4

DIVERSITY-ORIENTED SYNTHESIS

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4.1 INTRODUCTION

The deliberate synthesis of small molecule collections (libraries) that cover large areas of chemical space is described as diversity-oriented synthesis (DOS). These libraries are usually created with a view to discovering some novel biological activity but without a particular target in mind. Instead, it is hoped that the range of molecular architectures and potential bonding interactions present in the library can provide interesting and specific biological activity across a range of targets. This chapter will discuss the range of synthetic strategies applied to DOS, with particular reference to those carried out on solid phase.

4.2 SMALL MOLECULES AND BIOLOGY

The ability of small molecules to interact with biological macromolecules such as proteins in a selective, often reversible, and dose-dependent manner, and to exert specific effects, has led to them being regarded as powerful tools for the study of biological systems.[1,2] The use of small molecules in this manner to selectively perturb biological function underpins the whole of medicinal chemistry as well as forming the basis for the field of chemical genetics.[3]

Solid-Phase Organic Synthesis: Concepts, Strategies, and Applications, First Edition.
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The discovery of novel molecular entities or structural classes capable of these selective interactions represents a significant challenge. In cases where the biological target is well defined, rational design of potential ligands is often possible, particularly when the structure of a natural substrate is known. However, for other recondite disease states or if a novel mode of binding is sought, this is not possible, and the discovery of novel therapeutic agents largely relies on the screening of large collections of small molecules. Clearly, the composition, in terms of the structures of the molecules included in these collections, is an extremely important consideration.[4] The greater the structural variation between compounds, the higher the likelihood of achieving a broad-ranging and distinct biological activity across the library.[5,6] The presence of multiple structural classes or scaffolds within a library being tested against a single target also increases the likelihood of discovering a molecule capable of binding in a novel manner.[7]

The molecules that comprise these libraries, or indeed any compound collections, may be obtained from natural (natural products) or nonnatural (chemical synthesis) sources. If all known natural products are taken into account, they represent an extremely diverse and complex collection of molecules. They also show a wide range of biological activities and have been used medicinally for millennia. However, despite this, it is not realistic or even desirable to produce large libraries consisting solely of natural products, predominately due to difficulties in sourcing, isolating, and identifying the bioactive components, as well as purifying and chemically derivatizing these often extremely complex molecular structures. Therefore, in terms of producing large numbers of compounds for biological screening, deliberate chemical synthesis is considered the most efficient approach.

With the advent of combinatorial chemistry in the 1990s, their came the use of split–pool techniques that, when combined with advances in automation, made possible the efficient synthesis of literally millions of compounds.[8] These libraries, however, were generally made up of broadly similar structures, with any variation between molecules resulting from appendage alteration on building blocks assembled around a common scaffold. Libraries of this sort have had limited success in the discovery of novel biologically active agents, a fact that is mainly attributed to the relative lack of diversity within the libraries.[9] Therefore, it is believed that the quality, in terms of structural complexity and diversity, of these libraries is as important, if not more so, than the number of the compounds synthesized.[4]

Many proprietary and commercially available libraries are synthesized in this combinatorial fashion and so suffer from these limitations. Another criticism of these libraries is that they may be too heavily biased toward certain predefined criteria such as the Lipinski rule of 5.[10] These rules for bioavailability have proved very useful in drug discovery; however, they may be unnecessarily limiting when it comes to the discovery of ligands for novel biological targets such as protein–protein interactions. Despite these limitations, many of the principles of combinatorial chemistry are shared by DOS.

A review from 1997 by Spaller et al. suggested that combinatorial libraries may be considered to fall into two categories: "focused" libraries where a number of closely related analogues based on a privileged structure are synthesized with a known target in mind, and "prospecting" libraries where an entirely new lead compound is sought and so the objective is to screen a large number of structurally varied molecules in the hope of finding a lead with a novel mode of action.[11] These so-called prospecting libraries can probably be considered to be the first examples of diversity-oriented syntheses as they were produced with similar aims of achieving high levels of structural variety and bioactive chemical space coverage. The term "diversity-oriented synthesis" was coined by Schreiber and coworkers and first appeared in the literature in 2000.[12,13] It was from this point that the ideas behind

diversity-oriented synthesis began to become formalized in terms of forward synthetic analysis and strategies.

4.3 DIVERSITY-ORIENTED SYNTHESIS, TARGET-ORIENTED SYNTHESIS, AND COMBINATORIAL CHEMISTRY

The aim of efficiently synthesizing large numbers of structurally diverse compounds is not easy to realize for a number of reasons. Principal among these is the fact that the synthetic challenge of producing a successful DOS must be approached from the opposite direction to traditional chemical synthesis.[4,12] In both target-oriented synthesis (TOS) (of natural or nonnatural products) and focused library synthesis, a target structure is in mind at the beginning of the campaign. This structure is then broken down rationally to simpler starting materials through the well-established process of retrosynthetic analysis. In DOS, this is not possible and any synthetic analysis that can be carried out must be done so in the forward direction; that is, once starting materials are chosen, the reactions that can be carried out on them to generate diverse structures must be carefully considered. Generally, DOS strategies make use of complexity generating reactions to quickly build up molecular scaffolds and product–substrate relationships where the product of a given reaction then provides a suitable substrate for the next.[12] Figure 4.1 shows the synthetic strategies involved in TOS, focused library synthesis, and DOS.

Another obvious difficulty when carrying out diversity-driven synthesis is the fact that any given reaction will always provide the same structural feature, at least when carried out in an intermolecular fashion. For example, the coupling of an amine with a carboxylic acid will always form a peptide bond and a classic Diels–Alder reaction will always produce a

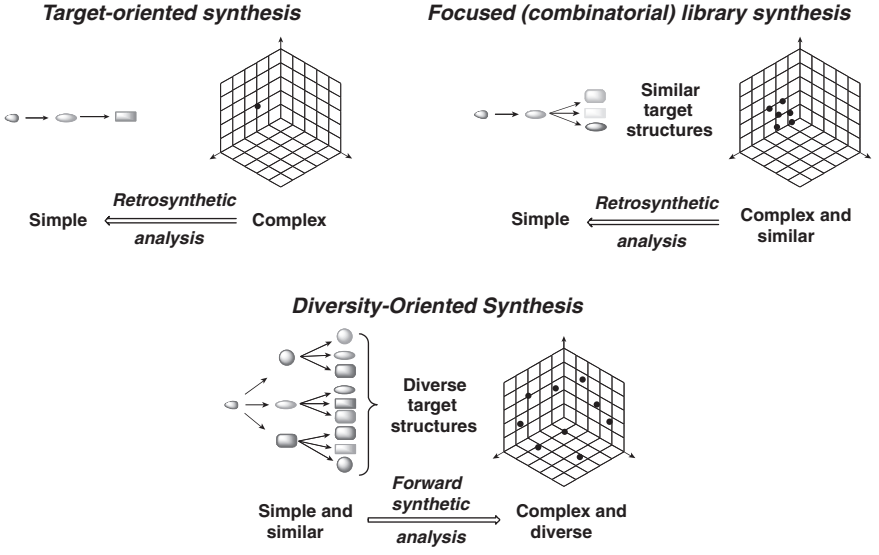


Figure 4.1. Planning strategies and end goals involved in target-oriented synthesis, focused library synthesis (combinatorial synthesis), and diversity-oriented synthesis. First two approaches use retrosynthetic analysis to design the synthesis of target compounds. Diversity-oriented synthesis uses forward synthetic analysis to produce libraries that occupy diffuse regions of chemical space.

cyclohexene or cyclohexadiene. This means that from a diversity generating point of view if the same reactions are to be carried out on a number of substrates, these substrates must be chosen very carefully. The next thing to consider is exactly what constitutes diversity.

