Modular Photocatalytic Synthesis of α-Trialkyl-α-Tertiary Amines

J. Henry Blackwell, Georgia R. Harris‡, Milo A. Smith‡, and Matthew J. Gaunt*

Yusuf Hamied Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge, CB2 1EW. United Kingdom.

ABSTRACT: Molecules displaying an α-trialkyl-α-tertiary amine motif provide access to an important and versatile area of biologically-relevant chemical space but are challenging to access through existing synthetic methods. Here we report an operationally straightforward, multi-component protocol for the synthesis of a range of functionally and structurally diverse α-trialkyl-α-tertiary amines, which makes use of three readily available components: dialkyl ketones, benzylamines and alkenes. The strategy relies on the of use visible-light-mediated photocatalysis with readily available Ir(III) complexes to bring about single-electron reduction of an all-alkyl ketimine species to an α-amino radical intermediate; the α-amino radical undergoes Giese-type addition with a variety of alkenes to forge the α-trialkyl-α-tertiary amine center. The mechanism of this process is believed to proceed through an overall redox neutral pathway that involves photocatalytic redox-relay of the imine, generated from the starting amine-ketone condensation, through to an imine-derived product. This is possible because the presence of a benzylic amine component in the intermediate scaffold drives a 1,5-hydrogen atom transfer step after the Giese addition to form a stable benzylic α-amino radical, which is able to close the photocatalytic cycle. These studies detail the evolution of the reaction platform, an extensive investigation of the substrate scope and preliminary investigation of some of the mechanistic features of this distinct photocatalytic process. We believe this transformation will provide convenient access to previously unexplored α-trialkyl-α-tertiary amine scaffolds that should be of considerable interest to practitioners of synthetic and medicinal chemistry in academic and industrial institutions.

INTRODUCTION

Molecules displaying an α-tertiary amine (ATA) motif — a nitrogen with an α-carbon bearing three C–C bonds — show versatile and tunable physicochemical and biological properties, making it an important structural unit that is found in a diversity of pharmaceutical agents and biologically-relevant natural products (Figure 1A).[1,2,3,4] The fully substituted carbon atom adjacent to the nitrogen atom impacts on amine basicity[5] and lipophilicity, and provides three exit vectors through which interactions with a biological receptor can be tuned. Furthermore, when coupled with the capacity to add up to two further substituents to the nitrogen atom, the presence of an α-tertiary amine can substantially impact the topology of molecules.

Topological complexity in pharmaceutical candidates has been shown to lead to a decrease in attrition of lead compounds and one way of achieving this is to increase the fraction of C(sp^3) atoms in a molecule.[6] In the context of the ATA scaffold, the incorporation of three functionalized α-alkyl substituents represents a particularly attractive class of C(sp^3)-rich amine scaffold. A number of compounds bearing α-trialkyl-ATA motifs are showing great promise as treatments across a range of disease areas (Figure 1B). The α-trialkyl-ATA feature is particularly prevalent in compounds acting on the nervous system. For example, β-hydroxy α-trialkyl-ATAs have been fundamental in the development of S1P receptor modulators, such as fingolimod (Gilenya), for the treatment of multiple sclerosis,[2a-b] with further studies suggesting that the ATA motif is thought to play a crucial role in the mechanism of action;[2c] fingolimod has indications in a number of other disease areas.[2d] The α-trialkyl-ATA Elayta is in phase II trials for the treatment of Alzheimer's disease.[2e-f] A number of kinase inhibitors, such CCT128930[4a] and PF-06843195,[4b] contain the α-trialkyl-ATA motif and have been utilized as candidates for the treatment of cancer. Despite the apparent importance of the α-trialkyl-ATA motif, they remain under represented structural features in pharmaceutical candidates, most likely because effective methods for their assembly remain limited. Therefore, the development of strategies for the streamlined synthesis of functionalized C(sp^3)-rich complex α-trialkyl-ATAs has been recognized as an important challenge in organic synthesis.[7]

The assembly of ATAs, in their broadest sense, is challenging because reactions to connect classical synthons arising from disconnecting around the α-center are usually hampered by steric effects in one of the components. Nevertheless, a number of innovative strategies have been developed to circumvent these challenges and deliver the ATA structure[1]. Methodologies which forge the α-tertiary center through formation of a C–N bond can be achieved through a number of different reaction types. For example, nucleophilic amination *via* Ritter-type reactions and metal-catalyzed hydroaminations constitute important approaches for the synthesis of ATAs.[1,8,9] Alternative C–N bond-forming methods that employ nitrogen as the electrophile have also shown great utility upon reaction with suitable carbon nucleophiles; nitrenes and metallonitrenoids can form C–N bonds on reaction with tertiary C(sp^3)–H bonds in saturated hydrocarbons.[10,11] Molecular rearrangements,[1a,12] in particular the Curtius reaction, have been utilized to great effect in converting readily available functional groups into α-trialkyl-ATAs within complex frameworks.

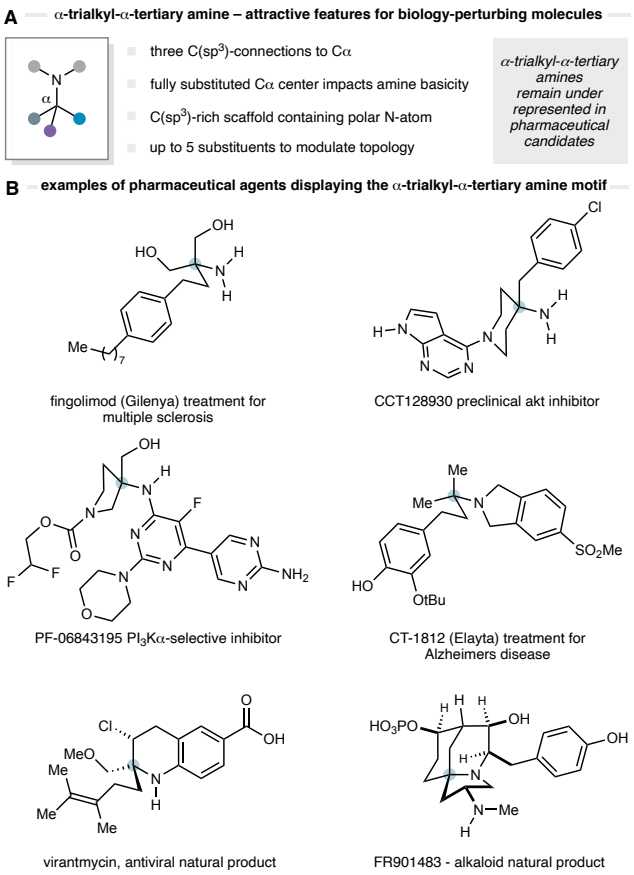


Figure 1. Pharmaceuticals displaying α-trialkyl-ATA motifs.

Disconnection at the C–C bond offers, arguably, the most effective approach to form the α-tertiary center.[1a,13,14] A cornerstone of such strategies is 1,2-addition of carbon-centered nucleophiles to ketimines. The most commonly adopted variation of this approach involves organometallic addition to N-activated ketimine derivatives. Ellman pioneered the use of a *tert*-butanesulfinamide auxiliary to activate the ketimine species and control the stereochemistry of the organometallic addition.[15] Whilst undeniably a powerful method, there are surprisingly few examples of the addition of an organometallic to dialkyl ketimines as a means to make α-trialkyl-ATA derivatives, likely due to sterically compromised reactivity and competitive α-deprotonation brought about by the basic nature of the nucleophile.[16] Recently, Dixon reported an indirect method for organometallic additions to dialkyl ketimine derivatives.[15h] Although tailored intermediates were required, the multi-step, one-pot transformation demonstrates a good substrate scope in α-trialkyl-ATAs.

An important contemporary strategy for the synthesis of ATAs has recently emerged that involves the reactions of α-amino radicals generated via visible-light-mediated photoredox catalysis (Figure 2A).[17] The α-amino radical is nucleophilic and represents the umpolung of the imine and, hence, affords an alternative C–C bond disconnection for the α-trialkyl-ATA motif that obviates the problems encountered using basic organometallics. There are two main approaches for generation of such radicals, in this context: direct α-hydrogen atom transfer (HAT) of primary amines and single-electron reduction of ketimines. Rovis, Schoenebeck and co-workers demonstrated a HAT-mediated α-alkylation of N-primary α-secondary amines using electron deficient alkenes. Enabled by a reversible reaction between the amine and CO_2, in situ carbamate formation lowers the bond dissociation energy of the α-C–H bond and engages a radical cation, which together facilitate an efficient HAT process.[18] In 2020, Cresswell and co-workers reported the direct coupling of a wide range of N-primary α-secondary amines with alkenes, this time employing a photocatalytically-generated azide radical as the electrophilic HAT reagent to enable α-amino radical formation.[19]

In the regime involving photocatalyst-mediated single-electron reduction of ketimines to α-amino radicals, the range of existing methods is more restricted. While aryl-substituted ketimines (on C and N) have been utilized in visible-light-mediated reductive coupling reactions,[20] all-alkyl ketimines have proven to be incompatible with this type of transformation to form α-trialkyl-ATAs owing to their very low reduction potentials,[21] which precludes α-amino radical formation. However, the modularity provided by an activation mode based on single-electron reduction of an in situ-generated ketiminium makes the successful realization of this process an important challenge for the synthesis of α-trialkyl-ATAs.

Here we report the development of an operationally straightforward and modular synthesis of a range of functionally and structurally diverse α-trialkyl-ATAs (Figure 2B). Visible-light-mediated photocatalytic single-electron reduction of a dialkyl-imine, generated in situ from a ketone and primary amine, forms an α-amino radical, which can engage a range of alkenes through Giese addition. The carefully designed process permits a redox-relay pathway through imine intermediates that leads to a redox neutral reaction without the need for any external reagents. The reaction's broad substrate scope provides convenient access to previously unexplored α-trialkyl-ATA scaffolds that should be of considerable interest to practitioners of synthetic and medicinal chemistry in academic and industrial institutions.

RESULTS & DISCUSSION

In 2018, our group reported a multicomponent alkene hydroaminoalkylation of olefins that leveraged photocatalytic single-electron reduction of alkyl iminium ions, derived from aliphatic aldehydes and benzylic secondary amines, to form α-amino radicals (Figure 3A).[22] Key to the success of this strategy was the alignment of a number of design features that enabled the orchestration of a complex mechanism: Hantzsch ester (HEH) quenches the excited state of the Ir(III)-photocatalyst to form a highly reducing $[Ir(II)]^-$ species, which promoted single-electron reduction of an alkyl iminium ion to form an α-amino radical; the α-amino radical undergoes Giese addition to an electron deficient alkene. The resulting radical underwent fast, thermodynamically driven 1,5-HAT to form a benzylic α-amino radical, which was ultimately reduced to form the product. While this alkene hydroaminoalkylation exhibited a broad substrate scope, it carried a number of limitations that could preclude its wider application: firstly, only highly activated or electron deficient alkenes were competent acceptors for the α-amino radical addition; secondly, the Hantzsch ester, while a critical enabling component, complicates the reaction from a mechanistic standpoint as well as being a poorly atom economic reagent considering it formally transfers a only single hydrogen atom; finally, condensation of ketones and secondary amines was prohibitively slow under the reaction conditions, meaning that α-trialkyl-ATAs were not directly accessible using this process.

