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Palladium catalysed queuing processes. Part 4: Termolecular cyclisation–anion capture cascades employing allene as a relay switch and secondary amines as nucleophiles☆

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Abstract—Pd(0) catalysed termolecular queuing processes involving oxidative addition to aryl or vinyl halides followed by cyclisation onto a proximate alkyne or alkene, allene (1 atm) insertion and capture of the resulting π-allyl palladium(II) species by secondary amines affords benzo-fused 5–8-membered rings in good yield.

1. Introduction

In earlier papers we outlined the general concept of relay switch reactants and their impact on our palladium catalysed queuing processes.[2] At present the most fully developed relay switches are carbon monoxide and allene, both of which have proved versatile building blocks in palladium catalysed processes,[3–7] whilst bicyclopropylidine is the most recent relay switch.[1]

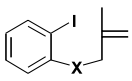
In this paper we describe full details of termolecular queuing cascades involving palladium catalysed cyclisation onto a proximate alkene/alkyne[8,9] followed by allene insertion and capture of the resulting π-allyl palladium(II) species by secondary amines (Scheme 1).

2. Cyclisation onto proximate alkenes

2.1. 5-*exo-trig* Processes

Initially we selected **1a–c** for evaluation as the 'zipper' molecules for the palladium catalysed cyclisation/allenylation/amination cascades (Scheme 1(a)). The reaction of **1a–c** with allene (1 bar) and pyrrolidine or piperidine (2 equiv.) in toluene at 110°C in the presence of Pd(0) (generated in situ from $Pd(OAc)_2$ (10 mol%) and triphenylphosphine (20 mol%)) was then investigated.

It was found convenient to carry out these reactions in a Schlenk tube since allene diffuses readily through an ordinary balloon. Under these conditions the reaction of **1a–c** proceeded according to Scheme 1(a) to afford **2–7** (Table 1, entries 1–6) in good yield.



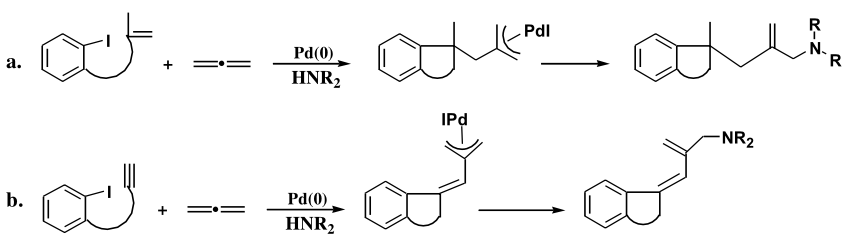
1

a. X = NMe, Y = CO

b. X = NTs, Y = CH_2

c. X = O, Y = CH_2

In this cascade potassium carbonate (2 equiv.) was employed as base together with tetraethylammonium



Scheme 1.

☆ See Ref. 1.

Keywords: nucleophiles; dienylamines; triazoline.

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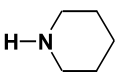
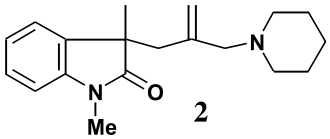
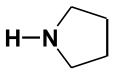
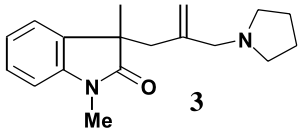
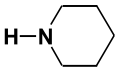
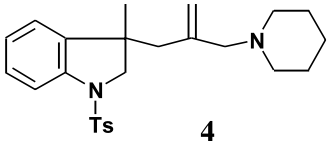
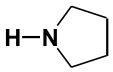
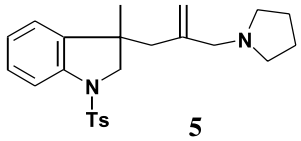
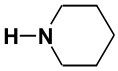
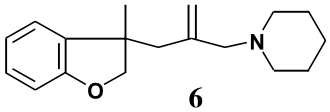
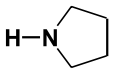
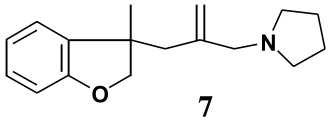
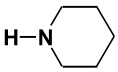
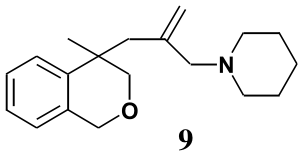
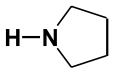
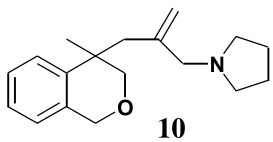
Table 1. Three component *exo-trig* cyclisation–allenylation–amination cascades

Entry	Zipper	Nucleophile	Product	Yield (%)[a]
1	**1a**		 **2**	82
2	**1a**		 **3**	76
3	**1b**		 **4**	66
4	**1b**		 **5**	72
5	**1c**		 **6**	66
6	**1c**		 **7**	60
7	**8**		 **9**	50[b]
8	**8**		 **10**	50[b]

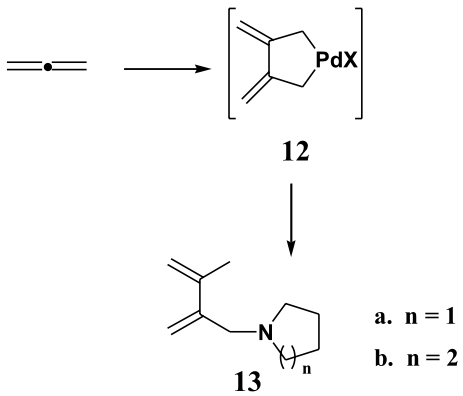
All reactions were carried out in toluene at 110°C for 25 h and employed 1 mol (**1a**–**c**), allene (1 bar), 10 mol% $Pd(OAC)_2$, 20 mol% PPh_3, 2 mol equiv. K_2CO_3, 1 mol equiv. $Et_4N^+Cl^-$ and 2 mol equiv. secondary amine.
[a] Isolated yield.
[b] Xylene, 140°C.

chloride (1 equiv.). Tetraalkylammonium chlorides are commonly used to accelerate the rates of Heck reactions.[8–13] Although the precise role of Et_4NCl remains unclear its mode of action is believed to involve three effects:

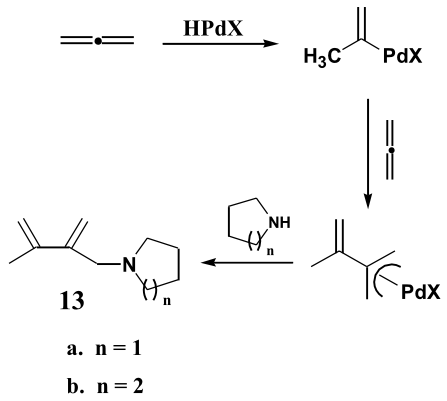
(i) it favours the conversion of RPdI species to RPdCl species in which the palladium centre is more electrophilic, thereby promoting coordination of the olefin to the metal and promoting cyclisation.
(ii) it results in the formation of polychloro palladium(0) anionic species which both stabilises the palladium(0) species and promotes oxidative addition.
(iii) in common with other quaternary ammonium salts, it acts as a phase transfer catalyst.

