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Skeletal editing through direct nitrogen deletion of secondary amines

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Synthetic chemistry aims to build up molecular complexity from simple feedstocks[1]. However, the ability to exert precise changes that manipulate the connectivity of the molecular skeleton itself remains limited, despite possessing substantial potential to expand the accessible chemical space[2,3]. Here we report a reaction that 'deletes' nitrogen from organic molecules. We show that *N*-pivaloyloxy-*N*-alkoxyamides, a subclass of anomeric amides, promote the intermolecular activation of secondary aliphatic amines to yield intramolecular carbon–carbon coupling products. Mechanistic experiments indicate that the reactions proceed via isodiazene intermediates that extrude the nitrogen atom as dinitrogen, producing short-lived diradicals that rapidly couple to form the new carbon–carbon bond. The reaction shows broad functional-group tolerance, which enables the translation of routine amine synthesis protocols into a strategy for carbon–carbon bond constructions and ring syntheses. This is highlighted by the use of this reaction in the syntheses and skeletal editing of bioactive compounds.

Retrosynthetic analysis is the cornerstone of synthesis. As chemical transformations are discovered, they can be evaluated in terms of the retrosynthetic disconnections that they enable, and the forward progress of synthesis—broadly speaking—can be assessed by inspection of the total set of available disconnections. Accordingly, the identification and realization of synthetically attractive transformations that represent inaccessible or otherwise underused molecular changes is paramount to the continued advancement of the chemical sciences, and as such the advancement of all allied fields that design and deploy purpose-built molecules. Molecular editing and late-stage functionalization have emerged as appealing strategies for the identification of such 'missing' transformations[4–7], and represent the ideals of modern synthesis—including the ability to build and tolerate complexity. However, their intellectual deployment has so far largely focused on C–H functionalization chemistry (peripheral editing). Conversely, modification of the underlying molecular skeleton (skeletal editing) has not achieved the same level of refinement, despite receiving increasing interest from many laboratories[8–12].

In our own assessment, such skeletal transformations represent a large untapped pool of potentially transformative chemical reactions, should they be realized (Fig. 1a). Among these, single-atom insertions and deletions are particularly attractive from the standpoint of retrosynthetic simplicity, in contrast to many known skeletal rearrangements for which complex patterns of reactivity require substantial skill and insight to recognize as disconnections. Indeed, many classic reactions—especially in the context of carbonyl chemistry—enable the insertion or deletion of carbon, nitrogen or oxygen into molecular skeletons (for example the Wolff, Favorskii and Bayer–Villiger rearrangements)[13,14]. Nonetheless, broadly speaking, accessible single-step skeletal transformations remain limited. Here we report a reaction that excises nitrogen atoms from secondary amines, liberating N_2 and forging a new C–C bond between the remaining molecular fragments.

Our approach was based on the mechanistic hypothesis outlined in Fig. 1b. This hypothesis was in turn supported by precedented chemistry of anomeric amides, which—in analogy to the anomeric centres of carbohydrates—bear two oxygen substituents on the amide nitrogen[15]. Bis-heteroatom-substituted amides have been studied in detail and display unusual pyramidalization at nitrogen as well as notable electrophilic reactivity[16]. In particular, *N*-methylaniline was observed to form a tetrazene product upon reaction with reagent **1a**, which is strongly suggestive of an isodiazene intermediate[15] (Fig. 1c). These latter species piqued our interest owing to their known N_2-extrusion reactivity, providing diradical species that undergo rapid, intramolecular C-C bond formation[17–19]. Classical routes to such intermediates involve multistep protocols that use hazardous reagents—one frequently used synthesis involves a sequence of *N*-nitrosation (requiring isolation of carcinogenic *N*-nitrosamine compounds), reduction to the 1,1-hydrazine and oxidation with stoichiometric mercuric oxide or lead tetraacetate[20]. We reasoned that the combination of anomeric amide reagents with suitable secondary amine nucleophiles would enable a single-step protocol for nitrogen deletion directly from secondary amines. Crucially, this would facilitate the examination of skeletal edits by circumventing the laborious and undesirable features of existing protocols[21,22].

From a retrosynthetic perspective, this strategy would enable aliphatic C–N bond-forming reactions to serve formally as C–C bond-forming surrogates. This is advantageous in part because of the reliability and broad scope of iminium-based transformations that feature prominently among the medicinal chemistry toolbox. For example, reductive amination consistently ranks in the top ten most-used reactions in drug discovery, and iminium-based cyclization methods are broadly applied for the synthesis of cyclic amines[23]. These methods have led to the proliferation of amines as feedstock chemicals, and thousands of derivatives are now commercially available[24,25].

