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Aerobic Palladium(II)-Catalyzed Dehydrogenation of Cyclohexene-1-carbonyl Indole Amides: An Indole-Directed Aromatization

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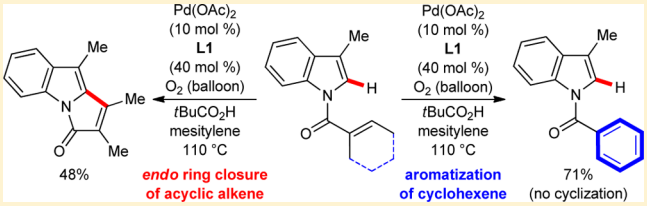
Supporting Information

ABSTRACT: A palladium(II)-catalyzed oxidative dehydrogenation of cyclohexene-1-carbonyl indole amides yielding the corresponding benzoylindoles is reported. The new aromatization is also applied to functionalized indoles such as tryptamine and tryptophan. The tethered indole is likely acting as a directing group for allylic C−H bond activation, and there is evidence for a mechanism proceeding through 1,3-diene formation followed by aromatization.



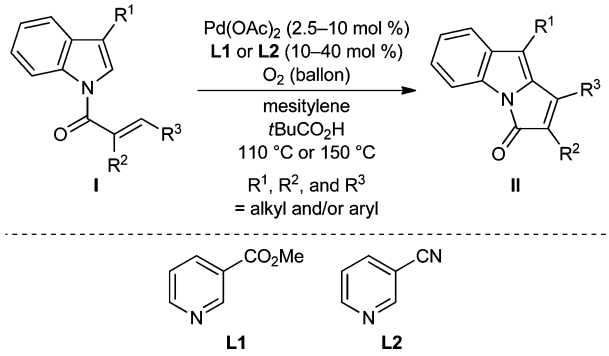
Molecular oxygen and likewise hydrogen are clearly attractive oxidizing and reducing agents, respectively. There are numerous reports on the selective hydrogenation of alkenes,[1] but examples of aerobic oxidation of alkanes to alkenes are scarce.[2] Aerobic oxidation of alcohols is well-investigated,[3] whereas selective aerobic dehydrogenation of alkanes remains elusive. A palladium(II)-catalyzed oxidative aromatization of cyclic alkenes, i.e., cyclohexenes, was reported by Trost and Metzner for the first time.[4] The dehydrogenation of substituted six-membered ring alkenes is a useful transformation as it provides access to arenes with challenging substitution patterns.[5] In this paper, we report the serendipitous finding of a remarkable indole-directed aerobic oxidative dehydrogenation of cyclohexene-1-carbonyl indole amides.

We recently disclosed a diastereoselective C-2 alkenylation of indoles with tri- and tetrasubstituted double bonds[6] by using a typical $Pd(OAc)_2$−pyridine ligand system for aerobic palladium(II) catalysis.[7] The important step in our two-step strategy is an *endo* cyclization of alkenes onto indoles temporarily tethered to the indole nitrogen atom by an amide linkage (**I**→**II**, Scheme 1).

We successfully applied this *endo* cyclization protocol to various di- and trisubstituted acyclic alkenes.[6] However, when precursor **1a** containing a cyclohexenyl group was subjected to the above reaction conditions, the expected ring closure to afford the 3*H*-pyrrolo[1,2-*a*]indole-3-one **4a** did not occur at all. Instead, benzoylindole **2a** derived from aromatization of the appended cyclohexenyl group was formed in 60% yield along with a trace amount of isoindolo[2,1-*a*]indole **3a** (**1a**→**2a** along with **3a**, Scheme 2). We suspect that the formation of **3a** resulted from the known double C−H bond activation of the intermediate benzoylindole (**1a**→**2a**→**3a** but not **1a**→**4a**→**3a**, Scheme 2).[8]

This unexpected result prompted us to further investigate the scope of this dehydrogenation reaction (Table 1). Additional

Scheme 1. Aerobic Palladium(II)-Catalyzed Intramolecular *Endo* Cyclization of Indoles



indole-tethered cyclohexenes **1b**−**g** were prepared by amide coupling of an indole and cyclohexene-1-carboxyl chloride. Optimizing experiments showed that all components of the $Pd(OAc)_2$−pyridine ligand−acid system as well as dioxygen as terminal oxidant are necessary; **L1** emerged from a screening of different pyridine ligands (as in ref 6) as optimum. Full conversion[9] was found for all substrates, but either substituents on the cyclohexene ring[10] (Table 1, entries 2−4 versus entry 1) or phenyl substitution at the indole C-3 position (Table 1, entry 5 versus entry 1) were detrimental to the reaction rate. The former is assumed to be due to hampered β-hydride elimination with ring substitution. Functionalized indoles such as tryptamine and tryptophan also reacted in reasonable yields[9] (Table 1, entries 6 and 7).

Moreover, benzoylindoles (**2a**−**g**) were all prone to subsequent double C−H bond activation, affording isoindolo-

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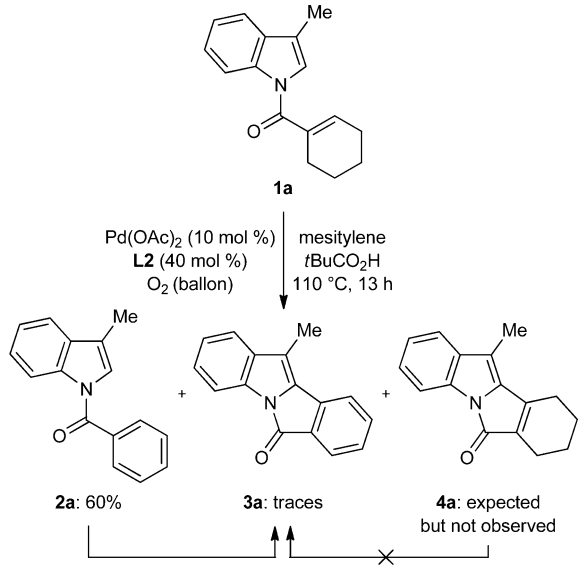
Scheme 2. Aerobic Palladium(II)-Catalyzed Dehydrogenation of a Cyclohexene-1-carbonyl Indole Amide



Scheme 3. Experiment Results for the Double C−H Coupling of Unsubstituted Indoles

