Towards the generalized iterative synthesis of small molecules

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Abstract | Small molecules have extensive untapped potential to benefit society, but access to this potential is too often restricted by limitations inherent to the highly customized approach that is currently used to synthesize this class of chemical matter. An alternative ‘building block approach’ — that is, generalized iterative assembly of interchangeable parts — has now proved to be a highly efficient and flexible method of constructing things ranging from skyscrapers and macromolecules to artificial intelligence algorithms. The structural redundancy found in many small molecules suggests that they possess a similar capacity for generalized building block-based construction. It is also encouraging that many customized iterative synthesis methods have been developed that already improve access to specific classes of small molecules. There has also been substantial recent progress towards the iterative assembly of many different types of small molecules, including complex natural products, pharmaceuticals, biological probes and materials, using common building blocks and coupling chemistry. Collectively, these advances suggest that a generalized building block approach for small-molecule synthesis may be within reach.

Small molecules can serve as powerful tools for improving society, with wide-ranging applications in medicine, science and technology. They make the world a more enjoyable place to see, touch, taste and smell, by acting as popular colourants, lotions, flavourings and perfumes. In fact, there is unlikely to be a household on the planet that is not positively affected by this class of chemical matter on a daily basis. Small molecules also possess substantial untapped potential to perform many frontier functions¹, including modulating protein–protein interactions⁵, allosterically modifying protein function⁶, acting as prostheses on the molecular scale⁷, serving as next-generation biological probes⁸–¹⁰, enabling miniaturized diagnostics¹¹–¹⁵, transducing energy¹⁶–¹⁹, emitting light²⁰, initiating self-healing²¹, acting as molecular magnets²², and enabling next-generation computing²³ and superconducting²⁴,²⁵. However, mainly owing to limitations in synthesis, much of this functional potential remains untapped. Eliminating this synthesis bottleneck thus represents both a major challenge and an extraordinary opportunity for the field of chemistry.

Currently, most small molecules are synthesized using customized approaches. For each target, a unique set of starting materials and a specialized sequence of different chemical reactions are developed de novo and then extensively optimized. This approach is a useful strategy for the large-scale production of a particular target. But it is also a laborious bottleneck for the discovery and optimization of new function, which depend on rapid access to many different chemical compounds. Although it is now widely considered possible to synthesize any physically accessible small molecule using this customized approach, both the design and execution phases of this process are time intensive, challenging to automate and inherently restricted to specialists.

In many other disciplines that share the challenge of assembling complex structures to access new functions, the development of a more generalized strategy that involves the iterative assembly of interchangeable building blocks has been transformative. Early examples can be found in Samuel Bentham’s pioneering use of interchangeable parts to facilitate the rapid repair of wooden pulley blocks, and Honoré Blanc’s²³ and Eli Whitney’s²⁵ modularization of musket production. Henry Ford dramatically increased the efficiency of this approach with the development of the assembly line, which revolutionized human transportation by making automobiles a household commodity. The building block approach is now recognized in a remarkably wide range of different areas, including architecture, computers, space stations, robotics, college curricula, music, smart technology apps and artificial intelligence algorithms. The advantages of building block-based construction for efficiency, flexibility and scalability are well-documented and widely appreciated. Perhaps even more exciting is the capacity of this approach to inspire and enable
innovation. This is evidenced by the explosion of applications for 3D printing and the joyful creativity that is unleashed in a child when they are handed their first bucket of Lego bricks.

During the latter half of the 20th century, iterative building block assembly was extended to the molecular scale, yielding automated synthesizers that now provide on-demand access to peptides and oligonucleotides. The corresponding impact has been substantial. To highlight just a few examples, automatically synthesized oligonucleotide probes that correspond to every gene in the human genome printed on a glass slide helped to usher in the era of genomics. Countless peptide- and oligonucleotide-based drug candidates were rapidly tested and optimized, yielding entirely new classes of therapeutics. Total synthesis of genes, proteins and even complete genomes became possible, launching the field of synthetic biology. Substantial recent progress in the automated iterative synthesis of oligosaccharides has also led to important advances in vaccine development.

Extending the building block method to small-molecule synthesis brings a unique set of challenges. The remarkable structural complexity and diversity of small molecules will require a greater number of building blocks, more versatile assembly reactions and new strategies for the generalized purification of intermediates. Encouragingly, many different iterative building block-based synthesis approaches have already increased access to particular molecules and regions of chemical space. Heading towards a more general platform, iteration of metal-mediated cross-coupling reactions has provided increasingly broad access to a diverse range of small molecules, and such a process has even been fully automated. Many challenges remain, but as progress in this direction enables access to previously untapped small-molecule functions, the impetus for finding solutions is expected to continue to grow.

Inherent modularity of small molecules

Small molecules are highly structurally diverse, which makes the development of a generalized building block approach for this class of chemical matter especially challenging. However, many types of small molecule are inherently modular, suggesting that such structures and their accompanying functions should be accessible using a generalized modular synthesis approach. Most natural products, which represent the source or inspiration for more than 50% of all human therapeutics, are derived from only a few major biosynthetic pathways that each involve the iterative assembly of a small number of discrete molecular building blocks. For example, polyketides are biosynthesized from malonyl-CoA and methyl malonyl-CoA, polyterpenes from isopentenyl pyrophosphate and dimethylallylpyrophosphate, fatty acids primarily from malonyl-CoA, non-ribosomal peptides from amino acids and polyphenylpropanoids from phenylpyruvic acid.

Even highly complex molecular structures from natural products can usually be traced back to these same modular pathways. Although the biosynthesis of many natural products also involves rearrangements, oxidations and cyclizations, there is still evidence that this inherent modularity translates to the final products. A recent analysis revealed that more than 75% of all polyene motifs found in natural products can be prepared using only twelve building blocks and one coupling reaction (Fig. 1b). Increasing evidence further suggests that natural product chemical space is bounded, enabling the consideration of generalized approaches for studying the complete natural productome. An expanded effort is now under way to find the minimal number of building blocks required to access most of the natural product chemical space.

Even many non-natural small molecules, which lack such biosynthetic constraints, still contain a remarkable degree of structural redundancy. For example, a 2014 analysis of 1,086 Food and Drug Administration (FDA)-approved small-molecule drugs revealed many recurring heterocyclic building blocks, including piperidine, pyridine and piperazine, cephem, pyrrolidine, pyrrolidine and thiazole. Seventeen additional heterocycles are found in at least ten drugs. This modularity suggests that much of the chemical space relevant to synthesizing pharmaceuticals should also be accessible from a defined set of building blocks. Material components also display a high degree of modularity. Despite performing a wide range of different functions, they are often composed of common repeating substructural motifs, such as oligoarenes, oligothiophenes and polystyrenes. Collectively, this inherent modularity suggests that a wide range of different molecular functions should be accessible by simply assembling building blocks that come from a finite set of common substructural motifs.

