Dearomative Photocatalytic Construction of Bridged 1,3-Diazepanes

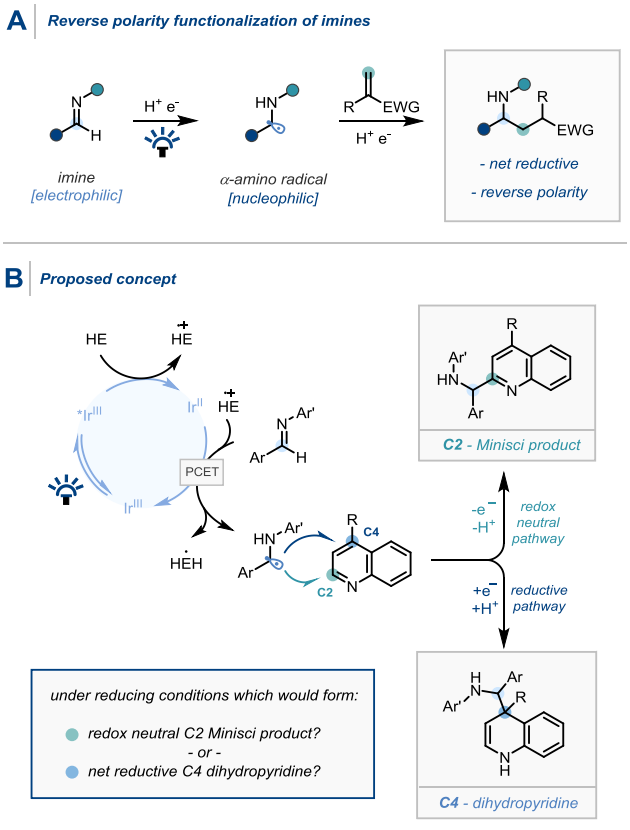
Jamie A. Leitch,[a] Tatiana Rogova, [a] Fernanda Duarte,[a] and Darren J. Dixon[a]**

Abstract: *The construction of diverse sp^3-rich skeletal ring systems is of importance to drug discovery programmes and natural product synthesis. Herein, we report the photocatalytic construction of 2,7-diazabicyclo[3.2.1]octanes (bridged 1,3-diazepanes) via a reductive diversion of the Minisci reaction. The fused tricyclic product is proposed to form via radical addition to the C4 position of 4-substituted quinoline substrates, with subsequent Hantzsch ester-promoted reduction to a dihydropyridine intermediate which undergoes in situ two-electron ring closure to form the bridged diazepane architecture. A wide scope of N-arylimine and quinoline derivatives was demonstrated and good efficiency was observed in the construction of sterically congested all-carbon quaternary centers. Computational and experimental mechanistic studies provide insights into the reaction mechanism and observed regioselectivity/diastereoselectivity.*

Introduction

Photocatalytic one-electron activation of organic substrates has granted access to complementary and/or unprecedented reactivity to established two-electron chemistry.[1] In this context, the generation and manipulation of α-amino radicals has become a prominent research focus in recent years.[2] Furthermore, the photocatalytic single electron reduction – often proton coupled electron transfer (PCET) reduction – of classically electrophilic imine derivatives,[3] has emerged as a new pathway to create such key α-amino radicals. These nucleophilic intermediates have been shown to then engage a variety of transformations including radical-radical coupling[4] and reaction with electrophilic species.[5] The latter of these methods represents challenging umpolung cross-electrophile coupling,[6] nevertheless recent research has established this technique as a valuable avenue towards decorated α-functionalized amines (Scheme 1A). Notwithstanding these advances, current methods largely rely on the use of classical electrophilic Michael acceptors such as acrylates, and (hetero)styrene derivatives, and accordingly, adapting this chemistry towards new classes of electrophiles such as heteroaromatic ring systems could bring new synthetic opportunities.

The functionalization of quinoline motifs has become a commonplace target in Minisci-type chemistry,[7] and reactivity at both C2 and C4 positions has been established, although often with selectivity issues arising in unbiased systems.[7d],[8] Whilst recent photocatalytic approaches have enabled selective C2 functionalization through hydrogen bonding networks,[8a] selective radical functionalization at the C4 position (without blocking the C2 position) still remains a challenge.[9] We reasoned that judicious choice of reaction conditions could permit an α-amino radical – created from PCET of an imine derivative enabled by a Hantzsch ester reductant and photocatalyst[10] – to add to a suitable Minisci acceptor such as lepidine (4-methylquinoline, Scheme 1B). Due to the reducing nature of the reaction medium required to form the α-amino radical (e. g. stoichiometric quantities of reductant), a question of regioselectivity arose with two possible products potentially accessible under the conditions. Firstly a classical redox neutral Minisci functionalization at C2 or secondly – in the case of C4 addition where rearomatization is not possible – the net reductive dearomatized dihydropyridine. Either way, unlocking new reactivity with abundant amine, aldehyde, and quinoline reagents to generate any C–C linked structures is of general synthetic interest, and herein we wish to report our findings.



