Article

Couple-close construction of polycyclic rings from diradicals

https://doi.org/10.1038/s41586-024-07181-x

Received: 17 October 2023

Accepted: 8 February 2024

Published online: 13 March 2024

Check for updates

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Heteroarenes are ubiquitous motifs in bioactive molecules, conferring favourable physical properties when compared to their arene counterparts[1–3]. In particular, semisaturated heteroarenes possess attractive solubility properties and a higher fraction of sp^3 carbons, which can improve binding affinity and specificity. However, these desirable structures remain rare owing to limitations in current synthetic methods[4–6]. Indeed, semisaturated heterocycles are laboriously prepared by means of non-modular fit-for-purpose syntheses, which decrease throughput, limit chemical diversity and preclude their inclusion in many hit-to-lead campaigns[7–10]. Herein, we describe a more intuitive and modular couple-close approach to build semisaturated ring systems from dual radical precursors. This platform merges metallaphotoredox C(sp^2)–C(sp^3) cross-coupling with intramolecular Minisci-type radical cyclization to fuse abundant heteroaryl halides with simple bifunctional feedstocks, which serve as the diradical synthons, to rapidly assemble a variety of spirocyclic, bridged and substituted saturated ring types that would be extremely difficult to make by conventional methods. The broad availability of the requisite feedstock materials allows sampling of regions of underexplored chemical space. Reagent-controlled radical generation leads to a highly regioselective and stereospecific annulation that can be used for the late-stage functionalization of pharmaceutical scaffolds, replacing lengthy de novo syntheses.

The introduction of saturation into pharmaceutical candidates often leads to improvements in a variety of medicinal properties[11–14]. Semisaturated fused ring systems in particular show enhanced solubility, target binding affinity and specificity, along with decreased toxicity when compared to their fully aromatic analogues[15]. However, the synthesis of these semisaturated ring scaffolds is typically an arduous process, requiring several steps, bespoke functionalized heterocycles, de novo synthesis of the aromatic fragment[16–19] and, for some simpler substrates, selective semireduction of a fused-aromatic precursor[20]. Numerous methods exist for (semi)saturated ring formation such as selective hydrogenation[21], classical cycloadditions (for example, Diels-Alder, dipolar [3+2])[22,23], photochemical [2+2][24], heterocycle syntheses (for example, Fischer, Paal–Knorr, Larock)[25], ring-closing olefin metathesis[26–29] and radical-type cyclizations[30–32]. However, fused semisaturated systems in particular can remain challenging to access due to synthetic inaccessibility of precursors or functional group incompatibilities with transition metal catalysts, especially in substrates containing basic nitrogen atoms. Methods for direct annulation from commercially available feedstocks would be exceptionally valuable because they would provide efficient access to semisaturated ring scaffolds en route to therapeutically relevant candidates for biological testing. Here, we report a new conceptual framework for the modularly controlled late-stage installation of saturated rings onto complex, polyfunctionalized aromatic scaffolds. This strategy uses a couple-close approach to provide a new avenue for complex substrate diversification and allow for substantial streamlining of challenging synthetic sequences (Fig. 1a).

This new strategy uses metallaphotoredox catalysis for the initial bond-forming step, a powerful tool that combines radical generation from native functional groups with the versatility of transition metal based cross-coupling[33–35]. Our group has a longstanding interest in synergistically merging nickel and photoredox catalysis to convert native functionalities into highly reactive open shell intermediates. Ring closure then occurs through a second radical transformation: a Minisci-type cyclization, in which a tethered carbon-centred radical alkylates the heteroaromatic ring[36]. Although this transformation originally required fairly oxidizing conditions, milder variants have since been developed including photoredox transformations[37,38]. We proposed that this general synthetic strategy could be used to achieve the proposed late-stage annulation protocol. Specifically, we imagined a diradical synthon that would be accessed through photoredox chemistry from highly abundant bifunctional radical precursor feedstocks, such as diols, haloacids and haloalcohols[39]. Recognizing that appropriate reagents must possess functionality suitable for sequential activation under mild and orthogonal conditions to ensure high regioselectivity and broad substrate scope, we chose to pursue a reagent-controlled approach to chemoselective radical generation. Specifically, we postulated that bromoalcohols and diols might serve

