Chapter 1
Multicomponent Reactions: Superior Chemistry Technology for The New Millennium

1.1 Introduction
Diversity-oriented synthesis (DOS) continues to grow as an area of importance in the disciplines of organic synthesis and chemical biology [1, 2]. A central goal of DOS is to create collections of structurally diverse molecules for evaluation in biological systems, hoping that a broader spectrum of diversity in the chemical library will lead to the generation of more information from biological screens. Of special interest are compounds that possess those molecular skeletons found in natural products and drug like molecules [3, 4]. Since the vast majority of natural products and drug like compounds possess heterocyclic sub-units, the ability to synthesize efficiently diverse heterocyclic compounds is critical.

Arguably, one of the most promising synthetic strategies for generating collections of small molecules by DOS involves the sequencing of multi-component reactions (MCRs) with subsequent transformations, including cyclizations and re-functionalizations that form new compounds possessing increased molecular complexity and diversity [5]. This process of sequencing MCRs with subsequent cyclizations is commonly referred to as the build/couple/pair strategy of DOS [6]. Ideally, the MCRs will be sufficiently versatile that each input for the MCR can incorporate a wide range of functionalities and substituents. Using the tactic of functional group pairing [7], the MCR adduct is then selectively transformed in ring-forming processes and re-functionalizations comprising the synthon [8] into the target heterocyclic structures. Moreover, the ring-forming reactions should be chosen so that the products they generate still contain functional handles that can be further derivatized by other carbon–carbon or carbon–heteroatom bond-forming reactions. The major advantage of combining MCRs with post-condensation modifications
relative to other strategies for DOS is that it enables access to a number of functionalized heterocyclic scaffolds in a short number of steps (Figure 1.1).

![Figure 1.1 Sequencing of MCRs with post condensation cyclizations to generate diverse scaffolds](image)

### 1.2 Background

MCRs have been known for over 100 years. Although it would be difficult to identify the first example of an MCR, the Hantzsch dihydropyridine (DHP) synthesis was reported in 1882, followed by the Biginelli 3CR in 1893 [9]. The first isocyanide-based MCRs were disclosed by Passerini (3CR) and Ugi (4CR) in 1921 and 1959, respectively. Many subsequent variants of the Passerini and Ugi reactions that capitalize on the unique reactivity of isonitriles have subsequently been described [5]. These and related MCRs gained prominence in the early 1990s with the advent of combinatorial chemistry and related library-synthesis strategies and the establishment of academic high-throughput screening (HTS) facilities [10]. During this time, MCRs have also found wide application in the synthesis of natural products [11] and other targets of interest [12, 13]. The pursuit of MCR products as biological probes, drug candidates and as synthetic intermediates has resulted in an intensified effort to find MCR catalysts. MCRs are striking in their ability to resist catalysis, as exemplified by
the fact that more than a century elapsed between the discovery of the Hantzsch and Biginelli MCRs and the first catalysts for these reactions (Figure 1.2). In these cases, the first asymmetric catalysts were described shortly thereafter. As such, current efforts often focus on the discovery of new catalyzed MCRs [14].

**Figure 1.2 Timeline of discovery of multicomponent reactions (MCRs) and catalysts**

MCRs fill a unique niche in the synthesis of libraries and the inextricable follow-up associated with the development of drugs and selective biological probes. First, MCRs provide the highest number of compounds for the least synthetic effort. A 3CR will provide 1000 compounds when 10 variants of each component are employed in a full matrix of combinations. Second, MCRs provide an inherent
measure of SAR information within a screening library by providing sets of compounds with related core structures. Third, ‘screening positives’ or ‘hits’ that emanate from MCRs provide a valuable starting point for follow-up as the rapid preparation of ‘focused’ libraries and scale up are ensured.

The use of MCRs for the preparation of diverse libraries carries the potential liability of having one core structure that is over-represented within a collection. The diversity of a library of MCR products is, on some level, limited by the structure of the appendages that emanate from the components. This liability is addressed by new variants of traditional MCRs that result in fundamentally different structures. Furthermore, the use of MCRs as a starting point for subsequent reactions that define the core connectivity of the components is a powerful approach to achieving efficiency and diversity. This tactic falls under the more general ‘build-couple-pair’ strategy that was recently delineated by Schreiber [6, 15].