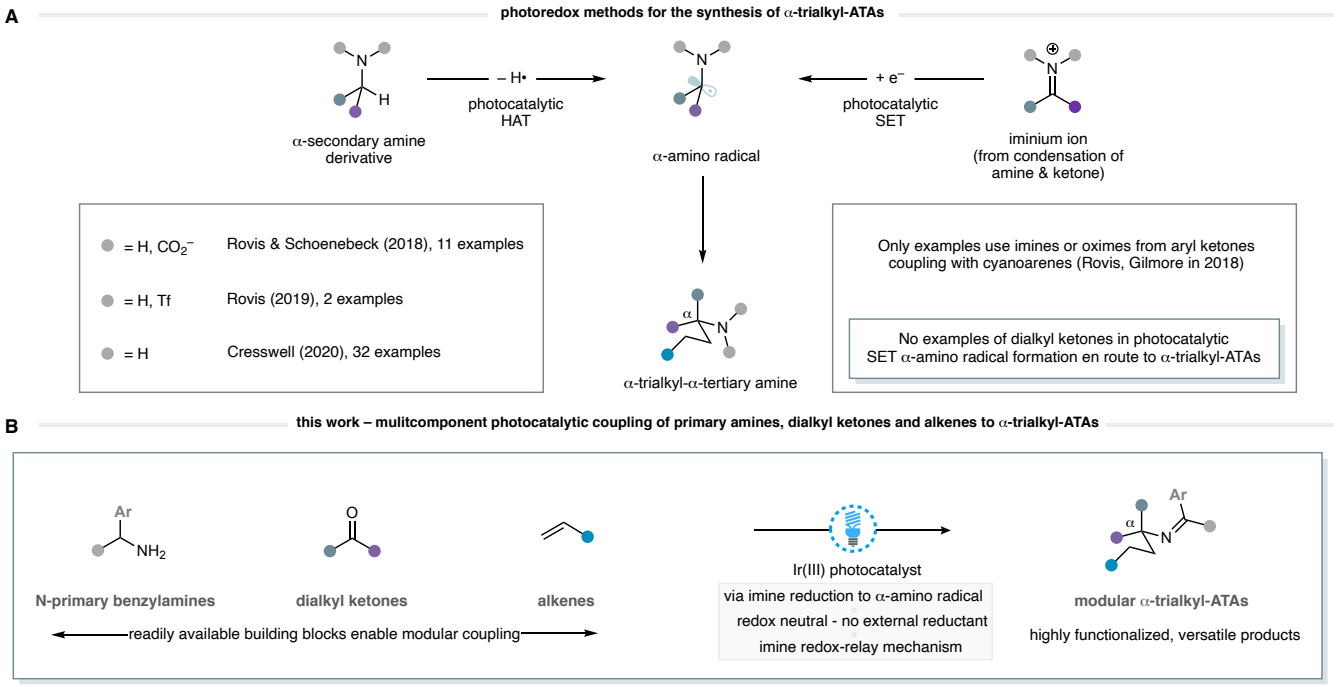


Figure 2. (A) Photoredox catalysis for the synthesis of α-trialkyl-ATAs. **(B)** Redox neutral photocatalytic strategy for the synthesis of α-trialkyl-ATAs.

Subsequent work from our group addressed some of these limitations,[23,24] but failed to provide a platform for a general intermolecular alkene hydroaminoalkylation to α-trialkyl-ATAs (Figure 3B-C). For example, an intramolecular variant of the original process accommodated cyclic ketones in combination with a range of homoallylic secondary amines to generate N-heterospirocycles (Figure 3B).[23] However, we believe the successful deployment of ketones, in this case, arises from the irreversible process-terminating HAT step to the exocyclic primary radical, which drives the equilibria of the discrete steps towards product formation. Importantly, this work revealed that the use of more reducing photocatalysts could change the nature of the quenching cycle, directly engaging the iminium species through single-electron reduction rather than being reduced by HEH (as in Figure 3A). As part of our total syntheses of (–)-FR901483 and (+)-TAN1251C,[24] we also showed that cyclic ketones could be utilized in a modified intermolecular alkene hydroaminoalkylation reaction (Figure 3C). There, the use of a primary amine circumvented the condensation problems associated with ketiminium formation, but the radical addition step required the use of a highly activated acceptor. Non-benzylic primary amines could be used because addition to the Karady-Beckwith alkene[25] generates a capdodative radical that cannot undergo the 1,5-HAT back on the amine framework, as required in our original work.[22]

Taken together, it was clear that the requirements of our previous alkene hydroaminoalkylation protocols (Figure 3) would preclude the sought-after process for a modular synthesis of α-trialkyl-ATAs and so we set out to redesign an activation platform that could draw from readily available ketone, amine and alkene feedstocks. Our previous work had highlighted three factors that would be important in a new design plan: (1) the use of a photocatalyst with a more reducing excited state may provide a pathway by which HEH could be removed from the reaction components; (2) the use of a primary amine would likely address problems associated with ketimine formation; and (3) the primary amine component would still require a benzylic substituent to drive the 1,5-HAT step designed to translocate the radical from the acceptor framework to the amine scaffold. While this latter feature was crucial in our original work, we speculated that it could function as a lynchpin mechanistic step for unlocking the desired modular α-trialkyl-ATA synthesis.

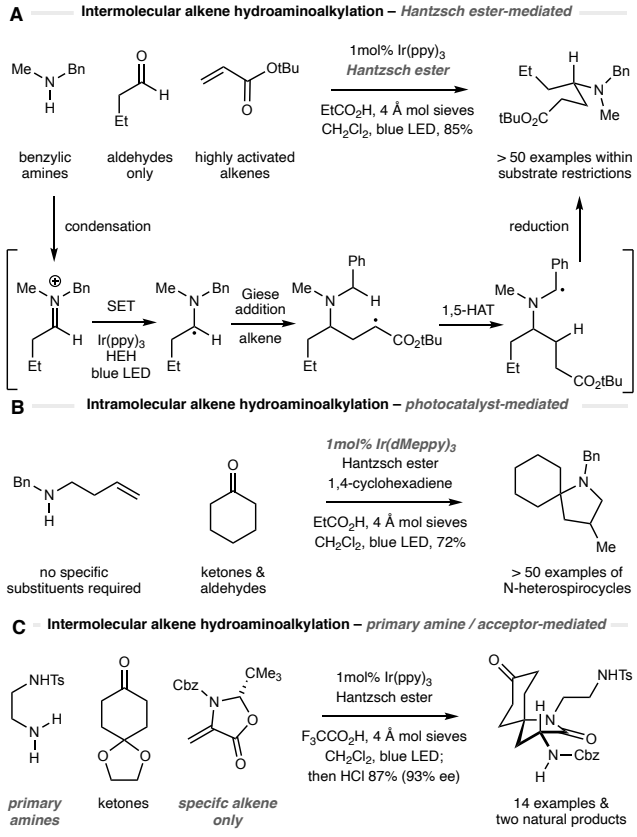


Figure 3. Previous work on alkene hydroaminoalkylation.

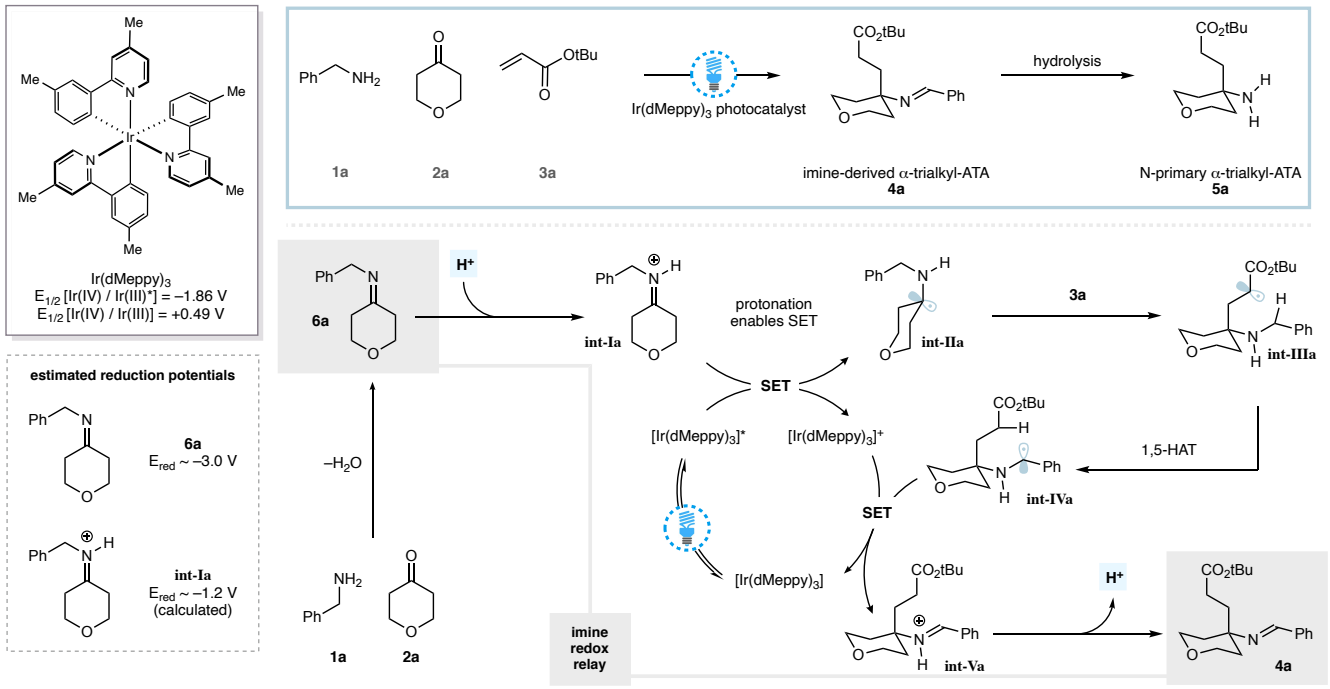
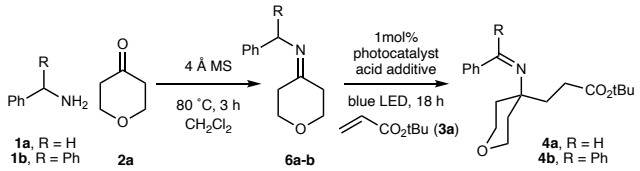


Figure 4. Strategy and reaction design for multicomponent photocatalytic α-trialkyl-ATA synthesis.[27,28]

Guided by these factors, we proposed a mechanistic blueprint that begins with condensation of a representative benzylamine (**1a**) and ketone (**2a**), which was expected to deliver imine **6a**. The reduction potential of all-alkyl ketimines, however, is predicted to be in the region of –3.0 V (vs. SCE in MeCN[21]; for comparison, the reduction potential of elemental Li is –3.05 V vs SHE[26]), placing it out of reach of most convenient reducing photocatalysts. Instead, we anticipated that protonation of **6a** to form ketiminium **int-Ia** would significantly lower the reduction potential and bring it into the range of the more reducing Ir(III)-photocatalysts such as $Ir(dMeppy)_3$ ($E_{1/2}[Ir(IV)/Ir(III)^*] = -1.86$ V vs SCE in CH_2Cl_2[23]), which we had shown was capable of effecting the single-electron reduction process in the intramolecular alkene hydroaminoalkylation (Figure 3B). Single-electron reduction of **int-Ia** affords α-amino radical **int-IIa**, which would engage the acrylate **3a** via Giese addition[29] to form radical **int-IIIa**. As demonstrated in our original work (Figure 3A), **int-IIIa** would be expected to undergo rapid 1,5-HAT, translocating the radical from the acrylate framework to form benzylic α-amino radical **int-IVa**. At this point, we envisioned that the oxidized form of the photocatalyst, $[Ir(dMeppy)_3]^+$ would take part in single-electron transfer from the benzylic α-amino radical, returning the photocatalyst to its ground state form and concurrently oxidizing **int-IVa** to the new ketiminium species **int-Va**. This step is distinct from our previous work, wherein a benzylic α-amino radical is reduced to the amine product, and formulates an important feature of this new design: starting material-derived ketimine **6a** is processed through to product aldimine **4a**, which represents a photocatalytic imine redox-relay process that renders the transformation redox neutral and obviates the need for any terminal reducing agents.

Guided by this design plan, our studies began with a series of reactions reaction involving irradiation (with a 40 W blue Kessil lamp) of a dichloromethane solution of imine **6a** (formed in situ by mixing benzylamine **1a**, ketone **2a** and 4 Å molecular sieves in advance of irradiation) and *tert*-butyl acrylate **3a** in the presence of 1mol% of $Ir(dMeppy)_3$ and a small range of acid additives (Table 1A, entries 1-3), according to our mechanistic hypothesis. The benzaldimine-derived α-trialkyl-ATA **4a** was obtained in all cases alongside amine **1a** and ketone **2a**, however, the highest assay yield was observed in a reaction with no acid additive (Table 1A, entry 4). While this result was surprising, given our mechanistic hypothesis requiring imine protonation, we proceeded to further optimize the conditions. The facile hydrolysis of the benzaldimine motif in product **4a**, coupled with isolation issues, lead us consider the use of alternative benzylamines that would deliver a more stable product. We reasoned that use of benzhydrylamine **1b** as the amine component would afford more stable benzophenone imine products (**4b**). Accordingly, we found that more consistent assay yields were obtained when using amine **1b** and the products were readily isolable after chromatographic purification (Table 1A, entry 5). Assessment of other photocatalysts confirmed our hypothesis that more reducing systems delivered a more efficient process, although it should be noted that the use of slightly less reducing (but commercially available) iridium complex $Ir(ppy)_3$ is also effective, delivering **4b** in a slightly lower but comparable yield (Table 1, entry 6). A control reaction in the absence of photocatalyst gave no product (Table 1A, entry 7; see SI for full details regarding control studies). Finally, we were pleased to find that pre-condensation to form the imine was not essential and a multicomponent reaction combining amine **1b**, ketone **2a**, alkene **3a**, photocatalyst and molecular sieves at the start of the process proceeded at no detriment to the yield of **4b**, substantially increasing the efficiency of the process (Table 1B).

