Multicomponent Reactions

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Highly Stereoselective Synthesis of Substituted Prolyl Peptides Using a Combination of Biocatalytic Desymmetrization and Multicomponent Reactions**

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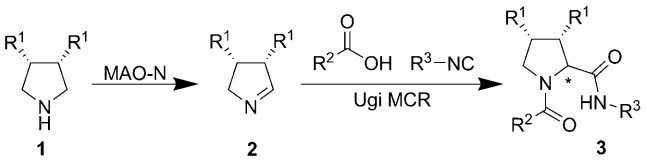
Multicomponent reactions (MCRs) offer the ability to rapidly and efficiently generate collections of structurally and functionally diverse organic compounds.[1] MCRs are important tools for both combinatorial chemistry and diversity-oriented synthesis, and thus play a significant role in the development of methodology for drug discovery.[2] Although MCRs are very efficient by their nature, the stereocontrol in these reactions is mostly not trivial.[3] For most MCRs, catalytic asymmetric methods to control the stereochemical outcome of the reaction are so far not available.

The Ugi reaction is undoubtedly one of the most widely applied MCRs.[4] It is of considerable interest owing to its exceptional synthetic efficiency and is widely used in the fields of modern combinatorial and medical chemistry.[1,2] The Ugi reaction involves a one-pot condensation of an aldehyde, an amine, a carboxylic acid, and an isocyanide to produce chiral α-acylaminoamides. However, as in most MCRs, controlling the newly formed stereocenter is highly complex.

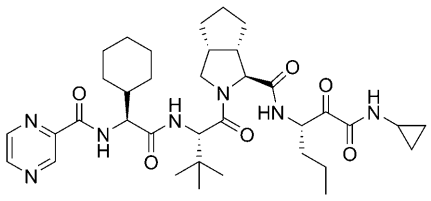
In 1982, Nutt and Joullié reported the use of an Ugi-type three-component reaction (3CR) that employed substituted 1-pyrrolines instead of the amine and aldehyde components to produce substituted prolyl peptides.[5] In that case and in later applications,[6] the (dia)stereoselectivities were poor or unpredictable at best, and the routes to the required substituted 1-pyrrolines were tedious and/or low-yielding.

Recently, Turner and co-workers reported the biocatalytic desymmetrization of 3,4-substituted *meso*-pyrrolidines with monoamine oxidase N (MAO-N) from *Aspergillus niger*[7] to yield optically active
1-pyrrolines in excellent yields and *ee* values.[8] As imines are intermediates for many common multicomponent reactions, the use of these optically active 1-pyrrolines in the Ugi MCR would be highly attractive given the excellent diastereoselectivity that can be achieved from the addition of nucleophiles to the imine, owing to its steric bulk.

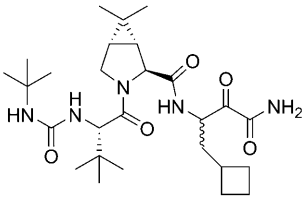
Herein, we report the development of a new MAO-N oxidation/MCR (MAO-MCR) sequence for the stereoselective synthesis of highly functionalized, optically pure 3,4-substituted prolyl peptides starting from simple cyclic *meso*-amines (Scheme 1). These peptides, with generic structure **3**, are of considerable interest in organocatalysis[9] and medicinal chemistry. Specifically, such substructures are key structural elements of the hepatitis C virus NS3 protease inhibitors telaprevir[10] and boceprevir[11] (Scheme 2).



Scheme 1. General MAO-MCR sequence.



telaprevir



boceprevir

Scheme 2. HCV NS3 protease inhibitors.

