Multicomponent synthesis of tertiary alkylamines by photocatalytic olefin-hydroaminoalkylation

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There is evidence to suggest that increasing the level of saturation (number of sp^3-hybridized carbon atoms) in small molecules increases the chance of success in the transition from discovery, through clinical studies, to drugs[1]. Due to their favorable physical properties, alkylamines have become ubiquitous features amongst pharmaceutical agents, small-molecule biological probes and pre-clinical candidates[2]. Despite their importance, amine synthesis is still dominated by two methods: *N*-alkylation and carbonyl reductive amination[3]. The increasing demand for such saturated polar molecules in drug-discovery, however, has continued to drive development of practical catalytic methods to synthesize complex saturated alkylamines[4-7]. In particular, processes that transform diverse, accessible feedstocks into structurally diverse sp^3-rich architectures provides a strategic advantage in complex alkylamine synthesis. Here, we report a multicomponent reductive photocatalytic technology that combines readily-available dialkylamines, carbonyls and alkenes to build architecturally complex and functionally diverse tertiary alkylamines in a single step. This olefin-hydroaminoalkylation process involves a visible-light-mediated reduction of in-situ generated iminium ions, selectively furnishing previously inaccessible alkyl-substituted α-amino radicals, which engage alkenes and lead to C(sp^3)–C(sp^3) bond formation. The operationally straightforward reaction exhibits broad functional group tolerance, facilitates the synthesis of drug-like amines not readily accessible by other methods and is amenable to late-stage functionalization applications, making it of interest in pharmaceutical research and other areas.

The physiological properties of tertiary aliphatic amines and their ability to interfere with natural neurotransmission pathways have rendered them highly effective pharmaceutical agents[8], in areas ranging

from treatment of neurodegenerative disorders (such as Alzheimer's disease)[9] to metabolic syndromes (such as obesity)[10] (Fig 1A). Traditionally, efforts for the synthesis of these molecules require multiple steps and tedious purifications, severely hampering efforts in drug-discovery. Therefore, the development of straightforward methods that enable the construction of complex tertiary amines from simple starting materials would have far-reaching implications in both the synthetic and medicinal chemistry community. While the abundance, diversity and predictable reactivity of sp^2-hybridized feedstocks has led to the emergence of new transition-metal catalyzed amine syntheses, namely the Buchwald-Hartwig amination[11] and olefin-hydroamination[12-14], strategies for more complex alkylamines are more limited[13-15]. We reasoned that an operationally-simple and mechanistically-distinct catalytic process involving available dialkylamines, olefins, and aliphatic carbonyl feedstocks would expand the capacity of olefin-hydroaminoalkylation-based strategies for the synthesis of tertiary alkylamines.

