Chapter-IV

Cu-catalyzed synthesis of C2-tetrasubstituted indolin-3-ones

4.1 Introduction

Indolin-3-ones are privileged scaffolds that function as intermediate for the synthesis of medicinally important compounds.[1-4] In particular, 2,2-disubstituted 1,2-dihydro-3*H*-indol-3-one, also known as pseudoindoxyls bearing C2 stereocenters have continually appeared in natural products such as Austamide (**I**), strobilanthoside A (**II**), isatisine A (**III**) and halichrome A (**IV**), as well as in many other biologically active synthetic compounds (Figure 1).[5-10] Besides, compounds with this skeleton have also exhibited exciting applications in the areas of fluorescence labeling and optoelectronic materials in recent years.[11-13]

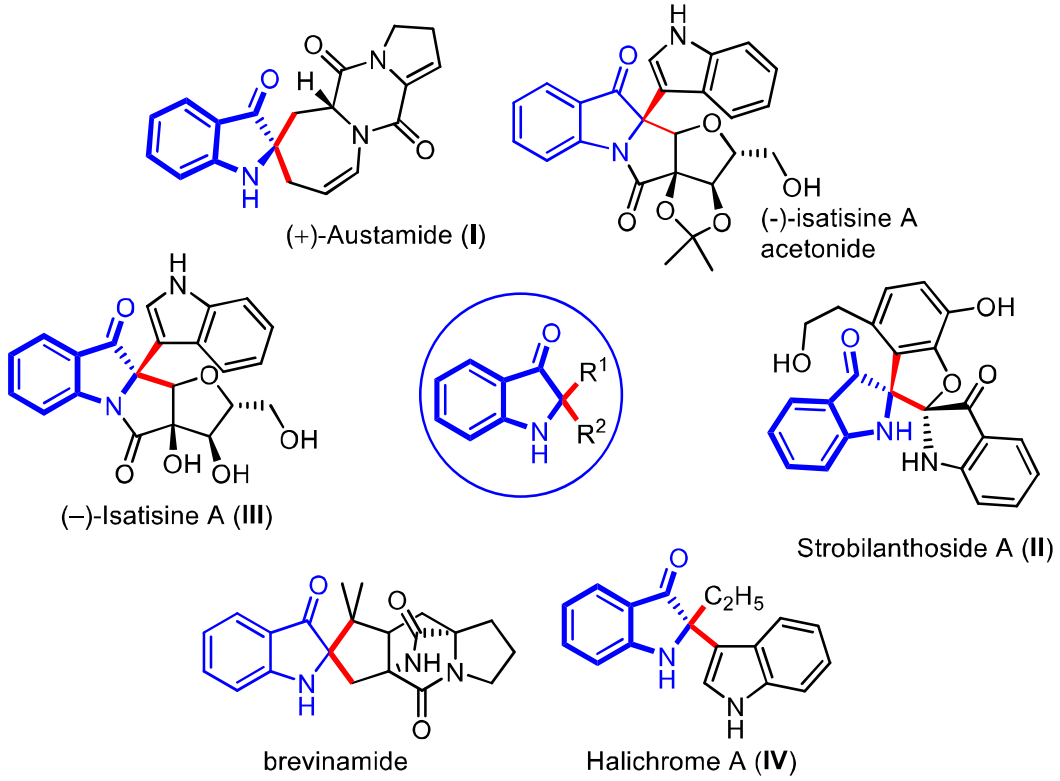
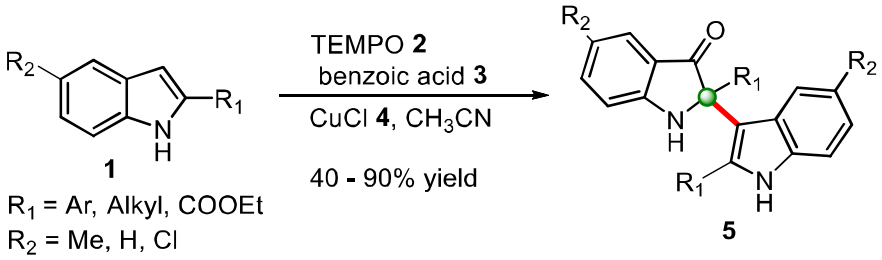


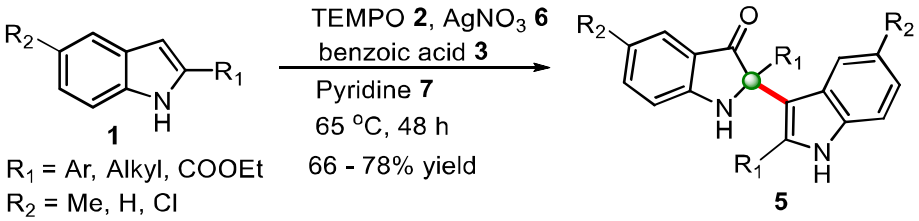
Figure 4.1 2-disubstituted indolin-3-one as essential core in natural products

Due to the broad utility of 2,2-disubstituted indolin-3-ones, several methods had been developed in the past few years, which includes; transition-metals catalyzed annulation reactions,[14-24] the cascade Fischer indolization/Claisen rearrangement,[25] and photo-oxidative rearrangements,[26-28] along with other methods.[29-30] Besides these methods, the chemoselective addition of various nucleophiles to 2-aryl-indol-3-one, an activated cyclic C-acylimine, is another exciting way to access 2,2-disubstituted indolin-3-one derivatives.[31-36] However, the synthesis of 2-aryl-3*H*-indol-3-ones requires troublesome multi-step and is not easily accessible.[37-40] To overcome this

problem, some attention has recently given to the chemistry of dearomative cascade reactions of 2-substituted indoles for the direct construction of C2-quaternary indoline-3-ones. In this context, initially, Cu-catalyzed self-dimerization of 2-substituted indoles **1** has been explored by Kong *et al*. to access indolin-3-one **5** decorated with quaternary carbon centers at the C-2 position using TEMPO **2** as oxidant catalyst and benzoic acid **3** as an additive in acetonitrile as solvent **(Scheme 4.1).**[41]

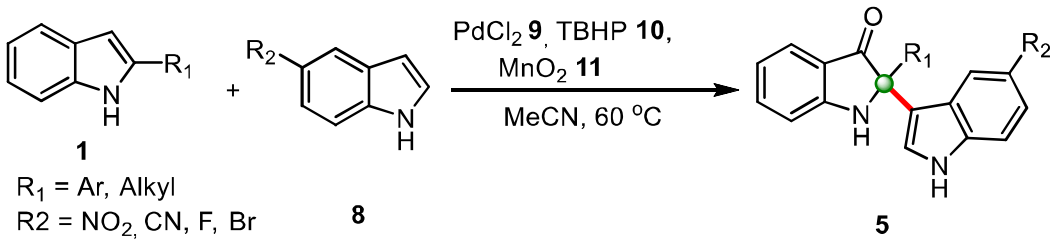


Scheme 4.1 TEMPO and Copper(I)chloride catalyzed self-dimerization of two substituted indole Lin *et al*. demonstrated the silver-catalyzed oxidative self-dimerization of 2-substituted indole derivatives **1** using TEMPO **2** as an oxidant in the presence of benzoic acid **3**. Thus 2,2-disubstituted indolin-3-one obtained with high regioselectivity moderate to excellent yields **(Scheme 4.2)**.[42] The whole procedure was carried out in pyridine **7** as solvent at 65 °C for 48 h using expensive chemical like-TEMPO, which makes this protocol less practical.



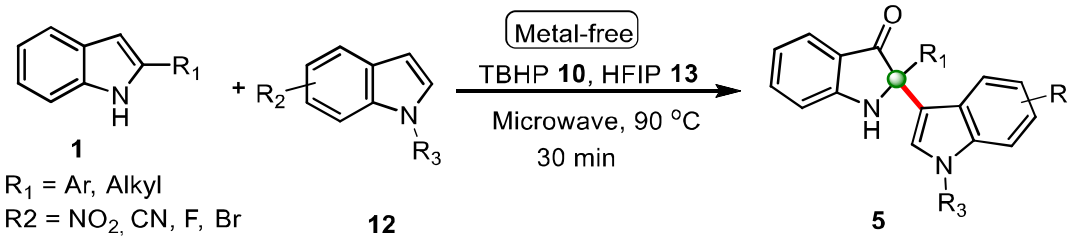
Scheme 4.2 Synthesis of 2-substituted indole derivatives by silver nitrate and TEMPO

On the other hand, cross-addition of indole to 2-substituted indole could be another way to achieve C2-quaternary indolin-3-ones; however, a difficult task to accomplish in terms of selectivity. In this context, Guchhait and coworkers developed an exciting and very first protocol for the Pd-catalyzed cross-addition of indoles to 2-substituted indoles to access 2,2-disubstituted indolin-3-ones **5** in a chemoselective fashion involving oxidative dearomatization of 2-aryl or 2-alky indoles **1** from TBHP (*t*-butyl hydrogen peroxide) **10**, Manganese dioxide **11**, and Kornblum−DeLaMare type reactions in acetonitrile at 60 °C **(Scheme 4.3)**.[43]

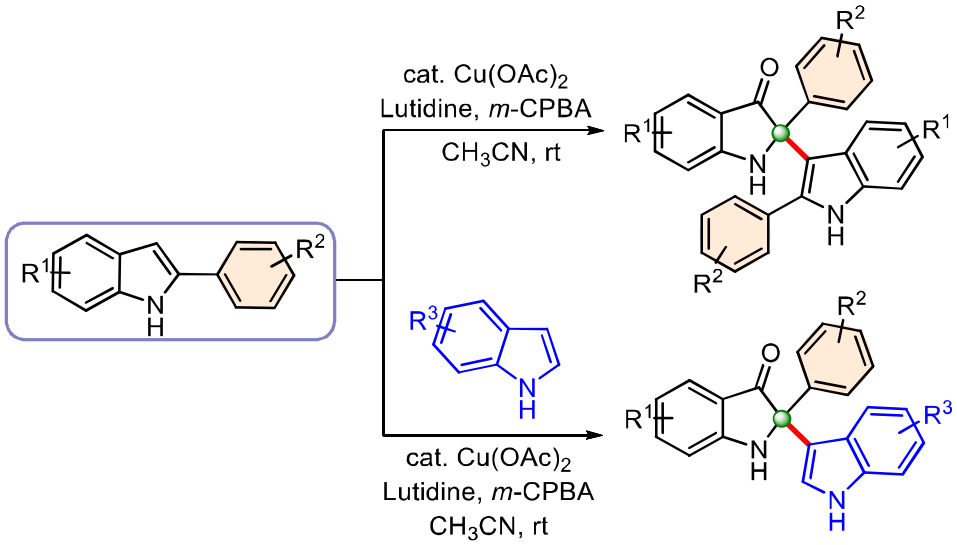


Scheme 4.3 Pd-catalyzed oxidative dearomatization of 2-aryl or 2-alkyl-indoles

Very recently, Yu and coworkers developed a straightforward metal-free method for the synthesis of indolin-3-one for the cross-addition of indoles **12** with 2-substituted indoles **1** to access a series of 2,2-disubstituted indolin-3-ones **5**. The following transformation was carried out in a microwave on a small scale at a high temperature (**Scheme 4.4**).[44]



Scheme 4.4 Microwave-assisted synthesis of 2,2-disubstituted indolin-3-ones



Scheme 4.5 Synthetic approaches from 2-aryl indoles to access 2,2-disubstituted indolin-3-ones

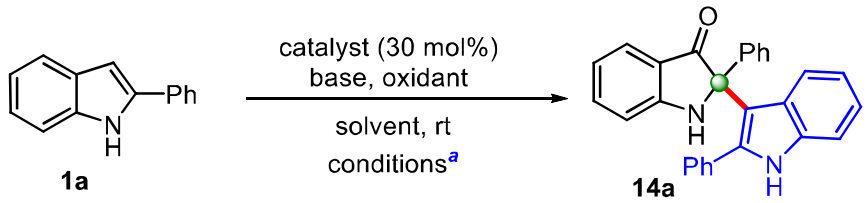
Due to the high significance of C2-quaternary indolin-3-ones, and limitations of the existing methods, the finding a direct path to these compounds through the self-dimerization of 2-substituted indoles or the cross-addition of indoles with 2-substituted indoles under mild conditions, is still highly desirable. Here, we present such a general and straight forward finding

for the synthesis of 2,2-disubstituted indole-3-ones from 2-aryl indoles through copper-catalyzed self-dimerization and cross-addition with indoles at room temperature **(Scheme 4.5)**.

