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Radical cyclisation reactions with indoles

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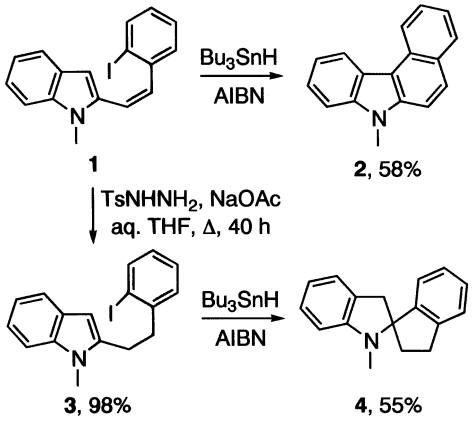
Abstract—Several radical cyclisation reactions involving indoles are described. Most notably, we have shown that radical additions to C3 of an indole are frequently facile. A dichotomy in the course of radical cyclisation reactions to C2 of the indole has also been exposed wherein 6-*endo*-trig cyclisations are propagated by the loss of a hydrogen atom from C2 while 5-*exo*-trig cyclisations are propagated by hydrogen atom abstraction at C3 from tributyltin hydride. Cyclisations involving the addition of indolyl radical intermediates to arenes have also been demonstrated.

Intramolecular additions of carbon centred radical intermediates to arenes and aromatic heterocycles have gained considerable prominence in recent years as they provide mild and often high yielding routes to condensed aromatic ring systems.[1,2] One unusual feature of such processes is that products derived from a non-reducing pathway are frequently observed even when tributyltin hydride is employed as a mediator.[1] In this letter we describe a series of radical cyclisation reactions in which an indole is employed as a radical acceptor.[3] Notably, cyclisations to C2 and C3 have each been accomplished providing access to various benzocarbazoles and indoline derivatives.

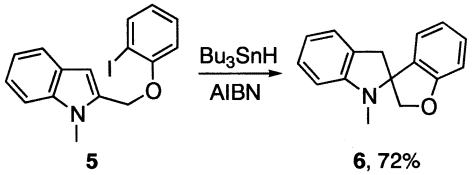
Our first objective was to see if radical cyclisations to C3 of an indole could be effected.[3j–k] To that end indoles **1** and **3** were prepared and treated with tributyltin hydride under standard radical forming conditions using 20 mol% AIBN as an initiator. For 2-styrylindole **1**, cyclisation occurred to C3 of the indole by a *6-endo*-trig pathway giving benzo[*c*]carbazole **2** in 58% yield, together with 26% recovered **1**. By contrast, **3** gave spirocycle **4** as the major product in 55% yield (Scheme 1). Spirocyclisation was more pronounced when an ether was used to conjoin the radical precursor to the indole;[4] **5** giving spirocycle **6** in 72% yield (Scheme 2).

A similar reactivity profile was noted with indoles **7** and **9**. While 3-styrylindole **7** underwent cyclisation to benzo[*a*]carbazole **8** in 90% yield, the analogous alkane **9** gave mainly spirocycle **12**, with benzocarbazole **13** accounting for the remainder of the mass balance. Notably, no products derived from rearrangement or fragmentation of the radical intermediate **10** were observed (Scheme 3).[5]

A fragmentation reaction was however observed when ether **14** was treated with tributyltin hydride. The primary product of the reaction was the expected spirocycle **18** derived from a 6-*exo*-trig spirocyclisation to C2



Scheme 1.



Scheme 2.

