Applications of Multicomponent Reactions to the Synthesis of Diverse Heterocyclic Scaffolds

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Abstract

The sequencing of multicomponent reactions (MCRs) and subsequent cyclization reactions is a powerful stratagem for the rapid synthesis of diverse heterocyclic scaffolds. The optimal MCR is sufficiently flexible that it can be employed to generate adducts bearing a variety of functional groups that may then be selectively paired to enable different cyclization manifolds, thereby leading to a diverse collection of products. The growing interest in diversity-oriented synthesis has led to increased attention to this paradigm for library synthesis, which has inspired many advances in the design and implementation of MCRs for the construction of diverse heterocyclic scaffolds.

Keywords

multicomponent processes; cyclization; diversity-oriented synthesis; heterocyclic compounds; molecular diversity

Introduction

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

Arguably, one of the most promising synthetic strategies for generating collections of small molecules by DOS involves the sequencing of multicomponent reactions (MCRs) with subsequent transformations, including cyclizations and refunctionalizations, that form new compounds possessing increased molecular complexity and diversity.[3] This process of sequencing MCRs with subsequent cyclizations is commonly referred to as the build/couple/ pair strategy of DOS.[4] Ideally, the MCRs will be sufficiently versatile that each input for the MCR can incorporate a wide range of functionalities and substituents. Using the tactic of functional group pairing,[5] the MCR adduct is then selectively transformed in ring forming processes and refunctionalizations comprising the synthome[6] into the target heterocyclic structures. Moreover, the ring forming reactions should be chosen so that the products they

generate still contain functional handles that can be further derivatized by other carbon-carbon or carbon-heteroatom bond forming reactions. The major advantage of combining MCRs with post-condensation modifications relative to other strategies for DOS is that it enables access to a number of functionalized heterocyclic scaffolds in a short number of steps.

The fields of DOS and MCRs have recently been extensively reviewed,[7] so this Concept Article will focus only on providing an overview of the applications of MCRs that have been sequenced with multiple ring-forming reactions that lead thereby to the synthesis of diverse heterocyclic scaffolds.

Applications of the Ugi Reaction

Since its original publication in 1959, the Ugi four component reaction (U-4CR) has emerged as the most well known and widely used MCR in organic synthesis.[3,8] The U-4CR is extraordinarily functional group tolerant, and each of the four components can contain functionality that can be used in subsequent transformations, thus allowing for access to a number of cyclization manifolds. It thus does not occasion surprise that a substantial body of work has been devoted to post condensation modifications of U-4CR adducts.[9] A brief overview showing some of the post-condensation cyclization manifolds accessible by the U-4CR is presented in Scheme 2.[10] Upon examining structures **9–16**, it is evident that considerable structural diversity can be generated in only two or three steps by sequencing the U-4CR with different cyclization reactions.

In 2005 El Kaïm and Grimaud reported a variation on the U-4CR referred to as the Ugi-Smiles coupling.[11] In the Ugi-Smiles process, an electron deficient phenol is substituted for the carboxylic acid normally used in the U-4CR. The Ugi-Smiles reaction works well with a variety of electron deficient phenols, including heterocyclic phenols like the pyrimidines **20** (Scheme 3). By incorporating different functional handles into **20**, various cyclization modes could be accessed. When an allyl group was incorporated into **20** (X = allyl), the products that were formed underwent sequential ring closing metathesis (RCM) and double bond isomerization to give **23**.[12] Similarly, an Ugi-Smiles/Heck cyclization pathway could be implemented when the iodopyrimidine **20** (X = I) was used, thus providing the pyrrolopyrimidine **24**.[13] Only the RCM and Heck reaction have been used to date to manipulate the products of Ugi-Smiles reactions, but there is clearly the potential for sequencing the Ugi-Smiles condensation with other reactions analogous to what has been done with adducts formed by the U-4CR.

Applications of the Petasis 3CR

The Petasis three component reaction, which has also been termed a boronic acid Mannich reaction, consists of the coupling of an aldehyde, amine, and boronic acid.[14] Schreiber has shown that the Petasis reaction can be nicely exploited to synthesize a multifunctional template that is suitable for further elaboration by a number of pathways (Scheme 4).[15] For example, coupling of lactol **25**, amine **26**, and boronic acid **27** gave **28** in good yield. The adduct **28** is already highly functionalized, but in order to maximize its potential, a subsequent propargylation of **28** to give **29** was implemented to provide the desired multifunctional template. The need for a subsequent elaboration of the initial MCR product reveals one of the drawbacks of the Petasis 3CR and illustrates why employing MCRs that can incorporate all the requisite functionality into the product of the MCR are preferred. This modest shortcoming notwithstanding, the highly functionalized amine **29** was readily elaborated by seven different selective functional group pairing reactions to generate the structurally distinct scaffolds **30–45**. Because several of these transformations exploit the enyne functionality found in **29**, this example highlights the utility of enyne motifs for generating diverse structures.

This elegant application of the Petasis 3CR to DOS represents one of the few examples where the potential of a MCR product was fully realized. Every functional handle in **29** was utilized in a subsequent ring forming reaction to give the targeted heterocycles **30–45**. This work nicely demonstrates the power of utilizing all of the functional handles in MCR adducts as a strategy for maximizing the number and types of scaffolds that can be accessed.