Scheme 1. Photoredox catalysis in reverse polarity synthesis, and proposed concept for quinoline functionalization

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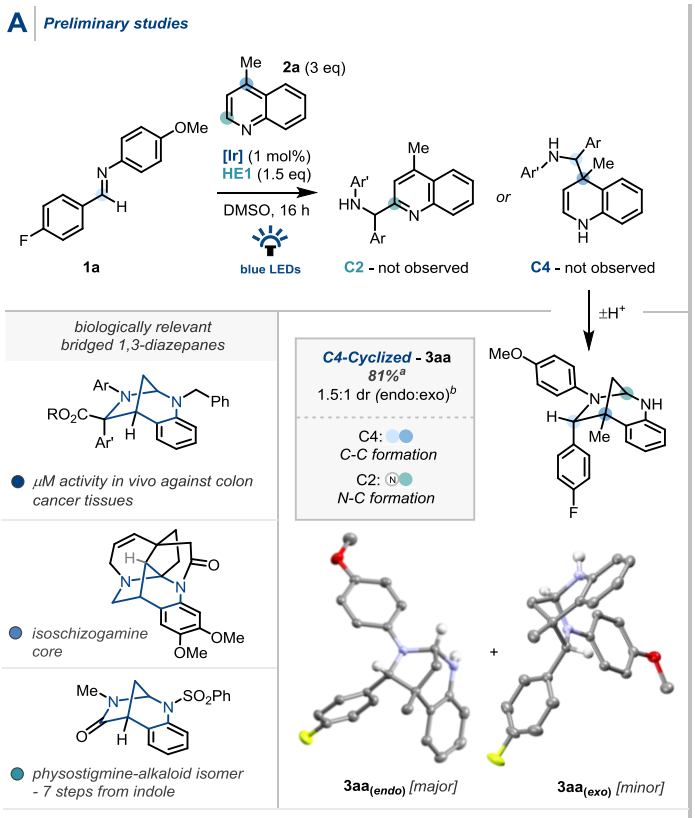
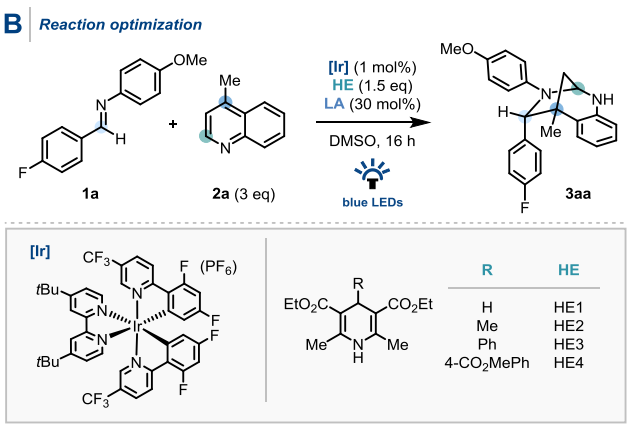
Results and Discussion

We began our investigation using fluorine tagged imine (**1a**), 4-methylquinoline (lepidine, **2a**), $[Ir(dFCF_3(ppy))_2(dtbbpy)]PF_6$ (1 mol%) as photocatalyst, the commercial Hantzsch ester (**HE1**) as stoichiometric reductant, in DMSO, under blue light irradiation (Scheme 2A). Excitingly, good reactivity was observed from preliminary experiments. Interestingly however, neither C2-Minisci product nor C4-dihydropyridine were formed; the major product isolated was a fused tricyclic 2,7-diazabicyclo[3.2.1]octane (or bridged 1,3-diazepane), the cycloisomerized adduct of the anticipated C4-dihydropyridine. This transformation constitutes a formal diversion from classical Minisci chemistry towards the dearomatization of the quinoline heterocycle, forming an unusual fused tricyclic framework possessing four new sp^3 carbon centres. It also exemplifies the synthetic utility that dearomative photochemistry can provide as a tool in upgrading abundant two-dimensional feedstock chemicals into structurally complex sp^3-rich three-dimensional frameworks,[11] a concept thoroughly explored in seminal work by Sarlah[12] and others.[13] Furthermore, photocatalytic dearomatization methods have potential benefits over other complementary approaches using the exhaustive hydrogenation of (hetero)arenes, notably in the formation of bridged heterocycles.[14],[15]

Although bridged 1,3-diazepane structures have been shown to possess *in vivo* anti-cancer activity;[16] and are present in natural products and corresponding analogues,[17] the heterocycle remains synthetically challenging to access. Accordingly, we were eager to further develop this quinoline dearomatization system as a novel access point to this underexplored architecture.[18]

Previously, our group has reported that the use of bespoke Hantzsch ester reductants can modulate reactivity and in turn increase product yield and / or improve diastereoselectivity.[5d],[5f],[19] A survey of Hantzsch ester reductants (Scheme 2B, entries 2-4) demonstrated that methyl carboxyphenyl derivative (**HE4**) led to increased conversion to product (90%) and to a higher diastereomeric ratio (1.9:1, for further optimization details, see supporting information). From a variety of additives, we were pleased to observe that certain Lewis acids increased the diastereoselectivity of this transformation, with zinc triflimide performing most effectively (entries 5-7). Sterically demanding Lewis acids – such as methylaluminium bis(2,6-di-tert-butyl-4-methylphenoxide) (MAD) – unfortunately led to a complex mixture of products.



