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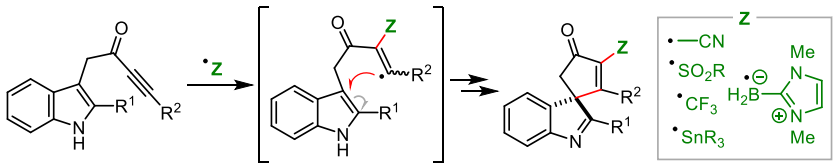
Indole-ynones as privileged substrates for radical dearomatizing spirocyclization cascades

Nantachai Inprung, Hon Eong Ho, James A. Rossi-Ashton, Ryan G. Epton, Adrian C. Whitwood, Jason M. Lynam, Richard J. K. Taylor, Michael J. James,* William P. Unsworth*

Department of Chemistry, University of York, Heslington, York, U.K., YO10 5DD



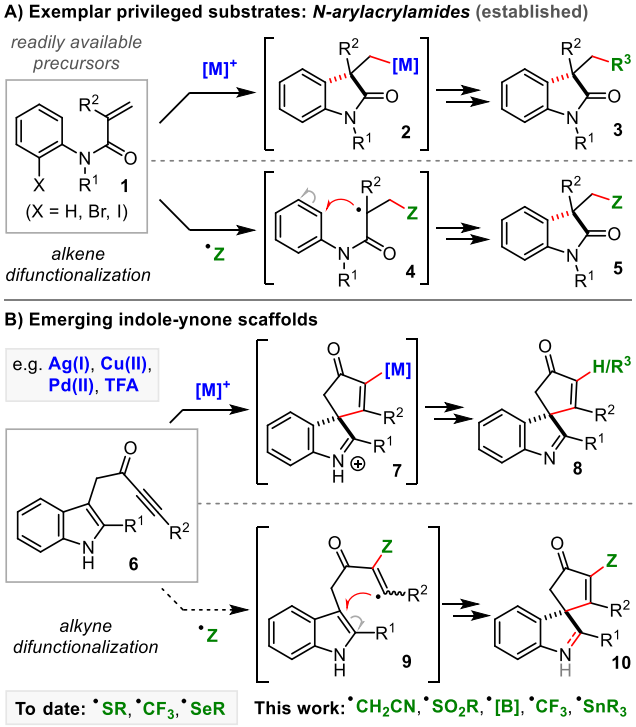
ABSTRACT: Indole-ynones have been established as general substrates for radical dearomatizing spirocyclization cascade reactions. Five distinct and varied synthetic protocols have been developed – cyanomethylation, sulfonylation, trifluoromethylation, stannylation and borylation – using a variety of radical generation modes, ranging from photoredox catalysis to traditional AIBN methods. The simple and easily prepared indole-ynones can be used to rapidly generate diverse, densely functionalized spirocycles and have the potential to become routinely used to explore radical reactivity. Experimental and computational investigations support the proposed radical cascade mechanism and suggest that other new methods are now primed for development.

Compound classes that expedite access to privileged biologically active scaffolds are highly prized in synthetic chemistry.[1] For example, *N*-arylacrylamides **1** are prominent precursors for the synthesis of biologically important 3,3-disubstituted oxindoles,[2] with a number of elegant (and asymmetric) metal-catalyzed strategies known (**1** → **2** → **3**, Scheme 1A).[3] Complementary radical-based strategies (**1** → **4** → **5**, Z = various, Scheme 1A) have also been developed.[4] Indeed, these methods are so well established that *N*-arylacrylamide-based radical addition-cyclization cascades have become a 'go-to' system with which to probe radical mechanisms and benchmark new (and old) methods for the reactions of radicals.[5]

The identification of new scaffolds with the utility of *N*-arylacrylamides therefore has great potential in synthetic and medicinal chemistry – both for their ability to facilitate the exploration of novel biologically relevant chemical space, and as testing grounds for new methodologies. Indole-ynones (**6**) are an emerging class of compounds that rival the versatile reactivity of *N*-arylacrylamides, most notably for the synthesis of spirocyclic indolenines.[6,7] A number of synthetic methods have been reported, by our groups and others, based on the reaction of the electron rich indole moieties with a tethered ynone group, promoted by alkyne activation with various reagent classes, including π-acids,[8] Brønsted acids,[9] palladium(II) complexes,[10] electrophilic halogenation reagents,[11] and others[12,13] (**6** → **7** → **8**, Scheme 1B).

