# Modular Synthesis of α-Branched Secondary Alkylamines via Visible-light-mediated Carbonyl Alkylative Amination

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**Abstract:** The development of methods for the assembly of α-branched secondary alkylamines 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 structural tolerance and limitations in each reaction component, we also report preliminary applications to the telescoped synthesis of α-branched N-heterocycles and a primary-selective N-alkylation protocol based on carbonyl alkylative amination. 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 distinct from established approaches.

## Introduction

Secondary alkylamines are one of the most commonly occurring functional motifs in small molecules that perturb biological processes.[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 straightforward, robust and modular preparations of secondary alkylamines remain a constant challenge to the synthetic organic chemistry community.[2,3] While catalytic methods are emerging for their synthesis, most notably, alkene hydroamination, photoredox-mediated reactions, hydrogenation, biocatalytic transformations, C–H activation, and others, the majority of secondary alkylamines are still prepared by carbonyl reductive amination (CRA) or N-alkylation.[4–13] A possible reason for this preference is that methods such as CRA 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.

The condensation of a primary alkylamine and a ketone adorned with alkyl substituents is usually reliable in forming a, herein termed, alkyl-imine, from which there are a plethora of reduction protocols to form the corresponding α-branched secondary alkylamine.[7] 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 CRA process. A potential solution to this problem could be realized via addition of a carbon nucleophile to an alkyl-aldimine rather than a hydride to the alkyl-ketimine; the steric features of the product α-branched secondary alkylamine could be partitioned between an aldehyde and the incoming carbon nucleophile rather than confined to the ketone unit alone. Despite almost 100 years of efforts 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.[5] Only when reactivity-augmenting auxiliary groups are deployed on either the amine or carbonyl component does an effective and general transformation result: organometallic additions to Ellman's *tert*-butanesulfinamide derivatives, for example, have become the benchmark for this type of reaction (Figure 1A).[14] Although one advantage of such auxiliaries is the opportunity to exert control over the stereochemistry at the newly-chiral α-amino carbon centre, they nonetheless suffer from the well-established drawbacks of auxiliary use, namely the requirement for installation and removal and associated issues with functional group compatibility, 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 significant challenge The main reason that organometallic additions to non-activated alkyl imines fail can be ascribed to two factors: 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. Most common organometallic reagents, with a few notable exceptions, are sufficiently basic to deprotonate the α-C–H bond in these alkyl-imine/iminium species and lead to the corresponding enamine; in contrast to their–