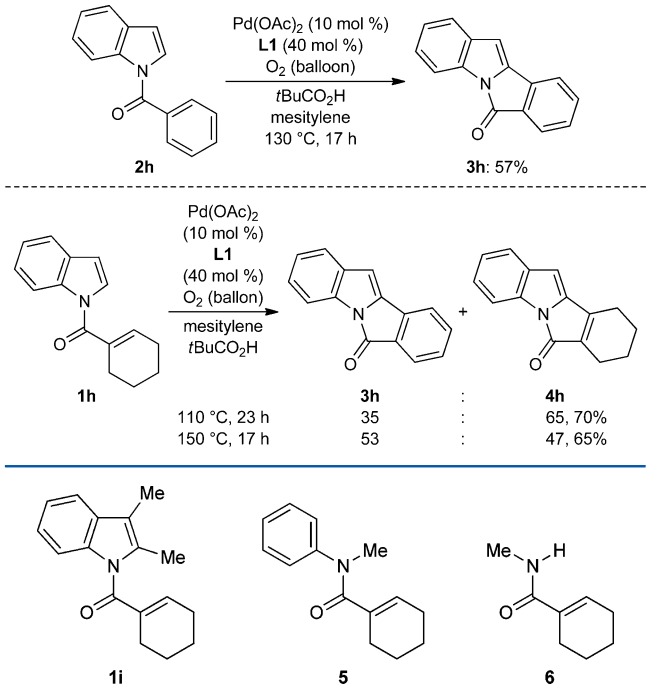
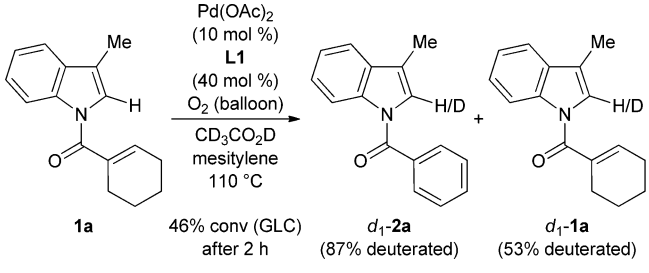


Figure 1. Groups not facilitating oxidative dehydrogenation.

Scheme 4. Control Experiment with Acetic Acid-d_4



[2,1-*a*]indoles **3a−g** in various quantities;[8] **3b** and **3c** derived from C-4-substituted cyclohexenes were even formed in substantial amounts (Table 1, entries 2 and 3). To verify the formation of **3** from **2**, parent benzoylindole **2h** was subjected to our standard dehydrogenation conditions, and **3h** formed in reasonable yield (Scheme 3, upper). The observation of a double C−H coupling in these systems is consistent with the previously reported examples.[8] Another interesting observation is that cyclohexene tethered to the unsubstituted indole **1h** yielded both **3h** and **4h** which was formed from the *endo* ring closure (Scheme 3, lower). We also observed the formation of expected **2h** by GLC analysis in these catalyses and were able to monitor its conversion into **3h**. We were also able to prove that **4h** is not converted into **3h** in an independent experiment. The rate of the oxidative C−C coupling with double C−H bond activation is faster for the parent indole than for 3-substituted indoles.

At present, we do not know the reasons for the difference in reactivity exerted by substitution at the indole C-3 carbon atom. Double C−H bond activation is fast, and *endo* cyclization is preferred over oxidative dehydrogenation in the absence of a substituent in that position.

To probe the role of the indole core or, more precisely, the C−H bond at the C-2 position in the dehydrogenation, we subjected C-2-substituted indole **1i** (Figure 1, left) to the standard protocol. No dehydrogenation but slow decomposition (30% after 16 h) was observed. Likewise, anilide **5** (middle) and enamide **6** (right) were also reluctant to undergo aromatization. While **5** was stable, **6** had decomposed to a certain extent (40% after 24 h). This set of test substrates corroborates the involvement of the indole C−H bond in the oxidation of cyclohexene and supports the directing group ability of indole. In addition, the amide carbonyl group is equally crucial for aromatization as deoxygenated **1a**, that is an indole tethered to a 1-cyclohexene-1-ylmethyl group, slowly decomposed (47% after 15 h).

Further insight was gained from an experiment with acetic acid-d_4 instead of pivalic acid (Scheme 4). After 2 h reaction time, the deuteration grade was high for both aromatized **2a**-d_1 and unreacted **1a**-d_1. While the result is not totally conclusive evidence for an indole-directed allylic C−H bond activation in the cyclohexene, it clearly demonstrates that palladium(II)-catalyzed C−H bond activation occurs reversibly at the indole C-2 position. $Pd(OAc)_2$ is necessary for deuterium incorporation. As to a tentative mechanism,[11] we believe that an indole-directed allylic C−H bond activation produces a π allyl palladium(II) complex that is followed by the formation of a 1,3-diene.[4] The latter is detected by GLC−MS analysis.[12] The 1,3-diene then transforms into the fully aromatized product. A mechanism for the oxidative coupling, via the double C−H bond activation, was previously discussed.[8b]

In summary, we discovered a new palladium(II)-catalyzed aerobic dehydrogenation of cyclohexenes connected to the nitrogen atom of indoles having a C−H bond at the C-2 position. Allylic C−H bond activation in the cyclohexene is assumed to occur intramolecularly subsequent to palladium(II)-mediated C−H bond activation of the indole, thereby directing the palladium(II) atom into the proximity of an allylic C−H bond. Yields are not outstanding but reasonable for such a transformation.

