

Chapter 2

Exploring Chemical Space: Recent Advances in Chemistry

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Abstract

Recent advances and concepts for exploring chemical space are highlighted in this chapter and show how the synthetic chemical world meets the demand of making large and relevant collection of new molecules for analyzing the biological world more closely.

Key words: Chemical space, Multicomponent reactions, Biology-oriented synthesis, Diversity-oriented synthesis, Divergent selectivity

1. Introduction

The terms chemical, biological, or pharmacological space have found widespread use in the last few years, more specifically in research programs involving high-throughput screening (HTS) (1–3); they encompass an even more global vision of the interconnectivity between chemistry and biology. Structural information obtained from chemical libraries in association with their performance in HTS bioassays can be qualitatively and quantitatively assessed according to descriptors, making possible data analysis and virtual screening (4). How can chemical space be defined in chemical biology or pharma arrays? Organic chemicals can be characterized by a wide range of descriptors, such as their physicochemical properties (molecular mass, lipophilicity, etc.) or their topological features (such as molecular structure, chirality, etc.). Lipinski's "rule of five" is a good example of how a chemical space can be defined in compliance with four physicochemical descriptors which are molecular weight, hydrogen-bond donors, hydrogen-bond acceptors, and lipophilicity (5). Lipinski's analysis of the World

Drug Index has revealed that an orally active drug has no more than one violation of the following criteria: molecular weight less than 500 Da, number of hydrogen-bond donors less than 5, number of hydrogen-bond acceptors less than 10, and log *P* less than 5. These descriptors taken as a whole and in accordance with the latter guidelines, define a chemical space for predicting orally active drugs. Another chemical space definition is illustrated by the representation of three-dimensional (3D) molecular shapes through descriptors. Recent advances in easily and reliably capturing topological data from molecules according to 3D shape descriptors have provided routine tools for synthetic chemists (6, 7). A recent example is the use of normalized principal moments of inertia (PMI) ratios that is becoming popular for analyzing molecular shape-based diversity (8). Biological targets, like biomacromolecules, are chiral and highly complex to ensure functional specificity. Indeed, recent analysis of structural complexity of libraries shows that collections of molecules with higher numbers of carbon sp^3 centers have a greater propensity for succeeding at various stages of the drug discovery process (9, 10). As sp^3 carbon is a major source of chirality and a source of molecular complexity and diversity in synthesis, carbon saturation can be used as a measurement of structural complexity. This is defined by the fraction sp^3 (F_{sp^3}), where $F_{sp^3} = (\text{number of } sp^3\text{-hybridized carbon} / \text{total carbon in the molecule})$ (9).

In terms of making collections of molecules for biological screening, synthetic chemists have to design a way of introducing and modulating descriptor features prior to synthesis. The choice of reactions also depends on whether the synthetic chemist works for academia or the pharma world as shown in Fig. 1. However, and more importantly, both institutions share preferential criteria for reactions which must be efficient, practical, robust, functionally tolerant (without the need for protecting groups), and combinatorial (for rapidly increasing diversity). The suitability of pathways for rapid and relevant analogue synthesis is essential for HTS assays. Whereas pharma company practice more often defines a focused and restricted chemical space prior to starting library synthesis (11, 12), a more exploratory paradigm aspires to cover a much broader chemical space; this may not be covered by existing HTS programs, and it is expected that new regions in chemical space will reveal new and potent biological targets (13–15).

This brief review places emphasis on (1) the use of stereoselective multicomponent reactions to access diverse and complex pure analogues in a powerful combinatorial way and (2) to review recent synthetic pathways and concepts devoted to exploring chemical space (both defined or expanded).

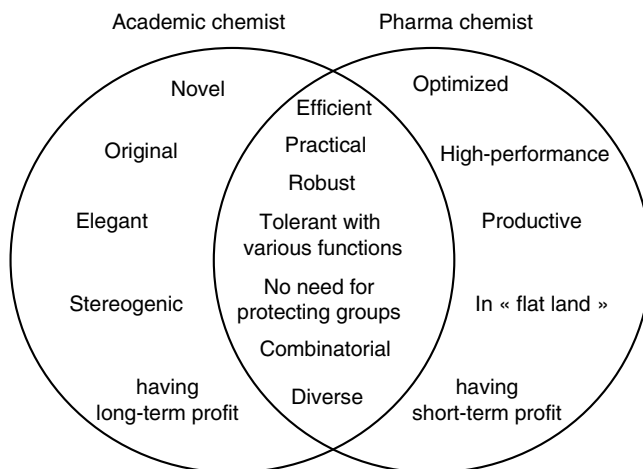


Fig. 1. Criteria required for a reaction to be selected in an array program from academic and pharma point of views.

2. Recent Advances in Stereoselective Multicomponent Reactions

Multicomponent reactions (MCRs) can be defined as three or more reactants that join together in a single synthetic step to form new products containing portions of all the components. These time and cost-effective reactions are powerful tools that are applicable to combinatorial and parallel syntheses in particular (16–20). However, MCRs for library synthesis are often selected to produce only high quantities of new compounds rather than high quality products (i.e., more diverse and chiral products in pure form). Thus, recent efforts have been made to offset this trend by building chirality into collections of new compounds with the help of efficient stereoselective MCRs (21).

2.1. Diastereoselective Multicomponent Reactions

Figure 2 represents four unique three-component reactions (3CR) (eq 1–4) in which one chiral center is set up on one reactant (symbolized by a dashed square) which can then induce a high diastereoselectivity. The first two reactions (eq 1 (22) and eq 2 (23)) are suitable for making chiral ethers **1** and **2** with *syn* configuration, whereas the last two reactions (eq 3 (24) and eq 4 (25, 26)) are designed to yield chiral amines displaying in either the *syn* **3** or *anti* **4** configuration.