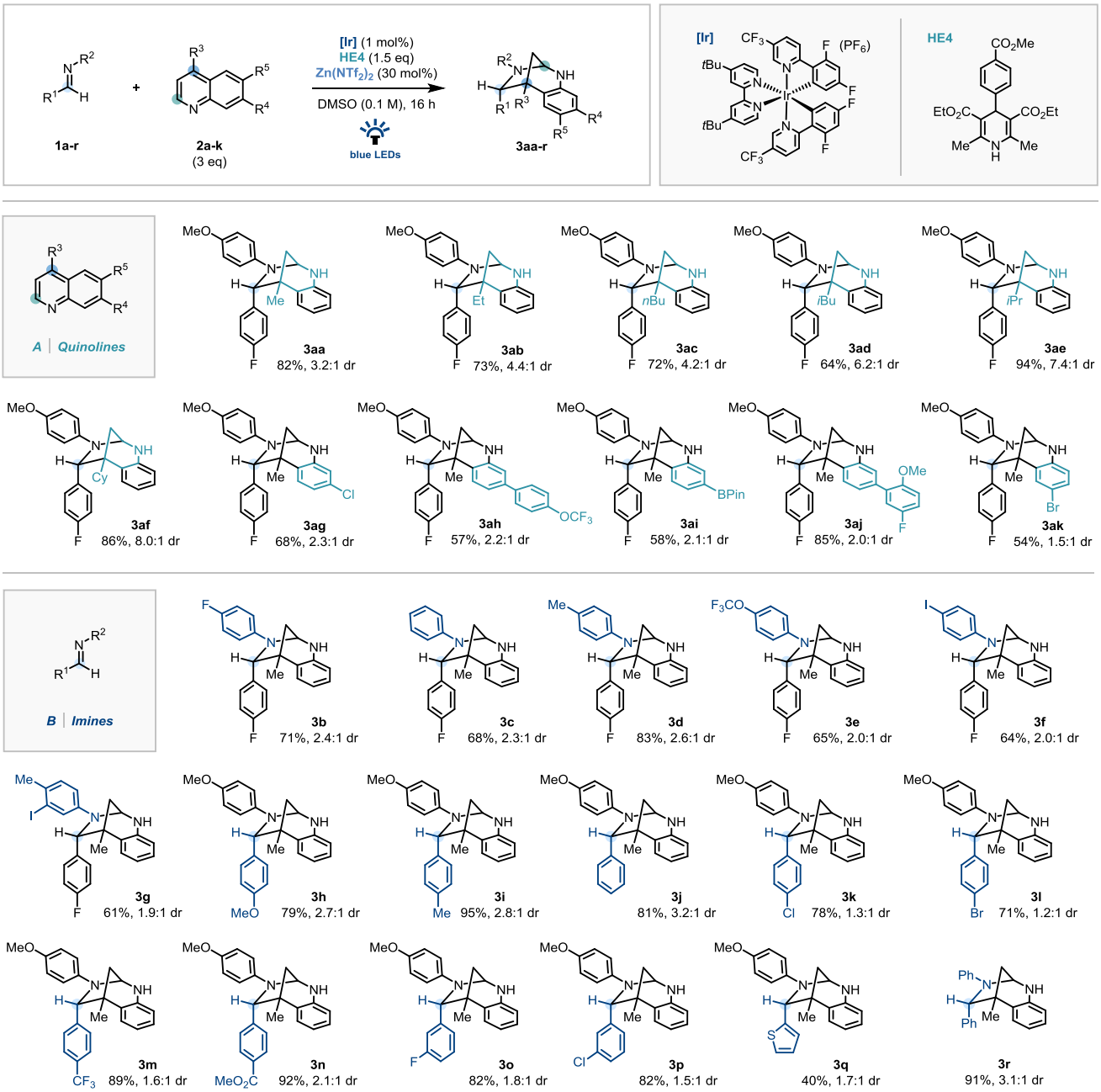


Entry	HE	LA	3aa[a]	dr[b]
1	HE1	-	81	1.5 : 1
2	HE2	-	77	2.0 : 1
3	HE3	-	88	1.5 : 1
4	HE4	-	90	1.9 : 1
5	HE4	$Sc(OTf)_3$	100	1.1 : 1
6	HE4	$Zn(OTf)_2$	94	2.5 : 1
7	**HE4**	**$Zn(NTf_2)_2$**	**94 (82)[c]**	**3.2 : 1**
8	*no iridium photocatalyst*		Trace	-
9	*no HE*		Trace	-
10	*no light*		-	-
11	***imine formed in situ***		**95**	**3.0 : 1**

[Ir] = $[Ir(dFCF_3)ppy)_2(dtbbpy)]PF_6$, HE1 = diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate. [a] = NMR yield determined by analysis of $^{19}F\{^1H\}$ NMR of crude reaction mixture. [b] Diastereoselectivity (endo:exo) determined *via* ^1H NMR analysis of the crude reaction mixture

General Conditions: **1a** (0.1 mmol), lepidine **2a** (0.3 mmol), $[Ir(dFCF_3)ppy)_2(dtbbpy)]PF_6$ (0.001 mmol, 1 mol%), Hantzsch ester (1.5 eq), DMSO (0.1 M), 16 h, under a nitrogen atmopshere under blue light irradiation using 18 W LED lamp. [a] Formation of **3a** calculated by direct conversion between SM and **3a** *via* $^1H\}^{19}F$ NMR including byproducts. [b] dr (endo:exo) was calculated *via* ^1H NMR analysis of the crude reaction mixture . [c] Isolated yield after silica gel column chromatography.