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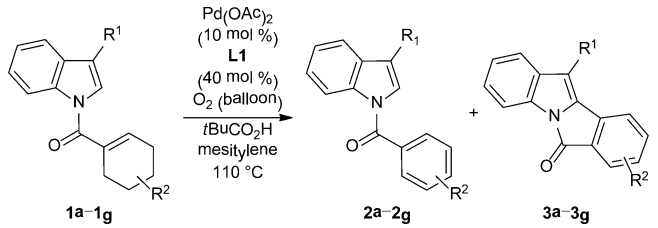
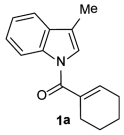
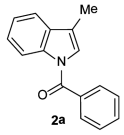
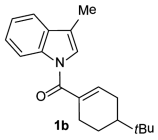
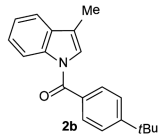
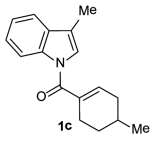
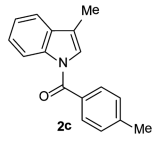
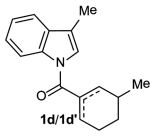
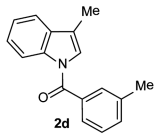
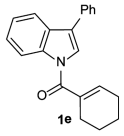
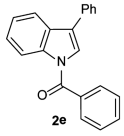
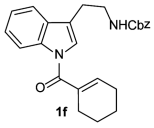
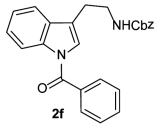
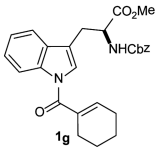
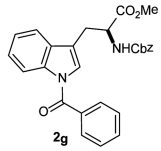
Table 1. Aerobic Palladium(II)-Catalyzed Aromatization of Indole-Tethered Cyclohexene-1-carbonyls[a]



entry	cyclohexene	conv [%][b]	t [h]	arene	yield [%][c,d]
1		100	22		71[e]
2		96	67		40 (10)
3		97	49		36 (22)
4[f]		98	39		41[e]
5		98	40		55[e]
6		99	26		45[e]
7		100	30		51[e]

[a]All reactions were conducted by using a $Pd(OAc)_2$:**L1** 1:4 ratio under O_2 atmosphere (balloon) with a substrate concentration of 0.125 M in mesitylene with added *t*-$BuCO_2H$ (30 equiv). [b]Conversion was monitored by GLC analysis. [c]Isolated yields. [d]Yield in the parentheses refers to the oxidative coupling product **3**. [e]Traces of oxidative coupling product **3** were observed. [f]Ratio of alkene regioisomers **1d** and **1d′** used (5-Me:3-Me = 69:31).

EXPERIMENTAL SECTION

General experimental details were reported before.[6] Literature-known compounds *N*-benzoylindole (**2h**),[8c] *N*-methyl-*N*-phenylcyclohex-1-enecarboxamide (**5**),[13] *N*-methylcyclolohex-1-enecarboxamide (**6**),[14] 4-*tert*-butylcyclohex-1-enecarboxylic acid (**7**),[15] 5-methylcyclohex-1-enecarboxylic acid/3-methylcyclohex-1-enecarboxylic acid (**9a**/**9a′**),[15] and 3-phenylindole (**10**)[16] were prepared according to reported procedures.

General Procedure for the Indole-Directed Oxidative Dehydrogenation. A flame-dried Schlenk tube is charged with $Pd(OAc)_2$ (10 mol %), tetracosane (40 mol %, internal standard), pivalic acid (30 equiv), **L1** (40 mol %), and compound **1** (1.0 equiv). The tube is then evacuated and backfilled with O_2 (three cycles), and mesitylene (0.125 M for **1**) is added. If compound **1** is a liquid, it is dissolved in mesitylene and the resulting solution is added. The reaction mixture is then heated to the indicated temperature and monitored by GLC analysis. The reaction mixture is cooled to room temperature, diluted with *tert*-butyl methyl ether, and washed with H_2O (1×) and saturated aqueous $NaHCO_3$ (1×). The aqueous layers are extracted with *tert*-butyl methyl ether (3×), and the combined organic phases are dried over Na_2SO_4. After evaporation of the solvents under reduced pressure, purification of the residue by flash column chromatography on silica gel (cyclohexane/*tert*-butyl methyl ether solvent mixtures as eluent) affords the title compound **2**.

***N*-Benzoyl-3-methylindole (2a, Table 1, Entry 1).** Prepared from **1a** (29.9 mg, 0.125 mmol, 1.00 equiv) according to the general

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procedure. Purification by flash column chromatography on silica gel (cyclohexane/*tert*-butyl methyl ether = 19:1) afforded analytically pure **2a** (20.8 mg, 71%) as a light yellow oil: GLC (HP-5MS) t_R = 22.3 min; R_f = 0.5 (cyclohexane/*tert*-butyl methyl ether = 5.5:1); IR and NMR spectra were in agreement with reported data;[17] HRMS (ESI) exact mass for $[M + Na]^+$ ($C_{16}H_{13}NONa$) calcd m/z 258.0889, found 258.0892.

***N*-(4-*tert*-Butylbenzoyl)-3-methylindole and 9-*tert*-Butyl-11-methyl-6*H*-isoindolo[2,1-*a*]indol-6-one (2b and 3b, Table 1, Entry 2).** Prepared from **1b** (36.9 mg, 0.125 mmol, 1.00 equiv) according to the general procedure. Purification by flash column chromatography on silica gel (cyclohexane/*tert*-butyl methyl ether = 19:1) afforded analytically pure **2b** (14.4 mg, 40%) as a light yellow solid (mp = 62−64 °C) along with **3b** (3.8 mg, 10%) as a yellow solid (mp = 173−175 °C). **2b**: GLC (HP-5MS) t_R = 25.9 min; R_f = 0.6 (cyclohexane/*tert*-butyl methyl ether = 9:1); IR (ATR) ν = 1676 (s, C═O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 1.38 (s, 9H), 2.26 (d, J = 1.3 Hz, 3H), 7.12 (q, J = 1.3 Hz, 1H), 7.33 (ddd, J = 8.8 Hz, J = 7.6 Hz, J = 1.2 Hz, 1H), 7.39 (ddd, J = 8.4 Hz, J = 7.3 Hz, J = 1.3 Hz, 1H), 7.52−7.55 (m, 3H), 7.66−7.69 (m, 2H), 8.41 (ddd, J = 8.2 Hz, J = 1.8 Hz, J = 0.7 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 9.8, 31.3, 35.2, 116.6, 117.6, 118.9, 123.7, 124.7, 125.0, 125.6, 129.2, 131.9, 132.1, 136.4, 155.4, 168.6 ppm; HRMS (ESI) exact mass for $[M + H]^+$ ($C_{20}H_{22}NO$) calcd m/z 292.1696, found 292.1690. **3b**: GLC (HP-5MS): t_R = 28.3 min; R_f = 0.6 (cyclohexane/*tert*-butyl methyl ether = 9:1); IR (ATR) ν = 1719 (s, C═O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 1.39 (s, 9H), 2.46 (s, 3H), 7.16 (ddd, J = 8.6 Hz, J = 7.6 Hz, J = 1.1 Hz, 1H), 7.27−7.29 (m, 1H), 7.35 (dd, J = 8.1 Hz, J = 1.7 Hz, 1H), 7.39 (ddd, J = 7.8 Hz, J = 1.9 Hz, J = 0.9 Hz, 1H), 7.57 (dd, J = 1.7 Hz, J = 0.6 Hz, 1H), 7.68 (dd, J = 8.1 Hz, J = 0.7 Hz, 1H), 7.86 (ddd, J = 8.0 Hz, J = 1.7 Hz, J = 0.8 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 9.8, 31.3, 35.6, 113.4, 114.9, 118.3, 120.2, 123.5, 125.2, 125.6, 126.5, 131.6, 133.7, 135.1, 135.5, 136.0, 157.8, 162.8 ppm; HRMS (ESI) exact mass for $[M + H]^+$ ($C_{20}H_{20}NO$) calcd m/z 290.1539, found 290.1531.

