Visible-light mediated carbonyl alkylative amination to all-alkyl α-tertiary amino acid derivatives.

J. Henry Blackwell, Roopender Kumar and Matthew J. Gaunt*

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

ABSTRACT: The all-alkyl α–tertiary amino acid scaffold represents an important structural feature in many biologically and pharmaceutically relevant molecules. Syntheses of this class of molecule, however, often involve multiple steps and requires activating auxiliary groups on the nitrogen atom or tailored building blocks. Here, we report a straightforward, single-step and modular methodology for the synthesis of all-alkyl α-tertiary amino esters. This new strategy uses visible light and a silane reductant to bring about a carbonyl alkylative amination reaction that combines a wide range of primary amines, α-ketoesters and alkyl iodides to form functionally diverse all-alkyl α-tertiary amino esters. Brønsted acid-mediated in situ condensation of primary amine and α-ketoester delivers the corresponding ketiminium species, which undergoes rapid 1,2-addition of an alkyl radical – generated from an alkyl iodide by the action of visible light and silane reductant – to form an aminium-radical cation. Upon a polarity-matched and irreversible hydrogen atom transfer from electron rich silane, the electrophilic aminium-radical cation is converted to an all-alkyl α-tertiary amino ester product. The benign nature of this process allows for broad scope in all three components and generates structurally and functionally diverse suite of α-tertiary amino esters that will likely have widespread use in academic and industrial settings.

INTRODUCTION

Unnatural amino acids and their derivatives constitute an important class of molecule, being pervasive as key motifs in a wide range of pharmaceutical agents, agrochemicals and biologically-relevant natural products (Figure 1A).[1] As a subset of these bifunctional scaffolds, α-tertiary amino acids (ATAAs) have emerged as a valuable variant of these molecules due to a number of distinct properties arising from their fully substituted carbon center. ATAAs, when incorporated into polypeptides or peptidomimetics, can have a dramatic effect on the physical properties of the molecule by influencing conformation, lipophilicity and proteolytic stability.[2] Beyond the amino acid functionality, the two non-hydrogen groups are projected along well-defined exit vectors, which can be exploited as a useful feature in the design of small molecules that interact with biological receptors. Finally, the intrinsic functionalities of ATAAs make them versatile precursors for the synthesis of more architecturally complex compounds. As a consequence, the development of new methodologies that allow streamlined access to α–tertiary amino acids has been an important challenge for chemical synthesis.[3]

Over the past 50 years a range of methodologies have been developed for the synthesis of ATAAs and can be divided (mainly) into four direct strategic bond disconnection strategies (Figure 1, B). By far the most frequently adopted strategy has involved bond disconnection of the ATAA back to an enolate equivalent and a carbon electrophile (Figure 1B, strategy 1). A benchmark protocol for this bond formation has been the coupling of enolates of Schiff base-derived α-amino esters with reactive or activated carbon electrophiles.[4,5] More recently, a wide range of transformations have been reported with enolate-type intermediates of azlactones in combination with Michael-type additions or with metal-activated π-electrophiles.[6] Notably, many of these reactions can be rendered enantioselective through the action of asymmetric catalysts. Disconnection through the C–N bond of ATAAs most conveniently reveals an enolate precursor (such as a malonate or enamine) and a nitrogen-based π-acceptor, such as a diimide (strategy 2).[7,8] Syntheses based on addition of acyl anion equivalents to ketimine derivatives have also proved to be effective for the preparation of ATAAs (strategy 3). Strecker-type reactions using cyanide anions to react with activated imine derivatives are the most frequently adopted variants of this transformation and can be rendered enantioselective.[9] Alternative approaches using 2-lithiated furans or carbamoyl anions as precursors to the carboxylate equivalent of ATAAs have also found success.[10] Finally, through a dipole-reversed disconnection variant of strategy 1, the addition of organometallic nucleophiles into imine derivatives of α-ketoesters can also produce ATAAs (strategy 4).[11] In addition to these direct methods for the synthesis of ATAAs, there exists a number of indirect methods involving the addition of alkyl groups to more highly functionalized substrates, followed by a structural rearrangement to form the fully substituted amino acid framework.[12]

Many of the protocols summarized in Figure 1B require the deployment of activating nitrogen auxiliaries, bespoke substrates or the inclusion of reactivity-inducing, but scope-limiting, functionality in one or more of the reaction components. This means that, while the preparation of many ATAAs have been served by methods based on these disconnection strategies, a number of additional chemical steps are needed to prepare the reactive 'high-energy' building blocks, such as activated imine derivatives or nitrogen electrophiles, and to convert products into the target molecules. Furthermore, there are certain classes of ATAAs to which direct access is non-trivial via these methods. All-alkyl ATAAs (*N*-alkyl α,α'dialkyl-amino acids) are difficult to access via concise synthetic sequences and yet derivatives of these molecules are often very important pharmaceutical candidates, for example as arginase inhibitors (Figure 1A).[13]