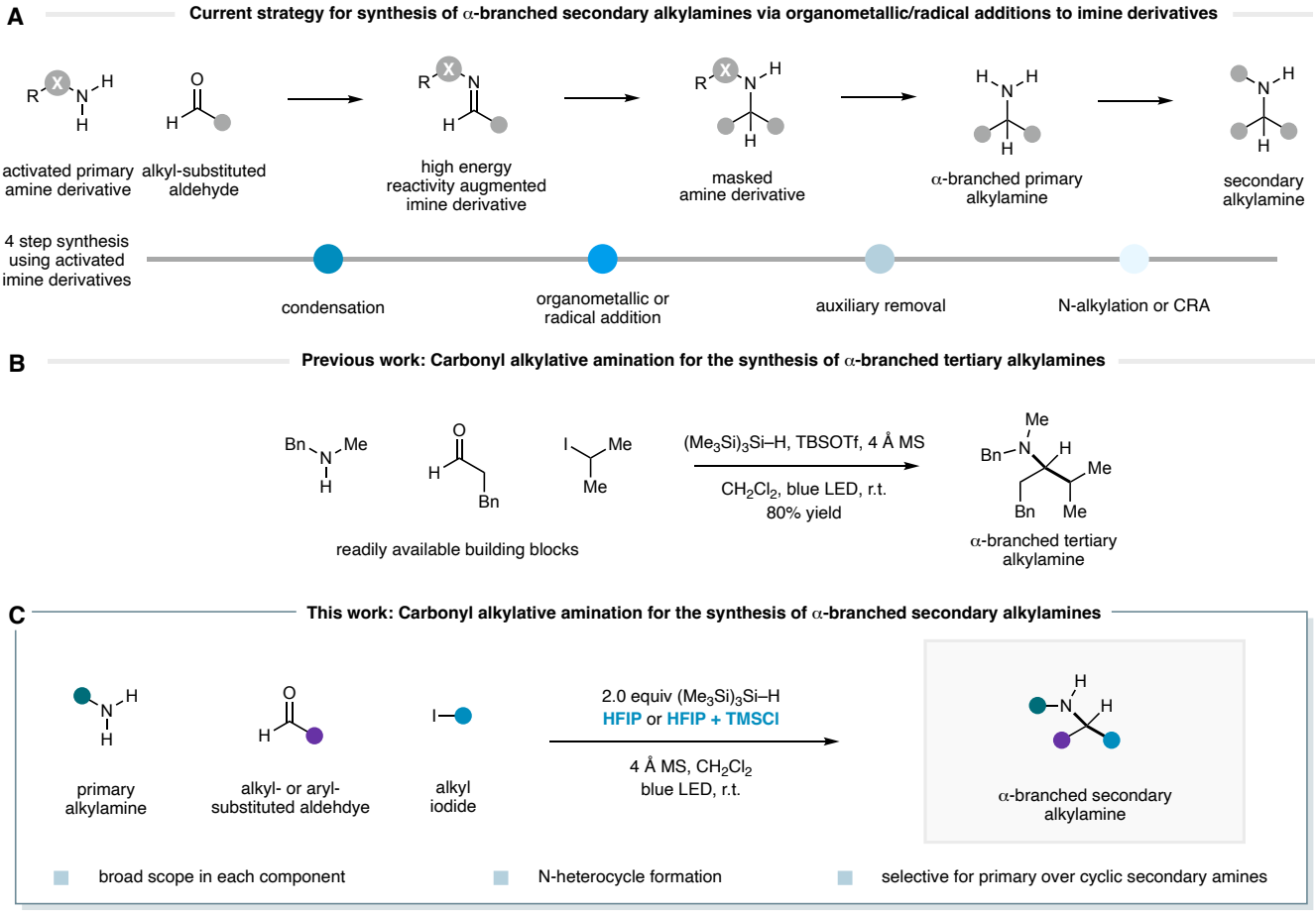



**Figure 1**. (**A**), Current strategies (auxiliary based methods which require protection and deprotection) to access α-branched secondary alkyl amines. (**B**) Carbonyl alkylative amination (CAA): a new strategy for the synthesis of α-branched tertiary alkylamines. (**C**) This work: CAA as a general method for highly complex and α-branched secondary alkylamines.

–carbon-oxygen congeners, the carbon-nitrogen double bond is insufficiently electrophilic for 1,2-addition to adequately compete with this deprotonation, thereby precluding the desired reaction.[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] The charge-neutral and non-basic nature of alkyl-radicals addresses the deprotonation problems associated with organometallic additions, however, their lower nucleophilicity often prevents efficient 1,2-addition to non-activated imines, and tailored activating substituents on the aldehyde or reactivity augmenting auxiliaries on the amine component are required. Furthermore, the nitrogen centred radical resulting from 1,2-addition to a C=N bond often needs stabilization by the N-substituent, meaning that auxiliary groups once again become prerequisite for an effective transformation.

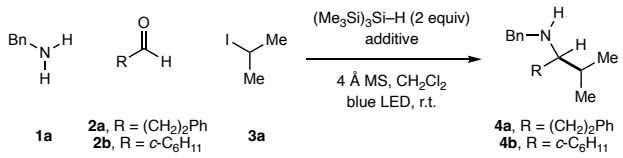
Our laboratory introduced a process called carbonyl alkylative amination (CAA) for the synthesis of tertiary alkylamines (Figure 1B).[16] In this reaction, visible-light and a silane mediate the addition of an alkyl-radical—generated from a non-activated alkyl iodide—to an unbiased and in situ generated all-alkyl iminium ion (formed from a secondary amine and aldehyde) to form a wide range of tertiary 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, following alkyl-radical addition to an iminium ion, enabled a rapid hydrogen atom transfer (HAT) to the resulting aminium radical cation to form a stable ammonium salt product. The addition of an alkyl-radical to a base-sensitive alkyl-substituted aldiminium ion represents a higher order variant of CRA and provides a particularly useful strategic bond forming reaction for the synthesis of α-branched tertiary alkylamines that would not be possible using the corresponding organometallic addition. While this reaction displayed excellent scope in the secondary amine, aldehyde and alkyl halide component, 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 (Figure 1C). This 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, and to enable selective alkylation of primary over cyclic secondary amines. This work substantially expands the scope

of carbonyl alkylative amination as a general strategy for alkylamine synthesis.

## Results and Discussion

Beginning with the reaction conditions of the CAA to form tertiary alkylamines,[16a] we investigated the synthesis of α-branched secondary alkylamines by irradiating (with a 40 W blue LED) a dichloromethane solution of benzylamine (1a, 1 equiv), hydrocinnamaldehyde (**2a**, 1.2 equiv) and 2-iodopropane (3.0 equiv) in the presence of $(Me_3Si)_3Si–H$ (2.0 equiv), TBSOTf (2.0 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). We subsequently conducted a screen of Lewis acids, the key results of which are presented in Table 1.




