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Freezing Imine Exchange in Dynamic Combinatorial Libraries with Ugi Reactions: Versatile Access to Templated Macrocycles

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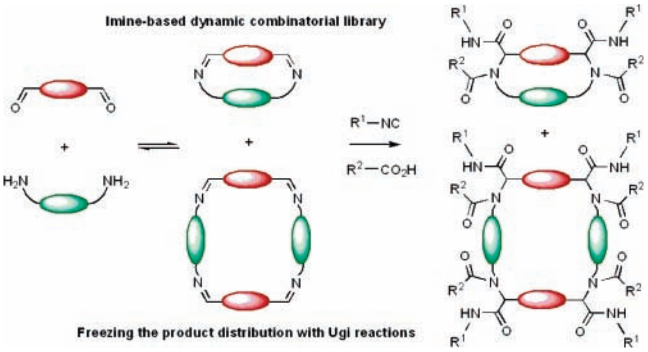
ABSTRACT



A novel approach to freeze the imine exchange process in dynamic combinatorial libraries by Ugi reactions was developed. Macrocyclic oligoimine libraries previously formed and altered by addition of metal templates are efficiently quenched by multiple multicomponent reactions. The approach may be considered as an alternative to the typical reduction with borohydrides and delivers polyazamacrocycles with variable side arms. High dilution is not required to achieve high yields.

Dynamic combinatorial chemistry (DCC) has evolved as a selection-based strategy to achieve novel supramolecular receptors, guests, and ligands.[1] Three different transimination reactions have been employed in DCC: hydrazone, oxime, and imine bond exchange.[1]

Despite the greater stability of hydrazones and oximes, the imine linkage still has preference for many authors due to the better availability of amino and oxo functions in natural and synthetic building blocks.[2,3] However, because of the instability of Schiff bases, the analysis of imine-based dynamic combinatorial libraries (DCLs) always requires a

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(1) For reviews, see: (a) Corbett, P. T.; Leclaire, J.; Vial. L.; West, K. R.; Wietor, J.-L.; Sanders, J. K. M.; Otto, S. *Chem. Rev.* **2006**, *106*, 3652. (b) Cheeseman, J. D.; Corbett, A. D.; Gleason, G. L.; Kazlauskas, R. J. *Chem.—Eur. J.* **2005**, *11*, 1709. (c) Ramström, O.; Bunyapaiboonsri, T.; Lohmann, S.; Lehn, J.-M. *Biochim. Biophys. Acta* **2002**, *1572*, 178. (d) Rowan, S. J.; Cantrill, S. J.; Cousins, G. R. L.; Sanders, J. K. M.; Stoddart, J. F. *Angew. Chem., Int. Ed.* **2002**, *41*, 898. (e) Lehn, J.-M. *Chem.—Eur. J.* **1999**, *5*, 2455.

(2) For examples of acyclic imine-based DCLs, see: (a) Zameo, S.; Vauzeilles, B.; Beau, J.-M. *Angew. Chem., Int. Ed.* **2005**, *44*, 965. (b) Bugaut, A.; Toulmet, J.-J.; Bayner, B. *Angew. Chem., Int. Ed.* **2004**, *43*, 3144. (c) Albrecht, M.; Janser, I.; Runsink, J.; Raabe, G.; Weis, P.; Fröhlich, R. *Angew. Chem., Int. Ed.* **2004**, *43*, 6662. (d) Hochgürtel, M.; Biesinger, R.; Kroth, H.; Piecha, D.; Hofmann, M. W.; Krause, S.; Shaaf, O.; Nicolau, C.; Eliseev, A. V. *J. Med. Chem.* **2003**, *46*, 356. (e) Karan, C.; Miller, B. L. *J. Am. Chem. Soc.* **2001**, *123*, 7455. (f) Huc, I.; Lehn, J.-M. *Proc. Natl. Acad. Sci. U.S.A.* **1997**, *94*, 2106.