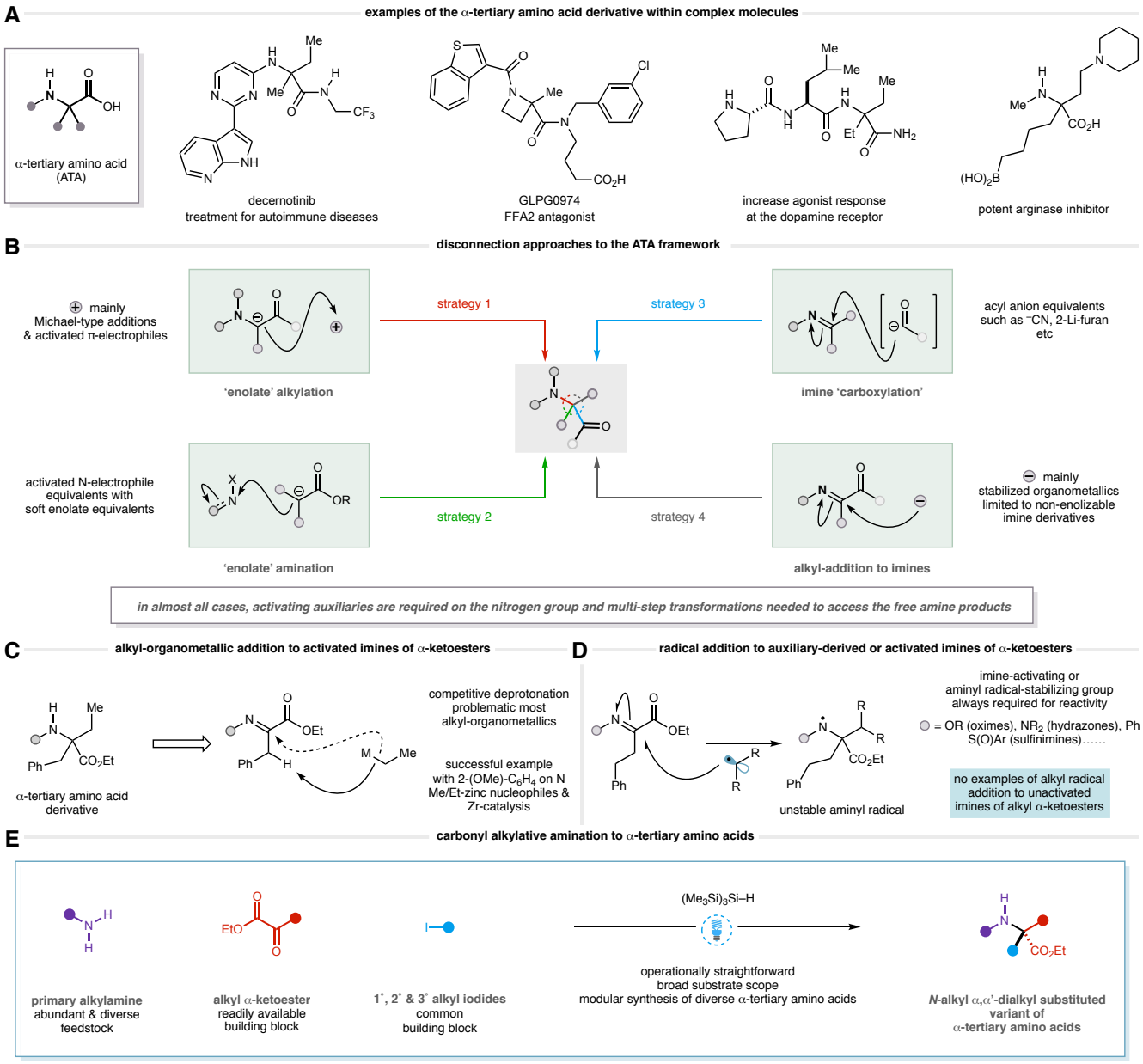


Figure 1. (A) Examples of ATAA-derived pharmaceutically relevant molecules; (B) Strategies (1-4) for the synthesis of ATAAs; (C) Alkyl-organometallic additions to imine-derivatives of α-keto esters: the problems arising competitive deprotonation and regioselective addition pathways; (D) Alkyl-radical additions to imine-derivatives of α-ketoesters; (E) Carbonyl alkylative amination as a straightforward method for the synthesis of all-alkyl ATAEs.

The synthesis of all-alkyl ATAAs is most commonly achieved via the classical O'Donnell-type Schiff base-enolate alkylation (strategy 1) but generally this protocol still requires activated carbon electrophiles for a successful reaction. To the best of our knowledge, no general examples exist for the C–N bond formation between nitrogen electrophiles and dialkyl-substituted enolate equivalents (see strategy 2) or acyl anion additions to dialkyl-ketimine-derivatives (see strategy 3). Transformations based on strategy 4 in Figure 1, however, would offer a seemingly straightforward synthesis of all-alkyl ATAAs. While the addition of alkyl-organometallics to the N-alkyl imine of an alkyl-substituted α-ketoester derivative appears to represent a logical approach to all-alkyl ATAAs, methods for the successful execution of the strategy (4) towards these targets are restricted. The C–H bonds adjacent to the imine-motif are acidic and are readily deprotonated by the basic organometallic reagent (Figure 1C). Furthermore, controlling the regioselectivity of the addition step is complicated by the viability of an alternative pathway wherein the alkyl-nucleophile adds to the N-atom of the imine-motif to form the corresponding enolate.[14] As a result, only a very limited number of examples exist for the addition of alkyl-organometallics reagents to imine derivatives of α-ketoesters, exemplified by the Zr-catalyzed method of Snapper and Hoveyda, which sees dimethyl- or diethyl zinc reagents add, enantioselectively, to ortho-anisidine-derived α-iminoesters.[11c] As a result, there remains a need to develop flexible, multicomponent methodologies for the synthesis of all-alkyl ATAAs from α-ketoester that exploit readily available alkyl nucleophiles and primary amine feedstocks in order to expedite further exploration of the chemical space around this important motif.

Given the limitations of basic organometallic reagents in reactions with substrates displaying acidic C–H bonds, interest has arisen in the addition of nucleophilic, but importantly charge neutral, alkyl radicals to activated imine derivatives. While radical addition to the carbon nitrogen double bond of *N*-activated glyoxalate-derived aldimines to make α–amino acid precursors is relatively well established,[15] only a limited number of analogous transformations have been reported for imine derivatives of α–ketoesters to generate ATAAs (Figure 1D).[16] Generally, these methodologies rely on the use of an auxiliary group on the *N*-atom of the imine derivative in order both activate the electrophile and stabilize the resulting aminium-derived radical. Furthermore, reactions of this type have only been demonstrated simple on α-ketoesters, such as ethyl pyruvate. Together, these stringent requirements significantly limit the modularity, efficiency, and hence, utility in the context of all-alkyl ATAA synthesis.

We reasoned that leveraging the intuitive nature of the bond disconnection outlined in strategy 4 with a radical carbonyl alkylative amination (CAA) process would effectively combine readily available primary amines, α-ketoesters and alkyl iodides to form a wide range of all-alkyl α–tertiary amino esters in a single step (Figure 1E). The potential efficacy of such a strategy is evidenced by the modular nature of this multi-component transformation that would exploit the combination of sets of established building blocks to access new product classes, which would require multistep syntheses using other methods. Here, we report the successful realization of this idea through the design, development and demonstration of a new visible-light mediated carbonyl alkylative amination method for the synthesis of all-alkyl α-tertiary amino esters (ATAEs). Factors that distinguish this method from previously documented transformations are its wide substrate scope within each component, the mild reaction conditions and the use of abundant building blocks requiring no activating or stabilizing auxiliary. Given the proclivity for C(sp^3)-rich polar scaffolds in pharmaceuticals candidates, we expect that this method will be of significant interest to practitioners of synthetic and medicinal chemistry in both academic and pharmaceutical industry settings.

