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Versatile Multicomponent Reaction Macrocycle Synthesis Using α-Isocyano-ω-carboxylic Acids

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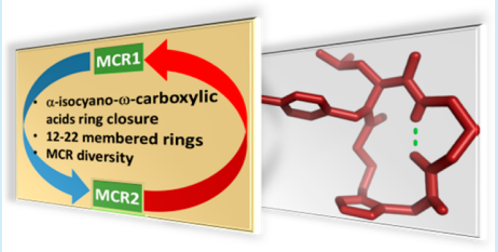
Supporting Information

ABSTRACT: The direct macrocycle synthesis of α-isocyano-ω-carboxylic acids via an Ugi multicomponent reaction is introduced. This multicomponent reaction (MCR) protocol differs by being especially short, convergent, and versatile, giving access to 12−22 membered rings.



Historically, chemists have always had a special affinity for macrocycles because of their abundance in natural products, their synthetic challenge, and their unusual properties.[1] In medicinal chemistry, however, fully synthetic macrocycles are a rather neglected class of compounds presumably due to their complex sequential synthesis and because they have generally not been classified as orally bioavailable and druglike until recent advancements in their synthesis and development. In particualar, several synthetic macrocycles were recently approved as drugs for unmet medical needs, e.g., to treat hepatitis C.[2] Specifically, macrocycles have huge potential in targeting modern postgenomic targets which are difficult to address by small molecules such as protein−protein interactions (PPI), currently a therapeutic domain mostly covered by antibodies.[3] Hence, macrocycles as intermediates between small molecules and biologics are useful to target flat, large, and featureless protein−protein interfaces.[4] Recent synthetic advancements in macrocycle synthesis include genetically encoded peptides,[5] phage display followed by organic-linker induced cyclization,[6] artificially made aminoacylated tRNAs,[7] stapled peptides,[8] or automated peptoid synthesis,[9] to name a few.[10] Perhaps the renaissance of macrocycles is also triggered by the recent introduction of several FDA-approved drugs and clinical stage development drugs, e.g., HCV NS5b polymerase inhibitor TMC647055.[4a,11] The latest advancements in macrocycles, however, indicate that that macrocycles are an underused compound class in medicinal chemistry. Therefore, methods allowing for rapid and diverse access toward cycles of different size, shape, and function are urgently needed to advance the field.

Macrocycles can also be accessed by multicomponent reactions (MCRs) as elaborated for the first time by Failli et al. using *N*,*C*-unprotected tri- and hexapeptides to synthesize bioactive cyclic hexapeptides.[12] Yudin et al. introduced formylaziridines as bifunctional Ugi starting materials to synthesize spectacular macrocycles.[13] Wessjohann et al. used homobifunctional starting materials to synthesize up to 36-membered macrocycles using Ugi reactions.[14] Others used Ugi− and Passerini−MCR to assemble macrocycles using a different method, e.g., ring-closing metathesis.[15] However, among the six topologically possible Ugi reaction promoted direct macrocyclizations (Scheme 1) only one has been realized so far.[12]

Here, we introduce the unprecedented use of α-isocyano-ω-carboxylic acids in macrocycle synthesis via the Ugi reaction. Synthetic and structural studies support the scope and usefulness of the approach. The finding is significant as a new versatile and very short synthetic method is added to the arsenal of macrocycle synthesis. Because of the convergent character of MCR, there is considerable potential to design the 3D shape and therefore biological activity of the macrocycles.

