Multicomponent Reactions

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Studies toward Scaffold and Stereochemical Diversity

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Multicomponent Reactions

Studies toward Scaffold and Stereochemical Diversity

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ter verkrijging van de graad Doctor aan
de Vrije Universiteit Amsterdam,
op gezag van de rector magnificus
prof.dr. L.M. Bouter,
in het openbaar te verdedigen
ten overstaan van de promotiecommissie
van de faculteit der Exacte Wetenschappen
op vrijdag 30 oktober 2009 om 13.45 uur
in het auditorium van de universiteit,
De Boelelaan 1105

door

Bas Groenendaal

geboren te Velsen

promotoren: prof.dr. ir. R.V.A. Orru
prof.dr. M.B. Groen

copromotor: dr. E. Ruijter

aan hen die mij dierbaar zijn

Contents

Chapter 1

General Introduction

1.1 Diversity oriented synthesis (DOS)

Chemical space, defined as the total descriptor space including all carbon-based molecules that in principle can be prepared, contains more than 10^{60} small organic molecules.[1] Only a very limited number of these have actually been made by Man and explored for potential useful properties, such as their biological relevance. This continues to drive synthetic chemists to develop novel reactions that can efficiently access unexplored regions of the chemical space.[2]

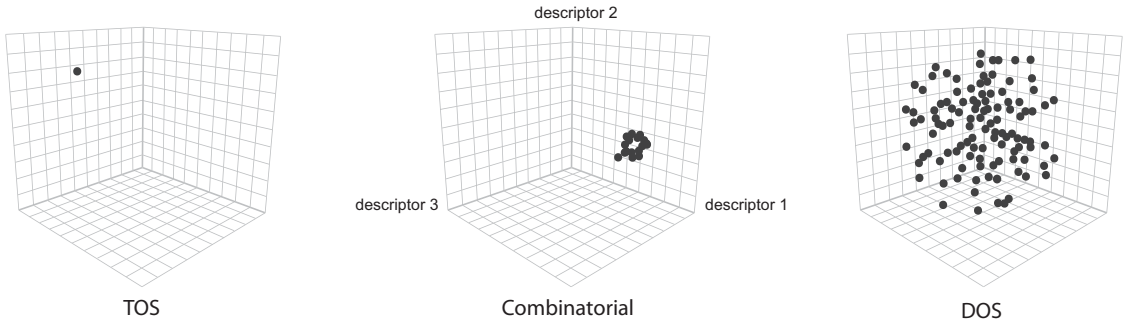


Figure 1: TOS, Combinatorial synthesis and DOS.

To access points (i.e. specific molecules) in this chemical space, three different strategies can be followed: target oriented synthesis (TOS), combinatorial synthesis or diversity oriented synthesis (DOS) (Figure 1). In TOS, focus lies on the synthesis of a single point in chemical space that has known (biological) properties. This type is used in, for example, natural product synthesis.[2] In combinatorial synthesis, a dense region of the chemical space is synthesized in proximity to a precise region known to have useful properties. Examples can be found in the synthesis of libraries of structurally similar products performed in the pharmaceutical industry. DOS aims to synthesize compounds with complex and diverse structures that cover a wide range of the chemical space and have unknown properties. In this way, potentially new small molecule drugs may be discovered.[2]

Thus for DOS to be effective, methods that allow the quick generation of scaffold diversity are essential. Multicomponent reactions (MCRs) represent one of the most powerful tools to easily access molecules showing both skeletal and decoration diversity.[3-5] As such, these reactions are also ideally suited to uncover unprecedented types of scaffolds.

1.2 Multicomponent reactions (MCRs)

By definition MCRs are reactions in which three or more readily available starting materials are combined in one pot generating a product that essentially contains all of the atoms of the starting materials (Figure 2).[6] They are a subclass of domino (or tandem) reactions, which are one-pot sequences of two or more reactions. The exploratory power of MCRs is very high and because they are highly flexible and efficient they can be considered as one of the most versatile classes of tandem reactions.[7] A reaction is said to have a high exploratory power if

during the reaction a large increase of structural complexity from starting materials to products is obtained and when a relatively large number of diversity points are covered.[7]

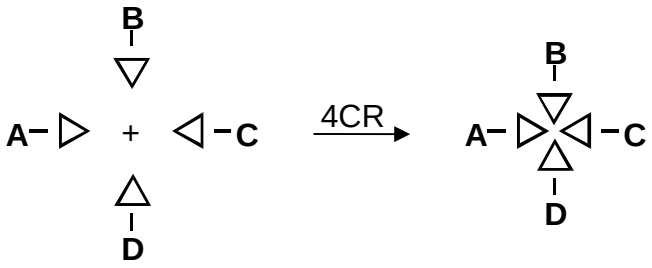


Figure 2: Schematic representation of a 4-component reaction.

Based on the reaction mechanism, MCRs can be divided into three subclasses (Table 1).[6] In type I MCRs, starting materials, intermediates and products are all in equilibrium. Because of these equilibria, the product found is often a mixture of starting materials and/or intermediates. Type II MCRs are similar to type I MCRs except that the final step is irreversible. The advantage of this type of MCRs is that the equilibria of all steps are pushed to the product because of the last irreversible step. This type is also the most successful one because possible side reactions are also reversible and the irreversibly formed product P predominates.[8]

Table 1: Different MCR types.

MCR type	General reaction equation
I	$A + B \rightleftharpoons C \rightleftharpoons \ldots O \rightleftharpoons P$
II	$A + B \rightleftharpoons C \rightleftharpoons D \ldots O \longrightarrow P$
III	$A \longrightarrow B + C \longrightarrow D \longrightarrow \ldots O \longrightarrow P$

Type III MCRs are the most rare: in this type, all reactions are irreversible. In preparative chemistry not many examples of type III MCRs are known.

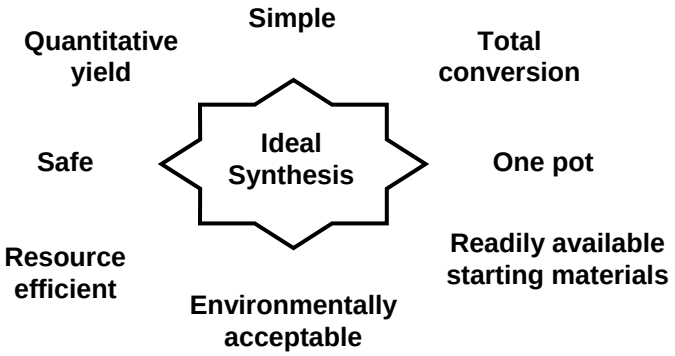
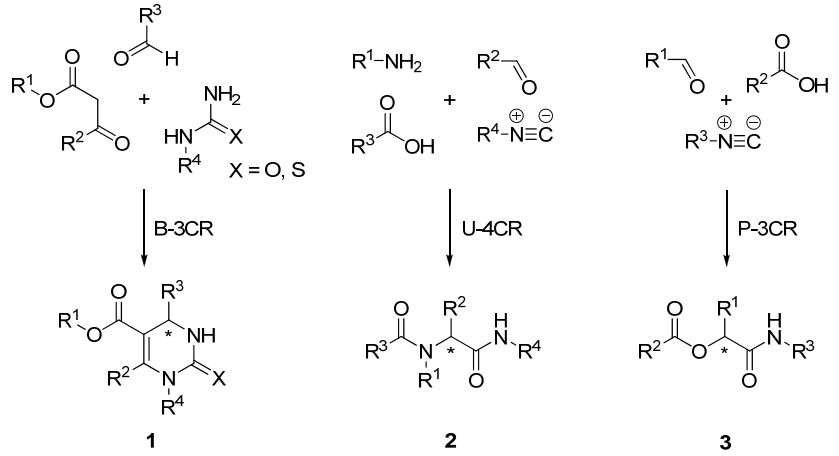


Figure 3: Ideal chemical synthesis.

The general features of MCRs compare favorably with the criteria that have been set for the ideal synthesis (Figure 3).[6] In the ideal synthesis, a target molecule is prepared from readily

available starting materials in one simple, safe, environmentally friendly and resource-efficient operation that proceeds in quantitative yield. MCRs come quite close because these reactions are highly convergent, selective and atom efficient.

Three of the most widely used and oldest MCRs are the Biginelli (B-3CR)[9,10], Ugi (U-4CR)[3,11] and Passerini (P-3CR)[12,13] reaction (Scheme 1). As these reactions are also relevant to this thesis they are described in more detail here.



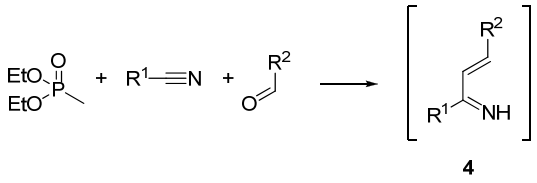
Scheme 1: Biginelli, Ugi and Passerini reaction.

The Biginelli reaction was first reported in 1893 by Biginelli and is an acid-catalyzed, three-component condensation of aldehydes, β-ketoesters and ureas yielding dihydropyrimidines (DHPMs) **1**.[9] Variation of all three inputs is possible, with the aldehyde being the component that can be varied most extensively, thus giving access to a broad range of differently functionalized DHPMs.[10] The exact reaction mechanism has been clarified by the group of Kappe in 1997 and it will be discussed in detail in Chapter 6. The DHPMs obtained via the Biginelli reaction are very interesting, biologically active compounds and applications can be found in their use as for example calcium channel modulators or α_1 adrenergic antagonists.[14]
The Ugi reaction was discovered in 1959 by Ivar Ugi and it originally consists of a one-pot combination of amines, aldehydes, carboxylic acids and isocyanides to form α-acylamino amides **2**.[11] There are almost no limitations in the inputs that can be used in the Ugi-reaction. The exact reaction mechanism is still under debate and the different possibilities will be discussed in more detail in Chapter 5. The reaction runs normally very fast at room temperature and it is best performed in polar, protic solvents like methanol or ethanol but also aprotic polar solvents like DMF or THF can be used.[6]
The Passerini reaction dates back to 1921 and involves the combination of aldehydes or ketones, carboxylic acids and isocyanides yielding α-acyloxy amides **3** (Scheme 1).[12] All three starting materials are highly variable but extremely sterically hindered or α,β-unsaturated ketones can not be used.[15] The reaction is usually carried out with high concentrations of starting materials, in inert aprotic solvents, at or below room temperature. The fact that the Passerini reaction is accelerated in aprotic, apolar solvents suggests a non-

ionic mechanism but kinetic studies led to different mechanistic suggestions.[16,17] The α-acyloxy amide moiety is a much found pattern in many natural products which makes the Passerini reaction a very suitable reaction for their synthesis.[6]

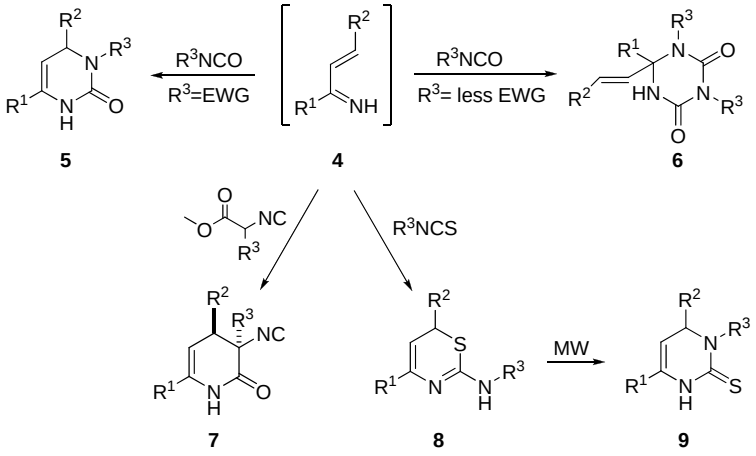
1.3 Modular reaction sequences

A MCR that was recently developed in our group involves the *in situ* formation of 1-azadienes **4**.[18,19] The 1-azadiene is formed via a reaction between diethyl methylphosphonate, a nitrile and an aldehyde (Scheme 2).



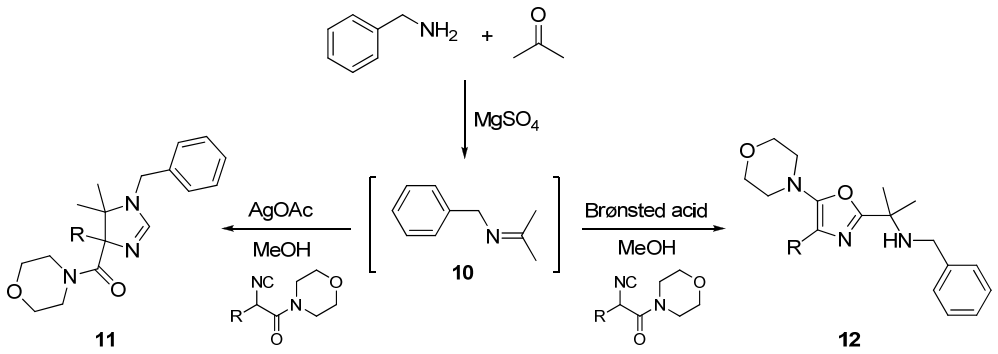
Scheme 2: MCR yielding 1-azadiene **4**.

The 1-azadiene can be used as a reactive intermediate in modular reaction sequences yielding various types of heterocycles.[18-21] Modular reaction sequences are a conceptually new approach to DOS combining MCRs with other complexity-generating reactions, like cycloadditions, condensations or even additional MCRs.



Scheme 3: Various types of heterocycles from 1-azadiene.

When the *in situ*-generated 1-azadiene is reacted with highly electron-deficient isocyanates, dihydropyrimidines **5** are formed (Scheme 3).[18,19] When reacted with isocyanates with less or no electronwithdrawing groups, triazinane diones **6** are formed.[21] With isothiocyanates, thiazines **8** are formed,[22] which can be converted into dihydropyrimidinethiones **9** *via* a Dimroth rearrangement. Finally, when reacted with isocyano esters, dihydropyridones **7** are formed.[20] An interesting feature of the latter reaction is that the isocyanide function stays intact during the reaction, leaving it available for further reactions.



Scheme 4: Imidazoles or oxazoles from same substrates.

Another modular sequence that is developed in our group involves the three-component synthesis of 2-imidazolines **11** or 2-substituted oxazoles **12** from the same set of substrates.[23] By choosing the appropriate reaction conditions either the imidazoline or the oxazole can be formed (Scheme 4). The amine and the ketone first form the imine **10** *in situ*. This imine then reacts with the isocyano amide to the desired type of heterocycle. When the reaction is performed in the presence of silver acetate, 2-imidazolines **11** are generated but in the presence of a weak Brøndsted acid, 2-substituted oxazoles **12** are generated (Scheme 4). This reaction can also be regarded as a modular reaction sequence with imine **10** as the reactive intermediate yielding two different types of heterocycles.

1.4 Outline of this thesis

MCRs are very useful reactions for the rapid generation of complex and diverse molecules in a very efficient way. In the research described in this thesis the potential of the 3CR toward 1-azadienes **4** for Diversity Oriented Synthesis is further explored. Especially the use of this reaction as a platform for the generation of structural or skeletal diversity is studied in more detail.
In addition, stereochemical aspects of MCRs are studied. Most MCRs proceed via relatively complex reaction mechanisms and control over the newly formed stereocenters is often not trivial. The use of biocatalysts and/or chiral Lewis-acid based catalysis was explored to address this general issue in MCR-chemistry.

Chapter 2 contains a literature survey about the synthesis and use of 1-azadienes in cycloaddition and multicomponent reactions towards *N*-heterocycles. Also the use of 1-azadienes in modular reaction sequences is discussed in more detail in this chapter.

In chapter 3, the development of a new MCR for the synthesis of an unexplored class of heterocycles, the triazinane diones, is described. The reaction conditions are optimized and a small library of different triazinane diones is prepared. Also, alternative methods to synthesize triazinane diones are explored.

In chapter 4, the triazinane dione scaffold is used in follow-up chemistry generating structurally diverse and complex products. After a simple alkylation, different synthetic handles are introduced to the initial scaffold generated by the MCR. Then additional complexity generating reactions like ring-closing metathesis, cycloaddition reactions or isonitrile-based MCRs were performed to provide highly complex (poly)heterocyclic scaffolds.

Chapter 5 is the first of two chapters that deal with the issues of stereoselectivity often encountered when using MCRs. In chapter 5 attempts are described to develop an enantioselective Ugi reaction. The chapter includes a study of critical reaction parameters and the influence of solvent, temperature and acid concentration on the reaction are studied. With the results of this study some initial progress was made towards an enantioselective Ugi reaction.

The research described in chapter 6 deals with the use of biocatalysis in combination with MCRs. A MCR-biocatalysis sequence was envisioned which should generate structurally complex, enantiopure products. The Biginelli reaction in combination with an esterase biocatalyst was studied in more detail. The product of a Biginelli-3CR contains an ester function, which can easily be hydrolyzed selectively to the corresponding carboxylic acid. The individual steps of the sequence are optimized, and subsequently a one-pot procedure was developed.

1.5 References and notes

1. Dobson, C. M. *Nature* **2004**, *32*, 824-828.
2. Burke, M. D.; Schreiber, S. L. *Angew. Chem. Int. Ed.* **2004**, *43*, 46-58.
3. Domling, A. *Chem. Rev.* **2006**, *106*, 17-89.
4. Zhu, J. *Eur. J. Org. Chem.* **2003**, 1133-1144.
5. Orru, R. V. A.; De Greef, M. *Synthesis* **2003**, 1471-1499.
6. Domling, A.; Ugi, I. *Angew. Chem. Int. Ed.* **2000**, *39*, 3168-3210.
7. Bienayme, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*, 3321-3329.
8. Weber, L.; Illgen, K.; Almstetter, M. *Synlett.* **1999**, 366-374.
9. Biginelli, P. *Gazz. Chim. Ital.* **1893**, *23*, 360-413.
10. Kappe, C. O. *QSAR Comb. Sci.* **2003**, *22*, 630-645.
11. Ugi, I.; Meyr, R.; Fetzer, U.; Steinbruckner, C. *Angew. Chem.* **1959**, *71*, 386.
12. Passerini, M. *Gazz. Chim. Ital.* **1921**, *51*, 126-129.
13. Banfi, L.; Riva, R. *Org. React.* **2005**, *65*, 1-140.
14. Kappe, C. O. *Eur. J. Med. Chem.* **2000**, *35*, 1043-1052.
15. Baker, R. H.; Schlesinger, A. H. *J. Am. Chem. Soc.* **1945**, *67*, 1499-1500.
16. Ugi, I.; Meyr, R. *Chem. Ber.* **1961**, *94*, 2229-2233.
17. Hagedorn, I.; Eholzer, U. *Chem. Ber.* **1965**, *98*, 936-940.
18. Vugts, D. J.; Jansen, H.; Schmitz, R. F.; de Kanter, F. J. J.; Orru, R. V. A. *Chem. Comm.* **2003**, 2594-2595.
19. Vugts, D. J.; Koningstein, M. M.; Schmitz, R. F.; de Kanter, F. J. J.; Groen, M. B.; Orru, R. V. A. *Chem. Eur. J.* **2006**, *12*, 7178-7189.
20. Paravidino, M.; Bon, R. S.; Scheffelaar, R.; Vugts, D. J.; Znabet, A.; Schmitz, R. F.; de Kanter, F. J. J.; Lutz, M.; Spek, A. L.; Groen, M. B.; Orru, R. V. A. *Org. Lett.* **2006**, *8*, 5369-5372.

21. Groenendaal, B.; Vugts, D. J.; Schmitz, R. F.; de Kanter, F. J. J.; Ruijter, E.; Groen, M. B.; Orru, R. V. A. *J. Org. Chem.* **2008**, *73*, 719-722.
22. Glasnov, T. N.; Vugts, D. J.; Koningstein, M. M.; Desai, B.; Fabian, W. M. F.; Orru, R. V. A.; Kappe, C. O. *QSAR Comb. Sci.* **2006**, *25*, 509-518.
23. Elders, N.; Ruijter, E.; De Kanter, F. J. J.; Groen, M. B.; Orru, R. V. A. *Chem. Eur. J.* **2008**, *14*, 4961-4973.

Chapter 2

1-Azadienes in Cycloaddition and Multicomponent Reactions toward N-heterocycles

This Chapter has been published in *Chem. Comm.* **2008**, 5474-5489.

2.1 Introduction

The number of novel molecular entities brought on the market as new drugs has decreased steadily over the past decades, while at the same time R&D expenditures increase exponentially. With resistance to drugs currently on the market on the rise, the demand for new active compounds is higher than ever. It is becoming increasingly evident that the nature of the compounds produced by combinatorial chemistry efforts in the past two decades does not fit a rational drug discovery approach. Both structural complexity and chemical diversity are central issues to address in the design and construction of compound collections in order to find and explore potential biological activities.

Natural products display much more scaffold diversity and structural complexity than purely synthetic compounds.[1-5] The diversity of natural compounds, which often contain at least one heterocyclic ring, has been an important inspiration for the development of many drugs.[6] As a result, many medicines are relatively small heterocyclic organic compounds. However, the range of easily accessible and suitably functionalized heterocyclic building blocks for the synthesis of structurally diverse libraries is very limited. As a result, the construction of even a small library of, *e.g.*, 1000 pharmaceutically relevant heterocycle-based compounds is still far from trivial.

To address the issues of complexity and diversity in the synthesis of libraries of biologically active small molecules, diversity-oriented synthesis (DOS)[7] in combination with complexity-generating reactions receives growing attention.[8-14] Again, the scaffold diversity found in natural products is an inspiration for DOS-based library generation.[15-26] Therefore, synthetic methodology for the creation of diverse natural product-like scaffolds based on heterocycles starting from a limited number of inputs is highly desirable. To achieve this, access to densely functionalized intermediates with multiple reactive sites for selective synthetic manipulation can be of key importance.

2.2 Properties of 1-azadienes

Many biologically active small molecules contain nitrogen heterocycles, which can present diverse arrays of pharmacophores in a semi-rigid framework of hydrogen bond donors and acceptors. 1-Azadienes are extremely versatile building blocks for the efficient *de novo* construction of such nitrogen heterocycles. They can serve as useful platforms to create structural diversity and complexity in only few reaction steps. The basis for this versatility lies in the various possible reactivities of 1-azadienes (see Figure 1). For example, the electron-rich nitrogen atom of the azadiene may react as a nucleophile. On the other hand, the α,β-unsaturated imine may act as an electrophile, in a 1,2-addition or in a Michael-type 1,4-addition. Finally, 1-azadienes can react as heterodienes in cycloaddition reactions. In addition, both the alkene and the imine functionality could, in principle, react as dienophiles, dipolarophiles or carbenophiles, giving rise to the formation of yet different types of N-heterocycles.

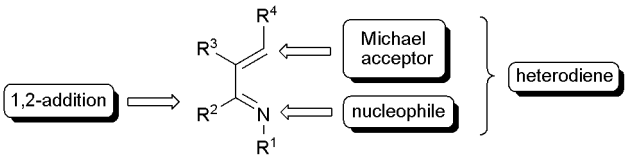


Figure 1: Different reactivities of 1-azadienes.

Although many possible reactivities of 1-azadienes can be distinguished, they often react with remarkable selectivity in specific cases. The reactivity that a 1-azadiene displays in a given reaction depends both on the reaction partner and on the nature of the substituents. More precisely, the electron density in the 1-azadienes is the important factor. Therefore, we classify 1-azadienes in three categories:
(1) *Electron-deficient 1-azadienes*, bearing electron-withdrawing substituents such as sulfonyl, acyl, or alkoxycarbonyl groups, typically on nitrogen. These tend to react primarily as electrophiles in 1,4-additions, but also react with electron-rich dienophiles in inverse electron-demand hetero Diels-Alder reactions.
(2) *Electron-rich 1-azadienes*, bearing electron-donating substituents such as alkyl, alkoxy, silyloxy, or dialkylamino groups, typically on nitrogen. These react mostly in hetero Diels-Alder reactions with electron-poor dienophiles, but they can also react as nitrogen nucleophiles.
(3) *1H-1-Azadienes*, lacking N-substituents, combine all reactivities of 1-azadienes. The type of reaction they participate in depends mostly on reaction partners and reaction conditions. Indeed, 1*H*-1-azadienes can be regarded as the synthetically most versatile type. A limiting factor in the application of 1*H*-1-azadienes is their low stability. In most reactions involving 1*H*-1-azadienes, they are generated *in situ* rather than isolated. This does, however, make them valuable reactive intermediates (see also Section 2.5).

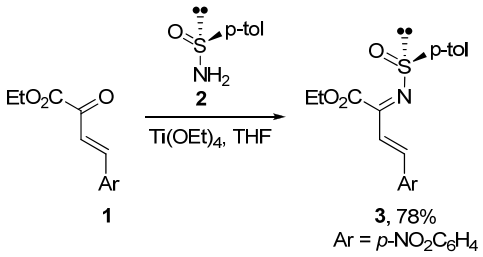
It should be noted that no strict rules can be applied to this classification, since 1-azadienes may carry both electron-withdrawing and electron-donating substituents. In most cases, the N-substituent typically has a profound influence on the reactivity. Therefore, we use the nature of the N-substituent as the basis for the above classification.
This chapter describes the use of 1-azadienes as reactive intermediates in the synthesis of various types of biologically relevant heterocycles. In some cases, the 1-azadienes are isolated and then used for further reactions. In many cases, however, the 1-azadienes are generated *in situ* and reacted with several types of reactants. First, the synthesis of 1-azadienes will be discussed, followed by their use in the synthesis of various classes of heterocycles. The focus will be on cycloaddition, electrocyclization, and multicomponent reactions.

2.3 Synthesis of 1-azadienes

1-Azadienes can be prepared in a number of ways and some examples in the recent literature are discussed here. A representative set of reactions rather than a complete overview of all the possible reactions that are used for this purpose is presented.

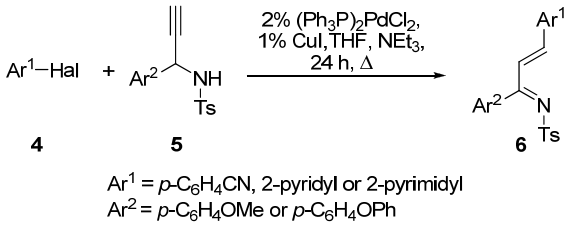
2.3.1 Synthesis of electron-deficient 1-azadienes

The most straightforward synthesis of 1-azadienes is the classical condensation reaction between an α,β-unsaturated carbonyl compound with an amine. A recent example by Palacios and co-workers is shown in scheme 1.[27] A direct condensation of (*S*)-*p*-toluene-sulfinimide **2** and β,γ-unsaturated α-ketoester **1** yields 1-azadiene **3** in 78% yield (Scheme 1).



Scheme 1: Synthesis of chiral sulfinimides.[27]

The reaction is performed in the presence of 2 equivalents of titanium tetraethoxide to activate the ketoester. The presence of an electron-withdrawing group at the γ-position of the α-ketoester seems to increase the reactivity of the carbonyl group leading to exclusive formation of the *N*-sulfinylimine. The resulting *N*-sulfinylimines were used in the synthesis of substituted pyridines.[27]



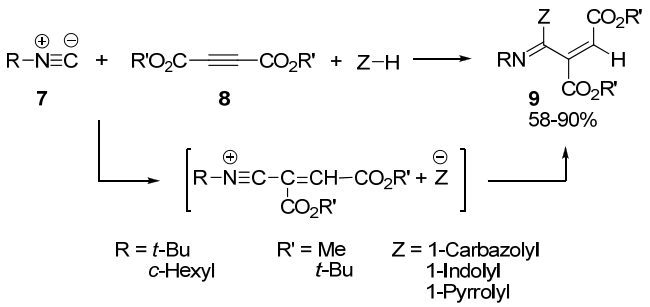
Scheme 2: *In situ* generation of azadienes by rearrangement of Sonogashira products.[28]

Another method for *in situ* generation of electron-deficient 1-azadienes is reported by Müller and co-workers (Scheme 2).[28] The 1-azadiene **6** is generated *in situ* from an electron-poor aryl halide **4** and a terminal propargylic *N*-tosylamine **5** via a cross-coupling/isomerization sequence. The sequence consists of a Pd^0/Cu^I catalyzed Sonogashira reaction followed by a slow base-catalyzed isomerization.

2.3.2 Synthesis of electron-rich 1-azadienes

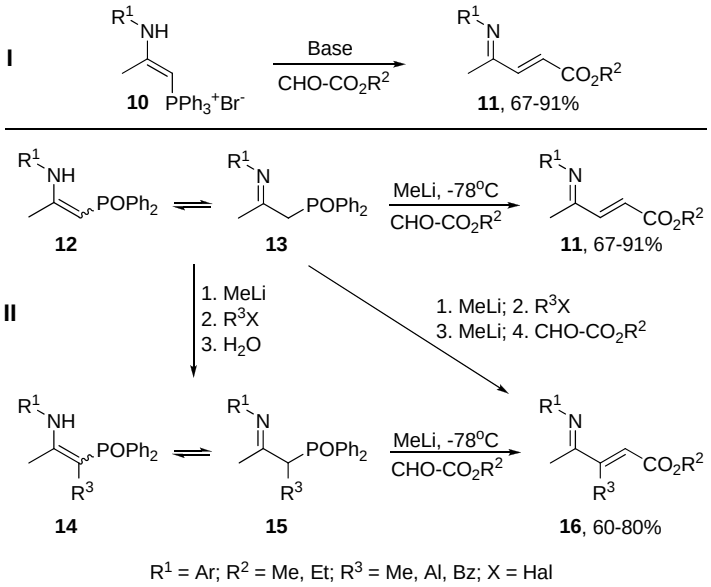
The synthesis of *N*-alkyl-1-azadienes has been reported most extensively and some recent examples are presented here.

The use of an isonitrile for the synthesis of 1-azadienes is reported by Yavari *et al*.[29] Addition of an alkyl isonitrile **7** to a dialkyl acetylenedicarboxylate **8** yields an intermediate that can be trapped by fairly strong NH-acids (Z-H) such as carbazole, indole or pyrrole to yield 1-azadienes **9** (Scheme 3).



Scheme 3: Synthesis of 1-azadienes by α-addition of NH-acids and alkynes to isocyanides.[29]

Using pyrrole as the NH-acid, only 1-azadienes were obtained, but with carbazole or indole highly functionalized ketenimines were formed as side products. The formation of the products results from an initial addition of the alkyl isocyanide to the acetylenic ester, followed by protonation of this adduct by the NH-acid (Z-H). The positively charged adduct can then be attacked at two positions by the nitrogen atom of the anion of the NH-acid. Direct addition leads to 1-azadienes, while conjugate addition leads to ketenimines (Scheme 3).



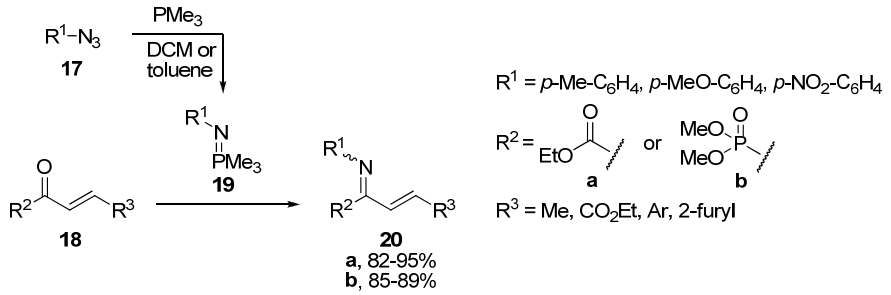
Scheme 4: Synthesis of 1-azadienes by Wittig-type reactions of imino- and enamino-ylides.[30]

The group of Palacios contributed considerably with several methods to synthesize N-substituted 1-azadienes. Examples of two different methods are given here. The first example reports the synthesis of α,β-unsaturated γ-imino esters by Wittig or Wittig-Horner reaction of alkyl glyoxylates and functionalized phosphonium salts or phosphine oxides, *via* methods **I** and **II**, respectively (Scheme 4).[30]

With method **I**, phosphonium salts **10** were deprotonated by a strong base followed by the addition of ethyl glyoxylate (R^2 = Et). After stirring at room temperature for 24 h, aqueous work-up and purification, the corresponding 1-azadienes **11** were obtained in good yields (67-91%). This methodology could also be used for the β-enamino or β-imino phosphine oxides

12 and **13** with MeLi as the base (**II**, scheme 4). The alkylated phosphine oxides **14** or **15** were used for the generation of 3-substituted 1-azadienes **16**. The alkylated phosphine oxides **14** and **15** were made from **12** and **13** by metallation and subsequent addition of alkyl halides and aqueous work-up. Wittig-Horner olefination of these phosphine oxides **14** and **15** with ethyl glyoxylate leads to the formation of the 1,3-disubstituted-1-azadienes **16**. This process can also be performed in a stepwise fashion from phosphine oxides **12** and **13**. The reaction is compatible with chiral substituents and with functional groups that can later be removed. The 1-azadienes are stable to air and moisture and can be purified, isolated and stored for several hours.

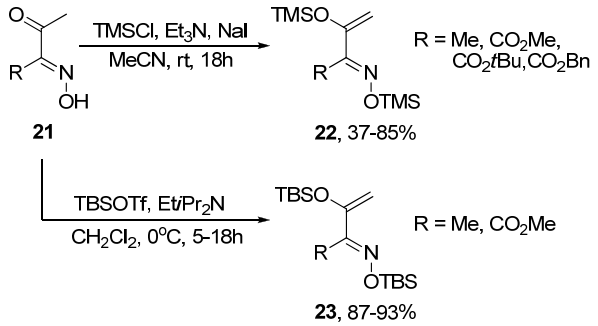
A second example reported by Palacios to arrive at 1-azadienes is the Staudinger reaction of β,γ-unsaturated α-ketoesters **18a** with phosphazenes **19**. The latter were prepared *in situ* by addition of trimethylphosphine to aryl azides **17** (Scheme 5).[31] The α-ketoesters were prepared via aldol- or Wittig-type condensation of aldehydes with the corresponding pyruvate-derived reagent.[32]



Scheme 5: Synthesis of 1-azadienes derived from α-ketoesters and α-ketophosphonates.[31,33]

The 1-azadienes **20a** were obtained as *syn/anti* mixtures in yields ranging from 82-95%. The stability of azadienes **20a** towards most common purification techniques like chromatography and distillation was very low, so they were used without purification in further steps. *Via* the same methodology, phosphorylated 1-azadienes **20b** can be made from *P*-trimethyl phosphazenes **19** and β,γ-unsaturated α-ketophosphonates **18b** in a regioselective fashion and in high yields (85-89%, Scheme 5).[33] The 1-azadienes **20b** bearing aromatic, heteroaromatic or alkoxy substituents in the β-position were stable and could be isolated using standard purification techniques, those derived from crotonaldehyde could not be isolated.

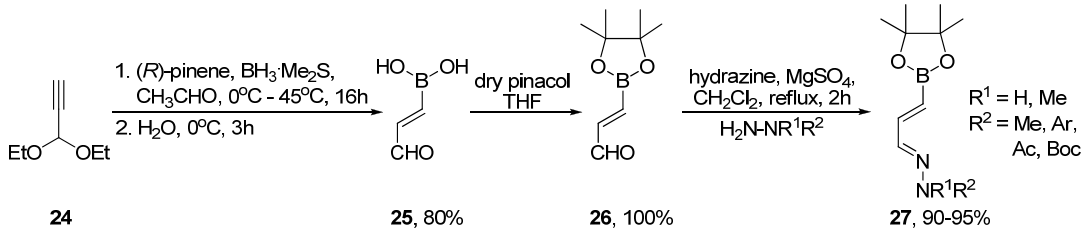
The procedures described above all yielded 1-alkyl-1-azadienes. However, 1-azadienes bearing R_2N- or RO- substituents at the 1-position are also relevant. A method reported by Fletcher *et al*. converts α,β-unsaturated oximes **21** to 1,3-bis(siloxy)-1-azadienes **22** by reaction with trimethylsilyl chloride in the presence of triethylamine and sodium iodide (Scheme 6).[34]



Scheme 6: Synthesis of highly electron-rich 1,3-bis(silyloxy)-1-azadienes.[34]

The yields of the reaction were quite good (37-85%), but the stability of the 1,3-bis(silyloxy)-1-azadienes proved to be quite low. Therefore, the TMS group was replaced by a TBS group. These corresponding 1,3-bis(silyloxy)-1-azadienes **23** could also be prepared from the α-ketooximes **21**, now by using TBSOTf, in excellent yields (87-93%). This method was also employed to generate analogous 1-(dimethylamino)-1-azadienes from butane-2,3-dione mono-hydrazone in good yields.

Hall and co-workers reported an approach to the synthesis of α,β-unsaturated hydrazones by the three-step sequence depicted in Scheme 7.[35] First, hydroboration of **24** with diisopinocampheylborane, followed by acetaldehyde-promoted oxidative dealkylation and hydrolysis afforded 3-boronoacrolein (**25**) in 80% yield. Then the corresponding boronic ester **26** was obtained quantitatively *via* a reaction of **25** with pinacol. Finally, the 1-azadienes **27** were formed in 90-95% yield by a condensation reaction with the required hydrazines using anhydrous magnesium sulfate as the drying agent.

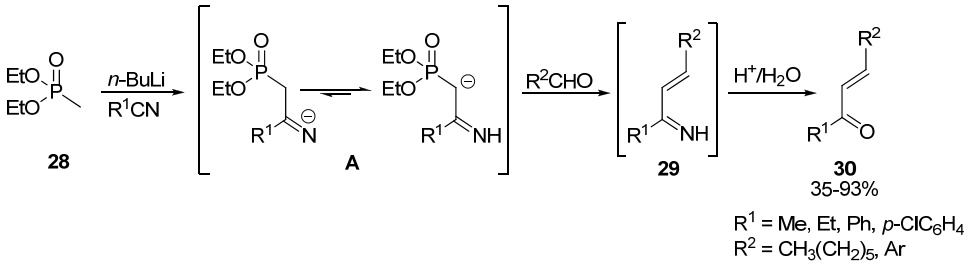


Scheme 7: Three-step synthesis of 1-(dialkylamino)-4-borono-1-azadienes.[35]

2.3.3 Synthesis of 1*H*-1-azadienes

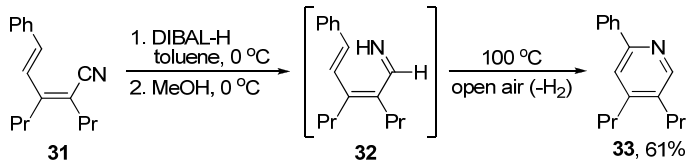
An efficient way of generating 1*H*-1-azadienes is reported by our laboratory.[36,37] The method is based on the chemistry reported by Lee and Oh in which a 1-azadiene (**29**) is generated from a phosphonate (**28**), a nitrile and an aldehyde, as an intermediate in the synthesis of α,β-unsaturated ketones **30** (Scheme 8).[38] A nitrile is added to the carbanion of diethyl methylphosphonate **28**, generating the intermediate ketimine anion **A**. This intermediate is then reacted with an aldehyde to give 1*H*-1-azadienes **29**. This method was first used by Lee and Oh[38] and later by Palacios and co-workers[39] to synthesize α,β-unsaturated ketones **30**. The

in situ generation of 1-azadienes also offers ample possibility for application in multicomponent reactions, exemplified by various reports from our group[36,37,40,41] and Kiselyov and co-workers[42,43] (see also Section 5.2).



Scheme 8: Multicomponent synthesis of 1-azadienes as intermediates in the preparation of α,β-unsaturated ketones.[38]

Another method for generating 1*H*-1-azadienes that involves the use of nitriles is their reduction with diisobutylaluminum hydride (DIBAL-H). Hiyama and co-workers used this method for the generation of 1*H*-1-azatrienes.[44] Thus, reduction of the nitrile **31** with DIBAL-H followed by protonation by MeOH leads to formation of 1-azatriene **32** (Scheme 9). Such 1*H*-1-azatrienes can then undergo electrocyclization followed by air oxidation at elevated temperature to give pyridine **33**.



Scheme 9: Generation of 1-azadienes and 1-azatrienes by DIBAL-H reduction of nitriles.[44]

2.4 The use of 1-azadienes in the synthesis of N-heterocycles

1-Azadienes have been employed in a range of different reactions to access a wide variety of N-heterocycles, including *e.g.* di- and tetrahydropyridines, pyrimidines, quinolines, thiazines, pyrroles, triazinane diones, and aziridines.

2.4.1 Cycloaddition reactions

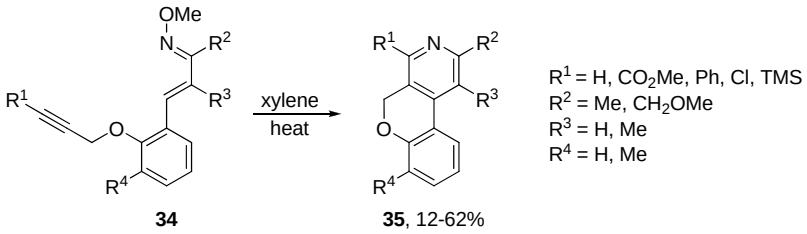
1-Azadienes are frequently applied in [4+2] or in [4+1] cycloadditions. In these reactions, the 1-azadienes usually serve as the heterodiene partner. However, both the imine and alkene functionality of 1-azadienes can also react as dienophiles, dipolarophiles or carbenophiles in *e.g.* [4+2], [2+3], or [2+1] cycloadditions. Here, we present an overview on the broad range of possible cycloadditions leading to various heterocycles.

2.4.1.1 [4+2] Cycloadditions/hetero Diels-Alder reactions

Many reports exist on the use of 1-azadienes in hetero Diels-Alder reactions giving six-membered heterocycles. This topic has been reviewed by Behforouz and Ahmadian in 2000[45] and Mahajan and co-workers in 2002.[46] The former report focuses on the hetero Diels-Alder reactions of 1-azadienes, while the latter is a review on the synthetic applications of azadienes in general. In this chapter, the literature that appeared after these reviews will be discussed. The substitution on the nitrogen atom defines the type of hetero Diels-Alder that occurs. Electron-rich 1-azadienes typically react in normal electron-demand hetero Diels-Alder reactions, while electron- deficient 1-azadienes react in inverse electron-demand hetero Diels-Alder reactions. This section is organized accordingly.

2.4.1.1.1 Normal electron-demand hetero Diels-Alder reactions

One of the most recent examples of this type is reported by Moody and co-workers.[47] They use an intramolecular hetero Diels-Alder reaction of α,β-unsaturated oxime ethers and acetylenic dienophiles in **34** for the synthesis of [*c*]-fused pyridines **35** (Scheme 10).

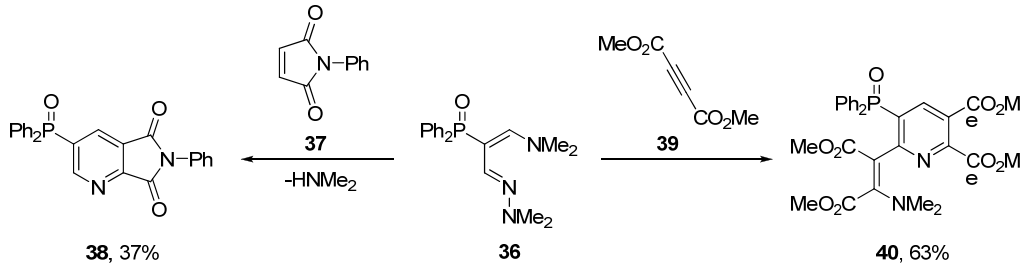


34 **35**, 12-62%

Scheme 10: Intramolecular hetero Diels-Alder cycloaddition leading to [*c*]-fused pyridines.[47]

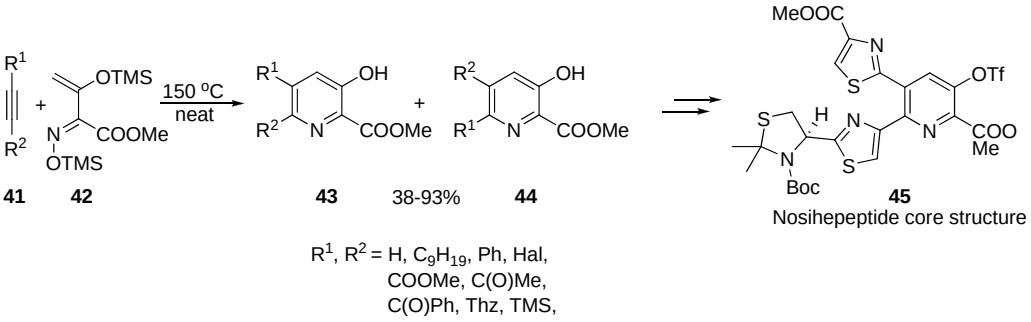
The α,β-unsaturated oxime ethers **34** (1-azadienes) were synthesized from the corresponding α,β-unsaturated ketones *via* a reaction with methoxylamine hydro-chloride and sodium acetate trihydrate. The yields of the pyridines **35** can be reasonable (12-62%); Optimal results were obtained with an electron-deficient acetylene functionality in **34**.

