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N-Heterocyclic carbene-catalyzed [4+2] cyclization of 2-bromo-2-enal with 3-alkylenyloxindoles: an efficient assembly of spirocarbocyclic oxindole

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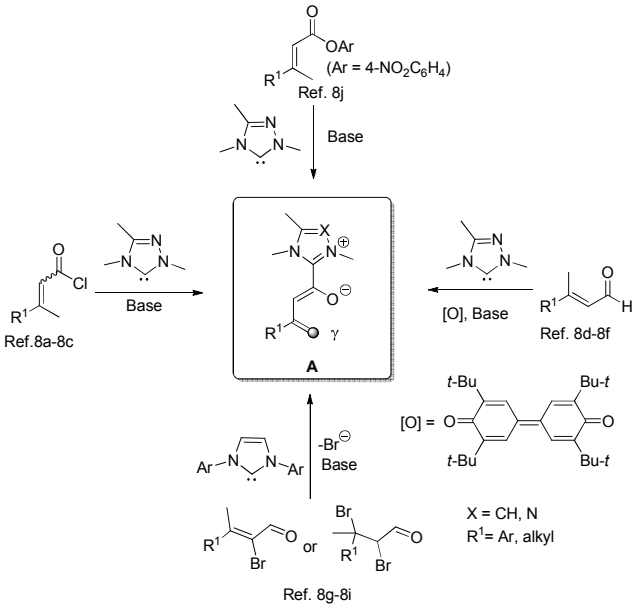
A NHC-catalyzed [4+2] cyclization of 2-bromo-2-enal bearing γ-H with 3-alkylenyloxindoles under mild reaction conditions gives spirocarbocyclic oxindoles containing one quaternary carbon in moderate to good yields with high diastereoselectivies. The easy availability of the starting materials, the concise assembly and the potential utilization value of the products make this strategy attractive in molecular biology and pharmacy.

Introduction

Over the past two decades, the application of N-heterocyclic carbenes (NHCs) in chemistry has developed rapidly.[1] NHC-catalyzed reactions have emerged as an particularly fruitful area of research in organic chemistry,[2] because of their wide utility as efficient organocatalysts to activate different types of aldehdyes,[3] ketones,[4] esters,[5] and nitroalkenes.[6] Due to the unique "Umpolung" in organic synthesis, umpolunging the aldehydes to acyl nucleophiles has become an important way to the synthesis of heterocyclic compounds in current research.[7] In addition to the classical a^1-d^1 umpulong of aldehydes for the benzoin reaction,[7f] Stetter reaction,[7g,7h] and a^3-d^3 umpulong of enals,[7i-7l] the NHC-catalyzed formation of NHC-bonded vinyl enolate **A** were developed successfully from readily available starting materials including a,β-unsaturated acyl chlorides,[8a-8c] oxidative γ-addition of enals,[8d-8f] α-bromo-α,β-unsaturated aldehyde or α,β-dibromoaldehyde,[8g-8i] and α,β-unsaturated esters (Scheme 1).[8j] These NHC-bonded vinyl enolates as a novel synthones can be converted into a variety of highly functionalized molecules in new manners.[8k-8m]



Scheme 1 Formation of NHC-bonded vinyl enolate

The functionalized spirocarbocyclic oxindole core is featured in many bioactive natural products as well as synthetic medicinally relevant compounds (Figure 1).[9] Many efficient methods have been devised toward the synthesis of spirooxindoles,[10] such as the [4+2] cyclization through double Michael addition,[11] and the three-component [2+2+2] cyclization.[12] In 2011, Wang and co-workers disclosed an effective double Michael reaction to access spriocyclic oxindoles with excellent enantioselectivities.[13] Later, Ramachary group presented a versatile method for the synthesis of drug-like six-membered spirooxindoles using an aminoenyne-catalysis.[9i]

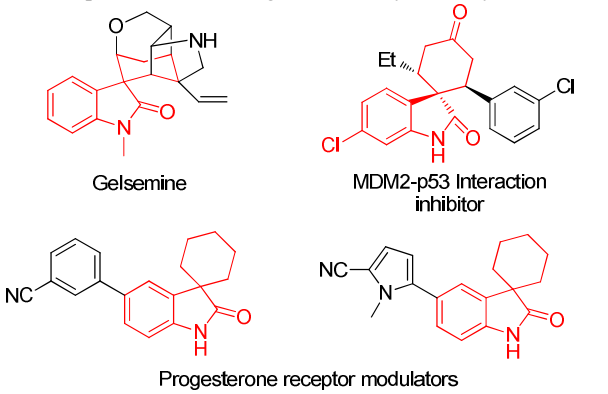
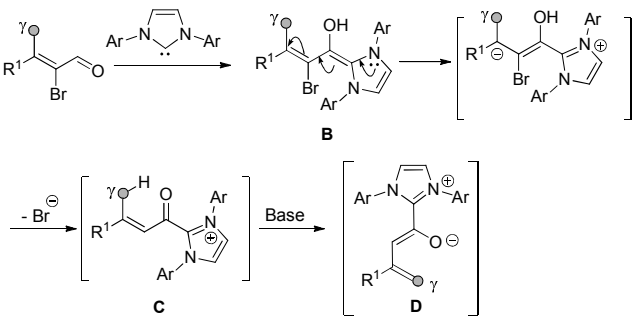


