#### A radical-polar crossover approach to complex nitrogen heterocycles via the triplet state

Zachariah Lockhart<sup>1</sup>, Mihai V. Popescu<sup>1,2</sup>, Juan V. Alegre-Requena<sup>2,3</sup>, Jay Ahuja<sup>1</sup>, Robert S. Paton<sup>2\*</sup>, Martin D. Smith<sup>1\*</sup>.

<sup>1</sup> Chemistry Research Laboratory, University of Oxford, 12 Mansfield Road, Oxford, OX1 3TA, UK.

<sup>2</sup> Department of Chemistry, Colorado State University, 1301 Center Ave, Ft. Collins, CO 80523-1872, USA.

6 7 <sup>3</sup> Dpto. de Química Inorgánica, Instituto de Síntesis Química y Catálisis Homogénea (ISQCH) CSIC-Universidad de 8 Zaragoza, C/ Pedro Cerbuna 12, Zaragoza 50009, Spain.

Email martin.smith@chem.ox.ac.uk; homepage: http://msmith.chem.ox.ac.uk/ robert.paton@colostate.edu; homepage: http://patonlab.colostate.edu/

### Abstract

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The transition from radical to ionic reactivity is a key design feature of many photochemical reactions, enabling 14 complex transformations not possible under either mechanistic regime alone. Ground-state alkenes are common 15 substrates in existing methods of this type, serving as radical acceptors to generate open-shell intermediates from 16 which the radical-polar crossover (RPC) event is oxidatively or reductively triggered by a photocatalyst. Here, we 17 describe an alternative RPC mechanism proceeding via an alkene triplet diradical. In this transformation, an iodine 18 radical liberated during a homolytic aromatic substitution step functions as a single electron oxidant to generate an 19 iminium electrophile that can be intercepted en route to complex natural product-like amines. An enantioselective 20 variant of the reaction, enabled by an oxidatively installed sulfinyl leaving group, points to the generality of this 21 underdeveloped pattern of diradical reactivity, paving the way to other triplet-state reactions that incorporate both 22 23 one- and two-electron bond-forming processes. 24

The addition of carbon-centered radicals to ground-state alkenes offers a versatile route for the formation of 25 26 challenging carbon–carbon bonds, and also enables an increase in molecular complexity through the onward reaction of the subsequently formed radical. This intermediate is often trapped in a radical termination step but may also react 27 *via* a polar (non-radical) step<sup>1</sup>. When the initial formation of radicals is mediated by an excited-state photocatalyst, 28 these intermediates can undergo a single-electron oxidation (to generate a cationic intermediate) or a single-electron 29 reduction (to generate an anionic intermediate). These ionic species may then engage in two-electron reactions to 30 yield diverse products (Figure 1). 31



Radical-polar crossover via an alkene triplet diradical (this work) - alkene as chromophore В





Figure 1. Photochemical approaches to radical-polar crossover (RPC) reactions. (A) Previous work: RPC can occur when alkenes function as 36 radical acceptors; subsequent one-electron oxidation or reduction leads to intermediates that can be trapped in two-electron bond-forming 37 processes. This reactivity can be exemplified in the reductive formation of cyclopropanes<sup>12,13</sup> and the oxidative generation of lactones<sup>14</sup> from 38 alkenes under photoredox catalysis. (B) This work: A transition from diradical to ionic reactivity occurring from the triplet excited state. 39 Following a regioselective radical cyclisation step, intersystem crossing (ISC) and single-electron transfer (SET) lead to an iminium salt that 40 can be intercepted through a polar nucleophilic mechanism. PC = photocatalyst; EWG = electron-withdrawing group; EnT = energy transfer; 41 NuY = nucleophile (e.g. 1-methylindole).