Another reaction generating fused pyridines was reported by Palacios *et al*.[48] Hetero Diels-Alder reaction of 1-dimethylamino-1-azadiene **36** containing a phosphine oxide group at C3 with the electron-deficient dienophile *N*-phenylmaleimide **37** gave fused pyridine **38** (Scheme 11). The 1-azadiene **36** can also react with the electron-deficient diethyl acetylenedicarboxylate **39** yielding the substituted vinyl pyridine **40**. The reaction towards the fused pyridine product **38** was achieved in the absence of solvent at 100°C. The yield was moderate (37%) and could not be increased by the addition of Lewis acids (BF_3, $AlCl_3$, $Cu(OTf)_2$, $InCl_3$ or $LiClO_4$). The synthesis of the substituted vinyl pyridine **40**, again in the absence of solvent, could be performed at room temperature, furnishing **40** in reasonable yield (63%).



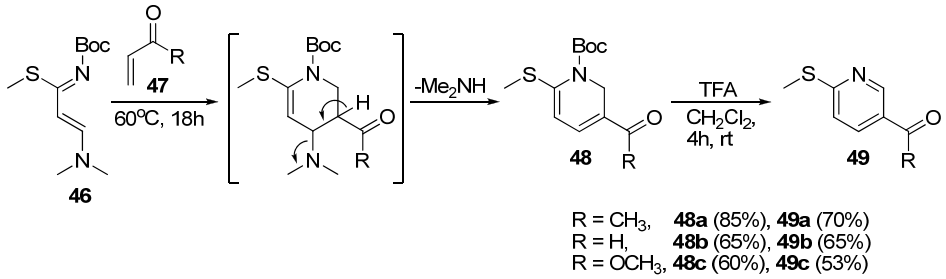
Scheme 11: Synthesis of pyridines by hetero Diels-Alder reactions of electron-rich 1-azadienes.[48]

Arndt and coworkers report the synthesis of 3-hydroxy-pyridines **43** *via* a hetero Diels-Alder reaction.[49] The products were applied to the synthesis of Nosihepeptide core structures **45**. The 1-azadiene, a silylated enol oxime **42**, can react with various alkynes **41** (Scheme 12).



Scheme 12: Hetero Diels-Alder reactions of electron-rich 1-azadienes with alkynes leading to 3-hydroxypyridine-2-carboxylates.[49]

In the reaction, mixtures of different regioisomers (**43** and **44**) were formed and the overall yield of the reaction varies from reasonable (38%) to good (93%). The choice of the diene and dienophile is flexible as long as electronically activated alkynes are employed, and the diene must not be further deactivated by steric bulk. The regioselectivity can be directed towards the 6-isomer **44** by using monosubstituted alkynyl ketones (R^1 = RC(O)-, R^2 = H). Fletcher *et al.* have used a similar strategy for the synthesis of polysubstituted pyridine derivatives.[34]

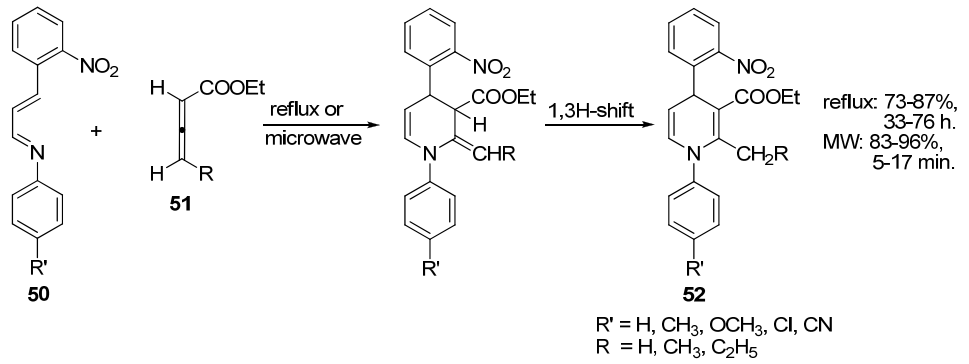


Scheme 13: Synthesis of 2-(methylthio)pyridines by hetero Diels-Alder reaction of 1-azadienes with α,β-unsaturated carbonyl compounds.[50]

Another method for the synthesis of substituted pyridines is reported by Deniaud and co-workers, who used the hetero Diels-Alder reaction of Boc-protected 1-azadiene **46** and acrylic

dienophiles **47** (Scheme 13).[50] In this way, they obtained dihydropyridines **48** by a cycloaddition and spontaneous deamination sequence. Aromatization to the pyridines **49** was then achieved by removal of the Boc-group using trifluoroacetic acid followed by spontaneous air oxidation. Three different R groups were used and the yields for both the dihydropyridines **48** (60-85%) and the pyridines **49** (53-70%) are reasonable to good.

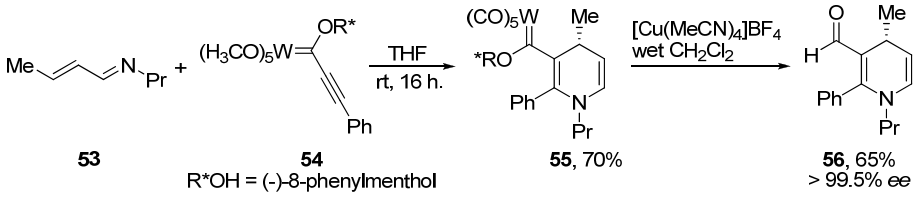
Dihydropyridines can also be prepared under microwave conditions. Singh *et al.* reported the thermal and microwave-assisted hetero Diels-Alder reactions between 1-azadienes **50** and allenic esters **51** for the synthesis of unsymmetrical substituted 1,4-dihydropyridines **52** (Scheme 14).[51]



Scheme 14: Synthesis of dihydropyridines by hetero Diels-Alder reaction of 1-azadienes with allenic esters.[51]

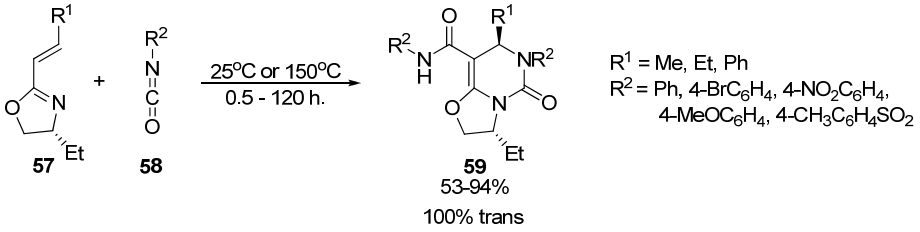
Using microwave irradiation instead of refluxing in dry benzene gave a faster and cleaner reaction, and the products were obtained in higher yields. The yields of **52** under normal reflux conditions vary between 73-87% while with microwave heating **52** could be isolated in 83-96%. Reaction times decreased notably, from 33-76 h under conventional heating conditions to 5-17 min using microwave heating.

Barluenga and co-workers report an enantioselective synthesis of 1,4-dihydropyridine **56** by reaction of the chiral alkynyl(alkoxy)carbene complex **54** with 1-azadiene **53** (Scheme 15).[52] The dihydropyridine complex **55** was isolated in 70% yield as a single regio- and diastereoisomer. The complex was demetallated and the chiral auxiliary removed by treatment with $[Cu(MeCN)_4]BF_4$ in wet dichloromethane giving the corresponding optically pure (*ee* > 99.5%) aldehyde **56** in 65% yield.



Scheme 15: Enantioselective hetero Diels-Alder reaction of 1-azadienes and optically pure alkynyl Fischer carbenes leading to dihydropyridines.[52]

An interesting use of 1-azadienes in natural product synthesis is reported by Elliott *et al.*, who developed a hetero Diels-Alder reaction for application in their studies towards the total synthesis of batzelladine A.[53-55] They showed that the hetero Diels-Alder reaction between 2-alkenyl-2-oxazolines **57** (as the 1-azadienes) and isocyanates **58** efficiently (53-94%) gives oxazolo[3,2-*c*]pyrimidines **59** (Scheme 16).

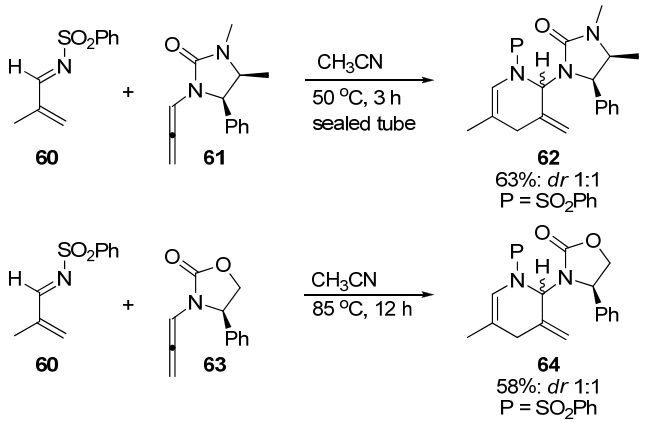


Scheme 16: Hetero Diels-Alder reaction yielding oxazolo[3,2-*c*]pyrimidines.[53-55]

Moreover, the reaction is completely diastereoselective. The *trans* isomers are the only diastereomers obtained. An interesting aspect of these oxazolopyrimidines is that the pure *cis* isomers are obtained upon heating of the pure *trans* isomer above their melting points.

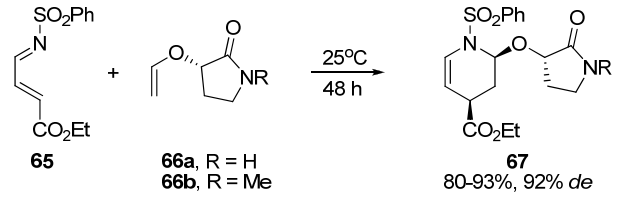
2.4.1.1.2 Inverse electron-demand hetero Diels-Alder reactions

N-Sulfonyl 1-azadienes are electron-deficient and therefore react as heterodienes in inverse electron-demand hetero Diels-Alder reactions. A number of reports have appeared on the use of these *N*-sulfonyl substituted 1-azadienes in the synthesis of heterocycles.[56-59] A recent example was reported by Hsung and co-workers.[56] The optically pure allenamides **61** and **63** can both react with the *N*-sulfonyl-1-azadiene **60** in a [4+2] cycloaddition reaction to give nitrogen heterocycles **62** and **64**, respectively (Scheme 17).[56] These were employed in the synthesis of aza-glycoside related heterocycles. Although the yields of **62** and **64** (63 and 58%, respectively) were good, formation of a 1:1 mixture of diastereomers was observed in both cases.



Scheme 17: Inverse electron-demand hetero Diels-Alder reaction of electron-deficient 1-azadienes with optically pure allenamides.[56]

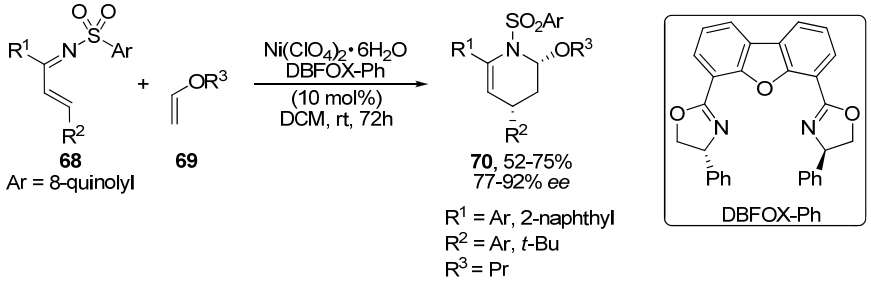
A diastereoselective, auxiliary-assisted, hetero Diels-Alder reaction reported by Boger and co-workers[57] employs *N*-sulfonyl-1-azadienes **65**. These can react with optically active enol ethers **66** and cycloadducts of type **67** are obtained with high diastereoselectivity (Scheme 18).



Scheme 18: Auxiliary-assisted asymmetric inverse electron-demand hetero Diels-Alder reaction.[57]

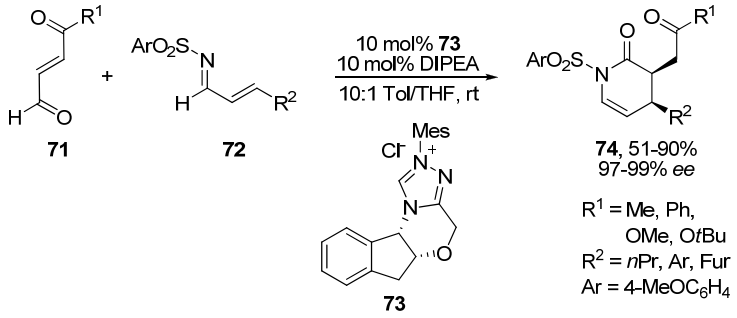
Three readily available enol ethers bearing chiral auxiliaries were tested along with standard reaction parameters like temperature, solvent, reactant concentration and substitution of the sulfonyl group. The best results were obtained with chiral auxiliaries **66a** and **66b**, which gave high *endo* and facial diastereoselectivity to yield **67** in 80-93% and 92% *de*.

An enantioselective hetero Diels-Alder reaction was reported by Carretero *et al*., who reacted *N*-sulfonyl-1-azadienes **68** with vinyl ethers **69** under the influence of a nickel catalyst and the chiral ligand DBFOX-Ph.[58] The reaction affords asymmetric piperidine derivatives **70** (Scheme 19). Carretero showed that combination of a propyl group (R^3) and the 8-quinolyl group (Ar) gave the optimal *ee* (91%). With this system in hand, the R^1 and R^2 group were varied and the products **70** were isolated in good yields (52-75%), high degrees of *endo* selectivity and with good *ee*'s (77-92%). Aryl substituents of varied electronic and steric nature at the *β*-position (R^2) are well tolerated and even a *tert*-butyl group was allowed. Variation of R^1 was more limited. *p*-Substituted aryl groups could be used, but with the more sterically demanding 2-naphthyl group, the *ee* dropped significantly (6%).



Scheme 19: Catalytic asymmetric inverse electron-demand hetero Diels-Alder reaction.[58]

Another example that makes use of a chiral catalyst is reported by Bode and co-workers, who use an optically pure *N*-heterocyclic carbene (NHC) to catalyze a hetero Diels-Alder reaction of **71** and **72** for the synthesis of optically enriched dihydro-pyridones **74** (Scheme 20).[59]



Scheme 20: N-Heterocyclic carbene-catalyzed asymmetric inverse electron-demand hetero Diels-Alder reaction.[59]

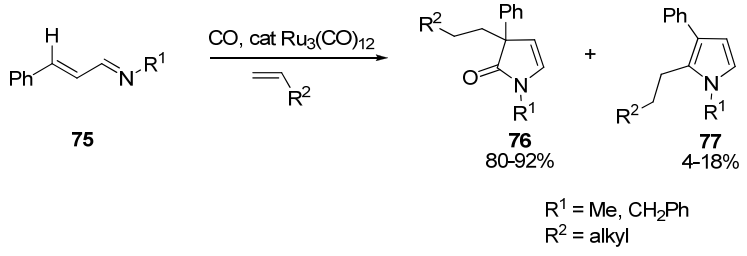
Combination of enals **71** and electron-poor 1-azadienes **72** in the presence of the NHC generated *in situ* from **73** efficiently affords the dihydropyridones **74** in yields ranging from 51-90% with *ee*'s of 97-99%. As the NHC catalyst precursor, a chiral triazonium salt with a sterically demanding mesityl group (**73**) was used. Electron-rich and electron-deficient, heterocyclic and aliphatic 1-azadienes **72** are tolerated. Also, a range of different enals **71** could be used. This is the first example of asymmetric organocatalysis in a hetero Diels-Alder reaction by a metal-free NHC.

2.4.1.2 Other cycloaddition reactions

In addition to the various types of hetero Diels-Alder reactions, 1-azadienes can also be involved in other cycloaddition reactions generating complex and diversely functionalized N-heterocycles.

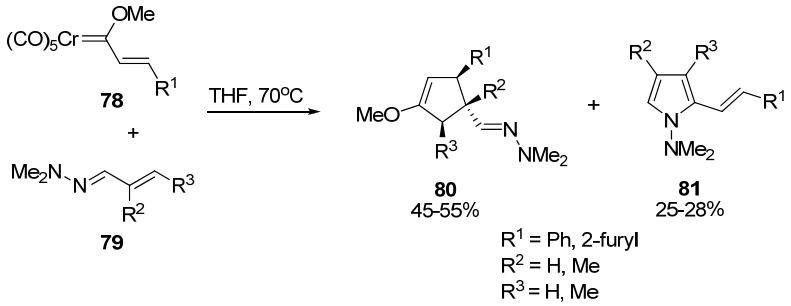
2.4.1.2.1 [4+1] and [2+3] cycloadditions

Imhof *et al.* reported a reaction between 1-azadiene **75**, CO and various alkenes in the presence of a catalytic amount of $Ru_3(CO)_{12}$ giving 1,3-dihydropyrrolone derivatives **76** (lactams).[60] Usually, small amounts of 2,3-disubstituted pyrroles **77** were observed as side products (Scheme 21). The yield of **76** increased with enhanced basicity of the azadiene nitrogen atom. Therefore, the 1-azadienes **75** with R^1 = Me or Bn performed best in this reaction and the yields of **76** are good to excellent (80-92%). A high *n/iso* ratio in **76** is only obtained when α-olefins with long alkyl chains as R^2 are used.



Scheme 21: Ru^0-catalyzed alkylative [4+1] cycloadditions leading to pyrrolones or pyrroles.[60]

The group of Barluenga reports the use of Fischer carbene complexes **78** and 1-amino-1-azadienes **79** for the synthesis of substituted cyclopentenes **80** (Scheme 22).[61]



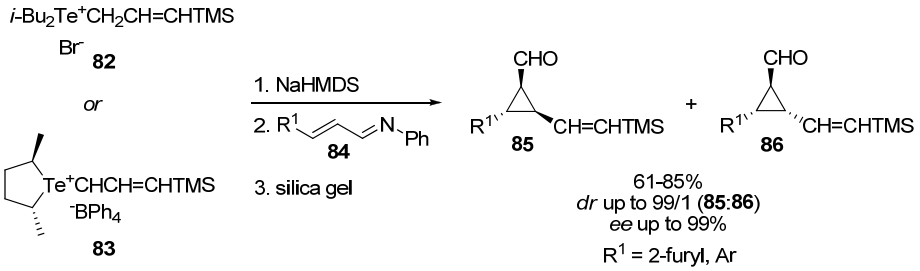
Scheme 22: [2+3] *vs.* [4+1] cycloaddition of 1-dimethylamino-1-azadienes and alkenyl Fischer carbenes affording cyclopentenes and pyrroles, respectively.[61]

Pyrroles **81** are formed as side products. The methoxy-cyclopentenes **80** are formed *via* a [2+3] cycloaddition generating two or three stereogenic centers (depending on R^1) in a single operation. The pyrroles **81** are formed *via* a [4+1] cyclization, a process that is rather uncommon for Fischer carbene complexes. Yields of **80** range from 45-55% and of **81** from 25-28%. The methoxycyclopentenes can be converted to the corresponding cyclopentanone hydrazones or cyclopentanone carboxaldehydes by treatment with 0.5 or 3 M aq. HCl, respectively.

The asymmetric version of this reaction involving enantiopure chromium carbene complexes derived from (−)-8-phenyl-menthol and (−)-8-(2-naphthyl)menthol has also been studied. This gave, next to the pyrrole side products, diastereomeric mixtures of the expected *trans*,*trans*- and *cis*,*cis*-cyclopentenes.

2.4.1.2.2 [2+1] Cycloadditions

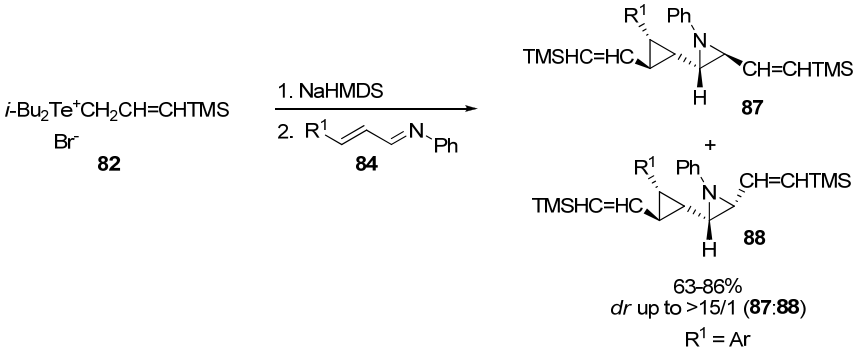
Zheng *et al.* reported the synthesis of vinylcyclopropane-carbaldehydes by reaction of tellurium ylides **82** and 1-azadienes **84** (Scheme 23).[62]



Scheme 23: [2+1] Cycloaddition between 1-azadienes and tellurium ylides leading to cyclopropanecarbaldehydes.[62]

Usually, reaction of ylides with 1-azadienes leads to aziridine formation *via* a 1,2-addition.[63] However, after deprotonation of the telluronium salt **82** by NaHMDS, the resulting tellurium ylides undergo a facile [2+1] cycloaddition between the C=C π-bond of the azadiene and the

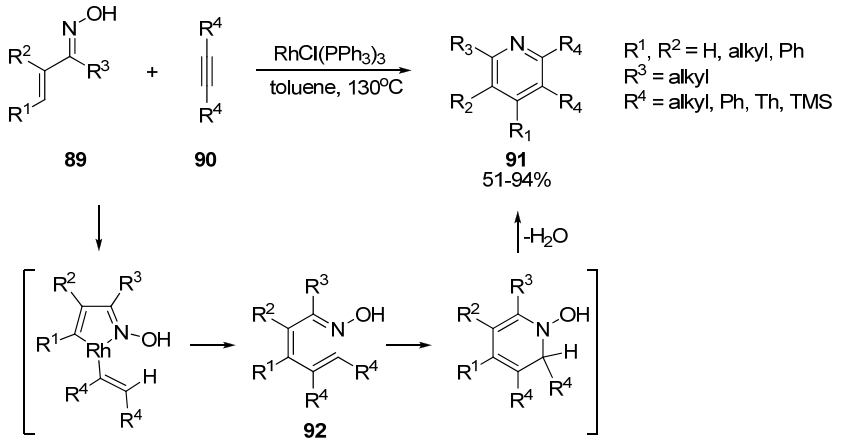
carbanion. The corresponding cyclopropane-carbaldehydes **85** and **86** were isolated in good yields (61-85%) and with excellent chemo- and diastereo-selectivity.[62] Both electron-withdrawing and electron-donating aryl groups (R^1) are tolerated. An asymmetric version of the reaction employs optically pure telluronium salt **83**. The desired cyclopropanes were isolated in good *ee* (95-99%). Interestingly, vinyl-cyclopropylaziridines **87** and **88** are obtained when a 3:1 ratio of telluronium salt **82** and 1-azadiene **84** is used (Scheme 24). The products with cumulated three-membered rings could be synthesized with good diastereoselectivity (*dr* up to 15/1) in reasonable to good yields (63-86%). Again, both electron-withdrawing and electron-donating R^1 groups are tolerated.



Scheme 24: Formation of cyclopropylaziridines by double [2+1] cycloaddition of tellurium ylides to 1-azadienes.[62]

2.4.2 The use of 1-azadienes in electrocylization reactions

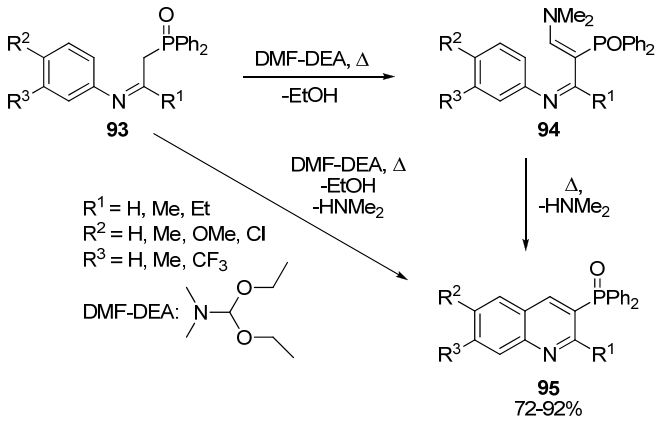
In addition to the cycloaddition reactions described above, 1-azadienes can be employed in electrocyclization processes as well. For example, Cheng and co-workers reported a Rh^I-catalyzed synthesis of substituted pyridine derivatives **91** from 1-hydroxy-1-azadienes **89** and alkynes **90** (Scheme 25).[64]



Scheme 25: Rh^I-Catalyzed β-alkenylation of 1-azadienes followed by electrocyclization/dehydration affording highly substituted pyridines.[64]

First, a rhodium-catalyzed chelation-assisted C-H activation of the 1-azadiene takes place. The formation of the product can be regarded as a β-alkenylation of the 1-azadiene to give a 1-azatriene intermediate (**92**), followed by a 6π-cyclization and dehydration. The product may also be formed *via* a Diels-Alder reaction followed by dehydration. However, performing the reaction without the rhodium catalyst did not give any cycloaddition product. Various substituents are allowed on both the 1-hydroxy-1-azadiene **89** and the acetylene **90**, affording the pyridines **91** in yields between 51-94%. When unsymmetrical internal alkynes are used, mixtures of regioisomers are obtained.

In another electrocyclization, Palacios *et al.* reported the synthesis of quinolinyl-phosphine oxides **95** from *N*-arylimines **93** (Scheme 26).[65]



Scheme 26: Synthesis of quinolinylphosphine oxides by electrocyclization of *N*-aryl-4-dimethylamino-1-azadienes.[65]

The reaction proceeds *via* the intermediate *N*-aryl-1-azadiene **94** that can be isolated. Formation of **94** can be explained by a condensation of the imine starting material with dimethylformamide diethyl acetal (DMF-DEA). The resulting 1-azadiene can then undergo electrocyclization to afford the quinoline **95** by heating to 110 °C in toluene. With this procedure in hand, a small library of quinolinylphosphine oxides **95** was prepared by heating *N*-arylimines with DMF-DEA in refluxing toluene (48 h). The yields are good to excellent (72-92%) and various types of substituents are tolerated. The aromatic ring can bear electron-donating and -withdrawing substituents (R^2 and R^3), while R^1 can be alkyl or H. The quinolinylphosphine oxides **95** can also be made directly from **93** and DMF-DEA without isolation and purification of the intermediate 1-azadiene **94**. Using similar methodology, quinolinyl phosphonates can also be prepared in good yields (68-82%).

2.5 Multicomponent reactions based on 1-azadienes

As already mentioned in the introduction, DOS-based methods receive considerable attention in the recent literature.[5,7,13,15-18,21-26] The challenge is to address diversity as well as complexity in compound collections in order to probe functional biological activity more

efficiently.[20] Synthetic methods that generate multiple molecular scaffolds from the same starting materials or intermediates are considered to be most effective to increase especially structural or skeletal diversity.[9] On the other hand, complexity is most commonly introduced by highly convergent reactions like the cycloaddition and electrocyclization reactions described in Section 4. Also multicomponent reactions (MCRs) are powerful reactions to generate complex molecules as they combine at least three simple, easily accessible building blocks in a one-pot process.[66-68]

A conceptually novel approach to DOS is the use of **modular reaction sequences** combining MCRs and other complexity-generating reactions. In these sequences, a densely functionalized reactive intermediate formed *via* an initial MCR reacts with different additional components yielding a diverse set of complex scaffolds (Figure 2). In this way, both the diversity and the complexity criteria can be met in the design and construction of compound libraries to identify small molecule modulators of biological systems. 1-Azadienes are such densely functionalized intermediates, which can react as nucleophiles, electrophiles and as dienophiles, dipolarophiles or carbenophiles. Moreover, 1-azadienes can be generated *via* MCR chemistry, as will be discussed in the following sections. Therefore, 1-azadienes are extremely well suited to explore the concept of modular reaction sequences in DOS.

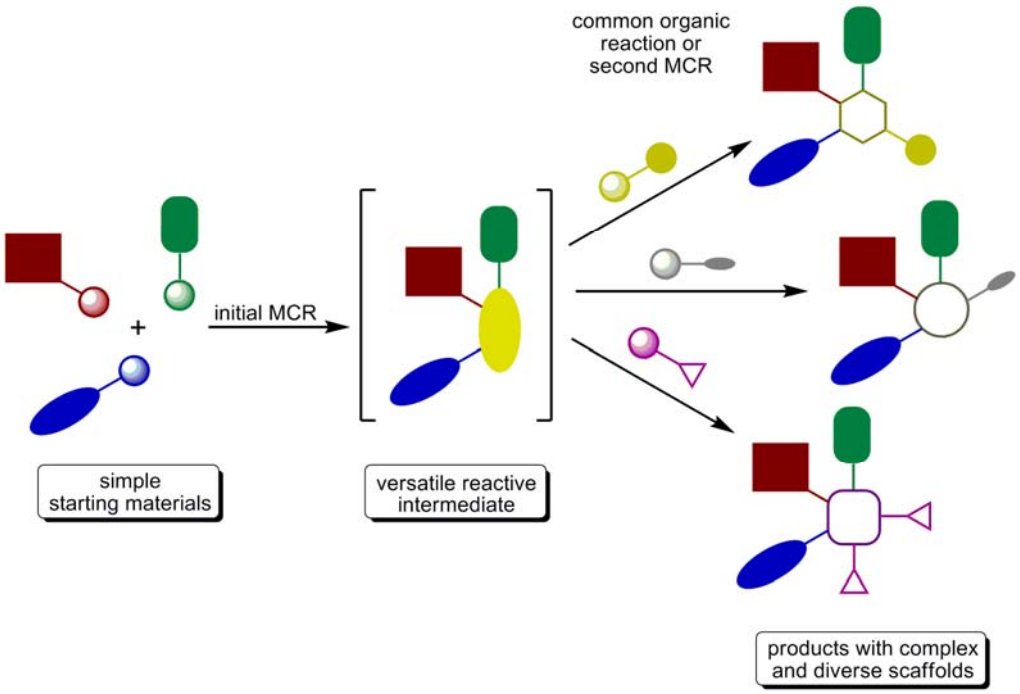
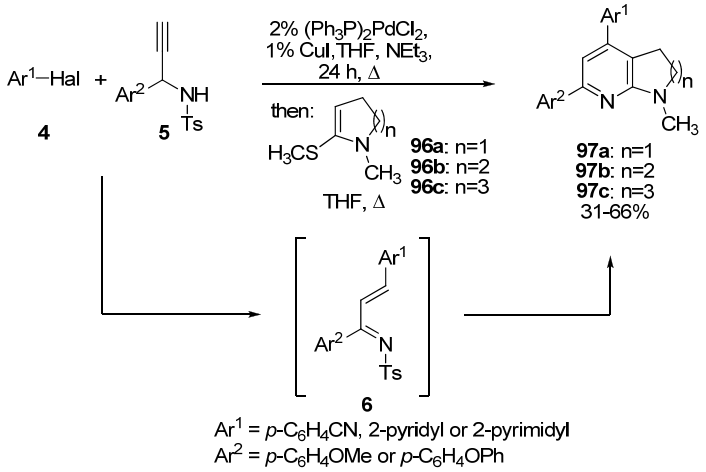


Figure 2: Modular reaction sequences.

2.5.1 *N*-substituted 1-azadienes in MCRs

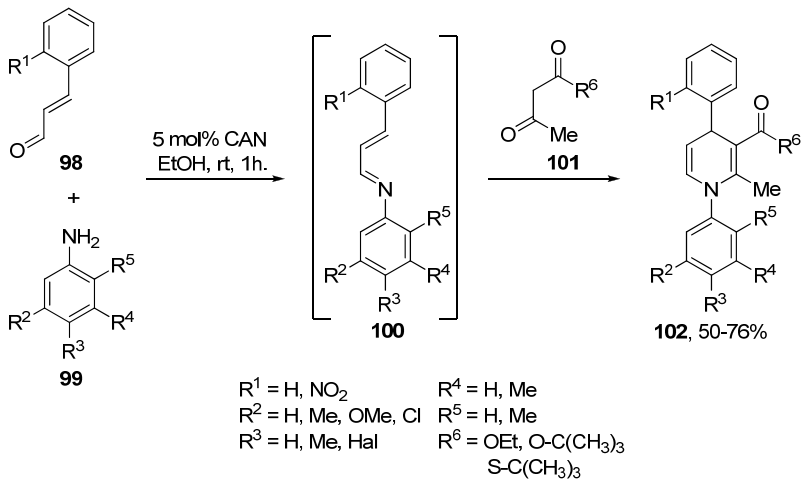
Müller and co-workers report a convenient method for a 1-azadiene-based MCR approach to pyrrolo[2,3,*b*]pyridines **97a**, [1,8]naphthyridines **97b** and pyrido[2,3-*b*]azepines **97c** (Scheme 27).[28] The 1-azadiene **6** is generated *in situ* from an electron-poor aryl halide **4** and a terminal propargyl *N*-tosylamine **5** *via* a coupling/isomerization sequence (see also Scheme 2). After

the 1-azadiene formation, the *N,S*-ketene acetal **96** is added and an inverse electron-demand hetero Diels-Alder reaction takes place, followed by aromatization yielding **97** in 31-66% (Scheme 27).



Scheme 27: Multicomponent synthesis of fused pyridines involving 1-azadienes generated *in situ* by isomerization of arylpropargylic sulfonamides.[28]

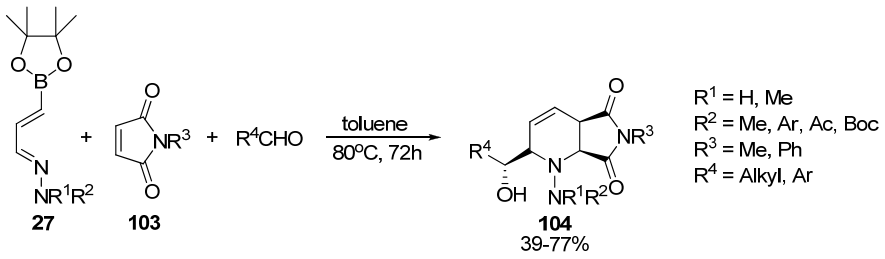
Sridharan *et al.* also reported an *in situ* synthesis of 1-azadienes **100**, by the condensation of α,β-unsaturated aldehydes **98** and aniline derivatives **99**. The azadienes are combined, in the same pot, with β-dicarbonyl compounds **101** yielding 1,4-dihydropyridines **102** (Scheme 28).[69]



Scheme 28: CAN-catalyzed three-component condensation leading to dihydropyridines.[69]

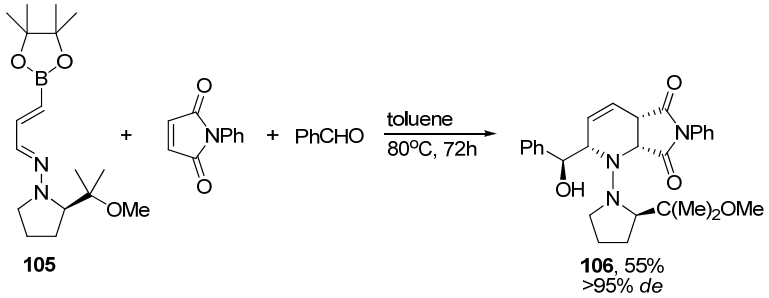
The reaction performs optimally by using 5 mol% ceric ammonium nitrate (CAN) in ethanol at room temperature for 1 h. The optimized reaction conditions were applied to a range of substrates yielding the 1,4-dihydropyridines **102** in reasonable to good yields (50-76%). Several types of electron-releasing and electron-withdrawing groups at all positions of the *N*-aryl group (R^2-R^5) are tolerated, including alkyl, alkoxy, bromo, chloro and fluoro subsituents. The 4-aryl group on the 1-azadiene **100** can also bear substituents (R^1) such as a

nitro group, but this can result in a lower yield. For the β-dicarbonyl compound (R^6), ethyl esters (R^6 = OEt) were the standard input. *tert*-Butyl esters can also be employed, but require a longer reaction time (2 h) and gave the corresponding dihydropyridine products in slightly lower yields. *tert*-Butyl β-keto thioesters (R^6 = S*t*Bu) can be efficiently applied in the reaction as well. Limitations of the reaction were found in the use of aliphatic amines or other α,β-unsaturated aldehydes than cinnamaldehyde derivatives, which resulted in complex reaction mixtures containing only small amounts of the desired product.



Scheme 29: Tandem hetero Diels-Alder/allylboration involving 4-borono-1-azadienes.[35]

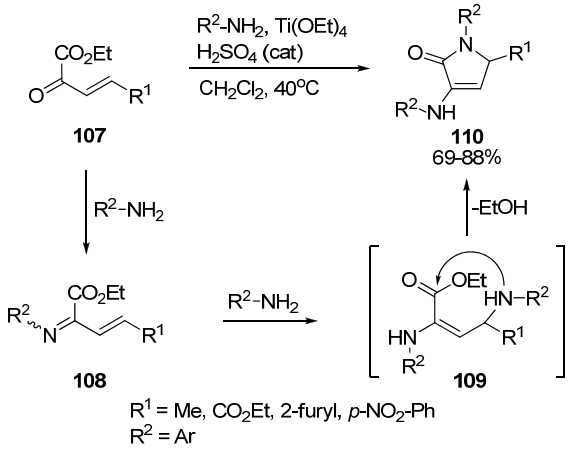
A MCR in which the 1-azadiene is not generated *in situ* is reported by Hall and co-workers.[35] They report a three-component reaction between 4-borono-hydrazono-dienes (1-azadienes) **27**, maleimides **103** and aldehydes for the synthesis of polysubstituted piperidines **104** *via* a tandem aza-[4+2]/allylboration reaction (Scheme 29). The required 4-borono-1-amino-1-azadienes **27** are efficiently synthesized *via* condensation of 3-boronoacrolein pinacol ester with hydrazines (see Scheme 7). Both mono- and disubstituted arylhydrazines can be used and even an acetyl or Boc group can be used as R^2. In the MCR itself, a wide variety of aldehydes (R^4) can be used including aliphatic aldehydes and electron-rich and electron-poor aromatic aldehydes. The maleimide substituent can also be varied (R^3 = Me, Ph). The yields of the products range from 39-77%. Another interesting feature of this approach is that the absolute stereochemistry can be controlled by using the appropriate chiral auxiliary.[70] Thus, when the L-proline derived 1-azadiene **105** is used, product **106** could be isolated in a remarkable >95% *de* (Scheme 30).



Scheme 30: Auxiliary-assisted asymmetric tandem hetero Diels-Alder/ allylboration.[35]

Palacios and co-workers also report a synthesis of lactams **110** that proceeds *via* an intermediate 1-azadiene **108** (Scheme 31).[32] Reaction of this 1-azadiene, which was isolated first, with one equivalent of *p*-toluidine in the presence of $Ti(OEt)_4$ and H_2SO_4 gave the cyclic

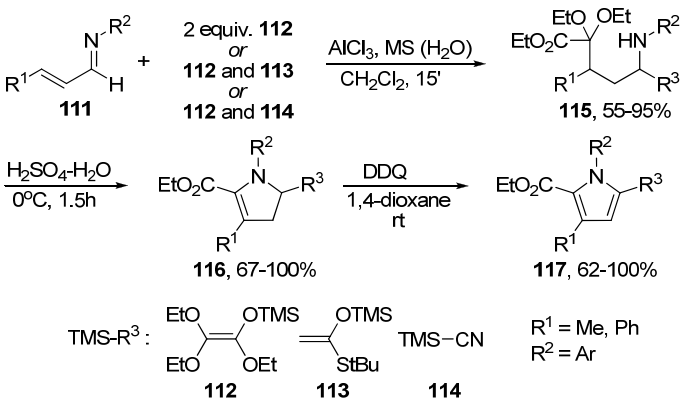
enamine (lactam) **110**. However, the authors optimized the reaction towards a one-pot procedure.



Scheme 31: Three-component condensation reaction towards aminolactams involving 1-azadienes as intermediates.[32]

The formation of lactam **110** can be explained by initial condensation of the amine and carbonyl component **107** affording 1-azadiene **108**. Subsequent conjugate addition of a second equivalent of amine yields the linear adduct **109**. This undergoes ring closure with loss of ethanol to give the final product **110**. A small array of lactams was made by reaction of β,γ-unsaturated α-keto esters with two equivalents of an amine in the presence of $Ti(OEt)_4$ and H_2SO_4 in refluxing dichloromethane, yielding only the cyclic products. The yields were moderate to good (69-88%) with $R^1 = CO_2R$, Me, or 2-furyl. Chiral amines can also be used, yielding a 1:1 mixture of diastereomers, which could be separated and isolated to give two optically pure lactams.

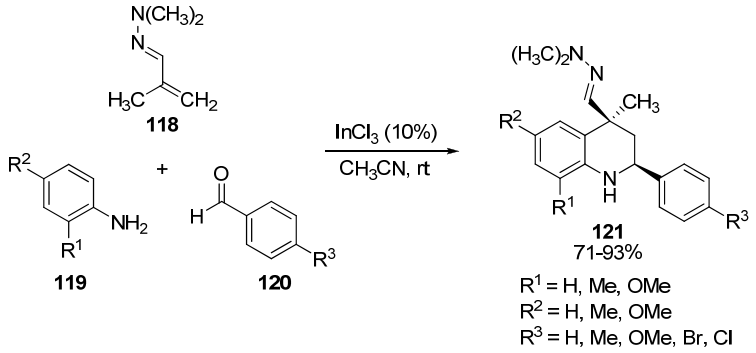
A three reaction sequence for the synthesis of pyrroles involving a 1-azadiene-based MCR was reported by Kawai *et al.* (Scheme 32).[71]



Scheme 32: Synthesis of highly substituted pyrroles involving a 1-azadiene-based multicomponent reaction.[71]

First, a double nucleophilic addition of α,α-dialkoxy ketene silyl acetals **112**, ketene silyl thioacetals **113** or trimethylsilyl cyanide **114** to the 1-azadienes **111** was performed yielding coupling products **115** in reasonable to excellent yields (55-95%). Next, acid-promoted cyclization and subsequent oxidation with DDQ gave the pyrroles **117**. This is actually a two-step process in which first dihydropyrroles **116** are formed in reasonable to excellent yields (67-100%) by treating the coupling products **115** with acid. These dihydropyrroles are then dehydrogenated under influence of DDQ yielding, also in reasonable to excellent yields (62-100%) the pyrroles **117**.

Sridharan *et al.* report a three-component reaction between 1-(dimethylamino)-1-azadiene **118**, anilines **119** and aromatic aldehydes **120** yielding tetrahydroquinolines **121** (Scheme 33).[72]

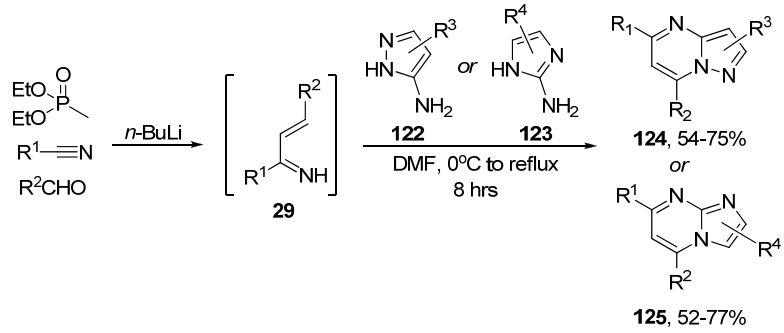


Scheme 33: Synthesis of tetrahydroisoquinolines involving a hetero Diels-Alder reaction where the 1-azadienes reacts as the dienophile.[72]

In the first step, **119** and **120** react to give a diarylimine. This diarylimine reacts as the diene in a Diels-Alder reaction with the 1-azadiene **118** as the dienophile. The use of 10% indium trichloride in the reaction resulted in the formation of C4 functionalized 1,2,3,4-tetrahydroquinolines **121** in good to excellent yields (71-93%). Both electron-donating and electron-withdrawing substituents R^1-R^3 are tolerated. The reaction proceeds in a diastereoselective fashion to give only the *cis* products **121**. This reaction is the first example of a 1-azadiene reacting as a dienophile in an aza-Diels-Alder reaction.

