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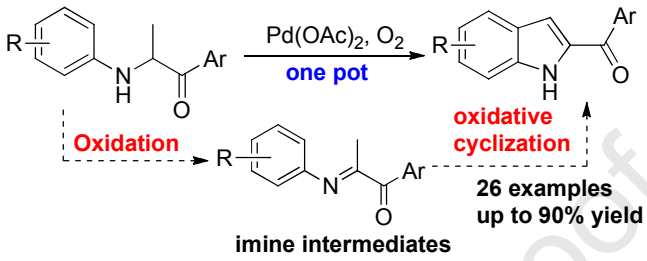

Palladium-Catalyzed Tandem Oxidative Annulation of α-Amino Ketones Leading to 2-aroylindoles

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Abstract

A simple synthesis of 2-aroylindoles via palladium-catalyzed tandem oxidative annulation directly from α-amino ketones has been developed. In this transformation, two-step reaction including oxidation of α-amino aetones to generate imine intermediates and subsequent palladium-catalyzed aerobic annulation to give 2-aroylindoles was compatible in one pot.

Keywords: 2-aroylindoles, α-amino ketones, palladium-catalyzed, oxidative annulations

1. Introduction

The indole nucleus is prevalent in many chemical substrates which exhibit a broad spectrum of biological activities, and is recognized as privileged motif in medicinal chemistry.[1] It is also used as a useful building block for the synthesis of extensive functional molecules in different fields.[2] Among them, 2-aroylindoles constitute a particularly important class of indole derivatives that widely existed in many biologically active molecules (Figure 1).[3] For examples, 2-aroyltrimethoxyindoles have been studied as analogues of the naturally occurring drug Combretastatin A4 and showed well inhibitory activity against the tubulin polymerization.[3a] 2-(4-Phenoxybenzoyl)indole derivatives have been identified as a novel structural class of calmodulin-dependent protein kinases (CaMKII) inhibitors.[3b] Therefore, the synthesis of 2-aroylindoles has aroused considerable interest from organic chemists and many successful cases by transition-metal-catalyzed reaction and other metal-free conditions were developed over the past decades.[4-6] Although the efforts have greatly enriched the development of indole synthesis, the direct and efficient procedure for 2-aroylindoles synthesis has been rarely reported.

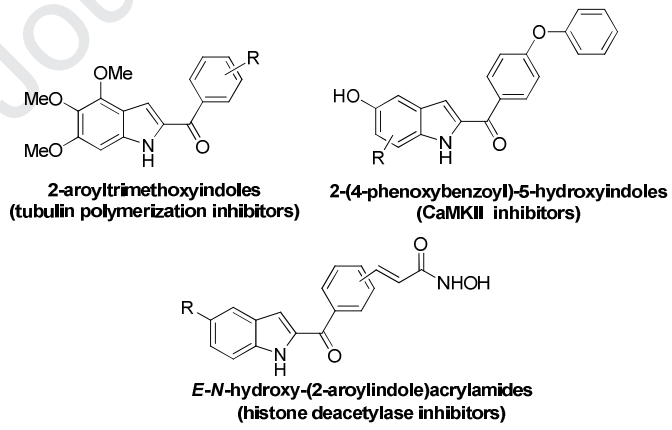
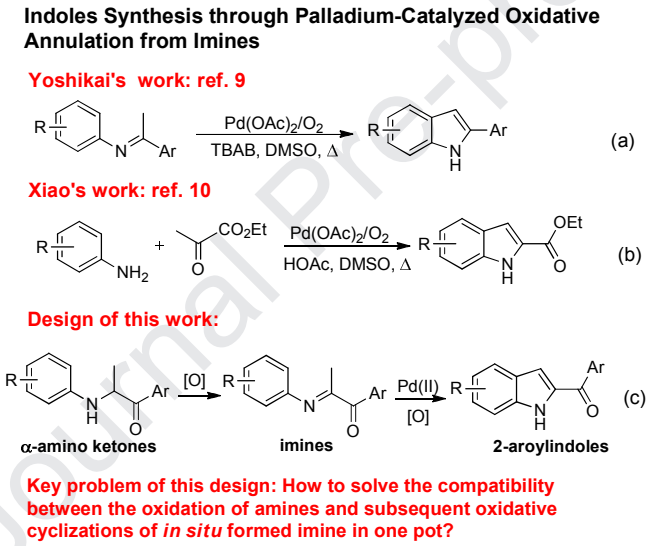


Figure 1. Examples of molecules which are of medicinal interest.

Recently palladium-catalyzed oxidative cross-coupling strategy has been one of the most fascinating strategies in organic synthesis.[7-8] Eespecially the successful methodologies have been applied to the synthesis of indoles from enamine or imine intermediates under $Pd(OAc)_2/O_2$ conditions (Scheme 1a and 1b).[9-10] However, for the

synthesis of 2-aroylindoles there was only one example in the work of Xiao group.[10b] Inspired by previous pioneering achievements,[10] we envisaged that 2-aroylindoles could be synthesized from α-amino ketones through palladium-catalyzed tandam oxidative annulation reaction (Scheme 1c). This idea is theoretically feasible and the key problem is how to accomplish the compatibility between the oxidation of α-amino ketones and subsequent oxidative annulation in one pot. Meanwhile, α-amino ketones can be readily obtained via a two-step procedure from widely existed anilines and phenylpropones (see SI). Herein, we report the direct and easy synthesis of 2-aroylindoles via palladium-catalyzed tandem oxidative annulation of α-amino ketones in one pot.



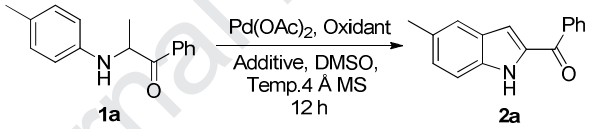
Scheme 1. Indoles Synthesis *via* Palladium-Catalyzed Oxidative Annulation Strategy.