Applications of the van Leusen 3CR

The van Leusen imidazole synthesis is a 3CR in which an aldehyde, an amine, and a substituted TosMIC reagent are combined to form a substituted imidazole in one pot. [16] When the substituents on the imidazole ring are suitably functionalized to allow subsequent cyclizations, polycyclic imidazole scaffolds, which are important owing to their presence in a number of natural products and biologically active compounds, may be readily prepared.[17]

The application of the van Leusen 3CR followed by subsequent ring closing reactions to the production of substituted imidazoles and fused imidazoles is nicely exemplified by the work of Djuric and co-workers (Scheme 5). By incorporating either two alkenes or an alkene and an alkyne into the starting materials, intermediates were prepared that could be cyclized by various RCM reactions.[18] For example, the imidazole **49** contains an enyne motif that was utilized in an enyne RCM to give **50**. Compounds amenable to further transformation via palladium-catalyzed ring closures were also readily generated by using an aryl halide as one of the inputs. Tricycle **54** was prepared via a sequential van Leusen/Heck reaction sequence,[19] and compounds such as **58** could be accessed via a Pd catalyzed C-H activation.[20] When an appropriately disposed azide and alkyne functionalities were incorporated as inputs in the reaction, intermediates were generated that underwent a spontaneous azide-alkyne cycloaddition to give fused triazolo imidazole scaffolds such as **61**.[21]

The van Leusen 3CR has considerable promise for preparing compounds that may be converted into diverse imidazole containing structures. However, there is but a solitary example wherein functionality is incorporated into the isocyanide input that might be exploited in subsequent cyclizations.[18a] The expansion of this methodology to include functional handles on the TosMIC derivative would significantly expand the scope of targets accessible by the van Leusen 3CR.

Applications of the Amide/Aldeyhde/Dienophile Reaction

A novel MCR developed by Beller involving the coupling of an amide, aldehyde, and dienophile (AAD reaction) has been used to prepare compounds that may be elaborated by post-condensation modifications.[22] For example, the AAD reaction of amide **62** with crotonaldehyde (**64**) and maleimide **63** provided the enyne **65** (Scheme 6).[23] Subsequent methylation of **65** provided **66**. As demonstrated by Schrieber (see Scheme 4), the enyne moiety is a versatile functional motif that may be transformed via different cyclizations manifolds by simply modifying reagents or catalysts to provide a variety of scaffolds. Accordingly, **66** could be converted into **67** via a ruthenium catalyzed Pauson-Khand reaction or into **68** by a palladium catalyzed Alder-ene reaction.

Alternatively, when the amide input also possessed an aryl halide group as found in **70**, substrates similar to **71** could be synthesized (Scheme 7).[24] Subsequent cyclization of **71** via a Heck reaction afforded the phenanthridone **72**. The phenanthridone core structure can be found in a number of alkaloids,[25] thus highlighting the broader utility of this method to access natural product-like structures.

Applications of the α,γ-Difunctionalization Reaction of β-Ketoamides

Spirocycles are present in a number of natural products and biologically active compounds, and they are consequently attractive targets for synthetic chemists.[26] Rodriguez has recently reported an interesting 3CR involving aldehydes **73**, β-ketoesters or amides **74**, and allylic or propargylic halides **75** that can be utilized for synthesizing spiroheterocyclic structures (Scheme 8).[27] By incorporating the appropriate functional groups in the intermediate adducts, a number of different cyclization modes could be accessed. For example, by a suitable combination of inputs, compounds **76** and **78** were prepared and cyclized via RCM into **77** and **79**, respectively. A similar 3CR was employed to prepare the vinyl bromide **80** that was converted via an intermolecular Heck reaction into diene **81**, which then underwent a Diels-Alder reaction with dimethyl acetylenedicarboxylate (DMAD) to give **82**. Pairing of the vinyl bromide and amide functionalities in **83** under conditions developed by Buchwald[28] yielded **84**.

Applications of the 4-Component Triazinane Dione Synthesis

Orru has recently developed a 4CR for the synthesis of triazinane diones by a process that entails the sequential combination of a phosphonate, nitrile, aldehyde, and two equivalents of an isocyanate.[29] While it has not been shown that the triazinane dione products themselves can be directly manipulated into other more complex heterocycles, an additional alkylation step affords substrates suitable for further cyclizations (Scheme 9).[30] The utility of this 4CR for heterocyclic synthesis can be illustrated by the combination of phosphonate **85**, benzonitrile, benzaldehyde, and phenyl isocyanate to yield **86** (R^1 = Ph), which underwent *N*-allylation to give an intermediate that was transformed into **88** by RCM. Use of 2-furonitrile as the nitrile input gave **87** (R^1 = furyl), which upon *N*-alkylation with **89** gave a compound that underwent a spontaneous intramolecular Diels-Alder to give **90**. While the need for a second alkylation step detracts somewhat from the overall efficiency and convenience, this methodology shows some promise as a quick entry into a diverse library of structures having triazinane dione subunits.

In all of these examples, only the alkyl halide and ester (or amide) incorporated functionality that was utilized in subsequent reactions. Further expansion of this methodology to access substrates suitable for additional modes of cyclization which utilize the aldehyde component would greatly enhance the usefulness of this methodology for the synthesis of diverse spiroheterocycles.

Applications of a Mannich-Type 4CR

In 2007 Martin published a 4CR that involved combining aldehydes, amines, acid chlorides, and nucleophiles to provide access to highly functionalized amide products that could be readily subjected to a variety of subsequent ring closures to give a diverse collection of heterocyclic scaffolds.[6] One of the important features of this approach to DOS is that there is considerable flexibility associated with the additional functionality that may be incorporated in each of the components. This allows for greater opportunity in the functional group pairing that is essential for transforming the initial adducts via different cyclization manifolds. A few examples will illustrate the potential of this novel strategy.