**1a** **2a**, R = $(CH_2)_2Ph$ **2b**, R = *c*-$C_6H_{11}$ **3a** **4a**, R = $(CH_2)_2Ph$ **4b**, R = *c*-$C_6H_{11}$

| Entry | R | Additive | Assay yield (%)[a] |
|---|---|---|---|
| 1 | $(CH_2)_2Ph$ | TBSOTf (2.0 equiv) | 0 |
| 2 | $(CH_2)_2Ph$ | none | 11 |
| 3 | $(CH_2)_2Ph$ | HFIP (2.5 equiv) | 29 |
| 4 | $(CH_2)_2Ph$ | TMSCl (2.0 equiv) | 37 |
| 5 | $(CH_2)_2Ph$ | HFIP + TMSCl | 52 (41) |
| 6 | *c*-$C_6H_{11}$ | none | 88 |
| 7 | *c*-$C_6H_{11}$ | TBSOTf (2.0 equiv) | 74 |
| 8 | *c*-$C_6H_{11}$ | HFIP (2.5 equiv) | 91 |
| 9 | *c*-$C_6H_{11}$ | TMSCl (2.0 equiv) | 78 |
| 10 | *c*-$C_6H_{11}$ | HFIP + TMSCl | 97 (86) |

**Table 1.** (**A**) Optimisation for carbonyl alkylative amination. [a]Assay yield determined by $^1H$ NMR using 1,1,2,2-tetrachloroethane as internal standard. Yield of isolated product shown in parentheses.

The use of 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) as an additive significantly improved the yield of **4a**, as did the use of trimethylsilyl chloride (TMSCl) (entries 3 and 4).[17,18] 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 the 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). 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). Interestingly, the combination of TMSCl and HFIP again proved optimal, providing **4b** in 97% assay yield which could be isolated in 86% yield after reverse phase chromatography on C18. Given the efficacy of both HFIP and TMSCl as additives in these studies, we evaluated the use of both additives for the majority of substrate combinations.

With optimal reaction conditions for the CAA process to form α-branched secondary amines in hand, we explored the scope of the transformation with respect to the primary amine component in combination with representative linear and α-branched aldehydes (**2a**-**b**) and isopropyl iodide (**3a**) (Figure 2). We report assay yields alongside isolated yields for all reaction products in order to accurately represent the reaction efficiency. A range of functionalized primary alkylamines were found to be compatible with the CAA process and produced generally good yields of α-branched secondary alkylamines (**4**) after isolation. Beyond the optimization substrate derived from benzylamine (**4b**), a series of linear primary alkylamines (**4c**-**e**), α-amino acids (**4f**), and amines containing electron-deficient (**4g**-**h**) and electron-rich heteroaryl (**4i**) groups all worked well in the CAA reaction. Throughout the course of our studies, we found that substrates featuring basic heterocycles typically benefitted from employing HFIP in co-solvent quantities (4:1 $CH_2Cl_2$/HFIP): imidazole-containing product **4h** was formed in quantitative yield under these conditions. The use of TMSCl was also of particular importance in this case; omission of TMSCl, or use of the standard equivalency of HFIP, resulted in low yields. Further observations of this CAA process include the accommodation of unprotected, potentially-competitive two-electron nucleophiles (**4c** – furan; **4i** – indole) in the primary alkylamine component. α-Branched primary amines were also good substrates and delivered the corresponding products that displayed α-branching on both substituents on the nitrogen atom of the secondary alkylamine (**4j**-**l**). An aromatic primary amine was also a competent substrate (**4m**).

