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Diversity-Oriented Synthesis

Towards the Optimal Screening Collection: A Synthesis Strategy**

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build/couple/pair · diversity-oriented synthesis · molecular diversity · small molecules · synthesis design

The development of effective small-molecule probes and drugs entails at least three stages: 1) a discovery phase, often requiring the synthesis and screening of candidate compounds, 2) an optimization phase, requiring the synthesis and analysis of structural variants, 3) and a manufacturing phase, requiring the efficient, large-scale synthesis of the optimized probe or drug. Specialized project groups tend to undertake the individual activities without prior coordination; for example, contracted (outsourced) chemists may perform the first activity while in-house medicinal and process chemists perform the second and third development stages, respectively. The coordinated planning of these activities in advance of the first small-molecule screen tends not to be undertaken, and each project group can encounter a bottleneck that could, in principle, have been avoided with advance planning. Therefore, a challenge for synthetic chemistry is to develop a new kind of chemistry that yields a screening collection comprising small molecules that increase the probability of success in all three phases. Although this transformative chemistry remains elusive, progress is being made. Herein, we review a newly emerging strategy in diversity-oriented small-molecule synthesis that may have the potential to achieve these challenging goals.

1. Introduction

Small organic molecules are valuable for treating diseases and constitute most medicines marketed today. Such molecules are also highly useful as probes to study, for example, the individual functions of multifunctional proteins, cell circuitry and animal physiology, and they are now being used in these contexts on an unprecedented scale (Figure 1). Consequently, their effect on life-science research in recent years has been dramatic, providing both new tools for understanding living systems and a smoother transition from biology to medicine.[1–6]

Small-molecule syntheses combined with small-molecule screens in an open data-sharing environment are beginning to illuminate the structural properties of small molecules most likely to affect assay performance.[*][7–11] A goal of this research is to guide the identification of candidate structures that are most likely to yield small-molecule leads in experi-

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[*] A thorough discussion of the performance of small molecules in disease-relevant screens is beyond the scope of this Minireview; however, we note that there is widespread agreement that current compound collections are lacking, and therefore that chemistry strategies that yield advances in higher performing small molecules are in great demand. Deficiencies in the performance of current compounds are evident in colloquialisms such as "undruggable targets" and "crowded intellectual property space" limiting "freedom to operate". The decline in drug-discovery successes, at least in part as a result of shortcomings in synthetic chemistry, has contributed to a global decline in the pharmaceutical industry's productivity and success.

ments that probe nearly any facet of human biology, including disease biology.[*]

Research in this area has also revealed the value of using compounds that are poised for optimization during follow-up studies, or for modification during, for example, target identification studies. An overall successful outcome will demand the manufacturing of optimized compounds for broad distribution or for preclinical or clinical investigations, and thus a third demand is that synthetic pathways should be short and efficient. Collectively, these points constitute a substantial challenge for the field of organic synthesis. Among others, what are the structural features of small molecules most likely to yield specific modulation of disease-relevant functions? How do we superimpose on these structural features ones that render the compounds most effectively poised for optimization and modification? How do we synthesize compounds with these features in ways that ensure process-friendly and scalable manufacturing of final, optimized variants? Can we identify strategies for the complete synthesis of the optimal screening deck?

[*] Collections of small molecules that can modulate any area of human biology are increasingly important in drug discovery since advances in small-molecule screening now allow drug hunters to search for compounds that induce state switching, for example, switching from a disease state to a healthy state, without any bias towards a specific target or pathway. Given the highly connected network structure of human cell circuitry, our expectation of the number of potential "therapeutic targets" is undergoing reanalysis, with projected numbers believed by some to be vastly larger than previously imagined.

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Planning and performing complete syntheses of natural products in the past resulted in the recognition and, occasionally, resolution of gaps in synthetic methodology.[12–18] The synergistic relationship between organic synthesis planning and methodology is even more significant as synthetic organic chemists tackle the new challenges noted above. The objects of synthesis planning, no longer limited by the biochemical transformations used by cells in synthesizing naturally occurring small molecules, require radically new strategies and methodologies.[19–22] Several efforts to identify planning concepts for syntheses of small molecules with at least some of the features described above have been reported recently.[23–34] These strategies include among others, "biology-oriented synthesis" (Waldmann),[35] "molecular editing" (Danishefsky),[36] and "libraries-from-libraries" (Houghten).[23] This Minireview draws attention to (and is limited to) a new concept that is evident in several particularly striking examples of diversity-oriented syntheses, in which the focus is on short syntheses of structurally complex and skeletally and stereochemically diverse small molecules poised for optimization.[*][**]

2. Planning Diversity Syntheses with the Build/Couple/Pair (B/C/P) Strategy

Previous summaries on approaches to stereochemical and skeletal diversity emphasized reagent-based differentiation pathways and substrate-based folding pathways. Some recent efforts in diversity syntheses have been particularly noteworthy, especially as they provide a systematic and general process for obtaining a dense matrix of stereochemically and skeletally diverse products in a small number of synthetic transformations. These efforts have a common strategic feature to which we draw attention herein. The strategy also gives access to products with modular origins and chemically orthogonal handles, which facilitate both systematic optimization and modification of the resulting products. We refer to this three-phase strategy as build/couple/pair (B/C/P):

1) Build: Asymmetric syntheses of chiral building blocks containing orthogonal sets of functionality suitable for subsequent coupling and pairing steps are performed; this process when combined with the "Couple" phase provides the basis for stereochemical diversity.

