# Copper-Catalysed Amination of Alkyl Iodides Enabled by Halogen-Atom Transfer

Bartosz Górski,[1†] Anne-Laure Barthelemy,[1†] James J. Douglas,[2] Fabio Juliá[1]* and Daniele Leonori[1]*

[1] *Department of Chemistry, University of Manchester, Oxford Road, Manchester M13 9PL, UK.*

[2] *Early Chemical Development, Pharmaceutical Sciences, R&D, AstraZeneca, Macclesfield, UK.*

† These authors contributed equally to this work.

* fabio.juliahernandez@manchester.ac.uk and daniele.leonori@manchester.ac.uk

**Despite the fact that nucleophilic displacement ($S_N2$) of alkyl halides with nitrogen nucleophiles is one of the first reactions introduced in organic chemistry teaching, its practical utilization is largely limited to unhindered (primary) or activated (α-carbonyl, benzylic) substrates. Here we demonstrate an alternative amination strategy where alkyl iodides are used as radical precursors instead of electrophiles. α-Aminoalkyl radicals enable the efficient conversion of the iodides into the corresponding alkyl radical by halogen-atom transfer (XAT) while copper catalysis assembles the $sp^3$ C–N bonds at room temperature. The process provides "$S_N2$-like" programmability and application in late-stage functionalization of several densely functionalized pharmaceuticals demonstrates its utility in the preparation of valuable *N*-alkylated drug analogues.**

**Introduction.** Nitrogen-rich molecules form the structural basis of almost every pharmaceutical and agrochemical lead as well as many other high-value products like food additives and organic materials.[1] A large fraction of these chemotypes contain bonds between nitrogenated residues and saturated carbons, which makes the development of methods for $sp^3$ C–N bond construction integral to both academia and industry (Scheme 1A).[2-4]

One classical method is *N*-alkylation using alkyl (pseudo)halides using text-book $S_N2$ (bimolecular nucleophilic substitution) chemistry, however, this reactivity has major limitations in complex molecular settings.[5] Indeed, while substitutions on primary substrates are easy to perform, extension to secondary and tertiary is challenging due to their increased steric hinderance. The requirement for forcing conditions (strong bases, high temperatures) often results in low yields and leads to competitive E2-elimination to alkene by-products. The intrinsic difficulties in $S_N2$ reactivity are underscored by the fact that among all the *N*-nucleophilic substitutions reported in the literature, 93% take place on primary alkyl halides while only 6% and 1% involve secondary and tertiary substrates respectively (Scheme 1B).[6] Furthermore, the limited pool of substitutions at secondary centres is largely biased towards the use of activated electrophiles (e.g. benzylic, α-carbonyl), making the frequency of nucleophilic displacement at unactivated secondary halides <1.5%. As a result, the preferred route to assemble C–N bonds on secondary $sp^3$-centers is largely based on the use of ketones via reductive aminations[7,8] but this is only feasible for the reaction of alkylamines and cannot be extended to other valuable *N*-nucleophiles like azoles, amides and carbamates.

The limitations of these polar approaches have recently triggered the exploration of alternative reactivity modes based on radical chemistry. In this context, copper catalysis has demonstrated a unique versatility in orchestrating coupling reactions involving carbon-radical intermediates.[5,9] The success of these transformations generally relies on the ability of Cu(II) complexes to trap carbon-radicals at near diffusion-controlled rates,[10] and then undergo facile reductive elimination from the

resulting high-valent Cu(III) species.[11] The potential of these two elementary steps to assemble a broad array of $sp^3$ C–Y bonds (Y= C, N, O, S, halogen) represents a powerful opportunity for modular fragment coupling.[12]

Despite these prominent features, copper catalysis has seen limited applications to the amination of unactivated alkyl halides.[13,14] As shown in Figure 1C, the overall amination using an [Cu(I)–amido] species would require initial single-electron transfer (SET) reduction of the halide, followed by radical capture to give the [alkyl–Cu(III)–amido] complex that undergoes fast reductive elimination. While radical recombination and reductive elimination are very facile, the low reduction potential of unactivated alkyl halides ($E_{red}$ < –2 V vs SCE) thwarts their activation by Cu(I) ultimately limiting synthetic applications. This lack of reactivity contrasts with the ubiquitous applicability of activated substrates, like α-carbonyl and benzylic halides,[15,16] that are much easier to reduce ($E_{red}$ > –1.5 V vs SCE) and therefore readily engage in Cu-catalysis.