4.4 MOLECULAR DIVERSITY

The terms "diversity" and DOS are used widely and with some legitimacy in the literature to describe the synthesis of compound collections. While it is true that any collection of more than one compound must contain some degree of diversity as the molecules are not identical, this is not really in the spirit of DOS, where the goal should be the incorporation of the maximum possible structural diversity within a given compound collection. To provide a visually gratifying and conceptually simple comparison of the degrees of molecular diversity incorporated into compound collections, Spandl et al. proposed the consideration of the molecular diversity spectrum (Figure 4.2), where one extreme is a single-molecule target-oriented synthesis and the other extreme is complete chemical space coverage.[14] In this context, the aim of diversity-oriented synthesis is to produce a compound collection that could qualitatively be considered to be toward the right-hand side of the spectrum. The consideration of molecular diversity on a sliding scale or spectrum such as this is useful in as much as it shows that when planning a DOS, one should aim to achieve the highest possible level of structural diversity; however, it does not really do very much toward defining molecular diversity. It is not possible to define molecular diversity absolutely and analysis performed using any degree of human intuition will by necessity involve some degree of subjectivity. However, there are two main ways in which molecular diversity is usually considered: first, the synthetic strategy can be analyzed as there are only a finite number of ways that diversity can be incorporated synthetically, and second diversity can be analyzed through the computational analysis of library compounds and their relative positions in chemical space (see below).

From a synthetic point of view, when planning a diversity-oriented synthesis, four potential types of molecular diversity to be incorporated are consistently highlighted in the literature:[1,4,14,15]

1. *Appendage or Building Block Diversity*: Variation resulting from the choice of starting materials or "building blocks" used, usually resulting in the variation of R-groups around a single scaffold. This is the approach most frequently used, almost by definition, in combinatorial libraries.
2. *Functional Group Diversity*: Variation of the functional groups present in a molecule generally but also at specific sites within the gross structure. This gives

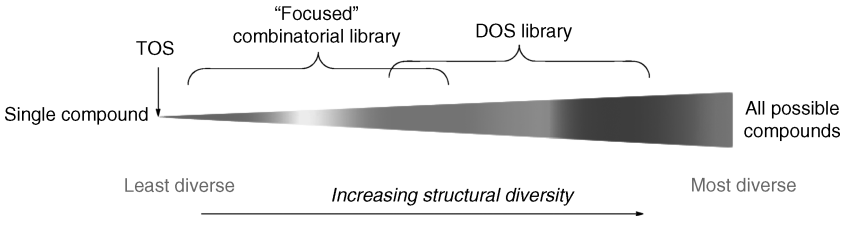


Figure 4.2. Molecular diversity spectrum: a representation of the relative degrees of molecular diversity achieved using TOS, focused library synthesis, and DOS.

the potential for interactions with different polar, apolar, or charged groups present in macromolecules.

3. *Stereochemical Diversity*: Variation in the orientation of functional groups and potential macromolecule-interacting elements. Clearly, it is very important as nature is a three-dimensional (3D) environment.
4. *Scaffold or Skeletal Diversity*: Variation in the overall molecular framework, typically considered to be variation in ring structures and other rigidifying elements, resulting in molecules with distinct scaffolds and consequently molecular shapes.

There is a widespread consensus that in terms of producing functionally (biologically) diverse molecules, the most important type of diversity that can be incorporated into a library is scaffold diversity.[1,16,17] The rationale behind this is that biomacromolecules are (on a molecular scale) large 3D environments with certain defined potential binding pockets and surfaces, and as such they will interact only with small molecules that have complementary 3D structure. Libraries that contain compounds based around distinct molecular scaffolds and so distinct 3D shape and structure should therefore cover a large range of potential binding partners.

4.4.1 Molecular Diversity and Chemical Space

Chemical space encompasses all theoretically possible compounds and is therefore to all extents and purposes infinite, limited only by the imagination of chemists and current synthetic methodology.[7,18,19] Molecules occupy discrete points and regions within chemical space based on their comparable physical and topological properties. The regions of chemical space that are populated by biologically active molecules are considered to comprise bioactive chemical space. Known biologically active molecules are usually aggregated into relatively small areas of chemical space and tend to be found in clusters of molecules that interact with particular targets. In the context of chemical space, it can be said that one of the aims of DOS is to discover novel regions of bioactive chemical space.

As chemical space theoretically comprises all possible compounds, it is clearly not possible to definitively measure it and the position of molecules within it. However, a representation of chemical space can be generated using large numbers of chemical descriptors. Such a representation is more correctly called multidimensional chemical descriptor space.[20] Chemical descriptors are usually based on the physical properties of a given molecule such as molecular weight and log *P* and also on topological features such as geometrical positions and orientations of bonds and groups within the molecule. The use of an algorithm based on a large number of chemical descriptors allows a molecule's position in that particular multidimensional chemical descriptor space to be calculated and this then provides an estimate of the position of a compound in the theoretical chemical space.

To give a visually accessible representation of this multidimensional descriptor space, it is necessary to use principal component analysis (PCA) to condense the multidimensional information into two- and three-dimensional scatter plots.[21] These plots provide the means to easily interpret the comparison of molecular diversity/chemical space coverage between given sets of compounds. They are not infallible, however, and it is conceivable that molecules' absolute and relative positions within the plot could vary depending on the chemical descriptors used. The use of large numbers of chemical descriptors though should minimize this. Figure 4.3 is an example of a chemical space analysis produced using chemical descriptors and PCA.

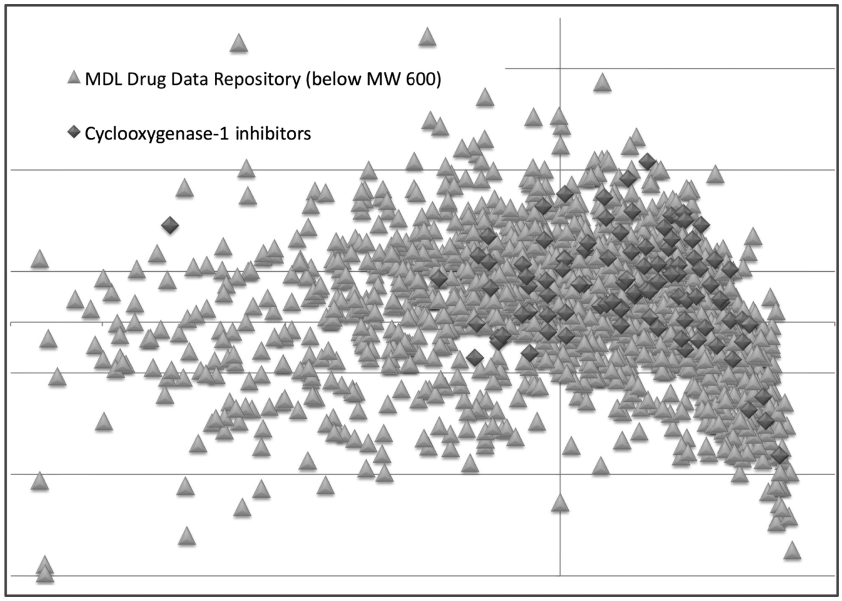


Figure 4.3. Chemical space analysis plot of cyclooxygenase-1 inhibitors (diamonds) and MDL Drug Repository compounds (triangles), created using chemical descriptors and principal component analysis. Plot shows that the cyclooxygenase-1 inhibitors occupy a fairly broad area of chemical space.

4.4.2 Synthetic Strategies for Creating Molecular Diversity

As mentioned previously, the challenge of creating molecular diversity is a considerable one, requiring strategies that differ from those used in the majority of traditional chemical synthesis. Since the conception of DOS, two distinct strategies for the generation of molecular and particularly skeletal diversity have been identified in the literature.[1] They are

1. The *reagent-based* approach, where subjecting a given molecule to a range of conditions allows the synthesis of a number of distinct compounds.
2. The *substrate-based* approach, where a number of starting materials containing "pre-encoded skeletal information" are transformed under the same reaction conditions into a range of different structures (Figure 4.4).

