

Highly Stereoselective Synthesis of Natural-Product-Like Hybrids by an Organocatalytic/Multicomponent Reaction Sequence**

Radell Echemendía, Alexander F. de La Torre, Julia L. Monteiro, Michel Pila, Arlene G. Corrêa, Bernhard Westermann, Daniel G. Rivera,* and Márcio W. Paixão*

Abstract: In an endeavor to provide an efficient route to natural product hybrids, described herein is an efficient, highly stereoselective, one-pot process comprising an organocatalytic conjugate addition of 1,3-dicarbonyls to α,β -unsaturated aldehydes followed by an intramolecular isocyanide-based multicomponent reaction. This approach enables the rapid assembly of complex natural product hybrids including up to four different molecular fragments, such as hydroquinolinone, chromene, piperidine, peptide, lipid, and glycoside moieties. The strategy combines the stereocontrol of organocatalysis with the diversity-generating character of multicomponent reactions, thus leading to structurally unique peptidomimetics integrating heterocyclic, lipidic, and sugar moieties.

The generation and decoration of privileged natural product scaffolds is a successful strategy for obtaining libraries of bioactive compounds.^[1] Scaffold decoration entails the utilization of both combinatorial and rationally designed approaches to functionalize biologically validated molecular targets. Scaffold generation, in contrast, focuses on the application of methodologies capable of generating structures which cover a larger part of the chemical and biological space.^[2] Since scaffold generation is pivotal during the early stage of drug discovery, issues like chemical efficiency, stereocontrol, and easy diversification are crucial in process development. Relevant strategies for exploring the broader chemical space by targeting dissimilar chemotypes, either

previously validated by nature or derived from chemists' synthetic expertise, include biology-,^[3] function-,^[4] and diversity-oriented^[5] syntheses.

Several methodologies relying on cascade or domino processes^[6] and multicomponent reactions (MCRs)^[7,8] are currently being applied to match or even surpass nature's synthetic ability to generate structurally complex and diverse scaffolds. Within the class of MCRs, isocyanide-based multicomponent reactions (I-MCRs) stand as powerful approaches^[8] comprising high chemical efficiency, convergency, and atom economy. Not surprisingly, I-MCRs have been intensively exploited in drug discovery and chemical biology programs targeting both scaffold decoration and generation.^[9] Moreover, the intrinsic characteristics of I-MCRs may be further improved when they are combined with either pre-^[10] or post-MCR^[11] modifications. However, most efforts have been devoted to the latter one,^[11,12] whereas examples describing pre-MCR modifications are quite seldom.^[10]

Looking at the repertoire of MCRs, one realizes the ubiquity of the carbonyl component, that is, ketones or aldehydes, in these reactions. Only recently, early efforts have been directed towards the implementation of an aminocatalytic asymmetric functionalization of such carbonyl functionalities followed by a subsequent MCR.^[11,13] Aminocatalysis has been applied with great success in the α -, β -, γ - and even ϵ -asymmetric functionalization of carbonyls.^[14] Hence, combination of aminocatalysis with the available repertoire of MCRs provides endless possibilities for scaffold generation. In an endeavor to demonstrate the potential of this concept, we focused on the development of a stereocontrolled organocatalytic/multicomponent sequence leading to compounds with skeletal complexity resembling natural products.

This article describes a highly stereoselective approach for the one-pot synthesis of complex natural product hybrids^[15] incorporating fragments such as hydroquinolines, chromenes, piperidines, peptides, lipids, and glycosides. The approach involves an asymmetric organocatalytic conjugate addition of dicarbonyl compounds to α,β -unsaturated aldehydes, followed by an intramolecular four-center three-component reaction including amine and isocyanide components.

We formulated two main selection criteria for the organocatalytic and multicomponent approaches. First, the organocatalytic process should provide enantiomerically enriched natural-product-like scaffolds having a pair of reactive functionalities suitable for a subsequent I-MCR. Second, we aimed at utilizing intramolecular I-MCRs, as these typically provide better stereocontrol as compared to their intermo-

[*] M. Sc. A. F. de La Torre, M. Sc. J. L. Monteiro, Prof. Dr. A. G. Corrêa, Prof. Dr. M. W. Paixão
Departamento de Química, Universidade Federal de São Carlos
São Carlos, 97105-900, SP (Brasil)
E-mail: mwpaixao@ufscar.br

