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Modular synthesis of α -branched secondary alkylamines *via* visible-light-mediated carbonyl alkylative amination†

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The development of methods for the assembly of secondary α -alkyl amines remains a central challenge to chemical synthesis because of their critical importance in modulating the physical properties of biologically active molecules. Despite decades of intensive research, chemists still rely on selective N-alkylation and carbonyl reductive amination to make most amine products. Here we report the further evolution of a carbonyl alkylative amination process that, for the first time, brings together primary amines, aldehydes and alkyl iodides in a visible-light-mediated multicomponent coupling reaction for the synthesis of a wide range of α -branched secondary alkylamines. In addition to exploring the tolerance and limitations in each reaction component, we also report preliminary applications to the telescoped synthesis of α -branched N-heterocycles and an N-alkylation protocol that is selective for primary over cyclic secondary amines. Our data support a mechanism involving addition of an alkyl radical to an uncharged alkyl imine which, to the best of our knowledge, has not previously been described. We believe that this method will enable practitioners of synthetic chemistry in academic and industrial settings to approach the synthesis of these important molecules in a manner that is streamlined compared to established approaches.

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Introduction

Secondary alkylamines are one of the most commonly occurring functional motifs in small molecules that perturb biological processes (Fig. 1A).¹ Their capacity to function as hydrogen bond donors or acceptors with proteins, as modulators of solubility and bioavailability on protonation, and as scaffolds to support small molecule topology makes them privileged features in pharmaceuticals and agrochemicals. Accordingly, the development of new methods that lead to robust and modular preparations of secondary alkylamines remains a constant challenge to the synthetic organic chemistry community.^{2,3} While catalytic methods are emerging for their synthesis, most notably, alkene hydroamination,⁴ photoredox-mediated reactions,⁵ hydrogenation,⁶ biocatalytic transformations,⁷ C–H activation,⁸ and others,⁹ the majority of secondary alkylamines are still prepared by carbonyl reductive amination¹⁰ or N-alkylation.^{11,12} A possible reason for this preference is that methods such as reductive amination offer an operationally straightforward, robust and widely explored means by which to prepare secondary alkylamines *via* the union of two classes of extensive and diverse building blocks, namely

primary amines and aldehydes or ketones. In reality, however, many of the established amine synthesis technologies often come up short in increasingly complex scenarios and so new robust synthetic methods for alkylamine synthesis are still needed.

The condensation of a primary alkylamine and a ketone adorned with alkyl substituents to form an alkyl imine is usually reliable, from which there are a plethora of reduction protocols to form the corresponding α -branched secondary alkylamine.¹⁰ In some cases, however, steric hindrance or adverse electronic effects on either the amine or ketone component can preclude alkyl imine formation, leading to failure of the reductive amination process. An alternative disconnection involves addition of a carbon nucleophile to an alkyl aldimine, thus partitioning the steric features of the product alkylamine between the two reacting components. Despite almost 100 years of effort towards a solution to this simple idea, a general method for the addition of organometallic nucleophiles to alkyl imines or iminium ions derived from primary alkylamines and alkyl-substituted aldehydes has largely eluded synthetic chemists.¹³ Only when reactivity-augmenting auxiliary groups are deployed on either the amine or carbonyl component does an effective and general transformation result (Fig. 1B). Organometallic additions to Ellman's *tert*-butanesulfinamide derivatives have become the benchmark for this type of reaction.¹⁴ While a distinct advantage of this auxiliary is the capacity to exert stereocontrol at the newly formed α -amino carbon centre, they nonetheless suffer

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Fig. 1 (A) The importance of secondary alkylamines in drug discovery and development. (B) Current strategies for the modular synthesis of α -branched alkylamines (auxiliary-based methods which require protection and deprotection). (C) Carbonyl alkylative amination (CAA) for the synthesis of α -branched tertiary alkylamines. (D) This work: CAA as a general method for the synthesis of complex α -branched secondary alkylamines. (E) This work: alkyl radical addition to neutral imines.