Figure 1 Medicinally important six-membered spirooxindoles

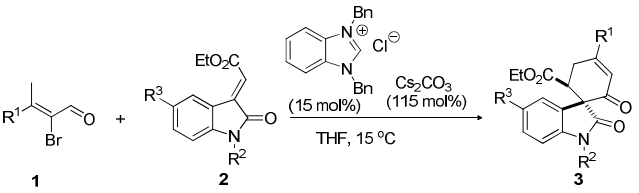
NHC-catalyzed assembly of spiroheterocyclic oxindole scaffolds was set up well. Chi *et al* put forward a catalytic procedure to synthesize spirocyclic oxindole δ-lactams via NHC-

catalyzed activation of α-aryl ester.[5c] Our group has also proposed the NHC-catalyzed [4+2] annulation of α-bromo-α,β-unsaturated aldehydes or α,β-dibromoaldehydes bearing γ-H with isatin derivatives to construct spirocyclic oxindole–dihydropyranone.[8h,8i] Compared with these efficient NHC-catalyzed [4+2] annulation of intermediate **A** with unsaturated C-O bonds, the corresponding reaction with unsaturated C-C bonds remains a challenge. Ye and co-workers disclosed a facile synthesis of spirocarbocyclic oxindoles through catalytic [4+2] cyclization of α,β-unsaturated acyl chlorides with 3-alkylenyloxindoles.[8c] Since the deprotonation of the intermediate **C** at the γ-position would give an intermediate **D** similar to **A** successfully (Scheme 2), we envisioned that the same structure of spirocarbocyclic oxindole could be assembled effectively via the reaction of α-bromo-α,β-unsaturated aldehyde with 3-alkylenyloxindoles catalyzed by NHC.



Scheme 2 Generation of NHC-bonded vinyl enolate from 2-bromo-2-enal with γ-H

To continue our strong interest in the cascade synthesis of heterocycles and NHC catalysis,[8h,8i,14] herein we shall report our preliminary results of NHC-catalyzed reaction of 2-bromo-2-enal bearing γ-H with 3-alkylenyloxindoles, which may give the desired spirocarbocyclic oxindoles with potential bioactivity efficiently (Scheme 3).

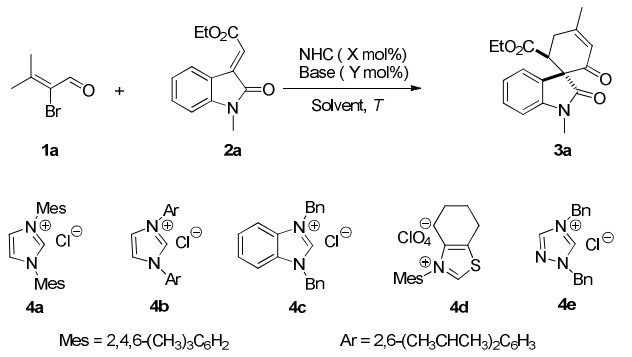


Scheme 3 This work

Results and Discussion

To test our hypothesis, the NHC-catalyzed [4+2] cyclization of 2-bromo-3-methylbut-2-enal **1a** and ethyl 2-(1-methyl-2-oxoindolin-3-ylidene) acetate **2a** were tested as a model reaction. The influences of precatalyst, bases, solvents and temperatures were investigated to optimize the reaction conditions. As shown in table 1, initially, different imidazolium, thiazolium and triazolium salts **4a**-**4e** were screened. We were happy to find that **4c** was the best precatalyst to give the desired cycloadduct **3a** in good yield (Table 1, entry 3). Then, Cs_2CO_3, K_2CO_3, t-BuOK, DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) and KOH were used to explore the scope of the base. The results showed that Cs_2CO_3 was preferable among the bases employed and t-BuOK could only give a poor yield of the desired product (Table 1, entries 6-9). An examination of the amount of catalyst and base indicated that 15 mol% of **4c** along with 115 mol% of Cs_2CO_3 was optimal to the reaction (Table 1, entries 14-15, 18-19). Solvent screening revealed that tetrahydrofuran (THF) was the best choice compared with trichloromethane, methylene dichloride (DCM), dimethylform amide (DMF), and toluene (Table 1, entries 10-13). The optimization of temperature demonstrated that 15 ^oC should be preferred to perform the NHC-catalyzed annulation (Table 1, entries 17).

