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# Organocatalytic Multicomponent Synthesis of $\alpha/\beta$ -Dipeptide Derivatives

Thomas Martzel,<sup>[a,c]</sup> Julien Annibaleto,<sup>[a,c]</sup> Pierre Millet,<sup>[a]</sup> Etienne Pair,<sup>[a]</sup> Morgane Sanselme,<sup>[b]</sup> Sylvain Oudeyer,<sup>[a]</sup> Vincent Levacher<sup>[a]</sup> and Jean-François Brière\*<sup>[a]</sup>

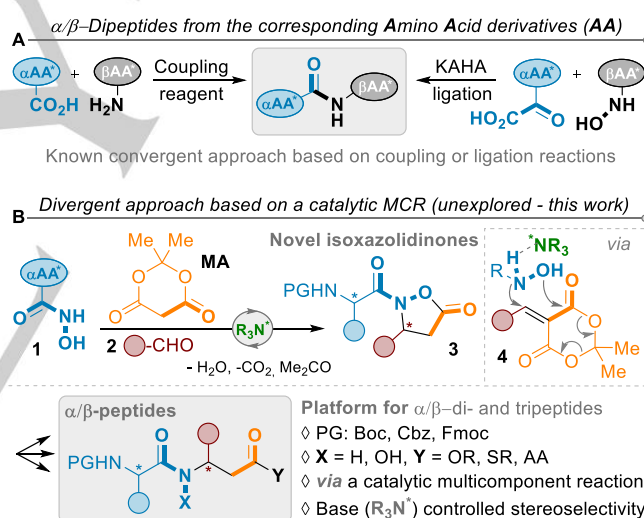
Dedication ((optional))

**Abstract:** A straightforward multicomponent Knoevenagel-aza-Michael-Cyclocondensation reaction involving readily available hydroxamic acid-derived from naturally occurring  $\alpha$ -amino acids allows a diversity-oriented synthesis of novel isoxazolidin-5-ones possessing an *N*-protected  $\alpha$ -amino acid pendant with good to high diastereoselectivities thanks to a match effect with a chiral organocatalyst. These diversely substituted heterocycles, easily isolated as a single diastereoisomer, proved to be versatile platforms for the formation of an array of  $\alpha/\beta$ -dipeptide fragments.

Naturally occurring peptides currently hold a privileged place for the development of bio-inspired ingredients in pharmaceutical industry.<sup>[1]</sup> In order to overcome the inherently sensitivity to proteolytic degradation of native peptides, while giving the opportunity to afford new properties and bio-tools to probe protein functions, synthetic chemists have tackled the elaboration of peptide analogues. In that peptidomimetic context,  $\beta$ -amino acids proved to be excellent building blocks for the elaboration of either  $\beta$ -peptides and hybrid  $\alpha/\beta$ -polyamino acids having not only an improved stability towards peptidases but also displaying unique secondary structures and pharmacological activities.<sup>[2]</sup> Furthermore, the  $\alpha/\beta$ -dipeptide fragments are not only a key elements of naturally occurring products,<sup>[3]</sup> but have met important successes in medicinal chemistry either in a linear form in case of cardiovascular diseases target for instance,<sup>[2b]</sup> or to construct cyclic-peptide architectures in which the 1,4-diazepane-2,5-diones, and heterocycles derived thereof, proved to be privileged platforms in a large array of pharmaceutical applications.<sup>[4]</sup> The attractiveness of these frameworks has fueled numerous research efforts dealing with the asymmetric synthesis of  $\beta$ -amino acids, and the elaboration of original derivatives is still of high added value.<sup>[3a],[5]</sup>

The synthesis of the  $\alpha/\beta$ -dipeptide motif essentially relies on the construction of the amide bond by means of coupling reagents, essentially stoichiometric, between suitably (orthogonal) protected and pre-elaborated  $\alpha$ -amino acids ( $\alpha$ AA) and  $\beta$ -amino

acids ( $\beta$ AA) derivatives (Scheme 1A).<sup>[6]</sup> Bode and co-workers have made a major achievement in this field, by developing the  $\alpha$ -ketoacid-hydroxylamine (KAHA) ligation between two pre-synthesized AA derivatives, one bearing a  $\alpha$ -keto acid pendant and another possessing an hydroxylamine *N*-terminus functional group.<sup>[7]</sup> Recently, Takemoto expended the portfolio of hydroxylamine-derived  $\beta$ AA to aspartic acid derivatives thanks to an organocatalytic aza-Michael addition to fumaric monoacid electrophiles.<sup>[8]</sup> This elegant strategy, making use of hydroxylamine functions as key building blocks for the elaboration of  $\beta$ AA, was applied to the elaboration of  $\alpha/\beta$ -dipeptides albeit with moderate diastereoselective ratio (dr).