These previous studies focused on two-electron processes, but in 2020, our group published the first radical-based spirocyclization of an indole-ynone. In this work, thiyl radicals generated *in situ* were shown to promote dearomatizing spirocyclization with concomitant C–S bond formation (**6** → **9** → **10**, Scheme 1B) via a hydrogen atom transfer based radical chain process.[14,15] Interestingly, the thiyl radical formation that initiates this process was shown to be promoted by visible-light-mediated photoexcitation of an intramolecular electron donor-acceptor (EDA) complex, formed between the indole and alkyne moieties in the indole-ynone **6**.[16,17] Soon afterwards, related radical spirocyclisation methods began to emerge from other groups. For example, Liu, Han and coworkers reported an efficient Cu(I)-catalyzed trifluoromethylation protocol, which proceeds via the formation of trifluoromethyl radicals from Togni's reagent (Z = CF_3).[18a] A similar cascade was also reported by Xu, Pan, Ma and coworkers; in this case, dearomatizing spirocyclization was promoted by selenyl radicals, formed via the homolysis of diselenides (Z = SeR).[18b]

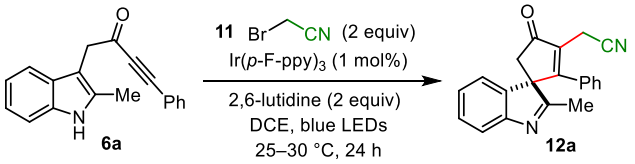
Scheme 1. Privileged substrates in synthetic chemistry.



We postulated that in addition to being versatile precursors for two-electron processes,[8,13,19] indole-ynones **6** may be similarly privileged substrates for radical cascade reactions.[20] Thus, herein we describe efforts to fully establish indole-ynones as general precursors for radical dearomatizing spirocyclization reactions. In total, five efficient, novel synthetic protocols have been established for dearomative cyanomethylation, sulfonylation, trifluoromethylation, stannylation and borylation. Demonstrating that spirocyclization can be achieved using a range of radical generation methods was also an important goal, and the new methods developed rely on various radical reaction modes ranging from traditional AIBN homolysis to more modern photoredox catalysis and EDA activation.

The first radical class utilized were cyanomethyl radicals.[21] Cyanomethyl radicals can be generated from bromoacetonitrile **11** via known photoredox catalysis methods.[22,23] Optimization results for the conversion of indole-ynone **6a** into spirocyclic indolenine **12a** are included in Table 1. Optimal conditions (entry 1) were identified based on the use of catalytic Ir(*p*-F-ppy)$_3$ (1 mol%) and 2,6-lutidine in DCE with blue light irradiation (25–30 °C, fan cooling). Light is essential for reactivity (entry 2) and the reaction is shut down by the addition of TEMPO (entry 3), which taken together strongly indicates that a light-promoted radical process operates. Changes to the quantity and identity of base led to inferior conversion (entries 4–7). Other photocatalysts were trialed (entries 8–11) but only Ir(III) catalysts resulted in satisfactory conversion into **12a**, with the relatively reducing catalyst Ir(*p*-F-ppy)$_3$ the most effective. Interestingly, modest conversion into **12a** was also observed in the absence of an added photocatalyst (entry 12), indicating that electron-donor-acceptor (EDA) complexes may also be photoexcited to initiate dearomative spirocyclization,[14] albeit with lower efficiency than the reaction with Ir(*p*-F-ppy)$_3$.