(3) For recent examples of macrocyclic imine-based DCLs, see: (a) González-Álvarez, A.; Alfonso, I.; Gotor, V. *Chem. Commun.* **2006**, 2224. (b) Gregoliñki, J.; Lisowski, J.; Lis, T. *Org. Biomol. Chem.* **2005**, *3*, 3161. (c) Katayev, E. A.; Pantos, G. D.; Reshetova, M. D.; Khrustalev, V. N.; Lynch, V. M.; Ustynyuk, Y. A.; Sessler, J. L. *Angew. Chem., Int. Ed.*, **2005**, *44*, 1. (d) González-Álvarez, A.; Alfonso, I.; López-Ortiz, F.; Aguirre, A.; García-Granda, S.; Gotor, V. *Eur. J. Org. Chem.* **2004**, 1117. (e) Storm, O.; Lüning, U. *Chem.—Eur. J.* **2002**, *8*, 793. (f) Star, A.; Goldberg, I.; Fuchs, B. *Angew. Chem., Int. Ed.* **2000**, *39*, 2685.

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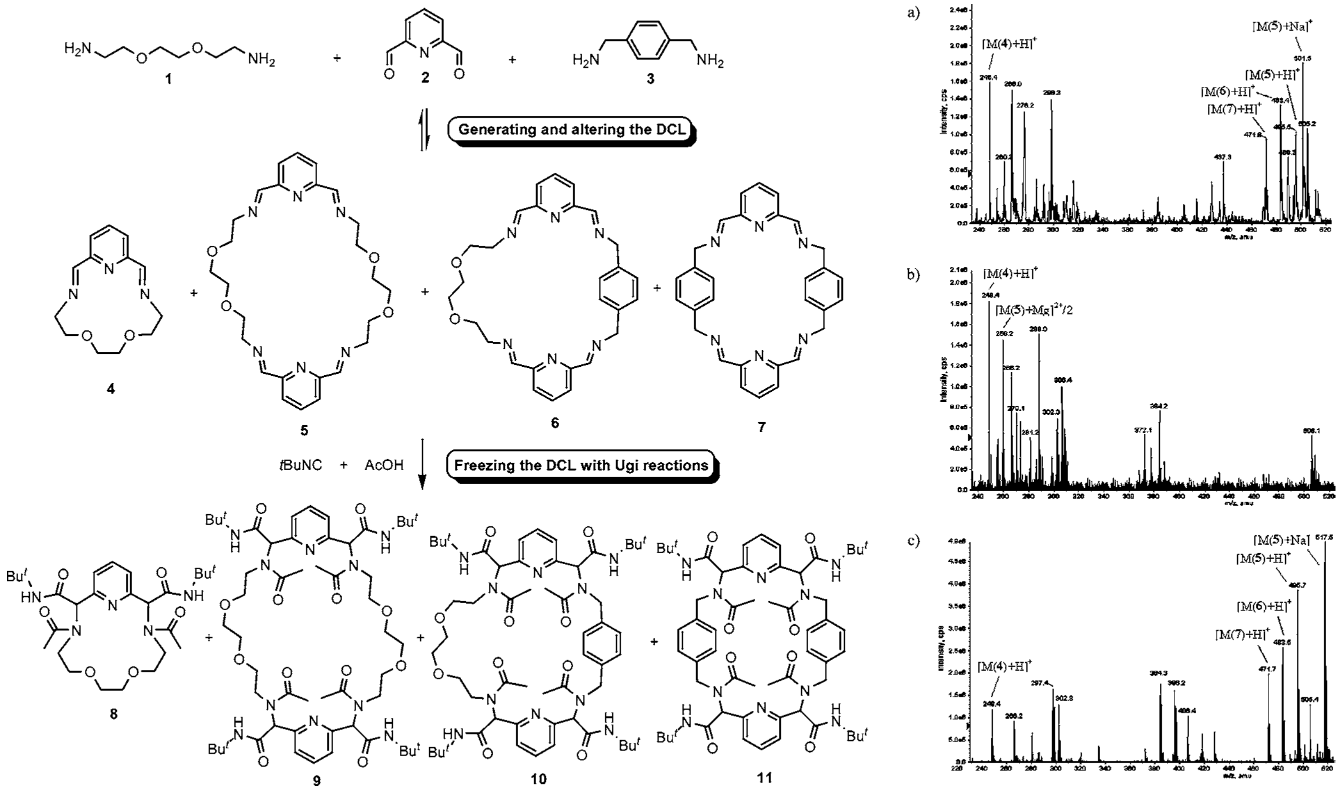
Scheme 1. Ugi-4CR-Based Quenching Approach of Macrocyclic Oligoimine-Based DCLs Built from **1**, **2**, and **3**



reduction step to allow the isolation of the library members. To our knowledge, switching-off the imine exchange by reduction is the only procedure performed to date to quench the dynamic process of this type of DCLs.[1−3]