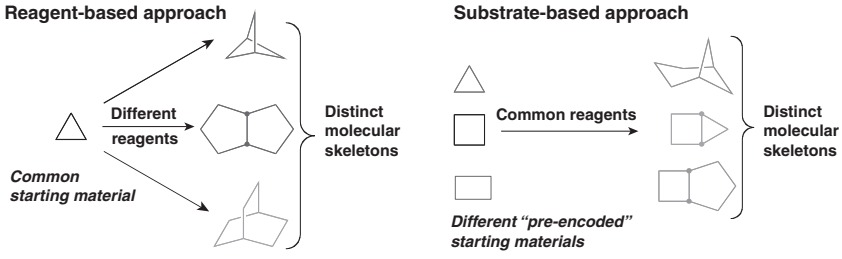


Figure 4.4. Two general strategies used to access chemical and skeletal diversity.

These strategies are not orthogonal to each other and many diversity-oriented syntheses will contain aspects of both. Reagent-based diversification, also known as a "*branching*" reaction pathway, can be used at any stage of a divergent synthesis, either during the early stages to produce diverse functionality or at the later stages to transform prefunctionalized molecules into distinct molecular scaffolds. There are generally considered to be two approaches to reagent-based diversification: (i) the use of the so-called pluripotent functionality where a single functional group can be transformed into distinct functional groups for further diversification or into distinct molecular scaffolds and (ii) the use of a densely functionalized molecule where different functional groups can be transformed under distinct reaction conditions, and this approach is usually used to pair functional groups and so create skeletal diversity. Substrate-based diversification is generally used in the later stages of a DOS to produce distinct molecular scaffolds by intramolecular reaction, and for this reason it is often referred to as a "folding" reaction pathway. While a DOS may contain aspects of both these approaches, generally the strategy used to produce skeletal diversity within the library is considered the most important.

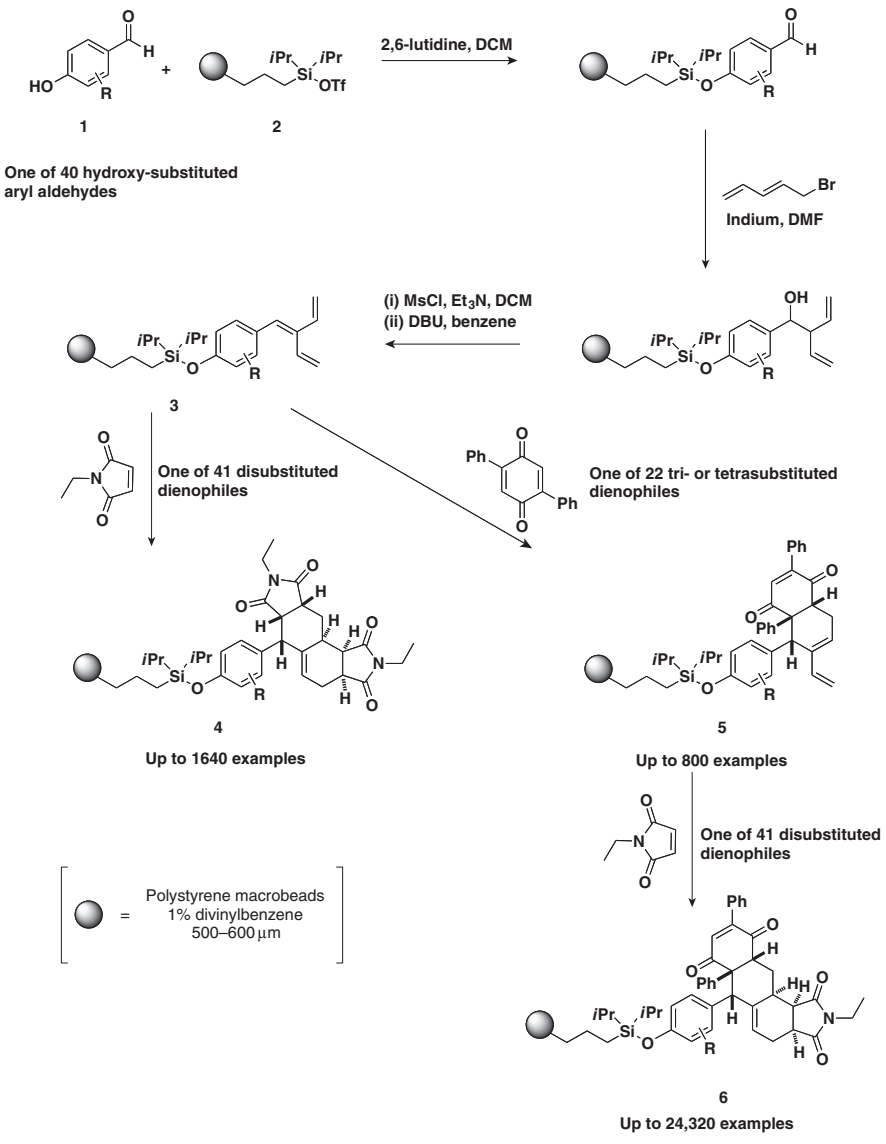
Some of these ideas were further refined by Schreiber when he suggested the use of the *build/couple/pair* strategy for the production of optimal small molecule collections for biological screening.[22] In the build stage, the required, ideally chiral, starting materials are synthesized or obtained from the chiral pool. These starting materials are then coupled to produce densely functionalized molecules; multicomponent reactions are often used at this stage to couple three or more building blocks together. The pair stage then involves the intramolecular reaction of attached functional groups, usually under reagent control, to generate diverse molecular skeletons. This approach has been widely adopted in the literature.[23–25]

4.5 DIVERSITY-ORIENTED SYNTHESIS ON SOLID PHASE

Solid-phase technology has been a consistent feature in the synthesis of DOS libraries over the past 10 years and it is likely that this trend will continue for years to come. It is worth noting though that many elegant examples of diversity-oriented syntheses have been carried out using fluorous technology as a means for generic purification[26,27] and many more carried out purely in solution with purification achieved by traditional methods.[24,28–30] The remainder of this chapter, however, will focus for the most part on those examples that have employed solid-phase technology to their advantage.

4.5.1 Reagent-Based Strategies

In an early example of a DOS, Kwon et al. took advantage of solid-phase synthesis to achieve the synthesis of a library consisting of up to 29,400 discrete compounds comprising 10 distinct polycyclic skeletons (Scheme 4.1).[31] This strategy relied on the use of consecutive Diels–Alder reactions performed on polymer-bound trienes. The polymer-bound trienes were synthesized in three steps: the reaction of hydroxyl-substituted aryl aldehydes (**1**) with a macrobead attached alkyl silyl triflate (**2**), the reaction of the aldehydes with indium dust and 5-bromo-1,3-pentadiene, and finally mesylation and elimination of the resulting benzylic alcohols to furnish the desired trienes (**3**). These trienes were then reacted with a number of dienophiles displaying a range of creativities to give highly complex polycyclic structures.



scheme 4.1. Consecutive Diels–Alder approach to DOS employed by Kwon et al.

The authors found that by varying the level of steric hindrance associated with the dienophiles, they were able to modify the outcome of the potential double Diels–Alder reaction. When disubstituted dienophiles such as maleimides were used, the double Diels–Alder reaction occurred smoothly to yield a tetracyclic skeleton (**4**). If tri- or tetrasubstituted dienophiles were used, only one Diels–Alder reaction occurred to give a bicyclic diene-containing skeleton (**5**) that could either be treated as a discrete product or reacted further with a more reactive dienophile to again give a tetracyclic structure (**6**).

