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Research Article

Exploring the Benefit of Diversity Oriented Synthesis (DOS) *vis-à-vis* Other Synthetic Tools – A Review

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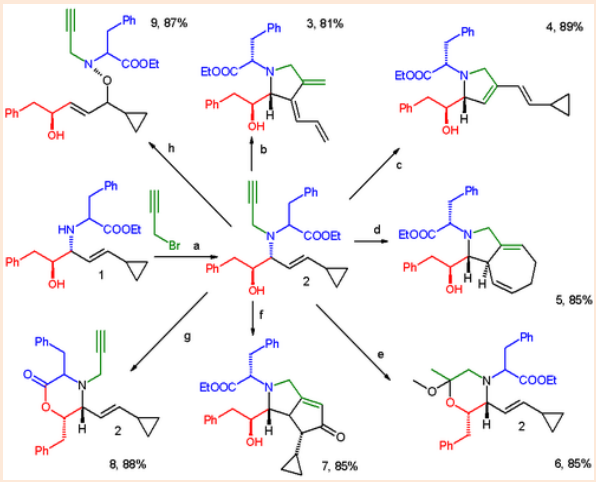
Abstract

This mini review letter discusses some basic concept of diversity oriented synthesis (DOS) which has evolved as an efficient and effective synthetic tool that has been very useful in the synthesis of structurally diverse libraries of compounds. This account also details some comparative advantages of the DOS over the other traditional synthetic tools, particularly the TOS, in the light of maximizing chemical space coverage and generating skeletal diversity. While exonerating the DOS as having far reaching impact for the discovery of small molecules with the desired properties in terms of the use of synthetic reagents, biological probes and catalyst application as applied in contemporary organic synthesis.

Keywords: Diversity, Target, Combinatorial, Structural, Synthesis



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Introduction

The evolution of combinatorial chemistry allowed for the synthesis of a huge stock of compounds. Indeed, a numbers of compounds are realizable by chemist on using split-pool combinatorial techniques [1]. However, a major drawback of combinatorial chemistry is that the compounds produced have a limited structural diversity. This is because only building block diversity is usually introduced. The structural diversity of the products obtained is due to the building blocks and starting scaffold. The resulting molecular framework is the same in every case. In order to achieve the highest levels of structural diversity: (*i*) the building blocks, (*ii*) the stereochemistry, (*iii*) the functional groups and, most importantly, (*iv*) the molecular framework must be varied. The pertinent questions that reside on the mind of the synthetic chemists are: Why do we need to synthesize structurally-diverse collections of compounds? And how do we synthesize structurally-diverse collections of small molecules? It is not obvious. Whereas, the synthesis of small molecules focused around a lead structure (the target molecule) is relatively easy: diversify a scaffold with different building blocks. It is evident from research studies that efficient synthesis of structurally diverse small molecules exhibiting a range of bioactivities has been distinguished from the traditional combinatorial chemistry and target oriented synthesis (*e.g.* natural product synthesis and focused 'library' synthesis) and thus termed *diversity-oriented synthesis*.

Diversity Oriented Synthesis (DOS)

There have been several definitions of DOS suggested, but in order to facilitate the present discussion the following definition will be adopted. "*Diversity-oriented synthesis involves the deliberate, simultaneous and efficient synthesis of more than one target compound in a diversity-driven approach to answer a complex problem"* [8]. Complexity in this text refers to binding, catalysis, phenotypic and synergistic effects *etc*. DOS describes a process whereby diverse collections of complex small molecules are synthesized in an efficient and deliberate manner [3,4] Although

complexity is not a prerequisite for diversity. It has been proposed to confer specificity in biological interactions [2]. There is, however, debate in the literature about this point [6,7]. In designing a DOS, analysis is performed in a forward sense and a strategy is developed whereby simple starting materials can be transformed into diverse and complex products. Unlike, in target oriented synthesis (TOS), where retrosynthetic analysis allows a complex product to be deconstructed in a backward sense. There is also a difference in the outcomes (and goals) of both approaches; whereas TOS aims to synthesize a molecule at a discrete point in chemical space. DOS aims to cover as diffuse an area as possible [5]. We would therefore like to suggest that DOS is a more "evolved" version of combinatorial chemistry. Thus, these terms are not mutually exclusive and the technologies overlap. DOS, however, does differ from *traditional* combinatorial chemistry as DOS does not target as selected an area of chemical space. An example of this selected targeting in *traditional* combinatorial chemistry would be in lead optimization for drug discovery. This comparison also serves to highlight another important issue, the subjectivity of diversity [4].