Scheme 2. Preliminary studies and subsequent optimization of photocatalytic dearomative construction of bridged 1,3-diazepanes.

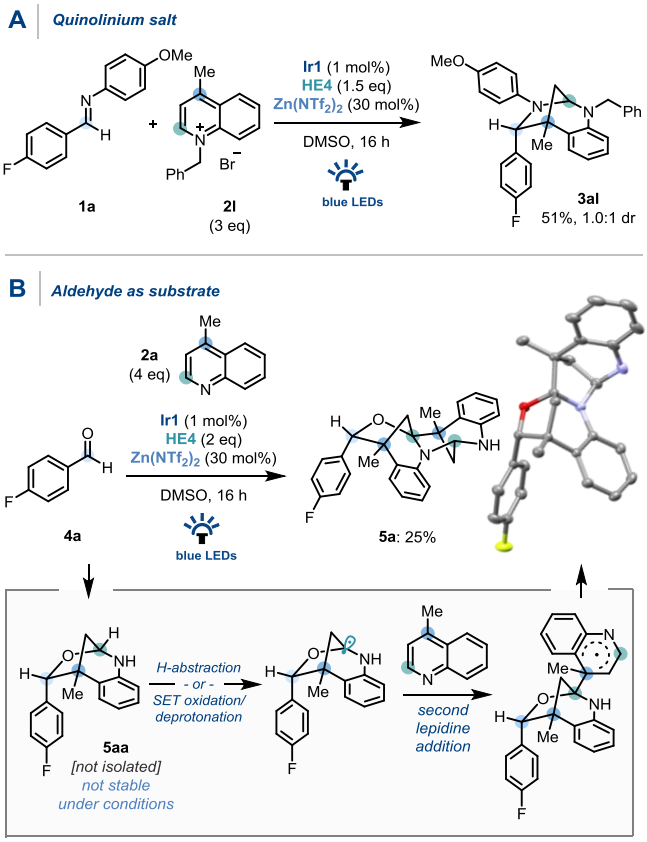


Scheme 3. Substrate scope for the dearomative photocatalytic construction of bridged 1,3-diazepanes

Importantly, control experiments elucidated that the iridium photocatalyst, the Hantzsch ester, and blue light irradiation were all essential for reactivity (entries 8-10). This methodology was also shown to be compatible with *in situ* formation of the imine (entry 11).[20]

With optimal conditions established for this, we explored how substitution patterns across the quinoline moiety affected product formation (Scheme 3A).[21][22] Pleasingly with increased steric demand at the 4-position, ethyl (**3ab**), *n*-butyl (**3ac**), and *i*-butylquinoline (**3ad**) substrates performed with greater diastereoselectivity and reaction efficiency was maintained.

Furthermore, isopropyl (**3ae**) and cyclohexyl (**3af**) derivatives were well-tolerated, with product structures obtained in high yields and excellent diastereoselectivity. When exploring substitution on the aryl moiety of the quinoline, this chemistry was shown to be amenable to functionalization at the 7-position (**3ag**-**3aj**), with starting materials readily prepared from commercially available 4,7-dichloroquinoline. Notably, the pinacol boronate derivative (**3ai**) was tolerated. Gratifyingly, C6-substitution was also amenable to substitution with 6-bromolepidine performing well, further incorporating functional handles into the product (**3ak**).



Scheme 4. (A) Use of the quinolinium salt. (B) Use of α-oxoradical in the methodology.

The imine component was then studied, initially with variation to the aniline fragment (Scheme 3B). A variety of functionality was well-tolerated in this methodology including trifluoromethoxyarene (**3e**) and iodoarenes (**3f**-**3g**). Furthermore the aldehyde fragment of the imine was varied, and a wide electronic profile tolerance varying from electron-releasing methoxy (**3h**) to electron withdrawing trifluoromethyl (**3m**) and ester derivatives (**3n**), was observed. *meta*-Substituted arenes (**3o**-**3p**) also performed efficiently as did a thiophene derivative (**3q**), albeit in reduced yield.

