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C–C bond-forming reactions of ground-state aryl halides under reductive activation

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ABSTRACT

Under basic conditions aryl halides can undergo $S_{RN}1$ reactions, BHAS reactions and benzyne formations. Appropriate complex substrates afford an opportunity to study inherent selectivities. $S_{RN}1$ reactions are usually favoured under photoactivated conditions, but this paper reports their success using ground-state and transition metal-free conditions. In benzene, the enolate salt **12**, derived by deprotonation of diketopiperazine **11**, behaves as an electron donor, and assists the initiation of the reactions, but in DMSO, it is not required. The outcomes are compared and contrasted with a recent photochemical study on similar substrates. A particular difference is the prevalence of hydride shuttle reactions under relatively mild thermal conditions.

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1. Introduction

Ar–C and Ar–heteroatom bond formations have long been key reactions in organic synthesis. Pd salts and related complexes have played an important role in this field, but other metals, notably copper, are central to some of these coupling processes. The 2010 Nobel Prize in Chemistry[1] was awarded to Heck,[2] Negishi[3] and Suzuki[4] for their pioneering studies on the former; whereas the Sonogashira reaction[5] is one of a host of other Ar–C coupling reactions that are now indispensable to organic chemistry. Furthermore, Buchwald's and Hartwig's studies of the synthesis of Ar–heteroatom bonds[6] have become extremely important, adding significantly to the much earlier discovery of the Ullmann synthesis.[7]

Alongside these pioneering reactions, transition metal-free couplings have emerged and are now witnessing spectacular growth.[8–10] With the increasing cost of transition metal catalysts, and the requirement for costly separation and recovery of heavy metals from waste-streams, the attractions of the transition metal-free couplings are clear. We consider below three types of reactions (Scheme 1) that can take place with aryl halides, all of which occur under basic conditions (other types of reaction that occur for restricted classes of aryl iodides, such as S_NAr, are not considered here): (i) the $S_{RN}1$ reactions developed by Bunnett and co-workers.[11] In this case, electron transfer to aryl halide **1** affords an aryl radical **3**, which couples with an anionic nucleophile to form radical anion **4**. This species transfers an electron to another molecule of aryl halide to form another aryl radical **3** and thereby propagates the chain reaction. In doing so, **4** is converted into product **5**. This family of reactions has shown expanded scope in recent years, mirroring the greater mechanistic understanding of the processes.[12–15] It includes both carbon–carbon and carbon–heteroatom bond formations. Rossi has been a pioneer of much of the recent development of the $S_{RN}1$ reaction.[13,14] His studies generally focus on reactions that are conducted under photoactivation conditions.[14]

(ii) benzyne coupling reactions, an area of rapid recent developments.[10,16] Base-induced elimination of hydrogen halide from a halobenzene **1** forms the benzyne **6**, which is attacked by a nucleophile to form aryl anion **7**. On protonation, this affords the product **5**.

(iii) the BHAS (base-promoted homolytic aromatic substitution) reaction.[8,9] Here, an aryl radical **3** adds to an arene; the new radical **8** is deprotonated to form an electron-rich radical anion **9**. Transfer of an electron from this species leads to the biaryl product **10**; the electron is transferred to another molecule of aryl halide **1** to form a new aryl radical **3**, continuing the chain.

For transition metal-free coupling chemistry to advance, complex substrates need to be studied, including those where different

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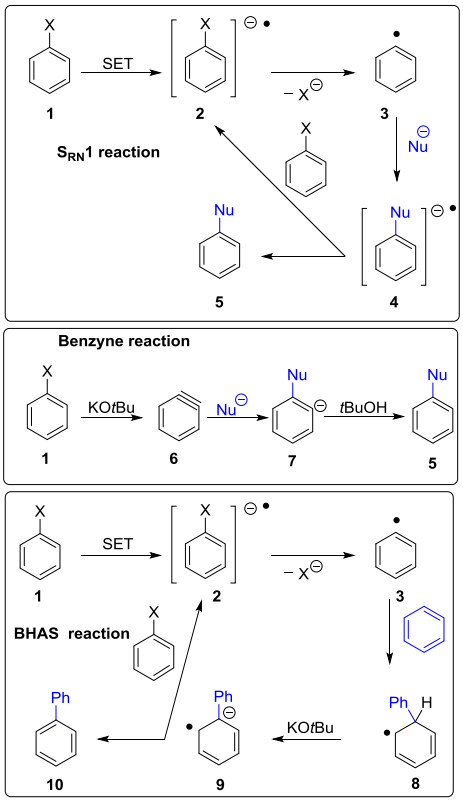
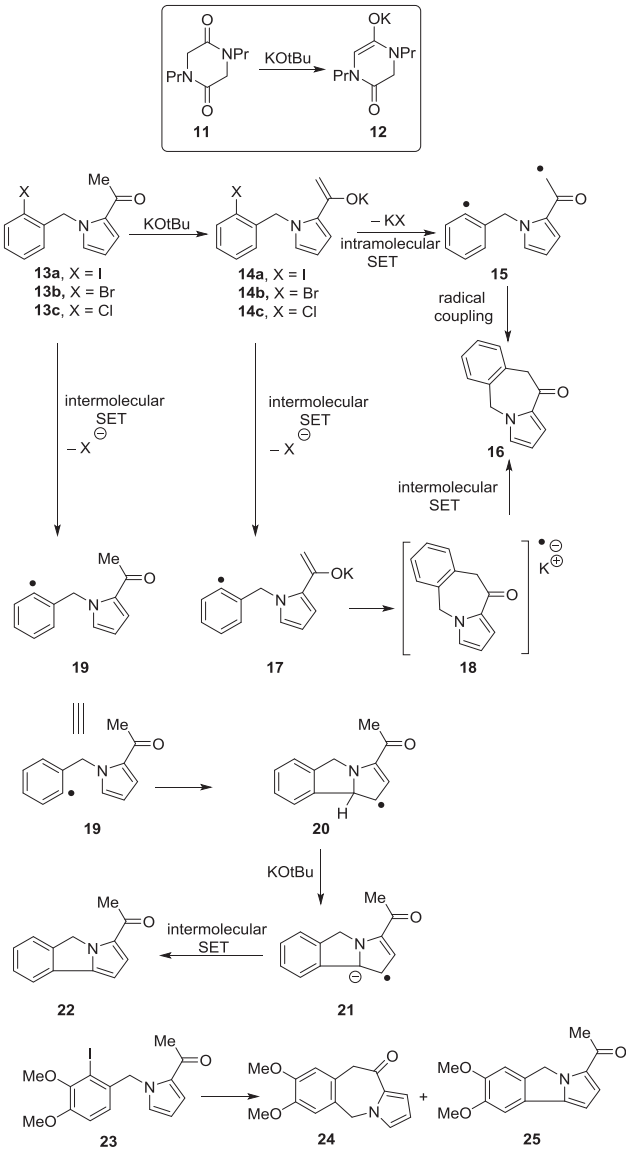


Scheme 1. Transition metal-free routes to formation of Ar–C and Ar–Heteroatom bond.

types of coupling reactions are in competition. Rossi and co-workers have conducted a recent study where aryl radicals have more than one option from the classes of reactions listed above.[13] The studies were conducted (i) under transition metal-free photoactivation conditions, or (ii) without photoactivation but in the presence of iron (II) salts and pinacolone. Our interest in coupling reactions that are conducted in the ground-state and under transition metal-free conditions attracted us to this area. We recently studied BHAS coupling reactions of arenes with aryl halides under more routine thermal conditions and using organic electron donors to initiate the reaction of the aryl halides.[9i,9m,9s,17] In this paper, we now report on a series of competing reactions for a selection of substrates that are carried out under thermal reaction conditions.

2. Results and discussion

Recent reports of BHAS coupling reactions use KO*t*Bu together with one of a wide variety of organic additives, to facilitate coupling of haloarenes with arenes under transition metal-free conditions.[8,9] We have previously shown that one of the most successful additives at initiating the BHAS pathway was *N*,*N*′-dipropyldiketopiperazine (DKP) **11**.[9m,9s] The enolate anion, **12**, derived by deprotonation of DKP **11** (Scheme 2), acts as an electron donor to the aryl halides in the initiation step. Most reactions reported in the literature that proceed via the BHAS mechanism are performed using benzene as the solvent, since benzene is the coupling partner in these reactions. In the few examples where aryl radicals couple to enolate anions via the $S_{RN}1$ pathway, the solvents used are DMSO or liquid ammonia or DMF.[14a,15] Given that the polarity of the medium is expected to play an important role in facilitating electron transfer reactions, the reaction outcomes in both benzene and DMSO were investigated and the results are compared throughout our studies.



Scheme 2. Potential reaction pathways involved in formation of **16**, **22**, **24** and **25**.

Our initial studies exposed substrates **13a**–**c** to these transition metal-free reaction conditions (Table 1). When **13a** was stirred at 120 °C for 1 h in the presence of KO*t*Bu and DKP **11**, and in either anhydrous benzene or anhydrous DMSO, two products were isolated. The major product in both benzene and DMSO was 5H-benzo[e]-pyrrolo[1,2-a]azepin-11(10H)-one **16**, which was isolated in 55% and 79% yields, respectively, and the minor product isolated was 3-acetyl-5H-pyrrolo[2,1-a]isoindole **22** in yields of 7% and 10%, respectively [Table 1: entries 1 and 2]. These products were isolated in yields that compared favourably to previous experiments under light irradiation or when iron salts were used as a catalyst [Table 1: entries *lit 1* and *lit 2*], and with the same preference for the formation of **16** as major product.[13] Blank reactions were performed without the DKP additive **11**, to observe how the enolate anion of DKP, **12**, influences the yields of the reaction. We note that the choice of solvent has a dramatic effect on the yields. A blank reaction in benzene, without the DKP additive **11**, afforded much lower yields of **16** compared to when DKP was present [Table 1: entry 3]. However, a blank reaction in DMSO showed the opposite trend, and **16** was achieved with higher yields of 90% when the DKP additive was omitted [Table 1: entry 4]. The difference in DMSO

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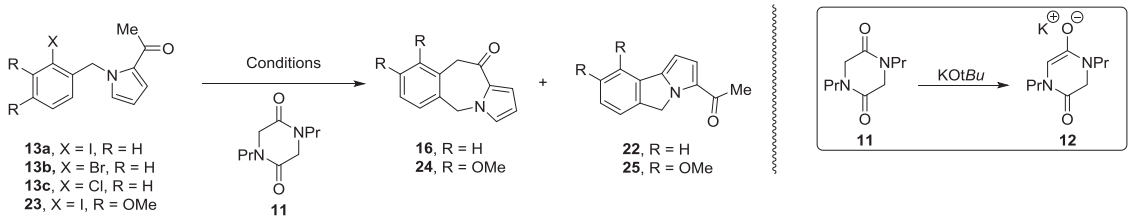
Table 1
Thermally activated Electron Transfer Reactions of 1-(2-halobenzyl)-2- acetylpyrrole **13a**–**c** and 1-(2-Iodo-3,4-dimethoxybenzyl)-2-acetylpyrrole **23**



