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Visible-light-induced intramolecular charge transfer in the radical spirocyclisation of indole-tethered ynones†

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Indole-tethered ynones form an intramolecular electron donor–acceptor complex that can undergo visible-light-induced charge transfer to promote thiyl radical generation from thiols. This initiates a novel radical chain sequence, based on dearomatising spirocyclisation with concomitant C–S bond formation. Sulfur-containing spirocycles are formed in high yields using this simple and mild synthetic protocol, in which neither transition metal catalysts nor photocatalysts are required. The proposed mechanism is supported by various mechanistic studies, and the unusual radical initiation mode represents only the second report of the use of an intramolecular electron donor–acceptor complex in synthesis.

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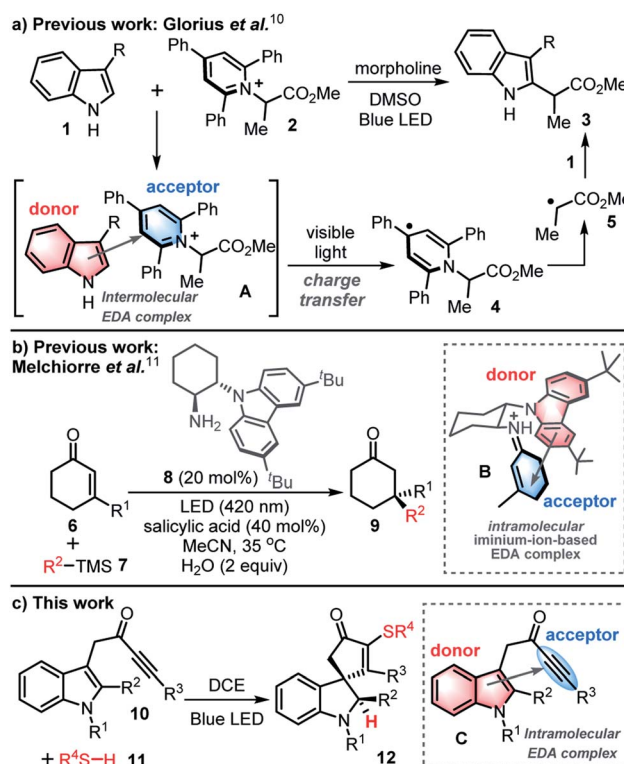
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Introduction

The use of visible-light-mediated photochemistry in synthesis has grown enormously in recent years,^{1,2} triggered by dramatic progress in the fields of photoredox catalysis,³ energy transfer⁴ and atom transfer processes.⁵ This has led to a renaissance in the use of single electron transfer (SET) processes in chemical synthesis, including renewed interest in the study of charge transfer in electron donor–acceptor (EDA) complexes.

The phenomenon of charge transfer was first postulated in the 1950s,^{6,7} but received relatively little attention in synthetic chemistry⁸ until a surge in interest in the last decade,⁹ with an illustrative example recently reported by Glorius and co-workers summarised in Scheme 1a.¹⁰ In this study, it was shown that the coupling of indoles **1** and pyridinium salt acceptors **2** can be performed in the absence of a transition metal catalyst or photocatalyst. Key to this process is the formation of an intermolecular EDA complex **A** between an indole (the donor) and a pyridinium salt (the acceptor); the EDA complex can then absorb visible light to promote charge transfer to form radical **4**, that can then fragment to give electrophilic radical **5** and couple with indole **1** to afford C-2 functionalised indole **3** via a radical chain process.

This report and others,^{9,10} highlight the value of *intermolecular* EDA-mediated charge transfer for the construction of challenging chemical bonds. However, until a 2018 report by



Scheme 1 EDA complexes in synthetic chemistry (a, b = previous work, c = this work). DCE = 1,2-dichloroethane. LED = light emitting diode.