Customized iterative synthesis

Iterative synthesis of small molecules from building blocks has already improved access to a diverse range of molecular structures. In each case, building blocks are consecutively added to a growing molecule by repeating a series of chemical transformations. The two main distinguishing characteristics of different iterative synthesis methods are the type of bond used to connect the building blocks and the reactions used to form that bond; both of these characteristics can be optimized for a given target or area of chemical space. Representative methods of iterative synthesis are summarized in Fig. 2 and Fig. 3 (natural products), and Fig. 4 (unnatural molecules), with building blocks highlighted in different colours. The schemes highlight the iterative section of often more complex syntheses (detailed reaction schemes are provided with corresponding figure numbering in Supplementary Fig. S1).

These examples reflect some of the most efficient routes for accessing particular regions of chemical space and, in some cases, they have led to important discoveries. However, the assembly chemistries can impose some practical limitations, such as imperfect stereoselectivity in bond formations or harsh reaction conditions. The synthesis of more complex targets can require many transformations to complete one iteration cycle, lowering
the overall yield and efficiency of the process. These methods also differ by how much structural variation is allowed in the building blocks, which is ultimately what determines the scope of molecules that can be made using an iterative method. Although these customized platforms all use different types of building blocks and assembly reactions and thus are limited with respect to their generality, they have substantially increased synthetic access to specific types of small-molecule structure.

Iterative approaches to naturally occurring molecules. Seminal work by Masamune and Sharpless established that an iterative multistep cycle could be applied to access all eight L-hexoses. Figure 2a shows the sequence applied to the synthesis of L-mannose as a representative example. The cycle begins with the asymmetric epoxidation of an allylic alcohol. In basic medium, the product rearranges to the more thermodynamically favourable terminal epoxide (Payne rearrangement), allowing for nucleophilic attack by sodium thiophenolate. A sequence of acetal protection of the nascent 1,2-diol followed by oxidation to the sulfoxide enables a Pummerer rearrangement to a gem-acetoxyxulfide. Subsequent hydrolysis through reductive (DIBAL) or basic (K₂CO₃/MeOH) conditions enables selective retention or inversion, respectively, of the C2 stereogenic centre in the formation of the corresponding aldehydes. Finally, Wittig olefination and aldehyde reduction produces allylic alcohols for further iteration. Changing the conditions of the two stereo-controlling steps, Sharpless asymmetric epoxidation and gem-acetoxyxulfide reduction, enables access to all eight L-hexoses. The versatility of this strategy has inspired
the development of further methods for the de novo enantioselective synthesis of sugars, and many iterative methods have similarly been developed to access various different classes of small molecule.

The modular nature of polypropionates has inspired several customized iterative synthesis methods to access even highly stereochemically complex products. In early examples by Evans and Paterson, substrate-controlled diastereoselective aldol reactions followed by stereodivergent ketone reductions provided efficient access to a library of stereotetrad motifs. Auxiliary cleavage and the regeneration of aldehyde intermediates enable both of these processes to be iterated. More recently, Crimmins developed a variant of the Evans oxazolidinone methodology that uses N-acylazaindolines as chiral auxiliaries to facilitate a more readily iterated aldol approach (Figure 2b). After a diastereoselective aldol reaction, cleavage of the chiral...
Figure 3 | Customized iterative synthesis of further naturally occurring small molecules. a | The iterative homoligation of boronic esters has been applied to the synthesis of (+)-kalkitoxin. b | A key intermediate in the convergent synthesis of coenzyme Q₁₀ was prepared by iterative palladium-catalysed couplings of alkylzinc reagents. c | Iterative Horner–Wadsworth–Emmons olefinations were applied to the synthesis of a key polyene fragment of amphotericin B. d | Synthesis of gonioicin through iterative THF ring formation. e | The ABCDEF ring system of yessotoxin and adriatxin has been prepared using an iterative oxiranyl anion strategy. f | Structure of natural product halichondrin B showing the four key substructures. Enbulin is an anticancer drug developed as a result of structure–activity relationship studies on the natural product. Detailed reaction schemes are included in Supplementary Fig. S2. TMS, trimethylsilyl; TBDPS, tert-butyldiphenylsilyl; TES, triethyloxysilyl; TIB, 2,4,6-trisopropyl benzoyl.
Figure 4 | Customized iterative synthesis of non-natural small molecules. a | Iterative arene homologation.  
   b | Iterative aryne cycloadditions have been used in the synthesis of polyacenes and dendrimers.  
   c | Phenylacetylene oligomers and dendrimers have been prepared by iterative Sonogashira-type reactions.  
   d | Extended iptycene structures have been prepared by iterative Diels–Alder-like cycloadditions.  
   e | Selective iterative cross-coupling of pre-installed boronate esters has been used to access polyarylated structures. Detailed reaction schemes are included in Supplementary Fig. S3.  

TMS, trimethylsilyl; DMAP, 4-dimethylaminopyridine; LAH, lithium aluminium hydride.
auxiliary directly generates an aldehyde, priming the substrate for further homologation. Notably, the same chiral building block can grant access to either stereoisomer of the syn aldol product depending on whether the additive is TiCl₄ or (−)-sparteine. During the synthesis of 6-deoxyerythronolide B, Crimmins iterated this sequence five times, setting off of the 11 stereocentres using a single type of reaction⁶⁹ (Supplementary Fig. S1b).

A related polyketide motif, the 1,3-poly unit, can also be prepared using several different types of iterative chemistry. Brown developed an iterative allylation reaction using chiral boranes to carry out highly enantioselective reactions with aldehydes⁶⁶–⁶⁸. The olefin motif of the resulting homoallylic alcohols can be oxidatively cleaved to reveal a new aldehyde for further allylation. This approach was used to generate the 1,3-poly fragment in the synthesis of passifloricin A⁶⁹ (Fig. 2c).

Recently, Krische and co-workers pioneered a highly efficient C–C bond-forming transfer hydrogenation strategy involving the in situ generation of an aldehyde and an organometallic nucleophile⁷⁰. Application of this iterative strategy in a two-directional manner expedited the construction of the key polyol portion of (+)-roxatins B⁷¹ (Fig. 2d). This methodology has proved to be highly versatile and readily scalable, enabling practical gram-scale access to stereochemically complex building blocks for a wide range of highly complex polyketide natural products⁷²–⁷⁴. This efficiency has further enabled the practical synthesis and testing of bryostatin derivatives, shedding new light on the relationship between potency and biological activity⁷⁵.