1.3 Hantzsch Reaction & Role of Catalyst

The Hantzsch reaction, which incorporates two di-carbonyl compounds, an amine and an aldehyde into a dihydropyridine (DHP), has been used extensively in many settings (Figure 1.3) [16]. Although this is a 4CR in the sense that four components are incorporated, the di-carbonyls are not independently variable and are incorporated twice to form symmetrical products. This limitation is avoided by pre-forming either an enamine or a knoevenagel product that can participate in a 3CR with a di-carbonyl and an aldehyde or amine, respectively.

As is the case with many MCRs, the discovery of catalysts for the Hantzsch reaction, asymmetric and otherwise, has only received recent attention. The first reported catalyst for the Hantzsch reaction appears to be Yb(OTf)₃, which was disclosed in 2005, nearly 120 years after the discovery of the reaction itself [17]. Subsequently, several other lewis acid additives were shown to catalyze the hantzsch reaction, along with proline and PhB(OH)₂ [17–20]. A lone example of asymmetric catalysis of the hantzsch reaction was recently reported by Evans and Gestwicki [21]. A survey of catalysts revealed that phosphonic acid (4) exhibited comparable activity to Yb(OTf)₃ and induced high enantioselectivity. Up till now, numerous literature citations exist relating to various attempts to improve the Hantzsch reaction using alternative catalysts and greener methods.
<table>
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<th>Catalyst</th>
<th>Yb(OTf)$_3$</th>
<th>CAN</th>
<th>L-proline</th>
<th>4</th>
<th>PhB(OH)$_2$</th>
<th>CeCl$_3$</th>
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<td>2</td>
<td>2</td>
<td>2</td>
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<td>10</td>
<td>10</td>
<td>10</td>
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<td>83-96</td>
<td>69-94</td>
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<td>MeCN</td>
<td>EtOH</td>
<td>MeCN</td>
</tr>
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<td>0.5-4</td>
<td>0.5</td>
<td>5</td>
<td>4-5</td>
<td>3-6</td>
</tr>
<tr>
<td>Temperature</td>
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<td>25 ºC</td>
<td>25 ºC</td>
<td>80 ºC</td>
<td>25 ºC</td>
</tr>
</tbody>
</table>

Figure 1.3 The Hantzsch reaction as a 3CR & Catalysis of the Hantzsch reaction

However, most of the research has been focused on the modification and optimization of the Hantzsch reaction to maximize reaction conversion, minimize reaction time and offer high purity 1,4-DHPs. At the same time, the oxidative aromatization of 1,4-DHPs to corresponding pyridines has also been extensively studied. A plethora of oxidants including air, catalyzed by RuCl$_3$ or Pd/C have been
applied in the aromatization reactions [22]. All of these studies seem to indicate that Hantzsch reaction has been well understood.

1.3.1 Recent advancement in the Hantzsch reaction

The Hantzsch reaction has undergone an extensive evolution in the last decade. Recent new variants include the use of amino heterocycles as the enamine component.

Figure 1.4  (A) New variants and applications of the Hantzsch 3CR  
(B) Divergent structural products from different conditions  
(C) Spirobicyclic products from the Hantzsch reaction
Aminopyridines and aminopyrazoles can function as the enamine component (Figure 1.4) [23-25]. The reactions of aminopyrazoles were found by Chebanov to produce different regioisomers (8 and 9, Figure 1.4) and a previously unknown ring-opened product (25) under different conditions [26].

The Hantzsch reaction has recently been employed in the one-pot synthesis of polycyclic products that result in a greater degree of three-dimensional shape variation [27]. Although the Hantzsch reaction typically produces compounds those are aromatic, or nearly so with regard to their degree of saturation, two new reactions defy this trend. Chebanov and Tu discovered that barbiturates react with two equivalents of aromatic aldehydes and aminopyrazoles or 2,6-diaminopyrimidine-4-one to produce densely substituted spirocyclic products 11 and 12, respectively (Figure 1.4) [28]. Chebanov’s reaction occurs under mild conditions and can be altered to allow the independent variation of the aldehyde components by pre-forming an alkylidene barbiturate that leads to 11.

### 1.4 The Biginelli Reaction

![Figure 1.5](image-url)

*Figure 1.5 (A) Biginelli products: a naturally occurring alkaloid and mitotic spindle kinesin inhibitor (B) Asymmetric catalysis of the Biginelli reaction*
The Biginelli reaction was relatively obscure for the first century that ensued after its discovery [29, 30]. Two events vaulted this reaction to prominence. In 1993, Overman disclosed a synthetic strategy for the synthesis of the tricyclic core of the guanidinium alkaloid ptلومycinlin (13) that is enabled by a diastereoselective variant of the Biginelli 3CR [31, 32].