RESULTS & DISCUSSION

Recently, our group reported a general method for 1,2-addition of alkyl-radicals to, in-situ generated, alkyl-substituted aldiminium ions through a process that was facilitated by visible-light irradiation (Figure 2A).[17] A critical factor in the successful execution of carbonyl alkylative amination (CAA) proved to be the rapid termination of the process by hydrogen atom transfer (HAT) between an intermediate aminium radical cation and tris(trimethylsilyl)silane [$(Me_3Si)_3Si$–H]. Notably, ketones proved recalcitrant to the carbonyl alkylative amination protocol, presumably because the condensation of secondary amine with the more sterically hindered carbonyl group of the ketone was slow compared to the other competing processes and that all-alkyl ketiminium ions are inherently less electrophilic than their aldehyde counterparts as a result of their four inductively donating alkyl substituents. With these limitations in mind and the overarching goal of developing a method for the synthesis of all-alkyl ATAEs, we reasoned that combining the use of primary amines with more electrophilic α-ketoesters and an activating Brønsted acid might circumvent the reactivity problems precluding our inability to add alkyl radicals to ketiminium ions (Figure 2B). Imine formation (to int I) and subsequent addition of the alkyl-radical (formed from alkyl iodide via visible light-mediated initiation) should be promoted in this design plan. Furthermore, the hydridic $(Me_3Si)_3Si$–H would be polarity-matched to the unstablized and, hence, reactive secondary N-alkyl aminium-radical cation (ARC, int II) emanating from the addition step, enabling a favorable HAT to form the product.

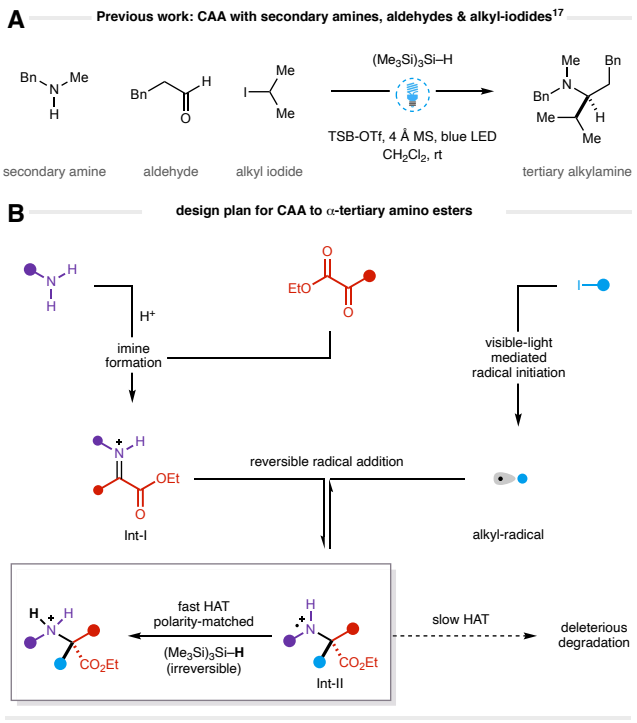


Figure 2. Initial proposal for CAA to all-alkyl ATAEs.

Investigations to form N-alkyl ATAEs began by employing the reaction conditions that had proved successful in our previously reported visible-light-mediated carbonyl alkylative amination protocol.[17] Surprisingly, visible-light irradiation of a reaction deploying $(Me_3Si)_3Si$–H, TBS–OTf and 4 Å molecular sieves to combine butylamine **1a**, α-ketoester **2a** and iso-propyl iodide **3a** failed to produce any of the desired product (Table 1, entry 1); modest reaction was observed on omission of TBS–OTf (entry 2). On testing alternate means to promote the reaction, the combination of 0.2 equivalents $EtCO_2H$, 4 Å molecular sieves and 3 equivalents of $(Me_3Si)_3Si$–H was found to affect CAA between **1a**, **2a** and **3a** to give a 39% yield of ATAE **4a**, when irradiated with a 40 W Kessel lamp for 6 h (entry 3); the addition of $EtCO_2H$ was believed to facilitate imine formation. An assessment of the reaction parameters ultimately revealed an optimal procedure that involved stirring a dichloromethane solution of primary amine **1a** (1 equivalent), α-ketoester **2a** (2 equivalents) and $EtCO_2H$ (1 equivalent) for 3 hours before adding iso-propyl iodide **3a** (3 equivalents) and $(Me_3Si)_3Si$–H (3 equivalents), and reaction under visible-light irradiation for 6 h, which produced an 85% yield (by ^{1}H NMR) of the desired ATAE **4a** (entry 5). The role of $(Me_3Si)_3Si$–H in orchestrating a successful reaction is likely linked to its ability to perform a kinetically and thermodynamically favored HAT to the reactive secondary N-alkyl aminium-radial cation (Figure 2B, Int II) and contrasts with previously reported radical additions to activated imine derivatives adorned with auxiliary groups, which consequently stabilize the corresponding aminium-radical cation and require more forcing conditions to terminate the process. As such, a visible-light enabled carbonyl alkylative amination to all-alkyl-ATAEs using $(Me_3Si)_3Si$–H obviates the need for auxiliary groups on the nitrogen atom of the imine electrophile and is directly responsible for the mild and straightforward conditions that lead to a successful reaction.