13a, X = I, R = H
13b, X = Br, R = H
13c, X = Cl, R = H
23, X = I, R = OMe

Entry number	Substrate (0.5 mmol, 1 equiv)	Additive (eq.)	Base (3 equiv) unless stated	Solvent	Conditions	Product (%)
lit1 [Ref. 13]	**13a**	—	KO*t*Bu (2 equiv)	$NH_3(l)$	*hv*, 2 h, −78 °C	**16** (38)
lit2 [Ref. 13]	**13a**	$FeCl_2$ (0.5)+Pinacolone (3)	KO*t*Bu (5 equiv)	DMSO	4.5 h, RT	**16** (84), **22** (11)
1	**13a**	**11** (0.1)	KO*t*Bu	PhH	1 h, 120 °C	**16** (55), **22** (7)
2	**13a**	**11** (0.1)	KO*t*Bu	DMSO	1 h, 120 °C	**16** (79), **22** (10)
3	**13a**	—	KO*t*Bu	PhH	1 h, 120 °C	**13a** (73),**16** (23), **22** (0)
4	**13a**	—	KO*t*Bu	DMSO	1 h, 120 °C	**16** (90), **22** (8)
5	**13a**	**11** (0.1)	KO*t*Bu	PhH	24 h, RT	No reaction
6	**13a**	**11** (0.1)	KO*t*Bu	DMSO	24 h, RT	**13a** (3), **16** (76), **22** (10)
7	**13a**	—	KO*t*Bu	DMSO	24 h, RT	**13a** (19), **16** (60), **22** (12)
8[a]	**13a**	—	KO*t*Bu	DMSO	24 h, RT	**13a** (13), **16** (70), **22** (10)
9	**13a**	—	LDA (1.2 equiv)	DMSO	1 h, 120 °C	**13a** (50), **22** (12)
10	**13b**	**11** (0.1)	KO*t*Bu (2 equiv)	PhH	1 h, 120 °C	No reaction
11	**13b**	**11** (0.1)	KO*t*Bu	DMSO	1 h, 120 °C	**16** (25)
12	**13b**	**11** (0.1)	KO*t*Bu (5 equiv)	PhH	16 h, 160 °C	**16** (30)
13	**13c**	**11** (0.1)	KO*t*Bu	DMSO	1 h, 120 °C	**16** (20)
14	**13c**	**11** (0.1)	KO*t*Bu	PhH	16 h, 160 °C	**16** (24)
15	**23**	**11** (0.1)	KO*t*Bu	DMSO	1 h, 120 °C	**24** (33), **25** (29)
16	**23**	—	KO*t*Bu	DMSO	1 h, 120 °C	**24** (17), **25** (12)

[a] Reaction was performed in the dark.

may not be due purely to polarity effects, as evidence mounts of the dimsyl anion as an electron donor.[18]

When using DMSO as a solvent (but not benzene—see Table 1: entry 5) the reactions could be achieved at lower temperatures. When the reaction was performed at room temperature (RT) in DMSO moderate to high yields of cyclized products were isolated both with and without the DKP **11** additive, respectively [Table 1: entries 6 and 7]. A reaction that was conducted in the dark provided confirmation that these reactions proceed via a ground-state SET pathway, with yields matching those carried out in the presence of ambient light [Table 1: entry 8]. So, even at RT, photochemical assistance is not needed for these $S_{RN}1$ reactions. When LDA was used as the base in the reaction, only the product **22** was isolated in low yields; the yield of **22** was comparable with the yield of **22** obtained in the presence of KO*t*Bu [Table 1: entry 9]. To test the effect of the halogen substituent, the substrates **13b**,**c** were also treated under transition metal-free reaction conditions. When **13b** was stirred at 120 °C for 1 h in the presence of KO*t*Bu and DKP **11**, in anhydrous benzene, **13b** did not react [Table 1: entry 10]. However under the same conditions in DMSO solvent, both **13b** and **13c** afforded **16** in low yields [Table 1: entries 11 and 13]. When either **13b** or **13c** was reacted under harsher reaction conditions, stirred at 160 °C for 16 h in the presence of KO*t*Bu and DKP **11**, in anhydrous benzene, the product **16** was achieved in low yield [Table 1: entries 12 and 14]. Finally the substrate **23** was treated with KO*t*Bu and DMSO, and stirred at 120 °C for 1 h, in the presence of DKP **11**, and afforded the products **24** and **25** in moderate yields [Table 1: entry 15]. In the absence of DKP under the same conditions, **23** yielded lower yields of **24** and **25** [Table 1: entry 16].

The proposed mechanism involves initial deprotonation of the substrates and additives by KOtBu (Scheme 2). Under the basic conditions, **13a**–**c** will exist in part as enolate **14a**–**c**, and similarly the DKP additive **11** will be partly converted to its enolate anion **12**. The enolate anion **12** acts as an electron donor, and will intermolecularly donate a single electron to **14a**–**c** to afford the aryl radical **17**. The aryl radical formed could undergo intramolecular cyclisation onto the enolate anion to form the seven-membered cyclic radical anion **18**. This radical anion **18** is electron-rich and can propagate the radical chain mechanism by donating an electron, to either **14a**–**c** or **13a**–**c**, and thus yield the seven-membered cyclic product **16**. The formation of the minor by-product **22** likely arises when an electron is donated intermolecularly to the substrate **13a**–**c**. SET (single electron transfer) to **13a**–**c** forms the aryl radical **19** which cyclises onto the pyrrole ring to form the intermediate radical **20**. Deprotonation of **20** affords the radical anion **21** and, after the transfer of an electron, the product **22** is formed (Scheme 2).

It was demonstrated that in DMSO, and to a slight extent in benzene, the substrate **13a** cyclises in the absence of the DKP additive **11** (Table 1: entries 3 and 4). The enolate anion of DKP is proposed to act as the electron donor, but the substrate also forms an electron-rich enolate species, **14a**, in the presence of KO*t*Bu. The relative effectiveness of the two potential electron donors, in this case the enolate anion of DKP **12** or the enolate anion present within **14a**, is often an important aspect in $S_{RN}1$ chemistry. Although two enolates are present, they are not necessarily of equal strength as electron donors. $S_{RN}1$ reactions are frequently dependent on traces of a more active electron donor (here **12**) to initiate the radical chain—this is known as 'entrainment'.[11,13,14,19] In non-polar solvents like benzene, where electron transfer from neutral species to form charged species is not facilitated, a stronger donor like **12** can play a powerful role in assisting the initiation of the chains. Polar solvents, like DMSO, favour SET reactions in which charged species are formed from neutral starting materials, and so, donors like **12** are not needed to initiate the reaction.[18] If the enolate anion within **14a**–**c** donated an electron intramolecularly to the LUMO in the haloaryl moiety, the diradical **15** would form upon the loss of an iodide anion. The diradical **15** would undergo radical coupling in the cyclisation to form product **16**. This route does not involve a radical chain.

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When substrate **13a** was treated with LDA, the lithium enolate salt analogous to **14a** formed. Based on the experiments above with KOtBu as base, the expected product was **16**. However only **22** and unreacted **13a** were observed. In this case, we expect full deprotonation of the substrate and hence a different rationalization than above for formation of **22**. Its formation may suggest that the tightly bound lithium enolate anions are less effective electron donors than the corresponding potassium enolates (differences between potassium salts and salts of lower alkali metals are pronounced in BHAS and other coupling reactions.[15,9v]) Intramolecular electron transfer from the lithium analogue of **14a** would have produced the (metal-free) diradical **15** that should behave as described above. Intermolecular electron transfer would create the lithium analogue of radical **17**; here, coupling of the aryl radical to the lithium enolate must again be harder than for the potassium enolate, whether for conformational or electronic reasons, so that coupling to the pyrrole occurs, finally on workup forming **22**.

The substrate **23** should follow the same type of mechanism as **13a**–**c** (Scheme 2) in the formation of products **24** and **25**. This substrate was important for mechanistic reasons. Our previous studies had shown that coupling of haloarenes to arenes can be initiated through formation of benzynes.[9i,9m] Since this substrate cannot form a benzyne, it confirms that the current transformations are not dependent on a benzyne route. Compared to the cyclisation of **13a**, lower yields of products were achieved in the cyclisation of **23**. The low yields may reflect the increased steric hindrance around the aryl radical that would arise from the methoxy substituents on the benzene ring.[9m] Alternatively, electron-rich substrate **23** should also have a higher LUMO, hence the initiation by electron transfer to the haloarene would be harder, and require more energy.

Table 2 illustrates the powerful effects that solvent and temperature can have on the reaction pathways that are followed. Substrates **26a**,**b** were synthesized and reacted under various conditions in the presence of KO*t*Bu and with either DMSO or benzene as the solvent.

Surprisingly, when **26a** was exposed to the thermal electron transfer conditions in DMSO, a completely different product, **30**, was isolated in moderate yield [Table 2: entry 2]. The product structure was confirmed by X-ray crystallography (Fig. 1). The formation of **30** also occurs in similar yields in the absence of the additive **11** [Table 2: entry 3]. When **26b** was subjected to similar reaction conditions, product **30** was isolated in lower yields, showing that changing the halogen to Br adversely affects the yield [Table 2: entry 4]. The reaction of **26a** in DMSO [Table 2: entry 5] at RT generated a mixture of products, **27**, **29** and **30** in low yields and a new product identified as **42** was obtained in moderate yields. Product **42** was only seen at RT, but its desaturation product, **30**, was seen at higher temperature [Table 2: entry 2]. When substrate **29**, which is the non-halogenated analogue of **26a**,**b** was subjected to the reaction conditions in DMSO, the starting material was recovered [Table 2: compare entries 7 and 5]. This substrate was used to provide added information about the mechanism of formation of products from **26a** (Scheme 3). Particularly interesting is the fact that by isolating pure **29** and subjecting it to these reaction conditions, this does not lead to isolation or detection of **30** or **42**, implying a role for the halogen of **26a**,**b** in the reactions of these substrates.

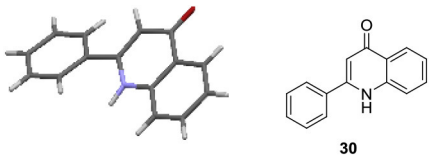
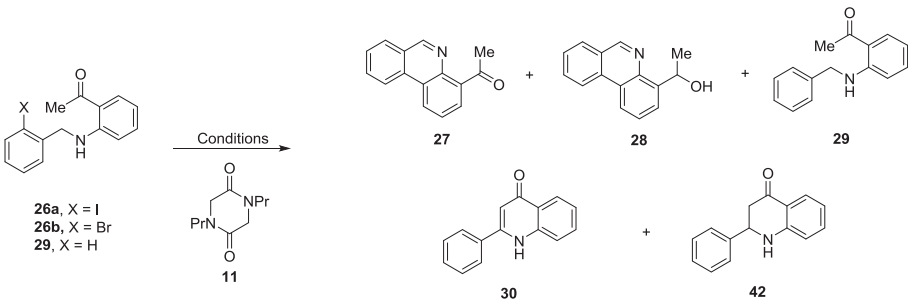


Fig. 1. The X-ray crystal structure of 2-phenylquinolin-4(1H)-one **30**.

In these reactions, we recognize that either deprotonation of **26a**,**b** of the N-H or of the C-H of the ketone can occur to form the enolate; in addition, an equilibrium is likely to exist between the

Table 2
Thermally activated electron transfer reactions of **26a,b** and the non-halogenated analogue **29**

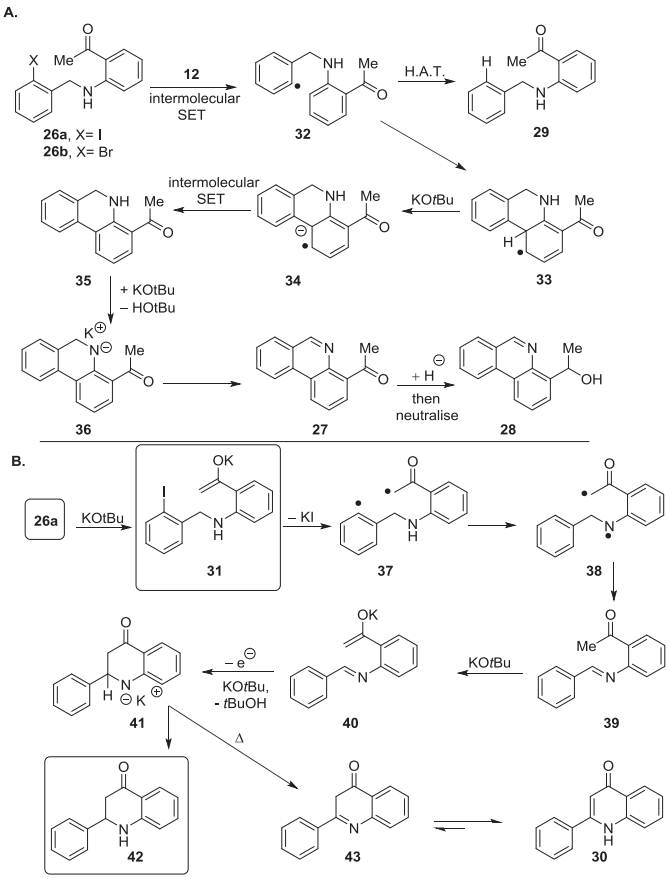


Entry number	Substrate (0.5 mmol, 1 equiv)	Additive (0.1 equiv)	Base (3 equiv) unless stated	Solvent	Conditions	Product (%)
lit3 [Ref. 13]	**26a**		KO*t*Bu	$NH_{3(l)}$	*hv*, 2 h, −78 °C	**27** (51)
1	**26a**	**11**	KO*t*Bu	PhH	1.5 h, 120 °C	**27** (10), **28** (21), **29** (8)
2	**26a**	**11**	KO*t*Bu	DMSO	1 h, 120 °C	**28** (trace), **30** (52)
3	**26a**	—	KO*t*Bu	DMSO	1 h, 120 °C	**30** (49)
4	**26b**	**11**	KO*t*Bu	DMSO	16 h, 120 °C	**30** (31)
5	**26a**	**11**	KO*t*Bu	DMSO	24 h, RT	**27** (14), **29** (16), **30** (23), **42** (42)
6	**29**	—	KO*t*Bu	PhH	1 h, 120 °C	No reaction
7	**29**	**11**	KO*t*Bu	DMSO	24 h, RT	No reaction

Under the thermal activation conditions in benzene solvent, **26a** afforded three products in low yields: the 6-membered cyclised product, 4-acetylphenanthridine, **27**, its dihydro derivative, **28** and the deiodinated but uncyclised product **29** [Table 2: entry 1].