2.2. Enantioselective Multicomponent Reactions

The preparation of optically pure collections of products by enantioselective MCR implies the action of efficient chiral catalysts. The Biginelli reaction that assembles aldehydes, urea/thio-urea, and enolizable carbonyls into dihydropyrimidinethiones **6** (Fig. 2, eq 5) has for a long time been selected as the MCR of

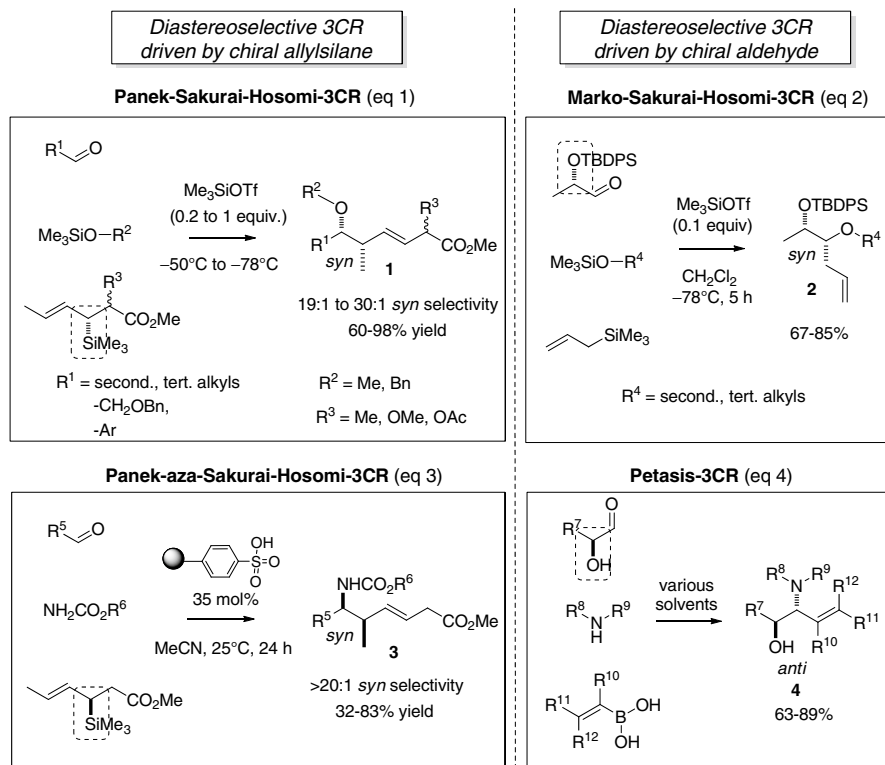


Fig. 2. Diastereoselective three-component reactions (3CR).

choice for gaining access to biologically active libraries (27). However, the control of stereochemistry in the formation of the new chiral center (symbolized by *) has been a long-standing challenge and has only recently been solved by the use of the Brønsted acid catalyst **5** having a broad tolerance of functional groups (eq 5) (28). Another milestone is the poor stereocontrol generally observed in MCR with isocyanide **7** (eq 6, see Fig. 3), a powerful functional group implicated in many MCR patterns (29). Interestingly, recent examples have shown that the enantioselective Passerini reaction can be efficiently catalyzed by chiral Lewis acids such as tridentate indan (pybox) Cu(II) **8** (eq 6) (30) or chiral salen-complex (31).

An enantioselective variant of Petasis reaction catalyzed by the chiral biphenol **10** was applied to the synthesis of optically active amines **11** (eq 7) (32). Enantioselective addition of alkyne catalyzed by the chiral copper-phosphine ligand in MCR offers a practical pathway to obtain homochiral propargylamines like **12** (eq 8) (33). The last decade has also witnessed the emergence of organocatalysts, derived from natural products like amino acids (with more emphasis

