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Cooperative *N*-heterocyclic carbene (NHC)/Lewis acid-mediated regioselective umpolung formal [3+2] annulations of alkynyl aldehydes with isatins

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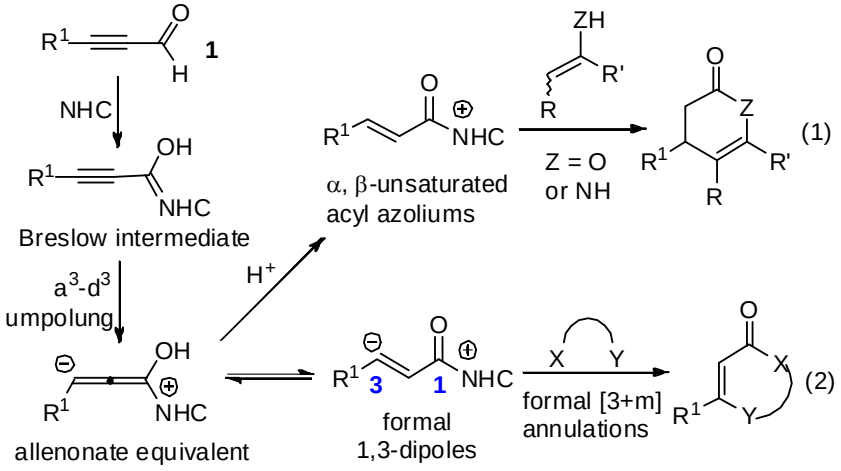
A novel and regioselective umpolung synthesis of spirooxindoles has been developed by cooperative NHC/Lewis acid-mediated formal [3+2] annulations of alkynyl aldehydes with isatins. In most cases, the reactions proceeded via a^3-d^3 umpolung of alkynyl aldehydes resulting in spirooxindole butenolides. In few cases, spirooxindole furan-3(2*H*)-ones were formed as major products via a^1-d^1 umpolung process by controlling the reaction temperature. These newly formed spirooxindoles could provide promising candidates for chemical biology and drug lead discovery.

N-Heterocyclic carbenes (NHCs) are efficient organocatalysts which can promote a large number of umpolung transformations of different types of aldehydes.[1] The most-investigated NHC-catalyzed umpolung reactions are involved in a^1-d^1 umpolung of aldehydes (such as Benzoin condensation[2] and Stetter reaction[3]) and a^3-d^3 umpolung of enals[4] which have offered unconventional access to a variety of organic molecules with diverse skeletons. In recent years, alkynyl aldehydes **1** have emerged as novel substrates applied in NHC-catalyzed reactions (Scheme 1). Following the pioneering work of redox esterification of alkynyl aldehydes **1**,[5] much emphasis has been laid on the application of α,β-unsaturated acyl azoliums generated from the sequential a^3-d^3 umpolung of Breslow intermediate[6] and β-protonation of allenonate equivalent (eq. 1, Scheme 1).[7] In contrast, few attention has been paid to NHC-catalyzed β -nucleophilic additions of allenonate intermediate which could be potentially employed as formal 1,3-dipoles to undergo formal [3+m] annulations (eq.

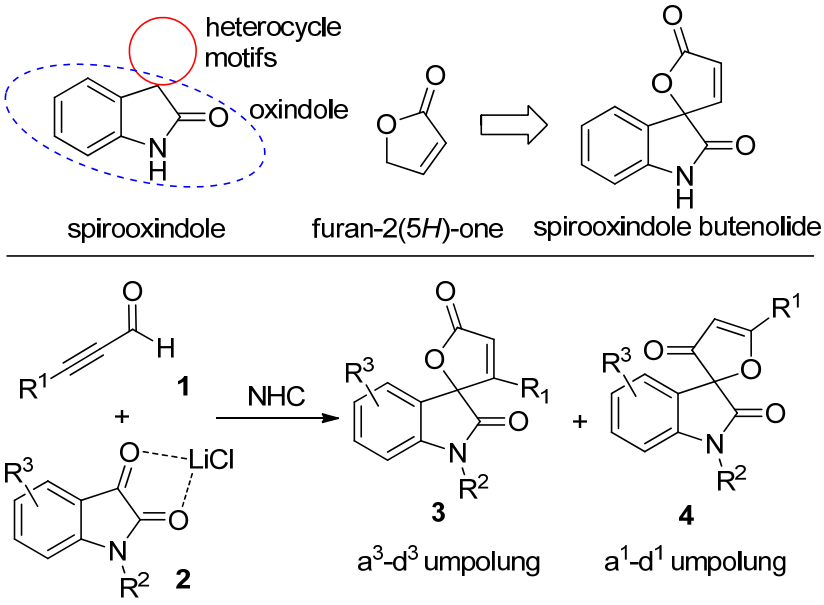
2, Scheme 2). Until recently, She[8] and Snyder[9] reported a^3-d^3 umpolung annulations of alkynyl aldehydes with ketones[8a, 9] and nitrosobenzenes[8b] respectively by a cooperative NHC/Lewis acid catalysis strategy[10] which has proved critical for some transformations. However, it is still in demand to further explore novel a^3-d^3 umpolung annulations of alkynyl aldehydes.



Scheme 1 Two reaction modes of alkynyl aldehydes with NHC catalysis.