2.2. 6-*exo-trig* Processes

We have briefly explored the palladium catalysed 6-*exo-trig* cyclisation/allenylation/amination cascades with substrate **8**. When **8** was treated with allene (1 bar) and pyrrolidine or piperidine (2 equiv.) in the presence of 10 mol% $Pd(OAc)_2$,

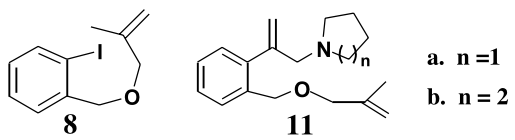


Scheme 2.



Scheme 3.

20 mol% triphenyl phosphine in toluene at 110°C the direct capture products **11a** and **11b**, respectively, were formed. In order to suppress formation of direct capture products the allene concentration in solution was decreased by both increasing the reaction temperature (140°C xylene) and decreasing the pressure of allene to 0.5 bar (at rt). Under these modified conditions the desired unsaturated amines **9** and **10** were both obtained in 50% yield (Table 1, entries 7 and 8).

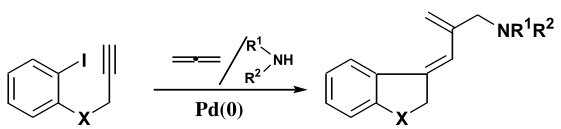


Common by-products from the reactions collected in Table 1 were the amino dienes **13a** and **b**. This type of product was first reported by Coulson in 1973[14] and he proposed that allene dimerisation occurs via complex **12** (Scheme 2). We have recently developed this process further with phenols[15] and active methylene compounds.[16]

3. Cyclisation onto proximate alkynes

3.1. 5-*exo-dig* Processes

A series of 5-*exo-dig* cyclisation/allenylation/amination cascades (Scheme 1(b)) were explored with alkynes **14a** and **b**.



14 a. X = O **15 - 18**

b. X = NSO_2Ph

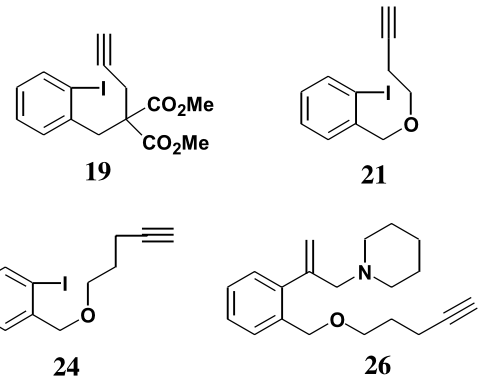
Reaction of **14a** and **b** with allene (1 bar) and secondary amines (2 equiv.) in the presence of a catalyst system comprising 10 mol% $Pd(OAc)_2$, 20 mol% PPh_3 and K_2CO_3 (1 mol equiv.) proceeded according to Scheme 1(b) to afford **15**–**18** in 60–67% yield (Table 2, entries 1–4). In the case of **18** the product consisted of a 1:1 mixture of *E* and *Z*-isomers.

The mechanism of formation of these types of products has been discussed by us[15,16] and in the case of **13a** and **b** an alternative to Scheme 2 is one involving a series of hydropalladation/carbopalladation/amination steps (Scheme 3).

3.2. 6-, 7- and 8-*exo-dig* Processes

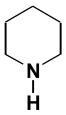
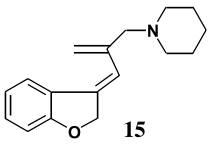
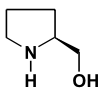
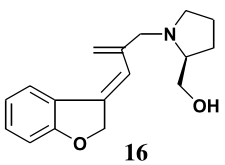
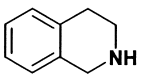
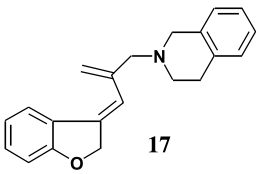
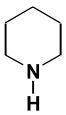
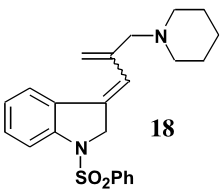
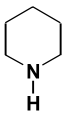
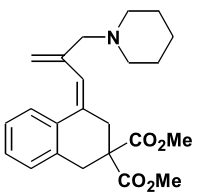
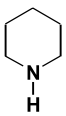
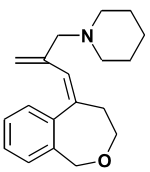
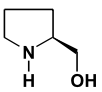
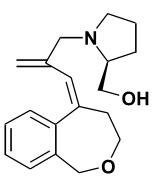
One example of a 6-*exo-dig* cyclisation/allenylation/amination cascade was studied. Thus carbocycle **20** was efficiently assembled in 73% yield from **19** (Table 2, entry 5) under the same conditions employed for **14**.

The (2-iodobenzyl)propargyl ether **21** undergoes a 7-*exo-dig* termolecular cascade under the same conditions. Trapping the π-allyl palladium(II) intermediate with piperidine afforded tetrahydro-2-benzoxepin **22** (68%) (Table 2, entry 6), whilst trapping with (*S*)-(+)-2-prolinol gave **23** (71%) (Table 2, entry 7).



Finally we explored the possibility of forming an eight membered ring using the above methodology. Thus **24** reacted (toluene 70°C, 20 h) with allene (1 bar) and piperidine (2 equiv.) to give 1:1.4 mixture of **25** and **26** in 43% combined yield (Table 2, entry 8). Hence formation of the tetrahydro-2-benzoxocin **25** was less efficient due to a slower rate of cyclisation allowing a competitive direct allenylation/amination process. A similar strategy to that

Table 2. Three component *exo-dig* cyclisation–allenylation–amination cascades

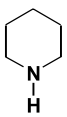
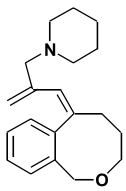
Entry	Zipper	Nucleophile	Product	Yield (%)[a]
1	**14a**		 **15**	61
2	**14a**		 **16**	67
3	**14a**		 **17**	61
4	**14b**		 **18**	60[b]
5	**19**		 **20**	73
6	**21**		 **22**	68
7	**21**		 **23**	71

employed to suppress formation of **11a**,**b** merits investigation in this case.