In an effort to address this issue, two main approaches have emerged in recent years, both relying on the use of photochemistry to aid the radical generation step. Fu and Peters reported pioneering works using photochemistry to engage unactivated alkyl and aryl halides in C–N bond formations.[17-19] In these examples, photoexcitation of the transient amido–Cu(I) complex (amido = carbazole, indole, amide) is required to access a highly reducing species from which SET reduction of the organic halides is possible. This strategy hinges on the photochemical performance of the amido–Cu(I) complex and therefore is highly dependent on the *N*-nucleophile structure and often requires high-energy UV-light irradiation (hν = 254 nm).[20]

An alternative avenue for copper-catalysed aminative cross-coupling relies on the combination with visible-light photoredox catalysis and the use of carboxylic acids or their activated derivatives as alkyl radical precursors.[21-23] In these cases, radical generation by SET reduction is facile ($E_{red}$ > –1.5 V vs SCE) but the extension of this approach to unactivated alkyl halides is challenging.

Overall, the limited capacity to access strong reducing species remains the key element restricting general application of copper catalysis in amination chemistry. From this perspective, a strategy able to circumvent the problematic alkyl halide SET reduction, while still benefitting from the ability of copper to forge $sp^3$ C–N bonds by reductive elimination, might provide a powerful tool towards the assembly of complex nitrogenated motifs.

Recently, ourselves[24,25] and the group of Doyle[26,27] have demonstrated that alkyl radicals can be accessed from the corresponding halides exploiting the ability of α-aminoalkyl radicals to trigger halogen-atom-transfer (XAT) reactions. This blueprint for radical generation is facilitated by the interplay of strong polar effects in the transition state of the halide abstraction step[28] and can be used as part of C–C bond-forming strategies like Giese alkylation and Heck-type olefination. We recently questioned if this reactivity mode could be integrated with copper-catalysis to enable $sp^3$ C–N bond formation. Such a strategy would benefit from a carbon-halogen bond activation step occurring outside the copper-cycle, independently from the nature of the *N*-nucleophile and also obviating for the need for additional photocatalysis.

Here, we describe the successful realisation of this proposal and demonstrate that integration of α-aminoalkyl-mediated XAT with copper catalysis is a practical and effective tool to achieve the *N*-alkylation of secondary alkyl iodides. This novel mode for $sp^3$ C–N bond formation is fast, operates under mild conditions, display broad functional group tolerance and can be used in the late-stage functionalization of complex bioactive materials.

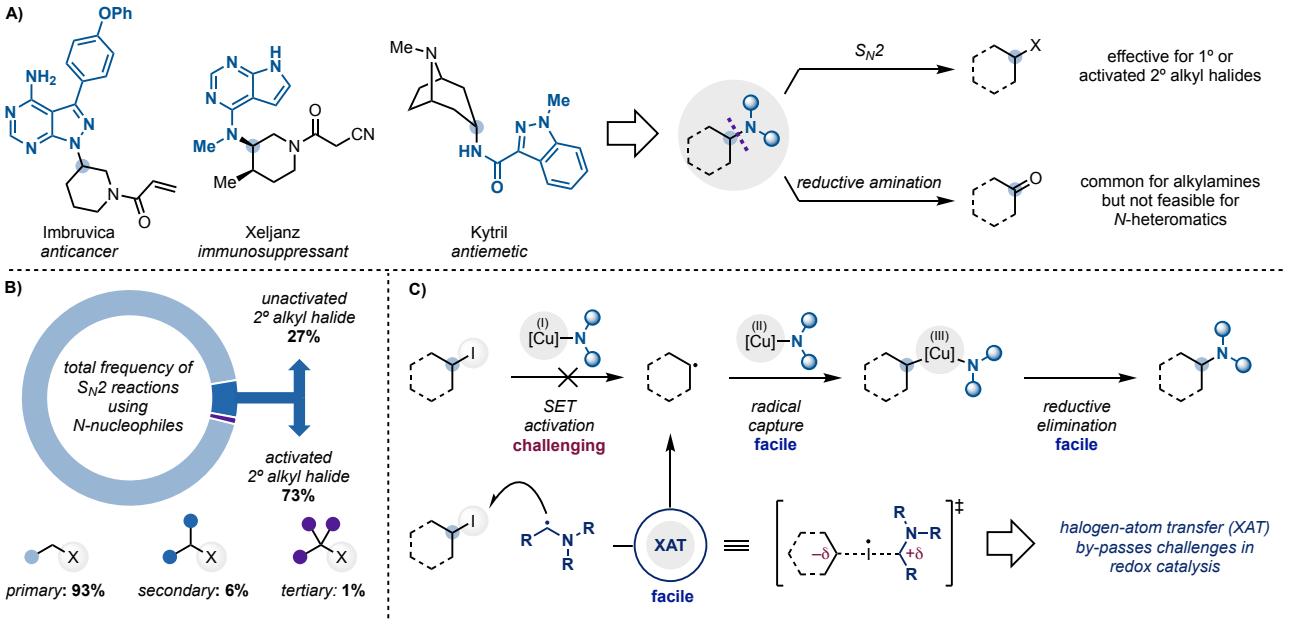



**Figure 1. (A)** Molecules containing $sp^3$ C–N bonds are widespread among many high-value materials. However, these bonds are still challenging to assemble. **(B)** Analysis of substitution reactions involving *N*-nucleophiles and alkyl halides. **(C)** The use of copper catalysis in the amination of unactivated alkyl halides is hampered by the initial SET reduction. Here we demonstrate that halogen-atom transfer (XAT) using α-aminoalkyl radicals can be used to by-pass this issue and enable catalytic $sp^3$ C–N bond formation.