When aldehyde **91** was sequentially reacted with allylamine, acetyl chloride, and allylzinc bromide, the amide **92** was obtained (Scheme 10). The two olefins in **92** were then paired via RCM, and the amide and ester paired in a Dieckmann cyclization to give the benzazepine dione **94**. Similarly, when propargyl amine was used as the amine input in the initial condensation reaction, the resulting amide **93** could be transformed by a tandem enyne RCM/cross-metathesis in the presence of styrene, a fifth input, followed by a Dieckmann cyclization to

give the benzazepine **95**. Changing the aldehyde component in the initial 4CR to *o*-bromobenzaldehyde (**52**) provided the intermediate amide **96**, which was elaborated by a RCM and a subsequent Heck reaction to give the bridged azatricycle **97** (Scheme 11).

By judiciously varying the inputs in this Mannich-type 4CR, a number of different cycloaddition manifolds become accessible (Scheme 12). For example, when *o*-azidobenzaldehyde (**60**) and propargylamine are among the components in the 4CR, the intermediate amide thus formed may undergo spontaneous azide/alkyne [3+2] dipolar cycloaddition to give triazoles such as **100**. Alternatively, use of acryloyl chloride as the acylating agent and 2,4-pentadienyltrimethylsilane (**102**) as the nucleophile can lead to intermediates that will undergo facile intramolecular Diels-Alder cycloaddition to give compounds related to **103**. When the nucleophile is the silyl enol ether **104** and the amine or acylating agent contains a carbon-carbon double or triple bond, adducts such as **105** are produced. Such compounds may be used as precursors to azomethine ylides or nitrones that will undergo spontaneous [3+2] dipolar cycloadditions to give bicycles **106** and **107**, respectively.

The utility of this Mannich-type 4CR for the facile synthesis of complex natural products has also been demonstrated (Scheme 13). Namely, the sequential reaction of piperonal (**108**) with methyl amine, the benzylic Grignard reagent **109**, and the acid chloride **110** delivered **111**, which underwent an acid catalyzed double cyclization to give the isopavine alkaloid (±)-roelactamine (**112**).

Conclusion

The sequencing of MCRs with subsequent ring forming reactions is truly one of the best methods for rapidly accessing heterocyclic scaffolds. When the MCRs that are employed are flexible enough to enable incorporation of a broad range of functional groups, and these functional groups are chosen so that a variety of post MCR transformations can be employed, then the structures of accessible scaffolds are greatly increased. The examples presented herein illustrate that with careful selection of the MCR inputs, a single MCR can be used to generate versatile intermediates that may be readily transformed into diverse collections of compounds. However, there remains the need to develop new MCRs that allow access to different scaffolds, as well as the need to find new functional group pairing processes to implement on the MCR products so compounds having natural product or drug like structures may be easily prepared.