**Scheme 1.** A new entry to  $\beta$ -amino acid derivatives.

Besides these convergent sequences, we tackled an alternative divergent approach in order to populate the chemical space within the biorelevant  $\alpha/\beta$ -dipeptide series (Scheme 1B). We reasoned that the multicomponent Knoevenagel-aza-Michael-Cyclocondensation (KMC) reaction would take place between readily available hydroxamic acids **1**,<sup>[9]</sup> derived from naturally occurring and enantiopure  $\alpha$ AA, various aldehydes **2** and Meldrum's acid (MA) as a C2-synthon (first point of diversity).<sup>[10],[11]</sup> Then, this strategy would afford a straightforward elaboration of novel isoxazolidin-5-ones **3**,<sup>[12]</sup> as masked  $\beta$ AA with an  $\alpha$ AA side chain, providing eventually versatile platforms to elaborate a library of  $\alpha/\beta$ -dipeptides (second point of diversity).<sup>[13],[14]</sup> In order to be synthetically useful, this sequence should demonstrate a significant functional group compatibility and furnish one stereoisomer. Thanks to the marked electrophilic

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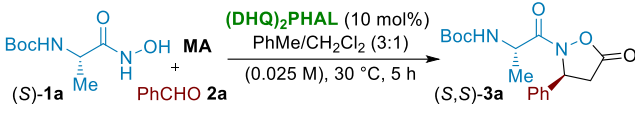
[c] These authors contributed equally to this work.

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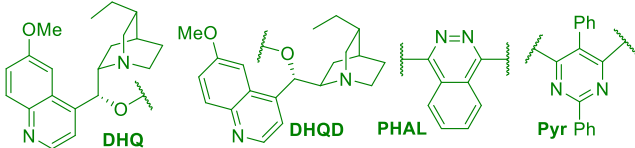
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reactivity of alkylidene **MA** intermediates **4**,<sup>[11],[15]</sup> we postulated that (1) a facile domino addition process of hydroxamic acids **1** would occur and (2) the C-N bond formation between **1** and **4** would be under the influence of both a chiral nucleophile **1** and a Brønsted base organocatalysts to favor the formation one stereoisomer (Scheme 1B). We are delighted to report on the unprecedented diastereoselective multicomponent reaction (MCR) giving rise to versatile isoxazolidin-5-ones **3** thanks to the match influence of a suited organocatalyst, en route to the elaboration of various original  $\alpha/\beta$ -dipeptide derivatives.

**Table 1.** Proof of principle and optimization.<sup>[a]</sup>



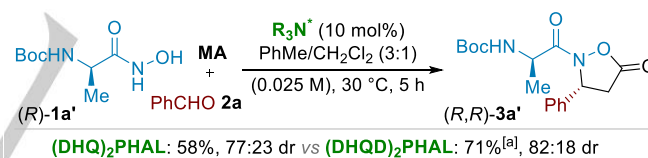
Entry	Deviation from the standard conditions	Yield [%]	dr <sup>[b]</sup>
1	Without catalyst	20 (55) <sup>[c]</sup>	57:43
2	Quinuclidine as catalyst	86	71:29
3	-	<b>75</b>	<b>86:14</b>
4	(DHQD) <sub>2</sub> PHAL as catalyst	82	74:26
5	(DHQ) <sub>2</sub> Pyr as catalyst	62	82:18
6	Quinine (QN) as catalyst	73	81:19
7	Quinidine (QD) as catalyst	66	48:52
8	MeCN (0.1 M) as solvent, 20 °C <sup>[d]</sup>	44	73:27
9	CH <sub>2</sub> Cl <sub>2</sub> (0.1 M) as solvent, 20 °C <sup>[d]</sup>	30	86:14
10	PhMe (0.1 M) as solvent, 20 °C <sup>[d]</sup>	traces	-
11	PhMe/CH <sub>2</sub> Cl <sub>2</sub> (3:1, 0.1 M) as solvent, 20 °C <sup>[d]</sup>	68	86:14



[a] Reaction conditions: **1a** (0.1 mmol), PhCHO **2a** (1 equiv), **MA** (1.5 equiv) in PhMe/CH<sub>2</sub>Cl<sub>2</sub> (3:1, 0.025 M) at 30 °C for 5 h. Yields of both diastereoisomers determined by <sup>1</sup>H NMR with an internal standard. [b] dr determined by <sup>1</sup>H NMR on the crude product. [c] Bimolecular reaction from benzylidene Meldrum's acid **4a**. [d] **MA** (1 equiv), (DHQ)<sub>2</sub>PHAL (20 mol%).