This general strategy was extended to other members of the natural product family and used in several biological studies of structurally related analogs [33]. Later in the decade (1999), a drug-like small molecule inhibitor (14, monastrol) of the mitotic spindle kinesin Eg5 was discovered at the Institute for Chemistry and Cell Biology [34]. This compound, which is formed in a single step by the Biginelli 3CR, contributed to both the popularity of the Biginelli reaction and of HTS in academic settings.

1.4.1 Asymmetric catalyst for biginelli reaction

The first Lewis acid catalyst for the Biginelli 3CR was reported in 2000 and five years later the first asymmetric catalyst emerged (Figure 1.5) [35-37]. In the ensuing years, three chemically distinct asymmetric catalysts were subsequently reported and a tabular comparison reveals that all perform comparably at room temperature, with (18) offering the shortest reaction times [38-41]. In addition, Biginelli 3CR products can be accessed in enantiomerically pure form an asymmetric Mannich reaction catalyzed by Cinchona alkaloids [42].

1.5 Isocyanide-based MCRs

The unique ability of isocyanides to serve as c-nucleophiles toward imines and aldehydes, resulting in nitrilium ion electrophiles, enables the Ugi 4CR and Passerini 3CR, respectively.

Like the Biginelli 3CR, Ugi and Passerini reactions have seen exponential growth in the number of publications on these reactions as interest in library synthesis has grown. These reactions served as an efficient tool in the synthesis of plenty of novel small organic molecules with high yields and shorter reaction times.

Recent synthetic applications include a one-step synthesis of tubuvaline (20) as part of a synthesis of several tubulisins and a short synthesis of dysibetaine (Figure 1.6) [43, 44].
1.5.1 New isonitriles and in situ preparation

One consistent drawback of isonitrile-based MCRs is the extreme stench associated with isonitriles. Two methods of circumventing this limitation of these useful reagents have been recently reported (Figure 1.7).

![Figure 1.6 Natural product synthesis based on Ugi reaction](image)

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![Figure 1.7 (A) Synthetic utility of pleasant smelling and convertible isonitriles](image)

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![Figure 1.7 (B) 'Isonitrile-free' Ugi reaction employing isonitriles that are generated in situ](image)

Figure 1.7 (B) 'Isonitrile-free' Ugi reaction employing isonitriles that are generated in situ
Pirrung has discovered a structural class of isonitriles that avoids this problem. Phenylisonitriles with \( o \)-acyl substituents, which are easily prepared from benzoxazole, have inoffensive odours [45]. These substrates readily undergo Ugi, Passerini, Grobke and Ugi-Smiles reactions [46]. Moreover, the Ugi products derived from these substrates are ‘convertible’, that is they are poised for conversion to esters (shown) and other useful intermediates [47]. El Kaim and Grimaud have devised a method for preparing isonitriles in situ for subsequent MCRs carried out in the same pot (Figure 1.7) [48].

1.5.2 Asymmetric catalysis

Schreiber and Zhu have each disclosed metal-based catalysts for asymmetric Passerini reactions (Figure 1.8) [49, 50]. Although both reactions proceed in similar yield and
selectivity, Zhu’s reaction has broader substrate scope as it does not require chelating aldehydes. That said, both reactions require carefully controlled reagent delivery and the use of a syringe pump.

Although a catalytic asymmetric Ugi 4CR is still lacking, several important advances have been reported (Figure 1.8). Ciufolini has observed that TiCl₄ serves as an efficient Ugi 4CR catalyst when used in methanol [51]. In this case, as with related observations with Sc(OTf)₃, the effect of the catalyst is not dramatic, that is reactions still proceed in the absence of catalyst in lower yield [52–54]. Catalysis by titanium is inferred by the fact that HCl is not an effective catalyst and Ti(Oi-Pr)₄, which cannot form HCl, is only slightly less effective than TiCl₄. The methyl ester products are the result of methanol intercepting a probable lactone intermediate. The product derived from glutamic acid 5-methyl ester (47) can be cyclized to either the pyroglutamate (48) or diketopiperazine (46) using acetic acid or TFA, respectively. A second advance was reported by List, who reasoned that water produced from the condensation of the aldehyde and amine components could take the place of a carboxylic acid as the nucleophilic component [55]. The resulting ‘Ugi 3CR’ is uniquely catalyzed by a phosphinic acid, whereas other protic and Lewis acids were ineffective.

1.6 The Petasis 3CR and related reactions

In 1997, Petasis described a new and mechanistically distinct 3CR that combines amines, aldehydes and vinylboronic or arylboronic acids (Figure 1.9) [56]. This reaction was shown to be diastereoselective when any one of the components employed was chiral [57, 58].