4. Further reaction of the dienylamines

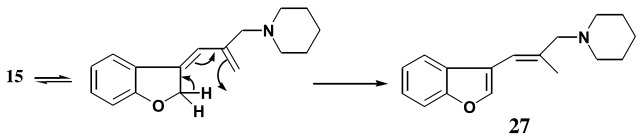
The potential of heterocyclic dienes to participate in Diels–Alder reactions has been briefly explored in thermal uncatalysed reactions. These dienes are not very reactive

Table 2 (*continued*)

Entry	Zipper	Nucleophile	Product	Yield (%)[a]
8	**24**		 **25**	43[c]

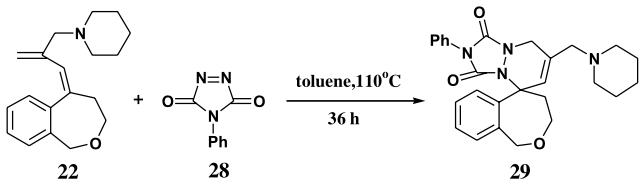
All reactions were carried out in toluene 70°C for 20 h and employed 1 mmol **14**–**24**, allen (1 bar), 10 mol% $Pd(OAc)_2$, 10 mol% PPh_3, 1 mol equiv. K_2CO_3 and 2 mol equiv. amine.
[a] Isolated yield.
[b] 1:1 mixture of *E*/*Z*-isomers.
[c] 1:1.4 mixture of **25** and **26**.

and this allows competitive processes to predominate in many cases. Thus **15** and *N*-methylmaleimide on heating in boiling toluene for 18 h afforded the benzofuran **27** in 84% yield. A plausible mechanism for this transformation involves *E*/*Z*-diene isomerisation which sets up the requisite geometry for a 1,5-H shift (Scheme 4).



Scheme 4.

When triazoline dione **28** was used as dienophile the Diels–Alder reaction occurred in moderate yield (Scheme 5). Thus **22** and **28** were reacted in toluene at 110°C over 36 h to afford cycloadduct **29** in 44% yield (Scheme 5).

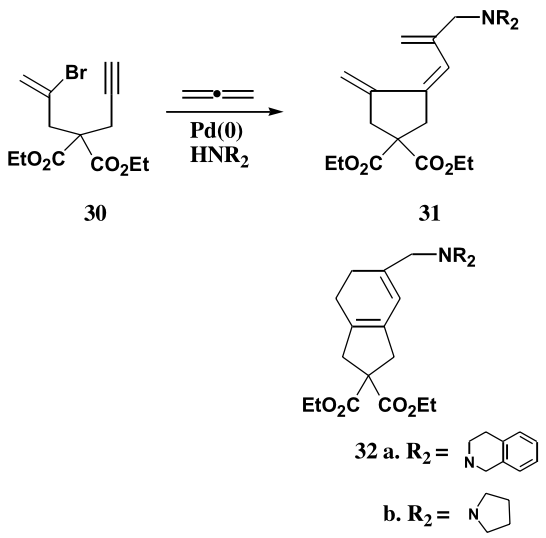


Scheme 5.

An interesting extended cascade resulted when the vinyl halide **30** was reacted with allene and either pyrrolidine or piperidine (MeCN, K_2CO_3 (1 mol equiv.), 70°C, 10 h)) using 10 mol% $Pd(PPh_3)_4$ as catalyst. The initial product **31** was not detected under these conditions but transformed into **32a** (77%) and **32b** (60%), respectively, by a 6π-electrocyclisation[16] (Scheme 6).

5. Conclusions

The three-component cascades result in the formation of three new bonds, a 5–8 membered ring and an allylic amine. The observation of direct capture products in the 6-*exo-trig* case but not in the 6-*exo-dig* cases attests to the faster rate of *exo-dig* cyclisations compared to *exo-trig* cyclisation. Adjusting the solution concentration of the allene suppresses direct capture products.



Scheme 6.

6. Experimental

Melting points were determined on a Kofler hot stage apparatus and uncorrected. Mass spectral data were obtained from a VG Autospec mass spectrometer operating at 70 eV. Nuclear magnetic resonance spectra were recorded on Bruker QE 300 and AM 400 machines operating at 300 and 400 MHz, respectively. Unless otherwise specified deuterochloroform was used as solvent with tetramethylsilane as internal standard. Microanalysis were obtained using a Carlo Erba MOD 11016 instrument. Thin layer chromatography was carried out on Whatman PGIL G/UV polyester plates coated with a 0.2 mm layer of silica gel 60 (Merck 9385). Column chromatography was performed with silica gel 60 (Merck 9385). Petroleum ether refers to the fraction with bp 40–60°C. Anhydrous toluene was commercially available (Aldrich). Compounds **1a–c**, **8**, **14a**,**b**, **21** and **19** have been previously prepared by us.[7,17–19]

6.1. General procedure A for three-component cyclisation allenylation/amination cascades of 1a–c and 8

A mixture of **1a–c** (or **8**) (0.5 mmol), secondary amine (1 mmol), $Pd(OAc)_2$ (0.05 mmol), PPh_3 (0.1 mmol) potassium carbonate (1 mmol) and Et_4NCl (0.5 mmol) in dry toluene (10 ml) was degassed using two freeze, pump, thaw cycles. Allene (1 bar) was incorporated into the Schlenk tube and the solution was heated at 110°C in an oil bath for 20 h. The solution was then concentrated and the residue purified by column chromatography to afford the product.

6.1.1. 3-Methyl-3-(2-piperidin-1-ylmethyl-allyl)-1-(toluene-4-sulfonyl)-2,3-dihydro-1*H*-indole 2. Prepared by general procedure A. Flash chromatography eluting with 1:1 v/v petroleum ether 40–60°C containing 1% aqueous ammonia afforded the product (82%) as pale yellow needles, mp 64–65°C. Found: C, 76.25; H, 8.95; N, 9.4. $C_{19}H_{26}N_2O$ requires C, 76.5; H, 8.5; N, 9.4%. δ_H 7.25 (m, 2H, ArH), 7.05 (t, 1H, J=7.0 Hz, ArH), 6.8 (d, 1H, J=7.0 Hz, ArH), 4.65 and 4.75 (2×s, 2×1H, C=CH_2), 3.2 (s, 3H, NCH_3), 2.6 and 2.75 (2×d, 2H, J=12.0 Hz, CH_2 N), 2.1 and 2.3 (2×d, 2H, J=12.6 Hz, CH_2C=C), 1.85–2.1 (br m, 4H, $N(CH_2)_2$) and 1.3–1.55 (m, 9H, $(CH_2)_3$ and CH_3). m/z (%): 298 (M^+, 0.5), 297 (1), 214 (1), 138 (100), 98 (30), 84 (16).

