Organic LETTERS

Letter

pubs.acs.org/OrgLett

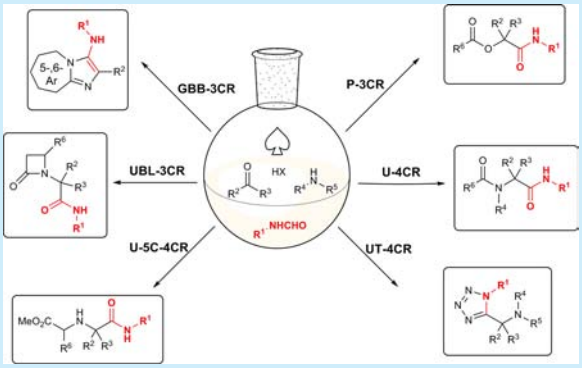
Efficient Isocyanide-less Isocyanide-Based Multicomponent Reactions

Constantinos G. Neochoritis, Silvia Stotani, Bhupendra Mishra, and Alexander Dömling*

University of Groningen, Department of Drug Design, A. Deusinglaan 1, 9713 AV Groningen, The Netherlands

Supporting Information

ABSTRACT: Isocyanides are the "Jekyll and Hyde" of organic chemistry allowing for extremely interesting transformations that are not only extremely odorous but also noxious. Therefore, an isocyanide-less isocyanide-based multicomponent reaction (IMCR) has been developed, and this protocol is expected to replace many of the old procedures in the future not only in IMCR but in other areas of organic chemistry as well.

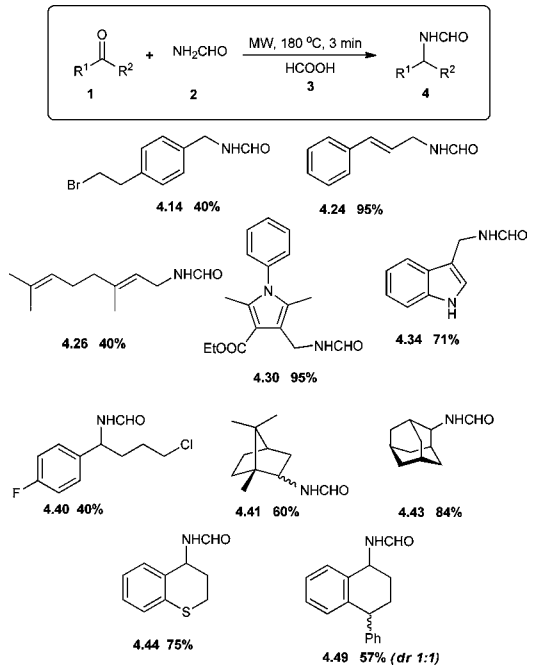


Isocyanides have been first described by Lieke in 1859 and now form the basis of a large and very useful group of reactions in organic chemistry, in particular in isocyanide-based multicomponent reactions (IMCRs).[1] Two decades ago, IMCRs experienced a renaissance, and they are now regularly used to produce diversity-oriented compound libraries for pharmaceutical or material science.[1] Isocyanides, exhibiting an interesting reactivity toward both electro- and nucleophiles adding onto the isocyanide-carbon, comprise a very unusual functional organic group and undergo outstanding chemical transformations.[1,2] At the same time, the compound class of isocyanides is notorious for its intensive stench. Early isocyanide chemists used to work on the roofs of chemical laboratories to avoid the isocyanide stench.[3] Reports of isocyanide toxicity complement the picture of a bad compound class.[4] One can speculate that this property severely hampers progress in isocyanide chemistry. Although a few *in situ* isocyanide formation IMCRs have been described, they are rather limited in substrate scope and examples. For example, El Kaïm et al. formed benzyl isocyanides from the benzyl halide by treatment with AgCN and subsequently performed the Ugi reaction in one pot.[5] Fédou et al. have used an *in situ* epoxide to isocyanide transformation in an MCR of very limited structural diversity.[6] Seebach et al. used one *in situ* generated isocyanide by reacting a formamide with diphosgene and used it in the Passerini reaction.[7] Sharma et al. described a microfluidic system to perform odorless isocyanide chemistry.[8] Here we introduce the general use of formamides to produce complex IMCR products by *in situ* isocyanide formation and IMCR in the same flask. This one-pot procedure is more general, leading to more diverse product types and is supported by more examples than any previously reported case.[5−9] Moreover, we report for the first time a modified Leuckart−Wallach procedure to rapidly generate many different formamides from aldehydes and ketones, the precursors of isocyanides. The findings are significant as (1) the scope of IMCR is greatly increased, (2) the isolation of toxic and bad smelling isocyanides is avoided, and (3) the overall time to products is considerably shortened, as several steps of conventional IMCR procedures are deleted. The majority of isocyanide syntheses use the classical 2-step sequence by Ugi: primary amine → formamide → isocyanide.[10] The Hoffman procedure of carbene-mediated isocyanide formation directly from primary amines is also popular, especially since the introduction of phase transfer catalysis.[11] The reductive amination of oxocomponents **1** with formamide **2** and formic acid **3**, also known as the Leuckart−Wallach reaction, has however never been established as a general synthesis pathway to isocyanides.[12] This is surprising, since often the oxocomponents leading to an isocyanide via Leuckart−Wallach are much cheaper than the corresponding primary amines used for the classical synthesis pathways (Ugi, Hoffmann). Furthermore, the structural diversity and accessibility of oxocomponents is higher compared to primary amines. Here we show that the Leuckart−Wallach reaction, using conventional heating and requiring longer reaction times or using microwave and shorter reaction times, can be used to produce formamides from virtually all tested >50 oxocomponents in moderate to excellent yields (Scheme 1, Supporting Information (SI)). The synthesis can be easily performed in parallel using suitable metal block heaters (SI movie). The reaction is scalable and has been performed on a 50 g scale, for example, to produce **4.43** in good yields. The formamides produced by the Leuckart−Wallach reaction can be