from the well-established drawbacks of auxiliary use, namely the requirement for installation and removal steps, and poor overall atom economy. Several additional steps are also required to form secondary or tertiary amine products, with cyclic tertiary amine motifs presenting a notable challenge. The main reason that organometallic additions to non-activated alkyl imines fail lies with the low pK_a of the C–H bonds

adjacent to the carbon–nitrogen double bond, and the low electrophilicity of the carbon–nitrogen double bond. As a result, the treatment of alkyl imine/iminium species with organometallic reagents typically results in deprotonation of the acidic α -C–H as the major process, leading to formation of the corresponding enamine instead of the desired 1,2-addition product.^{14b}



As an alternative, carbon-centred radicals have been shown to effectively add to a range of activated surrogates, such as hydrazones, oximes, carbamoyl and sulfonyl imines.¹⁵ However, although the charge-neutral and non-basic nature of alkyl radicals addresses the deprotonation problems associated with organometallic additions, tailored activating substituents on nitrogen are still required, in this case to promote radical 1,2-addition by stabilising the resulting nitrogen-centred radical.

Our laboratory has a longstanding interest in the development of methods for the direct synthesis of alkylamines that avoid the use of reactivity-enhancing auxiliaries. Recently, we introduced a process called carbonyl alkylative amination (CAA) for the synthesis of complex alkylamines from feedstock alkylamines, carbonyls and alkyl iodides (Fig. 1C).¹⁶ In this reaction, visible-light and a silane mediate the addition of an alkyl radical—generated from a non-activated alkyl iodide—to an *in situ* generated all-alkyl iminium ion to form a wide range of complex alkylamines. Central to the success of this process was the multifaceted role of the silane, which not only facilitated a unique alkyl-radical initiation step but also enabled a rapid hydrogen atom transfer (HAT) to an aminium radical cation intermediate to form the product as its ammonium salt. The addition of an alkyl radical to a highly reactive alkyl-substituted iminium ion represents a higher order variant of reductive amination and provides a particularly useful strategic bond forming reaction for the synthesis of alkylamines that would not be possible using the corresponding organometallic addition. The Qin laboratory recently reported a mechanistically distinct multicomponent platform for alkylamine synthesis using alkyl boronates as the alkyl radical source.¹⁷ While our CAA platform displayed excellent scope in the secondary amine, aldehyde and alkyl halide components, significantly lower yields of product were observed when using primary amines (unless the imine was derived from highly activated α -ketoesters) and precluded a general strategy for the synthesis of different types of alkylamine.^{16b}

Herein, we report a reaction platform to accommodate the synthesis of α -branched secondary alkylamines through the modular coupling of primary amines with aldehydes and alkyl iodides (Fig. 1D).^{16d} In contrast to our previous work on radical additions to iminium ions, and to the multitude of prior reports suggesting that reactivity-augmenting auxiliaries (or Lewis acid activation) are essential for effective intermolecular radical addition to imines,¹⁵ we present evidence that the reaction proceeds *via* visible-light and silane-mediated radical addition to an uncharged alkyl imine (Fig. 1E). In turn, this addition step forms a neutral aminyl radical, which undergoes HAT with the silane reagent. The reaction exhibits a good scope across the three components and offers a practical process for the synthesis of a wide range of α -branched secondary alkylamines. Furthermore, we demonstrate how the reaction can be adapted to generate saturated nitrogen heterocycles, to enable selective alkylation of primary over cyclic secondary amines, and to effect telescoped multicomponent processes to functionally and structurally diverse α -branched secondary alkylamine derivatives. This work substantially expands the scope of carbonyl

alkylative amination towards its establishment as a general strategy for alkylamine synthesis.