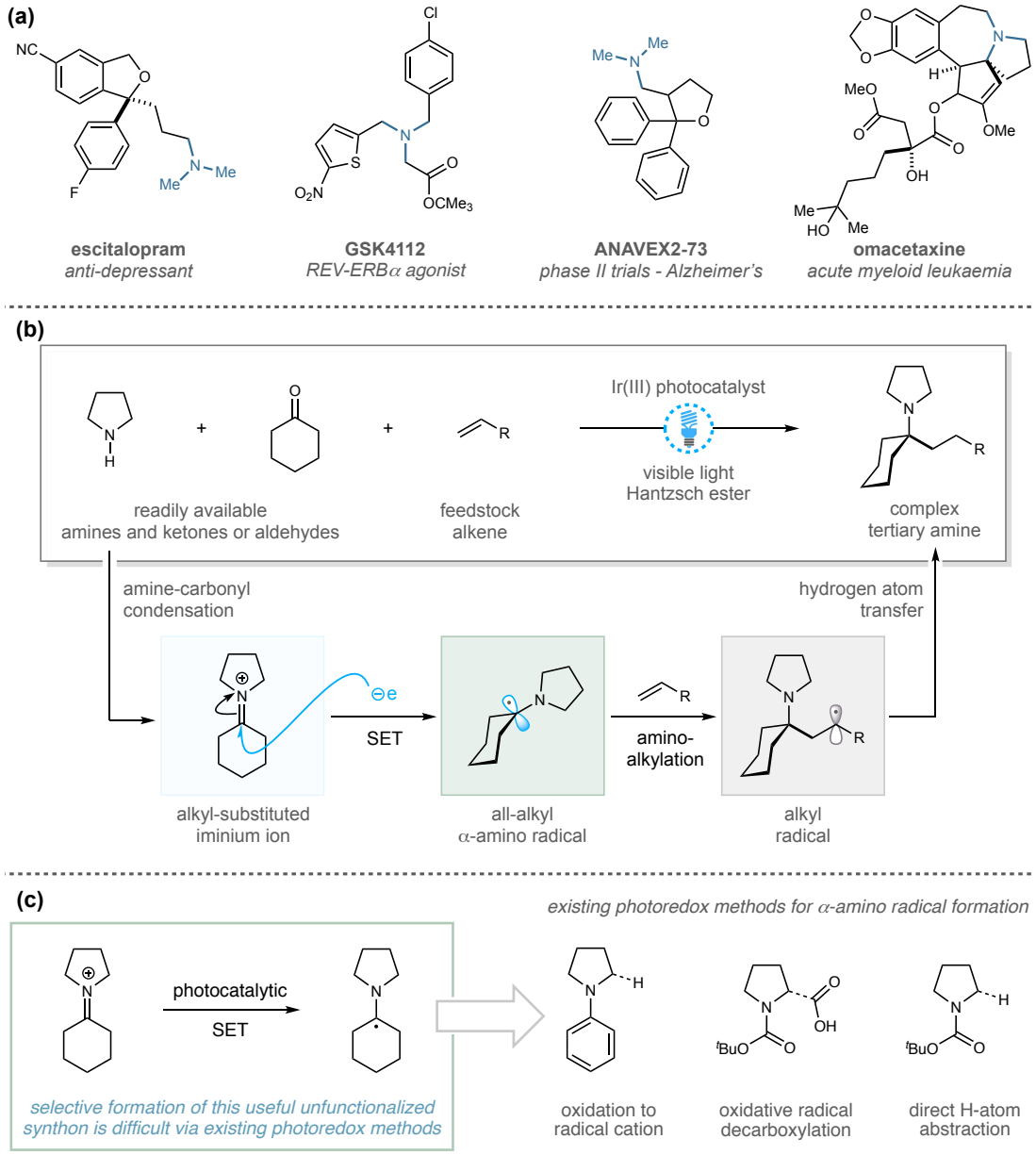

Fig 1. (a). Importance of tertiary amines. **(b)**. Multicomponent photocatalytic olefin-hydroaminoalkylation to tertiary alkylamines via the selective formation of alkyl-substituted α-amino radicals. **(c).** Existing catalytic photoredox methods for the generation of α-amino radicals.

We proposed that an electrophilic iminium ion, formed through the well-established union of secondary alkylamines and alkyl-substituted carbonyls, could be susceptible to a catalytic single electron reduction process (Fig 1B). The resulting α-amino radical could then engage a third reaction component, such as an alkene, in a subsequent C(sp^3)–C(sp^3) cross-coupling process. However, few methods report the generation of 'all-alkyl' α-amino radicals from pre-formed iminium ions, and each suffers from issues of practical application[16, 17]. Moreover, their subsequent addition to alkenes has been limited to specific intramolecular examples. To overcome these problems, we envisioned, firstly, that a visible-light-activated photocatalyst could mediate single-electron transfer (SET) to an in-situ generated alkyl-substituted iminium ion, generating

the desired α-amino radical under mild reaction conditions (Fig 1B). Secondly, we considered that a polarity-matched hydrogen atom transfer (HAT) from a suitable reagent could facilitate the cross-coupling to the alkene by intercepting the resulting alkyl-substituted radical. An important feature of this proposed catalytic activation pathway is the regiospecific positioning of the newly formed α-amino radical, made possible by the SET to the iminium ion, regardless of the groups surrounding the reactive center. Selective formation of an 'all-alkyl' α-amino radical would not be possible via the related photocatalytic approaches without the use of pre-functionalized starting materials or inherently selective substrates (Fig 1C)[18-20].

