

Carbon-to-nitrogen atom swap enables direct access to benzimidazoles from drug-like indoles

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ABSTRACT

The ability to selectively edit organic molecules at the atomic level has the potential to streamline lead discovery and optimization in the pharmaceutical and agrochemical industry. While numerous atom insertion and deletion reactions have recently been reported, examples of single atom swaps remain scarce due to the challenge of orchestrating the selective cleavage and formation of multiple chemical bonds around the same atom. We herein report a method for the carbon-to-nitrogen atom swap in *N*-alkyl indoles, allowing for the direct conversion of indoles to the corresponding benzimidazoles. The reaction leverages the innate reactivity of the indole scaffold to engage in an initial oxidative cleavage step, followed by oxidative amination, Hofmann-type rearrangement and cyclization. This complex sequence of steps is mediated by the simple combination of commercially available PIDA and ammonium carbamate as nitrogen atom source. The reaction tolerates a wide range of functional groups which is demonstrated by the interconversion of 15 drug-like molecules implying its immediate applicability across a wide range of discovery programs. Furthermore, it shows how leveraging the innate reactivity of a common heterocycle can unlock otherwise challenging skeletal editing reactions.

Main Text

Selectively editing organic molecules at the atomic level has been a longstanding vision of organic chemists.¹ Besides the conceptual appeal of this paradigm, it also bears disruptive potential for the rapid discovery and synthesis of key molecules in diverse areas such as pharmaceuticals, agrochemicals, fragrances or organic materials.² Inspired by venerable organic transformations, like the Beckmann rearrangement, and equipped with new synthetic tools, chemists have recently developed creative approaches to directly edit the core skeleton of molecules.³ For example, numerous methods to insert,⁴⁻⁸ or delete single atoms,⁹⁻¹¹ such as carbon and nitrogen from a molecular framework have recently been disclosed. As an alternative approach to traditional, orthogonal syntheses, these methods represent a straightforward strategy for scaffold diversification. Circumventing labor-intensive *de novo* synthesis by making use of already existing libraries offers tremendous potential to rapidly identify and optimize leads while assessing valuable structure-activity relationships (SARs) and thus, accelerate drug discovery (Figure 1 A). Among skeletal editing strategies, the swap between two atoms is arguably the most challenging variant as it involves the selective sequential cleavage and formation of strong bonds around the same atom. At the same time, this type of transformation is the most appealing from a medicinal chemist's point of view due to minimal changes in the molecule's topology, accounting for its utility in SARs.^{12,13} Recently, various groups reported promising strategies for single atom exchange reactions which expand the toolbox of late-stage editing methodologies. Besides isotope exchange reactions,¹⁴⁻¹⁷ net N-to-C,¹⁸⁻²⁰ O-to-N,^{13,21} as well as C-to-N^{12,22,23} swaps have been disclosed (Figure 1 B). The latter are particularly desirable with regard to the notion of

“necessary nitrogen atoms”²⁴ and their potential to facilitate nitrogen atom scans of the respective parent compound. However, these are among the most challenging reactions to develop, because it is a daunting task to surgically perform and orchestrate a sequence of carbon atom excision, nitrogen insertion, and ring closure, all while not altering any other peripheral functional groups. A strategy to circumvent this challenge is to pre-install an azide onto an arene, which - upon nitrene generation - can insert into benzene rings ultimately forming pyridines.²³ A complementary strategy can convert quinoline *N*-oxides, a specific class of *N*-heterocycles, to quinazolines in a three-step protocol.¹² The creativity and complexity of these protocols not only underscore the challenges mentioned above, but also reveal numerous critical limitations in the state-of-the-art: 1) the vast majority of (hetero)arenes cannot be employed for a C-to-N swap; 2) substrate pre-activation (versus using the “native” heterocycle) is necessary, limiting their applicability, particularly with regard to late-stage derivatization of drug-like molecules.