Table 1 Optimization of the reaction conditions



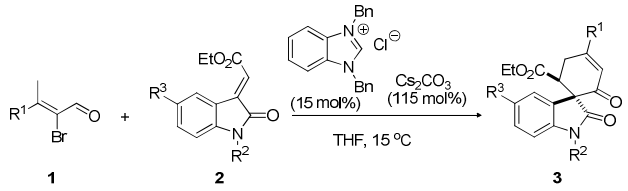
Entry	Precat. (X mol%)	Base (Y mol%)	Solvent	T (^oC)	Yield [a] (%)	dr[c]
1	**4a**(20)	Cs_2CO_3(120)	THF	25	41	5:1
2	**4b**(20)	Cs_2CO_3(120)	THF	25	39	8:1
3	**4c**(20)	Cs_2CO_3(120)	THF	25	59	>20:1
4	**4d**(20)	Cs_2CO_3(120)	THF	25	26	2:1
5	**4e**(20)	Cs_2CO_3(120)	THF	25	37	3:1
6	**4c**(20)	K_2CO_3(120)	THF	25	55	4:1
7	**4c**(20)	t-BuOK(120)	THF	25	N.R.[b]	-
8	**4c**(20)	DBU(120)	THF	25	32	7:1
9	**4c**(20)	KOH(120)	THF	25	29	4:1
10	**4c**(20)	Cs_2CO_3(120)	DMF	25	25	2:1
11	**4c**(20)	Cs_2CO_3(120)	CH_2Cl_2	25	40	9:1
12	**4c**(20)	Cs_2CO_3(120)	toluene	25	15	-
13	**4c**(20)	Cs_2CO_3(120)	$CHCl_3$	25	33	15:1
14	**4c**(10)	Cs_2CO_3(110)	THF	25	42	>20:1
15	**4c**(15)	Cs_2CO_3(115)	THF	25	60	>20:1
16	**4c**(15)	Cs_2CO_3(115)	THF	10	45	>20:1
17	**4c**(15)	Cs_2CO_3(115)	THF	15	63	>20:1
18	**4c**(15)	Cs_2CO_3(100)	THF	15	52	>20:1
19	**4c**(15)	Cs_2CO_3(130)	THF	15	38	>20:1

[a] isolated yield. [b] N.R.= no reaction. [c] determined by ^1H NMR (400 MHz) of the reaction mixture.

With the optimized reaction conditions in hand, we turned our attention to explore the scope of the reaction from α-bromo-α,β-unsaturated aldehydes **1** and 3-alkylenyloxindoles **2**. 3-Alkylenyloxindoles bearing different substituents, including electron-rich (5-methyl, 5-methoxy) and electron-poor (5-bromo,

5-fluoro) groups reacted smoothly with 2-bromo-3-methylbut-2-enal **1a** to generate products (**3a-3n**) in moderate to good yields (45-70%) and high diastereoselective (≥ 7:1 dr, Table 2, entries 1–14). 3-Alkylenyloxindoles with aromatic ring substituted by electron-donating group could provide a better yield of the product in comparison with those with an electron-withdrawing substituent on them. Besides, different substituted groups on the N-atom of 3-alkylenyloxindoles influenced the reactivity and the product yield slightly. Then, to survey the scope of *a*-bromoenal, 2-bromo-3,4-dimethylpent-2-enal and 2-bromo-3-phenylbut-2-enal were subjected to this protocol and the isopropyl group was well tolerated for the desired cycloadducts was obtained in good yields with high diastereoselectivities (>20:1 dr, Table 2, entry 15). These results highlighted the wide application scope of this NHC-catalyzed [4+2] reaction.

Table 2 Synthesis of spirocyclic oxindole



Entry	R^1	R^2	R^3	Product	Yield(%)[a]	d.r.[b]
1	Me	Me	H	**3a**	63	>20:1
2	Me	Et	H	**3b**	61	>20:1
3	Me	allyl	H	**3c**	53	>20:1
4	Me	Bn	H	**3d**	57	>20:1
5	Me	Me	Me	**3e**	70	7:1
6	Me	Et	Me	**3f**	67	>20:1
7	Me	allyl	Me	**3g**	53	>20:1
8	Me	Bn	Me	**3h**	60	>20:1
9	Me	Me	OMe	**3i**	68	>20:1
10	Me	Et	OMe	**3j**	65	>20:1
11	Me	allyl	OMe	**3k**	55	>20:1
12	Me	Bn	OMe	**3l**	66	>20:1
13	Me	Me	Br	**3m**	45	7:1
14	Me	Me	F	**3n**	50	>20:1
15	iPr	Me	H	**3o**	60	>20:1
16	Ph	Me	H	**3p**	0	-

[a] isolated yield. [b] Determined by ^{1}H NMR spectroscopy (400 MHz).

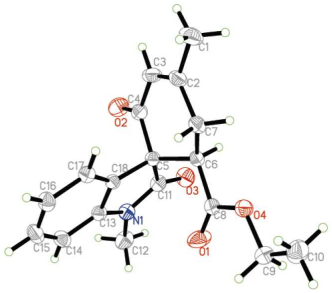
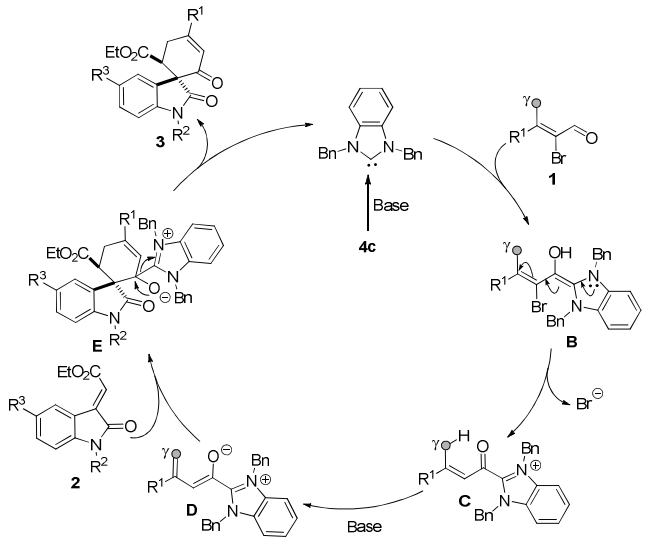