Herein we report the use of the Ugi four-component reaction (Ugi-4CR) to freeze the exchange process of imine-based DCLs. The Ugi-4CR is the one-pot condensation of a primary amine, an oxo component, a carboxylic acid, and an isocyanide to afford a N-substituted peptide backbone.[4] This process is recognized as a multicomponent reaction (MCR) of type II, that is, a sequence of reversible steps that is ended by an irreversible one. Therefore, we envisaged its applicability in DCC by considering that imine-based DCLs could be created and frozen subsequently by addition of an acid and an isocyanide. In previous reports of MCR-based macrocyclizations,[5] classic or pseudo high dilution conditions were typically required to accomplish the macrocyclization. However, high dilution was not used in the current approach, taking advantage of the known template effect of diverse metal ions in the assembly of macrocyclic oligoimines under thermodynamic control.[3] It must be noted that the main goal of this study is not to find novel template effects or to add new metal-ion-based amplification procedures for DCLs. Instead, the focus is on demonstrating that MCRs of type II, especially the Ugi-4CR and its variations, are capable of efficiently switching-off the imine exchange and thus freezing the product distribution. Therefore, previously reported systems devised to form and alter imine-based DCLs by addition of varied templates were chosen to accomplish this goal. These make use of the recognized metal ion coordination capability of pyridine and imine moieties[6,7] which enables the amplification of different library members by using metal ions of different ionic radii.

Scheme 1 summarizes the first entry to the generation, alteration, and freezing of macrocyclic oligoimine-based DCLs with Ugi-4CRs. Three replicas of these DCLs were prepared by mixing dialdehyde **2** (10 mM) with diamines **1** and **3** (5 mM each) and stirred for 8 h to reach equilibrium. Two of them were subsequently treated with 1 equiv of $MgCl_2 \times 6H_2O$ or $BaCl_2 \times 2H_2O$ and stirred at 40 °C to re-equilibrate the system. Mg^{II} and Ba^{II} ions were chosen due to their known ability to stabilize macrocyclic oligoimines of different ring sizes.[3,6] Stirring DCLs treated with

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these metal ions for a longer time at room temperature will result in the formation of some precipitate (i.e., saturated coordination complex). To avoid this, the DCLs should be quenched immediately after the re-equilibration time. The reversible character of the imine formation under these conditions has been proven previously. However, as the instability of the imine bond does not allow quantification of the DCL composition by HPLC, direct ESI-MS analysis was chosen to evaluate the changes in the library composition induced by the addition of the metal ion templates.

The equilibrated DCLs were quenched by addition of a 3-fold excess of an isocyanide and a carboxylic acid with subsequent stirring of the reaction mixture for 4 h. The final composition of the static libraries (see also HPLC analysis in the Supporting Information) is in agreement with the distribution prior to the quenching (see ESI-MS in Scheme 1). All frozen library members were isolated by preparative HPLC to assess quantitative and qualitative information of the static library composition. Table 1 shows the individual and overall yields of the amide-based macrocycles **8**−**11** emanating from the Ugi-4CRs at every imine bond of the macrocyclic oligoimines **4**−**7**. The structures of these peptoid macrocycles were confirmed by FT-ICR-MS and NMR, albeit the latter is of limited value as some macrocycles are formed as diastereomeric mixtures.

