Modular synthesis of heterobenzylic amines via Carbonyl Azinylative Amination

Alex A. Rafaniello[†], Roopender Kumar[†] & Matthew J. Gaunt*

ABSTRACT

The synthesis of α-alkyl, α'-2-azinyl amines by addition of 2-heteroaryl-based nucleophiles to alkyl substituted iminium ion is typically a challenging synthetic transformation due to mismatched reactivities and competing deprotonation adjacent to the carbon-nitrogen double bond. Here, we report a solution to this problem through the development of a multicomponent coupling process wherein a putative 2-azinyl indium nucleophile, generated *in situ* from the corresponding 2-iodo heteroarene and indium powder, adds to an iminium ion that is also formed directly in the reaction. This modular and operationally straightforward carbonyl azinylative amination (CAzA) displays a broad scope, does not require a transition metal catalyst and only a metal reductant is needed to generate a reactive 2-azinyl nucleophile in the reaction. Beyond the addition to iminium ions, the 2-azinylation of polyfluoromethyl ketones to form the corresponding tertiary alcohols is also disclosed. Together, the products of these reactions possess a high degree of functionality, are typically challenging to synthesize by other methods, and contain motifs recognized as privileged in the context of pharmaceuticals and agrochemicals.

INTRODUCTION

Nitrogen-containing heteroarenes are present in 11 of the top 25 most frequently occurring ring systems in U.S. approved drugs.[1–2] Of these, Lewis basic azines, such as pyridines, pyrimidines, quinazolines and pyrazines, are some of the most prevalent structural units and share the unique properties that make this type of aromatic heterocycle an attractive component in drug molecules – namely, hydrogen bond-acceptor ability and the capacity to interact *via* nonpolar interactions.[1] Moreover, the nitrogen atom in azine ring systems can confer considerable improvement of key pharmacological parameters, including biochemical potency, binding affinity, aqueous solubility and metabolic stability.[2–4] The presentation of an azine feature connected through the 2-position to an alkylamine substituent – a so-called α-alkyl 2-azinyl amine – represents an attractive polar scaffold in the design of pharmaceutical and agrochemical candidates due to the density of polar functionality, multiple diversification points for analogue synthesis and a balance of C(sp^3) and C(sp^2) carbon frameworks. Accordingly, the α-alkyl 2-azinyl amine motif can be found in a variety of biologically and medicinally relevant molecules (Fig. 1A). For example, introduction of the α-amine moiety to a 2-alkyl-pyrimidine scaffold enabled improved physical properties and cell permeability for an inhibitor of human immunodeficiency virus type-1 (HIV-1) integrase, which led to the identification of a potentially clinically useful antiretroviral agent.[5] Despite broad interest in the α-alkyl 2-azinyl amine feature, the availability of surprisingly few general and concise methods for their preparation appears to have hindered their wider utilization.

Arguably, the most straightforward approach to this scaffold is *via* reductive amination of a 2-azine-substituted alkyl ketone. However, due to poor reaction kinetics in the condensation step and/or competitive enamine tautomerization, this

method can be capricious for many coupling combinations.[6] Moreover, 2-azine-substituted ketones are rarely readily available and require their own, often cumbersome, syntheses. Beyond this, most approaches to the synthesis of α-alkyl 2-azinyl amines can be divided into two generic classes of reaction that exploit one or two electron processes: (a) 1,2-additions of open- and closed-shell nucleophiles to activated 2-azinyl imines (Fig. 1B[i]),[7–13] and (b) coupling reactions of α-amino radicals with activated 2-azine derivatives (Fig. 1B[ii–iv]). While the former approach has enabled the synthesis of a range of α-alkyl 2-azinyl amine derivatives, these methods often require activation through the incorporation of a high energy auxiliary on the imine nitrogen atom in order to instil the required reactivity towards the nucleophile.[7,9–14] The incorporation and removal of this auxiliary adds two further steps to the route required to make the parent α-alkyl 2-azinyl primary amine by this strategy. Furthermore, these approaches often require preformation and isolation of the 2-azinyl imine species.

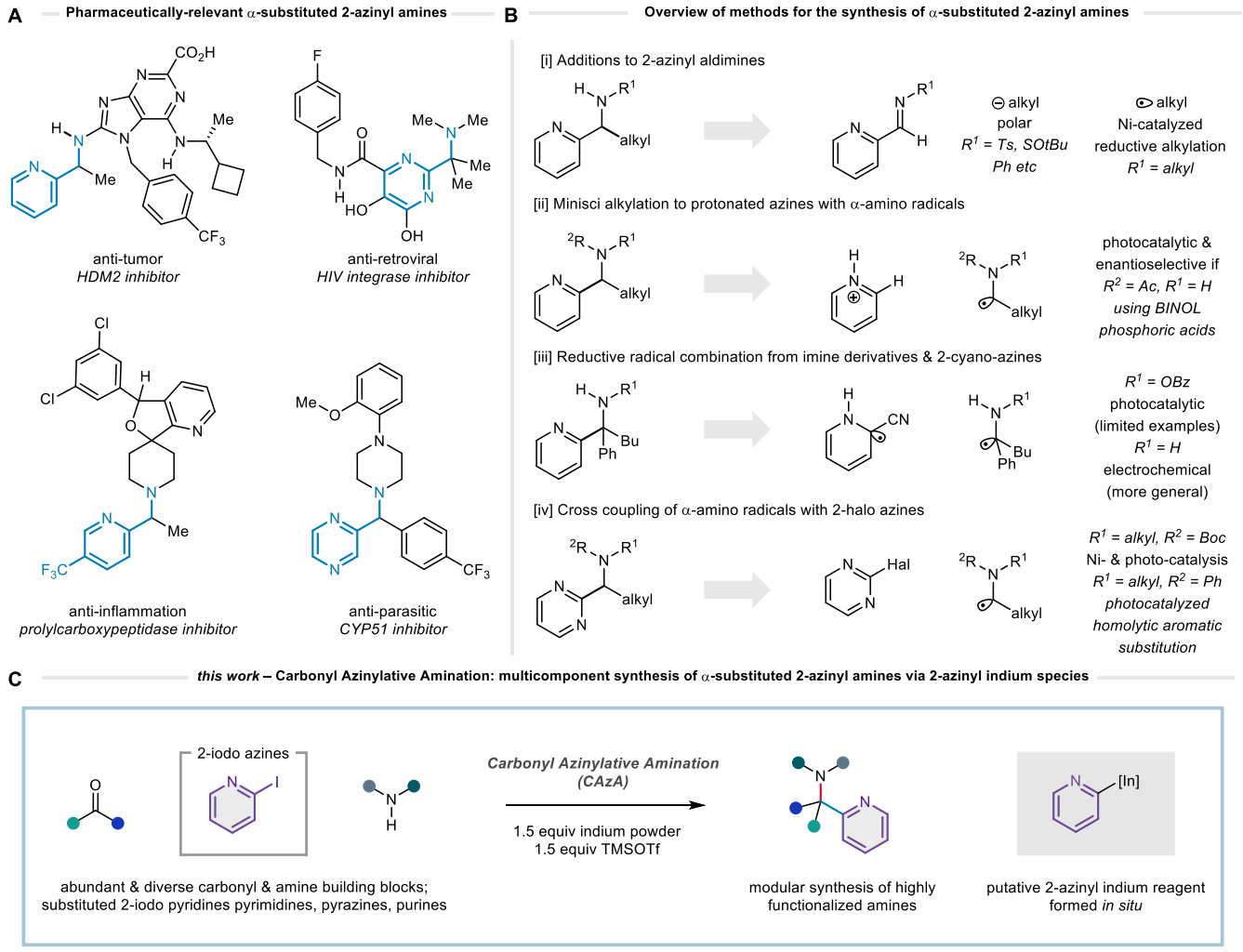


Figure 1. (**A**) Selected pharmaceutical compounds containing the α-heteroaryl amine motif. (**B**) Established approaches to the α-alkyl 2-azinyl amine scaffold. (**C**) Carbonyl Azinylative Amination: a straightforward modular strategy for the synthesis of α-alkyl 2-azinyl amines.

Despite these limitations, perhaps the best-in-class example of this strategy is the use of Ellman sulfinylimines, the 1,2-addition reactions of which displays a broad scope in aldimine and organometallic component and also provides an effective means for the synthesis of enantioenriched α-alkyl 2-azinyl amines.[8] Examples of analogous reactions that do not require the use of activating groups on the imine are scarce and display very specific substrate requirements, which

limits scope and utility of such reactions. Notable examples of 1,2-additions of alkyl radicals to non-activated 2-azinyl imines were reported by Bode and co-workers,[11–12] however these were limited to intramolecular examples for the synthesis of 2-azinyl piperidine or piperazine products. Reisman *et al.* have reported an efficient Ni-catalyzed reductive alkylation of pre-formed N-alkyl 2-azinyl imines, using secondary alkyl or benzyl halides and mediated by a stoichiometric metal reductant, which provided an effective preparation of a range of α-alkyl 2-azinyl secondary amines (Fig. 1B[i]).[9] A ligand centred radical on a Ni-coordinated imine complex is thought to combine with an alkyl radical, forming the N-alkyl 2-azinyl amine after decomplexation. 2-Azinyl-substituted imines, which typically react as electrophiles, could conceivably be used to access α-amino radical species *via* single electron reduction processes and coupled with electrophilic partners. While this appears as an attractive transformation for an umpolung synthesis of heterobenzylic amines, Dixon *et al.* demonstrated that the addition of a 2-pyridyl substituted α-amino radical to an activated alkene acceptor was particularly sluggish due to the electron-deficiency of the radical nucleophile.[14]

