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Ynones in dearomative spirocyclisation processes; a review

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ABSTRACT

This review concentrates on our research into the discovery of novel ynone-based dearomative spirocyclisation processes, whilst placing the new chemistry into the context of existing knowledge. The genesis of the research programme, the development of efficient synthetic routes to prepare the novel natural products spirobacillene A (**1**) and spirobacillene B (**2**), utilised the dearomative spirocyclisation of indole ynones. This stimulated a much wider study to explore the reactivity of ynones in dearomative spirocyclisation processes more generally. Routes to generate a wide range of spirocycles were subsequently developed, with dearomative reactions of ynones tethered to indoles, benzofurans, benzisoxazoles, pyrroles, pyridines, isoquinolines, pyrazines, cyclic ketimines, and anisoles all discussed herein, with these reactions initiated by catalytic Ag(I), Cu(II), Pd(0), visible light and many other reagents. Asymmetric variants of some of the reactions are also discussed, as is further elaboration of the spirocyclic products to give carbazoles, quinolones, polycycles and other useful synthetic building blocks. Finally, applications of the new methodology in natural product synthesis (*e.g.* spirobacillene A, lasubine II and indolizidine 209D) are described.

1. Introduction

The synthesis and functionalisation of indoles [1,2] is synthetically important given the prevalence of indole derivatives in pharmaceuticals, agrochemicals, biological probes and in various other industrial applications [3]. Our York groups have had a long-standing interest in the development of novel routes to indoles, oxindoles and related heterocyclic systems [4a-b], and also in spirocycle synthesis [4c-g], especially via dearomative methods [5,6]. However, our involvement in indole functionalisation using ynones was initiated not by our prior work, but by a publication by Kwon and coworkers in 2012, describing the isolation of novel natural products, spirobacillene A (**1**) and spirobacillene B (**2**), from the extremophile bacterium *Lysinibacillus fusiformis* [7]. Both spirobacillene structures are based on completely novel carbon frameworks within the natural product field. In addition, spirobacillene A (**1**) was found to display inhibitory activity against the production of nitric oxide and reactive oxygen species [7]. We therefore initiated a synthetic programme based on the spirobacillenes and the approach which eventually proved to be successful [8] is summarised in Scheme 1.

Our successful total synthesis of spirobacillene A (**1**) [8] had as its cornerstone the spirocyclisation of indole ynone **3**; treatment of ynone **3** with an excess of $SnCl_2.2H_2O$ cleanly gave the key spirocyclic dienone product **4** in excellent yield. This reaction is proposed to operate via activation of the alkyne towards nucleophilic attack from the electron-rich anisole moiety via its *para*-position, hence leading to spirocyclisation; this transformation is described in more detail later in the review (see Scheme 34) with an improved synthesis of spirocycle **4** also included later (see Scheme 36). Further synthetic elaborations (not shown) then generated the desired natural product **1** [8]. A preliminary study was then carried out on the complementary indole 3-ynone **5a**, which revealed that spirocyclisation of this substrate can also be achieved using the same $SnCl_2.2H_2O$ conditions, but in this case, spirocyclisation took place via nucleophilic attack from the C-3 position of the electron-rich indole moiety, furnishing spirobacillene B analogue **6a** in 55 % yield [9]. Both strategies were inspired by related dearomative spirocyclisation transformations [5,10], utilising the activation of alkynes tethered to electron-rich aromatic systems; most relevant is the seminal report from Larock and coworkers in 2005 [10a].

Thus, complementary approaches to both natural product scaffolds from structurally similar ynone precursors had been established. The remarkable ease of both novel reaction types piqued our interest further and prompted us to initiate a larger research programme to explore the reactivity of ynones in dearomative spirocyclisation processes much more generally. Little did we know at the onset how these initial results

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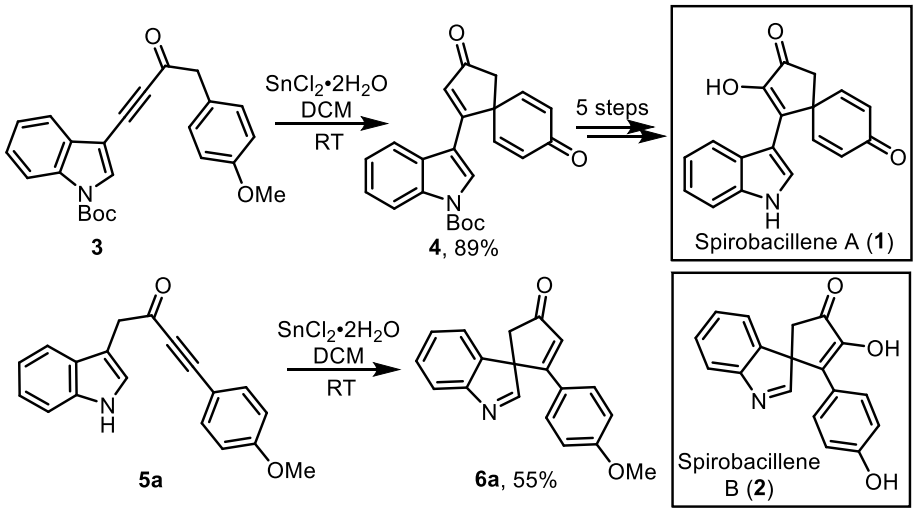


Scheme 1. Total Synthesis of spirobacillene A (**1**) and synthesis of spirocycle **6a**, an analogue of spirobacillene B (**2**).

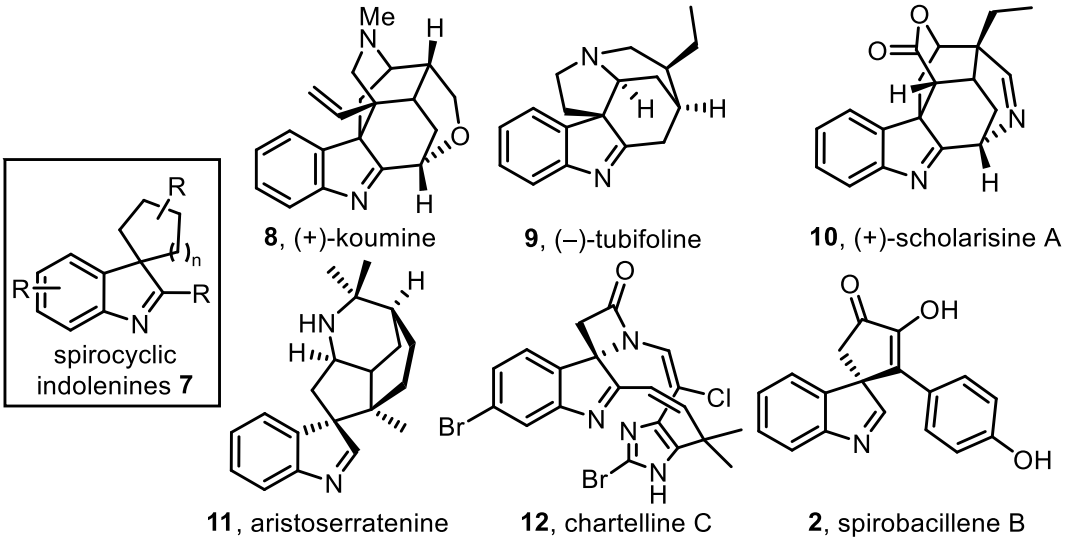


Fig. 1. Spirocyclic indolenine natural products.

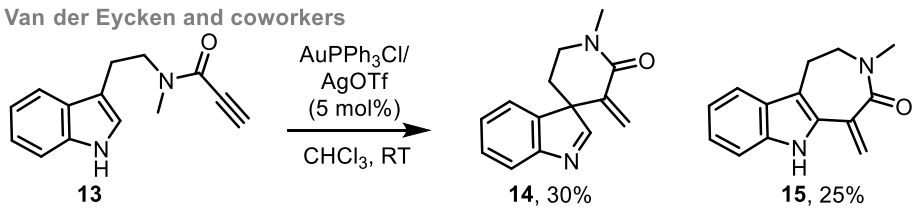
would take us on a journey of discovery through the myriad new ynone methodologies detailed in this review!

The review commences with a discussion of the optimisation and scope of indole 3-ynone dearomative spirocyclisation processes using metal catalysis (including asymmetric variants). Photochemical/radical approaches to the dearomative spirocyclisation of indole 3-ynones are then discussed, including a recent extension to benzisoxazole-ynones. An overview of cascade sequences which lead to further diversification of the spirocyclic products giving a range of heterocyclic and polycyclic products are then reviewed. Finally, extension of the dearomative spirocyclisation procedure to other heterocyclic- and carbocyclic-ynones (derived from benzofurans, pyrroles, pyridines, isoquinolines, pyrazines, cyclic ketimines, anisoles and phenols) are then overviewed, along with applications in natural product synthesis. The review is not intended be comprehensive and is largely focused on our own contributions to discover new dearomative processes using ynones tethered to aromatics and heteroaromatics. However, selected contributions from other groups that informed our own studies are also covered, especially those that most influenced our thinking and reaction design.

2. Optimisation of indole 3-ynone dearomative spirocyclisations

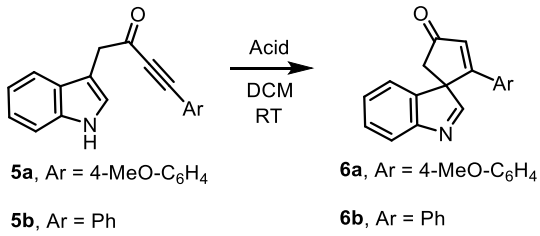
Having discovered the novel dearomatision/spirocyclisation of indolyl ynone **5a**, and knowing the value of the resulting spirocyclic indolenines (also known as spiroindolenines or spirocyclic 3*H*-indoles), we set out to explore this unusual transformation further. Rigid, three-dimensional molecular scaffolds, particularly those containing nitrogen heterocycles, have attracted significant attention in drug discovery research in recent years [6,11]; this interest is partly driven by a desire to examine under-explored regions of three-dimensional chemical space [12]. Spirocyclic indolenines **7** are therefore important systems in this context [12c], and they also have significant therapeutic potential in their own right, exemplified in a range of biologically active natural products (**2**, **8**–**12**, Fig. 1) [7,13]. In addition, the versatile reactivity of spirocyclic indolenines allows ready access to other important heterocycles, including indolines, oxindoles, carbazoles and others [1,2,14], as will be discussed in more detail later.

We started by seeking to explore further the synthesis of spirocyclic indolenines via the process outlined for their preparation in Scheme 1 (**5a** → **6a**). The ability to generate such compounds by dearomative spirocyclisation processes from simple indoles seemed attractive; however, a cautionary approach was suggested when literature precedents



Scheme 2. Gold catalysed dearomative spirocyclisation of indole-tethered propargylic amide **13** [15].

Table 1
Optimisation of the dearomative spirocyclisation of ynones **5a/b**.



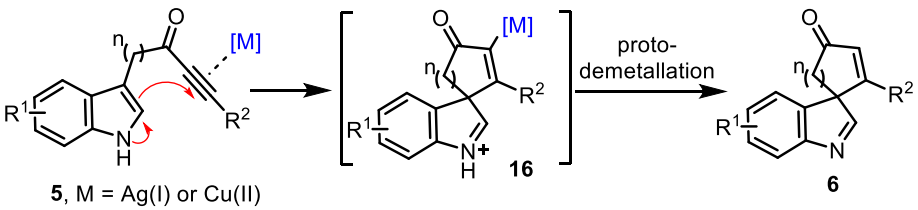
Entry	Starting material	Acid	Equivalents/Time [h]	Yield
1	**5a**	none	0/20	0 %
2	**5a**	PPh_3AuCl	0.1/1	**6a**, trace
3	**5a**	PPh_3AuCl/ AgOTf	0.1/1	**6a**, 0 %
4	**5a**	$Cu(OTf)_2$	1/20	**6a**, 80 %
5	**5a**	$Cu(OTf)_2$	0.01/8.5	**6a**, 89 %
6	**5a**	$AgNO_3$	0.01/2.5	**6a**, 97 %
7	**5a**	AgOTf	0.1/1	**6a**, 95 %
8	**5a**	AgOTf	0.01/0.5	**6a**, 100 %
9	**5a**	TfOH	0.01/1	**6a**, trace
10	**5b**	$AgNO_3{\cdot}SiO_2$	0.01/0.5	**6b**, 98 %

were studied [15–18]. A significant problem with this type of transformation appeared to be the proclivity with which the spirocyclic products undergo 1,2-migration under acidic conditions to restore aromaticity. An illustrative example of this was reported by Van der Eycken's group (Scheme 2) [15]: spirocyclic indolenine **14** was formed in 30 % yield when alkyne **13** was treated with $AuPPh_3Cl/AgOTf$, alongside a second major product, indole **15**, which may have resulted from the 1,2-migration and rearomatisation of **14** (or alternatively via direct C-2 cyclisation, although this 7-membered ring cyclisation pathway is perhaps less likely). Indeed, while processes involving the electrophilic activation of alkynes had been well-studied at this time [16], Van der Eycken's example was, to the best of our knowledge, the highest yielding acid-catalysed spirocyclisation of its type reported in the literature; in related processes, aromatic C-2 annulated indole products such as compound **15** are reported far more often (and not only with indoles – a similar tendency to form annulated products rather than spirocycles is observed across a range of heteroaromatics) [17,18].

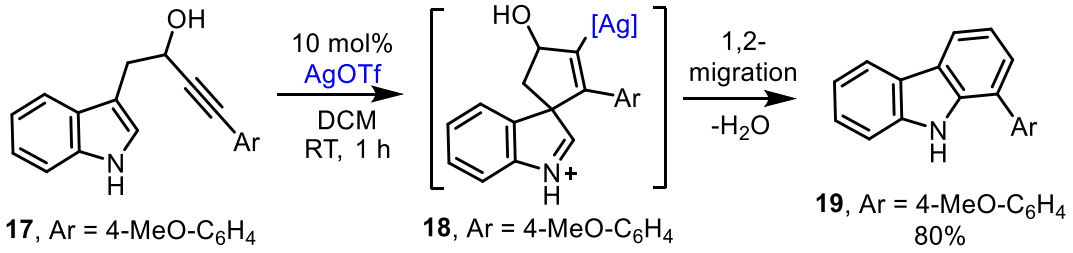
Despite this precedent, the relatively straightforward synthesis of spirocycle **6a** encouraged us that suitably mild conditions to enable selective spirocycle formation could be found and enable the development of a general method. We therefore set out to re-evaluate the spirocyclic indolenine synthesis shown in Scheme 1 (starting with **5a** → **6a**), with an initial emphasis on devising a catalytic process, to replace the use of super-stoichiometric $SnCl_2{\cdot}2H_2O$. The initial optimisation studies evaluated a range of Brønsted-, Lewis- and π-acids to activate the alkyne, with selected examples shown in Table 1 (entries 1–10) [9].

Perhaps surprisingly, the widely-used gold π-acid PPh_3AuCl (both with and without AgOTf) [16c,d]' [19] was ineffective (entries 2 and 3) [20], but $Cu(OTf)_2$, $AgNO_3$ and AgOTf all worked well (entries 4–8), with the use of 0.01 equivalents of AgOTf in DCM at RT being optimal, giving spirocyclic indolenine **6a** in quantitative yield (entry 8). The use of TfOH (Table 1, entry 9) produced only trace amounts of spirocycle **6a**, along with other unidentified impurities and unreacted **5a** (*ca.* 90 %). This result would appear to rule out the possibility that the successful reactions using metal triflate salts are catalysed by adventitious triflic acid via 'hidden Brønsted acid catalysis' [21]. Subsequent studies [22] showed that silica-supported silver nitrate ($AgNO_3{\cdot}SiO_2$) also catalyses the same transformation in high yield (Table 1, entry 10, **5b** → **6b**). Mechanistic studies indicated that in this latter case, silver nanoparticle formation occurs on the silica surface and that there is an additional synergistic effect from the silica support itself which enhances the reactivity [22]. The role of silver nanoparticles in the silica-free AgOTf reaction has not been studied further to date. The general mechanistic hypothesis for the Ag(I) or Cu(II)-catalysed conversion of indoles **5** into spirocyclic indolenines **6** is summarised in Scheme 3.

The stability of the spirocyclic product in these reactions is noteworthy, given the relative ease of 1,2-rearrangement referred to earlier (cf. Scheme 2). It seems likely that the ynone carbonyl is essential to the successful spirocyclisation, by stabilising intermediate **16** with respect to subsequent migratory rearrangement. This hypothesis was strengthened by the contrasting reactivity of the corresponding propargyl alcohol **17** (Scheme 4); treatment of compound **17** with 0.1 equivalents of AgOTf for 1 h at RT resulted in its complete conversion into the known carbazole **19**, presumably via an initial spirocyclisation to **18**, followed by 1,2-migration and dehydration. The relative ease of the migration in the conversion of **18** into **19** is likely to be driven by the higher migratory aptitude of the more electron-rich alkene in intermediate **18** compared to the enone sub-unit present in the analogous ynone derived intermediate **16**. More discussion of synthetic scope and mechanism of this carbazole-forming reaction is included later in the review; see Section 7a [9,23,24].



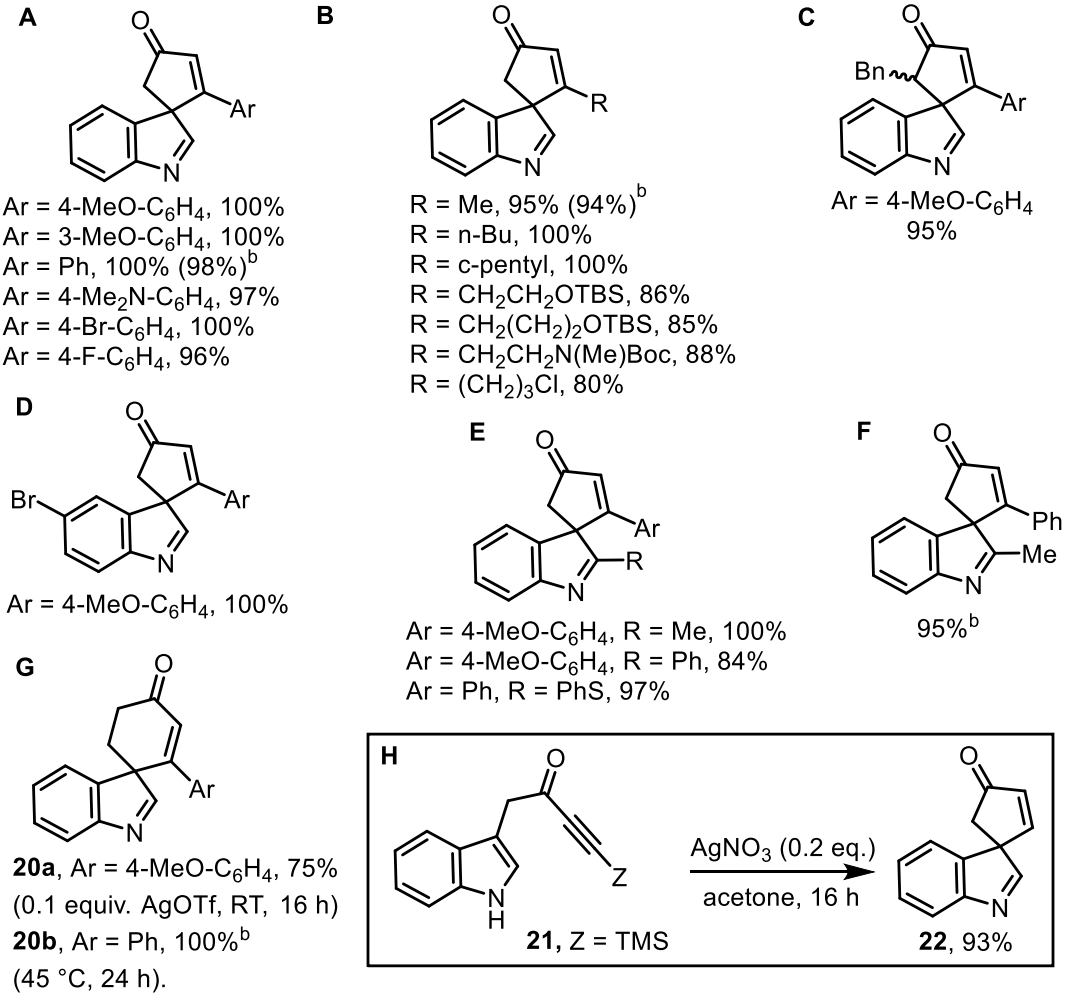
Scheme 3. Proposed mechanism for π-acid catalysed dearomative spirocyclisation of indole ynones **5**.



Scheme 4. Conversion of indole-tethered propargyl alcohol **17** into carbazole **19**.