This radical-polar crossover (RPC) is the basis of many photoredox processes and has enabled a wide range of 42 impactful transformations<sup>2-7</sup>. In contrast, RPC reactions have not been exploited where alkenes act as a *chromophore* 43 rather than a radical acceptor<sup>8-11</sup>. Here we describe an alternative RPC strategy involving the photochemical activation 44 of an alkene by direct excitation or triplet energy transfer, whereupon a homolytic aromatic substitution mechanism 45 gives rise to an iminium salt that can be trapped intra- or intermolecularly by two-electron nucleophiles. This 46 photocyclization-cation trapping cascade<sup>15,16</sup> leads to the generation of complex three-dimensional templates 47 containing an array of functional groups with high levels of diastereoselectivity. 48

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We have previously examined the energy transfer-mediated isomerization of N-aryl enaminones<sup>17</sup>, and observed that 50 an outlier in their reactivity was that *ortho*-iodinated substrate 1 led to the exclusive formation of indole 2 as a single 51 regioisomer without ipso-H diradical cyclization products 3 in detectable quantities (Figure 2). It was hypothesised 52 that this product arises from either the cyclization of a photolytically generated aryl radical onto the enone in a 5-53 endo-trig<sup>18</sup> fashion or a selective ipso-I substitution and net-eliminative cyclization process upon excitation of the 54 enone to its triplet state<sup>19-21</sup>. Eliminative photocyclizations such as this have previously been applied in the generation 55 of aromatic systems in natural products and the development of new materials<sup>22,23</sup>. We designed *N*-allyl substrate 4 56 to probe the formation of an aryl radical, reasoning that a 5-exo-trig mode would be competitive with any other 57 cyclization. In the presence of an iridium sensitizer and 467 nm light, 4 yielded indole 5 (86% yield) and bridged 58 59 cyclobutane 6 (10% yield); 5-exo-trig cyclization products 7 were not observed.

Discovery of a regioselective eliminative photocyclization:



Figure 2 Overview of reaction development. (A) Observation of an unexpected product leads to the development of an eliminative alkene difunctionalization. (B) Tethering an intramolecular radical acceptor indicates that the intermediacy of an aryl radical is unlikely and the observed reactivity is more consistent with a triplet-state mechanism. (C) Reaction design and validation. The formation of an iminium salt as the primary photoproduct of the reaction is supported by the isolation of hemiaminal 11 upon the direct irradiation of a  $\beta$ -methylated substrate, 67 10, in which re-aromatization is prevented; treating the former compound with trifluoroacetic acid enables the identification of the putative 68 iminium ion intermediate as enol 12. X = H or I; NuY = nucleophile.

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This result is consistent with energy transfer activation of the enone in 4 and subsequent *ipso-I* cyclization to yield 70 5, with competitive [2+2] cycloaddition onto the *N*-allyl group to yield  $6^{24}$ . A control experiment in which 4 was 71 reduced using a neutral organic super-electron donor<sup>25</sup> gave a mixture of 5-exo- and 5-endo-trig aryl radical 72 cyclization products, demonstrating the viability of both cyclization modes whenever the aryl radical in question is 73 generated thermally (see SI). Thus, the failure to observe 5-exo-trig products upon sensitized irradiation of 4 suggests 74 that an aryl radical does not form under photochemical activation of this and related compounds. Instead, a 75 mechanism involving the regioselective cyclization of an alkene triplet diradical is more likely. We reasoned that 76 such a process would lead initially to a radical pair, 8, which could be expected, upon ISC and SET, to form an 77 iminium iodide salt, 9. Thus, provided re-aromatization is prevented, it should be possible to effect a net-eliminative 78 difunctionalization of the alkene functional group in compounds such as 10 through the thermal trapping of this 79 cationic photoproduct with different two-electron nucleophiles. This triplet-state approach would constitute a distinct 80 but complementary strategy to existing radical-polar crossover processes. To explore this possibility, substrate 10, 81 which absorbs weakly in the visible region and bears a methyl substituent at the enone  $\beta$ -position, was synthesized 82 and irradiated with 427 nm light in an acetonitrile-water mixture; in the absence of photocatalyst and presence of 83 potassium acetate, this yielded hemiaminal 11 in 89% yield as a single diastereoisomer. The observed product is 84 consistent with in situ base-promoted hydrolysis of an iminium salt; this putative intermediate was formally generated 85 and characterized by NMR spectroscopy as enol species 12 by treating the hemiaminal product with trifluoroacetic 86 acid in acetonitrile- $d_3$  solution. 87