The second generic class of transformations includes those based on bond forming reactions between an activated 2-azine fragment and an α-amino radical. For example, variations on the Minisci reaction, wherein a net oxidative C–H functionalization of a protonated azine with an α-amino radical at the 2- or 4-position, have emerged for the assembly of the α-alkyl 2-azinyl amine scaffold.[15–19] Most notably, Phipps and co-workers have reported a series of powerful transformations that couple N-acetyl amino acid redox active esters or N-acetylated amines with a range of azines to form α-alkyl 2-azinyl N-acetyl amides through a BINOL-phosphoric acid and photocatalytic coupling reaction in good yields and with high enantioselectivity (Fig. 1B[ii]).[18–19] Rovis and co-workers showed that a limited number of 2-cyano pyridines undergo reductive coupling with a butyrophenone-derived oximes or NH-imines under photocatalytic or electrochemical conditions, respectively, to form α-phenyl, α'-butyl 2-pyridyl amines (Fig. 1B[iii]), although the yields were frequently low.[20–21] Finally, Doyle, MacMillan and co-workers have demonstrated the utility of visible-light mediated photocatalysis for the synthesis of α-azinyl pyrrolidines or morpholines from various 2-halo azines, *via* its merger with Ni-catalysis,[22–23] or by employing a homolytic aromatic substitution pathway (Fig. 1B[iv]).[24]

Despite the recent advancements (*vide supra*), there remain several strategic gaps in the synthetic chemist's toolbox for the general preparation of α-alkyl 2-azinyl amines. For example, it is surprising that the, apparently, straightforward addition of 2-azine organometallics, such as heteroaryl-Grignard or -lithium reagents, to non-activated imines has not been successfully exploited, a deficiency that is possibly due to the diminished nucleophilicity and frequent instability of these reagents.[25–26] There also remains a paucity of multicomponent processes that are capable of generating modular functionally and structurally complex variants of the pharmaceutically privileged α-alkyl 2-azinyl amine scaffold from readily available building blocks.

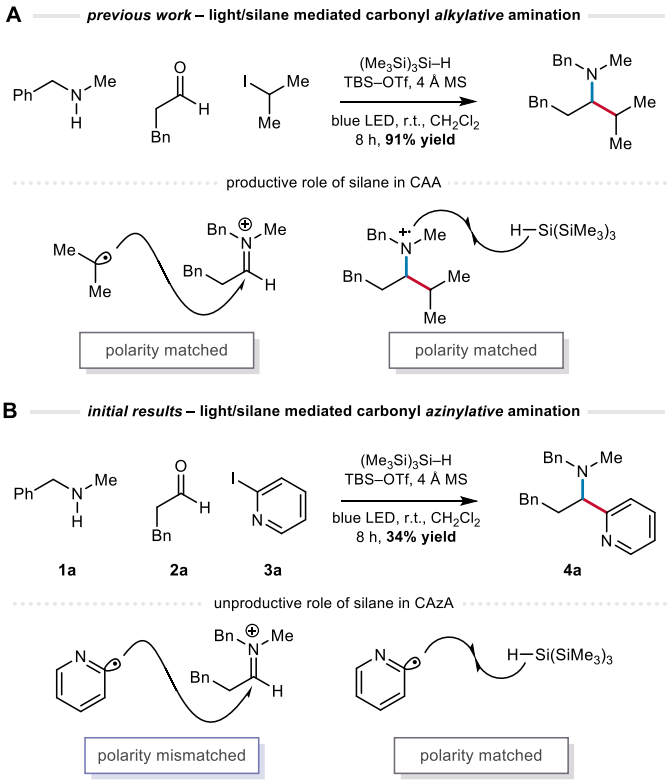
Herein, we report the development of an operationally straightforward and general multicomponent method that addresses some of the key strategic gaps in the synthesis of α-alkyl 2-azinyl amines (Fig. 1C). In this modular reaction, an iminium ion, which is generated *in situ* from an aldehyde and a secondary amine, is coupled with a 2-iodo azine *via* the intermediacy of a putative 2-azinyl indium nucleophile (also generated *in situ*). A broad range of tertiary amine products containing many pharmaceutically-relevant structural and functional features can be formed *via* these tandem C–N and C–C bond forming steps from abundant amine and carbonyl feedstocks and readily available 2-iodo azines. This work also reveals the underexplored utility of a 2-azinyl-anion equivalent that we believe manifests in the form of the organoindium species, and which is demonstrated through its reactions with other common synthetically versatile

functionalities. Considering the demonstrated importance and interest in nitrogen-rich scaffolds, we believe these methods will be of substantial interest to the synthetic community in both industrial and academic settings.

RESULTS AND DISCUSSION

Reaction Discovery and Optimization

In 2020, our group disclosed carbonyl alkylative amination (CAA) method for tertiary alkylamine synthesis (Fig. 2A).[27] Through this visible light-mediated process, a range of alkyl radicals add to *in situ* generated all-alkyl-iminium ions and the resulting aminium radical cation undergoes rapid hydrogen atom transfer (HAT) with a silane to form the tertiary alkylamine product, released after workup. This transformation allows for remarkably facile access to an array of complex amines from abundant and diverse building blocks and can be extended to the synthesis of α-tertiary amino acid derivatives and α-fluoromethyl tertiary amines.[28–29] Continuing the evolution of the generic CAA strategy, we speculated that leveraging 2-iodo azines, as precursors to heteroarene radical coupling partners, may be amenable to this photochemical protocol and provide a convenient means to generate α-alkyl 2-azinyl amines.



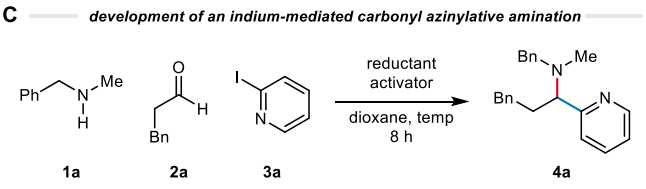


Table 1. Selective optimization for the multicomponent CAzA reaction

entry	reductant (equiv)	activator	temp. (˚C)	yield **4a** (%)[a]
1	Zn (1.5)	TMSOTf	r.t.	16
2	Zn (1.5)	TMSOTf	60	trace
3	Zn (2.0)	TMSOTf	r.t.	16
4	Zn (3.0)	TMSOTf	r.t.	24
5	In (1.5)	TMSOTf	r.t.	33
6	In (1.5)	TMSOTf	70	85 (67[b])
7	In (1.5)	TMSCl	70	trace
8	In (1.5)	TFA	70	20
9	In (1.5)	none	70	14
10	none	TMSOTf	70	0

[a]Yields of **4a** were determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as an internal standard. [b]Yield of isolated product **4a** after purification by silica gel chromatography.

Figure 2. (**A**) Tertiary alkylamine synthesis *via* visible-light & silane-driven Carbonyl Alkylative Amination (CAA). (**B**) Preliminary results for a visible-light & silane driven Carbonyl Azinylative Amination (CAzA) for the synthesis of α-alkyl 2-azinyl tertiary amines. (**C**) Selected optimization for the multicomponent carbonyl azinylative amination reaction.

We recognized that the generation of a 2-azinyl radical under the mild reaction conditions used for the alkyl radicals would be substantially more challenging due to the higher energy nature of the heteroaryl radical species. Indeed, our extensive preliminary studies were largely unsuccessful, with only a modest yield of the desired α-alkyl 2-azinyl amine **4a** obtained (Fig. 2B). In the proposed mechanism for the visible light-mediated CAA reaction tris(trimethylsilyl)silane [$(Me_3Si)_3Si–H$] fulfils a multifaceted role: it is integral to radical initiation, quenches the aminium radical cation on the amine nitrogen

atom after radical addition to the iminium ion and carries the radical chain through halogen atom transfer (XAT) with the alkyl iodide.[30] We speculated that the poor outcome of the CAzA reaction under these conditions was due to rapid, competitive hydrogen atom transfer (HAT) of the 2-pyridyl radical (BDE of pyridine ~ 100 kcal mol^{-1}) with $(Me_3Si)_3Si–H$ (BDE = 84 kcal mol^{-1}). To avoid the use of $(Me_3Si)_3Si–H$, and guided by the pioneering studies of Rieke on the formation of heteroleptic alkylzinc reagents,[31] we initially considered that a stronger single electron reducing agent might facilitate the formation of the desired 2-pyridyl radical from the parent 2-iodo pyridine. However, in line with the observations of Rieke, then subsequent reduction of the incipient heteroaryl radical with a second equivalent of a metal may lead to the corresponding 2-pyridyl organometallic species, which has not previously been explored in terms of its reactivity towards electrophilic all-alkyl iminium species, to the best of our knowledge.