Received: March 16, 2015
Published: March 31, 2015

DOI: 10.1021/acs.orglett.5b00759
Org. Lett. 2015, 17, 2002−2005

Scheme 1. Modified Leuckart–Wallach Formamide Procedure and Representative Examples with Yields



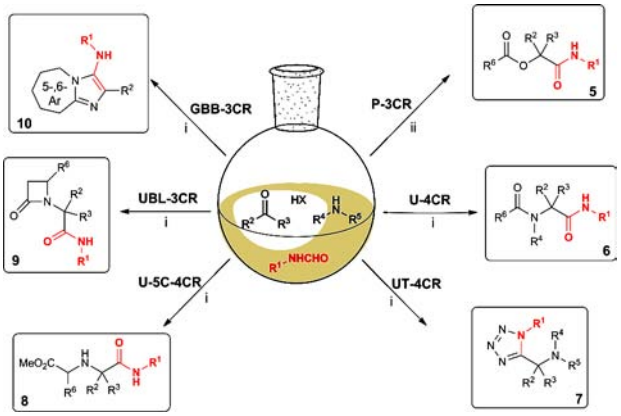
used to produce unprecedented and otherwise difficult to access isocyanides (SI Table 1).

For example, the primary amines for the formamides shown in Scheme 1 are very expensive as compared to the oxo precursor, difficult to access, or not commercially available. However, we were interested to leverage the Leuckart–Wallach produced formamides **4** to develop an *in situ* IMCR without tedious synthesis and isolation of the foul smelling and toxic isocyanides. Thus, we first optimized the reaction conditions by testing different dehydrating agents, temperatures, and solvent systems. After experimentation and screening conditions (SI Tables 2,3), triphosgene (0.4 equiv) with Et_3N (2.4 equiv) in dichloromethane (0.5 M) proved to be the best dehydrating system for the isocyanide formation and superior to the one precedence in literature.[7] Subsequent addition of the complementary MCR components (each 1.3 equiv) in methanol as a cosolvent gave good to excellent yields of the MCR products in 24 h at room temperature in most of the cases and were used as general reaction conditions. With these optimized reaction conditions in hand, we have chosen six well described IMCRs to test if the *in situ* isocyanide formation and IMCR can be performed in one pot and provide a competitive advantage (Scheme 2). Surprisingly, the unrelated MCRs worked well using just one set of general reaction conditions. For each of the six different scaffolds we selected diverse starting materials to give realistic insight into the scope and limitations.

The Passerini 3-CR is a well-established MCR with applications for example in the field of natural product synthesis, material science, or drug photocaging.[13] Our *in situ* procedure allows for diverse syntheses of products **5.1**–**5.5** in yields between 48% to 58% (Scheme 3). The substrate scope includes ketones, aldehydes, (hetero)aromatic aldehydes, and functional groups such as phenols and tertiary amines.