This differed markedly from the photoactivated conditions,[13] which afforded solely **27** in moderate yields [Table 2: entry *lit3*].

neutral and deprotonated forms. Scheme 3A proposes a possible route for the formation of **27**, starting with an electron transfer from the DKP enolate **12** to **26a**,**b**. The resulting aryl radical, **32**, cyclises onto the neighbouring aryl ring via the BHAS mechanism and generates the intermediate **33**. The rate of cyclisation of radical **32** must be competitive with hydrogen atom transfer (H.A.T.); the

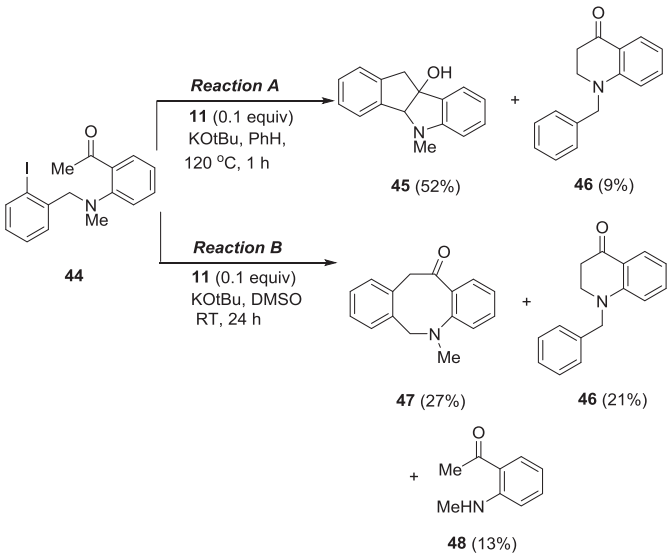


Scheme 3. The proposed reaction pathways of substrate **26**.

hydrogen abstraction will quench **32** to generate the observed product **29**. Deprotonation of **33** yields the radical anion **34**, which will form **35**, by donating an electron to the starting substrate **26a**, which goes on to propagate the radical chain. Deprotonation of the N–H proton of **35**, followed by hydride loss forms the product **27**, which was the only product reported under photoactivation.[13] Hydride loss has been observed from alkoxides under the conditions of the coupling reactions;[9m] in this case, the aromaticity of the nitrogen-containing ring in the product **27** provides additional driving force. The proposal that a hydride is eliminated from **36** to form **27** is supported by the isolation of **28**; this compound can form when **27** behaves as the hydride acceptor for another molecule of **36**.

When the reaction is performed in DMSO, the major product is either **30** or **42**, depending on the temperature of the reaction. It is proposed that in DMSO the substrate **26a** will be present to some extent in its enolate anionic form, **31** (Scheme 3B). Since the isolated yields of **30** were similar both with and without the DKP additive **11**, we proposed that this enolate anion **31** is capable of undergoing intramolecular SET, whereby an electron is donated from the enolate anion moiety to its haloaryl moiety. This would yield the diradical species **37**. An 8-membered ring could form by the combination of the radicals, however it appears that this process must be slower than an alternative process. One possibility is that a [1,4]-hydrogen atom transfer by the aryl radical would form intermediate **38**.[20] Instead of radical combination between the two electrophilic species in **38**, hydrogen atom transfer occurs to form a conjugated imine **39**. In the presence of KOtBu the enolate anion formation will occur to give **40**, 6-*endo*-cyclisation would afford salt **41**, which would yield **42** by proton transfer either during the reaction or on work up. On the other hand, exposure of **41** to heat could lead to loss of hydride, consistent with the conversion of **36** to **27** discussed earlier, and leads to **43**. Tautomerism would then afford **30**. In addition, trace amounts of **28** were also observed in DMSO, which proceeds via the same mechanism as proposed above (Scheme 3A). Recently, Long et al. published an alternative synthesis of analogues of **30** using TEMPO and KO*t*Bu in DMSO, but our route must occur by a different mechanism.[21]

The final substrate tested was substrate **44** (Scheme 4), which is analogous to **26a** except that the nitrogen of the tether is methylated to favour selective deprotonation to form the enolate anion. Under UV irradiation conditions, this substrate led, in Rossi's hands, to the formation of the 8-membered ring **47** (78%), in preference to a 6-membered cyclisation, that would have been analogous to that seen in the formation of **27** from **26a**. We wanted to probe the effect of this methylation under our ground-state conditions.



Scheme 4. The reaction conditions and products arising from SET to substrate **44**.

When **44** was treated with KO*t*Bu and **11** in benzene at 120 °C, tetracycle **45** was isolated as a novel compound, the structure of which was confirmed using X-ray single crystal structure determination (Fig. 2), and additionally **46** was isolated in low yield [Scheme 4: reaction A]. However when the reaction was performed in DMSO at RT, this tetracycle **45** was not observed [Scheme 4: reaction B]. The products isolated were **46**, similar to when the reaction was performed in benzene, **47** (which was the only product observed when the reaction was performed using photoirradiation[13]) and **48**.

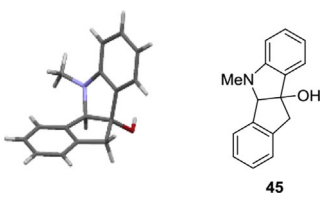
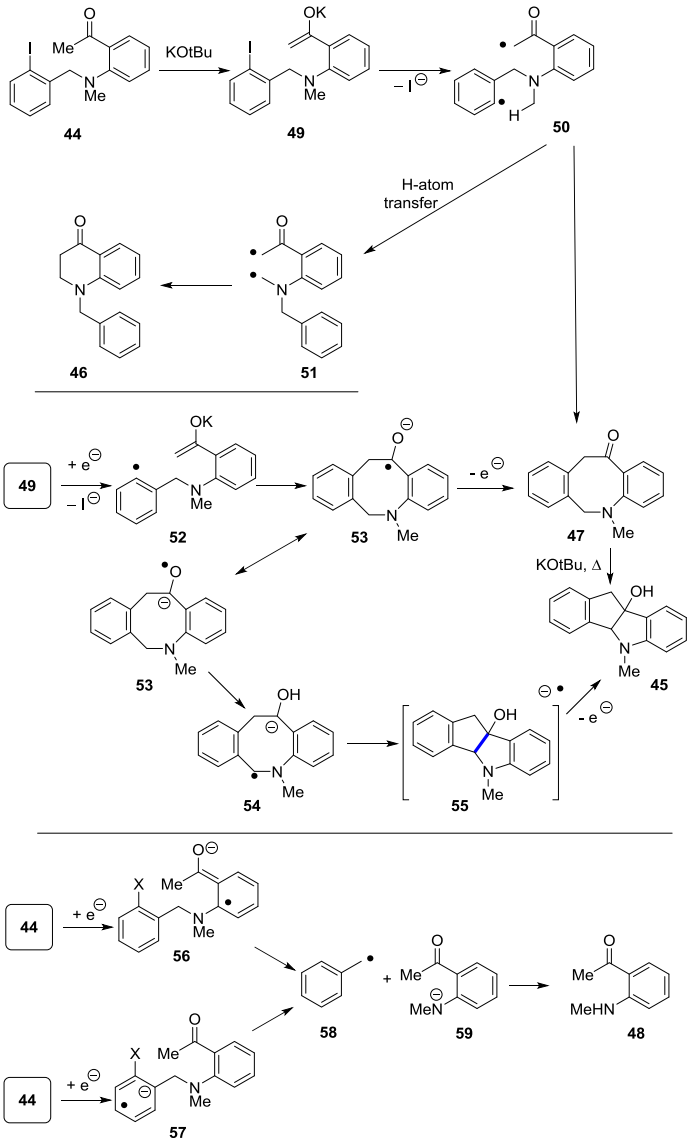


Fig. 2. The X-ray crystal structure of the (4b*R*,9b*S*)-5-methyl-4b,10-dihydro-indeno [1,2-b]indol-9b(5H)-ol **45**.

Possible mechanisms for forming the products are shown in Scheme 5. Electron transfer within enolate **49** affords the diradical

50. This diradical could directly close to form the 8-membered ring in **47**. Alternatively, hydrogen atom transfer through a favoured 6-centred transition state would give diradical **51**, that cyclises rapidly to form ketone **46**. Of course, more than one mechanistic pathway may have relevance. Intermolecular electron transfer to enolate **49** would yield radical anion **52**. Coupling of the radical to the anion would give **53**, which could transfer an electron (to another molecule of **44**) to give product **47**.



Scheme 5. The proposed reaction pathways of substrate **44**.

Two possible routes are shown (and one of them is discussed below) for the formation of tetracycle **45**. We took purified **47** and converted this to **45** in the presence of KO*t*Bu. The 5-membered ring product **45** was not observed in DMSO at room temperature, which suggests that the application of heat is required to convert the 8-membered product **47** to the cyclic product **45** (Scheme 5).

Formation of **48** was not observed in the photochemical study. This compound can arise by cleavage of the bond between the benzylic N and the benzylic C atoms. This cleavage can be triggered from the radical anions **56** and/or **57**, which can form by electron transfer to either of the arene rings of **44**. (The radical anions **56** and **57** are shown, where substituent X=I or H; in our experience, deiodination of arenes is an easier reaction than cleavage of benzylic C–N bonds, and so we suspect that deiodination to X=H occurs first). Such reactions have recently been observed using powerful organic electron donors,[22] but this is the first observation of such reactions under KO*t*Bu-facilitated coupling conditions.

3. Conclusion

In conclusion, the present work reports the results of our studies on thermally initiated reactions of various substrates using the additive DKP **11** and KO*t*Bu, in DMSO or benzene. Entrainment with enolate **12** is of benefit in the less polar benzene solvent, but generally not so in the more polar DMSO. Although $S_{RN}1$ reactions are normally conducted under photochemical activation, the substrates represented here show that activation also occurs efficiently when ground-state conditions are used.[15]

4. Experimental section

The electron transfer reactions were carried out within a glove box (Innovative Technology Inc., U.S.A.) under nitrogen atmosphere, and performed in oven-dried or flame-dried apparatus. All the reagents were obtained from commercial suppliers and used without further purification unless stated otherwise. A Büchi rotary evaporator was used to concentrate the reaction mixtures. Column chromatography was performed using Prolabo 35–70 μm particle size silica gel 60 (200–400 mesh). Thin Layer Chromatography (TLC) was performed using Merck silica gel 60 F_{254} pre-coated aluminium plates. Visualisation was achieved under UVP mineralight UVG-11 lamp and by using methanolic vanillin or phosphomolybdic acid to develop them. Melting points were determined using a GallenKamp 'Griffen Melting Point Apparatus'. ^{1}H NMR spectra were obtained at 400 MHz (Bruker AV400) or 500 MHz (Bruker AV500) and ^{13}C NMR spectra were obtained at 100 MHz (Bruker AV400) or 125 MHz (Bruker AV500) using broadband decoupled mode. Spectra were recorded in either deuterated chloroform ($CDCl_3$) or deuterated dimethyl sulfoxide (DMSO-d_6), depending on the solubility of the compounds. Chemical shifts are reported in parts per million (ppm) calibrated on the residual non-deuterated solvent signal, and the coupling constants, *J*, are reported in Hertz (Hz). The peak multiplicities are denoted using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; sx, sextet; m, multiplet; br s, broad singlet; dd, doublet of doublets; td, triplet of doublets. GC–MS data were recorded using an Agilent Technologies 7890A GC system coupled to a 5975C inert XL EI/CI MSD detector. Separation was performed using the DB5MS-UI column (30 m×0.25 mm×0.25 μm) at a temperature of 320 °C, using helium as the carrier gas. Positive Chemical Ionisation (PCI^+) was used with methane as the ionization gas and a voltage of 952.941 V. High-resolution mass spectrometry (HRMS) was performed at the University of Wales, Swansea, in the EPSRC National Mass Spectrometry Centre. Accurate mass was obtained using nanospray ionization (NSI) or atmospheric pressure chemical ionisation (APCI) with a LTQ Orbitrap XL mass spectrometer. Infra-Red spectra were recorded using Shimadzu FTIR Spectrophotometer (Model IRAffinity-1) with a MIRacle Single Reflection Horizontal ATR Accessory.

