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Toward Generalization of Iterative Small Molecule Synthesis

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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 customized approach currently used to synthesize this class of chemical matter. In contrast, the “building block approach”, i.e., generalized iterative assembly of interchangeable parts, has now proven to be a highly efficient and flexible way to construct things ranging all the way from skyscrapers to 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 improve access to specific classes of small molecules. There has also been substantial recent progress toward 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.

Introduction

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 colorants, lotions, flavorants, and perfumes. In fact, there is probably not a household on the planet that is not positively impacted by this class of chemical matter on a daily basis. Small molecules also possess substantial untapped potential to perform many frontier functions,[1] including modulating protein-protein interactions,[2] allosterically modifying protein function,[3] acting as prostheses on the molecular scale,[4,5] serving as next-generation biological probes,[6–9] enabling miniaturized diagnostics,[10] transducing energy,[11–16] emitting light,[17] initiating self-healing,[18] acting as molecular magnets,[19] enabling next generation computing,[20] and superconducting.[21–22] However, largely due to limitations in synthesis, much of this functional potential remains largely untapped. Eliminating this synthesis bottleneck thus

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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 also a laborious bottleneck for the discovery and optimization of new function, which depends 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, a widespread innovation is the development of a more generalized strategy involving the iterative assembly of interchangeable building blocks. Early examples can be found in Samuel Bentham's pioneering use of interchangeable parts to facilitate the rapid repair of wooden pulley blocks[23] and Honore Blanc's[24] and Eli Whitney's[25] 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.[26] The building block approach is now recognized in a remarkably wide range of different areas, including architecture,[27] computers,[28] space stations,[29] robotics,[30] college curricula,[31] music,[32] smart technology apps,[28] and artificial intelligence algorithms.[33] The advantages of building block-based construction on efficiency, flexibility, and scalability are well-documented and widely appreciated.[34] Perhaps even more exciting is the capacity of this approach to inspire and enable innovation. This is evidenced in the explosion of applications for 3D printing[35–38] and the joyful creativity unleashed in a child when 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[39] and oligonucleotides[40]. The corresponding impact has been transformative. To highlight just a few examples, automatically synthesized oligonucleotide probes corresponding to every gene in the human genome printed on a glass slide helped usher in the era of genomics.[41–42] Countless peptide- and oligonucleotide-based drug candidates were rapidly tested and optimized yielding entirely new classes of therapeutics.[43–44] Total synthesis of genes, proteins, and even complete genomes became possible, launching the field of synthetic biology.[45–47] Substantial recent progress in the iterative synthesis of oligosaccharides has also led to important impacts in vaccine development.[48–49]

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 substrate-general purification conditions. Encouragingly, many different iterative building block-based synthesis approaches have already increased access to

particular molecules and regions of chemical space. Heading towards an even more general platform, iteration of metal-mediated cross-coupling reactions has provided unprecedented access to a diverse range of small molecules and even demonstrated the possibility of automated synthesis. Many challenges remain, but as progress in this direction enables access to previously untapped small molecule functions, the impetus for finding solutions will continue to grow.

Many small molecules are inherently modular

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 molecules 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 of inspiration for more than half of all human therapeutics,[50,51] are derived from just a few major biosynthetic pathways that each involve the iterative assembly of a small number of discrete molecular building blocks (Figure 1a). 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 natural product molecular architectures can usually be traced back to these same modular pathways. Although many natural product biosyntheses also involve rearrangements, oxidations, and cyclizations, there is still evidence that this modularity shows up in the final products. A recent analysis revealed that more than 75% of all the polyene motifs found in natural products can be prepared with just 12 building blocks and one coupling reaction (Figure 1b).[52] Increasing evidence further suggests that natural product chemical space is bounded,[53] enabling consideration of generalized approaches for studying the complete natural productome.[54] An expanded effort is now underway to find the minimal number of building blocks required to access most natural product chemical space.[55]

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 1086 FDA approved small molecule drugs showed many recurring heterocyclic building blocks (Figure 1c), including piperidine (72 drugs), pyridine (62 drugs), piperazine (59 drugs), cephem (41 drugs), pyrrolidine (37 drugs), and thiazole (30 drugs).[56] Sixteen additional heterocycles appear in at least 10 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. Materials 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 (Figure 1d). 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.

Many customized iterative synthesis methods have already been developed

Iterative synthesis of small molecules from building blocks has already streamlined 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 for different iterative synthesis methods are the type of bond used to connect 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 Figure 2 (natural products) and Figure 3 (unnatural molecules), with building blocks highlighted in different colors.

These examples reflect some of the most efficient routes for accessing particular regions of chemical space, and in some cases they have led to impactful discoveries. Still, 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 with an iterative method. Although these customized platforms each use different kinds 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 structures.

Seminal work by Masume and Sharpless established that an iterative four step cycle could be applied to access all eight L-hexoses (Figure 2a for illustrative examples). The cycle begins with asymmetric epoxidation of an allylic alcohol. In basic medium, the product rearranges to the more thermodynamically favorable 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-acetoxysulfide. Subsequent hydrolysis through reductive (DIBAL) or basic (K_2CO_3/MeOH) conditions allows selective retention or inversion of the C2 stereogenic center in formation of the corresponding aldehydes. Finally, Wittig olefination and aldehyde reduction produces allylic alcohols for further iteration. Changing the conditions of the two stereocontrolling steps, Sharpless asymmetric epoxidation and gem-acetoxysulfide reduction, allows for 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,[57] and many iterative methods have likewise been developed to access various different classes of small molecules.

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.[58–60] Auxiliary cleavage and regeneration of aldehyde intermediates allows both of these processes to be iterated. More recently, Crimmins developed a variant of the Evans oxazolidinone methodology[61] that employs N-acylthiazolidinethiones as chiral auxiliaries to

facilitate a more readily iterated aldol approach (Figure 2b).[62–63] After a diastereoselective aldol reaction, cleavage of the chiral 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 if the additive is TiC4or (−)-sparteine. In his synthesis of 6-deoxyerythronolide B, Crimmins iterated this sequence five times, setting 10 of the 11 stereocenters using a single type of reaction.[64]

A related polyketide motif, the 1,3-polyol unit, can also be prepared using several different types of iterative chemistry. Brown developed an iterative allylboration reaction using chiral boranes to carry out highly enantioselective reactions with aldehydes.[65–67] The olefin motif of the resulting homoallylic alcohols can be oxidatively cleaved to reveal a new aldehyde for further allylation. This approach was employed to generate the 1,3-polyol fragment in the synthesis of passifloricin A (Figure 2c).[68]

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 nucleophile.[69] Application of this iterative strategy in a two-directional manner expedited construction of the key polyol portion of (+)-roxaticin (Figure 2d).[70] This methodology has proven 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 products.[71–73] This efficiency has further enabled practical synthesis and testing of bryostatin derivatives, shedding new light on the relationship between potency and biological activity.[74]

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 provides access to all possible stereochemical variants,[75–76] and Theodorakis has applied this methodology in the total synthesis of (−)-borrelidin (figure 2e).[77–78]

Minnaard and Feringa have recently developed an alternative iterative three step protocol to access *syn* deoxypropionate motifs based on catalytic asymmetric conjugate additions (Figure 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 center. 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 stereocenters to be installed with excellent levels of stereoselectivity, enabling the first total synthesis of phthioceranic acid[79] as well as the first total synthesis of sulfolipid-1.[80]

Breit has also developed an iterative zinc-catalyzed sp^3-sp^3 coupling method for the synthesis of deoxypropionates (Figure 2g).[81] Treatment of an alkyl Grignard with $ZnCl_2$ generates a triorganozincate species ($R_3ZnMgCl$), which displaces a secondary triflate to generate a new carbon-carbon 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 alkyl lithium 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 greater than 99% diastereomeric excess. In addition to the aforementioned work by Myers, Minnaard, and Breit, the modular nature of polydeoxypropionates has also inspired the development of several other iterative synthesis strategies.[82–83]

Aggarwal's versatile approach for iterative synthesis of various stereochemically complex Csp^3-rich motifs is demonstrated with his route to (+)-kalkitoxin (Figure 2h).[84] This approach leverages the stereospecificity of the 1,2-metallate rearrangement of boronate complexes[85] to install both stereochemistry and functionality *via* 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 as well as three methyl-bearing stereocenters derived from the requisite enantiomerically-pure lithiated benzoates.[86] Amination followed by amide formation furnished the core of (+)-kalkitoxin in an overall 52% yield. This same approach has been used to synthesize baulamycin A,[87] tatanan A,[88] fluorohexestrol,[89] and C30 botryococcene[90] and many other targets.[91] More broadly, the versatility of this homologation method, which tolerates a diversity of 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 shapes.[86]

Polyisoprenoids are attractive targets for iterative synthesis due to the numerous 1,5-related trisubstituted olefins spanning their structures. Negishi has developed an iterative and convergent synthesis for these motifs and applied it to the synthesis of coenzyme Q_{10} (Figure 2i). A one pot iterative cycle begins with formation of a primary alkylzinc iodide followed by a chemoselective cross-coupling with a diiodo building block. Two more iterations and a further coupling with a diene containing building block installs five of the trisubstituted olefins of coenzyme Q10. To enable convergent synthesis, the TMS-protected alkyne also serves as an attachment. TMS deprotection subsequent carbometalation-iodonation generates a new vinyl iodide which undergoes a strategic and convergent cross-coupling with an earlier homologue. A final round of deprotection, hydrozirconation-iodination, and cross-coupling gave coenzyme Q10 in only 11 steps.