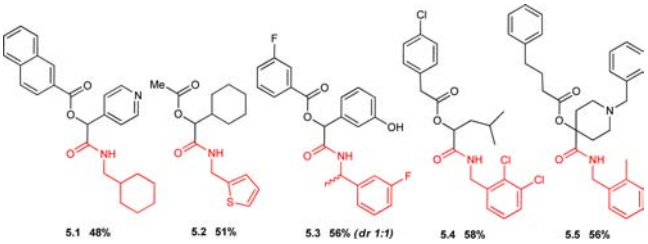
The classical Ugi-4CR is the basis of an enormous number of secondary scaffolds and has found widespread application

Scheme 2. Isocyanide-less IMCRs Leading to Six Different Scaffolds[a]



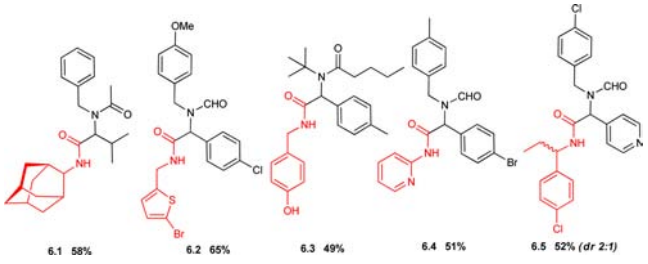
[a]Reactions and conditions: Triphosgene/Et_3N in DCM at 0 °C and then amine/oxo/acid component in MeOH (i) or DCM (ii) at rt for 24–48 h.

Scheme 3. Isocyanide-less Passerini 3-CR (P-3CR)



throughout the field of chemistry.[14,1] In our hands, the substrate scope of the *in situ* method is not distinguishable from the procedure using the isolated isocyanides (Scheme 4),

Scheme 4. Isocyanide-less Ugi 4-CR (U-4CR)

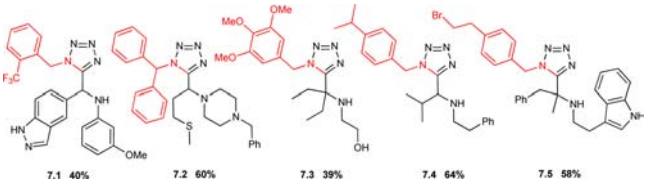


affording **6.1**–**6.5** in 49–87% yield for example. Additionally, 2-pyridyl isocyanide derived product **6.4** which, using the classical approach, is not very accessible, underscoring the utility of the *in situ* procedure. Aniline derived, and especially heteroaromatic, isocyanides are difficult to synthesize, very unstable, and prone to polymerization. So far, they were only isolated as complexes with copper(I) bromide and could thus not be used in IMCR chemistry.[15]

The Ugi tetrazole variation (UT-4CR) recently became popular in the search for bioactive compounds such as inhibitors of γ-aminobutyric acid transporters.[16] The substrate scope includes diverse substituted aldehydes and ketones, substituted formamides, and a multitude of primary and secondary amines yielding the 1,5-disubstituted tetrazoles, e.g. **7.1**–**7.5** in yields of 39–64% (Scheme 5).

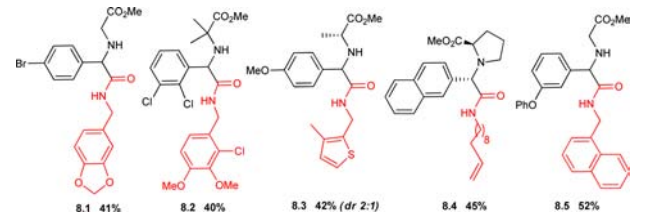
DOI: 10.1021/acs.orglett.5b00759
Org. Lett. 2015, 17, 2002–2005

Scheme 5. Isocyanide-less Ugi 4-CR Tetrazole Variation (UT-4CR)



The Ugi 5-center-4-component reaction (U-5C-4CR) of free α-amino acids, aldehydes, an alcohol, and an isocyanide stereoselectively yields yet another scaffold, iminodicarboxylic acid monoamide monoesters.[17] The IMCR is used for example in the industrial syntheses of the clinical oxytocine receptor antagonists Epelsiban and Atosiban.[18] Moreover, it constitutes the basis of several scaffolds now found in the screening decks of the European Lead Factory library.[19] The substrate scope of our *in situ* variant is not distinct from the original procedure using isolated isocyanides, e.g. **8.1**−**8.5** (Scheme 6). Stereoinduction in the proline derivative **8.4** is excellent, and only one diastereomer could be isolated.