In the ensuing decade, several variants have been described. Kobayashi demonstrated a related reaction involving aldehydes, ammonia, and allylboronic acids [59]. The Kobayashi reaction occurs at a lower temperature as it proceeds by allylic transposition. Although the Petasis reaction requires a nucleophilic group in the α-position or β-position of the aldehyde carbonyl, unsubstituted benzaldehydes will form the analogous 3CR products in the presence of a palladium catalyst [60].

The high level of diastereoselection conferred by α-alkoxy aldehydes, paired with tolerance of additional hydroxy groups without protection, has allowed this reaction to serve as a key transformation in the recent syntheses of sialic acids (e.g.
(A) Petasis

\[
\begin{align*}
\text{R}_1\text{H} + \text{HO}_2\text{B} &+ \text{NH}_2 \rightarrow \text{EtOH} & 25^\circ C \\
(49) & \quad (50) \\
\text{Kobayashi} & \\
\text{R}_1\text{H} + \text{NH}_3 \rightarrow \text{EtOH} & 25^\circ C \\
(52) & \quad (53) \\
\text{R}_1\text{H} + \text{Pd, H}_2\text{O} & 12h, 100^\circ C \\
(55) &
\end{align*}
\]

\(\text{R}_1, \text{R}_2, \text{R}_3 = \text{Aromatic}\)

Figure 1.9 (A) Petasis and related boronic acid-based MCRs

(B) Enantioselective catalysis of boronic acid-based 3CRs

1.6.1 Catalysis for Petasis reaction based 3CRs

Two asymmetric catalysts have been reported for 3CRs that involve nucleophilic addition of vinylboronic acids (Figure 1.9). Takemoto has shown that a thiourea with a pendant amino alcohol is an effective catalyst for a 3CR between quinolines, acylating agents and boronic acids [63]. A directly catalytic and asymmetric variant of the Petasis reaction was reported by Schaus using a VAPOL-type chiral biphenol [64].
1.6.2 Molecular diversity from boronic acid-based 3CRs

The combination of allylboronic acids, amines and aldehydes has found application in the synthesis of heterocyclic products (Figure 1.10).

Szabo used a palladium catalyst to generate allylboronic esters in situ, which are then allowed to react with amines and glycolic acid to undergo a reaction analogous to that reported by Kobayashi [65]. When the substrate has a methyl ester substituent, a subsequent cyclization is observed to form a lactam (Figure 1.10). A related strategy was used by Hall for lactam synthesis wherein methyl ester-substituted allylboronic esters form exo-methylene lactams in a one-pot reaction with
ammonia and aldehydes (Figure 1.10) [66]. The products could be further diversified by N-arylation, Heck, or conjugate addition reactions catalyzed by copper, palladium or rhodium, respectively.

Gracias et al. employed the Kobayashi allylation strategy in the preparation of a series of diazaspirocycles (Figure 1.10) [67]. Cyclic piperidones and related ketones were treated with amines and an allylboronic ester to provide dienes that were subsequently cyclized using Grubbs’ ruthenium catalyst. The two-step process provided the spirobicyclic products in good overall yield.

1.7 New MCRs

Many new MCRs have been reported in recent years. In addition to the new variants of ‘classical’ MCRs mentioned in the previous four sections, we highlight here, a sampling of interesting new MCRs reported in the past five years. We have chosen four arbitrary categories that capture a cross-section of reactivity and result in a broad array of structures.

1.7.1 MCRs based on anhydride annulation

Although anhydrides typically serve as mild acylating agents for the formation of amides and esters, there are recent examples of MCRs where anhydrides undergo annulation reactions (Figure 11) [68]. Early observations on the reactions of succinic and homophthalic anhydrides with imines revealed the propensity of anhydrides to serve as C-nucleophiles [69–71].

Yadav first reported accessing the same products from the component parts of the imine in a 3CR with homophthalic anhydride [72]. A recent report of highly efficient catalysis from Wang demonstrates that aldehydes, amines and homophthalic anhydride react smoothly in the presence of Yb(OTf)₃ to form the kinetically favored cis isoquinolones [73].