Spirooxindoles[11] represent interesting and attractive frameworks for synthesis owing to their biological activities and applications for drug lead discovery. Most spirooxindoles are characterized by a spiro fusion at the 3-position of oxindole ring with diverse heterocycle motifs (Scheme 2). Furan-2-(5*H*)-one is a privileged heterocyclic structure existing in various natural products with a broad range of biological activities.[12] Thus, fusion of oxindole core with furan-2-(5*H*)-one motif could give rise to spirooxindole butenolides which may provide promising candidates for chemical biology and drug lead discovery. However, the synthesis of spirooxindoles butenolides is still a challenge and only a few protocols have been documented.[13] Since isatins[13d, 14] are usually used as privileged molecules in design and synthesis of spiro-fused cyclic compounds due to the highly reactive C-3 carbonyl group, we envisioned that the cooperative NHC/Lewis acid-catalyzed umpolung annulations of alkynyl aldehydes **1** with isatins **2** might afford spirooxindoles butenolides. Actually, two regioisomers **3** and **4** via two different umpolung processes (a^3-d^3 and a^1-d^1) were observed (Scheme 2). Nevertheless, regioselective a^3-d^3 umpolung of alkynyl aldehydes could be achieved in most cases by controlling the

reaction conditions and *N*-substituents of isatins **2**. In few cases, a^1-d^1 umpolung products could also be obtained as major products by lowering the reaction temperature. As a continuation of our exploration of NHC-catalyzed chemistry of alkynyl aldehydes to synthesize diverse heterocycles,[7d, 7h] we herein wish to report the regioselective umpolung formal [3+2] annulations of alkynyl aldehydes **1** with isatins **2** for the synthesis of spirooxindoles **3** and **4**.

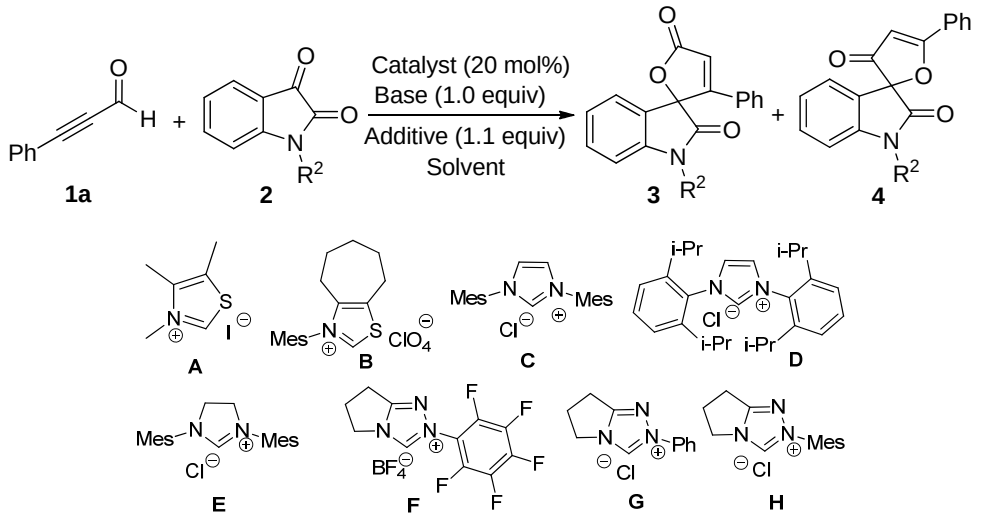


Scheme 2 The cooperative NHC/Lewis acid-catalyzed umpolung annulations of alkynyl aldehydes **1** with isatins **2**

Our explorations began with examining the efficiency of several carbene precursors **A**-**H** for the reaction of 3-phenylpropioaldehyde **1a** with N-Bn substituted isatin **2a** (Table 1). The reaction did not work at all in the presence of NHCs derived from precursors **A**-**G** even if LiCl was used as a Lewis acid (entry 1). Fortunately, a mixture of a^3-d^3 umpolung product **3a** and a^1-d^1 umpolung product **4a** was obtained in lower combined yield when carbene precursor **H** was employed in the presence of LiCl (entry 3). Subsequent screening of various bases showed that DIPEA was the optimal one resulting in 43% yield and high regioselectivity (entries 4-8). However, further examination of a variety of Lewis acids and solvents failed to improve the yield and regioselectivity (entries 9-14). At this point, we assumed that *N*-substituents of isatins **2** might have certain impact on the yield and regioselectivity. We then tried other three different *N*-substituted isatins **2b**-**d** (entries 15-18). Surprisingly, the

reaction of *N*-Me substituted isatin **2d** with **1a** in 1,4-dioxane at 40℃exclusively afforded a^3-d^3 umpolung product **3d** in 75% yield which was finally established as our optimal reaction conditions for following substrate scope exploration (entry18). The structure of the products was established by spectroscopic analysis and further confirmed by X-ray crystallography of **3d** (Figure 1). [15]

Table 1 Optimization of the reaction conditions and evaluation of *N*-substituents of isatins **2**[a]



Entry	R^2, **2**	Cat.	Base	Sol.	Add.	Temp. (^{o}C)	Time (h)	Yield of **3**, **4** (%)[b]
1	Bn, **a**	**A-G**	DBU	THF	none or LiCl	40	10	**a**, 0, 0
2	Bn, **a**	**H**	DBU	THF	none	40	8	**a**, 0, 0
3	Bn, **a**	**H**	DBU	THF	LiCl	40	1	**a**, 10, 21
4	Bn, **a**	**H**	*t*BuOK	THF	LiCl	40	1.5	**a**, <10, 37
5	Bn, **a**	**H**	*t*BuOLi	THF	LiCl	40	1.5	**a**, <10,34
6	Bn, **a**	**H**	Cs_2CO_3	THF	LiCl	40	21	**a**, 14,19
7	Bn, **a**	**H**	Et_3N	THF	LiCl	40	3	**a**, 42, 0
8	Bn, **a**	**H**	DIPEA	THF	LiCl	40	2	**a**, 43, 0
9	Bn, **a**	**H**	DIPEA	THF	$LiBF_4$	40	40	**a**, 0, 0
10	Bn, **a**	**H**	DIPEA	THF	Mg(*t*BuO)$_2$	40	4	**a**, 15, 15
11	Bn, **a**	**H**	DIPEA	THF	Ti(*i*PrO)$_4$	40	7	**a**, 11, 0
12	Bn, **a**	**H**	DIPEA	DCM	LiCl	40	5	**a**, 26, <10
13	Bn, **a**	**H**	DIPEA	DMF	LiCl	40	7.5	**a**, 15, 39
14	Bn, **a**	**H**	DIPEA	1,4-dioxane	LiCl	65	24	**a**, 37, 0
15	Bz, **b**	**H**	DIPEA	THF	LiCl	25	1.5	**b**, <10, 0
16	Boc, **c**	**H**	DIPEA	THF	LiCl	25	1	**c**, <10, 0
17	Me, **d**	**H**	DIPEA	THF	LiCl	40	24	**d**, 38, 15
18	*Me, **d***	***H***	*DIPEA*	*1,4-dioxane*	*LiCl*	*40*	*24*	***d**, 75, 0*

