

Cite this: *Chem. Sci.*, 2022, 13, 11074

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## A switchable redox annulation of 2-nitroarylethanols affording *N*-heterocycles: photoexcited nitro as a multifunctional handle†

Bin Wang,<sup>‡a</sup> Hongyuan Ren,<sup>‡a</sup> Hou-Ji Cao,<sup>‡a</sup> Changsheng Lu<sup>‡\*a</sup> and Hong Yan<sup>‡\*a</sup>

The efficient transformation of nitroaromatics to functional molecules such as *N*-heterocycles has been an attractive and significant topic in synthesis chemistry. Herein, a photoexcited nitro-induced strategy for switchable annulations of 2-nitroarylethanols was developed to construct *N*-heterocycles including indoles, *N*-hydroxyl oxindoles and *N*-H oxindoles. The metal- and photocatalyst-free reaction proceeds through intramolecular redox C–N coupling of branched hydroxyalkyl and nitro units, which is initiated by a double hydrogen atom abstraction (*d*-HAA) process. The key to the switchable reaction outcomes is the mediation of a diboron reagent by its favorable oxy-transfer reactivity to *in situ* generated nitroso species. The utility of this protocol was well demonstrated by broad substrate scope, excellent yields, functional group tolerance and wide applications. Finally, detailed mechanistic studies were performed, and kinetic isotope effect (KIE) experiments indicate that the homolysis of the C–H bond is involved in the rate-determining step.

Received 27th June 2022  
Accepted 15th August 2022

DOI: 10.1039/d2sc03590a

rsc.li/chemical-science

### Introduction

*N*-Heterocycles are ubiquitous skeletons of various biologically active and pharmaceutical substances.<sup>1</sup> Among them, indole<sup>2</sup> and oxindole<sup>2a,3</sup> are privileged skeletons, which have attracted chemists for over a century and remained sustained topics in synthetic chemistry with high value-added features. Although a considerable collection of synthetic methods for these skeleton molecules has been developed, there is still a continuous thirst for highly efficient strategies to create these functional substructures while maximizing atom economy.<sup>4</sup> Besides, new application scenarios also issue new challenges to the development of these methodologies, such as the modularity for pharmaceutical synthesis<sup>5</sup> and facile conditions for biocompatible synthesis.<sup>6</sup> Given the widespread availability and easy preparation of nitroarenes, the most straightforward protocol to construct *N*-heterocycles is using nitro as the nitrogen source.<sup>4c,7</sup> A few renowned reactions<sup>8</sup> for the synthesis of indoles have witnessed the potential of nitroarenes, especially for *ortho*-branched ones which possess robust features for reductive cyclization.

More recently, switchable transformations of *ortho*-branched nitroarenes to indoles or oxindoles by metal-free methods were reported by Radosevich's group<sup>9</sup> and Driver's group,<sup>10</sup> which provided new perspectives for the construction of these *N*-heterocycles (Scheme 1A). Compared to these strategies starting from *ortho*-vinyl or -carbonyl nitroarenes, the redox cyclization of *ortho*-hydroxyalkyl nitroarenes could offer a more facile and practical choice for the synthesis of the corresponding *N*-heterocycles.<sup>11</sup> However, the tactic using an *ortho*-branched hydroxyalkyl moiety as both a C-precursor and a hydrogen donor under metal-free conditions is still undeveloped. This tactic could circumvent the use of problematic reductants such as sensitive Grignard reagents,<sup>8c,12</sup> pressured CO gas,<sup>13</sup> hazardous organophosphine reagents<sup>7c,9,14</sup> and stoichiometric metal reductants.<sup>7a,b,15</sup> Moreover, exogenous hydrogen donors for reductive cyclization of nitroarenes are no longer needed.

The recent development of the activation of alcohols into  $\alpha$ -carbon-centered or oxygen-centered radical fragments by photo-redox catalysis contributed to valuable transformations of alcohols,<sup>16</sup> which were otherwise unattainable. The photocatalytic hydrogen atom transfer (HAT) strategy for activating an electron-rich  $\alpha$ -C–H bond of alcohols is commonly facilitated *via* hydrogen-bond interaction or deprotonation of the hydroxyl group<sup>17</sup> (Scheme 1B). Besides, the proton-coupled electron transfer (PCET) strategy for activating the O–H bond of alcohols is heavily dependent on the combination of a Brønsted base with an oxidant to remove a proton and an electron from the O–H bond, respectively<sup>18</sup> (Scheme 1B). Inspired by these profound strategies for radical generation, we envisaged that the

