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Synthesis of indoles and polycyclic amides via ruthenium(II)-catalyzed C–H activation and annulation

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Received (in XXX, XXX) Xth XXXXXXXX 200X, Accepted Xth XXXXXXXX 200X 5 DOI: 10.1039/b000000x

Ruthenium(II)-catalyzed oxidative coupling of NH protic amides with alkynes has been developed for the synthesis of diversity of complex structures, such as *N*-acyl indole and tricyclic amide derivatives.

Transition-metal-catalyzed C-H activation is an efficient and straightforward tool for the construction of various heterocyclics from simple substrates, which is generally difficult to obtain by using traditional synthetic methods.¹ In particular, chelation 10 assisted strategy has emerged as one of the most powerful methodologies in rhodium or ruthenium catalyzed C-H activation.² Among them, NH protic amides as important directing groups have been successfully utilized in catalytic C-H activation to synthesize complex products, probably due to either ¹⁵ the C-aryl or N-aryl ring can potentially undergo C-H activation.³ For example, N-substituted isoquinolones or 2-pyridones were efficiently synthesized from oxidative coupling of N-substituted benzamides or acrylamides (both N-aryl and N-alkyl) and alkynes at the ortho position of the C-ring using rhodium or ruthenium 20 catalysts (Scheme 1, eq 1).4,5 In addition, carbonyl group of amides can facilitate activation of the ortho C-H bond to afford N-acyl indole derivatives with alkynes by rhodium catalyst and N-acyl pyrrole by ruthenium catalyst, when C-alkyl was employed (Scheme 1, eqs 2 and 3).^{6,7} Satoh and Miura and Li 25 have independently developed a rhodium(III)-catalyzed facile synthesis of tricyclic amides by double C-H activation of primary benzamides with alkynes (Scheme 1, eq 4).^{4b,4c,8}

Despite the significant developments, the substrate scope is still limited, and rhodium catalysts are most used, while ³⁰ ruthenium catalysts have been less exploited.⁹ Therefore, revealing new reactions under less-expensive ruthenium catalysis is highly desirable. Very recently, Ackermann reported ruthenium(II) complexes enabled oxidative C–H bond functionalizations with anilines to provide various indoles ³⁵ (Scheme 1, eq 5).^{9d} Our continuous interest is in metal-catalyzed

diverse reactivity C–H bond activation process of amides as chelation-assisted groups. Herein, we describe a novel

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ruthenium(II)-catalyzed C–H bond activation of NH protic amides with alkynes which gives *N*-acyl indole derivatives using 40 *O*-atom to direct cyclometalation at the *ortho* C–H activation, and tricyclic amide derivatives when primary benzamides were used



Scheme 1 Selective C-H bond activation of NH protic amides.

Results and Discussion

We set out our studies with the screening of reaction conditions ⁵⁰ between *N*-phenylacetamide (**1a**) and diphenylacetylene (**2a**) (Table 1). We initially chosen copper salts as an additive under the catalyst of $[\text{RuCl}_2(p\text{-cymene})]_2$, while $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ just gave the desired product **3aa** in 8% yield (entries 1 and 2).

Table 1 Optimization of the reaction conditions^a

Ph [RuCl ₂ (<i>p</i> -cymene)] ₂ (5 mmol %)					
	Ö Ph	oxidant, additive			~
1a 2a		AI, 1211		3aa ^{Ph}	
Entry	Oxidant/[equiv]	Additive/[equiv]	Solvent	T[°C]	Yield ^b [%]
1	$Cu(OAc)_2 \cdot H_2O/1.0$	-	toluene	110	8
2	Cu(OTf) ₂ /1.0	-	toluene	110	N.R.
3	$Cu(OAc)_2 \cdot H_2O/1.0$	AgSbF ₆ /0.6	toluene	110	N.R.
4	Cu(OAc)2·H2O/1.0	AgBF ₄ /0.6	toluene	110	Trace
5	$Cu(OAc)_2 \cdot H_2O/1.0$	AgPF ₆ /0.6	toluene	110	17
6	Cu(OAc)2·H2O/1.0	CH ₃ SO ₂ OAg/0.6	toluene	110	31
7	Cu(OAc) ₂ ·H ₂ O/1.0	CH ₃ SO ₂ OAg/1.0	toluene	110	29
8	Cu(OAc)2·H2O/1.0	CH ₃ SO ₂ OAg/0.3	toluene	110	36
9	Cu(OAc)2·H2O/0.6	CH ₃ SO ₂ OAg/0.3	toluene	110	57
10	Cu(OAc)2·H2O/0.3	CH ₃ SO ₂ OAg/0.3	toluene	110	37
11	Cu(OAc)2·H2O/0.6	CH ₃ SO ₂ OAg/0.3	DCE	110	57
12	Cu(OAc)2·H2O/0.6	CH ₃ SO ₂ OAg/0.3	tAmOH	110	Trace
13	Cu(OAc)2·H2O/0.6	CH ₃ SO ₂ OAg/0.3	dioxane	110	47
14	Cu(OAc)2·H2O/0.6	CH ₃ SO ₂ OAg/0.3	DMF	110	N.R.
15	Cu(OAc)2·H2O/0.6	CH ₃ SO ₂ OAg/0.3	THF	110	41
16 ^[c]	Cu(OAc)2·H2O/0.6	CH ₃ SO ₂ OAg/0.3	toluene	110	87
17 ^[c]	Cu(OAc)2·H2O/0.6	CH ₃ SO ₂ OAg/0.3	toluene	100	73
18 ^[c]	Cu(OAc)2·H2O/0.6	CH ₃ SO ₂ OAg/0.3	toluene	120	80
19 ^[c,d]	Cu(OAc)2·H2O/0.6	CH ₃ SO ₂ OAg/0.3	toluene	110	42

^{*a*} Reaction conditions unless otherwise specified: 0.05 mmol of **1a**, 0.055 mmol of **2a**, 5 mmol 9 (of [BuCl (a summon)] = 0.6 mL of solvent 12 h

mmol of 2a, 5 mol % of [RuCl₂(*p*-cymene)]₂, 0.6 mL of solvent, 12 h, 5 under Ar atmosphere. ^{*b*} Isolated yield. ^{*c*} 0.10 mmol of 1a, 0.05 mmol of 2a. ^{*d*} 2.5 mol % of [RuCl₂(*p*-cymene)]₂.

