
Frontier of Chemistry
Exploring Chemical Space
Shuli Mao
04/12/2008

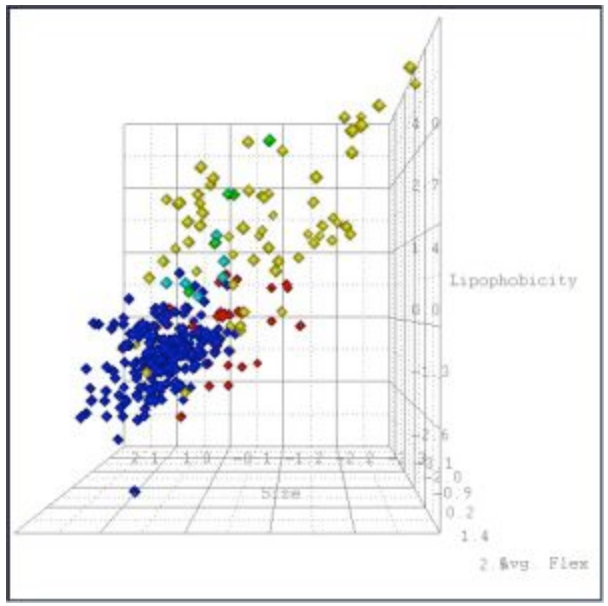
What is chemical space?

Chemical space is the space spanned by all possible (i.e. energetically stable) stoichiometrical combinations of electrons and atomic nuclei and topologies (isomers) in molecules and compounds in general.

-----wilkipedia

Chemical space is defined as the total descriptor space that encompasses all the small carbon-based molecules that could in principle be created. (Descriptors: molecular mass, liphophilicity and topological features, etc.)

-----Dobson, C. M. **Chemical space and biology** *Nature* **2004**, *432*, 824.



Why we need to explore chemical space?

The estimated number of small carbon-based compounds is on the order of 10^{60}. However, only a minute fraction of this chemical space has been explored. Given the vastness of chemical space, we need to explore chemical space efficiently to find biologically relevant chemical space (space in which biologically active compounds reside).

Dobson, C. M. **Chemical space and biology** *Nature* **2004**, *432*, 824.

- To understand biological systems especially in unknown area

- To develop potential drugs

From 1994 to 2001, only 22 drugs that modulate new targets were approved. So far, less than 500 human proteins have been targeted by current drugs, which is a small portion of human proteins.

Lipinski, C; Hopkins, A. **Navigating chemical space for biology and medicine** *Nature* **2004**, *432*, 855.

How to explore chemical space?

Three approaches:

(A) Target-Oriented Synthesis

(B) Focused Synthesis (Medicinal Chemistry/ Combinatorial Chemistry)

(C) Diversity-Oriented Synthesis

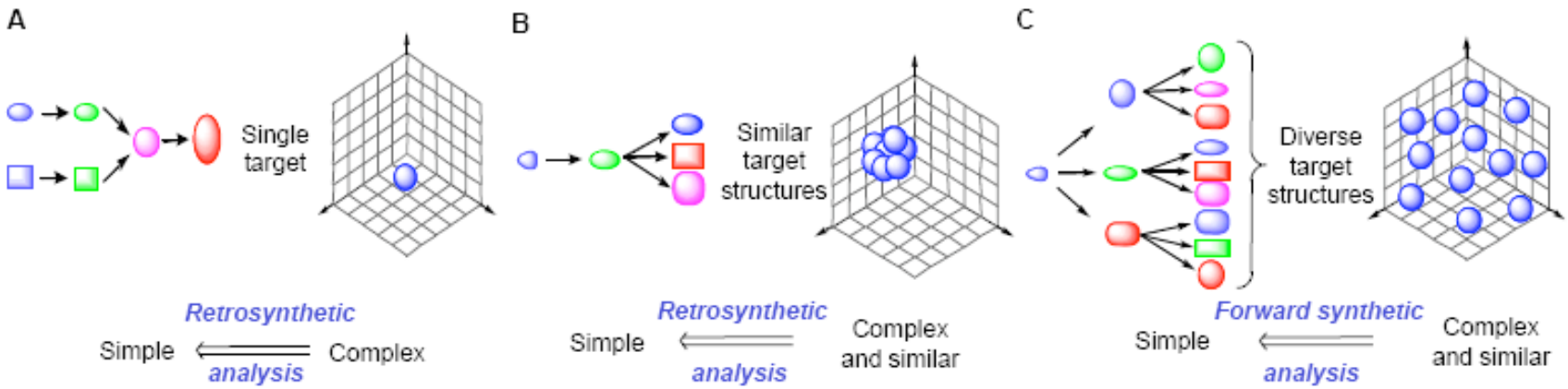
Burke, M. D.; Schreiber, S. L. **A planning strategy for diversity-oriented synthesis** *Angew. Chem. Int. Ed.* **2004**, *43*, 46.

Comparison of Three Approaches

(A) Target-Oriented Synthesis

(B) Focused Synthesis (Medicinal Chemistry/ Combinatorial Chemistry)

(C) Diversity-Oriented Synthesis



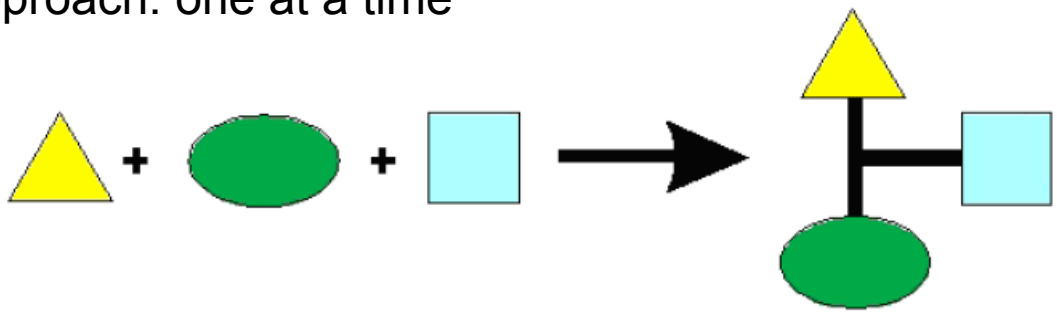
Thomas, G. L.; Wyatt, E. E.; Spring, D. R. **Enriching chemical space with diversity-oriented synthesis** *Curr Opin Drug Dis Dev* **2006**, *9*, 700.

Combinatorial Chemistry

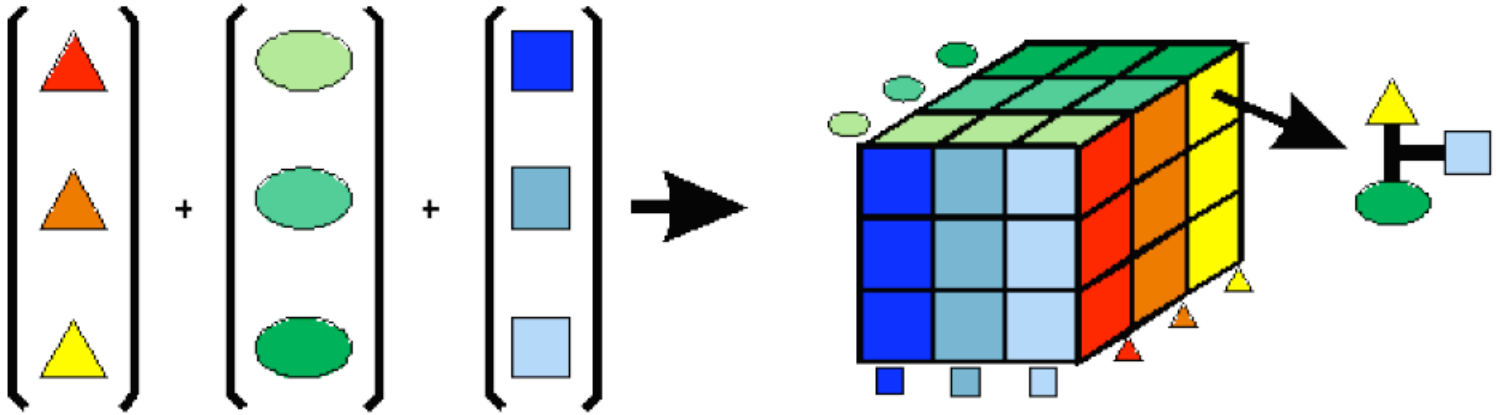
The rapid synthesis and screening of a large number of different compounds at the same time - instead of one-at-a-time-manner- to identify agents with desired functional properties

Classical VS. Combinatorial Approach

Classical approach: one at a time



Combinatorial approach: many at a time



www.aae.enscm.fr/anciens/94-mc/combchem.htm

Synthetic Strategies towards Combinatorial Libraries

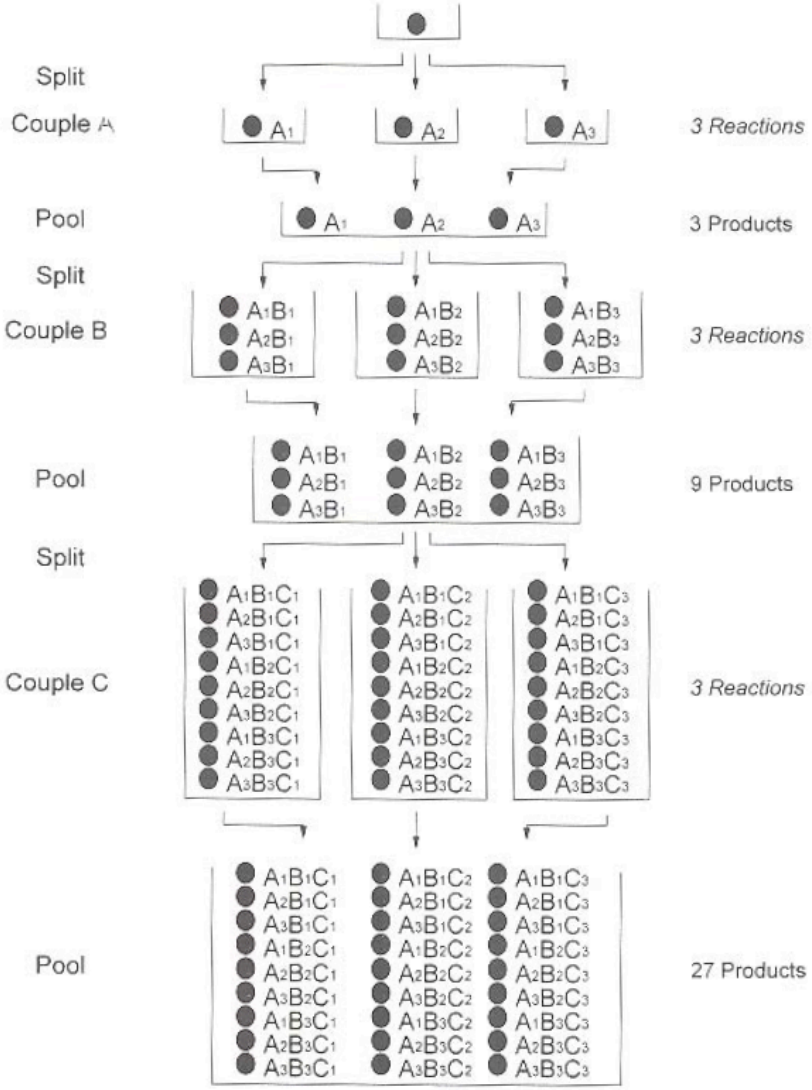
(A) Split-pool synthesis

Furka and co-workers pioneered the split-pool synthesis method for the synthesis of large peptide libraries in 1988; this approach is termed divide, couple and recombine synthesis by other workers