[a] All reactions were performed on a 0.3 mmol scale with 2.5 equiv. of **1a**, 1.0 equiv. of **2**, 20 mol % of a carbene precursor, 1.0 equiv. of a base, 1.1 equiv. of an additive and 200 mg of 4 Å MS in 0.1 M in a solvent under N_2. [b] Isolated yield based on **2**. DBU = 1,8-diazabicyclo[5.4.0]-undec-7-ene; Mes = 2,4,6-$(CH_3)_3C_6H_2$; DIPEA = *N*,*N*-diisopropylethylamine.

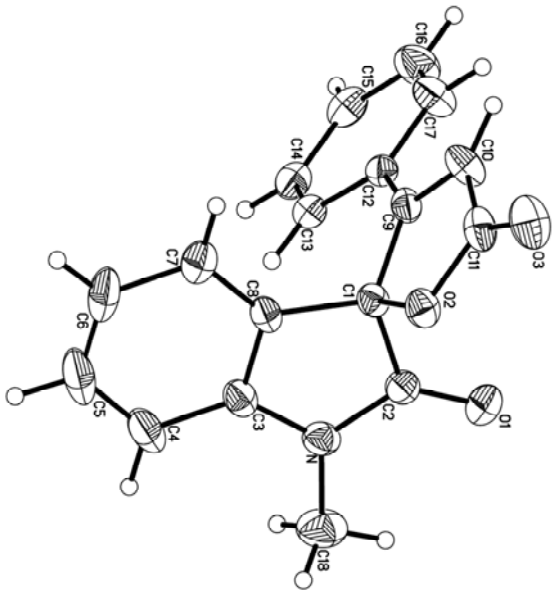
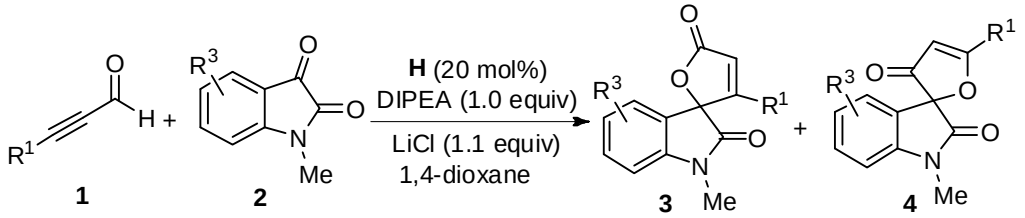


Figure 1 X-ray crystal structure of **3d**.

After establishing the optimized conditions, we focused on expansion of the reaction scope (Table 2). Firstly, the variation of isatins **2** was evaluated. A wide range of isatins **2** except **2m** were found suitable for the a^3-d^3 umpolung [3+2] annulations to get spirooxindole butenolides **3e-l** in 30-90% yield at 40℃ or 65℃ (entries 2-10). In few cases, spirooxindoles **4f-h** and **4j** formed via a^1-d^1 umpolung pathway were obtained as major products by lowering the reaction temperature to 10℃ (entries 3-5 and entry 7). Subsequently, a variety of alkynyl aldehydes **1** were tested to evaluate the generality of this protocol. Alkynyl aldehydes **1b-g** with substituents at 3- or 4-positions of phenyl rings were tolerant to the reaction, only affording a^3-d^3 umpolung products in 41-83% yield (entries 11-16). The reaction of 3-(2-chlorophenyl)propiolaldehyde **1h** did not work perhaps owing to the steric effect of hindered 2-Cl group (entry 17). Surprisingly, 3-heteroaromatic-substituted alkynyl

aldehyde **1i** and 3-aliphatic-substituted alkynyl aldehyde **1j** were also subject to a^3-d^3 umpolung process in moderate yield (entries 18-19).

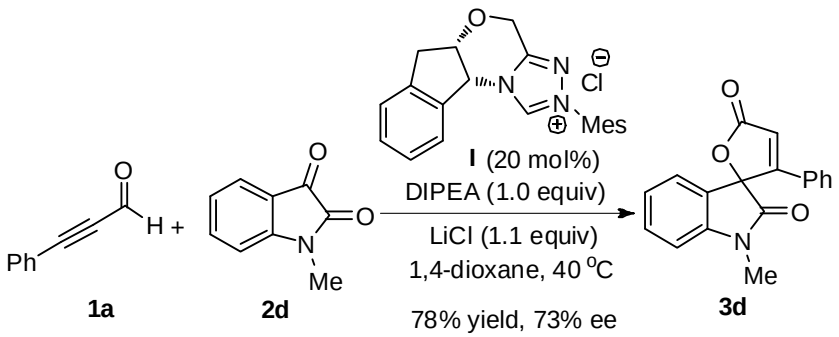
Table 2 Scope of the reaction [a]



