Maximizing Synthetic Efficiency: Multi-Component Transformations Lead the Way

Hugues Bienaymé,*[a] Chris Hulme,[b] Gilles Oddon,[a] and Philippe Schmitt[a]

Abstract: With the emergence of high-throughput screening in the pharmaceutical industry in the early 1990's, organic chemists were faced with a new challenge: how to prepare large collections of molecules (the libraries) to "feed" the high-throughput screen? The unique exploratory power of some reactions (such as the 40 year-old Ugi four-component condensation) was soon recognized to be extremely valuable to produce libraries in a time- and cost-effective manner. Over the last five years, industrial and academic researchers have made these *powerful* transformations into one of the most efficient and cost-effective tools for combinatorial and parallel synthesis.

Keywords: combinatorial chemistry · heterocycles · multicomponent reactions · productivity · synthetic efficiency

Drug Discovery: The New Paradigm

With increased economical pressure on the pharmaceutical and agrochemical industries, and the ensuing emergence of high-throughput screening of drug candidates, corporate synthetic chemists were faced with one of their greatest challenges: producing large collections of molecules, as diverse and structurally distinct as possible, in a time- and cost-effective manner.

The cost and mass production aspects of this paradigm were solved through parallel automated synthesis, and by systematic exploration of the chemical pool (combinatorial chemistry).[1] These techniques are now commonplace and have set new productivity standards in most major life-science industries.

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Generating a large collection of molecules is a requirement, but is by no means the sole criterion in rating the quality of a library of molecules. Besides size, the optimization of several other parameters is important. Among them, the diversity criterion is of the utmost importance.

One way to enhance the sampling quality of the chemical pool is to maximize the number of chemical reactions transposed to systematic exploration. In the selection of the reactions to transpose they are not all equal and of the same potential value. A good reaction to employ would be one that uses the best advantage of the systematic exploration by having a maximum number of variation centers and, for a given variation center, a maximum number of variations attainable. Among this class of reactions the multi-component reactions (M-CRs), which could be briefly defined as reactions in which at least three chemical functionalities join through covalent bonds, are particularly suited to fulfill these criteria (Figure 1).[2]

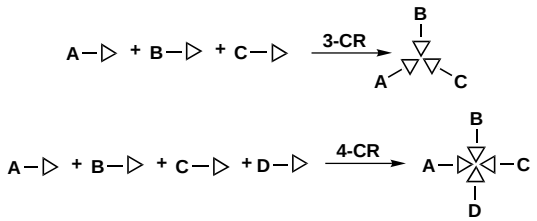

Figure 1. Multi-component reactions.

A rapid look at the literature will convince the most skeptical that M-CRs are becoming increasingly popular. This interest upsurge is best illustrated by the number of articles published per year in the area (Figure 2).[3] Although not yet as popular as the field of solid-phase synthesis, it is reasonable to believe that this field will continue to grow as both the academic and industrial sectors are directing their efforts towards more efficient drug-discovery processes.[4] The objective of the present article is to highlight how and why M-CRs have gained a special place in the arsenal of the synthetic chemist to deal with the new paradigm of drug discovery.[5]

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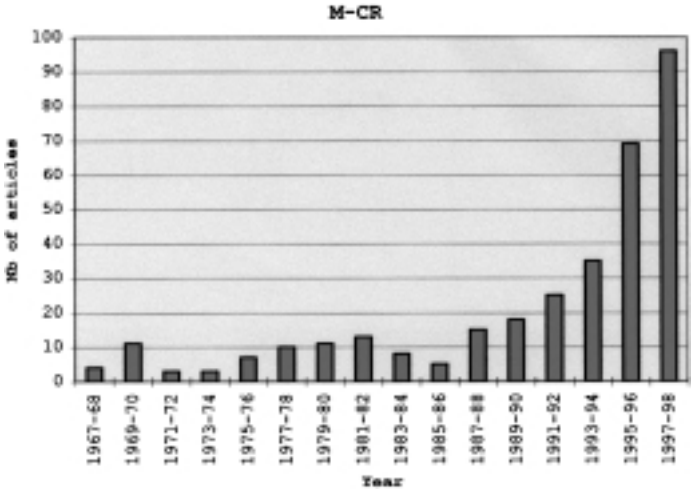

Figure 2. Number of publications per year on M-CRs.

M-CRs

Reactions with high exploratory power: If drug blockbusters were gold, drug discovery chemists could be depicted as prospectors, exploring a yet unknown landscape, collecting soil samples as numerous and distant from each other as possible. But the chemical pool, which contains all the structures one could draw given a infinite amount of time, is by no way a landscape or even a infinite surface, but more like a *n*-dimensional space with *n* being a user-defined number of parameters (chemoinformaticians would call them metrics) representing to the best of our affordable means the qualities and physico-chemical properties of a drug candidate. Chemical reactions are our medium of travel from place to place and, already mentioned, they are not all equal in doing their job. In choosing an efficient reaction/vehicle, one would prefer a reaction that starts from simple synthons to produce an *optimum complexity* product[6] and a reaction *versatile* enough to allow a maximum number of new structures to be reached by systematic variation of reactants. A reaction that induces a large increase of structural complexity from starting materials to products and which possess a high degree of versatility would be said to have a high *exploratory power*.