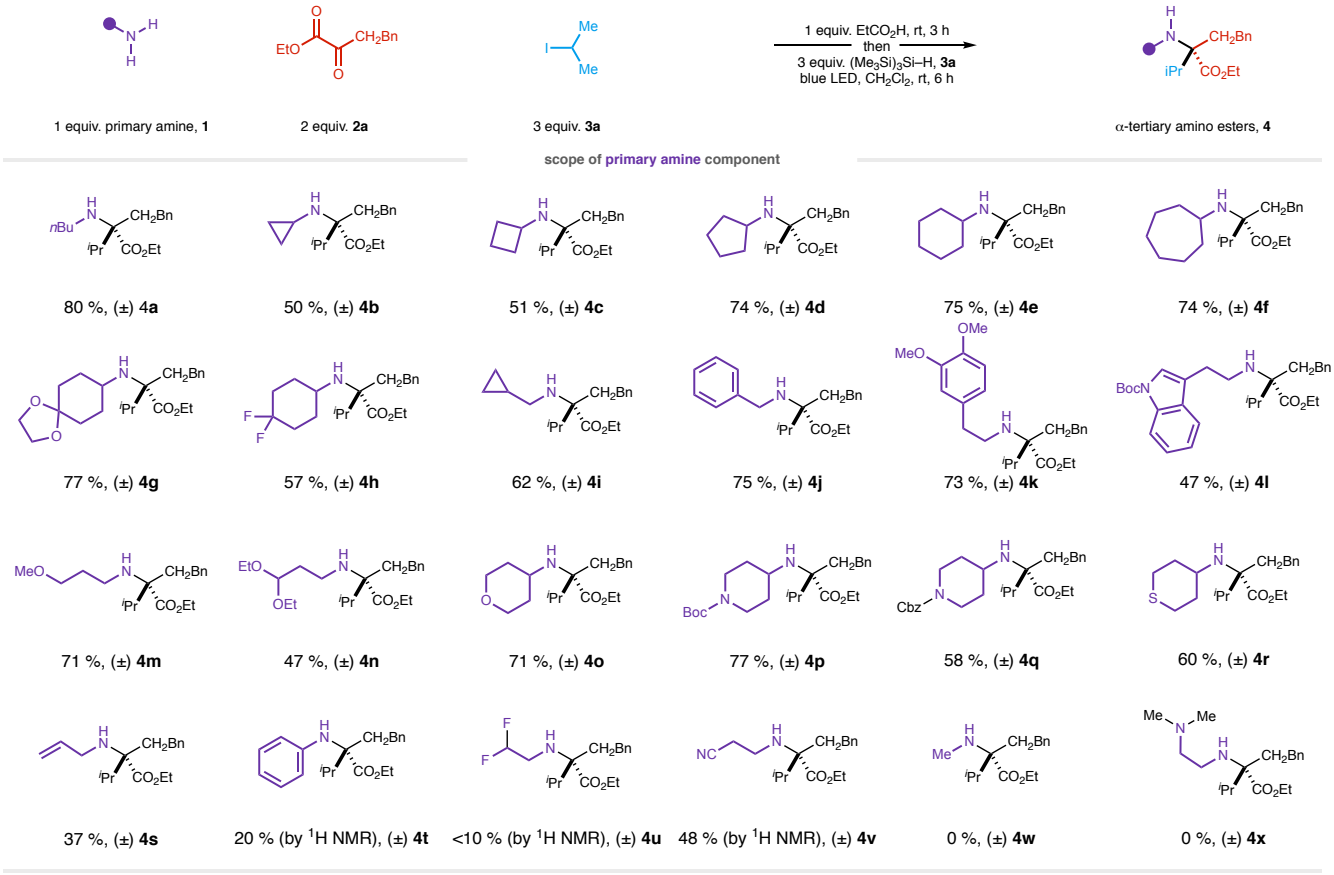
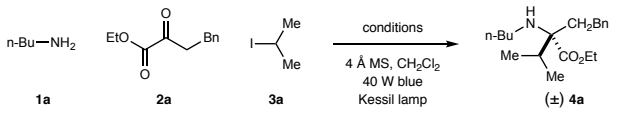


Figure 3. Scope of the carbonyl alkylative amination to ATAEs in the primary amine component.

Table 1. Selected optimization for CAA to all-alkyl ATAEs



	$R_3Si–H$ (3 equiv)	Acid (equiv)	Solvent	Yield* **4a**, %
1	$(Me_3Si)_3Si–H$	TBS-OTf (1 equiv)	CH_2Cl_2	0
2	$(Me_3Si)_3Si–H$	–	CH_2Cl_2	15
3	$(Me_3Si)_3Si–H$	$EtCO_2H$ (0.2 equiv)	CH_2Cl_2	39
4	$(Me_3Si)_3Si–H$	$EtCO_2H$ (0.2 equiv)	CH_2Cl_2	53†
5	$(Me_3Si)_3Si–H$	$EtCO_2H$ (1 equiv)	CH_2Cl_2	85†
6	$Et_3Si–H$	$EtCO_2H$ (1 equiv)	CH_2Cl_2	0
7	$Ph_3Si–H$	$EtCO_2H$ (1 equiv)	CH_2Cl_2	0
8	$PhSiH_3$	$EtCO_2H$ (1 equiv)	CH_2Cl_2	0
9	$(Me_3Si)_3Si–H$	$EtCO_2H$ (1 equiv)	MeCN	28
10	$(Me_3Si)_3Si–H$	$EtCO_2H$ (1 equiv)	DCE	61
11	$(Me_3Si)_3Si–H$	$EtCO_2H$ (1 equiv)	MeOH	0
12	$(Me_3Si)_3Si–H$	$EtCO_2H$ (1 equiv)	EtOAc	15
13	$(Me_3Si)_3Si–H$	$EtCO_2H$ (1 equiv)	THF	10

* Yields were determined by ^1H NMR using 1,1,2,2-tetrachloroethane as internal standard. † Primary amine **1a**, α-ketoester **2a** and $EtCO_2H$ were stirred for 3 hours before the addition of iso-propyl iodide **3a** and $(Me_3Si)_3Si–H$ and irradiation with visible-light.

Equipped with a set of optimized reaction conditions, the scope of the carbonyl alkylative amination to all-alkyl ATAEs was first explored by varying the amine component using α-ketoester **2a** and isopropyl iodide **3a** as representative coupling partners. A variety of primary amines, containing a range of different structural and functional features, were found to be highly effective in the reaction (Figure 3, **4a**-**4r**). In addition to deployment of butylamine **1a**, the primary amine component could incorporate cyclic hydrocarbon substituents with the reaction providing good yields throughout (**4b**-**4f**). Amines with linear substituents displaying cyclopropyl, benzyl and distal electron rich arene and heteroarenes, ether and acetal features produced the all-alkyl ATAEs in good to moderate yields (**4i**-**4n**). The benzylamine example provides a product that can be readily transformed into the corresponding primary amine and will be useful for downstream diversification, for example to non-alkyl N-substituted ATAEs (Figure 1A). A selection of α-branched alkylamines substituted with saturated heterocyclic groups also performed well as coupling partners (**4o**-**4r**). Of particular note was the deployment of a N-Boc-protected piperidine-derived primary amine, which gave an orthogonally protected ATAE suitable for further functionalization using classical transformations. We identified some primary amines that generated product, but in low yield (**4s**-**4x**). In particular, reactions with aniline or alkyl amines with proximal electron withdrawing groups or amines bearing electron

deficient aromatic moieties resulted in by-product formation arising from reductive amination. The use of methylamine proved to be problematic due to difficulties associated with handling a gaseous reagent on laboratory scale; unfortunately, the use of the commercial hydrochloride salt was complicated by its insolubility in the reaction solvent and resulted in no reaction.