Scheme 6. Isocyanide-less Ugi 5-Center-4-Component Reaction (U-5C-4CR)



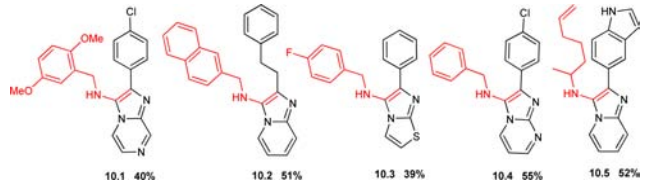
The reaction of β-amino acids in the Ugi reaction yields strained β-lactams and has found widespread applications in the synthesis of β-lactam antibiotics.[20] A wide variety of substrates can undergo the reaction toward **9.1**-**9.5** in good yields ranging from 49% to 90% (Scheme 7). The 3-aroyl or 3-aryl substituted

Scheme 7. Isocyanide-less Ugi-β-lactam 3-CR (UBL-3CR)

β-amino acids often have poor alcohol solubility, requiring extended Ugi reaction times and often giving low yields. The *in situ* procedure, however, is advantageous as considerable higher yields of **9.4** and **9.5** could be isolated after only 24 h of reaction times. When running the reaction for the derivative **9.4** under standard conditions with pure cyclohexyl isocyanide (1.0 mmol scale, 1 M solution), we obtained the product after 24 h only in 42% yield as opposed to 77% with the current *in situ* method. We believe that salt effects increase the solubility of the β-amino acid and thus give higher yields of the β-lactam.

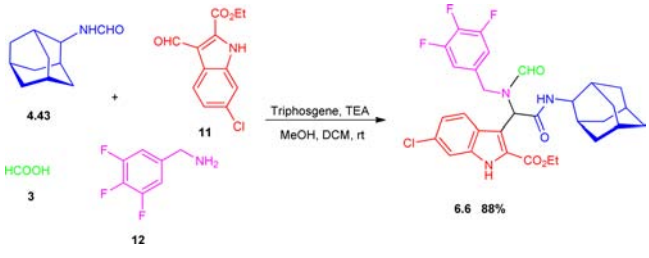
Lastly, we investigated the Gröbcke−Blackburn−Bienaymé variant GBB-3CR of the Ugi MCR.[21] GBB-3CR products have been recently described as GPCR ligands, *M. tuberculosis* glutamine synthetase, kinase, and bromo domain inhibitors, just to name a few applications.[22] For the GBB-3CR, many different catalysts are known and we used the initially described $HClO_4$ to accelerate the reaction. We found that aromatic, as well as aliphatic, formamides can be used as isocyanide precursors in the *in situ* variant. Different heteroaromatic 5- and 6-membered amidines reacted with aliphatic and aromatic aldehydes in moderate to good yields (Scheme 8).

Scheme 8. Isocyanide-less Gröbcke−Blackburn−Bienaymé 3-CR (GBB-3CR)



A "real life" application of the isocyanide-less U-4CR is shown in Scheme 9 where we synthesized in one step, with very

Scheme 9. Example of an Application of the Isocyanide-less U-4CR To Synthesize a Highly Potent p53-MDM2 Antagonist



good yield (88%) , an example of a recently discovered highly potent class of antagonists of the protein−protein interaction between p53 and MDM2.[23] Gratifyingly, during this reaction the product **6.6** precipitates and a simple filtration/washing step is sufficient to obtain the product in excellent purity.

Another application of our *in situ* method is the protecting group free access to photoinducible probe **7.6**, a bioisostere of the important neurotransmitter glycine. Photocleavable tetrazole was synthesized, via an UT-4CR, using the Leuckart−Wallach accessible *o*-nitro formamide (Scheme 10).

Scheme 10. Example of an Application of the Isocyanide-less UT-4CR To Synthesize a Photocleavable Tetrazole Derivative

It can be hypothesized that noxious and malodorous properties are severely hampering progress in isocyanide chemistry, a compound class highly under-used in organic chemistry. Therefore, we developed the isocyanide-less isocyanide-based multicomponent reaction (IMCR). We described a rapid and highly diverse formamide synthesis via

DOI: 10.1021/acs.orglett.5b00759
Org. Lett. 2015, 17, 2002−2005

a modified Leuckart−Wallach procedure, with conversion *in situ* into isocyanides, which can be reacted in the same pot in different isocyanide-based MCRs. The broad applicability of the procedure is exemplified with multiple highly diverse examples of six different unrelated MCR scaffolds. We found the yields and substrate scope to be comparable, or superior, to the original procedures using isolated isocyanides. Highly stereoselective transformations are also possible. This *in situ* procedure comprises a major milestone in the rapidly advancing field of isocyanide chemistry in general, and specifically in IMCR, since it avoids the isolation of the unpleasant isocyanides and reduces the time to the product without compromising structural and scaffold diversity.