Various kinds of silver salts were added in the presence of Cu(OAc)₂·H₂O in the reaction, in which CH₃SO₂OAg exhibited ¹⁰ good reactivity and improve the yield to 31% (entries 3-6). In

Table 2 The scope of substituted amides^a



¹⁵ ^a Reaction conditions unless otherwise specified: 0.10 mmol of **1a**, 0.05 mmol of **2**, 5 mol % of [RuCl₂(*p*-cymene)]₂, 0.6 equiv of Cu(OAc)₂·H₂O, 0.3 equiv of CH₃SO₂OAg, 0.6 mL of toluene, 110 °C, 12 h, under Ar atmosphere. Yields are reported for the isolated products. ^b 0.3 equiv of Cu(OAc)₂·H₂O.

²⁰ addition, the reaction can be carried out with good efficiency when 0.6 equiv of Cu(OAc)₂·H₂O and 0.3 equiv of CH₃SO₂OAg were used (entries 7-10). Among the test of the solview Article Chines gave the same activity as toluene (entries 11-15). To our delight, the yield was raised to 87% when excess amide 1a was used
²⁵ (entry 16). The reaction temperature was very essential in the catalyst system (entries 17 and 18). The yield was significantly diminished when the catalyst loading of [RuCl₂(*p*-cymene)]₂was reduced (entry19). In addition, we also tried the reaction conditions (KPF₆ as the additive) which was reported by ³⁰ Ackermann, but only got **3aa** in 10% yield.^{9d}

With the optimal conditions in hand, we began to explore the scope and limitation of substituted amides (Table 2). Methyl substituent at the *ortho-*, *meta-* and *para-*positions of the phenyl ring reacted smoothly providing corresponding products in good ³⁵ to moderate yields (**3ba-3da**). In addition, **1e** proceeded smoothly, proving the product **3ea** in 70% yield. Substrates bearing electron-rich or electron-poor groups at the *para-*position (**1f-1i**) gave good reactivity. Although *N-*alkyl groups are generally tolerated, steric effects of the *N-*alkyl group seems to play an ⁴⁰ important role. *N-*isopropyl substrate **1k** is much less efficient under the same conditions, leading to **3ka** in only 40% yield.

Table 3 The scope of substituted alkynes^a



⁴⁵ ^a Reaction conditions unless otherwise specified: 0.10 mmol of **1a**, 0.05 mmol of **2**, 5 mol % of [RuCl₂(*p*-cymene)]₂, 0.6 equiv of Cu(OAc)₂·H₂O, 0.3 equiv of CH₃SO₂OAg, 0.6 mL of toluene, 110 °C, 12 h, under Ar atmosphere. Yields are reported for the isolated products. ^b 0.3 equiv of Cu(OAc)₂·H₂O.

The scope of the alkynes reactant was subsequently investigated in Table 3. N-phenylacetamide **1a** reacted with

2|Journal Name, [year], [vol], 00-00

various alkynes, with either electron-donating or –with drawing diaryl groups, to form expected products in good yields (**3ab-3af**). The reaction was successfully expanded to dialkyl acetylene **2g**, but generating the product in 33% yield. A single isomer **3ah** was isolated by using **2h** as a coupling partner. In addition, unsymmetrically disubstituted alkyne **2i** gave products in good yield albeit with excellent regioselectivity. However, terminal alkynes couldn't react in the standard reaction.





^{*a*} Reaction conditions unless otherwise specified: 0.05 mmol of **4**, 0.175 mmol of **2a**, 7.5 mol % of [RuCl₂(p-cymene)]₂, 2.2 equiv of Cu(OAc)₂·H₂O, 2.0 equiv of Na₂CO₃, 0.5 mL of PhCl, 110 °C, 16 h, 15 under Ar atmosphere. Yields are reported for the isolated products.

Next, various substituted primary benzamides were tested in the catalyst system (Table 4).¹⁰ Primary benzamide **4a** react differently between *N*-substituted secondary benzamides due to ²⁰ two alkyne units are oxidatively incorporated to give tricyclic products **5aa**. The electronic effects of diverse *para*-substituted groups slightly impacted the reaction efficiency (**5ba-5ea**), while **5da** was obtained in 35% yield. Substituent in the *meta*-position of the phenyl ring (**4f**) was a suitable coupling partner for the ²⁵ coupling reaction. In contrast, substrate **4g** furnished the corresponding product in only 18% yield, probably owing to strong steric effects.

A plausible catalytic cyclewas posposed (Scheme 2). C–H first undergoes insertion by ruthenium(II) complex to form six-³⁰ membered ruthenacycle **I**. Subsequently, alkyne coordinates to a ruthenium species to give intermediate **II**, which undergo migratory insertion with alkyne to provide ruthenacycle **III**. Finally, reductive elimination generates the product **3aa**, and reoxidation regenerates the ruthenium(II) complex.