4.2 Results and discussions

Copper-catalyzed transformations are one of the most studied methods in synthetic chemistry due to their efficiency, good functional group tolerance.[45-47] In this context, Cu-catalyzed tandem oxidative reactions of 2-aryl indole-3-ones, in situ generated from 2-arylindoles, have been developed to synthesize 2-arylbenzoxazinone,[48] and polyhydropyrido[1,2-a]indoles/tetracyclic quinazolinones.[49] Encouraged by these relevant precedents, we envisaged that a general copper-catalyzed method could be developed for the self-dimerization 2-substituted indoles and cross-addition with indoles through the in situ generations of indol-3-ones under mild conditions. Herein, we describe the successful implementation of the process.

Table 4.1 Optimization of the reaction conditions[a]

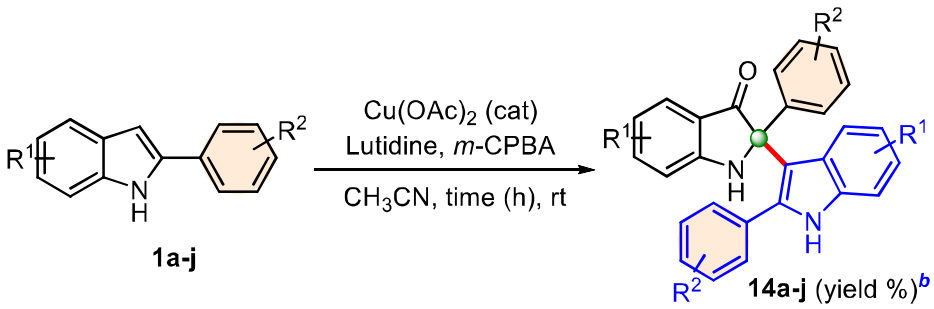


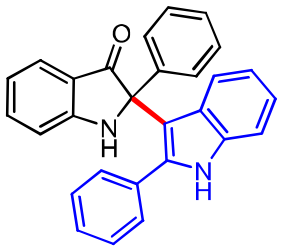
Entry	Solvent	Catalyst	Base	Oxidant	Time (h)	Yield (%)[b]
1	Toluene	CuCl	Py	$K_2S_2O_8$	24	n.r.
2	Toluene	CuCl	Py	Oxone	24	n.r.
3	Toluene	CuCl	Py	Air	24	<10
4	DMSO	CuCl	Py	Air	24	<10
5	CH_3CN	CuCl	Py	TBHP	24	34
6	CH_3CN	CuCl	Py	Oxone	24	25
7	CH_3CN	CuCl	Py	Air	24	30
8	CH_3CN	CuCl	Lutidine	TBHP	22	45
9	CH_3CN	CuCl	K_2CO_3	TBHP	24	20
10	CH_3CN	CuCl	Lutidine	*m*-CPBA	20	52
11	CH_3CN	$Cu(OAc)_2$	Lutidine	TBHP	20	63
12	**CH_3CN**	**$Cu(OAc)_2$**	**Lutidine**	***m*-CPBA**	**18**	**75**
13	CH_3CN	$Cu(OAc)_2$	Lutidine	H_2O_2	18	43
14[c]	CH_3CN	$Cu(OAc)_2$	Lutidine	*m*-CPBA	24	65
15	CH_3CN	-	Lutidine	*m*-CPBA	24	n.r.
16	CH_3CN	$Cu(OAc)_2$	-	*m*-CPBA	24	n.r.

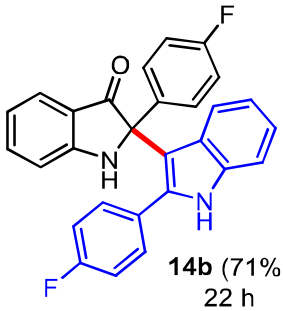
[a]Unless otherwise indicated the reaction was carried out with (i) 2-phenylindole **1a** (0.5mmol), solvent (3.0 mL), catalyst (30 mol%), base (1.0 mmol), oxidant (0.3mmol), reaction time (h) at rt. [b]Isolated yield of **14a** refer to **1a**, [c]$Cu(OAc)_2$(15mmol%) was used.

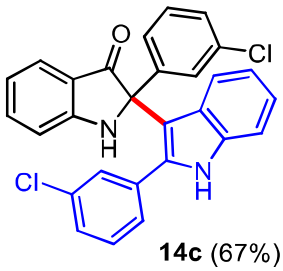
We begin this study for the oxidative cross-dimerization of 2-phenyl indole **1a** as model substrates to prepare 2-phenyl-2-(2-phenyl-1*H*-indol-3-yl)indolin-3-ones **14a**. In this context, optimization of the reaction conditions was carried out by employing several bases, oxidizing agents, catalysts, and solvents, and the results are shown in **(Table 4.1)**. Initially, reaction failed to work, when **1a** was treated with catalysts CuCl (30 mol%), pyridine with; $K_2S_2O_8$ **(entry 4.1, Table 4.1)**, oxone **(entry 2, Table 4.1)**. Trace amount (<10%) of **14a** was obtained with air as oxidants in toluene **(entry 3, Table 4.1)** and DMSO **(entry 4, Table 4.1)** as solvents, respectively. However, product **14a** was obtained with low yield (34%), when the reaction was carried out with CuCl (cat.), pyridine, and TBHP (*tert*-butyl hydroperoxide) in CH_3CN **(entry 5, Table 4.1)** at room temperature. Next, additional efforts were made to improve the reaction yields either by changing the oxidants, base, and catalysts **(entries 6-11, Table 4.1)**. An improvement in the reaction yields was observed by employing Lutidine, in place of pyridine, with TBHP (45%) **(entry 8, Table 4.1)**, and with *m*-CPBA (*meta*-chloroperbenzoic acid) (52%) **(entry 10, Table 4.1)**. The dimerized product **14a** was obtained with moderate yield (63%) when $Cu(OAc)_2$ **(entry 11, Table 4.1)** was employed in place of CuCl as a catalyst with TBHP as oxidant, which was again improved to 75% yield by using *m*-CPBA as oxidant **(entry 12, Table 4.1)**. Any additional change in the reaction conditions either; by changing oxidant **(entry 12, Table 4.1)** or lowering the catalyst loading **(entry 14, Table 4.1)** failed to improve the reaction yield. The reaction failed to produce any dimerization product in the absence of a catalyst **(entry 15, Table 4.1)**, and base **(entry 16, Table 4.1)**. Thus, we preferred to perform this reaction to yield cross-dimerized product **14a** under the standardized conditions **(entry 12, Table 4.1)**. Moreover, reaction only furnished 2-indoles substituted 3-oxindole **14a** through the addition of indole as a nucleophile at the C2-position in situ generated indol-3-one in a chemoselective fashion.

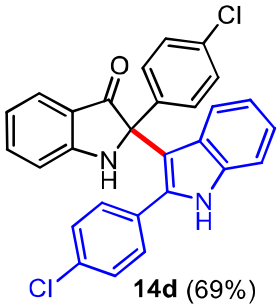
Table 4.2 Substrate scope for the self-dimerized synthesis of C2-quaternary indolin-3-ones