When a compound collection is synthesized, since the composite molecules are not identical, diversity, to a greater or lesser extent, is incorporated; the racemic synthesis of enantiomers could even be classified as a DOS. As a result of this subjectivity, and the free use of the terms "diversity" and "DOS" in the literature, considering diversity as a spectrum may be useful. In one extreme of the "molecular diversity spectrum" would be where maximal chemical space coverage has been achieved and, in the other extreme, would be a TOS (**Figure 1**) [4]. It should be the goal of a DOS to synthesize, in a qualitative sense, collections as near to the right-hand side of the "diversity spectrum" as possible [4]. It should be noted that DOS and TOS are different strategies with different goals. The above serves to compare the diversity achieved using either approach regardless of the eventual aim; it is not to be implied that DOS is better than TOS as it generates more diversity, merely that, to maximize chemical space coverage, skeletal diversity is essential. It is this skeletal diversity that can be incorporated using the DOS (and not the traditional combinatorial chemistry) approach to library synthesis.

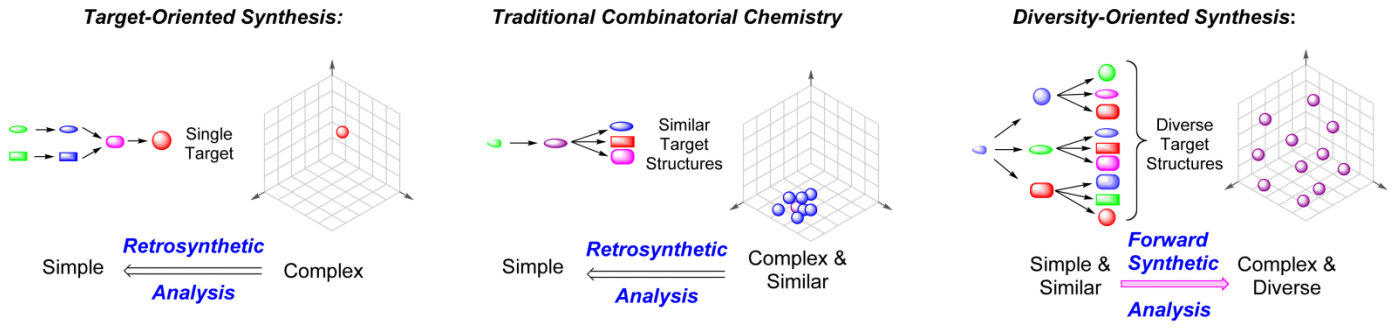


Figure 1 An overview of the strategies and approaches of TOS compared to (DOS); the former aims to prepare molecules at discrete points in chemical space, whereas the latter strives to cover as much of chemical space as possible. The partition between DOS and combinatorial chemistry is less clear cut. DOS does, however, differ from traditional combinatorial chemistry (or focused library synthesis). In these latter approaches, a discrete region of chemical space is interrogated, the chemical space around a lead compound, for example.

