



# Towards the Optimal Screening Collection: A Synthesis Strategy

## Citation

### Published version

<https://doi.org/10.1002/anie.200703073>

## Link

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Published in final edited form as:

*Angew Chem Int Ed Engl.* 2007 December 17; 47(1): 48–56. doi:10.1002/anie.200703073.

## Diversity-Oriented Syntheses Using the Build/Couple/Pair Strategy\*\*

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### Abstract

The development of effective small-molecule probes and drugs entails a discovery phase, often requiring the synthesis and screening of candidate compounds, an optimization phase requiring the synthesis and analysis of structural variants, and a manufacturing phase requiring the efficient, large-scale synthesis of the optimized probe or drug. In the pharmaceutical industry, the original chemistry team-based approach is evolving to a bucket brigade-based approach where, increasingly, contracted (outsourced) chemists perform the first activity while in-house medicinal and process chemists, respectively, perform the second and third activities. The up-front coordination of these activities tends not to be optimized – each has a life of its own and each can result in a bottleneck. Therefore, a challenge for the field of synthetic chemistry is to develop a new kind of chemistry that yields small molecules that increase the probability of success in all subsequent facets of the probe- and drug-discovery pipelines, including discovery, optimization and manufacturing. Whereas this transformative chemistry remains elusive, progress is being made. Here, we review a newly emerging strategy in diversity-oriented small-molecule synthesis that may have the potential to achieve these challenging goals in the future.

### Keywords

diversity; oriented synthesis; build/couple/pair; functional group pairing; molecular diversity; synthesis design

### 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 (see *Sidebar*).

Consequently, their effect on life-science research in recent years has been dramatic,

\*\*The NIGMS-sponsored Center of Excellence in Chemical Methodology and Library Development (Broad Institute CMLD) enabled this research. T.E.N is grateful to the Alfred Benzon Foundation for a Postdoctoral Research Scholarship.

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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.<sup>i</sup>[7–9][10][11] A goal of this research is to guide the identification of candidate structures most likely to yield small-molecule leads in experiments probing nearly any facet of human biology, including disease biology.<sup>ii</sup>

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 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 having these features in ways that ensure process-friendly and scalable manufacturing of final, optimized variants?

Planning and performing multi-step syntheses of natural products in the past resulted in the recognition of and, periodically, resolution in 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 having at least some of the features described above have been reported in recent years.[23–34] These strategies include among others, “biology-oriented synthesis” (Waldmann),[35] “molecular editing” (Danishefsky),[36] and “libraries-from-libraries” (Houghten).[23] This review draws attention to (and is limited to) a new concept that is evident in several particularly striking examples of diversity-oriented syntheses, where the focus is on short syntheses of structurally complex and skeletally and stereochemically diverse small molecules poised for optimization.[iii][iv]

<sup>i</sup>A thorough discussion of the performance of small molecules in disease-relevant screens is beyond the scope of this Review; however, we note here 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 I.P. space” limiting “freedom to operate”. The decline in drug-discovery successes, at least in part due to shortcomings in synthetic chemistry, has contributed to a global decline in the pharmaceutical industry’s productivity and success.

<sup>ii</sup>Having collections of small molecules that can modulate any area of human biology is 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.

<sup>iii</sup>Efficient optimization of the properties of small molecules by structural modification in follow-up studies benefit from syntheses that are short and modular, with structures of the candidates possessing orthogonal chemical functionality that enable appending of substituents 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.

<sup>iv</sup>This review 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. Here, we simply note that the latter is by itself a challenging and important science requiring creative input by chemists.

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

In previous summaries, approaches to stereochemical and skeletal diversity using *reagent-based differentiation* pathways and *substrate-based folding* pathways have been emphasized. Some recent efforts in diversity syntheses have been particularly noteworthy, especially since 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 in this Review. The strategy also allows for products having modular origins and chemically orthogonal handles, both facilitating 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 provides the basis for stereochemical diversity.
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 J. 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 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 (*vide infra*). 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 that join the building blocks and result in compounds having 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 represents a substantial synthetic challenge given 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 (SAR) from primary screening data. Stereochemistry-based SAR can provide important clues that facilitate optimization and modification studies following the discovery of a small-molecule lead. Achieving the full matrix of all possible stereoisomeric products is exceedingly challenging during the pairing phase when reactions are used that proceed with diastereoface selectivity, as will be seen in subsequent illustrations, although in principle is a challenge that might be overcome with the advent of new chiral catalysts that impose their diastereochemical will in a way that

overrides substrate-controlled preferences. Currently, full stereochemical control in the overall process is most readily achieved by using coupling and pairing reactions having no stereochemical consequence, thereby relying on full stereochemical control achieved during the build phase. In practice, the merits of increased structural complexity and more complete stereochemical matrices are most often balanced (Figure 1).[v]

In the pair phase, intramolecular coupling reactions are performed that join strategically placed appendages in the building blocks and result in compounds having diverse skeletons. Here, the power of modern synthesis, especially using the broad range of functional group preferences of different transition metals, can be exploited to achieve a dense combinatorial matrix of functional group pairings in the cyclization reactions (see, e.g., Kumagai et al. [39]). This process yields skeletal diversity in the resulting products. Ideally, functional group-pairing reactions are selected that are successful independent 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 using the B/C/P concept identifies 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 for 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 using several different strategies (Figure 2).

Assigning functional groups either polar or non-polar status, three modes are possible: (i) polar/polar; e.g., amine/ester to form a lactam; (ii) non-polar/non-polar; e.g., alkene/alkene ring-closing metathesis to generate a cycloalkene, and (iii) polar/non-polar; e.g., alcohol/alkyne cycloacetalization enabled by alkynophilic metal activation. Functional group-pairing reactions may also include the intermolecular incorporation of other molecular fragments, e.g., a Pauson-Khand reaction involving an alkene/alkyne pairing with incorporation of CO, or the acetalization of two hydroxyl groups with incorporation of an external aldehyde.