***N*-(4-Methylbenzoyl)-3-methylindole and 9,11-Dimethyl-6*H*-isoindolo[2,1-*a*]indol-6-one (2c and 3c, Table 1, Entry 3).** Prepared from **1c** (31.6 mg, 0.125 mmol, 1.00 equiv) according to the general procedure. Purification by flash column chromatography on silica gel (cyclohexane/*tert*-butyl methyl ether = 19:1) afforded analytically pure **2c** (11.2 mg, 36%) as a light yellow solid (mp = 107−109 °C) along with **3c** (6.8 mg, 22%) as a yellow solid (mp = 135−137 °C). **2c**: GLC (HP-5MS) t_R = 23.6 min; R_f = 0.6 (cyclohexane/*tert*-butyl methyl ether = 9:1). IR (ATR) ν = 1664 (s, C═O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 2.25 (d, J = 1.3 Hz, 3H), 2.46 (s, 3H), 7.09 (q, J = 1.3 Hz, 1H), 7.31−7.34 (m, 3H), 7.38 (ddd, J = 8.4 Hz, J = 7.2 Hz, J = 1.3 Hz, 1H), 7.52−7.55 (m, 1H), 7.60−7.65 (m, 2H), 8.37 (ddd, J = 8.2 Hz, J = 1.8 Hz, J = 0.7 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 9.8, 21.7, 116.6, 117.7, 118.9, 123.7, 124.6, 125.0, 129.3, 129.4, 131.9, 132.2, 136.5, 142.4, 168.6 ppm; HRMS (ESI) exact mass for $[M + Na]^+$ ($C_{17}H_{15}NONa$) calcd m/z 272.1046, found 272.1045. **3c**: GLC (HP-5MS): t_R = 25.8 min; R_f = 0.6 (cyclohexane/*tert*-butyl methyl ether = 9:1); IR (ATR) ν = 1704 (s, C═O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 2.43 (s, 3H), 2.44 (s, 3H), 7.10 (d, J = 7.8 Hz, 1H), 7.15 (t, J = 7.5 Hz, 1H), 7.27−7.29 (m, 1H), 7.36−7.38 (m, 2H), 7.63 (d, J = 7.7 Hz, 1H), 7.85 (d, J = 8.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 9.6, 22.2, 113.3, 115.1, 120.2, 122.0, 123.5, 125.3, 126.5, 129.0, 131.6, 133.7, 134.8, 135.5, 135.9, 144.5, 162.6 ppm; HRMS (ESI) exact mass for $[M + H]^+$ ($C_{17}H_{14}NO$) calcd m/z 248.1070, found 248.1070.

***N*-(3-Methylbenzoyl)-3-methylindole (2d, Table 1, Entry 4).** Prepared from **1d**/**1d′** (31.6 mg, 0.125 mmol, 1.00 equiv) according to the general procedure. Purification by flash column chromatography on silica gel (cyclohexane/*tert*-butyl methyl ether = 19:1) afforded analytically pure **2d** (12.7 mg, 41%) as a light yellow oil: GLC (HP-5MS) t_R = 23.3 min; R_f = 0.6 (cyclohexane/*tert*-butyl methyl ether = 9:1); IR (ATR) ν = 1672 (s, C═O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 2.25 (d, J = 1.3 Hz, 3H), 2.45 (s, 3H), 7.06 (q, J = 1.3 Hz, 1H), 7.33 (ddd, J = 8.7 Hz, J = 7.6 Hz, J = 1.3 Hz, 1H), 7.36−7.40 (m, 3H), 7.48−7.50 (m, 1H), 7.52−7.54 (m, 2H), 8.37 (ddd, J = 8.2 Hz, J = 1.8 Hz, J = 0.7 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 9.8, 21.5, 116.6, 117.8, 118.9, 123.7, 124.6, 125.0, 126.2, 128.4, 129.6, 131.9, 132.4, 135.1, 136.4, 138.6, 168.7 ppm; HRMS (ESI) exact mass for $[M + H]^+$ ($C_{17}H_{16}NO$) calcd m/z 250.1226, found 250.1224.

***N*-Benzoyl-3-phenylindole (2e, Table 1, Entry 5).** Prepared from **1e** (37.6 mg, 0.125 mmol, 1.00 equiv) according to the general procedure. Purification by flash column chromatography on silica gel (cyclohexane/*tert*-butyl methyl ether = 19:1) afforded analytically pure **2e** (20.4 mg, 55%) as a light yellow solid: mp =143−145 °C (lit.[18] 151−153 °C); GLC (HP-5MS) t_R = 29.5 min; R_f = 0.57 (cyclohexane/*tert*-butyl methyl ether =5.5:1); IR (ATR) ν = 1677 (s, C═O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.36−7.47 (m, 6H), 7.53−7.57 (m, 2H), 7.60−7.62 (m, 3H), 7.78−7.80 (m, 2H), 7.86 (ddd, J = 7.8 Hz, J = 1.2 Hz, J = 0.7 Hz, 1H), 8.48 (ddd, J = 8.2 Hz, J = 1.4 Hz, J = 0.7 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 116.8, 120.0, 123.6, 124.4, 124.5, 125.5, 127.6, 128.1, 128.8, 129.0, 129.3, 129.5, 132.1, 133.5, 134.7, 136.9, 168.8 ppm; HRMS (ESI) exact mass for $[M + H]^+$ ($C_{21}H_{16}NO$) calcd m/z 298.1226, found 298.1219.