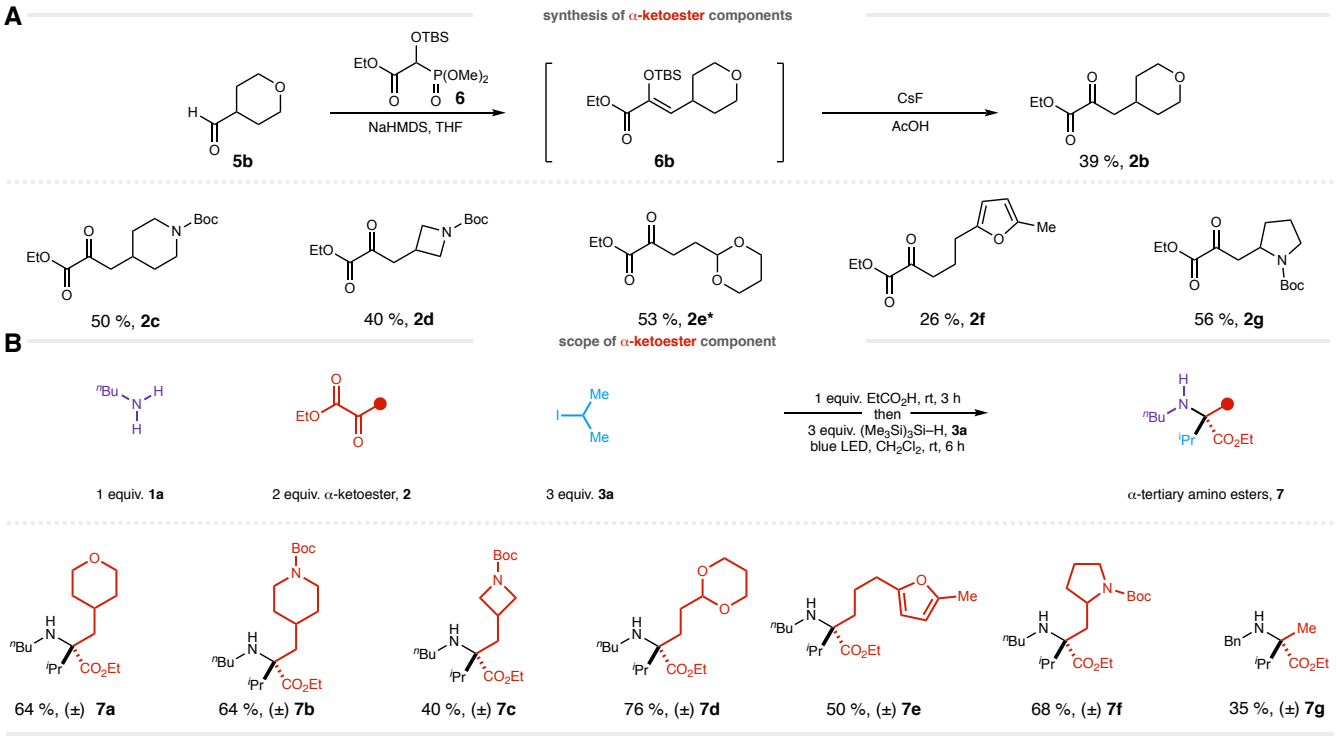


Figure 4. (A) Synthesis of the α-ketoester component based on a modified literature protocol (yield over two steps from aldehyde).[18] *Substrate was prepared by addition of the corresponding Grignard reagent into diethyl oxalate.[18b] (B) Scope of the CAA to ATAEs in the α–ketoester component.

We also noted that amines displaying proximal basic sites, such as pendant tertiary amine, failed to record any product formation, most likely due to the electron withdrawing effects of the inevitably protonated functionality under the reaction conditions.

Next, we examined the preliminary scope in the nature of the α-ketoester component. First, an efficient protocol for the assembly of these substrates was required. By adapting procedures reported by the groups of Overman[18a] and Yo and Wang,[18b] we were able to effectively render these versatile building blocks readily available by following a straightforward two step method starting from a representative aldehyde (**5b**) and an α-(OTBS)-substituted Wadsworth-Horner-Emmons reagent (**6**). A variety of aldehydes were smoothly transformed to the tri-substituted enol silane in good to yields. Treatment of this intermediate with CsF and one equivalent of acetic acid afforded the desired α-ketoesters (Figure 4A, **2b-d,f,g**) in synthetically useful yields.[18a]

We were pleased to find that a range of α-ketoesters worked well in the CAA reaction when assessed using *n*-butylamine **1a** and isopropyl iodide **3a** as representative coupling partners (Figure 4B, **7a**-**7g**). Notable features of this study included the suitability of saturated heterocyclic substituents in the α-ketoester component, which provide versatile products displaying structural and functional features that will be useful for the synthesis of small bioactive molecules to interact with biological receptors. Interestingly, the use of the prolinyl-derived α-ketoester lead to the observation of a 4:1 diastereomeric ratio of the products from the CAA reaction (**7f**). The diastereoselectivity observed in this reaction is surprising given that the controlling stereogenicity is in the β-position to reacting centre, suggesting that the prolinyl-N-Boc substitutent may engage the protonated imine through an 8-membered ring hydrogen bonding interaction, leading to facial selectivity in the cyclic species during the radical addition. We also found that ethyl pyruvate worked in the reaction to form the corresponding AATE (**7g**), although the yield with this α-ketoester was lower. We believe the high enamine content of the corresponding α-iminoesters may be compromising the reactivity of this substrate. Still, the deployment of this substrate provides immediate access to the methyl-substituted AATE framework that frequently appears in pharmaceutically-relevant compounds. [1] Furthermore, low yields (less than 10 % assay yield) of the desired product were obtained when β-branched α-ketoesters were employed.