4.1. Experimental procedures and characterisation of substrates

4.1.1. 1,4-Dipropylpiperazine-2,5-dione ***11***.[9m] In a round-bottomed flask with anhydrous dichloromethane (30 mL) under argon at

0 °C, chloroacetyl chloride (4 mL, 50 mmol) and propylamine (8.64 mL, 105 mmol, 2.1 equiv) were simultaneously added dropwise, and the reaction mixture was stirred at 0 °C for 15 min. The reaction mixture was diluted with diethyl ether (200 mL) and a solid precipitated out of solution. The reaction mixture was filtered and the solid was washed with diethyl ether. The filtered solution was concentrated in vacuo and again diluted with diethyl ether (200 mL) and filtered. The filtered solution was concentrated in vacuo to yield the crude product 2-chloro-*N*-propylacetamide (6.72 g, 99%) as a pale yellow oil which was used without further purification. In a round-bottomed flask, 2-chloro-*N*-propylacetamide (6.604 g, 48.7 mmol) was diluted with anhydrous tetrahydrofuran (30 mL). At 0 °C, a suspension of sodium hydride in mineral oil (60%, 1.95 g, 48.7 mmol, 1 equiv) in anhydrous tetrahydrofuran (20 mL) was added dropwise to the reaction mixture via cannula. The reaction mixture was stirred at 0 °C for 10 min, then at RT for 3.5 h. The reaction mixture was quenched by dropwise addition of water and diluted with diethyl ether (150 mL). The reaction mixture was dried over anhydrous sodium sulfate. The filtered solution was concentrated in vacuo and purified by column chromatography (30%–100% ethyl acetate in petroleum ether) to yield 1,4-dipropylpiperazine-2,5-dione **11** (0.696 g, 14%) as pale yellow crystals, and recovered 2-chloro-*N*-propylacetamide (3.26 g, 49%).

Compound **11**: mp 54–59 °C; [Found: (ESI$^+$) 199.1438. $C_{10}H_{19}N_2O_2^+$ $(M+H)^+$ requires 199.1438]; ν_{max}(film)/cm^{-1} 2964, 2932, 2872, 1647, 1483, 1335, 1308, 1277, 1204, 1055; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92–0.95 (6H, m, 2×C*H*$_3$), 1.56–1.62 (4H, m, 2×C*H*$_2$), 3.37 (4H, t, *J*=7.5 Hz, 2×C*H*$_2$), 3.96 (4H, s, C*H*$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.3 (CH_3), 20.0 (CH_2), 47.7 (CH_2), 50.0 (CH_2), 163.7 (C); *m/z* (ESI$^+$) 199.1438 (MH^+, 100%).

4.1.2. 1-(1-(2-Iodobenzyl)-1H-pyrrol-2-yl)ethan-1-one ***13a***. In an oven-dried round-bottomed flask, (2-iodophenyl)methanol (8.2 g, 35 mmol) was dissolved in anhydrous dichloromethane (60 mL). At 0 °C, PBr_3 (1.32 mL, 14 mmol, 0.4 equiv) was added slowly into the reaction flask, and the reaction mixture was stirred at 0 °C for 30 min, then at RT overnight. The reaction mixture was quenched with water (20 mL) and extracted with dichloromethane (3×20 mL). The combined organic phases were washed with water (2×50 mL), brine (50 mL) and dried over anhydrous sodium sulfate. The filtered solution was concentrated in vacuo to yield the crude product 1-(bromomethyl)-2-iodobenzene (9.37 g, 90%) as white crystals, which was used without further purification. In an oven-dried three-necked flask equipped with condenser, sodium hydride in mineral oil (60%, 0.720 g, 18 mmol, 1.2 equiv) was suspended in anhydrous DMF (5 mL). At 0 °C, a solution of 1-(1H-pyrrol-2-yl)ethan-1-one (1.64 g, 15 mmol) in anhydrous DMF (10 mL) was added slowly into the reaction mixture, which was stirred at 0 °C for 5 min, then at RT for 1 h. A solution of 1-(bromomethyl)-2-iodobenzene (5.12 g, 17.25 mmol, 1.15 equiv) in anhydrous DMF (10 mL) was added dropwise to the reaction mixture, which was stirred at 60 °C overnight. The reaction mixture was cooled to RT, quenched dropwise with water (80 mL) and extracted with ethyl acetate (3×50 mL). The combined organic phases were washed with water (2×100 mL), brine (50 mL) and dried over anhydrous sodium sulfate. The filtered solution was concentrated in vacuo and purified by column chromatography (0%–10% diethyl ether in petroleum ether) to yield 1-(1-(2-iodobenzyl)-1H-pyrrol-2-yl)ethan-1-one **13a** (3.90 g, 80%) as off-white crystals; mp 99–100 °C (lit.[13]: 100.3–101.5 °C); [Found: (HRMS-ESI$^+$) 326.0034. $C_{13}H_{13}INO^+$ $(M+H)^+$ requires 326.0042]; ν_{max}(film)/cm^{-1} 3109, 2359, 2342, 1634, 1533, 1468, 1433, 1397, 1331, 1252, 1094, 1011, 947, 752, 743, 720; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43 (3H, s, C*H*$_3$), 5.57 (2H, s, C*H*$_2$), 6.22–6.24 (1H, m, Ar*H*), 6.47 (1H, dt, *J*=8, 0.8 Hz, Ar*H*), 6.84–6.85 (1H, m, Ar*H*), 6.92–6.96 (1H, m, Ar*H*), 7.05 (1H, dd, *J*=4.0, 1.6 Hz, Ar*H*), 7.21 (1H, t, *J*=7.6, 1.2 Hz, Ar*H*), 7.84 (1H, d, *J*=8.0, 1.2 Hz, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.3 (CH_3), 57.9 (CH_2), 97.6 (C), 109.0 (CH), 120.4 (CH), 127.3 (CH), 128.7 (CH), 129.1 (CH), 130.5 (CH), 130.7 (C), 139.5 (CH), 140.9 (C), 188.5 (C). The spectral data of **13a** were consistent with the literature data.[13]

4.1.3. 1-(1-(2-Bromobenzyl)-1H-pyrrol-2-yl)ethan-1-one ***13b***. In an oven-dried three-necked flask equipped with condenser, sodium hydride in mineral oil (60%, 0.240 g, 6 mmol, 1.2 equiv) was suspended in anhydrous DMF (5 mL). At 0 °C, a solution of 1-(1H-pyrrol-2-yl)ethan-1-one (0.546 g, 5 mmol) in anhydrous DMF (5 mL) was added slowly into the reaction flask, which was stirred at 0 °C for 5 min, then at RT for 1 h. A solution of 1-(bromomethyl)-2-bromobenzene (1.44 g, 5.75 mmol, 1.15 equiv) in anhydrous DMF (5 mL) was added dropwise to the reaction mixture, which was stirred at 60 °C overnight. The reaction mixture was cooled to RT, quenched dropwise with water (60 mL) and extracted with ethyl acetate (3×40 mL). The combined organic phases were washed with water (20 mL), brine (20 mL) and dried over anhydrous sodium sulfate. The filtered solution was concentrated in vacuo and purified by column chromatography (0%–5% diethyl ether in petroleum ether) to yield 1-(1-(2-bromobenzyl)-1H-pyrrol-2-yl) ethan-1-one **13b** (1.20 g, 86%) as pale-yellow crystals; mp 90–91 °C (lit.[13]: 80–81 °C); [Found: (HRMS-ESI$^+$) 278.0176. $C_{13}H_{13}^{79}BrNO^+$ $(M+H)^+$ requires 278.0175]; ν_{max}(film)/cm^{-1} 1651, 1528, 1470, 1439, 1422, 1398, 1356, 1325, 1244, 1086, 1024, 943, 758, 741, 677; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43 (3H, s, C*H*$_3$), 5.65 (2H, s, C*H*$_2$), 6.22–6.24 (1H, m, Ar*H*), 6.52–6.54 (1H, m, Ar*H*), 6.88–6.89 (1H, m, Ar*H*), 7.04–7.06 (1H, m, Ar*H*), 7.09–7.13 (1H, m, Ar*H*), 7.15–7.19 (1H, m, Ar*H*), 7.56 (1H, dd, *J*=7.6, 1.2 Hz, Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.4 (CH_3), 53.0 (CH_2), 108.9 (CH), 120.4 (CH), 122.5 (C), 127.9 (2×CH), 128.9 (CH), 130.6 (CH), 130.7 (C), 132.8 (CH), 138.0 (C), 188.5 (C); *m/z* (ESI$^+$) 280.0153 (MH^+, Br^{81}, 100%), 278.0176 (MH^+, Br^{79}, 100). The spectral data of **13b** were consistent with the literature data.[13]

4.1.4. 1-(1-(2-Chlorobenzyl)-1H-pyrrol-2-yl)ethan-1-one ***13c***. In an oven-dried three-necked flask equipped with condenser, sodium hydride in mineral oil (60%, 0.240 g, 6 mmol, 1.2 equiv) was suspended in anhydrous DMF (5 mL). At 0 °C, a solution of 1-(1H-pyrrol-2-yl)ethan-1-one (0.546 g, 5 mmol) in anhydrous DMF (5 mL) was added slowly into the reaction flask, which was stirred at 0 °C for 10 min, then at RT for 1 h. A solution of 1-(bromomethyl)-2-chorobenzene (0.75 mL, 5.75 mmol, 1.15 equiv) in anhydrous DMF (5 mL) was added dropwise to the reaction mixture, which was stirred at 60 °C overnight. The reaction mixture was cooled to RT, quenched dropwise with water (40 mL) and extracted with ethyl acetate (3×30 mL). The combined organic phases were washed with water (30 mL), brine (30 mL) and dried over anhydrous sodium sulfate. The filtered solution was concentrated in vacuo and purified by column chromatography (0%–2% ethyl acetate in petroleum ether) to yield 1-(1-(2-chlorobenzyl)-1H-pyrrol-2-yl)ethan-1-one **13c** (0.717 g, 61%) as pale yellow crystals; mp 77–80 °C (lit.[13]: 69–70 °C); [Found: (GC-CI) 234.1. $C_{13}H_{13}ClNO^+$ $(M+H)^+$ requires 234.0680]; ν_{max}(film)/cm^{-1} 2980, 1647, 1468, 1397, 1331, 1244, 1086, 1038, 945, 745, 694, 633, 615; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43 (3H, s, C*H*$_3$), 5.68 (2H, s, C*H*$_2$), 6.22 (1H, dd, *J*=4, 2.8 Hz, Ar*H*), 6.61 (1H, d, *J*=7.6 Hz, Ar*H*), 6.89–6.90 (1H, m, Ar*H*), 7.04–7.05 (1H, m, Ar*H*), 7.11–7.21 (2H, m, Ar*H*), 7.37 (1H, dd, *J*=8, 1.2 Hz, Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.4 (CH_3), 50.5 (CH_2), 108.9 (CH), 120.5 (CH), 127.2 (CH), 127.8 (CH), 128.7 (CH), 129.5 (CH), 130.6 (C), 130.7 (CH), 132.6 (C), 136.4 (C), 188.5 (C); *m/z* (ESI$^+$) 236.1 (MH^+, Cl^{37}, 32%), 234.1 (MH^+, Cl^{35}, 100). The spectral data of **13c** were consistent with the literature data.[13]