Results and discussion

Beginning with the reaction conditions developed for CAA to form tertiary alkylamines,^{16a} we investigated the synthesis of α -branched secondary alkylamines by irradiating a dichloromethane solution of benzylamine (**1a**, 1 equiv.), hydrocinnamaldehyde (**2a**, 1.2 equiv.) and 2-iodopropane **3a** (3 equiv.) with a 40 W blue LED in the presence of $(\text{Me}_3\text{Si})_3\text{Si-H}$ (2 equiv.), TBSOTf (2 equiv.) and 4 Å MS. These conditions produced a complex mixture of degradation products, and none of the desired α -branched secondary amine **4a** was detected by ¹H NMR analysis of the crude reaction mixture (entry 1, Table 1). Surprisingly, when TBSOTf was omitted, **4a** was formed in 11% assay yield (entry 2). Assuming formation of an iminium ion to be a requirement for effective product formation (see Fig. 1C) we subsequently conducted a screen of acid additives, the key results of which are presented in Table 1. The use of 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) significantly improved the yield of **4a**, as did the use of trimethylsilyl chloride (TMSCl) (entries 3 and 4).^{18,19} The combination of these two additives gave **4a** with an assay yield of 52%, which proved to be optimal for this combination of amine and aldehyde.

To our surprise, changing linear aldehyde **2a** to the α -branched aldehyde cyclohexanecarboxaldehyde (**2b**) resulted in a greatly enhanced yield of the corresponding α -branched secondary amine **4b** in the absence of any additive (entry 6), highlighting a significant difference in the reactivity of structurally distinct carbonyls. The use of TBSOTf, again, had a detrimental effect on the reaction and, in contrast to the case of **2a**, so did the addition of TMSCl (entries 7 and 9). The addition of HFIP gave a small boost in the yield (entry 8).

Table 1 Selected optimisation for carbonyl alkylative amination

Entry	R	Additive	Assay yield ^a (%)
1	(CH ₂) ₂ Ph	TBSOTf (2.0 equiv.)	0
2	(CH ₂) ₂ Ph	None	11
3	(CH ₂) ₂ Ph	HFIP (2.5 equiv.)	29
4	(CH ₂) ₂ Ph	TMSCl (2.0 equiv.)	37
5	(CH ₂) ₂ Ph	HFIP + TMSCl	52 (41)
6	<i>c</i> -C ₆ H ₁₁	None	88
7	<i>c</i> -C ₆ H ₁₁	TBSOTf (2.0 equiv.)	74
8	<i>c</i> -C ₆ H ₁₁	HFIP (2.5 equiv.)	91
9	<i>c</i> -C ₆ H ₁₁	TMSCl (2.0 equiv.)	78
10	<i>c</i> -C ₆ H ₁₁	HFIP + TMSCl	97 (86)

^a Assay yield determined by ¹H NMR using 1,1,2,2-tetrachloroethane as internal standard. Yield of isolated product shown in parentheses.



of the steric hindrance in both α -tertiary primary amine and α -branched dialkyl ketone components, which may preclude the incorporation of more delicate functionality. Finally, we found that Hantzsch dihydropyridine and steroid-derived alkylamine-containing pharmaceuticals were effective substrates for the CAA reaction, delivering the corresponding products in good yield (**4p–q**). It is particularly notable that the CAA reaction tolerates the presence of unprotected protic functionality (**4d**, **4i**, **4j**, **4p**) which would be incompatible with organometallic approaches to these structures.

Next, the scope of the reaction in the aldehyde component was examined using benzylamine (**1a**) in combination with isopropyl iodide (**3a**, Fig. 3). The CAA reaction accommodated the use of alkyl-substituted aldehydes featuring α -branching (**4r–v**) and could incorporate useful functionalities. The successful transformation of an aldehyde containing a cyclopropyl motif to the expected amine product (**4v**) proceeded without any products arising from β -scission of the strained ring, suggesting that the reaction is unlikely to proceed *via* an α -amino radical intermediate.²⁰ A series of benzaldehydes also performed well in the CAA reaction (to **4w–y**). Although aryl iodides can undergo halogen-atom transfer with the silyl radicals generated under our reaction conditions, reaction with alkyl iodides is generally faster;²¹ α -branched secondary amine product **4y** derived from 3-iodobenzaldehyde could be obtained in good yield with the aryl iodide moiety intact. Products containing Lewis-basic heterocycles could be readily accessed in good yields through the use of heteroarene-derived aldehydes (**4z–aa**) with HFIP as co-solvent. Unbranched aldehydes were generally poor substrates when using benzylamine