Topologically, there are six pathways to form (macro)cycles based on bifunctional starting materials in the classical Ugi-4CR reaction (Scheme 1). We decided to focus here on the cyclization using bifunctional α-isocyano-ω-carboxylic acids **3** to leverage the most versatile building blocks, primary amine **2** and oxo component **1**, for incorporation into the macrocycle **4** (Scheme 2). Therefore, we synthesized six α-isocyano-ω-carboxylic acids of different lengths (n = 9−15) from their commercial amino acids (Supporting Information, S-5). Using

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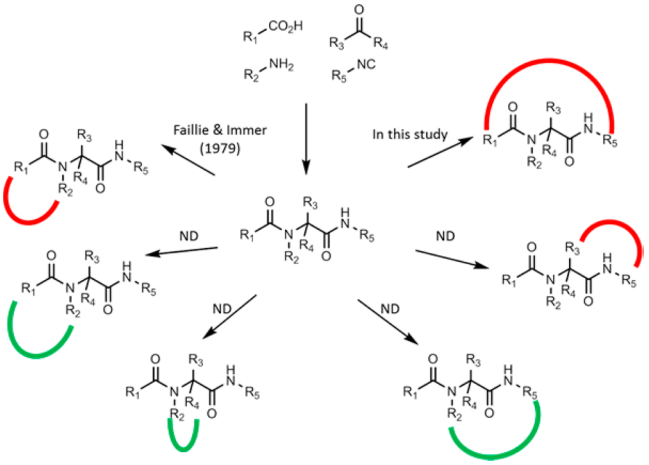
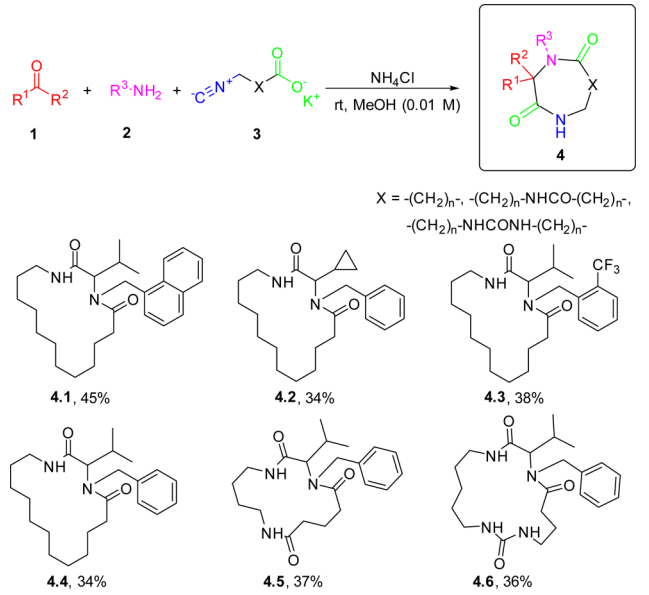
Scheme 1. Current State of Direct Macrocyclizations Using U-4CR[a]



[a]ND not described.

Scheme 2. Ugi/U-4CR-Derived Macrocycle Synthesis Pathway and Some Examples with Macrocyclization Yields after Purification



1-isocyano-12-dodecanoic acid, which can be accessed in three steps from the commercial amino acid, and together with isobutyraldehyde and benzylamine, we extensively screened different conditions and optimized temperature, solvent, time, additives, and concentration (SI, Table 1−3). Methanol as solvent in 0.01 M dilution, 16 h at rt, was found to be optimal. Surprisingly, the free isocyano carboxylic acid did not work, but we employed the corresponding K salt with 1.5 equiv of NH_4Cl additive, which worked nicely; therefore, the same conditions were used subsequently. The advantageous effect of additives in the Ugi reaction, although poorly understood, has been reported in the literature.[16] We used α-isocyano-ω-carboxylic acids of different lengths to yield 12−16-membered macrocycles after the Ugi ring closure (Scheme 2 and S-15). Next, we investigated the scope and limitations of the Ugi macrocyclization step regarding the oxo and amine components (**4.1**−**4.4**). Side chains with aliphatic, small, bulky, and aromatic substituents can be introduced. We also investigated different sized and substituted α-isocyano-ω-carboxylic acids including additional amide and urea motifs (**4.5** and **4.6**).