A stepwise, one-pot photocatalytic alkene hydroaminoalkylation



Entry	Amine	Photocatalyst	Acid	Yield 4a
1	**1a**	$Ir(dMeppy)_3$	F_3CCO_2H	43%
2	**1a**	$Ir(dMeppy)_3$	$EtCO_2H$	13%
3	**1a**	$Ir(dMeppy)_3$	TBSOTf	54%
4	**1a**	$Ir(dMeppy)_3$	–	80%
5	**1b**	$Ir(dMeppy)_3$	–	85%
6	**1b**	$Ir(ppy)_3$	–	75%
7	**1b**	–	–	0

B optimized multicomponent photocatalytic alkene hydroaminoalkylation

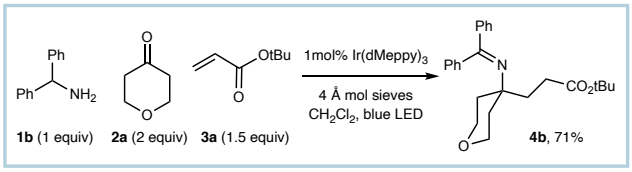


Table 1. (A) Selected optimization for stepwise, one-pot alkene hydroaminoalkyltion to α-trialkyl-ATAs. Yields were determined by ^1H NMR using 1,1,2,2-tetrachloroethane as an internal standard. **(B)** Optimized reaction conditions for direct multicomponent transformation. Yield is quoted for isolated product.

With optimal conditions in hand, the scope of the alkene hydroaminoalkylation protocol to form α-trialkyl-ATAs was investigated (Figure 5). The scope in the ketone component was first investigated and we were pleased to observe that a functionally and structurally rich suite of cyclic ketones were successful substrates in the reaction (Figure 5A). Five to seven membered ring ketones were competent substrates in the reaction, although compared to cyclohexanone the reaction of cyclopentanone and cycloheptanone gave lower yields of product (**4c**-**e**). A range of functionalized 6-membered ring ketones, incorporating O, S and N-heteroatoms gave access to versatile α-trialkyl-ATA scaffolds in good yields (**4b**, **4f**-**j**). Compared to the lower yielding cyclopentanone example, the corresponding 3-pyrrolidinone gave satisfactory yields of the 5-membered ring heterocyclic amine product (**4k**). Conversely, the product (**4l**) of the reaction using the corresponding *N*-Cbz azetidinone was obtained in a low yield, which we conjecture results from more challenging condensation and tautomerization processes in the strained heterocycle. Acyclic ketones were also good substrates, although it was found that pre-condensation with the less bulky benzylamine **1a** gave superior results and allowed for a broader scope in this subclass of substrates (Figure 5B). Furthermore, we also found that cleavage of the aldimine motif to the primary amine led to the more straightforward isolation of these products (**5m**-**x**) in higher yields. Accordingly, following this modified protocol revealed that a selection of linear and α-branched ketones bearing a variety of functionality could be converted to the α-trialkyl-ATA products; a ketone containing a distal ester group cyclized on isolation to the corresponding lactam (**5v**). Whilst reactions with acetone and 3-pentanone gave good assay yields of product (**5m** and **5w**), isolation proved challenging. It is thought that this is due to partial spontaneous lactamization of the free amine onto the *tert*-butyl ester of the acrylate framework, which had not been observed in other substrates. Notably, no intramolecular addition was observed onto the internal alkene in the case when 6-methylhept-5-en-2-one was employed to form **5u**, even in the absence of *tert*-butyl acrylate. The sterically encumbered tropinone scaffold also worked well under these conditions and provided **5x** as a single diastereomer. Tri-substiuted ketones were found to be poor substrates in the transformation. We attribute this to a combination of three factors; condensation hampered by steric hindrance, a challenging giese addition forging vicinal quaternary centres and 1,3-allylic strain limiting enamine formation (*vide infra*).

Next the scope of the α-trialkyl-ATA synthesis protocol was explored with respect to the alkene component (Figure 6); a wide range of alkenes delivered α-trialkyl-ATAs with good yields. The classical Giese addition electron-deficient alkene acceptors, phenyl vinyl sulfone, methyl vinyl ketone and even di-substituted cyclopentenone and benzyl methacrylate could be employed to give the desired products (Figure 6A, **7a**,**b**,**e**,**f**) in excellent yields. Vinyl pinacol borane gave access to the borylated product in good yield (**7d**), providing a useful handle for further diversification.[30] Electron-deficient alkynes were also found to be competent coupling partners, giving access to the trans- alkene product exclusively (**7c**). The discovery that the use of benzhydrylamine as the amine component led to superior yields in the hydroaminoalkylation reaction further strengthened our plan to exhibit a broad scope with respect to the alkene; 1,5-HAT of the radical formed following addition of the α-amino radical to the alkene would, if benzhydrylamine was used, lead to the formation of the highly stabilized open shell species that we reasoned would provide an increased thermodynamic driving force for the forward reaction in preference to β-scission or further additions to an alkene. We were pleased to observed that when styrene was tested under this new reaction regime, a good yield of the phenethyl-substituted α-trialkyl-ATA was obtained (Figure 6B, **7g**). In contrast, the same reaction using benzylamine delivered approximately 15% yield of product accompanied by an intractable mixture of oligomerization products. By extending irradiation time and increasing the number of equivalents of acceptor from 1.5 to 3 equivalents, the use of benzhydrylamine **1b** led to a range of styrenes being successfully engaged as coupling partners (**7h**-**m**). A clear electronic trend was observed in the yields of these reactions, with electron rich styrenes giving lower yields and electron deficient styrenes leading to higher yields. Furthermore, 2-, 3- and 4-vinyl pyridines were employed in modest to good yields (**7n**-**r**), without the need for external acceptor activation.[31]

While the benzyl/benzhydryl amine component of the reaction originated as a design feature to drive a more challenging Giese-addition with a broad range of alkenes, we wondered if we could exploit variation of this reaction component to incorporate an additional dimension of modularity into the reaction products. As such, we evaluated a selection of benzylamines in the reaction with 4-oxotetrahydropyran (**2a**) and *tert*-butylacrylate (**3a**) (Figure 6C). To enable facile isolation of the reaction products with the benzylamine moiety intact, the aldimine products were reduced to the corresponding secondary amine by treatment with sodium borohydride in methanol. The process was tolerant towards a range of substituents as well as amenable to the use of heteroaromatic benzylamines and gave their corresponding secondary amines in synthetically useful yields (**8a**-**f**).

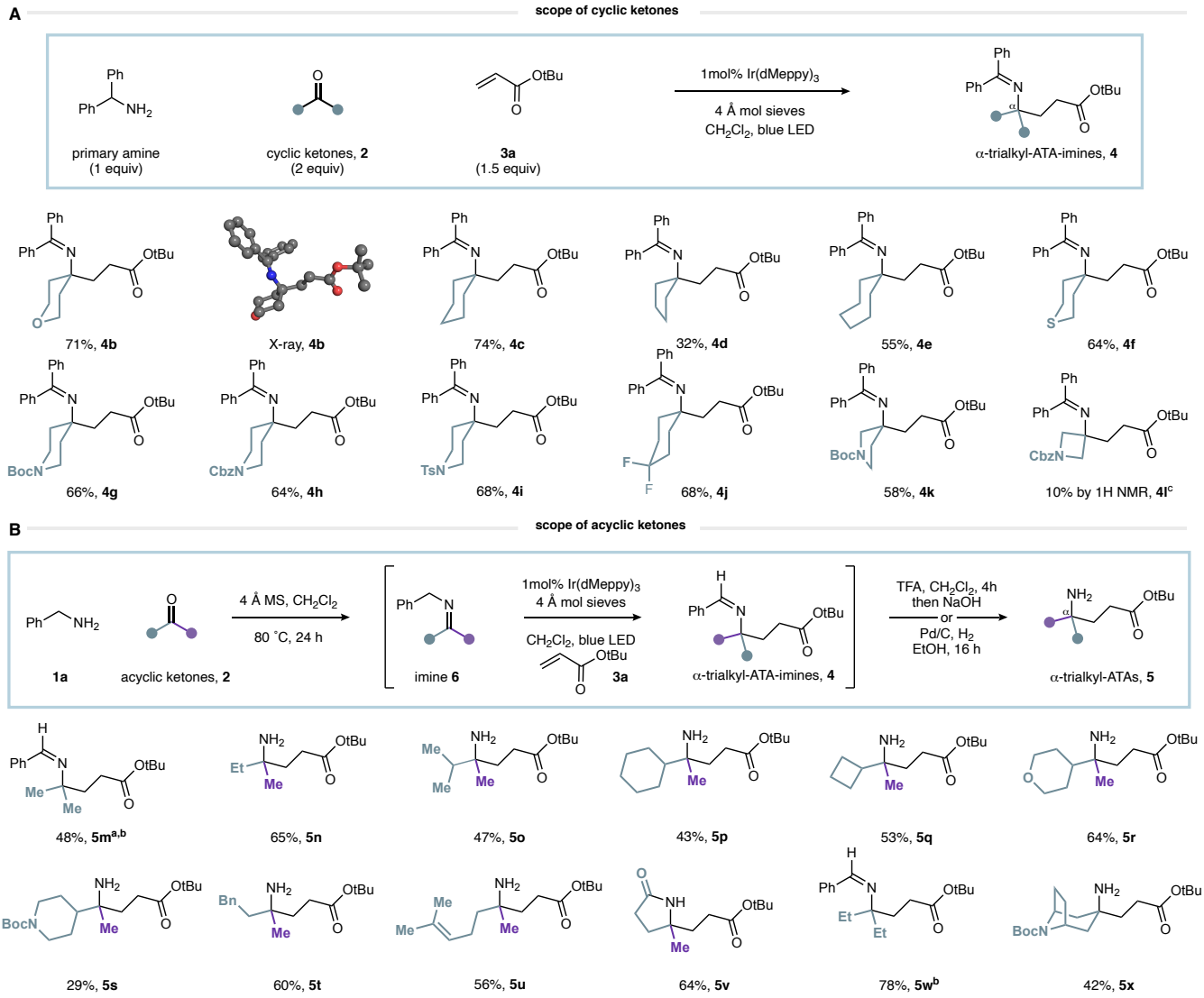


Figure 5. Scope of the photocatalytic α-tertiary amine synthesis in the ketone component. **(A)** Cyclic ketones. **(B)** Acyclic ketones. [a]Reaction using 3 Å MS. [b]Assay yield of aldimine product by ^{1}H NMR, taken with reference to 1,1,2,2-tetrachloroethane as an internal standard. [c]Reaction with 20 mol% TFA added.

To demonstrate the utility of the photocatalytic α-trialkyl-ATA synthesis, we targeted the preparation of a selection of molecules relevant to the treatment of disease (Figure 7). Fingolimod (Gilenya, **9**) is an important multiple sclerosis treatment and the figurehead of a broad class of S1P receptor modulators bearing the α-trialkyl-ATA motif,[32] and has also been identified as a potential new lead for heart failure therapeutics.[2d] The new intermolecular alkene hydroaminoalkylation procedure enables disconnection of fingolimod back to the commercial starting materials benzhydrylamine (**1b**), ketone **2x** and 4-octylstyrene (**3r**). Treatment of these reagents with the standard photocatalytic reaction conditions for 48 h, followed by an acidic aqueous workup delivered fingolimod in 17% yield (Figure 7A). Although the yield of this transformation is modest, it is notable for its practical simplicity and amenability towards the synthesis of analogues of fingolimod which, through our new procedure, are directly accessible in a single synthetic step.