Long polyene chains are another modular structure found in natural products. However, these motifs are often sensitive to many common reagents (e.g. protic and Lewis acids) and conditions (e.g. light and oxygen), rendering their synthesis challenging. In a landmark synthesis of the complex polyene macrolide amphotericin B, Nicolaou employed an iterative Horner-Wadsworth-Emmons strategy to complete the all-*trans*-polyene motif. Starting from an aldehyde, the first triene unit was installed using a diene-containing phosphonate (Figure 2j).[92] 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 K_2CO_3/18-crown-6 formed the desired cyclic heptaene, completing the carbocyclic core of amphotericin B.[93]

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 be both practical and expeditious. For example, Uenishi and co-workers developed an iterative protocol for the stereoselective synthesis of linked tetrahydrofuran (THF) rings (Figure 2k).[94] The iterative sequence commences with formation of a homoallylic alcohol through Grignard addition to an aldehyde or epoxide, followed by cross-metathesis with a stereodefined 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-threo-trans* and *trans-threo-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 inherent modularity within structurally complex polycyclic ether natural products to enabling their iterative construction (Figure 2l).[95] 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-catalyzed, 6-endo cyclization. A five-step sequence then generated a new triflate for further iteration. Six repetitions of this protocol led to efficient construction of the ABCDEF-ring fragments of yessotoxin and adriatoxin, with the stereochemistry of the cyclic ethers dialed in through selection of the appropriate oxirane building blocks. This iterative oxiranyl anion strategy has further been employed for the synthesis of hemibrevetoxin B,[96] gambierol,[97] and even gymnocin-A with 14 contiguous fused rings.[98] Other iterative synthesis strategies have also been developed for polycyclic eithers, including iterative ring closing metathesis/hydroboration, iterative reductive cyclizations, and iterative oxonium ylide formation/[2,3]-shift processes.[99]

Kishi's highly impactful synthesis of halichondrin B utilized iterative Nozaki-Hiyama-Kishi (NHK) reactions interspaced by tailoring steps to build cyclic ether moieties in a recursive fashion (Figure 2m). This strategy allowed highly complex building blocks to be efficiently assembled in an iterative manner.[88] Other family members of the halichondrin family could also be accessed by incorporating variant building blocks into a similar synthetic sequence.[100] This efficient and modular synthesis enabled Kishi and coworkers to discover that half of halichondrin B, the portion that contains the macrocycle, is nearly equipotent as an anticancer agent to the exceptionally potent natural product. A close variant of this iterative synthesis was successfully scaled up by chemists at Eisai to produce enough of this portion of the molecule, dubbed Eribulin, to enable its clinical utlization. Significant benefits were observed for patients with metastatic breast cancer and liposarcoma, leading to FDA approval of Eribulin for treatment of these cancers in 2010 and 2016, respectively.[101–102]

Beyond natural products, iterative assembly methods have also enabled the synthesis of many other types of inherently oligomeric materials (Figure 3). For instance, 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 allenoate (Figure 3a).[103] 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 the best available organic p-type semiconductor, but larger members could be even more useful.[104] Excellent syntheses of octacene and nonacene derivatives have been carried out by Echavarren,[105–106] and Bettinger and coworkers have developed a building block method using iterative Diels Alder reactions (Figure 3b).[107] Combination of 5,6,7,8-tetramethylenebicyclo[2.2.2]oct-2-ene and an aryne dienophile generated by treatment of 1,2-dibromobenzene with *n*-BuLi led to formation of a cycloadduct with a terminating diene moiety. This was treated with an aryne generated from 1,2,4,5-tetrabromobenzene, resulting in a product terminating in another dibromide moiety. One more iteration of aryne formation and cycloaddition gave a stable precursor to octacene. After a sequence of aromatization and oxidation reactions, exposure to low wavelength UV-light generated octacene for characterization and some initial studies.

While 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 using Sonogashira coupling.[108–109] Moore's work highlights a critical advance enabling 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. Here, a bifunctional building block can be selectively activated in two different ways; a dialkyltriazene can be converted to an iodide, or a TMS protecting group can be removed to reveal a reactive terminal alkyne (Figure 3c). These two differently activated building blocks can then be assembled *via* Sonagashira coupling to form an advanced intermediate containing a dialkyltriazene and a protected alkyne at opposite termini. Repeating this process of using advanced intermediates as building blocks allows for exponential molecule growth. In such a manner, it is possible to generate repeating tetramers, octamers, and longer oligomers with control of the sequence of building blocks. Additionally, building blocks with other functional groups can also be incorporated to prepare diverse oligomeric products.[110]

Moore has also developed a convergent approach to iterative synthesis for the assembly of large dendrimers (Figure 3d).[111–113] Compared to his strategy for making oligomers (Figure 3c), this dendrimer method is different in two fundamental respects. Here, the building blocks can only be activated in one way, by unmasking a TMS group to reveal a reactive terminal alkyne for Sonogashira coupling. However, exponential molecule growth can still be achieved *via* a double Sonogashira coupling onto a trifunctional monomer containing two bromines. Four iterations of TMS deprotection and double Sonogashira coupling allowed for rapid construction of a monodedron containing 31 building blocks.[111] This double Sonogashira approach is capable of quickly making large molecules, but it also lacks versatility needed to make unsymmetrical targets. Such a limitation is not problematic for dendrimer synthesis, but it does illustrate that convergent iterative synthesis can be most versatile when it has two separate masking and deprotection strategies for orthogonal functional groups (Figure 3c).

Iterative synthesis methods have also been developed for molecules of defined threedimensional 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 rearomatization to form a new anthracene unit for further iteration (Figure 3e). This cycle was then repeated to form longer iptycenes in a modular fashion.[114]

Many methods have recently been developed which allow near-identical boronic esters to be chemoselectively functionalized, and Crudden has harnessed this selectivity to facilitate a fundamentally different approach to iterative synthesis (Figure 3f). Instead of generating new positions for appending building blocks during each iteration cycle, Crudden has preinstalled all of the attachment points in advance. In a one-pot procedure, a Csp^2-Csp^2 coupling of an aryl boronic ester was followed by group selective cross coupling of a Csp^3 primary boronic ester. Simple filtration through silica gel enabled a Csp^3 cross coupling of the remaining secondary boronic acid in the presence of Ag_2O, creating a defined polyarylated structure.[115]

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 reaction (Figure 3g). The product rotaxane has a terminus containing a TIPS-protected alkyne. Cleavage of the silyl group and iteration of this reaction allows for the incorporation of different macrocyclic moieties.[116]

Each of these examples represent important advances toward 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 (Figure 3c-d) that allow for even more efficient molecule growth. There is tradeoff; the more convergent an iterative synthesis method, the more limited its scope of targets. In contrast, divergent approaches to a iterative synthesis have the greatest potential to accelerate discovery of new function. It is evident from several divergent iterative synthesis methods[59, 76, 81, 86, 117] that the greater the potential for structural variation in the building blocks, the greater the scope of possible products. Given the arguments that most small molecules could be made from a defined set of molecular building blocks, is it possible to develop a suitably general iterative synthesis method?

Advances towards a general platform for iterative small molecule synthesis

A 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 whilst being very 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 employ non-toxic and shelf-stable building blocks, are highly efficient and stereospecific, and 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 couplings has placed them among the most widely employed reactions in both academic and industrial synthesis groups. Most recently, this scope has been extended to include a wide range of Csp^3 and Xsp^3 coupling partners,[118–120] including even stereospecific Csp^3 cross-couplings of stereochemically defined chiral non-racemic building blocks, originally pioneered by Crudden.[121–131] These new methods, combined with anticipated major additional advances in the area of sp^3 cross-coupling over the next few decades, suggest that iterative cross-coupling 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 just 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 required the development of methodology for reversibly attenuating the reactivity of such building blocks toward metal-mediated coupling (Figure 4a).[108–109]

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 (Figure 4b). Under normal cross-coupling conditions, these arylsilanes are “switched off” and unreactive towards transmetalation, but upon deprotection of a strategically-positioned neighboring alcohol, 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 oligoarenylsilanes.[132]

Suginome reported an alternative method for switching off organometallic coupling partners (Figure 4c). Complexing boronic acids with the 1,8-diaminonaphthalene (DAN) group decreases the Lewis acidity of the p orbital of the sp^2-hybridized boron atom *via* electron donation from neighboring lone pairs on planar nitrogen atoms. The resulting BDAN compounds are stable to anhydrous as well as aqueous biphasic cross-coupling conditions, but exposure to strong aqueous HCl or H_2SO_4 removes the DAN group and releases the corresponding boronic acid. This iterative building block-based method has been applied in the synthesis of oligoarenes[133] and oligo(phenylenevinylene)s.[134]

Parallel 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 sp^2 to sp^3 (Figure 4d).[135] MIDA boronates[136] represent a very promising platform for generalized building block-based molecule synthesis. It is of course possible that even better strategies are yet to be discovered for reversibly attenuating the reactivity of organometallic building blocks. Such enabling advances would be a very exciting opportunity for generalized synthesis of small molecules and the discovery of new

molecular functions. However, due the collective efforts of many different research groups, the MIDA boronate platform currently represents the most well-developed strategy for iteration of metal-mediated couplings.