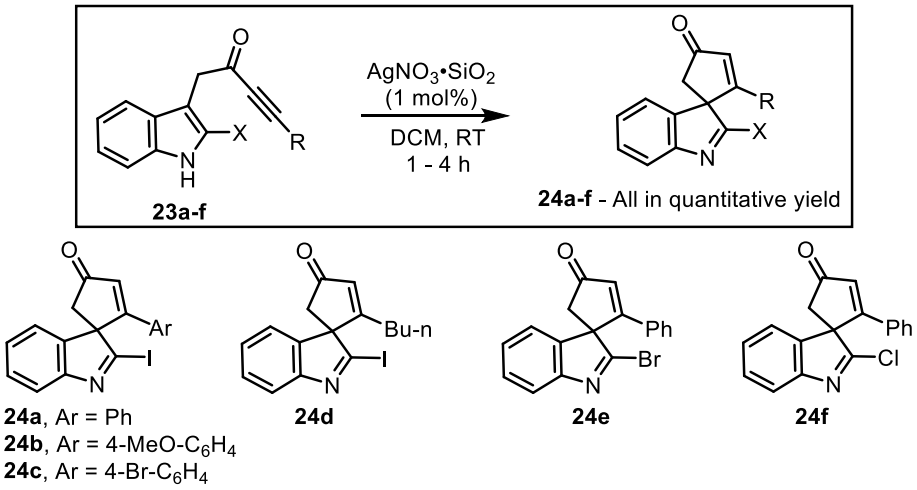
Table 2

[a] Dearomative spirocyclisation of indolyl ynones: reaction scope. [a]All reactions performed using 0.01 equiv. AgOTf in DCM (0.1 M) at RT unless stated.[9,23,24.] [b]Carried out using silica-supported silver nitrate in place of AgOTf.[22].



The indolyl ynone dearomative spirocyclisation was shown to be very general in scope (Table 2) [9,22–24]. Thus, the method is applicable to a range of electronically diverse aryl substituents in addition to the original *p*-methoxyphenyl example **6a** (Table 2A). Alkyl-substituted ynones were similarly good substrates, producing a range of simple and cyclo-alkyl spirocycles (Table 2B). Additional substitution around the indole system is also well tolerated: for example, benzyl- and bromo-substituted spirocycles were each formed in excellent yields (Tables 2C and 2D). 2-Substituted indoles were also compatible with this procedure, giving disubstituted spirocycles using the standard conditions (Tables 2E and 2F); these results were pleasing as the proximity of the substituents on the 2-position of the indole to the reaction site could possibly have impeded the reaction. Cyclohexenone spirocycles were also formed from the corresponding homologous ynones (**20a** and **20b**, Table 2G); in these cases, however, the reactions were slower and more forcing conditions were required to obtain good yields. Attempts to prepare the unsubstituted spirocycle **22** were hampered by the instability of the unsubstituted terminal alkyne (**21**, Z = H). However, success was achieved via a desilylation/spirocyclisation sequence, by stirring ynone **21** (**21**, Z = TMS) with 0.2 equivalents of $AgNO_3$ in acetone, to successfully generate spirocyclic cyclopentenone **22**.

In a variant of the above process (Scheme 5), readily available 2-haloindole ynones **23a–f** were also shown to undergo successful spirocyclisation, with indoleninyl halides **24a–f** all formed in quantitative yield



Scheme 5. Ag(I)-catalysed dearomative spirocyclisation of 2-halo indolyl ynones.

using silica-supported silver nitrate as catalyst (Scheme 5).[25]

The halo-spirocycles **24** were surprisingly stable to air and moisture and could be stored in a freezer for several months without noticeable decomposition. Indoleninyl iodide **24a**, an easy-to-handle solid that could be readily prepared on a gram scale, was used as the main test substrate for diversification studies with a range of nucleophiles and used to prepare a wide array of spirocyclic products **25a–n** (Scheme 6). Three distinct reaction modes were demonstrated: hydrolysis to the corresponding oxindoles (**A**), nucleophilic substitution with sulfur- and nitrogen-nucleophiles to give adducts (**B**), and transition-metal-catalysed cross-coupling to generate products (**C**) possessing a new C–C bond at C-2 [25].

3. Extension to indole-tethered propargylic alcohols

As described above, propargyl alcohol substrate **17** is converted into carbazole **19** under the standard Ag(I)-catalysed spirocyclisation conditions [9]; this conversion is thought to be driven by the proclivity of spirocyclic intermediate **18**, to rearrange via 1,2-migration and dehydration to produce an aromatic product (see Scheme 4 above) [26]. However, subsequent optimisation established that treatment of propargyl alcohol **17** with both catalytic $AgNO_3$ and additional catalytic Ag_2O, enabled spirocyclisation to take place without subsequent rearrangement, producing spirocycle **26a** in 95 % yield (Scheme 7). The inclusion of Ag_2O (a mild base) is thought to reduce likelihood of spirocycle rearrangement, which is known to be promoted by acidic conditions [26]. Thus, the divergent synthesis of spirocycles (Scheme 7) and carbazoles (Schemes 4 and 17) can be achieved from the same starting material, via subtle variations to the reaction conditions. The scope of this alcohol spirocyclisation procedure is summarised below, with good reactivity observed for electron-rich, electron-neutral and electron-poor aromatic examples (**26b–e**). C-2 substituted indoles (**26f**) and silyl protected alcohols (*e.g.* **26g**) could also be incorporated. Similarly, simple alkyl and cyclopropyl spirocycles were produced in excellent yields (**26h**,**i**), as were spirocycles containing tertiary alcohols (**26j**,**k**). In all cases, excellent yields of the spirocyclic products were isolated, although little diastereocontrol was observed with the products being isolated as approximately 1:1 mixtures of diastereoisomers.

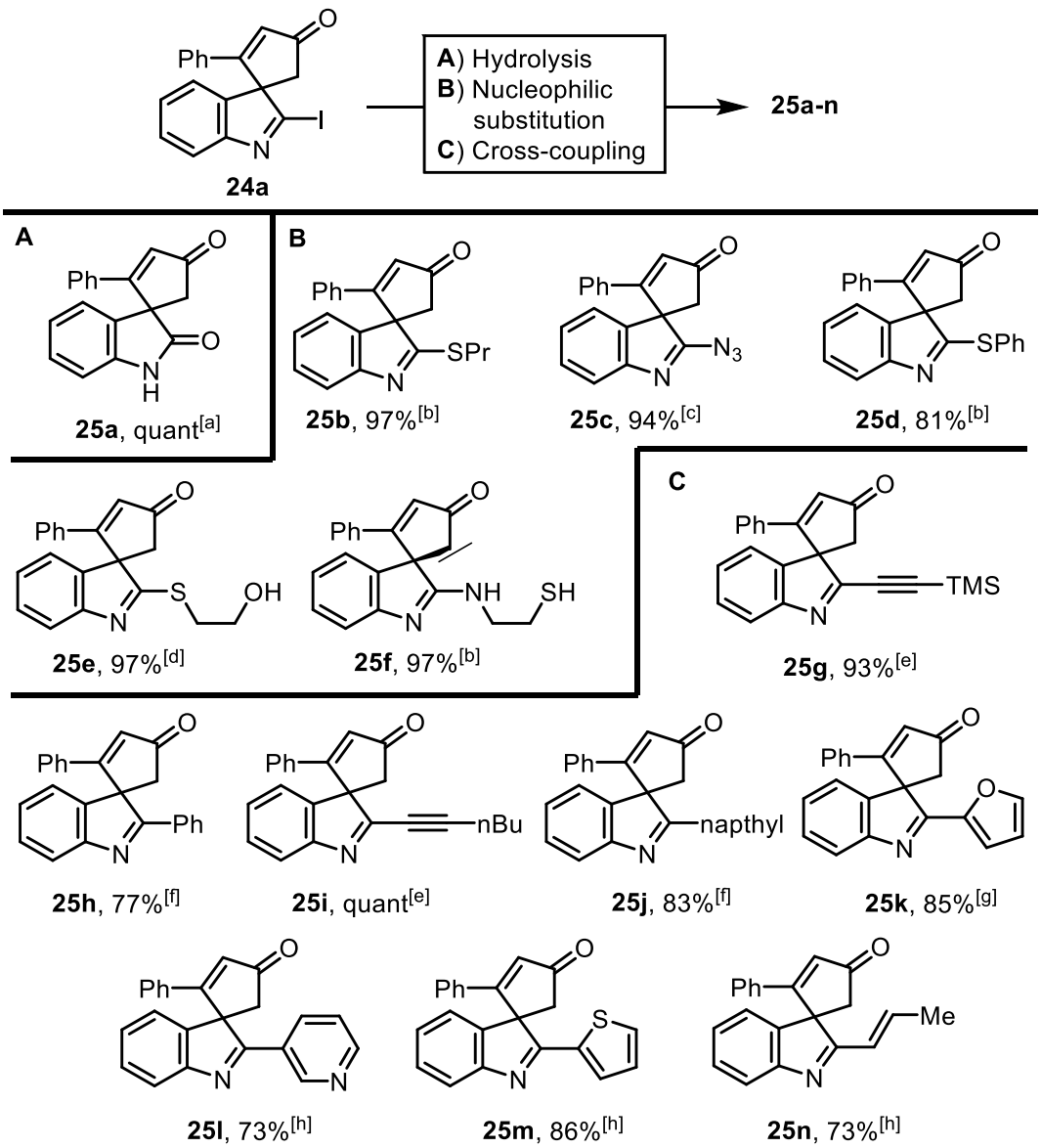
4. Asymmetric indole-ynone spirocyclisations

It was also established that Ag(I) salts of chiral phosphoric acids (CPAs) [27] can be used as catalysts for asymmetric indole-ynone spirocyclisations [9]. Six simple Ag(I) salts of commercially available BINOL-based CPAs were investigated as catalysts (not shown) and various conditions were screened. The highest *er* observed using 9-phenanthryl-derivative **A**, which gave spirocycle **6a** in quantitative yield, and in 89:11 *er*. These conditions were then extended to other ynones (Scheme 8B). Gratifyingly, in all cases the spirocyclic products were obtained in high yields (**6b–f**, 62–100 %) and with good enantioselectivities (*er* 70:30–89:11) illustrating the likely generality of this asymmetric procedure. In addition, the *er* of compounds **6a** and **6c** could be readily enriched (to 98:2 *er*) following recrystallisation from ethyl acetate/hexane. The fact that these promising enantiomeric ratios could be achieved by screening a relatively small number of commercially available CPAs indicates that further optimisation studies could generate still higher *er's*. The major enantiomer formed in reactions using the (*R*)-CPA catalysts was shown to be the (*S*)-spirocycle (illustrated in Scheme 8) based on X-ray crystallographic studies on spirocycle **6c** [9].

5. Palladium-catalysed indole-ynone spirocyclisations

As shown in Scheme 3, the spirocyclisation protocols discussed so far involve alkyne activation with a π-acidic catalyst, most usually Ag(I)-based, followed by nucleophilic attack by the tethered indole to form a vinyl metal intermediate (**16**), and then fast protodemetallation. The ease with which vinyl silver species undergo protodemetallation [28] is key to efficient catalyst turnover. However, the fast protodemetallation meant that, in our hands, all efforts to trap intermediate **16** (or related intermediates) with an external electrophile other than a proton failed, meaning that tetrasubstituted alkenes cannot be accessed via these Ag (I)-catalysed procedures. Indeed, at the time this work was carried out, there were no published methods which allowed such a transformation to be performed via the interception of an organometallic intermediate; notably, however, methods based on dearomatising spirocyclisation reactions using electrophilic halogenation reagents have been developed, and the resulting vinyl halides can be used in subsequent cross-coupling reactions [29].

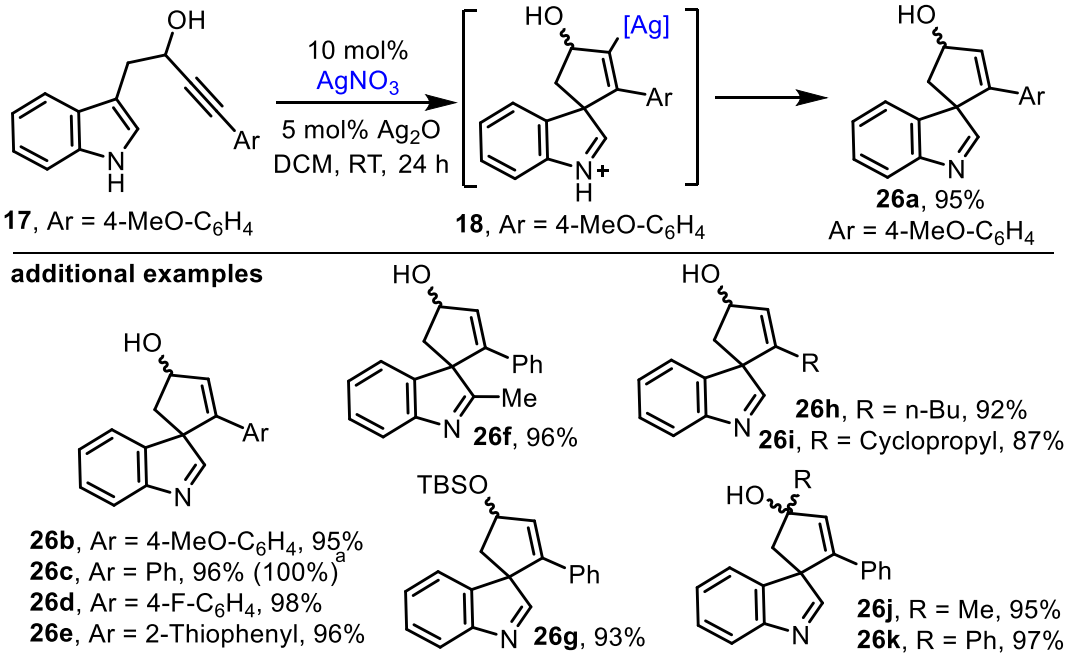
To address this limitation, we explored the use of other π-acidic catalysts in which the transiently-formed vinyl metal species might undergo cross-coupling processes, thus generating spirocyclic products containing tetrasubstituted alkenes in a single synthetic operation [30]. Initial studies concentrated on the dearomatising spirocyclisation/cross-coupling sequence using indole **27** and 4-iodotoluene **28** to make spirocycle **29a**, exploring the use of various Pd complex/ligand combinations under basic conditions. Selected results of this study are summarised in Table 3. We were delighted to observe that the cross-coupled spirocycle **29a** could be accessed using this palladium-catalysed method, although in some cases the



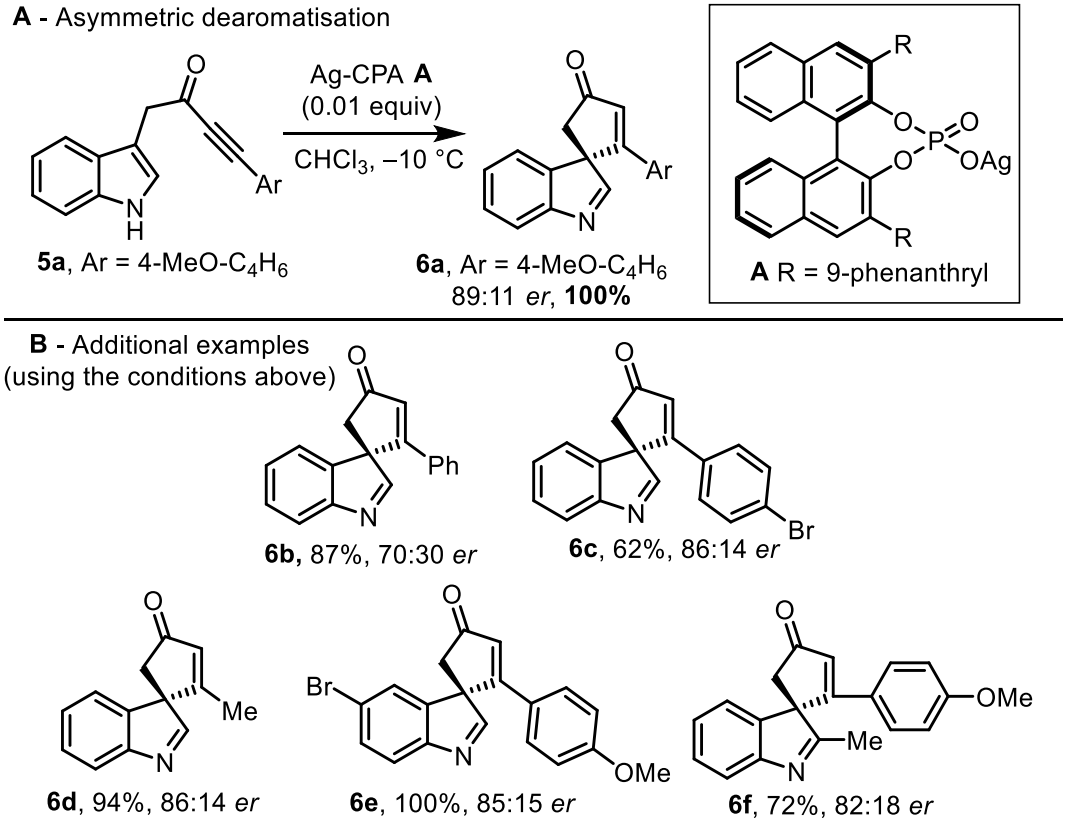
Scheme 6. Functionalisation of indoleninyl iodide **24a**. [a] 10 % HCl (aq), THF, RT, 4 h [b] thiol, Cs_2CO_3, MeCN, RT, 2–4 h [c] NaN_3, DMF, 60 °C, 1.5 h [d] 2-mercapto ethanol, Et_3N, MeCN, RT, 22 h [e] Alkyne, iPr_2NH, $PdCl_2(PPh_3)$, CuI, THF, RT, 1.5 h [f] arylboronic acid, $Pd(PPh_3)_4$, K_2CO_3, toluene/water, 80 °C, 16–20 h [g] 2-(tributylstannyl)furan, $Pd(PPh_3)_4$, dioxane, 100 °C, 21 h [h] stannane, *trans*-PdBr(*N*-Succ)$(PPh_3)_2$, toluene or dioxane, 100–130 °C, 17–48 h.

proto-demetallation by-product **6g** was also formed. However, the use of either $Pd(PPh_3)_4$ or commercially available *trans*-PdBr(*N*-succinimide)$(PPh_3)_2$ (Catcat) [31] with triethylamine proved effective at preventing the by-product production, giving up to 94 % conversion into the desired cross-coupled spirocycle **29a** (entries 3–9). The use of 2 mol% Catcat (entry 9) was found to be optimal; the catalyst loading could be reduced further still giving reasonable conversion into **29a** (see entry 10, 1 mol %) but some of the starting material **27a (**ca. 5 %) remained under these conditions. Both base (entry 11) and catalyst (entry 12) were demonstrated to be essential to the success of this conversion, and no direct C-3 arylation was observed, despite this being a well-established dearomative process for indoles [32].

We went on to investigate the generality of the optimised reaction conditions (entry 9 of Table 3) and these studies are summarised in Table 4. Indoles with C-2 substituents were first studied. It was shown that changes at various positions of the indole scaffold were well tolerated, with spirocycles **29a**–**h** all being prepared in very good yields (Table 4A). Spirocycles **30a**–**e** were also produced efficiently from indole precursors without a C-2 substituent (Table 4B), and importantly, there was no evidence of competing C-2 substituted side-products being formed (*i.e.* carbazole-type frameworks; see later). This procedure is also compatible with more challenging cross-coupling partners (Table 4C). For example, aryl iodides substituted with morpholine-, methoxy-, carboethoxy- and alkyl groups at the 2- and 4-positions were all shown to couple efficiently (**31a**–**c**, **31f**–**g**). Aniline coupling partners were less straightforward, with 4-iodoanilines **13e** and **13f** giving no cross-coupling products; however, some anilines are compatible, as demonstrated by the successful coupling of 3-iodoaniline, which afforded **31h** in excellent yield. Isatin (**31i**), pyrazine (**31l**) and pyridine coupling partners (**31j**–**m**) all worked well, which is significant given the medicinal importance of these nitrogen-containing heterocycles. Coupling to sp^3 hybridised benzyl and naphthylene methyl halides was also successful giving adducts **31n**–**p**, although it seems that alkyl halides lacking β-hydrogen atoms are required; the corresponding reactions using iodo-cyclopentane and 3-bromo-1-phenyl propane (not shown in the Table) both failed to deliver any of the expected cross-coupled products. In addition, successful spirocyclisation/cross-coupling with installation of thiophene (**31q**), cyclopentenone (**31r**), alkyne (**31s**),



Scheme 7. Dearomative spirocyclisations of indole propargyl alcohols. All reactions performed using 10 mol% $AgNO_3$ and 5 mol% Ag_2O in DCM at RT unless stated [26]. [a]Carried out using silica-supported silver nitrate [22].

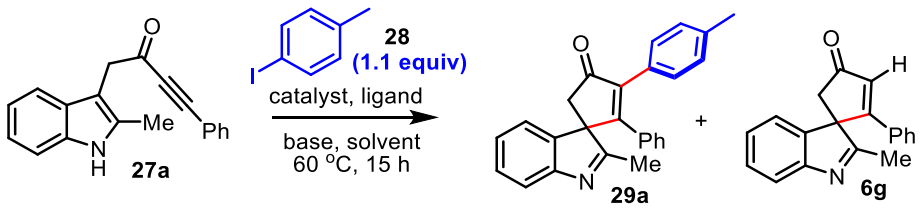


Scheme 8. Asymmetric spirocyclisation of indolyl ynones. All reactions were performed using 0.09–0.30 mmol of **5a** in chloroform (0.1 M), 0.01 equiv. of the specified CPA catalyst and stirred at either RT or −10 °C for 16 h unless otherwise stated. Enantiomeric ratios were measured by HPLC using a Chiralpak IB column, eluting with 10 % IPA in hexane.

pyrazole (**31t**) and naphthyl (**31u**) groups were all successful; in the case of naphthyl derivative **31u**, this was prepared using an aryl triflate, confirming that triflates can also be used as coupling partners in this process.