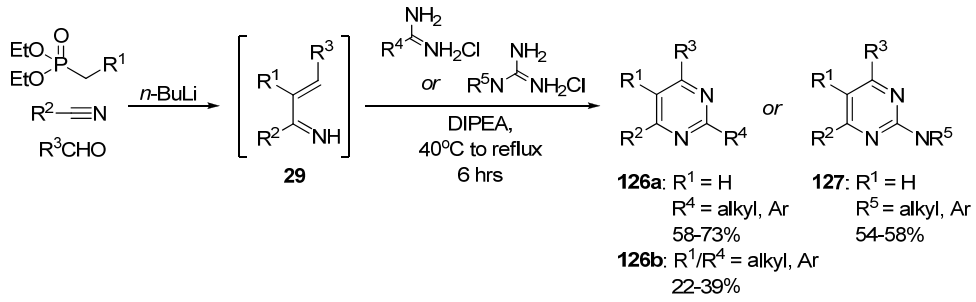
2.5.2 1*H*-1-Azadienes in MCRs

The Oh method that was discussed in Scheme 8 for the *in situ* generation of 1*H*-1-azadienes[38] **29** was used by Kiselyov and Smith in a MCR for the synthesis of polysubstituted pyrazolo- and imidazolopyrimidines. The 1-azadiene **29**, generated from diethyl methylphosphonate, a nitrile and an aldehyde, was combined in the same pot with amino heterocycles **122** and **123**, respectively (Scheme 34).[43]



Scheme 34: Multicomponent reaction of *in situ*-generated 1-azadienes with 5-aminopyrazoles and 2-aminoimidazoles to afford pyrazolo- and imidazolopyrimidines, respectively.[43]

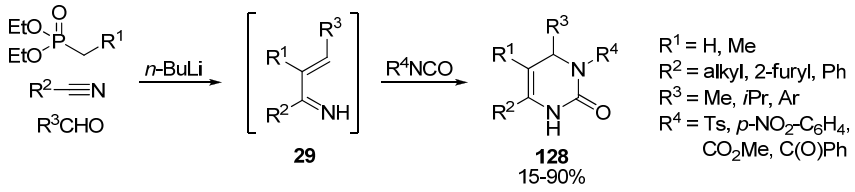
The reaction of **29** with 5-amino pyrazoles **122** gives pyrazolo [1,5-*a*]pyrimidines **124** while the one-pot combination of **29** with imidazoles **123** affords imidazo[1,2-*a*]pyrimidines **125**. Yields were reasonable to good (52-77%) and in both reactions, the electronic nature of the aryl substituents (donating or withdrawing) did not significantly affect the yield.



Scheme 35: Multicomponent reaction of *in situ*-generated 1-azadienes with amidines or guanidines to give highly substituted pyrimidines.[42]

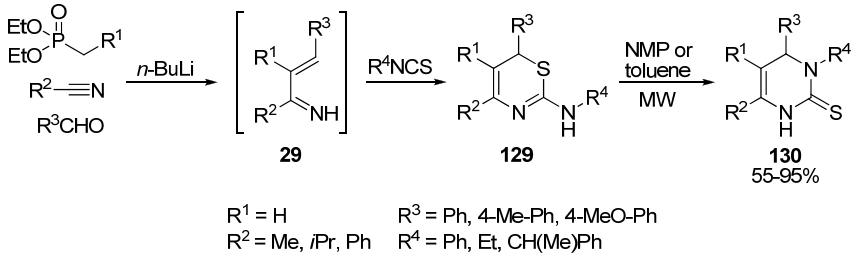
In another one-pot procedure also reported by Kiselyov, a similar 1-azadiene is reacted with amidine or guanidine derivatives yielding polysubstituted pyrimidines **126** or 2-amino pyrimidines **127** (Scheme 35).[42] Different aromatic nitriles (R^2) and aromatic aldehydes (R^3) with electron-donating and electron-withdrawing substituents can be used, as well as various alkyl and aryl groups on the amidine and guanidine derivatives (R^4/R^5). Yields of the products range from reasonable to good, 54-73%. The phosphonate can also be substituted (R^1) to give 5-substituted pyrimidines. However, this is limited to small alkyl groups and the yields drop significantly to 22-39% when the steric bulk is increased from methyl to phenyl or *iso*-butyl.

Our group recently reported a multicomponent reaction between 1*H*-1-azadienes **29** and isocyanates bearing a strong electron-withdrawing group yielding dihydropyrimidinones **128** (Scheme 36).[36,37] As stated, **29** was generated *in situ* using the modified Oh protocol[38] from diethyl methylphosphonate, a nitrile and an aldehyde.



Scheme 36: Multicomponent reaction of *in situ*-generated 1-azadienes with electron-deficient isocyanates to give dihydropyrimidones.[36,37]

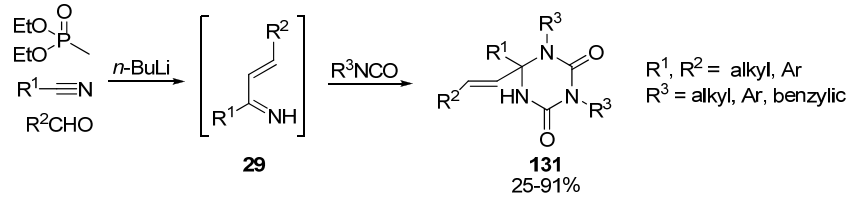
A broad range of different R^2 and R^3 groups can be introduced on the dihydro-pyrimidinone scaffold with yields of the isolated product ranging from 15-90%. However, variation of R^1 is limited (only H or Me). In the isocyanate input, highly electron-withdrawing R^4 groups are needed. In a modification of this method, isothiocyanates were employed instead of isocyanates.[73] This results in the formation of thiazines **129**, which can be converted into dihydropyrimidinethiones **130** *via* a Dimroth rearrangement.[74] This rearrangement was achieved under microwave irradiation in batch or continuous flow format (Scheme 37).



Scheme 37: Multicomponent reaction of *in situ*-generated 1-azadienes with isothiocyanates leading to aminothiazines and dihydropyrimidinethiones.[73]

Three different rearrangement protocols were developed that lead to **130** in 55-95% isolated yield. Solvents of choice are either toluene or 1-methyl-2-pyrrolidone (NMP) and reaction temperatures range between 120 °C and 210 °C.

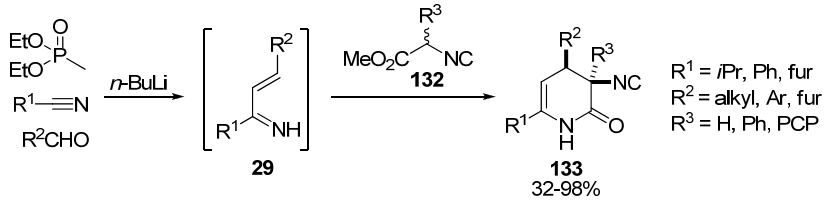
Another very useful variation of these MCRs combines *in situ* generated 1-azadienes **29** with isocyanates bearing less electron-withdrawing (aryl) or even electron-donating (alkyl) substituents.[41] In this case, the initial addition product of the 1*H*-1-azadiene on the isocyanate does not undergo electrocyclization as in the synthesis of dihydropyrimidinones **128**[36,37] or aminothiazines **129**.[73] Instead, the intermediate acts as a nucleophile and reacts with a second equivalent of isocyanate. The second addition product then cyclizes in a 1,2-fashion to afford triazinane diones **131**, a rather unexplored class of *N*-heterocycles (Scheme 38).



Scheme 38: Multicomponent synthesis of triazinane diones.[41]

The reaction is quite flexible and isolated yields of the corresponding triazinane diones are moderate to excellent (25-91%). (Hetero)aromatic and aliphatic R^1/R^2 substituents and benzylic and aromatic R^3 substituents could be introduced successfully. As is shown here, isocyanates are versatile reagents in these 1-azadiene-based MCRs for the synthesis of different heterocycles. They are used in other MCRs as well.[75,76]

The *in situ*-generated 1*H*-1-azadienes **29** can also react with α-acidic isocyanides **132**, yielding dihydropyridones **133** (Scheme 39).[40] The interesting feature of this reaction is that the isocyanide function stays intact during the reaction, leaving it available in **133** for further differentiation in, for example, additional multicomponent reactions.



Scheme 39: Multicomponent reaction of *in situ*-generated 1-azadienes with α-isocyano esters leading to 3-isocyano-3,4-dihydropyridones.[40]

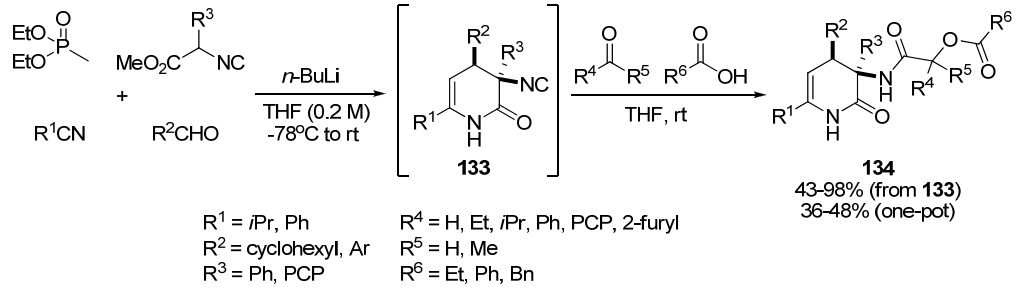
Furthermore, the products were isolated solely as the 3,4-*cis* diastereomer (*i.e.*, with R^2 and R^3 in *trans* orientation). The choice of the aldehyde (R^2) is crucial for this reaction. Aromatic, heteroaromatic and α,β-unsaturated aldehydes give the expected dihydropyridones, but aliphatic and highly electron-deficient aldehydes do not give the desired product. Different nitriles can also be used. Aromatic, heteroaromatic and aliphatic nitriles give good results, but primary aliphatic nitriles should be avoided. The isocyano ester can also be varied, even towards those lacking additional electron-withdrawing α-substituents. The yields of the reaction are reasonable to excellent (32-98%).

2.6 A platform for further complexity generation and DOS

The results presented in the previous sections illustrate that 1-azadienes are indeed very versatile building blocks in the synthesis of a wide variety of N-heterocycles. Especially the *in situ* generation of 1*H*-1-azadienes as first reported by Lee and Oh[38] offers a highly versatile platform for the development of 1-azadiene-based MCRs. This is clearly exemplified by contributions from Kiselyov[42,43] and our group.[36,37,40,41,73] The high variability in terms of substitution pattern and resulting scaffold structures makes it a highly attractive complexity-generating strategy to achieve skeletal diversity in DOS. The strategy can be made even more attractive for DOS by incorporating handles for subsequent additional complexity-generating reactions, like ring-closing metathesis, cycloadditions or even a second MCR.

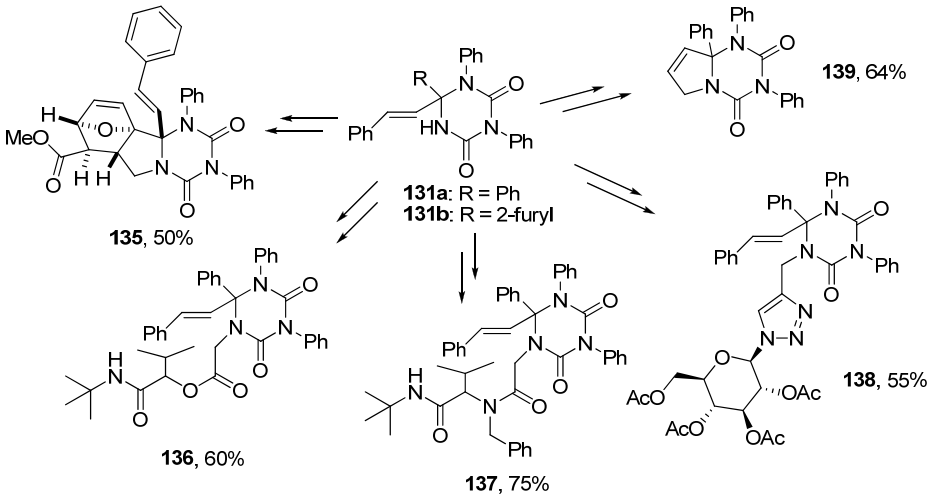
One example of such an approach was recently reported by our laboratory.[77] As shown in Scheme 39, an azadiene-based MCR leading to isocyano-functionalized 3,4-dihydropyridin-2-ones **133** was developed.[40] These products can immediately be used in isocyanide-based

multicomponent reactions (I-MCRs). One such reaction is the Passerini reaction and combination of the two MCRs would lead to the generation of conformationally constrained depsipeptides **134**.[77]



Scheme 40: One-pot combination of a 1-azadiene-based multicomponent reaction affording isocyano-functionalized dihydropyridones with Passerini reaction: a formal six-component reaction.[77]

Thus, 3,4-dihydropyridin-2-ones **133** were reacted with a range of commercially available aldehydes and acids under standard Passerini reaction conditions (CH_2Cl_2, rt). The expected depsipeptides **134** were successfully obtained in reasonable to excellent yields (43-98%) as 1:1 mixtures of diastereomers (Scheme 40). With these results in hand, we turned to study the combination of both MCRs in one pot, resulting in a six-component reaction. The whole sequence was performed in THF, which is a slight modification of the Passerini-3CR. The one-pot synthesis of depsipeptide **134a** (R^1,R^4 = *i*Pr, R^2 = PMP, R^3 = Ph, R^5 = H, R^6 = Et) was first investigated and this compound could be isolated in 40% yield, the same yield as for the overall yield obtained *via* the two-step procedure (41%). In addition, three other examples of this six-component procedure were performed all with approximately the same yields (36-48%).



Scheme 41: Rapid generation of molecular diversity and complexity by combining a multicomponent reaction leading to triazinane diones with additional complexity-generating reactions, including ring-closing metathesis, [2+3] cycloaddition, isocyanide-based multicomponent reactions (I-MCRs) and tandem alkylation/intramolecular Diels-Alder cycloaddition.[78]

Because of the ease of alkylation of the free NH, triazinane diones resulting from a 1-azadiene-based MCR (Scheme 38) can also be used for various types of follow-up chemistry.[78] We selected six different reactions to create a set of highly diverse and complex compounds. For all reactions, a simple alkylation reaction was performed to introduce a handle for further functionalization. Passerini, Ugi, Cu^{I}-catalyzed [2+3] cycloaddition, ring-closing metathesis, and intramolecular Diels-Alder reactions were selected for complexity generation (Scheme 41). The alkylation reactions were easy to perform and typically proceeded in 50-75% yield. Next, the various types of follow-up reactions were performed yielding the diverse and complex molecules **135-139** shown in scheme 41. The yields of the reactions were reasonable to good (50-75%), but, more importantly, we have shown that the triazinane scaffold can be a valuable tool for making diverse and complex small molecules.

2.7 Conclusions

1-Azadienes are densely functionalized building blocks or intermediates that can react as nucleophiles, electrophiles and as dienophiles, dipolarophiles or carbenophiles. In this chapter we discussed various applications of 1-azadienes in cycloaddition, electrocyclization, and multicomponent reactions for the efficient construction of a broad range of N-heterocycles. The use of 1-azadienes to generate complexity and diversity is highlighted. They prove excellent platforms to address skeletal diversity in DOS. Especially in combination with MCR-based strategies, 1-azadienes represent a challenging array of functionalities that can be employed to explore chemical space efficiently and identify small molecular probes for biology.

2.8 References and notes

1. Feher, M.; Schmidt, J., M. *J. Chem. Inf. Comput. Sci.* **2003**, *43*, 218-227.
2. Henkel, T.; Brunne, R. M.; Mueller, H.; Reichel, F. *Angew. Chem. Int. Ed* **1999**, *38*, 643-647.
3. Koch, M. A.; Schuffenhauer, A.; Scheck, M.; Wetzel, S.; Casaulta, M.; Odermatt, A.; Ertl, P.; Waldmann, H. *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 17272-17277.
4. Wessjohann, L. A.; Ruijter, E.; Garcia-Rivera, D.; Brandt, W. *Mol. Div.* **2004**, *9*, 171-186.
5. Clardy, J.; Walsh, C. *Nature* **2004**, *432*, 829-837.
6. Newman, D. J.; Cragg, G. M. *J. Nat. Prod.* **2007**, *70*, 461-477.
7. Schreiber, S. L. *Science* **2000**, *287*, 1964-1969.
8. Burke, M. D.; Berger, E. M.; Schreiber, S. L. *Science* **2003**, *302*, 613-616.
9. Burke, M. D.; Berger, E. M.; Schreiber, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 14095-14104.
10. Burke, M. D.; Schreiber, S. L. *Angew. Chem. Int. Ed.* **2004**, *43*, 46-58.
11. Goess, B. C.; Hannoush, R. N.; Chan, L. K.; Kirchhausen, T.; Shair, M. D. *J. Am. Chem. Soc.* **2006**, *128*, 5391-5403.
12. Mitchell, J. M.; Shaw, J. T. *Angew. Chem. Int. Ed.* **2006**, *45*, 1722-1726.
13. Spandl, R. J.; Bender, A.; Spring, D. R. *Org. Biomol. Chem.* **2008**, *6*, 1149-1158.
14. Kumar, N.; Kiuchi, M.; Tallarico, J. A.; Schreiber, S. L. *Org. Lett.* **2005**, *7*, 2535-2538.
15. Arya, P.; Quevillon, S.; Joseph, R.; Wei, C.-Q.; Gan, Z.; Parisien, M.; Sesmilo, E.; Reddy, P. T.; Chen, Z.-X.; Durieux, P.; Laforce, D.; Campeau, L.-C.; Khadem, S.; Couve-Bonnaire, S.; Kumar, R.; Sharma, U.; Leek, D. M.; Daroszewska, M.; Barnes, M. L. *Pure Appl. Chem.* **2005**, *77*, 163-178.
16. Boldi, A. M. *Curr. Opin. Chem. Biol.* **2004**, *8*, 281-286.

17. Breinbauer, R.; Manger, M.; Scheck, M.; Waldmann, H. *Curr. Med. Chem* **2002**, *9*, 2129-2145.
18. Breinbauer, R.; Vetter, I. R.; Waldmann, H. *Angew. Chem. Int. Ed* **2002**, *41*, 2878-2890.
19. Dobson, C. M. *Nature* **2004**, *432*, 824-828.
20. Haggarty, S. J. *Curr. Opin. Chem. Biol.* **2005**, *9*, 206-303.
21. Ortholand, J.-Y.; Ganesan, A. *Curr. Opin. Chem. Biol.* **2004**, *8*, 271-280.
22. Reayi , A.; Arya, P. *Curr. Opin. Chem. Biol.* **2005**, *9*, 240-247.
23. Stockwell, B. R. *Nature* **2004**, *432*, 946-954.
24. Ulaczyk-Lesanko, A.; Hall, D. G. *Curr. Opin. Chem. Biol.* **2005**, *9*, 266-276.
25. Wessjohann, L. A.; Ruijter, E. *Top. Curr. Chem.* **2004**, *243*, 137-184.
26. Kaiser, M.; Wetzel, S.; Kumar, K.; Waldmann, H. *Cell. Mol. Life. Sci* **2008**, *65*, 1186-1201.
27. Palacios, F.; Vicario, J.; Aparicio, D. *Tetrahedron Lett.* **2007**, *48*, 6747-6750.
28. Schramm, O. G.; Oeser, T.; Muller, T. J. J. *J. Org. Chem.* **2006**, *71*, 3494-3500.
29. Yavari, I.; Djahaniani, H.; Nasiri, F. *Monatsh. Chem.* **2004**, *135*, 543-548.
30. Palacios, F.; Aparicio, D.; Garcia, J.; Rodriguez, E.; Fernandez-Acebes, A. *Tetrahedron* **2001**, *57*, 3131-3141.
31. Palacios, F.; Vicario, J.; Aparicio, D. *J. Org. Chem.* **2006**, *71*, 7690-7696.
32. Palacios, F.; Vicario, J.; Aparicio, D. *Eur. J. Org. Chem.* **2006**, 2843-2850.
33. Palacios, F.; Vicario, J.; Maliszewska, A.; Aparicio, D. *J. Org. Chem.* **2007**, *72*, 2682-2685.
34. Fletcher, M. D.; Hurst, T. E.; Miles, T. J.; Moody, C. J. *Tetrahedron* **2006**, *62*, 5454-5463.
35. Toure, B. B.; Hoveyda, H. R.; Tailor, J.; Ulaczyk-Lesanko, A.; Hall, D. G. *Chem. Eur. J.* **2003**, *9*, 466-474.
36. Vugts, D. J.; Jansen, H.; Schmitz, R. F.; de Kanter, F. J. J.; Orru, R. V. A. *Chem. Comm.* **2003**, 2594-2595.
37. Vugts, D. J.; Koningstein, M. M.; Schmitz, R. F.; de Kanter, F. J. J.; Groen, M. B.; Orru, R. V. A. *Chem. Eur. J* **2006**, *12*, 7178-7189.
38. Lee, K.; Oh, D. Y. *Synthesis* **1991**, 213-214.
39. Palacios, F.; Retana, A. M. O. d.; Pascual, S.; Oyarzabal, J. *J. Org. Chem.* **2004**, *69*, 8767-8774.
40. Paravidino, M.; Bon, R. S.; Scheffelaar, R.; Vugts, D. J.; Znabet, A.; Schmitz, R. F.; de Kanter, F. J. J.; Lutz, M.; Spek, A. L.; Groen, M. B.; Orru, R. V. A. *Org. Lett.* **2006**, *8*, 5369-5372.
41. Groenendaal, B.; Vugts, D. J.; Schmitz, R. F.; de Kanter, F. J. J.; Ruijter, E.; Groen, M. B.; Orru, R. V. A. *J. Org. Chem.* **2008**, *73*, 719-722.
42. Kiselyov, A. S. *Tetrahedron Lett.* **2005**, *46*, 1663-1665.
43. Kiselyov, A. S.; Smith II, L. *Tetrahedron Lett.* **2006**, *47*, 2611-2614.
44. Nakao, Y.; Yada, A.; Ebata, S.; Hiyama, T. *J. Am. Chem. Soc.* **2007**, *129*, 2428-2429.
45. Behforouz, M.; Ahmadian, M. *Tetrahedron* **2000**, *56*, 5259-5288.
46. Jayakumar, S.; Ishar, M. P. S.; Mahajan, M. P. *Tetrahedron* **2002**, *58*, 379-471.
47. Hurst, T. E.; Miles, T. J.; Moody, C. J. *Tetrahedron* **2008**, *64*, 874-882.
48. Palacios, F.; Aparicio, D.; Lopez, Y.; de los Santos, J. M.; Ezpeleta, J. M. *Tetrahedron* **2006**, *62*, 1095-1101.
49. Lu, J.-Y.; Arndt, H.-D. *J. Org. Chem.* **2007**, *72*, 4205-4212.
50. Robin, A.; Julienne, K.; Meslin, J. C.; Deniaud, D. *Tetrahedron Lett.* **2004**, *45*, 9557-9559.
51. Singh, L.; Ishar, M. P. S.; Elango, M.; Subramaniam, V.; Gupta, V.; Kanwall, P. *J. Org. Chem.* **2008**, *73*, 2224-2233.
52. Barluenga, J.; de la Rua, R. B.; de Saa, D.; Ballesteros, A.; Tomas, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 4981-4983.
53. Elliott, M. C.; Kruiswijk, E. *J. Chem. Soc. Perkin Trans. 1* **1999**, 3157-3166.
54. Elliott, M. C.; Kruiswijk, E.; Willock, D. J. *Tetrahedron* **2001**, *57*, 10139-10146.
55. Elliott, M. C.; Long, M. S. *Org. Biomol. Chem.* **2004**, *2*, 2003-2011.
56. Berry, C. R.; Hsung, R. P. *Tetrahedron* **2004**, *60*, 7629-7636.
57. Clark, R. C.; Pfeiffer, S. S.; Boger, D. L. *J. Am. Chem. Soc.* **2006**, *128*, 2587-2593.
58. Esquivias, J.; Arrayas, R. G.; Carretero, J. C. *J. Am. Chem. Soc.* **2007**, *129*, 1480-1481.
59. He, M.; Struble, R.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 8418-8420.
60. Donnecke, D.; Imhof, W. *Tetrahedron* **2003**, *59*, 8499-8507.

61. Barluenga, J.; Ballesteros, A.; Santamaria, J.; Tomas, M. *J. Organomet. Chem.* **2002**, *643-644*, 363-368.
62. Zheng, J.-C.; Liao, W.-W.; Sun, X.-L.; Dai, L.-X. *J. Am. Chem. Soc.* **2005**, *127*, 12222-12223.
63. Morton, D.; Pearson, D.; Field, R. A.; Stockman, R. A. *Org. Lett.* **2004**, *6*, 2377-2380.
64. Parthasarathy, P.; Jeganmohan, M.; Cheng, C.-H. *Org. Lett.* **2008**, *10*, 325-328.
65. Palacios, F.; Aparicio, D.; Vicario, J. *Eur. J. Org. Chem.* **2002**, 4131-4136.
66. Domling, A.; Ugi, I. *Angew. Chem. Int. Ed.* **2000**, *39*, 3168-3210.
67. Domling, A. *Chem. Rev.* **2006**, *106*, 17-89.
68. Orru, R. V. A.; de Greef, M. *Synthesis* **2003**, 1471-1499.
69. Sridharan, V.; Perumal, P. T.; Avendano, C.; Menendez, J. C. *Tetrahedron* **2007**, *63*, 4407-4413.
70. Beaudegnies, R.; Ghosez, L. *Tetrahedron: Asymmetry* **1994**, *5*, 557-560.
71. Shimizu, M.; Takahashi, A.; Kawai, S. *Org. Lett.* **2006**, *8*, 3585-3587.
72. Sridharan, V.; Perumal, P. T.; Avendano, C.; Menendez, J. C. *Org. Biomol. Chem.* **2007**, *5*, 1351-1353.
73. Glasnov, T. N.; Vugts, D. J.; Koningstein, M. M.; Desai, B.; Fabian, W. M. F.; Orru, R. V. A.; Kappe, C. O. *QSAR Comb. Sci.* **2006**, *25*, 509-518.
74. El Ashry, E. S. H.; El Kilany, Y.; Rashed, N.; Assafir, H. *Adv. Heterocycl. Chem.* **2000**, *75*, 79-165.
75. Strubing, D.; Neumann, H.; Hubner, S.; Klaus, S.; Beller, M. *Org. Lett.* **2005**, *7*, 4321-4324.
76. Church, T. L.; Byrne, C. M.; Lobkovsky, E. B.; Coates, G. W. *J. Am. Chem. Soc.* **2007**, *129*, 8156-8162.
77. Paravidino, M.; Scheffelaar, R.; Schmitz, R. F.; de Kanter, F. J. J.; Groen, M. B.; Ruijter, E.; Orru, R. V. A. *J. Org. Chem.* **2007**, *72*, 10239-10242.
78. Groenendaal, B.; Ruijter, E.; de Kanter, F. J. J.; Lutz, M.; Spek, A. L.; Orru, R. V. A. *Org. Biomol. Chem.* **2008**, *6*, 3158-3165.

Chapter 3

A Multicomponent Synthesis of Triazinane Diones

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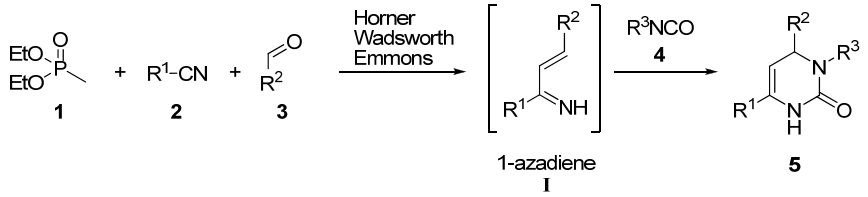
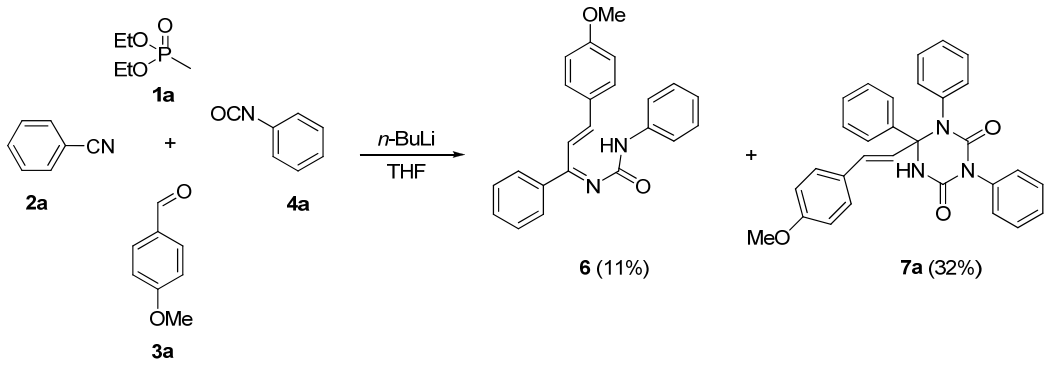
3.1 Introduction

Chemical space, defined as the total descriptor space including all carbon-based molecules that in principle can be prepared, contains more than 10^{60} small organic molecules.[1] Only a very limited number of these have been actually made by man and explored for potential useful properties, like their biological relevance. This continues to drive synthetic chemists to develop novel reactions that can efficiently access unexplored regions of the chemical space. Especially appreciated are those methods that allow the quick generation of scaffold diversity.[2] Multicomponent reactions (MCRs) represent one of the most powerful tools to easily access molecules showing both skeletal and decoration diversity.[3-5] As such, these reactions are also ideally suited to uncover thus far unprecedented types of scaffolds. Recently, we described a novel four-component reaction (4-CR) that combines phosphonates **1**, nitriles **2**, aldehydes **3** and isocyanates **4** to afford functionalized 3,4-dihydropyrimidine-2-ones (DHPMs, **5**) efficiently (Scheme 1).[6,7] The MCR most likely proceeds via 1-azadienes of type **I** that can undergo facile aza Diels-Alder (aza-DA) cycloaddition with isocyanates **4**, equipped with an electron withdrawing substituent, to give DHPMs of type **5**.



Scheme 1: Synthesis of dihydropyrimidines (DHPMs).

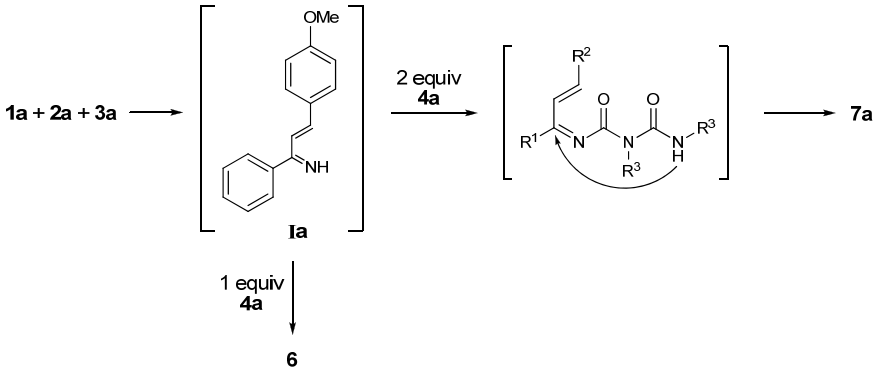
The thermodynamic driving force for a (concerted) aza-DA reaction of such 1-azadienes is, compared to butadienes or 2-azadienes, much lower.[8] Consequently, this results in a much lower reactivity toward dienophiles. Therefore, Diels-Alder reactions with 1-azadienes usually proceed sluggishly and are of limited synthetic significance.[9] During our initial studies, we observed the formation of non-cyclized **6** together with triazinane dione **7a** when diethyl methylphosphonate **1a**, benzonitrile **2a**, 4- methoxybenzaldehyde **3a**, and PhNCO **4a** were combined (Scheme 2).[6]



Scheme 2: Formation of non-cyclized **6** and triazinane dione **7a**.

The corresponding DHPM **5a** was not formed in this case. 6,6-Dialkyl/aryl-subsituted triazinane diones such as **7** are a hitherto unexplored class of heterocyclic scaffolds and only scattered reports exist on their synthesis.[10-14] This led us to examine the reaction pathway more closely in order to optimize the MCR towards these highly interesting and novel cyclic urea derivatives.

Most likely, triazinane dione **7a** is formed *via* the pathway depicted in Scheme 3. Deprotonation of the phosponate **1a** with *n*-BuLi and subsequent reaction with **2a** yields the corresponding intermediate ketimine. A subsequent Horner-Wadsworth-Emmons reaction of this ketimine and **3a** results in the formation of the azadiene **Ia**. The isolation of the linear urea derivative **6** strongly supports a step-wise reaction mechanism, in which **6** can be formed from an addition reaction of **Ia** to **4a** followed by a 1,3-H-shift. Moreover, formation of the triazinane dione can be rationalized by the addition of a second equivalent of **4a** followed by ring closure to afford the thermodynamically favored six-membered cyclic urea derivative.



Scheme 3: Mechanism for the formation of triazinane diones.

3.2 Results and discussion

3.2.1 Reaction optimization

The moderate isolated yield of **7a** (32%) encouraged us to further optimize the reaction and explore the scope of this interesting multicomponent procedure. For convenience, the combination of **1a**, **2a**, benzaldehyde **3b**, and **4a** was employed to optimize the reaction conditions toward the corresponding triazinane dione **7b**. As a starting point the general conditions for the efficient formation of the DHPM derivative **5b** were chosen.[7] Not surprisingly, the standard conditions afforded mostly **5b** and the desired triazinane dione **7b** was observed in only 20% yield (Table 1; entry 1). However, when product formation was followed in time by HPLC analysis it became clear that the formation of **7b** was instantaneous. The conversion to **7b** was at its maximum only minutes after addition of **4a** and decreased slowly over time.

Table 1: Optimization of the formation of **7b**.

Entry	equiv of 4a	Reaction time	Yield (%)	Work-up[a]
1	1.1	18 h	20%	A
2	1.1	5 min	29%	A
3	2.2	5 min	80%	A
4	2.2	5 min	91%	B

[a](A) After addition of Et_2O, the reaction mixture was washed with water and brine. Drying the organic phase and evaporation of the solvents followed by column chromatography afforded pure **7b**. (B) After partial evaporation of the solvents, water was added to the reaction mixture. The product precipitated and after filtering and washing with cold Et_2O, pure **7b** was obtained directly.

Thus, immediate workup after the addition of the final isocyanate component already showed a significant improvement of the yield of **7b** (entry 2, 29%). The MCR was further optimized by slight modification of the workup procedure and using 2.2 equiv of isocyanate **4a**. Addition of water during workup caused precipitation of the product from the reaction mixture, and **7b** could simply be filtered off and washed with diethyl ether to yield the pure product in 91% isolated yield (entry 4).

3.2.2 Scope study

With this optimized procedure in hand, the scope of the reaction toward a range of differently substituted triazinane diones was studied. As becomes clear from Figure 1, the reaction is quite flexible and isolated yields of the corresponding triazinane diones **7** are usually reasonable to good (13-91%).

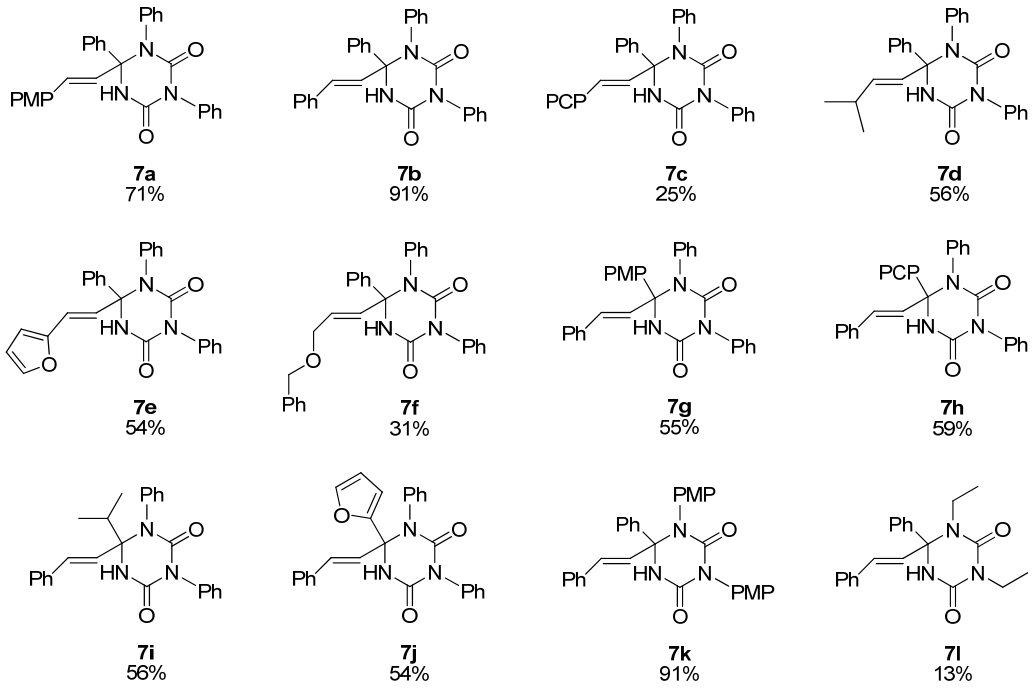


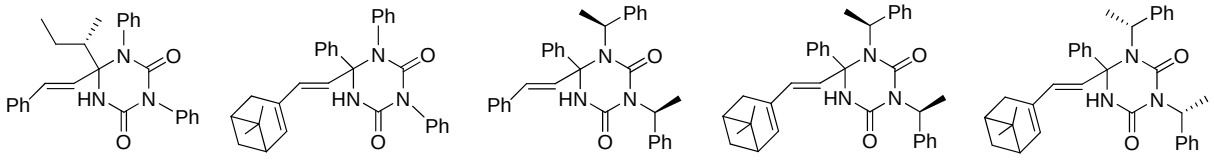
Figure 1: Range of differently substituted triazinane diones.
PMP = *p*-methoxyphenyl, PCP = *p*-chlorophenyl.

Successful inputs include nitriles (**2**) and aldehydes (**3**) with (hetero)aromatic and aliphatic substituents R^1 and R^2. For the isocyanate input (**4**) benzylic and aromatic substituents R^3 are

compatible in this reaction. The reaction employing an isocyanate with an aliphatic R^3 group is less efficient (**7l**, 13%).

3.2.3 Use of chiral inputs

Although the MCR proceeds smoothly using either an optically pure nitrile, aldehyde, or isocyanate, the observed diastereoselectivities are not very encouraging (**7m-o**, Figure 2). With (*S*)-2-methylbutyronitrile, low stereoinduction is perhaps not surprising considering the rather basic reaction conditions. On the other hand, for the DHPM synthesis the use of the optically pure (*R*)-myrtenal was relatively successful and a *de* up to 85% was observed.[7] However, application of (*R*)-myrtenal did not result in a diastereoselective formation of the corresponding triazinane dione **7n**. The best (albeit still moderate) diastereoselectivity was observed when (*S*)-α-methyl benzyl isocyanate was combined with **1a**, **2a** and **3a** under the standardized conditions for the formation of **7o** (*de* = 33%).



7m 25% 3% *de* | **7n** 45% 11% *de* | **7o** 50% 33% *de* | **7p** 59% 67% *de* | **7q** 62% 33% *de*

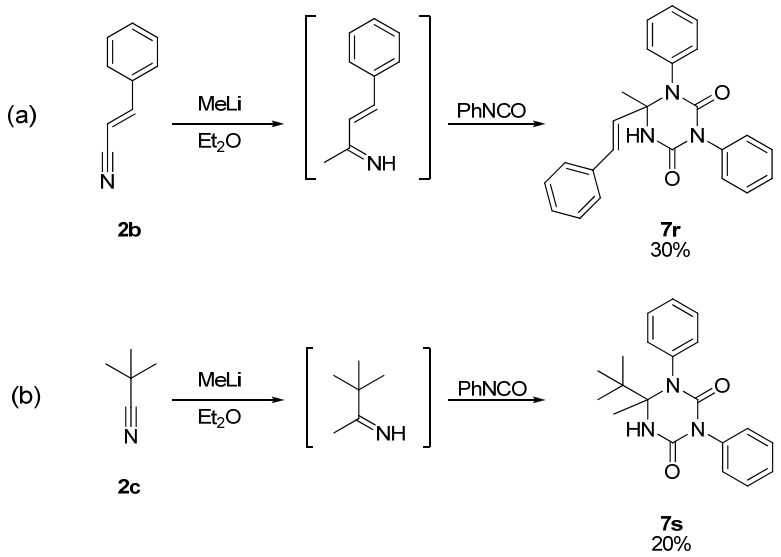
Figure 2: Chiral inputs in the triazinane dione MCR.

To investigate if the *de* could be further increased by using two chiral inputs in one reaction, a match/mismatch study was conducted. For this, (-)-myrtenal and the *R* and *S* –enantiomer of α-methyl benzyl isocyanate where used together with benzonitrile. A chiral nitrile was not used because, as can be seen from Figure 2, the lowest *de* was obtained when using a chiral nitrile. When using a combination of (-)-myrtenal and (*S*)-α-methyl benzyl isocyanate, **7p** was obtained with a *de* of 67%. When using (-)-myrtenal and (*R*)-α-methyl benzyl isocyanate, **7q** was obtained with a *de* of 33%. So in the case of **7p** the chiral inputs showed a match with each other resulting in a significant increase of the *de*. In the case of **7q** there is no match but also no mismatch as the *de* obtained was still 33%.

3.2.4 Alternative methods for the synthesis of triazinane diones

As for the DHPM synthesis, the most limiting input in the MCR for triazinane diones is, however, the phosphonate input. From our earlier studies it is known that only the use of diethyl methylphosphonate or diethyl ethylphosphonate resulted in efficient formation of the crucial 1-azadiene intermediate **I**.[7] Partly based on some literature precedents,[15-20] some alternative methods were investigated for the *in situ* generation of 1-azadienes **I** and their subsequent trapping by PhNCO **4a**. Attempts starting from α,β-unsaturated aldehydes, like the addition of appropriate Grignard reagents to nitriles or reduction of α,β-unsaturated nitriles with DIBAL-H were not successful and gave mixtures of unidentified products. The only procedure that indeed led to the formation of a triazinane dione is depicted in Scheme 4a.

Thus, the reaction of α,β-unsaturated nitrile **2b** with MeLi and subsequent reaction with PhNCO **4a** gave the corresponding triazinane dione **7r**, albeit in only 30% isolated yield.
Alternatively, efficient triazinane dione formation may occur by trapping an intermediate imine, instead of a 1-azadiene, with an appropriate isocyanate. Indeed, when MeLi was added to the nitrile **2c** followed by the addition of PhNCO **4a** the desired product **7s** was obtained, but again only in a disappointing 20% yield (Scheme 4b). Since our MCR efficiently affords quite a range of differently functionalized triazinane diones we did not pursue further in this direction.



Scheme 4: Alternative route towards triazinane diones.

3.3 Conclusions

In conclusion, we have developed a flexible multicomponent synthesis of a range of differently functionalized triazinane diones. Our approach opens the way to more detailed studies of the general and biological properties of these cyclic urea-type scaffolds, which have hitherto remained unexplored.

3.4 Experimental section

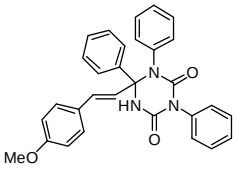
General information

All reactions were carried out under an inert atmosphere of dry nitrogen. THF and Et_2O were dried and distilled from sodium benzophenone prior to use. Benzonitrile, isobutyronitrile and isobutyraldehyde were distilled before use. Diethyl methyl-phosphonate was made according to literature.[7] Other commercially available chemicals were used as purchased. Thin Layer Chromatography (TLC) was performed using Merck aluminium TLC sheets (Silica gel 60 F_{254}) and compounds were visualized using UV-detection (254 nm) and colouring with an anisaldehyde solution (6 mL *p*-Anisaldehyde, 7 mL acetic acid and 7 mL sulfuric acid in 120 mL of EtOH). Column chromatography was performed using Silicycle Silia-P Flash Silica Gel (40-63 μm) and mixtures of (cyclo)hexane and EtOAc. Melting points were measured using a Stuart Scientific SMP3 melting point apparatus and are uncorrected. Infrared (IR) spectra were obtained from KBr, using a Perkin Elmer FT-IR Spectrometer Spectrum 1000 and wavelengths (ν) are reported in cm^{-1}. ^1H and ^{13}C nuclear magnetic resonance

(NMR) spectra were recorded on a Bruker Avance 400 (400.13 MHz and 100.61 MHz respectively) or a Bruker Avance 250 (250.13 MHz and 62.90 MHz respectively) with chemical shifts (δ) reported in ppm downfield from tetramethylsilane. (HR)MS-EI data were measured using a Finnigan Mat 900 spectrometer at 70 eV. HRMS-FAB data were measured using a JEOL JMS SX/SX 102A four sector mass spectrometer, coupled to a JEOL MS-MP9021D/UPD system program.

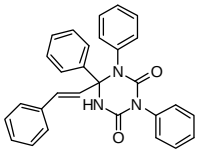
General procedure for the synthesis of triazinane diones

To a solution of diethyl methylphosphonate (152 mg, 1.0 mmol) in dry THF (5 mL) at -78 ºC was added *n*-BuLi (1.2 mmol, 1.6 M in hexanes), and this mixture was stirred for 1.5 hours at this temperature. The nitrile was added, and stirring was continued at -78 ºC for 45 min. Then the reaction mixture was warmed up to -40 ºC and stirred for 1 h, and subsequently warmed to -5 ºC and stirred for 30 min. The aldehyde was then added and the reaction mixture was stirred at -5 ºC for 30 min, warmed to room temperature, and stirred for an additional 1.5 h. The isocyanate was then added and after 5 min, the reaction was worked up by removing half of the solvent by evaporation under reduced pressure and addition of water (10 mL). In some cases, triazinane diones **7** either crystallized directly from this mixture or crystallized upon standing overnight at 5 ºC. Pure products were obtained by filtration and washing of the residu with cold Et_2O. In cases were triazinane diones **7** did not crystallize from the reaction mixture, the products were purified by flash chromatography or by recrystallization from hexane/EtOAc. For compounds **7e,g-k**, the products were coevaporated with Et_2O and dried 48 h under vacuum (10^{-2} mbar) to remove traces of solvent.



