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Organocatalytic Multicomponent Synthesis of α/β-Dipeptide Derivatives

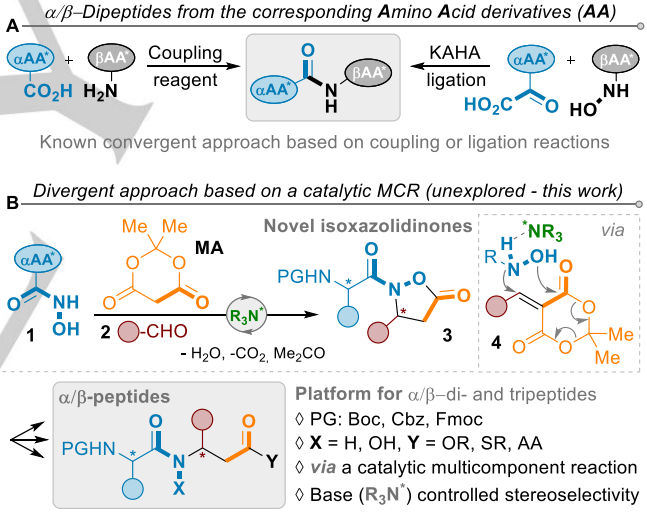
Thomas Martzel,[a,c] Julien Annibaletto,[a,c] Pierre Millet,[a] Etienne Pair,[a] Morgane Sanselme,[b] Sylvain Oudeyer,[a] Vincent Levacher[a] and Jean-François Brière*[a]

Dedication ((optional))

Abstract: A straightforward multicomponent Knoevenagel-aza-Michael-Cyclocondensation reaction involving readily available hydroxamic acid-derived from naturally occurring α-amino acids allows a diversity-oriented synthesis of novel isoxazolidin-5-ones possessing an *N*-protected α-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 α/β-dipeptide fragments.

Naturally occurring peptides currently hold a privileged place for the development of bio-inspired ingredients in pharmaceutical industry.[1] 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, β-amino acids proved to be excellent building blocks for the elaboration of either β-peptides and hybrid α/β-polyamino acids having not only an improved stability towards peptidases but also displaying unique secondary structures and pharmacological activities.[2] Furthermore, the α/β-dipeptide fragments are not only a key elements of naturally occurring products,[3] but have met important successes in medicinal chemistry either in a linear form in case of cardiovascular diseases target for instance,[2b] 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.[4] The attractiveness of these frameworks has fueled numerous research efforts dealing with the asymmetric synthesis of β-amino acids, and the elaboration of original derivatives is still of high added value.[3a],[5]

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



Scheme 1. A new entry to β-amino acid derivatives.

Besides these convergent sequences, we tackled an alternative divergent approach in order to populate the chemical space within the biorelevant α/β-dipeptide series (Scheme 1B). We reasoned that the multicomponent Knoevenagel-aza-Michael-Cyclocondensation (KMC) reaction would take place between readily available hydroxamic acids **1**,[9] derived from naturally occurring and enantiopure αAA, various aldehydes **2** and Meldrum's acid (**MA**) as a C2-synthon (first point of diversity).[10],[11] Then, this strategy would afford a straightforward elaboration of novel isoxazolidin-5-ones **3**,[12] as masked βAA with an αAA side chain, providing eventually versatile platforms to elaborate a library of α/β-dipeptides (second point of diversity).[13],[14] 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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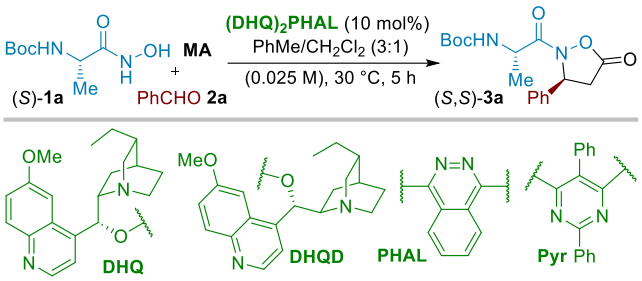
reactivity of alkylidene **MA** intermediates **4**,[11],[15] we postulated that (1) a facile domino addition process of hydroxamic acids **1** would occur and (2) the C-N bond formation between **1** and **4** would be under the influence of both a chiral nucleophile **1** and a Brønsted base organocatalysts 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 α/β-dipeptide derivatives.