In order to introduce more complexity and flexibility and to better cover the substitution potential of the macrocycle, we investigated the possibility of assembling the overall macrocycle by the union of two orthogonal MCRs, e.g., the linker α-isocyano-ω-carboxylic acids by MCR-1 and the subsequent macro ring closure by MCR-2 (Figure 1).[17] An MCR of great

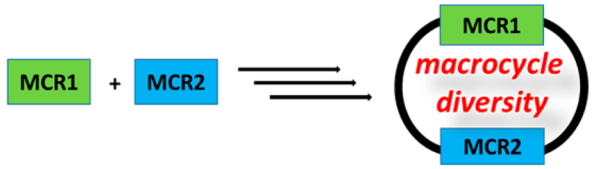
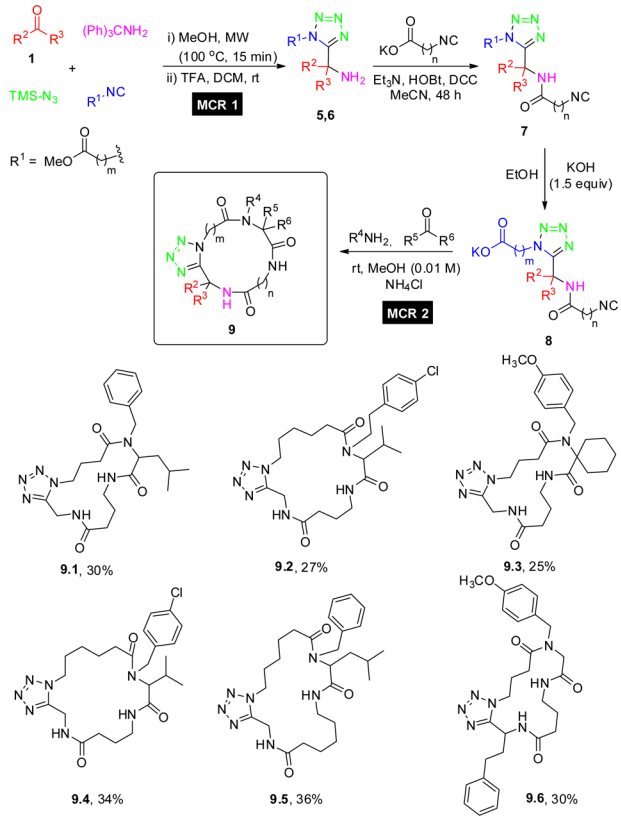


Figure 1. Synthetic platform to rapidly access diverse macrocycles by the union of two MCRs.

interest due to its bioisosteric *cis*-amide character is the Ugi tetrazole reaction (U-T-MCR).[18] A general, fast, and efficient synthesis of these building blocks that does not require more than five sequential reaction steps is depicted in Scheme 3 with

Scheme 3. Tetrazole Ugi/U-4CR-Derived Macrocycle Synthesis Pathway with Exemplary Structures and Cyclization Yields



the used reaction conditions. In the first U-T-MCR, an aldehyde, tritylamine, $TMSN_3$, and a bifunctional ester protected amino acid derived isocyanides are reacted to give α-amino tetrazole **5**. Next, the amine is deprotected to give **6**, and an isocyano carboxylic acid is coupled to yield **7**. The macrocyclic ring closure by the second MCR (U-4CR) with

