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Applications of Multicomponent Reactions for the Synthesis of Diverse Heterocyclic Scaffolds

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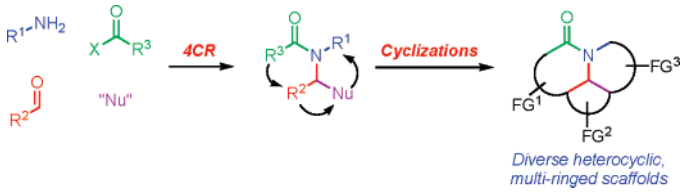
ABSTRACT



A four-component coupling process involving sequential reactions of aldehydes, primary amines, acid chlorides, and nucleophiles has been developed to prepare multifunctional substrates that may be employed in subsequent ring-forming reactions to generate a diverse array of functionalized heterocyclic scaffolds. This new approach to diversity-oriented synthesis was then applied to the first total synthesis of the isopavine alkaloid (±)-roelactamine.

Diversity-oriented synthesis (DOS) continues to be an area of importance at the interface of the fields of organic synthesis and chemical biology.[1] At the heart of DOS are the synthetic methods needed for the efficient generation of collections of functionally and stereochemically diverse small molecules, especially those possessing skeletons found in natural products or drug-like molecules.[2] Perhaps the most promising and powerful method for generating these collections of molecules is by sequencing multicomponent reactions (MCRs) with subsequent transformations that further increase molecular complexity and diversity.[3] Ideally, the MCRs that are implemented should be versatile so that any combination of functional groups can be incorporated into the reaction products. This capability will enable maximal use of ring-forming processes and refunctionalizations that comprise the synthome, which is the set of all reactions available to the chemist for the synthesis of small molecules, to transform these key intermediates into target structures.

The venerable isocyanide-based Ugi four-component reaction (4CR)[4] has been widely utilized for the rapid assembly of functionalized intermediates that may be readily transformed by Diels−Alder reactions,[5] Heck cyclizations,[6] ring-closing metathesis (RCM),[7] dipolar cycloadditions,[8] nucleo-

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(3) Marcaccini, S.; Torroba, T. *Multicomponent Reactions*; Zhu, J., Bienayme, H., Eds.; Wiley-VCH: Wienheim, 2005; pp 33. (b) Dömling, A. *Chem. Rev.* **2006**, *106*, 17.

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(7) (a) Beck, B.; Larbig, G.; Mejat, B.; Magnin-Lachaux, M.; Picard, A.; Herdtweck, E.; Dömling, A. *Org. Lett.* **2003**, *5*, 1047. (b) Hebach, C.; Kazmaier, U. *Chem. Commun.* **2003**, 596. (c) Banfi, L.; Basso, A.; Guanti, G.; Riva, R. *Tetrahedron Lett.* **2003**, *44*, 7655. (d) Piscopio, A. D.; Miller, J. F.; Koch, K. *Tetrahedron* **1999**, *55*, 8189. (e) Krelaus, R.; Westermann, B. *Tetrahedron Lett.* **2004**, *45*, 5987. (f) Anthoine-Dietrich, S.; Banfi, L.; Basso, A.; Damonte, G.; Guanti, G.; Riva, R. *Org. Biomol. Chem.* **2005**, *3*, 97. (g) Kazmaier, U.; Hebach, C.; Watzke, A.; Maier, S.; Mues, H.; Huch, V. *Org. Biomol. Chem.* **2005**, *3*, 136.

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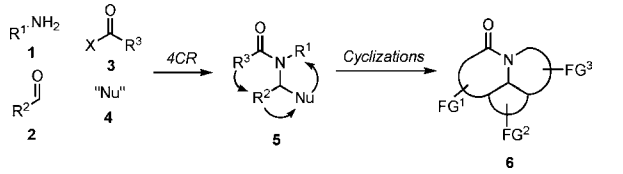
philic aromatic substitution,[9] and other reactions to generate a number of heterocyclic structures. Post-condensation reactions used in conjunction with the van Leusen[10] and Petasis[11] 3-component reactions have also been exploited to fabricate novel molecules for biological screening.[12]