Research in the Shaw group has uncovered a mechanistically related 4CR wherein amines, aldehydes, thiols and maleic anhydrides react in high yield and with high diastereoselectivity to form g-lactams with up to three contiguous stereogenic centers [74].
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Figure 1.11 (A) Anhydride-based MCRs
(B) A catalytic variant of the Williams spirooxindole MCR and a new spiropyranlyoxindole-forming MCR
1.7.2 Sprio-oxidnole-forming MCRs

Spirooxindoles are prominent substructures in natural products and in medicinal leads [75]. The synthesis of pyrrolidinyl products using an auxiliary-controlled approach was first demonstrated by Williams in a synthesis of spirotryprostatin A [76]. Gong recently reported the first catalytic variant using 2-aminodiethyl-malonate (93, Figure 1.11) [38, 77]. This substructure is often prepared using the established azomethine ylide cycloaddition reaction of alkylidene oxindoles. This strategy was central to the success of a diverse library reported by Schreiber [78]. Scheidt described a complementary approach to the synthesis of spirooxindoles from imines, alkylidene oxindoles and ethylidiazocacetate requiring syringe-pump addition of the latter reagent to the reaction mixture. More recently, Stephenson has developed a new 3CR of dicarbonyl compounds and isatins leading to pyranyl structure 101 (Figure 1.11) [79]. This reaction shows excellent chemoselectivity for the ‘crossed’ product of a variety of differentially reactive dicarbonyls, one of which is usually a ketoester. A nearly simultaneous publication from Bazgir describes a related MCR in which an amine is also incorporated [80].

1.7.3 MCRs forming carbocyclic products

Although most MCRs rely on the formation of heterocycles and/or carbon-heteroatom bonds, there are several recent reactions that exploit the differential reactivity of various alkenes and alkynes to engage in MCRs. Organocatalysis has featured prominently in the discovery of catalytic MCRs and proline derivative 104 has been applied in two related reactions (Figure 1.12). Melchiorre demonstrated that alkylidene oxindoles will undergo annulation reaction with two aldehydes sequentially when one is unsaturated [81]. The resulting spirocyclohexene product has four new stereogenic centers and is formed in high enantioselectivity and diastereoselectivity. A related reaction was reported by Gong wherein two molecules of acrolein react with an alcohol and a nitrostyrene [82]. Although the latter reaction amounts to a 4CR with one component that is employed twice and cannot be varied, this reaction is an interesting complement to the spirooxindole-forming organocatalysis MCR. The requirement of many different functional groups for MCRs, including many that are either nucleophilic and/or Lewis basic, precludes the broad use of transition metal catalysts.
One recent and notable exception is the 3CR of a benzyne precursor, alkyne and enoate reported by Xie [83]. High chemoselectivity for the crossed combination of all three inputs is observed as is high regioselectivity (Figure 1.12). A related transformation employing stoichiometric quantities of thallium has been shown to produce phenanthrenes [84]. As has been the case with organocatalysts and Lewis acids, transition metal catalysis will likely increase in frequency as an MCR strategy.

1.7.4 MCRs forming tricyclic products

A few recent examples highlight the power of MCRs to create complex products featuring the linear, angular or bridged fusion of three or more rings (Figure 1.12). Marque showed that amino alcohols, maleate esters and electron rich furan
carboxaldehydes react in a single step to produce fused 5-5-6 products 145 (Figure 1.12) [85]. Bridged tricyclic amides are made possible by the reaction of diketones, acrolein and nucleophile-terminated amines [86].

Rodriguez demonstrated this process with diamines, amino alcohols and aminopropyl pyrrole. Single diastereomers were observed in all cases. Finally Li has found a remarkable synthesis of angularly fused tricyclic products derived from cyclic ketones, aldehydes and cyanoacetamide (Figure 12) [87].

As with the previous examples, single diastereomers were observed in which three rings are formed in high yield. Although each of these new MCRs employs only two variable components, these reactions rapidly access unique polycyclic architectures.

1.7.5 Future possibilities with MCRs
MCRs have become a staple for the synthesis of diverse compounds for screening libraries and the recent increase in the discovery of new reactions, catalytic and otherwise, suggests that this will be the case indefinitely. The preceding examples identify three clear areas for growth: firstly, the prospective use of catalysts in the discovery of new MCRs; secondly, the development of new synthesis strategies using MCRs as a starting point (e.g. ‘buildcouple- pair’); and thirdly, the exploration of MCRs using non-traditional reactivity. Although most MCRs use amines and/or aldehydes, it is clear that there is much left to be discovered in the reactivity of functional groups not yet employed in most MCRs.

1.8 Objectives
These interesting findings from literature survey of MCRs prompted us to further elaborate scope of this new technology, in order to synthesize three different heterocycles of medicinal interest.
1.9 References and notes


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[64] Lou, S.; Schaus, S. E. *Journal of the American Chemical Society* **2008**, *130*, 6922.