### 3. Diversity Syntheses Using B/C/P Strategies

A B/C/P synthetic pathway using consecutive rhodium-catalyzed cyclization-cycloaddition reactions, which have been 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  $\alpha$ -diazo ketocarbonyl and indole moieties were incorporated at defined positions around a common template (**1**  $\rightarrow$  **2**). In subsequent rhodium-mediated 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 (Figure 3; C  $\rightarrow$  A, A  $\rightarrow$  B and A  $\rightarrow$  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

<sup>v</sup>We use the term skeleton loosely to denote rigidifying elements in small molecules; these can be atom connectivities that yield either linked, fused, bridged and/or spiro rings, or acyclic conformational elements that provide substantial rigidification through the avoidance of non-bonded interactions.

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, requiring a new generation of chiral catalysts, rendering advances along this line a daunting challenge.

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 (Figure 4). [42] The study is noteworthy since 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 aldehydes, followed by diastereoselective enolate alkylation using phosphazene bases and ortho-substituted benzyl bromides, to assemble a collection of oxazolines **13** poised for 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. Notably, 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 follow-up 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 non-natural  $\alpha$ -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 papers by Meldal and co-workers, building blocks were connected by using standard peptide coupling procedures to yield masked peptide aldehydes of general structure **22** (Figure 5). 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 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 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, non-racemic monomers **32–33** were prepared from racemic *N*-Boc vinylglycinol via enzymatic esterification. Functional group manipulations provided alcohols (including the achiral propargylic alcohol **34**) and their corresponding benzoates, where the *N*-Boc groups were converted to nucleophilic *N*-brosyl (in the two-mers) or *N*-nosyl (in the three-mers) groups. In the couple phase, building blocks (monomers) were combined by using the Fukuyama-Mitsunobu reaction into linear dimers and trimers having polar benzoate, *N*-brosyl, and *N*-nosyl groups, and non-polar alkene and alkyne groups. The build phase focused on joining only the non-polar groups using Ru-catalyzed metathesis reactions (alkene/alkene and alkene/alkyne). In this pathway, the polar groups, in addition to enabling

the couple phase, are used to facilitate optimization studies following the discovery of leads in small-molecule screens. From three pairs of monomers, all nine possible 2-mers ( $3 \times 3$ ) and a subset of the 27 possible 3-mers ( $3 \times 3 \times 3$ ) were synthesized and subjected to common sets of functional group-pairing reactions, yielding many types of novel skeletons, some of which are illustrated in Figure 6. A near complete matrix of stereochemical isomers in the final products resulted by simple iterative coupling of (*R*)- and (*S*)-stereoisomeric building blocks since 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 following  $6\pi$ -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, commonly involving the need to control face selectivity in each of two unsaturated partners.

The recent study that led J. Porco and co-workers to suggest the term “functional group pairing” is illustrated in Figure 7.[37] Building blocks such as  $\beta$ -nitrostyrenes **49** and  $\alpha$ -substituted malonates **50** were easily synthesized in the build phase. In the couple phase, building blocks were joined via an asymmetric Michael addition catalyzed by Cinchona alkaloid derivative **60**. Although asymmetric induction was high (>90%), the preferential formation of only one of 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 by the three pairings 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]; Figure 8). 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 (Figure 9). Beller and co-workers used aldehyde/amide/dienophile (AAD)-type multicomponent reactions in the couple phase,[46] followed by catalyst (Pd)- and reagent ( $\text{Co}_2(\text{CO})_8$ )-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 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 have many distinct skeletons. This diverging reaction pathway is based on alkynyl allenes (Figure 10).[48, 49] In these studies, a common template **76** was converted into structurally distinct skeletons: cross-conjugated triene skeletons **77** were formed via rhodium-catalyzed allenic Alderene reactions, two modes of allenic Pauson-Khand reactions were developed to afford either 4-alkylidene or  $\alpha$ -alkylidene cyclopentenones **78–79**, 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 Figure 11. The Petasis three-component (boronic acid Mannich reaction) of (*R*)- or (*S*)- $\alpha$ -hydroxy aldehydes (protected as lactols) **81**, (*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, selectively pairing the non-polar 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), selectively pairing the non-polar with polar functional groups, is illustrated by the synthesis of **89**, **90** and **92**, respectively. NaH-mediated lactonization, selectively pairing polar functional groups, is illustrated by the formation of **91**, which in turn was converted, using transition metal-catalyzed functional group-pairing reactions, to multicyclic compounds **95–98** having distinct and diverse skeletons.

This B/C/P pathway begins with a build phase yielding four types of building blocks, with the (*R*)- and (*S*)-stereoisomers of the two chiral building blocks being easily synthesized. The couple phase uses a reaction that creates one new stereogenic carbon. The diastereoface selectivity of the transient imine is dictated by the  $\alpha$ -hydroxyl substituent without regard to the stereochemistry of the  $\alpha$ -amino substituent of the amino ester and yielding the *anti*-aminoalcohol. This 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 in this review, 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 – valued in target-oriented synthesis but a shortcoming in diversity-oriented synthesis when not coupled to methods to access all possible stereoisomers.

## 4. Future

We've suggested in this review 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 having different origins, including from pathways guided by the B/C/P strategy (Figure 12). 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. For the moment, this will remain an activity driven by theoretical considerations since insufficient data exist, particularly with respect to compounds derived from the B/C/P strategy. 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 their parts.

## Acknowledgments

Colleagues at the Chemical Biology Program, Chemical Biology Platform, and CMLD at the Broad Institute of Harvard and MIT are gratefully acknowledged for many stimulating discussions, especially Damian W. Young, Lisa Marcaurelle, Annaliese K. Franz, Ryan E. Looper, Alexander M. Taylor, John Rearick, Xiang Wang, David A. Spiegel, Teruhisa Tokunaga, Takuya Uchida, Jared T. Shaw, Jeremy R. Duvall, B. Lawrence Gray, and Mike A. Foley.