Some years ago we discovered a multicomponent reaction that featured vinylogous Mannich reactions of electron-rich dienes with *N*-acyl iminium ions generated in situ by *N*-acylation of imines to give adducts that were readily transformed into complex indole alkaloids.[13] In the context of DOS, we envisioned that a related four-component process involving the combination of an amine **1**, an aldehyde **2**, and an acylating agent **3** might generate a reactive *N*-acyl iminium ion that could be subsequently trapped with a nucleophile **4** to give a highly functionalized amide **5** (Scheme 1).[14] In a variant of this protocol, the nucleophile

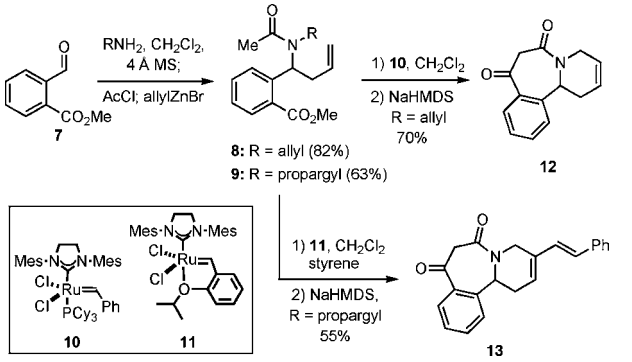
Scheme 1. Sequential MCR/Cyclization Strategy for DOS



could be added to an intermediate imine, and the amine thus formed could be *N*-acylated to furnish **5**.[15] This experimental flexibility together with the ready availability of numerous reactants **1**−**4** allows for the incorporation of high levels of functional and structural diversity in the products **5**, so that a number of different subsequent cyclizations might be performed to generate an array of heterocyclic scaffolds in only a few steps from commercially available starting materials. Furthermore, because there are numerous methods for effecting the enantioselective addition of many types of nucleophiles to C=N double bonds,[16] there is an opportunity to prepare amides of general type **5** in enantiomerically pure form.

To establish the underlying feasibility of this approach to DOS, we initiated exploratory studies, some representative examples of which are summarized herein. In these experiments, we focused on combining unsaturated amines, aryl aldehydes, simple acid chlorides, and allylic and π-nucleophiles to prepare adducts that could be further transformed by cyclizations involving RCM, Dieckmann and Heck reactions, and Diels−Alder and dipolar cycloadditions. For example, methyl 2-formylbenzoate (**7**) was condensed with either allyl or propargyl amine to give intermediate imines that were treated sequentially with acetyl chloride and allylzinc bromide to furnish adducts **8** and **9**, each in a one pot operation (Scheme 2). In a slight modification of this

Scheme 2. Sequential MCR/RCM/Dieckmann Cyclization and MCR/RCM/CM/Dieckmann Cyclization



procedure, we discovered that **9** could be isolated in 76% yield if the crude intermediate imine was isolated prior to acylation and allylation. Compound **8** was then converted into the benzazepine **12** via a RCM using Grubbs catalyst **10** followed by a Dieckmann cyclization. In a related process, **9** was transformed via an enyne RCM/CM cascade that was catalyzed by the Hoveyda−Grubbs catalyst (**11**)[17] and in which styrene served as a fifth component to give an intermediate that was cyclized by a Dieckmann condensation to give **13**. These two examples illustrate how simply changing one of the inputs for the 4CR allows for differential processing of the initial adduct into targets of varying complexity. Importantly, the keto amide and alkene groups in **12** and **13** serve as potential initiation sites for further diversification.

The nature of the aldehyde component may also be altered to access other cyclization manifolds and different heterocyclic systems. For example, use of 2-bromobenzaldehyde (**14**) in the 4CR generates substrates amenable to Heck cyclizations (Scheme 3). To this end, the tertiary amide **15**

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(16) For a review of enantioselective additions to C=N bonds, see: Friestad, G. K.; Mathies, A. K. *Tetrahedron* **2007**, *63*, 2541.

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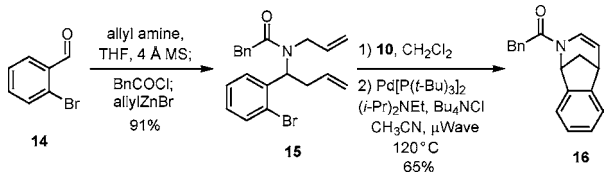
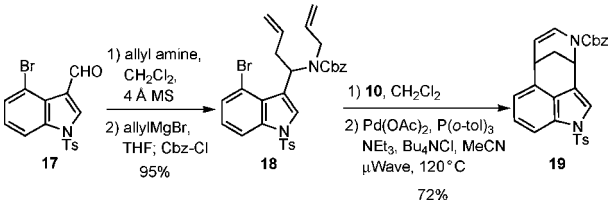
Scheme 3. Sequential MCR/RCM/Heck Reaction



was synthesized and subjected to a two step sequence of cyclizations involving first a RCM and then a Heck reaction to give **16**.