Figure 2 X-ray crystal structure of **3a**

All of the products were characterized by IR, NMR and HRMS. In addition, the structure of compound **3a** was established by X-ray diffraction unambiguously (Fig. 2).[15]

A plausible catalytic cycle of this NHC catalyzed [4+2] annulations is illustrated in Scheme 4. Breslow intermediate **B** was generated from the reaction of 2-bromo-2-enal with the NHC, then it was transformed into **C** through $a^3 \rightarrow d^3$ umpolung and debromination. The acylazoliumion **C** was deprotonated at *γ*-position to give the vinyl enolate **D** in the presence of base. Then intermediate **D** reacted with 3-alkylenyloxindole **2** in a Diels–Alder type reaction or a non-concerted nucleophilic addition reaction with subsequent intramolecular cyclization to give zwitterionic intermediate **E**. The collapse of zwitterion **E** afforded final cycloadduct **3** and released the catalyst.



Scheme 4 Plausible catalytic cycle

Conclusions

In summary, we developed a NHC-catalyzed [4+2] cyclization of *α*-bromo-*α*,*β*-unsaturated aldehydes bearing *γ*-H with 3-alkylenyloxindoles under mild reaction conditions to give spirocarbocyclic oxindoles containing one quaternary carbon in good yields with high diastereoselectivies. Studies aimed at the expansion the reaction scope and the further development of analogous cyclization reactions of *α*-bromo-*α*,*β*-unsaturated aldehydes are under way in our lab.

Experimental section

Typical procedure for the NHC-catalyzed reaction of *α*-bromo-*α*,*β*-unsaturated aldehydes with 3-alkylenyloxindoles

To an oven-dried 25 mL vial equipped with a stir bar, precatalyst **4C** (49 mg, 0.15 mmol) and anhydrous Cs_2CO_3 (374 mg) were added in. Freshly distilled THF (10 mL) was added to the mixture. The mixture was stirred at room temperature for 5 mins. Then 2-bromo-2-enal, 3-alkylenyloxindole 2 (1 mmol) was successively added. The mixture was stirred at 15 °C until

completion (monitored by TLC). The solvent was removed under reduced pressure and the crude product was purified by chromatography on silica gel (mixtures of petroleum ether/ethyl acetate, 3:1, v/v).

ethyl 1',4-dimethyl-2,2'-dioxospiro[cyclohex[3]ene-1,3'-indoline]-6-carboxylate 3a

White solid; M.P: 158-160 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 7.6 Hz, 1H, ArH), 7.05 (d, J = 7.2 Hz, 1H, ArH), 6.97 (t, J = 7.2 Hz, 1H, ArH), 6.88 (d, J = 7.6 Hz, 1H, ArH), 6.06 (s, 1H, CH=), 3.98 - 3.82 (m, 3H, CH_2, CH), 3.31 (s, 3H, CH_3), 3.09-2.99 (m, 1H, CH_2), 2.88 (dd, J = 19.6, 6.0 Hz, 1H, CH_2), 2.17 (s, 3H, CH_3), 2.07 (s, 1H, CH_3), 0.97 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.1, 175.7, 170.0, 160.5, 145.1, 129.2, 126.6, 125.4, 123.1, 122.3, 108.7, 61.1, 60.2, 44.3, 30.4, 26.7, 24.4, 13.8; IR (potassium bromide) (ν, cm^{-1}): 1731, 1713, 1660, 1606, 1493, 1470, 1377, 1251, 1209, 1130, 1025, 969, 777, 695, 541; HRMS (ESI) m/z: Calcd. for $[M+Na]^+C_{18}H_{19}NNaO_4$: 336.1212; found: 336.1212.

ethyl 1'-ethyl-4-methyl-2,2'-dioxospiro[cyclohex[3]ene-1,3'-indoline]-6-carboxylate 3b