Our initial experiments to probe this hypothesis focused on the use of zinc powder, without any further additives classically used to aid the generation of such reagents,[32] to form the corresponding pyridyl-zinc iodide (Fig. 1C). We were pleased to observe that stirring a mixture of *N*-methylbenzylamine (**1a**), hydrocinnamaldehyde (**2a**) and 2-iodopyridine (**3a**) in a dichloromethane solution with 1.5 equivalents of zinc powder and trimethylsilyl trifluoromethanesulfonate (TMSOTf, to facilitate iminium ion formation) at room temperature afforded α-substituted 2-pyridyl amine **4a** in 16% assay yield (AY), as determined by ^{1}H NMR spectroscopy (Table 1, entry 1). Raising the temperature of the reaction resulted in only trace amounts of the desired product being formed (entry 2) and no significant benefit was observed when changing the equivalents of Zn (entries 3 & 4). We noted that the use of indium powder, whose first ionization potential of +5.8 eV indicates a good single electron reductant (compare with that of Na [+5.1 eV] and Zn [+9.4 eV]),[33] gave comparable yields to those obtained with zinc (entry 5, also see Supplementary Information, Table S1), and when the reaction was stirred at elevated temperature a substantially higher yield of **4a** was obtained (see Supplementary Information, Table S2). Following further exploration of the reaction parameters around this lead result, a set of optimal conditions were identified that consistently produced high assay yields of the desired amine **4a** (entry 6): vigorous stirring of a 1,4-dioxane solution containing amine **1a** (1 equiv.), aldehyde **2a** (1.5 equiv.), 2-iodo pyridine **3a** (2 equiv.), indium powder (1.5 equiv.) and TMSOTf (1.5 equiv.) at 70 ˚C for 8 h afforded amine **4a** in 85% assay yield, which after isolation and purification by silica gel chromatography provided 67% yield of the desired product. A cursory screen of alternate Lewis and Brønsted acids revealed a particular dependence on the use of TMSOTf (entries 7–8, also see Supplementary Information, Table S3). Control experiments revealed that both indium and TMSOTf were vital for the success of the reaction (entries 9–10). We believe that TMSOTf is playing multiple roles in the reaction, including aiding iminium ion formation, enhancing the reactivity of the carbon-iodine bond through coordination to the adjacent pyridine nitrogen and activating the indium metal (see Supplementary Information, Section 9.1).[34] Under the optimized conditions a reaction using 2-bromopyridine gave an assay yield of 20% and no product was formed with 2-chloropyridine (returning only the starting material) highlighting the importance of the 2-iodo group and the relative reactivity of the weaker carbon–iodine bond with respect to indium insertion.

The insertion of indium into reactive allyl halides, propargyl halides and α-halo esters *via* Barbier or Reformatsky-type activation modes is well precedented.[35] Furthermore, the activation of aryl halides using elemental indium alongside additives such as LiCl and Co catalysts has enabled the use of arylindiums in a variety of transition metal-catalyzed cross coupling processes.[34,36] In contrast to these methods, the use of indium metal for the insertion into 2-azinyl halides to form the corresponding heteroarylindium species and their subsequent role in productive carbon-carbon bond forming reactions is limited to a solitary report, to the best of our knowledge.[37] In this case, an indium mediated addition of 2-iodopyridine to neat aldehyde at 75 ˚C generated the corresponding 1,2-addition product, although no details were provided on the nature of the putative 2-pyridyl nucleophile. In contrast, the mild and operationally straightforward reaction

conditions afforded by the near equimolar multicomponent coupling reaction of our new CAzA reaction offer a modular and potentially general entry into highly functionalized and structurally complex 2-azinyl tertiary alkylamines. Although the CAzA process requires 1.5 equivalents of indium powder as a reductant, it is notable that no other metal additives or catalysts are required. This draws an interesting distinction to related, but mechanistically disparate, reductive processes that form similar products reported by the groups of Reisman and Doyle, in particular.[9,23] In these cases, a transition metal catalyst is required in addition to the use of a stoichiometric quantity of a metal reductant to afford the desired products.

Exploration of reaction scope

With an optimized set of reaction conditions in hand, we explored the scope of this transformation by first varying the amine component, using cyclohexanecarboxaldehyde (Fig. 3, **1b**) and 2-iodopyridine (**3a**) as representative coupling partners. Both assay yield and yield of isolated product are quoted in all cases to provide a measure of reaction efficiency separated from isolation of materials, which is frequently problematic with tertiary alkylamines. A range of cyclic, bicyclic, spirocyclic and heterocyclic secondary amines were smoothly converted to the corresponding α-alkyl 2-azinyl tertiary alkylamines (Fig. 3, **4b-4j**, **4r-4w**), allowing for the incorporation of a broad selection of pharmaceutically ubiquitous features arising from the diversity of the abundant secondary alkylamine feedstock. Primary amines and anilines, however, consistently performed poorly in the reaction, frequently resulting in complex product mixtures. For example, using *p*-anisidine (**1l**) as the amine component gave the corresponding secondary amine product **4l** with a low assay yields and challenging purification precluded accurate yield determination (see Supplementary Information, Section 7.2). However, *N*-methyl-*p*-anisidine (**1k**) was capable of coupling to give N-aryl tertiary amine **4k** in good yield, suggesting an important role of the intermediate iminium ion. N,N-dialkylamines displaying linear functionalized alkyl substituents, including aromatic and tetrazole containing groups, gave tertiary amines **4m-4q**. The use of benzyl and allylamine derivatives gives rise to products that can be readily transformed to the corresponding primary and secondary amines (**4n**, **4q**) for downstream diversification. Several secondary amine-containing drugs, drug fragments and a natural product were accommodated in the reaction, producing tertiary amine derivatives **4r-4w** and demonstrating a compatibility of the reaction with more complex functionality. We were pleased to find that, in many cases, amines with multiple Lewis basic functionalities were well tolerated in this reaction. As an additional feature, the reaction was found to be amenable to the use of amine hydrochloride salts – a form in which they are often supplied – by lowering the amount of TMSOTf required to substoichiometric levels; the hydrochloride salt is presumed to assist the iminium ion formation and hence there is less reliance on the TMSOTf additive to promote this step.

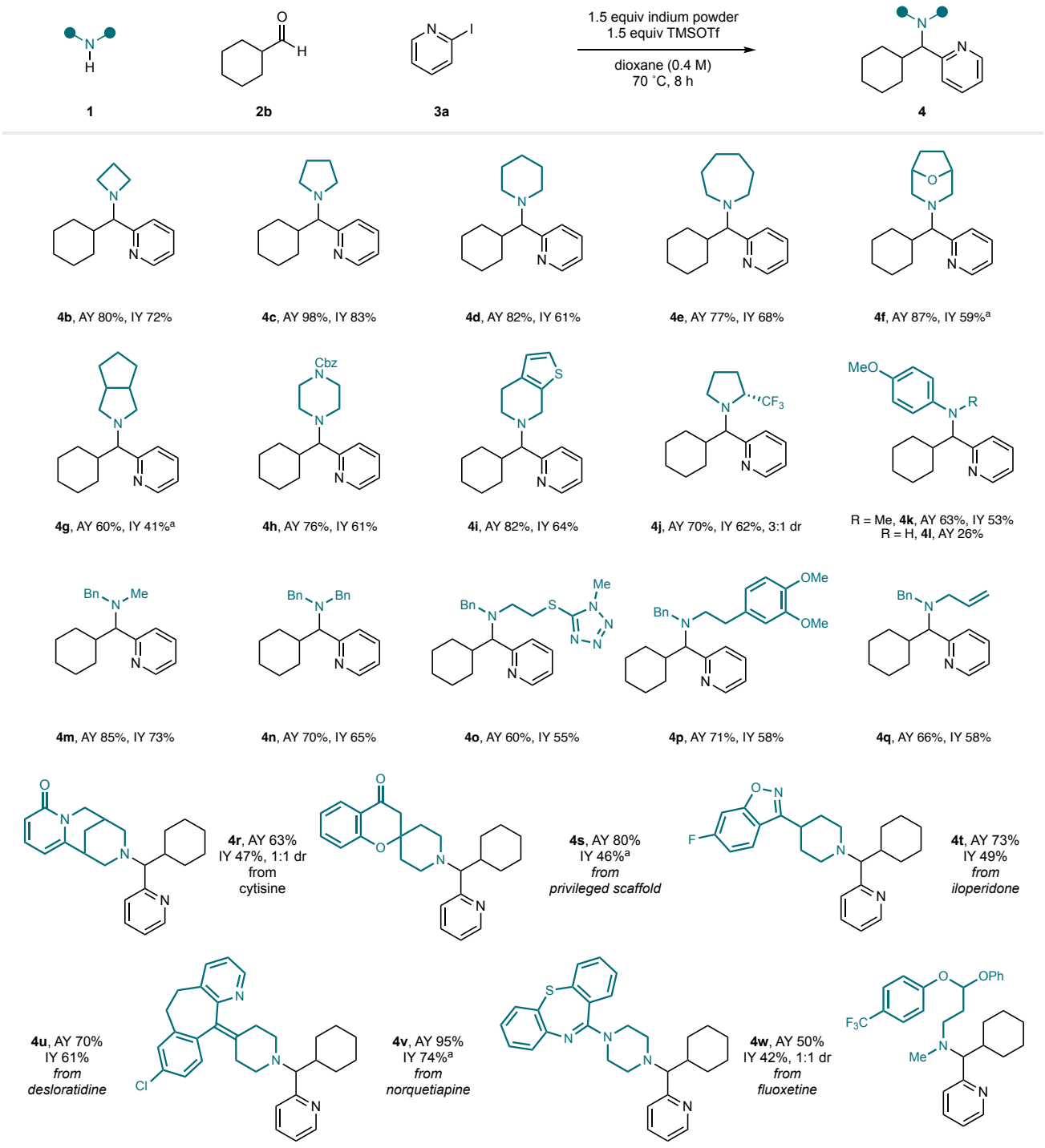


Figure 3. Scope of carbonyl azinylative amination reaction in the secondary amine component. [a]Amine•HCl salt was used in combination with 0.5 equiv of TMSOTf.

Next, we surveyed the scope of the reaction in the aldehyde component using amine **1x** and 2-iodopyridine **3a** as representative coupling partners (Fig. 4A). Accordingly, a variety of aliphatic (Fig. 4, **2x-2ai**) and aromatic (**2aj-2ap**) aldehydes were successfully coupled in the carbonyl azinylative amination reaction to give amine products which we, upon inspection, would expect to possess favorable pharmacokinetic properties as orally available agents: molecular weights ranging from 300–500 Da and between five to eight H-bond acceptors.[38] Both linear aldehydes and α-branched aldehydes, including carbocycle and heterocycle-containing, were readily converted to amines **4x-4ai**. The reaction of a substituted

cyclopropyl aldehyde resulted in formation of the expected amine **4ae** without any trace of strained ring-opening products.[40] This radical clock experiment suggests that the reaction pathway does not go through an indium-mediated iminium reduction to an α-amino radical and subsequent addition-elimination to the 2-iodo pyridine. A range of aromatic and heteroaromatic aldehydes could be used, giving rise to (hetero)benzhydrylamine derivatives **4aj-4ap**. These amines, which contain the α-aryl, α'-2-azinyl methylamine motif but can be challenging to access by traditional methods.[39] Some heteroaromatic aldehydes, such as 2-pyridinecarboxaldehyde, lead to poor yields of the desired products (**2aq**) and reductive amination was observed as the predominant reaction pathway. However, use of several Lewis-basis heteroaryl aldehydes generated the methylamine motive substituted with two heteroarenes in synthetically useful yields (**2ao-p**, **2ar**), the products of which display up to seven heteroatoms.