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Melchiorre and co-workers,^{11,12} there were no reports of the use of photon-absorbing *intramolecular* EDA complexes being used in synthesis. In this seminal study, an enantioselective radical conjugate addition reaction is described that relies on visible-light-excitation of a chiral iminium-ion based intramolecular EDA complex **B**, itself formed *in situ* from a ketone **6** and organocatalyst **8** (Scheme 1b).¹¹

Herein, a new synthetic method based on *intramolecular* EDA complexation and charge transfer is reported for only the second time. Thus, a novel radical dearomatising spirocyclisation¹³ of indole-tethered ynones **10** (ref. 14) and thiols **11** is described for the formation of spirocyclic indolines **12** with concomitant C–S bond formation (Scheme 1c).¹⁵ The reactions are catalyst-free and proceed *via* a thiyl radical-based chain process, that is thought to be self-initiated by the ynone starting material **10**, through visible-light-induced charge transfer of an intramolecular EDA complex **C**. A wide range of sulfur-containing spirocycles **12** have been prepared using this mild, high yielding synthetic procedure. This unusual photocatalyst-free method to initiate radical chemistry was discovered by serendipity, and could easily have gone unnoticed, if not for the recent surge in interest in the study of charge transfer in electron donor–acceptor (EDA) complexes.

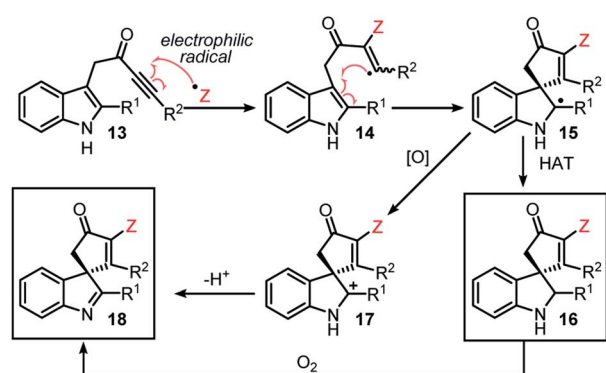
Results and discussion

The original aim of this project was to develop a radical spirocyclisation protocol based on more well-established methods for radical generation. We postulated that indole-tethered ynones **13** would react with electrophilic radicals *via* regioselective addition to the alkyne group (**13** → **14**), before cyclising on to the indole at its 3-position to form a spirocyclic radical intermediate (**14** → **15**). Radical **15** could then go on to form either spirocyclic indoline **16** *via* hydrogen atom transfer (HAT), or spirocyclic indolenine **18** *via* single electron oxidation followed by proton loss (Scheme 2). Oxidation of **16** to **18** in the presence of molecular oxygen, or other oxidants, was also predicted to be viable. Confidence in this general idea was raised by reports of radical-based dearomative processes involving phenol- and anisole-tethered alkynes.^{16,17} These studies confirm that electrophilic radicals can react with ynones with the

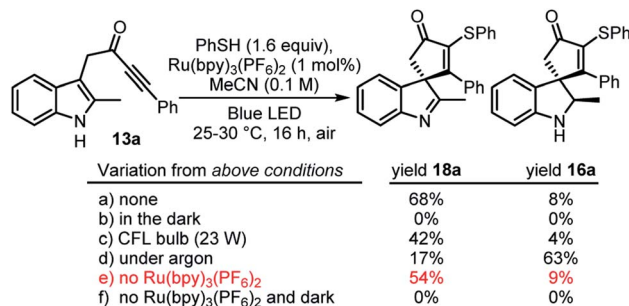
desired regioselectivity, and that the so-formed radical species can go on to react with tethered aromatics; however, to the best of our knowledge, such a strategy had not been applied to indole-tethered alkynes prior to this report.