Indoles and related π -excessive *N*-heterocycles (e.g., aza-indoles) are prime examples of desirable substrates for the development of a C-to-N swap. They are present in a large number of commercial drugs (ranking #6 of the most frequently appearing *N*-heterocycles among FDA-approved drug molecules as of 2024),²⁵ owing to their abundance in naturally occurring alkaloid compounds. Despite their wide-spread application in drug development programs, indoles are considered challenging scaffolds in modern drug discovery campaigns as they tend to be oxidized easily at their metabolic soft spots (i.e., 2- and 3-position) to highly reactive metabolites, leading to undesirable absorption-distribution-metabolism-excretion (ADME) and/or toxicity profiles.²⁶ Changing from a more electron rich heterocycle, like an indole, to a less electron rich one, such as a benzimidazole, often has a positive effect on pharmacokinetics (Figure 1 C top) by removing metabolic soft spots and decreasing Phase I (cytochrome-P450-enzyme) oxidations, ultimately improving the success rate in lead optimization campaigns.²⁷⁻²⁹ In addition, easy remodeling of indole drugs to benzimidazoles would allow for a rapid library extension and thus, open new avenues for lead identification and optimization due to a substantial change in the drug’s pharmacological properties, and the introduction of a new target binding site with the potential of boosting potency (Figure 1 C bottom). However, there is currently no method to directly convert indoles into benzimidazoles through a C-to-N swap, despite the enormous synthetic potential of such a process to perform late-stage diversification campaigns. Ideally, such a reaction would directly convert “native” indole substrates, without any pre-functionalization, under simple reaction conditions to ensure rapid adoption by synthetic practitioners.³⁰

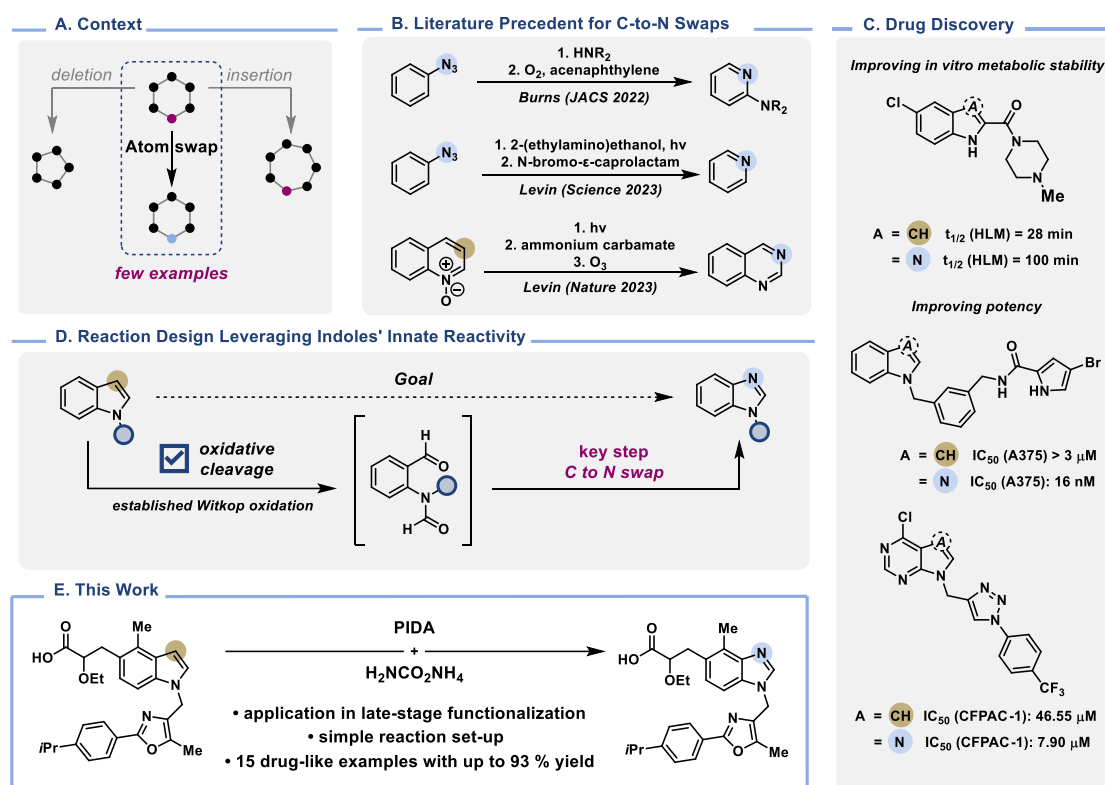


Figure 1. A. Context of the work. B. Literature precedents for carbon-to-nitrogen atom swaps. C. Examples of the “necessary nitrogen” effect by exchanging a carbon atom for a nitrogen atom.^{31–33} D. Reaction design for the direct transformation of indoles to benzimidazoles via the Witkop Oxidation intermediate. E. Developed carbon-to-nitrogen atom swap methodology using ammonium carbamate and phenyliodine(III) diacetate (PIDA).