It was also recognized that the use of orthogonally functionalized (hetero)aromatic alkene acceptors could deliver N-primary α-trialkyl-ATAs primed for cyclization via C–N bond formation, enabling rapid access to a class of N-aryl α-trialkyl-spiroheterocyclic-ATAs, which are under-represented as scaffolds in pharmaceutical candidates, most likely due to a lack of tractable methods for their synthesis. In this regard, a range of heterocyclic ketones were successfully employed in the alkene hydroaminoalkylation reaction with benzhydrylamine and either 2-bromostyrene (**3s**) or 2-fluoro-3-vinylpyridine (**3t**) to give α-trialkyl-ATAs **10a-e** (Figure 7B). Cyclization of α-trialkyl-ATAs **10a-b** (derived from 2-bromostyrene) was accomplished using a palladium-mediated intramolecular Buchwald-Hartwig C–N bond formation, affording 1,2,3,4-tetrahydroquinolines (THQ's) **11a-b** displaying the α-trialkyl-ATA motif embedded within its framework. The generic THQ-pharmacophore is well established in a variety of contexts in medicinal chemistry, however, those displaying an α-trialkyl-ATA motif are scarce and so expedient access to new derivatives is desirable.[33]

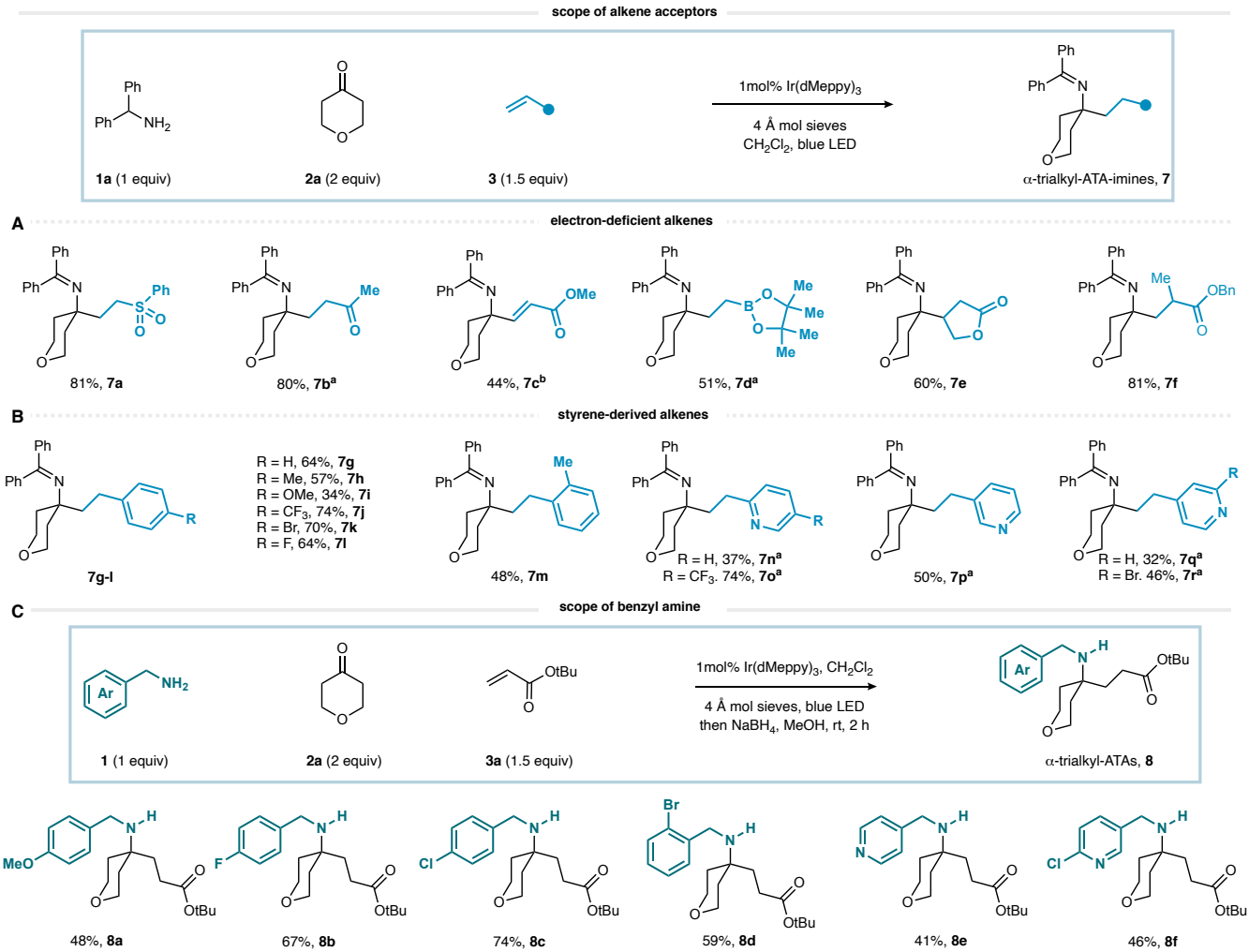


Figure 6. (A) Scope of reaction in electron deficient acceptors. Reactions for 18 h unless stated. **(B)** Scope of reaction with styrenes. (3 equivalents of alkene used, reactions for 48 h) **(C)** Scope of reaction in benzylamine component. [a]For optimal conversion the ketone and amine were stirred at 80 °C for 3 h before being subjected to the photocatalysis conditions. [b]Reaction for 24 h.

Similarly, cyclization of α-trialkyl-ATAs **10c-e** by exploiting C–N bond-forming S_NAr ring closure onto the pendant 2-fluoropyridine motif is able to generate a new heterospirocyclic framework; stirring amines **10c-e** at 120 °C in DMF in the presence of Hünig's base afforded 1,2,3,4-tetrahydronaphthyridines (THN's) **11c-e** in satisfactory yields. Although less thoroughly explored, the THN motif has also found application in medicinal chemistry, in particular as an arginine mimetic.[34] THN's **11c-e** are low molecular weight, polar-structures, with three-dimensionality imparted by the α-tertiary amine motif, and orthogonal amine functionalities available for fragment growing, placing them in highly attractive but unexplored lead-like chemical space.[35] Notably, the THN motif contains similar polar functionality to classical kinase hinge-binding small molecules, such as 7-deazapurines, while offering tunable substituents (via the α-trialkyl-ATA motif) which project towards the hydrophobic pocket of interest in these proteins.[36] In addition to the medicinal value of our products, Schiff bases have been utilized as ligands for many transition metals, with the resultant complexes having broad scoping applications due to their promising catalytic, biological and chemotherapeutic activities.[37] We suggest that the α-tertiary imine products generated by our transformation could serve as interesting scaffolds for future ligand design, with the redox neutral process enabling rapid access to a range of structurally diverse and sterically hindered imines challenging to access via classical methods.

To probe the likely pathway of this photocatalytic alkene hydroaminoalkylation protocol, a series of preliminary mechanistic experiments were carried out. The standard reaction was performed with ketone **2a**, alkene **3a** and α-deuterobenzhydrylamine (d_1-**1b**) as the amine component. The corresponding imine product d_1-**4a** was obtained with essentially quantitative deuterium incorporation at the position next to the ester functionality, strongly supporting the operation of a 1,5-HAT step (Figure 8A). To probe to the intermediacy of an α-amino radical, imine **13** was prepared via the condensation of 3-butenylamine **12** and ketone **2a** and submitted to the standard reaction conditions (Figure 8B); heterospirocycle **14** was formed in moderate yield, which presumably arises from intramolecular 5-*exo*-trig ring closure of an α-amino radical intermediate onto the pendant alkene, followed by a HAT process to the resulting primary exocyclic radical.[23] It was presumed that the hydrogen atom required for this final HAT step originates from either imine **13** or excess ketone **2a**. Therefore, we tested a reaction in the presence of 1,4-cyclohexadiene (1,4-CHD) as an exogenous HAT source, which showed a significant increase in the assay yield of **14**.

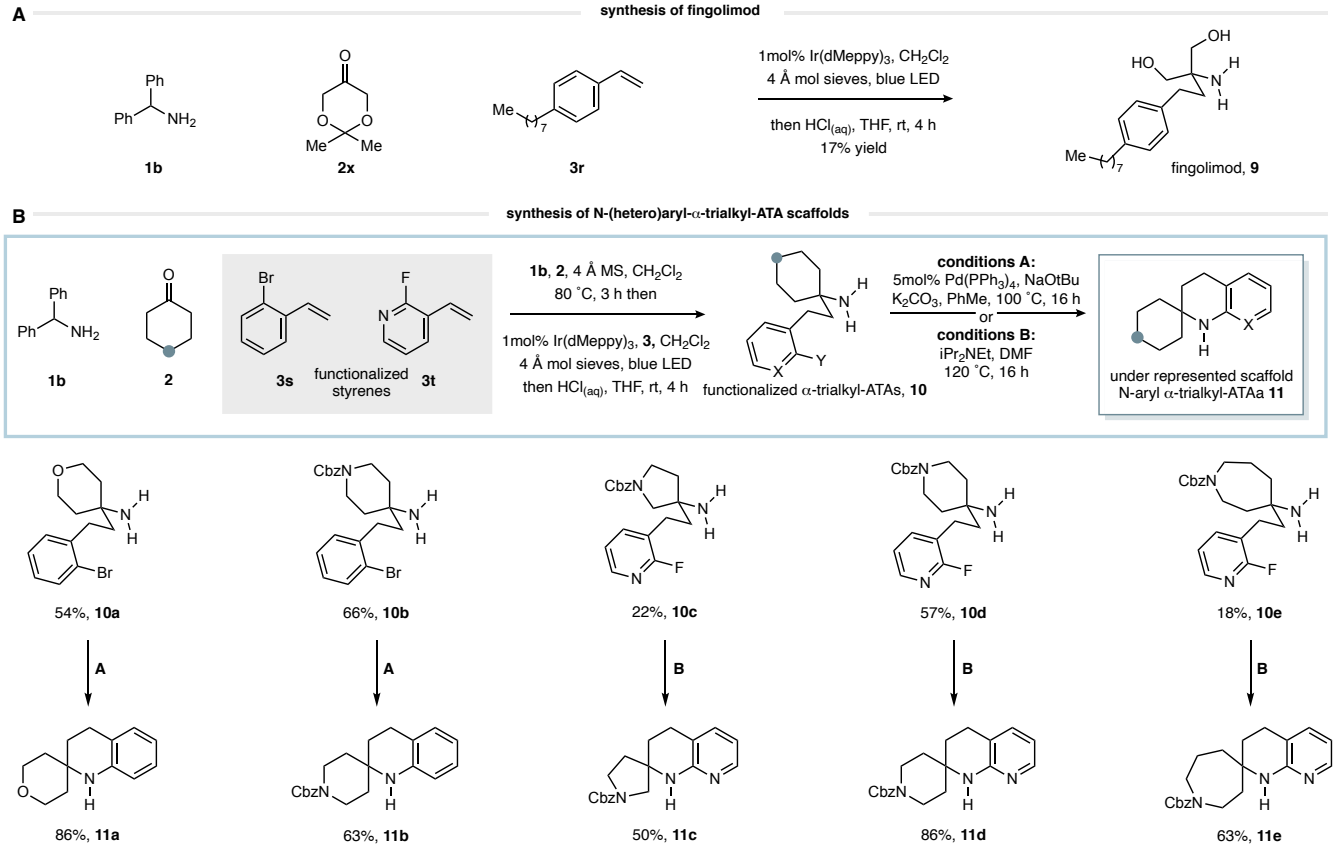
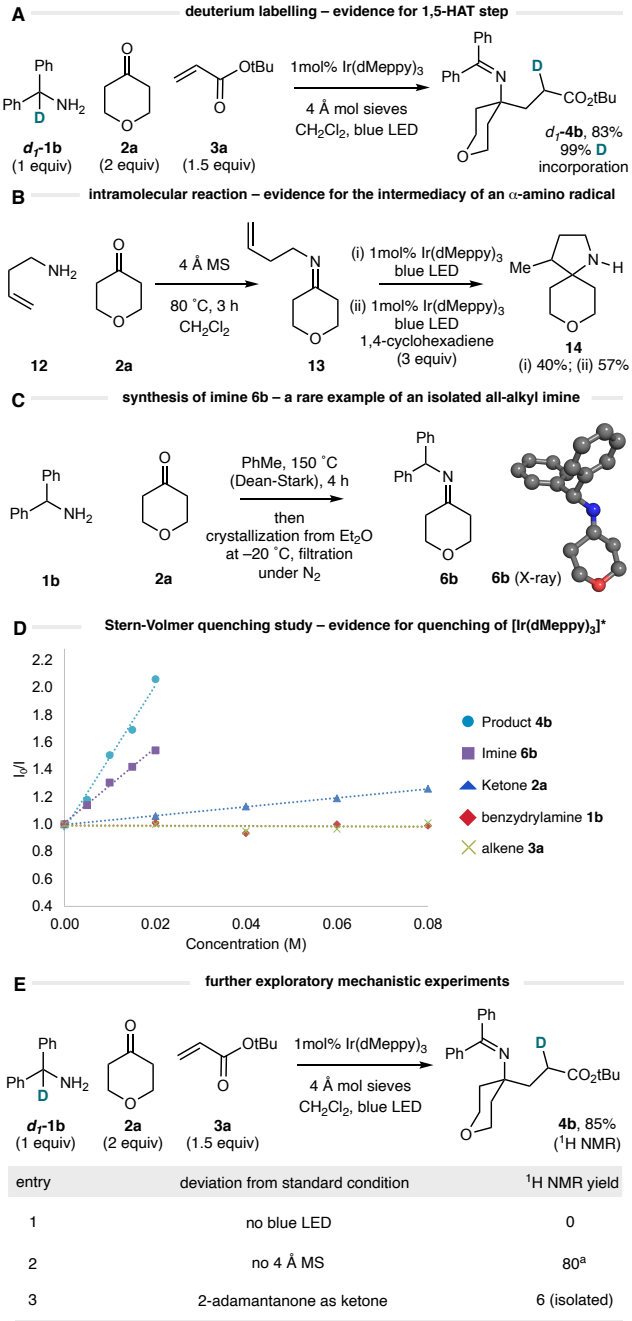


Figure 7. Applications of photocatalytic α-trialkyl-ATA synthesis. **(A)** One-step synthesis of fingolimod. **(B)** Synthesis of cyclic N-(hetero)aryl-α-trialkyl-ATA scaffolds, which are under-represented in medicinal chemistry.