6.1.2. 1,3-Dimethyl-3-(2-pyrrolidin-1-ylmethyl-allyl)-1,3-dihydro-indole-2-one 3. Prepared by general procedure A. Flash chromatography eluting with 9:1 v/v dichloromethane–methanol containing 2% aqueous ammonia afforded the product (76%) as pale yellow prisms, mp 77–78°C. Found: C, 76.0; H, 8.75; N, 9.55. $C_{18}H_{24}N_2O$ requires C, 76.0; H, 8.45; N, 9.85%. δ_H 7.25 (m, 2H, ArH), 7.05 (t, 1H, J=7.2 Hz, ArH), 6.8 (d, 1H, J=7.2 Hz, ArH), 4.6 and 4.75 (2×s, 2×1H, C=CH_2), 3.2 (s, 3H, NCH_3), 2.75 and 2.6 (2×d, 2×1H, J=12.05 Hz, CH_2N), 2.55 and 2.4 (2×d, 2H, J=12.3 Hz, CH_2C=C), 2.2 (br m, 4H, $N(CH_2)_2$), 1.7 (br m, 4H, $(CH_2)_2$) and 1.4 (s, 3H, CH_3). m/z (%): 284 (M^+, 0.1), 214 (1), 124 (100), 84 (19) and 70 (8).

6.1.3. 3-Methyl-3-(2-pyrrolidin-1-ylmethyl-allyl)-1-(toluene-4-sulfonyl)-2,3-dihydro-1*H*-indole 4. Prepared by general procedure A. Flash chromatography eluting with 1:1 v/v petroleum ether–ether containing 1% aqueous ammonia afforded the product (66%) as colourless amorphous powder, mp 85–88°C. Found: C, 70.35; H, 7.65; N, 6.4. $C_{25}H_{32}N_2O_2S$ requires C, 70.75; H, 7.55; N, 6.6%. δ_H 7.7 (d, 2H, J=8.1 Hz, ArH), 7.6 (d, 1H, J=8.1 Hz, ArH), 7.25–7.1 (m, 3H, ArH), 7.05 (d, 1H, J=7.5 Hz, ArH), 7.0 (t, 1H, J=7.5 Hz, ArH), 4.7 and 4.9 (2×s, 2×1H, C=CH_2), 3.55 and 4.0 (2×d, 2×1H, J=10.0 Hz, CH_2NTs), 2.2–2.5 (m, 4H, NCH_2, CH_2C=C), 2.35 (s, 3H, $ArCH_3$), 2.2–1.9 (br m, 4H, $N(CH_2)_2$), 1.3–1.55 (br m, 6H, $(CH_2)_3$) and 1.05 (s, 3H, CH_3). m/z (%): 424 (M^+, 0.2), 423 (1), 339 (1), 269 (100), 184 (63), 138 (99) and 98 (61).

6.1.4. 3-Methyl-3-(2-pyrrolidin-1-ylmethyl-allyl)-1-(toluene-4-sulfonyl)-2,3-dihydro-1*H*-indole 5. Prepared by general procedure A. Flash chromatography eluting with 95:5 v/v dichloromethane–methanol containing 1% aqueous ammonia afforded the product (72%) as pale yellow needles, mp 93–94°C. Found: C, 69.95; H, 7.4; N, 6.5, S, 8.1. $C_{24}H_{30}N_2O_2S$ requires C, 70.2; H, 7.3; N, 6.8; S, 7.8%. δ_H 7.75 (d, 2H, J=7.4 Hz, ArH), 7.6 (d, 1H, J=8.0 Hz, ArH), 7.25–7.15 (m, 3H, ArH), 7.05 (d, 1H, J=7.4 Hz, ArH), 7.0 (t, 1H, J=7.4 Hz, ArH), 4.65 and 4.9 (2×s, 2×1H, C=CH_2), 3.55 and 4.05 (2×d, 2×1H, J=10.0 Hz, CH_2NTs), 2.7 and 2.5 (2×d, 2H, J=11.0 Hz, NCH_2), 2.2–2.45 (m, 6H, $N(CH_2)_2$ and CH_2C=C), 2.4 (s, 3H, $ArCH_3$), 1.7 (br, 4H, $(CH_2)_2$ and 1.1 (s, 3H, CH_3). m/z (%): 410 (M^+, 0.2), 339 (1), 255 (72), 184 (53), 124 (100) and 84 (51).

6.1.5. 1-[2-(3-Methyl-2,3-dihydro-benzofuran-3-ylmethyl)-allyl]-pyrrolidine 6. Prepared by general procedure A. Flash chromatography eluting with 9:1 v/v petroleum ether–ether containing 1% aqueous ammonia afforded the product (60%) as a pale yellow oil. Found: C, 79.5; H, 9.2; N, 5.2. $C_{18}H_{25}NO$ requires C, 79.7; H, 9.2; N, 5.2%. δ_H 7.75 (d, 1H, J=8.0 Hz, ArH), 7.1 (m, 2H, ArH), 6.85 (t, 1H, J=7.3 Hz, ArH), 4.8 and 5.0 (2×s, 2×1H, C=CH_2), 4.2 and 4.6 (2×d, 2×1H, J=8.0 Hz, OCH_2), 2.55 (s, 2H, CH_2N), 2.3 and 2.65 (2×d, 2×1H, J=13.6 Hz,

$CH_2C{=}C$), 2.0–2.3 (br m, 4H, $N(CH_2)_2$), 1.3–1.5 (m, 6H, $(CH_2)_3$) and 1.3 (s, 3H, CH_3). *m/z* (%): 270 (M^+-1, 3), 186 (23), 139 (63), 98 (100) and 84 (44).