The proposed mechanism for this merged spirocyclisation/cross-coupling protocol is discussed in detail in the publication [30], with the two possibilities considered to be most plausible (cycles 1 and 2) summarised in Scheme 9. Both proposals rely on alkyne activation by a

Table 3
Selected optimisation results for the merged Pd-catalysed cross coupling and dearomative spirocyclisation of indole ynones.



entry	catalyst (X mol%)	base	solvent	yield [%][a] 29a	6g
1	$Pd(PPh_3)_2Cl_2$ (5)	K_2CO_3 (2 equiv)	PhMe	31	53
2	$Pd(OAc)_2$ (5), PCy_3 (10)	K_2CO_3 (2 equiv)	PhMe	41	42
3	$Pd(PPh_3)_4$ (5)	K_2CO_3 (2 equiv)	PhMe	90	0
4	$Pd(PPh_3)_4$ (5)	Et_3N (2 equiv)	PhMe	91	0
5	Catcat (5)	Et_3N (2 equiv)	PhMe	91	0
6[b]	$Pd(PPh_3)_4$ (2)	Et_3N (2 equiv)	PhMe	73	0
7[b]	Catcat (2)	Et_3N (2 equiv)	PhMe	91	0
8[b]	Catcat (2)	Et_3N (1.1 equiv)	PhMe	91	0
9[b]	Catcat (2)	Et_3N (1.1 equiv)	MeCN	94	0
10	Catcat (1)	Et_3N (1.1 equiv)	MeCN	78	0
11[b]	Catcat (2)	–	MeCN	0	22
12[b]	–	Et_3N (1.1 equiv)	MeCN	0	0

[a] Yield determined by ^1H NMR, using CH_2Br_2 as an internal standard.
[b] Reaction time 5 h. Catcat = *trans*-PdBr(*N*-succinimide)$(PPh_3)_2$.

π-acidic Pd complex in the key step, with the Pd complex believed to mimic Ag(I) in the original studies. Oxidative addition into the aryl iodide (either before or after spirocyclisation) is thought to facilitate the cross-coupling, with reductive elimination completing the catalytic cycle.

6. Photochemical indole-ynone spirocyclisations and extension to benzisoxazoles

Later studies uncovered a photochemical variant of the indole-ynone spirocyclisation method [33]. The original aim of this project was to devise a radical spirocyclisation protocol based on well-established radical generation procedures (Scheme 8). It was anticipated that indole-tethered ynones **32** would react with electrophilic radicals via regioselective addition to the alkyne (**32** → **33**), before cyclisation on to the C-3 position of the indole to generate a spirocyclic radical intermediate (**33** → **34**). Radical **34** could then give either spirocyclic indoline **35** via hydrogen atom transfer (HAT), or generate spirocyclic indolenine **37** via single electron oxidation followed by the loss of a proton (Scheme 10). Oxidation of **35** to **37** by molecular oxygen, or another oxidant, also seemed possible.

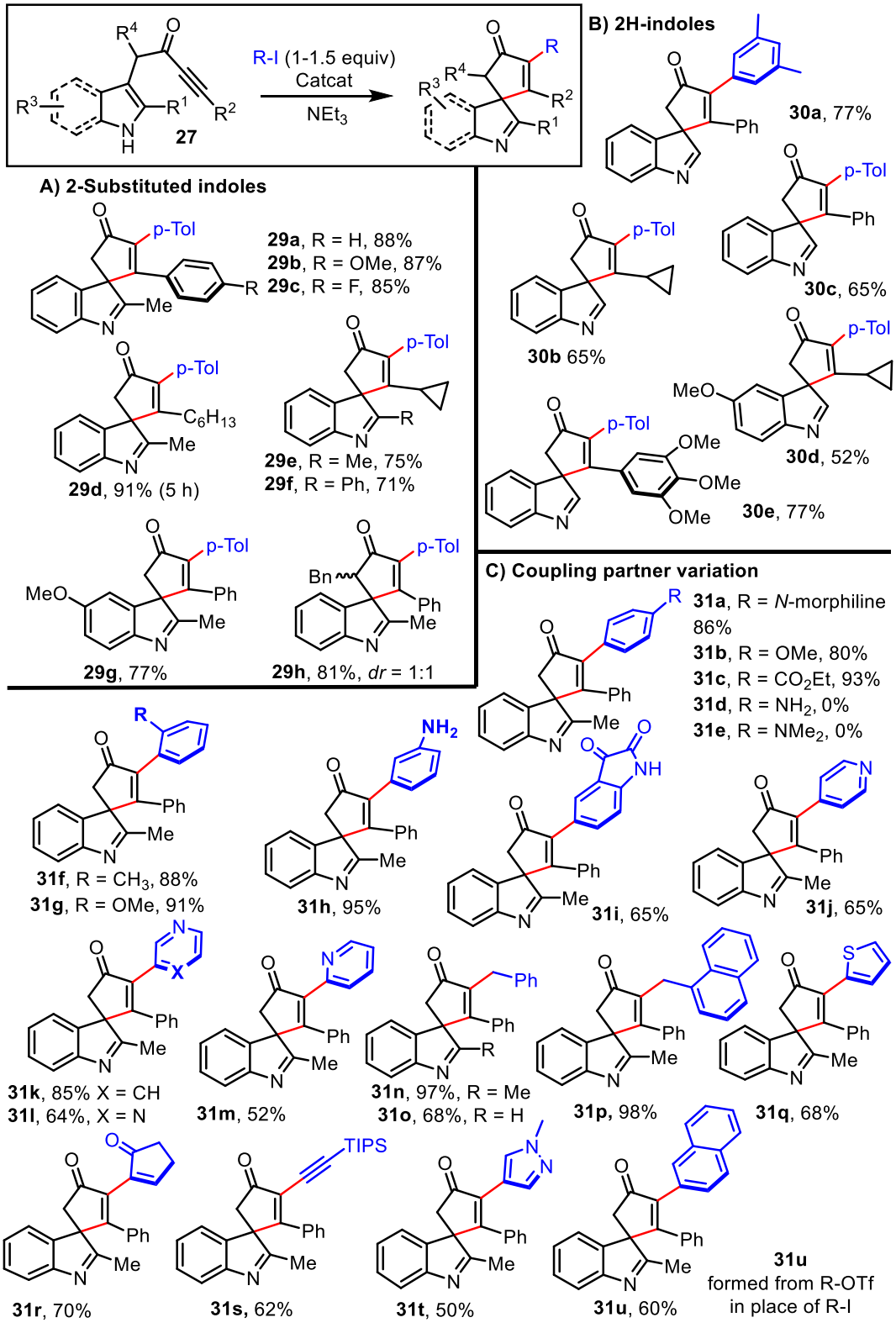
This investigation commenced by studying the reaction of ynone **27a** with a thiyl radical generated from thiophenol *in situ*. A photoredox catalytic approach was originally chosen for thiyl radical generation [34]; the combination of thiophenol, catalytic $Ru(bpy)_3(PF_6)_2$ and irradiation with a blue LED lamp (λ_{max} = 455 nM, 60 W) at rt under air, successfully converted the indole-tethered ynone **27a** into spirocyclic indolenine **37a** in good yield along with indoline **35a** being isolated as a minor by-product (Table 5, entry a). Control experiments revealed that light is essential for reaction (Table 5, entry b) and that oxygen is required for the efficient formation of **37a** (indoline **35a** is the major product in the absence of oxygen, see Table 5, entry c). However, surprisingly, it was also observed that a mixture of both products **37a** and **35a** was formed under blue LED irradiation, but in the absence of a photocatalyst (Table 5, entry d).

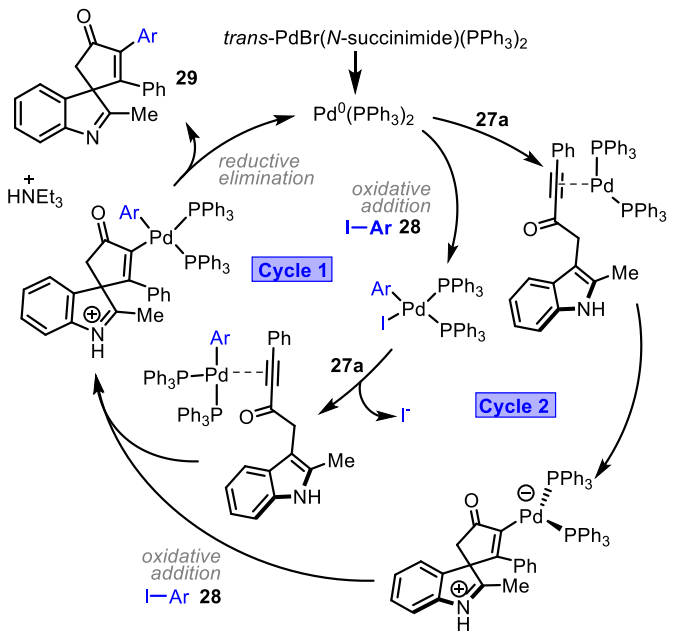
The unexpected discovery that spirocyclisation can be accomplished in the absence of a photocatalyst was interesting, both from a mechanistic standpoint, and in view of the practical and environmental advantages of avoiding metal-based catalysts. Additional optimisation was carried out, and it proved more straightforward to access indoline products **35** (via an overall redox-neutral reaction) rather than indolenines **37** (an overall oxidative process). Therefore, the reactions were carried out under argon rather than air, and a change of the solvent from acetonitrile to 1,2-dichloroethane also proved advantageous. These optimised conditions were applied to a range of substrates, and the results are summarised in Table 6. As can be seen, this photochemical transformation is broad in scope, in terms of both the indole-ynone and the thiol [33].

Changes to the substituent on the indole nitrogen (R^1=NH and NMe), the indole 2-position (R^2) and the ynone terminus (R^3) were all tested, and the reactions worked well (12 examples, **35a–l,** 45–99 %). In C-2 substituted examples (**35a–f**) the products were isolated as the single diastereoisomer shown. A wide range of thiols were also tested, and these reactions generally worked very well (20 examples, **38a–38t**, 36–99 %). The most electron-rich examples typically were the highest yielding. Aliphatic thiols could also be coupled using the standard procedure (**38i–38n**); this is despite the higher S–H bond dissociation energy for alkyl thiols (~87 $kcalmol^{-1}$ vs 72–82 $kcalmol^{-1}$ for aryl thiols), which can adversely affect their reactivity in radical reactions [35]. More complex thiols also work well using the standard procedure, including 1,3-propanedithiol (**38r**), cysteine derived systems (**38q** and **38s**) and an α-tocopherol-derived thiol (to produce **38t**).

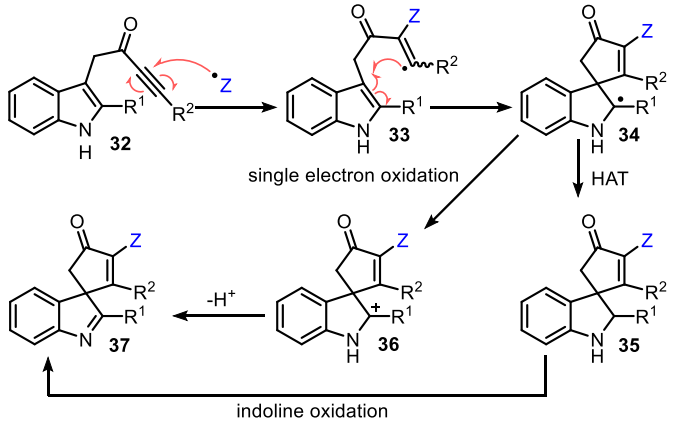
Studies were also carried out to provide information as to how these reactions operate without an obvious photocatalyst [33]. A number of possibilities were considered, all involving the activation of one of the starting materials by visible-light. The proposed sequence considered most likely is summarised in Scheme 11. Thus, it is proposed that the reaction is initiated by the formation of an intramolecular charge transfer electron donor-acceptor (EDA) complex **39a′**, followed by visible light absorption to give a photo-excited state, depicted as the charge transfer complex **39b** [36]. In most cases, this complex would be expected to relax to reform EDA complex **39a′** via back electron transfer (BET). However, this open shell excited state **39b** could also abstract a hydrogen atom from the thiol, thereby forming a small amount of the

Table 4
Substrate Scope for the Merged Pd-Catalysed Cross-Coupling and Dearomative Spirocyclisation of Indole Ynones. Catcat = *trans*-PdBr(*N*-succinimide)(PPh_3)$_2$.





Scheme 9. Mechanistic possibilities for merged spirocyclisation/cross-coupling.



Scheme 10. Radical indole-ynone spirocyclisation approach.

thiyl radical, which is needed to start a radical cascade (Scheme 11a). From here, a more typical radical chain process is thought to operate (Scheme 11b), which likely proceeds by the addition of thiyl radical to the ynone (**39a** → **39c**), spirocyclisation (**39c** → **39d**) and hydrogen atom abstraction from the thiol (**39d** → **40**) to propagate the chain. Quantum yield measurements (φ = 19.8) support the operation of a chain process.

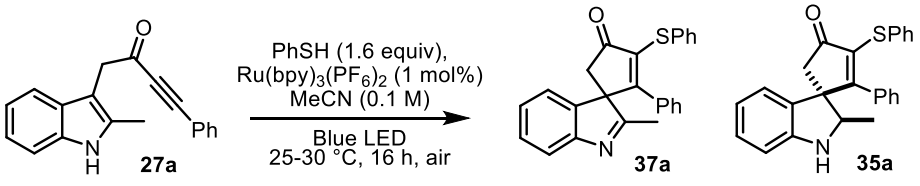
After demonstrating that indole-ynones particpate well in reactions with thiyl radicals, we then proceded to establish that the same substrates are good precursors for radical dearomatising spirocyclisation cascades more generally [37]. This was achieved by exploring a series of related transformations that proceed via different radical types. Five distinct and diverse synthetic procedures were developed in total – cyanomethylation (**41**, Scheme 12A), sulfonylation (**42**, Scheme 12B), trifluoromethylation (**43**, Scheme 12C), stannylation (**44**, Scheme 12D) and borylation (**45**, Scheme 12E). These procedures utilise a variety of radical generation modes, ranging from photoredox catalysis to traditional AIBN methods. Using this suite of procedures, indole ynones can provide convienient access to libraries of densely functionalised spirocycles using conceptually similar radical-based protocols.

It is believed that a key reason the indole ynones are so effective in radical cascade reactions, as outlined above, is their ability to form partially stabilised, intermediate radicals upon spirocyclisation. For example, when indole-tethered ynones **46** react with different radical species, they can form spirocyclic α-amino radicals **47**, which are stabilised by two-centre three-electron (2c,3e) π-bonding interactions (Scheme 13a). Based on this rationale, it was reasoned that the radical dearomative spirocyclisation of comparatively electron-deficient heteroarenes might be achieved if related stabilising interactions could be built into the intermediate spirocyclic radical. This analysis instigated a study of radical additions to benzisoxazole-tethered ynones **48**; here, radical spirocyclisation would produce a nitrogen-centred radical **49**, stabilised by 2c,3e-bonding with the lone pair of electrons on the adjacent oxygen atom [38].

In the above example, thiyl radical addition proceeds by a radical chain process under thermal conditions without the need for photochemical activation. The scope of this dearomative spirocyclisation cascade was explored (Scheme 14). A range of arylthiols were utilised and a wide variety of substituted benzenethiols could be used to generate spirocycles **49a**–**n**, many in >90 % yields. Such reactions were easy to scale up and spirocycle **49a** was isolated in 93 % yield when the reaction was carried out with 1.0 mmol of ynone **48a**. Unfortunately, however, limited reactivity was observed when alkylthiols were employed (spirocycles **49o**–**q** were isolated in low yields or as trace amounts), which may be due to the higher BDE of the alkyl thiol S–H bond. Dithiols such as 1,4-benzenedithiol were compatible, however, and this reagent produced spirocycle **49r** in excellent yield, as a ~1:1 diastereoisomeric mixture. Finally, aryl substitution on the ynone substituent was well-tolerated giving methoxy- and fluoro-substituted spirocycles **49s**,**t** in high yields [38].

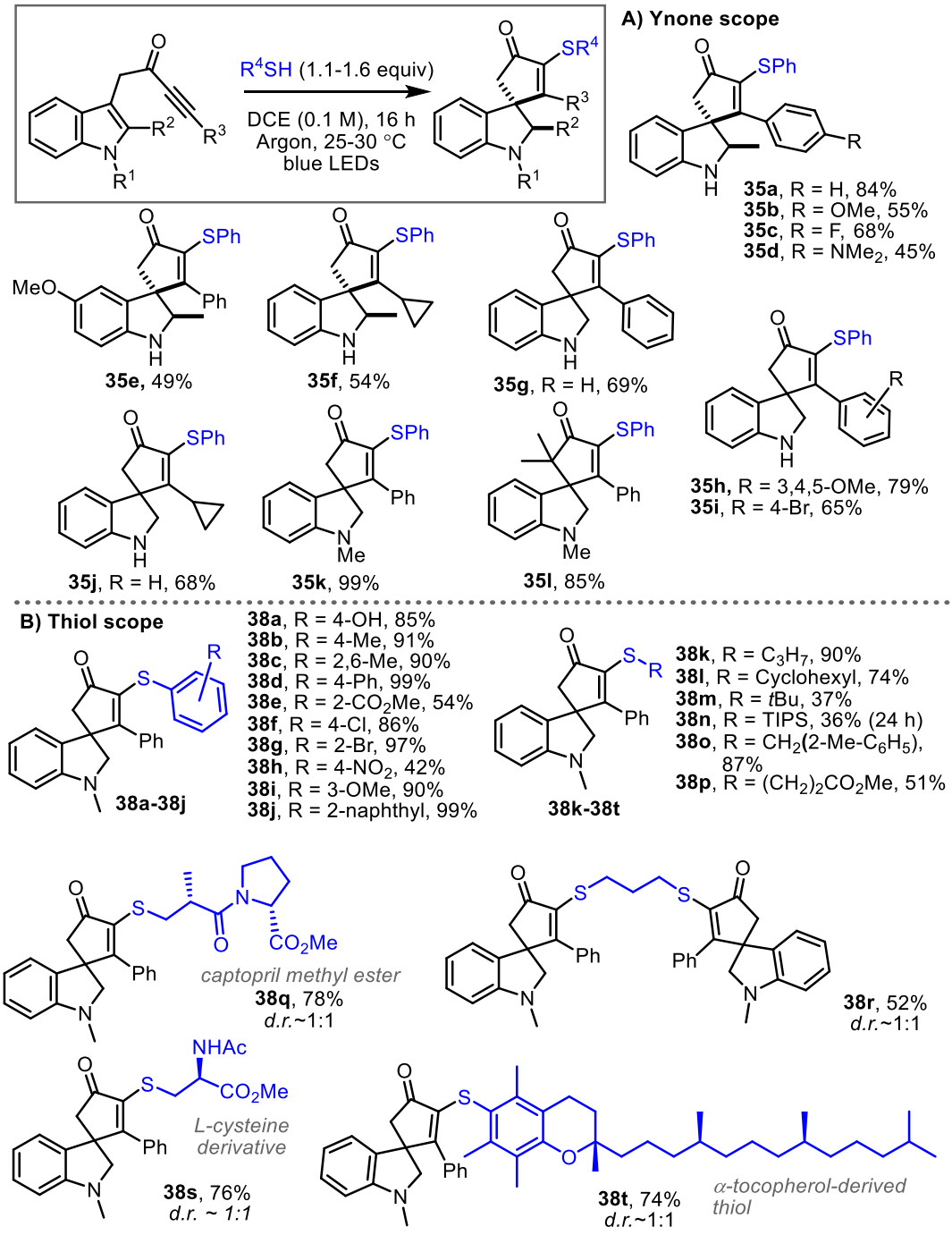
The novel spirocyclic oxazolines **49** undergo facile N–O reduction with H_2/Pd–C and the resulting amino alcohols can be recyclised to give the corresponding 3-oxazinanes, cyclic carbamates and cyclic

Table 5
Photoredox approach to the spirocyclisation of indole ynone **27a** with thiyl Radicals.



Variation from *above conditions*	yield **37a**	yield **35a**
a) none	68%	8%
b) in the dark	0%	0%
c) under argon	17%	63%
d) no $Ru(bpy)_3(PF_6)_2$	54%	9%

Table 6
Scope of the photochemical indole-ynone Spirocyclisation.