[*] Efficient optimization of the properties of small molecules by structural modification in follow-up studies benefit from syntheses that are short and modular, whereby structures of the candidates possess orthogonal chemical functionality that allows substituents to be appended onto their core skeletons. Diversifying structures of small molecules by altering stereochemistry and skeletal arrays rather than by altering appendages has been a central tenet of the more successful endeavors in diversity syntheses.

[**] This Minireview focuses on the strategic planning of B/C/P pathways and the demonstration of their experimental feasibility rather than on the implementation of the pathways on a scale and purity required for small-molecule screening. The latter is by itself a challenging and important science that requires creative input by chemists.

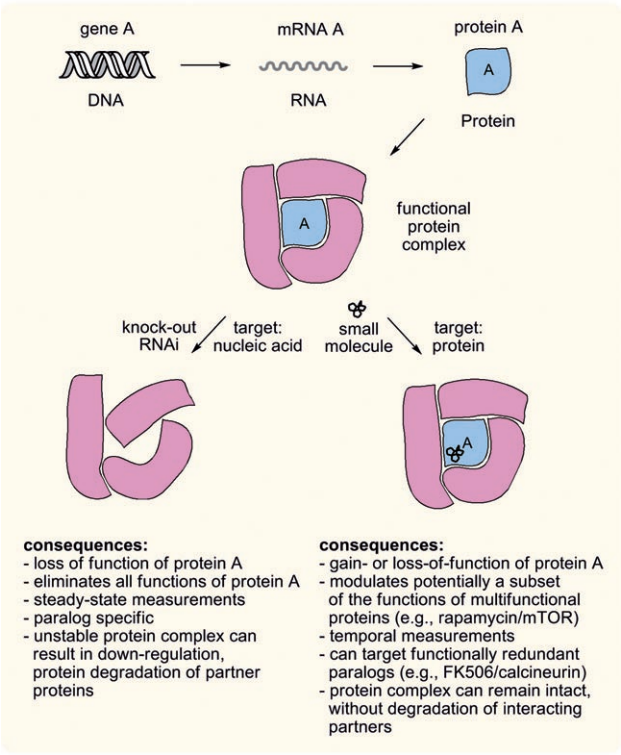


Figure 1. Differences between nucleic-acid- and small-molecule-based modulation of protein function, emphasizing the reasons why small molecules are being used with increased frequency.

2) Couple: Intermolecular coupling reactions that join the building blocks are performed—ideally either without stereochemical consequences or with complete control of all possible stereochemical outcomes.
3) Pair: Intramolecular coupling reactions that join pairwise combinations of functional groups incorporated in the "build" phase (what Porco and co-workers have termed functional-group-pairing reactions[37]) are performed; this process provides the basis for skeletal diversity.

In the build phase, building blocks are synthesized. Chiral building blocks can be prepared by using either enantio- and diastereoselective reactions or compounds from the "chiral pool". Chiral building blocks ideally are synthesized in every possible stereoisomeric form. To minimize the overall number of synthetic steps, functional groups needed for subsequent coupling and pairing reactions should be embedded within these building blocks, although, in practice, additional steps have been performed immediately after the coupling process to introduce new functional groups for functional-group-pairing reactions. In the simplest form of the B/C/P strategy, all stereogenic elements of the final products reside within the chiral building blocks and are obtained by a simple mix-and-match process.[38]

In the couple phase, intermolecular coupling reactions are performed, which join the building blocks and result in compounds with a dense array of functional groups that can undergo intramolecular reactions in distinct pairwise combinations. To achieve the full matrix of all possible stereoisomeric products, coupling reactions are used that either generate no new stereogenic elements or that can provide every possible stereoisomeric outcome. Of course, the latter is a substantial synthetic challenge in view of the current limitations in synthetic methodology (e.g., we still lack general methods to obtain selectively products of Diels–Alder reactions derived from *exo*-transition states). Although the formation of new stereocenters in the coupling and pairing steps generally provide a higher degree of complexity in the products, which is a feature common to many naturally occurring small molecules, incomplete collections of stereoisomers impair efforts to extract powerful stereochemistry-based structure/activity relationships (SARs) from primary screening data. Stereochemistry-based SARs can provide important clues for the optimization and modification studies that follow the discovery of a small-molecule lead. Achieving the full matrix of all possible stereoisomeric products is exceedingly challenging during the pair phase when reactions are used that proceed with diastereoface selectivity. In principle, this challenge might be overcome by new chiral catalysts that impose strong diastereochemical control of the reaction and override the usual substrate control. Currently, full stereochemical control in the overall process is most readily achieved by using coupling and pairing reactions that have no stereochemical consequence, thereby relying on full stereochemical control during the build phase. In practice, the merits of increased structural complexity and more complete stereochemical matrices are most often balanced (Figure 2).