With evidence in hand for the photochemical generation of an iminium cation, we sought to explore the scope of the 89 reaction with respect to the nucleophilic coupling partner (Table 1A). Thus, irradiation of  $\beta$ -methyl substrate 10 with 90 91 427 nm light in the presence of N-methylindole in a polar solvent mixture gave the complex heterocycle 13 as a single diastereoisomer in 81% yield and >40:1 ratio of eliminative to non-eliminative cyclization. The N-substituent 92 on the indole is not necessary for reactivity, and 14 can be isolated in 83% yield by addition of 1H-indole as the 93 94 nucleophile. Other  $\pi$ -rich heterocycles are also reactive: addition of 2,4-dimethylpyrrole yields 15 (68% yield), while 3-methoxythiophene affords 16 (44% yield) and 2-methylfuran leads to 17 (59% yield). Potassium trifluoroborate 95 salts may also be used as nucleophiles in a process reminiscent of the borono-Petasis reaction<sup>26,27</sup>, enabling the formal 96 addition of furan (18, 55% yield), styrenes (19, 66% yield) and alkynes (20, 53% yield). Reduction of the iminium 97 98 cation through addition of triethylsilane led to 21 (80% yield); this process also enables the synthesis of deuterated analogue 22 (79% yield, >99% D). Addition of allyltrimethylsilane to form 23 was also successful (80% yield). The 99 trimethylsilyl enol ether derived from acetophenone could be employed in anhydrous nitromethane solvent and in 100 the presence of sodium trifluoroacetate, generating 1,4-diketone 24 (57% yield), which was examined by single-101 crystal X-ray diffraction. Toluenesulfonylmethyl isocyanide (TosMIC) added smoothly in aqueous acetonitrile to 102 produce amide 25 in 74% yield and with complete diastereoselectivity. We were also able to move beyond the 103 formation of carbon-carbon bonds. Performing the reaction in the presence of diethylphosphite led to the formation 104 105 of aminophosphonate 26 in 57% yield as the cis-diastereomer (19:1 d.r.). Water (to afford 11 in 89% yield) and methanol (to give 27 in 77% yield) are also proficient trapping agents in the presence of bases. The potential of this 106 process to generate complex natural product-like<sup>28</sup> heterocycles was demonstrated by tethering a nucleophile to 107 enable an intramolecular cyclization. Irradiation of 28, which bears a pendent carbamate functional group, led to the 108 formation of bridged tetracycle **29** in 88% yield, the structure of which was confirmed through X-ray crystallography. 109 We were also able to install different substituents in the enone  $\beta$ -position with minimal impact to the efficiency of 110 the cyclization process: a  $\beta$ -ethyl substrate was irradiated in the presence of TosMIC to yield **30** in 64% yield (Table 111 1B). An N-acyl piperidinyl substituent was also tolerated, yielding 31 in 42% yield. Different N-substitution patterns 112 are also possible: products bearing *N*-allyl **32** (alongside 6% of a competitive [2+2] product) and *N*-benzyl **33** groups 113 were effectively generated in yields of 42% and 53%, respectively. We were able to exemplify the regioselective 114 nature of this transformation through the incorporation of substituents at either meta-position. The cyclization of a 115 5-chloro-2-iodo substrate and subsequent trapping with TosMIC afforded 34 (62% yield) without formation of the 116 alternative regioisomer in detectable quantities; in a similar fashion a 3-methyl-2-iodo substrate cyclizes 117 regioselectively to yield 35 (58% yield). The introduction of para-substituents on the aromatic ring is also possible. 118 Whilst para-nitro product 36 was generated in moderate yield (29%) with substantial starting substrate recovery, 119 120 other groups in this position cyclize effectively: para-N-acetyl 37 (69% yield), para-bromo 38 (79% yield) and paraiodo **39** (72% yield) products were all formed efficiently. 121