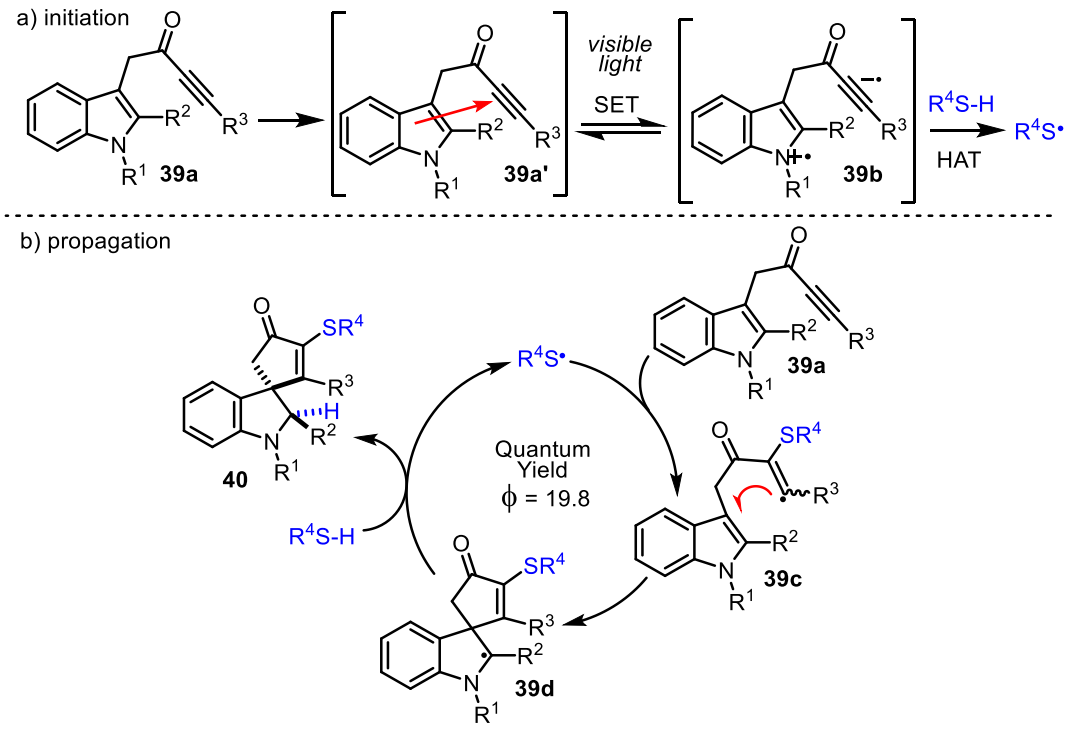


thionocarbamates (not shown) [38].

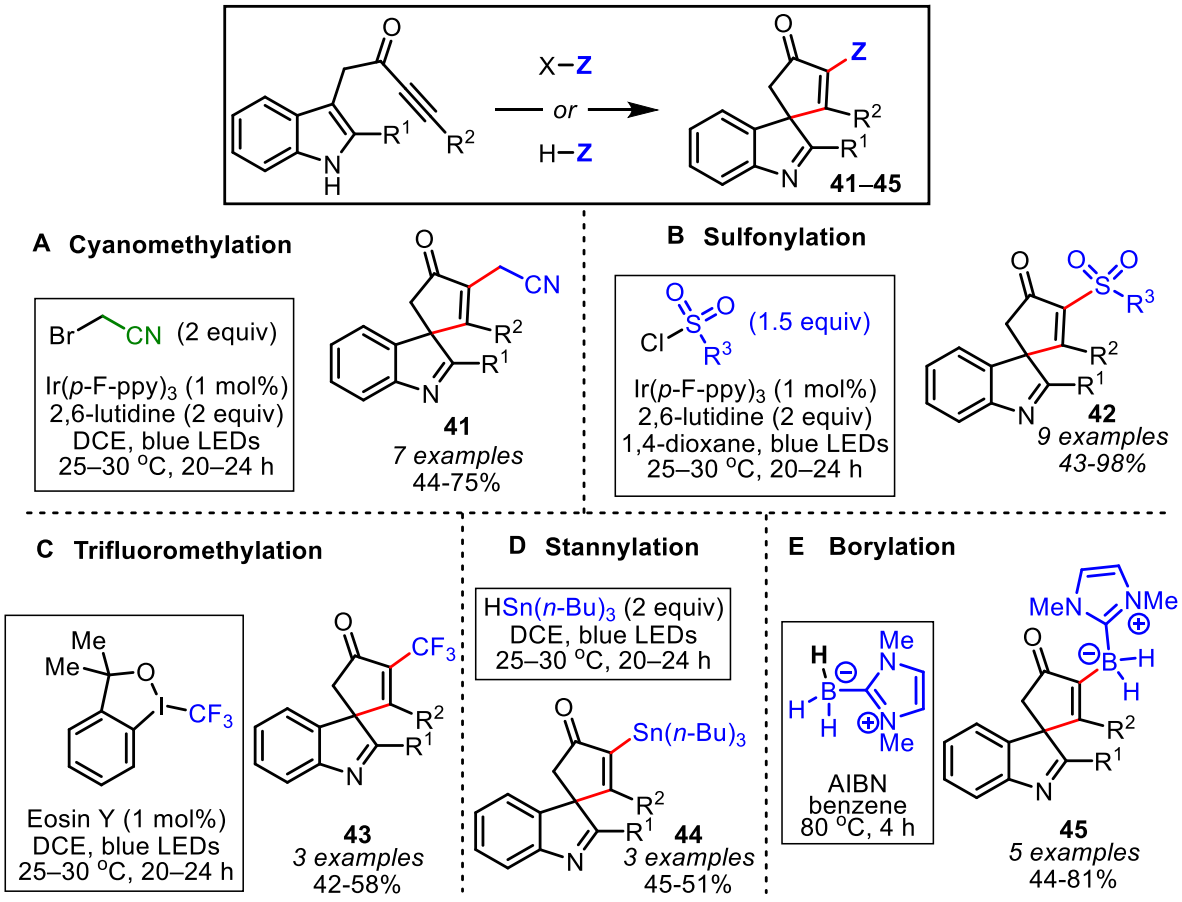
7. Controlled indole-ynone-derived spirocycle rearrangements; heterocyclic diversification

a Carbazoles

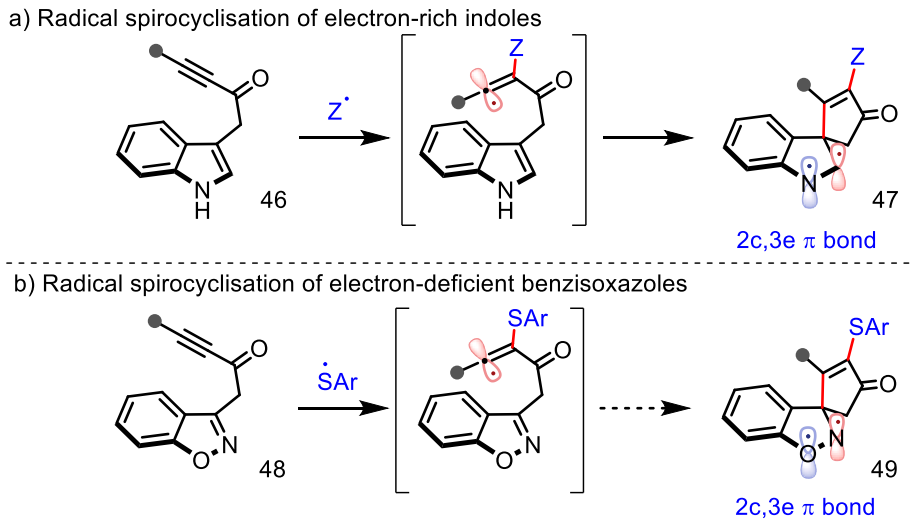
As mentioned earlier, a significant challenge with dearomative spirocyclisations is the readiness with which the spirocyclic products can undergo 1,2-migration to form annulated bicyclic products and restore aromaticity, which for indole systems typically results in the formation of carbazoles. This is well-illustrated in the reactions of indolic propargyl alcohols such as compound **17** (Scheme 4), although notably the 1,2-migration can be minimised by using the basic conditions outlined in Scheme 7 [9]. However, carbazoles are important products in their own right, and hence the conversion of indolic propargyl alcohols **17** directly into carbazoles is a potentially valuable process; therefore, the optimisation of the indolic propargyl alcohol to carbazole transformation was explored. The scope of this method is shown in Scheme 15, with catalytic AgOTf in THF successful in most cases [26]. Good functional group compatibility was generally observed, with carbazoles derived from aryl and alkyl substituted alkynes being formed in high yields in most cases. Most examples employed secondary alcohols but tertiary alcohols are also compatible starting materials (**50e**). Notably,



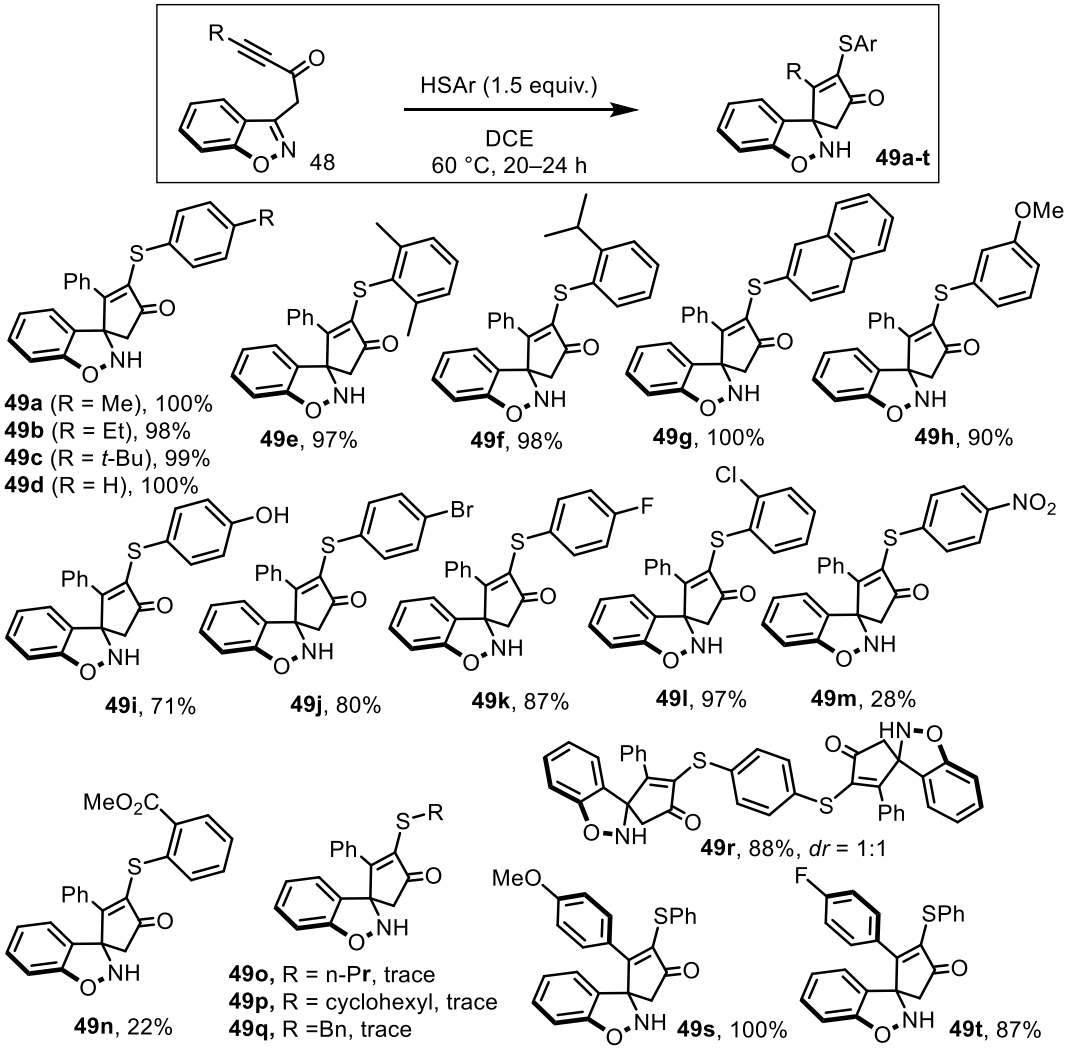
Scheme 11. Radical indole-ynone spirocyclisation: proposed mechanism.



Scheme 12. Diverse radical indole-ynone spirocyclisation procedures.

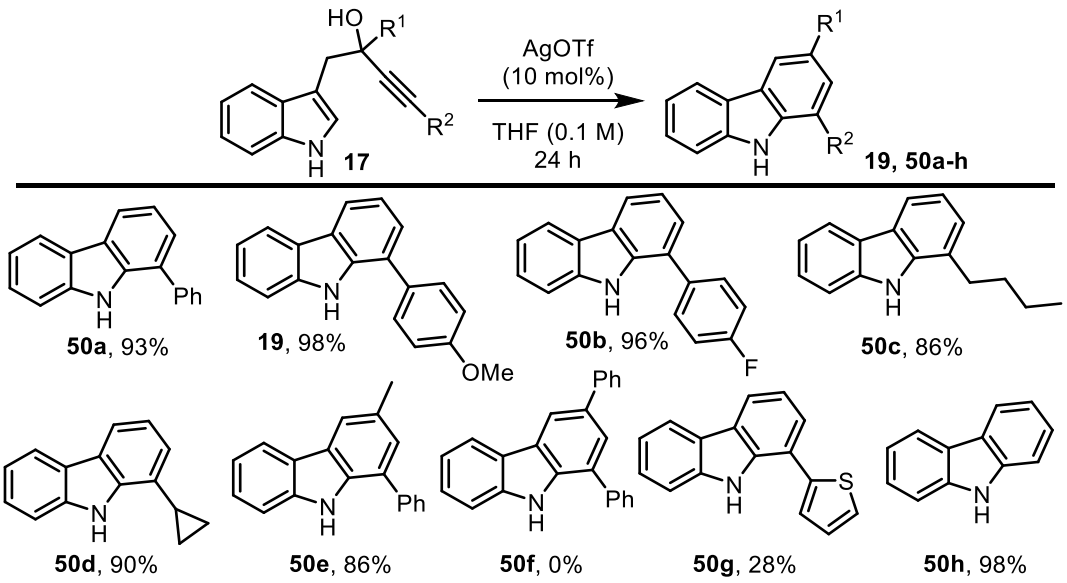


Scheme 13. a) Radical spirocyclisation of electron-rich indoles; b) Radical spirocyclisation of electron-deficient benzisoxazoles.

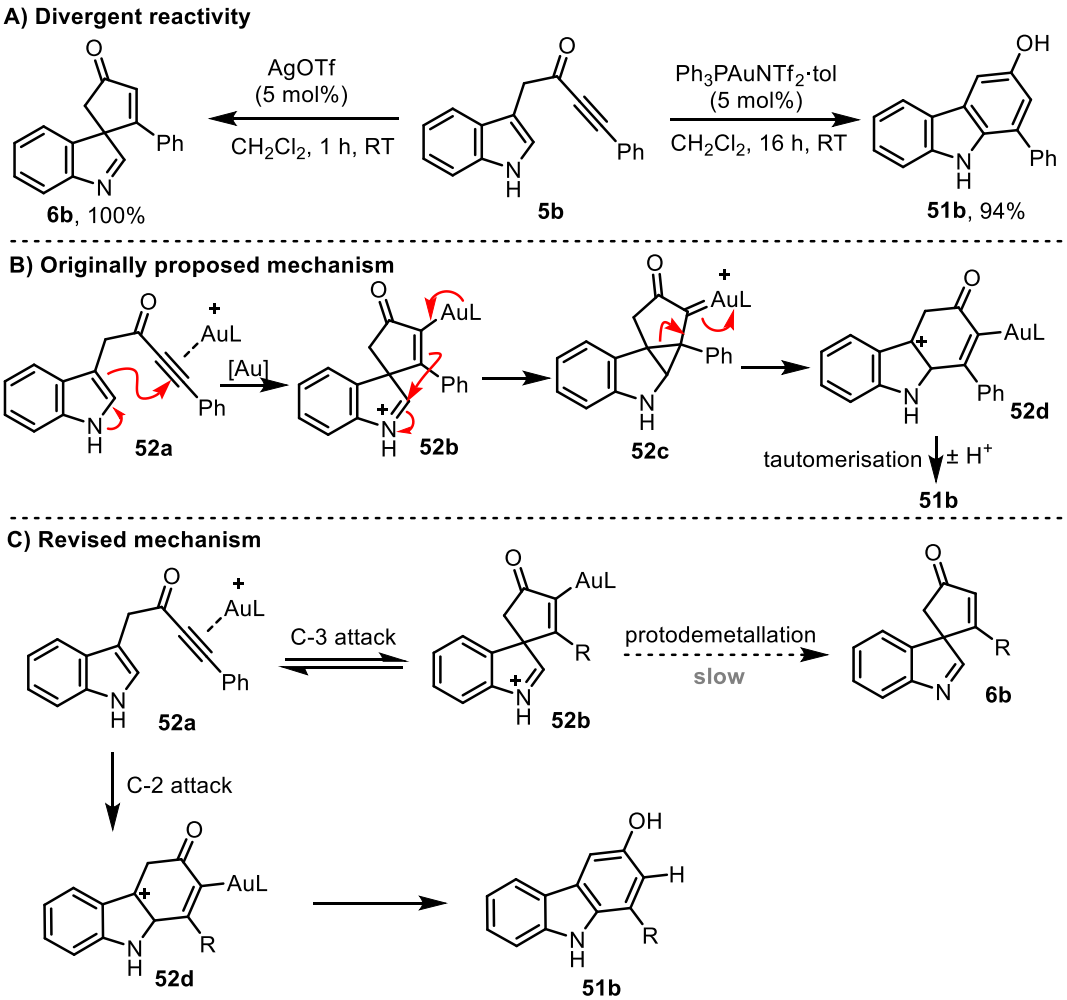


Scheme 14. Scope of the radical dearomative benzisoxazole spirocyclisation cascade.

the parent carbazole **50h** could be readily prepared from the unsubstituted terminal alkyne starting material as well as from its TMS-derivative. The carbazole products were always formed as single regioisomers, with the regiochemical outcome consistent with the 1, 2-migration of the alkenyl group from a spirocyclic intermediate (cf. **26** in Scheme 7), or via direct C-2 annulation.

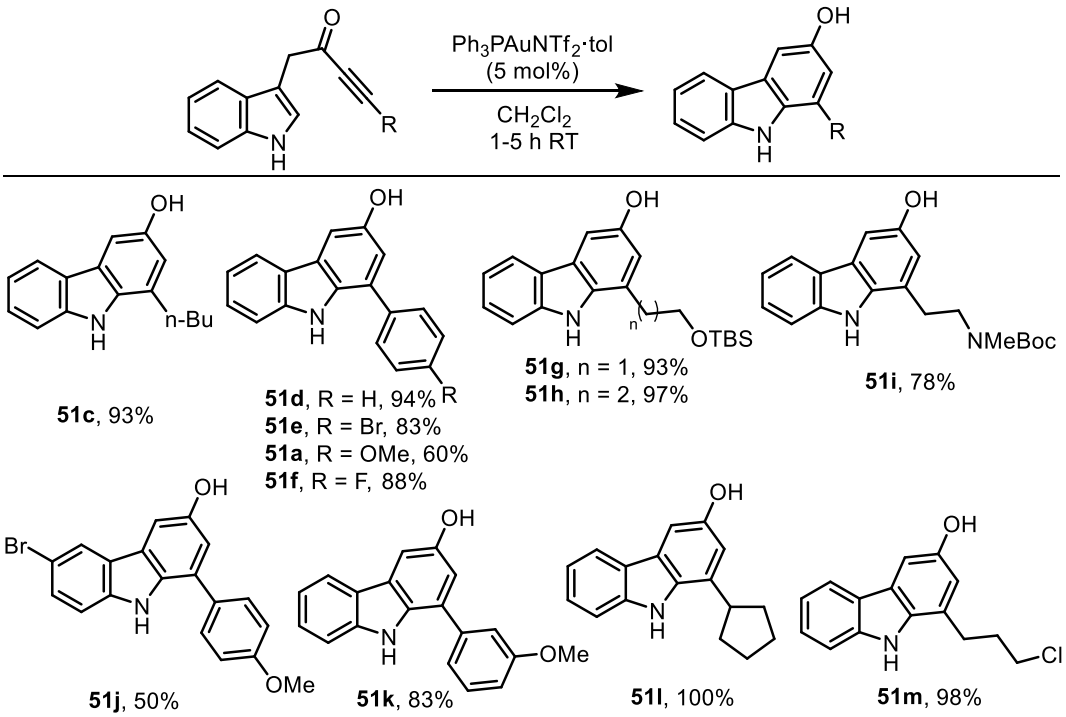


Scheme 15. Scope of the conversion of indolic propargyl alcohols **17** into carbazoles.