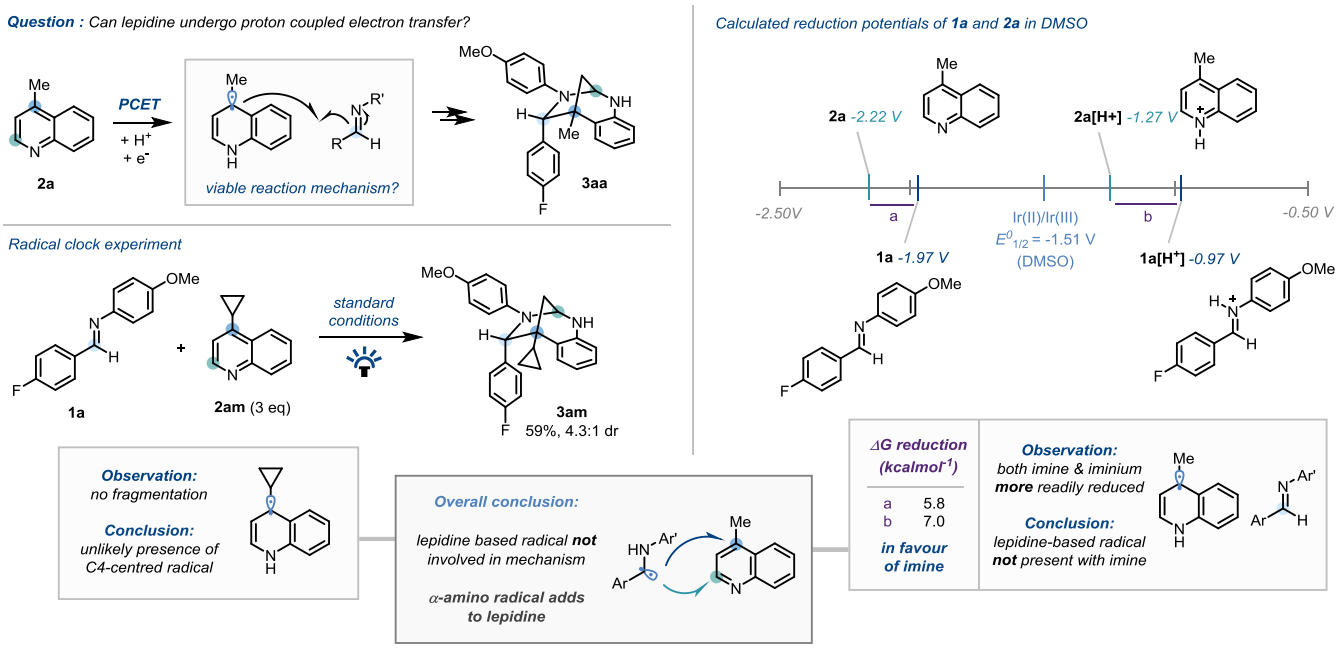
As previous reports on quinoline dearomatization have required pre-activation of the quinoline substrate as *N*-alkyl quinolinium salt to permit reaction efficiency,[16b],[18c] we reasoned that this salt could also engage in this chemistry. Pleasingly when *N*-benzyl lepidinium bromide (**2l**) was exposed to the dearomatization conditions, the *N*-benzyl diazepane structure was also observed, although any diastereoselectivity witnessed previously was suppressed (**3al**, Scheme 4A). The addition of the Lewis acid remained beneficial to this transformation, suggesting that zinc coordination to the nitrogen atom on the α-amino radical rather than the quinoline moiety could be relevant.

Recent research in the area has demonstrated that aldehydes react similarly in reductive photocatalytic conditions to imine substrates.[4],[5] Accordingly, we investigated whether an aldehyde substrate was also amenable to this dearomative chemistry to give the corresponding hemiaminal adduct (Scheme 4B). Interestingly, however, when 4-fluorobenzaldehyde (**4a**) was submitted to the reaction conditions a fused tetracyclic structure **5a** was observed as the major product amongst a mixture of other compounds. This complex molecular architecture is derived from the formal addition of two lepidine molecules to an α-oxoradical. We propose that this takes place initially *via* formation of the hemiaminal product (analogous to that observed in the case of the imine). Subsequent direct or indirect net loss of a hydrogen atom provides the open shell α-amino radical which can then participate in C–C bond formation at the C4 position of a secondary lepidine molecule. Subsequent reduction followed by *in situ* cyclization affords the structurally complex sp^3-rich fused hexacyclic **5a**. Single crystal X-ray diffraction analysis of this structure confirmed the bridgehead connectivity, with notably two C–C bond formations at C4 taking place, along with the construction of two connected quaternary centres.

Mechanistic Studies

Determination of active radical species. Whilst the single electron reduction of imine derivatives has become well established,[4],[5] a few recent reports[9b],[23] have demonstrated that quinoline / pyridinium molecules can be activated in redox pathways to create heteroarene-centred radicals. An alternative mechanism was plausible, in which proton coupled electron transfer of a lepidine molecule would result in a C4-centred radical on the lepidine and which could viably add to an imine molecule (Scheme 5, left). To study this, first we conducted a radical clock experiment using 4-cyclopropyllepidine (**2am**) where the presence of a stabilized C4-radical would lead to favourable fragmentation of this cyclopropyl unit to the primary radical. Interestingly, the diazepane product was still formed in good yield and dr (**3am**) with the cyclopropyl unit remaining intact and no fragmentation adducts were observed.[24]

Furthermore we computed the redox potentials of **2a** and **1a** relative to the catalyst (Scheme 5, right, see supporting information for further details). Values of –2.22 V and –1.97 V were obtained for **2a** and **1a** respectively, which are outside the reduction capacity of $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (calculated as $E^{red}_{1/2}$ $[Ir^{III}/Ir^{II}]$ = –1.51 V in DMSO (vs. –1.37 V in MeCN).[1a],[25] This suggests that H-bond interactions and/or a certain degree of protonation is essential for raising the reduction potential of these molecules into an accessible range.[10] Whilst predicting the extent of imine protonation at the event of electron transfer is challenging,[26] calculation of the reduction potentials for both the imine (**1a**) and lepidine species (**2a**), in both their neutral and protonated forms, provides an estimate of the operating window. As expected, protonation raises the reduction potentials (easier to reduce) for both **1a** and **2a** species into the operating range of the photocatalyst [Ir]. The fact that the reduction potential of iminium **1a[H$^+$]** is 0.30 V higher than the protonated **2a[H$^+$]** counterpart strongly suggests that the active radical species is formed from the imine starting material **1a** rather than the lepidine coupling partner **2a**.