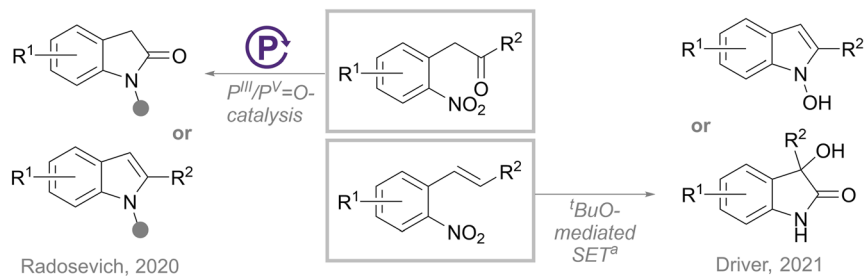
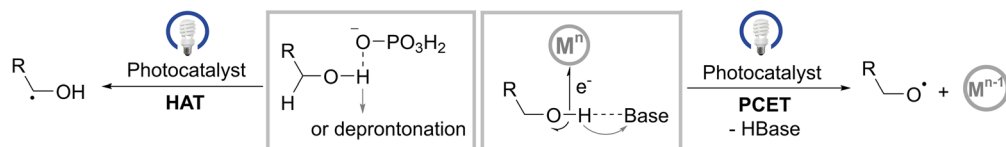
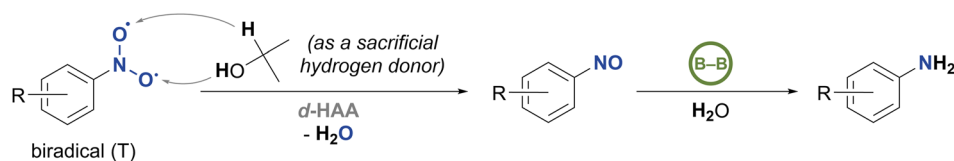
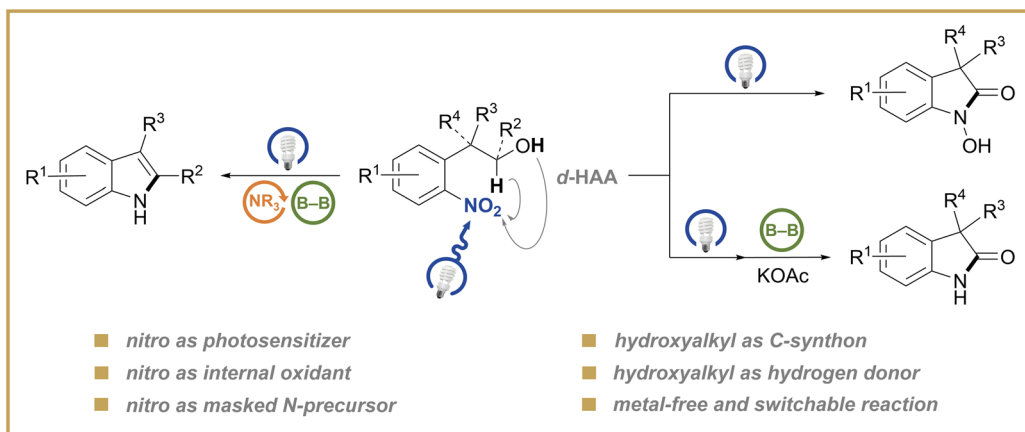
<sup>a</sup>State Key Laboratory of Coordination Chemistry, Jiangsu Key Laboratory of Advanced Organic Materials, School of Chemistry and Chemical Engineering, Nanjing University, Nanjing 210023, China. E-mail: hyan1965@nju.edu.cn

<sup>b</sup>School of Chemistry and Chemical Engineering, Henan Normal University, XinXiang, Henan 453007, China. E-mail: houjica@ sina.cn

† Electronic supplementary information (ESI) available. CCDC 2163566, 2163568, 2163569 and 2163570. For ESI and crystallographic data in CIF or other electronic format see <https://doi.org/10.1039/d2sc03590a>

‡ Equal contribution.