Benzyl [2-(1-Benzoyl-1*H*-indol-3-yl)ethyl]carbamate (2f, Table 1, Entry 6). Prepared from **1f** (50.3 mg, 0.125 mmol, 1.00 equiv) according to the general procedure. Purification by flash column chromatography on silica gel (cyclohexane/*tert*-butyl methyl ether = 2:1) afforded analytically pure **2f** (22.4 mg, 45%) as a colorless oil: GLC (HP-5MS) t_R = 26.5 min; R_f = 0.52 (cyclohexane/*tert*-butyl methyl ether = 1:2); IR (ATR) ν = 3334 (s, NH), 1677 (s, C═O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 2.90 (t, J = 6.7 Hz, 2H), 3.50 (td, J = 6.7 Hz, J = 5.7 Hz, 2H), 4.99 (t, J = 5.7 Hz, 1H), 5.09 (s, 2H), 7.13 (s, 1H), 7.30−7.36 (m, 6H), 7.39 (ddd, J = 8.3 Hz, J = 7.3 Hz, J = 1.1 Hz, 1H), 7.50 (t, J = 7.6 Hz, 2H), 7.60 (m, 2H), 7.70 (m, 2H), 8.40 (ddd, J = 8.2 Hz, J = 1.7 Hz, J = 0.7 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 25.7, 40.6, 66.7, 116.7, 118.9, 119.0, 123.9, 124.9, 125.3, 128.1, 128.2, 128.6, 128.7, 129.1, 130.7, 131.9, 134.7, 136.5, 136.6, 156.4, 168.5 ppm; HRMS (ESI) exact mass for $[M + Na]^+$ ($C_{25}H_{22}N_2O_3Na$) calcd m/z 421.1523, found 421.1512.

(*S*)-Methyl 2-[[(Benzyloxy)carbonyl]amino]-3-(1-benzoyl-1*H*-indol-3-yl)propanoate (2g, Table 1, Entry 7). Prepared from **1g** (57.6 mg, 0.125 mmol, 1.00 equiv) according to the general procedure. Purification by flash column chromatography on silica gel (cyclohexane/*tert*-butyl methyl ether = 2:1) afforded analytically pure **2g** (29.1 mg, 51%) as a white solid: mp = 128−130 °C; GLC (HP-5MS) t_R = 29.4 min; R_f = 0.33 (cyclohexane/*tert*-butyl methyl ether = 2:1); IR (ATR) ν = 3320 (s, NH), 1734 (m, C═O), 1679 (s, C═O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 3.18 (dd, J = 14.7 Hz, J = 5.4 Hz, 1H), 3.27 (dd, J = 14.7 Hz, J = 5.5 Hz, 1H), 3.60 (s, 3H), 4.72 (ddd, J = 7.8 Hz, J = 5.5 Hz, J = 5.4 Hz, 1H), 5.07 (d, J = 12.4 Hz, 1H), 5.09 (d, J = 12.4 Hz, 1H), 5.38 (d, J = 7.8 Hz, 1H), 7.09 (s, 1H), 7.27−7.35 (m, 6H), 7.39 (ddd, J = 8.3 Hz, J = 7.2 Hz, J = 0.9 Hz, 1H), 7.49 (m, 3H), 7.59 (tt, J = 7.3 Hz, J = 1.3 Hz, 1H), 7.69 (m, 2H), 8.37 (ddd, J = 8.3 Hz, J = 1.7 Hz, J = 0.7 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 27.9, 52.5, 54.1, 67.1, 116.3, 116.6, 118.8, 124.0, 125.4, 125.8, 128.1, 128.3, 128.6, 128.7, 129.2, 130.8, 132.0, 134.6, 136.2, 136.3, 155.7, 168.4, 172.0 ppm; HRMS (ESI) exact mass for $[M + Na]^+$ ($C_{27}H_{24}N_2O_5Na$) calcd m/z 479.1577, found 479.1574; $[\alpha]^{20}_D$ +47.8 (c 1.0, $CHCl_3$).

6*H*-Isoindolo[2,1-*a*]indol-6-one (3h, Scheme 3). Prepared from **2h** (44.2 mg, 0.200 mmol, 1.00 equiv) according to the general procedure. Purification by flash column chromatography on silica gel (cyclohexane/*tert*-butyl methyl ether = 32:1) afforded analytically pure **3h** (25.0 mg, 57%) as a yellow solid: mp =157−159 °C (lit.[8a] 154−155 °C); GLC (HP-5MS) t_R = 22.9 min; R_f = 0.47 (cyclohexane/*tert*-butyl methyl ether = 5.5:1); IR and NMR spectra were in agreement with reported data;[8b] HRMS (ESI) exact mass for $[M + H]^+$ ($C_{15}H_{10}NO$) calcd m/z 220.0757, found 220.0755.

7,8,9,10-Tetrahydro-6*H*-isoindolo[2,1-*a*]indol-6-one (4h, Scheme 3). Prepared from **1h** (28.2 mg, 0.125 mmol, 1.00 equiv) according to the general procedure. Purification by flash column chromatography on silica gel (cyclohexane/*tert*-butyl methyl ether = 19:1) afforded a mixture of **3h** and **4h** (19.2 mg, 70%): GLC (HP-5MS) t_R = 23.2 min; R_f = 0.47 (cyclohexane/*tert*-butyl methyl ether = 5.5:1); IR (ATR) ν = 1697 (s, C═O) cm^{-1}; ^1H NMR (400 MHz,

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$CDCl_3$) δ = 1.73−1.79 (m, 4H), 2.28−3.32 (m, 2H), 2.40−2.44 (m, 2H), 6.24 (d, J = 0.5 Hz, 1H), 7.03 (ddd, J = 8.6 Hz, J = 7.6 Hz, J = 1.0 Hz, 1H), 7.21 (ddd, J = 8.6 Hz, J = 7.5 Hz, J = 1.1 Hz, 1H), 7.26−7.29 (m, 1H), 7.64 (ddd, J = 7.9 Hz, J = 1.1 Hz, J = 0.8 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 20.6, 21.7, 21.8, 22.4, 104.1, 112.1, 122.5, 122.7, 126.7, 134.0, 134.6, 134.7, 142.2, 144.2, 165.6 ppm; HRMS (ESI) exact mass for $[M + H]^+$ ($C_{15}H_{14}NO$) calcd m/z 224.1070, found 224.1066.