White solid; M.P: 163.9-164.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (t, J = 7.6 Hz, 1H, ArH), 7.03 (d, J = 7.6 Hz, 1H, ArH), 6.93 (t, J = 7.6 Hz, 1H, ArH), 6.87 (d, J = 8.0 Hz, 1H, ArH), 6.02 (s, 1H, CH=), 3.98 - 3.81 (m, 5H, 2 × CH_2 + CH), 3.03 (dd, J = 19.6, 11.6 Hz, 1H, CH_2), 2.86 (dd, J = 19.6, 6.4 Hz, 1H, CH_2), 2.14 (s, 3H, CH_3), 1.32 (t, J = 7.2 Hz, 3H, CH_3), 0.93 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.0, 175.3, 170.0, 160.4, 144.2, 129.1, 126.9, 125.3, 123.2, 122.0, 108.8, 61.0, 60.1, 44.2, 35.1, 30.4, 24.4, 13.7, 12.4; IR (potassium bromide) (ν, cm^{-1}): 2982, 1727, 1654, 1607, 1469, 1374, 1244, 987, 759, 550; HRMS (ESI) m/z: Calcd. for $[M+Na]^+$ $C_{19}H_{21}NNaO_4$: 350.1368 found: 350.1366.

ethyl 1'-allyl-4-methyl-2,2'-dioxospiro[cyclohex[3]ene-1,3'-indoline]-6-carboxylate 3c

White solid; M.P: 131.1-132.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (t, J = 7.6 Hz, 1H, ArH), 7.03 (d, J = 7.6 Hz, 1H, ArH), 6.94 (t, J = 7.6 Hz, 1H, ArH), 6.84 (d, J = 8.0 Hz, 1H, ArH), 6.03 (s, 1H, CH=), 5.94 - 5.85 (m, 1H, CH=), 5.43 (d, J = 17.2 Hz, 1H, CH_2=), 5.25 (d, J = 10.4 Hz, 1H,CH_2=), 4.51 (dd, J = 16.4, 4.4 Hz, 1H, CH_2), 4.31 (dd, J = 16.8, 5.2 Hz, 1H, CH_2), 4.01 - 3.83 (m, 3H, CH_2+CH), 3.04 (dd, J = 20.0, 11.6 Hz, 1H, CH_2), 2.88 (dd, J = 19.6, 6.4 Hz, 1H, CH_2), 2.15 (s, 3H, CH_3), 0.95 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.9, 175.4, 170.0, 160.4, 144.3, 130.9, 129.1, 126.8, 125.3, 123.1, 122.2, 117.8, 109.6, 61.1, 60.3, 44.2, 42.7, 30.5, 24.4, 13.8; IR (potassium bromide) (ν, cm^{-1}): 2980, 1726, 1655, 1364, 1245, 1000, 942, 761, 582; HRMS (ESI) m/z: Calcd. for $[M+Na]^+$ $C_{20}H_{21}NNaO_4$: 362.1368 found: 362.1352.

ethyl 1'-benzyl-4-methyl-2,2'-dioxospiro[cyclohex[3]ene-1,3'-indoline]-6-carboxylate 3d

White solid; M.P: 118.7-120.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J = 7.6 Hz, 2H, ArH), 7.36 (t, J = 7.6 Hz, 2H, ArH), 7.28 (t, J = 6.0 Hz, 1H, ArH), 7.16 (t, J = 7.6 Hz, 1H, ArH), 7.06 (d, J = 7.6 Hz, 1H, ArH), 6.93 (t, J = 7.6 Hz, 1H, ArH), 6.71 (d, J = 8.0 Hz, 1H, ArH), 6.08 (s, 1H, CH=), 5.27 (d, J = 15.6 Hz, 1H, CH_2), 4.78 (d, J = 15.6 Hz, 1H, CH_2), 4.02 - 3.92 (m, 2H, CH_2), 3.87 - 3.79 (m, 1H, CH), 3.09 (dd, J = 19.6, 11.6 Hz, 1H, CH_2), 2.92 (dd, J = 19.6, 6.0 Hz, 1H, CH_2), 2.18 (s, 3H, CH_3), 0.91 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.0, 175.9, 170.1, 160.6, 144.2, 135.5, 129.1, 128.7, 127.5, 127.4, 126.9, 125.3, 123.1, 122.3, 109.8, 61.1, 60.3, 44.2, 44.1, 30.5, 24.4, 13.7; IR (potassium bromide) (ν, cm^{-1}): 2938, 1731, 1655, 1486, 1346, 1240, 1184, 747, 705, 572; HRMS (ESI) m/z: Calcd. for $[M-H]^-$ $C_{24}H_{22}NO_4$: 388.1549 found: 388.1577.

ethyl 1',4,5'-trimethyl-2,2'-dioxospiro[cyclohex[3]ene-1,3'-indoline]-6-carboxylate 3e

White solid; M.P: 171.3-172.5°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, J = 8.0 Hz, 1H, ArH), 6.81 (s, 1H, ArH), 6.74 (d, J = 8.0 Hz, 1H, ArH), 6.03 (s, 1H, CH=), 3.98 - 3.81 (m, 3H, CH_2 + CH), 3.26 (s, 3H, CH_3), 3.03 (dd, J = 20.0, 12.4 Hz, 1H, CH_2), 2.84 (dd, J = 20.0, 6.4 Hz, 1H, CH_2), 2.27 (s, 3H, CH_3), 2.16 (s, 3H, CH_3), 0.95 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.1, 175.6, 170.1, 160.5, 142.7, 131.7, 129.5, 126.7, 125.4, 123.9, 108.4, 61.0, 60.3, 44.3, 30.4, 26.6, 24.4, 21.2, 13.8; IR (potassium bromide) (ν, cm^{-1}): 2920, 1730, 1662, 1499, 1368, 1277, 1224, 1039, 832, 557; HRMS (ESI) m/z: Calcd. for $[M-H]^-$ $C_{19}H_{20}NO_4$: 326.1392 found: 326.1431.