2. Results and Discussion

At the outset of our design, we chosen the α-amino ketone **1a** to screen the feasibility using $Pd(OAc)_2$ (10 mol%), $Cu(OAc)_2$ (3.0 equiv.), 4 Å MS (60 mg) and TBAB (2.0 equiv.) in anhydrous DMSO at 60 ^oC for 12 h (Table 1).[10a] To our delight, **1a** could be converted into the desired indole product **2a** in 49% yield (Entry 1). Then different conditions were explored. First, considering two kinds of different oxidation processes in one pot, the conditions using different oxidants (1.0 equiv.) and molecular oxygen (O_2) as the co-oxidant were investigated (Entries 2-7). The best

result was obtained under 1.0 equiv. of $Cu(OAc)_2$ and O_2 atmosphere, other oxidative systems were inferior. Much to our pleasure, using O_2 as the sole oxidant also could gave the target product in 73% yield, very similar to the condition employing $Cu(OAc)_2$ (1.0 equiv.) and O_2 (Entry 8 versus entry 2). The addition of TBAB was important and improved the reaction efficiency (Entry 8 versus entry 9). Further optimization of the temperature showed the yield could be increased to 88% at 80 ^oC (Entry 11 versus entries 10, 12). It should be pointed that an elevated reaction temperature (100 ^oC) caused dramaticly decreased yield (Entry 12). At last, we also examined the conditions for indole synthesis using a carboxylic acid-promoted Pd(II)-catalytic system reported by Xiao group.[10b] Replacing the additive TBAB with 4 equiv of AcOH or PivOH, the reaction also proceeded and the desired product was isolated in moderate yield (Entries 13-14).

Table 1. Optimization of Reaction Conditions on Palladium(II)-catalyzed Oxidative Annulation. [a]

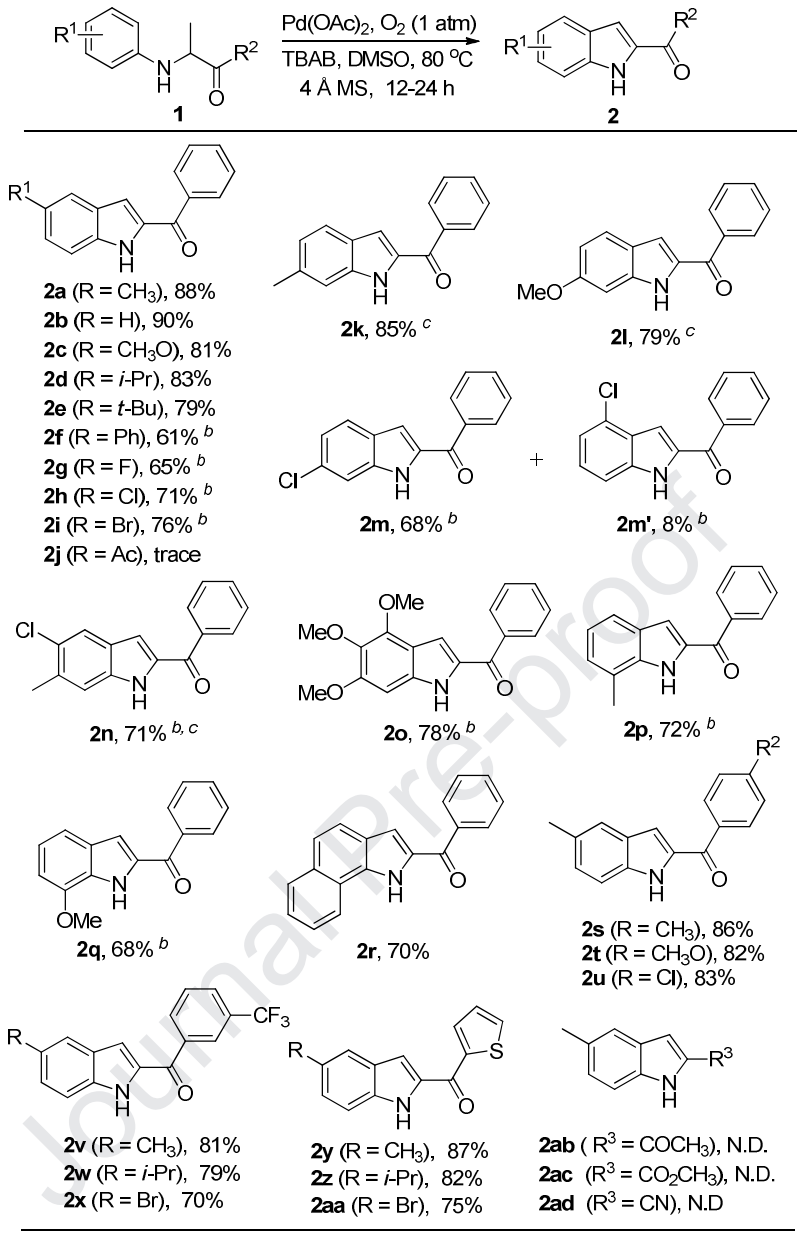


1a **2a**

Entry	Oxidant (equiv.)	Additive	Temp	Yield **2a** (%)
1	$Cu(OAc)_2$ (3.0)	TBAB	60 ^oC	49
2	$Cu(OAc)_2$ (1.0)/O_2	TBAB	60 ^oC	75
3	$CuCl_2$ (1.0)/O_2	TBAB	60 ^oC	trace
4	AgOAc (1.0)/O_2	TBAB	60 ^oC	28
5	TBHP (1.0)/O_2	TBAB	60 ^oC	19
6	^{t}-BuONO (1.0)/O_2	TBAB	60 ^oC	trace
7	BQ(1.0) / O_2	TBAB	60 ^oC	22
8	O_2	TBAB	60 ^oC	73
9	O_2	-	60 ^oC	36
10	O_2	TBAB	40 ^oC	49
11	**O_2**	**TBAB**	**80 ^oC**	**88**
12	O_2	TBAB	100 ^oC	13
13[b]	O_2	HOAc	80 ^oC	72
14[c]	O_2	PivOH	80 ^oC	56

[a] Reaction conditions: **1a** (0.2 mmol), $Pd(OAc)_2$ (10 mol%), Oxidant, TBAB (2.0 equiv.) and 4 Å MS (60 mg) in 1.0 mL of anhydrous DMSO for 12 h. [b] HOAc (4.0 equiv.). [c] PivOH (4.0 equiv.).