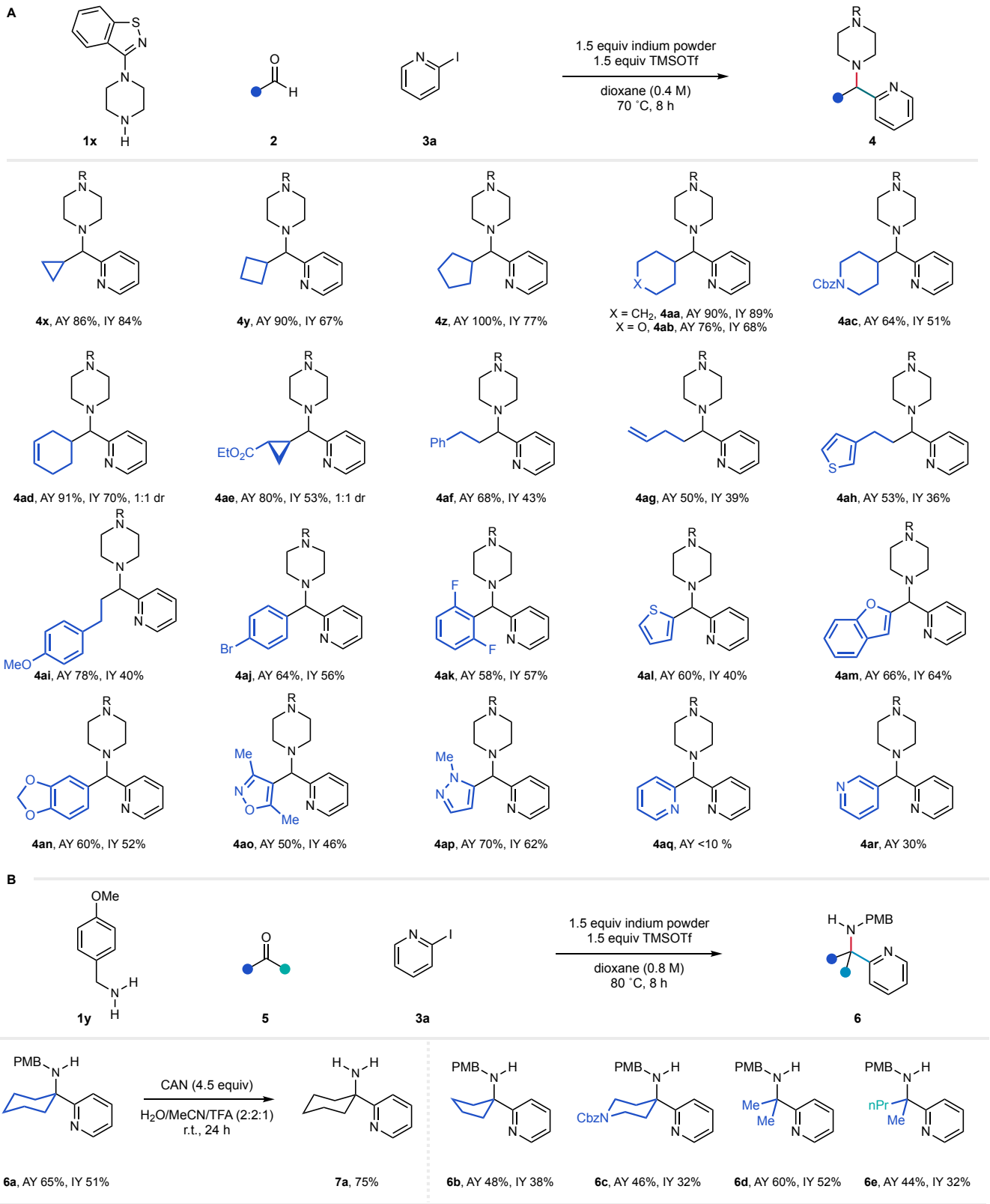


Figure 4. (A) Scope of carbonyl azinylative amination reaction in the aldehyde component. **(B)** Synthesis of α,α'-dialkyl, α''-2-pyridyl tertiary amines.

The CAzA reaction could also accommodate the use of a ketone to deliver a synthesis of α-2-azinyl α-tertiary amines (ATAs). Molecules bearing an ATA motif – a nitrogen with an adjacent fully substituted carbon atom – are prevalent

among pharmaceuticals and bioactive molecules but efficient methods for their synthesis have remained elusive.[8,12,20,21,28,41–49] While the addition of organometallic nucleophiles to N-activated ketimine derivatives is well established, reports of the addition of non-activated organometallics to non-activated all-alkyl ketimines are exceptionally rare.[7,41–43] Preliminary investigations guided us towards the use of primary amines for this transformation to overcome the challenging condensation between aliphatic ketones and secondary amines that had yielded none of the desired product in our investigations to date. Surprisingly, we found that ketimines derived from primary benzylamines were uniquely reactive in this process and delivered the α-2-azinyl ATA in modest but synthetically useful yield, given the challenging nature of the transformation (Fig. 4B). We found that increasing the equivalents of the ketone component and the reaction concentration enabled a range of cyclic and linear ketones (Fig. 4B, **5a-e**) to be successfully coupled with 4-methoxybenzylamine (**17**) and 2-iodopyridine (**3a**) to give α-2-azinyl α-tertiary amines (ATAs), **6a-6e**. The use of the CAzA method to assemble these sterically congested and functionality-dense amines represents a rare example of C(sp^3)-rich ATA synthesis by addition of an organometallic nucleophile to non-activated ketimines. Removal of the para-methoxybenzyl (PMB) protecting group from amine **6a** was achieved by an oxidative reaction using ceric ammonium nitrate (CAN) under acidic conditions, giving **7a**, which demonstrated a streamlined approach to the synthesis of 2-azinyl α,α'-dialkyl primary amines.

With respect to the 2-iodo azine component, the scope of the reaction was explored using morpholine (**1z**) and cyclohexanecarboxaldehyde (**2b**) as representative coupling partners, under the same optimized reaction conditions (Fig. 5). We identified that a range of 2-iodo azines performed well in the carbonyl azinylative amination reaction. Using a selection of di- and tri-substituted 2-iodopyridines, we were able to prepare the corresponding α-alkyl 2-azinyl amines (Fig. 5, **8a–j**), bearing substituents at the 3-, 4-, 5- and 6-position of the pyridine ring. The chemo- and regioselective activation of the 2-iodo group in the presence of other bromide and iodide substituents demonstrates the mild nature of the indium activation process and allowed for the synthesis of substrates such as **8b**-**e**, bearing versatile handles for downstream functionalization. Other functional handles, such as allyloxy (**8i**), ester (**8j**) and carbamate (**8r**) groups could be incorporated into the heterobenzylic amine scaffold. A variety of 2-iodopyrimidines were successfully applied to give amines **5k–5n**. Other heterocycles were smoothly incorporated into the tertiary amine scaffold, including pyrazine (**8o**), isoquinoline (**8p**), furopyridine (**8q**) and pyrrolopyrimidine (**8r**) rings, all of which have found a broad utility in drug design and synthesis as pharmacophores for molecular recognition.[50–52] 3-Iodopyridine (**3s**) could be used to give amine **8s**, albeit in a lower yield to its 2-pyridyl counterpart (**8a**) offering an interesting insight to the nature of activation of differentially substituted iodo azines; azines with an iodide in the 2-position are more reactive that the 3-iodo and 4-iodo congeners. Pentafluoroiodobenzene (**3v**) was shown to undergo successful coupling with an iminium to give amine **8v** with a perfluorophenyl substituent. This suggests that sufficient electron deficiency of the aromatic ring could preclude the requirement for 2-iodo azines, and possibly expand the scope of this transformation. This hypothesis was supported by the unsuccessful coupling of more electron-rich heteroarenes (see Supplementary Information, Section 7.2). It was noted that with most examples, isolated yields were 5–15% lower than assay yields due to mass loss upon silica gel chromatography, which is commonly encountered with alkylamines.