Table 1. Cyanomethylation optimization[a]



entry	deviation from standard conditions[a]	12a (%)[b]	6a (%)[b]
1	none	75[c]	12[c]
2	without light	0	99
3	with TEMPO (2 equiv)	0	99
4	without 2,6-lutidine	13	52
5	2,6-lutidine (1 equiv)	40	42
6	2,4,6-collidine (2 equiv)	60	15
7	K_2CO_3 (2 equiv)	40	42
8	Ir(ppy)$_3$ (1 mol%)	60	6
9	Ru(bpy)$_3$(PF$_6$)$_2$ (1 mol%)	0	74
10	Eosin Y (1 mol%)	0	80
11	10-phenyl phenothiazine (1 mol%)	7	93
12	without photocatalyst	31	56

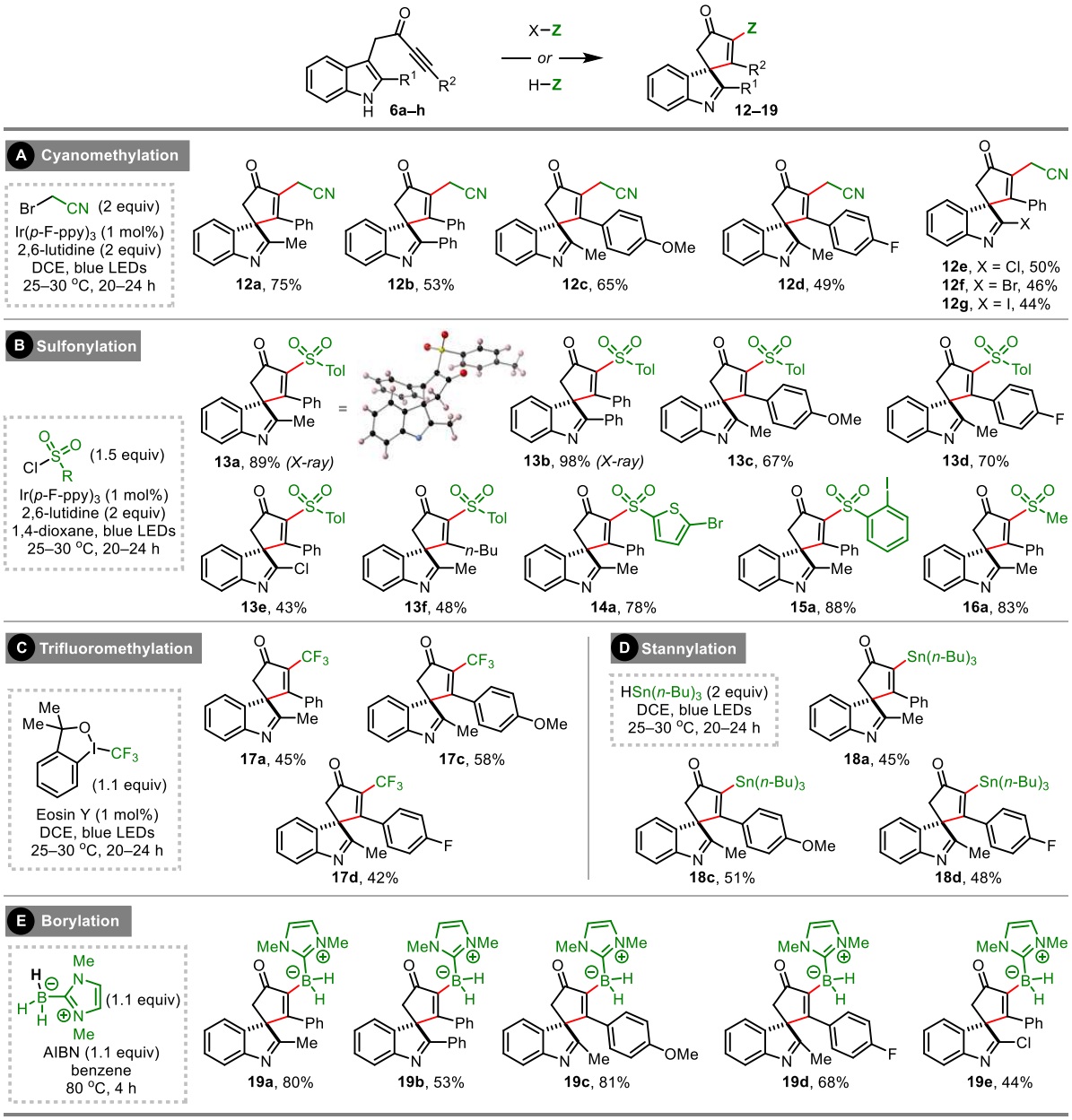
[a] Standard conditions: Ir(*p*-F-ppy)$_3$ (1 mol%), 2,6-lutidine (2 equiv), DCE (0.1 M), RT, blue LED, on 0.2 mmol scale. [b] Yields based on ^{1}H-NMR analysis of the unpurified reaction mixture using CH_2Br_2 as an internal standard unless stated. [c] Isolated yield following column chromatography.