First, we turned our attention to finding the most suitable conditions for the Ugi-type MCR. As methanol is usually the solvent of choice in the Ugi reaction, we decided to do a solvent screen to determine if there would be any solvent effect on the diastereomeric ratio (d.r.). The reaction of racemic 3-azabicyclo[3.3.0]oct-2-ene (*rac*-**4**, synthesized according to a literature procedure[8]), benzoic acid, and

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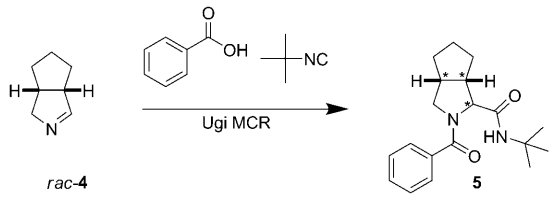
tert-butyl isocyanide was selected as the model reaction. Various solvents were screened at room temperature (Table 1), and dichloromethane and toluene gave the best

Table 1: Solvent and temperature dependence of the d.r. of the Ugi-type 3CR of *rac*-**4**, benzoic acid, and *tert*-butyl isocyanide.[a]



rac-**4** **5**

Entry	Solvent	d.r.[b] (RT)	d.r. (4 °C)	d.r. (−40 °C)
1	H_2O	87:13	–[c]	–[c]
2	buffer[d]	87:13	–[c]	–[c]
3	MeOH	90:10	92:8	91:9
4	CH_2Cl_2	92:8	93:7	90:10
5	DMSO	87:13	–[c]	–[c]
6	DMF	89:11	–[c]	–[c]
7	toluene	92:8	93:7	–[e]
8	TFE	90:10	–[c]	–[c]

[a] All reactions were performed with 0.073 mmol of imine *rac*-**4** and 0.1 mmol of benzoic acid and *tert*-butyl isocyanide and run until conversion of the imine was complete. Reaction mixtures were stirred for 24 h at the appropriate temperature. [b] Based on GC analysis. [c] Not tested. [d] 100 mM KPO_4 buffer, pH 8.0. [e] Reaction too slow for accurate determination. DMF = *N*,*N*-dimethylformamide, TFE = 2,2,2-trifluoroethanol.

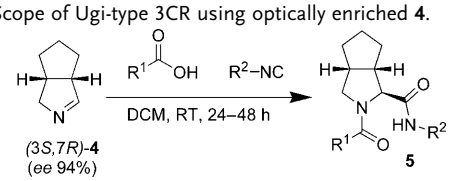
diastereomeric ratios. These solvents were also subjected to screening at lower temperatures. Table 1 shows that dichloromethane at 4 °C gave the best diastereomeric ratio. The yields were comparable for dichloromethane and methanol in contrast to toluene where the yields were lower (data not presented). Because of the only marginal improvement in diastereomeric ratio at 4 °C we decided to perform our MAO-MCR sequence in CH_2Cl_2 at room temperature.

Enantiomerically enriched cyclic imine (3*S*,7*R*)-**4** was prepared by MAO-N-catalyzed desymmetrization of the corresponding pyrrolidine derivative[8] in very good yield and *ee* (85 %, 94 % *ee*). The *ee* could be improved to 97 % by recrystallization during workup.

With the chiral imine **4** in hand, we turned our attention to the Ugi-type 3CR. Different carboxylic acids and isocyanides were used to generate substituted prolyl peptides **5a**–**g** in good yield and d.r. with very good *ee* (Table 2).

Excellent diastereoselectivity was observed for all reactions (Table 2). Crystallographic analysis of **5f** (Figure 1) determined the absolute configuration (as the stereochemistry at the C3 and C4 positions, resulting from the biotransformation, has been reported previously[8]), and showed that attack by the isocyanide occured from the sterically less-hindered face. The 2,3-*trans* relationship is in agreement with the generally accepted mechanism of the Ugi reaction, in which the stereodetermining step is the direct nucleophilic attack of the isocyanide on the imine (or iminium) carbon. The extraordinarily high selectivity for the 2,3-*trans* isomer is

Table 2: Scope of Ugi-type 3CR using optically enriched **4**.