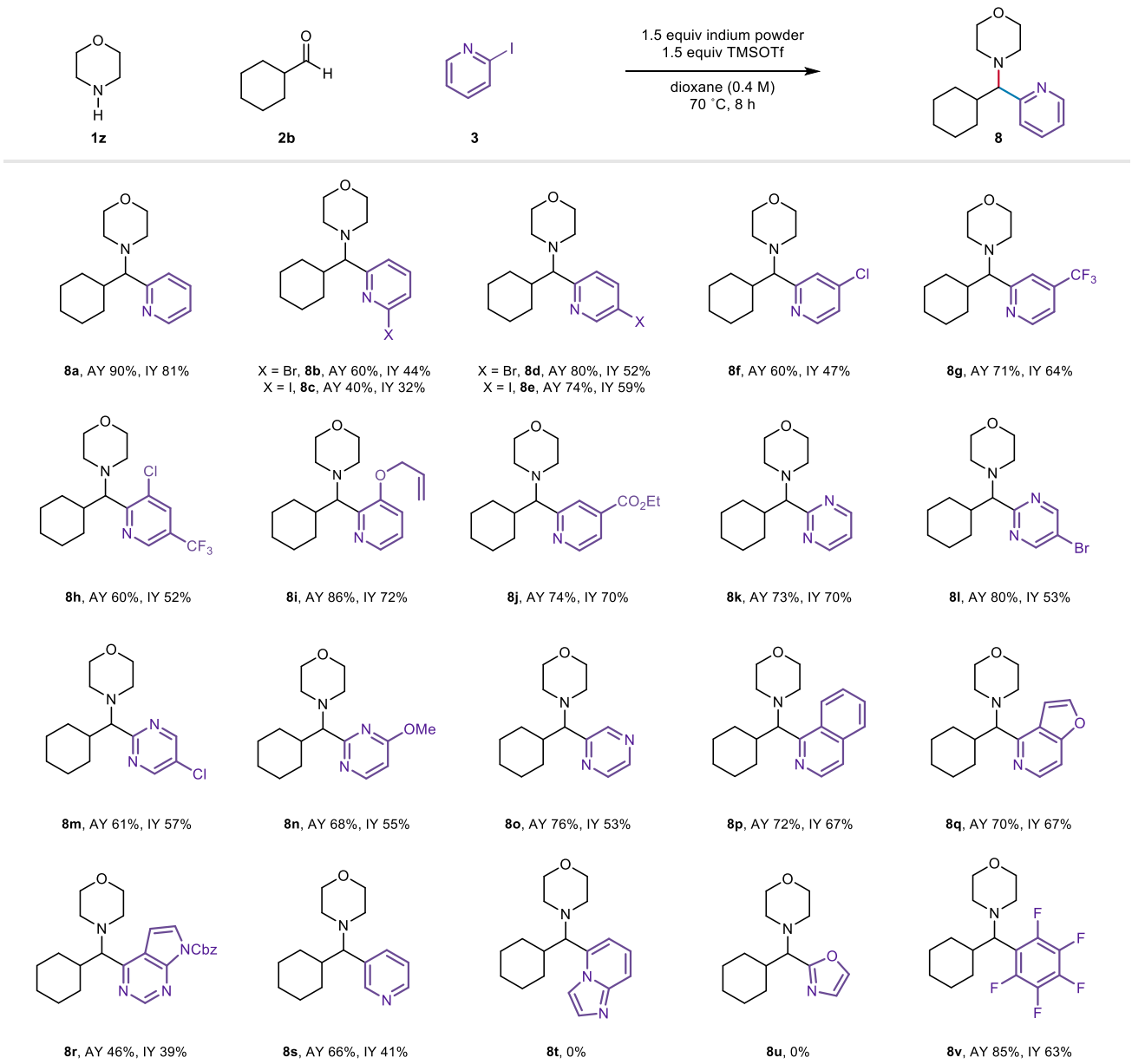


Figure 5. Scope of carbonyl azinylative amination reaction in the 2-iodo azine component.

Having established a broad scope for the carbonyl azinylative amination, we questioned whether the native ketone could serve as a competent electrophile for the putative organoindium nucleophile, therefore enabling a complementary process for the synthesis of the corresponding tertiary alcohols substituted with a 2-azinyl group (Fig. 6A). The corresponding 2-pyridyl Grignard reagents have been shown to add to ketones in modest yield (usually less than 50%). In our initial survey of reaction conditions, we found that the use of TMSOTf was poorly effective in the addition of the putative 2-pyridyl indium to ketones. We were pleased to discover that 2-iodopyridine (**3a**) reacted with 4-tetrahydropyranone (**5a**) in the presence of a catalytic amount (25 mol%) of (±)-camphorsulfonic acid (CSA) in a THF solution to provide tertiary alcohol **9a** in an adequate assay yield. Unfortunately, however, other non-activated acyclic ketones exhibited very poor reactivity, resulting in low yields of the corresponding tertiary alcohols and perhaps reflects the mild nature of the putative 2-pyridyl indium species. Perhaps unsurprisingly, more reactive aliphatic and aromatic aldehydes could be employed as effective electrophiles under these conditions, giving rise to secondary alcohols **9b** and **9c**.

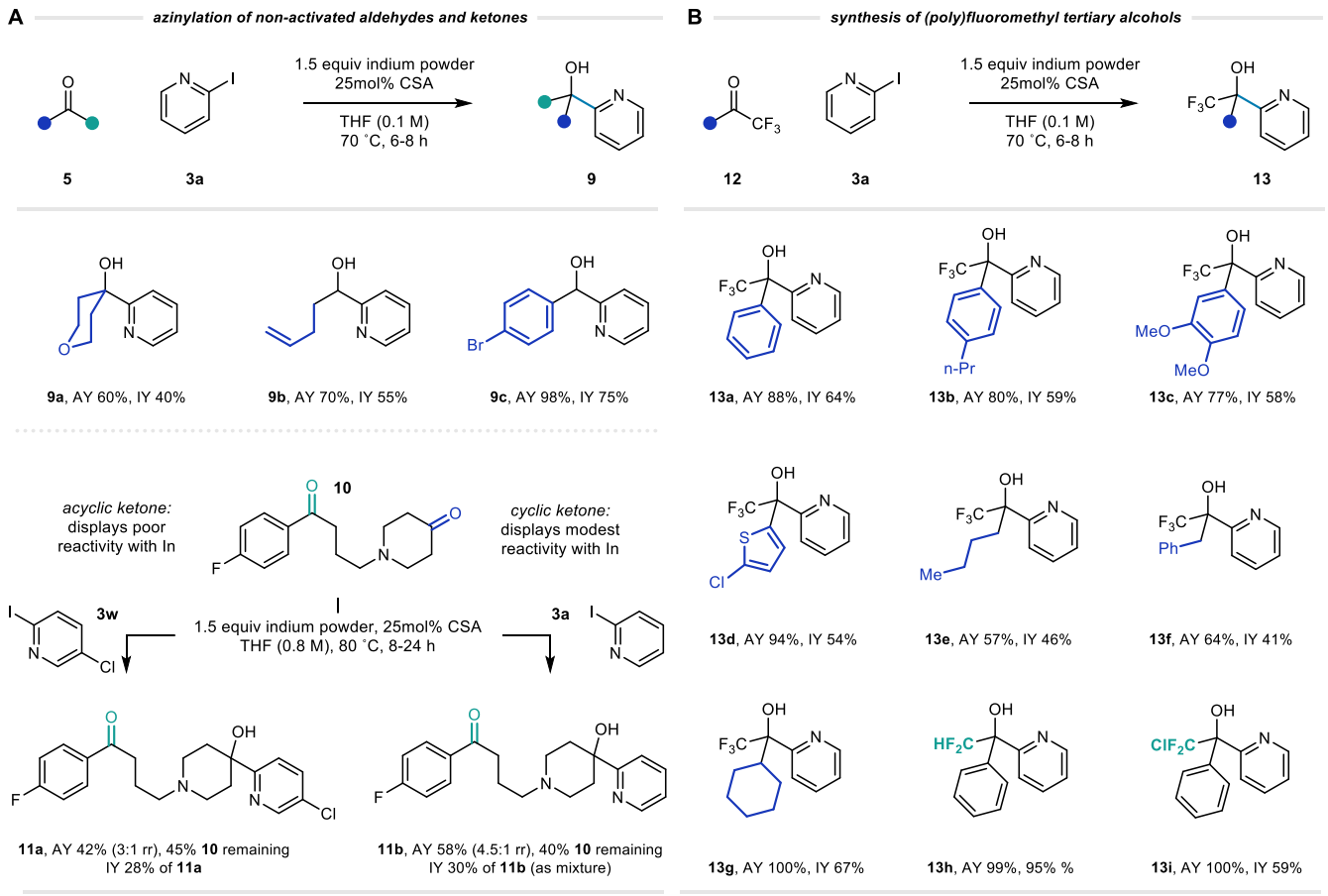


Figure 6. (A) Indium-mediated 2-pyridylation of aldehydes and ketones and the synthesis of pharmaceutically-relevant butyrophenone derivatives. **(B)** Indium-mediated 2-pyridylation of perfluoromethyl ketones.

While there appears to be little to no benefit to using 2-pyridyl indiums in the addition to carbonyls over the more conventional Grignard reagent, we sought to establish whether our method provided any chemoselectivity over classical organometallic reagents. We selected dione **10** as a substrate to investigate this potentially useful facet of 2-azinyl-indium reagents. Butyrophenones are a class of antipsychotic drugs with applications in the treatment of schizophrenia or as sedatives in veterinary settings.[53] They all feature a phenylbutanone chain and marketed members of this drug class, such as haloperidol, contain an aryl-substituted tertiary alcohol on the piperidine ring. The selective 2-azinylation of the piperidinone unit in dione **10** would provide a streamlined strategy for the synthesis of an aza-haloperidol analogue and other butyrophenone derivatives. Based on our results of adding 2-pyridyl indium reagents to ketones, we reasoned that the cyclic ketone may react in preference to the acyclic carbonyl. Harnessing the disparity of this intrinsic selectively of the putative 2-pyridyl indium species allowed for site selective heteroarylation of diketone **10** using 2-iodo-5-chloropyridine (**3w**) at slightly elevated temperature and concentration to give tertiary alcohol **11a,** which is an analogue of haloperidol containing a single carbon-to-nitrogen bioisosteric replacement, as a 3:1 mixture of regioisomers. Pleasingly, 2-iodopyridine (**3a**) showed similar selectivity with our diketone precursor **10**, to furnish the alcohol **11b**, a further analogue of haloperidol. While the yields of **11a** and **11b** were modest, the alcohol products were readily isolable from their product mixtures, and much of the remaining mass balance could be attributed to unreacted starting material which could be recovered (see Supplementary Information, Section 5.2). As a control reaction, we tested the same 2-azinylation reaction with the Grignard reagent derived from **3w** and observed only trace amounts of the desired product **11a** with the reaction forming an intractable mixture, which also precluded regioselectivity determination. In contrast, the conditions developed

in this report allow for the selective installation of an α-2-azinyl tertiary alcohol in a single step, which remains the key challenge in the synthesis of butyrophenone drugs,[54] demonstrating a streamlined method for the generation of analogues of this important scaffold.