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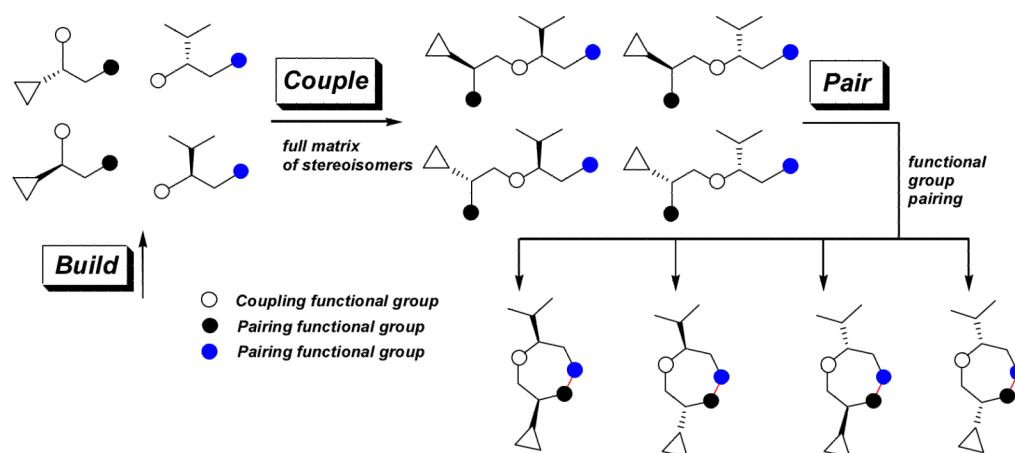
## Biographies

Thomas E. Nielsen completed his PhD in 2002 at the Technical University of Denmark (DTU) under the supervision of Professor David Tanner. From 2003–2005 he carried out postdoctoral studies with Professor Morten Meldal at the Carlsberg Laboratory. In 2006, he joined the Chemical Biology Program at the Broad Institute of Harvard and MIT as a postdoctoral fellow under the supervision of Professor Stuart L. Schreiber. Among his recent honors, he has received the Bert L. Schram Award from the European Peptide Society (2004), an ESCS Young Investigator Award from the European Society of Combinatorial Sciences (2005), and a Research Scholarship from the Alfred Benzon Foundation (2006).



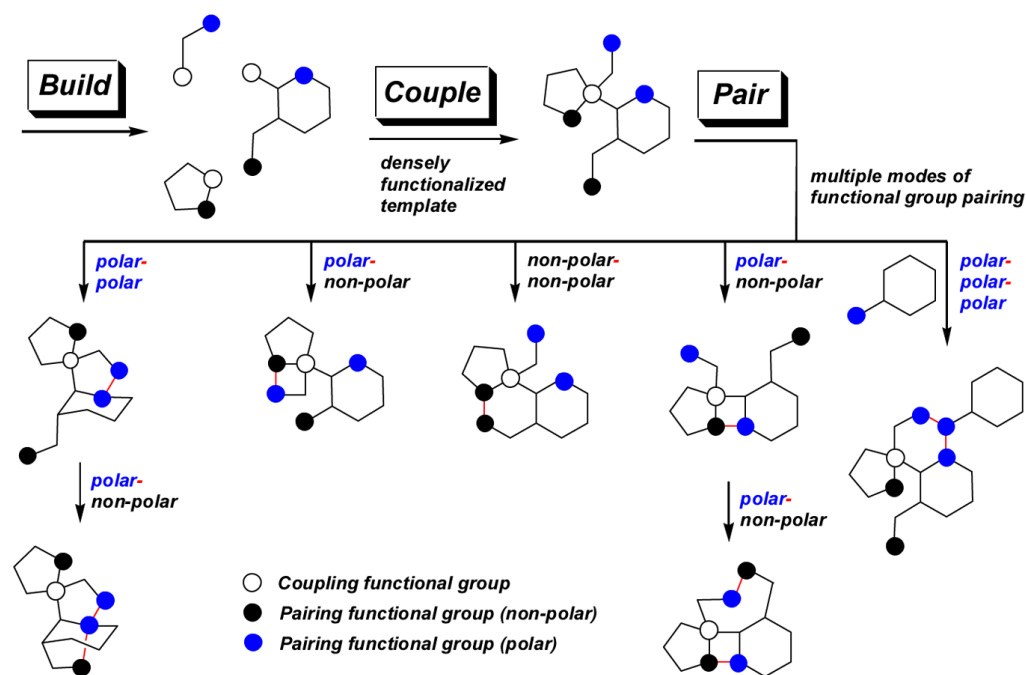
Stuart L. Schreiber is the Morris Loeb Professor in the Department of Chemistry and Chemical Biology at Harvard University and an Investigator with the Howard Hughes Medical Institute at the Broad Institute of Harvard and MIT, where he is also the Director of Chemical Biology (formerly the Harvard ICCB) and its affiliated, NCI-sponsored Initiative for Chemical Genetics (ICG) and NIGMS-sponsored Center for Chemical Methodology and Library Development (CMLD). His research aims to develop systematic ways to explore biology and medicine using small molecules.