By combinatorial variation of the dienophiles and polymer-bound aldehydes used, the synthesis of 29,400 compounds was possible, broken down into 800 bicyclic dienes and 28,600 potential tetracycles. Further skeletal variation was achieved using different heterocyclic dienophiles for some examples. This work effectively illustrates the scale of

synthetic campaigns that can be attempted on solid phase; however, by current standards, it shows a relatively low level of skeletal diversity for such a large number of compounds.[27,32]

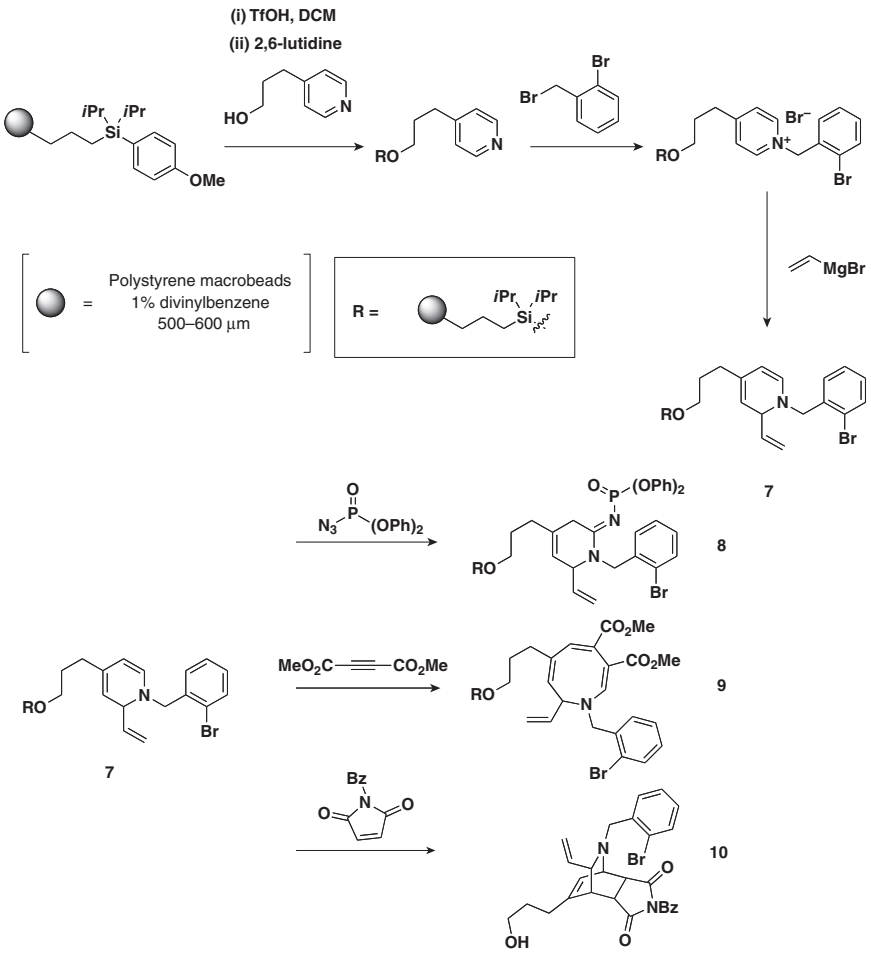
Work by Taylor et al. from 2004 neatly illustrates another potential advantage of solid-phase synthesis; this work was based on the generation of reactive dihydroisoquinoline and dihydropyridine intermediates to be used in further reactions.[33] These species are known to be unstable when stored for any period of time, even under "seemingly inert" conditions; however, once attached to a solid support, they proved immune to degradation even after storage for 30 days at room temperature.

These intermediates, which were bound to a polymer support *via* a silicon-based linker similar to the one used by Kwon et al., were generated in a three-step reaction sequence. Both the dihydroisoquinoline and the dihydropyridine were synthesized following the same sequence and were subjected to identical subsequent reactions; however, for clarity only the dihydropyridine route will be discussed here. First, 3-(4-pyridyl)propan-1-ol was attached covalently to the macrobead using a standard procedure, the pyridine was then alkylated with 2-bromobenzyl bromide, and finally the resulting iminium salt was trapped with vinylmagnesium bromide. The resulting dihydropyridine **(7)** was then able to partake in a number of reactions, including a 1,3-dipolar cycloaddition with an electron-deficient azide followed by extrusion of molecular nitrogen to give **8**, a [2 + 2] cycloaddition with dimethyl acetylenedicarboxylate (DMDA) followed by ring expansion to give eight-membered ring **9,** and a Diels–Alder reaction with *N*-benzylmaleimide to generate bridged bicycle **10** (Scheme 4.2).

This methodology produced 12 distinct molecular skeletons, all of which possessed a pendant hydroxyl group resulting from cleavage of the solid support, which allowed the use of microarray technology for protein binding assays.

Work from 2008 by Thomas et al. used an imidazolidone linker to immobilize their enone substrate onto a silyl polystyrene support (Scheme 4.3).[34] Besides simplifying purification, this linker allowed two-point binding of a chiral catalyst for a subsequent Diels–Alder reaction and also gave the opportunity for divergent cleavage to increase the appendage diversity of the library. The exocyclic acyl group could be cleaved by hydrolysis, forming the acid, reduced to the aldehyde, esterified, or reacted with an amine to form an amide. The initial reagent-based strategy for this DOS was to treat the alkene as a pluripotent functional group that was able to partake in three initial branching reactions: [3 + 2] cycloaddition, dihydroxylation, and [4 + 2] cycloaddition. These initial products were then transformed into 242 discrete compounds consisting of 18 distinct molecular scaffolds, including a novel *cis–trans*-fused 7-5-7 tricycle (**11**) generated by ring-opening–ring-closing metathesis of a decorated norbornene (**12**).

The compounds produced in this library were screened for their effects on three strains of UK epidemic *Staphylococcus aureus*: methicillin-susceptible *S. aureus* (MSSA) and two strains of methicillin-resistant *S. aureus* (EMRSA 15 and EMRSA 16). Three compounds from the library were found to restrict the growth of these strains; the most potent compound "gemmacin" (Table 4.1) showed considerably higher activity against the strains of MRSA than the widely used antibiotics erythromycin and oxacillin. In the original DOS, gemmacin was made racemically, but the enantiomerically pure compounds were subsequently synthesized and showed comparable activity, with (−)-gemmacin being slightly more potent. Studies were carried out to discover the mode of action of (−)-gemmacin and the results of an assay to test the generation of reactive oxygen species proved positive, suggesting that gemmacin may act as a selective cell membrane disruptor. The discovery of gemmacin is a good example of how the DOS approach can be used to discover new structural classes of biologically active molecules.[34,35]