The scope of the reaction with respect to the alkyl iodide was assessed using *n*-butylamine **1a** and α-ketoester **2a**. Secondary alkyl iodides based on saturated cyclic and heterocyclic groups were smoothly coupled under the optimized reaction conditions to deliver the all-alkyl ATAE products in good yields (Figure 5A, **8a**-**8g**). However, when primary and tertiary iodides were subjected to these conditions, diminished conversions to products were observed. In the case of primary iodides, the decreased conversion of the reaction was deemed to be a result of the decreased nucleophilicity of primary radicals relative to secondary alkyl radicals.[19] With tertiary alkyl iodides, the increased steric demands on the addition were thought to be detrimental to the yield. Therefore, for reactions employing these more challenging substrate classes, modifications to the optimized conditions were identified: a solution of butylamine **1a** (1 equivalent), α-ketoester **2a** (2 equivalents) and $EtCO_2H$ (0.2 equivalents)

in dichloromethane was stirred for 4 h before the addition of the iodide **3a** (3 equivalents) and TBS-OTf (1 equivalent) and irradiation with visible light for 6 hours (Figure 5B). We believe that the use of TBS-OTf increases the reactivity of the ketiminium ion through counteranion exchange, overcoming the challenges described previously in regards to the addition of the less reactive alkyl radicals. (vida supra). As a result, high conversions could be obtained for primary and tertiary alkyl halides displaying a variety of structural and functional features (Figure 5B, **8h**-**8n**). Notably, the use of tertiary alkyl halides delivers all-alkyl AATEs with vicinal fully substituted centers, which are difficult to access by other methods.

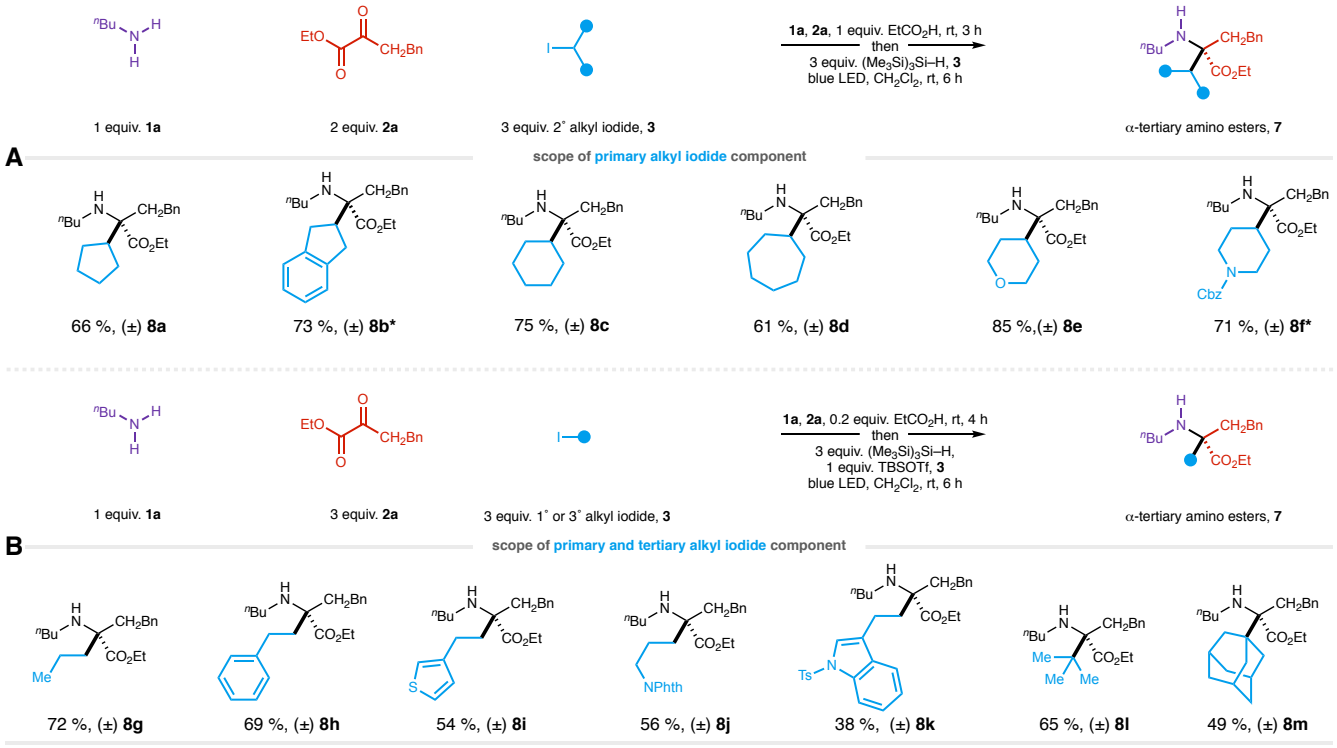


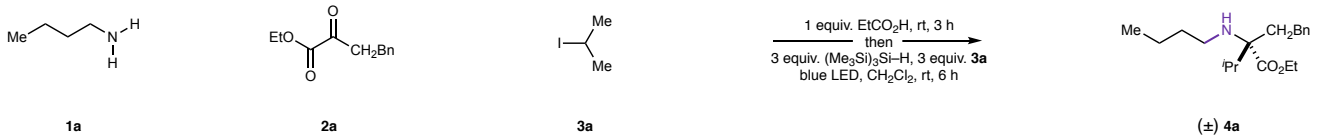
Figure 5. (A) Scope of the carbonyl alkylative amination to ATAEs in the 2° alkyl iodide component; *0.2 equivalents $EtCO_2H$ and 1 equivalent TBS-OTf employed (B) Scope of the carbonyl alkylative amination to ATAEs in the 1° & 3° alkyl iodide component.

Having established a broad scope for the synthesis of all-alkyl ATAEs, attention was focused the mechanism of this CAA reaction. Control experiments established visible-light and $(Me_3Si)_3Si–H$ as essential components of the reaction (Table 2, entries 1 & 2). Moreover, since oxygen is known to generate the silyl radical,[20] we tested the efficiency of the reaction under air in the absence of light: no product was observed, underscoring the pivotal role played by visible-light (entry 3). The reaction yield was greatly diminished when $EtCO_2H$ was omitted, supporting its previously hypothesized role in aiding imine formation and activation via protonation (entry 4). An experiment conducted in the absence of light, but at 80 °C, showed no reaction indicating that a thermal radical initiation pathway was not operational (entry 5). The intermediacy of a free radical was supported by a TEMPO trapping experiment, which resulting in complete inhibition of CAA (entry 6). A more detailed analysis of the role of visible light revealed the reaction still proceeded with high conversion to product when a 420 nm bandpass filter was employed (entry 7), suggesting that the reaction is not initiated by traces of UV-light mediating homolysis of the carbon-iodine bond.[17,21] Interestingly, the reaction did not proceed when a 455 nm wavelength bandpass filter was employed (entry 8), indicating that a narrow range of light is required in order to facilitate initiation. This feature is in contrast to observations in our previous work.[17] While the nature of the initiation of the radical chain is not well understood, we believe that it is analogous to the mode of initiation disclosed in our previous report; visible-light activates an EDA-type complex between enamine, alkyl halide and $(Me_3Si)_3Si–H$. However, it should be noted that, in this case we were unable to observe the relevant bathochromic shift when studying combinations of the relevant reaction components, possibly due to the low concentration of the active complex. This, of course, could suggest the initiation operates by an alternative, as yet unknown, pathway.