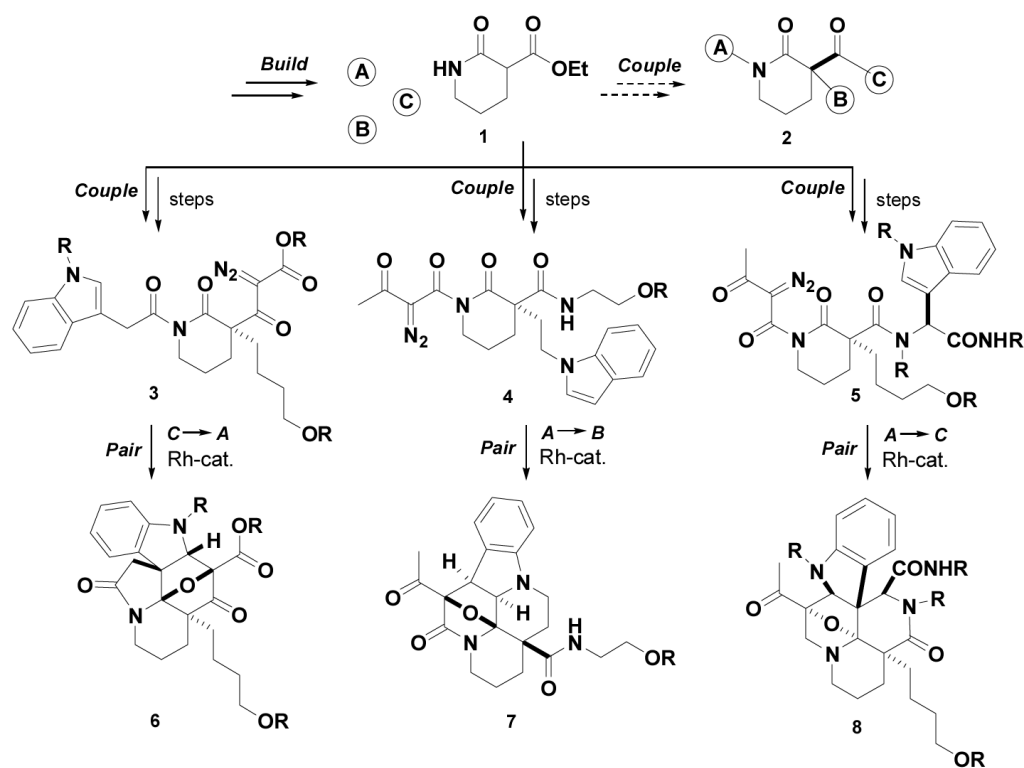


**Figure 1.**

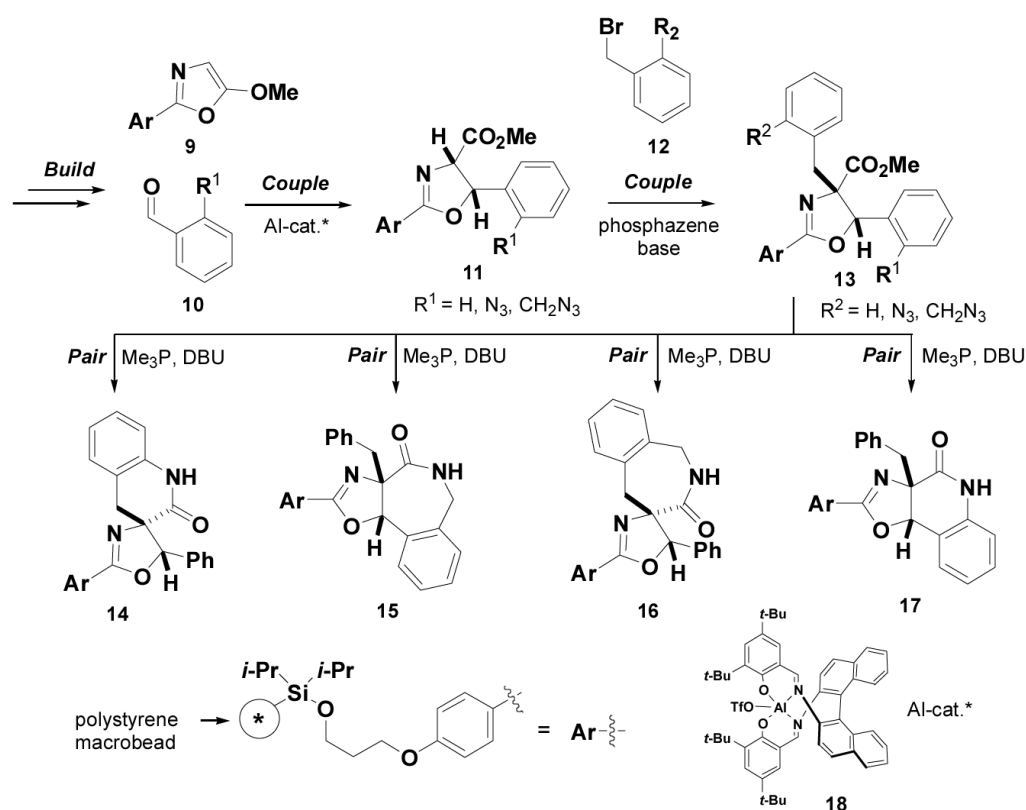
Stereochemical diversity using the build/couple/pair strategy: the complete matrix of stereoisomeric products results from mixing and matching all stereoisomeric building blocks. The couple and pair steps may increase stereochemical diversity if new stereocenters are created, ideally with the ability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



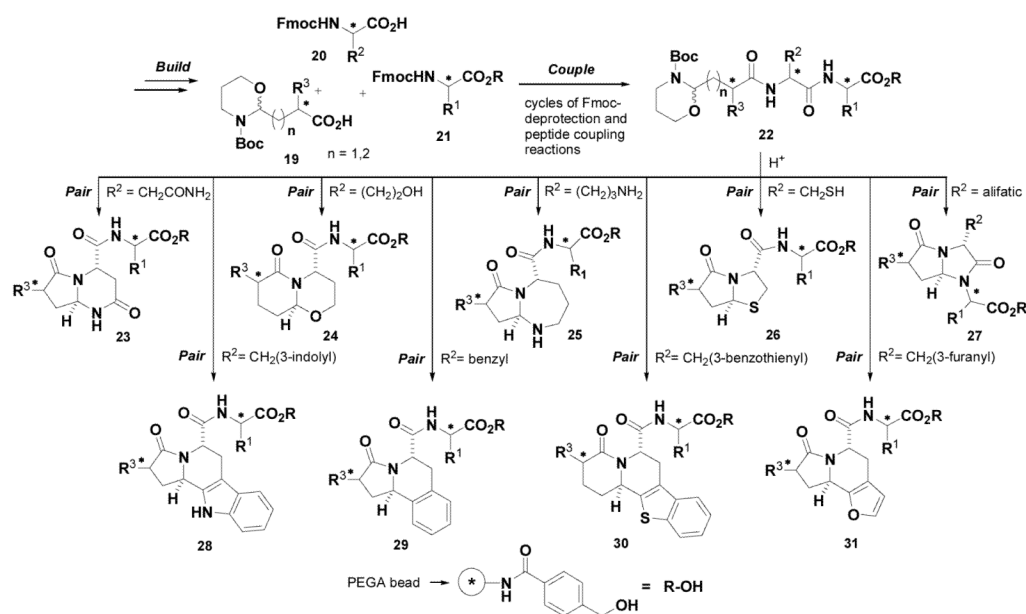
**Figure 2.** Skeletal diversity using the build/couple/pair strategy: in the pair phase, chemoselective and intramolecular joining of strategically positioned polar (blue), and non-polar (black) functional groups affords diverse skeletons.