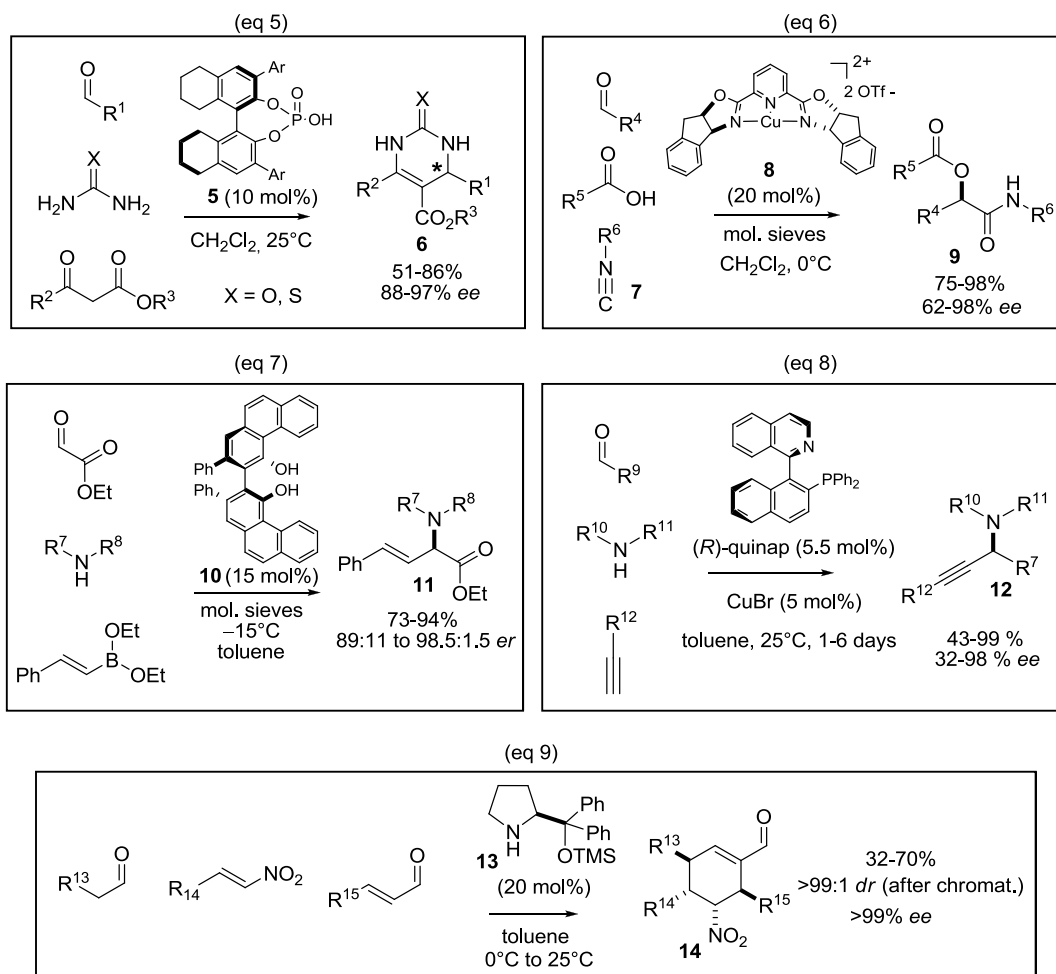


Fig. 3. Enantioselective MCRs.

on proline), as an impressive, though simple, tool for catalyzing various enantioselective MCRs (34, 35). Starting from three simple achiral reactants and in the presence of a catalytic amount of prolinol derivative **13**, a six-membered ring was created with the stereocontrol of four new chiral centers giving access to the optically pure product **14** (36).

3. Recent Concepts in the Exploration of Chemical Space

3.1. Focused Structural Diversity: Biology-Oriented Synthesis

Protein folds and natural product scaffolds are highly conserved in nature. From this observation, Waldmann proposes a concept termed biology-oriented synthesis (BIOS) (37–39). The idea rests on the hypothesis that proteins showing similar tertiary and quaternary structures (similar folding) should have the propensity

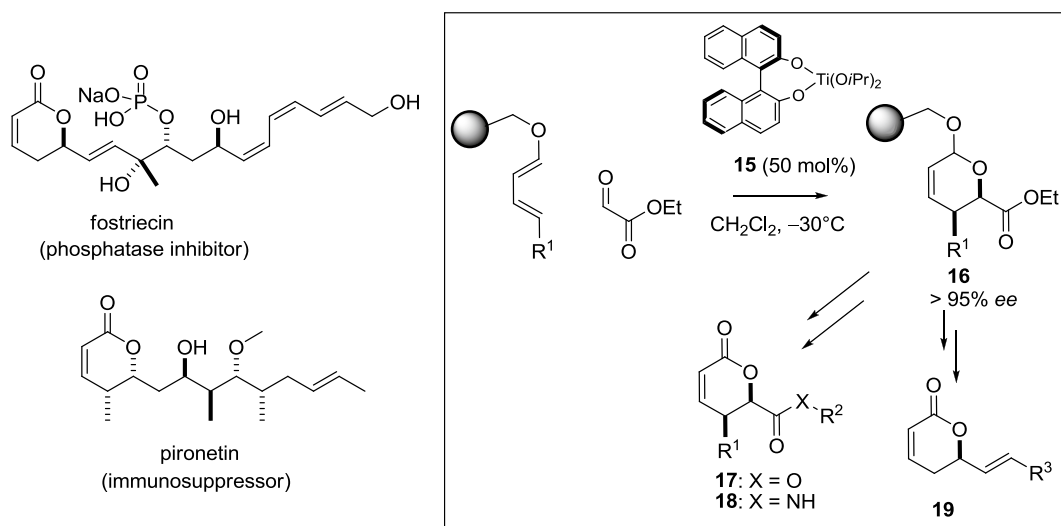


Fig. 4. Solid-phase synthesis of biologically relevant products inspired by natural α,β -unsaturated δ -lactones.

to bind natural products with similar scaffolds. Thus, synthetic chemists have to design pathways that connect natural scaffolds to each other according to a biologically prevalidated scaffold tree. In addition, natural product scaffolds are structurally complex and rich in chiral centers; they also cover chemical space that is distinct from most existing synthetic libraries (40, 41). Furthermore, nature provides efficient biomimetic reactions or pathways from which inspiration can be drawn to make compound collections (42).

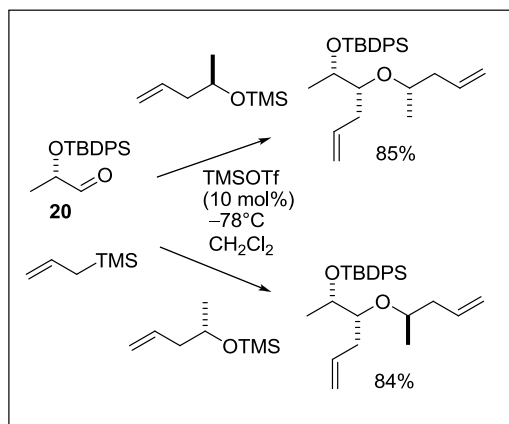
A α,β -unsaturated δ -lactone library, inspired by bioactive natural products such as fostricin and pironetin (Fig. 4), has been synthesized on a solid support in a highly enantioselective manner using the Lewis acid Ti-(*R*)-BINOL catalyst **15** (43). After subsequent transformations, a collection of 50 analogues containing structures **17**, **18**, and **19** were subjected to biological evaluation in phenotype-based screens. A few of them have been shown to be modulators of cell cycle progression and inhibitors of viral entry into cells.