MIDA boronates have many advantageous physical and chemical features. They are readily purified by silica gel chromatography and/or recrystalization and typically are indefinitely stable on the benchtop as free-flowing crystalline solids.[135] Moreover, many alkyl-, vinyl-, and arylboronic acids can be directly converted to their MIDA boronate counterparts in quantitative yield under mild conditions. To drive the MIDA complexation to completion, water can be removed simply *via* toluene azeotrope with a Dean-Stark trap[136] or by addition of a drying agent like magnesium sulfate. MIDA boronates are inert to anhydrous cross-coupling reactions, but they can be quickly deprotected under mild aqueous basic conditions. Deprotection can proceed through two different mechanisms: (1) under strong aqueous base, rate-limiting attack of hydroxide on the carbonyl carbon, or (2) under weakly basic or neutral aqueous conditions, slower rate-limiting attack of water on the boron-nitrogen bond.[137] This mechanistic divergence is consistent with extensive reaction kinetics, kinetic isotope effects, ^{18}O labelling, and computational data. In-situ slow release of MIDA boronates has been advantageous for many reactions including couplings of unstable heteroarylboronates,[138,139] polymerization reactions,[140–141] asymmetric methodologies,[142] the synthesis of organic photovoltaics,[143] and a one-pot homologation of boronic acids.[144]

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 (Figure 5). For example, many standard oxidations (Figure 5a), reductions (Figure 5b), and protecting group manipulations (Figure 5c) are well-tolerated.[145–151] Numerous other common synthetic transformations leave MIDA boronates intact, including aldol reactions,[145] carbonyl olefination reactions,[145] Mitsunobu reactions,[145] electrophilic substitution reactions,[149, 152] hydroborations and –stannylations,[151] Diels Alder cycloadditions (Figure 5j),[151, 153] and cyclopropanations.[147] A variety of transition metal-catalyzed reactions are also well-tolerated (Figure 5g), including Heck reactions,[147, 154] Grubbs metathesis,[147] Sonagashira couplings,[151] and Suzuki cross-couplings.[135]

MIDA boronates are not without limitations in terms of scope and application. A large number of Suzuki-Miyaura cross coupling reactions require the use of aqueous base which cause hydrolsis of othe MIDA boronate, and Buchwald-Hartwig aminations can involve the use of strong base which is incompatible with the acidic protons on the backbone of the MIDA ligand. The former point is a significant limitation as the majority of recent important advances in Csp^3 coupling involve aquoues basic reaction conditions thus preventing their use in MIDA-boronate based ICC.

A few of the many recent advances in this area are highlighted here. By harnessesing the ability of MIDA to rehybridize boron from sp^2 to sp^3, Zard has used vinyl MIDA boronates as acceptors for xanthate-derived radicals.[155] The resulting α-boryl radicals are sufficiently destabilized to ensure that the reaction is irreversible. Making use of similar vinyl MIDA boronate substrates, Wang has developed a new oxidative difunctionalization reaction.[146]

After treating with SIBX along with either a fluorinating or trifluoromethylating 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 kinetically amphoteric molecules containing MIDA boronates and electrophilic ketones/aldehydes, Yudin has developed syntheses of borylated pyridazines/pyrroles,[156] imidazoles,[148] thiazoles,[149] imidazo[1,2-a]pyridines,[157] and many other motifs.[158] Watson has also developed a synthesis of 2-borylated indoles/benzofurans involving a palladium catalyzed cascade reaction with ethynyl BMIDA and 2-iodoanilines.[159] Similarly, borylated indolenes and benzofurans have been synthesized through gold-catalyzed intramolecular cyclizations onto alkynes.[160] 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 adehydes (Figure 5k), which without MIDA complexation would rearrange to the O-boryl enolates. Yudin has pioneered the application of this unique class of molecules by exploiting the amphoteric nature of the boron centre and the aldehyde.[161] This has served as a platform for the synthesis of a variety of heterocycles and functionalized boronic esters and even the formation of complex tertiary organoboronates through Tsuji-Trost allylations.[162]

Beyond the synthesis of simple achiral and racemic building blocks, chiral non-racemic MIDA ligand varients (Figure 5l) can direct diastereoselective epoxidation of vinyl boronates, to generate stereoisomerically pure oxyranyl boronates.[163] Futhermore, 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 acids.[164]

Iterative cross-coupling with MIDA boronates

Leveraging these many advantageous features, iterative cross-coupling (ICC) of MIDA boronates has now been applied by many research groups to synthesize a wide range of structurally-diverse small molecules (Figure 6).[135, 145, 163, 165–178] This 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 macro- and polycyclic frameworks for which inherent modularity is less obvious. Moreover, many of these syntheses took advantage of common off-the-shelf MIDA boronate building blocks many of which are now commercially available. Collectively, this rapidly growing collection of successful applications of ICC to make a wide range of complex small molecules suggests 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 Figure 7. Ratanhine was the first natural product to be synthesized by ICC (Figure 7a).[135] 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 myxalamide A (Figure 6b).[171] A key challenge in this synthesis was construction of the central *trans-trans-cis-trans* tetraene, as such motifs are difficult to install in a stereocontrolled fashion. The capacity of olefinic stereochemical 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 problem.[165–166, 179] Specifically in this case, a *cis*-bifunctional vinyl MIDA boronate building block was iteratively cross-coupled to unite the two key fragments of the polyene core of myxalamide A in a stereospecific fashion. Moreover, no protecting groups were required, as the cross-coupling reactions proceeded in the presence of two free alcohols.

This same concept of leveraging stereospecific cross-couplings to transfer pre-installed stereochemistry from pre-fabricated building blocks into products has been extended to stereogenic Csp^3 centers as well. For the glucagon receptor inhibitor (Figure 7c), the presence of several Csp^3 carbons offered strategic disconnection points. The first two building blocks were assembled by a Csp^3 coupling between an aryl iodide and a primary alkylzinc reagent.[163] In the second coupling reaction, an enantiomerically-enriched benzylic boronate was then subjected to Crudden's stereoretentive Csp^3 coupling to yield the targeted chiral pharmaceutical candidate in a very simple manner.[121]

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 these conditions can be incompatible with MIDA boronates. Hamann and coworkers have pioneered a strategy that selectively protects MIDA boronates *in situ* through enolization with LiHMDS at low temperatures.[180] This more robust Li-MIDA enolate enabled the authors to perform an efficient one-pot ICC synthesis of the histamine H3 agonist through iterative C-N then C-C coupling reactions (Figure 7d). This Li-MIDA enolate strategy may have applications beyond C-N coupling where strong base causes loss/cleavage of the MIDA protecting group.

Even some highly complex small molecules have been prepared *via* ICC. For example, the natural product peridinin is a norcarotenoid containing several complex functional groups and stereochemical elements, including a butenolide, an epoxide, and an allene motif. Because of the mild and stereospecific nature of ICC, all of these functional groups and stereochemical elements were preinstalled in the four complex building blocks and faithfully translated into the final product, yielding the first fully stereocontrolled synthesis of peridinin.[167] Each MIDA boronate intermediate, including even 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 for 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, Csp^3-rich polycyclic natural products often involves an actionable two-part strategy: assembly of building blocks into a linear precursor and then a cyclization reaction to transform this linear molecule into a complex (poly)cyclic skeleton.[181] In theory, ICC could be employed in a similar linear-to-cyclized approach. This was confirmed in the synthesis of the pentacyclic core of secodaphnane natural products (Figure 7f).[178] Two cycles of Csp^3 couplings 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.[182]

A linear-to-cyclized strategy was also employed by Vosberg to make other highly complex polycyclic natural product frameworks, including the ethyl ester of the tetracyclic natural product cryptobeilic acid D (Figure 7g). 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 tetraene was primed for an $8\pi/6\pi$ electrocylization cascade to generate a fused 4-6 ring system, which led to the completion of cryptobeilic acid D after some additional final steps (Figure 7g).[176]

This linear-to-cyclized strategy has also enabled biological studies of clinically-relevant natural products. Having served for over 50 years as the last line of defense against invasive and drug-resistant fungal infections, the polyene macrolide amphotericin B (AmB) still suffers from dose-limiting side effects. With the goal of gaining a better understanding of AmB's mechanism of toxicity, an AmB derivative lacking a single hydroxyl group was synthesized *via* ICC followed by macrocyclization (Figure 7h). This new compound, C35deOAmB, lacked the ability to form ion channels yet 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 product.[183] This discovery helped build a strong foundation for ongoing efforts to rationally optimize the therapeutic index of AmB.[184–185] 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 scale.[4–5] MIDA boronates have been employed independent of iteration on a wide range of other small molecule synthesis applications as well.[140–141, 143, 150, 180, 186–193]

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 synthesis approaches to an automated format.[194–197] While this

approach has the advantage of utilizing known manual solutions, it necessitates the automation of many different kinds of chemical reactions, each of which requires different types of reagents, conditions, optimization protocols, reaction vessels, and/or purification protocols.