***N*-Cyclohexene-1-carbonyl-3-methylindole (1a, Table 1, Entry 1).** Prepared from 3-methylindole (0.520 g, 3.96 mmol, 1.00 equiv) and cyclohex-1-enecarboxylic acid (1.0 g, 7.9 mmol, 2.0 equiv) according to the reported procedure.[6] Purification by flash column chromatography on silica gel (cyclohexane/*tert*-butyl methyl ether = 49:1) afforded analytically pure **1a** (0.84 g, 88%) as a light yellow solid: mp =113−115 °C; GLC (HP-5MS) t_R = 22.6 min; R_f = 0.5 (cyclohexane/*tert*-butyl methyl ether =5.5:1); IR (ATR) ν = 1664 (s, C═O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.70−1.83 (m, 4H), 2.25−2.31 (m, 2H), 2.28 (d, J = 1.1 Hz, 3H), 2.43−2.47 (m, 2H), 6.25−6.26 (m, 1H), 7.23 (q, J = 1.1 Hz, 1H), 7.29 (ddd, J = 8.7 Hz, J = 7.7 Hz, J = 1.3 Hz, 1H), 7.35 (ddd, J = 8.3 Hz, J = 7.3 Hz, J = 1.3 Hz, 1H), 7.51 (ddd, J = 7.6 Hz, J = 1.5 Hz, J = 0.7 Hz, 1H), 8.36 (ddd, J = 8.2 Hz, J = 1.3 Hz, J = 0.7 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 9.8, 21.6, 22.1, 25.3, 25.6, 116.5, 117.0, 118.8, 123.4, 124.3, 124.8, 132.0, 134.4, 135.9, 136.0, 169.9 ppm; HRMS (ESI) exact mass for $[M + Na]^+$ ($C_{16}H_{17}NONa$) calcd m/z 262.1202, found 262.1210.

***N*-(4-*tert*-Butylcyclohexene-1-carbonyl)-3-methylindole (1b, Table 1, Entry 2).** Prepared from 3-methylindole (0.240 g, 1.83 mmol, 1.00 equiv) and 4-*tert*-butylcyclohex-1-enecarboxylic acid[15] (**7**, 0.500 g, 2.74 mmol, 1.50 equiv) according to the reported procedure.[6] Purification by flash column chromatography on silica gel (cyclohexane/*tert*-butyl methyl ether = 19:1) afforded analytically pure **1b** (0.324 g, 60%) as a white solid (mp = 103−105 °C): GLC (HP-5MS) t_R = 26.2 min; R_f = 0.6 (cyclohexane/*tert*-butyl methyl ether = 5:1); IR (ATR) ν = 1667 (s, C═O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.94 (s, 9H), 1.26−1.44 (m, 1H), 1.98−2.08 (m, 2H), 2.28 (d, J = 1.3 Hz, 3H), 2.31−2.46 (m, 2H), 2.59−2.65 (m, 1H), 6.29−6.32 (m, 1H), 7.23 (q, J = 1.3 Hz, 1H), 7.30 (ddd, J = 8.7 Hz, J = 7.7 Hz, J = 1.3 Hz, 1H), 7.35 (ddd, J = 8.3 Hz, J = 7.3 Hz, J = 1.3 Hz, 1H), 7.50−7.57 (m, 1H), 8.36 (ddd, J = 8.2 Hz, J = 1.3 Hz, J = 0.7 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 9.8, 23.7, 27.0, 27.2, 27.3, 32.4, 43.5, 116.5, 117.0, 118.8, 123.4, 124.3, 124.8, 132.0, 134.2, 136.1, 136.5, 169.8 ppm; HRMS (ESI) exact mass for $[M + H]^+$ ($C_{20}H_{26}NO$) calcd m/z 296.2009, found 296.2015.

***N*-(4-Methylcyclohexene-1-carbonyl)-3-methylindole (1c, Table 1, Entry 3).** Prepared from 3-methylindole (0.280 g, 2.13 mmol, 1.00 equiv) and 4-methylcyclohex-1-enecarboxylic acid[15] (**8**, 0.600 g, 4.28 mmol, 2.00 equiv) according to the reported procedure.[6] Purification by flash column chromatography on silica gel (cyclohexane/*tert*-butyl methyl ether = 19:1) afforded analytically pure **1c** (0.404 g, 75%) as a white solid: mp = 58−60 °C; GLC (HP-5MS) t_R = 23.2 min; R_f = 0.6 (cyclohexane/*tert*-butyl methyl ether = 9:1); IR (ATR) ν = 1665 (s, C═O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.05 (d, J = 6.3 Hz, 3H), 1.37−1.42 (m, 1H), 1.75−1.92 (m, 3H), 2.27 (d, J = 1.2 Hz, 3H), 2.34−2.52 (m, 3H), 6.25−6.26 (m, 1H), 7.21 (d, J = 1.2 Hz, 1H), 7.29 (ddd, J = 8.7 Hz, J = 7.6 Hz, J = 1.3 Hz, 1H), 7.35 (ddd, J = 8.6 Hz, J = 7.4 Hz, J = 1.4 Hz, 1H), 7.50 (ddd, J = 7.6 Hz, J = 1.4 Hz, J = 0.6 Hz, 1H), 8.35 (ddd, J = 8.3 Hz, J = 1.8 Hz, J = 0.7 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 9.8, 21.7, 25.7, 27.8, 30.4, 33.8, 116.5, 117.1, 118.8, 123.4, 124.2, 124.8, 132.0, 134.1, 135.5, 136.1, 169.9 ppm; HRMS (ESI) exact mass for $[M + H]^+$ ($C_{17}H_{20}NO$) calcd m/z 254.1539, found 254.1538.