Acknowledgments

## References

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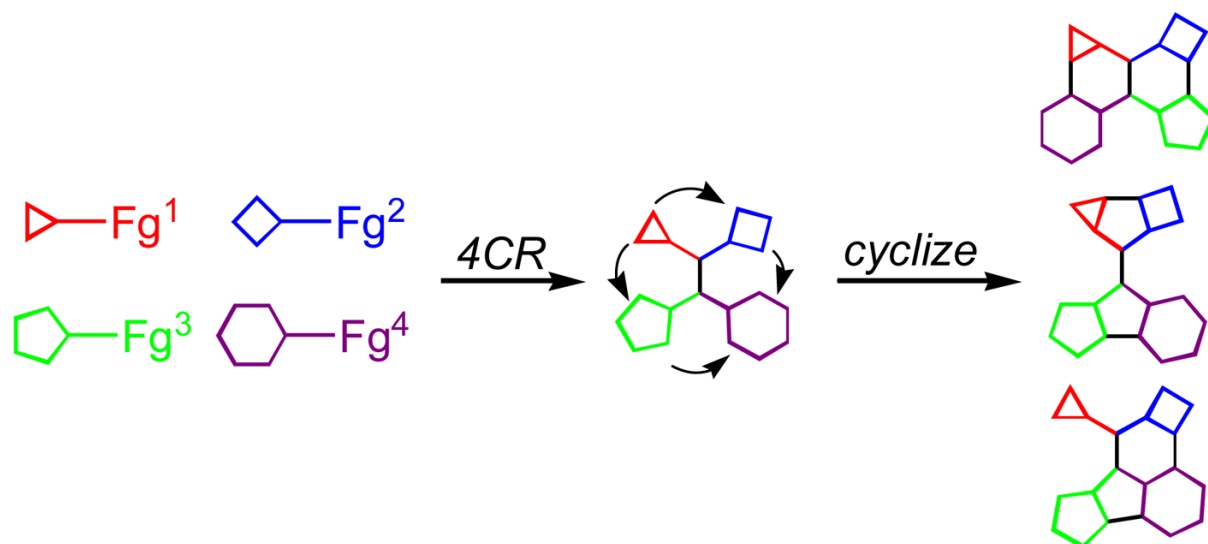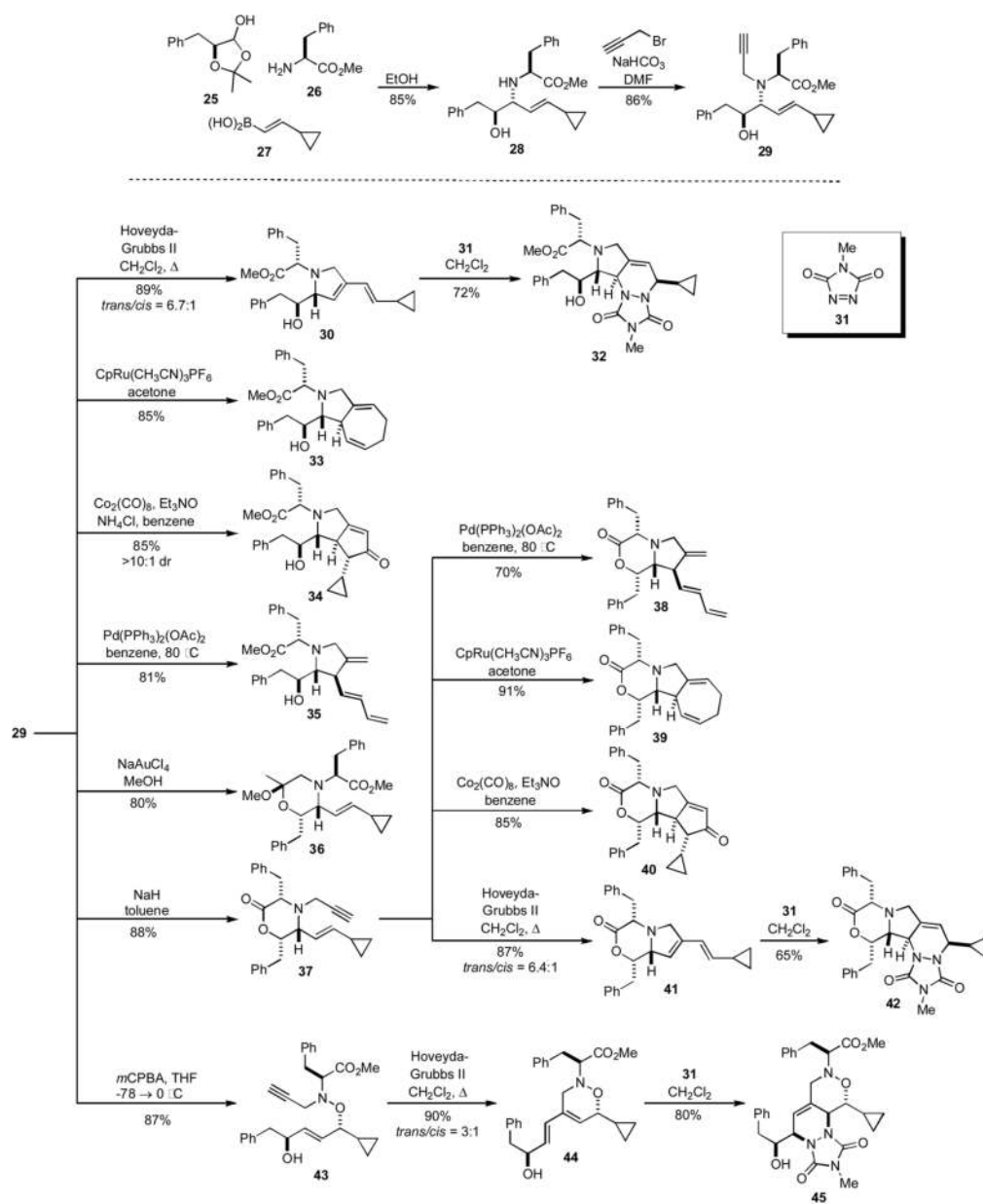
Scheme 1.
Sequencing of MCRs with post condensation cyclizations to generate diverse scaffolds.
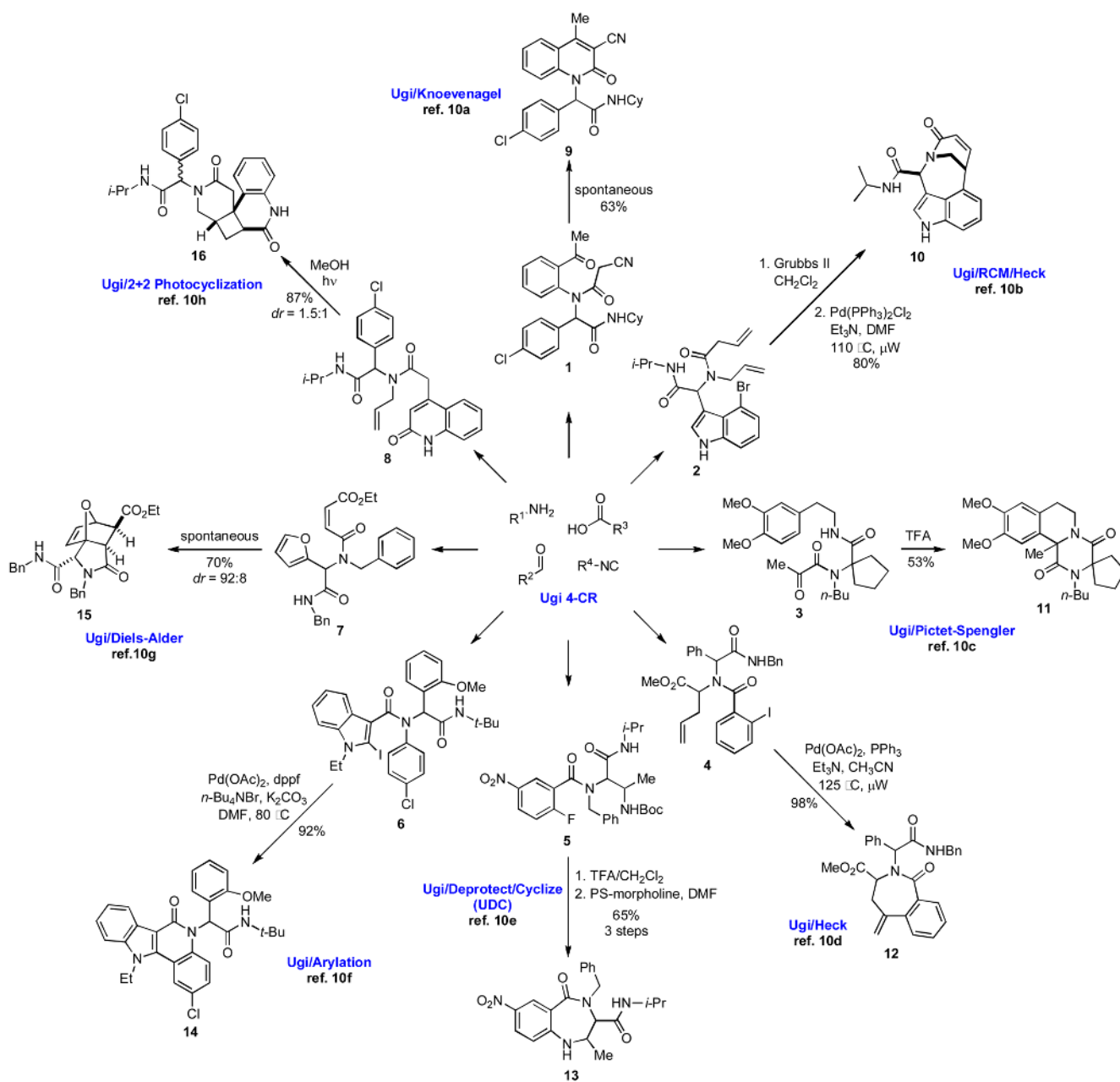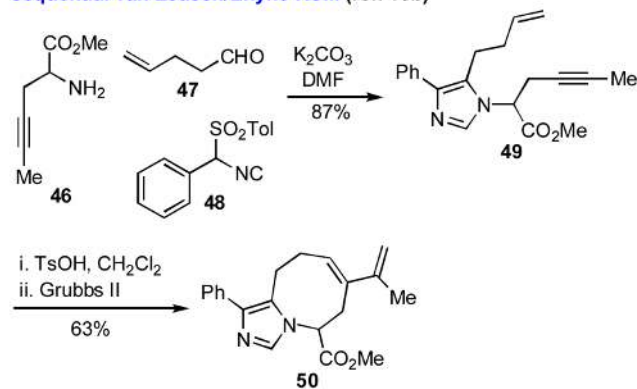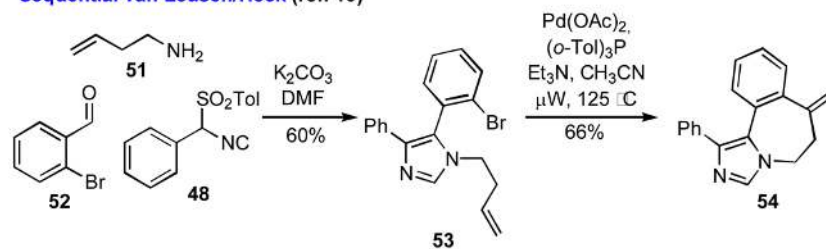