Polydeoxypropionates are an important subclass of the polyketide family, but the absence of functional handles has rendered their stereoselective synthesis challenging. Myers has developed a robust iterative alkylation protocol using stoichiometric ephedrine-based auxiliaries that provide access to all possible stereochemical variants⁷⁶–⁷⁷, and Theodorakis has applied this methodology to the total synthesis of (−)-borrelidin⁷⁸–⁷⁹ (Fig. 2e).

Minnaard and Feringa⁸⁰ have recently developed an alternative iterative three-step protocol to access syn deoxypropionate motifs based on catalytic asymmetrical conjugate additions (Fig. 2f). Starting from an α,β-unsaturated thioester, a highly enantioselective 1,4-addition of MeMgBr in the presence of a chiral copper catalyst sets the first methyl-bearing stereogenic centre. A reduction and Wittig olefination sequence generates a new α,β-unsaturated thioester for further 1,4-addition reactions. Repetition of these three steps allows seven methyl stereocentres to be installed with excellent levels of stereoselectivity, enabling the first total synthesis of phthioceranic acid⁸⁰, as well as the first total synthesis of sulfolipid-1 (REF 81).

Breit has also developed an iterative zinc-catalysed sp²–sp³ coupling method for the synthesis of deoxypropionates⁸² (Fig. 2g). Treatment of an alkyl Grignard with ZnCl₂ generates a triorganozincate species (R₂ZnMgCl), which displaces a secondary triflate to generate a new C–C bond with inversion of configuration. Reduction of the ester followed by conversion to a primary alkyl chloride enables further iteration. The lack of reactivity with alkyllithium species suggests that magnesium coordination to the triflate may play a role in Lewis acid activation of the electrophile. Using this iterative method, Breit was able to access a library of different diastereomers of trideoxypropionates, all in >99% diastereomeric excess. The modular nature of polydeoxypropionates has also inspired the development of several other iterative synthesis strategies⁸³,⁸⁴.

Aggarwal’s versatile approach for the iterative synthesis of various stereochemically complex Cap³-rich motifs is demonstrated with his route to (+)-kalkitoxin (FIG. 5a). This approach leverages the stereospecificity of the 1,2-metallate rearrangement of boronate complexes⁸⁵ to install both stereochemistry and functionality through iterative chain extension of boronic esters. In a one-pot procedure, a boronic ester was subjected to a series of six homologations, installing three methylene spacer units and three methyl-bearing stereocentres derived from the requisite enantiomerically pure lithiated benzoates⁸⁶. Amination followed by amide formation furnished the core of (+)-kalkitoxin in an overall 52% yield. The same approach has been used to synthesize baulamycin A⁸⁷, tatanan A⁸⁸, fluorohexestrol⁹⁰ and C30 botryococcene⁹¹, among many other targets⁹². More broadly, the versatility of this homologation method, which tolerates diverse structural variation in its building blocks, opens the door for divergent synthesis. This can be seen in Aggarwal’s assembly-line production method of hydrocarbons with tailored shapes⁹³.

Polyisoprenoids are attractive targets for iterative synthesis due to the numerous 1,5-trisubstituted olefin motifs spanning their structures. Negishi⁹⁴ has developed an iterative and convergent synthesis for these motifs and applied it to the synthesis of coenzyme Q₁₀ (FIG. 5b). A one-pot iterative cycle begins with the formation of a primary alkylzinc iodide followed by a chemoselective cross-coupling with a diiodo building block. Two further iterations followed by coupling with a diene-containing building block installs five of the trisubstituted olefins of coenzyme Q₁₀. To enable convergent synthesis, the trimethylsilyl (TMS)-protected alkyl also serves as an attachment point. TMS deprotection and subsequent carbometalation–iodination generates a new vinyl iodide that undergoes a strategic and convergent cross-coupling with an earlier homologue. A final round of deprotection, hydroxirazonation–iodination and cross-coupling gives coenzyme Q₁₀ in only 11 steps. Only part of the iterative sequence is shown in the figure, but a detailed reaction scheme is available in Supplementary Fig. S2b (FIG. 5b).

Long polyene chains are another modular structure found in natural products. However, these motifs are often sensitive to many common reagents (for example, protic and Lewis acids) and conditions (for example, light and oxygen), rendering their synthesis challenging. In a landmark total synthesis of the complex polyyne macroide amphotericin B (AmB), Nicolaou used an iterative Horner–Wadsworth–Emmons (HWE) strategy to complete the all-trans-polyene motif. Starting from an aldehyde, the first triene unit was installed using a diene-containing phosphonate⁹⁴ (FIG. 3c). Subsequent conversion of the terminal ethyl ester into an aldehyde set
the stage for a second homologation using the phosphonate building block. Deprotection and redox modification furnished a hexaenal, which was esterified with a highly functionalized carboxylic acid containing a phosphonate to generate the open-chain molecule. An intramolecular HWE reaction initiated by K₂CO₃/18-crown-6 formed the desired cyclic heptaene, completing the carbocyclic core of AmB²⁸ (Supplementary Fig. S2c).

Developing iterative routes to complex, polycyclic molecules represents a substantial challenge, but provided that common repeating units and assembly methods can be established, iterative synthesis can both be practical and expeditious. For example, Uenishi and co-workers developed an iterative protocol for the stereoselective synthesis of linked tetrahydrofuran (THF) rings⁹⁸ (Fig. 5d). The iterative sequence commences with the formation of a homoallylic alcohol through Grignard addition to an aldehyde or epoxide, followed by cross-metathesis with a stereoregulated allylic alcohol. Pd(II)-mediated ring closure forms the THF ring and, finally, ozonolysis of the resultant olefin forms an aldehyde to allow further iteration. Synthesis of either trans-three-trans or trans-three-cis THF rings is simply a case of exchanging the allylic alcohol building blocks during the metathesis stage of the iterative cycle.

Mori and co-workers leveraged the modularity inherent in structurally complex polycyclic ether natural products to enable their iterative construction⁹⁹ (Fig. 5e). In this approach, diastereomerically pure oxiranyl anions were utilized to displace primary tosylates, and the resulting epoxy sulfone products were then subjected to an acid-catalysed 6-endo cyclization. A five-step sequence then generated a new trflate for further iteration. Six repetitions of this protocol led to the efficient construction of the ABCDEF-ring fragments of yessotoxin and adriatin, with the stereochemistry of the cyclic ethers introduced through the selection of the appropriate oxirane building blocks. This iterative oxiranyl anion strategy has further been used for the synthesis of hemibrevetoxin B⁰⁰, gambierol⁰⁰ and even gymnoca-A with 14 contiguous fused rings⁰⁰. Other iterative synthesis strategies have also been developed for polycyclic ethers, including iterative ring closing metathesis–hydroboration, iterative reductive cyclizations, and iterative oxonium ylide formation-[2,3]-shift processes⁰¹.