3.2. Expanded Structural Diversity: Diversity-Oriented Synthesis

Rather than being directed toward a single and defined biological target, diversity-oriented synthesis (DOS) (13, 44–49) aims at making collections of structurally diverse molecules to gain access to wider, and often unexplored, chemical space. Thus, new strategies for library design deal with the challenge of maximizing stereochemical, appendage, and skeletal diversity within a minimal number of steps. These approaches make use of the concepts of *divergent selectivity* in either stereochemistry, reactivity, or by combination of both using short synthetic pathways.

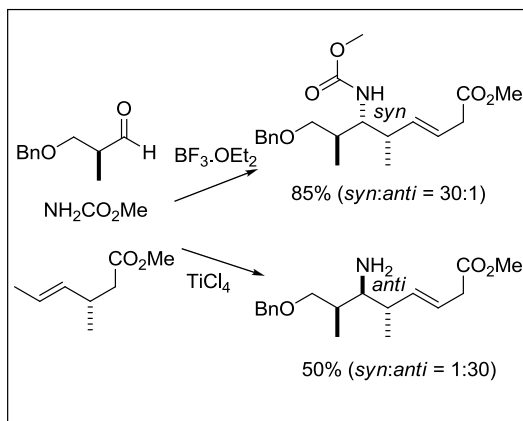
*Divergent diastereoselective 3CR
dominated by chiral aldehyde*

Sakurai-Hosomi-3CR (eq 10)

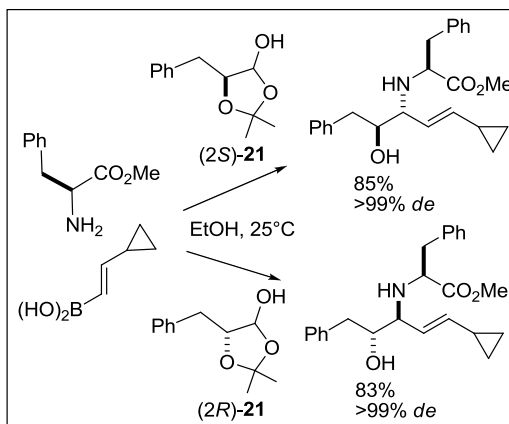


*Divergent diastereoselective 3CR
driven by reagent*

Aza-Sakurai-Hosomi-3CR (eq 12)



Petasis-3CR (eq 11)



*Divergent diastereoselective 3CR
driven by steric effect*

Roush "one-pot" reaction (eq 13)

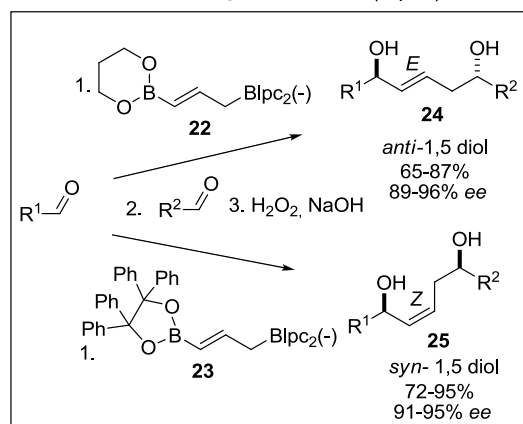


Fig. 5. Divergent diastereoselective three-components and "one-pot" reactions.

**3.2.1. Divergent
Diastereoselective
Multicomponent Reactions**

The difference between two diastereomers can be seen as the difference between the spatial orientation of their appendages. Divergent diastereoselective MCR is a straightforward method which gives rise to a unique diastereomer in each vessel. One strategy rests on the use of two chiral reactants where one chiral inductor dominates the other. Two examples are represented in Fig. 5 where the chiral aldehydes **20**, **(2S)-21**, and **(2R)-21** act as the dominant stereogenic inductor (eq 10 (**23**) and eq 11 (**50**)). Use of different reagents can also end up forming two distinct diastereoselectivities (eq 12 (**51**)). In Roush's "one-pot" double allylboration reaction