A major advantage of iterative cross-coupling 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 reach highly generalized conditions, as was previously achieved for iterative peptide[198] and oligonucleotide synthesis,[199] and is now being increasingly realized for oligosaccharides.[200]

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 (Figure 8a).[178] Regardless of size, functional group content, and polarity, MIDA boronates show minimal mobility when eluting with MeOH:Et_2O, but simply switching the solvent to THF causes rapid elution. This was the key to developing a generalized “catch-and-release” purification platform (Figure 8a). A crude reaction is first loaded onto a silica gel plug and washed with 1.5% MeOH in Et_2O 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 purification was readily transformed 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 (Figure 8b).[178] This synthesis machine proved capable of making natural products from every major biosynthetic pathway (crocacin C, β-parinaric acid, all-*trans*-retinal, and ratanhine) and many natural product derivatives (Figure 8c). In additional, materials components (oligophenylene and oligothiophene), pharmaceuticals (PDE472, B-Raf kinase inhibitor), 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 ratanhine, the automated synthesizer was capable of combining four sets of variant building blocks in all possible combinations to make 20 unique structural derivatives of the parent natural product (Figure 8d). 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 a network of Csp^3-linkages. However, by integrating the aforementioned biomimetic “linear-to-cyclized” strategy, even Csp^3-rich

cyclic and polycyclic natural products can be accessed *via* automated synthesis (Figure 8e). For the macrocyclic natural product citreofuran, 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 enantio- 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 natural product secodaphnane core. This strategy of combining 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, while 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 iterative assembly of building blocks has repeatedly accelerated the discovery of new functions. The recent development of automated synthesis platforms for oligopeptides and oligonucleotides removed the synthetic barrier and led to countless discoveries and applications. Small molecules are very different from biopolymers. Given that their structures are far more diverse and complex, the development of a highly general building block synthesis of small molecules will require solving a unique set of challenges. Principally, this endeavor will require very efficient and versatile ways of both making and coupling a wide range of building blocks corresponding 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 led to important discoveries. However, a general platform for small molecule synthesis would be far more impactful. As an important step in that direction, iterative cross-coupling with MIDA boronates has already enabled the synthesis of many different kinds of small molecules in a fully automated fashion.

Continued progress towards this goal will depend on the development of new chemical methodologies. The last several decades have seen tremendous progress in the expansion of cross-coupling chemistry, including even stereocontrolled Csp^3 coupling methods. Another important avenue of investigation will be integration of customized iterative approaches into a generalized synthesis platform, as they represent especially efficient routes to specific areas of chemical space. These advances will enable generalized synthesis strategies to become capable of making a wider range of different small molecules, and resulting discoveries of new molecular functions will inspire further efforts to improve the versatility of generalized synthesis. It is worth noting that customized synthesis still 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. It is thus exciting to imagine how removing the bottleneck to discovering new molecular functions will in turn

create more opportunities for chemists to find the best ways of making those functions available to society.

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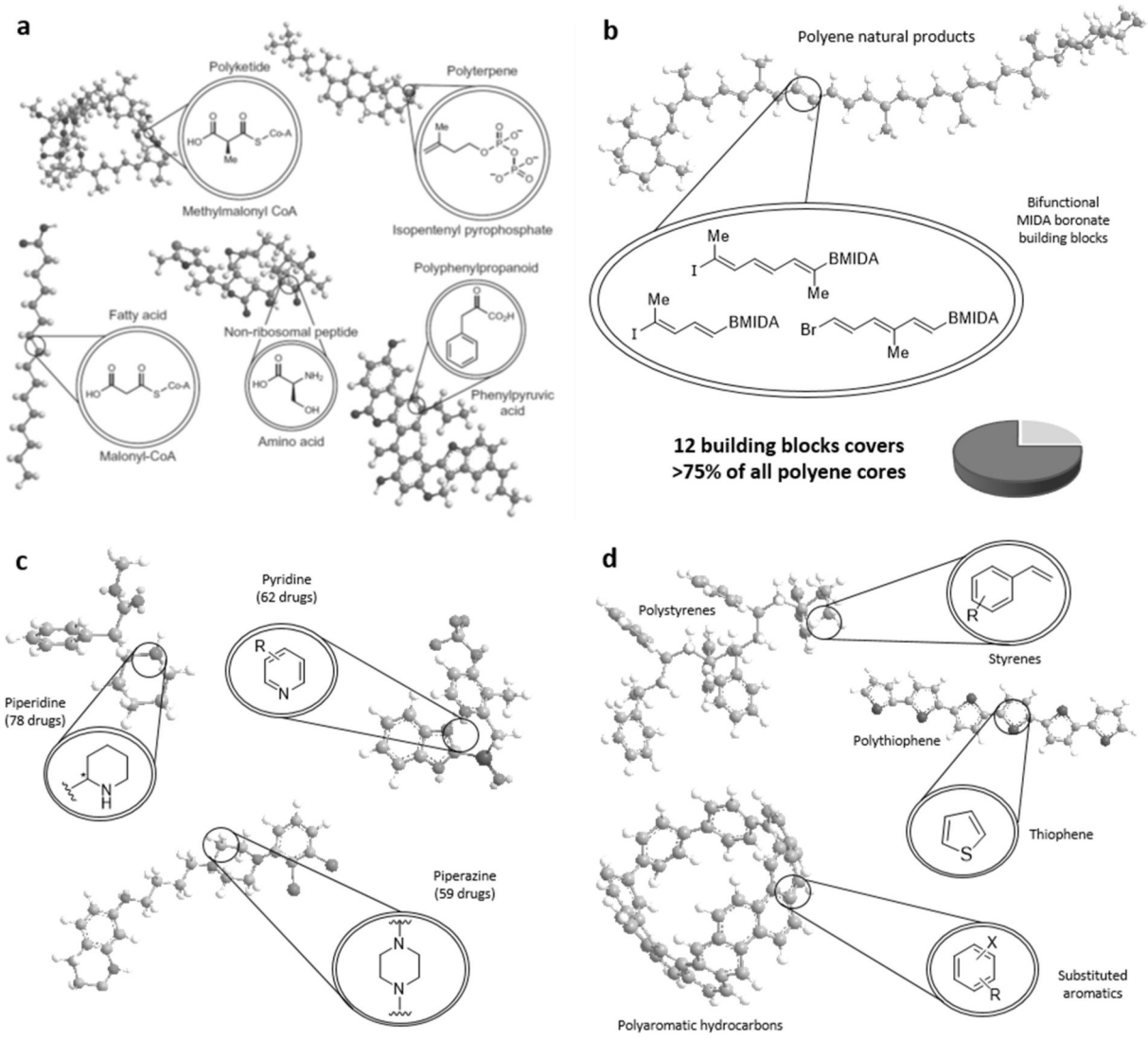
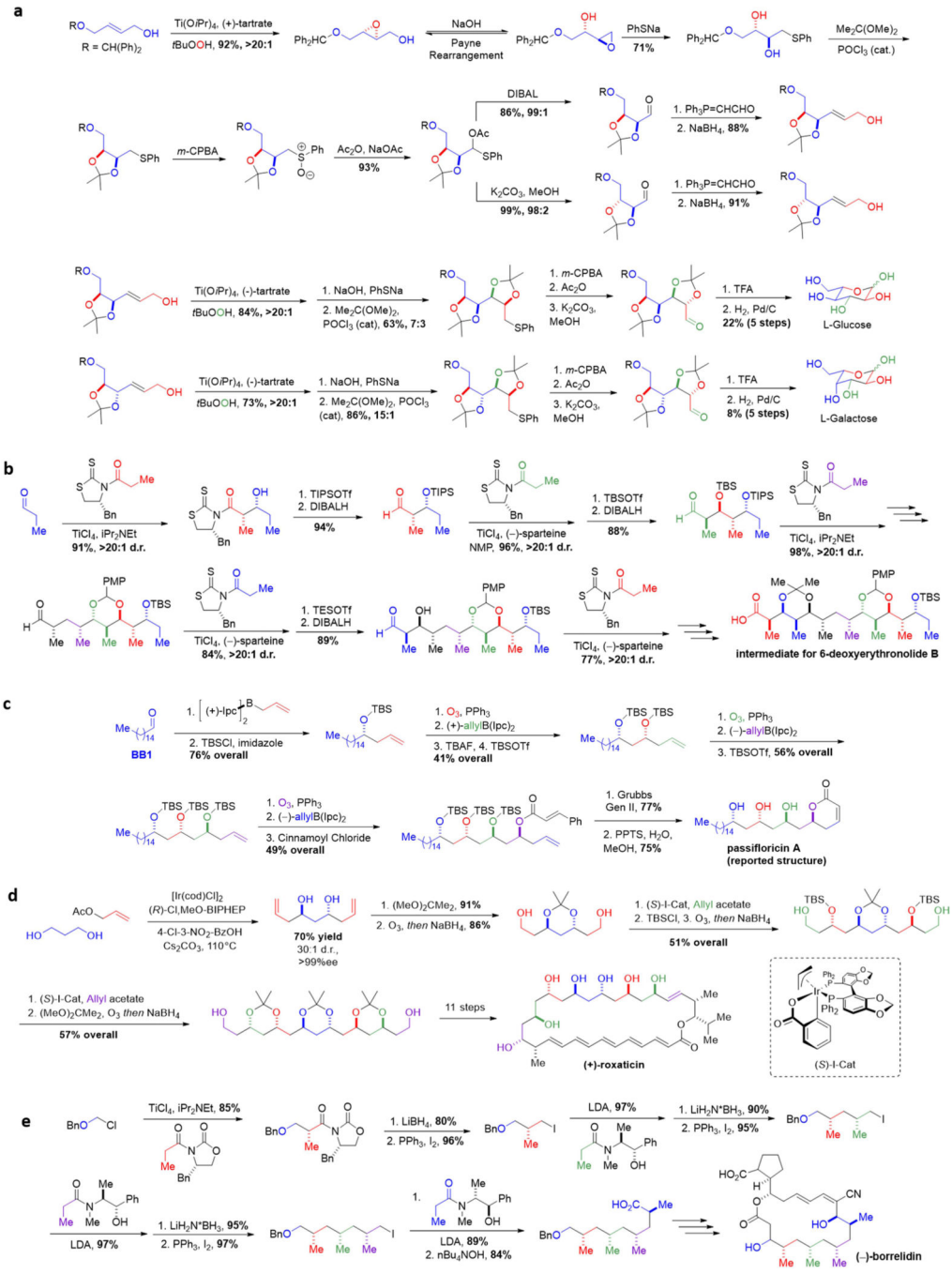
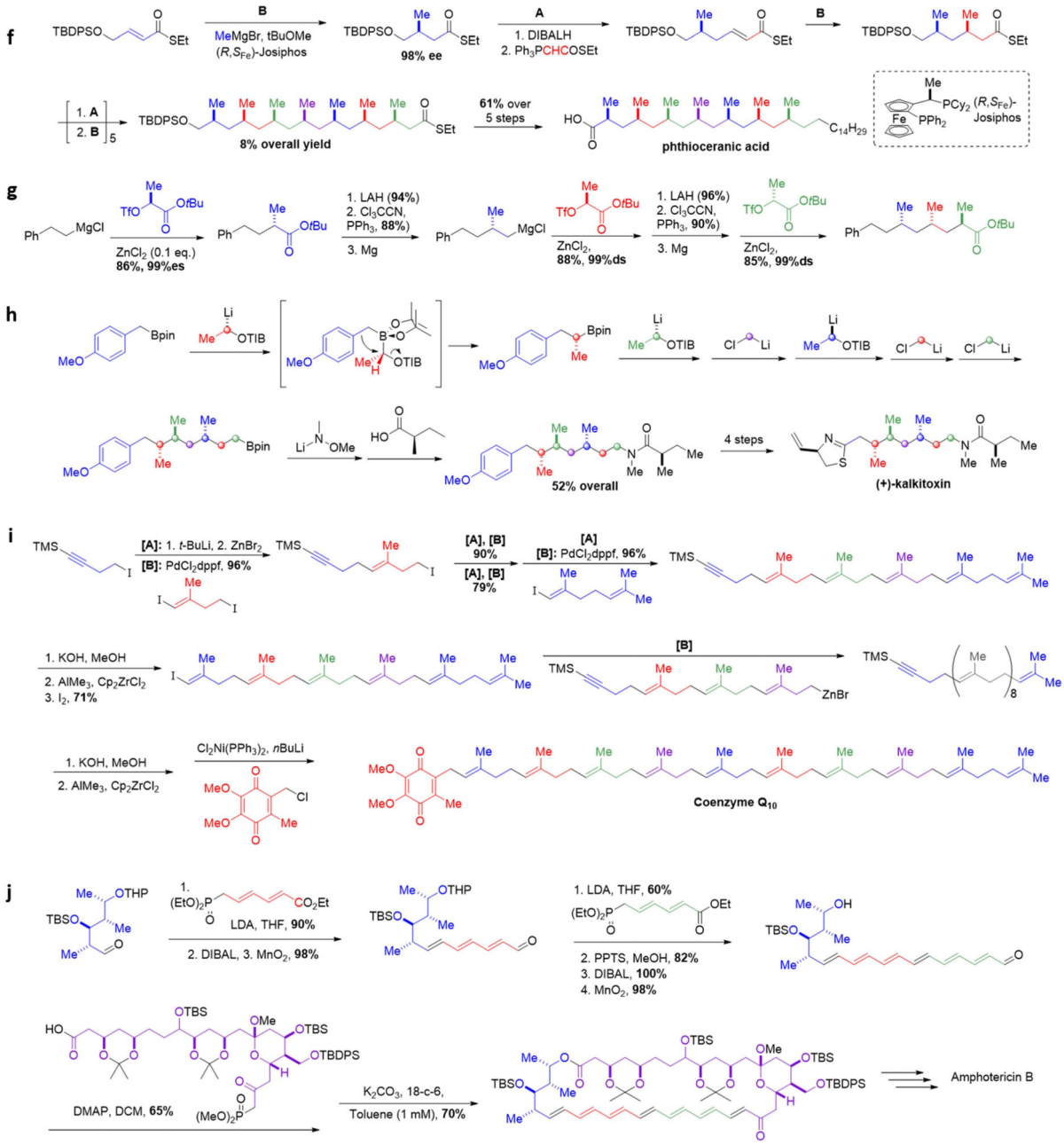