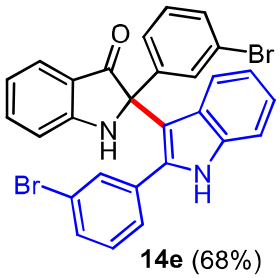


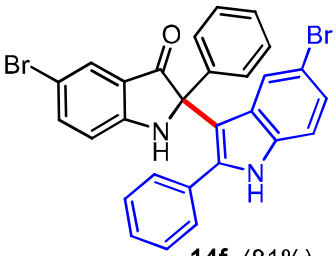

14a (75%)
18 h

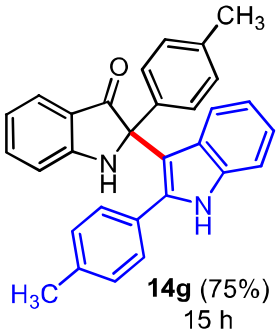

14b (71%)
22 h

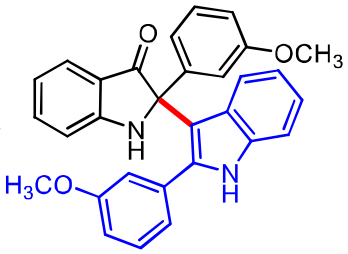

14c (67%)
16 h

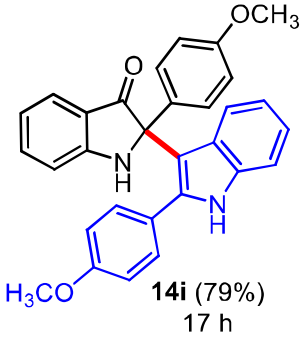

14d (69%)
18 h

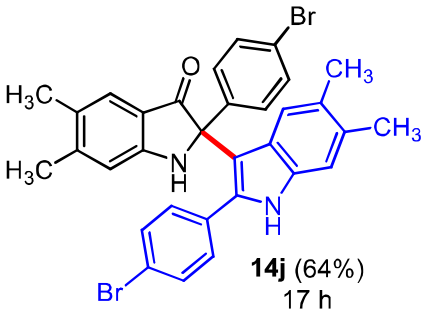

14e (68%)
20 h

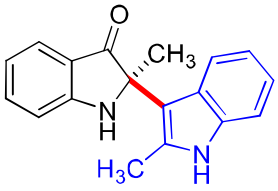

14f, (81%)
16 h


14g (75%)
15 h


14h (82%)
19 h


14i (79%)
17 h

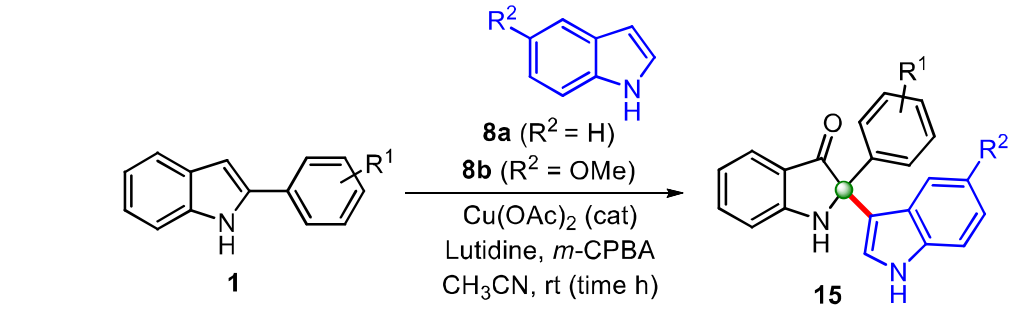

14j (64%)
17 h

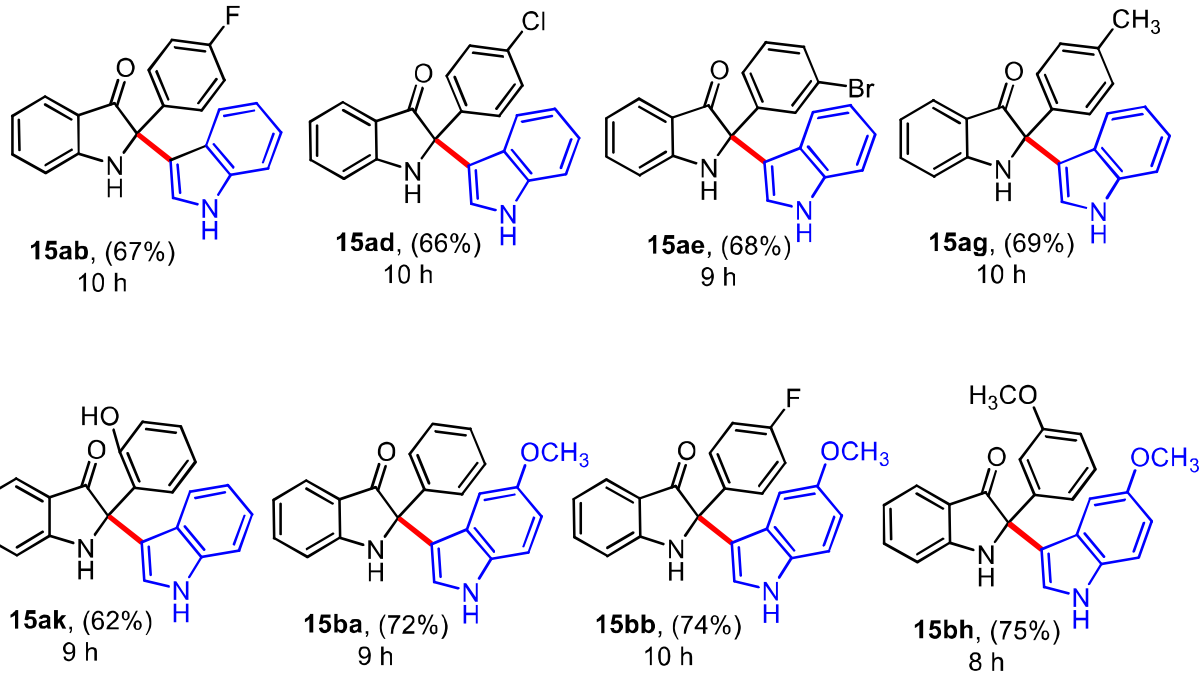

2k (71%)
14 h

[a]Unless otherwise indicated the reaction was carried out with (i) 2-phenylindole **1** (0.5mmol), CH_3CN (3.0 mL), $Cu(OAc)_2$ (30 mol%), Lutidine (1.0 mmol), *m*-CPBA (0.3mmol), reaction time at rt. [b]Isolated yield of **14** refers to **1**.

Next, we explored the generality of our developed cross-dimerization protocol with variously substituted 2-aryl indoles **1a-k** under standardized conditions, and results are shown in **Table 4.2**. The reaction was found to be quite general concerning the substituents on both the aryl-rings of 2-aryl-indole **1** and accomplished within 15-22 h at room temperature to furnish similar cross-dimerized products, i.e., 2-indoles substituted 3-oxindoles **14** in good to high yields (68-82%). Initially, halo-substituents like 4-F, 3-Cl, 4-Cl, 3-Br substitutions on the phenyl ring of 2-aryl indole **1b**, **1c**, **1d**, and **1e** gave similar products **14b** (71%), **14c** (67%), **14d** 69%), and **14e** (68%), respectively. The electron-donating substituents like $–OCH_3$ and $–CH_3$ on the phenyl ring of 2-aryl indoles furnished similar products **14g**, **14h**, and **14i** with relatively higher yields (75-82%) than the substrates with electron-withdrawing groups. The product **14f** obtained in high yields (81%) when 5-Bromo-2-phenyl-1*H*-indole **1f** was employed under standardized conditions. Moreover, densely substituted 2-aryl indole **1j** could furnish corresponding cross-dimerized product **14j** with 64% yields, due to the presence of internal steric hindrance. In the case of 2-methyl indole as substrate, corresponding dimerized product **2k** was also obtained with good yield (71%). Thus, the developed method found to be general w.r.t., the alkyl/aryl substituents at the C2-position of indoles. We also extended this developed protocol for the cross addition of indoles **8** at the C2-position of 2-arylindole **1**, and the results are shown in (**Table 4.3)**. Pleasingly, cross-addition of indoles furnished similar products in good to high yields, in all the cases, under similar reaction conditions. Initially, indole **8a** reacted with 2-aryl indoles (**1b**, **1d**, **1e**) substituted with electron-withdrawing groups (**–**F, **–**Cl, **–**Br) and furnished corresponding cross-addition products **15ab** (67%), **15ad** (66%), and **15ae** (68%), respectively. Similarly, products **15ag** (69%) and **15ak** (62%) were obtained, when simple indole **8a** reacted with 2-aryl indoles **1g** and **1k** substituted with electron-donating groups ($–CH_3$, –OH), respectively. Moreover, 5-Methoxy indole **8b** furnished corresponding cross-addition products **15ba** (72%), **15bb** (74%), and **15bh** (75%) with improved yields, when treated with 2-phenylindole **1a** and other substituted 2-aryl indoles (**1b** and **1h**), respectively, in the presence of $Cu(OAc)_2$ (cat.), *m*-CPBA (1.0 equiv), and Lutidine (2.0 equiv) as base at room temperature. Interestingly, the cross-addition reaction of indoles was observed to be relatively faster as compared to the cross-dimerization. In general, the self-dimerization product yields were found slightly more that than the cross-addition reactions because in the case of cross-addition of indoles we also observed a trace amount (<10%) of self-dimerized products in almost all the cases.

Table 4.3 Substrate scope for the synthesis of Indolin-3-ones through cross indole-addition

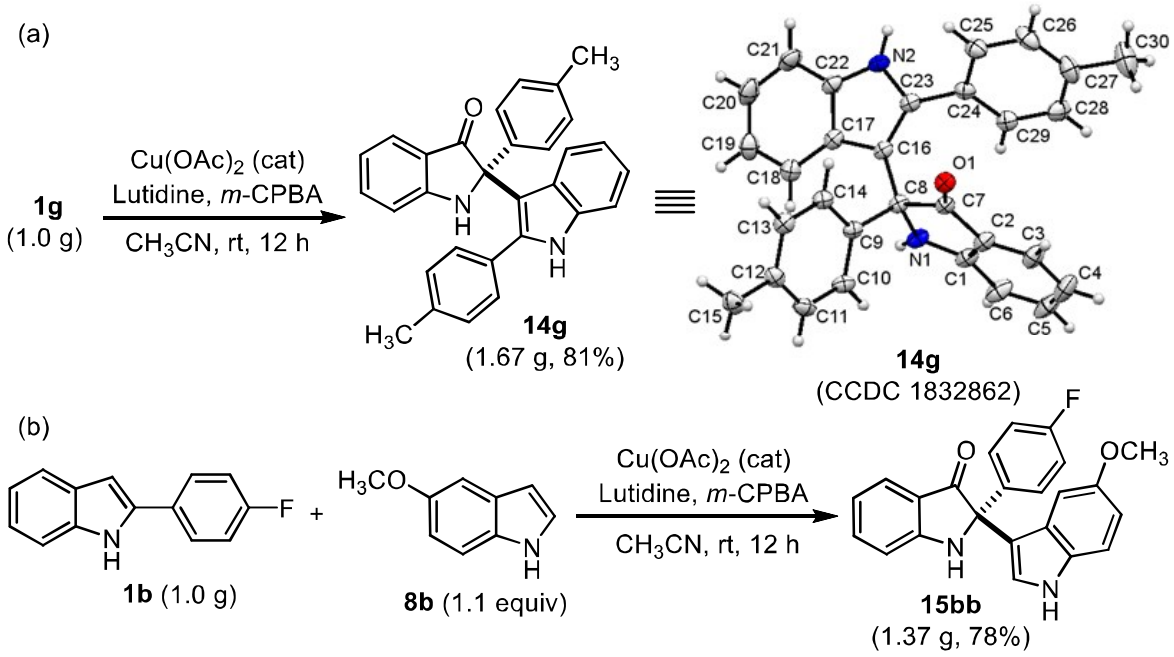




[a]Unless otherwise indicated, the reaction was carried out with (i) 2-phenylindole **1** (0.5mmol), indole **8** (0.55 mmol), CH_3CN (3.0 mL), $Cu(OAc)_2$ (30 mol%), Lutidine (1.0 mmol), *m*-CPBA (0.5 mmol), reaction time (h) at rt. [b] Isolated yield of **15** refer to **1**.

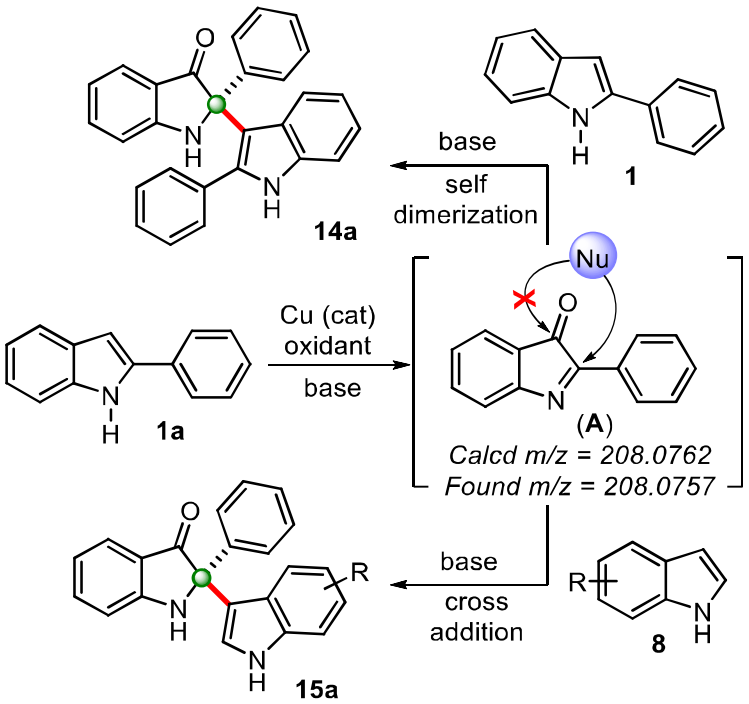
The practical use of this method was also demonstrated to access both cross-dimerization of 2-arylindole and cross-addition of indole with 2-arylindole products on a gram-scale without much variation in yield, as shown in **(Scheme 4.6)**. Pleasingly, the gram-scale reaction successfully afforded **14g** with a higher yield (81%) **(Scheme 4.5a)** as compared to the small-scale response **(Table 4.2)**. The single-crystal X-ray diffraction analysis confirmed the structure of cross-dimerized product **14g**.[50] Moreover, 2,2-disubstituted indole-3-one **15bb** was isolated with a

78% yield, when cross-addition of 2-substituted indole **1b** was performed with 4-methoxy indole **8b**, under standardized conditions **(Scheme 4.6b)**.