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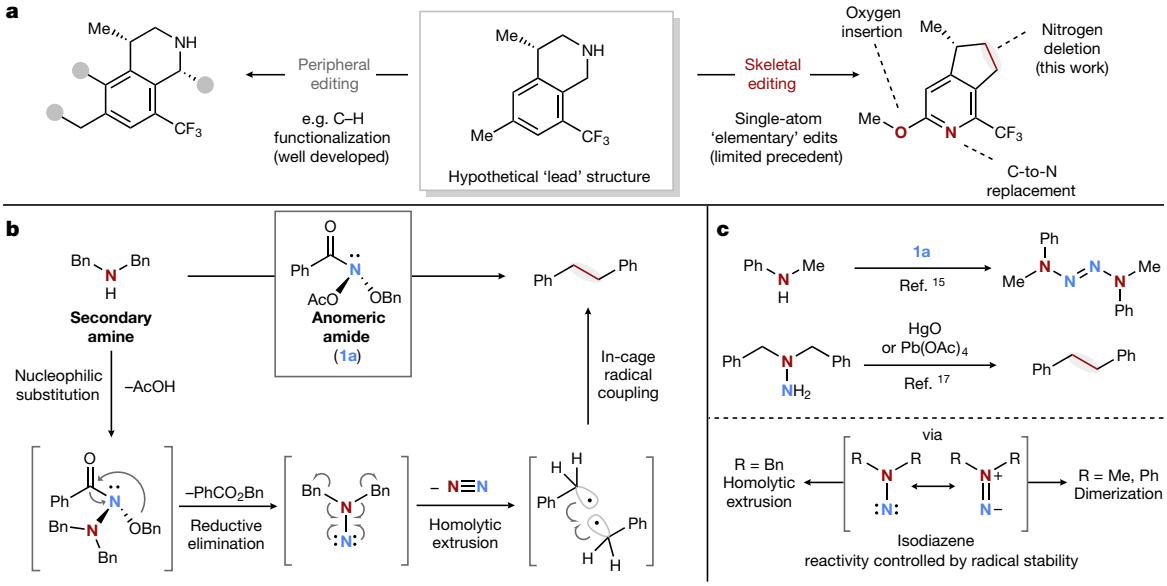

Fig. 1 | Background. a, Conceptual overview of skeletal editing and peripheral editing techniques as used in molecular optimization campaigns. **b**, Mechanistic hypothesis for direct nitrogen deletion enabled by anomeric amide reagents. **c**, Precedent for isodiazene generation from anomeric amides, and for nitrogen extrusion from isodiazenes.

Our investigation began with the *N*-benzyloxy-*N*-acetoxybenzamide **1a** (ref. [15]) (Fig. 2a). Reaction with the model substrate **2a** in tetrahydrofuran solution at 45 °C resulted in a 35% yield of nitrogen deletion product **3a**. However, acetamide **4a** was observed as a major side product, which probably formed through competitive substitution at the acyl carbon. To ameliorate this, we synthesized the *N*-pivaloxy derivative **1b**. When used under identical conditions, none of the corresponding pivalamide side product **4b** could be detected and **3a** was produced in an improved yield of 57%. Further evaluation of substituent effects revealed that *para*-trifluoromethyl-substituted reagent **1c** reacted more rapidly, leading to complete conversion of **2a** within 5 h, in comparison to the 18-h reaction time required for **1b**. This was representative of a general trend: a competition Hammett study revealed a slope of 0.60 (corresponding to the reaction constant ρ) when rate data were plotted against the electrophilic substituent constant (σ^+)[26] (Fig. 2b). However, the preparation of reagents that are more electron-poor than **1c** failed using our standard procedure. Anomeric amide **1c** is straightforward to prepare on a multigram scale: a three-step sequence from commercially available reagents furnishes 28 g of material in 78% overall yield with no chromatographic purification.