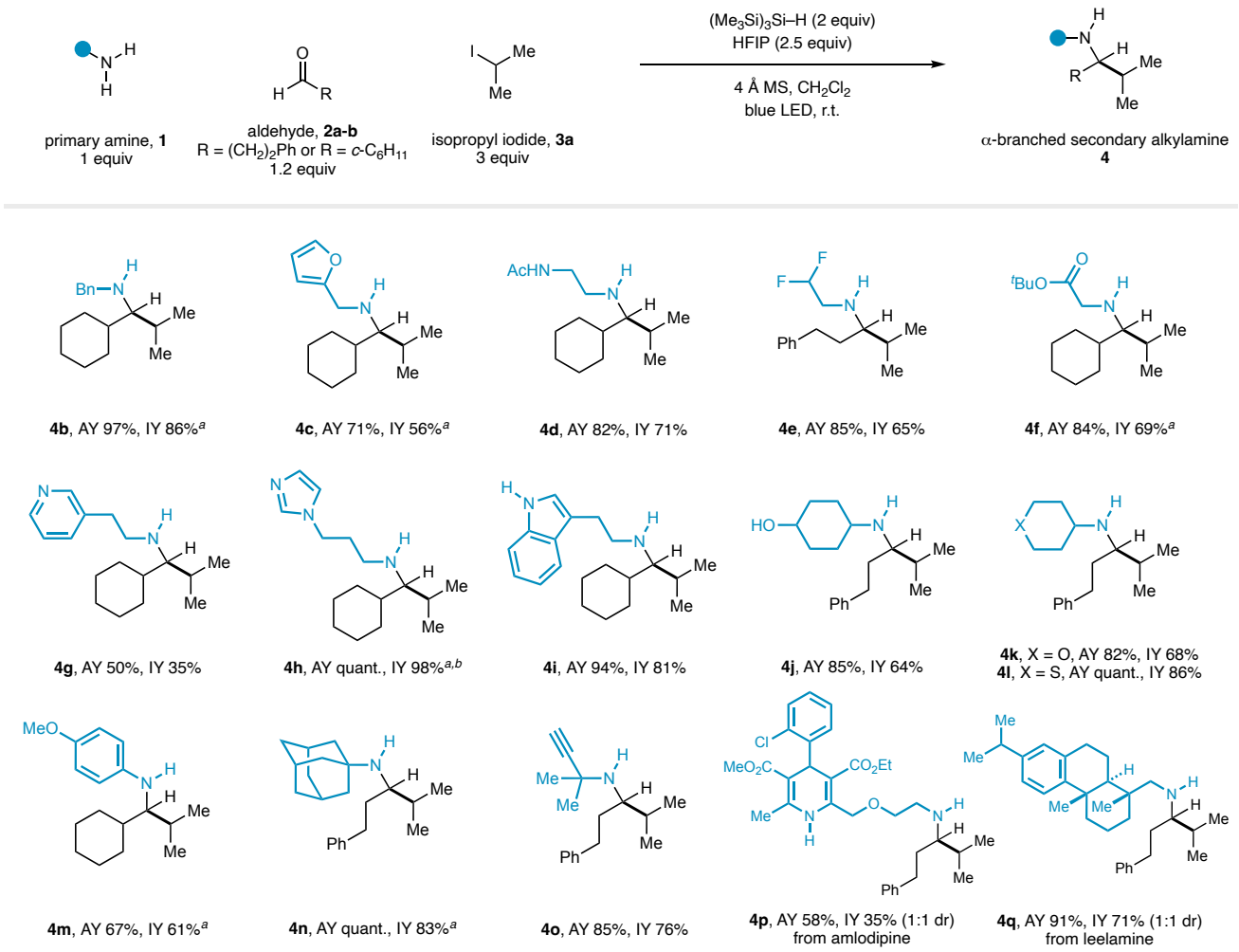



**Figure 2**. Scope of the primary amine component in CAA to α-branched secondary alkylamines. [a] TMSCl (2 equiv) used as an additive. [b] 4:1 $CH_2Cl_2$/HFIP used as solvent.

Importantly, α-tertiary primary alkylamines are competent substrates in this CAA reaction, the use of which forges extremely hindered secondary alkylamines in good yields (**4n-o**). The synthesis of this type of product via classical carbonyl reductive amination would require forcing conditions for the imine formation step because of the steric hinderance 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**, Figure 3). The CAA reaction was well-tolerant of alkyl aldehydes featuring α-branching (**4q-u**), and could accommodate 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, strongly suggesting that the reaction does not proceed via an α-amino radical intermediate. A series of benzaldehydes also performed well in the CAA reaction (to **4w-y**). Although aryl iodides are susceptible to reduction by the silyl radicals generated under our reaction conditions, reduction of alkyl iodides is generally faster; accordingly, we observed that α-branched secondary amine product **4y** derived from 3-iodobenzeldehyde could be obtained in good yield with the aryl iodide moiety intact.[19] 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. Although unbranched aldehydes were generally poor substrates when using benzylamine as the amine (entries 1–5, Table 1), while evaluating the scope in the amine component we noticed that the performance of these substrates was markedly improved when α-branching was present in the amine (e.g. **4j-l**, **4n-o**).