Next, the role of the photocatalyst was investigated. Stern-Volmer quenching studies performed,[38] independently, on solutions of benzhydryl amine **1b**, ketone **2a**, alkene **3a**, 'starting' imine **6b** and 'product' imine **4b** in the presence of Ir(dMeppy)$_3$ revealed that imine **6b**, whose structure was confirmed by X-ray diffraction of a single crystal (Figure 8C), is an effective quencher of the excited state of Ir(dMeppy)$_3$ (Figure 8D).[39] While product imine **4b** is a more effective quencher, this process is presumably reversible and is evidently unproductive on account of the fact that no derivatives of **4b** were observed over the course of our studies. When considering that the reduction potentials of all-alkyl imines, such as **6b**, have been reported to be lower than –3.0 V vs. SCE in MeCN[21] its quenching of the excited state photocatalyst was surprising considering that the redox potential ($E_{1/2}$ [Ir(IV)/Ir(III*)]) of [Ir(dMeppy)$_3$]* is –1.86 V vs. SCE in CH_2Cl_2.[23] Our mechanistic hypothesis exploited a protonation event that would convert imine **6a** to the iminium **int-Ia** (Figure 4), which would have a substantially more accessible reduction potential (reduction potential for related iminium **int-Ib** computed to be –1.2 V).[20a,28] The results of the Stern-Volmer quenching study, however, raised the question of the source of this proton, given our optimization experiments had shown that the reaction performed more effectively in the absence of either strong or weak Brønsted acid additives (Table 1, entries 1-4). It was deemed possible that the 4 Å molecular sieves that were present in the reaction could act either as a Lewis acid or a source of protons resulting from their interaction with water. However, when the imine was isolated (by Dean-Stark condensation and without contact with 4 Å molecular sieves, followed by crystallization) and subjected to the reaction in the absence of 4 Å molecular sieves, the reaction still produced 80% of **4b** (Figure 8E, entry 2).

This led us to consider where else in the reaction mechanism a proton could be generated, even in catalytic or trace quantities. On closer examination of the ^{1}H NMR spectrum (in CD_2Cl_2) of starting imine 6b, we noticed that there was approximately 4% of the enamine tautomer present in the solution. Single-electron oxidation of enamines has frequently been reported in a variety of photocatalytic transformations;[40] moreover, enamines have been reported to have oxidation potentials as low as +0.32 V (vs SCE in MeCN),[41] which should be accessible to [Ir(dMeppy)$_3$]* (calculated $E_{1/2}$ [Ir(III*)/Ir(II)] = +0.33 V vs. SCE in MeCN[41]). Therefore, we deemed it possible that the observed low concentration of enamine 15 may be responsible for reductively quenching the excited state of the photocatalyst (Figure 9). As a result, enamine 15 would be converted into its corresponding radical cation (int-VIb), which will dramatically decrease the pK_a of the N–H bond.[43] If imine 6b is protonated by the enamine radical cation int-VIb, then the single-electron reduction would be feasible with either [Ir(dMeppy)$_3$]$^-$ (resulting from the reductive quenching step; calculated $E_{1/2}$ [Ir(III)/Ir(II)] = –1.96 V vs. SCE in MeCN[42]) or [Ir(dMeppy)$_3$]*.[28,44] Therefore, our current mechanistic hypothesis involves initiation by single-electron oxidation of the enamine 15 (by the excited state of the photocatalyst [Ir(dMeppy)$_3$]*), to its radical cation int-VIb, the now-acidic N–H bond of which permits protonation of imine 6b to form ketiminium int-Ib. Int-Ib can now be reduced by [Ir(dMeppy)$_3$]$^-$ (formed from enamine oxidation) to the α-amino radical int-IIb and also reforms the ground state Ir(III) photocatalyst. Giese addition between the alkene 3a and α-amino radical int-IIb and subsequent 1,5-HAT generates the diphenyl-substituted α-amino-radical int-IVb.



entry	deviation from standard condition	^{1}H NMR yield
1	no blue LED	0
2	no 4 Å MS	80[a]
3	2-adamantanone as ketone	6 (isolated)

Figure 8. Mechanistic investigations. [a] Reaction with isolated imine **6b** (see **C**)

This radical can then be oxidized by $[Ir(dMeppy)_3]^*$, not just closing the photocatalytic cycle by regenerating the reducing species $[Ir(dMeppy)_3]^-$ but also forming product-like ketiminium ion **int-Vb**, which undergoes proton transfer with the starting imine **6b** to render the process catalytic in proton and complete the redox-relay transformation. Unfortunately, test reactions to probe this pathway were inconclusive. For example, while a reaction using 2-adamantanone–chosen as it cannot form its corresponding enamine–worked, it only generated a small amount of α-trialkyl-ATA product (Figure 8E, entry 3). At this point, we cannot rule out other pathways and a discussion of alternative mechanistic possibilities, such as energy transfer, are provided in the supporting information. Further studies into this complex mechanism are ongoing and will reported in due course.

CONCLUSION

In summary we have designed a flexible, multicomponent strategy for the synthesis of α-trialkyl-α-tertiary amines from readily available precursors. This protocol allows for the rapid preparation of a wide variety of functionally and structurally diverse α-trialkyl-α-tertiary amines, thus offering immediate access to a motif that is otherwise challenging to assemble in such a modular fashion.[7] In addition to an extensive substrate scope in each component, the utility of the process has been further demonstrated through the straightforward synthesis of a range of N-aryl spiroheterocyclic α-trialkyl-α-tertiary amine scaffolds that are underexplored and offers access to new pharmaceutically-relevant chemical space. The mechanism of the process involves an imine redox-relay pathway that ensures a redox neutral transformation. Key to the success of the process, we believe, is an initiation step involving single-electron oxidation of an enamine intermediate to a (NH)-enamine radical cation, through which imine protonation and hence activation takes place and enables reduction of the resulting ketiminium ion to the α-amino radical. Overall, we believe that the flexibility and simplicity of the newly developed protocol will make this procedure of interest to chemists in both industrial and academic environments, and in particular to practitioners of medical chemistry where this transformation provides access to a class of underexplored amine scaffolds.[45]

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at: All experimental procedures, extended mechanistic discussion and compound characterization (including 1H & 13C NMR spectra, IR, HRMS and X-ray data) are available in the document (PDF)

AUTHOR INFORMATION

Corresponding Author

* Professor Matthew Gaunt; mjg32@cam.ac.uk

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. ‡These authors contributed equally and are listed alphabetically.

Funding Sources

Funding sources are the following: Studentship to (J.H.B. and G.R.H) through the AstraZeneca–Cambridge PhD Programme; EPSRC Centre for Doctoral Training – SynTech EPS024220/1 for studentship (M.A.S); Royal Society for Wolfson Merit Award (M.J.G.).

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

We are grateful to Dr. Charlene Fallon (AstraZeneca), Dr. Claudia De Fusco (AstraZeneca) and Dr Jennifer Nelson (AstraZeneca) for useful discussion. We thank Dr. Andrew Bond for X-ray diffraction experiments on compounds **4b**, **6b**, **11a, S1**.

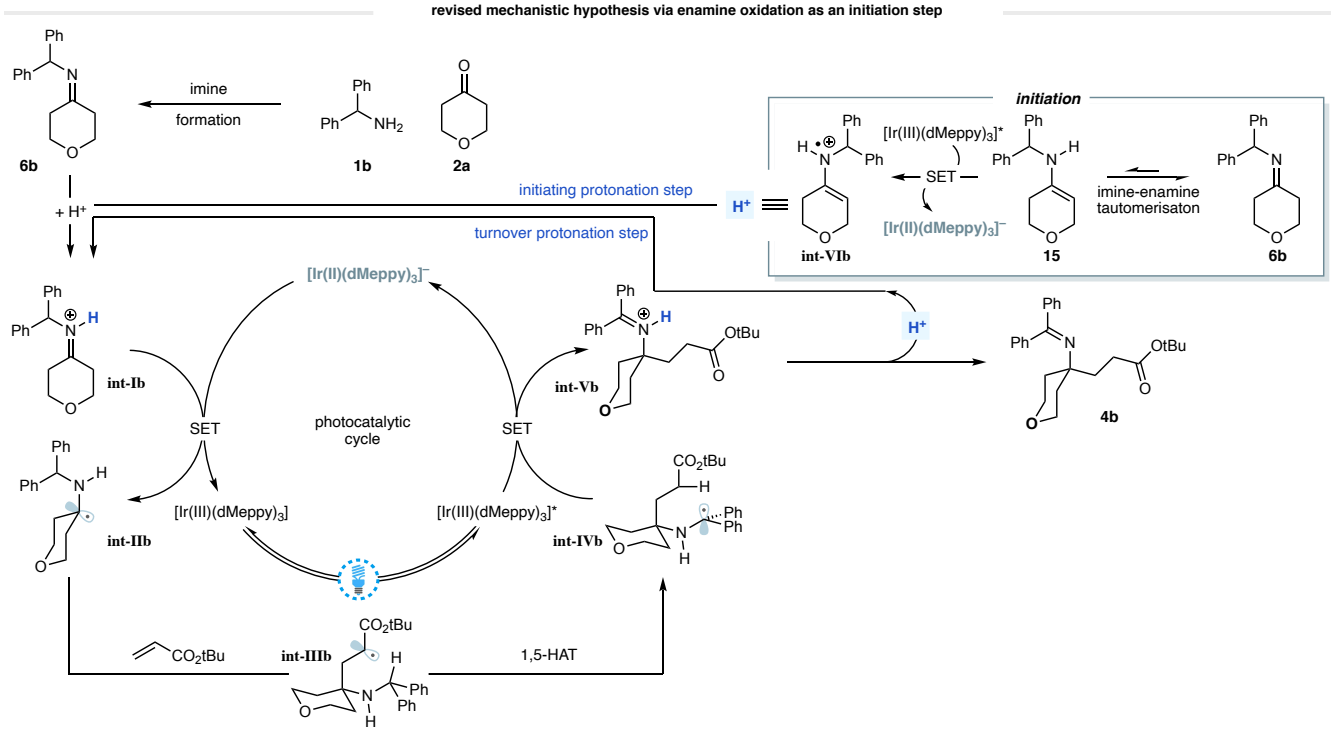


Figure 9. Revised mechanistic hypothesis

REFERENCES

(1) (a) For excellent reviews pertinent to ATA synthesis see: Clayden, J.; Donnard, M.; Lefranc, J.; Tetlow, D. J. Quaternary Centres Bearing Nitrogen (α-Tertiary Amines) as Products of Molecular Rearrangements. *Chem. Commun.* **2011**, *47*, 4624. (b) Hager, A.; Vrielink, N.; Hager, D.; Lefranc, J.; Trauner, D. Synthetic Approaches towards Alkaloids Bearing α-Tertiary Amines. *Nat. Prod. Rep.* **2016**, *33*, 491–522.

(2) (a) Subei, A. M.; Cohen, J. A. Sphingosine 1-Phosphate Receptor Modulators in Multiple Sclerosis. *CNS Drugs,* **2015**, *29*, 565. (b) Xiao, Z.; Yang, M. G.; Dhar, T. G. M.; Xiao, H.-Y.; Gilmore, J. L.; Marcoux, D.; McIntyre, K. W.; Taylor, T. L.; Shi, H.; Levesque, P. C.; et al. Aryl Ether-Derived Sphingosine-1-Phosphate Receptor ($S1P_1$) Modulators: Optimization of the PK, PD, and Safety Profiles. *ACS Med. Chem. Lett.* **2020**, *11*, 1766–1772. (c) Fujita, T.; Inoue, K.; Yamamoto, S.; Ikumoto, T.; Sasaki, S.; Toyama, R.; Yoneta, M.; Chiba, K.; Hoshino, Y.; Okumoto, T. Fungal Metabolites. Part 12. Potent Immunosuppressant, 14-Deoxomyriocin, (2S,3R,4R)-(E)-2-Amino-3,4-dihydroxy-2-hydroxymethyleicos-6-enoic acid and Structure-Activity Relationships of Myriocin Derivatives. *J. Antibiot.* **1994**, 47, 216-224. (d) Parijat, P.; Kondacs, L.; Alexandrovich, A.; Gautel, M.; Cobb, A. J. A.; Kampourakis, T. High Throughput Screen Identifies Small Molecule Effectors That Modulate Thin Filament Activation in Cardiac Muscle *ACS Chem. Biol.* **2021**, *16*, 1, 225–235. (e) Rishton, G.; Catalano, S. M.; Look, G. C. Isoindoline Compositions and Methods for Treating Neurodegenerative Disease, WO 2015/116923 A1, **2015**. (f) Pilot Clinical Study of CT1812 in Mild to Moderate Alzheimer's Disease Using EEG, ClinicalTrials.gov identifier NCT04735536, accessed 27 February **2021**.