**Figure 3.**

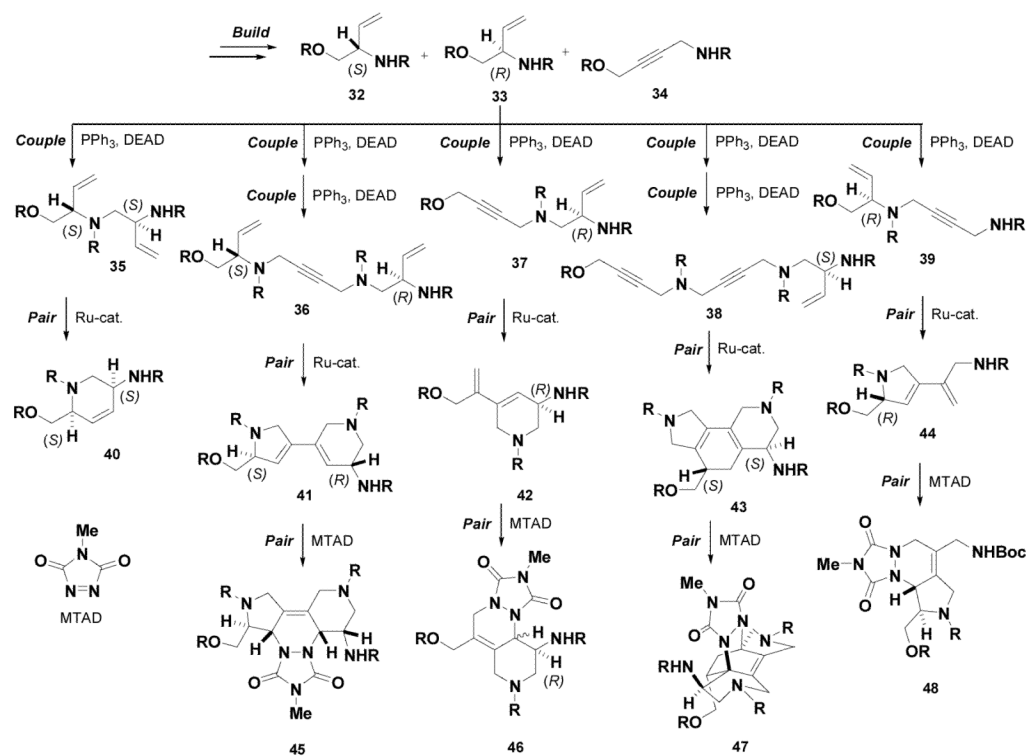
Positioning of paired functional groups in the couple phase and performing Rh-catalyzed cycloadditions in the pair phase results in diverse skeletons containing indolizidines. The notation  $A \rightarrow B$  is short for: carbonyl ylide on site A reacts with dipolarophile on site B.

**Figure 4.**

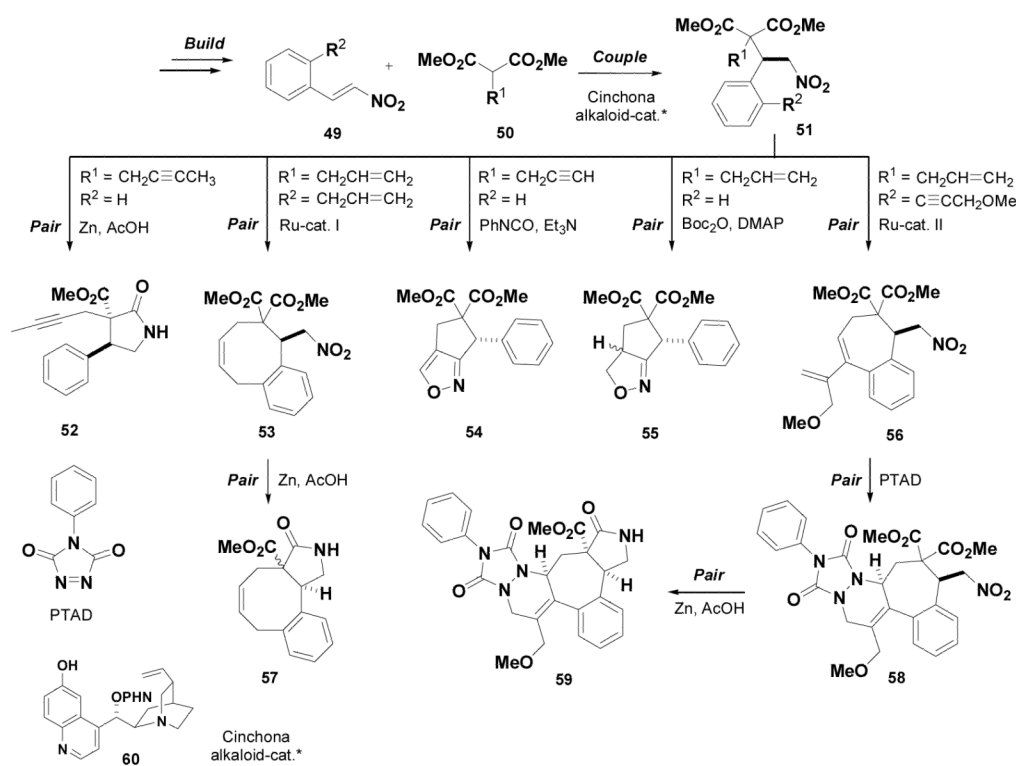
Solid-phase, catalytic enantioselective Suga-Ibata reactions and diastereoselective enolate alkylations in the couple phase (coupling functional groups: oxazole/aldehyde; enolate/benzyl bromide) were followed by Staudinger-type reductive cyclizations in the pair phase (pairing functional groups: azide/methyl ester).