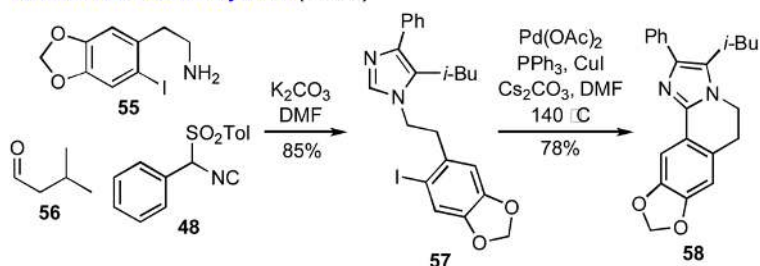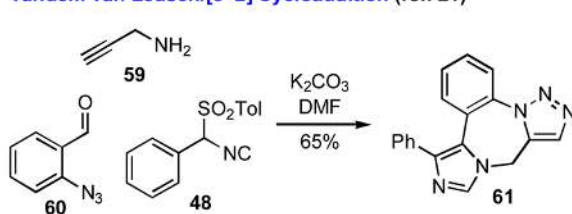
Scheme 2.
An overview of the U-4CR post condensation cyclizations.
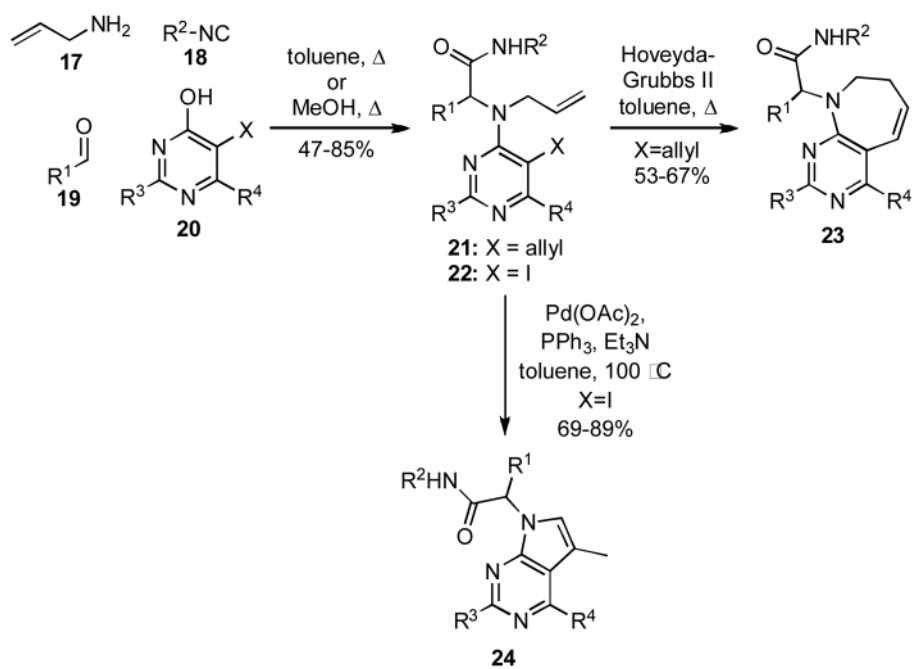
Scheme 3.
Sequential Ugi-Smiles/RCM or Ugi-Smiles/Heck
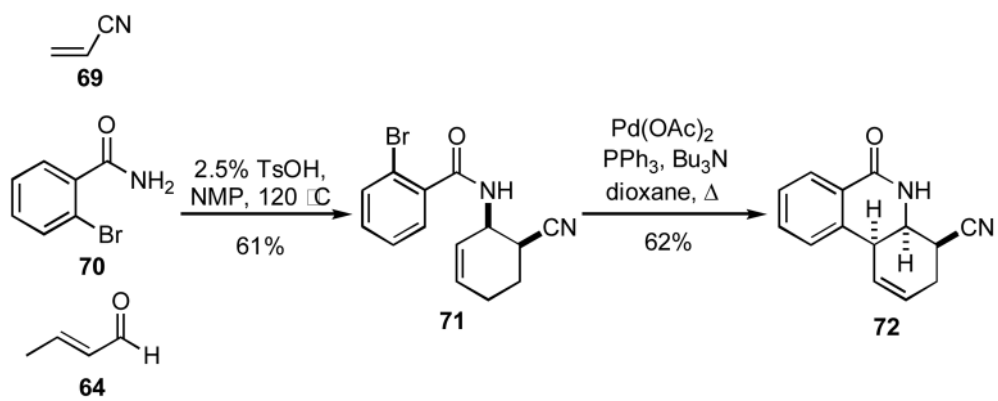
Scheme 4.
Schreiber's use of the Petasis 3CR for the synthesis of 15 distinct heterocyclic scaffolds.