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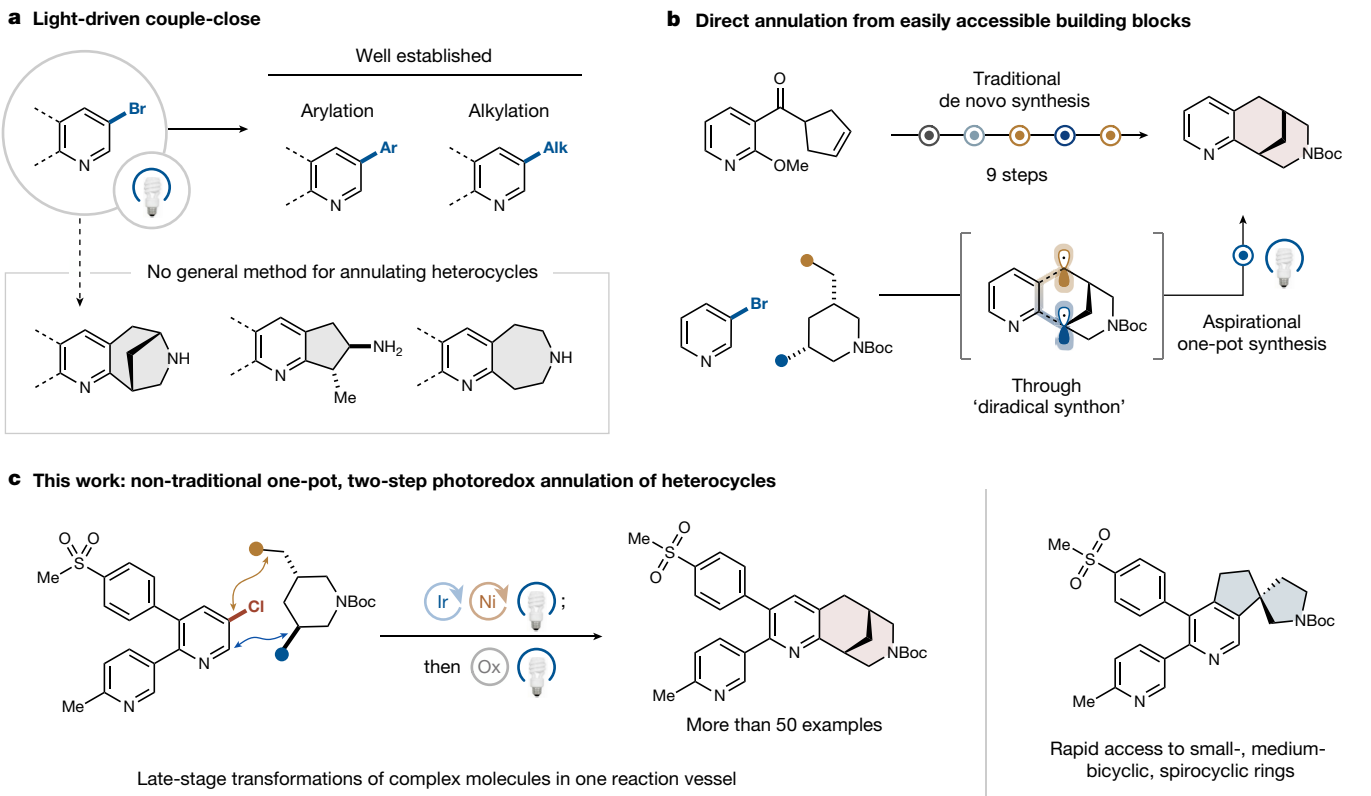

Fig. 1 | Direct annulation from bifunctional fragments. a, Photoredox catalysis enables various chemical transformations; however, annulation has not been explored. **b**, Traditional methods of constructing rings require lengthy synthesis. **c**, The success of ring construction relies on the successful merger between dual photoredox catalysis and nickel catalysis methods in a one-pot fashion. This fragment stapling method can be used for late-stage ring construction of drugs. Boc, *tert*-butyloxycarbonyl.

as suitable bifunctional radical precursors. Notably, alkyl halides and alcohols are simple, abundant and stable functional motifs. These functional groups can be converted to the corresponding radicals by mild and orthogonal protocols involving silyl radical-mediated halogen atom transfer[40,41] or deoxygenative homolytic fragmentation enabled by *N*-heterocyclic carbene (NHC)-based reagents[42]. Moreover, selective alcohol activation of a polyol substrate can be achieved using steric principles, thereby potentially unlocking abundant unsymmetrical diols as valuable diradical synthons. Under our proposed model, selective radical coupling with one of the functional handles would serve to append the fragment onto the aromatic coupling partner. The resulting system would then be primed for subsequent intramolecular radical cyclization (Fig. 1b).

With this design, we proceeded to interrogate whether simple bromoalcohols and diols could be suitable building blocks for regiocontrolled synthesis of structurally complex semisaturated targets. Initial efforts were focused on first tethering the alkyl fragment by means of deoxygenative metallaphotoredox cross-coupling followed by the appropriate secondary activation to facilitate radical annulation (Fig. 1c).