This study began by examining the reaction of ynone **13a** with a thiyl radical generated from thiophenol *in situ*. Thiyl radicals are versatile reactive intermediates in synthetic radical chemistry¹⁸ and we reasoned that the derived products could be relevant in drug discovery, in view of the prevalence of vinyl sulfides in bioactive compounds.¹⁹ A photoredox catalysis approach originally was chosen to generate the thiyl radical,²⁰ which led to the development of the conditions summarised in Scheme 3 (see ESI† for full optimisation). Thus, the combination of thiophenol, catalytic Ru(bpy)₃(PF₆)₂ and irradiation with a blue LED lamp (λ_{max} = 455 nm, 60 W) at rt under air, enabled the conversion of indole-tethered ynone **13a** into spirocyclic indolenine **18a** in reasonable yield *via* an overall oxidative dearomative process (Scheme 3, a). Product **18a** was synthesised along with indoline **16a** as minor side-product, with **16a** believed to be an intermediate on the route to indolenine **18a**.²² Control experiments revealed that oxygen is required for the efficient formation of **18a** (indoline **16a** is the major product in the absence of oxygen, Scheme 3, d) and more intriguingly, a mixture of both products **18a** and **16a** is formed even *in the absence of any photocatalyst* (Scheme 3, e). In the absence of light, no reaction occurs (Scheme 3, f). This indolenine-forming reaction was also found to work on other ynone starting materials (5 examples, see ESI† page S8 for details).

The unexpected discovery that spirocyclisation can be achieved without Ru(bpy)₃(PF₆)₂ was intriguing, both from a mechanistic standpoint, and in view of the clear practical and environmental benefits of avoiding metal-based photocatalysts. We therefore decided to explore this process in more detail and started by establishing whether the photocatalyst-free reaction conditions could be applied to other substrates. Additional optimisation was performed at this point (see ESI†), and based on this, the decision was made to prioritise the synthesis of indoline products **16/19** (*via* overall redox neutral reactions, *c.f.* Scheme 3, d) rather than indolenines **18** (overall oxidative processes, *c.f.* Scheme 3, a).²³ Thus, the reactions were performed under argon rather than air; another change to the



Scheme 2 Planned reaction courses.



Scheme 3 Control reactions; all yields are based on comparison to an internal standard in the ¹H NMR spectrum of the unpurified reaction mixture except for 'a' which is an isolated yield. CFL = compact fluorescent lamp.



conditions was to switch the solvent from acetonitrile to 1,2-dichloroethane (see ESI† for further optimisation details).