A. Representative strategies for reductive cyclization of *ortho*-branched nitroarenes to indoles or oxindolesB. Reported radical strategies for activation of  $\alpha$ -C-H or O-H bonds of hydroxylC. Diboron-mediated reduction of nitroarenes to anilines using <sup>i</sup>PrOH as a sacrificial H-donor (our previous work, 2022)D. Switchable cyclization of 2-nitroarylethanol involving a photoexcited nitro-induced  $d$ -HAA process (this work)Scheme 1 Research backgrounds and this work. <sup>a</sup> SET: single electron transfer.

photoexcited nitro might act as a potential dual HAT-functionality for the activation of both  $\alpha$ -C-H and O-H bonds of hydroxyl owing to its nature as a biradical in the triplet state,<sup>19</sup> and we describe this process as double hydrogen atom abstraction ( $d$ -HAA). As a preliminary attempt for this hypothesis, our previous work achieved a tandem reduction of nitroarenes to anilines triggered by a  $d$ -HAA process with isopropanol<sup>20</sup> (Scheme 1C). However, in the reaction, alcohol serves a sacrificial and disposable reductant, which limits further evolution of the nitro-triggered radical process. In order to provide more reaction possibilities for the  $d$ -HAA process and construct a diversity of functionalized molecules by using this reaction platform, we tried new designs in an intramolecular setting. Herein, we disclose a redox annulation of 2-nitroarylethanol via a photoexcited nitro-triggered  $d$ -HAA process under blue-light irradiation, which delivers diboron-switched indoles, *N*-hydroxyl oxindoles or

*N*-H oxindoles (Scheme 1D) in good to excellent yields. This reaction does not need any metal catalyst or photocatalyst, and three characteristics stand out as given below: (1) nitro serves as a masked nitrogen precursor, as well as an internal photosensitive and oxidative functionality; (2) the branched hydroxyalkyl serves as an internal carbon precursor and a double hydrogen donor ( $\alpha$ -C-H and O-H); (3) the *in situ* generated nitrosoarene and *N*-hydroxylaniline intermediates may undergo diboron-based deoxygenation,<sup>20,21</sup> thus avoiding the addition of extra activators.<sup>22</sup> The different usages of a diboron reagent could lead to different products (Scheme 1D).

## Results and discussion

We started our study with the reaction of 2-(2-nitrophenyl)ethan-1-ol (**1a**) in the presence of a base catalyst and a diboron reagent



under the irradiation of 400 nm blue LEDs. A broad screening of conditions gave the optimal conditions containing *N,N*-diisopropylethylamine (DIPEA, 20 mol%) as the catalyst, bis(neopentyl glycolato)diboron ( $B_2nep_2$ , 2.2 equiv.) as the reductant, THF/MeOH with an 8/1 ratio as co-solvents, under a nitrogen atmosphere and at room temperature for 12 h, delivering the product **2a** in 82% isolated yield (Table 1, entry 1). Deviations from the standard conditions were manipulated by varying the reaction parameters to validate the superiority of the optimal conditions. In this regard, other solvents have been screened including oxygenated and chlorinated hydrocarbons, such as 1,4-dioxane, toluene, dichloroethane, and acetonitrile instead of THF/MeOH, but led to lower yields (Table 1, entry 2 and Table S1†). Altering the ratio of mixed THF/MeOH or using THF as the solvent diminished the yield of **2a** (Table S1†). A decreased yield of **2a** was observed if  $B_2nep_2$  was replaced by  $B_2(OH)_4$  due to the competitive formation of *N*-hydroxyoxindole (Table 1, entry 3 and Table S1†). A detrimental effect on the yield of **2a** was also observed while other diboron reagents such as bis(pinacolato)diboron ( $B_2pin_2$ ) and bis(catecholato)diboron ( $B_2cat_2$ ) were examined (Table 1, entry 4 and Table S1†). When the amount of  $B_2nep_2$  was reduced instead of 2.2 equiv., a diminished yield of **2a** was observed (Table 1, entries 5 and 6 and Table S1†). To check the effect of other catalytic bases,  $Et_3N$ ,  $K_2CO_3$ , and  $KO^tBu$  were examined, which led to lower yields (Table 1, entry 7 and Table S1†). Notably, the yield of **2a** dropped without the addition of DIPEA (Table 1, entry 8). The control experiments further demonstrated that the diboron reagent and light are indispensable for the redox cyclization process (Table 1, entries 9 and 10), and air is a detrimental factor (Table 1, entry 11).

The substrate scope of the metal-free and photoinduced cyclization of 2-nitroarylethanol for the preparation of indoles

Table 1 Optimization studies for the synthesis of indoles<sup>a</sup>



Entry	Deviation from the standard conditions	Yield <sup>b</sup> /%
1	None	82
2	Other solvents instead of the mixed solvents	<70
3 <sup>c</sup>	$B_2(OH)_4$ instead of $B_2nep_2$	62
4	Other diboron reagents instead of $B_2(OH)_4$ or $B_2nep_2$	<30
5	0.5 equiv. instead of 2.2 equiv. $B_2nep_2$	35
6	1.0 equiv. instead of 2.2 equiv. $B_2nep_2$	52
7	Other catalytic bases instead of DIPEA	<60
8	Without DIPEA	40
9	Without $B_2nep_2$	Trace
10	In the dark	0
11	In air	48

<sup>a</sup> Standard reaction conditions: **1a** (0.2 mmol), DIPEA (0.04 mmol),  $B_2nep_2$  (0.44 mol), THF/MeOH (8/1, 0.45 mL),  $N_2$ , rt, under the irradiation of blue LEDs (400 nm), 12 h. <sup>b</sup> Isolated yields of **2a**. <sup>c</sup>  $B_2(OH)_4$ : tetrahydroxydiboron;  $B_2nep_2$ : bis(neopentylglycolato) diboron.