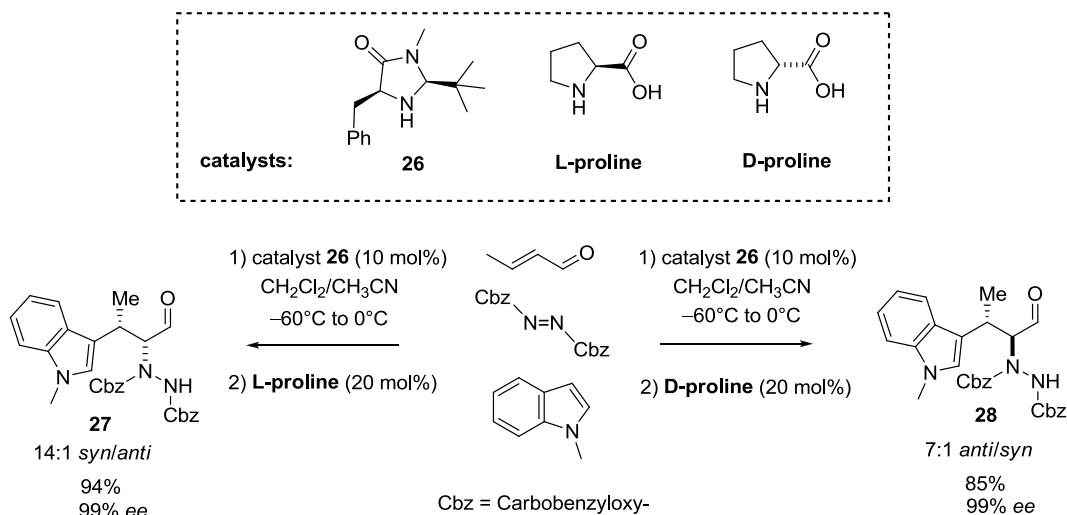


Fig. 6. Dual catalyst system in enantioselective and diastereodivergent 3CR.

sequence ([52](#)), the difference in steric hindrance between boronate esters **22** and **23** results in orienting the stereochemistry to form either (*E*)-1,5-*anti* diols **24** or (*Z*)-1,5-*syn* diols **25**, respectively.

3.2.2. Enantioselective Diastereodivergent Multicomponent Reactions

Starting from achiral reactants, dual and highly enantioselective catalyst system can govern the overall stereodivergent process. Ingenious examples in the field of organocatalysis have been reported ([53](#)). For instance, the combination of catalyst **26** and homochiral proline (Fig. 6) led to an optically pure diastereomeric product, either **27** and **28**, depending upon whether L or D proline was used ([54](#)).

3.2.3. The Build/Pair Strategy

The diversity-generating process can also be conducted over two steps with a Build/Pair strategy. Ideally, the first step would involve a MCR which assembles and installs (the Build) combinations of fragments having all the diversity and functionality required for performing divergent post-transformations (the Pair) ([55](#)). The Ugi-four-component reaction (Ugi-4CR) is a powerful build process involving an isocyanide group **29** (Fig. 7) as key reactant which forms peptide-like products such as **30**, **31**, **32**, and **33**. Subsequent conversions into novel skeletons are then possible to give diverse new scaffolds such as **34**, **35**, **36**, and **37**. Identification of lead compounds as antagonists of protein Bcl-x_L has been reported using such a Build/Pair approach ([56](#)).

3.2.4. The Build/Couple/ Pair Strategy

After the build process the diversity potential can be enriched by adding a new fragment with functionalities which offer new pairing combinations with existing functional groups (Couple). An illustration of this Build/Couple/Pair strategy is shown in Fig. 8 ([57](#)).

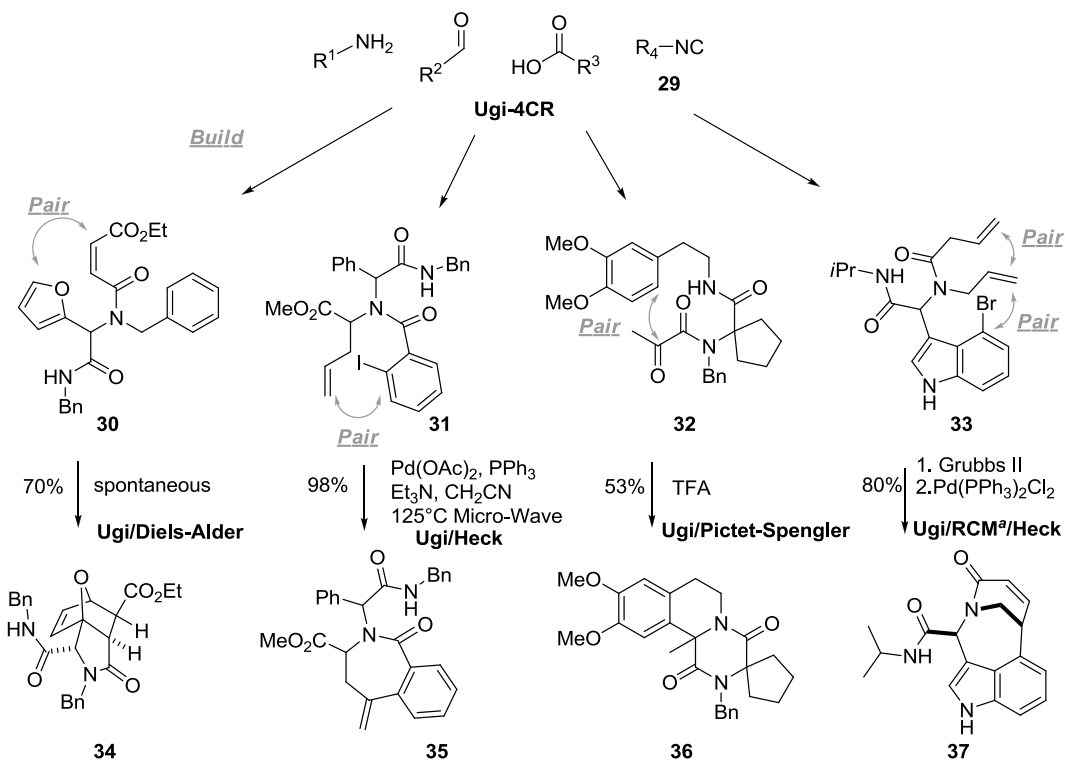


Fig. 7. Build/Pair strategy with Ugi-four-components reactions (Ugi-4CR) and their post-transformations. *RCM*^a ring closure metathesis.