Entry	R^1, **1**	R^3, **2**	T (℃)	Time (h)	Yield of **3**, **4** (%)[b, c]
1	Ph, **a**	H, **d**	40	24	**d**, 75, 0
2	Ph, **a**	4-Cl, **e**	65	48	**e**, 90, 0
3	Ph, **a**	5-F, **f**	65	10	**f**, 67, 0 (<10, 45)
4	Ph, **a**	5-Cl, **g**	65	12	**g**, 53, 15 (<5, 47)
5	Ph, **a**	5-Br, **h**	40	7	**h**, 30, 33 (0, 42)
6	Ph, **a**	5-Me, **i**	65	24	**i**, 47[d], 0
7	Ph, **a**	6-Cl, **j**	65	10	**j**, 63, 0 (<10, 46)
8	Ph, **a**	7-Me, **k**	65	72	**k**, 37, 0
9	Ph, **a**	7-Cl, **l**	65	2	**l**, 40, 14
10	Ph, **a**	4,6-Me_2, **m**	65	20	**m**, trace, 0
11	(4-Me)Ph, **b**	H, **d**	65	20	**n**, 71, 0
12	(4-OMe)Ph, **c**	H, **d**	10	72	**o,** 42, 0
13	(4-F)Ph, **d**	H, **d**	65	20	**p**, 33, 0
14	(4-Cl)Ph, **e**	H, **d**	40	48	**q**, 63, 0
15	(3-Me)Ph, **f**	H, **d**	65	30	**r**, 83, 0
16	(3-Cl)Ph, **g**	H, **d**	65	72	**s**, 41[e], 0
17	(2-Cl)Ph, **h**	H, **d**	40	24	**t**,trace, 0
18	2-furyl, **i**	H, **d**	10	26	**u**, 56, 0
19	$Ph(CH_2)_2$, **j**	H, **d**	10	48	**v**, 58, 0

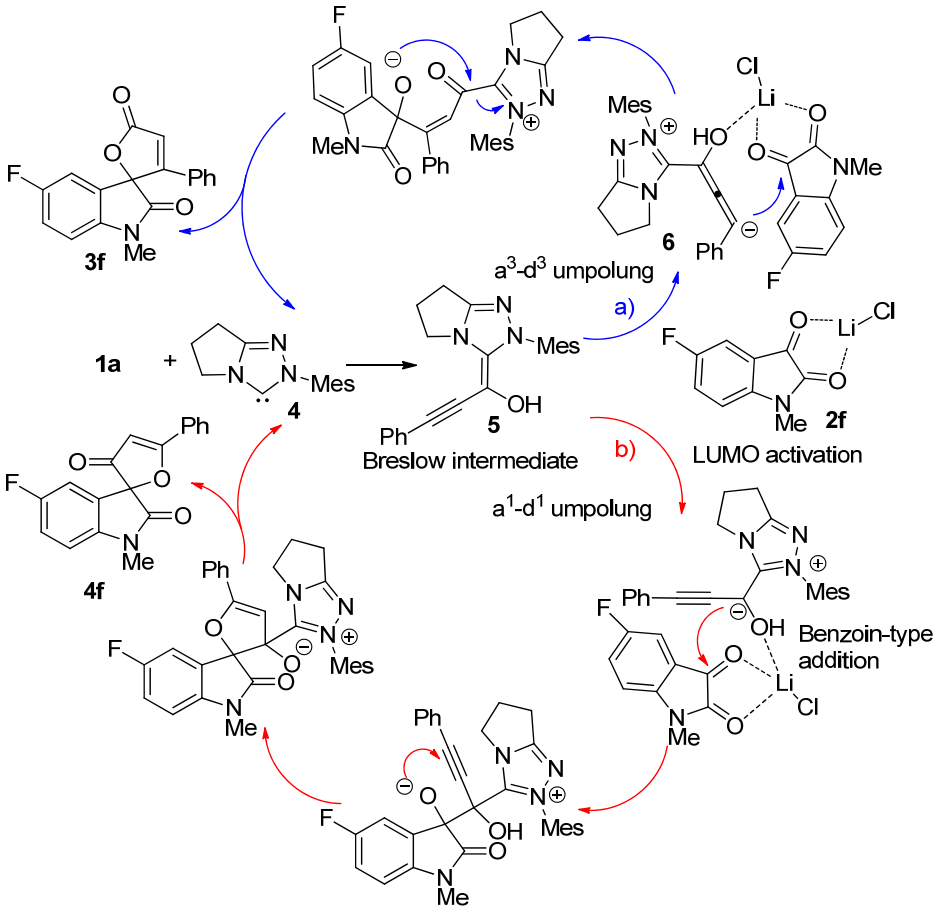
[a] All reactions were performed on a 0.3 mmol scale with 2.5 equiv. of **1**, 1.0 equiv. of **2**, 20 mol % of **H**, 1.0 equiv. of DIPEA, 1.1 equiv. of LiCl and 200 mg of 4 Å MS in 0.1 M in 1,4-dioxane, under N_2. [b] Isolated yield based on **2**. [c] Isolated yield in the parentheses was obtained under 10℃. [d] 70% conversion, [e] 61% conversion.

Preliminary enantioselective studies of the formal [3+2] annulation between alkynyl **1a** and isatin **2d** has also been undertaken using **I** as the chiral carbene precursors, and a^3-d^3 umpolung product **3d** was obtained as the single regioisomer in 78% yield with a promising 73% e.e. value (Scheme 3).



Scheme 3 Preliminary enantioselective studies of the annulation of alkynyl **1a** and isatin **2d**.

A plausible mechanism for the regioselective umpolung annulations is proposed based on the model reaction of alkynyl aldehyde **1a** with isatin **2f**. Initially, NHC **4** was generated upon deprotonation of carbene precursor **H** with DIPEA followed by addition to alkynyl **1a** to produce Breslow intermediate **5**. Coordination of LiCl with isatin **2f** enhanced the electrophility of 3-carbonyl of **2f** by lowering LUMO energy. This alkali metal salt effect has been observed to promote new C-C bond formation in many NHC-catalyzed reactions.[8a, 10b] For a^3-d^3 umpolung process (path a), concurrent coordination of LiCl to isatin **2f** and Breslow intermediate facilitated the nucleophilic addition of β-carbon anion of allenolate equivalent to the activated carbonyl as shown in **6**. Subsequent intramolecular cyclization afforded the formal [3+2] adduct **3f** accompanied with release of NHC **4** for next catalytic cycle. For a^1-d^1 umpolung process (path b), the annulation occurred via Benzoin-type addition of Breslow intermediate to the carbonyl of **2f**, followed by intramolecular Michael addition and release of NHC **4** to give product **4f**.