Kishi’s important synthesis of halichondrin B⁰³ used iterative Nozaki–Hiyama–Kishi (NHK) reactions interspaced by tailoring steps to build cyclic moieties in an iterative fashion (Fig. 5i). This strategy allowed highly complex building blocks to be efficiently assembled in an iterative manner. Other family members of the halichondrin family could also be accessed by incorporating variant building blocks into a similar synthetic sequence⁰². This efficient and modular synthesis enabled Kishi and co-workers to perform a structure–activity relationship study and discover that the macrocyclic portion of halichondrin B was almost as equipotent as an anti-cancer agent as the natural product itself. A close variant of the synthesis was successfully scaled up by chemists at Eisai to produce enough of this fragment, dubbed eribulin, to enable its clinical study. Significant benefits were observed for patients with metastatic breast cancer and liposarcoma, leading to the FDA approval of eribulin for the treatment of these cancers in 2010 and 2016, respectively⁰³,⁰⁴.

Iterative approaches to oligomeric small molecules.

Beyond natural products, customized iterative assembly methods have also enabled the synthesis of many other types of inherently oligomeric materials (Fig. 4). For example, polyaromatic hydrocarbons have numerous applications in solar cells and light-emitting diodes but can often prove challenging to prepare when site-specific functionalization is required. Kwon and co-workers have developed an efficient strategy for the iterative synthesis of polyaromatic hydrocarbons through the union of a 1,2-dialdehyde and ethyl allenolate⁰⁵ (Fig. 4a). Oxidative modification of the annulated product furnishes a 2,3-dialdehyde that is primed for another annulation reaction. This iterative cycle rapidly generates 2,3-substituted anthracene and tetracene structures.

The synthesis of larger acenes is complicated by their higher reactivity, but these structures are highly sought after for their applications in organic electronic materials. For example, pentacene is currently the best available organic p-type semiconductor, but larger members could be even more useful⁰⁶. Excellent syntheses of octacene and nonacene derivatives have been carried out by Echavarren⁰⁷,⁰⁸ and Bettinger and co-workers have developed a building block–based approach using iterative Diels–Alder reactions⁰⁸ (Fig. 4b). Combination of 5,6,7,8-tetramethylenecyclo[2.2.2]oct-2-ene and an arylene dienophile, generated by the treatment of 1,2-dibromobenzene with n-BuLi, led to the formation of a cycloaduct with a terminating diene moiety. This was treated with an arylene generated from 1,2,4,5-tetramethylenecyclobutene, resulting in a product terminating in another dibromide moiety. An additional iteration of arylene formation and cycloadition generated a stable precursor to octacene. After a sequence of aromatization and oxidation reactions, exposure to low-wavelength UV light generated octacene for functional studies.

Although most iterative synthesis methods are based on the linear assembly of building blocks, Moore and co-workers have developed a convergent iterative synthesis of phenylacetylene oligomers (Fig. 4c; left) using Sonogashira coupling⁰⁹,¹⁰,¹¹. Moore’s work highlights a crucial advance that enables the application of iterative synthesis in a convergent fashion, the ability to orthogonally protect and deprotect each of the two different functional groups required for building block assembly (Supplementary Fig. S3c). Here, a bifunctional building block can be selectively activated in two different ways: a dialkylationzene can be converted to an iodide or a TMS protecting group can be removed to reveal a reactive terminal alkyne. These two differently activated building blocks can then be assembled via Sonogashira coupling to form an advanced intermediate containing a dialkylationzene and a protected alkyne at opposite termini. Repeating this process of using advanced intermediates as building blocks enables exponential molecular growth. In such a manner, it is possible to generate
repeating tetramers, octamers and longer oligomers with precise control of the sequence of building blocks. Additionally, building blocks with other functional groups can also be incorporated to prepare diverse oligomeric products with a range of important functions112.

Moore has also developed a convergent approach to iterative synthesis for the assembly of large dendrimers113–115 (Fig. 4c; right). Compared with the strategy for making oligomers, this dendrimer method is different in two respects. In this case, the building blocks are activated in a single direction, by unmasking a reactive terminal alkyne for Sonogashira coupling through the removal of a TMS protecting group. However, exponential molecule growth can still be achieved via double Sonogashira coupling onto a trifunctional monomer containing two bromines. Four iterations of TMS deprotection and double Sonogashira coupling enabled the rapid construction of a monodendron containing 31 building blocks115. This double Sonogashira approach is capable of quickly making large molecules, but generating unsymmetrical targets represents an additional challenge. Such a limitation is not problematic for dendrimer synthesis, and these examples illustrate that convergent iterative synthesis can be most versatile when it has two separate masking and deprotection strategies for orthogonal functional groups.

Iterative synthesis methods have also been developed for molecules with defined 3D architectures. Iptycenes are of interest in materials science and supramolecular chemistry due to their structural rigidity and three-dimensionality. Swager and co-workers devised an iterative solid-state synthesis of extended iptycenes in which a Diels–Alder reaction between anthracene and 1,4-anthraquinone was followed by reaeromatization to form a new anthracene unit for further iteration (Fig. 4d). This cycle was then repeated to form longer iptycenes in a modular fashion116.

Many methods have recently been developed to enable boronic esters to be chemoselectively functionalized. For example, Cruden discovered and harnessed such selectivity to facilitate a different approach to iterative synthesis (Fig. 4e). Instead of generating new positions for appending building blocks during each iteration cycle, all of the attachment points were pre-installed in advance. In a one-pot procedure, a Csp²–Csp² coupling of an aryl boronic ester was followed by group-selective cross-coupling of a Csp¹ primary boronic ester. Simple filtration through silica gel enabled a Cruden Csp¹ cross-coupling of the remaining secondary boronic ester in the presence of Ag₂O, creating a defined polarylated structure117.

Iterative synthesis has also been applied to create mechanically interlocked molecules. In Goldup’s iterative synthesis of oligo[n]rotaxanes, copper-templating via a bipyridyl-containing macrocycle is harnessed to control a three-component click reaction118 (Supplementary Fig. S3g). The product rotaxane has a terminus containing a trisopropyl (TIPS)-protected alkyne. Cleavage of the silyl group and iteration of this reaction allow for the incorporation of different macrocyclic moieties119.