ethyl 1'-ethyl-4,5'-dimethyl-2,2'-dioxospiro[cyclohex[3]ene-1,3'-indoline]-6-carboxylate 3f

White solid; M.P: 101-104 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (d, J = 7.6 Hz, 1H, ArH), 6.83 (s, 1H, ArH), 6.78 (d, J = 8.0 Hz, 1H, ArH), 6.04 (s, 1H, CH=), 4.02 - 3.80 (m, 5H, 2 × CH_2 + CH), 3.05 (dd, J = 19.6, 11.6 Hz, 1H, CH_2), 2.86 (dd, J = 19.6, 6.0 Hz, 1H, CH_2), 2.28 (s, 3H, CH_3), 2.17 (s, 3H, CH_3), 1.32 (t, J = 7.2 Hz, 3H, CH_3), 0.96 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.2, 175.2, 170.1, 160.3, 141.8, 131.4, 129.4, 127.0, 125.4, 124.0, 108.5, 61.0, 60.2, 44.2, 35.1, 30.4, 24.4, 21.1, 13.8, 12.4; IR (potassium bromide) (ν, cm^{-1}): 2978, 1739, 1719, 1661, 1496, 1368, 1187, 824, 641, 595; HRMS (ESI) m/z: Calcd. for $[M+H]^+$ $C_{20}H_{24}NO_4$: 342.1705 found: 342.1684.

ethyl 1'-allyl-4,5'-dimethyl-2,2'-dioxospiro[cyclohex[3]ene-1,3'-indoline]-6-carboxylate 3g

White solid; M.P: 123.9-124.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (d, J = 7.6 Hz, 1H, ArH), 6.82 (s, 1H, ArH), 6.73 (d, J = 8.0 Hz, 1H, ArH), 6.03 (s, 1H, CH=), 5.93-5.83 (m, 1H, CH=), 5.42 (d, J = 17.2 Hz, 1H, CH=), 5.24 (d, J = 10.4 Hz, 1H, CH=), 4.49 (dd, J = 16.8, 4.0 Hz, 1H, CH_2), 4.28 (dd, J = 16.8, 4.0 Hz, 1H, CH_2), 4.01 - 3.84 (m, 3H, CH_2), 3.04 (dd, J = 19.6, 11.6 Hz, 1H, CH_2), 2.87 (dd, J = 19.6, 6.4 Hz, 1H, CH_2), 2.26 (s, 3H, CH_3), 2.17 (s, 3H, CH_3), 0.96 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.0, 175.4, 170.1, 160.4, 141.8, 131.6, 131.0, 129.3, 126.9, 125.3, 123.9, 117.6, 109.3, 61.1, 60.3, 44.2, 42.7, 30.4, 24.4, 21.1, 13.8; IR (potassium bromide) (ν, cm^{-1}): 1735, 1720, 1662, 1495, 1363, 1212, 1187, 931, 826, 633; HRMS (ESI) m/z: Calcd. for $[M+Na]^+$ $C_{21}H_{23}NNaO_4$: 376.1525 found: 376.1545.

ethyl 1'-benzyl-4,5'-dimethyl-2,2'-dioxospiro[cyclohex[3]ene-1,3'-indoline]-6-carboxylate 3h

White solid; M.P: 158.9-159.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 7.6 Hz, 2H, ArH), 7.35 (t, J = 7.6 Hz, 2H, ArH), 7.29 - 7.25 (m, 1H, ArH), 6.96 (d, J = 8.0 Hz, 1H, ArH), 6.85 (s, 1H, ArH), 6.59 (d, J = 8.0 Hz, 1H, ArH), 6.07 (s, 1H, CH=), 5.26 (d, J = 16.0 Hz, 1H, CH_2), 4.74 (d, J = 16.0 Hz, 1H, CH_2), 4.01 -

3.93 (m, 2H, CH_2), 3.88 - 3.80 (m, 1H, CH), 3.09 (dd, J = 19.6, 11.6 Hz, 1H, CH_2), 2.91 (dd, J = 19.6, 6.0 Hz, 1H, CH_2), 2.25 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 0.92 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.1, 175.8, 170.2, 160.6, 141.71, 135.6, 131.7, 129.4, 128.7, 127.4, 127.4, 126.9, 125.3, 123.9, 109.5, 61.1, 60.4, 44.2, 44.1, 30.5, 24.5, 21.1, 13.8; IR (potassium bromide) (v, cm^{-1}): 1726, 1661, 1368, 1215, 1187, 1027, 824, 724, 583; HRMS (ESI) m/z: Calcd. for $[M+Na]^+$ $C_{25}H_{25}NNaO_4$: 426.1681 found: 426.1680.

ethyl 5'-methoxy-1',4-dimethyl-2,2'-dioxospiro[cyclohex[3]ene-1,3'-indoline]-6-carboxylate 3i