With reagent **1c** in hand, we endeavoured to explore the scope and limitations of this process in terms of both the functional-group compatibility and the structural diversity. To address the former, we evaluated a series of substituted dibenzylamines and their heteroaromatic analogues, all of which were prepared through reductive amination and bore various medicinally relevant functionality. As shown in Fig. 3, the functional-group tolerance of this methodology is high, and includes both basic nitrogen heterocycles (**3j**–**3m**), unprotected protic functionality (**3h**, **3i**), and reducing or Lewis basic functionality (**3c, 3f, 3g, 3l**). This is particularly notable considering the presence of several highly reactive intermediates in our proposed mechanism, and highlights the chemoselectivity of the anomeric amide reagents.

With respect to structural variation, cyclic amines offer a unique opportunity to promote ring contractions that give access to new molecular skeletons. Although atom deletion might ostensibly be considered to be a simplifying transformation, ring contractions highlight the power of these transformations to instead build molecular

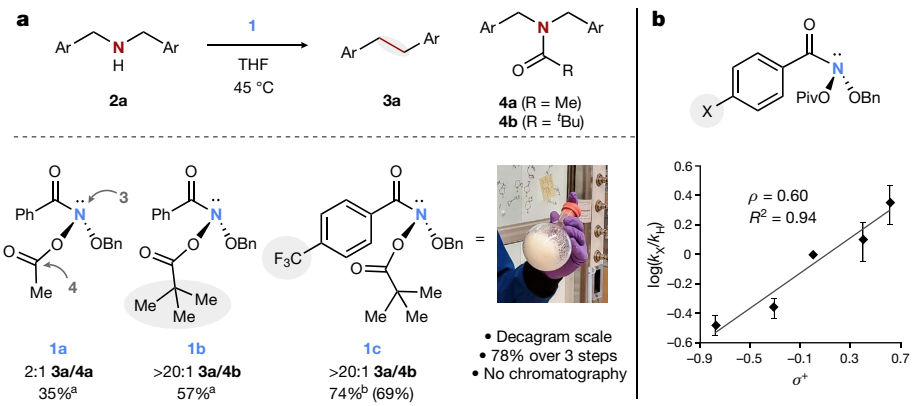

Fig. 2 | Development of an anomeric amide reagent. a, Optimization of the reagent structure for direct nitrogen deletion. The yields stated are NMR yields, with isolated yields given in parentheses. [a]18 h, [b]5 h. Ar, *p*-bromophenyl; THF, tetrahydrofuran. **b**, Hammett plot (s.d., $n = 3$) indicating the electronic origin of the increased rate of reaction with reagent **1c**. k_X/k_H, the ratio of the rate of reaction with different substituents at X to the rate when X = H in a one-pot direct competition experiment. Piv, pivaloyl.