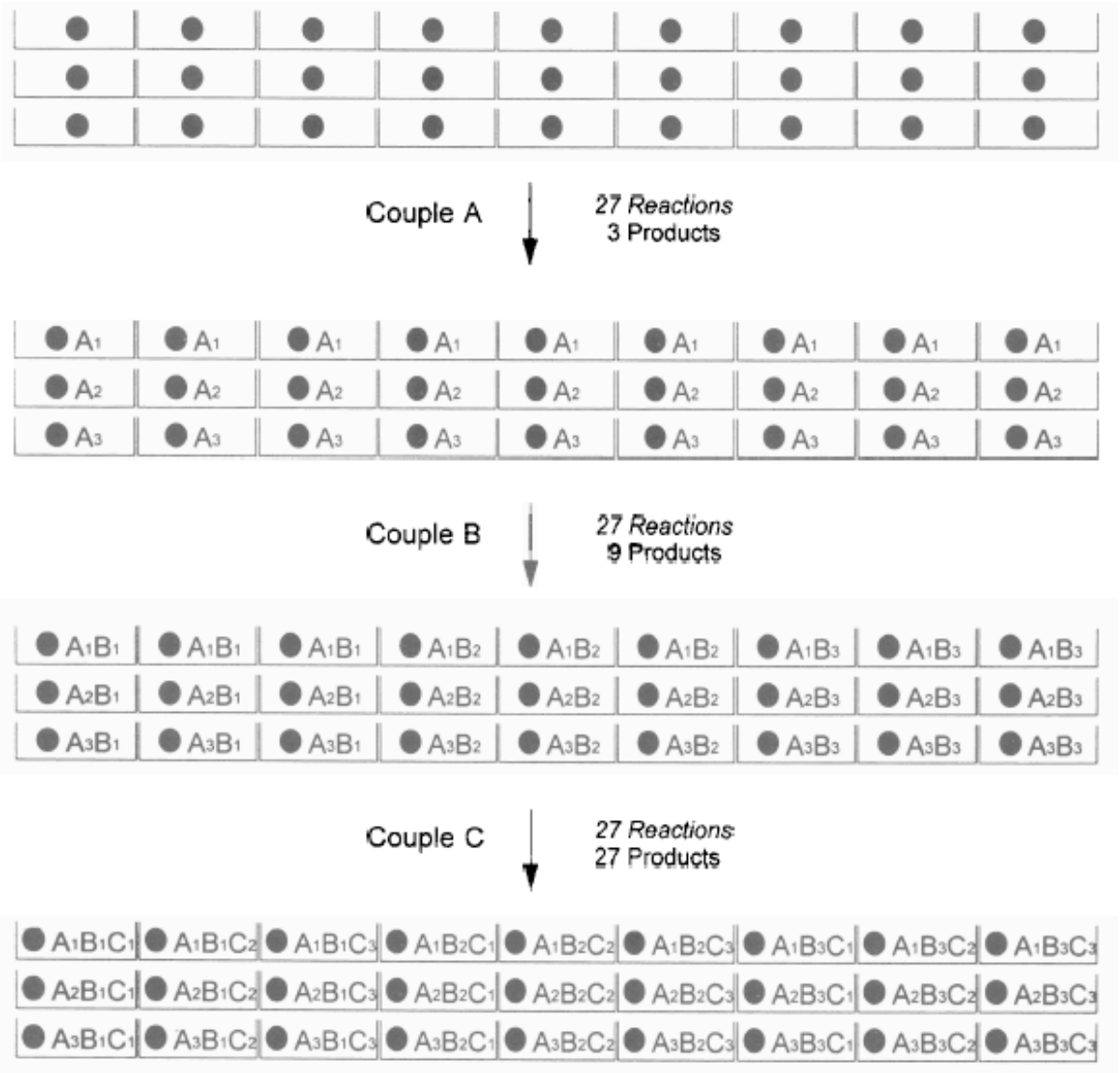
(B) Parallel synthesis

Jung, G. **Combinatorial Chemistry:synthesis, analysis, screening; 1999**

Split-Pool Synthesis (One-Bead-One-Compound)



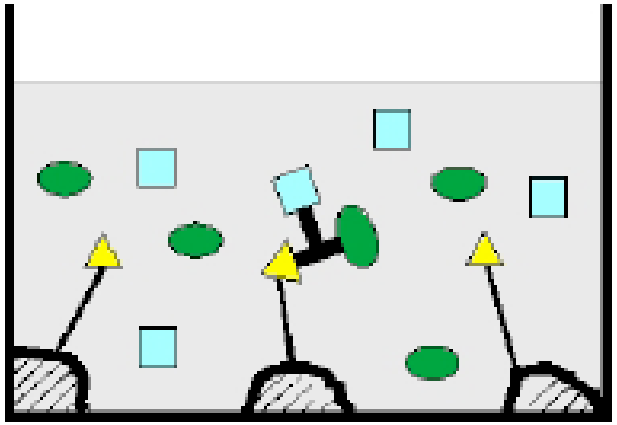
Parallel Synthesis (One-Vessel-One-Compound)



Synthetic Methodology for Organic Library Construction

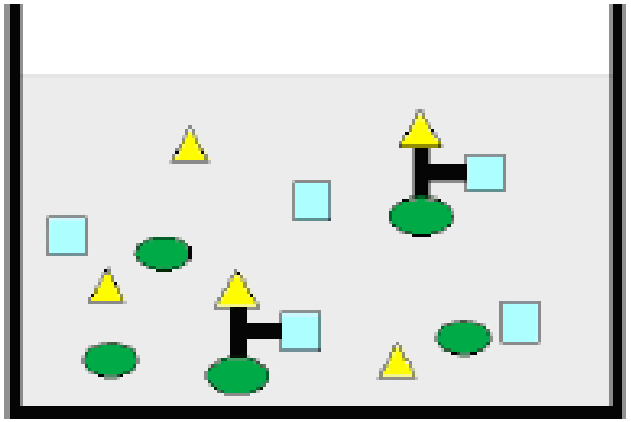
- Solid-Phase Synthesis
- Solution-Phase Synthesis

Solid-phase synthesis



Heterogeneous

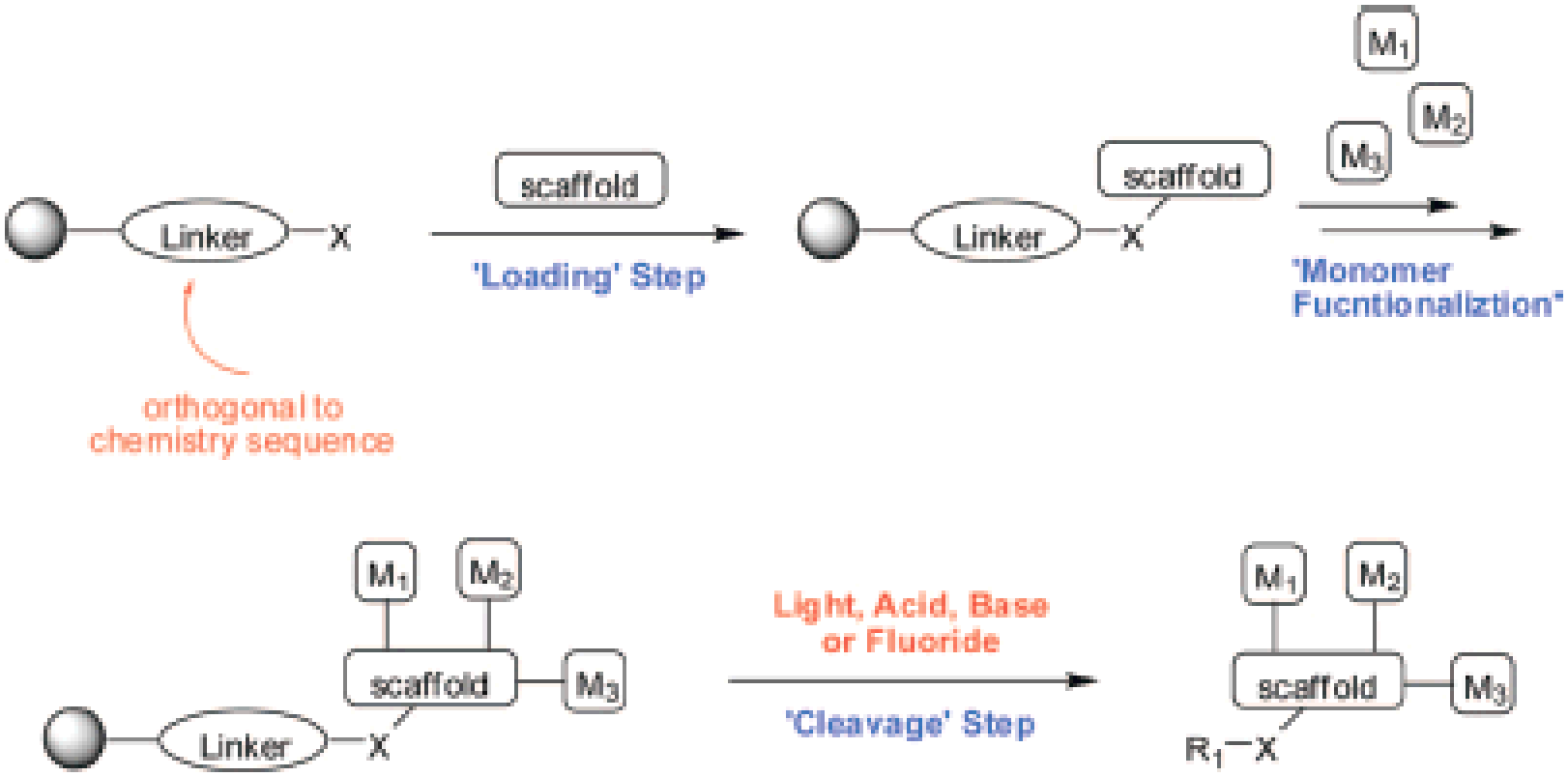
Solution-phase synthesis



Homogeneous

Solid-Phase Synthesis

Compound under construction is covalently attached to a swollen insoluble solid support (usually a resin bead) by a linker that can be cleaved under specific conditions with an appropriate reagent to give the target compound in solution later on.



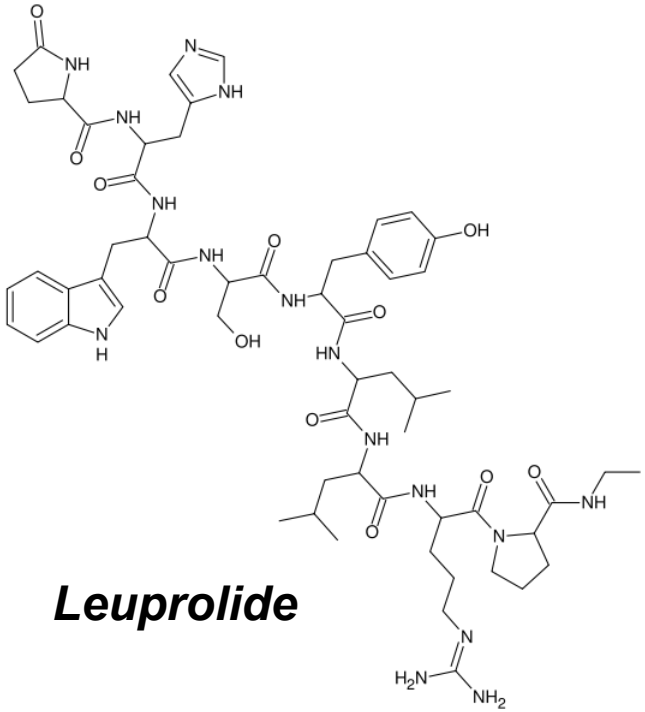
Kennedy, J. P.; Williams, L.; Bridges, T. M.; Daniels, R. N.; Weaver, D.; Lindsley, C. W. **Application of combinatorial science on modern drug discovery** *J. Com. Chem.* **2008**, *ASAP.*

Solid-Phase Peptide Synthesis (SPPS)

"Merrifield's publication of SPPS method completely revolutionized the field, both from the perspective of accelerating research and discovery, and also because of its now widespread use for the manufacture of peptides for use as active pharmaceutical ingredients (APIs)."