By standing with our image of the chemical pool depicted as a plane, one could fully describe a chemical reaction as a vector with a length proportional to the increase of structural complexity it produces from reactants to products, in which the angle (θ) is related to the actual reagents being used. A reaction with a high versatility, or scope, would have a high degree of tolerance of, or compatibility with, the initial reagents and thus many different values of θ would be feasible. The exploratory power of a reaction could then be defined as the surface area described by the vector as θ varies within the tolerable $\Delta\theta$ range. By using this classification the one-pot transformation of an acyclic squalene derivative into a pentacyclic alkaloid would be associated with very large increase of molecular complexity, but the structural constraints imposed on the reactants would be so great that only a very few derivatives would be attainable (Figure 3).[8] The corresponding surface area would be rather

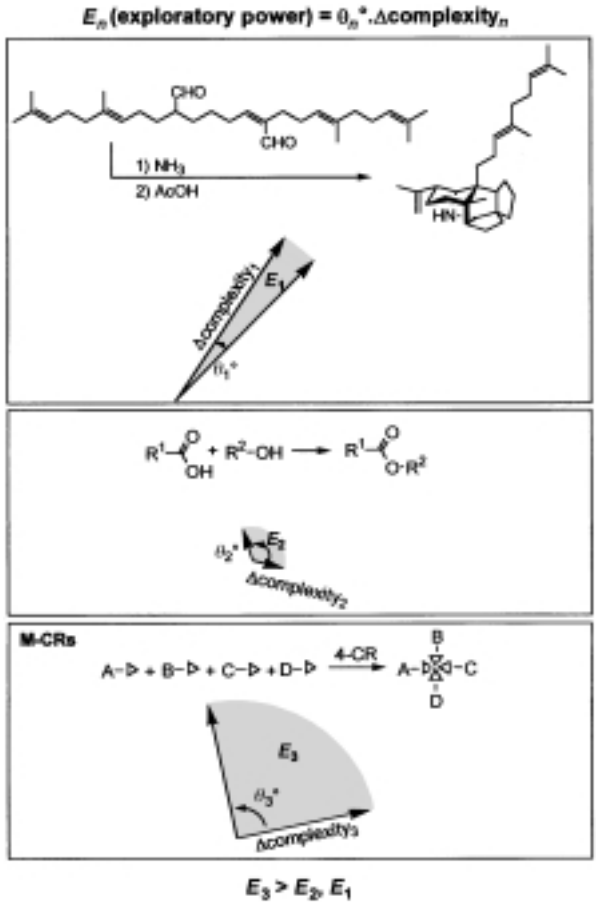

Figure 3. Exploratory power of various classes of reactions.

small despite a quite long associated vector. On the other hand the formation of an ester from an alcohol and an acid would offer a large $\Delta\theta$ as many alcohols and acids are available for that reaction. However, the corresponding increase of molecular complexity would only be modest as it is only related to the complexity of two reagents and the formation of a single bond. For the combinatorial chemist, both of these reactions would be considered as having a low to medium exploratory power and be probably disregarded if used in a single-step process. In contrast, an average M-CR would be associated with a long vector as at least three reagents and several newly created bonds would contribute to the product molecular complexity, and a large $\Delta\theta$ as many reagents combinations would be allowed (Figure 3).

In addition to their high exploratory power, M-CRs possess several attributes of synthetic efficiency.

- Selectivity: even though diversity is a goal, one expects to form only a single product from a given set of inputs.
- Atom economy: the valuable property of transformations in which adducts are composed of the exact sum of the reactants.[9] Maximizing atom economy avoids wasteful atom loss from the starting materials.[9a]
- Convergence: a synthesis route is said to be convergent when it tends to maximize the overall yield by minimizing the number of consecutive steps for each building block.[10] Accordingly, an M-CR, as a synthetic route, is the ultimate in maximal convergence.

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From a practical standpoint, understanding why these transformations have found such deep interest by the combinatorial community is simple: a single-step transformation is needed to synthesize a target compound. In most cases the reactions will be robust enough to give high yields by simply mixing reagent solutions at room temperature; this allows large molecular collections to be prepared with minimal man power. Therefore, together with a high exploratory power, multi-component reactions may be defined as productive according to industrial standards (number of samples produced per unit of time, per chemist).

Finally, as is clear from the previous discussion, exploratory powerful reactions require a combination of qualities that makes their discovery and development a difficult goal to achieve (Figure 4). Nevertheless, the intensive research effort

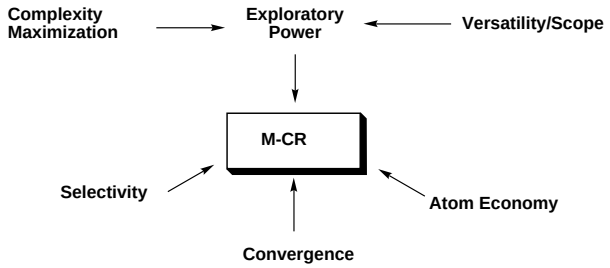


Figure 4. Attributes of powerful transformations make M-CRs highly efficient reactions in the context of combinatorial synthesis.

currently undertaken towards the discovery of new M-CRs is driven by the considerable economical value attached to them.