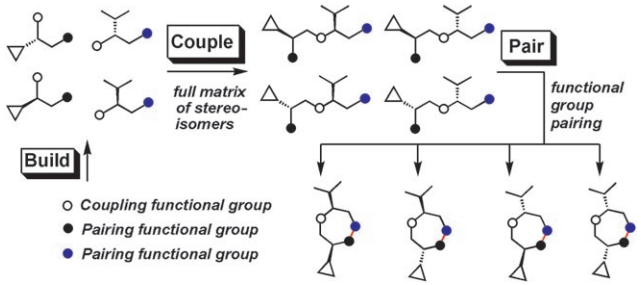


Figure 2. Generation of stereochemical diversity with the build/couple/pair strategy: the complete matrix of stereoisomeric products results from mixing and matching all stereoisomeric building blocks. The couple and pair steps may increase stereochemical diversity if new stereocenters are created, ideally with the ability to achieve all possible stereochemical outcomes selectively.

In the pair phase, intramolecular coupling reactions are performed that join strategically placed appendages in the building blocks and result in compounds with diverse skeletons.[*] For this purpose, the power of modern synthesis, especially the functional group preferences of different transition metals, can be exploited to achieve a dense combinatorial matrix of functional group pairings in the

[*] We use the term skeleton loosely to denote rigidifying elements in small molecules; these can be atom connectivities that yield either linked, fused, bridged or spiro rings, or acyclic conformational elements that provide substantial rigidification by avoiding non-bonded interactions.

cyclization reactions (see, for example, reference [39]). This process yields skeletal diversity in the resulting products. Ideally, functional-group-pairing reactions are selected that are successful regardless of the stereogenic elements in the substrates, thereby providing a cross-matrix of stereochemical isomers (resulting from the build phase) and skeletal variants (resulting from the pair phase).

An early step in planning synthetic routes with the B/C/P concept is identifying templates that display combinations of functional groups suitable for pairwise, intramolecular cyclization reactions. Multicomponent reactions are appealing coupling reactions for the synthesis of such templates, especially ones under the stereochemical control of catalysts or additives. Functional groups used in the subsequent pairing reactions should be strategically positioned so as to allow as many ring-closing modes as possible. The new functional groups that result from pairing reactions are valued for their ability to participate in either additional functional-group-pairing reactions or follow-up appending processes during optimization studies. Selective coupling of pairs of functional groups ("chemoselectivity") in functional-group-pairing reactions may be achieved by several different strategies (Figure 3).

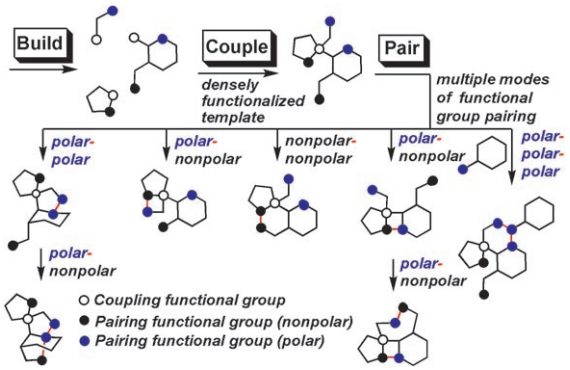
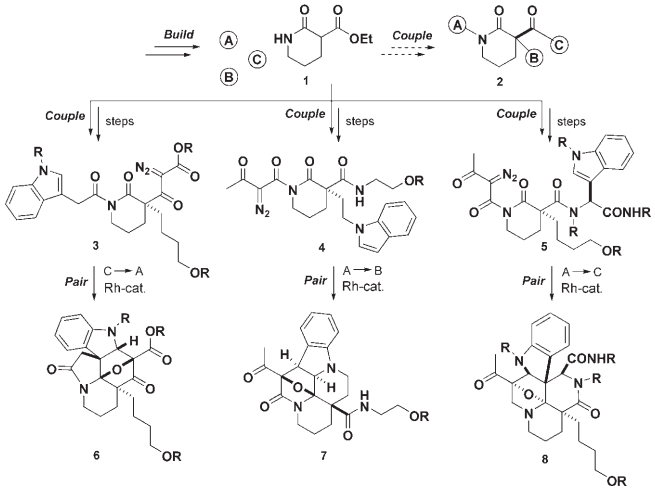


Figure 3. Generation of skeletal diversity with the build/couple/pair strategy: in the pair phase, chemoselective and intramolecular joining of strategically positioned polar (blue), and nonpolar (black) functional groups affords diverse skeletons.

Three categories of functional group couplings are: 1) polar/polar (e.g., amine/ester to form a lactam); 2) nonpolar/nonpolar (e.g., alkene/alkene ring-closing metathesis to generate a cycloalkene), and 3) polar/nonpolar (e.g., alcohol/alkyne cycloacetalization enabled by alkynophilic metal activation). Functional-group-pairing reactions may also include the intermolecular incorporation of other molecular fragments, for example, a Pauson–Khand reaction involving an alkene/alkyne pairing with incorporation of CO, or the acetalization of two hydroxy groups with incorporation of an external aldehyde.

