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PAPER

CH activation and CH_2 double activation of indolines by radical translocation: Understanding the chemistry of the indolinyl radical†

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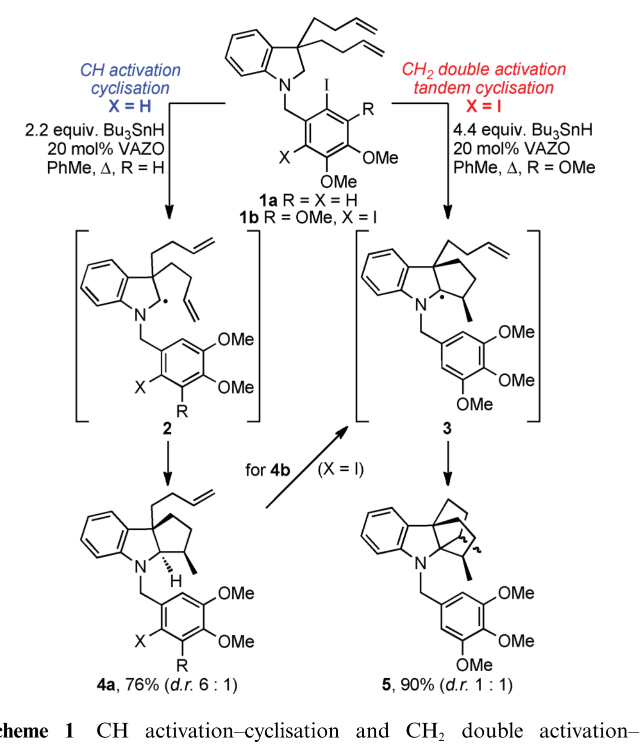
CH activation and CH_2 double activation of indolines at C2 may be achieved efficiently through radical translocation. The fate of the C2 indolinyl radical is dictated by the substitution at C3. Fragmentation, cyclisation and tandem cyclisation reactions leading to indole, azaheterocycle and azapropellane formation, respectively, are reported.

Introduction

Indoles and indolines have long been considered ‘privileged structures’ in medicinal chemistry owing to their ubiquitous presence in natural and pharmaceutical products. Consequently, their synthesis and functionalisation have been widely studied.[1–4] In recent years the introduction of transition metal-catalysed cross-coupling and CH bond activation strategies has provided useful methods for the direct introduction of aryl, alkyl, vinyl and alkynyl substituents.[5] In addition, the ability to induce intramolecular radical additions to both C2 and C3 of an indole and to metallate indolines at C2 with strong bases are notable advances.[3,6] CH activation of indolines leading to carbon-to-carbon bond formation is less well developed than for indoles, having been demonstrated under both transition metal catalysis[4] and, in a single example, through radical translocation and capture of samarium(II) iodide.[7] Herein we describe a detailed examination of the chemistry of the C2 indolinyl radical in which we exposed and exploited various fates including cyclisation, C3-fragmentation and tandem cyclisation reactions leading to annulation, indole and azapropellane formation, respectively.

Results and discussion

Before embarking on the study we sought an efficient method for the generation of C2 indolinyl radical intermediates. Translocation of an aryl radical tethered through the nitrogen seemed an appropriate starting point as this tactic has a proven track-record in other saturated nitrogen heterocyclic ring systems.[8] Thus, with indoline **1a** we were pleased to find that on treatment with Bu_3SnH under standard radical-forming conditions the envisioned arene to indoline radical translocation outpaced cyclisation to C7 to give **4a** in 76% yield as a 6 : 1 mixture of diastereomers (Scheme 1).[9,10] Moreover, when the same method was applied to the analogous diiodide **1b** it yielded azapropellane **5** as a 1 : 1 mixture of diastereoisomers in 90% yield, the result of a double activation–tandem radical cyclisation at C2.



Scheme 1 CH activation–cyclisation and CH_2 double activation–tandem cyclisation reactions. VAZO®–88: 1,1′-azobis (cyclohexane-1-carbonitrile).

The outcome was equally clear cut with indoline **6**, where the C2 radical intermediate **8** underwent fragmentation to indole **7** rather than cyclisation to the proximal arene to form **9** (Scheme 2).