Further evidence for the proposed radical addition to a ketiminium ion was accrued from a free-radical clock experiment (Figure 6A). The reaction of cyclopropylmethyliodide **3b** with **1b** and **2a** provided the expected terminal alkene-derived product **9** in modest yield, reflecting the β-scission of the cyclopropylmethyl radical in advance of addition to the iminium ion. However, we also observed the formation of two diastereomers of a trisubstituted pyrrolidine product, **10a** and **10b** (2:1 diastereomeric ratio). These products are consistent with a mechanism first involving radical addition of the linear alkenyl primary radical (from β-scission of the cyclopropylmethyl radical) to the ketiminium ion to form the corresponding aminium-radical cation (Int-I). This intermediate would then engage the pendent terminal alkene via 5-*exo*-trig ring closure delivering the incipient exocyclic radical, which then undergoes HAT with $(Me_3Si)_3Si–H$.[22] The radical nature of the ring closure and subsequent HAT was confirmed by a reaction employing $(Me_3Si)_3Si–D$, which showed deuterium incorporation into the methyl group of each diastereomer of the pyrrolidine product (Figure 6B, *d*-**10a** & *d*-**10b**) (see Supporting Information for full details).[23] Taken together,

these experiments suggest that, because no intact cyclopropyl product was observed, the rate of addition of the alkyl radical to the ketiminium ion is slower than the rate of opening of the cyclopropylmethyl radical ($k = 1 \times 10^8\ s^{-1}$ at 25 °C).[24] Furthermore, the observed ratio of linear to cyclized product (1:3) suggests the rate of HAT from $(Me_3Si)_3Si–H$ to the aminium-radical cation is comparable to that of the 5-*exo*-trig ring closure of an aminium radical cation onto a pendant alkene ($k \approx 10^7$-$10^8\ M^{-1}s^{-1}$).[25] Overall, we believe that these data support a mechanism whereby radical addition to intermediate ketiminium delivers *N*-centered radical cation (Int-II), followed by rapid HAT to $(Me_3Si)_3Si–H$. This delivers the ammonium salt of the desired ATAE as well as the $(Me_3Si)_3Si•$, which propagates the radical chain (Figure 6C).

Table 2. Control experiments



1a 2a 3a (±) 4a

Entry	Deviation from standard	Yield (%)	Entry	Deviation from standard	Yield (%)
1	No light	0	5	No light, stirring at 80 °C	0
2	No $(Me_3Si)_3Si–H$	0	6	With 1 equiv. TEMPO	0
3	Under air & no light	0	7	Long pass filter (>420nm)	0
4	No propionic acid	15	8	Long pass filter (>450nm)	60

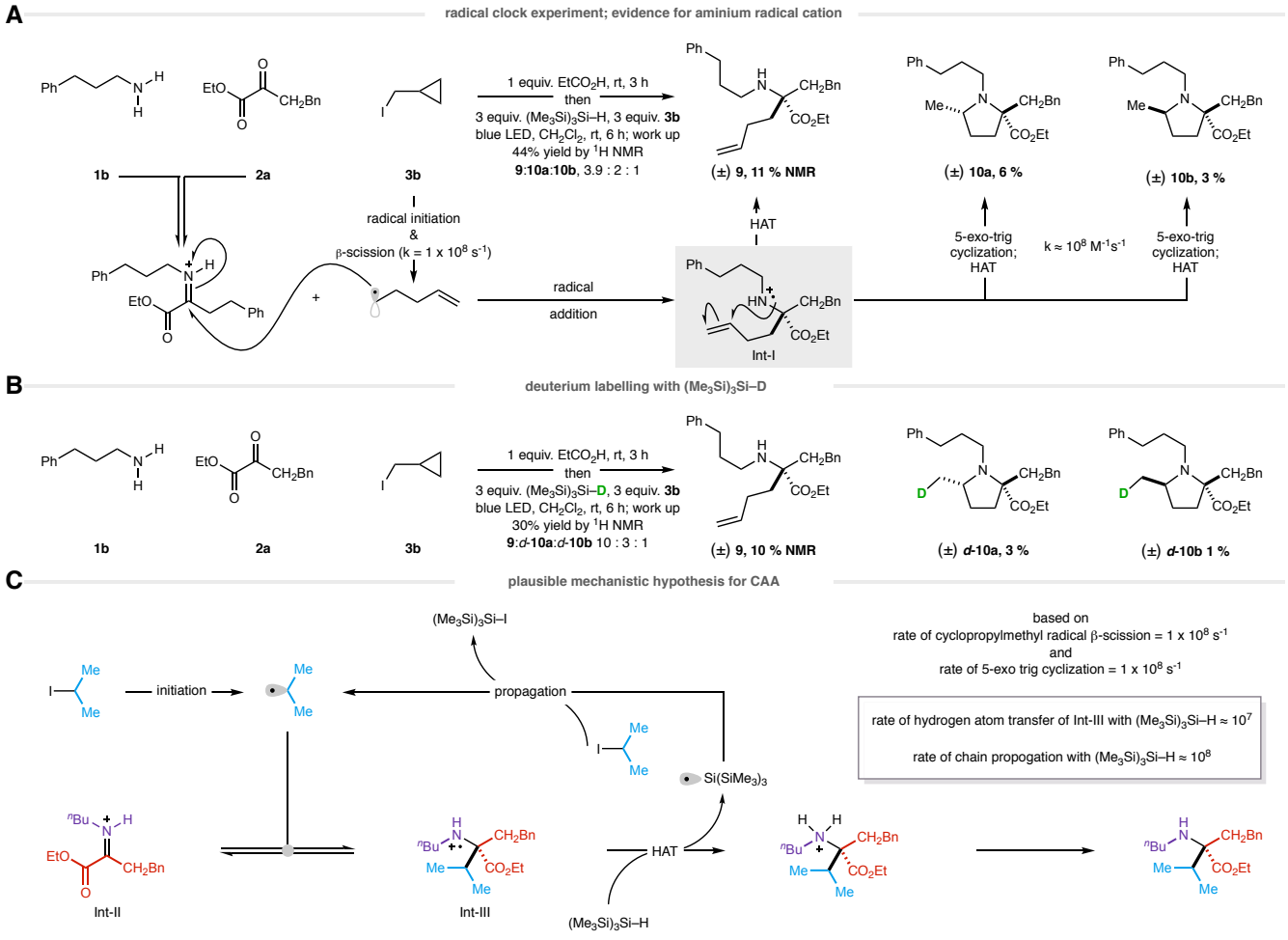


Figure 6. Mechanistic experiments (A) Intercepting the aminium radical cation intermediate. (B) Deuterium labelling experiments. (C) Plausible mechanism based on exploratory experiments.