At the onset, it was shown that the model MCR involving the *N*-Boc alanine hydroxamic acid **1a** (Boc- $\alpha$ -AlaNH<sub>2</sub>OH), **MA** and benzaldehyde **2a** furnished after 5 hours the corresponding isoxazolidinone **3a** in 20% yield (determined by <sup>1</sup>H NMR) as 57:43 mixture of diastereoisomers namely with virtually no stereoselection (entry 1, Table 1). By performing the di-component reaction with benzylidene Meldrum's acid **4a**, the putative intermediate involved into the formal domino aza-Michael-cyclocondensation process (see Scheme 1), similar poor dr was obtained with a better 55% yield (entry 1). The facility with which this MCR takes place is worthy of note, likely thanks to the high electrophilic reactivity of benzylidene MA,<sup>[15]</sup> but the ability of a catalyst to accelerate this process and promote a stereoselective sequence remains an issue.<sup>[10]</sup> To our delight the use of 10 mol% of a Brønsted base like the achiral quinuclidine allowed to improve significantly the yield to 86% and dr (71:29,

entry 2). A large screening of organocatalysts (see SI) showed that the commercially available and chiral amine (DHQ)<sub>2</sub>PHAL turned out to be the more efficient catalyst leading to good 86:14 dr in 75% yield in 5 hours (entry 3 versus entries 4-7). Early optimization endeavors (see SI) showed that less polar solvents like CH<sub>2</sub>Cl<sub>2</sub> (entries 8-9) benefited to the level of stereoselection, while a mixture of PhMe/CH<sub>2</sub>Cl<sub>2</sub> was required for solubility issue (entries 10-11). Noteworthy, isoxazolidone **3a** proved to be somewhat unstable during the purification by silica-gel column chromatography but also in the presence of the Brønsted base in solution (*vide infra*). Then, some decomposition events occur during longer or forcing reaction conditions leading to erratic outcomes. However, the use of more diluted conditions and a slight excess of **MA** prevent the decomposition of product **3a** (thanks to its high acidity, pK<sub>a</sub> = 4.8 in H<sub>2</sub>O)<sup>[11],[16]</sup> even at 30 °C, a temperature allowing both a faster process and a decrease of the amount of catalyst from 20 to 10 mol% while giving improved yield of 75% and the same dr in 5 hours (entries 3 vs 11, Table 1). This shows the key role of **MA** to secure soft reaction conditions. Interestingly, it was observed a match/mismatch effect between chiral Cinchona-derived organocatalysts and (S)-Boc- $\alpha$ -AlaNH<sub>2</sub>OH **1a** (Table 1, entries 3-4 and 6-7) which demonstrated that quinine versus quinidine derivatives were more competent to give (S,S)-isoxazolidinone **3a** with a good dr. Accordingly, it was proven that quinidine derived (DHQD)<sub>2</sub>PHAL catalyst was able to transform the (R)-Boc- $\alpha$ -AlaNH<sub>2</sub>OH enantiomer **1a'** into isoxazolidinone (R,R)-**3a'** in 71% yield and 82:18 dr contrary to (DHQ)<sub>2</sub>PHAL catalyst giving **3a'** only in 58% yield and 77:23 dr (Scheme 2). Eventually, it was validated that this MCR took place with no racemization and provided the major isoxazolidinones **3a** and **3a'** as a single enantiomer (>99:1 er, see SI).



**Scheme 2.** Molecular diversity towards a versatile synthesis of **3a'** - the other enantiomer of isoxazolidinone **3a**. Yields of both diastereoisomers determined by <sup>1</sup>H NMR with an internal standard. [a] 47% isolated yield after column chromatography.