Scheme 4 Proposed mechanism for the regioselective umpolung annulation of alkynyl aldehyde **1a** and isatin **2f**.

In summary, we have described regioselective umpolung formal [3+2] annulations of alkynyl aldehydes **1** with isatins **2** to give spirooxindole butenolides **3** in moderate to high yields via a^3-d^3 umpolung process. In few cases, a^1-d^1 umpolung spirooxindoles **4** could be obtained as major products in moderate yields by controlling the reaction temperature. Further investigation on an enantioselective synthesis of this protocol and exploration of new chemistry of alkynyl aldehydes are currently underway.

Experimental section

General Methods. All reactions were carried out under an atmosphere of nitrogen in dry glassware, and were monitored by analytical thin-layer chromatography (TLC), which was visualized by ultraviolet light (254 nm). All solvents were obtained from commercial sources and were purified according to standard procedures. Purification of the products was accomplished by flash chromatography using silica gel (200~300

mesh). All NMR spectra were recorded with a spectrometer at 300 MHz or 500 MHz (^{1}H NMR) in $CDCl_3$: chemical shifts (δ) are given in ppm, coupling constants (J) in Hz, the solvent signals were used as references (residual $CHCl_3$ in $CDCl_3$: δ_H = 7.26 ppm, δ_c = 77.0 ppm). The e.e. value was determined by chiral HPLC.

General experimental procedure

To an oven-dried 25 mL three-necked glassware was charged with alkynyl aldehyde **1** (0.75 mmol), isatin **2** (0.3 mmol), LiCl (14 mg, 0.33 mmol), carbene precursor **H** (16 mg, 0.06 mmol) and 200 mg of 4 Å MS. Then THF (3 mL) was added followed by addition of DIPEA (39 mg, 0.3 mmol). The resulting mixture was stirred at certain temperature under nitrogen atmosphere for a period of time. After completion of the reaction as monitored by TLC, the mixture was cooled to room temperature. The solvent was evaporated under reduced pressure and the residue was purified by chromatography on silica gel to afford the products **3** and **4**.

3a. White solid, MP: 140-141℃. ^{1}H NMR (500M, $CDCl_3$): δ 6.88-7.33 (m, 14H), 6.65 (s, 1H), 5.12 and 4.76 (2×d, J = 14.4 Hz, 2H). ^{13}C NMR (125M, $CDCl_3$): δ 171.2, 170.0, 163.1, 143.5, 134.7, 131.8, 131.4, 129.1, 128.9, 128.1, 127.6, 125.1, 123.9, 123.8, 116.9, 110.4, 86.5, 44.6. HRMS (ESI) calcd for $C_{24}H_{18}NO_3$ $(M+H)^+$: 368.1281, found 368.1283. IR (KBr): ν 3089, 3062, 1768, 1733, 1610, 1489, 1359, 1298, 1240, 1186, 1026 cm^{-1}.

4a. White solid, MP: 227-228℃. ^{1}H NMR (300M, $CDCl_3$): δ 7.96 (d, J = 7.3 Hz, 2H), 7.53-7.67 (m, 3H), 7.04-7.39 (m, 8H), 6.79 (d, J = 7.8 Hz, 1H), 6.24 (s, 1H), 5.07 and 4.89 (2×d, J = 15.9 Hz, 2H). ^{13}C NMR (75M, $CDCl_3$): δ 196.8, 187.9, 169.1, 144.3, 134.7, 133.4, 131.1, 128.9, 128.1, 127.8, 127.6, 127.1, 123.9, 123.8, 123.4, 110.2, 100.4, 89.3, 44.3. HRMS (ESI) calcd for $C_{24}H_{18}NO_3$ $(M+H)^+$: 368.1281, found 368.1283. IR (KBr): ν 3128, 2921, 1729, 1693, 1605, 1564, 1488, 1340, 1168, 1046 cm^{-1}.

3d. White solid, MP: 194-195℃. ^{1}H NMR (300M, $CDCl_3$): δ 7.46 (m, 1H), 7.36 (m,

1H), 7.24-7.29 (m, 2H), 7.08-7.20 (m, 4H), 6.99 (d, J = 7.8 Hz, 1H), 6.66 (s, 1H), 3.31 (s, 3H). ^{13}C NMR (75M, $CDCl_3$): δ 171.2, 169.9, 162.9, 144.4, 131.9, 131.5, 129.2, 128.9, 126.9, 125.0, 124.0, 123.8, 116.9, 109.5, 86.4, 27.1. HRMS (ESI) calcd for $C_{18}H_{14}NO_3$ $(M+H)^+$: 292.0968, found 292.0967. IR (KBr): v 3127, 2932, 1775, 1727, 1611, 1574, 1493, 1470, 1448, 1422, 1368, 1348, 1303, 1235, 1200, 1136, 1099, 1058, 1006 cm^{-1}.

3e. White solid, MP: 196-197℃. ^{1}H NMR (300M, $CDCl_3$): δ 6.86-7.35 (m, 8H), 6.66 (s, 1H), 3.27 (s, 3H). ^{13}C NMR (75M, $CDCl_3$): δ 170.9, 169.3, 162.0, 145.9, 133.0, 132.9, 131.4, 129.2, 129.0, 126.5, 124.8, 120.5, 118.3, 107.7, 86.0, 27.3. HRMS (ESI) calcd for $C_{18}H_{13}ClNO_3$ $(M+H)^+$: 326.0578, found 326.0583. IR (KBr): v 3188, 2874, 1767, 1731, 1609, 1461, 1335, 1241, 1199, 1124, 1011 cm^{-1}.