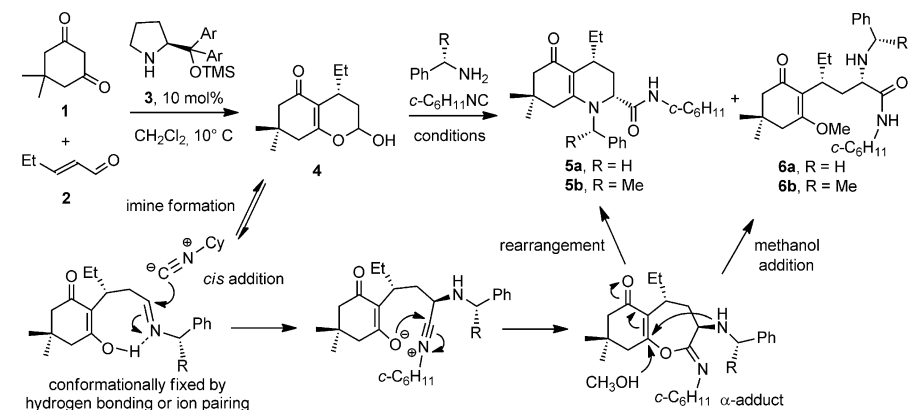
M. Sc. R. Echemendía, M. Sc. M. Pila, Prof. Dr. D. G. Rivera
Center for Natural Products Research
Faculty of Chemistry, University of Havana
Zapata y G, 10400, La Habana (Cuba)
E-mail: dgr@fq.uh.cu

Prof. Dr. B. Westermann
Department of Bioorganic Chemistry
Leibniz Institute of Plant Biochemistry
Weinberg 3, 06120 Halle (Saale) (Germany)
and
Martin-Luther-University, Halle Wittenberg, Institute of Chemistry
Kurt-Mothes-Str. 2, 06120 Halle (Germany)

[**] D.G.R. is grateful to FAPESP for a visiting professor grant (2013/21599-8). The authors also kindly acknowledge financial support from CNPq (INCT-Catálise), CAPES/MES-Cuba, and FAPESP. Dr. S. S. van Berkel is also acknowledge for his fruitful suggestions.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201412074>.

Table 1: Screening of the one-pot organocatalytic conjugate addition/four-center three-component reaction sequence to 2-amido-hydroquinolin-6-ones and concise reaction mechanism.



Entry ^[a]	R	Conditions ^[b]	5/6 Yield [%] ^[c]	5 d.r. (<i>cis/anti</i>) ^[d]	5 ee [%] ^[e]
1	H	MeOH, RT ^[f]	39/25	54:46	92
2	Me	MeOH, MW ^[g]	42/28	> 99:1	> 99
3	H	toluene, MW ^[g]	n.r.	—	—
4	Me	CH ₂ Cl ₂ , RT ^[f]	n.r.	—	—
5	H	TFE, RT ^[f]	77/0	58:42	93
6	Me	TFE, MW ^[g]	75/0	> 99:1	> 99
7	Me	CH ₂ Cl ₂ /TFE, RT ^[f,h]	64/0	> 99:1	> 99
8	Me	CH ₂ Cl ₂ /TFE, MW ^[g,h]	71/0	> 99:1	> 99

[a] First step performed with **1** (1 equiv) and **2** (1.3 equiv). [b] Second step performed either with benzyl or (*S*)- α -methylbenzyl amine (1.3 equiv) and cyclohexylisocyanide (1.3 equiv). [c] Yield of isolated product after two steps. [d] Determined by ¹H NMR analysis of the crude reaction mixture and confirmed by HPLC. [e] Determined by chiral-phase HPLC analysis. [f] Conducted at room temperature (RT) for 36 h. [g] Conducted under microwave irradiation (MW) for 15 minutes at 70°C. [h] Addition of TFE to the reaction mixture containing CH₂Cl₂ to make a 1:1 (v/v) mixture. Ar = 3,5-(CF₃)₂-C₆H₃, MW = microwave, TFE = trifluoroethanol, TMS = trimethylsilyl.

lecular versions.^[10,17] As shown in Table 1, the first procedure is an organocatalytic cascade developed independently by the groups of Rueping^[18] and Jørgensen.^[19] The cascade process comprises the asymmetric conjugate addition of 1,3-cycloalkanediones to α,β -unsaturated aldehydes followed by acetalization, thus enabling the installation of two reactive functionalities onto a single skeleton. Dimedone (**1**) and 2-pentenal (**2**) were initially selected for the organocatalytic conjugate addition as the first step in the multicomponent sequence. Reaction conditions originally described by Rueping et al.,^[18b] employing 10 mol % of the catalyst diarylprolinol silyl ether **3**, successfully produced the chromenone **4**. This intermediate fulfills the requisite of being a biologically relevant core for scaffold diversification as well as having two functionalities suitable for I-MCRs, that is, an aldehyde and a conjugated enol.

Both racemic and enantiomerically enriched **4** were prepared and subsequently subjected to the I-MCR by treatment with a primary amine and an isocyanide. Such a multicomponent process resembles the Ugi–Smiles reaction,^[20] which has been previously implemented with heterocyclic and conjugated enols^[21] as surrogates of the classic phenol component. However, neither intramolecular variant of this type of I-MCR nor combinations with a pre-MCR organocatalytic process have been reported so far.