(3) (a) Vuckovic, S.; Prostran, M.; Ivanovic, M.; Dosen-Micovic, L.; Todorovic, Z.; Nesic, Z.; Stojanovic, R.; Divac, N.; Mikovic, Z. Fentanyl Analogs: Structure-Activity-Relationship Study. *Curr. Med. Chem.* **2009**, *16*, 2468–2474. (b) Tyler, M. W.; Yourish, H. B.; Ionescu, D. F.; Haggarty, S. J. Classics in Chemical Neuroscience: Ketamine. *ACS Chem. Neurosci.* **2017**, *8*, 1122. (c) Yang, J.; Wang, N.; Yang, C.; Shi, J.; Yu, H.; Hashimoto, K. Serum Interleukin-6 Is a Predictive Biomarker for Ketamine's Antidepressant Effect in Treatment-Resistant Patients With Major Depression. *Biol. Psychiatry* **2015**, *77*, e19. (d) World Health organization List of Essential Medicines, https://list.essentialmeds.org/?query=ketamine, accessed 27 February **2021**.

(4) (a) Yap, T. A.; Walton, M. I.; Hunter, L.-J. K.; Valenti, M.; Brandon, A. de H.; Eve, P. D.; Ruddle, R.; Heaton, S. P.; Henley, A.; Pickard, L.; Vijayaraghavan, G.; Caldwell, J. J.; Thompson, N. T.; Aherne, W.; Raynaud, F. I.; Eccles, S. A.; Workman, P.; Collins, I.; Garrett, M. D. Preclinical Pharmacology, Antitumor Activity, and Development of Pharmacodynamic Markers for the Novel, Potent AKT Inhibitor CCT128930. *Mol. Cancer Ther.* **2011**, *10*, 360–371. (b) Cheng, H.; Orr, S. T. M.; Bailey, S.; Brooun, A.; Chen, P.; Deal, J. G.; Deng, Y. L.; Edwards, M. P.; Gallego, G. M.; Grodsky, N.; Huang, B.; Jalaie, M.; Kaiser, S.; Kania, R. S.; Kephart, S. E.; Lafontaine, J.; Ornelas, M. A.; Pairish, M.; Planken, S.; Shen, H.; Sutton, S.; Zehnder, L.; Almaden, C. D.; Bagrodia, S.; Falk, M. D.; Gukasyan, H. J.; Ho, C.; Kang, X.; Kosa, R. E.; Liu, L.; Spilker, M. E.; Timofeevski, S.; Visswanathan, R.; Wang, Z.; Meng, F.; Ren, S.; Shao, L.; Xu, F.; Kath, J. C. Structure-Based Drug Design and Synthesis of PI3Kα-Selective Inhibitor (PF-06843195). *J. Med. Chem.* **2021**, *64*, 644–661.

(5) Morgenthaler, M.; Schweizer, E.; Hoffmann-Röder, A.; Benini, F.; Martin, R. E.; Jaeschke, G.; Wagner, B.; Fischer, H.; Bendels, S.; Zimmerli, D.; Schneider, J.; Diederich, F.; Kansy, M.; Müller, K. Predicting and Tuning Physicochemical Properties in Lead Optimization: Amine Basicities. *Chem. Med. Chem.* **2007**, *2*, 1100–1115.

(6) (a) Lovering, F.; Bikker, J.; Humblet, C. Escape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success. *J. Med. Chem*. **2009**, *52*, 6752–6756. (b) Ritchie, T. J.; Macdonald, S. J. F. The Impact of Aromatic Ring Count on Compound Developability – Are Too Many Aromatic Rings a Liability in Drug Design? *Drug Discov. Today* **2009**, *14*, 1011–1020. (c) Ritchie, T. J.; MacDonald, S. J. F.; Young, R. J.; Pickett, S. D. The Impact of Aromatic Ring Count on Compound Developability: Further Insights by Examining Carbo- and Hetero-Aromatic and -Aliphatic Ring Types. *Drug Discov. Today* **2011**, *16*, 164–171. (d) Lovering, F. Escape from Flatland 2:

Complexity and Promiscuity. *Med. Chem. Comm.* **2013**, *4*, 515.

(7) Campos, K. R.; Coleman, P. J.; Alvarez, J. C.; Dreher, S. D.; Garbaccio, R. M.; Terrett, N. K.; Tillyer, R. D.; Truppo, M. D.; Parmee, E. R. The Importance of Synthetic Chemistry in the Pharmaceutical Industry. *Science,* **2019**, 363, eaat0805.

(8) (a) Sasaki, T.; Nakanishi, A.; Ohno, M. Synthesis of Adamantane Derivatives. 56. Reaction of 1-Adamantyl Chloride with Trimethylsilyl Pseudohalide. *J. Org. Chem.* **1981**, *46*, 5445–5447. (b) Masutani, K.; Minowa, T.; Hagiwara, Y.; Mukaiyama, T. Cyanation of Alcohols with Diethyl Cyanophosphonate and 2,6-Dimethyl-1,4-Benzoquinone by a New Type of Oxidation–Reduction Condensation. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 1106–1117. (c) Mascal, M.; Hafezi, N.; Toney, M. D. 1,4,7-Trimethyloxatriquinane: S_N2 Reaction at Tertiary Carbon. *J. Am. Chem. Soc.* **2010**, *132*, 10662–10664. (d) Michaudel, Q.; Thevenet, D.; Baran, P. S. Intermolecular Ritter-Type C–H Amination of Unactivated sp^3 Carbons. *J. Am. Chem. Soc*. **2012**, *134*, 2547–2550. (e) Pronin, S. V.; Reiher, C. A.; Shenvi, R. A. Stereoinversion of Tertiary Alcohols to Tertiary-Alkyl Isonitriles and Amines. *Nature,* **2013**, *501*, 195–199. (f) Fei, J.; Wang, Z.; Cai, Z.; Sun, H.; Cheng, X. Synthesis of α-Tertiary Amine Derivatives by Intermolecular Hydroamination of Unfunctionalized Alkenes with Sulfamates under Trifluoromethanesulfonic Acid Catalysis. *Adv. Synth. Catal.* **2015**, *357*, 4063–4068. (g) Kiyokawa, K.; Watanabe, T.; Fra, L.; Kojima, T.; Minakata, S. Hypervalent Iodine(III)-Mediated Decarboxylative Ritter-Type Amination Leading to the Production of α-Tertiary Amine Derivatives. *J. Org. Chem.* **2017**, *82*, 11711–11720.

(9) (a) Gui, J.; Pan, C.; Jin, Y.; Qin, T.; Lo, J. C.; Lee, B. J.; Spergel, S. H.; Mertzman, M. E.; Pitts, W. J.; Cruz, T. E. La; Schmidt, M. A.; Darvatkar, N.; Natarajan, S. R.; Baran, P. S. Practical Olefin Hydroamination with Nitroarenes. *Science,* **2015**, *348*, 886–891. (b) Zheng, J.; Qi, J.; Cui, S. Fe-Catalyzed Olefin Hydroamination with Diazo Compounds for Hydrazone Synthesis. *Org. Lett.* **2016**, *18*, 128–131. (c) Zhu, K.; Shaver, M. P.; Thomas, S. P. Chemoselective Nitro Reduction and Hydroamination Using a Single Iron Catalyst. *Chem. Sci.* **2016**, *7*, 3031–3035. (d) Bahamonde, A.; Al Rifaie, B.; Martín-Heras, V.; Allen, J. R.; Sigman, M. S. Enantioselective Markovnikov Addition of Carbamates to Allylic Alcohols for the Construction of α-Secondary and α-Tertiary Amines. *J. Am. Chem. Soc.* **2019**, *141*, 8708–8711. (e) Musacchio, A. J.; Lainhart, B. C.; Zhang, X.; Naguib, S. G.; Sherwood, T. C.; Knowles, R. R. Catalytic Intermolecular Hydroaminations of Unactivated Olefins with Secondary Alkyl Amines. *Science,* **2017**, *355* (6326), 727–730.

(10) For excellent reviews and key publications see: (a) Díaz-Requejo, M. M.; Pérez, P. J. Coinage Metal Catalyzed C–H Bond Functionalization of Hydrocarbons. *Chem. Rev.* **2008**, *108*, 3379–3394. (b) Liang, C.; Collet, F.; Robert-Peillard, F.; Müller, P.; Dodd, R. H.; Dauban, P. Toward a Synthetically Useful Stereoselective C–H Amination of Hydrocarbons. *J. Am. Chem. Soc.* **2008**, *130*, 343–350. (c) Collet, F.; Dodd, R. H.; Dauban, P. Catalytic C–H Amination: Recent Progress and Future Directions. *Chem. Commun.* **2009**, *34*, 5061-5074. (d) Collet, F.; Lescot, C.; Liang, C.; Dauban, P. Studies in Catalytic C–H Amination Involving Nitrene C–H Insertion. *Dalt. Trans.* **2010**, *39*, 10401–10413. (e) Barman, D. N.; Liu, P.; Houk, K. N.; Nicholas, K. M. On the Mechanism of Ligand-Assisted, Copper-Catalyzed Benzylic Amination by Chloramine-T. *Organometallics,* **2010**, *29*, 3404–3412. (f) Du Bois, J. Rhodium-Catalyzed C–H Amination. An Enabling Method for Chemical Synthesis. *Org. Process Res. Dev.* **2011**, *15*, 758–762. (g) Ochiai, M.; Miyamoto, K.; Kaneaki, T.; Hayashi, S.; Nakanishi, W. Highly Regioselective Amination of Unactivated Alkanes by Hypervalent Sulfonylimino-λ^3-Bromane. *Science,* **2011**, *332*, 448–451. (h) Roizen, J. L.; Harvey, M. E.; Du Bois, J. Metal-Catalyzed Nitrogen-Atom Transfer Methods for the Oxidation of Aliphatic C–H Bonds. *Acc. Chem. Res.* **2012**, *45*, 911–922. (i) Lescot, C.; Darses, B.; Collet, F.; Retailleau, P.; Dauban, P. Intermolecular C–H Amination of Complex Molecules: Insights into the Factors Governing the Selectivity. *J. Org. Chem*. **2012**, *77*, 7232–7240. (j) Hennessy, E. T.; Betley, T. A. Complex N-Heterocycle Synthesis via Iron-Catalyzed, Direct C–H Bond Amination. *Science,* **2013**, *340*, 591–595. (k) Betz, K. N.; Chiappini, N. D.; Du Bois, J. Intermolecular sp^3-C–H Amination for the Synthesis of Saturated Azacycles. *Org. Lett.* **2020**, *22*, 1687–1691. (l) Chiappini, N. D.; Mack, J. B. C.; Du Bois, J. Intermolecular C(sp^3)–H Amination of Complex Molecules. *Angew. Chem. Int. Ed*. **2018**, *57*, 4956–4959.

(11) For reviews and key references see: (a) Greck, C.; Drouillat, B.; Thomassigny, C. Asymmetric Electrophilic α-Amination of Carbonyl Groups. *European J. Org. Chem.*, **2004**, *2004*, 1377–1385. (b) Janey, J. M. Recent Advances in Catalytic, Enantioselective α Aminations and α Oxygenations of Carbonyl Compounds. *Angew. Chem. Int. Ed*. **2005**, *44*, 4292–4300. (c) Smith, A. M. R.; Hii, K. K. (Mimi). Transition Metal Catalyzed Enantioselective α-Heterofunctionalization of Carbonyl Compounds. *Chem. Rev.* **2011**, *11*, 1637–1656. (d) Zhou, F.; Liao, F.-M.; Yu, J.-S.; Zhou, J. Catalytic Asymmetric Electrophilic Amination Reactions To Form Nitrogen-Bearing Tetrasubstituted Carbon Stereocenters. *Synthesis,* **2014**, *46*, 2983–3003. (e) Ohmatsu, K.; Ando, Y.; Nakashima, T.; Ooi, T. A Modular Strategy for the Direct Catalytic Asymmetric α-Amination of Carbonyl Compounds. *Chem,* **2016**, *1*, 802–810. (f) Trost, B. M.; Tracy, J. S.; Lin, E. Y. Asymmetric Electrophilic Amination and Hydrazination of Acyclic α-Branched Ketones for the Formation of α-Tertiary Amines and Hydrazines. *ACS Catal.* **2019**, *9*, 11082–11087.