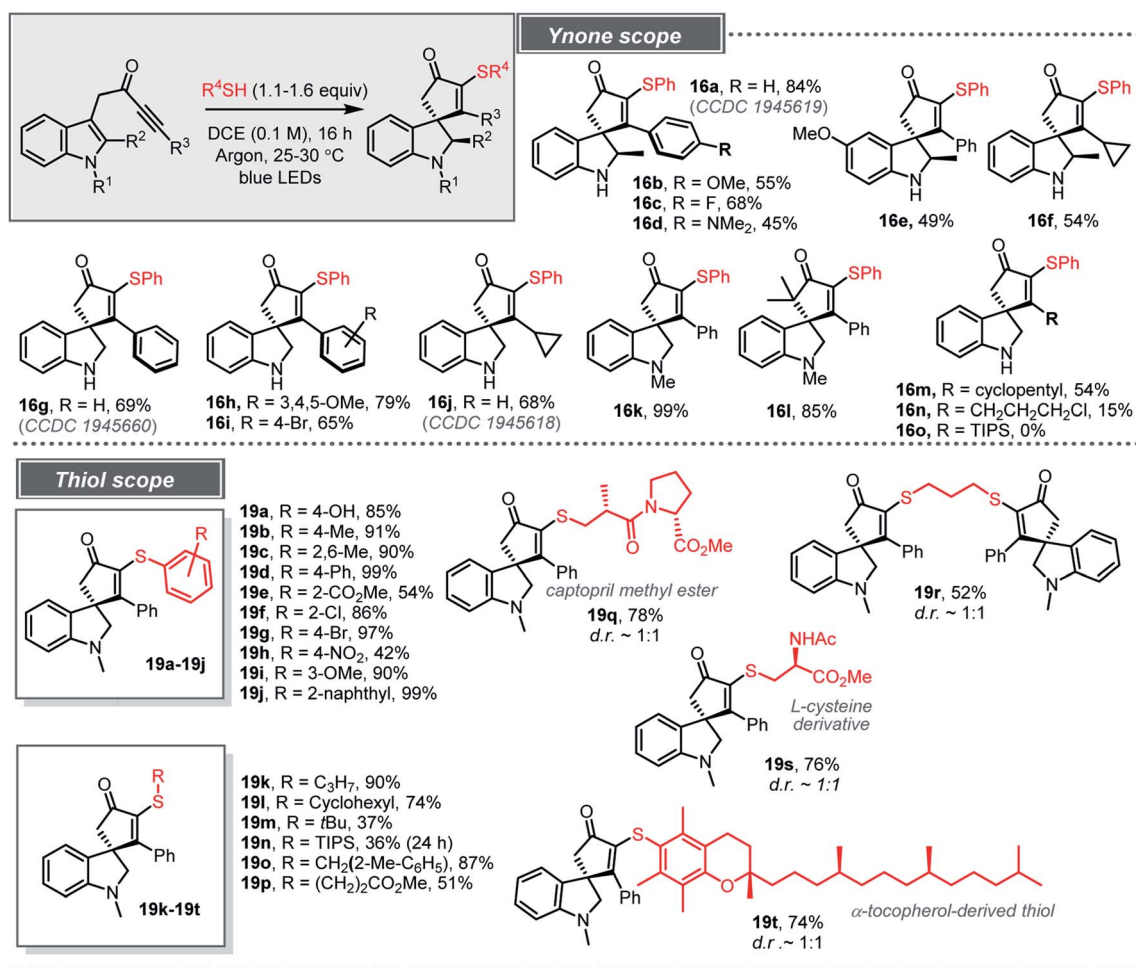
The optimised conditions were then tested across a range of indole-tethered ynones and thiols, and the results summarised in Scheme 4 confirm that the reaction is broad in scope. Changes to the substituent on the indole nitrogen (NH and NMe), the indole 2-position and the ynone terminus (R^3) were all tolerated (**16a–n**, 15–99%), with bulky TIPS-substituted ynone **13o** (to form **16o**) the only unsuccessful example. In cases where the indole C-2 position is substituted (**16a–f**) the products were isolated as the single diastereoisomer shown, with the assignment of relative stereochemistry based on X-ray crystallographic data for **16a**.^{24,25}

The reactions also work well with a range of thiols (20 examples, **19a–19t**, 36–99%). Various electronically diverse, substituted arylthiols were well-tolerated (**19a–19j**), with the more electron-rich examples typically the highest yielding. We were also pleased to observe that aliphatic thiols are compatible with the standard procedure (**19k–19p**); the S–H bond dissociation energy (BDE) for alkyl thiols (~ 87 kcal mol^{−1}) is usually higher than related aryl thiols (72–82 kcal mol^{−1}), which can adversely affect their reactivity in radical reactions.¹⁸ More

complex thiols have also been shown to work well using the standard procedure, including 1,3-propanedithiol (to make dimeric product **19r**), a protected cysteine derivative and a peptide-like thiol (to make **19q** and **19s**) and an α -tocopherol-derived thiol (to make **19t**).

Having established the synthetic method, attention then turned to understanding how the reactions operate in the absence of photocatalyst. We reasoned that visible-light activation of one of the starting materials must play a key role. Based on precedent, several possibilities could be envisaged:^{26,27} (1) light-induced homolytic cleavage of the thiol S–H bond to generate a thiyl radical would account for the observed reactivity, as this could start a radical chain reaction, as outlined earlier in Scheme 2; (2) similar reactivity could also originate from homolytic S–S bond cleavage of trace disulfides present in the thiol reagent; (3) photoexcitation of the alkyne to its triplet state could form an open-shell species theoretically capable of initiating radical chemistry.