Scheme 2 Substrate scope for the synthesis of indoles and other products. <sup>a</sup>Standard conditions: 0.2 mmol scale reaction in THF/MeOH (8/1, 0.45 mL), DIPEA (0.04 mmol, 20 mol%),  $B_2nep_2$  (0.44 mmol, 2.2 equiv.), blue LED,  $N_2$ , rt, 12 h; isolated yields. <sup>b</sup> $B_2(OH)_4$  (0.44 mmol) instead of  $B_2nep_2$ . <sup>c</sup> Without the addition of DIPEA.



was explored under the above optimal reaction conditions (Scheme 2). Most of our substrates of 2-nitroarylethanols were either commercially accessible or easily prepared in one step (ESI S1.1†), which differentiate from those substrates used in some reported methods such as *o*-nitrostyrenes<sup>7c,10,23</sup> and *o*-nitrobenzyl ketone analogues<sup>9,24</sup> that were prepared by noble metal-catalysis. A broad range of substrates bearing electron-donating and electron-withdrawing substituents installed at the phenyl group were evaluated. These substrates exhibited good to excellent reactivity, affording functionalized indoles **2a–2k** in 62–92% isolated yields. It is noteworthy that halogen substituents, especially for iodo, which could be utilized as coupling handles for late-stage modification, were intact (**2b**, **2d**, **2e**, **2h**, and **2m**), in contrast to the reported dehalogenation.<sup>25</sup> This can presumably be attributed to the nitro-triggered direct intramolecular 1,2-double-hydrogen atom abstraction (1,2-*d*-HAA) of the hydroxyalkyl moiety, which could avoid reactive hydride dehalogenation. In addition, the alkynyl-substituted substrate was also converted to the corresponding C4-substituted indole in 78% yield (**2i**), which is difficult to directly prepare by traditional methods.<sup>26</sup> C7-functionalized indoles were also produced in satisfactory yields (**2j** and **2aa** in Scheme 4), whereas scarcely reported synthetic methods were qualified for this target.<sup>8c,12</sup> Fortunately, this annulative method was applicable to the challenging 6-azaindoles (**2l** and **2m**), notwithstanding moderate yields were obtained due