3f. White solid, MP: 173-175℃. ^{1}H NMR (300M, $CDCl_3$): δ 7.14-7.35 (m, 8H), 6.66 (s, 1H), 3.30 (s, 3H). ^{13}C NMR (75M, $CDCl_3$): δ 170.7, 169.7, 162.4, 159.6 (d, $J_{C\text{-}F}$ = 243.0 Hz, 1C), 140.3, 131.6, 129.3, 128.6, 126.8, 118.3 (d, $J_{C\text{-}F}$ = 23.0 Hz, 1C), 116.9, 113.1 (d, $J_{C\text{-}F}$ = 25.0 Hz, 1C), 110.3, 110.2, 85.9, 27.2. HRMS (ESI) calcd for $C_{18}H_{13}FNO_3$ $(M+H)^+$: 310.0874, found 310.0876. IR (KBr): v 3145, 2987, 1772, 1735, 1614, 1492, 1270, 1206 cm^{-1}.

4f. White solid, MP: 159-160℃. ^{1}H NMR (300M, $CDCl_3$): δ 7.90 (d, J = 7.3 Hz, 2H), 7.62 (m, 1H), 7.50-7.55 (m, 2H), 7.13 (m, 1H), 6.93 (m, 1H), 6.87 (m, 1H), 6.14 (s, 1H), 3.19 (s, 3H). ^{13}C NMR (75M, $CDCl_3$): δ 196.2, 187.9, 168.5, 159.3 (d, $J_{C\text{-}F}$ = 241.0 Hz, 1C), 141.2, 133.5, 128.9, 127.8, 127.5, 124.9 (d, $J_{C\text{-}F}$ = 8.3 Hz, 1C), 117.5 (d, $J_{C\text{-}F}$ = 24.0 Hz, 1C), 112.2 (d, $J_{C\text{-}F}$ = 25.5 Hz, 1C), 109.9 (d, $J_{C\text{-}F}$ = 7.5 Hz, 1C), 100.3, 88.8, 26.9. HRMS (ESI) calcd for $C_{18}H_{13}FNO_3$ $(M+H)^+$: 310.0874, found 310.0876. IR (KBr): v 2956, 2922, 2852, 1734, 1700, 1608, 1569, 1493, 1382, 1270, 1162, 1105, 1046 cm^{-1}.

3g. White solid, MP: 197-198℃. ^{1}H NMR (300M, $CDCl_3$): δ 7.31-7.39 (m, 2H), 7.20-7.24 (m, 2H), 7.06-7.11 (m, 3H), 6.86 (d, J = 8.5 Hz, 1H), 6.60 (s, 1H), 3.25 (s, 3H). ^{13}C NMR (75M, $CDCl_3$): δ 170.7, 169.6, 162.3, 142.9, 131.9, 131.6, 129.5, 129.4, 128.6, 126.9, 125.4, 117.1, 110.5, 85.8, 27.3. HRMS (ESI) calcd for $C_{18}H_{13}ClNO_3$ $(M+H)^+$: 326.0578, found 326.0583. IR (KBr): v 3182, 3050, 2841, 1779, 1732, 1610, 1488, 1338, 1229, 1104, 1007, 928 cm^{-1}.

4g. White solid, MP: 186-187℃. ^{1}H NMR (300M, $CDCl_3$): δ 7.88-7.90 (m, 2H), 7.61 (m, 1H), 7.50-7.55 (m, 2H), 7.39 (dd, J = 8.2, 2.2 Hz, 1H), 7.15 (d, J = 2.2 Hz, 1H), 6.86 (d, J = 8.5 Hz, 1H), 6.21 (s, 1H), 3.26 (s, 3H). ^{13}C NMR (75M, $CDCl_3$): δ 196.2, 188.3, 168.2, 143.6, 133.8, 131.2, 129.1, 128.8, 128.0, 127.6, 125.2, 124.6, 110.2, 100.4, 88.6, 27.1. HRMS (ESI) calcd for $C_{18}H_{13}ClNO_3$ $(M+H)^+$: 326.0578, found 326.0582. IR (KBr): v 3192, 3089, 2856, 1737, 1688, 1604, 1567, 1491, 1451, 1348, 1106 cm^{-1}.

3h. White solid, MP: 207-208℃. ^{1}H NMR (300M, $CDCl_3$): δ 7.52 (dd, J = 8.3, 2.0 Hz, 1H), 7.34 (m, 1H), 7.20-7.24 (m, 3H), 7.05-7.08 (m, 2H), 6.81 (d, J = 8.5 Hz, 1H), 6.60 (s, 1H), 3.24 (s, 3H).^{13}C NMR (75M, $CDCl_3$): δ 170.6, 169.5, 162.6, 143.4, 134.8, 131.8, 129.3, 128.7, 128.2, 126.9, 125.8, 117.2, 116.6, 110.9, 85.9, 27.3. HRMS (ESI) calcd for $C_{18}H_{13}BrNO_3$ $(M+H)^+$: 370.0073, found 370.0079. IR (KBr): v 3156, 3088, 3892, 1733, 1688, 1604, 1565, 1488, 1374, 1172, 1103 cm^{-1}.

4h. White solid, MP: 201-202℃. ^{1}H NMR (300M, $CDCl_3$): δ 7.81-7.84 (m, 2H), 7.55 (m, 1H), 7.43-7.49 (m, 3H), 7.21 (d, J = 1.6 Hz, 1H), 6.75 (d, J = 8.4 Hz, 1H), 6.14 (s, 1H), 3.18 (s, 3H). ^{13}C NMR (75M, $CDCl_3$): δ 196.2, 188.0, 168.4, 144.3, 134.1, 133.6, 129.1, 127.9, 127.6, 127.2, 125.5, 115.9, 110.6, 100.4, 88.6, 26.9. HRMS (ESI) calcd for $C_{18}H_{13}BrNO_3$ $(M+H)^+$: $C_{18}H_{13}BrNO_3$, found 370.0075. IR (KBr): v 3155, 2898, 1774, 1734, 1608, 1486, 1336, 1288, 1103, 1006 cm^{-1}.