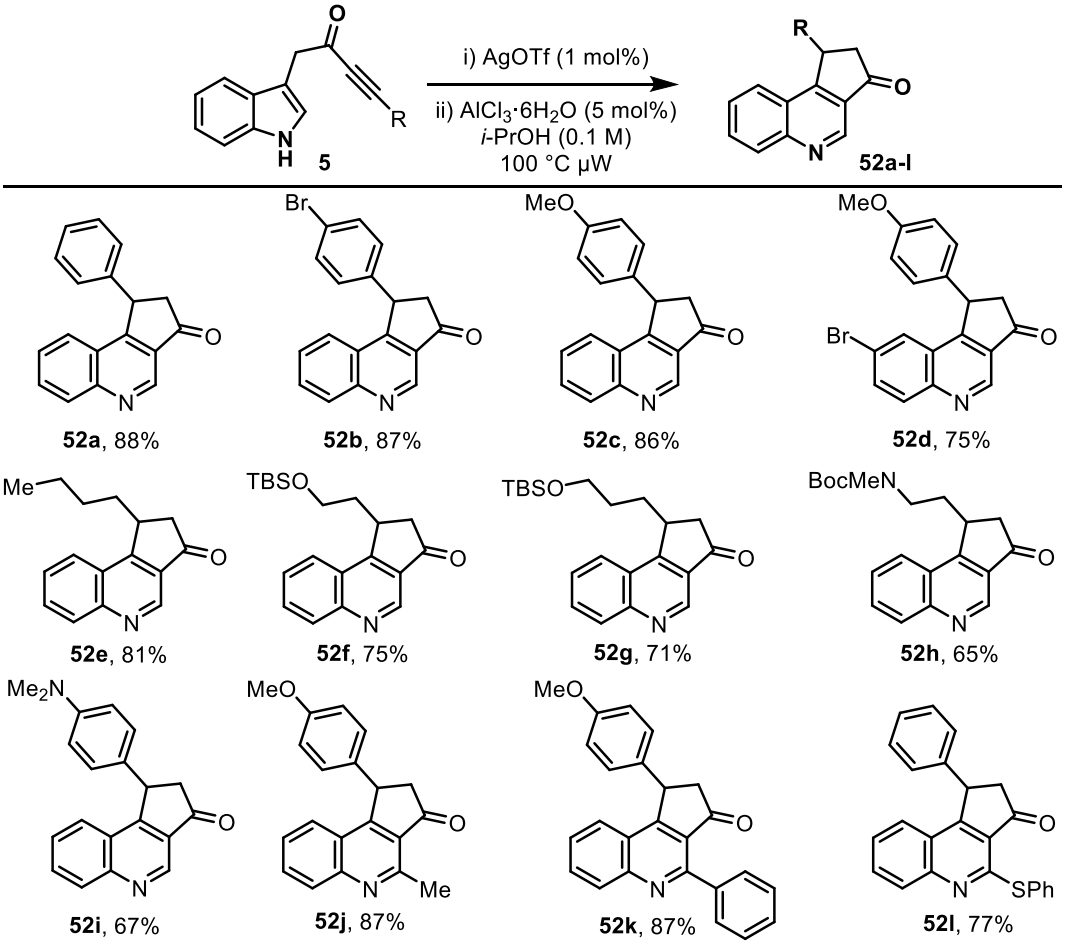


Scheme 16. Gold(I) catalysed conversion of indole ynone **5b** into carbazole **51b**: mechanistic proposals.

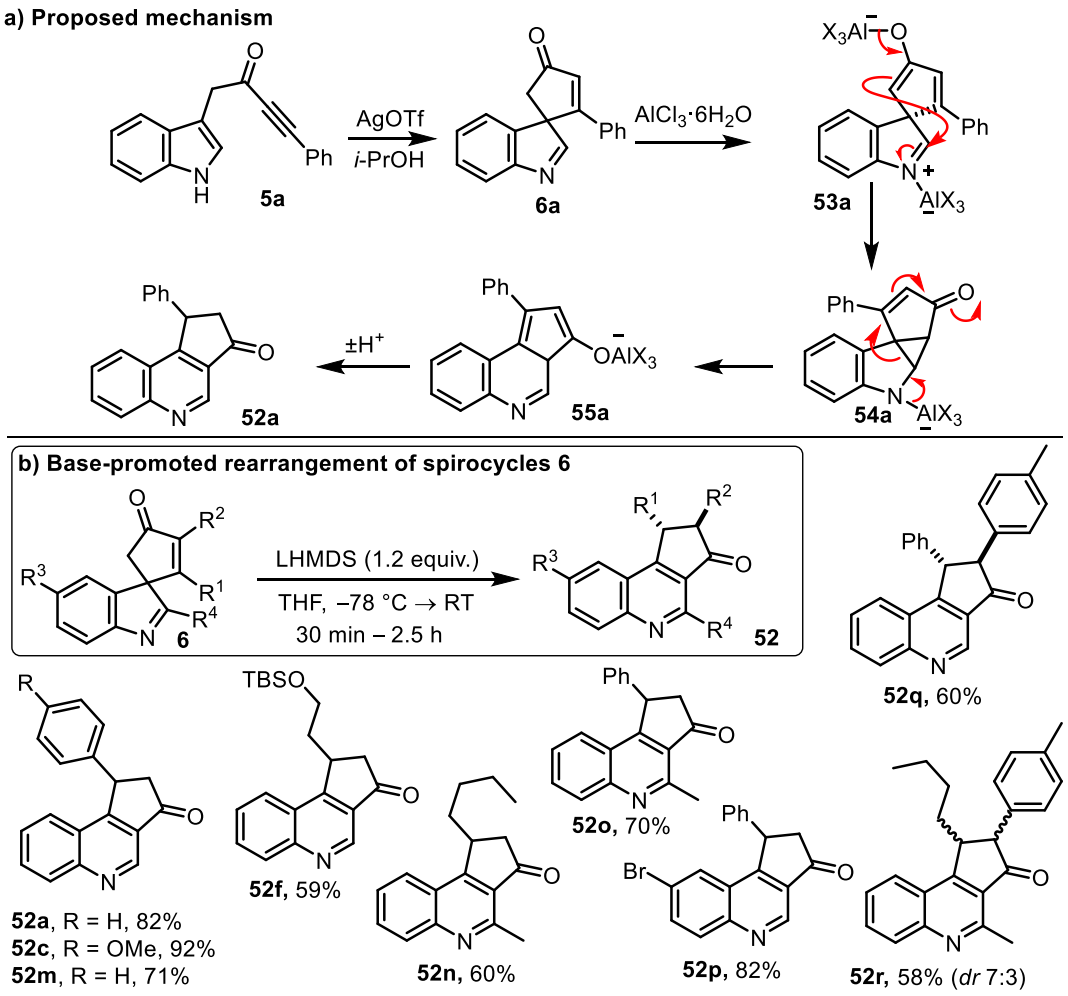
Subsequently, we went on to investigate the preparation of hydroxyl-carbazoles **51** directly and selectively from indole-ynones **5** (Scheme 16) [23]. The conversion of indole-ynones into spirocyclic indolenines using Ag(I) π-acid catalysis had already been established (*e.g.* **5a** → **6a**, Scheme 16A; see Section 2 for more details), and it was proposed that the gold(I) catalyst $Ph_3PAuNTf_2$·tol might promote the initial



Scheme 17. Gold(I) catalysed conversion of indole ynones **5** into carbazoles **51b**: substrate scope.



Scheme 18. Conversion of indole ynones **5** into quinolines **52a–l**: substrate scope.



Scheme 19. a) Proposed mechanism for the conversion of indole ynones **5** into quinolines **52**; b) Base-promoted rearrangement of spirocyclic indolenines **6**.

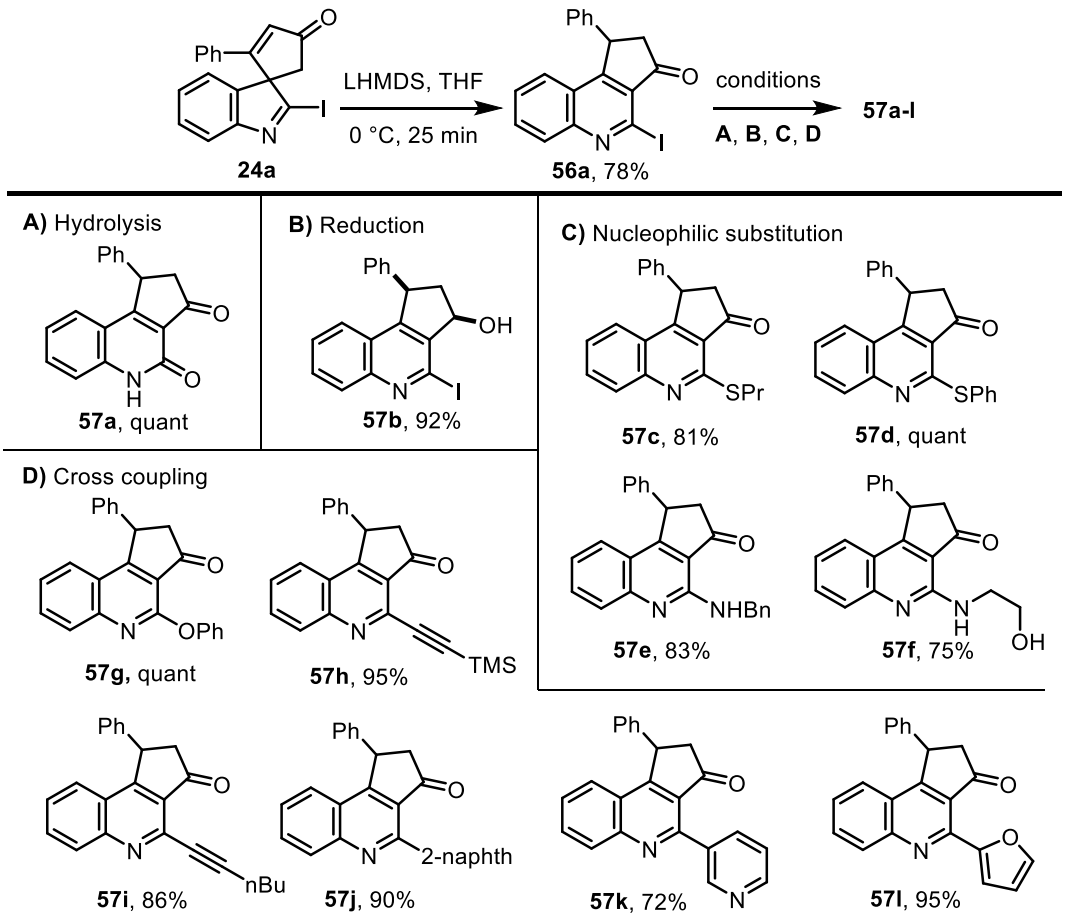
spirocyclisation reaction in a related manner, but it was hoped that the vinyl gold intermediate (**52b**, Scheme 16B) might undergo 1,2-migration, based on the known reactivity of similar vinyl gold and gold carbenoid species (*e.g.* as was seen in the example from van der Eycken's group earlier in Scheme 2) [16c]. This conversion was successful (94 % yield of **51b**), with the reaction mechanism originally proposed depicted in Scheme 16B. No reaction occurs when spirocycle **6b** is treated with $Ph_3PAuNTf_2$·tol under the same conditions, indicating that carbazole **51b** is not formed simply via the rearrangement of spirocycle **6b**, with this observation being consistent with the mechanism depicted in the original manuscript. However, the mechanism of the proposed 1, 2-migration was later questioned, following computational studies using a DFT approach [24]. No transition state connecting spirocycle **52b** with intermediates **52c/52d** could be located using any of the DFT methods employed. By contrast, the conversion of **52a** into **52b** was calculated to be facile. Therefore, it was thought that if protodemetallation of **52b** (**52b** → **6b**) is slow, then the formation of **52b** from **52a** would probably be reversible. The revised mechanism in Scheme 16C is therefore now thought to be more likely [24]; reversible interconversion of **52a** and **52b** promotes, over time, cyclisation via the less reactive C-2 position of **52a** to form **52d**, thereby enabling conversion into the thermodynamic reaction product, carbazole **51b** [39].

Having established efficient conditions for the conversion of indole-ynone **5b** directly into carbazole **51b** using gold-catalysis, the scope of the transformation was studied (Scheme 17) [23,24]. As illustrated in Scheme 17, good to excellent yields of carbazoles **51a–m** were obtained from a wide range aryl and alkyl alkynes, with substitution on the indole ring, and reactive side chains on the alkyne (*e.g.* alkyl chloride **51m**), proving compatible.

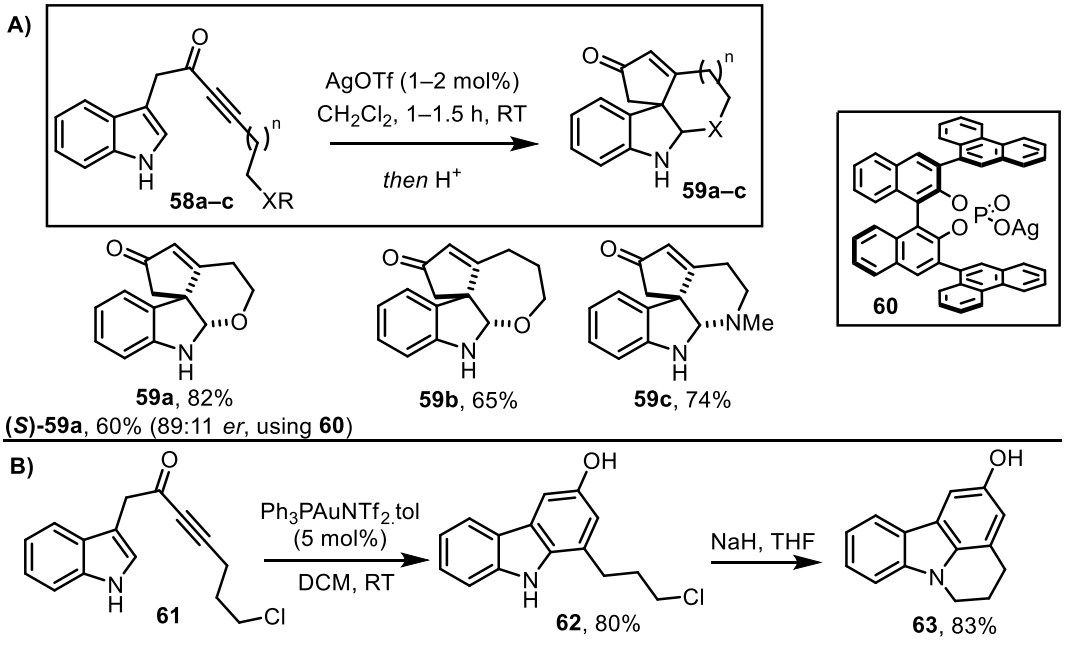
b Quinolines

A third divergent reaction pathway was also discovered starting from indole-ynones **5**, which enabled the synthesis of annulated quinolines via a novel rearrangement process (Scheme 18) [23]. In this procedure, indole-ynones **5** were first treated with catalytic AgOTf in *iso*-propanol, to promote spirocyclisation (as described earlier, see Table 2). This was then followed by the addition of 5 mol% of $AlCl_3.6H_2O$ and microwave heating, promoting a rearrangement to generate quinolines **52a–l** (Scheme 18). This transformation was discovered by serendipity; the Al (III)-based reaction conditions were originally employed to cleave a TBS protecting group, with the generation of quinoline product (**52f**) totally unexpected! However, the rearrangement to quinolones was found to be general and efficient route to quinolines **52a–l**. Subsequently, Van der Eycken and co-workers developed a transition metal-free variant of this transformation using Brønsted acids to effect rerrangement [40].

The proposed mechanism for the conversion of ynones **5** into quinolines **52** is shown in Scheme 19a, exemplified by ynone **5a**. Following Ag(I)-mediated spirocyclisation in the usual way (**5a** → **6a**, see Table 2 for more details on this step), it is suggested that the Al(III) catalyst promotes enolate formation (**6a** → **53a**); subsequent intramolecular attack by the enolate on the activated, electrophilic imine moiety (**53a** → **54a**) would form a cyclopropane intermediate **54a**. Then, cyclopropane fragmentation (**54a** → **55a**) is thought to promote the crucial ring

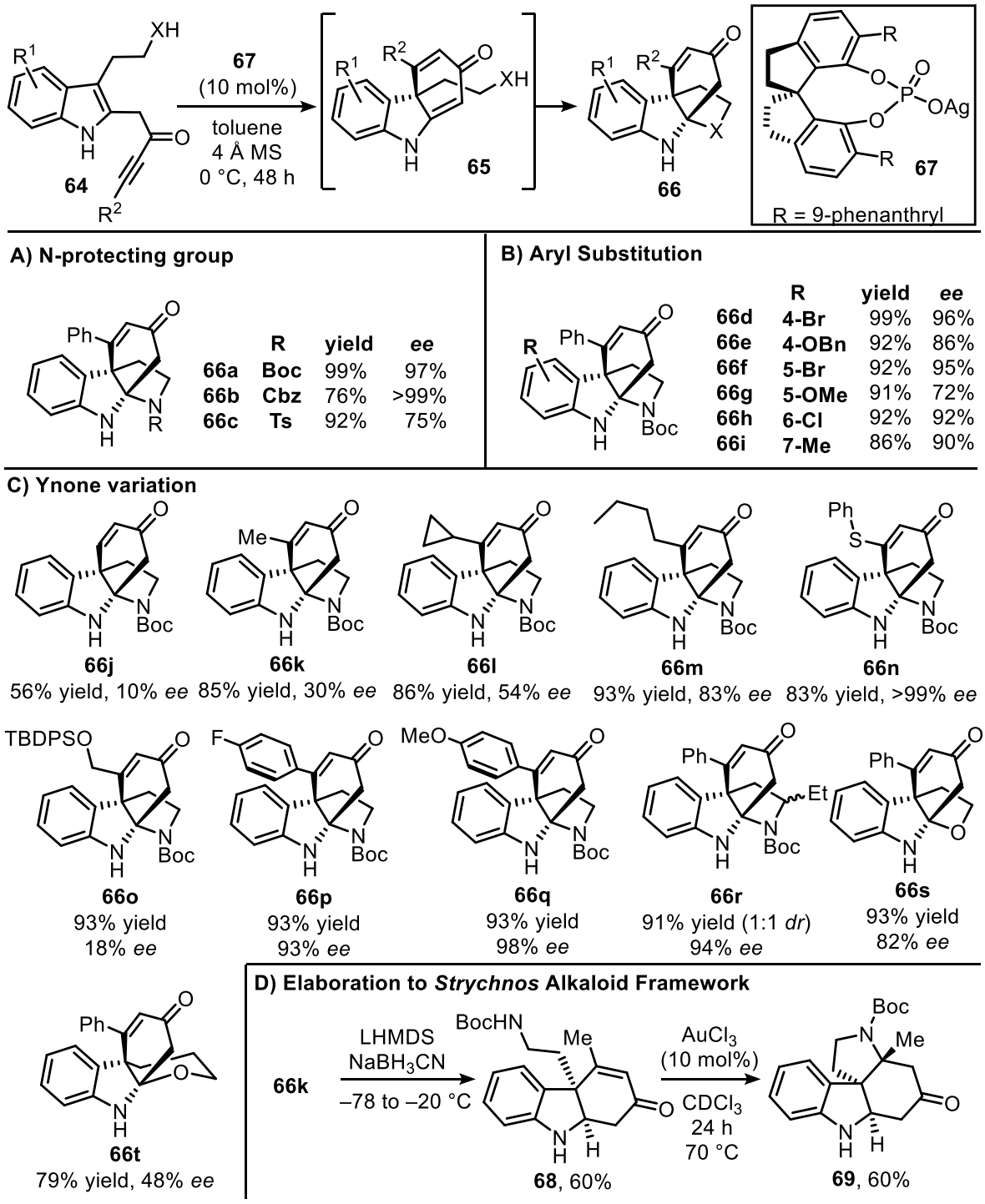


Scheme 20. Formation and versatile reactivity of iodo-quinoline **56a**.



Scheme 21. Synthesis of polycyclic products.

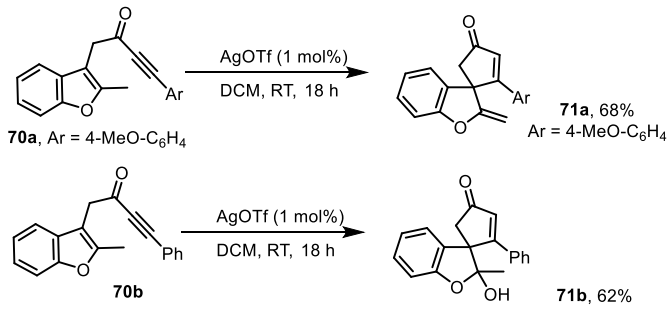
expansion step, with subsequent rearomatisation via 1,5-hydride migration completing the synthesis. Van der Eycken's Brønsted acid promoted variant seems likely to proceed via a similar mechanism, but via an enol, rather than an enolate, intermediate. Further support for this previously unprecedented rearrangement proceeding via an enolate was obtained when it was demonstrated that treatment of spirocycle **6a** with LHMDS in THF (*i.e.* conditions which seem certain to result in enolate formation), also led to the generation of quinoline **52a** (81 %,



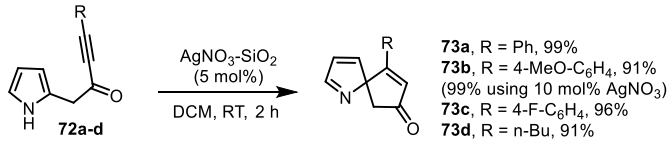
Scheme 22. Synthesis of polycyclic products from C-2 indole ynones via a cascade reaction.

Scheme 19b) [23]. In more recent studies [41], Density Functional Theory (DFT) was used to shed further light on this rearrangement. DFT indicates that both the base- and acid-mediated variants likely proceed via enolate/enol intermediates as proposed, and that the ease with which the enolate/enol is produced appears to be crucial in explaining the kinetic outcomes (thereby explaining why the base-promoted variant occurs under milder conditions than the acid-promoted variant). From a synthetic viewpoint, several additional examples of the base-mediated transformation were carried out using the LHMDS procedure (Scheme 19b) [41]. Good to excellent yields of quinoline products **52** were observed in all examples.

This type of base-mediated rearrangement was subsequently found to be applicable to indoleninyl halide **24a** generating the cyclopentanone-annulated iodo-quinoline **56a** in 78 % yield (Scheme 14) [25]. Iodo-quinoline **56a** was then employed in further reactions to illustrate the utility of such compounds as versatile building blocks. Hydrolysis with aqueous HCl gave 2-quinolone **57a** in quantitative yield (Scheme 20A) and a chemo- and diastereo-selective reduction using $NaBH_4$ efficiently gave alcohol **57b** (92 %, Scheme 20B). In addition, sulfur and amine nucleophiles successfully displaced iodide (Scheme 20C) and a range of Pd-catalysed cross-coupling methods proceeded in good to excellent yields (Scheme 20D). Full synthetic details of all of



Scheme 23. Dearomative spirocyclisation of benzofuran-ynones.