We were mindful of several factors that could impede the development of the photocatalytic olefin-hydroaminoalkylation process. In contrast to protonated imines and iminium ions conjugated with multiple aromatic substituents ($E_{1/2}^{red}$ = –0.8 to –1.2 V vs. SCE in acetonitrile)[21], which have been shown to partake in a limited range of reductive coupling reactions[22, 23], the reduction potential of an 'all-alkyl'-iminium ion could be up to –2.0 V[21] and would require a highly reducing photocatalyst that may be incompatible with resident functionality. Moreover, alkyl-iminium ions are known to exist in (often unfavorable) equilibrium with the corresponding enamines, which can also undergo SET reactions to form radical species, presenting competing pathways[24]. Finally, the addition of α-amino radicals to simple alkenes is known to be low-yielding due to oligomerization of the resulting radical[25]. We hereby report a comprehensive strategy for the modular and efficient construction of complex tertiary alkylamines via photocatalytic olefin-hydroaminoalkylation.

The initial evaluation of the proposed amine synthesis focused on a reaction between butyraldehyde **1a**, dibenzylamine **2a**, butyl acrylate **3a** and Hantzsch ester **4a** catalyzed by $Ir(ppy)_3$, under the action of visible-light (Fig 2A). Optimized reaction conditions were readily established (for a detailed account of the optimization study: see supplementary materials, S7), using 1mol% $Ir(ppy)_3$ and a 40 W blue-LED for 2 hours at room temperature. Under these conditions, near-equimolar quantities of aldehyde, amine and alkene with 1.5 equivalents of Hantzsch ester in a 0.1 M solution of dichloromethane containing molecular sieves and 20mol% of propionic acid formed desired amine **5a**, which was isolated in 84% yield after chromatography (Fig 2B). We were delighted by the remarkable selectivity displayed in this reaction; only trace quantities of

the reductive amination side product were observed, which presumably resulted from HAT to the α-amino radical from **4a**[26].