3i. White solid, MP: 194-195℃. ^{1}H NMR (300M, $CDCl_3$): δ 7.13-7.36 (m, 6H), 6.99 (m, 1H), 6.87 (m, 1H), 6.64 (s, 1H), 3.28 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (75M, $CDCl_3$): δ 171.2, 169.9, 162.9, 141.9, 133.9, 132.2, 131.4, 129.2, 128.9, 127.0, 125.7, 123.8, 116.8, 109.2, 86.5, 27.1, 20.9. HRMS (ESI) calcd for $C_{19}H_{16}NO_3$ $(M+H)^+$: 306.1125, found 306.1128. IR (KBr): ν 3167, 2886, 1779, 1726, 1611, 1498, 1347, 1202, 1105, 1005 cm^{-1}.

3j. White solid, MP: 197-198℃. ^{1}H NMR (300M, $CDCl_3$): δ 7.31-7.39 (m, 2H), 7.20-7.23 (m, 2H), 7.05-7.10 (m, 3H), 6.86 (d, J = 8.3 Hz, 1H), 6.60 (s, 1H), 3.25 (s, 3H). ^{13}C NMR (75M, $CDCl_3$): δ 170.7, 169.3, 162.3, 142.7, 131.9, 131.6, 129.5, 129.3, 128.7, 126.9, 125.5, 117.1, 110.4, 85.7, 27.2. HRMS (ESI) calcd for $C_{18}H_{13}ClNO_3$ $(M+H)^+$: 326.0578, found 326.0581. IR (KBr): ν 3175, 2902, 1779, 1732, 1610, 1488, 1337, 1228, 1104, 1006 cm^{-1}.

4j. White solid, MP: 184-185℃. ^{1}H NMR (300M, $CDCl_3$): δ 7.88-7.91(m, 2H), 7.62 (m, 1H), 7.50-7.55 (m, 2H), 7.39 (dd, J = 8.5, 2.0 Hz, 1H), 7.16 (d, J = 1.8 Hz, 1H), 6.86 (d, J = 8.5 Hz, 1H), 6.21 (s, 1H), 3.26 (s, 3H). ^{13}C NMR (75M, $CDCl_3$): δ 196.2, 188.0, 168.5, 143.9, 133.6, 131.2, 129.1, 128.8, 127.9, 127.6, 125.2, 124.5, 110.2, 100.3, 88.7, 27.0. HRMS (ESI) calcd for $C_{18}H_{13}ClNO_3$ $(M+H)^+$: 326.0578, found 326.0582. IR (KBr): ν 3088, 2875, 1736, 1685, 1607, 1567, 1489, 1346, 1173, 1104, 1047 cm^{-1}.

3k. White solid, MP: 189-190℃. ^{1}H NMR (300M, $CDCl_3$): δ ^{13}C NMR (75M, $CDCl_3$): δ 7.25-7.38 (m, 3H), 7.12-7.18 (m, 3H), 6.92-6.99 (m, 2H), 6.62 (s, 1H), 3.54 (s, 3H). ^{13}C NMR (75M, $CDCl_3$): δ 171.2, 170.6, 162.9, 141.9, 135.6, 131.3, 129.1, 128.9, 126.9, 124.2, 123.9, 122.8, 121.1, 116.8, 85.9, 30.4, 18.9. HRMS (ESI) calcd for $C_{19}H_{16}NO_3$ $(M+H)^+$: 306.1125, found 306.1129. IR (KBr): ν 3183, 2856, 1762, 1716, 1617, 1449, 1359, 1198, 1114, 1043 cm^{-1}.

3l. White solid, MP: 165-167℃. ^{1}H NMR (300M, $CDCl_3$): δ 7.31-7.38 (m, 4H), 7.00-7.14 (m, 4H), 6.65 (s, 1H), 3.66 (s, 3H). ^{13}C NMR (75M, $CDCl_3$): δ 170.7, 170.2, 162.5, 140.3, 134.1, 131.6, 129.3, 128.6, 126.9, 126.4, 124.7, 123.5, 117.1, 116.7, 85.5, 30.5. HRMS (ESI) calcd for $C_{18}H_{13}ClNO_3$ $(M+H)^+$: 326.0578, found 326.0582. IR (KBr): ν 3249, 2912, 1759, 1731, 1610, 1463, 1336, 1205, 1115, 1051 cm^{-1}.

3n. White solid, MP: 181-182℃. ^{1}H NMR (300M, $CDCl_3$): δ 7.44 (t, J = 7.8 Hz, 1H), 7.15 (d, J = 7.5 Hz, 1H), 6.96-7.09 (m, 6H), 6.59 (s, 1H), 3.27 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (75M, $CDCl_3$): δ 171.4, 170.0, 162.8, 144.3, 142.1, 131.8, 129.9, 126.9, 126.0, 124.9, 123.9, 115.8, 109.3, 86.2, 27.0, 21.3. HRMS (ESI) calcd for $C_{19}H_{16}NO_3$ $(M+H)^+$: 306.1125, found 306.1128. IR (KBr): ν 3188, 2895, 1762, 1733, 1607, 1467, 1364, 1235, 1190, 1000 cm^{-1}.

3o. White solid, MP: 200-201℃. ^{1}H NMR (300M, $CDCl_3$): δ 7.45 (m, 1H), 6.98-7.17 (m, 5H), 6.76 (d, J = 8.4 Hz, 2H), 6.53 (s, 1H), 3.75 (s, 3H), 3.30 (s, 3H). ^{13}C NMR (75M, $CDCl_3$): δ 171.5, 170.1, 162.3, 162.1, 144.3, 131.8, 128.7, 124.9, 124.2, 124.0, 121.2, 114.6, 114.3, 109.4, 86.0, 55.3, 27.0. HRMS (ESI) calcd for $C_{19}H_{16}NO_4$ $(M+H)^+$: 322.1074, found 322.1078. IR (KBr): ν 3185, 2885, 1763, 1725, 1607, 1511, 1269, 1190, 1005 cm^{-1}.