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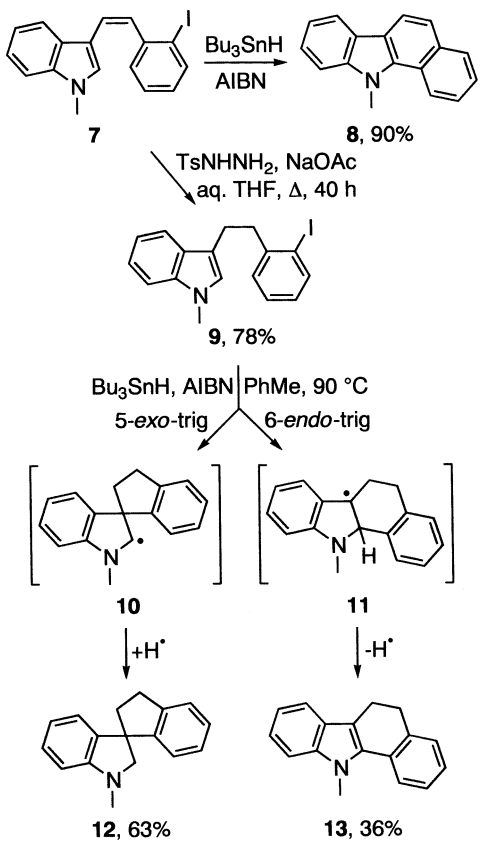
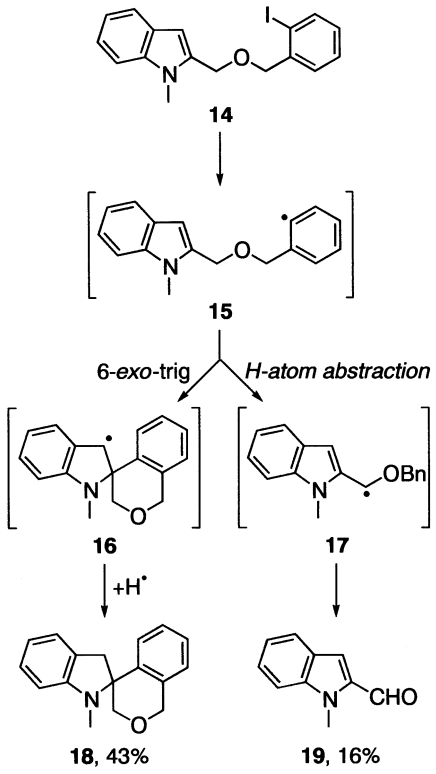


Scheme 3.



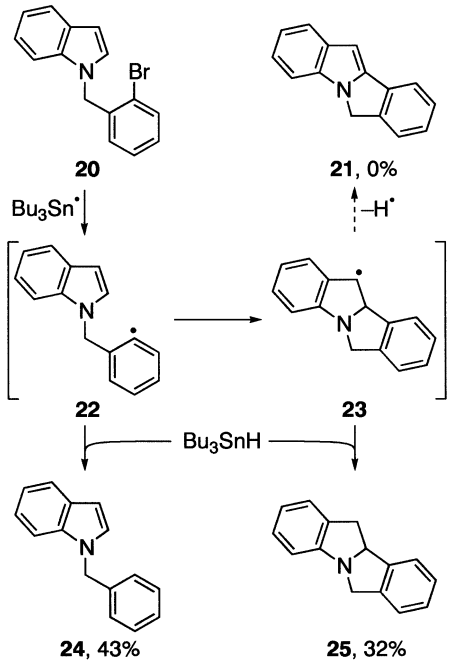
Scheme 4.

of the indole. The only other product to have been identified conclusively was aldehyde **19**, which is presumably formed by hydrogen atom abstraction, viz. **15**→**17**. Ejection of $PhCH_2^{\bullet}$, or intermolecular trapping with molecular oxygen, then facilitates collapse to aldehyde **19** (Scheme 4).

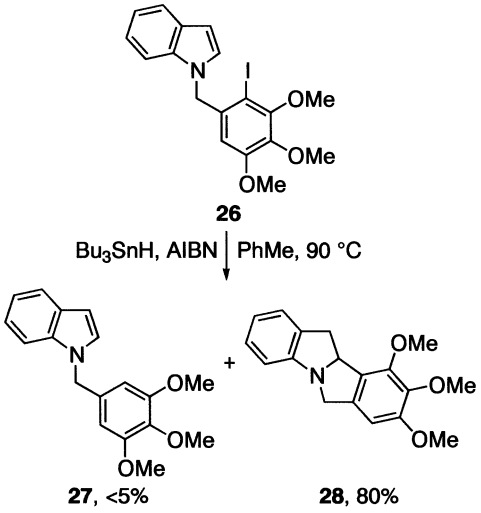
Our attention next turned to radical cyclisation reactions of *N*-(*o*-halobenzyl)indoles. Pleasingly, when a toluene solution of **20** was heated at 90°C with tributyltin hydride and 20 mol% AIBN, the product mixture comprised of *N*-benzylindole **24** and 10b,11-dihydro-6*H*-isoindolo[2,1-*a*]indole **25**.[6] In stark contrast to the cyclisation **9**→**13**, radical intermediate **23** was quenched by tributyltin hydride rather than suffer loss of a hydrogen atom leading to **21** (Scheme 5). It is also pertinent to note that attempts to effect an analogous five ring closure to a pyridine had given only products derived from carbon to halogen bond reduction.[5] It therefore seemed appropriate to study this reaction in more detail.

We soon established that the efficiency of such 5-*exo*-trig radical cyclisations to indoles was strongly influenced by substituents on the arene ring. Thus, while the unsubstituted arene **20** gave dihydroisoindoloindole **25** in a modest 32% yield, the corresponding trimethoxy derivative **26** gave **28** in 80% yield (Scheme 6). The stereochemical course of such reactions was also influenced by arene substitution (Scheme 7, Table 1).[7] This observation can be attributed to steric factors, with hydrogen atom abstraction from tributyltin hydride favouring the course of lowest steric demand.