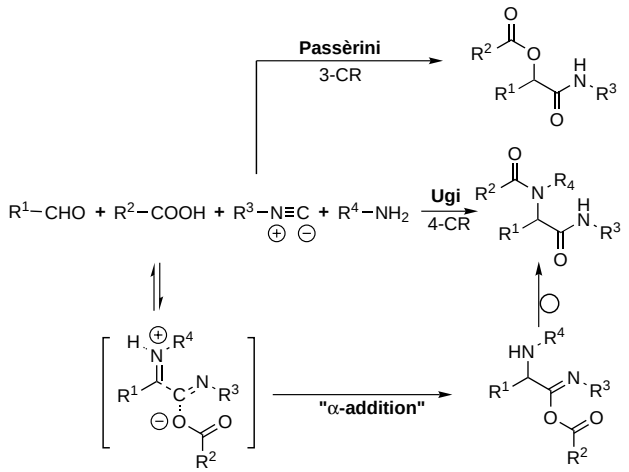
M-CR in practice: Combinatorial collections are typically composed of 10^2-10^3 members (for focused or targeted libraries)[11] and 10^4-10^5 members (for generic libraries). Powerful transformations should allow facile and rapid access to both such directed and large generic libraries.

There is, however, a general consensus today regarding the structural nature of pharmaceutical libraries: combinatorial chemists are tending to move away from peptides and other oligomeric libraries (which were massively generated in the first years of combinatorial chemistry), to focus on heterocyclic low-molecular-weight molecules (i.e., the so-called "drug-like" molecules). The movement is clearly motivated by several reasons, specifically the generally poor bioavailability and biostability of peptides and their derivatives, and the difficulty in optimizing these flexible structures once a hit has been identified. On the other hand, constrained structures provide more workable "structure–activity relationship" (SAR) data about protein/ligand interactions. These considerations are at the basis of a recent upsurge in the interest of powerful heterocyclic M-CRs, as will be shown below.

Exploratory power is not the sole advantage of such reactions. Other benefits of these approaches are highlighted below :

- The time devoted to chemistry development (often the major constituent of overall library generation) will be shorter than with a multi-step process.
- The mean library purity will be higher, as side-products will not accumulate with the number of steps: that is, the shorter, the better.
- These one-step or "multi-step, one-pot" procedures are often compatible with a solution-phase approach to library generation. In these cases, common drawbacks associated with the use of resins (e.g., troublesome monitoring of the reaction advancement, requirement of anchoring functions that limit the input diversity, linker and resin compatibility, etc.) are avoided.
- The "hit to lead" transition (i.e., the rapid acquisition of primary SAR), or the lead optimization (vs. various pharmacological parameters) may be shortened, if the same chemistry is used throughout the process.
- Ultimately, one might speculate that an M-CR-based industrial process would be more cost-effective than an multi-step route owing to the higher degree of convergence associated with the corresponding synthetic pathway.

Multi-component and cascade processes:[2] The most famous, and truly powerful reaction is the Ugi four-component reaction (U-4CR, Scheme 1).[12] Its uniqueness was recog-



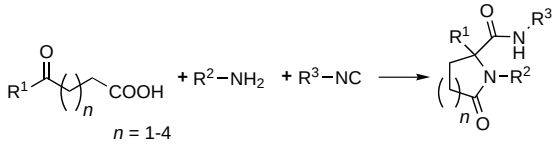
Scheme 1. The Ugi and Passérini multi-component condensations.

nized early on, even well before the introduction of combinatorial methods: "If, for example, 40 each of the different components are reacted with one another, the result is $40^4 = 2\,560\,000$ reaction products..".[12b]

The key in this case lies in the unique property of the isocyanide function to undergo an "α-addition" process. From the initial isocyanide carbon, after transition from the divalent (isocyanide reactant) to the tetravalent state (imidate adduct), two new covalent bonds are created. In the Passérini and Ugi reactions, which are conceptually related, this α-addition step takes place between an electrophilic species (an aldehyde or an immonium salt) and a heteroatomic nucleophile (a carboxylate ion). The isocyanide function can thus be viewed as a stable synthetic equivalent of a vinylidene carbene. This behavior, a truly multi-component event, is at the basis of the success of the Ugi reaction and other powerful isocyanide-based transformations in combinatorial chemistry.