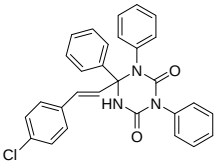
Triazinane dione 7a

Following the general procedure, reaction between diethyl methyl-phosphonate (152 mg, 1.0 mmol), benzonitrile (113 mg, 1.1 mmol), *p*-methoxy-benzaldehyde (150 mg, 1.1 mmol) and phenyl isocyanate (262 mg, 2.2 mmol), followed by crystallization from hexane/EtOAc afforded **7a** (340 mg, 71%) as a white solid. ^{1}H NMR (400 MHz, CDCl3): δ (ppm) 7.59-7.57 (m, 2H), 7.39-7.33 (m, 7H), 7.30 (d, *J* = 8.7 Hz, 1H) , 7.20-7.11 (m, 7H), 6.91 (d, *J* = 15.7 Hz, 1H), 6.89 (d, *J* = 8.7 Hz, 1H), 6.39 (d, *J* = 15.9 Hz, 2H). 6.16 (s, 1H), 3.83 (s, 3H); ^{13}C NMR (101 MHz, CDCl3): δ (ppm) 160.3, 152.9, 152.5, 139.9, 137.7, 135.0, 132.4, 129.7 (2C), 129.5, 129.2 (2C), 128.9 (2C), 128.7 (2C), 128.6 (2C), 128.37 (2C), 128.35, 127.7, 127.6 (2C), 127.5, 125.6, 114.3 (2C), 75.8, 55.4; HRMS (FAB) calculated for $C_{30}H_{25}N_3O_3$ (MH^+) 476.1974, found 476.1970. IR (KBr): 3435 (m), 3207 (w), 3090 (w), 1720 (s), 1680 (s), 1513 (m), 1435 (s), 1321 (m), 1256 (m), 741 (m), 694 (m), 592 (m), 536 (m). Melting point: 177.4- 178.4 °C.



Triazinane dione 7b

Following the general procedure, reaction between diethyl methyl-phosphonate (152 mg, 1.0 mmol), benzonitrile (113 mg, 1.1 mmol), benzaldehyde (117 mg, 1.1 mmol) and phenyl isocyanate (262 mg, 2.2 mmol) afforded crude **7b**. The crude product precipitated out of the reaction mixture after evaporation of half of the solvent and addition of water (10 mL). Subsequent washing with cold Et_2O gave **7b** (406 mg, 91%) as a white solid. ^{1}H NMR (400 MHz, CDCl3): δ (ppm) 9.32 (s, 1H), 7.62-7.60 (m, 2H), 7.47-7.30 (m, 11H), 7.24-7.12 (m, 5H), 7.06-7.04 (m, 2H), 6.78 (d, *J* = 16.0 Hz, 1H), 6.62 (d, *J* = 16.0 Hz, 1H). ^{13}C NMR (63 MHz, DMSO-d6): δ (ppm) 153.5, 152.9, 141.3, 138.9, 136.6, 136.1, 132.8, 130.7 (2C), 130.3 (2C), 129.8, 129.7 (2C), 129.7, 129.4, 129.4 (2C), 129.3 (2C), 129.2 (2C), 128.6, 128.6 (2C), 128.1, 127.8 (2C), 76.2. HRMS (FAB) calculated for $C_{29}H_{23}N_3O_2$ (MH^+) 446.1869, found 446.1872. IR (KBr): 3436 (m), 3208 (w), 3085 (w), 1721 (s), 1682 (s), 1493 (m), 1443 (s), 1330 (m), 752 (m), 694 (m), 596 (m), 535 (m). Melting point: 169.0-170.9 °C (decomp.).

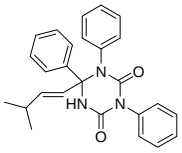


Triazinane dione 7c

Following the general procedure, reaction between diethyl methyl-phosphonate (152 mg, 1.0 mmol), benzonitrile (113 mg, 1.1 mmol), *p*-chloro-benzaldehyde (155 mg, 1.1 mmol) and phenylisocyanate (262 mg, 2.2 mmol), followed by column chromatography (hexane/EtOAc = 4:1, gradient), afforded **7c** (118 mg, 25%) as a light yellow foam. ^{1}H

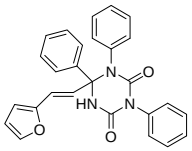
NMR (250 MHz, $CDCl_3$): 7.63-7.13 (m, 19H), 6.98 (d, *J* = 15.9 Hz, 1H), 6.56 (d, *J* = 15.9 Hz, 1H), 6.18 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): 153.6, 152.9, 140.2, 138.0, 135.3, 135.1, 134.0, 131.9, 130.6, 130.1 (2C), 129.9, 129.7 (2C), 129.6, 129.5 (2C), 129.3 (2C), 129.2, 129.1, 128.8 (2C), 128.6 (2C), 128.1, 127.8, 127.0, 76.0. HRMS (FAB) calculated for $C_{29}H_{22}ClN_3O_2$ (MH^+) 480.1479, found 480.1476. IR (KBr): 3309 (w), 3065 (w), 2959 (w), 1713 (s), 1682 (s), 1493 (m), 1431 (s), 1315 (m), 758 (m), 694 (m), 590 (m). Meltingpoint: 99.6-102.9 °C.

Triazinane dione 7d



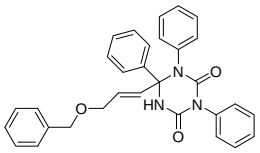
Following the general procedure, reaction between diethyl methyl-phosphonate (152 mg, 1.0 mmol), benzonitrile (113 mg, 1.1 mmol), isobutyraldehyde (79 mg, 1.1 mmol) and phenylisocyanate (262 mg, 2.2 mmol), followed by crystallization from hexane/EtOAc afforded **7d** (230 mg, 56%) as a white solid. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.54-7.51 (m, 2H), 7.38-7.32 (m, 6H), 7.24-7.12 (m, 5H), 7.09-7.07 (m, 2H), 6.17 (s, 1H), 6.01 (dd, *J* = 15.5, 6.9 Hz, 1H), 5.76 (dd, *J* = 15.5, 1.3 Hz, 1H), 2.43-2.37 (m, 1H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.98 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 153.4, 153.0, 142.5, 140.8, 138.3, 135.4, 130.1 (2C), 129.6, 129.5 (2C), 129.2 (2C), 129.0 (2C), 128.9 (2C), 128.7, 127.9, 127.8 (2C), 126.9, 75.7, 31.4, 22.4, 22.3. HRMS (EI, 70 eV) calculated for $C_{26}H_{25}N_3O_2$ (M^+) 411.1947, found 411.1947. IR (KBr): 3442 (m), 3206 (w), 3086 (w), 1724 (s), 1683 (s), 1494 (m), 1446 (s), 1322 (m), 758 (m), 695 (m), 596 (m), 537 (m). Meltingpoint: 184.0-185.7 °C (decomp.).

Triazinane dione 7e



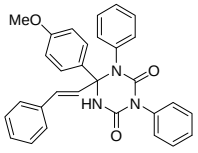
Following the general procedure, reaction between diethyl methyl-phosphonate (152 mg, 1.0 mmol), benzonitrile (113 mg, 1.1 mmol), furfural (105 mg, 1.1 mmol) and phenylisocyanate (262 mg, 2.2 mmol) afforded **7e** (235 mg, 54%) as a light brown solid. The crude product precipitated out of the reaction mixture after evaporation of half of the solvent and addition of water (10 mL). ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 9.29 (s, 1H), 7.69 (m, 1H), 7.59-7.56 (m, 2H), 7.40-7.32 (m, 6H), 7.24-7.21 (m, 2H), 7.17-7.13 (m, 3H), 7.05-7.03 (m, 2H), 6.66 (d, *J* = 3.3 Hz, 1H), 6.63 (d, *J* = 15.9 Hz, 1H), 6.53 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.39 (d, *J* = 15.9 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ (ppm) 152.4, 152.0, 150.5, 143.8, 140.3, 137.9, 135.6, 129.7 (2C), 129.4 (2C), 128.8, 128.42 (2C), 128.39 (2C), 128.3 (2C), 127.7, 127.6 (2C), 127.2, 126.4, 120.4, 111.9, 111.0, 75.3. HRMS (EI, 70 eV) calculated for $C_{27}H_{21}N_3O_3$ (M^+) 435.1583, found 435.1583. IR (KBr): 3440 (w), 3205 (w), 3092 (w), 1720 (s), 1680 (s), 1492 (m), 1444 (s), 1332 (m), 746 (m), 707 (m), 594 (m), 534 (m). Meltingpoint: 182.1-183.1 °C (decomp.).

Triazinane dione 7f



Following the general procedure, reaction between diethyl methyl-phosphonate (152 mg, 1.0 mmol), benzonitrile (113 mg, 1.1 mmol), benzyloxyacetaldehyde (165 mg, 1.1 mmol) and phenylisocyanate (262 mg, 2.2 mmol), followed by column chromatography (hexane/EtOAc 4:1. gradient) afforded **7f** (154 mg, 31%) as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.43-7.00 (m, 20H), 6.59 (s, 1H), 6.12-6.06 (m, 2H), 4.35 (s, 2H), 4.05-4.01 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 153.5, 152.9, 140.1, 138.3, 138.1, 135.4 131.5, 130.7, 130.0 (2C), 129.7, 129.6 (2C), 129.2 (2C), 129.0 (4C), 128.9 (2C), 128.7, 128.2, 128.0 (2C), 127.93, 127.90 (2C), 75.8, 72.8, 69.3. HRMS (EI, 70 eV) calculated for $C_{31}H_{27}N_3O_3$ (M^+) 489.2052, found 489.2052. IR (KBr): 3214 (w), 3063 (w), 2853 (w), 1722 (s), 1679 (s), 1495 (m), 1446 (m), 1321 (m), 1115 (w), 760 (m), 696 (m), 597 (w), 538 (w). Meltingpoint: 150.6-152.4 °C (decomp.).

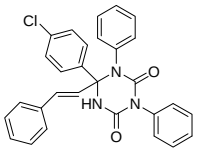
Triazinane dione 7g



Following the general procedure, reaction between diethyl methyl-phosphonate (152 mg, 1.0 mmol), *p*-methoxy-benzonitrile (146 mg, 1.1 mmol), benzaldehyde (117 mg, 1.1 mmol) and phenylisocyanate (262 mg, 2,2 mmol) afforded **7g** (259 mg, 55%) as a white solid. The crude product precipitated out of the reaction mixture after evaporation of half of the

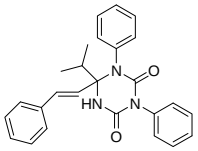
solvent and addition of water (10 mL). Subsequent washing of the crude with cold Et_2O gave **7g** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 9.22 (s, 1H), 7.51-7.48 (m, 4H), 7.40-7.31 (m, 6H), 7.24-7.14 (m, 5H), 7.09-7.07 (m, 2H), 6.93-6.82 (m, 2H), 6.80 (d, *J* = 15.9 Hz, 1H), 6.67 (d, *J* = 15.9 Hz, 1H), 3.74 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6): δ (ppm) 159.2, 152.5, 152.0, 138.1, 135.8, 135.3, 131.9, 131.5 (2C), 129.8 (2C), 129.4 (2C), 129.3, 129.2 (2C), 128.8 (2C), 128.5, 128.4 (2C), 128.3 (2C), 127.7, 127.1, 126.9 (2C), 113.4, 75.1, 55.1. HRMS (FAB) calculated for $C_{30}H_{25}N_3O_3$ (MH^+) 476.1974, found 476.1970. IR (KBr): 3216 (w), 3065 (w), 1721 (s), 1676 (s), 1494 (s), 1442 (s), 1326 (s), 1257 (s), 1177 (s), 1033 (m), 836 (m), 754 (s), 695 (s), 590 (m), 541 (m). Meltingpoint: 201.6-203.8 °C (decomp.).

Triazinane dione 7h



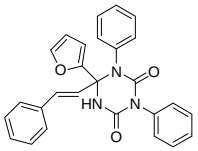
Following the general procedure, reaction between diethyl methyl-phosphonate (152 mg, 1.0 mmol), *p*-chloro-benzonitrile (151 mg, 1.1 mmol), benzaldehyde (117 mg, 1.1 mmol) and phenylisocyanate (262 mg, 2.2 mmol) afforded **7h** (285 mg, 59%) as a white solid. The crude product precipitated out of the reaction mixture after evaporation of half of the solvent and addition of water (10 mL). Subsequent washing of the crude with cold Et_2O gave **7h** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 9.34 (s, 1H), 7.63-7.61 (m, 3H), 7.51-7.44 (m, 4H), 7.41-7.31 (m, 6H), 7.26-7.14 (m, 4H), 7.09-7.07 (m, 2H), 6.80 (d, *J* = 16.0 Hz, 1H), 6.66 (d, *J* = 16.0 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ (ppm) 152.4, 151.9, 139.2, 137.8, 135.6, 135.1, 133.4, 132.1, 129.8 (2C), 129.8 (2C), 129.4 (2C), 128.9, 128.8, 128.7, 128.6, 128.5, 128.5 (2C), 128.2, 127.7, 127.3, 127.0 (2C), 115.6, 113.8, 74.9. HRMS (FAB) calculated for $C_{29}H_{22}ClN_3O_2$ (MH^+) 480.1479, found 480.1476. IR (KBr): 3206 (w), 3089 (w), 1723 (s), 1685 (s), 1492 (s), 1439 (s), 1332 (m), 1093 (m), 836 (m), 753 (m), 692 (m), 597 (m), 534 (m). Meltingpoint: 188.9-190.8 °C (decomp.).

Triazinane dione 7i

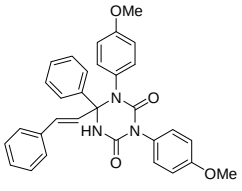


Following the general procedure, reaction between diethyl methyl-phosphonate (152 mg, 1.0 mmol), isobutyronitrile (76 mg, 1.1 mmol), benzaldehyde (117 mg, 1.1 mmol) and phenylisocyanate (262 mg, 2.2 mmol) afforded **7i** (231 mg, 56%) as a white solid. The crude product precipitated out of the reaction mixture after evaporation of half of the solvent and addition of water (10 mL). Subsequent washing of the crude with cold Et_2O gave **7i** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.62 (s, 1H), 7.44-7.28 (m, 13H), 7.19-7.17 (m, 2H), 6.84 (d, *J* = 16.0 Hz, 1H), 6.07 (d, *J* = 16.0 Hz, 1H), 2.22-2.19 (m, 1H), 1.21 (d, *J* = 6.6 Hz, 3H), 0.90 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6): δ (ppm) 152.3, 151.7, 137.3, 135.8, 135.6, 130.9 (2C), 130.5, 130.3, 129.4 (2C), 128.7 (4C), 128.4 (2C), 128.2, 128.0, 127.5, 126.8 (2C), 76.0, 35.4, 16.3, 16.2. HRMS (EI, 70 eV) calculated for $C_{26}H_{25}N_3O_2$ (M^+) 411.1947, found 411.1947. IR (KBr): 3440 (w), 3207 (w), 3096 (w), 2970 (w), 1713 (s), 1669 (s), 1481 (s), 1469 (s), 1357 (s), 1290 (m), 971 (m), 752 (m), 699 (m), 596 (m), 542 (m). Meltingpoint: 209.1-211.8 (decomp.).

Triazinane dione 7j

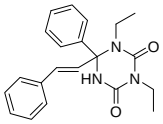


Following the general procedure, reaction between diethyl methyl-phosphonate (152 mg, 1.0 mmol), 2-furonitrile (102 mg, 1.1 mmol), benzaldehyde (117 mg, 1.1 mmol) and phenylisocyanate (262 mg, 2.2 mmol) afforded **7j** (235 mg, 54%) as a yellow solid. The crude product precipitated out of the reaction mixture after evaporation of half of the solvent and addition of water (10 mL). Subsequent washing of the crude with cold Et_2O gave **7j** as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 9.28 (s, 1H), 7.84-7.84 (m, 1H), 7.47-7.27 (m, 12H), 7.20-7.18 (m, 2H), 7.11-7.09 (m, 2H), 6.87 (d, *J* = 16.0 Hz, 1H), 6.62 (dd, *J* = 3.3, 0.6 Hz, 1H), 6.51 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.46 (d, *J* = 16.0 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ (ppm) 152.2, 151.8, 151.4, 137.3, 135.7, 135.1, 133.0, 130.0, 129.5 (2C), 128.7 (2C), 128.6, 128.5 (2C), 128.53 (2C), 128.47 (2C), 127.8, 127.7, 127.0 (2C), 126.0, 110.7, 110.4, 70.7. HRMS (EI, 70 eV) calculated for $C_{27}H_{21}N_3O_3$ (M^+) 435.1583, found 435.1583. IR (KBr): 3378 (w), 3223 (m), 3066 (w), 1721 (s), 1678 (s), 1494 (m), 1451 (s), 1328 (m), 746 (m), 695 (m), 592 (m), 556 (m). Meltingpoint: 198.8-200.6 °C (decomp.).



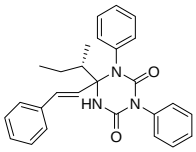
Triazinane dione 7k

Following the general procedure, reaction between diethyl methyl-phosphonate (152 mg, 1.0 mmol), benzonitrile (113 mg, 1.1 mmol), benzaldehyde (117 mg, 1.1 mmol) and *p*-methoxy-phenylisocyanate (328 mg, 2.2 mmol) afforded **7k** (460 mg, 91%) as a light yellow solid. The crude product precipitated out of the reaction mixture after evaporation of half of the solvent and addition of water (10 mL). Subsequent washing of the crude with cold Et_2O gave **7k** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 9.22 (s, 1H), 7.61-7.58 (m, 2H), 7.48-7.46 (m, 2H), 7.42-7.30 (m, 6H), 7.09-7.04 (m, 2H), 6.96-6.90 (m, 4H), 6.80-6.74 (m, 3H), 6.64-6.60 (m, 1H), 3.74 (s, 3H), 3.65 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6): δ (ppm) 158.5, 157.8, 152.7, 152.3, 140.6, 135.3, 131.5, 131.1 (2C), 130.6, 130.3 (2C), 129.0, 128.8 (2C), 128.7, 128.5, 128.4, 128.2 (2C), 127.6 (2C), 126.9 (2C), 113.7 (2C), 113.5 (2C), 75.2, 55.2, 55.1. HRMS (FAB) calculated for $C_{31}H_{27}N_3O_4$ (MH^+) 506.2080, found 506.2080. IR (KBr): 3216 (w), 3084 (w), 1720 (s), 1677 (s), 1511 (s), 1443 (s), 1329 (m), 1298 (m), 1249 (s), 1170 (m), 1033 (m), 830 (m), 751 (m), 696 (m), 566 (m). Meltingpoint: 199.2-201.1 °C.



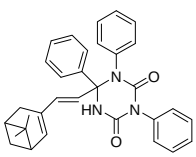
Triazinane dione 7l

Following the general procedure, reaction between diethyl methyl-phosphonate (152 mg, 1.0 mmol), benzonitrile (113 mg, 1.1 mmol), benzaldehyde (117 mg, 1.1 mmol) and ethylisocyanate (156 mg, 2.2 mmol), followed by column chromatography (hexane/EtOAc 4:1) afforded **7l** (44 mg, 13%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.46-7.44 (m, 2H), 7.35-7.19 (m, 8H), 6.53 (d, *J* = 15.9 Hz, 1H), 6.36 (d, *J* = 15.9 Hz, 1H), 6.16 (s, 1H), 3.70 (q, *J* = 7.0 Hz, 2H), 3.41-3.36 (m, 1H), 3.12-3.07 (m, 1H), 1.02 (t, *J* = 7.0 Hz, 3H), 0.90 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 153.1, 152.9, 140.4, 135.5, 133.0, 130.0, 129.3 (2C), 129.20 (2C), 129.18, 128.0, 127.9 (2C), 127.4 (2C), 75.3, 41.2, 36.6, 14.9, 14.3. HRMS (EI, 70 eV) calculated for $C_{21}H_{23}N_3O_2$ (M^+) 349.1790, found 349.1790. IR (KBr): 3282 (w), 2977 (w), 1713 (s), 1641 (s), 1490 (s), 1373 (m), 1292 (m), 753 (m), 695 (m). Meltingpoint: 138.8-139.6 °C.



Triazinane dione 7m

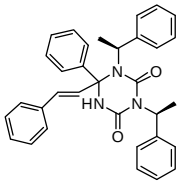
Following the general procedure, reaction between diethyl methyl-phosphonate (152 mg, 1.0 mmol), (*S*)-(+)-2-methylbutyronitrile (91 mg, 1.1 mmol), benzaldehyde (117 mg, 1.1 mmol) and phenylisocyanate (262 mg, 2.2 mmol), followed by column chromatography (hexane/EtOAc 9:1. gradient) afforded **7m** (106 mg, 25%) as a 52:48 mixture of diastereomers as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.43-7.10 (m, 30H), 6.90 (d, *J* = 16.0 Hz, 1H), 6.87 (d, *J* = 15.9 Hz, 1H), 6.29 (s, 1H), 6.21 (s, 1H), 5.94 (d, *J* = 16.0 Hz, 1H), 5.85 (d, *J* = 16.0 Hz, 1H), 2.20-2.15 (m, 1H), 1.83-1.72 (m, 2H), 1.39-1.25 (m, 6H), 1.04-0.97 (m, 2H), 0.87 (t, *J* = 14.7 Hz, 3H), 0.81 (t, *J* = 12.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 153.4, 153.4, 152.9, 152.6, 137.2, 135.8, 125.8, 135.3, 131.8, 131.4, 130.6, 130.4, 129.7, 129.6 (2C), 129.5 (4C), 129.5 (2C), 129.3 (2C), 129.3 (2C), 129.2 (2C), 129.0 (2C), 129.0 (2C), 128.9, 128.7 (2C), 127.3 (2C), 127.3 (2C), 43.7, 42.9, 23.8, 23.6, 13.4, 13.3, 12.7, 12.3. HRMS (EI, 70 eV) calculated for $C_{27}H_{27}N_3O_2$ (M^+) 425.2103, found 425.2103. IR (KBr): 3373 (w), 3234 (w), 2970 (w), 1718 (s), 1676 (s), 1449 (m), 1340 (w), 973 (w), 754 (m), 695 (m), 592 (w), 549 (w). Meltingpoint: 160.6-162.1 °C (decomp.).



Triazinane dione 7n

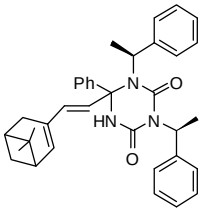
Following the general procedure, reaction between diethyl methyl-phosphonate (152 mg, 1.0 mmol), benzonitrile (113 mg, 1.1 mmol), (*R*)-(-)-myrtenal (165 mg, 1.1 mmol) and phenylisocyanate (262 mg, 2.2 mmol), followed by column chromatography (hexane/EtOAc 9:1. gradient) afforded **7n** (219 mg, 45%) as a 56:44 mixture of diastereomers as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.46-7.36 (m, 4H), 7.32-7.23 (m, 13H), 7.18-6.99 (m, 15H), 6.53 (d, *J* = 15.7 Hz, 1H), 6.45 (s, 1H), 6.39 (s, 1H), 6.37 (d, *J* = 10.8 Hz, 1H), 5.70-5.61 (m, 4H), 2.38-2.22 (m, 8H), 2.06 (s, 2H), 1.22 (s, 3H), 1.20 (s, 3H), 1.05 (dd, *J* = 8.8, 8.7 Hz, 2H), 0.66 (s, 3H), 0.62 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 153.6, 153.5, 153.4, 153.1, 153.0, 145.1, 145.1, 141.3, 140.4,

138.3, 138.2, 137.4, 135.4, 135.3, 134.3, 130.5, 130.1, 129.9, 129.6, 129.6, 129.5, 129.2, 129.1, 129.1, 129.0, 129.0, 128.9, 128.9, 128.6, 128.1, 127.9, 127.7, 127.6, 127.0, 124.2, 124.0, 41.8, 41.2, 41.2, 38.6, 38.2, 32.5, 31.6, 26.6, 25.2, 22.9, 21.2, 21.1. HRMS (EI, 70 eV) calculated for $C_{32}H_{31}N_3O_2$ (M^+) 489.2416, found 489.2416. IR (KBr): 3234 (w), 3093 (w), 2951 (w), 1721 (s), 1676 (s), 1493 (s), 1445 (s), 1324 (m), 1211 (m), 973 (m), 765 (m), 698 (m), 595 (m), 535 (w). Meltingpoint: 187.2-190.4 °C (decomp.).



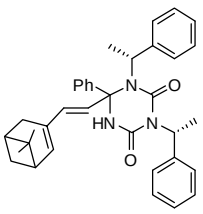
Triazinane dione 7o

Following the general procedure, reaction between diethyl methyl-phosphonate (152 mg, 1.0 mmol), benzonitrile (113 mg, 1.1 mmol), benzaldehyde (117 mg, 1.1 mmol) and (*S*)-(-)-1-phenylethylisocyanate (324 mg, 2.2 mmol), followed by column chromatography (hexane/EtOAc 9:1, gradient) afforded **7o** (249 mg, 50%) as a 66:33 mixture of diastereomers as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.54-7.52 (m, 1H), 7.39-7.38 (m, 1H), 7.32-7.09 (m, 14H), 7.05-6.88 (m, 6H), 6.67 (s, 1H), 6.62 (d, *J* = 15.9 Hz, 1H), 6.36 (d, *J* = 16.0 Hz, 1H), 6.32 (s, 1H), 6.28 (d, *J* = 16.0 Hz, 1H), 6.19 (d, *J* = 15.9 Hz, 1H), 5.57-5.53 (m, 1H), 1.71 (d, *J* = 7.1 Hz, 3H), 1.66 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 153.7 (2C), 153.2, 153.0, 152.7, 142.6, 142.3, 141.6, 140.7, 140.6, 135.6, 135.5, 133.2, 130.2, 129.7, 129.4, 129.2, 129.1, 129.0, 129.0, 128.7, 128.5, 128.4, 128.3, 128.2, 128.1, 128.1, 128.1, 128.0, 127.6, 127.5, 127.5, 127.4, 127.3, 127.2, 126.7, 126.6, 76.4, 57.9, 56.9, 51.6, 51.5, 31.3, 20.6, 20.3, 17.0, 16.9. HRMS (EI, 70 eV) calculated for $C_{33}H_{31}N_3O_2$ (M^+) 501.2416, found 501.2416. IR (KBr): 3388 (w), 3206 (w), 3062 (w), 2974 (w), 1712 (s), 1668 (s), 1448 (s), 1372 (m), 1283 (m), 757 (m), 696 (m), 554 (w). Meltingpoint: 89.9-91.6 °C.



Triazinane dione 7p

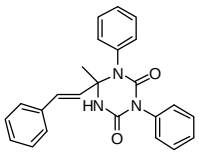
Following the general procedure, reaction between diethyl methyl-phosphonate (304 mg, 2.0 mmol), benzonitrile (226 mg, 2.2 mmol), (*R*)-(-)-myrtenal (330 mg, 2.2 mmol) and (*S*)-(-)-1-phenylethyl-isocyanate (648 mg, 4.4 mmol), followed by column chromatography (hexane/EtOAc 6:1, gradient) afforded **7p** (642 mg, 59 %) as a 83:17 mixture of diastereomers as a lightyellow foam. Diastereomer 1: ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.29-7.07 (m, 15H), 6.40 (s, 1H), 6.25 (d, *J* = 15.7 Hz, 1H), 5.75 (d, *J* = 15.7 Hz, 1H), 5.70 (s, 1H), 5.61 (q, *J* = 7.0 Hz, 1H), 4.67 (bs, 1H), 2.54-2.48 (m, 2H), 2.44-2.42 (m, 1H), 2.39-2.39 (m, 1H), 2.19 (bs, 1H), 1.77 (d, *J* = 7.0 Hz, 3H), 1.70 (d, *J* = 7.1 Hz, 3H), 1.38 (s, 3H), 1.23 (d, *J* = 8.2 Hz, 1H), 0.87 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 153.2, 152.8, 144.7, 142.1, 141.3, 140.6, 134.6, 129.1, 128.5 (2C), 128.3, 128.0 (2C), 127.8 (2C), 127.6 (2C), 127.0 (2C), 126.8 (2C), 126.7, 126.2, 123.1, 76.1, 56.2, 51.1, 41.4, 40.9, 37.9, 32.1, 31.3, 26.2, 20.9, 19.7, 16.6. $[\alpha]^{20}_D$ = -100 (*c* = 1.0 in $CHCl_3$). Diastereomer 2: ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.37-7.11 (m, 15H), 6.11 (d, *J* = 15.7 Hz, 1H), 5.90 (s, 1H), 5.68 (q, *J* = 5.7 Hz, 1H), 5.65 (d, *J* = 15.1 Hz, 1H), 5.49 (s, 1H), 4.35 (q, *J* = 7.0 Hz, 1H), 2.41-2.34 (m, 3H), 2.20-2.12 (m, 2H), 1.76 (d, *J* = 4.1 Hz, 3H), 1.74 (d, *J* = 4.2 Hz, 3H), 1.27 (s, 3H), 1.11 (d, *J* = 8.8 Hz, 1H), 0.77 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 152.5, 152.0, 144.6, 142.5, 141.4, 140.9, 133.6, 129.5, 128.8 (2C), 128.6, 128.2 (2C), 128.0, 127.8 (2C), 127.5 (2C), 127.5, 127.0, 126.9 (2C), 126.3, 123.3, 76.4, 57.4, 50.9, 41.2, 40.8, 37.7, 32.0, 31.2, 26.1, 20.7, 20.5, 16.7. $[\alpha]^{20}_D$ = -42 (*c* = 1.0 in $CHCl_3$). HRMS (FAB) calculated for $C_{36}H_{40}N_3O_2$ (MH^+) 546.3121, found 546.3123. IR (neat): 3193 (w), 3064 (w), 2933 (w), 1710 (s), 1662 (s), 1467 (s), 1371 (m), 1274 (m), 909 (m), 731 (m), 696 (m), 554 (m).



Triazinane dione 7q

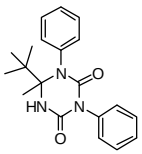
Following the general procedure, reaction between diethyl methyl-phosphonate (304 mg, 2.0 mmol), benzonitrile (226 mg, 2.2 mmol), (*R*)-(-)-myrtenal (330 mg, 2.2 mmol) and (*R*)-(+)-1-phenylethyl-isocyanate (648 mg, 4.4 mmol), followed by column chromatography (hexane/EtOAc 6:1. gradient) afforded **7q** (679 mg, 62 %) as a 66:33 mixture of diastereomers as an orange sticky oil. Diastereomer 1: ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.30-6.98 (m, 16H), 6.34 (d, *J* = 15.7 Hz, 1H), 5.72 (s, 1H), 5.70 (d, *J* = 15.7 Hz, 1H), 5.56 (q, *J* = 6.9 Hz, 1H), 4.80 (bs, 1H), 2.54-2.36 (m, 4H), 2.19 (bs, 1H), 1.76 (d, *J* = 7.0 Hz, 3H), 1.73 (d, *J* = 7.1 Hz, 3H), 1.37 (s, 3H), 1.25 (d, *J* = 8.1 Hz, 1H), 0.87 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm)

153.8, 153.6, 152.9, 144.8, 142.1, 141.1, 134.3, 128.6, 128.5, 128.4 (2C), 128.1, 128.0 (2C), 127.5 (2C), 127.3 (2C), 126.9 (2C), 126.8, 126.1, 123.0, 76.0, 56.3, 51.1, 41.5, 40.8, 37.8, 32.1, 31.4, 26.9, 26.3, 21.0, 19.7, 16.4. $[\alpha]^{20}_D$ = +62 (*c* = 1.0 in $CHCl_3$). Diastereomer 2: ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.50-7.09 (m, 16H), 6.06 (d, *J* = 15.7 Hz, 1H), 5.64 (d, *J* = 16.4 Hz, 1H), 5.61 (q, *J* = 7.0 Hz, 1H), 5.47 (s, 1H), 4.50 (q, *J* = 7.1 Hz, 1H), 2.41-2.27 (m, 3H), 2.17-2.10 (m, 2H), 1.80 (d, *J* = 7.1 Hz, 3H), 1.71 (d, *J* = 7.0 Hz, 3H), 1.27 (s, 3H), 1.09 (d, *J* = 8.9 Hz, 1H), 0.76 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 153.0, 152.3, 144.6, 142.7, 141.4, 141.2, 134.8, 132.7, 129.2, 128.8 (2C), 128.2 (2C), 128.0, 127.7 (2C), 127.3 (3C), 126.9, 126.8 (2C), 126.2, 123.7, 76.5, 57.4, 50.9, 41.2, 40.8, 37.6, 32.0, 31.2, 26.1, 20.8, 20.6, 16.7. $[\alpha]^{20}_D$ = +36 (*c* = 1.0 in $CHCl_3$). HRMS calculated for $C_{36}H_{40}N_3O_2$ (MH^+) 546.3121, found 546.3123. IR (neat): 3206 (w), 3065 (w), 2936 (w), 1709 (s), 1663 (s), 1447 (s), 1371 (m), 1268 (m), 909 (m), 729 (s), 695 (s), 550 (m).



Triazinane dione 7r

Dry Et_2O (2 ml) was cooled to -78 ºC and MeLi (625 μL, 1.6M in Et_2O) was added. Cinnamonitrile (129 mg, 1.0 mmol) dissolved in dry Et_2O (2 ml) was added dropwise to this solution over a period of 30 minutes and the mixture was then stirred at -78ºC for 3 hours and at room temperature for 1 hour. Phenyl isocyanate (217 μL, 2.0 mmol) was added and after 5 minutes the reaction was worked up by addition of H_2O (10 mL). Solid materials were filtered of and washed with cold Et_2O, dissolved in DCM and evaporated. Both the solid material and the Et_2O-wash contained product so they were purified together by column chromatography (hexane/EtOAc 2:1) to afford **7r** (115 mg, 30%) as a yellow solid. ^{1}H NMR (400 MHz, CDCl3): 7.41-7.25 (m, 15H), 6.80 (d, *J* = 15.9 Hz, 1H)., 6.41 (d, *J* = 15.9 Hz, 1H), 5.94 (s), 1.59 (s, 3H). ^{13}C NMR (101 MHz, CDCl3): 153.1, 152.4, 136.9, 135.2, 135.0, 130.1 (2C), 129.5, 129.3 (2C), 129.2 (2C), 128.9 (2C), 128.8 (2C), 128.7, 128.6, 128.3, 126.9 (2C), 70.6, 26.7. HRMS (EI, 70 eV) calculated for $C_{24}H_{21}N_3O_2$ (M^+) 383.1634, found 383.1632. IR (KBr): 3270 (w), 2925 (w), 1716 (s), 1674 (s), 1461(m), 1329 (m), 968 (w), 760 (m), 698 (m). Melting point: 223.0-223.6 °C (decomp.).



Triazinane dione 7s

Dry Et_2O (2 ml) was cooled to -78 ºC and MeLi (625 μL, 1.6M in Et_2O) was added. Trimethylacetonitrile (83 mg, 1.0 mmol) dissolved in dry Et_2O (2 ml) was added dropwise to this solution over a period of 30 minutes and the mixture was then stirred at -78ºC for 3 hours and at room temperature for 1 hour. Phenyl isocyanate (217 μL, 2.0 mmol) was added and after 5 minutes the reaction was worked up by addition of H_2O (10 mL). Solid materials were filtered of and washed with cold Et_2O, dissolved in DCM and evaporated. Both the solid material and the Et_2O-wash contained product so they were purified together by column chromatography (hexane/EtOAc 4:1) to afford **7s** (67 mg, 20%) as a white solid. ^{1}H NMR (400 MHz, CDCl3): 7.39-7.25 (m, 10H), 6.07 (s, 1H), 1.52 (s, 3H), 1.20 (s, 9H). ^{13}C NMR (101 MHz, CDCl3): 153.1, 152.0, 138.8, 135.1, 132.7, 130.9, 128.8 (2C), 128.7 (2C), 128.7, 128.5, 128.3, 125.1, 76.3, 44.1, 26.5 (3C), 24.8. HRMS (EI, 70 eV) calculated for $C_{20}H_{23}N_3O_2$ (M^+) 337.1790, found 337.1790. IR (KBr): 3206 (m), 3099 (m), 2978 (m), 1722 (s), 1677 (s), 1457 (s), 1325 (s), 769 (s), 700 (s), 589 (m), 562 (m). Melting point: 219.2-220.2 °C (decomp.).

3.5 References and notes

1. Dobson, M. *Nature* **2004**, *32*, 824-828.
2. Burke, M. D., Schreiber, S. L. *Angew. Chem. Int. Ed.* **2004**, *43*, 46-58.
3. Dömling, A. *Chem. Rev.* **2006**, *106*, 17-89.
4. Zhu, J. P. *Eur. J. Org. Chem.* **2003**, 1133-1144.
5. Orru, R. V. A. ; De Greef, M. *Synthesis* **2003**, 1471-1499.
6. Vugts, D. J. ; Jansen, H. ; Schmitz, R. F.; de Kanter, F. J. J. ; Orru, R. V. A. *Chem. Comm.* **2003**, 2594-2595.
7. Vugts, D. J.; Koningstein, M. M.; Schmitz, R. F. ; de Kanter, F. J. J. ; Groen, M. B. ; Orru, R. V. A. *Chem. Eur. J*. **2006**, *12*, 7178-7189.

8. Jung, M. E.; Shapiro, J. J. *J. Am. Chem. Soc.* **1980**, *102*, 7862-7866.
9. Behforouz, M.; Ahmadian, M.; *Tetrahedron* **2000**, *56*, 5259-5288.
10. Etienne, A.; Bonte, B. *Bull. Soc. Chim. Fr.* **1975**, *5-6*, 1419-1423.
11. Etienne, A.; Lonchambon, G.; Giraudeau, P. *Comptes rendus*, **1977**, *285*, 321-324.
12. Vovk, M. V.; Dorokhov, V. I.; Zhitomir, S-kh. *Izv. Vyssh. Ucheb. Zaved. Khim. Khim. Tekhnol.* **1992**, *35*, 28-31.
13. Vovk, M. V. *Russ. J. Org. Chem*. **1996**, *32*, 767-768.
14. Nazarenko, K. G.; Shvidenko, K. V.; Pinchuk, A. M.; Tolmachew, A. A. *Monatsh. Chem*. **2005**, *136*, 211-215.
15. Toye, T.; Ghosez, L. *J. Am. Chem. Soc.* **1975**, *97*, 2276-2277.
16. Blechert, S.; Wirth T. *Tetrahedron Lett*. **1991**, *32*, 7237.
17. Langhals, H.; Ruchardt, C. *Chem. Ber.* **1981**, *114*, 3831-3854.
18. Babler, J. H.; Marcuccilli, C. J. *Tetrahedron Lett*. **1987**, *28*, 4657-4660.
19. Klein Gebbink, E. A.; Stork, G. A.; Jansen, B. J. M.; de Groot, A. *Tetrahedron* **1999**, *55*, 11077-11094.
20. Sulmon, P.; De Kimpe, N.; Schamp, N. J. *Chem. Soc. Chem. Comm*. **1985**, *11*, 715-716.

Chapter 4

Generation of Molecular Diversity Using a Complexity-Generating MCR-Platform toward Triazinane Diones

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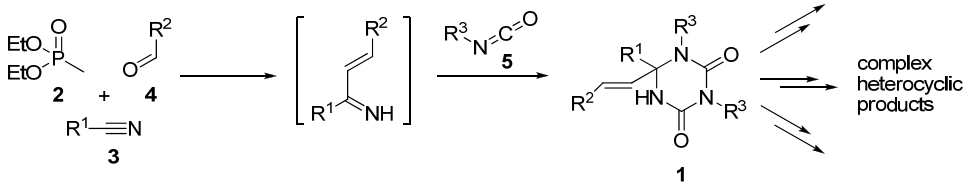
4.1 Introduction

Recent advances in genomics, proteomics, metabolomics, and structural biology highlight a clear need for small molecules that can modulate biological processes.[1] Combinatorial synthesis is undisputed as an enabling tool to access the required small-molecule based compound collections. Although the benefit for drug discovery seems obvious, the actual hit rates for new drug candidates have decreased steadily over the past decade.[2] It has become clear that not only the number of molecules but also the structural diversity and molecular complexity of the chosen scaffolds are key issues to address in the design of a compound library.[3,4]

Rapid generation of diverse sets of complex molecules can be achieved by employing diversity-oriented synthetic strategies in combination with complexity-generating reactions.[5] Multicomponent reactions (MCRs), which combine in one pot at least three simple building blocks,[6-8] provide a most powerful platform to access diversity as well as complexity in a limited number of reaction steps. Here we describe modular reaction sequences based on our previously reported MCR chemistry[9-11] in combination with other common organic reactions or even with a second MCR.

The MCR platform that we chose for this work is a one-pot synthetic protocol towards triazinane diones **1**, a rather unexplored class of heterocyclic scaffolds (Scheme 1).[9-11] The four-component reaction (4CR) combines phosphonate **2**, nitriles **3**, aldehydes **4** and isocyanates **5** and proceeds with remarkable efficiency and flexibility. Furthermore, subsequent alkylation of **1** proved successful and allows attachment of additional synthetic handles.



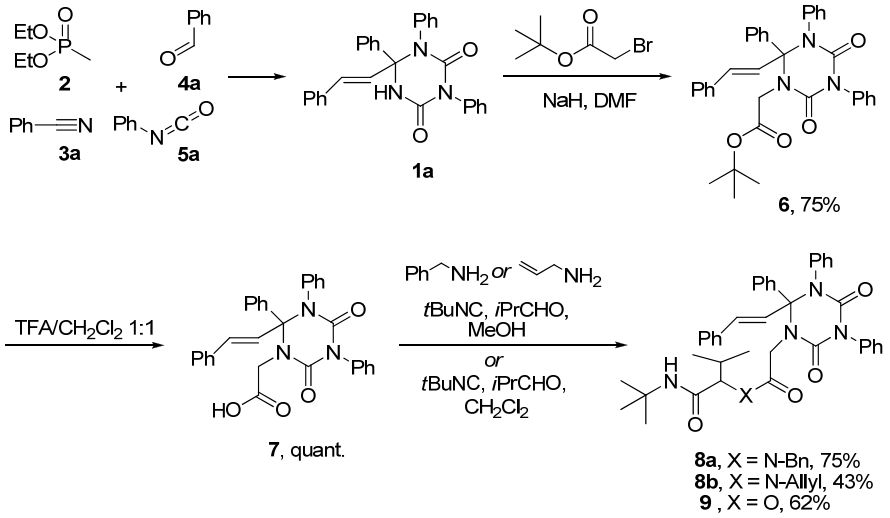
Scheme 1: 4CR for triazinane diones as versatile platform for complexity generation.

Combination of this 4CR with additional complexity-generating reactions, *e.g.*, ring-closing metathesis (RCM),[12-14] cycloaddition reactions (Huisgen[15,16] or Diels-Alder[17]), or isonitrile-based MCRs (I-MCR)[6] enables rapid access to highly complex (poly)hetero-cyclic scaffolds with pharmaceutically interesting cores.

4.2 Results and discussion

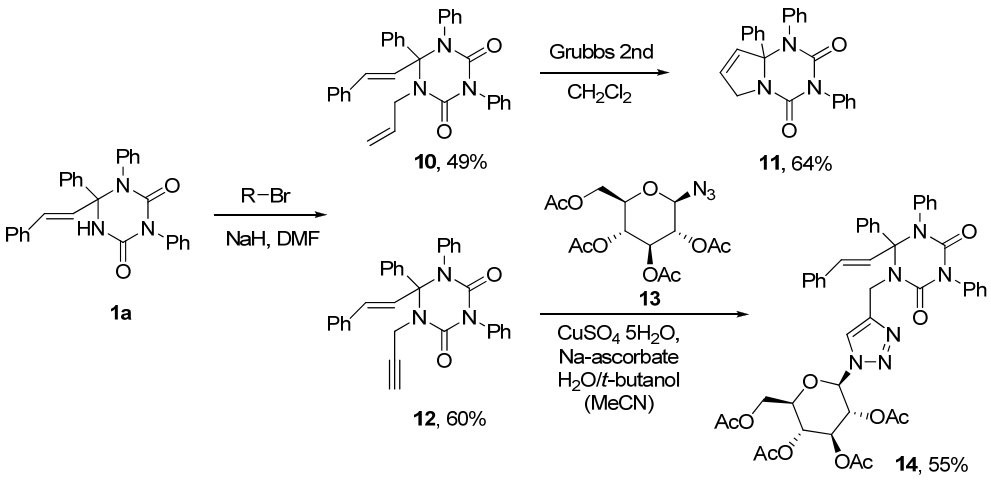
The triazinane dione **1a** was chosen as the heterocyclic platform and our attention initially focused on the combination with additional MCRs. The isonitrile-based Ugi four-component (U-4CR)[6-8,18] and Passerini three-component (P-3CR)[19,20] reactions, widely used to generate complex peptide-like products, were considered as candidate reactions to achieve fast complexity generation. Thus, as described before,[9] the 4CR of **2**, **3a**, **4a** and **5a** gave the triazinane dione **1a** efficiently. The amide NH was alkylated (NaH, *tert*-butyl 2-bromoacetate,

DMF) to give *tert*-butyl ester **6** in 75% yield. Subsequently, removal of the *tert*-butyl group with TFA in CH_2Cl_2 afforded carboxylic acid **7** in quantitative yield.