Peptide APIs: yearly sales in excess of **$12 billion** with a growth rate of **~4%** and majority **(>50%)** are prepared via SPPS

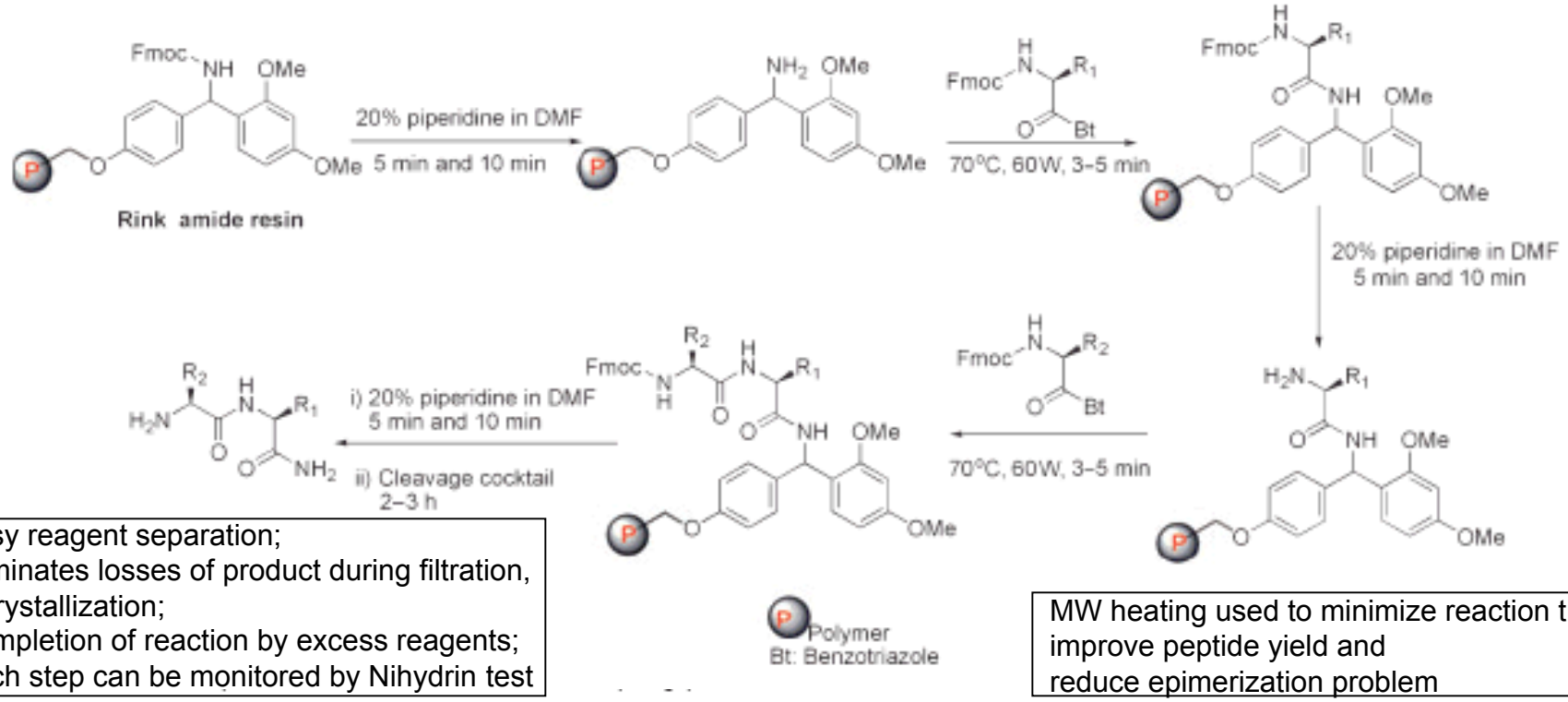
Leuprolide: a blockbuster drug with worldwide sales in excess of **$2 billion/year** is prepared via SPPS



Leuprolide

Verlander, M. **Industrial applications of solid-phase peptide synthesis-a status report** *Int. J. Pep. Res. Ther.* **2007**, *13*, 75.

Microwave-Assisted SPPS



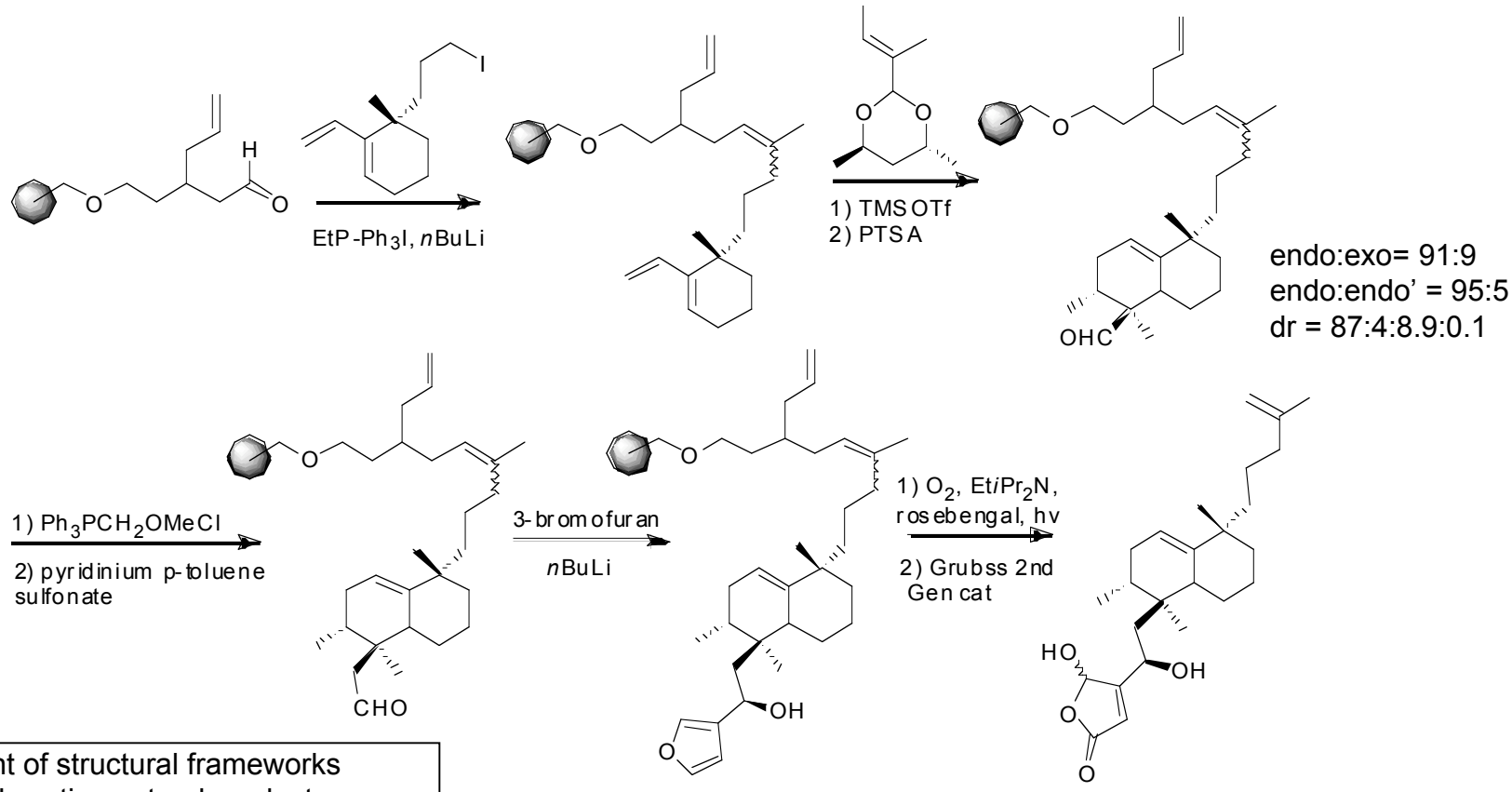
Easy reagent separation;
Eliminates losses of product during filtration, recrystallization;
Completion of reaction by excess reagents;
Each step can be monitored by Nihydrin test

MW heating used to minimize reaction time, improve peptide yield and reduce epimerization problem

	Conventional SPPS	Automated SPPS	Microwave-assisted SPPS	Our present SPPS method
Reagents used	PyBOP, PyBroP, HOBt, DIC, DCC, HATU, HBTU	PyBOP, PyBroP, HOBt, DIC, DCC, HATU, HBTU	PyBOP, PyBroP, HOBt, DIC, DCC, HATU, HBTU	*N*-Fmoc-protected(α-aminoacyl)benzotriazoles **2a–g**
Coupling time (min)	45–360[10–12]	60[13]	1.5[a]–60[14–17]	3–15
Reagent excess	3–10 equivalents	3–16 equivalents	3–16 equivalents	5 equivalents
Moisture sensitivity	Sensitive	Sensitive	Sensitive	Not sensitive

Katritzky, A. R. **Microwave-assisted solid-phase peptide synthesis utilizing N-Fmoc-protected (α-aminoacyl)benzotriazoles** *Chem. Bio. Drug. Des.* **2007**, *70*, 465.

Solid-Phase Synthesis of Dysidiolide Analogs as Phosphastase Inhibitors

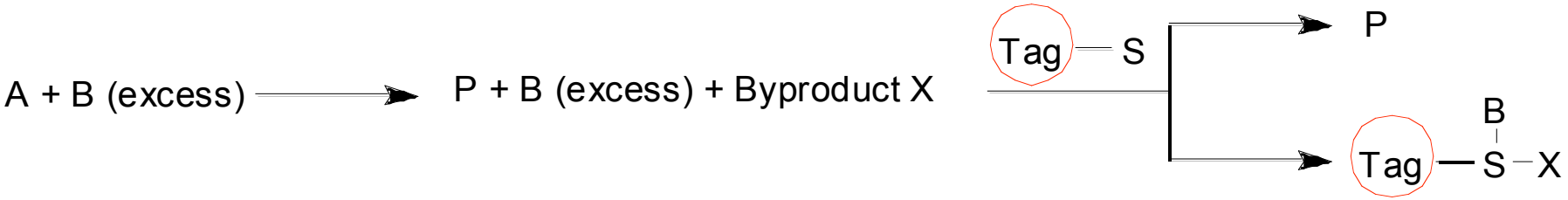


Employment of structural frameworks of biologically active natural products as a guilding principle for library development

Overall yield: 14% (11 steps);
average yield: 84% per step

Waldmann et al **Natural products are biologically validated starting points in structure space for compound library development: solid-phase synthesis of dysidiolide-derived phosphatase inhibitors** *Angew. Chem. Int. Ed.* **2002**, *41*, 307.

Solution-Phase Synthesis



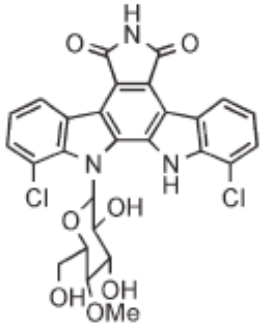
Tag	Method of Phase Separation
Polymer	Filtration
Ionizable group	pH adjusted LLE or ion-exchange SPE
Fluorous tag	3-Phase LLE (heavy) or fluorous SPE (light)

Scavenging reagents were used to form either covalent or ionic bond with excess reagents or reaction byproduct;
In general terms, scavenging can be considered a 'phase-switching" technique, wherein a chemoselective reaction
Is employed to switch the phase of one product relative to another by virtue of a "tag" attached to the scavenging reagent.

