyl)-1H-indol-3-yl]cyclobutanone (4g)

Yield: 283 mg (93%); colorless oil.

FTIR (film): 2984, 1789, 1458, 1227, 1144, 908 cm⁻¹.

¹H NMR (600 MHz, CDCl₃): δ = 7.49 (d, *J* = 7.9 Hz, 1 H), 7.18 (s, 1 H), 7.15–7.08 (m, 2 H), 7.03 (dd, *J* = 11.0, 3.9 Hz, 1 H), 7.00 (s, 1 H), 6.71 (dd, *J* = 8.2, 2.4 Hz, 1 H), 6.63 (d, *J* = 7.6 Hz, 1 H), 6.59 (s, 1 H), 5.15 (s, 2 H), 4.74–4.57 (m, 1 H), 3.66 (s, 3 H), 3.19 (dddd, *J* = 18.0, 10.7, 8.3, 2.5 Hz, 1 H), 3.04 (dddd, *J* = 17.5, 9.6, 4.9, 2.7 Hz, 1 H), 2.53 (qd, *J* = 10.7, 4.9 Hz, 1 H), 2.12 (dtd, *J* = 10.9, 9.6, 8.2 Hz, 1 H).

¹³C NMR (151 MHz, CDCl₃): δ = 208.9, 159.9, 138.9, 136.8, 129.8, 127.0, 125.2, 122.1, 119.4, 119.2, 119.1, 112.7, 112.7, 111.0, 109.8, 57.0, 55.1, 49.9, 45.0, 18.4.

HRMS (ESI): *m/z* [M + Na]⁺ calcd for C₂₀H₁₉NNaO₂: 328.1313; found: 328.1314.

2-[1-(Naphthalen-2-ylmethyl)-1H-indol-3-yl]cyclobutanone (4h)

Yield: 295 mg (91%); brown solid; mp 76 °C.

FTIR (film): 2952, 1790, 1612, 1463, 1352, 1200, 1072 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 7.77 (m, 3 H), 7.61–7.55 (m, 2 H), 7.48–7.40 (m, 2 H), 7.29 (d, *J* = 8.1 Hz, 1 H), 7.26–7.21 (m, 1 H), 7.20–7.14 (m, 1 H), 7.13–7.08 (m, 2 H), 5.39 (s, 2 H), 4.80–4.67 (m, 1 H), 3.25 (dddd, *J* = 17.8, 10.6, 8.3, 2.5 Hz, 1 H), 3.11 (dddd, *J* = 17.5, 9.6, 4.9, 2.7 Hz, 1 H), 2.60 (qd, *J* = 10.6, 4.9 Hz, 1 H), 2.19 (ddt, *J* = 10.9, 9.6, 8.2 Hz, 1 H).

¹³C NMR (126 MHz, CDCl₃): δ = 208.8, 136.9, 134.7, 133.3, 132.8, 128.6, 127.8, 127.6, 127.1, 126.3, 126.0, 125.6, 125.2, 124.8, 122.1, 119.4, 119.3, 111.1, 109.8, 57.0, 50.2, 45.0, 18.4.

HRMS (ESI): *m/z* [M + Na]⁺ calcd for C₂₃H₁₉NNaO: 348.1364; found: 348.1371.

2-(1-Benzyl-5-chloro-1H-indol-3-yl)cyclobutanone (4i)

Yield: 275 mg (89%); yellow oil.

FTIR (film): 3073, 1783, 1441, 1224, 1018, 990 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 7.44 (d, *J* = 1.3 Hz, 1 H), 7.20 (dd, *J* = 10.6, 7.1 Hz, 3 H), 7.05 (t, *J* = 7.8 Hz, 2 H), 7.04–6.99 (m, 3 H), 5.14 (s, 2 H), 4.59 (td, *J* = 8.1, 2.2 Hz, 1 H), 3.19 (dddd, *J* = 18.9, 10.6, 8.4, 2.4 Hz, 1 H), 3.09–2.92 (m, 1 H), 2.52 (qd, *J* = 10.7, 4.9 Hz, 1 H), 2.07 (tt, *J* = 10.8, 8.3 Hz, 1 H).

¹³C NMR (126 MHz, CDCl₃): δ = 208.4, 137.0, 135.3, 129.3, 128.9, 128.2, 127.9, 127.1, 126.9, 126.7, 125.4, 122.6, 118.9, 111.0, 110.9, 56.8, 50.4, 45.3, 18.5.