6.1.6. 1-[2-(3-Methyl-2,3-dihydro-benzofuran-3-ylmethyl)-allyl]-pyrrolidine 7. Prepared by general procedure A. Flash chromatography eluting with 1:1 v/v petroleum ether–ether containing 1% aqueous ammonia afforded the product (61%) as a pale yellow oil. Found: C, 79.1; H, 8.8; N, 5.2. $C_{17}H_{23}NO$ requires C, 79.4; H, 8.95; N, 5.45%. δ_H 7.1 (m, 2H, ArH), 6.85 (t, 1H, *J*=7.3 Hz, ArH), 6.75 (d, 1H, *J*=8.0 Hz, ArH), 4.8 and 5.0 (2×s, 2×1H, $C{=}CH_2$), 4.2 and 4.6 (2×d, 2×1H, *J*=8.5 Hz, OCH_2), 2.7 and 2.75 (2×d, 2H, *J*=9.0 Hz, NCH_2), 2.3–2.6 (m, 6H, $CH_2C{=}C$) and $N(CH_2)_2$), 1.75 (br m, 4H, $(CH_2)_2$) and 1.4 (s, 3H, CH_3). *m/z* (%): 256 (M^+-1, 6) 186 (17), 125 (51), 84 (100) and 70 (44).

6.1.7. 1-[2-(4-Methyl-isochroman-4-ylmethyl)-ally]-piperidine 9. Prepared from **8** by general procedure A. Flash chromatography eluting with 9:1 v/v petroleum ether–ether containing 1% aqueous ammonia afforded the product (50%) as a pale yellow oil. Found: C, 80.0; H, 9.5; N, 4.65. $C_{19}H_{27}NO$ requires C, 80.0; H, 9.45; N, 4.9%. δ_H 7.4 (d, 1H, *J*=7.5 Hz, ArH), 7.1–7.2 (m, 2H, ArH), 6.9 (d, 1H, *J*=7.5 Hz, ArH), 4.8 and 5.0 (2×s, 2×1H, $C{=}CH_2$), 4.8 (s, 2H, $PhCH_2O$), 3.5 and 3.9 (2×d, 2×1H, *J*=11.5 Hz, OCH_2), 2.3–2.65 (m, 4H, $CH_2C{=}C$ and NCH_2), 2.1 (br m, 4H, $N(CH_2)_2$), 1.3–1.6 (m, 6H, $(CH_2)_3$) and 1.25 (s, 3H, CH_3). *m/z* (%): 285 (M^+, 1.8), 139 (43), 98 (100) and 84 (44).

6.1.8. 1-[2-(4-Methyl-isochroman-4-ylmethyl)-ally]-pyrrolidine 10. Prepared from **8** by general procedure A. Flash chromatography eluting with 95:5 v/v dichloromethane–methanol containing 1% aqueous ammonia afforded the product (50%) as a pale yellow oil. Found: C, 79.6; H, 9.5; N, 5.4. $C_{18}H_{25}NO$ requires C, 79.7; H, 9.2; N, 5.2%. δ_H 7.35 (d, 1H, *J*=7.3 Hz, ArH), 7.1–7.2 (m, 2H, ArH), 6.95 (d, 1H, *J*=7.5 Hz, ArH), 4.8 and 5.05 (2×s, 2×1H, $C{=}CH_2$), 4.8 (s, 2H, $PhCH_2O$), 3.5 and 3.9 (2×d, 2H, *J*=11.5 Hz, OCH_2), 2.75 and 2.85 (2×d, 2H, *J*=13.8 Hz, CH_2N), 2.3–2.6 (m, 6H, $CH_2C{=}C$ and $N(CH_2)_2$), 1.75 (br m, 4H, $(CH_2)_2$) and 1.25 (s, 3H, CH_3). *m/z* (%): 271 (M^+, <1), 124 (43), 119 (18), 91 (12), 84 (100) and 70 (45).

6.2. General procedure B for cascade cyclisation–allene insertion–anion capture reactions of 14, 19, 21 and 24

A Schlenk flask containing a mixture of aryl halide (1.2 mmol), secondary amine (2.4 mmol), K_2CO_3 (1.2 mmol), $Pd(OAc)_2$ (0.12 mmol) and PPh_3 (0.24 mmol) in toluene (15 ml) was evacuated (water pump) and then filled with nitrogen two times. After a third evacuation the flask was filled with allene (1 bar) and the mixture was heated at 70–75°C (oil bath temperature) for 17–20 h. The solvent was evaporated under reduced pressure, the residue dissolved in CH_2Cl_2, washed with water, dried ($MgSO_4$), filtered and the filtrate evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, petroleum ether–ether–ammonia) to afford the product.

6.2.1. 1-[2-Benzofuran-(3*E*)-ylidenemethyl-ally]-piperidine 15. Prepared by general procedure B. The product (61%) was isolated as a pale yellow oil. Found: C, 79.8; H, 8.15; N, 5.3. $C_{17}H_{21}NO$ requires C, 80.0; H, 8.24; N, 5.49%. δ_H 7.91 (d, 1H, *J*=8.0 Hz, ArH), 7.18 (t, 1H, *J*=7.5 Hz, ArH), 6.82 (m, 2H, ArH), 5.88 (s, 1H, =CH), 5.44 (s, 1H, =CH), 5.32 (s, 1H, =CH), 5.11 (d, 2H, *J*=2.5 Hz, CH_2O), 3.01 (s, 2H, CH_2N), 2.37 (bs, 4H, piperidine H), 1.58 (m, 4H, piperidine H), 1.42 (m, 2H, piperidine H). δ (^{13}C NMR): 165.2, 141.9, 135.9, 130.3, 124.3, 120.1, 118.9, 115.8, 110.6, 76.1, 65.4, 54.6, 25.9 and 24.4. *m/z* (%): 255 (M^+, 41), 240 (6), 172 (21), 157 (10), 136 (12), 128 (23), 115 (11), 98 (100), 84 (15), 77 (7) and 55 (13). Found HRMS: 255.1629, $C_{17}H_{21}NO$ requires: 255.1623.

6.2.2. {1-[2-Benzofuran-(3*E*)-ylidenemethyl-ally]-pyrrolidine-2-yl}-methanol 16. Prepared by general procedure B. The product (67%) was isolated as a pale yellow oil. Found HRMS: 271.1564, $C_{17}H_{21}NO_2$ requires: 271.1572. δ_H 7.91 (d, 1H, *J*=8.0 Hz, ArH), 7.18 (t, 1H, *J*=7.4 Hz, ArH), 6.83 (m, 2H, ArH), 5.84 (s, 1H, =CH), 5.42 (s, 1H, =CH), 5.37 (s, 1H, =CH), 5.12 (d, 2H, *J*=2.6 Hz, CH_2O), 3.65 (dd, 1H, *J*=3.5, 10.7 Hz, pyrrolidine H), 3.48 (d, 1H, *J*=13.3 Hz, CH_2N), 3.39 (d, 1H, *J*=10.6 Hz, pyrrolidine H). 3.11 (m, 1H, pyrrolidine H), 2.95 (d, 1H, *J*=13.3 Hz, CH_2N), 2.78 (bs, 1H, OH), 2.66 (m, 1H, pyrrolidine H), 2.34 (q, 1H, *J*=7.6 Hz, pyrrolidine H) and 1.62–1.98 (m, 4H, pyrrolidine H). *m/z* (%): 271 (M^+, 13), 240 (100), 171 (66), 150 (12), 128 (19), 114 (35), 84 (18), 70 (11) and 43 (8).