In our design (Figure 1 D), we aimed to avoid the use of pre-activation strategies to develop an operationally simple C-to-N swap in indoles. The most efficient approach would therefore be to leverage the innate reactivity of the native indole skeleton to initiate this process. We thus envisaged a strategy in which the oxidative cleavage (Witkop Oxidation)^{34,35} of the electron rich indole ring could be used for the initial ring-cleavage step to access a dicarbonyl intermediate. Next, we would need to excise a carbon unit and replace it with a nitrogen atom, before the final ring closure, to form the aromatic benzimidazole product. All steps would need to be orchestrated in a single reaction to maximize practicality and truly allow for a direct indole to benzimidazole conversion without altering the peripheral functional groups.

Herein, we describe the successful development of such a C-to-N swap reaction in which native indole and azaindole substrates are directly converted to the corresponding benzimidazoles and azabenzimidazoles using inexpensive, commercially available reagents. This highly functional group tolerant reaction was demonstrated on a large number of drug-like molecules, unambiguously showcasing its potential for the immediate discovery of new medically relevant compounds (Figure 1 E).

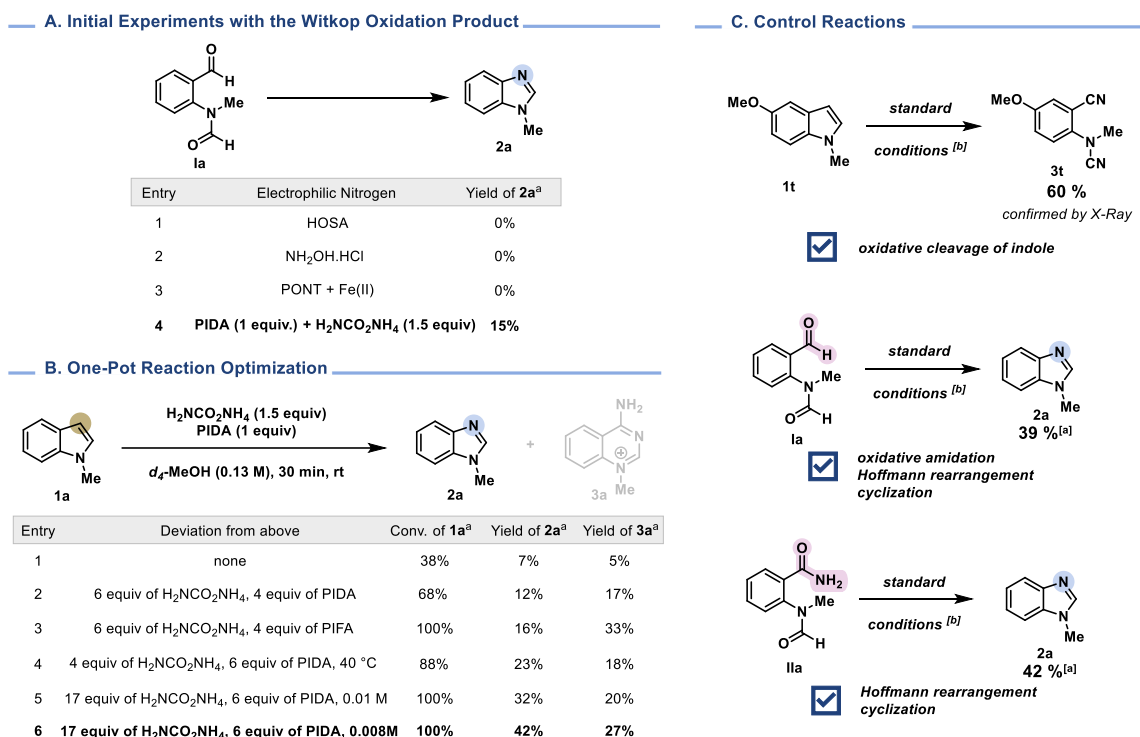


Figure 2. Reaction development. A. Experiments with *N*-(2-formylphenyl)-*N*-methylformamide **1a** to access methylbenzimidazole **2a**. Reactions were performed on 0.10 mmol scale. B. Optimization of the carbon-to-nitrogen atom swap with methylindole **1a** as model substrate. Reactions were performed on 0.10 mmol scale. C. Control experiments with different possible reaction intermediates. [a] Conversion and yields were determined using ¹H-NMR spectroscopy of the crude reaction mixture using 1,2-dimethoxyethane (1,2-DME) as an internal standard. [b] Standard conditions refer to PIDA (6.0 equiv) and ammonium carbamate (17.0 equiv) in *d*₄-MeOH (0.008 M) at room temperature performed on 0.10 or 0.25 mmol scale.