Each of these examples represents an important advance towards efficient and flexible synthetic access to specific types of small-molecule motifs. In most cases, the iterative syntheses proceed in a linear way, but there are also multiple strategies for convergent iterative methods (Fig. 4c) that enable even more efficient molecule growth. There is a trade-off: the more convergent an iterative synthesis method, the more limited its scope of targets. By contrast, divergent approaches to iterative synthesis have the greatest potential to accelerate the discovery of new function, but may require more steps. It is evident from several divergent iterative synthesis methods8,60,77,82,85,112 that the greater the potential for structural variation in the building blocks, the greater the scope of possible products. This suggests that highly generalized coupling chemistry may provide an opportunity for more generalized iterative synthesis approaches to be achieved.

A general platform for iterative synthesis

A more general iterative platform for small-molecule synthesis requires a common type of assembly chemistry that can form a wide range of different types of C–C and C–X bonds while being tolerant of many functional groups. Although many methods fall short of the high bar required to enable generalized synthesis, metal-mediated cross-coupling represents an exceptionally attractive candidate. The Suzuki–Miyaura and Buchwald–Hartwig couplings, in particular, can use non-toxic and shelf-stable building blocks, are highly efficient and stereospecific, and can proceed under mild reaction conditions with high levels of functional group tolerance. Moreover, the scope of both C–C and C–X bonds that can be formed using such methodology is already very broad and continues to expand, and the versatility of these types of coupling has placed them among the most widely used reactions in both academic and industrial synthesis groups. Most recently, this scope has been extended to include a wide range of Csp¹ and Xsp¹ coupling partners111–121, even including stereospecific Csp² cross-couplings of stereochemically defined chiral non-racemic building blocks, a concept that was pioneered by Cruden122–124. These new methods, combined with the anticipated major additional advances in the area of sp³ cross-coupling over the next few decades, suggest that iterative cross-coupling (ICC) could represent a generalizable approach for building block-based small-molecule synthesis.

In such a platform, the complex problem of molecular construction can be simplified into simply making and coupling building blocks. In theory, all the required functional groups, oxidation states and stereochemistry can be pre-installed into such building blocks and then faithfully translated into the growing target structure using only mild and stereospecific cross-coupling reactions. Achieving this goal requires compatible bifunctional building blocks that can be iteratively assembled in a precisely controlled manner. This in turn requires the development of methods for reversibly attenuating the reactivity of such building blocks towards metal-mediated coupling.110,111 (Fig. 5a).

Several approaches to achieve such reactivity attenuation have leveraged the sensitivity of Lewis acidic organometallic coupling partners in different ways.
Hiyama has devised a strategy for reversibly attenuating the reactivity of arylsilanes using specially designed organo[2-hydroxymethyl]phenyl dimethylsilanes (Fig. 5b). Under normal cross-coupling conditions, these arylsilanes are ‘switched off’ and unreactive towards transmetalation, but upon deprotection of a strategically positioned neighbouring alkoxy, the resulting intramolecular O–Si coordination activates the silane and promotes cross-coupling. Using this method of building block assembly in an iterative fashion, Hiyama completed the synthesis of highly conjugated linear oligoarylenilsilanes.

Sugino reported an alternative method for switching off organometallic coupling partners (Fig. 5c). Complexing boronic acids with the 1,8-diaminonaphthalene (DAN) group decreases the Lewis acidity of the ρ-orbital of the sp2-hybridized boron atom via electron donation from neighbouring lone pairs on planar nitrogen atoms. The resulting BDAN compounds are stable to both anhydrous and aqueous biphasic cross-coupling conditions, but exposure to strong aqueous HCl or H2SO4 removes the DAN group and releases the corresponding boronic acid. This iterative building block-based method has been applied to the synthesis of oligoarenes and oligo(phenylenevinylenes).

Work by our group identified that complexation with the trivalent ligand N-methyliminodiacetic acid (MIDA) can alternatively attenuate boronic acid reactivity by rehybridizing the boron atom from sp2 to sp3 [Ref. 138] (Fig. 5d). As described below, MIDA boronates represent a very promising platform for generalized building block-based molecular synthesis, and the collective efforts of many different research groups have continued to expand the scope of this approach. Continued advances in these and other methods to reversibly attenuate the reactivity of organometallic building blocks are set to continue to enable generalized synthesis of small molecules and the discovery of new molecular functions.
MIDA boronates have many advantageous physical and chemical features. They are readily purified by silica gel chromatography and/or recrystallization and are usually indefinitely stable on the benchtop as free-flowing crystalline solids. Moreover, many alkylboronic, vinylboronic and arylboronic acids can be directly converted to their MIDA boronate counterparts in quantitative yields under mild conditions. To drive the MIDA complexation to completion, water can be removed simply via toluene azeotrope with a Dean–Stark trap or by the addition of a drying agent such as magnesium sulfate. MIDA boronates are inert to anhydrous cross-coupling reactions, but they can be quickly deprotected under mild azeotropic conditions. Deprotection can proceed through two different mechanisms: either under a strong aqueous base in which a rate-limiting attack of hydride occurs on the carbonyl carbon, or under weakly basic or neutral aqueous conditions in which a slower rate-limiting attack of water occurs on the B–N bond. This mechanistic divergence is consistent with extensive reaction kinetics, kinetic isotope effects, ¹⁸O labelling and computational studies. In situ slow release of MIDA boronates has been advantageous for many reactions, including couplings of unstable heteroarylboronates, polymerization reactions, asymmetric methodologies, the synthesis of organic photovoltaics and a one-pot homologation of boronic acids.

The durability of MIDA boronates to a wide range of different reagents and reaction conditions further facilitates the synthesis of otherwise challenging to access boronate building blocks from simple boron-containing starting materials (Box 1; Supplementary Fig. S4). For example, many standard oxidations, reductions and protecting group manipulations are well-tolerated. Numerous other common synthetic transformations leave MIDA boronates intact, including aldehyde reactions, carbonyl olefination reactions, Mitsunobu reactions, electrophilic substitution reactions, hydroborations and hydrostannylation, Diels–Alder cycloadditions and cyclopropanations. A variety of transition metal-catalysed reactions are also well-tolerated, including Heck reactions, Grubbs alkene metathesis, Sonagashira couplings and Suzuki cross-couplings.

MIDA boronates are, however, not without their limitations in terms of scope and application. A large number of Suzuki–Miyaura cross-coupling reactions require the

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**Box 1 | Reaction conditions compatible with MIDA boronates**

*N*-Methylimidodiacetic boronic acid esters (MIDA boronates) have been found to be compatible with a wide range of standard reaction conditions. It is this broad stability profile that makes them especially suited to applications in building block style iterative synthesis. Detailed reaction conditions are included in Supplementary Fig. S4.