White solid; M.P: 139.2-140.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 - 6.75 (m, 2H, ArH), 6.65 (s, 1H, ArH), 6.03 (s, 1H, CH=), 4.00 - 3.83 (m, 3H, CH_2 + CH), 3.75 (s, 3H, OCH_3), 3.26 (s, 3H, CH_3), 3.00 (dd, J = 19.6, 11.6 Hz, 1H, CH_2), 2.86 (dd, J = 19.7, 6.0 Hz, 1H, CH_2), 2.14 (s, 3H, CH_3), 0.98 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.9, 175.3, 170.0, 160.5, 155.5, 138.7, 127.9, 125.3, 112.0, 108.7, 61.1, 60.5, 55.8, 44.2, 30.3, 26.7, 24.4, 13.8; IR (potassium bromide) (v, cm^{-1}): 2978, 1740, 1715, 1655, 1498, 1363, 1252, 1034, 808, 589; HRMS (ESI) m/z: Calcd. for $[M+Na]^+$ $C_{19}H_{21}NNaO_5$: 366.1317 found: 366.1302.

ethyl 1'-ethyl-5'-methoxy-4-methyl-2,2'-dioxospiro[cyclohex[3] ene-1,3'-indoline]-6-carboxylate 3j

White solid; M.P: 114.2-115.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 (s, 2H, ArH), 6.67 (s, 1H, ArH), 6.03 (s, 1H, CH=), 4.03 - 3.95 (m, 1H, CH), 3.94 - 3.88 (m, 2H, CH_2), 3.85 - 3.78 (m, 2H, CH_2), 3.75 (s, 3H, OCH_3), 3.01 (dd, J = 19.6, 11.6 Hz, 1H, CH_2), 2.87 (dd, J = 19.6, 6.4 Hz, 1H, CH_2), 2.15 (s, 3H, CH_3), 1.32 (t, J = 7.2 Hz, 3H, CH_3), 0.99 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.9, 174.8, 170.0, 160.5, 155.2, 137.7, 128.2, 125.3, 112.1, 111.8, 108.8, 61.1, 60.3, 55.8, 44.1, 35.2, 30.4, 24.4, 13.8, 12.4; IR (potassium bromide) (v, cm^{-1}): 2975, 1737, 1655, 1495, 1353, 1176, 1037, 802, 762, 590; HRMS (ESI) m/z: Calcd. for $[M+Na]^+$ $C_{20}H_{23}NNaO_5$: 380.1474 found: 380.1474.

Ethyl 1'-allyl-5'-methoxy-4-methyl-2,2'-dioxospiro[cyclohex[3] ene -1,3'-indoline]-6-carboxylate 3k

White solid; M.P: 101.7-102.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77 (s, 2H, ArH), 6.67 (s, 1H, ArH), 6.04 (s, 1H, CH=), 5.94 - 5.84 (m, 1H, CH=), 5.44 (d, J = 17.6 Hz, 1H, CH=), 5.26 (d, J = 10.3 Hz, 1H, CH_2=), 4.50 (dd, J = 16.4, 3.2 Hz, 1H, CH_2), 4.31 (dd, J = 16.4, 4.0 Hz, 1H, CH_2), 4.05 - 3.87 (m, 3H, CH_2, CH), 3.75 (t, 3H, OCH_3), 3.02 (dd, J = 19.6, 11.6 Hz, 1H, CH_2), 2.89 (dd, J = 19.6, 6.4 Hz, 1H, CH_2), 2.15 (s, 3H, CH_3), 1.00 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.8, 175.1, 170.0, 160.6, 155.3, 137.7, 131.0, 128.1, 125.2, 117.7, 111.9, 111.8, 109.6, 61.1, 60.4, 55.8, 44.1, 42.8, 30.4, 24.4, 13.8; IR (potassium bromide) (v, cm^{-1}): 2987, 1716, 1651, 1488, 1361, 1185, 930, 827, 742, 592; HRMS (ESI) m/z: Calcd. for $[M+Na]^+$ $C_{21}H_{23}NNaO_5$: 392.1474 found: 392.1446.

ethyl 1'-benzyl-5'-methoxy-4-methyl-2,2'-dioxospiro[cyclohex[3]ene-1,3'-indoline]-6-carboxylate 3l

White solid; M.P: 125.3-126.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 7.6 Hz, 2H, ArH), 7.36 (t, J = 7.6 Hz, 2H, ArH), 7.29 - 7.26 (m, 1H, ArH), 6.68 - 6.65 (m, 2H, ArH), 6.59 (d, J = 8.0 Hz, 1H, ArH), 6.07 (s, 1H, CH=), 5.26 (d, J = 15.6 Hz, 1H, CH_2), 4.74 (d, J = 15.8 Hz, 1H, CH_2), 4.05 - 3.94 (m, 2H, CH_2), 3.91 - 3.82 (m, 1H, CH), 3.71 (s, 3H, OCH_3), 3.05 (dd, J = 19.6, 11.6 Hz, 1H, CH_2), 2.92 (dd, J = 19.6, 6.4 Hz, 1H, CH_2), 2.18 (s, 3H, CH_3), 0.96 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.8, 175.5, 170.0, 160.6, 155.4, 137.6, 135.5, 128.7, 128.1, 127.5, 127.4, 125.21, 112.0, 111.8, 109.8, 61.1, 60.5, 55.7, 44.3, 44.0, 30.5, 24.4, 13.8.; IR (potassium bromide) (v, cm^{-1}): 1719, 1657, 1495, 1436, 1224, 1194, 1023, 858, 780, 627; HRMS (ESI) m/z: Calcd. for $[M+Na]^+$ $C_{25}H_{25}NNaO_5$: 442.1630 found: 442.1613.