***N*-(5-Methylcyclohexene-1-carbonyl)-3-methylindole and *N*-(3-Methylcyclohexene-1-carbonyl)-3-methylindole (1d and 1d′, Table 1, Entry 4).** Prepared from 3-methylindole (0.280 g, 2.13 mmol, 1.00 equiv) and a 69:31 mixture of 5-methylcyclohex-1-enecarboxylic acid and 3-methylcyclohex-1-enecarboxylic acid[15] (**9a** and **9a′**, 0.600 g, 4.28 mmol, 2.00 equiv) according to the reported procedure.[6] Purification by flash column chromatography on silica gel (cyclohexane/*tert*-butyl methyl ether = 19:1) afforded analytically pure **1d** and **1d′** as a 69:31 regioisomeric mixture (0.377 g, 70%) as a colorless oil: GLC (HP-5MS) t_R = 22.9 min, 23.1 min; R_f = 0.6 (cyclohexane/*tert*-butyl methyl ether = 9:1); IR (ATR) ν = 1674 (s, C═O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.06 (d, J = 6.5 Hz, 3H), 1.10 (d, J = 7.0 Hz, 1.4H), 1.30−1.35 (m, 2H), 1.78−1.83 (m, 4H), 1.98−2.01 (m, 1.5H), 2.21−2.34 (m, 8H), 2.39−2.42 (m, 2H), 2.53−2.58 (m, 1H), 6.11−6.12 (m, 0.4H), 6.25−6.28 (m, 1H), 7.21−7.29 (m, 1.5H), 7.29 (ddd, J = 8.5 Hz, J = 7.6 Hz, J = 1.2 Hz, 1.8H), 7.35 (ddd, J = 8.5 Hz, J = 7.4 Hz, J = 1.4 Hz, 1.8H), 7.49−7.51 (m, 1.6H), 8.35 (m, 1.4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 9.8, 9.9, 21.0, 21.1, 21.7, 25.6, 25.7, 28.3, 29.9, 30.4, 30.6, 33.8, 116.5, 117.1, 117.2, 118.8, 123.4, 124.2, 124.8, 132.0, 133.6, 134.0, 135.6, 136.1, 141.4, 169.9, 170.0 ppm; HRMS (ESI) exact mass for $[M + H]^+$ ($C_{17}H_{20}NO$) calcd m/z 254.1539, found 254.1532.

***N*-Cyclohexene-1-carbonyl-3-phenylindole (1e, Table 1, Entry 5).** Prepared from 3-phenylindole[16] (**10**, 0.400 g, 2.07 mmol, 1.00 equiv) and cyclohex-1-enecarboxylic acid (3.31 g, 2.48 mmol, 1.20 equiv) according to the reported procedure.[6] Purification by flash column chromatography on silica gel (cyclohexane/*tert*-butyl methyl ether = 19:1) afforded analytically pure **1e** (0.31 g, 50%) as a light yellow oil: GLC (HP-5MS) t_R = 29.9 min; R_f = 0.57 (cyclohexane/*tert*-butyl methyl ether = 5.5:1); IR (ATR) ν = 1680 (s, C═O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.70−1.76 (m, 2H), 1.78−1.83 (m, 2H), 2.25−2.30 (m, 2H), 2.47−2.51 (m, 2H), 6.38−6.41 (m, 1H), 7.31−7.42 (m, 3H), 7.45−7.49 (m, 2H), 7.57 (s, 1H), 7.62−7.65 (m, 2H), 7.82 (ddd, J = 7.8 Hz, J = 0.8 Hz, J = 0.6 Hz, 1H), 7.83 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 21.6, 22.0, 25.5, 25.6, 116.6, 119.8, 122.7, 123.9, 124.2, 125.1, 127.4, 128.0, 128.9, 129.5, 133.7, 134.3, 136.5, 137.2, 170.0 ppm; HRMS (ESI) exact mass for $[M + H]^+$ ($C_{21}H_{20}NO$) calcd m/z 302.1539, found 302.1535.

Benzyl [2-(cyclohexene-1-carbonyl-1*H*-indol-3-yl)ethyl]-carbamate (1f, Table 1, Entry 6). Prepared from indol-3-ylethylcarbamic acid benzyl ester (0.778 g, 2.64 mmol, 1.00 equiv) and cyclohex-1-enecarboxylic acid (0.500 g, 3.96 mmol, 1.50 equiv) according to the reported procedure.[6] Purification by flash column chromatography on silica gel (cyclohexane *tert*-butyl methyl ether = 2:1) afforded analytically pure **1f** (0.504 g, 50%) as a colorless oil: GLC (HP-5MS) t_R = 26.8 min; R_f = 0.52 (cyclohexane/*tert*-butyl methyl ether = 1:2); IR (ATR) ν = 3347 (s, NH), 1672 (s, C═O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.70−1.80 (m, 4H), 2.25−2.28 (m, 2H), 2.42−2.46 (m, 2H), 2.93 (t, J = 6.9 Hz, 2H), 3.54 (m, 2H), 4.85 (br s, 1H), 5.11 (s, 2H), 6.27−6.30 (m, 1H), 7.27−7.37 (m, 8H), 7.54 (d, J = 7.7 Hz, 1H), 8.34 (ddd, J = 8.2 Hz, J = 1.2 Hz, J = 0.7 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 21.5, 22.0, 25.4, 25.5, 25.7, 40.7, 66.7, 116.6, 118.0, 118.7, 123.5, 124.7, 124.9, 128.1, 128.2, 128.6, 130.8, 134.2, 136.2, 136.6, 136.7, 156.5, 169.8 ppm; HRMS (ESI) exact mass for $[M + Na]^+$ ($C_{25}H_{26}N_2O_3Na$) calcd m/z 425.1836, found 425.1832.