With the optimal conditions (Table 1, entry 11), the scope about the palladium-catalyzed tandem oxdative annulation of α-amino ketones is shown in Scheme 2. First, a series of substitutents on the phenyl rings of aniline motif were tested and the results showed electron-donating groups and weak electron-withdrawing groups were suitable for the reaction, giving the corresponding 2-aroylindoles in good to excellent yields (**2a**-**i**, **2k**-**r**). However, for the substrates with the weak electron-withdrawing group on aniline ring (**2f**-**i**, **2m**-**n**) longer reaction time was required. In this condition, strong electron-withdrawing acetyl group (**2j**) did not give the desired product. These phenomena were different from those already reported results about *N*-aryl imine intermediates for the synthesis of indoles.[10a] The possible reason may be the difficulty of the first step oxidation of α-amino ketones. This oxidative annulation reaction also had good region-selectivity. α-Amino ketones derived from *m*-methyl, -methoxy and –chloro could afford the relevant indole products at the less-hindered position in good yields (**2k**, **2l**, **2n**), while the reaction of *m*-chloro substitute on aniline motif was accompanied by a minor amount (8%) of the regioisomer (**2m** and **2m'**). Substituents at the *ortho* positions of the aniline-derived moieties were tolerated and the desired products were obtained in good yields (**2p**-**2r**). Then substitutents on the phenyl rings of ketone motif were screened. As expected, different aryl ketone motifs were suitable for constructing corresponding indoles with satisfactory yield (**2s**-**2aa**). However, the current catalytic system was inapplicable to non-aromatic ketone substrates (**2ab, 2ac, 2ad**)



Scheme 2. Substrate scope. [a] Reaction conditions: **1** (0.2 mmol), $Pd(OAc)_2$ (10 mol%), TBAB (2.0 equiv.), O_2 (1 atm) and 4 Å MS (60 mg) in 1.0 mL of anhydrous DMSO for 12 h. [b] Reaction time was 24 h. [c] Trace of regioisomeric product was detected by ^{1}HNMR. N.D. = Not Detected.

Although current reaction conditions were similar to previous reports and detailed mechanisms were discussed,[10] other further mechanistic insights should be known in this catalytic cycle. First, to elucidate the oxidation process of α-amino ketone and the key intermediate, **1b** was performed in the absence of $Pd(OAc)_2$ condition and imine intermediate **1b'** could be generated (eq 1).

This indicated the palladium catalyst was not imperative for the first oxidation step, but it may be used as a promoter in oxidation process can't be excluded. When the imine intermediate **1b'** was conducted in standard conditions for 8 h, the target product was isolated in 89% yield (eq 2). To further verify the intermediate **1b'**, a time−yield profile of α-amino ketone **1b** under the optimal conditions was depicted in Figure 2. The substrate **1b** was consumed to form imine **1b'** which was then transferred to the product **2b**. Meanwhile, **1b'** was accumulated to a maximum yield in about 3 h and then gradually converted into product **2b** in 12 h. These results indicate that **1b'** was the key intermediate for indole synthesis.

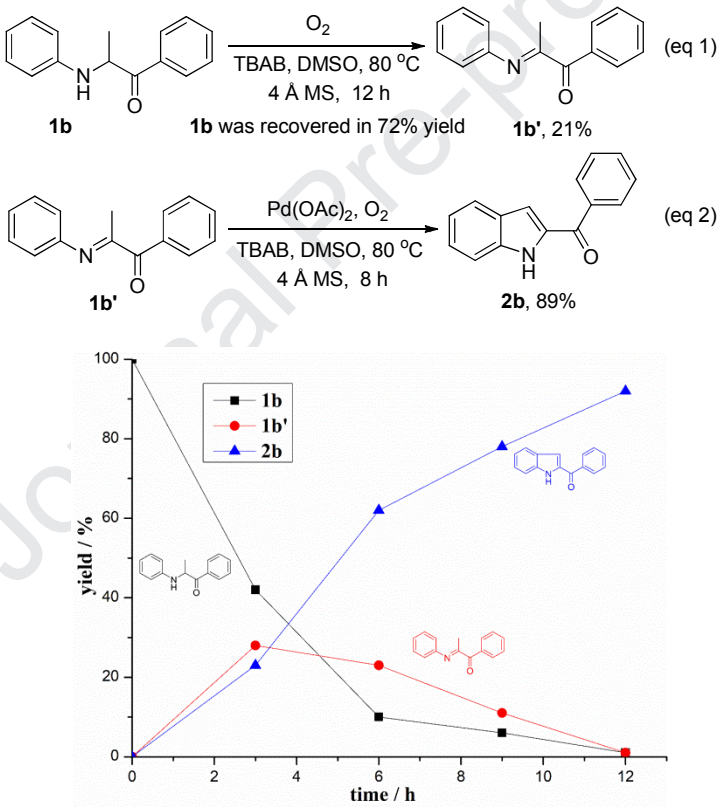
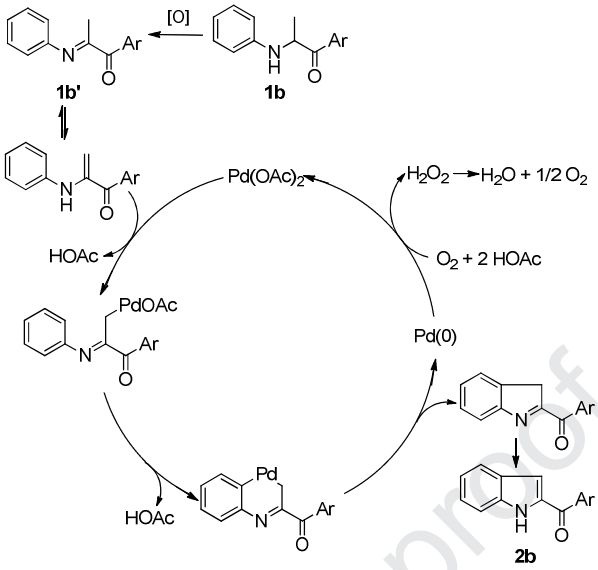


