Photocatalytic Generation of Alkyl Carbanions from Alkenes

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Abstract

Organometallic reagents are routinely used as fundamental building blocks in organic chemistry to rapidly diversify molecular fragments via carbanion intermediates. However the catalytic generation of carbanion equivalents particularly from sp^3-hybridized alkyl scaffolds, remains an underdeveloped goal in chemical synthesis. To align with the demands of modern synthetic protocols, a general method for the catalytic generation of alkyl carbanions must operate under benign reaction conditions and access commercially available feedstock chemicals. Alkenes constitute an attractive source of latent alkyl carbanion equivalents, however methods for the conversion of carbon-carbon π-bonds into carbanions is challenged by the need for precious metals and aggressive stoichiometric reductants. Here we disclose an approach for the controlled generation of 2-electron carbon nucleophiles via single electron reduction of aryl alkenes, facilitated by the highly reducing environment of multiphoton photoredox catalysts. We demonstrate that alkene radical anions engage in catalytic, metal free, intermolecular C-C bond-forming reactions with carbonyl derivatives, in a manner analogous to Grignard reagents. Under this reaction manifold, the alkene can be considered a dicarbanion synthon offering new opportunities for orthogonal diversification. This concept was illustrated by the development of four distinct C-C bond forming reactions with aromatic alkenes: hydroalkoxylation, hydroamidation, aminoalkylation and carboxyaminoalkylation, to generate a range of valuable and complex scaffolds.

Introduction

More than a century ago, Victor Grignard reported that metalated organic reagents react with carbon electrophiles to form new carbon-carbon (C-C) bonds.[1] The generation and reaction of nucleophilic carbanions from organometallic reagents have since played a defining role in chemical synthesis, facilitating the rapid assembly of higher order intermediates and complex target molecules. Despite the tremendous impact that stoichiometric organometallic reagents have had on chemical synthesis, the production of fine chemical, pharmaceutical and advanced material products via metalated organic reagents is complicated by challenges associated with safety, the generation of waste metal salts and the need for aggressive low-valent metal terminal reductants.[2] Further disadvantages include reaction conditions and the need to employ expensive or scarce organohalide starting materials as carbanion precursors.

The development of catalytic methods to generate carbanions is an attractive strategy to overcome the limitations of traditional stoichiometric organometallic coupling protocols.[2] Historically, the catalytic generation of carbon

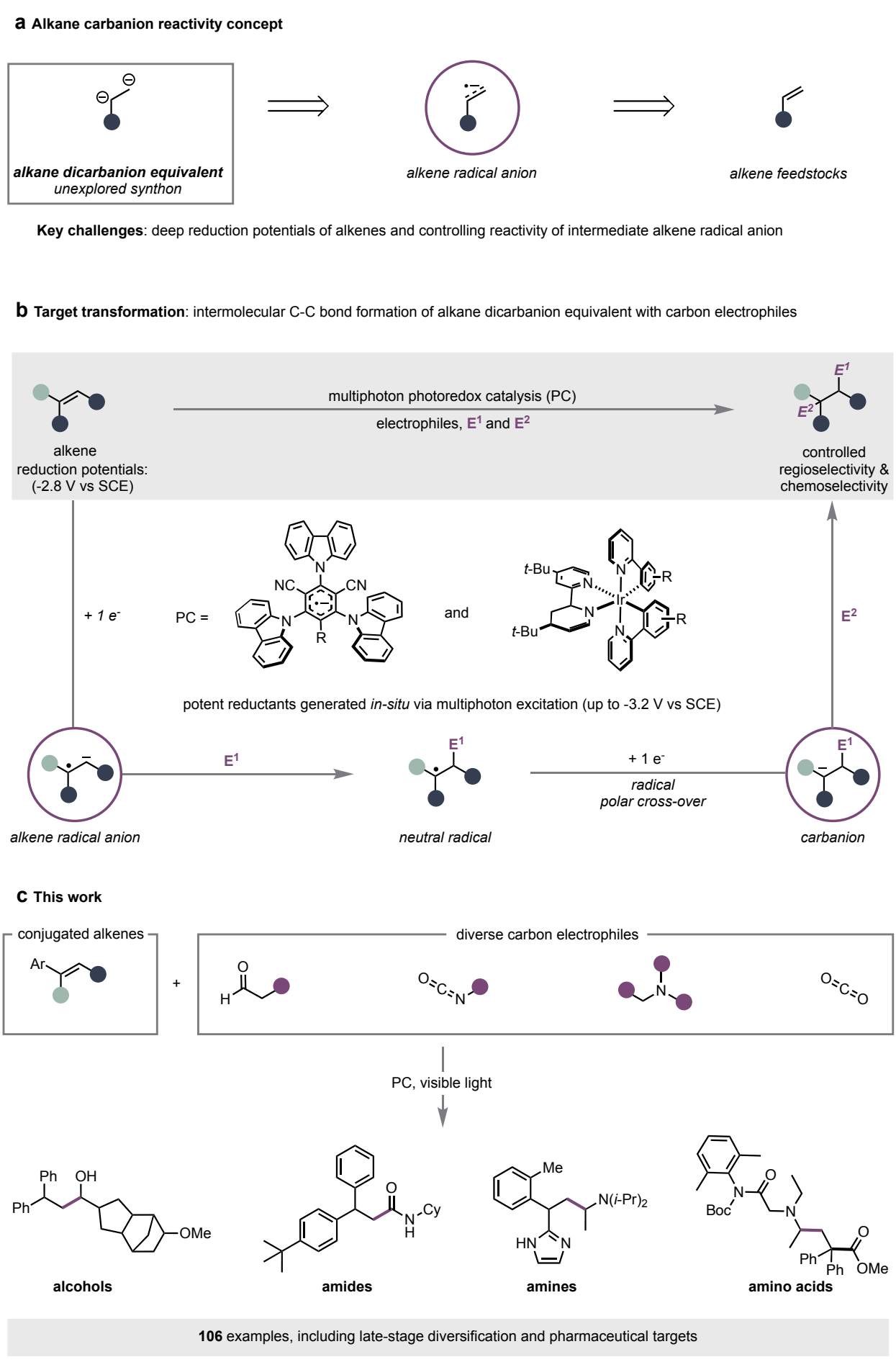

Fig. 1. Development of the alkane carbanion reactivity concept.

nucleophiles in the absence of stoichiometric metals has been advanced by protocols that furnish acyl anion equivalents via carbonyl umpolung strategies.[3-5] Although effective, these protocols are generally limited to installation of carbonyl functional groups and lack the versatility of classical organometallic reagents. In contrast, alkyl carbanion equivalents offer greater structural diversity, however methods for their catalytic generation remain scarce.[6-9]

Synthetic chemists have explored π-unsaturated systems as latent alkyl carbanion equivalents under transition metal catalysed conditions.[2] *In-situ* insertion of a metal hydride into an alkene generates an nucleophilic organometallic intermediate, capable of direct coupling with carbon electrophiles.[10-13] These reactions, however, typically require hazardous stoichiometric reductants such as silanes, boranes or hydrogen gas. Furthermore, owing to high basicity of organometallic intermediates the scope of carbon electrophiles is predominantly limited to aromatic or sterically hindered aldehydes to avoid unwanted aldol condenzation pathways. Despite current limitations, the generation of alkyl carbanion equivalents from alkenes is particularly attractive as they are feedstock material obtained at tonne scales from the petroleum industry and agricultural sector. The structural diversity and abundance of alkenes is highlighted by the commercial availability of approximately 330,000 derivatives,[14] making alkenes an ideal progenitor pool for carbanion building blocks.

Recent advances in reductive photoredox catalysis have enabled the generation of radical anions from π-unsaturated systems.[5,15-29] Pioneering studies from König established that the radical anion derived from heterocycles and naphthalene was sufficiently nucleophilic to engage CO_2 and a limited range of ketone electrophiles.[25] This method was extended to a single example of an alkene (styrene) viably forming a nucleophilic radical anion, however the alkene remained intact in the final product, limiting substrate scope to formation of C(sp^2) architectures. Previous work in our laboratory[15] and later by Nicewicz[23] has shown that vinyl radical anions are viably generated by highly reducing photocatalysts. Under this mechanistic manifold, the high onset of reduction for C-C π-bonds (up to – 3.0 V vs SCE) is overcome by the *in-situ* generation of a potent photoreductant via sequential visible-light multiphoton excitation of iridium[30] or acridinium[31] photoredox catalysts. These vinyl radical anions undergo reaction with alkyl ketones, however the inherent moderate nucleophilicity narrows intermolecular reactivity to a small number of ketones or to thermodynamically biased intramolecular reactions with substrates bearing tethered alkenes and ketones or aldehydes. This approach is further complicated by the closely matched onset of reduction for alkyl ketones and unactivated aryl alkenes, which leads to competing and wanted reactivity dervived from ketyl radical formation. Thus, despite these advances, a general platform that accommodates the direct catalytic and chemoselective generation of alkyl carbanions directly from alkene feedstock chemicals, and their viable reaction with a range of carbon electrophiles remains an unmet goal in chemistry.

To address these limitations and unlock the full potential of alkenes as latent alkyl carbanion equivalents, we reimagined the alkene as a dicarbanion synthon (Fig 1A). In this way, a carbanion can be considered to reside at the α or β carbons of the former π-system and offer new opportunities for the regioselective functionalization of weakly nucleophilic alkenes with electrophiles. Central to this strategy is the generation of an alkene radical anion and we hypothesized that the highly nucleophilic carbanion could readily undergo rapid nucleophilic attack with a weak electrophile, and the resultant neutral radical could undergo radical polar crossover[32] followed by quenching, to furnish the functionalized alkane (Fig 1B). To achieve this design goal, we postulated that the highly reducing environment of multiphoton photoredox catalysts served two important roles; firstly enabling the facile yet controllable generation of radical anions from diverse alkenes, and secondly promoting a kinetically favoured rapid polar

crossover of the neutral radical species subsequent to coupling with a electrophile, to generate a second carbanion that could be readily quenched by a proton source or further diversified via a second electrophilic species.