4.1.5. 1-(1-(2-Iodo-3,4-dimethoxybenzyl)-1H-pyrrol-2-yl)ethan-1-one, ***23***. In an oven-dried round-bottomed flask, (2-iodo-3,4-

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dimethoxyphenyl)methanol (2.94 g, 10 mmol) was dissolved in anhydrous dichloromethane (20 mL). At 0 °C, PBr_3 (0.38 mL, 4 mmol, 0.4 equiv) was added slowly into the reaction flask, and the reaction mixture was stirred at 0 °C for 30 min, then at RT overnight. The reaction mixture was quenched with water (20 mL) and extracted with dichloromethane (3×15 mL). The combined organic phases were washed with water (25 mL), brine (25 mL) and dried over anhydrous sodium sulfate. The filtered solution was concentrated in vacuo to yield the crude product 1-(bromomethyl)-2-iodo-3,4-dimethoxybenzene (3.57 g, 90%) as off-white crystals which was used without further purification. In an oven-dried round-bottomed flask equipped with condenser, sodium hydride in mineral oil (60%, 0.352 g, 8.81 mmol, 1.2 equiv) was suspended in anhydrous DMF (5 mL). At 0 °C, a solution of 1-(1H-pyrrol-2-yl) ethan-1-one (0.800 g, 7.34 mmol) in anhydrous DMF (5 mL) was added slowly into the reaction mixture, which was stirred at 0 °C for 5 min, then at RT for 1 h. A solution of 1-(bromomethyl)-2-iodo-3,4-dimethoxybenzene (3.01 g, 8.44 mmol, 1.15 equiv) in anhydrous DMF (10 mL) was added dropwise to the reaction mixture, which was stirred at 60 °C overnight. The reaction mixture was cooled to RT, quenched dropwise with water (40 mL) and extracted with ethyl acetate (3×30 mL). The combined organic phases were washed with water (50 mL), brine (50 mL) and dried over anhydrous sodium sulfate. The filtered solution was concentrated in vacuo and purified by column chromatography (0%–20% ethyl acetate in petroleum ether) to yield *1-(1-(2-iodo-3,4-dimethoxybenzyl)-1H-pyrrol-2-yl)ethan-1-one* ***23*** (1.75 g, 62%) as off-white crystals; mp 89–90 °C; [Found: (HRMS-ESI$^+$) 386.0250. $C_{15}H_{17}INO_3^+$ $(M+H)^+$ requires 386.0248]; ν_{max}(film)/cm^{-1} 1641, 1479, 1460, 1397, 1290, 1265, 1225, 1144, 1086, 1022, 947, 743, 631; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (3H, s, C*H*$_3$), 3.82 (3H, s, C*H*$_3$), 3.85 (3H, s, C*H*$_3$), 5.54 (2H, s, C*H*$_2$), 6.20–6.21 (1H, m, Ar*H*), 6.28 (1H, d, *J*=8.4 Hz, Ar*H*), 6.76 (1H, d, *J*=8.4 Hz, Ar*H*), 6.82–6.83 (1H, m, Ar*H*), 7.04–7.05 (1H, m, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.4 (CH_3), 56.2 (CH_3), 57.6 (CH_3), 60.4 (CH_2), 96.8 (C), 108.8 (CH), 112.7 (CH), 120.4 (CH), 123.2 (CH), 130.3 (C), 130.7 (C), 133.7 (CH), 149.0 (C), 151.8 (C), 188.5 (C).

4.1.6. 1-(2-((2-Iodobenzyl)amino)phenyl)ethan-1-one ***26a***. To an oven-dried high-pressure sealed tube was added 1-(bromomethyl)-2-iodobenzene (1.48 g, 5 mmol), 1-(2-aminophenyl)ethan-1-one (1.22 mL, 10 mmol, 2 equiv), K_2CO_3 (2.07 g, 15 mmol, 3 equiv) and acetonitrile (5 mL). The reaction mixture was stirred at 85 °C for 3 days. The reaction mixture was cooled to RT, diluted with H_2O (20 mL) and extracted with dichloromethane (3×20 mL). The combined organic phases were washed with brine (60 mL) and dried over anhydrous sodium sulfate. The filtered solution was concentrated in vacuo and purified by column chromatography (5% ethyl acetate in petroleum ether) to yield 1-(2-((2-iodobenzyl) amino)phenyl)-ethan-1-one **26a** (1.18 g, 67%) as a yellow solid; mp: 137–138 °C (lit.[13]: 128.3–129.3 °C); [Found: (HRSM-ESI$^+$) 352.0188. $C_{15}H_{15}INO^+$ $(M+H)^+$ requires 352.0193]; ν_{max}(film)/cm^{-1} 3296, 2359, 2342, 1626, 1570, 1516, 1435, 1418, 1356, 1331, 1248, 1229, 1173, 1150, 1013, 955, 743, 667; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.62 (3H, s, C*H*$_3$), 4.43 (2H, d, *J*=6 Hz, C*H*$_2$), 6.53 (1H, d, *J*=8 Hz, Ar*H*), 6.61–6.65 (1H, m, Ar*H*), 6.94–6.98 (1H, m, Ar*H*), 7.27–7.32 (3H, m, Ar*H*), 7.79 (1H, dd, *J*=8.0, 1.2 Hz, Ar*H*), 7.86 (1H, d, *J*=7.6 Hz, Ar*H*), 9.39 (1H, br s, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.1 (CH_3), 52.1 (CH_2), 98.4 (C), 112.4 (CH), 114.9 (CH), 118.2 (C), 128.2 (CH), 128.6 (CH), 129.1 (CH), 132.9 (CH), 135.2 (CH), 139.6 (CH), 140.3 (C), 150.8 (C), 201.3 (C). The spectral data of **26a** were consistent with the literature data.[13]

4.1.7. 1-(2-((2-Bromobenzyl)amino)phenyl)ethan-1-one ***26b***. To an oven-dried 3-necked flask was added 1-(bromomethyl)-2-bromobenzene (1.25 g, 5 mmol), 1-(2-aminophenyl)ethan-1-one (1.22 mL, 10 mmol, 2 equiv), K_2CO_3 (2.07 g, 15 mmol, 3 equiv) and acetonitrile (10 mL). The reaction mixture was stirred at 85 °C for 22 h. The reaction mixture was cooled to RT, diluted with water (30 mL) and extracted with ethyl acetate (3×30 mL). The combined organic phases were washed with water (30 mL) and brine (30 mL) and dried over anhydrous sodium sulfate. The filtered solution was concentrated in vacuo and purified by column chromatography (2%–4% diethyl ether in petroleum ether) to yield *1-(2-((2-bromobenzyl)amino)phenyl)ethan-1-one* **26b** (1.14 g, 75%) as yellow crystals; mp 141–143 °C; [Found: (HRMS-ESI$^+$) 304.0328. $C_{15}H_{15}^{79}BrNO^+$ $(M+H)^+$ requires 304.0332]; ν_{max}(film)/cm^{-1} 3291, 2924, 2359, 1634, 1572, 1516, 1437, 1418, 1356, 1250, 1229, 1152, 1024, 955, 745, 677; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.63 (3H, s, C*H*$_3$), 4.53 (2H, s, C*H*$_2$), 6.56–6.58 (1H, m, Ar*H*), 6.61–6.66 (1H, m, Ar*H*), 7.10–7.15 (1H, m, Ar*H*), 7.23 (1H, td, *J*=7.6, 1.2 Hz, Ar*H*), 7.28–7.33 (2H, m, Ar*H*), 7.57 (1H, dd, *J*=8.0, 1.2 Hz, Ar*H*), 7.79 (1H, dd, *J*=8.0, 1.6 Hz, Ar*H*), 9.40 (1H, br s, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.1 (CH_3), 47.1 (CH_2), 112.4 (CH), 114.9 (CH), 118.2 (C), 123.2 (C), 127.7 (CH), 128.6 (CH), 128.8 (CH), 132.9 (CH), 132.9 (CH), 135.2 (CH), 137.5 (C), 150.8 (C), 201.3 (C); *m/z* (ESI$^+$) 306.0304 (MH$^+$, Br^{81}, 96%), 304.0328 (MH$^+$, Br^{79}, 100).

4.1.8. 1-(2-((2-Iodobenzyl) (methyl)amino)phenyl)-ethan-1-one ***44***. To an oven-dried round-bottomed flask containing K_2CO_3 (3.46 g, 25 mmol, 1 equiv) suspended in anhydrous DMF (15 mL), was added 1-(2-aminophenyl)ethan-1-one (3.04 mL, 25 mmol) under argon atmosphere and reaction mixture was stirred at RT for 15 min. A solution of MeI (1.56 mL, 25 mmol, 1 equiv) in anhydrous DMF was added dropwise to the reaction mixture. The reaction mixture was stirred at RT for 3 days. The reaction mixture was diluted with H_2O (60 mL) and extracted with ethyl acetate (3×40 mL). The combined organic phases were washed with water (50 mL) and brine (50 mL) and dried over anhydrous sodium sulfate. The filtered solution was concentrated in vacuo and purified by column chromatography (3%–5% ethyl acetate in petroleum ether) to yield 1-(2-(methylamino)phenyl)ethan-1-one (1.98 g, 53%) as yellow crystals. To an oven-dried high-pressure sealed tube was added 1-(bromomethyl)-2-iodobenzene (1.48 g, 5 mmol), 1-(2-(methylamino) phenyl)ethan-1-one (895 mg, 6 mmol, 1.1 equiv), K_2CO_3 (1.38 g, 10 mmol, 2 equiv) and acetonitrile (5 mL). The reaction mixture was stirred at 85 °C for 4 days. The reaction mixture was cooled to RT, diluted with H_2O (20 mL) and extracted with dichloromethane (3×15 mL). The combined organic phases were washed with brine (40 mL) and dried over anhydrous sodium sulfate. The filtered solution was concentrated in vacuo and purified by column chromatography (5% ethyl acetate in petroleum ether) to yield 1-(2-((2-iodobenzyl) (methyl)amino)phenyl)ethan-1-one **44** (1.45 g, 79%) as orange crystals; mp 66–68 °C; [Found: (ESI$^+$) 366.1]; ν_{max}(film)/cm^{-1} 1668, 1503, 1221, 1211, 1119, 1015, 953, 750; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.63 (3H, s, C*H*$_3$), 2.78 (3H, s, C*H*$_3$), 4.31 (2H, s, C*H*$_2$), 6.95–7.00 (2H, m, Ar*H*), 7.02 (1H, d, *J*=8.0 Hz, Ar*H*), 7.25–7.38 (3H, m, Ar*H*), 7.46 (1H, dd, *J*=7.6, 1.6 Hz, Ar*H*), 7.85 (1H, dd, *J*=8, 0.8 Hz, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.7 (CH_3), 42.8 (CH_3), 64.4 (CH_2), 99.6 (C), 118.9 (CH), 120.8 (CH), 128.4 (CH), 129.1 (CH), 129.4 (CH), 129.6 (CH), 132.0 (CH), 132.9 (C), 139.5 (C), 139.8 (CH), 151.0 (C), 203.3 (C). The spectral data of **44** were consistent with the literature data.[13]