Figure 1. Modularity in small molecules

a Biosynthesis of natural products from building blocks. **b** Coverage of > 75% of polyene natural product chemical space using 12 bifunctional halo MIDA boronate building blocks. **c** Common heteroaryl motifs found in pharmaceuticals. **d** Modularity in organic materials.





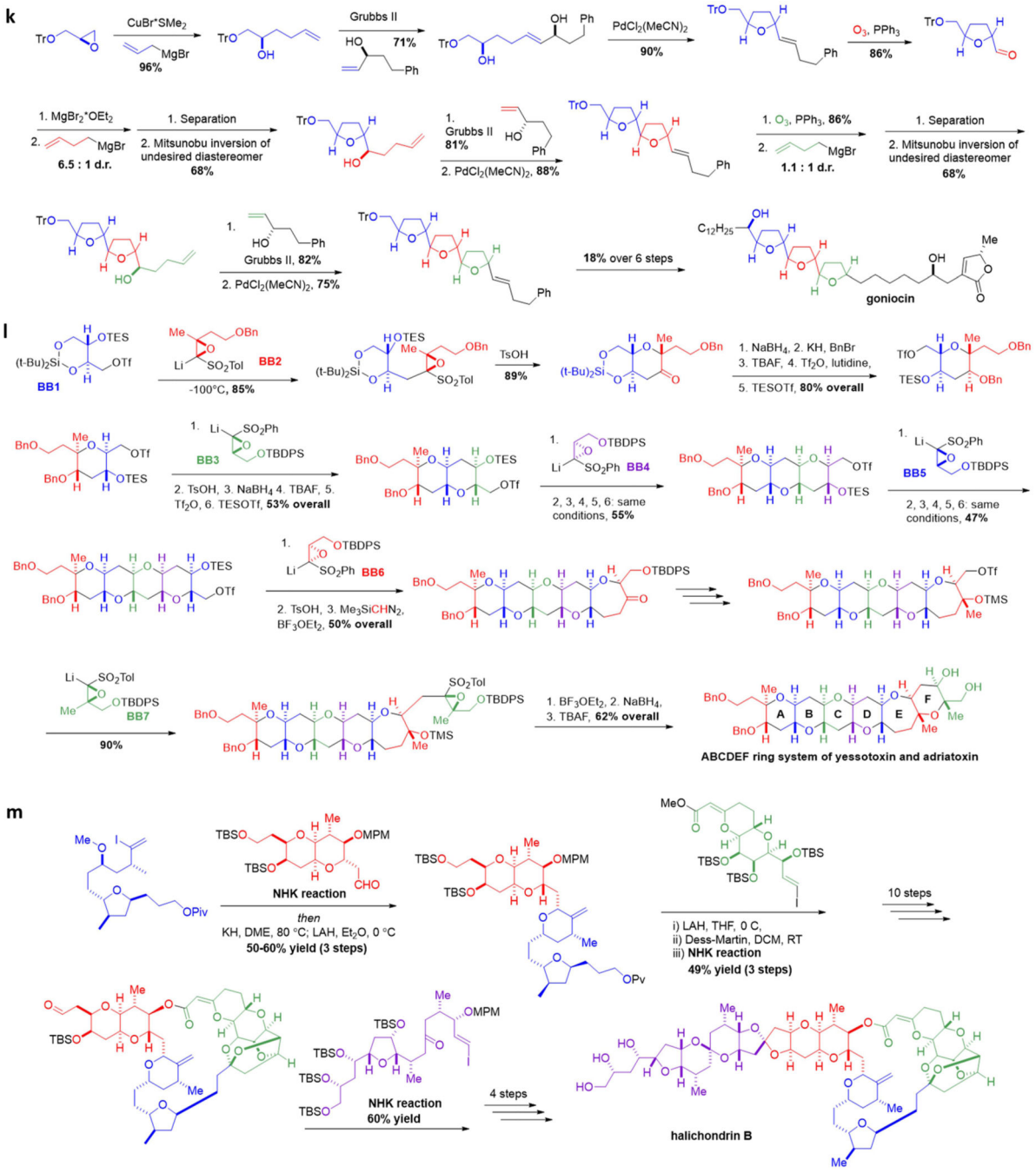


Figure 2. Customized iterative synthesis of naturally occurring small molecules

a Aldohexose synthesis via iterative Sharpless epoxidation. **b** Formal synthesis of 6-deoxyerythronolide B *via* iterative aldol reactions. **c** Passifloricin A synthesis *via* iterative allylboration. **d** |(+)-Roxaticin *via* iterative C-C bond forming transfer hydrogenation. **e (−)-**Borrelidin *via* iterative Myers' alkylation. **f** Phthioceranic acid *via* iterative conjugate addition. **g** Iterative synthesis of polydeoxypropionates via stereospecific displacement of tosylates. **h** (+)-Kalkitoxin *via* iterative homologation of boronic esters. **i** Coenzyme Q_{10} via iterative palladium-catalyzed couplings of alkylzinc reagents. **j** Amphotericin B *via* iterative

Horner-Wadsworth-Emmons olefinations. **k** Synthesis of goniocin *via* iterative THF ring formation. **l** ABCDEF ring system of yessotoxin and adriatoxin *via* iterative oxiranyl anion strategy. **m** Halichondrin B *via* iterative NHK reactions.