Our proposed tactic firstly assumes a distonic-like character of alkene radical anions, where the carbanion and radical spin density are separated and reside on two different carbon atoms of the former π-system. Secondly, our approach exploits the anticipated differential reactivity of the carbanion and neutral radical species of the initially formed alkene radical anion. We therefore anticipate two kinetically resolved processes; a rapid nucleophilic attack of the anion to generate a stabilized neutral radical, which could then be rapidly reduced to a carbanion and elaborated in an orthogonal fashion. This strategy would avoid complex side reactions arising from the neutral radical species, including homocoupling, or hydrogen-atom transfer (HAT), which are often encountered in electrochemical or reductive-quenching photocatalysis.[33,34]

Herein we report a new and general strategy that exploits the radical anion of vinylarenes as the linchpin for the facile generation of alkyl dicarbanion equivalents and their coupling with electrophilic coupling partners under visible light irradiation. Inspired by the commercial availability and structural diversity of vinylarenes, the synthetic potential of this approach to alkyl carbanion generation is demonstrated by the discovery of four new C-C bond forming reactions. Firstly the development of a method for the intermolecular alkene-aldehyde coupling of alkenes with aliphatic aldehydes is established. Detailed mechanistic studies confirm the “alkene first” mechanism which was achieved by careful tuning of the catalyst properties. Secondly, a metal-free approach for the synthesis of amides via a direct addition of an alkene to isocyanates was developed. Thirdly, a distinct approach to the synthesis of tertiary and secondary aliphatic amines was uncovered, that relies upon simultaneous oxidative C-H activation of amines, and reductive alkene activation of vinylarene derivatives, enabling intermolecular aminoalkylation of range of electron neutral- and electron-rich vinylarene derivatives. To showcase the utility of our developed methodology, we synthesized a selection of H_1-antihistamine drugs, in one step, from readily available tertiary and secondary amines and alkenes, and demonstrated late-stage functionalization of six pharmaceutical agents. This method was then extended to the preparation of γ-amino acids via chemoselective alkene dicarbofunctionalization protocol with amines and CO_2 in continuous flow.

Results and Discussion

Alkene – Aldehyde Coupling

Addition of carbon nucleophiles to aldehydes is a valuable transformation, owing to the prevalence of secondary alcohols as synthetic handles for further elaboration into complex molecular scaffolds. Direct alkylation of aldehydes under photoredox conditions is typically accomplished via single electron reduction of an aldehyde to a nucleophilic ketyl radical, which is trapped by an electron deficient alkene coupling partner.[35-37] The deeply negative redox potentials of carbonyl compounds, high nucleophilicity of ketyl radicals, and their propensity to undergo Pinacol-type coupling limits the scope to reactions between aromatic aldehydes and electron deficient alkenes.[38-41] In a notable exception, Nicewicz and co-workers demonstrated that aliphatic aldehydes engage in intramolecular cyclizations with styrene derivatives.[23] We postulated that radical anions derived from aromatic alkenes could undergo nucleophilic addition to neutral aliphatic aldehydes, to generate *anti*-Markovnikov secondary alcohols without competing aldol condensation pathways. Facile reduction of the resultant benzylic radical to the corresponding carbanion followed by

quenching with proton sources, enables the controlled and selective hydrofunctionalization of alkenes, in which the alkene functions as latent alkyl carbanion equivalent in the absence of transition metal catalysts.

Reaction development. Investigation commenced with the development of a reductive alkene-aldehyde coupling between 1,1-diphenylethylene **1a** ($E_{p/2}$ = -2.38 V vs SCE) and propionaldehyde **2a** ($E_{p/2}$ = -2.45 V vs SCE). It was reasoned that the controlled generation of the alkene radical anion should promote selective addition to the aldehyde and suppress unwanted decomposition pathways. To achieve effective concentrations of the radical anion that avoids unproductive reactivity, selection of a catalyst with sufficient negative reduction potentials but slow rates of single electron transfer is critical to reaction development. To this end, heteroleptic Ir complexes capable of generating potent photoreductants via the tandem photocatalytic cycle[30] were unexpectedly unproductive with trace product observed (Figure S1, SI). Dicyanobenzene donor-acceptor complexes exhibit deep reduction potentials (E^{red} < -3.0 V vs SCE) via consecutive photoinduced electron transfer (conPET).[42,43] The archetypal 4CzIPN gave improved yields of **3a** (15%; Fig 2 and Figure S1, SI) relative to the closed shell Ir complex; however, this was accompanied by significant decomposition. We reasoned that switching to a less reducing catalyst with increased steric bulk to supress rates of SET would improve the yield. Pleasingly, 3-^{t}BuCzFIPN (E^{red} = - 1.21 V vs SCE), delivered improved yields and exceptional levels of selectivity for the targeted reaction. On the other hand, the use of highly reducing 3-DPA2FPN (E^{red} = - 1.92 V vs SCE) resulted in complete decomposition, further confirming that a slow onset of alkene reduction is required for the controlled generation of the radical anion. Further parameter exploration (catalyst equivalents, aldehyde stoichiometry, solvent and reaction concentration) identified optimized reaction conditions; 2 mol% of the 3-^{t}BuCzFIPN catalyst, 3 equivalents of aldehyde and 1.1 equivalents of ^{i}Pr$_2$NEt as the reductive quencher in DMA at 0.05 M concentration. Irradiation with 14W 448 nm LEDs for 15 hours produced the desired alcohol **3a** in 76% isolated yield. The reaction displayed full selectivity for anti-Markovnikov hydrofunctionalization, with no evidence for the competing oxidation of the benzylic radical or functionalization of the subsequent carbanion.

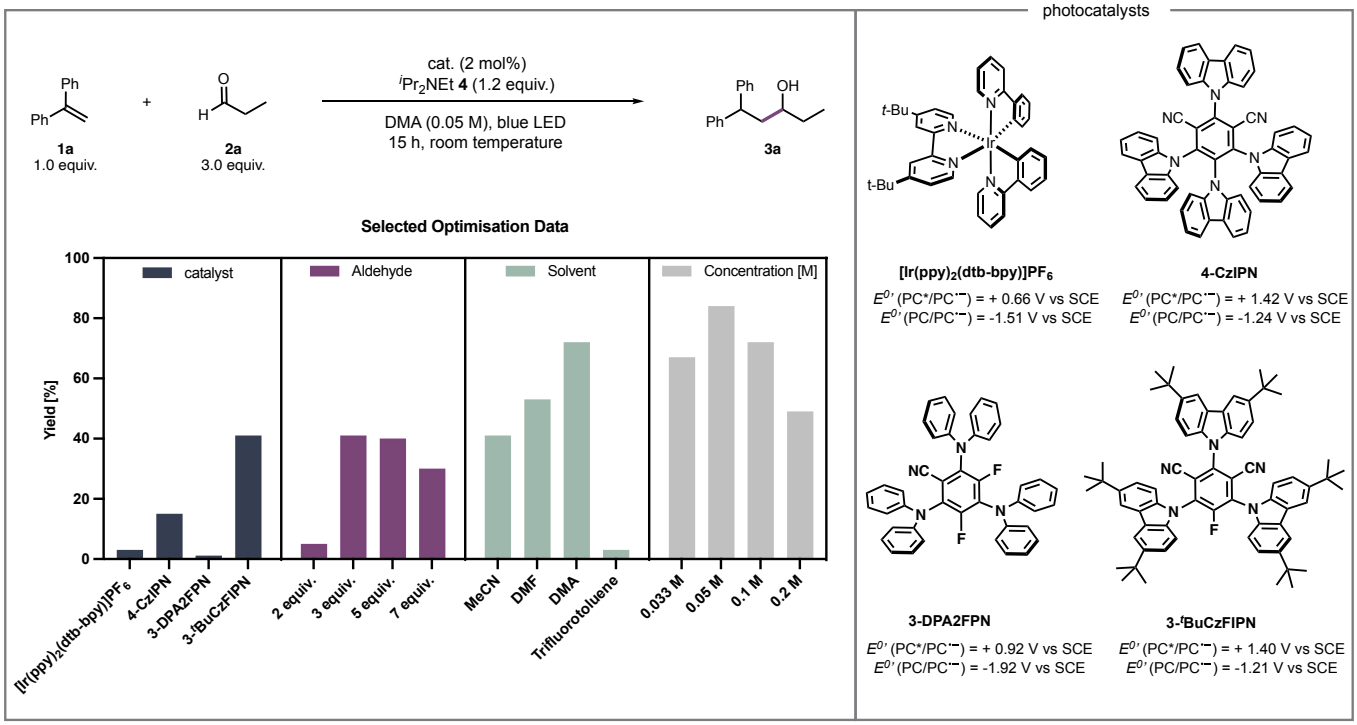

Fig. 2. Selected optimization data for the development of alkene – aldehyde coupling reaction via alkene radical anion.

Reaction scope. Following systematic optimization, we investigated the synthetic scope of the method with respect to arylalkene (Fig. 3). Intially, a series of 1,1-diarylethylenes were reacted with propionaldehyde **2a** to furnish the corresponding sterically congested secondary alcohols (**3a** - **3l**), bearing a 1,1-diaryl-pentanol framework. The protocol efficiently generated alcohol products, with notably high yields for electron rich alkenes bearing methyl (**3e** – **3g**) and methoxy (**3b** – **3c**) substituents. Electron deficient alkenes afforded the alcohols in moderate yields (up to 55%), and is attributed to attenuated nucleophilicity of alkene radical anion. This sensitivity to electron withdrawing effects is in direct contrast to the traditional Giese reactions, in which electron deficient alkenes react at faster rates with nucleophilic radicals, such as ketyl radicals,[44] and now offers opportunities engage electron-rich alkenes in radical cross coupling protocols. Furthermore, the mildness of the method is highlighted by the chemoselectivity for alkene reduction the presence of other reducible functional groups, including aryl chlorides (**3k** – $E_{p/2}$ = ~ -2.72 V vs SCE)[31] and amides (**3j**). We next investigated reaction compatibility with aliphatic aldehydes (Fig. 3). The coupling of 1,1-diphenylethylene with aliphatic aldehydes generated the expected 1,1-diaryl-pentanols in overall good yields. Aldehydes displaying secondary and tertiary carbons at the β-position reacted efficiently (**4d**-**4g** up to 79% yield). Remarkably, challenging sterically congested aldehydes bearing α-tertiary carbons were viable (**4n** – **4p**), with the exception of the isobutyraldehyde derived alcohol (**4m**). Pleasingly aldehydes that bore saturated and unsaturated heterocyclic subunits were compatible (**4g**, **4h** and **4o**) and those decorated with unactivated alkene (**4i** – **4j**) and alkyne (**4k**) bonds did not undergo competitive reduction. Notably, the reactions with these saturated aldehydes did not evidence side-products derived from competing 5-exo or 6-exo radical cyclization pathways that would be expected from the generation of an aldehydic ketyl radical.[35] On this basis, we next performed a detailed mechanistic investigation of the reaction.

