Strain-release amination

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To optimize drug candidates, modern medicinal chemists are increasingly turning to an unconventional structural motif: small, strained ring systems. However, the difficulty of introducing substituents such as bicyclo[1.1.1]pentanes, azetidines, or cyclobutanes often outweighs the challenge of synthesizing the parent scaffold itself. Thus, there is an urgent need for general methods to rapidly and directly append such groups onto core scaffolds. Here we report a general strategy to harness the embedded potential energy of effectively spring-loaded C–C or C–N bonds with the most oft-encountered nucleophiles in pharmaceutical chemistry, amines. Strain-release amination can diversify a range of substrates with a multitude of desirable bioisosteres at both the early and late stages of a synthesis. The technique has also been applied to peptide labeling and bioconjugation.

Fig. 1. Synthetic methods for incorporating small, strained ring systems. (A) Revisiting the retrosynthetic disconnection of an important scaffold in medicinal chemistry, bicyclo[1.1.1]pentan-1-amine 1. (B) Strain-release amination: “any-stage” functionalization of lead compounds in drug discovery.

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connections that rely on the native activation of strained C–C bonds.

**Application of propellane strain-release amination**

As mentioned above, efforts in this area were initiated on account of the practical difficulties encountered at Pfizer in procuring large quantities of bicyclo[1.1.1]pentan-1-amine 2 (Fig. 2A). The tendency of propellane A to react with strong nucleophiles such as t-BuLi and aryl Grignard reagents inspired our approach (17, 18). Extensive exploration (see table S1) identified Davies-type amine nucleophiles (Bn2N-Li) (19) as a good starting point, furnishing 9 in ~20% yield. The key breakthrough was the finding that the corresponding turboamide (20) (Bn2NMgCl•LiCl) led to clean formation of 9 even on a >100 g scale. The use of PhLi leads to reproducible, scalable, and clean formation of propellane A. The dibenzyl group was then easily removed, and the HCl salt of 2 was precipitated (30 g scale). This protocol was successfully scaled up at an outsourcing vendor and can now be used in a process setting to deliver bicyclo[1.1.1]pentan-1-amine-containing clinical candidates economically on scale.

With a reliable route to stock solutions of propellane A (after codistillation with Et2O, solution is stable for weeks to months at −20°C or −78°C, respectively), the scope of this direct “propellerization” was explored (Fig. 2B). Strain-release amination of A using a variety of in situ–derived turbo amides delivered a wide range of tertiary amines containing the valuable bicyclo[1.1.1]pentane bioisosteric motif. Figure 2 illustrates 29 different amines varying in complexity that can be easily accessed. In cases when the reaction did not go to completion, the starting amine could be recovered (e.g., 16, 24, 38). The method tolerates a variety of functional groups, including acetals (16), benzyl ethers (17), ketals (23), and Lewis-basic groups (21, 22, 27, 28, 30–32, 37, 38).

![Fig. 2. "Propellerization" of amine-containing substrates.](http://science.sciencemag.org/) Isolated yields are reported. (A) An improved synthesis of the known bicyclo[1.1.1]pentan-1-amine. (B) A general “propellerization” of amines enabled by strain-release reagents. (C) Substrate scope of amine-containing substrates.

**Conditions:** *Amine substrate (1 equiv.); †The HCl salt of the amine starting material was used; ‡Conditions: Amine substrate (2 equiv.); §The extra equivalent of the amine starting material was recovered in ca. 90% yield (See SM for details); ‖rt = room temperature
Late-stage incorporation of this challenging bioisostere onto six different commercial drugs (Fig. 2C, 33-38) obviated otherwise laborious multistep sequences to access these analogs. The use of turbo-amides is key to enabling the “any-stage” functionalization of both simple and complex amines with A. We anticipate that the path to these bioisosteres will find immediate and widespread use in medicinal chemistry. Indeed, this chemistry has already been field-tested at Pfizer (for example, compounds 14, 15, 17, 19, 21, and 30 were prepared at Pfizer for use in ongoing programs).

**Introduction of azetidine via strain release**

The documented use of azetidines as a tactic to both rigidify amine backbones and serve as phenyl bioisosteres inspired the evaluation of a similar approach (1, 20). Like the propellane systems, access to amino-azetidines is largely limited to a building-block approach that relies on the multistep synthesis of protected azetidinones (21). Strain-release amination of B was therefore evaluated as a means to simplify the preparation of such compounds. Isolated examples of the addition of nucleophiles to B are known but require superstoichiometric amounts of Lewis acids and only work with dibenzyl amine, anilines, and thios (22). As depicted in Fig. 3, the addition of in situ–generated turbo-amides to a solution of in situ–generated B leads cleanly to azetidinylated products (42–59) that are subsequently trapped with a variety of acylating agents to simplify isolation and handling (free azetidines can be generated if desired). Using this protocol, azetidines were directly appended to 18 different amines varying in complexity, including three pharmaceutical agents.