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**Table 1.** Scope of the reaction with respect to (A) the nucleophilic coupling partner (NuY) and (B) structural modifications to the prototypical126substrate. Reaction conditions (unless otherwise stated): 10 or corresponding substrate (0.3 mmol, 1.0 eq.), NuY (0.9 mmol, 3.0 eq.), solvent(s)127(v/v) (0.05 M) [TosMIC (3.0 eq.) and MeCN-H2O (9:1) for all reactions in (B)], room temperature (r.t.), 2 x Kessil PR160L 427 nm lamps,12818 h.  $^{a}$ 5.0 eq. NuY.  $^{b}$ 1.5 eq. NuY.  $^{c}$ 6 h reaction time.  $^{d}$ 90 min reaction time.  $^{e}$ This compound was isolated and characterized without129chromatographic purification owing to its instability on silica and alumina gels; the reported yield was measured for a 0.1 mmol-scale reaction130by quantitative <sup>1</sup>H NMR spectroscopy against dimethyl terephthalate.  $^{f}$ 2 h reaction time.  $^{g}$ 3 h reaction time.  $^{h}$ 21 h reaction time.  $^{i}$ Yield based131on recovered starting material.

Although we had satisfactorily demonstrated that the reaction does not proceed *via* an aryl radical, the origin of the underlying regioselectivity was challenging to interpret and hence we applied a combination of experimental and computational techniques to this problem. UV–visible absorption spectroscopy revealed a band centered at *ca*. 345 nm that extends above 400 nm for  $\beta$ -methyl substrate **10**; due to its weakly absorbing nature, this was assigned to an  $n\pi^*$  transition between the ground and first excited singlet (S<sub>1</sub>) state, in accordance with previous photophysical studies of cyclohexenones and their derivatives<sup>29-31</sup>. Since intersystem crossing from this state is known to be fast for cyclic enones<sup>32,33</sup>, we expect that bond formation proceeds *via* the T<sub>1</sub> state.

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Figure 3. Experimental and computational mechanistic investigations. (A) A sensitization experiment is consistent with the reaction proceeding *via* the triplet state. Conversions and yields were measured by quantitative <sup>1</sup>H NMR spectroscopy against dimethyl terephthalate. (B) Proposed reaction mechanism, in which an irreversible *ipso*-I cyclization step is selectivity-determining. (C) Potential energy surfaces for the *ipso*-H and *ipso*-I cyclization pathways available to intermediate <sup>3</sup>A, computed at M06-2X-D3/Def2-QZVPP(SMD=MeCN)//M06-2X-D3/Def2-TZVP(SMD=MeCN). (D) Intrinsic reaction coordinate (IRC) computed for TS-I; amu = atomic mass units. (E) Computed structures of transition states TS-I-III and triplet intermediate <sup>3</sup>B. Distances, *d*, in Å are indicated by dotted lines. WBO = Wiberg bond order;  $\rho_S$  = natural spin density; MECP = minimum energy crossing point.

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This tenet is consistent with the substantial rate acceleration observed (without change in product distribution) for the photocyclization of **40** ( $E_T \approx 48$  kcal mol<sup>-1</sup>) in the presence of catalytic Ir(dFppy)<sub>3</sub> ( $E_T = 60.1$  kcal mol<sup>-1</sup>)<sup>34</sup>. Upon irradiation with a 467 nm Kessil lamp in acetonitrile solution, indole **41** was formed in 99% yield under these conditions; in contrast, a significantly lower yield of 13% (14% conversion) was obtained in the photocatalyst's absence (Figure 3A). The iridium complex is not sufficiently oxidizing ( $E_{1/2}[Ir^{III*}/Ir^{II}] = +0.39$  V vs. SCE) or reducing 155  $(E_{1/2}[Ir^{IV}/Ir^{III*}] = -1.23 \text{ V } vs. \text{ SCE})$  in the excited state to activate **40** (whose half-wave oxidation and reduction 156 potentials were measured as +1.10 V and -2.04 V, respectively, vs. SCE) by single-electron transfer, implicating 157 triplet energy transfer as the mode of catalysis. Additional evidence for triplet state generation in the absence of 158 sensitizer includes the observation of a competing [2+2]-photocycloaddition (known to be a fast triplet process<sup>35,36</sup>) 159 in the reaction to form **32**, as well as a substantial reduction in conversion (and attendant formation of oxidative 160 degradation products) observed when **10** was irradiated in the presence of oxygen<sup>37,38</sup>; see SI for more detail.