Although we considered all of these scenarios to be unlikely under the influence of blue light (based on the energy typically needed to homolyse S–H/S–S bonds or to electronically excite alkynes),^{18,27} control experiments were nonetheless designed to



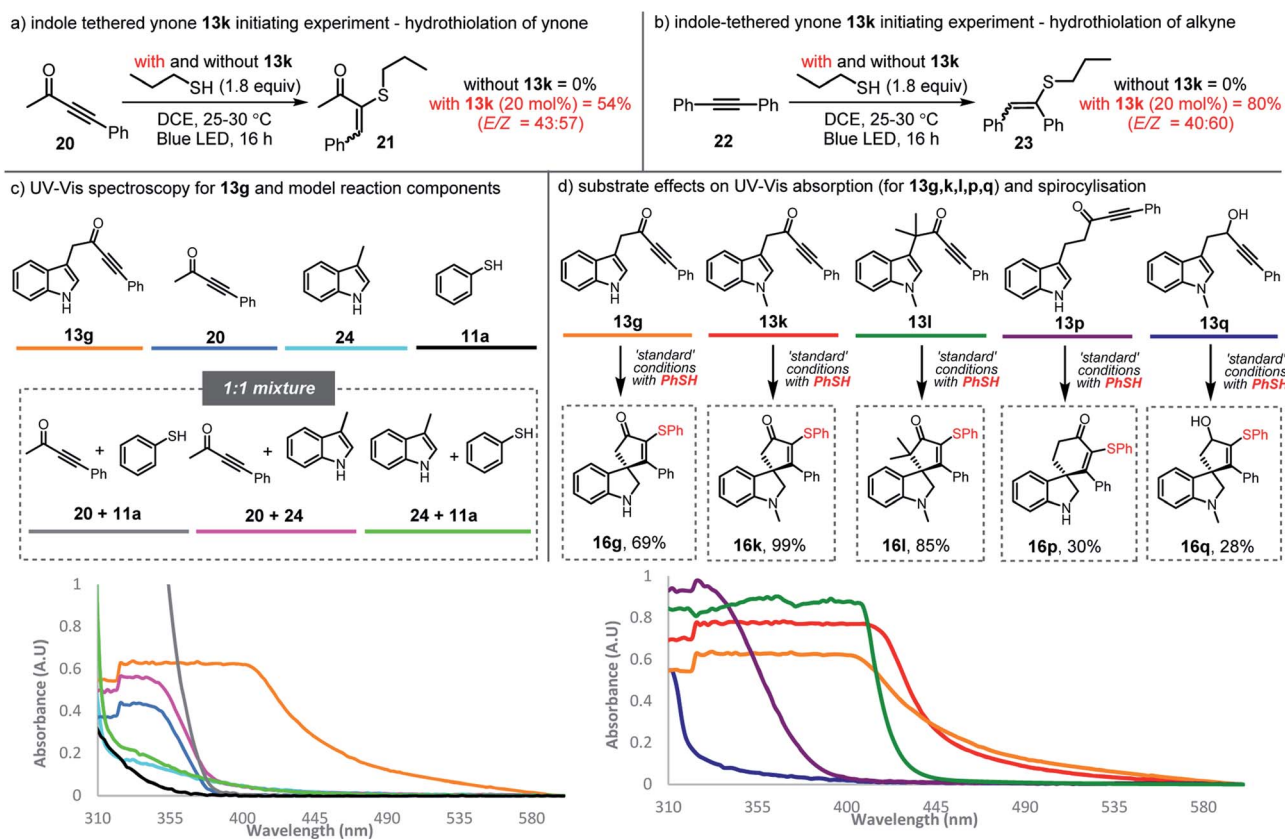
Scheme 4 Light induced charge-transfer radical spirocyclisation. Isolated yields following column chromatography are given.