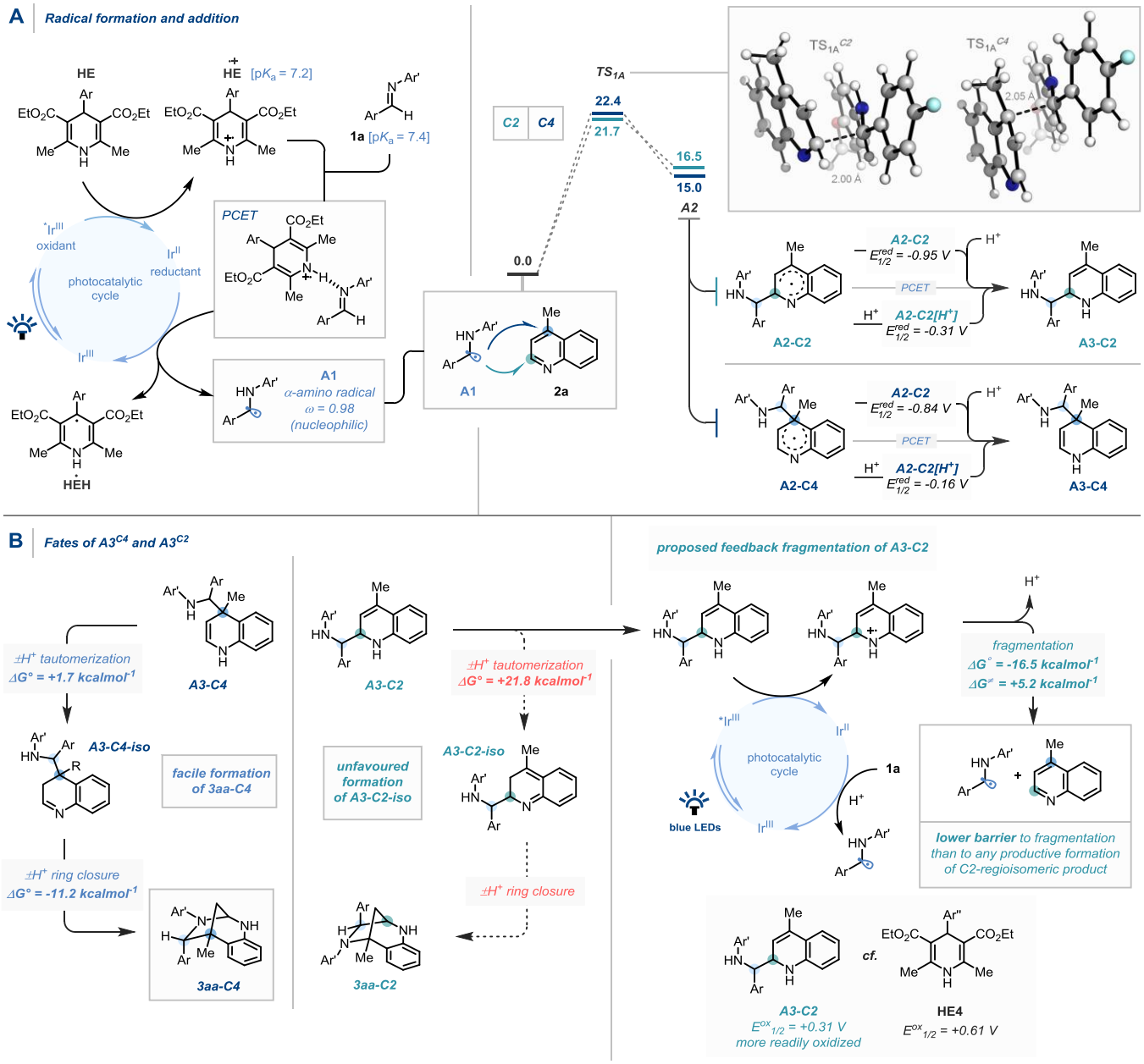
Scheme 5. Study into the nature of the radical species operating in the mechanism.

This result along with experimental studies allows us to rule out the presence of a lepidine based radical. On studying the pK_{BH+} value of the substrate (**1a**, pK_{BH+} = 7.4) we suggest that the partially oxidized Hantzsch ester radical cation (pK_a = 7.2) is acidic enough to facilitate the proton coupled electron transfer event to deliver the key nucleophilic α-amino radical (**A1**, ω = 0.98,[27] Scheme 6A, left).