**Reaction design and optimization.** A detailed description of the reaction design for this XAT-Cu mediated amination is provided in Fig. 2A using the coupling of 4-iodo-*N*-Boc-piperidine **1** with 3-chloroindazole **2**. Starting with a Cu(I) catalyst, base-aided azole coordination is expected to afford the [Cu(I)–**2**] complex **A**. At this stage, we postulated that the known ground-state SET between Cu(I) and a peroxide **B** could be used to simultaneously obtain a [Cu(II)–**2**] complex **C** and an electrophilic O-radical **D**.[29] This species would have the appropriate philicity and reactivity profile to undergo HAT selectively at the α-*N* position of alkyl amine **E**.[30] The activated nature (BDE = 91 kcal/mol)[31] and hydridic character of this C–H bond should lead to a polarity matched process resulting in the α-aminoalkyl radical **F**. This species is the key agent for the homolytic activation of iodide **1** through XAT and would generate the alkyl radical **G** (and iminium **H**). At this point, fast capture of radical **G** by **C** would provide the high-valent [alkyl–Cu(III)–**2**] species **I** from which reductive elimination is facile. This last step would forge the targeted $sp^3$ C–N bond in **3** and regenerate the Cu(I) catalyst. The realisation of this approach is not without challenges as it requires the synchronised interplay of SET → HAT → XAT steps and indeed examination of this mechanistic pathway revealed three major aspects potentially hampering reactivity. Since α-aminoalkyl radicals are electron rich species ($E_{ox}$ ~ –1.1 V vs SCE),[30] XAT needs to be faster than both oxidation of **F** by peroxide **B** (leading to **H**) and also capture of **F** by the Cu(II) species **C**, which would result in aminal-type by-products. Furthermore, radical capture of alkyl radical **G** by **C** needs to outcompete a potential H-abstraction from amine **E** which would result in dehalogenation.[6]

With this mechanistic picture in mind, the model reaction between iodide **1** and azole **2** was evaluated. After screening of reaction conditions, we identified an effective protocol leading to the formation of **3** in high yield in just 1 hour at room temperature (Fig. 2B). This process uses $[Cu(CH_3CN)_4]PF_6$ as the catalyst, *n*-$Bu_3N$ as the α-aminoalkyl radical precursor, TMS-protected cumyl peroxide