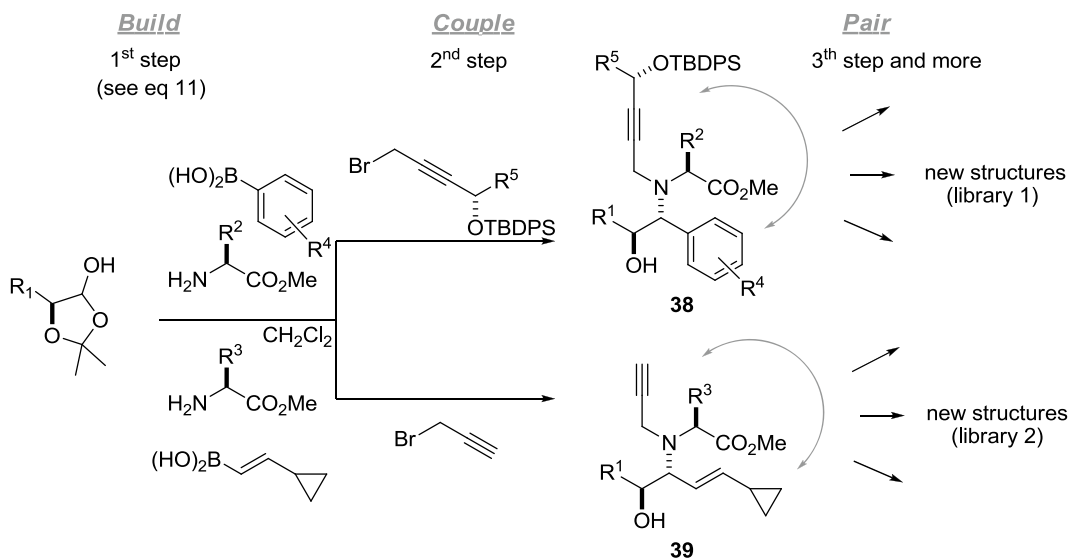


Fig. 8. Build/Couple/Pair strategy to expand 3D shape diversity.

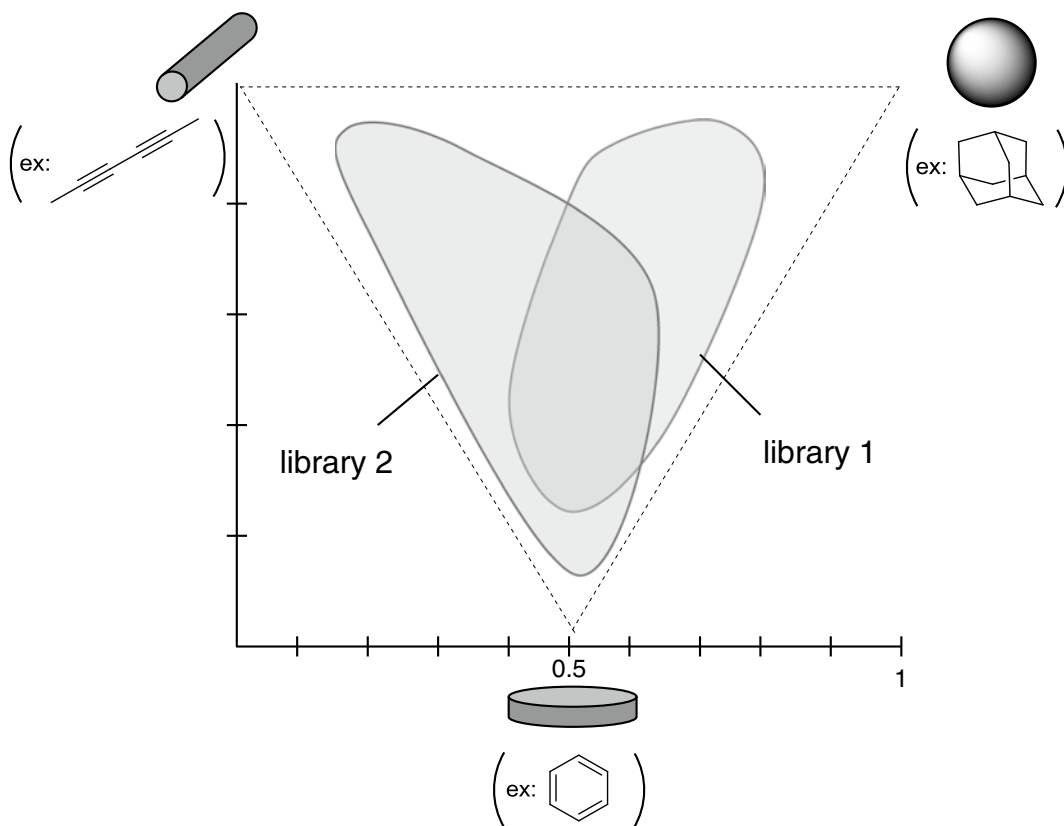


Fig. 9. Molecular shape analysis of libraries 1 and 2 by normalized principal moments of inertia (PMI) ratio plots.

Interestingly, the description of shape using normalized PMI ratios (Fig. 9) reveals that the collection of molecules issued from **38** (library 1) populates a structural region between sphere and disc shaped, whereas compounds issued from **39** (library 2) are more located in rod and disc-like regions. In this example, DOS strategy has succeeded in covering a large chemical space using no more than 73 compounds, with only five steps required for the longest synthetic pathways.

An aldol-based Build/Couple/Pair strategy has recently been applied for the discovery of new histone deacetylase inhibitors (58).