Initial experiments using methanol, toluene, or dichloromethane in the second reaction step were unsatisfactory, as the first solvent gave a mixture of products and the two latter ones did not lead to any product formation (Table 1, entries 1–4). The products **5** and **6** were formed in a ratio of about 1.5:1 when methanol was used, as a result of the competition between the rearrangement of the α -adduct (i.e., migration of the amine component) and the addition of methanol to the conjugated position. As shown in Table 1, the intermediate α -adduct is a rigid, fused bicyclic system, in which the low conformational flexibility may disfavor the amine migration, thus enabling the attack of a nucleophilic solvent like methanol. To circumvent this problem, TFE was used and led to the 2-amido-hydroquinolin-6-one **5** as the sole product in good yield (Table 1, entry 5). Importantly, the use of microwave irradiation enabled the reaction to proceed in similar chemical efficiency and significantly shorter reaction times, that is, 15 minutes at 70°C (entry 6). Since the second step did not proceed in CH₂Cl₂, we evaluated the possibility of implementing a one-pot

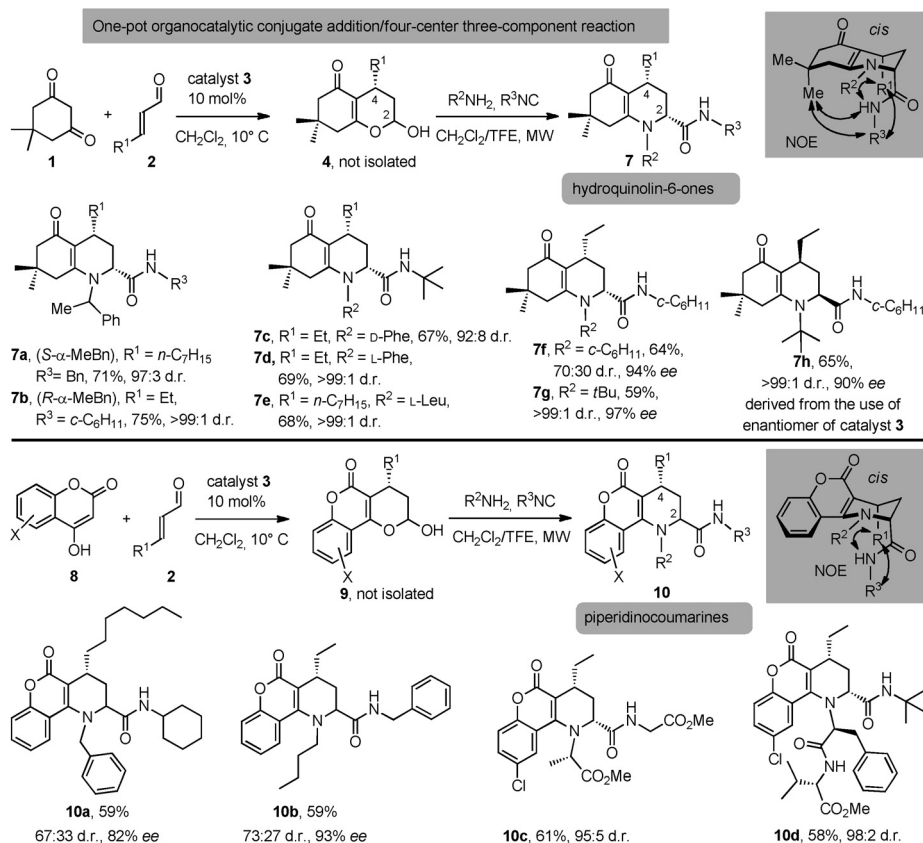
sequence by addition of TFE after formation of organocatalytic product **4**, thus carrying out the second step in the solvent mixture CH₂Cl₂/TFE (1:1, v/v). To our delight, both the yield and stereoselectivity remained high in this one-pot process comprising the organocatalytic step and the I-MCR (entries 7 and 8). Importantly, the presence of secondary amine catalyst **3** did not interfere in the I-MCR, as no product including this fragment was detected.