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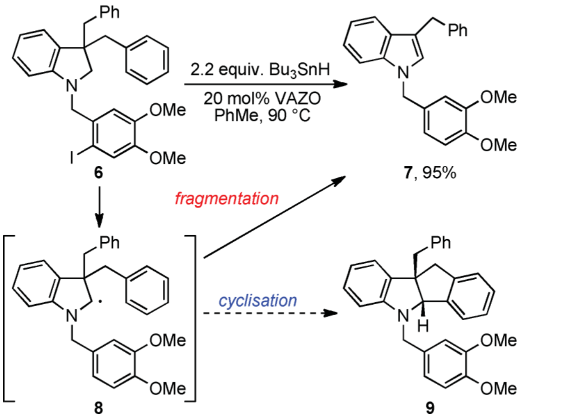
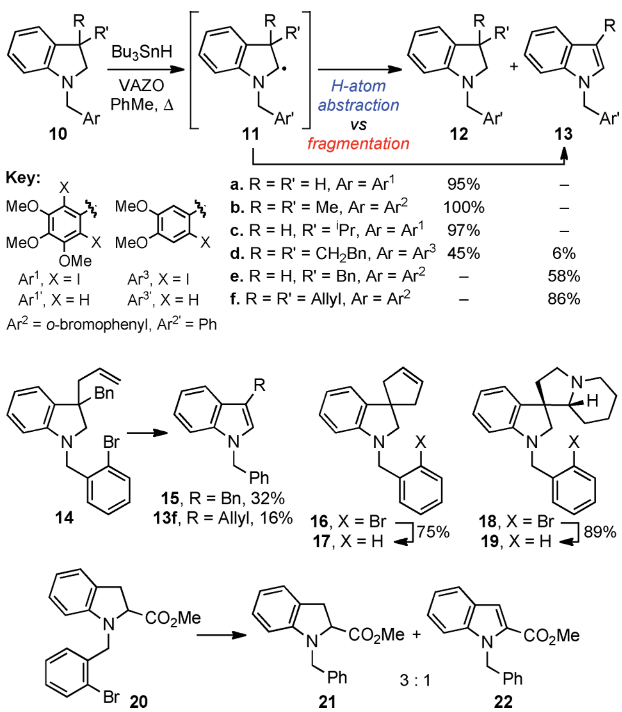
† Electronic supplementary information (ESI) available: Experimental details for the procedures described herein and for the preparation of starting materials are given, along with characterisation data and copies of recorded ^1H and ^{13}C NMR spectra. See DOI: 10.1039/c1ob05527e



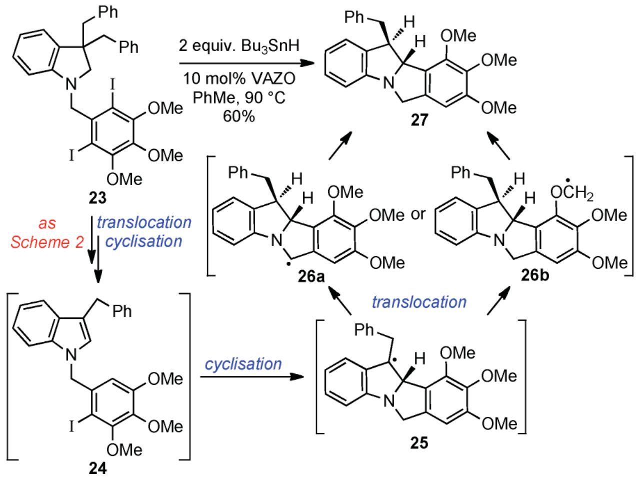
Scheme 2 Fragmentation of a C3 benzyl substituent.