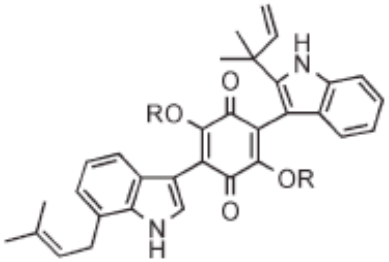
Kennedy, J. P.; Williams, L.; Bridges, T. M.; Daniels, R. N.; Weaver, D.; Lindsley, C. W. **Application of combinatorial science on modern drug discovery** *J. Com. Chem.* **2008**, *ASAP.*

Solution-Phase Synthesis Using Fluorous Tag

Antitumor

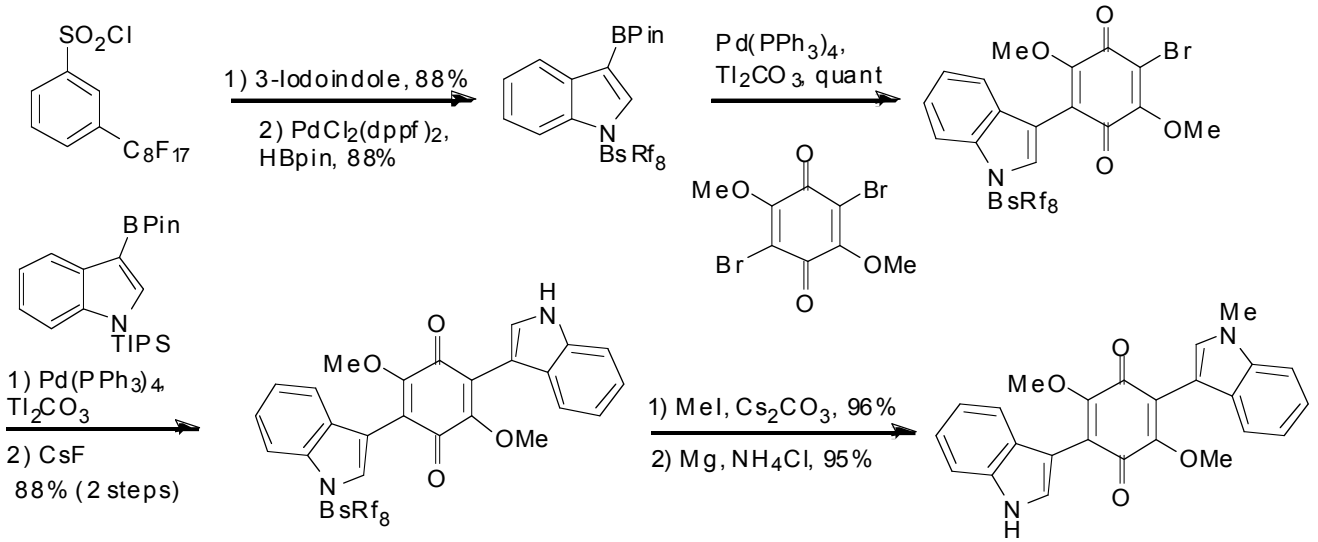


Rebeccamycin



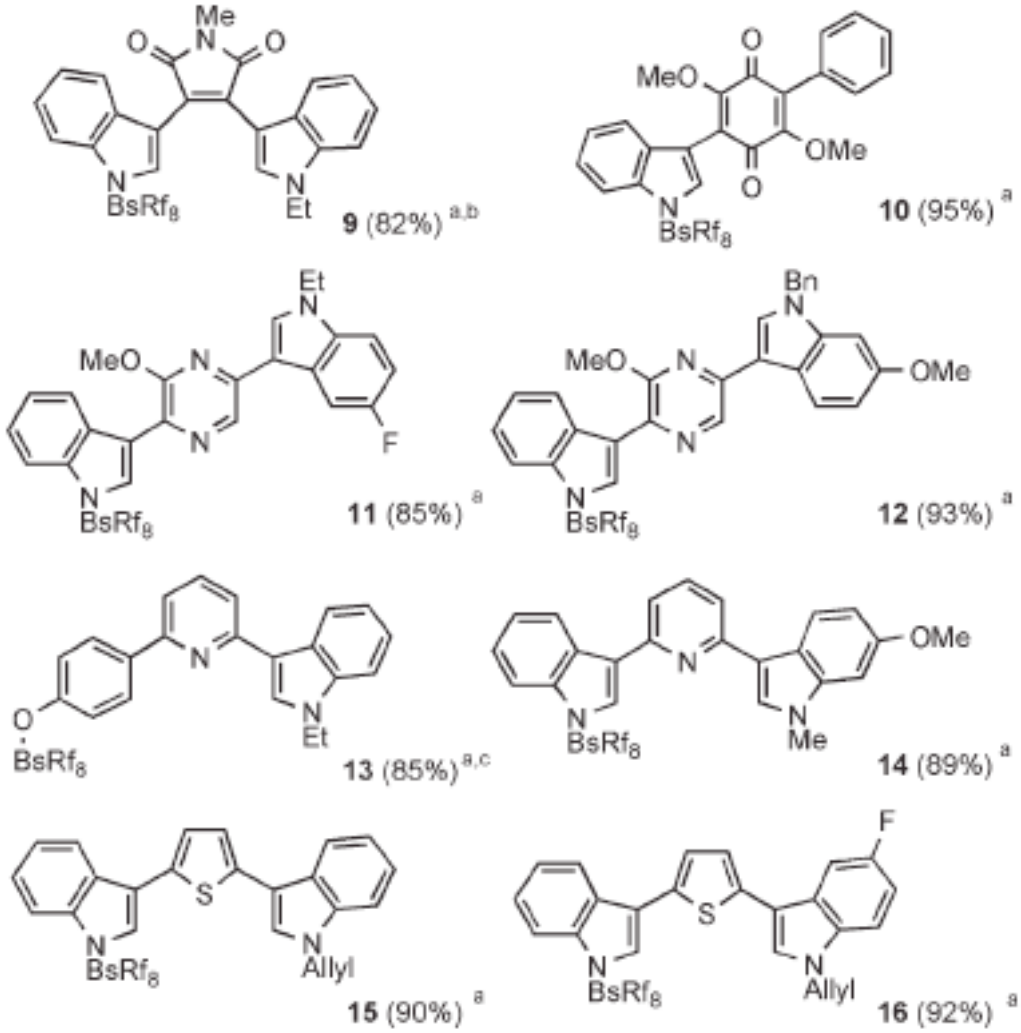
R = Me, Asterriquinone B1
= H, Demethyl Asterriquinone B1

Insulin receptor activator



Kasahara, T.; Kondo, Y. **Fluorous-tagged indolylboron for the diversity-oriented synthesis of biologically-attractive bisindole derivatives** *Chem. Commun.* **2006**, 891.

Solution-Phase Synthesis Using Fluorous Tag



Solid-phase synthesis of bisindole derivatives is hard to monitor, fluorous synthesis made it easier; Pd-cat coupling is used consecutively; New sulfonamide type tag (Rf_8-Bs) was developed.

Comparison of Combinatorial Library and DOS Library

- Combinatorial library:

  (a) Tens of thousand to millions of compounds;

  (b) Structures are not very complex

  (c) May have a specific target

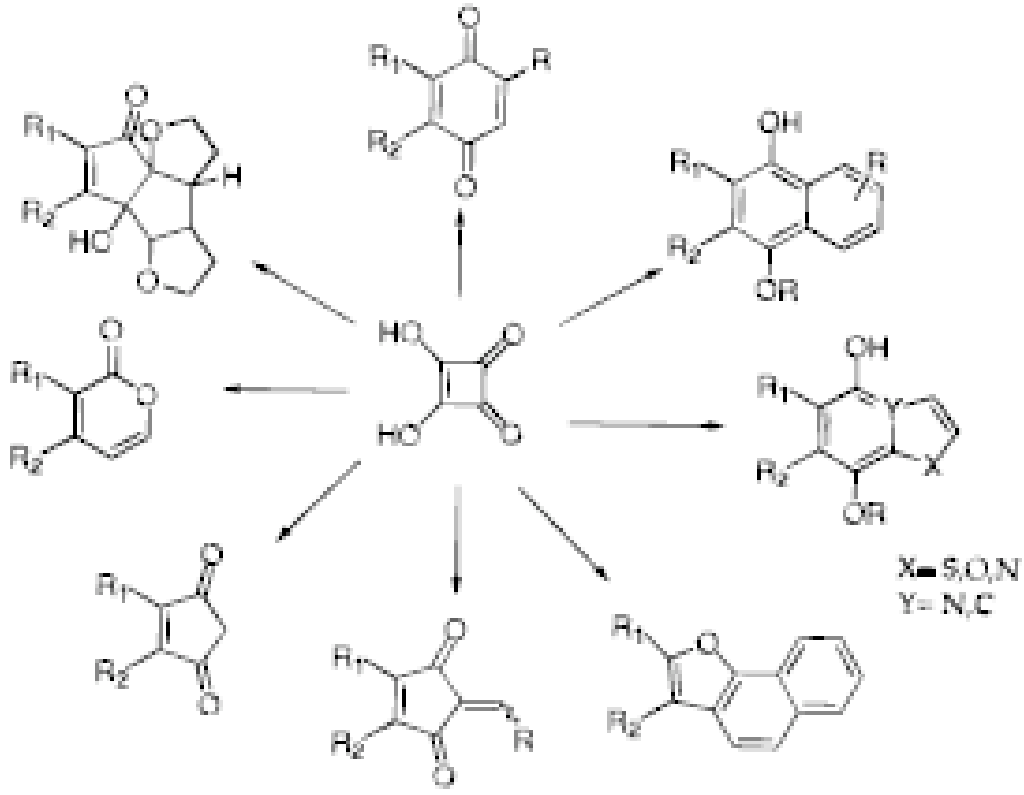
- DOS library:

  (a) Tens to hundreds of compounds;

  (b) Most have cyclic architectures with many stereocenters and resemble natural product;

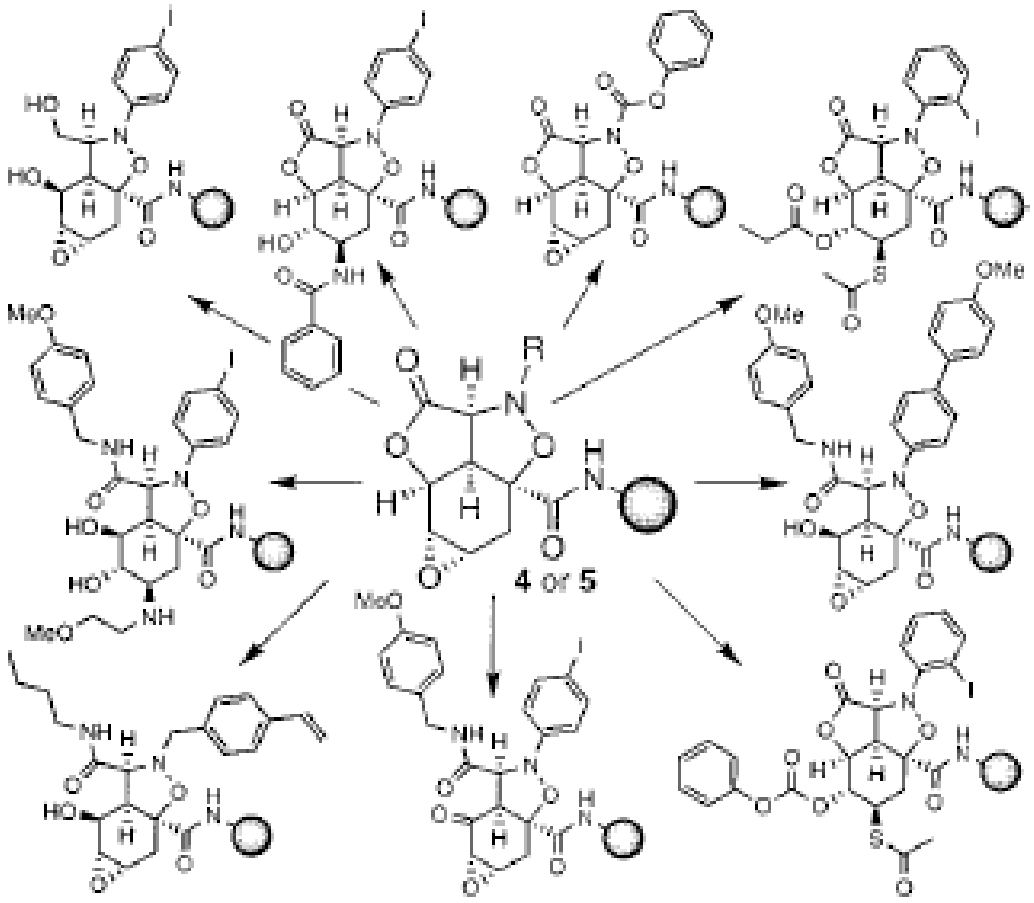
  (c) DOS are utilized as small-molecule chemical probes for understanding cellular processes and are not biased toward a specific biological target

Diversity-Oriented Synthesis-1st Example



Tempest, P. A.; Armstrong, R. W. **Cyclobutenedione derivatives on solid support: toward multiple core structure libraries** *J. Am. Chem. Soc.* **1997**, *119*, 7607.

Diversity-Oriented Synthesis



Tan, D. S.; Foley, M. A.; Shair, M. D.; Schreiber, S. L. **Stereoselective synthesis of over two million compounds having structural features both reminiscent of natural products and compatible with miniaturized cell-based assays** *J. Am. Chem. Soc.* **1998**, *120*, 8565.