Table 1. Results of the Ugi-4CR-Based Quenching Approach of DCLs in Scheme 1 Equilibrated without and with Metal Ions

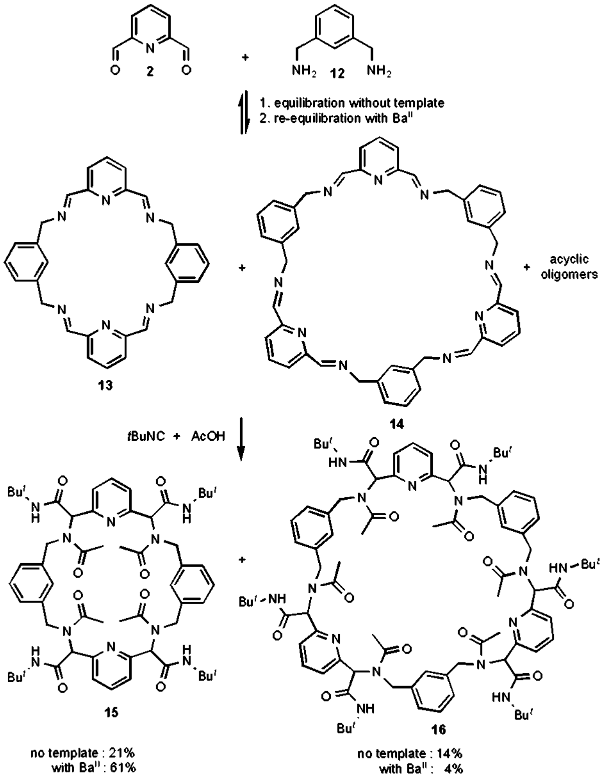
	yields (%)				
product	**8**	**9**	**10**	**11**	Σ
no template	16	6	2	13	**37**
Mg^{II}	69	7	6	3	**85**
Ba^{II}	8	23	29	26	**86**

In the absence of the metal ions, all macrocycles **4**−**7** were formed (ESI-MS in Scheme 1a) as demonstrated by the isolation of all final macrocycles **8**−**11**, albeit in low yields ranging from 2 to 16% for the individual compounds. Addition of Mg^{II} ions provoked a drastic change in the library composition shifting the equilibrium toward macrocyclic diimine **4** (Scheme 1b). Accordingly, macrocycle **8** was obtained as the major product in 69% yield. Minor amounts of the other members could be isolated from the quenched library by preparative HPLC. This result demonstrates not only the amplification of the [1 + 1] diimine **4** at the expense of the phenylene and the [2 + 2] products **5**−**7** but also the ability of the Ugi quenching approach to freeze the imine exchange efficiently. Similarly, addition of Ba^{II}, re-equilibration of the DCL, and quenching with Ugi-4CRs led to another final composition. In this case, ESI-MS analysis (Scheme 1c) showed the presence of all oligoimines **4**−**7**, but with the tetraimine macrocycles **9**−**11** being amplified as indicated in Table 1. Indeed, the larger radius of Ba^{II} is the key feature for favoring the formation of the [2 + 2] products **5**−**7**, thereby eventually leading to the amplification of the corresponding Ugi products.

It was important to assess whether the Ugi-4CRs are also suitable to act in the presence of precipitated metal−macrocycle complexes. On one hand, precipitation disturbs equilibration and is undesired in ideal DCL systems; at the same time, it can be a useful driving force toward one product. To check the quenching power of Ugi-4CRs in such nonideal cases, a parallel DCL with Ba^{II} was prepared, re-equilibrated, and set aside at lower temperature for a longer period to allow precipitation of the coordination complex. Interestingly, the precipitate was completely dissolved within a few minutes after addition of acid and isocyanide and stirring at room temperature to give the expected frozen library, demonstrating the excellent performance of the Ugi-4CRs.

To further demonstrate the efficient and reliable character of this process to freeze imine exchange in macrocyclic systems, whether taking part in coordination processes or not, more demanding systems were sought, such as quenching processes that require the performance of even more than four (simultaneous?) four-component reactions. Hence, two identical DCLs were built from dialdehyde **2** and diamine **12** (10 mM each), giving rise to a mixture of cyclic oligomers (and noncyclic ones) as shown in Scheme 2. After equilibration, one of the libraries was treated with $BaCl_2 \times 2H_2O$ and re-equilibrated as described before. The behavior of both DCLs was analyzed by ESI-MS, showing the expected changes in the solution exposed to the metal template (see the Supporting Information); that is, Ba^{II} clearly enhanced