Scheme 4.6 Practical utility at the gram-scale synthesis of **14g** and **15bb**. Single crystal X-ray structure of **14g** (The thermal ellipsoids are drawn at the 50% probability level)

4.3 Plausible mechanism



Scheme 4.7 Plausible way of reaction for the synthesis of 2,2-disubstituted indole-2-ones through in situ generations of indole-3-one confirmed by HRMS.

Based on previous reports and our findings, a tentative mechanism for the synthesis of self-dimerized2-phenyl-2-(2-phenyl-1*H*-indol-3-yl)indolin-3-ones **14** and cross-addition 2-(1*H*-indol-3-yl)-2-phenylindole-3-ones**15** is drawn, as shown in (**Scheme 4.7)**. Initially, the copper-catalyzed oxidation of 2-phenylindole **1a** to intermediate 2-phenylindole-3-one (**A**), which was confirmed by in situ HRMS data. This intermediate (**A**) undergoes a chemoselective C2-addition with another 2-phenylindole **1a** to furnished self-dimerization product **14a**. Whereas, for the cross-addition product **15**, intermediate (**A**) was trapped with another indole moiety.

4.4 Conclusion

In summary, we have developed an efficient and general protocol for the synthesis of 2-phenyl-2-(2-phenyl-1*H*-indol-3-yl)indolin-3-ones through the self-dimerization of 2-aryl indoles and 2-(1*H*-indol-3-yl)-2-phenylindolin-3-ones through cross-addition of indole on 2-aryl indoles through copper-catalyzed in situ generated indole-3-ones in a regioselective manner under mild conditions. This simple strategy provides convenient access to indolin-3-ones bearing C2-quaternary center in good to high yields. The developed protocol utilized nontoxic and readily available materials and practically viable at the gram-scale synthesis.

4.5 Experimental Procedure

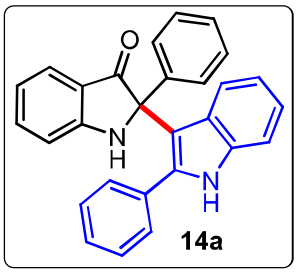
All reactions were observed using Thin-layer chromatography (on SiO_2 gel F254 plates) under standard conditions. The desired compounds were purified through Flash column chromatography packed with silica gel (100-200 meshes size) as the stationary phase and eluting solvent, hexane-ethyl acetate solvent mixture was used as mobile phase. Melting points were determined in open capillary tubes on an EZ-Melt Automated melting point apparatus and are uncorrected. NMR spectra were recorded on a Bruker AV 400 spectrometer. Chemical shifts were reported in parts per million (ppm) using deuterated solvent or tetramethylsilane (TMS) as an internal standard. High-resolution mass spectra (HRMS-ESI) were recorded using quadrupole time-of-flight (Q-TOF) mass spectrometer (Applied Biosystem). All the chemicals were obtained from the commercial supplier and were used without purification.

4.6 Typical procedure for thesynthesis of oxidative dimerized product 14

To a stirred solution of 2-phenylindole **1** (0.5 mmol) in CH_3CN (3.0 mL) was added Lutidine (1.0 mmol), $Cu(OAc)_2$ (30 mol%) and *m*-CPBA (*meta*-chloroperoxybenzoic acid, 0.3 mmol) successively at room temperature. The combined reaction mixture was stirred at the same temperature until TLC confirmed the complete consumption of starting material. Subsequently, the reaction was quenched with H_2O (3.0 mL) and stirred with EtOAc (10 mL). The organic layer was separated, and the aqueous layer was again extracted with EtOAc (5.0 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 anhydrous, and concentrated under reduced pressure. Column chromatography purification through silica gel by eluting the mixture of hexane/EtOAcgave corresponding dimerized product **14** as mainly yellow solid with 67-82% yields.

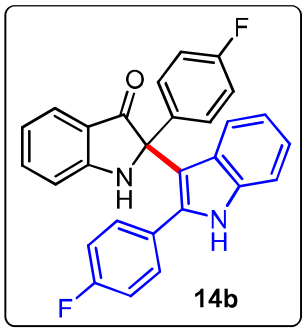
4.7 Characterization data of synthesized compounds (14a-14j)

2-phenyl-2-(2-phenyl-1*H*-indol-3-yl)indolin-3-one (14a) Yellow solid (mg 165, 75% yield, mp = 207-212 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.17 (s, 1H), 6.71 (d, *J* = 8.2 Hz, 1H), 6.80 (t, *J* = 7.7 Hz, 1H), 6.91-6.93 (m, 1H), 7.00 (d, *J* = 8.0 Hz, 1H), 7.10–7.20 (m, 8H), 7.23-7.27 (m, 1H), 7.32 (d, *J* = 8.1 Hz, 1H), 7.40 (d, *J* = 7.7 Hz, 1H), 7.42–7.46 (m, 1H), 7.48-7.51 (m, 2H), 8.11 (s, 1H).^{13}C NMR (100 MHz, $CDCl_3$) δ 72.0, 110.7, 112.0, 112.2, 119.1, 120.0, 120.4, 121.5, 122.3, 125.4 (2C), 127.2 (2C), 127.3, 127.5, 127.6 (2C), 128.2 (2C), 129.7 (2C), 133.2, 135.5, 137.0, 137.1, 140.3, 159.4, 200.3. HRMS (ESI-TOF)*m/z*: Calcd for $C_{28}H_{21}N_2O$ $[M+H]^+$ 401.1654, Found 401.1637.



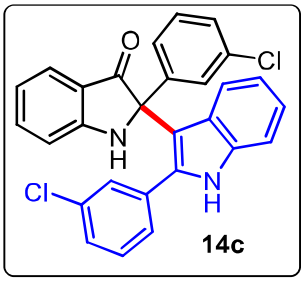
14a

2-(4-fluorophenyl)-2-(2-(4-fluorophenyl)-1H-indol-3-yl)indolin-3-one (14b) Yellow solid (175 mg, 71% yield, mp = 175-180 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.20 (s, 1H), 6.77–6.95 (m, 8H), 7.05 (dd, *J* = 8.8, 5.2 Hz, 2H), 7.14–7.18 (m, 1H), 7.29–7.37 (m, 2H), 7.45–7.51 (m, 3H), 8.16 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 71.3, 110.8, 112.4, 112.6, 114.5, 114.7, 114.9, 115.1, 119.6, 120.2, 120.4, 121.0, 122.6, 125.4, 127.1, 128.9, 128.9, 131.5, 131.6, 135.4, 135.8 (2C), 136.0, 137.4, 159.2, 162.4 (d, *J*= 246 Hz), 162.6 (d, *J* = 246 Hz), 200.1. HRMS (ESI-TOF) *m/z*: Calcd for $C_{28}H_{19}F_2N_2O$ $[M+H]^+$437.1465, Found 437.1445.



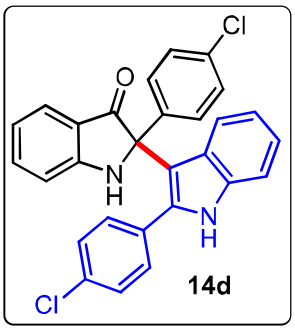
14b

2-(3-Chlorophenyl)-2-(2-(3-Chlorophenyl)-1*H*-indol-3-yl)indolin-3-one (14c) Yellow solid



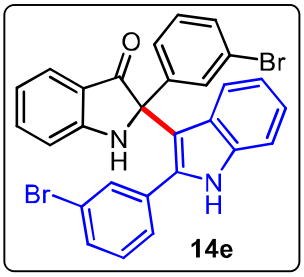
(157 mg, 67% yield, mp = 160-164 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.21 (s, 1H), 6.86–6.91 (m, 2H), 6.94 (d, *J* = 4.0 Hz, 2H), 7.02 (m, 5H), 7.15–7.21 (m, 2H), 7.33 (d, *J* = 8.1 Hz, 1H), 7.38 (dt, *J* = 8.0 Hz, 4.0 Hz, 1H), 7.46 (d, *J* = 7.3 Hz, 1H), 7.50–7.55 (m, 2H), 8.20 (s, 1H).^{13}C NMR (100 MHz, $CDCl_3$) δ 71.3, 111.0, 112.3, 112.6, 120.0, 120.4, 120.4, 120.9, 122.8, 125.4, 125.8, 126.9, 127.1, 127.7, 127.8, 128.4, 128.8, 129.4, 129.9, 133.6, 134.0, 134.5, 135.5, 135.9, 137.7, 141.93, 159.3, 199.9. HRMS (ESI-TOF) Calcd for $C_{28}H_{19}Cl_2N_2O$ *m/z*: $[M+H]^+$ 469.0874, Found 469.0848.

2-(4-chlorophenyl)-2-(2-(4-chlorophenyl)-1*H*-indol-3-yl)indolin-3-one (14d) Yellow solid



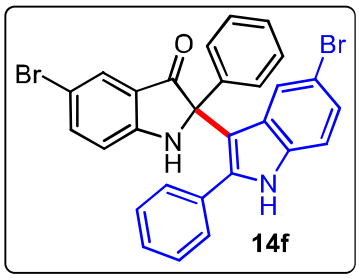
(161 mg, 69% yield, mp = 197–201 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.20 (s, 1H), 6.85–6.93 (m, 3H), 6.95-6.99 (m, 1H), 7.04 (d, *J* = 8.5 Hz, 2H), 7.13 (d, *J* = 8.5 Hz, 2H), 7.17–7.22 (m, 3H), 7.38 (dd, *J* = 13.9, 7.9 Hz, 2H), 7.47 (d, *J* = 8.7 Hz, 2H), 7.50–7.55 (m, 1H), 8.14 (s, 1H).^{13}C NMR (100 MHz, $CDCl_3$) δ 71.40, 110.9, 112.5, 119.7, 120.3, 120.4, 121.0, 122.7, 125.4, 127.1, 127.8 (2C), 128.3 (2C), 128.6 (2C), 131.0 (2C), 131.2, 132.0, 133.6, 134.5, 135.5, 135.8, 137.5, 138.6, 159.2, 199.7. HRMS (ESI-TOF) *m/z*: Calcd for $C_{28}H_{19}Cl_2N_2O$ $[M+H]^+$469.0874,Found 469.0853.