4. Conclusion

Targeting defined or expanded chemical space has inspired chemical and conceptual innovations that facilitate and forge close links between chemistry and biology. This cross disciplinary approach strives to reveal hidden connections between drugs (chemical space defined by small molecules) and diseases (space defined by biological targets) and will certainly provide even more promising discoveries in near future.

References

1. Dobson CM (2004) Chemical space and biology. *Nature* 432:824–828
2. Lipinski C, Hopkins A (2004) Navigating chemical space for biology and medicine. *Nature* 432:855–861
3. Paolini GV, Shapland RHB, van Hoorn WP et al (2006) Global mapping of pharmacological space. *Nat Biotechnol* 24:805–815
4. Reymond J-L, van Deursen R, Blum LC et al (2010) Chemical space as a source for new drugs. *Med Chem Comm* 1:30–38
5. Lipinski CA, Lombardo F, Dominy BW et al (1997) Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv Drug Deliv Rev* 23:3–25
6. Putta S, Beroza P (2007) Shape of things: computer modelling of molecular shape in drug discovery. *Curr Top Med Chem* 7:1514–1524
7. Nicholls A, McGaughey GB, Sheridan RP et al (2010) Molecular Shape and Medicinal Chemistry: A Perspective. *J Med Chem* 53:3862–3886
8. Sauer WHB, Schwarz MK (2003) Molecular Shape Diversity of Combinatorial Libraries: A Prerequisite for Broad Bioactivity. *J Chem Inf Comput Sci* 43:987–1003
9. Lovering F, Bikker J, Humblet C (2009) Escape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success. *J Med Chem* 52:6752–6756
10. Clemons PA, Bodycombe NE, Carrinski HA et al (2010) Small molecules of different origins have distinct distributions of structural complexity that correlate with protein-binding profiles. *Proc Natl Acad Sci USA* 107:18787–18792
11. Cooper TWJ, Campbell IB, Macdonald, SJF (2010) Factors Determining the Selection of Organic Reactions by Medicinal Chemists and the Use of These Reactions in Arrays (Small Focused Libraries). *Angew Chem Int Ed* 49: 8082–8091
12. Hopkins AL, Bickerton GR (2010) Drug discovery. Know your chemical space. *Nat Chem Biol* 6:482–483
13. Burke MD, Schreiber SL (2004) A planning strategy for diversity-oriented synthesis. *Angew Chem Int Ed* 43:46–58
14. Jacoby E, Mozzarelli A (2009) Chemogenomic strategies to expand the bioactive chemical space. *Curr Med Chem* 16:4374–4381
15. Dandapani S, Marcaurelle LA (2010) Grand Challenge Commentary: Accessing new chemical space for ‘undruggable’ targets. *Nat Chem Biol* 6:861–863
16. Pulici M, Cervi G, Martina K et al (2003) Use of multicomponent, domino, and other one-pot syntheses on solid phase: Powerful tools for the generation of libraries of diverse and complex compounds. *Comb Chem High Throughput Screen* 6:693–727
17. Ulaczyk-Lesanko A, Hall DG (2005) Wanted: New multicomponent reactions for generating libraries of polycyclic natural products. *Curr Opin Chem Biol* 9:266–276
18. Sunderhaus JD, Martin SF (2009) Applications of multicomponent reactions to the synthesis of diverse heterocyclic scaffolds. *Chem Eur J* 15:1300–1308
19. Toure BB, Hall DG (2009) Natural Product Synthesis Using Multicomponent Reaction Strategies. *Chem Rev* 109:4439–4486
20. Biggs-Houck JE, Younai A, Shaw JT (2010) Recent advances in multicomponent reactions for diversity-oriented synthesis. *Curr Opin Chem Biol* 14:371–382
21. Ramon DJ, Yus M (2005) Asymmetric multicomponent reactions (AMCRs): The new frontier, *Angew Chem Int Ed* 44:1602–1634
22. Panek JS, Yang M, Xu F (1992) Diastereoselective additions of chiral (E)-crotylsilanes to in situ generated oxonium ions: a direct asymmetric synthesis of functionalized homoallylic ethers. *J Org Chem* 57:5790–5792
23. Pospisil J, Kumamoto T, Marko IE (2006) Highly diastereoselective silyl-modified sakurai multicomponent reaction. *Angew Chem Int Ed* 45:3357–3360
24. Lipomi DJ, Panek JS (2005) Three-Component, Room Temperature Crotylation Catalyzed by Solid-Supported Bronsted Acid: Enantioselective Synthesis of Homoallylic Carbamates. *Org Lett* 7:4701–4704
25. Petasis NA, Zavialov IA (1998) Highly Stereocontrolled One-Step Synthesis of anti-beta -Amino Alcohols from Organoboronic Acids, Amines, and alpha -Hydroxy Aldehydes. *J Am Chem Soc* 120:11798–11799
26. Candeias NR, Montalbano F, Cal PMSD et al (2010) Boronic Acids and Esters in the Petasis-Borono Mannich Multicomponent Reaction. *Chem Rev* 110:6169–6193
27. Kappe CO (2000) Recent Advances in the Biginelli Dihydropyrimidine Synthesis. New Tricks from an Old Dog. *Acc Chem Res* 33:879–888
28. Chen X-H, Xu X-Y, Liu H et al (2006) Highly Enantioselective Organocatalytic Biginelli Reaction. *J Am Chem Soc* 128:14802–14803