The Utility of DOS in the Chemical Space

In the face of a challenging goal, how can a DOS be designed compared to TOS? In target-oriented synthesis (TOS), retrosynthetic analysis is employed to find an efficient and convergent route using complexity-generating reactions (**Figure 2**), which construct efficiently structural complexity such as the Diels–Alder reaction, where two C–C bonds are made regioselectively (Alder rule), stereospecifically *syn*, stereoselectively (*endo vs. exo*) and enantioselectively (if a chiral mediator is exploited). Unlike, in the DOS which requires a planning algorithm to deliver an efficient but divergent route. Complexity-generating reactions are again important for efficiency (multi-component-coupling, cascade and tandem complexity-generating reactions); however, pathways need to be identified that give structurally diverse targets. In order to design a synthetic pathway leading to a collection of compounds with different scaffolds requires the use of branch points, where a common substrate is used in different reactions that give different atomic skeletons. For example, nature takes acetyl CoA and makes terpenes, steroids, polyketides, *etc*, by branching

pathways leading to each structural class. The synthesis of structurally diverse and complex collections of small molecules still remains a major puzzle to the synthetic chemist [8].

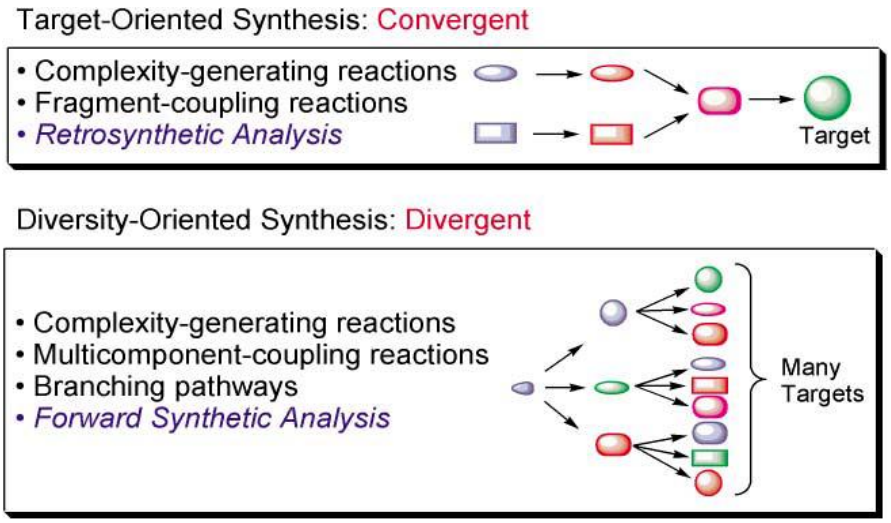


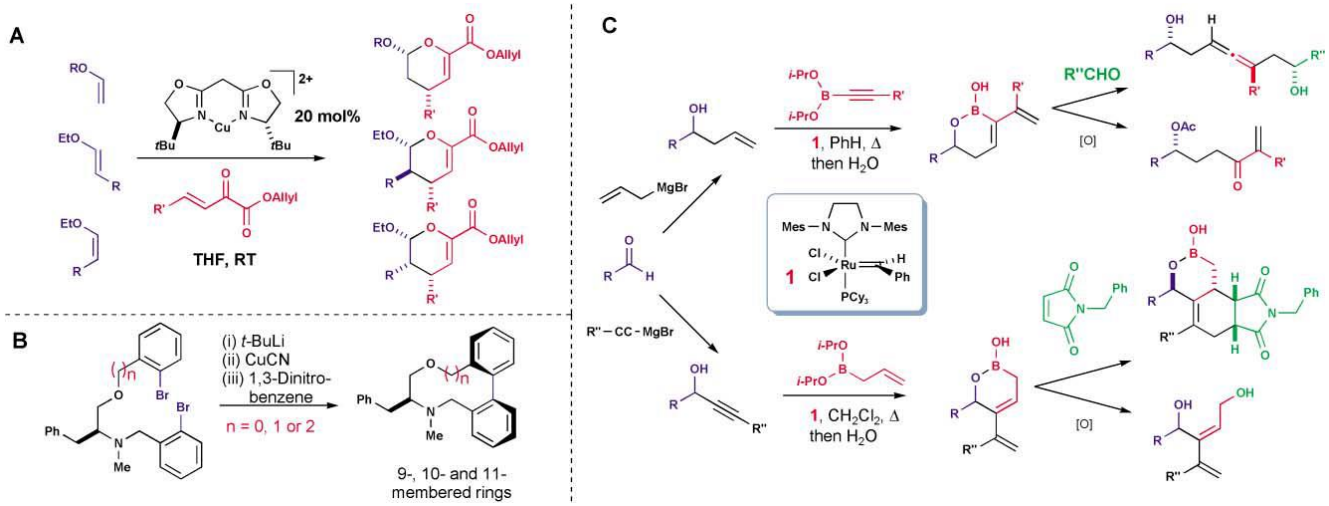
Figure 2 Comparison of target-oriented synthesis (TOS) *versus* diversity-oriented synthesis (DOS). Note there is no necessity for a solid-support (*e.g.*on polystyrene beads) to perform diversity-oriented synthesis; however, solid-supported synthesis has the advantages of generic purification (filter and wash) and synthetic efficiency using splitpool strategies [12]. No specific meaning is implied by the colours or shapes except that each unit represents a different compound