In order to test the viability of our hypothesis and evaluate possible reaction conditions, we initially focused on possible rearrangement reactions starting from the Witkop Oxidation product **1a**, as this compound is readily accessible from the oxidative cleavage of the corresponding methyl indole **1a**.³⁶ In these preliminary experiments, we explored a range of conditions that are known to facilitate Beckmann or Hofmann-type rearrangements, as well as conditions for the electrophilic amination of hydrocarbons (e.g., Fe(II)/PONT,³⁷ iodoniitrenes), aiming at detecting the formation of the corresponding benzimidazole **2a**. While most conditions failed to give the desired product, a combination of a hypervalent iodine reagent and ammonium carbamate gave the first positive results, allowing the formation of *N*-methylbenzimidazole **2a** in 15% ¹H-NMR yield (Figure 2 A).

Given that hypervalent iodine reagents can also be used for the oxidative cleavage of indoles,^{38,39} we directly attempted a one-pot reaction from indoles under the same reaction conditions. Excitingly, we obtained a low but promising ¹H-NMR yield of 7% of the desired product **2a** allowing the direct conversion of methyl indole **1a** to the corresponding benzimidazole product (Figure 2 B). Further optimization of this reaction led to an improved ¹H-NMR yield of 42% when more equivalents of ammonium carbamate and oxidant were employed at lower reaction concentration (see SI for details). Notably, 27% of 4-amino-1-methylquinazolin-1-ium **3a** was also obtained as a side-product but could easily be separated from the desired product of the reaction (see SI for details).

Intrigued by the possibility to realize this cascade transformation, involving multiple bond cleaving and reforming steps under a single set of reaction conditions, we next conducted several control experiments (Figure 2 C). When 5-methoxy-1-methyl indole **1t** was subjected to the reaction conditions, a dinitrile species **3t** was isolated as a major side product, presumably originating from the overoxidation of the Witkop intermediate, confirming the occurrence of oxidative cleavage in the process. Next, we subjected a series of compounds to the reaction conditions to evaluate their chemical competence as possible intermediates. The Witkop substrate **1a** gave the desired product in similar yield (39 % compared to 42%

with **1a** as starting material), supporting its possible intermediacy in the overall one-pot process. We envisage that under our reaction conditions this compound could next be converted to a primary amide through an oxidative amidation pathway in analogy to a literature-known process.⁴⁰ We thus probed whether amide **1la** could be a competent intermediate, and again obtained the desired product **2a** in a similar yield. Mechanistically, this intermediate could then undergo a Hofmann-type rearrangement, which is also known to be mediated by hypervalent iodine reagents,^{41,42} and a final cyclization step could explain the benzimidazole product formation.