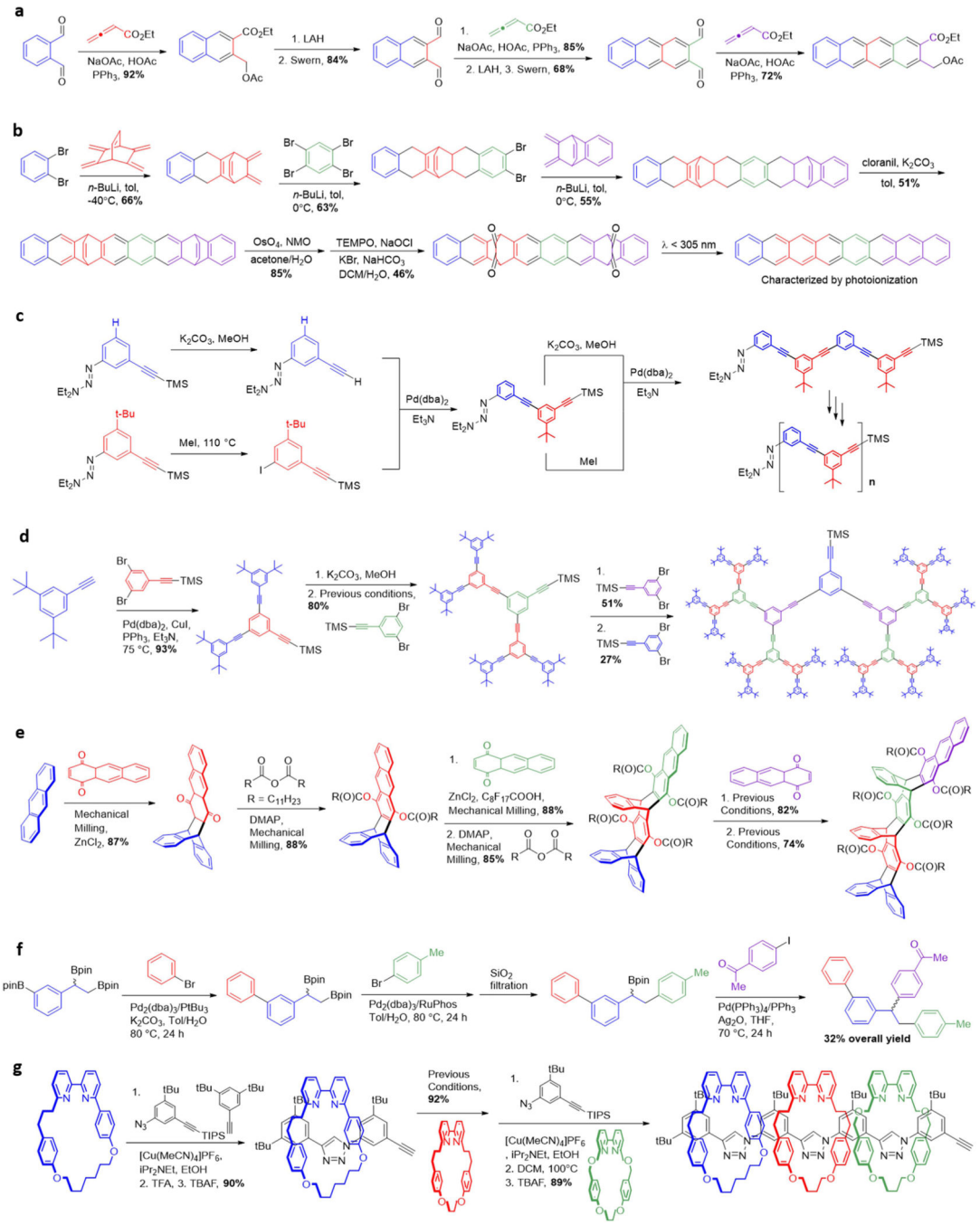


Figure 3. Customized iterative synthesis of non-natural small molecules

a Iterative arene homologation. **b** Iterative synthesis of octacene. **c** Iterative convergent synthesis of phenylacetylene oligomers. **d** Iterative convergent synthesis of hydrocarbon dendrimers. **e** Iterative synthesis of extended iptycenes. **f** Iterative arylation of multiply borylated compounds. **g** Iterative synthesis of rotaxanes.

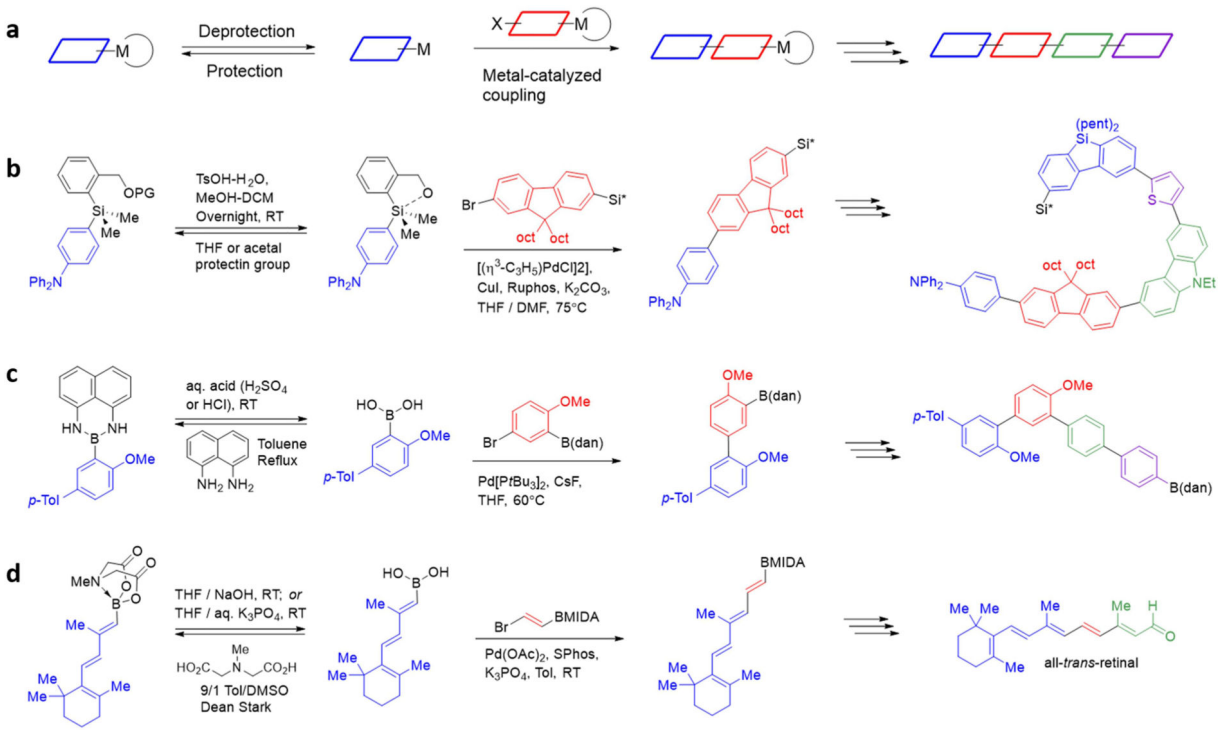
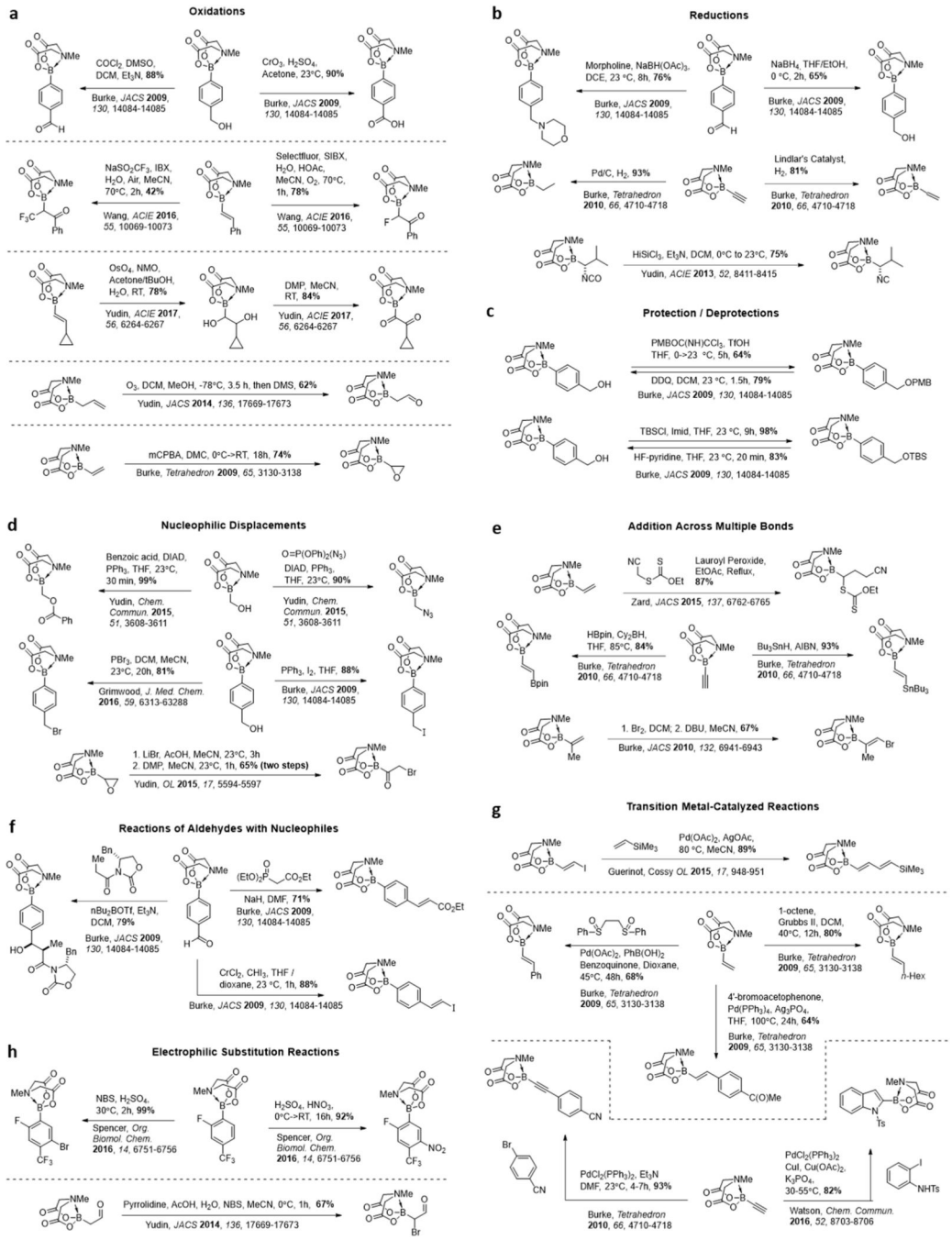