In contrast to the modest reactivity of alkyl ketones, we observed that the more reactive ketone, 2,2,2-trifluoroacetophenone (**12a**), was an effective electrophile for heteroarylation, giving α-trifluoromethyl-α'-(2-pyridyl) tertiary alcohol **13a** in reasonable yield (Fig. 6B). Indeed, a variety of fluoromethyl ketones could be successfully coupled with 2-iodopyridine (**3a**) to give fluorinated tertiary alcohols displaying aryl (**13a-c**, **13h-i**), heteroaryl (**13d**), benzyl (**13f**), and alkyl (**13e-g**) substituents. These results distinguish this method for the synthesis of perfluoromethylated tertiary alcohols from other protocols involving the use of organometallic reagents. For example, with readily enolizable (trifluoromethyl)alkylketones, which themselves are non-trivial to prepare, classical heteroaryl organometallic reagents participate in competitive and unproductive deprotonation at the acidic α-position meaning that products are formed in low yields.[55] Alternative approaches based on additions to highly reactive 2-azinyl(trifluoromethyl)ketones using alkyl organometallic reagents that contain hydridic β-hydrogens are rarely straightforward and can result in carbonyl reduction over alkyl addition.[56–59] This indium mediated ketone addition offers a single step solution to the synthesis of a class of tertiary alcohols that are difficult to prepare by other means. The successful synthesis of the difluoromethyl (CHF_2) variant (**13h**) is particularly noteworthy because this motif has attracted considerable interest in medicinal chemistry, as a lipophilic hydrogen bond donor and bioisostere of hydroxyl and thiol groups.[58]

Preliminary mechanistic investigations

When considering the possible reactive species involved in the key C–C bond forming step, we envisioned two possible scenarios: (i) addition of a pyridyl radical, formed through indium-mediated single electron reduction of the 2-iodo azine, to an iminium ion; or (ii) addition of a 2-azinyl indium species, which could be formed either by oxidative addition of In metal to the 2-iodo azine or *via* sequential indium-mediated single electron reductions, to an iminium ion. Note that initial N-silylation of the azine to form an N-trimethylsilyl azinium species was directly observable by ^{1}H NMR analysis (see Supplementary Information, Section 9.1) and assumed to be important for activation of the iodo azine. To probe a radical pathway, we reasoned that addition of a 2-pyridyl radical to an iminium ion would result in an aminium radical cation. However, the exclusive formation of **9b**, formed from an aldehyde bearing a pendant alkene, suggests an open shell pathway is not central to the key addition step as rapid *5-exo-trig* cyclization ($k = 10^8$–10^9 s^{-1} to **14**)[59] would be expected in the event of a 2-pyridyl radical pathway (Fig. 7A). A 2-pyridyl radical bearing a 3-allyloxy substituent has been shown to undergo rapid addition to the pendant alkene.[60] However, when subjected to our standard conditions, the use of 2-iodo pyridine **3i** resulted in the formation of desired tertiary amine **5i** in 86% assay yield alongside pyridine **15** resulting from protodeiodination (Fig. 7B) but no trace of the product from radical cyclization onto the alkene motif (**16**). In contrast, pyridine **3x**, displaying a pendant ketone motif, was involved in two competing pathways under our reaction conditions: the desired 2-pyridylation to furnish amine **5x** and intramolecular addition of the 2-pyridyl carbon atom to the pendant ketone to give cyclized product **17**, which provides evidence in support of a polar mechanism involving a 2-pyridyl indium species (Fig. 7C).

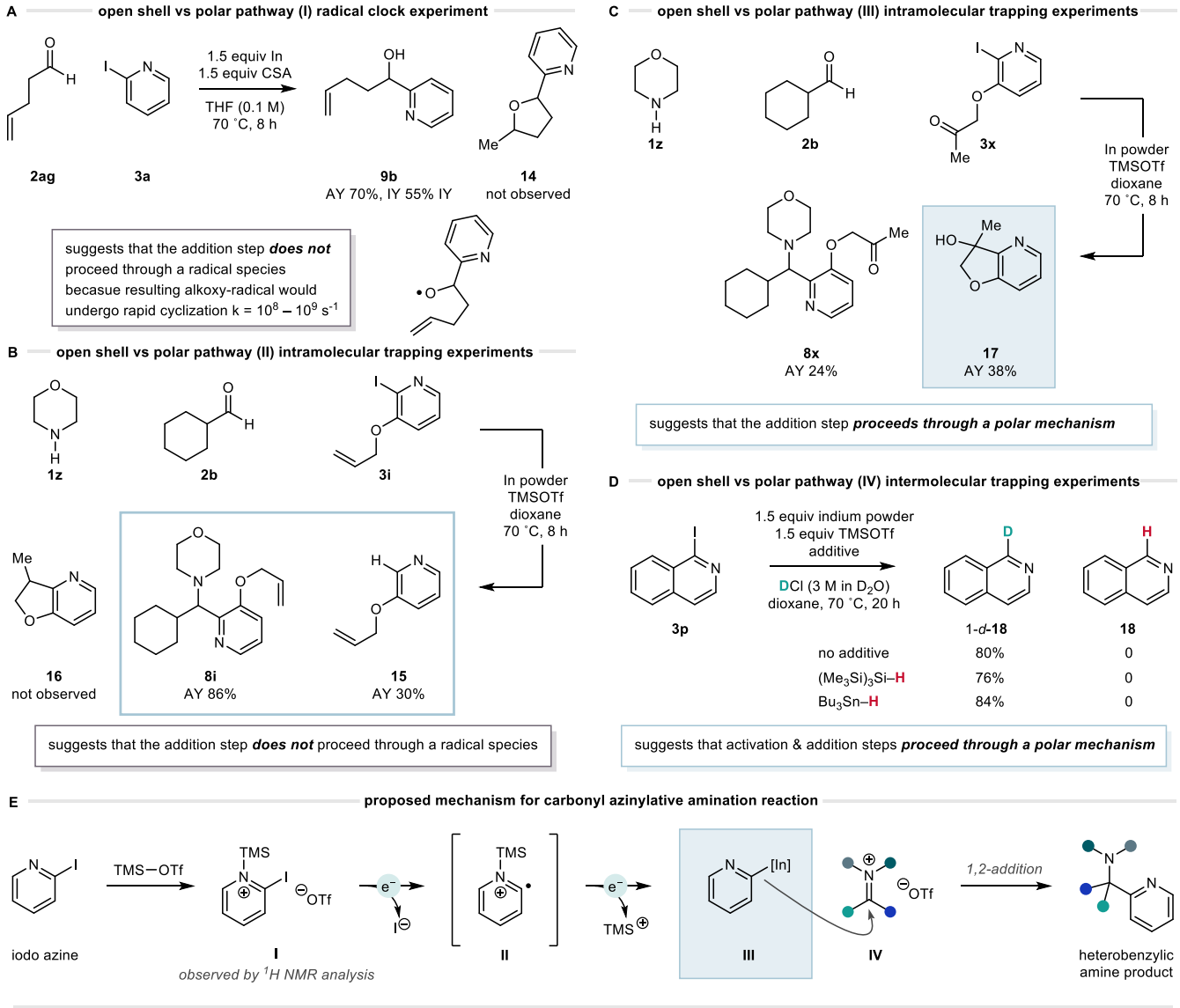


Figure 7. Mechanistic studies. **(A)** Radical clock experiments. **(B)** Intramolecular cyclization to probe radical mechanism. **(C)** Intramolecular cyclization to probe polar mechanism. **(D)** Intermolecular competition experiments to probe for polar or radical pathway. (**E**) A plausible pathway for a polar mechanism.

A reaction involving the presence of excess deuterium chloride in a stirred mixture of 1-iodoisoquinoline **3p**, indium powder and TMSOTf resulted in the complete conversion to 1-deuteroisoquinoline (1-*d*-**18**) (Fig. 7D). It is notable that stirring the reaction at 70 °C for 20 h was required to achieve complete deuteration. Organoindium species are typically characterised by their mild reactivity and kinetic inertness to deprotonative processes;[35] while the CAzA reaction does not proceed effectively in protic solvent (see Supplementary Information, Table S2), it appears that the reactive azinyl indium species does share these properties, to an extent. In the presence of classical hydrogen atom transfer reagents, the reaction still produced exclusively the deuterated product over isoquinoline (**18**). Given the high calculated electron affinity of the 2-pyridinium radical cation (Int. **II**, Fig. 7E) [6.59 eV] (calculated at the BLYP/aug-cc-pVDZ//BLYP/cc-pVDZ level of theory),[61] we can reason that following single electron reduction of the corresponding TMS-activated 2-iodo-azinium cation (Int. **I**), a successive single electron reduction process to generate the organoindium reagent (Int. **III**) would outcompete undesired HAT to quench the azinium radical cation. Together, these data suggest that the formation of a putative

2-azinyl indium species and its addition to an electrophile (Int. **IV**) proceed *via* a polar mechanism. For further discussion and experiments investigating the reaction mechanism, see the Supplementary Information, Section 9.