A key feature of this approach is the different stereochemical outcome derived from variation of the primary amine. As illustrated in Table 1, the use of benzylamine led to almost no diastereoselectivity in the I-MCR, thus producing **5a** as a mixture of diastereoisomers (entries 1 and 5). Conversely, the utilization of the chiral (*S*)- α -methylbenzyl amine provided the enantiomerically pure product **5b** with an excellent diastereoselectivity (> 99:1). The relative configurations of **5a,b** were determined by NMR analysis on the basis of the absolute configuration at C4 of **4**, as previously assessed by X-ray analysis.^[18] The solid-state structures showed the axial orientation (directing toward the α face) of the substituent at position 4 in **4**. In the first instance, the two diastereoisomers of **5a**, derived from benzyl amine, were isolated and analyzed by NMR spectroscopy. In the major stereoisomer of **5a** (and also in the only one of **5b**), various NOE couplings between hydrogen atoms of the ethyl chain at

position 4 and the substituent at position 2 were found. Similarly, strong NOE couplings were observed between the amide substituent at position 2 and one of the geminal methyl groups of the fused bicyclic skeleton. These results unambiguously prove the *cis* configuration in which both substituents at positions 2 and 4 have a pseudo-axial orientation directed toward the α -face of the hydroquinolin-6-one skeleton. As highlighted in Scheme 1, these NOE couplings are only possible because of the 1,3 and 1,5-diaxial interactions of the amide substituent at C2, the substituent at position 4, and the geminal axial methyl group. In contrast, the minor stereoisomer of **5a** showed a strong NOE coupling between the hydrogen at C2 and the ethyl group at C4, thus indicating the *trans* configuration of substituents at positions 2 and 4.

As shown in Table 1, the diastereoselection of this process derives from the preferential addition of the isocyanide to the conformationally fixed imine (or iminium ion) by the same face of ethyl group (*cis* addition). Further addition of the enolate oxygen atom leads to the α -adduct featuring the *trans* disposition between the ethyl group and the exocyclic amine moiety. Finally, migration of the amine (rearrangement) generates the piperidine ring with the *cis* configuration of the amide substituent at C2 with respect to the ethyl group at C4. Additional evidence that the stereocontrol lies at the isocyanide addition step is that the acyclic side-product **6b**, derived from methanol addition, was obtained with the same diastereoselectivity of **5b**, whilst formation of side-product **6a** proceeded with poor stereoselection, as for **5a**. To gain deeper insight into stereoselectivity, we implemented the reaction sequence with variation of the four different components.

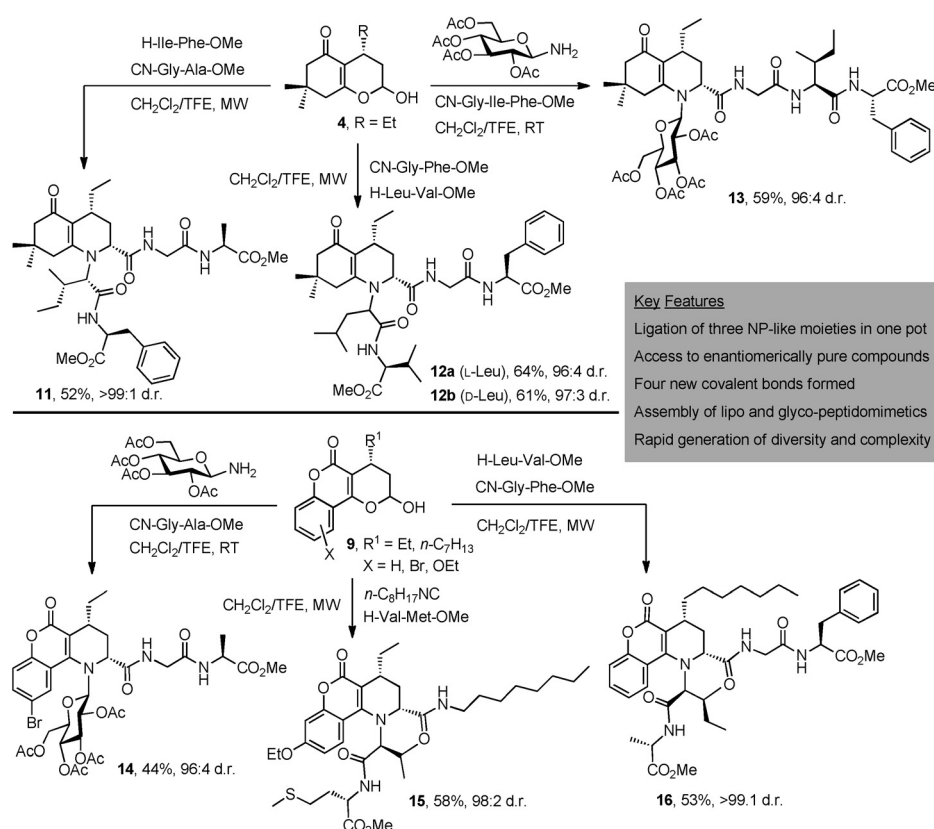
For this, we focused on the one-pot synthesis of more complex molecular hybrids having a piperidine core structure. Piperidine-containing alkaloids, including the tetrahydroquinolines and tetrahydroisoquinolines, represent an important class of natural products displaying a wide variety of pharmacological activities.^[22] As shown in Scheme 1, the hybrid scaffolds **7** and **10** were produced by variation of four structural elements, that is, the 1,3-dicarbonyl and aldehyde incorporated in the organocatalytic step, as well as the amine and isocyanide in the I-MCR. As before, the one-pot processes were performed without isolation of intermediates **4** and **9**, but simply carrying out the subsequent I-MCR through addition of TFE, the amine, and isocyanide compo-