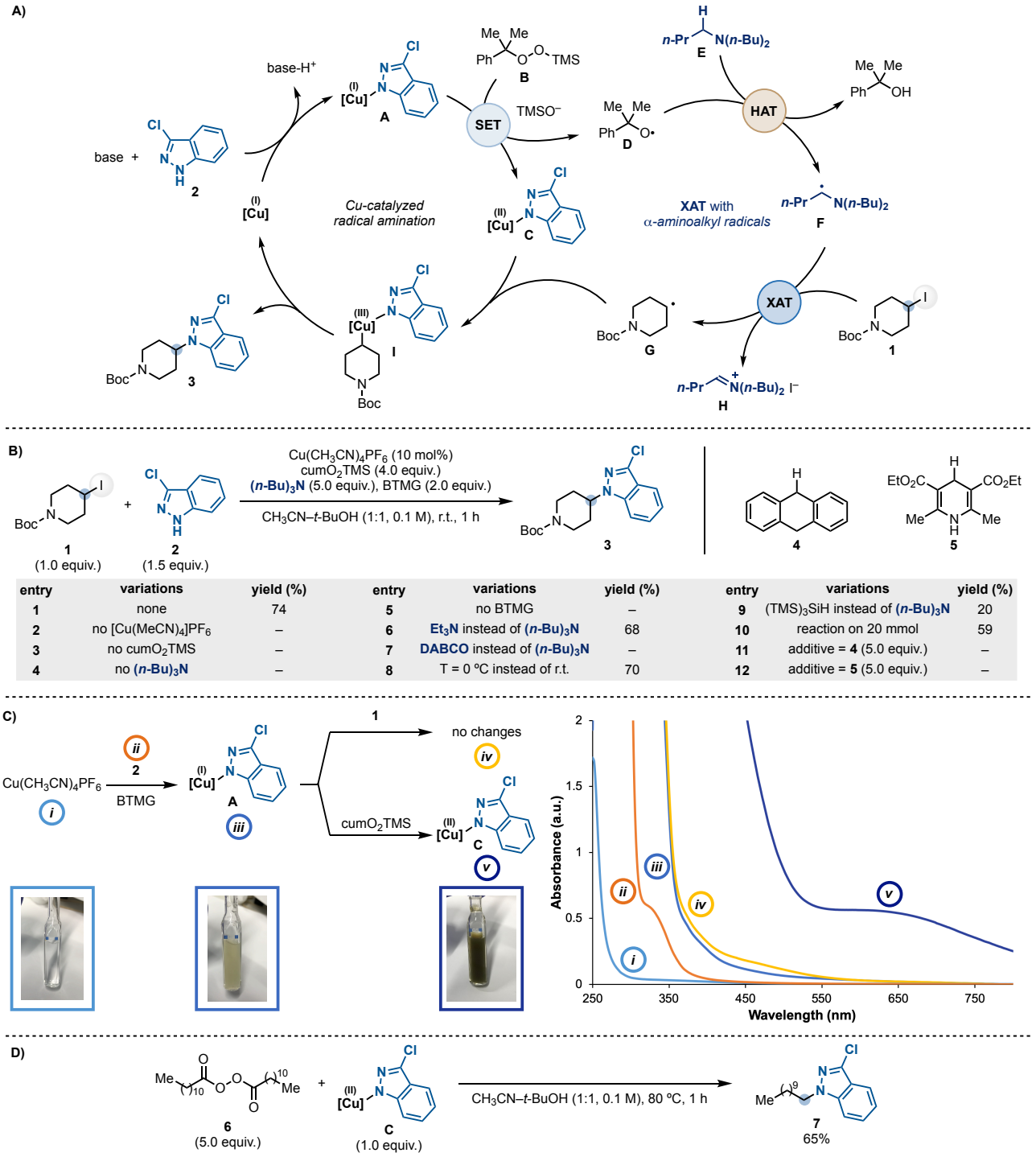
(cumOOTMS) as the oxidant and BTMG (2-*tert*-butyl-1,1,3,3-tetramethylguanidine) as the base in $CH_3CN$–*t*-BuOH solvent. Full details on the optimization are discussed in the Supplementary Material, but some experiments were of high relevance: (1) Control reactions demonstrated that all components (copper catalyst, amine, oxidant and base) were required in order to obtain the product (see entries 2–5). (2) Although *n*-$Bu_3N$ provided the highest reaction yield, other amines were compatible as long as they led to the generation of an α-aminoalkyl radical (see entries 6 and 7). (3) The coupling was also efficient at 0 ºC (entry 8), which is in contrast with the high temperatures (T > 100 ºC) generally required in processes based on Cu/peroxide systems for $sp^3$ C–H functionalization.[32,33] (4) Finally, the use of supersilane,[34] which is frequently adopted as XAT reagent in both classical radical chemistry as well as modern photoredox-based approaches,[35] resulted in low yields owing to competitive dehalogenation (entry 9).

In terms of reproducibility and scalability, the process was insensitive to the presence of water and was run in the laboratory of AstraZeneca up to multi-gram-scale (20 mmol), providing similar yields of **3** (entry 10). Peroxides are often problematic reagents due to their potentially exothermic decomposition. Prior to scale-up, safety assessments performed at AstraZeneca demonstrated the cumOOTMS can be handled safely and does not have explosive properties (DSC analysis showed an exotherm at T > 107 ºC), thus alleviating the initial concerns associated with the scale-up of this methodology.[6]

**Mechanistic studies.** Under our reaction conditions α-aminoalkyl radical **F** is generated by HAT on *n*-$Bu_3N$. The inclusion of additives with weaker and hydridic C–H bonds should therefore interfere with this step and, by outperforming the amine in the reaction with **D**, suppress the coupling process.[32] Indeed, when 5.0 equivalents of 9,10-dihydroanthracene **4** ($BDE_{C–H}$ = 76 kcal/mol)[36] or the Hantzsch ester **5** ($BDE_{C–H}$ = 69 kcal/mol)[37] were incorporated, no product was detected and the alkyl iodide was largely recovered (Fig. 2B, entries 11 and 12). Together with the lack of reactivity observed when amines without α-*N* C–H bonds were employed;[6] these competition experiments prove the fundamental role of the **F** in the C–I bond activation step.