Scheme 2 Proposed catalytic cycle

Conclusion

In summary, NH protic amides coupled with alkynes ⁴⁰ provided *N*-acyl indole derivatives and tricyclic amide derivatives in high selectivity, indicating that the selectivity of the coupling of amides with alkynes is substrate-dependent. In particular, the method in the context broadens the scope of metal-catalyst to cost-effective ruthenium. Given the wide products in this ⁴⁵ versatility reaction system, this approach is also likely to find utility in the synthesis of diversity of complex structures.

Acknowledgments

We are grateful for the financial support from the NSFC (21202106), Sichuan University "985 project-Science and ⁵⁰ technology innovation platform for novel drug development".

Experimental

General remarks

NMR data were obtained for ¹H at 400 MHz or 600 MHz, and for ¹³C at 100 MHz or 151 MHz. Chemical shifts were reported in ppm from tetramethylsilane with the solvent resonance as the internal standard in CDCl₃ solution. ESI HRMS was recorded on a Waters SYNAPT G2 and Water XEVO G2 Q-ToF. UV detection was monitored at 220 nm. TLC was performed on ⁶⁰ glass-backed silica plates. Column chromatography was performed on silica gel (200-300 mesh), eluting with ethyl acetate and petroleum ether. *N*-phenylacetamide, benzamide and alkynes were commercially available.

General procedure for synthesis of indoles, polycyclic amides 65 and Characterization data

- *N*-phenylacetamide **1a** (13.5 mg, 0.1 mmol), diphenylacetylene **2a** (8.9 mg, 0.05 mmol), $[RuCl_2(p-cymene)]_2$ (1.5 mg, 5 mmol %), Cu(OAc)₂·H₂O (6.0 mg, 0.6 equiv) and CH₃SO₂OAg (3.0 mg, 0.3 equiv) were stirred in toluene (0.6 mL) at 110 °C for 12 h. After
- ⁷⁰ completion, the reaction mixture was purified by flash chromatography eluting with ethyl acetate and petroleum ether (1:20) to give the product **3aa** as a white solid (13.5 mg, 87%).^{6a} Benzamides **4a** (6.1 mg, 0.05 mmol), diphenylacetylene **2a** (31.2 mg, 0.175 mmol), [RuCl₂(*p*-cymene)]₂ (2.3 mg, 7.5 mmol %), 75 Cu(OAc)₂·H₂O (22.0 mg, 2.2 equiv) and Na₂CO₃ (10.6 mg, 2.0 mg,
- equiv) were stirred in chlorobenzene (0.5 mL) at 110 °C for 16 h.

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After completion, the reaction mixture was purified by flash chromatography eluting with ethyl acetate and petroleum ether (1:30) to give the product **5aa** as a yellow solid (10.2 mg, 43%).¹⁰ **1-(2,3-diphenyl-1***H***-indol-1-yl)ethanone (3aa).** 12 h, 87% yield,

- ⁵ white solid; m.p. 148.7-150.2 °C; IR (KBr): v = 3053, 2922, 2851, 1694, 1612, 1512, 1448, 1307 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 8.46 (d, J = 8.0 Hz, 1H), 7.56 (d, J = 7.6 Hz, 1H), 7.41 (t, J = 7.6 Hz, 1H), 7.37~7.32 (m, 5H), 7.30~7.25 (m, 4H), 7.24~7.21 (m, 2H), 2.00 (s, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 171.6,
- ¹⁰ 136.8, 135.0, 133.1, 132.9, 130.8, 130.1, 129.3, 128.6, 128.2, 126.9, 125.5, 123.8, 123.4, 119.6, 116.2, 27.9 ppm. ESI HRMS: calcd. for C₂₂H₁₇NO+H 312.1388, found 312.1384.

1-(5-methyl-2,3-diphenyl-1*H***-indol-1-yl)ethanone (3ba)**. 12 h, 76% yield, pale yellow solid; m.p. 182.0-183.8 °C; IR (KBr): $\upsilon =$

¹⁵ 3057, 2921, 2856, 1693, 1608, 1512, 1462, 1311 cm^{-1.} ¹H NMR (400 MHz, CDCl₃) δ 8.34 (d, J = 8.4 Hz, 1H), 7.34~7.39 (m, 6H), 7.27~7.20 (m, 6H), 2.43 (s, 3H), 1.99 (s, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 171.4, 135.1, 135.1, 133.4, 133.2, 133.1, 130.8, 130.1, 129.5, 128.6, 128.2, 126.9, 126.8, 123.3, 119.4, ²⁰ 116.0, 27.9, 21.4 ppm. ESI HRMS: calcd. for C₂₃H₁₉NO+H

326.1545, found 326.1547.

1-(6-methyl-2,3-diphenyl-1H-indol-1-yl)ethanone (3ca). 12 h, 64% yield, pale yellow solid; m.p. 129.1-130.5 °C; IR (KBr): $v = 3059, 2920, 2854, 1693, 1614, 1512, 1480, 1311 \text{ cm}^{-1}$. ¹H NMR ²⁵ (400 MHz, CDCl₃) δ 8.29 (s, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.34