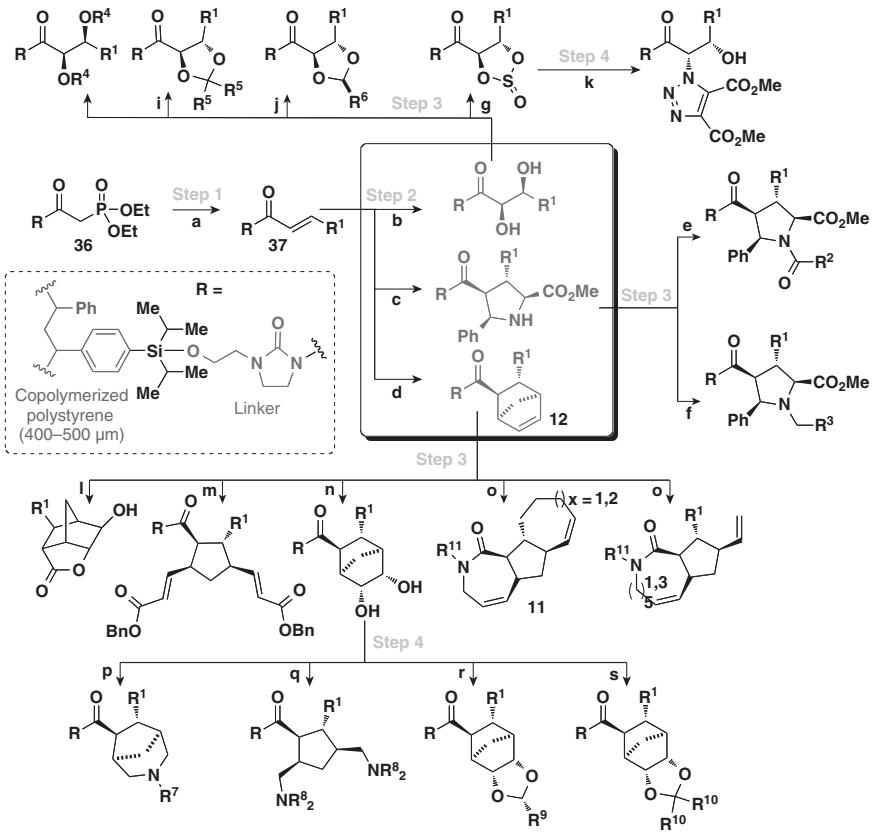


scheme 4.2. Taylor et al.'s use of supported dihydropyridines in DOS.

4.5.2 Substrate-Based Strategies

In the first formal example of a substrate-based diversification strategy, Burke et al. made use of the Achmatowicz reaction to generate a range of molecular skeletons in a combinatorial fashion.[36] Their strategy was based on the use of macrobead-bound 2,5-disubstituted furan species; the functionalization of the attached alkyl chains then provided the necessary pre-encoded skeletal information for the "folding" of these furan species into vastly different structures. Under oxidative conditions, the relatively stable furans can be transformed into highly electrophilic enedione species. The pre-encoded skeletal information was manifested by the presence of one, two, or zero nucleophilic hydroxyl groups that could then trap the reactive intermediate intramolecularly to generate monocyclic, bridged bicyclic, and linear species, respectively (Scheme 4.4).

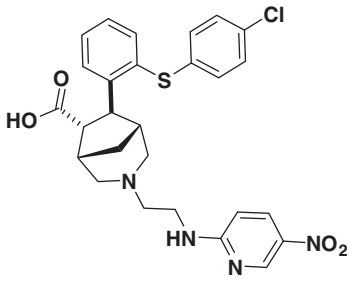
The enedione intermediate was generated under mild oxidative conditions using *N*-bromosuccinimide (NBS) and pyridinium *para*-toluenesulfonic acid (PPTS) and, once formed, the intramolecular reactions occurred spontaneously. The diol substrates underwent the expected NBS-mediated ring expansion followed by bicycloketalization to give [3.2.1]bicycle **13**, the single hydroxyl substrates underwent the same ring expansion



scheme 4.3. Diversity-oriented synthesis of 242 compounds based of 18 discrete molecular frameworks by Thomas et al. Conditions: (a) LiBr, 1,8-diazabicyclo[5.4.0]undec-7-ene, R^1CHO, MeCN; (b) (R)-QUINAP, AgOAc, i-Pr_2NEt, THF, $-78°C \rightarrow 25°C$; (c) AD-mix, (DHQD)PHAL, THF:H2O (1:1); (d) chiral bis(oxazoline), $Cu(OTf)_2$, 3 MS, CH_2Cl_2, C_5H_6; (e) R^2COCl, DMAP, pyridine, CH_2Cl_2; (f) R^3CHO, BH_3 ⩤ pyridine, MeOH; (g) $SOCl_2$, pyridine, CH_2Cl_2, 40°C; (h) R^4Br, Ag_2O, CH_2Cl_2, 40°C; (i) $R^5C(O)R^5$, TsOH, DMF, 65°C; (j) R^6CHO, TsOH, DMF, 65°C; (k) NaN_3, DMF, 100°C, and then dimethyl acetylenedicarboxylate, PhMe, 65°C; (l) mCPBA, CH_2Cl_2 then MeOH, 65°C; (m) $CH_2{=}CHCO_2Bn$, PhMe, 120°C, Grubbs II, $CH_2{=}CH_2$; (n) OsO_4, NMO, $CH_3C(O)CH_3$:H_2O (10:1); (o) RNH_2, Me_2AlCl, PhMe, 120°C, then NaH, $R^{11}X$, DMF, THF, and finally PhMe, 120°C, Grubbs II, $CH_2{=}CH_2$; (p) $NaIO_4$, THF:H_2O (1:1) and then R^7NH_2, $NaB(OAc)_3H$, CH_2Cl_2; (q) $NaIO_4$, THF:H_2O (1:1) and then R^8NHR^8, $NaB(OAc)_3H$, CH_2Cl_2; (r) R^9CHO, DMF, TsOH, 60°C; (s) $R^{10}C(O)R^{10}$, DMF, TsOH, 60°C. DMF = *N*,*N*-dimethylformamide; THF = tetrahydrofuran; DMAP = *N*,*N*-dimethyl-aminopyridine; (DHQD)PHAL = hydroquinidine 1,4-phthalazinediyl diether; mCPBA = *meta*-chloroperbenzoic acid; Ts = *para*-toluenesulfonyl; Grubbs II = 1,3-(bis(mesityl)-2-imidazolidinylidene)dichloro(phenylmethylene)(tricyclohexylphosphine)ruthenium; NMO = 4-methylmorpholine *N*-oxide.

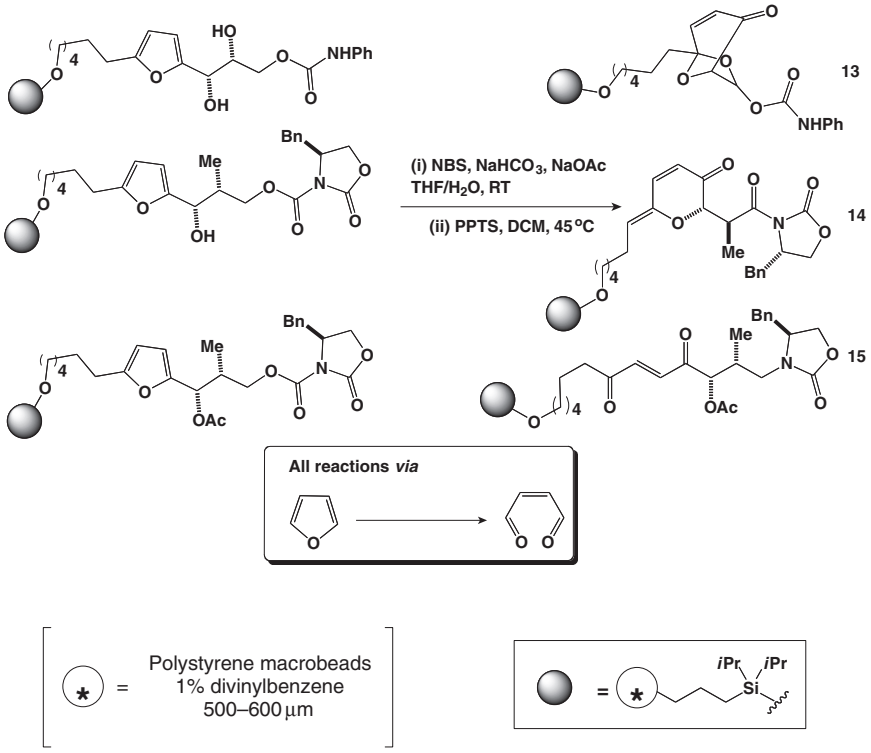
followed by PPTS-mediated dehydration to give alkylidene pyran-3-one **14**, and finally the acetylated substrates gave the corresponding *trans*-enediones (**15**) resulting from furan ring opening followed by olefin isomerization. Following this strategy and using combinatorial variation of building blocks, they were able to produce a library of ∼1260 compounds.