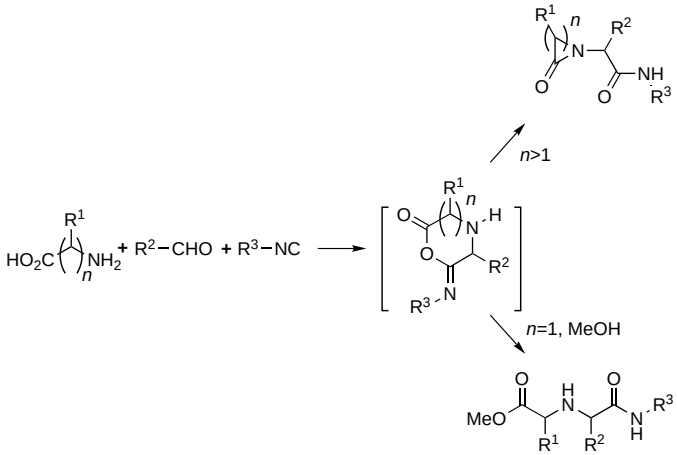
The Ugi-4CR can be (and has been extensively) used for the generation of both large generic and smaller focused libraries.[13]

Constrained Ugi adducts: Ugi adducts are peptide-like by nature and, therefore, as mentioned above, can be problematic with respect to bioavailability. A simple, yet efficient, way to access pharmacologically more relevant heterocyclic structures by using the Ugi reaction is to tether two reaction partners. For instance, various ring-size lactams can be prepared by linking the carbonyl and the carboxylic acid inputs through a variable spacer (Scheme 2).[14]



Scheme 2. Three-component synthesis of substituted lactams.

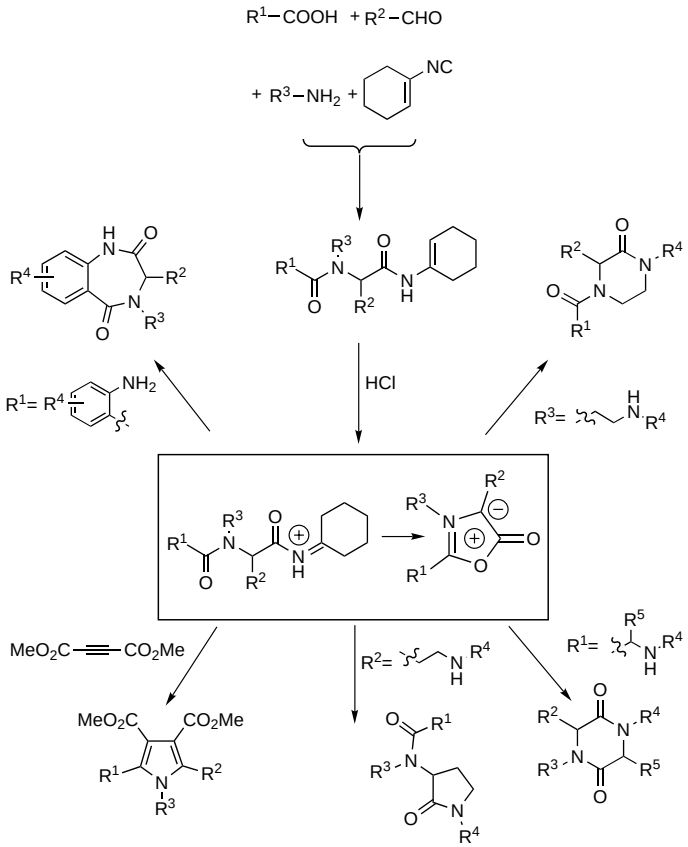
Similarly, β- and higher lactams are produced from β- and higher aminoacids. With α amino acids, aminodiacetic adducts are obtained through the solvent interception of the activated *O*-acylimidate intermediates (this latter reaction has been designated the Ugi 5-center 4-component reaction, Scheme 3).[12b, 15]



Scheme 3. The Ugi lactam and aminodiacetic adduct syntheses.

Neglecting the diversity, which could be introduced by using a variety of alcohols as solvents, the number of inputs (variables) are reduced in both cases from four to three. However, this strategy is still viable for the production of rather large libraries ($\geq$10000 compounds) if all inputs including the bifunctional reactants are readily available (either commercially, or easily synthesized).

An alternative strategy for ring closure consists of post-condensation modification or what is sometimes referred to as a secondary reaction.[13a] In this case a latent activating substituent must be introduced as part of one of the inputs (preferably the isocyanide) to cope with the relatively unreactive nature of amide bonds.[16] 1-*cyclo*-Hexenylisocyanide (the so-called convertible isocyanide), for instance, has been used for this purpose. Protonation of the enamide functionality, generates a transient activated *N*-acyliminium ion, which can undergo further ring closure with expulsion of a *cyclo*-hexyliminium cation to either form a münchnone intermediate or the corresponding methyl ester. *N*-BOC deprotection and cyclization of the internal amino-nucleophile affords a range of potential biologically relevant products including 1,4-benzodiazepine-2,5-diones,[17] diketo- and ketopiperazines,[18] and lactams.[19] If no internal nucleophile is present, this münchnone can still be trapped by an external dipolarophile to yield poly-substituted pyrroles (Scheme 4).[20]



Scheme 4. Post-condensation modifications of Ugi adducts.

Similarly, access to ring systems can be accomplished by "programming" one of the inputs for a second in situ transformation. A combination of a modified Ugi four-component condensation (with hydrazoic acid) with a subsequent Michael addition – elimination process yields bicyclic tetrazoles in a two-step one-pot protocol by using an isocyanide input that contains the requisite β-dimethylaminoacrylate moiety (Scheme 5). Thus, rather elaborated and rigid molecules can be prepared directly from simple precursors.[21]

Other isocyanide-based multi-component transformations: Recent reports have revealed that the reactivity of the isocyanide functionality can be exploited in alternative ways.