Scheme 24. Dearomative spirocyclisation of 2-substituted pyrroles.

these transformations are described in the original publisation [25].

c Polycycle Synthesis

Polycyclic compounds can also be accessed from indole precursors using modified variants of the procedures outlined above. For example, tetracyclic scaffolds **59a**–**c** were obtained by reaction of functionalised indole-ynones **58a**–**c** with AgOTf followed by acid-mediated protecting group cleavage/imine cyclisation in one-pot (Scheme 21) [23]. The tetracyclic products were synthesised as the single diastereoisomers shown, and in addition, **(*S*)-59a** was prepared in enantioenriched form (89:11 *er*) by using the (*R*)-CPA silver(I) salt **60** in place of AgOTf. The *er* of **(*S*)-8h** could be increased to ~100:0 by recrystallisation (ethanol) and its structure was confirmed using X-ray crystallography. Similarly, indole-ynone **61** was readily converted into the functionalised carbazole **62** using the Au(I)-mediated spirocyclisation/rearrangement protocol and then cyclisation to produce the tetracyclic product **63** was accomplished by treatment with sodium hydride [24].

Other polycyclic products were prepared using a conceptually similar approach starting from indoles with the ynone attached to the indole 2-position (**64**) [42]. On treatment with chiral silver(I) chiral phosphoric acid salt **67**, a range of indole derivatives **64** were converted into polycyclic products **66** via initial cyclisation through the indole 3-position (**65**). In most cases, high yields and *er* were obtained using this procedure (**66a–S**cheme 22A–C). This method was developed, in part, due to its potential for the generation of frameworks found in *strychnos* alkaloids; for example, polycycle **66k** was converted into the alkaloid analogues **68** and **69** (Scheme 22D). A racemic, Au(I)-catalysed, procedure to prepare the same family of polycycles was also developed and reported later (not shown) [43].

8. Extension of ynone cyclisations to other aromatic systems

Indole-ynones of the types described above have been the main focus of this research programme. However, synthetic applications of ynones tethered to other heteroaromatic, aromatic and non-aromatic rings, have also been explored. These are reviewed in this section, starting with benzannulated heterocycles and then covering applications in monocyclic heterocyclic and carbocyclic systems.

a Benzofuran-Ynones

Only two examples involving benzofuran spirocyclisation have been reported (Scheme 23) [9,22]. With benzofuran **70a**, the unusual spirocyclic enol ether **71a** was isolated in reasonable yield using catalytic AgOTf [9]. In a later study [22], the use of silica-supported $AgNO_3$ gave the corresponding hemi-acetal **71b** from ynone **70b** (unsupported $AgNO_3$ gave no conversion to **71b**, even after 24 h). These examples show that, provided there is a method by which neutralisation of the intermediate oxonium ion (analogous to **16** in Scheme 3) can be achieved, stable spirocyclic products can be obtained from benzofuran ynones. In these examples this occurs via either deprotonation or nucleophilic trapping.

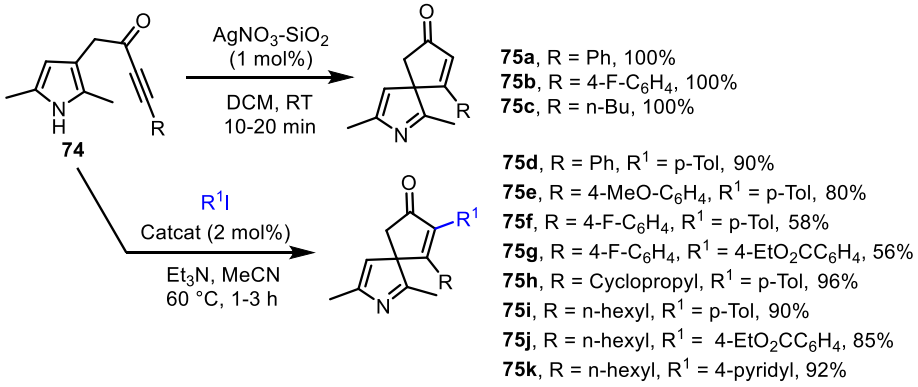
b Pyrrole-Ynones

(i)2-Substituted Pyrroles

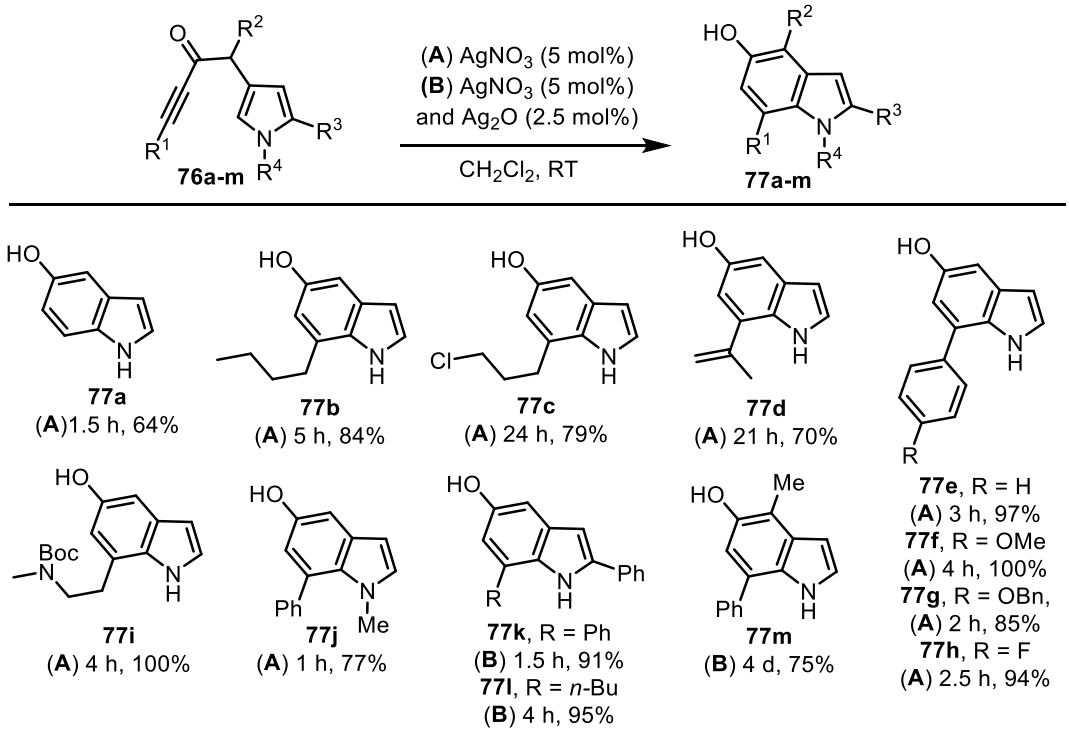
Pyrrole-ynones also undergo dearomatising spirocyclisation, with initial studies concentrating on 2-substituted pyrroles **72a–d** as shown in Scheme 24 [9,22]. Silica-supported $AgNO_3$ gave excellent yields of spirocyclic products **73a–d** in all four of the examples studied.

(ii) 3-Substituted Pyrroles

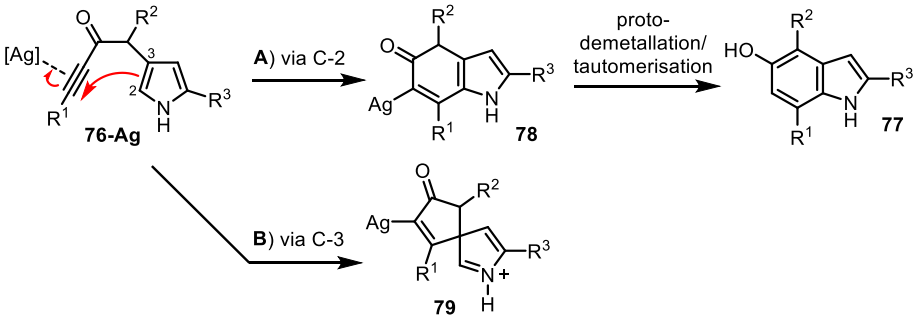
Similar Ag(I) catalysed conditions were also applicable to the spirocyclisation of 3-substituted pyrrole-ynones (Scheme 25) [22]. In three examples (**75a–c**), quantitative yields of the expected spirocyclic products were obtained using silica-supported $AgNO_3$ as catalyst, with lower yields observed for the unsupported catalyst (not shown). 3-Substituted pyrrole-ynones were also successfully utilised in the palladium-catalysed spirocyclisation/cross-coupling cascade originally developed for indole-ynones (**75d–k**, Scheme 25; for the analogous indole study see above, Table 4) [30]. The 2- and 5-methyl substituents present in substrates **74** were essential as analogous starting materials lacking this substitution pattern did not undergo spirocyclisation; these results are significant nonetheless, given the rarity of dearomatising



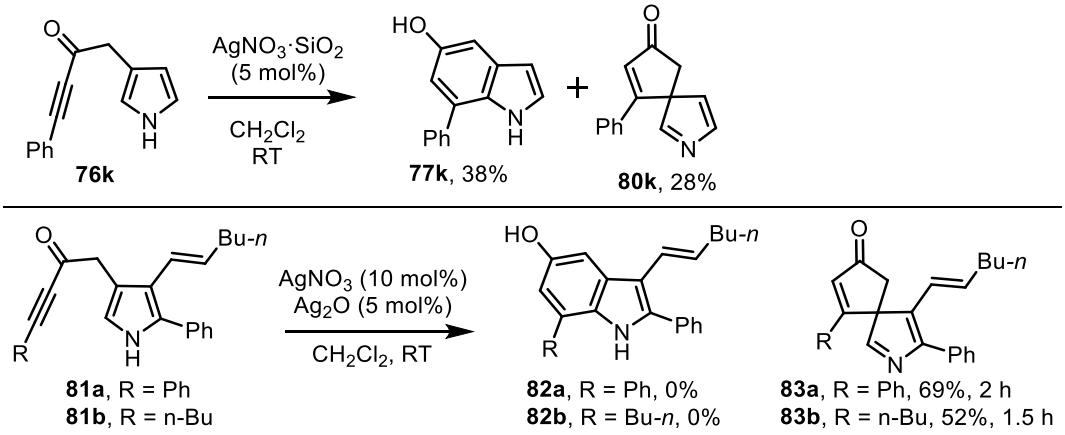
Scheme 25. Dearomative spirocyclisation of 3-substituted pyrroles.



Scheme 26. Conversion of 3-substituted pyrroles **76** into indoles **77**.



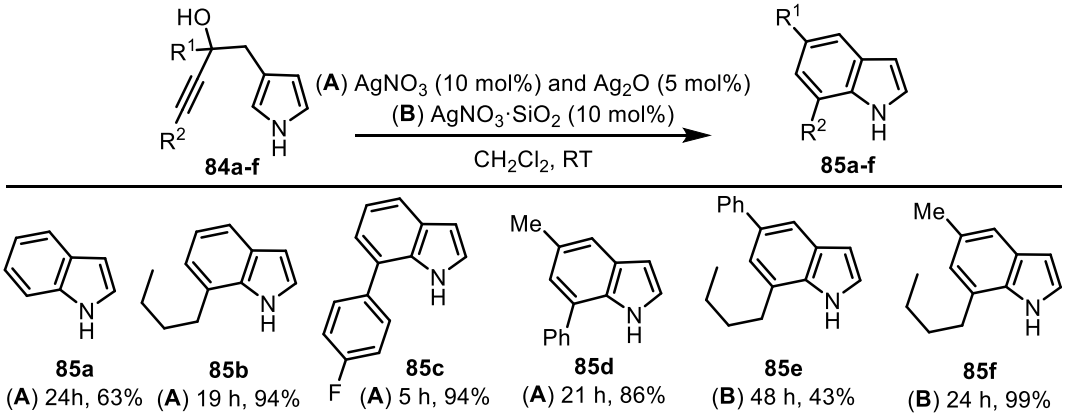
Scheme 27. Mechanistic possibilities in conversion of 3-substituted pyrroles **76** into indoles **77**.



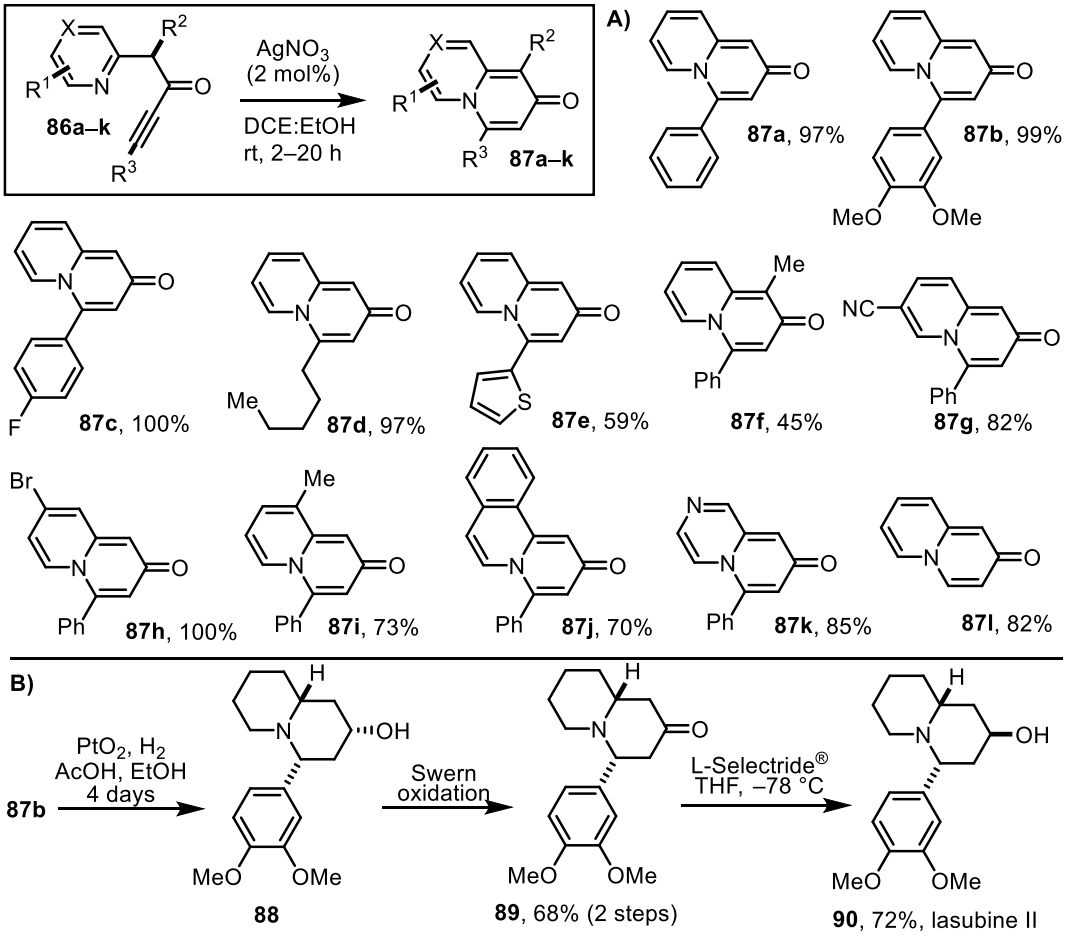
Scheme 28. Dearomative spirocyclisation of 3-substituted pyrroles **76** to form spirocycles.

spirocyclisation reactions of 3-pyrroles.

Later studies showed that pyrrole-3-ynones lacking a 2-substituent **76a–m** undergo efficient Ag(I)-catalysed cyclisation/rearrangement to provide a novel route to give 5-hydroxy-indoles **77a–m** (Scheme 26) [44]. Notably, most methods for the preparation of indoles involve annulation on to a benzene precursor to assemble the pyrrole portion



Scheme 29. Dearomative spirocyclisation of ynols **84** to form indoles **85**.

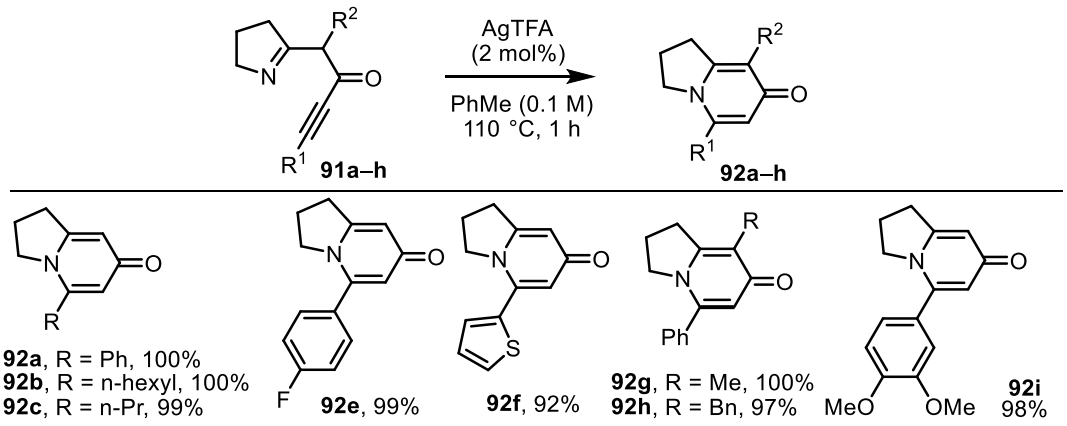


Scheme 30. Ag(I) catalysed cyclisation of ynone-tethered aza-aromatics.

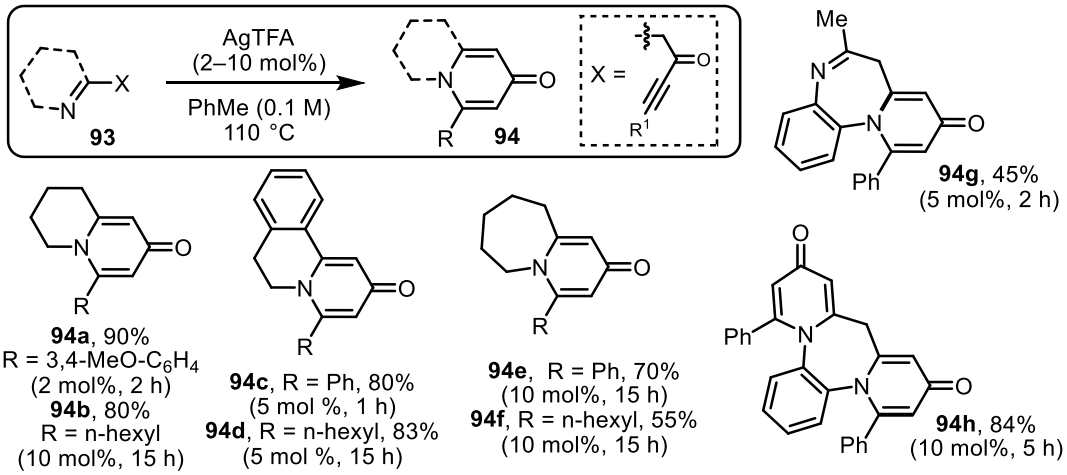
[1]; this ynone method is unusual in that pyrrole precursors are employed as starting materials with the benzene ring being constructed in a subsequent step. This observation led us term this method a 'back-to-front' indole synthesis [44].

In terms of the likely mechanism of these cyclisation reactions, two main pathways were considered, as shown in Scheme 27. Firstly, coordination of the alkyne unit of **76** to the active π-acidic silver species (to form **76-Ag**) can activate it towards attack by the electron-rich pyrrole ring, either via the pyrrole C-2 position (**76-Ag** → **78**) or via its C-3 position (**76-Ag** → **79**). Route **A**, cyclisation via C-2 was initially considered to be the most likely, given the well-accepted wisdom that pyrroles are more nucleophilic through C-2 than C-3, and the fact that this was judged to be the less sterically hindered of the two alternative pathways. Attack at C-2 is also the most direct route to the product, as from intermediate **78** protodemetallation and tautomerisation completes the formation of indole **77**. Route **B** illustrates a second possibility, that was initially considered to be less likely, with cyclisation proceeding via C-3 to form a spirocyclic intermediate **79**, followed by rearrangement via an overall 1,2-migration to form the indole scaffold **77**.

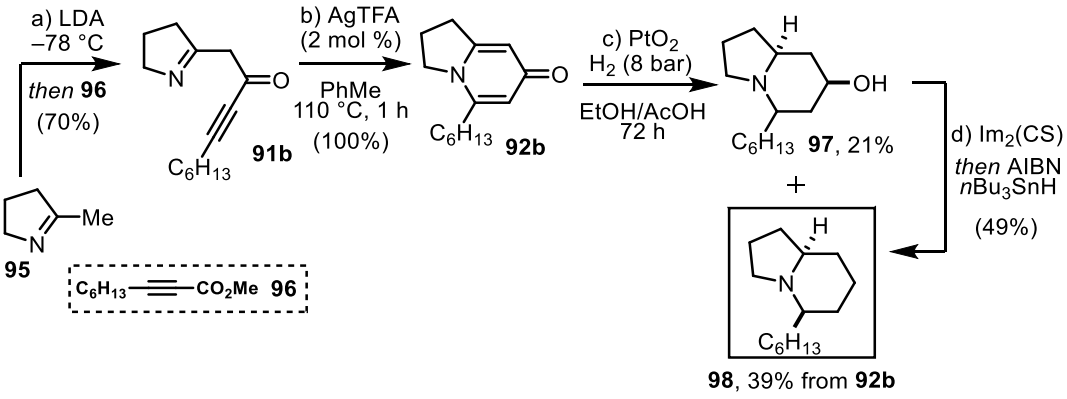
However, additional experimental results forced a mechanistic rethink (Scheme 28). With certain conditions for the conversion of



Scheme 31. Substrate scope for Ag(I)-catalysed cyclisation of pyrroline-tethered ynones.