**Oxidations**
- Swern (COCl₂, DMSO, NEt₃)
- Jones (CrO₃, H²SO₄)
- Oxidative fluorination (Selectfluor, SinB, AcOH)
- Oxidative trifluoromethylation (NaSO₂CF₃, IBX)
- Dihydroxylation (OsO₄)
- Dess–Martin oxidation (Dess–Martin periodinane) ¹⁵¹
- Ozonolysis (O₃)
- Epoxidation (m-CPBA)

**Reductions**
- Aldehyde reduction (NaBH₄)
- Reductive amination (NaBH₄.OAc)
- Alkene hydrogenation (H₂, Pd/C)
- Alkene semi-hydrogenation (H₂, Lindlar catalyst)
- Isocyanate reduction (HSICl₂, Et₃N)

**Protection/deprotection**
- p-Methoxybenzylolation (PMB) (PMBOC/NH/CCl₃/DDQ)
- tert-butylidemethylsilylation (TBS) (TBSI, imidazole/ HF/pyridine)

**Nucleophilic displacement**
- Mitsunobu (DIAD, PhP₃, benzoic acid, diphenylphosphonylazide)
- Bromination (PhBr₂)
- Iodination (PhP₃I₃)
- Epoxide opening (LiBr, AcOH)

**Nucleophilic addition to aldehydes**
- Evans asymmetric aldole (‘Bu₂BOT, Et₃N)
- Horner–Wadsworth–Emmons reaction (Et₂O, P(O)
- CH₃CO₂Et, NaH)
- Takai olefination (CrCl₂, CH₂J)

**Electrophilic substitution**
- Aromatic bromination (N-bromosuccinimide (NBS), H₂SO₄)
- Aromatic nitration (HNO₃, H₂SO₄)
- Aldehyde α-bromination (Pyridoline, AcOH, NBS)

**Addition across multiple bonds**
- Xanthate radical addition (Lauroyl peroxide O-ethyl S-(isocyanomethyl) carbonodithioate)
- Hydroboration (HBPn)
- Hydrostannylation (Bu₃SnH, AIBN)
- Bromination (Br₂)

**Transition metal catalysed reactions**
- Heck coupling (Pd(OAc)₂, AgOAc, Pd(PPh₃)₃, Ag₂PO₃)
- Sonogashira coupling (PdCl₂(PPh₃)₃, Cu, CuOAc, K₂PO₃)
- Olefin metathesis (Grubbs II)
use of an aqueous base, which causes the hydrolysis of MIDA boronates, and Buchwald–Hartwig aminations can involve the use of strong bases that are incompatible with the acidic protons on the backbone of the MIDA ligand. As many Csp3 cross-coupling methods involve aqueous basic reaction conditions, these important limitations currently prevent the use of these reactions in MIDA boronate-based ICC.

Only a few of the many recent advances in MIDA boronate-based building block synthesis from many different research groups are highlighted in this Review. By harnessing the ability of MIDA to rehybridize boron from sp2 to sp3, Zard used vinyl MIDA boronates as acceptors for xanthate-derived radicals159. The resulting α-boryl radicals are sufficiently destabilized to ensure that the reaction is irreversible. Making use of similar vinyl MIDA boronate substrates, Wang160 developed a new oxidative difunctionalization reaction. After treating with SIBX along with either a fluorinating or a trifluoromethylation reagent, the resulting α-boryl ketones can be converted to highly functionalized furans bearing MIDA boronates. A variety of other heterocycle-forming reactions have also been developed using MIDA boronate-containing substrates. Making use of amphoteric molecules containing MIDA boronates and electrophilic ketones or aldehydes, Yudin developed syntheses of a wide range of otherwise challenging to access borylated building blocks, including pyridazines and pyroles161, imidazoles162, thiazoles163, imidazo[1,2-α]pyridines164, and many other motifs165. Watson166 has also developed a synthesis of 2-borylated indoles and benzofurans involving the use of a palladium-catalyzed cascade reaction with ethynyl BMIDA and 2-iodoanilines. Similarly, borylated indolines and benzofurans have been synthesized through gold-catalyzed intramolecular cyclizations onto alkenes167. These reactions are expanding the collection of MIDA boronate building blocks available for small-molecule construction, and hundreds of MIDA boronates are already commercially available.

The protection of boron with the MIDA ligand has also enabled previously inaccessible borylated molecules to be created such as α-boryl aldehydes162,164, which without MIDA complexation would rearrange to O-boryl enolates. Yudin and our group have explored applications of this unique class of molecules by exploiting the divergent reactivity of the aldehyde and MIDA boronate motifs163,164. Yudin has extensively expanded this platform to enable the efficient synthesis of a variety of heterocycles and functionalized boronic esters and even the formation of complex tertiary organoboronates through Tsuji–Trost allylations166.

Beyond the synthesis of simple achiral and racemic building blocks, chiral non-racemic MIDA ligand variants can direct diastereoselective epoxidation of vinyl boronates to generate stereoisomerically pure oxyaryl boronates167. Furthermore, installation of enantiopure chiral MIDA ligands onto racemic boronic acids generates diastereomers that can be separated via column chromatography to ultimately yield enantiomerically pure boronic acids168.

**ICC with MIDA boronates.** Leveraging these many advantageous features, the ICC of MIDA boronates has now been applied by many research groups to the synthesis of a wide range of structurally diverse small molecules19,149,167,169–182 (Fig. 6, Supplementary Fig. S5). This rapidly growing list includes natural products from every major biosynthetic pathway, pharmaceuticals, biological probes and materials components. Moreover, these completed syntheses include linear molecules for which the capacity for iterative building block-based assembly is more apparent, as well as an increasing number of highly complex macrocyclic and polycyclic frameworks for which the inherent modularity is less obvious. Moreover, many of these syntheses took advantage of common off-the-shelf MIDA boronate building blocks, hundreds of which are now commercially available. Collectively, this rapidly growing collection of successful applications of ICC for making a wide range of complex small molecules suggests that the opportunity to drive functional discovery with this type of chemical matter will be increasingly accessible.

A few illustrative examples are highlighted in detail in Fig. 7. Ratanhine was the first natural product to be synthesized by ICC179 (Fig. 7a). Notably, the mild nature of the deprotection and coupling reactions preserved even hydrolytically sensitive functional groups such as esters. The stability of MIDA also assisted in several additional ways. The benzofuran building block, which in its boronic acid form is prone to decomposition, proved to be bench-stable under air. Even couplings that required elevated temperatures of 80 °C tolerated the MIDA boronate and proceeded in high yield.