- (s, 5H), 7.30~7.25 (m, 3H), 7.23~7.20 (m, 2H), 7.13 (d, J = 8.0 Hz, 1H), 2.53 (s, 3H), 1.98 (s, 3H) ppm. ¹³C NMR (151 MHz, CDCl₃) δ 171.4, 136.9, 135.4, 134.1, 133.0, 132.8, 130.5, 129.7, 128.3, 128.2, 127.9, 126.8, 126.6, 124.9, 123.0, 118.9, 116.0, ³⁰ 27.7, 21.8 ppm. ESI HRMS: calcd. for C₂₃H₁₉NO+Na 348.1364, found 348.1362.
- **1-(7-methyl-2,3-diphenyl-1***H***-indol-1-yl)ethanone (3da).** 12 h, 50% yield, pale yellow solid; m.p. 130.1-132.9 °C; IR (KBr): $\upsilon = 3044$, 2925, 2853, 1707, 1617, 1542, 1512, 1446, 1283 cm⁻¹. ¹H
- ³⁵ NMR (400 MHz, CDCl₃) δ 7.46 (d, J = 7.2 Hz, 1H), 7.35 (s, 5H), 7.30~7.16 (m, 7H), 2.44 (s, 3H), 2.06 (s, 3H) ppm. ¹³C NMR (151 MHz, CDCl3) δ 172.9, 135.2, 134.8, 133.2, 132.1, 130.6, 129.8, 129.8, 128.4, 128.3, 127.9, 127.3, 126.4, 124.3, 123.0, 121.0, 117.3, 28.4, 21.1 ppm. ESI HRMS: calcd. for ⁴⁰ C₂₃H₁₉NO+H 326.1545, found 326.1554.
- **1-(6-chloro-2,3-diphenyl-1***H***-indol-1-yl)ethanone (3ea).** 12 h, 70% yield, yellow solid; m.p. 139.2-141.3 °C; IR (KBr): v = 3024, 2925, 2854, 1702, 1602, 1561, 1513, 1456, 1306 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 8.52 (s, 1H), 7.46 (d, J = 8.0 Hz, 1H),
- $_{45}$ 7.39~7.36 (m, 3H), 7.35~7.32 (m, 2H), 7.30~7.26 (m, 4H), 7.20~7.18 (m, 2H), 1.99 (s, 3H) ppm. 13 C NMR (100 MHz, CDCl₃) δ 171.5, 137.0, 135.4, 132.6, 132.5, 131.4, 130.7, 129.9, 128.9, 128.7, 128.4, 127.8, 127.2, 124.3, 123.0, 120.3, 116.5, 27.8 ppm. ESI HRMS: calcd. for C₂₂H₁₆ClNO+Na 368.0818, 50 found 368.0811, 370.0796.
- **1-(5-methoxy-2,3-diphenyl-1***H***-indol-1-yl)ethanone (3fa).** 12 h, 59% yield, pale orange solid; m.p. 186.3-188.5 °C; IR (KBr): v = 3005, 2958, 2930, 2832, 1692, 1606, 1544, 1512, 1468, 1370, 1297 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 8.39 (d, *J* = 8.8 Hz,
- ⁵⁵ 1H), 7.36~7.31 (m, 5H), 7.29~7.24 (m, 3H), 7.22~7.19 (m, 2H), 7.03~6.99 (m, 2H), 3.82 (s, 3H), 1.98 (s, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 171.2, 156.7, 135.7, 133.1, 133.0, 131.6, 130.8, 130.2, 130.0, 128.6, 128.6, 128.3, 126.9, 123.3, 117.3,

113.9, 102.2, 55.8, 27.8 ppm. ESI HRMS: calcd. for $_{60}$ C₂₃H₁₉NO₂+H 342.1494, found 342.1511.