The scope and limitation of this novel MC-strategy was next addressed (Table 2). Pleasingly, carrying out the reaction for 24 hours on a larger scale secured the complete transformation of Boc- $\alpha$ -AlaNH<sub>2</sub>OH **1a** into isoxazolidinone **3a** in 88:12 dr (99% of NMR yield for both diastereoisomers). Importantly, the two diastereoisomers of isoxazolidinone **3a** could be separated by flash column chromatography, as a general behavior in this series, leading to the major (S,S)-**3a** in 71% isolated yield (slight drop of the theoretical yield of 88%).<sup>[17]</sup> Starting from isovaleraldehyde **2b**, a facile synthesis of the corresponding isoxazolidinone **3b**, having  $\beta$ Leu backbone (homologated  $\beta^3$ -Leucine), occurred in excellent dr > 95:5 and 96% yield for the pure major stereoisomer. As a rule of thumb, in comparison to the use of aromatic aldehydes such as **2a**, the isoxazolidinones **3** derived from aliphatic aldehydes **2** turned out to be more stable which allows (1) an easy purification by chromatography and (2) to carry out the reaction in higher

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concentration.<sup>[18]</sup> The MCR was applied successfully to *N*-Cbz- $\alpha$ AlaNH<sub>2</sub> **1b** (**3c-3d**, 64-85%, 83:17-89:11 dr)<sup>[19]</sup> and *N*-Fmoc- $\alpha$ AlaNH<sub>2</sub> **1c** (**3e**, 86%, 93:7 dr) to provide the corresponding **3c-3e** with good to excellent stereoselectivities and yields. Then, various  $\beta$ hLeu-derived isoxazolidinones were constructed from isovaleraldehyde and Boc-protected proteinogenic  $\alpha$ AA such as  $\alpha$ Phe (**3f**, 71%, 89:11 dr),  $\alpha$ Val (**3f**, 93%, >95:5 dr) and  $\alpha$ Pro (**3i**, 63%, 75:25 dr) with yields ranging from 63% to 93%. It was also shown that *N*-Boc glycine hydroxamic acid afforded the corresponding isoxazolidinone **3h** in excellent 93% yield but low 58:42 er. In line with previous observations, this highlights a moderate capability of (DHQ)<sub>2</sub>PHAL catalyst to promote an enantioselective process from an achiral  $\alpha$ AANHOH.<sup>[10a],[20]</sup>

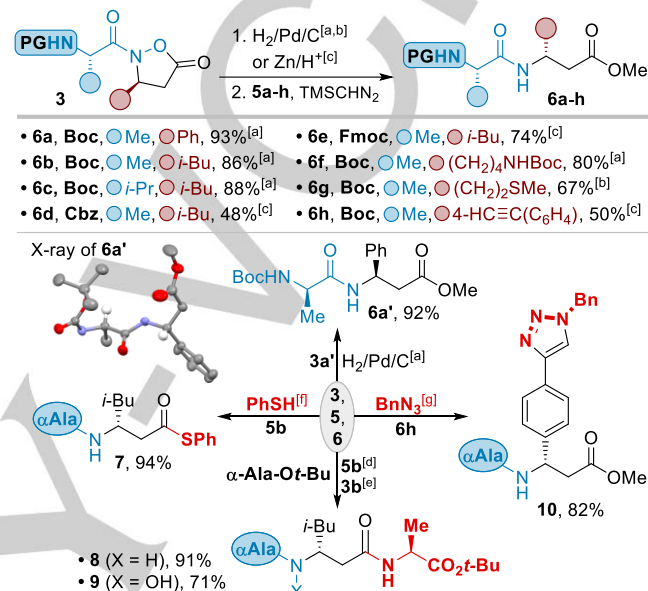
Table 2. Scope and limitations.<sup>[a]</sup>

Reaction 1		Reaction 2	
From PG- $\alpha$ AlaNH <sub>2</sub> <b>1a-1c</b>		From <i>i</i> -BuCHO <b>2b</b>	
• PG = Boc • PG = Cbz • PG = Fmoc		• PG = Boc • PG = Cbz • PG = Fmoc	
• Ph • <i>i</i> -Bu <sup>[b]</sup>		• Ph • <i>i</i> -Bu <sup>[b]</sup>	
• Bn (Boc- $\alpha$ Phe) • <i>i</i> -Pr (Boc- $\alpha$ Val) • H (Boc- $\alpha$ Gly) <sup>[d]</sup>		• Bn (Boc- $\alpha$ Phe) • <i>i</i> -Pr (Boc- $\alpha$ Val) • H (Boc- $\alpha$ Gly) <sup>[d]</sup>	
• R = F <b>3j</b> , (99%), 64%, 92:8 dr • R = OMe <sup>[c]</sup> <b>3k</b> , (91%), 51%, 88:12 dr • R = C $\equiv$ CH <b>3l</b> , (99%), 68%, 90:10 dr		• (Boc- $\alpha$ Pro), <b>3i</b> • (91%), 63%, 75:25 dr	
• <b>3m</b> , (99%) • <b>3n</b> , (99%) • <b>3o</b> , (99%) • <b>3p</b> , (80%) <sup>[c]</sup> • <b>3q</b> , (73%) <sup>[c]</sup>		• <b>3a</b> , (99%), 71%, 88:12 dr • <b>3b</b> , (99%), 96%, >95:5 dr • <b>3c</b> , (57%), 40%, 82:18 dr • <b>3c</b> , (82%), 64%, 83:17 dr • <b>3d</b> , (99%), 85%, 89:11 dr • <b>3e</b> , (99%), 86%, 93:7 dr	
• <b>3r</b> , (25%) • <b>3s</b> , (65%) <sup>[c]</sup>		• <b>3t</b> , (25%) • <b>3s</b> , (65%) <sup>[c]</sup>	