CONCLUSION

In summary, we have developed an operationally straightforward protocol for the synthesis of highly functionalized α-alkyl 2-azinyl tertiary amines from readily accessible or commercially available feedstock components. This procedure offers practical access to a complex structural unit that is often challenging to assemble in such a modular fashion. The carbonyl azinylative amination protocol is run under mild and operationally straightforward conditions, enabling a broad scope in all three reaction components. A notable feature of this reaction platform is its independence from the need for a transition metal catalyst, which is usually required to generate a reactive aryl species in other related processes. Beyond the reaction with iminium ions, the 2-azinylation of aldehydes and electron-poor ketones was also realized, under modified conditions, delivering a collection of heterobenzylic alcohols. Additionally, the platform can be adapted to the synthesis of tertiary alcohols containing both di- or trifluoromethyl and heteroaryl substituents, which may be of use in the search for biologically active molecules. Our preliminary studies lead is to believe the reaction invokes a 2-azinyl indium species, which undergoes nucleophilic addition to a C=X electrophile. These findings reveal previously unexplored aspects of the reactivity of heteroleptic 2-azinylindium reagents, which may present further applications of interest to synthetic chemists working in academic and industrial settings.

METHODS

General procedure for the multicomponent synthesis of heterobenzylic amines employing secondary amines, aldehydes and iodo azines

An oven dried vial (Biotage Microwave Process Vial 10 mL, equipped with gas-tight pierceable caps) was charged with a magnetic stirring bar and indium powder (0.60 mmol, 1.5 equiv). The vial was sealed, evacuated and backfilled with N_2 (3 cycles). To this was added dry dioxane (1.0 mL) followed by amine or amine hydrochloride (0.40 mmol, 1.0 equiv), aldehyde (0.60 mmol, 1.5 equiv) and 2-iodo azine (0.80 mmol, 2.0 equiv) followed by trimethylsilyl trifluoromethanesulfonate (0.60 mmol, 1.5 equiv with neutral amines, or 0.20 mmol, 0.5 equiv with amine hydrochloride salts) *via* microsyringe. The reaction vial was heated at 70 °C with vigorous stirring for 8 h. The crude reaction mixture was cooled and diluted with CH_2Cl_2 (20 mL), 10% aq. NaOH (15 mL) was added, and the resultant mixture was stirred vigorously for 10 min, until the aqueous layer appeared cloudy white. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography using a mixture of ethyl acetate and petroleum ether (with 5% v/v triethylamine), or a mixture of methanol and dichloromethane (with 5% v/v triethylamine), to give the α-alkyl 2-azinyl amine product.

DATA AVAILABILITY

All experimental procedures, extended mechanistic discussion and compound characterization (^{1}H and ^{13}C NMR spectra, IR and MS data) are available in the Supplementary Information.

AUTHOR INFORMATION

Corresponding Author

*Matthew. J. Gaunt – Yusuf Hamied Department of Chemistry, University of Cambridge, Cambridge CB2 1EW, United Kingdom.
ORCID: 0000-0002-7214-608X
Email: mjg32@cam.ac.uk

Author Contributions

†A.A.R. & R.K. contributed equally to the research described in this Article.

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REFERENCES

1. Vitaku, E., Smith, D. T. & Njardarson, J. T. Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals. *J. Med. Chem.* **57**, 10257–10274 (2014).

2. Ling, Y., Hao, Z., Liang, D., Zhang, C., Liu, Y. & Wang, Y. The Expanding Role of Pyridine and Dihydropyridine Scaffolds in Drug Design. *Drug Des. Devel. Ther.* **15**, 4289–4338 (2021).
3. Verheij, M. H. P., Thompson, A. J., van Muijlwijk-Koezen, J. E., Lummis, S. C. R., Leurs, R. & de Esch, I. J. P. Design, synthesis, and structure−activity relationships of highly potent 5-HT_3 receptor ligands. *J. Med. Chem.* **55**, 8603−8614 (2012).
4. Zheng, X., Bauer, P., Baumeister, T., Buckmelter, A. J., Caligiuri, M., Clodfelter, K. H., Han, B., Ho, Y., Kley, N., Lin, J., Reynolds, D. J., Sharma, G., Smith, C. C., Wang, Z., Gragovich, P. S., Oh, A., Wang, W., Zak, M., Gunzner-Toste, J., Zhao, G., Yuen, P. & Bair, K. W. Structure-Based Identification of Ureas as Novel Nicotinamide Phosphoribosyltransferase (Nampt) Inhibitors. *J. Med. Chem.* **56**, 4921–4937 (2013).
5. Pace, P., Di Francesco, M. E., Gardelli, C., Harper, S., Muraglia, E., Nizi, E., Orvieto, F., Petrocchi, A., Poma, M., Rowley, M., Scarpelli, R., Laufer, R., Paz, O. G., Monteagudo, E., Bonelli, F., Hazuda, D., Stillmock, K. A. & Summa, V. Dihydroxypyrimidine-4-carboxamides as Novel Potent and Selective HIV Integrase Inhibitors. *J. Med. Chem.* **50**, 2225–2239 (2007).
6. Abdel-Magid, A. F. & Mehrman, S. J. A Review on the Use of Sodium Triacetoxyborohydride in the Reductive Amination of Ketones and Aldehydes. *Org. Proc. Res. Dev.* **10**, 971–1031 (2006).
7. Bloch, R. Additions of Organometallic Reagents to C=N Bonds: Reactivity and Selectivity. *Chem. Rev.* **98**, 1407–1438 (1998).
8. Cogan, D. A., Liu, G. & Ellman, J. Asymmetric synthesis of chiral amines by highly diastereoselective 1,2-additions of organometallic reagents to *N-tert*-butanesulfinyl imines. *Tetrahedron* **55**, 8883−8904 (1999).
9. Turro, R. F., Brandstätter, M. & Reisman, S. E. Nickel-Catalyzed Reductive Alkylation of Heteroaryl Imines. *Angew. Chem. Int. Ed.* e202207597 (2022).
10. Patel, N. R., Kelly, C. B., Siegenfeld, A. P., Molander, G. A. Mild, Redox-Neutral Alkylation of Imines Enabled by an Organic Photocatalyst. *ACS Catal.* **7**, 1766–1770 (2017).
11. Luescher, M. U. & Bode, J. W. Catalytic Synthesis of N-Unprotected Piperazines, Morpholines, and Thiomorpholines from Aldehydes and SnAP Reagents. *Angew. Chem. Int. Ed.* **54**, 10884–10888 (2015).
12. Hsieh, S. & Bode, J. W. Silicon Amine Reagents for the Photocatalytic Synthesis of Piperazines from Aldehydes and Ketones. *Org. Lett.* **18**, 2098–2101 (2016).
13. Garrido-Castro, A. F., Gini, A., Maestro, M. C. & Alemán, J. Unlocking the direct photocatalytic difluoromethylation of C=N bonds. *Chem. Commun.* **56**, 3769–3772 (2020).
14. de Arriba, A. L. F., Urbitsch, F. & Dixon, D. J. Umpolung synthesis of branched α-functionalized amines from imines *via* photocatalytic three-component reductive coupling reactions. *Chem. Commun.* **52**, 14434–11437 (2016).
15. Proctor, R. S. J., Davis, H. J. & Phipps, R. J. Catalytic enantioselective Minisci-type addition to heteroarenes. *Science* **360**, 419–422 (2018).
16. Proctor, R. S. J., Chuentragool, P., Colgan, A. C. & Phipps, R. J. Hydrogen Atom Transfer-Driven Enantioselective Minisci Reaction of Amides. *J. Am. Chem. Soc.* **143**, 4928–4934 (2021).
17. Fu, M., Shang, R., Zhao, B., Wang, B. & Fu, Y. Photocatalytic decarboxylative alkylations mediated by triphenylphosphine and sodium iodide. *Science* **363**, 1429–1434 (2019).
18. Grainger, R., Heightman, T. D., Ley, S. V., Lima, F. & Johnson, C. N. Enabling synthesis in fragment-based drug discovery by reactivity mapping: photoredox-mediated cross-dehydrogenative heteroarylation of cyclic amines. *Chem. Sci.* **10**, 2264–2271 (2019).

19. Garza-Sanchez, R. A., Tlahuext-Aca, A., Tavakoli, G. & Glorius, F. Visible Light-Mediated Direct Decarboxylative C–H Functionalization of Heteroarenes. *ACS Catal.* **7**, 4057–4061 (2017).

20. Nicastri, M. C., Lehnherr, D., Lam, Y., DiRocco, D. A. & Rovis, T. Synthesis of Sterically Hindered Primary Amines by Concurrent Tandem Photoredox Catalysis. *J. Am. Chem. Soc.* **142**, 987–998 (2020).

21. Lehnherr, D., Lam, Y., Nicastri, M. C., Liu, J., Newman, J. A., Regalado, E., DiRocco, D. A. & Rovis, T. Electrochemical Synthesis of Hindered Primary and Secondary Amines via Proton-Coupled Electron Transfer. *J. Am. Chem. Soc.* **142**, 468–478 (2020).

22. Zuo, Z., Ahneman, D. T., Chu, L., Terrett, J. A., Doyle, A. G. & MacMillan, D. W. C. Merging photoredox with nickel catalysis: Coupling of α-carboxyl sp^3-carbons with aryl halides. *Science* **345**, 437–440 (2014).

23. Heinz, C., Lutz, J. P., Simmons, E. M., Miller, M. M., Ewing, W. R. & Doyle, A. G. Ni-Catalyzed Carbon–Carbon Bond-Forming Reductive Amination. *J. Am. Chem. Soc.* **140**, 2292–2300 (2018).

24. Prier, C. K. & MacMillan, D. W. C. Amine α-heteroarylation *via* photoredox catalysis: a homolytic aromatic substitution pathway. *Chem. Sci.* **5**, 4173–4178 (2014).

25. Weidmann, N., Nishimura, R. H. V., Harenberg, J. H. & Knochel, P. Halogen–Lithium Exchange of Sensitive (Hetero)aromatic Halides under Barbier Conditions in a Continuous Flow Set-Up. *Synthesis* **53**, 557–568 (2021).