HRMS (ESI): *m/z* [M + Na]⁺ calcd for C₁₉H₁₆ClNNaO: 332.0818; found: 332.0821.

2-(2-Methyl-1H-indol-3-yl)cyclobutanone (4j)

Yield: 173 mg (87%); yellow oil.

FTIR (film): 2989, 1788, 1457, 1231, 1144 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 7.83 (br s, 1 H), 7.33 (d, *J* = 7.8 Hz, 1 H), 7.25 (d, *J* = 6.5 Hz, 1 H), 7.10 (t, *J* = 7.1 Hz, 1 H), 7.08–7.01 (m, 1 H), 4.67 (ddt, *J* = 10.7, 8.6, 2.2 Hz, 1 H), 3.28 (dddd, *J* = 19.3, 10.5, 8.7, 2.0 Hz, 1 H), 3.23–3.12 (m, 1 H), 2.52 (qd, *J* = 10.8, 4.8 Hz, 1 H), 2.40–2.34 (m, 1 H), 2.33 (s, 3 H).

¹³C NMR (126 MHz, CDCl₃): δ = 210.1, 135.3, 131.9, 127.3, 121.3, 119.5, 118.1, 110.4, 107.2, 57.0, 45.0, 18.3, 12.1.

HRMS (ESI): *m/z* [M + Na]⁺ calcd for C₁₃H₁₃NNaO: 222.0895; found: 222.0899.

2-(2-Phenyl-1H-indol-3-yl)cyclobutanone (4k)

Yield: 219 mg (84%); colorless oil.

FTIR (film): 3054, 2989, 1789, 1623, 1456, 1227, 1112, 1024 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 8.06 (br s, 1 H), 7.38–7.34 (m, 5 H), 7.31–7.29 (m, 1 H), 7.17–7.16 (m, 1 H), 7.14–7.13 (m, 1 H), 7.06–7.03 (m, 1 H), 4.87–4.66 (m, 1 H), 3.31–3.02 (m, 2 H), 2.52–2.30 (m, 2 H).

¹³C NMR (126 MHz, CDCl₃): δ = 201.8, 136.1, 129.8, 129.1, 129.0, 123.0, 122.8, 120.4, 120.2, 119.5, 119.0, 111.2, 111.1, 57.5, 45.1, 18.3.

HRMS (ESI): *m/z* [M + Na]⁺ calcd for C₁₈H₁₅NNaO: 284.1051; found: 284.1053.

2-[2-(*p*-Tolyl)-1H-indol-3-yl]cyclobutanone (4l)

Yield: 250 mg (91%); colorless oil.

FTIR (film): 3007, 1790, 1502, 1460, 1134, 1028 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 8.07 (br s, 1 H), 7.44 (d, *J* = 7.9 Hz, 1 H), 7.39 (d, *J* = 8.1 Hz, 2 H), 7.37 (d, *J* = 8.1 Hz, 1 H), 7.28 (d, *J* = 7.9 Hz, 2 H), 7.21–7.17 (m, 1 H), 7.13–7.09 (m, 1 H), 4.90–4.71 (m, 1 H), 3.35–3.12 (m, 2 H), 2.55–2.45 (m, 2 H), 2.42 (s, 3 H).

¹³C NMR (126 MHz, CDCl₃): δ = 209.9, 138.2, 136.2, 135.9, 129.6, 128.4, 127.7, 127.4, 122.3, 120.0, 119.3, 111.1, 107.6, 57.6, 45.0, 21.2, 18.3.

HRMS (ESI): *m/z* [M + Na]⁺ calcd for C₁₉H₁₇NNaO: 298.1208; found: 298.1211.

2-(3-Methyl-1H-indol-2-yl)cyclobutanone (4m)

Yield: 189 mg (95%); yellow oil.

FTIR (film): 3390, 3053, 2919, 1789, 1704, 1612, 1462, 1386, 1238 cm⁻¹.

¹H NMR (600 MHz, CDCl₃): δ = 7.49 (dd, *J* = 7.9, 3.5 Hz, 1 H), 7.13 (dd, *J* = 7.8, 2.3 Hz, 2 H), 7.05 (ddd, *J* = 7.9, 5.6, 2.4 Hz, 1 H), 6.83 (d, *J* = 0.8 Hz, 1 H), 5.67–5.45 (m, 1 H), 3.11–3.03 (m, 1 H), 2.99–2.91 (m, 1 H), 2.66 (d, *J* = 3.0 Hz, 1 H), 2.62 (ddd, *J* = 21.5, 10.9, 4.4 Hz, 1 H), 2.22 (s, 3 H).