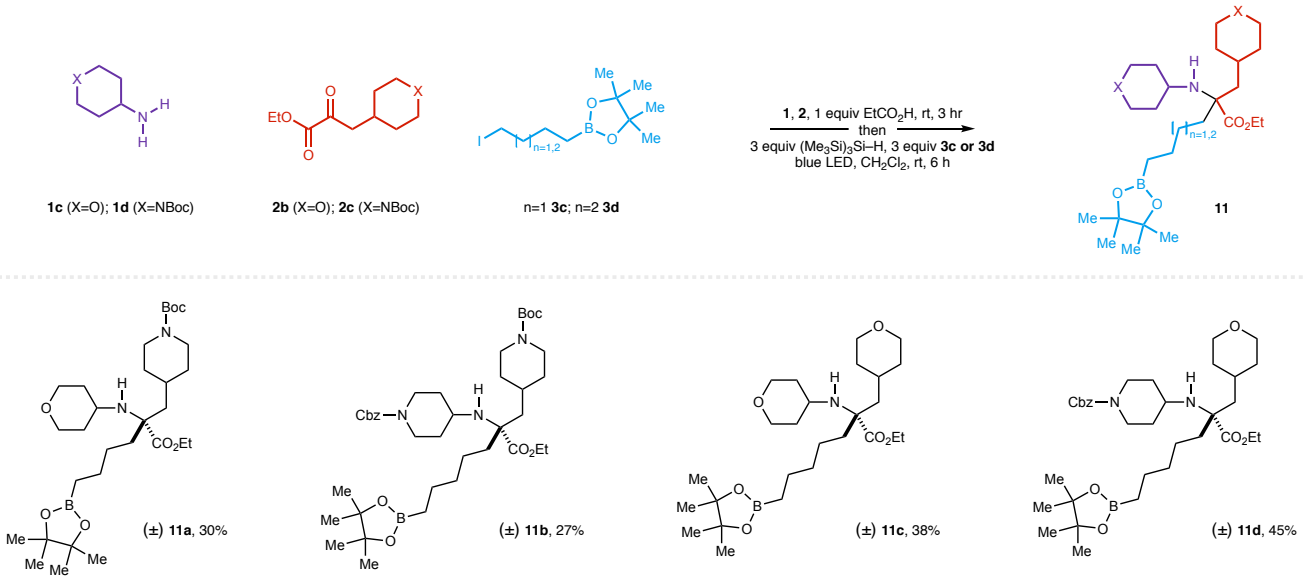


Figure 7. Application of CAA toward the concise and flexible synthesis of AATE-derived arginase inhibitor analogues

Finally, we sought to highlight the utility of the newly developed radical alkylation through the synthesis of all-alkyl ATAEs that resemble established ω-borono-α–amino acid arginase inhibitors (Figure 7).[13] Generally, the synthesis of these important compounds relies on time consuming multistep procedures, which also limits the modularity and flexibility that would ideally be inherent in approaches to such molecules.[26] Selecting two primary amines and two α-ketoesters we were able to use the CAA reaction to combine these building blocks with 4-(Bpin)-butyl iodide (to **11a**) and 5-(Bpin)-butyl iodide (to **11b**-**11d**) to generate analogues of all-alkyl ω-borono-α–amino ester scaffolds. Four highly functionalized molecules, all containing the core components of arginase inhibitors, were produced in in a modest but synthetically useful yield in a single step from the readily available precursors.

CONCLUSION

In summary, we have developed a modular protocol for the synthesis of α–tertiary amino ester derivatives. This procedure employs readily accessible or commercially available feedstocks to deliver a suite of functionally and structurally diverse products, which would otherwise be difficult to access under such mild conditions in a single synthetic sequence. Our newly developed ATAE protocol addresses many of the issues associated with the use high energy auxiliary-activated imine derivatives and tailored intermediates that facilitate reactivity and offers a practical one step protocol for rapid and straightforward assembly of these important molecules. Importantly, the visible-light-mediated CAA protocol requires neither photocatalyst or chemical initiators, rendering the process exceptionally mild and enables a broad scope in all three components.[6,16,22b] Though this CAA process was found to be robust in each reaction components, certain limitations were identified: amines bearing electron withdrawing groups adjacent to the nitrogen center were found to undergo significant levels of reductive amination; highly reactive alkyl radicals, such as that generated from iodomethane, were found to undergo rapid hydrogen atom transfer with $(Me_3Si)_3Si–H$, leading to competitive dehydrohalogenation; and β-branched α-ketoesters returned low yields of product, presumably due to deactivating steric hindrance around the iminium ion. Although in some of these cases, synthetic usable yields were returned, our future studies will focus on addressing these problems towards the development of a more general process. Despite these limitations, the broad utility of the reaction is still demonstrated by a substantial substrate scope that generates highly functionalized and synthetically versatile ATAEs, which would be difficult to prepare by other methods. From a mechanistic perspective, radical clock and deuterium labelling experiments suggest the intermediacy of an aminium radical cation as a productive intermediate in this carbonyl alkylative amination, but also exemplify its innate reactivity towards pendant π–acceptors. Despite the low yields observed for 5-exo trig cyclisation of aminium radical cation onto a pendent alkene, this transformation represents a rare example of the multicomponent assembly of a complex pyrrolidine scaffold, which has the potential to offer flexible access to this pharmaceutically relevant azacyclic scaffold. Moreover, we were able to display the utility of this transformation by the rapid assembly of analogues of an important class of arginase inhibitor. As such, we anticipate that this platform will facilitate modular, rapid access to this privileged classed of hindered unnatural amino acids, which are likely to be of interest to practitioners of synthetic and medicinal chemistry in academic and industrial settings.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at:

All experimental procedures and compound characterization are available in the document (PDF)

AUTHOR INFORMATION

Corresponding Author

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

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