6.2.3. 2-[2-Benzofuran-(3*E*)-ylidenemethyl-ally]-1,2,3,4-tetrahydro-isoquinoline 17. Prepared by general procedure B. The product (61%) was isolated as a pale yellow oil. Found HRMS: 303.1629, $C_{21}H_{21}NO$ requires: 303.1623. δ_H 7.96 (d, 1H, *J*=8.1 Hz, ArH), 7.03–7.18 (m, 4H, ArH), 6.93 (m, 1H, ArH), 6.78 (m, 2H, ArH), 5.95 (s, 1H, =CH), 5.52 (s, 1H, =CH), 5.43 (s, 1H, =CH), 5.11 (d, 2H, *J*=2.6 Hz, CH_2O), 3.65 (s, 2H, NCH_2Ar), 3.25 (s, 2H, $=CCH_2N$), 2.87 (t, 2H, *J*=5.6 Hz, CH_2N) and 2.74 (t, 2H, *J*=5.6 Hz, $ArCH_2$). δ (^{13}C NMR): 165.3, 141.6, 136.3, 134.8, 134.4, 130.4, 128.7, 126.6, 126.1, 125.6, 124.4, 124.2, 120.1, 118.5, 116.3, 110.7, 76.1, 64.3, 56.2, 50.4 and 29.0. *m/z* (%): 303 (M^+, 33), 286 (6), 184 (23), 172 (28), 157 (11), 146 (100), 132 (42), 117 (22), 103 (11), 91 (14), 84 (42), 77 (12) and 42 (24).

6.2.4. 1-Benzenesulfonyl-3-[2-piperidin-1-ylmethyl-prop-2-en-(*E*)-ylidene]-2,3-dihydro-1*H*-indole 18. Prepared by general procedure B. The product (60%) was isolated as a pale yellow oil. Found HRMS: 394.1711, $C_{23}H_{26}N_2O_2S$ requires: 394.1715. δ_H 7.89 (d, 1H, *J*=7.8 Hz, ArH), 7.81 (d, 2H, *J*=7.8 Hz, ArH), 7.76 (d, 1H, *J*=7.8 Hz, ArH), 7.54 (m, 1H, ArH), 7.42 (t, 2H, *J*=7.8 Hz, ArH), 7.22 (t, 1H, *J*=7.8 Hz, ArH), 6.89 (t, 1H, *J*=7.8 Hz, ArH), 5.89 (s, 1H, =CH), 5.27 (s, 2H, =CH), 4.56 (d, 2H, *J*=2.6 Hz, CH_2 ring), 2.95 (s, 2H, CH_2N), 2.34 (bs, 4H, piperidine H), 1.55 (m, 4H, piperidine H), 1.41 (m, 2H, piperidine H). *m/z* (%): 394 (M^+, 8), 311 (13), 253 (100), 168 (57), 154 (24), 141 (12), 98 (97), 86 (16), 77 (50), 69 (8) and 41 (22).

6.2.5. 4-[2-Piperidine-1-ylmethyl-prop-2-en-(*Z*)-ylidene]-3,4-dihydro-1*H*-naphthalene-2,2-dicarboxylic acid dimethyl ester 20. Prepared by general procedure B. The product (73%) was isolated as a pale yellow oil.

Found HRMS: 383.2077, $C_{23}H_{29}NO_4$ requires: 383.2096. δ_H 7.57 (d, 1H, J=7.9 Hz, ArH), 7.14 (m, 2H, ArH), 7.03 (m, 1H, ArH), 5.99 (s, 1H, =CH), 5.07 (s, 1H, =CH), 5.00 (s, 1H, =CH), 3.75 (s, 6H, CO_2CH_3), 3.31 (s, 2H, CH_2N), 2.92 (s, 4H, $ArCH_2$+CH_2C=), 2.37 (m, 4H, piperidine H), 1.58 (m, 4H, piperidine H) and 1.42 (m, 2H, piperidine H). δ (^{13}C NMR): 171.2, 142.4, 134.6, 134.3, 132.4, 128.4, 128.3, 128.1, 127.6, 125.1, 116.3, 64.2, 55.1, 54.6, 52.7, 40.0, 35.0, 25.9 and 24.4. m/z (%): 383 (M^+, 14), 352 (4), 324 (5), 179 (9), 165 (19), 136 (17), 98 (85), 86 (7), 71 (36), 57 (42) and 43 (100).

6.3. General procedure C for the synthesis of 21 and 24

NaH (4.3 mmol, 60% in mineral oil) was added to a stirred solution of alcohol (4-pentyn-1-ol or 3-butyl-1-ol, 4.0 mmol) in DMF (35 ml) at 0°C. Stirring was continued for 30 min followed by dropwise addition of 2-iodobenzyl chloride (4.0 mmol) in DMF (3 ml). The mixture was stirred for a further 15 h allowing it to warm to room temperature. Ether was then added, the mixture washed with saturated brine, the organic layer dried ($MgSO_4$), filtered and the filtrate evaporated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, petroleum ether–ether) to afford the product.

6.3.1. 1-(But-3-ynyloxymethyl)-2-iodo-benzene 21. Prepared by general procedure C. The product (61%) was isolated as a colourless oil. Found: C, 46.05; H, 3.7. $C_{11}H_{11}OI$ requires: C, 46.15; H, 3.85. δ_H 7.83 (d, 1H, J=7.8 Hz, ArH), 7.46 (d, 1H, J=7.8 Hz, ArH), 7.38 (t, 1H, J=7.8 Hz, ArH), 6.99 (t, 1H, J=7.8 Hz, ArH), 4.54 (s, 2H, $ArCH_2O$), 3.67 (t, 2H, J=7.1 Hz, OCH_2), 2.58 (m, 2H, OCH_2CH_2) and 2.02 (t, 1H, J=0.3 Hz, CH). m/z (%): 286 (M^+, 7), 258 (7), 231 (30), 217 (100), 159 (26), 129 (27), 105 (9), 90 (57), 63 (22) and 39 (34).