as the amine (entries 1–5, Table 1) and we currently do not have an explanation for this phenomenon. However, while evaluating the scope in the amine component, the performance of unbranched aldehydes was markedly improved when α -branching was present in the amine (*e.g.* **4j–l**, **4n–o**), suggesting a subtle steric effect is at play. Accordingly, with 4-amino-tetrahydropyran (**1b**) as the amine, product **4ab** containing a remote alkene was formed from (\pm)-citronellal in excellent yield. The use of 4-pentenal as the aldehyde provided α -branched secondary amine **4ac**, and no products derived from radical 5-*exo*-trig cyclisation were detected. This result contrasts to our previous study^{16b} and suggests that, under the present conditions, the isopropyl radical adds to imine **Int-I** to form neutral aminyl radical **Int-II** (Fig. 4), rather than proceeding *via* cationic intermediates (Fig. 1C). Performing the same reaction in the presence of 2 equivalents of TMSCl led to the formation of pyrrolidine product **4ac'** in addition to **4ac**. Pyrrolidine **4ac'** presumably arises from radical addition to iminium ion **Int-III** to form aminium radical cation **Int-IV** which, in contrast to **Int-II**, cyclises with a rate comparable to that of hydrogen atom transfer from the silane reductant.²² ¹H and ¹³C NMR studies suggest that iminium ion **Int-III** is formed quantitatively from imine **Int-I** in the presence of 2 equiv. TMSCl (see ESI†), lending further support to the involvement of two distinct mechanistic pathways. Moreover, HFIP is not required to promote radical addition to the neutral imine (entry 6, Table 1). To the best of our knowledge, the intermolecular addition of alkyl radicals to non-activated, uncharged, alkyl-substituted imines, has not previously been reported.¹⁵



Fig. 3 Scope of the aldehyde component in CAA to α -branched secondary alkylamines. ^a 4 : 1 CH_2Cl_2 /HFIP used as solvent. n.d. = not determined.





Fig. 4 Evidence for distinct mechanistic pathways. Conditions as Fig. 3 with and without TMSCl. Isolated yields. Values for rate constants taken from ref. 22e and given as $k_{\text{HAT}}/\text{M}^{-1} \text{ s}^{-1}$ and $k_{\text{cycl.}}/\text{s}^{-1}$. THP = 4-tetrahydropyranyl.

The scope in the alkyl iodide component was explored using benzylamine (**1a**) in combination with hydrocinnamaldehyde (**2a**) or cyclohexanecarboxaldehyde (**2b**) (Fig. 5). Linear alkyl fragments derived from primary alkyl iodides could be added to the *in situ*-generated imine intermediates to form a selection of α -branched secondary alkylamines displaying a variety of functionality in generally good yields (**4ad–4ak**). In these cases, we found the addition of two equivalents TMSCl to be beneficial—we speculate that this effect originates from the lower nucleophilicity of primary alkyl radicals, wherein full

protonation (by *in situ*-generated HCl) of the intermediate aldimine to generate a more electrophilic species is advantageous.

Methyl iodide was productive in this process, but the yield of the amine product (**4ad**) was low and proved inseparable from a reductive amination by-product. By products of a formal reductive amination were commonly observed in low-yielding reactions; several possible mechanisms for their formation are provided in the ESI.† We were pleased to find that the fluoromethyl radical (derived from fluoriodomethane) engaged in effective radical addition under these conditions, giving β -fluoroamine **4ah** in synthetically useful yield.^{16c} A C–Cl bond was retained through the reaction to deliver **4ai**, which contains an electrophilic functional handle suitable for further elaboration, and use of an alkyl iodide derived from ethylene glycol provided protected γ -amino alcohol **4aj**. Pleasingly, incorporation of a ketone into the iodide component, which could theoretically compete with the aldehyde in the condensation step, resulted in the formation of aminoketone product **4ak** in good yield. Cyclic secondary alkyl iodides of varying ring sizes and substitution were also good substrates (forming **4al–am**) and even tertiary alkyl iodides generated the hindered amine products (**4an–ao**) in good yield. As observed in the scope of the amine and aldehyde components, classical reductive amination methods to form **4an–ao** would be challenging due to the difficulty in performing condensations at hindered ketones. Although a range of alkyl iodides are competent in this CAA reaction, our studies highlighted this as the component having the greatest impact on the success of the reaction. Specifically, the reaction is sensitive to the nucleophilicity of the carbon-centred radical; less nucleophilic radicals (such as primary