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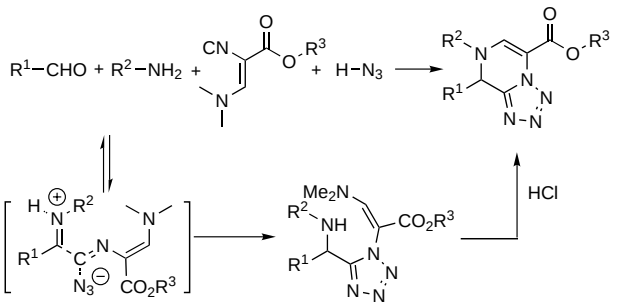
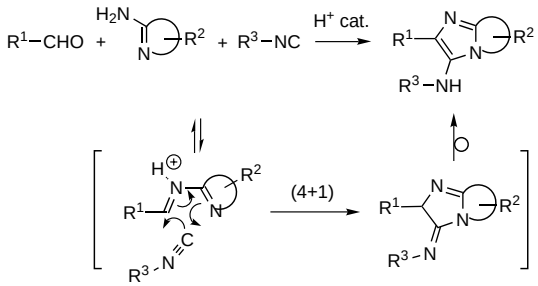


Scheme 5. A "two-step, one-pot" fused-tetrazole synthesis.

An entropically-favored [4+1] cycloaddition (or cheletropic addition) to protonated 1,3-diazadienes has been exploited in a very efficient synthesis of a variety of amino-3-imidazoles. The isocyanide behaves in classical fashion (iminium electrophile and heteroatomic nucleophile), but the structural diversity generated is original (heteroaromatic ring formation) and of great value to combinatorial synthesis (Scheme 6).[22]



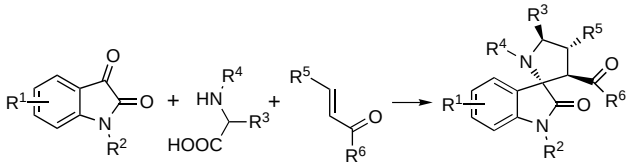
Scheme 6. The amino-3-imidazole three-component synthesis.

The exploratory power of such heterocyclic three-component syntheses is remarkable; over 30000 elaborated heterocycles have currently been synthesized by solution phase techniques in our laboratory, mostly from commercially available or readily synthesized building blocks, in a reasonable time-span.[22a]

From the various examples shown above, it is quite clear that the unique reactivity pattern of isocyanides can be utilized through conceptually similar, but structurally different reactions (though all contain at least one nitrogen atom). It is expected that, as interest in this field grows, new reports of isocyanide related M-CRs will emerge. One new area of powerful transformations to recently appear is the concept of the union of M-CRs (for example double Ugi reactions developed by Ugi).[13, 17]

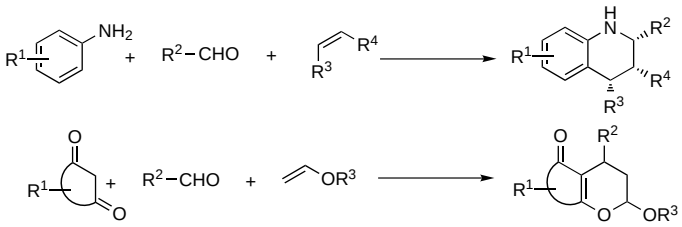
Other multi-component or cascade transformations: Examples of multi-component processes used for the generation of libraries are often based on a simple disconnection principle. Thus, reactive intermediates used in known two-component condensations are "reassembled" in situ from two simpler and available precursors through a high yielding process (usually an imine formation or a Knoevenagel condensation).

Azomethin-ylids for example can be disconnected into α amino acids and aldehydes or ketones.[23] In situ interception of these species with substituted olefins yields pyrrolidines and is a simple way to transform a classical two-component 1,3-dipolar cycloaddition into a three-component reaction. Using this procedure, 25600 compounds have been prepared (from a potential pool of an estimated 400000 compounds) from isatins, α amino acids, and chalcones (Scheme 7).[24]



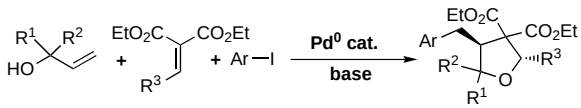
Scheme 7. A pyrrolidine three-component synthesis.

Similarly, electron-deficient heterodienes involved in inverse electron-demand [4+2] cycloadditions can be simply disconnected into widely available precursors (e.g., primary anilines/aldehyde and 1,3-diketones/aldehydes, Scheme 8)[25, 26]



Scheme 8. [4+2] Cycloadditions with heterodienes generated in situ.

Interestingly, a cascade of a Michael addition and an olefin nucleophile carbo-functionalization catalyzed by palladium, have been demonstrated for the synthesis of substituted tetrahydrofurans (Scheme 9).[27] So far, these metal-catalyzed



Scheme 9. A palladium-catalyzed multi-component tetrahydrofuran synthesis.

multi-component processes remain rare.[28] They hold, however, great promise for the rapid construction of structures that are not readily accessible through other means.