Scheme 2: Alkylation and then U-4CR or P-3CR reactions.

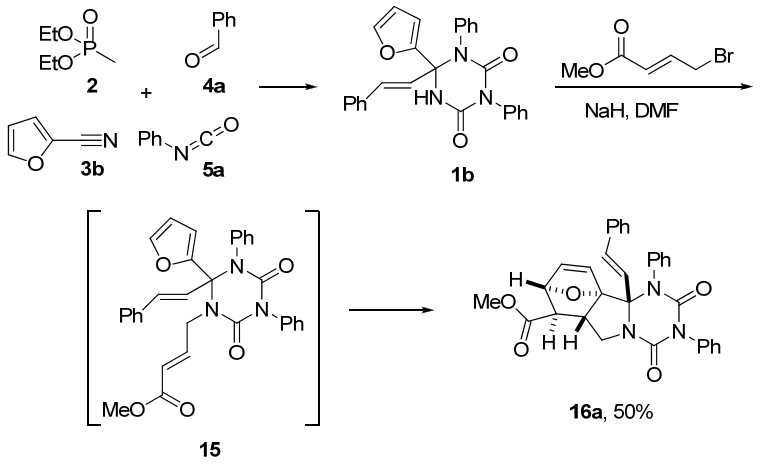
The acid 7 was employed in either an U-4CR or a P-3CR (Scheme 2). The U-4CR was performed in MeOH at room temperature using isobutyraldeldehyde, benzyl-amine or allylamine, the triazinane dione acid **7** and *tert*-butyl isocyanide. This indeed gave the expected peptide-derived triazinane diones **8a** and **8b**, respectively, in reasonable to good isolated yields. The P-3CR of isobutyraldehyde, acid **7** and *tert*-butyl isocyanide was performed in CH_2Cl_2 at room temperature and afforded the corresponding peptide-like **9** in 62% isolated yield. Thus, combination of our 4CR and these isonitrile-based MCRs in a short synthetic sequence (four steps) allows for rapid construction of rather complex, peptide-functionalized heterocycles. Both the initial 4CR, which generates the heterocyclic scaffold, as well as the U-4CR and the P-3CR are easy to perform and compatible with a large variety of differently functionalized inputs. This makes this four-step sequence amenable for a combinatorial set-up to generate libraries of peptidyl triazinane diones of type **8** or **9**.



Scheme 3: Alkylation and then RCM or click reactions.

Next, our attention focused on the construction of highly functionalized bi-or polycyclic ring systems. Combination of the initial triazinane dione-generating 4CR with RCM or cycloaddition reactions was envisioned as a powerful strategy to achieve this goal. Thus, allylation of **1a** to afford **10** and subsequent RCM using the 2nd generation Grubbs' catalyst[21] in CH_2Cl_2 resulted in the bicyclic triazinane dione **11** (64%, Scheme 3).

To further explore the potential of the triazinane dione scaffold as a versatile platform for additional cyclization reactions, a [2+3] Huisgen cycloaddition (click reaction)[22-24] was considered. Propargylation of the free NH in **1a** (NaH, propargyl bromide, DMF; Scheme 3) gave the desired product **12** in 60% isolated yield. Then, the click reaction of **12** and readily available β-glucosyl azide derivative **13** was performed in a H_2O/*t*-BuOH/MeCN mixture with $CuSO_4$ and sodium ascorbate as the catalyst and co-catalyst, respectively.[22] The cycloaddition product **14** was obtained in a reasonable yield of 55%. Again, combination of our initial 4CR for triazinane diones and these cyclization protocols allow rapid complexity generation in a short synthetic sequence (three steps). The RCM and the [2+3] Huisgen cycloaddition are well established and robust reactions that are compatible with a wide variety of different functionalities. This opens the way for easy generation of diversified sets of xanthine-like[25] annelated bicyclic cores **11** or non-natural nucleoside mimics of type **14**.[26]



Scheme 4: A domino alkylation-IMDA reaction.

Furthermore, a strategy based on the 4CR for triazinane diones and an intramolecular Diels-Alder (IMDA) reaction was envisioned to access the desired diversity and complexity of functionalized polycyclic ring systems in a highly efficient manner.[27] For this purpose, we decided to introduce the required dienophile on a furan-functionalized triazinane dione (**1b**) platform. The four-component synthesis of **1b** proceeded smoothly following the general procedure reported by us earlier.[9] Next, reaction of **1b** with methyl *E*-4-bromo-2-butenoate in DMF after deprotonation with NaH would lead to **15**, which could then be subjected to heating to give the IMDA product. However, the anticipated IMDA reaction appears to proceed readily at room temperature and occurs immediately after alkylation of 1b with the dienophile. The intermediate alkylation product **15** was not observed. Thus, the desired

polycyclic IMDA product **16a** is formed in a very efficient one-pot domino process and could be isolated in 50% yield (Scheme 4). The structure of **16a** including the relative stereochemistry is predicted by orbital symmetry considerations and was unambiguously confirmed by NOESY and X-ray crystal structure determination (Figure 1).

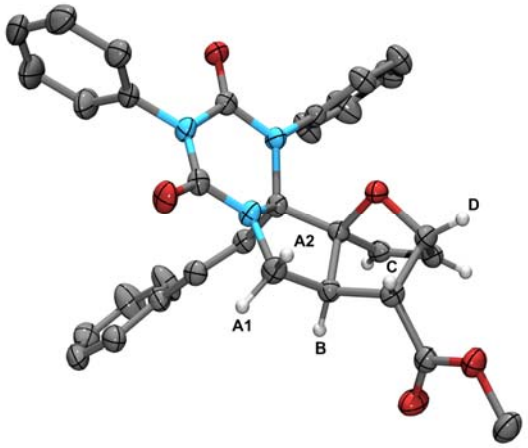
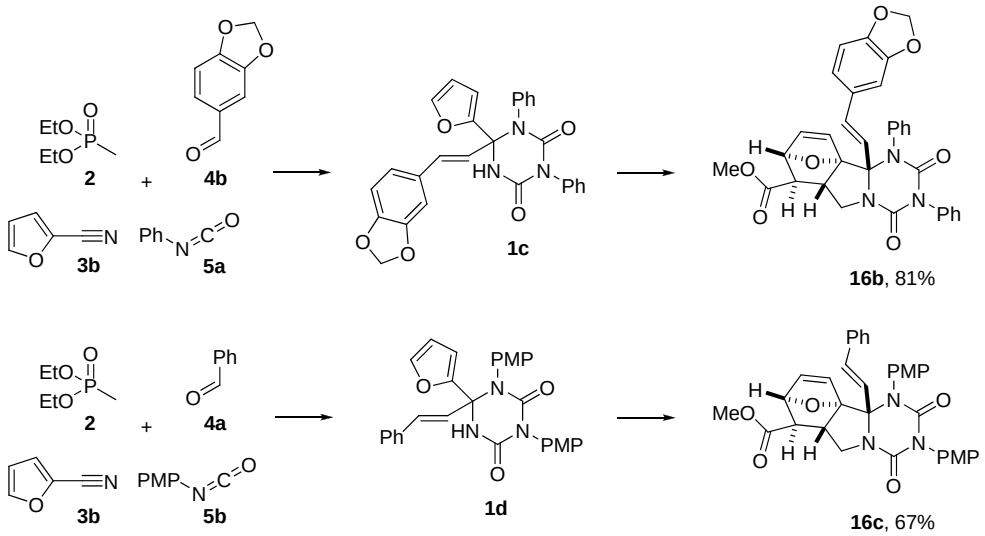


Figure 1: Displacement ellipsoid plot of racemic **16a**, drawn at the 50% probability level, indicating the stereochemistry between hydrogens **A1**-**A2**, **A1**-**B**, **A2**-**C**, **B**-**C** and **C**-**D**. Other hydrogen atoms are omitted for clarity.

Other furan-functionalized triazinane diones underwent similar efficient spontaneous IMDA cyclization after alkylation with methyl *E*-4-bromo-2-butenoate. Thus, alkylation of **1c**, prepared efficiently via the 4CR of **2**, furonitrile **3b**, piperonal **4b** and **5a**, resulted in smooth in situ IMDA cyclization to give **16b** in high yield. Similarly, alkylation of **1d**, prepared via the 4CR of **2**, **3b**, **4a** and *p*-methoxyphenyl isocyanate **5b**, afforded **16c** (Scheme 5).



Scheme 5: Two more examples of the domino alkylation/IMDA reaction.
PMP = *p*-methoxyphenyl.

The structures of **16b** and **16c** were assigned on the basis of NOE intensities between the hydrogens **A1**-**A2**, **A1**-**B**, **A2**-**C** and **B**-**C** (Figure 1), which have a similar build-up rate as the

NOE intensities between the corresponding hydrogens in **16a**. Also, the coupling constants of the various hydrogens in **16a** (**A1**-**B** = 9.5 Hz; **A2**-**B** = 7.3 Hz; **B**-**C** = 2.9 Hz; **C**-**D** = 4.8 Hz) are comparable to those observed in **16b** and **16c**, indicating that the relative stereo-chemistry of all three compounds is the same.
Thus, combination of our 4CR with an alkylation/IMDA domino reaction yields a very efficient strategy to access highly functionalized polycyclic cores in only two reaction steps.

4.3 Conclusions

In summary, the 4CR for triazinane diones provides a versatile platform that can be applied in combination with additional MCRs, RCM, [2+3] cycloaddition and IMDA reactions. This results in very short reaction sequences (maximum of four) to generate both diversity and complexity. In some cases, diversification is based solely on the *N*-alkyl functionality, while in other cases various functional groups on the triazinane dione participate in the secondary reactions, thus leading to increased scaffold diversification. Combination of both approaches leads to higher overall diversity and therefore to a better coverage of chemical space. This strategy will prove useful in the design of combinatorial libraries based on highly functionalized heterocyclic small molecules.

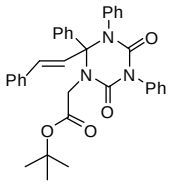
4.4 Experimental section

General information

All reactions were carried out under an inert atmosphere of dry nitrogen. THF was dried and distilled from sodium/benzophenone prior to use, CH_2Cl_2 was dried and distilled from $CaCl_2$ prior to use. Other commercially available chemicals were used as purchased. Thin Layer Chromatography (TLC) was performed using aluminium TLC sheets (Silica gel 60 F254) and compounds were visualized using UV-detection (254 nm) and colouring with an anisaldehyde solution (6 mL *p*-anisaldehyde, 7 mL acetic acid and 7 mL sulfuric acid in 120 mL of EtOH) or a CER-MOP solution (5 g molybdophosphoric acid, 2 g cerium (IV) sulfate and 16 mL sulfuric acid in 184 mL of H_2O). Column chromatography was performed using Flash Silica Gel (40-63 μm) and mixtures of cyclohexane and EtOAc. Melting points are uncorrected. Infrared (IR) spectra were obtained from pure samples and wavelengths (ν) are reported in cm^{-1}. ^1H nuclear magnetic resonance (NMR) spectra were recorded at 400.13 MHz or 250.13 MHz and ^{13}C NMR spectra at 100.61 MHz or 62.90 MHz with chemical shifts (δ) reported in ppm downfield from tetramethylsilane. HRMS-FAB data were measured using a four sector mass spectrometer.

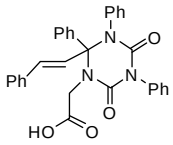
General procedure I: Alkylation of triazinane diones

NaH (1.1 equivalent, 0.12 M) was added to a flame-dried Schlenk vessel and dry DMF was added. This suspension was cooled to 0ºC after which the triazinane dione (1.0 equivalent. 0.11 M) was added. The mixture was then stirred for 1.5 h at 0ºC after which the appropriate allylic or propargylic bromide was added (1.1 equivalent, 0.12 M). The reaction mixture was then allowed to warm to room temperature overnight, after which the reaction was worked up. DMF was removed by evaporation and the crude material was dissolved in EtOAc. This organic fraction was washed twice with water, then with brine, dried (Na_2SO_4), filtrated and concentrated by evaporation of the solvent under reduced pressure. The crude product was purified by column chromatography (cyclohexane/EtOAc).



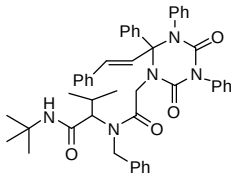
***tert*-Butyl ester 6**

Following general procedure I, reaction between triazinane dione **1a** (1.00 g, 2.20 mmol) and *tert*-butyl 2-bromoacetate (340 mg, 2.40 mmol) followed by column chromatography (cyclohexane/EtOAc = 2:1), afforded **6** (945 mg, 75%) as a white foam. ^{1}H NMR (400MHz, $CDCl_3$): 7.45-7.58 (m, 2H), 7.09-7.36 (m, 18H), 6.61 (s, 2H), 4.03 (s, 2H), 1.39 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): 167.7, 153.2, 152.5, 138.6, 138.2, 135.4, 135.1, 135.0, 129.9 (2C), 129.5, 129.2 (2C), 129.0, 128.9 (2C), 128.7 (2C), 128.7 (2C), 128.6 (2C), 128.3 (2C), 128.1, 127.5, 127.0 (2C), 126.4, 81.9, 81.2, 48.2, 27.9 (3C). HRMS (FAB) calculated for $C_{35}H_{34}N_3O_4$ (MH^+) 560.2549, found 560.2543. IR (neat): 2978 (w), 1713 (s), 1676 (s), 1493 (m), 1433 (s), 1321 (m), 1229 (m), 1148 (s), 752 (s), 692 (s).



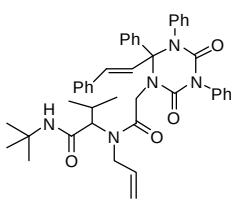
Triazinane dione acid 7

tert-Butyl ester **6** (900 mg, 1.6 mmol) was dissolved in CH_2Cl_2 (2 mL) and trifluoroacetic acid (2 mL) was added. This mixture was stirred for 45 minutes after which the solvent and excess trifluoroacetic acid were removed by evaporation under reduced pressure. This afforded crude **7** as white solid (806 mg, quant.) without further purification being necessary. ^{1}H NMR (250MHz, $CDCl_3$): 7.61-7.57 (m, 2H), 7.40-7.11 (m, 18H), 6.76 (d, J = 16.0 Hz, 1H), 6.62 (d, J = 15.9 Hz, 1H), 4.20 (s, 2H). ^{13}C NMR (101MHz, DMSO-d_6): 169.5, 152.9, 152.2, 138.8, 138.5, 136.1, 135.5, 134.3, 130.1, 129.8, 129.6 (2C), 129.3, 129.3, 129.3 (2C), 129.0 (2C), 129.0 (2C), 128.9 (2C), 128.7, 128.4, 127.6, 127.6 (2C), 127.1, 125.8, 81.5, 47.8. HRMS (FAB) calculated for $C_{31}H_{26}N_3O_4$ (MH^+) 504.1923, found 504.1916. IR (neat): 2818 (w), 2567 (w), 1784 (m), 1705 (s), 1636 (s), 1491 (m), 1460 (m), 1445 (s), 1334 (m), 1253 (m), 1213 (s), 1146 (s), 756 (s), 692 (s), 590 (s). Melting point: 181.3-181.9 ºC (decomp.).



Ugi product 8a

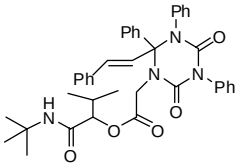
Benzylamine (107 mg, 1.0 mmol) and isobutyraldehyde (72 mg, 1.0 mmol) were dissolved in MeOH (5 mL) containing Na_2SO_4 (500 mg). This mixture was stirred for 2 h at room temperature, after which the acid **7** (252 mg, 0.5 mmol) was added. This mixture was then stirred for an additional 30 minutes after which *tert*-butyl isocyanide (42 mg, 0.5 mmol) was added. The reaction was stirred overnight and then worked up by addition of H_2O (25 mL) and extraction with EtOAc (3×25 mL). The combined organic fractions were washed with brine (25 mL), dried (Na_2SO_4), filtered and concentrated by evaporation of the solvent under reduced pressure. The crude product was purified by column chromatography (cyclohexane/EtOAc 4:1, gradient) affording **8a** (281 mg, 75 %) as a white foam as a 1:1 mixture of diastereomers and rotamers. NMR spectra were recorded at 403K to resolve the rotamers, but this did not have a good resolving effect on the NMR spectra. Therefore, quantification of the signals could not be achieved. ^{1}H NMR (400 MHz, DMSO-d_6, 403K): 7.64 (bs), 7.57 (bs), 7.47-7.46 (m), 7.40 (bs), 7.38 (bs), 7.34-7.11 (m), 6.90-6.85 (m), 6.51 (d, J = 16.1 Hz), 6.40 (d, J = 15.6 Hz), 6.26 (d, J = 15.2 Hz), 6.23 (d, J = 16.0 Hz), 4.85 (bs), 4.81 (bs), 4.78 (bs), 4.74 (bs), 4.61 (bs), 4.57 (bs), 4.47 (bs), 4.44 (bs), 4.11 (bs), 2.27-2.22 (m, 1H), 1.18 (s), 1.09 (bs), 0.91 (d, J = 6.5 Hz), 0.88 (bs), 0.74 (d, J = 6.6 Hz), 0.65 (bs). ^{13}C NMR (101 MHz, DMSO-d_6, 403K): 168.5, 168.4, 167.8, 151.8, 151.8, 151.4, 151.4, 139.5, 139.5, 137.9, 137.9, 135.5, 135.4, 135.3, 135.2, 134.4, 129.5, 129.5, 128.3, 128.3, 128.0, 127.9, 127.8, 127.8, 127.8, 127.7, 127.1, 127.0, 126.9, 126.9, 126.8, 126.5, 126.5, 126.1, 125.7, 80.2, 80.1, 65.3, 49.8, 49.7, 47.7, 47.6, 27.6, 27.5, 27.2, 27.1, 18.3, 18.1, 18.0. HRMS (FAB) calculated for $C_{47}H_{50}N_5O_4$ (MH^+) 748.3863, found 748.3862. IR (neat): 3341 (w), 3065 (w), 2965 (w), 1717 (m), 1653 (s), 1491 (m), 1437 (s), 1302 (m), 1219 (m), 756 (m), 711 (m), 692 (s), 590 (m).



Ugi product 8b

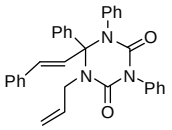
Allylamine (145 mg, 0.75 mmol) and isobutyraldehyde (53 mg, 0.75 mmol) were dissolved in MeOH (1 mL) containing Na_2SO_4 (50 mg). This mixture was stirred for 2 h at room temperature, after which the acid **7** (180 mg, 0.38 mmol) was added. This mixture was then stirred for an additional 30 minutes after which *tert*-butyl isocyanide (32 mg, 0.38 mmol) was added. The reaction was stirred overnight and then worked up by addition of H_2O (10 mL) and extraction with EtOAc (3×10 mL). The combined

organic fractions were washed with brine (30 mL), dried (Na_2SO_4), filtered and concentrated by evaporation of the solvent under reduced pressure. The crude product was purified by column chromatography (cyclohexane /EtOAc 2:1, gradient) affording **8b** (112 mg, 43%) as a white foam as a 1:1 mixture of diastereomers and rotamers. NMR spectra were recorded at 403K to resolve the rotamers, but this did not have a good resolving effect on the NMR spectra. Therefore, quantification of the signals could not be achieved. ^{1}H NMR (400 MHz, DMSO-d_6, 403K): 7.68-7.65 (m), 7.52-7.39 (m), 7.33-7.28 (m), 7.24-7.16 (m), 7.08 (bs), 7.02 (bs), 6.89-6.87 (m), 6.53 (d, J = 16.1 Hz), 6.49 (d, J = 16.0 Hz), 6.32 (d, J = 16.0 Hz), 5.63 (bs), 5.09-5.04 (m), 4.93-4.86 (m), 4.66-4.62 (m), 4.38 (d, J = 17.2 Hz), 4.29 (d, J = 17.0 Hz), 4.04 (s), 4.02 (s), 2.19-2.14 (m), 1.23 (s), 1.19 (bs), 0.90 (d, J = 6.4 Hz), 0.71 (d, J = 6.7 Hz), 0.69 (bs). ^{13}C NMR (101 MHz, $CDCl_3$): 169.6, 169.5, 168.9, 168.8, 153.3, 153.2, 152.7, 152.7, 138.3, 138.2, 135.8, 135.4, 135.4, 135.1, 134.9, 133.6, 133.2, 130.0, 129.3, 129.1, 129.1, 129.0, 128.9, 128.8, 128.7, 128.7, 128.7, 128.6, 128.6, 128.1, 128.0, 127.5, 127.4, 127.2, 127.1, 126.9, 126.9, 126.8, 117.1, 116.9, 116.8, 81.2, 81.1, 51.3, 51.2, 47.9, 47.8, 28.5, 28.2, 26.8, 26.6, 19.5, 19.5, 18.7. HRMS (FAB) calculated for $C_{43}H_{48}N_5O_4$ (MH^+) 698.3706, found 698.3702. IR (neat): 2924 (m), 2853 (w), 1751 (s), 1709 (m), 1672 (m), 143 (m), 1441 (m), 1367 (m), 1221 (s), 1037 (s), 912 (m), 731 (m), 694 (m), 596 (w).



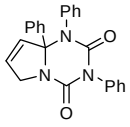
Passerini product 9

To a suspension of isobutyraldehyde (54 mg, 0.75 mmol) and **7** (252 mg, 0.50 mmol) in CH_2Cl_2 (5 mL) was added *tert*-butyl isocyanide (62 mg, 0.75 mmol). Within a minute the reaction mixture became clear and it was then stirred overnight after which the solvent was removed by evaporation under reduced pressure. The crude product was purified by column chromatography yielding **9** (203 mg, 62 %) as a white foam as a 1:1 mixture of diastereomers. Diastereomer a: ^{1}H NMR (400MHz, $CDCl_3$): 7.62 (dd, J = 8.1, 1.9 Hz, 2H), 7.40-7.32 (m, 12H), 7.15-7.10 (m, 6H), 6.86 (d, J = 16.0 Hz, 1H), 6.60 (d, J = 16.0 Hz, 1H), 6.31 (s, 1H), 4.86 (d, J = 3.5 Hz, 1H), 4.16 (d, J = 16.2 Hz, 1H), 4.00 (d, J = 16.2 Hz, 1H), 2.34-2.27 (m, 1H), 1.37 (s, 9H), 0.89 (d, J = 7.6 Hz, 3H), 0.87 (d, J = 7.2 Hz, 3H). ^{13}C NMR (101MHz, $CDCl_3$): 168.0, 167.6, 153.8, 152.0, 138.2, 137.4, 135.1, 135.1, 134.7, 129.9, 129.3, 129.2 (2C), 129.0 (2C), 129.0 (2C), 128.9 (2C), 128.8 (2C), 128.7 (2C), 128.6 (2C), 128.4, 127.5, 127.1 (2C), 125.7, 81.6, 79.4, 51.4, 48.1, 30.2, 28.3 (3C), 18.9, 16.5. Diastereomer b: ^{1}H NMR (250MHz, $CDCl_3$): 7.58-7.09 (m, 20H), 6.95 (d, J = 16.0 Hz, 1H), 6.81 (d, J = 15.9 Hz, 1H), 6.46 (s, 1H), 4.93 (d, J = 3.2 Hz, 1H), 4.12 (d, J = 16.6 Hz, 1H), 3.94 (d, J = 16.6 Hz, 1H), 2.48-2.35 (m, 1H) 1.15 (s, 9H), 0.99 (d, J = 6.9 Hz, 6H). ^{13}C NMR (101MHz, $CDCl_3$): 168.0, 167.7, 153.7, 152.0, 138.2, 137.3, 135.1, 134.8, 134.4, 129.9, 129.2, 129.1 (2C), 129.0 (2C), 128.9 (2C), 128.8 (2C), 128.8 (2C), 128.6 (2C), 128.5 (2C), 128.4, 127.4, 127.2 (2C), 125.8, 81.6, 79.4, 51.4, 48.5, 30.1, 28.2 (3C), 19.1, 16.4. HRMS (FAB) calculated for $C_{40}H_{43}N_4O_5$ (MH^+) 659.3233, found 659.3237. IR (neat): 3349 (w), 2967 (w), 1716 (s), 1663 (s), 1437 (s), 1319 (m), 1192 (m), 756 (s), 692 (s), 588 (m).



***N*-Allyltriazinane dione 10**

Following general procedure I, reaction between triazinane dione **1a** (500 mg, 1.12 mmol) and allyl bromide (150 mg, 1.24 mmol) followed by column chromatography (cyclohexane/EtOAc = 2:1), afforded **10** (267 mg, 49%) as a white foam. ^{1}H NMR (400MHz, $CDCl_3$): 7.57-7.55 (m, 2H), 7.38-7.06 (m, 18H), 6.61 (s, 2H), 5.96-5.89 (m, 1H), 5.14 (ddt, J = 10.2, 1.4, 1.4 Hz, 1H), 5.05 (ddt, J = 17.1, 1.4, 1.4 Hz, 1H), 4.20 (ddt, J = 15.7, 5.2, 1.6 Hz, 1H), 3.98 (ddt, J = 15.6, 6.3, 1.3 Hz, 1H) ^{13}C NMR (101 MHz, $CDCl_3$): 153.4, 152.7, 138.7, 138.3, 135.5, 135.1, 135.0, 134.0, 129.6 (2C), 129.4, 129.2 (2C), 129.0, 128.9 (2C), 128.7 (2C), 128.6 (4C), 128.5 (2C), 128.1, 127.3, 127.0 (2C), 126.5, 117.2, 81.7, 49.0. HRMS (FAB) calculated for $C_{32}H_{28}N_3O_2$ (MH^+) 486.2182, found 486.2176. IR (neat): 3061 (w), 1716 (s), 1670 (s), 1491 (m), 1420 (s), 1314 (m), 1281 (m), 754 (s), 692 (s), 588 (m).

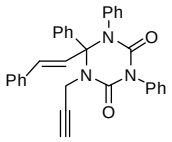


RCM product 11

Grubbs 2nd generation catalyst (22 mg, 0.026 mmol) was added to a solution of 10 (125 mg, 0.26 mmol) in CH_2Cl_2 (4.5 mL, dry) and this mixture was heated to reflux for 2 h. Then the solvent was removed by evaporation under reduced pressure. The crude product was purified by column chromatography (cyclohexane/EtOAc = 2:1) affording **11** (63 mg, 64%) as a grey solid. ^{1}H NMR

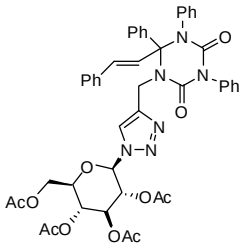
(250MHz, $CDCl_3$): 7.49-7.28 (m, 13H), 7.15-7.12 (m, 2H), 6.25 (d, *J* = 6.3 Hz, 1H), 5.83 (d, *J* = 6.3 Hz, 1H), 4.77 (d, *J* = 16.2 Hz, 1H), 4.53 (d, *J* = 16.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): 152.5, 150.6, 141.1, 137.5, 135.3, 130.2, 129.3 (2C), 129.0, 129.0 (4C), 128.7 (2C), 128.7 (2C), 128.3, 128.2, 127.8, 125.6 (2C), 84.7, 54.0. HRMS (FAB) calculated for $C_{24}H_{20}N_3O_2$ (MH^+) 382.1556, found 382.1560. IR (neat): 3067 (w), 2872 (w), 1717 (s), 1684 (s), 1443 (s), 1319 (m), 1194 (w), 760 (m), 731 (m), 694 (m). Melting point: 199.5-200.1 ºC (decomp.).

_N_-Propargyltriazinane dione 12



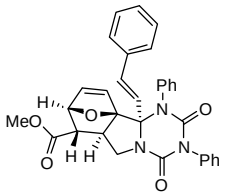
Following general procedure I, reaction between triazinane dione **1a** (500 mg, 1.12 mmol) and propargyl bromide (148 mg, 1.24 mmol) followed by column chromatography (cyclohexane/EtOAc = 2:1), afforded **12** (326 mg, 60%) as a yellow foam. ^{1}H NMR (250MHz, $CDCl_3$): 7.61-7.57 (m, 2H), 7.44-7.32 (m, 13H), 7.19-7.12 (m, 5H), 6.99 (d, *J* = 15.9 Hz, 1H), 6.82 (d, *J* = 16.0 Hz, 1H), 4.43 (dd, *J* = 17.5, 2.4 Hz, 1H), 3.96 (dd, *J* = 17.5, 2.4 Hz, 1H), 2.30 (t, *J* = 2.4 Hz, 1H). ^{13}C NMR (63 MHz, $CDCl_3$): 153.0, 152.6, 138.4, 137.5, 135.3, 135.1, 134.5, 129.7, 129.4 (HSQC), 129.2 (2C), 129.1, 129.0 (2C), 129.0 (HSQC), 128.9 (2C), 128.8 (2C), 128.8 (2C), 128.6 (2C), 128.3, 127.3, 127.2 (2C), 126.1, 81.7, 79.8, 72.0, 35.4. HRMS (FAB) calculated for $C_{32}H_{26}N_3O_2$ (MH^+) 484.2025, found 484.2032. IR (neat): 3287 (w), 3061 (w), 1713 (s), 1674 (s), 1491 (m), 1431 (s), 1310 (m), 1281 (m), 752 (s), 691 (s), 586 (m).

Triazole 14



12 (100 mg, 0.21 mmol) and **13** (78 mg, 0.21 mmol) were added to a mixture of H_2O/*t*-BuOH (1:1, 400µl:400µl). Sodium ascorbate (17 mg, 0.084 mmol) and $CuSO_4{\cdot}5H_2O$ (10 mg, 0.042 mmol) were added to the white suspension and this was stirred for 2.5 h. Then, acetonitrile (400 µl) was added and the mixture was stirred overnight. An additional batch of sodium ascorbate and $CuSO_4{\cdot}5H_2O$ were added to the clear yellow solution and the mixture was stirred for another 2 h. The reaction was worked up by adding H_2O (10 mL) and extraction with CH_2Cl_2 (2×20 mL). The combined organic fractions were dried (Na_2SO_4) and concentrated by evaporation of the solvent under reduced pressure. The crude product was purified by column chromatography (cyclohexane/EtOAc = 2:1, gradient) affording **14** (99 mg, 55%) as a light yellow sticky oil as a 1:1 mixture of dia-stereomers. Diastereomer a: ^{1}H NMR (400 MHz, $CDCl_3$): 8.00 (s, 1H), 7.62-7.60 (m, 2H), 7.44-7.28 (m, 12H), 7.21-7.13 (m, 4H), 7.08-7.06 (m, 2H), 6.89 (d, *J* = 16.0 Hz, 1H), 6.51 (d, *J* = 15.9 Hz, 1H), 5.83-5.81 (m, 1H), 5.46-5.43 (m, 2H), 5.28-5.23 (m, 1H), 4.91 (d, *J* = 15.2 Hz, 1H), 4.69 (d, *J* = 15.0 Hz, 1H), 4.32 (dd, *J* = 12.6, 4.5 Hz, 1H), 4.26-4.15 (m, 1H), 4.02-3.98 (m, 1H), 2.10 (s, 3H), 2.10 (s, 3H), 2.08 (s, 3H), 2.04 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): 170.4, 169.9, 169.1, 168.3, 153.2, 152.4, 144.8, 139.0, 138.1, 135.7, 135.3, 135.0, 129.6 (2C), 129.3, 129.1 (2C), 128.8, 128.7 (2C), 128.6 (4C), 128.4 (2C), 128.1, 128.1 (2C), 127.3, 127.1 (2C), 127.0, 123.2, 85.7, 81.7, 75.0, 72.5, 70.3, 67.5, 61.4, 41.0, 20.6, 20.4 (2C), 19.8. Diastereomer b: ^{1}H NMR (400 MHz, $CDCl_3$): 7.89 (s, 1H), 7.63-7.56 (m, 2H), 7.44-7.28 (m, 12H), 7.21-7.20 (m, 4H), 7.15-7.08 (m, 2H), 6.96 (d, *J* = 16.0 Hz, 1H), 6.60 (d, *J* = 16.0 Hz, 1H), 5.85-5.82 (m, 1H), 5.46-5.42 (m, 2H), 5.27-5.24 (m, 1H), 4.82 (d, *J* = 15.2 Hz, 1H), 4.69 (d, *J* = 15.1 Hz, 1H), 4.32 (dd, *J* = 12.7, 4.7 Hz, 1H), 4.17-4.13 (m, 1H), 4.01-3.97 (m, 1H), 2.09 (s, 3H), 2.09 (s, 3H), 2.08 (s, 3H), 2.05 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): 170.4, 169.8, 169.1, 168.6, 153.4, 152.4, 144.7, 138.5, 138.1, 135.3, 135.3, 135.0, 129.6 (2C), 129.4, 129.0 (2C), 128.8, 128.7 (2C), 128.7 (2C), 128.6 (2C), 128.5 (2C), 128.3 (2C), 128.1, 127.3, 127.1 (2C), 126.9, 122.7, 85.7, 81.8, 75.0, 72.6, 70.3, 67.5, 61.3, 41.0, 20.6, 20.4 (2C), 20.0. HRMS (FAB) calculated for $C_{46}H_{45}N_6O_{11}$ (MH^+) 857.3146, found 857.3146. IR (neat): 3350 (w), 3067 (w), 2967 (w), 2247 (w), 1713 (s), 1655 (s), 1493 (m), 1441 (s), 1304 (m), 1223 (m), 1186 (m), 909 (s), 727 (s), 692 (s), 646 (m), 690 (m), 519 (m).

Diels-Alder product 16a



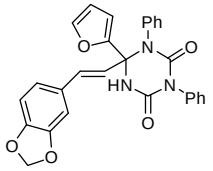
Following general procedure I, reaction between triazinane dione **1b** (250 mg, 0.57 mmol) and methyl *E*-4-bromo-2-butenoate (113 mg, 0.63 mmol) followed by column chromatography (cyclohexane /EtOAc = 2:1), afforded **16a** (144 mg, 47%) as a yellow

solid. **16a** was crystallized by slow evaporation of an EtOAc-solution. ^{1}H NMR (400MHz, $CDCl_3$): 7.51-7.32 (m, 12H), 7.26-7.23 (m, 3H), 6.98 (d, *J* = 15.7 Hz, 1H), 6.61 (d, *J* = 15.8 Hz, 1H), 6.10 (dd, *J* = 5.9, 1.6 Hz, 1H), 6.00 (d, *J* = 5.9 Hz, 1H), 5.33 (dd, *J* = 4.8, 1.6 Hz, 1H), 4.20 (dd, *J* = 11.3, 9.5 Hz, 1H), 3.75 (dd, *J* = 11.7, 7.3 Hz, 1H), 3.63 (s, 3H), 3.26 (dd, *J* = 4.8, 2.9 Hz, 1H), 2.61 (ddd, *J* = 9.4, 7.3, 2.9 Hz, 1H). ^{13}C NMR (101MHz, $CDCl_3$): 170.8, 152.7, 150.5, 136.3, 135.3, 134.7, 133.8, 133.2, 133.0 (2C), 129.3 (4C), 129.1 (3C), 128.8 (2C), 128.5, 128.2, 127.2 (3C), 132.2, 98.8, 80.4, 77.1, 52.9, 52.2, 50.2, 42.7. HRMS (FAB) calculated for $C_{32}H_{28}N_3O_5$ (MH^+) 534.2029, found 534.2031. IR (neat): 3013 (w), 1717 (s), 1676 (s), 1449 (s), 1319 (m), 1213 (m), 754 (m), 694 (m). Melting point: 194.9-195.4 ºC (decomp.).

Crystallographic Data for 16a

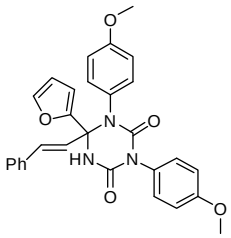
$C_{32}H_{27}N_3O_5$, Fw = 533.57, yellow plate, 0.36 x 0.36 x 0.12 mm^3, monoclinic, $P2_1/c$ (no. 14), a = 9.8195(1), b = 25.2307(3), c = 11.4069(2) Å, β = 112.6460(5)°, V = 2608.20(6) Å^3, Z = 4, D_x = 1.359 g/cm^3, μ = 0.09 mm^{-1}. 28707 Reflections were measured on a Nonius Kappa CCD diffractometer with rotating anode (graphite monochromator, λ = 0.71073 Å) up to a resolution of $(\sin\theta/\lambda)_{max}$ = 0.65 Å^{-1} at a temperature of 150 K. The reflections were corrected for absorption and scaled on the basis of multiple measured reflections with the program SORTAV[28] (0.95-0.99 correction range). 5961 Reflections were unique (R_{int} = 0.0497). The structure was solved with Direct Methods (program SHELXS-97[29]) and refined with SHELXL-97[29] against F^2 of all reflections. Non hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were located in difference Fourier maps. Methyl and phenyl hydrogen atoms were refined with a riding model; all other hydrogen atoms were refined freely with isotropic displacement parameters. 398 Parameters were refined with no restraints. R1/wR2 [I > 2σ(I)]: 0.0464/0.1247. R1/wR2 [all refl.]: 0.0716/0.1416. S = 1.085. The maximum residual electron density peak has a height of 0.84 e/Å^3 and a distance of 2.34 Å to the closest atom H33. Geometry calculations and checking for higher symmetry was performed with the PLATON program[30].

Triazinane dione 1c



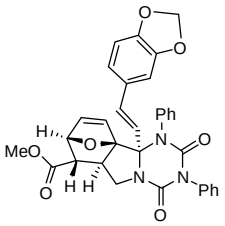
Triazinane dione **1c** was prepared by the method reported by Groenendaal *et al*.[9] Reaction between diethyl methyl-phosphonate (730 mg, 5.0 mmol), furonitrile (510 mg, 5.5 mmol), piperonal (826 mg, 5.5 mmol) and phenylisocyanate (1.31 g, 11.0 mmol), followed by column chromatography (cyclohexane/EtOAc 4:1) afforded **1c** (1.47 g, 61%) as a brown solid. ^{1}H NMR (250 MHz, $CDCl_3$): 7.52-7.51 (m, 1H), 7.45-7.27 (m, 8H), 7.52-7.13 (m, 2H), 6.83 (d, *J* = 15.9 Hz, 1H), 6.76 (s, 3H), 6.46 (dd, *J* = 3.4, 0.8 Hz, 1H), 6.40 (dd, *J* = 3.4, 1.9 Hz, 1H), 6.11 (d, *J* = 15.8 Hz, 1H), 6.10 (s, 1H), 5.97 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): 152.7, 152.0, 151.7, 148.4, 148.1, 143.5, 136.8, 134.8, 133.4, 129.9 (2C), 129.1, 129.1 (2C), 128.7 (4C), 128.2, 128.1, 123.3, 122.4, 110.7, 110.0, 108.4, 105.8, 101.3, 71.0. HRMS (FAB) calculated for $C_{28}H_{22}N_3O_5$ (MH^+) 480.1559, found 480.1562. IR (neat): 3160 (w), 3069 (w), 2899 (w), 1709 (s), 1667 (s), 1489 (m), 1444 (s), 1325 (m), 1251 (s), 1036 (s), 929 (m), 748 (m), 692 (s), 560 (s). Melting point: 205.8-206.4 ºC (decomp.).

Triazinane dione 1d



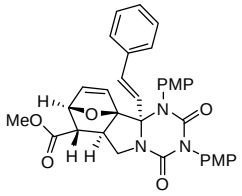
Triazinane dione **1d** was prepared by the method reported by Groenendaal *et al*.[9] Reaction between diethyl methyl-phosphonate (730 mg, 5.0 mmol), furonitrile (510 mg, 5.5 mmol), benzaldehyde (585 mg, 5.5 mmol) and *p*-methoxyphenyl isocyanate (1.64 g, 11.0 mmol), afforded **1d** (1.30 g, 52%) as a light brown solid. The crude product precipitated out of the reaction mixture after evaporation of half of the solvent and addition of water (10 mL). Subsequent washing of the crude product with cold Et_2O gave **1d** as a light brown solid. ^{1}H NMR (400 MHz, DMSO-d_6): 9.16 (s, 1H), 7.82 (dd, *J* = 1.6, 0.6 Hz, 1H), 7.46 (d, *J* = 7.2 Hz, 2H), 7.39-7.32 (m, 3H), 7.07 (d, *J* = 8.9 Hz, 2H), 7.01 (d, *J* = 8.8 Hz, 2H), 6.95 (d, *J* = 8.9 Hz, 2H), 6.85 (d, *J* = 15.9 Hz, 1H), 6.83 (d, *J* = 9.0 Hz, 2H), 6.56 (dd, *J* = 3.3, 0.8 Hz, 1H), 6.49 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.45 (d, *J* = 16.0 Hz, 1H), 3.77 (s, 3H), 3.70 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6): 158.9, 158.7, 152.7, 152.4, 152.1, 144.3, 135.6, 133.1, 131.6 (2C), 130.8 (2C), 130.2, 129.1 (2C), 129.0, 128.7, 127.4 (2C), 126.6, 114.1 (4C), 111.1, 110.6, 71.0, 55.6, 55.5. HRMS (FAB) calculated for $C_{29}H_{26}N_3O_5$ (MH^+)

496.1872, found 496.1868. IR (neat): 3215 (w), 3065 (w), 2905 (w), 1717 (s), 1670 (s), 1508 (s), 1437 (m), 1296 (m), 1240 (s), 1028 (m), 826 (m), 743 (m), 554 (m). Melting point: 195.6-196.3 ºC (decomp.).



Diels-Alder product 16b

Following general procedure I, reaction between triazinane dione **1c** (250 mg, 0.52 mmol) and methyl *E*-4-bromo-2-butenoate (140 mg, 0.78 mmol) followed by column chromatography (cyclohexane/ EtOAc = 2:1), afforded **16b** (150 mg, 81%, based on recovered starting material) as an orange solid. ^{1}H NMR (400MHz, $CDCl_3$): 7.47-7.29 (m, 8H), 7.23-7.20 (m, 2H), 6.98 (d, *J* = 1.5 Hz, 1H), 6.93 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.86 (d, *J* = 16.1 Hz, 1H), 6.84 (d, *J* = 7.7 Hz, 1H), 6.41 (d, *J* = 15.6 Hz, 1H), 6.09 (dd, *J* = 5.9, 1.6 Hz, 1H), 6.02 (s, 2H), 5.97 (d, *J* = 5.9 Hz, 1H), 5.32 (dd, *J* = 4.8, 1.5 Hz, 1H), 4.16 (dd, *J* = 11.3, 9.6 Hz, 1H), 3.72 (dd, *J* = 11.5, 7.4 Hz, 1H), 3.62 (s, 3H), 3.25 (dd, *J* = 4.8, 2.9 Hz, 1H), 2.58 (ddd, *J* = 9.8, 7.3, 2.8 Hz, 1H). ^{13}C NMR (101MHz, $CDCl_3$): 170.7, 152.6, 150.4, 148.6, 148.3, 136.2, 135.2, 133.7, 133.1, 132.4 (2C), 129.2 (4C), 128.9, 128.7 (4C), 128.4, 128.0, 122.6, 121.1, 108.6, 105.8, 101.4, 98.4, 80.2, 52.8, 52.0, 50.0, 42.6. HRMS (FAB) calculated for $C_{33}H_{28}N_3O_7$ (MH^+) 578.1972, found 578.1932. IR (neat): 2955 (w), 2899 (w), 1713 (s), 1676 (s), 1449 (s), 1319 (m), 1254 (m), 1036 (m), 912 (m), 760 (m), 729 (m), 696 (m). Melting point: 161.8-162.5 ºC (decomp.).