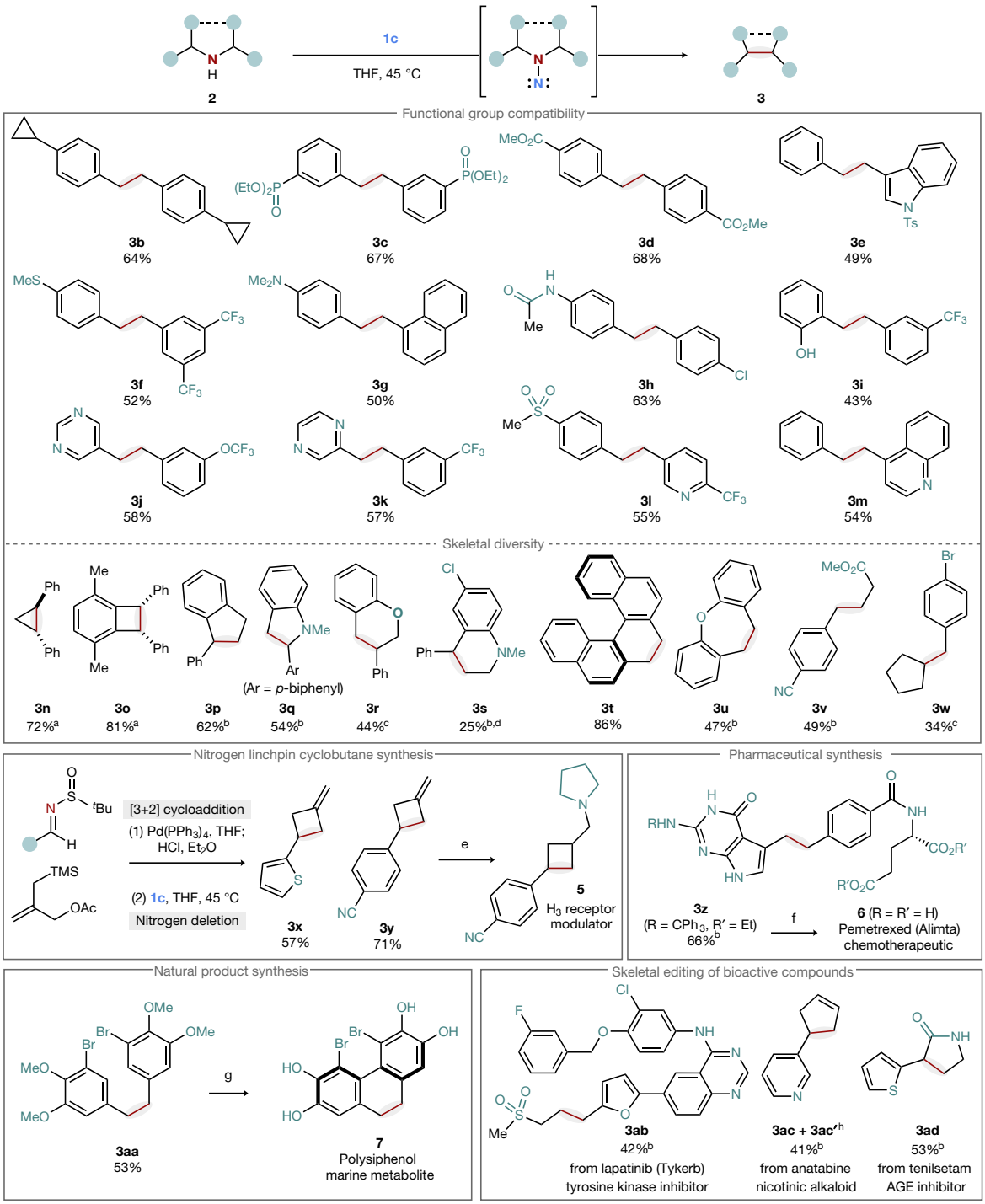

Fig. 3 | Scope of the nitrogen-deletion reaction promoted by reagent 1c. Conditions: **2** (1.0 equivalent), **1c** (1.5 equivalents), THF (0.2 M). The yields stated are isolated yields for nitrogen deletion. [a]**3n** and **3o** formed stereospecifically, *trans*-**3n** from *trans*-**2n** and *cis*-**3o** from *cis*-**2o**. [b]2 equivalents trimethylamine were added. [c]2 equivalents **1c**. [d]Reaction conducted at 25 °C. [e]**3y**, 9-borabicyclo(3.3.1)nonane, $NaBO_3$ (3:1 diastereomeric ratio); 4-toluenesulfonyl chloride, pyridine; pyrrolidine, K_2CO_3, 42% yield over 3 steps. [f]AcOH, H_2O; 1 M NaOH, THF/H_2O, 56% yield over 2 steps. [g]$PhI(OCOCF_3)_2$, $F_3B{\cdot}OEt_2$; BBr_3, see ref. [32]. [h]1.7:1 mixture of cyclopentene and vinylcyclopropane isomers were isolated. TMS, trimethylsilyl; Ts, tosyl.

complexity, wherein the nitrogen atom can serve as a traceless linchpin for the initial ring synthesis, yielding the $(n-1)$ carbon framework after nitrogen deletion. Contractions of azetidines to cyclopropanes, pyrrolidines to cyclobutanes, piperidines to cyclopentanes, azepanes to cyclohexanes, and azocanes to cycloheptanes—as well as their heterocyclic analogues—can all be achieved using reagent **1c**. It should be noted that steric effects can preclude reactivity altogether: whereas **2n** and **2o** react smoothly, acyclic bis(α-secondary)amines and α-tertiary amines are typically inert to the present conditions[27]. Notably, conjugated radicals are not a strict requirement on both substituents for efficient reactivity, as demonstrated by **2p**, **2s**, **2v**, **2w**, **2ab** and **2ad**, for which benzylic substitution is present on only one of the two reacting aliphatic substituents; in acyclic systems a single benzylic centre is sufficient, whereas for cyclic systems, two stabilizing elements are necessary for productive C–C bond formation, either one on each terminus or both on the same reactive centre. In cases in which the