Scheme 2. Ugi-4CR-Based Quenching Approach of Macrocyclic Oligoimine-Based DCLs Built from **2** and **12**



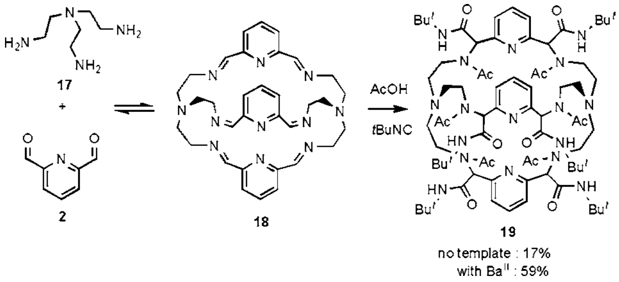
no template : 21%
with Ba^{II} : 61%

no template : 14%
with Ba^{II} : 4%

the amount of tetraimine **13**. At this point, the challenge was to preserve this amplification by quenching the DCL with four and six (!) Ugi-4CRs. Notably, the Ugi quenching approach was capable of transferring the imine distribution into the final oligoamide products **15** and **16**. Thus, macrocycle **16** was formed by six simultaneous Ugi-4CRs with 24 new bonds in the overall process.

Encouraged by these promising results, we turned to a similar DCL, this time containing a macrobicyclic system (i.e., a cryptand) obtained by [2 + 3] Schiff base condensations.[7] As depicted in Scheme 3, two parallel experiments for the assembly of cryptand **18** from triamine **17** (10 mM) and dialdehyde **2** (15 mM) were prepared by stirring both building blocks at room temperature. One of them was subsequently exposed to Ba^{II} and stirred at 40 °C for 4 h to allow the metal-ion-driven re-equilibration. It must be noted that the success of this procedure is not based on high dilution but on the ability of the metal ion to shift the equilibrium toward cryptand **18** through the formation of a coordination complex. Both experiments were analyzed by ESI-MS and subsequently frozen with Ugi-4CRs. The more favorable formation of **18** in the presence of the template, as revealed by ESI-MS, translated to the remarkably improved isolated yield of the final product, peptoid-type cryptand **19**. This again demonstrates the capability of the multiple Ugi-4CRs to freeze all imine bonds (close to) simultaneously, as the product and the proposed most advanced, partially reacted intermediates en route from **18** to **19** do not complex the metal ion as well as **18** if the highly lipophilic and sterically demanding *tert*-butylisonitrile is employed.

Scheme 3. Ugi-4CR-Based Quenching Approach of a Macrobicyclic Oligoimine Assembled from **2** and **17**



At this point, it must be mentioned that due to the usually indiscriminating nature of the Ugi-4CR, with achiral imines and templates, diastereomeric mixtures of isomeric macrocycles are formed. However, in diversity-oriented discovery experiments, such indiscrimination can be considered an advantage. In the future, the use of nonracemic templates may allow induction of the stereoselective formation of macrocycles.

In conclusion, we have developed a useful procedure to freeze imine-based DCLs by performing multiple Ugi-4CRs. The process is highly efficient to switch-off the imine exchange even in complex macro(multi)cycles, although its scope is not limited to cyclic oligoimines. In addition, it allows access to peptide-like receptors and ligands exhibiting binding properties different from the typical polyazamacrocycles obtained by reduction. The findings offer a promising prospect toward the use of other isonitriles and acids bearing further binding motifs, as well as for using other MCRs in DCC, such as the Petasis[8] reaction and the Staudinger [2 + 2] ketene−imine cycloaddition,[9] which both include reversible imine formation steps followed by an irreversible reaction.

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Supporting Information Available: Experimental and spectroscopic data of all compounds. HPLC and ESI-MS analyses of the DCLs. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) For review, see: Petasis, N. A. In *Multicomponent Reactions*; Zhu, J., Bienaymé, H., Eds.; Wiley-VCH: Weinheim, Germany, 2005; pp 119−223.

(9) For review, see: Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Eur. J. Org. Chem.* **1999**, 3223.