Diels-Alder product 16c

Following general procedure I, reaction between triazinane dione **1d** (250 mg, 0.50 mmol) and methyl *E*-4-bromo-2-butenoate (135 mg, 0.76 mmol) followed by column chromatography (cyclohexane/EtOAc = 2:1), afforded **16c** (125 mg, 67%, based on recovered starting material) as a white solid. ^{1}H NMR (400MHz, $CDCl_3$): 7.47-7.37 (m, 6H), 7.13 (d, *J* = 8.9 Hz, 2H), 6.93 (d, *J* = 15.8 Hz, 1H), 6.88 (d, *J* = 9.0 Hz, 2H), 6.58 (d, *J* = 15.7 Hz, 1H), 6.11 (dd, *J* = 5.9, 1.6 Hz, 1H), 5.99 (d, *J* = 5.9 Hz, 1H), 5.33 (dd, *J* = 4.9, 1.6 Hz, 1H), 4.17 (dd, *J* = 11.2, 9.5 Hz, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 3.73 (dd, *J* = 11.3, 7.5 Hz, 1H), 3.62 (s, 3H), 3.25 (dd, *J* = 4.8, 2.9 Hz, 1H), 2.56 (ddd, *J* = 9.5, 7.2, 2.8 Hz, 1H). ^{13}C NMR (101MHz, $CDCl_3$): 170.7, 159.2, 159.0, 153.0, 150.7, 134.7, 133.8, 133.1, 132.7 (2C), 130.1 (3C), 129.2, 128.9 (3C), 128.8, 127.9, 127.1 (3C), 123.1, 114.0 (2C), 113.5 (2C), 98.4, 80.2, 55.3, 52.8, 52.0, 50.2, 42.4. HRMS (FAB) calculated for $C_{34}H_{32}N_3O_7$ (MH^+) 594.2240, found 594.2242. IR (neat): 2955 (w), 2837 (w), 1713 (s), 1676 (s), 1510 (s), 1456 (s), 1296 (m), 1248 (s), 1169 (m), 1032 (m), 829 (m), 731 (m). Melting point: 198.7-199.3 ºC (decomp.).

4.5 References and notes

1. Arve, L.; Voigt, T.; Waldmann, H. *QSAR Comb. Sci*. **2006**, *25*, 449-456.
2. Newman, D. J.; Cragg G. M. *J. Nat. Prod.* **2007**, *70*, 461-477.
3. Dobson, C. M. *Nature* **2004**, *432*, 824-828.
4. Clardy, J.; Walsh, C. *Nature* **2004**, *432*, 829-837.
5. Burke, M. D.; Schreiber S. L. *Angew. Chem. Int. Ed.* **2004**, *43*, 46-58.
6. Dömling A. *Chem. Rev.* **2006**, *106*, 17-89.
7. Zhu, J. *Eur. J .Org. Chem.* **2003**, 1133-1144.
8. Orru, R. V. A.; De Greef, M. *Synthesis* **2003**, 1471-1499.
9. Groenendaal, B.; Vugts, D. J.; Schmitz, R. F.; De Kanter, F. J. J.; Ruijter, E.; Groen, M. B; Orru, R. V. A. *J. Org. Chem.* **2008**, *73*, 719-722.
10. Vugts, D. J.; Jansen, H.; Schmitz, R. F; De Kanter, F. J. J.; Orru, R. V. A. *Chem. Comm.* **2003**, 2594-2595.
11. Vugts, D. J.; Koningstein, M. M.; Schmitz, R. F.; De Kanter, F. J. J.; Groen, M. B.; Orru, R. V. A. *Chem. Eur. J.* **2006**, *12*, 7178-7189.
12. Grubbs, R. H. *Angew. Chem. Int. Ed.* **2006**, *45*, 3760-3765.
13. Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed.* **2005**, *44*, 4490-4527.
14. Hoveyda, A. H.; Zhugralin, A. R. *Nature* **2007**, *450*, 243-251.

15. Dedola, S.; Nepogodiev, S. A.; Field, R. A. *Org. Biomol. Chem.* **2007**, *5*, 1006.
16. Gil, M. V.; Arévalo, M. J.; López, Ó. *Synthesis* **2007**, 1589-1620.
17. For an excellent review on furan-based Diels-Alder chemistry, see: Kappe, C. O.; Murphree, S. S.; Padwa, A. *Tetrahedron* **1997**, *53*, 14179-14233.
18. Ugi, I.; Meyr, R.; Fetzer, U.; Steinbrückner, C. *Angew. Chem.* **1959**, *71*, 386.
19. Passerini, M. *Gazz. Chim. Ital*. **1921**, *51*, 126-129.
20. Banfi, L.; Riva, R. *Organic Reactions*, **2005**, *65*, 1-140.
21. Scholl, M.; Ding, S.; Lee, C.W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953-956.
22. Wilkinson, B. L.; Bornaghi, L. F.; Poulsen, S. A.; Houston, T. A. *Tetrahedron* **2006**, *62*, 8115-8125.
23. Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2001**, *40*, 2004-2021.
24. Tornoe, C. W.; Christensen C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057-3064.
25. For example, see: Baraldi, P. G.; Fruttarolo, F.; Tabrizi, M. A.; Romagnoli, R.; Preti, D. *Expert Opin. Drug Discovery*, **2007**, *2*, 1161-1183.
26. For example, see: Mathé, C.; Gosselin, G. *Antivir. Res.* **2006**, *71*, 276-281.
27. Fokas, D.; Patterson, J. E.; Slobodkin G.; Baldino, C. M. *Tetrahedron Lett.* **2003**, *44*, 5137-5140.
28. Blessing, R. H. *J. Appl. Crystallogr.* **1997**, *30*, 421-426.
29. Sheldrick, G. M. *Acta Crystallogr., Sect. A* **2008**, *64*, 112-122.
30. Spek, A. L. *J. Appl. Crystallogr.* **2003**, *36*, 7-13.

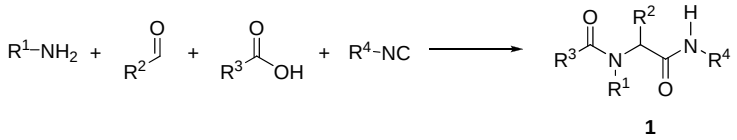
Chapter 5

Mechanistic Studies toward a Stereoselective Ugi Reaction

5.1 Introduction

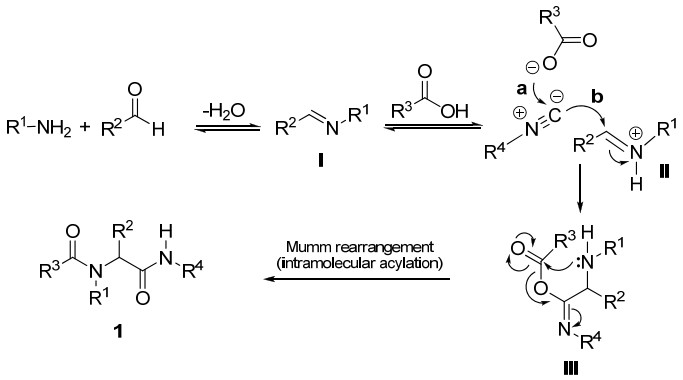
5.1.1 Ugi reaction

The Ugi four component reaction (U-4CR) was first described by I. Ugi *et al*. in 1959.[1] It is one of the most widely studied MCRs.[2-4] The reason for this is the combination of the high degree of molecular diversity introduced, and the substantial increase in structural complexity gained in this reaction. This makes the Ugi reaction extremely well-suited for the construction of focused libraries of peptide-like compounds, which are relevant for pharmaceutical applications.



Scheme 1: General Ugi reaction.

In the U-4CR, primary or secondary amines, aldehydes or ketones, carboxylic acids and isonitriles react to form α-aminoamides **1** (Scheme 1). Even after almost 50 years, the exact reaction mechanism of the U-4CR still remains unclear. There are two possible pathways: a direct mechanism (Scheme 2) and a stepwise mechanism (Scheme 3).[5,6] In both pathways the first step is a condensation of the carbonyl component with the amine to form the imine (**I**). Upon addition of the carboxylic acid, a proton transfer from the carboxylic acid to the imine will occur, giving the iminium ion **II**. This increases the electrophilicity of the original imine dramatically. In the direct mechanism there are now three possibilities: (i) steps **a** and **b** occur simultaneously. Addition of the carboxylate anion to the empty p-orbital of the isocyanide carbon (step **a**) and simultaneous attack of the filled s-orbital of the isocyanide carbon on the activated imine (step **b**) result in the α-adduct **III** (Scheme 2). (ii) First step **a** occurs and then step **b** or (iii) first step **b** occurs and then step **a** (Scheme 2).

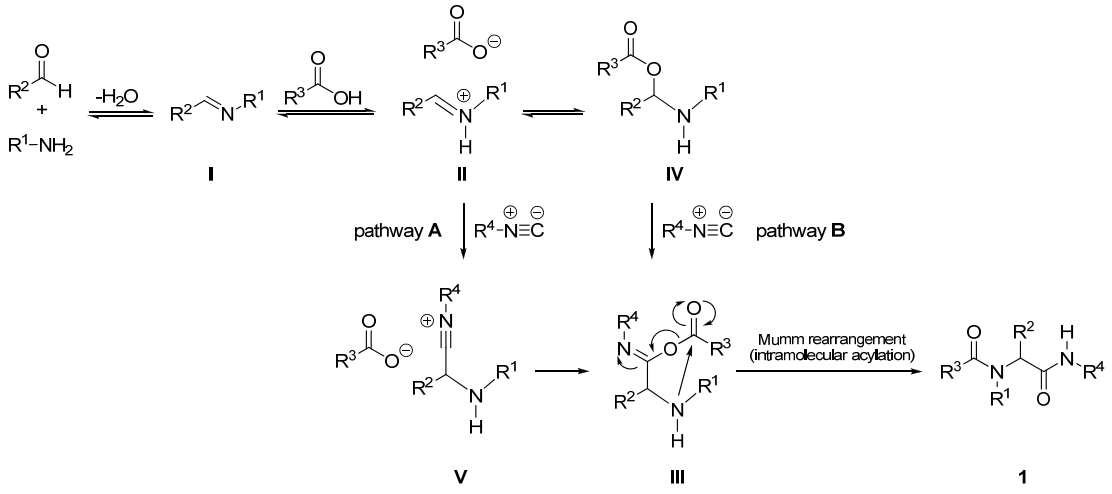


Scheme 2: Direct reaction mechanism for the U-4CR.

In the stepwise mechanism (Scheme 3), the protonated imine **II** is in equilibrium with reactive intermediate **IV**, which can be formed by nucleophilic attack of the carboxylate to the

iminium carbon. These intermediates are in mobile equilibrium with the starting materials. Two different pathways (**A** and **B**) can now lead to the formation of α-adduct **III**. Pathway **A** proceeds via a two-step addition of the isocyanide to the imminium ion **II**, and involves formation of the nitrilium ion **V**. Also a direct addition of the isocyanide to intermediate **IV** can be imagined (pathway **B**). In the latter pathway (**B**), the isocyanide carbon atom itself may insert in the C-O bond of **IV** or the isocyanide reacts with **IV** as an oriented ion pair (Scheme 3).[5]

In both the concerted and the stepwise mechanism the α-adduct **III** is formed, which is an O-acyl isoamide that can be regarded as an activated acid moiety. Therefore acyl transfer to the nucleophilic secondary amine can take place to give the final Ugi product (**1**). This type of intramolecular acylation was first described by O. Mumm in 1910, and is therefore called the Mumm rearrangement.[7]



Scheme 3: Stepwise reaction mechanism for the U-4CR.

Not many reports have appeared in literature that study in detail the reaction mechanism of the U-4CR. The concerted mechanism as proposed in Scheme 2 is in clear analogy to the mechanism of the Passerini reaction (P-3CR). In this reaction a carboxylic acid, an isonitrile and an aldehyde or ketone are combined.[8] No amine component is introduced and the oxo input serves as the electrophile. The use of a chiral isocyanide led to excellent *de*'s for the P-3CR but not for the U-4CR.[9] Also the U-4CR runs better in polar solvents like methanol whereas the P-3CR is faster in apolar solvents like dichloromethane and diethylether. This suggests that both reactions proceed via totally different mechanisms.[6] A study using (*S*)-α-methyl-benzylamine as chiral auxiliary revealed two competing mechanisms based on pathway B of the stepwise mechanism (Scheme 3) since products with opposite stereoselectivity were obtained.[10,11] The difference between both mechanisms lies in the fact that the iminium ion **II** is attacked by the carboxylate anion from either the top or the bottom side, giving opposite isomers of intermediate **IV**. Substitution by the isonitrile with inversion of configuration then leads to the same product but with opposite stereochemistry.[10] Thus the results reported in literature which are mentioned here are not very conclusive about the exact mechanism.

5.1.2 Stereoselective Ugi-reaction

In the Ugi reaction one chiral center is formed. Although many studies describe the formation of optically enriched α-aminoamides **1** via stereoselective U-4CRs, no general asymmetric procedure is available and mixtures of stereoisomers are often obtained. To achieve stereo induction in the U-4CR, three different approaches can be imagined. In one approach chiral starting materials are employed. This approach is also named the diastereoselective approach. To arrive at an asymmetric U-4CR optically pure amines, aldehydes, carboxylic acids and isonitriles have been examined as chiral inputs.[12] The use of chiral isonitriles did not lead to any diastereoselectivity.[9] The results obtained using optically active aldehydes were also disappointing, since no diastereoselectivity was observed.[13] Also, when optically active carboxylic acids were used in the U-4CR the final products were obtained as a 1:1 mixture of diastereomers. However in most cases the separation of compounds was achieved by selective crystallization or flash chromatography.[14] Chiral amines proved the most successful inputs. The use of different α-chiral benzylic amines (**2ab**, Figure 1) led to the formation of Ugi products in excellent diastereoselectivity (*de* up to 98%), depending on the amine used.[15-18] Amines **2a** and **2b** can also be regarded as auxiliaries because they can be removed by catalytic hydrogenation.[6]

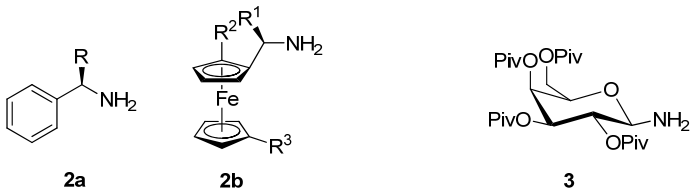


Figure 1: Chiral amines used in the U-4CR.

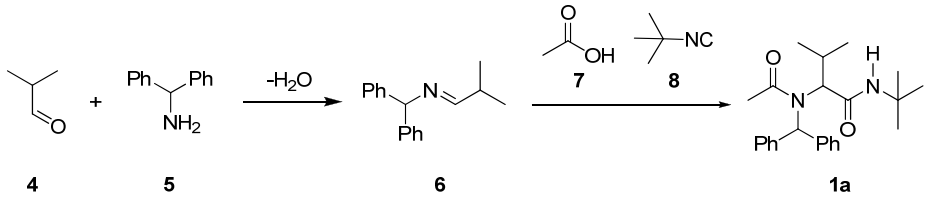
The second approach is the use of chiral auxiliaries. The optically active side groups are introduced to one of the starting materials prior to the Ugi reaction. After the reaction these auxiliaries have to be removed from the product. This makes this approach much less atom efficient and less suitable for application for library synthesis. An example is the use of galactopyranosyl amine derivative **3** (Figure 1) in the presence of $ZnCl_2$ reported by Kunz.[19] The *de*'s were around 90% in all of the reported cases.

Finally, the use of chiral catalysts can be considered. In this way the enantioselective formation of α-aminoamides **1** should be possible. To date no catalytic enantioselective methods for the U-4CR have been reported. The design of a suitable catalyst for an enantioselective U-4CR critically depends on our understanding of the exact reaction mechanism. As discussed above, the mechanism is still under debate. Therefore, we set out a thorough study of critical reaction parameters and studied the influence of solvent, temperature, and acid concentration on the performance of the U-4CR. This should lead to the selection of optimal conditions for a screening of potential asymmetric catalysts.

5.2 Results and discussion

5.2.1 Mechanistic study

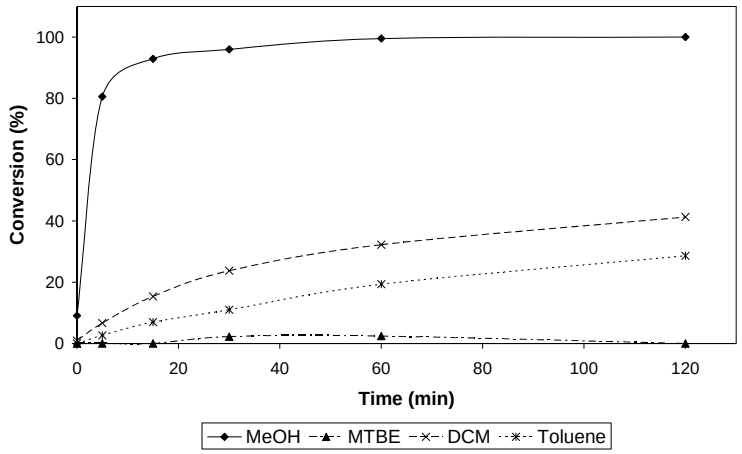
The reaction between isobutyraldehyde (**4**), benzhydrylamine (**5**), acetic acid (**7**) and *tert*-butylisocyanide (**8**) was chosen as the model reaction for this study (Scheme 4). In all reaction pathways that are considered reasonable the initial formation of an imine (**I**, scheme 2 and 3) is involved. Therefore, in all reactions the preformed imine **6** was used as the initial input. Imine **6**, acetic acid **7** and *tert*-butylisocyanide **8** were used in a 1:1:1 molar ratio, in a 66 mM concentration with respect to the imine. In all ractions 4-nitrobiphenyl was used as and internal standard to facilitate HPLC analysis.



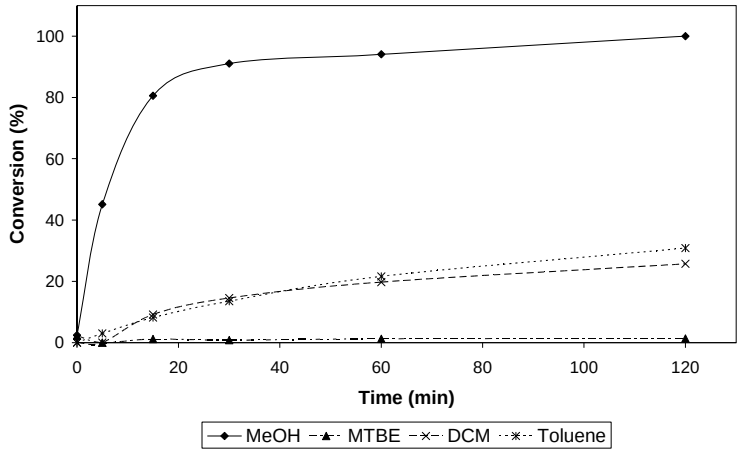
Scheme 4: Model reaction.

5.2.1.1 Solvent and temperature

First, the influence of the temperature was investigated in different solvents. For this, the U-4CR was performed in four different solvents (methanol, dichloromethane, toluene and methyl *tert*-butylether) at four different temperatures (-20°C, -5°C, 10°C and 25°C). Product formation was monitored in time by HPLC analysis. From all data obtained, only the graphs for -5°C and 25°C are shown (See graph 1 and 2).



Graph 1: Product formation at -5ºC.



Graph 2: Product formation at 25ºC.

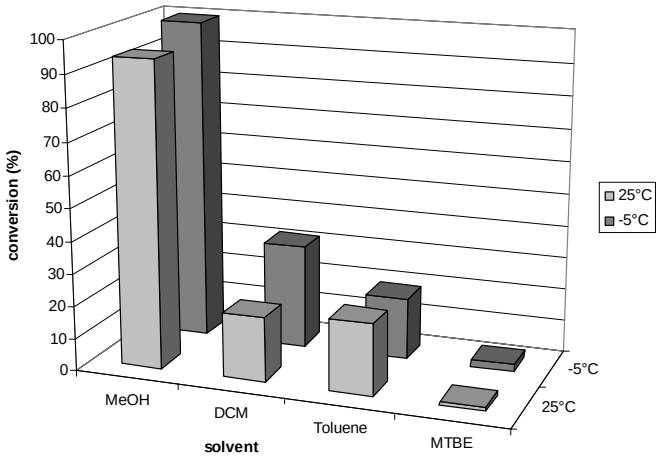


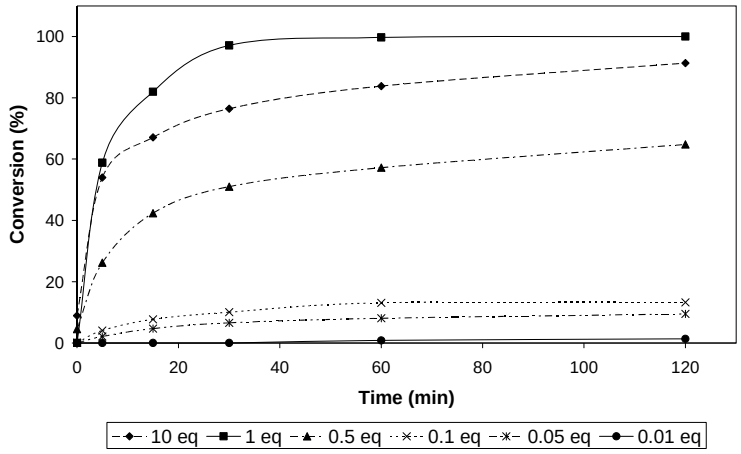
Figure 2: Conversion after 60 min. at -5ºC and 25ºC .

In Figure 2, the conversions after 60 minutes at -5ºC and 25ºC in the different solvents are depicted. As can be seen, the best conversion at -5ºC is obtained in the polar protic solvent methanol followed by dichloromethane and non-polar toluene. In MTBE the conversion is only minimal. The same trend can be seen at 25ºC but conversion in toluene is some what higher than in dichloromethane at this temperature.

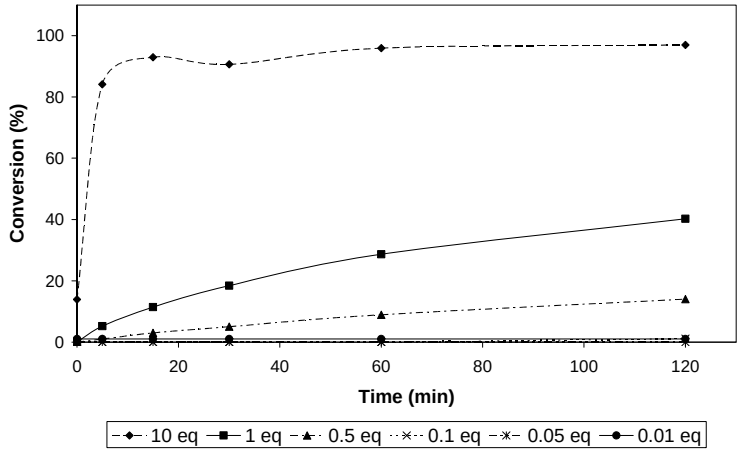
Remarkable is that the reaction proceeds faster at lower temperatures in MeOH. This effect is known for aqueous media in MCR chemistry where the relatively apolar reactants are surrounded by water and aggregate.[20] This causes regions where the concentration of reactants is higher, with reaction acceleration as a result. A similar effect may play a role here using methanol as a quite polar solvent. At lower temperatures the inputs of the U-4CR stay better coagulated. For effective asymmetric induction, the U-4CR should not run too fast in a certain solvent. If the uncatalyzed (background) reaction is running fast it will be difficult to run the catalyzed reaction with high enantioselectivity. Dichloromethane and toluene seem therefore reasonable solvents to use at a temperature of -5°C. Another reason to perform the reaction at -5°C is that at a lower temperatures the transition state for the enantioselective reaction is lowered which may result in a higher *ee*.[21]

5.2.1.2 Acid concentration

It should become clear, from the mechanism, at which stage in the U-4CR (asymmetric) catalysis may be possible. In both proposed mechanisms (Scheme 2 and 3) protonation of the imine seems important. Therefore, the influence of the acid concentration on the reaction was studied to explore options for an acid-catalyzed Ugi reaction. The standard reaction as described above was performed in dichloromethane and methanol at different [H^+]. In these experiments, the concentration of H^+ was varied but the amount of carboxylate was held constant at 1.0 equivalent. In order to reach full conversion a stoichiometric amount of acetate is needed. Therefore, at acid concentrations below 66 mM, additional sodium acetate was added to allow the reaction to complete conversion (see graph 3 and 4). As can be seen from graph 3 the reaction stops at a conversion that corresponds to the amount of H^+ added, and thus does not run to completion. It should be noted that NaOAc is (very) poorly soluble in DCM (graph 4).



Graph 3: Product formation in MeOH at -5ºC with different acid concentrations.



Graph 4: Product formation in DCM at -5ºC with different acid concentrations.

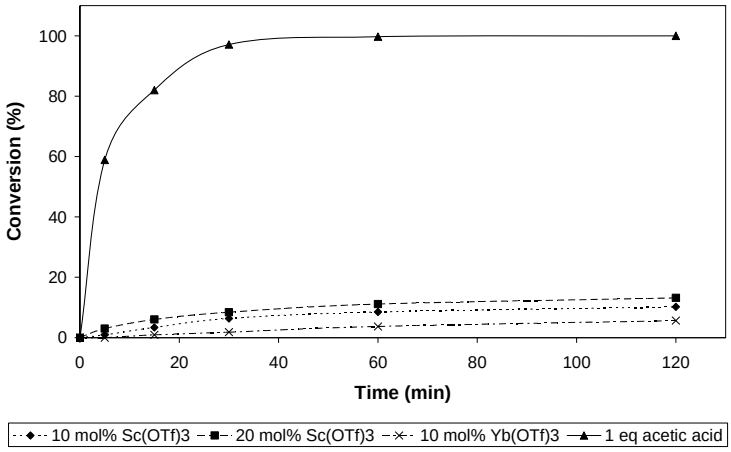
From these experiments it was concluded that the α-aminoamide **1a** can not be formed in this reaction by using a catalytic amount of acid, in the presence of stoichiometric acetate anion. A proton is essential for the formation of the product. When all available protons are consumed, the reaction stops. Therefore, we considered the addition of an additional external proton donor, that can protonate the product upon formation. The proton donor should not protonate (activate) the initially formed imine, but merely should protonate the final product.
Ammonium chloride has been used as a proton donor in the U-4CR.[22] In this study, ammonium acetate was chosen as the proton donor, because it bears an acidic proton on the ammonium ion and at the same time the acetate anion that is needed for reaction. This procedure was only investigated in methanol because of the insolubility of ammonium acetate in both dichloromethane and toluene. We first performed the standard reaction in the presence of only ammonium acetate and no additional acid, however, formation of **1a** was observed within 2 hours. Thus the ammonium ion is apparently acidic enough to protonate and thus activate the imine.

5.2.2 Lewis acids

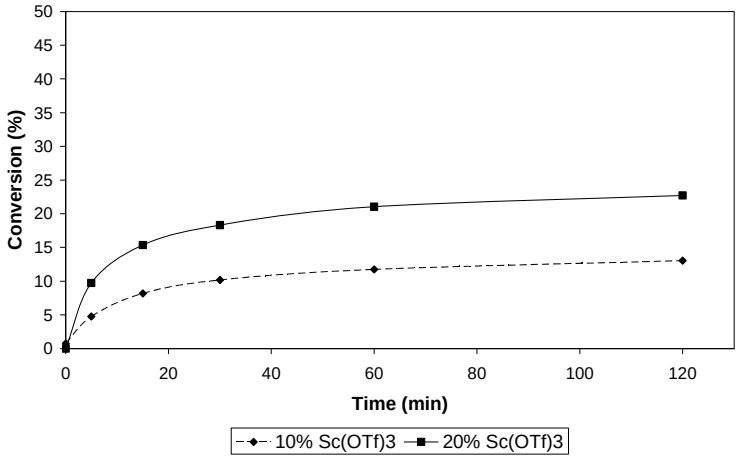
We now turned our attention to procedures that completely avoid the use of free H^+. However, activation of the imine **6** is essential for the formation of **1a** as was shown above and in literature.[23]

5.2.2.1 Water stable Lewis acids

It is known from literature that certain Lewis acids can activate imines, but a problem is that they are often water sensitive.[24] As in the Ugi reaction imine formation occurs with formation of 1 equiv. of water, the use of such sensitive Lewis acids is not efficient. Moreover, the use of sensitive Lewis acids would make the Ugi reaction much less suitable for combinatorial applications. However, rare earth metal Lewis acids based on Sc(III) or Yb(III) have been reported to be quite stable in aqueous environments.[25] Therefore, we decided to investigate formation of **1a** in the model reaction by using water stable Lewis acids in the presence of 1 equivalent sodium acetate in MeOH. We reasoned that the protic solvent MeOH should be able to deliver the proton required to complete the formation of **1a** after the final Mumm rearrangement. The results of using different molar % of scandium trifluoromethanesulfonate ($Sc(OTf)_3$) and ytterbium trifluoromethanesolfonate ($Yb(OTf)_3$) are depicted in graph 5 and 6. Both Lewis acids are able to activate the imine and formation of product **1a** was indeed observed. However, from graph 5 it becomes clear that the use of scandium triflate results in higher conversions towards **1a** than the reaction using ytterbium triflate. In both cases the reaction rate is much lower in comparison to the reaction using acetic acid, and in all cases the reaction does not reach completion.



Graph 5: Product formation in MeOH at -5ºC with $Sc(OTf)_3$ and $Yb(OTf)_3$.



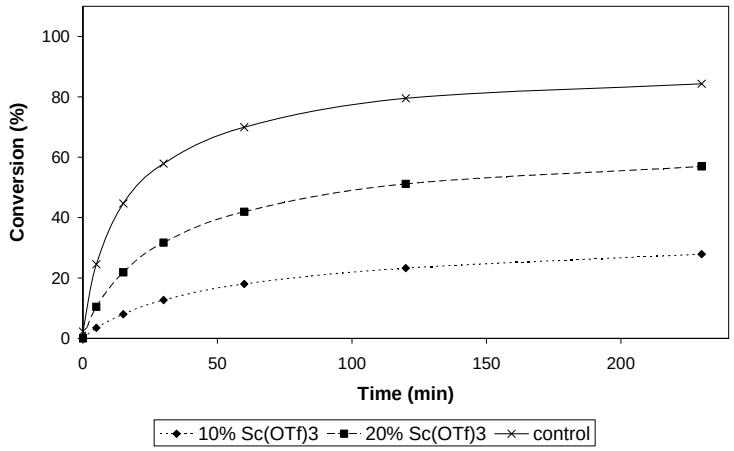
Graph 6: Product formation in MeOH at 20ºC with $Sc(OTf)_3$.

When the reaction was performed at 20°C, the conversion to **1a** levels at the mol percentage of scandium triflate that was added. This suggests that a 1:1 ratio of Lewis acid and imine **6** is required to proceed to complete formation of **1a**. However, when a stoichiometric amount of scandium triflate was used not the desired Ugi product **1a** but a product with a mass of M^+=353 was formed. This corresponds to the mass of **10** (scheme 5), which is a known side product in Ugi reactions, where methanol acts as the nucleophile instead of the carboxylate anion.[26] Under these conditions, **10** was formed in 10%, the rest was unreacted starting material.

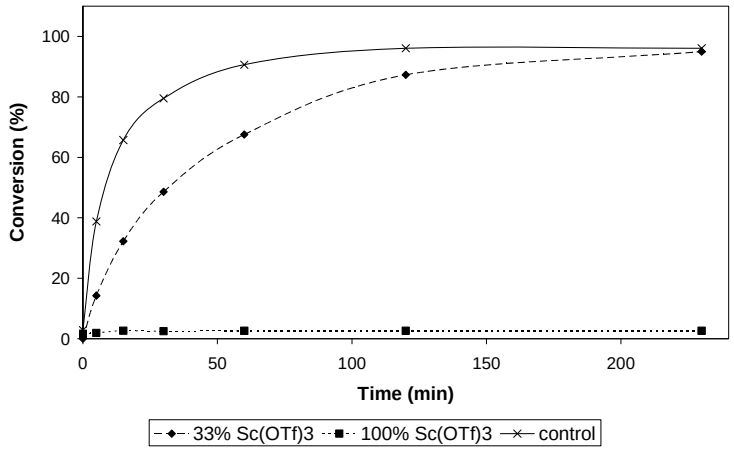
Scheme 5: Side reaction with MeOH as the nucleophile.

5.2.2.2 Scandium triflate in trifluoroethanol

A protic solvent that is both much less nucleophilic than methanol and a better proton donor may be trifluoroethanol (TFE). This solvent has been frequently applied in U-4CRs.[23]
When the reaction of **6** with **7** and **8** was performed in TFE at 20ºC under otherwise similar conditions as described above in the presence of $Sc(OTf)_3$, HPLC-analysis indeed showed considerable conversion to the desired α-aminoamide **1a**. In order to compare the results obtained using trifluoroethanol as the solvent with those obtained in MeOH, the experiments in the presence of 10 and 20 % scandium triflate were repeated in trifluoroethanol at -5°C. The results are shown in graph 7.



Graph 7: Product formation in TFE at -5ºC with $Sc(OTf)_3$.



Graph 8: Product formation in TFE at -5ºC with $Sc(OTf)_3$.

The reaction proceeds faster in TFE and shows better conversions compared to the reactions performed in MeOH. With 10 mol% of $Sc(OTf)_3$ the conversion to **1a** at -5ºC in MeOH is 10% (graph 5) while in TFE 28% (Graph 7) of the starting material is converted to **1a**. With 20 mol% of $Sc(OTf)_3$ the conversion to **1a** at -5ºC in MeOH is 13% (graph 5) while in TFE 57% (Graph 7) of the starting material is converted to **1a**. The higher acidity of

trifluoroethanol (pK_a = 11.4) compared to methanol (pK_a = 15.5) may account for this. The protic solvents act as a proton donor till an equilibrium is reached between the solvent and the product. Because of the higher acidity of trifluoroethanol, more product can be formed before the equilibrium is reached.
However, using 100 % scandium triflate in TFE only a trace amount of product **1a** is formed (Graph 8). A stoichiometric amount of scandium triflate apparently blocks reaction, but the reason for this is still unclear. The product analogous to **10**, which was formed when using a stoichiometric amount of scandium triflate in methanol, was not observed when using trifluoroethanol, most likely due to the reduced nucleophilicity of TFE compared to MeOH.
Graph 7 shows that the reaction using 10 % scandium triflate stops at the formation of 28 % of **1a**, and the reaction using 20 % scandium triflate stops at 57% conversion. We reasoned that when using 33 % scandium triflate (conversion is three times the catalyst loading) the reaction could run to completion and indeed **1a** was formed in 95% which is the same as the control experiment (Graph 8). In the control experiment, acetic acid is used in stead of Lewis acid and sodium acetate.

If we now consider the three possible reaction mechanisms mentioned in the introduction and compare our results with the proposed mechanisms we can conclude that all three mechanisms are in principle possible. This is because in all three cases the imine (**I**) that is formed in the first step (Scheme 2 and 3) requires activation before any further reaction can occur. As we have shown, this activation can either be achieved using a Brønsted acid or a Lewis acid. When using Brønsted acid, the reaction stops when all H^+ is consumed so the imine can no longer be activated. Maximum conversion can be achieved by using 33 mol% of $Sc(OTf)_3$. Initially it was presumed that the three triflate groups of the $Sc(OTf)_3$ were all substituted by an imine molecule thus explaining why maximum conversion could be achieved with 33 mol% $Sc(OTf)_3$. But when using 100 mol% $Sc(OTf)_3$ no reaction was observed.

5.2.3 Chiral scandium complexes

In summary, the Ugi-type reaction of **6**, **7** and **8** to give product **1a** can be forced to completion using a substoichiometric amount (33 %) of scandium triflate in TFE at -5ºC. At this temperature the reaction is relatively slow, which makes these conditions good starting point to screen for asymmetric catalysts. The influence of chiral ligands in the presence of scandium triflate for chiral induction was tested. For this the Sc(III) Lewis acid is complexed in situ to the chiral ligand to generate a chiral Lewis acid complex.[27,28]
Three ligands were chosen for initial experiments (Figure 2). Pybox **11** in combination with Cu(II) gave reasonable chiral induction in the Passerini reaction.[29] Binap **12** is widely applied in transition metal catalysis and is used in various types of enantioselective reactions involving imines like aza-Diels-Alder[30] and Mannich-type[31] reactions. The ferrocene ligand **13** in combination with Au(I) was used before in addition reactions of isocyanoacetates to sulfonylimines yielding 2-imidazolines.[32]

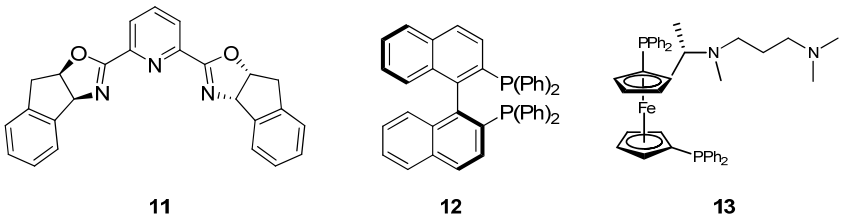
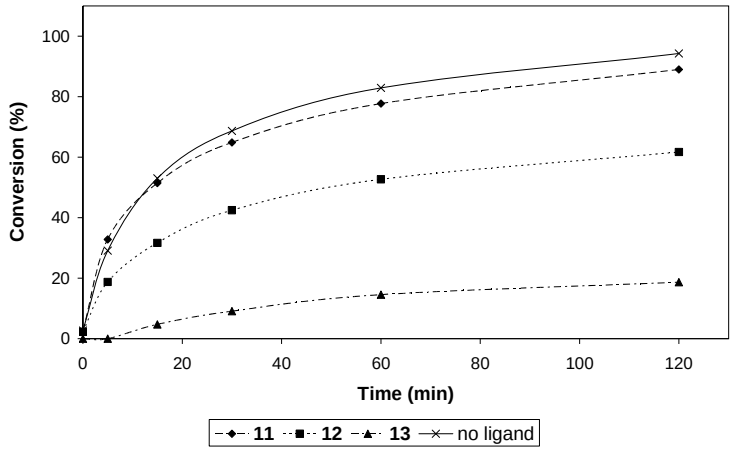


Figure 2: Tested chiral ligands.

For each reaction, one of the ligands (**11**, **12** or **13**) was combined with $Sc(OTf)_3$ in a 1:1 ratio and precomplexed by stirring for 10 minutes at -5ºC in TFE. Then, imine **6** was added, followed by **7** and **8**. Formation of **1a** was followed in time.



Graph 9: Product formation in TFE at -5ºC with 33% $Sc(OTf)_3$ and chiral ligands **11**-**13**.

Formation of **1a** in the presence of $Sc(OTf)_3$ and chiral ligands is slower compared to reactions with only $Sc(OTf)_3$. This effect is most pronounced for the reactions using **11** and **13**. Direct determination of the *ee* of the α-aminoamide **1a** from the reaction mixture by means of chiral HPLC would be most convenient. In this way *ee*'s could be followed in time. However, chiral separation of the enantiomers of **1a** proved sluggish. The ligand systems showed comparable retention times to **1a** on a Chiracel OD-H column. Therefore, we decided to work up the reaction and isolate the product (after 2h) before chiral analysis. The enantiomers of the isolated product could be efficiently separated with chiral HPLC and results are summarized in table 1. As a consequence, only *ee* data at t=120 min. could be obtained and the *ee* vs. time data are not available. The results in table 1 show that in dichloromethane, as expected, no product is formed (entries 4 and 5). Also no product was isolated using trifluoroethanol, scandium triflate and the ligand **13** (entry 3). Only trace amounts of **1a** were detected after 120 min. However, some chiral induction was observed when the reaction was performed in trifluoroethanol in the presence of 33% scandium triflate and either Pybox (**11**) or Binap (**12**) as ligand. Although not high, the *ee*'s are reproducable and since stereoselectivity of any kind using chiral catalysts has not been reported for the Ugi reaction the results are promising. A recent report described complexation times of 1-2 h at

40ºC for scandium triflate and Pybox.[33] Therefore, some experiments (entry 1 and 2) were repeated with longer complexation time (1h at 40ºC), however, conversion did not increase and *ee*'s were not determined.

Table 1: Results with chiral $Sc(OTf)_3$/ligand complexes.

Entry	Solvent	Ligand	Yield (%)[a]	*ee*
1	TFE	**11**	45	10
2	TFE	**12**	60	8
3	TFE	**13**	-	-
4	DCM	**11**	-	-
5	DCM	**12**	-	-

[a] Based on isolated yield corrected for samples taken from the reaction mixture.

After this initial ligand screen, we decided to apply another class of chiral ligands, the BINOL ligands. These ligands can coordinate efficiently to $Sc(OTf)_3$[24] and the ligands (**14-17**) that were screened for potential asymmetric catalysis are depicted in Figure 3.

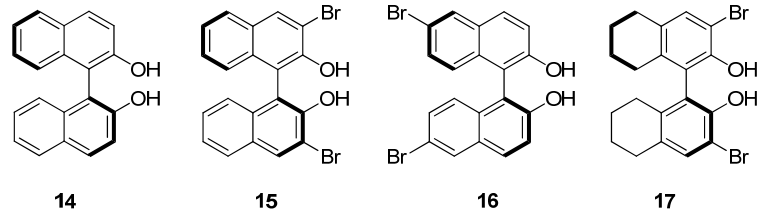


Figure 3: BINOL ligands.

When using BINOL ligands **14-17** with scandium triflate for asymmetric catalysis, a co-catalyst (*N*-methylpiperidine) was used to generate the chiral ligand-complex.[34]
Thus, an initial screening of the BINOL ligands **14-17** in combination with *N*-methylpiperidine and $Sc(OTf)_3$ was conducted. The standard reactions were performed in a 1:1 mixture of dichloromethane and trifluoroethanol due to solubility problems. As for the chiral ligands **11-13**, first the chiral complex was formed by stirring a mixture of BINOL ligand, *N*-methylpiperidine and scandium triflate for 1.5 hours at room temperature. Next, the mixture was cooled to -5ºC and the imine **6** was added. Sodium acetate was added after 30 minutes and after an additional 5 minutes the isocyanide **8**. The reactions were monitored in time with chiral HPLC. Unfortunately in all cases no product formation was observed at all.

5.3 Conclusions

In methanol the Ugi reaction proceeds too fast to study any catalysis. From a solvent/temperature screening, dichloromethane and toluene at -5 °C seemed reasonable conditions to study chiral catalysis. It was also found that the reaction can be accelerated using methanol at low temperatures, and that the reaction does not reach completion using a catalytic amount of acetic acid in the presence of 1 equivalent acetate.
Scandium triflate in combination with 1 equivalent sodium acetate was found to be a good Lewis acid for activation of the imine. Using a substoichiometric amount of 33% $Sc(OTf)_3$ in

trifluoroethanol, the reaction can be driven to completion. In trifluoroethanol the reaction proceeds faster in comparison to methanol because of the lower pK_a. In dichloromethane no product is formed.
Initial tests using $Sc(OTf)_3$ in combination with chiral ligands yielded a maximum *ee* of 10% in a reasonable yield (45-60%).

5.4 Experimental section

General information

Unless stated otherwise, all reagents were obtained from commercial suppliers and used without further purification. All solvents were used directly from the manufacture bottle without degassing or drying. All reactions were carried out in oven-dried glassware under nitrogen atmosphere. Reaction progress was monitored by HPLC according to general procedure C unless stated otherwise. All products were purified by flash column chromatography using Screening Devices 230-400 mesh silica unless otherwise noted. All reactions were carried out using a Radleys Discovery Technologies cooled parallel synthesizer. ^{1}H NMR and ^{13}C NMR data were obtained with a Bruker NMR 250/63 MHz, or Bruker NMR 400/100 MHz in $CDCl_3$.

General procedure A: Kinetic experiments with different solvents at different temperatures

To an oven dried vial were added: 1.0 equiv imine, 1.0 equiv of carboxylic acid, 1.5 g Na_2SO_4 and solvent (resulting in 66 mM with respect to the imine) containing 0.83 mg/mL 4-nitrobiphenyl as internal standard. This mixture was brought to the desired temperature and stirred for 30 min. after which 1.0 equiv of isonitrile was added to the solution. The reaction was monitored in time by taking samples for HPLC analysis at t=0, 5, 15, 30, 60 and 120 min. Samples were obtained by withdrawing 100 μL MeOH in a syringe followed by 100 μL reaction mixture and adding this to a HPLC vial containing 1 mL 1:1 H_2O:ACN (10% Et_3N). If the solution was cloudy it was filtered over an 0.45 μm teflon HPLC filter before injection into the HPLC

General procedure B: Kinetic experiments with carboxylic acid

To an oven dried vial were added: 1.0 equiv imine, 1.5 g Na_2SO_4 and solvent (resulting in 66 mM with respect to the imine) containing 0.83 mg/mL 4-nitrobiphenyl as internal standard. This mixture was brought to the desired temperature, followed by the addition of the appropriate amount of sodium carboxylate and/or carboxylic acid (combined 1.0 equiv). After stirring for 30 min, 1.0 equiv of isonitrile was added to the solution, and the reaction was monitored in time by taking samples for HPLC analysis at t=0, 5, 15, 30, 60 and 120 min. Samples were obtained by withdrawing 100 μL MeOH in a syringe followed by 100 μL reaction mixture and adding this to a HPLC vial containing 1 mL 1:1 H_2O:ACN (10% Et_3N). If the solution was cloudy it was filtered over an 0.45 μm teflon HPLC filter before injection on the HPLC.