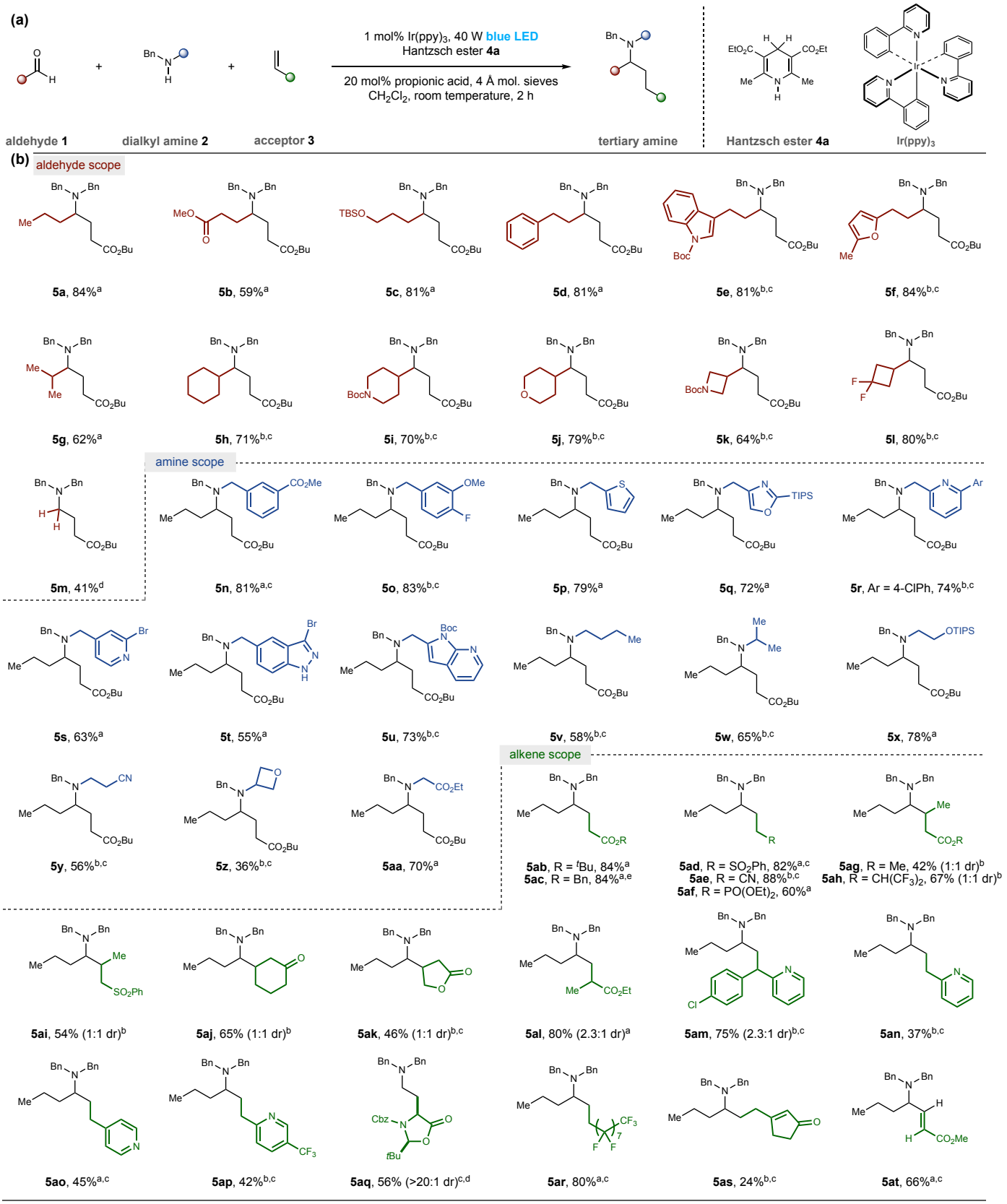

Fig 2. (a). Optimized conditions for photocatalytic olefin-hydroaminoalklyation. **(b)**. Scope of photocatalytic olefin-hydroaminoalklyation. [a]amine/aldehyde/acceptor (1:1.1:1.1) and **4a** (1.5 equiv.). [b]amine/aldehyde/acceptor (1:2:2) and **4a** (1.5 equiv.). [c]conducted using methoxyethyl-Hantzsch ester (1.5 equiv.). [d]conducted using paraformaldehyde (5 equiv.), preheated for 1 hour. [e]4 mmol scale. ppy = 2-phenylpyridinato; Boc = *t*-butyloxycarbonyl; TIPS = triisopropylsilyl; Cbz = benzyloxycarbonyl.

With the optimized conditions, we found that a variety of linear aldehydes reacted efficiently to give amines **5a**-**5f**, including those bearing electron-rich heteroarenes (**5e**, **5f**), in good yields (Fig 2B). Aldehydes displaying α-branching produced the expected amines **5g**-**5l** in good yield; notable examples included saturated heterocycles and strained ring features commonly found in pharmaceutical agents. The α-amino radical formed from formaldehyde and dibenzylamine was effective in the reaction, producing γ-aminobutyric acid derivative **5m**; unfortunately, benzaldehyde-derived iminium ions failed to deliver the desired cross-coupling products. Next, we found that benzylamine derivatives containing a multitude of functionalized aryl and heteroaryl groups were amenable to the reaction and gave good yields of the corresponding amines (**5n**-**5u**). Amines displaying linear and branched alkyl-substituents, as well as ester, hydroxyl and nitrile functionality, worked well to give amines **5v**-**5aa**. The photocatalytic process was effective with a range of electron-deficient alkenes. A reaction with benzyl acrylate **3c** could be adapted to a gram-scale process, delivering 1.4 g of product **5ac** in 84% yield. Notably, acrylonitrile (giving **5ae**) proved a suitable coupling partner, despite being prone to oligomerization in radical reactions. Substituents at either the α- or β-positions on the alkene (**5ag-5ak**) could be accommodated despite the lower electrophilicity and greater steric demand of these acceptors, with a diastereoselectivity of 2.3:1 observed in the reaction of methacrylate to form **5al**. Vinyl pyridine derivatives also proved to be viable acceptors (giving **5am**-**5ap**) allowing facile access to chlorphenamine derivative **5am**. By employing a chiral dehydroalanine derivative, the α-amino radical addition to this acceptor led to enantioenriched non-proteogenic amino acid derivative **5aq** in good yield. We also found that perfluorinated alkenes, dienes, and electron-deficient alkynes functioned well as acceptors (giving **5ar**-**5at**); the reaction with methyl propiolate delivered (*E*)-allylic amine **5at** in 66% yield as a single geometric isomer.