3. Diversity Syntheses with B/C/P Strategies

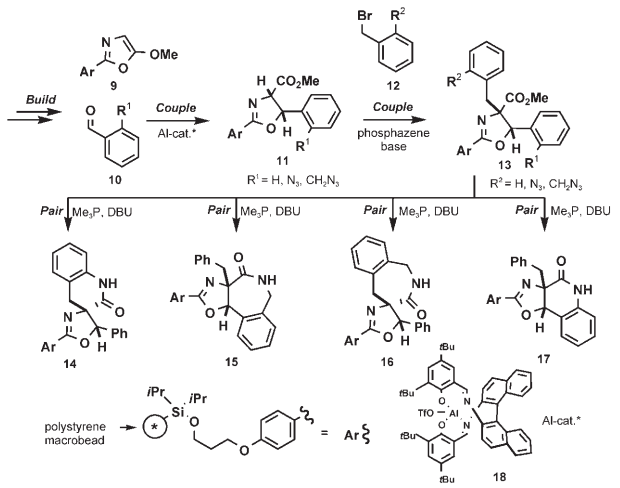
A B/C/P synthetic pathway involving consecutive rhodium-catalyzed cyclization and cycloaddition reactions, which were developed by Padwa and co-workers,[40] was used to generate several complex skeletons reminiscent of naturally occurring indole alkaloids.[41] In the coupling phase, different combinations of α-diazoketocarbonyl and indole moieties were incorporated at defined positions around a common template (Scheme 1; **1**→**2**). In subsequent rhodium-mediated



Scheme 1. Positioning of paired functional groups in the couple phase and performing Rh-catalyzed cycloadditions in the pair phase results in diverse skeletons containing indolizidines. The notation A→B denotes the reaction of the carbonyl ylide on site A with the dipolarophile on site B.

functional-group-pairing reactions, intermediate carbonyl ylides underwent 1,3-dipolar cycloaddition reactions with the electron-rich 2,3-double bond of neighboring indoles. In theory, this approach could comprise six modes of cyclization, of which three were demonstrated (Scheme 1; C→A, A→B, and A→C). The pair phase of this pathway involves the use of a common reagent to achieve functional group pairing (an example of a substrate-based folding pathway[20]). The variation in skeletons results from the differing positions of the alkene and diazo partners. The stereochemical orientation of the reacting functional groups in **3**–**5** around the lactam core effectively dictate a single relative face selectivity, and thus this pathway illustrates the difficulty of achieving stereochemical diversity in the pair phase. Overcoming the intrinsic diastereoface selectivities inherent to these substrates will likely be extremely challenging, as a new generation of chiral catalysts will be required.

In a conceptually related B/C/P pathway developed by Shaw and Mitchell, azido and methyl ester moieties were strategically positioned around a small heterocyclic template (Scheme 2).[42] The study is noteworthy as few metal-catalyzed asymmetric transformations to date have been adapted to high-throughput solid-phase synthesis of biologically active small molecules. For the coupling phase, the authors carefully optimized the Al-catalyzed asymmetric Suga–Ibata reaction of oxazole **9** with *ortho*-substituted aromatic adehydes, followed by diastereoselective enolate alkylation using phosphazene bases and *ortho*-substituted benzyl bromides, to assemble a collection of oxazolines **13** that are poised for

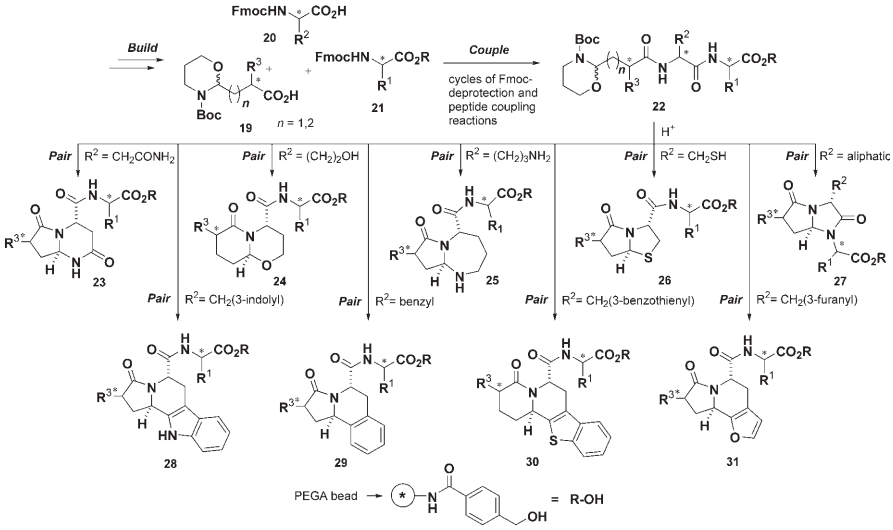


Scheme 2. Solid-phase, catalytic enantioselective Suga–Ibata reactions and diastereoselective enolate alkylations in the couple phase (coupling of oxazole/aldehyde and enolate/benzyl bromide) and subsequent Staudinger-type reductive cyclizations in the pair phase (pairing of azide/methyl ester). DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; Tf = trifluoromethanesulfonyl.