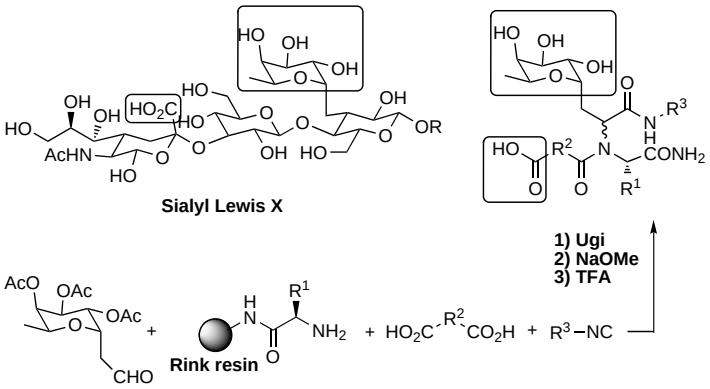
Purity and purification: For libraries prepared from multi-component processes, the crucial issue of products purity (or mean product purity) must be addressed.

Yields and overall purities are strongly affected by the nature of the reactants and reaction conditions. In fact, crude product purity may vary enormously throughout a library made from diverse inputs and, if no purification is performed, could contribute to erroneous and misleading biological data. Hence, purification is often part of the library design strategy and must be studied at an early stage during chemistry development.

Two major strategies have been used to increase the mean library purity: supporting one input on a resin, or effecting a

parallel solution-phase "high-throughput purification".[29] In both approaches, satisfying purities are insured by simple way of filtration work-ups, which removes excess reagents and any by-products that do not posses the linked or tagged input.

As illustrated below, the choice of supported input is often governed by the target structure (Scheme 10). A 192 compound library of sialyl Lewis X glycomimetics was prepared



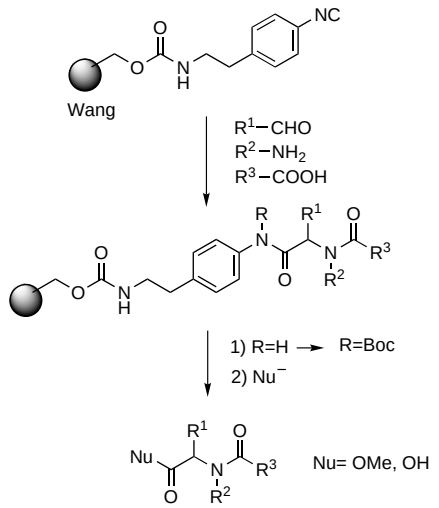
Scheme 10. Sialyl Lewis X "glycomimetic" productive synthesis.

by utilization of a series of diverse amines bound on polystyrene beads (Rink amide linker) and properly designed building blocks. Consistent purities of over 95%, were observed across this small library.[30]

For generic libraries, use of the isocyanide input is often the best choice. It belongs to the most restricted reagent class as a mere 20 representatives are available from commercial sources (though they are readily prepared from primary amines).[12b, 31] This limited commercial availability does put limits on the attainable diversity. Product diversity in libraries derived from early resin-bound isonitriles, for example, was lowered by constraints on the linker and clipping strategies, often leaving final products poisoned with isonitrile solvolysis by-products.[32]

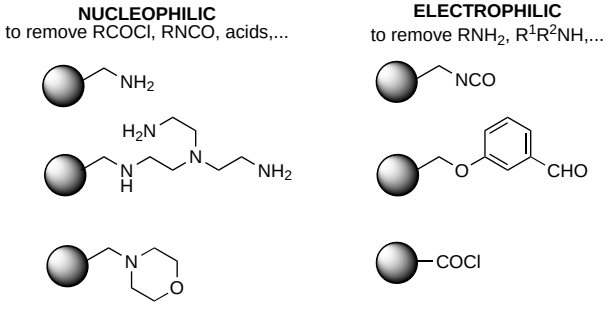
A new isocyanide safety-catch linker has, therefore, been recently developed to release the multi-component adduct through *N*-BOC activation (the safety-catch) and subsequent hydrolysis, or esterification, of the amide carbonyl. This transformation allows the generation of a methyl ester, which can be further manipulated in solution to give a range of known heterocyles (benzodiazepine-2,5-diones, keto- and diketopiperazines, dihydroquinoxalines, Scheme 11).[33] The methoxide safety-catch clipping strategy and subsequent solution-phase cyclization offer similar advantages to a traceless linker as no functionality derived from clipping remains at the end of the synthetic protocol.

Solution-phase purification techniques are especially useful and provide a complement to the solid-phase-supported technique. With productivity in mind, parallel purification techniques must not compromise the synthesis output. This implies that the minimum number of operations per sample is required (maximum of two). Hence, traditional chromatographic techniques, even automated, are prohibitive for large libraries (>1000 samples). Three techniques are usually used for work-up of solution-phase syntheses.



Scheme 11. Supported Ugi condensation with a "safety-catch" linker.