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We proceeded to study the reaction mechanism with density functional theory (DFT) at the M06-2X-D3/def2-162 QZVPP//M06-2X-D3/def2-TZVP level (Figure 3B). Once the triplet state <sup>3</sup>A (which has an adiabatic triplet energy 163 of 48.3 kcal mol<sup>-1</sup>) is reached, a conrotatory ring-closure to form a new C-C bond can proceed either *ipso*- to the 164 iodine substituent (via TS-I to furnish intermediate <sup>3</sup>B) or at the unsubstituted position (via TS-II leading to 165 intermediate <sup>3</sup>C). Computation predicts selective attack at the carbon bearing the iodine substituent ( $\Delta\Delta G^{\ddagger} = -0.4$  kcal 166 mol<sup>-1</sup>); this selectivity is maintained across several commonly employed DFT levels of theory, albeit to varying 167 degrees (see SI). We further performed single-point corrections using multiconfiguration methods 168 (NEVPT2:CASSCF(10,10)/Def2-TZVP) that indicated greater selectivity ( $\Delta\Delta G^{\ddagger} = -2.6 \text{ kcal mol}^{-1}$ ), suggesting that 169 the competition between TS-I and TS-II is selective towards the formation of intermediate <sup>3</sup>B in an irreversible and 170 highly exergonic fashion (40.7 kcal mol<sup>-1</sup>). Intrinsic reaction coordinate (IRC) calculations performed from TS-I 171 revealed that the minimum energy path directly connects intermediate  ${}^{3}A$  to  ${}^{3}B$  without forming a stable  $\sigma$ -172 intermediate (Figure 3D). Natural bond orbital (NBO) analysis of TS-I revealed a Wiberg bond order (WBO) of 0.28 173 for the forming C–C bond, indicative of an early TS (Figure 3E). The WBO of the C–I bond is 0.90, and the natural 174 175 spin density on iodine 0.13, suggesting partial bond-breaking in the TS. That the *ipso-I* cyclization (via TS-I) is concerted is consistent with its lower activation energy (vs TS-II): the partial breaking of the C-I bond in the 176 transition structure enables the stabilization of one of the unpaired electrons on the iodine atom. Second-order 177 perturbation theory analysis of natural bonding orbitals indicated donation into the  $\sigma^*_{C-I}$  orbital from adjacent C–C 178  $\sigma$  and  $\pi$  bonds of the aromatic system worth 14.6 kcal mol<sup>-1</sup>, consistent with a direct and concerted radical *ipso*-I 179 substitution mechanism.<sup>39-41</sup> Similarities can be drawn between this mechanism and that of recently identified 180 concerted nucleophilic aromatic substitutions, where a lone pair assists the elimination of a bromide atom in a 181 concerted fashion<sup>42,43</sup>. The resulting triplet radical pair  ${}^{3}\mathbf{B}$  is expected to undergo spontaneous intersystem crossing 182 as one of the unpaired electrons is fully localized on a heavy iodine atom, with the putative singlet radical pair being 183 able to undergo a facile outer-sphere single electron transfer (SET) ( $\Delta G^{\ddagger} = 6.0 \text{ kcal mol}^{-1}$ ) to form the experimentally 184 observed iminium iodide product, <sup>1</sup>B. In contrast, regioisomeric cyclization via TS-II to form triplet diradical  ${}^{3}C - a$ 185 pathway that could account for the formation of trace side-products in some reactions but that otherwise is not 186 observed experimentally – was found to be only mildly exergonic (-3.9 kcal mol<sup>-1</sup>). This intermediate could undergo 187 intersystem crossing to ground state zwitterion <sup>1</sup>C, passing through a relatively high minimum energy crossing point 188 of 9.6 kcal mol<sup>-1</sup>, affording product <sup>1</sup>D via an intramolecular hydrogen transfer (**TS-III**,  $\Delta G^{\ddagger} = 20.9$  kcal mol<sup>-1</sup>). 189 190