Figure 4. Approaches to Iterating Metal-Mediated Coupling Reactions

a Reversible attenuation of organometallic reactivity enables iterative coupling. **b** Iterative Hiyama couplings by reversible silane activation. **c** Iterative Suzuki couplings by reversible protection with 1,8-diaminonaphthalene (dan). **d** Iterative Suzuki couplings by reversible protection with *N*-methyliminodiacetic acid (MIDA).



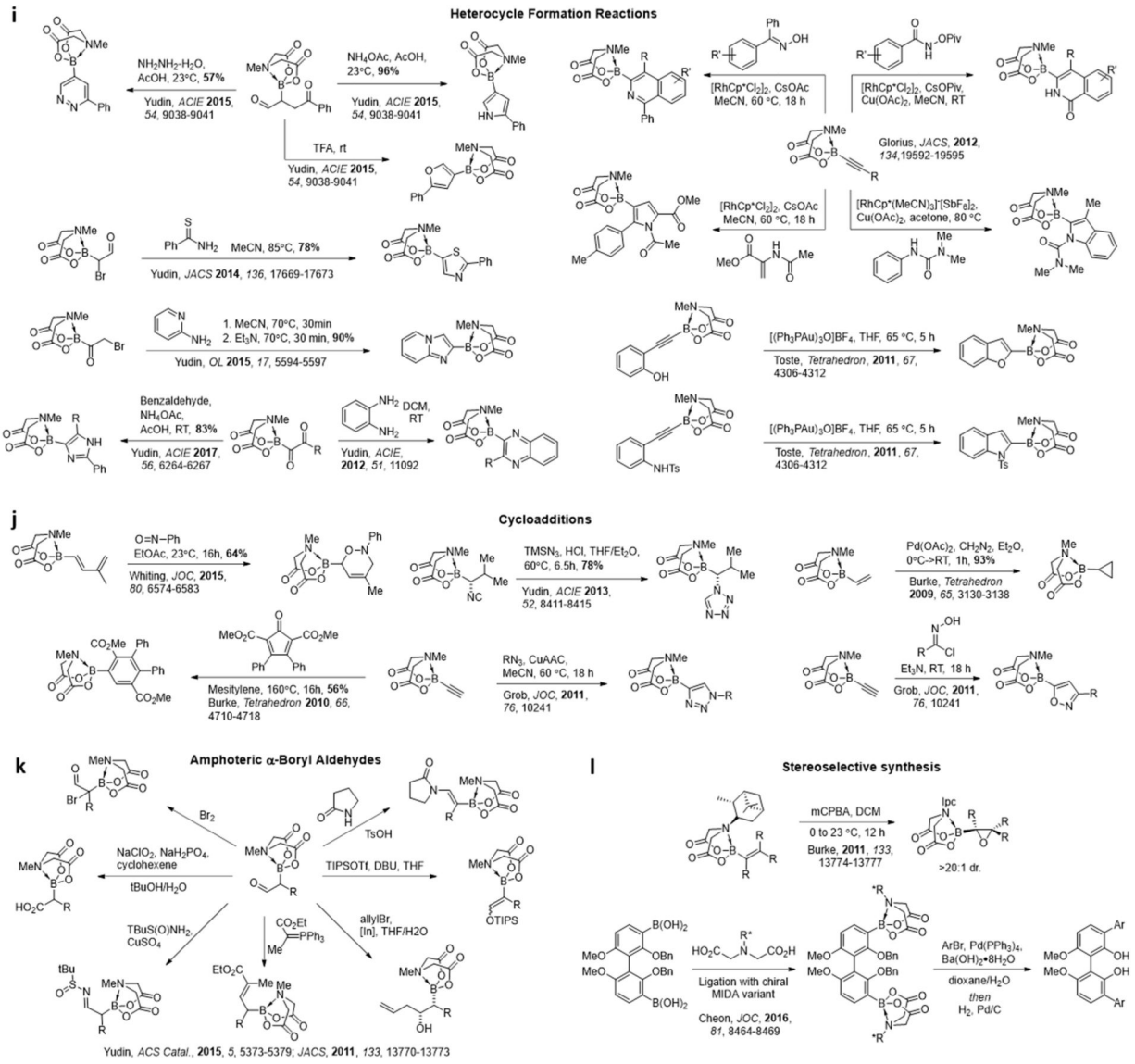


Figure 5. Reaction conditions that tolerate. MIDA boronates

a Oxidations. **b** Reductions. **c** Protections and Deprotections. **d** Nucleophilic Displacements. **e** Addition across multiple bonds. **f** Reactions of aldehydes with nucleophiles. **g** Transition metal-catalyzed reactions. **h** Electrophilic substitution reactions. **i** Heterocycle formation reactions. **j** Cycloadditions. **k** Reactions of α-boryl aldehydes. **l** Stereoselective synthesis with chiral MIDA variants

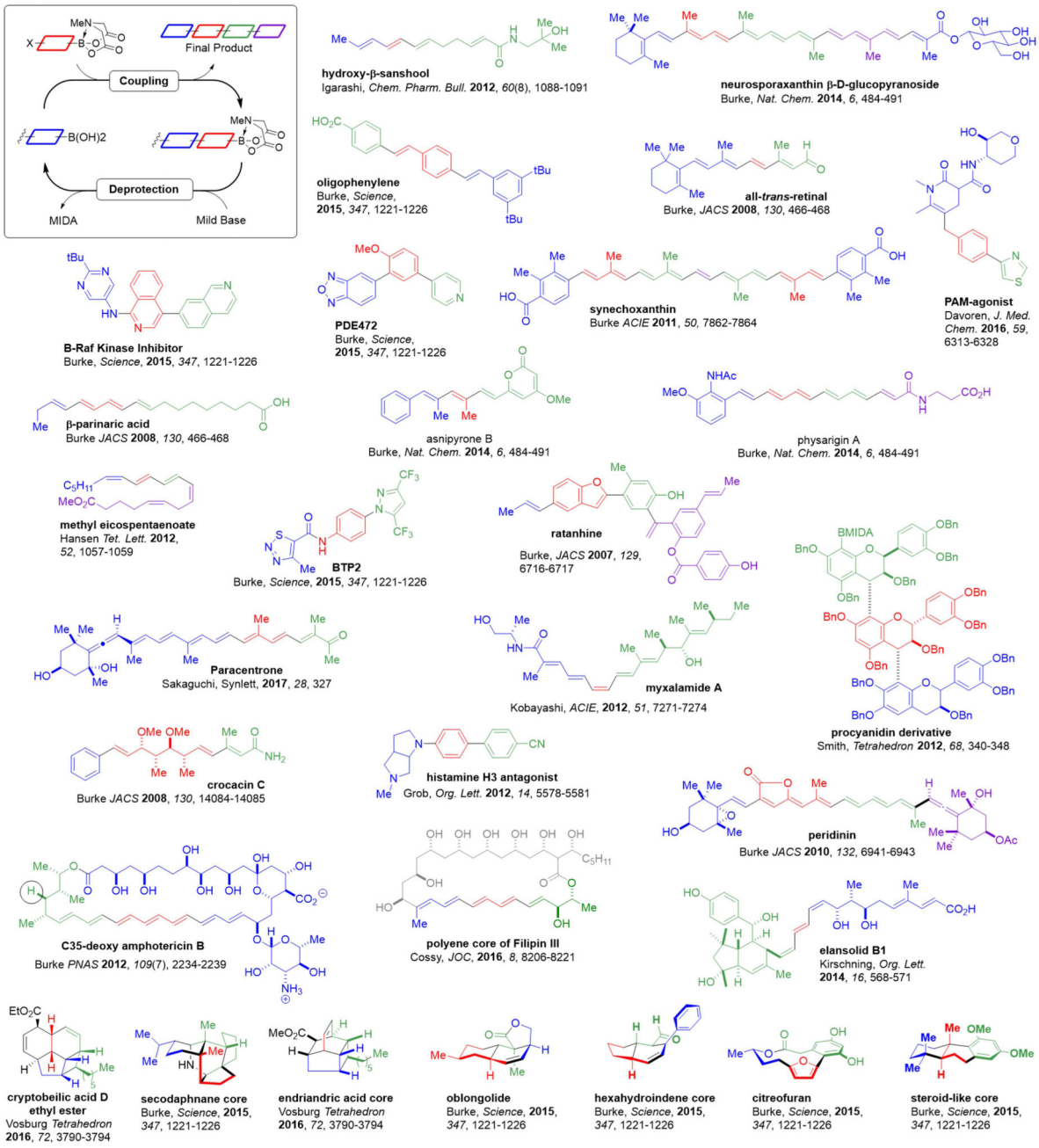


Figure 6.