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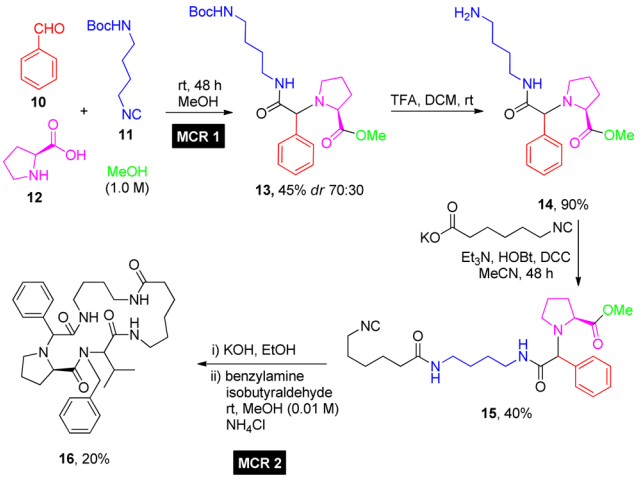
another equivalent of primary amine and oxo component takes place with the optimized conditions to yield **9**. The overall reaction sequence is quite general, and some representatives out of a total of 26 macrocycles with ring sizes between 12 and 20 are shown in Scheme 3 (see also S-15). The substrate scope of the two Ugi MCR variations is great, including aromatic, aliphatic, and heteroaromatic oxo components as aldehydes and ketones and substituted aromatic, or aliphatic amines (**9.1**−**9.6** and S-15).

Next, we chose another well-established Ugi MCR to introduce diversity into the macrocycle linker portion: the U-5C-4CR.[19] In the U-5C-4CR, an unprotected α-amino acid is reacting with an oxo component and an isocyanide in methanol to yield imino dicarboxylic acid mono amides, often with very high stereoinduction by the α-amino acid component.[19,20] We used diamine-derived monoisocyanide **11**[21] in order to provide the isocyano-ω-carboxylic acid linker **15**, which was macrocyclized with the help of a second MCR, the classical U-4CR, to yield the 21-membered **16**. The overall synthesis exemplified in Scheme 4 is not more than five steps and could result in very

Scheme 4. Mixed U-5C-4CR/U-4CR Strategy Derived Macrocycle Synthesis Pathway toward 16



diverse macrocycles of different sizes and substitution patterns. We demonstrate the above strategy by using (*S*)-proline **12** achieving good diastereoselectivity in compound **13**. The two diastereomers were separated by chromatography, and the major **13** was reacted further in a sequence involving N-deprotection, coupling, saponification, and macrocycle formation via U-4CR to yield **16**. In both the tetrazole Ugi/U-4CR and U-5C-4CR/U-4CR strategies (Schemes 3 and 4), the presence of an additive for the final MCR ring closure is necessary.

Several X-ray structures of macrocycles of different size involving different MCR assembly routes and different substituents give some first insight into possible solid-state conformations (Figure 2). The simple rather flat macrocycle **4.5**, for example, shows the potential to interact with a flat protein surface often found in protein−protein interactions. The alignment of four different tetrazole moiety containing macrocycles in Figure 2A impressively shows the wide special distribution of the macrocycles in the solid phase. Three examples in Figure 2 (**9.1**, **9.9**, and **9.10**) exemplify the potential of intramolecular hydrogen bonding to potentially stiffen the macrocycle and to also increase hydrophobicity, a