26. Cook, X. A. F., de Gombert, A., McKnight, J., Pantaine, L. R. E. & Willis, M. C. The 2-Pyridyl Problem: Challenging Nucleophiles in Cross-Coupling Arylations. *Angew. Chem. Int. Ed.* **60**, 11068–11091 (2021).

27. Kumar, R., Flodén, N. J., Whitehurst, W. G. & Gaunt, M. J. A general carbonyl alkylative amination for tertiary amines. *Nature* **581**, 415–420 (2020).

28. Blackwell, J. H., Kumar, R. & Gaunt, M. J. Visible-Light-Mediated Carbonyl Alkylative Amination to All-Alkyl α-Tertiary Amino Acid Derivatives. *J. Am. Chem. Soc.* **143**, 1598–1609 (2021).

29. Deneny, P. J., Kumar, R., Gaunt, M. J. Visible light-mediated radical fluoromethylation *via* halogen atom transfer activation of fluoroiodomethane. *Chem. Sci.* **12**, 12812–12818 (2021).

30. Juliá, F., Constantin, T. & Leonori, D. Applications of Halogen-Atom Transfer (XAT) for the Generation of Carbon Radicals in Synthetic Photochemistry and Photocatalysis. *Chem. Rev.* **122**, 2292–2352 (2022).

31. Zhu, L., Wehmeyer, R. M. & Rieke, R. D. The Direct Formation of Functionalized Alkyl(aryl)zinc Halides by Oxidative Addition of Highly Reactive Zinc with Organic Halides and Their Reactions with Acid Chlorides, α,β-Unsaturated Ketones, and Allylic, Aryl, and Vinyl Halides. *J. Org. Chem.* **56**, 1445–1453 (1991).

32. Boudet, N., Sase, S., Sinha, P., Liu, C., Krasovskiy, A. & Knochel, P. Directed Ortho Insertion (DoI): A New Approach to Functionalized Aryl and Heteroaryl Zinc Reagents. *J. Am. Chem. Soc.* **129**, 12358–12359 (2007).

33. Pitts, M. R., Harrison, J. R. & Moody, C. J. Indium metal as a reducing agent in organic synthesis. *J. Chem. Soc., Perkin Trans. 1*, 955–977 (2001).

34. Chen, Y. & Knochel, P. Preparation of Aryl and Heteroaryl Indium(III) Reagents by the Direct Insertion of Indium in the Presence of LiCl. *Angew. Chem. Int. Ed.* **47**, 7648–7651 (2008).

35. Shen, Z., Wang, S., Chok, Y., Xu, Y. & Loh, T. Organoindium Reagents: The Preparation and Application in Organic Synthesis. *Chem. Rev.* **113**, 271–401 (2013).

36. Adak, L. & Yoshikai, N. Cobalt-Catalyzed Preparation of Arylindium Reagents from Aryl and Heteroaryl Bromides. *J. Org. Chem.* **76**, 7563–7568 (2011).

37. Fukuda, E., Takahasi, Y., Hirasawa, N., Sugimoto, O. & Tanji, K. Dehalogenation and Barbier-type hydroxyalkylation of -deficient haloheterocycles using indium. *Heterocycles* **77**, 1163–1170 (2009).

38. Lipinski, C. A., Lombardo, F., Dominy, B. W., Feeney, P. J. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv. Drug Delivery Rev.* **46**, 3–26 (2001).

39. Conn, E. L., Perry, M. A., Shi, K., Wang, G., Hoy, S., Sach, N. W., Qi, W., Qu, L., Gao, Y., Xu, Y. & Schmitt, D. C. Identification of parallel medicinal chemistry protocols to expand branched amine design space. *Org. Biomol. Chem.* **20**, 3747–3754 (2022).

40. Bowry, V. W., Lusztyk, J. & Ingold, K. U. Calibration of a New Horologery of Fast Radical "Clocks". Ring-Opening Rates for Ring- and α-Alkyl-Substituted Cyclopropylcarbinyl Radicals and for the Bicyclo[2.1.0]pent-2-yl Radical. *J. Am. Chem. Soc.* **113**, 5687–5698 (1991).

41. Ciganek, E. Tertiary Carbinamines by Addition of Organocerium Reagents to Nitriles and Ketimines. *J. Org. Chem.* **57**, 4521−4527 (1992).

42. Wang, D. K., Dai, L. X., Hou, X. L. & Zhang, Y. Mg and Zn Mediated Allylation of Imines with Allyl Bromide. *Tetrahedron Lett.* **37**, 4187−4188 (1996).

43. Siau, W.-Y. & Bode, J. W. One-step synthesis of saturated spiorocyclic N-heterocycles with SNAP reagents and ketones. *J. Am. Chem. Soc.* **136**, 17726−17729 (2014).

44. Trowbridge, A., Reich, D. & Gaunt, M. J. Multicomponent synthesis of tertiary alkylamines by photocatalytic olefin-hydroaminoalkylation. *Nature* **561**, 522–527 (2018).

45. Flodén, N. J., Trowbridge, A., Willcox, D., Walton, S. M., Kim, Y. & Gaunt, M. J. Streamlined Synthesis of C(sp^3)-Rich N-Heterospirocycles Enabled by Visible-Light-Mediated Photocatalysis. *J. Am. Chem. Soc.* **141**, 8429–8430 (2019).

46. Blackwell, J. H., Harris, G. R., Smith, M. A. & Gaunt, M. J. Modular Photocatalytic Synthesis of α-Trialkyl-α-Tertiary Amines. *J. Am. Chem. Soc.* **143**, 15946–15959 (2021).

47. Askey, H. E., Grayson, J. D., Tibbetts, J. D., Turner-Dore, J. C., Holmes, J. M., Kociok-Kohn, G., Wrigley, G. L. & Cresswell, A. J. Photocatalytic Hydroaminoalkylation of Styrenes with Unprotected Primary Alkylamines. *J. Am. Chem. Soc.* **143**, 15936–15945 (2021).

48. Ye, J., Kalvet, I., Shoenebeck, F. & Rovis, T. Direct α-alkylation of primary aliphatic amines enabled by CO2 and electrostatics. *Nature Chem.* **10**, 1037–1041 (2018).

49. Jeffrey, J. L., Petronijević, F. R. & MacMillan, D. W. C. *J. Am. Chem. Soc.* **137**, 8404–8407 (2015).

50. Luo, C., Ampomah-Wireko, M., Wang, H., Wu, C., Wang, Q., Zhang, H. & Cao, Y. Isoquinolines: Important Cores in Many Marketed and Clinical Drugs. *Anticancer Agents Med. Chem.* **21**, 811–824 (2021).

51. Hornberger, K. R., Berger, D. M., Crew, A. P., Dong, H., Kleinberg, A., Li, A., Medeiros, M. R., Mulvihill, M. J., Siu, K., Tarrant, J., Wang, J., Weng, F., Wilde, V. L., Albertella, M., Bittner, M., Cooke, A., Gray, M. J., Maresca, P., May, E., Meyn, P., Peick Jr, W., Romashko, D., Tanowitz, M. & Tokar, B. Discovery and optimization of 7-aminofuro[2,3-*c*]pyridine inhibitors of TAK1. *Bioorg. Med. Chem. Lett.* **23**, 4517–4522 (2013).

52. El-Gamal, M. & Anbar, H. S. Recent advances of pyrrolopyridines derivatives: a patent and literature review. *Expert. Opin. Ther. Pat.* **27**, 591–606 (2017).

53. Miyamoto, S., Duncan, G. E., Marx, C. E. & Liebermann, J. A. Treatments for schizophrenia: a critical review of pharmacology and mechanisms of action of antipsychotic drugs. *Mol Psychiatry* **10**, 79–104 (2005).

54. Kook, C. S., Reed, M. F. & Digenis, G. A. Preparation of fluorine-18-labeled haloperidol. *J. Med. Chem.* **18**, 533–535 (1975).

55. Manolikakes, S. M., Jaric, M., Karaghiosoff, K. & Knochel, P. Metalated N-heterocyclic reagents prepared by the frustrated Lewis pair TMPMgCl·BF3 and their addition to aromatic aldehydes and activated ketones. *Chem. Commun.* **49**, 2124–2126 (2013).

56. McBee, E.T., Pierce, O. R. & Higgins, J. F. The Reducing Action of Grignard Reagents on Fluorinated Carbonyl Compounds. *J. Am. Chem. Soc.* **74**, 1736–1737 (1952).

57. Kani, R., Inuzuka, T., Kubota, Y. & Funabiki, K. One-Pot Successive Turbo Grignard Reactions for the Facile Synthesis of α-Aryl-α-Trifluoromethyl Alcohols. *Eur. J. Org. Chem.* **2020**, 4487–4493 (2020).

58. Zafrani, Y., Yeffet, D., Sod-Moriah, G., Berliner, A., Amir, D., Marciano, D., Gershonov, E. & Saphier, S. Difluoromethyl Bioisostere: Examining the "Lipophilic Hydrogen Bond Donor" Concept. *J. Med. Chem.* **60**, 797–804 (2017).

59. Hartung, J. & Gallou, F. Ring Closure Reactions of Substituted 4-Pentenyl-l-oxy Radicals. The Stereoselective Synthesis of Functionalized Disubstituted Tetrahydrofurans. *J. Org. Chem.* **60**, 6706–6716 (1995).

60. Dahlén, A., Petersson, A. & Hilmersson, G. Diastereoselective intramolecular SmI_2–H_2O–amine mediated couplings. *Org. Biomol. Chem.* **1**, 2423–2426 (2003).

61. Widjaja, F., Jin, Z., Nash, J. J. & Kenttämaa, H. I. Direct Comparison of Solution and Gas-Phase Reactions of the Three Distonic Isomers of the Pyridine Radical Cation with Methanol. *J. Am. Chem. Soc.* **134**, 2085–2093 (2012).