Fragmentation of C3 allyl substituents was also facile (*viz.* **10f** → **13f**) and outpaced fragmentation of a C3 benzyl in the competition experiment **14** → **15** + **13f**.[11] Interestingly, no fragmentation was observed with spirocyclopentene **16**, which returned the product of halide reduction **17** (presumably *via* translocation and H-atom abstraction). Methyl, alkyl, aminoalkyl and hydrogen atoms at C3 resisted fragmentation (Scheme 3), though in the latter case this did compete with H-atom abstraction from tributyltin hydride when the C2 radical intermediate was stabilised by conjugation (*viz.* **20** → **21** + **22**).[12] Fragmentation of homobenzyl substituents at C3 was also observed as a minor pathway in the reaction **10d** → **12d** + **13d**, which unexpectedly gave rise to a complex product mixture.



Scheme 3 A study of C3 fragmentation reactions.

Finally, with the conversion of indoline **23** to the fused azaheterocycle **27** we have been able to show how the CH-activation/fragmentation sequence can be used to set up radical cyclisation reactions (Scheme 4). Interestingly, the product was given as a single diastereoisomer with delivery of a hydrogen atom to the concave face of intermediate **25**. It therefore seems likely that this too involves radical translocation to **26a** or **26b** providing an opportunity for further diversification.



Scheme 4 An alternative CH activation–cyclisation strategy leading to a fused azaheterocycle.

Conclusions

In summary, access to the C2-indolinyl radical is conveniently given by translocation of an aryl radical tethered to its nitrogen centre. The fate of that radical intermediate is dictated by the substitution at C3. Hydrogen, methyl, 1°- and 2°-alkyl and homoallyl substituents at C3 are resistant to fragmentation, providing an opportunity to exploit the C2-indolinyl radical in cyclisation and tandem cyclisation reactions. By contrast, benzyl and allyl substituents at C3 readily cleave in such circumstances leading to the corresponding indole. That fate extends, in part, to hydrogen atoms at C3 when the C2-indolinyl radical is stabilised by conjugation. The CH-activation/fragmentation sequence provides further opportunities for extension, as exemplified by the conversion of indoline **23** to the fused azaheterocycle **27**.

Experimental†

General techniques

Unless specified, commercially reagents were used without further purification. All reactions were carried out in oven-dried glassware under an atmosphere of argon. Toluene, THF and diethyl ether were freshly distilled from a purple solution of sodium and benzophenone. Dichloromethane and chloroform were freshly distilled from CaH_2. Flash column chromatography was performed using silica gel (60A Particle Size 30–70 micron) with the stated solvent system. Chromatographic purification of organotin-containing reaction mixtures was performed using 10% w/w anhydrous K_2CO_3 in silica gel.[13] Melting points were recorded on a Reichert Austria apparatus and are uncorrected. Infrared spectra were recorded neat as a film or compressed solid using the ATR/golden gate method and are quoted in wavenumbers (cm^{-1}). ^1H NMR spectra were recorded on either a Bruker AV-300 (300 MHz) or DPX-400 (400 MHz) spectrometer operating at 298 K. ESI mass spectra were recorded using a VG Platform Quadrupole Electrospray Ionisation mass spectrometer, measuring mono-isotopic masses (mode: ES+ or ES–). EI and CI spectra were measured on a Thermoquest Trace MS.