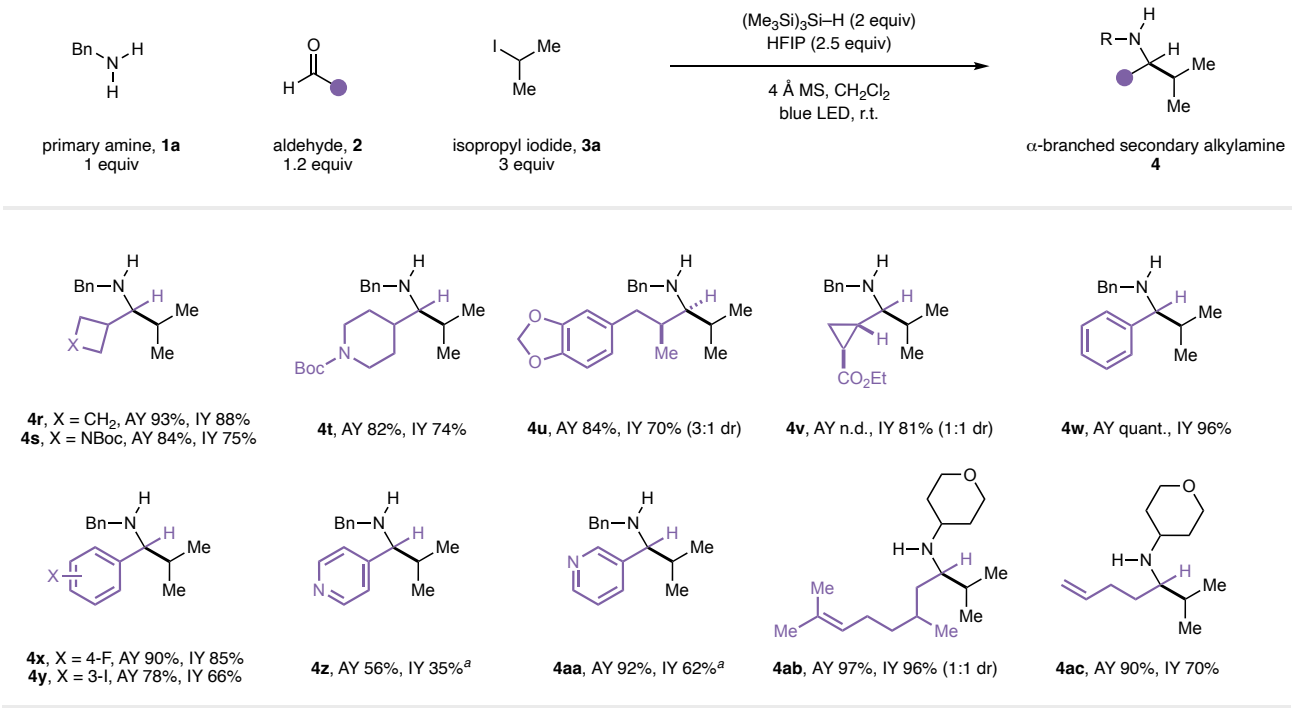



**Figure 3**. Scope of the aldehyde component in CAA to α-branched secondary alkylamines. [a] 4:1 $CH_2Cl_2$/HFIP used as solvent.

Accordingly, with 4-aminotetrahydropyran as the amine, product **4ab** containing a remote alkene was formed from (±)–citronellal in excellent yield. The use of 4-pentenal as the aldehyde provided α-branched secondary amine **4ac** as the sole product, with no products derived from radical 5-*exo*-trig cyclisation detectable. This result contrasts to our previous study[16b] and suggests that, under the present conditions, the isopropyl radical adds to an uncharged imine, rather than cationic iminium, C=N bond. Indeed, 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 a competing mechanism involving formation of an aminium radical cation (***Int-II***) which, in contrast to the corresponding neutral aminyl radical (***Int-I***), cyclises with a rate comparable to that of hydrogen atom transfer from the silane reductant (Figure 4).[20]

The scope in the alkyl iodide component was explored using benzylamine (**1a**) in combination with hydrocinnamaldehyde (**2a**) or cyclohexanecarboxaldehyde (**2b**) (Figure 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-aj**). 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, in our hands, proved inseparable from the reductive amination by-product. We were pleased to find that the fluoromethyl radical (derived from fluoroiodomethane) 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 assay yield, although we were unable to obtain a pure sample of this material. Cyclic secondary alkyl iodides of varying ring sizes and substitution were also good substrates (forming **4ak-al**) and even tertiary alkyl iodides generated the hindered amine products (**4am-an**) in good yield.