Small molecules made via iterative cross-coupling with MIDA boronate building blocks.

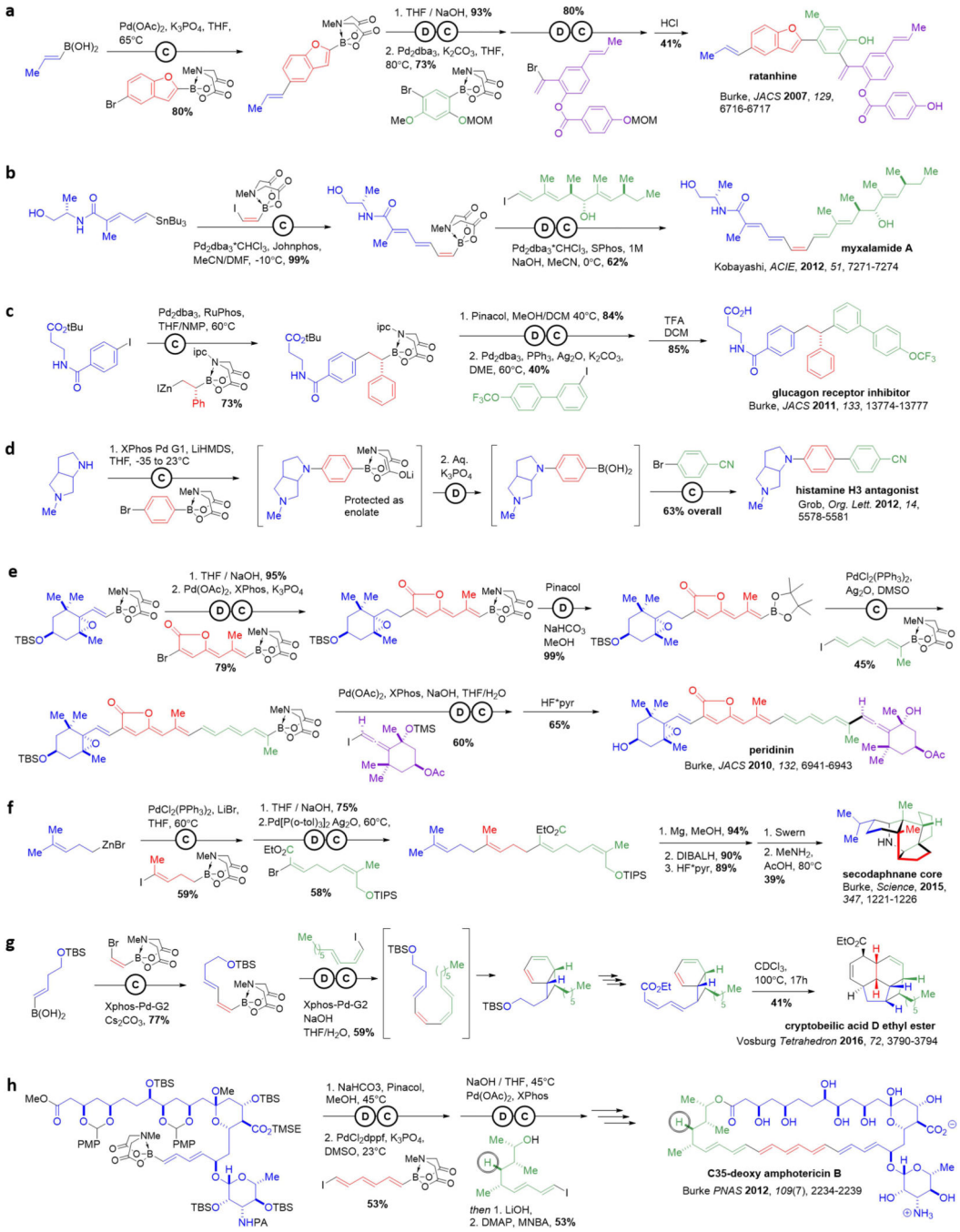


Figure 7. Illustrative examples of iterative cross-coupling

a Ratanhine. **b** Mixalamide A. **c** Glucagon receptor inhibitor. **d** Histamine H3 antagonist. **e** Peridinin. **f** Secodaphnane core via biomimetic linear-cyclized strategy. **g** Cryptobeilic acid D methyl ester. **h** C35-deoxy amphotericin B.

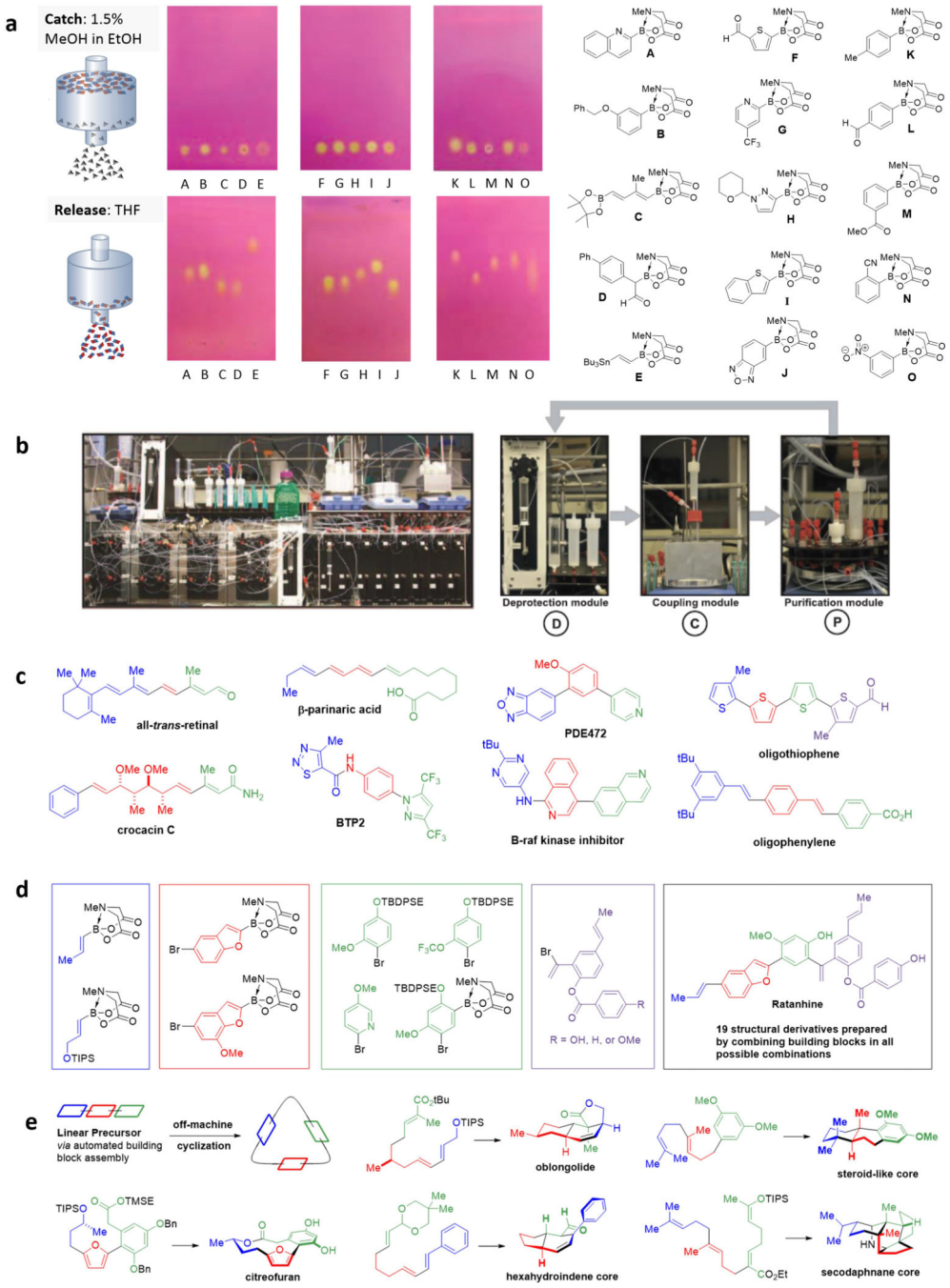


Figure 8. Automated Synthesis Machine

a Binary affinities of MIDA boronates for silica gel enable catch-and-release purification. **b** Design of a machine for automated iterative cross-coupling. **c** Linear small molecules prepared by using automated iterative cross-coupling. **d** Automated synthesis of ratanhine and 19 derivatives. **e** Linear-to-cyclized strategy for automated synthesis of complex natural products.