TABLE 4.1. Gemmacin and the Comparable effects of the Enantiomers of Gemmacin, Erythromycin, and Oxacillin on Three Strains of *S. aureus*

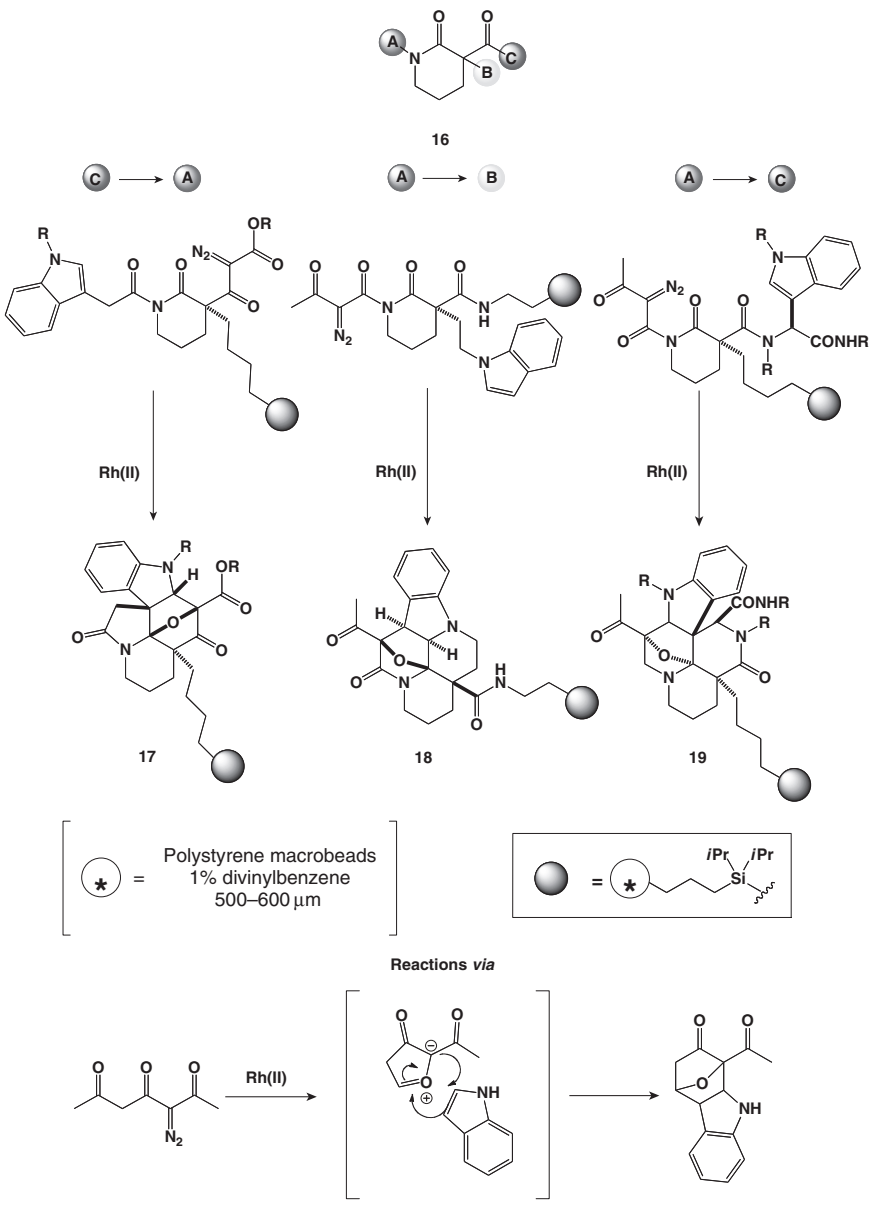


(–)-Gemmacin

	MIC (μg/mL)		
	MSSA	EMRSA 15	EMRSA 16
(±)-Gemmacin	2	16	32
(−)-Gemmacin	Not determined	8	16
(+)-Gemmacin	Not determined	16	32
Erythromycin	0.5	>64	>64
Oxacillin	0.5	>32	>32



scheme 4.4. Use of the Achmatowicz reaction in a folding pathway for DOS by Burke et al.



scheme 4.5. Oguri and Schreiber's DOS of polycyclic alkaloid scaffolds using a folding pathway based on an intramolecular 1,3-dipolar cycloaddition.

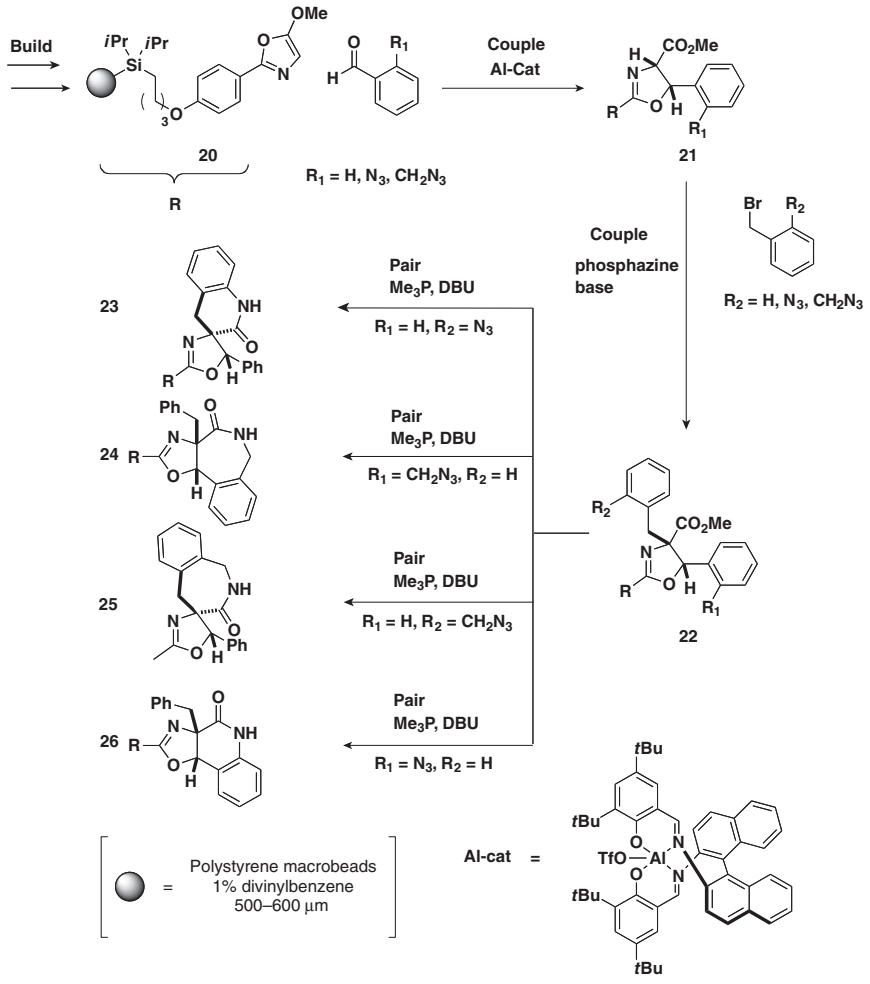
Another outstanding example of a folding reaction pathway carried out on solid phase comes from Oguri and Schreiber's work on the DOS of polycyclic indole alkaloid-like scaffolds (Scheme 4.5).[37] By attaching different reactive groups, an α-diazocarbonyl, an indole, and a solid support, at three different points (A, B, and C) around a common piperidinone scaffold (**16**), they were able to create a range of pentacyclic scaffolds (**17–19**) by pairing the reactive groups attached to different positions. The pairing reaction used in this case was an extremely effective complexity generating reaction, based on methodology developed by Padwa and Mejia-Oneto.[38] The reaction involves the initial generation

of a rhodium carbenoid from the α-diazocarbonyl species, and this carbenoid then cyclizes with an adjacent carbonyl group to give a cyclic carbonyl ylid that is able to undergo 1,3-dipolar cycloaddition with the electron-rich 2,3-double bond of the attached indole moieties.