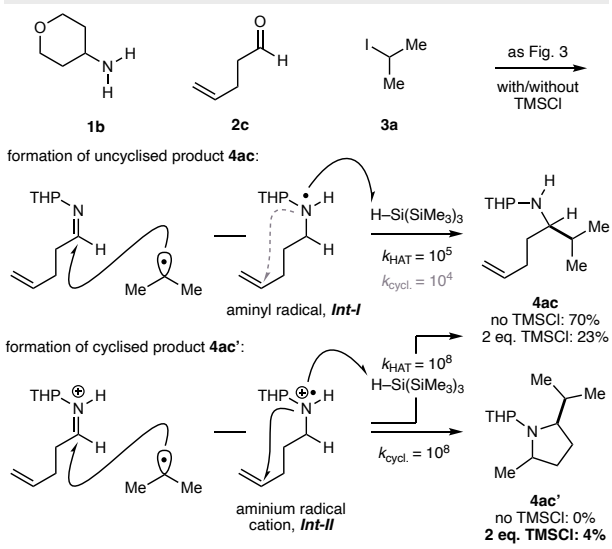



**Figure 4**. Formation of cyclised product **4ac'**.

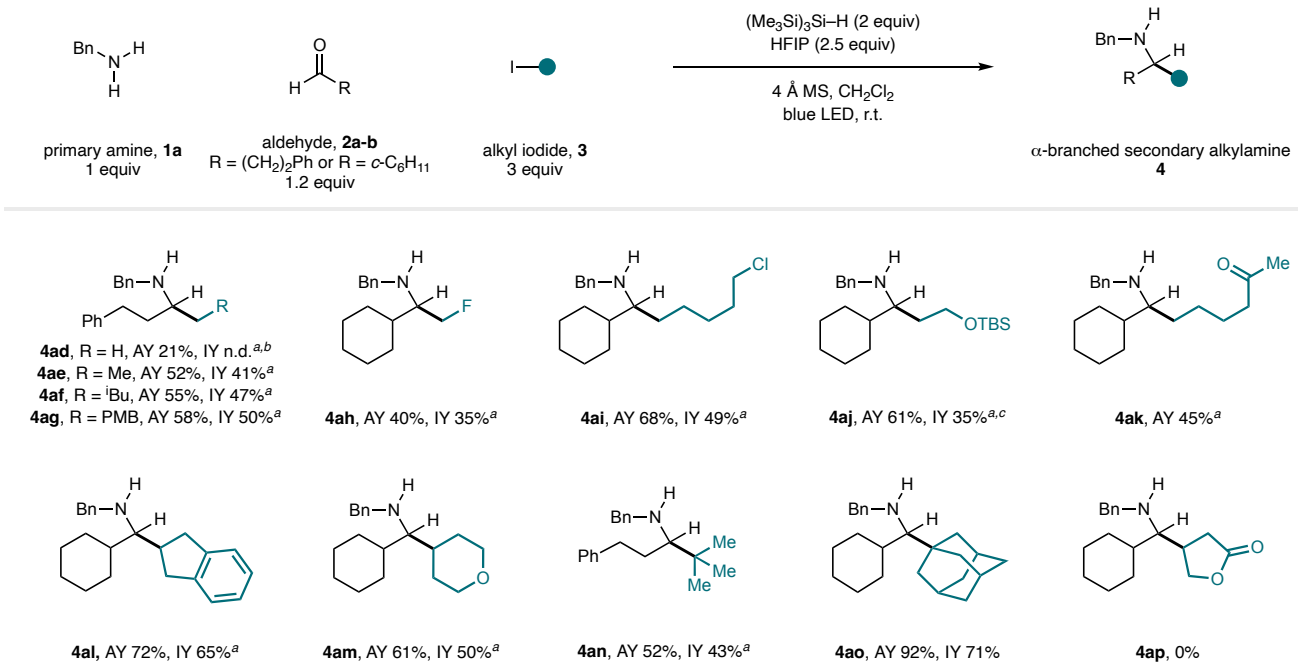



**Figure 5**. Scope of the alkyl iodide component in CAA to α-branched secondary alkylamines. [a] TMSCl (2 equiv) used as an additive. [b] It was not possible to separate **4ad** from the reductive amination side-product. [c] 13 mol% ethyl 2-methyl-2-iodopropionate used as additive. PMB = 4-methoxybenzyl.

As observed in the scope of the amine and aldehyde components, classical reductive amination methods to form **4an-o** 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; in the case of less nucleophilic radicals (such as primary radicals and/or those bearing proximal electron-withdrawing groups), reductive amination is observed as a significant by-product. For example, the use of 3-iodo-γ-butyrolactone gave exclusively the product of reductive amination; none of desired product **4ao** was observed.

Given the efficiency with which the α-branched secondary alkylamines could be assembled via this visible-light-driven 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 pendant 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. Evaluating this process using *p*-anisidine (**1b**), 4-fluorobenzaldehyde (**2c**) and chloroiodomethane (**5a**), we found heating the β-chloro amine CAA derivative **6a** in the presence of $^{t}$BuOK for 30 min gave the α-branched aziridine **7a** in good yield (Figure 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-chloro amine CAA product **6d** in the presence of base and catalytic sodium iodide in acetonitrile for 2 h. We note the high yields (≥ 70%) of the CAA reaction when using functionalised alkyl iodides **5a-c** with amine **1b** and aldehydes **2c** and **2e**, demonstrating that consistently high efficiency can be achieved with challenging alkyl iodides under our conditions with favourable amine and aldehyde coupling partners. 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 (**5a-c**) represents a valuable approach that is complementary to existing methods. Moreover, we 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. Indeed, a reaction using primary alkylamine **1c**, 5-chloropentanal (**2f**), and isopropyl iodide followed by cyclisation of the ε-chloro amine CAA product provided α-branched piperidine **7f** in 64% yield over two steps (Figure 6B). These results suggest that a straightforward and general multicomponent approach to saturated nitrogen heterocycles may be possible with further optimization—studies in this regard are ongoing and will be reported in due course.