Figure 2. Selective time course of the reaction.

Based on the above results and previous studies,[9-10] a plausible reaction mechanism was proposed in scheme 3. First, α-amino ketone **1b** was oxidized to imine intermediate **1b'**, followed by tautomerization to generate corresponding enamine which electrophilically attacked by $Pd(OAc)_2$. Then similar catalytic cycle occured to afford the indole product as depicted in the work of Yoshikai group

including intramolecular C-H palladation, reductive elimination of palladacycle and tautomerization. [10a]



Scheme 3. Proposed mechanism.

3. Conclusion

In conclusion, we have developed an efficient and simple protocol for direct 2-aroylindoles synthesis from α-amino ketones. This reaction includes an oxidation of amine to afford imine intermediates *in situ* and then palladium-catalyzed oxidative annulation process to give the 2-aroylindoles in one pot. Further synthetic applications are currently underway in our laboratory.

4. Experimental section

4.1. General information

All reactions were carried out under O_2 atmosphere in dry conditions. Flash Column chromatography was performed using 200-300 mesh silica gel, SiO_2. ^1H NMR and ^{13}C NMR spectra were measured on a 600 MHz spectrometer (Agilent DD2 600Hz, ^1H: 600 MHz, ^{13}C: 150 MHz) using $CDCl_3$ as the solvent at room temperature. Multiplicities are recorded as: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, m = multiplet, br = broad. High-resolution mass spectra (HRMS) were recorded on a BRUKER VPEXII spectrometer with ESI mode.

Melting point was measured with melting point instrument.

4.2. Synthesis of α-amino ketones (**1**)

To a solution of acetone (10.0 mL) was added aniline (1.0 mmol), α-bromo ketone (1.2 mmol), K_2CO_3 (2.0 mmol), KI (0.1 mmol), then the reaction was stirred at room temperature for 18 h under air condition. After the reaction was complete, the solvent was evaporated in vacuo, and the residue was directly separated by flash column chromatography on a silica gel to give the α-amino ketone (**1**).

4.3. Synthesis of 2-aroylindoles (**2**)

A mixture of α-amino ketone (0.2 mmol), $Pd(OAc)_2$ (0.02 mmol), TBAB(0.4 mmol), O_2 (1 atm), 4 Å MS (60 mg) in anhydrous DMSO (1.0 mL) were stirred at 80 ^oC for 12 h or 24 h. After the reaction was finished, the mixture was diluted with ethyl acetate (100 mL) and then washed with saturated brine (20 mL*3 times), the organic phase was concentrated under reduced pressure. The residue was purified by flash column chromatography on a silica gel using petroleum ether/ethyl acetate as the eluent to give the desired product **2**.

4.3.1. (5-Methyl-1*H*-indol-2-yl)(phenyl)methanone (**2a**)[11a]

White solid (41.4 mg, 88% yield). ^1H NMR (600 MHz, $CDCl_3$): δ 9.56 (br, 1H), 8.01 (d, *J* = 7.2 Hz, 2H), 7.63 (t, *J* = 7.2 Hz, 1H), 7.54 (t, *J* = 7.2 Hz, 2H), 7.49 (s, 1H), 7.40 (d, *J* = 8.4 Hz, 1H), 7.22 (d, *J* = 8.4 Hz, 1H), 7.09 (s, 1H), 2.46 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 187.2, 138.1, 136.1, 134.4, 132.2, 130.3, 129.2, 128.6, 128.4, 128.0, 122.3, 112.4, 111.9, 21.4.

4.3.2. (1*H*-Indol-2-yl)(phenyl)methanone (**2b**)[11a]

Yellowish solid (39.8 mg, 90% yield). ^1H NMR (600 MHz, $CDCl_3$): δ 9.52 (br, 1H), 8.01 (d, *J* = 7.8 Hz, 2H), 7.73 (d, *J* = 7.8 Hz, 1H), 7.63 (t, *J* = 7.2 Hz, 1H), 7.54 (t, *J* = 7.2 Hz, 2H), 7.50 (d, *J* = 8.4 Hz, 1H), 7.38 (t, *J* = 7.2 Hz, 1H), 7.18 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 187.2, 138.0, 137.6, 134.4, 132.3, 129.2, 128.5, 127.8, 126.5, 123.2, 121.0, 112.8, 112.2 ;

4.3.3. (5-Methoxy-1*H*-indol-2-yl)(phenyl)methanone (**2c**)[11a]

Yellow solid (40.7 mg, 81% yield). ^1H NMR (600 MHz, $CDCl_3$): δ 9.42 (br, 1H), 7.99 (d, *J* = 7.2 Hz, 2H), 7.62 (t, *J* = 7.8 Hz, 1H), 7.53 (t, *J* = 7.8 Hz, 2H), 7.39 (d, *J* =