Sequential van Leusen/Enyne RCM (ref. 18b)

Sequential van Leusen/Heck (ref. 19)

Tandem van Leusen/Arylation (ref. 20)

Tandem van Leusen/[3+2] Cycloaddition (ref. 21)

Scheme 5.
Diverse heterocyclic scaffolds accessible by the van Leusen 3CR.
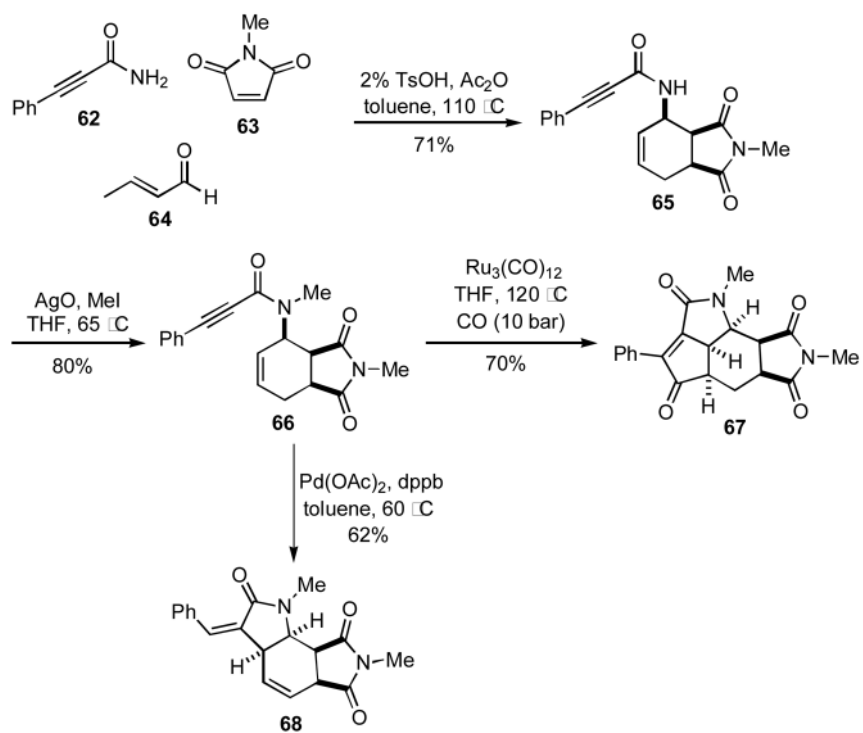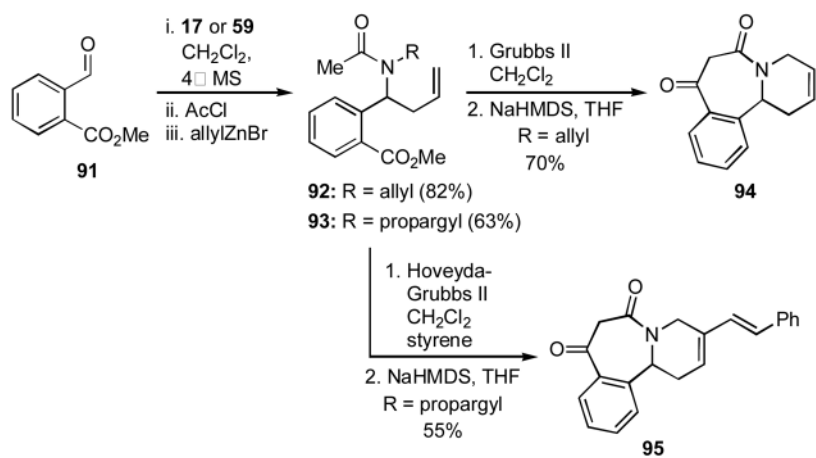
Scheme 6.
Sequential AAD/Pauson-Khand and AAD/Alder-ene reactions.