Next, we sought to use UV/Vis absorption spectroscopy to obtain further information on some of the individual steps involved in the copper catalytic cycle (Fig. 2C). When a colourless solution of $[Cu(MeCN)_4]PF_6$ was treated with **2** in the presence of BTMG, a pale yellow solution was formed. The formation of [Cu(I)–**2**] **A** was possible only in the presence of the base as also confirmed by $^1H$ NMR spectroscopy.[6] The addition of alkyl iodide **1** to this solution did not lead to any significant change in the UV/Vis spectrum and the foreseen lack of reactivity between **A** and **1** was also demonstrated by stoichiometric experiments.[6] In contrast, addition of cumOOTMS resulted in an immediate colour change to dark green which corresponded to the appearance of a new absorbance band centred at ~600 nm, matching those reported for other amido–[Cu(II)] complexes.[38,39] This supports the formation of [Cu(II)–**2**] **C** which was further confirmed by comparison with a sample of [Cu(II)–**2**] complex (obtained by mixing $Cu(OTf)_2$ + **2** + BTMG).

Finally, to validate the last step of the copper catalytic cycle, we studied the stoichiometric reaction of **C** with alkyl radicals, generated by thermal decomposition of lauroyl peroxide **6**. As shown in Fig. 2D, the successful formation of **7** provides evidence supporting the proposed radical metalation on [Cu(II)–**2**], followed by reductive elimination that complete our proposed mechanism for $sp^3$ C–N bond assembly.[32]




| entry | variations | yield (%) | entry | variations | yield (%) | entry | variations | yield (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | none | 74 | 5 | no BTMG | – | 9 | $(TMS)_3SiH$ instead of $(n\text{-}Bu)_3N$ | 20 |
| 2 | no $[Cu(MeCN)_4]PF_6$ | – | 6 | $Et_3N$ instead of $(n\text{-}Bu)_3N$ | 68 | 10 | reaction on 20 mmol | 59 |
| 3 | no $cumO_2TMS$ | – | 7 | DABCO instead of $(n\text{-}Bu)_3N$ | – | 11 | additive = **4** (5.0 equiv.) | – |
| 4 | no $(n\text{-}Bu)_3N$ | – | 8 | T = 0 °C instead of r.t. | 70 | 12 | additive = **5** (5.0 equiv.) | – |

**Figure 2. (A)** The proposed mechanism for the amination of 2º alkyl iodides requires the merge of copper-catalysis with XAT reactivity. **(B)** Optimization of the amination process between iodide **1** and *N*-nucleophile **2** and relevant control reactions. **(C)** UV/Vis absorption spectroscopy studies support the individual steps in the catalytic cycle. **(D)** Experiments probing the ability of alkyl radicals to undergo amination by reacting with [Cu(II)–*N*-nucleophile] species.

**Substrate Scope.** The optimized reaction conditions were then applied to a wide variety of *N*-nucleophiles using **1** as the coupling partner (Fig. 3). *N*-Alkylation of azoles is still a recognized challenge in synthetic chemistry, so we were pleased to see that many systems were compatible with our process. This included differentially substituted indazoles (**8**–**11**) and indoles (**12**–**15**), which could incorporate handles for further cross-coupling like chloride, bromide and ester functionality. Pleasingly we succeeded in alkylating a protected tryptophan residue (**16**) and also accessed **17**,

which is a synthetic intermediate for the preparation of the antineoplastic enzastaurin.[40] Carbazole (**18**) and pyrrole (**19**) could be used, as well as a functionalised 7-deazapurine (**20**), which is a common scaffold in many blockbuster drugs like pevonedistat (anticancer).

Aminopyridines are motifs frequently encountered in drug development campaigns and could also be alkylated in high yields. Electronic (**21**–**26**) and steric (**27**) perturbation of the system did not hamper reactivity, and we also succeeded in using the less nucleophilic *N*-phenyl derivative (**28**). Other systems that underwent efficient coupling with **1** were 2-aminoquinoline (**29**), several 2-amino-pyrimidines (**30**–**32**), 2-amino-pyrazine (**33**) as well as 2-aminopyrrolo[2,1-*f*][1,2,4]triazine (**34**), which is found in the structure of many commercial drugs, including remdesivir, an antiviral considered for the treatment of COVID19 infections.[41]

We then considered the possibility of using this chemistry to convert alkyl iodides into primary amines, something challenging with ammonia owing to known over-alkylation issues. Pleasingly, we could engage commercially available benzophenoneimine[42,43] as an effective surrogate providing **35** that, upon simple deprotection, gave primary amine **36**.

The use of carbamates/amides in this coupling process proved difficult (see below) but nonetheless we demonstrate efficient alkylation of a cyclic carbamate (**37**), as well as a β-lactam that gave **38** in near quantitative yield.

The Supplementary Material, contains information regarding additional control experiments run with each class of nucleophiles to rule out background $S_N2$ reactivity. In all cases, no product formation was detected when the reactions were run in the absence of copper catalyst and oxidant.