**Figure 5.**

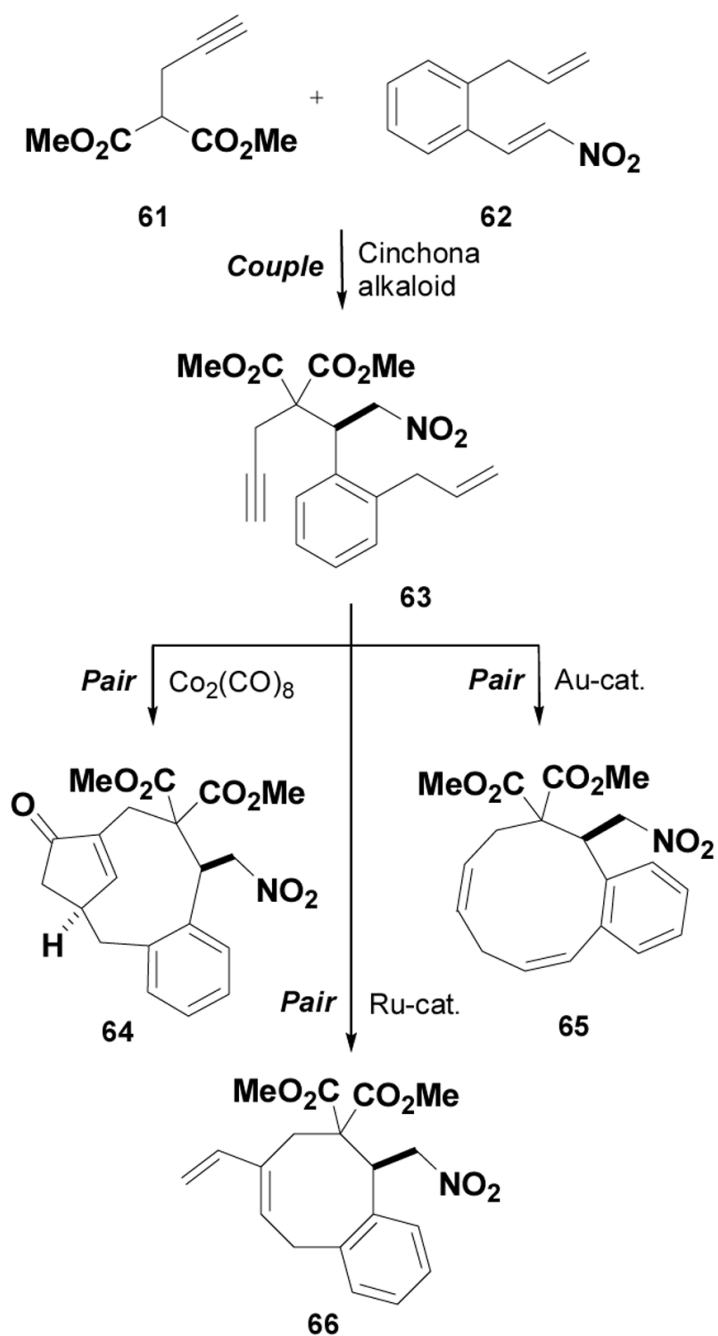
Solid-phase peptide deprotections and amide bond formations in the couple phase (coupling functional groups: amine/activated carboxylic acid) were followed by aldehyde-amide condensation and subsequent addition of a nucleophile to an iminium intermediate in the pair phase (pairing functional groups: *N*-acyliminium ion/heteroaromatic ring, aromatic ring, amine, carbamyl, amide, alcohol, thiol).

**Figure 6.**

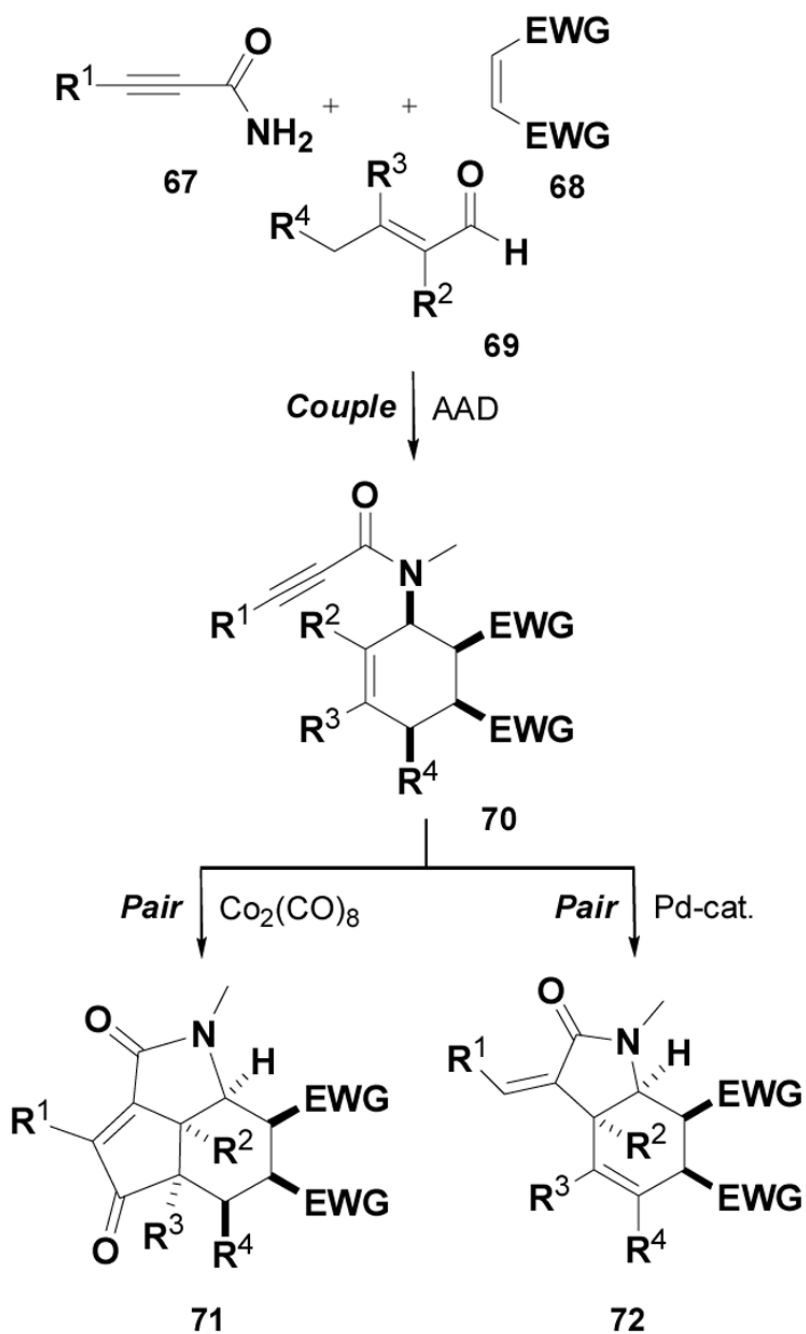
Fukuyama-Mitsunobu reactions in the couple phase (coupling functional groups: alcohol/*N*-brosyl or *N*-nosyl) were followed by Ru-catalyzed ring-closing metathesis reactions in the pair phase (pairing functional groups: alkene/alkene; alkene/alkyne). Diels-Alder cycloadditions were demonstrated as methods to enable subsequent optimization of additional skeletal diversification (pairing functional groups: diene/triazolinedione).



