Deconstructive functionalization involves carbon–carbon (C–C) bond cleavage followed by bond construction on one or more of the constituent carbons. For example, ozonolysis and olefin metathesis have allowed each carbon in C=C double bonds to be viewed as a functional group. Despite the substantial advances in deconstructive functionalization involving the scission of C=C double bonds, there are very few methods that achieve C(sp<sup>3</sup>)–C(sp<sup>3</sup>) single-bond cleavage and functionalization, especially in relatively unstrained cyclic systems. Here we report a deconstructive strategy to transform saturated nitrogen heterocycles such as piperidines and pyrrolidines, which are important moieties in bioactive molecules, into halogen-containing cyclic amine derivatives through sequential C(sp<sup>3</sup>)–N and C(sp<sup>3</sup>)–C(sp<sup>3</sup>) single-bond cleavage followed by C(sp<sup>3</sup>)–halogen bond formation. The resulting acyclic haloamines are versatile intermediates that can be transformed into various structural motifs through substitution reactions. In this way we achieve the skeletal remodelling of cyclic amines, an example of scaffold hopping. We demonstrate this deconstructive strategy by the late-stage diversification of proline-containing peptides.

The development of technologies that enable the late-stage diversification of bioactive, heterocycle-containing molecules (Fig. 1a) should facilitate access to underexplored chemical space. Over the past two decades, considerable effort has been dedicated to the development of methods to functionalize C–H bonds at a late stage; this has enabled the fine-tuning of substituents on nitrogen heterocycles and enhanced their functional-group diversity. In the medicinal chemistry community, there is a growing demand for methods that not only modify the periphery of molecules via C–H functionalization, but also modify their core framework in order to achieve skeletal diversity, a concept referred to as ‘scaffold hopping’. However, there are only a few methods known to achieve deconstructive functionalization, such as those involving unstrained cyclic amines. Recent example generates an aldehyde intermediate that can be further transformed to install C–O, C–C and C–N bonds.

In this context, ring-opening chlorination or bromination would generate versatile intermediates en route to diverse cyclic amines by coupling to a variety of nucleophiles (Fig. 1b). Furthermore, the deconstructive halogenation of proline-containing peptides would furnish versatile intermediates for the late-stage diversification of these medicinally important entities. Although ring-opening chlorination of cyclic amines is known, the existing methods to effect this transformation are limited to 3–5-membered, N-alkyl-substituted cyclic amines because of competing N-dealkylation. Recently, our laboratory introduced a silver-mediated deconstructive strategy to transform cyclic amine derivatives into fluorine-containing cyclic amine derivatives using Selectfluor, via the homolytic ring-opening of hemiaminal intermediates. On the basis of mechanistic insights gained from our deconstructive fluorination protocol, we questioned whether it would be possible to access acyclic chloro- and bromoamines from cyclic amines using our deconstructive strategy. Upon examination of existing reports on silver-catalysed halogenation reactions, we recognized that the simple replacement of Selectfluor with N-halo reagents such as N-chlorosuccinimide (NCS) or N-bromosuccinimide (NBS) would be unproductive, presumably owing to their lower oxidation potential. Therefore, a distinct approach would be required to oxidize Ag(I) to Ag(II) in order to achieve deconstructive bromination and chlorination.
Fig. 2 | Scope of the cyclic amine in the deconstructive halogenation reaction. Only isolated yields are shown. Reactions were performed on a 0.2-mmol scale (based on 1) under the conditions listed in Fig. 1c. b.r.s.m., based on recovered starting material. °5,6-dihydro-4H-1,3-oxazine was obtained (see Supplementary Information for details).

Fig. 3 | Applications of deconstructive halogenation. a, Skeletal remodelling of cyclic amines. b, Dehomologation of cyclic amines. °Yields in bracket represent the average yield per step.
Fig. 4 | Deconstructive chlorination of L-proline-containing peptides. a, Deconstructive diversification of tripeptide 21. b, The tolerance for oxidizable amino acid residues. c, Deconstructive chlorination of L-phenylalanine-containing tripeptide 30. d, Deconstructive fluorination of tripeptide 21. r.s.m., recovered starting material; Tf, trifluoromethanesulfonyl.