In a similar sequence of reactions, the protected indolecarboxaldehyde **17** was converted into **18** that was then elaborated into the bridged bicyclic tetracycle **19** by sequential RCM and Heck reactions (Scheme 4). Both **16** and **19**

Scheme 4. Sequential MCR/RCM/Heck Cyclization



possess functionality that might be exploited for additional diversification.

Having explored nucleophiles that enabled RCM as one of the possible cyclization manifolds, we turned our attention to other nucleophiles such as ketene acetals and enol ethers that would permit us to develop other cyclizations to create heterocyclic products. After some experimentation, we discovered that multicomponent reactions using these nucleophiles proceeded more efficiently when the imines were generated from the reactions of aldehydes with bis(trimethylsilyl)alkylamines in the presence of catalytic amounts in TMSOTf.[18] This tactic for imine formation is a nice complement to the more common reaction of an amine with an aldehyde.

Accordingly, treatment of the indolic aldehyde **17** with commercially available bis(trimethylsilyl)allylamine in the presence of 10 mol % TMSOTf smoothly provided an intermediate imine that was treated in situ with acetyl chloride and the silyl ketene acetal **20** to furnish the amide **21** in 72% yield (Scheme 4). When the bromoindole **21** was heated in a microwave oven in the presence of 10% $Pd(OAc)_2$, 20% PPh_3, and Et_3N, a Heck cyclization occurred giving **22a** in 85% yield and its isomer **22b** (12% yield). The ester and olefin functions would then serve as points for subsequent elaborations.

The use of silyl enol ethers as inputs in the 4CR generates aldehydes that can potentially be used in a variety of subsequent transformations. For example, such aldehydes

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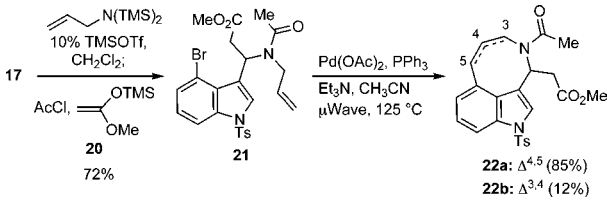
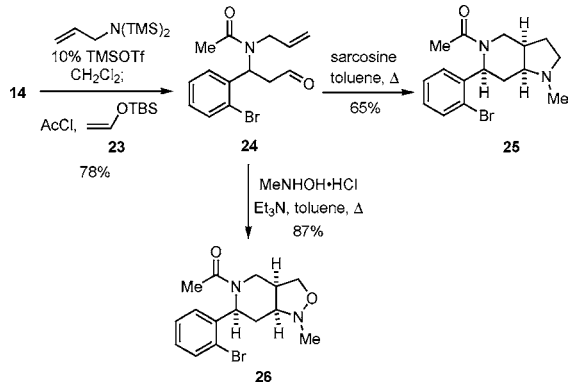
Scheme 5. Sequential MCR/Heck Cyclization



might be condensed with selected amines to generate 1,3-dipoles that would react with proximal double or triple bonds via [3+2] dipolar cycloadditions to generate diverse heterocyclic scaffolds. To investigate the feasibility of this strategy for DOS, the bromoaldehyde **14** was first treated with bis(trimethylsilyl)allylamine in the presence of catalytic amounts of TMSOTf, whereupon acetyl chloride and the enol ether **23** were added to deliver the adduct **24** in 78% yield (Scheme 6). When **24** was condensed with sarcosine in refluxing

Scheme 6. Sequential MCR/[3+2] Dipolar Cycloaddition

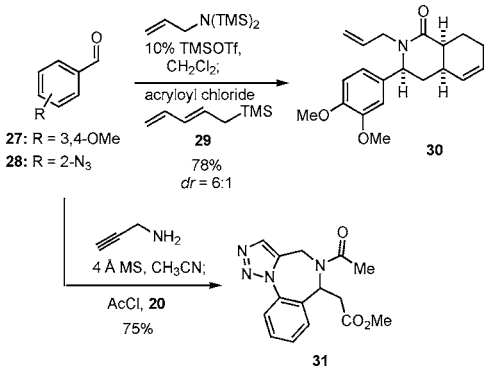


toluene, the intermediate azomethine ylide readily underwent a [3+2] cycloaddition to give **25**. Similarly, the reaction of **24** with *N*-methylhydroxylamine under the same conditions generated a nitrone that underwent facile [3+2] cycloaddition to provide **26**.[19] Both **25** and **26** are nicely functionalized for a number of further transfomations.