**Introduction of cyclobutane via strain release**

Given the variety of medicinal contexts in which cyclobutane derivatives have been enlisted (23), we next explored a strain-release approach for this motif. The goal was to generate a stable reagent that would enable both rapid and mild “cyclobutylation” of amines but also permit further functionalization of intermediate adducts. Cyclobutane and its substituted derivatives, since their first preparation in 1959 (24), have been the subject of many synthetic studies, most of which either engaged the strained system as a nucleophile or cleaved the center bond via a transition metal–mediated process (25, 26). Rather than pursuing the parent bicyclobutane (a gas at room temperature) (27), we appended an arylsulfonyl group as a means to both activate the strained C–C bond and render the reagent bench stable. Encouragingly, a few examples have been reported wherein benzylamine, when employed as a solvent, could be added to phenylsulfonyl-substituted bicyclo-

butanes at 140°C (28, 29). In seeking a reagent that would allow for more mild reaction conditions and the use of the amine as a limiting reagent, we synthesized a variety of substituted phenylsulfonylated bicyclobutanes (C2 to C7, Fig. 4) and evaluated them in a strain-release amination with amine 39. Not surprisingly, aryl sulfoles containing electron-withdrawing substituents were the most reactive, and the addition of LiCl further accelerated the amination. Removal of the arylsulfonyl group could be easily achieved in the same pot under mild reductive conditions (Mg, MeOH). This protocol was applied to 16 diverse amines with the use of reagent C7, including four commercial drugs, to append the cyclobutyl group (Fig. 4B). The reaction of C7 is chemoselective for amines in the presence of free hydroxyl groups; 71 could be prepared from 4-hydroxypiperidine in 43% yield over three steps (see supplementary materials for details). The arylsulfonyl group could also be used as a handle to generate other useful cyclobutane building blocks containing deuterium (77), alkyl (78), fluorine (79), and olefin (80) substituents. Strain-release amination is not limited to the three ring systems described here, as illustrated in Fig. 4D, wherein cyclopentane (30) could be easily appended to 1,2,3,4-tetrahydroisquinoline (81 → 83) and N-benzylpiperazine (84 → 85). Given these collective findings, we anticipate that a wide range of strained C–C bonds

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**Fig. 3.** “Azetidinylation” of amine-containing substrates. (A) A general “azetidinylation” of amines enabled by strain-release reagents. (B) Scope of amine-containing substrates.
will be amenable to amination and further functionalization.

Applications to peptide labeling

The “spring-loaded” electrophiles described herein exhibit a broad substrate scope for amination and inspired exploration of this platform in a more biologically relevant context. A model peptide (86, Fig. 5) was therefore prepared containing an assortment of proteinogenic nucleophilic functional groups and exposed to strain-release reagent C7 in a mixed organic/aqueous solvent system. Remarkably, complete selectivity was observed for labeling of the cysteine thiol [91% isolated yield of 88 after 5 hours; see HPLC (high-performance liquid chromatography) trace in Fig. 5B]. In the presence of cysteine-free amine 87, no background reaction was observed (Fig. 5C) after 24 hours. In marked contrast, the commonly employed maleimide electrophile led to multiple adducts with 87 after only 1 hour of exposure. The complete chemoselectivity observed for cysteine shows promise for the use of strain-release functionalization in a variety of contexts, such as site-selective bioconjugation (31–34) and peptide stapling (35–38). The efficient tagging of other thiols, including glutathione and cysteine methyl ester, attests to the generality of the approach (see supplementary materials for details).

Fig. 4. “Cyclobutylation” of amine-containing substrates. (A) A general “cyclobutylation” of amines with C7 enabled by strain-release reagents. (B) Substrate scope of amine-containing substrates. (C) Diversification of intermediate cyclobutylsulfone 76. (D) Installation of cyclopentane onto primary and secondary amines by strain-release amination.

Electrophilic covalent warheads for enzyme inhibition and activity-based protein profiling.

Outlook

The operational simplicity, mild reaction conditions, inexpensive preparation, and chemoselectivity exhibited by strain-release reagents A to C will facilitate their rapid adoption. More globally, an enormous variety of reagents based on this concept can be envisaged. For the task of procuring a specific target, this approach to bond formation will enable practitioners to refocus on the challenge of synthesizing a molecular scaffold rather than on the difficulty posed by small ring systems. We anticipate that this approach will also enable formation of distinct connections in the materials, polymer, and bioconjugation arenas.
REFERENCES AND NOTES


Fig. 5. Use of reagent C as a chemoselective cysteine tag for peptide and protein labeling.

(A) Reaction of C7 with functionalized peptides 86 and 87. (B) HPLC chromatogram depicting rapid and clean conversion of 86 to cysteine-labeled product 88 after 1 hour.

(C) Superior chemoselectivity of reagent C7 relative to maleimide 89 in the presence of cysteine-free peptide 87. (D) Reaction kinetics demonstrating the tunable functionalization of 86 with substituted arylsulfonfyl bicyclo-butane reagents.