The planned annulation proceeds by means of bromoalcohol or diol cross-coupling with the aromatic scaffold, followed by net oxidative intramolecular cyclization (see Extended Data Fig. 1 for a mechanistic scheme). On evaluating reaction conditions, we determined that modifications to the established deoxygenative arylation protocol would be required for each of these two bifunctional reagent classes. First, bromoalcohol cross-coupling required the use of non-nucleophilic mild amine base 2,2,6,6-tetramethylpiperidine, rather than more nucleophilic quinuclidine, to avoid deleterious alkylation side pathways. The resultant bromoalkyl pyridine intermediates underwent smooth cyclization in a one-pot manner on addition of tris(trimethylsilyl)silane as the halogen atom transfer reagent, $ZnCl_2$ as a Lewis acidic activator and acetonitrile as an additional solvent, with irradiation in an Integrated Photoreactor and atmospheric oxygen as the terminal oxidant. We next investigated the diol system. The diol cross-coupling required the use of a more nucleophilic base, quinuclidine, to enable rapid arylation. Then, the resulting hydroxyalkyl pyridines underwent cyclization in optimal yield by means of a second in situ alcohol activation (with $ZnCl_2$ as a Lewis acid activator but using $KClO_3$ as oxidant, and a methyl *tert*-butyl ether (MTBE)–dimethylacetamide (DMA) solvent mixture). Following independent optimization of each step with both the bromoalcohol and diol substrates, the one-pot protocol was performed in a single reaction vessel without notable loss in yield (see the Supplementary Information for optimization details).

Having developed optimized conditions for the one-pot radical annulations, we proceeded to investigate the scope of both reactions. Using *N*-Boc-(*S*)-2-amino-4-bromobutanol **2** as the bromoalcohol and *N*-Boc-*trans*-4-hydroxy-L-prolinol **3** as the diol, we were pleased to find that a range of structurally and electronically differentiated heterocycles underwent successful annulation (Fig. 2). Notably, the scaffolds shown here are sparsely reported in the literature and are challenging to synthesize by other methods; structurally similar fused or bridged systems require semiselective hydrogenation or multistep heterocycle synthesis. We examined the amenability of the transformation to a wide range of heterocycles, focusing our attention on over nine classes of heterocycles including non-traditional radical acceptors commonly found in drugs. Under our optimized conditions, bromopyridines with substitution at the 4 position underwent 2,3-annulation to generate 5,6,7,8-tetrahydroquinoline scaffolds (**4**–**8**, **15**–**18**), whereas 2-substituted pyridines were converted exclusively to the corresponding 5,6,7,8-tetrahydroisoquinolines (**9**, **10**, **19**, **20**). Electron-poor pyridines were generally effective with both