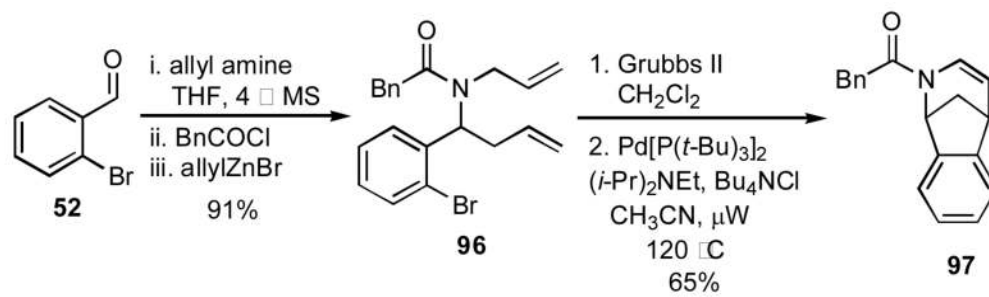**Scheme 7.**
Sequential AAD/Heck reaction.
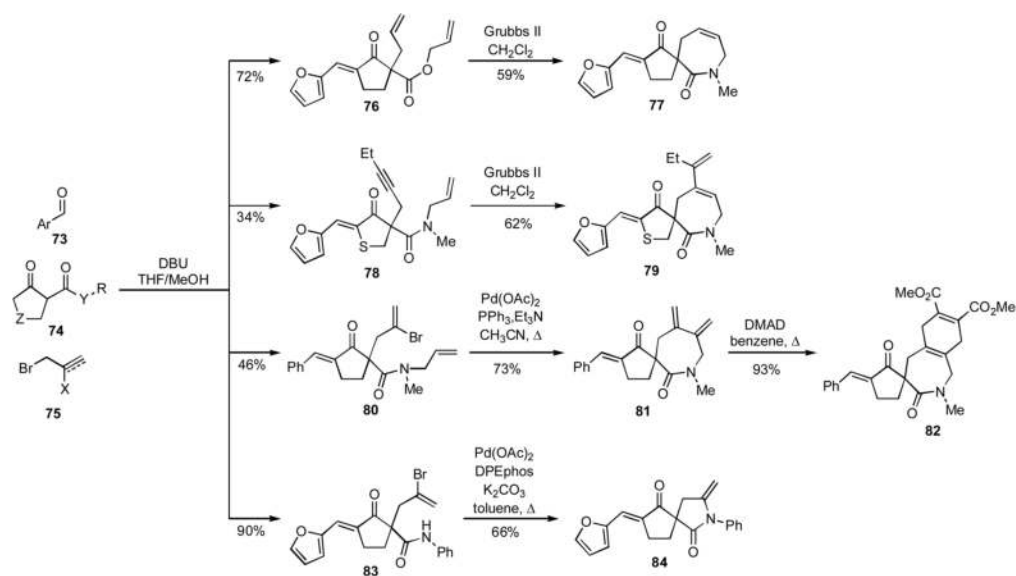
Scheme 8.
α,γ-Difunctionalization reaction of β-ketoamides and its application to the synthesis of spiroheterocycles.
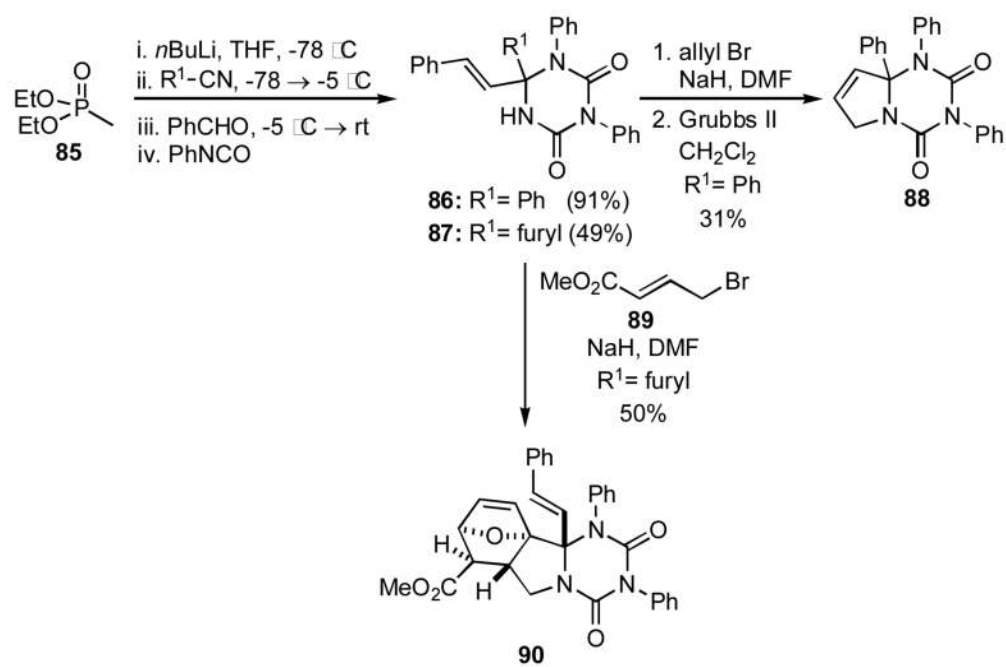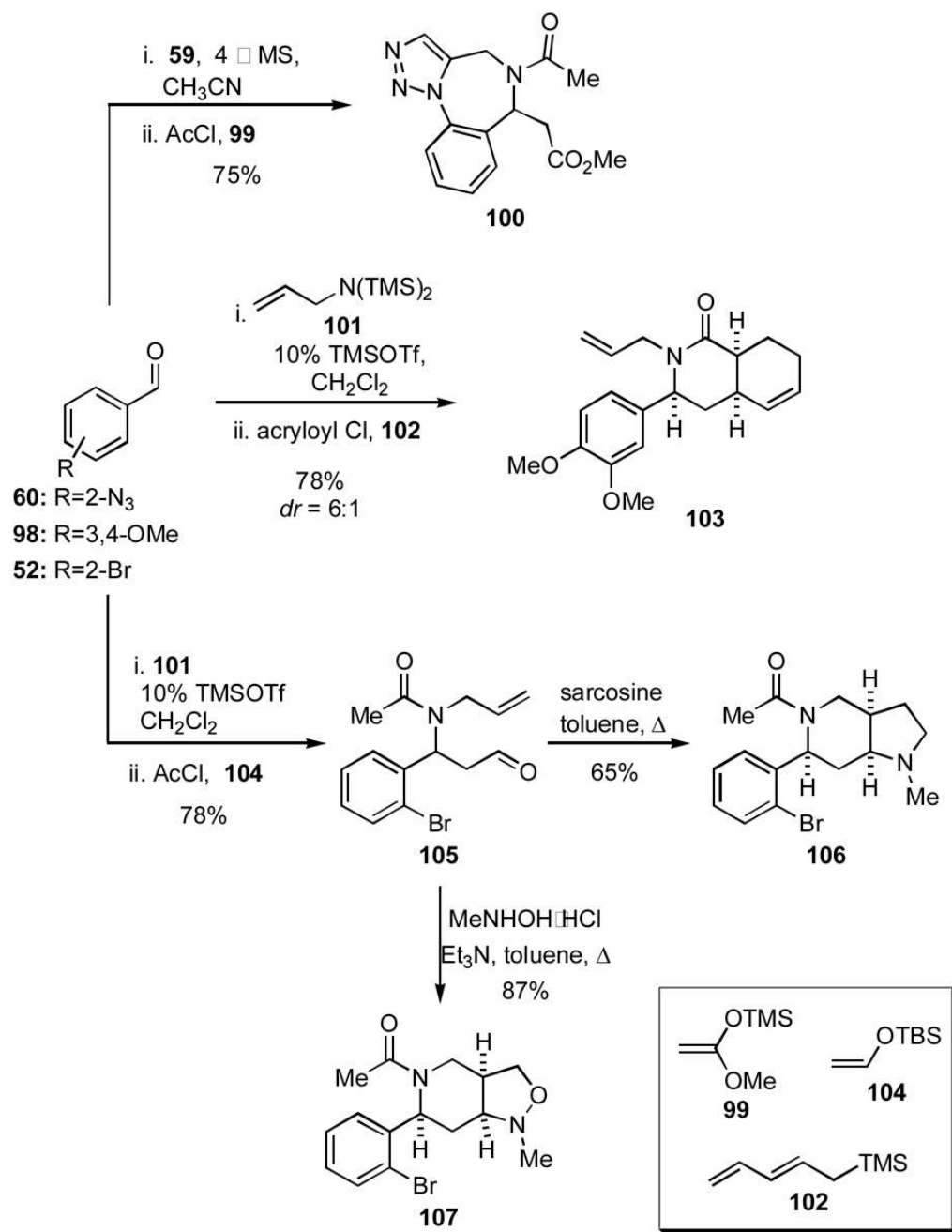
Scheme 9.