■ ASSOCIATED CONTENT

Supporting Information

Optimization, screening results, general procedures, characterization data of all the compounds, and a multimedia file (AVI) are included as Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: a.s.s.domling@rug.nl.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The work was financially supported from the NIH (1R01GM097082-01) and by Innovative Medicines Initiative (Grant Agreement No. 115489).

■ REFERENCES

(1) (a) Lieke, W. *Liebigs Ann.Chem.* **1859**, *112*, 316−321. (b) Wilson, R. M.; Stockdill, J. L.; Wu, X.; Li, X.; Vadola, P. A.; Park, P. K.; Wang, P.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2012**, *51*, 2834−2848. (c) Vlaar, T.; Ruijter, E.; Maes, B. U. W.; Orru, R. V. A. *Angew. Chem., Int. Ed.* **2013**, *52*, 7084−7097. (d) Lygin, A. V.; de Meijere, A. *Angew. Chem., Int. Ed.* **2010**, *49*, 9094−9124. (e) Zaretsky, S.; Adachi, S.; Rotstein, B. H.; Hickey, J. L.; Scully, C. C. G.; St. Denis, J. D.; Courtemanche, R.; Yu, J. C. Y.; Chung, B. K. W.; Yudin, A. K. *J. Org. Chem.* **2014**, *79*, 9948−9957. (f) De Moliner, F.; Bigatti, M.; Banfi, L.; Riva, R.; Basso, A. *Org. Lett.* **2014**, *16*, 2280−2283. (g) Kambe, T.; Correia, B. E.; Niphakis, M. J.; Cravatt, B. F. *J. Am. Chem. Soc.* **2014**, *136*, 10777−10782. (h) Dömling, A. *Chem. Rev.* **2006**, *106*, 17−89. (i) Dömling, A.; Wang, W.; Wang, K. *Chem. Rev.* **2012**, *112*, 3083−3135.

(2) Tumanov, V. V.; Tishkov, A. A.; Mayr, H. *Angew. Chem., Int. Ed.* **2007**, *46*, 3563−3566.

(3) Ugi, I., personal communication.

(4) Holmer, S. A.; Houlton, C. L.; Westmoreland, D. T. *J. Inorg. Biochem.* **1997**, *66*, 63−65.

(5) Kaim, L. El.; Grimaud, L.; Schiltz, A. *Org. Biomol. Chem.* **2009**, *7*, 3024−3026.

(6) Fédou, N. M.; Parsons, P. J.; Viseux, E. M. E.; Whittle, A. *J. Org. Lett.* **2005**, *7*, 3179−3182.

(7) Seebach, D.; Adam, G.; Gees, T.; Schiess, M.; Weigand, W. *Chem. Ber.* **1988**, *121*, 507−517.

(8) Sharma, S.; Maurya, R. A.; Min, K.-I.; Jeong, G.-Y.; Kim, D.-P. *Angew. Chem., Int. Ed.* **2013**, *52*, 7564−7568.

(9) Guchhait, S. K.; Priyadarshani, G.; Chaudhary, V.; Seladiya, D. R.; Shah, T. M.; Bhogayta, N. P. *RSC Adv.* **2013**, *3*, 108670−10874.

(10) Ugi, I.; Fetzer, U.; Eholzer, U.; Knupfer, H.; Offermann, K. *Angew. Chem., Int. Ed.* **1965**, *4*, 472−484.

(11) (a) Hofmann, A. W. *Liebigs Ann. Chem.* **1867**, *144*, 114−120. (b) Weber, W. P.; Gokel, G. W.; Ugi, I. K. *Angew. Chem., Int. Ed.* **1972**, *11*, 530−531.

(12) (a) Leuckart, R. *Chem. Ber.* **1885**, *18*, 2341−2344. (b) Wallach, O. *Chem. Ber.* **1891**, *24*, 3992−3993. (c) Kitamura, M.; Lee, D.; Hayashi, S.; Tanaka, S.; Yoshimura, M. *J. Org. Chem.* **2002**, *67*, 8685−8687. (d) Loupy, A.; Monteux, D.; Petit, A.; Aizpurua, J. M.; Domínguez, E.; Palomo, C. *Tetrahedron Lett.* **1996**, *37*, 8177−8180. (e) Musatov, D. M.; Starodubtseva, E. V.; Turova, O. V.; Kurilov, D. V.; Vinogradov, M. G.; Rakishev, A. K.; Struchkova, M. I. *Russ. J. Org. Chem.* **2010**, *46*, 1021−1028.