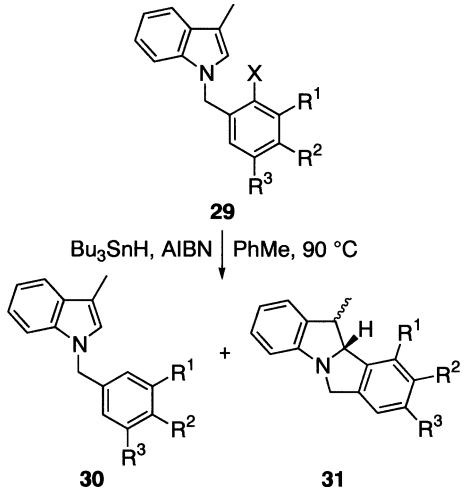
Cyclisations wherein the indole serves as a radical donor and the arene as a radical acceptor have also been examined.[8] For *cis*-3-iodo-2-styrylindole **32**, the



Scheme 5.

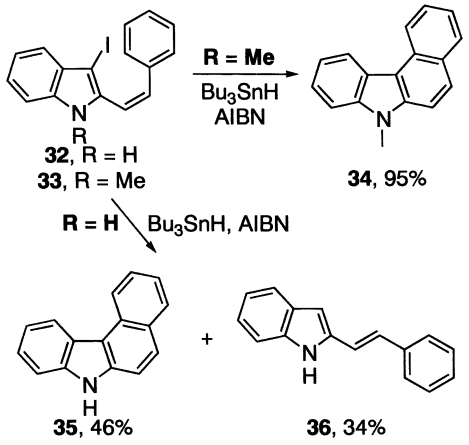


Scheme 6.



Scheme 7.

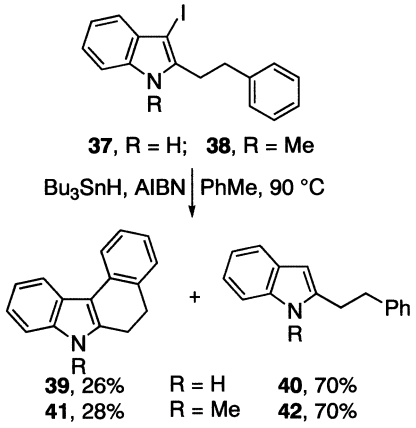
expected benzocarbazole **35** was given in a modest 46% yield together with *trans*-2-styrylindole **36** (34%). Remarkably, under the same reaction conditions the analogous *N*-methyl derivative **33** gave benzocarbazole **34** in 95% yield (Scheme 8)! The result suggests that isomerisation of the alkene, by addition and elimination of $Bu_3Sn^{\bullet}$, only competes with carbon to halogen bond homolysis when the alkene tether is conjugated to the indole ring system. Substituents on nitrogen render this conformation less favourable and hence retard the rate at which the byproduct is formed.



Scheme 8.

The *cis*-alkene tether was found to be essential for achieving efficient cyclisation reactions with this system; 3-iodoindoles **37** and **38** giving benzocarbazoles **39** and **41**, respectively, in low yield. The products of halide reduction, **40** and **42**, accounted for much of the mass balance in each case (Scheme 9).

In conclusion, several radical cyclisation reactions involving indoles have been studied. Most notably, we have shown that radical additions to C3 of an indole can be achieved in good yield through both 5-*exo*-trig spirocyclisation (e.g. **9**→**12**) and 6-*endo*-trig *ortho*-cyclisation of a suitably functionalised *cis*-2-styrylindole derivative (e.g. **1**→**2**). A dichotomy in the course of radical cyclisation reactions to C2 of the indole has also been exposed. While 6-*endo*-trig cyclisation reactions



Scheme 9.

Table 1. Summary of reactions illustrated in Scheme 7[7]

Entry	R^1	R^2	R^3	X	**30** (%)	**31** (%)	α-:β-CH_3
a	H	H	H	Br	11	38	1:1
b	H	H	H	I	16	35	1:1
c	H	OCH_2O		Br	26	54	3:2
d	H	OMe	OMe	I	30	56	2:1
e	OMe	OMe	OMe	I	10	66	1:3

(e.g. **9**→**11**) are propagated by the loss of a hydrogen atom from C2, 5-*exo*-trig cyclisations (e.g. **22**→**23**) are propagated by hydrogen atom abstraction from tributyltin hydride. Finally, cyclisation reactions involving the addition of indolyl radical intermediates to arenes have been demonstrated.

Acknowledgements

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