4.5.3 Build/Couple/Pair Strategies

The above work by Oguri and Schreiber can be considered to be an example of the build/couple/pair strategy as the initial building blocks A, B, and C must first be built, then coupled to the piperidinone template, and finally the reactive functionality paired intramolecularly to yield the products. Another example of the build/couple/pair strategy incorporating a folding pathway can be found in the work of Mitchell and Shaw (Scheme 4.6).[39]

In their work, the build phase involved the synthesis of a solid-supported methoxy oxazole (**20**) and various azide-decorated aromatic aldehydes and benzyl bromides. The methoxy oxazole was then able to take part in an enantioselective Suga–Ibata reaction with

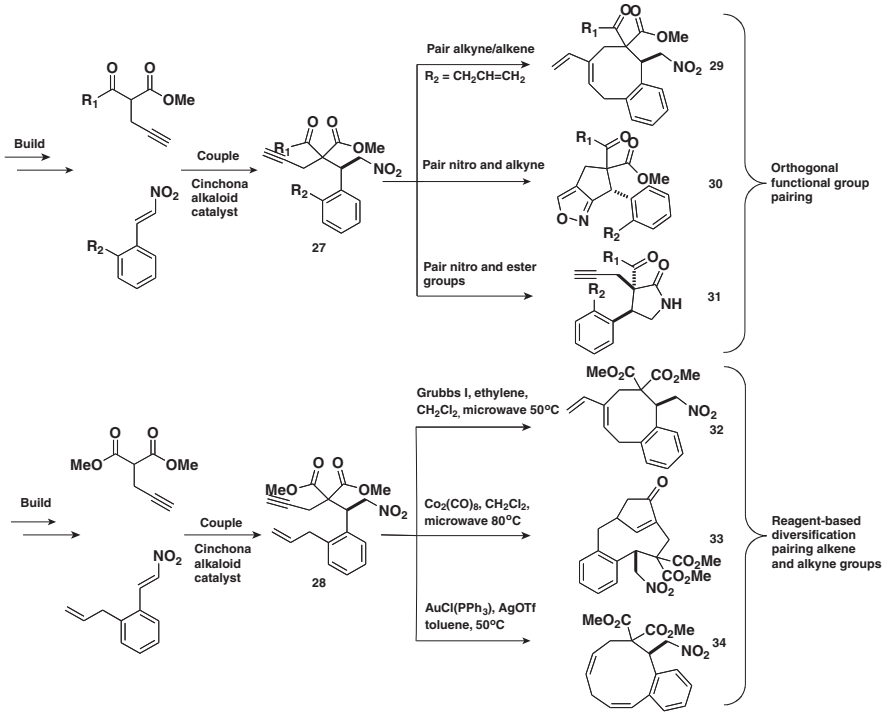


scheme 4.6. Mitchell and Shaw's folding pathway to produce fused and spirotricyclic compounds.

the aryl aldehydes to give **21**, the enolate of which was then alkylated with the benzyl bromides to give **22**. These substrates were then subjected to Staudinger-type reductive cyclization conditions to give tricycles **23–26**. This folding pathway is appealing from a skeletal diversity generating standpoint because depending on how the azide functionality is attached, the process can generate fused and spirocyclic compounds that have very different 3D structures and shapes. The authors also draw attention to the fact that the relative configurations of six- and seven-membered ring lactams give rise to significantly different dihedral angles associated with the two substituents attached to the oxazoline core of the final structures, resulting in further 3D chemical space coverage within the compound collection. These two examples are illustrations of the use of the build/couple/pair strategy in combination with a substrate-based approach to skeletal diversity construction.

A particularly elegant example of the build/couple/pair strategy combined with reagent-based skeletal diversity construction can be found in the solution-phase work carried out by Comer et al. (Scheme 4.7).[28] Their strategy involved the synthesis of a number of substituted β-nitrostyrenes and alkylated 1,3-dicarbonyls in the build phase that were then coupled by enantioselective Michael addition of the dicarbonyls to the β-nitrostyrenes using a cinchona alkaloid-derived organocatalyst to give densely functionalized molecules such as **27** and **28**.

They were then able to generate skeletal diversity by two different reagent-based strategies, by pairing different functionality orthogonally and pairing the same functional groups using different reagents. The functional groups available for pairing were (depending on the particular substrate) alkene, alkyne, and nitro and ester groups. The alkene and alkyne groups could be paired by enyne metathesis to give conjugated dienes such as



scheme 4.7. Functional group pairing strategy used by Comer et al.

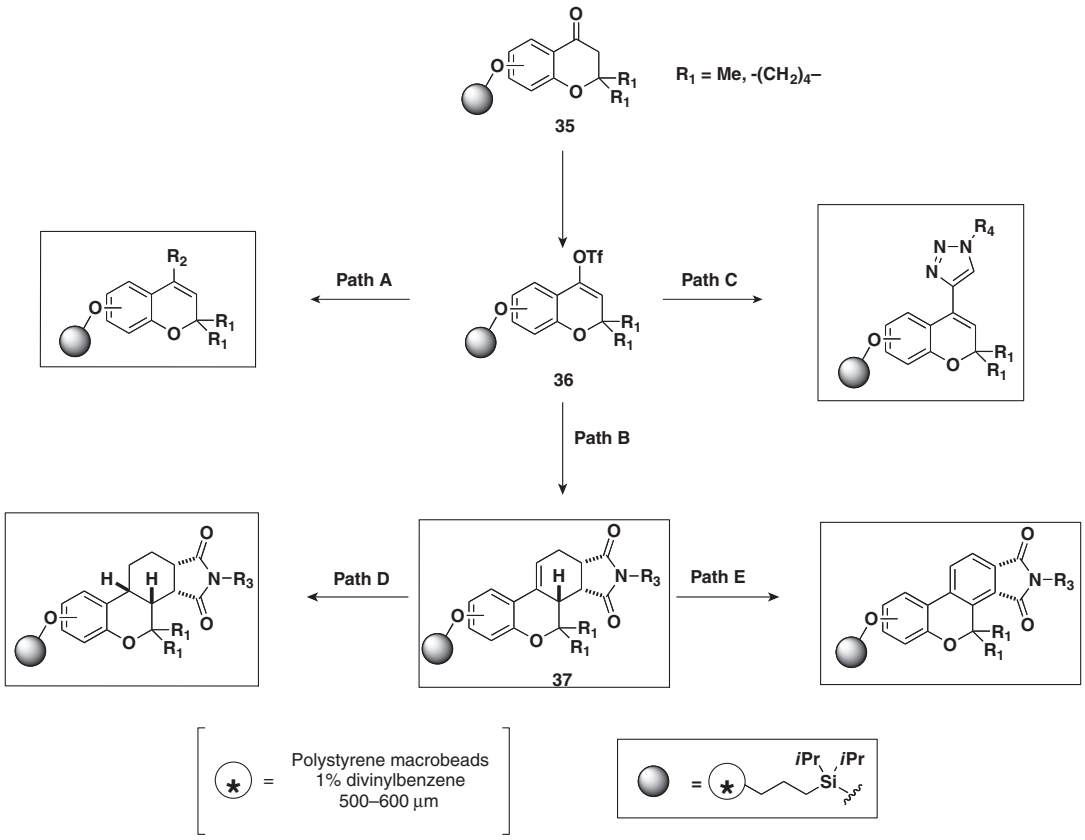
29, the nitro and alkyne groups could be paired by cycloaddition to give isoxazole-containing bicycles such as **30**, and the nitro and ester groups could be paired to give lactams such as **31**.