¹³C NMR (151 MHz, CDCl₃): δ = 203.6, 135.8, 128.9, 122.8, 121.9, 119.4, 119.2, 112.2, 109.1, 68.5, 41.8, 20.2, 9.5.

HRMS (ESI): *m/z* [M + Na]⁺ calcd for C₁₃H₁₃NNaO: 222.0895; found: 222.0901.

3-[2-(2-Oxocyclobutyl)-1H-indol-3-yl]propionic Acid Methyl Ester (4n)

Yield: 211 mg (78%); colorless oil.

FTIR (film): 3418, 2973, 2881, 1781, 1721, 1622, 1462, 1397, 1087, 912 cm⁻¹.

¹H NMR (600 MHz, CDCl₃): δ = 7.50 (d, *J* = 7.9 Hz, 1 H), 7.13–7.10 (m, 2 H), 7.05 (ddd, *J* = 7.9, 5.9, 2.1 Hz, 1 H), 6.86 (s, 1 H), 5.54 (ddd, *J* = 10.5, 4.1, 2.1 Hz, 1 H), 3.59 (s, 3 H), 3.11–3.01 (m, 1 H), 2.99 (t, *J* = 7.8 Hz, 2 H), 2.97–2.90 (m, 1 H), 2.60 (t, *J* = 7.8 Hz, 2 H), 2.59–2.56 (m, 1 H), 2.26–2.18 (m, 1 H).

¹³C NMR (151 MHz, CDCl₃): δ = 203.2, 173.6, 135.8, 127.8, 122.7, 122.0, 119.6, 119.0, 115.2, 109.3, 68.4, 51.5, 41.8, 34.5, 20.4, 20.0.

HRMS (ESI): *m/z* [M + Na]⁺ calcd for C₁₆H₁₇NNaO₃: 294.1106; found: 294.1112.

N,N-Diethyl-3-[2-(2-oxocyclobutyl)-1H-indol-3-yl]propionamide (4o)

Yield: 230 mg (74%); yellow oil.

FTIR (film): 3412, 2977, 2889, 1781, 1627, 1460, 1298, 1089, 1086 cm⁻¹.

¹H NMR (600 MHz, CDCl₃): δ = 7.52 (d, *J* = 7.9 Hz, 1 H), 7.14–7.07 (m, 2 H), 7.04 (ddd, *J* = 8.0, 4.9, 3.1 Hz, 1 H), 6.87 (s, 1 H), 5.55 (ddd, *J* = 10.4, 3.9, 2.0 Hz, 1 H), 3.30 (dd, *J* = 14.0, 7.0 Hz, 2 H), 3.12 (dd, *J* = 14.2, 7.1 Hz, 2 H), 3.08–3.04 (m, 1 H), 3.02 (dd, *J* = 9.0, 6.9 Hz, 2 H), 2.93 (dddd, *J* = 14.9, 12.3, 7.4, 5.3 Hz, 1 H), 2.63–2.59 (m, 1 H), 2.60–2.57 (m, 2 H), 2.23 (dt, *J* = 20.0, 9.9 Hz, 1 H), 1.02 (t, *J* = 7.0 Hz, 3 H), 0.99 (t, *J* = 7.1 Hz, 3 H).

¹³C NMR (151 MHz, CDCl₃): δ = 203.3, 171.7, 135.7, 127.9, 122.8, 121.9, 119.5, 119.0, 115.9, 109.3, 68.4, 41.8, 41.7, 40.1, 33.6, 20.8, 19.9, 14.1, 12.9.

HRMS (ESI): *m/z* [M + Na]⁺ calcd for C₁₉H₂₄N₂NaO₂: 335.1735; found: 335.1737.

2-[3-(2-Nitro-1-phenylethyl)-1H-indol-2-yl]cyclobutanone (4p)

Yield: 304 mg (91%); colorless oil.