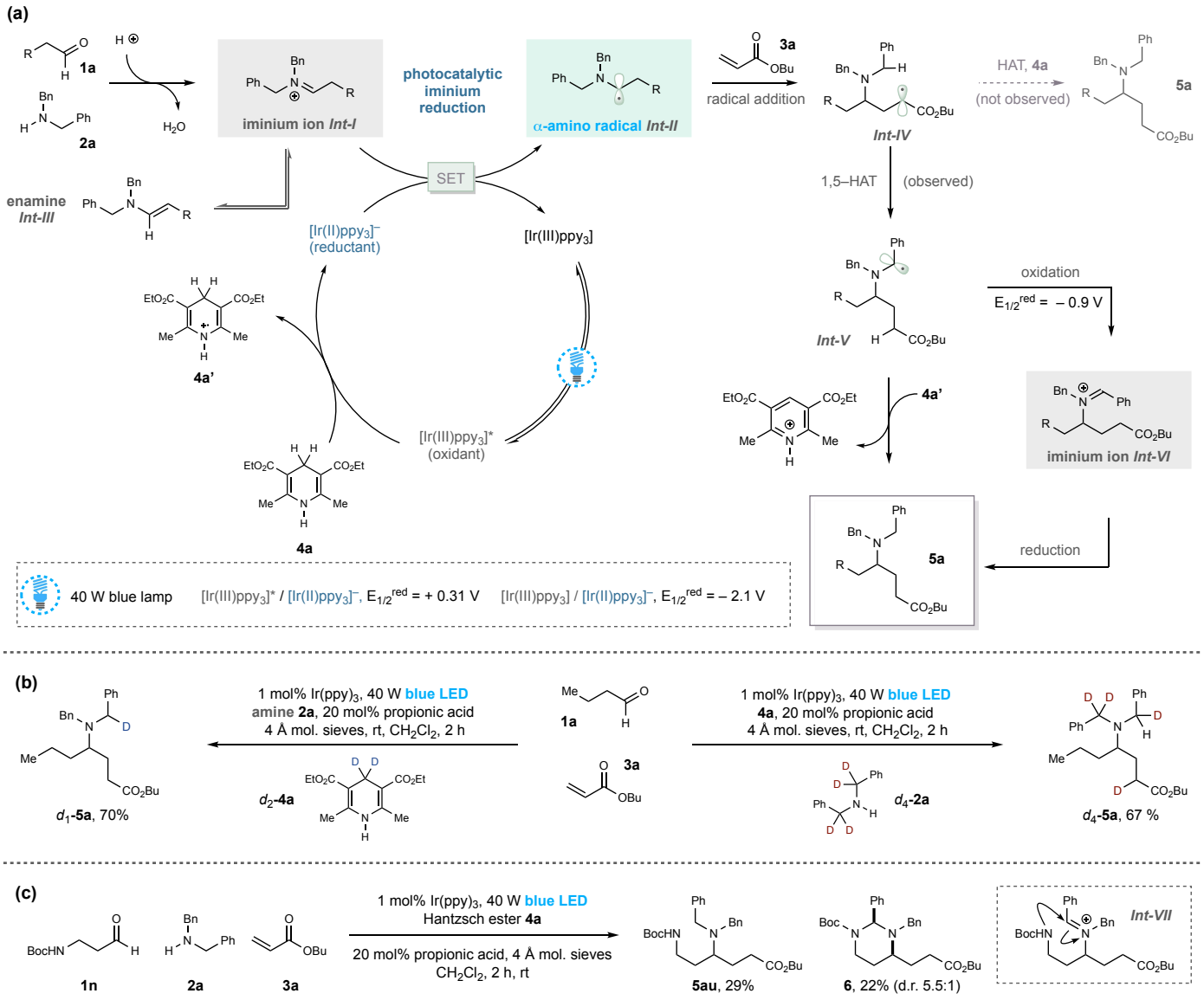

Fig 3. **(a)** Proposed mechanism for the photocatalytic olefin-hydroaminoalkylation. **(b)**. Deuterium-labelling studies. **(c)**. Evidence for iminium ion redox-relay mechanism.

Our mechanistic proposal for the photocatalytic olefin-hydroaminoalkylation is shown in Fig 3A. The reaction begins with visible-light excitation of $Ir(ppy)_3$ to the long-lived photoexcited *Ir(III) species (τ = 1.9 μs)[27]. While this species may be sufficiently reducing [Ir(IV)/*Ir(III), $E_{1/2}^{red}$ = –1.73 V vs. SCE in acetonitrile][27] to undergo SET to alkyl-iminium ion *Int-I*, we recognized that *$Ir(III)ppy_3$ is efficiently quenched by Hantzsch ester **4a** [*Ir(III)/Ir(II), $E_{1/2}^{red}$ = +0.31 V vs. SCE in acetonitrile][27] leading to $[Ir(II)ppy_3]^-$ and the corresponding Hantzsch ester-radical cation **4a'**. Importantly, $[Ir(II)ppy_3]^-$ is sufficiently reducing [Ir(III)/Ir(II), $E_{1/2}^{red}$ = –2.19 V vs. SCE in acetonitrile][27] to undergo SET with the full range of alkyl-iminium ions[21], leading to α-amino radical *Int-II*. We identified enamine *Int-III* as the predominant species in the ^{1}H NMR of the reaction mixture, which we believe is an off-cycle precursor to the iminium ion *Int-I*; the acid

maintains a low concentration of iminium *Int-I* by protonation of the enamine. The α-amino radical *Int-II* now engages the polarity-matched acrylate **3a**, creating a carbon-carbon bond and α-ester radical *Int-IV*. Given the propensity for mono-substituted α-ester radical *Int-IV* to undergo oligomerization[25], we anticipated that an intramolecular 1,5-HAT to the benzylic position may act