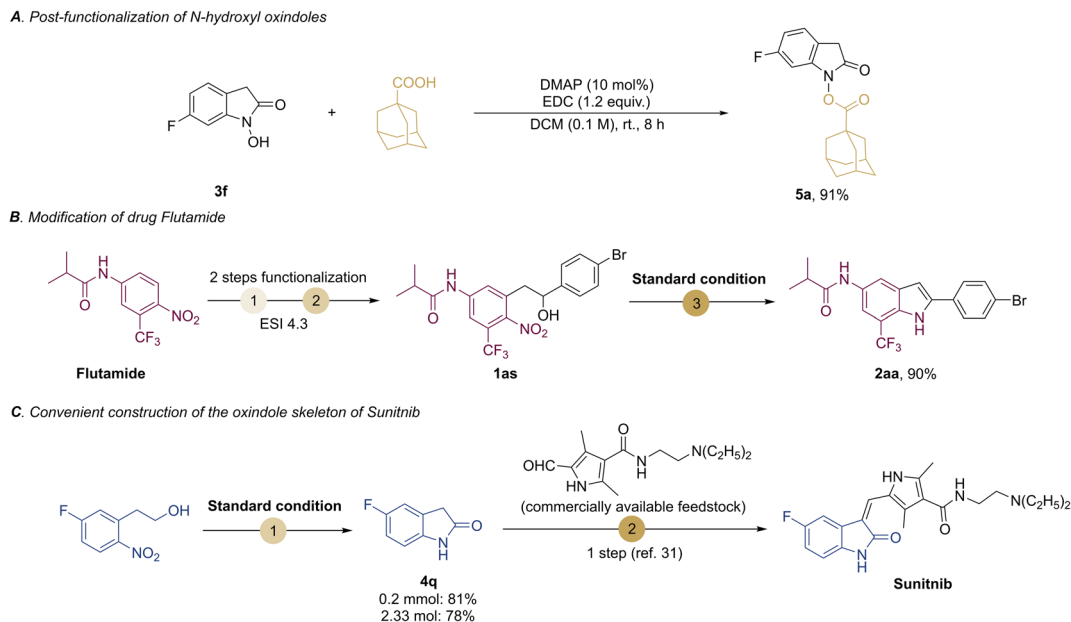
to the low reactivity of these electron-deficient pyridines.<sup>27</sup> To assess the generality toward C2-functionalized indoles, panels of substituents at the  $\alpha$ -position of hydroxyl were inspected under slightly modified conditions. It turned out that C2-alkyl or aryl functionalized indoles (**2n–2w**) were obtained in quantitative yields, exhibiting insensitivity toward sterically hindered tertiary alkyl (**2n**), cyclopropyl (**2o**) and polycyclic (**2q**) substituents. This system also demonstrates remarkable compatibility with sensitive groups including aldehyde (**2t**), cyano (**2u**), alkene (**2p**, **2q**), and ether (**2r**). To further validate the practicality of this method, we extrapolated this strategy to the synthesis of the aggregation-induced emission (AIE)<sup>28</sup> molecule (**2y**) and medicinal skeletons (**2x**, **2z** and **2aa** in Scheme 4) in moderate to excellent yields. In particular, the AIE molecule **2y** can be employed as a specific lipid droplet (LD) probe as it could colocalize perfectly with the commercial LD dye of Nile Red and Pearson's correlation coefficient can reach 90.49% (Fig. S10†). Therefore, various indole derivatives including interesting functionalities can be readily synthesized by this methodology, demonstrating its practicability. To our surprise, the  $\beta$ -aryl-substituted substrates release the reactivity of the  $\beta$ -C–H bond to form a benzylic radical, which delivers  $\alpha,\beta$ -dihydroxyl-substituted amines in good yields (**2ab–2ae** in Scheme 2).

To our delight, the aforementioned competitive *N*-hydroxyl oxindoles could become the sole products just by removal of the



**Scheme 3** Substrate scope for the synthesis of *N*-hydroxyl oxindoles and *N*-free oxindoles. <sup>a</sup>0.2 mmol scale reaction in THF/MeOH (8/1, 0.45 mL), a blue LED, N<sub>2</sub>, rt, 6 h; isolated yields. <sup>b</sup>10 mmol scale. <sup>c</sup>5 mmol scale. <sup>d</sup>The reaction was performed via a one-pot, two-step procedure (ESI S4.1†): 0.2 mmol scale reaction in THF/MeOH (8/1, 0.45 mL), blue LED, N<sub>2</sub>, rt, 6 h; after 6 h, the solvent was evaporated and the subsequent reaction was performed in the same pot, B<sub>2</sub>(OH)<sub>4</sub> (0.3 mmol, 1.5 equiv.), KOAc (0.4 mmol, 2.0 equiv.), MeOH (0.2 M), 50 °C, 2 h, isolated yields.





Scheme 4 Synthetic applications.

diboron reagent from the standard conditions (Table S2† and Scheme 3, left). This reaction system does not need any additive and exhibits admirable functional group compatibility toward group-abundant *N*-hydroxyl oxindole molecules, including halogen-(**3b**, **3d–3f**, **3m**, and **3o**), cyano-(**3g**), thienyl-(**3i**), alkynyl-(**3l**) and ester-(**3r**) bearing products. Spiro-*N*-hydroxyoxindoles with a five-membered ring (**3p**) and even a strained four-membered ring (**3q**) were readily afforded in 85% and 82% isolated yields, respectively. Substrates with either electron-withdrawing or electron-donating groups performed well regardless of substituents embedded either on the phenyl ring or the benzylic site. Potentially bio-active hetero-tricyclic molecule **3r** was isolated in 90% yield, which shows the practicality of this method. Unexpectedly, the substrate with a cyclohexyl substituent in the benzylic position underwent incredible oxy-transfer and intramolecular rearrangement, finally leading to spiro-[cyclohexane-1, 2'-indolin]-3'-one (**3s**) in an isolated yield of 92%. To test the scalability of our *N*-hydroxyl oxindole synthesis, we conducted the preparation of **3a**, **3b**, and **3f** on the gram-scale and obtained 70–85% isolated yields. In our system, with exclusive conversion of the substrates, the products could be easily isolated and purified by using a pad of silica gel or by quick recrystallization in chloroform. Although this class of skeletons is widely present in natural products and pharmaceuticals, for example, as calcium channel blockers or agents possessing anti-angiogenic and analgesic effects, only few synthetic methods of *N*-hydroxyl oxindoles have been described.<sup>29</sup> Thus, these results imply the utility of the protocol developed here. Moreover, hydroxyl attached at the nitrogen site of *N*-OH oxindoles can obviously serve as a diversified handle for post-functionalization of O–H or N–O bonds. However, it has not yet been reported as a leaving group to access *N*-H oxindoles.