FTIR (film): 2919, 1701, 1456, 1225, 1153, 907, 738 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 7.36 (dd, *J* = 18.2, 8.0 Hz, 1 H), 7.28–7.22 (m, 5 H), 7.14 (t, *J* = 4.1 Hz, 2 H), 7.06–6.98 (m, 1 H), 6.92 (d, *J* = 27.1 Hz, 1 H), 5.59 (dt, *J* = 17.0, 5.3 Hz, 1 H), 5.09 (td, *J* = 7.9, 4.5 Hz, 1 H), 4.97 (ddd, *J* = 12.6, 7.3, 5.3 Hz, 1 H), 4.86 (ddd, *J* = 17.8, 12.5, 8.6 Hz, 1 H), 3.20–3.15 (m, 1 H), 2.98–2.95 (m, 1 H), 2.67–2.65 (m, 1 H), 2.28–2.24 (m, 1 H).

¹³C NMR (126 MHz, CDCl₃): δ = 202.7, 138.9, 134.4, 128.9, 127.7, 125.2, 124.3, 123.2, 122.9, 121.1, 118.9, 114.0, 109.4, 84.8, 79.4, 68.6, 27.5, 21.4.

HRMS (ESI): *m/z* [M + Na]⁺ calcd for C₂₀H₁₈N₂NaO₃: 357.1215; found: 357.1221.

2-[5-Methyl-3-(2-nitro-1-phenylethyl)-1H-indol-2-yl]cyclobutane (4q)

Obtained as a 55:45 mixture of diastereoisomers.

Yield: 313 mg (90%); colorless oil.

FTIR (film): 3013, 2980, 2232, 1789, 1785, 1644, 1470, 1229, 1148, 1012 cm⁻¹.

Isomer A

¹H NMR (500 MHz, CDCl₃): δ = 7.25–7.24 (m, 4 H), 7.20–7.17 (m, 3 H), 7.00 (m, 1 H), 6.97–6.95 (s, 1 H), 5.53 (d, *J* = 8.2 Hz, 1 H), 5.07–5.03 (m, 1 H), 4.99–4.91 (m, 1 H), 4.90–4.80 (m, 1 H), 3.17–3.04 (m, 1 H), 3.03–2.91 (m, 1 H), 2.67–2.55 (m, 1 H), 2.31 (s, 3 H), 2.27–2.21 (m, 1 H).

¹³C NMR (126 MHz, CDCl₃): δ = 202.6, 138.9, 134.4, 129.7, 129.0, 128.9, 127.7, 127.5, 124.3, 122.9, 118.8, 114.0, 109.4, 79.4, 68.6, 28.5, 27.5, 21.3, 20.0.

HRMS (ESI): *m/z* [M + Na]⁺ calcd for C₂₁H₂₀N₂NaO₃: 371.1372; found: 371.1379.

Isomer B

¹H NMR (500 MHz, CDCl₃): δ = 7.25–7.23 (m, 4 H), 7.19–7.17 (m, 2 H), 7.13–7.12 (m, 1 H), 7.02 (d, *J* = 4.5 Hz, 1 H), 6.82 (s, 1 H), 6.66–6.23 (m, 1 H), 5.07–5.04 (m, 1 H), 4.99–4.90 (m, 1 H), 4.89–4.80 (m, 1 H), 3.07–3.06 (m, 1 H), 2.98–2.95 (m, 1 H), 2.76–2.74 (m, 1 H), 2.32 (s, 3 H), 2.27–2.19 (m, 1 H).

¹³C NMR (126 MHz, CDCl₃): δ = 202.7, 138.9, 134.4, 129.7, 129.0, 128.9, 127.7, 125.2, 122.9, 121.1, 118.9, 114.0, 109.4, 84.9, 68.7, 41.9, 28.4, 21.4, 20.1.

HRMS (ESI): *m/z* [M + Na]⁺ calcd for C₂₁H₂₀N₂NaO₃: 371.1372; found: 371.1377.

1-(5-Nitro-1H-indol-3-yl)cyclopropanecarbaldehyde (3r)

Yield: 170 mg (74%); yellow solid.

All analytical data were in good accordance with reported data.¹⁶

3-(1-Formylcyclopropyl)-1H-indole-4-carbonitrile (3s)

Yield: 170 mg (81%); colorless oil.

All analytical data were in good accordance with reported data.¹⁶

3-(1-Formylcyclopropyl)-1H-indole-5-carboxylic Acid Methyl Ester (3t)

Yield: 218 mg (90%); colorless oil.

FTIR (film): 3472, 2961, 1785, 1711, 1620, 1437, 1261, 1096 cm⁻¹.