One implication of a diradical cyclization mechanism is that leaving groups other than iodine should also be viable; 191 moreover, radical addition to the arene would represent the stereodetermining step of any asymmetric variant. 192 Reactions involving the loss of sulfur-centred radicals are well-studied, particularly in the context of Smiles-type 193 rearrangements<sup>44-47</sup>. An elegant example of this class of reaction was recently reported by the Nevado group<sup>48</sup>, who 194 showed that the addition of radicals generated under photoredox catalysis to enantioenriched N-arylsulfinyl 195 acrylamides initiates a stereospecific radical sulfinyl Smiles rearrangement<sup>49</sup>. Inspired by these precedents, we 196 synthesized an enantioenriched N-aryl enaminone substrate, (+)-43, bearing an ortho-sulfinyl substituent in 75% 197 yield and 98:2 e.r. from the corresponding sulfide, 42, under Kagan oxidation conditions (Figure 4)<sup>50</sup>. Pleasingly, 198 when irradiated in the presence of triethylsilane and trifluoroacetic acid in acetonitrile solution, this compound 199 underwent eliminative photocyclization with transfer of chirality from sulfur to carbon, delivering the expected 200 201 iminium reduction product, (-)-21, in 75% yield and 96:4 e.r.

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Figure 4. Enantioselective visible-light-mediated cyclization with loss of a sulfur-based leaving group. Reaction conditions: (i) Substrate 45 (1.0 eq.), Ti(Oi-Pr)<sub>4</sub> (1.0 eq.), (+)-diethyl L-tartrate (2.0 eq.), H<sub>2</sub>O (1.0 eq.), *t*-BuOOH (2.0 eq.), CH<sub>2</sub>Cl<sub>2</sub> ([42] = 0.1 M), -20°C, 21 h. (ii) Substrate (+)-43 (0.1 mmol), Et<sub>3</sub>SiH (0.5 mmol), CF<sub>3</sub>CO<sub>2</sub>H (0.3 mmol), Kessil PR160L 427 nm lamp, MeCN ([(+)-43] = 0.05 M), r.t., 12 h. Enantiomeric ratio (e.r.) determined by chiral stationary phase HPLC.

In conclusion, we have discovered that the incorporation of an *ortho*-iodine substituent is an effective strategy for 210 transitioning from diradical to jonic reactivity during photocyclizations of the N-aryl enaminone substrate class. 211 Quantum calculations in conjunction with experimental mechanistic investigations identify an irreversible *ipso*-I 212 substitution process in the triplet state as the central step of this complexity-generating cascade, which marks a 213 strategic departure from the cycloaddition and isomerization reactions typical of excited-state alkenes. Intersystem 214 crossing and single-electron transfer within the radical pair resulting from *ipso*-substitution lead to the formation of 215 216 an iminium iodide salt as the primary photoproduct of the reaction, which can be intercepted thermally by a variety of two-electron nucleophiles. The intermediacy of an alkene triplet diradical circumvents the need for a photolabile 217 bond to achieve regioselective cyclization, permitting control over the absolute stereochemistry of the  $C(sp^3)$ -rich 218 indoline products through the use of an *ortho*-sulfinyl group in place of iodine. We anticipate that the reactivity 219 described herein will inspire the development of other triplet-state reactions incorporating radical-polar crossover. 220

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## 233 Data Availability

All data (experimental procedures, characterization data and cartesian coordinates for all DFT calculations) supporting the findings of this study are available within the article and its supplementary information. Crystallographic data for compounds **24** and **29** have been deposited with the Cambridge Crystallographic Data Centre under deposition numbers 2243733 and 2243732 respectively. These data can be obtained free of charge from www.ccdc.cam.ac.uk/data request/cif

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