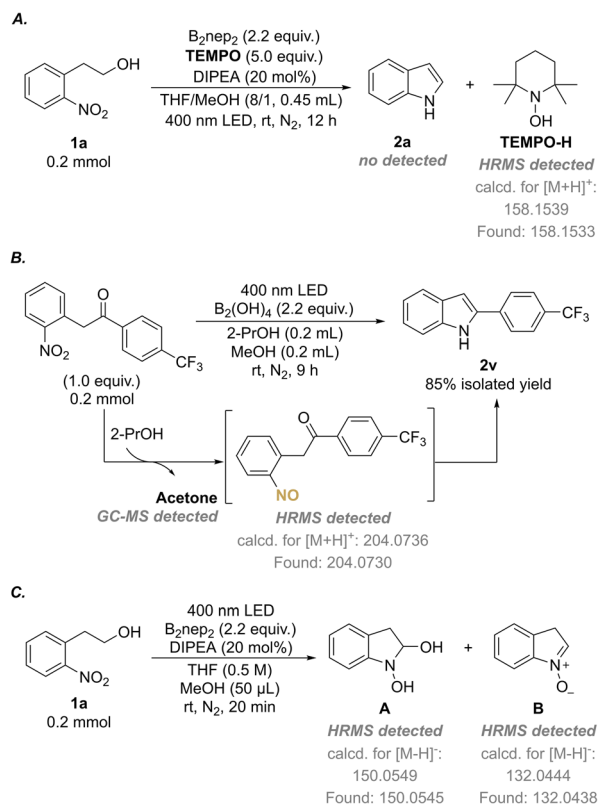
Next, we demonstrated the switchability of our reaction with respect to the formation of *N*-H oxindoles *via* a one-pot two-step

procedure (Table S3† and Scheme 3, right). A range of *N*-H oxindole products were achieved through a subsequent transborylative deoxygenation of *in situ* generated *N*-OH oxindoles under a weakly basic condition. Substrates containing sensitive groups, including iodo (**4b**), cyano (**4f**), oxaboron (**4h**), and alkynyl (**4m**) were accommodated perfectly, yielding *N*-H oxindoles exclusively with the reducible functionalities intact upon borylation. It is noteworthy that the method could provide value-added 3,3-spiro-oxindole (**4p**) at a lower cost compared to the precedent methods.<sup>1b</sup>

Then we provide representative synthetic applications to signify the practicality of our protocols. To show the unique features of the *N*-OH oxindoles, the post-functionalization of the O–H bond of compound **3f** led to the *N*-esterification product **5a** in 91% yield (Scheme 4A). Besides, starting from the drug Flutamide, our methodology can transform it into the indole product **2aa** (Scheme 4B). This may provide a useful strategy to access potential lead compounds for medicinal chemistry and structure–activity relationship studies without the need of *de novo* synthesis.<sup>30</sup> To further demonstrate the synthetic utility of our methods, we exemplified the synthesis of Sunitinib, a multitargeted receptor of tyrosine kinase for the treatment of cancer.<sup>31</sup> Using our protocol first to prepare 5-fluoroindolin-2-one (**4q**), and then one more step could lead to Sunitinib (Scheme 4C), in contrast to the 5 steps required for the synthesis of Sunitinib in the literature.<sup>31</sup> Of note, our reaction could be scaled up to 2.3 mmol without loss of efficiency for **4q** (78% yield).

To shed insight into the mechanisms of the switchable annulation reactions of 2-nitroarylethanol, a series of mechanistic investigations were conducted (Scheme 5 and ESI†). First, the UV-Vis absorption spectra of **1a**, B<sub>2</sub>nep<sub>2</sub>, and a mixture of **1a** and B<sub>2</sub>nep<sub>2</sub> (molar ratio = 1 : 2.2) were recorded (Fig. S12†). No spectral shift was observed for the mixture *versus* the individual





**Scheme 5** Mechanistic studies. (A) Radical-quenching experiment for the synthesis of indole. (B) Annulation of *o*-nitrobenzyl ketone with an exogenous H-donor. (C) HRMS analysis of the proposed intermediates.

species, which indicates that no electron-donor acceptor (EDA) was involved between **1a** and  $B_2nep_2$ . Then we turned our attention to investigate the radical nature of the reactions. The addition of 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) as a radical scavenger under standard conditions resulted in no production of the target product **2a**, but the formation of TEMPO-H, as detected by HRMS (Scheme 5A, ESI 5.1†). This indicates that the radical reaction is quenched. The same phenomenon was observed in the synthesis of *N*-OH oxindole, as only a trace amount of **3a** was obtained if TEMPO was added



**Fig. 1** Light on-off experiments for the synthesis of *N*-OH oxindole (the reaction was performed in a sealed NMR tube and NMR yields were shown, ESI 5.3†).