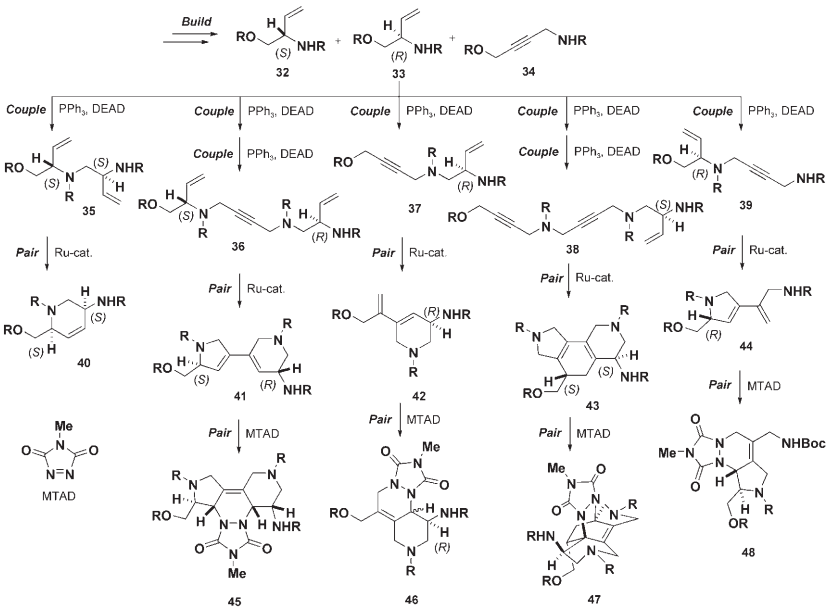
functional-group-pairing reactions. Treatment with trimethylphosphine/DBU allowed cyclization of the azido and methyl ester moieties in the pair phase, thus generating a collection of spiro- and fused tricyclic lactam ring systems. The overall reaction sequence proceeds with near-quantitative conversions and excellent enantio- and diastereoselectivities. However, stereochemical diversity is limited by the inability to alter face selectivities in the Suga–Ibata and enolate alkylation reactions. In subsequent library syntheses, stereochemical diversity was partially addressed by using each enantiomer of the catalyst, and the appending potential of the newly generated lactam amide NH moiety was explored in a series of efficient alkylation and acylation reactions.

Protected natural and nonnatural α-amino acids are readily available from synthetic and commercial sources. Benefiting from decades of optimization of peptide synthesis methods, such building blocks readily fulfill the B/C/P criterion of full stereochemical control in the coupling phase. In a series of studies by Meldal and co-workers, building blocks were connected by using standard peptide coupling procedures to yield masked peptide aldehydes of general structure **22** (Scheme 3). Treatment with acid liberates the corresponding aldehyde, which immediately condenses with the amide backbone to generate an *N*-acyliminium intermediate. By changing nucleophilic moieties positioned in the side chain R^2 of a strategically positioned amino acid residue, new ring systems were formed by cyclization to the *N*-acyliminium intermediates.[43–45] In these reactions, for example, the intramolecular *N*-acyliminium Pictet–Spengler cyclization leading to **28**–**31**, the hydrogen atom in the newly formed stereogenic site always bears a *cis* relationship to R^2. As the relative stereochemical orientations of the R^1 and R^3 substituents are not interfering with the *N*-acyliminium cyclization, 8 of 16 possible stereoisomers of the resulting products **23**–**31** are accessible by using this approach. Complete stereochemical diversification is again thwarted by the current inability to overcome the substrate-controlled face selectivity posed by the *N*-acyliminium intermediates.

A recently described B/C/P pathway relied on the iterative coupling of three simple monomer units, each prepared in electrophilic and nucleophilic forms.[38] In the build phase, nonracemic monomers **32** and **33** were prepared from racemic *N*-Boc-vinylglycinol through enzymatic esterification (Scheme 4). Functional group manipulations provided alcohols (including the achiral propargylic alcohol **34** (R = H)) and their corresponding benzoates, and the *N*-Boc groups were converted into nucleophilic *N*-brosyl (in the dimers) or *N*-nosyl (in the trimers) groups (brosyl = *para*-bromobenzenesulfonyl). In the couple phase, building blocks (monomers) were combined by using the Fukuyama–Mitsunobu reaction into linear dimers and trimers with polar benzoate, *N*-brosyl, and *N*-nosyl groups, and nonpolar alkene and alkyne groups. The pair phase focused on joining only the nonpolar groups by using Ru-catalyzed metathesis reactions (alkene/alkene and alkene/alkyne). In this pathway, the polar groups, as well as enabling the couple phase, are used to facilitate optimization studies after the discovery of leads in small-molecule screens. From three pairs of monomers, all nine possible dimers (3 × 3) and a subset of the 27 possible trimers (3 × 3 × 3) were synthesized and subjected to common



Scheme 3. Solid-phase peptide deprotections and amide bond formations in the couple phase (coupling of amines with activated carboxylic acids) and subsequent aldehyde–amide condensation and addition of a nucleophile to an iminium intermediate in the pair phase (pairing of *N*-acyliminium ion/heteroaromatic ring, aromatic ring, amine, carbamyl, amide, alcohol, thiol).