6.3.2. 1-Iodo-2-(pent-4-ynyloxymethyl)-benzene 24. Prepared by general procedure C. The product (85%) was isolated as a colourless oil. Found: C, 47.7; H, 4.25. $C_{12}H_{13}OI$ requires: C, 48.0; H, 4.33. δ_H 7.82 (d, 1H, J=8.0 Hz, ArH), 7.42 (d, 1H, J=8.0 Hz, ArH), 7.35 (t, 1H, J=8.0 Hz, ArH), 6.98 (t, 1H, J=8.0 Hz, ArH), 4.48 (s, 2H, $ArCH_2O$), 3.66 (t, 2H, J=6.1 Hz, OCH_2), 2.37 (m, 2H, $OCH_2CH_2CH_2$), 1.96 (t, 1H, J=2.8 Hz, CH) and 1.87 (q, 2H, J=6.4 Hz, $CH_2CH_2CH_2$). m/z (%): 300 (M^+, 7), 285 (36), 252 (11), 231 (37), 217 (1000), 173 (23), 145 (39), 131 (24), 117 (13), 90 (67), 78 (22) and 41 (28).

6.3.3. 1-{2-[3,4-Dihydro-1*H*-benzo-[*o*]oxepin-(5*Z*)-ylidenemethyl]-allyl}-piperidine 22. The product (68%) was isolated as a pale yellow oil. Found HRMS: 283.1928. $C_{19}H_{25}NO$ requires: 283.1936. δ_H 7.15 (m, 4H, ArH), 6.11 (s, 1H, =CH), 4.97 (s, 1H, =CH), 4.79 (s, 1H, =CH), 4.66 (s, 2H, $ArCH_2O$), 4.03 (bm, 2H, CH_2O), 2.66 (s, 2H, CH_2N), 2.47 (t, 2H, J=5.1 Hz, CH_2C=), 2.04 (bs, 4H, piperidine H) and 1.23–1.58 (m, 6H, piperidine H). m/z (%): 283 (M^+, 42), 254 (15), 230 (8), 198 (17), 185 (6), 167 (14), 155 (28), 136 (42), 128 (30), 115 (27), 98 (100), 84 (40) and 55 (35).

6.3.4. (1-{2-[3,4-Dihydro-1*H*-benzo-[*o*]oxepin-(5*Z*)-ylidenemethyl]-allyl}-pyrrolidine-2-yl)-methanol 23. The product (71%) was isolated as a pale yellow oil. Found HRMS: 299.1878. $C_{19}H_{25}NO_2$ requires: 299.1885. δ_H 7.19 (m, 4H, ArH), 6.09 (s, 1H, =CH), 5.03 (s, 1H, =CH), 4.72 (s, 1H, =CH), 4.63 (s, 2H, $ArCH_2O$), 4.03 (bs, 2H, CH_2O), 3.51 (dd, 1H, J=3.5, 9.0 Hz, pyrrolidine H), 3.32 (bd, 1H, pyrrolidine H), 3.19 (d, 1H, J=13.2 Hz, CH_2N), 2.93 (m, 1H, pyrrolidine H), 2.71 (d, 2H, J=13.5 Hz, CH_2N), 2.51 (t, 2H, J=4.4 Hz, CH_2C=), 2.11 (m, 1H, pyrrolidine H) and 1.89–1.62 (m, 4H, pyrrolidine H). m/z (%): 299 (M^+, 1), 268 (100), 169 (7), 153 (13), 141 (18), 128 (18), 114 (38), 91 (7), 77 (5), 70 (17), 57 (8) and 41 (15).

6.3.5. (1-{2-[4,5-Dihydro-1*H*-benzo-[*o*]oxepin-(6*Z*)-ylidenemethyl]-allyl}-piperidine 25. The product (25%) was isolated as a pale yellow oil. Found HRMS: 297.2086. $C_{20}H_{27}NO$ requires: 297.2093. δ_H 7.24 (m, 3H, ArH), 7.03 (m, 1H, ArH), 6.09 (s, 1H, =CH), 4.81 (s, 1H, =CH), 4.62 (s, 3H, $ArCH_2O$+=CH), 3.75 (m, 2H, CH_2O), 2.60 (bs, 2H, CH_2N), 2.49 (bm, 2H, CH_2C=), 2.04 (bs, 4H, piperidine H), 1.71 (m, 2H, $CH_2CH_2CH_2$) and 1.24–1.58 (m, 6H, piperidine H). m/z (%): 297 (M^+, 37), 268 (46), 212 (11), 199 (11), 183 (10), 177 (8), 167 (12), 153 (13), 145 (9), 136 (26), 128 (13), 115 (10), 98 (100), 85 (11), 69 (6), 57 (12) and 43 (26).

6.3.6. 1-[2-(2-Pent-4-ynyloxymethyl-phenyl)-ethyl]-piperidine 26. The product (18%) was isolated as a pale yellow oil. Found HRMS: 297.2090. $C_{20}H_{27}NO$ requires: 297.2093. δ_H 7.45 (m, 1H, ArH), 7.25 (m, 2H, ArH), 7.19 (m, 1H, ArH), 5.42 (s, 1H, =CH), 5.05 (d, 1H, J=1.4 Hz, =CH), 4.49 (s, 2H, $ArCH_2O$), 3.54 (t, 2H, J=6.1 Hz, CH_2O), 3.11 (s, 2H, CH_2N), 2.45 (bm, 4H, piperidine H), 2.33 (m, 2H, CH_2CH_2C), 1.94 (t, 1H, J=2.8 Hz, CH), 1.82 (q, 2H, J=6.7 Hz, $CH_2CH_2CH_2$), 1.51–1.61 (m, 4H, piperidine H) and 1.38–1.51 (m, 2H, piperidine H). m/z (%): 297 (M^+, 5), 230 (56), 145 (24), 129 (17), 115 (15), 98 (100), 84 (46), 69 (7), 55 (16) and 41 (25).