Diversity-Oriented Synthesis

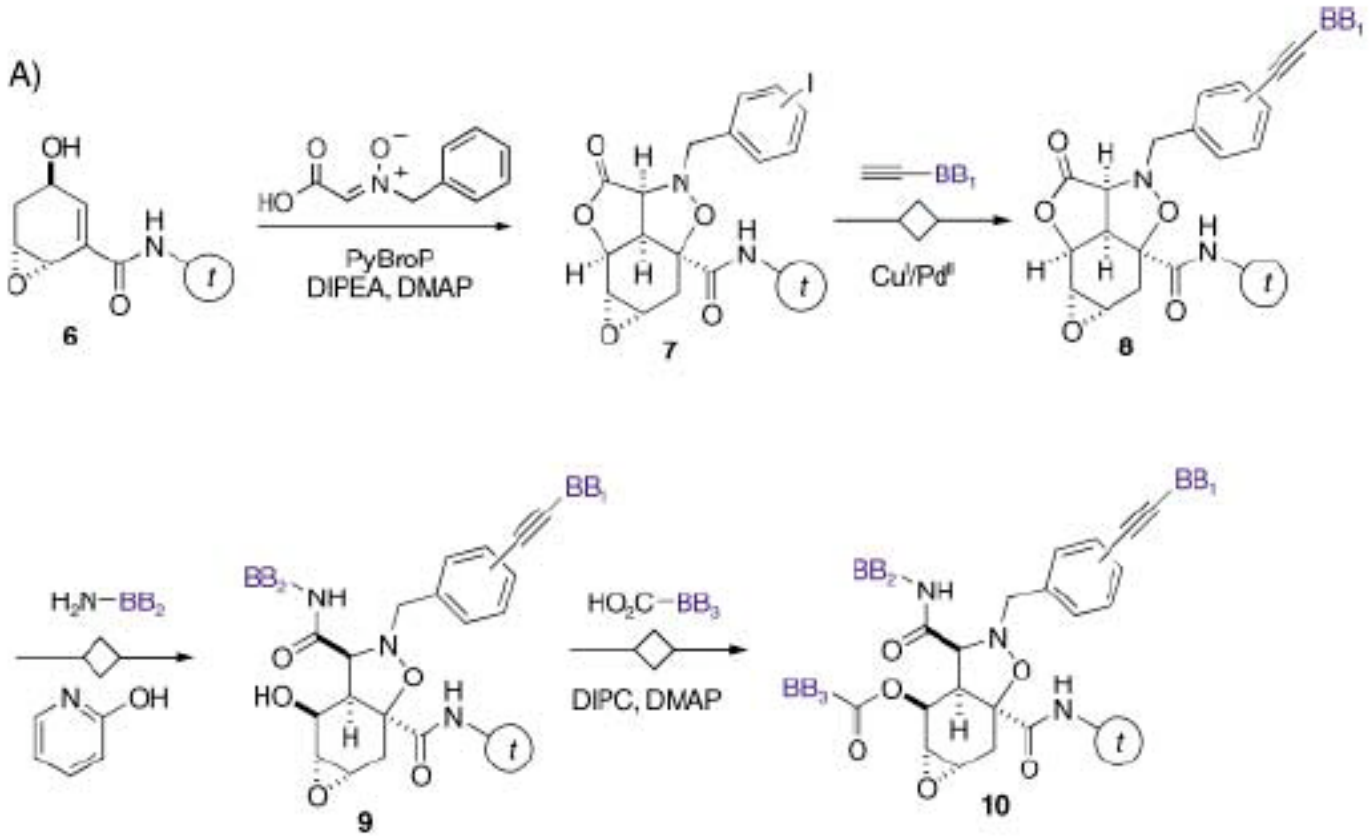
DOS aims at generating natural product-like compounds that are (a) easy to access, (b) rich in dense, chiral functional groups, and (c) rich in stereochemically and three-dimentional, skeletally diverse architectures.

- Appendage diversity
- Stereochemical diversity
- Skeleton diversity

Appendage Diversity

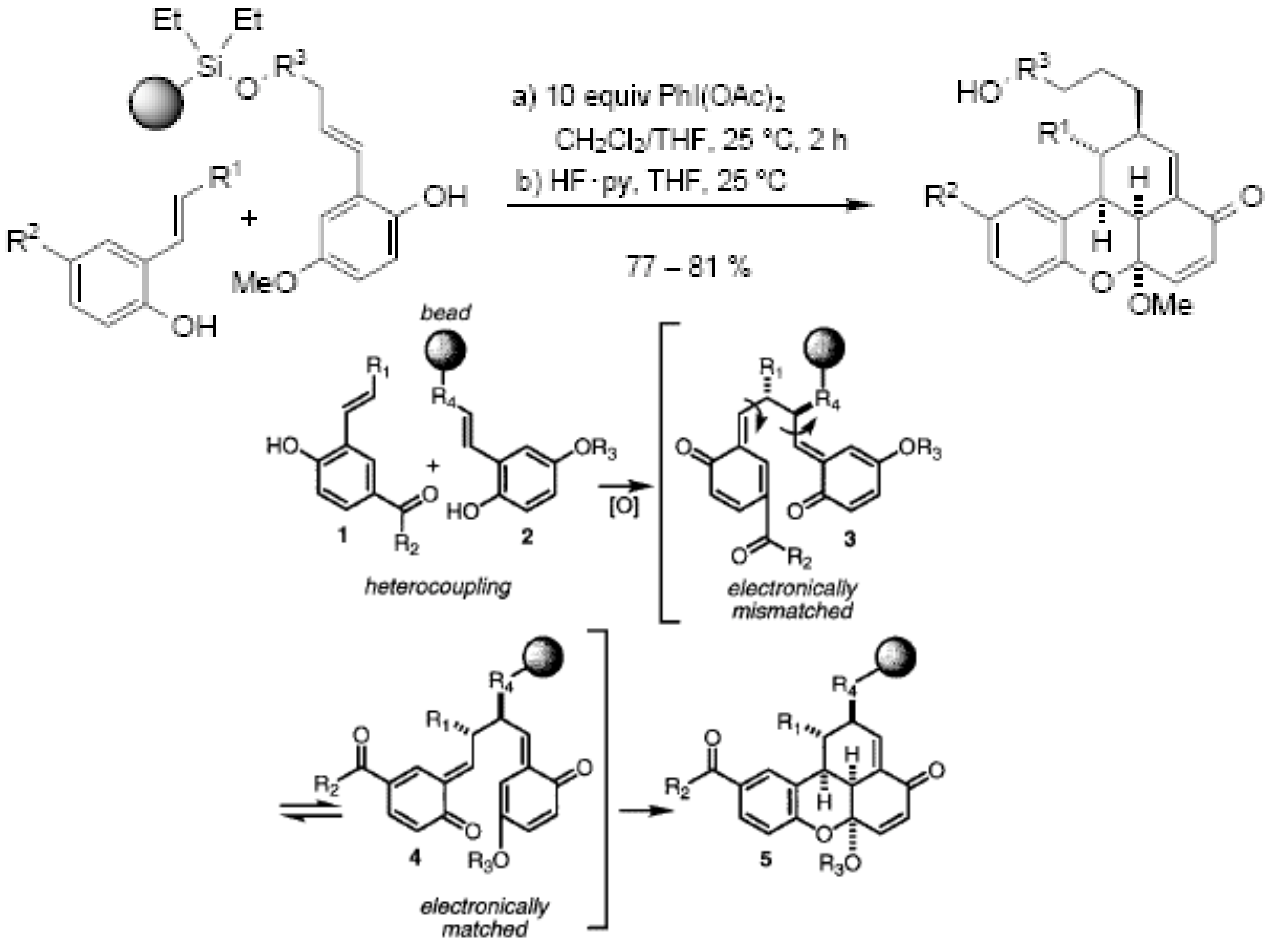
- Using coupling reactions to attach different appendages to a common molecular skeleton
- A split-pool synthesis can be used when a molecular skeleton has multiple reactive sites with potential for orthogonal functionalization

Appendage Diversity



Tan, D. S.; Foley, M. A.; Shair, M. D.; Schreiber, S. L. **Stereoselective synthesis of over two million compounds having structural features both reminiscent of natural products and compatible with miniaturized cell-based assays** *J. Am. Chem. Soc.* **1998**, *120*, 8565.

Appendage Diversity



Four substituents can be varied.

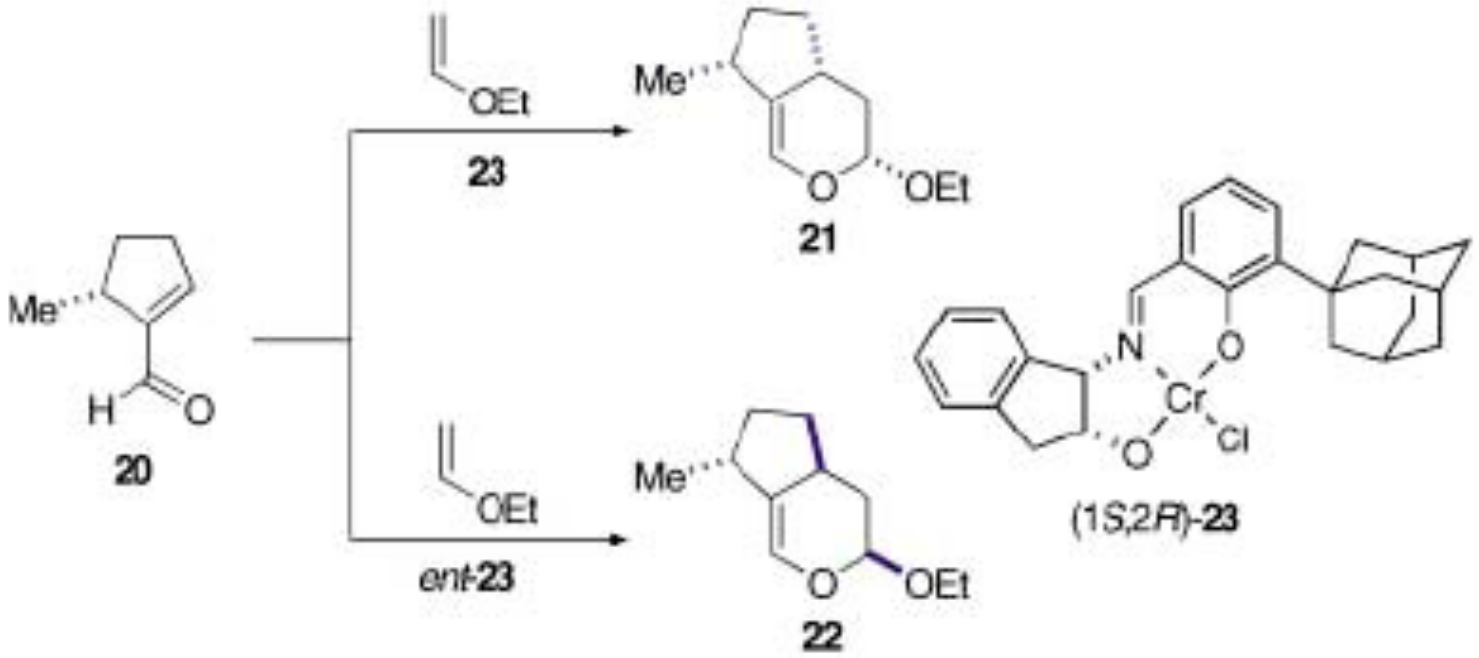
Lindsley, C. W.; Chan, L. K.; Goess, B. C.; Joseph, R.; Shair, M. D. **Solid-phase biomimetic synthesis of carpanone-like molecules** *J. Am. Chem. Soc.* **2000**, *122*, 422.