9.0 Hz, 1H), 7.09 (t, *J* = 2.4 Hz, 2H), 7.06 (dd, *J* = 9.0, 2.4 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 187.0, 154.8, 138.1, 134.8, 133.1, 132.3, 129.2, 128.4, 128.1, 118.4, 113.1, 112.3, 102.8, 55.7;

4.3.4. (5-*iso*-Propyl-1*H*-indol-2-yl)(phenyl)methanone (**2d**)

Yellow solid (43.7 mg, 83% yield), mp 142.3-143.6 ^{o}C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.37 (br, 1H), 7.99 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.62 (t, *J* = 7.2 Hz, 1H), 7.54-7.52 (m, 3H), 7.41 (d, *J* = 8.4 Hz, 1H), 7.29 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.11 (d, *J* = 1.2 Hz, 1H), 3.01 (sep, *J* = 7.2 Hz, 1H), 1.31 (d, *J* = 7.2 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 187.1, 141.8, 138.1, 136.3, 134.5, 132.2, 129.2, 128.4, 127.9, 126.4, 119.6, 112.7, 112.0, 34.1, 24.4. HRMS (ESI) m/z [M+H$^+$] calcd for $C_{18}H_{18}NO$ 264.1388, found 264.1382.

4.3.5. (5-(*tert*-Butyl)-1*H*-indol-2-yl)(phenyl)methanone (**2e**)

Yellow solid (43.8 mg, 79% yield), mp 139.0-140.2 ^{o}C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.44 (br, 1H), 8.00 (d, *J* = 7.2 Hz, 2H), 7.69 (s, 1H), 7.62 (t, *J* = 7.8 Hz, 1H), 7.54 (t, *J* = 7.8 Hz, 2H), 7.49 (dd, *J* = 9.0, 1.8 Hz, 1H), 7.44 (d, *J* = 9.0 Hz, 1H), 7.15 (d, *J* = 1.8 Hz, 1H), 1.40 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 187.1, 144.0, 138.1, 135.9, 134.5, 132.2, 129.2, 128.4, 127.6, 125.4, 118.4, 113.0, 111.8, 34.6, 31.6. HRMS (ESI) m/z [M+H$^+$] calcd for $C_{19}H_{20}NO$ 278.1545, found 278.1541.

4.3.6. Phenyl(5-phenyl-1*H*-indol-2-yl)methanone (**2f**)

Yellow solid (36.3 mg, 61% yield), mp 161.4-162.5 ^{o}C. ^{1}HNMR (600 MHz, $CDCl_3$): δ 9.45 (br, 1H), 8.02 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.92 (s, 1H), 7.66-7.63 (m, 4H), 7.57-7.55 (m, 3H), 7.46 (t, *J* = 7.2Hz, 2H), 7.35 (t, *J* = 7.2 Hz, 1H), 7.22 (d, *J* = 0.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 187.1, 141.7, 138.0, 137.0, 135.0, 134.6, 132.4, 129.2, 128.8, 128.5, 128.3, 127.3, 126.8, 126.6, 121.3, 113.0, 112.4. HRMS (ESI) m/z [M+H$^+$] calcd for $C_{21}H_{16}NO$ 298.1232, found 298.1237.

4.3.7. (5-Fluoro-1*H*-indol-2-yl)(phenyl)methanone (**2g**)

Yellowish solid (31.1 mg, 65% yield), mp 181.1-182.3 ^{o}C. ^{1}HNMR (600 MHz, $CDCl_3$): δ 9.67 (br, 1H), 8.00 (d, *J* = 7.8 Hz, 2H), 7.64 (t, *J* = 7.2 Hz, 1H), 7.55 (t, *J* = 7.2 Hz, 2H), 7.45 (dd, *J* = 9.0, 4.2 Hz, 1H), 7.35 (dd, *J* = 9.0, 1.2 Hz, 1H), 7.16-7.13 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): *δ* 187.1, 158.2 (d, *J* = 235.5 Hz), 137.8, 135.7,

134.2, 132.5, 129.2, 128.5, 127.8 (d, *J* = 10.5 Hz), 115.7 (d, *J* = 27.0 Hz), 113.2 (d, *J* = 9.0 Hz), 112.4 (d, *J* = 6.0 Hz), 107.2 (d, *J* = 22.5 Hz). HRMS (ESI) m/z [M+H^+] calcd for $C_{15}H_{11}FNO$ 240.0825, found 240.0822.

4.3.8. (5-Chloro-1*H*-indol-2-yl)(phenyl)methanone (**2h**)[11a]

White solid (36.3 mg, 71% yield). ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.61 (br, 1H), 7.99 (d, *J* = 7.2 Hz, 2H), 7.69 (s, 1H), 7.64 (t, *J* = 7.8 Hz, 1H), 7.55 (t, *J* = 7.8 Hz, 2H), 7.43 (d, *J* = 9.0 Hz, 1H), 7.33 (dd, *J* = 9.0, 1.2 Hz, 1H), 7.09 (d, *J* = 1.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 187.1, 137.7, 135.8, 135.4, 132.6, 129.2, 128.6, 128.55, 127.0, 126.7, 122.3, 113.4, 111.8.

4.3.9. (5-Bromo-1**H**-indol-2-yl)(phenyl)methanone (**2i**)[11a]

White solid (45.6 mg, 76% yield). ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.57 (br, 1H), 7.99 (d, *J* = 8.4 Hz, 2H), 7.85 (s, 1H), 7.64 (t, *J* = 7.2 Hz, 1H), 7.55 (t, *J* = 7.2 Hz, 2H), 7.45 (dd, *J* = 9.0, 1.8 Hz, 1H), 7.38 (d, *J* = 9.0 Hz, 1H), 7.09 (d, *J* = 1.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 187.1, 137.6, 136.0, 135.2, 132.6, 129.4, 129.3, 129.2, 128.6, 125.5, 114.1, 113.7, 111.6.