Kobayashi developed an efficient ICC-based synthesis to the natural product mxyalamide A138 (Supplementary Fig. S6b). A key challenge in this synthesis was the construction of the central trans-trans-cis-trans tetrane, as such motifs are difficult to install in a stereocontrolled fashion. The capacity of olefinic stereocchemical elements pre-installed in shelf-stable bifunctional MIDA boronate building blocks to be faithfully translated into growing targets by using mild and stereospecific cross-coupling methods simplifies this type of complex problem169,171,183. In this specific case, a cis-bifunctional vinyl MIDA boronate building block was iteratively cross-coupled to unite the two key fragments of the polylene core of mxyalamide A in a stereospecific fashion. Moreover, no protecting groups were required, as the cross-coupling reactions proceeded in the presence of two free alcohols.

The same concept of leveraging stereospecific cross-couplings to transfer pre-installed stereochemistry from pre-fabricated building blocks into products has also been extended to stereogenic Csp3 centres. During the synthesis of a glucagon receptor inhibitor, the presence of several Csp3 carbons offered strategic disconnection points (Supplementary Fig. S6c). The first two building blocks were assembled by a Csp3 coupling between an aryl iodide and a primary alkylzinc reagent147. In the second coupling reaction, an enantiomerically enriched benzylboronate was then subjected to Cruden’s stereoretentive Csp coupling to yield the targeted chiral pharmaceutical candidate in a very simple manner124.
Figure 6 | Small molecules made via iterative cross-coupling with MIDA boronate building blocks. a | A generic scheme for iterative cross-coupling. Molecules with a linear polyene core represent the largest group of molecules that have so far been prepared via an N-methyliminodiacetic acid (MIDA) boronate-derived iterative synthetic route\(^{146,147,149,151,153-155}\). Linear precursors synthesized via an MIDA boronate route have been converted into the polycyclic core structures of several natural products\(^{148,149}\). b | Linear polyene core. Neurosporaxanthin [β-glucopyranoside\(^{154}\)] See also: * Physarin A\(^{160}\) * β-Parinaric acid\(^{162}\) * Synechoxanthin\(^{172}\) * Aspironpyrene B\(^{162}\) * Methyl eicosapentaenoate\(^{177}\) * All-trans-retinal\(^{182}\) * Hydroxy-[β-sanshool\(^{171}\) c | Polypene natural products and drugs are obvious targets of such an iterative Suzuki-type method\(^{146,147,155,156,158}\). d | Polypene substructures of larger molecules, such as amphoterin B\(^{172}\), filipin III\(^{174}\), elansolid B1 [REF. 178], myxalamide A\(^{179}\) and crocin B\(^{180}\), have also been prepared using the MIDA-boronate method. Detailed molecular structures are included in Supplementary Fig. 55.

Another powerful reaction in the synthesis of pharmaceutical compounds is C–N bond formation; however, strong bases are sometimes required for less reactive amines and, as described above, these conditions can be incompatible with MIDA boronates. Hamann and co-workers pioneered a strategy that selectively protects MIDA boronates in situ by eutolization with Li[N(SiMe\(_3\))]\(_2\) (LiHMDS) at low temperatures\(^{184}\). This more robust Li-MIDA enolate enabled an efficient one-pot ICC synthesis of the histamine H\(_3\) agonist through iterative C–N and then C–C coupling reactions (FIG. 7b). This Li-MIDA enolate strategy may have other applications beyond C–N coupling where use of a strong base causes loss or cleavage of the MIDA protecting group.

Even some highly complex small molecules have been prepared via ICC. For example, the natural product peridinin (FIG. 7c) is a norcarotenoid that contains several complex functional groups and stereochemical elements, including a butenolide, an epoxide and an allene motif. Because of the mild and stereospecific nature of MIDA-boronate ICC, all of these functional groups and stereochemical elements were pre-installed in the four complex building blocks and faithfully translated into the final product, yielding the first fully stereocontrolled synthesis of peridinin\(^{171}\). Each MIDA boronate intermediate, including the final heptaenyl MIDA boronate, proved stable to chromatography and storage. Although the boronic acid in the final coupling reaction proved unstable to isolation, an in situ deprotection of the MIDA boronate allowed the coupling to proceed both in high yield and with complete stereoretention.

Polycyclic molecules present an especially formidable challenge for building block-based construction. However, the biosynthesis of complex, Cs\(^+\)-rich polycyclic natural products often involves an actionable two-part strategy: the assembly of building blocks into a
Figure 7 | Illustrative examples of iterative MIDA boronate cross-coupling. A generic scheme for iterative cross-coupling is shown in part a. Detailed reaction schemes are shown for the synthesis of ratanidine\textsuperscript{139} (part b), a histamine H3 antagonist\textsuperscript{140} (part c) and peridinin\textsuperscript{171} (part d). Detailed reaction schemes are included in Supplementary Fig. S6. MIDA, N-methyliminodiacetic acid; TBS, tert-butylimidemethylsilyle; THF, tetrahydrofuran; TMS, trimethylsilyl. C and D represent coupling and deprotection steps respectively.

linear precursor and then a cyclization reaction to transform this linear molecule into a complex (poly)cyclic skeleton\textsuperscript{185}. In theory, ICC could be used in a similar linear-to-cyclized approach. This was confirmed by the synthesis of the pentacyclic core of secodaphnane natural products\textsuperscript{182} (Fig. 8a). Two cycles of Csp\textsuperscript{4} coupling were initially used to construct a linear precursor, which was then subjected to a bioinspired cyclization cascade involving amine condensation and intramolecular Diels–Alder and Prins cyclizations\textsuperscript{186}. 
An exceptionally efficient linear-to-cyclized approach was also used by Vosburg to make highly complex polycyclic natural product frameworks, including the ethyl ester of the tetracyclic natural product cryptobelic acid D179 (Supplementary Fig. S6). Vosburg and co-workers used all commercially available MIDA boronate building blocks to stereospecifically construct the complex trans-cis-cis-trans-tetraene linear precursor. This tetrane was primed for an 8/6" electrolycycloization cascade to generate a fused 4–6 ring system, which ultimately led to the completion of cryptobelic acid D180.

This linear-to-cyclized strategy has also enabled biological studies of clinically relevant natural products. AmB has served for more than 50 years as a last line of defence against invasive and drug-resistant fungal infections, but it has dose-limiting side effects. With the goal of gaining a better understanding of the mechanism of toxicity of AmB, an AmB derivative lacking a single hydroxyl group was synthesized via ICC followed by macrocyclization187 (Fig. 8b). This new compound, C35deOAmB, lacked the ability to form ion channels but retained its toxicity to fungal pathogens, overturning decades of prior thinking about the primary mechanism of action of this clinically vital but unfortunately highly toxic natural product187. This discovery helped to build a strong foundation for ongoing efforts to rationally optimize the therapeutic index of AmB188,189. It also enabled the ion channel-forming capacity of this natural product to be rationally separated from its cell-killing effects. This, in turn, facilitated the development of small molecules that replace missing protein ion channels and thereby restore physiology, akin to acting as prostheses on the molecular scale189.