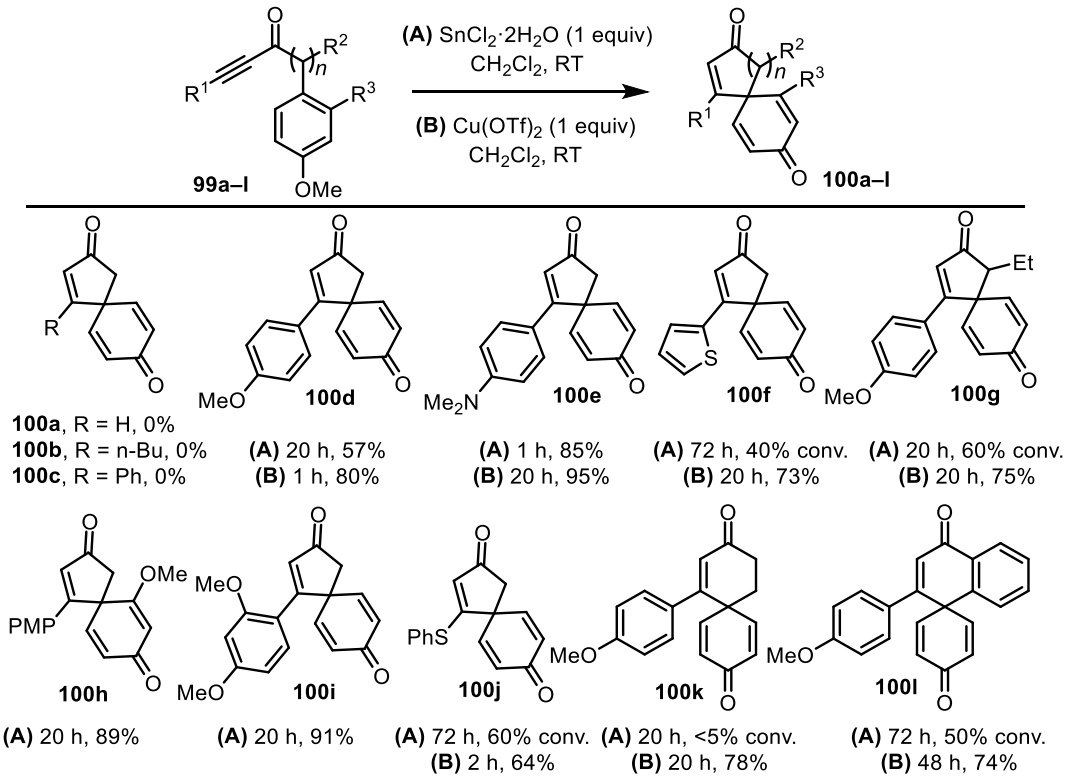
Scheme 32. Ag(I) catalysed cyclisation of ynone-tethered aza-aromatics.



Scheme 33. Synthesis of (±)-indolizidine 209D **98**.

pyrrole-ynone **76k** into indole **77k**, spirocycle **80k** was observed as a by-product. In addition, pyrrole-ynones **81a** and **81b** were converted into spirocycles **83a** and **83b** selectively, without any formation of indoles **82a** and **82b**. Re-subjecting the spirocycles **83a** and **83b** to the reaction conditions gave no discernible reaction, even at reflux temperature, indicating their stability. These observations suggest that a vinyl silver intermediate (cf. **79**) is essential for the 1,2-migration to occur (either via a concerted 1,2-migration or by way of a reversible ring closing/ring opening pathway, similar to that in Scheme 16C). Surprisingly, given the usual wisdom that pyrroles are most reactive via their C-2 position, Density Functional Theory (DFT) studies indicated that for ynones of type **76**, cyclisation via C-3 is the lowest energy pathway. Therefore, in view of this, and the isolation of spirocycles **80k** and **83a,b**, it seems reasonable to conclude that pyrrole-ynones **76** likely react via the pyrrole C-3 position, before undergoing subsequent rearrangement in most cases. Whether the subsequent rearrangement takes place via a concerted 1,2-migration or reversible ring opening/ring closing is not currently known.

The corresponding cyclisation reactions of ynol derivatives **84** were also studied as these produce the parent indoles **85** without hydroxyl



Scheme 34. Substrate scope of Sn(II) and Cu(I)-catalysed dearomatisation of anisole-tethered ynones. PMP = *para*-methoxyphenyl.

substitution (Scheme 29) [44]. In these systems, the optimum catalyst system proved to be 10 mol% $AgNO_3$ and 5 mol% Ag_2O, or silica-supported $AgNO_3$, giving a range of indoles **85a–f** (Scheme 29).

c Pyridine-, Isoquinoline-, and Pyrazine-ynones

Ynones linked to other nitrogen containing ring systems – including pyridine, isoquinoline- and pyrazine-ynones – can also be employed in related silver(I) catalysed cyclisation reactions (Scheme 30A) [45]. Similar cyclisation reactions have been reported to take place under thermal conditions [46], but these thermal conditions are in contrast to the milder (RT) and scalable catalytic Ag(I) method illustrated here. Initially, a diverse range quinolizinones **87a–i** were prepared from pyridines, mostly in excellent yield, with variation of the substituent on the alkyne, the alkyl chain and on the pyridine ring. This methodology was then extended to afford the isoquinoline- and pyrazine-derived products **87j** and **87k** in high yield. Finally, the fully unsubstituted quinolizinone **87l** was prepared in excellent yield from a TMS-ynone using $AgNO_3$ (20 mol%) to promote a one-pot desilylation−cyclisation sequence. Quinolizinone **87b** was then employed as the cornerstone of a novel dearomatisation route to prepare 0.53 g of the alkaloid lasubine II **90** in 5 steps and 36 % overall yield (Scheme 30B) [45].

d Pyrroline-Ynones and Ynones Derived from Related Cyclic Ketimines

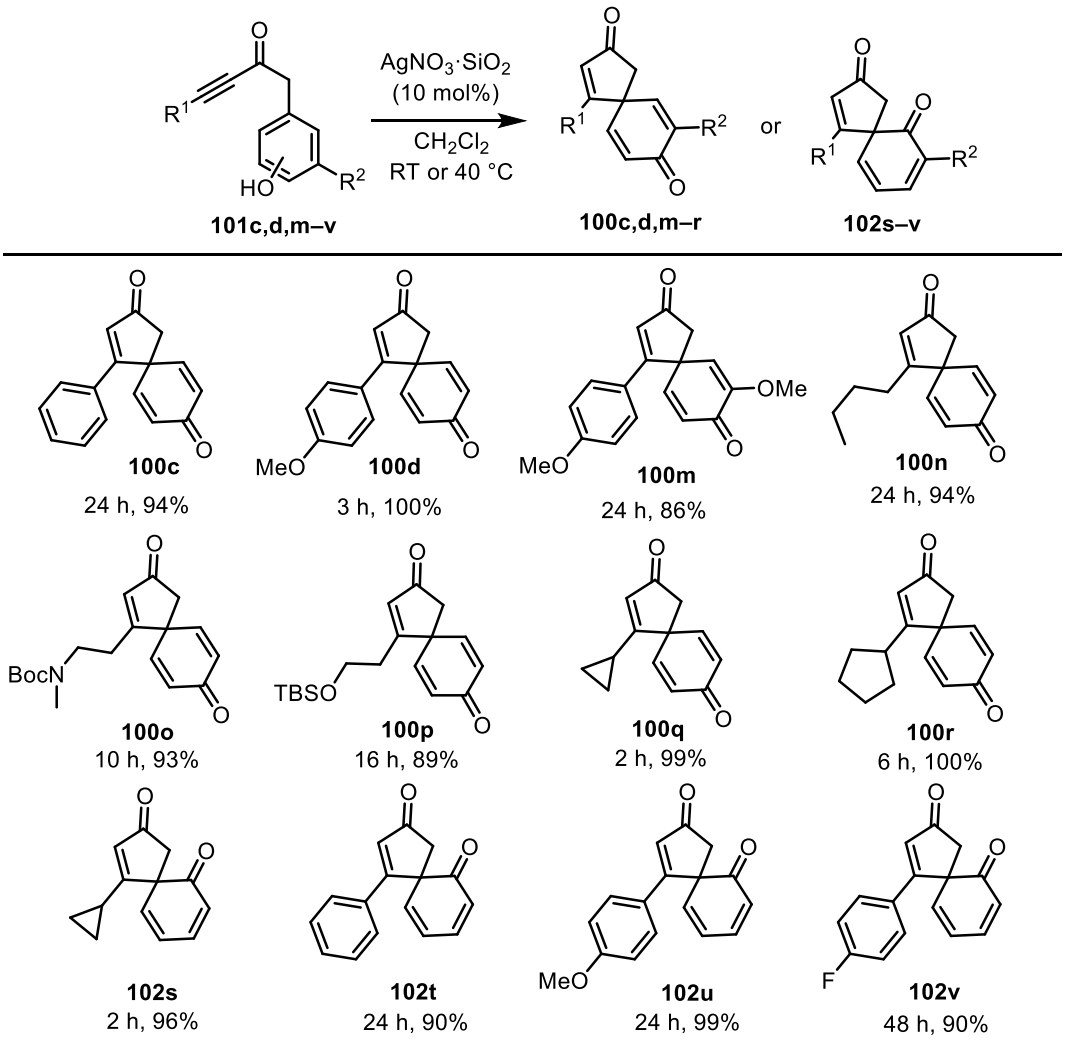
An efficient Ag(I)-catalysed π-acid activation procedure for the cyclisation of cyclic ketimine-tethered ynones has also been developed providing a novel route to annulated 4-pyridones. Initial studies involved the cyclisation of pyrroline-linked ynones **91** (Scheme 31), which are readily prepared by acylation of 2-methyl-1-pyrroline [47]. As can be seen, cyclisation using silver trifluoroacetate (AgTFA) proceeded efficiently, with both alkyl and aryl substituted alkynes, giving bicyclic products **92a-92f**; additional substituents on the ynone tether were also compatible with the standard method giving products **92g** and **92h**. All of the examples proceeded in excellent yields (92−100 %) using catalytic AgTFA (2 mol%).

This type of ynone cyclisation was also extended to other cyclic ketimines **93** (Scheme 32) [47]. Firstly, two dihydropiperidine ketimines and two benzannulated variants were converted into cyclised products **94a–d** in 80–90 % yields using catalytic AgTFA. Extension to 7-membered cyclic ketimines was also successful giving products **94e**,**f**, as were the diazepine examples **94g**,**h**, the latter via an efficient double cyclisation procedure.

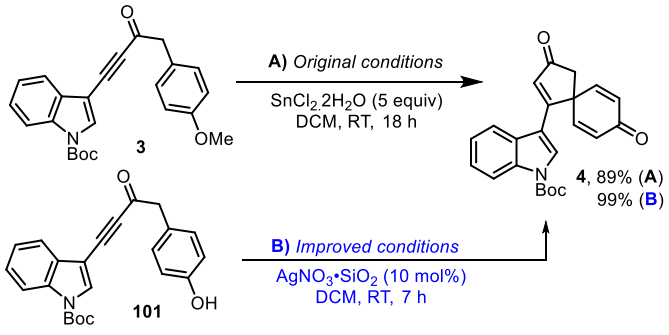
The utility of this Ag(I)-catalysed pyrroline-ynone cyclisation sequence was illustrated with a short total synthesis of indolizidine 209D (Scheme 33) [47], a bioactive alkaloid isolated from the skin secretions of the *Dendrobates* family of neotropical frogs. The synthesis commenced with the deprotonation of 2-methyl-1-pyrroline **95** followed by acylation using ester **96** to provide ynone **91b** in 70 % yield. Then, AgTFA-catalysed ynone cyclisation gave the required bicyclic product **92b** in quantitative yield as described above. Hydrogenation of compound **92b** using platinum(IV) oxide as catalyst (with hydrogen at 8 bar), gave a 1:2 mixture of hydroxylated product **97** and the fully saturated target molecule (±)-indolizidine 209D (**98**). The products were readily separated (21 % for **97** and 39 % for **98**), and each was isolated as a single diastereoisomer. Moreover, the yield of the natural product could be increased by subjecting the partially reduced by-product **97** to standard Barton−McCombie deoxygenation conditions, which gave an additional quantity of (±)-indolizidine 209D **98**.

e **Benzenoid Systems**

A range of *para*-substituted-anisoles linked to ynones **99** were shown to undergo dearomative spirocyclisation to generate spirocyclic dienones **100** upon treatment with either $SnCl_2{\cdot}2H_2O$ or $Cu(OTf)_2$ (Scheme 16) [9,48]. Initial results with unsubstituted and alkyl substituted ynones **99a** and **99b** were disappointing, however, with both failing to react with $SnCl_2{\cdot}2H_2O$ (Scheme 34, **100a** and **100b**) under the conditions used during the total synthesis of spirobacillene A shown earlier in Scheme 1. The phenyl substituted ynone **99c** also failed to react at room



Scheme 35. Substrate scope of Ag(I)-catalysed dearomatisation of phenol-tethered ynones.



Scheme 36. Improved synthesis of spirocycle **4** using Ag(I) catalysis.

temperature, although a small amount of cyclisation occurred when the reaction was heated at reflux. A reasonable explanation for these unsuccessful reactions is that electron-rich alkynes are required to more readily interact with the acidic additives, thereby facilitating spirocyclisation. The additional results in Scheme 34 support this theory; several substituted cyclopentenones **100d-j** were prepared from electron-rich alkynes **99d–j** (n = 1), as were the corresponding cyclohexenones **100k,l** from alkynes **99k,l** (n = 2), albeit the latter reactions were much slower. The simplicity of this synthetic method and its mild reaction conditions are positive aspects of the procedure, although the need for relatively large quantities of Sn(II) or Cu(II) reagents, and the requirement for electron-rich ynones, were identified as areas with potential for improvement.

The Sn(II)/Cu(I)-catalysed reactions shown in Scheme 34 were developed before we identified Ag(I)-catalysts as being generally superior for indole ynone dearomative spirocyclisation reactions. The same trend was seen for the benzenoid system (Scheme 35) [48]. Switching the nucleophilic component in the starting material from an anisole to the analogous phenol, and using silica-supported $AgNO_3$ (10 mol%) in CH_2Cl_2 at RT as catalyst, gave efficient dearomative spirocyclisation (Scheme 35) [22,48]. This approach enables the catalytic spirocyclisation of both *para*- and *ortho*-substituted phenols **101c,d,m-r** and **101s-v**, to give cyclopentenones **100c,d,m-r** and **102s-v**, respectively. Initial asymmetric studies were also reported producing **102t**, albeit in low *er* [48].

The superior reactivity of Ag(I) salts in dearomative ynone spirocyclisation reactions is illustrated in the final example in this review, in which we return to one of the two reactions that initiated the ynone research programme – the conversion of ynone **3** into spirocycle **4**. Our published synthesis of spirocyclic dienone **4**, a key intermediate en route to spirobacillene A, required five equivalents of $SnCl_2{\cdot}2H_2O$ and an 18 h reaction time to generate the product **4** in 89 % yield [8]. By contrast, the same product **4** was generated from phenol **103** in near quantitative yield in just 7 h using 10 mol% $AgNO_3{\cdot}SiO_2$ (Scheme 36).[48]

9. Summary

A wide range of novel dearomatising reactions have been developed for the efficient generation of synthetically useful spirocyclic and heterocyclic building blocks from simple heteroaromatic precursors with tethered ynone side chains. The reactions, usually catalysed by Ag(I), are easy to perform, usually proceed at RT, and are insensitive to both air and moisture. Initial studies were carried out on indole-3-ynones, and asymmetric, palladium-catalysed and photochemical variants were subsequently developed. In addition, the synthetic versatility of the indole-derived spirocycles was illustrated with facile, catalyst-controlled, selective conversion into carbazoles, quinolines and polycyclic systems. The ynone chemistry was subsequently extended to several other heterocyclic systems (pyrroles, pyridines, isoquinolines, pyrazines, cyclic ketimines etc.) as well as to anisoles and phenols producing spirocyclic dienones. The scope of the ynone methodology, illustrated throughout this review, is now broad and well-established, and preliminary applications in natural product synthesis have been explored. Our hope is that this review will inspire new methodological discoveries, particularly in terms of extensions to new aromatic systems and optimised asymmetric variants, as well as applications in the synthesis of natural products and bioactive target molecules.

CRediT authorship contribution statement

Richard J.K. Taylor: Writing – review & editing, Writing – original draft, Visualization, Conceptualization. **William P. Unsworth:** Writing – review & editing, Writing – original draft, Visualization, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

References

[1] For reviews on indole synthesis, see: a) J. Bergman and T. Janosik, in: A. R. Katritzky, C.A. Ramsden, E.F.V. Scriven, R.J.K. Taylor (Eds.), Volume 3 of Comprehensive Heterocyclic Chemistry III, Elsevier, Oxford, 2008, pp. 269–351 (Chapter 3).03;
b) A.K. Clarke, H.E. Ho, J.A. Rossi-Ashton, R.J.K. Taylor, W.P. Unsworth, Indole synthesis using silver catalysis, Chem. Asian J. 14 (2019) 1900–1911;
c) D.F. Taber, P.K. Tirunahari, Indole synthesis: a review and proposed classification, Tetrahedron 67 (2011) 7195–7210;
d) S. Cacchi, G. Fabrizi, Synthesis and functionalization of indoles through palladium-catalyzed reactions, Chem. Rev. 105 (2005) 2873–2920;
e) G.R. Humphrey, J.T. Kuethe, Practical methodologies for the synthesis of indoles, Chem. Rev. 106 (2006) 2875–2911;
f) J. Campo, M. Garcia-Valverde, S. Marcaccini, M.J. Rojo, T. Torroba, Synthesis of indole derivatives via isocyanides, Org. Biomol. Chem. 4 (2006) 757–765;
g) R. Vicente, Recent advances in indole syntheses: new routes for a classic target, Org. Biomol. Chem. 9 (2011) 6469–6480;
h) M. Inman, C.J. Moody, Indole synthesis – something old, something new, Chem. Sci. 4 (2013) 29–41.

[2] For reviews on indole elaboration reactions, see a) M. Shiri. Indoles in Multicomponent Processes (MCPs), Chem. Rev. 112 (2012) 3508–3549;
b) G.M. Ziarani, R. Moradi, T. Ahmadi, N. Lashgari, Recent advances in the application of indoles in multicomponent reactions, RSC Adv. 8 (2018) 12069–12103;
c) J. Wen, Z. Shi, From C4 to C7: innovative strategies for site-selective functionalization of indole C–H bonds, Acc. Chem. Res. 54 (2021) 1723–1736;
d) M. Bandini, A. Eichholzer, Catalytic functionalization of indoles in a new dimension, Angew. Chem., Int. Ed. 48 (2009) 9608–9644;
e) T.W. Lyons, M.S. Sanford, Palladium-Catalyzed ligand-directed C–H functionalization reactions, Chem. Rev. 110 (2010) 1147–1169;
f) G. Bartoli, G. Bencivenni, R. Dalpozzo, Organocatalytic strategies for the asymmetric functionalization of indoles, Chem. Soc. Rev. 39 (2010) 4449–4467;
g) R. Dalpozzo, Strategies for the asymmetric functionalization of indoles: an update, Chem. Soc. Rev. 44 (2015) 742–778;
h) S. Cacchi, G. Fabrizi, Update 1 of: synthesis and functionalization of indoles through palladium-catalyzed reactions, Chem. Rev. 111 (2011) PR215–PR283;
i) J.-B. Chen, Y.-X. Jia, Recent progress in transition-metal-catalyzed enantioselective indole functionalizations, Org. Biomol. Chem. 15 (2017) 3550–3567.

[3] For reviews on the applications of indole derivatives, see: M. d'Ischia, A. Napolitano and A. Pezzella, in: A.R. Katritzky, C.A. Ramsden, E.F.V. Scriven, R.J. K. Taylor (Eds.), -388 in Volume 3 of Comprehensive Heterocyclic Chemistry III, Elsevier, Oxford, 2008, p. 353 (Chapter 3).04;
b) G.W. Gribble, Recent developments in indole ring synthesis—methodology and applications, Eur. J. Med. Chem. 183 (2019) 111691. J. Chem. Soc. Perkin Trans. 1 (2000), 1045–1075; Y. Wan, Y. Li, C. Yan, M. Yan, Z. Tang. Indole: A Privileged Scaffold for the Design of Anti-Cancer Agents;
d) K. Urbina, D. Tresp, K. Sipps, M. Szostak, Recent advances in metal-catalyzed functionalization of indoles, Adv. Synth. Catal. 363 (2021) 2723–2739;
e) P. Kumar, P.J. Nagtilak, M. Kapur, Transition metal-catalyzed C–H functionalizations of indoles, New J. Chem. 45 (2021) 13692–13746;
f) J.A. Leitch, Y. Bhonoah, C.G. Frost, Beyond C2 and C3: transition-metal-catalyzed C–H functionalization of indole, ACS Catal. 7 (2017) 5618–5627.