as a kinetic trap to form stabilized radical *Int-V*[28]. Finally, we expected that the Hantzsch ester or its radical cation **4a**/**4a'** would participate in a HAT reaction with *Int-V*, to form amine **5a**. A reaction using deuterium-labelled Hantzsch ester d_2-**4a** (Fig 3B) confirmed our hypothesis; deuterium was incorporated exclusively at the benzylic position of amine d_1-**5a**, showing that 1,5-HAT occurred prior to interception with **4a**/**4a'**. This theory was further corroborated using labelled dibenzylamine d_4-**2a**, wherein a deuterium was transferred to the position adjacent to the ester in amine d_4-**5a**. We also found that an aldehyde bearing a β-nucleophilic group (**1n**) underwent cyclization onto the benzylic position to form **6**, as a side reaction in the formation of **5au** (Fig 3C). This result suggests that the α-aminobenzyl radical (*Int-V*) can undergo oxidation [$E_{1/2}^{red} = -0.9$ V vs. SCE in acetonitrile][29] to iminium *Int-VI*, which is accessible to a range of oxidants, such as *Ir(III)[27]. Notably, selective reduction of benzaldiminium ion *Int-VI*, over the initially formed iminium *Int-I,* can be accounted for by its inability to form a stable enamine intermediate compared to the interconversion between *Int-I* and *Int-III*. The reduction of *Int-VI* could proceed by a 2-electron process with **4a** or photocatalytic SET and HAT. Interestingly, a pathway whereby iminium *Int-I* is translated into a new iminium species *Int-VI* represents an overall mechanism that can be described as a redox-relay of iminium ions, which, to the best of our knowledge, has not been previously reported.