examine these possibilities. The experiments were based on the hydrothiolation of simple alkynes; thus, each of alkynes **20** and **22** were reacted with *n*-propane thiol under blue LED irradiation at RT, but no conversion into vinyl sulfides **21** and **23** was observed, with the alkynes fully recovered in each case (Schemes 5a and 5b). The lack of hydrothiolation in these experiments supports the idea that the initiation mechanisms suggested above are invalid; thiyl radicals seem not to be formed directly from the thiol reagent (or trace amounts of disulfides) in the presence of either of these alkynes, and the lack of reactivity observed with ynone starting material **20**, appears to rule out simple triplet excitation of the ynone functionality under blue light radiation. Instead, these results suggest that the indole-tethered ynone moiety **13** itself is critical to the observed reactivity. Indeed, compelling evidence that supports the involvement of the ynone in initiating thiyl radical chemistry was obtained when alkynes **20** and **22** were again reacted with *n*-propane thiol, but this time with the addition of substoichiometric (20 mol%) ynone **13k**; under these conditions, hydrothiolation products **21** and **23** were obtained in 54% and 80% yields, respectively.

Normally, neither ynones nor 3-substituted indoles would be expected to absorb visible light wavelength photons. However, the ynones **13** used in this study tend to be yellow in colour, and indeed, ynone **13g** was found to absorb relatively strongly at

around 455 nm (the λ_{max} of the light source) when analysed using UV-Vis spectroscopy (orange line, Scheme 5c; for the emission spectra of **13g** see the ESI†). In contrast, model ynone **20** (blue line), 3-substituted indole **24** (cyan line), and thiophenol **11a** (black line) displayed little/no absorption in the same region. Equimolar mixtures of these compounds (**20** + **11a** in grey, **20** + **24** in pink and **24** + **11a** in green) did absorb in the visible region when measured at 0.02 M, although interestingly, when mixed at much higher concentration (>0.5 M) a significant bathochromic shift was observed for a mixture of ynone **20** and indole **24**, indicating that the intermolecular interaction of these components can influence their absorption properties, albeit at concentrations well above those used in the synthetic reactions (see ESI, Scheme S3†). The addition of thiol **11a** does not appear to influence the absorbance, with near-identical UV-Vis spectra obtained for both ynone **13k** and a mixture of **20** and **24**, with and without the inclusion of **11a** (see ESI Scheme S4†).

The ability of the indole ynone starting materials **13** to absorb visible light around 455 nm appears to correlate well with the success of the radical cascade processes, as illustrated by the data presented in Scheme 5d. For example, alkynes **13p** and **13q**, showed low absorption at 455 nm (purple and blue lines respectively) and both the conversion and yields for these reactions were much lower than those for the standard substrates (*c.f.* Scheme 4).²⁸ In contrast, ynones **13g**, **13k** and



Scheme 5 (a) Hydrothiolation of ynone **20**; (b) Hydrothiolation of alkyne **22**; (c) UV-Vis spectroscopy studies of indole-tethered ynone **13g** compared with model reaction components; (d) UV-Vis spectroscopy of indole-tethered ynones (**13g**, **13k**, **13l**, **13p**) and propargylic alcohol **13q**. All UV-Vis experiments were performed in anhydrous 1,2-dichloroethane (0.02 M).

13l, which all reacted efficiently to form **16g**, **16k** and **16l** with full conversion and in good yields, show a clear red-shift into the visible region (orange, red and green lines respectively).²⁹

We postulate that through-space interactions explain the enhanced visible light absorption of the reactive ynone systems, *via* formation of an intramolecular EDA complex of the form **C** (Scheme 6a) that enables the ynone to absorb relatively long wavelength visible light and initiate thiyl radical chemistry. A through bond process (*i.e.* involving conjugation *via* enolate formation)³⁰ was also considered as a possible explanation for the red shift of typical ynone substrates, but was ruled out on the basis of the UV-Vis data and successful reaction of non-enolisable ynone **13l**. The formation of an intramolecular EDA complex is also supported by time-dependent density functional theory (TDDFT) calculations performed on ynone **13k**, which predicted a peak at 441 nm with an oscillator strength of 0.050 (Scheme 6b). This peak is composed entirely of a charge transfer excitation between the π orbitals of the indole HOMO and ynone LUMO (Scheme 6b).