Limitations of Appendage Diversity

Compounds having a common molecular skeleton display chemical information similarly in 3D space, thus limiting the pool of potential binding partners to only those macromolecules with a complementary 3D binding surface

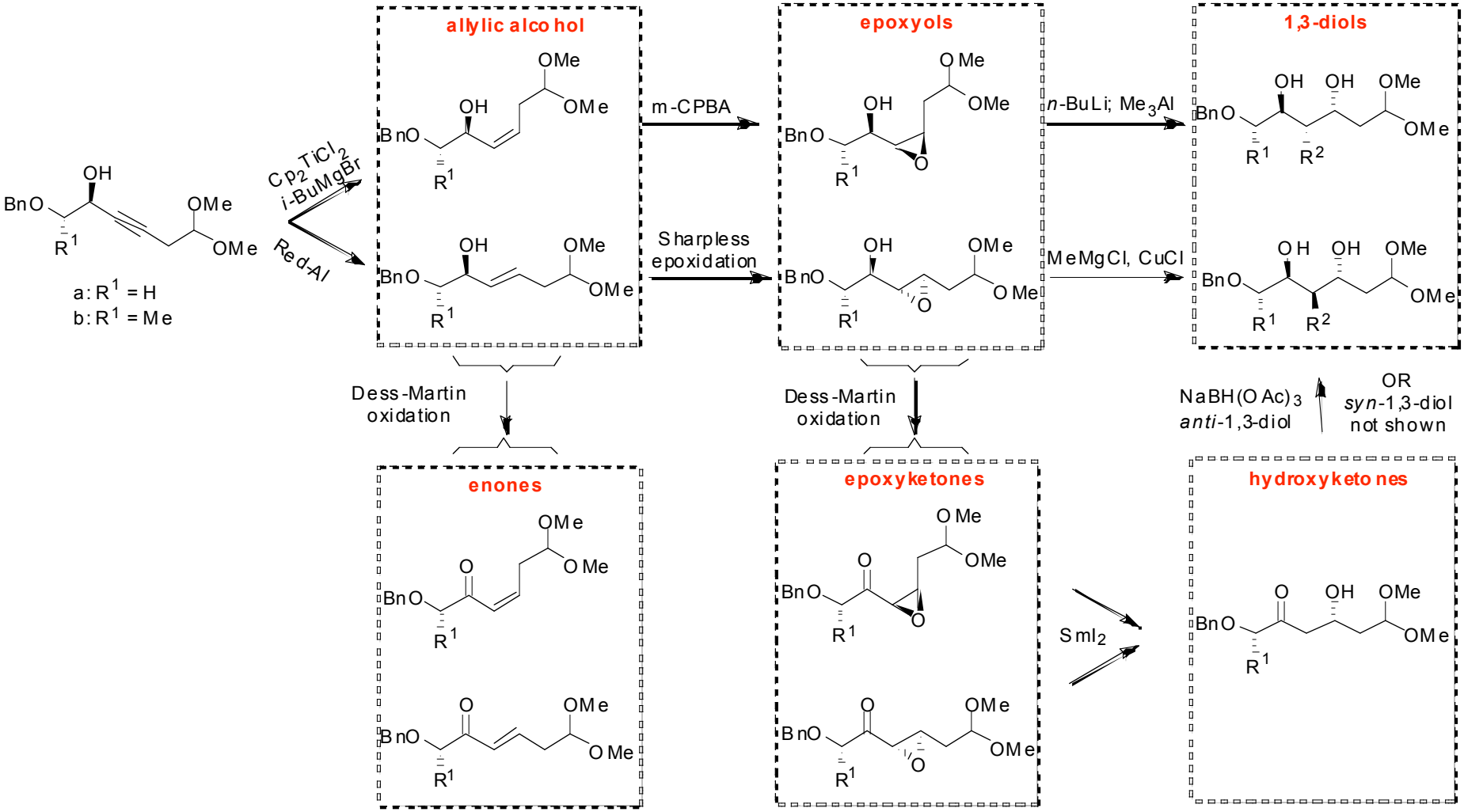
Stereochemical Diversity

- Increase the number of relative orientations of potential macromolecule-interacting elements in small molecules
- Require powerful reagents that can override substrate bias and deliver diastereomeric products with very high selectivity



Chavez, D. E.; Jacobsen, E. N. **Catalyst-controlled inverse-electron-demand hetero-Diels-Alder reactions In the enantio- and diastereoselective synthesis of iridoids natural products** *Org. Lett.* **2003**, *5*, 2563.

Stereochemical Diversity



Shang, S.; Iwadare, H.; Macks, D. E.; Ambrosini, L. M.; Tan, D. S. **A unified synthetic approach to polyketides having both skeletal and stereochemical diversity** *Org. Lett.* **2007**, *9*, 1895.

Skeletal Diversity

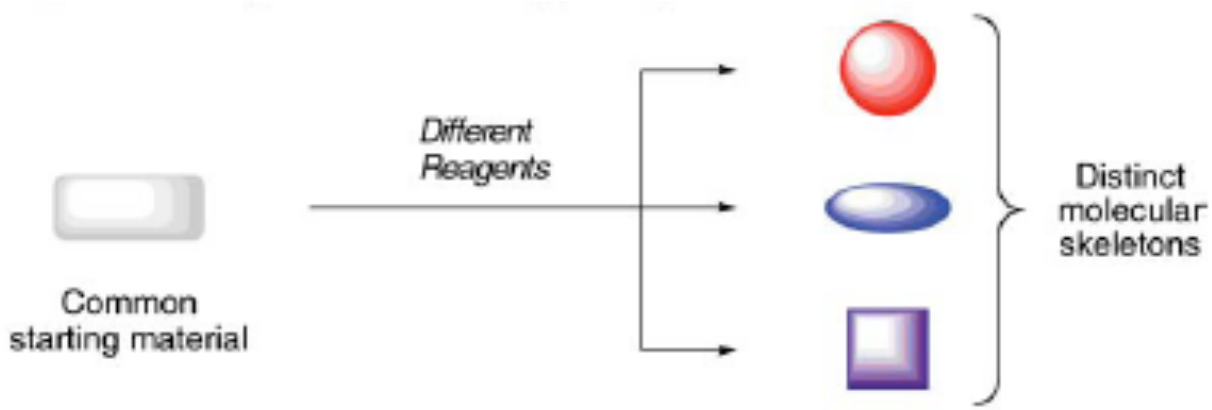
- Products with many distinct molecular skeletons are particularly effective at achieving a diverse display of chemical functionality in 3D space
- Differentiating processes

  Strategy 1: Pluripotent functional group strategy

  Strategy 2: Multiple group pairing strategy
- Folding processes

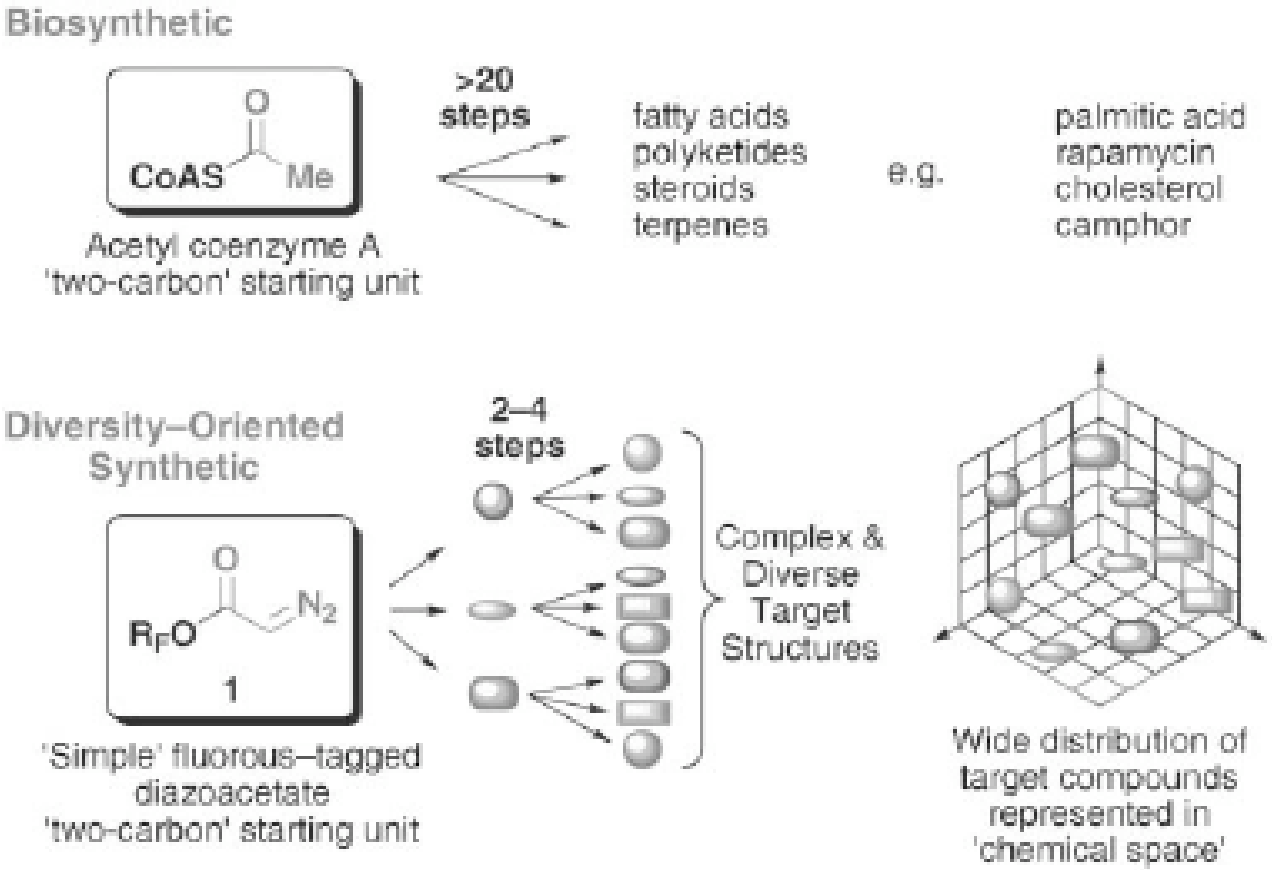
Differentiating Processes

- Using different reagents to transform a common substrate with the potential for diverse reactivity



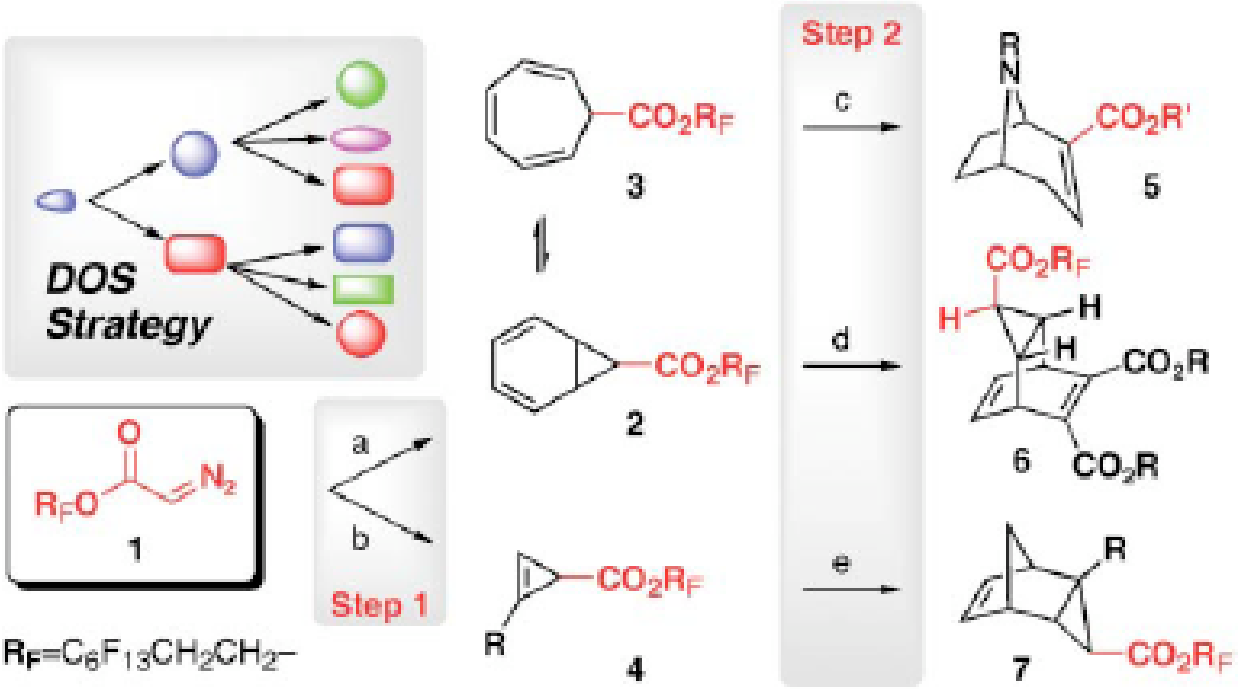
Strategy 1: Pluripotent functional group strategy
Strategy 2: Multiple group pairing strategy

Pluripotent Functional Group Strategy



Wyatt, E. E.; Fergus, S.; Galloway, W.; Bender, A.; Fox, D. J.; Plowright, A. T.; Jessiman, A. S.; Welch, M.; Spring, D. R. **Skeletal diversity construction via a branching synthetic strategy** *Chem. Commun*. **2006**, *3296*.