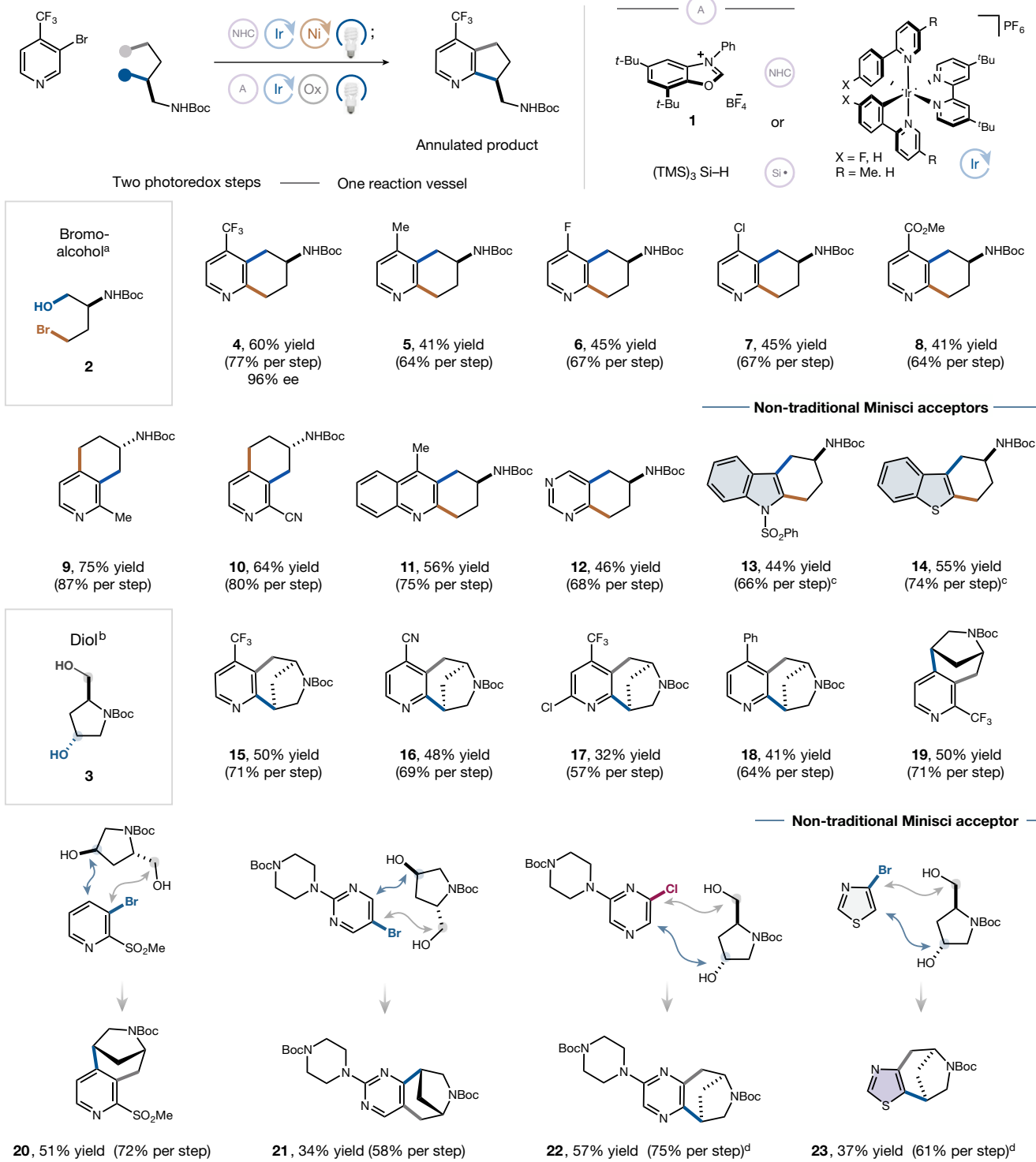

Fig. 2 | Annulation with diverse heteroaryl halide precursors. All yields are isolated unless otherwise indicated. See Supplementary Information for full reaction conditions for each substrate. [a]Standard bromoalcohol conditions: 1 equiv. heteroaryl bromide, 1.4 equiv. bromoalcohol, NHC and pyridine, 1.5 mol% Ir photocatalyst, 5–10 mol% $NiBr_2$•dtbbpy, 1.4 equiv. 2,2,6,6-tetramethylpiperidine, MTBE/DMA (1:1, 0.05 M), blue LEDs, 2 h then add 1 equiv. $(TMS)_3SiH$, 5 equiv. $ZnCl_2$, MTBE/DMA/MeCN (1:1:4, 0.017 M), open to air, blue LEDs, 12 h. [b]Standard diol conditions: 1 equiv. heteroaryl halide, 1 equiv. diol, 1.2–1.3 equiv. NHC and pyridine, 1.5 mol% Ir photocatalyst, 8 mol% $NiBr_2$•dtbbpy, 1.75 equiv. quinuclidine, MTBE/THF (1:1, 0.05 M), blue LEDs, 5 h then 1.6 equiv NHC and pyridine, 1.5 mol% Ir photocatalyst, 3 equiv. quinuclidine, 2.5 equiv. $ZnCl_2$, 2 equiv. $KClO_3$, MTBE/DMA (1:1, 0.05 M), blue LEDs, 6 h. [c]Assay yield from ^{1}H NMR. [d]22.5 mol% phthalimide was added to the cross-coupling step. Boc, *tert*-butyloxycarbonyl; *t*-Bu, *tert*-butyl; TMS, trimethylsilyl.

the bromoalcohol and diol coupling partners: 2,3- and 3,4-annulated products were formed efficiently across both steps for either transformation (**4**, **6**–**8**, **10**, **15**–**17**, **19**, **20**, 32–64% yield, 57–80% yield per step). Electroneutral and electron-rich pyridines were also annulated in good yield (**5**, **9** and **18**, 41–75% yield, 64–87% per step). Beyond pyridine substrates, other aromatic heterocycles were amenable to