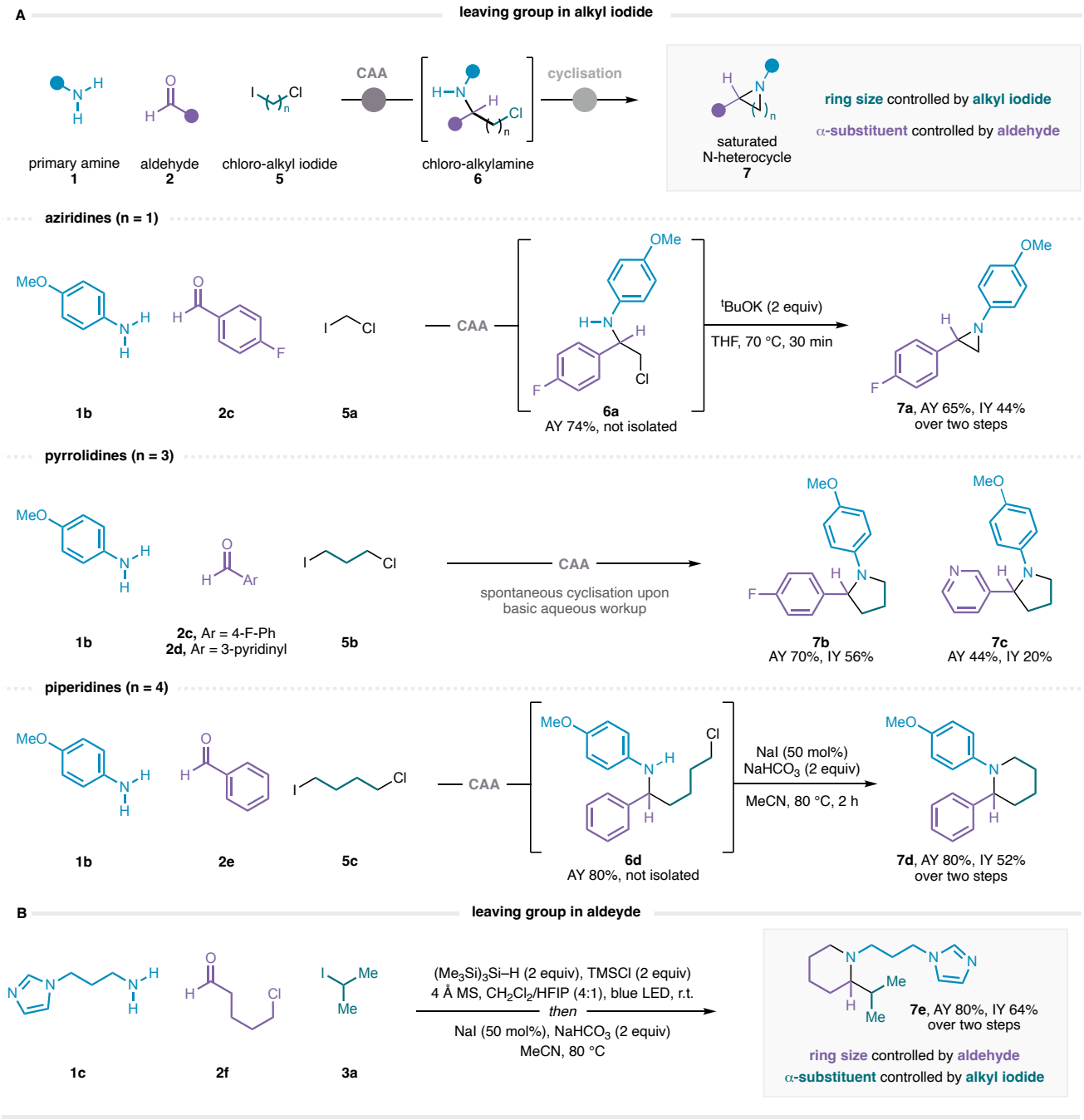



**Figure 6**. (**A**) Preliminary scope of chloroalkyl iodides in the application of carbonyl alkylative amination to α-branched saturated N-heterocycles. (**B**) Example of an alternative carbonyl alkylative amination strategy using 5-chloropentanal to generate α-branched piperidines.

A longstanding challenge in amine synthesis has been the development of alkylation processes that are selective between primary and secondary amines.[21] 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-aminomethylpiperidisne (**9a**) to the HFIP-mediated CAA reaction with cyclohexane carboxaldehyde (**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 (Figure 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, $^1$H 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 obtain pure diamine **10a** in low yield (see Supporting Information) we were unable to find conditions that provided **10a** 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-**10a**), which could be isolated in 66% yield via chromatography on neutral alumina (Figure 7B).