4.3.10. (6-Methyl-1*H*-indol-2-yl)(phenyl)methanone (**2k**)

Yellow solid (40.0 mg, 85% yield), mp 136.0-137.0 ^{o}C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.36 (br, 1H), 7.99 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.63-7.58 (m, 2H), 7.53 (t, *J* = 7.8 Hz, 2H), 7.26 (s, 1H), 7.12 (dd, *J* = 1.8, 0.6 Hz, 1H), 7.00 (dd, *J* = 8.4, 1.2 Hz, 1H), 2.49 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 187.0, 138.2, 138.1, 137.0, 134.0, 132.2, 129.2, 128.4, 125.7, 123.3, 122.8, 113.0, 111.7, 22.1. HRMS (ESI) m/z [M+H^+] calcd for $C_{16}H_{14}NO$ 236.1075, found 236.1080.

4.3.11. (6-Methoxy-1*H*-indol-2-yl)(phenyl)methanone (**2l**)

Yellow solid (39.7 mg, 79% yield), mp 161.5-162.7 ^{o}C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.54 (br, 1H), 7.98 (dd, *J* = 7.8, 1.2 Hz, 2H), 7.61 (tt, *J* = 7.2, 1.2 Hz, 1H), 7.57 (d, *J* = 9.0 Hz, 1H), 7.52 (t, *J* = 7.8 Hz, 2H), 7.11 (dd, *J* = 2.4, 1.2 Hz, 1H), 6.89 (d, *J* = 1.8 Hz, 1H), 6.83 (dd, *J* = 9.0, 2.4 Hz, 1H), 3.87 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 186.5, 159.8, 139.0, 138.3, 133.7, 132.1, 129.1, 128.4, 124.1, 122.2, 113.6, 113.0, 93.5, 55.5. HRMS (ESI) m/z [M+H^+] calcd for $C_{16}H_{14}NO_2$ 252.1025, found 252.1032.

4.3.12. (6-Chloro-1*H*-indol-2-yl)(phenyl)methanone (**2m**)[11a]

White solid (34.8 mg, 68% yield). ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.53 (br, 1H), 7.99 (d, *J* = 7.2 Hz, 2H), 7.64 (t, *J* = 7.2 Hz, 2H), 7.55 (t, *J* = 7.8 Hz, 2H), 7.49 (s, 1H), 7.15-7.13 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 187.0, 137.72, 137.71, 135.0, 132.5, 132.4, 129.2, 128.5, 126.3, 124.2, 122.2, 112.6, 112.0.

4.3.13. (4-Methyl-1*H*-indol-2-yl)(phenyl)methanone (**2m'**)[11a]

White solid (4.1 mg, 8% yield); ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.47 (br, 1H), 8.02 (d, *J* = 7.2 Hz, 2H), 7.65 (t, *J* = 7.2 Hz, 1H), 7.57 (t, *J* = 7.8 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 1H), 7.29 (t, *J* = 7.2 Hz, 1H), 7.25 (t, *J* = 1.2 Hz, 1H), 7.18 (d, *J* = 7.8 Hz, 1H).

4.3.14. (5-Chloro-6-methyl-1*H*-indol-2-yl)(phenyl)methanone (**2n**)

Yellow solid (38.3 mg, 71% yield), mp 207.2-208.2 ^{o}C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.43 (br, 1H), 7.98 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.69 (s, 1H), 7.63 (t, *J* = 7.2 Hz, 1H), 7.54 (t, *J* = 7.8 Hz, 2H), 7.34 (s, 1H), 7.05 (d, *J* = 1.2 Hz, 1H), 2.50 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 187.0, 137.9, 136.5, 134.9, 134.7, 132.4, 129.2, 128.5, 128.0, 126.9, 122.6, 113.4, 111.9, 21.2. HRMS (ESI) m/z [$M+H^+$] calcd for $C_{16}H_{13}ClNO$ 270.0686, found 270.0690.

4.3.15. Phenyl(4,5,6-trimethoxy-1*H*-indol-2-yl)methanone (**2o**)[11b]

Yellow solid (48.6 mg, 78% yield). ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.58 (br, 1H), 7.98 (d, *J* = 7.8 Hz, 2H), 7.61 (t, *J* = 7.8 Hz, 1H), 7.52 (t, *J* = 7.2 Hz, 2H), 7.19 (d, *J* = 1.2 Hz, 1H), 6.65 (s, 1H), 4.10 (s, 3H), 3.91 (s, 3H) , 3.87 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 186.2, 155.2, 147.1, 138.2, 136.3, 135.4, 133.1, 132.1, 129.1, 128.4, 116.3, 111.3, 89.0, 61.5, 61.0, 56.1.

4.3.16. (7-Methyl-1*H*-indol-2-yl)(phenyl)methanone (**2p**)[11a]

White solid (33.9 mg, 72% yield). ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.31 (br, 1H), 8.00 (dd, *J* = 7.8, 1.2 Hz, 2H), 7.63 (tt, *J* = 7.8, 1.2 Hz, 1H), 7.58-7.53 (m, 3H), 7.18-7.17 (m, 2H), 7.09 (t, *J* = 7.2 Hz, 1H), 2.57 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 187.3, 138.1, 137.4, 134.1, 132.3, 129.2, 128.4, 127.4, 126.7, 121.5, 121.3, 120.8, 113.4, 16.7.