Experimental and computational mechanistic studies: alkene – aldehyde coupling

To gather insights into this reaction involving a nucleophilic alkene-derived radical anion with a neutral aliphatic aldehyde a series of experimental and computational mechanistic studies were performed. First, to differentiate between the proposed “alkene first” reduction and the competitive “aldehyde first” pathway, we subjected aldehyde **2c** to standard reaction conditions in the absence of diarylethylene **1a**. ^{1}H NMR spectroscopic analysis of the crude reaction mixture showed minimal conversion (< 5%) of the aldehyde (Fig 4a and S10). Furthermore, in the reaction between aldehyde **2i**, bearing an terminal alkene poised for the radical 5-*exo-trig* cyclization, no evidence for the cyclized product **7** was found (Figure 4b). Together, these results suggest that aliphatic aldehydes are stable to the reaction conditions, and ketyl radicals are unlikely to be involved in C-C bond formation, despite the closely matched reduction potential of propionaldehyde **2a** ($E_{p/2}$ = -2.45 V vs SCE) and diphenylethylene **1a** ($E_{p/2}$ = -2.38 V vs SCE) (Figure S6). Secondly, we sought evidence for single electron transfer from the dicyanobenzene photocatalyst 3^{t}BuCzFIPN to the alkene via the established conPET mechanism for cyanoarene dyes.[42,43] The properties of the catalyst in the ground and excited state were first evaluated with cyclic voltammetry and UV-Vis spectroscopy. The ground $E_{1/2}$ ($PC^n/PC^{\bullet-}$) = -1.21 V vs SCE and excited state reduction potential ($E(PC^*/PC^{\bullet+})$ = - 1.12 V vs SCE) were found to be insufficient to promote single electron reduction of 1,1-diphenylethylene **1a** ($E_{p/2}$ = -2.38 V vs SCE) or propionaldehyde **2a** ($E_{p/2}$ = -2.45 V vs SCE). Steady-state luminescence quenching experiments confirmed an absence of photocatalyst phosphorescence quenching in the presence of 1,1-diphenylethylene **1a** or propionaldehyde **2a**, excluding direct electron or energy transfer from the excited state (Figure 4c). Conversely, phosphorescence intensity from triplet excited photocatalyst 3^{t}BuCzFIPN was quenched in the presence of ^{i}Pr$_2$EtN

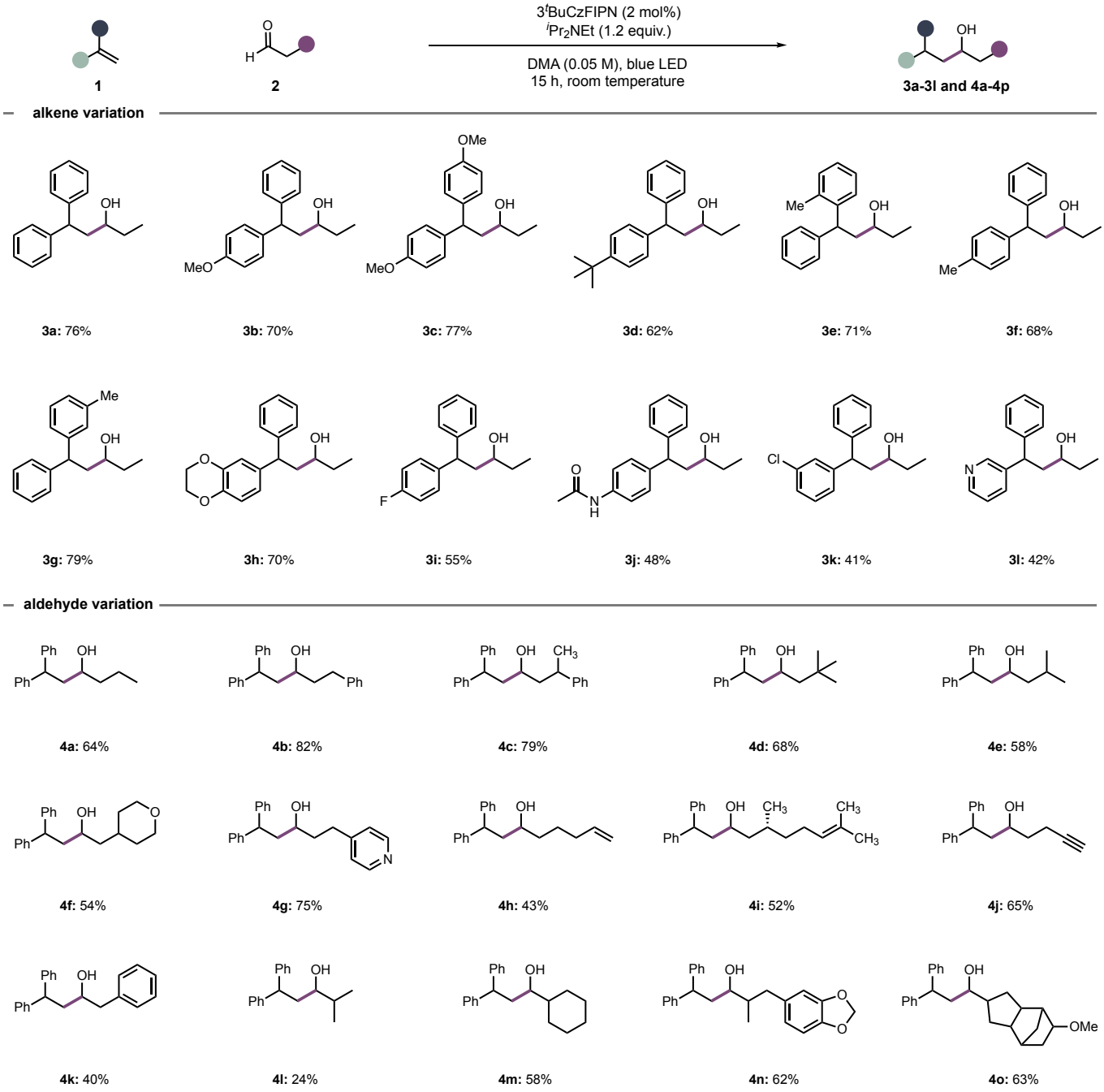

Fig. 3. Photoredox catalyzed hydroalkoxylation of alkenes. **General conditions**: alkene (0.1 mmol, 1.0 equiv.), 3^{t}BuCzFIPN (2 mol%), ^{i}Pr$_2$EtN (1.2 equiv.), DMA (0.05 M in substrate), r.t., 24 h, 14 W Blue LEDs (448 nm). Isolated yields.

4, confirming generation of the catalyst radical anion, [3-^{t}BuCzFIPN]$^{\bullet-}$, (PC$^{\bullet-}$), under experimental conditions. Furthermore, consistent with previous studies,[43] we observed facile bleaching of PC$^{\bullet-}$ in the presence of ^{i}Pr$_2$EtN **4** and blue light, with concomitant hypsochromal shift of emission from 577 to 450 nm (Figure 4d).The photodegraded product was identified as 3,6-di-*tert*-butylcarbazole **8** (Figure S10); however, control experiments revealed that **8** was not an effective photocatalyst for alkene-aldehyde coupling, generating less than 14% yield of the product and resulting in extensive decomposition of the alkene (Scheme S1). The photodegradation was markedly impeded in the presence of 1,1-diphenylethylene **1a**, providing further evidence that **8** was not the active catalytic species (Figure