Synthetic procedures

8b-But-3-enyl-4-(3,4-dimethoxybenzyl)-3-methyl-1,2,3,3a,4,8b-hexahydrocyclopenta[*b*]indole (4a). A solution of **1a** (200 mg, 0.40 mmol), tributyltin hydride (0.24 mL, 0.87 mmol) and VAZO (20 mg, 0.08 mmol) in toluene (20 mL) was heated at reflux for 4 h, then cooled and concentrated *in vacuo*. Purification by column chromatography (10% w/w anhydrous K_2CO_3–silica;[13] 10% diethyl ether in petroleum ether) afforded the *title compound* as a brown oil (120 mg, 0.31 mmol, 76%), as a 6 : 1 mixture of diastereoisomers. ^{1}H NMR (400 MHz, $CDCl_3$) *major diastereoisomer* δ 7.48 (app. td, J = 7.9, 1.1 Hz, 1H), 7.43 (dd, J = 7.3, 1.1 Hz, 1H), 7.34–7.28 (m, 3H), 7.13 (app. td, J = 7.3, 0.6 Hz, 1H), 6.87 (d, J = 7.9 Hz, 1H), 6.16 (ddt, J = 16.7, 10.7, 6.1 Hz, 1H), 5.39–5.31 (m, 2H), 5.04 (d, J = 15.9 Hz, 1H), 4.65 (d, J = 15.9 Hz, 1H), 4.34 (s, 3H), 4.25 (s, 3H), 4.11 (d, J = 5.8 Hz, 1H), 2.59–2.46 (m, 2H), 2.45–2.35 (m, 2H), 2.34–2.02 (m, 4H), 1.82 (m, 1H), 1.57 (d, J = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *major diastereoisomer* δ 153.2 (C), 148.9 (C), 148.0 (C), 138.8 (CH), 136.3 (C), 131.2 (C), 127.3 (CH), 122.8 (CH), 119.8 (CH), 117.1 (CH), 113.9 (CH_2), 111.0 (CH) 110.9 (CH), 107.0 (CH), 75.0 (CH), 56.9 (C), 55.8 (CH_3), 55.7 (CH_3), 53.3 (CH_2), 41.5 (CH), 40.9 (CH_2), 40.6 (CH_2), 32.6 (CH_2), 30.1 (CH_2), 14.9 (CH_3). IR (neat) ν_{max} 3077, 3003, 2929, 2856, 2827, 1601, 1513, 1485, 1461. LRMS-CI (m/z, %): 378 (30), 151 (100). HRMS-ES$^+$ (m/z): [M + H]$^+$ calcd for $C_{25}H_{32}NO_2$ 378.2428; found, 378.2428.

2 - Aza - 2 - (3,4,5 - trimethoxybenzyl) - 8,11 - dimethylbenz[*c*]tri - cyclo[3,3,3,0^{1,5}] undecane (5). A solution of **1b** (300 mg, 0.46 mmol), tributyltin hydride (0.55 mL, 2.02 mmol) and VAZO (23 mg, 0.09 mmol) in toluene (20 mL) was heated at reflux for 16 h, then cooled and concentrated *in vacuo*. Purification by column chromatography (10% w/w anhydrous K_2CO_3–silica;[13] 5–10% diethyl ether in petroleum ether) afforded the *title compound* as a white solid (170 mg, 0.41 mmol, 90%) as a 1 : 1 mixture of diastereoisomers. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.04 (dd, J = 7.3, 1.0 Hz, 1H), 7.05 (dd, J = 7.3, 1.0 Hz, 1H), 6.92 (app. td, J = 7.7, 1.4 Hz, 1H), 6.91 (app. td, J = 7.7, 1.4 Hz, 1H), 6.63 (app. tt, J = 7.3, 1.0 Hz, 1H + 1H), 6.57 (br. s, 1H + 1H), 6.53 (br. s, 1H + 1H), 6.01 (d, J = 7.6 Hz, 1H), 5.95 (d, J = 7.6 Hz, 1H), 4.72 (d, J = 16.8 Hz, 1H), 4.44 (s, 1H + 1H), 4.25 (d, J = 16.8 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.79 (s, 6H), 3.78 (s, 6H), 2.19–1.97 (m, 4H + 4H), 1.94–1.76 (m, 2H + 2H), 1.75–1.57 (m, 2H + 2H), 1.54–1.32 (m, 2H + 2H), 1.26 (d, J = 6.9 Hz, 3H), 1.11 (d, J = 6.9 Hz, 3H), 0.92 (d, J = 7.0 Hz, 3H + 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.4 (2 × C), 152.6 + 151.8 (C), 138.5 + 137.9 (C), 135.3 (C), 135.1 (C), 127.2 + 127.2 (CH), 122.7 + 122.5 (CH), 117.3 + 117.0 (CH), 107.5 (CH), 105.7 (CH), 103.8 + 103.7 (CH), 91.4 + 87.4 (C), 67.5 + 64.3 (C), 61.1 (CH_3), 56.3 + 56.2 (2 × CH_3), 52.8 + 50.8 (CH_2), 44.0 + 43.6 (2 × CH), 41.5 + 41.1 + 40.1 (2 × CH_2), 35.0 + 34.3 + 33.8 (2 × CH_2), 16.4 + 15.2 + 15.1 (2 × CH_3). IR (neat) ν_{max} 2933, 2868, 2848, 1687, 1588, 1499. LRMS-ES$^+$ (m/z, %): 408 (50), 228 (100). HRMS-ES$^+$ (m/z): [M + Na]$^+$ calcd for $C_{26}H_{33}NNaO_3$ 430.2353; found, 430.2349.