4.3.17. (7-Methoxy-1*H*-indol-2-yl)(phenyl)methanone (**2q**)

White solid (34.2 mg, 68% yield), mp 158.3-159.5 ^{o}C. ^{1}H NMR (600 MHz,

$CDCl_3$): δ 9.40 (br, 1H), 7.99 (d, J = 7.2 Hz, 2H), 7.62 (t, J = 7.2 Hz, 1H), 7.53 (t, J = 7.8 Hz, 2H), 7.30 (d, J = 8.4 Hz, 1H), 7.13 (d, J = 2.4 Hz, 1H), 7.08 (t, J = 7.8 Hz, 1H), 6.77 (d, J = 7.2 Hz, 1H), 4.00 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 186.9, 146.7, 138.1, 134.1, 132.3, 129.2, 129.0, 128.9, 128.4, 121.5, 115.3, 112.7, 105.1, 55.5. HRMS (ESI) m/z [M+H$^+$] calcd for $C_{16}H_{14}NO_2$ 252.1025, found 252.1025.

4.3.18. (1*H*-Benzo[g]indol-2-yl)(phenyl)methanone (**2r**)

Yellow solid (38.0 mg, 70% yield), mp 181.1-182.0 ^{o}C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 10.38 (br, 1H), 8.29 (d, J = 7.8 Hz, 1H), 8.05 (d, J = 7.8 Hz, 2H), 7.92 (d, J = 7.8 Hz, 1H), 7.68 (d, J = 9.0 Hz, 1H), 7.64 (t, J = 7.8 Hz, 1H), 7.60- 7.52 (m, 5H), 7.29 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 186.5, 138.2, 134.1, 133.2, 132.6, 132.2, 131.6, 129.2, 129.0, 128.5, 126.2, 124.2, 122.5, 121.8, 121.4, 121.0, 114.2. HRMS (ESI) m/z [M+H$^+$] calcd for $C_{19}H_{14}NO$ 272.1075, found 272.1073.

4.3.19. (5-Methyl-1*H*-indol-2-yl)(p-tolyl)methanone (**2s**)

White solid (42.9 mg, 86% yield), mp 164.1-165.2 ^{o}C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.49 (br, 1H), 7.93 (d, J = 7.8 Hz, 2H), 7.48 (s, 1H), 7.38 (d, J = 8.4 Hz, 1H), 7.34 (d, J = 7.8 Hz, 2H), 7.20 (dd, J = 8.4, 1.2 Hz, 1H), 7.08 (d, J = 1.2 Hz, 1H), 2.47 (s, 3H), 2.46 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 186.9, 143.0, 136.0, 135.5, 134.6, 130.2, 129.4, 129.1, 128.4, 128.0, 122.3, 112.0, 111.8, 21.6, 21.4. HRMS (ESI) m/z [M+H$^+$] calcd for $C_{17}H_{16}NO$ 250.1232, found 250.1229.

4.3.20. (4-Methoxyphenyl)(5-methyl-1*H*-indol-2-yl)methanone (**2t**)

Grayish-white solid (43.5 mg, 82% yield), mp 191.3-192.8 ^{o}C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.38 (br, 1H), 8.03 (d, J = 8.4 Hz, 2H), 7.48 (s, 1H), 7.37 (d, J = 8.4 Hz, 1H), 7.19 (d, J = 8.4 Hz, 1H), 7.07 (d, J = 1.2 Hz, 1H), 7.02 (d, J = 9.0 Hz, 2H), 3.91 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 185.8, 163.1, 135.8, 134.6, 131.5, 130.8, 130.2, 128.2, 128.1, 122.2, 113.8, 111.8, 111.3, 55.5, 21.4. HRMS (ESI) m/z [M+H$^+$] calcd for $C_{17}H_{16}NO_2$ 266.1181, found 266.1179.

4.3.21. (4-Chlorophenyl)(5-methyl-1*H*-indol-2-yl)methanone (**2u**)

Yellow solid (44.8 mg, 83% yield), mp 210.4-211.3 ^{o}C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.35 (br, 1H), 7.94 (d, J = 7.8 Hz, 2H), 7.51 (d, J = 7.8 Hz, 2H), 7.48 (s, 1H), 7.37 (d, J = 8.4 Hz, 1H), 7.22 (d, J = 8.4 Hz, 1H), 7.05 (s, 1H), 2.45 (s, 3H); ^{13}C

NMR (150 MHz, $CDCl_3$): δ 185.7, 138.7, 136.4, 136.2, 134.1, 130.6, 128.9, 128.8, 128.0, 122.38, 122.35, 112.3, 111.9, 21.4. HRMS (ESI) m/z [$M+H^+$] calcd for $C_{16}H_{13}ClNO$ 270.0686, found 270.0681.

4.3.22. (5-Methyl-1*H*-indol-2-yl)(3-(trifluoromethyl)phenyl)methanone (**2v**)

Yellow solid (49.1 mg, 81% yield), mp 198.2-199.4 ^oC. ^1H NMR (600 MHz, $CDCl_3$): δ 9.34 (br, 1H), 8.24 (s, 1H), 8.16 (d, *J* = 7.8 Hz, 1H), 7.87 (d, *J* = 7.8 Hz, 1H), 7.68 (t, *J* = 7.8 Hz, 1H), 7.50 (s, 1H), 7.39 (d, *J* = 8.4 Hz, 1H), 7.24 (d, *J* = 8.4 Hz, 1H), 7.05 (s, 1H), 2.46 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 185.5, 138.7, 136.3, 133.8, 132.3 (q, *J* = 1.0 Hz), 131.1(q, *J* = 32.7 Hz), 130.8, 129.2, 129.1, 128.7 (q, *J* = 3.6 Hz), 128.0, 126.0 (q, *J* = 3.6 Hz), 123.7 (q, *J* = 271.0 Hz), 122.5, 112.7, 111.9, 21.4. HRMS (ESI) m/z [$M+H^+$] calcd for $C_{17}H_{13}F_3NO$ 304.0949, found 304.0950.