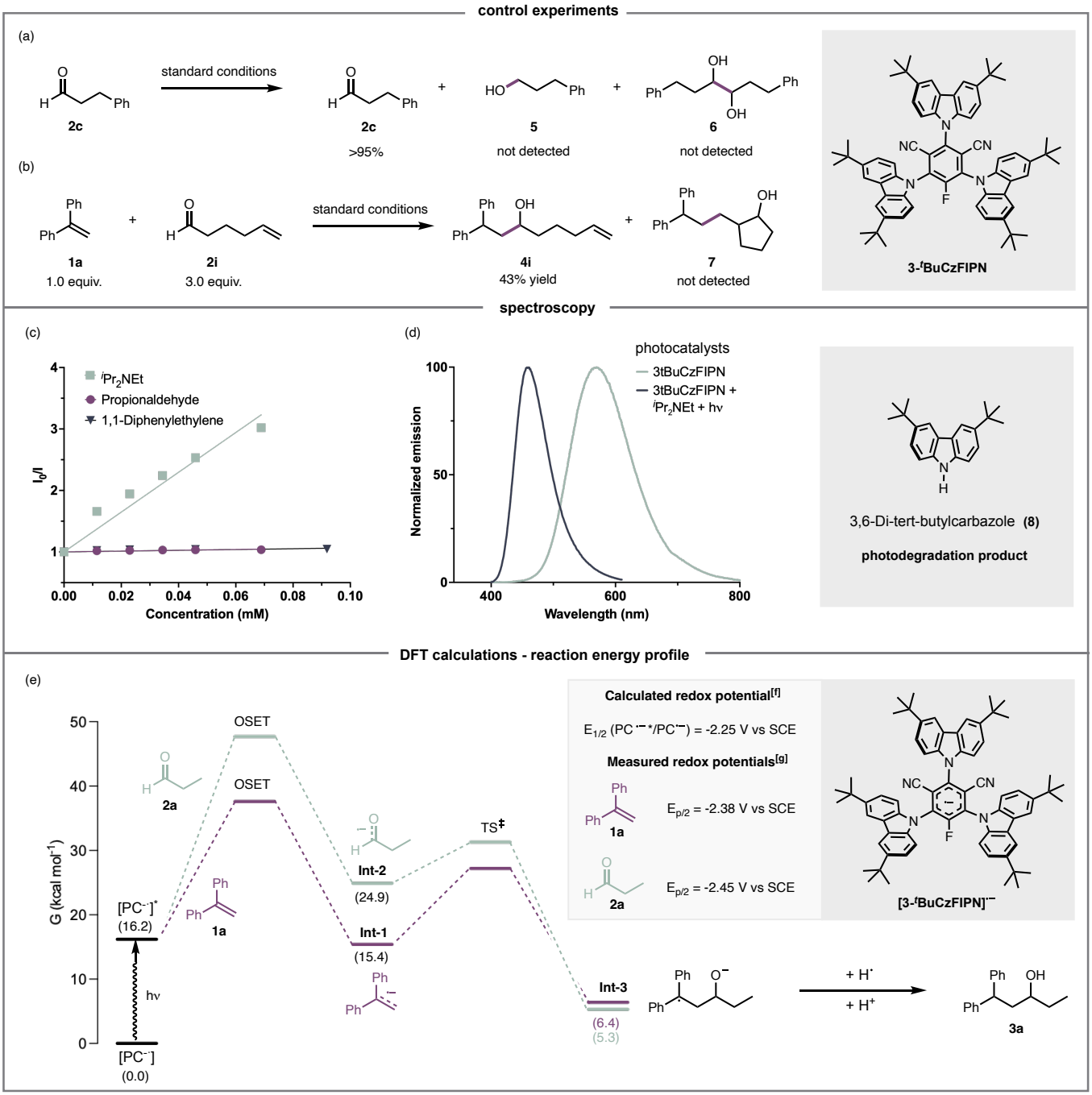

Fig. 4. Mechanistic investigation (a) Control experiment: direct reduction of an aldehyde using 3^{t}BuCzFIPN as the catalyst (b) Control experiment: competition with the 5-exo-trig cyclization using 3^{t}BuCzFIPN as the catalyst. (c) Quenching of [3^{t}BuCzFIPN]* emission by 1,1-diphenylethylene **1a** and ^{i}Pr$_2$NEt, **4** (d) Emission from [3^{t}BuCzFIPN]* and the spectroscopic evidence for photodegradation under irradiation with blue light in the presence of ^{i}Pr$_2$NEt (e) Calculated reaction profiles (kcal mol^{-1}, 298.15K) at the wB97XD/ma-def2TZVP//wB97XD/6-31G(d) level of theory using SMD to model the dimethylacetamide solvent environment, see the SI for further details. (f) Redox potential of the excited radical anion was calculated at the wB97XD/ma-def2TZVP//wB97XD/6-31G(d) level of theory using SMD to model the dimethylacetamide solvent environment (see Table S8 for further details). (g) Cyclic voltammogram of 1,1-diphenylethylene and propanal, were measured in degassed acetonitrile (Bu_4NPF_6 as the supporting electrolyte), scan rate = 0.1 Vs^{-1}, reported relative to SCE using Fe+/0 couple as an internal standard (see Figure S7 for further details).

S9). To gain further insight into the catalytic cycle and the observed chemoselectivity, properties of the putative (PC $^{\bullet-}$)* were evaluated by density functional theory (DFT) calculations (see SI for detail). The excited state oxidation potential of (PC $^{\bullet-}$)* was estimated to be -2.25 V vs SCE, which corresponds to the D_1 state (Figure 4e). Calculated outer-sphere electron transfer barriers for the single electron reduction of each substrate **1a** and **2a** by the (PC $^{\bullet-}$)*

revealed that the Marcus barrier for the outer sphere electron transfer for propionaldehyde **2a** is 10.1 kcal mol^{-1} greater than 1,1-diphenylethylene **1a** (Figure 4e). This implies a favourable kinetic contributon for single electron transfer to an aromatic alkene over the aldehyde, despite closely matching reduction potentials (Figure S7, SI). Taking the above results together, it is plausible that the radical anion **Int-1** derived from 1,1-diphenylethylene **1a** undergoes carbanionic nucleophilic addition to an aldehyde ($\Delta G^{\ddagger}$ = 11.8 kcal mol^{-1}, ΔG = 6.4 kcal mol^{-1}) to generate a distonic radical anion **Int-3** which is instantenously reduced and protonated by residual water to afford the corresponding secondary alcohol product **3a**.

Alkene – Isocyanate Coupling

Amides represent an important functional group in numerous classes of pharmaceuticals, agrochemicals and natural products, and the development of catalytic methods to generate versatile amide bonds is of ongoing interest.[45-47] Isocyanates are a reactive and atom-economical, yet heavily underutilized reagents for the synthesis of amide bonds.[48,49] The highly electrophilic heterocumulene carbon atom enables facile reaction with organometallic reagents, however these approaches are prone to diminished chemoselectivity and functional group compatibility.[50] Despite complete atom economy and conceptual simplicity, the catalytic conversion of alkene derivatives to amides using isocyanates is largely unprecedented and limited to two catalytic examples.[51,52] Recognising that alkene radical anions are viable alkyl carbanion equivalents, we proposed that addition to isocyanate to generate amide bonds, in a manner analogous to Grignard reagents, should proceed smoothly. The investigation was initiated by reacting 1,1-diphenylethylene **1a** with phenyl isocyanate **9g** under previously optimized reaction conditions (Fig. 3 *vide supra*). Following a detailed optimization, the desired amide **10l** was furnished in 31% yield (Table S2, SI) and this remarkable transformation represents the first example of a direct alkene hydroamidation strategy in the absence of metal salts. As shown in Fig. 5, electron neutral (product **10a**) and electron rich diarylethylenes (product **10b** to **10f**) could be easily converted to the corresponding cyclohexylamides. Similarly alkyl isocyanates were efficiently converted to amides **10g** to **10l** with 1,1-diphenylethylene **1a**.

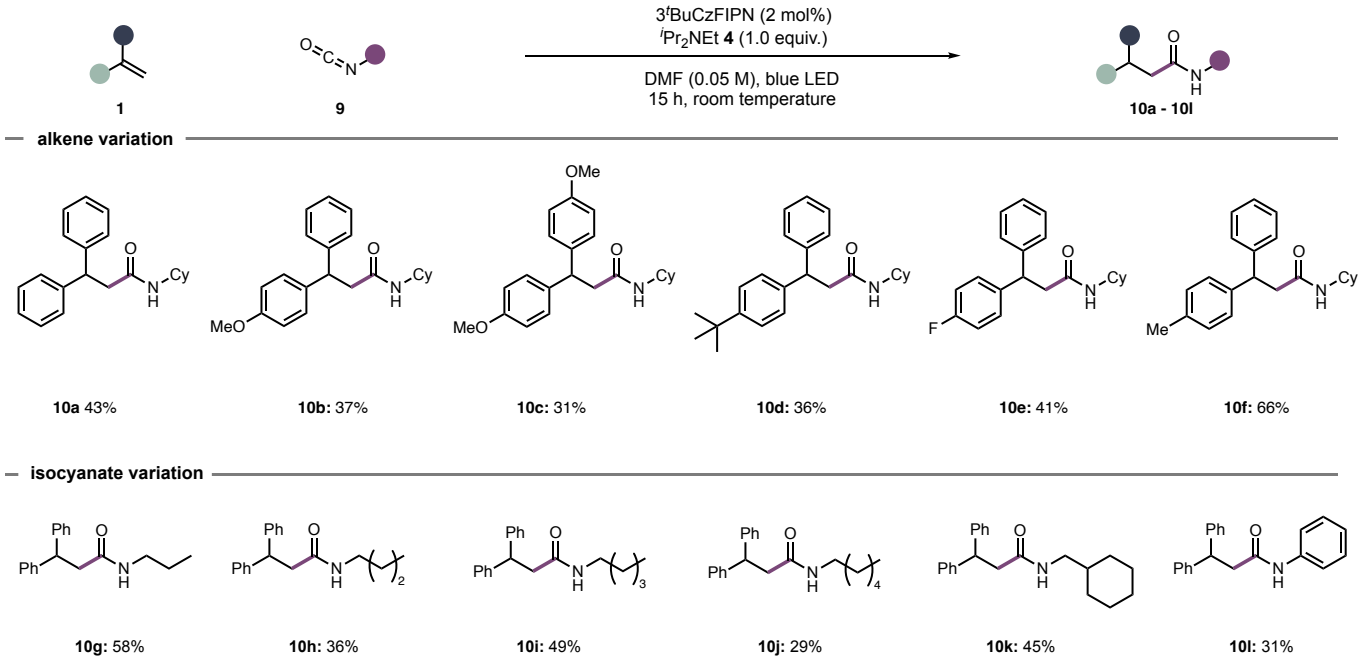

Fig. 5. Photoredox catalyzed hydroamidation of alkenes. **General conditions**: alkene (0.1 mmol, 1.0 equiv.), 3^{t}BuCzFIPN (2 mol%), ^{i}Pr$_2$EtN (1.0 equiv.), DMF (0.05 M in substrate), r.t., 24 h, 14 W Blue LEDs (448 nm). Isolated yields.

Alkene Hydroaminoalkylation

Next we turned our attention to the addition of alkyl carbanion equivalents to imine electrophiles. The addition of carbon nucleophiles to imine derivatives is a fundamental strategy for the synthesis of secondary and tertiary amines.[53] It is typically accomplished using either enolate nucleophiles (Mannich reaction), or organometallic reagents. An alternative approach, under photoredox conditions, is based on the addition of alkyl radicals to electrophilic imine derivatives.[54-57] This strategy has been successfully executed using either isolated imine precursors or *in-situ* generated transient iminium ions via condensation of aldehydes or ketones and secondary amines (Fig. 1). Photoredox generation of iminium ions directly from tertiary amines, via two consecutive single electron oxidations, and its subsequent functionalization with 2-electron nucleophiles, is also well established.[58] Pioneering studies by Stephenson demonstrated that iminium ions, identified as byproducts in the reaction using tertiary amines as reductants, could be trapped by a variety of nucleophiles under photoredox conditions.[59,60] Nonetheless, it is not compatible with the use of alkyl radicals due to the competing reductive hydrogen atom transfer. We questioned whether the iminium ion, generated *in situ* by oxidation of the sacrificial reductant, could be controllably intercepted by the alkene radical anion to generate arylpropylamine derivatives. This simultaneous oxidative C-H activation of amines, and reductive π activation of vinylarenes derivatives would enable a mechanistically distinct approach to the synthesis of tertiary and secondary amines with a range of electron neutral and electron rich vinylarenes derivatives, with selectivity complementary to that of Giese-type radical addition. Central to this reaction design is the multiphoton photoredox catalysis, which possess a broad redox window capable of simualtenously oxidizing an amine and reducing a vinyl arene. This tactic enables the simultaneous *in situ* generation of a highly electrophilic iminium species and the alkyl carbanion equivalent from vinyl arenes. We envisioned that the strong electrostatic interaction between the alkene radical anion and the iminium cation could drive the direct nucleophilic addition in a manner analogous to the reactivity with aldehydes and isocynates (*vide supra*).