(3*S*,7*R*)-**4** (*ee* 94%) **5**

Entry	Product	R^1	R^2	*t* [h]	Yield [%]	d.r.[a]	*ee* [%][b]
1	**5a**	Me	*t*Bu	48	73	93:7	95[c]
2	**5b**	Ph	*t*Bu	24	80	93:7	94
3	**5c**	furyl	*i*Pr	48	75	92:8	94
4	**5d**	Ph	*i*Pr	24	78	92:8	94
5	**5e**	Me	Bn	48	71	92:8	94
6	**5f**	Ph	Bn	24	81	92:8	97[c]
7	**5g**	*i*Pr	*t*Bu	48	83	93:7	97[c]

[a] d.r. determined by GC analysis. [b] *ee* determined by HPLC and GC analysis. [c] Partial crystallization of imine.

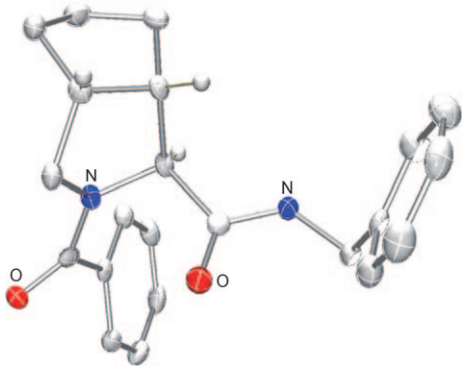


Figure 1. Single-crystal structure of **5f**. Displacement ellipsoids are drawn at the 50 % probability level.[14]

in sharp contrast with other reports, where stereoinduction is poor[6a–e] or the 2,3-*cis* isomer is preferentially formed.[6f,g]

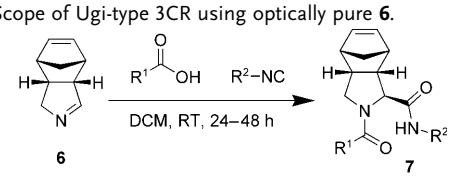
All other pyrrolidines **5** were assigned the same absolute stereochemistry as **5f**, based on analogy of the ^{1}H NMR spectroscopic data.

Subsequently, the sterically demanding imine **6** was prepared by MAO-N-catalyzed desymmetrization in 84 % yield and > 99 % *ee*, and was used in a series of Ugi-type 3CRs. To our delight, substituted prolyl peptides **7** were obtained as single diastereomers in > 99 % *ee* (Table 3, entries 1–8).

To confirm that the stereochemical outcome of the reaction was solely determined by the starting chiral imine, we reacted **6** with *t*BuNC and either Fmoc-Pro-OH or Fmoc-D-Pro-OH to give **8** and **9**, respectively (Scheme 3a). In both cases, only one diastereomer was formed.[12] Likewise, we reacted **6** with benzoic acid and either (*S*)- or (*R*)-α-methylbenzylamine to give **10** and **11**, respectively, as single diastereomers. ^{1}H NMR analysis indicated that the shown 2,3-*trans* isomers were selectively formed in all cases.

We then reacted imine **6** with Fmoc-D-Pro-OH and methyl 3-isocyanopropionate, which, after treatment with NaOH in methanol/dichloromethane,[13] afforded **12** as a single stereoisomer (Scheme 3b). Compound **12** strongly resembles H-D-

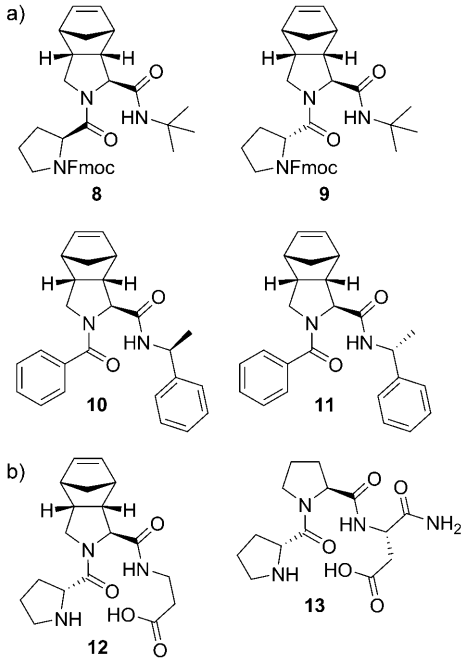
Table 3: Scope of Ugi-type 3CR using optically pure **6**.