(ESI 5.1†). Combined with the control experiment in the dark (Table 1, entry 10), we assume that the photoinduced hydrogen atom abstraction (HAA) process is involved in the annulation reaction. Moreover, the light on-off experiments showed that no transformation could occur in the dark and constant irradiation is required for completion of the reaction (Fig. 1 and ESI 5.3†).

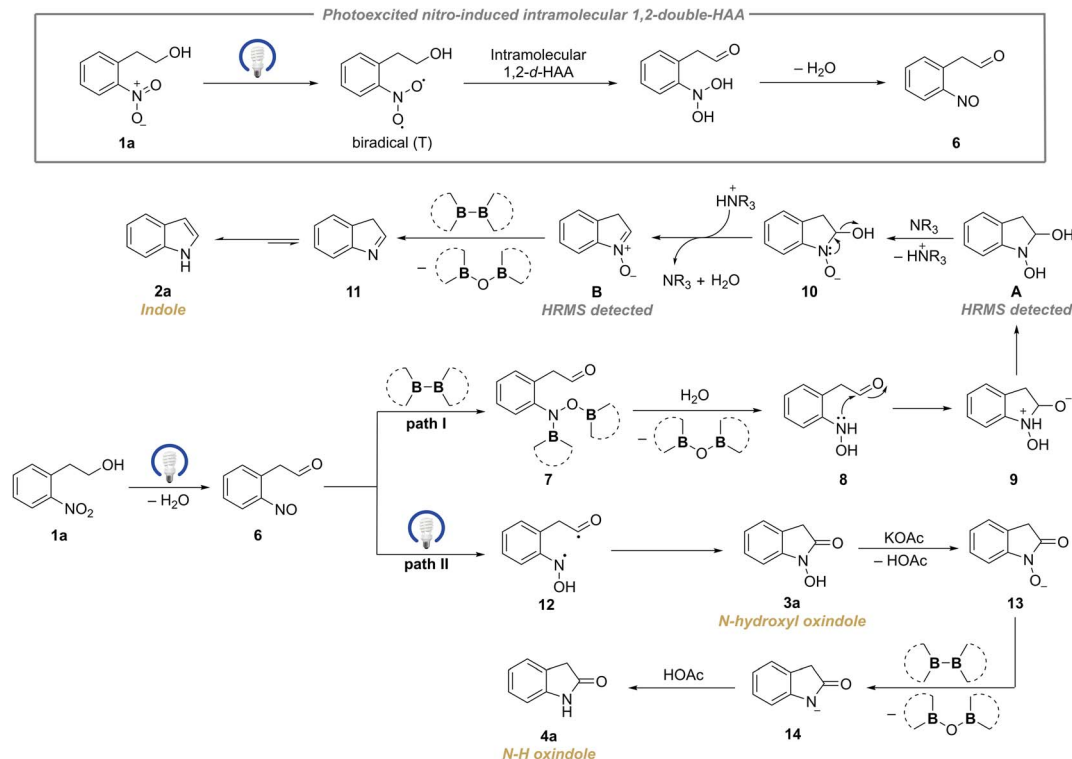
According to the previous reports concerning the reduction of nitroarenes to nitroso compounds,<sup>19,19a,20</sup> we assume that nitroso and carbonyl might be the outcomes of the *d*-HAA process. Therefore, we designed the less fast intermolecular HAA reaction to verify this hypothesis and try to detect the active nitroso species. In doing so, the reductive cyclization of *o*-nitrobenzyl ketone using 2-PrOH as a hydrogen donor was examined. As a result, not only the indole product **2v** was obtained in 85% isolated yield, accompanied by the generation of acetone as detected by GC-MS (Scheme 5B, Fig. S23†), but the nitroso intermediate was also detected in the reaction mixture by HRMS (Scheme 5B, Fig. S22†). Moreover, we also attempted to experimentally detect more possible intermediates involved in the redox-cyclization reaction and we were successful to catch the proposed intermediates **A** and **B**<sup>32</sup> by HRMS analysis (Scheme 5C, Fig. S21†).