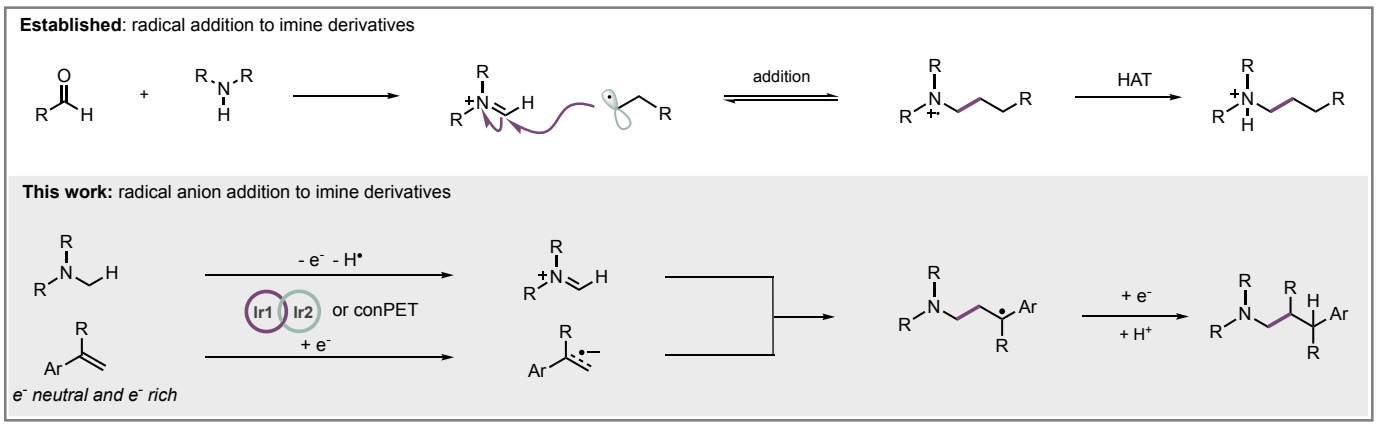

Fig. 6. Evolution of a strategy for the hydroaminoalkylation reaction via alkene radical anion

Reaction optimization

We first examined aminoalkylation of 1,1-diphenylethylene **1a** with diisopropylmethylamine **11** to generate Diisopromine **12a**, an antispasmodic drug. The use of 3^{t}BuCzFIPN as the catalyst resulted in formation of the desired product **12a** in low yield (35%) with a simultaneous exhaustive alkylation to give **13** in 14% yield (Table S3, SI). Appreciable decomposition observed in the ^{1}H NMR of the crude reaction mixture was attributed to detrimental oxidation and hydrolysis of the aminoalkylated products. We postulated that the decomposition pathway was attributable to the highly positive reduction potential of the photocatalyst ($PC^*/PC^{\bullet-}$ = + 1.42 V vs SCE). Consequently,

dicyanobenzene derived catalysts with lower excited state redox potentials were investigated. The use of less oxidising 3-DPAFIPN ($PC^*/PC^{\bullet-}$ = +1.06 V vs SCE) resulted in a slight increase in yield of **12a** (49%) and **13** (21%). Moving to 3-DPA2FPN ($PC^*/PC^{\bullet-}$ = +0.92 V; $PC/PC^{\bullet-}$ = - 1.92 V vs SCE) which possesses a less oxidising and strongly reducing potential, led to diminished yields of both products and extensive decomposition, implying that reaction efficacy was contingent upon controlled reduction of 1,1-diphenylethylene and simultaneous rates of tertiary amine oxidation. This postulate was further corroborated by catalyst 3CzClIPN ($PC^*/PC^{\bullet-}$ = +1.56 V; $PC/PC^{\bullet-}$ = - 1.16 V vs SCE) generating the desired product with full selectivity for **12a**, albeit with high degree of decomposition and incomplete conversion of the starting material. Thus, we hypothesized that the relative concentration of carbanion and iminium electrophile is key to viable C-C bond formation. On this basis it was considered imperative to fine-tune the excited and ground state potentials of the photocatalyst independently, to achieve a rate of generation of the alkene radical anion that enables addition to the electrophile without unproductive reactivity. Consequently, we turned our attention to the tandem photoredox catalytic cycle of heteroleptic Ir complexes and the archetypal catalyst $[Ir(dFppy)_2(dtb\text{-}bpy)]PF_6$ [$(Ir^{III})^*/Ir^{II}$ = + 0.98 V vs SCE; Ir^{III}/Ir^{II} = -1.42 V vs SCE] remarkably generated the aminoalkylated adduct **12a** in 81% ^{1}H NMR yield.

Reaction scope

With optimized conditions established, we sought to evaluate the scope with respect to alkene while employing *N,N*-diisopropylethylamine **4** as the coupling partner. As shown in Fig. 7, electron deficient (product **12c**) and electron rich diarylethylenes reacted smoothly with amine **4**, where the reaction was insensitive to the electronic properties of the carbanion, even for very electron rich coupling partners (**12f – 12j**). To further demonstrate synthetic value, α-alkyl and styrene derivatives were evaluated and the deeply negative reduction potentials of these alkenes (< 2.8 V vs SCE) necessitated photocatalytic systems with aggressive reduction potentials. Accordingly, $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ and surprisingly, the organocatalyst 4CziPN were compatible with this class of substrates. 4CzIPN was particularly effective for the most electron rich and sterically hindered alkenes (**12o, 12q** – **12s**). Significantly, β-substituted styrene was also a competent coupling partner, generating a sterically crowded C-C bond in **12s** in a good yield, with full selectivity for the substitution at the β-position. The reaction was compatible with competitively reducible groups, incuding aryl halides **12w**.

Next, attention was directed to the substrate scope with respect to the amine using 1,1-diphenylethylene **1a** as the alkene coupling partner and a range of commercially available tertiary amines. Sterically hindered amines, such as *N*-methyl tetramethylpiperidine and *N,N*-dicyclohexylmethylamine reacted exceptionally well under the optimized reaction conditions, generating **13b** and **13c** in remarkably high yields. The reaction was compatible with reducible functional groups including nitrile (**13g**), ester (**13k** and **13n**) and ketone (**13o**) functionalities, as well as protic groups present on an unprotected primary amine (**13e**) and an unprotected alcohol (**13f**). Amines substituted with vinyl groups reacted in a lower yield of 35% (**13d**), however a basic heterocycle such as pyridine was exceptionally tolerated (**13i**). In all cases, regioselectivity was excellent. Consistent with the classic redox chemistry of amines,[61,62] the reaction was selective for the primary methyl position in the presence of secondary and tertiary C-H bonds. The chemoselectivity of this protocol is further reflected by the preferential monoalkylation observed for amines with multiple primary methyl groups (**13e – 13j**), with only trace quantities of bisalkylation found in the mass spectra of the crude reaction mixtures. Pleasingly, aqueous trimethylamine was also compatible with the reaction conditions, generating the pharmaceutically significant *N,N*-dimethyl scaffold (product **13j**) in 52% yield.

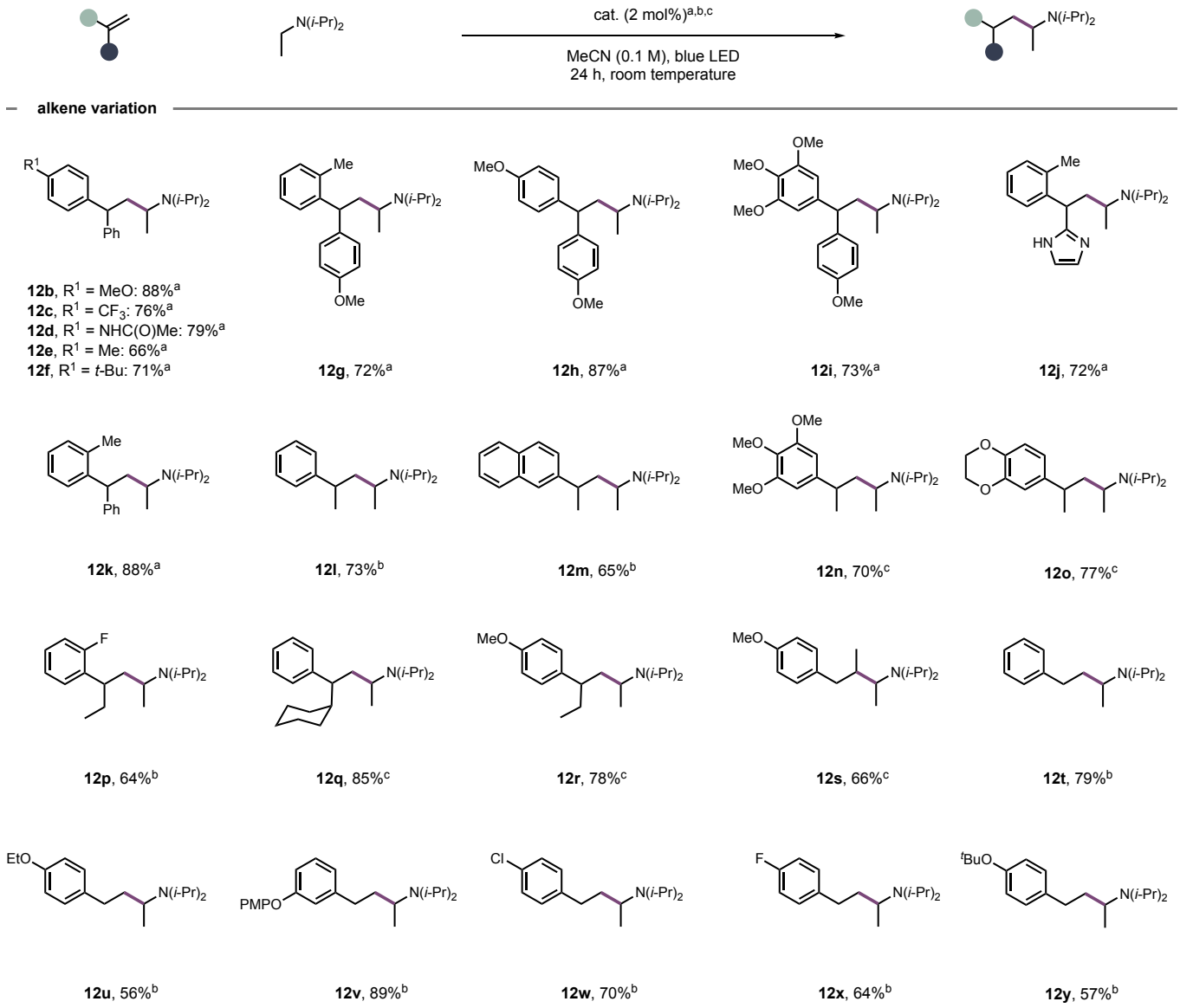

Fig. 7. Photoredox catalyzed aminoalkylation of alkenes[a,b] [a] General conditions A: alkene (0.2 mmol, 1.0 equiv.), $[Ir(dFppy)_2(dtb\text{-}bpy)]PF_6$ (2 mol%), $^iPr_2EtN$ (3.0 equiv.), CH_3CN (0.1 M in substrate), r.t., 24 h, 14 W Blue LEDs (448 nm) [b] General conditions B (products: alkene (0.2 mmol, 1.0 equiv.), $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (2 mol%), $^iPr_2EtN$ (3.0 equiv.), CH_3CN (0.1 M in substrate), r.t., 24 h, 40 W Blue LEDs (440 nm) [c] General conditions C: alkene (0.2 mmol, 1.0 equiv.), 4-CzIPN (2 mol%), $^iPr_2EtN$ (3.0 equiv.), CH_3CN (0.1 M in substrate), r.t., 24 h, 40 W Blue LEDs (440 nm) [d] Isolated yields.