6.3.7. 1-[(*E*)-3-(2,3-Dihydro-benzofuran-3-yl)-2-methyl-allyl]-piperidine 27. A mixture of diene (**21**) (0.064 g, 0.25 mmol) and NMM (0.31 g, 0.27 mmol) in toluene (5 ml) was boiled under reflux for 18 h. The solvent was evaporated under reduced pressure and the residue purified by column chromatography (SiO_2, 7:3:0.1 v/v/v petroleum ether–ether–ammonia) to afford the product (0.054 g, 84%) as a colourless oil that solidified upon standing, mp 39–40.5°C. Found: C, 79.95; H, 8.25; N, 5.3. $C_{17}H_{21}NO$ requires: C, 80.0; H, 8.24; N, 5.49. δ_H 7.63 (s, 1H, ArH), 7.59 (d, 1H, J=7.8 Hz, ArH), 7.44 (d, 1H, J=8.0 Hz, ArH), 7.25 (m, 2H, ArH), 6.39 (s, 1H, =CH), 3.03 (s, 2H, CH_2N), 2.38 (bs, 4H, piperidine H), 1.93 (s, 3H, CH_3), 1.56–1.63 (m, 4H, piperidine H) and 1.41–1.52 (m, 2H, piperidine H). m/z (%): 255 (M^+, 83), 240 (31), 172 (62), 157 (21), 143 (20), 128 (57), 115 (19), 98 (100), 84 (60), 75 (15) and 43 (82).

6.3.8. 2′-Phenyl-7′-(piperidin-1-ylmethyl)-3,4-dihydro-1*H*-1′*H*,8′*H*-spiro[2-benzoxepine-5,5′-[1,2,4]triazolo[1,2-*a*]pyridazine]-1′,3′(2′*H*)-dione 29. A mixture of diene (**21**) (0.048 g, 0.17 mmol) and triazoline dione (**28**) (0.032 g, 0.19 mmol) in toluene (3 ml) was boiled under reflux for 24 h. An additional amount of (**28**) (0.016 g, 0.09 mmol) was then added and the mixture heated under reflux for a

further 12 h. The solvent was evaporated under reduced pressure and the residue purified by column chromatography (SiO_2, 50:1 v/v ether–ammonia) to afford the product (0.034 g, 44%) as a viscose oil. Found HRMS: 458.2327, $C_{27}H_{30}N_4O_3$ requires 458.2318. δ_H 7.08–7.59 (m, 9H), 6.03 (s, 1H), 5.02 (d, 1H, J=15.1 Hz), 4.70 (d, 1H, J=15.1 Hz), 4.49 (d, 1H, J=15.9 Hz), 4.20 (d, 1H, J=16.9 Hz), 3.97 (m, 2H), 3.39 (m, 1H), 3.00 (m, 2H), 2.31 (bs, 4H), 2.05 (dd, 1H, J=4.1, 13.9 Hz), 1.42–1.62 (m, 4H) and 1.38–1.42 (m, 2H). *m/z* (%): 458 (100), 373 (37), 339 (6), 282 (28), 255 (7), 225 (19), 182 (7), 167 (13), 154 (8), 141 (10), 112 (42), 98 (55), 84 (50), 69 (39), 55 (24) and 45 (21).

6.4. General procedure for the cascade cyclisation–allene insertion–anion capture reaction of vinyl halide zipper (30)

A Schlenk flask with a mixture of vinyl halide (0.3 mmol), secondary amine (0.6 mmol), K_2CO_3 (0.3 mmol) and $Pd(PPh_3)_4$ (0.03 mmol) in acetonitrile (15 ml) was evacuated (water pump) and then filled with nitrogen two times. After the third evacuation the flask was filled with allene and the mixture was heated at 70–75°C (oil bath temperature) for 17–20 h. The solvent was evaporated under reduced pressure, the residue dissolved in CH_2Cl_2, washed with water, dried ($MgSO_4$), the solvent evaporated under reduced pressure and the residue purified by column chromatography (SiO_2, petroleum ether–ether–ammonia) to afford the product.

6.4.1. 6-(3,4-Dihydro-2*H*-quinolin-1-ylmethyl)-1,3,4,5-tetrahydro-indene-2,2-dicarboxylic acid diethyl ester 32a. The product (77%) was isolated as a colourless oil. Found: C, 73.2; H, 7.7; N, 3.2. $C_{25}H_{31}NO_4$ requires: C, 73.35; H, 7.58; N, 3.42). δ_H 7.11 (m, 3H, ArH), 7.09 (m, 1H, ArH), 5.81 (s, 1H, =CH), 4.21 (q, 4H, J=7.2 Hz, O*CH*$_2$Me), 3.58 (s, 2H, ArNCH$_2$), 3.10 (s, 2H, CH$_2$N), 3.02 (bs, 4H, ArNCH$_2$), 2.88 (t, 2H, J=6.2 Hz, CH$_2$N), 2.69 (t, 2H, J=6.0 Hz, ArCH$_2$), 2.31 (bt, 2H, CH$_2$C=), 2.19 (bt, 2H, CH$_2$C=) and 1.25 (t, 6H, J=7.0 Hz, OCH$_2$*Me*). δ (^{13}C NMR): 172.3, 135.4, 135.1, 134.4, 131.8, 130.0, 128.6, 126.6, 126.0, 125.5, 120.2, 64.2, 61.5, 59.0, 58.5, 56.2, 50.6, 43.1, 41.3, 29.0, 26.0, 23.4 and 14.0. *m/z* (%): 409 (M$^+$, 45), 336 (15), 275 (11), 201 (33), 171 (28), 145 (32), 132 (56), 104 (28), 84 (100) and 47 (30).

6.4.2. 6-Pyrrolidine-1-ylmethyl-1,3,4,5-tetrahydro-indene-2,2-dicarboxylic acid diethyl ester 32b. The product (60%) was isolated as a colourless oil. Found: C, 68.95; H, 8.5; N, 3.85. $C_{20}H_{29}NO_4$ requires: C, 69.16; H, 8.36; N, 4.03). δ_H 5.75 (s, 1H, =CH), 4.20 (q, 4H, J=6.9 Hz, O*CH*$_2$Me), 3.04 (2×s, 6H, CH$_2$CCH$_2$+CH$_2$N), 2.46 (bm, 4H, pyrrolidine H), 2.29 (m, 2H, CH$_2$C=), 2.20 (m, 2H, CH$_2$C=), 1.78 (m, 4H, pyrrolidine H) and 1.24 (t, 6H, J=7.2 Hz, OCH$_2$*Me*). δ (^{13}C NMR): 172.3, 136.6, 131.1, 130.1, 118.9, 62.3, 61.4, 58.5, 54.3, 43.0, 41.3, 26.3, 23.4 and 14.0. *m/z* (%): 347 (M$^+$, 87), 346 (100), 302 (8), 274 (48), 201 (62), 175 (27), 129 (64), 109 (38), 84 (61) and 70 (42).

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