2-(3-bromophenyl)-2-(2-(3-bromophenyl)-1*H*-indol-3-yl)indolin-3-one (14e) Yellow solid



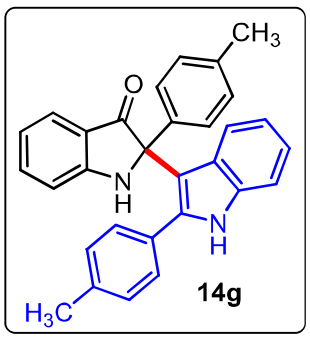
(168 mg, 68% yield, mp = 122–126 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.25 (s, 1H), 6.90–6.93 (m, 2H), 6.97 (d, *J* = 3.9 Hz, 2H), 7.00–7.06 (m, 2H), 7.11 (d, *J* = 7.7 Hz, 1H), 7.17–7.21 (m, 2H), 7.26–7.27 (m, 1H) , 7.33–7.38 (m, 2H), 7.44 (d, *J* = 7.9 Hz, 1H), 7.48 (d, *J* = 7.7 Hz, 1H), 7.53-7.57 (m, 1H), 7.71 (t, *J* = 1.8 Hz, 1H), 8.27 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 71.3, 111.0, 112.3, 112.7, 120.1, 120.3, 120.4, 120.9, 121.8, 122.3, 122.8, 125.5, 126.2, 126.9, 128.1, 129.0, 129.7, 129.9, 130.7, 131.3, 132.7, 134.7, 135.5, 135.9, 137.7, 142.1, 159.3, 199.9. HRMS (ESI-TOF) *m/z*: Calcd for $C_{28}H_{19}Br_2N_2O$ $[M+H]^+$ 556.9864, Found 556.9836.

5-Bromo-2-(5-bromo-2-phenyl-1*H*-indol-3-yl)-2-phenylindolin-3-one (14f) Yellow solid (225 mg, 81% yield, mp = 148–153 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.13 (s, 1H), 6.58 (d, *J* = 8.5 Hz, 1H), 7.04 (d, *J* = 1.4 Hz, 1H), 7.11–7.15 (m, 2H), 7.19–7.25 (m, 7H), 7.29–7.33(m, 1H), 7.41–7.43 (m, 2H), 7.48–7.51 (m, 2H), 8.15 (s, 1H).^{13}C NMR (100 MHz, $CDCl_3$) δ 72.5, 111.2, 111.4, 112.1, 113.3, 113.7, 121.7, 124.0, 125.4, 127.0 (2C), 127.7, 127.9 (2C), 128.1, 128.5 (2C), 128.7, 128.9, 129.6 (2C), 132.6, 134.1, 138.1, 139.5, 139.7, 157.5, 198.6. HRMS (ESI-TOF) *m/z*: Calcd for $C_{28}H_{19}Br_2N_2O$ $[M+H]^+$ 556.9864, Found 556.9836.



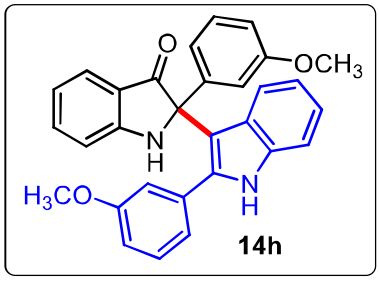
14f

2-(*p*-tolyl)-2-(2-(p-tolyl)-1*H*-indol-3-yl)indolin-3-one (14g) Yellow solid (215 mg, 75% yield, mp = 159-161 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.27 (s, 3H), 2.33 (s, 3H), 5.17 (s, 1H), 6.68 (d, *J* = 8.2 Hz, 1H), 6.78 (t, *J* = 7.4 Hz, 1H), 6.89–7.05 (m, 8H), 7.13 (t, *J* = 8.0 Hz, 1H), 7.28 (d, *J* = 8.1 Hz, 1H), 7.34–7.40 (m, 3H), 7.41–7.45 (m, 1H), 8.10 (s, 1H).^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 21.2, 71.9, 110.6, 111.8, 112.1, 118.8, 119.7, 120.3, 121.6 (2C), 122.1, 125.3, 127.1 (2C), 127.4, 128.3 (2C), 128.9 (2C), 129.5, 130.3, 135.4, 136.9, 137.0, 137.1, 137.4, 137.9, 159.1, 200.4. HRMS (ESI-TOF) *m/z*: Calcd for $C_{30}H_{25}N_2O$ $[M+H]^+$429.1967, Found 429.1961.



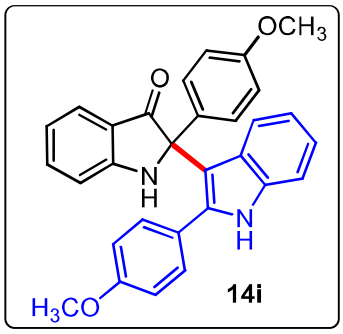
14g

2-(3-Methoxyphenyl)-2-(2-(3-Methoxyphenyl)-1*H*-indol-3-yl)indolin-3-one (14h) Yellow solid (188 mg, 82% yield, mp = 206–210 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.56 (s, 3H), 3.67 (s, 3H), 5.20 (s, 1H), 6.64 (m, 1H), 6.69–6.74 (m, 2H), 6.78–6.83 (m, 3H), 6.94 (t, *J* = 7.3 Hz, 1H), 7.05–7.17 (m, 6H), 7.32 (d, *J* = 8.2 Hz, 1H), 7.42–7.47 (m, 2H), 8.10 (s, 1H).^{13}C NMR (100 MHz, $CDCl_3$) δ 54.9, 55.1, 71.9, 110.6, 111.7, 112.2, 112.8, 113.1, 114.7 (2C), 119.2, 119.7, 120.0, 120.4, 121.50, 121.7, 122.3, 125.3, 127.3, 128.8, 129.1, 134.5, 135.4, 136.9, 137.1, 141.9, 158.6, 159.2, 159.3, 200.1. HRMS (ESI-TOF) *m/z*: Calcd for $C_{30}H_{25}N_2O_3$ $[M+H]^+$ 461.1865, Found 461.1843.

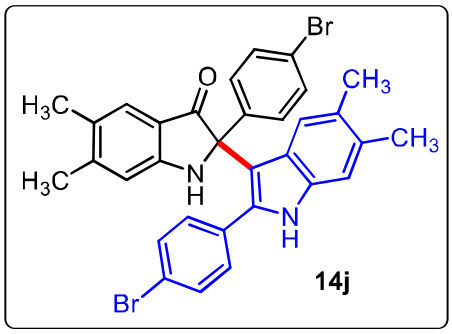


14h

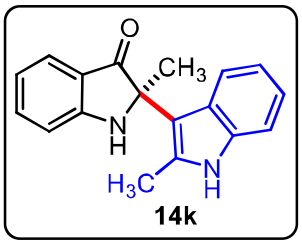
2-(4-Methoxyphenyl)-2-(2-(4-Methoxyphenyl)-1*H*-indol-3-yl)indolin-3-one (14i) Yellow solid (181 mg, 79% yield, mp = 102–105 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.73 (s, 3H), 3.77 (s, 3H), 5.18 (s, 1H), 6.65 (d, *J* = 8.7 Hz, 2H), 6.71–6.74 (m, 3H), 6.78 (t, *J* = 7.2 Hz, 1H), 6.90–6.99 (m, 2H), 7.02 (d, *J* = 8.7 Hz, 2H), 7.11–7.15 (m, 1H), 7.30 (d, *J* = 8.1 Hz, 1H), 7.37–7.46 (m, 4H), 8.07 (s, 1H).^{13}C NMR (100 MHz, $CDCl_3$) δ 55.2, 55.3, 71.6, 110.6, 112.1, 112.2, 113.1 (2C), 113.6 (2C), 119.0, 119.8, 120.5, 121.5, 122.1, 125.4, 125.5, 127.5, 128.4 (2C), 130.9 (2C), 132.4, 135.4, 137.0, 136.8, 159.0, 159.1, 159.5, 200.6. HRMS (ESI-TOF) *m/z*: Calcd for $C_{30}H_{25}N_2O_3$ $[M+H]^+$ 461.1865, Found 461.1851.



2-(4-Bromophenyl)-2-(2-(4-bromophenyl)-5,6-dimethyl-1*H*-indol-3-yl)-5,6-dimethylindolin 3-one (14j) Yellow solid (196 mg 64% yield,mp = 192-195 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.16 (s, 3H), 2.21 (s, 3H), 2.30 (s, 3H), 2.31 (s, 3H), 4.94 (s, 1H), 6.66 (d, *J* = 8.7 Hz 2H), 6.94 (d, *J* = 8.4 Hz, 2H), 7.11 (s, 1H), 7.16 (s, 1H), 7.25 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.7 Hz, 2H), 7.36 (d, *J* = 8.7 Hz, 2H), 7.85 (s, 1H).^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 20.3 (2C), 21.3, 71.7, 111.1, 112.1, 113.4, 118.8, 121.0, 121.5, 122.4, 125.0, 125.4, 126.3, 128.9, 129.0 (2C), 130.6 (2C), 131.1 (2C), 131.3 (2C), 131.9, 132.0, 134.5, 134.9, 139.7, 148.2, 158.5, 199.3. HRMS (ESI-TOF) *m/z*: $[M+H]^+$Calcd for $C_{32}H_{27}Br_2N_2O$ 613.0490, Found 615.0433.



2-methyl-2-(2-methyl-1H-indol-3-yl)indolin-3-one (14k) Yellow solid (145 mg, 71% yield, mp = 151-153°C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.95 (s, 3H), 2.45 (s, 3H), 5.05 (s, 1H), 6.89–6.92 (m, 2H), 6.96–7.00 (m, 1H), 7.07–7.11 (m, 1H), 7.24–7.28 (m, 1H), 7.42 (dd, *J* =8.1, 1.0 Hz, 1H), 7.52-–7.56 (m, 1H), 7.73 (dd, *J* =8.1 Hz, 1.0 Hz, 1H), 7.90(s, 1H).^{13}C NMR (100 MHz, CDCl3) δ 14.6, 25.1, 67.14, 109.5, 110.4, 111.4, 112.4, 119.1, 119.5, 119.7, 121.2, 125.3, 127.4, 132.6, 134.9, 137.4, 159.5, 204.3. HRMS (ESI-TOF) *m/z*: Calcd for $C_{18}H_{17}N_2O$ $[M+H]^+$ 277.1341, Found 277.1334.

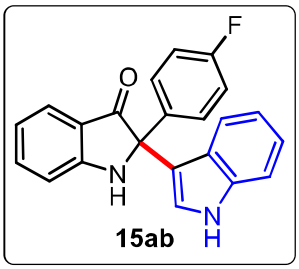


4.8 Typical procedure for the synthesis of 15

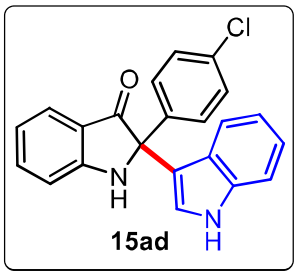
To a stirred solution of 2-phenylindole **1** (0.5 mmol) in CH_3CN (3.0 mL) was added Lutidine (1.0 mmol), $Cu(OAc)_2$ (30 mol%) and *m*-CPBA (0.5mmol) successively, followed by substituted indole **8** (1.1 equiv.) at room temperatureand progress of the reaction was monitored by TLC. Once the reaction was over, it was quenched with water (3.0 mL) and stirred with EtOAc (10 mL). The organic layer was separated, and the aqueous layer was again extracted with EtOAc (5.0 mL). The combined organic extracts were washed with brine and dried over anhydrous Na_2SO_4, followed by concentrated in the vacuum after filtration. Purification through silica-gel column chromatography by eluting the mixture of hexane/EtOAcgave corresponding product **15** as mainly yellow solid with 62-75% yields.