Scheme 1. One-pot synthesis of hydroquinolin-6-one and piperidinocoumarine hybrids by an organocatalytic conjugate addition/I-MCR sequence. Yields are those of the isolated products. The d.r. values were determined by ¹H NMR analysis of the crude reaction mixture and confirmed by HPLC. The ee values were determined by HPLC analysis on a chiral stationary phase.

nents immediately after completion of the organocatalytic step. This diversity-oriented approach gives rise to a unique class of hydroquinolin-6-one and piperidinocoumarine hybrids substituted at positions 1, 2, and 4.

The stereoselectivity of the multicomponent sequence leading to the hexahydroquinolinones **7** and piperidinocoumarines **10** proved to be excellent when the amine is chiral (α -MeBn and amino acids), whereas unbranched *n*-butyl- and benzylamines provided poor stereocontrol. Again, NMR evidence proved the *cis* configuration for major isomers. The use of either *S*- or *R*- α -methylbenzyl amine as well as either D- or L-amino acid methyl esters provided the same stereodifferentiation to the *cis* isomers of the hybrids **7a–e**. An interesting result was obtained when the bulky character of the achiral amine was increased from cyclohexyl to *tert*-butylamine. Thus, cyclohexylamine gave the compound **7f** with moderate diastereoselectivity, while the highly crowded *tert*-butylamine rendered **7g** with excellent diastereoselectivity. This outcome confirms that not only chiral amines, but also achiral ones with great steric congestion at the α -position reinforce the stereoselection in this I-MCR. An additional experiment proceeding through the enantiomer of intermediate **4** (prepared using the enantiomer of catalyst **3**) resulted in the highly stereoselective formation of **7h**, which is the enantiomer of **7g** as revealed by chiral-phase HPLC and optical rotation analysis. This result is consistent with a sub-



Scheme 2. One-pot stereoselective synthesis of natural product hybrids including hydroquinolinone, chromene, lipidic, peptidic, and saccharidic moieties. Yields are those of the isolated products. The d.r. values were determined by ^1H NMR analysis of the crude reaction mixture and confirmed by HPLC. The *ee* values were determined by HPLC analysis on a chiral stationary phase.

strate-controlled reaction and confirms the great stereofacial selectivity of the isocyanide addition. Although the origin of the stereocontrol^[23] remains to be determined, it is clear that the magnitude of the diastereoselectivity for the *cis* product is dependent on the steric bulk of the amine. Computational modeling may aid in elucidating the mechanistic insights that explain such a stereocontrol.^[24]

Having demonstrated the efficacy of the organocatalytic/I-MCR sequence for the stereoselective preparation of molecular hybrids, we focused on the generation of further skeletal diversity and complexity through variation of the amine and isocyanide components. To this end, we investigated the possibility of incorporating natural product fragments of peptidic, lipidic, and saccharidic nature into piperidine-based hybrid architectures. Scheme 2 illustrates the one-pot approach leading to the hydroquinolin-6-one and piperidinocoumarin hybrids **11–16** utilizing the enantiomerically enriched chromenone **4** and piranocoumarin **9**. As before, enantiomerically pure hybrids were produced in an excellent diastereomeric ratio, with the *cis* isomers as major products. The use of epimeric dipeptides having either L- or D-Leu at the N-terminus generates the hybrids **12a** and **12b**, respectively, and both feature the *cis* configuration.

In conclusion, we developed a highly stereoselective and one-pot sequence leading to complex natural-product-like

hybrids. From a synthetic point of view, the present approach can be regarded as an asymmetric multicomponent ligation process^[25] which integrates up to four different molecular fragments into a single skeleton. This report confirms that the asymmetric aminocatalytic functionalization of carbonyl compounds is an effective pre-MCR process capable of providing enantiomerically enriched building blocks for subsequent multicomponent diversification. The versatility of this diversity-oriented strategy relies on the vast number of 1,3-dicarbonyls and α,β -unsaturated aldehydes which could be combined with amines and isocyanides of biomolecular nature. Such a facile variation of reaction components combines the great levels of molecular complexity available with low synthetic cost. Finally, we envision that other iminium, enamine, and N-heterocyclic carbene organocatalytic processes may be combined with varied MCRs, hence expanding the repertoire of stereoselective multicomponent cascade reactions.