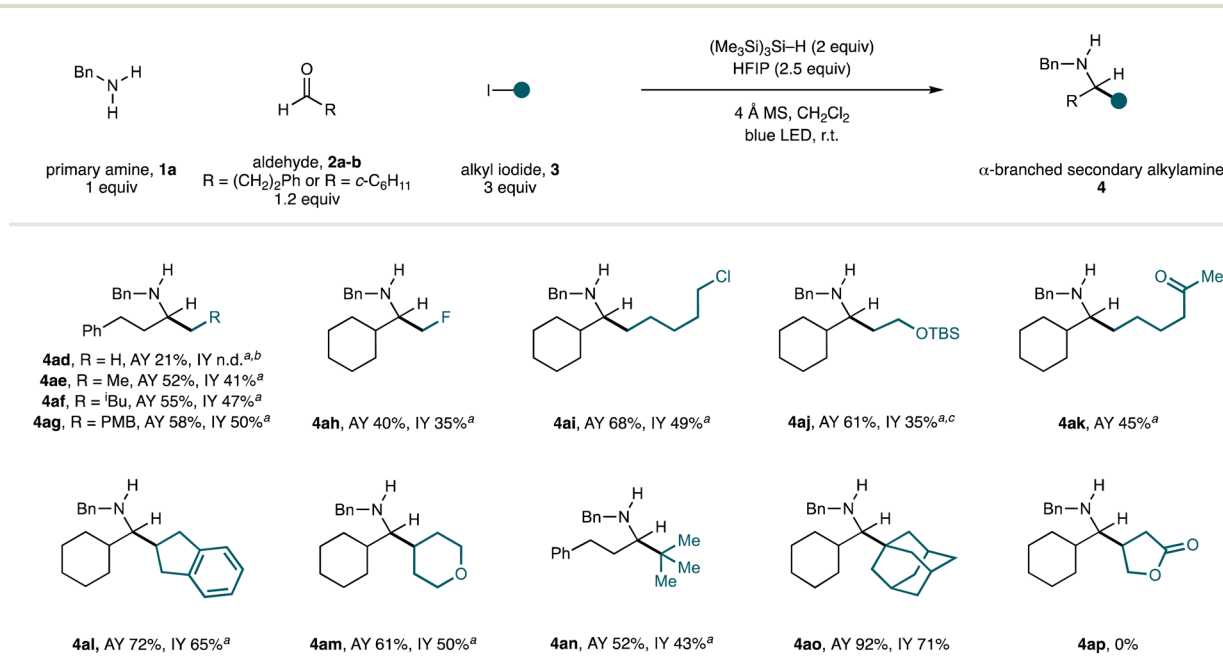


Fig. 5 Scope of the alkyl iodide component in CAA to α -branched secondary alkylamines. ^a TMSCl (2 equiv.) used as an additive. ^b It was not possible to separate **4ad** from the reductive amination side-product. ^c 13 mol% ethyl 2-methyl-2-iodopropionate used as additive. PMB = 4-methoxybenzyl. n.d. = not determined.



radicals and/or those bearing proximal electron-withdrawing groups), lead to reductive amination being observed as a significant by-product.