(*S*)-Methyl 2-[[(Benzyloxy)carbonyl]amino]-3-(cyclohexene-1-carbonyl-1*H*-indol-3-yl)propanoate (1g, Table 1, Entry 7). Prepared from *N*-carbobenzyloxy-L-tryptophan methyl ester (0.838 g, 2.38 mmol, 1.00 equiv) and cyclohex-1-enecarboxylic acid (0.600 g, 4.76 mmol, 2.00 equiv) according to the reported procedure.[6] Purification by flash column chromatography on silica gel (cyclohexane/*tert*-butyl methyl ether = 2:1) afforded analytically pure **1g** (0.75 g, 68%) as a white solid: mp = 126−128 °C; GLC (HP-5MS) t_R = 29.7 min; R_f = 0.33 (cyclohexane/*tert*-butyl methyl ether = 2:1); IR (ATR) ν = 3340 (s, NH), 1735 (s, C═O), 1692 (s, C═O), 1668 (s, C═O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.67−1.80 (m, 4H), 2.20−2.26 (m, 2H), 2.41−2.4 (m, 2H), 3.18 (dd, J = 14.8 Hz, J = 5.6 Hz, 1H), 3.26 (dd, J = 14.8 Hz, J = 5.5 Hz, 1H), 3.68 (s, 3H), 4.75 (ddd, J = 8.1 Hz, J = 5.6 Hz, J = 5.5 Hz, 1H), 5.08 (d, J = 12.5 Hz, 1H), 5.11 (d, J = 12.5 Hz, 1H), 5.34 (d, J = 8.1 Hz, 1H), 6.25−6.26 (m, 1H), 7.24−7.26 (m, 2H), 7.31−7.36 (m, 6H), 7.47 (d, J = 7.7 Hz, 1H), 8.32 (ddd, J = 8.2 Hz, J = 1.2 Hz, J = 0.7 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 21.5, 22.0, 25.4, 25.5, 28.0, 52.6, 54.0, 67.1, 115.3, 116.5, 118.7, 123.6, 125.1, 125.6, 128.1, 128.3, 128.6, 130.9, 134.1, 135.9, 136.2, 137.1, 155.7, 169.8, 172.1 ppm; HRMS (ESI) exact mass for $[M + Na]^+$ ($C_{27}H_{28}N_2O_5Na$) calcd m/z 483.1890, found 483.1886; $[\alpha]^{20}_D$ +40.4 (c 1.0, $CHCl_3$).

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***N*-Cyclohexene-1-carbonylindole (1h, Scheme 3).** Prepared from indole (0.300 g, 2.55 mmol, 1.00 equiv) and cyclohex-1-enecarboxylic acid (0.386 g, 3.06 mmol, 1.20 equiv) according to the reported procedure.[6] Purification by flash column chromatography on silica gel (cyclohexane/*tert*-butyl methyl ether = 19:1) afforded analytically pure **1h** (0.286 g, 50%) as a colorless liquid: GLC (HP-5MS) t_R = 21.6 min; R_f = 0.48 (cyclohexane/*tert*-butyl methyl ether = 5.5:1); IR (ATR) ν = 1676 (s, C═O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 1.72−1.81 (m, 4H), 2.26−2.29 (m, 2H), 2.45−2.49 (m, 2H), 6.31−6.34 (m, 1H), 6.58 (dd, J = 7.7 Hz, 0.7 Hz, 1H), 7.27 (ddd, J = 8.4 Hz, J = 7.6 Hz, J = 1.1 Hz, 1H), 7.35 (ddd, J = 8.3 Hz, J = 7.3 Hz, J = 1.3 Hz, 1H), 7.46 (d, J = 3.7 Hz, 1H), 7.58 (ddd, J = 7.7 Hz, J = 1.3 Hz, J = 0.8 Hz, 1H), 8.37 (ddd, J = 8.2 Hz, J = 1.7 Hz, J = 0.8 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 21.6, 22.1, 25.4, 25.6, 107.8, 116.4, 120.8, 123.6, 124.7, 127.4, 130.9, 134.2, 135.8, 136.9, 170.2 ppm; HRMS (ESI) exact mass for $[M + H]^+$ ($C_{15}H_{16}NO$) calcd m/z 226.1226, found 226.1225.

***N*-Cyclohexene-1-carbonyl-2,3-dimethylindole (1i, Figure 1).** Prepared from 2,3-dimethylindole (0.296 g, 2.04 mmol, 1.00 equiv) and cyclohex-1-enecarboxylic acid (0.515 g, 4.08 mmol, 2.00 equiv) according to the reported procedure.[6] Purification by flash column chromatography on silica gel (cyclohexane/*tert*-butyl methyl ether = 49:1) afforded analytically pure **1i** (0.31 g, 60%) as a light yellow solid: mp = 49−51 °C; GLC (HP-5MS) t_R = 23.0 min; R_f = 0.5 (cyclohexane/*tert*-butyl methyl ether = 5.5:1); IR (ATR) ν = 1662 (s, C═O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 1.69−1.76 (m, 2H), 1.77−1.83 (m, 2H), 2.20 (d, J = 0.7 Hz, 3H), 2.20−2.25 (m, 2H), 2.40 (d, J = 0.7 Hz, 3H), 2.45−2.50 (m, 2H), 6.38−6.41 (m, 1H), 7.16 (ddd, J = 9.3 Hz, J = 7.2 Hz, J = 2.0 Hz, 1H), 7.17 (ddd, J = 9.1 Hz, J = 7.2 Hz, J = 1.9 Hz, 1H), 7.40−7.44 (m, 1H), 7.56−7.61 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 8.7, 13.1, 21.6, 22.2, 24.8, 25.9, 113.7, 114.1, 118.1, 121.9, 122.8, 130.7, 132.8, 135.8, 136.5, 140.3, 171.2 ppm; HRMS (ESI) exact mass for $[M + H]^+$ ($C_{17}H_{20}NO$) calcd m/z 254.1539, found 254.1533.

4-Methylcyclohex-1-enecarboxylic Acid (8). Prepared from 4-methylcyclohexanone (5.0 g, 44 mmol, 1.0 equiv) and bromoform (44.4 g, 176 mmol, 4.00 equiv) according to the reported procedure,[15] affording analytically pure **8** (4.93 g, 80%) as a white solid: mp = 115−117 °C; GLC (HP-5MS) t_R = 10.9 min; IR (ATR) ν = 1670 (s, C═O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 0.98 (d, J = 6.5 Hz, 3H), 1.20−1.25 (m, 1H), 1.75−1.85 (m, 3H), 2.14−2.24 (m, 1H), 2.27−2.42 (m, 2H), 7.08−7.11 (m, 1H), 11.8 (br s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 21.5, 24.5, 27.6, 30.4, 33.9, 132.0, 135.0, 170.8 ppm; HRMS (ESI) exact mass for $[M + H]^+$ ($C_8H_{13}O_2$) calcd m/z 141.0910, found 141.0907.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

GLC−MS traces on 1,3-diene formation as well as copies of ^1H and ^{13}C NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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