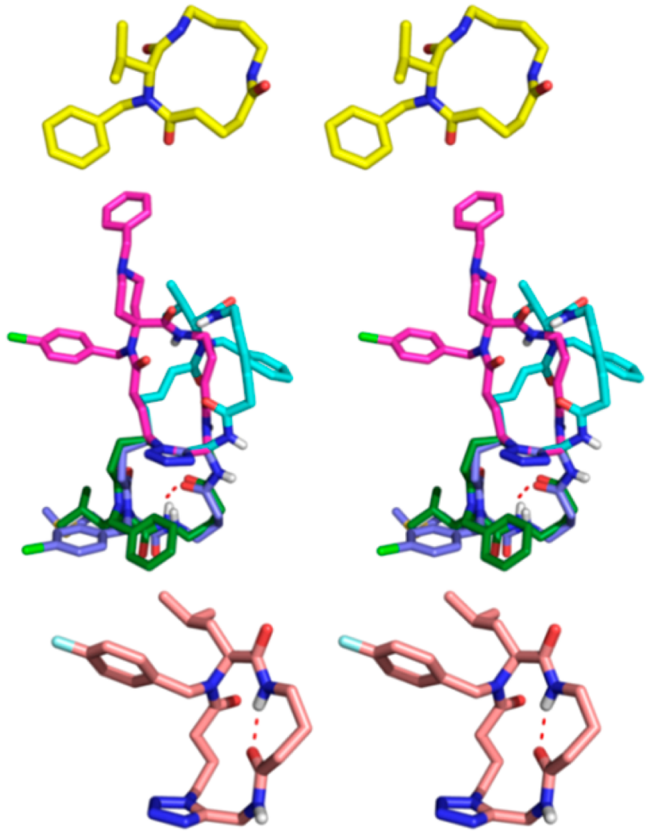


Figure 2. Examples of MCR-derived macrocyles inthe solid state. Top: macrocycle **4.5** with a simple unsubstituted linker. Middle: Stereoview of four aligned tetrazole motif macrocycles of different sizes (20-membered **9.7**, cyan; 16-membered **9.1**, green; 16-membered **9.8**, pink; 16-membered **9.9**, purple) as derived from X-ray structures. The ring amide groups are suited to form intermolecular as well as intramolecular hydrogen bonds (bottom, **9.10**) and by virtue of the synthetic approach can be shifted along the macrocycle or hidden. Rendering using PyMol.

mechanism recently reported to increase bioavailability of macrocycles.[22] In particular, the introduction of γ-amino acid linkers such as in **9.1**, **9.9**, and **9.10** has been recognized to increase passive membrane penetration through intramolecular hydrogen bonding. Another important recent finding is that selective *N*-alkylation of amide groups in the macrocycle can also increase membrane penetration.[23] Classically, this is done by a peptoid approach, while we are using here an MCR approach which allows for differential and broad substitution of secondary amides. Clearly, increasing the understanding of folding and conformation of big cycles as well as rules and strategies to mimic secondary structure elements such as α-helices, β-sheets, and loops will help in the rational design of potent and selective macrocyclic drugs for uncommon targets.[24]

In conclusion, we introduce here a general, unprecedented, rapid, and highly diverse macrocycle synthesis pathway via MCR, while the final ring closure is performed via Ugi-4CR of α-isocyano-ω-carboxylic acids. The number of steps to generate highly decorated macrocycles of size 12−21 generally does not exceed five sequential steps from simple building blocks. The moderate yields found can be justified by the immense potential this synthetic approach has and the resulting use in the discovery of novel tool compounds and leads. The herein introduced MCR approach allows for the flexible introduction

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of linker motives, which have been described to facilitate passive membrane permeation to potentially increase oral bioavailability. Further macrocyclic scaffold examples of different combinations of MCRs as well as targeted applications for protein−protein interactions are currently being investigated in our laboratory and will be reported shortly.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02419.

Optimization, screening results, general procedures, and characterization data of all compounds (PDF)
Crystal structure determinations (ZIP)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

We dedicate this work to Ivar Ugi, the father of modern multicomponent reaction chemistry.

■ REFERENCES

(1) (a) Stoll, M. *Helv. Chim. Acta* **1948**, *31*, 1082−1086. (b) Hunsdiecker, H.; Erlbach, H. *Chem. Ber.* **1947**, *80*, 129−137. (c) Cram, D. J.; Steinberg, H. *J. Am. Chem. Soc.* **1951**, *73*, 5691−5704. (d) Giordanetto, F.; Kihlberg, J. J. *J. Med. Chem.* **2014**, *57*, 278−295.

(2) Raboisson, P.; de Kock, H.; Rosenquist, Å.; Nilsson, M.; Salvador-Oden, L.; Lin, T. I.; Roue, N.; Ivanov, V.; Wähling, H.; Wickström, K.; Hamelink, E.; Edlund, M.; Vrang, L.; Vendeville, S.; Van de Vreken, W.; McGowan, D.; Tahri, A.; Hu, L.; Boutton, C.; Lenz, O.; Delouvroy, F.; Pille, G.; Surleraux, D.; Wigerinck, P.; Samuelsson, B.; Simmen, K. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4853−4858.