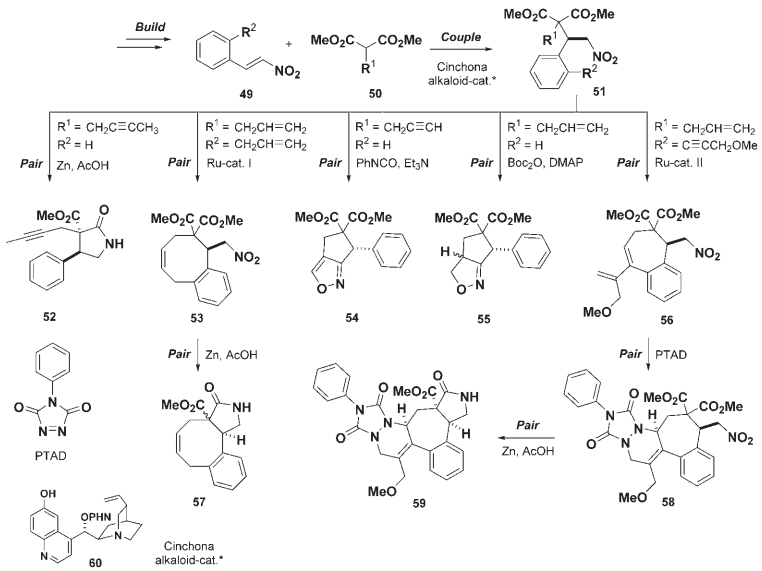
Scheme 4. Fukuyama–Mitsunobu reactions in the couple phase (coupling of alcohol/*N*-brosyl or *N*-nosyl groups) and subsequent Ru-catalyzed ring-closing metathesis reactions in the pair phase (pairing of alkene/alkene and alkene/alkyne). Diels–Alder cycloadditions were demonstrated as methods to enable subsequent optimization of additional skeletal diversification (pairing of diene/triazolinedione). DEAD = diethyl azodicarboxylate.

sets of functional-group-pairing reactions to yield many types of novel skeletons, some of which are illustrated in Scheme 4. A near-complete matrix of stereochemical isomers in the final products resulted by simple iterative coupling of *R* and *S* stereoisomeric building blocks, as both the coupling and pairing reactions proceed without the introduction of new stereogenic sites (neglecting the generation of small-ring Z-cycloalkenes). The stereogenic sites of the end products **40**–**44** are those originating from the monomer building blocks, with the single exception of **43**, which results from a substrate-controlled 1,5-hydride shift after 6π-electrocyclization of the initially formed ene/yne/yne metathesis product.

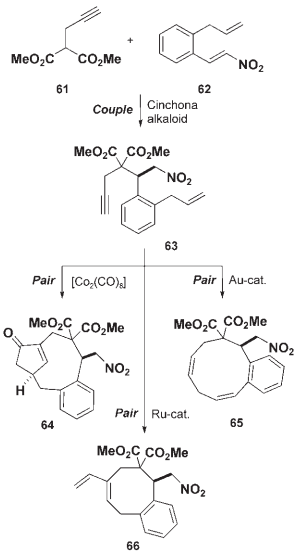
The dienes **41**–**44** that result from ene/yne metathesis reactions can be used as appending sites during optimization or modification studies, but they can also serve as sites for additional skeletal diversification. In the latter mode, however, the reported Diels–Alder reactions suffer from the ideal outcome in that they are under strict substrate control, thereby yielding only a subset of the possible stereoisomeric products. This shortcoming again illustrates the need in synthetic chemistry for general methods to control the absolute face selectivities of substrates in cycloaddition reactions, which commonly the control of face selectivity in both of unsaturated partners.

The recent study that led Porco and co-workers to suggest the term "functional group pairing" is illustrated in Scheme 5.[37] Building blocks such as β-nitrostyrenes **49** and α-substituted malonates **50** were easily synthesized in the build phase. In the couple phase, building blocks were joined by an asymmetric Michael addition catalyzed by Cinchona alkaloid derivative **60**. Although asymmetric induction was high (> 90 %), the preferential formation of only one of the two enantiomers was described. Combinations of functional groups were positioned with defined stereochemical orientations around the resulting core element, thus enabling diverse functional-group-pairing reactions. These densely functionalized templates also undergo consecutive functional group-pairing reactions, as illustrated in Scheme 5 by the three pairing reactions leading to fused pentacycle **59**.