Our scope evaluation demonstrated wide compatibility with many classes of *N*-reagents, notoriously difficult in classical $S_N2$ settings. In terms of limitations, we did not succeed in extending this chemistry to less nucleophilic benzamide (e.g. **39**) and aniline (**40**). UV/Vis absorption spectroscopy studies were therefore conducted to understand and identify the recalcitrant step in the copper catalytic cycle that was thwarting reactivity. In general, coordination of the *N*-nucleophile to Cu(I) and/or the oxidation of the resulting species are currently believed to be the limiting steps, potentially resulting in unproductive pathways for the alkyl iodide like dehalogenation or elimination.[6] This lack of reactivity has however provided a substantial opportunity for the chemoselective alkylation of complex materials (see below) that would have been very challenging using ionic approaches.

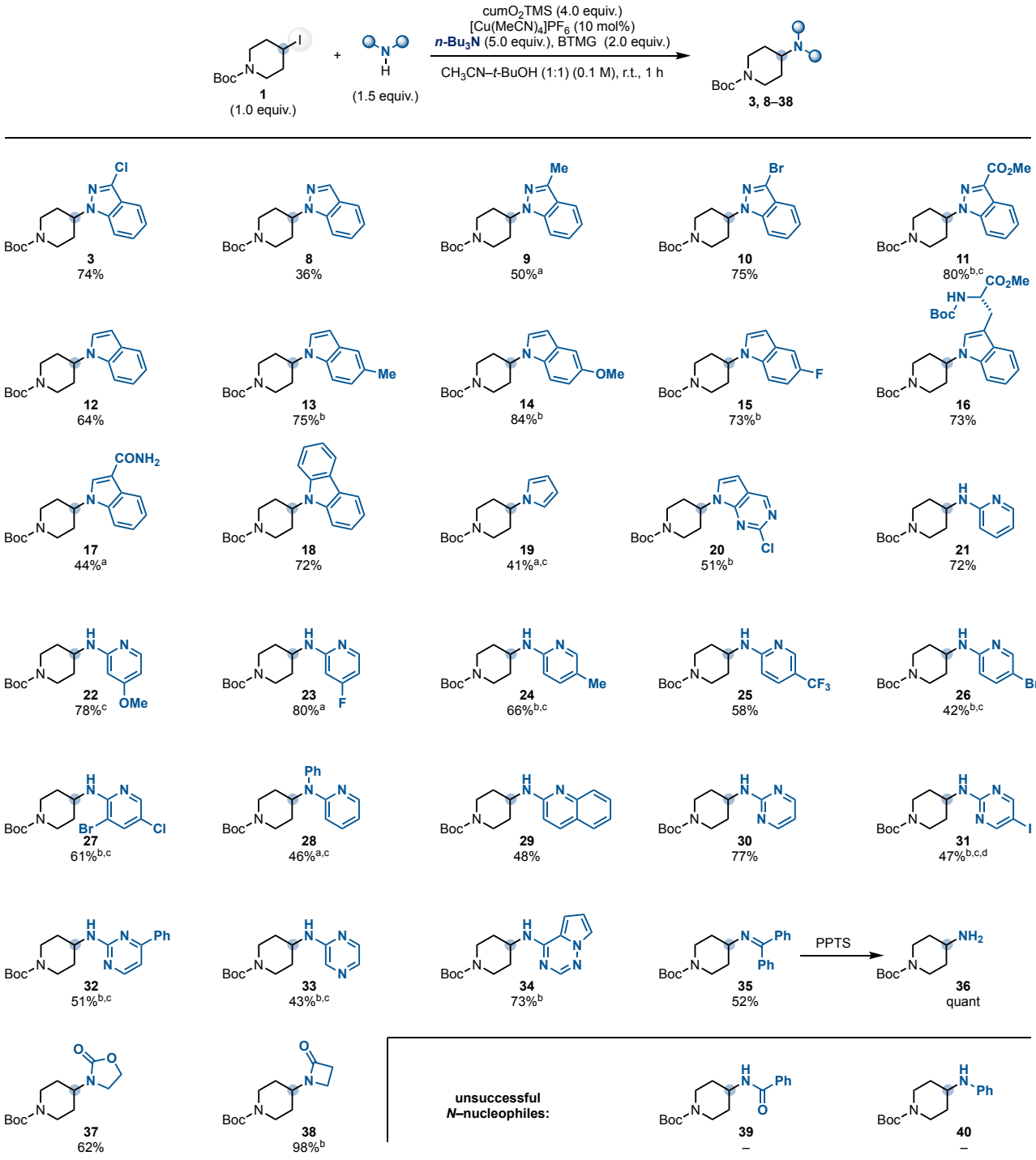



**Figure 3**. Scope of the *N*-nucleophilic partner for the amination of iodide **1**. [a] Reaction performed using CuI as the [Cu(I)] catalyst. [b] Reaction performed using CuCl as the [Cu(I)] catalyst. [c] Reaction performed at 0 ºC. [d] Reaction performed using DMF–$CH_3CN$ (9:1) as the solvent.