To gain more solid data concerning the reaction mechanism, the intermolecular kinetic isotope effect (KIE) experiments were performed by using the reactions of equivalent molar **1a** and the deuterium-labeled substrate [**D**]-**1a** under the standard conditions (Scheme 6 and ESI 5.5†). Two  $k_H/k_D$  values were obtained as  $k_H/k_D = 5.0$  for the *N*-OH oxindole formation, and  $k_H/k_D = 3.8$  for the indole formation. The KIE studies suggest that the homolytic cleavage of the  $\alpha$ -C-H bond is the rate-determining step for the formation of both *N*-OH oxindole and indole, which conforms to the primary kinetic isotope effect (PKIE). The difference of the two KIE values also suggest that the formation



**Scheme 6** Kinetic isotope effect (KIE) experiments.





Scheme 7 Proposed mechanisms for the generation of indoles, N-OH oxindoles and N-H oxindoles.

of *N*-hydroxyl oxindoles may be related to dual homolysis of  $\alpha$ -C-H bonds.<sup>33</sup>

Based on the above mechanistic experiments and previous reports,<sup>19,20,34</sup> the plausible mechanisms were proposed (Scheme 7). If ground-state nitroarene (1a) is exposed to appropriate irradiation, it could be photoexcited to the long-lived triplet state (T), which has a biradical character.<sup>19</sup> Then the active biradical participates in an intramolecular double hydrogen atom abstraction (*d*-HAA) from the adjacent hydroxyalkyl, affording the nitroso intermediate 6 (as illustrated in Scheme 7, top). Thereafter the key species 6 could switch two paths dependent on a diboron reagent. In Path I, the quick diborylation of the nitroso intermediate results in 7 which gives rise to 8 upon hydrolysis.<sup>21</sup> Then intramolecular nucleophilic addition occurs to yield 9, whose subsequent proton transfer would produce species A (detected by HRMS, ESI 5.6<sup>†</sup>). A undergoes sequential deprotonation and dehydration under the catalysis of tertiary amine to deliver 10 and species B (detected by HRMS, ESI 5.6<sup>†</sup>).<sup>32</sup> Next, the *N*-oxide B undergoes the oxygen-transfer process assisted by a diboron reagent to release 11 which undergoes a fast tautomerization to give the indole product 2a. In Path II, the nitroso species 6 could undergo a photoinduced intramolecular 1,6-HAT process to yield 12, which subsequently gives rise to the *N*-OH oxindole 3a via an intramolecular radical coupling. After sequential deprotonation, deoxygenation by a diboron reagent and protonation, 3a delivers the *N*-H oxindole 4a (Scheme 7). Additionally, the mechanisms for the rearrangement reactions of  $\beta$ -cyclohexyl and  $\beta$ -aryl-substituted substrates via 1,3-double hydrogen atom

abstraction (1,3-*d*-HAA) were rationally explained which leads to 2ab–2ae and 3s (ESI 5.8, Fig. S24<sup>†</sup>).

## Conclusions

In conclusion, we developed a metal- and photocatalyst-free toolbox for intramolecular annulation of 2-nitroarylethanol under blue-light irradiation, to deliver a diversity of indoles, *N*-hydroxyl oxindoles and *N*-H oxindoles in good to excellent yields. A notable feature of the strategy is a photoexcited nitro-triggered double hydrogen atom abstraction (*d*-HAA) process, which initiates the intramolecular redox C–N coupling of the nitro unit and the *ortho*-hydroxyalkyl moiety. Using the concept of nitro-triggered *d*-HAA for the synthesis of *N*-heterocycles is novel and unprecedented. This work also demonstrates the practical applications as an efficient methodology in the synthesis of important molecules of indoles and oxindoles. Moreover, abundant nitro-triggered radical chemistry is involved in this protocol. This prompts us to extend the concept to other robust synthetic studies.

## Data availability

The data that support the findings of this study are available in the ESI<sup>†</sup> or on request from the corresponding author.

## Author contributions

B. Wang discovered the reductive cyclization reaction of 1a and guided the synthesis. On this basis, B. Wang and H. Ren



conducted the experiments. B. Wang wrote the draft. H. Ren analysed the experimental data and wrote the ESI.† H. Yan, C. Lu and H.-J. Cao designed this project, directed the study and wrote the manuscript.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

We thank the National Natural Science Foundation of China (21820102004 and 91961104) and the Ministry of Science and Technology (2021YFE0114800). We are also grateful to Prof. Zhuangzhi Shi, Prof. Shaolin Zhu, Prof. Jin Xie and Prof. Shouyun Yu for their helpful suggestions.

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