- Simple liquid–liquid extraction has been used, but is only applicable in a limited number of cases (i.e., when the partition coefficient between two non-miscible liquids, usually water and an organic solvent, is substantially different for the reactants and the adduct). Variations around this theme, such as the non-miscibility of fluorinated solvents in other organic solvents, has been used to purify molecules bearing a fluorinated tag.[34]
- Solid-phase scavengers are another option. Covalent or ionic bonds are created between two complementary functional groups, one linked on a support, the other to be removed from the reaction mixture. Quantitative reactions, such as imine formation, amide or urea formation, protonation, and so forth are used to remove excess amount of amines, aldehydes, ketones, acids, or acid chlorides. Mixtures of different scavengers can also be used owing to the virtue of phase segragation even when the supported functions are not chemically compatible. A selection of scavenger resins is presented below (the support may be either polystyrene or silica).[29, 35]



- Solid-phase extraction is used when two complementary functions exist between the product to be purified and the support. Usually, noncovalent interactions (ionic, hydrophobic) are involved to temporarily sequester the product on solid-phase. All molecules that do not posses this complementary function are subsequently washed away, and the product released in a subsequent operation.

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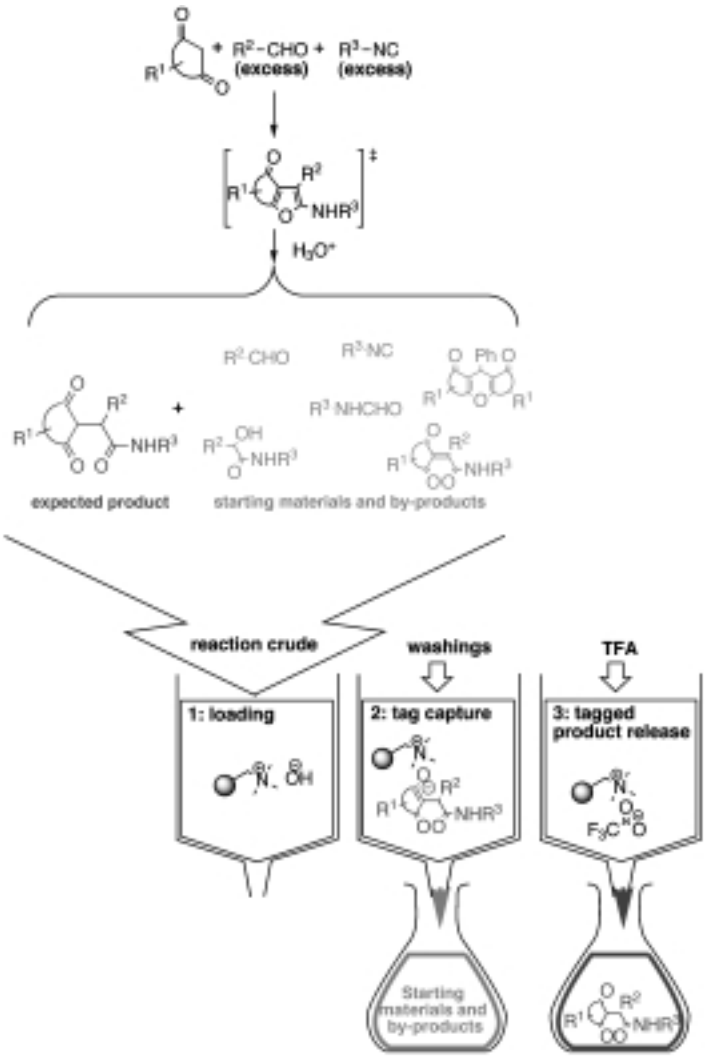
The following example is illustrative of the last purification strategy, which is often more efficient than the scavenger resin approach (Scheme 12).[36]



Scheme 12. High-throughput purification protocol of 1,3-diketones.

Preparation of a collection of 2-substituted 1,3-diketones has been undertaken in our laboratory by mixing a variety of 1,3-diketones with various aldehydes and isonitriles. As prior screening of the synthetic conditions had revealed that the expected products could often not be obtained with a good yield ($\leq 30\,\%$), transposition of this reaction to parallel synthesis had to take into account a powerful purification technique to separate both starting materials and by-products from the expected compounds. Satisfactory purification (purities often above 90%) was achieved after proper selective extraction of the acidic expected product on anion-exchange cartriges, intensive washings of starting materials and by-products, and subsequent product release by elution with dilute trifluoroacetic acid.

The majority of the purification techniques described herein are well documented, although their applications in the field of traditional organic synthesis is underdeveloped.[37] The recent growth of interest in ion-exchange chromatography, solid-phase extraction, or related techniques clearly emphasizes the development of highly efficient and easy to automate purification protocols. In this process, one should keep in mind that compatibility with a range of functionally different molecules is of extreme importance. Neglecting this aspect will rapidly replace the former synthesis bottleneck with a purification bottleneck!

Together with chemistry, purification is now heading towards more "efficiency".