(3) Khoury, K.; Holak, T. A.; Dömling, A. Protein−Protein Interactions in Drug Discovery. *Methods and Principles in Medicinal Chemistry*; Wiley-VCH: Weinheim, 2013; Vol. *56*, pp 129−164.

(4) (a) Marsault, E.; Peterson, M. L. *J. Med. Chem.* **2011**, *54*, 1961−2004. (b) Driggers, E. M.; Hale, S. P.; Lee, J.; Terrett, N. K. *Nat. Rev. Drug Discovery* **2008**, *7*, 608−624.

(5) (a) Gartner, Z. J.; Tse, B. N.; Grubina, R.; Doyon, J. B.; Snyder, T. M.; Liu, D. R. *Science* **2004**, *305*, 1601−1605. (b) Smith, J. M.; Vitali, F.; Archer, S. A.; Fasan, R. *Angew. Chem., Int. Ed.* **2011**, *50*, 5075−5080.

(6) (a) Baeriswyl, V.; Calzavarini, S.; Gerschheimer, C.; Diderich, P.; Angelillo-Scherrer, A.; Heinis, C. *J. Med. Chem.* **2013**, *56*, 3742−3746. (b) Heinis, C.; Rutherford, T.; Freund, S.; Winter, G. *Nat. Chem. Biol.* **2009**, *5*, 502−507.

(7) Wang, L.; Schultz, P. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 34−66.

(8) Verdine, G. L.; Hilinski, G. J. *Drug Discovery Today: Technol.* **2012**, *9*, e41−e47. (b) Sawyer, T. K.; Guerlavais, V.; Darlak, K.; Feyfant, E. *Macrocycles in Drug Discovery*; The Royal Society of Chemistry: London, 2015; pp 339−366.

(9) (a) Culf, A. S.; Čuperlović-Culf, M.; Léger, D. A.; Decken, A. *Org. Lett.* **2014**, *16*, 2780−2783. (b) Butterfoss, G. L.; Yoo, B.; Jaworski, J. N.; Chorny, I.; Dill, K. A.; Zuckermann, R. N.; Bonneau, R.; Kirshenbaum, K.; Voelz, V. A. *Proc. Natl. Acad. Sci. U. S. A.* **2012**, *109*, 14320−14325. (c) Mäde, V.; Els-Heindl, S.; Beck-Sickinger, A. G. *Beilstein J. Org. Chem.* **2014**, *10*, 1197−1212.

(10) (a) Yudin, A. K. *Chem. Sci.* **2015**, *6*, 30−49. (b) White, C. J.; Yudin, A. K. *Nat. Chem.* **2011**, *3*, 509−524.

(11) (a) Vendeville, S.; Lin, T.-I.; Hu, L.; Tahri, A.; McGowan, D.; Cummings, M. D.; Amssoms, K.; Canard, M.; Last, S.; Van den Steen, I.; Devogelaere, B.; Rouan, M.-C.; Vijgen, L.; Berke, J. M.; Dehertogh, P.; Fransen, E.; Cleiren, E.; Van der Helm, L.; Fanning, G.; Van Emelen, K.; Nyanguile, O.; Simmen, K.; Raboisson, P. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 4437−4443. (b) Cummings, M. D.; Lin, T. I.; Hu, L.; Tahri, A.; McGowan, D.; Amssoms, K.; Last, S.; Devogelaere, B.; Rouan, M. C.; Vijgen, L.; Berke, J. M.; Dehertogh, P.; Fransen, E.; Cleiren, E.; Van der Helm, L.; Fanning, G.; Van Emelen, K.; Nyanguile, O.; Simmen, K.; Raboisson, P.; Vendeville, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 4637−4640.