Notably, in the absence of primary methyl groups, the reaction was completely selective for secondary C-H bonds, with excellent selectivity for monoalkylated products **13l** – **13o**. Functionalization of the unsubstituted propyl and ethyl side chains was exclusively observed in products **13n** and **13o**. This is especially significant in the case of compound **13o**, in which alkylation of the more activated α-carbonyl C-H bond could be readily accomplished via an enolate intermediate.

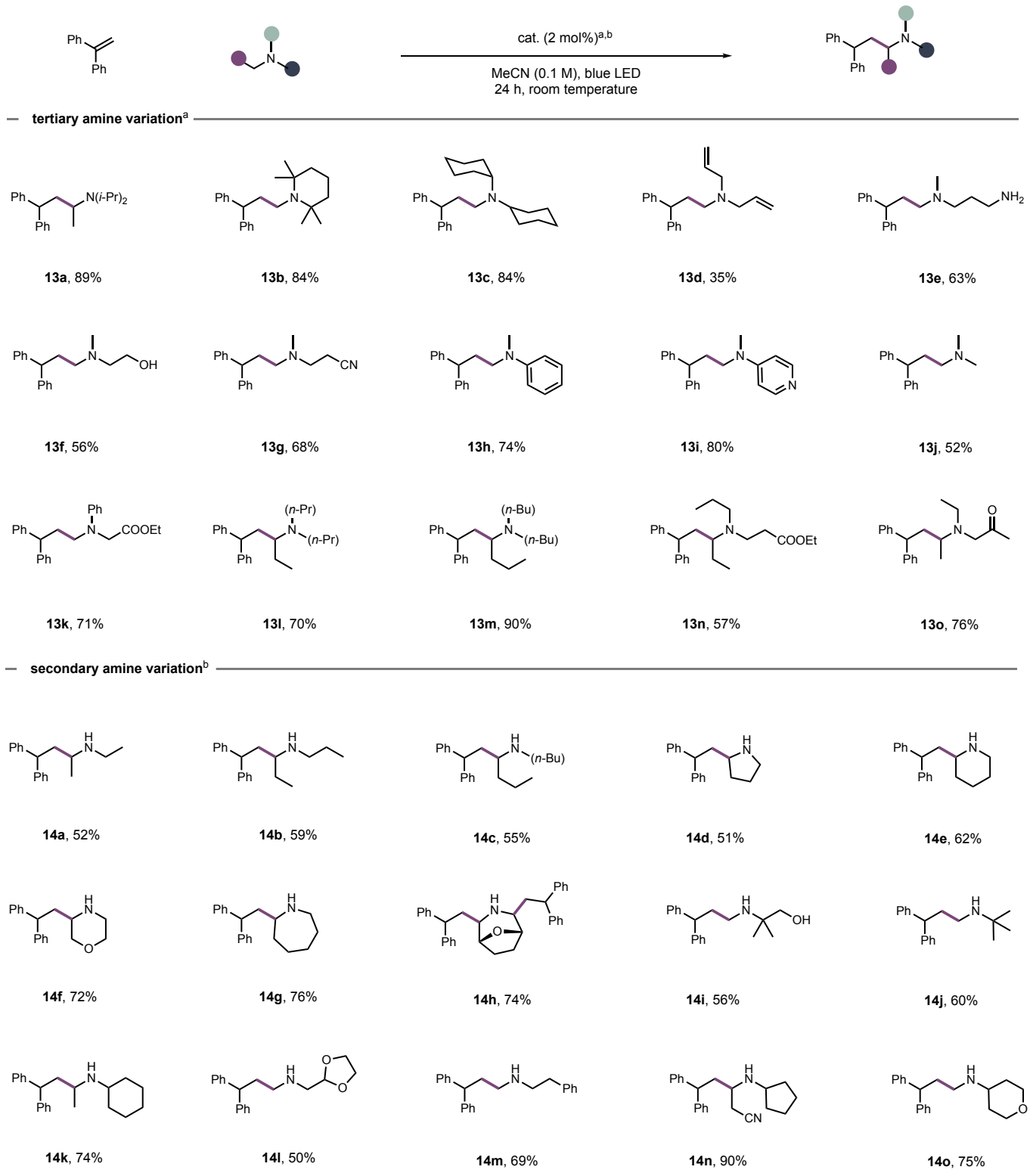

Fig. 8. Amine scope[a,b] [a] General conditions for 3° amines: 1,1-Diphenylethylene (0.2 mmol, 1.0 equiv.), $[Ir(dFppy)_2(dtb\text{-}bpy)]PF_6$ (2 mol%), amine (3.0 equiv.), CH_3CN (0.1 M in substrate), r.t., 24 h, 14 W Blue LEDs (448 nm) [b] General conditions for 2° amines: 1,1-Diphenylethylene (0.2 mmol, 1.0 equiv.), $[Ir(dF\text{-}4\text{-}Meppy)_2(dtb\text{-}bpy)]PF_6$ (2 mol%), amine (4.0 equiv.), CH_3CN (0.1 M in substrate), r.t., 48 h, 80 W Blue LEDs (440 nm) [c] Isolated yields.

We next turned our attention to unprotected secondary amines as coupling partners, which are largely incompatible with most 2-electron and photocatalytic C-H bond functionalization methodologies.[63,64] In the presence of α,β-

unsaturated alkenes, secondary amines undergo competitive aza-Michael addition, while the use of electron rich alkenes leads to the direct hydroamination reaction.[65-67] Re-optimization of the reaction conditions enabled the synthesis of **14a** in 59% isolated yield (see SI for details). Acyclic, symmetrical amines reacted efficiently to generate monoalkylated products **14b** and **14c** in good yields, with no correlation between the length of the alkyl side chain and yield. Symmetrical cyclic amines were also amenable to the reaction conditions. Pyrrolidine, piperidine, morpholine and azepane gave the corresponding alkylated products **14d – 14g** in moderate to high yields. High levels of selective monoalkylation were observed in all cases except for the bicyclic compound **14h**, where bisalkylated product was exclusively isolated. Sterically hindered amines substituted with one trialkyl group reacted in good yields (products **14i** and **14j**). The reaction was selective for the primary methyl position in the presence of a secondary C-H bonds (**14l** and **14m**). Oxygen-containing heterocycles (**14k** and **14o**), nitrile (**14n**) and unprotected alcohol (**14i**) functional groups were exceptionally tolerated.

Experimental mechanistic studies: alkene hydroaminoalkylation

First, we questioned whether a simple Giese reaction between the α-amino radical and ground state alkene could be responsible for the formation of product **13a** under the established reaction conditions (Figure 9, path A.1). Electron neutral and rich styrene derivatives have been generally deemed incompatible with Giese-type reactivity owing to high nucleophilicity of α-amino radicals, which are subject to significant polar effects in the transition state.[56] Yoon and co-workers reported that the addition of an α-amino radical across a Michael acceptor is the rate limiting step in the absence of a Brønsted acid co-catalyst.[68] Similarly, pioneering studies by Melchiorre demonstrated that α-amino methylation of alkenylpyridines requires a synergistic merger of photoredox and Brønsted-acid catalysis to transiently generate a highly reactive, electrophilic pseudo-iminium ion intermediate, and minimal radical conjugate addition proceeds in the absence of co-catalyst.[69] In addition to polarity contributions, inefficient single electron reduction of the resulting α-carbonyl radical to a carbanion often necessitates the use of polarity matched hydrogen atom transfer (HAT) reagent to avoid oligomerization pathways.[56] The reported redox potential of a benzylic radical, **Int-6** ($E_{1/2}^{red}$ = -1.34 V vs SCE)[70] and that of reduced [Ir(dFppy)$_2$(dtb-bpy)]PF$_6$ (Ir^{III}/Ir^{II} = -1.42 V vs SCE) suggests that back electron transfer to **Int-6** should be thermodynamically favoured. Interestingly, a catalyst screen revealed no correlation between ground state redox properties and yield of **13a**. The highly reducing catalyst, [Ir(ppy)$_2$(dtb-bpy)]PF$_6$ (Ir^{III}/Ir^{II} = -1.51 V vs SCE), led to substantial reduction in the yield of aminoalkylated product **13a** and concomitant generation of reduced alkane **15**. Furthermore, the use of a highly oxidising, yet weakly reducing consecutive photoinduced electron transfer(conPET) photocatalyst, 3CzClIPN ($PC/PC^{\bullet-}$ = -1.16 V vs SCE) generated a mixture of the α-amino adduct (in 30% yield) and the reduced alkene (in 12% yield). Contrastingly, [Ru(bpy)$_3$]Cl$_2$, with a less negative ground state reduction potential (Ru^{II}/Ru^{I} = -1.33 V vs SCE) and a well-established propensity to oxidise tertiary amines from the excited state, afforded a full recovery of the alkene starting material and no evidence of product **13a** was observed (Table 1, entry 4). Similarly, no conversion of the alkene occured with the highly reducing homoleptic [Ru(phen)$_3$](PF$_6$)$_2$ (Ru^{II}/Ru^{I} = -1.38 V vs SCE) and *fac*-Ir(dFppy)$_3$ (Ir^{III}/Ir^{II} = -2.11 V vs SCE) catalysts (Table 1, entry 5-6). Furthermore, other heteroleptic Ir complexes containing the dtb-bpy ligand such as [Ir(dFppy)$_2$(dtb-bpy)]PF$_6$ (Ir^{III}/Ir^{II} = -1.42 V vs SCE) and [Ir(dF-4-Me)ppy)$_2$(dtb-bpy)]PF$_6$ (Ir^{III}/Ir^{II} = -1.44 V vs SCE) afforded very high yields of the desired α-amino adduct (Table 1, entry 7-8).