(13) (a) Passerini, M.; Simone, L. *Gazz. Chim. Ital.* **1921**, *51*, 126−129. (b) Solleder, S. C.; Meier, M. A. R. *Angew. Chem., Int. Ed.* **2014**, *53*, 711−714. (c) Szymański, W.; Velema, W. A.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2014**, *53*, 8682−8686. (d) Isaacson, J.; Kobayashi, Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 1845−1848. (e) Faure, S.; Hjelmgaard, T.; Roche, S. P.; Aitken, D. J. *Org. Lett.* **2009**, *11*, 1167−1170.

(14) (a) Ugi, I.; Steinbrückner, C. *Chem. Ber.* **1960**, *72*, 267−268. (b) Dömling, A.; Ugi, I. *Angew. Chem.* **2000**, *112*, 3300−3344.

(15) Mironov, M. A.; Mokrushin, V. S. *Russian Journal of Organic Chemistry (Translation of Zhurnal Organicheskoi Khimii)* **1999**, *35*, 693−697.

(16) (a) Ugi, I.; Steinbrückner, C. *Chem. Ber.* **1961**, *94*, 734−742. (b) Schaffert, E. S.; Höfner, G.; Wanner, K. T. *Bioorg. Med. Chem.* **2011**, *19*, 6492−6504. (c) Patil, P.; Khoury, K.; Herdtweck, E.; Dömling, A. *Org. Lett.* **2014**, *16*, 5736−5739.

(17) (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.* **1996**, *35*, 173−175.

(18) (a) Borthwick, A. D.; Liddle, J.; Davies, D. E.; Exall, A. M.; Hamlett, C.; Hickey, D. M.; Mason, A. M.; Smith, I. E. D.; Nerozzi, F.; Peace, S.; Pollard, D.; Sollis, S. L.; Allen, M. J.; Woollard, P. M.; Pullen, M. A.; Westfall, T. D.; Stanislaus, D. J. *J. Med. Chem.* **2012**, *55*, 783−796. (b) Borthwick, A. D. *J. Med. Chem.* **2010**, *53*, 6525−6538.

(19) (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.

(20) Ugi, I. *Angew. Chem., Int. Ed.* **1982**, *21*, 810−819.

(21) (a) Groebke, K.; Weber, L.; Mehlin, F. *Synlett* **1998**, 661−663. (b) Blackburn, C.; Guan, B.; Fleming, P.; Shiosaki, K.; Tsai, S. *Tetrahedron Lett.* **1998**, *39*, 3635−3638. (c) Bienaymé, H.; Bouzid, K. *Angew. Chem., Int. Ed.* **1998**, *37*, 2234−2237.

(22) (a) Reutlinger, M.; Rodrigues, T.; Schneider, P.; Schneider, G. *Angew. Chem., Int. Ed.* **2014**, *53*, 582−585. (b) Odell, L. R.; Nilsson, M. T.; Gising, J.; Lagerlund, O.; Muthas, D.; Nordqvist, A.; Karlén, A.; Larhed, M. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4790−4793. (c) Akritopoulou-Zanze, I.; Wakefield, B. D.; Gasiecki, A.; Kalvin, D.; Johnson, E. F.; Kovar, P.; Djuric, S. W. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1480−1483. (d) McKeown, M. R.; Shaw, D. L.; Fu, H.; Liu, S.; Xu, X.; Marineau, J. J.; Huang, Y.; Zhang, X.; Buckley, D. L.; Kadam, A.; Zhang, Z.; Blacklow, S. C.; Qi, J.; Zhang, W.; Bradner, J. E. *J. Med. Chem.* **2014**, *57*, 9019−9027.

(23) Huang, Y.; Wolf, S.; Beck, B.; Köhler, L.-M.; Khoury, K.; Popowicz, G. M.; Goda, S. K.; Subklewe, M.; Twarda, A.; Holak, T. A.; Dömling, A. *ACS Chem. Biol.* **2014**, *9*, 802−811.

DOI: 10.1021/acs.orglett.5b00759
Org. Lett. 2015, 17, 2002−2005