General procedure C: Kinetic experiments with Lewis acid

To an oven dried vial were added: 1.0 equiv imine and solvent (66 mM with respect to the imine) containing 0.83 mg/mL 4-nitrobiphenyl as internal standard. This mixture was brought to the desired temperature, followed by the addition of the appropriate amount of Lewis acid. After stirring for 30 min, 1.0 equiv. sodium acetate was added to the mixture and stirring was continued for five minutes. At this point 1.0 equiv of isonitrile was added and the reaction was monitored in time by taking samples for HPLC analysis at t=0, 5, 15, 30, 60 and 120 min. Samples were taken by taking up 100 μL MeOH in a syringe followed by 100 μL reaction mixture and adding this to a HPLC vial containing 1 mL 1:1 H_2O:ACN (10% Et_3N). If the solution was cloudy it was filtered over an 0.45 μm teflon HPLC filter.

General procedure D: HPLC analysis

All samples were measured on a Shimadzu HPLC system equipped with a photo diode array detector. The method is listed in table 2. Retention times for the compounds of interest are shown in table 3. Peak areas were normalized by calculating a correction factor from the internal standard which is set to a peak area of 100,000 mAu^2.

Table 2: HPLC method used

Parameter	Value
Column	Shant laboratories Pathfinder MR, Silica 100 5 μm RP column 4.6*150 mm.
Eluent	MeCN / 20mM NH_4OAC pH = 4.50
Gradient	Hold 2 min 50:50. In 8 min. to 90:10 and hold 4 min. In 6 min. to 50:50 and hold 10 min.
Flow	1 mL/min
Runtime	30 minutes
Detection	250 nm

Table 3: Retention times

Compound	Retention time (min.)
Imine (**6**)	1.96
Ugi product (**1a**)	5.30
Internal standard (4-nitrobiphenyl)	7.18

General procedure E: Chiral HPLC analysis

All samples were measured on a Shimadzu HPLC system equipped with a photo diode array detector. The method is listed in table 4. Retention times for the enantiomers of **1a** are shown in table 5. Capacity factors of the two enantiomers using the above method are k'_1 = 0:12 and k'_2 = 0:20. The enantiomers are separated with a resolution of 1.28 calculated with the formula:

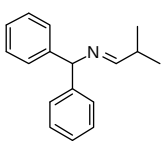
$$R = \frac{1.177 \cdot (t_{r1} - t_{r2})}{b_{0.5(1)} + b_{0.5(2)}}$$

Table 4: HPLC method used for chiral separation

Parameter	Value
Column	Chiracel OD-H
Eluent	*n*-hexane (0.05% diethylamine):isopropanol
Gradient	Isocratic 90:10
Flow	0.7 mL/min
Runtime	20 minutes
Detection	180 nm

Table 5: Retention times enantiomers of **1a**.

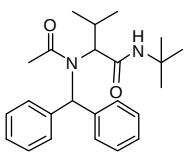
Compound	Retention time (min.)
Enantiomer a	4.35
Enantiomer b	4.66



Synthesis of imine 6

To a flame dried round bottom flask were added: 1.1 equiv isobutyraldehyde (4.52 g, 63 mmol), 1.0 equiv diphenylmethanamine (10.22 g, 57 mmol), Na_2SO_4 and diethylether (distilled from sodium) under nitrogen (resulting in 2.3M aldehyde). The solution was stirred at room temperature for 18 hours. After reaction completion (TLC), the mixture was filtered, and solvent was removed under reduced pressure yielding 13.53 g **6** (57 mmol, 100%) as a yellow oil. The product was not further purified. ^1H NMR (250 MHz, $CDCl_3$): δ (ppm) 7.74 (d, J = 2.5 Hz, 1H), 7.40-7.25 (m, 10H),

5.36 (s, 1H), 2.62-2.55 (m, 1H), 1.15 (d, J = 6.8 Hz, 6H); ^{13}C NMR (63 MHz): δ (ppm) 170.24, 144.28, 128.94 (4C), 128.16 (4C), 127.48 (4C), 78.39, 34.70, 19.94. HRMS: calculated for $C_{17}H_{19}N$ (M^+): 237.1517, found 237.1508.



Synthesis of Ugi product 1a

To a flame dried round bottom flask were added: 2.0 equiv imine **6** (237 mg, 1 mmol), 1.0 equiv acetic acid (30 mg, 0.5 mmol) and MeOH (resulting in 0.13 mM acetic acid). The solution was stirred at room temperature for 30 min, after which it was cooled to 0°C and 1.0 equiv of *tert*-butylisonitrile (42 mg, 0.5 mmol) was added. After half an hour the solution was allowed to warm to room temperature, and water (25 mL) was added to the solution. The mixture was extracted with EtOAc (3 x 12.5 mL). The organic layers were combined, washed with H_2O (12.5 mL), brine (12.5 mL) and dried over $MgSO_4$. The mixture was filtered, followed by the removal of solvent under reduced pressure. Isolation of the product by flash column chromatography using cyclohexane:EtOAC:Et_3N 4:1:0.01 yielded 160 mg **1a** (0.42 mmol, 85%) as an off white solid. ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 7.37-7.19 (m, 12H), 6.38 (s, 1H), 2.71 (bs, 1H) 2.02 (s, 3H), 1.39 (s, 9H), 0.78 (d, *J* = 6.4 Hz, 3H), 0.55 (d , *J* = 6.4 Hz, 3H); ^{13}C NMR (63 MHz): δ (ppm) 174.08, 171.04, 139.06 (2C), 131.17, 129.15 (4C), 128.82 (2C), 127.87(4C), 60.14, 58.60, 29.01 (3C), 28.23, 25.38, 20.36, 20.19. HRMS: calculated for $C_{24}H_{32}N_2O_2$ (M^+): 380.2464, found 380.2453.

Influence of temperature and solvent on the reaction

The experiment was set up according to general procedure A. 1.0 equiv imine **6** (237 mg, 1.0 mmol) and 1.0 equiv of acetic acid (60 mg, 1.0 mmol) were dissolved in 15.0 mL solvent containing 0.83 mg/mL 4-nitrobiphenyl. The solution was brought to the desired temperature and stirred for half an hour after which 1.0 equiv of *tert*-butylisonitrile (83 mg, 1.0 mmol) was added. Samples were taken at time points defined in general procedure A. These samples were analyzed by HPLC according to general procedure D.

Solvents screened: methanol, dichloromethane, toluene and methyl *tert*-butylether.

Temperatures screened: -20ºC, -5 ºC, 10 ºC and 25 ºC.

Influence of the acid concentration on the reaction in MeOH or DCM

The experiment was set up according to general procedure B. 1.0 equiv imine **6** (237 mg, 1.0 mmol) was dissolved in 15.0 mL methanol or dichloromethane containing 0.83 mg/mL 4-nitrobiphenyl. After cooling down the solution to -5ºC, sodium acetate and/or acetic acid was added to the solution according to table 6.

Table 6: Used amounts of acetic acid / sodium acetate.

Compound	**10 eq.**	**1 eq.**	**0.5 eq.**
Acetic acid	600 mg (10 mmol)	60 mg (1.0 mmol)	30 mg (0.5 mmol)
Sodium acetate	-	-	41 mg (0.5 mmol)

Compound	**0.1 eq.**	**0.05 eq.**	**0.01 eq.**
Acetic acid	6 mg (0.1 mmol)	3 mg (0.05 mmol)	0.6 mg (0.01 mmol)
Sodium acetate	74 mg (0.9 mmol)	78 mg (0.95 mmol)	81 mg (0.99 mmol)

After stirring for 30 min, 1.0 equiv *tert*-butylisonitrile (83 mg, 1.0 mmol) was added, and samples were taken at time points defined in general procedure B. These samples were analyzed by HPLC according to general procedure D.

Influence of ammonium acetate as proton donor on the reaction

The experiment was set up according to general procedure B. 1.0 equiv imine **6** (237 mg, 1.0 mmol) was dissolved in 15.0 mL methanol containing 0.83 mg/mL 4-nitrobiphenyl. After cooling down the solution to -5ºC,

1.0 equiv ammonium acetate (77 mg, 1.0 mmol) was added to the solution. After stirring for 30 min, 1.0 equiv *tert*-butylisonitrile (83 mg, 1 mmol) was added, and samples were taken at time points defined in general procedure A. These samples were analyzed by HPLC according to general procedure D.

Influence of scandium triflate (10, 20%) and ytterbium triflate (10%) on the reaction

The experiment was set up according to general procedure C. 1.0 equiv imine **6** (119 mg, 0.5 mmol) was dissolved in 7.5 mL methanol or trifluoroethanol. After bringing the solution to -5º C or 20 ºC, scandium or ytterbium triflate was added to the solution according to table 7.

Table 7: Used amounts of Lewis acid.

Lewis acid	10 %	20 %
$Sc(OTf)_3$	24.6 mg (0.05 mmol)	49.2 mg (0.1 mmol)
$Yb(OTf)_3$	15.5 mg (0.05 mol)	-

After stirring for 30 min, 1.0 equiv sodium acetate (41 mg, 0.5 mmol) was added to the solution. After five minutes 1.0 equiv *tert*-butylisonitrile (42 mg, 0.5 mmol) was added, and samples were taken at time points defined in procedure C. These samples were analyzed by HPLC according to general procedure D.

Influence of scandium triflate (33, 100%) on the reaction

The experiment was set up according to general procedure C. 1.0 equiv imine **6** (600 mg, 0.25 mmol) was dissolved in 3.75 mL methanol or trifluoroethanol containing 0.83 mg/mL. 4-nitrobiphenyl. After bringing the solution to -5ºC, scandium triflate was added to the solution according to table 8.

Table 8: Used amounts of Lewis acid.

Lewis acid	33 %	100 %
$Sc(OTf)_3$	36.9 mg (0.083 mmol)	123 mg (0.25 mmol)

After stirring for 30 min, 1.0 equiv sodium acetate (20 mg, 0.25 mmol) was added to the solution. After five minutes 1.0 equiv *tert*-butylisonitrile (21 mg, 0.25 mmol) was added, and samples were taken at time points defined in procedure C. These samples were analyzed by HPLC according to general procedure D. Additional samples were taken after 230 minutes.

Influence of scandium triflate/ligand complex on the reaction

To an oven-dried vial was added 3.75 mL triflouroethanol containing 0.83 mg/mL 4-nitrobiphenyl. 0.33 equiv scandium triflate (36.9 mg, 0.083 mmol) and 0.33 equiv ligand according to table 9 were added to the solution.

Table 9: Used amounts of ligand.

Ligand	amount
Pybox (**11**)	33 mg, 0.083 mmol
Binap (**12**)	52 mg, 0.083 mmol
Ferrocene (**13**)	58 mg, 0.083 mmol

This solution was stirred. After 10 minutes, 1.0 equiv imine **6** (60 mg, 0.25 mmol) was added to the solution, which was stirred for half an hour, whereafter 1.0 equiv sodium acetate (20 mg, 0.25 mmol) was added to the solution. After 5 min. 1.0 equiv *tert*-butylisonitrile (21 mg, 0.25 mmol) was added, and samples were taken at time points defined in general procedure C. These samples were analyzed by HPLC according to general procedure D. After 24 h the reactions were quenched by pouring the solution into 25 mL water. The aqueous layer was extracted with EtOAc (3 x 12.5 mL). The organic layers were combined, washed with water, and brine, and dried ($MgSO_4$). After filtration the solvent was removed under reduced pressure. The crude products were purified using flash column chromatography. The *ee*'s were determined according to general procedure E.

Influence of scandium triflate/BINOL complex on the reaction

0.33 equiv. scandium triflate (37 mg, 0.083 mmol), 0.40 equiv. (0.100 mmol) axial chiral binaphtyl ligand according to table 10 and 0.80 equiv *N*-methylpiperidine (20 mg, 0.200 mmol) were dissolved in DCM:TFE (1:1, 3.0 mL).

Table 10: Used amounts of BINOL-ligands.

Ligand	amount
(*S*)-(-)-1,1'-Binaphtol (**14**)	29 mg, 0.100 mmol
(*S*)-(-)-3,3'-Dibromo-1,1'-Bi-2-naphtol (**15**)	44 mg,0.100 mmol
(*S*)-(+)-6,6'-Dibromo-1,1'-Bi-2-naphtol (**16**)	44 mg, 0.100 mmol
(*S*)-(-)-3,3'-Dibromo-5,5',6,6',7,7',8,8'-octahydro-(1,1'-binaphtalene)-2,2'-diol (**17**)	29 mg, 0.100 mmol

The mixture was stirred for 1.5 h at room temperature. 1.0 equiv imine **6** (59 mg, 0.25 mmol) was added and the solution was cooled to -5 ^{o}C and stirred for 30 min. 1.0 equiv sodium acetate (20 mg, 0.25 mmol) was added and after 5 min 1.0 equiv *tert*-butyl isocyanide (21 mg, 0.25 mmol) was added. Samples (100 μL) were taken at 0, 5, 15, 30, 60 and 120 min, together with 200 μL of MeOH and added to 1 mL of 1:1 H_2O:MeOH + 10% Et_3N. Samples were analyzed using HPLC-diode array detector (cyclobond 2000, 225nm, 83:17 MeCN:NH_4OAc, 0.02 M, pH 4.5)

5.5 References and notes

1. Ugi, I.; Meyr, R.; Fetzer, U.; Steinbruckner, C. *Angew. Chem.* **1959**, *71*, 386.
2. Domling, A. *Chem. Rev.* **2006**, *106*, 17-89.
3. Zhu, J. *Eur. J. Org. Chem.* **2003**, 1133-1144.
4. Orru, R. V. A.; De Greef, M. *Synthesis* **2003**, 1471-1499.
5. Gokel, G.; Ludke, G.; Ugi, I. In *Isonitrile Chemistry*; Ugi, I., Ed.; Academic Press: New York, 1971, p 145-199.
6. Zhu, J.; Bienayme, H. *Multicomponent reactions*; WILEY-VCH Verlag GmbH Co: Weinheim, 2005.
7. Mumm, O. *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 886-893.
8. Passerini, M. *Gazz. Chim. Ital.* **1921**, *51*, 126-129.
9. Bock, H.; Ugi, I. *J. Prakt. Chem.* **1997**, *339*, 385-389.
10. Ugi, I.; Kaufhold, G. *Liebigs Ann. Chem.* **1967**, *709*, 11-28.
11. Ugi, I.; Offermann, K.; Herlinger, H.; Marquarding, D. *Liebigs Ann. Chem.* **1967**, *709*, 1-10.
12. Ramon, D. J.; Yus, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 1602-1634.
13. Tsuchida, K.; Mizuno, Y.; Ikeda, K. *Heterocycles* **1981**, *15*, 883-887.
14. Rossen, K.; Sager, J.; DiMichelle, L. M. *Tetrahedron Lett.* **1997**, *38*, 3183-3186.
15. Urban, R.; Ugi, I. *Angew. Chem. Int. Ed.* **1975**, *14*, 61-62.
16. Ugi, I.; Offermann, K. *Angew. Chem. Int. Ed.* **1963**, *2*, 624.
17. Hebach, C.; Kazmaier, U. *Chem. Comm.* **2003**, 596-597.
18. Ahmadian, H.; Nielsen, B.; Bruner-Osborne, H.; Johansen, T. N.; Stensbl, T. B.; Slk, F. A.; Sekiyama, N.; Nakanishi, S.; Krogsgaard-Larsen, P.; Madsen, U. *J. Med. Chem.* **1997**, *40*, 3700-3705.
19. Kunz, H.; Pfrengle, W. *J. Am. Chem. Soc.* **1988**, *110*, 651-652.
20. Pirrung, M. C.; Das Sarma, K. *Tetrahedron* **2005**, *61*, 11456-11472.
21. Rothenberg, G. *Catalysis*; Wiley-VCH Verlag GmbH & Co.: Weinheim, 2008.
22. Bonne, D.; Dekhane, M.; Zhu, J. *Org. Lett.* **2004**, *6*, 4771-4774.
23. Domling, A.; Ugi, I. *Angew. Chem. Int. Ed.* **2000**, *39*, 3168-3210.
24. Yamamoto, H. *Lewis Acids in Organic Synthesis*; Wiley VCH: Weinheim, 2000; Vol. 2.
25. Kobayashi, S.; Manabe, K. *Pure Appl. Chem.* **2000**, *72*, 1373-1380.
26. Godet, T.; Bonvin, Y.; Vincent, G.; Merle, D.; Thozet, A.; Ciufoline, M. A. *Org. Lett.* **2004**, *19*, 3281-3284.
27. Liang, G.; Trauner, D. *J. Am. Chem. Soc.* **2004**, *126*, 9544-9545.

28. Kitajima, H.; Ito, K.; Katsuki, T. *Tetrahedron* **1997**, *53*, 17015-17028.
29. Andreana, P. R.; Liu, C. C.; Schreiber, L. *Org. Lett.* **2004**, *23*, 4231-4233.
30. Yao, S.; Saaby, S.; Hazell, R. G.; Jorgensen, K. A. *Chem. Eur. J.* **2000**, *6*, 2435-2448.
31. Fujii, A.; Hagiwara, E.; Sodeoka, M. *J. Am. Chem. Soc.* **1999**, *121*, 5450-5458.
32. Zhou, X.-T.; Lin, Y.-R.; Dai, L.-X.; Sun, J.; Xia, L.-J.; Tang, M.-H. *J. Org. Chem.* **1999**, *64*, 1331-1334.
33. Evans, D. A.; K.R., F. *Org. Lett.* **2006**, *8*, 2249-2252.
34. Kobayashi, S.; Araki, M.; Hachiya, I. *J. Org. Chem.* **1994**, *59*, 3758-3759.

Chapter 6

Combining Biocatalysis with Multicomponent Reactions

6.1 Introduction

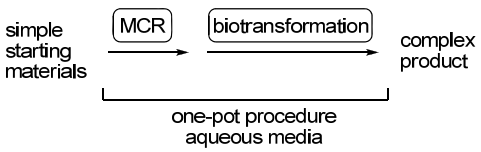
As has become clear from the preceding chapters, multicomponent reactions (MCRs) are very atom- and step efficient organic transformations by nature. The products formed are structurally complex compared to the relatively simple starting materials and often contain new stereocenters. The mechanistic pathways that lead to product formation are fairly complex and therefore control over formation of these stereocenters is mostly not trivial. Although many reports exist on asymmetric MCRs many of them are based on the use of chiral auxiliaries or chiral inputs.[1] Such an approach, however, reduces the exploratory power of a given MCR significantly and, moreover, stoichiometric amounts of chiral starting material are required. As a consequence, additional reaction steps are needed to remove and/or recover the chiral auxiliary.

The most convenient way to perform highly flexible asymmetric MCRs would involve the application of a chiral catalyst. Only small amounts of chiral resources are then required to produce substantial quantities of the desired optically active product. No additional reaction steps are needed to remove and/or regenerate chiral auxiliaries and waste production is minimized. At the same time the original high exploratory power of the MCR is retained. So far, for most MCRs, catalytic asymmetric methods to control the stereochemistry are not available.[1]

The use of catalytic systems from nature for the transformation of synthetic molecules, commonly referred to as biocatalysis, has found wide-spread application in the fine-chemical, pharmaceutical and food industry.[2,3] Both whole cells, cell organelles and purified enzymes can be employed to selectively produce high yields of specific products with low energy use and minimal waste generation. Biocatalysis continues to gain momentum and is now a key component in the toolbox of many organic and process chemists.[4]

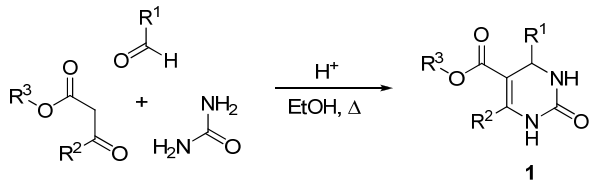
The stereoselectivity of many biocatalysts excellently complements the chemoselectivity of MCRs, and the possibility of combining these methods in a one-pot procedure opens opportunities for truly sustainable production methods. Despite the potential of both MCRs and biocatalysis, their combination in one-pot processes has hardly been described.[5] This is mainly due to the fact that MCRs are most commonly performed in organic solvents. However, recent studies demonstrate that many of the classical MCRs (Biginelli, Ugi, Passerini, Strecker and Mannich) can be performed in aqueous media and are thus in principle compatible with biocatalysis.[6-9]

In the research described in this chapter we explored possibilities to combine (i) MCR methodology and (ii) biocatalysis preferably in a one-pot set-up. Starting from simple building blocks we could access relatively complex products with potential medicinal value (Scheme 1).



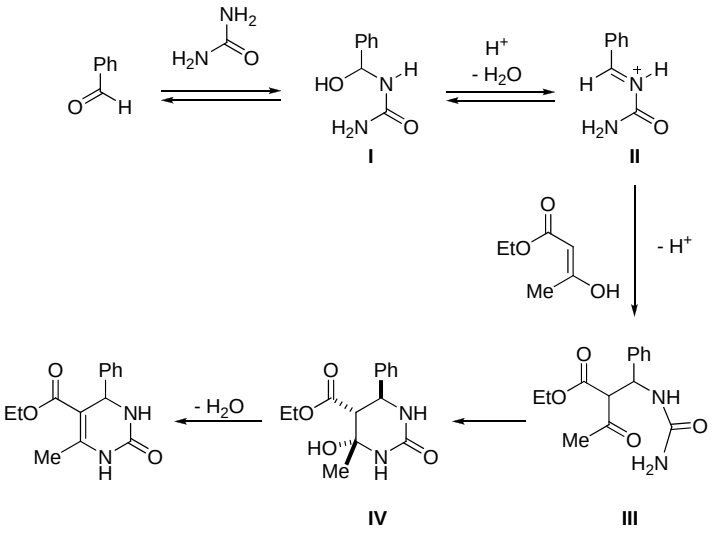
Scheme 1: Combination of MCRs and biocatalysis leading to complex products.

Conceptually many different types of MCR/biocatalysis combinations are possible. However, to demonstrate the power of this approach, we have focused on the enzymatic kinetic resolution of dihydropyrimidone (DHPM) esters of type **1**, which are conveniently formed via a Biginelli reaction (Scheme 2). In this three-component reaction, first reported in 1893 by P. Biginelli, aldehydes, β-ketoesters and urea react under acidic conditions to give DHPMs **1**.[10]



Scheme 2: Original Biginelli reaction.

The mechanism of the reaction was under debate for several decades until 1997, when the group of Kappe conducted a series of NMR experiments (Scheme 3).[11] They could show that the key intermediate in the Biginelli reaction is *N*-acyliminium ion intermediate **II** which is formed by the acid catalyzed reaction between the aldehyde and the urea component. The iminium ion is then attacked by the nucleophilic enol form of the β-ketoester yielding open-chain ureide **III**, which cyclizes to cyclic urea **IV**. The final DHPM product is then formed by acid-catalyzed elimination of water.[12]

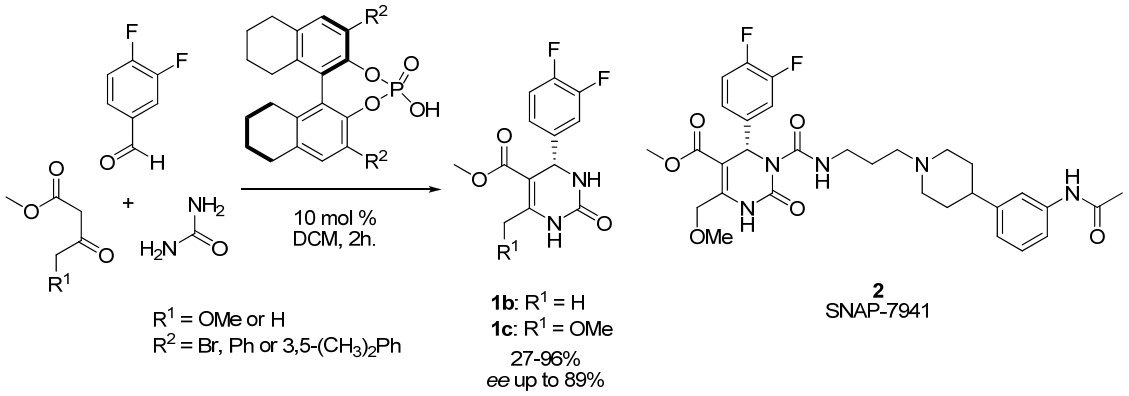


Scheme 3: Mechanism of the Biginelli reaction.

The relatively easy experimental procedure of the Biginelli-3CR (B-3CR), which involves just refluxing the starting materials in ethanol with a catalytic amount of HCl, has made this reaction very popular.[13] Early examples of the reaction mostly involved the use of β-ketoesters, aromatic aldehydes and urea. Since then however, all three building blocks have been varied successfully, giving access to a large number of different DHPMs.[14]

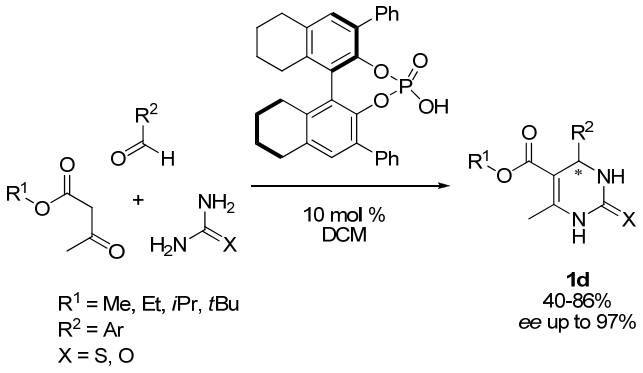
DHPMs display a broad range of biological effects like antitumor and anti-inflammatory activities, making them very interesting targets for the pharmaceutical industry.[15] The DHPMs

that result from the Biginelli-3CR have a chiral center at C4. Usually only one of the enantiomers shows the desired biological activity. Methods to enantioselectively make DHPM are highly desirable. Two recent examples are reported by the groups of Schaus and Gong.[16,17] The group of Schaus reported an enantioselective synthesis of the dihydropyrimidine core of SNAP-7941 (**2**), a potent melanin concentrating hormone receptor antagonist, via a chiral phosphoric acid-catalyzed Biginelli reaction (Scheme 4).[16]



Scheme 4: Enantioselective Biginelli reaction of SNAP-7941 core.

The reaction proceeds in moderate to good yields (27-96%) with good *ee*'s (up to 98%). The group of Gong also used a chiral phosphoric acid for their enantioselective Biginelli reaction (Scheme 5).[17]



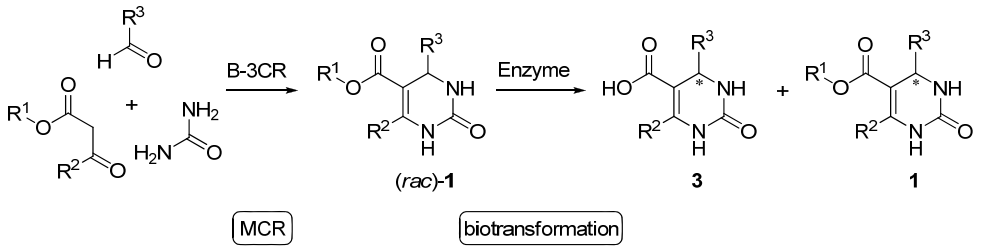
Scheme 5: Organocatalytic enantioselective Biginelli reaction.

Yields of the reaction were moderate to good (40-86 %) with excellent *ee*'s (up to 97%). If you compare both results it looks like the system of the group of Gong is better, but in fact the *ee*'s for comparable products are in the same range. Small differences in *ee* might be caused by the different reaction stoichiometries that are used.

Several examples of Biginelli reactions in aqueous media have been reported in literature. The group of Suzuki reported a Biginelli reaction in pure water using metal triflimides such as $Ni(NTf_2)_2$, $Cu(NTf_2)_2$ and $Yb(NTf_2)_3$ as the catalysts.[18] Addition of a Brønsted acid gave the DHPMs in yields ranging from 65 to >95% after 24 hours at room temperature. The group of

Varma reported a microwave-assisted, aqueous Biginelli reaction with polystyrene sulfonic acid (PSSA) as the catalyst. Typical yields are between 86 and 92 % after 20 minutes of reaction time at 80ºC.[19] Finally, Yadav *et al.* reported the use of $Ag_3PW_{12}O_{40}$ as a new, water-tolerant heteropolyacid for the Biginelli reaction. Yields, in water, range between 80 and 93 % with reaction times between 3.5 and 4.5 hours.[6] In all three examples combinations of aromatic aldehydes, methyl or ethyl acetoacetate and urea were used.

We envisioned that selective hydrolysis of the ester functionality in the Biginelli products **1** should be possible using specific hydrolases such as esterases, which are known to hydrolyze functionalized esters. Unfortunately there are not many esterases known that have been used for the selective hydrolysis of (carboxylic) esters. Some examples are pig and horse liver esterase, acetylcholine esterase and cholesterol esterase.[3] Of these, the pig liver esterase is most widely used in synthetic procedures.[20] It is normally used in aqueous solutions because of its instability in organic solvents. However, some methods have been reported in biphasic or organic media, but then the enzyme is either immobilized or co-lyophilized.[20] However, proteases and lipases can also hydrolyze carboxylic esters. Useful examples of proteases are α-chymotrypsin, subtilisin, a protease from *Aspergillus oryzae*[3] and an example of a lipase is *Candida rugosa* lipase.[21]
Combination of an aqueous Biginelli three component procedure for *rac*-**1** and subsequent in situ enzyme catalyzed kinetic resolution should give access to the optically pure esters **1** and the corresponding carboxylic acids **3** (Scheme 6). In the kinetic resolution, one of the enantiomers of the racemic Biginelli product **1** is converted to the corresponding carboxylic acid while the other enantiomer remains unaffected (Scheme 6).

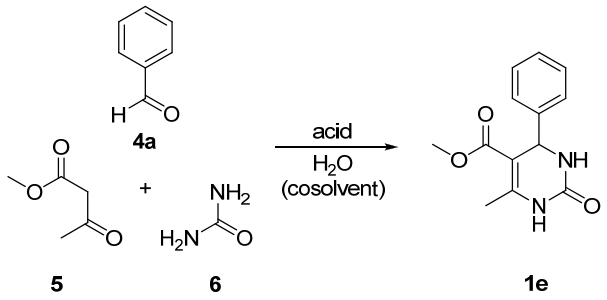


Scheme 6: Envisioned one-pot MCR/biotransformation sequence.

6.2 Results and discussion

6.2.1 Aqueous Biginelli reaction

The reaction conditions reported by Yadav *et al.* for their $Ag_3PW_{12}O_{40}$ –catalyzed aqueous Biginelli reactions[6] were chosen as a starting point for our studies. As the standard reaction inputs benzaldehyde (**4a**), methyl acetoacetate (**5**) and urea (**6**) were chosen, yielding the known DHPM **1e** after the Biginelli-3CR (Scheme 7). We selected the methyl ester because it is most likely to be a good substrate for a wide range of hydrolases.[3]



Scheme 7: Aqueous Biginelli reaction.

After some initial test experiments it became clear that the silver/tungsten catalyst of Yadav could not be used for this standard Biginelli 3-CR as separation of the catalyst from the Biginelli product **1e** proved very difficult. We felt that remainders of the silver salt of the heteropolyacid catalyst would hamper the esterase catalyzed hydrolysis in the following step of the MCR/biotransformation sequence. Therefore, another water-soluble acid catalyst was required. A range of water-soluble, organic acids that are known to be compatible with many common biocatalysts were selected. L-tartaric acid, L-malic acid, ascorbic acid, trizma acid, and phosphonoacetic acid all catalyzed efficiently the Biginelli reaction and gave the desired ester **1e** efficiently. As the use of L-tartaric acid as the catalyst led to the cleanest reaction as judged by TLC, this became the acid catalyst of choice for further optimization of our aqueous Biginelli reaction. The reaction stoichiometry was optimized (table 1) and the use of 1.0 equivalent of L-tartaric acid, 2.0 equivalents of urea, and 1.0 equivalent of both benzaldehyde and methyl acetoacetate gave optimal yields of **1e** (entry 2). The reaction was best performed in a 3:1 mixture of water/acetonitrile compared to the use of pure water (entry 9, table 1). The isolated yield of dihydropyrimidine **1e** was 85%.

Table 1: Optimization of aqueous Biginelli reaction.

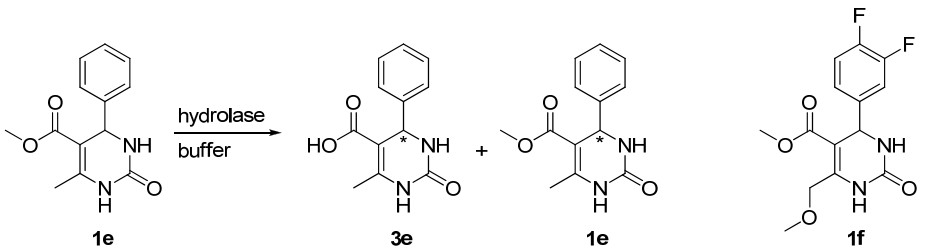
Entry	equiv. urea	equiv. tartaric acid	yield (%)
1	1.0	1.0	49
2	2.0	1.0	85
3	3.0	1.0	80
4	4.0	1.0	83
5	2.0	0.25	49
6	2.0	0.5	61
7	2.0	2.0	82
8	1.0	2.0	54
9	2.0	1.0	48[a]

All reactions were performed with 1.0 equiv. of aldehyde and 1.0 equiv. of β-ketoester in H_2O/MeCN (3:1) as the solvent. [a] Reaction performed in pure H_2O.

6.2.2 Biotransformation

With a useful procedure for the Biginelli-3CR under aqueous conditions in hand, we now turned our attention to the next step in the MCR/biocatalysis sequence: the enzyme catalyzed hydrolysis of racemic **1e**. This should proceed via a kinetic resolution to generate the corresponding enantiomerically pure ester **1e** and its acid derivative **3e**. A small range of

different hydrolases was selected and screened for optimal (activity and) selectivity. Selection of specific hydrolases was based on their known ability to hydrolyze bulky esters[3] and a report by Sidler *et al.* who performed a kinetic resolution using hydrolases with a similar Biginelli ester (**1f**, scheme 8) as our Biginelli-ester substrate **1e**.[22] Screening was focused to select conditions that would make this biocatalytic hydrolysis compatible with a one-pot procedure including the preceeding Biginelli reaction.

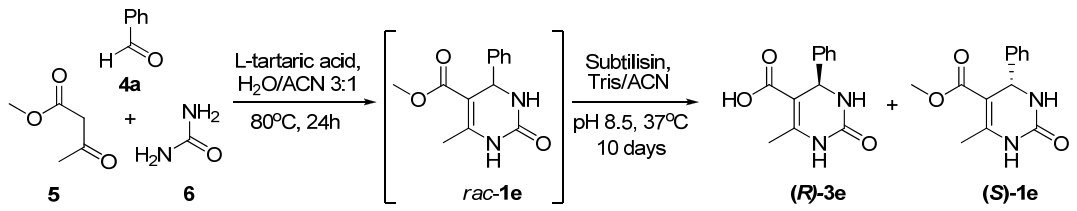


Scheme 8: Biotransformation.

Thus, seven different commercial hydrolases were screened for selective hydrolysis of racemic ester **1e**. In general we used a solution of 6.8 mM **1e** in the appropriate buffer system (pH 8.5). α-Chymotripsin from Bovine Pancreas, Proteinase K, a protease from *Aspergillus oryzae*, a protease from *Streptomyces gryseus*, esterase from porcine liver (PLE), all gave very poor conversions and, at best, only moderate *ee*'s of the desired optically active ester or corresponding acid. However, the use of subtilisin from *Bacillus licheniformis* (Sigma) or from *Bacillus lentus* (Genencor Purafect 4000L) both afforded the ester product and the corresponding acid in reasonable to good conversion (as judged by TLC). Subtilisin from *Bacillus lentus* performed best (high conversion rate with high *ee*) and was the biocatalyst of choice for the kinetic resolution of *rac*-**1e**. The biotransformation performed most optimal in Tris buffer at pH 8.5 and a temperature of 37 ºC. These conditions seem compatible with the above described optimized conditions for the aqueous Biginelli reaction, although the reaction time for full conversion (50%) is relatively long and takes at least 10 days. With this enzyme, the (*R*)-enantiomer of the acid **3e** is obtained in 89% *ee* while the (*S*)-enantiomer of the ester **1e** (92% *ee*) remains unaffected.[22]

6.2.3 One-pot Biginelli 3CR/Subtilisin sequence

With the two individual reactions of the MCR/biocatalysis sequence established, attention was now focused on combining them in a one-pot procedure. (Scheme 9)



Scheme 9: MCR/biotransformation sequence in one pot.

First, the Biginelli-3CR of **4a**, **5** and **6** was performed under the optimized conditions with L-tartaric acid as the catalyst and heating overnight at 80ºC. The crude reaction mixture from this Biginelli reaction was then diluted with the Tris-buffer/ACN mixture. The pH was adjusted to 8.5 and the mixture was heated to 37ºC. Then, the solution of subtilisin from *Bacillus lentus* was added (78635 units/mmol[23]). The hydrolysis reaction was run for eleven days resulting in a conversion of 43%. To our satisfaction this one-pot procedure gave the acid (*R*)-**3e** in 89% *ee*, while the remaining (*S*)-ester **1e** was recovered in 92% *ee* (based on chiral HPLC analysis) (Figure 1). This corresponds to an E-value of 52, which is quite acceptable for preparative use.[3]

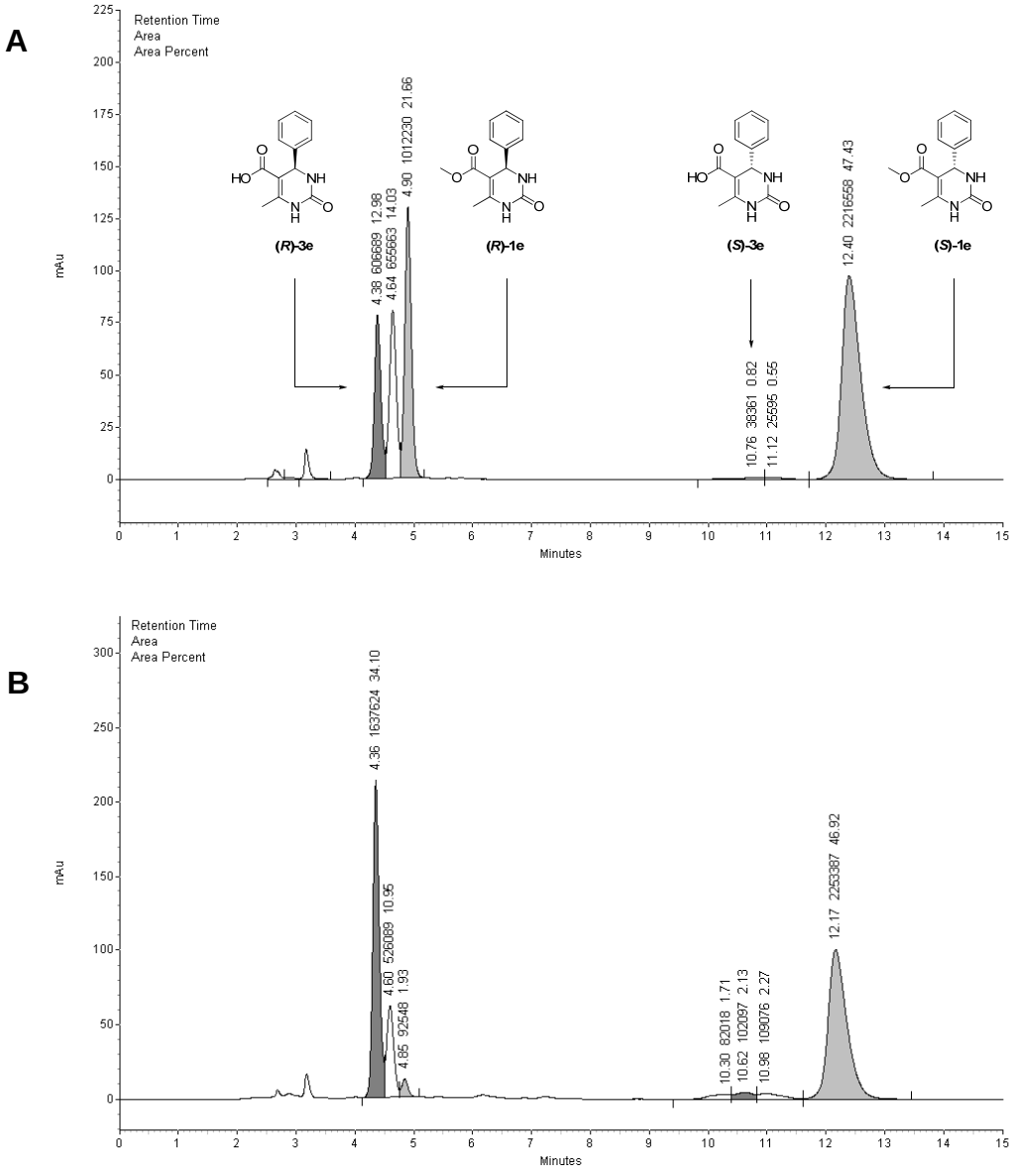
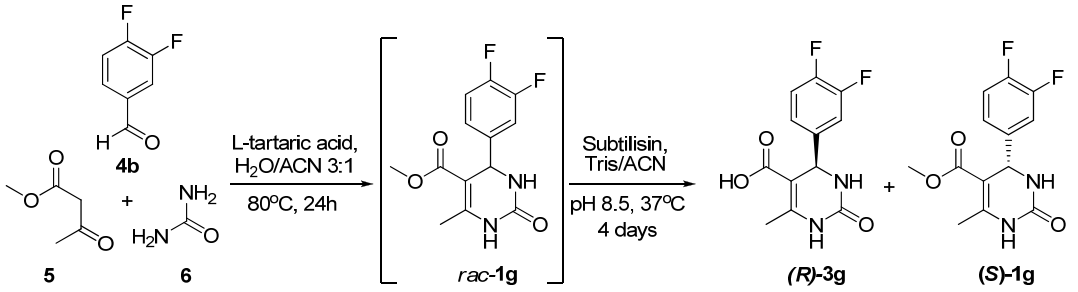


Figure 1: HPLC traces of the biotransformation after 4 days (top) and 11 days (bottom). Acids are dark-grey, esters light grey.

Two HPLC traces of the biotransformation are shown in Figure 1. Trace A is taken 4 days after addition of the subtilisin from *Bacillus lentus* very clearly showing the two enantiomers

of the ester **1e** (light grey) and the (*R*)-acid **3e** (dark grey) generated during the biotransformation. Trace B is taken after 11 days of biocatalytic conversion showing almost complete conversion of the ester (*R)*-**1e** to the acid(*R*)-**3e** while only a minute amount of (*S*)-**3e** is formed. This demonstrates that direct, one-pot combination of the Biginelli-3CR performed under aqueous conditions with a biocatalytic hydrolysis of the resulting racemic ester **1e** was established.



Scheme 10: MCR/biotransformation sequence using 3,4-difluorobenzaldehyde.

We also studied the combination of 3,4-difluorobenzaldehyde (**4b**), methyl acetoacetate (**5**) and urea (**6**) and a subsequent biohydrolysis. (Scheme 10) The Biginelli reaction was again conducted using L-tartaric acid and the components were stirred overnight at 80°C as described above. Subsequently, the biohydrolysis was run during 4 days after which a conversion of the racemic ester **1g** of 49% was reached. The selectivity of this reaction was quite good and the corresponding acid (*R*)-**3g** was obtained in 92% *ee* while the remaining ester (*S*)-**1g** was formed in 86% *ee* (E-value of 70). Apparently, the Biginelli ester **1g** is a much better substrate for the subtilisin from *Bacillus lentus* compared to ester **1e**.

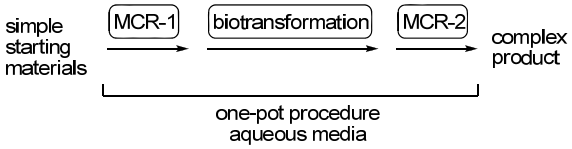
When the actual yield of the Biginelli reaction described above with 3,4-difluorobenzaldehyde **4b** was determined, it became clear that the optimized aqueous Biginelli conditions were not very suitable for the synthesis of Biginelli ester **1g**, which could be isolated in only 19% yield. So, a more general set of reaction conditions had to be found for the aqueous Biginelli reaction. Kappe has shown that the Biginelli reaction can be performed very efficiently under microwave irradiation conditions with the additional benefit of relatively short reaction times.[24] However, we could not use the Lewis acid catalyst that gave optimal results in the procedure of Kappe (ytterbium triflate ($Yb(OTf)_3$)) because test experiments revealed a clear negative effect on the activity of the subtilisin enzyme. Therefore, a series of additional acid catalysts (HCl, H_3PO_4, H_2SO_4 and trifluoroacetic acid (TFA)) were screened in the microwave-assisted standard Biginelli reaction giving **1e** and compared with the performance of L-tartaric acid as in the procedure described above. When using TFA as the acid catalyst the yield of *rac*-**1e** proved to be even higher as compared to the procedure using the L-tartaric acid. The conditions of the microwave-assisted Biginelli reaction were further optimized and with a 30 minutes hold time at a reaction temperature of 120°C the highest yields for both Biginelli ester **1e** (90%) and Biginelli ester **1g** (70%) were obtained. As solvent, acetonitrile was used just like in the protocol of Kappe and co-workers.