[a] Reaction conditions: **1** (0.3 mmol), RCHO **2** (1 equiv), **MA** (1.5 equiv) in PhMe/CH<sub>2</sub>Cl<sub>2</sub> (3:1, 0.025 M) at 30 °C for 24 h. Isolated yields of the pure major diastereoisomer after column chromatography. In parentheses, yields of both diastereoisomers determined by <sup>1</sup>H NMR with an internal standard. dr determined by <sup>1</sup>H NMR on the crude product. [b] 5 mol% of catalyst on 1 mmol scale gives **3b** (89%, 94:6 dr), **3d** (86%, 89:11), **3e** (80%, 94:6 dr), **3r** (47%, 94:6 dr). [c] 20 mol% of catalyst. [d] Absolute configuration was not determined for **3h**.

An array of both aromatic aldehydes (**3j-3l**, 51-68%, 88:12 to 92:8 dr), linear and cyclic aliphatic aldehydes (**3m-3p**, 69-91%, 85:15 to > 95:5 dr) proved to be compatible with this multicomponent KaMC process, encompassing the construction of  $\beta$ hPhe **3n** and  $\beta$ hLeu **3o** precursors. Isoxazolidinones with ether **3q** ( $\beta$ hSer, 61%, 83:17 dr), thioether **3r** ( $\beta$ hMet, 41%, >95:5 dr) and NHBoc **3s** ( $\beta$ hLys, 44%, 89:11 dr) pendants could be isolated in diastereomeric pure form albeit in slightly lower yields

even with 20 mol% of catalyst, due to the instability of these aldehydes that results in an incomplete reaction. Although the homologous tryptophane derivative **3t** ( $\beta$ hTrp) could be constructed with excellent > 95:5 dr, a low conversion was observed leading to a moderate 19% isolated yield. Worthy of note, several MCR could be carried out on 1 mmol scale to give the isoxazolidinones **3b**, **3d**, **3e** and **3r** with rather similar yields and dr by means of only 5 mol% of (DHQ)<sub>2</sub>PHAL as organocatalyst.



**Scheme 3.** Chemical transformations into  $\alpha/\beta$ -dipeptides. Reaction conditions: [a] H<sub>2</sub>, Pd/C (1 atm), *i*-PrOH, 30 °C for **6a-b**; 15 atm, RT for **6c**, 1 atm, 50 °C for **6f** and TMSCHN<sub>2</sub>, MeOH, RT. [b] H<sub>2</sub>, Pd(OH)<sub>2</sub>/C (20 atm), *i*-PrOH/EtOAc (2:1), MeOH, RT. [c] Zn (40-80 equiv), THF/H<sub>2</sub>O/AcOH, 40 °C, and TMSCHN<sub>2</sub>, MeOH, RT. [d] From **3b**, HCl- $\alpha$ AlaO*t*-Bu, *i*-Pr<sub>2</sub>NEt, DMAP (0.5 equiv), DMF, RT. [e] From **5b**, HCl- $\alpha$ AlaO*t*-Bu, *i*-Pr<sub>2</sub>NEt, EDC-HCl, HOBT, CH<sub>2</sub>Cl<sub>2</sub>, RT. [f] PhSH, DCC, HOBT, CH<sub>2</sub>Cl<sub>2</sub>, RT. [g] BnN<sub>3</sub>, Na-Ascorbate, CuSO<sub>4</sub>·5H<sub>2</sub>O (20 mol%), *t*-BuOH/H<sub>2</sub>O, RT.