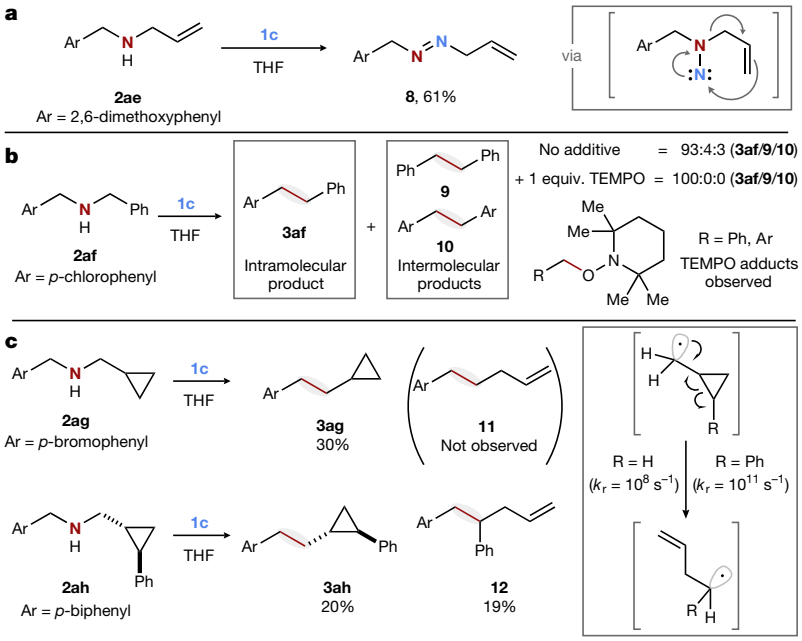

Fig. 4 | Mechanistic experiments. a, Evidence for the isodiazene intermediate via competitive rearrangement to a 1,2-diazene. **b**, Product ratios in a trapping experiment with TEMPO demonstrate the scavenging of intermolecular products, suggesting largely in-cage C–C bond formation. **c**, A radical clock experiment also suggests largely in-cage radical recombination.

requisite stabilizing elements are lacking, side reactions can predominate, including rearrangement of the isodiazene to a hydrazone. For a more detailed analysis of limitations, see Supplementary Fig. 2 and its associated analysis in the Supporting Information.

As noted above, connecting this methodology to existing amine syntheses enables fundamentally new retrosynthetic logic: [3+2] cycloaddition can be used to construct pyrrolidines **2x** and **2y**, and subsequent nitrogen deletion affords cyclobutanes **3x** and **3y**[28]. **3y** can be further elaborated to the histamine H_3 receptor modulator **5** through stepwise, formal hydroamination, highlighting the potential for this method to benefit medicinal chemistry[29,30]. This method also enables the synthesis of the folate antimetabolite pemetrexed (**6**, via the protected precursor **3z**), which is used as a chemotherapeutic in the treatment of lung cancer[31]. In this synthesis, reductive amination unites the two functional-group-laden halves of the molecule, and nitrogen deletion subsequently forges the central C–C bond, again highlighting the functional-group compatibility of this method. We have further used our method to provide an accelerated synthesis of the atropoisomeric marine metabolite polysiphenol, **7**, intercepting the known synthetic intermediate **3aa**[32]. The previously reported preparation of **3aa** relies on hydrogenation of a stilbene, the preparation of which—via olefination—requires diverging a common aldehyde intermediate to prepare the corresponding ylide over 3 steps. By contrast, our synthesis enables conversion of the aldehyde to the bibenzyl dimer (via an amine linchpin) without the need to divert half of the material through a phosphonium synthesis. Finally, we performed skeletal editing on several bioactive compounds, including the tyrosine kinase inhibitor lapatinib[33], the nicotinic alkaloid anatabine[34], and the advanced glycation end product inhibitor tenilsetam[35]. The chemoselective nitrogen deletion of lapatinib in particular exemplifies the merits of a skeletal-editing approach, as preparation of derivative **3ab** would otherwise require repetition of the entire synthetic sequence for the preparation of lapatinib from the beginning, starting from a des-amino analogue of the sidearm.

Mechanistically, we anticipated that this transformation would follow the pattern outlined in Fig. 1b, namely: bimolecular nucleophilic substitution of the pivaloxy group of **1c** by the amine; formal reductive elimination of the benzoate ester to afford an isodiazene intermediate[36,37]; N_2 loss to generate a geminate radical pair; and C–C bond-forming radical recombination. However, because we are using more-electron-rich amine nucleophiles and have modified several features of the anomeric amide, this expected pathway might not be operative. Nonetheless, we have garnered preliminary evidence for this proposed mechanism.