The intramolecular Diels−Alder reaction is another powerful reaction for the synthesis of complex molecules, so we selected inputs that would enable such transformations on the intermediate MCR adducts. For example, we discovered that when pentadienyl trimethylsilane **29** and acryloyl chloride were added to the imine generated in situ from the reaction of 3,4-dimethoxybenzaldehyde (**27**) with bis(trimethylsilyl)allylamine in the presence of 10 mol % TMSOTf, the resulting product underwent spontaneous

(19) The stereochemistry of **25** was established by correlating its NMR spectra with those of the corresponding aryl iodide, which was prepared similarly and the structure of which was established by X-ray analysis of its hydrochloride salt. The structure of **26** was also verified by X-ray analysis of its hydrochloride salt.

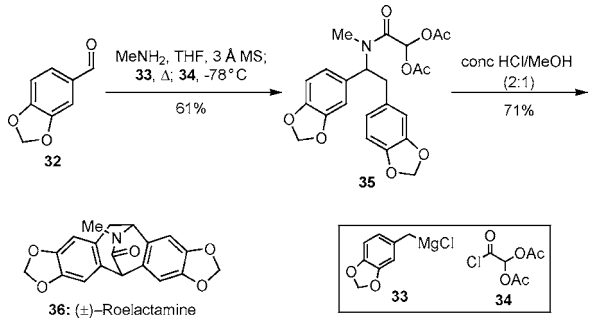
Scheme 7. Tandem MCR/Diels−Alder and Dipolar Cycloadditions



[4+2] cyclization to give **30** in 78% yield (Scheme 7).[20] The stereochemistry of **30** was established by hydride reduction to the corresponding amine and X-ray analysis of its methiodide salt. In a related cascade reaction, condensation of 2-azidobenzaldehyde (**28**) with propargyl amine furnished an imine that was treated with acetyl chloride and the ketene acetal **20** to furnish the triazole **31** via a [3+2] dipolar cycloaddition.

The preceding examples nicely highlight how adducts obtained from multicomponent reactions involving amines, aldehydes, acylating agents, and organometallic reagents can be rapidly transformed by cascade reactions to generate polycyclic heterocycles that are endowed with useful functionality for further manipulation and diversification. The versatility of this strategy for DOS may be further exemplified by its application to natural product synthesis. In particular, we envisioned that such a four-component reaction might be exploited to assemble compounds such as **35**, which might serve as precursors of the doubly benzanulated azabicyclo[3.2.2]nonane core structures found in the isopavine family of alkaloids.[21,22] Gratifyingly, we discovered that the condensation of piperonal (**32**) with methylamine provided an imine in situ that was allowed to react

Scheme 8. First Synthesis of (±)-Roelactamine (**36**)



sequentially with the benzyl Grignard reagent **33** and then the acid chloride **34** to provide **35** (Scheme 8). When **35** was treated with concentrated HCl/MeOH (2:1), it underwent facile double cyclization to give (±)-roelactamine (**36**), an alkaloid that was isolated in 1992 from *Roemeria refracta* DC.[23]

In summary, we have developed a novel approach for DOS that may be applied to the facile synthesis of a broad range of functionalized heterocycles. The key element of the strategy is a one pot process incorporating four components to assemble highly functionalized templates that may be transformed via various cyclization manifolds into a diverse collection of functionalized heterocyclic scaffolds containing several new rings. The flexibility associated with each of the inputs of the MCR allows for the incorporation of a broad range of functional groups and substituents that serve as initiation points for further diversification. The utility of this strategy for DOS was further exemplified by its application to the first synthesis of the isopavine alkaloid (±)-roelactamine (**36**). Applications of this methodology to the synthesis of novel libraries of heterocycles may be easily envisioned.

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Supporting Information Available: Representative experimental procedures for conducting multicomponent reactions and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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