- **1-(5-chloro-2,3-diphenyl-1***H***-indol-1-yl)ethanone (398) 5 \times 10^{-10} (500) 10.10 \times 10^{-10}**
- ⁶⁵ 7.38~7.34 (m, 6H), 7.30~7.26 (m, 3H), 7.18 (d, J = 6.4 Hz, 2H), 1.98 (s, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 171.4, 136.2, 135.1, 132.5, 132.4, 130.7, 130.6, 129.9, 129.4, 128.9, 128.7, 128.4, 127.2, 125.6, 122.7, 119.1, 117.4, 27.8 ppm. ESI HRMS: calcd. for C₂₂H₁₆CINO+Na 368.0818, found 368.0821, 370.0804.
- ⁷⁰ **1-(5-iodo-2,3-diphenyl-1***H***-indol-1-yl)ethanone (3ha).** 12 h, 83% yield, pale yellow solid; m.p. 223.9-225.4 °C; IR (KBr): v = 3055, 2930, 1698, 1603, 1578, 1515, 1441, 1301 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 8.23 (d, J = 8.8 Hz, 1H), 7.86 (s, 1H), 7.68~7.66 (m, 1H), 7.38~7.37 (m, 3H), 7.34~7.31 (m, 3H), 7.29~7.25 (m,
- $_{75}$ 2H), 7.19~7.17 (m, 2H), 1.98 (s, 3H) ppm. $^{13}\mathrm{C}$ NMR (100 MHz, CDCl₃) δ 171.5, 136.1, 135.7, 133.9, 132.4, 132.4, 131.6, 130.7, 130.0, 128.9, 128.7, 128.4, 128.3, 127.2, 122.3, 118.2, 87.8, 27.9 ppm. ESI HRMS: calcd. for C₂₂H₁₆INO+Na 460.0174, found 460.0177.
- ⁸⁰ **1-(5-nitro-2,3-diphenyl-1***H***-indol-1-yl)ethanone (3ia).** 12 h, 34% yield, yellow solid; m.p. 152.9-154.6 °C; IR(KBr): v = 3061, 2922, 2851, 1715, 1611, 1575, 1519, 1445, 1336, 1295 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 8.52 (d, J = 9.2 Hz, 1H), 8.45 (s, 1H), 8.29~8.26 (m, 1H), 7.42~7.39 (m, 3H), 7.38~7.36 (m, 2H),
- 85 7.35~7.31 (m, 3H), 7.22~7.20 (m, 2H), 2.03 (s, 3H) ppm. $^{13}\mathrm{C}$ NMR (100MHz, CDCl₃) δ 171.6, 144.4, 139.6, 137.7, 131.8, 131.6, 130.6, 129.9, 129.4, 129.3, 128.9, 128.7, 127.7, 123.5, 120.6, 116.3, 116.0, 27.9 ppm. ESI HRMS: calcd. for $C_{22}H_{16}N_2O_3+Na$ 379.1059, found 379.1053.
- ⁹⁰ 1-(2,3-diphenyl-1*H*-indol-1-yl)propan-1-one (3ja). 12 h, 50% yield, pale yellow solid; m.p. 145.4-147.5 °C; IR (KBr): υ = 3063, 2984, 2937, 2875, 1696, 1609, 1565, 1485, 1447, 1274 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 8.41 (d, *J* = 8.4 Hz, 1H), 7.56 (d, *J* = 7.6 Hz, 1H), 7.42~7.39 (m, 1H), 7.36~7.32 (m, 5H), 7.29~7.25
- ⁹⁵ (m, 4H), 7.22~7.20 (m, 2H), 2.20 (q, J = 7.2 Hz, 2H), 1.02 (t, J = 7.6 Hz, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 175.8, 136.8, 134.8, 133.2, 133.1, 130.6, 130.1, 129.2, 128.6, 128.5, 128.2, 126.9, 125.4, 123.6, 123.1, 119.6, 115.8, 33.2, 9.4 ppm. ESI HRMS: calcd. for C₂₃H₁₉NO+Na 348.1364, found 348.1373.
- ¹⁰⁰ **1-(2,3-diphenyl-1***H***-indol-1-yl)-2-methylpropan-1-one (3ka).** 12 h, 40% yield, pale yellow solid; m.p. 123.2-125.0 °C; IR (KBr): v = 3023, 2966, 2929, 2871, 1697, 1617, 1564, 1511, 1447, 1272 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 8.20 (d, J = 8.0Hz, 1H), 7.57 (d, J = 7.6 Hz, 1H), 7.40~7.28 (m, 10H), 7.26~7.22
- ¹⁰⁵ (m, 2H), 2.55~2.48 (m, 1H), 0.97 (d, J = 6.8 Hz, 6H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 180.1, 137.0, 134.5, 133.4, 132.8, 130.2, 130.1, 129.1, 128.6, 128.4, 128.3, 126.9, 125.2, 123.3, 122.3, 119.6, 114.8, 37.2, 19.0 ppm. ESI HRMS: calcd. for C₂₄H₂₁NO+Na 362.1521, found 362.1524.
- ¹¹⁰ **cyclohexyl(2,3-diphenyl-1***H***-indol-1-yl)methanone (3la).** 12 h, 75% yield, pale yellow solid; m.p. 142.3-143.9 °C; IR (KBr): υ = 3053, 2929, 2849, 1699, 1604, 1562, 1507, 1447, 1312 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 8.25 (d, *J* = 8.4 Hz, 1H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.39~7.23 (m, 12H), 2.15 (t, *J* = 7.2 Hz, 1H), 115 1.63~1.56 (m, 3H), 1.48~1.34 (m, 4H), 1.08 (q, *J* = 12.8 Hz, 1H), 0.69 (q, *J* = 12.8 Hz, 2H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ

4|Journal Name, [year], [vol], 00-00

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178.7, 136.9, 134.7, 133.3, 133.0, 130.3, 130.1, 129.0, 128.6, 128.4, 128.2, 126.8, 125.1, 123.3, 122.3, 119.5, 115.1, 46.7, 29.1, 25.5, 25.4 ppm. ESI HRMS: calcd. for $C_{27}H_{25}NO+Na$ 402.1834, found 402.1834.