The alkyl iodide scope was evaluated using **2** as the nucleophile and our conditions proved general for a broad array of iodides (Fig. 4A). Both cyclic and acyclic systems were successfully engaged as demonstrated by the formation of **41–45**, which also contain HAT-activated benzylic and α-O positions. Several heterocyclic building blocks were evaluated and this included protected 3- and 4-iodo-piperidines (**46** and **47**) which increased the number of functionalities tolerated. Notably, the chemoselective activation of alkyl vs aryl iodides is demonstrated in **47**, which would be difficult by other strategies based on either SET or metal-mediated oxidative addition. This method also enabled coupling of **2** with 4-iodo(thio)pyranes (**48** and **49**), 2-iodo-*N*-Boc-azetidine (**50**) and 2-iodo-oxetane

(**51**). Spirocyclic fragments[44] are now popular in medicinal chemistry campaign to increase the $sp^3$ content in organic leads[45] and our methodology successfully led to the formation of **52** and **53** in good yield while 3-substitued cyclobutyl iodides gave **54** and **55**.

The majority of alkyl iodides used in the scope are commercial building blocks, however a powerful application was found by the preparation of novel nitrogenated scaffolds exploiting secondary alcohols via the Appel reaction and several olefins after iodo-functionalizations. For example, hydroxyl group-containing alkaloid nortropine and 3α-cholestane were used to obtain indazole products **56** and **57** as single diastereomers. Furthermore, iodo-etherification and -fluorination of cyclohexene enabled formation of valuable vicinal α-O and α-F derivatives **58** and **59**, while iodolactonization then amination of norbornene carboxylic acid gave **60** in good yield. In all cases, the diasteroselectivity of the initial iodo-functionalization was inconsequential as the substrates underwent stereoconvergent amination at the less hindered side. Hence, olefin iodo-functionalization represents a powerful gateway to quickly enlarge the pool of substrates available to this aminative coupling which cannot be accessed using, for example, radical strategies based on activated carboxylic acids.

Figure 4B depicts several examples of how this reaction can be applied at a late-stage for the *N*-alkylation of many complex bioactive materials. We succeeded in the selective and high-yielding alkylation of the indole ring in the sleep hormone melatonin in the presence of a tethered *N*-acetamide group (**61**). The oxazolidinone ring in metaxalone (**62**), a widely used muscle relaxant, and the antitussive fenspiride (**63**), were alkylated in high yield. The successful formation of **63** also demonstrate compatibility with tertiary amine functionalities, which are often problematic in photoredox catalysis. The migraine treatment medicine zolmitriptan is an interesting example due to the presence of both free indole and oxazolidinone. Our reaction conditions enabled a complete discrimination between these two nucleophilic sites resulting in the chemoselective alkylation of the azole framework (**64**).

We then applied the method to the alkylation of complex 2-aminopyridine- and 2-amino-pyridimidine-based drugs imiquimod and trimethoprim that gave **65** and **66** in good to excellent yield. In the latter case double alkylation of both nucleophilic $NH_2$ groups was possible by increasing the equivalents of 4-iodopirane. Another example of chemoselective *N*-alkylation, is provided by the formation of **67** from the antiretroviral lamivudine. The success of this example is remarkable as reactivity was exclusive at the 4-aminopyridinone core in the presence of a primary alcohol, two activated positions for HAT and a thioether. Finally, we obtained preliminary results demonstrating applicability of the coupling process in the alkylation of tryptophan residues in small peptides (**68**).