4.9 Characterization data of synthesized compounds (15ab-15bh)

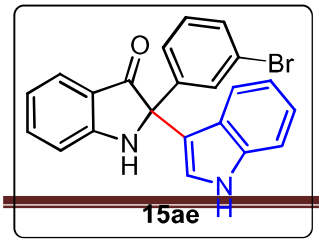
2-(4-Fluorophenyl)-2-(1*H*-indol-3-yl)indolin-3-one (15ab) Yellow solid (114 mg, 67% yield, mp = 206-210 ºC).^{1}H NMR (400 MHz, $CDCl_3$) δ 5.36 (s, 1H) 6.90–7.06 (m, 5H), 7.15–7.13 (m, 3H), 7.41 (d, *J* = 8.2 Hz, 1H), 7.50–7.60 (m, 3H), 7.72 (d, *J* = 7.7 Hz, 1H), 8.20 (s, 1H).^{13}C NMR (100 MHz, $CDCl_3$) δ 70.7, 111.7, 113.0, 115.1, 115.3, 115.5, 119.5 (2C), 119.9, 120.2, 122.7, 123.6, 125.46, 125.6, 128.5, 128.6, 135.3, 136.9, 137.6(2C), 160.5, 200.3. HRMS (ESI-TOF)*m/z*: Calcd for $C_{22}H_{16}FN_2O$ $[M+H]^+$ 343.1246, Found 343.1236.



2-(4-Chlorophenyl)-2-(1*H*-indol-3-yl)indolin-3-one (15ad) Yellow solid(118 mg, 66% yield, mp = 123-126ºC). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.35 (s, 1H), 6.91 (t, *J* = 8.2 Hz, 2H), 6.98–7.03 (m, 1H), 7.12–7.13 (m, 2H), 7.17–7.21 (m, 1H), 7.24–7.26 (m, 2H), 7.37 (d, *J* = 8.2 Hz, 1H), 7.49–7.53 (m, 3H), 7.69 (d, *J* = 7.7 Hz, 1H), 8.26 (s, 1H).^{13}C NMR (100 MHz, $CDCl_3$) δ 70.7, 111.7, 113.1, 115.1, 119.4 (2C), 119.9, 120.1, 122.6, 123.6, 125.3, 125.6, 128.2(2C), 128.5(2C), 133.6, 136.9, 137.7, 138.1, 160.5, 200.1. HRMS (ESI-TOF)*m/z*: Calcd for $C_{22}H_{16}ClN_2O$ $[M+H]^+$ 359.0951, Found 359.0951.

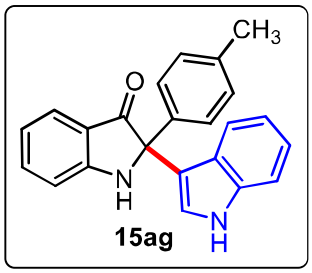


2-(3-Bromophenyl)-2-(1*H*-indol-3-yl)indolin-3-one (15ae) Yellow solid (137 mg, 68% yield, mp = 135-138 ºC). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.38 (s, 1H), 6.92–9.97 (m, 2H),7.01–7.05 (m, 1H),7.15–7.23 (m, 4H), 7.38–7.44 (m, 2H), 7.48–7.52 (m, 1H), 7.52-7.56 (m, 1H), 7.72 (d, *J* = 7.7 Hz, 1H),

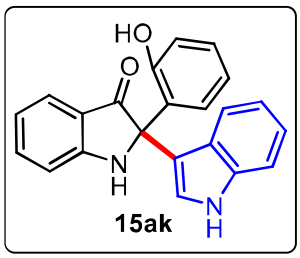


7.81 (t, *J* = 3.6 Hz, 1H),8.30 (s, 1H).^{13}C NMR (100 MHz, $CDCl_3$) δ 70.7, 111.8, 113.2, 115.0, 119.4, 119.4, 120.0, 120.2, 122.5, 122.7, 123.7, 125.3, 125.6, 126.0, 129.4, 130.0, 130.8, 136.9, 137.8, 142.0, 160.5, 199.9. HRMS (ESI-TOF)*m/z*: Calcd for $C_{22}H_{16}BrN_2O$ $[M+H]^+$403.0446, Found 403.0441.

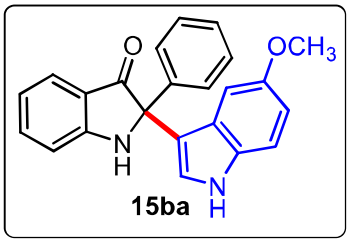
2-(1H-indol-3-yl)-2-(p-tolyl)indolin-3-one (15ag) Yellow solid (122 mg, 69% yield, mp = 103-107°C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.31 (s, 3H), 5.39 (s, 1H), 6.86–6.91 (m, 2H), 6.95–7.01 (m, 1H), 7.09–7.11 (m, 3H), 7.14-7.19 (m, 2H), 7.34 (d, *J* = 8.1 Hz, 1H), 7.43 (d, *J* = 8.2 Hz, 2H), 7.47-751 (m, 1H), 7.69 (d, *J* = 7.3 Hz, 1H), 8.29 (s, 1H).^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 71.2, 111.7, 112.8, 115.5, 119.5, 119.5, 119.8, 119.9, 122.4, 123.8, 125.6 (2C), 126.7 (2C), 129.2 (2C), 136.5, 136.9, 137.4, 137.5, 160.5, 200.9. HRMS(ESI-TOF)*m/z*: Calcd for $C_{23}H_{18}N_2O[M+H]^+$ 339.1497, Found 339.1492.



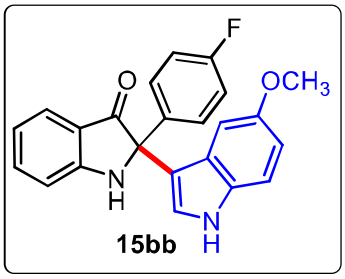
2-(2-Hydroxyphenyl)-2-(1*H*-indol-3-yl)indolin-3-one(15ak) Yellow solid (105 mg, 62% yield, mp = 107-111 °C).^{1}H NMR (400 MHz, $CDCl_3$) δ 2.08 (s, 1H), 5.42 (s, 1H), 6.90–7.01 (m, 6H),7.09 (d, *J* = 7.9 Hz, 1H),7.12–7.16 (m, 1H),7.23–7.31 (m, 2H), 7.56-7.60 (m, 1H), 7.71 (dd, *J* = 7.9 Hz, 1.6 Hz, 1H), 7.76 (d, *J* = 7.8 Hz, 1H), 8.39 (s, 1H).^{13}C NMR (100 MHz, $CDCl_3$) δ 71.6, 111.8, 113.4, 113.7, 118.8, 119.0, 120.1, 120.2, 120.7, 124.0, 124.5, 124.9,125.6,128.1, 129.9, 136.8, 138.7,156.0, 160.1, 171.3, 204.0. HRMS (ESI-TOF)*m/z*: Calcd for $C_{22}H_{17}N_2O_2$ $[M+H]^+$341.1290, Found 341.1286.



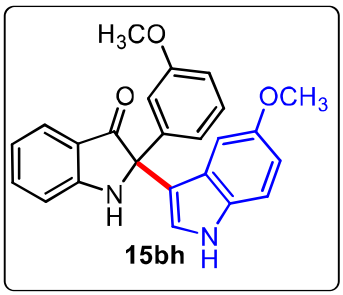
2-(5-Methoxy-1*H*-indol-3-yl)-2-phenylindolin-3-one (15ba) Yellow solid (128 mg, 72% yield, mp = 91-94°C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.63 (s, 3H), 5.39 (s, 1H), 6.58 (d, *J* = 2.2 Hz, 1H), 6.85 (dd, *J* = 8.8 Hz, 2.4 Hz, 1H), 6.92 (t, *J* = 7.4 Hz, 1H), 6.96 (d, *J* = 8.2 Hz, 1H),7.12 (d, *J* = 2.6 Hz, 1H), 7.26–7.34 (m, 4H), 7.51–7.55 (m, 1H),7.62 (dd, *J* = 8.0 Hz, 1.5 Hz, 2H), 7.72 (d, *J* = 7.7 Hz, 1H),8.14 (s, 1H).^{13}C NMR (100 MHz, $CDCl_3$) δ 55.5, 71.2, 101.8, 112.3, 112.3, 112.8, 115.4, 119.6, 119.7, 124.4, 125.5, 126.0, 126.84 (2C), 127.7, 128.4 (2C), 131.9, 137.5, 139.3, 154.2, 160.5, 200.1. HRMS (ESI-TOF)*m/z*: Calcd for $C_{23}H_{19}N_2O_2[M+H]^+$ 355.1446, Found 355.1429.



2-(4-Fluorophenyl)-2-(5-methoxy-1*H*-indol-3-yl)indolin-3-one (15bb) Yellow solid (137 mg, 74% yield, mp = 201-204°C).[1]H NMR (400 MHz, $CDCl_3$) δ 3.65 (s, 3H), 5.37 (s, 1H), 6.55 (d, *J* = 2.3 Hz, 1H), 6.85 (dd, *J* = 8.8 Hz, 2.4 Hz, 1H), 6.91–7.03 (m, 4H), 7.09 (d, *J* = 2.6 Hz, 1H), 7.27 (d, *J* = 9.6 Hz, 1H), 7.52-7.60 (m, 3H), 7.72 (d, *J* = 7.7 Hz, 1H), 8.19 (s, 1H). [13]C NMR (100 MHz, $CDCl_3$) δ 55.6, 70.7, 101.7, 112.3, 112.4, 113.1, 115.1, 115.2, 115.3, 119.7, 119.9, 124.4, 125.5, 125.9, 128.6, 128.7, 132.0, 135.1, 137.7, 154.1, 160.5, 162.5 (d, *J* = 246 Hz),200.6. HRMS (ESI-TOF)*m/z*: Calcd for $C_{23}H_{18}FN_2O_2[M+H]^+$ 373.1352, Found 373.1334.



2-(5-Methoxy-1*H*-indol-3-yl)-2-(3-methoxyphenyl)indolin-3-one (15bh) Yellow solid (140 mg, 75% yield, mp = 91-95°C). [1]H NMR (400 MHz, $CDCl_3$) δ 3.62 (s, 3H), 3.74 (s, 3H), 5.32 (s, 1H), 6.59 (d, *J* = 2.4 Hz, 1H), 6.80–6.84 (m, 2H), 6.89 (t, *J* = 7.7 Hz, 1H), 6.93 (d, *J* = 8.2 Hz, 1H), 7.11 (d, *J* = 2.7 Hz, 1H), 7.16–7.21 (m, 2H), 7.23–7.25 (m, 1H), 7.27 (s, 1H) 7.48–7.52 (m 1H), 7.69 (d, *J* = 7.7 Hz, 1H), 8.01 (s, 1H).[13]C NMR (100 MHz, $CDCl_3$) δ 55.2, 55.6, 71.1, 101.9, 112.2, 112.3, 112.8 (2C), 112.9, 115.5, 119.3, 119.6, 119.9, 124.4, 125.5, 126.0, 129.3, 131.9, 137.4, 141.0, 154.0, 159.6, 160.4, 200.4. HRMS (ESI-TOF)*m/z*: Calcdfor $C_{24}H_{21}N_2O_3$ $[M+H]^+$385.1552, Found 385.1535.