Having an array of novel isoxazolidinones **3** in hand, decorated with various functionalities, the transformations of **3** into  $\alpha/\beta$ -dipeptide derivatives was undertaken in order to probe the versatility of these masked  $\beta$ AA platforms (Scheme 3). By means of adapted palladium catalyzed N-O bond hydrogenolysis, followed by esterification of the obtained acids **5**, in order to facilitate the purification step, several *syn*- $\alpha/\beta$ -dipeptides-OMe **6a-6c** (86-93%),<sup>[19]</sup> together with NHBoc **6f** (Boc- $\alpha$ Ala-Boc- $\beta$ hLys, 80%) and SMe **6g** (Boc- $\alpha$ Ala-Boc- $\beta$ hMet, 67%) derivatives were easily synthesized. This straightforward strategy was also applied to the formation of (*R,R*)-dipeptide **6a'** in 92% yield.<sup>[19]</sup> On the other hand, by means of orthogonal Zn/AcOH deprotection conditions, the elaboration of *N*-Cbz and *N*-Fmoc  $\alpha$ Ala- $\beta$ hLeu dipeptides **6d** (48%) and **6e** (74%) respectively was allowed.<sup>[10b]</sup> Product **6h**, displaying a sensitive but useful terminal alkyne moiety, was accessible in 50% yield under these reductive conditions (Zn/AcOH) and successfully transformed into triazole **10** in 82% yield, thanks to the copper-catalyzed 1,3-dipolar cycloaddition protocol. The readily available Boc- $\alpha$ Ala- $\beta$ hLeu carboxylic acid **5b** (used as a crude product) was subjected to

peptide-coupling reagents to give rise to the formation of either thioester **7** (94%), suited for further native ligation processes, or  $\alpha/\beta/\alpha$ -tripeptide **8** in 91% yield. Interestingly, taking advantage of the reactivity of the N-EWG isoxazolidinone framework,<sup>[12], [17b], [7c]</sup> the direct ring opening event of **3b** with *tert*-butyl-alanine furnished the  $\alpha/\beta/\alpha$ -tripeptide **9**, similar to **8** but with a N-OH functionality known to be a valuable moiety to complex metal in bio-environment.<sup>[21]</sup>

In summary, we have developed a multicomponent synthesis of novel isoxazolidin-5-ones possessing an N- $\alpha$ -amino acid. Thanks to the high reactivity of transient alkylidene Meldrum's acids, a smooth and diastereoselective domino addition reaction takes place upon the match influence of a commercially available quinine derived organocatalyst allowing to achieve good to excellent dr. The corresponding isoxazolidin-5-ones, easily obtained as single diastereoisomer after purification, proved to be versatile platforms for the diversity-oriented synthesis of an array of  $\alpha/\beta$ -dipeptides, as useful fragment in medicinal chemistry.

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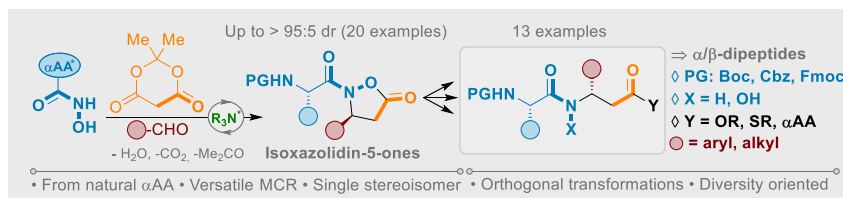
**Keywords:** amino acid • asymmetric synthesis • isoxazolidinone • Meldrum's acid • organocatalysis