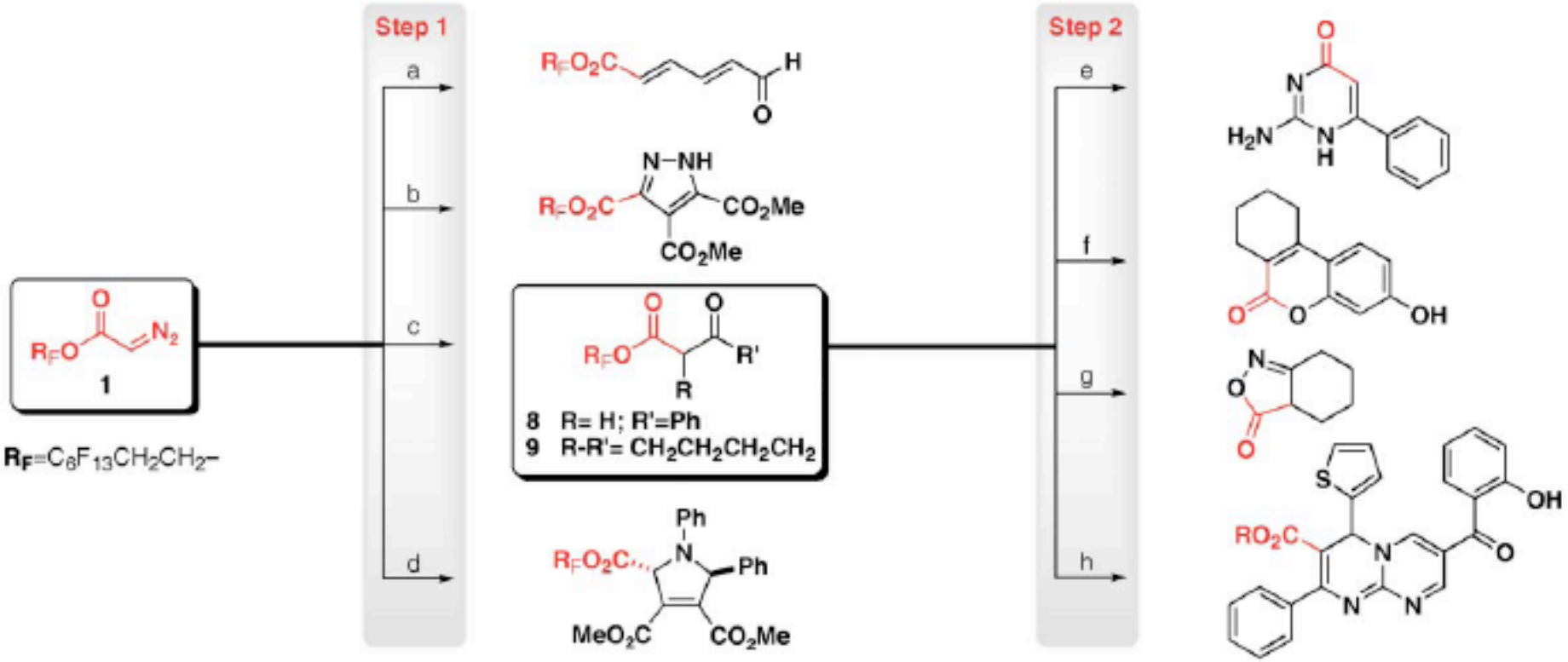
Pluripotent Functional Group Strategy



(a) C_6H_6, $Rh_2(O_2CCF_3)_4$, 70%; (b) RCCH, $Rh_2(OAc)_4$, [BuCCH, 57%];
(c) RNH_2, NaOH then MeOH, H_2SO_4, [$MeNH_2$, 35%]; (d) dienophile [DMAD, 59%]; (e) C_5H_6, 92%

Wyatt, E. E.; Fergus, S.; Galloway, W.; Bender, A.; Fox, D. J.; Plowright, A. T.; Jessiman, A. S.; Welch, M.; Spring, D. R. **Skeletal diversity construction via a branching synthetic strategy** *Chem. Commun*. **2006**, *3296*.

Pluripotent Functional Group Strategy



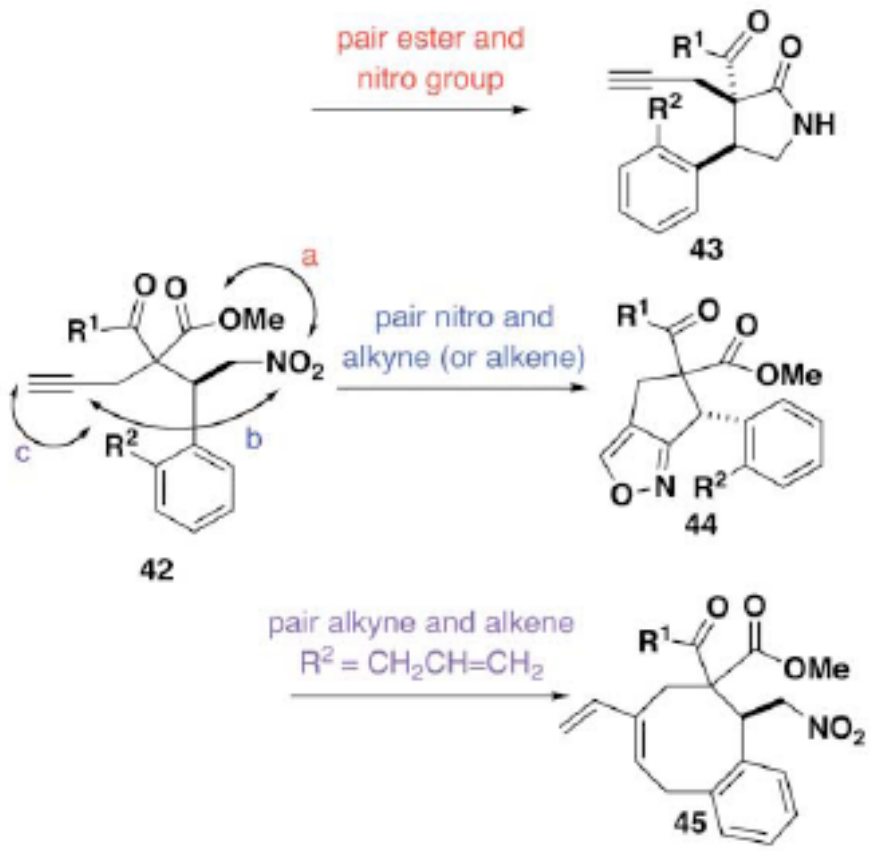
(a) $Rh_2(OAc)_4$, furan, then I_2, 60% (91%); (b) DMAD, 84% (88%); (c) LDA, RCOR', then $Rh_2(OAc)_4$; **8:** 49% (90%); **9**: 68% (97%); (d) PhCHO, $PhNH_2$, then DMAD, $Rh_2(OAc)_4$, dr = 20:1, 51% (80%); (e) Guanidine carbonate 62% (96%); (f) Resorcinol, H_2SO_4, 74% (95%); (g) NH_2OH, 77% (89%); (h) Thiophene-2-carboxaldehyde, guanidine carbonate, Then 3-formylchromone, 43% (98%) Yield and purity (in brackets)

Phenotypic screening showed that a high number of the compounds modulate the growth of pathogenic strains of methicillin resistant Staphylococcus aureus (MRSA): 100 μM (29%), 50 μM (6%), 25 μM (4%), 10 μM (2%). The most active ones have MIC 3.56 and 6.05 μg/mL.

Multiple Group Pairing Strategy

Skeletal diversity was achieved by chemoselective activation of different pairs of functional groups

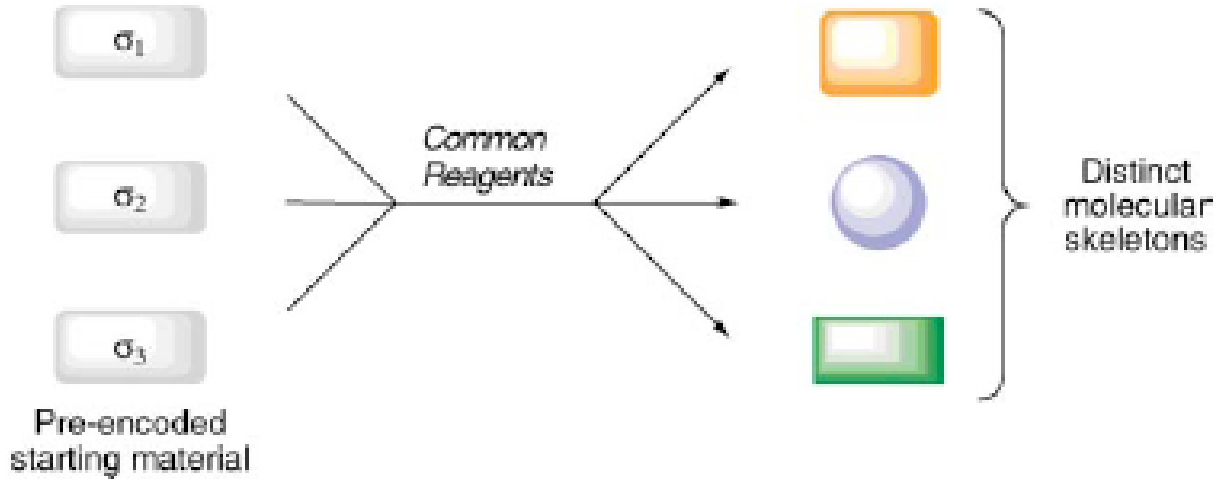
Obtained by Cinchona catalyzed enantioselective Michael addition



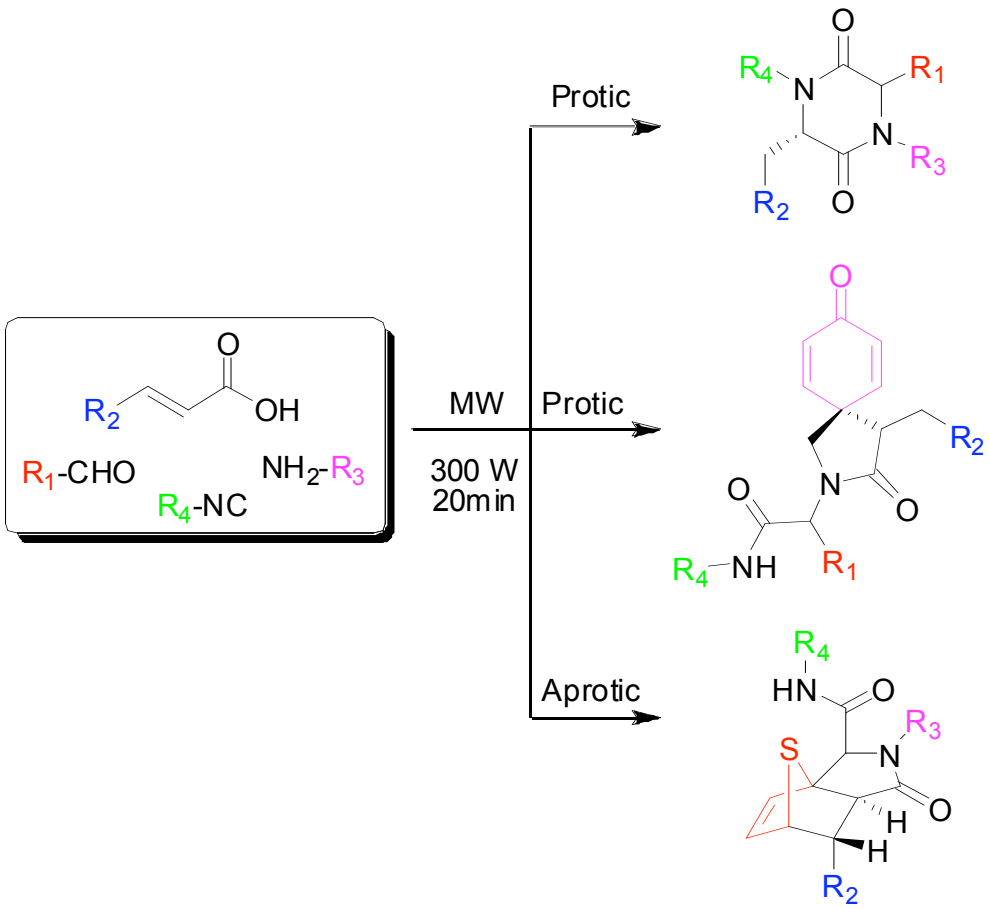
Comer, E.; Rohan, E.; Deng, L.; Porco, J. A., Jr. **An approach to skeletal diversity using functional group pairing of multifunctional scaffolds** *Org. Lett.* **2007**, *9*, 2123.