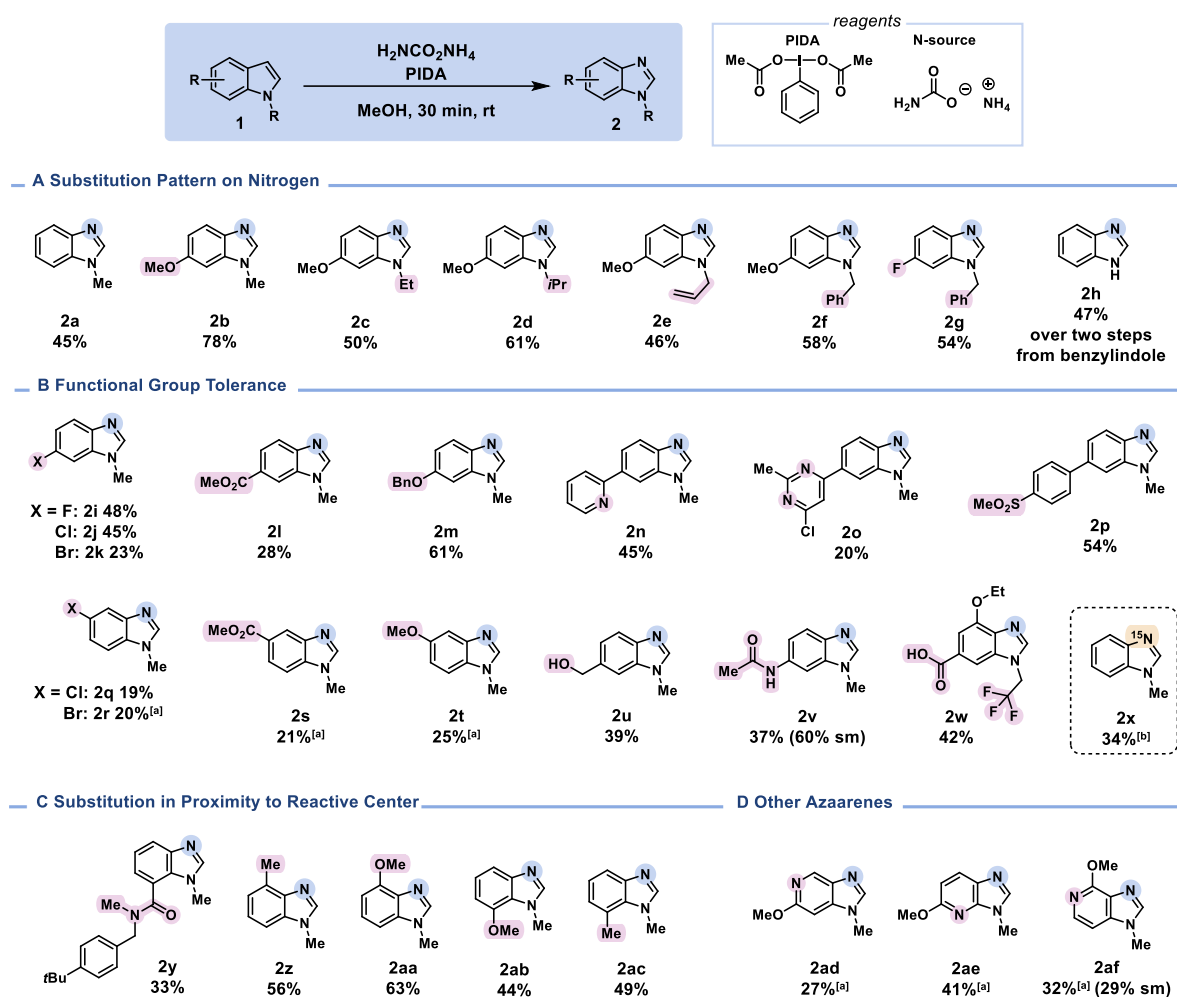


Figure 3. Substrate scope for the carbon-to-nitrogen atom swap. Yields are given for isolated products unless stated otherwise. Recovered starting material (sm) is stated in brackets. Reaction conditions: indole (0.10-0.25 mmol) and ammonium carbamate (17.0 equiv) were dissolved in methanol (0.008 M) in a pressure tube. After 15 min of stirring, PIDA (6.0 equiv) was added, and the reaction mixture was stirred for another 15 min at rt. [a] To achieve further conversion, monitored by ¹H-NMR after solvent evaporation, an additional portion of the reagents and solvent was added. [b] Modified reaction conditions were used: ¹⁵N-ammonium chloride (17.0 equiv), K₂CO₃ (17.0 equiv), PIDA (6.0 equiv) in 0.008 M methanol.

With the optimized reaction conditions in hand, we set out to explore the functional group tolerance and synthetic utility of this transformation. The reaction tolerates different alkyl-groups on the indole nitrogen, giving the corresponding benzimidazoles in good yields (Figure 3 A). Little influence of steric hindrance of those groups was observed, and this generality is important in the context of late-stage skeletal editing of drug-like molecules (*vide infra*). Groups which are commonly used as protecting groups, i.e., the benzyl-group in molecule **1h**, were also well tolerated under the reaction conditions, allowing for an atom swap-dealkylation sequence to access the free NH benzimidazole product **2h** in 47% isolated yield over two steps.