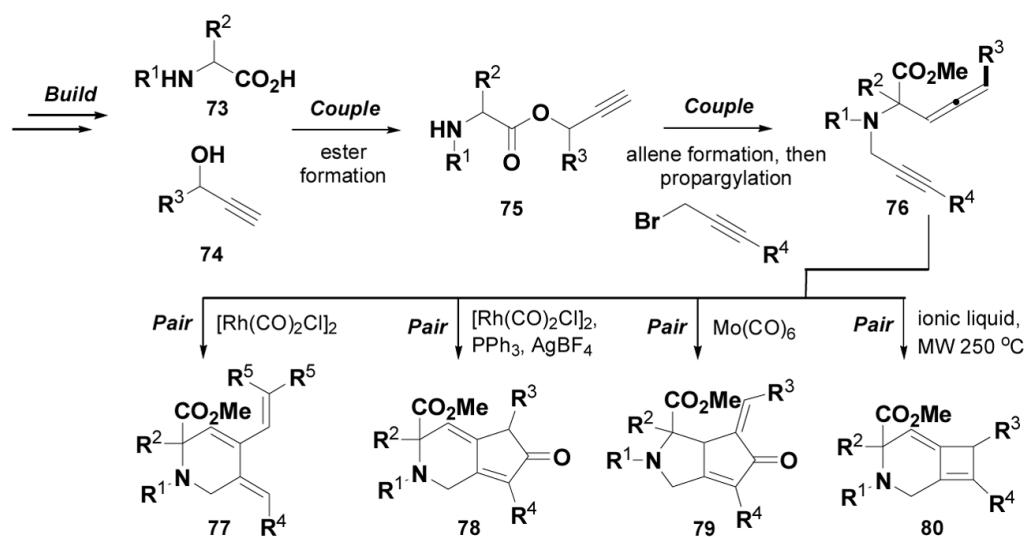
**Figure 7.** Enantioselective Michael additions in the couple phase (coupling functional groups: malonate/nitroalkene) were followed by nitro reduction/lactamizations (nitro/ester), Diels-Alder cycloadditions (diene/triazolinedione), and 1,3-dipolar cycloadditions (nitro/alkene, nitro/alkyne) in the pair phase.



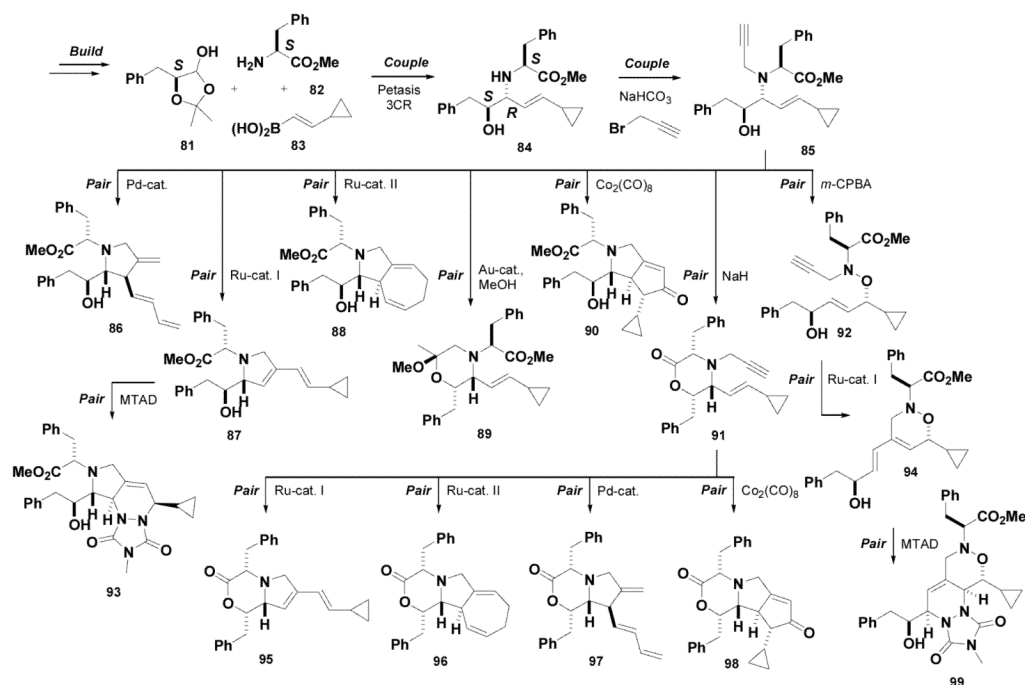
**Figure 8.** Three skeletons formed via metal-mediated functional group-pairing reactions of an enyne substrate.