Next, the generality of the cyanomethylation reaction was explored (Scheme 2A).[24] A selection of indole-tethered ynones **6a–g** were prepared and tested using the optimized conditions, and all were converted into spirocyclic indolenines **12a–g** in 44–75% yield; this series includes 2-halo substituted systems, which furnished synthetically useful spirocyclic indoleninyl halides **12e–g**.[8d] Attempts to perform the reaction on indole-ynones without a 2-substitutent (*i.e.* R^1 = H in the general scheme) were not successful however, with these reactions complicated by competing radical addition to the indole ring.

Attention then turned towards the development of reactions based on other radical types. In total, four additional distinct reaction classes have been developed (Scheme 2B–E), with additional synthetic and optimization details included in the Supporting Information. First, known photoredox-catalyzed methods for the generation of sulfonyl radicals using sulfonyl chlorides[25] were adapted and used to prepare sulfonylated spirocycles **13–16** in good to excellent yields (9 examples, 43–98%, Scheme 2B).[26] This series confirms that switching to other reactive radical species can be achieved remarkably easily, with high yields obtained.[27] A transition-metal-free method for the synthesis of trifluoromethylated spirocycles was also developed, that complements the copper-catalyzed reaction reported by Liu, Han and coworkers featured in Scheme 1B.[18a] Here, Togni's reagent was used with the photoredox catalyst Eosin Y to form trifluoromethylated spirocycles **17a**,**c–d** in 42–65% yield (Scheme 2C). Note that in this system, control reactions show that product **17a** could be obtained in reduced yield in the absence of an added photocatalyst, or in the dark, indicating that EDA complex activation[14,28] may also enable trifluoromethyl radical formation alongside the Eosin Y catalyzed pathway.

In addition, a remarkable additive-free stannylative dearomatizing spirocyclization reaction was developed, which can be performed simply by irradiating a mixture of the indole-ynone and tributyltin hydride in DCE with blue LEDs (Scheme 2D). Using these mild conditions, stannylated spirocyclic indolenines **18a**,**c**–**d** were formed in 45–51% yield. In line with our previous work with thiols,[14] we propose that these reactions were initiated either via a hydrogen atom transfer or an ET event between the photoexcited indole-ynone and tributyltin hydride to generate a tributyltin radical. The potential to develop other unconventional additive-free dearomatizing spirocyclization reactions of this type highlights the still relatively untapped synthetic utility of this substrate class. Finally, we have also shown that similar reactivity can be promoted using classical thermal radical generation conditions. AIBN in refluxing benzene was used to generate *N*-heterocyclic carbene (NHC) boryl radicals[29] that go on to form borylated spirocycles **19a–e** in 44–81% yield (Scheme 2E). Diversification of these products was also briefly explored, in which we confirmed that borylated spirocycle **19a** could be converted into a pinacol ester and undergo subsequent Suzuki-Miyaura cross coupling (see Supporting Information).