Indoles with electron-donating functional groups, including methoxy- and amide-groups, allowed access to the corresponding atom swap products **2b** and **2v** in good yields. Benzimidazoles with

electron-withdrawing groups, such as halogens (**2i** to **2k** and **2q** and **2r**), esters (**2l** and **2s**), or sulfones (**2p**), were obtained in moderate to good yields. Moreover, indoles bearing a free alcohol (**2u**) or pyridine substituents (**2n**) performed well and gave the desired benzimidazole. Despite being structurally simple, the access to several of these benzimidazoles is restricted given the limitations in common benzimidazole syntheses *via* condensation reactions⁴³ or selectivity issues in the *N*-alkylation of benzimidazoles.⁴⁴ For both electron-donating and -withdrawing substituents, substitution in the 5-position (**2q** to **2t**) decreased the yield due to the formation of the dinitrile derivative of the Witkop intermediate as a side product (*vide supra*). In those cases, it was necessary to add a second portion of reagents to achieve full starting material conversion. Indoles with substituents in proximity to the reactive center, i.e. substituents in 4- or 7-positions (**2y** to **2ac**), were also efficiently transformed into the corresponding benzimidazoles (Figure 3 C). To our delight, the C-to-N atom swap could also be successfully applied to various aza-indoles (**2ad** to **2af**, Figure 3 D). This further expands the synthetic utility of our method since protocols to access those imidazopyridines remain scarce regardless of their high relevance in medicinal chemistry.²⁵ Despite the broad generality of this method, nitro, nitrile, and boronic ester functional groups were not tolerated (see SI for details). A slightly modified protocol allowed for the synthesis of ¹⁵N-labeled methyl benzimidazole **2x**.