As an illustration of how to design a diversity-oriented synthesis D. R Spring reported a synchronise detail on the benefit of complexity-generating reactions together with branching pathways [8]. Perhaps, if they take was to make chiral compounds; hence, it requires that the inclusion of stereochemistry is vital (**Scheme 1A**).

Catalytic asymmetric reactions are most useful since the stereochemical outcome of the reaction is determined by the enantiomer of the catalyst added, whereas when chiral auxilaries require two substrates to give both enantiomers. Cyclic, bicyclic and polycyclic compounds are often relatively rigid (*e.g.* steroids), which can minimise loss of conformational entropy on binding to a protein/reagent/substrate; however, cyclisation strategies need to be considered carefully, especially with medium and large ring sizes (**Scheme 1B**).

TOS has shown us that medium and large ring formation can be unpredictable, with subtle changes in substrate substituents, solvent and other conditions being important for reaction success. In DOS, methodology has to be used or developed that will work on a wide range of substrates and be compatible with a wide range of functional groups. Thus, methodology development for DOS is more demanding than for just a total synthesis, for example, where often the method has to work with only one substrate. With methods for controlling stereochemistry and efficient, reliable, general synthetic methodology already determined, branching pathways are then conceived. Branch points are devised by choosing reactions that take the same substrate functional group to furnish different functionalities, stereochemistry and molecular frameworks (**Scheme 1C**).

Building blocks are then chosen that contribute best to the structural diversity of products. For instance, if six aldehyde building blocks are required, then structurally diverse ones are chosen, *e.g.* acetaldehyde (small alkyl), trimethylacetaldehyde (large alkyl), benzaldehyde (aromatic), furfural (heteroaromatic), glucose (hydrophilic), and dodecanal (hydrophobic). Within just a few steps a single substrate can be modified into structurally-complex and structurally-diverse outcomes. The key to the structural complexity is the complexity-generating reactions; the key to the structural diversity is the branch points and building blocks [8].



Scheme 1 Diversity-oriented synthesis strategies. **A**: Example of enantioselective catalysis in DOS. The copper bis(oxazoline) Lewis acid catalyses the inverse electron demand heterocycloaddition of a broad range of vinyl ethers and β,γ-unsaturated ketoesters with outstanding efficiency and selectivity [5]. **B**: Example of ring formation in DOS. A wide range of substituted acyclic precursors could be cyclised to give biaryl-containing medium rings efficiently and atropdiastereoselectively [11]. **C**: Example of branching pathways in DOS. Structurally-complex and diverse products are synthesized elegantly by annulation reactions of alcohols and boronic esters (transesterification then ring-closing ene-yne metathesis), followed by divisional, complexity-generating steps [10].

Conclusion

The emergence of DOS of small molecules has been very resourceful, particularly in the application of new strategies to generate appendage and skeletal diversity. In recent years, enormous progress has been made that utilizes fragment-based molecular descriptors to determine the structural diversity of collections of small molecules [9]. However, if the benefit of the DOS is to be made more useful generally the process of selective small molecule discovery to modulators must be enhanced. Since accessing diverse regions of chemical space still represents a significant but potentially rewarding challenge for organic chemists.

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