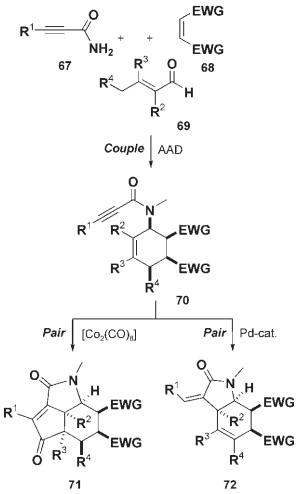
This study illustrates that certain functional group combinations may pair in different ways through the use of different catalysts and reagents (an example of a reagent-based differentiation pathway;[20] Scheme 6). This gain in synthetic efficiency of functional-group-pairing reactions leading to multiple skeletons has been the tenet of other recent approaches to complex small molecules (Scheme 7). Beller and co-workers used aldehyde/amide/dienophile (AAD)-type multicomponent reactions in the couple phase,[46] followed by catalyst- (Pd) and reagent ($[Co_2(CO)_8]$)-controlled reactions of an enyne substrate **70** in the pair phase.[47] In this study, structurally diverse and complex small molecules **71**–**72** are created efficiently, with potential for multiple attachment chemistries, but the lack of chiral building block and the inability to access more than one



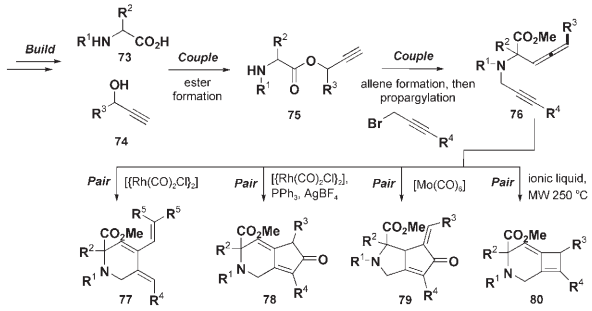
Scheme 5. Enantioselective Michael additions in the couple phase (coupling of malonate/nitroalkene) and subsequent nitro reduction/lactamizations (nitro/ester), Diels–Alder cycloadditions (diene/triazolinedione), and 1,3-dipolar cycloadditions (nitro/alkene, nitro/alkyne) in the pair phase. DMAP = 4-dimethylaminopyridine.



Scheme 6. Three skeletons formed by metal-mediated functional-group-pairing reactions of an enyne substrate.



Scheme 7. Multicomponent aldehyde/amide/dienophile reactions used in the couple phase and metal-mediated cyclizations used in the pair phase.



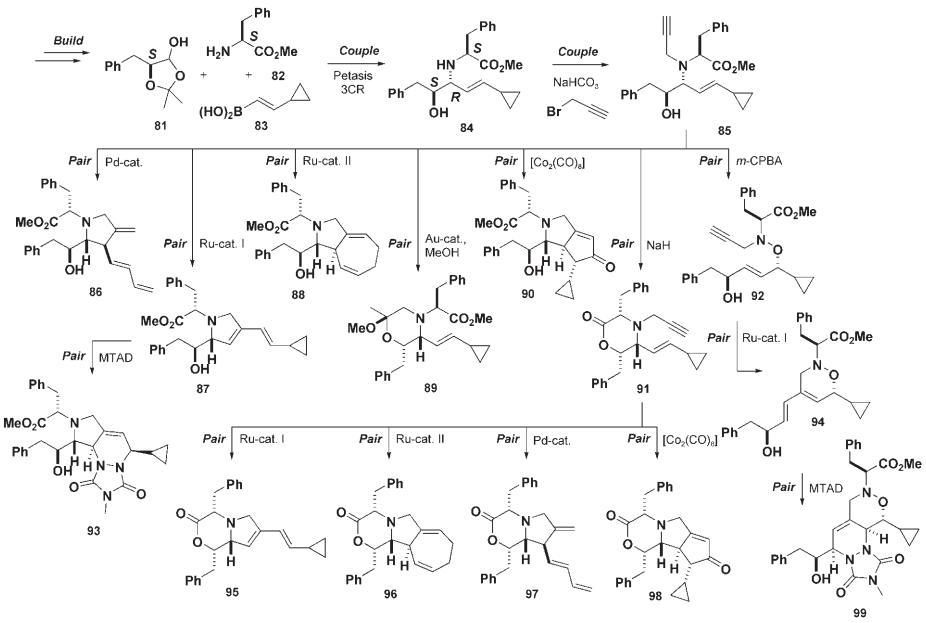
Scheme 8. Four skeletons formed by metal-mediated functional-group-pairing reactions of alkynyl allenes.

stereoisomer in the couple and build phases represent shortcomings of this B/C/P pathway.

The Brummond group has explored a B/C/P pathway that exploits the ability of distinct metals and ligands to convert a central core element into products that have many distinct skeletons. This diverging reaction pathway is based on alkynyl allenes (Scheme 8).[48,49] The common template **76** was converted into four structurally distinct skeletons: cross-conjugated triene skeletons **77** were formed by rhodium-catalyzed allenic Alder–ene reactions, two modes of allenic Pauson–Khand reactions were developed to afford either 4-alkylidene **78** or α-alkylidene cyclopentenones **79**, and a thermal [2+2]-cycloaddition was used to yield the bicyclo[4.2.0]octadiene ring system **80**.