With respect to the first step, a minimal solvent effect was observed. Initial rates were only slightly perturbed across solvents whose Reichardt polarity index E_T^N ranged from 0.309 (dichloromethane) to 0.099 (toluene); this suggests that the initial nucleophilic substitution is probably S_N2-like, in line with the ρ value measured in the Hammett study discussed above. A crossover experiment using reagents with distinct benzoyl and alkoxy substituents (Supplementary Fig. 12) led to the exclusive formation of benzoate esters corresponding to intramolecular C–O bond formation, and no crossover products were detected. This indicates that the second step of the transformation is an intramolecular process. Although we cannot conclusively rule out an ionic mechanism that involves fast intramolecular recombination, previous computational studies have demonstrated concerted, formal reductive elimination to be an accessible pathway in *N*-alkoxyhydrazine thermolyses[36,37]. The involvement of an isodiazene intermediate is supported by the formation of the rearranged 1,2-diazine product **8** from allylamine **2ae**, arising from [2,3]-sigmatropic rearrangement of the intermediate isodiazene[38] (Fig. 4a).

Evidence for the subsequent extrusion process comes from an analysis of product distributions in asymmetric substrates (Fig. 4b). The formally intramolecular products (**3**) for non-symmetric substrates are favoured in all cases—well above the statistically anticipated 1:2:1 ratio that would arise from a free-radical process, as was recently observed for a Ni-catalysed deamination of benzylic ammonium salts—which suggests a largely in-cage recombination process[39]. The variable amounts (1–10% yield depending on the substrate used) of the corresponding symmetric ('intermolecular') products (**9**,**10**) are effectively scavenged by the addition of 2,2,6,6-tetramethylpiperidin-1-yl-oxyl (TEMPO), whereas the intramolecular coupling product shows minimal perturbation by such scavengers.

Radical clock experiments were conducted using (cyclopropyl) methyl-substituted amines to gain further insight into the radical recombination process (Fig. 4c). The parent compound (**2ag**) undergoes nitrogen deletion without detectable rearrangement, whereas a phenyl-substituted analogue (**2ah**) yields products both with and without rearrangement of the cyclopropane. Despite the poor mass balance in these reactions (see Supplementary Fig. 17 for identified side products), the results are nonetheless consistent with predominantly in-cage recombination (rate of rearrangement, k_r, is around $10^8\ s^{-1}$ for the cyclopropyl methyl radical)[40], with partial rearrangement of **2ah** suggesting that the in-cage C–C bond-forming mechanism involves radical species. Although estimates of cage-escape rates differ, the rate of rearrangement of the intermediate cyclopropylmethyl radical derived from substrate **2ah** ($k_r \approx 10^{11}\ s^{-1}$) is roughly similar to that of such processes[41]. However, we cannot categorically exclude a competitive non-radical pathway for the formation of **3ah**. Given the high-energy species involved in this reaction, it is likely that dynamic effects strongly influence the partitioning of the isodiazene intermediate. This is further evidenced by the exclusive formation of *cis*-**3o** from *cis*-**2o**, in contrast to the *trans* product diastereomer that is predicted by a Woodward–Hoffman analysis of the putative *ortho*-quinodimethane intermediate, which suggests that the initially formed diradical intermediate never relaxes to a fully planar conformation[42].

In summary, we have developed an anomeric amide reagent that enables straightforward nitrogen deletion of secondary amine substrates. The reaction relies on the facile in situ generation of an isodiazene intermediate, which extrudes N_2 and forms a new C–C bond. We have demonstrated the high functional-group tolerance of this method and its application to ring contractions of cyclic amines. This transformation should serve as a valuable tool for structural optimization in a variety of contexts, adding to the growing catalogue of skeletal-editing technologies.

Online content

Any methods, additional references, Nature Research 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/s41586-021-03448-9.

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Data availability

All data are available from the corresponding author upon reasonable request.

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Author contributions S.H.K., K.J.B. and B.D.D. designed and conducted experiments, and collected and analysed the data. M.D.L. supervised the research, conceived of the project and wrote the manuscript with input from all authors.

Competing interests Reagent **1c** is under development for commercialization with Sigma-Aldrich (product number 919799), but the authors have retained no financial interest and no patents have been filed.

Additional information

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