In this context, benzylamines not only overcome the inherent challenges posed by the addition of α-amino radicals to electron-deficient alkenes, but also act as a protecting group for primary and secondary alkylamines. Nonetheless, we reasoned that use of an alkene which would produce a less-electrophilic radical should favor direct reaction with the Hantzsch ester-radical cation **4a'**, obviating the need for the 1,5-HAT process, and hence permitting the use of a variety of dialkylamines. To test this, 1,1-diphenylethylene was

combined with aldehyde **1a** and 4-phenyl piperidine under the standard conditions. Pleasingly,

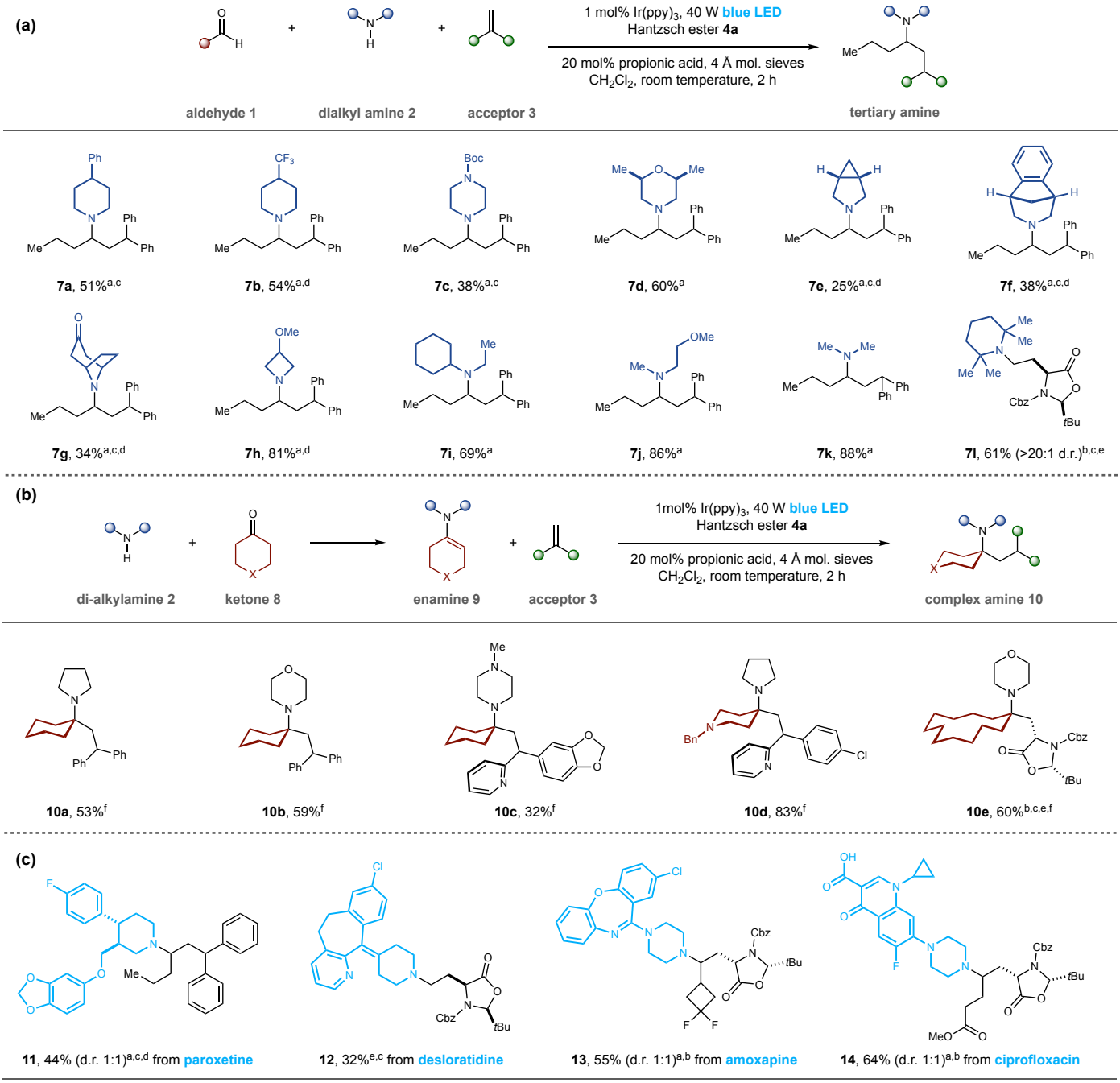

Fig 4. **(a)**. Scope of non-benzylic amines for photocatalytic olefin-hydroaminoalkylation **(b)**. The synthesis of alkyl substituted α-tertiary amines from dialkyl ketones. **(c)**. Late-stage photocatalytic olefin-hydroaminoalkylation with pharmaceutical agents. [a]conducted using amine/aldehyde/acceptor (1:2:2), and **4a** (1.5 equiv.). [b]conducted using acceptor (1.5 equiv.). [c]conducted using methoxyethyl-Hantzsch ester (1.5 equiv.). [d]using amine hydrochloride and Et_3N (1 equiv.). [e]conducted using paraformaldehyde (5 equiv.), preheated for 1 hour. [f]conducted using enamine (1 equiv.) and acceptor (2 equiv.).

the desired tertiary amine **7a** was formed in 51% yield (Fig 4A). Other amine heterocycles were also compatible with this alkene acceptor, giving the amine products (**7b**-**7k**) in good yield; 1,1-diarylpropylamines are key motifs commonly found in H_1-antihistamines[30]. Among these examples, a number of amines found in pharmaceuticals formed the corresponding complex tertiary amines (**7c**-**7h**), demonstrating the potential to

forge ‘drug-like’ molecules in a single step from readily available materials. The use of non-benzylic amines was not restricted to reactions with 1,1-diarylethenes; the union of tetramethylpiperidine, formaldehyde and a dehydroalanine acceptor proceeded smoothly to form amine **7l** as a single diastereomer.