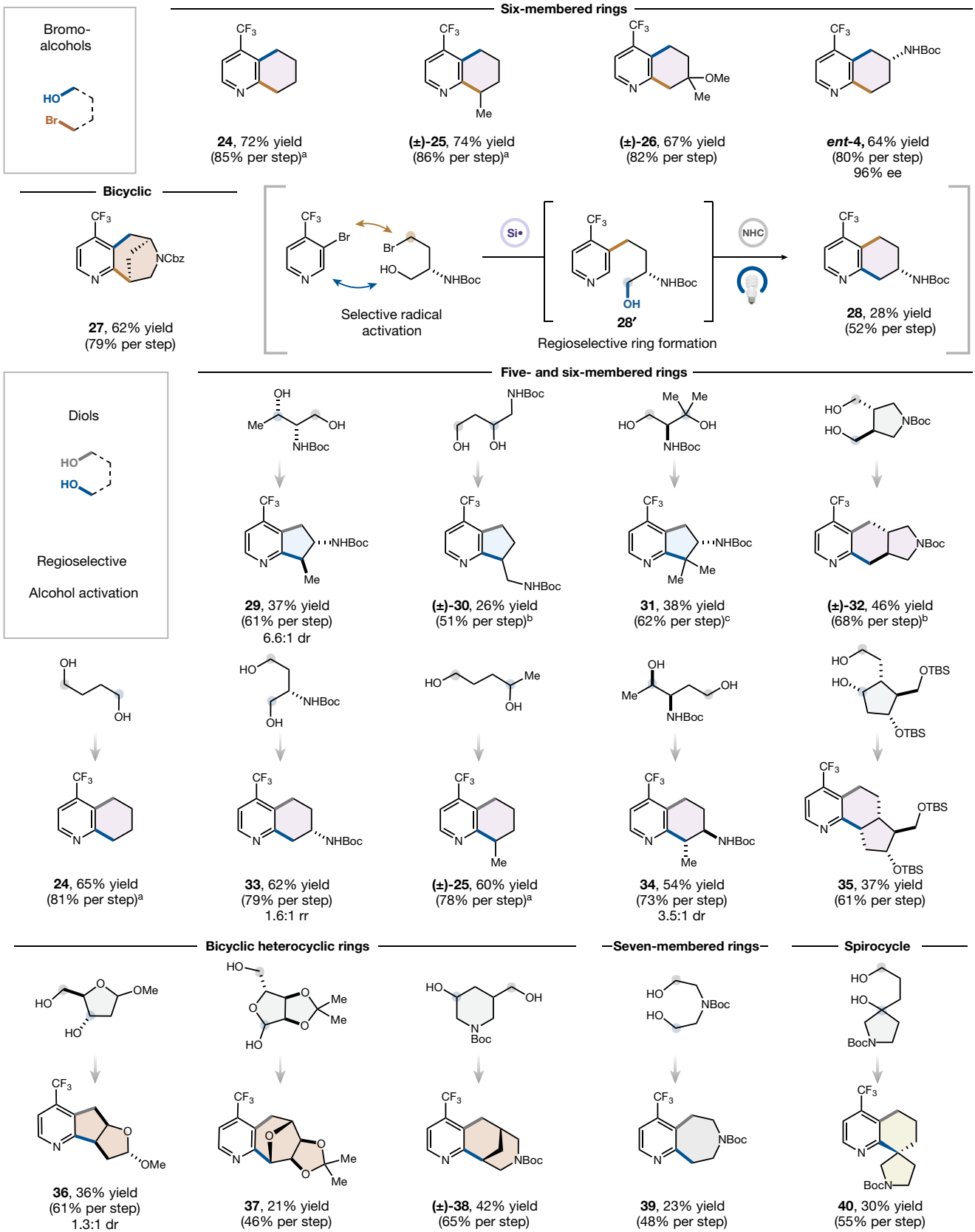

Fig. 3 | Numerous complex bifunctional linker precursors can be used in this transformation. All yields are isolated unless otherwise indicated. See Supplementary Information for full reaction conditions for each substrate. [a]Assay yield from ^{1}H or ^{19}F NMR. [b]22.5 mol% phthalimide was added. [c]1 equiv. phthalimide was added. Boc, *tert*-butyloxycarbonyl; TBS, *tert*-butyldimethylsilyl; Cbz, benzyloxycarbonyl.