In addition to the already mentioned enyne metathesis to give **32**, the enyne functionality in **28** could also be paired using a cobalt-mediated Pauson–Khand reaction to give **33** and gold(I)-catalyzed cycloisomerization to give **34**. These reactions constitute an attractive branching pathway, and enyne cyclizations such as these are widely used in DOS. Another point to note about this particular pathway is that each of these products can be used in further reactions: **32** can undergo Diels–Alder reaction, the α,β-unsaturated ester **33** can undergo conjugate addition, and the 10-membered ring of cycloisomerization product **34** can be fused to a five-membered lactam by the subsequent pairing of the ester and nitro groups.

4.6 DIVERSITY-ORIENTED SYNTHESIS AROUND PRIVILEGED SCAFFOLDS

The above examples cover the range of planning strategies that are generally applied to "pure" diversity-oriented syntheses both in solid phase and in solution. Another planning strategy widely used is DOS around privileged scaffolds.[40–42] In this approach, divergent synthesis is applied around a core structure or scaffold with well-established biological activity. In many ways, DOS around a privileged scaffold is somewhat of a contradiction in terms as clearly the overall diversity of any library produced will be limited by the presence of a single core structure in all the compounds synthesized. Therefore, it is fair to say that rather than being purely diversity driven, these libraries can be considered to be more focused, both in their synthetic planning and end goals, than those produced from more authoritarian DOS. Despite this, DOS around a privileged scaffold is an effective way of exploring areas of prevalidated chemical space, with the aim of achieving increased potency and selectivity for a given target. If one were to consider the molecular diversity spectrum, then the libraries produced from this approach would be expected to lie somewhere between traditional combinatorial and DOS libraries. However, there are many situations where the DOS around privileged scaffold approach is especially applicable.

A recent example of DOS around a privileged scaffold can be found in the work of Park and coworkers (Scheme 4.8).[43] In a follow-up to previous work on DOS around the benzopyran scaffold,[44] they synthesized a library of 434 compounds on a solid support, the average purity of which, with no further purification, was 85%. Their synthetic effort began with the synthesis of eight distinct solid-supported chromanones (**35**), and these compounds differed in the substitution around the aromatic ring, and consequently the position of the linker unit, and also in the substituent R_1 that could comprise geminal dimethyl groups or a spirocyclopentane moiety. These compounds then underwent triflation to generate vinyl triflates (**36**), which were then subjected to several palladium-catalyzed transformations: Suzuki coupling (path A), Stille coupling with tributyl(vinyl)tin followed by a subsequent Diels–Alder reaction with substituted maleimides (path B), and Negishi coupling with an alkynyl zinc species followed by copper-catalyzed azide–alkyne cycloaddition with a range of azides (path C). The Diels–Alder products (**37**) were then able to undergo substrate-controlled asymmetric hydrogenation (path D) and aromatization (path E). Following this scheme, they generated five core molecular scaffolds based on the benzopyran motif; further appendage diversity around these scaffolds was then achieved through the choice of coupling partner.



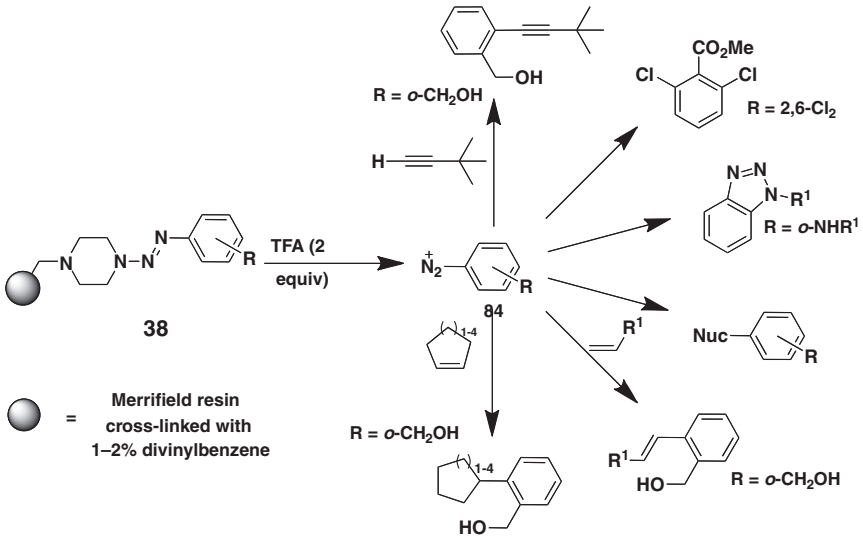
scheme 4.8. DOS around a privileged benzopyran scaffold.

4.7 DIVERSITY LINKER UNITS IN SOLID-PHASE ORGANIC SYNTHESIS

The majority of linker units used in the examples discussed in this chapter can be cleaved, under a single set of conditions, to leave behind a single functional group, usually a hydroxyl group. However, in the work of Thomas et al., the linker could be cleaved in four different ways to incorporate further appendage diversity into the library; therefore, it can be considered to be an example of a *diversity linker unit*.[45] The use of such linkers could be of great value to the field of DOS as introducing further molecular diversity and potential complexity at the cleavage stage of a solid-phase library synthesis would add considerably to the overall step efficiency and economy of the process.

The linker unit used by Thomas et al. was fairly limited in the degree of diversity that it could introduce; however, it is possible to generate a high degree of diversity, even including scaffold diversity, during the cleavage of certain linker units. This is well illustrated by the triazine-based linker **38** developed by Brase and coworkers. Treatment of this linker with TFA generates a highly reactive electrophilic aryl diazonium salt that can be intercepted by a range of nucleophiles to generate a diverse array of structures including aryl cycloalkanes and benzotriazoles (Scheme 4.9).[46,47]

Another class of linkers or more specifically cleavage strategies with potential application to DOS are those strategies that involve cleavage with concomitant ring closure

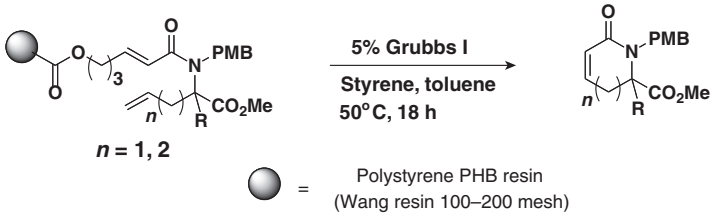


scheme 4.9. Diversity linker unit; cleavage produces a highly electrophilic diazonium species that can be intercepted by a range of nucleophiles.

to give cyclic structures. An example of such a process can be found in the work of Veerman et al., who used ring-closing metathesis (RCM) to release linear amides from solid support, while simultaneously synthesizing six- and seven-membered ring lactams (Scheme 4.10).[48] This strategy is valuable for DOS as it allows the incorporation of further skeletal diversity into a library of compounds.

4.8 CONCLUSIONS

In the 10 years since the DOS concept was first formally described, a number of imaginative strategies for the creation of libraries of structurally complex and diverse molecules have been developed. The synthesis of libraries that cover large areas of chemical space has proved a challenging yet rewarding endeavor, with extremely diverse compound collections being successfully created. Over the years, solid-phase synthesis has proved to be a useful enabling technology for DOS, allowing multistep syntheses to be performed efficiently, and any purification necessary is performed simply and generically. Indeed, all the largest DOS libraries produced have taken advantage of solid-phase techniques. The creative use of



scheme 4.10. Cyclative cleavage strategy to yield cyclic products by RCM.

solid-phase synthesis and linker units has allowed syntheses that would otherwise not be possible and also provided additional handles for reactivity on immobilized substrates.

In the future, the ideas that underpin DOS, such as maximal chemical space coverage and efficient complex structure generation, will remain. However, we may also see DOS being used in a more focused way, directed toward the synthesis of novel or unusual chemical structures and architectures, and used more in the field of fragment-based drug discovery. Whatever directions DOS takes in the future, it is likely that solid-phase synthesis will remain integral to the field.

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