A detailed mechanistic proposal for our reaction sequence is depicted in Fig. 1c. We theorized that, consistent with existing precedent, Ag(I) would be oxidized to Ag(II) in the presence of persulfate anion, with concomitant disproportionation of the persulfate anion into a sulfate dianion and a sulfate radical anion. N-acylated cyclic amines 1 would then undergo a hydrogen-atom transfer with the resulting sulfate radical anion to give an α-amino radical. Subsequent oxidation by Ag(II) via single-electron transfer would lead to iminium ion A. An alternative pathway is also possible, in which an Ag(II) species oxidizes N-acylated cyclic amines (for example, 1a: \( E^{\circ} = +2.02 \) V vs SCE) (Supplementary Fig. 1) to the radical cation via single-electron transfer, followed by hydrogen-atom transfer using the sulfate radical anion to generate the same iminium ion, A. The resulting iminium ion A would then be trapped by H₂O to give hemiaminal B. The heterolytic cleavage of the C–N bond would then occur through an equilibrium between hemiaminal B and aldehyde C, the latter being subsequently oxidized to carboxylic acid D, setting the stage for a silver-catalysed...
decarboxylative halogenation\textsuperscript{17,22}. This strategy would represent a general method for deconstructive diversification, as the electrophile is independent of the initial redox cycle.

We commenced our investigations of the proposed deconstructive halogenation by evaluating a broad range of silver salts, halogenating reagents and solvent combinations. After extensive screening we identified the optimized conditions shown in Fig. 1c, using cheap and commercially available silver nitrate, ammonium persulfate and NCS in a 1:9 (v/v) mixture of acetone:H$_2$O at room temperature. Upon subjecting N-pivaloylpiperidine (1a) to the optimized conditions, we obtained 81% yield of the desired acyclic chlorinated product 2a. Similarly, a bromine atom could be readily incorporated to afford 4a in 54% yield by changing the electrophilic halogenating reagent to NBS. It is worth noting that this method can be performed without the strict exclusion of air. Control experiments established the importance of both silver and persulfate, as no formation of the desired chlorinated product was observed in the absence of the silver salt or the persulfate additive. The optimized conditions use four equivalents of silver nitrate, with lower quantities leading to reduced yields—presumably owing to substrate and/or product inhibition by binding to the silver salt (Supplementary Table 1).

With the optimized conditions in hand, we proceeded to investigate the scope of the deconstructive halogenation process (Fig. 2). An N-substituted piperidine derivative bearing a tert-butoxycarbonyl group (Boc, 1b) gave the desired chlorinated products in a combined 52% yield of 2b along with formimide product 3b, which results from homolytic C–C bond cleavage of hemiaminal B\textsuperscript{16}. Unlike the bulky pivaloyl group, which favours linear aldehyde C over hemiaminal B in the equilibration of the two species, the less sterically congested Boc group presumably favours B (Fig. 1c). Bromination using NBS led to a mixture of mono and dibrominated products 5b and 6b in 65% combined yield. Upon switching the group on nitrogen to benzoyl (Bz, 1c), secondary amide products 2c and 4c were obtained as the major products along with formimide products 3c and 5c. In all cases, the secondary amide product and corresponding formimide are easily separated. Saturated heterocycles with various ring sizes (1d–1f) underwent deconstructive halogenation in moderate to good yields (55%–77% combined yield), although the deconstructive bromination of 1d led to 5,6-dihydropyridine 4d (Supplementary Information)\textsuperscript{29}. Substituents at the 2- and 4-position on piperidines are also well tolerated (1g–1i, 53%–80%). Polycyclic compounds such as 1j are also readily functionalized, paving the way for late-stage derivatization in more complex polycyclic frameworks. Halogenated amino acid derivatives (2k, 2l and 4k) are accessed in three steps from l-proline and l-pipeolic acid, which may serve as versatile intermediates to other unnatural amino acids.

Next, the skeletal remodelling of piperidine scaffolds bearing other reactive groups was examined (Fig. 3a). Oxidative ring-opening of 7 followed by the coupling of the pendant 2-nitrobenzenesulfonylamide (NsNH) nucleophile with the incipient aldehyde group in 8 ultimately yielded the corresponding lactam 9. The choice of halogenating reagent led to divergence in the products that were formed. For example, when carboxylic acid 10 was subjected to the deconstructive chlorination conditions, dichloro compound 11 was obtained through decarboxylative\textsuperscript{17} and deconstructive chlorination, and was directly transformed to azetidine 12 via double nucleophilic displacement with NsNH$_2$. Alternatively, when NBS was used as the halogenating agent, in situ-generated alkyl bromide 13 reacted with the carboxylic acid group to form the corresponding lactone 14 in 44% yield.