[4] a) J.R. Donald, R.J.K. Taylor, Tandem meinwald rearrangement/fischer indolisation: a one pot conversion of epoxides into indoles, Synlett (2009) 59–62;
b) P. Drouhin, R.J.K. Taylor, A copper-mediated oxidative coupling route to 3H- and 1H-indoles from N-aryl enamines, Eur. J. Org. Chem. (2015) 2333–2336;
c) A. Perry, R.J.K. Taylor, Oxindole synthesis by direct C-H, Ar-H coupling, Chem. Commun. (2009) 3249–3251;
d) J.R. Donald, R.J.K. Taylor, W.F. Petersen, A low-temperature, transition metal-free cross dehydrogenative coupling protocol for the synthesis of 3,3-disubstituted oxindoles, J. Org. Chem. 82 (2017) 11288–11294;
e) W.P. Unsworth, R.J.K. Taylor, Upenamide, Trials and tribulations, Org. Biomol. Chem. 11 (2013) 7250–7261;
f) S.J. Chambers, G. Coulthard, W.P. Unsworth, P. O'Brien, R.J.K. Taylor, From heteroaromatic acids and imines to azaspirocycles: stereoselective synthesis and 3D shape analysis, Chem. Eur J. 22 (2016) 6496–6500;
g) T.E. Hurst, R. Gorman, P. Drouhin, R.J.K. Taylor, Application of copper(II)-Mediated radical cross-dehydrogenative coupling to prepare spirocyclic oxindoles and to a formal total synthesis of sataxaptan, Tetrahedron 74 (2018) 6485–6496.

[5] For reviews on dearomative spirocyclisation, see: a) C.-X. Zhuo, W. Zhang, S.-L. You. Catalytic asymmetric dearomatization reactions, Angew. Chem. Int. Ed. 51 (2012) 12662–12686;
b) W.-T. Wu, L. Zhang, S.-L. You, Catalytic asymmetric dearomatization (CADA) reactions of phenol and aniline derivatives, Chem. Soc. Rev. 45 (2016) 1570–1580;
c) J. Bariwal, L.G. Voskressensky, E.V. Van der Eycken, Recent advances in spirocyclization of indole derivatives, Chem. Soc. Rev. 47 (2018) 3831–3848;
d) W.C. Wertjes, E.H. Sothgate, D. Sarlah, Recent advances in chemical dearomatization of nonactivated arenes, Chem. Soc. Rev. 47 (2018) 7996–8017;
e) C. Zheng, S.-L. You, Catalytic asymmetric dearomatization (CADA) reaction-enabled -total synthesis of indole-based natural products, Nat. Prod. Rep. 36 (2019) 1589–1605;
f) W.-C. Yang, M.-M. Zhang, J.-G. Feng, Recent advances in the construction of spiro compounds via radical dearomatization, Adv. Synth. Catal. 362 (2020) 4446–4461;
g) C. Zheng, S.-L. You, Advances in catalytic asymmetric dearomatization, ACS Cent. Sci. 7 (2021) 423–444;
h) D. Bag, S.D. Sawant, Heteroarene-tethered functionalized alkyne metamorphosis, Chem. Eur J. 27 (2021) 1165–1218;
i) N. Li, Z. Shi, W.-Z. Wang, Y. Yuan, K.-Y. Ye, Electrochemical dearomative spirocyclization, Chem. Asian J. 18 (2023) e202300122.

[6] For reviews on the synthesis and applications of spirocycles, see: a) F. Buttard, X. Guinchard. Spiroindoles as Intermediates/Products in Transition Metal-Catalyzed Dearomatization of Indoles, ACS Catal. 13 (2023) 9442–9475;
b) Y. Zheng, C.M. Tice, S.B. Singh, The use of spiro-cyclic scaffolds in drug discovery, Bioorg. Med. Chem. Lett. 24 (2014) 3673–3682;
c) K. Fominova, T. Diachuk, D. Granat, T. Savchuk, V. Vilchynskyi, O. Svitlychnyi, V. Meliantsev, I. Kovalchuk, E. Litskan, V.V. Levterov, V.R. Badlo, R.I. Vas-kevych, A.I. Vaskevych, A.V. Bolbut, V.V. Semeno, R. Iminov, K. Shvydenko, A. S. Kuznetsova, Y.V. Dmytriv, D. Vysochyn, V. Ripenko, A.A. Tolmachev, O. Pavlova, H. Kuznietsova, I. Pishel, P. Borysko, P.K. Mykhailiuk, Oxa-spirocycles: synthesis, properties and applications, Chem. Sci. 12 (2021) 11294–11305;
d) A. Ding, M. Meazza, H. Guo, J.W. Yang, R. Rios, New development in the enantioselective synthesis of spiro compounds, Chem. Soc. Rev. 47 (2018) 5946–5996.

[7] H.B. Park, Y. Kim, J.K. Lee, K.R. Lee, H.C. Kwon, A. Spirobacillenes, B, unusual spiro-cyclopentenones from Lysinibacillus fusiformis KMC003, Org. Lett. 14 (2012) 5002–5005.

[8] a) W. P Unsworth, J.D. Cuthbertson, R.J.K. Taylor, The total synthesis of spirobacillene, A. Org. Lett. 15 (2013) 3306–3309. For an alternative approach for the total syntheses of spirobacillenes A and B published around the same time, using an oxidative coupling strategy, see:;
b) H. Yang, J. Feng, Y. Tang, Biomimetic total syntheses of spirobacillenes A and B, Chem. Commun. 49 (2013) 6442–6444.

[9] M.J. James, J.D. Cuthbertson, P. O'Brien, R.J.K. Taylor, W.P. Unsworth, Silver(I) or copper(II)-Mediated dearomatization of aromatic ynones: direct access to spirocyclic scaffolds, Angew. Chem. Int. Ed. 54 (2015) 7640–7643.

[10] a) X. Zhang, R.C. Larock, Synthesis of Spiro[4.5]trienones by Intramolecular ipso-Halocyclization of 4-(p-Methoxyaryl)-1-alkynes, J. Am. Chem. Soc. 127 (2005) 12230–12231;
b) B.-X. Tang, D.-J. Tang, S. Tang, Q.-F. Yu, Y.-H. Zhang, Y. Liang, P. Zhong, J.-H. Li, Selective synthesis of spiro[4,5]trienyl acetates via an intramolecular electrophilic ipso-iodocyclization process, Org. Lett. 10 (2008) 1063–1066;
c) Q.-F. Yu, Y.-H. Zhang, Q. Yin, B.-X. Tang, R.-Y. Tang, P. Zhong, J.-H. Li, Electrophilic ipso-Iodocyclization of N-(4-Methylphenyl)propiolamides: selective Synthesis of 8-Methyleneazaspiro[4,5]trienes, J. Org. Chem. 9 (2008) 3658–3661;
d) B.-X. Tang, Q. Yin, R.-Y. Tang, J.-H. Li, Electrophilic ipso-cyclization of N-(p-Methoxyaryl)propiolamides involving an electrophile-exchange process, J. Org. Chem. 73 (2008) 9008–9011;
e) T. Dohi, D. Kato, R. Hyodo, D. Yamashita, M. Shiro, Y. Kita, Discovery of stabilized bisiodonium salts as intermediates in the carbon–carbon bond formation of alkynes, Angew. Chem. Int. Ed. 50 (2011) 3784–3787.

[11] a) E.M. Carreira, T.C. Fessard, Four-membered ring-containing spirocycles: synthetic strategies and opportunities. Route to three-dimensional fragments using diversity-oriented synthesis, Chem. Rev. 114 (2014) 8257–8322;
b) A.W. Hung, A. Ramek, Y. Wang, T. Kaya, J.A. Wilson, P.A. Clemons, D. W. Young, Route to three-dimensional fragments using diversity-oriented synthesis, Proc. Natl. Acad. Sci. USA 108 (2011) 6799–6804;
c) A. Sveiczer, A.J.P. North, N. Mateu, S.L. Kidd, H.F. Sore, D.R. Spring, Spirocycles as rigidified sp3-rich scaffolds for a fragment collection, Org. Lett. 21 (2019) 4600–4604.

[12] a) J.-L. Reymond, M. Awale, Exploring chemical space for drug discovery using the chemical universe database, ACS Chem. Neurosci. 3 (2012) 649–657;
b) A.W. Hung, A. Ramek, Y. Wang, T. Kaya, J.A. Wilson, P.A. Clemons, D. W. Young, Route to three-dimensional fragments using diversity-oriented synthesis, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 6799–6804;
c) M.J. James, W.P. Unsworth P, O'Brien, R.J.K. Taylor, Synthesis of spirocyclic indolenines, Chem. Eur J. 22 (2016) 2856–2881.

[13] a) E. Chupakhin, O. Babich, A. Prosekov, L. Asyakina, M. Krasavin, Spirocyclic motifs in natural products, Molecules 24 (2019) 4165;
b) L.K. Smith, I.R. Baxendale, Total syntheses of natural products containing spirocarbocycles, Org. Biomol. Chem. 13 (2015) 9907–9933.

[14] M.E. Welsch, S.A. Snyder, B.R. Stockwell, Privileged scaffolds for library design and drug discovery, Curr. Opin. Chem. Biol. 14 (2010) 347–361.

[15] V.A. Peshkov, O.P. Pereshivko, E.V. Van der Eycken, Synthesis of azocino[5,4-b] indoles via gold-catalyzed intramolecular alkyne hydroarylation, Adv. Synth. Catal. 354 (2012) 2841–2848.

[16] a) S.F. Kirsch, Construction of heterocycles by the strategic use of alkyne π-activation in catalyzed cascade reactions, Synthesis 20 (2008) 3183–3204;
b) M. Álvarez-Corral, M. Muñoz-Dorado, I. Rodríguez-García, Silver-mediated synthesis of heterocycles, Chem. Rev. 108 (2008) 3174–3198. ; For more recent reviews, see:;
c) R. Dorel, A.M. Echavarren, Gold(I)-Catalyzed activation of alkynes for the construction of molecular complexity, Chem. Rev. 115 (2015) 9028–9072;
d) D. Campeau, D.F.L. Rayo, A. Mansour, K. Muratov, F. Gagosz, Gold-Catalyzed reactions of specially activated alkynes, allenes, and alkenes, Chem. Rev. 121 (2021) 8756–8867.

[17] J. Badorrek, D. Enders, C.C.J. Loh, G. Raabe, Merging organocatalysis and gold catalysis: enantioselective synthesis of tetracyclic indole derivatives through a sequential double friedel–crafts type reaction, Chem. Eur J. 17 (2011) 13409–13414;
(b) D. Benito, D.R. Carbery, S.J. Heffernan, M.F. Mahon, M.E. Queru, A. C. Silvanus, J.P. Tellam, B.I. Andrews, A.J. Hennessy, Double gold-catalysed annulation of indoles by enynones, Adv. Synth. Catal. 355 (2013) 1149–1159.

[18] (a) J.G. Rodriguez, Y. Benito, F. Temprano, Synthesis of spiro[cycloalkane-1,3′-[3H]indoles] from cycloalkanecarbaldehydes. Acid-catalyzed rearrangement to cycloalkano[b]indoles, J. Heterocycl. Chem. 22 (1985) 1207–1210;
(b) K.G. Liu, A.J. Robichaud, J.R. Lo, J.F. Mattes, Y. Cai, Rearrangement of 3,3-disubstituted indolenines and synthesis of 2,3-substituted indoles, Org. Lett. 8 (2006) 5769–5771;
(c) A.S.K. Hashmi, W. Yang, F. Rominger, Gold(I)-Catalyzed rearrangement of 3-Silyloxy-1,5-enynes: an efficient synthesis of benzo[b]thiophenes, dibenzothiophenes, dibenzofurans, and indole derivatives, Chem. Eur J. 18 (2012) 6576–6580.

[19] A. Furstner, P.W. Davies, Catalytic carbophilic activation: catalysis by platinum and gold π acids, Angew. Chem. Int. Ed. 46 (2007) 3410–3449, 46.

[20] A complex mixture of products was formed when the mixed $AuPPh_3Cl/AgOTf$ catalyst system used in the work of Van der Eycken was tested.

[21] T.T. Dang, F. Boeck, L. Hintermann, Hidden Brønsted acid catalysis: pathways of accidental or deliberate generation of triflic acid from metal triflates, J. Org. Chem. 76 (2011) 9353–9361.

[22] A.K. Clarke, M.J. James, P. O'Brien, R.J.K. Taylor, W.P. Unsworth, Silica-supported silver nitrate as a highly active dearomatising spirocyclisation catalyst: synergistic alkyne activation by silver nanoparticles and silica, Angew. Chem. Int. Ed. 55 (2016) 13798–13802.

[23] J.T.R. Liddon, M.J. James, A.K. Clarke, P. O'Brien, R.J.K. Taylor, W.P. Unsworth, Catalyst-driven scaffold diversity. Selective synthesis of spirocycles, carbazoles and quinolines from indolyl ynones, Chem. Eur J. 22 (2016) 8777–8780.

[24] J.T.R. Liddon, J.A. Rossi-Ashton, A.K. Clarke, J.M. Lynam, R.J.K. Taylor, W. P. Unsworth, Divergent reactivity of indole-tethered ynones with Ag(I) and Au(I) catalysts: a combined synthetic and computational study, Synthesis 50 (2018) 4829–4836.

[25] J.T.R. Liddon, A.K. Clarke, R.J.K. Taylor, W.P. Unsworth, Preparation and reactions of indoleninyl halides: versatile scaffolds for the synthesis of spirocyclic indole derivatives, Org. Lett. 18 (2016) 6328–6333.

[26] M.J. James, R.E. Clubley, K.Y. Palate, T.J. Procter, A.C. Wyton, P. O'Brien, R.J. K. Taylor, W.P. Unsworth, Silver(I)-Catalysed dearomatization of alkyne-tethered indoles: divergent synthesis of spirocyclic indolenines and carbazoles org, Letture 17 (2015) (2015) 4372–4375.

[27] a) G.L. Hamilton, E.J. Kang, M. Mba, F.D. Toste, A powerful chiral counterion strategy for asymmetric transition metal catalysis, Science 317 (2007) 496–499;
b) M. Terada, F. Li, Y. Toda, Chiral silver phosphate catalyzed transformation of ortho-alkynylaryl ketones into 1H-isochromene derivatives through an intramolecular-cyclization/enantioselective-reduction sequence, Angew. Chem. Int. Ed. 53 (2014) 235–239;
c) Y. Wang, K. Zheng, R. Hong, Chiral silver phosphate-catalyzed cycloisomeric kinetic resolution of α-allenic alcohols, J. Am. Chem. Soc. 134 (2012) 4096–4099.

[28] G. Fang, X. Bi, Silver-catalysed reactions of alkynes: recent advances, Chem. Soc. Rev. 44 (2015) 8124–8173.

[29] P. Fedoseev, G. Coppola, G.M. Ojeda, E.V. Van der Eycken, Synthesis of spiroindolenines by intramolecular ipso-iodocyclization of indol ynones, Chem. Commun. 54 (2018) 3625–3628.

[30] H.E. Ho, M.J. James, T.C. Stephens, T.C. Payne P, O'Brien, R.J.K. Taylor, W. P. Unsworth, Merging π-acid and Pd catalysis: dearomatising spirocyclisation/cross coupling cascade reactions of alkyne-tethered aromatics, ACS Catal. 9 (2019) 504–510.

[31] a) C.M. Crawforth, S. Burling, I.J.S. Fairlamb, R.J.K. Taylor, A.C. Whitwood, Bromobis(triphenylphosphine)(N-succinimide)palladium(II) as a novel catalyst for stille cross-coupling reactions, Chem. Commun. (2003) 2194–2195;
b) I.J.S. Fairlamb, R.J.K. Taylor, J.L. Serrano, G. Sánchez, Halide and pseudohalide effects in Pd-catalysed cross-coupling reactions, New J. Chem. 30 (2006) 1655–1704;
c) M.J. Burns, I.J.S. Fairlamb, A.R. Kapdi, P. Sehnal, R.J.K. Taylor, Simple palladium(II) precatalyst for Suzuki−Miyaura couplings: efficient reactions of benzylic, aryl, heteroaryl, and vinyl coupling partners, Org. Lett. 9 (2007) 5397–5400.

[32] K.-J. Wu, L.X. Dai, S.-L. You, Palladium(0)-Catalyzed dearomative arylation of indoles: convenient access to spiroindolenine derivatives, Org. Lett. 14 (2012) 3772–3775.

[33] H.E. Ho, A. Pagano, J.A. Rossi-Ashton, J.R. Donald, R.G. Epton, J.C. Churchill, M. J. James, P. O'Brien, R.J.K. Taylor, W.P. Unsworth, Visible-light-induced intramolecular charge transfer in the radical spirocyclisation of indole-tethered ynones, Chem. Sci. 11 (2020) 1353–1360.

[34] M.S. Oderinde, M. Frenette, D.W. Robbins, B. Aquila, J.W. Johannes, Photoredox mediated nickel catalyzed cross-coupling of thiols with aryl and heteroaryl iodides via thiyl radicals, J. Am. Chem. Soc. 138 (2016) 1760–1763.

[35] N.A. Romero, D.A. Nicewicz, Mechanistic insight into the photoredox catalysis of anti-markovnikov alkene hydrofunctionalization reactions, J. Am. Chem. Soc. 136 (2014) 17024–17035.

[36] a) Z.-Y. Cao, T. Ghosh, P. Melchiorre, Enantioselective radical conjugate additions driven by a photoactive intramolecular iminium-ion-based EDA complex, Nat. Commun. 9 (2018) 3274;
b) M.J. James, F. Strieth-Kalthoff, F. Sandfort, F.J.R. Klauck, F. Wagener, F. Glorius, Visible-light-mediated charge transfer enables C−C bond formation with traceless acceptor groups, Chem. Eur J. 25 (2019) 8240–8244.

[37] N. Inprung, H.E. Ho, J.A. Rossi-Ashton, R.G. Epton, A. Whitwood, J.M. Lynam, R.J. K. Taylor, M.J. James, W.P. Unsworth, Indole-ynones as privileged substrates for radical dearomatising spirocyclization cascades, Org. Lett. 24 (2022) 668–674.

[38] N. Inprung, A.C. Whitwood, R.J.K. Taylor, M.J. James, W.P. Unsworth, Radical dearomatising spirocyclisation of benzisoxazole-tethered ynones, Eur. J. Org. Chem. (2023) e202300603.

[39] For additional insight into the question of direct indole C-2 annulation versus 1,2-migration from C-3, see: C. Zheng, Z.-L. Xia, S.-L. You. Unified Mechanistic Understandings of Pictet-Spengler Reactions, Chem 4 (2018) 1952–1966.

[40] P. Fedoseev, E. Van Der Eycken, Temperature switchable Brønsted acid-promoted selective syntheses of spiro-indolenines and quinolines, Chem. Commun. 53 (2017) 7732–7735.

[41] Synthetic and mechanistic studies into the rearrangement of spirocyclic indolenines into quinolones; R. G. Epton, A. K. Clarke, R. J. K. Taylor, J. M. Lynam, W. P. Unsworth, Eur. J. Org. Chem. (2019) 5563–5571.

[42] J.A. Rossi-Ashton, A.K. Clarke, R.J.K. Taylor, W.P. Unsworth, Modular synthesis of polycyclic alkaloid scaffolds via an enantioselective dearomative cascade, Org. Lett. 22 (2020) 1175–1181.

[43] A.K. Clarke, J.A. Rossi-Ashton, R.J.K. Taylor, W.P. Unsworth, Synthesis of polycyclic scaffolds via a gold-catalysed dearomative cyclisation cascade, Tetrahedron 76 (2020) 131392.

[44] A.K. Clarke, J.M. Lynam, R.J.K. Taylor, W. P Unsworth, "Back-to-Front" indole synthesis using silver(I) catalysis: unexpected C-3 pyrrole activation mode supported by DFT, ACS Catal. 8 (2018) 6844–6850.

[45] M.J. James, N. Grant, P. O'Brien, R.J.K. Taylor, W.P. Unsworth, Catalytic dearomatization approach to quinolizidine alkaloids: five step total synthesis of (±)-Lasubine II, Org. Lett. 18 (2016) 6256–6259.

[46] a) V. Boekelheide, J.P. Lodge, A study of some quinolizone derivatives, J. Am. Chem. Soc. 73 (1951) 3681–3864;
b) X. Fan, Y. He, X. Zhang, J. Wang, Sustainable and selective synthesis of 3,4-dihydroquinolizin-2-one and quinolizin-2-one derivatives via the reactions of penta-3,4-dien-2-ones, Green Chem. 16 (2014) 1393–1398. P. S. Shinde, A. C.

Shaikh, N. T. Patil. Efficient access to alkynylated quinalizinones via the gold(i)-catalyzed aminoalkynylation of alkynes. Chem. Commun. 52 (2016) 8152–8155.
[47] H.E. Ho, M.J. James, P. O'Brien, R.J.K. Taylor, W.P. Unsworth, Ag(I)-Catalysed synthesis of azabicyclic alkaloid frameworks from ketimine-tethered ynones: total synthesis of indolizidine 209D, Org. Lett. 20 (2018) 1439–1443.
[48] A.K. Clarke, J.T.R. Liddon, J.D. Cuthbertson, R.J.K. Taylor, W.P. Unsworth, Dearomatisation approaches to spirocyclic dienones via the electrophilic activation of alkynes, Org. Biomol. Chem. 15 (2017) 233–245.