Equipment: One attractive feature of the multi-component reactions is the relative ease of its automation. Unique reactions may be run in parallel by solution- or solid-phase protocols in a 96-well format (8×12). Dispensing of reagents is facile and rapid with a range of commercially available automated 96-well or *X*, *Y* dispensers (Tom-tech™, Rapid Plate™, Hydra 96™, Gilson, etc.). Especially noteworthy are commercially available Calypso™ reaction frame assemblies (Charybdis technologies) that, when combined with a 96-well filter plate (Polyfiltronics™), allow automation of a range of solid-phase syntheses and parallel purification techniques (see Figure 5 for a representative example of a 96-well reactor).[38]

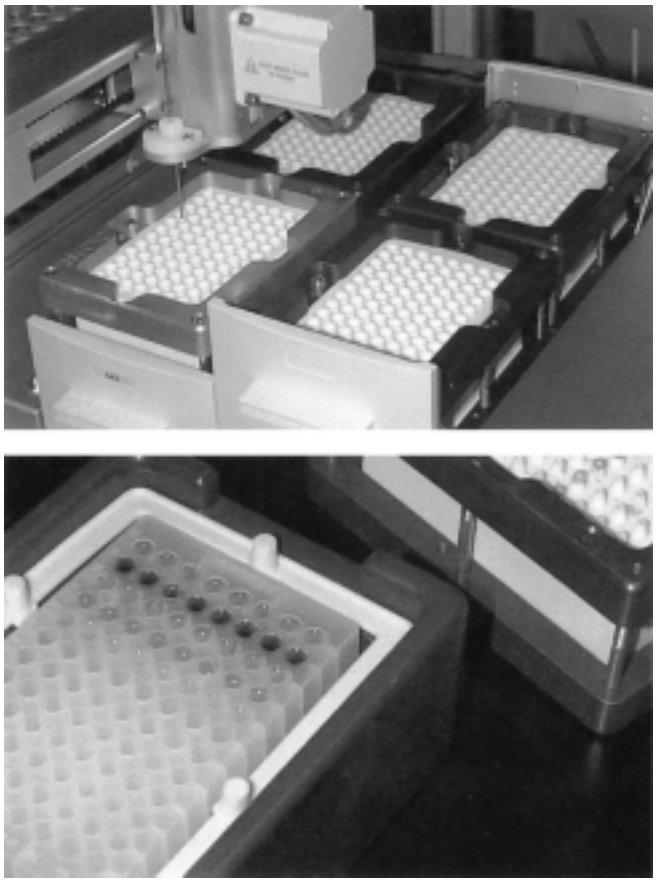


Figure 5. 96-well reactors and collector plates.

Most of these automated tools are conceptually simple and the range of operational conditions they tolerate may be quite restricted (temperature, stirring efficacy, gas tightness, chemical compatibility, etc.). When optimizing the chemistry of a specific compound class, these constraints must be kept in

mind. Consequently, powerful transformations that are also operationally friendly, and thus can be used with any reactor type, offer a special bonus and should be considered with extra attention.

Conclusion

Most of the truly powerful reactions illustrated above stem from the rich isocyanide chemistry. Forty years have elapsed from the early days of peptide-like Ugi products to the more recent elaborate heterocycles. The last five years have witnessed an explosion of reports in the area, demonstrating the renewed deep interest brought by the scientific community for that topic. What will be next? One can speculate that development of alternatives to isonitriles would pave the way to fruitful new reactions.

Access to new and elaborate constrained structures through secondary reactions is also an area of probable development, as is further study of cascade of M-CRs. Original cascades of "traditional" transformations, for instance, may also serve the cause of generating collections of novel polysubstituted carbon frameworks.[39]

Equally reasonable is to speculate that combinatorial or parallel methods may be aimed at discovering new multicomponent condensations that are of special value. The combinatorial principle, so powerful for the discovery of new biologically active molecules, has a clear potential to address the study of chemical reactivity! After all, truly original multicomponent processes are rare and to a certain extent unpredictable events. Thus, any methodology aiming at exploring the "chemical reaction landscape" will be welcome.[40]

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[4] The recent rise of interest for M-CRs, is best exemplified by the first international conference on the topic (M-CR 2000) to take place in München (Germany) in October 2000.

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[6] The benefit of using a *complexity-inducing reaction*, even though intuitively understandable, is difficult to rationalize and certainly deserves a word of explanation. The very concept of *structural complexity*, once applied to molecules, can accept several definitions of various degree of empiricism and relevancy in the context of drug discovery. It is not the purpose of the present article to compare the different definitions *of structural complexity* available in the literature,[7] let us only consider *complexity* as a function of molecular weight, number and order of chemical bonds, stereocenters, heteroatoms, cycles, and overall symmetry among other parameters. In the present context of drug design, a successful drug candidate will achieve a task of predefined refinement, notably by interacting simultaneously with several complementary functions in a receptor binding pocket or by exhibiting a combination of properties and reactivities, which correlates with the presence of several structural features in a well-defined spatial arrangement. One might therefore anticipate that elaborated tasks need a sufficient level of drug *complexity* to be successfully achieved. As the demand on drug efficacy will continue to expand in the years to come, there is little doubt that structural complexity of future drugs will follow (gene-targeted antisens drugs certainly pave the way in that direction).

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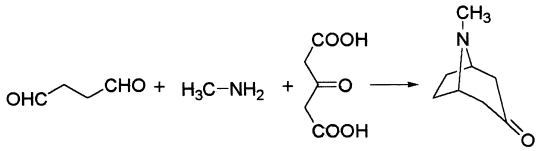

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