(12) (a) Failli, A.; Immer, H.; Götz, M. *Can. J. Chem.* **1979**, *57*, 3257−3261. (b) Vasco, A. V.; Pérez, C. S.; Morales, F. E.; Garay, H. E.; Vasilev, D.; Gavín, J. A.; Wessjohann, L. A.; Rivera, D. G. *J. Org. Chem.* **2015**, *80*, 6697−6707.

(13) (a) Hili, R.; Rai, V.; Yudin, A. K. *J. Am. Chem. Soc.* **2010**, *132*, 2889−2891. (b) Jebrail, M. J.; Ng, A. H. C.; Rai, V.; Hili, R.; Yudin, A. K.; Wheeler, A. R. *Angew. Chem., Int. Ed.* **2010**, *49*, 8625−8629.

(14) Wessjohann, L. A.; Voigt, B.; Rivera, D. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4785−4790.

(15) (a) Beck, B.; Larbig, G.; Mejat, B.; Magnin-Lachaux, M.; Picard, A.; Herdtweck, E.; Dömling, A. *Org. Lett.* **2003**, *5*, 1047−1050. (b) Masson, G.; Neuville, L.; Bughin, C.; Fayol, A.; Zhu, J. In *Synthesis of Heterocycles via Multicomponent Reactions II*; Orru, R. V. A., Ruijter, E., Eds.; Springer: Berlin, 2010; Vol. *25*, pp 1−24.

(16) (a) Janvier, P.; Sun, X.; Bienaymé, H.; Zhu, J. *J. Am. Chem. Soc.* **2002**, *124*, 2560−2567. (b) Bonne, D.; Dekhane, M.; Zhu, J. *Org. Lett.* **2004**, *6*, 4771−4774. (c) Pirrung, M. C.; Sarma, K. D. *Synlett* **2004**, *8*, 1425−1427. (d) Pirrung, M. C.; Sarma, K. D. *J. Am. Chem. Soc.* **2004**, *126*, 444−445.

(17) Zarganes-Tzitzikas, T.; Chandgude, A.; Dömling, A. *Chem. Rec.* **2015**, DOI: 10.1002/tcr.201500201.

(18) Zhao, T.; Boltjes, A.; Herdtweck, E.; Dömling, A. *Org. Lett.* **2013**, *15*, 639−641.

(19) (a) Demharter, A.; Hörl, W.; Herdtweck, E.; Ugi, I. *Angew. Chem.* **1996**, *108*, 185−187. (b) Demharter, A.; Hörl, W.; Herdtweck, E.; Ugi, I. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 173−175.

(20) (a) Khoury, K.; Sinha, M. K.; Nagashima, T.; Herdtweck, E.; Dömling, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 10280−10283. (b) Sinha, M. K.; Khoury, K.; Herdtweck, E.; Dömling, A. *Org. Biomol. Chem.* **2013**, *11*, 4792−4796.

(21) Dömling, A.; Chi, K. Z.; Barrére, M. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2871−2874.

(22) Bockus, A. T.; Lexa, K. W.; Pye, C. R.; Kalgutkar, A. S.; Gardner, J. W.; Hund, K. C. R.; Hewitt, W. M.; Schwochert, J. A.; Glassey, E.; Price, D. A.; Mathiowetz, A. M.; Liras, S.; Jacobson, M. P.; Lokey, R. S. *J. Med. Chem.* **2015**, *58*, 4581−4589.

(23) Schwochert, J.; Turner, R.; Thang, M.; Berkeley, R. F.; Ponkey, A. R.; Rodriguez, K. M.; Leung, S. S. F.; Khunte, B.; Goetz, G.; Limberakis, C.; Kalgutkar, A. S.; Eng, H.; Shapiro, M. J.; Mathiowetz, A. M.; Price, D. A.; Liras, S.; Jacobson, M. P.; Lokey, R. S. *Org. Lett.* **2015**, *17*, 2928−2931.

(24) Gavenonis, J.; Sheneman, B. A.; Siegert, T. R.; Eshelman, M. R.; Kritzer, J. A. *Nat. Chem. Biol.* **2014**, *10*, 716−723.

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