(12) (a) Ihara, M.; Takahashi, M.; Niitsuma, H.; Taniguchi, N.; Yasui, K.; Fukumoto, K. Enantioselective Construction of a Quaternary Asymmetric Carbon Center: A Versatile Synthesis of α-Alkyl, α-Amino Acids. *J. Org. Chem.* **1989**, *54*, 5413–5415. (b) Iosub, V.; Haberl, A. R.; Leung, J.; Tang, M.; Vembaiyan, K.; Parvez, M.; Back, T. G. Enantioselective Synthesis of α-Quaternary Amino Acid Derivatives by Sequential Enzymatic Desymmetrization and Curtius Rearrangement of α,α-Disubstituted Malonate Diesters. *J. Org. Chem.* **2010**, *75*, 1612–1619. (c) Ha, M. W.; Lee, M.; Choi, S.; Kim, S.; Hong, S.; Park, Y.; Kim, M.; Kim, T.-S.; Lee, J.; Lee, J. K.; Park, H. Construction of Chiral α-Amino Quaternary Stereogenic Centers via Phase-Transfer Catalyzed Enantioselective α-Alkylation of α-Amidomalonates. *J. Org. Chem.* **2015**, *80*, 3270–3279. (d) Gokada, M. R.; Hunter, R.; Andrijevic, A.; Petersen, W. F.; Samanta, S.; Venter, G.; Rees-Jones, S. Quaternized α, α′-Amino Acids via Curtius Rearrangement of Substituted Malonate–Imidazolidinones. *J. Org. Chem.* **2017**, *82*, 10650–10658. (e) Szcześniak, P.; Pieczykolan, M.; Stecko, S. The Synthesis of α,α-Disubstituted α-Amino Acids via Ichikawa Rearrangement. *J. Org. Chem.* **2016**, *81*, 1057–1074. (f) Leonard, D. J.; Ward, J. W.; Clayden, J. Asymmetric α-Arylation of Amino Acids. *Nature,* **2018**, *562*, 105–109. (g) Abas, H.; Mas-Roselló, J.; Amer, M. M.; Durand, D. J.; Groleau, R. R.; Fey, N.; Clayden, J. Asymmetric and Geometry-Selective A-Alkenylation of α-Amino Acids. *Angew. Chem. Int. Ed.* **2019**, *58*, 2418–2422.

(13) For reviews and key references concerning the alkylation of enolate equivalents of amino acids see: (a) Schöllkopf, U. Enantioselective Synthesis of Non-Proteinogenic Amino Acids via Metallated Bis-Lactim Ethers of 2,5-Diketopiperazines. *Tetrahedron,* **1983**, *39*, 2085–2091. (b) Seebach, D.; Fadel, A. N,O-Acetals from Pivalaldehyde and Amino Acids for the α -Alkylation with Self-Reproduction of the Center of Chirality. Enolates of 3-Benzoyl-2-(Tert-Butyl)-1,3-Oxazolidin-5-One. *Helv. Chim. Acta.* **1985**, *68*, 1243–1250. (c) Maruoka, K.; Ooi, T. Enantioselective Amino Acid Synthesis by Chiral Phase-Transfer Catalysis. *Chem. Rev.* **2003**, *103*, 3013–3028. (d) Lygo, B.; Andrews, B. I. Asymmetric Phase-Transfer Catalysis Utilizing Chiral Quaternary Ammonium Salts: Asymmetric Alkylation of Glycine Imines. *Acc. Chem. Res.* **2004**, *37*, 518–525. (e) Ooi, T.; Maruoka, K. Recent Advances in Asymmetric Phase-Transfer Catalysis. *Angew. Chem. Int. Ed.* **2007**, *46*, 4222–4266. (f) Hashimoto, T.; Maruoka, K. Recent Development and Application of Chiral Phase-Transfer Catalysts. *Chem. Rev.* **2007**, *107*, 5656–5682. (g) Nájera, C.; Sansano, J. M. Catalytic Asymmetric Synthesis of α-Amino Acids. *Chem. Rev.* **2007**, *107*, 4584–4671. (h) Shirakawa, S.;

Maruoka, K. Recent Developments in Asymmetric Phase-Transfer Reactions. *Angew. Chem. Int. Ed.* **2013**, *52*, 4312–4348. (i) O'Donnell, M. J. Benzophenone Schiff Bases of Glycine Derivatives: Versatile Starting Materials for the Synthesis of Amino Acids and Their Derivatives. *Tetrahedron* **2019**, *75*, 3667–3696

(14) (a) Anderson, J. C.; Skerratt, S. Synthesis of α,α-disubstituted unnatural amino acid derivatives using the aza-[2,3]-Wittig sigmatropic rearrangement *J. Chem. Soc. Perkin Trans.* **2002**, *1*, 2871–2879. (b) Li, W. D. Z.; Wang, Y. Q. A Novel and Efficient Total Synthesis of Cephalotaxine, *Org. Lett.* **2003**, *5*, 2931–2934. (c) Soheili, A.; Tambar, U. K. Synthesis of (±)-Amathaspiramide F and Discovery of an Unusual Stereocontrolling Element for the [2,3]-Stevens Rearrangement, *Org. Lett.* **2013**, *15*, 5138–5141. (d) Li, F.; He, F.; Koenigs, R. M.; Catalyst-Free [2,3]-Sigmatropic Rearrangement Reactions of Photochemically Generated Ammonium Ylides, *Synthesis* **2019**, *51*, 4348–4358.

(15) For excellent reviews and key publications pertinent to the addition organometallics to imines and ketimines see: (a) Ciganek, E. Tertiary Carbinamines by Addition of Organocerium Reagents to Nitriles and Ketimines. *J. Org. Chem.* **1992**, *57*, 4521–4527. (b) Wang, D. K.; Dai, L. X.; Hou, X. L.; Zhang, Y. Mg and Zn Mediated Allylation of Imines with Allyl Bromide. *Tetrahedron Lett.* **1996**, *37*, 4187–4188. (c) Bloch, R. Additions of Organometallic Reagents to C=N Bonds: Reactivity and Selectivity. *Chem. Rev.* **1998**, *98*, 1407–1438. (d) Cogan, D. A.; Ellman, J. A. Asymmetric Synthesis of α,α-Dibranched Amines by the Trimethylaluminum-Mediated 1,2-Addition of Organolithiums to Tert -Butanesulfinyl Ketimines. *J. Am. Chem. Soc.* **1999**, *121*, 268–269. (e) McMahon, J. P.; Ellman, J. A. Highly Stereoselective Addition of Organometallic Reagents to N-Tert-Butanesulfinyl Imines Derived from 3- and 4-Substituted Cyclohexanones. *Org. Lett.* **2004**, *6*, 1645–1647. (f) Yamada, K.; Tomioka, K. Copper-Catalyzed Asymmetric Alkylation of Imines with Dialkylzinc and Related Reactions. *Chem. Rev.* **2008**, *108*, 2874–2886. (g) Robak, M. T.; Herbage, M. A.; Ellman, J. A. Synthesis and Applications of Tert –Butanesulfinamide. *Chem. Rev.* **2010**, *110*, 3600–3740. (h) Vasu, D.; Fuentes de Arriba, A. L.; Leitch, J. A.; De Gombert, A.; Dixon, D. J. Primary α-Tertiary Amine Synthesis via α-C-H Functionalization. *Chem. Sci.* **2019**, *10*, 3401–3407. (i) Jackl, M. K.; Schuhmacher, A.; Shiro, T.; Bode, J. W. Synthesis of N,N-Alkylated α-Tertiary Amines by Coupling of α-Aminoalkyltrifluoroborates and Grignard Reagents. *Org. Lett.* **2018**, *20*, 4044–4047. For examples of radical-based strategies, see: (j) Siau, W.-Y.; Bode, J. W. One-step synthesis of saturated spiorocyclic N-heterocycles with SNAP reagents and ketones. *J. Am. Chem. Soc.* **2014**, *136*, 17726–17729. (k) Hsieh, S.-Y.; Bode, J. W. Siliconamine reagents for the photocatalytic synthesis of piperazines from aldehydes and ketones. *Org. Lett.* **2016**, *18*, 2098–2101. (l) Saito, F.; Trapp, N.; Bode, J. W. Iterative assembly of polycyclic saturated heterocycles from monomeric building blocks. *J. Am. Chem. Soc.* **2019**, *141*, 5544–5554.

(16) (a) Stork, G.; Dowd, S. R.; A New Method for the Alkylation of Ketones and Aldehydes: The C-Alkylation of the Magnesium Salts of N-Substituted Imines *J. Am. Chem. Soc.* **1963**, 85, 2178–2180. (b) Colgan, D. A.; Liu, Guangcheng; Ellman, J. A. Asymmetric Synthesis of Chiral Amines by Highly Diastereoselective 1, 2-Additions of Organometallic Reagents to N-Tert-Butanesulfinyl Imines. *Tetrahedron*, **1999**, *55*, 8883–8904.

(17) (a) Trowbridge, A.; Walton, S. M.; Gaunt, M. J. New Strategies for the Transition-Metal Catalyzed Synthesis of Aliphatic Amines. *Chem. Rev.* **2020**, *120*, 2613–2692. (b) Leitch, J. A.; Rossolini, T.; Rogova, T.; Andrew, J.; Maitland, P.; Dixon, D. J. α-Amino Radicals via Photocatalytic Single-Electron Reduction of Imine Derivatives. *ACS Catal.* **2020**, *10*, 2009–2025.

(18) (a) Ye, J.; Kalvet, I.; Schoenebeck, F.; Rovis, T. Direct α-Alkylation of Primary Aliphatic Amines Enabled by CO_2 and Electrostatics. *Nat. Chem.* **2018**, *10*, 1037–1041. (b) Ashley, M. A.; Yamauchi, C.; Chu, J. C. K.; Otsuka, S.; Yorimitsu, H.; Rovis, T. Photoredox-Catalyzed Site-Selective α-C(Sp^3)–H Alkylation of Primary Amine Derivatives. *Angew. Chem. Int. Ed.* **2019**, 58 , 4002–4006.

(19) Ryder, A. S. H.; Cunningham, W. B.; Ballantyne, G.; Mules, T.; Kinsella, A. G.; Turner-Dore, J.; Alder, C. M.; Edwards, L. J.; McKay, B. S. J.; Grayson, M. N.; Cresswell, A. J. Photocatalytic α-Tertiary Amine Synthesis via C–H Alkylation of Unmasked Primary Amines. *Angew. Chem. Int. Ed.* **2020**, *59*, 14986–14991.

(20) (a) Rong, J.; Seeberger, P. H.; Gilmore, K. Chemoselective Photoredox Synthesis of Unprotected Primary Amines Using Ammonia. *Org. Lett*. **2018**, *20*, 4081–4085. (b) Nicastri, M. C.; Lehnherr, D.; Lam, Y.; DiRocco, D. A.; Rovis, T. Synthesis of Sterically Hindered Primary Amines by Concurrent Tandem Photoredox Catalysis. *J. Am. Chem. Soc.* **2020**, *142*, 987–998.

(21) Root, D. K.; Smith, W. H. Electrochemical Behaviour of Selected Imine Derivatives, Reductive Carboxylation, α-Amino Acid Synthesis. *J. Electrochem. Soc.* **1982**, *129*, 1231.

(22) Trowbridge, A.; Reich, D.; Gaunt, M. J. Multicomponent Synthesis of Tertiary Alkylamines by Photocatalytic Olefin-Hydroaminoalkylation. *Nature,* **2018**, *561*, 522–527.

(23) Flodén, N. J.; Trowbridge, A.; Willcox, D.; Walton, S. M.; Kim, Y.; Gaunt, M. J. Streamlined Synthesis of C(sp^3)-Rich N-Heterospirocycles Enabled by Visible-Light-Mediated Photocatalysis. *J. Am. Chem. Soc.* **2019**, *141*, 8426–8430.

(24) Reich, D.; Trowbridge, A.; Gaunt, M. J. Rapid Syntheses of (−)-FR901483 and (+)-TAN1251C Enabled by Complexity-Generating Photocatalytic Olefin Hydroaminoalkylation. *Angew. Chem. Int. Ed.* **2020**, *59*, 2256–2261.