4.10 Representative ^{1}H and ^{13}C NMR of **(14g and 15ag)** are shown in **(Figure 4.2 and 4.3)**.

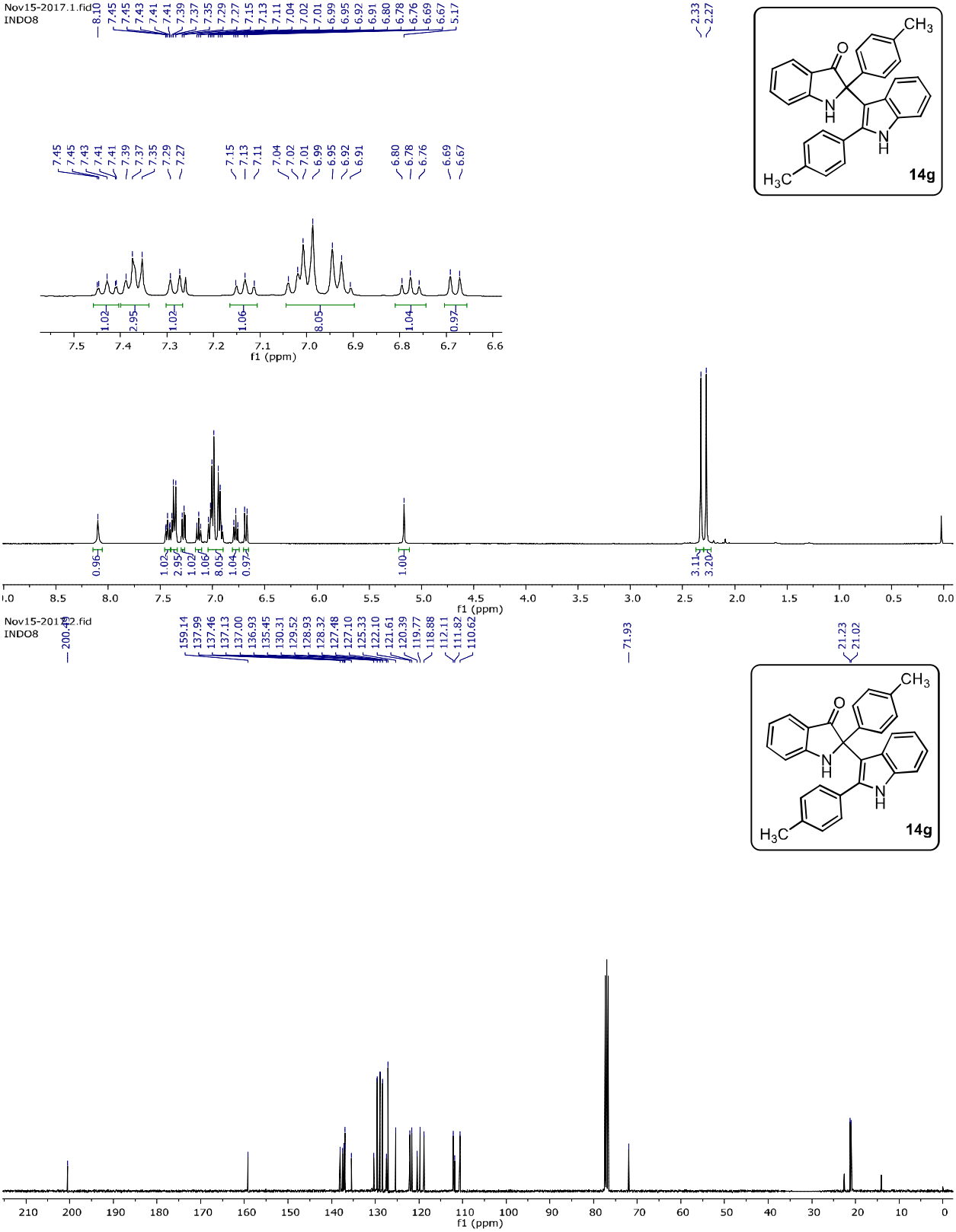


Figure 4.2 ^{1}H and ^{13}C NMR spectra of 2-(p-tolyl)-2-(2-(p-tolyl)-1H-indol-3-yl)indolin-3-one **(14g)**

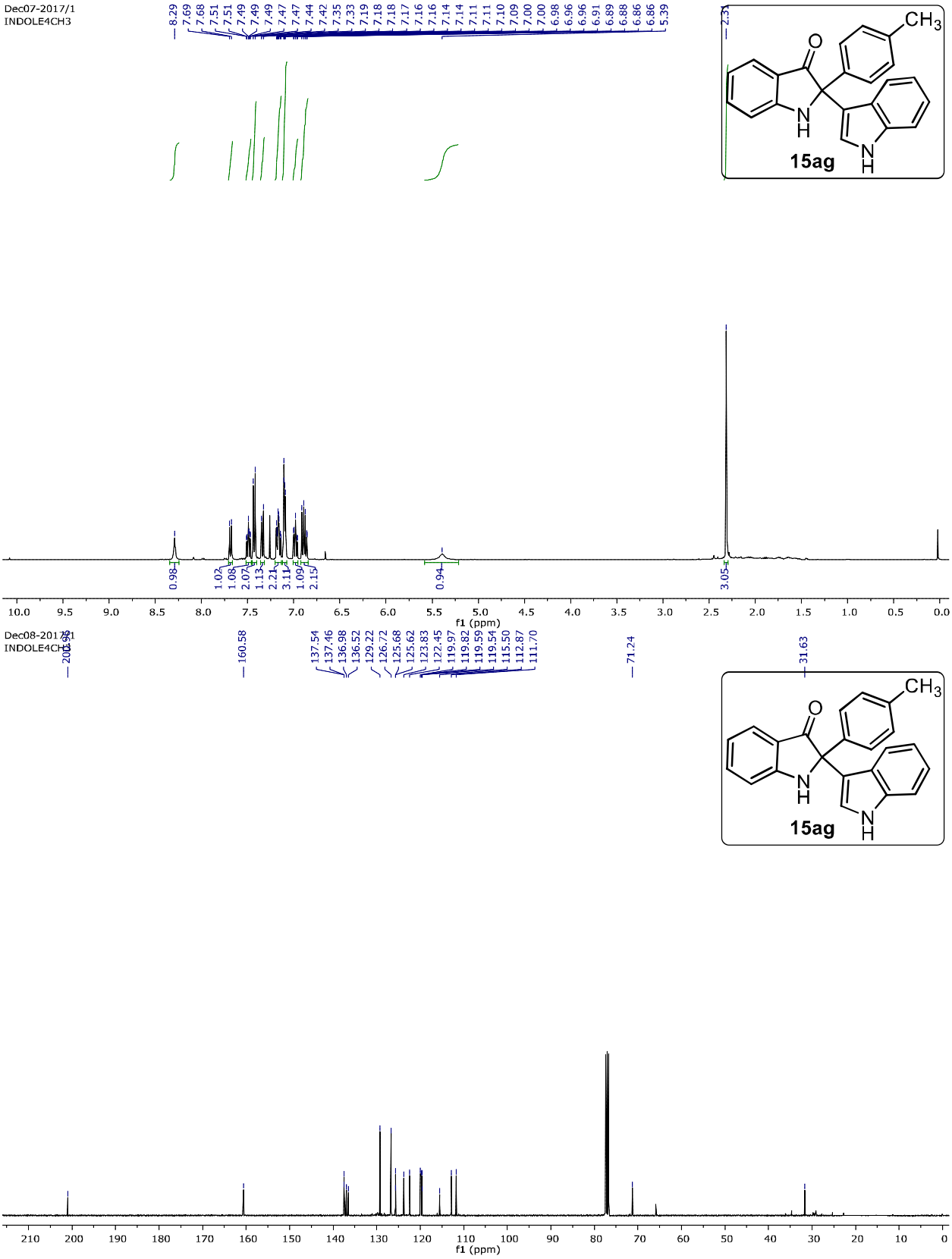
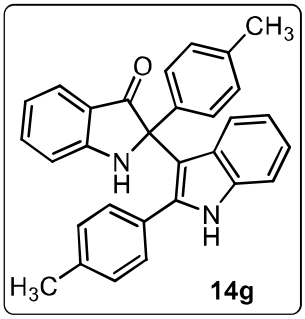


Figure 4.3^{1}H and ^{13}C NMR spectra of 2-(1H-indol-3-yl)-2-(p-tolyl)indolin-3-one **(15ag)**

4.11 Crystal structure determination of 14g

Crystal structure of 2-(*p*-tolyl)-2-(2-(p-tolyl)-1*H*-indol-3-yl)indolin-3-one (14g)

(CCDC No.1832862) Single crystals of2-(*p*-tolyl)-2-(2-(p-tolyl)-1*H*-indol-3-yl)indolin-3-one



($C_{61}H_{49}Cl_3N_4O_2$) was selected on aXtaLAB Pro: Kappa dual offset/far diffractometer. The crystal was kept at 93(2) K during data collection. Using Olex2, the structure was solved with the ShelXT structure solution program using Intrinsic Phasing and refined with the ShelXL refinement package using Least Squares minimization.

Crystal Data for $C_{61}H_{49}Cl_3N_4O_2$ (M =976.39 g/mol): triclinic, space group P-1 (no. 2), a = 13.13930(10) Å, b = 14.65600(10) Å, c = 15.47680(10) Å, α = 110.2300(10)°, β = 91.2620(10)°, γ = 108.1490(10)°, V = 2629.10(4) Å^3, Z = 2, T = 93(2) K, μ(CuKα) = 1.943 mm^{-1}, *Dcalc* = 1.233 g/cm^3, 28497 reflections measured (7.156° ≤ 2Θ ≤ 149.04°), 10338 unique (R_{int} = 0.0246, R_{sigma} = 0.0226) which were used in all calculations. The final R_1 was 0.0623 (I >2σ(I)) and wR_2 was 0.1867 (all data).