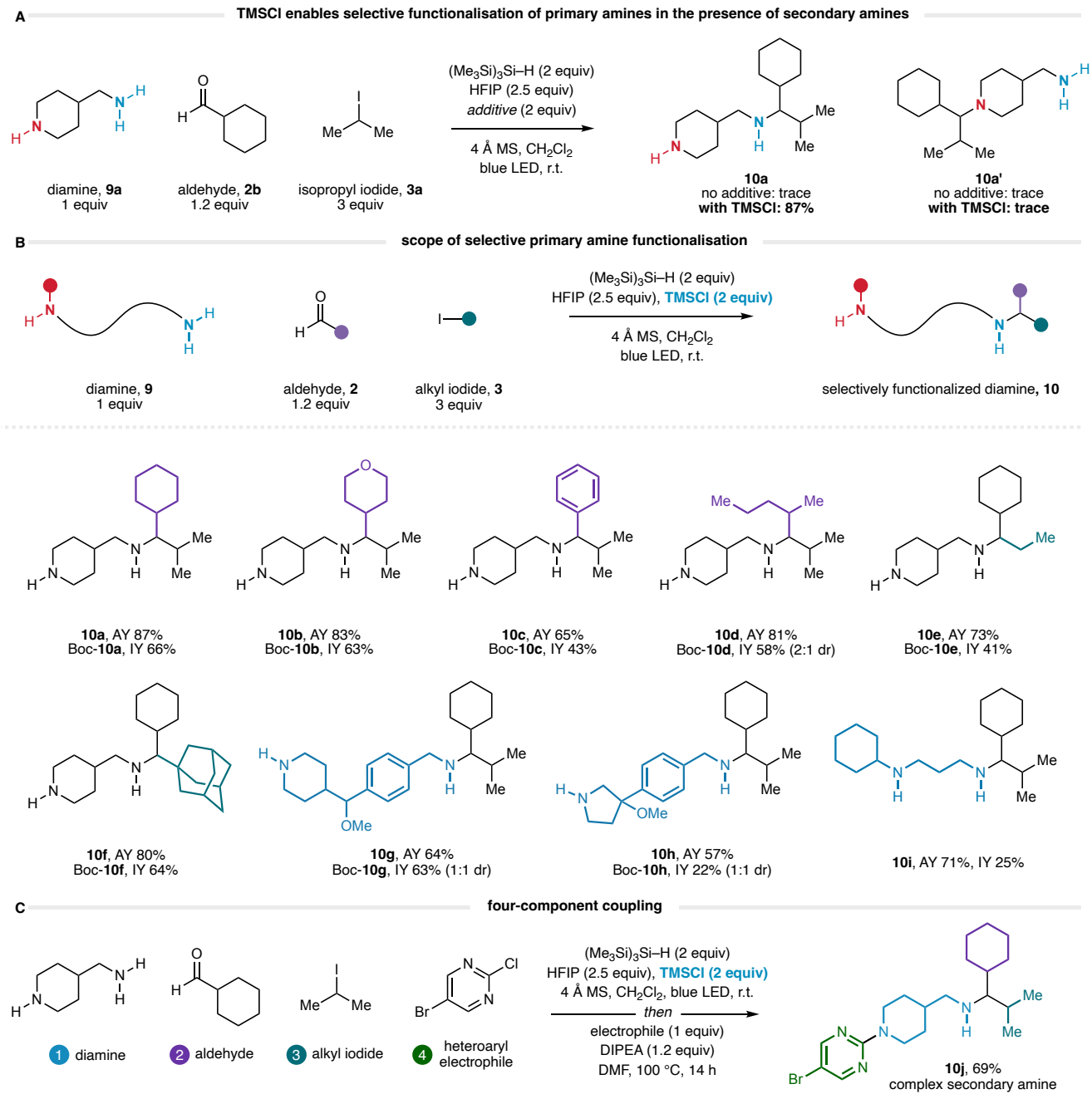



**Figure 7**. (**A**) TMSCl enables selective functionalization of primary amines in the presence of secondary amines. (**B**) Selective N-alkylation of diamines using CAA. (**C**) Selective functionalization of diamine **10a** to effect a formal four-component coupling.

As such, all diamines generated through this reaction were isolated as their mono-Boc derivatives. Although analysis of the crude CAA reaction mixture by $^1$H 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. 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; however, studies in this regard are ongoing and will be reported in due course. The selective reactivity of the starting diamine was replicated over several combinations of aldehyde and alkyl iodide to form the desired products **10b-10f** with a scope reflecting that of the standard reaction: heterocyclic (**10b**), aromatic (**10c**) and acyclic (**10d**) aldehydes could be incorporated, as could primary (**10e**) and tertiary (**10f**) alkyl iodides. We were pleased to find that 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 (**10g**). A diamine containing a benzylamine as the primary amine and a pyrrolidine as the secondary amine also reacted selectively at the benzylamine nitrogen (**10h**), 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. However, some selectivity was observed in a sterically biased system, and compound **10i** was obtained in a good assay yield. Furthermore, we note that the use of α-branched aldehydes is required in order 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 **10a** (obtained from SCX filtration of the crude reaction mixture) to 100 °C in the presence of a heteroaryl electrophile (Figure 7C). We were pleased to find that arylation took place exclusively at the piperidine nitrogen, providing **10j** 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.

## Conclusion

In summary, we have developed a visible-light and silane-mediated mediated carbonyl alkylative amination method for the synthesis of 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. 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. 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.

## Supporting Information

The authors have cited additional references within the Supporting Information.

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**Keywords:** Alkylamines • Imines • Radicals • Multicomponent • Heterocycles

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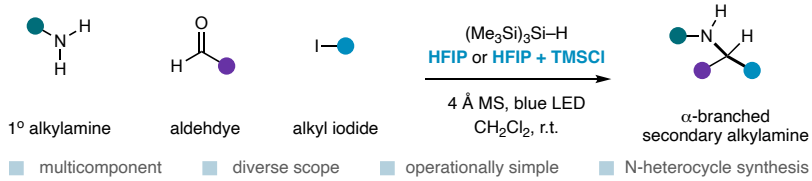
## Entry for the Table of Contents




We report a multicomponent method for the preparation of α-branched secondary alkylamines from readily available starting materials. In addition to exploring the scope in each component, we show that appropriately-functionalised starting materials can provide straightforward access to saturated N-heterocycles. We also report preliminary findings regarding a selective reaction at primary amines in the presence of cyclic secondary amines.

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