ethyl 5'-bromo-1',4-dimethyl-2,2'-dioxospiro[cyclohex[3]ene-1,3'-indoline]-6-carboxylate 3m

White solid; M.P: 180.5-181.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (dd, J = 8.4, 2.0 Hz, 1H, ArH), 7.10 (d, J = 2.0 Hz, 1H, ArH), 6.77 (d, J = 8.4 Hz, 1H, ArH), 4.74 - 4.67 (m, 1H, CH), 4.00 -3.90 (m, 2H, CH_2), 3.42 (dd, J = 11.2, 7.2 Hz, 1H, CH), 3.26 (s, 3H, CH_3), 2.83 - 2.68 (m, 2H, CH_2), 2.07 (s, 3H, CH_3), 1.07 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 169.9, 144.7, 133.9, 131.8, 128.2, 127.7, 122.2, 115.0, 109.5, 73.9, 61.1, 54.6, 43.4, 32.6, 26.7, 23.2, 13.9; IR (potassium bromide) (v, cm^{-1}): 1733, 1694, 1605, 1488, 1367, 1181, 1085, 1026, 821, 618; HRMS (ESI) m/z: Calcd. for $[M-H]^-$ $C_{18}H_{17}BrNO_5$: 390.0341 found: 390.0368.

ethyl 5'-fluoro-1',4-dimethyl-2,2'-dioxospiro[cyclohex[3]ene-1,3'-indoline]-6-carboxylate 3n

White solid; M.P: 152.7-153.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 - 6.99 (m, 1H, ArH), 6.82 - 6.78 (m, 2H, ArH), 6.06 (s, 1H, CH=), 4.01 - 3.88 (m, 3H, CH_2, CH), 3.29 (s, 3H, CH_3), 3.03 - 2.87 (m, 2H, CH_2), 2.18 (s, 3H, CH_3), 1.01 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.4, 175.3, 169.8, 160.7, 158.6 (J_{CF} = 240.0 Hz), 141.2 (J_{CF} = 2.0 Hz), 127.8 (J_{CF} = 8.0 Hz), 125.3, 115.3 (J_{CF} = 23.3 Hz), 111.5 (J_{CF} = 25.0 Hz), 109.0 (J_{CF} = 8.0 Hz), 61.2, 60.4 (J_{CF} = 1.6 Hz), 44.2, 30.3, 26.8, 24.4, 13.8; IR (potassium bromide) (v, cm^{-1}): 1726, 1664, 1630, 1495, 1335, 1174, 1122, 1058, 1026, 818; HRMS (ESI) m/z: Calcd. for $[M+H]^+$ $C_{18}H_{19}FNO_5$: 332.1298 found: 332.1287.

ethyl 4-isopropyl-1'-methyl-2,2'-dioxospiro[cyclohex[3]ene-1,3'-indoline]-6-carboxylate 3o

White solid; M.P: 141.2-142.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.27 (m, 1H, ArH), 7.01 (dd, J = 7.6, 1.2 Hz, 1H, ArH), 6.95 (td, J = 7.2, 0.8 Hz, 1H, ArH), 6.86 (d, J = 7.6 Hz, 1H, ArH), 6.05 (t, J = 1.2 Hz, 1H, CH=), 4.00 - 3.81 (m, 3H, CH_2, CH), 3.29 (s, 3H, NCH_3), 3.08-2.99 (m, 1H, CH_2) 2.90 (dd, J = 19.2, 6.0 Hz, 1H, CH_2), 2.64-2.57 (m, 1H, CH), 1.25 (t, J = 6.6 Hz, 6H, CH_3), 0.95 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.7, 175.7, 170.2, 169.7, 145.1, 129.2, 126.6, 123.0, 122.6, 122.3, 108.7, 61.1, 60.7, 44.5, 35.9, 27.2, 26.6, 21.0, 20.6, 13.8; IR (potassium bromide) (v, cm^{-1}): 2963, 1724, 1715, 1655, 1606, 1493, 1346, 1249, 1189, 1093, 759; HRMS (ESI) m/z: Calcd. for $[M+Na]^+$ $C_{20}H_{23}NNaO_4$: 364.1525 found: 364.1545.

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Notes and references

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‡ Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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15 The crystal of compounds **3a** was prepared from the solution in petroleum ether/ethyl acetate/ ethyl alcohol with trace of acetone. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 1016169. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, CambridgeCB21EZ, UK (fax: +44 1223 336033 or email: deposit@ccdc.cam.ac.uk).