We envisioned that the use of dialkylketones would be an important extension to the photocatalytic process, since these reactions would give rise to α-tertiary amine products[31]. Conscious that the formation of ketiminium ions often require more forcing conditions, we reasoned that protonation of a pre-formed enamine **9** would provide a more accessible source of alkyl-ketiminium ions, since alkyl-enamines can be readily prepared on gram scale in one step (Fig 4B). Under the standard conditions, a range of alkyl enamines underwent smooth cross-coupling with alkene acceptors to form α-tertiary amines (**10a**-**10e**). The olefin-hydroaminoalkylation method was able to generate complex α-tertiary alkylamines scaffolds, in a single step, which would be difficult to assemble via classical methods.

Given that dialkylamine motifs are present in a range of small molecule drugs and pre-clinical candidates, late-stage functionalization of such molecules would be a powerful demonstration of the utility of this process. To confirm this strategy, we selected four pharmaceutical agents and subjected them to the photocatalytic reaction (Fig 4C). Each of these architecturally complex amines underwent smooth olefin-hydroaminoalkylation with a variety of aldehydes to furnish the tertiary amine products (**11**-**14**). In particular, the combination of desloratidine with formaldehyde and a chiral dehydroalanine acceptor forms a single diastereomer of the tertiary amine derivative (**12**), constituting a potentially useful linker-strategy through which further functionalization of drug scaffolds could be realized.

We expect that the operational simplicity, efficacy and broad scope of this highly selective multicomponent photocatalytic amine synthesis will find widespread use among organic chemistry end users in both academia and industry. Moreover, we believe that the convenience with which this method generates underexplored alkyl-substituted α-amino radicals will inspire further advances in the synthesis of complex tertiary amine scaffolds.

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