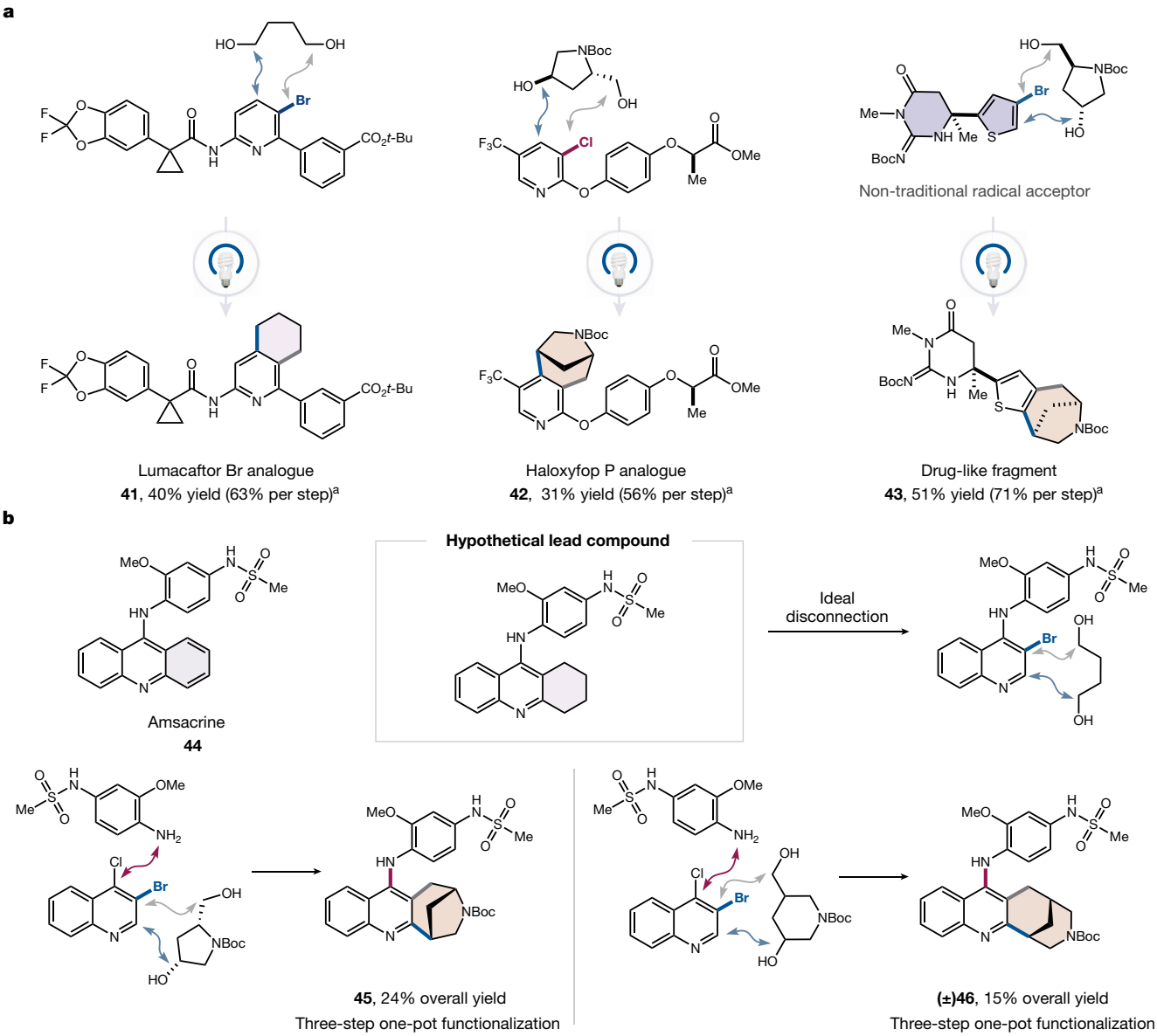

Fig. 4 | Numerous complex drug precursors can be used in this transformation. a, This protocol can also be applied to late-stage functionalization of pharmaceutical variants, such as Lumacaftor Br and Haloxyfop P. All yields are isolated; see Supplementary Information for exact conditions. **b**, The saturated analogue of Amsacrine can be made across diverse linkers in a three-step, one-pot fashion. [a]22.5 mol% phthalimide was added to the cross-coupling step.

annulation. Azarenes, such as quinolines (**11**), pyrimidines (**12** and **21**) and pyrazines (**22**), underwent the one-pot sequence in moderate to good yields (34–57% yield, 58–75% per step). Notably, non-traditional radical acceptor heterocycles were also competent substrates, with indoles (**13**), benzothiophenes (**14**) and thiazoles (**23**) (37–55% yield, 61–74% per step) all proving to be effective in the transformation. Success with these electronically mismatched heterocycles indicates an important lesson: otherwise electronically unfavourable radical additions can prove viable in intramolecular settings.

We next turned our attention to the bifunctional radical precursors. We were pleased to find that a range of bromoalcohols performed well as annulation partners (Fig. 3). Simple 4-bromobutanol provided the unfunctionalized-alkyl backbone **24** in excellent yield across both steps (76% yield, 87% per step). We were able to incorporate substituents on the bromobutanol chain, including a fully substituted carbon centre, en route to functionalized six-membered rings (**25** and **26**, 67–74% yield, 82–86% per step). The *S*-enantiomer of standard bromoalcohol **2** furnished enantiomeric amine-containing product ***ent*-4** (64% yield, 80% per step) with complete retention of stereochemistry. Bicyclic systems were readily accessible, including prolinol-derived **27** (62% yield, 79% per step). Notably, identical substrate combinations could be used to generate regioisomeric products by inverting the sequence of functional group activation. Thus, initial debrominative cross-coupling of standard bromoalcohol **2** followed by deoxygenative radical cyclization afforded the 7-aminotetrahydroquinoline product with complete regiocontrol (**28**, 28% yield, 52% yield per step). In principle, the same sequence inversion strategy should be applicable to any bromoalcohol substrate, potentially providing controlled access to several products with distinct functional group patterns from a smaller set of substrates.