- [1] a) A. Groß, C. Hashimoto, H. Sticht, J. Eichler, *Frontiers in Bioengineering and Biotechnology* **2016**, *3*; b) R. Gopalakrishnan, A. I. Frolov, L. Knerr, W. J. Drury, E. Valeur, *J. Med. Chem.* **2016**, *59*, 9599.
- [2] a) G. Lelais, D. Seebach, *Peptide Science* **2004**, *76*, 206; b) M.-I. Aguilar, A. W. Purcell, R. Devi, R. Lew, J. Rossjohn, A. I. Smith, P. Perlmutter, *Org. Biomol. Chem.* **2007**, *5*, 2884; c) D. Seebach, J. Gardiner, *Acc. Chem. Res.* **2008**, *41*, 1366; d) L. M. Johnson, S. H. Gellman, in *Methods in Enzymology*, Vol. 523 (Ed.: A. E. Keating), Academic Press, **2013**, pp. 407; e) C. Cabrele, T. A. Martinek, O. Reiser, L. Berlicki, *J. Med. Chem.* **2014**, *57*, 9718; f) G. A. Eddinger, S. H. Gellman, *Angew. Chem. Int. Ed.* **2018**, *57*, 13829; *Angew. Chem.* **2018**, *130*, 14025.
- [3] a) E. Juaristi, V. A. Soloshonok, Editors, *Enantioselective Synthesis of  $\beta$ -Amino Acids*, Second Edition, **2005**; b) F. Kudo, A. Miyanaga, T. Eguchi, *Nat. Prod. Rep.* **2014**, *31*, 1056.
- [4] For selected examples, see: a) C. Yuan, R. M. Williams, *J. Am. Chem. Soc.* **1997**, *119*, 11777; b) A. Nefzi, J. M. Ostresh, R. A. Houghten, *Tetrahedron Lett.* **1997**, *38*, 4943; c) J. C. D. Müller-Hartwieg, K. G. Akyel, J. Zimmermann, *Journal of Peptide Science* **2003**, *9*, 187; d) Y.-M. Zhang, X. Fan, S.-M. Yang, R. H. Scannevin, S. L. Burke, K. J. Rhodes, P. F. Jackson, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 405; e) A. Moure, G. Sanclimens, J. Bujons, I. Masip, A. Alvarez-Larena, E. Pérez-Payá, I. Alfonso, A. Messeguer, *Chem. Eur. J.* **2011**, *17*, 7927; f) E. Jiménez-González, C. Gabriela Ávila-Ortiz, R. González-Olvera, J. Vargas-Caporalí, G. Dewynter, E. Juaristi, *Tetrahedron* **2012**, *68*, 9842; g) Y. Chen, Y. Zhou, J.-H. Li, J.-Q. Sun, G.-S. Zhang, *Chinese Chem. Lett.* **2015**, *26*, 103; h) S. Popovic, L. Wijsman, I. R. Landman, M. F. Sangster, D. Pastoors, B. B. Veldhorst, H. Hiemstra, J. H. van Maarseveen, *Eur. J. Org. Chem.* **2016**, *2016*, 443; i) L. Fanter, C. Müller, D. Schepmann, F. Bracher, B. Wünsch, *Bioorg. Med. Chem.* **2017**, *25*, 4778.
- [5] For review, see: a) J.-A. Ma, *Angew. Chem. Int. Ed.* **2003**, *42*, 4290; *Angew. Chem.* **2003**, *115*, 4426; b) B. Weiner, W. Szymański, D. B. Janssen, A. J. Minnaard, B. L. Feringa, *Chem. Soc. Rev.* **2010**, *39*, 1656; c) S. M. Kim, J. W. Yang, *Org. Biomol. Chem.* **2013**, *11*, 4737.
- [6] For emerging coupling reagents for amide bond formation, see: a) R. M. de Figueiredo, J.-S. Suppo, J.-M. Campagne, *Chem. Rev.* **2016**, *116*, 12029; b) K. Hollanders, B. U. W. Maes, S. Ballet, *Synthesis* **2019**, *51*, 2261.
- [7] a) J. W. Bode, R. M. Fox, K. D. Baucom, *Angew. Chem. Int. Ed.* **2006**, *45*, 1248; *Angew. Chem.* **2006**, *118*, 1270; b) M. E. Juárez-García, S. Yu, J. W. Bode, *Tetrahedron* **2010**, *66*, 4841; c) Y.-L. Huang, R. Frey, M. E. Juárez-García, J. W. Bode, *Heterocycles* **2012**, *84*, 1179; d) J. W. Bode, *Acc. Chem. Res.* **2017**, *50*, 2104.
- [8] K. Michigami, H. Murakami, T. Nakamura, N. Hayama, Y. Takemoto, *Org. Biomol. Chem.* **2019**, *17*, 2331.
- [9] J. Zhu, Q. Wang, M.-X. Wang, in *Multicomponent Reactions in Organic Synthesis*, Wiley-VCH Verlag GmbH & Co. KGaA, **2014**.
- [10] For early discovery of the MCR to form racemic isoxazolidin-5-ones from achiral aldehydes and N-oxycarbonyl-hydroxylamines, see: a) C. Berini, M. Sebban, H. Oulyadi, M. Sanselme, V. Levacher, J.-F. Brière, *Org. Lett.* **2015**, *17*, 5408–5411; b) A. Le Foll Devaux, E. Deau, E. Corrot, L. Bischoff, V. Levacher, J.-F. Brière, *Eur. J. Org. Chem.* **2017**, 3265.