3-Benzyl-1-(3,4-dimethoxybenzyl)-1*H*-indole (7). A solution of **6** (350 mg, 0.61 mmol), tributyltin hydride (0.36 mL, 1.34 mmol) and VAZO (0.12 mmol, 30 mg) in toluene (25 mL) was heated at reflux for 16 h, then cooled and concentrated *in vacuo*. Purification by column chromatography (10% w/w anhydrous K_2CO_3–silica;[13] 5% diethyl ether in petroleum ether) afforded the *title compound* as a brown oil (210 mg, 0.58 mmol, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (dd, J = 7.8, 0.9 Hz, 1H), 7.38–7.31 (m, 4H), 7.26–7.21 (m, 3H), 7.14 (ddd, J = 7.8, 6.9, 1.0 Hz, 1H), 6.93 (s, 1H), 6.86 (d, J = 8.1 Hz, 1H), 6.75 (dd, J = 8.1, 1.9 Hz, 1H), 6.71 (d, J = 1.9 Hz, 1H), 5.27 (s, 2H), 4.20 (s, 2H), 3.92 (s, 3H), 3.83 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.3 (C), 148.5 (C), 141.4 (C), 136.9 (C), 130.2 (2 × C), 128.6 (2 × CH), 128.3 (2 × CH), 126.4 (CH), 125.8 (CH), 121.7 (CH), 119.3 (CH), 119.2 (CH), 119.0 (CH), 114.8 (C), 111.3 (CH), 110.1 (CH), 109.6 (CH), 55.9 (CH_3), 55.8 (CH_3), 49.7 (CH_2), 31.5 (CH_2). IR (neat) ν_{max} 3052, 3027, 2999, 2933, 2901, 2823, 1514, 1463, 1452. LRMS-ES$^+$ (m/z, %): 258 (100). HRMS-ES$^+$ (m/z): [M + H]$^+$ calcd for $C_{24}H_{24}NO_2$ 358.1802; found, 358.1804.

Methyl 1-benzylindoline-2-carboxylate (21) and methyl 1-benzyl-1*H*-indole-2-carboxylate (22). A solution of **20** (569 mg, 1.64 mmol), tributyltin hydride (0.97 mL, 3.61 mmol) and VAZO (81 mg, 0.33 mmol) in toluene (50 mL) was heated at reflux for 18 h, then cooled and concentrated *in vacuo*. Purification by column chromatography (10% w/w anhydrous K_2CO_3–silica;[13] 2–5% diethyl ether in petroleum ether) afforded firstly **22** as a colourless oil (102 mg, 0.38 mmol, 24%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, J = 8.1 Hz, 1H), 7.44 (s, 1H), 7.41 (d, J = 8.1 Hz, 1H), 7.36 (dd, J = 6.6, 1.1 Hz, 1H), 7.28 (d, J = 7.5 Hz, 1H), 7.33–7.17 (m, 3H), 7.10 (m, 2H), 5.89 (s, 2H), 3.91 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.3 (C), 139.5 (C), 138.2 (C), 128.5 (2 × CH), 127.3 (CH), 127.1 (C), 126.2 (2 × CH), 126.1 (C), 125.3 (CH), 122.7 (CH), 120.8 (CH), 111.1 (CH), 110.8 (CH), 51.6 (CH_3) 47.8 (CH_2). IR (neat) ν_{max} 3062, 3031, 2857, 1706, 1605, 1518, 1248, 1191. LRMS-EI (70 eV, m/z, %): 265 (57), 233 (12), 206 (6), 188 (4), 91 (100). HRMS-ES$^+$ (m/z): [M + Na]$^+$ calcd for $C_{17}H_{15}NNaO_2$ 288.0995; found, 288.0994. Then **21** as a pale yellow oil (290 mg, 1.09 mmol, 67%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.14 (m, 5H), 7.02–6.93 (m, 2H), 6.62 (app. td, J = 7.4, 0.7 Hz, 1H), 6.39 (d, J = 7.8 Hz, 1H), 4.44 (d, J = 15.4 Hz, 1H), 4.25 (d, J = 15.4 Hz, 1H), 4.19 (dd, J = 10.3, 8.1 Hz, 1H), 3.59 (s, 3H), 3.31 (dd, J = 15.9, 10.3 Hz, 1H), 3.12 (dd, J = 15.9, 8.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3 (C), 151.3 (C), 137.7 (C), 128.4 (2×CH), 127.8 (2×CH), 127.7 (CH), 127.2 (CH), 126.8 (C), 124.1 (CH), 118.1 (CH), 107.2 (CH), 65.2 (CH), 52.1 (CH_2), 52.0 (CH_3), 33.4 (CH_2). IR (neat) ν_{max} 3053, 3027, 2950, 2849, 1733, 1605, 1484, 1195, 1156. LRMS-EI (70 eV, m/z, %): 267 (25), 208 (54), 117 (17), 91 (100). HRMS-ES$^+$ (m/z): [M + Na]$^+$ calcd for $C_{17}H_{17}NNaO_2$ 290.1151; found, 290.1156.