4.3.23. (5-*iso*-propyl-1*H*-indol-2-yl)(3-(trifluoromethyl)phenyl)methanone (**2w**)

Yellow solid (52.3 mg, 79% yield), mp 202.1-203.3 ^oC. ^{1}HNMR (600 MHz, $CDCl_3$): δ 9.49 (br, 1H), 8.26 (s, 1H), 8.18 (d, *J* = 7.2 Hz, 1H), 7.88 (d, *J* = 7.8 Hz, 1H), 7.68 (t, *J* = 7.8 Hz, 1H), 7.56 (s, 1H), 7.43 (d, *J* = 8.4 Hz, 1H), 7.32 (d, *J* = 8.4 Hz, 1H), 7.10 (s, 1H), 3.03 (sep, *J* = 7.2 Hz, 1H) , 1.32 (d, *J* = 7.2 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 185.5, 142.1, 138.8, 136.7, 133.9, 132.3, 131.1 (q, *J* = 33.0 Hz), 129.1, 128.6, 127.9, 127.0, 126.0, 123.7 (q, *J* = 271.5 Hz), 119.7, 113.1, 112.1, 34.1, 24.3. HRMS (ESI) m/z [$M+H^+$] calcd for $C_{19}H_{17}F_3NO$ 332.1262, found 332.1265.

4.3.24. (5-Bromo-1*H*-indol-2-yl)(3-(trifluoromethyl)phenyl)methanone (**2x**)

Yellow solid (51.5 mg, 70% yield), mp 231.0-232.2 ^oC. ^{1}HNMR(600 MHz, $CDCl_3$): δ 9.62 (br, 1H), 8.24 (s, 1H), 8.17 (d, *J* = 7.8 Hz, 1H), 7.90 (d, *J* = 7.2 Hz, 1H), 7.88 (s, 1H), 7.69 (t, *J* = 7.8 Hz, 1H), 7.47 (dd, *J* =1.2, 9.0 Hz, 1H), 7.39 (d, *J* = 8.4 Hz, 1H), 7.07 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 185.5, 138.2, 136.3, 134.6, 132.3, 131.3 (q, *J* = 33.0 Hz), 130.0, 129.2, 129.1, 129.0, 126.0, 125.6, 123.7 (q, *J* = 270.0 Hz), 114.4, 113.8, 112.0. HRMS (ESI) m/z [$M+H^+$] calcd for $C_{16}H_{10}BrF_3NO$ 367.9898, found 367.9896.

4.3.25. (5-Methyl-1*H*-indol-2-yl)(thiophen-2-yl)methanone (**2y**)

Yellow solid (42.0 mg, 87% yield), mp 129.4-130.6 ^oC. ^{1}HNMR (600 MHz,

$CDCl_3$): δ 9.37 (br, 1H), 8.03 (dd, *J* = 3.6, 0.6 Hz, 1H), 7.70 (dd, *J* = 5.4, 1.2 Hz, 1H), 7.51 (s, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.35 (d, *J* = 1.8 Hz, 1H), 7.23-7.20 (m, 2H), 2.46 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 177.8, 142.6, 135.9, 134.2, 133.0, 132.8, 130.4, 128.5, 128.1, 128.0, 122.3, 111.8, 110.2, 21.4. HRMS (ESI) m/z [M+H$^+$] calcd for $C_{14}H_{12}NOS$ 242.0640, found 242.0643.

4.3.26. (5-*iso*-propyl-1*H*-indol-2-yl)(thiophen-2-yl)methanone (**2z**)

Yellow solid (41.2 mg, 82% yield), mp 134.3-135.4 ^{o}C. ^{1}HNMR (600 MHz, $CDCl_3$): δ 9.57 (br, 1H), 8.05 (dd, *J* = 3.6, 1.2 Hz, 1H), 7.71 (dd, *J* = 4.8, 0.6 Hz, 1H), 7.57 (s, 1H), 7.44 (d, *J* = 8.4 Hz, 1H), 7.40 (d, *J* = 1.2 Hz, 1H), 7.29 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.23 (dd, *J* = 3.6, 4.2 Hz, 1H) , 3.03 (sep, *J* = 7.2 Hz, 1H) , 1.33 (d, *J* = 7.2 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 177.8, 142.6, 141.8, 136.2, 134.3, 133.0, 132.8, 128.0, 127.9, 126.3, 119.5, 112.0, 110.5, 34.1, 24.4. HRMS (ESI) m/z [M+H$^+$] calcd for $C_{16}H_{16}NOS$ 270.0953, found 270.0949.

4.3.27. (5-Bromo-1*H*-indol-2-yl)(thiophen-2-yl)methanone (**2aa**)

Yellow solid (45.9 mg, 75% yield), mp 207.1-208.2 ^{o}C. ^{1}HNMR (600 MHz, $CDCl_3$): δ 9.58 (br, 1H), 8.04 (d, *J* = 3.6 Hz, 1H), 7.88 (s, 1H), 7.74 (d, *J* = 4.8 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.38 (d, *J* = 9.0 Hz, 1H), 7.35 (s, 1H) , 7.24 (t, *J* = 4.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 177.6, 142.2, 135.8, 135.0, 133.6, 133.2, 129.4, 129.3, 128.2, 125.4, 114.2, 113.7, 109.4. HRMS (ESI) m/z [M+H$^+$] calcd for $C_{13}H_9BrNOS$ 305.9588, found 305.9584.

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at

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Highlights:

efficient synthesis of 2-aroylindoles from α-amino ketones

palladium-catalyzed tandam oxidative reactions in one pot

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Declaration of interests

√ ☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

No