Given the efficiency of this visible-light-mediated CAA process, we questioned whether deployment of an alkyl iodide containing a tethered leaving group might enable a subsequent cyclization to form α -substituted N-heterocyclic frameworks in a multicomponent fashion. Specifically, after the CAA process, cyclization *via* displacement of a pendent chloride would generate a cyclic amine bearing N-substitution controlled by choice of amine, α -substitution controlled by choice of aldehyde, and ring size controlled by choice of the chloroalkyl iodide reagent. The ability to obtain α -branched N-heterocycles directly from feedstock amines and aldehydes with a programmable ring size dictated by choice of a commercial bifunctional lynchpin would represent a valuable approach that is complementary to existing methods. Accordingly, the CAA reaction of *p*-anisidine, 4-fluorobenzaldehyde and chloriodomethane (5a) successfully delivered β -chloro-amine 6a, and heating this compound in the presence of ^tBuOK for 30 min effected cyclisation to give the α -branched aziridine 7a in good yield (Fig. 6A). Chromatographic

purification of the intermediate chloro-amines was not required, although we observed higher yields when removing excess silane, alkyl iodide and aldehyde by strong cation exchange (SCX) filtration before performing the cyclisation. The use of 1-chloro-3-iodopropane (5b) delivered pyrrolidines 7b and 7c directly after basic aqueous workup without the need for a separate cyclisation procedure, reflecting the facile 5-*exo* ring-closure of saturated 5-membered rings. Piperidine 7d was obtained by heating ϵ -chloroamine CAA product 6d in the presence of base and sodium iodide in acetonitrile for 2 h. We note the high yields ($\geq 70\%$) of the CAA reaction when using functionalised alkyl iodides 5a–c with amine 1c and benzaldehydes, demonstrating that consistently high efficiency can be achieved with challenging alkyl iodides under our conditions with favourable amine and aldehyde coupling partners.

We also recognized that the leaving group need not be confined to the alkyl iodide component, and that the same annulation strategy should be effective with the aldehyde component carrying the chloride leaving group and the alkyl iodide component carrying the eventual α -substituent. A reaction using primary alkylamine 1d, 5-chloropentanal (2e), and



Fig. 6 Preliminary scope of chloro-alkyl iodides in the application of carbonyl alkylative amination to α -branched saturated N-heterocycles. (A) Leaving group in alkyl iodide. CAA conditions given for the formation of 7b and 7c also apply to the formation of 6a and 6d. ^a 4 : 1 CH₂Cl₂/HFIP used as solvent. (B) Leaving group in aldehyde.





Fig. 7 (A) TMSCl enables selective functionalization of primary amines in the presence of secondary amines. (B) Selective N-alkylation of diamines using CAA. (C) Selective functionalization of diamine **9a** to effect a formal four-component coupling.

isopropyl iodide followed by cyclisation of the ϵ -chloro-amine CAA product provided α -branched piperidine **7e** in 64% yield over two steps (Fig. 6B). These results suggest that a straightforward and general multicomponent approach to saturated nitrogen heterocycles may be possible with further optimization, and studies in this regard are ongoing and will be reported in due course.

A longstanding challenge in amine synthesis has been the development of alkylation processes that are selective between primary and secondary amines.²³ With this in mind, we questioned how a molecule containing both a primary and a secondary amine would react under the new conditions. Accordingly, we submitted 4-aminomethylpiperidine (**8a**) to the

HFIP-mediated CAA reaction with cyclohexanecarboxaldehyde (**2b**) and isopropyl iodide (**3a**) and were surprised to find that only trace quantities of product arising from the CAA reaction (at either amine) could be observed (Fig. 7A). Given the effectiveness of TMSCl as an additive in the main substrate scope, we also evaluated the reaction in the presence of two equivalents of TMSCl. Remarkably, ¹H NMR analysis of the crude reaction mixture appeared to show the formation of a single product in 87% assay yield. While we were able to isolate diamine **9a** in low yield (see ESI[†]) we were unable to find purification conditions that provided this compound in a yield commensurate with the assay. However, selective protection of the piperidine nitrogen as the Boc-carbamate gave the corresponding mono-Boc



diamine (Boc-9a), which could be isolated in 66% yield *via* chromatography on neutral alumina (Fig. 7B). As such, all diamines generated through this reaction were isolated as their mono-Boc derivatives. Although analysis of the crude CAA reaction mixture by ¹H NMR shows a remarkably clean reaction profile, analysis by LCMS elucidates that the reaction is not perfectly selective, and by-products derived from reductive amination and CAA reactivity can be observed (see ESI† for details). Nonetheless, the fact that products derived from a single CAA reaction at the primary amine can be isolated from the reaction mixture in yields typically exceeding 50% demonstrates a significant bias for the formation of these products. At the present stage of development, the origin of this unexpected selectivity remains unclear; several mechanistic possibilities are discussed in the ESI.†