- ⁵ **1-(2,3-di-p-tolyl-1***H***-indol-1-yl)ethanone (3ab).** 12 h, 71% yield, white solid; m.p. 170.0-171.8 °C; IR (KBr): $v = 3016, 2939, 2861, 1687, 1590, 1504, 1448, 1311 cm^{-1}$. ¹H NMR (400 MHz, CDCl₃) δ 8.44 (d, J = 8.4 Hz, 1H), 7.54 (d, J = 7.6 Hz, 1H), 7.39 (t, J = 7.6 Hz, 1H), 7.30~7.25 (m, 1H), 7.23~7.21 (m, 2H), 7.17~7.13 (cm) 7.11 7.00 (cm) 7.
- 10 (m, 2H), 7.11~7.09 (m, 4H), 2.37 (s, 3H), 2.33 (s, 3H), 1.99 (s, 3H) ppm. $^{13}\mathrm{C}$ NMR (100 MHz, CDCl₃) δ 171.7, 138.5, 136.8, 136.5, 135.0, 130.6, 130.1, 130.0, 129.9, 129.5, 129.3, 129.0, 125.3, 123.7, 123.0, 119.5, 116.2, 28.0, 21.4, 21.2 ppm. ESI HRMS: calcd. for C_{24}H_{21}NO+H 340.1701, found 340.1700.
- ¹⁵ **1-(2,3-di-m-tolyl-1***H***-indol-1-yl)ethanone (3ac).** 12 h, 77% yield, pale yellow oil; IR (KBr): v = 3033, 2961, 2860, 1695, 1608, 1515, 1449, 1307 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 8.45 (d, J = 8.0 Hz, 1H), 7.56 (d, J = 7.6 Hz, 1H), 7.39 (t, J = 7.6 Hz 1H), 7.29 (t, J = 7.2 Hz, 1H), 7.25~7.21 (m, 1H), 7.18~7.12 (m, 4H), 20 7.08~7.04 (m, 2H), 6.99 (d, J = 7.6 Hz, 1H), 2.32 (s, 3H), 2.29 (s, 3H), 2.00 (s, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 170.7, 137.2, 136.6, 135.7, 134.1, 132.0, 131.9, 130.3, 129.7, 128.3, 128.3, 127.4, 127.0, 126.9, 126.6, 126.1, 124.3, 122.7, 122.2, 118.6, 115.1, 26.9, 20.4, 20.3 ppm. ESI HRMS: calcd. for 25 C₂₄H₂₁NO+Na 362.1521, found 362.1520.
- **1-(2,3-di-o-tolyl-1***H***-indol-1-yl)ethanone (3ad).** 12 h, 80% yield.pale yellow solid; m.p. 85.1-86.9 °C; IR(KBr): v = 3034, 2952, 2860, 1695, 1606, 1516, 1448, 1307 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 8.45 (d, J = 8.0 Hz, 1H), 7.56 (d, J = 7.6 Hz, 1H), 7.42~7.38 (m, 1H), 7.31~7.28 (m, 1H), 7.25~7.21 (m, 1H), 7.18~7.12 (m, 4H), 7.08~7.05 (m, 2H), 6.99 (d, J = 7.6 Hz, 1H), 2.32 (s, 3H), 2.29 (s, 3H), 2.00 (s, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 171.8, 138.2, 137.7, 136.8, 135.1, 133.0, 132.9, 131.4, 130.7, 129.4, 129.4, 128.4, 128.1, 127.9, 127.7, 127.1, 125.4, ³⁵ 123.7, 123.3, 119.6, 116.2, 27.9, 21.5, 21.4 ppm. ESI HRMS: calcd. for C₂₄H₂₁NO+Na 362.1521, found 362.1521.
- **1-(2,3-bis(4-methoxyphenyl)-1***H***-indol-1-yl)ethanone (3ae).** 12 h, 80% yield, pale yellow solid; m.p. 148.6-150.1 °C; IR (KBr): υ = 3066, 2955, 2837, 1701, 1610, 1568, 1504, 1451, 1300, 1249 ⁴⁰ cm^{-1.} ¹H NMR (400 MHz, CDCl₃) δ 8.45 (d, *J* = 8.4 Hz, 1H), 7.54 (d, *J* = 7.6 Hz, 1H), 7.39 (t, *J* = 7.6 Hz, 1H), 7.30 (d, *J* = 7.6 Hz, 1H), 7.27~7.23 (m, 2H), 7.15 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 8.4 Hz, 2H), 6.84 (d, *J* = 8.4 Hz, 2H), 3.83 (s, 3H), 3.80 (s, 3H), 2.01 (s, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 171.7, 159.8, ⁴⁵ 158.4, 136.7, 134.6, 132.0, 131.1, 129.5, 125.4, 125.3, 125.2,
- 123.7, 122.7, 119.4, 116.2, 114.1, 113.8, 55.3, 55.2, 27.3 ppm. ESI HRMS: calcd. for $C_{24}H_{21}NO_3+Na$ 394.1419, found 394.1423. **1-(2,3-bis(4-chlorophenyl)-1***H***-indol-1-yl)ethanone (3af).** 12 h, 59% yield, pale yellow solid; m.p. 204.2-205.8 °C; IR (KBr): $v = s_0$ 3062, 2957, 2853, 1698, 1598, 1557, 1447, 1301 cm⁻¹. ¹H NMR
- ⁵⁰ 3062, 2957, 2853, 1698, 1598, 1557, 1447, 1501 cm⁻. H NMR (400 MHz, CDCl₃) δ 8.41 (d, J = 8.4 Hz, 1H), 7.49 (d, J = 7.6 Hz, 1H), 7.40 (t, J = 7.6 Hz, 1H), 7.38~7.36 (m, 2H), 7.33~7.30 (m, 2H), 7.28~725 (m, 3H), 7.13 (d, J = 8.0 Hz, 2H), 2.06 (s, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 171.0, 136.8, 135.0, 133.9,
- $_{55}$ 133.2, 131.9, 131.3, 131.2, 129.1, 128.9, 128.7, 125.9, 124.0, 122.7, 119.4, 116.2, 28.1 ppm. ESI HRMS: calcd. for $C_{22}H_{15}Cl_2NO+Na$ 402.0428, found 402.0443, 404.0373.

1-(2,3-dibutyl-1H-indol-1-yl)ethanone (3ag). 12 h, 33% yield,

yellow oil; IR (KBr): v = 3048, 2957, 2930, 2863, 1703, 1602, 1578, 1518, 1460, 1311 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 7.76~7.74 (m, 1H), 7.49~7.47 (m, 1H), 7.25~7.22 View Article 7048 (t, J = 7.6 Hz, 2H), 2.76 (s, 3H), 2.64 (t, J = 7.6 Hz, 2H), 1.62~1.52 (m, 4H), 1.44~1.37 (m, 4H), 0.97~0.93 (m, 6H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 170.0, 138.3, 135.7, 130.9, 123.3,

⁶⁵ 122.6, 120.1, 118.7, 114.5, 32.5, 32.4, 27.7, 26.8, 23.7, 22.9, 22.8, 14.0, 13.9 ppm. ESI HRMS: calcd. For C₁₈H₂₅NO+Na 294.1834, found 294.1840.

ethyl 1-acetyl-2-phenyl-1*H*-indole-3-carboxylate (3ah). 12 h, 26% yield, pale yellow solid; m.p. 104.5-106.1 °C; IR (KBr): v = 70 3057, 2987, 2945, 2897, 1796, 1707, 1608, 1555, 1515, 1446, 1290, 1240, 1178 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 8.32 (d, J = 7.2 Hz, 1H), 8.23~8.20 (m, 1H), 7.51~7.48 (m, 5H), 7.42~7.40 (m, 2H), 4.20 (q, J = 7.6 Hz, 2H), 1.92 (s, 3H), 1.16 (t, J = 7.6 Hz, 3H) ppm. ¹³C NMR (151 MHz, CDCl₃) δ 171.7, 164.2, 143.6,

 $_{75}$ 136.2, 132.6, 130.4, 129.5, 128.3, 126.9, 125.7, 124.5, 121.7, 115.6, 112.4, 60.1, 27.8, 14.0 ppm. ESI HRMS: calcd. for $C_{19}H_{17}NO_3+Na$ 330.1106, found 330.1102.