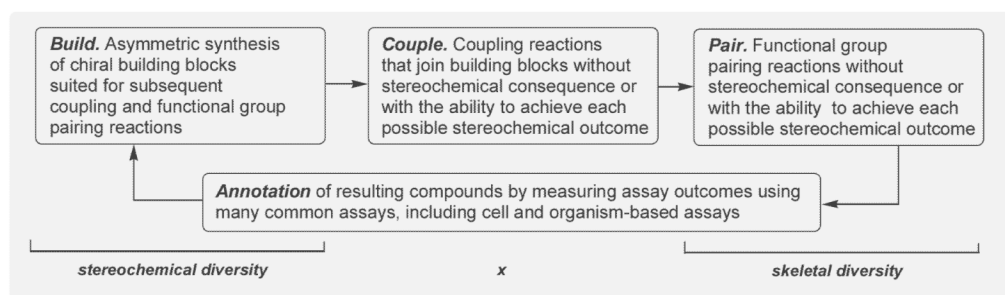
**Figure 9.** Multicomponent aldehyde/amide/dienophile reactions used in the couple phase and metal-mediated cyclizations used in the pair phase.



**Figure 10.** Four skeletons formed via metal-mediated functional group-pairing reactions of alkyne allenes.

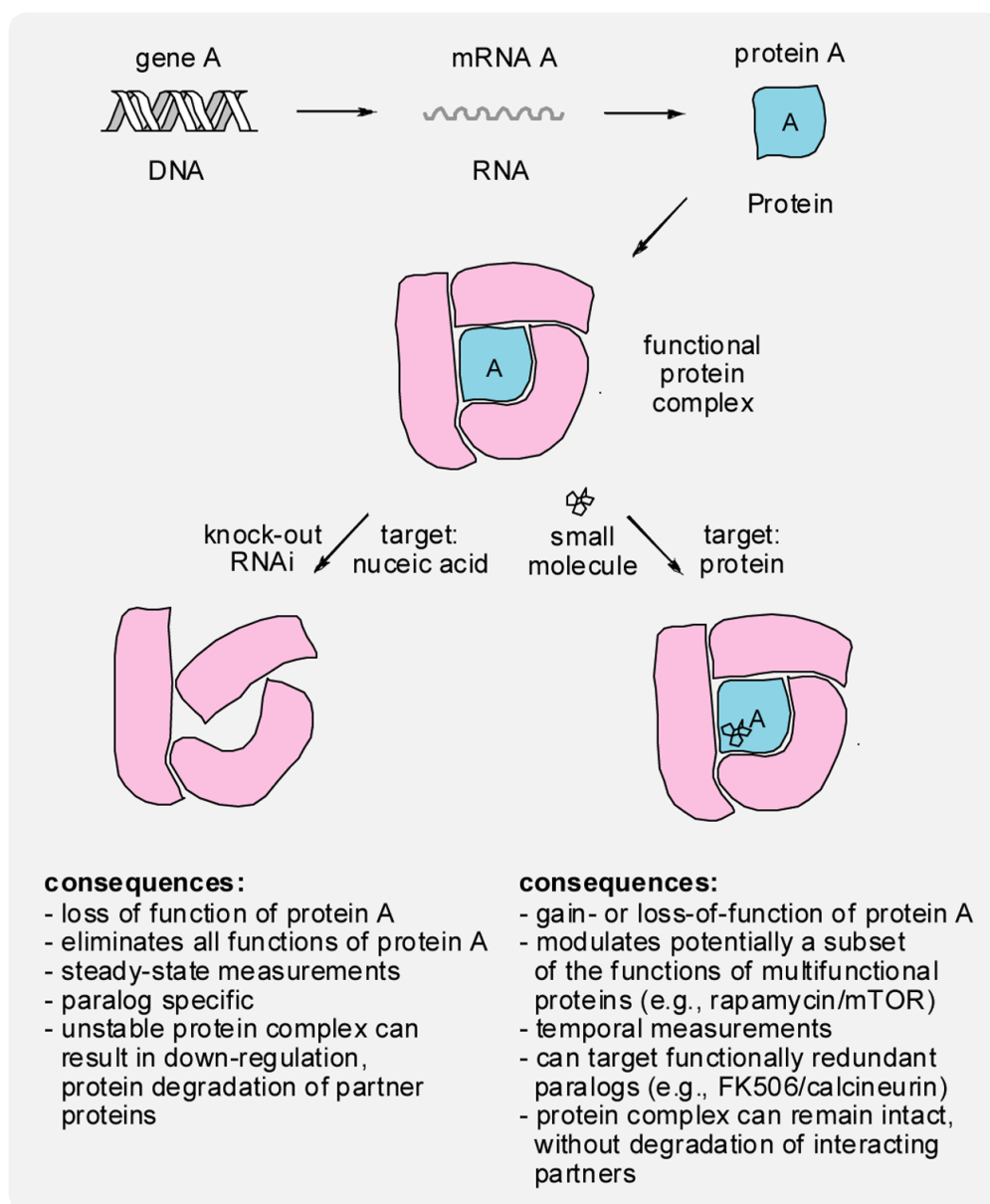
**Figure 11.**

Petasis 3-component reactions in the couple phase (coupling functional groups:  $\alpha$ -hydroxy aldehyde, amine, vinylboronic acid) were followed by reagent-controlled reactions leading to multiple skeletons in the pair phase (polar pairing functional groups: hydroxyl, amino, ester; non-polar pairing functional groups: alkene, alkyne, cyclopropane).



**Figure 12.**

Small molecules originating from different sources, including from synthetic pathways using the Build/Couple/Pair strategy described in this review, are being annotated by their performance in large numbers of common small-molecule screens. Chemical research is entering an important new phase where intuition and bias concerning the specialness of different types of compounds can, in the near future, be replaced by quantitative analyses.



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