Diols with differing substitution patterns were also found to be effective regioselective annulation partners. Diols composed of one primary and one secondary or tertiary hydroxyl group participated in regioselective annulation due to the sterically controlled nature of NHC-based

alcohol activation. The 2,3-cyclopentenopyridine scaffolds could be generated from simple primary–secondary and primary–tertiary diols (**29**–**31**, 26–38% yield, 51–62% per step). Notably, five-membered ring product **29** was derived from the biologically relevant, enantiopure building block Boc-D-threoninol, whereas product **31** demonstrates the ability of this annulation protocol to generate quaternary carbon centres, forming a sterically congested α,α-disubstituted product. A diverse array of 1,4 diols also proved to be competent coupling bifunctional linkers in the annulation protocol, allowing construction of semisaturated six-membered rings in good yields (**24** and **32**, 46–65% yield, 68–81% per step). An L-homoserine derived diol, composed of two primary alcohols connected by an asymmetric linker, showed a slight preference for cross-coupling with the less sterically encumbered alcohol, affording **33** in a 1.6:1 regioisomeric ratio (rr). A homothreonine derived diol was also found to be an effective substrate for the transformation (**34**, 54% yield, 73% per step). (−)-Corey's lactone derived precursor afforded fused ring in good yield (**35**, 37% yield, 61% per step). Notably, bicyclic nitrogen and oxygen-containing systems **36**, **37** and **38** were obtained in useful yields (21–42% yield, 46–65% per step), with **36** and **37** deriving from 2-deoxyribose and ribose, respectively. A pyridine fused azepane was formed in synthetically useful yields (**39**, 23% yield, 48% per step). Last, a diol consisting of a primary and tertiary hydroxyl group was likewise successful in the two-step procedure to afford the new spirotricyclic product **40** (30% yield, 55% per step).

Finally, we subjected several structurally complex pharmaceutical agents to our annulation protocol (Fig. 4). Semisaturated analogues of Lumacaftor[43], a pharmaceutical involved in the treatment of cystic fibrosis and the herbicide Haloxyfop P methyl ester were generated in one pot in good yields (**41**, **42**, 31–40% yield, 56–63% per step). Furthermore, thiophene X13, a compound from the Merck informer library[44] underwent radical annulation in good yield (**43**, 51% yield, 71% per step). To further demonstrate the synthetic value of this technology, partially saturated fused analogues of an anticancer agent, Amsacrine **44** (ref. 45), were prepared in a three-step, one-pot fashion (**45**, **46**, 15–24% overall yield). The amenability of this new chemistry to complex drug molecules demonstrates the potential of this transformation to achieve late-stage diversification in pharmaceutically relevant settings.

In conclusion, we report here a convergent strategy for assembling challenging semisaturated fused heterocyclic systems with a dual radical disconnection approach. A nickel-catalysed radical cross-coupling followed by radical alkylation of the heteroaryl core allows for use of commercially abundant haloheterocycles and bromoalcohols or diols as coupling partners, obviating tedious synthetic sequences while allowing for the use of chiral and biologically derived starting materials. A diverse range of fused and bridged semisaturated scaffolds can be synthesized, including many previously synthetically inaccessible ring systems and several pharmaceutical derivatives. Consequently, we anticipate that this protocol will be of substantial value to practitioners of organic synthesis.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41586-024-07181-x.

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Data availability

All data are available in the main text or in the Supplementary Information.

Acknowledgements We thank J. Balsells, R. Lambert, B. Boyle and C. Gould for helpful discussion and for assistance in the preparation of this manuscript. A.L. also thanks C. Seath, H. Sakai, O. Garry and J. Xie for assistance in manuscript preparation. A.L. and C.J.O. thank the Ted Taylor family for a graduate fellowship. Research reported in this publication was supported by the National Institute of General Medical Sciences (NIGMS) under grant no. R35 GM134897-04, the Princeton Catalysis Initiative, Janssen R&D and gifts from Merck, Bristol Myers Squibb, Genentech, GenMab and Pfizer. The content is solely the responsibility of the authors and does not necessarily represent the official views of NIGMS.