The same ratio of starting materials was used: 1 equivalent of **4a** or **4b**, 1 equivalent of **5**, 2 equivalents of **6** and 1 equivalent of acid, in our case TFA. In both cases, the products crystallized from the reaction mixture as a white solid and could easily be obtained by filtration.

However, to our disappointment, the B-3CR/biotransformation sequence to afford the optically active Biginelli esters **1e** and **1g** and their corresponding carboxylic acids **3e** and **3g** did not perform very well in the presence of TFA. The activity of the Subtilisin enzyme decreased significantly and large amounts of enzyme solution (131058 units/mmol[23]) were required to run the sequence to completion Further experimentation is required to optimize this microwave-assisted B-3CR/ biotransformation protocol.

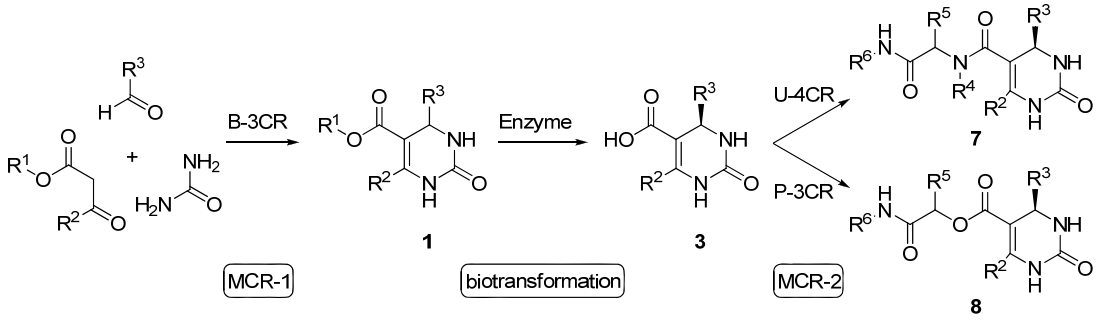
6.3 Outlook

An interesting extension of the above protocol would be the combination of the above described Biginelli-Subtilisin sequence with an additional MCR. This leads to a one-pot MCR/biotransformation/MCR-sequence (Scheme 11) in which the biotransformation is used to address the stereochemical issues and the MCRs to address the issues of structural diversity and complexity.



Scheme 11: Envisioned MCR/biotransformation-MCR sequence.

We envisioned as the key intermediate in the sequence the enantiomerically pure acids (*R*)-**3**. These could be combined with for example an Ugi-4CR or a Passerini 3-CR. The specific reaction sequence is depicted in Scheme 12. The ultimate goal is to perform all three reactions in one pot, in aqueous media.



Scheme 12: Planned one-pot sequence.

This reaction sequence leads to a class of interesting peptidic dihydropyrimidones (**7, 8**, scheme 12), which bear (some) structural resemblance to the class of biologically active compounds shown in Scheme 4 (**2**)[16] and Figure 2 (**9** and **10**). The compound L-771,668 (**10**)

is a potential antagonist for the treatment of benign prostatic hyperplasia.[22] The MAL3-analogs **9** inhibit the Hsp40-Hsp-70-interaction, which is involved in a large number of human diseases including cancer and cystic fybrosis.[25]

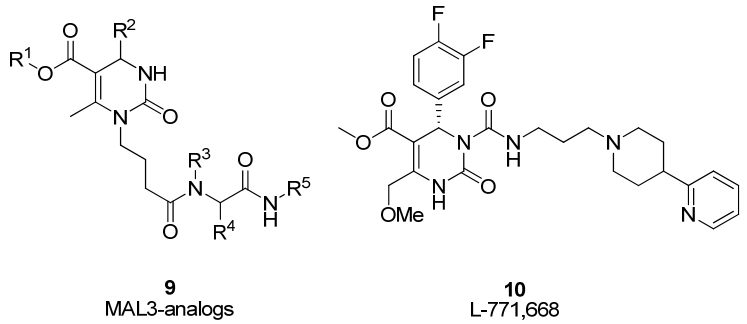
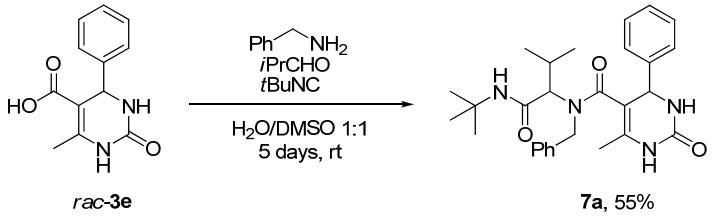


Figure 2: Biologically active compounds with structural resemblance to **7** and **8**.

We initially focused was on the combination of our one-pot Biginelli-subtilisin sequence with an Ugi-4CR. From literature it is known that the Ugi-reaction can be performed in aqueous media.[26] These conditions were the starting point to study the Ugi-4CR using our Biginelli acid **1e** together with standard Ugi inputs.



Scheme 13: Aqueous Ugi reaction.

Thus isobutyraldehyde, benzylamine, the racemic Biginelli *rac*-**3e** acid and *tert*-butyl isocyanide (Scheme 13) were combined using a 1:1 mixture of phosphate buffer and DMSO (for solubility reasons). The reaction was performed in the presence of glucose (1 M) as an additive as Pirrung *et al.* reported an aggregation effect (with glucose or LiOH) resulting in enhanced reaction rates.[26] Nevertheless, under these conditions the Ugi-4CR still proceeded sluggishly. The Ugi product **7a** could be isolated in 55% yield after 5 days at room temperature. This result shows that an Ugi-4CR with the racemic Biginelli acid **3e** is possible under aqueous conditions.

To further investigate the Biginelli-3CR-subtilisin-Ugi-4CR sequence, sufficient amounts of chemically and optically pure acids **3e** and **3g** were required. However, it proved difficult to isolate the optically enriched acids (*R*)-**3e** and (R)-**3g** from the reaction mixture after the biotransformation. The problems arise from the large amount of enzyme used in the biohydrolysis. The work-up after the Biginelli-3CR-biohydrolysis step requires further attention to establish the one-pot formation of **7a** efficiently.

6.4 Conclusions

The individual steps of the Biginelli-subtilisin sequence have been established. The aqueous Biginelli reaction is performed best in a water/acetonitrile (3:1) mixture with L-tartaric acid as the acid catalyst and overnight stirring at 80°C, resulting in an isolated yield of 85%. The biotransformation is performed best using the hydrolase subtilisin from *Bacillus lentus* (Genencor Purafect 4000L). Direct connection of this Biginelli reaction and biotransformation (resulting in a one-pot sequence) proved to be possible in good conversions and *ee*'s for both the acid and the ester.
Further optimization of especially work-up procedures are essential to fully exploit this one-pot MCR/biocatalysis procedure for the efficient synthesis of biologically relevant target compounds.

6.5 Experimental section

General information

All commercially available chemicals and enzymes were used as purchased. All enzymes were used in pure form except for the Subtilisin from *Bacillus lentus* (Genencor Purafect 4000L) which was purchased as a solution in water (5.2-6.0% w/w) also containing propylene glycol (30.0-50.0% w/w) and sodium formate (6.0-10.0% w/w). Thin Layer Chromatography (TLC) was performed using Merck aluminium TLC sheets (Silica gel 60 F_{254}) and compounds were visualized using UV-detection (254 nm) and staining with an anisaldehyde solution (6 mL *p*-Anisaldehyde, 7 mL acetic acid and 7 mL sulfuric acid in 120 mL of EtOH). Column chromatography was performed using Silicycle Silia-P Flash Silica Gel (40-63 μm) and mixtures of (cyclo)hexane and EtOAc. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance 400 (400.13 MHz and 100.61 MHz respectively) or a Bruker Avance 250 (250.13 MHz and 62.90 MHz respectively) with chemical shifts (δ) reported in ppm downfield from tetramethylsilane. Enantiomeric excess (*ee*) was determined on a Shimadzu Prominence, equipped with a DAD detector and a Shimadzu SIL-20A auto-injector following the method described in table 2. Microwave reactions were performed in a monomode microwave (MW) reactor equipped with an autosampler (CEM Explorer). The temperature was controlled throughout the reaction and was assessed by measuring the surface temperature at the bottom of the reaction vessel by means of an infrared sensor. In all cases capped vessels were used, allowing the pressure to build up. The pressure was evaluated by measuring the bulging of the septum, but never exceeded 17.2 bars.

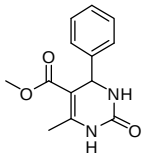
Table 2: HPLC method used for chiral separation.

Parameter	Value
Column	Astec Chirobiotic-T column, 250 x 4.6 mm
Eluent	20mM NH_4OAc buffer (pH 4.50) / MeCN
Gradient	Isocratic 65:35
Flow	1.0 mL/min
Runtime	20 minutes
Oven temperature	25 ºC
Detection	275 nm

General procedure I: Aqueous Biginelli reaction

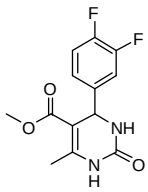
An aldehyde (1.0 equivalent, 1.0 M), urea (2.0 equivalents, 2.0 M) and L-tartaric acid (1.0 equivalent, 1.0 M) were dissolved in a 3:1 mixture of water/acetonitrile and this mixture was stirred for 10 minutes at room temperature. Then methyl acetoacetate (1.0 equivalent, 1.0 M) was added and the mixture was stirred overnight

at 80ºC. The product was collected either by filtration or by extraction of the reaction mixture with EtOAc followed by column chromatography of the crude product.



Biginelli ester 1e [27]

Employing general procedure I, reaction between benzaldehyde (530 mg, 5.0 mmol), methylacetoacetate (580 mg, 5.0 mmol) and urea (600 mg, 10.0 mmol) in the presence of L-tartaric acid (750 mg, 5.0 mmol) afforded Biginelli ester **1e** (1.05 g, 85 %) as a white solid. Biginelli product **1e** crystallized from the reaction mixture and could be collected by suction filtration and washing with a small volume (5-10 mL) of a 1:1 hexane/EtOAc solution to remove impurities. The resultant white crystals were dried by suction filtration. ^{1}H NMR (250 MHz, DMSO-d_6): 9.19 (s, 1H), 7.73 (s, 1H), 7.35-7.22 (m, 5H), 5.14 (s, 1H), 3.53 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (63 MHz, DMSO-d_6): 166.7, 153.1, 149.5, 145.5, 129.3 (2C), 128.1, 127.0 (2C), 99.9, 54.7, 51.6, 18.7. t_r = 4.85 min (*R*-enantiomer), t_r = 12.17 min (*S*-enantiomer).

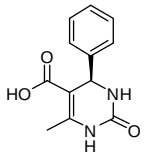


Biginelli ester 1g [28]

Employing general procedure I, reaction between 3,4-difluoro-benzaldehyde (710 mg, 5.0 mmol), methyl-acetoacetate (580 mg, 5.0 mmol) and urea (600 mg, 10.0 mmol) in the presence of L-tartaric acid (750 mg, 5.0 mmol), followed by extraction with EtOAc (3 x 15 mL) and column chromatography (cyclohexane/EtOAc 1:1, gradient) afforded Biginelli ester **1g** (274 mg, 19%) as a white solid. ^{1}H NMR (250 MHz, DMSO-d_6): 9.29 (s, 1H), 7.80 (s, 1H), 7.43-7.05 (m, 3H), 5.16 (s, 1H), 3.54 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (63 MHz, DMSO-d_6): 166.0, 152.2, 150.8, 150.0, 147.1, 142.7, 123.2, 117.8, 115.5, 98.7, 53.4, 51.2, 18.2. t_r = 4.94 min (*R*-enantiomer), t_r = 10.19 min (*S*-enantiomer).

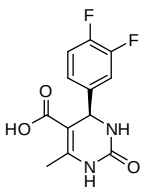
General procedure II: Biginelli-Biotransformation sequence

First, the Biginelli reaction was performed with the aldehyde (2.5 mmol), methylacetoacetate (290 mg, 2.5 mmol) and urea (300 mg, 5 mmol) in the presence of L-tartaric acid (375 mg, 2.5 mmol) in a mixture of H_2O/ACN (3:1, 2.5 mL), stirring overnight at 80 °C. After the aqueous Biginelli reaction the reaction mixture was diluted with acetonitrile (34 mL) and H_2O (243 mL) and Trizma HCl (320 mg, 2.0 mmol) and Trizma base (1.36 g, 11.2 mmol) were added. The pH was adjusted to 8.5 and the mixture was heated to 37 ºC for 30 minutes. The pH was again adjusted to 8.5 after which the enzyme (89 g, 2427 units/mL[23]) was added. The biotransformation was run until it reached maximum conversion, which was monitored in time by means of chiral HPLC analysis following the method described in table 2. HPLC samples were prepared by taking 1.5 mL of reaction mixture, which was acidified to pH 2~3, extracted with EtOAc (3 x 5.0 mL), concentrated by evaporation under reduced pressure and dissolved in acetonitrile.



Biginelli acid (*R*)-3e [29]

Employing general procedure II, enzymatic hydrolysis of Biginelli ester **1e** by Subtillisin from *Bacillus lentus* took 11 days to reach 43% conversion and afforded Biginelli acid **(*R*)-3e** in 89 % *ee*. ^{1}H NMR (250 MHz, DMSO-d_6): 11.80 (bs, 1H), 9.05 (s, 1H), 7.64 (s, 1H), 7.34-7.20 (m, 5H), 5.11 (s, 1H), 2.24 (s, 3H). ^{13}C NMR (63 MHz, DMSO-d_6): 168.0, 153.3, 148.6, 145.7, 129.2 (2C), 128.0, 127.1 (2C), 100.7, 54.9, 18.6. t_r = 4.36 min (*R*-enantiomer), t_r = 10.62 min (*S*-enantiomer).

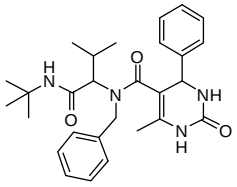


Biginelli acid (*R*)-3g [30]

Employing general procedure II, enzymatic hydrolysis of Biginelli ester **1g** by Subtillisin from Bacillus Lentus took 4 days and afforded Biginelli acid **(*R*)-3g** with a conversion of 49% and an *ee* of 92%. ^{1}H NMR (250 MHz, DMSO-d_6): 12.0 (bs, 1H), 9.14 (s, 1H), 7.71 (s, 1H), 7.38 (m, 1H), 7.20 (m, 1H), 7.08 (m, 1H), 5.13 (d, J = 2.8 Hz, 1H), 2.24 (s, 3H). ^{13}C NMR (63 MHz, DMSO-d_6): 167.9, 153.0, 149.3, 143.4, 123.6, 118.5, 118.2, 116.2, 115.9, 100.0, 64.0, 18.7. t_r = 4.37 min (*R*-enantiomer), t_r = 8.97 min (*S*-enantiomer)

General procedure III: Microwave experiments

A glass microwave vial was equipped with a magnetic stirring bar and the aldehyde (2.5 mmol, 1.0 eq.), methylacetoacetate (2.5 mmol, 1.0 eq.), urea (5.0 mmol, 2.0 eq.), TFA (2.5 mmol, 1.0 eq.) and acetonitrile (2.5 mL). This mixture was heated in a microwave reactor (power 200 W, ramp time 2.0 min, hold time 30 min at 120ºC) and subsequently the products, were filtered off and washed with a crushed ice-ethanol mixture to remove impurities. Biginelli esters **1e** and **1g** were isolated in yields of 90 and 70 %, respectively.



Ugi product 7a

Isobutyraldehyde (40 mg, 0.43 mmol), benzylamine (60 mg, 0.56 mmol) and racemic Biginelli acid **1e** (100 mg, 0.43 mmol) were added to a solution of phosphate buffer (4.0 mL, 6.8mM, pH = 8.5) and DMSO (4.0 mL) containing glucose (1.0 M). The resulting reaction mixture was shaken for 2 hours after which *tert*-butylisocyanide (47 mg, 0.56 mmol) was added. The reaction mixture was shaken for 5 days and subsequently diluted with H_2O (15 mL) and extracted with EtOAc (3 x 30 mL). The combined organic fractions were washed with brine (2 x 20 mL), dried (Na_2SO_4), filtrated and concentrated under reduced pressure. The crude product was purified by column chromatography using a gradient of MeOH in CH_2Cl_2 (1% - 5%) to give the Ugi product **7a** (0.24 mmol, 55%) as a white solid as a 50:50 mixture of diastereomers. ^{1}H NMR (400 MHz, DMSO-d_6, 360 K) 8.25 (s, 1H), 8.18 (s, 1H), 7.33-6.99 (m, 24H), 5.13 (s, 1H), 4.95 (s, 1H), 4.82 (d, J = 15.2 Hz, 1H), 4.69 (d, J = 15.3 Hz, 1H), 4.59 (d, J = 15.3 Hz, 1H), 4.50 (d, J = 15.2 Hz, 1H), 4.07-4.00 (m, 1H), 3.87 (s, 1H), 2.28-2.24 (m, 2H), 1.78 (s, 3H), 1.66 (s, 3H), 1.26 (s, 9H), 1.25 (s, 9H), 0.89-0.86 (m, 6H), 0.74 (d, J = 6.6 Hz, 3H), 0.67 (d, J = 6.5 Hz, 3H). ^{13}C NMR (63 MHz, DMSO-d_6): 171.1, 170.7, 170.1, 169.9, 153.9 (2C), 142.9, 142.6, 136.5 (2C), 134.0 (2C), 129.5-127.4 (20C), 106.4, 106.2, 58.6 (2C), 58.3 (2C), 51.2 (2C), 51.0 (2C), 29.0 (3C), 28.9 (3C), 27.5 (2C), 20.6, 20.3, 20.2, 19.8, 17.3, 16.9. HRMS (ESI) calculated for $C_{28}H_{37}N_4O_3$ (MH^+) 477.2860, found 477.2862.

6.6 References and notes

1. Ramon, D. J.; Yus, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 1602-1634.
2. Drauz, K.; Waldmann, H. *Enzyme catalysis in organic synthesis*; Second ed.; Wiley-VCH Verlag GmbH: Weinheim, 2002.
3. Faber, K. *Biotransformations in organic chemistry*; 4th ed.; Springer, 1999.
4. Pollard, D. J.; Woodley, J. M. *Trends Biotechnol.* **2007**, *25*, 66-73.
5. Znabet, A. Literature thesis, Vrije Universiteit, 2006.
6. Yadav, J. S.; Subba Reddy, B. V.; Sridhar, P.; Reddy, J. S. S.; Nagaiah, K.; Lingaiah, N.; Saiprasad, P. S. *Eur. J. Org. Chem.* **2004**, 552-557.
7. Pirrung, M. C.; Das Sarma, K. *J. Am. Chem. Soc.* **2004**, *126*, 444-445.
8. Surendra, K.; Srilakshmi Krishnaveni, N.; Mahesh, A.; Rama Rao, K. *J. Org. Chem.* **2006**, *71*, 2532-2534.
9. Loh, T.-P.; Wei, L.-L. *Tetrahedron Lett.* **1998**, *39*, 323-326.
10. Biginelli, P. *Gazz. Chim. Ital.* **1893**, *23*, 360-413.
11. Kappe, C. O. *J. Org. Chem.* **1997**, *62*, 7201-7204.
12. Kappe, C. O. *Acc. Chem. Res.* **2000**, *33*, 879-888.
13. Kappe, C. O. In *Multicomponent reactions*; Zhu, J., Bienaymé, H., Eds.; Wiley-VCH Verlag GmbH: Weinheim, 2005.
14. Kappe, C. O. *QSAR Comb. Sci.* **2003**, *22*, 630-645.
15. Kappe, C. O. *Eur. J. Med. Chem.* **2000**, *35*, 1043-1052.
16. Goss, J. M.; Schaus, S. E. *J. Org. Chem.* **2008**, *73*, 7651-7656.
17. Chen, X.-H.; Xu, X.-Y.; Liu, H.; Cun, L.-F.; Gong, L.-Z. *J. Am. Chem. Soc.* **2006**, *128*, 14802-14803.
18. Suzuki, I.; Suzumura, Y.; Takeda, K. *Tetrahedron Lett.* **2006**, *47*, 7861-7864.
19. Polshettiwar, V.; Varma, R. S. *Tetrahedron Lett.* **2007**, *48*, 7343-7346.

20. Dominguez de Maria, P.; Garcia-Burgos, C. A.; Bargeman, G.; Van Gemert, R. W. *Synthesis* **2007**, 1439-1452.
21. Sobolev, A.; Franssen, M. C. R.; Vigante, B.; Cekavicus, B.; Zhalubovskis, R.; Kooijman, H.; Spek, A. L.; Duburs, G.; De Groot, A. *J. Org. Chem.* **2002**, *67*, 401-410.
22. Sidler, D. R.; Barta, N.; Li, W.; Hu, E.; Matty, L.; Ikemoto, N.; Campbell, J. S.; Chartrain, M.; Gbewonyo, K.; Boyd, R.; Corley, E. G.; Ball, R. G.; Larsen, R. D.; Reider, P. J. *Can. J. Chem.* **2002**, *80*, 646-652.
23. One unit will hydrolyze casein to produce color equivalent to 1.0 μmole (181 μg) of tyrosine per minute at pH 7.5 at 37 ºC (color by Folin & Ciocalteu's reagent).
24. Desai, B.; Dallinger, D.; Kappe, C. O. *Tetrahedron* **2006**, *62*, 4651-4664.
25. Fewell, S. W.; Smith, C. M.; Lyon, M. A.; Dumitrescu, T. P.; Wipf, P.; Day, B. W.; Brodsky, J. L. *J. Biol. Chem.* **2004**, *279*, 51131-51140.
26. Pirrung, M. C.; Das Sarma, K. *Tetrahedron* **2005**, *61*, 11456-11472.
27. Yamamoto, K.; Chen, Y. G.; Buono, F. *Org. Lett.* **2005**, *7*, 4673-4676.
28. Essa, H.; Sidler, D. R.; Dolling, U.-H. *J. Org. Chem.* **1998**, *63*, 3454-3457.
29. Valverde, M. G.; Dallinger, D.; Kappe, C. O. *Synlett.* **2001**, 741-744.
30. Barrow, J. C.; Nanternet, P. G.; Selnick, H. G.; Glass, K. L.; Rittle, K. E.; Gilbert, K. F.; Steele, T. G.; Homnick, C. F.; Freidinger, R. M.; Ransom, R. W.; Kling, P.; Reiss, D.; Broten, T. P.; Schorn, T. W.; Chang, R. S. L.; O'Malley, S. S.; Olah, T. V.; Ellis, J. D.; Barrish, A.; Kassahun, K.; Leppert, P.; Nagarathnam, D.; Forray, C. *J. Med. Chem.* **2000**, *43*, 2703-2718.

Summary

Multicomponent reactions

Studies toward Scaffold and Stereochemical Diversity

Multicomponent reactions (MCRs) are highly flexible, convenient reactions to rapidly generate complex and diverse small molecules. As such they are very suitable to access unexplored regions of chemical space in a Diversity Oriented Synthetic (DOS) approach. They also form the basis for modular reaction sequences, a conceptual new approach to DOS, which consists of a combination of MCRs and other complexity-generating reactions, like cycloadditions, condensations or even additional MCRs. In these sequences a densely functionalized reactive intermediate, like a 1-azadiene, is formed *via* an initial MCR that can react with different additional components yielding a diverse set of complex scaffolds. However, an inherent problem of using MCRs is the lack of stereocontrol over newly formed stereocenters.

The research described in this thesis focuses on two different subjects: (i) the use of MCRs for the generation of scaffold diversity *via* modular reaction sequences using 1-azadienes and (ii) possible approaches toward stereoselective MCRs.

1-Azadienes in cycloaddition and multicomponent reactions towards N-heterocycles

1-Azadienes are extremely versatile building blocks for the efficient synthesis of nitrogen heterocycles, which can be found in many biologically active small molecules. The reason for this versatility is the various possible reactivities of 1-azadienes (see Figure 1).

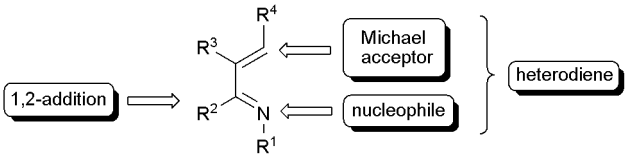
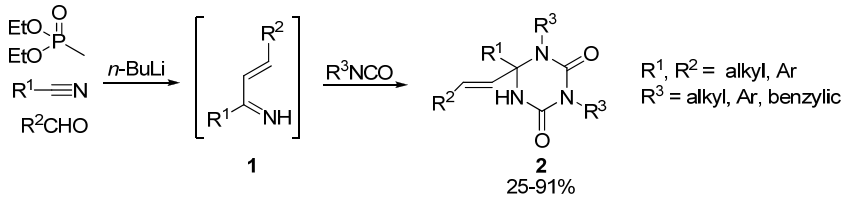


Figure 1: Different reactivities of 1-azadienes.

1-Azadienes can react as nucleophiles, electrophiles and as dienophiles, dipolarophiles or carbenophiles. In chapter 2, various applications of 1-azadienes in cycloaddition, electrocyclization, and multicomponent reactions for the efficient construction of a broad range of N-heterocycles are described. The 1-azadienes are reactive intermediates in these syntheses and are either generated *in situ* or isolated and then used for further reactions. Also the use of 1-azadienes to generate complexity and diversity in several scaffolds is highlighted. They prove excellent platforms to address skeletal diversity in DOS. Especially in combination with MCR-based strategies, 1-azadienes represent a challenging array of functionalities that can be employed to explore chemical space efficiently and identify small molecular probes for biology.

A multicomponent synthesis of triazinane diones

One type of N-heterocycle that can be formed from the 1-azadiene *via* a MCR is the triazinane dione (**2**, Scheme 1). Reaction between diethyl methylphosphonate, a nitrile and an aldehyde yields 1-azadiene **1**, which is then reacted with 2 equivalents of isocyanate yielding the triazinane dione **2** (Scheme 1).



Scheme 1: Multicomponent synthesis of triazinane diones.

First, the reaction conditions were optimized and after that a study of the scope of compatible inputs was conducted. This yielded a small library of 17 different triazinane diones in reasonable to good yields (25-91%). (Hetero)aromatic and aliphatic substituents on the nitrile and aldehyde can be used and benzylic and aromatic substituents on the isocyanate are tolerated. Chiral inputs can also be used in the reaction resulting in a maximum *de* of 67% of the triazinanedione **2**.

Generation of molecular diversity using a complexity-generating MCR-platform toward triazinane diones

Next, research was conducted to investigate if the triazinane dione scaffold could be used as a platform for the generation of diverse sets of relatively complex small molecules. For this, the triazinane dione was first alkylated to afford a scaffold with an appropriate synthetic handle to allow follow-up chemistry.

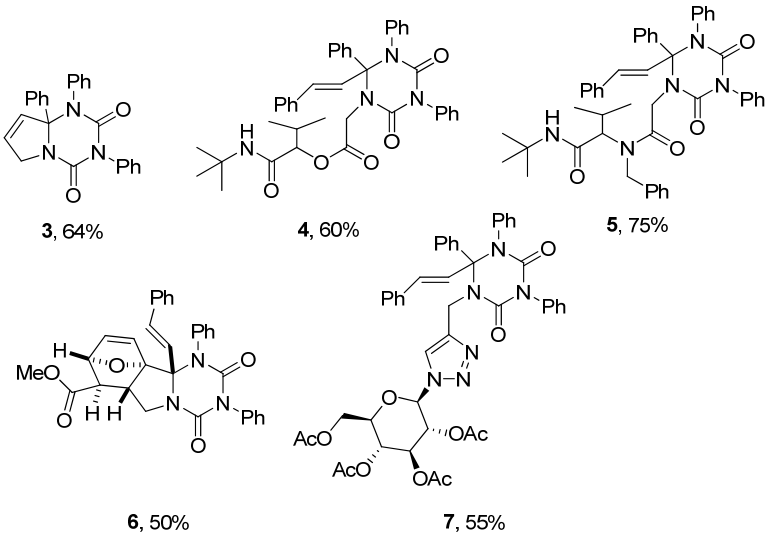
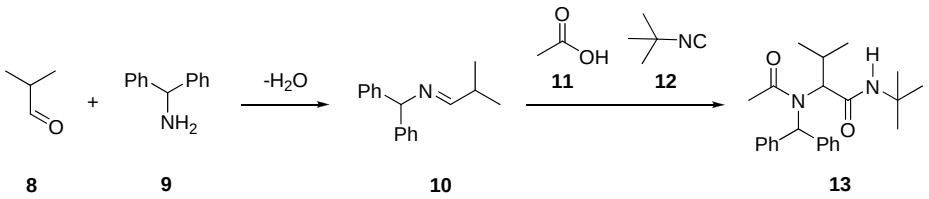


Figure 2: Different scaffolds obtained.

Then additional complexity-generating reactions were performed, like the ring-closing metathesis, cycloaddition reactions (Huisgen or Diels-Alder) and isonitrile-based MCRs (Passerini or Ugi). All five different products (**3-7**, Figure 2) could be obtained in good yields (50-75%) in very short reaction sequences (maximum of four). This nicely demonstrates that the triazinane dione core **2** is indeed a versatile platform to generate efficiently both diversity and complexity.

Mechanistic studies toward a stereoselective Ugi reaction

The research described in chapter 5 deals with studies toward a stereoselective Ugi-reaction (U-4CR) using chiral catalysts. The design of a suitable catalyst for an enantioselective U-4CR depends on our understanding of the exact reaction mechanism. Therefore, a thorough study of critical reaction parameters was required. A model reaction (Scheme 2) was chosen to study the influence of solvent, temperature and acid concentration on the performance of the U-4CR. This should lead to the selection of optimal conditions for a screening of potential asymmetric catalysts.



Scheme 2: Standard Ugi-reaction.

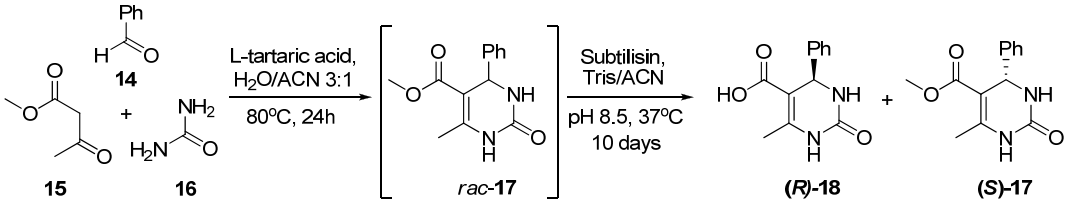
The study revealed that in methanol the U-4CR proceeds too fast to study any catalysis. However, a combination of dichloromethane or toluene and a temperature of -5 °C seemed reasonable conditions to study asymmetric catalysis. It was also found that the reaction can be accelerated using methanol at low temperatures, and that the reaction does not reach completion using a catalytic amount of acetic acid in the presence of 1 equivalent of acetate.
Next, a suitable Lewis acid for activation of the imine proved scandium triflate, which, in combination with 1 equivalent of sodium acetate afforded the Ugi-product in reasonable to good yields. Using a substoichiometric amount (33%) of $Sc(OTf)_3$ in trifluoroethanol, the reaction can be driven to completion. Initial screening of several chiral ligands in combination with $Sc(OTf)_3$ yielded **13** with a maximum of 10% *ee* in a reasonable yield (45-60%).

Combining biocatalysis with multicomponent reactions

Another approach to address the problem of stereoselectivity in MCRs would be the combination of them with biocatalysis in a one-pot procedure. As biocatalysis is normally performed in aqueous media, also MCRs are needed that can be performed in aqueous media. Recent studies have demonstrated that many of the classical MCRs (Biginelli, Ugi, Passerini, Strecker and Mannich) can be performed in aqueous media and are thus in principle compatible with biocatalysis. We envisioned a MCR/biotransformation sequence (Scheme 3)

combining an aqueous Biginelli reaction with a specific hydrolase that hydrolyzes the ester functionality in the Biginelli product **17** (Scheme 3). In the kinetic resolution, one of the enantiomers of the racemic Biginelli product **17** is converted to the corresponding carboxylic acid while the other enantiomer remains unaffected.

First, the individual steps of the Biginelli-hydrolase sequence were established. The aqueous Biginelli reaction is performed best in a 3:1 water/acetonitrile mixture with L-tartaric acid as the acid catalyst and overnight stirring at 80°C, resulting in an isolated yield of 85%. The biotransformation is performed best using the hydrolase subtilisin from *Bacillus lentus* (Genencor Purafect 4000L).



Scheme 3: MCR/biotransformation sequence in one pot.

Direct connection of this Biginelli reaction and biotransformation (resulting in a one-pot sequence) proved to be possible in good conversions and *ee*'s for both the acid and the ester.

In conclusion, major challenges still remain in solving stereoselectivity issues in MCRs. On the other hand, however, this research has demonstrated that MCRs provide an ever-expanding toolbox for the generation of scaffold diversity *via* modular reaction sequences.

Samenvatting

Multicomponentreacties

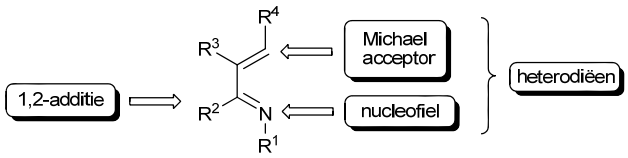
Studies naar Diversiteit in Ringstructuur en Stereochemie

Multicomponentreacties (MCRs) zijn zeer handige reacties om snel complexe en diverse kleine moleculen te genereren. Als zodanig zijn ze zeer geschikt om onbekende gebieden van de chemische ruimte te verkennen in een Diversiteit Georiënteerde Synthetische (DOS) benadering. Ze vormen ook de basis voor modulaire reactiesequenties, een conceptueel nieuwe benadering voor DOS, die bestaat uit een combinatie van MCRs en andere complexiteitgenererende reacties, zoals cycloaddities, condensaties of zelfs additionele MCRs. In deze sequenties wordt via een eerste MCR een rijk gefunctionaliseerd reactief intermediair, zoals een 1-azadiëen, gevormd dat kan reageren met verschillende additionele componenten waardoor een diverse set van complexe ringstructuren wordt gevormd. Een inherent probleem van het gebruik van MCRs is echter het gebrek aan stereocontrole over nieuw gevormde stereocentra.

Het onderzoek beschreven in dit proefschrift richt zich op twee verschillende onderwerpen: (i) het gebruik van MCRs voor het genereren van diverse ringstructuren via modulaire reactie sequenties gebruik makend van 1-azadiënen en (ii) mogelijke benaderingen voor stereochemische MCRs.

1-Azadiënen in cycloaddities en multicomponentreacties naar N-heterocycli

1-Azadiënen zijn zeer veelzijdige bouwstenen voor het efficiënt synthetiseren van stikstofheterocycli die gevonden kunnen worden in veel biologisch actieve kleine moleculen. De reden voor deze veelzijdigheid is de verschillende mogelijke reactiviteiten van 1-azadiënen (zie Figuur 1).



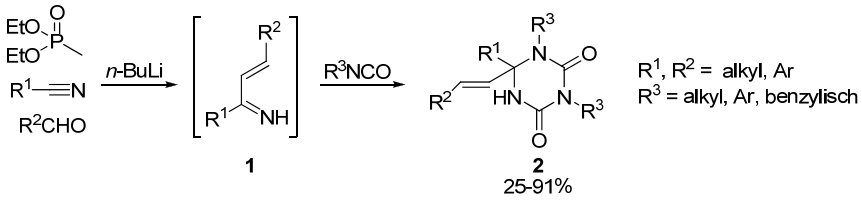
Figuur 1: Verschillende reactiviteiten van 1-azadiënen.

Ze kunnen reageren als nucleofielen, electrofielen en als dienofielen, dipolarofielen of carbenofielen. In hoofdstuk 2 worden verschillende toepassingen van 1-azadiënen in cycloaddities, electrocyclisaties, en multicomponentreacties beschreven voor de efficiënte constructie van een breed scala aan N-heterocycli. De 1-azadiënen zijn reactieve intermediairen in deze syntheses en worden of *in situ* gemaakt of geïsoleerd en vervolgens gebruikt in vervolgreacties. Ook het gebruik van 1-azadiënen voor het genereren van complexiteit en diversiteit wordt besproken. Ze blijken uitstekende platforms te zijn om skelet

diversiteit te genereren in DOS. Vooral in combinatie met op MCRs gebaseerde strategieën, vertegenwoordigen 1-azadiënen een breed scala aan functionaliteiten die gebruikt kunnen worden om de chemische ruimte efficiënt te verkennen en om kleine biologische moleculaire probes te identificeren.

Een multicomponent synthese van triazinaandionen

Eén type N-heterocyclus die gevormd kan worden vanuit een 1-azadiëen via een MCR is het triazinaandion (**2**, Schema 1). Reactie tussen diethyl methylphosphonaat, een nitril en een aldehyde geeft 1-azadiëen **1** die vervolgens verder kan reageren met 2 equivalenten isocyanaat tot het triazinaandion **2** (Schema 1).

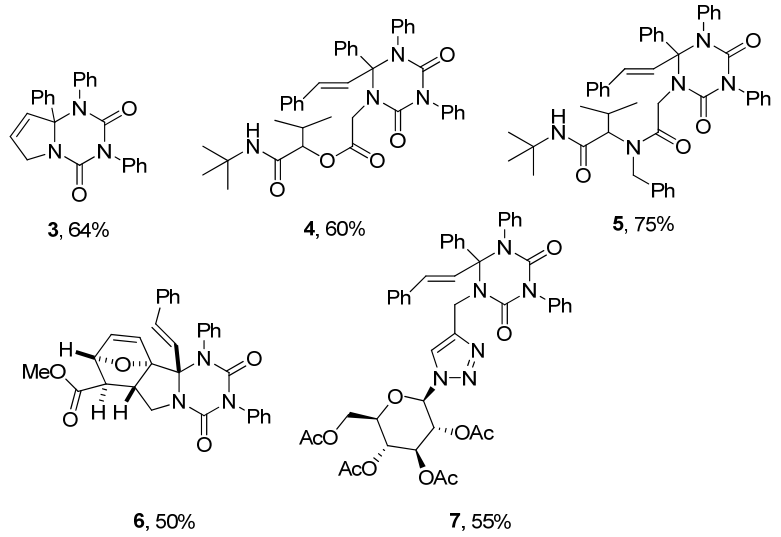


Schema 1: Multicomponent synthese van triazinaandionen.

Eerst werden de reactiecondities geoptimaliseerd en vervolgens werd een scope studie uitgevoerd leidend tot een kleine bibliotheek van 17 verschillende triazinaandionen in redelijke tot goede opbrengsten (25-91%). (Hetero)aromatische en alifatische substituenten op het nitril en aldehyde kunnen worden gebruikt en benzylische en aromatische substituenten op het isocyanaat worden getolereerd. Chirale inputs kunnen ook gebruikt worden in de reactie, resulterend in een maximale *de* van 67%.

Genereren van moleculaire diversiteit met behulp van een complexiteit-genererend MCR-platform naar triazinaandionen

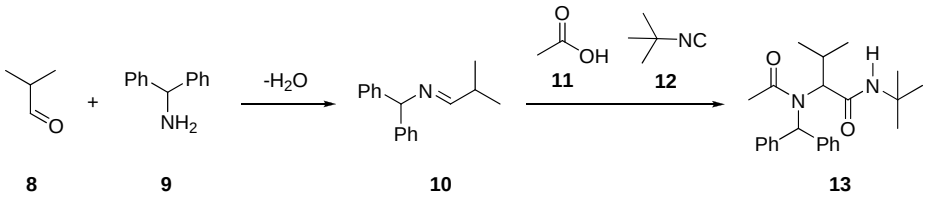
Vervolgens werd onderzoek gedaan naar het gebruik van de triazinaandion-ringstructuur als een platform voor het verkrijgen van diverse en complexe kleine moleculen. Hiervoor moest het triazinaandion eerst gealkyleerd worden, zodat met het juiste synthetische handvat vervolgchemie mogelijk werd.
De additionele complexiteitgenererende reacties die gekozen werden waren ringsluitings-metathese, cycloadditie reacties (Huisgen of Diels-Alder) en op isonitril gebaseerde MCRs (Passerini of Ugi). Alle vijf verschillende ringstructuren (**3**-**7**, Figuur 2) konden verkregen worden in goede opbrengsten (50-75%) in zeer korte reactie sequenties (maximaal 4 stappen). Dit bewijst dat het triazinaandion een veelzijdig platform is om diversiteit en complexiteit te verkrijgen.



Figuur 2: Verschillende verkregen ringstructuren.

Mechanistische studies naar een stereoselectieve Ugi reactie

Het onderzoek beschreven in hoofdstuk 5 beschrijft studies naar een stereoselectieve Ugi-reactie (U-4CR) met behulp van chirale katalysatoren. Het ontwerpen van een geschikte katalysator voor een enantioselectieve U-4CR hangt af van onze kennis van het exacte reactiemechanisme. Daarom werd een gedegen studie van de essentiële reactieparameters uitgevoerd. Een modelreactie (Schema 2) werd gekozen om de invloed van oplosmiddel, temperatuur en zuurconcentratie op de prestaties van de U-4CR te onderzoeken. Dit zou moeten leiden tot de selectie van optimale condities om potentiële asymmetrische katalysatoren te screenen.



Schema 2: Standaard Ugi-reactie.

Uit de studie kwam naar voren dat de U-4CR in methanol te snel verloopt om katalyse te kunnen bestuderen. Echter, een combinatie van dichloormethaan of tolueen met een temperatuur van -5 °C leken redelijke condities om chirale katalyse te bestuderen. Het bleek ook dat de reactie versneld kan worden bij gebruik van methanol bij lage temperaturen, en dat de reactie niet volledig verloopt als een katalytische hoeveelheid azijnzuur wordt gebruikt in aanwezigheid van 1 equivalent acetaat.

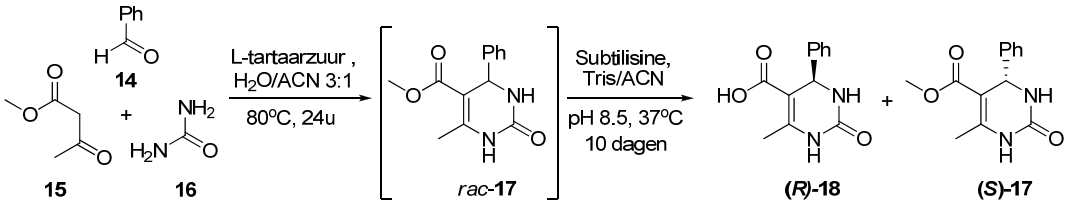
Vervolgens werd gevonden dat Scandium triflaat een geschikt Lewis zuur is om het imine te activeren en dat, in combinatie met 1 equivalent natriumacetaat, goede opbrengsten aan Ugi-product bereikt konden worden. Bij gebruik van een substoichiometrische hoeveelheid van

33% $Sc(OTf)_3$ in trifluorethanol, kan de reactie volledig verlopen. Screening van een serie aan chirale liganden in combinatie met $Sc(OTf)_3$ liet zien dat **13** in een maximale *ee* van 10% en in een redelijke opbrengst (45-60%) gevormd werd.

Combinatie van biokatalyse met multicomponentreacties

Een andere benadering om het probleem van stereoselectiviteit in MCRs op te lossen zou kunnen zijn om ze te combineren met biokatalyse in een éénpots-procedure. Omdat biokatalyse normaal uitgevoerd wordt in waterig milieu zijn ook MCRs nodig die uitgevoerd kunnen worden in waterig milieu. Recente studies hebben aangetoond dat veel van de klassieke MCRs (Biginelli, Ugi, Passerini, Strecker en Mannich) uitgevoerd kunnen worden in waterig milieu en deze zijn dus in principe te combineren met biokatalyse. Er werd een MCR/biotransformatie sequentie (Schema 3) bedacht die een Biginelli reactie in waterig milieu combineert met een specifiek hydrolase dat de ester functionaliteit in het Biginelli produkt **17** hydrolyseert (Schema 3). In de kinetische resolutie wordt één van de enantiomeren van het racemisch Biginelli produkt **17** omgezet naar het overeenkomstige carbonzuur terwijl de andere enantiomeer ongemoeid blijft.

Als eerste werden de individuele stappen van de Biginelli-hydrolase sequentie geoptimaliseerd. De Biginelli reactie in waterig milieu verliep het best in een mengsel van water/acetonitril (3:1) met L-tartaarzuur als de zuur-katalysator en overnacht roeren bij 80°C. De geïsoleerde opbrengst bedroeg 85%. De biotransformatie verliep het best met het hydrolase subtilisine van *Bacillus lentus* (Genencor Purafect 4000L).



Schema 3: MCR/biotransformatie sequentie in één pot.

Het direct koppelen van de Biginelli reactie en de biotransformatie (resulterend in een éénpotssequentie) bleek mogelijk in goede conversies en *ee*'s voor zowel het zuur als de ester.

Samenvattend moet er nog veel gebeuren om het probleem van de stereoselectiviteit in MCRs op te lossen. Dit onderzoek heeft echter wel aangetoond dat MCRs een zeer handig hulpmiddel zijn voor het genereren van diverse ringstructuren via modulaire reactiesequenties.

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Bas