Given the aforementioned importance of scaffold hopping in cyclic systems\textsuperscript{32,38}, we have also pursued the ring contraction of piperidines (Fig. 3b). There are few reports that detail the ring contraction of piperidines to pyrrolidines\textsuperscript{24–26}. Deconstructive bromination of N-benzoyl piperidine (1c) with dibromohydrindotin followed by cyclization of the resulting bromoamine with sodium tert-butoxide furnished N-benzoyl pyrrolidine (15) in 89% yield in just two steps (94% average yield per step), with only one chromatographic purification step. Notably, this process can also be conducted in one pot, albeit in lower yield (unoptimized) owing to the competing displacement of the newly installed halogen group by the imide byproduct from the halogenating reagent. This ring-contraction process also proceeds for a series of simple cyclic amines, such as 2- and 4-methyl substituted piperidines and azepane (16, 18 and 20, 35%–60% yield over two steps). These results demonstrate a powerfully direct approach to achieving deep-seated structural modifications.

The virtue of this method is evident in the deconstructive functionalization and diversification of peptides\textsuperscript{27}. As shown in Fig. 4a, l-proline-containing tripeptide 21 underwent ring-opening chlorination in 41% yield, along with 15% of recovered starting material. Chlorinated peptide 22 is easily transformed into a variety of products. For example, treatment of 22 with sodium methylylinate afforded 23 in 91% yield, constituting the conversion of a proline residue into the corresponding methionine residue in only two steps. Alternatively, C–N bond formation can be achieved by the treatment of 22 with sodium azide, and in this way a proline residue or polypeptides that bear a cyclic amine (for example, l-pipeolic acid) can be converted into a site for azide-based biothogonal click chemistry\textsuperscript{28}. In a demonstration of this strategy, 22 was azidated and then subjected to copper-catalysed azide–alkyne cycloaddition to afford triazole 24 in 72% yield over two steps. In addition, C–O bond formation is also easily achieved by displacement of the halogen group with benzoic acid. Treatment of 22 with NaCN in dimethylformamide led to nitrile 26 as the major product along with 5,6-dihydro-4H-1,3-oxazine 27 in 36% yield, demonstrating the feasibility of C–C bond formation. Cyclized product 27 is obtained as the sole product when 22 is treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

Additionally, we evaluated the functional-group tolerance of the deconstructive chlorination process. As shown in Fig. 4b, a variety of dipeptides bearing potentially oxidizable amino acid residues participate in this deconstructive protocol (29a–29f, 19%–44%). It is worth noting that the proline residue can be preferentially oxidized over the benzylic position (29a, 29b) and C–H bonds of the activated aliphatic side chains bearing oxygen heteroatoms (29e, 29f). A dipeptide bearing a methionine residue underwent deconstructive chlorination with oxidation of the thioether to the corresponding sulphone (29g). Therefore, like many other oxidative processes\textsuperscript{29,30}, deconstructive halogenation leads to a competing reaction with the sulfur group of methionine. Additionally, deconstructive chlorination of the challenging tripeptide substrate 30 proceeded to furnish ring-opened product 31 in a 16% yield, along with 62% of recovered starting material (Fig. 4c). Given that the current methodology involves a mechanistic change compared with our previous deconstructive fluorination strategy\textsuperscript{16}—namely the incorporation of a heterolytic C–N cleavage (B→C, Fig. 1c)—the over-oxidation of the hemiaminal intermediate B is generally avoided, as evidenced by the ring-opening fluorination of 21 to give fluorinated tripeptide 32 using this new method (Fig. 4d). Despite the lower yields obtained in the presence of these reactive residues, the deconstructive protocol provides an expedient approach to a novel range of peptides without the need for their de novo synthesis.

Saturated heterocycles remain a prevalent structural motif that is found in a large percentage of bioactive organic molecules such as pharmaceuticals. We anticipate that deconstructive functionalization strategies will provide access to wide-ranging structural diversity at a late stage in the preparation of bioactive molecules.

**Data availability**

All data supporting the findings of this study are available within the paper and its Supplementary Information, or from the corresponding author upon reasonable request.

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Author contributions J.B.R. and Y.K. conceived the research and designed the experiments. J.B.R., Y.K. and L.T.G. performed the experiments. R.S. directed the project. J.B.R., Y.K. and R.S. wrote the manuscript.

Competing interests J.B.R., Y.K., L.T.G. and R.S. are listed as inventors on an initial patent application describing the silver-mediated deconstructive halogenation of cyclic amines and subsequent transformations (052103-515P01US).

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