Keywords: carbohydrates · diversity-oriented synthesis · multicomponent reactions · organocatalysis · synthetic methods

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 7621–7625
Angew. Chem. **2015**, *127*, 7731–7735

- [1] a) S. Rizzo, H. Waldmann, *Chem. Rev.* **2014**, *114*, 4621; b) K. Kumar, H. Waldmann, *Angew. Chem. Int. Ed.* **2009**, *48*, 3224; *Angew. Chem.* **2009**, *121*, 3272; c) D. J. Newman, G. M. Cragg, **2012**, *75*, 311; d) J. Clardy, C. Walsh, *Nature* **2004**, *432*, 829.
- [2] a) R. S. Bon, H. Waldmann, *Acc. Chem. Res.* **2010**, *43*, 1103; b) L. A. Marcaurelle, C. W. Johannes, *Prog. Drug Res.* **2008**, *66*, 187; c) S. Shang, D. S. Tan, *Curr. Opin. Chem. Biol.* **2005**, *9*, 248; d) P. Arya, R. Joseph, D. T. H. Chou, *Chem. Biol.* **2002**, *9*, 145.
- [3] a) S. Wetzel, R. S. Bon, K. Kumar, H. Waldmann, *Angew. Chem. Int. Ed.* **2011**, *50*, 10800; *Angew. Chem.* **2011**, *123*, 10990; b) R. Breinbauer, I. R. Vetter, H. Waldmann, *Angew. Chem. Int. Ed.* **2002**, *41*, 2878; *Angew. Chem.* **2002**, *114*, 3002.
- [4] P. A. Wender, V. A. Verma, T. J. Paxton, T. H. Pillow, *Acc. Chem. Res.* **2008**, *41*, 40.
- [5] a) S. L. Schreiber, *Science* **2000**, *287*, 1964; b) M. D. Burke, S. L. Schreiber, *Angew. Chem. Int. Ed.* **2004**, *43*, 46; *Angew. Chem.* **2004**, *116*, 48; c) T. E. Nielsen, S. L. Schreiber, *Angew. Chem. Int. Ed.* **2008**, *47*, 48; *Angew. Chem.* **2008**, *120*, 52; d) R. J. Spandl, A. Bender, D. R. Spring, *Org. Biomol. Chem.* **2008**, *6*, 1149.
- [6] a) L. F. Tietze, G. Brasche, K. Gerike, *Domino Reactions in Organic Chemistry*, Wiley-VCH, Weinheim, **2006**; b) D. Enders, C. Grondal, M. R. M. Hüttl, *Angew. Chem. Int. Ed.* **2007**, *46*,