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Gain modulation by graphene plasmons in aperiodic lattice lasers

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Two-dimensional graphene plasmon-based technologies enable the development of fast, compact, and inexpensive active photonic elements because, unlike plasmons in other materials, graphene plasmons can be tuned via the doping level. Such tuning is harnessed within terahertz quantum cascade lasers to reversibly alter their emission. This is achieved in two key steps: first, by exciting graphene plasmons within an aperiodic lattice laser and, second, by engineering photon lifetimes, linking graphene’s Fermi energy with the round-trip gain. Modal gain and hence laser spectra are highly sensitive to the doping of an integrated, electrically controllable, graphene layer. Demonstration of the integrated graphene plasmon laser principle lays the foundation for a new generation of active, programmable plasmonic metamaterials with major implications across photonics, material sciences, and nanotechnology.

A mong the many intriguing properties of graphene, its plasmonic characteristics are some of the most fascinating and potentially useful (1, 2). Long-lived, tunable intrinsic graphene surface plasmons (SPs) have already been demonstrated in a number of experiments (3–9), including optical modulators (10, 11), providing the potential for applications (12, 13). In contrast to the noble metals that are usually used in SP devices (13, 14), graphene’s Fermi energy, $E_F$, and carrier concentration, $n_e$ (and therefore its conductivity and SP mode properties), can be altered, for example, by electrical gating and surface doping (3, 15, 16). Consequently, the behavior of graphene SP-based structures can be modified in situ, without the need for structural device changes. In particular, graphene’s optical and plasmonic properties are tunable in the terahertz (THz) spectral region (3, 17), giving rise to the possibility of compact electrically controllable THz optical components (18). We incorporated graphene into a plasmonic THz laser microcavity to dynamically modulate round-trip modal gain values and therefore laser emission via $E_F$. In this way, gated graphene becomes a powerful tool with which to control the fundamental properties of a laser—a tool that is potentially extremely fast and all electrical in nature, with negligible electrical power requirements. The interaction between light and matter can be altered by manipulating the electromagnetic density of states (DOS) using a microresonator (19, 20). By incorporating a photonic lattice or plasmonic structure into a laser, one can control the frequency and amplification of resonant modes and hence manipulate the properties of lasing emission (21–23). Furthermore, by breaking the regularity of these structures it is possible to modulate the photon DOS and hence light-matter interaction at several frequencies simultaneously. This technique was used recently to develop an aperiodic distributed feedback (ADFB) cavity laser with a lattice that is in essence a computer-generated hologram (24, 25). The hologram digitally encodes the Fourier transform of a desired optical filter function (multiple reflection resonances within the gain bandwidth of the laser), enabling photonic DOS manipulation at precise filter frequencies. In real space, a typical hologram lattice contains a multitude of phase shifts; the locations and sizes of scattering sites and defects are set such that via coherent backscattering the device enters a slow light regime. Transfer matrix method (TMM) calculations of the group delay transfer function (which is intrinsically linked to the photonic DOS) of an ADFB microcavity under the influence of gain reveal infinite-gain singularities [fig. S4; see (26) for further details]. These singularities represent the frequency and gain values at which self-oscillation occurs. The ADFB microcavity can produce coherent amplification of the cavity photons via stimulated emission processes because of the build-up of phase coherence at the singularities (20). ADFB structures were realized in THz quantum cascade lasers (QCLs)—extremely long wavelength semiconductor lasers with active regions based on precisely engineered inter-subband transitions (27). Such ADFB THz QCLs provide an ideal proving ground for graphene-controlled gain modulation because they use SP-based waveguides (at a metal-semiconductor interface, Fig. 1A) (28). The first crucial step is to excite two-dimensional (2D) plasmons in an integrated, atomically thin graphene sheet to take full leverage of the computer-generated hologram principle. Hologram pixels are introduced to the QCL waveguide as plasmonic scattering sites along the longitudinal axis of the laser ridge (Fig. 1B). By depositing an electrically gateable graphene film onto these devices, our goal is to switch the THz SP at each pixel “on” or “off” by tuning $n_e$, thereby altering the photonic DOS and the degree to which the THz inter-subband gain spectra follows the hologram response. For example, by modulating the hologram pixel scattering strength we approach the DOS singularities, resulting in a dramatic increase of light-matter interaction within the QCL gain media (20). Photon lifetimes (and hence modal gain values) are thereby enhanced, leading to selective enhancement of competing laser modes and a concomitant suppression of others. A hologram with relatively weak feedback was chosen so that any subtle influence of graphene plasmons on laser emission was not hidden by

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SUPPLEMENTARY MATERIALS

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Materials and Methods

Fig. S1 to S6

Tables S1 to S6

References (39–68)

NMR Spectra

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Opening one ring to tack on another

Curious chemists have long sought to learn just how tightly carbon atoms can be bound together. For instance, it’s possible to form a bond between two opposite corners of an already strained four-membered ring to make an edge-sharing pair of triangles. Gianatassio et al. have now devised a general use for these and related molecular curiosities. They show that appropriately modified nitrogen centers can pop open the most highly strained bond, leaving the more modestly strained ring motif intact. In this way, small rings can emerge as a convenient diversifying element in compounds, including new pharmaceutical candidates.

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