4.1.9. 1-(2-(Benzylamino)phenyl)ethan-1-one ***29***. To an oven-dried high-pressure sealed tube was added (bromomethyl)benzene (0.855 g, 5 mmol), 1-(2-(aminomethyl)phenyl)ethan-1-one (0.73 mL, 6 mmol, 1.1 equiv), K_2CO_3 (1.38 g, 10 mmol, 2 equiv) and acetonitrile (5 mL). The reaction mixture was stirred at 85 °C for 3 days. The reaction mixture was cooled to RT, diluted with H_2O (20 mL) and extracted with dichloromethane (3×20 mL). The combined organic phases were washed with brine (40 mL) and

dried over anhydrous sodium sulfate. The filtered solution was concentrated in vacuo and purified by column chromatography (20%–40% toluene in hexane) to yield 1-(2-(benzylamino)phenyl) ethan-1-one **29** (0.482 g, 43%) as yellow crystals; mp 83–85 °C (lit.[23]: 79–81 °C); [Found: (HRMS-ESI$^+$) 226.1227. $C_{15}H_{16}NO^+$ $(M+H)^+$ requires 226.1226]; ν_{max}(film)/cm^{-1} 3323, 1638, 1566, 1514, 1493, 1418, 1362, 1244, 1225, 1165, 1024, 953, 747, 729, 706, 692, 667; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.61 (3H, s, C*H*$_3$), 4.47 (2H, d, *J*=5.6 Hz, C*H*$_2$), 6.59–6.63 (1H, m, Ar*H*), 6.65 (1H, d, *J*=8.8 Hz, Ar*H*), 7.24–7.34 (5H, m, Ar*H*), 7.77 (1H, dd, *J*=8, 1.6 Hz, Ar*H*), 9.31 (1H, br s, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.1 (CH_3), 46.8 (CH_2), 112.3 (CH), 114.5 (CH), 118.0 (C), 127.1 (2×CH), 127.3 (CH), 128.8 (2×CH), 132.8 (CH), 135.2 (CH), 138.8 (C), 151.0 (C), 201.1 (C). The spectral data of **29** were consistent with the literature data.[23]

4.2. General procedure for electron transfer reactions

Substrate (0.5 mmol) and **11** (0 or 0.1 equiv) were added to a pressure tube. Base and anhydrous solvent were added into the tube in the glove box. The tube was then sealed properly and then removed from the glove box. The reaction was carried out at the given temperature for the given reaction time. The reaction was stopped and the pressure tube was cooled to RT. The reaction mixture was quenched with either water or saturated aqueous ammonium chloride (20 mL) and extracted with diethyl ether or dichloromethane or ethyl acetate (3×20 mL). The combined organic layers were then washed with water (15 mL) and brine (15 mL) and dried over anhydrous sodium sulfate. The filtered solution was concentrated in vacuo and purified by column chromatography to yield products.

4.2.1. Table 1; entry 1. **13a** (0.163 g, 0.5 mmol) was treated with **11** (10 mg, 0.05 mmol, 0.1 equiv), KOtBu (0.168 g, 1.5 mmol, 3 equiv) and anhydrous benzene (5 mL) under the general reaction procedure at 120 °C for 1 h. The reaction mixture was quenched with water and extracted with diethyl ether. Purification (10%–20% ethyl acetate in petroleum ether) yielded 5,10-dihydro-11H-benzo[e] pyrrolo[1,2-a]azepin-11-one **16** (54 mg, 55%) as a pale green solid and 1-(5H-pyrrolo[2,1-a]isoindol-3-yl)ethan-1-one **22** (7.2 mg, 7%) as a yellow solid.

For 5,10-dihydro-11H-benzo[e]pyrrolo[1,2-a]azepin-11-one **16**: mp 176–177 °C (lit.:[24] 174–176 °C); [Found: (HRMS-ESI$^+$) $(M+H)^+$ 198.0911. $C_{13}H_{12}NO$ (M+H) requires 198.0913]; ν_{max}(film)/cm^{-1} 2963, 2359, 2342, 1636, 1520, 1489, 1466, 1398, 1337, 739, 72, 677; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.09 (2H, s, C*H*$_2$), 5.26 (2H, s, C*H*$_2$), 6.15–6.17 (1H, m, Ar*H*), 6.94–6.95 (1H, m, Ar*H*), 7.10–7.12 (1H, m, Ar*H*), 7.25–7.35 (4H, m, Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 49.1 (CH_2), 53.7 (CH_2), 109.2 (CH), 118.6 (CH), 127.5 (CH), 127.9 (CH), 128.3 (CH), 129.3 (CH), 129.9 (CH), 132.4 (C), 134.3 (C), 135.2 (C), 184.4 (C). The spectral data of **16** were consistent with the literature data.[13,24]

For 1-(5H-pyrrolo[2,1-a]isoindol-3-yl)ethan-1-one **22**: mp 128–129 °C; [Found: (HRMS-ESI$^+$) $(M+H)^+$ 198.0913. $C_{13}H_{12}NO$ (M+H) requires 198.0913]; ν_{max}(film)/cm^{-1} 2922, 2359, 2342, 1626, 1614, 1476, 1439, 1395, 1306, 1262, 1192, 1138, 1098, 1067, 1026, 1017, 963, 924, 747, 718, 696, 655; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.48 (3H, s, C*H*$_3$), 5.22 (2H, s, C*H*$_2$), 6.41 (1H, d, *J*=4 Hz, Ar*H*), 7.07 (1H, d, *J*=4.4 Hz, Ar*H*), 7.30–7.34 (1H, m, Ar*H*), 7.38–7.42 (1H, m, Ar*H*), 7.49–7.51 (1H, m, Ar*H*), 7.63 (1H, d, *J*=7.6 Hz, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.0 (CH_3), 53.2 (CH_2), 100.2 (CH), 120.2 (CH), 121.7 (CH), 123.5 (CH), 127.1 (CH), 128.1 (CH), 129.2 (C), 131.9 (C), 142.1 (C), 144.8 (C), 187.4 (C). The spectral data of **22** were consistent with the literature data.[13]

4.2.2. Table 1; entry 2. **13a** (0.163 g, 0.5 mmol) was treated with **11** (10 mg, 0.05 mmol, 0.1 equiv), KOtBu (0.168 g, 1.5 mmol, 3 equiv) and anhydrous DMSO (2 mL) under the general reaction procedure at 120 °C for 1 h. Reaction contents mixture was with saturated ammonium chloride and extracted with dichloromethane. Purification (5%–25% ethyl acetate in hexane) yielded 5,10-dihydro-11H-benzo[e]pyrrolo[1,2-a]azepin-11-one **16** (77.8 mg, 79%) as a pale-brown solid and 1-(5H-pyrrolo[2,1-a]isoindol-3-yl)ethan-1-one **22** (9.6 mg, 10%) as pale brown crystals.

4.2.3. Table 1; entry 3. **13a** (0.163 g, 0.5 mmol) was treated with KOtBu (0.168 g, 1.5 mmol, 3 equiv) and anhydrous benzene (5 mL) under the general reaction procedure at 120 °C for 1 h. Reaction mixture was quenched with saturated ammonium chloride and extracted with dichloromethane. Purification (5%–20% ethyl acetate in hexane) yielded 5,10-dihydro-11H-benzo[e]pyrrolo[1,2-a] azepin-11-one **16** (22.9 mg, 23%) as pale yellow crystals and recovered starting material, **13a**, (118.9 mg, 73%) as yellow crystals.

4.2.4. Table 1; entry 4. **13a** (0.163 g, 0.5 mmol) was treated with KOtBu (0.168 g, 1.5 mmol, 3 equiv) and anhydrous DMSO (2 mL) under the general reaction procedure at 120 °C for 1 h. Reaction mixture was quenched with water and extracted with ethyl acetate. Purification (5%–20% ethyl acetate in hexane) yielded 5,10-dihydro-11H-benzo[e]pyrrolo[1,2-a]azepin-11-one **16** (88.6 mg, 90%) as pale brown crystals and 1-(5H-pyrrolo[2,1-a]isoindol-3-yl) ethan-1-one **22** (7.6 mg, 8%) as brown crystals.

4.2.5. Table 1; entry 5. **13a** (0.163 g, 0.5 mmol) was treated with **11** (10 mg, 0.05 mmol, 0.1 equiv), KOtBu (0.168 g, 1.5 mmol, 3 equiv) and anhydrous benzene (5 mL) under the general reaction procedure at RT for 24 h. Reaction mixture was quenched with saturated aqueous ammonium chloride and extracted with dichloromethane. The filtered solution was concentrated in vacuo and an NMR and TLC of the crude mixture showed only starting material, **13a**, was present, with trace amounts (<5%) of possible cyclized product.

4.2.6. Table 1; entry 6. **13a** (0.163 g, 0.5 mmol) was treated with **11** (10 mg, 0.05 mmol, 0.1 equiv), KOtBu (0.168 g, 1.5 mmol, 3 equiv) and anhydrous DMSO (2 mL) under the general reaction procedure at RT for 24 h. Reaction mixture was quenched with saturated aqueous ammonium chloride and extracted with dichloromethane. Purification (5%–25% ethyl acetate in hexane) yielded 5,10-dihydro-11H-benzo[e]pyrrolo[1,2-a]azepin-11-one **16** (74.9 mg, 76%) as off-white crystals and 1-(5H-pyrrolo[2,1-a]isoindol-3-yl) ethan-1-one **22** (9.5 mg, 10%) as off-white crystals, and recovered starting material **13a** (4.7 mg, 3%) as pale brown solid.

4.2.7. Table 1; entry 7. **13a** (0.163 g, 0.5 mmol) was treated with KOtBu (0.168 g, 1.5 mmol, 3 equiv) and anhydrous DMSO (2 mL) under the general reaction procedure at RT for 24 h. Reaction mixture was quenched with saturated aqueous ammonium chloride and extracted with dichloromethane. Purification (5%–25% ethyl acetate in hexane) yielded 5,10-dihydro-11H-benzo[e]-pyrrolo[1,2-a]azepin-11-one **16** (58.8 mg, 60%) as off-white crystals and 1-(5H-pyrrolo[2,1-a]isoindol-3-yl)ethan-1-one **22** (12.1 mg, 12%) as off-white crystals, and recovered starting material **13a** (30.9 mg, 19%) as pale brown crystals.

4.2.8. Table 1; entry 8. **13a** (0.163 g, 0.5 mmol) was treated with KOtBu (0.168 g, 1.5 mmol, 3 equiv) and anhydrous DMSO (2 mL) under the general reaction procedure at RT for 24 h, in the dark. Reaction mixture was quenched with saturated aqueous ammonium chloride and extracted with dichloromethane. To the crude reaction mixture was added 1,3,5-trimethoxybenzene (42 mg; 0.25 mmol) as an internal standard. The yields were deduced from NMR analysis to be 5,10-dihydro-11H-benzo[e]

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pyrrolo[1,2-a]azepin-11-one **16** (70%) and 1-(5H-pyrrolo[2,1-a]isoindol-3-yl)ethan-1-one **22** (10%), and starting material **13a** (13%).

4.2.9. Table 1; entry 9. To a flame-dried round-bottomed flask was added freshly distilled diisopropylamine (0.1 mL, 0.7 mmol, 1.4 equiv) and anhydrous THF (1 mL) which was put under argon atmosphere and cooled to −78 °C. A solution of n-butyllithium in hexane (2.38 N, 0.25 mL, 0.6 mmol, 1.2 equiv) was added to generate lithium diisopropylamine in situ. This LDA solution was added via cannula to a flame-dried 3-neck flask, containing a solution of **13a** (0.163 g, 0.5 mmol) in anhydrous THF (2 mL), under argon atmosphere at −78 °C. The reaction mixture was stirred at −78 °C for 1 h, then at RT for 1 h. The THF was removed from the reaction mixture by vacuum, leaving a residue. In the glovebox the residue was dissolved in anhydrous DMSO (2 mL) and transferred to a sealed tube. The reaction mixture was heated to 120 °C and stirred for 1 h. The reaction mixture was quenched with saturated aqueous ammonium chloride (10 mL) and extracted with dichloromethane (4×10 mL). The combined organic phases were dried over anhydrous sodium sulfate. To the crude reaction mixture was added 1,3,5-trimethoxybenzene (42 mg; 0.25 mmol) as an internal standard. The yields were deduced from NMR analysis to be 1-(5H-pyrrolo[2,1-a]isoindol-3-yl)ethan-1-one **22** (12%), and starting material **13a** (50%).

4.2.10. Table 1; entry 10. **13b** (0.139 g, 0.5 mmol) was treated with **11** (10 mg, 0.05 mmol, 0.1 equiv), KOtBu (0.168 g, 1.5 mmol, 3 equiv) and anhydrous benzene (5 mL) under the general reaction procedure at 120 °C for 1 h. Reaction mixture was quenched with water and extracted with diethyl ether. NMR and TLC of the crude mixture showed only starting material **13b** was present.