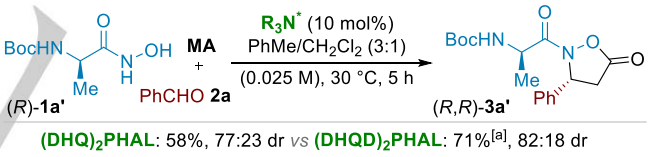
Table 1. Proof of principle and optimization.[a]



Entry	Deviation from the standard conditions	Yield [%]	dr[b]
1	Without catalyst	20 (55)[c]	57:43
2	Quinuclidine as catalyst	86	71:29
3	**-**	**75**	**86:14**
4	**(DHQD)$_2$PHAL** as catalyst	82	74:26
5	**(DHQ)$_2$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[d]	44	73:27
9	CH_2Cl_2 (0.1 M) as solvent, 20 °C[d]	30	86:14
10	PhMe (0.1 M) as solvent, 20 °C[d]	traces	-
11	PhMe/CH_2Cl_2 (3:1, 0.1 M) as solvent, 20 °C[d]	68	86:14

[a] Reaction conditions: **1a** (0.1 mmol), PhCHO **2a** (1 equiv), **MA** (1.5 equiv) in PhMe/CH_2Cl_2 (3:1, 0.025 M) at 30 °C for 5 h. Yields of both diastereoisomers determined by ^{1}H NMR with an internal standard. [b] dr determined by ^{1}H NMR on the crude product. [c] Bimolecular reaction from benzylidene Meldrum's acid **4a**. [d] **MA** (1 equiv), **(DHQ)$_2$PHAL** (20 mol%).

At the onset, it was shown that the model MCR involving the *N*-Boc alanine hydroxamic acid **1a** (Boc-αAlaNHOH), **MA** and benzaldehyde **2a** furnished after 5 hours the corresponding isoxazolidinone **3a** in 20% yield (determined by ^{1}H NMR) as 57:43 mixture of diastereoisomers namely with virtually no stereoinduction (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,[15] but the ability of a catalyst to accelerate this process and promote a stereoselective sequence remains an issue.[10] 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)$_2$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_2Cl_2 (entries 8-9) benefited to the level of stereoinduction, while a mixture of PhMe/CH_2Cl_2 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 eratic 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_a = 4.8 in H_2O)[11],[16] 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-αAlaNHOH **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)$_2$PHAL** catalyst was able to transform the (*R*)-Boc-αAlaNHOH enantiomer **1a'** into isoxazolidinone (*R*,*R*)-**3a'** in 71% yield and 82:18 dr contrary to **(DHQ)$_2$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 isoxazolidones **3a** and **3a'** as a single enantiomer (>99:1 er, see SI).



(DHQ)$_2$PHAL: 58%, 77:23 dr *vs* **(DHQD)$_2$PHAL**: 71%[a], 82:18 dr

Scheme 2. Molecular diversity towards a versatile synthesis of **3a'** - the other enantiomer of isoxazolidinone **3a**. Yields of both diastereoisomers determined by ^{1}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-αAlaNHOH **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%).[17] Starting from isovaleraldehyde **2b**, a facile synthesis of the corresponding isoxazolidinone **3b**, having βhLeu backbone (homologated β^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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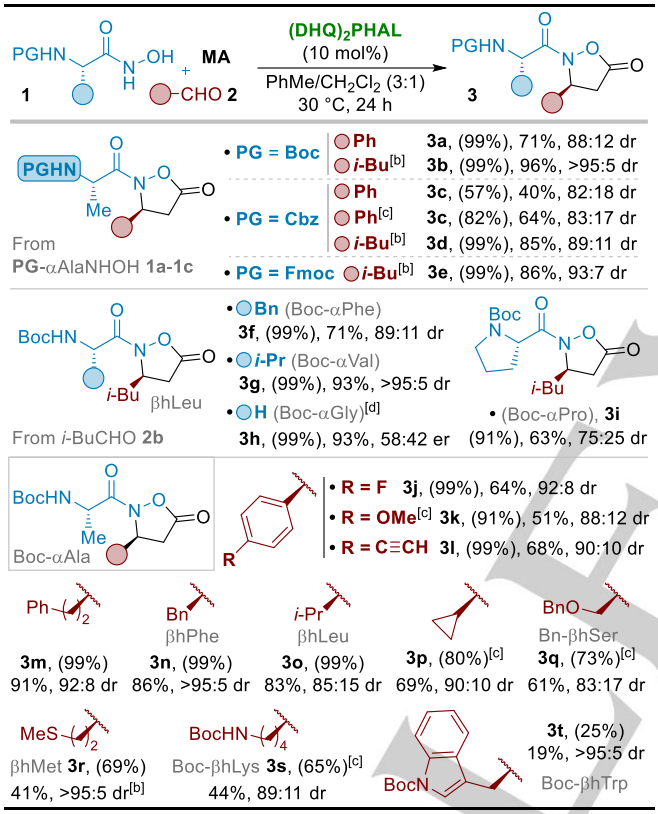
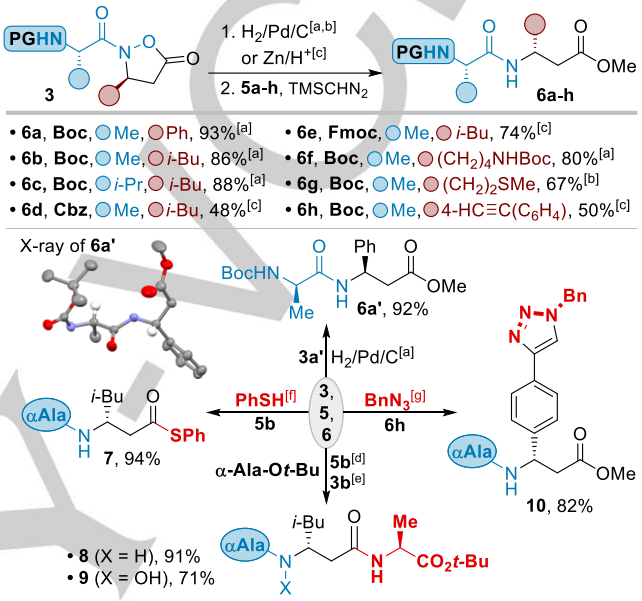
concentration.[18] The MCR was applied successfully to *N*-Cbz-αAlaNHOH **1b** (**3c**-**3d**, 64-85%, 83:17-89:11 dr)[19] and *N*-Fmoc-αAlaNHOH **1c** (**3e**, 86%, 93:7 dr) to provide the corresponding **3c**-**3e** with good to excellent stereoselectivities and yields. Then, various βhLeu-derived isoxazolidinones were constructed from isovaleraldehyde and Boc-protected proteinogenic αAA such as αPhe (**3f**, 71%, 89:11 dr), αVal (**3f**, 93%, >95:5 dr) and αPro (**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)$_2$PHAL** catalyst to promote an enantioselective process from an achiral αAANHOH.[10a],[20]