Drug-Like Substrates

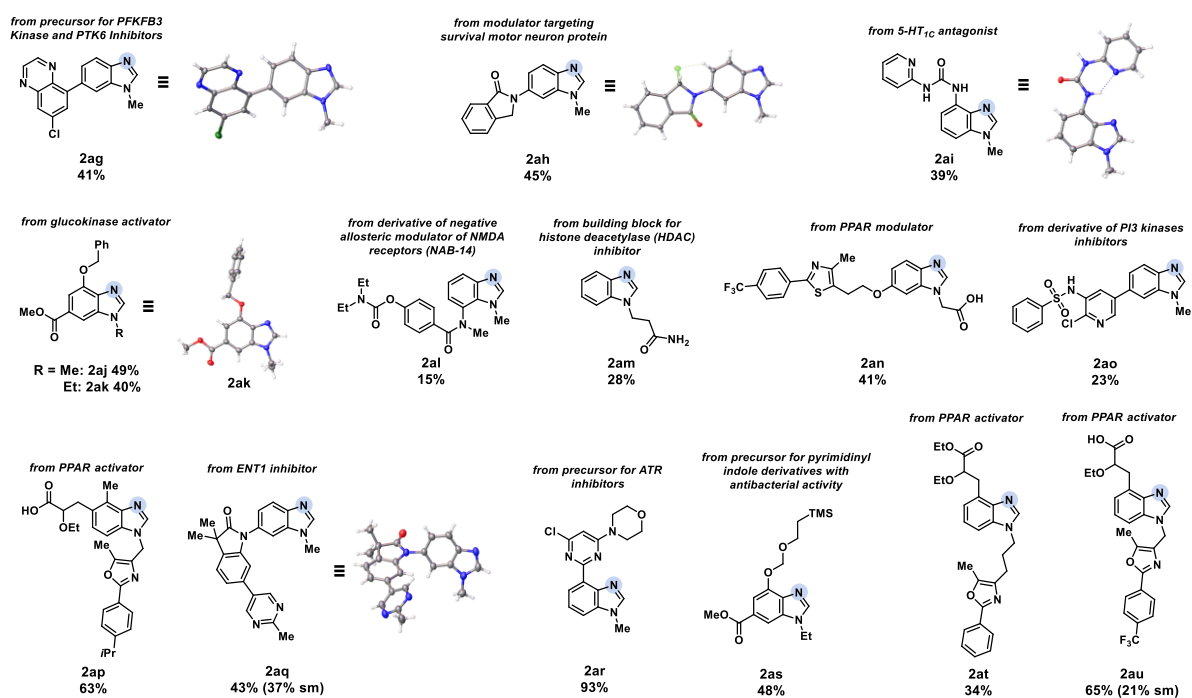


Figure 4. Carbon-to-nitrogen atom swap methodology applied to drug-like molecules. Reactions were performed on 0.10-0.35 mmol scale, depending on the availability of the substrate. Yields are given for isolated products unless stated otherwise. Recovered sm is stated in brackets. Reactions conditions: indole (0.10-0.35 mmol) and ammonium carbamate (17.0 equiv) were dissolved in methanol (0.008 M) in a pressure tube. After 15 min of stirring, PIDA (6.0 equiv) was added, and the reaction mixture was stirred for another 15 min at rt. [a] To achieve further conversion of the starting material, monitored by ¹H-NMR after solvent evaporation, an additional portion of solvent and reagents was added.

Since the above-described results clearly showed the potential of our methodology to access relevant benzimidazole building blocks while tolerating numerous functional groups, the main application area of this process would be for the late-stage diversification of drug-like compounds. We therefore tested our protocol on a wide range of complex, densely functionalized molecules (Figure 4). The corresponding benzimidazole **2ag** of a precursor derivative for a PFKFB3 kinase⁴⁵ and PTK6 inhibitor⁴⁶ was obtained in 41% isolated yield, demonstrating that other *N*-heterocycles remain intact under the reaction conditions. The skeleton of drug derivative **1ah** – a structural motif common in compounds known to target the survival motor neuron⁴⁷ – gave the corresponding benzimidazole product (**2ah**) in 45% isolated yield, leaving the lactam moiety untouched. Furthermore, a 5-HT_{1c}

antagonist analogue⁴⁸ was successfully transformed into the corresponding benzimidazole **2ai** in 39% isolated yield, demonstrating the reaction's compatibility with urea groups. The benzimidazole analogues of a glucokinase activator (**2aj**)⁴⁹ and a related derivative (**2ak**) could directly be accessed in 49% and 40% isolated yield, respectively. The derivative of NAB-14, a negative allosteric modulator of NMDA receptors,⁵⁰ afforded the corresponding atom swap product **2al** in 15% isolated yield. An HDAC inhibitor motif⁵¹ yielded the desired product **2am** in 28%, showing the reaction's tolerance to primary amides. Moreover, a PI3 kinase inhibitor⁵² **1ao** gave the corresponding benzimidazole derivative **2ao** in 23% isolated yield, further showcasing the functional group compatibility of the atom swap with medically relevant sulfonamides. To our delight, compound **1aq**, an ENT1 inhibitor,⁵³ gave the desired product **2aq** in 43% isolated yield. It was further demonstrated that valuable building blocks (compound **2an**, **2ar** and **2as**)⁵⁴ can be transformed into the corresponding benzimidazoles in up to 93% yield, underlining the broad functional group tolerance. Finally, a series of PPAR modulators (compound **2ap**, **2at** and **2au**) yielded the desired product in up to 65% isolated yield, showcasing the reactions compatibility with oxazoles and thiazoles and its applicability in SARs with advanced leads. The identity of **2ag**, **2ah**, **2ai**, **2ak** and **2aq** were unambiguously confirmed by single crystal X-ray analysis. Overall, the C-to-N atom swap shows excellent compatibility with functional groups relevant in medicinal chemistry and applicability to complex, drug-like molecules.

In summary, we have developed a reaction that can directly convert structurally complex *N*-alkyl indoles to the corresponding benzimidazoles in a single step using commercially available reagents without the need of pre-installed functional groups. Given the simple reaction conditions and the applicability to complex drug-like structures, we believe that this reaction will have an immediate impact on discovery programs in the pharmaceutical and agrochemical industry. This study also demonstrates that utilizing the innate reactivity of common heterocycles can pave the way for powerful new strategies in atom swapping reactions.

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DATA AND MATERIALS AVAILABILITY

X-ray data for compounds are freely available at the Cambridge Crystallographic Data Centre under deposition CCDC 2379390 and 2388835-2388840.

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AUTHOR CONTRIBUTIONS

A.-S.K.P. conceived the project. A.-S.K.P., Y.B., B.B.B., E.S. and O.G. conducted the experimental work and analyzed the data. B.M. supervised the research. A.-S.K.P. and B.M. wrote the manuscript with input from all authors.

COMPETING INTERESTS

The authors declare that they have no competing interests.