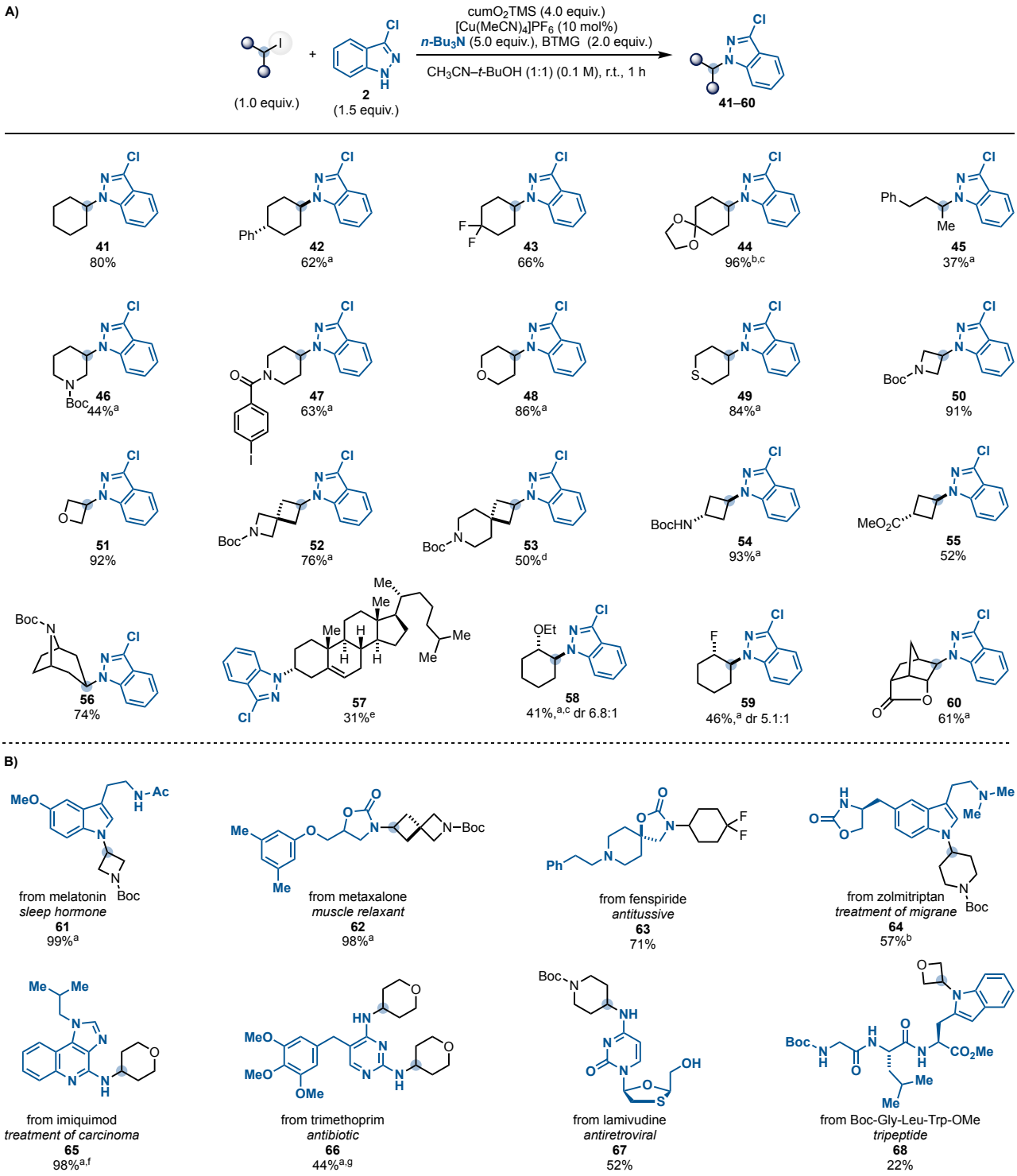



**Figure 4**. **(A)** Scope of the secondary alkyl iodide partner for the amination with *N*-nucleophile **2**. **(B)** Late-stage *N*-alkylations of complex and biologically active materials. [a] Reaction performed using CuCl as the [Cu(I)] catalyst. [b] Reaction performed using CuI as the [Cu(I)] catalyst. [c] Reaction performed at 0 ºC. [d] Reaction performed using CuI (1 mol%) as the [Cu(I)] catalyst. [e] Reaction performed using $CF_3$–$C_6H_5$:$CH_3CN$ (9:1) as the solvent. [f] Reaction performed using DMF:*t*-BuOH (9:1) as the solvent. [g] Reaction performed using DMF:$CH_3CN$ (9:1) as the solvent.

**Conclusions.** In summary, the integration of α-aminoalkyl radical-mediated XAT with copper catalysis has led to the development of an efficient strategy for the coupling of secondary alkyl iodides with *N*-nucleophiles. The utilization of this strategy eliminates the requirement for strong reductants

in the alkyl radical generation step. This reactivity occurs at room temperature under just one hour and enables the preparation of many complex building blocks elusive through $S_N2$ reactivity.

**Data Availability:** The authors declare that all data supporting the findings of this study are available within the supplementary information file. These include: reaction procedures, products characterization, safety studies, cyclic voltammograms, UV/Vis and NMR spectra.

**Acknowledgments:** D. L. thanks EPSRC for a Fellowship (EP/P004997/1) and a Research Grant (EP/T016019/1) and the European Research Council for a research grant (758427). We thank William Ashworth, Paul Gillespie, and Stuart Wells for performing safety studies. We thank Magnus Johansson (AstraZeneca) for useful discussions.

**Author contributions:** F. J. and D. L. designed the project and directed the work. B. G. and A. L. B. performed all the synthetic and mechanistic experiments. J. J. D performed the scale-up experiments. All the authors analysed the results and wrote the manuscript.

**Competing interests:** Authors declare no competing interests.

**Material & Correspondence:** Dr Fabio Juliá, fabio.juliahernandez@manchester.ac.uk; Prof Daniele Leonori, daniele.leonori@manchester.ac.uk.

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