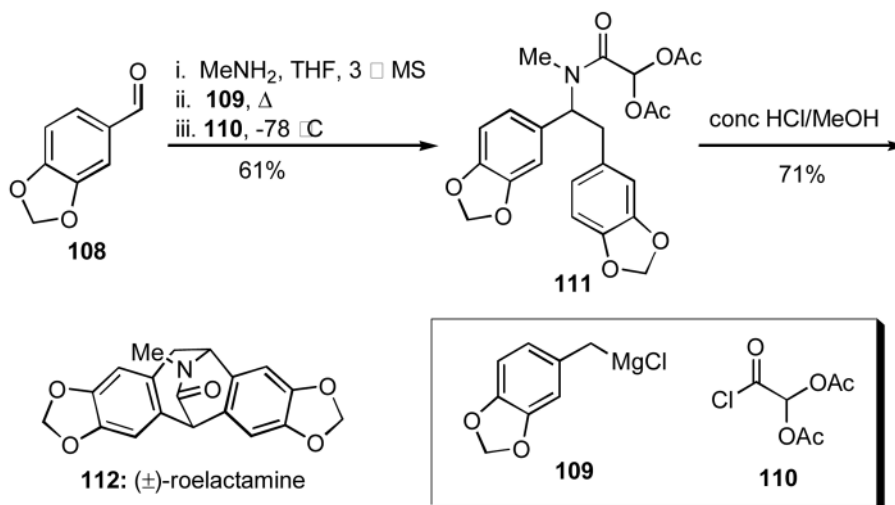A 4CR approach to the synthesis of diverse triazinane diones.

Scheme 10.
Sequential Mannich-type 4CR/RCM/Dieckmann Cyclization.

Scheme 11.
Sequential Mannich-type 4CR/RCM/Heck Cyclization.

Scheme 12.
Sequential Mannich-type 4CR/Cycloaddition.

Scheme 13.
Application of the Mannich-type 4CR to the synthesis of (±)-roelactamine.