- 1570; *Angew. Chem.* **2007**, *119*, 1590; c) C. Grondal, M. Jeanty, D. Enders, *Nat. Chem.* **2010**, *2*, 167; d) C. Vaxelaire, P. Winter, M. Christmann, *Angew. Chem. Int. Ed.* **2011**, *50*, 3605; *Angew. Chem.* **2011**, *123*, 3685.
- [7] a) S. Brauch, S. S. van Berkel, B. Westermann, *Chem. Soc. Rev.* **2013**, *42*, 4948; b) E. Ruijter, R. Scheffelaar, R. V. A. Orru, *Angew. Chem. Int. Ed.* **2011**, *50*, 6234; *Angew. Chem.* **2011**, *123*, 6358; c) B. Ganem, *Acc. Chem. Res.* **2009**, *42*, 463; d) B. B. Touré, D. G. Hall, *Chem. Rev.* **2009**, *109*, 4439; e) *Multicomponent Reactions* (Eds.: J. Zhu, H. Bienyamé), Wiley-VCH, Weinheim, **2015**.
- [8] a) A. Dömling, I. Ugi, *Angew. Chem. Int. Ed.* **2000**, *39*, 3168; *Angew. Chem.* **2000**, *112*, 3300; b) *Isocyanide Chemistry—Applications in Synthesis and Material Science* (Ed.: V. Nenajdenko), Wiley-VCH, Weinheim, **2012**; c) L. El Kaïm, L. Grimaud, *Tetrahedron* **2009**, *65*, 2153; d) A. Dömling, *Chem. Rev.* **2006**, *106*, 17; e) L. Banfi, R. Riva, *Org. React.* **2005**, *65*, 1.
- [9] a) P. Slobbe, E. Ruijter, R. V. A. Orru, *MedChemComm* **2012**, *3*, 1189; b) A. Dömling, W. Wang, K. Wang, *Chem. Rev.* **2012**, *112*, 3083; c) I. Akritopoulou-Zanze, *Curr. Opin. Chem. Biol.* **2008**, *12*, 324; d) C. Hulme, V. Gore, *Curr. Med. Chem.* **2003**, *10*, 51.
- [10] a) L. Banfi, A. Basso, L. Moni, R. Riva, *Eur. J. Org. Chem.* **2014**, 1989; b) Y. Yue, M.-X. Wang, D.-X. Wang, J. Zhu, *Angew. Chem. Int. Ed.* **2008**, *47*, 9454; *Angew. Chem.* **2008**, *120*, 9596.
- [11] For reviews, see: a) L. A. Wessjohann, C. R. B. Rhoden, D. G. Rivera, O. E. Vercillo, *Top. Heterocycl. Chem.* **2010**, *23*, 199; b) J. D. Sunderhaus, S. F. Martin, *Chem. Eur. J.* **2009**, *15*, 1300; c) S. Marcaccini, T. Torroba, in *Multicomponent Reactions* (Eds.: J. Zhu, H. Bienyamé), Wiley-VCH, Weinheim, **2005**, pp. 33–75.
- [12] For recent examples, see: a) F. De Moliner, M. Bigatti, L. Banfi, R. Riva, A. Basso, *Org. Lett.* **2014**, *16*, 2280; b) A. Kumar, Z. Li, S. K. Sharma, V. S. Parmar, E. V. van der Eycken, *Chem. Commun.* **2013**, *49*, 6803; c) S. G. Modha, A. Kumar, D. D. Vachhani, J. Jacobs, S. K. Sharma, V. S. Parmar, L. van Meervelt, E. V. van der Eycken, *Angew. Chem. Int. Ed.* **2012**, *51*, 9572; *Angew. Chem.* **2012**, *124*, 9710; d) Z. Xu, F. De Moliner, A. P. Cappelli, C. Hulme, *Angew. Chem. Int. Ed.* **2012**, *51*, 8037; *Angew. Chem.* **2012**, *124*, 8161; e) W. Wang, S. Ollio, E. Herdtweck, A. Dömling, *J. Org. Chem.* **2011**, *76*, 637; f) M.-A. Cano-Herrera, L. D. Miranda, *Chem. Commun.* **2011**, *47*, 10770; g) A. Znabet, J. Zonneveld, E. Janssen, F. J. J. De Kanter, M. Helliwell, N. J. Turner, E. Ruijter, R. V. A. Orru, *Chem. Commun.* **2010**, *46*, 7706.
- [13] a) S. Umbreen, M. Brockhaus, H. Ehrenberg, B. Schmidt, *Eur. J. Org. Chem.* **2006**, 4585; b) G. Dickmeiss, K. L. Jensen, D. Worgull, P. T. Franke, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2011**, *50*, 1580; *Angew. Chem.* **2011**, *123*, 1618; c) E. Riguet, *J. Org. Chem.* **2011**, *76*, 8143; d) A. M. Deobald, A. G. Correa, D. G. Rivera, M. W. Paixão, *Org. Biomol. Chem.* **2012**, *10*, 7681; e) F. Morana, A. Basso, R. Riva, V. Rocca, L. Banfi, *Chem. Eur. J.* **2013**, *19*, 4563; f) L. Moni, L. Banfi, A. Basso, A. Galatini, M. Spallarossa, R. Riva, *J. Org. Chem.* **2014**, *79*, 339.
- [14] For reviews, see: a) H. Jiang, L. Albrecht, K. A. Jørgensen, *Chem. Sci.* **2013**, *4*, 2287; b) I. D. Jurberg, I. Chatterjee, R. Tannert, P. Melchiorre, *Chem. Commun.* **2013**, *49*, 4869; c) P. Melchiorre, *Angew. Chem. Int. Ed.* **2012**, *51*, 9748; *Angew. Chem.* **2012**, *124*, 9886; d) M. Nielsen, D. Worgull, T. Zweifel, B. Gschwend, S. Bertelsen, K. A. Jørgensen, *Chem. Commun.* **2011**, *47*, 632; e) *Chem. Rev.* **2007**, *107*, 5413–5883 (special issue on organocatalysis); f) A. Dondoni, A. Massi, *Angew. Chem. Int. Ed.* **2008**, *47*, 4638; *Angew. Chem.* **2008**, *120*, 4716; g) D. W. C. MacMillan, *Nature* **2008**, *455*, 304; h) S. Bertelsen, K. A. Jørgensen, *Chem. Soc. Rev.* **2009**, *38*, 2178.