The selective reactivity of the starting diamine was replicated over several combinations of aldehyde and alkyl iodide to form the desired products 9b–f with a scope reflecting that of the standard reaction: heterocyclic (9b), aromatic (9c) and acyclic (9d) aldehydes could be incorporated, as could primary (9e) and tertiary (9f) alkyl iodides (Fig. 7B). This selectivity could be extended to a diamine containing a benzylamine as the primary amine and a piperidine as the secondary amine, with the CAA reaction taking place selectively at the benzylamine nitrogen (9g). A diamine containing a benzylamine as the primary amine and a pyrrolidine as the secondary amine also reacted selectively at the benzylamine nitrogen (9h), however, a challenging purification led to a diminished isolated yield. A limitation of this method is the necessity of a cyclic secondary amine to impart selectivity: diamines containing acyclic secondary amines reacted unselectively (see ESI† for details). However, some selectivity was observed in a sterically biased system, and compound 9i was obtained in a good assay yield. Furthermore, we note that the use of α -branched aldehydes is required to impart this primary-over-cyclic-secondary amine reactivity; use of unbranched aldehydes resulted in complex mixtures. Finally, given our ability to selectively protect the cyclic secondary amine in the presence of the acyclic α -branched secondary amine derived from the CAA reaction, we questioned whether it might be possible to selectively functionalize the cyclic amine to achieve a formal four-component coupling to complex diamine-derived products. Accordingly, we heated 9a (obtained from SCX filtration of the crude CAA reaction mixture) to 100 °C in the presence of a heteroaryl electrophile (Fig. 7C). We were pleased to find that S_NAr-type *N*-arylation took place exclusively at the piperidine nitrogen, providing 9j in 69% yield after chromatography. We believe that this four-component coupling demonstrates a powerful approach to the rapid assembly of complex nitrogen-containing scaffolds through the modular incorporation of commercial building blocks.

Conclusions

In summary, we have developed a visible-light and silane-mediated carbonyl alkylative amination method for the synthesis of α -branched secondary alkylamines from readily available primary alkylamines, aldehydes and alkyl iodides. This

multicomponent protocol exhibits a good scope and tolerates a wide range of functional groups on all the three components. Although the key silane reagent is used in excess, it is relatively cheap and its by-products easy to remove, representing an advantage compared to the stoichiometric reductants (such as Hantzsch ester) that are commonly used in catalytic visible-light-mediated protocols. Further synthetic utility of the new method is demonstrated through a one-pot synthesis of saturated nitrogen-containing heterocycles, the synthesis of which would require multi-step routes using established methods. The new carbonyl alkylative amination is also chemoselective in the reaction of primary amines over cyclic secondary amines and provides a rare example of selective *N*-alkylation of diamines, which remains an important challenge in chemical synthesis. Our mechanistic data suggest that alkyl radicals undergo efficient intermolecular addition to uncharged alkyl imines when using HFIP as the sole additive—a process that is rare, and possibly unique. Overall, the operationally straightforward CAA reaction provides a strategically distinct transformation for alkylamine synthesis that is complementary to—and in many cases, provides products that would be inaccessible *via*—carbonyl reductive amination. We believe this transformation will be of interest to practitioners of biologically-relevant molecule synthesis in academic and industrial settings.

Data availability

Data associated with this article, including experimental procedures and compound characterization, are available in the ESI.†

Author contributions

R. K. and M. J. G. conceived the project. M. A. S. and R. J. D. K. and B. R. conducted the experiments. M. A. S., R. J. D. K., B. R. and M. J. G. analysed the data. M. A. S. and M. J. G. wrote the manuscript.

Conflicts of interest

There are no conflicts to declare.

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