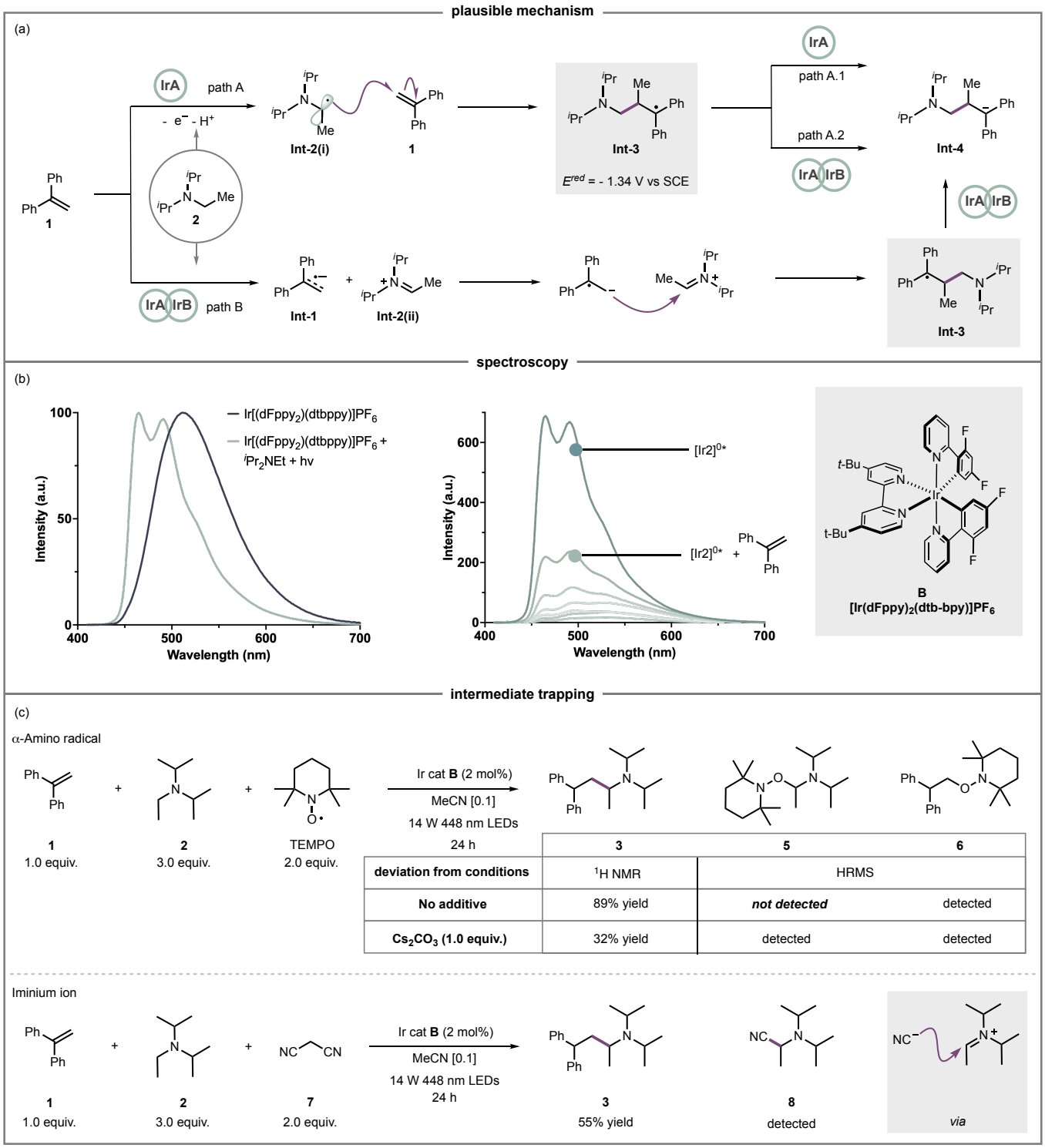

Fig. 9. Mechanistic investigation; (a) the proposed mechanistic pathways for the formation of α-amino adduct **13a** (b) Evidence for the formation of the second excited state, [IrB]⁰ state from [Ir(dFppy)$_2$(dtb-bpy)]PF$_6$ and its ability to interact with 1,1-diphenylethylene **1a** from the excited state (i) formation of [IrB]⁰ under reaction conditions (ii) Quenching of [IrB]⁰* emission by substrate **1a** (iii) Stern-Volmer plot for quenching of [IrB]⁰* by substrate **1a** (c) TEMPO trapping experiment in the absence and presence of added base (d) Iminium trapping experiment.

Combined, these results established a correlation between the *in-situ* formation of a potent photoreductant, via a tandem photoredox catalytic cycle or the consecutive photoinduced electron transfer (conPET), and formation of α-

amino adducts. Indeed, Stern-Volmer quenching experiments revealed that 1,1-diphenylethylene (**1a**) effectively quenched the phosphorescence of $[IrB]^{0*}$ derived from $[Ir(dFppy)_2(dtb\text{-}bpy)]PF_6$, consistent with one-electron reduction of 1,1-diphenylethylene **1** by the highly reducing catalytic species (Figure 9b). The reaction failed to generate any detectable product when amines containing a benzylic α-amino C-H positions were used as coupling partners, including tetrahydroisoquinoline derivatives. These amines are known to undergo facile oxidation and functionalization via both α-amino radical and iminium ion intermediates.[58,68] To understand this phenomena and further corroborate the proposed mechanism, we irradiated a solution of the Ir catalyst in the presence of a benzylic amines, *N*-benzyl-*N*-ethylaniline, and the emission profile characteristic of the $[IrB]^0$ complex was not observed with 10 minutes of excitation (Figure S14). This suggests that HAT from the excited photocatalyst to the tertiary amine with subsequent generation of the semi-saturated $[IrB]^0$ is inefficient. This could be rationalized by the significantly lower pK_a of benzylic α-C-H bonds[71] promoting facile generation of stabilized α-amino radicals, which should be unreactive in the context of this reaction.

We next questioned whether formation of alkene radical anions were responsible for the generation of product **13a**. The highly reducing photoredox conditions may promote facile reduction of the benzylic radical **Int-6** to carbanion (**Int-7,** path A.2) preventing competing reaction pathways and turn over the catalytic cycle. We first sought evidence for the involvement of α-amino radical intermediates. Selective formation of α-amino radicals from aminium radical cations is promoted by the addition of inorganic bases, which deprotonate the C-H bond adjacent to nitrogen.[72-74] Reaction conducted in the presence of one equivalent of K_2HPO_4 resulted in an increase concentration of reduced 1,1-diphenylethane **15** up to 10% by ^1H NMR spectroscopic analysis and this was accompanied by a corresponding reduction in the yield of **13a** (Table 1, entry 11) Furthermore, the reaction was effectively suppressed by the addition of 1 equivalent of Cs_2CO_3, with 50% of the starting material remaining in the crude reaction mixture, and 18% of the reduced product **15** (Table 1, entry 12). To gain further insight into the effect of Cs_2CO_3 we performed radical trapping experiments. Addition of one equivalent of radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) to the standard reaction mixture did not inhibit formation of product **13a**. Significantly, TEMPO adduct with the α-amino radical **16** was not detected by HRMS analysis. Contrastingly, 1 equivalent of Cs_2CO_3 and TEMPO, suppressed the generation of product **13a** and accompanied by concomitant formation of the TEMPO adduct of α-amino radical **16**. These results are consistent with the well-established ability of inorganic bases to promote formation of α-amino radicals, but also implies that α-amino radical are not significant intermediates in this reaction. It should be noted that in the absence and with the addition of Cs_2CO_3, a peak with m/z = 338.2476 was identified at the baseline, which matches with a TEMPO adduct of diphenylethylene **17** (*m/z* = 338.2478). This suggests that the reduction of diphenylethylene to the corresponding radical anion of alkene is not affected by added base. Subsequently, we performed this reaction in the presence of malonitrile **18** as a source of cyanide anion, to trap the putative iminium ion **Int-5(ii)**.[75] Reaction performed with 3 equivalents of malonitrile resulted in reduced yield of adduct **13a** (55% by ^1H NMR), while mass spectrometry revealed formation of α-cyano adduct **19**. Additionally, a reaction performed in a mixture of methanol and water influenced a further decrease in the yield of **13a** to 18%, with concomitant hydrolysis of the intermediate iminium ion in aqueous solution. These results strongly imply that the iminium ion **Int-5(ii)**, and not an α-amino radical **Int-5(i)**, participates in the key C-C bond forming step with 1,1-diphenylethylene **1a**.

Synthetic application: Alkene Hydroaminoalkylation

Tertiary and secondary aliphatic amine motifs are ubiquitous in small molecule drugs and natural products. To demonstrate the versatility of our developed methodology in generating biologically active amines, we synthesized a selection of H_1-antihistamine drugs based on 3,3-diarylpropylamine scaffold, in a one step manipulation, from readily available tertiary and secondary amines and alkenes (Fig. 10a). The simplicity and practicality of this protocol is further exemplified through the scaled up hydroaminoalkylation of Diisoproimine **12a** (Figure 10c) in flow without erosion of yield. The reaction was run continuously giving 1.26 g of the desired product in 79 % yield. To showcase the utility of our method towards late-stage functionalization, six pharmaceutical agents were used as the amine coupling partners under the optimized reaction conditions (Fig. 10b). All reacted efficiently and selectively to furnish alkylated products **25 – 30**. Topical anaesthetic lidocaine underwent selective alkylation at the less activated C-H bond on one of the ethyl side chains in the presence of the α-carbonyl C-H bond (product **25**). Drugs containing multiple α-amino sides, clomipramine (**27**) and desipramine (**30**), reacted selectively at the aliphatic primary methyl group, consistent with lower reactivity of aniline derivatives. Notably, dehalogenation was not observed for clomipramine derived **27**, highlighting the remarkable mildness and commensurate chemoselectivity of the method.