Author contributions D.W.C.M. conceived the work. A.L. and C.J.O. developed the couple-close protocol and experimental strategy. C.B.K. and M.C.B. helped design experiments and provided guidance. All authors discussed the results and contributed to editing the manuscript and preparing the Supplementary Information.

Competing interests D.W.C.M. declares a competing financial interest with respect to the Integrated Photoreactor. The remaining authors declare no competing interests.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41586-024-07181-x.

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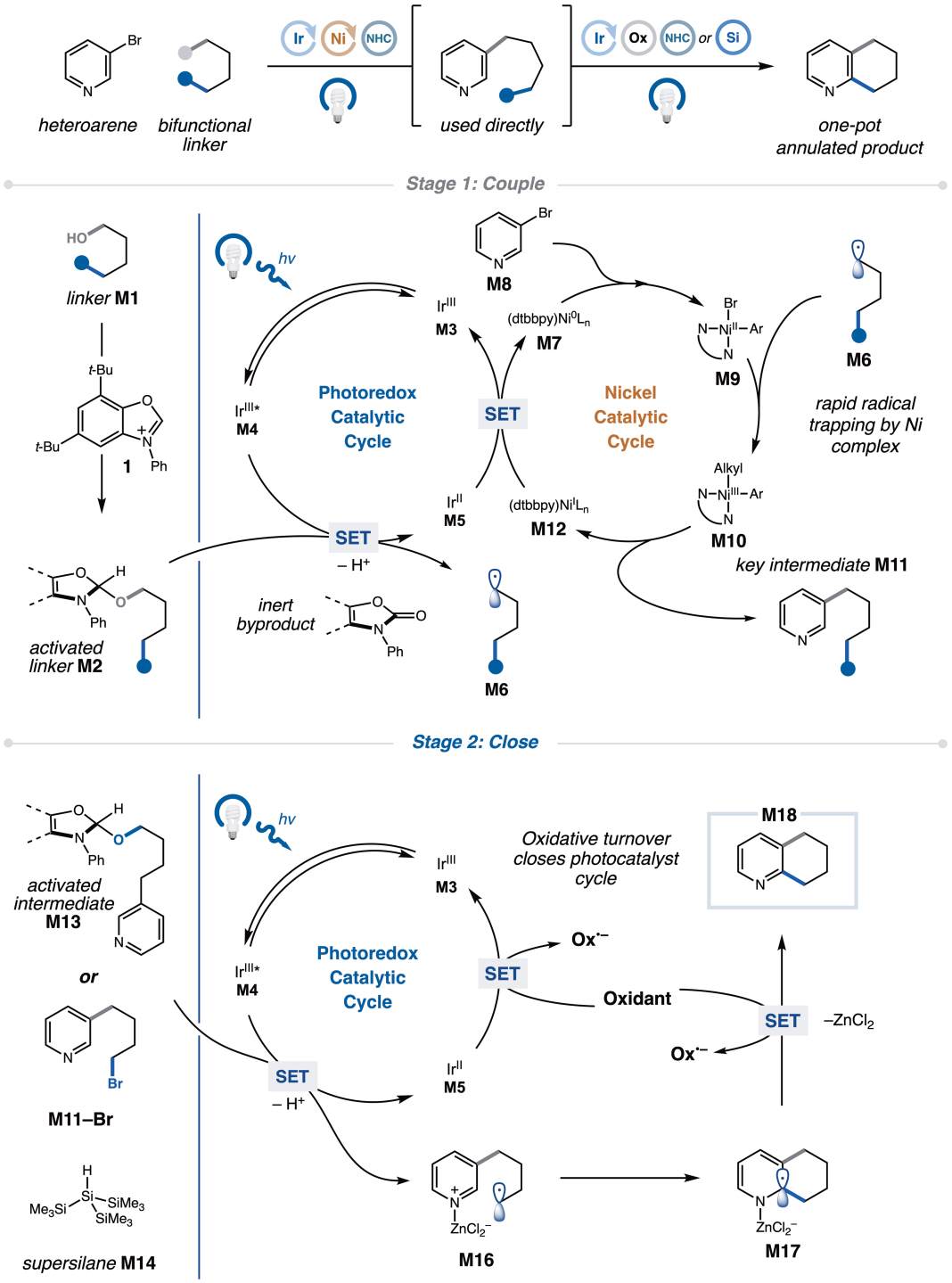
Peer review information *Nature* thanks the anonymous reviewers for their contribution to the peer review of this work.



Extended Data Fig. 1 | Proposed mechanistic scheme for the couple-close annulation reaction. Metallaphotoredox cross-coupling (stage 1) is followed in the same reaction vessel by a photoredox-catalysed Minisci reaction (stage 2) to generate challenging semisaturated heterocyclic products. See Supplementary Information for a full description of the proposed mechanism.