11-Benzyl-8,9,10-trimethoxy-10b,11-dihydro-6*H*-isoindolo [2,1-*a*]indole (27). A solution of **23** (500 mg, 0.68 mmol), tributyltin hydride (3.01 mmol, 0.81 mL) and VAZO (0.14 mmol, 33 mg) in toluene (40 mL) was heated at reflux for 16 h, then cooled and concentrated *in vacuo*. Purification by column chromatography (10% w/w anhydrous K_2CO_3–silica;[13] 5% diethyl ether in petroleum ether) afforded the *title compound* as a colourless oil (160 mg, 0.40 mmol, 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.36 (m, 4H), 7.31 (m, 1H), 7.17 (app. dt, J = 7.5, 1.3 Hz, 1H), 6.87–6.80 (m, 2H), 6.78 (ddd, J = 7.9, 7.2, 0.8 Hz, 1H), 6.51 (s, 1H), 5.06 (br. s, 1H), 4.55 (dd, J = 14.6, 1.3 Hz, 1H), 4.48 (d, J = 14.6 Hz, 1H), 4.18 (br. dt, J = 7.5, 1.9 Hz, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.70 (s, 3H), 3.16 (dd, J = 13.3, 8.2 Hz, 1H), 3.07 (dd, J = 13.3, 7.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1 (C), 154.1 (C), 149.5 (C), 140.9 (C), 140.0 (C), 135.0 (C), 134.0 (C), 129.7 (2 × CH), 128.2 (2 × CH), 127.8 (CH), 127.1 (C), 126.1 (CH), 124.8 (CH), 120.3 (CH), 112.0 (CH), 101.3 (CH), 74.7 (CH), 60.8 (CH_3), 60.3 (CH_3), 59.4 (NCH_2), 56.1 (CH_3), 48.1 (CH), 43.2 (CH_2). IR (neat) ν_{max} 3032, 2995, 2938, 2856, 1597. LRMS-CI (m/z, %): 388 (80), 296 (100), 280 (15), 195 (20), 167 (20), 91 (30). HRMS-ES$^+$ (m/z): $[M + H]^+$ calcd for $C_{25}H_{26}NO_3$ 388.1907; found, 388.1901.

Acknowledgements

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9 The reaction can also be mediated by tris(trimethylsilyl)silane (TTMSS) and an example related to those in Scheme 1 is presented in the ESI†.

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12 Competition between H-atom abstraction from tributyltin hydride and indole formation is also manifest in related radical cyclisations to indoles [ref. 6]. We note that where an intermediate indolinyl radical is stabilised by conjugation, these reactions show a greater tendency to follow the 'oxidative' cyclisation pathway leading to indoles.

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