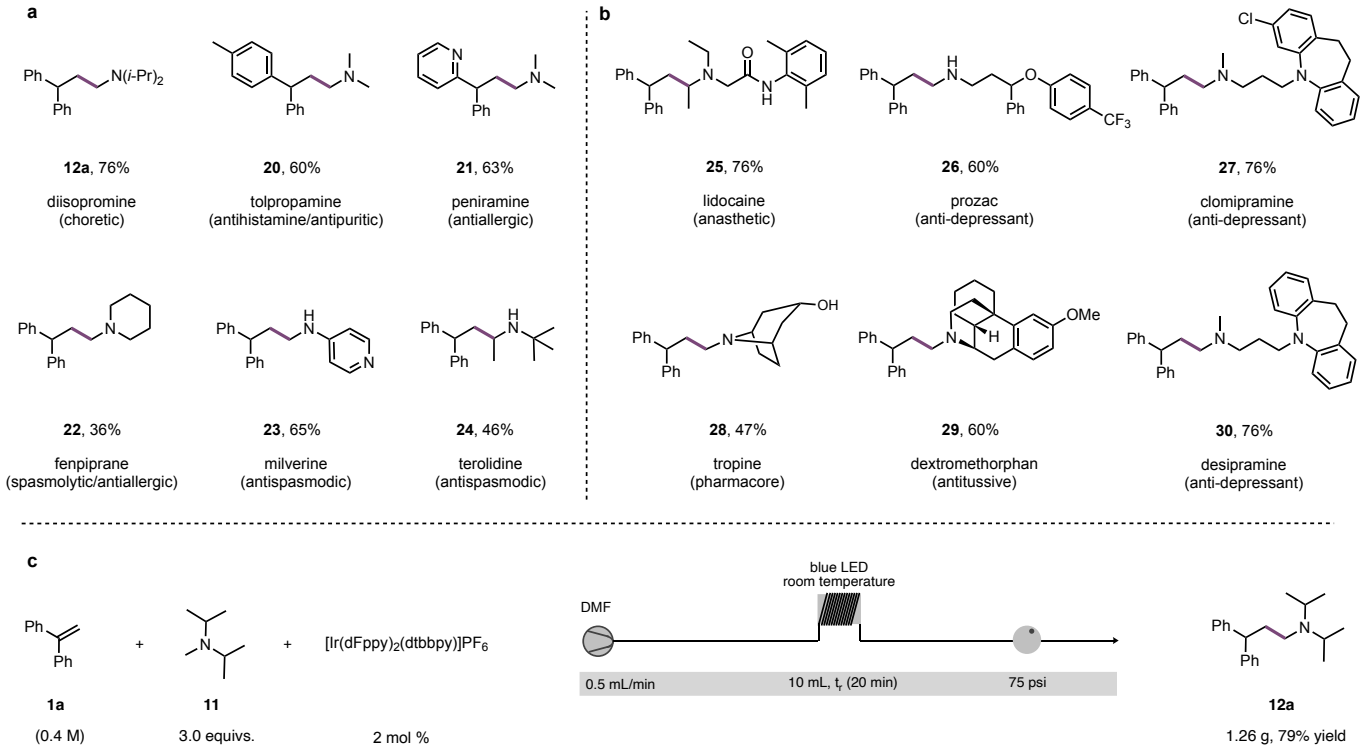

Fig. 10. Synthetic application of alkene aminoalkylation: (A) late-stage functionalization of pharmaceutical agents, (B) synthesis of pharmaceuticals and (C) scale up synthesis of Diisopromine in flow.

Alkene – Carbodifunctionalization

We envisioned the alkene as a dicarbanion synthon, with differential reactivity of the primary alkyl carbanion and the stabilized benzylic carbanion. Thus, we questioned whether these separate reactive sites could be elaborated in an orthogonal fashion with two different electrophilic coupling partners. Given the fast rates of aminoalkylation, and the reported ability of the benzylic anions to undergo nucleophilic addition to CO_2,[24,25,76-78] we proposed to extend the newly established aminoalkylation protocol towards synthesis of γ-aminobutyric acid scaffold. γ-Aminobutyric acids

have attracted significant interest as precursors for the synthesis of biologically active α,β- and β,γ-hybrid peptides.[79] Previous examples of photoredox catalyzed difunctionalization of aromatic alkenes to generate γ-aminobutyric acid derivatives were limited to *N,N*-dimethyl anilines that can be intercepted by facile Giese addition with less activated alkenes.[79-81] Remarkably, the use of sterically hindered alkyl amines such as *N,N*-diisopropylethylamine has not been reported in this context. The key feature of our design plan is continuous flow chemistry, incorporating tube-in-tube gas/liquid reactor to enable controlled delivery of carbon dioxide. Precise control over CO_2 concentration was crucial for high levels of chemoselectivity, to avoid bis carboxylation pathway of the alkene radical anion.[82] Furthermore, given the importance of γ-aminobutyric acid in medicinal and biological chemistry, we opted to develop a metal free protocol, using a conPET mechanism of dicyanobenzene derivatives.

Initial screening revealed that a highly reducing 3DPAFIPN catalyst was optimal to ensure that the kinetics of alkene reduction was compatible with flow conditions. Further optimization of the reaction parameters with 1,1-diphenylethylene and 4 equivalents of *N,N*-diisopropylethylamine, 9 bar CO_2 gas pressure and 20 min. residence time in the photoreactor furnished the corresponding γ-aminobutyric acid **31** in 54% yield. Diverting to the less sterically hindered triethylamine improved the yield to 77% (product **32**). The diisopromine derivative **33** reacted moderately well under the reaction conditions, delivering the corresponding amino acid in 33% yield. The reaction conditions were compatible with Boc-protected lidocaine (**34**) enabling facile selective late stage functionalization of this active pharmaceutical ingredient. Pleasingly, unsubstituted arylalkenes and α-alkyl styrene derivatives were compatible, delivering a diverse library of γ-aminobutyric acids in acceptably moderate yields, within a rapid 20 minute reaction time. This protocol establishes the alkene as a dicarbanion synthon, and opportunities can be envisaged where the alkyl carbanion and benzylic carbanion can be reacted with a range of differentiated carbon electrophiles for dicarbofunctionalization.

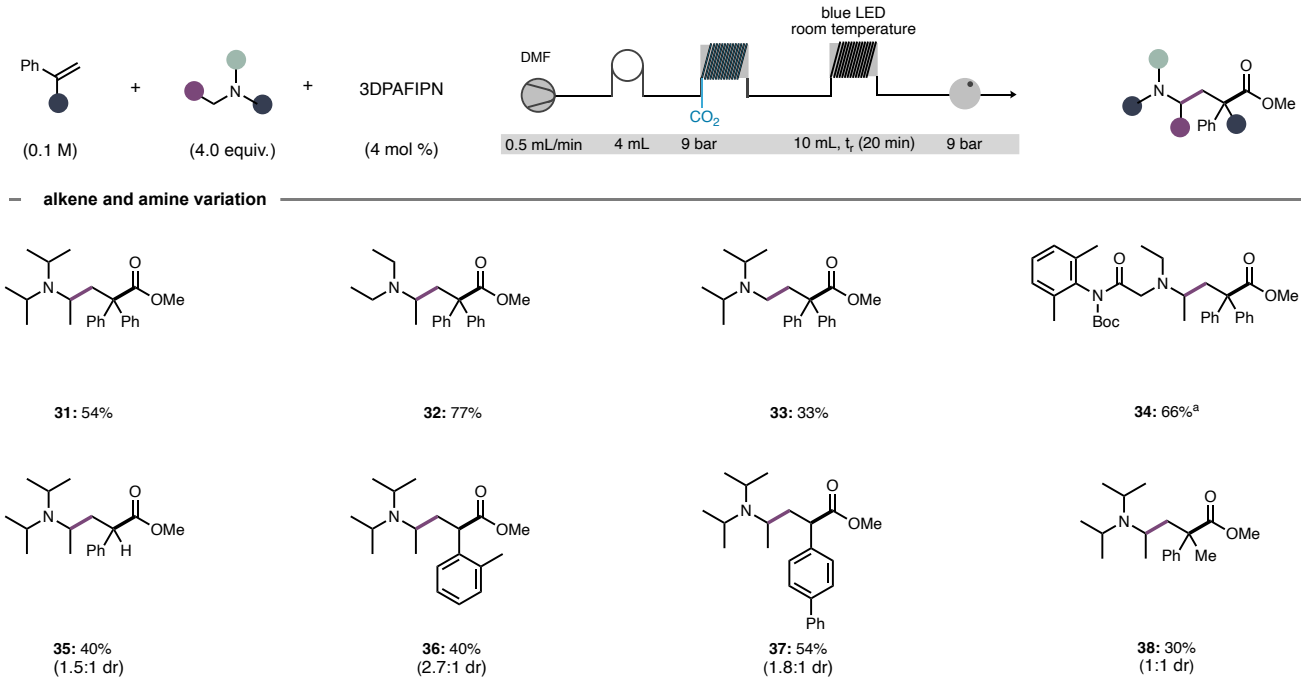

Fig. 11. γ-Aminobutyric acids scope. **General conditions**: alkene (0.4 mmol, 1.0 equiv.), 3DPAFIPN (4 mol%), amine (4.0 equiv.), DMF (0.1 M in substrate), 60 W Blue LEDs (440 nm); 9 bar CO_2 pressure; 20 min photoreactor residence time. Isolated yields.

Conclusion

In summary, we have identified a strategy to access latent alkyl carbanion equivalents from alkenes under visible light photocatalysis. We found that unlike conventional photoredox methods, the potent reducing environment of multiphoton photoredox catalysis reliably generates alkyl carbanions via alkene radical anion linchpins. This operationally simple method represents a new approach to the regioselective functionalization of weakly nucleophilic alkenes with carbon electrophiles. This mild and scalable procedure provide access to previously unattainable 1,2-dicarbanion synthons from readily available alkene feedstock chemicals. We demonstrate the potential generality of this platform as a mild source of alkyl carbanion building blocks through synthesis of new alcohol, amide, amine and amino acid products via intermolecular C-C bond-forming reactions with carbonyl electrophiles, in a manner analogous to conventional organometallic reagents. Experimental and computational studies support a mechanism involving the controlled generation an alkene radical anion that undergoes nucleophilic addition to a carbon electrophile, followed by a kinetically favoured rapid polar crossover of the neutral radical species, to generate a second carbanion that is readily quenched by a proton source or further diversified via a second electrophile. We anticipate that this sets the stage for the future development of a wide variety of alkene hydro- and di-functionalization strategies by reimagining the alkene as an alkyl dicarbanion synthon. This could inspire the synthesis of complex intermediates or targets with weak electrophiles in absence of stoichiometric reductants using only visible light mediated catalysis, that are currently beyond the scope of conventional alkene functionalization approaches.

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Author Contributions

A.P., M.L.C. (UoM) and T.H.H. designed the project. M.L.C (UoM) T.H.H., A.J.K., L.J.F. and J.A.F., performed the experiments and collected the data. M.L.C. (Flinders) and L.N.P. performed the computational experiments and analysed the data. A.P., M.L.C. (UoM) and M.L.C. (Flinders) analysed the data and contributed to writing the manuscript.

Competing Interests

The authors declare no competing interests.