MIDA boronates have also been used independently of iteration in a wide range of other small-molecule synthesis applications143–144,146,153,184,190–197.

**Automation of small-molecule synthesis**

The automation of small-molecule synthesis has the potential to dramatically improve the efficiency with which new molecular functions can be discovered and optimized. It also represents an actionable path for...
bringing the power of making small molecules to non-specialists. One strategy for automating small-molecule synthesis involves translating current customized synthetic approaches into an automated format\textsuperscript{198–201}. Although this approach has the advantage of utilizing known manual solutions, it necessitates the automation of many different types of chemical reaction, each of which requires different reagents, conditions, optimization protocols, reaction vessels and/or purification protocols.

A major advantage of ICC is that, once the necessary building blocks are in hand, it only requires the same two reactions — deprotection and coupling — to complete the molecular assembly process. This presents the strategic opportunity for collective efforts to be deployed to extensively optimize these two reactions and, ultimately, to reach highly generalized conditions, as was previously achieved for iterative peptide\textsuperscript{202} and oligonucleotide synthesis\textsuperscript{203}, and is now being increasingly realized for oligosaccharides\textsuperscript{204}.

It is also notable that every intermediate in a MIDA boronate-based ICC sequence contains the same common MIDA boronate functional group. It was recognized that this could potentially serve as a handle for generalized purification. In this vein, MIDA boronates were discovered to possess an unusual binary affinity for silica gel with certain pairs of eluents\textsuperscript{192} (FIG. 9a). Regardless of size, functional group content or polarity, MIDA boronates show minimal mobility when eluting with MeOH:Et\textsubscript{3}O, but simply switching the solvent to THF causes rapid elution. This was the key to developing a generalized ‘catch-and-release’ purification platform. A crude reaction is first loaded onto a silica gel plug and washed with 1.5% MeOH in Et\textsubscript{3}O to remove any excess reagents, catalysts or other impurities. Then, by simply switching the solvent to THF, the purified MIDA boronate is rapidly released. This methodology was readily converted into a general automated purification module.

This catch-and-release purification module was then combined with a deprotection module and a cross-coupling module to create a machine capable of carrying out each step of ICC in a fully automated fashion\textsuperscript{199}. This synthesis machine (FIG. 9b) proved capable of making natural products from every major biosynthetic pathway (crocacin C, β-parinaric acid, all-trans-retinal and rathanine) and many natural product derivatives. In addition, materials components (oligophenylene and oligothiophene), pharmaceuticals (PDE472 and BRAF kinase inhibitors), and biological probes (BTP2) were also made in the same fully automated fashion. In each case, all the functional groups, oxidation states and stereochemical information were pre-installed into the corresponding building blocks and then faithfully translated to the products via automated stereospecific couplings.

Another advantage of building block-based synthesis is the ability to rapidly prepare many different structural derivatives of a targeted compound. For the natural product rathanine, the automated synthesizer was capable of combining four sets of variant building blocks in all possible combinations to make 19 unique structural derivatives of the parent natural product (FIG. 9c). All 20 of these syntheses were completed without any customized optimization of the conditions for deprotection or coupling.

It is not immediately obvious that the same building block-based approach can be used to create complex polycyclic scaffolds consisting of an intricate network of Csp\textsuperscript{3}-linkages. However, by integrating the abovementioned biomimetic ‘linear-to-cyclized’ strategy (FIG. 9d), even Csp\textsuperscript{3}-rich cyclic and polycyclic natural products can be accessed using automated synthesis. For the macrocyclic natural product citrofuran, the fully automated assembly of building blocks into a linear precursor set the stage for an atropdiastereoselective Mitsunobu cyclization. In the case of oblongolide, the stereochemical information encoded in the building blocks was faithfully translated through the automated assembly of the linear precursor and then used to direct the subsequent diastereoselective polycyclization. A steroid-like core was made through an automatically assembled linear precursor followed by a catalyst-promoted enantioselective and diastereoselective cation-π cyclization. The same first two building blocks were also used to achieve the automated synthesis of the linear precursor for the pentacyclic secodaphnane natural product core. This strategy of combining the automated assembly of prefabricated molecular building blocks with biomimetic cyclization reactions has substantial potential to remove the synthetic bottleneck to accessing many other complex, biologically relevant natural products. Thus, although many important challenges remain, the scope of the now fully automated MIDA boronate-based ICC is already substantial and rapidly expanding.

**Summary and prospectus**

Over the past several centuries, the strategy of the iterative assembly of building blocks has repeatedly accelerated the discovery of new functions on many scales. The recent development of automated synthesis platforms for oligopeptides and oligonucleotides, and increasingly for oligosaccharides, removed the synthetic barrier and led to countless discoveries and applications of these classes of chemical matter. Small molecules are different, and the development of a highly general building block synthesis for this type of chemical matter will require solving a unique set of challenges. That said, increasing evidence suggests that this is a solvable problem.

Achieving this goal will require very efficient and versatile ways of both making and coupling a wide range of building blocks that correspond to some of the most common substructural motifs found in small molecules. For specific classes of small molecules, customized iterative strategies have already demonstrated some of this potential and have led to important discoveries. A more general platform for small-molecule synthesis now represents a highly attractive and accessible target. As an important step in this direction, ICC with MIDA boronates has already enabled the synthesis of many different types of small molecules in a fully automated fashion.

Continued progress towards this goal will depend on the development of advanced chemical methodologies. The past several decades have seen tremendous progress in the expansion of cross-coupling chemistry,
even including stereocontrolled Cp′ coupling methods. Another important opportunity involves the integration of customized iterative approaches into more generalized synthesis platforms, as some of these customized approaches represent especially efficient routes to specific areas of chemical space. These advances will enable generalized synthesis strategies to make an increasingly broad range of different small molecules, and the resulting discoveries of new molecular functions will inspire further efforts to improve the versatility of generalized synthesis.

It is worth noting that customized synthesis retains many practical advantages in the scale-up of routes to particular target compounds, where a premium is placed on step-count, atom economy and overall efficiency. Thus, removing the synthesis bottleneck on the discovery scale will create many more opportunities for chemists to find the best ways of making exceptionally functional molecules practically accessible at scale.

Given the extraordinary untapped potential that small molecules have in terms of helping to solve some of the most important problems facing society, it is exciting to consider the prospect of generalized and automated synthesis platforms bringing the power of synthesis to non-specialists. There are many great ideas out there just waiting to be harnessed.