Thus, a mechanism is proposed in which the formation of an EDA complex **C** is followed by visible light absorption to form a photoexcited state, loosely represented as charge transfer complex **25**. This species may simply relax to reform EDA complex **C** *via* back electron transfer, or alternatively, the open shell excited state **25** could abstract a hydrogen atom from the thiol **11**, thus generating the thiyl radical needed to start a radical cascade (Scheme 6a).³¹ At this point, a more typical

radical chain process can operate (Scheme 6c), which likely proceeds by the addition of thiyl radical to the ynone (**10** \rightarrow **26**), spirocyclisation (**26** \rightarrow **27**) and hydrogen atom abstraction from thiol **11** (**27** \rightarrow **12**), thus enabling chain propagation. Quantum yield measurements ($\phi = 19.8$)³² support operation through a chain process.^{33,34}

Conclusions

In summary, a new dearomative method for the synthesis of sulfur-containing spirocyclic indolines is described, based on the reaction of indole-tethered ynone with thiyl radicals generated *in situ* from thiols. The reactions are promoted by visible light, operate at RT under mild reaction conditions and need neither a transition metal catalyst nor added photocatalyst to proceed efficiently across a wide range of substrates. The reaction is thought to be self-initiated³⁵ with visible-light-mediated photoexcitation of an intramolecular EDA complex formed between the indole and ynone moieties in the starting material leading to the formation an open shell excited charge-transfer complex, capable of abstracting a hydrogen atom from the thiol and initiating radical chain propagation.

To the best of our knowledge, this is only the second report that details the use of intramolecular EDA complexes in synthesis. This rare radical activation mode was uncovered entirely by serendipity,³⁶ and this is a feature of the discovery that we are keen to highlight, as we believe that intramolecular EDA complexes likely play key roles in other synthetic methods, but can go (or have gone) unnoticed.^{36d} As awareness of the value of charge transfer processes in synthetic chemistry grows, we believe that many important new methods of this type will be discovered, both through design and by serendipity.

Conflicts of interest

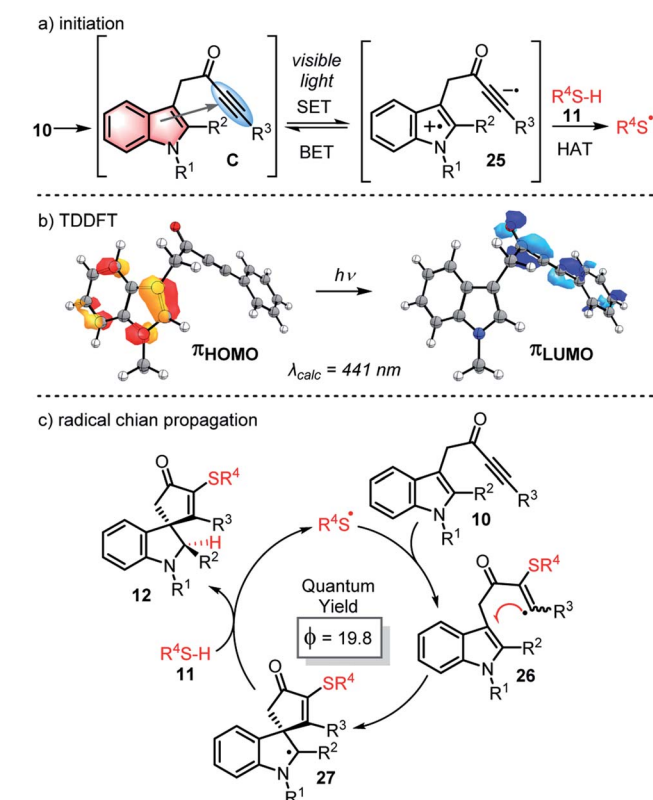
There are no conflicts to declare.