C4/C2 selectivity. Having identified the active radical species we then investigated the regioselectivity of C–C bond formation via computational methods. Although partial protonation may be relevant for the transformation; for simplicity, our initial model considered radical addition to a neutral lepidine molecule.[28]

Initially the addition of the α-amino radical to either the C2 or C4 position of the lepidine coupling partner was explored. Density Functional Theory (DFT) calculations at the SMD(DMSO)-ωB97X-D/6-311++G(d,p)//SMD(DMSO)-ωB97X-D/6-31G(d) level of theory show that the C2 position is slightly preferred, albeit within computational error ($\Delta G^{\ddagger}_{(C2)}$ = 21.7 vs $\Delta G^{\ddagger}_{(C4)}$ = 22.4 kcal mol^{-1}).[29] The resulting radical aromatic intermediates **A2-C4** & **A2-C2** are high in energy (cf. **A1** and **2a**), with the C4 intermediate slightly more stable (16.5 vs 15.0 kcal mol^{-1} for C2 and C4 respectively, Scheme 6A). These results suggest a reversible radical addition, where both pathways could be populated under thermodynamic control. Subsequently, the radical aromatic intermediates **A2-C4** & **A2-C2** undergo formal addition of a hydrogen atom to afford the dihydropyridine. The redox potentials associated with this process showed that **A2-C4** is more readily reduced than **A2-C2** ($E^{red}_{1/2}$ = –0.85 V vs –0.95 V for **A2-C4** and **A2-C2** respectively). A similar trend is observed for the protonated A2 intermediate (**A2[H$^+$]**) ($E^{red}_{1/2}$ = –0.16 V vs -0.31 V for **A2-C4[H$^+$]** and **A2-C4[H$^+$]** respectively). It is noteworthy that all four are sufficiently oxidizing to take an electron from the Hantzsch ester intermediate HEH· ($E^{ox}_{1/2}$ = –1.15 V). This transformation likely takes place as a concerted PCET, with the true reduction potentials for **A2-C2** and **A2-C4** lying between the two calculated values.

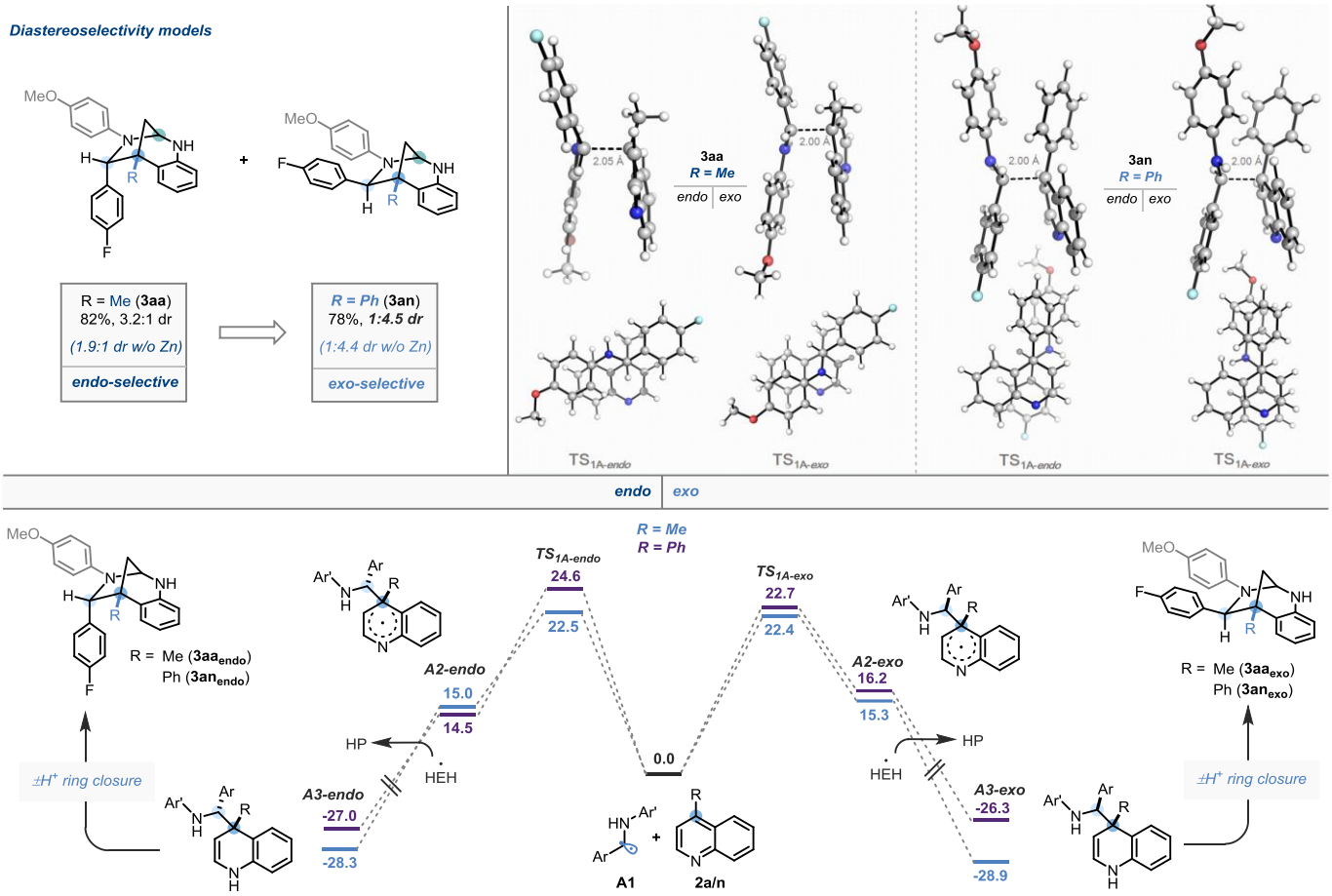
Furthermore, we investigated the plausible fates of dihydropyridines **A3-C4** and **A3-C2** (Scheme 6B). We observed that the tautomerization and subsequent ring closure of **A3-C4** to form **3aa-C4** is energetically facile (ΔG° = –11.2 kcalmol^{-1}), indicating why the dihydropyridine structure is not detected. Control experiments deduced that both diastereomers of this framework are stable to further re-subjection to the reaction conditions with or without Hantzsch ester. In contrast, tautomerization from **A3-C2** is substantially less favourable (ΔG° = +21.8 kcalmol^{-1}), suggesting this structure has no plausible downhill two-electron pathway. Despite this, from our previous calculations we were aware that this substrate can undergo single electron oxidation to the corresponding radical cation ($E^{ox}_{1/2}$ = +0.31 V). In fact this substrate is more readily oxidized than the Hantzsch ester reductant (**HE4**) ($E^{ox}_{1/2}$ = +0.61 V). For these reasons, we hypothesize that **A3-C2** will competitively quench the photoexcited iridium(III) species ($E^{ox}_{1/2}$ = +1.21 V) in favour of the Hantzsch ester. As the reaction conditions are net reducing we expect no further oxidation to the Minisci product. Following the single electron oxidation, there is a low energetic barrier to fragmentation of this radical cation intermediate to the corresponding α-amino radical and lepidine ($\Delta G^{\ddagger}$ = +5.2 kcalmol^{-1}, ΔG° = –16.5 kcalmol^{-1}). Aligned to previous reports detailing the reversibility in Minisci-type radical additions, we conclude that this fragmentation pathway is fully plausible.[7d],[8a]