Folding Processes

- Transform substrates having different appendages that pre-encode skeletal information (called σ elements) into products having distinct molecular skeletons using common reaction conditions

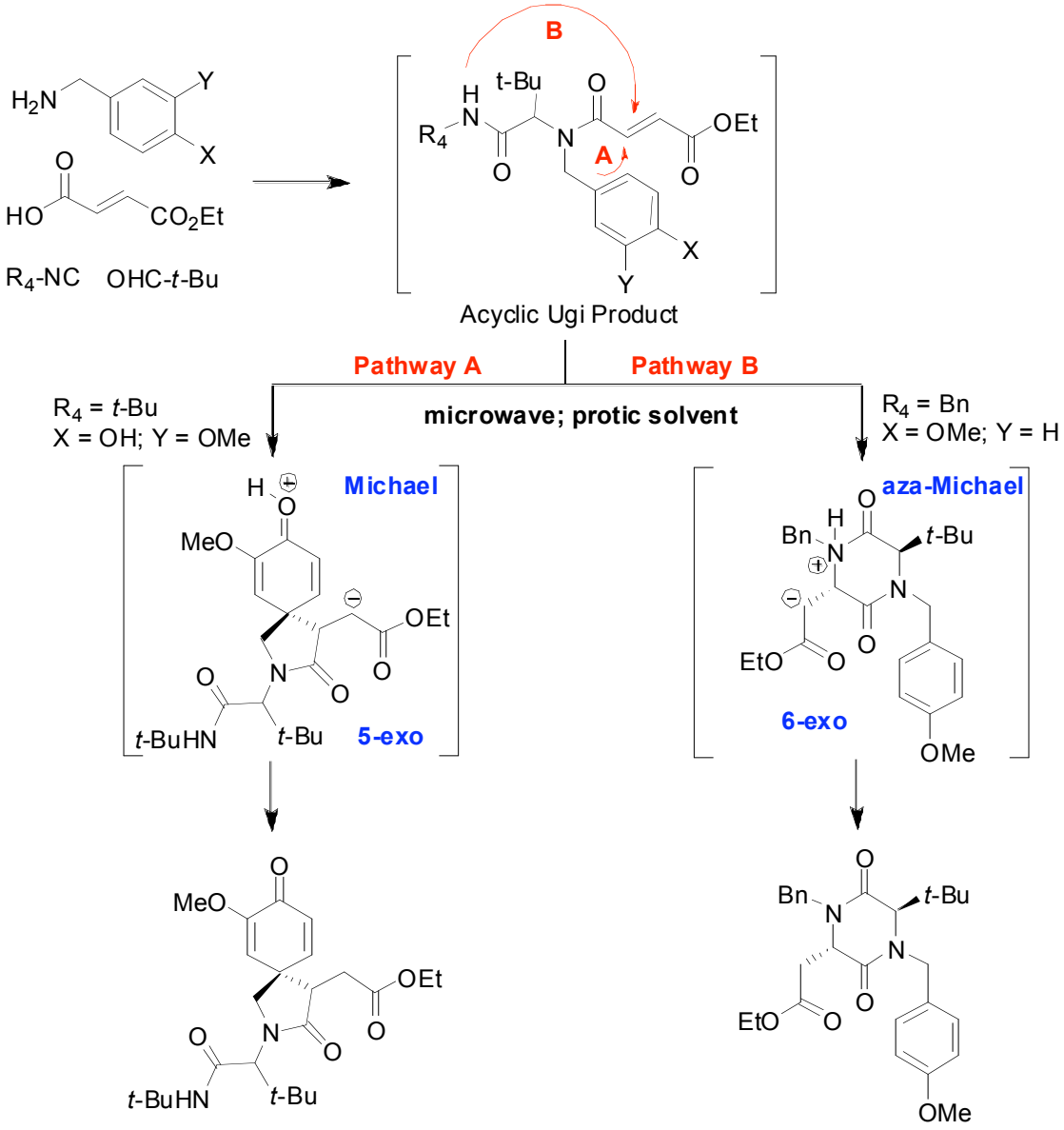


Folding Processes

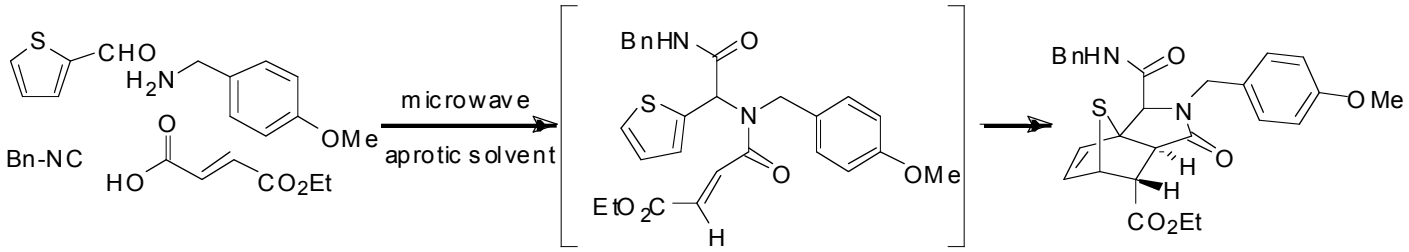


Santra, S.; Andreana, P. R. **A one-pot, microwave-influenced synthesis of diverse small molecules by multicomponent reaction cascades** *Org. Lett.* **2007**, *9*, 5035.

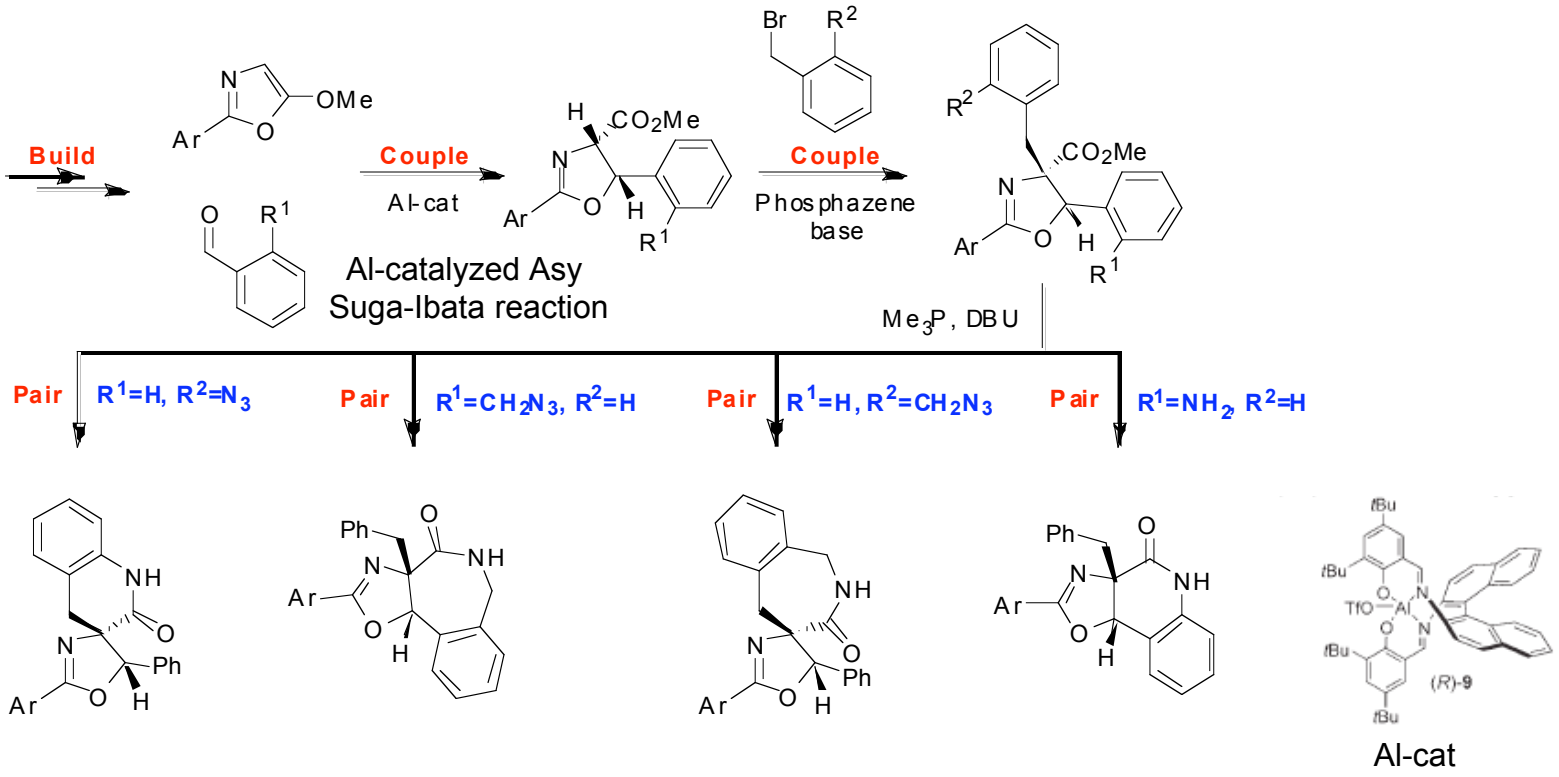
Mechanism


B
A
Acyclic Ugi Product
Pathway A
Pathway B
microwave; protic solvent
R4 = t-Bu
X = OH; Y = OMe
R4 = Bn
X = OMe; Y = H
Michael
5-exo
aza-Michael
6-exo
R4-NC
OHC-t-Bu

Mechanism


S
CHO
H2N
OMe
Bn-NC
O
HO
CO2Et
microwave
aprotic solvent
BnHN
O
S
N
O
OMe
EtO2C
H
BnHN
O
S
N
OMe
O
H
H
CO2Et

Build/Couple/Pair (B/C/P) Strategy

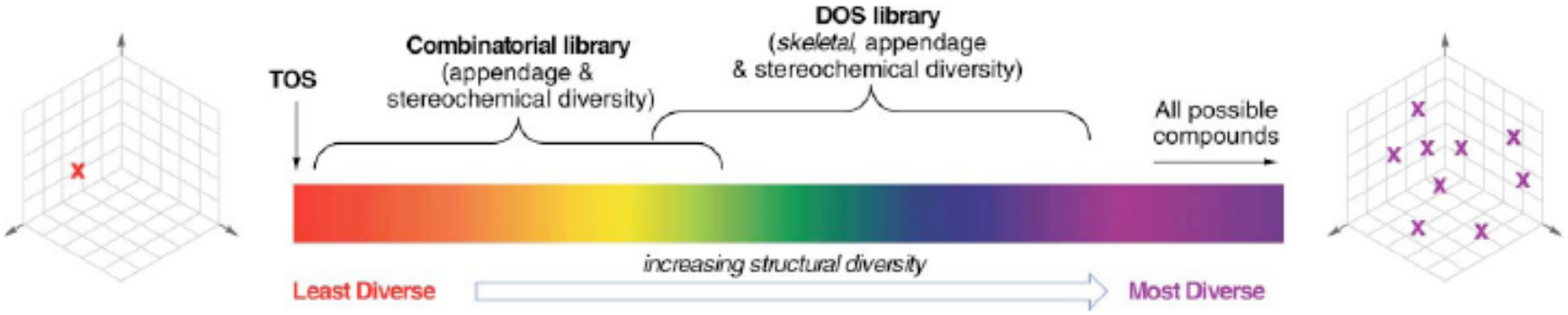


Nielsen T. E.; Schreiber, S. L **Towards the optimal screening collection: a synthesis strategy** *Angew. Chem. Int. Ed.* **2008**, *47*, 48.

Mitchell, J. M.; Shaw, J. T. **A structurally diverse library of polycyclic lactams resulting from systematic Placement of proximal functional groups** *Angew. Chem. Int. Ed.* **2006**, *45*, 1722.

Conclusion

TOS, focused synthesis and DOS are all important approaches to explore chemical space. They all play very important role in studying biological systems and discovering drugs.



"Although no longer in the spotlight and heralded as the savior of the drug industry, combinatorial chemistry is alive and well: actually, combinatorial science is more prevalent and widespread than ever before."
-----Craig W. Lindsley

DOS is a new and challenging field, the development of it will lead to the discovery of new chemistry as well as new entities in the chemical space; however, whether it is the most efficient and successful way or not needs to be evaluated in the future.