1-(2-(tert-butyl)-3-phenyl-1*H*-indol-1-yl)ethanone (3ai); 1-(3-(tert-butyl)-2-phenyl-1H-indol-1-yl)ethanone (3ai'); (3ai:3ai'

- ⁸⁰ = **17:1**). 12h, 45% yield, pale yellow solid; m.p. 86.3-87.9 °C; IR (KBr): $v = 3060, 2994, 2963, 2918, 2864, 1713, 1584, 1516, 1454, 1295 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) <math>\delta$ **3ai**: 7.48~7.12 (m, 9H), 2.87 (s, 3H), 1.34 (s, 9H) ppm; **3ai**': 8.44 (d, J = 8.0 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.48~7.12 (m, 7H), 1.50 (s, 3H),
- ⁸⁵ 1.25 (s, 9H) ppm. ¹³C NMR (151 MHz, CDCl₃) δ 174.9, 145.5, 136.5, 134.8, 131.4, 130.8, 128.2, 127.1, 123.6, 123.0, 121.8, 119.8, 111.4, 35.2, 32.1, 31.1, 29.9, 28.3 ppm.^{6a}
 5 (12 trick end 8W is environmentation [22 ending sequence]

5,6,13-triphenyl-8*H*-isoquinolino[3,2-a]isoquinolin-8-one

- (5aa). 16 h, 43% yield, yellow solid; m.p. 296.5-297.9 °C; IR % (KBr): v = 3021, 1673, 1595, 1540, 1477, 1309 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 8.26 (d, J = 8.0 Hz, 1H), 7.62~7.58 (m, 1H), 7.56~7.53 (m, 5H), 7.44 (t, J = 7.6 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.28~7.20 (m, 3H), 7.18~7.12 (m, 5H), 7.08 (s, 5H), 6.88 (t, J = 7.6 Hz, 1H) ppm. ¹³C NMR (151 MHz, CDCl₃) δ 162.2,
- $_{95}$ 138.6, 137.1, 137.1, 136.2, 136.1, 133.8, 133.0, 132.3, 132.1, 131.4, 129.6, 129.0, 128.8, 128.4, 128.1, 127.9, 127.6, 127.4, 127.1, 126.9, 126.8, 126.6, 126.4, 126.3, 125.8, 125.6, 125.5, 116.9 ppm. ESI HRMS: calcd. for $\rm C_{35}H_{23}NO+Na$ 496.1677, found 496.1674.

100 11-chloro-5,6,13-triphenyl-8H-isoquinolino[3,2-a]isoquinolin-8-one (5ba). 16 h, 56% yield, yellow solid; m.p. 334.2-336.1 °C; IR (KBr): v = 3025, 1667, 1591, 1529, 1449, 1317 cm⁻¹. ¹H NMR $(400 \text{ MHz}, \text{CDCl}_3) \delta 8.19 \text{ (d}, J = 8.4 \text{ Hz}, 1\text{H}), 7.58 \sim 7.50 \text{ (m}, 5\text{H}),$ 7.38 (d, J = 8.4 Hz, 1H), 7.32~7.23 (m, 4H), 7.19~7.11 (m, 5H), ¹⁰⁵ 7.08 (s, 5H), 6.89 (t, J = 7.6 Hz, 1H) ppm. ¹³C NMR (151 MHz, CDCl₃) δ 161.5, 139.0, 138.4, 137.9, 136.9, 136.0, 135.9, 135.2, 133.1, 132.0, 131.3, 129.9, 129.3, 129.1, 128.8, 128.8, 128.4, 127.9, 127.2, 127.2, 127.0, 126.9, 126.9, 126.8, 126.4, 125.7, 123.9, 115.8 ppm.ESI calcd. 124.8 HRMS: for 110 C₃₅H₂₂ClNO+H508.1468, found 508.1468, 510.1452.

11-methoxy-5,6,13-triphenyl-8*H***-isoquinolino[3,2-a] isoquinolin-8-one (5ca).** 16 h, 40% yield, yellow solid; m.p. 301.6-303.1 °C; IR (KBr): v = 3021, 2938, 2839, 1670, 1604, 1540, 1475, 1279, 1217 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 8.19 115 (d, J = 8.8 Hz, 1H), 7.54~7.50 (m, 5H), 7.27~7.21 (m, 3H), 7.16~7.09 (m, 5H), 7.06 (s, 5H), 7.03~7.00 (m, 1H), 6.86 (t, J =

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Journal Name, [year], [vol], 00-00 |5

8.0 Hz, 1H), 6.71 (d, *J* = 2.4 Hz, 1H), 3.75 (s, 3H) ppm. ¹³C NMR (151 MHz, CDCl₃) δ 162.9, 161.7, 139.2, 138.7, 137.3, 136.3, 136.2, 134.6, 133.2, 132.1, 131.5, 129.7, 129.7, 129.1, 128.8, 128.5, 128.1, 127.9, 127.5, 127.1, 126.9, 126.7, 126.3, 126.2, s 125.6, 119.9, 116.6, 115.1, 107.5, 55.3 ppm. ESI HRMS: calcd.