(25) Beckwith, A. L. J.; Chai, C. L. L. Diastereoselective Radical Addition to Derivatives of Dehydroalanine and of Dehydrolactic Acid. *J. Chem. Soc. Chem. Commun*. **1990**, *11*, 1087–1088.

(26) Atkins, P.; De Paula, J. Atkins' Physical Chemistry, 9th ed.; Oxford University Press, 2010; p 928.

(27) Jung, S.; Kang, Y.; Kim, H. S.; Kim, Y. H.; Lee, C. L.; Kim, J. J.; Lee S. K.; Kwon, S. K.; Effect of Substitution of Methyl Groups on the Luminescence Performance of Ir^{III} Complexes: Preparation, Structures, Electrochemistry, Photophysical Properties and Their Applications in Organic Light-Emitting Diodes (OLEDs) *Eur. J. Inorg. Chem.*, **2004**, *2004*, 3415–3423.

(28) Reduction potential of iminium ion **int-Ib** calculated at (U)B3LYP/6-31G(d,p) in MeCN (CPCM).

(29) Kanegusuku, A. L. G.; Roizen, J. L. Recent Advances in Photoredox-Mediated Radical Conjugate Addition Reactions: An Expanding Toolkit for the Giese Reaction. *Angew. Chem. Int. Ed.* **2021**. DOI: 10.1002/anie.202016666.

(30) Fyfe, J. W. B.; Watson, A. J. B. Recent Developments in Organoboron Chemistry: Old Dogs, New Tricks. *Chem*. **2017**, *3*, 31–55.

(31) Lee, K. N.; Lei, Z.; Ngai, M. Y. β-Selective Reductive Coupling of Alkenylpyridines with Aldehydes and Imines via Synergistic Lewis Acid/Photoredox Catalysis. *J. Am. Chem. Soc*. **2017**, *139*, 5003–5006.

(32) Sanford, M. Fingolimod: A Review of Its Use in Relapsing-Remitting Multiple Sclerosis, *Drugs*, **2014**, *74*, 1411–1433.

(33) (a) DeMont, E. H.; Gosmini, R. L. Tetrahydroquinolines Derivatives as Bromodomain Inhibitors. EP2010/066701 (WO/ 2011/054848), 2011. (b) Hewings, D. S.; Rooney, T. P. C.; Jennings, L. E.; Hay, D. A.; Schofield, C. J.; Brennan, P. E.; Knapp, S.; Conway, S. J. Progress in the Development and Application of Small Molecule Inhibitors of Bromodomain–Acetyl-Lysine Interactions. *J. Med. Chem.* **2012**, *55*, 9393–9413. (c) Quan, M. L.; Wong, P. C.; Wang, C.; Woerner, F.; Smallheer, J. M.; Barbera, F. A.; Bozarth, J. M.; Brown, R. L.; Harpel, M. R.; Luettgen, J. M.; et al. Tetrahydroquinoline Derivatives as Potent and Selective Factor XIa Inhibitors. *J. Med. Chem.* **2014**, *57*, 955–969. (d) Li, Y.-S.; Liu, X.-Y.; Zhao, D.-S.; Liao, Y.-X.; Zhang, L.-H.; Zhang, F.-Z.; Song, G.-P.; Cui, Z.-N. Tetrahydroquinoline and Tetrahydroisoquinoline Derivatives as Potential Selective PDE4B Inhibitors. *Bioorg. Med. Chem. Lett.* **2018**, *28*, 3271–3275. (e) Gnanasekaran, K. K.; Pouland, T.; Bunce, R. A.; Darrell Berlin, K.; Abuskhuna, S.; Bhandari, D.; Mashayekhi, M.; Zhou, D. H.; Benbrook, D. M. Tetrahydroquinoline Units in Flexible Heteroarotinoids (Flex-Hets) Convey Anti-Cancer Properties in A2780 Ovarian Cancer

Cells. *Bioorg. Med. Chem.* **2020**, *28*, 115244. (f) A Reaxys structure search for the THQ scaffold returned 57,451 results. Limiting this to α-difuctionalised THQs returned 2,606 results (5% of all THQ scaffolds). Limiting further to a-spirocyclic substitution returned 249 results (0.004% of all THQ scaffolds). Accessed 23/08/21

(34) (a) Wang, J.; Breslin, M. J.; Coleman, P. J.; Duggan, M. E.; Hunt, C. A.; Hutchinson, J. H.; Leu, C.-T.; Rodan, S. B.; Rodan, G. A.; Duong, L. T.; Hartman, G. D. Non-peptide αvβ3 antagonists. Part 7: 3-Substituted tetrahydro-[1,8]naphthyridine derivatives *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1049. (b) Manley, P. J.; Miller, W. H.; Uzinskas, I. N. PCT Int. 017959, 2001. (c) Nagarajan, S. R.; Khanna, I. K.; Clare, M.; Gasiecki, A.; Rogers, T.; Chen, B.; Russell, M.; Lu, H.-F.; Yi, Y.; Huff, R. M. U.S. Patent 0092538, 2004. (d) Hatley, R. J. D.; Macdonald, S. J. F.; Slack, R. J.; Le, J.; Ludbrook, S. B.; Lukey, P. T. An Av-RGD Integrin Inhibitor Toolbox: Drug Discovery Insight, Challenges and Opportunities. *Angew. Chem. Int. Ed.* **2018**, *57*, 3298–3321. (e) Fairhurst, R. A.; Knoepfel, T.; Buschmann, N.; Leblanc, C.; Mah, R.; Todorov, M.; Nimsgern, P.; Ripoche, S.; Niklaus, M.; Warin, N.; et al. Discovery of Roblitinib (FGF401) as a Reversible-Covalent Inhibitor of the Kinase Activity of Fibroblast Growth Factor Receptor 4. *J. Med. Chem.* **2020**, *63*, 12542–12573. (f) Jackl, M. K.; Frietuss, I.; Bode, J. W. Synthesis of tetrahydronaphthyridines from aldehydes and HARP reagents via radical Pictet-Spengler reactions. *Org. Lett.* **2016**, *18*, 1713–1715. (f) (f) A Reaxys structure search for the THN scaffold returned 10,364 results. Limiting this to α-difuctionalised THNs returned 79 results (0.008% of all THN scaffolds). Limiting further to a-spirocyclic substitution returned 1 result (0.0001% of all THN scaffolds). Accessed 23/08/21.

(35) Nadin, A.; Hattotuwagama, C.; Churcher, I. Lead-Oriented Synthesis: A New Opportunity for Synthetic Chemistry. *Angew. Chem. Int. Ed.* **2012**, 51, 1114–1122.

(36) Xing, L.; Klug-Mcleod, J.; Rai, B.; Lunney, E. A. Kinase Hinge Binding Scaffolds and Their Hydrogen Bond Patterns. *Bioorganic Med. Chem*. **2015**, *23*, 6520–6527.

(37) (a) Abu-Dief, A. M.; Mohamed, I. M. A. A Review on Versatile Applications of Transition Metal Complexes Incorporating Schiff Bases. Beni-Suef Univ. J. Basic Appl. Sci. 2015, 4 (2), 119–133 (b) Kumar, S. Recent Advances in the Schiff Bases and N-Heterocyclic Carbenes as Ligands in the Cross-Coupling Reactions: A Comprehensive Review. Journal of Heterocyclic Chemistry. John Wiley & Sons, Ltd April 1, 2019, pp 1168–1230.

(38) Buzzetti, L.; Crisenza, G. E. M.; Melchiorre, P. Mechanistic Studies in Photocatalysis. *Angew. Chem. Int. Ed*. **2019**, *58*, 3730–3747.

(39) The sample of imine **6b** used in Stern-Volmer quenching studies was prepared via Dean Stark condensation in the absence of molecular sieves (see Figure 8C).

(40) (a) Jeffrey, J. L.; Petronijević, F. R.; Macmillan, D. W. C. Selective Radical-Radical Cross-Couplings: Design of a Formal β-Mannich Reaction. *J. Am. Chem. Soc*. **2015**, *137*, 8404–8407. (b) Terrett, J. A.; Clift, M. D.; MacMillan, D. W. C. Direct β-Alkylation of Aldehydes via Photoredox Organocatalysis. *J. Am. Chem. Soc.* **2014**, *136*, 6858–6861.

(41) Roth, H.; Romero, N.; Nicewicz, D. Experimental and Calculated Electrochemical Potentials of Common Organic Molecules for Applications to Single-Electron Redox Chemistry. *Synlett* **2015**, *27* (05), 714–723.

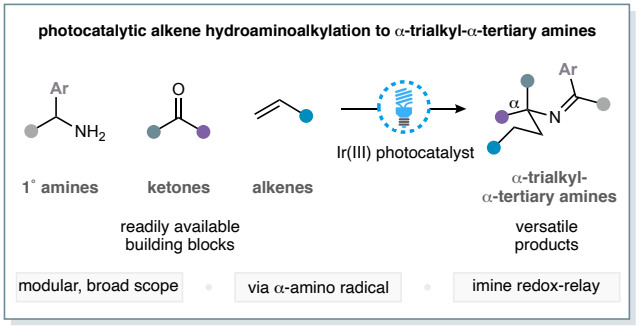
(42) Demissie, T. B.; Ruud, K.; Hansen, J. H. DFT as a Powerful Predictive Tool in Photoredox Catalysis: Redox Potentials and Mechanistic Analysis. *Organometallics* **2015**, *34*, 4218–4228.

(43) (a) Bordwell, F. G.; Cheng, J. P. Radical-Cation Acidities in Solution and in the Gas Phase. *J. Am. Chem. Soc.* **1989**, *111*, 1792–1795. (b) Zhu, L.; Wang, D.; Jia, Z.; Lin, Q.; Huang, M.; Luo, S. Catalytic Asymmetric Oxidative Enamine Transformations. *ACS Catal.* **2018**, *8*, 5466–5484. (c) Wang, D.; Zhang, L.; Luo, S. Enantioselective Decarboxylative α-Alkynylation of β-Ketocarbonyls *via* a Catalytic α-Imino Radical Intermediate. *Org. Lett*. **2017**, *19*, 4924–4927.

(44) Electron transfer to **6b** may also take place before full proton transfer has occurred, resulting in a proton-coupled electron transfer (PCET) mechanism. For other literature examples of PCET processes assisting imine reduction, see: (a) Fuentes de Arriba, A. L.; Urbitsch, F.; Dixon, D. J. Umpolung Synthesis of Branched α-Functionalized Amines from Imines via Photocatalytic Three-Component Reductive Coupling Reactions. *Chem. Commun.* **2016**, *52*, 14434–14437. (b) Qi, L.; Chen, Y. Polarity-Reversed Allylations of Aldehydes, Ketones, and Imines Enabled by Hantzsch Ester in Photoredox Catalysis. *Angew. Chem. Int. Ed.* **2016**, *55*, 13312–13315. (c) Rossolini, T.; Leitch, J. A.; Grainger, R.; Dixon, D. J. Photocatalytic Three-Component Umpolung Synthesis of 1,3-Diamines. *Org. Lett*. **2018**, *20*, 6794–6798. For general reviews on proton coupled electron transfer, see: (d) Weinberg, D. R.; Gagliardi, C. J.; Hull, J. F.; Murphy, C. F.; Kent, C. A.; Westlake, B. C.; Paul, A.; Ess, D. H.; McCafferty, D. G.; Meyer, T. J. Proton-Coupled Electron Transfer. *Chem. Rev*. **2012**, *112*, 4016–4093. (e) Miller, D. C.; Tarantino, K. T.; Knowles, R. R. Proton-Coupled Electron Transfer in Organic Synthesis: Fundamentals, Applications, and Opportunities. *Top. Curr. Chem.* **2016**, *374*, 30.

(45) We became aware that Professor Cresswell at the University of Bath was engaged in related studies towards photocatalytic amine synthesis. We are grateful to the Cresswell group for kindly agreeing to submit their results concurrently with our own studies, and thank them for their generosity and collegiality.

Authors are required to submit a graphic entry for the Table of Contents (TOC) that, in conjunction with the manuscript title, should give the reader a representative idea of one of the following: A key structure, reaction, equation, concept, or theorem, etc., that is discussed in the manuscript. Consult the journal's Instructions for Authors for TOC graphic specifications.


photocatalytic alkene hydroaminoalkylation to α-trialkyl-α-tertiary amines
Ar
NH2
O
Ir(III) photocatalyst
Ar
α
N
1˚ amines
ketones
alkenes
α-trialkyl-
α-tertiary amines
readily available
building blocks
versatile
products
modular, broad scope
via α-amino radical
imine redox-relay