3p. White solid, MP: 190-191℃. ^{1}H NMR (500M, $CDCl_3$): δ 7.52 (t, J = 7.7 Hz, 1H), 7.23 (d, J = 7.3 Hz, 1H), 7.15-7.18 (m, 3H), 6.99-7.04 (m, 3H), 6.65 (s, 1H), 3.35 (s, 3H). ^{13}C NMR (75M, $CDCl_3$): δ 170.9, 169.8, 164.3 (d, $J_{C\text{-}F}$ = 252.2 Hz, 1C), 161.6, 144.3, 132.1, 129.2, 129.1, 124.9, 124.1, 123.5, 116.8, 116.5 (d, $J_{C\text{-}F}$ = 21.9 Hz, 1C), 109.5, 86.2, 27.0. HRMS (ESI) calcd for $C_{18}H_{13}FNO_3$ $(M+H)^+$: 310.0874, found 310.0880. IR (KBr): ν 3165, 2927, 1752, 1722, 1612, 1508, 1368, 1239, 1208, 1006 cm^{-1}.

3q. White solid, MP: 165-166℃. ^{1}H NMR (300M, $CDCl_3$): δ 7.46 (m, 1H), 6.97-7.25 (m, 7H), 6.63 (s, 1H), 3.29 (s, 3H). ^{13}C NMR (75M, $CDCl_3$): δ 170.8, 169.7, 161.5,

144.3, 137.7, 132.1, 129.5, 128.2, 127.3, 125.0, 124.1, 123.4, 117.4, 109.5, 86.2, 27.1. HRMS (ESI) calcd for $C_{18}H_{13}ClNO_3$ $(M+H)^+$: 326.0578, found 326.0585. IR (KBr): *v* 3168, 3087, 2887, 1757, 1609, 1468, 1346, 1234, 1202, 1098, 1004 cm^{-1}.

3r. White solid, MP: 165-166℃. ^1H NMR (300M, $CDCl_3$): *δ* 7.45 (m, 1H), 6.96-7.15 (m, 6H), 6.81 (d, *J* = 6.6 Hz, 1H), 6.62 (s, 1H), 3.29 (s, 3H), 2.23 (s, 3H). ^{13}C NMR (75M, $CDCl_3$): *δ* 171.3, 169.9, 163.1, 144.3, 138.9, 132.2, 131.9, 129.0, 127.8, 124.9, 124.0, 123.8, 116.6, 109.3, 86.3, 27.0, 21.3. HRMS (ESI) calcd for $C_{19}H_{16}NO_3$ $(M+H)^+$: 306.1125, found 306.1128. IR (KBr): *v* 3136, 2895, 1771, 1727, 1610, 1470, 1356, 1193, 1006 cm^{-1}.

3s. White solid, MP: 157-158℃. ^1H NMR (300M, $CDCl_3$): *δ* 7.47 (m, 1H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.08-7.21 (m, 4H), 6.93-7.00 (m, 2H), 6.64 (s, 1H), 3.29 (s, 3H). ^{13}C NMR (75M, $CDCl_3$): *δ* 170.7, 169.6, 161.4, 144.3, 135.2, 132.2, 131.3, 130.6, 130.5, 127.1, 124.9, 124.8, 124.2, 123.2, 118.2, 109.5, 86.3, 27.1. HRMS (ESI) calcd for $C_{18}H_{13}ClNO_3$ $(M+H)^+$: 326.0578, found 326.0582. IR (KBr): *v* 3145, 3068, 2890, 1773, 1727, 1612, 1471, 1347, 1101, 1008 cm^{-1}.

3u. White solid, MP: 174-175℃. ^1H NMR (300M, $CDCl_3$): *δ* 7.33-7.40 (m, 2H), 7.21 (m, 1H), 7.05 (m, 1H), 6.84 (d, *J* = 7.2 Hz, 1H), 6.69 (m, 1H), 6.14 (s, 1H), 3.45 (s, 1H), 3.22 (s, 3H). ^{13}C NMR (75M, $CDCl_3$): *δ* 171.5, 156.9, 144.6, 143.4, 139.8, 130.5, 125.7, 123.7, 123.1, 119.8, 117.5, 108.5, 83.9, 72.7, 70.1, 26.4. HRMS (ESI) calcd for $C_{16}H_{11}NNaO_4$ $(M+Na)^+$: 304.0580, found 304.0587. IR (KBr): *v* 3258, 3146, 2879, 1726, 1616, 1493, 1371, 1293, 1216, 1140, 1009 cm^{-1}.

3v. White solid, MP: 137-138℃. ^1H NMR (300M, $CDCl_3$): *δ* 7.44 (m, 1H), 7.17-7.26 (m, 3H), 7.05-7.14 (m, 4H), 6.93 (d, *J* = 7.8 Hz, 1H), 6.12 (s, 1H), 3.26 (s, 3H), 2.74-2.91 (m, 2H), 2.34 (m, 1H), 2.18 (m, 1H). ^{13}C NMR (75M, $CDCl_3$): *δ* 171.8, 169.9, 167.7, 144.4, 139.4, 131.7, 128.6, 128.1, 126.5, 124.5, 123.8, 122.6, 117.3, 109.2, 87.7, 32.4, 28.4, 26.9. HRMS (ESI) calcd for $C_{20}H_{18}NO_3$ $(M+H)^+$: 320.1281,

found 320.1288. IR (KBr): *v*3258, 3132, 3067, 2856, 1768, 1722, 1613, 1466, 1365, 1190, 1104, 1005 cm^{-1}.

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[15] CCDC 987924 contains the supplementary crystallographic data for compound **3d**. The data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. For details of the crystallographic data see Supporting Information.