- for $C_{36}H_{25}NO_2+Na$ 526.1783, found 526.1780. **11-nitro-5,6,13-triphenyl-8H-isoquinolino[3,2-a]isoquinolin-8-one (5da).** 16 h, 35% yield, red solid; m.p. 348.5-349.7 °C; IR (KBr): $\upsilon = 3026$, 1666, 1605, 1578, 1519, 1456, 1340, 1293 cm⁻¹.
- ¹⁰ ¹H NMR (400 MHz, CDCl₃) δ 8.38 (d, J = 8.4 Hz, 1H), 8.22 (s, 1H), 8.15 (d, J = 8.4 Hz, 1H), 7.61~7.57 (m, 3H), 7.52~7.50 (m, 2H), 7.29~7.20 (m, 4H), 7.17~7.15 (m, 4H), 7.09 (s, 5H), 6.93 (t, J = 7.2 Hz, 1H) ppm. ¹³C NMR (151 MHz, CDCl₃) δ 160.8, 150.3, 137.7, 137.2, 136.4, 136.0, 135.8, 135.6, 133.1, 131.8,
- 150.5, 151.7, 151.2, 150.4, 150.6, 155.6, 155.6, 155.7, 151.6, 151.7, 151.6, 151.1, 151.1, 1
- **11-fluoro-5,6,13-triphenyl-8***H***-isoquinolino[3,2-a]isoquinolin-**²⁰ **8-one (5ea).** 16 h, 42% yield, yellow solid; m.p. 298.2-300.0 °C; IR(KBr): v = 3024, 1673, 1614, 1580, 1490, 1399, 1286 cm^{-1.} ¹H NMR (400 MHz, CDCl₃) δ 8.25 (dd, J = 6.4, 8.4 Hz, 1H), 7.59~7.53 (m, 3H), 7.51~7.49 (m, 2H), 7.28~7.21 (m, 3H), 7.19~7.12 (m, 6H), 7.08 (s, 5H), 6.98~6.95 (m, 1H), 6.89 (t, J = 6.4 successible for the second statement of th
- ²⁵ 7.6 Hz, 1H) ppm. ¹³C NMR (151 MHz, CDCl₃) δ 165.4(d, $J_{C-F} =$ 252 Hz), 161.4, 139.6 (d, $J_{C-F} =$ 10.0 Hz), 138.2, 137.0, 136.1, 136.0, 135.2, 133.2, 132.0, 131.4, 130.7 (d, $J_{C-F} =$ 10.0 Hz), 129.9, 129.1, 128.8, 128.8, 128.4, 127.9, 127.2, 127.1, 127.0, 126.9, 126.8, 126.4, 125.7, 122.3, 116.2, 115.0 (d, $J_{C-F} =$ 24.0 Hz), 110.6 ³⁰ (d, J = 24.0 Hz) ppm. ESI HRMS: calcd. for C₃₅H₂₂FNO+Na 514.1583, found 514.1581.
- **10-methyl-5,6,13-triphenyl-8***H***-isoquinolino[3,2-a]isoquinolin-8-one (5fa).** 16 h, 36% yield, yellow solid; m.p. 252.1-253.5 °C; IR (KBr): υ = 3025, 2923, 2852, 1669, 1606, 1537, 1467, 1326 ³⁵ cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 8.07 (s, 1H), 7.57~7.50 (m, 5H), 7.46~7.42 (m, 1H), 7.26~7.20 (m, 5H), 7.17~7.11 (m, 4H), 7.07 (s, 5H), 8.87 (t, *J* = 7.6 Hz, 1H), 2.45 (s, 3H) ppm. ¹³C NMR (151 MHz, CDCl₃) δ 162.2, 138.7, 137.2, 136.7, 136.2, 136.2, 134.8, 133.8, 132.9, 132.9, 132.1, 131.4, 129.6, 128.9, 128.8, ⁴⁰ 128.2, 128.0, 127.9, 127.8, 127.1, 127.0, 126.9, 126.7, 126.6, 126.2, 125.7, 125.6, 125.6, 117.0, 21.3 ppm.ESI HRMS: calcd. for C₃₆H₂₅NO+K526.1573, found 526.1573.
- 9-chloro-5,6,13-triphenyl-8H-isoquinolino[3,2-a]isoquinolin-
- **8-one (5ga).** 16 h, 18% yield, yellow solid; m.p. 229.7-230.6 °C; ⁴⁵ IR (KBr): υ = 3024, 1689. 1581, 1528, 1447, 1294 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 7.58~7.52 (m, 3H), 7.46~7.36 (m, 4H), 7.29~7.21 (m, 3H), 7.18~7.09 (m, 10H), 7.04~7.02 (m, 1H), 6.88 (*t*, *J* = 7.2 Hz, 1H) ppm. ¹³C NMR (151 MHz, CDCl₃) δ 161.5, 140.3, 138.7, 136.5, 136.4, 136.0, 134.3, 133.8, 133.4, 132.0,
- $_{50}$ 131.4, 131.3, 129.8, 129.0, 128.9, 128.7, 128.5, 128.1, 127.9, 127.4, 127.1, 127.0, 126.6, 126.2, 125.8, 125.5, 124.4, 122.2, 114.7 ppm.ESI HRMS: calcd. for $\rm C_{35}H_{22}CINO+Na$ 530.1288, found 530.1271, 532.1256.

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6|Journal Name, [year], [vol], 00-00