29. Doemling A (2006) Recent Developments in Isocyanide Based Multicomponent Reactions in Applied Chemistry. *Chem Rev* 106:17–89
30. Andreana PR, Liu CC, Schreiber SL (2004) Stereochemical Control of the Passerini Reaction. *Org Lett* 6:4231–4233
31. Wang S-X, Wang M-X, Wang D-X et al (2008) Catalytic enantioselective Passerini three-component reaction. *Angew Chem Int Ed* 47:388–391
32. Lou S, Schaus SE (2008) Asymmetric Petasis Reactions Catalyzed by Chiral Biphenols. *J Am Chem Soc* 130:6922–6923
33. Gommermann N, Koradin C, Polborn K et al (2003) Enantioselective, copper(I)-catalyzed three-component reaction for the preparation of propargylamines. *Angew Chem Int Ed* 42:5763–5766
34. Carlone A, Cabrera S, Marigo M et al (2007) A new approach for an organocatalytic multi-component domino asymmetric reaction. *Angew Chem Int Ed* 46:1101–1104
35. Grondal C, Jeanty M, Enders D (2010) Organocatalytic cascade reactions as a new tool in total synthesis. *Nat Chem* 2:167–178
36. Enders D, Huettl MRM, Grondal C et al (2006) Control of four stereocenters in a triple cascade organocatalytic reaction. *Nature* 441:861–863
37. Bon RS, Waldmann H (2010) Bioactivity-Guided Navigation of Chemical Space. *Acc Chem Res* 43:1103–1114
38. Koch MA, Schuffenhauer A, Scheck M et al (2005) Charting biologically relevant chemical space: A structural classification of natural products (SCONP). *Proc Natl Acad Sci USA* 102:17272–17277
39. Schuffenhauer A, Ertl P, Roggo S et al (2007) The Scaffold Tree - Visualization of the Scaffold Universe by Hierarchical Scaffold Classification. *J Chem Inf Model* 47:47–58
40. Feher M, Schmidt JM (2003) Property distributions: differences between drugs, natural products and molecules from combinatorial chemistry. *J Chem Inf Comput Sci* 43:218–227
41. Reayi A, Arya P (2005) Natural product-like chemical space: search for chemical dissectors of macromolecular interactions. *Curr Opin Chem Biol* 9:240–247
42. Kumar K, Waldmann H (2009) Synthesis of natural product inspired compound collections. *Angew Chem Int Ed* 48:3224–3242
43. Lessmann T, Leuenberger MG, Menninger S et al (2007) Natural Product-Derived Modulators of Cell Cycle Progression and Viral Entry by Enantioselective Oxa Diels-Alder Reactions on the Solid Phase. *Chem Biol* 14:443–451
44. Antonchick AP, Gerding-Reimers C, Catarinella M et al (2010) Highly enantioselective synthesis and cellular evaluation of spirooxindoles inspired by natural products. *Nat Chem* 2:735–740
45. Tan DS (2005) Diversity-oriented synthesis: exploring the intersections between chemistry and biology. *Nat Chem Biol* 1:74–84
46. Thomas GL, Wyatt EE, Spring DR (2006) Enriching chemical space with diversity-oriented synthesis. *Curr Opin Drug Discov Develop* 9:700–712
47. Peuchmaur M, Wong Y-S (2008) Expanding the chemical space in practice: diversity-oriented synthesis. *Comb Chem High Throughput Screen* 11:587–601
48. Dandapani S, Marcaurelle LA (2010) Current strategies for diversity-oriented synthesis. *Curr Opin Chem Biol* 14:362–370
49. Biggs-Houck JE, Younai A, Shaw JT (2010) Recent advances in multicomponent reactions for diversity-oriented synthesis. *Curr Opin Chem Biol* 14:371–382
50. Kumagai N, Muncipinto G, Schreiber SL (2006) Short synthesis of skeletally and stereochemically diverse small molecules by coupling Petasis condensation reactions to cyclization reactions. *Angew Chem Int Ed* 45:3635–3638
51. Schaus JV, Jain N, Panek JS (2000) Asymmetric synthesis of homoallylic amines and functionalized pyrrolidines via direct amino-crotylation of in situ generated imines. *Tetrahedron* 56:10263–10274
52. Flamme EM, Roush WR (2002) Enantioselective Synthesis of 1,5-anti- and 1,5-syn-Diols Using a Highly Diastereoselective One-Pot Double Allylboration Reaction Sequence. *J Am Chem Soc* 124:13644–13645
53. Westermann B, Ayaz M, van Berkel SS (2010) Enantiodivergent Organocascade Reactions. *Angew Chem Int Ed* 49:846–849
54. Simmons B, Walji AM, MacMillan DWC (2009) Cycle-Specific Organocascade Catalysis: Application to Olefin Hydroamination, Hydro-oxidation, and Amino-oxidation, and to Natural Product Synthesis. *Angew Chem Int Ed* 48:4349–4353
55. Sunderhaus JD, Martin SF (2009) Applications of multicomponent reactions to the synthesis of diverse heterocyclic scaffolds. *Chem Eur J* 15:1300–1308
56. Di Micco S, Vitale R, Pellicchia M et al (2009) Identification of Lead Compounds as Antagonists of Protein Bcl-xL with a Diversity-

- Oriented Multidisciplinary Approach. *J Med Chem* 52:7856–7867
57. Muncipinto G, Kaya T, Wilson JA et al (2010) Expanding Stereochemical and Skeletal Diversity Using Petasis Reactions and 1,3-Dipolar Cycloadditions. *Org Lett* 12:5230–5233
58. Marcaurelle LA, Comer E, Dandapani S et al (2010) An Aldol-Based Build/Couple/Pair Strategy for the Synthesis of Medium- and Large-Sized Rings: Discovery of Macrocyclic Histone Deacetylase Inhibitors. *J Am Chem Soc* 132:16962–16976

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