¹H NMR (600 MHz, CDCl₃): δ = 9.25 (s, 1 H), 8.30 (s, 1 H), 8.25 (s, 1 H), 7.86 (dd, *J* = 8.6, 1.6 Hz, 1 H), 7.30 (d, *J* = 8.6 Hz, 1 H), 7.10 (d, *J* = 2.1 Hz, 1 H), 3.86 (s, 3 H), 1.61 (q, *J* = 4.0 Hz, 2 H), 1.35 (q, *J* = 4.1 Hz, 2 H).

¹³C NMR (151 MHz, CDCl₃): δ = 201.1, 168.0, 138.8, 127.4, 125.4, 123.9, 122.1, 121.9, 114.8, 111.1, 51.8, 28.7, 15.8.

HRMS (ESI): *m/z* [M + Na]⁺ calcd for C₁₄H₁₃NNaO₃: 266.0793; found: 266.0798.

3-(1-Formylcyclopropyl)-1H-indole-4-carboxylic Acid Methyl Ester (3u)

Yield: 199 mg (82%); colorless oil.

All analytical data were in good accordance with reported data.¹⁶

3-(1-Formylcyclopropyl)-1H-indole-5-carbaldehyde (3v)

Yield: 155 mg (73%); colorless oil.

FTIR (film): 3348, 2960, 1726, 1665, 1611, 1258, 1094 cm⁻¹.

¹H NMR (600 MHz, CD₃OD): δ = 9.94 (s, 1 H), 9.17 (s, 1 H), 8.09 (d, *J* = 1.0 Hz, 1 H), 7.72 (dd, *J* = 8.5, 1.5 Hz, 1 H), 7.50 (d, *J* = 8.5 Hz, 1 H), 7.33 (s, 1 H), 1.70 (q, *J* = 3.8 Hz, 2 H), 1.48–1.43 (m, 2 H).

¹³C NMR (151 MHz, CD₃OD): δ = 203.0, 194.6, 141.9, 130.4, 129.2, 128.0, 125.7, 122.9, 115.6, 113.3, 30.0, 15.8.

HRMS (ESI): *m/z* [M + Na]⁺ calcd for C₁₃H₁₁NNaO₂: 236.0687; found: 236.0688.

1-(1-Benzyl-1H-pyrrol-2-yl)cyclopropanecarbaldehyde (3w)

Obtained as an 80:20 mixture of regioisomers.

Yield: 153 mg (68%); colorless oil.

FTIR (film): 2998, 2982, 1728, 1660, 1224, 1048, 1002, 980 cm⁻¹.

¹H NMR (600 MHz, CDCl₃): δ (major regioisomer) = 8.97 (s, 1 H), 7.23 (dt, *J* = 12.1, 2.9 Hz, 2 H), 7.19–7.18 (m, 2H), 6.88 (d, *J* = 1.8 Hz, 1 H), 6.67–6.59 (m, 1 H), 6.11–6.07 (m, 1 H), 6.03 (dt, *J* = 12.9, 6.4 Hz, 1 H), 4.98 (s, 2 H), 1.39 (q, *J* = 3.9 Hz, 2 H), 1.17 (q, *J* = 4.0 Hz, 2 H).

¹³C NMR (151 MHz, CDCl₃): δ (major regioisomer) = 200.2, 137.9, 129.4, 128.7, 127.6, 126.9, 122.9, 110.5, 107.3, 50.9, 29.5, 16.8.

HRMS (ESI): *m/z* [M + Na]⁺ calcd for C₁₅H₁₅NNaO: 248.1051; found: 248.1063.

2-(2-Hydroxy-4,6-dimethoxyphenyl)cyclobutanone (4x)

Yield: 190 mg (86%); colorless oil.

FTIR (film): 3412, 3023, 2988, 1787, 1462, 1228, 1144, 1021 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 6.31 (s, 1 H), 6.07–5.96 (m, 1 H), 5.92 (d, *J* = 2.3 Hz, 1 H), 4.74 (dd, *J* = 10.7, 8.3 Hz, 1 H), 3.74 (s, 3 H), 3.71 (s, 3 H), 3.16–3.02 (m, 2 H), 2.47–2.31 (m, 1 H), 2.20 (dq, *J* = 10.5, 8.5 Hz, 1 H).

¹³C NMR (126 MHz, CDCl₃): δ = 213.2, 160.2, 159.1, 155.2, 105.2, 94.1, 91.3, 55.5, 55.2, 55.1, 44.1, 18.0.

HRMS (ESI): *m/z* [M + Na]⁺ calcd for C₁₂H₁₄NaO₄: 245.0790; found: 245.0799.

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Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/s-0040-1706087>.

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