- [11] For reviews on catalytic transformations of alkylidene Meldrum's acids, see: a) A. M. Dumas, E. Fillion, *Acc. Chem. Res.* **2010**, *43*, 440; b) E. Pair, T. Cadart, V. Levacher, J.-F. Brière, *ChemCatChem* **2016**, *8*, 1882.
- [12] For a review on catalytic enantioselective syntheses of isoxazolidin-5-ones, see: J. Annibaleto, S. Oudeyer, V. Levacher, J.-F. Brière, *Synthesis* **2017**, *49*, 2117.
- [13] For rare examples of catalytic enantioselective synthesis (dicomponent) of  $\beta$ -substituted N-EWG isoxazolidin-5-ones, see: a) S. Postikova, T. Tite, V. Levacher, J.-F. Brière, *Adv. Synth. Catal.* **2013**, *355*, 2513; b) S. Izumi, Y. Kobayashi, Y. Takemoto, *Org. Lett.* **2016**, *18*, 696.
- [14] For dicomponent but two steps catalytic synthesis of  $\beta$ -substituted N-EWG isoxazolidin-5-ones, see: a) I. Ibrahem, R. Rios, J. Vesely, G.-L. Zhao, A. Córdova, *Chem. Commun.* **2007**, 849 (two steps); b) A. Pou, A. Moyano, *Eur. J. Org. Chem.* **2013**, 3103 (two steps); c) H.-T. Jiang, H.-L. Gao, C.-S. Ge, *Chinese Chem. Lett.* **2017**, *28*, 471 (two steps); d) J. Lai, S. Sayalero, A. Ferrali, L. Osorio-Planes, F. Bravo, C. Rodríguez-Escrich, M. A. Pericàs, *Adv. Synth. Catal.* **2018**, *360*, 2914 (two steps).
- [15] Benzylidene MA is  $10^{11}$  time more electrophilic than benzylidene malonate: O. Kaumanns, H. Mayr, *J. Org. Chem.* **2008**, *73*, 2738 and references cited therein.
- [16] For a recent example describing the use of a 1,3-diketone that buffer non-aqueous Solutions, see: M. Sohail, F. Tanaka, *Chem. Eur. J.* **2020**, *26*, 222.
- [17] The N-O bond reductive cleavage could be easily achieved on the mixture of diastereoisomers **3a**, but it turned out to be much more difficult to separate the two diastereoisomers of the obtained dipeptide **6a** on column chromatography. This shows the clear advantage of working with isoxazolidinone **3a** whose pure major (S,S)-diastereoisomer could be isolated. This easy separation of the mixture of diastereoisomers of isoxazolidinones **3** is a general rule in this series.
- [18] In case of aliphatic aldehydes such valeraldehyde **2b**, the catalyzed reaction (optimized conditions) could be performed with more concentrated conditions with only a moderate impact on dr (**3b**, 0.1 M, 99% NMR yield, 94:6 dr; 0.2 M, 99% NMR yield, 93:7 dr).
- [19] CCDC 1983122, 1983125, 1983123, 1983124 contains the supplementary crystallographic data for respectively compounds **3c** (minor diastereoisomer), **6a** (the two diastereoisomers both originated from major and minor stereoisomers **3a**), **6a'**.
- [20] For a rare example of enantioselective catalytic C-N bond formation to alkylidene Meldrum's acids, see: E. Pair, C. Berini, R. Noël, M. Sanselme, V. Levacher, J.-F. Brière, *Chem. Commun.* **2014**, *50*, 10218.
- [21] a) H. C. J. Ottenheijm, J. D. M. Herscheid, *Chem. Rev.* **1986**, *86*, 697; b) R. Rani, C. Granchi, *Eur. J. Med. Chem.* **2015**, *97*, 505.

## COMMUNICATION

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Thomas Martzel, Julien Annibaleto,  
Pierre Millet, Etienne Pair, Morgane  
Sanselme, Sylvain Oudeyer, Vincent  
Levacher and Jean-François Brière

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**Organocatalytic Multicomponent  
Synthesis of  $\alpha/\beta$ -Dipeptide  
Derivatives**

**The diversity:** A straightforward organocatalyzed multicomponent reaction (MCR) involving readily available hydroxamic acids-derived from naturally occurring  $\alpha$ -amino acids ( $\alpha$ AA) allows a stereoselective and diversity-oriented synthesis of novel isoxazolidin-5-ones as versatile platforms for the elaboration of  $\alpha/\beta$ -dipeptide fragments.