An additional use of multicomponent coupling reactions to display densely functionalized core elements capable of undergoing multiple functional-group-pairing reactions, entailing various reactive functional group combinations and consecutive pairing events, is shown in Scheme 9. The Petasis three-component reaction (boronic acid Mannich reaction) of (*R*)- or (*S*)-α-hydroxyaldehydes **81** (protected as lactols), (*R*)- or (*S*)-phenylalanine methyl ester **82**, and (*E*)-2-cyclopropylvinylboronic acid **83**, followed by propargylation of the resulting amine, was used in the couple phase. Subsequent reagent-controlled skeletal diversification reactions afforded a range of structurally complex small molecules. Pd- and Ru-based catalysts, which selectively pair the nonpolar alkene, alkyne, and cyclopropane functional groups of **85**, enable the cycloisomerization reactions leading to compounds **86**–**88**. *m*-CPBA-mediated Meisenheimer rearrangements (alkene with *N*-oxide), gold-catalyzed cycloketalizations (alkyne with hydroxy), and Pauson–Khand reactions (alkyne/alkene with CO), which selectively pair the nonpolar functional groups with the polar functional groups, are illustrated by the syntheses of **89**, **90**, and **92**, respectively. NaH-mediated lactonization, which selectively pairs polar functional groups, is illustrated by the formation of **91**, which in turn was converted into multicyclic compounds **95**–**98** with distinct and diverse skeletons by using transition-metal-catalyzed functional-group-pairing reactions.

This B/C/P pathway begins with a build phase that yields four types of building blocks. The *R* and *S* stereoisomers of the two chiral building blocks are easily synthesized. The couple phase uses a reaction that creates one new stereogenic carbon center. The diastereoface selectivity of the transient imine is dictated by the α-hydroxy substituent without regard to the stereochemistry of the α-amino substituent of the amino ester and yielding the *anti*-aminoalcohol. This selectivity enables the synthesis of four of the eight possible stereoisomers; again, the inability to synthesize the complete matrix of stereoisomers stems from the inability to override the intrinsic diastereoface selectivity of the imine addition (Petasis) reaction. As in other examples described herein, reactions in the pair phase that proceed with face selectivity are dependent on the bias imposed by the stereogenicity of the substrate. This yields highly stereoselective reactions—which are valued in target-oriented synthesis but a shortcoming in diversity-oriented synthesis when not coupled to methods to access all possible stereoisomers.



Scheme 9. Petasis three-component reactions in the couple phase (coupling of α-hydroxy aldehyde, amine, and vinylboronic acid) and subsequent reagent-controlled reactions leading to multiple skeletons in the pair phase (polar: hydroxyl, amino, ester; nonpolar: alkene, alkyne, cyclopropane). *m*-CPBA = *meta*-chloroperoxybenzoic acid.

4. The Future

We have suggested herein that the B/C/P strategy will yield small molecules with increased probability of success in the discovery, optimization, and manufacturing phases of probe- and drug-discovery research. How can we know if this is true?

At least with respect to the discovery phase, there is a clear path to an answer. Scientists who are contributing compounds and assays for small-molecule screens are performing a substantial body of chemical biology research in an open data-sharing environment. Public databases that provide access to the results of these experiments—especially ones such as ChemBank that offer both raw screening data and analysis tools to perform global analyses—are expected to provide the means to evaluate the performance of compounds from different origins, including from pathways guided by the B/C/P strategy (Figure 4). Indeed, pilot studies have already been performed that shine a light on this important issue.[8,50]

There are currently no efforts of which we are aware to evaluate quantitatively the role that the origins of compounds play on the ease and effectiveness of subsequent optimization and manufacturing experiments. We expect that progress in this area will benefit from public analysis environments, which enable the scientific community, especially the synthetic chemistry and chemical biology communities, to be more than the sum of its parts.

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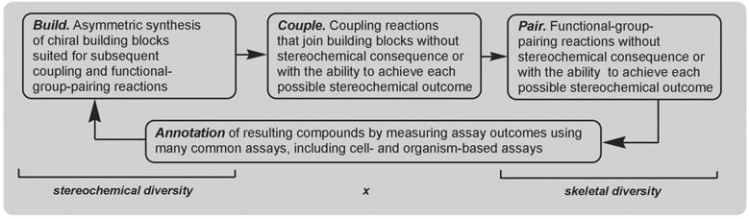

Figure 4. Small molecules originating from different sources, including from synthetic pathways using the build/couple/pair strategy described herein, are annotated by their performance in large numbers of common small-molecule screens. Chemical research could soon enter an important new phase in which intuition and bias concerning the effectiveness of different types of compounds are replaced by quantitative analyses.

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[10] ChemBank is a public, web-based informatics environment created by the Broad Institute's Chemical Biology Program and funded in a large part by the National Cancer Institute's Initiative for Chemical Genetics (ICG). This knowledge environment includes freely available data derived from small molecules and small-molecule screens, and resources for studying the data so that biological and medical insights can be gained. It is intended to guide chemists synthesizing novel compounds or libraries, to assist biologists searching for small molecules that perturb specific biological pathways, and to catalyze the process by which drug hunters discover new and effective medicines. For more

information, see: http://chembank.broad.harvard.edu.
[11] PubChem is a component of the Molecular Libraries Roadmap Initiative of the NIH and was established to provide information on the biological activities of small molecules. For more information, see: http://pubchem.ncbi.nlm.nih.gov.
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