4.2.11. Table 1; entry 11. **13b** (0.139 g, 0.5 mmol) was treated with **11** (10 mg, 0.05 mmol, 0.1 equiv), KOtBu (0.168 g, 1.5 mmol, 3 equiv) and anhydrous DMSO (2 mL) under the general reaction procedure at 120 °C for 1 h. Reaction mixture was quenched with saturated aqueous ammonium chloride and extracted with dichloromethane. Purification (2%–25% ethyl acetate in hexane) yielded 5,10-dihydro-11H-benzo[e]pyrrolo[1,2-a]azepin-11-one **16** (24.2 mg, 25%) as dark green crystals.

4.2.12. Table 1; entry 12. **13b** (0.139 g, 0.5 mmol) was treated with **11** (10 mg, 0.05 mmol, 0.1 equiv), KOtBu (0.281 g, 2.5 mmol, 5 equiv) and anhydrous benzene (5 mL) under the general reaction procedure at 160 °C for 16 h. Reaction mixture was quenched with water and extracted with diethyl ether. Purification (10–20% ethyl acetate in petroleum ether) yielded 5,10-dihydro-11H-benzo[e]pyrrolo[1,2-a]azepin-11-one **16** (29.3 mg, 30%) as a brown solid.

4.2.13. Table 1; entry 13. **13c** (0.117 g, 0.5 mmol) was treated with **11** (10 mg, 0.05 mmol, 0.1 equiv), KOtBu (0.168 g, 1.5 mmol, 3 equiv) and anhydrous DMSO (2 mL) under the general reaction procedure at 120 °C for 1 h. Reaction contents were quenched with saturated aqueous ammonium chloride and extracted with dichloromethane. Purification (2%–40% ethyl acetate in hexane) yielded 5,10-dihydro-11H-benzo[e]pyrrolo[1,2-a]azepin-11-one **16** (19.8 mg, 20%) as a brown solid.

4.2.14. Table 1; entry 14. **13c** (0.117 g, 0.5 mmol) was treated with **11** (10 mg, 0.05 mmol, 0.1 equiv), KOtBu (0.168 g, 1.5 mmol, 3 equiv) and anhydrous benzene (2 mL) under the general reaction procedure at 160 °C for 16 h. Reaction mixture was quenched with water and extracted with diethyl ether. Purification (5%–100% ethyl acetate in petroleum ether) yielded 5,10-dihydro-11H-benzo[e]pyrrolo[1,2-a]azepin-11-one **16** (23.5 mg, 24%) as a brown solid.

4.2.15. Table 1; entry 15. **23** (0.193 g, 0.5 mmol) was treated with **11** (10 mg, 0.05 mmol, 0.1 equiv), KOtBu (0.168 g, 1.5 mmol, 3 equiv) and anhydrous DMSO (2 mL) under the general reaction procedure at 120 °C for 1 h. Reaction mixture was quenched with water and extracted with diethyl ether. Purification (10%–30% ethyl acetate in petroleum ether) yielded *8,9-dimethoxy-5,10-dihydro-11H-benzo[e]pyrrolo[1,2-a]azepin-11-one* **24** (42.9 mg, 33%) as yellow crystals, *1-(8,9-dimethoxy-5H- pyrrolo[2,1-a]isoindol-3-yl)ethan-1-one* **25** (37.3 mg, 29%) as green crystals.

For *8,9-Dimethoxy-5,10-dihydro-11H-benzo[e]pyrrolo[1,2-a]azepin-11-one*, **24**; mp 184–187 °C; [Found: (HRMS-ESI$^+$) 258.1124. $C_{15}H_{16}NO_3$ $(M+H)^+$ requires 258.1125]; ν_{max}(film)/cm^{-1} 2924, 1638, 1491, 1398, 1341, 1279, 1267, 1076, 976, 812, 747, 689; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.81 (3H, s, C*H*$_3$), 3.85 (3H, s, C*H*$_3$), 4.15 (2H, s, C*H*$_2$), 5.19 (2H, s, C*H*$_2$), 6.14–6.16 (1H, m, Ar*H*), 6.75 (1H, d, *J*=8.4 Hz, Ar*H*), 6.92–6.93 (1H, m, Ar*H*), 7.05 (1H, d, *J*=8.4 Hz, Ar*H*), 7.09–7.11 (1H, m, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 41.1 (CH_2), 53.5 (CH_2), 56.0 (CH_3), 61.8 (CH_3), 109.1 (CH), 110.5 (CH), 118.4 (CH), 123.8 (CH), 127.6 (CH), 128.5 (C), 128.7 (C), 132.7 (C), 147.5 (C), 153.5 (C), 184.5 (C).

For *8,9-Dimethoxy-5,10-dihydro-11H-benzo[e]pyrrolo-[1,2-a]azepin-11-one*, **25**; mp 136–144 °C; [Found: (HRMS-ESI$^+$) 258.1126. $C_{15}H_{16}NO_3^+$ $(M+H)^+$ requires 258.1125]; ν_{max}(film)/cm^{-1} 2938, 1636, 1495, 1397, 1252, 1223, 1921, 1105, 1057, 1042, 1022, 934, 806, 774, 750, 694, 625; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.47 (3H, s, C*H*$_3$), 3.91 (3H, s, OC*H*$_3$), 3.99 (3H, s, OC*H*$_3$), 5.16 (2H, s, C*H*$_2$), 6.50–6.51 (1H, m, Ar*H*), 6.88 (1H, d, *J*=8.0 Hz, Ar*H*), 7.07–7.08 (1H, m, Ar*H*), 7.15 (1H, d, *J*=8.0 Hz, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.0 (CH_3), 52.8 (CH_2), 56.5 (CH_3), 60.9 (CH_3), 102.6 (CH), 112.0 (CH), 118.8 (CH), 121.7 (CH), 126.2 (C), 129.2 (C), 135.3 (C), 142.6 (C), 143.2 (C), 152.6 (C), 187.4 (C).

4.2.16. Table 1; Entry 16. **23** (0.193 g, 0.5 mmol) was treated with KOtBu (0.168 g, 1.5 mmol, 3 equiv) and anhydrous DMSO (2 mL) under the general reaction procedure at 120 °C for 1 h. Reaction mixture was quenched with water and extracted with ethyl acetate. Purification (20%–40% ethyl acetate in petroleum ether) yielded *8,9-dimethoxy-5,10-dihydro-11H-benzo[e]pyrrolo[1,2-a]azepin-11-one* **24** (21.2 mg, 17%) as pale brown crystals, *1-(8,9-dimethoxy-5H-pyrrolo[2,1-a]isoindol-3-yl)ethan-1-one* **25** (15.8 mg, 12%) as dark brown crystals.

4.2.17. Table 2; entry 1. **26a** (0.176 g, 0.5 mmol) was treated with **11** (10 mg, 0.05 mmol, 0.1 equiv), KOtBu (0.168 g, 1.5 mmol, 3 equiv) and anhydrous benzene (5 mL) under the general reaction procedure at 120 °C for 1.5 h. Reaction mixture was quenched with saturated aqueous ammonium chloride and extracted with dichloromethane. Purification (5%–100% ethyl acetate in petroleum ether, to 2% methanol in ethyl acetate) yielded 1-(phenanthridin-4-yl)ethanol **28** (22.9 mg, 21%) as an orange oil, 1-(2-(benzylamino) phenyl)ethan-1-one **29** (9.4 mg, 8%) as a yellow solid, and an impure sample of 1-(phenanthridin-4-yl)ethan-1-one **27** (37.6 mg). This impure mixture was purified by column chromatography (10%–100% dichloromethane in hexane) to yield 1-(phenanthridin-4-yl)ethan-1-one **27** (10.4 mg, 10%) as yellow crystals.

For 1-(Phenanthridin-4-yl)ethan-1-one, **27**; mp 91–94 °C (lit.[13]: 93.7–95.5 °C); [Found: (GC-CI) 222.2. $C_{15}H_{12}NO^+$ $(M+H)^+$ requires 222.0913]; ν_{max}(film)/cm^{-1} 2922, 2359, 2342, 1684, 1580, 1346, 1275, 1184, 1165, 1111, 889, 768, 747, 731, 720, 637; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.95 (3H, s, C*H*$_3$), 7.69–7.78 (2H, m, Ar*H*), 7.87–7.92 (2H, m, Ar*H*), 8.07–8.09 (1H, m Ar*H*), 8.62 (1H, d, *J*=8.0 Hz, Ar*H*), 8.69 (1H, dd, *J*=8.4, 1.2 Hz, Ar*H*), 9.32 (1H, s, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.0 (CH_3), 122.2 (CH), 124.3 (C), 125.2 (CH), 126.3 (C), 126.8 (CH), 127.8 (CH), 128.1 (CH), 129.0 (CH), 131.5

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(CH), 132.4 (C), 141.1 (C), 141.9 (C), 153.6 (CH), 205.2 (C). The spectral data of **27** were consistent with the literature data.[13]

For 1-(Phenanthridin-4-yl)ethanol, **28**; [Found: (HRMS-ESI$^+$) 246.0888. $C_{15}H_{13}NONa^+$ $(M+Na)^+$ requires 246.0889]; ν_{max}(film)/cm^{-1} 3320, 2967, 2922, 1614, 1587, 1516, 1445, 12612, 1231, 1159, 1098, 1069, 1053, 1007, 889, 752; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.77 (3H, d, J=6.8 Hz, CH_3), 5.47–5.52 (2H, m, Ar*H*), 7.62–7.67 (2H, m, Ar*H*), 7.73–7.76 (1H, m, Ar*H*), 7.87–7.92 (1H, m, Ar*H*), 8.09 (1H, d, J=8 Hz, Ar*H*), 8.52 (1H, dd, J=7.6, 2 Hz, Ar*H*), 8.64 (1H, d, J=8.4 Hz, Ar*H*), 9.25 (1H, s, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.8 (CH_3), 70.7 (CH), 121.5 (CH), 122.3 (CH), 124.7 (C), 126.1 (C), 126.1 (CH), 127.1 (CH), 127.8 (CH), 129.1 (CH), 131.4 (CH), 133.1 (C), 142.5 (C), 142.8 (C), 151.7 (CH).

For 1-(2-(Benzylamino)phenyl)ethan-1-one **29**; mp 83–85 °C (lit.[23]: 79–81 °C); [Found: (HRMS-ESI$^+$) 226.1227. $C_{15}H_{16}NO^+$ $(M+H)^+$ requires 226.1226]; ν_{max}(film)/cm^{-1} 3323, 1638, 1566, 1514, 1493, 1418, 1362, 1244, 1225, 1165, 1024, 953, 747, 729, 706, 692, 667; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.61 (3H, s, CH_3), 4.47 (2H, d, J=5.6 Hz, CH_2), 6.59–6.63 (1H, m, Ar*H*), 6.65 (1H, d, J=8.8 Hz, Ar*H*), 7.24–7.34 (5H, m, Ar*H*), 7.77 (1H, dd, J=8, 1.6 Hz, Ar*H*), 9.31 (1H, br s, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.1 (CH_3), 46.8 (CH_2), 112.3 (CH), 114.5 (CH), 118.0 (C), 127.1 (2×CH), 127.3 (CH), 128.8 (2×CH), 132.8 (CH), 135.2 (CH), 138.8 (C), 151.0 (C), 201.1 (C). The spectral data of **29** were consistent with the literature data.[23]

4.2.18. Table 2; entry 2. **26a** (0.176 g, 0.5 mmol) was treated with **11** (10 mg, 0.05 mmol, 0.1 equiv), KOtBu (0.168 g, 1.5 mmol, 3 equiv) and anhydrous DMSO (2 mL) under the general reaction procedure at 120 °C for 1 h. Reaction mixture was quenched with saturated aqueous ammonium chloride and extracted with dichloromethane. Purification (1%–100% ethyl acetate in hexane to 2% methanol in ethyl acetate) yielded 1-(phenanthridin-4-yl)ethanol **28** (trace) as an orange oil and 2-phenylquinolin-4(1H)-one **30** (57.1 mg, 52%) as pale-yellow solid.