- [15] a) L. F. Tietze, H. P. Bell, S. Chandrasekhar, *Angew. Chem. Int. Ed.* **2003**, *42*, 3996; *Angew. Chem.* **2003**, *115*, 4128; b) G. Mehta, V. Singh, *Chem. Soc. Rev.* **2002**, *31*, 324.
- [16] For a conceptual review on organocatalytic one-pot processes, see: L. Albrecht, H. Jiang, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2011**, *50*, 8492; *Angew. Chem.* **2011**, *123*, 8642.
- [17] a) S. S. van Berkel, B. G. M. Bögels, M. A. Wijdeven, B. Westermann, F. P. J. T. Rutjes, *Eur. J. Org. Chem.* **2012**, 3543; b) C. de Graaff, E. Ruijter, R. V. A. Orru, *Chem. Soc. Rev.* **2012**, *41*, 3969; c) D. J. Ramón, M. Yus, *Angew. Chem. Int. Ed.* **2005**, *44*, 1602–1634; *Angew. Chem.* **2005**, *117*, 1628–1661.
- [18] a) M. Rueping, E. Sugiono, E. Merino, *Angew. Chem. Int. Ed.* **2008**, *47*, 3046; *Angew. Chem.* **2008**, *120*, 3089; b) M. Rueping, E. Sugiono, E. Merino, *Chem. Eur. J.* **2008**, *14*, 6329; c) M. Rueping, E. Merino, E. Sugiono, *Adv. Synth. Catal.* **2008**, *350*, 2127; d) M. Rueping, E. Merino, E. Sugiono, *ChemCatChem* **2012**, *4*, 987.
- [19] P. T. Franke, B. Richter, K. A. Jørgensen, *Chem. Eur. J.* **2008**, *14*, 6317.
- [20] a) L. El Kaïm, L. Grimaud, J. Oble, *Angew. Chem. Int. Ed.* **2005**, *44*, 7961; *Angew. Chem.* **2005**, *117*, 8175; b) L. El Kaïm, M. Gizolme, L. Grimaud, J. Oble, *J. Org. Chem.* **2007**, *72*, 4169; c) R. Bossio, S. Marcaccini, P. Paoli, R. Pepino, C. Polo, *Synthesis* **1991**, 999.
- [21] a) T. G. Castellano, A. G. Neo, S. Marcaccini, C. F. Marcos, *Org. Lett.* **2012**, *14*, 6218; b) K. Akin, M. Gauriot, J. Totobenazara, N. Deguine, R. Deprez-Poulain, B. Deprez, J. Charton, *Tetrahedron Lett.* **2012**, *53*, 458; c) A. Massoudi, I. Amini, A. Ramazani, F. Z. Nasrabadi, Y. Ahmadi, *Bull. Korean Chem. Soc.* **2012**, *33*, 39; d) L. El Kaïm, L. Grimaud, *Mol. Diversity* **2010**, *14*, 855.
- [22] a) M. Shamma, J. L. Moniot, *The Isoquinoline Alkaloids, Chemistry and Pharmacology*, Academic Press, New York, **1972**; b) M. E. Welsch, S. A. Snyder, B. R. Stockwell, *Curr. Opin. Chem. Biol.* **2010**, *14*, 347.
- [23] For a recent stereoselective Ugi-Smiles-type reaction, see: A. Znabet, S. Blanken, E. Janssen, F. J. J. de Kanter, M. Helliwell, N. J. Turner, E. Ruijter, R. V. A. Orru, *Org. Biomol. Chem.* **2012**, *10*, 941.
- [24] For recent computational studies of related I-MCRs, see: a) L. Belding, S. Zaretsky, B. H. Rotstein, A. K. Yudin, T. Dudding, *J. Org. Chem.* **2014**, *79*, 9465; b) N. Chéron, R. Ramozzi, L. El Kaïm, L. Grimaud, P. Fleurat-Lessard, *J. Org. Chem.* **2012**, *77*, 1361.
- [25] For multicomponent ligations of sugars, peptides, and lipids, see: a) D. G. Rivera, A. V. Vasco, R. Echemendía, O. Concepción, C. S. Pérez, J. A. Gavín, L. A. Wessjohann, *Chem. Eur. J.* **2014**, *20*, 13150; b) K. Pérez-Labrada, I. Brouard, I. Mendez, L. Lambert, D. G. Rivera, *Eur. J. Org. Chem.* **2014**, 3671; c) D. G. Rivera, F. León, O. Concepción, F. E. Morales, L. A. Wessjohann, *Chem. Eur. J.* **2013**, *19*, 6417; d) D. G. Rivera, K. Pérez-Labrada, L. Lambert, S. Dörner, B. Westermann, L. A. Wessjohann, *Carbohydr. Res.* **2012**, *359*, 102; e) K. Pérez-Labrada, I. Brouard, I. Mendez, D. G. Rivera, *J. Org. Chem.* **2012**, *77*, 4660; f) T. Tanino, S. Ichikawa, *J. Org. Chem.* **2010**, *75*, 1366.

Received: December 16, 2014

Revised: March 19, 2015

Published online: May 12, 2015