Table 4.4 Crystal data and structure refinement for 14g

Identification code	**CCDC No.1832862**
Empirical formula	$C_{61}H_{49}Cl_3N_4O_2$
Formula weight	976.39
Temperature/K	93(2)
Crystal system	triclinic
Space group	P-1
a/Å	13.13930(10)
b/Å	14.65600(10)

c/Å	15.47680(10)
α/°	110.2300(10)
β/°	91.2620(10)
γ/°	108.1490(10)
Volume/Å^3	2629.10(4)
Z	2
ρ_{calc}g/cm^3	1.233
μ/mm^{-1}	1.943
F(000)	1020.0
Crystal size/mm^3	0.2 × 0.2 × 0.1
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	7.156 to 149.04
Index ranges	-15 ≤ h ≤ 16, -18 ≤ k ≤ 18, -19 ≤ l ≤ 13
Reflections collected	28497
Independent reflections	10338 [R_{int} = 0.0246, R_{sigma} = 0.0226]
Data/restraints/parameters	10338/0/635
Goodness-of-fit on F^2	1.069
Final R indexes [I>=2σ (I)]	R_1 = 0.0623, wR_2 = 0.1847
Final R indexes [all data]	R_1 = 0.0645, wR_2 = 0.1867
Largest diff. peak/hole / e Å^{-3}	0.49/-0.84

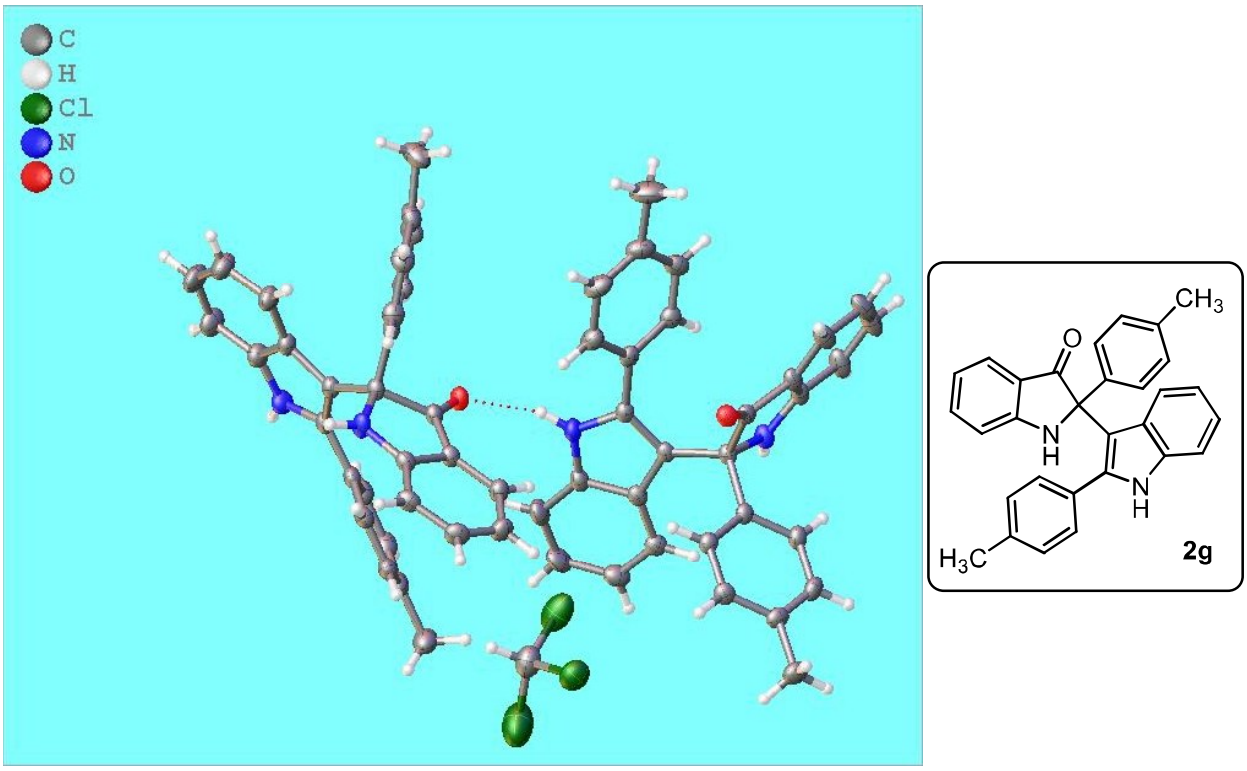


Figure 4.4 Single-crystal X-ray of **14g (CCDC No.1832862)**. The thermal ellipsoids are drawn at the 50% probability level. The compound was crystalized with $CHCl_3$.

4.12 Notes and references:

[1] Lee, J. H.; So, J.-H.; Jeon, J. H.; Choi, E. B.; Lee, Y.-R.; Chang, Y.-T.; Kim, C.-H.; Bae, M. A.; Ahn, J. H. *Chem. Commun*. **2011**, *47*, 7500.

[2] Parra, A.; Alfaro, R.; Marzo, L.; Moreno-Carrasco, A.; GarcíaRuano, J. L.; Alemán, J. *Chem. Commun*. **2012**, *48*, 9759.

[3] Kong, L.; Wang, M.; Zhang, F.; Xu, M.; Li, Y. *Org. Lett*. **2016**, *18*, 6124.

[4] Li, Y.-J.; Yan, N.; Liu, C.-H.; Yu, Y.; Zhao, Y.-L. *Org. Lett*. **2017**, *19*, 1160.

[5] Liu, J.-F.; Jiang, Z.-Y.; Wang, R.-R.; Zeng, Y.-T.; Chen, J.-J.; Zhang, X.-M.; Ma,Y.-B. *Org. Lett.* **2007**, *9*, 4127.

[6] Tan, C.-J.; Di, Y.-T.; Wang, Y.-H.; Zhang, Y.; Si, Y.-K.; Zhang, Q.; Gao, S.; Hu, X.-J.; Fang, X.; Li, S.-F.; Hao, X.-J. *Org. Lett*. **2010,** *12*, 2370.

[7] Kumar, C. V. S.; Puranik, V. G.; Ramana, C. V. *Chem. Eur. J*. **2012**, *18*, 9601.

[8] Abe, T.; Kukita, A.; Akiyama, K.; Naito, T.; Uemura, D. *Chem. Lett.* **2012**, *41*,728.

[9] Gu, W.; Zhang, Y.; Hao, X.-J.; Yang, F. M.; Sun, Q.-Y.; Morris-Natschke, S. L.; Lee, K.-H.; Wang, Y.-H.; Long, C.-L. *J. Nat. Prod*. **2014,** *77*, 2590.

[10] Lee, J.; Panek, J. S. *Org. Lett*. **2011**, *13*, 502.

[11] Wyrembak, P. N.; Hamilton, A. D. *J. Am. Chem. Soc*. **2009**, *131*, 4566.

[12] Matsumoto, S.; Samata, D.; Akazome, M.; Ogura, K. *Tetrahedron Lett*. **2009**, *50*, 111.

[13] Goriya, Y.; Ramana, C. V. *Chem. Commun*. **2013**, *49*, 6376.

[14] Wetzel, A.; Gagosz, F. *Angew. Chem., Int. Ed*. **2011**, *50*, 7354.

[15] Li, N.; Wang, T. Y.; Gong, L. Z.; Zhang, L. *Chem. Eur. J*. **2015**, *21*, 3585.

[16] Liu, R. R.; Ye, S. C.; Lu, C. J.; Zhuang, G. L.; Gao, J. R.; Jia, Y. X. *Angew. Chem., Int. Ed*. **2015**, *54*, 11205.

[17] Marien, N.; Luo, T.; Verniest, G. *Synlett*. **2017**, *28*, 934.

[18] Fu, W.; Song, Q. *Org. Lett*. **2018**, *20*, 393.

[19] Patel, P.; Ramana, C. V. *Org. Biomol. Chem*. **2011**, *9*, 7327.

[20] Zhou, P. X.; Zhou, Z. Z.; Chen, Z. S.; Ye, Y. Y.; Zhao, L. B.; Yang, Y. F.; Xia, X. F.; Luo, J. Y.; Liang, Y. M. *Chem. Commun*. **2013**, *49*, 561.

[21] Zhang, X. X.; Li, P.; Lyu, C.; Yong, W. X.; Li, J.; Pan, X. Y.; Zhu, X. B.; Rao, W. D. *Adv. Synth.Catal*. **2017**, *359*, 4147.

[22] Zhang, T.; Qi, Z.; Zhang, X.; Wu, L.; Li, X. *Chem. Eur. J*. **2014**, *20*, 3283.

[23] Kuppusamy, R.; Gandeepan, P.; Cheng, C. H. *Org. Lett*. **2015**, *17*, 3846.

[24] Mothe, S. R.; Novianti, M. L.; Ayers, B. J.; Chan, P. W. H. *Org. Lett*. **2014**, *16*, 4110.

[25] Xia, Z.; Hu, J.; Gao, Y. Q.; Yao, Q.; Xie, W. *Chem. Commun*. **2017**, *53*, 7485.

[26] Lerch, S.; Unkel, L.-N.; Brasholz, M. *Angew. Chem. Int. Ed*. **2014**, *53*, 6558.

[27] Ding, W.; Zhou, Q.-Q.; Xuan, J.; Li, T.-R.; Lu, L.-Q.; Xiao, W.-J. *Tetrahedron Lett*. **2014**, *55*, 4648.

[28] Bu, L.; Li, J.; Yin, Y.; Qiao, B.; Chai, G.; Zhao, X.; Jiang, Z. *Chem. Asian. J*. **2018**, *13*, 2382.

[29] Liu, Y.; Jr. McWhorter, W. W. *J. Org. Chem*. **2003,** *68*, 2618.

[30] Higuchi, K.; Sato, Y.; Kojima, S.; Tsuchimochi, M.; Sugiura, K.; Hatori, M.; Kawasaki, T. *Tetrahedron.* **2010**, *66*, 1236.

[31] Li, L.-Q.; Han, M.-Y.; Xiao, M.-X.; Xie, Z.-X. *Synlett*. **2011**, 12, 1727.

[32] Rueping, M.; Raja, S.; Nuñez, A. *Adv. Synth. Catal*. **2011**, 353, 563.

[33] Yin, Q.; You, S.-L. *Chem. Sci*. **2011**, *2*, 1344.

[34] Rueping, M.; Rasappan, R.; Raja, S. *Helvetica Chimica Acta*. **2012**, 95, 2296.

[35] Nakamura, S.; Matsuda, N.; Ohara, M. *Chem. Eur. J*. **2016**, *22*, 9478.

[36] Li, J.-S.; Liu, Y.-J.; Li, S.; Ma, J.-A. *Chem. Commun*. **2018**, *54*, 9151.

[37] Ling, K.-Q. *Synth. Commun*. **1995**, *25*, 3831.

[38] Liu, Y.; Jr. McWhorter, W. W. *J. Am. Chem. Soc*. **2003**, *125*, 4240.

[39] Liu, Q.; Chen, P.; Liu, G. *ACS Catal*. **2013**, *3*, 178.

[40] Najahi, E.; Valentin, A.; Fabre, P.-L.; Reybier, K.; Nepveu, F. *Eur. J. Med. Chem*. **2014**, *78*, 269.

[41] Kong, Y.-B.; Zhu, J.Y.; Chen, Z.-W.; Liu, L.-X. *Can. J. Chem.* **2014**, *92*, 269.

[42] Lin, F.; Chen, Y.; Wang, B.; Qin, W.; Liu, L. *RSC Adv.* **2015**, *5*, 37018.

[43] Guchhait, S. K.; Chaudhary, V.; Rana, V. A.; Priyadarshani, G.; Kandekar, S.; Kashyap, M. *Org. Lett*. **2016**, *18*, 1534.

[44] Jiang, X.; Zhu, B.; Lin, K.; Wang, G.; Su, W.-K.; Yu, C. *Org. Biomol. Chem*. **2019**, *17*, 2199.

[45] For review, see S. E. Allen, R. R. Walvoord, R. Padilla-Salinas, and M. C. Kozlowski, *Chem. Rev*. **2013**, *113*, 6234.

[46] Wendlandt, W. A.; Suess, A. M.; Stahl, S. S. *Angew. Chem., Int. Ed*. **2011**, *50*, 11062.

[47] Liu, Y.; Wan, J.-P. *Org. Biomol. Chem*. **2011**, *9*, 6873.

[48] Yamashita, M.; Iida, A. *Tetrahedron Letters*. **2014**, *55*, 2991.

[49] Yamashita, M.; Nishizono, Y.; Himekawa, S.; Iida, A. *Tetrahedron*. **2016**, *72*, 4123.

[50] The X-ray crystallographic structure for **14g** has been deposited at the Cambridge Crystallographic Data Centre (CCDC), under deposition numbers (CCDC 1832862).