Table 2. Scope and limitations.[a]



[a] Reaction conditions: **1** (0.3 mmol), RCHO **2** (1 equiv), **MA** (1.5 equiv) in PhMe/CH_2Cl_2 (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 ^{1}H NMR with an internal standard. dr determined by ^{1}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 βhPhe **3n** and βhLeu **3o** precursors. Isoxazolidinones with ether **3q** (βhSer, 61%, 83:17 dr), thioether **3r** (βhMet, 41%, >95:5 dr) and NHBoc **3s** (βhLys, 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** (βhTrp) 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)$_2$PHAL** as organocatalyst.



Scheme 3. Chemical transformations into α/β-dipeptides. Reaction conditions: [a] H_2, Pd/C (1 atm), *i*-PrOH, 30 °C for **6a-b**;15 atm, RT for **6c**, 1 atm, 50 °C for **6f** and $TMSCHN_2$, MeOH, RT. [b] H_2, $Pd(OH)_2$/C (20 atm), *i*-PrOH/EtOAc (2:1), 60 °C for **6g**. [c] Zn (40-80 equiv), THF/H_2O/AcOH, 40 °C, and $TMSCHN_2$, MeOH, RT. [d] From **3b**, HCl•AlaO*t*-Bu, iPr_2NEt, DMAP (0.5 equiv), DMF, RT. [e] From **5b**, HCl•AlaO*t*-Bu, *i*-Pr_2NEt, EDC•HCl, HOBt, CH_2Cl_2, RT. [f] PhSH, DCC, HOBt, CH_2Cl_2, RT. [g] BnN_3, Na•Ascorbate, $CuSO_4$•$5H_2O$ (20 mol%), *t*-BuOH/H_2O, RT.

Having an array of novel isoxazolidinones **3** in hand, decorated with various functionalities, the transformations of **3** into α/β-dipeptide derivatives was undertaken in order to probe the versatility of these masked βAA 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*-α/β-dipeptides-OMe **6a**-**6c** (86-93%),[19] together with NHBoc **6f** (Boc-αAla-Boc-βhLys, 80%) and SMe **6g** (Boc-αAla-Boc-βhMet, 67%) derivatives were easily synthesized. This straightforward strategy was also applied to the formation of (*R*,*R*)-dipeptide **6a'** in 92% yield.[19] On the other hand, by means of orthogonal Zn/AcOH deprotection conditions, the elaboration of *N*-Cbz and *N*-Fmoc αAla-βhLeu dipeptides **6d** (48%) and **6e** (74%) respectively was allowed.[10b] 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-αAla-βhLeu carboxylic acid **5b** (used as a crude product) was subjected to

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

In summary, we have developed a multicomponent synthesis of novel isoxazolidin-5-ones possessing an *N*-α-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 α/β-dipeptides, as useful fragment in medicinal chemistry.

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

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[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.

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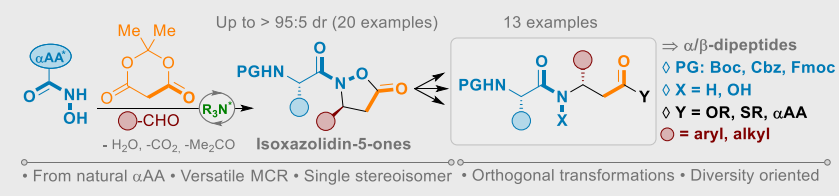

The diversity: A straightforward organocatalyzed multicomponent reaction (MCR) involving readily available hydroxamic acids-derived from naturally occurring α-amino acids (αAA) allows a stereoselective and diversity-oriented synthesis of novel isoxazolidin-5-ones as versatile platforms for the elaboration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

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

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Organocatalytic Multicomponent Synthesis of α/β-Dipeptide Derivatives

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