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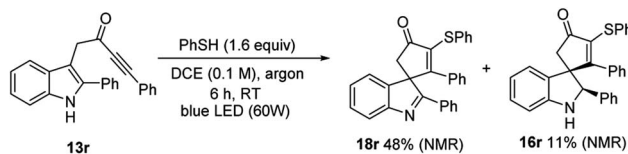
Scheme 6 (a) Proposed mechanism for initiation; (b) TDDFT calculations; (c) proposed propagation cycle.



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- 23 We reasoned that running the reactions under argon rather than air would lead to a more reproducible procedure, and we also know that spiroindolenines can be easily prepared by oxidation of the corresponding spiroindolines if required (see ESI†).
- 24 CCDC 1945619 (**16a**), 1945618 (**16j**), 1945660 (**16g**), 1645620 (**13g**), and 1645621 (**13k**) contain the crystallographic data, see ESI.†
- 25 When an analogous ynone substrate (**13r**) bearing a phenyl group at the indole C-2 position was tested, an inseparable mixture of indolenine product **18r** and indoline **16r** was obtained, as well as other minor impurities (the yields quoted below are based on NMR against an internal standard). The increased stability of the doubly benzylic radical that this reaction proceeds by, as well as the fact that this radical would be expected to undergo oxidation more easily, both account for the contrasting reactivity of this substrate compared with its alkyl substituted analogues. Although this reaction is not useful synthetically, the small amount of **16r** produced did appear to be formed as a single diastereoisomer, most likely with the same relative stereochemistry as that obtained for products **16b-f**.



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- 28 The structural features of **13p** and **13q** (the elongated tether in **13p** and reduction of the carbonyl group in **13q**) were designed to disrupt formation of the EDA complex that is proposed to enable charge transfer and the resulting reaction.
- 29 The blue LED spectral output is a bell curve centred at 455 nm, with sufficient irradiance in the 400–420 nm range to trigger slow radical initiation from substrates **13p** and **13q**. We believe these substrates to be competent thiyl radical chain carriers, as exemplified by the fact that an increase in yield for the conversion of **13q** → **16q**, from 28 to 65%, was observed upon the addition of 20 mol% of ynone **13k**, a substrate with a significantly higher absorbance at 455 nm.
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- 31 Unfortunately, we have been unable to obtain clear structural information on the fate of the initiator species **25** following HAT. Analysis of the unpurified reaction a typical reaction between ynone **13l** and thiophenol using



- ESI mass spectrometry led to the detection of peak representing a reduced version of the starting material (ynone **13I** + H₂ + H⁺), but no identifiable products could be isolated from the reaction.
- 32 For more details on the method used to calculate quantum yield, see ESI page S9,[†] and for important background on such methods, see: (a) M. A. Cismesia and T. P. Yoon, *Chem. Sci.*, 2015, **6**, 5426; (b) K. Liang, N. Li, Y. Zhang, T. Li and C. Xia, *Chem. Sci.*, 2019, **10**, 3049.
- 33 The proposed mechanism is further supported by deuterium labelling studies in which the reaction of ynone **13I** with PhSD was performed, with the expected deuterated product (**16I'**, see ESI, pages S12 and S13[†]) being obtained. No significant difference in rate of reaction was observed when comparing this reaction with the analogous reaction with PhSH, suggesting that the HAT step is not rate determining (also see ESI, pages S12 and S13[†]).
- 34 Attempts to provide additional evidence for the existence of the EDA complex using cyclic voltammetry were inconclusive (see ESI pages S15 and S16[†]).
- 35 For useful perspective on catalysis of radical reactions, including especially relevant discussion of the concept of 'smart initiation', see: A. Studer and D. P. Curran, *Angew. Chem., Int. Ed.*, 2016, **55**, 58.
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