Scheme 6. Mechanistic studies into C4 vs. C2 regioselectivity with *in silico* insights: (A) Radical addition. (B) Fates of both C2 and C4 dihydropyridine adducts.

As the reducing iridium(II) species formed above can then reduce a further molecule of **1a** through a PCET mechanism (with the proton lost in fragmentation), this feedback loop reforms an equivalent of the α-amino radical with no net exhaustion of reaction components. Whilst fragmentation is also feasible for **A3-C4** ($E^{ox}_{1/2}$ = +0.12 V), as no viable downstream path for **A3-C2** exists, we consider this mechanism responsible for the amplification of regioselectivity, with yields up to 95% of the experimentally observed C4 product.

Diastereoselectivity. Despite *endo* selectivity predominating throughout the scope, when 4-phenylquinoline (**1an**) was introduced as the coupling partner, a switch in diastereoselectivity was observed (Scheme 7). In this case, the *exo* isomer was favoured in a 4.5:1 dr (**3an**). The diastereomeric preference of the reaction is set by the initial addition of the α-amino radical **A1** into the respective quinolines **2a**/**2m** (**TS₁**). DFT calculations demonstrate that for **3aa** (derived from lepidine), the transition state energy difference was negligible between the *endo* and *exo* diastereomers. Conversely, for substrate **3an** (derived from 4-phenylquinoline), **TS$_{1\text{-}exo}$** is lower in energy by 1.9 kcal mol^{-1} with respect to **TS$_{1\text{-}endo}$**. A visual comparison (Scheme 7, top right) of the transition structures reveals that the phenyl substitution on quinoline **2n**, results in a change of orientation of the free α-amino radical species. This alternative conformation maximises π-π stacking interactions between the phenyl substituent on **2n** and the *N*-aryl group on the α-amino radical.



Scheme 7. Computed origins of diastereoselectivity

The degree of π-orbital overlap that could be achieved in the transition states of the **3an** *exo* and *endo* structures possibly has a greater effect on the energy difference than for the diastereomers of **3aa**. This change in atomic arrangement of radical addition accounts for the switch in diastereoselectivity.

Conclusion

In conclusion, a mild and practical method for the photocatalytic coupling of simple *N*-arylimines and quinolines into bridged 1,3-diazepane frameworks has been developed. This was achieved *via* diverting the classical Minisci reaction using net reducing conditions to permit dearomatization and cyclization events. The optimized method was shown to be tolerant of a range of functional groups with the formation of 31 examples of the fused tricyclic structure with yields up to 95% and diastereoselectivity up to 8.0:1 dr. Excellent regioselectivity for C–C bond formation at C4 was observed throughout the study. These results were rationalised *via* computational studies whereby a fragmentation/recycling method for unobserved C2 functionalized products into the C4 diazepane was postulated. This method offers a valuable step in the rapid construction of complex sp^3-rich heterocycles with demonstrable efficiency and regioselectivity. Further studies into new reactivity of related radical precursors are currently underway, and the results will be disclosed in due course.

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Keywords: Dearomatization, photocatalysis, quinoline, sp^3 framework, diazepane

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Graphical Abstract