Scheme 2. Radical spirocyclization cascades with diverse radicals generated via a range of methods.

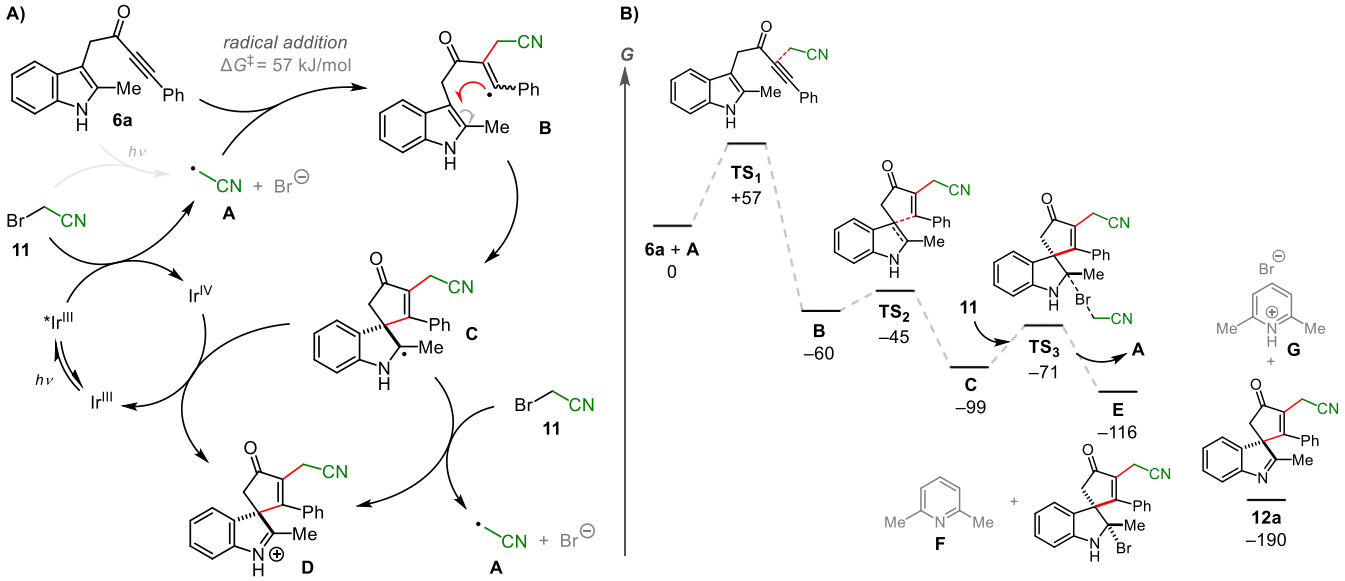


A proposed mechanism, exemplified on the initial cyanomethylation system, is presented in Scheme 3A. First, it is known that photoexcited Ir(III) complexes such as Ir(*p*-F-ppy)$_3$ are able to reduce bromoacetonitrile **11** to form cyanomethyl radical **A**,[23] which we presume initiates the radical cascade.[30] This is supported by Stern-Volmer luminescence quenching studies, which show that the photocatalyst Ir(*p*-F-ppy)$_3$ excited state is quenched by bromoacetonitrile (see Supporting Information). Next, we propose that cyanomethyl radical **A** reacts with the ynone moiety of **6a** to form vinylic radical **B**, which

cyclizes quickly to form α-amino alkyl radical **C**. Intermediate **C** may then either: i) be oxidized by an Ir(IV) species to regenerate the Ir(III) photoredox catalyst and form the spirocyclic product **D** (which is deprotonated in the presence of 2,6-lutidine); or ii) propagate a radical chain by reacting with **11** via halogen-atom transfer[31] or electron transfer[32] to form cyanomethyl radical **A** and spirocyclic product **D**.