For 2-Phenylquinolin-4(1H)-one, **30**; mp 252–255 °C (lit.:[25] 251–253 °C); [Found: (HRMS-ESI$^+$) 222.0915. $C_{15}H_{12}NO$ $(M+H)^+$ requires 222.0913]; ν_{max}(film)/cm^{-1} 2955, 2922, 2853, 1738, 1632, 1580, 1543, 1497, 1470, 1449, 1431, 1356, 1254, 1138, 839, 790, 754, 689, 662; ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.33 (1H, s, *CH*), 7.32–7.36 (1H, m, Ar*H*), 7.58–7.60 (3H, m, Ar*H*), 7.65–7.69 (1H, m, Ar*H*), 7.76 (1H, d, J=8.0 Hz, Ar*H*), 7.83–7.84 (2H, m, Ar*H*), 8.10 (1H, dd, J=8.0, 1.2 Hz, Ar*H*), 11.68 (1H, br s, N*H*); ^{13}C NMR (100 MHz, DMSO-d_6) δ 107.3 (CH), 118.7 (CH), 123.2 (CH), 124.7 (CH), 124.9 (C), 127.4 (2×CH), 129.0 (2×CH), 130.4 (CH), 131.8 (CH), 134.2 (C), 140.5 (C), 150.0 (C), 176.9 (C); ^{1}H–^{13}C HSQC 6.33/107.3, 7.33/123.2, 7.57/130.4, 7.57/128.9, 7.66/131.7, 7.76/118.7, 7.7.82/127.4, 8.11/124.7. X-ray crystallographic data is in the Supplementary data. The spectral data of **30** were consistent with the literature data.[25]

4.2.19. Table 2; entry 3. **26a** (0.176 g, 0.5 mmol) was treated with KOtBu (0.168 g, 1.5 mmol, 3 equiv) and anhydrous DMSO (2 mL) under the general reaction procedure at 120 °C for 1 h. Reaction mixture was quenched with water and extracted with ethyl acetate. Purification (5%–100% ethyl acetate in petroleum ether) yielded 2-phenylquinolin-4(1H)-one **30** (54.7 mg, 49%) as off-white crystals.

4.2.20. Table 2; entry 4. **26b** (0.152 g, 0.5 mmol) was treated with **11** (10 mg, 0.05 mmol, 0.1 equiv), KOtBu (0.168 g, 1.5 mmol, 3 equiv) and anhydrous DMSO (2 mL) under the general reaction procedure at 120 °C for 16 h. Reaction mixture was quenched with water and extracted with ethyl acetate. Purification (5%–100% ethyl acetate in petroleum ether) yielded 2-phenylquinolin-4(1H)-one **30** (33.8 mg, 31%) as a pale brown solid.

4.2.21. Table 2; entry 5. **26a** (0.176 g, 0.5 mmol) was treated with **11** (10 mg, 0.05 mmol, 0.1 equiv), KO*t*Bu (0.168 g, 1.5 mmol, 3 equiv) and anhydrous DMSO (2 mL) under the general reaction procedure at RT overnight. Reaction mixture was quenched with saturated aqueous ammonium chloride and extracted with dichloromethane. Purification (2%–100% dichloromethane in hexane, to 2% methanol in ethyl acetate) yielded 1-(phenanthridin-4-yl)ethan-1-one **27** (15 mg, 14%) as yellow crystals, 1-(2-(benzylamino)phenyl)ethan-1-one **29** (17.5 mg, 16%) as yellow crystals, 2-phenyl-2,3-dihydroquinolin-4(1H)-one **42** (46.4 mg, 42%) as yellow crystals and 2-phenylquinolin-4(1H)-one **30** (25.6 mg, 23%) as a pale yellow solid.

For 2-Phenyl-2,3-dihydroquinolin-4(1H)-one, **42**; mp 144–146 °C (lit.[26]: 148–149 °C); [Found: (GC-CI$^+$) 223.9]; ν_{max}(-film)/cm^{-1} 3331, 1653, 1603, 1479, 1330, 1302, 1153, 764, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.77–2.95 (2H, m, $COCH_2$), 4.49 (1H, br s, N*H*), 4.76 (1H, dd, J=13.6, 4.0 Hz, *CH*Ph), 6.71 (1H, d, J=8.4 Hz, Ar*H*), 6.78–6.82 (1H, m, Ar*H*), 7.32–7.48 (6H, m, Ar*H*), 7.81–7.90 (1H, m, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 46.6 (CH_2 or CH), 58.7 (CH_2 or CH), 116.1 (CH), 118.6 (CH), 119.2 (C), 126.8 (2×CH), 127.8 (CH), 128.6 (CH), 129.2 (2×CH), 135.6 (CH), 141.2 (C), 151.7 (C), 193.4 (C). The spectral data of **42** were consistent with the literature data.[26]

4.2.22. Table 2; entry 6. **29** (0.100 g, 0.5 mmol) was treated with KOtBu (0.168 g, 1.5 mmol, 3 equiv) and anhydrous benzene (5 mL) under the general reaction procedure at 120 °C for 1 h. Reaction mixture was quenched with saturated aqueous ammonium chloride and extracted with dichloromethane. NMR and TLC of the crude mixture showed only starting material **29** was present.

4.2.23. Table 2; entry 7. **29** (0.100 g, 0.5 mmol) was treated with **11** (10 mg, 0.05 mmol, 0.1 equiv), KOtBu (0.168 g, 1.5 mmol, 3 equiv) and anhydrous DMSO (2 mL) under the general reaction procedure at RT for 24 h. Reaction mixture was quenched with saturated aqueous ammonium chloride and extracted with dichloromethane. NMR and TLC of the crude mixture showed only starting material **29** was present.

4.2.24. Scheme 4; reaction A. **44** (0.183 g, 0.5 mmol) was treated with **11** (10 mg, 0.05 mmol, 0.1 equiv), KOtBu (0.168 g, 1.5 mmol, 3 equiv) and anhydrous benzene (5 mL) under the general reaction procedure at 120 °C for 1 h. Reaction mixture was quenched with saturated aqueous ammonium chloride and extracted with dichloromethane. Purification (25%–100% dichloromethane in hexane) yielded *((4bR,9bS)-5-methyl-4b,10-dihydroindeno[1,2-b]indol-9b(5H)-yl)oxonium* **45** (61.6 mg, 52%) and 1-benzyl-2,3-dihydroquinolin-4(1H)-one **46** (isolated but not pure) (<11.3 mg, <9%).

For *5-Methyl-4,10-dihydroindeno[1,2]indol-9(5H)-ol*, **45**; mp 102–106 °C; [Found: (HRMS$^+$) 238.1222. $C_{16}H_{16}NO^+$ $(M+H)^+$ requires 238.1226]; ν_{max}(film)/cm^{-1} 3304, 1668, 1609, 1489, 1373, 1314, 1263, 1219, 1123, 1057, 1040, 982, 745, 727, 654, 631; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.14 (1H, br s, O*H*), 3.07 (3H, s, CH_3), 3.44–3.53 (2H, m, CH_2), 4.73 (1H, s, C*H*), 6.46 (1H, d, J=8.0 Hz, Ar*H*), 6.71–6.75 (1H, m, Ar*H*), 7.16–7.25 (4H, m, Ar*H*), 7.36 (1H, dd, J=7.2, 0.8 Hz, Ar*H*), 7.43–7.45 (1H, m, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.8 (CH_3), 46.1 (CH_2), 82.7 (CH), 88.3 (C), 107.4 (CH), 117.8 (CH), 123.4 (CH), 125.4 (CH), 125.5 (CH), 127.1 (CH), 128.6 (CH), 130.1 (CH), 132.6 (C), 140.6 (C), 142.8 (C), 151.2 (C). X-ray crystallographic data are provided in the Supplementary data.

For 1-Benzyl-2,3-dihydroquinolin-4(1H)-one, **46**; mp 114–117 °C (lit.[27]: 111–114 °C); [Found: (GC-CI$^+$) 238.2. $C_{16}H_{16}NO^+$ $(M+H)^+$ requires 238.1226]; ν_{max}(film)/cm^{-1} 2918, 2907, 1661, 1603, 1497, 1449, 1346, 1289, 1229, 1198, 1180, 1121, 999, 856, 752, 731, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.74–2.78 (2H, m, CH_2), 3.58–3.62 (2H, m, CH_2), 4.57 (2H, s, CH_2), 6.69–6.75 (2H, m, Ar*H*), 7.29–7.37 (6H, m, Ar*H*), 7.92–7.95 (1H, m, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.2 (CH_2), 49.6 (CH_2), 55.4 (CH_2), 113.6 (CH), 117.1 (CH),

119.9 (C), 126.9 (2×CH), 127.6 (CH), 128.4 (CH), 129.0 (2×CH), 135.6 (CH), 137.4 (C), 151.9 (C), 193.7 (C). The spectral data of **46** were consistent with the literature data.[27]

4.2.25. Scheme 4; reaction B. **44** (0.183 g, 0.5 mmol) was treated with **11** (10 mg, 0.05 mmol, 0.1 equiv), KO*t*Bu (0.168 g, 1.5 mmol, 3 equiv) and anhydrous DMSO (2 mL) under the general reaction procedure at RT overnight. Reaction mixture was quenched with saturated aqueous ammonium chloride and extracted with dichloromethane. Purification (2%–25% ethyl acetate in hexane) to yield 2-phenylquinolin-4(1H)-one **47** (32.4 mg, 27%) as a yellow solid, 1-benzyl-2,3-dihydroquinolin-4(1H)-one **46** (25.2 mg, 21%) as a yellow oil and 1-(2-(methylamino)phenyl)ethan-1-one **48** (9.5 mg, 13%) as a yellow oil.

For 5-methyl-6,11-dihydrodibenzo[b,f]azocin-12(5H)-one, **47**; mp 102–106 °C (lit.[13]: 108–109 °C); [Found: (GC-CI$^+$) 238.1]; ν_{max}(film)/cm^{-1} 1661, 1591, 1487, 1350, 1285, 1163, 1088, 1009, 756, 735, 623; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.01 (3H, s, C*H*$_3$), 4.08 (2H, s, C*H*$_2$), 4.22 (2H, s, C*H*$_2$), 6.90–6.94 (1H, m, Ar*H*), 7.05 (1H, d, *J*=8.4 Hz, Ar*H*), 7.11 (1H, d, *J*=7.6 Hz, Ar*H*), 7.21–7.29 (3H, m, Ar*H*), 7.40–7.45 (1H, m, Ar*H*), 7.61 (1H, dd, *J*=7.6, 1.6 Hz, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.0 (CH_3), 48.3 (CH_2), 64.6 (CH_2), 115.2 (CH), 119.0 (CH), 127.2 (CH), 128.4 (CH), 128.8 (CH), 129.5 (CH), 130.9 (CH), 131.2 (C), 132.7 (CH), 135.3 (C), 135.8 (C) 153.0 (C), 210.9 (C). The spectral data of **47** were consistent with the literature data.[13]

For 1-(2-(methylamino)phenyl)ethan-1-one **48**; mp 45–47 °C (lit.[28]: 37–39 °C); [Found: (HRMS-ESI$^+$) 150.0910. $C_9H_{12}NO^+$ (M+H)$^+$ requires 150.0913]; ν_{max}(film)/cm^{-1} 3321, 1632, 1562, 1516, 1410, 1234, 1165, 951, 743, 652, 613; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.57 (3H, s, C*H*$_3$), 2.91 (3H, d, *J*=4.8 Hz, C*H*$_3$), 6.57–6.61 (1H, m, Ar*H*), 6.68–6.70 (1H, m, Ar*H*), 7.36–7.40 (1H, m, Ar*H*), 7.73–7.75 (1H, d, *J*=8, 1.6 Hz, Ar*H*), 8.78 (1H, br s, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.9 (CH_3), 29.3 (CH_3), 111.3 (CH), 113.9 (CH), 117.6 (C), 132.7 (CH), 135.1 (CH), 152.0 (C), 200.8 (C). The spectral data of **48** were consistent with the literature data.[28]

*4.2.26. Reaction of **47** with KOtBu.* **47** (0.010 g, 0.042 mmol) was treated with KOtBu (0.014 g, 0.126 mmol, 3 equiv) and anhydrous benzene (1 mL) under the general reaction procedure at 120 °C for 1 h. Reaction mixture was quenched with water and extracted with ethyl acetate. To the crude reaction mixture was added 1,3,5-trimethoxybenzene (0.025 mmol) as an internal standard. The yields were deduced from NMR analysis to yield *((4bR,9bS)-5-methyl-4b,10-dihydroindeno[1,2-b]indol-9b(5H)-yl)oxonium* **45** (31%) and starting material **47** (29%).

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2016.05.083.

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