6 **7**

Entry	Product	R^1	R^2	*t* [h]	Yield [%]	d.r.[a]	*ee* [%][b]
1	**7a**	Me	*t*Bu	48	83	>99:1	>99
2	**7b**	Ph	*t*Bu	24	82	>99:1	>99
3	**7c**	furyl	*i*Pr	48	75	>99:1	>99
4	**7d**	Ph	*i*Pr	24	78	>99:1	>99
5	**7e**	Me	Bn	48	78	>99:1	>99
6	**7f**	Ph	Bn	24	80	>99:1	>99
7	**7g**	*i*Pr	*t*Bu	48	81	>99:1	>99

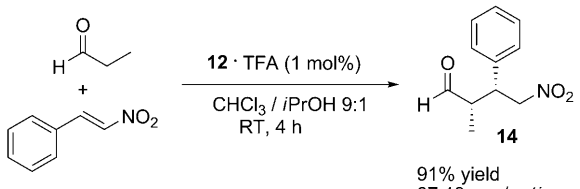
[a] d.r. determined by GC analysis. [b] *ee* determined by HPLC and GC analysis.



Scheme 3. a) Substituted prolyl peptides from optically pure acid or isocyanide inputs. b) Prolyl tripeptide organocatalysts. Fmoc = 9-fluorenylmethoxycarbonyl, Pro = proline, Asp = aspartic acid.

Pro-Pro-Asp-OH (**13**), which was described by Wennemers and co-workers to be a highly active and selective organocatalyst for conjugate additions of enolizable aldehydes and nitroolefins.[9] To our delight, peptide **12** catalyzed the reaction between propanal and nitrostyrene to give **14** (Scheme 4) in 91% yield, 87:13 *syn*/*anti* ratio, and 86% *ee* (compared to 90:10 *syn*/*anti* and 91% *ee* using **13**[9a]). Thus, our MAO-MCR sequence allows efficient asymmetric synthesis of proline derivatives containing all structural requirements for catalytic activity.

In conclusion, we have developed a highly efficient combination of MAO-N-catalyzed desymmetrization of cyclic *meso*-amines with the Ugi-type 3CR. This procedure is characterized by mild conditions, simple experiment procedures, and excellent yields and d.r. and *ee* values. We



Scheme 4. Organocatalytic asymmetric conjugate addition using **12**.

expect this methodology is applicable to a wide variety of 3,4-*cis*-substituted 1-pyrrolines and therefore of considerable synthetic value in the construction of arrays of otherwise hard-to-access 3,4-substituted prolyl peptides, for example, as Wennemers-type organocatalysts. Moreover, our methodology holds great promise for applications in medicinal chemistry, especially in the synthesis of novel hepatitis C drugs.

Experimental Section

Representative procedure: Acetic acid (55 mg, 52 μL, 0.91 mmol) and *tert*-butyl isocyanide (76 mg, 103 μL, 0.91 mmol) were added to a solution of imine **6** (93 mg, 0.70 mmol) in CH_2Cl_2. The reaction mixture was stirred for 24 h at RT. CH_2Cl_2 (8 mL) was added and the resulting mixture was washed with Na_2CO_3 (2 × 10 mL) and then dried ($MgSO_4$), filtered, and concentrated to give **7a** as a white solid, yield 83%, >99:1 d.r. (t_{major} = 18.179 min, GC for determination of d.r.); >99% *ee* [Daicel Chiralpak AD-H, hexane/2-propanol = 92:8, eluction rate 1.0 mL min^{-1}, λ = 220 nm, t_{major} = 5.319 min (chiral HPLC), t_{minor} = 6.587 min].

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