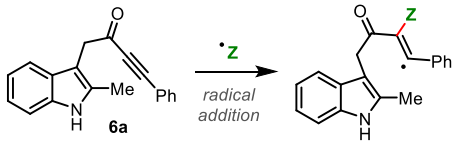
To gauge whether steps subsequent to radical formation could be limiting the reaction, DFT calculations of the individual steps were undertaken (Scheme 3B). Of these steps, the addition of the cyanomethyl radical is the slowest step (**TS₁**) and the calculated $\Delta G^{\ddagger}$ of 57 kJ/mol is accessible for a room temperature reaction. The analogous energy barrier was also calculated for each of the other four radical classes featured in this manuscript (*i.e.* sulfonyl, trifluoromethyl, stannyl and boryl radical addition to indole-ynone **6a**), as well as for the previously reported thiyl[14] and selenyl[18b] radical systems (Table 2, see the Supporting Information for further details). In all cases, this barrier was calculated to be lower in energy than that of the cyanomethyl system, strongly indicating that the radical addition step is not only viable, but likely to be facile across a range of radical species. For cyanomethylation, the subsequent radical spirocyclization through **TS₂** and bromine abstraction leading to chain propagation via **TS₃** have low free energies of activation and are therefore probably not rate controlling.

Scheme 3. Proposed radical spirocyclization mechanism with cyanomethyl radical.[a]



[a] Energies are Gibbs energies in kJ/mol and were calculated using the D3-B3LYP/def2-TZVPP//B3LYP/def2-SVP level of theory at 298 K with COSMO solvent correction in DCE.

Table 2. Calculated activation barriers[a] for the addition of radicals (·Z) to indole-ynone 6a.



·Z	ΔG‡
·—CN	57 kJ/mol
·Ts	42 kJ/mol
·CF_3	44 kJ/mol
·$SnMe_3$	34 kJ/mol
H_2B—NHC	35 kJ/mol
·SPh	15 kJ/mol
·SePh	17 kJ/mol

[a] Gibbs energies calculated using the D3-B3LYP/def2-TZVPP//B3LYP/def2-SVP level of theory at 298 K with appropriate COSMO solvent corrections.

Based on the above, we consider it likely that all reaction series developed herein operate via the same general mechanism; the exact nature of the oxidative step (**C** → **D** in Scheme 3A) will vary depending on the reagents used and reaction conditions on a case-by-case basis, and of course the radical initiation modes differ in each series. For clarity, full proposed mechanisms for each of the reactions in Scheme 2B–E are included in the Supporting Information. Having demonstrated the feasibility of the radical cascades using diverse reagents and conditions, both experimentally and computationally, it is likely that variants based on various other radical intermediates will also be feasible, and new methods will emerge in time. The development of any new radical spriocyclization of these types could be facilitated by virtual screening of the radical addition step for proposed radical species, using the DFT method established in this study. Of course, the ability of indole-ynones to undergo facile two-electron cyclization reactions means that it will be important to test for this possibility when developing new methods. Further, the opportunity to develop novel catalyst-free activation modes should also be possible based on photoexcitation of the indole-ynone itself.

In closing, we have demonstrated that indole-ynones are general precursors for radical dearomatizing spirocyclization cas-

cades through the development of five different synthetic protocols. These easily prepared reagents can be used to provide expedient access to libraries of densely functionalized spirocycles with rich biological potential. Our mechanistic studies indicate that many other cascade protocols of comparable/higher efficiency should be feasible using other radical classes and/or initiation modes. Moreover, we anticipate that these findings will facilitate the development and identification of other privileged substrate systems based on other heterocycle-ynone frameworks.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, characterization data, computational details, and copies of ^{1}H, ^{13}C, ^{11}B and ^{19}F NMR spectra for all compounds featured in this manuscript. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Authors

michael.james@york.ac.uk; william.unsworth@york.ac.uk

Author Contributions

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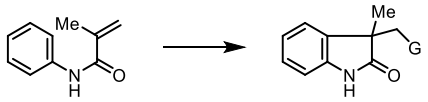

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